

Organic Chemistry

Core Principles

Noble Trex

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Introduction

Welcome to *Organic Chemistry: Core Principles*.

At the heart of every living organism, every life-saving pharmaceutical, and the vast majority of modern synthetic materials lies the element carbon. To study organic chemistry is to study the molecular architecture of the world around us. It is a discipline that bridges the fundamental laws of physics with the complex biological systems of life. This textbook is designed not merely as a repository of reactions, but as a guide to the logic inherent in nature's chemistry.

A common misconception among students is that organic chemistry is an exercise in rote memorization—an encyclopedic list of reagents and products to be committed to memory. This approach is neither sustainable nor enjoyable. Instead, this text presents organic chemistry as a structured language governed by a small set of fundamental physical principles. Just as learning a language requires understanding grammar before writing poetry, mastering organic chemistry requires understanding electron movement and structural stability before designing complex syntheses.

Our journey begins with the absolute foundations. In **Chapters 1 through 3**, we dismantle the molecule down to its atomic components. We explore how electrons are arranged in orbitals, how they form bonds through hybridization, and how these bonds dictate the three-dimensional shape of molecules in space. We emphasize that structure determines function; the static geometry of a molecule is the blueprint for its dynamic reactivity.

Building upon this structural framework, **Chapters 4 through 6** introduce the "engine" of organic chemistry: the mechanism. By defining reactivity through the lens of thermodynamics (stability) and kinetics (rate), and by quantifying these concepts using acid-base chemistry (pKa), we develop a predictive model for chemical change. Here, we introduce the curved arrow formalism—the chemist's primary tool for tracking electron flow. We will see that the vast majority of organic reactions are simply variations of nucleophiles attacking electrophiles.

With these mechanistic tools in hand, the middle portion of the text applies these principles to specific functional groups. We examine the rich chemistry of alkenes and alkynes, the redox chemistry of alcohols, and the fascinating world of organometallics. Interwoven with this reactivity is **Chapter 9**, which introduces spectroscopy. If reactions are the hands of the chemist, spectroscopy is the eyes, allowing us to see the invisible and confirm the structures we create using IR, MS, and NMR.

The latter third of the book tackles the most chemically versatile functional groups. We explore the stability of aromatic systems and the diverse reactivity of carbonyl compounds-aldehydes, ketones, carboxylic acids, and their derivatives. In **Chapter 13**, we bridge the gap between simple transformation and complex construction by exploring enolate chemistry, the primary method for forming carbon-carbon bonds.

Finally, **Chapter 14** serves as the capstone of this course: Synthetic Strategy. Here, we integrate every concept learned-from stereochemistry to protecting groups-to solve the puzzle of retrosynthesis. This is where science meets art, requiring creativity to design elegant routes to complex targets.

As you progress through these pages, I encourage you to look beyond the specific reaction at hand and search for the underlying pattern. Do not ask "What does this molecule do?" but rather "Where are the electrons flowing, and why?" By focusing on these core principles, you will find that the complex world of organic chemistry becomes not only manageable but truly beautiful.

Let us begin.

Chapter 1

Atomic Structure and Bonding

Organic chemistry is not merely a collection of molecules but a study of transformation and flow—specifically, the flow of electrons. This chapter lays the absolute foundation for understanding reactivity by exploring the quantum mechanical nature of the atom, the rules governing how atoms connect, and the distinct patterns of stability that emerge. By mastering these principles, from orbital shapes to resonance delocalization, you acquire the essential toolkit needed to predict how complex organic structures behave.

1.1 Electrons and Atomic Structure

Organic chemistry is largely the study of how and why electrons move. To predict reactivity (acid–base behavior, nucleophilicity/electrophilicity, stability of intermediates, and the shapes of molecules), we need a reliable picture of where electrons are likely to be and how tightly they are held by atoms. This section develops the quantum mechanical model of the atom, introduces orbitals as probability distributions, and then connects orbital occupancy to periodic trends—especially electronegativity—that govern bond polarity in organic molecules.

1.1.1 From classical pictures to quantum mechanics

Early atomic models (e.g., “planetary” electrons orbiting a nucleus) are appealing but ultimately fail because electrons do not behave like tiny classical particles with well-defined trajectories. Experiments such as atomic emission spectra show that atoms can absorb or emit only discrete (quantized) amounts of energy. A successful

model must explain both:

- **Quantized energies** (discrete spectral lines), and
- **Wave-like behavior** of electrons (diffraction and interference).

Quantum mechanics addresses this by describing an electron with a *wave function* $\psi(\mathbf{r})$, which contains information about the electron's energy and spatial distribution. The wave function itself is not directly observable, but the **probability density** is:

$$\rho(\mathbf{r}) = |\psi(\mathbf{r})|^2$$

Interpreting $|\psi|^2$ as a probability density means we should not imagine an electron “going around” the nucleus on a path. Instead, we speak of **orbitals**: regions of space where an electron is most likely to be found.

1.1.2 Orbitals as solutions to the Schrödinger equation

For a one-electron atom (hydrogen), the electron's allowed wave functions come from solving the time-independent Schrödinger equation:

$$\hat{H}\psi = E\psi$$

where $\hat{H}$ is the Hamiltonian operator (total energy operator), E is an allowed energy, and ψ is the corresponding wave function. The solutions are grouped into sets called **atomic orbitals**, labeled by quantum numbers. For organic chemistry, you do not need to solve the equation, but you must understand what its solutions imply:

- Only certain energies and orbital shapes are allowed.
- Orbitals have characteristic **sizes**, **shapes**, and **symmetries**.
- Orbitals may have **nodes** (surfaces where $\psi = 0$), which strongly influence shape and bonding.

1.1.3 Quantum numbers and what they mean chemically

An orbital is identified by three quantum numbers, and electrons carry a fourth:

- **Principal quantum number** $n = 1, 2, 3, \dots$: controls orbital energy and overall size (larger n generally means larger and higher energy).

- **Angular momentum quantum number** $\ell = 0, 1, 2, \dots, n - 1$: controls *shape*. The common letters are:

$$\ell = 0 \rightarrow s, \quad \ell = 1 \rightarrow p, \quad \ell = 2 \rightarrow d, \quad \ell = 3 \rightarrow f$$

- **Magnetic quantum number** $m_\ell = -\ell, \dots, 0, \dots, +\ell$: controls the orbital's *orientation* in space.
- **Spin quantum number** $m_s = +\frac{1}{2}$ or $-\frac{1}{2}$: an intrinsic electron property that allows two electrons to occupy the same orbital with opposite spins.

Two immediate chemical consequences follow:

- The number of orbitals in a subshell is $2\ell + 1$ (e.g., p has 3 orbitals: p_x, p_y, p_z).
- Each orbital can hold **at most two electrons** (because only two spin states exist).

1.1.4 Orbital phases and nodes: why sign matters

Although $|\psi|^2$ gives probability density, the *sign* (phase) of ψ also matters. In bonding, when two orbitals overlap:

- **Same phase overlap** (same sign) increases electron density between nuclei and is **bonding**.
- **Opposite phase overlap** (different sign) introduces a node between nuclei and is **antibonding**.

Thus, orbitals are often drawn with two colors (commonly red/blue) to indicate opposite phases. The colors do *not* mean charge; they are a sign convention for the wave function.

1.1.5 s and p orbitals: shapes and nodal structure

The orbitals most important for the bonding in typical organic molecules are the $2s$ and $2p$ orbitals of carbon, nitrogen, oxygen, and the other second-row elements.

s orbitals: spherical symmetry and radial nodes

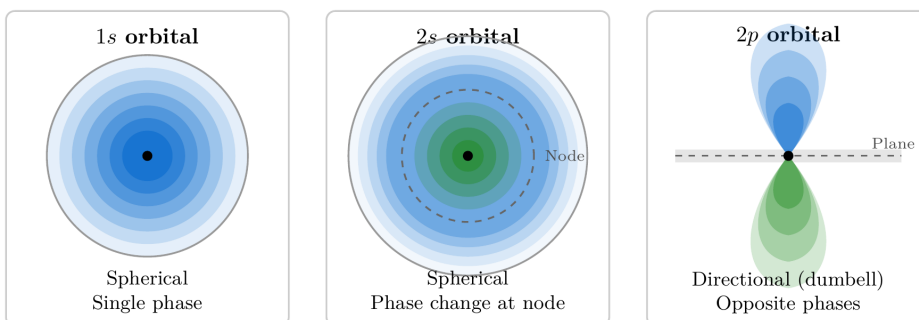
- An s orbital ($\ell = 0$) is **spherically symmetric**: probability density depends only on distance from the nucleus.
- The $1s$ orbital has **no nodes**.
- The $2s$ orbital has **one radial node**: a spherical surface where $\psi = 0$, separating an inner and outer region of opposite phase.

A useful mental picture is that the $2s$ orbital is not merely a “bigger $1s$ ”; it has *two lobes in the radial direction* (inner and outer) distinguished by a change in phase across the radial node.

p orbitals: directional bonding and nodal planes

- A p orbital ($\ell = 1$) has a characteristic **two-lobed** shape.
- Each p orbital has **one angular node**: a **nodal plane** passing through the nucleus where $\psi = 0$.
- The three p orbitals are oriented along mutually perpendicular axes: p_x , p_y , and p_z .

The nodal plane is central to organic chemistry because it controls how p orbitals overlap to form π bonds. For example, the side-by-side overlap of two parallel p orbitals produces a π bond with a nodal plane containing the internuclear axis.

A visual summary of $1s$, $2s$, and $2p$ orbitals

1.1.6 Electron configurations: placing electrons into orbitals

Real atoms contain multiple electrons, and electron–electron repulsions complicate the exact quantum mechanical treatment. Nevertheless, the orbital picture remains extremely useful when paired with three filling rules.

The Aufbau principle (“build-up”)

Electrons occupy the lowest-energy orbitals available, filling upward in energy. The familiar ordering for the first several shells is:

$$1s < 2s < 2p < 3s < 3p < 4s < 3d < 4p < \dots$$

In organic chemistry, the most frequently used valence orbitals are $2s$ and $2p$ (for C, N, O, F) and $3s$ and $3p$ (for Si, P, S, Cl).

The Pauli exclusion principle

No two electrons in the same atom can have the same set of four quantum numbers. A direct consequence is:

An orbital holds at most two electrons, and they must have opposite spins.

Hund’s rule

For orbitals of equal energy (degenerate orbitals), electrons occupy them singly with parallel spins before pairing. For example, in a p subshell, the three orbitals fill one-by-one before any pairing occurs. This minimizes electron–electron repulsion by maximizing spatial separation.

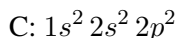
Orbital diagrams and electron configurations (examples)

It is helpful to use both notations:

- **Electron configuration** (compact bookkeeping, e.g., $1s^2 2s^2 2p^2$).

- **Orbital diagram** (shows spin pairing and Hund's rule explicitly).

Carbon ($Z = 6$).



In an orbital diagram, the $2p$ electrons occupy two different p orbitals with parallel spins (Hund's rule). These valence electrons are the starting point for understanding how carbon forms four bonds after orbital mixing (hybridization), introduced later.

Nitrogen ($Z = 7$) and oxygen ($Z = 8$).



Nitrogen has three unpaired $2p$ electrons (suggesting three bonding interactions in many structures), while oxygen has two unpaired $2p$ electrons and two paired electrons (often represented as two lone pairs in valence models). This connection between atomic electron configuration and typical bonding patterns is a central theme in organic chemistry.

1.1.7 Shielding, effective nuclear charge, and why valence electrons behave differently

Electrons do not feel the full attractive force of the nucleus because inner (core) electrons partially screen the nuclear charge. The **effective nuclear charge** Z_{eff} is a simplified way to express the net positive charge felt by a valence electron:

$$Z_{\text{eff}} \approx Z - \sigma$$

where Z is the atomic number and σ is a shielding constant (a measure of screening by other electrons).

Two qualitative but powerful ideas follow:

- **Across a period (left $\rightarrow$ right):** Z increases while shielding changes modestly (electrons are added to the same shell). Therefore Z_{eff} **increases**, pulling valence electrons closer.
- **Down a group (top $\rightarrow$ bottom):** valence electrons occupy higher n levels farther from the nucleus. Shielding increases substantially due to additional core shells, and the valence electrons are held **less tightly**.

These trends control atomic size and many related properties.

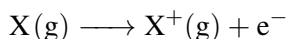
1.1.8 Periodic trends tied to orbital energies and sizes

Atomic radius

- **Across a period:** atomic radius generally **decreases** because increasing Z_{eff} contracts the valence orbitals.
- **Down a group:** atomic radius **increases** because valence orbitals have larger n and extend farther from the nucleus.

Ionization energy

The **first ionization energy** is the energy required to remove the most weakly held electron from a neutral atom in the gas phase:



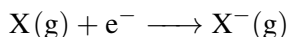
Trends:

- **Across a period:** ionization energy generally **increases** (electrons are held more tightly as Z_{eff} rises).
- **Down a group:** ionization energy generally **decreases** (valence electrons are farther away and more shielded).

Ionization energy relates to how strongly an atom retains electron density in bonds; it is one piece of the physical basis for electronegativity.

Electron affinity (qualitative)

Electron affinity measures the energy change when an electron is added to a neutral atom:



Many atoms (especially halogens) release energy upon gaining an electron (favorable electron affinity), consistent with their tendency to form anions and to withdraw electron density in polar covalent bonds.

1.1.9 Electronegativity: a rigorous definition for organic chemistry

What electronegativity is (and is not)

Electronegativity is the tendency of an atom *in a bond* to attract shared electron density toward itself. It is not directly measurable as a single experiment, so electronegativity values come from scales (e.g., Pauling) constructed to reproduce patterns in bond energies and other data.

Electronegativity is distinct from:

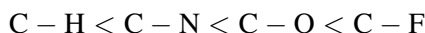
- **Electron affinity** (adding an electron to an isolated atom),
- **Ionization energy** (removing an electron from an isolated atom),
- **Formal charge** (a bookkeeping assignment in Lewis structures, not a direct measure of electron density).

Nevertheless, electronegativity correlates with ionization energy and electron affinity because all are influenced by Z_{eff} and orbital size.

Periodic trend in electronegativity

- **Across a period (left $\rightarrow$ right):** electronegativity generally **increases**. Valence orbitals are lower in energy and more contracted, so the atom attracts bonding electrons more strongly.
- **Down a group (top $\rightarrow$ bottom):** electronegativity generally **decreases**. Larger, more diffuse valence orbitals and stronger shielding reduce the pull on bonding electrons.

Second-row atoms (C, N, O, F) are especially important because their small, compact $2p$ orbitals overlap effectively, producing strong, directional covalent bonds central to organic structures. Their relatively high electronegativities also create pronounced bond polarities:



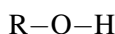
increasing in polarity as the heteroatom becomes more electronegative.

Electronegativity and bond polarity: the origin of partial charges

When two atoms of different electronegativities form a covalent bond, the shared electron density is drawn toward the more electronegative atom. We represent this with:

- **Partial charges** δ^+ and δ^-
- A **dipole arrow** pointing toward the more electronegative atom (with a plus sign at the tail)

For example, in an alcohol:



oxygen is more electronegative than both carbon and hydrogen, so electron density is polarized toward O. The C–O and O–H bonds are polar, which is why alcohols can hydrogen-bond and why the oxygen can act as a Lewis base. These reactivity patterns emerge directly from the quantum-based ideas: orbital energies, contraction, and Z_{eff} .

1.1.10 Why this matters for the rest of organic chemistry

The quantum mechanical model provides the conceptual machinery for everything that follows:

- **Lewis structures** depend on valence electron counts and typical bonding patterns rooted in electron configurations.
- **Resonance** and curved-arrow reasoning track electron density movement, which is meaningful only when we have a model for where electrons reside (orbitals and electron pairs).
- **Functional group reactivity** depends on bond polarity and the stability of electron-rich or electron-poor sites, governed by electronegativity and orbital energies.

In the next section, we will translate these orbital-based ideas into practical molecular representations using Lewis structures and formal charge, while keeping in mind that Lewis pictures are simplified projections of a deeper orbital reality.

1.2 Covalent Bonding and Lewis Structures

The quantum mechanical picture developed in the previous section explains *why* atoms hold electrons with different strengths (effective nuclear charge, orbital energies, electronegativity). In practice, organic chemists need a fast, reliable way to *count* valence electrons, *connect* atoms, and *evaluate* whether a proposed structure is reasonable. Lewis theory provides that framework.

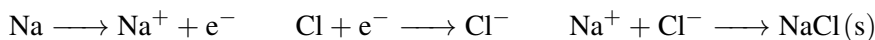
A Lewis structure is not a literal picture of orbitals; it is a **bookkeeping model** that tracks valence electrons as **bonding pairs** (lines) and **lone pairs** (dots). When used carefully—especially with **formal charge**—it becomes a powerful tool for predicting polarity, reactive sites, and plausible resonance patterns.

1.2.1 Bonding as electron sharing: ionic, covalent, and polar covalent

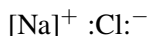
Bonds can be viewed on a continuum from electron transfer to equal sharing. The dominant factor is the **electronegativity difference** $\Delta\chi$.

Ionic bonding (electron transfer limit)

In the ionic limit, one atom donates electron density and another accepts it, producing ions held together by electrostatic attraction. A classic example is:



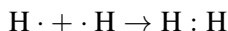
Lewis representations emphasize full charges:



Ionic bonding is most common between metals and nonmetals; it is not the dominant bonding pattern within typical organic molecules, but ionic *character* (partial charges) is ubiquitous.

Covalent bonding (equal sharing limit)

In the covalent limit, atoms share electron pairs. A simple example is hydrogen:



or, more commonly,



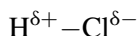
Each H “counts” the shared pair toward its duet (2 electrons), achieving a stable valence configuration.

Polar covalent bonding (the organic chemistry default)

Most bonds in organic molecules are **polar covalent**: electrons are shared but unequally. For example:



Chlorine is more electronegative, so the bond is polarized:



This polarization underlies the behavior of functional groups: electron-rich atoms (often O, N, halogens) act as Lewis bases/nucleophiles, while electron-poor atoms (often C attached to electronegative substituents) act as electrophiles.

1.2.2 Valence electrons and the octet rule (with realistic expectations)

Lewis structures focus on **valence electrons**: for main-group elements, these are the *s* and *p* electrons in the outermost shell.

The octet rule and duet rule

- **Second-row elements** (C, N, O, F) strongly prefer an **octet**: 8 electrons in their valence shell, resembling the noble gas configuration.
- **Hydrogen** follows the **duet rule**: 2 electrons (like He).

In organic chemistry, most stable neutral structures respect these rules, and deviations usually signal high reactivity (e.g., carbocations) or require careful justification (e.g., radicals).

Common octet patterns (typical valences)

These patterns appear so often that they serve as “sanity checks”:

- **Carbon:** 4 bonds, 0 lone pairs (neutral carbon in typical organics)
- **Nitrogen:** 3 bonds + 1 lone pair (neutral amines); 4 bonds (ammonium, positive)
- **Oxygen:** 2 bonds + 2 lone pairs (neutral alcohols/ethers); 1 bond (negative, alkoxide)
- **Halogens (F, Cl, Br, I):** 1 bond + 3 lone pairs (neutral)

These are not arbitrary; they follow from valence electron counts and the strong stabilization associated with filled $2s/2p$ shells for second-row atoms.

Important exceptions you must recognize

Incomplete octets (electron-deficient species).

- **Carbocations** (e.g., CH_3^+): carbon has only 6 valence electrons (three bonds, no lone pair). Such species are strongly electrophilic.
- **Boron compounds** (e.g., BF_3): boron commonly has 6 valence electrons and acts as a Lewis acid.

Odd-electron species (radicals). Species with an odd number of valence electrons cannot give all atoms full octets. Example: $\text{Cl}\cdot$ or organic radicals such as $\text{CH}_3\cdot$.

Expanded octets (third row and beyond). Elements like P, S, Cl can sometimes be drawn with more than 8 electrons. In early organic chemistry, the most relevant cases involve common hypervalent patterns for P and S (e.g., phosphates, sulfates). For many neutral organosulfur and organophosphorus compounds, octet-based Lewis structures still work well, but you should be aware that bonding descriptions may require resonance and/or more advanced models.

1.2.3 A systematic algorithm for drawing Lewis structures

Lewis structures should be drawn using a reproducible procedure. The following algorithm works for most main-group molecules and polyatomic ions encountered in organic chemistry.

Step 1: Determine the total number of valence electrons

Add valence electrons from each atom (using periodic table group numbers for main-group elements), and then adjust for charge:

- For a **negative charge** (-1), *add* 1 electron.
- For a **positive charge** ($+1$), *subtract* 1 electron.

Example: acetate ion, $\text{C}_2\text{H}_3\text{O}_2^-$.

$$\text{Valence } e^- = 2(\text{C} : 4) + 3(\text{H} : 1) + 2(\text{O} : 6) + 1 = 8 + 3 + 12 + 1 = 24$$

Step 2: Choose a skeletal structure (connectivity)

In organic chemistry, connectivity is often known from context or nomenclature. If not, a useful rule is:

- The **least electronegative** atom (except H) is often central.
- **Hydrogen is terminal** (forms one bond).
- **Halogens are terminal** in typical Lewis structures (form one bond).

For acetate, a sensible skeleton is $\text{H}_3\text{C}-\text{CO}_2^-$ (a methyl group attached to a carboxylate carbon).

Step 3: Connect atoms with single bonds

Each single bond represents **2 electrons**. Draw the skeleton with lines. Keep track of electrons used.

Example: CH_3CO_2^- . Skeleton single bonds: C–H (3), C–C (1), C–O (2) $\Rightarrow$ 6 single bonds = 12 electrons used.

Remaining electrons: $24 - 12 = 12$.

Step 4: Complete terminal atoms' octets (or duets)

Place lone pairs on terminal atoms first (typically O, halogens). Hydrogen is complete with one bond.

In acetate, place lone pairs on the two oxygens until each has an octet. With two C–O single bonds, each O currently has 2 electrons from the bond; each needs 6 more (three lone pairs), so both oxygens would require $2 \times 6 = 12$ electrons—exactly what remains.

At this stage, the structure has all atoms with octets *except* the carbonyl carbon might still have only four single bonds? Here it has four single bonds total? In CH_3CO_2^- skeleton, the carboxyl carbon is bonded to CH_3 and to two oxygens (3 single bonds total), so it has only 6 electrons around it (three bonds). That indicates we need a multiple bond.

Step 5: If the central atom lacks an octet, form multiple bonds

Convert a lone pair on a neighboring atom into a bonding pair (double bond), maintaining total electron count but increasing electron sharing to satisfy octets.

For acetate, convert one O lone pair into a π bond to give $\text{C}=\text{O}$. This yields one $\text{C}=\text{O}$ and one $\text{C}-\text{O}^-$ (with more lone pairs). This introduces **formal charges** that must be evaluated (next subsection) and also signals that **resonance** is important (covered in the following section).

Step 6: Check electron count and reasonable formal charges

A correct Lewis structure must:

- Use exactly the computed total valence electrons,
- Give appropriate octets/duets (with justified exceptions),
- Minimize unreasonable formal charges and charge separation.

1.2.4 Formal charge: definition, calculation, and meaning

Formal charge (FC) is a bookkeeping tool that assigns charges to atoms in a Lewis structure by assuming *equal sharing* of bonding electrons. It does **not** claim that charge is actually localized exactly that way; rather, it lets us compare alternative Lewis structures on consistent accounting grounds.

Formal charge formula

For an atom in a Lewis structure:

$$\text{FC} = V - \left(N + \frac{B}{2} \right)$$

where

- V = valence electrons of the free atom,
- N = nonbonding (lone-pair) electrons assigned to that atom,
- B = bonding electrons in bonds to that atom (2 per single bond, 4 per double bond, etc.).

Equivalent phrasing: *Formal charge equals valence electrons minus (lone-pair electrons + number of bonds)*. This shortcut works because each bond corresponds to one electron assigned to the atom under equal sharing.

Worked examples of formal charge

Example 1: water, H_2O . O has two lone pairs and two single bonds:

$$V(\text{O}) = 6, \quad N = 4, \quad B = 4$$

$$\text{FC}(\text{O}) = 6 - \left(4 + \frac{4}{2} \right) = 6 - (4 + 2) = 0$$

Each H: $V = 1$, $N = 0$, one bond $\Rightarrow B = 2$:

$$\text{FC}(\text{H}) = 1 - \left(0 + \frac{2}{2} \right) = 0$$

So H_2O is neutral with all FCs zero.

Example 2: hydroxide, HO^- . O has three lone pairs (6 electrons) and one bond:

$$\text{FC}(\text{O}) = 6 - \left(6 + \frac{2}{2} \right) = 6 - 7 = -1$$

H is 0. The negative charge resides formally on oxygen, consistent with oxygen's high electronegativity and common reactivity as a base/nucleophile.

Example 3: ammonium, NH_4^+ . N has four single bonds and no lone pairs:

$$\text{FC}(\text{N}) = 5 - \left(0 + \frac{8}{2}\right) = 5 - 4 = +1$$

Each H is 0. This is consistent with protonated amines being positively charged at nitrogen.

Example 4: carbon dioxide, CO_2 . The best Lewis structure is $\text{O}=\text{C}=\text{O}$, with each O having two lone pairs. For each O: $V = 6$, $N = 4$, $B = 4$ (double bond has 4 bonding electrons):

$$\text{FC}(\text{O}) = 6 - (4 + 2) = 0$$

For C: $V = 4$, $N = 0$, $B = 8$ (two double bonds):

$$\text{FC}(\text{C}) = 4 - (0 + 4) = 0$$

All zeros: strong indication this structure is preferred.

Rules of thumb for choosing among Lewis structures

When multiple Lewis structures satisfy octets and electron count, prefer structures that:

- **1. Minimize the magnitude of formal charges** (avoid ± 2 when possible),
- **2. Minimize charge separation** (avoid having both $+$ and $-$ if a neutral alternative exists),
- **3. Place negative formal charge on more electronegative atoms** (e.g., O rather than C),
- **4. Place positive formal charge on less electronegative atoms** when unavoidable (e.g., C rather than O).

These preferences align Lewis bookkeeping with the underlying physical reality that electronegative atoms stabilize electron density and that separated charges often cost energy.

1.2.5 How to count electrons correctly: common pitfalls

Many Lewis structure errors arise not from misunderstanding bonding, but from inconsistent counting. The following checkpoints prevent most mistakes.

Checkpoint 1: Sum of formal charges must equal the overall charge

After assigning FC values to all atoms:

$$\sum \text{FC} = \text{overall molecular/ionic charge}$$

If not, the structure is not consistent with the electron count.

Checkpoint 2: Second-row atoms should not exceed an octet

For C, N, O, F in particular, **do not draw five bonds to carbon** or three bonds plus a lone pair plus a double bond on nitrogen, etc., unless you are explicitly drawing a radical or an incomplete octet species. Octet violations in second-row elements are among the most common student errors.

Checkpoint 3: Hydrogens and halogens are nearly always terminal

In typical organic structures:

- H forms one bond and has no lone pairs.
- F, Cl, Br, I form one bond and have three lone pairs in neutral structures.

Checkpoint 4: Do not confuse formal charge with “real” charge density

Formal charge is a useful accounting device, but real electron density depends on electronegativity and bond polarization. For example, carbonyl oxygen in a neutral ketone has $\text{FC} = 0$, yet it is still partially negative ($\text{O}^{\delta-}$) and is commonly the nucleophilic site.

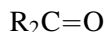
1.2.6 Lewis structures in organic chemistry: predicting reactive sites

Once a Lewis structure is drawn correctly, it immediately suggests likely reactivity patterns:

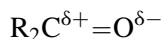
- **Lone pairs** (especially on O, N, halogens) identify potential **Lewis bases/nucleophiles**.
- **Positive formal charge** identifies strong **electrophiles** (e.g., carbocations, protonated carbonyls).

- **Polar bonds** (e.g., C–O, C–N, C–X) create electron-poor carbons that are often electrophilic.

Example: a carbonyl group (generic). A common Lewis representation is:



Even with all formal charges zero, electronegativity predicts polarization:



Thus, nucleophiles tend to attack the carbonyl carbon (electrophilic), while the oxygen tends to bind protons or metals (basic site). Later chapters will formalize these ideas using curved-arrow mechanisms.

1.2.7 Preview: when one Lewis structure is not enough

Some molecules are not adequately represented by a single Lewis structure without placing “uncomfortable” formal charges or implying unequal bonds. Carboxylates (RCO_2^-), allylic systems, and many conjugated π systems require **multiple valid Lewis structures** that differ only in electron placement, not in atom connectivity. This is the domain of **resonance**, developed in the next section.

For now, the key skill is to produce *valid* individual Lewis structures and to use formal charge to assess their plausibility. Resonance then becomes a controlled way to combine multiple valid contributors into a more accurate electron-distribution picture.

1.3 Resonance and Electron Delocalization

Lewis structures are indispensable for counting electrons and assigning formal charges, but they sometimes force an artificial choice: a single drawing may imply that electrons (and charges) are localized on one atom and one bond, even when the true electron density is spread over multiple atoms. **Resonance** is the systematic extension of Lewis theory that corrects this limitation.

In this section we develop three core ideas:

- A **resonance hybrid** (the real molecule) is not any one Lewis structure, but a weighted blend of multiple **resonance contributors**.

- Resonance is handled rigorously using **curved-arrow notation** that moves *electron pairs* without moving atoms.
- Resonance stabilizes molecules by **delocalizing charge and/or π electron density**, lowering energy relative to any single localized contributor.

1.3.1 What resonance is (and what it is not)

Definition of resonance contributors and the resonance hybrid

When two or more valid Lewis structures differ only in the placement of electrons (bond order and/or lone pairs) but have the *same atomic connectivity*, they are called **resonance contributors** (also called **canonical forms**). The actual electronic structure is the **resonance hybrid**.

Key consequences.

- The real molecule has **one geometry**. Contributors are not rapidly interconverting “isomers”; they are different drawings of the same species.
- Resonance contributors are separated by a double-headed arrow ($\leftrightarrow$), not an equilibrium arrow.
- Resonance affects **bond lengths, charge distribution, and stability**. For example, bonds may become intermediate in length between single and double.

Resonance does *not* move atoms

In resonance:

- **Atom positions and σ bonds do not change.**
- Only **π electrons** and/or **lone pairs** are relocated in the drawing.

A good practical rule is: *if you would need to redraw the molecular skeleton, you are not doing resonance.*

1.3.2 When resonance is needed: identifying delocalizable electron patterns

Resonance is common whenever you can draw more than one reasonable Lewis structure without violating octets (for second-row atoms) and without changing con-

nectivity. The most frequent patterns in organic chemistry are:

Adjacent π bonds (conjugation)

If a π bond is adjacent to another π bond (or to a p orbital), electrons can delocalize over a larger framework. This includes:

- conjugated dienes,
- aromatic rings (treated in later chapters),
- allylic cations/anions/radicals.

A lone pair adjacent to a π bond

A lone pair can donate into an adjacent π system, producing alternative contributors. Classic examples include:

- amides (RCONR_2),
- enols and phenols,
- anions next to carbonyls (enolates, covered later).

A positive charge adjacent to a lone pair or a π bond

A carbocation next to a π bond (allylic cation) is stabilized by delocalization of the positive charge.

Carbonyl-containing anions: carboxylates

Carboxylate ions (RCO_2^-) are among the most important resonance-stabilized species in organic chemistry. Their negative charge is distributed over two oxygens rather than localized on one.

1.3.3 Curved-arrow notation: the language of electron movement

Curved-arrow notation is the standard method for generating resonance contributors. It is also the foundation of reaction mechanisms. Mastering it here will pay dividends throughout the course.

What a curved arrow means

A curved arrow shows the movement of an **electron pair**:

- The **tail** starts at an electron source: a lone pair, a π bond, or a negative charge.
- The **head** points to where that electron pair ends up: forming a bond or becoming a lone pair.

In resonance, curved arrows *reassign* electrons within a fixed atomic framework.

Allowed moves in resonance (practical rules)

Most correct resonance steps can be built from these moves:

- **Move a π bond**: shift a double bond to an adjacent position.
- **Move a lone pair into a bond**: form a π bond next to it.
- **Move a bond onto an atom**: convert a π bond into a lone pair on one atom.

Conservation laws and constraints

A resonance step must obey all of the following:

- **Total number of electrons is conserved** (you are only moving them).
- **Total charge is conserved.**
- **Second-row atoms (C, N, O, F) must not exceed an octet.**
- **Connectivity is unchanged** (no atoms move; no σ bonds are broken/formed).

Common curved-arrow mistakes

- Starting an arrow at an atom rather than at a *pair of electrons*.
- Ending an arrow in empty space (unless explicitly creating a lone pair on an atom).
- Creating a structure where carbon has 10 electrons (five bonds) or oxygen has three bonds without a corresponding positive charge.
- Moving electrons in a way that breaks the *framework* (changing which atoms are connected).

1.3.4 Assessing resonance contributors: which ones matter most?

Not all contributors are equally important. The resonance hybrid is a *weighted* blend, and the most stable contributors contribute the most.

Major stability rules for contributors

Prefer contributors that:

- **Satisfy octets** for second-row atoms (especially C, N, O).
- **Minimize formal charge magnitude** (avoid ± 2 if possible).
- **Minimize charge separation** (avoid having both + and – when a less separated option exists).
- Place **negative charge on more electronegative atoms** ($O > N > C$).
- Place **positive charge on less electronegative atoms** when unavoidable ($C > N > O$).

These rules connect directly to the concepts from earlier sections: electronegativity and formal charge are the tools that let you judge whether a particular electron distribution is physically plausible.

Resonance and stability: the big picture

Resonance stabilizes a molecule because delocalization:

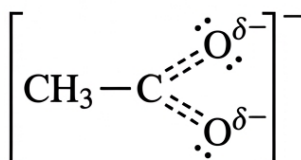
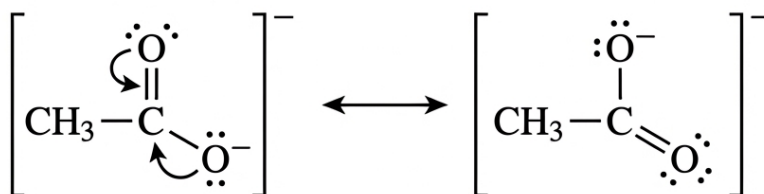
- spreads charge over a larger volume (reducing electrostatic energy),
- allows electron density to reside on atoms that stabilize it better (e.g., negative charge on oxygen),
- can increase bonding interactions overall (e.g., partial π bonding distributed across multiple atoms).

1.3.5 Canonical examples: acetate and the allyl cation

The two examples below illustrate the two most common resonance motifs in early organic chemistry:

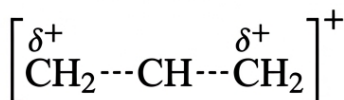
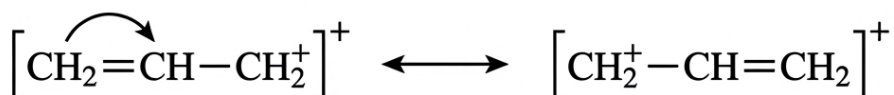
- **Carboxylate anion (acetate):** lone pair/ π bond delocalization over two oxygens.
- **Allyl cation:** π bond delocalization adjacent to a positive charge.

Acetate ion



Resonance hybrid
(electron delocalization over both O atoms)

Allyl cation



Resonance hybrid
(positive charge delocalized)

1.3.6 Interpreting the resonance hybrid: bond order and charge distribution

Resonance hybrids are often summarized with two experimentally meaningful consequences.

Partial bond order and bond length equalization

If two contributors differ only in the placement of a π bond between two positions, the hybrid often shows **intermediate bond order** in both positions.

- In the **acetate ion**, both C–O bonds are equivalent in the hybrid: each has partial double-bond character (bond order ≈ 1.5). This predicts that both C–O bond lengths are the same experimentally.
- In the **allyl cation**, the two C–C bonds are equivalent in the hybrid, each between single and double in character.

Delocalized charge

Resonance often spreads formal charge:

- In acetate, negative charge is shared by *both* oxygens (a major stabilizing factor, consistent with oxygen's high electronegativity).
- In the allyl cation, positive charge is distributed over the terminal carbons rather than confined to one carbon.

This delocalization is not merely aesthetic; it changes acidity/basicity, nucleophilicity/electrophilicity, and the energy barriers of reactions.

1.3.7 A disciplined procedure for drawing resonance forms

When asked to “draw resonance structures,” use the following procedure to stay rigorous.

Step 1: Verify the starting Lewis structure is valid

Before doing resonance, confirm:

- correct total valence electrons,
- correct connectivity,
- reasonable formal charges,
- octets satisfied (where expected).

Resonance cannot fix an invalid Lewis structure.

Step 2: Identify the electron source and sink

Find an electron pair that can move (lone pair or π bond) and an adjacent place it can go (an atom that can accept electron density without exceeding an octet).

Step 3: Push electrons with curved arrows

Use as many arrows as needed to keep octets satisfied. In many resonance steps, **two arrows** are required: one bond forms while another bond shifts to avoid overfilling an atom.

Step 4: Redraw the new contributor and re-check formal charges

After moving electrons:

- reassign formal charges,
- confirm electron count and octets,
- ensure only electrons moved (no atoms relocated).

1.3.8 Why resonance contributors differ in importance: acetate vs. less stable patterns

In acetate, the two main contributors are equivalent: each places the negative charge on an oxygen and gives all atoms octets. Therefore they contribute equally, producing a strongly delocalized anion.

By contrast, in many systems one contributor may be *minor* because it:

- introduces charge separation,

- places negative charge on carbon rather than oxygen,
- or violates octets.

The hybrid then resembles the major contributor more strongly. Thinking in terms of *weighted contributions* prevents a common misconception: resonance does not always mean “all forms are equally important.”

1.3.9 Resonance as a predictor of stability and reactivity

Resonance stabilization has immediate practical consequences in organic chemistry:

- **Stability of ions and intermediates:** carboxylates and allylic cations are more stable than comparable localized ions.
- **Acid–base behavior:** acids are stronger when their conjugate bases are resonance-stabilized (e.g., carboxylic acids vs. alcohols; treated in later chapters).
- **Site of reaction:** delocalization spreads electrophilic or nucleophilic character over multiple atoms, affecting where reagents attack.

At this stage, the most important outcome is conceptual: resonance is the bridge between simple Lewis bookkeeping and a more accurate picture of electron density. In the next section, we will build on this by learning to recognize functional groups—recurring structural patterns whose reactivity is largely controlled by bond polarity and resonance-enabled electron delocalization.

1.4 Introduction to Functional Groups

The previous sections developed a consistent framework for thinking about **electron distribution**: atomic electronegativity creates polar bonds, Lewis structures locate lone pairs and formal charges, and resonance explains how electron density can be delocalized across multiple atoms. Organic chemistry builds directly on these ideas by organizing molecules into families based on **functional groups**—specific atom-and-bond patterns that produce predictable reactivity.

A functional group is not merely a naming convenience. It is a structural motif that typically determines:

- where a molecule is **electron-rich** (nucleophilic/basic sites),
- where it is **electron-poor** (electrophilic/acidic sites),
- whether electrons are **localized** or **delocalized** (resonance),
- and what reactions are likely under common conditions (substitution, addition, elimination, oxidation/reduction).

This section is a recognition-and-classification guide. The goal is to learn to **see** functional groups inside larger structures and to connect each to a simple electron-picture: polar bonds, lone pairs, and π systems.

1.4.1 How to recognize functional groups in skeletal structures

Organic molecules are usually drawn in **skeletal (line-angle) form**. Recall the conventions:

- Each line endpoint or vertex is a **carbon** unless another element is shown.
- Hydrogens on carbon are usually omitted; they are implied to give carbon four bonds.
- **Heteroatoms** (O, N, halogens, S, P) are always written explicitly, and their attached hydrogens may be shown (e.g., HO, NH₂).
- Double and triple bonds are drawn explicitly and signal π electrons.

When scanning a structure, first locate:

- heteroatoms (O, N, halogens, S, P),
- multiple bonds (C=C, C#C, C=O, C#N),
- and aromatic rings (a conjugated π system).

Then match these features to named functional groups.

1.4.2 Hydrocarbon functional groups: carbon frameworks and π bonds

Hydrocarbons contain only C and H, but they already display important reactivity patterns depending on whether electrons are confined to σ bonds or include π bonds.

Alkanes (saturated hydrocarbons)

Alkanes have only single bonds (C–C and C–H). They are relatively nonpolar and generally less reactive in polar reactions because they lack strongly polarized bonds and lone pairs. They do participate in combustion and radical halogenation under appropriate conditions.

Alkenes (carbon–carbon double bonds)

Alkenes contain a C=C double bond (one σ and one π bond). The π bond is electron-rich and can act as a nucleophile toward strong electrophiles. Addition reactions across the double bond are a central theme in organic chemistry.

Alkynes (carbon–carbon triple bonds)

Alkynes contain a C#C triple bond (one σ and two π bonds). Like alkenes, they undergo addition reactions, but their geometry and acidity (for terminal alkynes) introduce additional patterns explored later.

Aromatics (aryl groups)

Aromatic rings (e.g., benzene) are conjugated cyclic π systems with unusual stability (aromaticity). They tend to undergo substitution rather than simple addition because addition would disrupt the aromatic π system.

1.4.3 Heteroatom functional groups: polarity, lone pairs, and common reactivity roles

Introducing heteroatoms changes electron distribution dramatically:

- Bonds to O and halogens are often strongly polar (C–O, C–X).
- O and N commonly carry lone pairs (nucleophilic/basic sites).
- Many heteroatom-containing groups participate in resonance (e.g., carbonyl derivatives, amides).

Oxygen-based functional groups**Alcohols** ($\text{R}-\text{OH}$).

Alcohols contain an $\text{O}-\text{H}$ bond and a $\text{C}-\text{O}$ bond. Oxygen bears two lone pairs and is electronegative, so alcohols are polar and can hydrogen-bond. The oxygen is typically the most nucleophilic site, while the $\text{O}-\text{H}$ proton can be weakly acidic.

Ethers ($\text{R}-\text{O}-\text{R}$).

Ethers have oxygen with two lone pairs but no $\text{O}-\text{H}$ bond, so they are less acidic than alcohols. Ethers are polar and often serve as solvents. Their oxygen can coordinate to Lewis acids and can be protonated in strong acid.

Carbonyl compounds (aldehydes and ketones)

A **carbonyl** group $\text{C}=\text{O}$ features:

- a polarized π bond ($\text{C}^{\delta+} = \text{O}^{\delta-}$),
- a nucleophilic oxygen (lone pairs),
- and an electrophilic carbon.

Aldehydes have at least one H on the carbonyl carbon ($\text{R}-\text{CHO}$); **ketones** have two carbon substituents ($\text{R}_2\text{C}=\text{O}$). Both commonly undergo nucleophilic addition.

Carboxylic acids ($\text{R}-\text{CO}_2\text{H}$).

Carboxylic acids contain a carbonyl plus a hydroxyl on the same carbon. Their conjugate bases (carboxylates) are resonance-stabilized, which is why carboxylic acids are substantially more acidic than alcohols. The carbonyl carbon is electrophilic, and the group participates in nucleophilic acyl substitution.

Esters ($\text{R}-\text{CO}_2\text{R}'$).

Esters are carboxylic acid derivatives in which the hydroxyl is replaced by OR' . They retain a carbonyl and participate in nucleophilic acyl substitution. Esters are common in fragrances, fats, and polymers.

Amides ($\text{R}-\text{CONR}_2$).

Amides are carboxylic acid derivatives with $-\text{NR}_2$ replacing $-\text{OH}$. Their key feature is resonance between the nitrogen lone pair and the carbonyl, which reduces nitrogen basicity and gives the $\text{C}-\text{N}$ bond partial double-bond character. Amides are foundational in peptides and proteins.

Nitrogen-based functional groups

Amines ($R-NH_2$, R_2NH , R_3N).

Amines contain a nitrogen with a lone pair. The lone pair is the primary reactive feature: amines are readily protonated and act as nucleophiles in substitution and addition reactions.

Nitriles ($R-C\equiv N$).

Nitriles contain a polarized triple bond. The carbon is electrophilic; the nitrogen has a lone pair but is relatively weakly basic due to high s-character and the strong electron-withdrawing effect of the triple bond. Nitriles can be converted into carboxylic acids and amines under appropriate conditions.

Halogen-containing functional groups

Alkyl halides ($R-X$, $X = F, Cl, Br, I$).

The $C-X$ bond is polarized ($C^{\delta+} - X^{\delta-}$). The carbon often behaves as an electrophile, and the halogen can serve as a leaving group. Alkyl halides are key substrates for substitution and elimination reactions.

Aryl halides ($Ar-X$).

Halogens attached directly to aromatic rings behave differently from alkyl halides because the carbon is part of an aromatic π system; nucleophilic substitution is more restricted and often requires activating groups or special conditions.

Sulfur- and phosphorus-based groups (brief survey)

Sulfur and phosphorus appear frequently in biologically relevant and synthetic molecules:

- **Thiols** ($R-SH$) are sulfur analogs of alcohols but often more nucleophilic and more acidic than corresponding alcohols.
- **Thioethers (sulfides)** ($R-S-R$) resemble ethers but are typically more polarizable and can be oxidized to sulfoxides or sulfones.
- **Phosphates** and related $P=O/P-O$ motifs are central in biochemistry (ATP, DNA backbone). Their reactivity is strongly influenced by charge and resonance.

These groups will be revisited when reactions that feature them become relevant.

1.4.4 A functional-group electron story for prediction

As you learn reactions, interpret each functional group with a small set of electron concepts:

- **Where are the lone pairs?**
- **Where are the polarized bonds?**
- **Where are the π bonds?**
- **Is there resonance stabilization?**

For example, consider an ester $\text{R}-\text{CO}_2\text{R}'$:

- the carbonyl carbon is electrophilic ($\text{C}^{\delta+}$),
- the two oxygens carry lone pairs,
- resonance distributes electron density and influences which bonds are strong or reactive.

This compact electron story is more predictive than memorizing reactions in isolation.

1.4.5 Functional group table (recognition, naming, and examples)

Major Functional Groups: Recognition and Naming Patterns

Category	Functional group	General structure	Naming (suffix/prefix)	Example
Hydrocarbons	Alkane	$R-CH_3$ / $R-CH_2-R$	-ane	ethane
	Alkene	$R-CH=CH-R$	-ene	propene
	Alkyne	$R-C\equiv C-R$	-yne	1-butyne
	Arene (aryl)	$Ar-H$ / $Ar-R$	-benzene (common)	toluene
Halogen-based	Alkyl halide	$R-X$ ($X = F, Cl, Br, I$)	fluoro-, chloro-, ...	bromoethane
Oxygen-based	Alcohol	$R-OH$	-ol	ethanol
	Ether	$R-O-R'$	alkoxy- (common)	diethyl ether
	Aldehyde	$R-CHO$	-al	ethanal
	Ketone	$R-C(=O)-R'$	-one	propanone
	Carboxylic acid	$R-C(=O)OH$	-oic acid	ethanoic acid
	Ester	$R-C(=O)OR'$	-oate	ethyl ethanoate
Nitrogen-based	Amine	$R-NH_2, R_2NH, R_3N$	-amine	ethylamine
	Amide	$R-C(=O)NR'_2$	-amide	acetamide
	Nitrile	$R-C\equiv N$	-nitrile	acetonitrile
Sulfur/Phosphorus	Thiol	$R-SH$	-thiol	ethanethiol
	Sulfide (thioether)	$R-S-R'$	thio- (common)	dimethyl sulfide
	Phosphate (generic)	$R-O-P(=O)(O^-)-O^-$	phosphate	methyl phosphate

R, R' = carbon substituents; Ar = aromatic ring; X = halogen.
General structures are shown schematically to emphasize recognition, not 3D geometry.

1.4.6 Strategy for mastering functional groups

To make functional-group knowledge usable, practice the following routine:

- **Name it:** identify the functional group and the key atoms.
- **Assign polarity:** mark likely δ^+ and δ^- based on electronegativity.
- **Locate lone pairs and π bonds:** decide where nucleophiles and electrophiles might be.
- **Ask about resonance:** can the lone pair or charge delocalize? If yes, expect altered basicity or acidity and bond character.

As the course proceeds, each major reaction family will be tied to a small set of functional groups. If you can quickly recognize the functional group and tell its electron story, you can usually predict the type of reaction that is likely to occur and the site where it occurs.

1.5 Problems

1.5.1 Quantum numbers, orbitals, and nodes

Answer all parts.

- **1.** For $n = 3$, list all allowed values of ℓ and, for each ℓ , list all allowed values of m_ℓ .
- **2.** How many orbitals are in the $3p$ subshell? How many electrons can that subshell hold?
- **3.** State (with a brief justification) the number of **radial nodes** and **angular nodes** expected for each of the following orbitals: $1s$, $2s$, $2p$, $3s$, $3p$.
- **4.** Two orbitals have the same principal quantum number n but different ℓ values. Explain qualitatively how their shapes differ and how this affects the directional character of bonding in organic molecules.

1.5.2 Electron configurations and orbital diagrams (Aufbau, Pauli, Hund)

For each species below, (i) write the ground-state electron configuration, and (ii) draw an orbital diagram for the valence shell showing correct spin placement.

(a) C (b) N (c) O (d) F (e) Ne

Then answer:

- **1.** Which of these neutral atoms has the largest number of unpaired electrons in the ground state?
- **2.** Using only the ideas of Z_{eff} and shielding, explain the trend in atomic radius across this series.

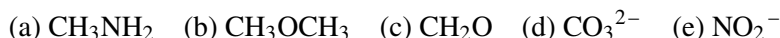
1.5.3 Effective nuclear charge and periodic trends

Without using numerical electronegativity values, rank each set in order (highest to lowest) and justify each ranking using concepts from the chapter (*effective nuclear charge, orbital size, shielding, electron configuration*).

- **1.** First ionization energy: Li, Be, B, C
- **2.** Atomic radius: C, N, O, F
- **3.** Electronegativity: C, N, O, F
- **4.** For the pair O vs. S, predict which has (i) the larger atomic radius, (ii) the higher electronegativity, and (iii) the more compact valence orbitals. Explain how these predictions are mutually consistent.

1.5.4 Lewis structures: algorithmic construction and electron counting

Draw complete Lewis structures (showing all lone pairs) for each species below. For each, explicitly show your valence-electron count and indicate whether each second-row atom satisfies an octet.



Then:

- **1.** Identify any species for which multiple valid Lewis structures (same connectivity, different electron placement) are possible.
- **2.** For each such species, state how many unique resonance contributors you can draw *that satisfy octets*.

1.5.5 Formal charge as a plausibility test

For each structure below, compute the formal charge on every atom. Then determine whether the structure is a reasonable major contributor, a minor contributor, or an invalid structure (explain your reasoning using the rules from the chapter).

(a) HNO_2 connectivity given as $\text{H}-\text{O}-\text{N}=\text{O}$.

Draw the Lewis structure consistent with this connectivity and compute all formal charges.

(b) CNO^- with connectivity $\text{C}-\text{N}-\text{O}$.

Consider two proposed structures:



For each, compute formal charges and decide which is more plausible and why.

(c) $\text{CH}_3\text{CO}_2^{-}$ (acetate).

Compute formal charges for the two principal resonance contributors and verify that the total formal charge matches the overall charge.

1.5.6 Resonance: generating contributors with curved arrows

For each species below, draw **all** important resonance contributors that obey octets for second-row atoms. Use curved arrows to show the electron-pushing steps connecting contributors.

- **1. Allyl anion** $\text{CH}_2=\text{CH}-\text{CH}_2^{-}$
- **2. Allyl radical** $\text{CH}_2=\text{CH}-\text{CH}_2\cdot$
- **3. Formate** HCO_2^{-}
- **4. Amide fragment** (connectivity fixed): $\text{H}_2\text{N}-\text{CHO}$ (formamide). Include the contributor that places positive charge on N and negative charge on O, and explain why it is relevant despite charge separation.

1.5.7 Ranking resonance contributors by stability

For each set below:

- **1.** Draw the resonance contributors indicated (or all reasonable contributors, if not specified).
- **2.** Rank contributors from most important (largest weight in the hybrid) to least important.
- **3.** Justify your ranking using: octet satisfaction, formal charge magnitude, charge separation, and placement of charge relative to electronegativity.

(a) Acetamide resonance.

Use the two key contributors for CH_3CONH_2 : the neutral $\text{C}=\text{O}$ form and the charge-separated $\text{C}-\text{O}^{-} / \text{C}=\text{N}^{+}$ form.

(b) Protonated carbonyl.

For $(\text{CH}_3)_2\text{C}=\text{OH}^+$ (protonated acetone), consider resonance contributors that place positive charge on oxygen vs. carbon. Rank and justify.

(c) Enolate-like motif (connectivity fixed).

For $\text{CH}_3-\text{CO}-\text{CH}_2^-$, draw contributors that place the negative charge on carbon vs. oxygen and rank them.

1.5.8 Bond polarity, partial charges, and reactive sites

For each molecule below, (i) draw a correct Lewis structure, (ii) indicate the most polarized bonds using δ^+/δ^- , and (iii) identify the most likely nucleophilic atom(s) and electrophilic atom(s) *based only on electron distribution*.

(a) CH_3Cl (b) CH_3OH (c) CH_3CHO (d) $\text{CH}_3\text{CO}_2\text{H}$ (e) CH_3CN

Finally, explain briefly why formal charge and partial charge can point to different atoms as “electron-rich,” using one example from this set.

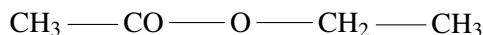
1.5.9 Functional group identification in complex structures

For each structure given below (drawn using chemfig skeletal notation), identify **all** functional groups present. Then, for each functional group, state (i) the most electron-rich atom, (ii) the most electron-poor atom (if applicable), and (iii) whether resonance is expected to be important.

(a)



(b)



(c)



(d)



1.5.10 Synthesis of concepts: choosing the best representation

This problem integrates orbital ideas, Lewis structures, formal charge, resonance, and functional-group recognition.

- **1.** Draw a valid Lewis structure for NO_3^- . Then draw **all** equivalent resonance contributors and the resonance hybrid.
- **2.** Compute formal charges for one contributor and explain why the negative charge is best placed on oxygen rather than nitrogen.
- **3.** Predict (qualitatively) whether all three N–O bond lengths should be equal or not, and justify using resonance arguments.
- **4.** Identify the functional group category for NO_3^- in the broad sense (*oxygen-rich anion*) and compare its charge delocalization to that of a carboxylate (RCO_2^-) discussed in the chapter.

Chapter 2

Molecular Geometry and Orbitals

While Lewis structures provide the necessary accounting for valence electrons, they flatten the vibrant, three-dimensional reality of organic molecules into static lines and dots. This chapter breathes life into those representations, demonstrating how atomic orbitals mix and reshape to determine the spatial architecture of matter. By mastering these geometric and orbital principles, students gain the ability to predict the physical properties and reactive potential of organic compounds solely from their structural formulas.

2.1 Valence Bond Theory and Hybridization

Organic chemistry relies on a simple observational fact: carbon most commonly forms four bonds, and those bonds are not arranged randomly in space. In Chapter 1, we used Lewis structures as a bookkeeping system for valence electrons and formal charges. That approach correctly predicts connectivity and many resonance patterns, but it does not (by itself) explain *why* a carbon atom forms four equivalent C–H bonds in methane, why alkenes are planar and resist rotation, or why alkynes are linear.

This section introduces **valence bond (VB) theory** and **hybridization** as a practical quantum-mechanical framework that connects electron configuration to *bond geometry* and *bond type*:

- σ **bonds** arise from **head-on overlap** of orbitals along the internuclear axis.
- π **bonds** arise from **side-on overlap** of parallel unhybridized p orbitals above and below a plane (or in two orthogonal planes for alkynes).

- **Hybrid orbitals** (sp^3 , sp^2 , sp) are directional combinations of atomic orbitals that maximize σ -bonding overlap and rationalize observed shapes.

2.1.1 Valence bond theory: bonds as localized orbital overlap

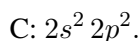
In VB theory, a covalent bond forms when two atomic orbitals (AOs) on different atoms overlap in space and a pair of electrons occupies the resulting region of high electron density. The key ideas are:

- **Orbital overlap and energy.** Greater overlap places electron density between nuclei more effectively, lowering potential energy (nucleus–electron attraction) and stabilizing the bond.
- **Directional bonding.** Orbitals are not spheres of electron “stuff”; they are wavefunctions with directionality and phase. Directional orbitals can form stronger bonds by aligning along the line connecting two nuclei.
- **Localization.** Unlike molecular orbital theory (introduced later), VB theory treats bonds as localized between pairs of atoms. This makes VB language (hybridization, σ/π bonds) extremely useful for organic structure and mechanism.

2.1.2 Orbital mixing and the need for hybridization

Carbon’s ground-state configuration and the tetravalency puzzle

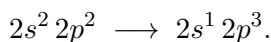
A neutral carbon atom has the valence-shell configuration



If one pictures bonding by pairing up unpaired electrons in *unmodified* atomic orbitals, carbon would appear to have only two half-filled orbitals (two unpaired electrons in the $2p$ subshell), suggesting only two bonds. Yet methane (CH_4) contains four equivalent C–H bonds arranged tetrahedrally.

VB theory resolves this by allowing two conceptual steps:

- **Promotion:** one $2s$ electron is promoted to a $2p$ orbital to give four unpaired electrons,



- **Hybridization:** the valence $2s$ and $2p$ orbitals *mix* (form linear combinations) to create new, equivalent, directional orbitals optimized for bonding.

Promotion costs energy, but the formation of four strong bonds more than compensates for this cost. The result is a lower-energy molecule overall.

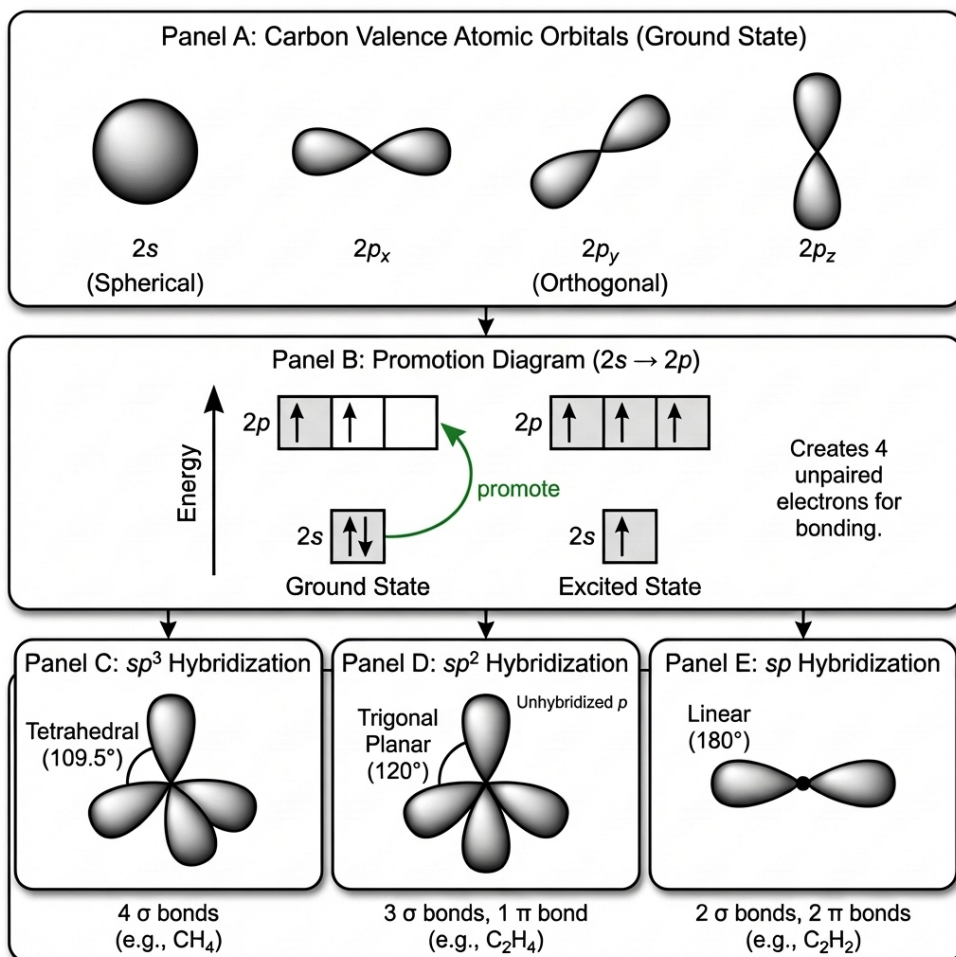
What does “mixing orbitals” mean?

Hybrid orbitals are **linear combinations** of atomic orbitals on the *same atom*. For carbon,

$$\psi_{\text{hybrid}} = c_s \psi_{2s} + c_x \psi_{2p_x} + c_y \psi_{2p_y} + c_z \psi_{2p_z},$$

with coefficients chosen so that the set of hybrids is orthonormal and oriented to minimize electron-pair repulsion while maximizing overlap with substituents.

Immediately after introducing orbital mixing, the following diagram summarizes (i) promotion and (ii) the geometries and remaining unhybridized p orbitals characteristic of sp^3 , sp^2 , and sp schemes.



2.1.3 The three common hybridization schemes

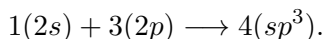
Hybridization is best treated as a model that correlates three things:

- the **number of electron domains** around an atom (regions of electron density used for σ bonding or lone pairs),
- the **geometry** that maximizes separation among those domains, and
- the **number of unhybridized p orbitals** left to form π bonds.

In most organic contexts, carbon uses sp^3 , sp^2 , or sp hybrids.

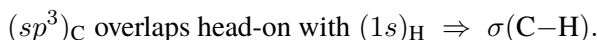
sp^3 hybridization: tetrahedral σ bonding

Construction and geometry. Mixing one s orbital with three p orbitals produces four equivalent sp^3 hybrids:



These four hybrids point toward the corners of a tetrahedron, with ideal angles of approximately 109.5° .

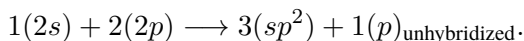
Bonding consequence. Each sp^3 hybrid has one large lobe (directional bonding lobe) and one small lobe of opposite phase. The large lobe points toward a bonding partner and forms a strong σ bond by head-on overlap. For methane, each C–H bond is a σ bond formed by overlap of a carbon sp^3 orbital with a hydrogen $1s$ orbital:



Key structural prediction. Atoms connected by single bonds (C–C or C–H) are often described as sp^3 at carbon (provided carbon makes four σ bonds and no π bonds). This does *not* mean the atom must be perfectly tetrahedral—substituent size and lone pairs on neighboring atoms can distort angles—but tetrahedral is the correct baseline model for saturated carbon centers.

 sp^2 hybridization: trigonal planar framework plus one π bond

Construction and geometry. Mixing one s orbital with two p orbitals yields three equivalent sp^2 hybrids in a plane:

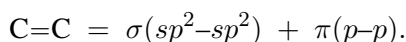


The three sp^2 orbitals arrange themselves trigonal planar with ideal angles near 120° . The remaining unhybridized p orbital is perpendicular to that plane.

How a double bond forms ($\sigma + \pi$). A carbon–carbon double bond consists of:

- one **σ bond** from head-on overlap of an sp^2 orbital on each carbon along the internuclear axis, and
- one **π bond** from side-on overlap of the two unhybridized, parallel p orbitals.

Symbolically:



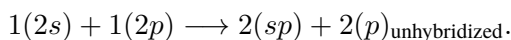
Planarity and restricted rotation. The π bond requires the two unhybridized p orbitals to remain parallel so their side-by-side overlap is maintained. Rotating one carbon relative to the other misaligns these orbitals and destroys π overlap. As a result:

- alkenes are **approximately planar** at the double bond (each sp^2 carbon is trigonal planar), and
- the $\text{C}=\text{C}$ bond exhibits a **rotation barrier** (a key prerequisite for E/Z stereoisomerism).

In contrast, a single σ bond is cylindrically symmetric about the internuclear axis, so rotation about a pure σ bond generally does not break the bond (though steric and hyperconjugative effects can create torsional preferences).

***sp* hybridization: linear σ framework plus two π bonds**

Construction and geometry. Mixing one s orbital with one p orbital yields two equivalent sp hybrids:

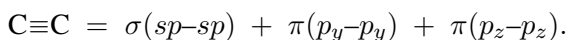


The two sp orbitals point in opposite directions, giving a linear arrangement with an ideal angle of 180° . Two unhybridized p orbitals remain; importantly, they are mutually perpendicular (for example, p_y and p_z).

How a triple bond forms ($\sigma + \pi + \pi$). A carbon–carbon triple bond consists of:

- one σ **bond** from head-on overlap of sp orbitals, and
- two π **bonds** from side-on overlap of each pair of parallel unhybridized p orbitals.

Thus,



Because the two π systems are orthogonal, the electron density of the triple bond is distributed in two perpendicular “belts” around the internuclear axis. This is the geometric origin of the characteristic linearity of alkynes.

2.1.4 σ bonds vs. π bonds: symmetry, overlap, and consequences

Head-on overlap and cylindrical symmetry of σ bonds

A σ bond results when two orbitals overlap directly along the internuclear axis. The electron density is concentrated *between* the nuclei and is symmetric with respect to rotation around the bond axis. This symmetry explains why, in many cases, rotation about a single bond does not require breaking the bond.

In organic molecules, common σ overlaps include:

- sp^3-1s (C–H in alkanes),
- sp^3-sp^3 (C–C single bonds),
- sp^2-sp^2 (the σ component of C=C),
- $sp-sp$ (the σ component of C $\equiv$ C),
- and mixed overlaps such as sp^2-sp^3 (e.g., alkene carbon to alkyl carbon).

Side-on overlap, nodal planes, and the fragility of π bonds

A π bond forms when two unhybridized p orbitals overlap side-by-side. Each p orbital has a nodal plane passing through the nucleus; the resulting π bond therefore has *zero* electron density along the internuclear axis and electron density above and below (or in two perpendicular regions for triple bonds).

Two consequences follow immediately:

- **Geometric requirement.** The orbitals must remain parallel for effective overlap. Twisting destroys overlap and destabilizes the bond.
- **Reactivity trend.** Because π electron density is more exposed (less concentrated directly between nuclei) than σ density, π bonds are often the first site of reaction with electrophiles in many organic transformations. (This reactivity connection will be developed mechanistically in later chapters.)

2.1.5 s -character, bond length, and bond strength

Hybrid orbitals differ in the fraction of s character mixed into them:

$$sp^3 : 25\% s, \quad sp^2 : 33\% s, \quad sp : 50\% s.$$

An s orbital is lower in energy and more penetrating (its electron density is, on average, closer to the nucleus) than a p orbital. Therefore, hybrids with greater s character hold bonding electron density closer to the nucleus.

A useful structural trend is:

More s character $\Rightarrow$ shorter and stronger σ bonds (all else equal).

This trend helps rationalize why $\text{C}\equiv\text{C}$ bonds are shorter than $\text{C}=\text{C}$ bonds, which are shorter than $\text{C}-\text{C}$ single bonds, and why terminal alkynes have relatively acidic $\text{C}-\text{H}$ bonds compared with alkenes and alkanes (a topic revisited in acid–base chapters).

2.1.6 How to assign hybridization in practice (within the VB framework)

Within VB theory, hybridization is a model for the orbitals used in σ bonding and for the count of remaining unhybridized p orbitals available for π bonding. A robust procedure for typical organic structures is:

- **1. Draw a correct Lewis structure** (including resonance where needed) to determine connectivity and whether π bonds are present.
- **2. Count electron domains** around the atom of interest: each σ bond counts as one domain; each lone pair counts as one domain (important for heteroatoms); a multiple bond counts as one domain for geometry (because it contains one σ bond plus π bond(s)).
- **3. Match domain count to hybridization** (most common cases):

$$4 \text{ domains} \Rightarrow sp^3, \quad 3 \text{ domains} \Rightarrow sp^2, \quad 2 \text{ domains} \Rightarrow sp.$$

- **4. Check for π bonds.** An sp^2 center must have one unhybridized p orbital available (one π bond possible); an sp center must have two (two π bonds possible, or one π bond plus another interaction in conjugated systems).

Example 1: Ethane, $\text{H}_3\text{C}-\text{CH}_3$. Each carbon forms four σ bonds (three $\text{C}-\text{H}$ and one $\text{C}-\text{C}$) and no π bonds $\Rightarrow$ 4 domains $\Rightarrow sp^3$.

Example 2: Ethene, $\text{H}_2\text{C}=\text{CH}_2$. Each carbon forms three σ bonds (two $\text{C}-\text{H}$ and one $\text{C}-\text{C}$ σ) and one π bond $\Rightarrow$ 3 domains $\Rightarrow sp^2$, with the unhybridized p orbital forming the π bond.

Example 3: Ethyne, $\text{HC}\equiv\text{CH}$. Each carbon forms two σ bonds (one C–H and one C–C σ) and two π bonds $\Rightarrow$ 2 domains $\Rightarrow sp$, with two unhybridized p orbitals forming the two π bonds.

2.1.7 A final unifying picture: hybridization as geometry plus bond-type bookkeeping

Hybridization language is most powerful when used for what it directly encodes:

- **Geometry of σ bonds:** sp^3 (tetrahedral), sp^2 (trigonal planar), sp (linear).
- **Count of π bonds possible at a center:** none for sp^3 , one for sp^2 , two for sp (using unhybridized p orbitals).
- **Rotation behavior:** free (or nearly free) rotation about a single σ bond versus restricted rotation when a π bond is present.

In the next section, we will abstract away from orbital composition and focus directly on *electron domain geometry* using VSEPR theory, which provides a fast and often accurate way to predict molecular shape and approximate bond angles, especially when lone pairs are present.

2.2 VSEPR Theory and Molecular Shape

In the previous section, hybridization connected orbital mixing to *idealized* bond geometries for common carbon centers: sp^3 (tetrahedral), sp^2 (trigonal planar), and sp (linear). Hybridization, however, is not the fastest way to predict shape in general—especially for heteroatoms that carry lone pairs and for structures where the dominant question is simply: *how are electron groups arranged in space?*

VSEPR theory (Valence Shell Electron Pair Repulsion) provides a complementary, largely electrostatic model:

Electron domains (regions of valence electron density) arrange themselves around a central atom to minimize Coulombic repulsion.

Despite its simplicity, VSEPR is remarkably effective for predicting *molecular shape* and *approximate bond angles*. In organic chemistry, this matters because geometry controls steric strain, conformational preferences, polarity, and the approach trajectories of reagents.

2.2.1 Electron domains: the core bookkeeping step

VSEPR analysis begins with a Lewis structure (or a set of resonance structures) and focuses on the **central atom**. One counts **electron domains** (also called electron groups):

- Each **single bond** counts as **one** domain.
- Each **multiple bond** ($C=C$, $C\equiv C$, $C=O$) counts as **one** domain (because it occupies one direction in space even though it contains σ and π components).
- Each **lone pair** counts as **one** domain.

Electron-domain geometry vs. molecular geometry. VSEPR distinguishes two related geometries:

- **Electron-domain geometry:** arrangement of *all* domains (bonding domains + lone pairs).
- **Molecular geometry (shape):** arrangement of *atoms* (bonding domains only); lone pairs are “invisible” but they still influence angles.

This distinction is essential. For example, water (H_2O) has four electron domains (two bonds, two lone pairs), so its electron-domain geometry is tetrahedral. But its *molecular* geometry is bent because only two of those domains correspond to atoms.

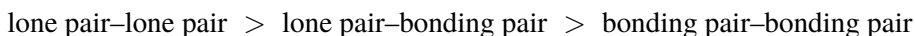
2.2.2 Why domains repel: an electrostatic and spatial picture

A useful mental model is to treat each electron domain as an “electron cloud” with negative charge. Like charges repel, so clouds spread out as much as possible on the surface of an imaginary sphere centered on the atom.

Two refinements improve predictions:

- **Domains differ in repulsive strength.** Lone pairs are attracted to only one nucleus, so they occupy more space near the central atom than bonding pairs, which are shared between two nuclei. Therefore, lone pairs generally repel more strongly.
- **Multiple bonds are bulkier than single bonds.** A double bond has a π electron density region in addition to its σ bond, so it typically repels adjacent domains more strongly than a single bond. VSEPR usually treats it as one domain, but expects *angle distortions* near multiple bonds.

These ideas lead to the common qualitative ordering:



in terms of repulsion (and thus in terms of how much a given interaction compresses nearby bond angles).

2.2.3 Steric number and the basic geometries (2–4 domains)

For most first-row main-group atoms in organic chemistry (C, N, O, F), the most common steric numbers are 2, 3, or 4, corresponding closely to the familiar linear, trigonal planar, and tetrahedral arrangements.

Steric number 2: linear electron-domain geometry

Domain count: 2 domains around the central atom.

Electron-domain geometry: linear, 180° .

Typical organic examples.

- An *sp* carbon in an alkyne: $\text{HC}\equiv\text{CH}$ (each carbon has 2 domains: C–H and $\text{C}\equiv\text{C}$).
- The central carbon in carbon dioxide, $\text{O}=\text{C}=\text{O}$ (2 domains: two double bonds).

Key point. With only two domains, there is essentially one way to maximize separation: place them opposite each other.

Steric number 3: trigonal planar electron-domain geometry

Domain count: 3 domains.

Electron-domain geometry: trigonal planar, ideal angles $\approx 120^\circ$.

Typical organic examples.

- An *sp*² carbon in an alkene: $\text{H}_2\text{C}=\text{CH}_2$.
- The carbonyl carbon in $\text{R}_2\text{C}=\text{O}$ (three domains: two single bonds to substituents and one double bond to oxygen).

- A carbocation center (R_3C^+) is commonly trigonal planar (three σ bonds, empty p orbital).

Angle distortions with multiple bonds. In a carbonyl, the $C=O$ domain often exerts greater repulsion than a $C-C$ single bond. As a result, $O=C-R$ angles can be slightly larger than $R-C-R$ angles, even though the electron-domain geometry remains trigonal planar.

Steric number 4: tetrahedral electron-domain geometry

Domain count: 4 domains.

Electron-domain geometry: tetrahedral, ideal angles $\approx 109.5^\circ$.

Typical organic examples.

- Saturated carbon centers in alkanes: CH_4 , C_2H_6 .
- Nitrogen in amines: R_3N (3 bonds + 1 lone pair).
- Oxygen in alcohols/ethers: $R-O-R'$ (2 bonds + 2 lone pairs).

The tetrahedral arrangement is the default for second-row atoms with four electron domains, but the *molecular shape* depends critically on how many of those domains are lone pairs.

2.2.4 From electron-domain geometry to molecular shape: lone pairs change angles

VSEPR predicts that when lone pairs are present, observed bond angles typically *decrease* relative to the ideal tetrahedral or trigonal planar values because lone pairs occupy more space and push bonding domains closer together.

Steric number 4 shapes: tetrahedral, trigonal pyramidal, bent

Consider a central atom A with steric number 4. The electron-domain geometry is tetrahedral in all cases below, but the molecular geometry changes with the number of lone pairs.

Case 1: 4 bonding domains (0 lone pairs).



Molecular geometry: tetrahedral; **ideal angle:** 109.5° . Example: methane, CH_4 .

Case 2: 3 bonding domains + 1 lone pair.



(E denotes a lone pair domain.)

Molecular geometry: trigonal pyramidal. Example: ammonia, NH_3 .

Angle trend: the $\text{H}-\text{N}-\text{H}$ angle is smaller than 109.5° (experimentally about 107°) because the lone pair repels the bonding pairs more strongly than bonding pairs repel each other.

Case 3: 2 bonding domains + 2 lone pairs.

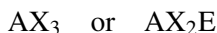


Molecular geometry: bent. Example: water, H_2O .

Angle trend: the $\text{H}-\text{O}-\text{H}$ angle is significantly smaller than 109.5° (experimentally 104.5°) because two lone pairs compress the bond angle more strongly.

Steric number 3 shapes: trigonal planar and bent

For steric number 3:



Electron-domain geometry: trigonal planar.

Case 1: AX_3 . Molecular geometry: trigonal planar ($\approx 120^\circ$). Examples: BF_3 (in general chemistry), sp^2 carbons in alkenes and carbonyls.

Case 2: AX_2E . Molecular geometry: bent, with bond angles $< 120^\circ$. Example: SO_2 (classic VSEPR example), or an sp^2 -like oxygen center in some resonance-stabilized systems. In organic chemistry, this situation appears less often as an isolated functional group center than the tetrahedral lone-pair cases (amines, alcohols), but the same logic applies.

2.2.5 Practical workflow for organic molecules

In organic structures, VSEPR is most useful as a rapid predictor of local geometry at each non-hydrogen atom. A consistent workflow is:

- **Start from a valid Lewis structure.** Include formal charges where needed. If resonance is important, use the resonance hybrid as your mental picture but count domains from a representative contributor.
- **Pick one atom at a time and count domains.**
- **Assign electron-domain geometry from the domain count.**
- **Convert to molecular shape by ignoring lone pairs.**
- **Apply distortion rules qualitatively:** lone pairs compress adjacent bond angles; multiple bonds tend to widen angles adjacent to them; bulky substituents can enlarge angles between them (steric effects), sometimes competing with lone-pair compression.

Example: methanol, CH_3OH . At carbon: 4 domains $\Rightarrow$ tetrahedral electron geometry $\Rightarrow$ tetrahedral molecular geometry around carbon (approximately 109.5°). At oxygen: 4 domains (2 bonds + 2 lone pairs) $\Rightarrow$ tetrahedral electron geometry, **bent** molecular geometry. The C–O–H angle is typically a bit less than 109.5° due to lone-pair compression.

Example: acetone, $(\text{CH}_3)_2\text{C}=\text{O}$. At the carbonyl carbon: 3 domains (two C–C single bonds + one C=O double bond) $\Rightarrow$ trigonal planar around that carbon ($\approx 120^\circ$). At oxygen: 3 domains if one counts C=O as one bonding domain plus two lone pairs $\Rightarrow$ trigonal planar electron-domain geometry at oxygen, consistent with a p orbital participating in the π bond and a local planar arrangement.

2.2.6 Brief extension: higher steric numbers (5 and 6 domains)

Although less central in introductory organic chemistry, atoms beyond the second row (especially P, S, and halogens in higher oxidation states) can exhibit steric numbers 5 or 6. VSEPR extends straightforwardly:

Steric number 5: trigonal bipyramidal electron-domain geometry

Geometry: three equatorial positions (120° apart) and two axial positions (180° apart, 90° to equatorial).

Lone-pair placement rule. Lone pairs preferentially occupy **equatorial** positions because equatorial domains experience fewer 90° interactions than axial domains.

Steric number 6: octahedral electron-domain geometry

Geometry: octahedral, with 90° angles between adjacent positions and 180° between opposite positions.

These extended cases will appear occasionally in functional groups and reagents (e.g., hypervalent iodine reagents, sulfur(VI) centers), but for most carbon-centered organic structures, steric numbers 2–4 dominate.

2.2.7 Connecting VSEPR to hybridization (without confusing the two)

It is tempting to treat VSEPR and hybridization as interchangeable. They are related, but conceptually distinct:

- **VSEPR** predicts geometry from electron-domain repulsion (a spatial/electrostatic argument).
- **Hybridization** describes the orbital types used for σ bonding (a VB orbital-mixing argument) and indicates how many unhybridized p orbitals remain for π bonding.

For many second-row atoms in typical organic bonding, the mapping is consistent:

$$2 \text{ domains} \leftrightarrow sp, \quad 3 \text{ domains} \leftrightarrow sp^2, \quad 4 \text{ domains} \leftrightarrow sp^3.$$

However, VSEPR can be applied even when hybridization language becomes less clear (expanded octets, highly ionic bonding, or delocalized resonance situations). In this chapter, VSEPR will serve as the primary tool for *shape and angle prediction*, while hybridization remains the primary tool for distinguishing σ and π bonding patterns and for anticipating rotation barriers and conjugation.

In the next section, we will connect molecular shape to **bond polarity** and **intermolecular forces**, showing how geometry and electronegativity combine to produce molecular dipoles and, ultimately, observable physical properties such as boiling point and solubility.

2.3 Bond Polarity and Intermolecular Forces

The previous sections developed two complementary ways of thinking about molecular structure: valence bond theory and hybridization connect *bonding orbitals* to

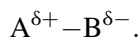
σ and π bonds, while VSEPR predicts *molecular shape* by minimizing repulsions among electron domains. In this section we add a third structural dimension: **unequal sharing of electrons**.

When atoms of different electronegativity form a bond, electron density is displaced toward the more electronegative atom. That displacement creates a **bond dipole**. Molecular geometry (from VSEPR) then determines whether bond dipoles cancel or add to give a **net molecular dipole**. Finally, these charge separations govern **intermolecular forces (IMFs)**—the non-covalent interactions that control boiling points, melting points, viscosity, solubility, and many recognition events in biology.

2.3.1 Electronegativity and the origin of bond polarity

Electronegativity as a predictor of electron-density displacement

Electronegativity is an atom's tendency to attract shared electrons in a chemical bond. In a heteronuclear bond A–B, if B is more electronegative than A, then the electron density shifts toward B, creating partial charges:



The bond is then **polar**. If the atoms have identical electronegativity (e.g., C–C, Cl–Cl), the bond is **nonpolar** (no permanent dipole).

In organic chemistry, a few comparisons are especially important:

$$\chi(\text{F}) > \chi(\text{O}) > \chi(\text{N}) \gtrsim \chi(\text{Cl}) > \chi(\text{C}) > \chi(\text{H}).$$

Thus C–F, C–O, and C–N bonds are typically polar, with C bearing partial positive charge.

Bond dipole moment: direction and notation

A **dipole moment** is a vector quantity, commonly denoted $\vec{\mu}$. For a single bond, the dipole vector points from the partial positive end to the partial negative end:



Chemists often draw a dipole arrow with a small “plus” or cross at the positive end. Quantitatively, the magnitude of a dipole moment is

$$\mu = q r,$$

where q is the magnitude of charge separation (not a full unit charge in most covalent bonds) and r is the distance between the charge centers. Dipole moments are commonly reported in Debye (D).

Important caution. Electronegativity difference is a *qualitative predictor* of polarity, not a complete calculation. Bond polarity depends on the molecular environment (inductive effects, resonance, hybridization, and nearby polar groups). Nevertheless, electronegativity trends give reliable first-order predictions.

2.3.2 From bond dipoles to molecular dipoles: vector addition and geometry

A molecule may contain several polar bonds. Whether the molecule has a net dipole depends on:

- the **magnitudes** of individual bond dipoles, and
- their **vector arrangement in space** (molecular geometry).

Dipole cancellation: the role of symmetry

If bond dipoles are arranged symmetrically, they can cancel.

Example: carbon dioxide, $\text{O}=\text{C}=\text{O}$. Each $\text{C}=\text{O}$ bond is strongly polar, but CO_2 is linear (VSEPR steric number 2 at carbon). The two equal and opposite bond dipoles cancel:

$$\vec{\mu}_{\text{net}} = \vec{\mu}_1 + \vec{\mu}_2 = 0.$$

Therefore CO_2 is nonpolar despite having polar bonds.

Example: carbon tetrachloride, CCl_4 . Each $\text{C}-\text{Cl}$ bond is polar, but the molecule is tetrahedral and symmetric. The four bond dipoles cancel, so CCl_4 has essentially no net dipole.

Dipole addition: bent and pyramidal molecules are often polar

When geometry is not fully symmetric, dipoles add to produce a net molecular dipole.

Example: water, H_2O . Oxygen is more electronegative than hydrogen, so each O–H bond is polar. VSEPR predicts a bent geometry (two lone pairs). The bond dipoles do not cancel, producing a strong net dipole directed roughly toward oxygen.

Example: chloromethane, CH_3Cl . The C–Cl dipole is not canceled by the three C–H dipoles (which are smaller and not arranged to cancel it). The molecule has a net dipole pointing approximately from the methyl group toward chlorine.

Geometry as the link. These examples illustrate why the previous section matters: VSEPR provides the 3D arrangement needed to do vector reasoning. In many organic problems, you do not need a numerical dipole; you need a qualitative prediction (polar vs. nonpolar, larger vs. smaller dipole) based on shape and electronegativity.

2.3.3 Inductive effects: polarity transmitted through σ bonds

Bond polarization can propagate through a chain by the **inductive effect**. Electronegative substituents withdraw electron density through σ bonds (a $-I$ effect), while electropositive substituents can donate electron density (a $+I$ effect). Inductive effects:

- are strongest near the substituent and decay with distance,
- stabilize or destabilize charged intermediates (important later for acidity and reactivity), and
- influence local partial charges, altering intermolecular interactions and solubility.

Example: halogenated alkanes. Replacing H with Cl or F increases local partial positive charge on nearby carbons, generally increasing molecular polarity and often increasing boiling point relative to the parent hydrocarbon (though molecular mass and shape also matter).

2.3.4 Intermolecular forces: types, physical origin, and typical strength order

Intermolecular forces (IMFs) are electrostatic interactions between molecules. They are weaker than covalent bonds, but they dominate many bulk properties because they act *between* molecules and therefore determine how easily molecules separate in the liquid and solid phases.

The major IMFs relevant to organic chemistry are:

- London dispersion forces (present in all molecules),
- dipole–dipole interactions (present in polar molecules),
- hydrogen bonding (a particularly strong, directional dipole interaction involving X–H bonds where X is N, O, or F).

Ion–dipole forces are also crucial in solutions (e.g., salts dissolving in water), but for neutral organic molecules the three listed above are the core set.

A typical qualitative strength trend (for similarly sized molecules) is:

London dispersion < dipole–dipole < hydrogen bonding.

This is a guideline, not a universal rule: very large nonpolar molecules can exhibit strong dispersion forces that exceed dipole interactions in smaller polar molecules.

2.3.5 London dispersion forces: instantaneous dipoles and polarizability

Physical origin

London dispersion forces arise from correlated fluctuations in electron density:

- At any instant, electrons in a molecule may be unevenly distributed, creating an *instantaneous* dipole.
- That dipole can induce a dipole in a neighboring molecule.
- The two induced dipoles attract.

Because this mechanism does not require permanent polarity, dispersion forces exist in *all* substances, including noble gases and hydrocarbons.

Factors that increase dispersion forces

Dispersion forces increase with:

- **Polarizability:** how easily an electron cloud is distorted. Larger atoms and molecules (more electrons, more diffuse valence shells) are more polarizable.
- **Surface area contact:** elongated or less-branched molecules can make more close contacts than compact, highly branched molecules.

Organic trend: branching lowers boiling point. For isomers with the same formula (similar molar mass), increased branching typically lowers boiling point because branching reduces surface area and therefore reduces dispersion interactions. For example, among C_5H_{12} isomers:

n-pentane (least branched) > isopentane > neopentane (most branched)

in boiling point (qualitative order).

2.3.6 Dipole–dipole interactions: alignment of permanent dipoles

Physical origin

In polar molecules with permanent dipoles, molecules can align so that the partial positive region of one is near the partial negative region of another. This **dipole–dipole** attraction is an orientation-dependent electrostatic interaction.

Thermal motion and averaging. In liquids, molecules are constantly rotating and colliding. Dipole–dipole interactions are therefore transient and dynamic. Even so, the time-averaged effect can significantly increase boiling point and affect solubility compared with nonpolar analogs.

Consequences for boiling points and solubility

Boiling point. All else equal, polar molecules tend to have higher boiling points than nonpolar molecules of comparable size because additional dipole–dipole attractions must be overcome to separate molecules into the gas phase.

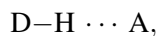
Solubility: “like dissolves like.” Polar solutes tend to dissolve in polar solvents because the solvent can stabilize the solute through dipole interactions. Nonpolar solutes dissolve best in nonpolar solvents where dispersion dominates.

This principle becomes quantitative when combined with hydrogen bonding: a molecule may be polar but still poorly soluble in water if it cannot hydrogen bond and has a large hydrophobic region.

2.3.7 Hydrogen bonding: a strong, directional dipole interaction

Definition and requirements

A **hydrogen bond** (H-bond) is an attractive interaction of the form



where:

- D (donor atom) is typically O, N, or F,
- H is covalently bound to D (O–H, N–H, F–H),
- A (acceptor atom) is an electronegative atom with a lone pair (commonly O or N, sometimes F).

Two key features make H-bonds distinctive:

- **Enhanced polarity of D–H.** The D–H bond is strongly polarized, giving hydrogen a substantial δ^+ character.
- **Directionality.** Hydrogen bonding is strongest when the D–H bond and the lone pair of A align approximately linearly (D–H $\cdots$ A close to 180°). This directional preference is a major reason H-bonds organize molecular structures in liquids, crystals, and biomolecules.

Donors and acceptors in common organic functional groups

Alcohols and phenols (R–OH).

- Donor: yes (has O–H).
- Acceptor: yes (oxygen lone pairs).

Ethers (R–O–R').

- Donor: no (no O–H).
- Acceptor: yes.

Amines (RNH₂, R₂NH, R₃N).

- Donor: primary and secondary amines yes (have N–H); tertiary amines no.
- Acceptor: most amines yes (nitrogen lone pair).

Carbonyl compounds (aldehydes, ketones, esters, amides).

- Donor: generally no (unless N–H in amides).
- Acceptor: usually the carbonyl oxygen is an acceptor (but in amides, resonance reduces basicity of the oxygen and nitrogen; H-bonding patterns can be more nuanced and are treated later).

Consequences: boiling points and water solubility

Hydrogen bonding increases boiling points dramatically compared with molecules of similar size that cannot hydrogen bond.

Example: ethanol vs. dimethyl ether. Both have formula C_2H_6O , but ethanol (CH_3CH_2OH) can hydrogen bond as a donor and acceptor, while dimethyl ether (CH_3OCH_3) can only accept. Ethanol therefore generally exhibits stronger intermolecular association and a higher boiling point.

Water solubility. Small molecules capable of hydrogen bonding often have significant water solubility because they can form favorable H-bonding interactions with water. As hydrocarbon content increases, hydrophobic surface area grows and solubility typically decreases even if a polar functional group is present.

2.3.8 Ranking intermolecular forces in real molecules: a structured approach

When comparing physical properties (especially boiling point and solubility), a reliable approach is:

- **Compare molecular size (molar mass) and polarizability.** Larger $\Rightarrow$ stronger dispersion.
- **Compare shape and surface area.** Less branched $\Rightarrow$ stronger dispersion.
- **Assess polarity (net dipole).** Use electronegativity + VSEPR geometry to predict whether dipoles cancel.
- **Check hydrogen-bonding capability.** Identify donors and acceptors; count how many and consider accessibility (sterics).

Example comparison (qualitative). Rank the expected boiling points: CH_3CH_3 (ethane), CH_3Cl (chloromethane), CH_3OH (methanol).

- Ethane: nonpolar; dispersion only; low boiling point.

- Chloromethane: polar; dispersion + dipole–dipole; higher.
- Methanol: polar and hydrogen bonding; highest.

2.3.9 Intermolecular forces and molecular recognition: a preview

In organic reactions and in biochemistry, non-covalent interactions often determine how molecules approach one another before any covalent bonds form. Dipole alignment, hydrogen bonding, and dispersion-driven packing can:

- pre-organize substrates in enzyme active sites,
- stabilize transition states through specific H-bonds,
- control conformations that expose or hide reactive sites.

Later chapters will connect these ideas to reactivity (through stabilization of charges and transition states) and to stereochemical outcomes (through three-dimensional approach trajectories).

In the next section, we will move from localized VB pictures to **molecular orbital theory**, developing a delocalized description of bonding that becomes essential for understanding conjugation, resonance stabilization, and frontier-orbital control of organic reactivity.

2.4 Molecular Orbital Theory and Conjugation

Valence bond (VB) theory and hybridization explain much of organic structure by describing bonds as localized overlaps of atomic orbitals: sp^3 centers form σ bonds in tetrahedral arrangements; sp^2 centers form a planar σ framework plus one unhybridized p orbital that can form a π bond; sp centers are linear and retain two p orbitals for two π bonds. VSEPR provided a rapid geometric method, and bond polarity connected electron distribution to intermolecular forces.

However, a purely localized bond picture becomes incomplete when π electrons are **shared over more than two atoms**. The classic examples are **conjugated systems** such as 1,3-butadiene ($\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$), allylic cations/anions, and many aromatic and carbonyl-adjacent structures. In these molecules, the experimentally observed stability and reactivity patterns reflect **delocalization** of electrons.

Molecular orbital (MO) theory treats electrons as occupying orbitals that belong to the **entire molecule** rather than to individual bonds. This section introduces the MO

framework using the **linear combination of atomic orbitals (LCAO)** approach, then develops **frontier molecular orbitals** (HOMO and LUMO) as a practical predictor of reactivity in conjugated organic molecules.

2.4.1 From atomic orbitals to molecular orbitals: the LCAO idea

Constructive and destructive interference

Atomic orbitals are wavefunctions, and wavefunctions can add or subtract. When two atomic orbitals overlap, their combination produces two molecular orbitals:

- a **bonding MO** from **constructive interference** (same phase overlaps), which increases electron density between nuclei and lowers energy;
- an **antibonding MO** from **destructive interference** (opposite phase overlaps), which introduces a node (a region of zero electron density) between nuclei and raises energy.

For two p orbitals forming a π system, we often write:

$$\psi_{\pi} = c_A\psi_{p,A} + c_B\psi_{p,B} \quad (\text{bonding})$$

$$\psi_{\pi^*} = c_A\psi_{p,A} - c_B\psi_{p,B} \quad (\text{antibonding})$$

The coefficients c_A and c_B depend on orbital energies and symmetry; for two identical atoms (like the two carbons of ethene), the coefficients are equal in magnitude.

Nodes and energy ordering

More nodes $\Rightarrow$ higher energy.

A node is a surface (often a plane) across which the wavefunction changes sign; it corresponds to zero probability density. Nodes reduce electron density in bonding regions, decreasing stabilization and raising orbital energy.

Electron filling: Aufbau and Pauli principles (as used in MO diagrams)

Electrons occupy molecular orbitals according to the same rules used for atomic orbitals:

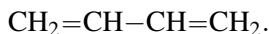
- **Aufbau principle:** fill lowest-energy orbitals first.
- **Pauli exclusion principle:** each orbital holds at most two electrons with opposite spin.
- **Hund's rule:** for degenerate orbitals (same energy), maximize unpaired spins before pairing. (In many introductory conjugated-system diagrams, degeneracy is absent, so Hund's rule plays a smaller role.)

2.4.2 π systems as a separate “subproblem”

In most organic molecules, the σ framework (built from hybrid orbitals) is strong and relatively localized. The π electrons are typically the most chemically responsive because they are higher in energy and more exposed. MO theory is therefore commonly applied first to the π **system** while treating the σ framework as a scaffold that:

- enforces planarity when conjugation is present (adjacent p orbitals must be parallel to overlap), and
- provides the atomic orbitals (p orbitals on sp^2 atoms) that combine into delocalized π MOs.

Conjugation (definition). A conjugated system has a continuous set of overlapping p orbitals (typically on adjacent sp^2 atoms), allowing π electrons to delocalize over three or more atoms. The simplest polyene example is 1,3-butadiene:



All four carbons are sp^2 hybridized, leaving one p orbital on each carbon. Those four p orbitals combine to form four π molecular orbitals.

2.4.3 1,3-Butadiene: four p orbitals give four π molecular orbitals

Counting orbitals and electrons

How many π MOs? In a conjugated system, the number of π molecular orbitals equals the number of atomic p orbitals combined. For 1,3-butadiene:

$$4 \text{ aligned } p \text{ orbitals} \Rightarrow 4 \pi \text{ MOs } (\psi_1, \psi_2, \psi_3, \psi_4).$$

How many π electrons? Each double bond contributes two π electrons. Butadiene has two double bonds, so it has 4 π electrons total.

Filling. The 4 π electrons occupy the lowest-energy MOs:

$$\psi_1^2 \psi_2^2 \psi_3^0 \psi_4^0.$$

Thus, the highest occupied molecular orbital (HOMO) is ψ_2 , and the lowest unoccupied molecular orbital (LUMO) is ψ_3 .

Nodal structure and qualitative shapes

The four π MOs can be ordered by nodes:

- ψ_1 : 0 nodes (most bonding, lowest energy).
- ψ_2 : 1 node.
- ψ_3 : 2 nodes (antibonding character begins to dominate).
- ψ_4 : 3 nodes (most antibonding, highest energy).

A convenient qualitative consequence is that conjugation spreads electron density across multiple atoms, lowering the overall energy of the occupied π orbitals compared with isolated double bonds. This stabilization is called **delocalization energy** (often also discussed as resonance stabilization). In MO language, the stabilization arises because electrons occupy orbitals (especially ψ_1 and ψ_2) that are bonding over **several** adjacent carbon–carbon links, not confined to one C=C.

2.4.4 Delocalization energy and the MO picture of conjugation

To see why conjugation stabilizes a molecule, compare two situations:

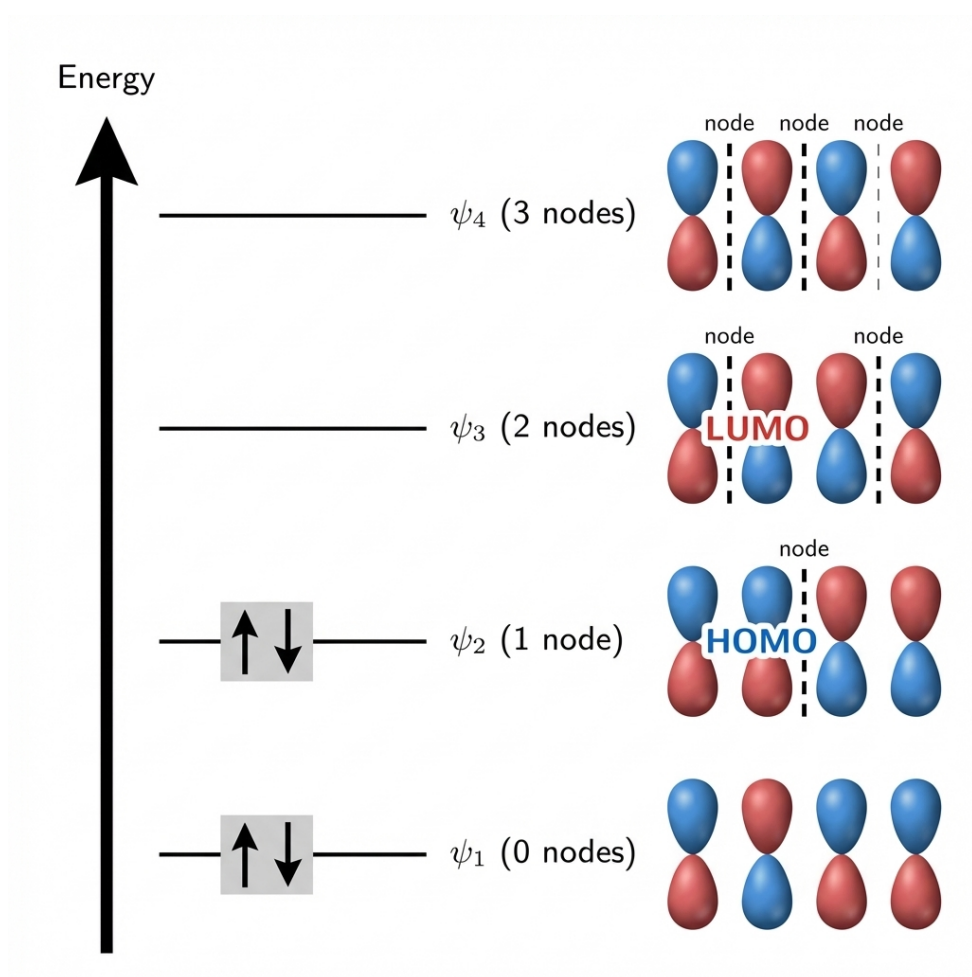
- **Isolated double bonds:** two separate π bonds (no interaction). Each has one bonding π orbital and one antibonding π^* orbital. Electrons occupy two separate bonding orbitals.
- **Conjugated double bonds:** four p orbitals interact simultaneously, producing two relatively low-energy occupied orbitals (ψ_1 and ψ_2) that are bonding across multiple carbon–carbon connections.

The net effect is that the electron distribution in a conjugated system is lower in energy than a simple sum of two isolated π bonds. This stabilization also has structural consequences: the **single** bond between the two double bonds in butadiene is shorter than a typical C–C single bond, reflecting partial π bonding character distributed through the chain.

Planarity requirement. Conjugation requires parallel alignment of adjacent p orbitals. Rotation about the central C–C bond in butadiene reduces p overlap and therefore reduces delocalization. This creates a conformational preference for the planar (or nearly planar) conformer.

2.4.5 Energy-level diagram for 1,3-butadiene (with HOMO and LUMO)

The following diagram summarizes the four π molecular orbitals of 1,3-butadiene, their relative energies, node counts, and occupancy, with HOMO and LUMO clearly indicated. It is placed here to accompany the discussion of delocalization energy and frontier orbitals.



2.4.6 Frontier molecular orbitals: HOMO and LUMO as reactivity handles

For many organic reactions, it is unnecessary to know **all** orbitals in detail. The most informative are the **frontier molecular orbitals (FMOs)**:

- **HOMO (Highest Occupied Molecular Orbital)**: the highest-energy orbital that contains electrons. It is often the best electron donor site and is closely connected to nucleophilicity.
- **LUMO (Lowest Unoccupied Molecular Orbital)**: the lowest-energy orbital

that is empty. It is often the best electron acceptor site and is closely connected to electrophilicity.

Why HOMO and LUMO matter: interaction and energy matching

When two molecules approach, new bonding interactions can form by overlap of a filled orbital on one molecule with an empty orbital on the other. The stabilizing interaction is strongest when:

- the donor orbital is high in energy (easier to donate electrons),
- the acceptor orbital is low in energy (easier to accept electrons),
- and the orbitals have compatible symmetry and good spatial overlap.

This is why a smaller HOMO–LUMO energy gap generally corresponds to higher reactivity (though many factors influence actual rates).

HOMO/LUMO shapes predict where reactions occur

In conjugated systems, the HOMO and LUMO are delocalized and have different amplitude (coefficient magnitude) on different atoms. Qualitatively:

- Positions with larger HOMO amplitude tend to be more reactive toward electrophiles (they are better electron donors).
- Positions with larger LUMO amplitude tend to be more reactive toward nucleophiles (they are better electron acceptors).

This idea becomes a practical tool in later chapters (conjugate addition, pericyclic reactions, and aromatic substitution), where regioselectivity can often be explained by matching the phases and coefficients of interacting FMOs.

2.4.7 MO interpretation of conjugation: stability and geometry revisited

MO theory provides a unified explanation for several observed features of conjugated molecules:

Stabilization by delocalization

Electrons in a conjugated π system occupy bonding orbitals that extend over multiple atoms, lowering their energy compared with a hypothetical localized description. This stabilization manifests as:

- increased thermodynamic stability,
- altered heats of hydrogenation (conjugated dienes release less heat than isolated dienes, reflecting initial stabilization),
- and bond-length equalization (partial double-bond character distributed across the chain).

Planarity as an orbital-overlap requirement

A conjugated chain typically prefers a planar (or near-planar) arrangement to maximize overlap among adjacent p orbitals. Twisting disrupts overlap, increasing energy by reducing the bonding character in occupied π orbitals.

Connection back to VB language

VB and MO descriptions are not competing **right vs. wrong** pictures; they emphasize different aspects:

- VB/hybridization is excellent for local structure, σ vs. π bonding, and mechanistic arrow-pushing intuition.
- MO theory is essential for delocalization, conjugation, and understanding reactivity in terms of electron donation/acceptance through HOMO/LUMO interactions.

Later, when resonance structures are used to rationalize stability and charge distribution, you can view resonance as a convenient representation whose underlying quantum-mechanical origin is delocalization in molecular orbitals.

2.4.8 Summary: what to retain for organic chemistry

By the end of this section, you should be able to use MO language in a practical, predictive way:

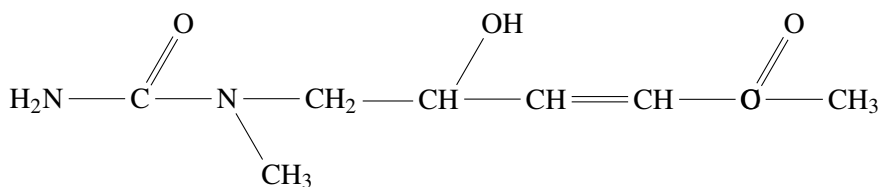
- **LCAO principle:** combining n aligned p orbitals yields n π MOs with increasing numbers of nodes and increasing energy.
- **Conjugation:** requires a continuous set of parallel p orbitals; it stabilizes molecules by delocalizing π electrons into lower-energy bonding MOs.
- **Frontier orbitals:** HOMO and LUMO dominate many interaction energies and often predict regioselectivity through orbital coefficients and phase matching.

The next section of this chapter consolidates these ideas through problems that integrate geometry (VSEPR), hybridization, dipole moments and intermolecular forces, and qualitative MO analysis of conjugated systems.

2.5 Problems

2.5.1 Hybridization and local geometry in a polyfunctional alkaloid-like framework

Consider the following polyfunctional skeleton (a simplified, alkaloid-like framework) given as a line-angle formula. Assume all atoms are neutral unless a formal charge is explicitly indicated.



- Assign the hybridization (sp^3 , sp^2 , or sp) of every non-hydrogen atom.
- For each non-hydrogen atom, state the expected VSEPR electron-domain geometry and the molecular geometry (shape).
- Identify which bonds in the structure have restricted rotation due to π bonding and briefly justify each.
- For the amide-like $C(=O)-N$ unit, predict whether the $C-N$ bond length is closer to a typical single bond or has partial double-bond character. State the orbital picture (VB/hybridization language) that supports your answer.

2.5.2 Dipole-moment ranking by 3D vector reasoning

Rank the following molecules in order of **increasing** net dipole moment magnitude. You must justify each comparison by explicitly considering both bond polarity and molecular geometry (VSEPR), indicating whether bond dipoles cancel or add.

(a) CO_2	(b) CH_2Cl_2	(c) CCl_4	(d) CH_3Cl
(e) CH_3OH	(f) BF_3	(g) NH_3	(h) H_2O

Include in your explanation:

- The electron-domain geometry at the central atom(s) used in your reasoning.
- A qualitative vector diagram description (e.g., “tetrahedral with three small C–H dipoles and one large C–Cl dipole”) for at least two of the molecules.

2.5.3 Bond-length comparison: amide vs. amine (resonance and orbital arguments)

Compare the C–N bond in acetamide (CH_3CONH_2) to the C–N bond in ethylamine ($\text{CH}_3\text{CH}_2\text{NH}_2$).

- Predict which C–N bond is shorter and provide a resonance-based argument (draw at least two major resonance contributors for the amide).
- Translate your resonance argument into an orbital picture: identify which orbitals must overlap to allow delocalization and state the geometric consequence (planarity vs. pyramidalization at nitrogen).
- Predict (qualitatively) the rotational barrier about the C–N bond in each compound and explain the difference using σ/π bonding language.

2.5.4 Allene (propadiene) in 3D: geometry, orbitals, and chirality

Allene ($\text{H}_2\text{C}=\text{C}=\text{CH}_2$) has a cumulated diene system. Answer the following.

- Determine the hybridization of the central carbon and each terminal carbon.
- Draw a 3D representation of allene showing the orthogonal arrangement of the terminal CH_2 groups. Indicate the two perpendicular π systems explicitly.

- Explain why substituted allenes can be chiral even in the absence of a stereogenic center, referencing (i) orthogonal π systems and (ii) the resulting 3D arrangement of substituents.

2.5.5 Boiling-point trends in C_5H_{12} isomers: dispersion and surface area

Three isomers of C_5H_{12} are shown below.



- Rank their boiling points from lowest to highest.
- Provide a detailed explanation based on London dispersion forces, explicitly relating your ranking to (i) molecular surface area, (ii) ability to pack in the liquid state, and (iii) polarizability (and why it is similar or different across the set).
- Predict which isomer has the lowest viscosity at room temperature and justify your answer in terms of intermolecular contact.

2.5.6 Qualitative MO diagram for the allyl cation

The allyl cation ($C_3H_5^+$) is a classic conjugated π system.

- Draw the three aligned p orbitals (one on each carbon) and construct the qualitative π MO diagram using LCAO: label the three π molecular orbitals, order them by energy, and indicate the number of nodes in each.
- Place the π electrons in the diagram for the allyl cation and identify the HOMO and LUMO.
- Using the MO coefficients (relative amplitudes) implied by your diagram, predict at which carbon(s) electrophilic attack would **most** stabilize the system, and justify your answer in frontier-orbital terms.

2.5.7 Identify HOMO and LUMO in an α, β -unsaturated ketone

Consider the conjugated enone methyl vinyl ketone, $CH_2=CH-CO-CH_3$.

- Identify the conjugated π system and count the number of p orbitals participating.
- Sketch a qualitative π MO energy diagram (no numbers required) and clearly label the HOMO and LUMO.
- Predict whether a nucleophile is more likely to react by **direct** addition to the carbonyl carbon (1,2-addition) or by **conjugate** addition to the β carbon (1,4-addition), **based only on HOMO/LUMO arguments**. State what additional factors (not required to compute) could shift the outcome in real reactions.

2.5.8 Why H_2O is 104.5° but CH_3OH has a larger $\text{C}-\text{O}-\text{H}$ angle

Water has an $\text{H}-\text{O}-\text{H}$ bond angle of about 104.5° . In methanol, the $\text{C}-\text{O}-\text{H}$ angle is larger (often close to 108° – 109°).

- Use VSEPR theory to explain why both water and methanol oxygen centers are based on a tetrahedral electron-domain geometry.
- Provide a detailed explanation for why the $\text{C}-\text{O}-\text{H}$ angle in methanol is larger than the $\text{H}-\text{O}-\text{H}$ angle in water, explicitly considering the following: (i) differences in lone pair-bond pair repulsions as substituents change; (ii) the relative “bulk” and electron-withdrawing character of CH_3 vs. H ; and (iii) how these factors distort bond angles away from the ideal tetrahedral value.
- Predict (qualitatively) how the $\text{C}-\text{O}-\text{H}$ angle would change in $(\text{CH}_3)_3\text{COH}$ (tert-butanol) relative to methanol and justify your prediction.

2.5.9 Orbital-overlap diagram for an alkyne: two orthogonal π systems

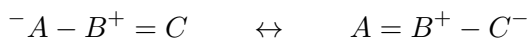
For acetylene ($\text{HC}\equiv\text{CH}$):

- Assign the hybridization of each carbon and identify which orbitals form the $\text{C}-\text{C}$ σ bond.
- Draw an orbital overlap diagram (qualitative) showing the $\text{C}-\text{C}$ σ bond from sp - sp head-on overlap, two distinct π bonds from side-on overlap of unhybridized p orbitals, and the fact that the two π systems are mutually perpendicular.

- Explain why rotation about the $\text{C}\equiv\text{C}$ axis does not change the overall bonding description in the same way as rotation about a $\text{C}=\text{C}$ bond, even though both contain π bonding (reference cylindrical symmetry of the overall electron density in the triple bond).

2.5.10 Formal charges and resonance: major contributor for a 1,3-dipolar species

A simplified 1,3-dipole can be represented by resonance forms of the type:



Consider the specific case of the azomethine ylide framework (use the connectivity shown; atoms are $\text{N}-\text{C}-\text{C}$):



where the dipolar form arises by charge separation across $\text{N}-\text{C}-\text{C}$. Answer the following.

- Draw two reasonable resonance contributors for a 1,3-dipolar $\text{N}-\text{C}-\text{C}$ system (one with negative charge adjacent to N and one with negative charge at the terminal carbon). Assign formal charges on each atom in each contributor.
- Using formal charge criteria (octet satisfaction, charge separation, and placing negative charge on more electronegative atoms), identify which contributor is expected to be the major one and justify.
- For the resonance hybrid, predict which atom would have the largest HOMO coefficient and which would have the largest LUMO coefficient qualitatively, and explain how this connects to nucleophilic vs. electrophilic sites in 1,3-dipoles.

Chapter 3

Stereochemistry and Conformations

While chemical structures are often drawn as static, two-dimensional figures, organic molecules exist as dynamic, three-dimensional objects. This chapter bridges the gap between flat representations and spatial reality, exploring how bond rotations and atomic arrangements dictate stability, physical properties, and biological activity. From the simple rotation of ethane to the complex folding of biomolecules, mastering the spatial relationships described here is essential for predicting how molecules interact in a chiral world.

3.1 Conformational Analysis of Acyclic Alkanes

In earlier discussions of covalent bonding and molecular structure, we emphasized that a σ bond (formed by end-to-end overlap) allows free rotation in principle. In practice, that rotation is not energetically uniform: as a bond rotates, the molecule passes through a family of distinct *conformations* (or *conformers*) that differ in energy. Conformational analysis is the quantitative description of (i) what conformers exist, (ii) why they have different energies, and (iii) how those energies determine the equilibrium mixture at a given temperature.

For acyclic alkanes, conformational effects arise mainly from changes in *torsional* and *steric* interactions during rotation about C–C single bonds. Although these conformers typically interconvert rapidly at room temperature, their energy differences still matter because conformational preferences influence reactivity, selectivity, and molecular recognition.

3.1.1 Conformations and the idea of a rotational energy profile

Consider rotation about a single C–C bond. At any instant, the atoms attached to the two carbons adopt a particular dihedral angle ϕ (the angle between two planes). A conformational energy profile is a plot of potential energy $E(\phi)$ versus dihedral angle ϕ , usually from 0° to 360° . The key features are:

- **Minima:** stable conformations (lower potential energy).
- **Maxima:** less stable conformations (higher potential energy) often corresponding to eclipsed arrangements.
- **Rotational barrier $\Delta E^\ddagger$:** the energy difference between a minimum and the adjacent maximum; this barrier controls how fast conformers interconvert.

It is important to distinguish two related but different ideas:

- **Conformational stability (thermodynamics):** which conformers are more populated at equilibrium?
- **Rotational barrier (kinetics):** how rapidly does the molecule interconvert among conformers?

3.1.2 Representations: Newman projections and sawhorse drawings

Because conformations are defined by rotation about a specific bond, we choose a viewpoint aligned with that bond.

Newman projection. A Newman projection looks *down* the bond of interest. The front carbon is drawn as a point (or small circle), and the back carbon as a larger circle; substituents are drawn as three bonds separated by 120° around each carbon.

Sawhorse representation. A sawhorse drawing shows the same conformational relationship from an oblique angle, often making it easier to connect to standard line-bond drawings. In practice, Newman projections are preferred for quantitative analysis because they map dihedral angles directly.

3.1.3 Strain terms that control conformational energy

For acyclic alkanes, conformational energies are dominated by three contributions:

Torsional strain

Torsional strain is the energetic penalty associated with *eclipsing* bonds (dihedral angles near 0° , 120° , 240°). In valence-bond terms, eclipsing conformations maximize repulsive interactions between electron density in adjacent σ bonds. In molecular orbital language, eclipsing also reduces stabilizing $\sigma \rightarrow \sigma^*$ hyperconjugative interactions that are best in staggered geometries. Regardless of language, eclipsed conformations are higher in energy than staggered ones.

Steric (van der Waals) strain

Steric strain arises when nonbonded atoms approach closer than their favorable van der Waals contact distance. In alkanes, this becomes especially important when larger substituents (e.g., CH_3) are brought near each other during rotation.

Angle strain (for comparison)

In acyclic alkanes, **angle strain** is minimal because bond angles can remain near the tetrahedral value ($\approx 109.5^\circ$). Angle strain becomes central in cycloalkanes (addressed in the next section), but it is not a primary driver of conformational preference in open-chain alkanes.

3.1.4 Ethane: the simplest case of torsional strain

Ethane illustrates torsional strain in its purest form because both carbons carry only hydrogens. Rotation about the C–C bond generates:

- **Staggered conformations** (minima): $\phi = 60^\circ, 180^\circ, 300^\circ$.
- **Eclipsed conformations** (maxima): $\phi = 0^\circ, 120^\circ, 240^\circ$.

All staggered conformations of ethane are equivalent by symmetry, as are all eclipsed conformations. The rotational barrier of ethane is modest, but the conceptual lesson is essential: even in a molecule with no “crowding” between large groups, eclipsing raises energy.

3.1.5 Butane: steric and torsional effects combine

n-Butane ($\text{CH}_3\text{--CH}_2\text{--CH}_2\text{--CH}_3$) is the first alkane in which rotation about a central bond produces *distinct* staggered conformations with different energies because

the rotating groups include methyl substituents.

We analyze rotation about the C_2-C_3 bond. In a Newman projection looking from C_2 to C_3 :

- Front carbon (C_2) bears CH_3 , H, H.
- Back carbon (C_3) bears CH_3 , H, H.

Key conformations and terminology

As the dihedral angle between the two methyl groups changes, three named arrangements are particularly important:

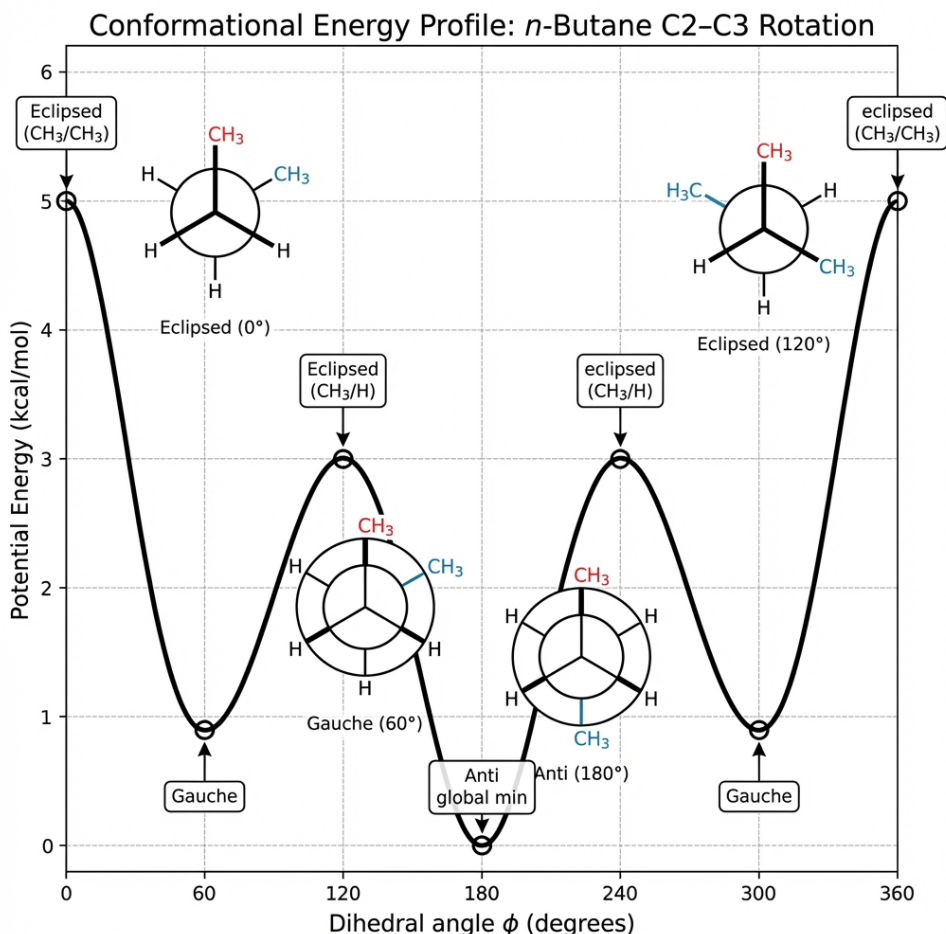
Anti (staggered, lowest energy). The methyl groups are opposite each other ($\phi = 180^\circ$). This minimizes steric interactions between methyl groups. Anti is the global minimum for butane.

Gauche (staggered, local minimum). The methyl groups are 60° apart ($\phi = 60^\circ$ or 300°). Gauche conformations remain staggered (so torsional strain is low), but the methyl groups experience increased steric repulsion because they are closer in space. Thus, gauche is higher in energy than anti.

Eclipsed (maxima). At $\phi = 0^\circ$, the methyl groups eclipse each other (CH_3/CH_3 eclipsing), giving the highest energy due to *both* torsional strain (eclipsing) and strong steric repulsion. At $\phi = 120^\circ$ and 240° , a methyl eclipses a hydrogen (CH_3/H eclipsing), which is still high energy but lower than CH_3/CH_3 eclipsing.

These relationships produce an energy ordering that is robust and foundational:

$$E(\text{anti}) < E(\text{gauche}) < E(\text{eclipsed } CH_3/H) < E(\text{eclipsed } CH_3/CH_3)$$



Interpreting the butane energy diagram: what each feature “means”

The butane profile encodes two intertwined ideas:

Staggered is not always equally stable. Both anti and gauche are staggered, so both minimize torsional strain. Their difference is largely *steric*: in the gauche conformer, the two methyl groups occupy closer regions of space, raising energy relative to anti.

Not all eclipsed conformations are equally unstable. At $\phi = 120^\circ$ and 240° , the worst eclipsing involves CH_3/H contacts. At $\phi = 0^\circ$ (and 360°), the CH_3 groups eclipse each other directly (CH_3/CH_3), producing the highest maximum. Thus, substituent size amplifies eclipsing penalties.

3.1.6 Thermodynamic populations: Boltzmann distribution of conformers

An energy profile is thermodynamic only when it is paired with the idea that conformers at equilibrium are populated according to their relative energies. For two conformers A and B at temperature T , the ratio of populations is given approximately by the Boltzmann relationship

$$\frac{N_B}{N_A} = \exp\left(-\frac{\Delta G_{B-A}^\circ}{RT}\right)$$

where $\Delta G_{B-A}^\circ = G_B^\circ - G_A^\circ$, R is the gas constant, and T is in kelvin.

In many introductory conformational discussions, we approximate $\Delta G^\circ \approx \Delta E$ (or ΔH°) to build intuition: lower potential energy $\Rightarrow$ more populated conformer. This approximation is often reasonable for simple acyclic alkanes because (i) conformers have similar bonding patterns and (ii) entropy differences among conformers are modest. However, a fully correct treatment uses ΔG° , not just ΔE .

Degeneracy matters: counting conformers correctly

For butane, there is one anti conformer (at 180°) but two equivalent gauche conformers (at 60° and 300°). Even if each gauche conformer is higher in energy than anti, the *total* population in the “gauche set” can still be substantial because there are two of them. A more careful population estimate includes a degeneracy factor g :

$$\frac{N_{\text{gauche, total}}}{N_{\text{anti}}} = \frac{g_{\text{gauche}}}{g_{\text{anti}}} \exp\left(-\frac{\Delta G_{\text{gauche-anti}}^\circ}{RT}\right) \quad (g_{\text{gauche}} = 2, g_{\text{anti}} = 1)$$

This is the conceptual bridge between an energy diagram and an experimentally meaningful statement like “anti predominates, but gauche is significantly populated at room temperature.”

Temperature effects: why higher energy conformers matter more at higher T

The exponential factor contains T in the denominator. As temperature increases, energy differences become *less decisive* (the distribution flattens), and higher-energy conformers become more populated. As temperature decreases, the distribution becomes more sharply concentrated in the lowest-energy conformer(s).

3.1.7 Rotational barriers and conformational interconversion

The energy maxima on the diagram correspond to rotational transition states (not isolable conformers). The barrier height $\Delta E^\ddagger$ between a minimum and the adjacent maximum governs the rate of interconversion. For acyclic alkanes at room temperature, these barriers are small enough that conformers interconvert rapidly on most laboratory time scales. Two consequences follow:

- **Conformers are usually not separable.** You typically observe an averaged signal (e.g., in NMR) unless temperature is lowered enough to slow exchange.
- **Equilibrium ideas still apply.** Even though the interconversion is fast, the fraction of molecules in each conformer at any instant reflects the underlying thermodynamics.

3.1.8 A structured workflow for conformational analysis of acyclic alkanes

When analyzing any acyclic alkane, a consistent approach prevents mistakes:

- **Choose the bond of interest** and draw a Newman projection looking down that bond.
- **Identify large substituents** on each carbon (e.g., CH_3 , CH_2CH_3 , tert-butyl).
- **Compare staggered conformations first:** find the arrangement that maximizes separation of the largest groups (often the global minimum).
- **Evaluate eclipsed conformations:** locate where the largest groups eclipse (often the global maximum).
- **Account for degeneracy:** count how many conformers belong to each energy class.
- **Translate energy differences into populations** using the Boltzmann distribution (using ΔG° when available).

3.1.9 Why conformational preferences matter beyond alkanes

Although this section uses alkanes as the simplest conformational system, the same logic becomes more consequential in functionalized molecules:

- In substituted systems, conformational preferences determine whether a reactive group is positioned for intramolecular reaction or properly aligned for orbital overlap.
- In stereoselective reactions, different conformers can lead to different stereochemical outcomes because they present different faces of a molecule to reagents.
- In cyclic molecules (next section), conformational constraints become even stronger: ring conformations can enforce or prevent eclipsing, and substituents can be locked into axial/equatorial environments with measurable energetic consequences.

Conformational analysis is therefore not an isolated topic; it is the thermodynamic and geometric foundation for stereochemical reasoning throughout organic chemistry.

3.2 Cycloalkanes and Chair Conformations

The previous section showed how rotation about σ bonds creates conformers with different energies, and how torsional and steric strain shape the conformational landscape of acyclic alkanes. Cycloalkanes add a new constraint: *a ring cannot freely rotate without changing its geometry*. As a result, cycloalkanes exhibit distinctive forms of strain and characteristic conformational pathways. This section develops a quantitative, structure-based understanding of (i) *ring strain* in small and medium rings and (ii) the unusually low-strain, highly mobile *chair* conformations of cyclohexane and its derivatives.

3.2.1 Ring strain: the energetic cost of forcing a ring into an unfavorable geometry

Ring strain is the extra energy a cyclic compound possesses relative to an unstrained (hypothetical) reference with similar bonding. It is not a single effect; it is best understood as the sum of three conceptually distinct contributions:

- **Angle strain (Baeyer strain):** deviation of C–C–C bond angles from the tetrahedral value ($\approx 109.5^\circ$) for sp^3 -hybridized carbons.

- **Torsional strain:** eclipsing interactions that occur when adjacent bonds are forced into (partially) eclipsed arrangements.
- **Steric (transannular) strain:** nonbonded atoms forced into close proximity, including across the ring (important in medium rings).

A key conceptual shift from acyclic conformations is that **angle and torsional strain become coupled**. In a ring, changing one dihedral angle typically requires changing others, and the ring may have only a limited number of accessible shapes.

3.2.2 Small rings: cyclopropane and cyclobutane

Cyclopropane: severe angle strain and “bent” bonding

A planar three-membered ring would require internal bond angles of 60° , far from 109.5° . This large deviation produces severe **angle strain**. In addition, if cyclopropane were composed of conventional localized σ bonds directed along internuclear axes, the geometry would be extremely unfavorable.

Cyclopropane is better described as having **bent (banana) bonds**: the bonding electron density is displaced outward from the ring center, allowing overlap in a geometry that is not perfectly head-on. Even with bent bonds, cyclopropane remains highly strained.

Torsional strain is also significant. If the ring is planar (as cyclopropane essentially is), many C–H bonds on adjacent carbons are close to eclipsed when viewed along a C–C bond. Thus, cyclopropane combines *maximum angle strain* with *substantial torsional strain*.

Cyclobutane: reduced angle strain but still significant torsional strain

A planar cyclobutane would have internal angles near 90° , still far from 109.5° , but less extreme than cyclopropane. Cyclobutane does not remain planar: it adopts a **puckered** (“butterfly”) conformation. Puckering slightly relieves torsional strain by reducing eclipsing of C–H bonds, at the cost of a modest increase in angle distortion. The observed conformation reflects the general principle that molecules adopt shapes that minimize ΔG by balancing multiple strain terms rather than optimizing only one.

3.2.3 Cyclopentane: conformational flexibility to reduce torsional strain

If cyclopentane were planar, it would have internal angles of 108° , very close to tetrahedral, implying minimal angle strain. However, a planar cyclopentane suffers from extensive torsional strain due to eclipsing C–H interactions around the ring.

Cyclopentane therefore adopts **nonplanar conformations**, primarily the **envelope** and **half-chair** forms. These conformations:

- greatly reduce torsional strain (more bonds become staggered-like),
- introduce only small angle distortions,
- interconvert rapidly through low-energy pathways.

This sets the stage for cyclohexane, which achieves an even more dramatic result: a conformation with essentially no angle strain and minimal torsional strain.

3.2.4 Cyclohexane: why the chair conformation is special

Cyclohexane is the prototypical “unstrained” cycloalkane because it can adopt conformations in which:

- C–C–C angles are near 109.5° (minimal angle strain),
- adjacent C–H and C–C bonds are largely staggered (minimal torsional strain),
- nonbonded contacts are not excessively crowded (minimal steric strain).

Common cyclohexane conformations

Cyclohexane has several named conformations, with the following qualitative stability order:

$$G(\text{chair}) < G(\text{twist-boat}) < G(\text{boat}) < G(\text{half-chair})$$

Chair. The **chair** is the lowest-energy form. It achieves near-tetrahedral bond angles and a predominantly staggered arrangement around each C–C bond. For conformational analysis, the chair is the reference point for cyclohexane and substituted cyclohexanes.

Boat and twist-boat. The **boat** form introduces steric and torsional penalties. Two key destabilizing features are:

- **Flagpole interactions:** steric repulsion between the two “bow” and “stern” hydrogens brought close together.
- **Increased eclipsing:** several adjacent bonds become partially eclipsed.

A slight distortion produces the **twist-boat**, which relieves some eclipsing and reduces flagpole repulsion, making it lower in energy than the boat but still higher than the chair.

Half-chair. The **half-chair** is a high-energy transition-region conformation along the ring-flip pathway; it features significant torsional strain and less favorable bond angles.

3.2.5 Axial and equatorial positions in the chair

The chair conformation introduces two distinct types of C–H (and C–substituent) bonds:

- **Axial bonds:** oriented approximately parallel to the ring’s vertical axis (alternating up and down around the ring).
- **Equatorial bonds:** oriented roughly around the “equator” of the ring, projecting outward around the ring perimeter.

Each carbon in cyclohexane has one axial and one equatorial substituent position. The important structural facts are:

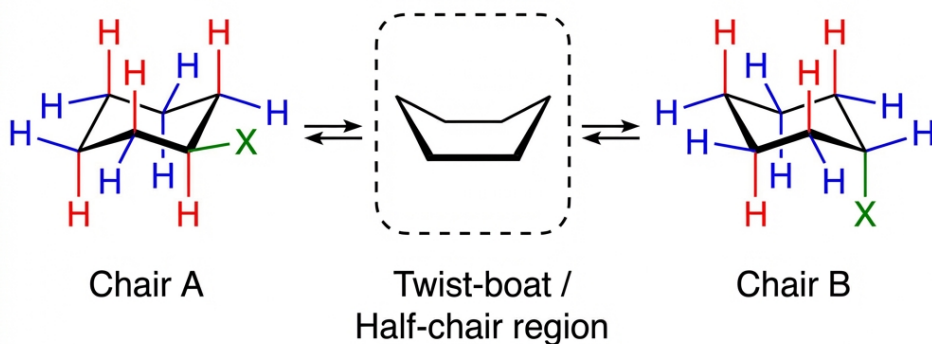
- Axial positions alternate up/down as you move around the ring.
- Equatorial positions also alternate up/down, but they point outward and are generally less crowded.
- **Up/down is not the same as axial/equatorial.** “Up” or “down” describes whether a substituent is on the same side of the average ring plane; “axial” or “equatorial” describes its orientation relative to the ring framework.

3.2.6 Ring flip: conformational mobility unique to cyclohexane

Cyclohexane is not locked into one chair. It undergoes a **ring flip** (chair $\rightleftharpoons$ chair) that interconverts two chair conformations of equal energy in unsubstituted cyclohexane. During a ring flip:

- every **axial** position becomes **equatorial**,
- every **equatorial** position becomes **axial**,
- **up/down orientation is retained** for a given substituent (an “up” substituent remains up, but may switch between axial up and equatorial up).

This last point is crucial for stereochemistry in rings: conformational change swaps axial/equatorial, but it does not invert the *configuration* (up vs. down) at a substituted carbon.



Red: axial positions in each chair

Blue: equatorial positions in each chair

Ring flip: axial $\leftrightarrow$ equatorial (up/down retained)

3.2.7 1,3-Diaxial interactions: why axial substituents are usually less stable

In substituted cyclohexanes, the two chair conformations are no longer equal in energy because a substituent may be axial in one chair and equatorial in the other. The energetic penalty for an axial substituent is primarily due to **1,3-diaxial interactions**.

What is a 1,3-diaxial interaction?

Place a substituent R in an axial position on carbon 1. On the same side of the ring (same “up” or same “down”), there are axial hydrogens on carbons 3 and 5. The axial R group is brought into close proximity with those axial hydrogens, producing steric repulsion akin to gauche-like crowding, but enforced by ring geometry.

Thus, an axial substituent experiences two significant steric contacts:



A-values: quantifying the axial penalty

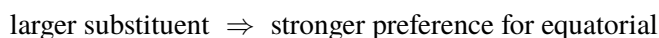
The energetic preference for equatorial placement is often expressed as an **A-value**:

$$A \equiv \Delta G^\circ = G^\circ(\text{axial}) - G^\circ(\text{equatorial})$$

A larger A -value means a stronger preference for equatorial placement.

Interpretation	What it tells you
$A > 0$	Equatorial conformer is more stable (typical for most substituents).
Larger A	Greater steric penalty for axial placement (bulkier groups).
Conformer ratio	$\frac{N_{\text{eq}}}{N_{\text{ax}}} = \exp\left(\frac{A}{RT}\right)$ (approx.).

Even without memorizing specific A -values, you should expect the qualitative trend:



A tert-butyl group is so bulky that it overwhelmingly prefers equatorial placement and can effectively “lock” the ring in the chair that keeps it equatorial.

3.2.8 Disubstituted cyclohexanes: cis/trans and conformational analysis

Substituted cyclohexanes introduce stereochemical relationships that must be described carefully. Two different classification schemes operate at the same time:

- **Conformation (axial/equatorial):** changes with ring flip.
- **Configuration (cis/trans):** does *not* change with ring flip.

Cis/trans in cyclohexanes

For cyclohexanes, **cis** means substituents are on the same side of the ring (both up or both down). **trans** means opposite sides (one up, one down). Because ring flip preserves up/down, cis remains cis and trans remains trans.

Diequatorial vs diaxial: the key stability question

For a given cis or trans isomer, one chair may place substituents in more favorable positions than the other. A highly useful heuristic is:

- **Diequatorial conformations are usually most stable.**
- **Diaxial conformations are usually least stable** (especially with bulky substituents).

Which isomer (cis or trans) can access a diequatorial conformation depends on substitution pattern (e.g., 1,2-; 1,3-; 1,4-) and the relative up/down orientations. The systematic procedure is:

- Draw one chair; assign substituents as up or down according to cis/trans.
- Translate each up/down assignment into axial or equatorial in that specific chair.
- Perform a ring flip and reassign: up remains up, down remains down, but axial/equatorial swap.
- Compare the two chairs by counting (and weighting) axial substituents using *A*-values or steric logic.

3.2.9 Fused rings: a preview with decalin

When two cyclohexane rings share an edge (a fused system), conformational mobility can be restricted. **Decalin** (bicyclo[4.4.0]decane) exists as *cis*- and *trans*-fused isomers. The fusion stereochemistry can limit or prevent a full ring flip because the shared bond and fusion geometry constrain the ring framework. This illustrates a general theme: cyclohexane is exceptionally flexible as a *single* ring, but connectivity (fusion, bridging, multiple substituents) can “freeze” conformations, making axial/equatorial placement a persistent structural feature rather than an averaging phenomenon.

3.2.10 Summary: what to remember and how to use it

Cyclohexane conformational analysis becomes powerful when you keep three statements separate and use them together:

- **Chair conformations minimize strain** (near-tetrahedral angles and near-staggered bonds).
- **Ring flip swaps axial and equatorial** but **retains up/down** orientation.
- **Axial substituents are destabilized by 1,3-diaxial interactions**; equatorial placement is usually favored, and the preference can be quantified with *A*-values.

These principles will be reused repeatedly: whenever a reaction or property depends on whether a group is axial or equatorial, the first step is to determine which chair conformations are accessible and which one dominates the equilibrium.

3.3 Chirality and Enantiomers

The previous sections developed the idea that molecules are three-dimensional objects whose σ -bond frameworks can adopt different shapes (conformations), and that those shapes have measurable energetic consequences. We now build on that three-dimensional viewpoint to introduce a deeper geometric property: *handedness*. Some molecular structures exist in two forms that are mirror images, yet cannot be made identical by any rotation or translation. This property is called **chirality**, and it is central to modern organic chemistry because chiral molecules interact differently with other chiral environments—including enzymes, receptors, and polarized light.

3.3.1 Chirality: mirror images that cannot be superimposed

A molecule is **chiral** if it is *not* superimposable on its mirror image. Two structures are **superimposable** if, after any combination of rotations and translations (but *not* breaking bonds), they can be made to coincide in three-dimensional space.

An operational test: “Can the mirror image be placed on top of the original?”

The most reliable mental model is the one used for hands: a left hand and a right hand are mirror images, but no rotation makes them identical. In the same way, a chiral molecule has a “left-handed” and a “right-handed” form.

The two non-superimposable mirror-image forms of a chiral molecule are called **enantiomers**. Enantiomers are distinct molecules: they are stereoisomers related as mirror images.

3.3.2 Symmetry and achirality

Plane of symmetry and center of inversion

A molecule is **achiral** if it *is* superimposable on its mirror image. Although there are several symmetry elements that guarantee achirality, one is especially important at this stage:

- If a molecule has an internal **plane of symmetry** (a mirror plane σ), it is achiral.

A plane of symmetry divides the molecule into two halves that are mirror images of each other. If such a plane exists, the mirror image of the whole molecule can be brought into coincidence with the original by rotation: the structure lacks handedness.

A **center of inversion** is another symmetry element that guarantees achirality: if for every point (x, y, z) there is an identical point $(-x, -y, -z)$ through a single inversion point, then the structure is achiral. In introductory organic chemistry, planes of symmetry are encountered more frequently than inversion centers, but both are useful in diagnosing chirality.

Conformations vs. configurations: an important warning

A molecule can have many conformations, but chirality is a property of the *three-dimensional arrangement at a given instant*. Two common sources of confusion are:

- **Chiral conformations vs. chiral molecules.** Some molecules without stereocenters can adopt chiral conformations (they lack a mirror plane in that conformation). However, if the molecule rapidly interconverts between enantiomeric conformations (a left-handed conformer and a right-handed conformer) under ordinary conditions, the *molecule as a whole* is usually treated as achiral in practice because it does not exist as isolable enantiomers.
- **Enantiomers are not conformers.** Conformers interconvert by rotation about σ bonds. Enantiomers require a change in configuration (for example, inversion at a stereocenter), which cannot be accomplished by simple bond rotations without passing through bond-breaking or a high-energy, symmetry-forbidden pathway.

In this section, our focus is on *configurational* chirality: stable, isolable enantiomers.

3.3.3 Stereocenters (chirality centers): a common origin of chirality

The most common structural feature producing chirality in organic molecules is a tetrahedral carbon attached to four different substituents. Such a carbon is called a **stereocenter** (or **chirality center**).

Definition: stereocenter at carbon

A carbon atom is a stereocenter if:

- it is tetrahedral (approximately sp^3),
- it is bonded to four *different* groups,
- interchanging any two substituents produces a stereoisomer.

If a molecule contains a single stereocenter and no other symmetry elements that eliminate chirality, it will exist as a pair of enantiomers.

What counts as “different” substituents?

Determining whether two substituents are different requires attention to *connectivity*. For example, on a tetrahedral carbon, $-\text{CH}_3$ and $-\text{CH}_2\text{CH}_3$ are different groups. Two $-\text{CH}_2\text{CH}_3$ groups are identical if they are connected in the same way to the stereocenter and lead through identical paths in the molecule. Later, the Cahn–Ingold–Prelog (CIP) rules will provide a systematic method for ranking substituents; here, the main point is conceptual: chirality requires *asymmetry*.

Chirality does not require carbon

Although the tetrahedral carbon stereocenter is the most common case, chirality can also arise from:

- **heteroatom stereocenters** (e.g., chiral sulfoxides, certain phosphines),
- **axial chirality** (e.g., substituted biphenyls with hindered rotation, allenes),
- **planar chirality** (certain metallocenes and constrained systems),
- **helical chirality** (helicenes).

These other sources share the same geometric essence: non-superimposable mirror-image arrangements.

3.3.4 Enantiomers: relationships and properties

Relationship definition

Two molecules are **enantiomers** if they are:

- stereoisomers,
- mirror images,
- non-superimposable.

If two stereoisomers are not mirror images, they are **diastereomers** (discussed in a later section).

What properties do enantiomers share?

In an *achiral* environment (no chiral reagents, solvents, catalysts, or surfaces), enantiomers have essentially identical:

- melting points and boiling points,
- densities and refractive indices,
- IR spectra and NMR spectra (in achiral solvents),
- most thermodynamic properties (e.g., ΔH , ΔS , ΔG) for achiral processes.

This similarity can be understood by noting that an achiral environment cannot “distinguish left from right”; it interacts with each enantiomer in an energetically equivalent way.

What properties differ?

Enantiomers differ in their behavior in *chiral* contexts, including:

- **optical activity** (interaction with plane-polarized light),
- **biological activity** (binding to enzymes and receptors),
- **reaction rates and equilibria** with chiral reagents/catalysts (enantioselective chemistry),
- **chromatographic behavior** on chiral stationary phases.

The most direct physical manifestation of chirality in a basic laboratory measurement is optical activity.

3.3.5 Optical activity and polarimetry

Plane-polarized light

Light is an electromagnetic wave. In ordinary light, the electric field oscillates in many planes perpendicular to the direction of travel. **Plane-polarized light** has its electric field constrained to oscillate in a single plane. A **polarizer** produces plane-polarized light.

Optically active substances rotate the plane of polarization

A chiral compound (as a pure enantiomer or an enantiomerically enriched sample) can rotate plane-polarized light. This phenomenon is **optical rotation**. It is measured using a **polarimeter**.

If the plane is rotated clockwise as viewed toward the light source, the compound is **dextrorotatory** and assigned a + sign. If the plane is rotated counterclockwise, the compound is **levorotatory** and assigned a – sign.

Rotation sign is not configuration

The + or – designation is an experimental property and does *not* reliably correlate with absolute configuration (which will later be labeled *R* or *S*). A common mistake is to assume, for example, that *R* always corresponds to +. There is no universal rule of that kind.

Specific rotation

The observed optical rotation depends on:

- path length l (typically in dm),
- concentration c (typically in g mL^{-1} for solutions),
- wavelength λ (commonly the sodium D line, 589 nm),
- temperature T ,
- solvent and sample purity.

To compare different measurements, the **specific rotation** $[\alpha]_{\lambda}^T$ is defined as

$$[\alpha]_{\lambda}^T = \frac{\alpha_{\text{obs}}}{l c}$$

where α_{obs} is the observed rotation in degrees, l is the path length in decimeters, and c is the concentration in g mL^{-1} .

For neat liquids, concentration may be replaced by density with an appropriate convention. Regardless of convention, the essential idea is that specific rotation normalizes optical rotation to standard conditions.

3.3.6 Racemic mixtures, enantiomeric excess, and optical purity

Racemic mixture

A **racemic mixture** (or **racemate**) contains equal amounts of the two enantiomers:

$$N_R = N_S$$

(Here R and S are placeholders for the two enantiomeric forms; the absolute configuration labels will be developed in the next section.) A racemic mixture is optically inactive:

$$\alpha_{\text{obs}} = 0$$

because the equal and opposite rotations cancel.

Enantiomeric excess (ee)

Most real samples are neither pure enantiomers nor perfectly racemic. The **enantiomeric excess** (ee) is a measure of the extent to which one enantiomer predominates. For a mixture of two enantiomers A and B ,

$$\text{ee} = \frac{|N_A - N_B|}{N_A + N_B} \times 100\%$$

If A is the major enantiomer, one often writes

$$\text{ee} = (\%A - \%B)$$

with the understanding that the sign indicates which enantiomer is in excess.

Relating ee to optical rotation (optical purity)

If the specific rotation of a *pure* enantiomer is known under the same conditions, then for many systems the rotation of a mixture is approximately proportional to ee:

$$\text{ee} \approx \frac{\alpha_{\text{obs}}}{\alpha_{\text{pure}}} \times 100\%$$

This proportionality holds because each enantiomer contributes an equal magnitude but opposite sign of rotation, and the net rotation reflects the imbalance between them.

A common calculation pattern

If a sample is 40% ee in favor of enantiomer *A*, then

$$\%A = \frac{100 + 40}{2} = 70\%, \quad \%B = \frac{100 - 40}{2} = 30\%$$

This conversion between ee and composition is used constantly in stereochemical problem-solving.

3.3.7 Physical meaning: why chirality is detectable

At a fundamental level, chirality becomes measurable when the probe or environment has a directional or handed character. Plane-polarized light has a defined plane; a chiral stationary phase has a handed surface; an enzyme active site is a chiral pocket. In each case, the interaction energy depends on three-dimensional fit. Two enantiomers are related by mirror reflection, so their fit in a chiral environment is generally not identical. That difference can appear as a different rotation angle, different binding affinity, or different reaction rate.

- **Chirality** is the property of having a non-superimposable mirror image.
- **Enantiomers** are pairs of non-superimposable mirror-image stereoisomers.
- A **plane of symmetry** guarantees **achirality**.
- Many chiral organic molecules contain a tetrahedral carbon **stereocenter** bonded to four different substituents.
- Enantiomers share most physical properties in **achiral** environments but differ in **chiral** contexts, notably in **optical activity**.
- **Specific rotation** and **enantiomeric excess** provide quantitative measures of chirality in the laboratory.

These ideas set up the next essential step: a systematic language for naming stereoisomers and assigning absolute configuration, so that “which enantiomer” is no longer ambiguous.

3.4 Stereochemical Descriptors: R/S and E/Z

The previous section established that many molecules exist as stereoisomers, including pairs of enantiomers that are non-superimposable mirror images. To communicate stereochemistry unambiguously, organic chemistry uses a standardized naming system. The most important elements of that system are the **Cahn–Ingold–Prelog (CIP)** priority rules and the resulting descriptors:

- *R* and *S* for tetrahedral stereocenters (and related stereogenic units),
- *E* and *Z* for alkene (and similar) geometric isomerism.

These descriptors replace ambiguous terms such as “left/right” or even “cis/trans” in cases where cis/trans is not uniquely defined (e.g., tri- and tetrasubstituted alkenes). This section develops the rules step-by-step and emphasizes a reliable workflow that minimizes common errors.

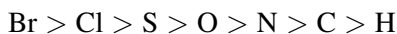
3.4.1 CIP priority rules: ranking substituents

Assigning *R/S* or *E/Z* begins the same way: rank substituents by priority using the CIP rules. The priority ranking is local and algorithmic; it does not depend on functional group “importance” or on the size of a substituent as a whole.

Rule 1: higher atomic number $\Rightarrow$ higher priority

Compare the atoms *directly attached* to the stereocenter (for *R/S*) or to each alkene carbon (for *E/Z*). The substituent whose directly attached atom has the higher atomic number gets higher priority.

Examples (directly attached atoms):



Thus, at a stereocenter bearing $-\text{OH}$, $-\text{CH}_3$, $-\text{Cl}$, and $-\text{H}$, the priorities start as $\text{Cl}(1) > \text{O}(2) > \text{C}(3) > \text{H}(4)$.

Rule 2: if directly attached atoms tie, compare the next set outward

If the directly attached atoms are the same (often carbon vs. carbon), compare the atoms attached to those atoms, moving outward one bond at a time until a difference is found.

How to compare “next atoms” correctly. For each substituent, list the atoms attached to the directly attached atom (excluding the stereocenter) in order of decreasing atomic number, and compare the lists term-by-term (lexicographically). The first point of difference determines priority.

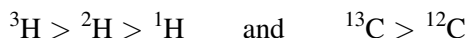
Example: compare $-\text{CH}_2\text{OH}$ vs. $-\text{CH}_3$. The directly attached atom is carbon in both cases (tie). Next atoms:

- For $-\text{CH}_2\text{OH}$: attached atoms to that carbon are O, H, H $\Rightarrow (O, H, H)$.
- For $-\text{CH}_3$: attached atoms are H, H, H $\Rightarrow (H, H, H)$.

Because $O > H$ at the first comparison, $-\text{CH}_2\text{OH}$ has higher priority than $-\text{CH}_3$.

Rule 3: isotopes

Isotopes are ranked by **mass number**, not by average atomic weight:



Rule 4: multiple bonds are treated as “phantom atoms”

A multiple bond is treated as if the atom were bonded to an equivalent number of duplicate atoms of the partner.

- A double bond $\text{C}=\text{O}$ is treated as carbon bonded to two oxygens for priority purposes.
- A triple bond $\text{C}\equiv\text{N}$ is treated as carbon bonded to three nitrogens.

This is a bookkeeping device that allows the same stepwise comparison method to work for alkenes, carbonyls, nitriles, and aromatics.

Example: $-\text{CHO}$ vs. $-\text{CH}_2\text{OH}$. Directly attached atom is carbon in both cases. Next atoms:

- $-\text{CHO}$: carbonyl carbon is treated as attached to O, O, H $\Rightarrow (O, O, H)$.
- $-\text{CH}_2\text{OH}$: carbon attached to O, H, H $\Rightarrow (O, H, H)$.

Because (O, O, H) outranks (O, H, H) , $-\text{CHO}$ has higher priority than $-\text{CH}_2\text{OH}$.

3.4.2 Assigning *R* and *S*: absolute configuration at a stereocenter

A tetrahedral stereocenter has four substituents that can be ranked 1 (highest) through 4 (lowest) by CIP rules. The *R/S* descriptor communicates the *absolute configuration*—a specific three-dimensional arrangement.

Core procedure (conceptual)

Once priorities 1 through 4 are assigned:

- Orient the molecule so that the lowest priority group (4) points *away* from you.
- Trace the path $1 \rightarrow 2 \rightarrow 3$.
- If the path turns clockwise, the stereocenter is *R* (from Latin *rectus*).
- If the path turns counterclockwise, the stereocenter is *S* (from Latin *sinister*).

Working with wedge/dash drawings

In wedge/dash notation:

- a **solid wedge** indicates a bond coming *toward* the viewer,
- a **hashed wedge** indicates a bond going *away* from the viewer,
- ordinary lines are in the plane of the page.

If group 4 is already on a dashed bond (away), the clockwise/counterclockwise test can be applied directly.

The “invert if 4 points toward you” rule. If group 4 is on a solid wedge (toward the viewer), you may still trace $1 \rightarrow 2 \rightarrow 3$, but the assignment is *reversed*:

$$\text{clockwise} \Rightarrow S, \quad \text{counterclockwise} \Rightarrow R$$

This reversal is a common source of mistakes; for reliability, many students prefer to reorient the drawing so that group 4 is away before deciding.

Working with Fischer projections (preview)

A Fischer projection is a standardized 2D representation of a tetrahedral carbon where:

- horizontal bonds come *out of the page* (toward),
- vertical bonds go *into the page* (away).

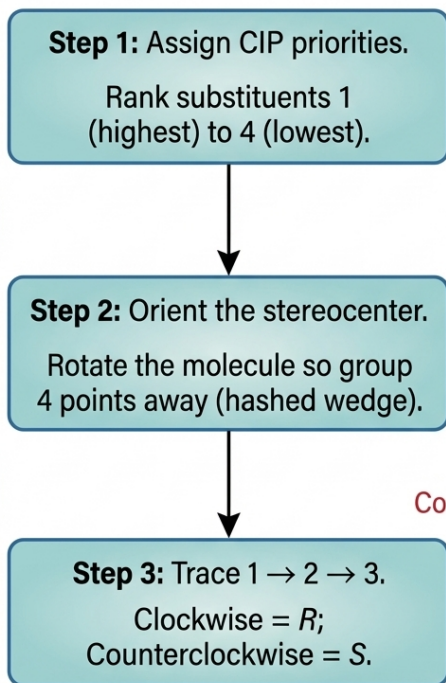
Thus, if the lowest priority group is on a horizontal position in a Fischer projection, it points toward you and the result must be inverted. Fischer projections will be used more extensively when we discuss molecules with multiple stereocenters.

Common pitfalls and how to avoid them

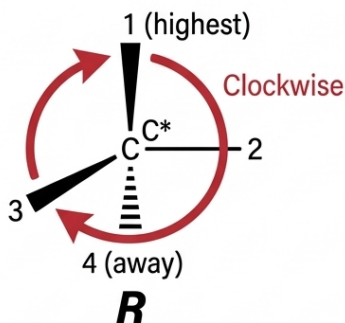
- **Comparing substituents by “size” instead of CIP rules.** Always compare atom-by-atom, outward from the stereocenter.
- **Forgetting the lowest-priority orientation.** The rule is defined with group 4 pointing away.
- **Doing illegal “moves” when reorienting.** Rotating the entire molecule in space is allowed; swapping two substituents at a stereocenter is not (a single swap inverts configuration).

3.4.3 Steering-wheel method: a reliable workflow

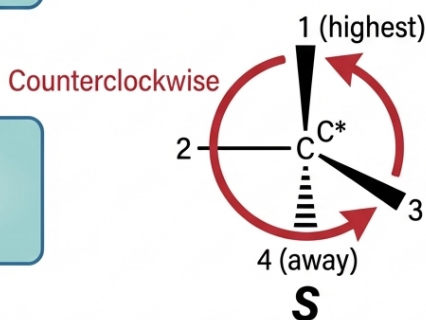
Immediately after applying CIP priorities, it is helpful to use a standardized visual workflow (often called the **steering wheel** rule) to keep the orientation step explicit. The goal is to reduce *R/S* assignment to a repeatable set of actions.



Example: Clockwise ⇒ *R*



Example: Counterclockwise ⇒ *S*



Note: If group 4 points *toward* you, the clockwise/counterclockwise result must be inverted. A safer method is to reorient the drawing so 4 is away before assigning *R* or *S*.

3.4.4 Assigning *E* and *Z*: alkene stereochemistry by CIP rules

Alkenes (C=C) are not freely rotating like σ bonds. Rotation about a double bond would require breaking the π bond, so substituents can be “locked” into distinct geometric arrangements. Historically, alkene stereochemistry was described as *cis* or *trans*, but that terminology becomes ambiguous for many substituted alkenes. The CIP system provides a general solution.

Definition of *E* and *Z*

For each alkene carbon, assign priorities to the two substituents using CIP rules. Then compare the positions of the two *higher-priority* substituents (one on each

carbon):

- *Z* (*zusammen*, together): the higher-priority substituents are on the *same* side of the double bond.
- *E* (*entgegen*, opposite): the higher-priority substituents are on *opposite* sides.

Step-by-step workflow for *E/Z*

- Identify the C=C bond of interest.
- On the left alkene carbon, rank its two substituents as high (1) and low (2) priority.
- On the right alkene carbon, rank its two substituents as high (1) and low (2) priority.
- If the two high-priority groups are on the same side, assign *Z*; if opposite, assign *E*.

Why *cis/trans* can fail

Cis/trans works cleanly only when each alkene carbon has exactly one substituent in common (often H), so that “same side” is unambiguous. For tri- and tetrasubstituted alkenes, there may be no obvious matching pair of substituents, and *cis/trans* becomes ill-defined. *E/Z* remains unambiguous because it relies on a defined ranking algorithm.

CIP with alkenes: multiple bonds appear naturally

When ranking substituents on an alkene carbon, you may need Rule 4 (multiple bonds). For example, comparing —CH_3 vs. —CHO attached to an alkene carbon requires treating C=O as if the carbonyl carbon is attached to two oxygens, which typically gives —CHO higher priority than —CH_3 .

3.4.5 Worked examples in words (how to think, not just what to do)

Example pattern for *R/S*: one stereocenter

When confronted with a single stereocenter:

- List the four substituents and identify the directly attached atoms.
- If there is a tie (usually carbon), expand outward atom-by-atom until resolved.
- Confirm which group is lowest (often H).
- Reorient mentally so the lowest group points away; then trace $1 \rightarrow 2 \rightarrow 3$.

If you can do these steps consistently, *R/S* assignment becomes routine rather than mysterious.

Example pattern for *E/Z*: the “two separate rankings” mindset

For alkenes, the most common mistake is trying to rank *all four* substituents at once. Do not do this. Instead:

- Rank the two groups on the left carbon only.
- Rank the two groups on the right carbon only.

Then compare the relative positions of the two winners (the two higher priorities). This separation keeps the logic clean.

3.4.6 Summary and readiness for multi-stereocenter systems

- The CIP rules provide an algorithmic method to rank substituents.
- *R/S* assigns the absolute configuration of a stereocenter by orienting group 4 away and reading the $1 \rightarrow 2 \rightarrow 3$ direction.
- *E/Z* assigns alkene stereochemistry by comparing the positions of the higher-priority substituents on each alkene carbon.

With these tools, we can now move beyond single stereocenters to molecules with multiple stereocenters, where additional stereoisomer relationships appear (diastereomers) and where symmetry can produce achiral stereoisomers (meso compounds).

3.5 Diastereomers and Meso Compounds

3.5.1 Stereoisomer relationships in molecules with multiple stereocenters

Definitions: enantiomers vs. diastereomers

Two molecules with the same connectivity can be related in one of several ways:

- **Identical:** the same molecule (superimposable in 3D).
- **Enantiomers:** non-superimposable mirror images.
- **Diastereomers:** stereoisomers that are *not* mirror images.
- **Constitutional isomers:** different connectivity (not stereoisomers).

For molecules with ≥ 2 stereocenters, **diastereomerism** becomes common. A practical working definition is:

Diastereomers differ in configuration at one or more stereocenters, but not all stereocenters (so they are not mirror images).

A key consequence: diastereomers have different physical properties

Unlike enantiomers (which have essentially identical properties in achiral environments), diastereomers usually differ in:

- melting and boiling points,
- solubility,
- NMR chemical shifts (even in achiral solvents),
- chromatographic behavior on *achiral* stationary phases,
- reactivity and selectivity in many reactions.

This difference is deeply practical: diastereomers are often separable by ordinary laboratory techniques, while enantiomers generally require a chiral environment for separation.

3.5.2 Counting stereoisomers: the 2^n rule and its limits

The 2^n maximum

For a molecule with n stereocenters, the *maximum* number of configurational stereoisomers is:

$$\text{maximum stereoisomers} = 2^n$$

This rule assumes that:

- each stereocenter can independently be R or S ,
- the molecule has no internal symmetry that makes some assignments equivalent.

When fewer than 2^n stereoisomers occur

The actual number can be less than 2^n when symmetry makes two nominally different configurations represent the *same* molecule, or when a configuration corresponds to an achiral **meso** form. Thus, symmetry is not an afterthought; it directly changes how many distinct stereoisomers exist.

3.5.3 Meso compounds: achiral molecules with stereocenters

Definition

A **meso compound** is an achiral molecule that:

- contains two or more stereocenters,
- has an internal symmetry element (most often a plane of symmetry),
- is superimposable on its mirror image.

A meso compound is therefore *not* optically active as a pure substance (it cannot exist as a pair of enantiomers), even though it contains stereocenters.

Why meso compounds are possible

At first, the phrase “achiral with stereocenters” seems contradictory. The resolution is that chirality is a property of the *whole molecule*, not of an individual stereocenter.

If the molecule contains an internal reflection symmetry that maps one stereocenter onto another in a compensating way, the overall structure can lack handedness.

A common pattern is:

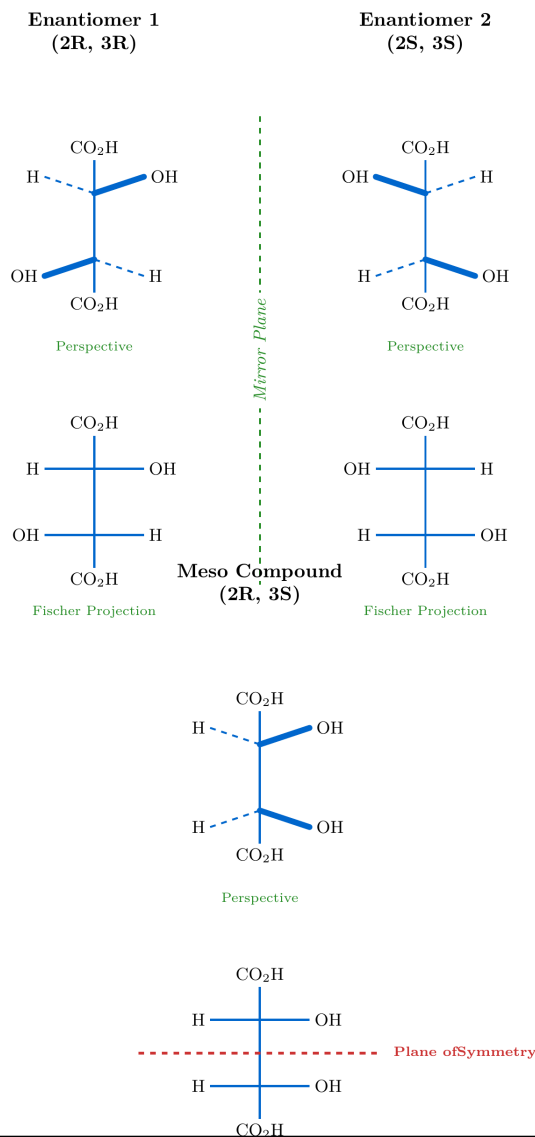
- two stereocenters have opposite configurations (R, S or S, R),
- the molecule is arranged such that a mirror plane interchanges the two halves.

3.5.4 Tartaric acid as the prototypical example

Tartaric acid $\text{HOOC}-\text{CH}(\text{OH})-\text{CH}(\text{OH})-\text{COOH}$ contains two stereocenters (C2 and C3). By the 2^n rule with $n = 2$, one might expect $2^2 = 4$ stereoisomers. In fact, tartaric acid has **three** distinct stereoisomers:

- a pair of enantiomers: $(2R, 3R)$ and $(2S, 3S)$,
- one meso form: $(2R, 3S)$, which is identical to $(2S, 3R)$ by symmetry.

The meso form is achiral because it possesses an internal plane of symmetry in an appropriate conformation/representation, causing its mirror image to be superimposable.

**Key Relationships:**

- (2R, 3R) and (2S, 3S) are enantiomers (non-superimposable mirror images).
- Meso-(2R, 3S) is a diastereomer of the enantiomers. It is achiral due to the internal plane of symmetry visible in the Fischer projection (substituents match on both sides).

3.5.5 How to decide whether two multi-stereocenter structures are enantiomers, diastereomers, or identical

A reliable classification procedure is:

Step 1: confirm identical connectivity

Verify that the two structures have the same atom-to-atom connections. If connectivity differs, the molecules are constitutional isomers and stereochemical comparison is not appropriate.

Step 2: assign configurations at all stereocenters

Use CIP rules to assign R/S at each stereocenter. For a molecule with two stereocenters, each structure can be labeled as (R, R) , (R, S) , (S, R) , or (S, S) (with position indices as needed, e.g., $(2R, 3S)$).

Step 3: compare the configuration strings

- If *all* stereocenters are inverted ($R \leftrightarrow S$) between the two molecules, they are **enantiomers** *unless* internal symmetry makes them identical (meso case).
- If *some but not all* stereocenters differ, the molecules are **diastereomers**.
- If the configuration assignments match at every stereocenter, the molecules are either **identical** or different conformations/drawings of the same compound.

Step 4: check for internal symmetry (meso possibility)

If a molecule has multiple stereocenters, especially in a symmetric framework, check whether it has an internal plane of symmetry or other symmetry element that would make it achiral. This step is essential when you encounter patterns like (R, S) and (S, R) : sometimes they are enantiomers, sometimes they are identical, depending on symmetry of the rest of the molecule.

3.5.6 Fischer projections as a tool for multi-stereocenter systems

Why Fischer projections are useful

For molecules with several stereocenters (notably carbohydrates and amino acids), Fischer projections provide a standardized representation that makes symmetry and relative stereochemistry easier to analyze. Key conventions:

- Vertical bonds point *away* from the viewer.
- Horizontal bonds point *toward* the viewer.
- The carbon chain is typically drawn vertically with the most oxidized carbon at the top.

Legal moves and their stereochemical consequences

In Fischer projections, certain transformations preserve configuration while others do not:

- **Rotation by 180° in the plane** gives the same molecule (allowed).
- **Rotation by 90°** changes configuration (not equivalent).
- **Single interchange of two substituents at a stereocenter** inverts that center.
- **Two interchanges** restore the original configuration (net even permutation).

These rules matter because recognizing meso forms and identifying enantiomeric pairs often depends on whether two drawings can be related by permitted operations.

3.6 Problems

3.6.1 Newman projections and conformational energy: 1-bromo-2-chloroethane

Consider $\text{BrCH}_2\text{--CH}_2\text{Cl}$ and rotation about the C--C bond.

- Draw a complete conformational analysis using Newman projections at $\phi = 0^\circ, 60^\circ, 120^\circ, 180^\circ, 240^\circ$, and 300° (view down $\text{C}_1\text{--C}_2$).

- Identify and clearly label all staggered and eclipsed conformations.
- Rank the conformations from lowest to highest energy, and justify the ranking using **torsional strain** and **steric/electrostatic** arguments.
- Sketch a qualitative potential energy diagram $E(\phi)$ consistent with your ranking and label the key conformers.

3.6.2 Boltzmann populations from conformational free-energy differences

An acyclic molecule exists as two rapidly interconverting conformers, *A* and *B*, with $\Delta G^\circ = G_B^\circ - G_A^\circ = +1.25$ kcal/mol at 298 K.

- Calculate the equilibrium ratio N_B/N_A at 298 K.
- Calculate the percent composition of *A* and *B* at 298 K.
- Repeat parts (1) and (2) at 350 K, and explain (in one or two sentences) why the population changes with temperature.
- If conformer *B* is doubly degenerate (two indistinguishable conformations with the same G°), incorporate degeneracy and recompute the populations at 298 K.

3.6.3 A-values and conformational equilibrium: bromocyclohexane

Bromocyclohexane exists as two chair conformers (Br axial vs. Br equatorial). Assume the axial penalty for bromine is $A = 0.55$ kcal/mol at 298 K, defined as

$$A = G^\circ(\text{axial}) - G^\circ(\text{equatorial}).$$

- Calculate the equilibrium ratio $N_{\text{eq}}/N_{\text{ax}}$ at 298 K.
- Calculate the percentage of the equatorial conformer.
- Predict qualitatively (no calculation required) whether the equatorial percentage increases or decreases at higher temperature, and explain why.
- Briefly describe (one paragraph) the structural origin of the axial penalty in terms of **1,3-diaxial interactions**.

3.6.4 Disubstituted cyclohexanes: *cis*/*trans* and major conformer determination

For *cis*-1-*tert*-butyl-4-methylcyclohexane:

- Draw both chair conformations. In each, label the axial and equatorial positions explicitly.
- Assign up/down orientation for each substituent consistent with the *cis*-1,4 relationship, and verify that up/down is retained upon ring flip.
- Determine which chair is the major conformer at room temperature. Your justification must explicitly reference (i) the large *A*-value of *tert*-butyl and (ii) the number/type of axial substituents in each chair.
- State whether the major conformer is expected to be overwhelmingly dominant or only modestly favored, and explain your reasoning.

3.6.5 Stereocenter identification in a complex structure (Taxol)

A skeletal structure of Taxol (paclitaxel) is provided by your instructor.

- Identify **all** stereocenters (tetrahedral stereogenic centers) in the structure.
- For each stereocenter, indicate whether it is part of a ring junction, adjacent to a heteroatom, or adjacent to a π -system (as a way of organizing your analysis).
- Determine whether any stereocenter could be “masked” (appear stereogenic in 2D but become non-stereogenic due to symmetry). Justify your conclusion.
- State the maximum number of stereoisomers predicted by the 2^n rule for the number n you found, and comment (qualitatively) on whether symmetry is likely to reduce this number for Taxol.

3.6.6 *R/S* assignment: L-threonine

L-threonine has the structure $\text{HO}-\text{CH}-\text{CH}(\text{NH}_2)-\text{CO}_2\text{H}$ with a CH_3 substituent on the β -carbon (i.e., $\text{HO}-\text{CH}(\text{CH}_3)-\text{CH}(\text{NH}_2)-\text{CO}_2\text{H}$). A wedge/dash drawing is provided by your instructor.

- Identify the stereocenters in L-threonine.

- Using CIP rules, assign priorities at each stereocenter and determine the absolute configurations (*R* or *S*).
- Clearly show (with brief written justification) how you handled any priority ties (e.g., carbon vs. carbon) by comparing outward atom sets.
- Explain why the letter “L” in the name does not, by itself, determine whether the configuration at the α -carbon is *R* or *S*.

3.6.7 *E/Z* assignment in a tri-/tetrasubstituted alkene (Tamoxifen)

A structure of Tamoxifen is provided by your instructor, with the central C=C bond highlighted.

- Assign CIP priorities on **each** alkene carbon (make two separate rankings).
- Determine whether the highlighted double bond is *E* or *Z*.
- Explain why a simple cis/trans descriptor is inadequate or ambiguous for this double bond (be specific about substitution pattern).
- If one substituent contains a phenyl ring, indicate how aromatic (multiple-bond) representations are treated under CIP rules for the purpose of ranking.

3.6.8 All stereoisomers of 2,3-dibromobutane: enantiomers, diastereomers, meso

For 2,3-dibromobutane, $\text{CH}_3\text{--CH(Br)--CH(Br)--CH}_3$:

- Draw all configurational stereoisomers using wedge/dash structures.
- Assign the *R/S* configuration at each stereocenter for every stereoisomer.
- Identify which pair are enantiomers, which are diastereomers, and whether any meso form exists.
- For any meso candidate, explicitly indicate the internal plane of symmetry (or explain why none exists).

3.6.9 Enantiomeric excess and composition from optical purity

A sample of 2-butanol is reported to be 40% enantiomeric excess in favor of (*S*)-2-butanol.

- Determine the percentage of (*S*)-2-butanol and (*R*)-2-butanol in the sample.
- If the specific rotation of pure (*S*)-2-butanol under the measurement conditions is $[\alpha] = +13.5^\circ$, predict the observed rotation α_{obs} for the sample using proportionality between rotation and ee.
- A second sample gives $\alpha_{\text{obs}} = +2.7^\circ$ under the same conditions. Determine its enantiomeric excess and composition.
- Briefly state one experimental reason (not a mathematical one) why optical rotation might underestimate true ee in practice.

3.6.10 From Fischer to chair: conformational interpretation of D-glucose

A Fischer projection of D-glucose is provided by your instructor.

- Convert the Fischer projection into the Haworth projection of α -D-glucopyranose and β -D-glucopyranose (show both anomers).
- Convert each Haworth projection into a cyclohexane chair conformation. Clearly label axial and equatorial substituents in each chair.
- Identify which anomer places more substituents in equatorial positions in its most stable chair, and use that to predict which anomer is more stable.
- Explain, using the “up/down retained” idea from ring flips, how the axial/equatorial designation could change without changing the anomeric configuration.

Chapter 4

Acids, Bases, and Equilibrium

While chemical structures appear static on the page, organic chemistry is defined by the dynamic flow of electrons. At the heart of this dynamism lies acid-base chemistry—the fundamental alphabet of reaction mechanisms. In this chapter, we transition from structural representation to reactivity prediction. By mastering the quantitative rigor of the pK_a scale and the qualitative power of structural stability analysis (ARIO), students gain the ability to predict not just the direction of equilibrium, but the very feasibility of reactions. We conclude by broadening our scope to Lewis acids and bases, the universal language connecting simple proton transfers to complex electrophile-nucleophile interactions.

4.1 Brønsted–Lowry Acids and Bases

In the previous chapter we developed a consistent way to represent molecules using Lewis structures, formal charge, and resonance. Those tools let us keep track of electrons—and in organic chemistry, *electron bookkeeping* is the fastest route to predicting reactivity. Acid–base chemistry is the first major reaction class where this bookkeeping becomes mechanistic: we will explicitly show where electron density starts, where it goes, and what new bonds and charges result.

4.1.1 The Brønsted–Lowry definition: proton transfer

A **Brønsted–Lowry acid** is a **proton donor**, and a **Brønsted–Lowry base** is a **proton acceptor**. An “acid–base reaction” in this framework is therefore a **proton-transfer reaction**.

It is essential to separate two ideas that are often conflated:

- **Acidity/basicity** is defined by *proton transfer* (Brønsted–Lowry).
- **Charge** is a *consequence* of proton transfer, not its definition. Neutral molecules can be acids (e.g., alcohols) and bases (e.g., amines).

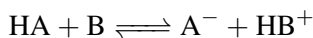
A proton (H^+) does not travel by itself in ordinary solution. Instead, proton transfer occurs when a base uses a lone pair (or a π bond) to form a new σ bond to hydrogen, while the acid's $\text{H}-\text{A}$ bond breaks and the electron pair remains with atom A . Mechanistically, **bond formation and bond breaking occur together** in a single elementary step for a simple deprotonation.

4.1.2 Conjugate acid–base pairs

When an acid donates a proton, it becomes its **conjugate base**. When a base accepts a proton, it becomes its **conjugate acid**. Conjugate pairs differ by exactly one proton:



A convenient general notation is:



Here, HA and A^- form one conjugate acid–base pair, and B and HB^+ form the other.

A key structural point. If an acid HA is neutral, its conjugate base is typically an anion (A^-). If a base B is neutral, its conjugate acid is typically a cation (HB^+). However, the conjugate relationship itself is independent of charge: it is defined only by gain/loss of H^+ .

4.1.3 Curved-arrow formalism for proton transfer (and strict charge conservation)

In organic mechanisms we depict **electron flow** using **curved arrows**. The arrow shows the movement of an *electron pair* (unless explicitly drawn as a fishhook for single-electron processes, which we will not use here).

Two non-negotiable rules govern curved-arrow notation in acid–base reactions:

- **An arrow must start at electrons:** a lone pair, a bond, or a negative charge (which represents a lone pair in excess).

- **An arrow must end at an atom or a bond where those electrons will reside.**

For a typical deprotonation $B + H-A \longrightarrow H-B + A^-$, there are *two* electron movements that must be shown:

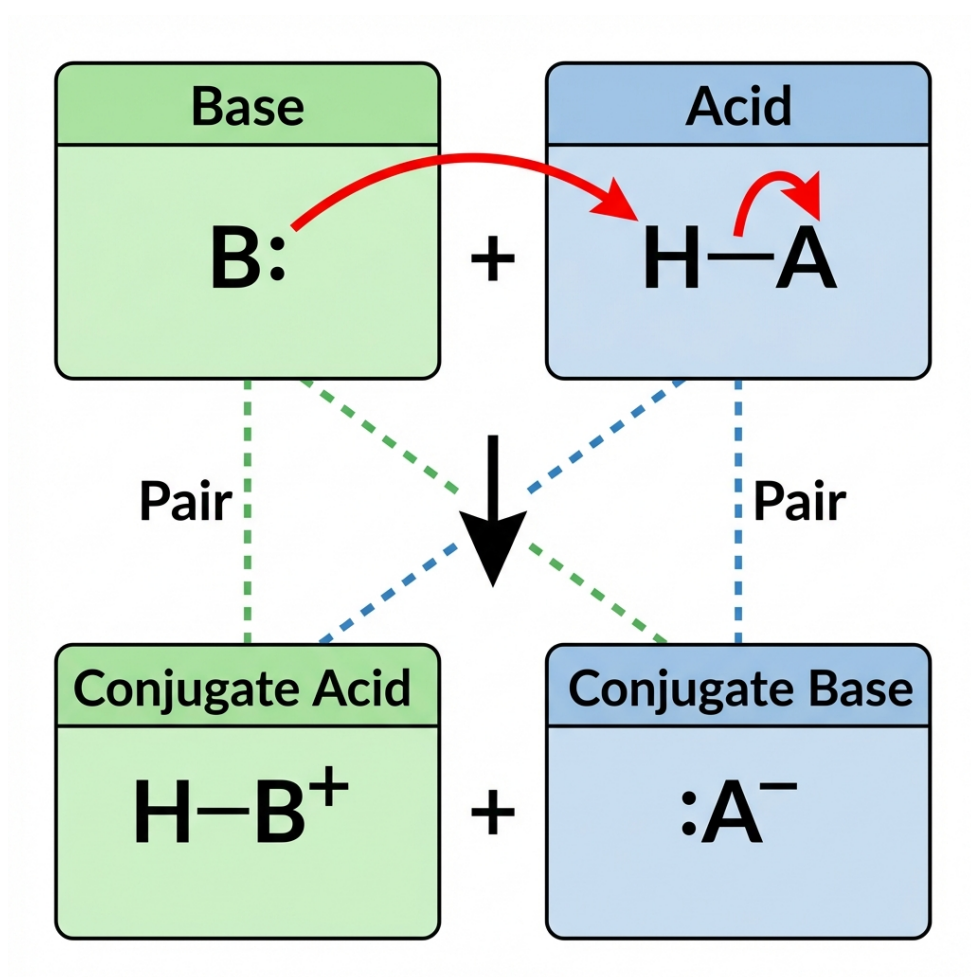
- The base donates a lone pair to H to form the new H–B bond.
- The H–A bond electrons move onto A as the bond breaks, generating (or increasing) electron density on A.

Charge conservation as a diagnostic. You should be able to check any acid–base mechanism by comparing total formal charge before and after the step. Total charge must be conserved. If it is not, then an arrow is missing, an arrow started from the wrong place, or a product charge has been assigned incorrectly.

4.1.4 General mechanism diagram: identifying the competing acid–base pairs

Immediately after identifying “the acid” and “the base,” train yourself to identify *both* conjugate pairs. Every Brønsted–Lowry reaction is a competition between two bases for a proton:

- B competes with A^- for H^+ .
- Equivalently, HA competes with HB^+ to donate H^+ .



4.1.5 How to identify acids and bases in practice

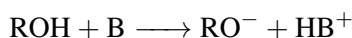
The Brønsted–Lowry definition is simple, but applying it requires recognizing *which atom actually gains or loses the proton*. A reliable approach is:

- **Locate the proton donor:** look for an H attached to an electronegative atom (common: $O-H$, $N-H$, $S-H$) or a positively charged center that can lose H^+ (e.g., R_3NH^+).
- **Locate the proton acceptor:** look for an available lone pair (common: $O:$, $N:$, X^-) or a π bond that can be protonated (common later: alkenes, carbonyls).

under strong acid).

- **Check feasibility by charge and octet:** after proton transfer, atoms should have reasonable valence (no five-bond carbon), and formal charges should follow from electron counting.

Example (generic, structure-focused). An alcohol can act as an acid because it possesses an O–H proton:



Here, oxygen becomes negatively charged after deprotonation because it receives the electron pair from the broken O–H bond. The base becomes positively charged because it uses a lone pair to form the H–B bond.

4.1.6 The role of solvent and the leveling effect

Brønsted–Lowry acid–base behavior is not only a property of the solute; it is also a property of the *medium*. In solution, the “free” acid or base is usually solvated, and proton transfer often occurs through solvent-assisted pathways (for example, through hydrogen-bonded networks).

A particularly important consequence is the **leveling effect**: in a given solvent, any acid stronger than the solvent’s conjugate acid will be converted (“leveled”) to that conjugate acid by complete proton transfer to the solvent. Likewise, any base stronger than the solvent’s conjugate base will be protonated (leveled) by the solvent.

- In water, very strong acids are all effectively limited by formation of H_3O^+ (hydronium).
- In water, very strong bases are limited by formation of HO^- (hydroxide) because stronger bases deprotonate water.

This matters operationally: when we say “HCl is a strong acid in water,” what we typically mean is that HCl transfers its proton essentially completely to water to give H_3O^+ and Cl^- . The mechanistic and equilibrium consequences of that statement will be quantified in the next section using K_a and pK_a . For now, the key message is that acid–base reactions should be interpreted as **competitions that take place in a specific solvent environment**.

4.1.7 Summary: what you must be able to do after this section

By the end of this section, you should be able to:

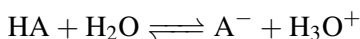
- Apply Brønsted–Lowry definitions to identify the acid (proton donor) and base (proton acceptor).
- Identify both conjugate acid–base pairs in any proton-transfer reaction.
- Draw a correct curved-arrow mechanism for a deprotonation/protonation step, with arrows starting at electron density and conserving total charge.
- Recognize that solvent can impose practical limits on observed acidity/basicity via the leveling effect.

4.2 Quantitative Acidity: the pK_a Scale

The Brønsted–Lowry model tells us *what* an acid–base reaction is (proton transfer) and how to draw it (curved arrows with charge conservation). The next step is to decide *how far* a proton-transfer reaction goes: does it strongly favor products, strongly favor reactants, or reach an appreciable mixture? This is an equilibrium question, and the quantitative language of equilibrium is K . The practical language chemists use for acidity is K_a and its logarithmic form pK_a .

4.2.1 From proton transfer to an equilibrium constant

Consider a generic acid in water:



This is simply the Brønsted–Lowry proton transfer written with H_2O as the base and H_3O^+ as its conjugate acid.

For the acid dissociation written above, the equilibrium constant expression is

$$K = \frac{a_{\text{A}^-} a_{\text{H}_3\text{O}^+}}{a_{\text{HA}} a_{\text{H}_2\text{O}}}$$

where a_i denotes *activity* (an effective concentration). In most introductory organic contexts we work in dilute aqueous solution and treat activities as approximately equal to molar concentrations, with one important simplification: because water is

the solvent, its activity is essentially constant (near 1). We therefore fold $a_{\text{H}_2\text{O}}$ into the constant and define the **acid dissociation constant**:

$$K_a \equiv \frac{a_{\text{A}^-} a_{\text{H}_3\text{O}^+}}{a_{\text{HA}}} \approx \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]}$$

Interpretation. K_a quantifies the extent to which HA transfers a proton to water. Larger K_a means the products A^- and H_3O^+ are favored at equilibrium, so the acid is *stronger*.

4.2.2 The pK_a definition and why it is useful

Acidities span an enormous range. For common acids, K_a values can vary by many orders of magnitude, which is inconvenient to compare directly. Chemists therefore use a logarithmic scale:

$$pK_a \equiv -\log_{10}(K_a)$$

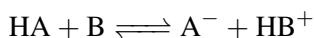
Because of the negative sign, the direction of “bigger” reverses:

- | |
|---|
| smaller $pK_a \Rightarrow$ larger $K_a \Rightarrow$ stronger acid |
|---|
- | |
|---|
| larger $pK_a \Rightarrow$ smaller $K_a \Rightarrow$ weaker acid |
|---|

Orders of magnitude are built in. A difference of 1.0 unit in pK_a corresponds to a factor of 10 in K_a . A difference of 5 pK_a units corresponds to a factor of 10^5 in K_a . This is the main practical advantage: you can compare acid strengths rapidly by subtraction.

4.2.3 Connecting pK_a to the direction of an acid–base equilibrium

Most acid–base steps in organic mechanisms are not written as dissociation into water. Instead, they are written as competition between two bases for a proton:



This is the general form introduced in the previous section.

To predict the direction of this proton transfer, we want an equilibrium constant K_{eq} for that specific proton transfer. The cleanest way to relate K_{eq} to pK_a is to use the fact that each side contains an acid:

- HA is the acid on the left, with $K_a(\text{HA})$ and $pK_a(\text{HA})$.
- HB^+ is the acid on the right, with $K_a(\text{HB}^+)$ and $pK_a(\text{HB}^+)$.

A key result (derivation below) is:

$$K_{\text{eq}} \approx \frac{K_a(\text{HA})}{K_a(\text{HB}^+)} = 10^{pK_a(\text{HB}^+) - pK_a(\text{HA})}$$

How to use the expression above quickly.

- Identify the two acids: the acid on the left (HA) and the conjugate acid on the right (HB^+).
- Compute $\Delta pK_a = pK_a(\text{acid on products}) - pK_a(\text{acid on reactants})$.
- Then $K_{\text{eq}} \approx 10^{\Delta pK_a}$.

This immediately gives a powerful qualitative rule:

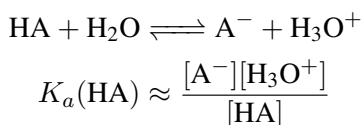
Acid–base equilibria favor the side with the *weaker* acid (higher pK_a) and the *weaker* base.

Why does “weaker acid” appear? Because the reaction proceeds in the direction that converts a stronger acid into a weaker acid, which corresponds to lowering the system’s free energy under the given conditions.

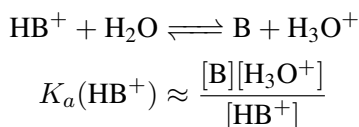
4.2.4 Derivation of the $K_{\text{eq}}-pK_a$ relationship

We derive the relation using two acid dissociation equilibria in the *same solvent* (so that H_3O^+ is the reference protonated species).

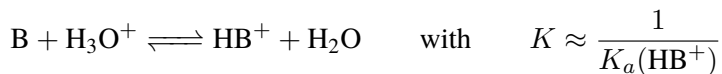
First write the dissociation of HA:



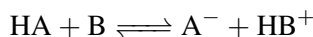
Next write the dissociation of HB^+ :



Now reverse the dissociation of HB^+ above to represent protonation of B by H_3O^+ :



If we add this reversed reaction to the dissociation of HA, H_3O^+ and H_2O cancel, and we obtain the net proton transfer:



The equilibrium constant for the sum of reactions is the product of equilibrium constants:

$$K_{\text{eq}} \approx K_a(\text{HA}) \times \frac{1}{K_a(\text{HB}^+)} = \frac{K_a(\text{HA})}{K_a(\text{HB}^+)}$$

Taking base-10 logarithms and using $pK_a = -\log_{10} K_a$ gives the expression above:

$$K_{\text{eq}} \approx 10^{pK_a(\text{HB}^+) - pK_a(\text{HA})}$$

Scope and assumptions. This derivation assumes that both pK_a values refer to the same solvent and comparable conditions. Mixing pK_a values from different solvents (e.g., water vs. DMSO) can give qualitatively wrong predictions because solvation can change relative acidities dramatically.

4.2.5 Link to thermodynamic favorability: ΔG° and K

Equilibrium constants are not just empirical numbers; they are directly connected to standard-state thermodynamics:

$$\Delta G^\circ = -RT \ln K_{\text{eq}}$$

where R is the gas constant and T is the absolute temperature.

Combining the expression $\Delta G^\circ = -RT \ln K_{\text{eq}}$ with the K_{eq} - pK_a relation above yields a direct connection between ΔpK_a and ΔG° . Since

$$\ln K_{\text{eq}} = \ln(10^{\Delta pK_a}) = \Delta pK_a \ln 10$$

we obtain:

$$\Delta G^\circ \approx -RT(\ln 10) \Delta pK_a$$

At 298 K, $RT \ln 10 \approx 5.71 \text{ kJ/mol}$ ($\approx 1.36 \text{ kcal/mol}$), so a one-unit difference in pK_a corresponds to a modest but meaningful change in free energy:

$$\Delta G^\circ \approx -(5.71 \text{ kJ/mol}) \Delta pK_a \quad (298 \text{ K})$$

Meaning for mechanism prediction.

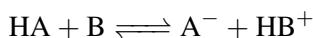
- If $\Delta pK_a = +3$, then $K_{\text{eq}} \approx 10^3$: products are favored by about a thousand-fold and ΔG° is negative.
- If $\Delta pK_a = -3$, then $K_{\text{eq}} \approx 10^{-3}$: reactants are favored by about a thousand-fold and ΔG° is positive.

In short, pK_a differences are not just “rules of thumb”; they are logarithmic encodings of equilibrium free-energy differences.

4.2.6 A practical equilibrium workflow for organic chemistry

When you see an acid–base step in a mechanism, use the following workflow.

Step 1: Write the proton-transfer reaction with conjugate pairs. For example:



Be explicit about which species is the acid on each side.

Step 2: Locate (or estimate) the relevant pK_a values. You need:

- pK_a of HA (acid on reactants),
- pK_a of HB^+ (acid on products, i.e., the conjugate acid of the base).

Step 3: Compute ΔpK_a and infer K_{eq} . Use the K_{eq} – pK_a relation above. Often you only need the sign and rough magnitude:

$$\Delta pK_a = pK_a(\text{HB}^+) - pK_a(\text{HA})$$

Step 4: Translate the number into a mechanistic conclusion. A useful (not absolute) guide:

- $|\Delta pK_a| \geq 3$: equilibrium is strongly biased (typically “goes to completion” for many purposes).
- $|\Delta pK_a| \approx 0$ to 2: appreciable mixture; reversibility is important.

Whether “goes to completion” is an appropriate statement also depends on concentrations, solvent, and whether subsequent steps remove products (Le Châtelier’s principle). Those considerations will recur throughout mechanistic chapters.

4.2.7 Common reference points (and what they communicate)

Without yet analyzing *why* different functional groups have different pK_a values (that is the subject of the next section), you should begin to internalize a few reference points because they anchor equilibrium predictions.

Acid (typical solvent)	pK_a	Interpretation for proton transfer
H_3O^+ (water)	≈ -1.7	Strong acid in water; stronger acids are leveled to H_3O^+ .
Carboxylic acid RCO_2H (water)	$\sim 4-5$	Deprotonated by bases whose conjugate acids have $pK_a \gg 5$.
Phenol $ArOH$ (water)	~ 10	Significantly less acidic than carboxylic acids; requires stronger base.
Water H_2O (water)	15.7	Defines hydroxide basicity scale in water.
Alcohol ROH (water)	$\sim 16-18$	Similar to water; deprotonation requires very strong bases.
Ammonium RNH_3^+ (water)	$\sim 9-11$	Amine conjugate acids; amines are bases in water.
Terminal alkyne $RC\equiv CH$ (DMSO)	~ 25	Much more acidic than alkanes; deprotonated by very strong bases.
Ammonia NH_3 (DMSO)	~ 38	Conjugate acid of NH_2^- is extremely weak; NH_2^- is very strong base.
Alkane RH (DMSO)	~ 50	Essentially non-acidic under ordinary conditions.

Two cautions.

- pK_a values depend on solvent; comparing numbers across solvents can mislead.

- Tables give typical values; substitution and structure can shift pK_a by several units. The next section will explain how and why.
- K_a is the equilibrium constant for acid dissociation; $pK_a = -\log_{10} K_a$.
- For $\text{HA} + \text{B} \rightleftharpoons \text{A}^- + \text{HB}^+$,

$$K_{\text{eq}} \approx 10^{pK_a(\text{HB}^+) - pK_a(\text{HA})}$$

so equilibria favor formation of the *weaker acid* (higher pK_a).

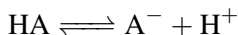
- Thermodynamics connects directly: $\Delta G^\circ = -RT \ln K_{\text{eq}}$, so pK_a differences encode free-energy differences ($\Delta G^\circ \approx -RT \ln 10 \Delta pK_a$).

4.3 Structural Effects on Acidity

In the previous section we learned how to *quantify* acidity using K_a and pK_a , and how to predict the direction of proton-transfer equilibria from ΔpK_a . This section answers the deeper structural question: *why* do some acids have lower pK_a values than others?

4.3.1 The central principle: acid strength tracks conjugate-base stability

For a Brønsted–Lowry acid HA,



the position of equilibrium depends strongly on how stable the conjugate base A^- is relative to HA. In practical terms:

A stronger acid has a more stable conjugate base.

Equivalently: the easier it is to accommodate negative charge in A^- , the more favorable deprotonation becomes (larger K_a , smaller pK_a).

This is not merely a slogan; it is a thermodynamic statement. If A^- is stabilized (lower free energy), the products of dissociation are stabilized, and the equilibrium shifts toward products.

4.3.2 The ARIO framework: a structured way to compare conjugate bases

To compare acidities efficiently, organic chemists often use the **ARIO** framework to evaluate conjugate-base stability:

- **A: Atom** — Where is the negative charge located? (electronegativity and polarizability/size)
- **R: Resonance** — Can the negative charge be delocalized by resonance?
- **I: Induction** — Do nearby electronegative atoms withdraw electron density through σ bonds?
- **O: Orbital** — What orbital bears the negative charge? (hybridization; s -character)

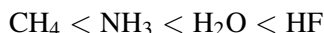
ARIO is most useful when applied in order. In many comparisons, resonance dominates everything else; in others, resonance is absent and atom/induction/orbital effects decide the outcome.

4.3.3 A — Atom effects (electronegativity and size)

Same row: electronegativity controls stability

When negative charge is on atoms in the same row of the periodic table (e.g., C, N, O, F), the more electronegative atom stabilizes negative charge better.

Example trend (conjugate bases implied):



Acidity increases left to right because F^- is far more stable than CH_3^- . The electrons in F^- are held at lower energy because fluorine is more electronegative.

Same group: size/polarizability controls stability

Down a group (e.g., O vs S), larger atoms stabilize negative charge better because the charge can be spread over a larger volume (lower charge density) and because larger atoms are more polarizable.

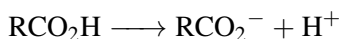
Thus, thiols (RSH) are typically more acidic than alcohols (ROH), even though sulfur is less electronegative than oxygen; the *size* effect dominates.

4.3.4 R — Resonance (delocalization is stabilization)

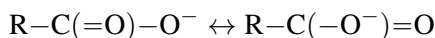
Resonance is often the single most important structural stabilizer of conjugate bases. Delocalization reduces the localization of negative charge on any one atom, lowering electrostatic energy and often enabling better solvation as well.

Resonance in carboxylates: two equivalent contributors

Deprotonation of a carboxylic acid gives a carboxylate:



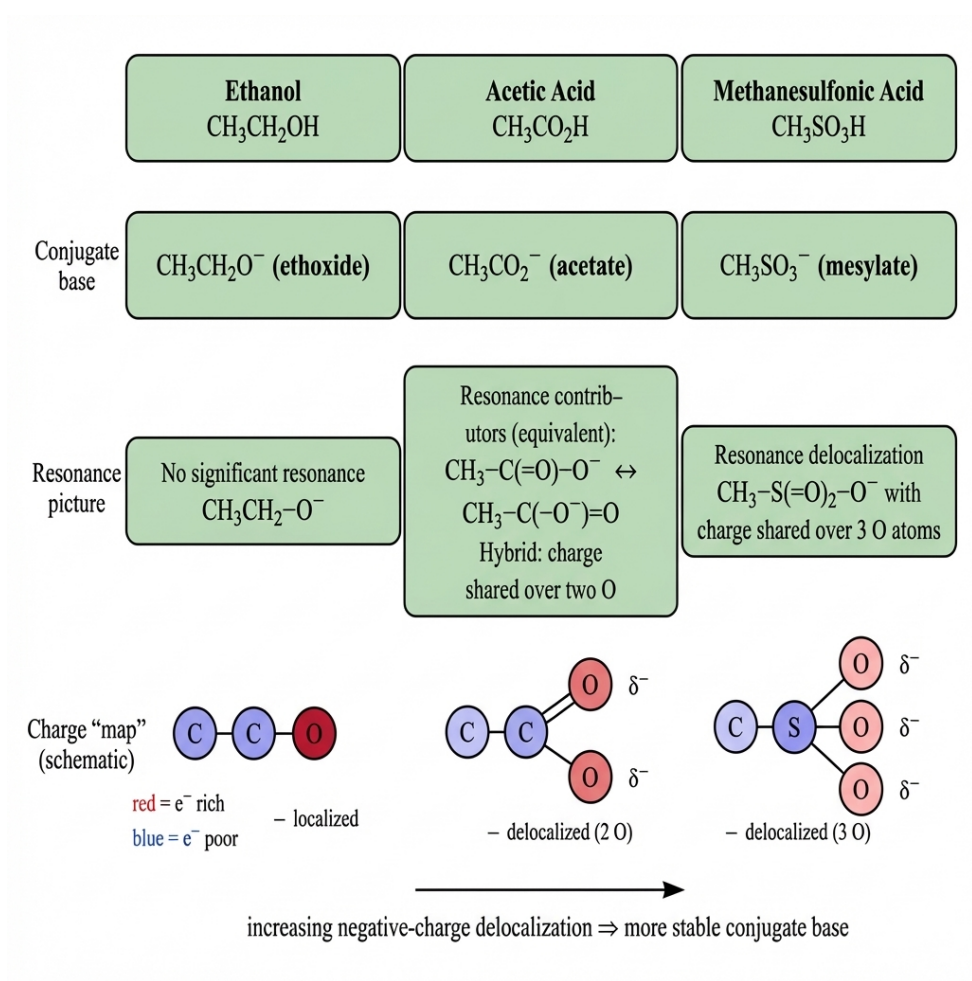
The conjugate base RCO_2^- has two major resonance contributors (equivalent when R is the same):



Because these contributors are equivalent, the resonance hybrid places substantial negative charge on *both* oxygens. The key consequence is that the conjugate base is much more stabilized than an alkoxide RO^- , where negative charge is localized on a single oxygen.

Resonance in sulfonates: delocalization over three oxygens

Sulfonic acids RSO_3H form sulfonate conjugate bases RSO_3^- . Here, negative charge can be distributed over three oxygen atoms, and the S center is in a high oxidation state, strongly biasing electron density toward oxygen. In many cases, this combination leads to exceptionally stable conjugate bases and very strong acids.



Interpreting the diagram. The “charge maps” are schematic, but they emphasize the central resonance lesson:

- **Ethoxide:** negative charge is largely localized on one oxygen.
- **Acetate:** negative charge is shared over two oxygens by resonance.
- **Mesylate (sulfonate):** negative charge is shared over three oxygens, and the sulfur center is strongly electron-withdrawing.

As delocalization increases, the conjugate base becomes more stable, and the corresponding acid becomes stronger (lower pK_a).

4.3.5 I — Induction (stabilization through σ -bond polarization)

Induction is the withdrawal (or donation) of electron density through σ bonds due to electronegativity differences. In acidity comparisons, we focus on **electron-withdrawing inductive effects** that stabilize anions.

The basic idea

If electronegative atoms (such as F, Cl, O, N, or groups like CF_3) are near the negatively charged site, they pull electron density away through the σ framework. This reduces electron density on the anionic atom, lowering its energy and stabilizing the conjugate base.

Distance dependence

Inductive effects diminish rapidly with distance. A substituent one bond away from the charged site has a much larger effect than one four bonds away. In practice:

- α -substituents (adjacent) matter a lot,
- β -substituents matter somewhat,
- beyond γ the effect is often small.

Example: fluorinated alcohols

A classic illustration is that $\text{CF}_3\text{CH}_2\text{OH}$ is more acidic than $\text{CH}_3\text{CH}_2\text{OH}$. The CF_3 group withdraws electron density inductively, stabilizing $\text{CF}_3\text{CH}_2\text{O}^-$ relative to $\text{CH}_3\text{CH}_2\text{O}^-$. The alcohol proton becomes easier to remove because its conjugate base is stabilized.

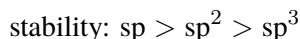
4.3.6 O — Orbital effects (hybridization and s -character)

Orbital effects matter when the atom bearing the negative charge can change hybridization, most prominently for carbanions. The guiding idea is:

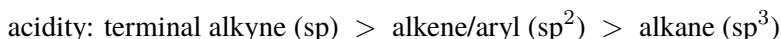
More s -character stabilizes negative charge.

An electron pair in an orbital with greater s -character is, on average, closer to the nucleus (lower energy).

Thus, for carbanions:



and correspondingly, for conjugate acids (protons on carbon):



This is why terminal alkynes ($\text{RC}\equiv\text{CH}$) are dramatically more acidic than alkenes or alkanes, even though all are C–H acids: the conjugate base places negative charge in an orbital with greater *s*-character.

4.3.7 Putting ARIO into practice: how to rank acidity systematically

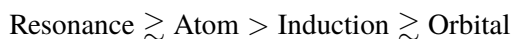
When comparing acids, always compare their conjugate bases.

Step-by-step method

- **Draw the conjugate base for each acid.** Make sure formal charges are correct.
- **Apply ARIO in order.** **Atom:** Is the negative charge on different atoms? If yes, that often decides the problem. **Resonance:** Can one conjugate base delocalize the charge more? If yes, resonance usually dominates. **Induction:** If resonance is similar/absent, compare electron-withdrawing groups and their distances. **Orbital:** If the charge is on carbon (or another atom with hybridization differences), compare *s*-character.
- **Conclude:** the more stable conjugate base corresponds to the stronger acid (lower pK_a).

A note on “dominance”

There is no universal numeric weight for A, R, I, and O, but in many organic contexts a useful heuristic is:



with the understanding that the actual outcome depends on the specific structures being compared.

4.3.8 Solvation and steric effects: why basicity can depend on solvent

So far, ARIO focuses on intrinsic electronic stabilization. In solution, a conjugate base is additionally stabilized (or destabilized) by **solvation**. Two qualitative solvent-phase ideas are especially useful:

Solvation stabilizes charge

Anions are stabilized by favorable ion–dipole interactions and hydrogen bonding to solvent molecules. Better solvation generally means a more stable conjugate base and (for a given acid) a stronger tendency toward deprotonation.

Steric hindrance can reduce solvation and increase basicity

Bulky bases can be *less solvated* and sometimes behave as stronger bases (and/or more selective bases) because their charge is not as effectively stabilized by the solvent. This becomes mechanistically important later when choosing bases to favor substitution vs. elimination pathways. The critical point here is conceptual: **solvation modifies conjugate-base stability**, so the same structural base can exhibit different effective basicity in different solvents.

4.3.9 Summary: structure → conjugate-base stability → acidity

- Acid strength is controlled by the stability of the conjugate base.
- The ARIO framework provides a disciplined way to evaluate that stability:
 - Atom:** electronegativity (across a row) and size/polarizability (down a group).
 - Resonance:** delocalization strongly stabilizes anions and often dominates.
 - Induction:** electron-withdrawing groups stabilize nearby negative charge; effects diminish with distance.
 - Orbital:** greater *s*-character stabilizes negative charge (especially for carbanions).
- Solvation and steric accessibility can shift effective basicity/acidity in solution, reinforcing that pK_a values must be compared within the same solvent system.

4.4 Lewis Acids and Bases

The Brønsted-Lowry model (proton transfer) and the pK_a framework (equilibrium position) allow us to predict when a base will remove a proton and how strongly the equilibrium will favor products. However, many of the most important organic reactions involve **no protons at all**. Carbonyl additions, substitutions at alkyl halides, and reactions of carbocations all involve the same fundamental event: an electron pair from one species forms a new bond to an electron-poor center. The **Lewis** definition generalizes acid-base chemistry to cover these processes.

4.4.1 Lewis definitions and their relationship to Brønsted-Lowry

A **Lewis base** is an **electron-pair donor**. A **Lewis acid** is an **electron-pair acceptor**.

This definition is broader than Brønsted-Lowry:

- Every Brønsted-Lowry base (proton acceptor) is a Lewis base because it uses an electron pair to bond to H^+ .
- Every Brønsted-Lowry acid (proton donor) is a Lewis acid because H^+ accepts an electron pair.
- The Lewis definition includes *non-proton* acids such as BF_3 , $AlCl_3$, metal cations (e.g., Zn^{2+}), and carbocations (e.g., $(CH_3)_3C^+$).

Proton transfer as a special case of Lewis acid-base chemistry. In Brønsted-Lowry protonation, the Lewis acid is H^+ (or, more realistically, H_3O^+ or $H-A$ in solution), and the Lewis base is the nucleophilic site that provides the electron pair. Thus, when you draw curved-arrow mechanisms for acid-base reactions, you are already doing Lewis acid-base chemistry; you are simply restricting the Lewis acid to be a proton source.

4.4.2 Lewis bases: identifying electron-pair donors in organic molecules

A Lewis base must have available electron density to donate. In organic chemistry, the most common Lewis bases are:

- **Lone pairs on heteroatoms** (typically O, N, S, halides)

- **π bonds** (alkenes, alkynes, aromatic rings) which can donate electron density into a new bond
- **Anionic centers** (alkoxides RO^- , carboxylates RCO_2^- , enolates, cyanide CN^-), which are often strong Lewis bases and strong nucleophiles

Availability matters. Not all lone pairs are equally available. A lone pair involved in resonance with a carbonyl (as in amides) is less available for donation than a lone pair on an amine. This resonance effect is one of the major links between the ARIO framework and Lewis basicity: **the same delocalization that stabilizes a conjugate base can reduce its donating ability (nucleophilicity).**

4.4.3 Lewis acids: identifying electron-pair acceptors

A Lewis acid must have an empty low-energy orbital (or a strongly polarized bond that can accept electron density into an antibonding orbital). Common classes include:

- **Cations** with empty orbitals: H^+ , carbocations R_3C^+ , metal cations
- **Electron-deficient neutrals** with incomplete octets: BF_3 , AlCl_3 , BH_3
- **Polarized σ bonds** that can accept electron density into σ^* : alkyl halides ($\text{C}-\text{X}$), protonated alcohols (ROH_2^+)
- **π systems with electrophilic carbon** (especially carbonyls): $\text{C}=\text{O}$ is polarized toward oxygen, leaving carbon electron-poor and susceptible to attack by Lewis bases

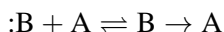
Electrophilicity is context-dependent. Whether a species behaves as an effective Lewis acid depends on its environment (solvent, substituents) and on what base it is reacting with. For example, a carbonyl carbon is a Lewis acid toward anionic nucleophiles, but it may be insufficiently electrophilic toward a weak neutral nucleophile unless activated (e.g., by protonation or coordination to a Lewis acid such as BF_3 or AlCl_3).

4.4.4 Lewis acid-base adducts and coordinate covalent bonds

When a Lewis base donates an electron pair to a Lewis acid, the immediate product is often called a **Lewis adduct** (or complex). The new bond is frequently described

as a **coordinate covalent bond** because both bonding electrons originate from the base.

A generic representation is:



where B is the Lewis base and A is the Lewis acid.

Important clarification. Once formed, a coordinate covalent bond is not fundamentally different from any other covalent bond. The “coordinate” label is a bookkeeping statement about bond formation, not a statement about the bond’s ultimate electronic nature.

4.4.5 Mechanistic unification: Lewis base = nucleophile; Lewis acid = electrophile

Organic reaction mechanisms are largely described as interactions between:

- **Nucleophiles:** electron-rich species that donate an electron pair to form a bond.
- **Electrophiles:** electron-poor species that accept an electron pair.

These terms are operational, but they align closely with the Lewis definitions:

Lewis base $\approx$ nucleophile

Lewis acid $\approx$ electrophile

This identification is powerful because it lets you interpret many “non-acid-base” reactions using the same curved-arrow logic developed for proton transfer:

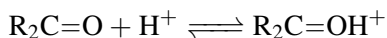
- Identify the electron source (Lewis base/nucleophile).
- Identify the electron sink (Lewis acid/electrophile).
- Draw a curved arrow from the electron source to the electrophilic atom.
- Account for any bond breaking needed to maintain valence and conserve overall charge.

4.4.6 How Lewis acidity and Brønsted acidity interact

Many transformations involve **activation by protonation** or **activation by Lewis-acid coordination**. These are conceptually parallel:

Protonation increases electrophilicity

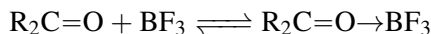
Protonation of a carbonyl oxygen increases the electrophilicity of the carbonyl carbon by increasing polarization of the C=O bond:



The carbonyl oxygen acts as a Lewis base; H^+ is the Lewis acid. The protonated carbonyl is then a much stronger electrophile toward nucleophiles (Lewis bases).

Lewis-acid coordination increases electrophilicity

Coordination of a Lewis acid (e.g., BF_3 , AlCl_3 , TiCl_4) to a carbonyl oxygen similarly withdraws electron density, making the carbonyl carbon more electrophilic:



Here oxygen donates a lone pair into an empty orbital on boron. The adduct often reacts faster with nucleophiles than the free carbonyl.

A practical mechanistic viewpoint. Protonation and Lewis-acid binding do not merely “add a positive charge”; they *lower the energy of the electrophile’s accepting orbital(s)* and/or increase bond polarization, making electron-pair donation more favorable.

4.4.7 Lewis acidity/basicity vs. Brønsted basicity: not always the same ordering

Students often expect a strong Brønsted base to be a strong nucleophile (Lewis base), but these properties can diverge.

Resonance: stabilized anions can be weak nucleophiles

A carboxylate RCO_2^- is often a relatively weak nucleophile compared to an alkoxide RO^- , even though both are anions. Resonance delocalization stabilizes the carboxylate (lower basicity and often lower nucleophilicity) and reduces the availability of electron density at any one atom for bond formation.

Solvent: protic solvents suppress nucleophilicity of small anions

In protic solvents, small hard anions (e.g., F^-) can be strongly hydrogen-bond solvated, reducing their nucleophilicity. Larger, more polarizable anions (e.g., I^-) are less tightly solvated and can be better nucleophiles under the same conditions. This solvent dependence will become central when we analyze substitution and elimination mechanisms.

Sterics: bulky bases can be poor nucleophiles

Bulky bases (e.g., tert-butoxide) can be strong Brønsted bases (high proton affinity) yet relatively poor nucleophiles toward crowded electrophiles due to steric hindrance to approach. This is a major reason bulky bases favor elimination over substitution in many systems.

4.4.8 Summary: why the Lewis framework matters

- The Lewis definitions generalize acid-base chemistry from proton transfer to *electron-pair transfer*.
- Brønsted-Lowry acid-base chemistry is a subset of Lewis acid-base chemistry in which the Lewis acid is H^+ .
- In mechanisms, **Lewis base $\approx$ nucleophile** and **Lewis acid $\approx$ electrophile**. Curved-arrow notation developed for proton transfer applies directly.
- Lewis-acid coordination and protonation are common activation strategies: they increase electrophilicity by withdrawing electron density and stabilizing accepting orbitals.
- Basicity and nucleophilicity are related but not identical; resonance, solvation, and sterics can separate them.

4.5 Problems**4.5.1 Inductive effects and electronegativity: ranking acidity**

Rank the following compounds in order of *increasing acidity* (lowest pK_a last). For each comparison, explicitly identify the conjugate base and state which ARIO factor(s) dominate (A, R, I, and/or O).

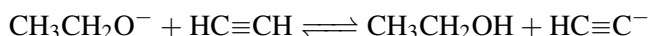
- 1. $\text{CH}_3\text{CH}_2\text{OH}$, $\text{ClCH}_2\text{CH}_2\text{OH}$, $\text{Cl}_2\text{CHCH}_2\text{OH}$, $\text{CF}_3\text{CH}_2\text{OH}$
- 2. $\text{CH}_3\text{CO}_2\text{H}$, $\text{ClCH}_2\text{CO}_2\text{H}$, $\text{Cl}_2\text{CHCO}_2\text{H}$, $\text{CF}_3\text{CO}_2\text{H}$
- 3. CH_3SH , CH_3OH , $(\text{CH}_3)_3\text{COH}$

Your final answer must include:

- a ranked list for each set,
- a one-sentence justification for each adjacent swap (why compound i is more acidic than compound $i + 1$).

4.5.2 K_{eq} from pK_a : ethoxide vs. acetylene

Consider the proton-transfer equilibrium:



Use the relationship

$$K_{\text{eq}} \approx 10^{pK_a(\text{acid on products}) - pK_a(\text{acid on reactants})}$$

Assume the following typical values in a consistent solvent set:

$$pK_a(\text{CH}_3\text{CH}_2\text{OH}) \approx 16, \quad pK_a(\text{HC}\equiv\text{CH}) \approx 25$$

- 1. Calculate K_{eq} (order of magnitude is sufficient).
- 2. State which side is favored and by approximately how many orders of magnitude.
- 3. Convert your result into an approximate ΔG° at 298 K using $\Delta G^\circ = -RT \ln K$.

4.5.3 Resonance and conjugate-base stabilization: phenol vs. cyclohexanol

- 1. Draw at least *four* valid resonance contributors for the conjugate base of phenol (PhO^-) and clearly indicate where the negative charge resides in each contributor.

- 2. Explain, using ARIO, why phenol is more acidic than cyclohexanol ($\text{C}_6\text{H}_{11}\text{OH}$), even though both deprotonate at oxygen.
- 3. Identify which resonance contributors are *major* and which are *minor*, and justify your classification using formal charge placement and octet considerations.

4.5.4 Lewis acid–base identification and curved-arrow mechanism: AlCl_3 with a ketone

Acetone reacts with aluminum trichloride to form a Lewis acid–base adduct.

- 1. Identify the Lewis acid and Lewis base.
- 2. Draw a curved-arrow mechanism showing formation of the coordinate bond (from electron source to electron sink).
- 3. Using words (no calculations), explain how coordination to AlCl_3 changes the electrophilicity of the carbonyl carbon.
- 4. Predict (qualitatively) how this coordination would affect nucleophilic addition of Cl^- to the carbonyl carbon.

4.5.5 Competing basic sites and site of protonation: amide vs. amine

Consider a molecule containing both an amide nitrogen and a tertiary amine nitrogen (e.g., a dimethylamide and a trialkylamine within the same molecule, separated by a carbon chain so they do not directly conjugate).

- 1. Predict which nitrogen is preferentially protonated under moderately acidic conditions.
- 2. Support your answer by comparing the conjugate acids using pK_a reasoning (you may use typical values: conjugate acid of a tertiary amine $pK_a \sim 9\text{--}11$; conjugate acid of an amide $pK_a \sim -1$ to 1).
- 3. Provide a resonance-based explanation for why the amide nitrogen is much less basic than the amine nitrogen.

4.5.6 Orbital (*s*-character) effects: acidity of C–H bonds

Rank the acidity (increasing acidity) of the indicated C–H sites, and justify the ranking using the orbital (O) component of ARIO. For each, draw the conjugate base and label the hybridization of the atom bearing the negative charge.

- 1. CH₃–CH₃ (alkane C–H), CH₂=CH₂ (alkene C–H), HC≡CH (terminal alkyne C–H)
- 2. Ph–CH₃ (benzylic C–H), HC≡C–CH₃ (propargylic C–H), Ph–H (aryl C–H)

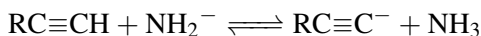
4.5.7 Mechanism drawing with charge conservation: intramolecular proton transfer

4-hydroxybutanoic acid can undergo an intramolecular proton transfer (via a hydrogen-bonded conformation) between the carboxylic acid and the alcohol group.

- 1. Draw a plausible intramolecular proton transfer step using curved arrows, explicitly showing bond breaking and bond formation.
- 2. Ensure that your mechanism strictly conserves overall charge.
- 3. Label the acid, base, conjugate acid, and conjugate base in the step you draw.
- 4. Briefly explain why intramolecular proton transfer can be faster than intermolecular proton transfer (focus on effective concentration and geometry, not kinetics math).

4.5.8 Quantitative deprotonation: is NaNH₂ strong enough?

Sodium amide (NaNH₂) is commonly used to deprotonate terminal alkynes:



Assume typical pK_a values in a consistent solvent set:

$$pK_a(\text{RC}\equiv\text{CH}) \approx 25, \quad pK_a(\text{NH}_3) \approx 38$$

- 1. Calculate K_{eq} for the deprotonation (order of magnitude).

- 2. State whether the deprotonation is expected to be essentially quantitative.
- 3. Explain your conclusion using the “weaker acid is favored” rule and the meaning of a large positive ΔpK_a .

4.5.9 Induction revisited: ethanol vs. 2,2,2-trifluoroethanol

2,2,2-trifluoroethanol ($\text{CF}_3\text{CH}_2\text{OH}$) is significantly more acidic than ethanol ($\text{CH}_3\text{CH}_2\text{OH}$).

- 1. Draw both conjugate bases ($\text{CH}_3\text{CH}_2\text{O}^-$ and $\text{CF}_3\text{CH}_2\text{O}^-$).
- 2. Using induction (I), explain why the CF_3 group stabilizes the conjugate base.
- 3. Predict how the acidity would change (increase, decrease, or stay similar) if the CF_3 group were moved one carbon farther from the oxygen (i.e., $\text{CF}_3\text{CH}_2\text{CH}_2\text{OH}$), and justify using distance dependence of induction.

4.5.10 Solvent effects and nucleophilicity: fluoride in protic vs. aprotic solvents

Fluoride is often described as a strong base but a weak nucleophile in protic solvents, while becoming a much stronger nucleophile in aprotic solvents.

- 1. Explain, using solvation concepts, why F^- is strongly solvated in protic solvents and how that affects its nucleophilicity.
- 2. Compare F^- and I^- as nucleophiles in protic solvents, focusing on polarizability and solvation.
- 3. Explain why the nucleophilicity trend among halides can change in aprotic solvents.
- 4. State clearly how these observations relate to (and differ from) Brønsted basicity trends.

Chapter 5

Mechanism Principles and Intermediates

If molecular structures are the nouns of chemistry, mechanisms are the verbs. In this chapter, we transition from static representations to dynamic processes, learning the rigorous language of curved arrows to track electron flow. We will uncover why some reactions occur instantly while others require heat, explore the fleeting existence of high-energy intermediates like carbocations, and use the Hammond Postulate to visualize the geometry of invisible transition states. Mastering these principles transforms organic chemistry from a list of reactions into a predictable system of logic.

5.1 Writing Mechanisms with Curved Arrows

Organic reaction mechanisms are a compact language for describing **how** bonds break and form. Up to this point, you have learned to represent molecules with Lewis structures (including formal charge) and to recognize functional groups. Curved-arrow notation (also called **electron-pushing formalism**) builds directly on those ideas: it is a set of strict, grammar-like rules for tracking **electron pairs** as they move from an **electron source** to an **electron sink**. When used correctly, curved arrows make mechanisms testable: every step conserves atoms, accounts for charge, and produces a chemically reasonable Lewis structure.

5.1.1 What a Curved Arrow Means: Electrons, Not Atoms

A curved arrow represents the movement of a specific set of electrons.

- A **full (double-barbed) curved arrow** indicates movement of an **electron pair** (two electrons).
- A **single-barbed (fishhook) arrow** indicates movement of a **single electron** and is used for radical mechanisms (treated later in this chapter).

In this section, we use only full curved arrows. The practical consequence is:

If you cannot point to the two electrons that are moving, you cannot draw the arrow.

Those electrons must come from a legitimate place in the Lewis structure: a lone pair, a bond (a σ bond or a π bond), or (less commonly) an anionic center best described as containing a lone pair.

5.1.2 The Source–Sink Rule (The Fundamental Grammar)

Every curved arrow has:

- **An electron source:** where the electrons **start**.
- **An electron sink:** where the electrons **end**.

Electron sources (things that **have** an electron pair available to donate) include:

- lone pairs (on heteroatoms such as O, N, halogens, S)
- π bonds (alkenes, alkynes, carbonyls, aromatic rings in appropriate contexts)
- σ bonds (in bond cleavage or rearrangement steps)
- negatively charged atoms (often best viewed as having an extra lone pair)

Electron sinks (places that can **accept** an electron pair) include:

- atoms with an incomplete octet (e.g., carbocations, BF_3)
- positively polarized atoms (electrophilic centers such as the carbon of a carbonyl)

- a proton (H^+) or an acidic $\text{H} - \text{X}$ bond
- the atom that will carry electrons in a heterolytic bond cleavage (the more electronegative partner or a stabilized leaving group)

The arrow tail must be drawn at the **source electrons** (a lone pair or a bond). The arrow head must point to the **sink** (an atom, a bond position, or a proton).

5.1.3 Bond Making, Bond Breaking, and the "One Step = One Picture" Rule

A mechanism is drawn as a sequence of discrete steps. Each step converts one valid Lewis structure into another valid Lewis structure (possibly via resonance forms). In most introductory mechanisms, a step should not do more than the following:

- form one new σ bond **and/or**
- break one σ bond (heterolytically) **and/or**
- shift a π bond (resonance or addition/elimination) **and/or**
- transfer a proton (acid–base step)

The number of curved arrows is determined by electron bookkeeping:

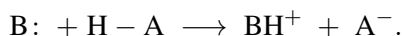
- If you **form** a bond using a lone pair, you **consume** that lone pair (it is no longer a lone pair in the product).
- If you **break** a bond heterolytically, the electron pair must **end up somewhere**: on one atom as a new lone pair (often creating a leaving group or an anion).
- If you **add** to a π bond (e.g., to a carbonyl), you typically need a second arrow to move the π electrons so an octet is not violated.

5.1.4 Heterolytic Bond Cleavage: Where Do the Electrons Go?

Most polar organic mechanisms use **heterolytic cleavage**, in which both electrons from a bond go to one atom. Curved-arrow notation makes heterolysis explicit:

- For cleavage of C–LG, the arrow tail begins on the σ bond, and the arrow head points to the leaving group atom (or the more electronegative atom). The leaving group departs with the electron pair.
- For cleavage of H–A in an acid, the arrow tail begins on a base lone pair and the arrow head points to H; a second arrow begins on the H–A bond and ends on A, giving A^- .

Example (generic deprotonation), written as electron flow:



In arrow language: $B: \rightarrow H$ and $H - A \rightarrow A$.

5.1.5 Bond Formation: "Attack" Means Electron Donation

Students often describe nucleophiles as "attacking" electrophiles. In curved-arrow grammar, **attack** has a specific meaning:

The nucleophile donates an electron pair to an electrophilic atom to form a new bond.

Thus, the arrow must start at a lone pair (or a bond) on the nucleophile and end at the electrophilic atom (or at the bond position being formed). This is why arrows do **not** start at positive charges: a positive charge indicates electron **deficiency**, not an electron pair available to move.

5.1.6 Resonance vs. Mechanism: Arrow Use Looks Similar but Means Different Things

Curved arrows are used in two related but distinct contexts:

Resonance arrows (within one structure)

Resonance describes **one** molecule represented by multiple Lewis structures. You use curved arrows to move π electrons or lone pairs to generate another resonance form. No atoms move, and no equilibrium arrow is implied between resonance contributors; they are not isolable species.

Mechanism arrows (between different species)

A mechanism step uses curved arrows to show electron movement that converts reactants into products. Here, the starting and ending drawings correspond to **different** chemical species (separated by a reaction arrow, often with reagents/conditions).

A practical diagnostic:

- If only electrons move **within** a single connectivity pattern and atoms are unchanged, you are likely drawing resonance.
- If a new bond forms or a bond breaks (changing connectivity), you are drawing a mechanism step.

5.1.7 Octets, Valence, and "Legal" Products

Curved arrows do not guarantee correctness unless the resulting structure is chemically plausible. After every step, perform three checks.

(1) Octet/valence check (especially for second-row atoms)

Carbon, nitrogen, oxygen, and fluorine generally obey the octet rule in stable intermediates.

- Carbon: typically 4 bonds (or 3 bonds + + charge; or 3 bonds + radical dot).
- Nitrogen: typically 3 bonds + lone pair (neutral) or 4 bonds (+).
- Oxygen: typically 2 bonds + 2 lone pairs (neutral) or 1 bond + 3 lone pairs (−) or 3 bonds + 1 lone pair (+).

If your arrows create a carbon with five bonds, you have missed a compensating bond-breaking arrow (common in additions to π bonds).

(2) Formal charge check

Electron movement changes formal charge.

- Donating a lone pair to make a bond typically makes the donor atom **more positive** (often by +1).

- Receiving an electron pair (e.g., when a bond breaks toward an atom) typically makes that atom **more negative**.

Your product charges must follow from the arrows. If you cannot justify each charge by electron bookkeeping, redraw the step.

(3) Atom conservation check

A mechanism never destroys atoms. If your step seems to "remove" an H or "add" an O without a reagent supplying it, something is wrong (often a missing acid/base species or omitted solvent molecule in a proton-transfer step).

5.1.8 Common Pitfalls (and How to Correct Them)

Pitfall 1: Starting an arrow at a positive charge

A + sign is not an electron source. Replace the erroneous arrow by identifying the true electron pair that will move (often a nucleophile lone pair or a π bond).

Pitfall 2: Ending an arrow in empty space

The arrow head must end on:

- an atom (forming a bond to that atom),
- a bond (creating a new π bond position, commonly used in resonance), or
- a hydrogen atom in a proton transfer.

Pitfall 3: Making a bond without breaking one when needed

When a nucleophile adds to a carbonyl carbon, carbon would exceed an octet unless the π electrons move to oxygen. Thus, addition to $C=O$ typically requires two arrows: $Nu : \rightarrow C$ and $C = O \rightarrow O$.

Pitfall 4: Moving atoms with arrows

Curved arrows move electrons only. If a group X leaves, the electrons in the C–X bond must be assigned to X (heterolysis) or split as radicals (fishhooks), depending on the chemistry. The group does not "carry itself away" by an arrow.

5.1.9 A Worked Micro-Example: Nucleophilic Attack on a Carbonyl (Electron Accounting)

Consider a generic nucleophile adding to a carbonyl group (the first step of many reactions, including additions and substitutions at acyl derivatives). The electron logic is:

- **Identify source:** the nucleophile has a lone pair (or a negative charge) $\Rightarrow$ it can donate.
- **Identify sink:** the carbonyl carbon is electrophilic due to polarization of the C=O bond $\Rightarrow$ it can accept.
- **Prevent octet violation:** if the nucleophile forms a new σ bond to carbon, the carbonyl π electrons must move to oxygen in the same step (a second arrow).
- **Update charges:** oxygen becomes more negative (alkoxide-like), while the nucleophile may become positively charged if it used a lone pair to bond.

This is not merely a drawing convention: it encodes conservation of electrons and predicts intermediate charge distribution, which in turn predicts subsequent steps (protonation of an alkoxide, expulsion of a leaving group, etc.).

5.1.10 Mechanism Writing as a Checklist Skill

When you write any step, train yourself to answer these questions explicitly:

- **What is the nucleophile (Lewis base) in this step?** Where is its electron pair?
- **What is the electrophile (Lewis acid) in this step?** Which atom is accepting electrons?
- **Do I need a second arrow to maintain octets?** (Common with π bonds, especially carbonyls.)
- **After the arrows, are all atoms reasonable in valence and formal charge?**

Curved-arrow mechanisms are often taught as an artistic skill, but they are better learned as a disciplined accounting method. If you consistently enforce the source–sink rule and verify the resulting Lewis structures, your mechanisms become logical consequences of structure rather than memorized drawings.

5.2 Thermodynamics and Kinetics

Curved-arrow mechanisms provide a *grammar* for proposing how electrons move. The next question is *which* of the many grammatically correct mechanisms is chemically plausible. Two distinct ideas guide that decision:

- **Thermodynamics** answers: *Which species are more stable?* and *Where does equilibrium lie?*
- **Kinetics** answers: *How fast is a step?* and *Which pathway is followed under given conditions?*

Confusing these is one of the most common sources of mechanistic error: a very stable product can form extremely slowly, and a fast-formed product can be less stable (and later equilibrate away).

5.2.1 Thermodynamics: Stability, Equilibrium, and ΔG

Thermodynamics concerns the **relative free energies** of reactants and products. At constant temperature and pressure, the key quantity is Gibbs free energy:

$$\Delta G = \Delta H - T\Delta S$$

where ΔH is the enthalpy change and ΔS is the entropy change.

Free energy and equilibrium constants

For a reaction written as Reactants $\rightleftharpoons$ Products,

$$\Delta G^\circ = -RT \ln K$$

Thus:

- If $\Delta G^\circ < 0$, then $K > 1$: products are favored at equilibrium (thermodynamically favored).
- If $\Delta G^\circ > 0$, then $K < 1$: reactants are favored at equilibrium.

Importantly, ΔG° and K do *not* tell you how fast equilibrium is achieved. They tell you only the energy difference between the initial and final states.

Thermodynamic stability in organic chemistry

In organic chemistry, “more stable” often correlates with:

- stronger bonds / more favorable bonding patterns (e.g., σ bonds replacing π bonds can be favorable *or* unfavorable depending on what forms)
- better charge distribution (less charge separation; negative charge on electronegative atoms; resonance stabilization)
- greater substitution / hyperconjugation (alkenes, carbocations, radicals; treated later in this chapter)

These trends help you estimate relative free energies even without numerical data.

5.2.2 Kinetics: Rates, Activation Free Energy, and $\Delta G^\ddagger$

Kinetics concerns how quickly reactants are converted to products. The rate of an elementary step is controlled primarily by the free energy of activation, $\Delta G^\ddagger$, the free-energy gap between the reactants (or intermediate) and the transition state.

Rate constants and the activation barrier

A convenient (and widely used) conceptual form is the Arrhenius equation:

$$k = Ae^{-E_a/RT}$$

where E_a is the activation energy. A more thermodynamically consistent expression for solution reactions is the Eyring equation, which uses $\Delta G^\ddagger$:

$$k = \frac{k_B T}{h} e^{-\Delta G^\ddagger/RT}$$

For our purposes, both emphasize the same key relationship:

A higher activation barrier means a slower step; a lower barrier means a faster step.

Transition states are not intermediates

- A **transition state** (TS) is the highest-energy point along a step. It is not isolable and is not drawn as a normal Lewis structure.

- An **intermediate** is a local minimum between steps. It has a finite lifetime (sometimes very short) and *can* often be drawn as a Lewis structure with reasonable valences.

The distinction matters mechanistically: intermediates can sometimes be trapped or observed; transition states cannot.

5.2.3 Reaction Coordinate Diagrams: The Shared Picture for Thermodynamics and Kinetics

A reaction coordinate diagram plots energy (typically Gibbs free energy) versus a generalized progress coordinate that traces bond-making and bond-breaking events. It is not a literal “distance” in space; it is a conceptual axis that orders structures from reactants to products.

Key features to identify

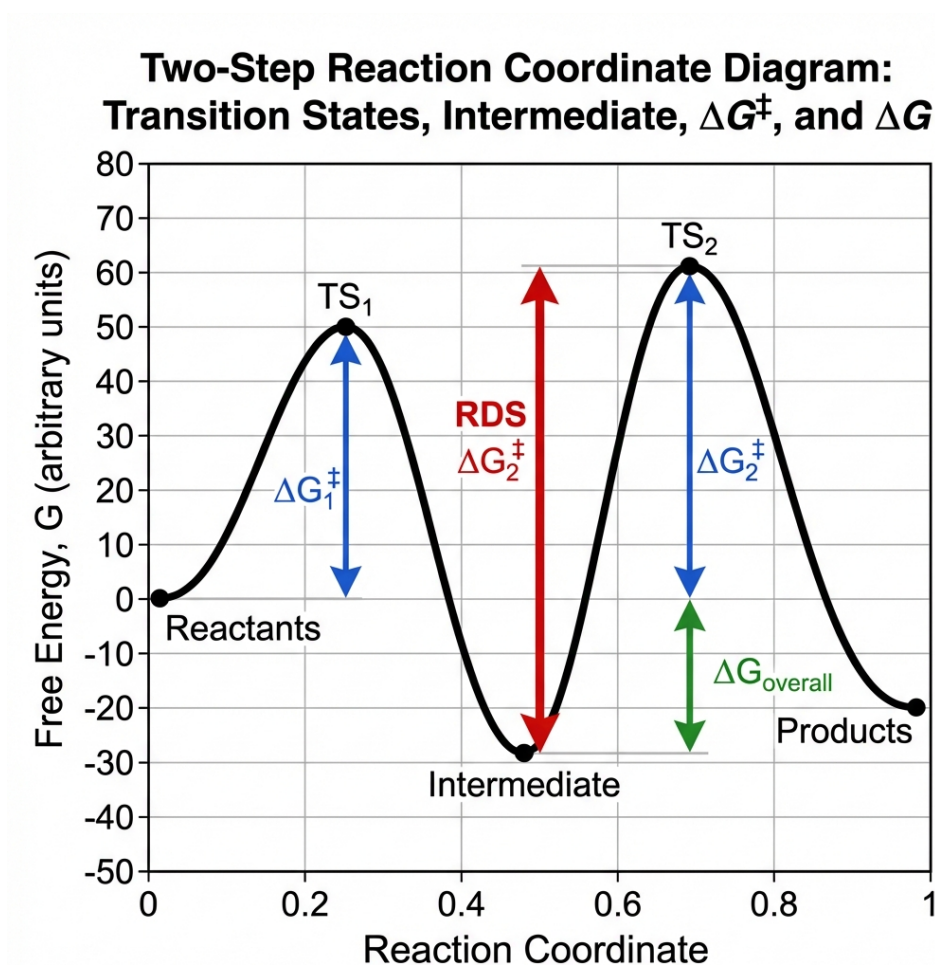
In any energy diagram, learn to locate and label:

- **Reactants** and **products** (endpoints)
- **Transition states** (peaks)
- **Intermediates** (valleys between peaks)
- **Activation free energies** $\Delta G^\ddagger$ for each step (vertical gaps from a minimum to the next peak)
- **Overall free energy change** ΔG (vertical gap from reactants to products)

These quantities answer different questions:

- ΔG answers: *Is the overall reaction thermodynamically favorable?*
- $\Delta G^\ddagger$ answers: *How fast is a given step?*

A two-step profile with an intermediate



Reading the diagram: what is fast, what is favored?

From a diagram like the one above:

- The **overall thermodynamic driving force** is given by $\Delta G_{\text{overall}} = G_{\text{products}} - G_{\text{reactants}}$. If products lie lower, the reaction is thermodynamically favorable.
- The **rate** is controlled by the **largest** activation barrier $\Delta G^\ddagger$ encountered from the currently occupied minimum. That step is the **rate-determining step (RDS)**.

A subtle but important point: the RDS is *not necessarily* the step with the highest absolute transition state energy. It is the step with the largest vertical gap from the preceding minimum. A high TS that is preceded by an even higher-energy intermediate can still correspond to a relatively small barrier.

5.2.4 Multi-Step Mechanisms: Overall Rate vs. Individual Steps

A typical organic mechanism consists of several elementary steps. Each step has its own rate constant and activation barrier. Two consequences follow.

The slowest step limits the overall rate

If one step has a much larger $\Delta G^\ddagger$ than the others, it dominates the timescale. This is why identifying the RDS is central to mechanistic reasoning.

Fast steps can still matter for selectivity

Even if a step is not rate-determining, it can control *which product forms* if multiple pathways compete from a common intermediate. Product distributions often depend on small differences in activation barriers between competing steps, even when both are “fast” relative to some earlier RDS.

5.2.5 Kinetic vs. Thermodynamic Control (Product Distribution Under Different Conditions)

Organic reactions often have more than one possible product. Two limiting regimes are especially important.

Kinetic control

Under kinetic control:

- the product ratio reflects **relative rates** of formation (relative $\Delta G^\ddagger$ values) from a common starting point
- the major product is the one formed through the **lower barrier** pathway, even if it is less stable

- typical conditions: lower temperature, short reaction times, irreversible trapping, strong driving force for the first-formed product to be removed from equilibrium

Thermodynamic control

Under thermodynamic control:

- products interconvert (directly or via intermediates), approaching equilibrium
- the major product is the **most stable** (lowest G) product, even if it forms more slowly
- typical conditions: higher temperature, longer reaction times, reversible steps, catalysts that allow equilibration

Mechanistically, this is not a vague rule of thumb: it is an energy-diagram statement. Kinetic control depends on the heights of barriers leading *to products*; thermodynamic control depends on the depths of the product wells.

5.2.6 How to Use Thermodynamics and Kinetics to Evaluate a Proposed Mechanism

When you propose a curved-arrow step, you should be able to justify it on both thermodynamic and kinetic grounds.

Thermodynamic plausibility checks

- Does the step generate an extremely unstable species (e.g., severe charge separation without stabilization)?
- Is there a clear driving force (formation of a strong bond, resonance stabilization, relief of strain, acid–base neutralization)?
- If the step is endergonic ($\Delta G > 0$), is it coupled to a subsequent strongly exergonic step that can pull the sequence forward?

Kinetic plausibility checks

- Does the step require an unlikely high-energy arrangement (e.g., breaking a strong bond without assistance, forming a bond to a poor electrophile)?

- Is there a more reasonable lower-barrier alternative (e.g., proton transfer before departure of a leaving group)?
- Does the step violate common kinetic patterns (e.g., attempting S_N2 at a sterically blocked center; attempting to expel a strong base as a leaving group)?

5.2.7 Summary: Two Questions, Two Answers

It is useful to keep the central distinction in a single sentence:

Thermodynamics compares *minima* (stabilities, equilibrium), while **kinetics** compares *barriers* (rates, rate-determining steps).

Curved arrows tell you *what electron movements are possible*. Energy diagrams help you decide *which* of those possibilities dominates under a given set of conditions. In the next sections, we will sharpen the “source and sink” idea into quantitative structure-based definitions of *nucleophiles* and *electrophiles*, and connect those definitions to reactivity trends.

5.3 Nucleophiles and Electrophiles

Curved-arrow notation provides a strict way to show *electron flow*: arrows start at an electron **source** and end at an electron **sink**. Thermodynamics and kinetics then tell us which electron-flow steps are plausible and which are fast. This section gives names to the most important sources and sinks in polar organic mechanisms:

- **Nucleophiles** are electron-pair donors (Lewis bases): they supply the electrons at the arrow tail.
- **Electrophiles** are electron-pair acceptors (Lewis acids): they provide the atom (or bond position) at the arrow head.

Mechanistic reasoning becomes much faster once you can reliably identify nucleophilic and electrophilic sites from structure, polarity, and steric environment.

5.3.1 Lewis Acids and Bases: Operational Definitions for Mechanisms

Nucleophile (Lewis base)

A **nucleophile** is a species (or a site within a species) that *donates* an electron pair to form a new bond. In arrow language: the curved arrow *starts* at the nucleophile.

Typical structural signatures of nucleophilicity include:

- **Lone pairs** on heteroatoms (e.g., HO^- , H_2O , NH_3 , RS^-)
- **Negative charge** (often strongly nucleophilic, though sterics and solvation can reduce it)
- **π electrons** (alkenes, arenes, enolates), which can act as nucleophiles toward strong electrophiles

Electrophile (Lewis acid)

An **electrophile** is a species (or site) that *accepts* an electron pair. In arrow language: the curved arrow *ends* at the electrophile.

Typical electrophilic signatures include:

- **Formal positive charge** (e.g., carbocations, protonated carbonyls)
- **Polarized bonds** where an atom is δ^+ (e.g., carbonyl carbon, alkyl carbon bonded to a leaving group)
- **Incomplete octet** (e.g., BF_3 , AlCl_3)

Common misconception: “nucleophile” is not synonymous with “negatively charged”

Many neutral molecules are effective nucleophiles (H_2O , ROH , NH_3 , R_3P), and some anions are weak nucleophiles under specific conditions (e.g., strongly resonance-stabilized anions). The correct question is always: *How available is the electron pair for bond formation?*

5.3.2 Locating Nucleophilic and Electrophilic Sites in a Molecule

Most molecules contain multiple potential donor and acceptor sites. Mechanisms become clear when you learn to identify the *reactive site* rather than labeling the

entire molecule.

Nucleophilic sites

A site tends to be nucleophilic if it has:

- **High electron density:** negative charge, lone pairs, π bonds.
- **An available orbital orientation:** a lone pair or π bond that can overlap with an electrophile's accepting orbital.
- **Sufficient accessibility:** low steric hindrance around the donor atom.

Examples:

- **Oxygen nucleophiles:** HO^- is strongly nucleophilic; H_2O is weaker because it is neutral and often strongly solvated.
- **Nitrogen nucleophiles:** amines are often good nucleophiles because N is less electronegative than O, so its lone pair is higher in energy (more donating).
- **Sulfur nucleophiles:** thiolates and neutral sulfides can be excellent nucleophiles because sulfur is larger and more polarizable (its electron cloud distorts easily during bond formation).

Electrophilic sites

A site tends to be electrophilic if it has:

- **Electron deficiency:** positive charge, δ^+ polarization, or an empty low-lying orbital.
- **A bond or orbital that can accept electron density:** commonly a σ^* (anti-bonding) orbital for substitution or a π^* orbital for addition.

Examples:

- **Carbonyl carbon:** in $\text{R}_2\text{C}=\text{O}$, the $\text{C}=\text{O}$ bond is polarized; carbon is δ^+ and has an accessible π^* orbital that accepts electron density in nucleophilic addition.

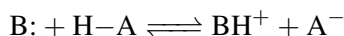
- **Alkyl carbon bearing a leaving group:** in $\text{R}-\text{CH}_2-\text{LG}$, the $\text{C}-\text{LG}$ bond polarization and the $\sigma_{\text{C}-\text{LG}}^*$ orbital make carbon electrophilic in substitution.
- **Protons:** H^+ is an extreme electrophile; acidic H atoms in $\text{H}-\text{X}$ bonds are electrophilic due to bond polarization.

5.3.3 Nucleophilicity vs. Basicity: Related but Not Identical

Both nucleophilicity and basicity describe electron-pair donation, but they refer to different *targets* and different experimental measurements.

Basicity is thermodynamic

A **base** donates an electron pair to H^+ . Basicity is quantified by an equilibrium constant (or pK_a of the conjugate acid):



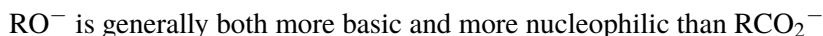
A stronger base gives a more favorable equilibrium for proton transfer.

Nucleophilicity is kinetic

A **nucleophile** donates an electron pair to an atom other than hydrogen (most often carbon). Nucleophilicity is quantified by a *rate* (how fast a bond forms) and depends strongly on conditions, especially solvent.

When nucleophilicity and basicity trend together

Within a related series and under fixed solvent conditions, nucleophilicity often increases with basicity because both correlate with a higher-energy, more donating electron pair. For example, among oxygen anions in a similar environment:



because the carboxylate is resonance-stabilized (lower electron-pair availability).

When nucleophilicity and basicity diverge

Two major reasons cause divergence:

- **Steric hindrance** can reduce nucleophilicity without greatly reducing basicity.
- **Solvent effects** can strongly suppress nucleophilicity of small, highly solvated anions.

Sterics: the “bulky base” concept

Bulky bases such as $(\text{CH}_3)_3\text{CO}^-$ (tert-butoxide) can be quite basic (readily abstract H^+) but relatively poor nucleophiles in substitution because approaching an electrophilic carbon requires close contact and precise orbital overlap. In contrast, proton transfer can occur at longer range and is less sensitive to steric congestion at the base center.

Solvent: protic vs. aprotic

In **polar protic** solvents (e.g., H_2O , ROH), anions are strongly solvated by hydrogen bonding. This solvation:

- stabilizes the nucleophile (lowering its free energy),
- and creates an energetic penalty for desolvation during bond formation,

often reducing nucleophilicity markedly.

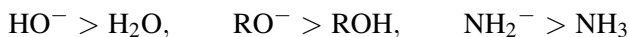
In **polar aprotic** solvents (e.g., DMSO, DMF, acetonitrile), anions are less strongly hydrogen-bond solvated, so their electron pairs are more available and nucleophilicity tends to increase.

5.3.4 Trends in Nucleophilicity: Charge, Electronegativity, and Polarizability

Nucleophilicity is best treated as a combination of electronic driving force and accessibility. The following trends are broadly useful in predicting behavior.

Effect of charge

All else equal, negatively charged nucleophiles are typically more nucleophilic than their neutral conjugates:



because the electron pair is higher in energy and more available for bond formation. However, strong solvation in protic solvents can diminish this advantage.

Effect of electronegativity (within a row of the periodic table)

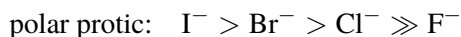
For nucleophiles in the same period, lower electronegativity typically increases nucleophilicity (more willing to donate):



Within a given row, a highly electronegative atom holds its electrons tightly, lowering nucleophilicity.

Effect of polarizability (down a group)

Down a group, atoms become larger and more polarizable. In many contexts (especially polar protic solvents), nucleophilicity can *increase* down the group even though basicity decreases:



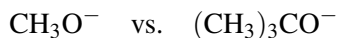
A useful physical picture is that a larger, softer electron cloud can distort and overlap with an electrophile more readily, and is less tightly solvated than small, hard anions like F^- .

5.3.5 Steric Effects: Accessibility Controls Many Reaction Pathways

Steric bulk can strongly reduce nucleophilicity by slowing the approach to the electrophilic center and reducing effective orbital overlap.

Steric hindrance at the nucleophile

Compare:



Both are oxygen anions and can be strong bases, but CH_3O^- is typically the better nucleophile in substitution because it is less hindered and can approach carbon more easily.

Steric hindrance at the electrophile

The electrophile's substitution pattern also matters. A crowded electrophilic carbon is harder to approach, making bimolecular bond-forming steps slower. This is one reason why different substitution patterns lead to different preferred reaction classes (developed later for S_N1 , S_N2 , E1, and E2).

5.3.6 Electrophilicity: What Makes an Atom Electron-Poor?

Electrophilicity is often introduced as “positive charge,” but most organic electrophiles are *neutral* and electrophilic because of bond polarization and orbital structure.

Bond polarization and partial charges

In a polarized bond C—X where X is more electronegative, the carbon often bears partial positive charge (δ^+), making it susceptible to nucleophilic attack. Similarly, the carbonyl group has a strong dipole, with a significantly electrophilic carbon.

Orbital view: σ^* and π^* acceptors

A more predictive (and mechanistically aligned) description uses acceptor orbitals:

- **Substitution:** nucleophiles donate into σ_{C-LG}^* , weakening the C—LG bond as the new C—Nu bond forms.
- **Addition to π systems:** nucleophiles donate into π^* (e.g., carbonyl π^*), forming a σ bond and shifting the π electrons (the two-arrow pattern emphasized earlier).

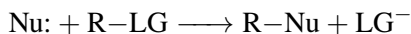
This orbital picture explains why electron-withdrawing substituents increase electrophilicity: they lower the energy of the acceptor orbital, increasing the driving force for donation.

5.3.7 Leaving Groups: The Hidden Partner in Many Electrophiles

Many electrophiles are only electrophilic because bond formation can be coupled to bond breaking. A **leaving group** (LG) is the fragment that departs with an electron pair when a bond breaks heterolytically.

Definition and mechanistic role

In a typical substitution step:



the nucleophile supplies electrons to form R–Nu, while the R–LG bond breaks and the leaving group takes the bonding electron pair.

Leaving group ability and conjugate base stability

A good leaving group is one that is stable after departure. In many cases, leaving group ability correlates inversely with basicity:

- **Weak bases** tend to be **good leaving groups** (their negative charge is stabilized).
- **Strong bases** tend to be **poor leaving groups**.

For example, I^- and Br^- are typically much better leaving groups than HO^- , because HO^- is a strong base and thus unstable as a free anion in many reaction contexts.

Practical consequence: activation of poor leaving groups

When a potential leaving group is too basic (e.g., $-\text{OH}$), reactions often proceed only after **activation**, commonly by protonation to form $-\text{OH}_2^+$, which can depart as neutral H_2O . This is a direct application of the curved-arrow “source–sink” rule: protonation changes the electron sink landscape and makes heterolytic cleavage feasible.

5.3.8 A Mechanistic Workflow: Identifying Roles Before Drawing Arrows

Before drawing any curved arrows in a polar mechanism, use this short workflow:

- **List nucleophilic sites:** locate lone pairs, anions, and π bonds; consider steric accessibility.
- **List electrophilic sites:** look for $+$ charge, δ^+ carbons (especially carbonyls and C–LG), and acidic protons.

- **Check coupling to leaving groups:** if a bond to the electrophilic carbon must break, decide whether the leaving group is plausible as drawn or requires activation.
- **Decide whether the key step is addition, substitution, or proton transfer:** this determines the typical arrow pattern (one arrow vs. two-arrow additions to π bonds).

This workflow links directly back to earlier sections: it tells you where arrows can start and end (curved-arrow grammar) and which plausible steps are likely fast or slow (kinetic barriers) and favorable or unfavorable (thermodynamic stability).

5.4 Carbocations and Radicals

In polar mechanisms, curved arrows often lead to intermediates in which carbon is *electron-deficient*. These intermediates are central to substitution, elimination, rearrangement, and many acid-catalyzed reactions. This section focuses on two such species:

- **Carbocations** (electron-pair deficient, formally positively charged carbon)
- **Carbon radicals** (single-electron deficient, neutral species with an unpaired electron)

Both are high-energy intermediates whose *structure* and *stability trends* strongly influence reaction pathways and product distributions (thermodynamics) as well as which steps are fast (kinetics).

5.4.1 Carbocations: Definition, Electron Count, and Geometry

What is a carbocation?

A **carbocation** is an organic species in which carbon bears a formal positive charge. In the simplest picture, the cationic carbon has:

- three σ bonds (to three substituents), and
- **only six valence electrons** around carbon (an incomplete octet),
- plus an **empty p orbital**.

Because it lacks a full octet, a carbocation is a strong electrophile: it is an electron sink in curved-arrow language.

Hybridization and shape

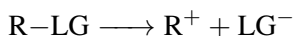
For a typical (classical) alkyl carbocation:

- the cationic carbon is approximately sp^2 -hybridized,
- the three σ bonds lie in a **trigonal planar** arrangement (bond angles near 120°),
- and the unhybridized p orbital is **perpendicular** to the plane and **empty**.

This geometry matters mechanistically: nucleophiles can approach from either face of the planar center, which connects directly to stereochemical outcomes in later chapters.

How carbocations arise in mechanisms

Carbocations commonly form by **heterolytic bond cleavage** in which a leaving group departs with an electron pair:



This step is often uphill in free energy unless the leaving group is very good and/or the cation is strongly stabilized. In energy-diagram terms, carbocation formation often corresponds to a high barrier and can be rate-determining.

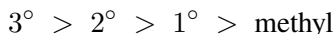
5.4.2 Carbocation Stability: The Core Trends

Carbocations are stabilized by any factor that *donates electron density* into the empty p orbital or *delocalizes* the positive charge. Three ideas are especially important:

- **Inductive effects** (electron donation through σ bonds)
- **Hyperconjugation** (overlap of filled σ orbitals with the empty p orbital)
- **Resonance** (delocalization of charge via π systems)

Alkyl substitution: $3^\circ > 2^\circ > 1^\circ > \text{methyl}$

A fundamental empirical ordering for simple alkyl carbocations is:



This trend reflects the cumulative stabilizing effects of alkyl groups (primarily hyperconjugation, with a smaller inductive component). A tertiary carbocation has more adjacent C–H and C–C σ bonds that can donate electron density toward the electron-deficient center.

Hyperconjugation: $\sigma \rightarrow p$ donation as a stabilizing interaction

Hyperconjugation is best viewed as an **orbital interaction**: a filled σ bonding orbital (commonly a C–H bond on a carbon adjacent to the cation) overlaps with the empty p orbital of the carbocation. This overlap allows electron density to be shared (delocalized) into the electron-deficient site, lowering the energy of the system.

Two key mechanistic consequences follow from this picture:

- Hyperconjugation requires **adjacent σ bonds**. More alkyl substitution means more adjacent C–H (and C–C) σ bonds that can align and donate into the empty p orbital.
- Hyperconjugation is **orientation-dependent**. If a σ bond cannot align reasonably with the empty p orbital (for conformational reasons), stabilization is reduced. (This idea becomes important in conformationally constrained systems.)

Resonance stabilization: allylic and benzylic carbocations

When a carbocation is adjacent to a π system, the positive charge can be delocalized by resonance, dramatically stabilizing the intermediate.

Allylic carbocation

An allylic carbocation has the cationic center adjacent to a double bond:



The empty *p* orbital overlaps with the adjacent π bond, allowing multiple resonance contributors in which the positive charge is shared over two carbons.

Benzylic carbocation

A benzylic carbocation ($\text{Ph}-\text{CH}_2^+$) is even more stabilized because the positive charge can delocalize into the aromatic ring, generating several resonance contributors.

Resonance stabilization often outweighs simple substitution effects. A primary benzylic carbocation can be more stable than a tertiary alkyl carbocation, depending on the system.

5.4.3 Carbocation Rearrangements: 1,2-Shifts Toward Greater Stability

Because carbocations are electron-deficient, they can undergo rearrangements that move the positive charge to a more stabilized position. These rearrangements are among the most important “mechanistic surprises” in introductory organic chemistry.

Why rearrangements occur

A rearrangement is favored when:

- the initial carbocation is relatively unstable (high in energy),
- a neighboring group can migrate with its bonding electron pair to generate a more stable carbocation,
- and the barrier for migration is competitive with other pathways (e.g., nucleophilic capture, elimination).

In energy-diagram terms, rearrangement is common when it leads to a significantly lower-energy intermediate, which can reduce subsequent activation barriers and redirect the mechanism.

The 1,2-hydride shift

A **1,2-hydride shift** is the migration of H^- (a hydride *unit*) from a carbon adjacent to the cationic center to the cationic carbon. Mechanistically, what migrates is a σ bond electron pair:

A curved arrow is drawn from the C–H σ bond to the carbocation center.

This forms a new C–H bond at the cationic carbon and moves the positive charge to the carbon that *lost* the hydride. The driving force is typically formation of a more substituted and/or resonance-stabilized carbocation.

The 1,2-methyl (alkyl) shift

A **1,2-alkyl shift** (often discussed as a methyl shift) is analogous: a C–C σ bond migrates with its electron pair to the carbocation center. The migrating group moves *as a unit*, but the arrow is still drawn from the σ bond (electron source) to the cation (electron sink).

What to predict: rearrangements follow stability gradients

In most introductory problems, assume rearrangements proceed (when possible) toward:

- higher substitution at the cationic center ($3^\circ > 2^\circ > 1^\circ$),
- resonance stabilization (allylic/benzylic),
- relief of ring strain (common in small rings).

However, rearrangements are not automatic: nucleophilic capture or elimination may occur first if those pathways are faster ($\Delta G^\ddagger$ lower). Thus, rearrangements are a kinetic competition problem, not only a thermodynamic one.

5.4.4 Carbon Radicals: Structure and Stability Trends (Brief Parallel)

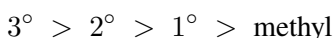
Radicals are intermediates with an unpaired electron. They are commonly formed by **homolytic** bond cleavage or by single-electron transfer processes (mechanistic details and fishhook arrows are treated later). Here we focus on structural features and stability trends that parallel carbocations.

Geometry and electron count

A typical alkyl radical $\text{R}_3\text{C}\cdot$ is often described as approximately sp^2 -like (nearly planar) with the unpaired electron occupying a p -like orbital. The geometry can be somewhat pyramidalized depending on substitution and environment, but the key mechanistic point is that a radical has a partially filled orbital that can participate in bond formation.

Stability order and hyperconjugation

Carbon radicals show a stability trend similar to carbocations:



The same conceptual explanation applies: hyperconjugation and inductive donation stabilize electron-deficient centers. Radicals are also strongly stabilized by resonance when allylic or benzylic.

Reactivity contrast: electrophilicity vs. selectivity

Although radicals and carbocations share stability patterns, they behave differently in mechanisms:

- Carbocations are strong electrophiles (electron-pair acceptors) and react readily with nucleophiles.
- Radicals often engage in chain reactions and can be less “charge-driven,” with selectivity strongly influenced by the stability of the radical intermediate and by transition-state character (connecting to the Hammond postulate in the next section).

5.4.5 Practical Mechanistic Guidance: Recognizing When These Intermediates Matter

When analyzing a mechanism, ask:

- **Does a step generate a positively charged carbon?** If so, consider substitution level and resonance; anticipate possible rearrangements.

- **Is there an adjacent carbon that could migrate (hydride or alkyl shift)?** If a more stable carbocation can form, rearrangement is plausible.
- **Are there strong nucleophiles present?** Fast nucleophilic capture can out-compete rearrangement.
- **Are conditions strongly acidic or strongly ionizing?** Such conditions often favor carbocation formation by stabilizing ions and improving leaving group ability.

Understanding carbocations and radicals turns curved-arrow mechanisms from a set of drawing rules into a predictive tool: once you know which intermediates are likely and how they reorganize, you can anticipate major products and common rearrangement outcomes rather than memorizing them.

5.5 The Hammond Postulate

Curved-arrow notation tells us *which electrons move*. Thermodynamics and kinetics tell us *how favorable* a step is (ΔG) and *how fast* it is ($\Delta G^\ddagger$). The remaining challenge is that the key structure governing rate and selectivity—the **transition state**—cannot be isolated or directly observed. The Hammond postulate provides a powerful bridge between *energetics* and *structure*: it allows us to infer whether the transition state of a step is “reactant-like” or “product-like” and to use that inference to predict selectivity trends.

5.5.1 Transition States Are “Invisible,” But Their Relative Structure Matters

A **transition state** (TS) is a first-order saddle point on the potential energy surface (a maximum along the reaction coordinate and a minimum along all other coordinates). It corresponds to the arrangement of atoms at the top of the activation barrier for an elementary step.

Two reminders from the kinetics section are crucial here:

- A TS is not an intermediate; it is not a minimum in energy and cannot be isolated.
- The rate of an elementary step depends exponentially on $\Delta G^\ddagger$, which is the free-energy difference between the reactant (or intermediate) well and the TS.

Although we cannot bottle a TS, we can still make useful statements about it. In many organic reactions, the TS geometry changes *gradually* along the reaction coordinate: as bonds begin to break and form, the structure continuously deforms from reactant-like to product-like. The Hammond postulate formalizes how the location of the TS along this deformation relates to the thermodynamics of the step.

5.5.2 Statement of the Hammond Postulate (Qualitative Form)

Hammond postulate: *For two successive points on a reaction coordinate, the structure with the more similar energy will be more similar in structure.*

In practice, we usually apply it to a transition state and the nearby stable species on the same step:

- **Exothermic step** ($\Delta G < 0$): the TS is **early** and **reactant-like**.
- **Endothermic step** ($\Delta G > 0$): the TS is **late** and **product-like**.

This is a structural interpretation of an energy diagram: a strongly downhill step has a TS closer in energy to reactants than to products, so the TS resembles reactants; a strongly uphill step has a TS closer in energy to products than to reactants, so the TS resembles products.

5.5.3 Early vs. Late Transition States: What “Resembles” Means Mechanistically

Meaning of an early (reactant-like) TS

If a TS is early, then:

- bonds that will form are only slightly formed,
- bonds that will break are only slightly broken,
- charge development is limited compared to the products of that step.

Thus, factors that stabilize the *products* of the step have a smaller effect on $\Delta G^\ddagger$, because the TS has not yet developed much of that product-like character.

Meaning of a late (product-like) TS

If a TS is late, then:

- bond formation is more advanced and/or bond breaking is more advanced,
- charge distribution and geometry more closely resemble the product(s) of that step,
- stabilization (or destabilization) of the step products strongly influences $\Delta G^\ddagger$, because the TS already “contains” much of that character.

Why this helps: selectivity is a transition-state property

Selectivity (which product forms faster) depends on comparing $\Delta G^\ddagger$ values for competing pathways. The Hammond postulate helps you decide whether a change that stabilizes a particular *intermediate or product* will also significantly stabilize the *transition state* leading to it.

5.5.4 Applying the Hammond Postulate to Reaction Steps Common in Organic Chemistry

Endothermic formation of unstable intermediates (carbocations and radicals)

Steps that *create* high-energy, electron-deficient intermediates are often endothermic. Two classic examples are:

- ionization to form a carbocation (leaving group departure in many $S_N1/E1$ contexts),
- hydrogen abstraction to form a carbon radical in radical chain halogenation (especially with less reactive halogen radicals).

If the step is endothermic, Hammond predicts a **late TS** that resembles the intermediate being formed. Consequence:

- Any factor that stabilizes the developing carbocation or radical (substitution, resonance, hyperconjugation) will also stabilize the TS and *lower* $\Delta G^\ddagger$, making that pathway faster.

This explains why, in many contexts, rates and selectivities track the stability trends of carbocations and radicals discussed earlier (e.g., tertiary > secondary > primary).

Exothermic capture of an intermediate

Once a carbocation has formed, reaction with a nucleophile (or deprotonation to form an alkene) is often exothermic. Hammond predicts an **early TS** for these fast, downhill steps. Consequence:

- Differences in product stability often matter less for the barrier of an exothermic capture step, because the TS is still close to the intermediate.

Thus, in multi-step mechanisms, *formation* of an intermediate (often endothermic) commonly controls selectivity more than *consumption* of that intermediate (often exothermic). This connects directly to the “rate-determining step” concept: the step with the largest barrier frequently corresponds to an endothermic formation of an electron-deficient species.

5.5.5 A Quantitative Mindset (Without Overpromising Precision)

The Hammond postulate is qualitative, not a calculator. It does not yield exact bond lengths or exact energies. However, it is highly predictive when used with care:

- It is most reliable when comparing *similar* reaction pathways (same general mechanism, similar reagents, similar solvent).
- It can fail or become ambiguous when the energy landscape changes shape substantially (e.g., different mechanisms, strong solvent participation, significant tunneling, or when multiple coordinates change in a complex way).

A safe operational use is:

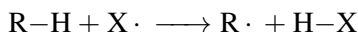
- Determine whether the step is *overall* exothermic or endothermic (even roughly).
- Assign early (reactant-like) vs. late (product-like) TS character.
- Decide whether stabilizing the product of that step would be expected to stabilize the TS (strong effect if TS is late; weak effect if TS is early).

5.5.6 Classic Application: Radical Halogenation Selectivity

Radical halogenation provides a clean example of Hammond reasoning because competing pathways differ mainly in the stability of the radical formed.

The key competition: abstraction of different C–H bonds

In a simplified chain propagation step, a halogen radical abstracts hydrogen:



Different C–H sites (primary, secondary, tertiary) compete to form different radicals $\text{R}\cdot$.

Hammond interpretation

If the hydrogen abstraction step is **endothermic**, the TS is **late** and radical-like; thus the barrier depends strongly on radical stability. The more stable radical (typically tertiary) forms through a lower barrier and is favored, giving higher selectivity.

If the hydrogen abstraction step is **exothermic**, the TS is **early** and reactant-like; thus radical stability has a smaller effect on the barrier, and selectivity decreases.

This logic explains the often-observed pattern: some halogenations are highly selective (favoring abstraction leading to the most stable radical), while others are less selective. The key is not “which product is more stable” but *how radical-like the TS is*, which is governed by the thermochemistry of the abstraction step.

5.5.7 Classic Application: Alcohol Dehydration and Carbocation Character

Acid-catalyzed dehydration of alcohols often proceeds by:

- protonation of –OH to make a better leaving group,
- loss of water to form a carbocation (in many cases),
- deprotonation to form an alkene.

The step that forms the carbocation by departure of water is frequently **endergonic** and has a **late TS** with substantial carbocation character. Hammond then predicts:

- substrates that form more stable carbocations (tertiary, allylic, benzylic) undergo dehydration more readily,
- rearrangements (1,2-hydride or 1,2-alkyl shifts) are plausible if they lead to a more stable carbocation, because the energy landscape strongly “rewards” carbocation stabilization.

5.5.8 Using Hammond Reasoning in Mechanistic Problem Solving

When faced with a selectivity question, especially in reactions involving carbocations or radicals, apply the following structured approach:

Step 1: Identify the competing elementary steps

Write the competing steps explicitly (even if only in words): e.g., “H abstraction at primary vs. tertiary carbon,” or “ionization to form secondary vs. tertiary carbocation.”

Step 2: Estimate whether the key step is exothermic or endothermic

Use chemical intuition:

- forming a high-energy intermediate (carbocation, many radicals) is often endothermic,
- forming a strong bond (e.g., H–X for some X) can make a step exothermic,
- significant charge separation without strong stabilization tends to be endothermic.

Step 3: Assign early/late TS character

Endothermic $\Rightarrow$ late TS (product-like). Exothermic $\Rightarrow$ early TS (reactant-like).

Step 4: Decide what controls the barrier

- Late TS: stability of the developing intermediate/product strongly affects $\Delta G^\ddagger$ (expect high selectivity based on intermediate stability).
- Early TS: intermediate/product stability weakly affects $\Delta G^\ddagger$ (expect reduced selectivity; other factors such as sterics and encounter frequency can dominate).

The Hammond postulate converts an energy statement into a structural statement:

- Exothermic step $\Rightarrow$ early, reactant-like TS $\Rightarrow$ product stabilization has limited influence on the barrier.

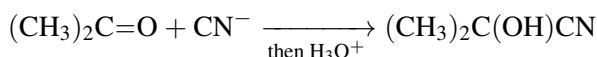
- Endothermic step $\Rightarrow$ late, product-like TS $\Rightarrow$ product (or intermediate) stabilization strongly lowers the barrier.

Combined with the stability trends for carbocations and radicals, Hammond reasoning becomes a practical tool for predicting which pathways are fastest and which products are favored—even when the decisive structures cannot be observed directly.

5.6 Problems

5.6.1 Problem 1: Curved-Arrow Grammar in a Multi-Step Addition (Carbonyl Chemistry)

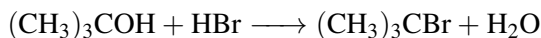
Consider the reaction of acetone with cyanide under acidic workup:



- Draw a complete, stepwise curved-arrow mechanism for the formation of the cyanohydrin, including **all** necessary proton-transfer steps and showing the correct intermediate(s).
- In the nucleophilic addition step, explicitly show **both** curved arrows required to avoid an octet violation.
- For each step, label the **electron source** and **electron sink** (tail and head of each arrow) in words.
- Identify the step(s) in which **formal charges change** and write the formal charge on each heteroatom after that step.

5.6.2 Problem 2: Curved-Arrow Mechanism with Leaving Group Activation (Alcohol as a Poor Leaving Group)

A tertiary alcohol undergoes acid-catalyzed substitution with bromide:



- Draw a stepwise curved-arrow mechanism consistent with polar (two-electron) arrow pushing.

- Your mechanism must include: protonation of the alcohol, formation of a carbocation intermediate, and nucleophilic capture by Br^- .
- For each step, state whether you expect it to be relatively **fast** or **slow** and justify using $\Delta G^\ddagger$ language (no numbers required).
- Identify which step is most likely the **rate-determining step** and explain why in terms of ion formation and leaving group ability.

5.6.3 Problem 3: Arrow-Pushing Diagnostics (Correct vs. Incorrect Mechanistic Arrows)

For each of the following proposed curved arrows, determine whether it is **valid** or **invalid**. If invalid, redraw the step correctly and explain the error using the arrow grammar rules from this chapter.

- An arrow that starts at a C^+ symbol and points to $:\text{OH}_2$.
- An arrow that starts at $:\text{NH}_3$ and points to a carbonyl carbon *without* a second arrow from $\text{C}=\text{O}$ to O .
- An arrow that starts at a C-LG σ bond and points to the carbon atom (rather than the leaving group atom).
- A proton transfer drawn with only one arrow: $:\text{B} \rightarrow \text{H}$ but no arrow from H-A to A .

For each case, provide the corrected arrow(s) and the resulting product structure(s) as valid Lewis structures.

5.6.4 Problem 4: Reaction Coordinate Diagram Interpretation (Two-Step Profile)

A reaction proceeds in two elementary steps with one intermediate. You are given the following free energies (arbitrary units) relative to reactants:

$$G(\text{reactants}) = 0, \quad G(\text{TS}_1) = +18, \quad G(\text{intermediate}) = +10, \quad G(\text{TS}_2) = +26, \quad G(\text{products}) = -8$$

- Sketch a reaction coordinate diagram labeling reactants, products, TS_1 , the intermediate, and TS_2 .

- Calculate $\Delta G_1^\ddagger$ and $\Delta G_2^\ddagger$ (relative to the preceding minimum in each step).
- Identify the **rate-determining step** and justify your answer.
- Calculate $\Delta G_{\text{overall}}$ and state whether the overall reaction is thermodynamically favorable.
- Based on the diagram, is the intermediate more likely to be “long-lived” or “short-lived”? Explain qualitatively using energy differences (no kinetics equations required).

5.6.5 Problem 5: Kinetic vs. Thermodynamic Control (Competing Products)

A reaction of a conjugated diene with HBr can give two products, $P_{1,2}$ and $P_{1,4}$. Under one set of conditions, $P_{1,2}$ dominates; under another, $P_{1,4}$ dominates. You are given these qualitative facts:

- $P_{1,4}$ is **more stable** than $P_{1,2}$ (lower G).
- Formation of $P_{1,2}$ has a **lower** $\Delta G^\ddagger$ than formation of $P_{1,4}$ from the common intermediate.
- Draw a schematic (qualitative) reaction coordinate diagram that shows a common intermediate leading to two different products with different $\Delta G^\ddagger$ and different product free energies.
- State which product is the **kinetic product** and which is the **thermodynamic product**, and explain in one or two sentences using the terms $\Delta G^\ddagger$ and ΔG .
- Predict which product is favored at **low temperature/short time** and which at **higher temperature/long time**, assuming reversibility is possible.
- Explain what experimental observation would convince you the reaction is under thermodynamic control (hint: time dependence, reversibility, or equilibrium).

5.6.6 Problem 6: Ranking Nucleophiles (Solvent-Dependent Trends)

Rank the nucleophiles in each set from **strongest** to **weakest nucleophile** under the stated solvent conditions. Provide a brief justification for each ranking that explicitly

mentions at least two of: charge, electronegativity, polarizability, solvation, and steric hindrance.

- In a **polar protic** solvent (e.g., methanol): F^- , Cl^- , Br^- , I^- .
- In a **polar aprotic** solvent (e.g., DMSO): F^- , Cl^- , Br^- , I^- .
- In a **polar aprotic** solvent: HO^- , CH_3O^- , $(\text{CH}_3)_3\text{CO}^-$, HS^- .
- In water: NH_3 , CH_3NH_2 , $(\text{CH}_3)_2\text{NH}$, $(\text{CH}_3)_3\text{N}$ (consider both electronic donation and steric access).

5.6.7 Problem 7: Leaving Group Ability and Conjugate Base Stability

For each pair, circle the **better leaving group** in a typical polar reaction (assume neutral or mildly acidic conditions unless otherwise stated). Then justify by comparing the **stability of the anion** (conjugate base) using at least one of: basicity, resonance, electronegativity, or polarizability.

- Cl^- vs. HO^-
- TsO^- (tosylate) vs. CH_3O^-
- Br^- vs. F^-
- H_2O vs. HO^- (explicitly state what prior activation step makes H_2O relevant as a leaving group)

Finally, explain why $-\text{OH}$ is often a poor leaving group in substitution and how acid can “turn it into” a good leaving group.

5.6.8 Problem 8: Carbocation Rearrangements (Hydride and Alkyl Shifts)

For each substrate below, assume conditions that allow carbocation formation (e.g., strong acid, good leaving group). Draw the carbocation that forms initially, then determine whether a rearrangement is expected. If so, show the rearrangement with curved arrows and draw the **rearranged carbocation** (the new intermediate).

- $(\text{CH}_3)_2\text{CH}-\text{CH}_2-\text{LG}$ where leaving group departure gives a primary carbocation adjacent to a secondary carbon.

- A cyclobutylmethyl system: (cyclobutyl)-CH₂-LG forming a carbocation adjacent to a strained ring.
- CH₃-CH(CH₃)-CH(LG)-CH₃ (identify whether hydride or methyl shift gives the more substituted carbocation).
- A benzylic system: Ph-CH₂-CH₂-LG (determine whether rearrangement can generate a benzylic carbocation and show how).

For each case, state the **stability argument** (substitution, resonance, strain relief) that drives or disfavors rearrangement.

5.6.9 Problem 9: Hammond Postulate and Transition-State Character

For each elementary step below, decide whether the transition state is expected to be **early** or **late**, and justify using the Hammond postulate by stating whether the step is likely **exothermic** or **endothermic**.

- Ionization step: $R-LG \rightarrow R^+ + LG^-$ for a substrate that forms a relatively unstable carbocation.
- Nucleophilic capture: $R^+ + Nu^- \rightarrow R-Nu$ where the nucleophile is strong and the carbocation is highly electrophilic.
- Radical hydrogen abstraction: $R-H + X\cdot \rightarrow R\cdot + H-X$ in a case where forming $R\cdot$ is energetically uphill.
- Proton transfer: $B: + H-A \rightarrow BH^+ + A^-$ where $H-A$ is a strong acid.

Then, for each case, state whether **stabilizing the product of the step** (carbocation, radical, conjugate base) would be expected to significantly lower $\Delta G^\ddagger$, and explain why.

5.6.10 Problem 10: Cumulative Mechanism and Product Prediction (Stability + Kinetics)

A secondary alkyl substrate $R-CH(LG)-CH_3$ is treated under conditions where both substitution and elimination are plausible. The reagent set is:



- Identify the likely major reaction class (S_N2 , S_N1 , E2, or E1) based on nucleophile/base strength, solvent type, and temperature. Justify succinctly.
- Propose a complete curved-arrow mechanism for the major pathway, including the key bond-making and bond-breaking event(s) in the rate-determining step.
- Predict the major product(s). If an alkene forms, indicate whether the more substituted (Zaitsev) or less substituted (Hofmann) alkene is expected to dominate, and justify using stability and steric arguments.
- If a carbocation pathway seems plausible as a minor pathway, state whether rearrangement could occur and what structural feature would be required for it to matter.

Chapter 6

Nucleophilic Substitution and Elimination

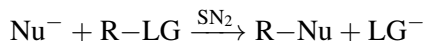
Every alkyl halide faces a chemical crossroads: to accept a new partner via substitution or to shed a proton and form a double bond via elimination. This chapter provides the rigorous theoretical framework required to navigate this choice. By dissecting the precise alignment of molecular orbitals, the stability of transient carbocation intermediates, and the subtle influence of solvent shells, we establish the rules that dictate whether a reaction proceeds through a concerted collision or a stepwise ionization. Mastery of these four pathways-SN1, SN2, E1, and E2-is fundamental to controlling the architecture of organic molecules.

6.1 Concerted Nucleophilic Substitution: The SN2 Mechanism

Nucleophilic substitution reactions convert one functional group into another by replacing a leaving group (LG) with a nucleophile (Nu⁻). In earlier discussions of polar reactivity, two foundational ideas were emphasized: (1) electron-rich sites (nucleophiles) donate electron density to electron-poor sites (electrophiles), and (2) the identity of the leaving group and the surrounding environment strongly influence feasibility and rate. The SN2 mechanism (substitution nucleophilic, bimolecular) is the paradigmatic case where these ideas combine into a single, stereochemically decisive elementary step.

6.1.1 Defining Features of SN2: A One-Step Substitution

An SN2 reaction proceeds through a **single concerted** elementary step in which bond formation to the nucleophile and bond cleavage to the leaving group occur simultaneously. A typical transformation can be written as:



where R–LG is an alkyl substrate bearing a leaving group.

Two features are immediately diagnostic:

Bimolecular kinetics. The rate depends on the concentration of both reactants:

$$\text{rate} = k[\text{Nu}][\text{R-LG}]$$

This empirical rate law is not merely a mathematical relation; it is mechanistic evidence that both nucleophile and substrate participate in the rate-determining event. In SN2, the single step is necessarily the rate-determining step, so the transition state must contain both species.

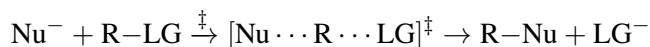
Concerted bond changes. In a concerted step, there is no discrete carbocation intermediate. The carbon center is never “free” to rearrange via hydride or alkyl shifts, and stereochemical information at the reacting carbon is transferred directly into the product in a predictable way (see the stereochemistry subsection).

6.1.2 Reaction Coordinate Picture and the SN2 Transition State

Although SN2 has only one step, it still passes through a high-energy configuration: the **transition state**. Conceptually, one can imagine a reaction coordinate that tracks two coupled changes:

- the C–Nu bond order increases from 0 to 1;
- the C–LG bond order decreases from 1 to 0.

At the transition state, both bonds are **partially formed/partially broken**. This is often depicted as:



The symbol $\ddagger$ emphasizes that this bracketed structure is not a stable intermediate; it cannot be isolated, and the reaction passes through it transiently.

Geometry at the transition state: a “trigonal bipyramidal-like” arrangement.

For a typical SN2 at an sp^3 carbon, the reacting center begins as tetrahedral. In the transition state, the nucleophile approaches along a specific axis, and the leaving group departs along the opposite axis. The result is often described as having *approximate* trigonal-bipyramidal character: the nucleophile and leaving group occupy the axial positions, while the three substituents on carbon occupy an equatorial plane. This should be understood as a geometric analogy rather than a claim that carbon becomes truly pentacoordinate in a stable sense. The defining point is that the nucleophile and leaving group are **collinear** with the carbon center at the highest-energy point.

6.1.3 Why Backside Attack Is Required: Stereoelectronic Control

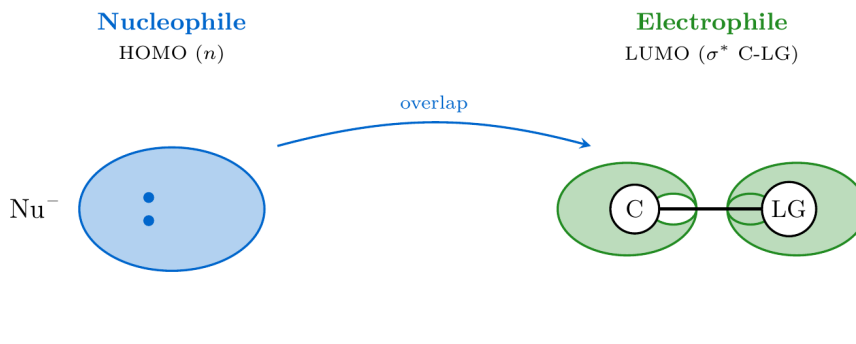
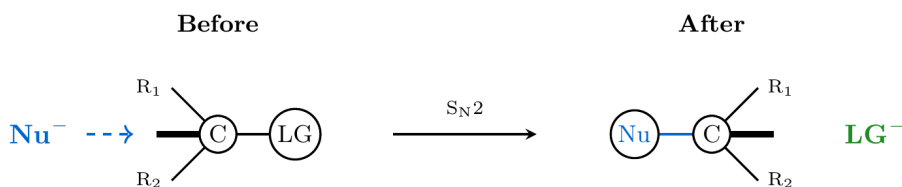
A striking and highly predictive feature of SN2 is that nucleophiles do not approach from any arbitrary direction. Instead, efficient substitution requires **backside attack**: the nucleophile approaches the electrophilic carbon from the side opposite the leaving group.

Orbital-level reason: overlap with the σ^* orbital. The C–LG bond has a bonding orbital (σ) and an antibonding orbital (σ^*). In a substitution, electron density from the nucleophile must be donated into an orbital that can accommodate it while simultaneously weakening the C–LG bond. The appropriate acceptor is the antibonding $\sigma^*(\text{C–LG})$ orbital.

Crucially, the σ^* orbital has a lobe on the carbon that is **largest and correctly phased on the backside** (opposite the leaving group). A frontside approach gives poor overlap (and strong repulsion with electron density in the C–LG bonding region), leading to a much higher activation barrier. Thus, backside attack is not a stylistic arrow-pushing convention; it is an orbital symmetry and overlap requirement.

Trajectory: alignment with the C–LG bond axis. The nucleophile approaches approximately 180° from the leaving group, maximizing overlap between:

- the nucleophile’s highest occupied molecular orbital (HOMO), typically a lone pair or a π -type electron pair; and
- the substrate’s lowest unoccupied molecular orbital (LUMO), which in this context is largely $\sigma^*(\text{C–LG})$.

Backside Attack: HOMO – LUMO Overlap**Stereochemical Consequence: Walden Inversion****6.1.4 Stereochemistry: Walden Inversion at a Stereogenic Center**

Because backside attack is required, S_N2 substitution at a stereogenic carbon occurs with **inversion of configuration** (Walden inversion). The simplest way to visualize this is to imagine an “umbrella flip”: as the nucleophile forms a bond from the backside, the three substituents on carbon reorganize to the opposite orientation relative to the incoming group.

What inverts, exactly? If the reacting carbon is stereogenic, its **absolute configuration** (R/S) may invert, but whether the label changes from R to S depends on the CIP priorities before and after substitution. The mechanistic guarantee is not “R becomes S”; it is that the tetrahedral arrangement undergoes inversion relative to the leaving group and incoming nucleophile.

Stereospecificity. S_N2 is **stereospecific**: a single reactant stereoisomer leads (ideally) to a single product stereoisomer, because the geometry of approach is con-

strained. This is in contrast to mechanisms that pass through planar intermediates, where multiple approach trajectories can erase stereochemical information.

6.1.5 Kinetics and the Transition State: Connecting Rate Law to Structure

The bimolecular rate law implies that the transition state contains both nucleophile and substrate. Transition state theory provides a useful conceptual link: the activation free energy $\Delta G^\ddagger$ depends on how difficult it is to bring the reactants into the specific geometry required for productive overlap (alignment along the Nu–C–LG axis) while accommodating charge redistribution.

Charge development in the transition state. In many SN2 reactions, electron density flows from nucleophile toward the carbon center and onward toward the leaving group. Consequently:

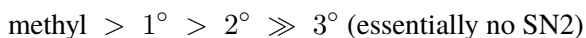
- the nucleophile becomes less negative (partial loss of electron density);
- the leaving group becomes more negative (partial gain of electron density);
- the carbon is simultaneously being bonded to two groups (partial “pentacoordinate” character).

How well the environment stabilizes this developing charge separation affects $\Delta G^\ddagger$ and thus the rate.

6.1.6 Steric Governance: Why Crowding Slows SN2

The SN2 transition state requires close approach of the nucleophile to the carbon center along the backside trajectory. Any substituents that block this path or raise repulsive interactions increase the activation barrier.

Substrate structure: methyl > primary > secondary $\gg$ tertiary. A central organizing principle is that SN2 rate decreases sharply as substitution at the reacting carbon increases:



This trend is best understood in terms of the transition state geometry:

- In methyl and primary substrates, the nucleophile can access the backside with minimal steric clash, allowing efficient HOMO–LUMO overlap.

- In secondary substrates, substituents partially block the approach and increase nonbonded repulsions in the crowded transition state, slowing the reaction.
- In tertiary substrates, the backside is sterically shielded; the required transition state becomes too high in energy for SN2 to compete effectively. Under many conditions, tertiary substrates react by pathways that do not require backside access (e.g., ionization followed by capture, or elimination under basic conditions).

Steric effects are amplified in the transition state. Steric crowding matters more in SN2 than one might predict from the reactants alone because the transition state forces multiple groups into closer proximity. In other words, substitution may not greatly destabilize the starting material, but it can disproportionately destabilize the transition state, thereby reducing rate.

Neopentyl effect (steric hindrance next to the reaction center). Steric blockage is not only determined by substitution at the reacting carbon (the α -carbon). Bulky substitution at the adjacent β -carbon can also dramatically slow SN2, even for formally primary substrates (e.g., neopentyl systems). The nucleophile must thread through the substituent environment to reach the backside, and β -branching narrows that approach corridor.

6.1.7 Nucleophile Strength Versus Base Strength: A Practical Distinction

Because SN2 rate depends directly on nucleophile concentration and identity, stronger nucleophiles generally react faster. However, “nucleophile strength” is not identical to “base strength.”

Why the distinction matters here. In substitution and elimination chemistry, a reagent may act as:

- a nucleophile (attacking carbon), promoting substitution; and/or
- a base (removing H^+), promoting elimination.

SN2 requires a nucleophile that can approach and donate electron density effectively to carbon. Highly basic, bulky reagents may be **poor** SN2 nucleophiles because steric hindrance prevents close approach, even if they are strong bases thermodynamically.

Sterically hindered nucleophiles. Bulky anions (conceptually: large, crowded electron donors) often show reduced SN2 rates because the transition state demands close-range orbital overlap. This steric limitation can redirect reactivity toward elimination pathways that require less direct access to the carbon center.

6.1.8 Leaving Group Ability: Lowering the Barrier by Stabilizing Departure

SN2 requires simultaneous bond breaking to the leaving group. Better leaving groups stabilize the negative charge they acquire upon departure and require less energy to cleave from carbon.

Leaving group ability is tied to anion stability. A good leaving group is typically the conjugate base of a strong acid (thus a weak base). When LG^- is stable, the transition state is stabilized because negative charge developing on the leaving group is less energetically costly. Conversely, strongly basic anions are generally poor leaving groups.

Mechanical consequence in SN2. Improving leaving group ability selectively lowers the activation energy for the concerted step by facilitating C–LG bond cleavage at the transition state, thereby increasing the rate constant k in the bimolecular rate law.

6.1.9 Solvent Effects: Protic Versus Aprotic Environments

Even though the elementary step is concerted, the surrounding medium can strongly influence SN2 rates by altering nucleophile reactivity and transition state stabilization.

Polar protic solvents slow many SN2 reactions. In polar protic solvents (those capable of hydrogen bonding), anionic nucleophiles are often strongly solvated. Solvation cages the nucleophile and lowers its effective reactivity by stabilizing it in the ground state. The nucleophile must shed some of this solvation to approach carbon closely, which increases $\Delta G^\ddagger$.

Polar aprotic solvents often accelerate SN2 reactions. Polar aprotic solvents can stabilize ions through dipole interactions without strongly hydrogen-bonding to anionic nucleophiles. This frequently leaves the nucleophile “freer” (less hindered by a tight solvation shell) and more reactive in backside attack. The key idea is that SN2 rates are sensitive to any factor that changes the energetic cost of organizing reactants into the required transition state geometry.

6.1.10 Summary: The SN2 Logic in One Coherent Picture

SN2 is best understood as the intersection of kinetics, stereochemistry, and stereoelectronics:

- **Kinetics:** the bimolecular rate law reflects a single, concerted rate-determining event involving both nucleophile and substrate.
- **Stereoelectronics:** productive reaction demands backside attack because the nucleophile HOMO must overlap with the substrate LUMO, $\sigma^*(\text{C-LG})$.
- **Stereochemistry:** backside attack enforces **Walden inversion**, making SN2 stereospecific.
- **Steric governance:** increasing substitution at (or near) the reacting carbon destabilizes the crowded transition state and can shut down SN2 entirely for tertiary centers.
- **Reactivity control:** better leaving groups and solvents that do not over-stabilize the nucleophile generally increase SN2 rates.

These principles will serve as essential reference points when we compare SN2 to stepwise substitution pathways and when we analyze substitution–elimination competition under varied conditions.

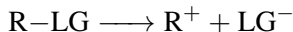
6.2 Stepwise Substitution and Carbocation Intermediates: The SN1 Mechanism

The SN2 mechanism established a key theme: substitution can be governed by strict stereoelectronic demands (backside attack into $\sigma^*(\text{C-LG})$) and by steric congestion at the reaction center. Those same factors that **disfavor** SN2—especially heavy substitution at the reacting carbon—often **favor** an alternative pathway: the SN1 mechanism (substitution nucleophilic, unimolecular). In SN1 chemistry, substitution occurs by a stepwise sequence in which the leaving group departs first to generate a carbocation intermediate, and only then does the nucleophile form the new bond.

6.2.1 Mechanistic Definition: Two Steps and a Carbocation Intermediate

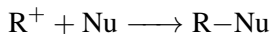
An SN1 reaction proceeds through two elementary steps (often followed by a rapid proton transfer if the nucleophile is neutral).

Step 1 (ionization, rate-determining): leaving group departure.

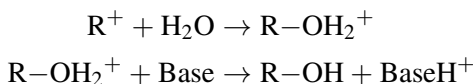


This step creates a carbocation (R^+). Because it involves bond cleavage and charge separation, it is typically the highest barrier step and therefore controls the overall rate.

Step 2 (capture): nucleophilic attack on the carbocation.



Common Step 3 (if Nu is neutral): deprotonation. If the nucleophile is a neutral molecule such as water or an alcohol, attack produces an oxonium intermediate that must be deprotonated:



Here “Base” is often the solvent itself or the leaving group anion.

6.2.2 Unimolecular Kinetics: Why the Rate Depends Only on the Substrate

The defining kinetic signature of SN1 is that the rate depends on the concentration of the substrate but not on the nucleophile:

$$\text{rate} = k[\text{R-LG}]$$

This follows directly from the mechanism: the slow step is ionization of R-LG . Nucleophile involvement occurs only after the rate-determining step has already produced the carbocation. Consequently, changes in nucleophile concentration typically have little effect on the observed rate (although nucleophile identity can influence product distributions through competition with solvent, and it can influence side reactions such as elimination).

6.2.3 Energy Landscape and the Meaning of “Stepwise”

Because $\text{S}_{\text{N}}1$ has an intermediate, its reaction coordinate contains (at minimum) two transition states separated by a local minimum corresponding to the carbocation:

- **First barrier:** forming R^+ and LG^- (ionization).
- **Intermediate well:** the carbocation (and associated ion pair/solvent cage).
- **Second barrier:** nucleophile capture (usually smaller than the first).

This energy profile has two crucial implications:

- Any factor that stabilizes the carbocation (or the developing charge separation in the first transition state) accelerates $\text{S}_{\text{N}}1$ by lowering $\Delta G^\ddagger$ for ionization.
- Because a discrete carbocation exists, rearrangements and competition with elimination become possible—features largely absent from $\text{S}_{\text{N}}2$.

6.2.4 Carbocation Structure: Planarity, Empty p Orbital, and High Reactivity

A classical carbocation at the reacting carbon is typically **sp^2 -hybridized** and approximately trigonal planar, with an empty p orbital perpendicular to the plane of the three substituents. Two consequences follow:

Electrophilicity. The empty p orbital can accept electron density from a nucleophile. Carbocations are therefore strong electrophiles.

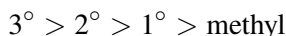
Stereochemical vulnerability. Because the cationic center is planar (or nearly planar), nucleophiles can approach from either face. This is the origin of the characteristic $\text{S}_{\text{N}}1$ stereochemical outcome discussed below.

6.2.5 Carbocation Stability: The Central Driving Force for $\text{S}_{\text{N}}1$

$\text{S}_{\text{N}}1$ reactions are favored when the substrate can form a sufficiently stable carbocation. The stability of R^+ is a thermodynamic concept, but it correlates strongly with the activation barrier for ionization because the first transition state resembles the separated ions to a significant extent (a Hammond-postulate-type relationship is often a helpful qualitative guide here: when ionization is endergonic, the transition state tends to be “product-like,” so stabilizing the carbocation stabilizes the transition state as well).

Inductive and Hyperconjugative Stabilization

For simple alkyl carbocations, stability generally increases with substitution:



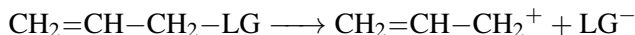
Inductive donation. Alkyl groups can donate electron density through σ -bond polarization, slightly stabilizing positive charge.

Hyperconjugation (dominant in many cases). Hyperconjugation is the delocalization of electron density from adjacent C–H or C–C σ bonds into the empty p orbital. More substituted carbocations have more adjacent σ bonds capable of donating electron density, providing greater stabilization.

Resonance Stabilization: Allylic and Benzylic Carbocations

Carbocations adjacent to π systems can delocalize the positive charge by resonance, often making them dramatically more stable than simple alkyl carbocations. Two common cases are:

Allylic carbocations.



The positive charge can be delocalized over the allylic framework.

Benzylic carbocations. Benzylic cations are stabilized by delocalization into the aromatic ring. This stabilization can strongly favor SN1 even when the carbon is only secondary by substitution count.

Why Primary Substrates Rarely Undergo SN1

Primary carbocations (RCH_2^+) are typically too unstable to form under ordinary conditions, so primary alkyl halides and sulfonates usually react by SN2 (if substitution occurs at all) rather than SN1. Two major exceptions illustrate the rule:

- **Resonance-stabilized primary cations** (e.g., benzylic/allylic primary systems).
- **Rearrangement-prone systems** where ionization is followed rapidly by rearrangement to a more stable carbocation (though if the initial ionization itself is prohibitively high in energy, rearrangement cannot rescue the pathway).

6.2.6 Solvation Effects: Stabilizing Charge Separation in the Rate-Determining Step

The ionization step creates (or at least develops) separated charge. Solvent effects are therefore often decisive in SN1 reactivity.

Polar Protic Solvents Lower the Ionization Barrier

Polar protic solvents (e.g., alcohols, water, carboxylic acids) can stabilize ions through strong solvation and hydrogen bonding:

- The developing LG^- is stabilized by hydrogen bonding to solvent H atoms.
- The developing R^+ is stabilized by dipole interactions and, in many cases, specific solvation.

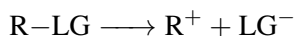
By stabilizing both ions (and the polar transition state leading to them), polar protic solvents lower $\Delta G^\ddagger$ for ionization and accelerate SN1.

Dielectric Constant Is Not the Whole Story

While high dielectric constant generally helps stabilize charge separation, SN1 rates depend not only on bulk polarity but also on the ability of the solvent to specifically solvate ions. Hydrogen bonding and strong ion–dipole interactions are particularly important for stabilizing LG^- and for reducing the energetic cost of generating an ion pair.

Ion Pairs and the Solvent Cage

The simplified equation



can conceal a real mechanistic subtlety: in many solvents, the departing leaving group does not instantly diffuse away. Instead, an **intimate ion pair** or **solvent-separated ion pair** may form, with LG^- lingering near R^+ within a solvent cage. This has two consequences:

- It can influence stereochemistry by partially blocking attack from one face.

- It can enable rapid recombination (return) that competes with nucleophile capture, effectively lowering the efficiency of substitution.

Thus, solvation is not merely “stabilizing”; it shapes the microenvironment in which the carbocation exists and reacts.

6.2.7 Stereochemistry of SN1: Racemization and Its Common Deviations

SN1 reactions at a stereogenic center characteristically yield loss of stereochemical purity, often described as racemization. The mechanistic origin is the planar carbocation intermediate.

Planar intermediate $\Rightarrow$ two faces accessible. If R–LG is chiral at the reacting carbon, ionization produces a planar R^+ . The nucleophile can attack from either face, giving both enantiomeric products:



Why “complete racemization” is not guaranteed. In many real systems, product mixtures show partial racemization (an enantiomeric excess remains). The most common reasons are:

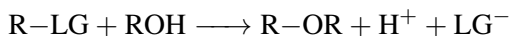
- **Ion pairing:** the leaving group anion remains closer to one face of the carbocation, hindering nucleophilic approach from that side and biasing attack.
- **Solvent cage effects:** restricted diffusion and oriented solvation can make one trajectory more accessible than the other.
- **Neighboring group participation (when present):** adjacent groups can form bridged intermediates that enforce stereochemical outcomes (a more advanced case that should be recognized as a deviation from the simplest SN1 picture).

The key takeaway is that SN1 erodes stereochemical information because the reaction passes through an intermediate with reduced geometric constraint, but the extent of stereochemical scrambling reports on how “free” the carbocation is in its solvated environment.

6.2.8 Nucleophile Identity: Weak Nucleophiles and Solvolysis

Because the nucleophile does not participate in the rate-determining step, SN1 reactions can occur with nucleophiles that would be too weak (or too heavily solvated)

to be effective in SN2. A common scenario is solvolysis, where the solvent acts as the nucleophile:



followed by proton transfer to give a neutral substitution product. In such reactions, changing the solvent changes the nucleophile and therefore changes the product identity, even if the overall rate is governed mainly by ionization.

6.2.9 Substrate and Leaving Group Requirements for SN1

SN1 is favored by substrates that can ionize and by leaving groups that depart readily.

Substrates

The most favorable substrates are those that form stable carbocations:

- **Tertiary alkyl substrates** (often fastest among simple alkyl systems).
- **Secondary substrates** (often viable under sufficiently ionizing conditions).
- **Benzylic and allylic substrates** (often exceptionally reactive due to resonance stabilization).

Methyl and most primary alkyl substrates generally do not undergo SN1 under typical conditions due to the instability of the corresponding carbocations.

Leaving groups

Leaving group ability remains crucial because ionization is the rate-determining step. Better leaving groups lower the barrier to C–LG bond cleavage and stabilize the departing anion. Poor leaving groups often prevent SN1 entirely unless they are activated (for example, by protonation in strongly acidic media to convert –OH into a better leaving group such as H₂O).

6.2.10 Competition and Side Processes: A Preview of What SN1 Enables

The formation of a carbocation intermediate means SN1 chemistry naturally competes with other pathways that also proceed via carbocations. Two outcomes are especially important:

- **E1 elimination:** deprotonation of the carbocation can form an alkene (discussed in detail in the elimination sections).
- **Rearrangements:** hydride or alkyl shifts can convert a less stable carbocation into a more stable one before nucleophile capture, changing the carbon skeleton of the product.

At this stage, the essential point is mechanistic: once a carbocation exists as an intermediate, multiple fates become accessible, and product analysis must consider these competing channels.

6.2.11 Summary: What Controls SN1 Reactivity and Outcomes

SN1 substitution is best summarized as substitution driven by **carbocation stability** and enabled by **solvation**:

- **Mechanism:** stepwise; ionization to a carbocation (rate-determining) followed by nucleophile capture (and often deprotonation).
- **Rate law:** $\text{rate} = k[\text{R-LG}]$, reflecting the unimolecular ionization step.
- **Substrate effect:** tertiary, resonance-stabilized (benzylic/allylic) substrates are most favorable; most primary substrates are unfavorable.
- **Solvent effect:** polar protic, strongly ionizing solvents accelerate SN1 by stabilizing charge separation and solvating LG^- and R^+ .
- **Stereochemistry:** planar carbocation intermediates lead to racemization or partial racemization, modulated by ion pairing and solvent cage effects.

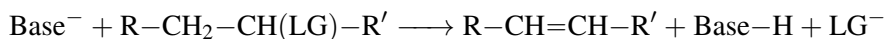
6.3 Concerted Elimination: Stereoelectronics of the E2 Reaction

The substitution mechanisms SN2 and SN1 highlight two complementary ideas: (1) concerted reactions impose strict geometric (stereoelectronic) demands and produce predictable stereochemical outcomes, and (2) stepwise reactions are governed by intermediate stability and solvation. Elimination reactions add a further dimension: a base can remove a β -proton while a leaving group departs, generating a π bond. In the *E2* mechanism (elimination, bimolecular), these events occur in a *single concerted step*, making E2 the elimination analogue of SN2. As with SN2, the transition

state geometry is not optional; it determines whether the reaction is fast, whether it occurs at all, and which alkene is formed.

6.3.1 Defining the E2 Mechanism: One Step, Two Bonds Broken, One π Bond Formed

A general E2 transformation can be represented as:



Here the base abstracts a β -hydrogen (a hydrogen on the carbon adjacent to the carbon bearing the leaving group), while the leaving group departs from the α -carbon. The product is an alkene formed between the α - and β -carbons.

Bimolecular kinetics. E2 reactions exhibit the characteristic second-order rate law:

$$\text{rate} = k[\text{Base}][\text{R}-\text{LG}]$$

Mechanistically, this indicates that both the base and the substrate participate directly in the rate-determining event—the single concerted transition state.

No carbocation intermediate. Because E2 is concerted, it avoids discrete carbocations (and thus avoids classical rearrangements). This distinguishes E2 from E1 and explains why E2 often dominates under strongly basic conditions even when ionization would be possible.

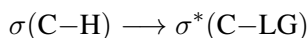
6.3.2 Stereoelectronic Requirement: Anti-Periplanar Geometry

The E2 mechanism is governed by a stringent stereoelectronic rule:

For a fast E2, the breaking C–H bond and the breaking C–LG bond must be anti-periplanar.

Orbital Basis: $\sigma(\text{C}-\text{H}) \rightarrow \sigma^*(\text{C}-\text{LG})$ **Donation**

The base removes H^+ , but at the electron-flow level, the key event is donation of electron density from the C–H σ bond into the C–LG antibonding orbital:



This interaction weakens the C–LG bond and simultaneously organizes electron density so that, as LG^- leaves, the remaining electron density becomes the new $\pi(\text{C}=\text{C})$ bond.

Why anti-periplanar? Maximum overlap between a donor orbital and an acceptor orbital occurs when the orbitals are properly aligned in space and phase. In an E2 transition state, the donor is the C–H σ bond orbital, and the acceptor is $\sigma^*(\text{C}–\text{LG})$ on the adjacent carbon. The anti-periplanar arrangement places these orbitals in the same plane and aligned in opposite directions (dihedral angle near 180°), producing the strongest stabilizing interaction and the lowest activation energy.

Syn-periplanar is possible but disfavored. A syn-periplanar arrangement (dihedral angle near 0°) can, in principle, also align orbitals, but it typically suffers from greater steric and torsional strain and poorer overall transition-state stabilization. In acyclic systems, free rotation generally allows adoption of the anti conformer, so anti elimination dominates.

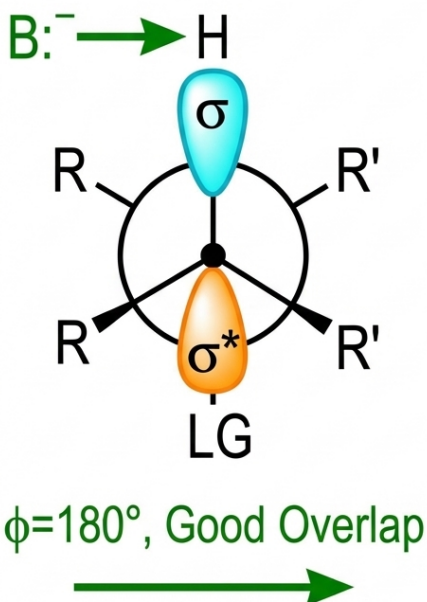
Newman Projections as the Working Tool

Because anti-periplanar geometry is defined by a dihedral angle, the most direct way to analyze E2 is to look down the forming alkene bond (the $\text{C}_\beta\text{--}\text{C}_\alpha$ bond) using a Newman projection:

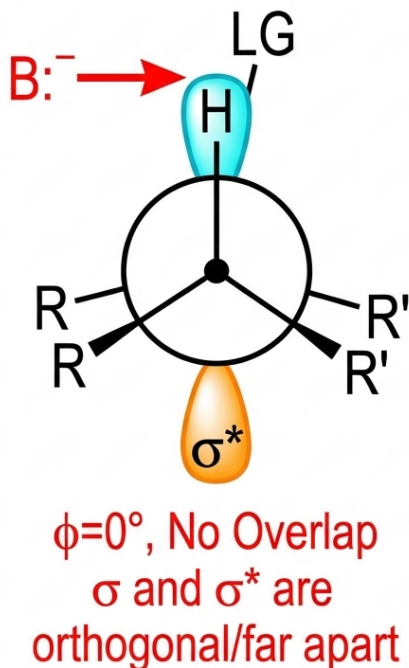
- The **front carbon** is usually taken as C_β (bearing the H to be removed).
- The **back carbon** is C_α (bearing the leaving group).

Then one checks whether a $\text{C}_\beta\text{--H}$ bond can be arranged anti to the $\text{C}_\alpha\text{--LG}$ bond. If yes, that conformer is the one that reacts fastest and largely determines the alkene stereochemistry.

Anti-periplanar (Fast E2)



Syn-periplanar (Disfavored)



6.3.3 Stereochemical Consequences: Conformation Controls Alkene Geometry

Because E2 is stereoelectronically constrained, *conformation determines configuration*. The alkene geometry (E vs. Z) that forms is often dictated by which anti-periplanar conformer is accessible and reacts fastest.

Acyclic Systems: Rotational Access to Anti Conformers

In open-chain substrates, rotation about the $C_{\beta}-C_{\alpha}$ bond usually allows the molecule to adopt an anti-periplanar arrangement. When multiple β -hydrogens exist, each can be anti to the leaving group in a different conformer. The major product commonly arises from the conformer that is both:

- accessible (low in energy), and
- aligned for a fast E2 (anti-periplanar C–H and C–LG bonds).

Cyclohexanes: The Trans-Diaxial Requirement

In cyclohexane systems, the anti-periplanar condition translates into a particularly important rule:

In a cyclohexane chair, E2 requires a trans-diaxial arrangement of the leaving group and the β -H.

This occurs because an axial C–LG bond can be anti to an axial C–H bond on the adjacent carbon. If the leaving group is equatorial, the necessary anti alignment is not available, and elimination is slow or impossible until a ring flip places the leaving group axial. Thus, conformational equilibria can gate E2 reactivity, sometimes overriding simple substitution-count arguments.

6.3.4 Regioselectivity: Zaitsev vs. Hofmann Products

Many substrates have more than one distinct β -carbon, so elimination can form different alkenes (regioisomers). E2 regioselectivity reflects the interplay of alkene stability and transition state accessibility.

Zaitsev's Rule: Preference for the More Substituted Alkene

Often, the major E2 product is the more substituted (more thermodynamically stable) alkene:

Zaitsev product: more substituted alkene (typically more stable)

This trend is rationalized by the greater stability of more substituted double bonds, commonly attributed to hyperconjugation and alkyl substitution stabilizing the π system.

When Hofmann Products Dominate: Steric and Stereoelectronic Control

In some situations, E2 gives the less substituted alkene (the *Hofmann product*):

Hofmann product: less substituted alkene (often favored by bulky base)

A particularly common cause is a **bulky base** (e.g., tert-alkoxide-type bases), which abstracts the most accessible β -hydrogen fastest. Even if the resulting alkene is less substituted, its formation can be kinetically favored because the transition state involves close approach of the base to the C–H bond. Steric congestion near the more substituted β site can therefore redirect deprotonation to a less hindered site.

A Practical View: E2 Selectivity is Transition-State Selectivity

For E2, it is useful to phrase regioselectivity as a competition between transition states:

- One transition state leads to the Zaitsev alkene: often lower in energy due to product stability and favorable electronic effects, but sometimes sterically hindered.
- Another transition state leads to the Hofmann alkene: often higher in product stability, but sometimes lower in activation energy when the corresponding β -H is more accessible (or when only that β -H can achieve the required anti-periplanar alignment).

Thus, predicting the major product requires checking both *which β -hydrogens exist* and *which of them can be anti to the leaving group in a reasonably populated conformer*.

6.3.5 E2 Versus SN2: Shared Bimolecularity, Different Geometric Demands

E2 and SN2 share important features:

- both are concerted,

- both are bimolecular in their rate laws,
- both are sensitive to steric congestion.

However, their geometric requirements differ:

- **SN2** requires backside attack at the electrophilic carbon along the C–LG axis.
- **E2** requires anti-periplanar alignment of C–H and C–LG bonds across the C_β – C_α bond.

This distinction is crucial in constrained systems: a substrate may be sterically accessible for substitution but conformationally locked against anti elimination, or vice versa.

6.3.6 Summary: The E2 “Checklist” for Prediction

E2 elimination is best predicted by systematically applying three questions:

- **Is a strong base present?** (E2 is promoted by strong bases and is bimolecular in base and substrate.)
- **Can the substrate adopt an anti-periplanar H_β and LG arrangement?** (Use Newman projections for acyclic systems; use the trans-diaxial rule for cyclohexanes.)
- **Which β -hydrogen abstraction pathway has the lower barrier?** (Balance Zaitsev alkene stability against steric accessibility and conformational availability; bulky bases often shift outcomes toward Hofmann products.)

With these principles, E2 becomes a strongly rule-governed reaction class: the product is not determined solely by “what alkene is most stable,” but by which specific C–H and C–LG bonds can be aligned to satisfy the stereoelectronic demands of the concerted transition state.

6.4 Stepwise Elimination: The E1 Mechanism and Competition

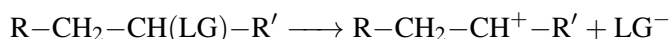
The SN1 mechanism introduced the central idea that ionization of a substrate to a carbocation can become the rate-determining step when the carbocation is sufficiently stabilized and the solvent is sufficiently ionizing. The E2 mechanism, in

contrast, showed that elimination can also occur by a concerted pathway that is strongly constrained by anti-periplanar geometry and promoted by strong bases. The **E1** mechanism (elimination, unimolecular) is the elimination analogue of SN1: it is **stepwise**, proceeds through a **carbocation intermediate**, and is therefore controlled by the same variables that govern SN1 ionization. Because SN1 and E1 share a common intermediate, they are inherently competitive pathways.

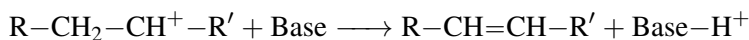
6.4.1 Mechanistic Definition: Ionization Followed by Deprotonation

A prototypical E1 reaction converts an alkyl substrate into an alkene by loss of LG^- and H^+ (or, more precisely, loss of the elements of H-LG). In its simplest form, E1 proceeds in two steps.

Step 1 (ionization, rate-determining): leaving group departure.



Step 2 (deprotonation): base removes a β -hydrogen to form the alkene.



In many E1 reactions, the “base” is the solvent (e.g., H_2O or ROH) or the leaving group anion itself. The deprotonation step is commonly fast relative to ionization.

6.4.2 Unimolecular Kinetics: Why E1 and SN1 Share the Same Rate Law

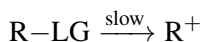
Because the slow step is ionization, E1 exhibits first-order kinetics in substrate:

$$\text{rate} = k[\text{R-LG}]$$

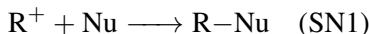
This is the same form as for SN1. In practice, observing a first-order rate law does not by itself distinguish SN1 from E1; it indicates that **ionization is rate-determining**, after which the carbocation can be intercepted either by nucleophilic attack (SN1) or by deprotonation (E1).

6.4.3 Energy Landscape: A Carbocation Branch Point

E1 and SN1 can be understood as diverging from a shared intermediate:



After the carbocation forms, two broad classes of fast events compete:



Thus, the product ratio is determined largely by the competition **after** the rate-determining step. This has an important practical implication: conditions can leave the overall rate nearly unchanged (still governed by ionization) while shifting the product distribution between substitution and elimination.

6.4.4 Substrate Requirements and Carbocation Stability: E1 Favors the Same Substrates as SN1

E1 is favored when formation of a carbocation is feasible. Therefore, the same stability arguments used for SN1 apply directly:

- **Tertiary substrates** readily form relatively stable tertiary carbocations and are common E1/SN1 candidates.
- **Secondary substrates** may undergo E1/SN1 under strongly ionizing conditions.
- **Primary substrates** rarely undergo E1 because primary carbocations are too unstable, except in resonance-stabilized systems (allylic/benzylic) or in special rearrangement contexts.

Leaving group ability remains crucial because it directly affects the ionization barrier.

6.4.5 Solvent and Base Strength: Why E1 Occurs Under “Weak Base” Conditions

A recurring pattern in laboratory and biological settings is that E1 is observed under conditions that are **not strongly basic**.

Ionization is the gating step. E1 requires ionization to R^+ . Strongly basic conditions are not necessary to form R^+ ; in fact, strongly basic reagents often promote E2 instead, because they can abstract a β -hydrogen in a single concerted step before ionization becomes competitive.

Polar protic solvents promote E1 by stabilizing ions. As with SN1, polar protic solvents stabilize both the developing carbocation and the leaving group anion (through ion–dipole interactions and hydrogen bonding), lowering $\Delta G^\ddagger$ for ionization and increasing the rate of carbocation formation. Once the carbocation forms, even a weak base such as solvent can remove a β -hydrogen.

Practical consequence: solvolysis conditions commonly yield mixtures. In ionizing, nucleophilic solvents such as H₂O or ROH, the same medium that stabilizes R⁺ can also act as:

- a nucleophile (favoring SN1 substitution), and
- a base (favoring E1 elimination).

This dual role makes E1 and SN1 difficult to separate cleanly without changing temperature, substrate structure, or solvent nucleophilicity/basicity.

6.4.6 Temperature and the Substitution–Elimination Competition

One of the most reliable levers for shifting an SN1/E1 mixture is temperature.

Why elimination tends to increase at higher temperature. The free energy barrier is $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$. While detailed entropy changes depend on the system, elimination often becomes relatively more favorable at higher temperature because:

- the formation of an alkene plus conjugate acid can be entropically favorable compared with a more tightly solvated substitution product in some media, and
- elimination products can be thermodynamically more stable in the presence of heat (particularly when conjugated or more substituted alkenes form).

Empirically, for many substrates under solvolysis-type conditions, raising temperature increases the fraction of elimination relative to substitution.

A useful working heuristic.

Higher temperature often shifts SN1/E1 mixtures toward E1.

This is not an absolute rule, but it is a strong trend in many common systems and is frequently used in synthetic planning.

6.4.7 Regioselectivity in E1: Zaitsev Products and Thermodynamic Control

Because E1 proceeds through a carbocation, it is not constrained by the anti-periplanar geometry requirement that governs E2. This difference has consequences for which alkene forms.

E1 often gives the more substituted (Zaitsev) alkene. Once the carbocation forms, deprotonation can occur at any adjacent β position that leads to an alkene. The major product is commonly the more substituted alkene because it is thermodynamically more stable:

E1 major product $\approx$ Zaitsev alkene (more substituted)

Why “thermodynamic control” is a reasonable approximation. In many E1 reactions, the deprotonation step is fast and reversible proton transfers may occur in the reaction medium. Combined with the fact that alkene stability differences can be significant, this often biases the outcome toward the most stable alkene. However, the extent of equilibration depends on acid/base conditions and on whether the alkene can be reprotonated under the reaction conditions.

6.4.8 Stereochemistry in E1: Less Stereospecific Than E2

E2 can be highly stereospecific because the elimination occurs from a single conformer with anti-periplanar alignment. E1 is generally **not** stereospecific.

Planar carbocation removes conformational constraints. The intermediate carbocation is approximately planar at the cationic center, and rotation about adjacent C–C single bonds can occur before deprotonation. As a result:

- both E and Z alkenes may form when applicable;
- the E:Z ratio often reflects relative alkene stability (E often favored due to lower steric repulsion) rather than a strict geometric requirement.

Important exception: conformationally restricted systems. In rigid ring systems, conformational constraints can still bias which β -hydrogens are accessible to the base and which alkene geometries are feasible. The key point is that E1 lacks the inherent anti-periplanar requirement, but it does not become “geometry-independent” in constrained frameworks.

6.4.9 Carbocation Rearrangements: The Defining Complication of E1

Because E1 proceeds through a discrete carbocation, rearrangements can occur before elimination.

Why rearrangements happen

Carbocations can lower their energy by converting into a more stable carbocation through a 1,2-shift:

- **1,2-hydride shift:** migration of H^- (with its bonding electron pair) from an adjacent carbon to the cationic center.
- **1,2-alkyl (methyl) shift:** migration of an alkyl group with its bonding electron pair.

These shifts are intramolecular and typically fast when they lead to a substantially more stable cation (e.g., secondary $\rightarrow$ tertiary, or formation of a resonance-stabilized cation).

How rearrangements change E1 outcomes

Rearrangement can change:

- the carbon skeleton of the product (“skeletal rearrangement”),
- which β -carbons are available for deprotonation,
- the identity of the major alkene regioisomer.

Thus, when E1 is possible, product prediction must include a check for plausible rearrangements **before** drawing elimination products.

A mechanistic caution

It is tempting to assume that elimination “simply removes a β -H next to the leaving group.” In E1, that is not necessarily correct because the leaving group departure can generate a carbocation that moves (by rearrangement) to a different carbon. Elimination then occurs from the **rearranged** carbocation, not from the initially ionized structure.

6.4.10 Competition Between E1 and SN1: A Structured Way to Think About Mixtures

When a carbocation forms in a nucleophilic solvent, both substitution and elimination are available. The competition can be organized by considering two questions.

Question 1: How fast is ionization? (Controls overall rate)

Ionization rate is increased by:

- more stable carbocations (tertiary, resonance-stabilized),
- better leaving groups,
- more ionizing solvents (often polar protic).

If ionization is slow, neither SN1 nor E1 will compete well with bimolecular pathways (SN2/E2) when strong nucleophiles/bases are present.

Question 2: Once the carbocation forms, which capture process is more likely? (Controls product ratio)

After R^+ forms, the outcome depends on relative rates of:

- **nucleophilic attack** (SN1) by solvent or added nucleophile, and
- **deprotonation** (E1) by solvent or base.

Trends that commonly favor **E1** relative to SN1 include:

- **higher temperature**,
- **more substituted carbocations** (which more readily form substituted alkenes),
- **poorer nucleophiles** (but still adequate bases) in the medium.

Trends that favor **SN1** relative to E1 include:

- **lower temperature**,
- **high nucleophile availability** (especially if the nucleophile is substantially better than the solvent),

- **conditions that suppress deprotonation** (e.g., very weakly basic, strongly solvating environments).

Because many solvents act as both nucleophile and base, clean selectivity can be difficult, and product mixtures are common.

6.4.11 E1 Versus E2: Distinguishing Features for Prediction

It is often necessary to decide whether elimination will be E1 or E2 under given conditions.

Key contrasts.

- **Base strength:** strong bases tend to favor E2; weak bases in ionizing solvents tend to favor E1 (if ionization is feasible).
- **Substrate structure:** tertiary substrates can undergo both; primary substrates generally undergo E2 (if elimination occurs) rather than E1.
- **Stereoelectronics:** E2 requires anti-periplanar geometry; E1 does not, and is therefore less stereospecific.
- **Rearrangements:** E1 can rearrange; E2 does not (because no carbocation exists).

6.4.12 Summary: E1 as Carbocation Chemistry with an Elimination Exit

E1 elimination is best viewed as “SN1 chemistry with deprotonation winning the race.” Its defining features are:

- **Mechanism:** stepwise; ionization to a carbocation (rate-determining), followed by deprotonation to form an alkene.
- **Rate law:** $\text{rate} = k[\text{R-LG}]$, reflecting unimolecular ionization.
- **Key controls:** carbocation stability and solvation (ionizing, often polar protic solvents).
- **Competition:** E1 and SN1 share an intermediate; product mixtures are common, with elimination often favored at higher temperature.

- **Selectivity:** E1 commonly yields Zaitsev alkenes and is not stereospecific; rearrangements can dominate product identity.

These principles set the stage for a unified decision framework: by combining substrate structure, nucleophile/base strength and steric bulk, leaving group quality, and solvent effects, one can predict when E1 will compete with or dominate over SN1 and when bimolecular pathways (SN2/E2) will take over.

6.5 Navigating the Energy Landscape: Predicting Pathway Selectivity

The preceding sections established four mechanistic archetypes—SN2, SN1, E2, and E1—each with its own kinetic signature and stereochemical logic. In real reactions, however, these pathways are not mutually exclusive. The same substrate can react by different mechanisms depending on the energetic accessibility of the relevant transition states. Predicting the **dominant** pathway is therefore an exercise in comparing barriers: which transition state is lowest under the given conditions?

This section presents a systematic framework for doing exactly that. The goal is not to memorize isolated “rules,” but to learn how each experimental variable reshapes the energy landscape and thus shifts the mechanistic outcome.

6.5.1 The Four Controlling Variables

For substitution and elimination at saturated carbon (typically sp^3 carbon bearing a leaving group), four variables account for most outcomes:

- **Substrate structure** (methyl, 1° , 2° , 3° ; and whether resonance stabilization is possible).
- **Nucleophile/base strength and steric bulk** (strong vs. weak; bulky vs. unhindered; nucleophilic vs. basic character).
- **Leaving group ability** (how readily LG^- departs).
- **Solvent type** (polar protic vs. polar aprotic; ionizing power; nucleophilicity/basicity of the solvent).

A disciplined prediction begins by identifying these variables, then asking which mechanistic barriers they lower most effectively.

6.5.2 Step 1: Start with the Substrate (It Sets the “Geometric Feasibility”)

Substrate structure determines whether certain transition states are feasible at all.

Methyl and Primary Substrates: Ionization Is Unfavorable

Methyl ($\text{CH}_3\text{--LG}$).

- **SN2:** strongly favored if a nucleophile is available (minimal steric hindrance).
- **E2/E1/SN1:** not relevant in most cases (no β -carbon for E2/E1; methyl carbocation is extremely unstable for SN1/E1).

Primary (1°) ($\text{RCH}_2\text{--LG}$).

- **SN2:** generally favored with good nucleophiles, especially in polar aprotic solvents.
- **E2:** competes when the reagent is a strong, especially bulky, base or when substitution is sterically slowed (e.g., β -branching such as neopentyl systems).
- **SN1/E1:** generally disfavored (primary carbocations are unstable), except in resonance-stabilized cases (allylic/benzylic primary substrates).

Secondary Substrates: The True Competition Case

Secondary (2°) substrates can plausibly access **all four** pathways. This is why prediction is most challenging here:

- SN2 is possible but slowed by sterics relative to primary.
- E2 is often competitive (strong base, accessible anti-periplanar H_β).
- SN1/E1 can occur in ionizing solvents if the carbocation is sufficiently stabilized.

Thus, for secondary substrates, reagent strength/bulk and solvent are often decisive.

Tertiary Substrates: Backside Attack Is Blocked

Tertiary (3°) substrates almost never undergo $\text{S}_\text{N}2$ because the required backside approach is sterically inaccessible and the $\text{S}_\text{N}2$ transition state is too crowded.

- **$\text{S}_\text{N}1/\text{E}1$:** often favored in polar protic, ionizing solvents because tertiary carbocations are relatively stable.
- **$\text{E}2$:** favored with strong bases; often dominates over $\text{S}_\text{N}1/\text{E}1$ when a strongly basic reagent is present.

Resonance-Stabilized Substrates: “Special Access” to $\text{S}_\text{N}1/\text{E}1$

Allylic and benzylic substrates (primary, secondary, or tertiary) often react unusually fast by $\text{S}_\text{N}1/\text{E}1$ because the carbocation intermediate is resonance-stabilized. In these cases, even substrates that are formally primary can exhibit significant $\text{S}_\text{N}1/\text{E}1$ character under ionizing conditions.

6.5.3 Step 2: Classify the Reagent as Nucleophile vs. Base, and as Bulky vs. Unhindered

The same reagent can be both a nucleophile and a base. Mechanistic selection often hinges on which role dominates in the transition state.

Strong Nucleophile, Not Too Basic (Promotes $\text{S}_\text{N}2$)

Reagents that are good electron-pair donors toward carbon but do not strongly favor proton abstraction tend to promote $\text{S}_\text{N}2$ when sterics allow. The key mechanistic idea is that $\text{S}_\text{N}2$ requires **orbital overlap at carbon** (backside attack) and is sensitive to crowding; if attack is feasible, a strong nucleophile lowers the $\text{S}_\text{N}2$ barrier directly.

Strong Base (Promotes $\text{E}2$)

$\text{E}2$ is promoted by strong bases because the transition state involves significant C–H bond breaking and proton transfer. Steric bulk often strengthens the bias toward elimination because bulky bases have difficulty approaching carbon for substitution but can still abstract relatively accessible β -hydrogens.

Bulky Reagents Shift Selectivity Toward Elimination

Bulky bases/nucleophiles tend to:

- **disfavor SN2** (sterically inhibited approach to the electrophilic carbon),
- **favor E2** (proton abstraction can occur at the least hindered β site),
- **increase Hofmann tendency** (less substituted alkene) when sterics dictate which H_β is accessible.

Weak Nucleophiles/Bases (Enable SN1/E1 Under Ionizing Conditions)

Weak nucleophiles/bases cannot efficiently drive bimolecular SN2/E2 unless the substrate is extremely activated. However, if the solvent and leaving group allow ionization, SN1/E1 can proceed because the rate-determining step is **substrate ionization**, not nucleophile/base attack.

6.5.4 Step 3: Check the Leaving Group (A Bad Leaving Group Can Override Everything)

The leaving group directly affects:

- **SN1/E1** rates (ionization barrier),
- **SN2/E2** rates (extent of C–LG bond breaking in the transition state).

A poor leaving group can suppress all four pathways unless it is activated (e.g., protonation of $-OH$ to form H_2O as a leaving group). When leaving group ability is low, mechanistic prediction becomes moot because reaction may be extremely slow or require different conditions.

6.5.5 Step 4: Solvent as an Energetic “Selector”

Solvent effects are most cleanly understood by asking which species the solvent stabilizes.

Polar Aprotic Solvents Favor SN2 (When a Strong Nucleophile Is Present)

Polar aprotic solvents stabilize cations well but do not strongly hydrogen-bond to anionic nucleophiles. This often leaves anionic nucleophiles more reactive (less solvated), lowering the SN2 barrier. The same logic can also accelerate E2 for anionic bases, but the key competition is usually SN2 vs. E2 and depends on base strength and steric bulk.

Polar Protic, Ionizing Solvents Favor SN1/E1

Polar protic solvents stabilize both R^+ and LG^- in the ionization step, lowering the barrier to carbocation formation. Once a carbocation exists, the solvent can act as nucleophile (SN1) and/or base (E1), often giving mixtures whose ratio is temperature-dependent and sensitive to nucleophile availability.

The Solvent Can Be a Reagent

In solvolysis, the solvent is the dominant nucleophile/base. This makes the mechanistic question inseparable from the choice of solvent, because changing solvent changes both:

- the ionization barrier (via solvation), and
- the identity of the nucleophile/base that captures the carbocation or removes H_β .

6.5.6 Putting It Together: A Practical Decision Procedure

A reliable prediction can be made by following a consistent sequence:

- **Identify substrate class:** methyl/1°/2°/3°; note allylic/benzylic stabilization.
- **Decide if SN2 is sterically feasible:** if 3°, essentially no SN2; if 2°, evaluate crowding and nucleophile strength.
- **Decide if ionization is feasible:** if 3° or resonance-stabilized and in ionizing solvent with good LG, SN1/E1 become plausible.
- **Classify the reagent:** strong nucleophile vs strong base; bulky vs unhindered; neutral vs anionic.

- **If strong base is present:** E2 becomes a leading candidate (especially for 2°/3°).
- **If weak nucleophile/base in polar protic solvent:** SN1/E1 likely (for 2°/3° or resonance-stabilized substrates).
- **Use temperature as a modifier:** higher temperature often increases elimination relative to substitution in SN1/E1 regimes.

6.5.7 A Compact Comparison Table (Mechanistic “Fingerprinting”)

Feature	SN2	E2	SN1/E1
Rate law	$k[\text{Nu}][\text{R}-\text{LG}]$	$k[\text{Base}][\text{R}-\text{LG}]$	$k[\text{R}-\text{LG}]$
Key intermediate	none	none	carbocation (R^+)
Stereochemical hallmark	inversion at C (stereospecific)	anti-periplanar requirement; often stereospecific in constrained systems	racemization/partial racemization (SN1); less stereospecific (E1)
Substrate bias	methyl, 1° $\gg$ 2°; not 3°	2°, 3°; 1° with strong base	3° $\gtrsim$ 2°; resonance-stabilized
Reagent bias	strong nucleophile, low steric bulk	strong base; bulky base favors elimination/Hofmann	weak nucleophile/base acceptable; solvent often participates
Solvent bias	polar aprotic often accelerates	varies; strong bases often used in aprotic media	polar protic/ionizing favors ionization
Rearrangements	no	no	yes (carbocation shifts possible)

6.5.8 Worked-Logic Examples (Without Full Problem Sets)

The following brief scenarios illustrate how the framework is applied.

Example A: Secondary Substrate + Strong, Unhindered Nucleophile in Polar Aprotic Solvent

A 2° substrate presents competition between SN2 and E2. A strong, unhindered nucleophile lowers the SN2 barrier, while the polar aprotic solvent keeps the nucleophile reactive. If the reagent is not strongly basic, SN2 often dominates; if it is strongly basic, E2 competes strongly. The mechanistic decision hinges on whether the reagent is primarily nucleophilic or basic under the chosen conditions.

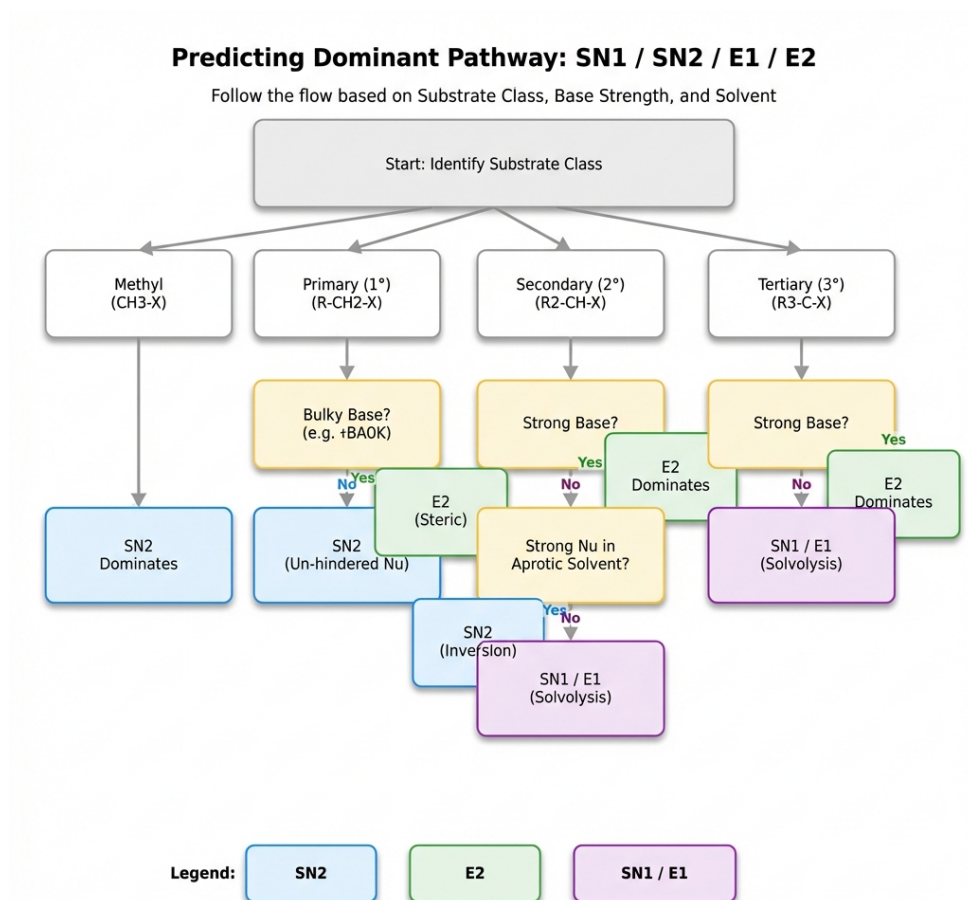
Example B: Tertiary Substrate + Strong Base

Tertiary substrates essentially exclude SN2. A strong base makes E2 fast and typically dominant. SN1/E1 may still occur in ionizing solvents, but strong base conditions usually shift the reaction toward E2 because a bimolecular proton abstraction transition state becomes lower in energy than ionization plus capture.

Example C: Tertiary Substrate in Polar Protic Solvent with Weak Nucleophile/Base

Ionization is feasible (stable tertiary carbocation; solvent stabilizes ions), but there is no strong base to enforce E2. The reaction proceeds through SN1/E1 competition: substitution by solvent nucleophilic attack versus elimination by solvent acting as base, with higher temperature often increasing the elimination fraction.

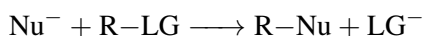
6.5.9 Master Decision Matrix / Flowchart (Summary Reference)



6.6 Problems

6.6.1 Problem 1: SN2 Kinetics, Stereochemistry, and Steric Effects

Consider the following three substitution reactions carried out at the same temperature in a polar aprotic solvent (e.g., DMSO), each with the same nucleophile concentration:



where Nu^- is a strong, unhindered nucleophile and LG is a good leaving group.

- Rank the substrates **by expected SN2 rate** (fastest to slowest): methyl, 1°, 2°, 3°.
- For a chiral 2° substrate (single enantiomer) undergoing substitution by SN2, state the **stereochemical outcome** at the reacting carbon and explain it using the $\sigma^*(\text{C-LG})$ backside-attack model.
- A primary substrate that is β -branched (neopentyl-like) is observed to react exceptionally slowly by SN2. Provide a **transition-state-based** explanation that distinguishes α -substitution from β -branching steric effects.
- Write the **rate law** expected for an SN2 mechanism and briefly justify it in terms of the composition of the transition state.

6.6.2 Problem 2: SN1 Mechanism, Solvation, and Stereochemical Outcome

A tertiary alkyl chloride $(\text{CH}_3)_3\text{C-Cl}$ is placed in a polar protic solvent containing H_2O and a small amount of ROH. A mixture of products is obtained.

- Propose a complete **stepwise mechanism** for substitution by H_2O (include ionization, nucleophilic capture, and any proton transfer steps).
- Predict and justify the **rate law** and identify the **rate-determining step**.
- Explain why polar protic solvents often **accelerate SN1** compared with polar aprotic solvents.
- If the substrate were chiral at the reacting carbon (assume a 3° stereogenic center for the sake of argument), predict the **stereochemical outcome** (racemization vs. partial racemization) and give a mechanistic explanation involving ion pairs/solvent cages.

6.6.3 Problem 3: E2 Anti-Periplanar Requirement and Newman Projection Analysis

A secondary alkyl bromide undergoes elimination in the presence of a strong base B^- . Two different alkenes (E/Z or regioisomers) are possible.

- Using Newman projections (viewing down the $\text{C}_\beta\text{-C}_\alpha$ bond), identify **all conformations** in which a β -hydrogen is anti-periplanar to Br.

- For each anti-periplanar conformation, indicate which β -hydrogen is abstracted and draw the corresponding alkene.
- Predict which alkene should be **major** under E2 conditions and justify your choice using (i) conformer populations, (ii) steric effects of the base (bulky vs. unhindered), and (iii) Zaitsev vs. Hofmann considerations.
- State whether E2 in this case is expected to be **stereospecific** and explain what feature of the mechanism controls stereochemical outcome.

6.6.4 Problem 4: Cyclohexane E2 and the Trans-Diaxial Constraint

Consider *cis*-1-bromo-2-methylcyclohexane subjected to strong base (assume conditions strongly favor E2 if geometrically possible).

- Draw the two chair conformations and identify which has Br **axial**.
- In the chair with axial Br, identify all β -hydrogens that are **trans-diaxial** to the leaving group.
- Predict the **major alkene** formed and specify whether it corresponds to the Zaitsev or Hofmann product.
- Explain how conformational equilibrium (ring flip) can be **rate-relevant** in cyclohexane E2 reactions even though the elimination step is concerted.

6.6.5 Problem 5: E1 Mechanism and SN1/E1 Competition in Solvolysis

A tertiary alkyl tosylate R–OTs is heated in aqueous ethanol. Both substitution and elimination products are observed.

- Propose mechanisms for both **SN1** and **E1** pathways starting from the same substrate. Clearly indicate the shared intermediate.
- Predict how increasing temperature (keeping concentrations constant) is expected to affect the **E1:SN1 product ratio**, and explain your reasoning using qualitative thermodynamic arguments.
- The substitution product is observed to be a mixture of stereoisomers (when applicable). Explain why this is consistent with SN1 and how ion pairing might bias the mixture away from perfect racemization.

- Give two experimental changes (solvent/reagent/temperature) that would likely shift the reaction toward **mostly substitution** and two changes that would shift it toward **mostly elimination**.

6.6.6 Problem 6: Carbocation Rearrangements in SN1/E1 Pathways

A secondary alkyl bromide is subjected to solvolysis conditions in a polar protic solvent, and the products include an alkene consistent with formation of a tertiary carbocation.

- Draw a plausible **carbocation rearrangement pathway** (choose either a 1,2-hydride shift or 1,2-methyl shift) from the initially formed secondary carbocation to a tertiary carbocation.
- From the rearranged carbocation, show how both **SN1** and **E1** products could form. Indicate which positions can be deprotonated to give distinct alkenes.
- Explain why rearrangements are common in SN1/E1 but are not expected in SN2/E2.
- Provide a structural feature of substrates that makes rearrangement **particularly likely** (e.g., proximity of a tertiary center, ring expansion possibility, resonance stabilization after shift).

6.6.7 Problem 7: Pathway Selectivity Decision Framework (Secondary Substrate)

For each set of conditions below, predict the **dominant mechanism** (SN1, SN2, E1, or E2) and the **major product class** (substitution vs. elimination). Provide a short justification referencing substrate structure, nucleophile/base strength and bulk, leaving group ability, and solvent effects.

- A 2° alkyl bromide with NaOEt in EtOH, heated.
- The same 2° alkyl bromide with NaI in acetone at room temperature.
- The same 2° alkyl bromide in H₂O/EtOH without added strong nucleophile/base.
- The same 2° alkyl bromide with KOtBu in *tert*-butanol.

In each case, indicate whether you expect the major alkene (if formed) to follow Zaitsev or Hofmann selectivity and why.

6.6.8 Problem 8: Competing β -Hydrogens and Product Stereochemistry (E2 vs E1)

A tertiary substrate R_3C-LG can form two different alkenes upon elimination: one more substituted (Zaitsev) and one less substituted (Hofmann). Two separate experiments are performed:

- Experiment A: strong, bulky base in a polar aprotic solvent.
- Experiment B: solvolysis in a polar protic solvent at elevated temperature (no strong base added).

For each experiment:

- Predict whether elimination proceeds predominantly by **E2** or **E1**.
- Predict whether the major alkene is more likely Zaitsev or Hofmann, and justify using transition-state accessibility versus thermodynamic alkene stability.
- State whether you expect a strong dependence on **conformation/anti-periplanar alignment** and explain why.

6.6.9 Problem 9: Stereochemical Tracking in Substitution (SN2 vs SN1)

A stereogenic secondary substrate $(R)-R^*-LG$ is reacted under two different sets of conditions that lead to substitution.

- Condition 1: strong nucleophile in a polar aprotic solvent.
- Condition 2: weak nucleophile in a polar protic, ionizing solvent.
- For each condition, predict whether substitution occurs by SN2 or SN1, and state the **expected stereochemical outcome** (inversion vs racemization/partial racemization).
- In the SN1 case, explain how an **intimate ion pair** could lead to partial retention or partial inversion, rather than perfect racemization.

- Propose an experiment (choice of nucleophile/solvent or isotopic labeling) that could help distinguish between SN2 and SN1 for this substrate.

6.6.10 Problem 10: Design a Synthesis by Mechanism Control

You are given a single starting material: a 2° alkyl substrate $R-CH(LG)-R'$ with a good leaving group, and you must selectively obtain one of the following targets:

- Target A: substitution product $R-CH(Nu)-R'$ with **inversion** at the reacting center.
- Target B: the **Zaitsev** alkene as the major product.
- Target C: the **Hofmann** alkene as the major product.
- Target D: substitution product obtained under conditions that plausibly proceed through a **carbocation** (and therefore do not preserve stereochemistry).

For each target, propose a set of reaction conditions (nucleophile/base identity and bulk, solvent type, and temperature) and justify mechanistically which pathway (SN2, E2, SN1, E1) you are selecting and which competing pathways you are suppressing.

Chapter 7

Addition Reactions of Alkenes and Alkynes

While sigma bonds form the rigid skeleton of organic molecules, the pi bond is the reservoir of electron density that drives reactivity. In this chapter, we transition from the stability of structure to the dynamics of transformation. We examine how the exposed electron cloud of alkenes and alkynes behaves as a nucleophile, inviting attack from electrophiles to forge new sigma bonds. This exploration is not merely a list of reactions but a study of mechanistic logic-balancing electronic stabilization (Markovnikov's rule) against steric constraints and orbital alignment (stereochemistry). By mastering these principles, students gain the ability to predict product outcomes and design synthetic pathways with precision.

7.1 Electrophilic Addition and Carbocation Stability

Alkenes are defined by a π bond: a region of electron density above and below the plane of the σ framework. In earlier chapters, we developed two ideas that now come together:

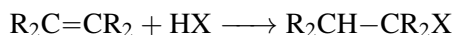
- **Polar bonds create electrophiles and nucleophiles.** In a polarized reagent such as HBr, hydrogen is electrophilic (δ^+) and bromine is nucleophilic (δ^-).
- **Curved-arrow notation tracks electron flow.** Electron-rich sites (Lewis bases) donate to electron-poor sites (Lewis acids).

Electrophilic addition is the characteristic reaction class of alkenes because the π

bond is a strong nucleophile and is relatively accessible to attack. The central goal of this section is to make Markovnikov's rule feel inevitable rather than memorized: the regiochemistry is a consequence of **carbocation stability** and the **energetics of the rate-determining step**.

7.1.1 The general two-step mechanism: π bond as nucleophile, X^- as nucleophile

The prototypical electrophilic addition is addition of a hydrogen halide, HX, to an alkene to form an alkyl halide:



Mechanistically, the reaction is most often described as a **two-step pathway**:

- **Protonation of the alkene** to form a carbocation intermediate (or, more precisely, an ion pair) and X^- .
- **Nucleophilic capture** of the carbocation by X^- to form the C–X bond.

In curved-arrow terms:

- The π electrons attack H of HX.
- The H–X bond electrons go to X, generating X^- .

Example: addition of HBr to 2-methylpropene

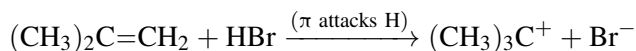
Consider 2-methylpropene (isobutene), $(CH_3)_2C=CH_2$. There are two possible regiochemical outcomes for addition of HBr:

- **Markovnikov product:** bromine ends up on the **more substituted** carbon, giving tert-butyl bromide, $(CH_3)_3CBr$.
- **Anti-Markovnikov regiochemistry (not the normal ionic pathway):** bromine ends up on the **less substituted** carbon, giving isobutyl bromide, $(CH_3)_2CHCH_2Br$.

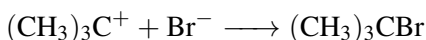
The key question is: **which carbocation forms during protonation?** Protonation can occur at either alkene carbon, but each choice places the positive charge on a different carbon.

Path A (Markovnikov): form a tertiary carbocation.

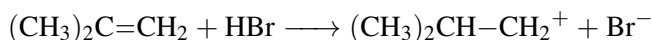
If H^+ adds to the terminal carbon (CH_2), the positive charge appears on the substituted carbon, giving a **tertiary carbocation**:



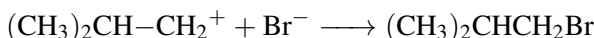
Then bromide rapidly traps the carbocation:

**Path B (formal anti-Markovnikov): form a primary carbocation.**

If H^+ adds to the substituted carbon, the positive charge would be placed on the terminal carbon, giving a **primary carbocation**:



followed by



In typical ionic electrophilic addition conditions, Path B is strongly disfavored because a primary carbocation is far higher in energy than a tertiary carbocation. The consequence is that the Markovnikov product dominates.

7.1.2 Markovnikov's rule as a consequence of the rate-determining step**Markovnikov's rule (for HX addition in the ionic mechanism):**

Hydrogen adds to the alkene carbon that already has more hydrogens (the less substituted carbon), placing the carbocation on the more substituted carbon, and the halide ultimately bonds to that more substituted carbon.

This "rule" is not an independent principle; it is a compact way of describing the outcome of a mechanism in which:

- Protonation is **rate-determining** (highest barrier).

- Carbocation stability controls which protonation pathway has the **lower activation free energy** $\Delta G^\ddagger$.

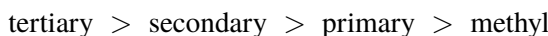
Because the carbocation (or carbocation-like) species is created in the slow step, any factor stabilizing the developing positive charge lowers the energy of the key transition state and increases the rate for that pathway. Therefore, **the major product generally comes from the pathway that forms the more stable carbocation intermediate.**

7.1.3 Carbocation stability: hyperconjugation and inductive effects

Carbocations are electron-deficient, with a formally positively charged carbon that is typically sp^2 -hybridized and planar, possessing an empty p orbital. Two major stabilizing effects dominate simple alkyl carbocations:

- **Hyperconjugation:** donation of electron density from adjacent σ (C–H or C–C) bonds into the empty p orbital. More adjacent σ bonds (more alkyl substituents) $\Rightarrow$ more hyperconjugative structures $\Rightarrow$ greater stabilization.
- **Inductive donation:** alkyl groups weakly donate electron density through σ bonds, reducing the electron deficiency at the cationic center.

This explains the common stability trend for simple alkyl carbocations:



In electrophilic addition of HX, this stability trend is translated directly into a **regioselectivity trend**: protonation pathways that lead to more substituted carbocations are faster and therefore dominate the product mixture.

7.1.4 Kinetic vs. thermodynamic control: what is actually being selected?

It is tempting to say “the more stable carbocation forms,” but the deeper statement is:

The faster pathway dominates because it has the lower $\Delta G^\ddagger$ for the rate-determining protonation.

This is primarily a matter of **kinetic control**:

- The product distribution reflects the relative **rates** of formation of competing intermediates (and then products).
- The intermediates need not be at equilibrium with each other.

However, the **thermodynamics of carbocation stability** strongly influences those rates through the structure and energy of the transition state. The bridge between “stability” (a thermodynamic idea) and “rate” (a kinetic idea) is the **Hammond postulate**.

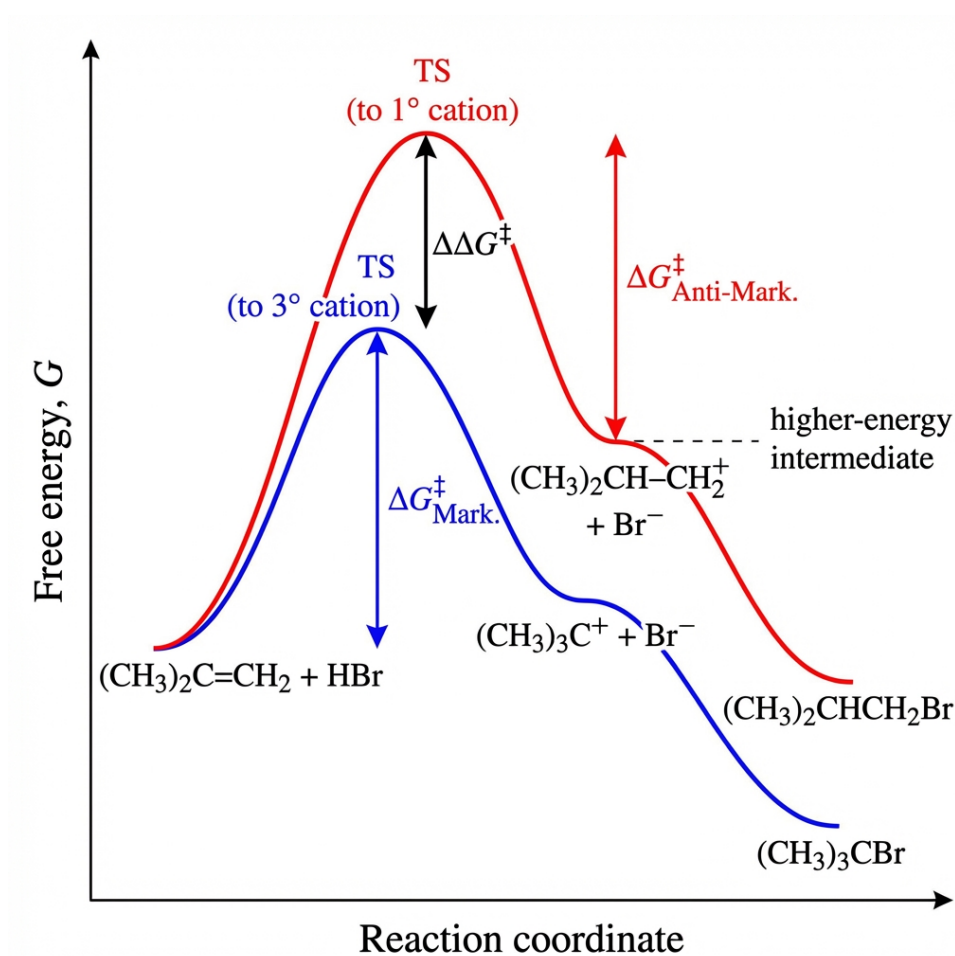
7.1.5 The Hammond postulate and Markovnikov selectivity

Hammond postulate: the structure of a transition state resembles the species (reactants or products) to which it is closer in energy.

Protonation of an alkene to form a carbocation is typically **endothermic** (it generates separated charge and a high-energy intermediate). For an endothermic step:

- The transition state is **late** and resembles the **carbocation intermediate**.
- Therefore, any factor stabilizing the carbocation also stabilizes the transition state, lowering $\Delta G^\ddagger$.

So, in competing protonations of an unsymmetrical alkene, the pathway that leads to the **more stable carbocation** also has the **lower activation barrier** and is faster. That is the mechanistic origin of Markovnikov’s rule.



7.1.6 Intermediates, transition states, and why “more substituted” matters

The diagram above summarizes a central pattern:

- Formation of the 3° carbocation (Markovnikov pathway) has a **lower** $\Delta G^\ddagger$ than formation of the 1° carbocation (formal anti-Markovnikov ionic pathway).
- Because protonation is the slow step, the product ratio reflects this $\Delta G^\ddagger$ difference. Even modest differences in $\Delta\Delta G^\ddagger$ can produce large selectivities.

Conceptually, you can think of protonation as “deciding” where the positive charge will develop. The alkene carbon that can best accommodate positive charge (via hy-

perconjugation and inductive donation from substituents) is the carbon that becomes cationic in the favored pathway. The proton therefore adds to the opposite carbon.

7.1.7 Stereochemical note: planar carbocations and racemization

A classical carbocation intermediate is planar at the cationic carbon. If nucleophilic capture occurs at a stereogenic carbocation center, attack can occur from either face, often leading to:

- a **racemic mixture** if a new stereocenter is created at the cationic carbon and no other stereochemical constraints exist, or
- a **mixture enriched by ion-pair effects** (the departing/associated counterion can partially block one face), especially in less polar solvents.

At this point, the key takeaway is mechanistic: **open** carbocations generally **erase** stereochemical information at the cation center because they are planar, whereas **bridged** intermediates (introduced later for halogenation and oxymercuration) can enforce stereochemical outcomes.

7.1.8 Carbocation rearrangements: a mechanistic consequence, not an exception

Because carbocations are real intermediates in many electrophilic additions, they can undergo **rearrangements** when a more stable carbocation is accessible by a 1,2-shift. Two common rearrangements are:

- **1,2-hydride shift** (migration of H^- with its bonding pair)
- **1,2-methyl shift** (migration of CH_3^- with its bonding pair)

These shifts are driven by the same stability logic used to predict Markovnikov regiochemistry: the system seeks a lower-energy carbocation before nucleophilic trapping. Practically, this means:

If your proposed mechanism contains a secondary or primary carbocation adjacent to a tertiary carbon, you should **actively consider** a rearrangement before the nucleophile attacks.

We will treat rearrangements in detail when comparing hydration methods, because alternative strategies can achieve Markovnikov hydration **without** rearrangement by avoiding open carbocations altogether.

7.1.9 Summary: how to predict regiochemistry for HX addition to alkenes

When an alkene undergoes electrophilic addition of HX under ionic conditions, use the following logic chain:

- **Identify the two protonation options.** Each option places the positive charge on a different carbon.
- **Rank the carbocations by stability** (resonance-stabilized > 3° > 2° > 1° > methyl; hyperconjugation/induction explain the alkyl trend).
- **Apply the Hammond postulate:** because protonation is endothermic, the lower-energy carbocation corresponds to a lower-energy transition state and thus a faster pathway.
- **Conclude Markovnikov regiochemistry:** the nucleophile ends up where the carbocation was formed (often the more substituted carbon), and the proton adds to the other carbon.

This mechanism-based approach replaces memorization: Markovnikov's rule is the observable consequence of carbocation-like transition states whose energies track carbocation stability.

7.2 Hydration Strategies: Acid-Catalysis and Oxymercuration

In the previous section, we established a general framework for electrophilic addition to alkenes: the π bond acts as a nucleophile, an electrophile adds first, and the regiochemical outcome is largely determined in the rate-determining step. We also saw the practical consequence of open carbocation intermediates: **rearrangements** can compete with nucleophilic capture.

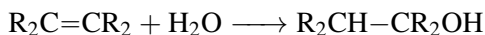
Hydration reactions apply the same principles to a particularly important transformation: **converting an alkene into an alcohol** by net addition of H and OH across

the double bond. Because the OH group is not itself a good electrophile for direct addition, hydration is carried out through **acid catalysis** (which generates a better electrophile) or through alternative electrophilic activation of the alkene. This section compares two widely used strategies:

- **Acid-catalyzed hydration:** Markovnikov addition via a carbocation intermediate, but often limited by rearrangements and equilibrium.
- **Oxymercuration–demercuration:** Markovnikov addition **without** rearrangement, via a bridged mercurinium ion.

7.2.1 What hydration accomplishes (and what must be controlled)

Hydration is formally:



Two selectivity issues immediately arise for unsymmetrical alkenes:

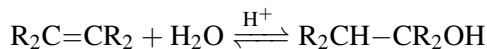
- **Regiochemistry:** does OH end up on the more substituted carbon (Markovnikov) or the less substituted carbon (anti-Markovnikov)?
- **Rearrangement:** does the mechanism create an open carbocation that can undergo 1,2-shifts before C–O bond formation?

Acid-catalyzed hydration and oxymercuration solve the first issue in the same direction (Markovnikov), but they differ dramatically on the second issue (rearrangements).

7.2.2 Acid-catalyzed hydration: Markovnikov addition via a carbocation

Overall transformation and typical conditions

Under strongly acidic aqueous conditions, alkenes can be hydrated to alcohols:

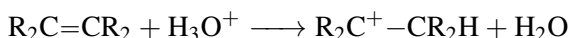


Common laboratory acids include H_2SO_4 or H_3PO_4 in water. The acid is a **catalyst**; the true electrophile is H_3O^+ (or a related protonated species), and water is the nucleophile.

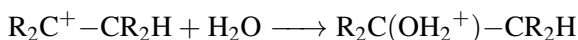
Mechanism: protonation, nucleophilic attack, deprotonation

The mechanism closely parallels HX addition:

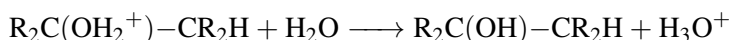
- **Protonation of the alkene** by H_3O^+ forms the **most stable carbocation** accessible by direct protonation (Markovnikov orientation).



- **Nucleophilic attack of water** on the carbocation forms a protonated alcohol (an oxonium ion).



- **Deprotonation** by water (or another base in solution) gives the neutral alcohol and regenerates acid catalyst.



Two points are worth emphasizing because they control product outcomes:

- The regiochemistry is determined in the **protonation step**, because that step determines where the positive charge develops (Hammond postulate reasoning from the previous section).
- Any time an **open carbocation** is formed, it may **rearrange** before nucleophilic capture.

Why acid-catalyzed hydration is often not ideal**(1) The reaction is reversible (equilibrium limitation).**

Acid-catalyzed hydration is the microscopic reverse of acid-catalyzed dehydration of alcohols (an elimination process). Consequently, hydration does not always go to completion:



The position of equilibrium depends on alkene substitution, temperature, and solvent composition. Practically, hydration is favored by:

- large excess of water,
- lower temperatures (to suppress dehydration),
- and alkenes that form more stable carbocations (which also tend to hydrate more readily).

(2) Carbocation rearrangements can change the carbon skeleton.

Because protonation generates a carbocation, the initially formed cation may undergo a 1,2-shift to a more stable cation before water attacks. This is not a special case; it is a mechanistic consequence of a high-energy intermediate seeking a lower-energy pathway.

A common pattern is:

- protonation gives a 2° carbocation adjacent to a 3° center,
- a **1,2-hydride shift** produces a 3° carbocation,
- water then attacks, giving a **rearranged alcohol**.

Representative example: hydration with rearrangement tendency.

Consider 3,3-dimethyl-1-butene, $\text{CH}_2=\text{CH}-\text{C}(\text{CH}_3)_3$. Direct Markovnikov protonation places the carbocation at C2 (secondary). But that cation sits adjacent to a quaternary carbon (C3) that can donate a hydride from C2? Here the realistic rearrangement pathway is a shift that produces a more substituted cation (the exact shift depends on the accessible migrating group and connectivity). The broader lesson is the important one for planning:

If acid-catalyzed hydration would proceed through a cation that is not the most stable cation available by a single 1,2-shift, expect competing rearranged products.

(3) Side reactions and polymerization are possible.

Carbocations are strong electrophiles. In some systems, the alkene itself (or other nucleophilic species present) can compete with water, leading to oligomerization/polymerization or other byproducts. These side reactions are most problematic when:

- carbocations are especially long-lived (less nucleophilic solvents, lower water activity),

- alkenes are highly substituted and form stabilized carbocations readily,
- or the substrate contains additional nucleophilic functional groups.

7.2.3 Oxymercuration–demercuration: Markovnikov hydration without rearrangement

Acid-catalyzed hydration succeeds when the carbocation pathway is clean, but fails when rearrangements or equilibrium limitations dominate. Oxymercuration–demercuration was developed as a solution to a very specific synthetic need:

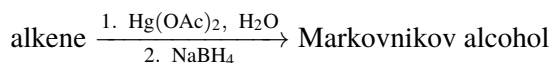
Add H and OH in Markovnikov fashion while avoiding free carbocations (and therefore avoiding rearrangements).

Reagents and overall transformation

The reaction is performed in two steps:

- **Oxymercuration:** $\text{Hg}(\text{OAc})_2$ in water (often THF/ H_2O as solvent mixture).
- **Demercuration:** NaBH_4 (typically in basic aqueous conditions).

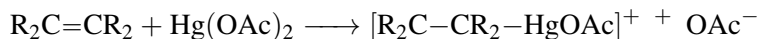
Net result:



The product regiochemistry matches acid-catalyzed hydration (Markovnikov), but the mechanism differs in a way that suppresses rearrangements.

Step 1: formation of a bridged mercurinium ion

Mercury(II) acetate behaves as an electrophile toward the alkene. Interaction of the alkene π electrons with Hg^{2+} forms a **three-membered cyclic mercurinium ion** (a bridged cationic intermediate). A simplified representation is:



Key mechanistic implication:

- The positive charge is **delocalized** over the three-membered ring, and there is **no open, freely rearranging carbocation**.

This is conceptually parallel to halonium ions in bromination/chlorination: a bridged intermediate constrains geometry and prevents 1,2-shifts that would require formation of a planar carbocation center.

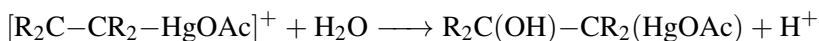
Regiochemistry: why the nucleophile attacks the more substituted carbon

Although the intermediate is bridged, it is not symmetrically charged. The more substituted carbon typically bears greater carbocation character (better able to stabilize positive charge through hyperconjugation/induction). Therefore, water attacks preferentially at the more substituted carbon, giving Markovnikov placement of OH.

Mechanistically:

- Water attacks the more substituted carbon of the mercurinium ion (opening the ring).
- Deprotonation yields an organomercury alcohol (C–O bond formed; C–HgOAc bond remains).

In a simplified form:

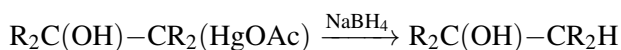


Stereochemical consequence: anti opening is typical

Because the nucleophile opens a bridged intermediate by backside attack (relative to the C–Hg bond being broken), the OH and HgOAc groups are introduced in an **anti** relationship in the oxymercuration step. After demercuration, the HgOAc group is replaced by H, so the final alcohol does not always display a simple anti/syn label relative to hydrogen addition as in hydroboration; nevertheless, the bridged intermediate is crucial for understanding why rearrangements do not occur.

Step 2: demercuration replaces –HgOAc with –H

In the second step, NaBH₄ reduces the carbon–mercury bond, replacing –HgOAc with hydrogen:



For our purposes, two practical conclusions matter more than the detailed radical/polar possibilities sometimes used to rationalize the reduction:

- The C–O bond formed in oxymercuration is retained.
- The overall transformation is **Markovnikov hydration without carbocation rearrangement**.

7.2.4 Comparative summary: choosing between acid-catalyzed hydration and oxymercuration

A concise way to compare these methods is to ask which mechanistic “price” you are paying to obtain the alcohol.

Acid-catalyzed hydration (H_3O^+)	Oxymercuration–demercuration
Markovnikov regiochemistry (via most stable carbocation)	Markovnikov regiochemistry (via mercurinium ion polarization)
Often proceeds through an open carbocation intermediate	Avoids open carbocation; bridged mercurinium ion
Rearrangements (hydride/methyl shifts) can occur	Rearrangements are strongly suppressed
Reversible; equilibrium can limit yield	Typically not equilibrium-limited in the same way
Possible side reactions from carbocations (polymerization, etc.)	Generally cleaner for rearrangement-prone substrates
Simple reagents (strong acid, water)	Uses mercury reagents; requires careful handling and waste disposal

7.2.5 Mechanistic decision-making: predicting when rearrangements will matter

When faced with an alkene hydration problem, use this checklist:

- **Draw the Markovnikov carbocation** that would form under acid catalysis.
- **Ask whether a 1,2-shift can give a more stable carbocation.** If yes, expect rearranged alcohols (often as major products).

- **If rearrangement is likely and Markovnikov alcohol is desired, choose oxymercuration–demercuration.**

This decision-making framework is not limited to hydration: it generalizes to many electrophilic additions. Whenever a method proceeds through a **bridged cationic intermediate** rather than an **open carbocation**, rearrangements become much less important, and stereochemical constraints become more predictable. In the next section, we will see the same core idea in halogenation, where halonium ions control both mechanism and stereochemistry.

7.3 Halogenation: Cyclic Intermediates and Stereocontrol

In the previous two sections, we saw how electrophilic addition to alkenes can proceed through *open carbocation* intermediates (e.g., HX addition and acid-catalyzed hydration), and how alternative pathways (e.g., oxymercuration) can avoid carbocation rearrangements by forming a *bridged* cationic intermediate. Halogenation reactions provide one of the clearest and most experimentally supported examples of the bridged-intermediate concept, and they add an additional layer of predictability: **stereochemical control**.

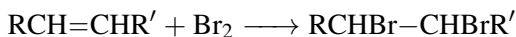
This section focuses on two related transformations:

- **Halogenation:** addition of X_2 (Br_2 or Cl_2) to form a vicinal dihalide.
- **Halohydrin formation:** addition of X and OH across an alkene when the halogenation is carried out in water (or alcohol).

Both proceed through **cyclic halonium ions**, which enforce **anti addition** by a back-side ring-opening mechanism.

7.3.1 Halogenation of alkenes: what is observed

When an alkene reacts with bromine or chlorine under non-nucleophilic conditions (e.g., Br_2 in CH_2Cl_2), the product is a vicinal dihalide:



Two experimental observations are central:

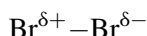
- **The reaction is stereospecific anti addition.** For cyclic alkenes, the two halogens end up on opposite faces (trans).
- **No carbocation rearrangements are seen.** Even substrates that readily rearrange under HX addition do not rearrange under Br₂ addition.

These outcomes are difficult to reconcile with an open carbocation mechanism, but they are directly explained by the halonium ion mechanism.

7.3.2 Mechanism: formation and opening of a halonium ion

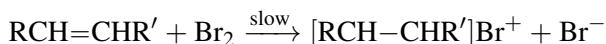
Step 1: electrophilic activation of X₂ and halonium formation

Although Br₂ is nonpolar overall, it is *highly polarizable*. As the alkene approaches, the π electrons repel electron density in Br–Br, inducing a dipole:



The alkene then behaves as a nucleophile and attacks Br^{δ+} while the Br–Br bond breaks to Br[–]. Crucially, the electrophilic bromine does not form a simple σ bond to one carbon and leave a free carbocation on the other. Instead, it forms a **three-membered bridged bromonium ion**.

Conceptually:



where $[\text{ }]\text{Br}^+$ indicates bromine bridging both alkene carbons.

Step 2: nucleophilic ring opening by backside attack (anti addition)

The bromonium ion is opened by nucleophilic attack of Br[–]. Because the bromine bridge blocks one face of the intermediate, nucleophilic attack occurs from the **opposite face** (backside), analogous to backside attack in S_N2 chemistry. This necessarily produces **anti stereochemistry** between the entering nucleophile and the leaving bromine bridge.

Two additional details are important:

- **Stereoelectronics:** maximal overlap occurs when the nucleophile attacks anti to the C–Br bond being broken, allowing donation into the antibonding orbital (σ^*).

- **Regiochemical bias (for unsymmetrical alkenes):** the more substituted carbon typically bears greater partial positive character in the bridged intermediate. Therefore, nucleophiles tend to attack the *more substituted* carbon of the halonium ion (especially with nucleophiles other than Br^- , such as water).

7.3.3 Stereochemical consequences: why halogenation is anti and stereospecific

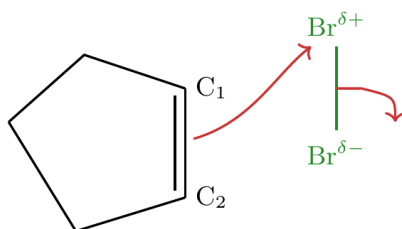
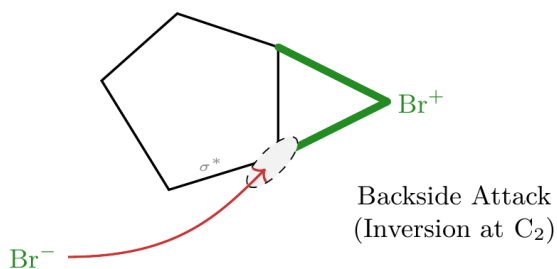
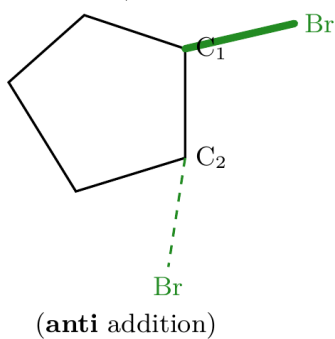
The cyclic halonium ion acts as a **stereochemical gatekeeper**. In an open carbocation pathway, the intermediate is planar and nucleophiles can attack from either face, leading to loss of stereochemical information. In contrast, the halonium ion:

- is **not planar at carbon** in the same way (it is a bridged structure),
- **blocks** nucleophilic approach from the same face as the halogen bridge,
- forces **backside attack**, producing **anti addition**.

For cyclic alkenes, this is often stated as: Br_2 addition gives **trans-1,2-dibromides** (or trans-1,2-dichlorides).

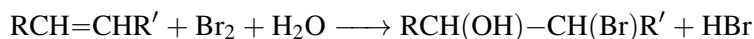
Worked stereochemical example: cyclopentene bromination

Cyclopentene is planar at the double bond in its dominant conformations, with two distinct faces (commonly drawn as “top” and “bottom”). Bromonium formation occurs on one face, and bromide must attack from the opposite face, yielding a trans product.

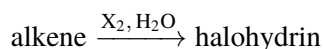
1. Cyclopentene + Bromine**2. Bromonium Ion****3. trans-1,2-dibromocyclopentane**

7.3.4 Halohydrin formation: X_2 in water gives X and OH

If bromination (or chlorination) is performed in water rather than an inert solvent, the major product is not the vicinal dihalide. Instead, the product is a **halohydrin**:



More generally:



This outcome follows directly from competition in the second step (ring opening of the halonium ion):

- The electrophilic step still forms a **halonium ion**.
- The nucleophile that opens the ring is the **solvent** (water), because it is present in overwhelming concentration.

Regiochemistry: why OH goes to the more substituted carbon

Ring opening of a halonium ion is not purely governed by sterics; it is also governed by charge distribution. The bridged intermediate can be viewed as having partial carbocation character at both carbons, but **the more substituted carbon better stabilizes positive charge**. Therefore:

In halohydrin formation, water attacks the **more substituted** carbon of the halonium ion, placing OH at the more substituted position (Markovnikov-like placement of OH).

After water attacks, deprotonation yields the neutral alcohol:



Thus, the product has:

- **anti stereochemistry** between X and OH (because opening is backside),
- **regioselective placement** of OH at the more substituted carbon.

Chlorohydrins and bromohydrins: practical notes

- $\text{Br}_2/\text{H}_2\text{O}$ is commonly used to form bromohydrins under mild conditions.
- $\text{Cl}_2/\text{H}_2\text{O}$ can form chlorohydrins, though chlorination can be more complex due to competing pathways in some substrates.
- Alcohol solvents (ROH) can substitute for water to give β -halo ethers via analogous ring opening.

7.3.5 Evidence for halonium ions (why the bridged mechanism is accepted)

The halonium ion mechanism is supported by multiple lines of reasoning that tie directly to outcomes you can predict:

- **Anti stereospecificity:** cyclic alkenes give trans dihalides/halohydrins, consistent with backside opening of a bridged intermediate.
- **No rearrangements:** the absence of hydride/methyl shifts indicates that a freely rearranging carbocation is not formed.
- **Regiochemistry in halohydrin formation:** preferential attack at the more substituted carbon fits a bridged intermediate with uneven charge distribution.

These features parallel oxymercuration: both reactions replace an open carbocation with a bridged cationic intermediate, thereby suppressing rearrangements and imposing stereochemical constraints.

7.3.6 Summary: predictive rules for X_2 additions

For routine product prediction, the halonium framework can be condensed into three reliable rules:

- **Halonium ion formation** is the key intermediate for Br_2 and Cl_2 additions to alkenes.
- **Ring opening is backside** $\Rightarrow$ **anti addition** (trans products in cycloalkenes).
- **In nucleophilic solvents, the solvent attacks:** X_2 in inert solvent $\Rightarrow$ vicinal dihalide (anti); X_2 in H_2O $\Rightarrow$ halohydrin: OH to the more substituted carbon, X to the less substituted carbon, overall anti.

These rules are not shortcuts to avoid mechanism; they are direct consequences of a specific mechanistic feature—a **cyclic electrophilic intermediate**—which you will encounter again in other addition reactions that control stereochemistry through constrained pathways.

7.4 Hydroboration-Oxidation: Syn-Anti-Markovnikov Addition

Acid-catalyzed hydration and oxymercuration–demercuration both deliver **Markovnikov** alcohols: the OH group ends up on the more substituted carbon of an unsymmetrical alkene. In the last section, halogenation introduced a second major mechanistic theme: **cyclic intermediates and concerted ring-opening** can impose strong **stereochemical control** and suppress rearrangements.

Hydroboration–oxidation is the complementary hydration strategy. It accomplishes a transformation that is difficult to obtain by ionic protonation mechanisms:

Net hydration of an alkene to give an anti-Markovnikov alcohol with syn stereochemistry.

Even more importantly, it does so through a **concerted** (single-step) addition that **does not form a carbocation**, so rearrangements are not an issue.

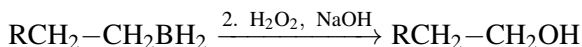
7.4.1 Overall transformation and reagents

Hydroboration–oxidation is a two-step sequence:

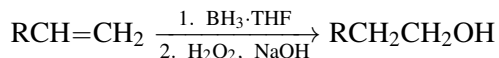
- **Hydroboration:** addition of borane across the alkene.



- **Oxidation:** replacement of the C–B bond by a C–O bond using hydrogen peroxide under basic conditions.



The net result is equivalent to adding H and OH across the double bond:



For a terminal alkene, the product is typically a **primary alcohol**.

7.4.2 Key outcomes to remember

Hydroboration–oxidation is characterized by three linked features:

- **Regiochemistry: anti-Markovnikov.** The OH group ends up on the **less substituted** alkene carbon.
- **Stereochemistry: syn addition.** The hydrogen and the OH group (introduced via boron, then replaced by oxygen) add to the same face of the alkene.
- **No carbocation rearrangements.** The mechanism avoids discrete cationic intermediates.

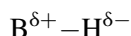
These are not independent “rules”; they all arise from the same mechanistic fact: **hydroboration is concerted**.

7.4.3 Step 1: Hydroboration is a concerted, four-center addition

Why BH_3 is an effective electrophile for alkenes

Borane, BH_3 , is electron-deficient (only 6 valence electrons around boron). In $\text{BH}_3 \cdot \text{THF}$, the Lewis base (THF) stabilizes borane but does not eliminate its electrophilicity; boron can still accept electron density from a π bond.

A useful polarization picture is:



Boron is electrophilic, and the B–H bond has hydridic character relative to boron. During addition to an alkene, electron density shifts in a way that simultaneously forms a C–B bond and a C–H bond.

The four-center transition state and syn addition

Hydroboration proceeds through a **single transition state** in which four atoms participate: the two alkene carbons, boron, and hydrogen. Two new σ bonds form at the same time:

- C–B forms at one alkene carbon.
- C–H forms at the other alkene carbon.

Because both bonds form in one step, boron and hydrogen necessarily add to the **same face** of the alkene. This enforces **syn addition**. There is no opportunity for backside attack on an intermediate (as in halonium opening), and no planar carbocation that could scramble stereochemistry.

Regiochemistry: why boron goes to the less substituted carbon

Hydroboration gives **anti-Markovnikov** regiochemistry because of a combination of **steric** and **electronic** effects in the transition state.

Steric factor (often dominant). Boron is larger than hydrogen, and BH_3 approaches the alkene as a unit. A transition state in which boron bonds to the more substituted carbon generally experiences greater steric crowding (more alkyl substituents near boron). Placing boron at the **less substituted** carbon reduces steric repulsion, lowering the transition-state energy.

Electronic factor (reinforcing). The hydroboration transition state is polarized: as the π bond donates electron density toward boron, partial positive character develops more strongly at one alkene carbon. The more substituted carbon better stabilizes partial positive character (via hyperconjugation/induction). Therefore, the hydride-like hydrogen is delivered preferentially to the **more substituted** carbon, while boron attaches to the **less substituted** carbon.

A concise way to state this is:

In the hydroboration transition state, the carbon receiving H is more cation-like; placing that developing positive character at the more substituted carbon is stabilizing. Therefore H goes to the more substituted carbon and B goes to the less substituted carbon.

After oxidation, the C–B bond becomes a C–O bond without changing the carbon framework, so the OH ends up where boron was: the **less substituted** carbon (anti-Markovnikov alcohol).

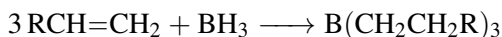
Why rearrangements do not occur

Rearrangements (hydride or alkyl shifts) require a discrete carbocation (or an intermediate with sufficient carbocation character and lifetime). Hydroboration does not generate such an intermediate: bond formation is concerted, and there is no stage at which a carbon bears a full positive charge and can reorganize by migration. Consequently:

- substrates that rearrange under acid hydration can often be hydrated cleanly by hydroboration–oxidation,
- regioselectivity is not “rescued” by rearrangement; it is determined in the transition state.

7.4.4 Stoichiometry note: why borane adds three times

A single BH_3 molecule contains three B–H bonds and can add across three alkene π bonds, ultimately forming a trialkylborane:



In practice, hydroboration is often carried out with $\text{BH}_3 \cdot \text{THF}$ (or bulky boranes to tune selectivity), but the mechanistic logic of concerted syn addition and anti-Markovnikov regiochemistry remains the same.

7.4.5 Step 2: Oxidation converts C–B into C–O with retention

Hydroboration installs boron at carbon; oxidation replaces boron with oxygen. The oxidation step uses H_2O_2 in basic solution (commonly NaOH) and can be understood as a two-part process:

- **Formation of a peroxyborate species** (boron is a Lewis acid and binds oxygen-containing nucleophiles readily under basic conditions).
- **Migration (rearrangement at boron) that transfers an alkyl group from boron to oxygen**, forming the C–O bond, followed by hydrolysis to give the alcohol.

The most important stereochemical consequence is:

The oxidation proceeds with retention of configuration at the carbon that migrates.

Therefore, the stereochemistry set in hydroboration is preserved: since hydroboration is syn, the overall hydroboration–oxidation sequence produces a **syn alcohol** (relative to the hydrogen added in step 1).

7.4.6 Stereochemical examples: syn addition on cyclic alkenes

Syn addition becomes especially visible in cyclic systems.

Example: cyclohexene. Hydroboration can occur from either face of the alkene, but within any one event, B and H add **syn**. Oxidation then replaces B with OH with retention, so the net result is **syn addition of H and OH** to cyclohexene.

Example: substituted cyclohexenes. For substituted rings, steric approach control can favor attack from the less hindered face, leading to diastereoselectivity. The mechanistic reason is straightforward: the borane approaches as a unit in a cyclic transition state, so the less hindered face is kinetically preferred. Regardless of facial selectivity, the **relative** stereochemistry of the newly added groups from a single addition remains syn.

7.4.7 Choosing among hydration methods: a planning perspective

At this point, we have three major ways to convert alkenes into alcohols, each with distinct selectivity control:

Method	Regiochemistry	Key mechanistic features
Acid-catalyzed hydration (H_3O^+)	Markovnikov	Open carbocation; rearrangements possible; reversible
Oxymercuration–demercuration	Markovnikov	Bridged mercurinium ion; rearrangements suppressed
Hydroboration–oxidation	Anti-Markovnikov	Concerted syn addition; no carbocation; oxidation with retention

Thus, hydroboration–oxidation is the method of choice when you need:

- a **primary alcohol** from a terminal alkene,
- **anti-Markovnikov** placement of OH,
- predictable **syn** stereochemistry,
- and a pathway that **avoids rearrangements**.

Hydroboration–oxidation is best understood as a mechanistically distinct hydration strategy:

- Hydroboration proceeds through a **concerted four-center transition state**, enforcing **syn** addition of H and B.
- Regiochemistry is **anti-Markovnikov** because transition-state steric and electronic effects place B on the less substituted carbon and H on the more substituted carbon.
- Oxidation with $\text{H}_2\text{O}_2/\text{NaOH}$ replaces the C–B bond with a C–O bond **with retention**, preserving the stereochemistry set in step 1.

The unifying theme across the chapter is now clear: **mechanism controls selectivity**. Open carbocations give Markovnikov addition but invite rearrangements and stereochemical loss; bridged intermediates and concerted additions avoid rearrangement and impose stereochemical constraints.

7.5 Alkyne Reactivity and Tautomerization

The previous sections established a general framework for addition to π bonds. For alkenes, we repeatedly used three mechanistic ideas:

- **Electrophilic activation of a π bond** initiates addition.
- **The nature of the intermediate** (open carbocation vs. bridged ion vs. concerted transition state) determines rearrangements and stereochemistry.
- **Regiochemistry** is often traceable to stability of developing positive charge (Markovnikov behavior) or to the structure of a concerted transition state (hydroboration).

Alkynes ($\text{C}\equiv\text{C}$) also undergo addition reactions, but several outcomes differ in systematic ways:

- Alkynes are **less reactive** toward electrophilic addition than comparable alkenes.
- Addition is often **stepwise** and can occur **twice** (because a triple bond contains two π bonds).

- When hydration occurs, the immediate product is an **enol**, which then converts to a **carbonyl compound** by **keto–enol tautomerization**.

This section develops these points carefully, with special emphasis on the stability problem that underlies much of alkyne behavior: **vinyllic carbocations are unusually unstable**.

7.5.1 Structure and bonding of alkynes: two π bonds and sp hybridization

An alkyne carbon is typically sp-hybridized, giving a linear geometry around the $\text{C}\equiv\text{C}$ axis. The triple bond consists of:

- one σ bond (from sp–sp overlap), and
- two mutually perpendicular π bonds (from two orthogonal p orbitals on each carbon).

Because there are *two* π bonds, electrophilic addition can occur once to produce an alkene (vinyl) product, and under more forcing conditions can occur a second time to produce a saturated product.

7.5.2 Why alkynes are generally less reactive than alkenes toward electrophiles

A common intuition is that “more π bonds means more nucleophilicity,” but reactivity depends on the *energy cost* of the first step as well as the availability of electrons.

Two factors reduce the rate of electrophilic addition to alkynes relative to alkenes:

- **Stability of intermediates/transition states:** protonation (or electrophilic attack) on an alkyne leads toward a **vinyllic cation** (positive charge on an sp carbon), which is much less stable than an alkyl carbocation.
- **Product stability considerations:** the first addition converts an alkyne into an alkene. This is often favorable overall, but it requires passage through a high-energy cationic region in the mechanism, increasing $\Delta G^\ddagger$.

The first point is the key mechanistic reason and is discussed next.

7.5.3 Vinyl carbocations: why they are unusually unstable

In alkene protonation, the developing carbocation is on an sp^2 carbon, and hyperconjugation from adjacent σ bonds can stabilize the cation. In alkyne protonation, the analogous intermediate would be a **vinyl carbocation** (a cation adjacent to, or directly on, a carbon–carbon double bond after the first addition step).

Two related stability issues arise:

- **Hybridization effect:** a positive charge on an sp carbon is higher in energy because sp orbitals have greater s -character. Greater s -character pulls electron density closer to the nucleus, leaving the carbon framework less able to distribute and stabilize electron deficiency in a simple cationic picture.
- **Hyperconjugation is less effective:** for a vinylic cation, the geometry and orbital alignment limit stabilizing donation from adjacent σ bonds compared to typical alkyl carbocations.

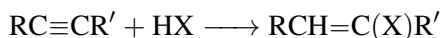
A practical consequence is straightforward and predictive:

Electrophilic additions to alkynes that require formation of a vinylic cation (or a strongly vinylic-cation-like transition state) are typically slower than the corresponding additions to alkenes, and they often require stronger conditions.

7.5.4 Addition of HX to alkynes: vinyl halides and geminal dihalides

One equivalent of HX: formation of a vinyl halide

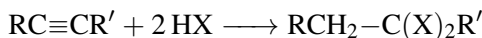
With one equivalent of HX (e.g., HBr, HCl, HI), an alkyne undergoes electrophilic addition to give a **vinyl halide** (an alkene bearing a halogen):



Regiochemistry for terminal alkynes is typically **Markovnikov-like** under ionic conditions: X ends up on the more substituted (internal) carbon, and H ends up on the terminal carbon. This parallels alkene chemistry, but the mechanistic barrier is higher because the first step approaches vinyl cation character.

Two equivalents of HX: geminal dihalides

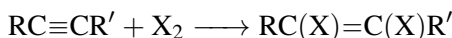
Because the first addition yields a π bond (a vinyl halide), a second equivalent of HX can add across that alkene. Under conditions where excess HX is present, the reaction often proceeds to a **geminal dihalide** (two halogens on the same carbon):



This outcome is a mechanistic consequence of the first halogen being electron-withdrawing, which polarizes the resulting alkene and can bias the second addition to place the new halogen on the same carbon (geminal pattern). In practice, the extent of double addition depends strongly on substrate and conditions; terminal alkynes frequently proceed readily to geminal dihalides when treated with excess HX.

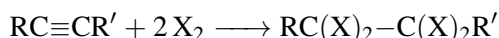
7.5.5 Addition of X_2 to alkynes: dihaloalkenes and tetrahalides

Alkynes also react with Br_2 or Cl_2 . The first equivalent yields a **dihaloalkene**:



The stereochemistry (E/Z) depends on conditions and the detailed mechanism (often involving a halonium-like intermediate even for alkynes), but the important high-level pattern is:

- **One equivalent** gives a **dihaloalkene**.
- **Two equivalents** give a **tetrahalide**:



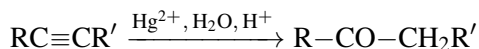
As with HX, the second addition occurs to the alkene formed after the first addition.

7.5.6 Hydration of alkynes: enol formation followed by tautomerization

Hydration is where alkynes diverge most sharply from alkenes in outcome. Adding H and OH across a triple bond initially produces an **enol** (an alkene with an OH group directly attached to a vinylic carbon). Enols are generally not the thermodynamic endpoint for simple systems because they convert to carbonyl compounds (ketones or aldehydes) by **keto–enol tautomerization**.

Overall outcomes: ketones (and aldehydes in special cases)

A common hydration protocol uses aqueous acid with a mercury(II) catalyst (often HgSO_4 in $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$):



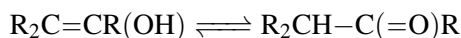
Key product patterns:

- **Internal alkynes** hydrate to give **ketones** (often as mixtures if the alkyne is unsymmetrical).
- **Terminal alkynes** under typical acid/mercury hydration conditions give **methyl ketones** (Markovnikov hydration of the triple bond $\Rightarrow$ enol $\Rightarrow$ ketone).

The mechanistic point emphasized here is not the catalyst detail, but the universal step that follows initial hydration:

**Why tautomerization occurs: thermodynamic driving force**

Keto–enol tautomerization is an isomerization that relocates a proton and shifts the π bond:



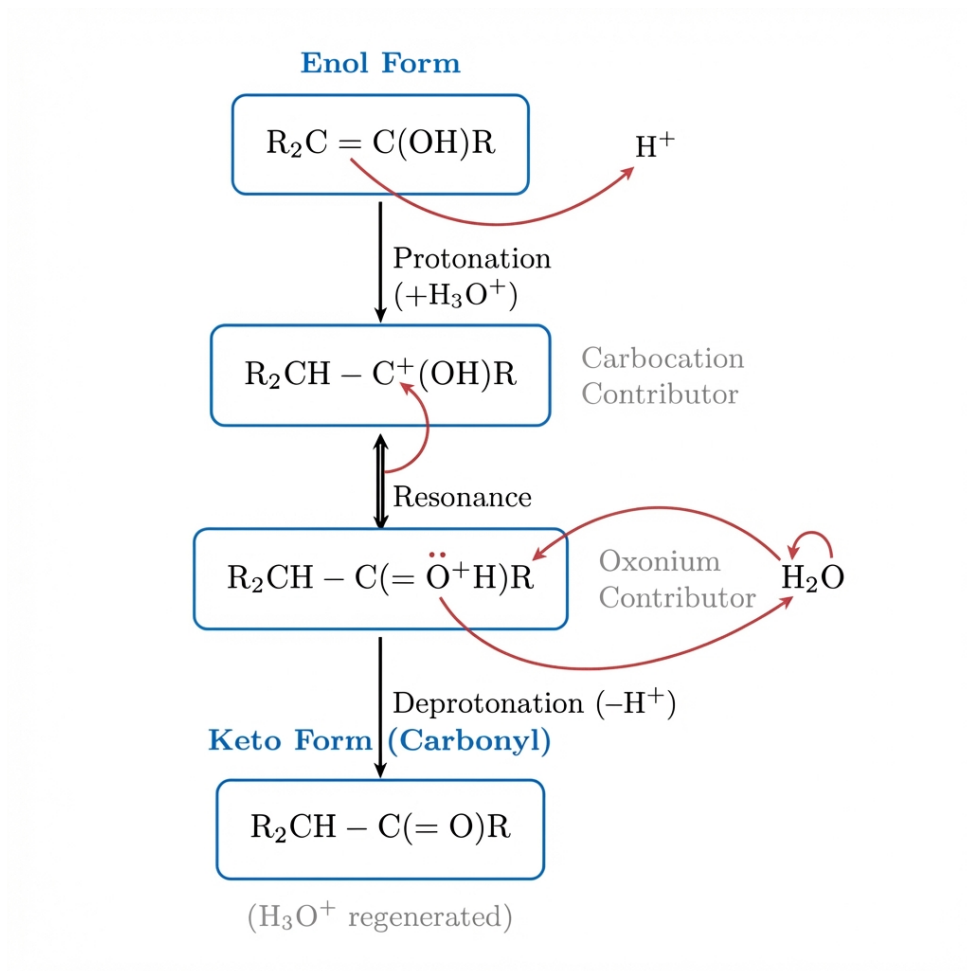
The carbonyl form is typically favored because the $\text{C}=\text{O}$ bond is strong and highly stabilized by polarization (and resonance description of the $\text{C}=\text{O}$ bond). Thus, the enol is often a transient intermediate that is difficult to isolate unless special stabilization is present (conjugation, intramolecular hydrogen bonding, aromaticity in the enol form, etc.).

7.5.7 Acid-catalyzed keto–enol tautomerization (mechanism)

Acid catalysis provides a low-barrier pathway for converting an enol into a carbonyl compound by shuttling protons and enabling rearrangement of π electrons. The essential sequence is:

- protonate the enol double bond to form a resonance-stabilized cation,
- deprotonate oxygen to form the carbonyl.

This mechanism should be practiced with careful curved-arrow bookkeeping, because it is a model for many acid-catalyzed rearrangements of π systems.



Interpreting the mechanism

Several conceptual points are worth highlighting:

- The protonation step occurs at the π bond of the enol (not at oxygen as the

only possibility). Protonation at carbon is what enables rearrangement of the π system toward a carbonyl.

- The “protonated intermediate” is best understood as a **resonance hybrid**: one contributor places positive charge on carbon (carbocation-like), and another places it on oxygen (oxonium-like).
- Deprotonation at oxygen restores neutrality and yields the carbonyl.

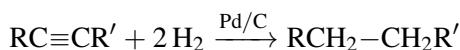
This is a prototypical example of using acid catalysis to interconvert π -bond locations through proton transfers.

7.5.8 Reduction of alkynes: contrasting *cis* and *trans* alkene synthesis

Although the central focus of this chapter is addition reactions, alkynes also illustrate an important selectivity principle in π -bond chemistry: **choice of reagent determines stereochemical outcome**. Reduction provides a concise contrast.

Catalytic hydrogenation: to alkanes (complete reduction)

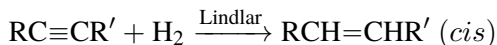
With H_2 and a metal catalyst (e.g., Pd/C, Pt, Ni), alkynes are typically reduced all the way to alkanes:



This is not usually used when the goal is a selectively reduced alkene.

Partial hydrogenation to *cis* alkenes

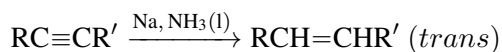
Using a poisoned catalyst (classically Lindlar’s catalyst), alkynes can be reduced to ***cis* alkenes** (syn addition of hydrogen on the catalyst surface):



The important idea is the same as in hydroboration: **syn delivery** of two atoms to a π bond produces a stereochemically defined product.

Dissolving metal reduction to trans alkenes

In contrast, reduction with Na (or Li) in liquid ammonia typically yields **trans alkenes**:



Mechanistically, this proceeds through stepwise electron transfer and protonation events, which favor anti addition overall. The broader message is consistent with the chapter's theme: **intermediate type determines stereochemical outcome**.

7.5.9 Summary: applying alkene logic to alkynes (and knowing what changes)

Alkynes participate in the same broad reaction classes as alkenes, but with predictable modifications:

- **Electrophilic additions** (HX, X₂) occur, often requiring stronger conditions because pathways approach **vinyl cation character**, which is high in energy.
- **Double addition** is common because the first addition produces an alkene that can undergo a second electrophilic addition, yielding geminal dihalides (from HX) or tetrahalides (from X₂).
- **Hydration** produces an **enol** initially, but the observed product is usually a **carbonyl compound** due to **keto–enol tautomerization**. Understanding tautomerization is therefore essential for predicting products of alkyne hydration.
- **Reductions** demonstrate reagent-controlled stereochemistry: syn partial reduction gives cis alkenes, while stepwise dissolving metal reduction gives trans alkenes.

With these principles, alkyne additions can be predicted using the same mechanistic reasoning developed earlier in the chapter, while accounting for the distinctive stability and tautomerization behavior of triple-bond systems.

7.6 Problems

7.6.1 HBr Addition to 1-Methylcyclohexene (Regiochemistry and Stereochemistry)

1-Methylcyclohexene is treated with HBr in an inert solvent at room temperature (no peroxides, no light).

- Draw the **major constitutional product** and justify the regiochemistry using a carbocation-stability argument (show the carbocation that is formed in the rate-determining step).
- Indicate the **stereochemical outcome**. If a mixture forms, specify whether it is racemic and identify the stereocenter(s) created.
- Predict whether any **rearranged products** are expected. If yes, propose a specific 1,2-shift pathway; if no, explain why not.

7.6.2 Acid-Catalyzed Hydration of 3,3-Dimethyl-1-butene (Rearrangements)

3,3-Dimethyl-1-butene is subjected to acid-catalyzed hydration using H_2SO_4 in water.

- Propose a complete curved-arrow mechanism for formation of the **major alcohol product(s)**, including protonation, nucleophilic attack by water, and deprotonation.
- Determine whether a **carbocation rearrangement** is expected. If so, specify whether a 1,2-hydride shift or 1,2-methyl shift occurs, and show the rearranged carbocation.
- Identify the **major** product and at least one plausible **minor** product, and state the mechanistic reason for the product distribution.

7.6.3 Oxymercuration-Demercuration vs. Hydroboration-Oxidation of 1-Hexene

1-Hexene is converted to alcohols under two different conditions:

- 1. $\text{Hg}(\text{OAc})_2$, H_2O (THF); 2. NaBH_4
- 1. $\text{BH}_3 \cdot \text{THF}$; 2. H_2O_2 , NaOH

For each sequence:

- Draw the major product and specify whether the regiochemistry is **Markovnikov** or **anti-Markovnikov**.
- For the oxymercuration case, draw the **key intermediate** responsible for suppressing rearrangements and briefly explain why rearrangements are not expected.
- For hydroboration, indicate the **relative stereochemistry** of addition (syn vs. anti) and explain how that stereochemistry is established in the mechanism.

7.6.4 Stereospecific Bromination of cis-2-Butene vs. trans-2-Butene

Two separate reactions are performed in CH_2Cl_2 :

- cis-2-butene + Br_2
- trans-2-butene + Br_2
- For each alkene, draw the major product(s) with correct stereochemistry. Use wedge/dash or Newman-style conventions as appropriate.
- Classify each product set as **meso**, **racemic**, or a **single enantiomer**, and justify your classification.
- Provide a brief mechanistic argument (halonium ion and backside attack) that explains the difference (or similarity) between the two outcomes.

7.6.5 Synthesis of 2-Pentanone from 1-Pentyne (Functional Group Interconversion)

Design a synthesis of 2-pentanone starting from 1-pentyne. You may use any inorganic reagents and standard catalysts discussed in this chapter.

- Propose reagents and conditions for each step.
- Show the expected major product after each step (structures required).

- Explain why the hydration gives a ketone rather than an isolable enol, and indicate the tautomerization step conceptually.

7.6.6 Halohydrin Formation from 1-Methylcyclopentene

1-Methylcyclopentene is treated with Br₂ in water.

- Draw the major halohydrin product(s) with correct regiochemistry and stereochemistry.
- Indicate which carbon receives OH and which receives Br, and justify using the charge distribution in the bromonium ion.
- State whether addition is **syn** or **anti**, and explain the stereochemical origin.

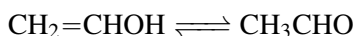
7.6.7 Rate Comparison: HCl Addition to an Alkene vs. an Alkyne (Mechanistic Rationale)

Consider the addition of HCl under comparable ionic conditions to:

- 1-hexene
- 1-hexyne
- Predict which substrate reacts faster and provide a mechanistic explanation based on the stability of the key cationic intermediate/transition state.
- Draw the relevant cation type(s) (alkyl carbocation vs. vinylic carbocation) and explain why one is higher in energy.
- For the alkyne, state whether you expect one or two equivalents of HCl to add under forcing conditions, and identify the likely product class (vinyl halide vs. geminal dihalide).

7.6.8 Mechanism: Tautomerization of Vinyl Alcohol to Acetaldehyde

Write a complete acid-catalyzed mechanism (curved arrows) for the tautomerization:



- Show protonation at the appropriate site, resonance stabilization of the key intermediate, and deprotonation to form the carbonyl.
- Clearly indicate how the π bond is relocated during the process.
- Identify which steps are acid-catalyzed and how the catalyst is regenerated.

7.6.9 Dissolving Metal Reduction of 2-Butyne (Stereochemical Outcome)

2-Butyne is treated with Na in liquid ammonia, followed by aqueous workup:



- Predict the major product and specify its alkene geometry (*E* or *Z*; cis or trans).
- Explain (conceptually) why this reduction gives that stereochemical outcome, contrasting it with catalytic hydrogenation on a metal surface.
- If the reaction is stopped early, discuss whether over-reduction to the alkane is expected under these conditions.

7.6.10 Multi-step Synthesis: Convert Acetylene into cis-2-Hexene

Design a synthesis of cis-2-hexene starting from acetylene ($\text{HC}\equiv\text{CH}$). Your plan must include:

- Construction of the C_6 carbon skeleton using appropriate carbon-carbon bond-forming steps consistent with acetylide chemistry (assume you may generate acetylide anions with strong base as needed).
- Formation of an internal alkyne precursor to cis-2-hexene.
- Selective partial reduction to the **cis** alkene (specify reagents and conditions).
- Structures for all major intermediates.

In addition, briefly state why your final reduction conditions give the **cis** alkene rather than the **trans** alkene.

Chapter 8

Oxidation, Reduction, and Organometallics

While functional group interconversions form the vocabulary of organic chemistry, the ability to construct carbon skeletons and manipulate oxidation states constitutes its grammar. In this chapter, we transcend simple substitution and elimination to explore reactions that fundamentally alter the electron density of carbon atoms. We begin by quantifying these changes through oxidation states, then survey powerful methods for oxidizing alcohols and alkenes and reducing carbonyls. Finally, we unlock the synthetic potential of organometallic reagents—transforming carbon from an electrophilic target into a nucleophilic architect capable of building complex molecular frameworks.

8.1 Oxidation States and Redox Agents

Organic chemistry relies heavily on patterns: functional groups interconvert in predictable ways, and those interconversions often correspond to *oxidation* (increasing the oxidation level of carbon) or *reduction* (decreasing it). In earlier chapters, you learned to recognize functional groups and to follow curved-arrow mechanisms. Here we add a quantitative bookkeeping tool—**carbon oxidation state**—that (1) unifies many seemingly different transformations under one principle and (2) helps you predict which reagents can accomplish a desired functional group change.

8.1.1 Why oxidation states matter in organic synthesis

In inorganic chemistry, oxidation states are often computed for atoms in ionic compounds. Organic molecules are covalent, so oxidation states are a *formalism*, not a physical charge. Nevertheless, this formalism is extraordinarily useful because it tracks electron *ownership* based on electronegativity and correlates directly with common functional group families:

- **More reduced carbon** has *more C–H bonds* and *fewer bonds to heteroatoms* (O, N, halogens).
- **More oxidized carbon** has *fewer C–H bonds* and *more bonds to electronegative atoms*, especially oxygen.

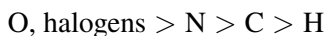
Many synthetic sequences can be planned as “move up” or “move down” an oxidation ladder, then perform a carbon–carbon bond-forming step at the appropriate oxidation level.

8.1.2 Rules for assigning oxidation states to carbon in organic molecules

To assign the oxidation state (OS) of a carbon atom in an organic molecule:

- **Step 1.** Break all bonds to carbon *homolytically* (split equally). A C–C bond contributes **0** to carbon’s OS because the electrons are shared between atoms of equal electronegativity.
- **Step 2.** Assign electrons in each C–X bond to the more electronegative atom. For a bond from carbon to a **more electronegative** atom (O, N, F, Cl, Br, I, S), carbon *loses* electron ownership: count **+1** for carbon per single bond. For a bond from carbon to **hydrogen** (less electronegative than carbon), carbon *gains* electron ownership: count **–1** for carbon per C–H bond.
- **Step 3.** Multiple bonds count multiple times. A C=O double bond counts as two C–O bonds (i.e., contributes **+2** to the carbon OS). A C≡N triple bond would count as three C–N bonds (contributes **+3**).
- **Step 4.** Sum contributions from all bonds to that carbon.

Electronegativity order (practical). For oxidation-state bookkeeping in this chapter, you can safely use:



Thus: C–O and C–X (X = halogen) raise carbon OS; C–H lowers carbon OS; C–C does not change carbon OS.

8.1.3 Worked examples: computing carbon oxidation state

Example 1: methane, CH₄. Carbon has four C–H bonds. Each C–H contributes –1:

$$\text{OS}(C) = 4(-1) = -4$$

Methane is therefore a very reduced form of carbon.

Example 2: methanol, CH₃OH. Carbon has three C–H bonds (3×-1) and one C–O bond (+1):

$$\text{OS}(C) = 3(-1) + 1(+1) = -2$$

Example 3: formaldehyde, H₂C=O. Carbon has two C–H bonds (2×-1) and one C=O double bond (+2):

$$\text{OS}(C) = 2(-1) + 2(+1) = 0$$

Example 4: formic acid, HCO₂H. The carbonyl carbon has one C–H bond (–1), one C=O (+2), and one C–O single bond to OH (+1):

$$\text{OS}(C) = (-1) + (+2) + (+1) = +2$$

Example 5: carbon dioxide, O=C=O. Two C=O double bonds contribute $2(+2) = +4$:

$$\text{OS}(C) = +4$$

This is the fully oxidized limit for carbon in common organic chemistry contexts.

8.1.4 The oxidation ladder: functional groups as oxidation levels

Once you can compute oxidation states, you can organize functional groups by the oxidation state of the key carbon (often the carbon bearing the functional group). The most useful “backbone” ladder for this chapter is:



This ladder is not merely a list: it encodes the net change in C–H vs. C–O bonds and predicts which transformations are oxidation (up the ladder) or reduction (down the ladder).

Ladder of Oxidation chart (with examples)

The following table summarizes representative functional-group rungs and the corresponding formal carbon oxidation states.

Functional group	Representative example	Carbon OS
Alkane	CH ₄	−4
Alcohol	CH ₃ OH	−2
Aldehyde	H ₂ C=O	0
Ketone	CH ₃ -C(=O)-CH ₃ (carbonyl C)	+2
Carboxylic acid	H-C(=O)-OH	+2
CO ₂	O=C=O	+4

8.1.5 Oxidation and reduction as changes in bonding patterns

A powerful habit is to translate “oxidation” and “reduction” into bond changes at the carbon center of interest:

- **Oxidation at carbon** typically means:

fewer C–H bonds and/or more C–O (or C–X) bonds

- **Reduction at carbon** typically means:

more C–H bonds and/or fewer C–O (or C–X) bonds

For example, converting a primary alcohol to an aldehyde replaces one C–H bond equivalent with a C=O bond (net increase in oxidation state by 2 for that carbon). Converting an aldehyde to a primary alcohol does the reverse (net reduction by 2).

8.1.6 Redox agents: definitions and practical interpretation

In organic chemistry, it is most useful to define agents by *what they do to the substrate*:

- An **oxidizing agent** accepts electron density overall; it *raises* the oxidation state of the organic substrate.
- A **reducing agent** donates electron density overall; it *lowers* the oxidation state of the organic substrate.

Chemically, the oxidant is reduced and the reductant is oxidized, but in synthesis planning you usually track only the substrate's change. A key synthetic idea is **chemoselectivity**: choosing a reagent that oxidizes (or reduces) one functional group in the presence of another.

8.1.7 Survey of common oxidizing agents (with “strength” and typical use)

Oxidants can be grouped by how aggressively they push a substrate “up” the oxidation ladder and by what functional groups they tolerate.

Chromium(VI) oxidants: strong, reliable, but harsh

Jones oxidation (chromic acid conditions). A common laboratory implementation uses CrO_3 in aqueous acid (often H_2SO_4) and acetone as solvent. Under these **aqueous** conditions:

- primary alcohols → **carboxylic acids**
- secondary alcohols → **ketones**
- aldehydes (if present) → **carboxylic acids**

Mechanistically, these oxidations proceed through formation of a **chromate ester** followed by elimination to the carbonyl. The presence of water is crucial: aldehydes hydrate to gem-diols, which are readily oxidized further to acids.

Scope and limitations. Cr(VI) oxidants are typically **not** compatible with many oxidation-sensitive groups and are operationally less desirable due to toxicity and waste concerns. Nonetheless, they remain conceptually important and are still encountered.

Mild, anhydrous alcohol oxidants: stopping at aldehydes

PCC (pyridinium chlorochromate). PCC is a Cr(VI) reagent commonly used in **anhydrous** organic solvents (e.g., dichloromethane). A central practical distinction from Jones conditions is the **absence of water**, which helps prevent overoxidation of aldehydes to acids:

- primary alcohols → **aldehydes** (often)
- secondary alcohols → **ketones**

PCC still uses chromium, but its typical behavior is milder and more chemoselective than aqueous chromic acid.

DMP and Swern oxidation (non-chromium, mild). Two widely used alternatives:

- **Dess–Martin periodinane (DMP):** a hypervalent iodine oxidant. Generally mild, often high-yielding, and frequently compatible with sensitive functionality.
- **Swern oxidation:** uses activated DMSO (e.g., oxalyl chloride + DMSO, then base). Particularly valuable for acid-sensitive substrates and for avoiding heavy-metal waste.

These reagents will be treated mechanistically in Section 8.2, but at this stage you should associate them with **selective oxidation of alcohols to carbonyl compounds under mild, anhydrous conditions**.

Oxidation of alkenes: adding oxygen or cleaving C=C bonds

Although alkenes are not a single rung on the simple carbonyl ladder, their oxidation is central in synthesis because it rapidly increases functionality.

Permanganate and osmium tetroxide (dihydroxylation).

- OsO_4 (with a co-oxidant) gives **syn-1,2-diols** from alkenes.
- KMnO_4 can also add oxygen across alkenes; under vigorous conditions it can proceed to **oxidative cleavage**.

Ozonolysis (oxidative cleavage). O_3 followed by an appropriate workup cleaves C=C bonds to carbonyl fragments. This is both a synthetic tool and a method for structural analysis. Details and mechanisms appear in Section 8.2.

A quick “oxidant strength” intuition

Rather than memorizing lists, build an intuition around two questions:

- **1.** Does the oxidant operate under aqueous/strongly acidic conditions? If yes, aldehydes often overoxidize to acids.
- **2.** Is the oxidant designed for selective alcohol-to-carbonyl conversion under anhydrous conditions? If yes, it often stops at aldehydes/ketones.

This is not a substitute for mechanism, but it is an excellent first-pass predictor.

8.1.8 Survey of common reducing agents (preview for Section 8.3)

Because this chapter treats oxidation and reduction as a unified theme, it is helpful to place key reductants on the same conceptual map, even though detailed chemoselectivity and mechanisms are developed later.

Catalytic hydrogenation: H_2 with a metal catalyst

- Typical catalysts: Pd/C, Pt, Ni.
- Most commonly: **reduces alkenes to alkanes** (decreases oxidation level by adding H across a π bond).
- Under appropriate conditions it can also reduce other functional groups, but in introductory synthesis planning you should primarily associate it with **C=C reduction**.

Hydride donors: NaBH_4 and LiAlH_4

- **NaBH_4** : typically reduces **aldehydes and ketones** to alcohols under relatively mild conditions.
- **LiAlH_4** : a much stronger hydride donor; reduces **aldehydes, ketones, esters, and carboxylic acids** (and many other derivatives) to alcohols, but is highly reactive toward water and protic groups.

At the planning level, a good rule is: NaBH_4 is selective and mild; LiAlH_4 is broad and powerful. Section 8.3 will explain these trends mechanistically and extend them to chemoselectivity across multiple functional groups.

8.1.9 Chemoselectivity and functional group compatibility: the central synthetic constraint

Organic molecules typically contain more than one functional group. The reagent that performs the desired redox change must do so without unwanted side reactions. Two recurring constraints dominate redox planning:

Constraint 1: Overoxidation and hydration. Primary alcohol $\rightarrow$ aldehyde is often challenging because aldehydes can be further oxidized (especially in water, where aldehydes form gem-diols). Thus:

- Aqueous, strong oxidants often give acids from primary alcohols.
- Anhydrous, “alcohol-to-carbonyl” oxidants often stop at aldehydes.

Constraint 2: Acid/base sensitivity. Some oxidants/reductants are strongly acidic, basic, or otherwise reactive toward functional groups that are not the redox target (e.g., acetals, epoxides, amines). Later sections will repeatedly return to the theme:

Choose reagents by both *redox power* and *compatibility*.

8.1.10 Summary: what to know before moving on

Before studying specific mechanisms and synthetic applications in Sections 8.2–8.6, you should be able to:

- **1.** Compute the oxidation state of a carbon atom by counting C–H as -1 , C–O/C–X as $+1$ (per bond), and C–C as 0 .
- **2.** Place common functional groups on an oxidation ladder and recognize oxidation vs. reduction as movement along that ladder.
- **3.** Predict, at a qualitative level, which oxidants are “strong” (often aqueous Cr(VI), permanganate) and which are “mild/anhydrous” (PCC, DMP, Swern).
- **4.** Recognize the major classes of reductants (catalytic hydrogenation, hydride donors) and anticipate that their selectivity will be a major focus of the next section.

8.2 Oxidation of Alcohols and Alkenes

Section 8.1 introduced oxidation state as a practical bookkeeping device: alcohol $\rightarrow$ carbonyl $\rightarrow$ carboxylic acid corresponds to a net increase in the oxidation level of carbon. This section turns that bookkeeping into **predictive mechanistic chemistry**. We will analyze (1) how common reagents oxidize alcohols and why reaction conditions determine whether a primary alcohol stops at an aldehyde or proceeds to a carboxylic acid, and (2) how alkenes are oxidized either by **addition** of oxygen across the π bond (dihydroxylation/epoxidation) or by **cleavage** of the double bond (ozonolysis and related oxidative cleavage).

8.2.1 General mechanistic motif: activate oxygen, then eliminate

Most alcohol oxidations share a unifying mechanistic theme:

- **1. Activation of the O–H (or O lone pairs)** to convert the poor leaving group –OH into a good leaving group (often via formation of a sulfonium, chromate, or iodinate ester).
- **2. Elimination** (often described as an E2-like step at carbon) that forms the π bond of the carbonyl and expels the leaving group.

The alcohol oxygen is the site of initial reaction because it is nucleophilic (lone pairs), and the C–O bond is already present; oxidation reorganizes electron density to create a C=O bond without breaking the carbon skeleton.

8.2.2 Oxidation of alcohols

Classifying alcohol substrates: what can be oxidized?

Primary vs. secondary vs. tertiary. Oxidation to a carbonyl requires removal of a hydrogen from the α -carbon (the carbon bearing the OH):

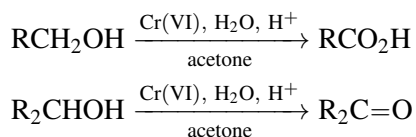
- **Primary alcohols** (RCH_2OH) have α -hydrogens and can be oxidized to aldehydes and (often) to carboxylic acids.
- **Secondary alcohols** (R_2CHOH) have an α -hydrogen and are oxidized to ketones.

- **Tertiary alcohols** (R_3COH) **lack** an α -hydrogen. They cannot be oxidized to carbonyl compounds without breaking a C–C bond; under harsh conditions they may undergo fragmentation rather than clean oxidation.

This structural requirement is one of the most important "mechanism-first" explanations for why tertiary alcohols behave differently.

Chromium(VI) oxidations: Jones reagent and related Cr(VI) systems

Typical conditions and outcomes. A prototypical strong Cr(VI) oxidation uses aqueous acid (often written as CrO_3 , H_2SO_4 , H_2O in acetone). Common outcomes:



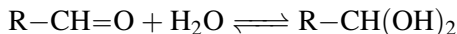
The key synthetic distinction is that **primary alcohols typically proceed to carboxylic acids** because the intermediate aldehyde is further oxidized under aqueous conditions.

Mechanism: chromate ester formation and elimination. Although the exact chromium species depend on pH and reagent source, the mechanistic steps for alcohol oxidation are consistent:

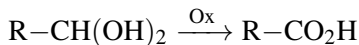
- **1. Chromate ester formation.** The alcohol oxygen attacks electrophilic chromium(VI), forming a C–O–Cr linkage (a chromate ester) after proton transfers.
- **2. Elimination to form the carbonyl.** A base (often water or another oxygen-bearing ligand) removes the α -hydrogen. As the C–H bond breaks, electrons form the C=O π bond while the O–Cr bond breaks, reducing chromium.

This elimination is commonly taught as an E2-like, concerted step that avoids discrete carbocation formation. The driving force is formation of a strong C=O bond coupled to reduction of Cr(VI) to lower oxidation states (often Cr(III) by the end of the process).

Why aldehydes overoxidize in water: the hydrate pathway. Aldehydes are uniquely prone to further oxidation because they reversibly form geminal diols (hydrates) in water:



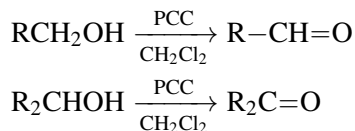
A gem-diol has an alcohol-like C–OH pattern and is readily oxidized by Cr(VI) (and many other oxidants) to a carboxylic acid:



Thus, **water does not just "accompany" the reaction; it creates a new oxidizable functional group.** This is the mechanistic reason that anhydrous oxidants can stop at aldehydes more reliably than aqueous oxidants.

PCC: anhydrous Cr(VI) oxidation that often stops at aldehydes

Typical outcomes. Pyridinium chlorochromate (PCC) is commonly used in non-aqueous solvents (e.g., CH_2Cl_2):



Mechanistic similarity to Jones oxidation. PCC also proceeds via chromate ester formation and elimination. The difference is primarily **reaction medium**:

- In anhydrous solvent, aldehyde hydration is suppressed, which reduces the rate of overoxidation.
- PCC conditions are often less strongly acidic and less water-rich than Jones conditions.

Practical caveat. Even with PCC, overoxidation can occur if water is present or if the aldehyde is unusually prone to oxidation. Mechanism-based thinking prevents overgeneralization: controlling water content and reaction time matters.

DMP and Swern oxidation: mild, non-chromium approaches

Dess–Martin periodinane (DMP). DMP is a hypervalent iodine reagent valued for mild conditions and broad functional group tolerance. The mechanistic logic paral-

lels Cr(VI): an **alkoxy-iodinane intermediate** forms (activation), then elimination produces the carbonyl. In synthesis planning, DMP is often chosen when:

- chromium waste is undesirable,
- acid-sensitive groups are present,
- selective oxidation to an aldehyde is needed.

Swern oxidation (activated DMSO). Swern oxidation typically uses a sequence such as $(\text{COCl})_2$ (or similar activator) + DMSO at low temperature, then base (often Et_3N). The key intermediate is an **alkoxysulfonium ion**, which undergoes base-promoted elimination to form the carbonyl and a sulfur-containing byproduct. In planning terms, Swern is powerful because it is:

- strongly **anhydrous** (good for stopping at aldehydes),
- often compatible with oxidant-sensitive functionality,
- mechanistically clean: activation $\rightarrow$ elimination.

Arrow-pushing details for Swern are deferred to a later figure in this chapter; for now, emphasize the shared activation–elimination motif.

Choosing an alcohol oxidant: a synthesis-oriented checklist

When selecting an oxidant, focus on what must be controlled:

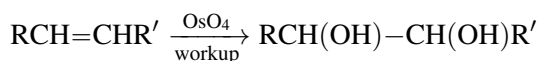
- **1. Target product: aldehyde vs. acid.**
 - Want $\text{RCH}_2\text{OH} \longrightarrow \text{RCHO}$: favor anhydrous, mild oxidants (PCC, DMP, Swern).
 - Want $\text{RCH}_2\text{OH} \longrightarrow \text{RCO}_2\text{H}$: favor aqueous/strong oxidants (Jones, KMnO_4 under appropriate conditions).
- **2. Functional group compatibility.** Acid/base sensitivity, oxidizable heteroatoms, and protecting groups often dominate the choice.
- **3. Operational constraints.** Temperature control, odor/toxicity, and waste handling can matter in real laboratory practice.

8.2.3 Oxidation of alkenes

In oxidation-state terms, an alkene is not a single rung but a versatile platform: oxidation can **add** oxygen functionality without changing the carbon skeleton, or **cleave** the π bond to create two carbonyl fragments. The mechanistic basis is the high electron density and polarizability of the π bond, which makes it reactive toward electrophilic oxidants.

Syn dihydroxylation: OsO₄ and related methods

Overall transformation and stereochemistry. Osmium tetroxide adds to alkenes to form vicinal diols with **syn** stereochemistry (both OH groups added to the same face):



If the alkene is cyclic, syn addition produces a **cis-1,2-diol**. If the alkene is acyclic, syn addition controls the relative stereochemistry of the new stereocenters (when applicable).

Mechanism: concerted cycloaddition to form an osmate ester. The key step is a concerted addition of OsO₄ across the π bond to form a cyclic **osmate ester**. Hydrolytic workup cleaves the Os–O bonds to release the diol. Important mechanistic consequences:

- Because addition is concerted, stereochemistry is predictable (syn).
- No carbocation intermediates are required; rearrangements are not expected.

Practical note. OsO₄ is highly toxic and often used catalytically with a co-oxidant to reoxidize osmium. Regardless of implementation, the mechanistic identity of syn addition is the key concept.

Permanganate dihydroxylation and oxidative cleavage

Cold, dilute KMnO₄: dihydroxylation. Under mild conditions, permanganate can also deliver syn dihydroxylation. In practice, KMnO₄ is less selective and can lead to overoxidation, so it is often presented as a conceptually similar but operationally harsher alternative.

Hot, concentrated KMnO_4 : oxidative cleavage. Under vigorous conditions, KMnO_4 can cleave alkenes, generating carbonyl-containing fragments. The identity of the fragments depends on substitution:

- A double-bond carbon bearing at least one H often ends as a **carboxylic acid** (further oxidation of an aldehyde intermediate).
- A fully substituted alkene carbon (no H) typically yields a **ketone**.
- Terminal alkenes frequently give CO_2 from the terminal carbon under strongly oxidative conditions.

The product pattern is best understood by combining (1) the idea that cleavage initially forms aldehydes/ketones and (2) the Section 8.1 principle that aldehydes readily oxidize further in strongly oxidative, aqueous environments.

Ozonolysis: oxidative cleavage with high structural information content

Why ozonolysis is special. Ozonolysis cleaves a $\text{C}=\text{C}$ bond and converts each alkene carbon into a carbonyl carbon. This is powerful because it:

- **simplifies structure** into smaller, interpretable fragments,
- often proceeds under relatively mild temperatures,
- can be tuned by workup conditions.

Mechanistic outline: molozonide $\rightarrow$ ozonide $\rightarrow$ carbonyl products. A mechanistically useful overview (without getting lost in pericyclic detail) is:

- **1. Cycloaddition of ozone** to the alkene forms a **molozonide** (an unstable 1,2,3-trioxolane).
- **2. Fragmentation/recombination** yields an **ozonide** (a more stable 1,2,4-trioxolane).
- **3. Workup** cleaves the ozonide to carbonyl compounds.

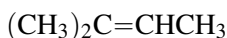
Reductive vs. oxidative workup. Workup conditions determine how far oxidation proceeds after cleavage:

- **Reductive workup** (e.g., $(\text{CH}_3)_2\text{S}$ or $\text{Zn}/\text{H}_2\text{O}$) tends to give **aldehydes and ketones**.
- **Oxidative workup** (e.g., H_2O_2) tends to oxidize aldehydes further to **carboxylic acids** (ketones remain ketones).

These outcomes again reflect the key principle: **aldehydes are easier to oxidize than ketones** under typical oxidative conditions.

Using ozonolysis for structure determination. Because each alkene carbon becomes a carbonyl carbon, the products "report" what substituents were attached to each alkene carbon.

For example, consider:



Cleavage yields acetone ($(\text{CH}_3)_2\text{C}=\text{O}$) from the fully substituted alkene carbon and acetaldehyde (CH_3CHO) from the alkene carbon bearing one hydrogen (under reductive workup). Even without memorizing this specific example, you can reason it out:

- carbon with two methyl substituents $\rightarrow$ ketone carbonyl with two methyl substituents;
- carbon with methyl and hydrogen substituents $\rightarrow$ aldehyde.

Epoxidation (preview link to later chapters and Section 8.6)

Alkenes can also be oxidized to epoxides using peracids (e.g., mCPBA). Mechanistically, epoxidation is concerted and stereospecific (the alkene geometry is retained in the epoxide). Although epoxides are not the final focus here, this oxidation is strategically important because epoxides are **activated** electrophiles for ring opening, which will be used extensively with organometallic nucleophiles in Section 8.6.

8.2.4 Comparing alkene oxidation pathways: addition vs. cleavage

It is useful to classify alkene oxidation by whether the carbon skeleton is preserved:

- **Addition oxidation** (skeleton preserved): dihydroxylation (OsO_4 , mild KMnO_4); epoxidation (peracids).

- **Cleavage oxidation** (skeleton broken): ozonolysis; strong KMnO_4 .

From a synthesis-planning perspective, addition is used to **install functionality** across a double bond; cleavage is used to **reorganize the carbon framework** or to reveal hidden structural information.

8.2.5 Summary: key outcomes to master

By the end of this section, you should be able to do the following reliably:

- **1.** Predict whether a given alcohol (1° , 2° , 3°) can be oxidized to a carbonyl without C–C bond cleavage.
- **2.** Explain alcohol oxidation mechanisms using the activation–elimination motif (chromate ester; activated DMSO or iodine(III) analogs).
- **3.** Predict when a primary alcohol oxidation will stop at an aldehyde versus proceed to a carboxylic acid, and explain the role of aldehyde hydration in overoxidation.
- **4.** Predict stereochemical outcomes of syn dihydroxylation of alkenes.
- **5.** Use ozonolysis logic to infer cleavage products from an alkene and to understand how workup conditions control aldehyde vs. acid formation.

8.3 Reduction of Carbonyl Compounds and Alkenes

Sections 8.1–8.2 framed oxidation and reduction as movement along an “oxidation ladder” for carbon. Oxidation increased the number of C–O (or C–X) bonds and decreased the number of C–H bonds; reduction did the reverse. In this section we focus on the complementary transformations: **reductions** that lower the oxidation state of carbon. Two mechanistic families dominate introductory organic synthesis:

- **Catalytic hydrogenation** (H_2 on a metal surface)—most important for π bonds such as alkenes.
- **Nucleophilic hydride delivery** (e.g., NaBH_4 , LiAlH_4)—most important for polarized π bonds such as carbonyls.

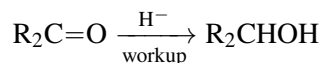
A central skill is **chemoselectivity**: predicting which functional group will be reduced (and which will be left untouched) under a given set of conditions.

8.3.1 Thermodynamic and mechanistic perspective: what “reduction” means here

At the carbon atom being transformed, reduction typically corresponds to:

- **Adding hydrogen** (increasing C–H bonding), and/or
- **Removing oxygen functionality** (decreasing the effective number of C–O bonds).

For carbonyl reductions, it is helpful to view the transformation as addition of H^- to carbon and H^+ to oxygen (even if the actual proton source is solvent during workup):

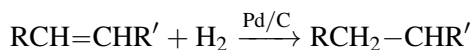


This shorthand emphasizes the polarity of the C=O bond: carbon is electrophilic, oxygen is basic.

8.3.2 Catalytic hydrogenation of alkenes

Overall transformation and stereochemical outcome

The simplest and most common hydrogenation reduces an alkene to an alkane:



Syn addition. Hydrogenation on a metal surface is effectively **syn** (both H atoms add to the same face of the alkene) because both hydrogens are delivered from the catalyst surface. Consequently:

- Hydrogenation of cyclic alkenes typically gives products consistent with syn addition.
- In acyclic systems, hydrogenation removes the double bond; stereochemical outcomes are most apparent when new stereocenters form.

Mechanistic sketch: adsorption and delivery from a surface

A detailed organometallic mechanism is beyond the scope of this chapter, but the essential steps are:

- **Adsorption of H₂** to the metal and dissociation to surface hydrides.
- **Adsorption of the alkene** onto the metal surface (interaction of the π bond with the metal).
- **Stepwise transfer of H atoms** from the surface to the two alkene carbons, followed by product desorption.

This model explains two practical observations:

- **Syn stereochemistry** (delivery from one surface face).
- **Sensitivity to sterics and poisoning**: strongly coordinating groups or impurities can inhibit adsorption and slow or stop the reaction.

Selectivity considerations for H₂/Pd-C

At the level needed here, H₂/Pd-C is best remembered as a reagent that **reliably reduces C=C bonds**. Under more forcing conditions it can reduce other groups, but for synthesis planning you should assume:

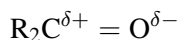
- **Alkenes**: readily reduced.
- **Simple carbonyls (aldehydes/ketones)**: typically *not* reduced by standard hydrogenation conditions used for alkenes.

Later chapters may address specialized catalysts and conditions (e.g., hydrogenation of carbonyls, imines, aromatic rings), but the foundational chemoselectivity pattern above is what will be used in this chapter's synthesis problems.

8.3.3 Hydride reductions of carbonyl compounds

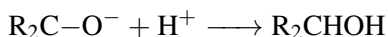
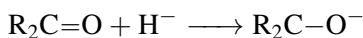
Why hydride is a natural reagent for carbonyls

The carbonyl group is polarized:



Thus, the carbonyl carbon is electrophilic. Nucleophilic hydride donors deliver H[−] (formally) to carbon, generating an alkoxide that is then protonated.

The generic two-step pattern is:



A common point of confusion is that H^- does not exist freely in solution. Instead, it is transferred from a reagent such as BH_4^- or AlH_4^- , where it is bound to boron or aluminum.

Sodium borohydride (NaBH_4): mild, selective carbonyl reduction

Typical scope. NaBH_4 commonly reduces:

- **Aldehydes** $\rightarrow$ primary alcohols
- **Ketones** $\rightarrow$ secondary alcohols

and it usually does so in protic solvents (e.g., methanol, ethanol) or mixed solvents.

Mechanism (conceptual).

- **Hydride transfer:** a B–H bond donates hydride to the carbonyl carbon, forming an alkoxide.
- **Protonation:** the alkoxide is protonated by solvent (or during aqueous workup) to yield the alcohol.

Why it is “mild.” Two interrelated ideas explain NaBH_4 ’s selectivity:

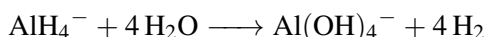
- **Reactivity of the donor.** Boron is less Lewis acidic than aluminum; B–H bonds are less polarized toward H^- than Al–H bonds, making hydride transfer less aggressive.
- **Electrophilicity of the acceptor.** Aldehydes and ketones are more electrophilic than esters and amides. A mild hydride donor can reduce aldehydes/ketones while leaving less electrophilic carbonyl derivatives largely unchanged.

Lithium aluminum hydride (LiAlH_4): strong, broad carbonyl reduction

Typical scope. LiAlH_4 reduces a much wider set of functional groups, including:

- aldehydes $\rightarrow$ primary alcohols
- ketones $\rightarrow$ secondary alcohols
- esters $\rightarrow$ primary alcohols (plus an alcohol from the leaving group)
- carboxylic acids $\rightarrow$ primary alcohols
- many acyl derivatives (acid chlorides, anhydrides) $\rightarrow$ alcohols

Key operational rule: LAH must be used under anhydrous conditions. Reaction with water is vigorous:



Therefore LAH reductions are typically performed in dry ethers (e.g., Et_2O , THF) followed by a careful aqueous workup.

Mechanism for aldehydes and ketones. For aldehydes and ketones, the mechanism mirrors NaBH_4 :

- hydride transfer to carbonyl carbon $\rightarrow$ alkoxide (often coordinated to Al)
- protonation during workup $\rightarrow$ alcohol

The difference is mainly **rate and driving force**: Al–H bonds are more hydridic.

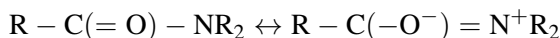
Mechanism for esters: addition–elimination then a second hydride addition. Ester reduction is a canonical example where mechanism *explains* stoichiometry and products.

Consider a generic ester $\text{RCO}_2\text{R}'$. The sequence is:

- **First hydride addition:** H^- adds to the ester carbonyl, forming a tetrahedral alkoxide intermediate.
- **Elimination:** the tetrahedral intermediate collapses, expelling OR'^- to form an aldehyde RCHO .
- **Second hydride addition:** the aldehyde is reduced to a primary alkoxide.
- **Workup:** protonation yields RCH_2OH and $\text{R}'\text{OH}$.

Thus, esters require *two* net hydride deliveries to reach the alcohol oxidation level.

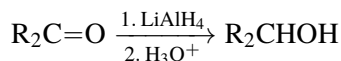
Why amides are harder to reduce. Amide carbonyls are less electrophilic due to resonance donation from nitrogen:



This stabilizes the carbonyl and raises the barrier to nucleophilic attack. LAH can reduce many amides (under appropriate conditions), but the reaction is generally more demanding than ester reduction and may require heating; NaBH₄ typically does not reduce amides.

Acid workup and the “hidden” role of protonation

Because hydride reagents are strongly basic, the immediate products of hydride transfer are usually metal-bound alkoxides. The alcohol product appears only after protonation. It is common to write reductions with two lines:



This notation encodes a mechanistic truth: step 1 is nucleophilic addition (reduction), step 2 is acid–base chemistry (protonation).

Competing reactions: reduction vs. acid–base quenching

Hydride reagents are both **nucleophiles** (deliver hydride to electrophiles) and **bases** (react with protic sites). Therefore, functional group compatibility is critical:

- Protic groups (e.g., ROH, RCO₂H, RNH) can **consume** hydride reagent by acid–base reaction.
- Carbonyl and related electrophiles **compete** for hydride transfer.

This dual nature is also the reason that LAH is a poor choice in the presence of unprotected alcohols or acids unless those groups are intended to be reduced/neutralized or are protected.

8.3.4 Chemoselectivity map: choosing between $\text{H}_2/\text{Pd-C}$, NaBH_4 , and LiAlH_4

Chemoselectivity table (core functional groups)

Reagent	Alkene (C=C)	Aldehyde (RCHO)	Ketone ($\text{R}_2\text{C}=\text{O}$)	Ester ($\text{RCO}_2\text{R}'$)	Amide (RCONR_2)
$\text{H}_2/\text{Pd-C}$		×	×	×	×
NaBH_4	×			×	×
LiAlH_4	×				*

Legend: = typically reduces × = typically does not reduce * = often reduces but may require forcing conditions.

Note: Actual outcomes depend on solvent, catalyst, temperature, and substrate structure.

8.3.5 Problem-solving strategies: predicting products and choosing reagents

Strategy 1: Identify the electrophile class and ask “is hydride addition plausible?”

- Aldehyde/ketone: strong $\text{C}^{\delta+}$ electrophile $\Rightarrow$ NaBH_4 works.
- Ester: less electrophilic and has a leaving group $\Rightarrow$ needs a stronger donor (LiAlH_4) and proceeds via addition–elimination.
- Amide: resonance-stabilized $\Rightarrow$ hardest; LiAlH_4 sometimes required with heat.

Strategy 2: Account for workup and proton sources

If a reagent is incompatible with protic groups, plan a two-stage sequence:

(anhydrous reduction) $\rightarrow$ (aqueous/acidic workup)

Do not “mix” LAH with aqueous acid in a single conceptual step; the workup is necessary but must occur *after* the hydride addition steps.

Strategy 3: Use oxidation level as a consistency check

After predicting a product, verify it against oxidation-state logic from Section 8.1:

- Carbonyl carbon (approximately 0 for aldehydes; +2 for ketones) $\rightarrow$ alcohol carbon (lower oxidation state).
- Alkene $\rightarrow$ alkane is reduction (adds H; lower oxidation level).

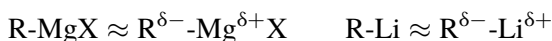
This “sanity check” catches many errors in multi-step synthesis planning.

8.4 Organolithium and Grignard Reagents

Sections 8.1–8.3 emphasized redox logic and polar reactivity: carbonyl carbons are electrophilic, hydride donors are nucleophilic, and catalytic hydrogenation reduces π bonds by adding hydrogen. In this section we introduce a different kind of “reduction” reagent—**organometallic reagents**—that are best understood not as hydride sources but as **carbon nucleophiles**. In synthesis, Grignard reagents and organolithium reagents are among the most powerful tools for **building C–C bonds**.

8.4.1 What makes organometallic reagents special? The polarity of the C–M bond

A Grignard reagent is typically written R–MgX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$); an organolithium reagent is written R–Li . In both cases, the C–M bond is highly polarized because Mg and Li are far less electronegative than carbon:



Thus, the carbon behaves as though it were a carbanion equivalent:

**Two consequences you must always keep in mind.**

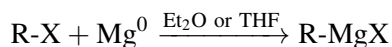
- **Strong nucleophiles.** R^- rapidly attacks electrophilic carbon centers (especially carbonyl carbons).
- **Strong bases.** R^- rapidly deprotonates acids—including weak acids by aqueous standards (alcohols, water, terminal alkynes, ammonium salts).

The second point is not a side note: it is the most common reason organometallic reactions fail.

8.4.2 Preparation: oxidative insertion into C–X bonds

Grignard reagent formation

A typical preparation is:



This is often described as **oxidative insertion**: Mg inserts into the C–X bond. Formally, Mg goes from oxidation state 0 to +2, while carbon becomes more nucleophilic (more reduced).

Mechanistic idea (qualitative). While detailed electron-transfer steps can be complex, a useful working model is:

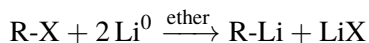
- single-electron transfer (SET) from Mg to R-X generates radical-like intermediates,
- recombination produces R-MgX.

This helps explain why:

- initiation can be slow (oxide layer on Mg),
- iodine or 1,2-dibromoethane can be used to “activate” Mg,
- radical side reactions can occasionally occur.

Organolithium formation

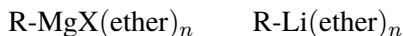
A common laboratory preparation is metal-halogen exchange or direct reaction with lithium metal:



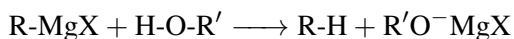
Organolithiums are generally **more reactive** (more basic and often more nucleophilic) than Grignard reagents. This increased reactivity expands scope but reduces functional group tolerance.

8.4.3 Solvent and water sensitivity: why ether solvents are used

Both Grignard and organolithium reagents are prepared and used in **dry, aprotic** solvents, most commonly ethers (diethyl ether, THF). Ethers stabilize the metal cation through Lewis basic coordination:



Absolute rule: avoid protic functional groups. Any O–H, N–H, or S–H bond will typically quench R–M:



Even trace moisture can destroy the reagent, converting valuable nucleophile into simple alkane R–H.

8.4.4 Core reactivity: nucleophilic addition to carbonyl compounds

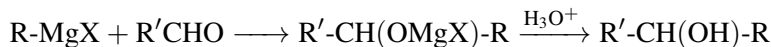
Additions to formaldehyde, aldehydes, and ketones

Organometallic reagents add to carbonyl compounds, forming new C–C bonds. After aqueous workup, the immediate alkoxide becomes an alcohol.

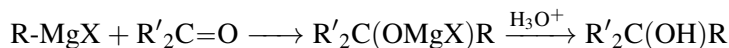
Formaldehyde gives primary alcohols (chain extension by one carbon).



Aldehydes give secondary alcohols.



Ketones give tertiary alcohols.



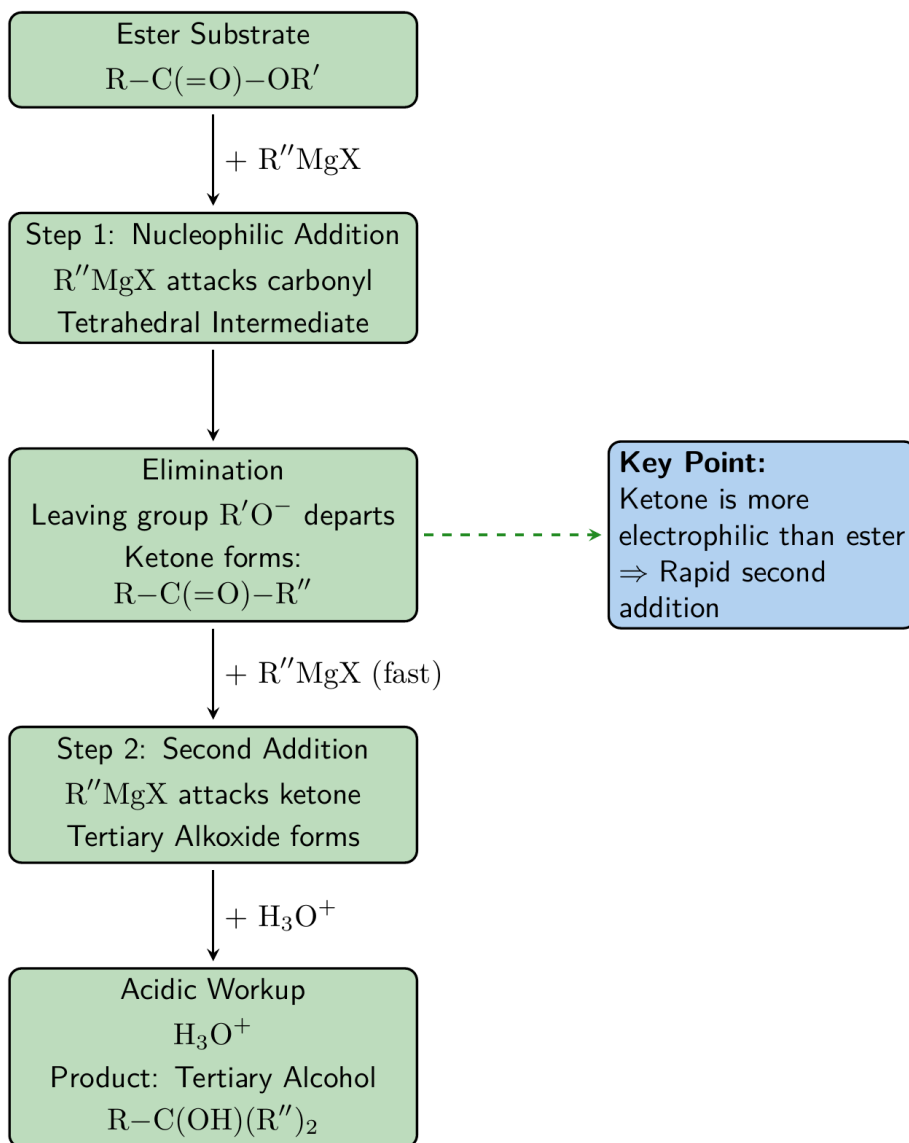
Stereochemical note. Addition to a planar carbonyl can occur from either face, so if a new stereocenter is formed and no chiral control exists, a racemic mixture is typical. In cyclic ketones, steric and conformational effects can bias attack from one face.

Reactivity with carboxylic acid derivatives: why esters behave differently

A key theme in this chapter is that mechanism determines chemoselectivity. Esters ($\text{RCO}_2\text{R}'$) have a carbonyl carbon that is electrophilic *and* a potential leaving group (OR'). Consequently, nucleophilic attack can be followed by elimination. For Grignard (or organolithium) reagents, this leads to a characteristic outcome:

- **Esters typically undergo double addition** to give **tertiary alcohols** after workup.

The mechanistic reason is that the first addition converts the ester into a ketone intermediate, and ketones are even more reactive toward organometallic addition than esters. Therefore, the ketone is generally not isolable under standard conditions.

Mechanism: Grignard addition to an ester (two-step sequence)

Stoichiometry and planning implication. Because the ketone intermediate reacts faster than the ester, you should assume that **two equivalents** of $R''-MgX$ (or $R''-Li$) are required for complete conversion to the tertiary alcohol. If only one equivalent is used, mixtures are common.

8.4.5 Basicity and incompatibilities: “things that kill” Grignards and organolithiums

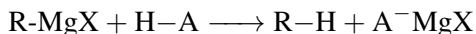
Organometallic reagents are incompatible with many functional groups. The most important incompatibilities can be classified mechanistically.

Acidic protons: fast quenching (acid-base)

Any group with a reasonably acidic proton will be deprotonated:

- H_2O , ROH , RCO_2H , RNH_2 , RSH
- terminal alkynes ($\text{RC}\equiv\text{CH}$) are deprotonated to acetylides

The consequence is loss of nucleophilic carbon:



In synthesis planning, this means that alcohols and acids often must be **protected** (or absent) before Grignard/organolithium addition is attempted.

Electrophiles other than carbonyls: competing pathways

Because R^- is broadly nucleophilic, it can react with many electrophiles. Some are useful (epoxide openings in Section 8.6), while others are problematic:

- CO_2 : useful, gives carboxylic acids after workup (“Grignard carboxylation”).
- Acid chlorides/anhydrides: often overreact, leading to tertiary alcohols (via ketone intermediates) unless conditions are carefully controlled.
- Alkyl halides: can undergo nucleophilic substitution or metal-halogen exchange depending on substrate and reagent.

Thus, organometallic reactions are powerful but require deliberate functional group management.

8.4.6 Organolithium vs. Grignard: practical differences

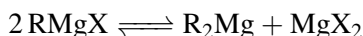
Both reagent classes behave as carbon nucleophiles, but they differ in typical behavior:

- **Organolithiums** (RLi) are generally more basic and more reactive; they can add to less electrophilic substrates and perform metal-halogen exchange efficiently.
- **Grignards** (RMgX) are often somewhat less reactive and can be easier to handle in many common additions to aldehydes/ketones.

A simple planning heuristic: If a Grignard reagent works, prefer it for simplicity; if the electrophile is less reactive or special reactivity is needed, consider an organolithium reagent.

8.4.7 The Schlenk equilibrium (conceptual overview)

In ether solution, Grignard reagents can participate in an equilibrium (the **Schlenk equilibrium**):



This matters because different magnesium species can have different reactivities and solubilities, and the position of the equilibrium depends on solvent, concentration, and the identity of R and X. For most introductory problems, you do not need to calculate this equilibrium; you do need to appreciate that “RMgX” is often a *mixture of related organomagnesium species*.

8.4.8 Summary: the organometallic mindset

- Grignard and organolithium reagents are best viewed as **carbanion equivalents** that are simultaneously **strong nucleophiles and strong bases**.
- They are prepared by **oxidative insertion** into C–X bonds and must be handled under **anhydrous** conditions in coordinating solvents (ethers).
- Their signature synthetic value is **C–C bond formation** via addition to carbonyls.
- **Esters undergo double addition** because the first addition-elimination produces a ketone intermediate that is rapidly attacked a second time.
- Functional group compatibility is the dominant constraint: **avoid protic sites and manage competing electrophiles**.

8.5 Gilman Reagents and Cuprates

Section 8.4 developed a powerful idea: the C–M bond in RLi and RMgX is highly polarized, so these reagents behave as strongly basic, strongly nucleophilic “R[−] equivalents.” That strength is both an advantage (fast C–C bond formation) and a limitation (poor functional group tolerance and frequent preference for direct addition to carbonyl carbons).

In this section we introduce a complementary class of organometallic reagents that are **softer** and typically **less basic**: **organocuprates**, especially lithium dialkylcuprates (Gilman reagents). Their signature value is **chemoselectivity**: they often perform *conjugate (1,4) addition* to α, β -unsaturated carbonyls and participate in *carbon–carbon coupling* reactions that are difficult with Grignard and organolithium reagents.

8.5.1 What is a Gilman reagent?

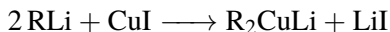
A **Gilman reagent** is a lithium dialkylcuprate, commonly written:



More generally, many useful cuprates have the form R₂CuLi or mixed forms such as RR'CuLi. You can think of these reagents as “organometallics with copper in the middle” that modulate reactivity compared to RLi and RMgX.

Preparation by transmetallation

A standard preparation uses an organolithium reagent and copper(I) iodide:



This process is an example of **transmetallation**: transfer of an organic group from one metal (Li) to another (Cu). In practice, the organolithium is generated first (often from an alkyl/aryl halide), then treated with CuI at low temperature.

Why start from organolithiums? Organolithiums readily form and readily transfer R groups. Copper(I) provides a relatively soft, polarizable center that changes the character of the carbon nucleophile: it becomes less basic and more selective.

8.5.2 Hard/soft intuition: why cuprates behave differently

A recurring pattern in synthesis is that **not all nucleophiles attack the same position on the same electrophile**. For α, β -unsaturated carbonyl compounds (enones, enals), there are two electrophilic sites:

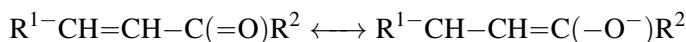
- the **carbonyl carbon** (1, 2-addition site),
- the **β -carbon** of the conjugated π system (1, 4-addition site).

Electrophilicity distribution in an enone

Consider a generic enone:



Resonance shows why the β -carbon is electrophilic:



In the second contributor, the β -carbon bears partial positive character. Thus, nucleophiles can attack either at the carbonyl carbon (giving an allylic alcohol after protonation) or at the β -carbon (giving a saturated carbonyl compound after protonation).

The “soft nucleophile” rule (practical form)

While the full hard/soft acid–base (HSAB) theory is more general, a useful synthesis-level guideline is:

Hard, strongly basic nucleophiles (e.g., RLi, RMgX) tend to give 1, 2-**addition** to enones.

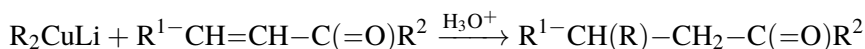
Softer, less basic nucleophiles (e.g., R_2CuLi) tend to give 1, 4-**addition** (conjugate addition).

Mechanistically, the softer nucleophile better stabilizes the more delocalized, π -system-centered transition state for conjugate addition, and copper can coordinate to the enone to facilitate selective delivery to the β -carbon.

8.5.3 Conjugate (1,4) addition to α, β -unsaturated carbonyls

Overall transformation

A Gilman reagent adds an R group to the β -carbon of an enone, and after protonation the product is a **saturated carbonyl compound**:



Net result.

- A new C–C bond forms at the β -carbon.
- The carbonyl group is **retained** (it is not converted to an alcohol).

This retention is often the strategic reason to choose a cuprate: it lets you functionalize the π system while preserving the carbonyl for subsequent transformations (e.g., reduction, enolate chemistry, further C–C bond formation).

Mechanistic outline (conceptual, synthesis-oriented)

A mechanistic description sufficient for planning is:

- **Conjugate addition:** the R group is delivered to the β -carbon, generating an enolate (or enolate-like) intermediate.
- **Protonation (or electrophilic trapping):** the enolate is protonated on workup to give the saturated carbonyl compound.

A key point is that conjugate addition does not require isolation of a discrete carbocation. The intermediate is best viewed as an enolate, which is stabilized by resonance with the carbonyl oxygen.

Stereochemical considerations

Conjugate addition can create stereocenters at the β -carbon. Without chiral control, mixtures are common. In cyclic enones, facial selectivity can arise due to sterics and conformational constraints, and conjugate addition often occurs from the less hindered face.

Synthetic advantage in ring systems. For cyclic enones, 1, 4-addition is a direct way to install substituents at the β -position, a transformation that may be difficult by other methods without multiple steps.

8.5.4 Why Grignards and organolithiums often give 1, 2-addition

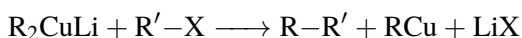
Recall from Section 8.4 that RMgX and RLi are strongly nucleophilic and strongly basic. For an enone, the carbonyl carbon is the “hardest,” most localized electrophilic site. Thus, these reagents frequently attack at the carbonyl carbon to give an alkoxide, which after protonation yields an **allylic alcohol** (a 1, 2-addition product):



This is not “wrong” reactivity—it is valuable when an allylic alcohol is desired. The point is that cuprates allow you to *choose* between two different products from the same starting material by selecting a different organometallic class.

8.5.5 Carbon–carbon coupling with cuprates: the Corey–House (Gilman) coupling

One of the most practically important uses of Gilman reagents is coupling with alkyl halides to form new C–C bonds:



This is often called the **Corey–House** or **Gilman coupling**. While the exact mechanism can depend on substrate and conditions, two mechanistic ideas provide a useful framework:

- **Oxidative addition** of $\text{R}'\text{-X}$ to a copper center increases the oxidation state of copper and attaches R' to copper.
- **Reductive elimination** forms the new $\text{R-R}'$ bond and returns copper to a lower oxidation state.

You should interpret these steps as a *metal-mediated assembly line* for forging C–C bonds that might be slow or messy via direct $\text{S}_{\text{N}}2$ substitution with strongly basic nucleophiles.

Why this coupling is synthetically useful.

- It can form C–C bonds under conditions where RLi or RMgX would be too basic and cause elimination or side reactions.
- It provides a controlled way to connect two carbon fragments.

Limitations (planning-level). Coupling works best when R'–X is suitable for substitution/oxidative addition (often primary halides). Secondary and tertiary halides can give competing elimination or rearrangement pathways. As always, substrate structure matters.

8.5.6 Cuprates as “moderated” nucleophiles: functional group tolerance and selectivity

Compared to RLi and RMgX, cuprates are typically:

- **less basic** $\Rightarrow$ less prone to deprotonating weakly acidic sites,
- **more chemoselective** $\Rightarrow$ more likely to react at the intended position (e.g., 1,4-addition),
- **still moisture sensitive** $\Rightarrow$ they must be handled under anhydrous conditions.

Do not overinterpret “less basic” as “safe in water”: cuprate chemistry still requires dry techniques and careful choice of solvent and temperature.

8.5.7 Strategic role in multistep synthesis

Cuprates often appear in sequences where you want to:

- build a carbon framework using organometallic methods,
- *avoid* excessive basicity or undesired 1,2-addition,
- preserve a carbonyl group for later transformations (reduction, enolate chemistry, aldol-type steps).

In retrosynthetic terms, conjugate addition with a Gilman reagent corresponds to disconnecting a C–C bond at the β -position of a saturated carbonyl compound back to an enone plus an R fragment that can be delivered as a cuprate.

- **Gilman reagents** (R_2CuLi) are prepared by **transmetallation** from organolithium reagents and CuI .
- They are **softer** nucleophiles than RLi and $RMgX$, leading to valuable **chemoselectivity**.
- Their hallmark transformation is **conjugate (1,4) addition** to α, β -unsaturated carbonyls, producing saturated carbonyl compounds while retaining the $C=O$.
- They also enable **C–C coupling** with alkyl halides (Corey–House/Gilman coupling), conceptually framed by oxidative addition and reductive elimination at copper.

8.6 Synthesis with Epoxides

Sections 8.4–8.5 introduced organometallic reagents as carbon nucleophiles and showed how changing the metal (Li/Mg vs. Cu) changes both basicity and selectivity. Epoxides provide a complementary electrophile class that is uniquely powerful in synthesis because ring opening can **create a C–C bond and install an alcohol in one step**. This section develops the mechanistic logic that determines **where** an epoxide opens (regioselectivity), **how** it opens (stereochemistry), and **why** epoxide opening is one of the most reliable chain-extension strategies in multistep synthesis.

8.6.1 Epoxides as activated electrophiles: strain and polarity

An epoxide is a three-membered cyclic ether. Two features make epoxides highly reactive toward nucleophiles:

- **Ring strain.** Three-membered rings have significant angle strain. Ring opening relieves this strain, providing a thermodynamic driving force.
- **Polar C–O bonds.** Oxygen is more electronegative than carbon, so the $C–O$ bonds are polarized, making carbon electrophilic and oxygen basic.

A simple but useful mental model is: epoxides behave like “masked” β -substituted alcohol derivatives. After opening, you obtain an alcohol whose position and substitution pattern are controlled by the opening mechanism.

8.6.2 Two mechanistic regimes: acid-catalyzed vs. base/nucleophile-catalyzed opening

Epoxide ring opening occurs under two broad sets of conditions, and the **regioselectivity rules are different**. The difference follows directly from mechanism.

Base/nucleophile-catalyzed opening: S_N2-like attack

Key mechanistic features. Under basic conditions (or with strong nucleophiles), the epoxide is attacked directly by the nucleophile:

- the nucleophile attacks from the **back side** of a C–O bond,
- the C–O bond breaks as the new C–Nu bond forms,
- the immediate product is an **alkoxide**, which is then protonated in workup.

This is mechanistically analogous to S_N2 substitution: steric hindrance strongly affects the transition state.

Regioselectivity rule (basic). In base/nucleophile-catalyzed epoxide opening, attack occurs at the *less substituted* (less hindered) epoxide carbon.

Stereochemistry rule (basic). Because the attack is S_N2-like: **The attacked carbon undergoes inversion of configuration.** In cyclic systems, this typically leads to **anti** (trans) relationships between the newly introduced nucleophile and the oxygen-derived substituent (after protonation).

Acid-catalyzed opening: protonation then “carbocation-like” regioselectivity

Key mechanistic features. Under acidic conditions, the epoxide oxygen is protonated first:



Protonation increases the leaving-group ability of oxygen and increases electrophilicity of the ring carbons. Nucleophilic attack then opens the ring.

Regioselectivity rule (acid). Acidic opening often resembles attack on the more substituted site because the transition state has partial positive charge development that is better stabilized at a more substituted carbon: **In acid-catalyzed epoxide opening, nucleophiles tend to attack the *more substituted* epoxide carbon.**

This should be understood as a competition between:

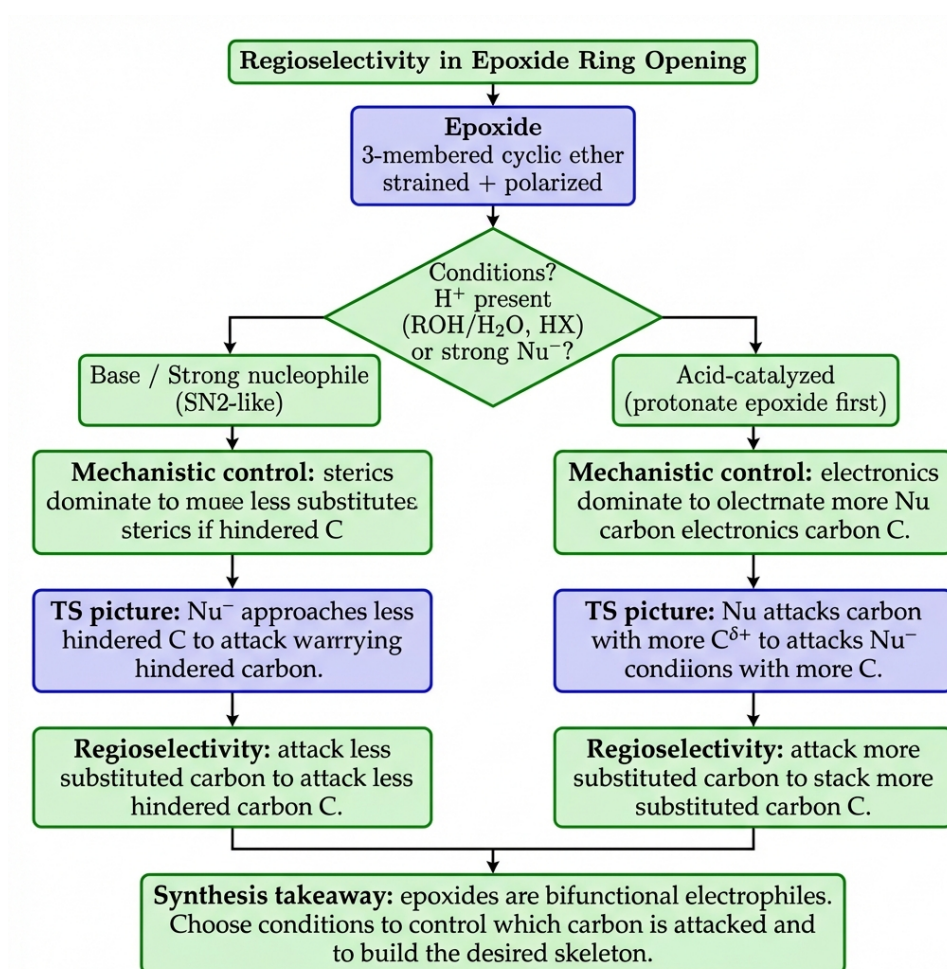
- **electronic control** (stabilizing positive charge at the more substituted carbon),

- **steric control** (hindrance can still matter, especially with bulky nucleophiles).

Stereochemistry rule (acid). Attack still occurs with **back-side character** relative to the C–O bond being broken, so the opening is **anti** overall. However, because the substrate is protonated and the transition state is more dissociative than in the basic case, stereochemical outcomes can be more complex in highly substituted systems. In typical introductory problems, you should assume: **Acid-catalyzed opening is anti and favors attack at the more substituted carbon.**

8.6.3 Regioselectivity map for epoxide opening

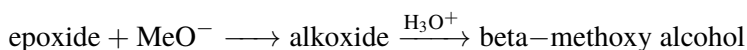
The following map summarizes the decision logic. Use it as a “mechanism-to-products” guide when predicting outcomes.



8.6.4 Base/nucleophile opening in detail: predictable S_N2 regioselectivity

Opening with simple nucleophiles: alkoxides, cyanide, halides

A generic example with methoxide:



In words: methoxide attacks the less substituted carbon, opens the ring anti, and after workup yields a β-methoxy alcohol.

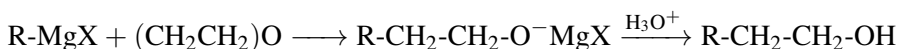
Common pitfall. Students often memorize “epoxides open at the less substituted

carbon” and apply it universally. That rule is *only* reliable under **basic** (or strongly nucleophilic, non-acidic) conditions.

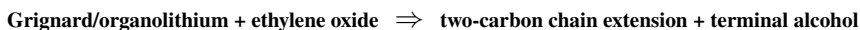
Opening with organometallic nucleophiles: Grignards and organolithiums

Epoxide opening is one of the most powerful ways to use Grignard and organolithium reagents for chain extension.

Overall transformation (two-carbon homologation). When an organometallic opens an epoxide, you add the R group and ultimately form an alcohol. With ethylene oxide (oxirane), the effect is especially clear: you extend the carbon chain by **two carbons**.



This is a standard synthetic tactic:



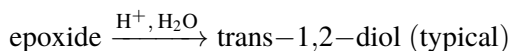
Mechanistic rationale. The organometallic acts as a strong nucleophile and attacks in an $\text{S}_{\text{N}}2$ -like manner at the less substituted epoxide carbon. For substituted epoxides, this gives high regiochemical control (attack at the less hindered carbon) and predictable inversion at the attacked center.

Compatibility reminder. Because RMgX and RLi are strongly basic (Section 8.4), these reactions must be performed in dry ether solvents, and the alcohol product appears only after aqueous workup.

8.6.5 Acid-catalyzed opening: attack at the more substituted carbon

Opening with water and alcohols: formation of trans diols and alkoxy alcohols

In acidic aqueous conditions, epoxides can be converted to diols:



In acidic alcohol (e.g., MeOH/H^+), epoxides often yield alkoxy alcohols.

Regiochemical logic. Protonation produces a better leaving group and increases positive character at the more substituted carbon. Nucleophilic attack then occurs

preferentially at that site. This is the same electronic principle that underlies many acid-catalyzed additions to alkenes: the pathway that stabilizes developing positive charge is favored.

Stereochemical logic. Even though the reaction has carbocation-like character, ring opening typically requires back-side attack relative to the breaking C–O bond, yielding anti opening. In cyclic epoxides, this often manifests as **trans** substitution patterns.

8.6.6 Synthesis design: using epoxide opening to assemble carbon skeletons

Epoxide opening is more than a functional group interconversion; it is a **carbon framework construction strategy**. The key features are:

- **C–C bond formation** (when the nucleophile is carbon-based).
- **Installation of an alcohol** (a functional handle for later oxidation/reduction).
- **Regioselective control** (choose basic vs acidic conditions).
- **Stereochemical predictability** (anti opening; inversion at the attacked carbon under basic conditions).

Retrosynthetic viewpoint

When you see a β -substituted alcohol (especially one that looks like it could arise from anti opening), consider disconnecting it back to an epoxide:

Retrosynthetic move: β -substituted alcohol $\Rightarrow$ epoxide precursor + nucleophile (often R^- equivalent).

This move is especially powerful when the nucleophile can be supplied as:

- a Grignard reagent (Section 8.4),
- an organolithium reagent (Section 8.4),
- or, in some contexts, a cuprate for moderated reactivity (Section 8.5), though epoxides are often sufficiently reactive that Grignards/lithiums are standard.

Combining epoxide opening with oxidation state planning

Because epoxide opening yields an alcohol, it dovetails naturally with the redox toolkit from Sections 8.1–8.3:

- After chain extension to an alcohol, you can oxidize to an aldehyde/ketone (Section 8.2) to enable further nucleophilic additions.
- Alternatively, you can reduce other functional groups first (Section 8.3) and then open epoxides to install an alcohol at a strategic location.

Thus, epoxide opening is often used as a **C–C bond-forming step that also “drops in” a controllable oxidation level**.

- Epoxides are reactive due to **ring strain** and **polar C–O bonds**; opening is strongly favored.
- **Basic/strong nucleophile conditions:** S_N2-like opening at the **less substituted carbon** with **inversion** and overall **anti** stereochemistry.
- **Acid-catalyzed conditions:** protonation increases electrophilicity; attack favors the **more substituted carbon** (electronic control) with overall **anti** opening.
- Epoxide opening with **Grignard/organolithium reagents** is a cornerstone method for **C–C bond formation** and, with ethylene oxide, accomplishes a **two-carbon chain extension** to a terminal alcohol.
- Epoxides integrate naturally into multistep synthesis by connecting **organometallic C–C bond formation** with **redox planning** (alcohol as a versatile intermediate).

Chapter 9

Spectroscopy and Structure Elucidation

If organic synthesis is the art of building molecules, structure elucidation is the logic of proving what has been built. This chapter transitions from the macroscopic study of reactions to the microscopic interrogation of molecular structure using electromagnetic radiation and magnetic fields. By correlating vibrational frequencies, mass-to-charge ratios, and nuclear spin states with molecular architecture, we develop the rigorous deductive framework necessary to identify unknown compounds with precision.

9.1 Infrared Spectroscopy

Infrared (IR) spectroscopy is one of the fastest ways to answer an early, high-impact question in structure elucidation: **what functional groups are present?** Whereas NMR emphasizes connectivity and detailed environments, IR focuses on **bond vibrations**. In practice, IR is used to (i) confirm or rule out functional groups suggested by formula/unsaturation, (ii) distinguish closely related functional groups (e.g., ketone vs. ester vs. acid), and (iii) assess hydrogen bonding and sample conditions (neat liquid, solution, solid).

9.1.1 What an IR spectrum measures: vibrational absorption

An IR spectrum plots the fraction of IR radiation absorbed as a function of *wavenumber* $\tilde{\nu}$ (in 1/cm). The wavenumber is proportional to frequency and energy:

$$E = h\nu = hc\tilde{\nu}$$

When a molecule absorbs IR light, it is promoted from one vibrational energy level to a higher one (most commonly $v = 0 \rightarrow 1$). Each normal mode of vibration (a concerted pattern of atomic motion) has a characteristic frequency.

The IR selection rule (why some vibrations absorb and others do not)

A vibration is IR-active if it produces a change in the molecular dipole moment:

$$\left(\frac{\partial \mu}{\partial Q} \right) \neq 0$$

where Q is the normal coordinate. Consequences:

- Strongly polar bonds that undergo a large dipole change during stretching (e.g., C=O) give strong absorptions.
- **Symmetric** vibrations in nonpolar molecules can be weak or absent (e.g., homonuclear O₂ has no IR absorption; C≡C in a **symmetric** internal alkyne is often weak).

9.1.2 A physical model for vibrational frequency: Hooke's law approximation

To connect peak position to molecular structure, treat a bond (or a localized stretching motion) as a spring. In the harmonic approximation, the stretching frequency depends on bond strength and mass:

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \quad \Rightarrow \quad \tilde{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}}$$

where k is an effective force constant (stiffer bond $\Rightarrow$ larger k) and μ is the reduced mass:

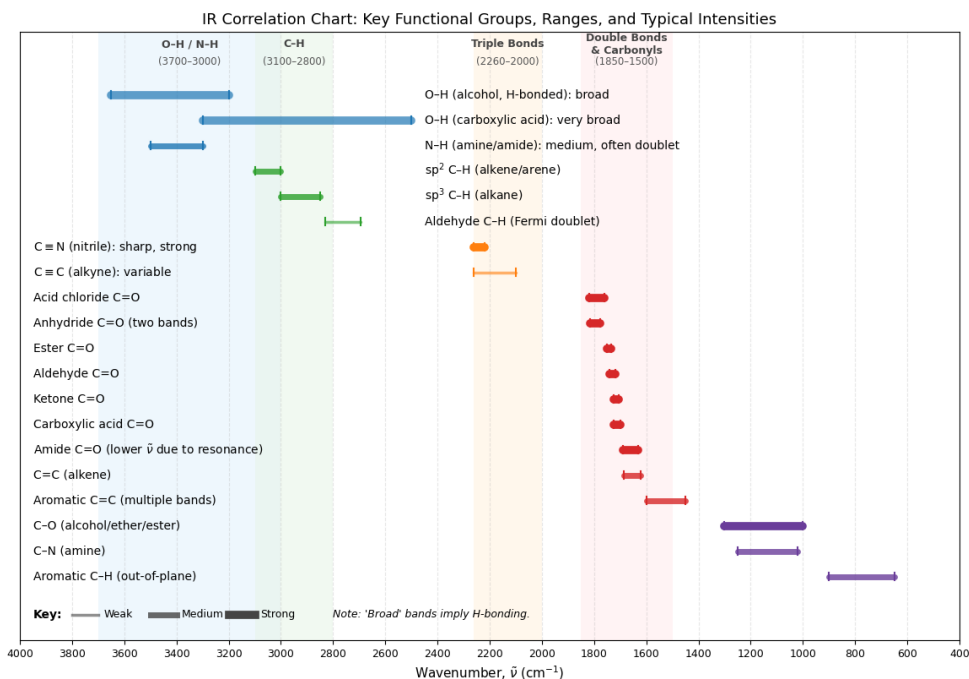
$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

This simple relationship explains many trends used every day in IR interpretation:

- **Bond order:** larger k for higher bond order, so

$$\tilde{\nu}(\text{C}\equiv\text{C}) > \tilde{\nu}(\text{C}=\text{C}) > \tilde{\nu}(\text{C}-\text{C})$$

- **Atom mass:** heavier atoms increase μ and lower frequency; thus C–H stretches appear at much higher wavenumber than C–D stretches, and C–H generally higher than C–O stretches.
- **Electronic effects:** resonance, conjugation, and inductive effects change effective bond order and thus k (especially important for C=O).



9.1.3 Reading an IR spectrum: regions and strategy

Although every molecule has many vibrational modes, IR interpretation becomes manageable by separating the spectrum into regions that differ in diagnostic value.

The diagnostic (functional group) region: 4000/ cm –1500/ cm

The region above $\sim 1500/\text{cm}$ is dominated by relatively simple stretching modes ($\text{X}-\text{H}$, $\text{C}\equiv\text{X}$, $\text{C}=\text{X}$, $\text{C}=\text{O}$) that are strongly tied to functional groups. Many structure problems are solved by answering three questions here:

- Is there an **O–H** or **N–H** stretch (broad or sharp; one or two bands)?
- Is there a **C=O** stretch (very strong; exact position depends on functional group and conjugation)?
- Is there evidence for **unsaturation** ($C=C$, $C\equiv C$, $C\equiv N$) and what type of C–H bonds are present (sp , sp^2 , sp^3)?

The fingerprint region: 1500/cm–400/cm

Below 1500/cm, spectra become crowded with bending vibrations and coupled motions. Individual peaks are less easily assigned, but the overall pattern is highly characteristic of a specific structure (hence **fingerprint**).

In functional group identification, the fingerprint region is most valuable for:

- **Confirmatory evidence** (e.g., strong C–O stretches support an ester or ether when a carbonyl is present).
- **Aromatic substitution clues** from C–H out-of-plane bending ($\sim 900/\text{cm}$ – $650/\text{cm}$), often used alongside NMR.

9.1.4 Characteristic absorptions and how to interpret them

The following subsections focus on the most diagnostically useful IR features for organic structure determination.

O–H stretching: alcohols vs. carboxylic acids

Alcohol O–H

Alcohols show an O–H stretch typically in the 3600/cm–3200/cm range. In neat liquids or concentrated samples, hydrogen bonding is common; it broadens the band and shifts it to lower wavenumber. In very dilute, non-hydrogen-bonding solvents, a sharper **free** O–H stretch near $\sim 3600/\text{cm}$ may be observed.

Carboxylic acid O–H

Carboxylic acids produce a **very broad** O–H absorption spanning roughly 3300/cm down to 2500/cm. The breadth arises from strong hydrogen bonding (often dimeric

association) that creates a distribution of O–H environments. A key practical point: this broad envelope can overlap C–H stretches, so the best confirmation of a carboxylic acid is the **combination** of (i) this broad O–H feature and (ii) a strong carbonyl near $\sim 1710/\text{cm}$.

N–H stretching: amines and amides

Amines and amides show N–H stretches around $3500/\text{cm}$ – $3300/\text{cm}$, usually less broad than alcohol O–H.

- **Primary** (RNH_2) often shows **two** bands (symmetric and asymmetric N–H stretching).
- **Secondary** (R_2NH) typically shows **one** band.
- **Tertiary** amines (R_3N) show **no** N–H stretch.

Amide N–H features can be broadened by hydrogen bonding, and are most compelling when paired with an amide carbonyl (see below).

C–H stretching: hybridization as a structural clue

The C–H stretching region is crowded but powerful for identifying hybridization:

- **sp C–H** (terminal alkyne) appears near $\sim 3300/\text{cm}$ and is often relatively sharp.
- **sp^2 C–H** (alkenes/arenes) appears just above $3000/\text{cm}$ (roughly $3100/\text{cm}$ – $3000/\text{cm}$).
- **sp^3 C–H** (alkanes) appears just below $3000/\text{cm}$ (roughly $2960/\text{cm}$ – $2850/\text{cm}$), usually as multiple bands.

Aldehyde C–H

Aldehydes show a distinctive pair of weak bands around $\sim 2830/\text{cm}$ and $\sim 2720/\text{cm}$ (often described as a “Fermi doublet”). This feature, together with a carbonyl near $\sim 1720/\text{cm}$, strongly supports an aldehyde.

Triple bonds: nitriles and alkynes

Nitriles (C#N)

The C $\equiv$ N stretch is typically sharp and strong in the 2260/cm–2220/cm region. Because few other functional groups absorb strongly there, a nitrile peak is among the clearest “single-peak diagnoses” in IR.

Alkynes (C#C)

The C $\equiv$ C stretch appears in the 2260/cm–2100/cm region but is often weak. Symmetry matters: an internal, symmetric alkyne may show a very weak or absent C $\equiv$ C absorption because the vibration causes little dipole change. A terminal alkyne is more readily recognized by the accompanying sharp sp C–H stretch near $\sim$ 3300/cm.

The carbonyl group: the most diagnostic stretch in IR

Carbonyl C=O stretching absorptions are usually **very strong** due to a large dipole change during stretching. The precise position is highly informative because it responds to electronic structure (force constant changes) and coupling.

A unifying idea: factors that shift $\tilde{\nu}(\text{C=O})$

- **Conjugation lowers $\tilde{\nu}$** (reduced effective bond order). For example, an α, β -unsaturated carbonyl typically absorbs at lower wavenumber than a saturated analog.
- **Electron-withdrawing substituents raise $\tilde{\nu}$** (increase effective bond order/polarization).
- **Ring strain can raise $\tilde{\nu}$** (e.g., small-ring ketones).
- **Resonance donation lowers $\tilde{\nu}$** strongly in amides, where N $\longrightarrow$ C=O resonance reduces carbonyl bond order.

Typical carbonyl ranges (most common cases)

While exact values vary with substitution and conjugation, the following are reliable starting points:

- **Ketones:** $\sim 1725/\text{cm}$ – $1705/\text{cm}$ (strong).
- **Aldehydes:** $\sim 1740/\text{cm}$ – $1720/\text{cm}$ (strong), plus aldehydic C–H doublet.
- **Carboxylic acids:** $\sim 1725/\text{cm}$ – $1700/\text{cm}$ (strong), plus very broad acid O–H.
- **Esters:** often $\sim 1750/\text{cm}$ – $1735/\text{cm}$ (strong), with strong C–O stretches in the fingerprint region ($\sim 1300/\text{cm}$ – $1000/\text{cm}$).
- **Amides:** $\sim 1690/\text{cm}$ – $1630/\text{cm}$ (strong), typically the **lowest** common carbonyl frequency due to resonance.
- **Acid chlorides:** $\sim 1820/\text{cm}$ – $1760/\text{cm}$ (very strong).
- **Anhydrides:** two strong carbonyl bands (commonly in the $\sim 1815/\text{cm}$ – $1775/\text{cm}$ region).

Carbonyl vs. alkene: intensity and context

Alkene C=C stretches ($\sim 1685/\text{cm}$ – $1620/\text{cm}$) are often medium to weak compared to carbonyls and can be missed in complex spectra. Aromatic C=C bands commonly appear around $\sim 1600/\text{cm}$ and $\sim 1500/\text{cm}$ (often multiple medium bands). Therefore, the presence of a very strong isolated peak near $\sim 1700/\text{cm}$ should immediately suggest a carbonyl-containing functional group.

9.1.5 Hydrogen bonding, peak breadth, and why “shape” matters

IR interpretation is not only about peak position; the **shape** (broad vs. sharp) and **intensity** (weak vs. strong) encode physical information.

Why hydrogen bonding broadens and shifts X–H stretches

In an O–H or N–H bond, hydrogen bonding weakens the X–H bond (lower effective k) and produces a distribution of bond strengths and environments. The result is:

- a shift to lower wavenumber (red shift),
- substantial broadening (many slightly different absorbing frequencies).

Thus, a broad band in the $3600/\text{cm}$ – $3200/\text{cm}$ region is often more informative than a sharp peak: it is evidence for hydrogen bonding and often implies the presence of a protic functional group.

Concentration and sample form effects (practical note)

Because hydrogen bonding depends on molecular association, the same compound can show different O–H shapes depending on whether the sample is a neat liquid, a concentrated film, or a dilute solution. When comparing spectra, always check measurement conditions if available.

9.1.6 A structured workflow for functional group identification

A disciplined approach prevents over-interpreting the fingerprint region too early.

- **Scan 3700/cm–3000/cm for O–H/N–H.** Note sharp vs. broad; one vs. two N–H bands.
- **Check 3100/cm–2800/cm for C–H hybridization.** Look for sp^2 above 3000/cm and sp^3 below 3000/cm; consider aldehydic C–H.
- **Look at 2260/cm–2000/cm for triple bonds.** A sharp strong peak suggests nitrile; a weak band may suggest alkyne (confirm with sp C–H at ~ 3300 /cm).
- **Interrogate 1850/cm–1650/cm for carbonyls and alkenes.** A strong peak near ~ 1700 /cm dominates interpretation; use position to classify carbonyl type and check for conjugation.
- **Use the fingerprint region for confirmation.** Seek supporting peaks (e.g., strong C–O for esters/ethers; aromatic out-of-plane bends for ring substitution patterns).

9.1.7 Worked micro-examples (interpretation without full structure solving)

The purpose of these brief examples is to show how a few diagnostic bands translate into functional group conclusions.

Example 1: broad O–H and strong carbonyl

Observed: very broad absorption 3300/cm–2500/cm plus strong C=O near 1710/cm.
Conclusion: **carboxylic acid** is strongly indicated (broad acid O–H + acid carbonyl).

Example 2: sharp strong band near 2250/cm

Observed: strong, sharp peak at 2245/cm; no O–H/N–H; no carbonyl. Conclusion: **nitrile** ($\text{C}\equiv\text{N}$) is likely.

Example 3: carbonyl near 1650/cm with N–H

Observed: N–H stretch near 3350/cm (one band) and strong carbonyl at 1655/cm. Conclusion: **amide** is likely (low-frequency carbonyl + N–H).

Example 4: aldehyde signature

Observed: strong C=O at 1725/cm plus weak bands at 2830/cm and 2720/cm. Conclusion: **aldehyde** is strongly supported.

9.1.8 Limitations and best practices

IR provides rapid functional group identification, but it rarely determines a full structure by itself.

- Many functional groups share overlapping ranges; use **multiple** peaks and shape/intensity together.
- The fingerprint region is powerful for comparison to reference spectra, but peak-by-peak assignment there is often ambiguous.
- Always combine IR with other data (molecular formula, MS, and NMR) to achieve complete structure elucidation.

9.2 Mass Spectrometry

Infrared spectroscopy is primarily a **functional group detector**: it tells you what kinds of bonds are present and highlights strongly polar vibrations such as C=O or O–H. Mass spectrometry (MS) answers a different set of first-order questions that are equally fundamental to structure elucidation:

- What is the **molar mass** of the unknown (and often its **molecular formula**)?
- What **substructures** are suggested by characteristic **fragment ions**?

- What **heteroatoms** are present, inferred from **isotope patterns** (especially Cl and Br)?

Unlike IR, MS does not measure an equilibrium property of a neutral molecule. It measures the masses of **gas-phase ions** generated from the analyte. Consequently, MS interpretation requires thinking in terms of **ion formation** and **ion stability**.

9.2.1 What a mass spectrum is: m/z and relative abundance

A mass spectrum is a plot of ion signal intensity (relative abundance) versus the mass-to-charge ratio, m/z .

- For most organic MS data discussed in this chapter, the dominant ions are **singly charged** ($z = +1$), so m/z is numerically equal to the ion's mass in atomic mass units (Da).
- The tallest peak is called the **base peak** and is assigned relative intensity 100. All other peak intensities are reported relative to it.

Key terms.

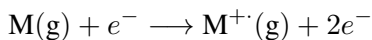
- **Molecular ion (M^+)**: the radical cation formed by removing an electron from the neutral molecule (common in electron impact ionization).
- **Quasi-molecular ions**: ions such as $[M + H]^+$, $[M + Na]^+$, or $[M - H]^-$ formed in soft ionization methods.
- **Fragment ion**: an ion produced by cleavage or rearrangement of a precursor ion.

9.2.2 Ionization methods: “hard” vs. “soft”

Before separation and detection, neutral molecules must be converted to ions. The ionization method strongly influences the appearance of the spectrum, especially whether a recognizable molecular ion is present.

Electron impact (EI): hard ionization and radical cations

In EI MS, a beam of high-energy electrons (classically 70 eV) ionizes gaseous analyte molecules:



EI deposits substantial internal energy, so the molecular ion often fragments extensively. This is a disadvantage if you only want molar mass, but it is a major advantage for **structural** information because fragments encode substructures.

When EI is most useful. EI works best for relatively small, volatile, thermally stable organic compounds. In many such cases, the EI fragmentation pattern is reproducible and searchable in spectral libraries.

Soft ionization (overview): preserving the molecular mass

Soft ionization methods aim to form ions with less excess internal energy, producing less fragmentation and making it easier to identify the parent mass. Common conceptual outcomes include:

- **Protonation:** $[M + H]^{+}$ (typical for many soft ionization modes).
- **Adduct formation:** $[M + Na]^{+}$ or $[M + NH_4]^{+}$ (common depending on conditions).
- **Deprotonation:** $[M - H]^{-}$ in negative-ion modes for acidic analytes.

Because this chapter emphasizes molecular weight determination and fragmentation logic, we will primarily use EI-style reasoning (clear fragmentation) while noting how to adapt to soft-ionization data by correctly identifying the quasi-molecular ion.

9.2.3 From ions to peaks: mass analysis and detection (magnetic sector principle)

Many instruments exist (quadrupole, time-of-flight, ion trap), but the core physical idea is the same: **ions are separated based on their mass-to-charge ratio**. A classic magnetic sector analyzer illustrates the physics cleanly.

An ion of charge q accelerated through a potential difference V gains kinetic energy:

$$\frac{1}{2}mv^2 = qV$$

In a magnetic field B , the ion follows a circular path because the magnetic Lorentz force provides centripetal force:

$$qvB = \frac{mv^2}{r}$$

Combining these gives a direct connection between the radius of curvature r and m/z :

$$\frac{m}{z} = \frac{q}{2V} B^2 r^2$$

Thus, at fixed B and V , different m/z ions reach different radii (or, equivalently, scanning B transmits different m/z to the detector). This is the operational meaning of “separation by m/z .”

9.2.4 Finding molar mass: the molecular ion and its pitfalls

The most direct route to molar mass is identifying the molecular ion peak (EI) or the quasi-molecular ion (soft ionization).

Recognizing $M^{+\cdot}$ in EI

If present, the molecular ion is the peak corresponding to the intact molecule after loss of one electron. Its m/z is (approximately) the nominal molecular mass. However:

- Some functional groups fragment so readily that $M^{+\cdot}$ is weak or absent (e.g., many tertiary alcohols, some highly branched alkanes).
- Conversely, aromatic and conjugated systems often show strong $M^{+\cdot}$ peaks because the radical cation is resonance-stabilized.

Therefore, identifying the molecular ion is not just “take the highest m/z peak.” One must check whether the apparent highest-mass peak could be an isotope peak ($M+1$, $M+2$) or an adduct (soft ionization).

Nominal mass vs. exact mass (preview)

In unit-resolution spectra, peaks appear at integer m/z values (nominal mass). High-resolution MS distinguishes exact masses and enables molecular formula determination by matching to the calculated exact mass. In this chapter, we focus on unit-resolution interpretation, but the conceptual hierarchy is:

molecular ion/quasi-molecular ion $\Rightarrow$ molar mass $\Rightarrow$ formula constraints $\Rightarrow$ fragmentation logic

9.2.5 The Nitrogen Rule: parity as a fast heteroatom diagnostic

The Nitrogen Rule is an extremely useful filter when the molecular ion is identifiable at unit resolution:

Nitrogen Rule (common case). For an organic molecule composed of C, H, N, O, S, halogens, and P: an **odd** nominal mass of M^{+} indicates an **odd number of nitrogen atoms**; an **even** nominal mass indicates zero or an even number of nitrogens.

The rule arises from valence/electron-count parity: introducing one nitrogen (odd valence electron count relative to CH framework) flips the parity of the molecular mass for typical organic compositions.

Practical use.

- If you see an M^{+} at $m/z = 121$ (odd), you should strongly suspect 1, 3, 5, ... nitrogens, with 1 nitrogen most common for small molecules.
- If $m/z = 120$ (even), nitrogen may be absent or present in pairs (0, 2, 4, ...).

A critical caveat: apply the rule to the **molecular ion** in EI. In soft ionization, the common ion is $[M + H]^+$, which shifts the parity by +1 and can mislead if you forget the proton.

9.2.6 Isotope patterns: reading M , $M + 1$, and $M + 2$

Even when the molecular ion is weak, isotope patterns provide robust evidence for elemental composition.

$M + 1$ and the carbon count estimate

Most organic molecules show a small $M + 1$ peak primarily due to ^{13}C (natural abundance $\approx 1.1\%$ per carbon). A rough estimate for the number of carbons is:

$$\frac{I(M+1)}{I(M)} \approx 0.011 \times n_C$$

For example, if $I(M + 1)/I(M) \approx 0.11$ (11%), then $n_C \approx 10$ (roughly). This estimate is approximate because other isotopes (^2H , ^{15}N , ^{17}O , ^{33}S) also contribute slightly, and because M and $M + 1$ intensities depend on how well M is measured.

$M + 2$ as a halogen fingerprint: Cl and Br

Halogens are uniquely easy to detect by their characteristic $M/M + 2$ clusters.

Chlorine. ^{35}Cl and ^{37}Cl occur in an approximate 3:1 ratio. A molecule with one chlorine often shows an M and $M + 2$ pair with intensities close to:

$$I(M) : I(M + 2) \approx 3 : 1$$

Two chlorines produce a three-peak cluster (M , $M + 2$, $M + 4$) with approximate binomial intensities 9 : 6 : 1.

Bromine. ^{79}Br and ^{81}Br occur in an approximate 1:1 ratio. One bromine yields:

$$I(M) : I(M + 2) \approx 1 : 1$$

Two bromines yield a 1 : 2 : 1 cluster at M , $M + 2$, and $M + 4$.

Iodine. Iodine is mostly ^{127}I , so it does not produce an $M + 2$ diagnostic pattern like Cl/Br. Instead, iodine-containing compounds often show characteristic iodine-containing fragment ions at high m/z values.

9.2.7 Fragmentation logic: why certain bonds break

Fragmentation is not random. It is guided by the stability of the ions (and radicals) produced. In EI, the precursor is typically a radical cation, M^+ , so fragments can be **even-electron** cations or **radical** cations depending on the pathway.

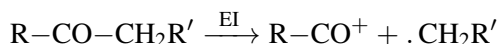
General principles that predict major fragments

- **Form the more stable cation.** Tertiary carbocations (or resonance-stabilized cations) tend to dominate over secondary and primary.
- **Resonance stabilization is decisive.** Allylic, benzylic, and acylium ions are commonly strong peaks.
- **Heteroatoms control cleavage.** Bonds adjacent to heteroatoms often cleave readily because the charge or radical can be stabilized by the heteroatom.

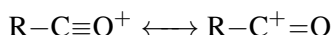
- **Neutral losses can be characteristic.** Loss of small neutrals (e.g., H₂O from alcohols, CO from certain carbonyl fragments) is common and can create recognizable peak spacings.

Alpha cleavage next to heteroatoms and carbonyls

Definition. **Alpha cleavage** is bond cleavage at the bond **alpha** to a functional group (the bond directly adjacent to the heteroatom or carbonyl carbon). For carbonyl compounds under EI, alpha cleavage is particularly important because it often produces an **acylium ion** that is resonance-stabilized:



The acylium ion is stabilized by resonance:



This stabilization makes the corresponding m/z peak intense and reliable for inference.

Interpretive payoff. If you can identify a strong acylium ion, its mass often corresponds to a recognizable acyl fragment (e.g., CH₃CO⁺, C₆H₅CO⁺), providing direct information about substituents on the carbonyl.

McLafferty rearrangement: a diagnostic rearrangement for carbonyls

When it occurs. A **McLafferty rearrangement** typically occurs in carbonyl compounds (aldehydes, ketones, esters, acids, amides) that possess at least one **γ-hydrogen** (a hydrogen three atoms away from the carbonyl carbon along an alkyl chain). Under EI, a six-membered transition-state-like rearrangement transfers the γ-hydrogen to the carbonyl oxygen while cleaving the α-β bond, producing an enol (neutral or radical) and a resonance-stabilized radical cation fragment.

Why it matters. The McLafferty rearrangement can generate a prominent peak that would be difficult to predict by simple bond cleavage alone. Seeing a strong McLafferty-type fragment is strong evidence for:

- the presence of a carbonyl functional group, and
- a chain long enough to supply a γ-hydrogen in an appropriate geometry.

9.2.8 Putting it together: a disciplined MS interpretation workflow

A workable procedure prevents common errors (misassigning isotope peaks as M , chasing minor fragments, or ignoring the ionization context).

- **Identify the ionization context.** Is the spectrum EI-like (many fragments, possible $M^{+•}$) or soft-ionization-like (dominant $[M + H]^+$, fewer fragments)?
- **Find the molecular ion or quasi-molecular ion.** In EI, look for a plausible $M^{+•}$ with supporting $M + 1$ and (if applicable) $M + 2$ peaks. In soft ionization, assign $[M + H]^+$ and subtract 1 to get M (for positive mode protonation).
- **Apply isotope logic.** Check for Cl/Br patterns; estimate carbon count from $M + 1$ if M is reliable.
- **Apply the Nitrogen Rule (if appropriate).** Use it as a constraint, not as a final answer.
- **Interpret major fragments.** Focus on the base peak and other high-intensity peaks; ask what stable cations they represent (benzylic, allylic, acylium, tertiary).
- **Look for signature rearrangements or losses.** Consider McLafferty rearrangement for carbonyls with γ -hydrogens; consider dehydration (-18) for alcohols, decarbonylation (-28) in some carbonyl-derived fragments, etc.
- **Cross-check with IR/NMR.** MS suggests mass and substructures; IR confirms functional groups; NMR will later resolve connectivity and hydrogen/-carbon environments.

9.2.9 Common interpretive pitfalls (and how to avoid them)

- **Mistaking $M + 2$ for M .** This is especially dangerous for brominated compounds, where M and $M + 2$ are similar in intensity. Always look for the paired peak two units away.
- **Assuming the base peak is the molecular ion.** The base peak is simply the most abundant ion; it is often a stable fragment (e.g., benzylic cation) rather than $M^{+•}$.
- **Applying the Nitrogen Rule to $[M + H]^+$.** For soft ionization, convert to M first.

- **Overfitting minor peaks.** Small peaks may reflect secondary fragmentations or background; prioritize strong, chemically interpretable ions.

9.2.10 A short, IR-connected example (conceptual integration)

Suppose IR indicates a strong C=O absorption near $\sim 1715/\text{cm}$ (carbonyl present). The MS then becomes more targeted:

- Look for a molecular ion consistent with the likely carbonyl class (and check for conjugation indicators in IR that might suggest an aromatic system, which often strengthens M^+).
- In EI, examine whether strong fragment peaks could be acylium ions (alpha cleavage) or a McLafferty fragment (requires a $\gamma\text{-H}$).

This illustrates the broader strategy of the chapter: each spectroscopic method constrains the hypothesis space so the next method can be interpreted more decisively.

9.3 Proton NMR: Chemical Shift and Integration

Infrared spectroscopy rapidly identifies functional groups by characteristic bond vibrations, and mass spectrometry constrains molar mass and substructures through fragmentation. Proton nuclear magnetic resonance (^1H NMR) adds a different kind of information: it reports how many *distinct proton environments* exist, how *electron density and bonding* influence those protons, and how many protons occupy each environment. In other words, ^1H NMR connects directly to *local structure*.

This section develops two core ideas:

- **Chemical shift** (δ): why protons resonate at different frequencies depending on their magnetic environment (shielding/deshielding).
- **Integration**: how peak areas encode relative numbers of protons.

(Spin–spin splitting and coupling patterns are treated in the next section.)

9.3.1 Nuclear spin, magnetic moments, and the origin of resonance

Spin and magnetic moments

Many nuclei possess an intrinsic angular momentum called *spin* (I). The proton has

$$I = \frac{1}{2}$$

A spinning charged particle behaves as a tiny magnet, characterized by a magnetic moment μ . When placed in a strong external magnetic field $\mathbf{B}_0$ (defined by the instrument), the magnetic moment has quantized orientations relative to $\mathbf{B}_0$.

For a spin- $\frac{1}{2}$ nucleus, there are two allowed energy states:

$$m_I = +\frac{1}{2} \quad (\text{lower energy, aligned with } \mathbf{B}_0) \quad \text{and} \quad m_I = -\frac{1}{2} \quad (\text{higher energy})$$

The energy gap between these states is proportional to the magnetic field strength:

$$\Delta E = \gamma \hbar B_0$$

where γ is the gyromagnetic ratio (a nucleus-specific constant).

Resonance and the Larmor frequency

A proton in a magnetic field precesses at the *Larmor frequency*:

$$\omega_0 = \gamma B_0 \quad \text{and} \quad \nu_0 = \frac{\omega_0}{2\pi} = \frac{\gamma B_0}{2\pi}$$

NMR occurs when radiofrequency (RF) radiation supplies energy matching ΔE ; the nucleus absorbs RF energy and transitions between the two spin states. The key point for structure elucidation is that the *effective* field experienced by the nucleus is not exactly B_0 ; it is modified by the electrons around the nucleus.

9.3.2 Shielding and deshielding: why chemical shifts exist

Local fields created by electrons

Electrons in a molecule circulate in response to the applied field B_0 , producing an induced magnetic field B_{ind} that typically opposes B_0 at the nucleus. The nucleus therefore experiences a *reduced* effective field:

$$B_{\text{eff}} = B_0 (1 - \sigma)$$

where σ is the *shielding constant*. Larger σ means greater shielding (smaller effective field), which lowers the resonance frequency.

Because the resonance frequency depends on B_{eff} , two chemically nonequivalent protons (different σ values) resonate at different frequencies and produce separate signals.

Definition of chemical shift (δ) and TMS reference

Absolute resonance frequencies scale with B_0 , so NMR reports *relative* resonance positions using the *chemical shift*:

$$\delta \text{ (ppm)} = \frac{\nu_{\text{sample}} - \nu_{\text{ref}}}{\nu_{\text{spectrometer}}} \times 10^6$$

The reference is almost always tetramethylsilane (TMS), assigned $\delta = 0.00$ ppm. TMS is convenient because:

- its protons are highly shielded (signal appears upfield, near 0 ppm),
- it is chemically inert toward many organic samples, and
- it is volatile and easily removed.

Upfield vs. downfield.

- **Upfield** (lower δ): more shielded protons, smaller B_{eff} , lower resonance frequency.
- **Downfield** (higher δ): more deshielded protons, larger B_{eff} , higher resonance frequency.

9.3.3 Structural factors that control δ

Chemical shift is a quantitative expression of how the molecular environment modifies electron circulation and local magnetic fields. Several recurring structural effects dominate ^1H chemical shifts.

Electronegativity and inductive deshielding

A proton on carbon adjacent to an electronegative atom is typically deshielded. Inductively withdrawing substituents reduce electron density around nearby C–H bonds, lowering shielding and moving the signal downfield.

A first approximation (with substantial dependence on substitution and solvent):

- $\text{R}-\text{CH}_2-\text{X}$ with $\text{X} = \text{O}, \text{N}, \text{halogen}$ often appears around $\delta \sim 2.5\text{--}4.5$ ppm.
- The effect decays with distance; β -protons are less affected than α -protons.

This inductive effect is one reason why recognizing $\text{CH}_3-\text{CH}_2-\text{O}^-$ fragments in ^1H NMR is so reliable: the methylene next to oxygen is shifted markedly downfield compared with a simple alkane methylene.

Hybridization: sp^3 vs. sp^2 vs. sp

Hybridization influences both electron distribution and susceptibility to anisotropic fields (discussed below). Typical trends:

- **Alkane** protons (sp^3): $\delta \sim 0.8\text{--}1.8$ ppm.
- **Allylic** protons (next to $\text{C}=\text{C}$): often $\delta \sim 1.6\text{--}2.4$ ppm.
- **Vinylic** protons (on $\text{C}=\text{C}$): typically $\delta \sim 4.5\text{--}6.5$ ppm.
- **Aromatic** protons: typically $\delta \sim 6.5\text{--}8.5$ ppm.
- **Terminal alkyne** proton ($\text{RC}\equiv\text{CH}$): often $\delta \sim 2\text{--}3$ ppm, notably *upfield* compared to vinylic protons due to anisotropy of the triple bond.

These ranges are not memorized as isolated facts; they become intuitive once anisotropy is understood: π systems create *direction-dependent* induced fields that can either deshield or shield protons depending on geometry.

Magnetic anisotropy in π -systems (ring currents and induced fields)

Core idea. In a π system, the applied field B_0 drives circulation of π electrons, producing a secondary induced field. This induced field is *anisotropic*: it depends on where the proton sits relative to the π electron cloud.

A useful mental model is to separate space around a π system into:

- **Deshielding regions**, where B_{ind} reinforces B_0 (B_{eff} increases $\Rightarrow$ downfield shift).
- **Shielding regions**, where B_{ind} opposes B_0 (B_{eff} decreases $\Rightarrow$ upfield shift).

Benzene (aromatic ring current). In an aromatic ring, circulating π electrons create a ring current. Protons on the ring perimeter lie in a region where the induced field reinforces B_0 , which is why aromatic protons are characteristically downfield (often $\sim 7\text{--}8$ ppm). In contrast, positions above or below the ring plane fall into a shielding region; this is why protons located above aromatic rings in certain geometries (e.g., in some cyclophanes or host–guest complexes) can appear unusually upfield.

Alkenes. For a $\text{C}=\text{C}$ bond, the anisotropy places vinylic protons in a deshielding region, pushing them downfield relative to alkanes.

Carbonyl anisotropy (conceptual note)

Carbonyl groups also create strong anisotropic fields. Protons *near* a carbonyl (especially α -protons) are often deshielded by a combination of inductive withdrawal and anisotropy; many α -to-carbonyl protons appear around $\delta \sim 2.0\text{--}2.7$ ppm. Aldehydic protons are strongly deshielded, typically $\delta \sim 9\text{--}10$ ppm, reflecting both the electron-withdrawing carbonyl and anisotropic effects.

Hydrogen bonding and exchangeable protons (OH, NH)

Protons on heteroatoms ($\text{O}\text{--}\text{H}$, $\text{N}\text{--}\text{H}$) can show highly variable chemical shifts because:

- hydrogen bonding deshields and broadens signals,
- rapid proton exchange can average environments and diminish coupling, and
- solvent and concentration strongly affect both exchange rate and hydrogen bonding network.

As a result, OH and NH chemical shifts are less reliable as precise structural markers than $\text{C}\text{--}\text{H}$ shifts. Their presence is still diagnostically valuable, especially when correlated with IR ($\text{O}\text{--}\text{H}/\text{N}\text{--}\text{H}$ stretches) and with chemical reactivity tests (e.g., D_2O exchange, discussed later in the chapter).

9.3.4 Counting signals: chemical equivalence and symmetry

Before interpreting chemical shifts, it is essential to know what a “signal” represents.

Chemical equivalence (practical definition)

Protons are **chemically equivalent** if they experience the same average electronic environment and thus have the same chemical shift. Equivalent protons contribute to the same NMR signal and integrate together.

Symmetry often creates equivalence. For example, in $(\text{CH}_3)_3\text{CCl}$ (tert-butyl chloride), all nine methyl protons are equivalent and produce one signal (ignoring coupling for now). In contrast, in $\text{CH}_3\text{CH}_2\text{Cl}$, the methyl and methylene protons are in different environments and produce two signals.

Magnetic equivalence (preview)

Even when two sets of protons have identical chemical shifts, they may or may not be magnetically equivalent with respect to coupling networks. This matters primarily for splitting patterns and is addressed in the next section. For the purposes of chemical shift and integration, treat each unique δ environment as a distinct signal.

9.3.5 Integration: peak area as a proton counting tool**Why integration measures number of protons**

In ^1H NMR, under quantitative acquisition conditions, the area under a resonance is proportional to the number of contributing nuclei:

$$\text{integral} \propto n_H$$

The instrument typically displays integrals as relative values (step-like traces) rather than absolute proton counts. The chemist converts these relative integrals into *whole-number ratios*.

From integral values to proton ratios

Suppose a spectrum shows three signals with integrals (arbitrary units):

$$1.52 : 1.01 : 3.02$$

Divide by the smallest value (1.01) to get:

$$1.50 : 1.00 : 2.99 \approx 3 : 2 : 6$$

Then reduce if possible:

$$3 : 2 : 6 \rightarrow 3 : 2 : 6 \quad (\text{already simplest})$$

These ratios suggest, for example, a CH₃ group (3 H), a CH₂ group (2 H), and two equivalent CH₃ groups (6 H), although chemical shift and splitting are needed to make a defensible assignment.

Normalization to a molecular formula

If a molecular formula is known (often from MS), integration can be normalized to absolute proton counts. For example, if MS suggests C₅H₁₂O (12 hydrogens total) and the NMR integrals reduce to a 3:2:2:3:2 pattern (sum = 12), then each ratio corresponds directly to proton counts without further scaling.

If the sum of the simplest integral ratio does not match the formula's hydrogen count, multiply all integrals by an integer factor to match the total. This is a powerful consistency check between MS and NMR.

Important limitations of integration

Integration is extremely reliable for C–H protons, but several situations require caution:

- **Exchangeable protons** (OH, NH) may integrate inaccurately due to exchange and broadening.
- **Overlapping peaks** can distort areas if resonances are not well separated.
- **Non-quantitative acquisition** (incorrect relaxation delay, saturation, or certain pulse sequences) can lead to systematic errors; routine structure elucidation spectra are usually suitable for relative integrals, but not guaranteed for rigorous quantitative work.

9.3.6 Typical ¹H chemical shift ranges (as a working map)

The table below provides a practical map for first-pass interpretation. Values are approximate; use the underlying principles (inductive effects, anisotropy, hydrogen bonding) to rationalize shifts rather than relying on memorization alone.

Proton environment	Typical δ (ppm)	Primary cause(s)
Alkyl $\text{R}-\text{CH}_3$, $\text{R}-\text{CH}_2^-$, R_3CH (sp^3)	0.8–1.8	High shielding in saturated carbon framework
Allylic $\text{C}=\text{C}-\text{CH}$ (next to alkene)	1.6–2.4	Proximity to π system + mild inductive effects
α to carbonyl $\text{R}-\text{CO}-\text{CH}$	2.0–2.7	Carbonyl inductive withdrawal + anisotropy
Benzylic $\text{Ar}-\text{CH}_3$, $\text{Ar}-\text{CH}_2^-$	2.2–3.0	Resonance/anisotropy near aromatic ring
$\text{C}\equiv\text{C}-\text{H}$ (terminal alkyne)	2.0–3.0	Triple-bond anisotropy (often shielding along bond axis)
$\text{C}-\text{O}-\text{CH}$ (ethers/alcohols), $\text{C}-\text{N}-\text{CH}$	3.0–4.5	Strong inductive deshielding by heteroatom
Vinylic $\text{C}=\text{C}-\text{H}$	4.5–6.5	Alkene anisotropy (deshielding region)
Aromatic $\text{Ar}-\text{H}$	6.5–8.5	Aromatic ring current deshielding
Aldehyde $-\text{CHO}$	9.0–10.5	Strong carbonyl anisotropy + inductive withdrawal
Carboxylic acid $-\text{CO}_2\text{H}$ (OH)	10–13 (broad)	Strong hydrogen bonding + deshielding; exchange

9.3.7 A compact interpretation workflow for ^1H chemical shift and integration

At this stage (before splitting analysis), the goal is to build a chemically consistent “inventory” of proton types.

- **Count signals** $\Rightarrow$ estimate number of distinct proton environments (symmetry clues).
- **Record chemical shifts** $\Rightarrow$ classify environments (alkyl, heteroatom-adjacent, vinylic, aromatic, aldehydic, etc.).
- **Use integrals** $\Rightarrow$ assign relative proton counts to each environment.
- **Cross-check with IR/MS constraints:** If IR shows O–H, expect an exchangeable proton (possibly broad) plus C–O–CH signals if an alcohol/ether

is present; if MS suggests a formula, verify that integral totals can be scaled to match total hydrogens.

9.3.8 Brief illustrative example (chemical shift + integration only)

Consider an unknown whose MS suggests $\text{C}_4\text{H}_{10}\text{O}$ (no unsaturation). The ^1H NMR shows:

- $\delta = 3.45$ ppm, integral ≈ 2 H
- $\delta = 1.60$ ppm, integral ≈ 2 H
- $\delta = 0.95$ ppm, integral ≈ 6 H

A consistent first-pass interpretation is:

- 2 H at 3.45 ppm: $-\text{CH}_2-\text{O}-$ (methylene adjacent to oxygen),
- 2 H at 1.60 ppm: internal alkyl $-\text{CH}_2-$,
- 6 H at 0.95 ppm: two equivalent methyl groups ($2 \times \text{CH}_3$) in a similar environment.

At this point, several constitutional isomers remain plausible; resolving which one is correct requires coupling/splitting analysis (next section) and, if available, ^{13}C NMR. The key achievement here is constructing a chemically coherent set of proton environments consistent with formula and functional group evidence.

9.4 Proton NMR: Splitting and Coupling

Chemical shift (δ) identifies types of proton environments and integration reports how many protons occupy each environment. These two features alone often narrow the set of plausible structures, but they do not directly reveal which groups are connected. Spin-spin coupling (also called *scalar coupling* or *J-coupling*) provides that connectivity information: it encodes which sets of protons are *neighbors through bonds*. In routine organic ^1H NMR, coupling patterns answer questions such as:

- Is a CH_3 group adjacent to CH_2 (ethyl pattern) or adjacent to CH (isopropyl pattern)?
- Are two vinylic protons *cis* or *trans* (from J values)?

- Are aromatic rings ortho-, meta-, or para-disubstituted (from coupling patterns and J magnitudes)?

This section develops the mechanism of coupling, the origin of multiplets, how to use the $n + 1$ rule when it applies, and how to move beyond it when protons are not equivalent.

9.4.1 What causes splitting: coupling through bonding electrons

Scalar coupling as an indirect interaction

In solution NMR, rapid molecular tumbling averages out through-space dipolar couplings for small molecules. The dominant interaction responsible for splitting is **scalar coupling**, transmitted *through bonds* by electrons (often described by the Fermi contact interaction).

A simple way to conceptualize it is:

A proton's local magnetic field depends not only on B_0 and its own electronic shielding, but also on the spin state of neighboring nuclei connected through bonds. Different neighbor spin states shift the resonance slightly, producing multiple closely spaced lines instead of a single peak.

The coupling constant J : what it measures and what it does not

The separation between adjacent lines in a multiplet is the **coupling constant** J , measured in Hertz (Hz). Two crucial facts:

- J is **field-independent** (in Hz). If you run the same compound at 300 MHz or 600 MHz, J stays the same.
- Chemical shift differences are commonly reported in **ppm** and are field-independent in ppm, but *field-dependent in Hz* because:

$$\Delta\nu \text{ (Hz)} = \Delta\delta \text{ (ppm)} \times \nu_0 \text{ (MHz)}$$

Therefore, increasing field strength spreads chemical shifts apart in Hz but leaves J unchanged. This generally makes spectra more “first-order” and easier to interpret.

9.4.2 First-order splitting and the $n + 1$ rule

A two-proton illustration: why a doublet forms

Consider a proton H_a coupled to one neighboring proton H_b . Because H_b is spin- $\frac{1}{2}$, it can be in either the α (aligned with B_0) or β (opposed to B_0) state. Each state slightly changes the effective field at H_a , giving two resonance conditions of equal probability. Thus H_a appears as a **doublet** with 1:1 intensities and line separation J_{ab} .

Generalization: coupling to n equivalent neighbors

If a proton couples to n *equivalent* neighboring protons (same J), the number of lines is:

$$\text{multiplicity} = n + 1$$

and the relative intensities follow Pascal's triangle (binomial coefficients).

Examples

- Coupling to $n = 2$ equivalent protons $\Rightarrow$ triplet (1:2:1).
- Coupling to $n = 3$ equivalent protons $\Rightarrow$ quartet (1:3:3:1).

Conditions for the $n + 1$ rule (and why it fails)

The $n + 1$ rule is a *first-order* approximation. It works well when:

- the coupled sets are well separated in chemical shift (in Hz), and
- the coupling partners are equivalent (or effectively equivalent) so that a single J describes the interaction.

A common practical criterion is:

$$\frac{\Delta\nu}{J} \gtrsim 10$$

where $\Delta\nu$ is the separation (Hz) between the centers of the two coupled resonances. When $\Delta\nu$ is not large compared to J , second-order effects distort line positions and intensities ("roofing," additional apparent complexity). This does not invalidate coupling as a concept, but it means simple first-order counting rules may mislead.

9.4.3 Common coupling pathways and typical J ranges

Coupling is most commonly observed over two or three bonds in organic molecules.

Vicinal coupling: ^3J (three bonds)

Vicinal coupling occurs across three bonds, e.g. $\text{H}-\text{C}-\text{C}-\text{H}$. It is the most frequently used for connectivity because most adjacent carbon frameworks create vicinal relationships.

Typical ranges:

- **Alkane vicinal** ($\text{H}-\text{C}-\text{C}-\text{H}$): $^3J \sim 6-8$ Hz (variable).
- **Vinylic** ($\text{H}-\text{C}=\text{C}-\text{H}$): ^3J is strongly geometry-dependent (cis vs. trans).

Geminal coupling: ^2J (two bonds)

Geminal coupling occurs between two protons on the same carbon, H_2C . In many simple, rapidly rotating systems, the two protons are equivalent and do not split each other. But if they are *diastereotopic* (chemically nonequivalent in a chiral or conformationally restricted environment), geminal coupling becomes visible. Typical geminal values:

$$^2J \sim 10-18 \text{ Hz} \quad (\text{sign can be positive or negative; magnitude is observed})$$

Long-range coupling: ^4J and beyond

Coupling can sometimes be observed over four bonds (and occasionally more), especially in π systems where orbital overlap enables transmission:

- **Allylic coupling** ($\text{H}-\text{C}=\text{C}-\text{C}-\text{H}$): often small, $^4J \sim 1-3$ Hz.
- **Aromatic meta coupling** can be a few Hz and is useful for substitution patterns.

9.4.4 Multiplet interpretation as connectivity information

Ethyl and isopropyl patterns (recognition tools)

Certain splitting patterns occur so frequently that they function as substructure “signatures.”

Ethyl group ($-\text{CH}_2\text{CH}_3$).

In an ideal first-order spectrum:

- CH_3 couples to two CH_2 protons $\Rightarrow$ **triplet** (integrates to 3 H).
- CH_2 couples to three CH_3 protons $\Rightarrow$ **quartet** (integrates to 2 H).
- Both multiplets share the same J value (typically ~ 7 Hz).

This paired triplet/quartet with matching J is among the strongest connectivity indicators in ^1H NMR.

Isopropyl group ($-(\text{CH}_3)_2\text{CH}-$).

- The methine CH couples to six equivalent methyl protons $\Rightarrow$ **septet** (1:6:15:20:15:6:1), integrates to 1 H.
- Each CH_3 group couples to one methine proton $\Rightarrow$ **doublet**, integrates to 6 H total (often two equivalent methyl groups give one doublet integrating to 6 H).

Multiplicity and equivalence: why “equivalent neighbors” matters

The $n + 1$ rule requires that the neighboring n protons be equivalent with respect to coupling (same J). When neighbors are *not* equivalent, splitting occurs in stages, producing patterns such as doublet of doublets (dd), triplet of doublets (td), etc. This is not a complication to be feared; it is an opportunity, because different J values often correspond to different geometrical relationships (cis/trans/geminal) and therefore carry rich structural information.

9.4.5 Complex splitting from non-equivalent couplings: the vinyl group

A classic example of non-equivalent coupling is the **vinyl group** $\text{CH}_2=\text{CH}^-$. Consider the alkene fragment $\text{H}_a\text{H}_b\text{C}=\text{CH}_c^-$. The vinylic proton H_c couples to the two nonequivalent protons on the adjacent carbon (H_a and H_b). Because one of these couplings is *trans* and the other is *cis*, the coupling constants differ significantly:

$$^3J_{\text{trans}} \approx 12\text{--}18 \text{ Hz} \qquad ^3J_{\text{cis}} \approx 6\text{--}12 \text{ Hz}$$

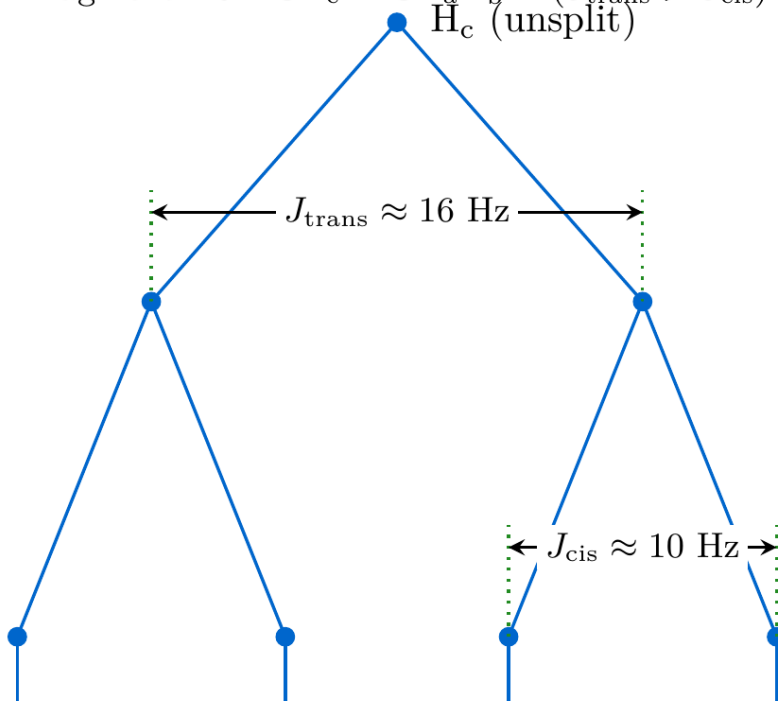
Additionally, the two protons on the terminal alkene carbon (CH_2) can show **geminal** coupling:

$${}^2J_{\text{gem}} \approx 10\text{--}18 \text{ Hz}$$

As a result, the vinylic proton H_c often appears as a **doublet of doublets (dd)**: first split by one neighbor (say trans), and each line split again by the other neighbor (cis). The key interpretive payoff is that the *two J values can be read directly from the multiplet*, providing stereochemical information.

Splitting Tree: Vinylic Proton (H_c)

Fragment: $R - CH_c = CH_aH_b$ ($J_{\text{trans}} > J_{\text{cis}}$)
 H_c (unsplit)



Observed Pattern: Doublet of doublets (dd)

Typical Coupling Constants (Vinyl Group):

- ${}^3J_{\text{trans}} \approx 11\text{--}18 \text{ Hz}$ (Large)
- ${}^3J_{\text{cis}} \approx 6\text{--}14 \text{ Hz}$ (Medium)
- ${}^2J_{\text{gem}} \approx 0\text{--}3 \text{ Hz}$ (Small, for terminal alkenes)

Reading stereochemistry from J : cis vs. trans alkenes

Because ^3J across a double bond depends strongly on geometry, J values provide direct evidence for alkene stereochemistry:

- **Trans** vinylic coupling is typically larger ($\sim 12\text{--}18$ Hz).
- **Cis** vinylic coupling is typically smaller ($\sim 6\text{--}12$ Hz).

Thus, when a vinylic proton appears as a doublet with $J \approx 16$ Hz, a trans relationship to the coupled partner is strongly suggested. When it appears as a doublet with $J \approx 10$ Hz, a cis relationship is more likely (with caveats for substitution and conjugation).

9.4.6 The Karplus relationship: coupling as a conformational probe

In saturated systems, vicinal coupling depends on the dihedral angle θ between the coupled C–H bonds. The qualitative form of the Karplus relationship is:

- ^3J is **largest** when $\theta \approx 180^\circ$ (anti).
- ^3J is **moderate to small** when $\theta \approx 60^\circ$ (gauche).
- ^3J is often **small** near $\theta \approx 90^\circ$.

A common empirical expression is:

$$^3J = A \cos^2 \theta + B \cos \theta + C$$

with constants A , B , and C depending on substituents and electronegativity. In practice, Karplus reasoning helps connect coupling constants to preferred conformations (especially in cyclic systems and constrained acyclic systems). For flexible acyclic molecules, rapid rotation averages coupling over accessible conformations, but informative trends often remain.

9.4.7 Second-order and practical complexities

Real spectra often deviate from ideal first-order patterns. Recognizing the source of complexity prevents misassignment.

Overlapping multiplets

If two signals partially overlap, the apparent splitting pattern can look more complex than it truly is. Integration may also become unreliable. In such cases, higher field data, selective decoupling, or 2D NMR methods (beyond the scope of this chapter) can help.

Diastereotopic protons and AB patterns (preview)

A CH₂ group adjacent to a stereocenter or in a rigid environment often has diastereotopic hydrogens. These two protons:

- have different chemical shifts,
- couple geminally to each other, and
- can couple differently to neighboring protons.

This creates AB or ABX-type patterns that do not follow simple $n + 1$ logic. The correct interpretation still relies on the same principles: identify coupling partners and measure J values, then build connectivity.

9.4.8 A structured workflow for using splitting to infer connectivity

When approaching an unknown ¹H NMR spectrum, a reliable sequence is:

- **Assign chemical shifts and integrals first** (from the previous section): identify candidate functional group neighborhoods and proton counts.
- **Read multiplicities qualitatively:** singlet, doublet, triplet, quartet, multiplet, etc.
- **Measure J values** for well-resolved multiplets: matching J values between two signals is strong evidence of mutual coupling (they are neighbors in the coupling network); vinylic J values can indicate cis/trans relationships.
- **Convert splitting to adjacency hypotheses:** for example, triplet (3H) + quartet (2H) with same $J \Rightarrow$ ethyl fragment; doublet (6H) + septet (1H) with same $J \Rightarrow$ isopropyl fragment; dd in vinyl region with $J \sim 16$ and 10 Hz $\Rightarrow$ vinylic proton coupled cis and trans to nonequivalent partners.
- **Check against IR/MS constraints:** ensure the inferred substructures are consistent with functional groups (IR) and formula/mass (MS).

9.4.9 Summary: what coupling contributes to structure elucidation

Chemical shifts tell you *what kinds* of proton environments exist; integration tells you *how many* protons are in each environment. Splitting and coupling tell you *which environments are connected* through two or three bonds, and J values can further report *geometry* (especially in alkenes) and *conformation* (via Karplus trends). Together, these three ^1H NMR observables form a tightly linked toolkit for constructing and validating molecular structures.

9.5 Carbon-13 NMR

Infrared spectroscopy quickly identifies functional groups, mass spectrometry constrains molar mass and substructures, and ^1H NMR provides detailed information about hydrogen environments, integrals, and connectivities through coupling. ^{13}C NMR extends these NMR principles to the *carbon framework* itself. Because most organic structures are ultimately defined by their carbon skeleton, ^{13}C NMR is the most direct spectroscopic “map” of the backbone: it tells you how many distinct carbons exist (symmetry), what *types* of carbons are present (sp^3 , sp^2 , carbonyl), and (with DEPT) how many hydrogens are attached to each carbon (CH_3 , CH_2 , CH , or quaternary).

At the same time, ^{13}C NMR introduces two practical challenges not prominent in ^1H NMR:

- **Low sensitivity** due to low natural abundance and a smaller magnetogyric ratio.
- **Extensive coupling** to attached protons unless decoupling methods are used.

9.5.1 Why ^{13}C is different from ^1H : abundance, sensitivity, and acquisition

Natural abundance and the consequence for signal strength

Carbon has two stable isotopes relevant to NMR:

- ^{12}C : $I = 0$ (NMR-inactive), $\sim 98.9\%$
- ^{13}C : $I = \frac{1}{2}$ (NMR-active), $\sim 1.1\%$

Thus, only about 1 in 90 carbon atoms is observable by ^{13}C NMR. This drastically reduces signal intensity compared with ^1H NMR, where essentially all hydrogens are ^1H .

Gyromagnetic ratio and intrinsic sensitivity

The ^{13}C gyromagnetic ratio is substantially smaller than that of ^1H . Because NMR signal strength scales strongly with γ (through both polarization and detection), ^{13}C is intrinsically less sensitive even before accounting for abundance. Practically, this means:

- ^{13}C NMR typically requires many scans (signal averaging).
- Sample concentrations are often higher than for ^1H NMR.
- Acquisition parameters (relaxation delays, decoupling) strongly influence whether peak areas are quantitative.

Relaxation and why ^{13}C integrals are usually not quantitative

In ^1H NMR, integrations are routinely reliable for proton counting (with reasonable acquisition settings). In contrast, ^{13}C peak areas are often *not* proportional to the number of carbons because:

- **Different T_1 relaxation times:** quaternary carbons and carbonyl carbons often relax slowly, requiring long delays to integrate quantitatively.
- **Nuclear Overhauser Effect (NOE)** under proton decoupling: carbon signals attached to hydrogens can be enhanced relative to quaternary carbons.

Therefore, in routine structure elucidation, ^{13}C NMR is used primarily for *counting distinct carbons* and *classifying carbon types*, not for integration.

9.5.2 Chemical shift in ^{13}C NMR: a backbone “functional group map”

Chemical shift scale and referencing

^{13}C chemical shifts are reported in ppm using the same δ definition as ^1H NMR (referenced indirectly to TMS). Because carbon chemical shifts span a much wider range (roughly 0–220 ppm for most organic compounds), ^{13}C NMR provides strong separation between carbon types.

Key ^{13}C chemical shift regions

A first-pass interpretation uses broad regions tied to bonding and functional groups: **sp^3 carbons (alkyl):** $\delta \sim 0\text{--}60$ **ppm.** Saturated carbons in alkanes and alkyl substituents typically appear upfield. Substitution and heteroatom effects shift positions:

- Simple alkyl carbons often fall in $\sim 10\text{--}40$ ppm.
- Carbons attached to electronegative atoms (e.g., C–O, C–N, C–X) are deshielded and commonly appear downfield in $\sim 40\text{--}90$ ppm depending on the heteroatom and substitution.

sp and sp^2 carbons (unsaturation): $\delta \sim 60\text{--}160$ **ppm.**

- Alkynes (sp) often appear around $\sim 65\text{--}90$ ppm.
- Alkenes and aromatics (sp^2) populate roughly $\sim 100\text{--}160$ ppm, with aromatic carbons often clustering in the $120\text{--}140$ ppm region.

Carbonyl carbons: $\delta \sim 160\text{--}220$ **ppm.** Carbonyl carbons are strongly deshielded, giving the most downfield signals in typical organic ^{13}C spectra.

- Esters, acids, amides: commonly $\sim 160\text{--}185$ ppm (variable, with amides often somewhat upfield relative to esters due to resonance).
- Aldehydes and ketones: commonly $\sim 190\text{--}220$ ppm.

These ranges are extremely useful for confirming carbonyl presence and helping distinguish carbonyl classes in conjunction with IR (carbonyl stretching frequency) and ^1H NMR (aldehydic proton at $\sim 9\text{--}10$ ppm, etc.).

9.5.3 Proton coupling in ^{13}C NMR and why decoupling is central**What a fully coupled ^{13}C spectrum would look like**

If ^{13}C spectra were recorded without proton decoupling, most carbon signals would be split by directly attached protons (one-bond coupling $^1J_{\text{CH}}$), producing complex multiplets:

- CH_3 carbon: quartet (coupled to 3 equivalent ^1H)
- CH_2 carbon: triplet

- CH carbon: doublet
- quaternary carbon: singlet

Although this seems analogous to the ^1H $n + 1$ rule, the coupling constants are large ($^1J_{\text{CH}}$ often on the order of 100–200 Hz), and additional longer-range couplings can further complicate patterns. The resulting spectrum is harder to interpret and less sensitive (signal spread across multiple lines).

Broadband proton decoupling: simplifying to singlets

The standard ^{13}C spectrum used for structure elucidation is **broadband proton-decoupled**. During acquisition, the instrument irradiates across the ^1H frequency range, rapidly flipping proton spins and averaging the carbon–proton scalar coupling to (approximately) zero. The main benefits are:

- Each distinct carbon appears as (approximately) a **singlet**, dramatically simplifying interpretation.
- Signal-to-noise improves because intensity is concentrated into one line rather than distributed across a multiplet.

Interpretive consequence. Because decoupled spectra remove splitting information, a basic ^{13}C spectrum does not directly reveal whether a carbon is CH_3 , CH_2 , CH , or quaternary. That information is recovered using polarization-transfer experiments such as DEPT.

9.5.4 Counting carbons: symmetry and the meaning of the number of signals

Distinct ^{13}C signals correspond to distinct carbon environments

In a broadband-decoupled ^{13}C spectrum, the number of peaks (signals) is the number of chemically distinct carbon environments. This makes ^{13}C NMR an efficient symmetry detector.

Example (conceptual). A molecule with formula C_6H_{14} could be any of several isomers. ^{13}C NMR distinguishes them quickly:

- *n*-hexane has fewer than six distinct carbon environments due to symmetry (terminal carbons equivalent, etc.).

- More branched isomers often reduce the number of distinct carbons further (greater symmetry), or increase it (reduced symmetry) depending on structure.

Thus, peak count is a structural constraint independent of ^1H integration and splitting.

Quaternary carbons: a common “missing peak” problem

Quaternary carbons (no attached hydrogens) frequently appear weaker in routine ^{13}C spectra because:

- they do not receive NOE enhancement under decoupling,
- they often relax slowly, and
- they may have less efficient polarization transfer in certain experiments.

Therefore, the absence or weakness of a quaternary carbon peak does not necessarily indicate absence of that carbon type; it may reflect acquisition sensitivity. DEPT experiments help identify quaternary carbons by their *absence* in DEPT spectra (see below).

9.5.5 DEPT spectroscopy: distinguishing CH_3 , CH_2 , CH , and quaternary carbons

Conceptual purpose of DEPT

DEPT (Distortionless Enhancement by Polarization Transfer) is designed to answer a specific question that broadband-decoupled ^{13}C does not: *how many hydrogens are attached to each carbon?* It does this by transferring polarization from abundant ^1H spins to ^{13}C and selecting signals based on the number of attached hydrogens.

DEPT spectra are typically interpreted *together* with the broadband-decoupled ^{13}C spectrum:

- The decoupled ^{13}C spectrum provides the complete list of carbon chemical shifts (including quaternary carbons).
- DEPT differentiates carbon multiplicity types among the protonated carbons.

DEPT-45, DEPT-90, and DEPT-135 (practical rules)

The most commonly used DEPT experiments are:

DEPT-45. Shows **all protonated carbons**: CH_3 , CH_2 , and CH appear (typically positive phase). Quaternary carbons do not appear.

DEPT-90. Shows **only CH** (methine) carbons. CH_3 and CH_2 are suppressed; quaternary absent.

DEPT-135. Shows CH_3 and CH as one phase (commonly drawn “upright”) and CH_2 as the opposite phase (commonly drawn “inverted”). Quaternary carbons are absent.

These rules are often summarized as:

- If it appears in decoupled ^{13}C but not in any DEPT $\Rightarrow$ **quaternary carbon** (including carbonyl carbons and substituted aromatic quaternaries).
- If it appears in DEPT-90 $\Rightarrow$ **CH**.
- If it appears inverted in DEPT-135 $\Rightarrow$ **CH_2** .
- If it appears in DEPT-135 upright but not in DEPT-90 $\Rightarrow$ **CH_3** .

How DEPT resolves common ambiguities

DEPT is especially useful in distinguishing isomers that have similar ^1H patterns but differ in carbon substitution. Examples of questions DEPT answers efficiently:

- Does an apparent alkyl region carbon at $\delta \sim 30$ ppm correspond to CH_3 , CH_2 , or CH ?
- Does a substituted aromatic ring contain quaternary carbons (ipso carbons) consistent with a substitution pattern?
- Is a carbonyl-bearing carbon adjacent to CH_2 or CH (important in distinguishing ester vs. ketone substitution patterns when combined with ^1H NMR)?

9.5.6 Interpreting ^{13}C NMR together with IR, MS, and ^1H NMR

A structure-elucidation workflow emphasizing complementarity

A disciplined multi-technique workflow uses each method for what it does best:

- **MS** gives M and often formula constraints (degrees of unsaturation, heteroatoms, halogens).
- **IR** identifies major functional groups (carbonyl, hydroxyl, amine, nitrile).
- **^1H NMR** identifies hydrogen environments, counts H's (integration), and connects neighbors (coupling).
- **^{13}C NMR** counts distinct carbons, classifies carbon types by chemical shift, and (with DEPT) assigns carbon multiplicities ($\text{CH}_3/\text{CH}_2/\text{CH}/\text{quaternary}$).

Degrees of unsaturation and ^{13}C “region checks”

If MS (or formula) indicates unsaturation, ^{13}C quickly tests whether it is due to:

- **Aromatic/alkene carbons** (signals in $\sim 100\text{--}160$ ppm),
- **Carbonyl carbons** (signals in $\sim 160\text{--}220$ ppm),
- **Alkyne carbons** (signals in $\sim 65\text{--}90$ ppm).

This is a fast consistency check: a molecule with multiple degrees of unsaturation but no sp^2 /carbonyl signals would be unusual and suggests either a misassigned formula or an atypical structure (e.g., multiple rings without double bonds).

9.5.7 Practical notes: solvents, referencing, and common artifacts

Solvents and solvent peaks (conceptual)

Deuterated solvents are used to avoid overwhelming ^1H signals and to provide a field-frequency lock. In ^{13}C spectra, the solvent often produces characteristic carbon peaks that must not be mistaken for sample carbons. Always consult the solvent peak positions when assigning ^{13}C spectra.

Why some carbons are weak or missing

If a peak expected from the formula is weak or absent, consider:

- quaternary carbons and carbonyl carbons often have lower intensity,
- insufficient relaxation delay (especially problematic for quantitative work),

- overlap (two carbons with similar shifts can coincide at unit resolution),
- low concentration or poor signal-to-noise.

9.5.8 Summary: what ^{13}C NMR contributes

^{13}C NMR provides a direct inventory of the carbon skeleton:

- **Number of signals** $\Rightarrow$ number of distinct carbon environments (symmetry constraint).
- **Chemical shift regions** $\Rightarrow$ carbon functional classes (sp^3 , sp/sp^2 , carbonyl; heteroatom substitution).
- **Broadband decoupling** $\Rightarrow$ simplified singlet spectrum for straightforward counting and classification.
- **DEPT** $\Rightarrow$ $\text{CH}_3/\text{CH}_2/\text{CH}$ discrimination and identification of quaternary carbons by absence.

Used alongside IR, MS, and ^1H NMR, ^{13}C NMR is often the final piece that locks a candidate structure into a uniquely consistent solution.

9.6 Problems

9.6.1 Problem 1: $\text{C}_4\text{H}_8\text{O}$ carbonyl unknown

An unknown compound has molecular formula $\text{C}_4\text{H}_8\text{O}$.

- **IR (neat, $1/\text{cm}$):** strong band at $1715/\text{cm}$; no broad absorption from $3600/\text{cm}$ to $3200/\text{cm}$; no bands near $2250/\text{cm}$.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 2.43 (quartet, $J = 7.2$ Hz, 2H); 2.13 (singlet, 3H); 1.03 (triplet, $J = 7.2$ Hz, 3H).
- **^{13}C NMR (100 MHz, CDCl_3 , δ ppm):** 205.5, 35.8, 30.1, 8.2.

Task: Determine the structure (give a condensed structural formula), assign each ^1H and ^{13}C signal to specific atoms, and state how the IR band at $1715/\text{cm}$ supports your assignment.

9.6.2 Problem 2: Bromoalkane from isotope clusters and integration

An unknown is a brominated alkane.

- **MS (EI):** two peaks at m/z 136 and 138 with approximately equal intensities; prominent fragments at m/z 57 and 41.
- **IR (neat, 1/cm):** no O–H/N–H; no C=O; strong sp^3 C–H stretches at 2960/cm to 2850/cm.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 3.42 (triplet, $J = 6.8$ Hz, 2H); 1.80 (quintet, $J = 6.8$ Hz, 2H); 1.37 (multiplet, 2H); 0.92 (triplet, $J = 7.2$ Hz, 3H).
- **^{13}C NMR (100 MHz, CDCl_3 , δ ppm):** 34.0, 32.8, 22.3, 13.9.

Task: Propose a single structure consistent with all data. Explicitly justify (i) the number of carbons, (ii) the presence of bromine and how many bromines, and (iii) the connectivity implied by the splitting pattern.

9.6.3 Problem 3: Distinguishing isomers of $\text{C}_5\text{H}_{10}\text{O}$ using DEPT and ^1H splitting

Two isomers, A and B, both have molecular formula $\text{C}_5\text{H}_{10}\text{O}$. Both show an IR carbonyl absorption, but their NMR data differ.

Compound A

- **IR (cm^{-1}):** strong 1715/cm; no broad O–H.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 0.93 (triplet, $J = 7.3$ Hz, 3H); 1.62 (sextet, $J = 7.3$ Hz, 2H); 2.41 (triplet, $J = 7.3$ Hz, 2H); 2.13 (singlet, 3H).
- **^{13}C NMR (δ ppm):** 208.0, 43.5, 29.8, 22.1, 8.0.
- **DEPT-135:** signals at 29.8 and 8.0 are positive; 43.5 and 22.1 are negative; 208.0 is absent.

Compound B

- **IR (cm^{-1}):** strong 1725/cm; no broad O–H.

- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 1.07 (doublet, $J = 6.6$ Hz, 6H); 2.72 (septet, $J = 6.6$ Hz, 1H); 2.12 (singlet, 3H).
- **^{13}C NMR (δ ppm):** 210.2, 34.6, 29.9, 18.9.
- **DEPT-135:** 29.9 and 18.9 are positive; 34.6 is positive; 210.2 is absent.

Task: Determine the structures of A and B, using the DEPT-135 results to specify which carbons are CH_3 , CH_2 , CH , and quaternary. Explain how the ^1H splitting patterns distinguish the two.

9.6.4 Problem 4: Aromatic substitution pattern from coupling constants

An unknown aromatic compound has formula $\text{C}_8\text{H}_{10}\text{O}$. (Assume one oxygen only.)

- **IR (cm^{-1}):** broad band at 3400/ cm ; aromatic $\text{C}-\text{H}$ near 3030/ cm ; bands at 1600/ cm and 1500/ cm ; strong band at 1250/ cm to 1050/ cm .
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 7.12 (doublet, $J = 8.6$ Hz, 2H); 6.83 (doublet, $J = 8.6$ Hz, 2H); 3.78 (singlet, 3H); 4.60 (broad singlet, 1H, disappears upon D_2O shake).
- **^{13}C NMR (δ ppm):** 159.2, 130.1, 114.2, 55.4 (plus two additional aromatic signals).

Task: Determine the aromatic substitution pattern (ortho, meta, or para) and propose a structure consistent with the oxygen-containing groups indicated. Explain how the ^1H aromatic splitting pattern supports your conclusion.

9.6.5 Problem 5: Degrees of unsaturation followed by IR/NMR correlation

An unknown has molecular formula $\text{C}_6\text{H}_{10}\text{O}_2$.

- **IR (cm^{-1}):** strong 1735/ cm ; strong 1240/ cm to 1050/ cm ; no broad $\text{O}-\text{H}$.
- **MS (EI):** molecular ion peak at m/z 114; notable fragment at m/z 43; notable fragment at m/z 88.

- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 4.12 (quartet, $J = 7.1$ Hz, 2H); 2.30 (triplet, $J = 7.5$ Hz, 2H); 1.62 (sextet, $J = 7.5$ Hz, 2H); 1.25 (triplet, $J = 7.1$ Hz, 3H).
- **^{13}C NMR (δ ppm):** 173.8, 60.5, 34.2, 24.6, 14.3.

Task: (i) Calculate the degrees of unsaturation, (ii) identify the functional group(s) supported by IR, and (iii) propose a structure consistent with the NMR and MS fragments. Assign each ^1H signal and explain why m/z 43 is plausible for this compound class.

9.6.6 Problem 6: Nitrogen Rule and exchangeable protons

An unknown has the formula $\text{C}_4\text{H}_9\text{NO}$.

- **MS (EI):** molecular ion at m/z 87.
- **IR (cm^{-1}):** strong band at 1650/ cm ; medium bands at 3350/ cm and 3180/ cm .
- **^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ ppm):** 7.65 (broad, 1H, disappears with D_2O); 6.95 (broad, 1H, disappears with D_2O); 2.15 (singlet, 3H); 1.10 (doublet, $J = 6.7$ Hz, 6H).
- **^{13}C NMR (δ ppm):** 169.5, 34.2, 22.5.

Task: Use the Nitrogen Rule to rationalize the molecular ion mass parity, identify the functional group implied by the IR at 1650/ cm and the two exchangeable protons, and propose a structure. Explain the origin of the 6H doublet and what it implies about the carbon skeleton.

9.6.7 Problem 7: Alkene stereochemistry from coupling constants (E vs. Z)

An unknown alkene has formula $\text{C}_5\text{H}_{10}\text{O}$. IR shows no carbonyl; a broad band near 3400/ cm is present.

- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 5.86 (doublet of doublets, $J = 15.6, 6.5$ Hz, 1H); 5.12 (doublet of doublets, $J = 15.6, 1.5$ Hz, 1H); 3.62 (triplet, $J = 6.5$ Hz, 2H); 2.05 (multiplet, 2H); 1.02 (triplet, $J = 7.4$ Hz, 3H); 1.75 (broad singlet, 1H, disappears with D_2O).

- **^{13}C NMR (δ ppm):** 137.0, 114.5, 62.4, 28.9, 13.8.

Task: Determine whether the alkene is more consistent with an *E* or *Z* relationship between the two vinylic protons, and propose a structure consistent with the alcohol evidence. Assign the two vinylic protons and explain the origin of each *J* value in the dd patterns.

9.6.8 Problem 8: Ester vs. carboxylic acid using chemical shifts and D_2O shake

Two unknowns, X and Y, both have formula $\text{C}_4\text{H}_8\text{O}_2$. Their IR spectra are similar in showing carbonyl absorption, but one is an ester and the other is a carboxylic acid.

Unknown X

- **IR (cm^{-1}):** strong 1740/ cm ; strong 1240/ cm to 1050/ cm ; no very broad 3300/ cm to 2500/ cm feature.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 4.12 (quartet, $J = 7.1$ Hz, 2H); 2.05 (singlet, 3H); 1.25 (triplet, $J = 7.1$ Hz, 3H).

Unknown Y

- **IR (cm^{-1}):** strong 1710/ cm ; very broad 3300/ cm to 2500/ cm .
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 11.2 (broad, 1H, disappears with D_2O); 2.34 (quartet, $J = 7.4$ Hz, 2H); 1.12 (triplet, $J = 7.4$ Hz, 3H).

Task: Identify which unknown is the ester and which is the carboxylic acid. For each, propose a structure and justify your assignment using (i) the IR diagnostic region, (ii) chemical shifts in the ^1H NMR, and (iii) the D_2O exchange behavior.

9.6.9 Problem 9: Full-spectrum unknown (IR, MS, ^1H , ^{13}C)

An unknown compound gives the following data:

- **MS (EI):** molecular ion at m/z 122; $M + 2$ is absent; $M + 1$ is about 6.6% of M .

- **IR (cm^{-1}):** strong 1715/cm; no broad O–H; aromatic bands at 1600/cm and 1500/cm; weak bands near 3030/cm; strong band near 750/cm.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 7.95 (doublet, $J = 8.0$ Hz, 2H); 7.45 (doublet, $J = 8.0$ Hz, 2H); 2.60 (singlet, 3H); 2.15 (singlet, 3H).
- **^{13}C NMR (δ ppm):** 197.5, 144.0, 134.5, 129.0, 127.0, 30.5, 26.8.

Task: (i) Estimate the number of carbons from the $M + 1/M$ ratio, (ii) propose a molecular formula consistent with m/z 122 and the IR data, and (iii) determine a structure consistent with the ^1H and ^{13}C NMR. Justify the aromatic substitution pattern implied by the ^1H spectrum.

9.6.10 Problem 10: Advanced MS fragmentation (McLafferty) plus anisotropy evidence in NMR

An unknown has molecular ion at m/z 128 in EI MS and shows a strong fragment at m/z 58. The IR spectrum shows a strong carbonyl at 1715/cm and no broad O–H/N–H.

- **MS (EI):** $M^{+\cdot} = 128$; prominent fragment at 58; additional notable fragment at 43.
- **^1H NMR (400 MHz, CDCl_3 , δ ppm):** 2.42 (triplet, $J = 7.4$ Hz, 2H); 2.10 (singlet, 3H); 1.62 (quintet, $J = 7.4$ Hz, 2H); 1.25 (sextet, $J = 7.4$ Hz, 2H); 0.92 (triplet, $J = 7.4$ Hz, 3H).
- **^{13}C NMR (δ ppm):** 208.5, 42.0, 30.0, 24.0, 22.0, 14.0.

Task: Propose a structure consistent with all spectra. Then, provide a mechanistic explanation for the fragment at m/z 58 via a McLafferty rearrangement (identify the required γ -hydrogen and the bond that breaks). Finally, use NMR reasoning to justify why the carbonyl-adjacent methylene appears downfield relative to the other alkyl methylenes, connecting your explanation to carbonyl anisotropy and inductive effects.

Chapter 10

Aromatic Compounds

Why does benzene resist the addition reactions typical of alkenes, opting instead to trade hydrogen for functional groups while preserving its ring? This chapter bridges quantum mechanics and synthetic utility, moving from the orbital symmetry arguments of Hückel's rule to the practical construction of complex molecular architectures via Electrophilic Aromatic Substitution. We will dissect the energetic trade-offs of the sigma-complex intermediate and learn to orchestrate multi-step syntheses by mastering the directing effects of substituents.

10.1 Aromaticity, Antiaromaticity, and Molecular Orbital Theory

In earlier chapters we developed three tools that will now converge into a single, unusually powerful idea:

- **Lewis structures and resonance** explain how electrons can be delocalized across multiple atoms.
- **Conjugation and orbital overlap** explain *when* such delocalization is possible (alignment of adjacent p orbitals).
- **Thermochemistry** (enthalpy changes) provides an experimental window into stability.

Aromaticity is the name we give to a *quantum-mechanical stabilization* that occurs when a cyclic, conjugated π system possesses a particular pattern of π molecular

orbitals (MOs) and electron occupancy. This stabilization is not merely “extra resonance” in the Lewis-structure sense; it is a direct consequence of how standing-wave solutions form on a ring of interacting p orbitals.

10.1.1 The structural prerequisites for aromaticity

Before applying any electron-counting rule, a molecule must be capable of supporting a continuous cyclic π system. Four structural prerequisites are commonly used as a checklist:

- **Cyclic:** the π system forms a closed loop.
- **Conjugated:** every atom around the loop has a p orbital (or can supply one) so that overlap is continuous.
- **Approximately planar:** the p orbitals must be parallel enough for effective overlap (planarity can be perfect or merely sufficient).
- **Appropriate π electron count:** the number of π electrons must allow *complete filling* of the bonding MOs without forcing electrons into a destabilizing occupancy pattern.

If (1)–(3) are not satisfied, the system is **nonaromatic** (neither especially stabilized nor destabilized by aromaticity rules). Only if the structure *can* be cyclically conjugated does the electron count determine whether the system is aromatic or antiaromatic.

10.1.2 The quantum-mechanical origin of the Hückel $4n + 2$ rule

Consider a ring of N atoms, each contributing one p orbital to a cyclic conjugated array. When these p orbitals combine, they form N π molecular orbitals with specific phase relationships around the ring. The key qualitative result of Hückel MO theory is that:

- there is always one **lowest-energy bonding MO** with no nodes around the ring,
- higher MOs have increasing numbers of nodes (phase changes),
- and, crucially for rings, there is a characteristic **degeneracy pattern** (pairs of MOs at the same energy) that depends on the symmetry of the polygon.

The most important practical consequence is the **closed-shell criterion**: a cyclic conjugated system is unusually stable when its π electrons can *completely fill all bonding π MOs* (two electrons per MO, opposite spins) *without leaving any electrons in nonbonding or antibonding orbitals*.

For a monocyclic, planar, conjugated polyene, this “closed-shell” condition occurs when the ring contains

$$4n+2 \text{ } \pi \text{ electrons (where } n = 0, 1, 2, \dots)$$

These are called **Hückel electron counts**. The most famous example is benzene: 6 π electrons corresponds to $n = 1$.

In contrast, when such a ring contains

$$4n \text{ } \pi \text{ electrons (where } n = 1, 2, \dots)$$

the degeneracy pattern forces electrons into a *destabilizing occupancy* that leaves the system either with:

- **partially filled degenerate nonbonding MOs** (open-shell, strongly destabilized), or
- **electron pairing in degenerate orbitals** that is still energetically unfavorable relative to a closed-shell alternative.

A planar, fully conjugated $4n$ ring is termed **antiaromatic**: it is destabilized relative to comparable noncyclic conjugated systems. Cyclobutadiene (4 π electrons) is the canonical example.

10.1.3 Frost circles (polygon method): a fast MO-energy diagram for cyclic π systems

The Hückel $4n + 2$ rule is not a numerology trick; it summarizes a recurring MO-energy pattern. **Frost circles** provide a rapid, visual way to obtain that pattern for a regular monocyclic conjugated ring:

- Draw a circle.
- Inscribe a regular N -gon (**one vertex per p orbital**).
- Orient the polygon with **one vertex at the bottom** (this ensures the lowest MO is nondegenerate).

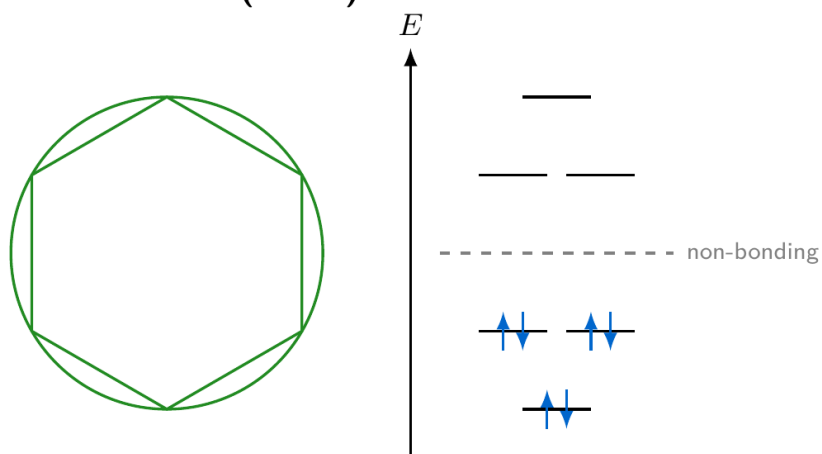
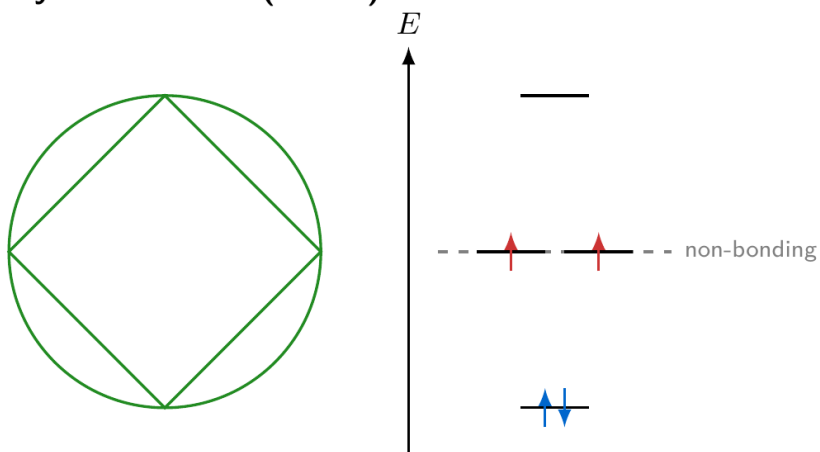
- Each vertex corresponds to a π MO energy level; vertices lower on the circle are lower in energy.
- Fill the levels with the system's π electrons (2 per level, following Hund's rule within degenerate sets).

The outcome immediately tells you whether the electron occupancy is **closed-shell** (aromatic) or **open-shell/degenerate at the Fermi level** (antiaromatic), assuming the ring is planar and fully conjugated.

Benzene vs. cyclobutadiene: the $4n + 2$ and $4n$ cases side by side

Benzene ($N = 6$) has three bonding MOs (one nondegenerate lowest, plus a degenerate pair), and three antibonding MOs. With 6 π electrons, all bonding MOs are filled: a closed shell.

Cyclobutadiene ($N = 4$) has one lowest bonding MO, one highest antibonding MO, and *two degenerate MOs at the nonbonding energy* (often drawn at α in Hückel notation). With 4 π electrons, after filling the lowest bonding MO (2 e^-), the remaining 2 electrons must occupy the degenerate nonbonding pair as *unpaired* electrons (Hund's rule) in the idealized square-planar picture. This is the hallmark of antiaromaticity: a cyclic conjugated system that cannot achieve a closed-shell configuration without moving electrons into higher-energy antibonding orbitals or distorting geometry to remove degeneracy.

Benzene (6π e⁻): Aromatic**Cyclobutadiene (4π e⁻): Antiaromatic**

10.1.4 Aromatic vs. antiaromatic vs. nonaromatic: precise definitions

With the MO picture in place, the modern definitions are:

- **Aromatic:** cyclic, conjugated, (approximately) planar π system with $4n + 2$ π **electrons**, yielding a **closed-shell** MO occupancy and a **thermodynamic stabilization** (lower energy than expected for a comparable acyclic conjugated system).
- **Antiaromatic:** cyclic, conjugated, (approximately) planar π system with $4n$ π **electrons**, yielding an **open-shell or destabilized** occupancy pattern and a **thermodynamic destabilization** (higher energy than expected).
- **Nonaromatic:** a system that fails cyclic conjugation and/or planarity, so the special aromatic/antiaromatic MO patterns do not apply.

A crucial practical point follows: **antiaromaticity is so unfavorable that many $4n$ systems distort to become nonaromatic.** Cyclobutadiene, for example, is experimentally observed to distort away from the square geometry, which reduces conjugation and lifts degeneracy, thereby escaping the worst antiaromatic penalty.

10.1.5 Counting π electrons correctly

Applying the $4n + 2$ rule requires correct identification of the electrons in the cyclic π system.

Carbons in double bonds

Each C=C contributes **2 π electrons** (one π bond). In benzene, three C=C bonds $\rightarrow$ 6 π electrons.

Lone pairs in a p orbital: when do they count?

A lone pair counts as part of the π system only if it resides in a p orbital aligned with the ring. This depends on the heteroatom's bonding pattern and hybridization.

- A heteroatom like **pyridine N** is sp^2 ; its lone pair is in an *in-plane* hybrid orbital and **does not** contribute to the aromatic π sextet. The nitrogen still contributes one p electron (like a C in the ring) to the π system.

- A heteroatom like **pyrrole N** uses its lone pair in the p orbital to complete the aromatic sextet; that lone pair **does** count (2π electrons).

Charges: anions and cations can create aromatic systems

Charges often change the π electron count in a way that enables aromaticity.

- **Cyclopentadienyl anion** (C_5H_5^-): five p orbitals around the ring; the negative charge supplies an extra pair in a p orbital, giving 6π electrons $\rightarrow$ aromatic.
- **Tropylium cation** (C_7H_7^+): seven p orbitals around the ring; the positive charge corresponds to an empty p orbital (one fewer electron), giving 6π electrons $\rightarrow$ aromatic.

10.1.6 Thermochemical evidence: heats of hydrogenation and “resonance energy”

Resonance structures suggest that benzene is stabilized, but thermochemistry allows us to *measure* that stabilization. The central idea is to compare a real compound's hydrogenation enthalpy to a hypothetical value predicted from “ordinary” isolated double bonds.

Heats of hydrogenation as a stability probe

Hydrogenation converts π bonds into σ bonds. The more stable the starting π system, the *less exothermic* (less negative) the hydrogenation enthalpy tends to be, because there is less energy “available” to be released upon destroying the π system.

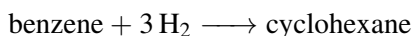
For a simple, unconjugated alkene, a typical heat of hydrogenation is approximately -120 kJ/mol (about -28 kcal/mol), though the exact value depends on substitution and conditions. If benzene behaved like a cyclohexatriene with three independent double bonds, one might naively expect approximately three times that magnitude.

Benzene: less exothermic than expected

Experimentally, hydrogenation of benzene to cyclohexane is *much less exothermic* than the “three isolated alkenes” expectation. The discrepancy is interpreted as **aromatic stabilization energy** (often called **resonance energy** in older terminology):

benzene starts at a lower energy than any localized “cyclohexatriene” picture would predict, so destroying aromaticity releases less heat.

A common thermochemical comparison is:



The key point is not the numerical value (which depends on measurement conventions) but the **direction of the discrepancy**: benzene is *stabilized* relative to a hypothetical localized model.

Cyclobutadiene: more reactive and effectively destabilized

A planar, fully conjugated 4π system would be expected to be **destabilized** (antiaromatic), hence *more exothermic* hydrogenation than expected for an ordinary conjugated diene. In practice, many $4n$ systems avoid strict planarity or continuous conjugation, becoming nonaromatic; nevertheless, the general trend holds: antiaromatic electron counts correlate with unusual instability and high reactivity.

What thermochemistry does (and does not) prove

Heats of hydrogenation provide **thermodynamic** evidence for stabilization/destabilization. However:

- They do not by themselves identify the electron count rule; the rule is a **quantum-mechanical** statement about MO occupancy.
- They must be interpreted using appropriate reference compounds (e.g., comparing to suitable alkenes/dienes).

Thus, thermochemistry is best viewed as experimental support for the MO-based definition of aromaticity.

10.1.7 Connecting MO theory to familiar resonance pictures

It is tempting to equate aromaticity with “having resonance structures,” but resonance alone is not sufficient:

- Many molecules have resonance yet are not aromatic (e.g., acyclic conjugated polyenes).

- Aromatic stabilization requires a **cyclic** conjugated network and a **closed-shell** π MO filling pattern.

Resonance structures remain valuable because they:

- help track **electron count** (where π electrons and lone pairs are),
- emphasize **delocalization** (which is consistent with MO descriptions),
- foreshadow **reactivity** patterns (aromatic systems resist reactions that would break aromaticity).

But the reason benzene is *unusually* stable is that its six π electrons fill exactly the set of bonding MOs predicted by cyclic MO theory.

10.1.8 A step-by-step decision workflow for aromaticity

For most monocyclic systems encountered in introductory organic chemistry, the following workflow is reliable:

- **Identify a ring and the candidate π system.**
- **Check conjugation:** is there a continuous set of p orbitals (including appropriate lone pairs/empty p orbitals)?
- **Check planarity:** can the ring be (approximately) planar?
- **Count π electrons** in the cyclic conjugated loop.
- **Apply $4n+2$ vs. $4n$:** $4n+2 \rightarrow$ aromatic (if conjugation and planarity are satisfied); $4n \rightarrow$ antiaromatic (if conjugation and planarity are satisfied; otherwise often nonaromatic by distortion).
- **Optionally confirm with a Frost circle** (especially helpful when you want to *see* whether the filling is closed-shell).

10.1.9 Preview: why aromaticity dominates aromatic reactivity

Aromatic stabilization is so significant that aromatic rings characteristically undergo reactions that *preserve* aromaticity whenever possible. This is the fundamental reason electrophilic aromatic substitution (EAS) proceeds by temporary loss of aromaticity followed by rapid rearomatization, rather than by simple addition as alkenes do. The next sections will build directly on the stability principles developed here.

10.2 The Mechanism of Electrophilic Aromatic Substitution (EAS)

The previous section established a central principle that governs nearly all chemistry of benzene and its derivatives: **aromaticity is a substantial thermodynamic stabilization**. As a result, reactions that would permanently destroy aromaticity (for example, simple *addition* across the ring as in alkene chemistry) are strongly disfavored. Aromatic rings therefore tend to react by pathways that *briefly* sacrifice aromaticity but *rapidly restore* it. The most important of these pathways is **electrophilic aromatic substitution (EAS)**.

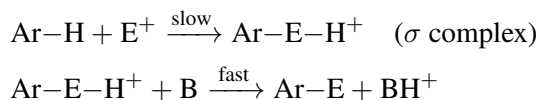
In EAS, the aromatic ring acts as a nucleophile toward a powerful electrophile. A new σ bond forms to the ring, and then a proton is lost to regenerate aromaticity. Overall, one substituent on the ring is replaced by an electrophile (**substitution**), not by net addition.

10.2.1 The general two-step mechanism: addition to form a σ complex, then elimination to restore aromaticity

Although the electrophile and conditions differ among EAS reactions, the core mechanism is the same:

- **Electrophile generation (activation step):** a reagent system produces a highly electrophilic species (often with the help of a Lewis or Brønsted acid).
- **Addition (rate-determining step):** the aromatic π system attacks the electrophile to form a σ **complex** (also called an **arenium ion** or **Wheland intermediate**). Aromaticity is lost in this step.
- **Elimination (fast re-aromatization):** a base removes the proton from the carbon bearing the electrophile; the π system is restored, and aromaticity returns.

A compact representation for benzene is:



Why the σ complex is the key intermediate

The σ complex contains one carbon that has changed from sp^2 to sp^3 hybridization, interrupting cyclic conjugation. The positive charge is **delocalized** over (typically) three ring carbons, giving several resonance contributors. This resonance stabilization makes the σ complex *possible*, but it remains much higher in energy than the aromatic starting material because aromatic stabilization has been sacrificed.

Two consequences follow immediately:

- **EAS has a high activation barrier.** Breaking aromaticity in the addition step is energetically costly.
- **Re-aromatization is strongly favored.** The elimination step returns the system to the aromatic energy minimum.

EAS versus alkene addition: same first step, different outcome

Alkenes typically undergo electrophilic addition because forming two new σ bonds is thermodynamically favorable, and there is no aromatic stabilization to lose. In contrast, if benzene were to undergo net addition (forming a nonaromatic cyclohexadienyl product), the product would be relatively high in energy compared to the aromatic starting material. Therefore, benzene substitutes rather than adds under typical electrophilic conditions.

10.2.2 Reaction coordinate perspective (energy diagram)

10.2.3 Step 1 in detail: generating a sufficiently strong electrophile

Benzene is *less nucleophilic* than typical alkenes because its π electrons are stabilized by aromaticity. Consequently, EAS usually requires generation of an unusually reactive electrophile, often by using:

- a **Lewis acid** (e.g., FeBr_3 , AlCl_3) to polarize a bond and promote heterolysis, or
- a **strong Brønsted acid** (often H_2SO_4) to protonate and dehydrate a precursor into a cationic electrophile.

The ring then attacks the electrophile to form the σ complex.

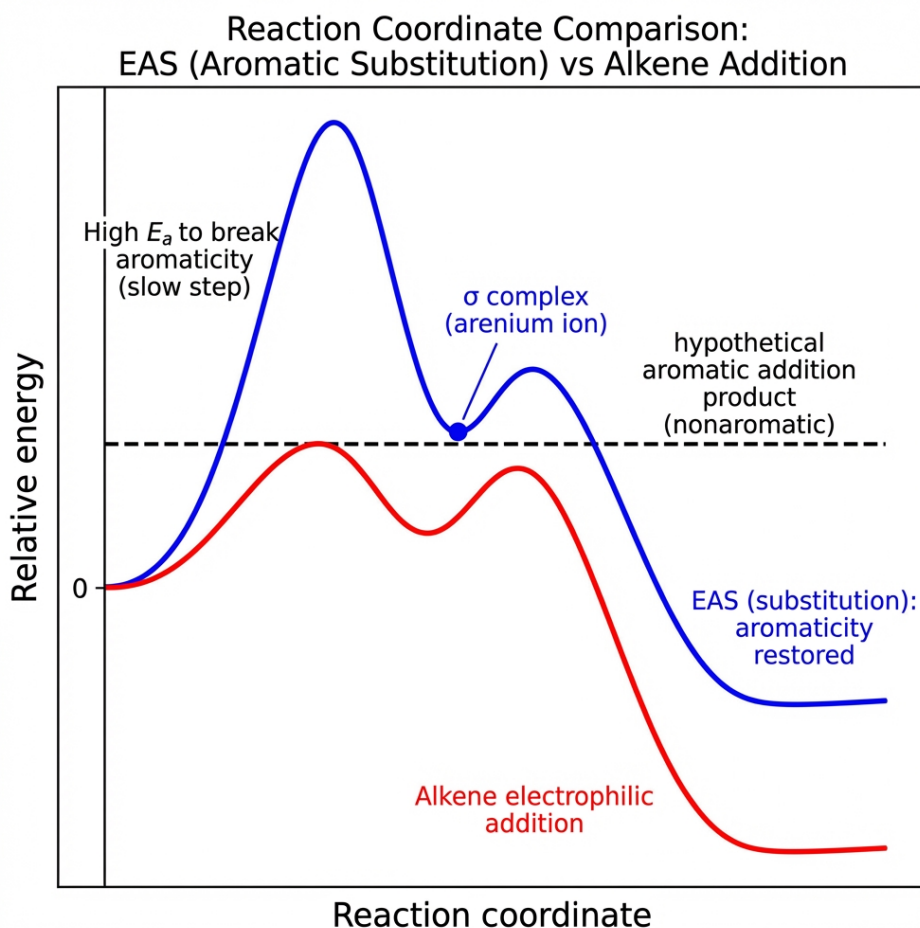


Figure 10.1: Qualitative reaction coordinate diagram showing why aromatic rings substitute rather than add. The rate-determining step in EAS is formation of the σ complex (loss of aromaticity), which has a high activation barrier. Rearomatization is strongly exergonic. In contrast, alkene addition has a lower barrier and leads to a stable addition product; a hypothetical *addition* product from benzene would be endergonic because it would remain nonaromatic.

10.2.4 Step 2 in detail: formation and resonance of the σ complex (arenium ion)

When benzene attacks E^+ , one carbon becomes sp^3 and bears both H and E. The positive charge is delocalized over the remaining conjugated portion of the ring. For monosubstituted benzene, the σ complex generally has three major resonance contributors, placing the positive charge at positions ortho and para to the new substituent (relative to the bond-formation site).

Two mechanistic points are repeatedly useful:

- **Bond formation precedes deprotonation.** EAS is not a concerted substitution; it is addition then elimination.
- **The slow step is electrophilic attack.** Any factor that stabilizes the σ complex (or lowers the energy of its transition state) increases the EAS rate. This is the foundation for substituent effects and directing groups in later sections.

10.2.5 Step 3: deprotonation and rearomatization

A base present in the reaction mixture removes the proton from the carbon bearing the electrophile:

- In halogenation, the base is often the counterion (e.g., $FeBr_4^-$) or halide (Br^- , Cl^-).
- In nitration and sulfonation, the base is typically HSO_4^- or another weak base in strongly acidic medium.

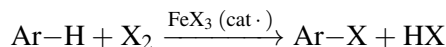
This deprotonation restores the aromatic π system and regenerates the acid catalyst (or a related catalytic species), which is why many EAS reactions are catalytic in Lewis acid (halogenations) or use a strongly acidic medium (nitration/sulfonation).

10.2.6 Specific EAS reactions

We now apply the general mechanism to three foundational EAS processes: halogenation, nitration, and sulfonation. In each case, focus on (i) **how the electrophile is generated**, (ii) **formation of the arenium ion**, and (iii) **rearomatization**.

10.2.7 Halogenation: bromination and chlorination of aromatic rings

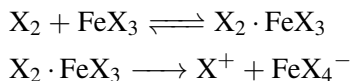
Overall transformation



with $X = \text{Br}$ or Cl and a Lewis acid such as FeBr_3 , FeCl_3 , or AlCl_3 .

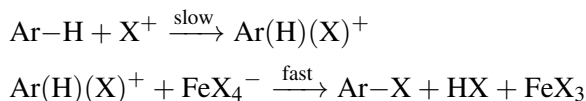
Electrophile generation by Lewis acid activation

Molecular halogens are electrophilic, but typically not electrophilic enough to react rapidly with benzene without activation. A Lewis acid coordinates to X_2 , polarizing the X-X bond and promoting heterolysis:



The species written as X^+ is a shorthand for a strongly electrophilic halogenating agent produced within the complex; the counterion FeX_4^- is weakly nucleophilic but serves as a base in the final step.

Arenium ion formation and deprotonation

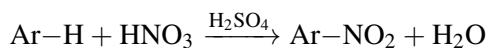


The Lewis acid is regenerated, consistent with its catalytic role.

Practical implications. Halogenation is typically **not** strongly exothermic at the point of forming the σ complex; the reaction is driven by the overall thermodynamics of forming strong bonds and, critically, by **rearomatization**. Reaction conditions must avoid overreaction in very activated rings, and halogenation is generally slower on deactivated rings.

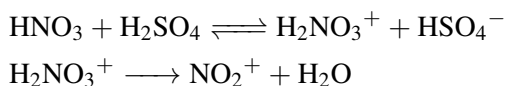
10.2.8 Nitration: installing the nitro group via the nitronium ion

Overall transformation



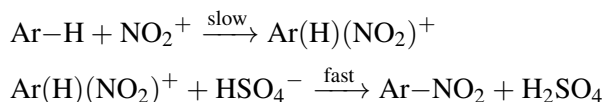
Generation of the electrophile: the nitronium ion NO₂⁺

The true electrophile in nitration is the **nitronium ion**, NO₂⁺. It is generated by strong acid activation of nitric acid in a mixed-acid system:

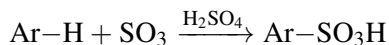


Two features make NO₂⁺ a powerful electrophile:

- it is positively charged and electron-poor,
- it is stabilized as a linear cation (often represented as O=N=O⁺), making its formation feasible in strongly acidic media.

Arenium ion formation and deprotonation

Practical implications. Nitration is a prototypical EAS because the electrophile is generated *in situ* and the acid catalyst is regenerated. The nitro group is strongly electron-withdrawing; once installed, it **deactivates** the ring toward further EAS, often helping to limit polysubstitution under controlled conditions.

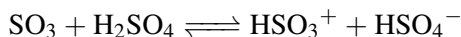
10.2.9 Sulfonation: reversible installation of SO₃H**Overall transformation**

In practice, sulfonation is performed using **fuming sulfuric acid** (oleum), which contains dissolved SO₃ in H₂SO₄.

Electrophile identity and activation

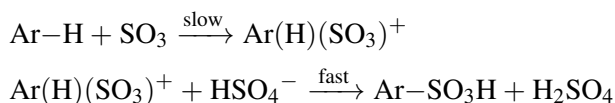
The electrophile is SO₃ (or its protonated form under strongly acidic conditions). Because SO₃ is neutral but highly polarized and has low-lying acceptor orbitals, it

can behave as a strong electrophile toward aromatic rings, especially when further activated by protonation:



Both SO_3 and HSO_3^+ can be viewed as effective sulfonating species depending on conditions; the essential point is that the medium provides a strongly electrophilic sulfur center.

Arenium ion formation and deprotonation



Reversibility: sulfonation as a functional “protecting” strategy

A distinguishing feature of sulfonation is that it is often **reversible**. Under hot, dilute aqueous acid conditions, aryl sulfonic acids can undergo **desulfonation**, restoring Ar-H . Mechanistically, this is best understood as the reverse of EAS:

- the ring is protonated (electrophilic attack by H^+) to form a cationic intermediate,
- SO_3 is eliminated,
- aromaticity is restored.

This reversibility makes $-\text{SO}_3\text{H}$ useful in multistep synthesis as a temporary substituent to block positions on the ring (a concept revisited in synthesis problems later).

10.2.10 Summary of the three protocols (electrophile, catalyst, and key feature)

10.2.11 Mechanistic takeaways that will matter for substituted rings

Two mechanistic facts will be repeatedly used in later sections on substituent effects and Friedel–Crafts reactions:

EAS reaction	Electrophile (active species)	Typical activating conditions	Mechanistic highlight
Halogenation (Cl ₂ , Br ₂)	X ⁺ generated from X ₂ by Lewis acid polarization	FeX ₃ or AlCl ₃ (cat.)	Lewis acid both generates electrophile and provides basic counterion for deprotonation (FeX ₄ ⁻).
Nitration	NO ₂ ⁺ (nitronium ion)	HNO ₃ /H ₂ SO ₄ (mixed acid)	Strong acid generates a discrete cationic electrophile; HSO ₄ ⁻ deprotonates to rearomatize.
Sulfonation	SO ₃ and/or HSO ₃ ⁺	SO ₃ /H ₂ SO ₄ (oleum)	Often reversible; can be undone by hot dilute acid (desulfonation).

Table 10.1: Core EAS protocols emphasized in this chapter: electrophile generation, conditions, and a key mechanistic feature.

- **The slow step is formation of the σ complex.** Anything that stabilizes the developing positive charge in the transition state (electron-donating substituents, resonance donation) accelerates EAS; electron-withdrawing substituents retard it.
- **Regioselectivity is decided in the addition step.** When a substituted benzene reacts, the positions that lead to the most stabilized σ complex (through resonance and inductive effects) are formed fastest and dominate the product distribution.

With the general EAS mechanism established and three key electrophile-generation strategies in hand, we are prepared to analyze carbon–carbon bond-forming EAS variants (Friedel–Crafts reactions) and, subsequently, the systematic directing effects of substituents.

10.3 Friedel–Crafts Alkylation and Acylation

Electrophilic aromatic substitution (EAS) provides a general strategy for functionalizing aromatic rings while preserving aromaticity. Among the most synthetically valuable EAS variants are the **Friedel–Crafts reactions**, which form new **C–C bonds** on an aromatic ring. Conceptually, Friedel–Crafts reactions are simply EAS in which the electrophile is a **carbocation equivalent** (alkylation) or an **acylium ion** (acylation).

Because benzene and substituted arenes are only modest nucleophiles (their π electrons are stabilized by aromaticity), Friedel–Crafts reactions generally require a strong **Lewis acid** catalyst to generate a sufficiently reactive electrophile. The mechanistic logic is the same as in other EAS reactions:

- generate an electrophile,
- attack by the aromatic ring to form the σ complex (rate-determining),
- deprotonate to restore aromaticity.

What makes Friedel–Crafts reactions distinctive are (i) the identity and behavior of the carbon-based electrophile and (ii) the **limitations** that follow from carbocation chemistry and Lewis acid complexation.

10.3.1 Friedel–Crafts alkylation: installing an alkyl substituent

Overall transformation

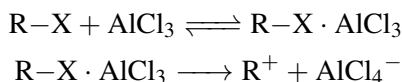
A typical Friedel–Crafts alkylation uses an alkyl halide and a Lewis acid:



Common Lewis acids include AlCl_3 , FeCl_3 , AlBr_3 , and BF_3 . Alkyl halides are most commonly chlorides or bromides.

Electrophile generation: carbocation (or “carbocation-like”) intermediates

The Lewis acid coordinates to the halide, polarizing the C–X bond and promoting heterolysis:

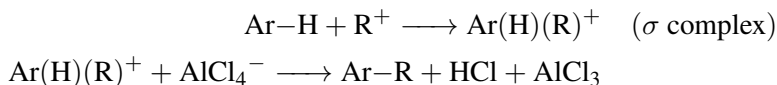


In many cases the electrophile is best viewed as an ion pair or a highly polarized complex rather than a long-lived “free” carbocation. Nonetheless, the **reactivity patterns** strongly resemble carbocation chemistry:

- more substituted carbocations form more readily and react faster,
- rearrangements (hydride/alkyl shifts) can occur if they lead to a more stable carbocation,
- primary carbocations are generally too unstable to form cleanly, often leading to rearrangement or failure.

EAS steps: arenium ion formation and deprotonation

Once a sufficiently electrophilic carbon center is present, the aromatic ring attacks:



The counterion AlCl_4^- (or a related chloride-containing species) typically serves as the base in the rearomatization step.

10.3.2 The central limitation of alkylation: carbocation rearrangements

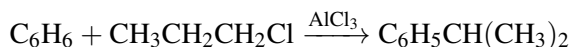
Why rearrangements occur

If the electrophile is (or resembles) a carbocation, it can undergo the familiar rearrangements discussed in substitution and elimination chemistry:

- **hydride shifts** (H^- migration),
- **alkyl shifts** (migration of CH_3^- or a larger alkyl group),

to form a more stable cation before the aromatic ring traps it.

Typical outcome. When a primary alkyl halide is used, the product is often the arene bearing a **rearranged** (more substituted) alkyl group. A classic example is attempted propylation:



Mechanistically, a secondary (isopropyl) carbocation is formed by hydride shift from a primary propyl cation equivalent, and the ring attacks the rearranged electrophile.

Rearrangements are a mechanistic competition

Two processes compete:

- **rearrangement of the cationic electrophile** to a more stable structure,
- **capture by the aromatic ring** to form the σ complex.

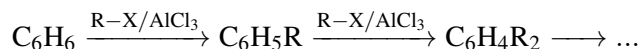
Rearrangement wins whenever it is fast relative to ring capture—which is common because aromatic attack has a high activation barrier (loss of aromaticity), whereas carbocation rearrangements can be extremely rapid.

10.3.3 Additional limitations of Friedel–Crafts alkylation

Polyalkylation: alkyl groups activate the ring

An alkyl group is weakly electron-donating (by hyperconjugation and inductive effects), making the ring **more reactive** toward EAS than benzene. Consequently,

once one alkyl group is installed, subsequent alkylations occur more readily, often producing mixtures of polyalkylated products:



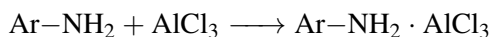
Suppressing polyalkylation typically requires careful control of stoichiometry (large excess of aromatic substrate) and reaction conditions, but complete selectivity is often difficult.

Failure on strongly deactivated rings

EAS requires the ring to attack an electrophile to form a σ complex. If the ring is strongly deactivated by electron-withdrawing substituents (e.g., $-\text{NO}_2$, $-\text{CF}_3$, $-\text{SO}_3\text{H}$, $-\text{C}(=\text{O})\text{R}$), the activation barrier for σ -complex formation becomes too high, and Friedel–Crafts alkylation commonly fails.

Lewis acid complexation with basic substituents

Substituents that are Lewis basic (especially amino groups) strongly bind Lewis acids such as AlCl_3 , forming stable complexes that remove electron density from the ring and/or deactivate the catalyst:

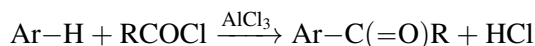


As a result, aniline and many other strongly basic aromatic compounds do not undergo clean Friedel–Crafts alkylation under standard conditions.

10.3.4 Friedel–Crafts acylation: installing an acyl group without rearrangement

Overall transformation

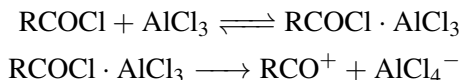
In Friedel–Crafts acylation, an aromatic ring is substituted by an **acyl group** (RCO^-) using an acyl chloride (or acid anhydride) and a Lewis acid:



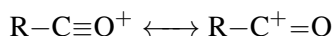
The product is an **aryl ketone**.

Electrophile generation: the acylium ion

The key to acylation is formation of the **acylium ion**, a resonance-stabilized cation:



The acylium ion is stabilized by resonance:



This stabilization makes the electrophile reactive yet **structurally constrained** compared to ordinary carbocations.

Why acylation does not rearrange

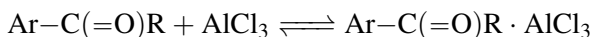
Acylium ions do not undergo hydride or alkyl shifts the way alkyl carbocations do, for two related reasons:

- The cation is delocalized over C and O, giving a low-energy resonance-stabilized structure rather than a localized, rearrangement-prone carbocation center.
- The electrophilic carbon is part of a **carbonyl framework**; rearrangement would disrupt the favorable resonance and is therefore strongly disfavored.

Thus, Friedel–Crafts acylation is the standard method for introducing a carbon chain onto an aromatic ring **without skeletal rearrangement**.

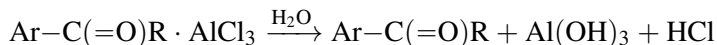
EAS steps and catalyst binding: why the Lewis acid is often required in stoichiometric amounts

After ring attack and deprotonation, the immediate product is often complexed to AlCl_3 through the carbonyl oxygen:



This complexation can be strong; as a practical matter, acylations frequently use **one equivalent** of AlCl_3 (or more) rather than strictly catalytic amounts. Workup with

water liberates the ketone and quenches the Lewis acid:



(Actual inorganic products depend on conditions; the essential point is that hydrolysis releases the ketone.)

10.3.5 A second major advantage of acylation: monoacylation is favored

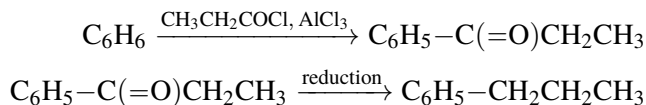
In contrast to alkyl groups, an acyl group ($-\text{C}(=\text{O})\text{R}$) is **electron withdrawing** (by induction and resonance). Once installed, it **deactivates** the ring toward further EAS. Consequently, Friedel–Crafts acylation tends to give predominantly **monoacylated** products under conditions where alkylation would yield polyalkylation mixtures.

10.3.6 Synthetic strategy: acylation–reduction to make unrearranged alkylbenzenes

Because alkylation can rearrange but acylation does not, a common synthetic workaround for making an unrearranged alkylbenzene is:

- **Friedel–Crafts acylation** to install $-\text{C}(=\text{O})\text{R}$,
- **reduction of the carbonyl** to $-\text{CH}_2\text{R}$.

For example:



Reductions commonly used in synthesis include Clemmensen reduction ($\text{Zn}(\text{Hg})/\text{HCl}$) or Wolff–Kishner reduction (NH_2NH_2 , base, heat); the choice depends on functional-group compatibility and reaction conditions.

	Friedel–Crafts alkylation	Friedel–Crafts acylation
Electrophile	Carbocation (or carbocation-like complex) from $R-X$ /Lewis acid	Acylium ion RCO^+ from $RCOCl$ (or anhydride)/Lewis acid
Key mechanistic risk	Rearrangements (hydride/alkyl shifts) common	No rearrangement (resonance-stabilized acylium)
Multiple substitution	Polyalkylation likely (alkyl activates ring)	Monoacylation favored (acyl deactivates ring)
Substrate limitations	Fails on strongly deactivated rings; problems with Lewis-basic groups (e.g., $-NH_2$)	Also sensitive to deactivated rings; Lewis-basic groups can still complex Lewis acids
Best use	Direct installation of stable, nonrearranging alkyl groups (e.g., tert-butylation)	Reliable installation of carbon skeletons; precursor to alkylbenzenes via reduction

Table 10.2: Comparison of Friedel–Crafts alkylation and acylation, emphasizing why acylation is the preferred route when rearrangement control or monosubstitution is required.

10.3.7 Summary: alkylation vs. acylation (mechanism and limitations)

10.3.8 Connection to upcoming topics: substituent effects and directing behavior

Friedel–Crafts reactions are EAS reactions; therefore, their rates and regioselectivities are governed by the same σ -complex stabilization arguments developed for EAS. In the next section, we formalize how substituents alter the energy of the σ complex (and its transition state), leading to predictable patterns of **activation vs. deactivation** and **ortho/para vs. meta directing** behavior.

10.4 Substituent Effects: Activation and Orientation

Electrophilic aromatic substitution (EAS) is governed by a single energetic bottleneck: **formation of the σ complex (arenium ion)**. In the previous sections we emphasized that this step is slow because it temporarily sacrifices aromatic stabilization, and that the σ complex is stabilized by resonance but remains high in energy. When a benzene ring already bears a substituent, that substituent changes:

- the **rate** of EAS (**activation vs. deactivation**), and
- the **position** where substitution occurs (**orientation or directing effects**).

Both effects arise from how the substituent perturbs the electron distribution of the ring and the stability of the σ complex and its transition state.

This section develops a unified framework: **compare the relative energies of the σ complexes formed by ortho, meta, and para attack**. The major product forms through the lowest-energy pathway (fastest formation of the most stabilized σ complex).

10.4.1 Two electronic effects that control EAS: inductive and resonance

Substituents influence aromatic reactivity primarily through two mechanisms. These effects often operate simultaneously; the observed behavior is the result of their competition.

Inductive effects (*I*): polarization through σ bonds

Inductive effects arise from electronegativity differences and are transmitted through σ bonds:

- **$-I$ (electron withdrawing inductively):** substituents such as $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CN}$, $-\text{SO}_3\text{H}$, $-\text{C}(=\text{O})\text{R}$, and halogens pull electron density away from the ring. This **deactivates** the ring toward electrophiles by reducing π electron density and destabilizing cationic intermediates.
- **$+I$ (electron donating inductively):** alkyl groups weakly donate electron density by polarization/hyperconjugation, increasing electron density in the ring (especially at ortho/para positions). This **activates** the ring modestly.

Inductive effects diminish with distance but can still be important in aromatic systems because the rate-determining step involves developing positive charge in the ring.

Resonance effects (*R*): donation or withdrawal through π conjugation

Resonance effects occur when a substituent has a lone pair or a π bond that can overlap with the ring p system.

- **$+R$ (resonance donation):** groups with a lone pair on an atom directly attached to the ring ($-\text{OH}$, $-\text{OR}$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$) can donate electron density into the ring by $n \rightarrow \pi$ conjugation. This strongly stabilizes σ complexes that place positive charge at positions conjugated with the substituent.
- **$-R$ (resonance withdrawal):** groups with a π -acceptor functionality adjacent to the ring ($-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}$, $-\text{CO}_2\text{R}$, $-\text{CHO}$, $-\text{CN}$, $-\text{SO}_3\text{H}$) withdraw electron density from the ring by conjugation, destabilizing σ complexes that place positive charge near the substituent.

Key idea: rate and regioselectivity follow σ -complex stability

For substituted benzenes, three different σ complexes are possible (ortho, meta, para). The substituent changes their relative energies. In many cases:

- **activation/deactivation** correlates with whether the substituent stabilizes/destabilizes the developing positive charge in the rate-determining step,

- **orientation** follows whichever pathway avoids the most unstable resonance contributor (for deactivators) or gains the most stabilizing contributor (for activators).

10.4.2 Classification of substituents by directing effects

Most substituents fall into one of three practical categories:

- **Activating, ortho/para-directing:** strong $+R$ donors (and alkyl groups).
- **Deactivating, meta-directing:** $-R$ and $-I$ withdrawers (carbonyls, nitro, sulfonic acid, cyano, etc.).
- **Deactivating, ortho/para-directing:** halogens (the special case).

The origin of these patterns becomes clear when we examine the resonance structures of the σ complex.

10.4.3 Theory of directing effects: the σ complex as the decision point

In EAS, the aromatic ring attacks an electrophile E^+ to form a σ complex. For a monosubstituted ring $Ar-Z$, the **site of attack** (ortho, meta, or para relative to Z) determines which resonance contributors are possible.

A systematic way to predict directing effects is:

- Draw the σ complex for ortho attack and write its resonance contributors.
- Do the same for meta and para attack.
- Identify any resonance contributor that is **especially stabilized** (e.g., by lone-pair donation) or **especially destabilized** (e.g., by placing positive charge adjacent to a strong electron-withdrawing group).
- The pathway that avoids severe destabilization or gains strong stabilization is favored.

Anisole ($Ph-OCH_3$): a strongly activating ortho/para director by $+R$ donation

In anisole (methoxybenzene), oxygen has lone pairs capable of overlap with the ring. In the σ complex formed by ortho or para attack, there exists a resonance contributor

in which the positive charge is placed on the carbon bonded to oxygen, allowing oxygen to donate a lone pair into the ring and **neutralize the carbocation by forming a π bond to the ring carbon**. This creates an **oxonium** resonance contributor (oxygen bears the positive charge), which is substantially stabilized relative to a ring carbocation.

Meta attack does *not* generate a resonance contributor that places the cation adjacent to the OCH_3 substituent in a way that allows this direct lone-pair donation into the cationic center. Thus, meta σ complexes lack the most stabilizing contributor and are higher in energy.

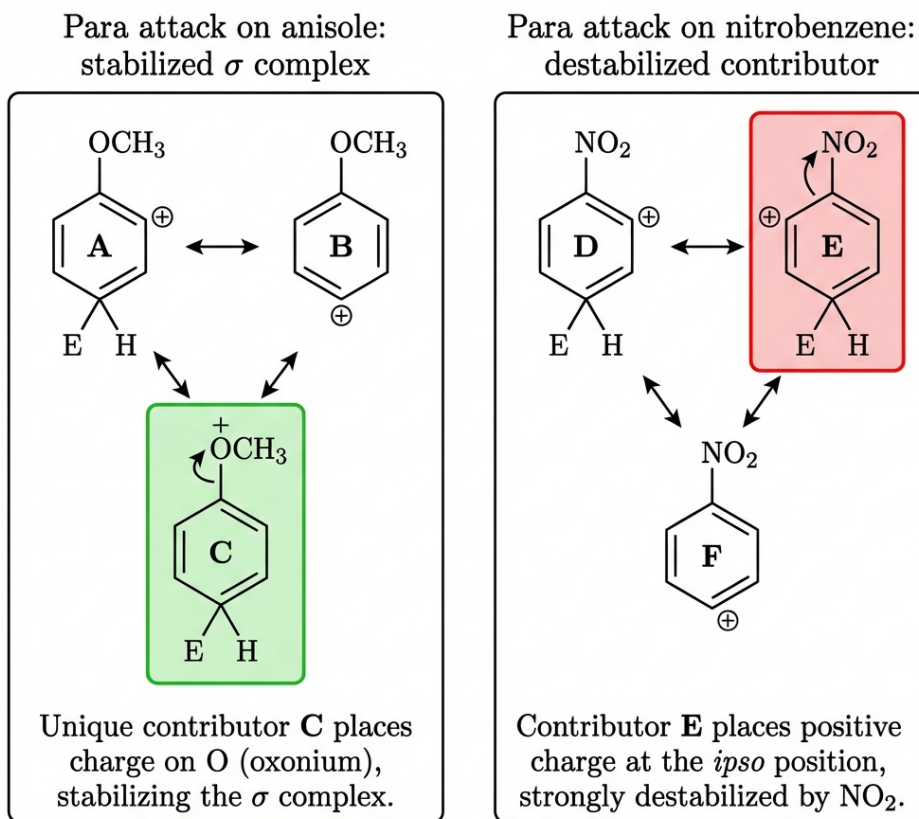
Nitrobenzene ($\text{Ph}-\text{NO}_2$): strongly deactivating and meta-directing by $-R$ and $-I$ effects

The nitro group is among the strongest deactivating substituents. It withdraws electron density:

- by **induction** ($-I$) due to electronegative oxygen atoms and the positively polarized nitrogen, and
- by **resonance** ($-R$) because the ring can conjugate with the NO_2 group, pulling π electron density away from the ring.

For ortho and para attack, one resonance contributor of the σ complex places the positive charge on the carbon directly bonded to the nitro group (or adjacent in a way that creates severe electron deficiency at that position). This is especially unfavorable because the nitro substituent already withdraws electron density; placing a positive charge at the position conjugated to NO_2 produces a resonance form that is strongly destabilized (often described qualitatively as placing two electron-withdrawing “demands” on the same region of the ring).

For meta attack, the resonance contributors avoid placing the positive charge on the carbon bearing NO_2 . Thus, meta attack avoids the **worst** contributor and becomes the preferred pathway, even though the ring is overall less reactive than benzene.



In *meta* attack, the σ -complex resonance set avoids placing + at the ipso carbon, so nitrobenzene is *meta*-directing despite overall deactivation.

10.4.4 From resonance pictures to observed outcomes: activation and orientation rules

Activators are usually ortho/para directors

Groups that donate electron density into the ring ($+R$ or $+I$) stabilize the σ complex formed by ortho and para attack because those pathways allow resonance contributors in which the positive charge is positioned where the substituent can donate electron density. This lowers the barrier to the rate-determining step.

Common activating ortho/para directors.

- Strongly activating ($+R$): $-\text{OH}$, $-\text{OR}$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{NR}_2$

- Moderately activating: $-\text{NHC}(=\text{O})\text{R}$ (amides; lone pair less available), $-\text{OC}(=\text{O})\text{R}$ (esters; lone pair less donating)
- Weakly activating ($+I$ /hyperconjugation): alkyl groups ($-\text{R}$)

Deactivators are usually meta directors

Groups that withdraw electron density ($-R$ and/or $-I$) destabilize cationic intermediates. The critical additional point is **which σ complex is destabilized the most**. Ortho and para attack on a ring bearing a $-R$ group typically produce at least one resonance contributor with positive charge at the ipso carbon (the carbon bearing the substituent), which is particularly unfavorable when the substituent is already pulling electron density away.

Thus, meta attack is favored because it avoids the most unstable contributor.

Common deactivating meta directors.

- Carbonyl-containing groups: $-\text{CHO}$, $-\text{COR}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}$, $-\text{CONH}_2$, $-\text{CONR}_2$
- Strongly withdrawing: $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NR}_3^+$

10.4.5 The special case: halogens are deactivating yet ortho/para-directing

Halogens (F, Cl, Br, I) combine two opposing effects:

- They are strongly $-I$ (electronegative), which withdraws electron density through σ bonds and **deactivates** the ring overall.
- They can donate by $+R$ (lone pair donation into the ring), which can stabilize ortho/para σ complexes relative to meta.

Because induction affects the entire reaction coordinate (making the ring less nucleophilic and raising the energy of cationic intermediates), halogenated benzenes react **more slowly than benzene**. However, among the possible σ complexes that *do* form, ortho and para pathways are relatively favored because resonance donation can stabilize those intermediates. The result is:

Halogens: deactivating but ortho/para directing.

This illustrates an important general lesson: **activation/deactivation and directing effects are related but not identical**. Directing reflects *relative* stabilization among competing σ complexes, whereas activation reflects the *overall* height of the rate-determining barrier relative to benzene.

10.4.6 Steric effects: why para often dominates over ortho

Electronic effects explain why a substituent directs to ortho/para or meta, but **sterics** often determine the ortho:para ratio. Ortho attack places the incoming electrophile near the existing substituent; bulky substituents therefore suppress ortho substitution. Para substitution is often favored when:

- the substituent is bulky (e.g., $-t\text{Bu}$),
- the electrophile is bulky (e.g., acylation with a large acylium ion),
- the reaction is under conditions where kinetic control exaggerates steric discrimination.

10.4.7 A quantitative viewpoint (conceptual): substituent effects on rate

Although a full quantitative treatment involves physical organic parameters, one qualitative statement is robust:

- **Anything that stabilizes the developing positive charge in the transition state to the σ complex accelerates EAS.**

Resonance donation is typically stronger than inductive donation, so $-\text{OR}$ and $-\text{NR}_2$ groups usually activate far more strongly than alkyl groups. Conversely, resonance withdrawal (nitro, carbonyls) strongly deactivates.

10.4.8 Practical prediction workflow for substituted benzenes

When asked to predict the major product of an EAS reaction on a substituted benzene, proceed as follows:

- **Classify the substituent** as: $+R$ donor (activating, ortho/para), $-R$ withdrawer (deactivating, meta), halogen (deactivating, ortho/para), or alkyl (weakly activating, ortho/para).

- **Choose the directed positions** (ortho/para or meta).
- **Account for sterics:** para often increases with bulk.
- **Check for reaction feasibility:** strongly deactivated rings may require harsher conditions or may fail in some protocols (notably Friedel–Crafts).

10.4.9 Summary table: activation and orientation

Substituent class	Typical examples	Net EAS behavior (relative to benzene)
Activating, ortho/para-directing (+ <i>R</i> donors; some + <i>I</i>)	–OH, –OR, –NH ₂ , –NHR, –NR ₂ , alkyl (– <i>R</i>)	Faster; ortho/para products favored (often para favored if sterically crowded).
Deactivating, meta-directing (– <i>R</i> and/or strong – <i>I</i>)	–NO ₂ , –SO ₃ H, –CN, –CF ₃ , –CHO, –COR, –CO ₂ R, –CO ₂ H, –NR ₃ ⁺	Slower; meta products favored (avoid worst σ -complex contributor).
Deactivating, ortho/para-directing (special case)	–F, –Cl, –Br, –I	Slower (strong – <i>I</i>), but ortho/para orientation (lone-pair + <i>R</i>).

Table 10.3: Summary of substituent effects on EAS rate (activation/deactivation) and regioselectivity (directing effects), interpreted through inductive and resonance stabilization of the σ complex.

In the final section of this chapter, you will apply these principles to multi-step synthesis planning and to mechanistic explanation problems that require explicit resonance structures of σ complexes.

10.5 Problems

10.5.1 Aromaticity classification with structural justification

Classify each of the following as **aromatic**, **antiaromatic**, or **nonaromatic**. For every case, you must (i) state whether the ring can be planar and fully conjugated, (ii) count the number of π electrons in the cyclic conjugated system, and (iii) justify the classification using Hückel's $4n + 2/4n$ rule and (when helpful) a Frost circle argument.

- **[10]annulene** ($C_{10}H_{10}$) in its lowest-energy conformation.
- **Azulene** (fused 5–7 ring system; overall formula $C_{10}H_8$).
- **Cyclopropenyl cation** ($C_3H_3^+$).
- **Cyclopentadienyl anion** ($C_5H_5^-$).
- **Tropylium cation** ($C_7H_7^+$).

Your final answers must clearly state which subset of electrons (including any lone pairs or charges) is counted toward aromaticity.

10.5.2 Frost circles and MO occupancy patterns

For each ring size N listed below, draw the Frost circle (polygon method), label the relative MO energy levels, and fill the MOs with the indicated number of π electrons. Then answer whether a *planar, fully conjugated* version of the system would be aromatic, antiaromatic, or neither, and briefly explain why.

- $N = 4$ with 4 π electrons.
- $N = 5$ with 6 π electrons.
- $N = 6$ with 8 π electrons.
- $N = 7$ with 6 π electrons.
- $N = 8$ with 10 π electrons.

Include at least one sentence in each case describing whether the configuration is closed-shell, and if not, whether degeneracy forces unpaired electrons in nonbonding orbitals.

10.5.3 Mechanism and product prediction: Friedel–Crafts alkylation with rearrangement

Provide a complete curved-arrow mechanism for the Friedel–Crafts reaction of benzene with **1-chloropropane** in the presence of $AlCl_3$. Your answer must:

- show electrophile generation (including Lewis acid complexation),

- account for the **major isomeric product** (including any rearrangement step),
- show formation of the σ complex and its rearomatization step,
- identify the base responsible for deprotonation.

Finally, explain in one paragraph why the rearranged product dominates over the unrearranged product.

10.5.4 Mechanistic explanation: why aniline fails in Friedel–Crafts reactions

Aniline ($\text{Ph}-\text{NH}_2$) is strongly activating toward many EAS reactions, yet it generally fails under typical Friedel–Crafts alkylation/acylation conditions with AlCl_3 .

- Propose a mechanistic explanation based on Lewis acid–base chemistry and its consequences for ring reactivity.
- Explain why this issue is less severe (or can be managed) for some other activated rings (e.g., anisole) under selected conditions.
- State one strategy (reagent choice or protecting-group logic) that could allow installation of a carbon substituent onto an aniline-derived ring.

10.5.5 Regioselectivity comparison: nitration of benzaldehyde vs. nitration of phenol

Predict the **major product(s)** (ortho/meta/para) for each nitration below. Provide a brief mechanistic justification in terms of σ -complex stabilization/destabilization (inductive and resonance effects), not merely a memorized directing rule.

- Nitration of benzaldehyde ($\text{Ph}-\text{CHO}$) using $\text{HNO}_3/\text{H}_2\text{SO}_4$.
- Nitration of phenol ($\text{Ph}-\text{OH}$) using $\text{HNO}_3/\text{H}_2\text{SO}_4$ under conditions mild enough to limit overreaction.

For each substrate, explicitly state which resonance contributor(s) in the σ complex are especially stabilizing or destabilizing.

10.5.6 Synthesis design: *m*-bromonitrobenzene from benzene

Design a multistep synthesis that converts benzene into ***m*-bromonitrobenzene**. Your synthesis must:

- use only EAS reactions and common functional-group interconversions discussed in this chapter (halogenation, nitration, sulfonation, Friedel–Crafts),
- specify reagents and conditions for each step,
- justify the order of substitution using directing effects.

If you use a temporary blocking group, state how it is installed and removed.

10.5.7 Synthesis design with directing-conflict resolution: *p*-bromonitrobenzene from benzene

Design a multistep synthesis that converts benzene into ***p*-bromonitrobenzene**. Because the nitro group is meta-directing and bromine is ortho/para-directing (but deactivating), your plan must explicitly address:

- which group must be installed first to achieve para substitution,
- how you will suppress formation of the ortho isomer (or how you will manage/select for para),
- whether a blocking-group strategy (e.g., sulfonation/desulfonation) is necessary and why.

Provide reagents and conditions for each step and a short rationale.

10.5.8 Mechanism proposal: desulfonation under hot dilute aqueous acid

Benzenesulfonic acid (Ph–SO₃H) can be converted back to benzene under hot, dilute aqueous acid conditions.

- Propose a step-by-step mechanism for **desulfonation** that is consistent with EAS principles (addition to form a cationic intermediate, then elimination to restore aromaticity).

- Identify the electrophile in the reverse direction and the leaving group that departs.
- Explain briefly why the process is favored at high temperature and in dilute aqueous conditions (qualitative thermodynamic argument).

10.5.9 Reactivity ranking toward EAS

Rank the following compounds in order of **increasing reactivity** toward a typical EAS reaction (e.g., bromination under Lewis-acid catalysis), and justify your ranking using inductive/resonance effects and the relative stability of the σ complex:

benzene, nitrobenzene, toluene, phenol, chlorobenzene

Your justification must address why halogens are deactivating yet ortho/para-directing, and why phenol is unusually reactive.

10.5.10 Synthetic strategy: propylbenzene without rearrangement

Direct Friedel–Crafts alkylation often rearranges when using primary alkyl halides. Propose a synthesis of **propylbenzene** ($\text{Ph}-\text{CH}_2\text{CH}_2\text{CH}_3$) from benzene that avoids skeletal rearrangement by using an **acylation–reduction** sequence.

- Specify the acylating reagent(s) and Lewis acid.
- Draw the key electrophile involved in acylation (including resonance structures of the acylium ion).
- Specify one suitable method to reduce the aryl ketone to the alkylbenzene and indicate why it does not cause rearrangement.

10.5.11 Resonance analysis problem: meta attack on nitrobenzene

Consider bromination of nitrobenzene under $\text{Br}_2/\text{FeBr}_3$. Draw the complete set of resonance contributors for the σ complex formed by attack at the **meta** position. Then:

- identify which contributors would occur for **ortho** and **para** attack that are **absent** in the meta case,

- explain why those missing contributors make ortho/para pathways higher in energy,
- connect your explanation explicitly to the placement of the positive charge relative to the NO_2 substituent.

Your final answer should clearly articulate the mechanistic origin of meta direction for strongly $-R$ groups.

Chapter 11

Aldehydes and Ketones

The carbonyl group is the cornerstone of organic synthesis, acting as a versatile electrophilic anchor that enables the construction of complex molecular architectures. This chapter moves beyond basic bonding models to explore how the polarization of the carbon-oxygen double bond dictates reactivity, strictly controlling the trajectory of nucleophilic attack. We will systematically examine the transformation of aldehydes and ketones into diverse functional groups—from the reversible equilibrium of acetals and imines to the irreversible generation of carbon-carbon bonds via organometallic and ylide reagents.

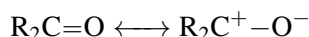
11.1 Carbonyl Structure, Bonding, and Reactivity

In earlier chapters, you developed three ideas that now converge in the chemistry of aldehydes and ketones: (1) *Lewis structures and resonance* as a way to represent electron distribution, (2) *hybridization and molecular geometry* as a predictor of structure, and (3) *acid–base reasoning and nucleophile/electrophile pairing* as a predictor of reaction direction. The carbonyl group ($\text{C}=\text{O}$) is a uniquely versatile functional group because its bonding pattern creates a strongly polarized π system with a low-lying acceptor orbital. This section builds a physical picture of *why* the carbonyl carbon is electrophilic and *how* structural and electronic factors tune that electrophilicity.

11.1.1 The carbonyl group as a polarized $\sigma + \pi$ system

A carbonyl functional group consists of one σ bond and one π bond between carbon and oxygen. Because oxygen is significantly more electronegative than carbon, both the σ and π electron densities are drawn toward oxygen. The consequence is a large bond dipole (often depicted as $\text{C}^{\delta+}=\text{O}^{\delta-}$) and a carbon atom that behaves as an electrophile toward nucleophiles.

A useful resonance picture captures the same idea:



The left contributor is the neutral double-bond form; the right contributor places formal positive charge on carbon and formal negative charge on oxygen. The true electronic structure is a hybrid: carbon is partially positive and oxygen is partially negative. This polarization is the origin of two hallmark reactivity patterns:

- **Nucleophilic attack at carbon:** electron-rich nucleophiles donate into an acceptor orbital centered largely on carbon.
- **Protonation or Lewis acid binding at oxygen:** electrophiles (e.g., H^+ , BF_3) bind oxygen and further increase carbon electrophilicity.

11.1.2 Hybridization and geometry: why the carbonyl carbon is planar

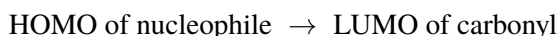
The carbonyl carbon in aldehydes and ketones is best described as sp^2 -hybridized. Three sp^2 hybrid orbitals on carbon form σ bonds (to oxygen and to the two substituents), arranged approximately trigonal planar with bond angles near 120° . The remaining unhybridized p orbital on carbon overlaps side-on with a p orbital on oxygen to form the π bond.

Two structural consequences are central for mechanism:

- **Planarity at the carbonyl carbon:** the carbonyl carbon and its three attached atoms lie in (or very near) a plane. This makes the carbonyl carbon accessible from either face (*Re* and *Si* faces), an idea that becomes crucial for stereochemical outcomes in nucleophilic addition.
- **Orthogonality of π and σ frameworks:** the π bond lies above and below the carbonyl plane, creating a directional target for nucleophilic approach.

11.1.3 Molecular orbital picture: HOMO/LUMO control of nucleophilic addition

Resonance explains polarization qualitatively, but molecular orbitals (MOs) explain *directionality* and *orbital interactions*. For most nucleophilic additions to carbonyls, the dominant interaction is:



The key acceptor orbital is the carbonyl π^* (antibonding) orbital. Its most important features are:

- **It is low in energy** relative to many other π^* orbitals because oxygen stabilizes the antibonding combination by mixing with low-lying oxygen-centered orbitals and because the C=O bond is strongly polarized.
- **It has a large coefficient on carbon.** Although the π bonding orbital is polarized toward oxygen, the π^* orbital often has substantial amplitude at carbon, making carbon the favored site for nucleophilic donation.
- **Population of π^* weakens the C=O bond.** Donation into π^* decreases π bond order and facilitates conversion of trigonal planar carbon to tetrahedral carbon in the addition product.

The dominant filled orbital on the carbonyl group itself is an oxygen lone pair (n), which can participate in spectroscopy ($n \rightarrow \pi^*$ transitions) and coordination chemistry (binding to Lewis acids). However, in *nucleophilic addition*, the oxygen lone pair is not the acceptor; it is the donor site for protonation and Lewis acid coordination, which indirectly increases electrophilicity.

11.1.4 The Bürgi–Dunitz trajectory: why nucleophiles attack at $\sim 107^\circ$

A nucleophile does not approach directly along the C=O bond axis (a “head-on” attack), nor does it approach exactly perpendicular to the carbonyl plane. Instead, experimental and computational studies show a preferred approach angle of about 107° relative to the C=O bond axis, known as the **Bürgi–Dunitz angle**.

This angle can be understood by combining two constraints:

(1) Maximize overlap with the π^* LUMO

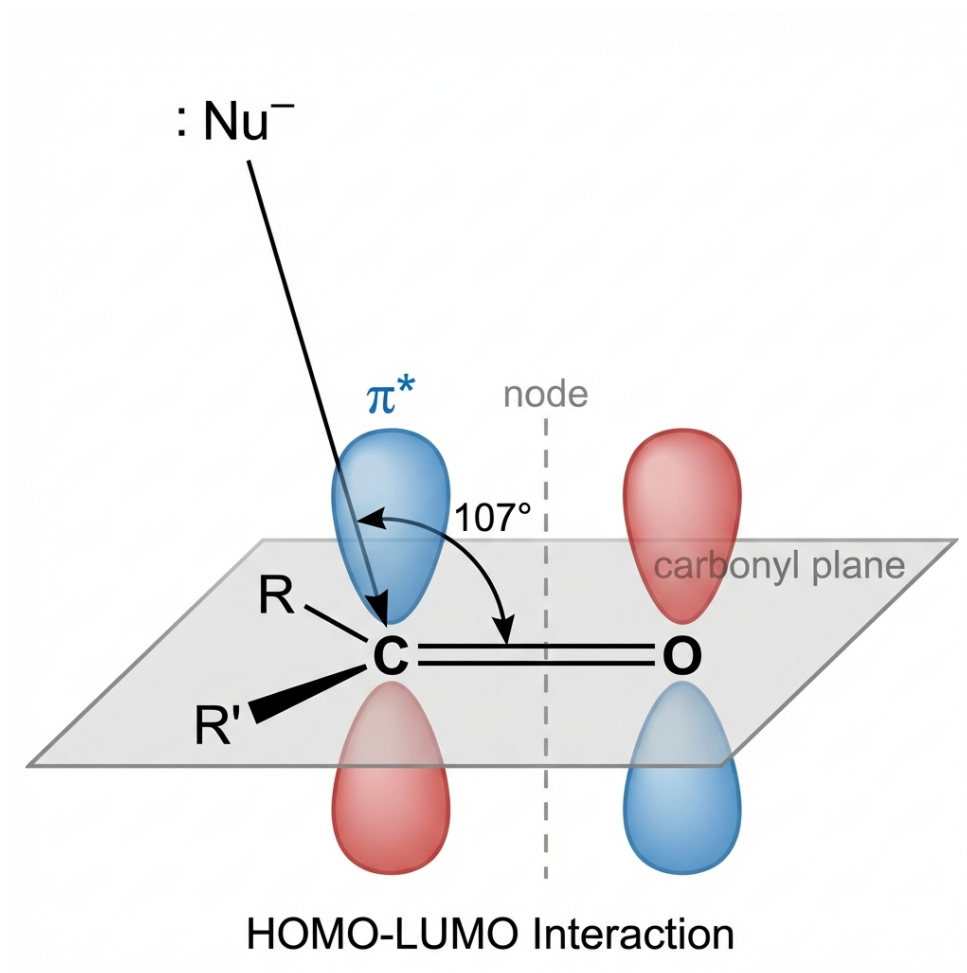
The π^* orbital has lobes above and below the carbonyl plane, with a phase relationship that makes it antibonding between C and O. A nucleophile approaches from a direction that aligns its donor orbital (often a lone pair) with the larger lobe of π^* on carbon. Approach within a specific cone of directions maximizes constructive overlap.

(2) Minimize repulsions and steric/electrostatic penalties

Direct approach along the C=O axis would place the nucleophile into regions of high electron density and would incur strong Pauli repulsion with occupied orbitals (including the π bond and oxygen lone pairs). A tilted approach reduces these repulsions while still maintaining strong donor–acceptor overlap.

The result is a trajectory that is oblique: close enough to the carbonyl carbon for good overlap with π^* , but angled to avoid unfavorable interactions. This geometric preference is not merely a curiosity; it helps explain:

- why addition proceeds with predictable facial selectivity in chiral environments,
- why bulky substituents near the carbonyl can strongly slow reactions (they block the preferred approach cone),
- why Lewis acid coordination (which changes orbital energies and shapes) can accelerate addition and alter selectivity.



11.1.5 Aldehydes vs. ketones: electronic and steric control of electrophilicity

Both aldehydes and ketones contain the same C=O unit, but aldehydes are generally *more reactive* toward nucleophilic addition than ketones. Two effects reinforce one another:

Steric effect (access to the Bürgi–Dunitz trajectory)

An aldehyde has one substituent and one hydrogen on the carbonyl carbon, whereas a ketone has two substituents. The nucleophile must approach the carbonyl carbon along a preferred cone of directions (near the Bürgi–Dunitz trajectory). Greater

substitution crowds that approach, raising the activation barrier. Thus, ketones are more hindered and typically add nucleophiles more slowly.

Electronic effect (inductive donation and hyperconjugation)

Alkyl substituents donate electron density by the inductive effect and by hyperconjugation, stabilizing positive charge. In the resonance contributor $R_2C^+-O^-$, the carbon bears partial positive character. Two electron-donating alkyl groups in ketones reduce that positive character (decrease δ^+ at carbon), thereby reducing electrophilicity relative to aldehydes, which have only one such substituent.

These effects can be summarized as:

typical electrophilicity: aldehyde > ketone

This trend is so robust that it is frequently used as a planning rule in synthesis: when a nucleophile is expected to react with one carbonyl group in the presence of another, the aldehyde is usually attacked preferentially.

11.1.6 Substituent effects: how structure tunes the carbonyl LUMO

The ease of nucleophilic addition correlates strongly with the energy and shape of the carbonyl LUMO (π^*). Lowering the LUMO energy strengthens HOMO→LUMO interaction and accelerates addition (all else being equal). Several common structural modifications shift electrophilicity in predictable ways.

Electron-withdrawing groups increase electrophilicity

Substituents that withdraw electron density (by induction and/or resonance) increase the partial positive character at carbon and typically lower the π^* energy. For example, an acyl group conjugated to strongly electron-withdrawing substituents tends to be more electrophilic. Although aldehydes and ketones lack a built-in leaving group (unlike acyl chlorides), inductive withdrawal still increases their susceptibility to nucleophilic addition.

Conjugation decreases electrophilicity but introduces new reactivity

If the carbonyl is conjugated with a π system (e.g., an α, β -unsaturated carbonyl), the π^* orbital mixes with the adjacent π orbitals. Delocalization stabilizes the carbonyl

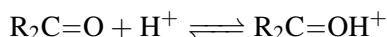
group and can reduce the *direct* electrophilicity at the carbonyl carbon. At the same time, it creates an additional electrophilic site at the β carbon (conjugate addition), which becomes important later when comparing 1,2- vs. 1,4-addition.

Even without detailed MO calculations, a practical takeaway is:

- conjugation often *stabilizes* carbonyls (lower reactivity toward simple 1,2-addition),
- but it also *redistributes* electrophilicity (new reaction pathways appear).

Protonation and Lewis acids: activating the carbonyl by lowering π^*

Protonation at oxygen (or coordination to a Lewis acid) is a powerful way to increase electrophilicity:



Binding an electrophile to oxygen pulls electron density away from the carbonyl, increasing δ^+ at carbon and lowering the π^* energy. In MO terms, coordination stabilizes the acceptor orbital and often increases its coefficient on carbon, both of which enhance nucleophilic addition rates. This is the fundamental reason acid catalysis accelerates many additions of weak nucleophiles (e.g., water, alcohols).

11.1.7 Thermodynamics vs. kinetics: electrophilicity is a kinetic concept

It is tempting to equate “more electrophilic” with “more product formed,” but electrophilicity primarily predicts *rate* (kinetics), not necessarily *position of equilibrium* (thermodynamics). Many oxygen and nitrogen nucleophiles add reversibly to aldehydes/ketones, forming tetrahedral adducts (hydrates, hemiacetals, carbinolamines). In such cases:

- **Electrophilicity controls how fast the adduct forms** (activation barrier for addition).
- **Stability of products controls how much adduct accumulates at equilibrium** (relative free energies of reactants and products).

For example, an aldehyde may hydrate faster than a ketone, yet the equilibrium extent of hydration also depends on sterics and on stabilization of the gem-diol by

substituents. Keeping these distinctions separate will prevent common mechanistic errors when interpreting reaction conditions.

11.1.8 A compact reactivity framework

When you need a quick prediction of carbonyl reactivity toward nucleophilic addition, you can organize the controlling factors as follows:

- **Orbital factor (LUMO energy and shape):** lower-energy, carbon-centered π^* means faster addition.
- **Electrostatic factor (partial positive charge at carbon):** greater δ^+ increases attraction to nucleophiles and stabilizes developing negative charge on oxygen in the transition state.
- **Steric factor (access to the Bürgi–Dunitz trajectory):** bulky substituents impede approach and slow reaction.
- **Activation by acids/Lewis acids:** oxygen binding increases electrophilicity by both electrostatic and MO effects.

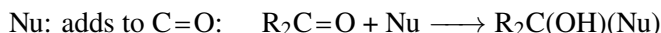
In the next section, these principles will be applied to specific nucleophiles. You will see that many mechanisms differ in their proton-transfer choreography, but they share a common core event: nucleophilic donation into the carbonyl π^* along a preferred trajectory, converting a planar sp^2 carbonyl carbon into a tetrahedral sp^3 center.

11.2 Nucleophilic Addition of Oxygen and Nitrogen Nucleophiles

The previous section established two ideas that will be used repeatedly here: (1) the carbonyl carbon is electrophilic because nucleophiles donate into the carbonyl π^* (LUMO), and (2) nucleophilic approach is stereoelectronically biased (Bürgi–Dunitz trajectory) and sterically sensitive (aldehydes typically react faster than ketones). In this section we focus on **heteroatom nucleophiles**—especially oxygen and nitrogen—and on a defining feature of their reactions with aldehydes and ketones: **many additions are reversible**. Reversibility means that *conditions* (acid/base catalysis, water removal, nucleophile excess) determine which functional group dominates at equilibrium.

11.2.1 A unified mechanism template: addition to form a tetrahedral intermediate

Hydration, hemiacetal/acetal formation, and imine/enamine formation share a common first event:



That tetrahedral species is an **addition intermediate** (often called a tetrahedral intermediate or, in amine chemistry, a **carbinolamine**). The key mechanistic tasks after addition are:

- **Proton transfers** to stabilize charges and to set up leaving groups.
- **Substitution at carbon** only when a good leaving group is created, typically H_2O (after protonation of $-\text{OH}$).

Two catalytic regimes recur:

Base-catalyzed addition (nucleophile activation dominates)

Base catalysis increases the fraction of the *more nucleophilic* form of the heteroatom reagent (e.g., HO^- rather than H_2O). Because leaving groups are poor under basic conditions (there is no easy way to convert $-\text{OH}$ into H_2O), base-catalyzed pathways are best suited for **simple addition** (e.g., hydrate formation) rather than **condensation** (addition followed by loss of water).

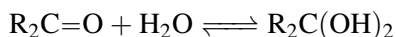
Acid-catalyzed addition/condensation (electrophile activation dominates)

Acid catalysis protonates the carbonyl oxygen, lowering the π^* energy and making the carbonyl carbon more electrophilic. Acid also enables **dehydration** by converting $-\text{OH}$ into H_2O , a good leaving group. For weak nucleophiles such as water and alcohols, acid catalysis is often essential; for amines, acid must be *carefully controlled* because excessive protonation converts the amine into RNH_3^+ or R_2NH_2^+ , which is not nucleophilic.

11.2.2 Hydration of aldehydes and ketones: gem-diols and their stability

What forms: hydrates (gem-diols)

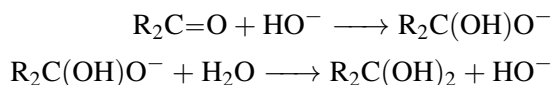
Addition of water to a carbonyl yields a **hydrate**, also called a **geminal diol**:



This is an equilibrium process. For many simple ketones, the equilibrium lies strongly to the left (carbonyl favored), whereas aldehydes hydrate more extensively.

Base-catalyzed hydration: fast addition, no dehydration

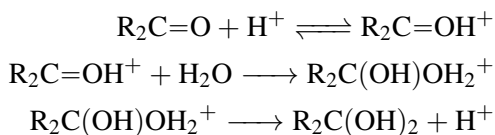
A minimal base-catalyzed mechanism is:



The base is regenerated: true catalysis. The first step is typically rate-determining for less reactive carbonyls because it requires nucleophilic attack on the electrophile.

Acid-catalyzed hydration: carbonyl activation and proton transfers

Acid catalysis shifts the burden away from nucleophile strength:



Water (a weak nucleophile) attacks efficiently only after carbonyl protonation.

What controls hydrate formation at equilibrium?

Hydration is favored when the tetrahedral product is stabilized relative to the planar carbonyl. Several trends are particularly important:

Aldehydes vs. ketones. Aldehydes hydrate more because (i) they are less sterically hindered, and (ii) ketone alkyl groups stabilize the carbonyl and reduce electrophilicity.

Electron-withdrawing substituents. Strong inductive withdrawal increases electrophilicity and stabilizes the hydrate. A classic extreme case is formaldehyde ($\text{H}_2\text{C}=\text{O}$), which hydrates extensively because it is unhindered and strongly electrophilic.

Conjugation and aromaticity. Conjugation stabilizes the carbonyl and often decreases hydrate fraction. Loss of conjugation upon hydration can be thermodynamically costly.

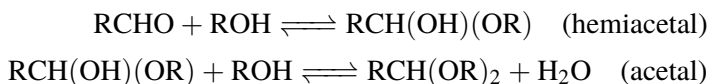
Why hydrates matter even when minor. Even if present in small amounts, hydrates can be mechanistically relevant (e.g., as transient forms under aqueous conditions) and spectroscopically observable in some cases. In biological settings, enzymes can stabilize the tetrahedral form, effectively increasing the functional importance of “minor” equilibria.

11.2.3 Addition of alcohols: hemiacetals and acetals

Alcohols react with aldehydes and ketones to give **hemiacetals** (one $-\text{OR}$ and one $-\text{OH}$ on the same carbon) and, upon further reaction, **acetals** (two $-\text{OR}$ groups). These are central to protecting-group strategy and to carbohydrate chemistry.

Definitions and general equilibria

For an aldehyde (analogous expressions apply to ketones):



Hemiacetal formation is an **addition** process; acetal formation is a **condensation** overall (addition followed by loss of water).

Why acetals require acid catalysis

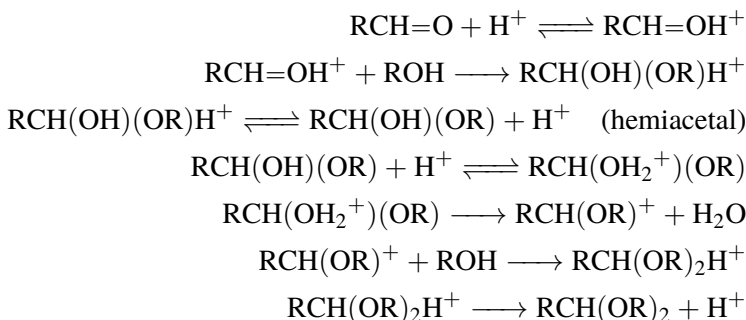
Under neutral or basic conditions, converting $-\text{OH}$ into a leaving group is difficult. Since acetal formation requires substitution of $-\text{OH}$ by $-\text{OR}$, it is strongly favored under **acidic** conditions where $-\text{OH}$ can be protonated and depart as H_2O .

Mechanism of acid-catalyzed acetal formation (stepwise logic)

A clear way to learn the mechanism is to track the *roles* of acid:

- **Activate the carbonyl for nucleophilic addition** (protonate oxygen).
- **Enable dehydration** (convert $-OH$ to H_2O).
- **Activate the oxocarbenium-like intermediate for capture by alcohol.**

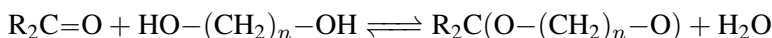
A representative sequence (aldehyde shown) is:



The cationic intermediate $RCH(OR)^+$ is often described as an **oxocarbenium ion** (or oxocarbenium-like species). It is strongly electrophilic and is rapidly trapped by alcohol.

Cyclic acetals: why five- and six-membered rings are favored

When a **diol** reacts with a carbonyl under acid catalysis, a cyclic acetal often forms:



Five- and six-membered cyclic acetals are commonly favored because they balance:

- **entropic advantage** (intramolecular ring closure after initial addition),
- **manageable ring strain** (minimal for 5–6 membered rings),
- **effective water removal** (driving equilibrium toward acetal).

Acetals as protecting groups: selective stability and selective removal

Acetals are widely used to protect aldehydes and ketones because they exhibit a complementary reactivity pattern:

- **Stable to many bases and many nucleophiles** (no electrophilic carbonyl carbon remains).

- **Acid-labile** (they are formed and cleaved under acid catalysis).

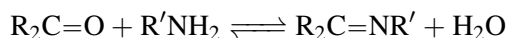
Thus, a carbonyl can be masked as an acetal to prevent reaction with strong nucleophiles (e.g., organometallic reagents) and later regenerated by aqueous acid. Importantly, protection is an *equilibrium manipulation*: it succeeds when water is removed (Dean–Stark, molecular sieves, or use of excess diol/alcohol), and deprotection succeeds when water is abundant.

11.2.4 Addition of ammonia derivatives: imines and enamines

Nitrogen nucleophiles add to carbonyls to give **imines** and **enamines**, which are among the most useful reversible “carbonyl derivatives” because they change both the polarity and the reactivity of the carbonyl carbon and its α -position.

Products and classification

- **Primary amines** (RNH_2) generally form **imines**:



(An imine is sometimes called a Schiff base, particularly for aromatic amines.)

- **Secondary amines** (R_2NH) generally form **enamines**:

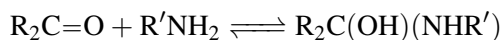


where the product contains a $\text{C}=\text{C}$ adjacent to NR_2 . (The exact alkene position depends on available α -hydrogens.)

Both transformations are **condensations**: addition followed by dehydration. As with acetals, dehydration requires acid, but here acid must be balanced against amine protonation.

The carbinolamine: the common tetrahedral intermediate

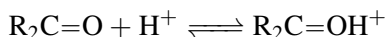
The first-formed addition product is a **carbinolamine** (also called a hemiaminal):



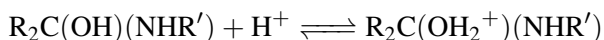
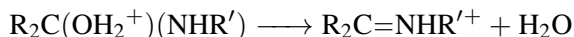
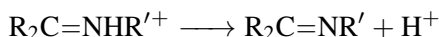
It is the nitrogen analogue of a hemiacetal. Carbinolamines are typically unstable relative to the imine/enamine under dehydrating conditions, but they can accumulate if dehydration is slow (especially at unsuitable pH).

Mechanism of imine formation (primary amine): addition then dehydration

A practical mechanistic outline is:

Step 1: carbonyl activation (optional but common).**Step 2: nucleophilic addition of the amine.**

followed by deprotonation at nitrogen to give the neutral carbinolamine $\text{R}_2\text{C}(\text{OH})(\text{NHR}')$.

Step 3: proton transfers to create a leaving group.**Step 4: elimination of water to form an iminium ion.****Step 5: deprotonation to yield the imine (C=N).****Mechanism of enamine formation (secondary amine): why the product differs**

Secondary amines cannot form a neutral imine because that would require nitrogen to have only three substituents including the carbon substituent and a hydrogen to remove in the final deprotonation step. In enamine formation, after dehydration an **iminium ion** still forms, but the path to neutrality is different:

- Addition forms a carbinolamine (with NR_2).
- Dehydration yields an iminium ion $\text{R}_2\text{C}=\text{NR}_2^+$.
- A base removes an α -hydrogen from the carbon adjacent to the iminium carbon, forming a $\text{C}=\text{C}$ bond and giving the enamine.

Thus, an enamine is best viewed as the **tautomeric partner** of an iminium ion, formed by deprotonation at carbon rather than at nitrogen.

pH dependence: why “mild acid” is optimal for imines/enamines

Amine condensations are highly sensitive to acid strength and concentration. Three competing needs must be balanced:

- **Need for electrophile activation:** some protonation of the carbonyl increases the rate of addition.
- **Need for a leaving group:** dehydration requires protonation of $-OH$ to make H_2O .
- **Need for a nucleophilic amine:** if the medium is too acidic, the amine is protonated to RNH_3^+ or $R_2NH_2^+$ and becomes a poor nucleophile, slowing the very first addition step.

Therefore, imine and enamine formations are typically performed with **catalytic acid** under conditions that also **remove water** (molecular sieves or azeotropic distillation). Water removal drives equilibrium to products and prevents hydrolysis from dominating.

Reversibility: hydrolysis regenerates the carbonyl

Imines, enamines, and acetals are all reversible under appropriate conditions because the carbonyl is thermodynamically accessible in water. For imines and enamines, hydrolysis is essentially the reverse sequence:



This reversibility is useful in synthesis and in biological chemistry, but it also means that isolation and storage of these functional groups may require dry conditions.

11.2.5 Comparative reactivity and practical trends**Aldehydes vs. ketones revisited (now in reversible equilibria)**

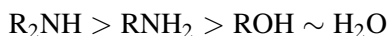
The same steric and electronic factors that control addition rates also influence equilibria indirectly:

- **Rates:** aldehydes typically form hemiacetals, acetals, carbinolamines, and iminium ions faster than ketones.

- **Equilibria:** aldehydes often show higher equilibrium conversions to hydrates and imines than ketones, though specific outcomes depend strongly on substituents and on water removal.

Strength of nucleophile vs. need for catalysis

A rough ordering of common neutral nucleophiles toward carbonyls (ignoring sterics and specific activation) is:



Because water and alcohols are weak nucleophiles, their reactions generally require acid activation of the carbonyl. Amines are more nucleophilic but demand careful pH control so the nucleophile is not quenched by protonation.

Driving reversible reactions: Le Châtelier in functional group form

Because these are equilibria, synthetic success is often a matter of shifting the equilibrium:

- **To form acetals, imines, enamines:** remove water and/or use excess nucleophile; use catalytic acid (but not so much that amines are fully protonated).
- **To regenerate carbonyls:** add water (often aqueous acid for acetals and imines; sometimes aqueous base works for certain substrates), and avoid dehydrating conditions.

11.2.6 Mechanistic checkpoints: common pitfalls and how to avoid them

Pitfall 1: attempting dehydration under basic conditions

Under base, $-\text{OH}$ is not a good leaving group. If the target transformation requires loss of water (acetal, imine, enamine), an acid-catalyzed pathway (or an alternative activation strategy) is needed.

Pitfall 2: using too much acid with amines

Strongly acidic media can stop imine/enamine formation by converting the nucleophilic amine to its ammonium salt. Optimal conditions usually involve a weak acid

(or buffered conditions) plus dehydration.

Pitfall 3: forgetting reversibility during workup

Many condensation products hydrolyze during aqueous workup, especially if acid is present. Planning must include whether the intermediate must survive water exposure, or whether hydrolysis is actually desired to “unmask” the carbonyl.

11.2.7 Summary: a map of reversible heteroatom additions

It is useful to view these reactions as a network connected by a single electrophile-the carbonyl-and by a single key intermediate-a tetrahedral addition product:

- **Water addition** → hydrate (gem-diol): reversible; favored by electrophilic, unhindered carbonyls.
- **Alcohol addition** → hemiacetal: reversible; usually acid-catalyzed for weak alcohol nucleophiles.
- **Alcohol condensation** → acetal: reversible; requires acid and dehydration; acetals protect carbonyls.
- **Amine addition** → carbinolamine: reversible; dehydration gives iminium species.
- **Amine condensation** → imine (primary amine) or enamine (secondary amine): reversible; requires mild acid and water removal.

11.3 Carbon Nucleophiles: Grignard, Organolithium, and Wittig Reactions

The previous section emphasized that additions of oxygen and nitrogen nucleophiles to aldehydes and ketones are often **reversible** and therefore strongly dependent on equilibrium control (pH, water removal, nucleophile excess). In contrast, many **carbon nucleophiles** used to form C–C bonds are sufficiently basic and reactive that their reactions with carbonyl compounds are typically **effectively irreversible** under synthetic conditions. The reason is twofold: (1) the nucleophile is very strong (high-energy HOMO), and (2) the tetrahedral alkoxide product is often strongly stabilized

after aqueous workup (protonation) and cannot readily revert to the carbonyl without an oxidant.

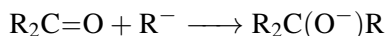
This section focuses on three foundational tools for carbonyl C–C bond formation:

- organomagnesium halides (Grignard reagents),
- organolithium reagents,
- Wittig reagents (phosphorus ylides) for carbonyl-to-alkene conversion.

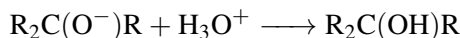
11.3.1 General principles: why strong carbon nucleophiles add irreversibly

Thermodynamic and practical irreversibility

Consider addition of a carbanion equivalent R^- to a carbonyl:



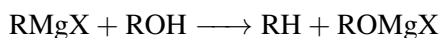
The reverse reaction would require expelling R^- , which is a **very strong base** and an extremely poor leaving group. Under ordinary conditions this is disfavored both kinetically and thermodynamically. In practice, the alkoxide is then protonated during workup:



Protonation removes the basic alkoxide and “locks in” the addition product.

Chemoselectivity is often acid–base selectivity

A crucial difference between carbon nucleophiles like $RMgX$ or RLi and weaker nucleophiles (water, alcohols, amines) is that organometallic reagents are also **strong bases**. They will react rapidly with **any** suitably acidic proton source:

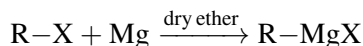


Thus, the primary selectivity question is often: **Is there an acidic proton present that will quench the reagent before it can add to the carbonyl?** This is why reactions must be performed under anhydrous conditions and why functional group compatibility is limited unless protection strategies are used.

11.3.2 Grignard reagents: structure, preparation, and reactivity

Preparation and physical picture

Grignard reagents are organomagnesium halides, commonly written RMgX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$). They are typically prepared by oxidative insertion of Mg into a carbon–halogen bond:



The traditional solvent is diethyl ether or THF, which coordinates to magnesium and stabilizes reactive species.

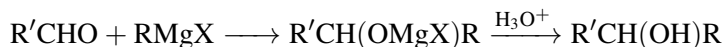
It is often helpful to think of a Grignard reagent as a **polar covalent** C-Mg bond with substantial carbanion character at carbon:



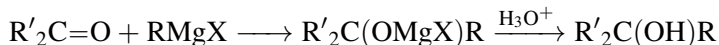
This **carbanion equivalent** is what attacks the electrophilic carbonyl carbon.

Addition to aldehydes and ketones: alcohol formation after workup

For aldehydes:



For ketones:



The product class is diagnostic:

- **Formaldehyde** ($\text{H}_2\text{C}=\text{O}$) gives **primary** alcohols after addition.
- **Other aldehydes** give **secondary** alcohols.
- **Ketones** give **tertiary** alcohols.

Mechanistic note. The key bond-forming step is nucleophilic addition into the carbonyl π^* , producing an alkoxide. The tetrahedral intermediate is not typically isolated because it is strongly basic and reactive; it is “revealed” as an alcohol only after aqueous workup.

Stereochemical outcome: formation of a new stereocenter

If addition to an aldehyde or ketone creates a stereogenic center, the nucleophile can attack either carbonyl face. In an **achiral** environment with an achiral substrate, a racemic mixture typically results. Diastereoselectivity can arise when the carbonyl compound is already chiral or conformationally biased, because the Bürgi–Dunitz approach trajectory is more accessible from one face than the other.

Functional group compatibility and the need for protection

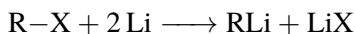
Because Grignard reagents are strong bases, they are incompatible with functional groups containing acidic hydrogens or easily attacked electrophiles. Common problematic groups include:

- $-\text{OH}$, $-\text{NH}$, $-\text{SH}$ (acidic protons),
- $-\text{CO}_2\text{H}$ (acidic and electrophilic),
- $-\text{C}(=\text{O})\text{X}$ derivatives (often react even faster than aldehydes/ketones),
- water (destroys the reagent).

A classic solution is **carbonyl protection** as an acetal (from the previous section), which survives strongly basic nucleophiles and can later be removed under aqueous acid.

11.3.3 Organolithium reagents: increased basicity and reactivity**Preparation and characteristics**

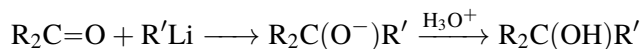
Organolithium reagents (RLi) are typically prepared by lithium–halogen exchange or by direct insertion into $\text{R}-\text{X}$ using lithium metal:



The $\text{C}-\text{Li}$ bond is highly polar, and RLi reagents are generally **more basic and more reactive** than the corresponding Grignard reagents.

Addition to carbonyls: similar products, harsher constraints

Organolithiums add to aldehydes and ketones to give the same classes of alcohols after workup:



However, greater basicity implies:

- more stringent exclusion of moisture and protic impurities,
- more frequent side reactions (e.g., deprotonation at α -positions, addition to less activated electrophiles),
- greater sensitivity to temperature and solvent coordination.

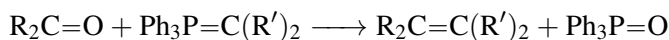
Choosing between RMgX and RLi

A practical comparison:

- Use **Grignard reagents** for many standard carbonyl additions when functional group sensitivity is manageable; they are often easier to handle.
- Use **organolithium reagents** when higher reactivity is needed or when a specific organolithium is more readily available than the corresponding Grignard, but expect narrower functional group tolerance.

11.3.4 Carbonyl-to-alkene conversion: the Wittig reaction**Why the Wittig reaction is different**

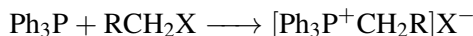
Grignard and organolithium reagents form C–C bonds by addition to a carbonyl and yield alcohols after protonation. The **Wittig reaction** also forms a C–C bond to the carbonyl carbon, but its net outcome is **replacement of the C=O group by a C=C double bond**:



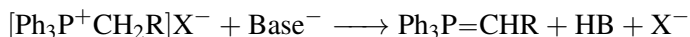
The strong thermodynamic driving force is the formation of P=O in triphenylphosphine oxide.

Step 1: ylide formation (phosphorus ylide as a carbanion equivalent)

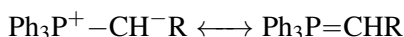
Wittig reagents are generated from **phosphonium salts**:



A strong base deprotonates the carbon adjacent to phosphorus:



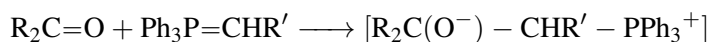
The product $\text{Ph}_3\text{P}=\text{CHR}$ is a **ylide**, often represented by resonance forms:



The carbanion-like carbon is the nucleophilic site that attacks the carbonyl.

Step 2: addition to the carbonyl and betaine formation

The ylide carbon adds to the carbonyl carbon, producing a zwitterionic intermediate commonly called a **betaine**:



This intermediate can cyclize to a four-membered ring.

Step 3: oxaphosphetane formation and collapse

A defining mechanistic feature of the Wittig reaction is the **oxaphosphetane**, a four-membered ring containing C, O, P, and the ylide carbon. Its collapse yields the alkene and $\text{Ph}_3\text{P}=\text{O}$. This ring formation/collapse is often depicted as a formal $[2 + 2]$ cycloaddition/fragmentation sequence.

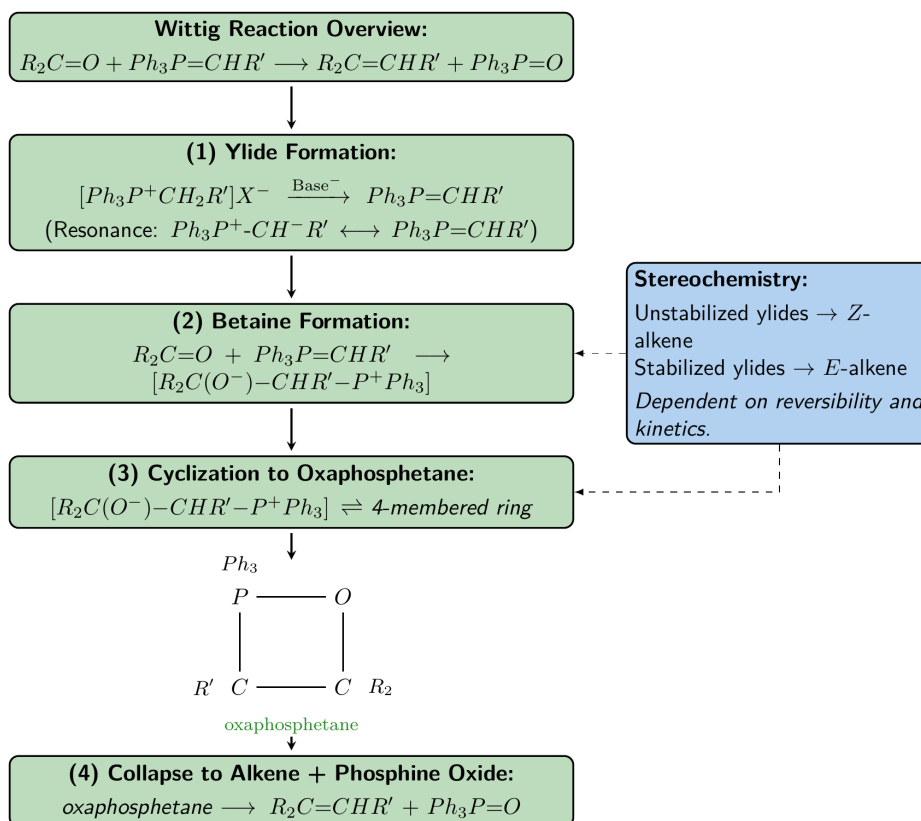
Stereochemical trends: Z vs. E alkenes and ylide stability

The Wittig reaction often produces mixtures of alkene stereoisomers. Two widely used qualitative trends are:

- **Unstabilized ylides** (alkyl-substituted; no strong electron-withdrawing group adjacent to the ylide carbon) often give more **Z**-alkene.

- **Stabilized ylides** (adjacent to electron-withdrawing groups such as CO_2R , COR , CN) often give more **E**-alkene.

These tendencies are connected to the energies and lifetimes of intermediates (betaine/oxaphosphetane) and to whether the reaction pathway is more kinetic or more thermodynamically controlled. While the full stereochemical model can be complex, the synthetic message is clear: **ylide substitution and stabilization strongly influence alkene geometry**.



11.3.5 Horner–Wadsworth–Emmons (HWE): a brief extension

A widely used variant replaces phosphonium ylides with phosphonate-stabilized carbanions (often generated from phosphonates). These reagents frequently provide improved control and often favor **E**-alkenes. Mechanistically, they proceed through related addition/cyclization steps, but the reagents and byproducts differ (phosphate-derived leaving groups rather than $\text{Ph}_3\text{P}=\text{O}$).

11.3.6 Planning C–C bond formation at carbonyls: a synthesis checklist

When selecting among Grignard/organolithium/Wittig, the following questions provide a robust decision framework:

- **Do you want an alcohol or an alkene?** For an alcohol: use RMgX or RLi addition, then workup. For an alkene: use Wittig (or HWE) olefination.
- **Is there an acidic proton or incompatible electrophile present?** If yes, consider protection (e.g., acetal for carbonyls, silyl ether for alcohols) or choose a different strategy.
- **Is chemoselectivity needed among multiple carbonyls?** Aldehydes are typically attacked faster than ketones. More substituted carbonyls are slower due to sterics and reduced electrophilicity. Lewis acids can alter selectivity but may also react with organometallics; compatibility must be evaluated.
- **Is stereochemical control required?** Organometallic additions can create stereocenters; control depends on substrate bias or chiral auxiliaries/catalysts (beyond the present scope). Wittig/HWE choice and ylide stabilization influence *E/Z* alkene geometry.

Strong carbon nucleophiles transform aldehydes and ketones into more complex carbon frameworks by forming C–C bonds:

- **Grignard and organolithium reagents** add to carbonyls to give alkoxides that become alcohols upon workup; these reactions are usually effectively irreversible and strongly constrained by acid–base compatibility.
- **Wittig reagents** convert carbonyls into alkenes through betaine and oxaphosphetane intermediates, driven by formation of a strong $\text{P}=\text{O}$ bond; ylide stability influences alkene stereochemistry.

These reactions complement the reversible heteroatom additions of the previous section and set the stage for redox chemistry of carbonyls, where electrophilicity is modulated not by nucleophile strength but by hydride delivery and migratory rearrangements.

11.4 Oxidation and Reduction of Carbonyl Compounds

The preceding sections developed two complementary ways that carbonyl compounds form new bonds: reversible nucleophilic addition by heteroatoms (hydrates, acetals, imines/enamines) and typically irreversible C–C bond formation by strong carbon nucleophiles (Grignard/organolithium, Wittig). In this section we turn to a third central reactivity class: **redox transformations** of aldehydes and ketones. Here the carbonyl group is not simply an electrophile for addition; instead, it is a functional group whose *oxidation state* can be moved up or down in a controlled and diagnostically useful way.

Two themes unify the redox chemistry:

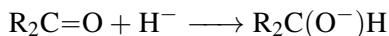
- **Reduction** of a carbonyl to an alcohol is commonly achieved by *hydride transfer* (a nucleophilic delivery of H^- equivalent) or by catalytic hydrogenation.
- **Oxidation** of aldehydes (and, by special methods, ketones) typically proceeds through pathways that convert the carbonyl carbon into a more oxidized functional group, most commonly a carboxylic acid derivative; ketone oxidation has distinct mechanistic features (e.g., Baeyer–Villiger oxidation).

Throughout, we will interpret mechanisms using the electronic structure principles already established: nucleophiles donate into the carbonyl π^* orbital, protonation/Lewis acids increase electrophilicity, and tetrahedral intermediates form when the carbonyl carbon changes from sp^2 to sp^3 .

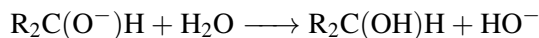
11.4.1 Reduction of aldehydes and ketones by metal hydrides

Hydride reagents as nucleophiles: the key step is addition

The defining bond-forming step in hydride reduction is:



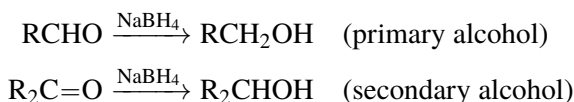
Hydride (H^-) is a strong nucleophile toward carbonyls, and the immediate product is an alkoxide. A subsequent protonation step converts the alkoxide to an alcohol:



Thus, carbonyl reduction by hydride is mechanistically analogous to Grignard/organolithium addition, except that the nucleophile is H^- equivalent and the product is an alcohol rather than a C–C coupled alcohol.

Sodium borohydride (NaBH₄): mild, selective hydride donor

NaBH₄ is widely used to reduce aldehydes and ketones to alcohols under relatively mild conditions. Typical outcomes:

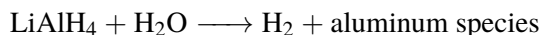


Mechanistic outline. A borohydride delivers hydride to the carbonyl carbon to form an alkoxide; the oxygen may coordinate to boron to form a borate complex. Protonation (from alcohol solvent, water, or aqueous workup) releases the alcohol and converts boron-containing intermediates to borate byproducts.

Why NaBH₄ is “mild.” The B–H bonds in BH₄[–] are less polar and less reactive than Al–H bonds in aluminum hydrides, so NaBH₄ generally reduces aldehydes and ketones efficiently but is less reactive toward many other functional groups. This allows useful chemoselectivity in multifunctional molecules.

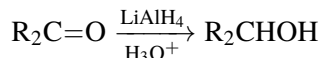
Lithium aluminum hydride (LiAlH₄): powerful, moisture-sensitive hydride donor

LiAlH₄ is a significantly stronger hydride donor than NaBH₄. It reduces aldehydes and ketones rapidly, but it is also highly reactive toward water and other protic functional groups:



Therefore it must be used under strictly anhydrous conditions, typically followed by a controlled aqueous workup.

For aldehydes and ketones, the net transformation is the same as with NaBH₄:



Practical implication of high reactivity. In synthesis planning, LiAlH₄ is chosen when the substrate is less reactive, when other reducible groups are present that NaBH₄ would leave untouched (beyond the scope here), or when a rapid and complete reduction is needed. However, its strong basicity and protic incompatibility frequently necessitate protecting groups.

Aldehydes vs. ketones: reactivity trends persist

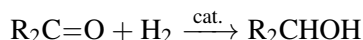
In both NaBH_4 and LiAlH_4 reductions, aldehydes are typically reduced faster than ketones, reflecting the same steric and electronic factors that govern nucleophilic addition in general. In mixed-carbonyl substrates, hydride may reduce an aldehyde selectively in the presence of a ketone under carefully chosen conditions.

Stereochemical considerations: hydride delivery creates alcohol stereocenters

Reduction of a prochiral ketone forms a new stereocenter at the alcohol carbon. Without a chiral reagent or chiral environment, the two faces of the carbonyl are attacked with similar probability, giving a racemic mixture. Diastereoselectivity arises when the substrate is already chiral (or conformationally biased), because one face of the carbonyl may be sterically or electronically more accessible along the preferred nucleophilic approach trajectory.

11.4.2 Catalytic hydrogenation of aldehydes and ketones**Net reaction and typical conditions**

Catalytic hydrogenation reduces a carbonyl to an alcohol using H_2 and a metal catalyst (commonly Pt, Pd, Ni, or specialized catalysts):



This method avoids stoichiometric metal-hydride reagents but often requires pressure and carefully chosen catalysts to achieve chemoselectivity.

Mechanistic picture (conceptual)

A simplified conceptual mechanism involves:

- adsorption of the carbonyl compound and H_2 onto the metal surface,
- activation (dissociation) of H_2 into surface-bound hydrogen atoms,
- transfer of hydrogen to the carbonyl carbon and oxygen (stepwise or concerted, depending on catalyst and conditions),
- desorption of the alcohol.

From the standpoint of functional group logic, the key point is that catalytic hydrogenation is a **two-electron reduction** of the carbonyl carbon with **net addition of** H_2 across the $\text{C}=\text{O}$ unit.

When hydrogenation is chosen

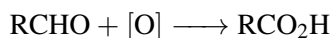
Hydrogenation is particularly useful when:

- large-scale reduction is desired (reagents are inexpensive; byproducts minimal),
- functional group compatibility allows it (some groups may also be hydrogenated),
- a catalytic approach is preferred over stoichiometric hydride reagents.

11.4.3 Oxidation of aldehydes to carboxylic acids

Why aldehydes oxidize readily

Aldehydes (RCHO) are readily oxidized to carboxylic acids (RCO_2H):



In oxidation-state terms, the aldehyde carbon is increased in oxidation level by converting the $\text{C}-\text{H}$ bond into a $\text{C}-\text{O}$ bond. Mechanistically, many oxidations proceed through formation of a **gem-diol** (hydrate) or a related tetrahedral intermediate, which is then further oxidized.

A crucial contrast:

- **Aldehydes** have a hydrogen on the carbonyl carbon and can be oxidized without breaking a $\text{C}-\text{C}$ bond.
- **Ketones** lack that hydrogen and are generally resistant to simple oxidation; oxidation often requires $\text{C}-\text{C}$ bond migration or cleavage.

Chromium-based oxidations (conceptual overview)

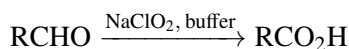
Classical oxidants (e.g., chromic acid conditions) convert aldehydes to carboxylic acids efficiently. While the detailed mechanism depends on the oxidant form, a com-

mon conceptual element is formation of a **chromate ester** (or analogous activated intermediate) followed by a redox step that increases the oxidation state at carbon.

Because chromium reagents involve toxicity and disposal concerns, modern practice often uses alternative oxidants when feasible.

Pinnick oxidation: selective aldehyde-to-acid conversion

A widely used mild method for converting aldehydes to carboxylic acids is the **Pinnick oxidation** (often involving sodium chlorite under buffered conditions):



A key synthetic advantage is **chemoselectivity**: aldehydes can often be oxidized in the presence of other oxidation-sensitive groups under appropriately controlled conditions. The buffering helps avoid side reactions and controls the speciation of the oxidant.

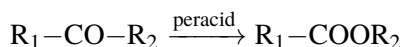
Aldehydes in air: practical sensitivity

Many aldehydes slowly oxidize upon exposure to oxygen (often via radical pathways) to give carboxylic acids. This is a practical reminder that aldehydes are intrinsically easier to oxidize than ketones and should be stored and handled accordingly, especially for sensitive analytical work.

11.4.4 Oxidation of ketones: Baeyer–Villiger oxidation to esters

Net reaction

The most important oxidation of ketones that preserves the carbon skeleton is the **Baeyer–Villiger oxidation**, which converts ketones to esters (and cyclic ketones to lactones) using a peracid (e.g., mCPBA):



This is not a simple “oxygen insertion” in an abstract sense; it is a mechanistically specific rearrangement in which **one substituent migrates** from carbon to oxygen.

Mechanism: Criegee intermediate and rearrangement

A mechanistically useful step-by-step outline is:

Step 1: nucleophilic addition of the peracid to the carbonyl. The peracid oxygen (the terminal peroxide oxygen) attacks the carbonyl carbon, forming a tetrahedral adduct. This step resembles nucleophilic addition to a carbonyl, except the nucleophile is part of an oxidant.

Step 2: formation of the Criegee intermediate. Proton transfers and bond reorganization give a tetrahedral species often called the **Criegee intermediate**, in which the carbonyl carbon is attached to an –OOH-derived group and to the original substituents.

Step 3: rearrangement (migration) with O–O bond cleavage. One of the substituents (R_1 or R_2) migrates from carbon to the adjacent oxygen while the O–O bond breaks, yielding the ester and a carboxylic acid byproduct (from the peracid). This step is stereoelectronically organized: the migrating group moves with retention of configuration at the migrating center (when it is chiral), consistent with a concerted migration.

Migratory aptitude: which group moves?

In unsymmetrical ketones, the identity of the migrating group determines which ester forms. A widely used qualitative order (highest migratory ability to lowest) is:



Two practical interpretations follow:

- More substituted alkyl groups often migrate preferentially over less substituted ones.
- A phenyl group can compete strongly with secondary alkyl groups.

Migratory aptitude reflects how well the migrating group stabilizes positive charge development in the rearrangement transition state and how readily it can align for migration.

Cyclic ketones give lactones

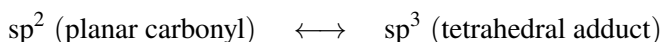
When the ketone is cyclic, migration inserts oxygen adjacent to the carbonyl carbon and expands the functional group into a **lactone**. Ring size and substitution influence

which bond migrates, and thus which lactone regioisomer predominates.

11.4.5 Connecting redox to earlier carbonyl chemistry: mechanistic and strategic links

Tetrahedral intermediates recur across reaction classes

Hydride reductions, hydration, acetal formation, imine formation, and Baeyer–Villiger oxidation all pass through tetrahedral carbon intermediates. The carbonyl carbon repeatedly toggles between:



This structural change is one reason carbonyl chemistry is so rich: many reagents can access the same geometric intermediate, but different subsequent steps (proton transfers, leaving group formation, migration) direct the outcome.

Chemoselectivity: reduction vs. oxidation choices

A synthesis plan often hinges on whether a carbonyl is being used as an electrophile to **build** structure, or as a functional handle to **adjust** oxidation level. For example, a non-exhaustive set of possibilities includes:

- A ketone can be **reduced** to an alcohol (increase C–H character) without changing carbon connectivity.
- A ketone can be **oxidized** by Baeyer–Villiger to an ester (insert oxygen and change functional group class), enabling subsequent substitution chemistry elsewhere in a synthesis sequence.
- An aldehyde can be **oxidized** to a carboxylic acid, which then opens access to acyl derivatives and amide/ester formation (topics treated in later chapters).

Reduction and oxidation of aldehydes and ketones provide high-leverage transformations that complement nucleophilic additions:

- **Hydride reductions** (NaBH_4 , LiAlH_4) convert aldehydes and ketones to alcohols through nucleophilic hydride addition to the carbonyl and protonation of the resulting alkoxide.

- **Catalytic hydrogenation** reduces carbonyls to alcohols using H_2 on a metal surface, often valuable for scale and atom economy.
- **Aldehyde oxidation** readily yields carboxylic acids; selective methods such as Pinnick oxidation are synthetically important.
- **Ketone oxidation** commonly proceeds by Baeyer–Villiger oxidation to esters/lactones via a rearrangement in which one substituent migrates; migratory aptitude controls regiochemistry.

With these redox tools, aldehydes and ketones can be used not only as electrophilic reaction partners but also as strategic “redox nodes” in multistep synthesis.

11.5 Problems

11.5.1 Problem 1: Ranking carbonyl electrophilicity and addition rate

Rank the following carbonyl compounds in order of **increasing** rate of nucleophilic addition by MeO^- under identical conditions (assume the reaction is kinetically controlled and the nucleophile is not protonated). Provide a brief justification for each comparison using steric effects, inductive effects, and conjugation arguments.

- 1. $(\text{CH}_3)_2\text{C}=\text{O}$ (acetone)
- 2. CH_3CHO (acetaldehyde)
- 3. $(\text{CH}_3)_3\text{CCHO}$ (pivaldehyde)
- 4. PhCHO (benzaldehyde)
- 5. $\text{CH}_3\text{COCH}_2\text{CH}_3$ (2-butanone)
- 6. $\text{CH}_2=\text{CHCHO}$ (acrolein, α, β -unsaturated aldehyde)

Then, for the same set, rank the equilibrium extent of hydration in water (fraction present as gem-diol), and explain why the ranking may differ from the kinetic ranking.

11.5.2 Problem 2: Bürgi–Dunitz trajectory and stereochemical prediction

A prochiral ketone R^1COR^2 is reduced with $NaBH_4$ to give a secondary alcohol. Assume R^1 is larger than R^2 and that the substrate adopts a conformation that minimizes steric interactions.

- 1. Using a 3D drawing (Newman-style or wedge–dash), propose the most reasonable approach of hydride consistent with a Bürgi–Dunitz angle of approximately 107° .
- 2. Predict which face (**Re** or **Si**) is attacked preferentially under substrate-control and what major enantiomer (or diastereomer, if applicable) would result. Clearly state any assumptions.
- 3. Explain how Lewis acid activation of the carbonyl oxygen might change the rate and potentially the facial selectivity.

11.5.3 Problem 3: Mechanism of cyclic acetal formation (with full curved-arrow logic)

Provide a complete acid-catalyzed mechanism (all key intermediates and proton-transfer steps) for formation of a 1,3-dioxolane acetal from cyclohexanone and ethylene glycol in the presence of catalytic H_2SO_4 .

- 1. Draw the overall reaction using mhchem notation and a chemfig structure for the cyclic acetal.
- 2. Show the hemiacetal intermediate and identify the step in which H_2O becomes a leaving group.
- 3. Explain why removal of water drives the reaction forward and why the same acetal is readily hydrolyzed under aqueous acid.

11.5.4 Problem 4: Grignard addition in a multifunctional molecule (chemoselectivity and protection)

Consider the substrate $HO(CH_2)_3CHO$ (4-hydroxybutanal). You are asked to convert it into $HO(CH_2)_3CH(OH)CH_3$ (a diol) using a Grignard reagent as the carbon source for the methyl group.

- 1. Explain why direct treatment of the substrate with CH_3MgBr fails (or gives undesired products).
- 2. Propose a viable multistep sequence that uses an appropriate protecting group strategy (choose between protecting the alcohol, the aldehyde, or both) to achieve the target diol after workup.
- 3. For each step, specify reagents and conditions, and identify the key intermediate functional groups.

11.5.5 Problem 5: Wittig synthesis planning (selecting reagents and predicting E/Z)

Design a Wittig reaction that converts cyclohexanone into an exocyclic alkene of the form cyclohexylidene- CHCH_3 (i.e., an alkene where the ring carbonyl carbon becomes part of the $\text{C}=\text{C}$ bond, and the external alkene carbon bears H and CH_3).

- 1. Identify a suitable phosphonium salt precursor and the base needed to form the ylide.
- 2. Write the full Wittig transformation (ketone + ylide $\rightarrow$ alkene + $\text{Ph}_3\text{P}=\text{O}$).
- 3. Predict whether the ylide is “stabilized” or “unstabilized” and discuss the expected stereochemical outcome (if E/Z is meaningful in your product). If stereochemistry is not applicable, explain why.

11.5.6 Problem 6: Acid-catalyzed enamine formation (mechanism and pH dependence)

Provide a full mechanism for formation of an enamine from cyclohexanone and pyrrolidine under catalytic acid conditions.

- 1. Show the carbinolamine (hemiaminal) intermediate and the iminium ion intermediate.
- 2. Clearly indicate the proton transfers required to convert $-\text{OH}$ into H_2O and to enable the final deprotonation step that generates the enamine.
- 3. Explain why strongly acidic conditions can suppress enamine formation even though acid is needed for dehydration.

11.5.7 Problem 7: Baeyer–Villiger product prediction (migratory aptitude and regiochemistry)

Predict the major Baeyer–Villiger oxidation product(s) for each ketone below using a peracid (e.g., mCPBA). For each, indicate which group migrates and justify your choice using migratory aptitude and stereoelectronic reasoning.

- 1. $\text{CH}_3\text{COCH}_2\text{CH}_3$ (2-butanone)
- 2. acetophenone (PhCOCH_3)
- 3. 2-methylcyclohexanone
- 4. bicyclic ketone: norbornan-2-one (2-norbornanone) (assume the usual rigid framework)

For the cyclic cases, state whether ring expansion occurs and identify the lactone size formed.

11.5.8 Problem 8: Multistep synthesis with acetal protection (functional group interconversion)

Propose a synthesis of 3-phenyl-3-pentanol ($\text{PhC}(\text{OH})(\text{CH}_3)(\text{CH}_2\text{CH}_3)$) starting from benzaldehyde and any necessary inorganic reagents and carbon sources (you may use Grignard or organolithium chemistry). Your route must include at least one step in which a carbonyl group is protected as an acetal to control chemoselectivity.

- 1. Provide the full sequence of steps with reagents.
- 2. Identify where protection is essential and what undesired reaction it prevents.
- 3. Indicate the point in the sequence where the acetal is hydrolyzed back to the carbonyl.

11.5.9 Problem 9: Spectroscopic identification of an unknown ketone (IR and NMR reasoning)

An unknown compound has formula $\text{C}_5\text{H}_{10}\text{O}$ and shows a strong IR absorption near 1715 cm^{-1} . The ^1H NMR (assume CDCl_3) shows:

- a triplet integrating to 3H near 0.9 ppm,
 - a quartet integrating to 2H near 2.4 ppm,
 - a singlet integrating to 3H near 2.1 ppm,
 - a multiplet integrating to 2H near 1.5 ppm.
1. Propose a structure consistent with these data and justify your assignment.
 2. Predict the ^{13}C NMR chemical shift region for the carbonyl carbon and the number of distinct carbon signals expected (ignoring accidental equivalence).
 3. Explain how the spectrum would change if the compound were an aldehyde instead of a ketone (identify at least two diagnostic differences).

11.5.10 Problem 10: Challenge mechanism and synthesis linkage (Robinson annulation precursor step)

A key step toward a Robinson annulation precursor involves generating an α, β -unsaturated carbonyl compound and then forming a C–C bond at the carbonyl β -position (conjugate addition). While full Robinson annulation chemistry is beyond this chapter, you can analyze the carbonyl-centered steps using principles developed here.

1. Starting from cyclohexanone, propose a sequence that converts it into an α, β -unsaturated ketone (enone) using an enamine intermediate (from a secondary amine) as a key step. Clearly specify reagents and conditions and show the enamine-forming step.
2. For the conjugate addition step, choose an appropriate carbon nucleophile equivalent (not necessarily RMgX or RLi) that would favor 1,4-addition over 1,2-addition, and justify your choice in terms of nucleophile “hard/soft” character and electrophile structure.
3. Provide a mechanistic sketch (key intermediates only) that explains why strongly basic organolithium reagents often give predominant 1,2-addition to enones, whereas softer nucleophiles can favor 1,4-addition.

Chapter 12

Carboxylic Acids and Derivatives

While aldehydes and ketones react primarily via nucleophilic addition, the presence of a potential leaving group on the carbonyl carbon of carboxylic acid derivatives unlocks a distinct and versatile pathway: nucleophilic acyl substitution. This chapter systematically explores the chemistry of the acyl group, establishing a rigorous hierarchy of reactivity based on leaving group basicity—from highly reactive acid halides to kinetically stable amides. By mastering the addition-elimination mechanism, students will understand the chemical principles governing diverse processes, from the laboratory synthesis of complex esters to the stability of peptide bonds in biological systems.

12.1 Acidity, Structure, and Synthesis of Carboxylic Acids

Carboxylic acids (RCO_2H) are among the most frequently encountered functional groups in organic chemistry. Their importance stems from two linked features:

- the **polar, resonance-stabilized** electronic structure of the carboxyl group, and
- their ability to serve as **central branching points** in synthesis, because many other functional groups can be formed from (or converted into) carboxylic acids and their derivatives.

This section connects structure to reactivity by explaining (i) why carboxylic acids are much more acidic than alcohols, (ii) how substituents and environment tune acidity, and (iii) the major synthetic routes that reliably install the $-\text{CO}_2\text{H}$ group.

12.1.1 The Carboxyl Group: Geometry, Bonding, and Resonance

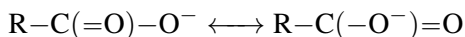
Planarity and π -bonding

The carboxyl group is best understood as a conjugated system containing a carbonyl ($\text{C}=\text{O}$) adjacent to a heteroatom bearing a lone pair (the hydroxyl oxygen). The atoms $\text{O}-\text{C}-\text{O}$ are approximately coplanar, and the carbonyl carbon is **trigonal planar** (approximately 120° bond angles), consistent with an sp^2 -hybridized carbon.

In a simple localized picture, one draws a $\text{C}=\text{O}$ double bond and a $\text{C}-\text{O}$ single bond. Experimentally, however, the two $\text{C}-\text{O}$ bond lengths in the **carboxylate** conjugate base are essentially equal, indicating that the π -electron density is delocalized over both $\text{C}-\text{O}$ bonds.

Resonance structures of the carboxylate

Deprotonation of a carboxylic acid gives a carboxylate anion, RCO_2^- . Two major resonance contributors distribute the negative charge over two oxygens:



In each contributor, one oxygen bears formal charge -1 , but the **resonance hybrid** has partial negative charge on **both** oxygens and partial double-bond character in **both** $\text{C}-\text{O}$ bonds.

This delocalization is the single most important structural reason carboxylic acids are significantly more acidic than alcohols.

12.1.2 Acidity: Why Carboxylic Acids Are Stronger Acids than Alcohols

A $\text{p}K_a$ -based comparison

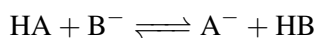
Typical aqueous $\text{p}K_a$ values (approximate, but diagnostically useful) are:



A difference of ~ 12 $\text{p}K_a$ units corresponds to an equilibrium constant ratio of about 10^{12} . Thus, in water, carboxylic acids are deprotonated by relatively weak bases (e.g., HCO_3^-), whereas alcohols are not.

Conjugate-base stability is the key

Acidity trends in organic molecules are best rationalized by the stability of the conjugate base. Deprotonation equilibria can be written as



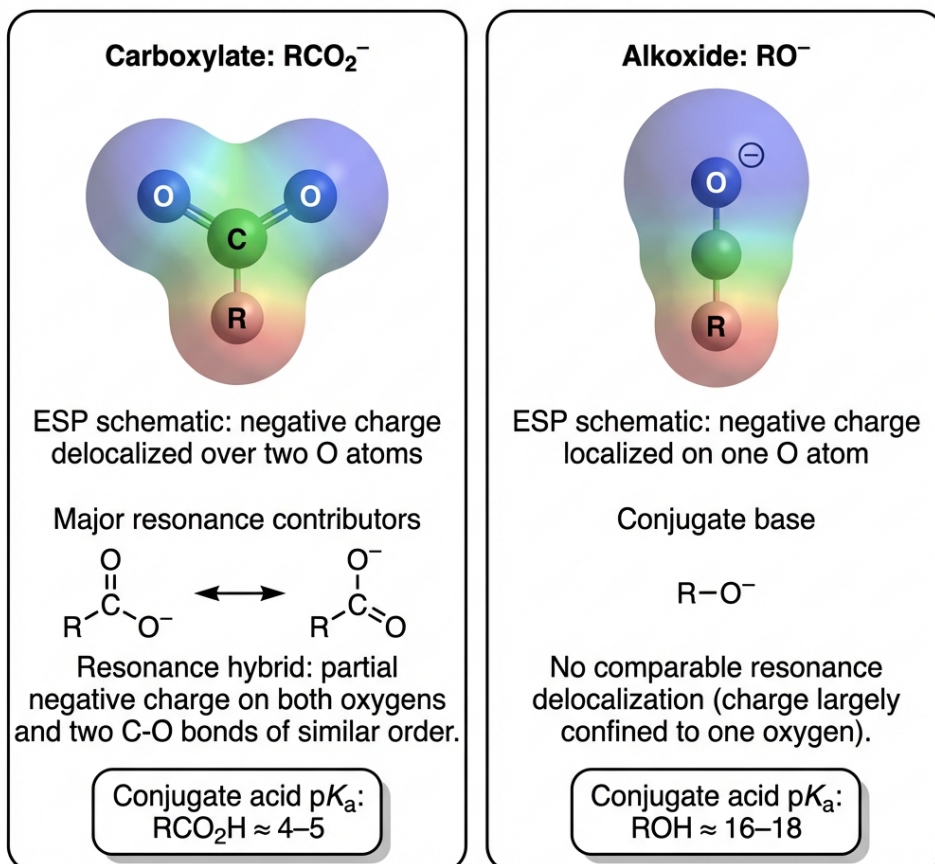
The more stabilized A^- is relative to HA , the more the equilibrium favors products and the lower the $\text{p}K_{\text{a}}$.

For carboxylic acids, stabilization of RCO_2^- is achieved primarily by:

- **Resonance delocalization:** the negative charge is shared by two electronegative oxygen atoms.
- **Inductive effects:** the carbonyl group (and substituents on R) withdraw electron density through σ bonds, reducing the energy of the anion.
- **Solvation:** the anion is well solvated in polar protic solvents because charge is distributed over two oxygens and can accept multiple hydrogen bonds.

By contrast, an alkoxide RO^- has its negative charge **localized** on a single oxygen and lacks the additional resonance stabilization available to carboxylates.

Charge delocalization $\Rightarrow$ more stable conjugate base $\Rightarrow$ stronger acid



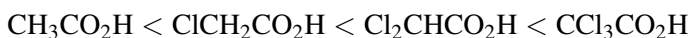
12.1.3 Factors That Control Carboxylic Acid Strength

Although resonance stabilization is common to nearly all carboxylates, $\text{p}K_a$ values **vary** with substituents, hybridization, and medium. The main effects can be organized into a small set of principles.

Inductive effects: electron-withdrawing groups stabilize the carboxylate

Substituents that withdraw electron density through σ bonds ($-I$ effect) stabilize RCO_2^- by reducing electron density on the already negative oxygens. This lowers the conjugate base energy and increases acidity (lowers $\text{p}K_a$).

A classic example is the haloacetic acid series:



Each additional chlorine increases acidity because the $-I$ effect becomes stronger.

Distance dependence

Inductive effects diminish rapidly with distance. For substituted carboxylic acids, an electron-withdrawing group on the α -carbon (adjacent to CO_2H) has a much larger effect than the same group on the β - or γ -carbon.

Resonance effects from conjugation with π systems

If the CO_2H group is conjugated with a π system that can withdraw electron density by resonance (e.g., an aromatic ring bearing electron-withdrawing substituents), acidity can increase. Conversely, resonance donation into the carbonyl can slightly decrease acidity by destabilizing the anion relative to the acid (the details depend on geometry and substituent orientation).

A particularly important special case is the comparison between:

- **Aliphatic carboxylic acids** (e.g., acetic acid), and
- **Benzoic acids** (aryl carboxylic acids), whose acidity is strongly affected by ring substituents.

Substituent effects in benzoic acid derivatives are often quantified with Hammett σ constants; conceptually, the key idea is that substituents that stabilize negative charge (by $-I$ and/or $-R$) increase acidity.

Hybridization and electronegativity effects adjacent to the carboxyl group

When R contains an sp -hybridized carbon near the carboxyl group (e.g., propiolic acid, $\text{HC}\equiv\text{CCO}_2\text{H}$), acidity is enhanced relative to an sp^3 -substituted acid, because sp carbons are more electronegative and exert a stronger inductive withdrawing effect.

Solvent and intramolecular hydrogen bonding

Measured $\text{p}K_a$ values depend on the solvent. Polar protic solvents stabilize ions effectively through solvation and hydrogen bonding, which generally increases apparent acidity for functional groups that form well-solvated anions. Additionally, some substituted acids form **intramolecular** hydrogen bonds that can stabilize either

the acid or the conjugate base; the net effect on acidity depends on which state is stabilized more strongly.

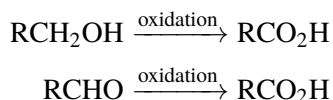
12.1.4 Carboxylic Acids as Synthetic Targets: Major Preparative Routes

Carboxylic acids are commonly made by reactions that either (i) **oxidize** a precursor already containing the appropriate carbon skeleton, or (ii) **form a new C–C bond** to install the carboxyl carbon (often using CO_2 as the electrophile). The methods below are foundational because they are broadly applicable and appear repeatedly in synthesis design.

12.1.5 Oxidation Routes to Carboxylic Acids

Oxidation of primary alcohols and aldehydes

Primary alcohols and aldehydes are direct precursors to carboxylic acids:



Conceptually, oxidation increases the number of bonds from carbon to heteroatoms (especially oxygen) and decreases C–H bonds. In practice, many oxidants accomplish this transformation; the unifying synthetic idea is:

- **Primary alcohol** → **aldehyde** → **carboxylic acid** is often a **two-step oxidation level change**, but strong oxidants can carry out the full conversion in one operation.
- **Aldehydes** are generally easier to oxidize than primary alcohols because they already contain a carbonyl and are readily converted (often even by air in some cases) to acids.

Functional group compatibility (strategic note)

Because oxidation changes the oxidation state and can affect other sensitive groups (alkenes, sulfides, benzylic positions, etc.), synthesis planning often involves choosing oxidants that are strong enough to reach the acid but selective enough to avoid undesired side reactions.

Oxidative cleavage of alkenes and alkynes

Oxidative cleavage breaks a π bond and converts the carbons of the double/triple bond into carbonyl-containing products. Under sufficiently oxidative conditions, carboxylic acids can form.

Alkenes

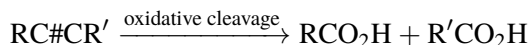
For a terminal alkene, cleavage can produce CO_2H at the substituted carbon and CO_2 (or a one-carbon oxidation product) from the terminal carbon, depending on conditions:



For internal alkenes, both carbons can become carboxylic acids if each bears at least one hydrogen initially (the exact product distribution depends on substitution pattern and reagents).

Alkynes

Alkynes can be oxidatively cleaved to carboxylic acids as well:



Terminal alkynes often yield RCO_2H plus CO_2 (from the terminal carbon).

Synthetic utility

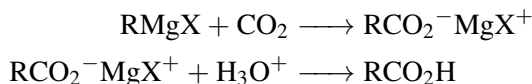
Oxidative cleavage is valuable for:

- **Retrosynthesis:** a target diacid can suggest an internal alkyne or alkene precursor.
- **Skeleton editing:** cleavage reactions can “split” carbon frameworks in a predictable way.

12.1.6 Carbon–Carbon Bond-Forming Routes: Carboxylation Chemistry

Carboxylation of Grignard reagents (and organolithiums)

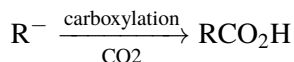
A powerful and general method to create carboxylic acids is carboxylation of an organometallic reagent using carbon dioxide:



Mechanistically, the carbon in CO_2 is electrophilic (polarized $\text{O}=\text{C}=\text{O}$), and the carbanion-like carbon in RMgX acts as a nucleophile, forming a new C–C bond to the carbon of CO_2 . Acidic workup protonates the carboxylate to give the carboxylic acid.

One-carbon homologation

This transformation is especially important because it **adds one carbon** to the carbon skeleton:



Thus, it is a standard method for homologation by a single carbon.

Practical constraints (conceptual)

Organometallic reagents are strong bases and nucleophiles, so they are incompatible with functional groups containing acidic protons (e.g., OH, NH, SH, terminal alkynes) and with many electrophilic carbonyl groups unless protected or otherwise managed. In synthesis planning, carboxylation is chosen when the substrate can survive strong basic conditions.

12.1.7 Other Common Synthetic Entries to Carboxylic Acids (Context and Continuity)

While oxidation and organometallic carboxylation are the primary routes emphasized in this chapter, two additional entries are frequently encountered and conceptually reinforce the role of carboxylic acids as “oxidation-level endpoints” of carbonyl chemistry:

- **Hydrolysis of nitriles:** $\text{RCN} \xrightarrow{\text{H}_2\text{O}, \text{H}^+ \text{ or } \text{OH}^-} \text{RCO}_2\text{H}$ (often requiring heat).
Nitriles act as masked carboxylic acids.

- **Hydrolysis of activated derivatives:** acyl halides and anhydrides react readily with water to give carboxylic acids. This will be developed later when nucleophilic acyl substitution is introduced.

These methods foreshadow a central theme of acyl chemistry: once a carbonyl carbon is activated toward nucleophilic attack, interconversion among acid derivatives (and formation of acids) becomes straightforward under appropriate conditions.

12.1.8 Summary: Structure–Acidity–Synthesis Connections

- **Electronic structure:** the carboxylate anion is stabilized by resonance, distributing negative charge over two oxygen atoms and equalizing C–O bond character.
- **Acidity control:** carboxylic acids are far more acidic than alcohols primarily because their conjugate bases are resonance-stabilized; inductive and resonance substituent effects fine-tune pK_a values.
- **Synthesis:** carboxylic acids are commonly made by oxidation (from primary alcohols or aldehydes; by oxidative cleavage) and by C–C bond formation via carboxylation of organometallic reagents with CO_2 .

These ideas provide the foundation for understanding why carboxylic acids and their derivatives undergo **nucleophilic acyl substitution** and why reactivity trends across derivatives correlate strongly with the stability of the leaving group and the electrophilicity of the acyl carbon, developed in subsequent sections.

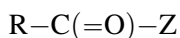
12.2 The Nucleophilic Acyl Substitution Mechanism

In the previous section, carboxylic acids were introduced as stable, resonance-stabilized functional groups whose conjugate bases (carboxylates) are unusually stable. That same resonance stabilization has an important consequence for **reactivity**: although carboxylic acids and their derivatives contain a carbonyl group, they typically **do not** undergo simple nucleophilic **addition** in the way aldehydes and ketones do. Instead, most reactions at the acyl carbon proceed by an **addition–elimination pathway** called **nucleophilic acyl substitution**. This mechanism is the defining reaction class for acid derivatives.

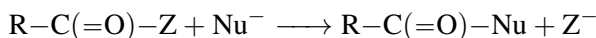
12.2.1 The General Reaction Class: Substitution at an Acyl Carbon

Acyl compounds and leaving groups

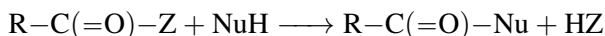
An **acyl compound** contains an acyl group $\text{R}-\text{C}(=\text{O})-$. Carboxylic acid derivatives can be represented generically as



where Z is a heteroatom-based substituent that can potentially act as a leaving group (e.g., Cl, $-\text{OCOR}$, $-\text{OR}$, $-\text{NR}_2$). The defining transformation is:



or, under neutral conditions,



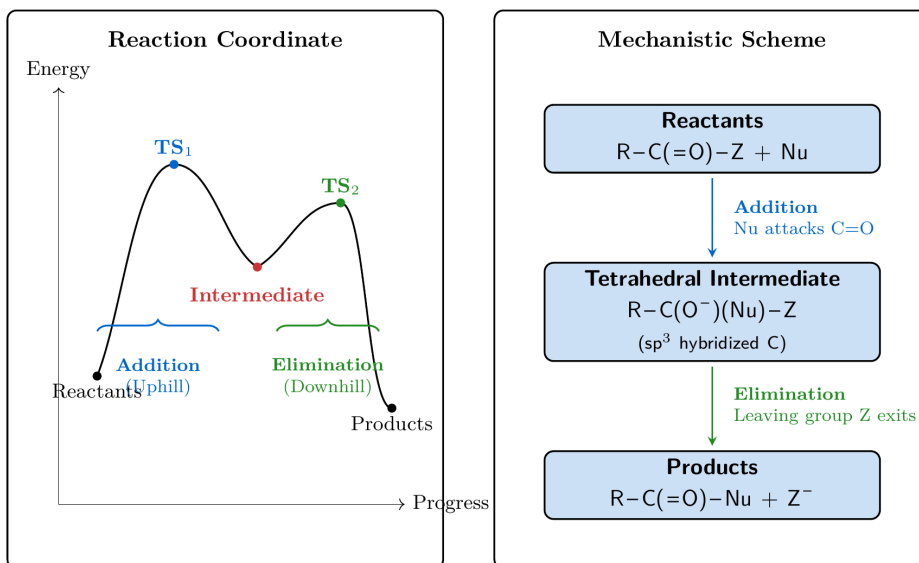
Thus, the nucleophile replaces Z at the acyl carbon.

Why substitution (not addition) is possible

Aldehydes and ketones ($\text{R}_2\text{C}=\text{O}$) lack a leaving group attached to the carbonyl carbon, so nucleophilic attack produces a tetrahedral alkoxide that cannot eliminate a substituent to re-form the carbonyl without breaking a strong C–C or C–H bond. Therefore they typically stop at **addition** products.

By contrast, acyl derivatives $\text{R}-\text{C}(=\text{O})-\text{Z}$ **do** contain a potential leaving group Z. After nucleophilic attack, the tetrahedral intermediate can collapse, expelling Z and restoring the carbonyl. This re-formation of the strong C=O π bond provides a powerful thermodynamic driving force.

12.2.2 Core Mechanism: Addition to Form a Tetrahedral Intermediate, Then Elimination



Step 1: Nucleophilic addition to the carbonyl (formation of the tetrahedral intermediate)

The acyl carbon is electrophilic because the C=O bond is polarized (δ^+ at carbon, δ^- at oxygen). A nucleophile donates electron density into the carbonyl carbon, and the carbonyl π bond shifts onto oxygen to give an anionic oxygen (or, under acidic conditions, a neutral oxygen after proton transfers). The key structural outcome is:

- carbon changes from **trigonal planar** (sp²) to **tetrahedral** (sp³-like),
- oxygen bears increased electron density (often formal negative charge under basic conditions),
- both Nu and Z are now attached to the same carbon, making the intermediate **poised** for elimination.

This tetrahedral intermediate is the mechanistic “pivot point” of acyl chemistry.

Step 2: Collapse of the tetrahedral intermediate (elimination of the leaving group)

The tetrahedral intermediate can collapse when the oxygen lone pair re-forms the carbonyl π bond. Because carbon cannot exceed an octet, one substituent must leave as the π bond forms. If Z is a sufficiently good leaving group, the dominant pathway is expulsion of Z^- (or HZ after proton transfer), producing the substituted acyl compound $R-C(=O)-Nu$.

Driving force: re-forming the carbonyl

Re-forming a strong $C=O$ bond is generally favorable. Thus, once the tetrahedral intermediate is formed, collapse is often fast **provided** the leaving group is not too basic.

12.2.3 Two Mechanistic Regimes: Acid Catalysis vs Base/Neutral Conditions

Nucleophilic acyl substitution is a **mechanistic family** rather than a single set of arrow-pushing steps. Proton transfers may occur before, during, or after addition and elimination. Two limiting regimes are particularly important.

Base-promoted or strongly nucleophilic conditions

Under basic conditions, nucleophiles are often anionic (Nu^-) and addition is fast. The tetrahedral intermediate is commonly an oxyanion. Elimination requires that Z^- be a plausible leaving group and that formation of Z^- is not prohibitively unfavorable.

A common feature is that **proton transfers occur as separate steps** (e.g., deprotonation of NuH to Nu^- , or acid workup after the substitution is complete).

Acid-catalyzed conditions

In acid, the carbonyl oxygen can be protonated, increasing electrophilicity of the acyl carbon and enabling addition by weaker neutral nucleophiles (e.g., H_2O , ROH). Acid also can convert poor leaving groups into better ones by protonation (e.g., turning $-OR$ into $-ROH$, which is a better leaving group than $-OR^-$).

Acid catalysis therefore often:

- accelerates **addition** (by activating the carbonyl), and

- facilitates **elimination** (by making Z less basic and more willing to leave).

12.2.4 The Central Selectivity Principle: Leaving-Group Basicity Controls Reactivity

Leaving group ability and derivative stability

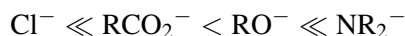
The outcome of the collapse step depends strongly on leaving-group ability. A simple and powerful rule is:

The better the leaving group Z, the more reactive the acyl derivative.
Leaving-group ability is inversely related to basicity.

Thus, Cl^- (very weak base) is an excellent leaving group, while NR_2^- (very strong base) is a very poor leaving group. This leads directly to the standard reactivity order of carboxylic acid derivatives toward nucleophilic acyl substitution:



The order can be rationalized by comparing the basicity of the leaving group:



As leaving-group basicity increases, elimination from the tetrahedral intermediate becomes less favorable, and the derivative is correspondingly less reactive.

Addition–elimination versus addition-only: the conceptual boundary

A useful way to distinguish aldehyde/ketone chemistry from acyl-derivative chemistry is:

- **Aldehydes/ketones:** nucleophilic **addition** dominates because there is no leaving group on the carbonyl carbon.
- **Acyl derivatives:** nucleophilic **acyl substitution** dominates because tetrahedral intermediates can collapse by expelling Z.

The presence of Z does not guarantee substitution (because Z may be too poor a leaving group), but it creates a mechanistic possibility that fundamentally reshapes reactivity patterns.

12.2.5 Energy Profile Interpretation: What the Diagram Predicts

The reaction coordinate diagram in the figure provides three predictive insights:

Two transition states are typical

Because the mechanism proceeds through a discrete tetrahedral intermediate, two barriers are expected:

- **TS₁ (addition):** nucleophile approaches and the C=O π bond is disrupted.
- **TS₂ (elimination):** the carbonyl is re-formed and the leaving group departs.

The rate-determining step depends on Z and Nu

For reactive derivatives (good leaving groups such as Cl), elimination is usually easy once the intermediate forms; TS₁ (addition) often controls the rate. For less reactive derivatives (poor leaving groups such as OR or especially NR₂), TS₂ (elimination) can become high, making collapse difficult. In such cases, conditions that improve leaving-group ability (often acid catalysis) become essential.

The tetrahedral intermediate is a “decision point”

The intermediate can sometimes revert to reactants (loss of nucleophile) rather than proceed to products (loss of leaving group). Which path dominates depends on:

- relative nucleophile versus leaving-group ability,
- relative stabilization of the intermediate (solvent, substituents),
- protonation state (acid/base conditions).

12.2.6 Summary: The Mechanistic Template for All Acid Derivative Chemistry

Nucleophilic acyl substitution can be reduced to a small number of mechanistic commitments:

- **Addition:** nucleophile attacks an electrophilic acyl carbon, converting trigonal planar carbonyl carbon into a tetrahedral intermediate.

- **Elimination:** the intermediate collapses to re-form the carbonyl, expelling a leaving group.
- **Reactivity is governed by leaving-group basicity:** weaker bases leave more readily, making the derivative more reactive.

This template will be applied repeatedly in the following sections to specific derivatives (acyl chlorides, anhydrides, esters, and amides), where the key differences are not the overall mechanism but the conditions required to make addition and elimination feasible and selective.

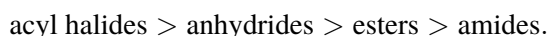
12.3 Chemistry of Acyl Chlorides and Anhydrides

The previous section established nucleophilic acyl substitution as a two-step addition–elimination process controlled largely by leaving-group ability. Acyl chlorides and anhydrides sit at the **most reactive** end of the acid-derivative series because their leaving groups (Cl^- and RCO_2^-) are weak bases. As a result, these derivatives are best viewed as **activated acyl donors**: they are rarely chosen for long-term stability, but they are exceptionally useful intermediates for rapidly converting a carboxylic acid into esters, amides, and other derivatives under mild conditions.

12.3.1 Reactivity Overview and the “Downhill” Logic of Acyl Substitution

Reactivity order revisited

The standard reactivity trend toward nucleophilic acyl substitution is



A practical interpretation is that converting *from left to right* is typically straightforward (“downhill” in reactivity), while converting *from right to left* often requires activation.

Activated intermediates for synthesis

Carboxylic acids themselves are relatively unreactive toward many neutral nucleophiles (e.g., alcohols, amines) because:

- the carbonyl is less electrophilic than in acyl chlorides (due to resonance and inductive differences), and
- nucleophiles are frequently *protonated* by the acid (especially amines), reducing nucleophilicity.

Transforming RCO_2H into RCOCl or $(\text{RCO})_2\text{O}$ circumvents both limitations by increasing electrophilicity and providing a better leaving group.

12.3.2 Acyl Chlorides: Structure, Preparation, and General Properties

Structure and electrophilicity

An acyl chloride has the functional group $\text{R}-\text{C}(=\text{O})-\text{Cl}$. Two features make it highly reactive:

- **Strong induction:** chlorine withdraws electron density inductively ($-I$), increasing the partial positive charge at the acyl carbon.
- **Excellent leaving group:** Cl^- is a weak base and leaves readily during collapse of the tetrahedral intermediate.

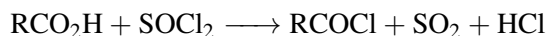
Therefore, the addition step is facilitated (more electrophilic carbonyl), and the elimination step is strongly favored (good leaving group).

Synthesis of acyl chlorides from carboxylic acids

Direct conversion $\text{RCO}_2\text{H} \longrightarrow \text{RCOCl}$ is an *activation* step. The most common reagents are thionyl chloride (SOCl_2), phosphorus trichloride (PCl_3), and oxalyl chloride ($(\text{COCl})_2$). The reactions are typically performed under anhydrous conditions.

Using thionyl chloride (SOCl_2)

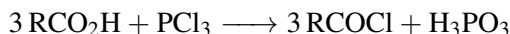
A commonly summarized transformation is:



The formation of gaseous byproducts (SO_2 and HCl) is synthetically convenient because their removal helps drive the reaction forward.

Using PCl₃ (or related phosphorus chlorides)

A representative overall stoichiometry is:



In practice, details depend on the exact phosphorus reagent and conditions, but the key outcome is replacement of –OH by –Cl at the acyl carbon.

Using oxalyl chloride ((COCl)₂)

Oxalyl chloride is another widely used chlorinating agent:



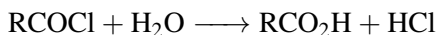
As with SOCl₂, gaseous byproducts help pull the equilibrium toward product. (Catalytic additives are often used to accelerate the reaction, but the essential synthetic idea is the same: activate –OH so it can be replaced by –Cl.)

Why direct substitution at RCO₂H is not feasible

A carboxylic acid does not simply undergo –OH substitution by Cl[–] because –OH is a very poor leaving group in acyl substitution unless it is first activated (e.g., converted into a better leaving group via formation of an intermediate chlorosulfite, phosphoryl intermediate, etc.). Chlorinating agents succeed by temporarily converting the hydroxyl group into a leaving group that *can* depart during collapse of a tetrahedral intermediate.

Practical handling: moisture sensitivity

Acyl chlorides react rapidly with water to regenerate the carboxylic acid:



Thus, they are typically prepared and used without prolonged exposure to moisture. In multistep synthesis, acyl chlorides are frequently generated *in situ* and immediately consumed by the intended nucleophile.

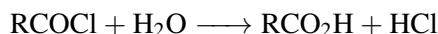
12.3.3 Nucleophilic Acyl Substitution Reactions of Acyl Chlorides

Because acyl chlorides are highly electrophilic and contain an excellent leaving group, they react with a wide range of nucleophiles. The mechanistic pattern is consistent:

- nucleophilic addition to form a tetrahedral intermediate,
- elimination of Cl^- to re-form $\text{C}=\text{O}$,
- acid–base steps to manage HCl (when NuH is used).

A recurring practical issue is that HCl is formed and must be neutralized or otherwise controlled to prevent protonation of the nucleophile or side reactions.

Hydrolysis: formation of carboxylic acids



Alcoholysis: formation of esters

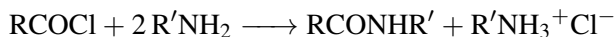


In practice, a base (often a tertiary amine such as pyridine or an equivalent acid scavenger) is commonly used to remove HCl . This maintains nucleophile strength and prevents acid-catalyzed side processes.

Key synthetic advantage

Compared to Fischer esterification ($\text{RCO}_2\text{H} + \text{R}'\text{OH} \rightleftharpoons \text{RCO}_2\text{R}' + \text{H}_2\text{O}$), acyl chloride esterification is generally:

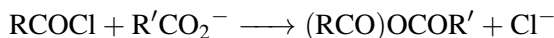
- faster,
- less equilibrium-limited (no water is produced as the leaving group),
- effective with sterically hindered alcohols in many cases.

Aminolysis: formation of amides

Two equivalents of amine are often used: one acts as the nucleophile, and the second neutralizes the HCl formed. Alternatively, an external base can be used.

Why acyl chlorides are excellent for amide synthesis

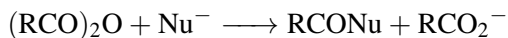
Direct conversion $\text{RCO}_2\text{H} \longrightarrow \text{RCONHR}'$ is difficult because the amine is protonated by the carboxylic acid to form an ammonium carboxylate salt, which is much less nucleophilic and typically requires harsh dehydration conditions to form an amide. Activation to an acyl chloride bypasses this acid–base “dead end” and enables mild amide formation.

Formation of anhydrides from acyl chlorides

This is a straightforward nucleophilic acyl substitution where $\text{R}'\text{CO}_2^-$ is the nucleophile and Cl^- is the leaving group.

12.3.4 Carboxylic Anhydrides: Structure, Preparation, and Reactivity**Structure and leaving group**

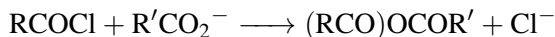
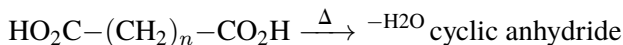
An anhydride contains the functional group $\text{R}-\text{C}(=\text{O})-\text{O}-\text{C}(=\text{O})-\text{R}'$. Its key reactivity feature is that the leaving group upon substitution is a *carboxylate*:



Because RCO_2^- is resonance-stabilized (weakly basic relative to alkoxides and amide anions), it is a decent leaving group, making anhydrides reactive but typically less reactive than acyl chlorides.

Synthesis of anhydrides

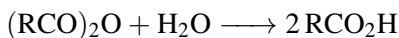
Two common synthetic entries are:

(1) From acyl chlorides and carboxylates**(2) Dehydration of carboxylic acids (when feasible)**

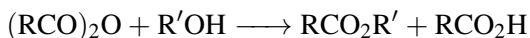
Intramolecular cyclization is favored when it forms 5- or 6-membered rings (low entropic penalty relative to larger rings, and favorable geometry).

General reactivity patterns

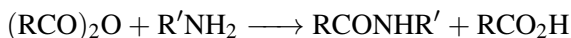
Anhydrides react with the same nucleophile classes as acyl chlorides, but typically require somewhat more forcing conditions (or stronger nucleophiles) because the electrophilicity is lower and the leaving group is less ideal than Cl^- .

12.3.5 Nucleophilic Acyl Substitution Reactions of Anhydrides**Hydrolysis: formation of carboxylic acids**

Mechanistically, water attacks one carbonyl, the tetrahedral intermediate collapses, and a carboxylate is expelled. Proton transfer then yields two acids (or an acid plus carboxylate depending on pH).

Alcoholysis: formation of esters

One acyl group is transferred to the alcohol, and the other becomes a carboxylic acid. Because a molecule of acid is produced, conditions may become acidic over time; bases or catalysts may be used to maintain nucleophile strength when needed.

Aminolysis: formation of amides

As with acyl chlorides, the mechanistic sequence is addition–elimination, followed by proton transfer. The byproduct is a carboxylic acid (not HCl), so anhydrides are often easier to handle than acyl chlorides in contexts where chloride salts or strong acid generation is undesirable.

12.3.6 Chemoselectivity and Practical Synthesis Design

Converting a less reactive derivative into a more reactive one is difficult

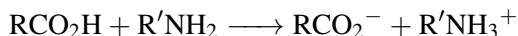
Because acyl substitution is governed by leaving-group ability, reactions tend to proceed “downhill” from reactive to less reactive derivatives. For example:



is typically feasible (with appropriate nucleophiles), but the reverse direction generally requires activation (e.g., converting an acid or ester into an acyl chloride before forming an amide).

Acylation versus acid–base neutralization

Amines pose a special issue: they are both nucleophiles and bases. With carboxylic acids, the dominant process is often salt formation:



which suppresses nucleophilic acyl substitution. Acyl chlorides and anhydrides avoid this trap by providing an electrophile that reacts rapidly at carbonyl carbon; although proton transfer still occurs, the substitution is fast enough to compete effectively.

Which reagent should you choose?

A useful strategic summary is:

- **Choose an acyl chloride** when you need maximum reactivity (hindered nucleophiles, low temperature, short reaction times) and can control moisture and HCl generation.
- **Choose an anhydride** when you want high reactivity but with easier handling (no HCl), or when the byproduct acid is acceptable or even useful (e.g., as an internal acid catalyst).

12.3.7 Summary: Why Acyl Chlorides and Anhydrides Matter

Acyl chlorides and anhydrides are best understood as **synthetic “activation” forms** of carboxylic acids. Their high reactivity follows directly from the nucleophilic acyl substitution mechanism:

- rapid nucleophilic addition to the electrophilic acyl carbon,
- facile collapse of the tetrahedral intermediate because Cl^- or RCO_2^- is a weak base and a good leaving group.

Because they enable reliable conversion to esters and amides under mild conditions, these derivatives serve as primary workhorses for constructing the acyl-containing functional groups that dominate biological molecules, polymers, pharmaceuticals, and materials.

12.4 Esters, Amides, and Nitriles: Synthesis and Hydrolysis

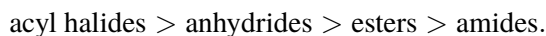
Acyl chlorides and anhydrides are highly reactive because they possess excellent leaving groups. In contrast, **esters** and especially **amides** are *more stable* derivatives: they react more slowly and typically require catalysis (acid or base), higher temperatures, or activation to undergo nucleophilic acyl substitution. **Nitriles** are often grouped with carboxylic acid derivatives because they can be transformed into carboxylic acids (and related derivatives) by hydrolysis, though their mechanistic pathway differs from the classic addition–elimination sequence at a carbonyl.

This section focuses on (i) how esters and amides are made, (ii) how and why ester hydrolysis differs under acidic versus basic conditions, and (iii) why amide hydrolysis is comparatively difficult. We conclude with nitriles as “masked” carboxylic acids.

12.4.1 Stability and Reactivity: Why Esters and Amides Are Less Reactive

Leaving-group basicity and the reactivity order

From nucleophilic acyl substitution principles, leaving-group basicity is central:



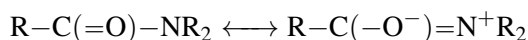
The leaving groups in ester and amide substitution are:



both of which are strong bases (poor leaving groups). As a result, the collapse of the tetrahedral intermediate to expel RO^- or NR_2^- is intrinsically disfavored unless proton transfers convert these into better leaving groups (ROH or HNR_2) or reaction conditions irreversibly remove products.

Resonance donation reduces electrophilicity

Amides are especially stable because the nitrogen lone pair donates strongly into the carbonyl:

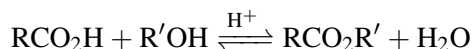


This resonance decreases the partial positive charge at the carbonyl carbon, reducing its electrophilicity and slowing nucleophilic attack. Esters exhibit analogous donation from oxygen, but it is weaker than donation from nitrogen; hence esters are more reactive than amides.

12.4.2 Esters: Synthesis

Fischer esterification (acid-catalyzed, reversible)

The most fundamental ester synthesis is the **Fischer esterification**:



This reaction is an equilibrium process. The mechanistic and strategic implications are inseparable:

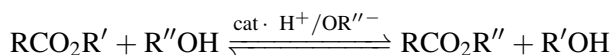
- Mechanistically, acid activates the carbonyl and enables ROH (a weak neutral nucleophile) to add.
- Thermodynamically, the reaction is reversible; yield depends on shifting equilibrium.

How to drive Fischer esterification to higher yield Le Châtelier's principle provides practical control:

- Use an **excess of the alcohol** (if inexpensive and easy to remove).
- **Remove water** as it forms (Dean–Stark apparatus with a water-immiscible solvent, molecular sieves, or azeotropic distillation where appropriate).
- In some cases, convert the acid into a more reactive derivative (acyl chloride/anhydride) when equilibrium limitations are unacceptable or the substrate is acid-sensitive.

Transesterification (acid- or base-catalyzed, equilibrium)

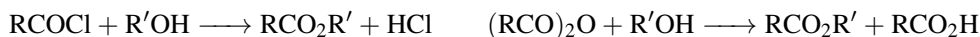
Esters can exchange their alkoxy group with another alcohol:



This is also typically an equilibrium process; driving force is obtained by using excess incoming alcohol or removing one product alcohol.

Ester formation from activated derivatives (practical alternative)

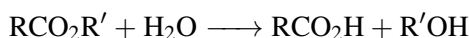
When mild conditions or high yields are essential, esters are commonly prepared from acyl chlorides or anhydrides:



These routes are usually faster and less equilibrium-limited than Fischer esterification.

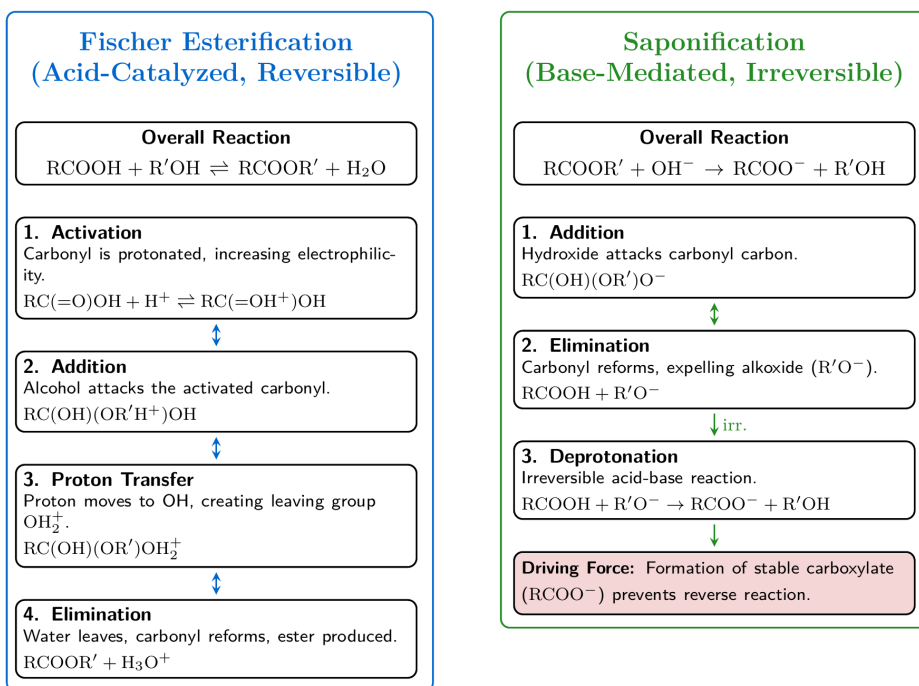
12.4.3 Ester Hydrolysis: Acidic vs Basic Conditions

Ester hydrolysis converts an ester back into a carboxylic acid (or its carboxylate salt) and an alcohol:



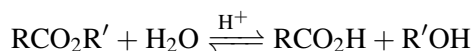
Despite the same net stoichiometry, acid-catalyzed and base-promoted hydrolysis differ profoundly in *mechanism, reversibility, and driving force*.

12.4.4 Mechanistic Comparison: Fischer Esterification vs Saponification



Acid-catalyzed ester hydrolysis (reverse of Fischer)

Under acidic conditions, ester hydrolysis is simply the reverse of Fischer esterification:

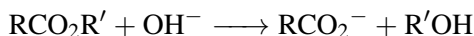


Key implications:

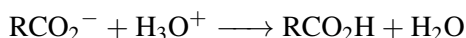
- The reaction is **reversible** and therefore equilibrium-limited.
- Acid catalysis improves leaving-group ability by protonating $-\text{OR}'$ to $-\text{OR}'\text{H}^+$, so $\text{R}'\text{OH}$ can depart.
- Water is the nucleophile; because it is a weak neutral nucleophile, heating is often required for less reactive esters.

Base-promoted ester hydrolysis (saponification)

Base-promoted hydrolysis is:



and after aqueous acid workup:



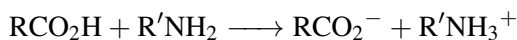
The crucial feature is the **irreversible acid–base step** that forms a resonance-stabilized carboxylate. Once RCO_2^- forms, it is much less electrophilic than the original ester and does not readily re-form the ester under basic conditions. This “product trapping” is why saponification is generally driven to completion.

A practical comparison (conditions and outcomes)

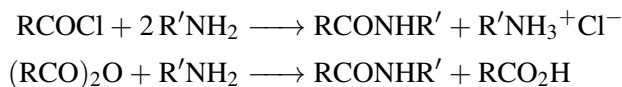
Feature	Acid-catalyzed hydrolysis	Base-promoted hydrolysis (saponification)
Nucleophile	H_2O (weak)	OH^- (strong)
Reversibility	Reversible (equilibrium)	Effectively irreversible (product trapping as RCO_2^-)
Leaving group	$\text{R}'\text{OH}$ after protonation	$\text{R}'\text{O}^-$ leaves, then proton transfer occurs
Typical conditions	H_3O^+ , heat	OH^- , heat (often milder than acid for many substrates)
Immediate product	RCO_2H	RCO_2^- (acid workup gives RCO_2H)

12.4.5 Amides: Synthesis and Hydrolysis**Amide synthesis: why activation is usually needed**

A naïve “direct” reaction between a carboxylic acid and an amine typically gives an ammonium carboxylate salt:



Because the amine is protonated, nucleophilic attack at the carbonyl is strongly suppressed. Therefore, reliable amide synthesis usually proceeds by **activating the acid** (commonly as an acyl chloride or anhydride, as discussed in the previous section), followed by aminolysis:



These are practical examples of “downhill” acyl substitution: a more reactive derivative is converted into a less reactive (more stable) amide.

Why amides are unusually stable

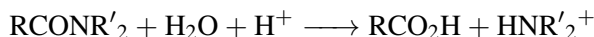
Amide stability has two complementary origins:

- **Resonance donation from nitrogen** decreases carbonyl electrophilicity.
- **A very poor leaving group** would be required in the reverse direction (NR_2^-).

As a result, amides require stronger conditions to hydrolyze than esters.

Acid-catalyzed amide hydrolysis (to carboxylic acids)

A representative net reaction is:



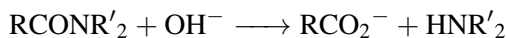
Conceptually, acid catalysis helps in two ways:

- protonation increases electrophilicity of the carbonyl, enabling water addition;
- protonation of nitrogen-containing groups converts them into better leaving groups (departure as $\text{R}'_2\text{NH}$ or, more realistically under strongly acidic conditions, as $\text{R}'_2\text{NH}_2^+$ after proton transfer steps).

Even so, the reaction is typically slow and often requires heating.

Base-promoted amide hydrolysis (to carboxylate salts)

Under strongly basic conditions:



Like saponification of esters, formation of the carboxylate product helps drive the process. However, because amide carbonyls are less electrophilic and because the leaving group is intrinsically poor, base-promoted amide hydrolysis generally requires harsher conditions than ester saponification (higher temperature, longer times).

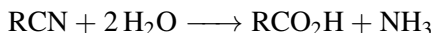
Take-home comparison: ester vs amide hydrolysis

- Esters hydrolyze under mild acid or base.
- Amides typically require strong acid or strong base and heat.

12.4.6 Nitriles: “Masked” Carboxylic Acids

Functional group relationship

A nitrile (RCN) is not an acyl derivative in the strict $R-C(=O)-Z$ sense, but it occupies a closely connected oxidation level and can be transformed into carboxylic acids by hydrolysis:



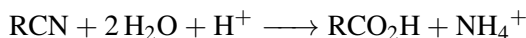
In practice, this occurs under acidic or basic conditions and often proceeds through an **amide intermediate**:



Thus, nitriles function as synthetically convenient precursors to acids, especially because $C\equiv N$ can be installed by CN^- substitution chemistry and then “unmasked” as $-CO_2H$ later.

Acidic hydrolysis of nitriles

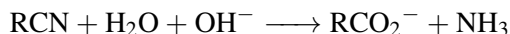
A simplified net transformation is:



Acidic conditions activate the nitrile toward addition by protonation, followed by water addition and subsequent steps leading to the amide and then the acid. Heating is frequently required.

Basic hydrolysis of nitriles

Under basic conditions, a common net outcome is:



followed by acid workup to yield RCO_2H . As with ester saponification, carboxylate formation helps “lock in” the product, but nitrile hydrolysis still often requires elevated temperatures due to the stability of the $\text{C}\equiv\text{N}$ bond and the multistep pathway.

12.4.7 Summary: How Stability Controls Conditions and Outcomes

- **Esters** are moderately stable: they undergo nucleophilic acyl substitution under acid or base catalysis. Fischer esterification and acid hydrolysis are **reversible**; saponification is **driven to completion** by irreversible carboxylate formation.
- **Amides** are highly stable: resonance donation from nitrogen strongly reduces electrophilicity, and NR_2^- is an extremely poor leaving group. Hydrolysis therefore requires **strong** conditions (acid or base, typically with heat).
- **Nitriles** are valuable synthetic surrogates for carboxylic acids: hydrolysis (often via an amide intermediate) converts RCN into RCO_2H under acidic or basic conditions, usually with heating.

Together, these trends extend the central theme of the chapter: acyl chemistry is governed by the addition–elimination framework, tuned by leaving-group basicity and resonance effects, and made synthetically powerful through strategic use of activation and equilibrium control.

12.5 Problems

12.5.1 Problem 1: Acidity and inductive effects (ranking and justification)

Rank the following carboxylic acids in order of **increasing** acidity (lowest pK_a last). Provide a brief justification using inductive effects and distance dependence (no numerical pK_a values needed).

- $\text{CH}_3\text{CO}_2\text{H}$ (acetic acid)

- $\text{ClCH}_2\text{CO}_2\text{H}$ (chloroacetic acid)
- $\text{ClCH}_2\text{CH}_2\text{CO}_2\text{H}$ (3-chloropropanoic acid)
- $\text{FCH}_2\text{CO}_2\text{H}$ (fluoroacetic acid)
- $\text{CF}_3\text{CO}_2\text{H}$ (trifluoroacetic acid)

In your answer, explicitly address (i) electronegativity versus number of halogens and (ii) the effect of moving the halogen from the α - to the β -carbon.

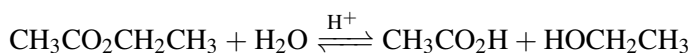
12.5.2 Problem 2: Substituent effects on benzoic acid acidity

Consider the following substituted benzoic acids: *p*-methoxybenzoic acid, *p*-nitrobenzoic acid, *m*-nitrobenzoic acid, and benzoic acid.

- Rank them in order of increasing acidity.
- For each substituent (OMe and NO_2), indicate whether inductive effects, resonance effects, or both are responsible for the trend.
- Explain why the *meta* and *para* nitro substituents do not influence acidity to the same extent.

12.5.3 Problem 3: Detailed mechanism—acid-catalyzed ester hydrolysis

Write a complete curved-arrow mechanism (all key proton transfers included) for the acid-catalyzed hydrolysis of ethyl acetate to acetic acid and ethanol:

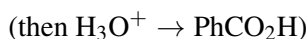
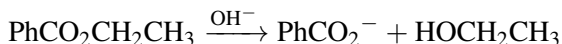


Your mechanism must:

- show formation and collapse of the tetrahedral intermediate,
- explicitly show how $-\text{OCH}_2\text{CH}_3$ is converted into a good leaving group,
- end with regeneration of the acid catalyst (H^+).

12.5.4 Problem 4: Detailed mechanism—base-promoted ester hydrolysis (saponification)

Write a complete curved-arrow mechanism for base-promoted hydrolysis of ethyl benzoate under aqueous NaOH, followed by acid workup:



Your mechanism must:

- show nucleophilic attack by OH^- and the tetrahedral intermediate,
- show elimination of EtO^- ,
- include the key *irreversible* acid–base step that drives the reaction to completion,
- indicate the products present *before* and *after* acidic workup.

12.5.5 Problem 5: Predicting products of acyl chloride reactions (chemoselectivity)

For each reaction below, predict the major organic product(s). If an acid scavenger/base is required for a clean reaction, specify one appropriate choice. Assume typical laboratory conditions and that reactions are run to completion.

- $\text{CH}_3\text{CH}_2\text{COCl} + \text{H}_2\text{O}$
- $\text{CH}_3\text{CH}_2\text{COCl} + \text{CH}_3\text{OH}$
- $\text{CH}_3\text{CH}_2\text{COCl} + (\text{CH}_3)_2\text{NH}$
- $\text{PhCOCl} + \text{HOCH}_2\text{CH}_2\text{NH}_2$ (2-aminoethanol), one equivalent of nucleophile

For part (d), address whether acylation occurs preferentially at oxygen or nitrogen under basic conditions, and explain your reasoning.

12.5.6 Problem 6: Mixed anhydride formation and selective acyl transfer

You wish to prepare a mixed anhydride $\text{RCO}-\text{O}-\text{COR}'$ from an acyl chloride and a carboxylate, then use it to acylate an amine.

- Propose reagents and conditions to form $\text{RCO}-\text{O}-\text{COR}'$ from RCOCl and $\text{R}'\text{CO}_2\text{H}$.
- Then propose conditions to convert $\text{RCO}-\text{O}-\text{COR}'$ into an amide using $\text{R}''\text{NH}_2$.
- In a mixed anhydride, acyl transfer can occur at either carbonyl. Provide two structural or electronic factors that would bias acylation to occur at one acyl group over the other.

12.5.7 Problem 7: Designing a Fischer esterification to maximize yield

You are tasked with preparing isopropyl cyclohexanecarboxylate from cyclohexanecarboxylic acid and isopropanol using Fischer esterification.

- Write the balanced equilibrium reaction.
- Propose a concrete strategy (apparatus or procedural choices) to maximize ester yield. Choose *two* distinct methods to shift equilibrium and justify each.
- Explain why using catalytic acid is necessary and why strong base would be counterproductive under Fischer conditions.

12.5.8 Problem 8: Multi-step synthesis—polyamide formation from simple precursors

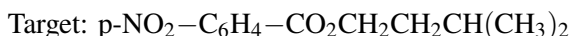
Design a plausible synthetic sequence to prepare a linear polyamide (nylon-like) from *two* bifunctional monomers: one diamine and one diacid (or a derivative of a diacid).

- Choose specific monomers (e.g., $\text{H}_2\text{N}-(\text{CH}_2)_n-\text{NH}_2$ and $\text{HO}_2\text{C}-(\text{CH}_2)_m-\text{CO}_2\text{H}$, with specified n and m).
- Explain why direct heating of the diamine with the diacid gives an ammonium carboxylate salt and why activation is usually required for efficient amide bond formation.

- Propose an activation method (e.g., conversion to a diacyl chloride or use of an anhydride) and write the repeating-unit formation step as a reaction.
- Identify the byproduct(s) formed during polymerization and describe how their removal (or neutralization) affects the extent of polymerization.

12.5.9 Problem 9: Retrosynthetic analysis of a complex ester

Provide a retrosynthetic plan (key disconnections and forward reagents) for the following target:



(*2-methylpropyl* group attached via a CH_2CH_2 spacer; interpret as an ester of *p*-nitrobenzoic acid with 3-methyl-1-butanol, i.e., isoamyl alcohol.)

- Give at least *two* distinct forward syntheses: one using Fischer esterification and one using an activated acid derivative (acyl chloride or anhydride).
- For each route, state the key conditions needed to obtain good yield and minimize side reactions.
- Explain which route you would choose if the alcohol were acid-sensitive and why.

12.5.10 Problem 10: Competing carbonyl reactivity—ketone vs ester in one molecule

Consider the bifunctional compound $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ (a molecule containing both a ketone and a methyl ester).

- Predict which carbonyl (ketone or ester) is more reactive toward nucleophilic *addition* by NaBH_4 and justify mechanistically.
- Predict which carbonyl is more reactive toward nucleophilic *acyl substitution* by MeO^- in methanol, and justify using leaving-group logic and the tetrahedral intermediate concept.
- Propose a reagent/condition set that would selectively hydrolyze the ester to a carboxylic acid *without* reducing the ketone, and explain why this selectivity is reasonable.

- Propose a reagent/condition set that would selectively reduce the ketone *without* hydrolyzing the ester, and explain why this selectivity is reasonable.

Chapter 13

Enolates and C-C Bond Formation

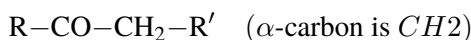
Up to this point, our study of carbonyls has focused largely on attack at the electrophilic carbonyl carbon. In this chapter, we shift our gaze to the neighboring position—the alpha-carbon—unlocking one of the most powerful toolsets in organic synthesis: the ability to form carbon-carbon bonds. By exploiting the acidity of alpha-protons, we transform carbonyl compounds into nucleophilic enolates, capable of attacking other electrophiles to build complex carbon skeletons from simple precursors. Mastery of these principles allows chemists to construct the cyclic frameworks and polyfunctional chains found in nature’s most intricate molecules.

13.1 Alpha-Acidity and Enolization

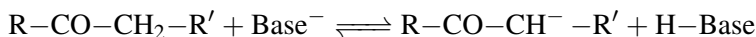
13.1.1 Why “alpha” matters: carbonyls as acidity amplifiers

In earlier chapters, we treated acidity largely as a property of heteroatom–hydrogen bonds (e.g., RO–H, RCO₂–H) and learned that resonance stabilization of a conjugate base is a dominant factor in lowering a compound’s pK_a . Carbonyl compounds extend this logic into *carbon acids*: certain C–H bonds become acidic enough to be deprotonated by strong bases because the resulting carbanion is *not* a localized carbanion—it is an *enolate*, a resonance-stabilized anion delocalized between carbon and oxygen.

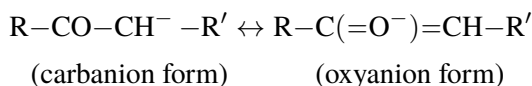
An α -hydrogen is a hydrogen on the carbon adjacent to a carbonyl group. For a generic carbonyl compound



removal of an α -proton generates an enolate:



but the anion is best represented as a *resonance hybrid* (Section on resonance):



The oxyanion resonance contributor is particularly stabilizing because it places negative charge on electronegative oxygen and preserves a strong C=C π -bond.

13.1.2 Resonance, inductive effects, and pK_a : a practical hierarchy

The acidity of α -hydrogens depends on how well the conjugate-base enolate is stabilized. Two ideas work together:

- **Resonance delocalization:** negative charge can be shared between α -carbon and oxygen.
- **Inductive withdrawal and additional carbonyls:** electron-withdrawing groups and additional carbonyls further stabilize the anion, often dramatically.

Table 1 summarizes commonly used approximate pK_a values in water (or values that closely track typical trends). These are *benchmarks* for reasoning about equilibrium direction in proton-transfer steps.

Compound type (typical example)	pK_a of α -H (approx.)	Key stabilization feature
Simple alkane $R-CH_3$	~ 50	No resonance stabilization
Terminal alkyne $RC\equiv CH$	~ 25	sp hybridization (greater s -character)
Aldehyde $R-CHO$	16–18	Enolate resonance; less alkyl donation
Ketone $R-CO-R'$	19–21	Enolate resonance; more alkyl donation than aldehydes
Ester $R-CO_2R'$	24–26	Enolate resonance reduced by π -donation from $-OR$
Nitrile $R-C\equiv N$	~ 25	Anion stabilized by $C\equiv N$ (less than carbonyl)
β -Dicarbonyl (1,3-dicarbonyl) $R-CO-CH_2-CO-R'$	9–13	Charge delocalized over two carbonyls; strong enol/enolate stabilization
Malonate diester $RO_2C-CH_2-CO_2R$	13	Two carbonyls; useful “activated methylene”
Acetoacetic ester $CH_3CO-CH_2-CO_2Et$	11	Two carbonyls; highly stabilized enolate

Table 13.1: Approximate α -proton acidities and the dominant stabilization rationale. Values vary with solvent and substitution; the *ordering* is the crucial tool for mechanism and synthesis.

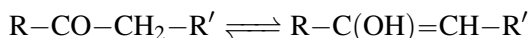
Interpretation.

- **Aldehydes are typically more α -acidic than ketones** because ketones possess two electron-donating alkyl groups that destabilize the anion relative to an aldehyde (one alkyl group and one hydrogen).
- **Esters are less α -acidic than ketones** because the $-OR$ substituent donates electron density by resonance into the carbonyl, diminishing the carbonyl's electron-withdrawing power and making the enolate less stabilized.
- **1,3-dicarbonyl compounds are dramatically more acidic** because the enolate can delocalize negative charge onto *two* carbonyl oxygens. This is why “active methylene” compounds are central to C–C bond-forming reactions later in the chapter.

13.1.3 Enols vs. enolates: two faces of the same α -carbon reactivity

Carbonyl compounds can appear in two interconvertible forms:

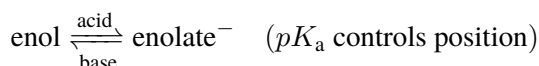
- **Keto form:** carbonyl $C=O$
- **Enol form:** alkene + alcohol $C=C-OH$



This is **keto-enol tautomerism**. The enol is usually a minor component for simple aldehydes/ketones, but it is mechanistically important because:

- under acidic conditions, *enols* are the nucleophilic species that react (e.g., α -halogenation under acid);
- under basic conditions, *enolates* are the nucleophilic species that react (e.g., aldol and alkylation).

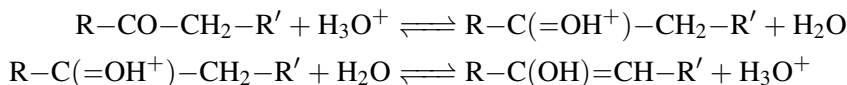
A common misconception is that “the enol” and “the enolate” are interchangeable. They are connected, but not identical:



Because typical α - pK_a values for ketones are near 20, only a tiny fraction of a ketone exists as enolate in the presence of moderate bases (e.g., RO^-). In contrast, strongly basic reagents (e.g., LDA) can produce enolates in high concentration.

13.1.4 Acid-catalyzed enol formation: mechanism and kinetic logic

In acidic media, the carbonyl oxygen is protonated first, which increases the acidity of the α -hydrogens and makes deprotonation feasible by a weak base (often solvent, such as water). A representative mechanism is:

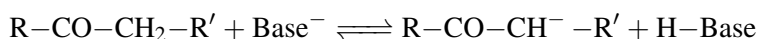


Key features.

- **The acid is a catalyst.** It is consumed in the first step and regenerated in the second.
- **The enol is formed by deprotonation at the α -carbon of a protonated carbonyl.** Protonation makes the α -C–H bond far more acidic by stabilizing the developing negative character through resonance.
- **Acidic conditions favor electrophilic reactions at the α -position that proceed via the enol.** The enol is neutral but nucleophilic at the α -carbon, and it reacts with electrophiles compatible with acid (e.g., Br₂ under acidic α -halogenation).

13.1.5 Base-mediated enolate formation: equilibria and the “conjugate-acid rule”

Under basic conditions, deprotonation at the α -carbon gives an enolate directly:



Whether this equilibrium lies to the right is governed primarily by relative pK_a values:

$$K \approx 10^{pK_a(\text{H-Base}) - pK_a(\alpha\text{-H})}$$

Conjugate-acid rule (practical form). To form an enolate in high yield, choose a base whose conjugate acid has a substantially *higher* pK_a than the carbonyl's α -hydrogens.

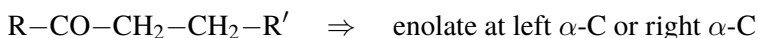
- **Alkoxide bases** (e.g., EtO[−]) have conjugate acids with $pK_a \sim 16$ (ethanol), so they do *not* fully deprotonate simple ketones ($pK_a \sim 20$). Instead, they establish an equilibrium containing mostly starting carbonyl with a small, reactive enolate fraction.
- **LDA (lithium diisopropylamide)** has a conjugate acid with $pK_a \sim 36$, so it can deprotonate ketones essentially irreversibly under typical conditions, generating a high concentration of enolate.

Why partial enolate formation can still be synthetically useful. Many C–C bond-forming reactions (aldol addition/condensation, Claisen condensation) are reversible at early steps. A small amount of enolate can be sufficient if it reacts quickly with an

electrophile and the downstream steps pull equilibrium forward. Thus, “not fully deprotonated” does *not* mean “unreactive”—it means the system is under **equilibrium control**, which is central to regioselectivity.

13.1.6 Regioselectivity: kinetic vs. thermodynamic enolates

Unsymmetrical ketones typically have two distinct α -positions, producing two possible regioisomeric enolates:



Controlling which enolate predominates is one of the most important practical skills in enolate chemistry.

Definitions

- **Kinetic enolate:** the enolate formed *faster* (lower activation barrier). It typically results from deprotonation at the α -position that is *less substituted* and/or *less sterically hindered*.
- **Thermodynamic enolate:** the enolate that is *more stable* (lower free energy). It typically corresponds to the *more substituted* double bond in the enolate (more substituted alkene-like component) and is favored when the system can equilibrate.

Kinetic control: strong, bulky base; low temperature; short time

Typical conditions: LDA, -78°C (dry THF), fast addition, short reaction time.

Mechanistic rationale. LDA is:

- **Strong** enough to deprotonate essentially irreversibly under these conditions.
- **Sterically hindered** and **poorly nucleophilic**, minimizing side reactions (e.g., nucleophilic addition to carbonyl).

At low temperature, proton transfer is fast and the reverse protonation (enolate $\rightarrow$ carbonyl) is disfavored kinetically. Deprotonation occurs at the α -site that can be reached with the least steric penalty, leading to the kinetic enolate.

Thermodynamic control: smaller base; higher temperature; reversible proton transfer

Typical conditions: an alkoxide base (NaOEt, KOtBu in some contexts), higher temperature, longer time, and a protic or equilibrating medium.

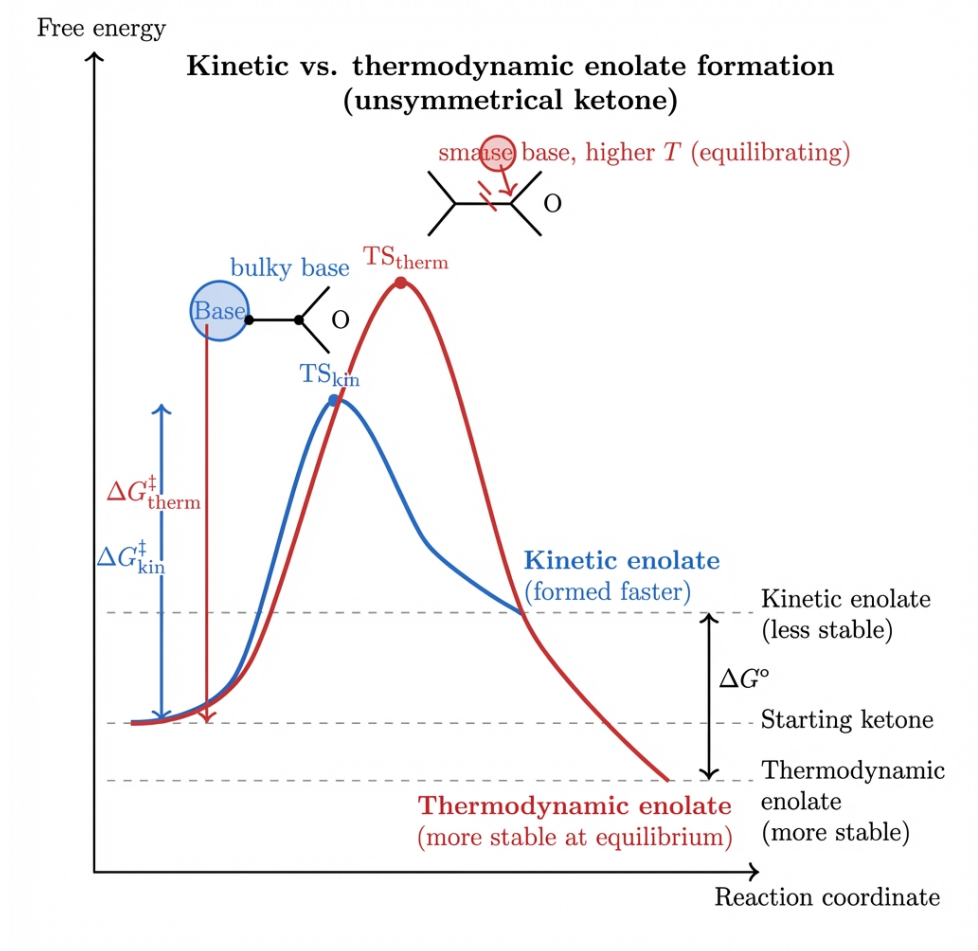
Mechanistic rationale. When deprotonation/reprotonation is reversible and sufficiently rapid, the enolate mixture equilibrates. The more stable enolate accumulates, even if it forms more slowly. Stability commonly correlates with greater substitution of the C=C component and better hyperconjugative stabilization (an alkene-like argument applied to the enolate resonance system).

Synthetic meaning: choose conditions to choose products

Because enolates are nucleophiles, the identity of the enolate often determines *where* a new C–C bond forms (alkylation, aldol, Michael). Therefore, controlling enolate regioselectivity is equivalent to controlling the regiochemistry of subsequent C–C bond formation.

Energy-coordinate picture of kinetic vs. thermodynamic control

The contrast between pathways is summarized by an energy coordinate diagram: the kinetic pathway has a lower transition state (forms faster) but leads to a higher-energy product; the thermodynamic pathway has a higher barrier but leads to a lower-energy (more stable) product under equilibrium conditions.



13.1.7 Operational control: what you actually change in the flask

Students often learn “LDA gives kinetic enolate” and stop there. In practice, regioselectivity is controlled by a *set* of coupled experimental variables:

Base identity and counterion

- **Bulky, strong bases** (LDA, LiHMDS) favor kinetic deprotonation and minimize nucleophilic addition to carbonyls.

- **Smaller bases** (alkoxides) allow equilibration and can favor the thermodynamic enolate.
- **Counterion effects** (Li^+ , Na^+ , K^+) influence aggregation and coordination to oxygen, changing both rate and selectivity. Lithium enolates are often more tightly coordinated (more “organized”), which can accentuate kinetic selectivity in aprotic solvents.

Temperature

- Lower temperature reduces reversibility and slows equilibration; the first-formed enolate can be trapped (kinetic control).
- Higher temperature accelerates proton exchange and allows the system to approach equilibrium (thermodynamic control).

Solvent and protic vs. aprotic media

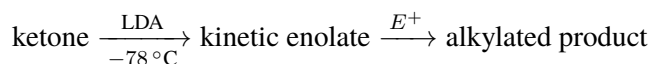
- **Aprotic solvents** (THF, ether) help maintain reactive, “naked” enolates and support strong bases like LDA.
- **Protic solvents** increase opportunities for proton exchange and can promote equilibration but also quench strong bases and enolates; they are generally incompatible with preformed lithium enolates.

Order of addition and trapping

A common kinetic strategy is:

- generate the enolate at low temperature with LDA;
- then add the electrophile so that the enolate is trapped faster than it can equilibrate.

Conceptually:



The essential idea is **separation of steps**: first *form* the enolate selectively, then *react* it.

13.1.8 A final conceptual anchor: enolization is reversible unless you make it not

Enolization (whether via enol or enolate) is typically a reversible process. Selectivity emerges from which pathway dominates under the chosen conditions:

- **Reversible, equilibrating conditions** $\Rightarrow$ thermodynamic control (*most stable* enolate dominates).
- **Irreversible or effectively irreversible formation + rapid trapping** $\Rightarrow$ kinetic control (*fastest formed* enolate dominates).

This framework will be used throughout the remainder of the chapter: *every* major C–C bond-forming reaction of carbonyl compounds (alkylation, aldol, Claisen, Michael) depends on generating an enol/enolate under conditions that control both **how much** nucleophile is present and **which** nucleophile (which regioisomer, and later, which geometry) is formed.

13.2 Alpha-Halogenation and Alkylation

13.2.1 From enolization to α -functionalization: the general strategy

Section 13.1 established two complementary ways to access nucleophilic α -carbon reactivity:

- **Acidic conditions** generate small amounts of **enol** (neutral nucleophile at the α -carbon).
- **Basic conditions** generate **enolate** (anionic nucleophile; generally much more reactive).

α -Functionalization reactions exploit these intermediates by reacting them with electrophiles. Two broad classes dominate synthetic practice:

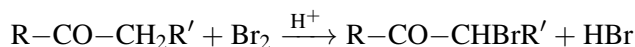
- **α -Halogenation:** installation of Cl, Br, or I at the α -position.
- **α -Alkylation:** C–C bond formation via S_N2 reaction between an enolate and an alkyl electrophile.

A unifying idea runs through both: **the α -carbon becomes nucleophilic only after enolization/enolate formation**. The choice of conditions determines **which nucleophile exists** (enol vs. enolate) and therefore controls selectivity, overreaction, and side pathways.

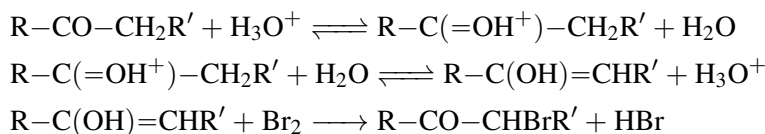
13.2.2 α -Halogenation of carbonyl compounds

Acid-catalyzed α -halogenation: enol as the nucleophile

Under acidic conditions, carbonyl compounds halogenate at the α -position through their enol tautomer. A typical transformation is:



Mechanistic outline. The mechanism consists of two coupled catalytic cycles: enol formation (acid-catalyzed) and electrophilic halogenation of the enol.

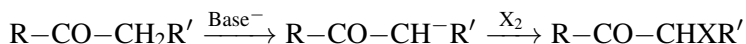


Why acid often gives monohalogenation. After one α -halogen is installed, the product $\text{R}-\text{CO}-\text{CHXR}'$ is typically **less able to enolize under acidic conditions** than the starting carbonyl (the enol content and rate of enol formation can decrease). Because the electrophile (Br_2) reacts with the **enol**, and enol formation is usually rate-limiting, further halogenation is not automatically fast. In practice, careful control of halogen equivalents favors monohalogenation.

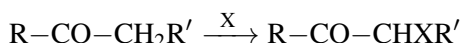
Selectivity note. Acidic halogenation proceeds through the enol, so regioselectivity mirrors the regioselectivity of enol formation under those conditions (thermodynamic tendencies are common because enolization is reversible). For unsymmetrical ketones, the more substituted (thermodynamic) enol is often favored.

Base-promoted α -halogenation: enolate as the nucleophile and the problem of polyhalogenation

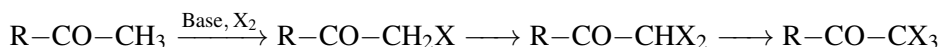
In basic media, enolate formation is straightforward, and enolates react rapidly with halogen electrophiles:



Why polyhalogenation is common under base. A crucial difference from the acid case is that α -halogenation **increases** the acidity of the remaining α -hydrogens:



The X substituent is inductively electron-withdrawing, stabilizing the enolate derived from the monohalogenated product. Therefore, after the first halogenation, the product is **more** easily deprotonated, making subsequent halogenations faster. The result is a typical sequence:

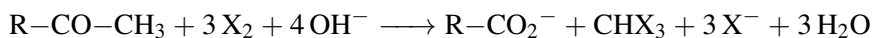


This behavior is not a curiosity; it is the foundation of the haloform reaction.

13.2.3 The haloform reaction: exhaustive halogenation and C-C bond cleavage

Overall transformation

Methyl ketones (and substrates that can be oxidized to methyl ketones under the reaction conditions) undergo the haloform reaction in base with X_2 (Cl_2 , Br_2 , or I_2):



where CHX_3 is the haloform (e.g., CHI_3 is iodoform, a yellow solid).

Mechanistic logic

The haloform reaction has two conceptual phases:

- **Exhaustive α -halogenation** to form a trihalomethyl ketone R-CO-CX_3 .

- **Nucleophilic acyl substitution (addition–elimination)** by OH^- , expelling CX_3^- , which is then protonated to CHX_3 .

Why CX_3^- can be a leaving group here. A typical alkyl carbanion is a terrible leaving group, but CX_3^- is unusually stabilized by the strong inductive effects of three halogens. This stabilization makes expulsion feasible in the tetrahedral intermediate collapse.

Synthetic takeaway. The haloform reaction is best viewed as a **diagnostic and cleavage reaction** for methyl ketones rather than a method for α -functionalization. If your goal is α -monohalogenation, strongly basic conditions are usually the wrong choice.

13.2.4 The Hell–Volhard–Zelinsky (HVZ) reaction: α -halogenation of carboxylic acids

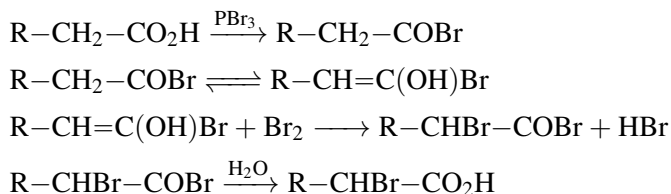
The challenge: carboxylic acids do not enolize efficiently

Carboxylic acids have α -hydrogens, but direct α -halogenation of $\text{R}-\text{CH}_2-\text{CO}_2\text{H}$ is not straightforward because:

- Under acidic conditions, enol formation from a carboxylic acid is much less favorable than from an aldehyde/ketone.
- Under basic conditions, the carboxylic acid is deprotonated first to $\text{R}-\text{CH}_2-\text{CO}_2^-$, and the resulting carboxylate is far less susceptible to the types of activation needed for electrophilic halogenation at α -carbon.

Solution: temporarily convert the acid into an acyl halide

The HVZ reaction accomplishes α -bromination or α -chlorination of carboxylic acids by using PBr_3 (or PCl_3) and Br_2 (or Cl_2), followed by hydrolysis:



Mechanistic logic (why it works). Acyl halides enolize much more readily than

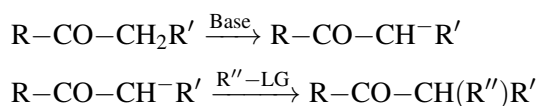
carboxylic acids, enabling electrophilic halogenation through the enol. Hydrolysis restores the carboxylic acid at the end.

Synthetic value. α -Halo carboxylic acids are versatile intermediates: the α -C–X bond can be substituted by nucleophiles (forming α -amino acids, α -hydroxy acids, etc.), and the α -halo group can participate in elimination or further transformations.

13.2.5 α -Alkylation of enolates: C–C bond formation by S_N2

The fundamental step

Direct alkylation is one of the most conceptually simple uses of enolates:



where R'' -LG is an alkyl electrophile (typically an alkyl halide or sulfonate ester), and the C–C bond forms via S_N2 .

Mechanistic requirement: S_N2 compatibility. Because enolates are strong nucleophiles and strong bases, the electrophile must be chosen to favor substitution over elimination:

- **Best:** methyl and primary halides/tosylates (MeI, EtBr, BnBr, allylic/benzylic halides).
- **Often problematic:** secondary halides (competition with E2).
- **Avoid:** tertiary halides (essentially E2 only; S_N2 is blocked).
- **Not appropriate:** aryl/vinyl halides (do not undergo S_N2).

Choice of base and conditions: preformed vs. equilibrium enolates

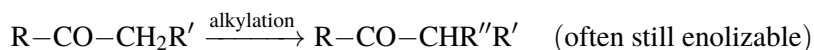
Two operational modes are common:

Mode A: preformed (directed) enolate alkylation. Generate the enolate with a strong, non-nucleophilic base (e.g., LDA) in an aprotic solvent at low temperature, then add the electrophile. This is the standard method for controlling enolate **regioselectivity** in unsymmetrical ketones (kinetic vs. thermodynamic control from Section 13.1).

Mode B: equilibrium enolate alkylation. Use an alkoxide base (or similar) that establishes an enolate equilibrium. This can be practical when the substrate is relatively acidic (e.g., 1,3-dicarbonyls) or when selectivity is not an issue. However, equilibration can allow undesired pathways such as overalkylation or condensation side reactions.

The problem of polyalkylation

Why it happens. After one alkylation, the product often still has at least one α -hydrogen and can form an enolate again:



Moreover, the first alkyl group can increase substitution at the α -carbon and sometimes stabilize the more substituted enolate, making subsequent alkylation feasible.

Strategies to minimize polyalkylation.

- Use **strong base to form a specific enolate** and then **add electrophile slowly** (or use controlled stoichiometry).
- Use **one equivalent** of base and electrophile when feasible, and quench promptly after consumption.
- Use substrates designed to be **alkylated once and then “turned off”** by a subsequent irreversible step (hydrolysis/decarboxylation in malonic ester and acetoacetic ester syntheses).

13.2.6 Regioselectivity in alkylation: which α -carbon reacts?

For unsymmetrical carbonyl compounds, alkylation regioselectivity is determined upstream: **which enolate is present**.

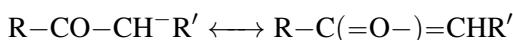
Guiding principle.

- If the enolate formation step is **selective and irreversible (kinetic control)**, alkylation reports that selectivity.
- If enolate formation is **reversible (thermodynamic control)**, the enolate mixture can equilibrate, and the alkylation outcome reflects the dominant enolate under those conditions.

Because alkylation is often faster than proton exchange once the electrophile is present, many procedures are designed to **separate** enolate formation (controlled) from electrophile trapping (fast).

13.2.7 C-alkylation vs. O-alkylation: an enolate is ambident

Enolates possess two nucleophilic sites in their resonance description:



Thus, alkylation can occur at:

- **Carbon (C-alkylation):** forms a new C–C bond at the α -carbon (usually desired in synthesis).
- **Oxygen (O-alkylation):** forms an enol ether $\text{R}-\text{C}(=\text{CHR}')-\text{ORR}'$ (often undesired unless specifically targeted).

What tends to favor C- vs. O-alkylation (qualitative).

- **Hard electrophiles** (e.g., Me_3SiCl) often react at oxygen (O-silylation), producing silyl enol ethers.
- Typical $\text{S}_{\text{N}}2$ alkyl halides often give predominantly **C-alkylation**, especially for lithium enolates in aprotic solvents, but mixtures can occur depending on substrate, counterion, solvent, and electrophile.

13.2.8 Activated methylene compounds as robust alkylation partners

Direct alkylation of simple ketones can be complicated by regioselectivity, self-condensation, and polyalkylation. In contrast, 1,3-dicarbonyl compounds (“activated methylenes”) are:

- **More acidic** ($pK_{\text{a}} \sim 9-13$), so mild bases generate substantial enolate.
- **Resonance-stabilized**, often giving cleaner $\text{S}_{\text{N}}2$ alkylation.

These properties underpin the malonic ester and acetoacetic ester syntheses (developed later in this chapter) as reliable methods for building carbon skeletons while avoiding uncontrolled multiple alkylations.

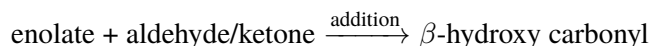
13.2.9 Summary: choosing conditions to choose outcomes

- **Acidic α -halogenation** proceeds via enols and often favors monohalogenation.
- **Basic α -halogenation** proceeds via enolates and often leads to polyhalogenation; methyl ketones can undergo the **haloform** cleavage reaction.
- The **HVZ reaction** enables α -halogenation of carboxylic acids by transient conversion to an acyl halide, halogenation via the enol, and hydrolysis.
- **Enolate alkylation** forms C–C bonds by S_N2 and works best with methyl/primary electrophiles; polyalkylation and competing E2 are central practical limitations.
- Regioselective alkylation is achieved by controlling enolate formation (kinetic vs. thermodynamic), then trapping with an electrophile.

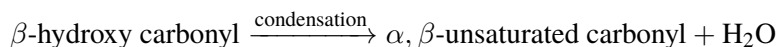
13.3 The Aldol Condensation

13.3.1 What the aldol reaction accomplishes

The aldol reaction is a cornerstone of carbonyl chemistry because it forms a new C–C bond *and* installs functional groups that can be exploited in subsequent steps. In its simplest form, an enolate (or enol equivalent) adds to another carbonyl compound to give a β -hydroxy carbonyl compound (an “aldol”):



Under conditions that promote dehydration, the β -hydroxy carbonyl compound loses water to yield an α, β -unsaturated carbonyl compound (a conjugated enone or enal):



It is essential to distinguish these two stages:

- **Aldol addition** refers specifically to C–C bond formation producing the β -hydroxy carbonyl.

- **Aldol condensation** refers to aldol addition *followed by* dehydration (net loss of H_2O).

The chemistry developed in Sections 13.1 and 13.2 now becomes operational: the reaction begins by generating an enolate (or enol), and the success of the overall process depends on controlling enolate formation and subsequent steps.

13.3.2 Carbonyl polarity revisited: why the aldol is an “addition” reaction

Carbonyl groups are polarized ($\text{C}^{\delta+}=\text{O}^{\delta-}$), making the carbonyl carbon electrophilic. Enolates are nucleophilic at the α -carbon (and also at oxygen). In the aldol addition, the key bond formed is between:

- the α -carbon of the enolate (nucleophile), and
- the carbonyl carbon of the acceptor (electrophile).

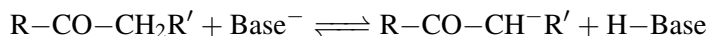
Thus, the aldol addition is best classified as a **nucleophilic addition to a carbonyl**—not a substitution—because aldehydes and ketones generally lack a leaving group on the carbonyl carbon.

13.3.3 Base-catalyzed aldol addition: the reversible C–C bond-forming step

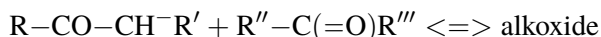
Generic mechanism

Consider an aldehyde or ketone $\text{R}-\text{CO}-\text{CH}_2\text{R}'$ that can form an enolate, reacting with a second carbonyl compound $\text{R}''-\text{C}(=\text{O})\text{R}'''$. The base-catalyzed aldol addition proceeds in three conceptual steps:

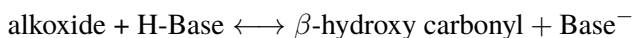
- **Enolate formation (acid–base):**



- **Carbonyl addition (C–C bond formation):**



- **Protonation (regenerates catalyst):**



Reversibility is a defining feature. For many aldol reactions under basic conditions, **steps 1–3 are reversible**. The reverse of the aldol addition is called the **retro-aldol** reaction, which cleaves the C–C bond adjacent to the carbonyl under suitable conditions. This reversibility has two major consequences:

- Product distributions can reflect equilibria (especially at higher temperature).
- Conditions that remove product (or convert it into a more stable species, such as a conjugated enone) can drive the overall process forward.

Why aldehydes are usually more reactive aldol acceptors than ketones

Aldehydes are typically better electrophiles than ketones for two reasons already familiar from nucleophilic addition chemistry:

- **Sterics:** aldehydes have one alkyl substituent and one hydrogen; ketones have two alkyl substituents.
- **Electronics:** alkyl groups donate electron density (inductively and by hyper-conjugation), reducing electrophilicity at the carbonyl carbon.

As a result, many practical aldol reactions use an aldehyde as the electrophile (acceptor), even when a ketone provides the enolate (donor).

13.3.4 From aldol addition to aldol condensation: dehydration and conjugation as the driving force

Thermodynamic incentive: conjugated π -systems

The dehydration step produces an α, β -unsaturated carbonyl compound. Conjugation between the alkene and carbonyl lowers the product's energy, providing a strong thermodynamic driving force:



Therefore, heating or otherwise promoting dehydration often shifts the overall equilibrium toward condensation products.

Base-promoted dehydration typically proceeds by an E1cB mechanism

Under basic conditions, dehydration of a β -hydroxy carbonyl compound often occurs by **E1cB** (elimination unimolecular conjugate base):

- Base removes an α -hydrogen to form an enolate-like anion.
- The anion then expels OH^- (a poor leaving group) to form the conjugated α, β -unsaturated carbonyl.

This is feasible because the intermediate anion is stabilized (enolate resonance), and the product is conjugated.

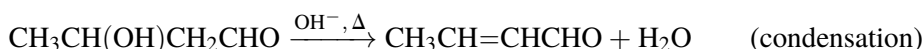
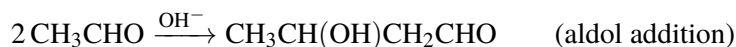
Why not E2? E2 elimination requires a good leaving group and a concerted pathway. In aldol dehydration under base, the leaving group would be OH^- , which is poor. E1cB provides an alternative: first make a stabilized anion, then eliminate.

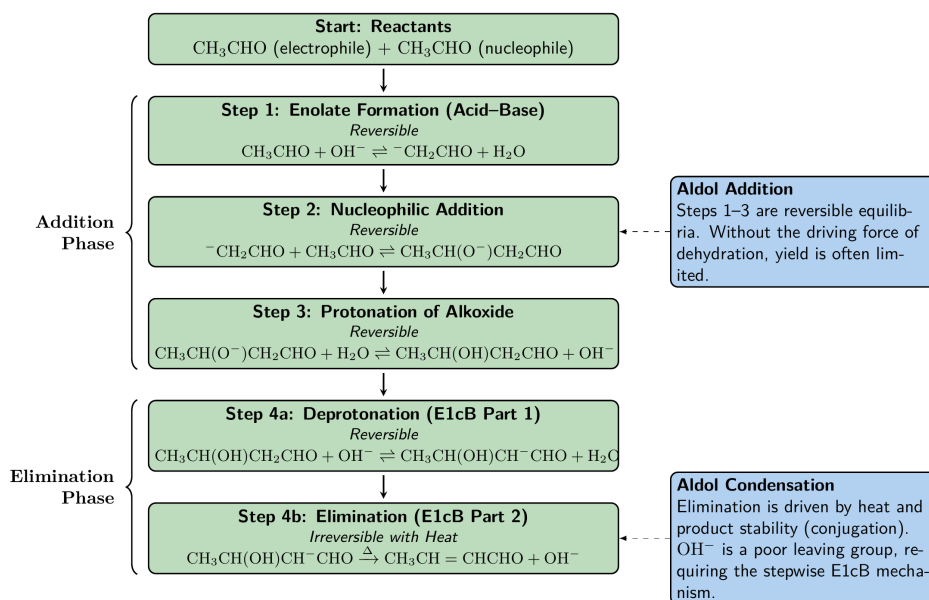
Reversibility and “irreversibility” in practice. While the dehydration can be reversible in principle, in practice it is often *effectively irreversible* when:

- the enone is strongly stabilized by conjugation (especially if extended conjugation forms), and/or
- water is removed, or the conditions (heat) continuously convert aldol to enone faster than rehydration occurs.

13.3.5 Step-by-step mechanism: base-catalyzed aldol condensation

To make the logic concrete, consider the self-aldol condensation of acetaldehyde (as a representative aldehyde). The same pattern applies broadly to enolizable aldehydes and ketones.



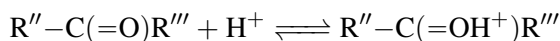
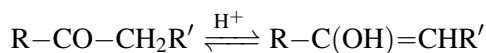


13.3.6 Acid-catalyzed aldol reactions: enol nucleophiles and complementary selectivity

Aldol chemistry can also be catalyzed by acid, but the mechanistic *roles* switch:

- The nucleophile is the **enol** (formed under acid catalysis).
- The electrophile is a **protonated carbonyl**, which is even more electrophilic.

A simplified logic is:



enol + protonated carbonyl $\longrightarrow$ β -hydroxy carbonyl (after deprotonation)

Practical contrast with base-catalyzed conditions.

- Acidic conditions can reduce the concentration of strongly basic anionic intermediates, which can be beneficial when sensitive functional groups are present.

- However, controlling which partner becomes the nucleophile (enol) can be difficult if both carbonyl compounds can enolize.

For most synthetic planning in this chapter, the base-catalyzed aldol is the primary model because it connects directly to enolate generation and regioselectivity control (Section 13.1).

13.3.7 Crossed (mixed) aldol reactions: controlling “who attacks whom”

When two different carbonyl compounds are combined under aldol conditions, up to four products may be possible:

- self-aldol of compound A,
- self-aldol of compound B,
- crossed aldol (A enolate + B carbonyl),
- crossed aldol (B enolate + A carbonyl).

Without planning, this leads to complex mixtures.

Strategy 1: use a non-enolizable carbonyl electrophile

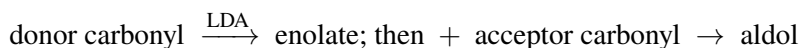
A carbonyl compound lacking α -hydrogens cannot form an enolate and therefore can serve only as the electrophile. Typical examples include:

- benzaldehyde (PhCHO; no α -H on the aromatic carbon),
- formaldehyde (HCHO; no α -carbon at all).

Then only the enolizable partner generates the nucleophile, biasing the reaction toward a single crossed product.

Strategy 2: preform the enolate (directed crossed aldol)

A powerful approach is to generate the enolate of one partner first (often with LDA at low temperature), then add the electrophile. Conceptually:



This avoids competition from the acceptor forming its own enolate and provides strong control over regiochemistry (kinetic vs. thermodynamic enolates) and, in advanced settings, stereochemistry.

13.3.8 Intramolecular aldol reactions: ring formation as a built-in selectivity element

If a molecule contains two carbonyl groups positioned appropriately, enolate formation at one carbonyl can lead to intramolecular attack on the other. Intramolecular reactions are often favored entropically relative to intermolecular combinations because the reacting partners are tethered.

Ring-size preference. Intramolecular aldol reactions most readily form **five- and six-membered rings**, which generally balance favorable geometry with low strain. After cyclization (aldol addition), dehydration frequently yields cyclic enones—highly useful building blocks in synthesis.

13.3.9 Predicting when dehydration occurs: aldol addition vs. condensation products

Whether a reaction stops at the β -hydroxy carbonyl (addition product) or proceeds to the α, β -unsaturated carbonyl (condensation product) depends on conditions and substrate:

- **Heat** strongly favors dehydration.
- **More substituted systems** often dehydrate more readily because the resulting alkene is more stable.
- **Conjugation gain** is a key driver; dehydration is especially favorable when it creates extended conjugation (e.g., aryl-conjugated enones).
- **Milder, colder conditions** and rapid workup can favor isolation of aldol addition products, particularly when dehydration would be slow or when the β -hydroxy product is stabilized (e.g., by hydrogen bonding or lack of a suitable anti-periplanar geometry in constrained systems).

13.3.10 Summary: a mechanistic “map” for aldol chemistry

- **Generate an enolate (or enol).** The availability and identity of the enolate depend on α -acidity and enolization conditions.
- **Add to a carbonyl (aldol addition).** This C–C bond-forming step is commonly reversible under base catalysis.
- **Decide whether to dehydrate (aldol condensation).** Under base, dehydration commonly follows an E1cB pathway and is driven by conjugation; with heat it is often effectively irreversible.
- **Control selectivity in crossed aldols.** Use non-enolizable electrophiles or preformed enolates to avoid mixtures.

This mechanistic framework will reappear in later sections as we compare aldol chemistry (addition) to Claisen chemistry (substitution) and integrate conjugate additions in Michael and Robinson annulation sequences.

13.4 Claisen Condensations

13.4.1 Positioning the Claisen condensation among enolate reactions

The aldol reaction (Section 13.3) is a **nucleophilic addition** of an enolate to an aldehyde or ketone, because those carbonyls lack a leaving group. Esters, in contrast, *do* possess a potential leaving group (OR^-). As a result, when an ester is the electrophile, enolate attack is typically followed by **elimination** of an alkoxide, giving a **nucleophilic acyl substitution** rather than a simple addition product.

The **Claisen condensation** is the prototypical reaction in which an **ester enolate** (nucleophile) attacks an **ester carbonyl** (electrophile) to form a β -keto ester. The term “condensation” reflects that two molecules combine with net loss of an alkoxide (and, after workup, net loss of a proton overall).

13.4.2 Overall transformation and product class

Self-Claisen condensation (one ester)

A simple schematic representation is:



More commonly (and more clearly), the product is described as a β -keto ester:



where the CH_2 between carbonyls is strongly acidified (a point that will matter immediately for the mechanism).

Dieckmann condensation (intramolecular Claisen)

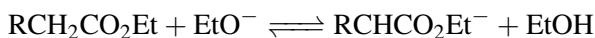
If a diester contains two ester groups tethered appropriately, an intramolecular Claisen condensation forms a cyclic β -keto ester. This is called the **Dieckmann condensation** and is the ester analog of an intramolecular aldol reaction.

13.4.3 Mechanistic core: a substitution reaction driven by a final deprotonation

Step-by-step mechanism (base-catalyzed, followed by workup)

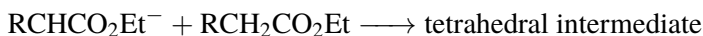
Consider a representative ester $\text{RCH}_2\text{CO}_2\text{Et}$ undergoing a Claisen condensation under EtO^- (ethoxide) in ethanol.

Step 1: Enolate formation (acid–base).

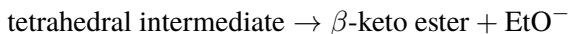


This equilibrium is not overwhelmingly favorable for many simple esters (recall α - pK_a of esters is typically ~ 24 – 26), but a small concentration of enolate is sufficient to initiate the substitution sequence.

Step 2: Nucleophilic acyl substitution (addition to the ester). The ester enolate attacks the carbonyl carbon of a second ester molecule:

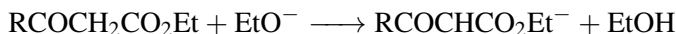


Step 3: Collapse of the tetrahedral intermediate (elimination). The tetrahedral intermediate collapses to re-form the carbonyl and expel ethoxide:



At this point, the carbonyl product has been formed, and one might imagine the reaction is complete. However, without an additional driving force, this step (like other acyl substitutions) could remain reversible.

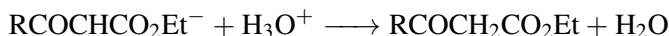
Step 4: The driving force—deprotonation of the β -keto ester (often essentially irreversible). The newly formed β -keto ester contains an α -C–H between two carbonyls ($-\text{CO}-\text{CH}_2-\text{CO}_2\text{Et}$). This hydrogen is far more acidic ($pK_a \sim 11-13$) than the alcohol conjugate acid of ethoxide (EtOH , $pK_a \sim 16$). Therefore ethoxide rapidly and strongly deprotonates the β -keto ester product:



This *product deprotonation* accomplishes two critical things:

- It removes neutral product from the equilibrium mixture as its stabilized enolate, **driving the condensation forward**.
- It explains why Claisen reactions are typically not merely catalytic in base: at least one equivalent of base is effectively “consumed” by converting product into its enolate salt until an acidic workup is performed.

Step 5: Acidic workup (protonation). The reaction mixture is then treated with aqueous acid to protonate the enolate and isolate the neutral β -keto ester:



Why Claisen products form: the “thermodynamic trap” concept

A useful mental model is that the Claisen condensation uses **acyl substitution** to form a β -keto ester, then **locks** that product in place as an enolate. Because the β -dicarbonyl enolate is unusually stabilized, product formation becomes a thermodynamic trap.

This logic closely parallels aldol condensation: the aldol addition is often reversible, and dehydration (to a conjugated enone) drives the net process forward. In the Claisen case, the driving force is not dehydration but **formation of a highly stabilized enolate from the product**.

13.4.4 The “two α -hydrogens” requirement and what it really means

Textbooks often state that a Claisen condensation requires that the starting ester have **at least two α -hydrogens**. The mechanistic reason is subtle but precise.

Correct mechanistic statement

To undergo a self-Claisen condensation efficiently, the ester must be able to:

- form an enolate to attack another ester (*needs at least one α -H*), and
- after C–C bond formation and elimination, *still allow deprotonation of the product* at the position between the two carbonyls (the driving force step).

For a self-Claisen, those requirements often translate into “two α -H on the starting ester” because one α -hydrogen is effectively “replaced” during C–C bond formation, and the product must still have an acidic hydrogen to be deprotonated and trapped as the enolate.

Consequence: esters without sufficient α -hydrogens fail or give poor yields

If an ester has no α -hydrogen ($\text{RCO}_2\text{R}'$ where R is non-enolizable, such as Ph in benzoate), it cannot form the nucleophilic enolate donor and cannot participate as the donor in a Claisen condensation.

If an ester can form an enolate but the resulting β -keto ester product cannot be deprotonated (or deprotonation is not strongly favorable), the critical driving-force step is missing and the reaction tends to be reversible and unproductive.

13.4.5 Base choice: why the alkoxide should match the ester**The “matching alkoxide” rule**

Claisen condensations are commonly performed with an alkoxide base that matches the ester alkoxy group:



Reason: avoid transesterification. Alkoxides are nucleophiles as well as bases. If you use a mismatched alkoxide (e.g., MeO^- with an ethyl ester), nucleophilic acyl substitution at the ester can exchange the OR group (transesterification), leading to mixtures of ester types and complicating product distributions and purification.

Why strong non-alkoxide bases are not the default

One might ask why not use LDA, which cleanly generates enolates. In Claisen chemistry, alkoxide bases are often preferred because:

- the electrophile is an ester (prone to nucleophilic acyl substitution), and
- matching alkoxide conditions minimize side reactions and keep the system simple.

That said, directed Claisen-type acylations using preformed enolates and activated acylating agents (e.g., acid chlorides) are important in synthesis, but the canonical Claisen condensation as introduced here emphasizes the alkoxide/ester pairing.

13.4.6 Crossed Claisen condensations: controlling which ester is the donor

As with crossed aldol reactions, mixing two different enolizable esters can produce complex mixtures. Crossed Claisen condensations are therefore designed to enforce selectivity.

Strategy 1: use a non-enolizable ester as the electrophile

An ester lacking α -hydrogens cannot act as an enolate donor but can serve as the electrophile. Examples include:

- aryl esters such as PhCO_2Et (benzoate esters),
- formate esters HCO_2R (no α -carbon).

Then only the enolizable ester forms the enolate donor, biasing the crossed product.

Strategy 2: use different functional group reactivity (acylating agents)

In more advanced practice, a preformed ester enolate is reacted with a more reactive acyl derivative (acid chloride, anhydride) to force acylation. Mechanistically this is still nucleophilic acyl substitution, but the electrophile is more activated than an ester, improving yields and selectivity. This idea anticipates acylation chemistry beyond the scope of the basic Claisen condensation, but the mechanistic logic is identical.

13.4.7 Dieckmann condensation: intramolecular Claisen to form rings

Intramolecular Claisen condensation is called the **Dieckmann condensation**. It typically converts a diester into a cyclic β -keto ester.

Ring-size preference

As with intramolecular aldol reactions, five- and six-membered rings form most readily because they minimize strain and allow favorable orbital overlap in the key C–C bond-forming step. The product is again a β -dicarbonyl system whose enolate is stabilized, so the same “product deprotonation drives the reaction” logic applies.

Workup and downstream chemistry

The cyclic β -keto ester can be:

- further alkylated at the acidic α -position (Section 13.2 logic),
- hydrolyzed and decarboxylated (a common theme for β -keto esters), yielding cyclic ketones after loss of CO_2 .

These transformations turn the Dieckmann condensation into a practical route to cyclic ketones.

13.4.8 Common pitfalls and diagnostic reasoning

Pitfall 1: using hydroxide as base

Hydroxide (HO^-) can promote ester hydrolysis (saponification), competing with Claisen condensation. Alkoxide bases in the corresponding alcohol solvent are preferred to suppress hydrolysis.

Pitfall 2: expecting “catalytic base”

Because the product is deprotonated strongly, a Claisen condensation generally requires:

- at least one equivalent of base to generate and maintain the product enolate, followed by
- an acidic workup to obtain the neutral β -keto ester.

If you omit acid workup, the isolated species may be the enolate salt rather than the neutral product.

Pitfall 3: choosing an ester without a viable driving-force deprotonation

If the product cannot be deprotonated at the α -position between carbonyls, the reaction often stalls. Always identify the acidic hydrogen that will be removed in the driving-force step.

13.4.9 Summary: the Claisen condensation as “enolate acyl substitution + product trapping”

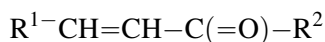
- **Nucleophile:** an ester enolate (formed under alkoxide base).
- **Electrophile:** an ester carbonyl (substitution-capable).
- **Key mechanistic class:** nucleophilic acyl substitution (addition to carbonyl, then elimination of OR^-).
- **Driving force:** deprotonation of the β -keto ester product to a stabilized enolate (often necessitating stoichiometric base and acid workup).
- **Variants:** crossed Claisen (selectivity by design) and Dieckmann (intramolecular ring formation).

With these ideas in place, we can now extend enolate chemistry from direct carbonyl additions and acyl substitutions to *conjugate additions* (Michael reactions), culminating in multi-step annulations that build cyclic frameworks efficiently.

13.5 Michael Addition and Robinson Annulation**13.5.1 Why conjugate addition is the next step after aldol and Claisen chemistry**

The aldol reaction (Section 13.3) taught enolates as nucleophiles in **1,2-addition** to carbonyl groups (attack at the carbonyl carbon). The Claisen condensation (Section 13.4) showed enolates in **acyl substitution** at esters. Both reactions involve nucleophilic attack at a carbonyl carbon.

α, β -Unsaturated carbonyl compounds (enones and enals) introduce a new pattern: the electrophilic character is distributed over two positions due to conjugation:



These substrates can react by:

- **1,2-addition** at the carbonyl carbon (“direct addition”),
- **1,4-addition** at the β -carbon (“conjugate addition”), giving a product in which the carbonyl remains intact.

The **Michael addition** is the prototypical 1,4-addition of an enolate (or other stabilized carbon nucleophile) to an α, β -unsaturated carbonyl compound. It is one of the most powerful ways to form C–C bonds *while preserving a carbonyl group* for later transformations—a feature that becomes crucial in the Robinson annulation.

13.5.2 Electronic structure of enones: why the β -carbon is electrophilic

An enone is conjugated, and resonance places positive charge at the β -carbon:



This resonance form is not a “real” structure, but it communicates an important reactivity fact: the β -carbon can behave like an electrophilic site because electron density can be drawn through the conjugated π -system into the carbonyl.

A mechanistically useful way to think about 1,4-addition is:

- nucleophile attacks at β -carbon,
- the π -system shifts, generating an enolate at the carbonyl end,
- protonation yields the saturated carbonyl product.

13.5.3 1,2- vs. 1,4-addition: “hard” and “soft” nucleophiles (qualitative)

A persistent question is: *what determines whether an enone undergoes 1,2- or 1,4-addition?* While a full treatment involves kinetics, thermodynamics, solvent, and metal counterion effects, a useful organizing principle is the hard/soft (HSAB) idea:

- The carbonyl carbon is a **harder** electrophilic site (localized, strongly polarized).
- The β -carbon is a **softer** electrophilic site (more diffuse electrophilicity distributed by resonance).

Accordingly:

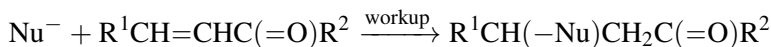
- **Hard nucleophiles** (e.g., RMgBr, RLi, H^- from LiAlH_4 in many contexts) tend to favor **1,2-addition**.
- **Soft nucleophiles** (e.g., enolates of 1,3-dicarbonyls, thiolates, and many organocuprates R_2CuLi) tend to favor **1,4-addition**.

A practical caution. This is a guideline, not a law. For enolates, the balance can shift with counterion (Li vs. Na vs. K), solvent, temperature, and substrate. In this chapter, we focus on the most common and synthetically central outcome: **enolates often perform conjugate (1,4) addition to enones**, producing a new C–C bond at the β -position.

13.5.4 The Michael addition: mechanism and synthetic meaning

Overall transformation

A generic Michael addition couples a stabilized enolate donor to an enone acceptor:

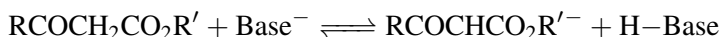


The product is a β -substituted carbonyl compound. Importantly, the carbonyl group remains, enabling further enolate chemistry.

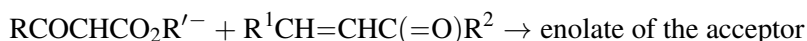
Step-by-step mechanism (base-catalyzed)

Let the Michael donor be an enolate derived from a 1,3-dicarbonyl compound (a common choice because of its high α -acidity and resonance stabilization). The mechanistic sequence is:

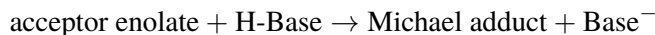
Step 1: Generate the donor enolate.



Step 2: Conjugate (1,4) attack at the β -carbon.



Conceptually, the nucleophile forms a bond to the β -carbon, and electron density shifts to oxygen, giving an enolate on the acceptor fragment.

Step 3: Protonation regenerates a neutral carbonyl.**Why 1,3-dicarbonyl compounds are excellent Michael donors**

From Section 13.1, 1,3-dicarbonyl compounds have unusually acidic α -hydrogens ($pK_a \sim 9 - 13$). This makes it easy to generate a significant concentration of enolate under mild base, and the resonance-stabilized enolate is nucleophilic but not excessively basic. This combination reduces side reactions and promotes selective C–C bond formation.

Why Michael addition is often viewed as “polarity inversion” at the β -carbon

In an enone, the β -carbon behaves electrophilically due to conjugation. Thus, Michael addition allows the formation of a C–C bond at a site that is not electrophilic in a simple alkene. The enone acts as an “activated alkene” whose β -carbon is an acceptor for nucleophilic attack.

13.5.5 Michael addition sets up intramolecular aldol: the Robinson annulation logic

The **Robinson annulation** is a classic three-part sequence:

- **Michael addition** to form a 1,5-dicarbonyl-type intermediate (often called a Michael adduct),
- **intramolecular aldol addition** to form a ring,
- **dehydration** to form a conjugated cyclic enone.

This sequence is powerful because it **constructs a six-membered ring** (often fused to an existing ring) while installing an α, β -unsaturated carbonyl functionality that is a versatile handle for further chemistry.

13.5.6 The Robinson annulation: mechanistic roadmap**Typical partners**

A common and instructive pairing is:

- **Michael donor:** an enolizable ketone (often cyclohexanone) or a 1,3-dicarbonyl compound.
- **Michael acceptor:** an α, β -unsaturated ketone, frequently methyl vinyl ketone (MVK, $\text{CH}_2=\text{CHCOCH}_3$).

Stage 1: Michael addition creates a 1,5-dicarbonyl framework

After the donor enolate adds to the acceptor at the β -position, the product contains a carbonyl from the donor and a carbonyl from the acceptor separated by three carbons (a 1,5-relationship). This spacing is ideal for forming a six-membered ring by intramolecular aldol reaction, because a 1,5-dicarbonyl can cyclize by forming a bond between the α -carbon of one carbonyl and the carbonyl carbon of the other.

Stage 2: Intramolecular aldol addition closes the ring

Under base, an enolate forms at one carbonyl within the Michael adduct and attacks the other carbonyl intramolecularly (Section 13.3, intramolecular aldol). Ring closure is typically favored when it produces a five- or six-membered ring; in the Robinson annulation, the architecture is designed to favor a six-membered ring.

Stage 3: Dehydration yields a conjugated enone

The aldol product is a β -hydroxy carbonyl embedded in a ring. Under the reaction conditions (often heat), it dehydrates—commonly by an E1cB pathway, as discussed in Section 13.3—to form a conjugated cyclohexenone or bicyclic enone. Conjugation provides a major thermodynamic driving force and often renders this final step effectively irreversible.

13.5.7 Selectivity and conditions: practical control elements

Chemoselectivity: why Michael addition can outcompete direct aldol with enones

An enone contains a carbonyl, so one might expect enolates to attack it by 1,2-addition (aldol-type). Michael addition becomes dominant when:

- the nucleophile is sufficiently **soft** (e.g., stabilized enolates),

- the conditions favor reversible equilibration and the product distribution is pulled by subsequent steps (intramolecular aldol and dehydration),
- steric and electronic factors reduce the rate of 1,2-addition relative to 1,4-addition.

Regioselectivity: enolate formation still matters

All the tools from Section 13.1 remain relevant. If the Michael donor has multiple α -positions, kinetic vs. thermodynamic enolate control can influence where the new bond forms. In Robinson annulation settings, substrates are often chosen so that enolate formation is effectively directed (e.g., cyclohexanone forming an enolate at equivalent α -positions), simplifying outcomes.

A strategic viewpoint

Robinson annulation is not merely a named reaction; it is a design principle:

Use conjugate addition to connect fragments, then use intramolecular aldol to cyclize, then dehydrate to lock in conjugation.

This viewpoint helps in retrosynthesis: if you see a cyclohexenone embedded in a polycyclic structure, consider disconnecting it into a Michael donor and an enone acceptor.

13.5.8 End-of-section schematic: the Robinson annulation as a bond-construction map

The figure below summarizes the logic of the Robinson annulation, highlighting (i) the Michael donor fragment, (ii) the Michael acceptor fragment, and (iii) the new bonds formed across the sequence. Carbon-tracing is emphasized so that you can follow how two acyclic (or monocyclic) partners become a bicyclic enone.

13.5.9 Summary: how Michael addition and Robinson annulation extend enolate chemistry

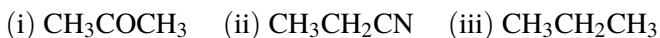
- Conjugated carbonyl compounds (enones/enals) possess two electrophilic sites, enabling **1,2-** and **1,4-addition**.
- **Michael addition** is 1,4-addition of a stabilized nucleophile (often an enolate) to the β -carbon of an enone, producing a new C–C bond while retaining a carbonyl group.
- The **Robinson annulation** combines a Michael addition with an intramolecular aldol condensation to efficiently build **six-membered rings** and **bicyclic enones**.
- Mechanistically, the annulation is best understood as a designed sequence in which each step creates the functional arrangement required for the next: Michael addition creates a 1,5-dicarbonyl, intramolecular aldol closes the ring, and dehydration locks in conjugation.

13.6 Problems

13.6.1 Problem 1: α -Acidity ranking in multifunctional molecules

For each set below, rank the indicated hydrogens in order of **increasing acidity** (least acidic $\rightarrow$ most acidic). For every ranking, justify your answer using resonance, inductive effects, hybridization, and (where relevant) the number and type of electron-withdrawing groups that can stabilize the conjugate base.

- **Set A (carbonyl vs. nitrile vs. simple alkane):** Rank the most acidic hydrogen in each compound:



- **Set B (ester vs. ketone vs. 1,3-dicarbonyl):** Rank the α -hydrogens:



- **Set C (competing α -sites):** For the unsymmetrical ketone $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_3$ (2-hexanone), rank the acidity of the α -hydrogens on the methyl side vs. the propyl side, and explain how this relates (or does not relate) to kinetic vs. thermodynamic enolate formation.

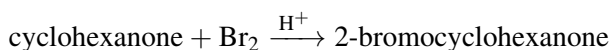
13.6.2 Problem 2: Kinetic vs. thermodynamic enolate prediction and trapping

Consider the ketone $\text{CH}_3\text{COCH}_2\text{CH}(\text{CH}_3)_2$ (4-methyl-2-pentanone, “MIBK”). It has two distinct α -positions.

- **1.** Draw both possible enolate regioisomers (show at least one resonance form for each).
- **2.** Predict which enolate is favored under each condition set below, and justify in terms of sterics, temperature, reversibility, and base identity.
- **(a)** LDA, THF, -78°C , then CH_3I .
- **(b)** NaOEt, EtOH, reflux, then CH_3I .
- **3.** For each condition set, draw the major alkylation product(s). State whether you expect monoalkylation vs. significant polyalkylation and why.

13.6.3 Problem 3: Mechanism and selectivity in acid-catalyzed α -halogenation

Provide a complete curved-arrow mechanism for the monobromination of cyclohexanone under acidic conditions:



Your mechanism must explicitly show:

- **1.** formation of the enol (including protonation of the carbonyl and deprotonation at α -carbon),
- **2.** electrophilic bromination of the enol,
- **3.** regeneration of the acid catalyst.

Then answer: why does this reaction often stop at *monohalogenation* under acidic conditions, whereas polyhalogenation is common under basic conditions?

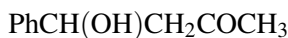
13.6.4 Problem 4: Designing a malonic ester synthesis to a target carboxylic acid

Design a synthesis of 3-methylbutanoic acid (isovaleric acid), $(\text{CH}_3)_2\text{CHCH}_2\text{CO}_2\text{H}$, using a malonic ester synthesis strategy starting from diethyl malonate $\text{EtO}_2\text{CCH}_2\text{CO}_2\text{Et}$.

- 1. Specify reagents and conditions for each step (base, electrophile, hydrolysis, decarboxylation).
- 2. Identify the key $\text{S}_{\text{N}}2$ alkylation step and justify your choice of alkyl halide (structure and leaving group).
- 3. Explain how the sequence avoids uncontrolled polyalkylation and why decarboxylation occurs upon heating.

13.6.5 Problem 5: Crossed aldol reaction planning and product prediction

You are asked to form the following β -hydroxy carbonyl compound selectively (drawn here in condensed form):



- 1. Propose a crossed aldol *addition* (not condensation) that produces this compound as the major product. Choose appropriate donor and acceptor carbonyl partners.
- 2. Provide conditions that minimize self-aldol side reactions and dehydration. Explain why your conditions favor the β -hydroxy product rather than the enone.
- 3. Provide a mechanistic justification for why benzaldehyde (PhCHO) is frequently used as an aldol acceptor in crossed aldols.

13.6.6 Problem 6: Claisen condensation feasibility and mechanism

For each substrate set below, determine whether a Claisen condensation is feasible under standard alkoxide conditions. If feasible, draw the major β -keto ester product

and provide a stepwise mechanism (enolate formation, nucleophilic acyl substitution, product deprotonation, acid workup). If not feasible, explain *precisely* which mechanistic requirement fails.

- (a) $\text{EtO}_2\text{CCH}_2\text{CH}_3$ (ethyl propionate) under NaOEt/EtOH .
- (b) PhCO_2Et (ethyl benzoate) under NaOEt/EtOH .
- (c) A crossed Claisen attempt: $\text{EtO}_2\text{CCH}_2\text{CH}_3 + \text{PhCO}_2\text{Et}$ under NaOEt/EtOH . Predict the major product (if any) and justify.
- (d) A Dieckmann case: $\text{EtO}_2\text{C}-(\text{CH}_2)_5-\text{CO}_2\text{Et}$ under NaOEt/EtOH . Predict the ring size formed and draw the cyclic β -keto ester product.

13.6.7 Problem 7: Robinson annulation retrosynthesis and forward synthesis

A target molecule contains a fused bicyclic cyclohexenone motif characteristic of a Robinson annulation product. You are given the following target in words: *a bicyclic enone formed by annulation of a cyclohexanone ring with a three-carbon enone fragment*. (You may sketch a generic fused bicyclic enone consistent with Robinson annulation if desired.)

- 1. Propose a retrosynthetic disconnection that breaks the product into a Michael donor and a Michael acceptor.
- 2. Choose a specific Michael acceptor consistent with standard Robinson annulations (e.g., methyl vinyl ketone or a substituted enone) and justify.
- 3. Provide a forward synthesis plan including: enolate formation conditions, Michael addition, intramolecular aldol, and dehydration conditions.
- 4. State where (which bond) the Michael addition forms, and where the aldol cyclization forms the second key C–C bond.

13.6.8 Problem 8: Distinguishing 1,2- vs. 1,4-addition outcomes

Consider the enone 2-cyclohexen-1-one. Predict the major product(s) under each reagent set. For each, specify whether 1,2- or 1,4-addition dominates, and provide a mechanistic rationale using the concepts of hard/soft nucleophiles and enolate/protonation steps where relevant.

- 1. CH_3MgBr , then H_3O^+ .
- 2. Lithium diethylcuprate $(\text{Et})_2\text{CuLi}$, then H_3O^+ .
- 3. The sodium enolate of diethyl malonate $(\text{EtO}_2\text{CCH}^-\text{CO}_2\text{Et})$ added to 2-cyclohexen-1-one, then aqueous workup.

13.6.9 Problem 9 (challenge): Tandem enolate sequence design with selectivity constraints

Design a multi-step synthesis (4–7 steps) to convert cyclohexanone into a substituted cyclohexenone that contains one new β -substituent introduced by a Michael addition and one new α -substituent introduced by enolate alkylation, with the constraint that the α -substituent must be installed *regioselectively* (kinetic vs. thermodynamic control) and the final product must be an α, β -unsaturated ketone.

Your answer must include:

- 1. the order of operations (which bond formation first and why),
- 2. reagents/conditions for each step (bases, electrophiles, temperature control),
- 3. a discussion of how you avoid (or manage) competing aldol self-condensation and polyalkylation,
- 4. a final dehydration step (if applicable) and justification for driving-force considerations.

Chapter 14

Synthetic Strategy

Organic synthesis represents the culmination of chemical knowledge, where reaction mechanisms and structural theory converge to build complex molecular architectures. This chapter moves beyond individual transformations to the strategic planning required to construct target molecules efficiently and elegantly. It introduces the rigorous logic of retrosynthetic analysis, the tactical use of functional group interconversions, and the nuanced control of chemoselectivity and stereochemistry, transforming the student from an observer of reactions to a molecular architect.

14.1 Retrosynthetic Analysis

Organic synthesis is not merely a catalog of reactions; it is a *planning discipline*. In earlier chapters, you learned individual reaction classes (addition, substitution, elimination, oxidation–reduction) and how to justify mechanisms with curved-arrow notation. The central challenge in synthesis is that a target molecule (often dense with functionality and stereochemistry) can rarely be made by simply “starting from something similar” and performing a few obvious transformations. Instead, successful synthesis begins with a different mindset: **work backward** from the **Target Molecule (TM)** to progressively simpler precursors until you reach **available starting materials**.

This backward-planning method is called **retrosynthetic analysis**. The key tool is the **disconnection** approach: you imagine breaking a bond in the target structure in a way that corresponds to a known, reliable forward reaction that can make that bond.

14.1.1 Core idea: plan backward, execute forward

A forward synthesis answers: “If I have starting materials A and B, what product do I obtain under certain conditions?” Retrosynthesis asks the inverse question:

Given the Target Molecule, what simpler precursors could reasonably be combined (or transformed) to form it?

In retrosynthetic analysis, you repeatedly apply two moves:

- **Disconnection (bond analysis):** Choose a bond in the TM to “break” to reveal simpler fragments.
- **Functional group and polarity analysis:** Decide what functional groups and *polarity pattern* must be present in the fragments so that a *known forward reaction* can form the broken bond.

The result is a **retrosynthetic tree** (or network) that maps one complex structure into a set of simpler precursors. After the backward plan is convincing, you reverse direction and write the **forward synthesis** with specific reagents and conditions.

14.1.2 Terminology and notation

Target Molecule (TM)

The **Target Molecule (TM)** is the compound you want to synthesize. Retrosynthesis begins with the TM drawn clearly, including functional groups, stereochemistry, and any protecting groups if relevant.

Retrosynthetic arrow

Retrosynthetic steps are written with a **double-lined arrow**:



This arrow does *not* represent an equilibrium or a mechanistic step. It means: “can be made from,” or more precisely, “could plausibly be derived from.”

Disconnection and the disconnection bond

A **disconnection** is the conceptual breaking of a bond in the TM to generate simpler fragments. The bond chosen is the **disconnection bond**. A good disconnection bond is one that:

- corresponds to a **known bond-forming reaction** (e.g., aldol addition, SN2 alkylation, Friedel–Crafts acylation, Suzuki coupling);
- produces fragments that are **stable and accessible**;
- simplifies the structure substantially (reduces ring complexity, decreases substitution density, or breaks a key branch point).

Synthons (idealized fragments)

After a disconnection, the fragments first appear as **synthons**: *idealized* pieces that capture the **polarity requirement** for bond formation.

A synthon is **not necessarily a real molecule**. Many synthons are written with **formal charges** to indicate nucleophilic or electrophilic character:

- **Donor synthon**: nucleophilic fragment, often written as C^- , O^- , N^- .
- **Acceptor synthon**: electrophilic fragment, often written as C^+ , or a polarized carbonyl carbon.

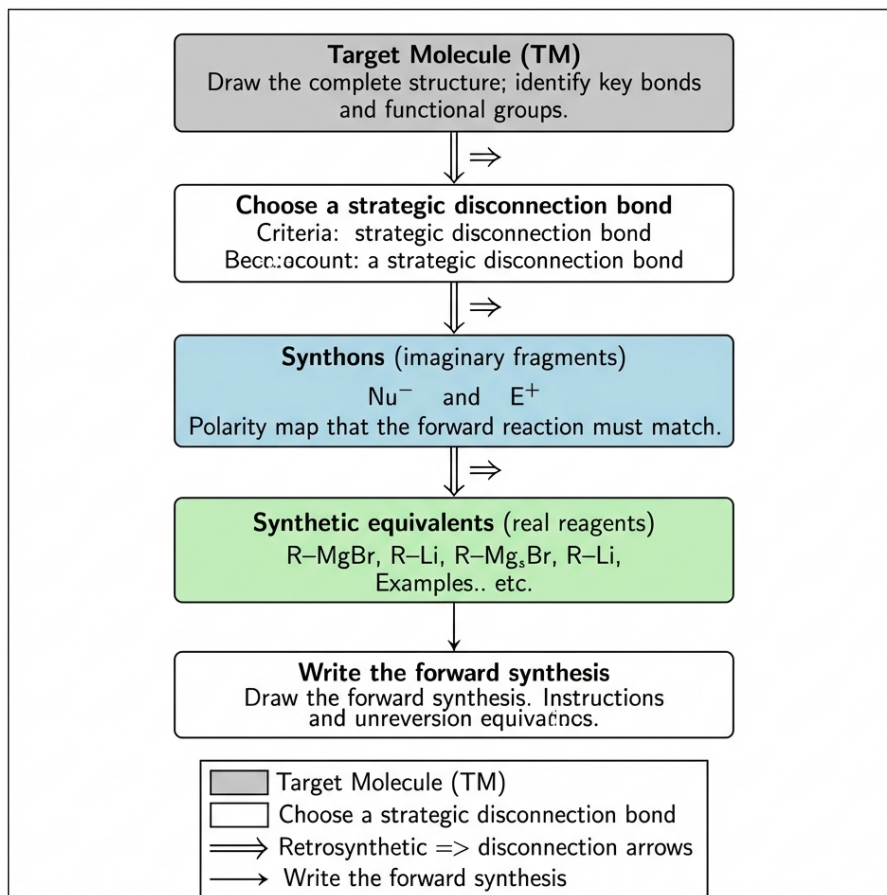
Synthetic equivalents (real reagents)

A **synthetic equivalent** is a *real, isolable reagent* that behaves like a synthon in the forward direction. For example:

- A C^- synthon might correspond to a **Grignard reagent** $R-MgBr$, an **organo-lithium** $R-Li$, or an **enolate** generated from a carbonyl compound.
- A C^+ synthon might correspond to an **alkyl halide** $R-X$, an **epoxide**, or a **carbonyl compound** (electrophilic at the carbonyl carbon).

The intellectual flow is therefore:

TM $\Rightarrow$ synthons (imaginary polarity fragments) $\Rightarrow$ synthetic equivalents (real reagents).



14.1.3 How to choose a strategic disconnection

A retrosynthetic plan is only as good as its disconnections. Beginners often disconnect “any” bond and then struggle to justify how that bond could be formed selectively. A strategic disconnection is chosen with forward chemistry in mind.

Disconnect at a bond that a known reaction forms

In practice, most disconnections map to a small set of reliable bond constructions. Common categories include:

- **Polar C–C bond formation** ($\text{Nu}^- + \text{E}^+ \longrightarrow \text{C} - \text{C}$): aldol and related enolate

additions, Grignard/organolithium additions to carbonyls, SN2 alkylation of enolates or other stabilized nucleophiles.

- **Aromatic substitution or acylation:** electrophilic aromatic substitution (EAS) steps can be planned via acylation/alkylation patterns.
- **Radical or pericyclic disconnections:** used when polarity-based logic fails, but typically reserved for later chapters or advanced cases.
- **Cross-coupling logic:** disconnect a biaryl or vinyl–aryl bond to two partners that could be coupled (e.g., organoboron + aryl halide), recognizing that the exact catalytic system is part of forward planning.

A useful planning habit is: *do not accept a disconnection unless you can immediately name at least one forward reaction family that makes the bond with the correct connectivity.*

Exploit symmetry and hidden symmetry

Symmetry reduces synthetic complexity because it reduces the number of distinct pieces you must make. If the TM contains two identical halves (or near-identical motifs), consider a disconnection that yields identical or similar precursors.

Even when a molecule is not globally symmetric, it may contain **local symmetry**: repeating subunits, equivalent positions on an aromatic ring, or two substituents that can be installed by the same transformation.

Disconnect at branching points (convergency)

A **branch point** is a carbon (or heteroatom) where multiple substituents converge. If you can disconnect at a branch point, you often obtain two fragments of similar complexity—a hallmark of **convergent synthesis**. Convergent plans are attractive because they can:

- shorten the *longest linear sequence* of steps;
- allow parallel preparation of fragments;
- increase overall yield relative to purely linear routes.

Prefer disconnections that reveal stable functional groups

A disconnection that produces unstable fragments (e.g., a free vinylic cation synthon without a clear equivalent) is usually a warning sign. Synthons may be “charged” on paper, but the corresponding synthetic equivalents must be chemically reasonable.

14.1.4 Polarity (synthon) analysis: donor vs. acceptor

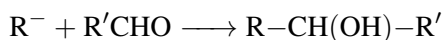
After selecting a bond to disconnect, assign which side should behave as a nucleophile and which as an electrophile in the forward direction. This polarity assignment is the heart of retrosynthetic thinking.

A simple example: secondary alcohol from carbonyl addition

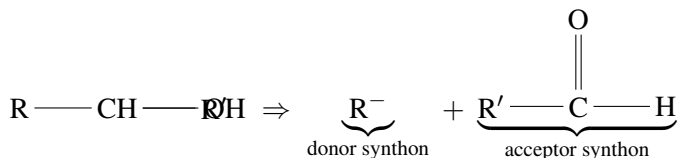
Suppose the TM contains a secondary alcohol motif:



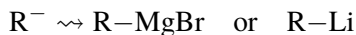
A common forward method is nucleophilic addition to an aldehyde:



Retrosynthetically:



Then convert synthons to **synthetic equivalents**, e.g.,



This illustrates the central workflow: the synthon step tells you *what polarity is required*; the synthetic equivalent step tells you *how to realize that polarity with real reagents*.

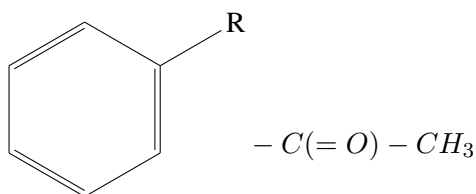
Umpolung (polarity inversion) as a planning signal

Sometimes the most obvious polarity assignment is not feasible because the corresponding synthetic equivalent is unstable or unavailable. This motivates **umpolung** strategies (polarity inversion), where you reverse the donor/acceptor roles using special reagents (e.g., acyl anion equivalents). At this stage, you do not need a full catalog of umpolung reagents; the planning lesson is:

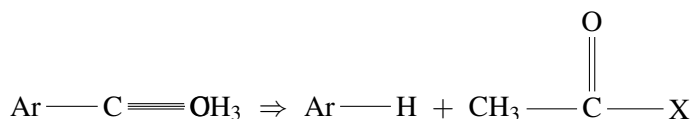
If you can write a synthon but cannot name a realistic synthetic equivalent, reconsider the disconnection or consider polarity inversion.

14.1.5 An annotated retrosynthetic example (C–C bond formation)

Consider a target that can be represented as a simple aryl ketone (a common motif in pharmaceuticals and materials):



A strategic bond to disconnect is the bond between the carbonyl carbon and the aromatic ring (aryl–acyl bond). Retrosynthetically:



where X is a leaving group in the synthetic equivalent (e.g., Cl).

Interpretation:

- The synthon logic is Ar^- (donor) plus CH_3CO^+ (acceptor).
- A realistic forward reaction is **Friedel–Crafts acylation** using an **acyl chloride** (synthetic equivalent for CH_3CO^+) with a Lewis acid catalyst.

This example illustrates a recurring retrosynthetic pattern: **disconnect a bond that a named reaction reliably forms**, then choose the functionalized precursor (here, acyl chloride) that operationally delivers the required electrophile.

14.1.6 Iterative simplification: building a retrosynthetic tree

Retrosynthesis is not a single disconnection; it is an **iterative simplification process**. Each round should:

- reduce molecular complexity (fewer rings, fewer stereocenters, fewer functional groups, or simpler substituents);
- increase the likelihood of reaching **commercially available** or **easily prepared** precursors.

A practical way to organize work is to draw a **retrosynthetic tree**:

- The TM at the top.
- Each disconnection produces one or two branches (precursors).
- Continue disconnecting until each branch ends at “known” starting points: simple aromatics, small carbonyl compounds, alkyl halides, organometallic precursors, etc.

14.1.7 Common pitfalls (and how to avoid them)

Pitfall 1: disconnecting without a forward reaction in mind

If a disconnection does not map to a plausible forward bond construction, it is not strategic. Always be able to answer: *How will I form that bond selectively, given the other functional groups present?*

Pitfall 2: ignoring chemoselectivity and functional group compatibility

Retrosynthesis can seduce you into thinking only about connectivity. In reality, every forward step must be compatible with existing functional groups. Early in your planning, note *incompatible pairs* (e.g., strong base with unprotected alcohols or acidic α -hydrogens; strong nucleophiles with sensitive electrophiles). When incompatibilities appear, you have two options:

- choose a different disconnection (different bond-forming logic), or
- plan for later chapters’ tools: functional group interconversions and protecting groups.

Pitfall 3: confusing synthons with reagents

Synthons are *polarity placeholders*. Do not write a forward step that uses a synthon directly. Always translate synthons into synthetic equivalents and confirm that those equivalents are stable and compatible with the substrate.

14.1.8 A minimal “checklist” for a good retrosynthetic step

Before accepting any retrosynthetic arrow, verify:

- **Bond construction:** A named reaction class can form the disconnected bond.
- **Polarity:** The donor/acceptor roles are chemically reasonable.
- **Synthetic equivalents:** Real reagents exist to represent each synthon.
- **Selectivity risk:** No obvious chemoselectivity or regioselectivity catastrophe is being ignored.
- **Net simplification:** The precursors are truly simpler than the TM.

Retrosynthetic analysis is therefore best viewed as a disciplined translation between three representations of a synthesis problem:

structure (TM) $\Rightarrow$ polarity (synthons) $\Rightarrow$ reality (synthetic equivalents).

Once you can move fluently among these representations, multistep synthesis becomes less about guessing and more about systematic design.

14.2 Functional Group Interconversion (FGI)

Retrosynthetic analysis identifies *which bonds* must be made and suggests *which fragments* (synthetic equivalents) can be coupled to build the carbon skeleton. In real synthesis, however, the fragments you can readily obtain often do *not* possess the exact functional groups needed for the key bond-forming step. This is where **functional group interconversion (FGI)** becomes a strategic tool.

Functional Group Interconversion (FGI) is the deliberate transformation of one functional group into another in order to:

- **enable** a critical bond-forming reaction (by creating the necessary electrophile, nucleophile, leaving group, or directing group),

- **adjust oxidation state** to match what is required at a given stage, and
- **unmask or restore functionality** after the carbon skeleton has been assembled.

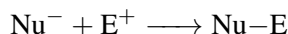
FGI is not “decoration.” It is often the difference between a theoretically plausible retrosynthetic disconnection and a practical forward synthesis.

14.2.1 FGI as a bridge between synthons and real chemistry

In retrosynthesis, synthons are defined by *polarity* (donor vs. acceptor). In forward synthesis, reagents require *specific functional groups*. FGI is the translation layer between these two viewpoints.

Polarity demands often imply specific functional groups

Consider the common synthon pair:



In the laboratory, the electrophile E^+ is rarely a “bare” cation; it is typically realized as one of the following:

- **alkyl electrophile:** $\text{R}-\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{OTs}, \text{OMs}$)
- **carbonyl electrophile:** aldehyde/ketone $\text{R}_2\text{C}=\text{O}$
- **acyl electrophile:** acyl chloride/anhydride/activated ester $\text{RCOCl}, (\text{RCO})_2\text{O}$

Likewise, a nucleophilic Nu^- synthon is realized as:

- **organometallics:** $\text{R}-\text{MgBr}, \text{R}-\text{Li}$
- **enolates/enolate equivalents:** generated from carbonyls
- **heteroatom anions:** $\text{RO}^-, \text{RS}^-, \text{R}_2\text{N}^-$

FGI is how you convert what you *have* (e.g., an alcohol) into what the bond-forming step *needs* (e.g., a good leaving group, or an aldehyde, or an enolate precursor).

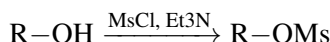
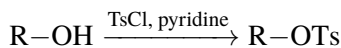
14.2.2 Two strategic roles of FGI in multistep synthesis

It is useful to separate FGI into two broad strategic roles. Many real syntheses use both.

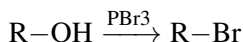
FGI #1: *Activation before a key bond-forming step*

An **activation FGI** modifies a functional group so that it participates in the next step with the desired reactivity pattern.

Example A: alcohol $\rightarrow$ leaving group (for substitution or elimination) Alcohols are common starting materials, but $-\text{OH}$ is typically a poor leaving group in neutral/basic conditions. If the plan requires an $\text{S}_{\text{N}}2$ step ($\text{Nu}^- + \text{R-LG} \longrightarrow \text{R-Nu}$), an alcohol may need to be converted to a sulfonate ester:



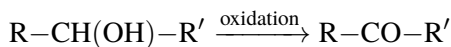
or to an alkyl halide:



Strategic note: “Alcohol $\rightarrow$ tosylate” is not a random transformation. It is performed because it *creates the synthetic equivalent of an alkyl electrophile* required by a retrosynthetic disconnection.

Example B: carbonyl $\leftrightarrow$ enolate precursor (for C–C bond formation) Aldol and related reactions require an enolate donor. If your fragment lacks an acidic α -position (or has the wrong carbonyl), you may need FGI to introduce or reposition carbonyl functionality before the bond-forming step.

For instance, if you need an enolate derived from a ketone but you possess the corresponding alcohol:



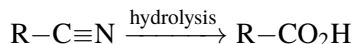
followed by base to form an enolate:



FGI #2: Unmasking (or “restoration”) after skeleton construction

After major bond formations, the molecule may contain functional groups in protected or “latent” forms chosen for stability or selectivity during earlier steps. A second class of FGIs restores the desired functionality.

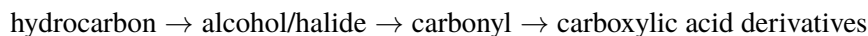
A simple case is the conversion of a nitrile (often used as a robust handle) into a carboxylic acid:



Here, the nitrile can survive conditions that might destroy an acid derivative, then later be unmasked to the acid oxidation level.

14.2.3 Oxidation state as a planning language for FGI

FGI is easiest to manage when you treat carbon functional groups as members of **oxidation-level families**. While exact oxidation numbers are rarely calculated in day-to-day synthesis planning, the *relative ladder* is enormously useful:

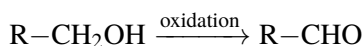


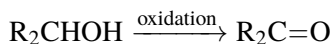
Moving “up” the ladder generally requires **oxidation**; moving “down” requires **reduction**. The central planning questions become:

- At what stage should oxidation be introduced (early vs. late)?
- Can the required oxidation/reduction be done *chemoselectively* in the presence of other functional groups?
- Does the planned bond-forming step require a specific oxidation level (e.g., carbonyl electrophile; enolate donor)?

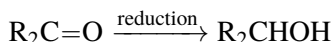
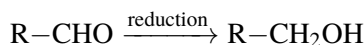
Common and strategically important oxidation-level interconversions

The following interconversions are so frequently used that they function as “moves” in synthesis design. The emphasis here is not on reagent memorization, but on *what each move enables*.

Alcohol $\leftrightarrow$ carbonyl



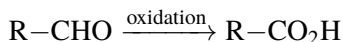
and the reverse:



Strategic uses:

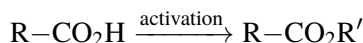
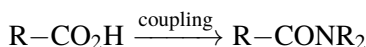
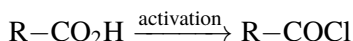
- Oxidize to a carbonyl to create an **electrophile** (for nucleophilic addition) or a **donor precursor** (enolate chemistry).
- Reduce a carbonyl to an alcohol to **quench electrophilicity** and improve stability/handling, or to prepare for conversion to a leaving group.

Aldehyde → carboxylic acid (often irreversible under harsh conditions)



Strategic note: This is often treated as a “one-way” move in many sequences. Once at the acid level, returning to the aldehyde typically requires multistep activation and controlled reduction. Therefore, introducing acids too early may impose later penalties (extra steps and selectivity challenges).

Carboxylic acid → activated derivatives (acyl electrophiles)



Strategic uses:

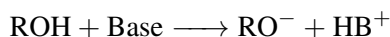
- Create **acyl electrophiles** to form amides/esters (key bonds in medicinal chemistry).
- Control reactivity: acyl chlorides are highly reactive; esters and amides are less reactive.

14.2.4 FGI as a polarity-switching tool (without “umpolung” machinery)

Even when you are not using formal polarity inversion chemistry, FGIs often *functionally* change polarity behavior by changing **mechanistic mode**.

Converting a poor nucleophile into a strong nucleophile

An alcohol (ROH) is weakly nucleophilic in many contexts; its conjugate base (RO[−]) is much stronger. The “FGI” here is deprotonation:



Strategic use: This transforms an alcohol into a competent nucleophile for Williamson ether synthesis (an S_N2 bond formation).

Converting a weak electrophile into a strong electrophile

A carbonyl is electrophilic, but an acid derivative can be tuned. For example, converting a carboxylic acid to an acyl chloride dramatically increases electrophilicity at the carbonyl carbon. This is an activation FGI that enables acyl substitution under milder conditions.

14.2.5 Deciding when to perform FGI: early vs. late

There is no universal rule, but there are recurring strategic patterns.

Late-stage FGI minimizes functional group exposure

If a functional group is sensitive (e.g., aldehydes are prone to over-oxidation, polymerization, or unwanted addition), it may be advantageous to introduce it late. This reduces the number of steps during which the sensitive group must survive.

Early-stage FGI can simplify downstream selectivity

Sometimes an early oxidation state change makes later steps cleaner. For example, converting an alcohol to a carbonyl early can:

- remove a protic site that complicates strong-base chemistry,

- create a handle for enolate formation,
- provide a directing influence in certain reactions (context-dependent).

FGI should be justified by a downstream payoff

A useful discipline is to annotate each planned FGI with its purpose:

“Perform FGI X because it enables bond-forming step Y or avoids selectivity problem Z.”

If you cannot state the payoff clearly, the FGI may be unnecessary (and unnecessary steps are the primary source of low overall yields in multistep synthesis).

14.2.6 A compact “strategy table” of high-frequency FGIs

14.2.7 FGI and the “hidden cost” of selectivity

FGIs are deceptively simple on paper. In multistep settings, their main difficulty is not whether the transformation is known, but whether it can be performed **selectively**:

- **Chemoselectivity:** will an oxidant react with one alcohol without oxidizing another? will reduction stop at an aldehyde rather than over-reducing?
- **Regioselectivity:** will elimination give the desired alkene regioisomer?
- **Stereoselectivity:** will reduction or addition set the correct relative/absolute configuration?

This is why synthesis design treats FGIs as *strategic* rather than mechanical. A route with many FGIs can still be excellent if each one is selective and enables a high-value bond construction; conversely, a route with “few steps” can fail if one necessary FGI cannot be done cleanly.

14.2.8 A planning workflow that integrates FGI with retrosynthesis

When you propose a retrosynthetic disconnection, immediately ask the following forward-looking questions:

- **What functional groups must be present** on each fragment to realize the synthons as synthetic equivalents?

Starting group	FGI target	Strategic reason in synthesis planning
R–OH	R–X, R–OTs, R–OMs	Create a good leaving group to enable SN2 substitution or elimination; realize an alkyl electrophile synthon.
R–CH ₂ OH	R–CHO	Generate a carbonyl electrophile for nucleophilic addition or a precursor for further oxidation/state adjustments.
R ₂ CHOH	R ₂ C=O	Create a carbonyl for enolate formation (aldol-type C–C bond formation) or for controlled reductions/additions.
R–CHO	R–CO ₂ H	Reach acid oxidation level for later activation to amides/esters; often done when carbon skeleton is complete due to relative irreversibility.
R–CO ₂ H	R–COCl, activated ester, amide	Increase acyl electrophilicity to form C–N or C–O bonds (acyl substitution) under practical conditions.
Carbonyl compound	alcohol	Quench electrophilicity; set stereochemistry via reduction; prepare for leaving-group formation (alcohol → sulfonate).

Table 14.1: Common functional group interconversions and their typical strategic purpose in multistep synthesis.

- If those groups are not present in available precursors, **what FGIs** will install them?
- **When** should each FGI occur (before or after skeleton assembly) to minimize selectivity risk?

14.3 Chemoselectivity and Protecting Groups

Retrosynthetic analysis tells us *which bonds* to form, and functional group inter-conversion (FGI) tells us how to *prepare the functional groups* required for those bond-forming steps. In real molecules, however, functional groups rarely appear one at a time. A typical intermediate contains multiple nucleophiles, electrophiles, acids/bases, and π -systems. The central planning question becomes:

How can we make one transformation occur at one site in the presence of other, potentially reactive sites?

Two complementary strategies address this problem:

- **Chemoselectivity:** choose reagents/conditions that react preferentially with one functional group over another.
- **Protecting groups:** temporarily mask a functional group so it does not participate, then remove the mask later.

A strong synthesis plan prioritizes *intrinsic chemoselectivity* first and uses protecting groups only when necessary. Protecting groups increase step count and decrease overall yield, but they can make otherwise impossible sequences feasible.

14.3.1 Chemoselectivity: controlling *what* reacts

Chemoselectivity is the preferential reaction of a reagent with one functional group in the presence of others. When chemoselectivity is high, you can perform FGIs and bond-forming steps without elaborate protection/deprotection sequences.

Where chemoselectivity comes from: a practical hierarchy

Chemoselectivity usually derives from one (or more) of the following differences:

- **Intrinsic reactivity (electrophilicity/nucleophilicity):** aldehydes are typically more reactive than ketones; acid chlorides are more reactive than esters; esters are often more reactive than amides.
- **Acid–base properties:** a reagent may selectively deprotonate the most acidic site (e.g., terminal alkyne vs. alcohol vs. α -carbonyl).
- **Sterics and accessibility:** a bulky reagent may approach a less hindered site preferentially (e.g., selective silylation of a primary alcohol over a tertiary alcohol).
- **Coordination/directing effects:** Lewis acids or metals can bind to one site and “deliver” reactivity there.
- **Kinetics vs. thermodynamics:** reaction time/temperature can favor the faster-forming product (kinetic control) or the more stable product (thermodynamic control).

A synthesis planner should treat these as adjustable “dials”: reagent identity, solvent, temperature, order of addition, and protecting group choices all shift selectivity.

Example chemoselectivities that inform synthesis planning

The following are representative patterns that guide decision-making. They are written as *planning heuristics* rather than exhaustive rules.

Reductions: aldehyde vs. ester

A molecule containing both an aldehyde and an ester presents a selectivity challenge because both are electrophilic carbonyls. Many reducing agents reduce aldehydes faster than esters. The planning insight is:

If you need to reduce only the aldehyde in the presence of an ester, seek conditions where aldehyde reduction is rapid and ester reduction is slow.

If that selectivity cannot be achieved cleanly, the ester may need protection (or the sequence order must be changed so the ester is installed later).

Acyl substitution: acid chloride vs. ester vs. amide

In nucleophilic acyl substitution, reactivity often decreases in the order:



Thus, if your intermediate contains both an acid chloride and an ester, a nucleophile will generally attack the acid chloride first. This can be exploited to form one bond selectively *before* converting the remaining acyl group to a less reactive derivative.

Acid–base selectivity: which proton is removed?

If a molecule contains an alcohol and a carbonyl with α -hydrogens, the choice of base and conditions determines whether you generate an alkoxide (for O-alkylation) or an enolate (for C–C bond formation). In synthesis planning, this is not just mechanism trivia: it determines which bond you can make next.

14.3.2 Protecting groups: controlling *what cannot* react

When chemoselective conditions are unavailable (or unreliable at scale), the synthetic chemist often turns to **protecting groups**. A protecting group is a functional group modification introduced *solely* to prevent a site from reacting during one or more steps, with the expectation that it will later be removed to regenerate the original functional group.

Protecting groups are strategic liabilities (but sometimes necessary)

Every protecting group operation typically adds at least:

- one step to install the protecting group,
- one step to remove it,
- purification and yield loss at each step,
- additional constraints on reagent compatibility (the protecting group must survive other steps).

Therefore, the decision to protect should be justified explicitly:

Protect only when (i) chemoselectivity fails and (ii) the protected route meaningfully increases the probability of success.

General criteria for a good protecting group

A protecting group should meet four planning criteria:

- **Easy installation** in high yield under mild conditions.
- **Stability** under the planned reaction conditions (bases, acids, oxidants, reductants, heat).
- **Selective removal** (deprotection) without damaging other functional groups.
- **Orthogonality**: the ability to remove one protecting group in the presence of another (especially when multiple groups are protected).

14.3.3 Protecting groups in action: why “naive” routes fail

The underlying problem: competing nucleophiles

A common scenario is a substrate containing *two nucleophilic sites*, such as an amino alcohol. Suppose you want to form an *ether* by alkylating the oxygen with an alkyl halide, but the molecule also contains an amine. Amines are often more nucleophilic than alcohols, so direct exposure to an alkyl halide can give a mixture (N-alkylation, O-alkylation, multiple alkylations).

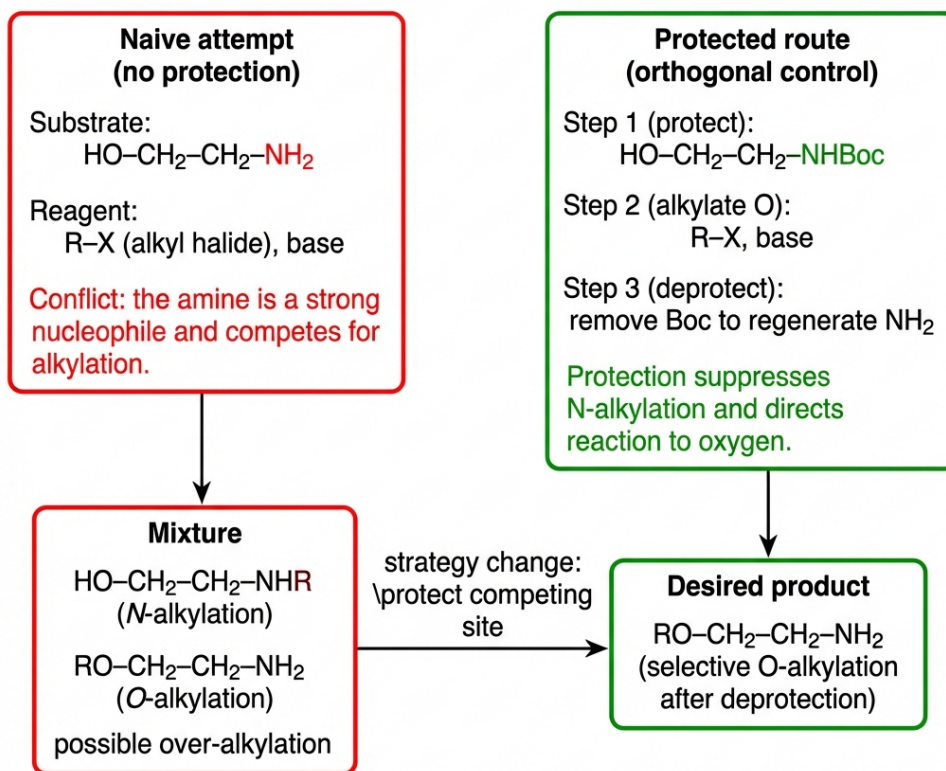
In such cases, protecting the amine (to reduce or eliminate its nucleophilicity) can channel the reaction to the oxygen.

Comparative scheme: unprotected vs. protected route (conceptual)

The following diagram illustrates the planning logic: a naive attempt produces a mixture because two sites compete, whereas a protected route blocks one site and yields the desired single product.

Competing functional groups: naive vs. protected strategy

Amino alcohol + alkyl halide: O-alkylation desired, but N-alkylation competes.

**14.3.4 Common protecting group families and what they are for**

A protecting group should be chosen because it solves a particular selectivity problem *under the conditions you anticipate*. The discussion below focuses on the *logic of choice*.

Protecting alcohols

Alcohols are common and can be problematic because they:

- are nucleophilic (can compete in substitution/acylation),

- are acidic enough to be deprotonated by strong bases (interfering with enolate formation),
- can coordinate to metals (affecting selectivity),
- can be oxidized under conditions intended for other sites.

Silyl ethers (e.g., TMS, TBDMS/TBS, TBDPS)

Silyl ethers are widely used because they are easy to install and often stable toward bases and many nucleophiles. Their deprotection can be tuned (more robust silyl groups require stronger conditions).

Planning logic: choose a silyl ether when you need an alcohol to survive *basic* conditions (e.g., organometallic additions, enolate chemistry), or when you need orthogonality among multiple alcohols (bulky vs. less bulky silyl groups can sometimes be selectively removed).

Acetals as alcohol-protecting motifs (via carbonyl protection)

Although acetals are usually discussed as carbonyl protecting groups, they also function as a way to “store” diols (cyclic acetals) or to mask reactive carbonyl chemistry that would otherwise affect alcohol transformations.

Protecting carbonyl compounds

Carbonyls (aldehydes and ketones) are electrophilic and can react undesirably with nucleophiles, reducing agents, and organometallics.

Acetals/ketals

Carbonyls can be protected as acetals/ketals, which are typically:

- **stable to base** and many nucleophiles,
- **cleaved by acid** (in aqueous acid, often).

Planning logic: use carbonyl protection when you need to run strongly basic or nucleophilic chemistry elsewhere (e.g., generate an enolate on a different carbonyl, perform organometallic addition to another electrophile) without the protected carbonyl being attacked.

Thioacetals (advanced option)

Thioacetals can be more robust than acetals under some conditions. In planning terms, they represent a “higher-stability” carbonyl mask when acetals fail, but their installation/removal may be less benign to sensitive functionality.

Protecting amines

Amines are often the most challenging functional group for chemoselectivity because they are:

- strongly nucleophilic (compete in alkylation/acylation),
- basic (protonation state changes reactivity),
- capable of binding catalysts/metals and altering reaction outcomes.

Boc and Cbz (carbamate protecting groups)

Carbamate protections (Boc, Cbz) reduce nucleophilicity and modulate basicity, making amines less likely to engage in unwanted substitution or addition.

Planning logic:

- Protect an amine when an electrophile intended for another nucleophile (e.g., an alcohol) would otherwise react at nitrogen.
- Choose protection with an eye toward deprotection conditions and compatibility with other protecting groups (**orthogonality**).

14.3.5 Orthogonality: managing multiple protecting groups rationally

In complex molecules, you may need to protect more than one functional group—or even multiple instances of the same type (e.g., two alcohols). **Orthogonality** means that each protecting group can be removed under conditions that leave the others intact.

Orthogonality is a planning constraint, not an afterthought

A route can fail if you protect early with a group that later cannot be removed without destroying a newly installed bond or functional group. Therefore, protecting groups

should be selected by *working backward* from the final deprotection sequence:

- What functional groups must be present at the end?
- Which will be introduced late (and must survive deprotection)?
- Therefore, which protecting groups can be removed under mild, selective conditions compatible with the late-stage functionality?

A practical orthogonality mindset

Rather than memorizing deprotection reagent lists, cultivate a qualitative map:

- Some protections are **acid-labile**.
- Some are **base-labile**.
- Some are **fluoride-labile**.
- Some are **hydrogenolysis-labile** (removed under H₂ and a catalyst).

Good orthogonal sets are chosen so that each deprotection uses a different “trigger,” allowing sequential unmasking.

14.3.6 Decision-making: a synthesis planner’s algorithm

When you confront a multifunctional intermediate, a disciplined planning approach prevents unnecessary protecting group steps.

Step 1: attempt chemoselectivity first

Ask:

- Is one functional group intrinsically more reactive?
- Can you change the protonation state to suppress one site (e.g., protonate an amine to reduce nucleophilicity)?
- Can you use a bulky reagent to favor the less hindered site?
- Can you alter the order of operations (perform the sensitive step earlier or later)?

Step 2: if chemoselectivity fails, protect the *problem* group

Protect the group that causes side reactions—not necessarily the group you intend to react. In the amino-alcohol example, protecting the amine (the more nucleophilic site) enables selective O-alkylation.

Step 3: choose protecting groups with removal in mind

Before committing, verify:

- the protecting group survives all planned steps in between,
- its deprotection is compatible with the final molecule and other protections,
- the deprotection will not reverse key stereochemistry or induce rearrangements.

14.3.7 Protecting groups and step economy: the yield perspective

Because overall yield is multiplicative, extra steps are costly. If each step proceeds in 90% yield, then:

$$(0.90)^5 \approx 0.59, \quad (0.90)^{10} \approx 0.35$$

Adding two protecting group steps (installation and removal) can noticeably reduce material throughput, even when individual steps are “high yielding.” Thus, protecting groups are justified when they:

- prevent catastrophic mixtures that would lower yield far below 90%,
- enable convergent fragment coupling that improves overall efficiency,
- allow a key transformation to proceed with high selectivity and reliable purification.

14.3.8 Summary: integrating selectivity into synthetic strategy

Chemoselectivity and protecting groups are not separate topics from retrosynthesis and FGI; they are the operational constraints that determine whether a retrosynthetic plan is *executable*. A robust synthesis plan therefore proceeds as follows:

- Use retrosynthesis to identify strategic bond constructions.
- Use FGIs to prepare the necessary functional groups and oxidation levels.
- Evaluate chemoselectivity at each step; modify reagents, conditions, and step order to achieve control.
- Introduce protecting groups only when necessary, and choose them to be stable, removable, and orthogonal.

With these tools, the synthesis planner can manage complex molecules in which many functional groups compete—not by hoping for selectivity, but by *designing* it.

14.4 Stereochemical Control in Synthesis

Retrosynthetic analysis focuses on connectivity: which bonds must be formed and which functional groups must be interconverted to enable those bond constructions. Chemoselectivity and protecting-group logic then address a second practical constraint: *which site reacts*. A third constraint is often the most demanding of all:

When a reaction can form more than one stereoisomer, how do we design a route that delivers the *desired* stereoisomer selectively?

This section develops the strategic logic of stereochemical control. The unifying idea is that stereochemistry is not “added at the end.” It is controlled (or lost) at specific steps, and your route must be engineered so that those steps are intrinsically selective.

14.4.1 Why stereochemical control is a planning problem

Many synthetic transformations either:

- create new stereocenters (e.g., additions to carbonyls, epoxidations, reductions), or
- set relative stereochemistry between existing stereocenters (e.g., aldol additions, hydrogenations, cyclizations), or

- erode stereochemical information through racemization or epimerization (e.g., base-promoted enolization at α -stereocenters).

Therefore, stereochemical planning begins by identifying **stereochemical decision points**:

- Which steps *create* stereocenters?
- Which steps *could* scramble stereochemistry?
- Which steps *must* deliver a specific relative or absolute configuration?

A useful mindset is to treat each key bond formation as a **3D event**: you are not only forming a bond, you are choosing a face, a conformation, and often a transition-state geometry.

14.4.2 Language: relative vs. absolute stereochemical control

Relative stereocontrol (diastereoselectivity)

Relative stereocontrol means that the product is formed with a preferred *relationship* between stereocenters (syn/anti; cis/trans; erythro/threo), regardless of which enantiomer is formed. This is quantified by **diastereomeric ratio** (dr).

Relative control is often sufficient if the synthesis begins with a chiral pool starting material and the existing stereocenter biases formation of new ones.

Absolute stereocontrol (enantioselectivity)

Absolute stereocontrol means favoring one enantiomer over the other, quantified by **enantiomeric excess** (ee). Achieving high ee typically requires a **chiral influence external to the substrate**, such as:

- a chiral catalyst (reagent control),
- a chiral auxiliary (temporary chiral directing group),
- a chiral starting material (substrate control via the chiral pool).

A planning rule: diastereoselectivity is usually easier than enantioselectivity

Diastereoselectivity can be achieved by existing stereocenters in the substrate, by conformational bias, and by simple steric/electronic effects. Enantioselectivity requires that the reaction environment be chiral in a consistent way across many molecules reacting in solution. Consequently, enantioselective steps tend to be more sensitive to conditions and may require optimization, but they can dramatically shorten routes by avoiding resolution steps.

14.4.3 Three strategic modes of stereocontrol

Most stereochemical solutions in synthesis fall into three categories. Effective route design often combines them.

Mode 1: substrate control (the molecule controls its own outcome)

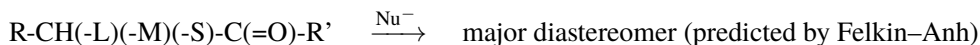
In **substrate-controlled** reactions, an existing stereocenter (or a rigid conformation) biases the approach of the reagent to one face of a π -system or carbonyl. This yields preferential formation of one diastereomer.

1,2-induction: additions to chiral carbonyl compounds

When a nucleophile adds to an aldehyde or ketone adjacent to a stereocenter, the two faces of the carbonyl are diastereotopic. A practical model for predicting the favored face is the **Felkin–Anh model**.

Felkin–Anh (qualitative): consider a carbonyl compound bearing an α -stereocenter with substituents L (large), M (medium), and S (small). The favored conformation places the largest group L roughly orthogonal to the carbonyl to minimize unfavorable interactions, and nucleophilic attack occurs from the less hindered face, typically opposite L.

A simplified planning representation is:



Strategic use: if you can introduce a stereocenter early (chiral pool or enantioselective step), you can often leverage it repeatedly to set adjacent stereocenters via 1,2-induction, reducing the need for external chiral reagents.

1,3-induction and conformational bias

Stereocenters further away can also exert influence if the substrate adopts a preferred conformation (e.g., in cyclic systems). In synthesis planning, rigid ring systems are valuable because they convert subtle stereochemical preferences into strong diastereoselectivity.

Mode 2: reagent control (a chiral reagent/catalyst controls the outcome)

In **reagent-controlled** reactions, a chiral reagent or catalyst delivers enantioselectivity even when the substrate is achiral (or when substrate bias is weak).

Why reagent control is strategically powerful

Reagent control can:

- create chirality “from scratch” at a late stage (useful when early chirality would be lost or scrambled),
- reduce reliance on chiral pool starting materials,
- avoid classical resolution (wasting material).

Strategic caution: reagent control must be matched to functional-group compatibility

Chiral catalysts and reagents often impose constraints: solvent, temperature, additives, and the presence of coordinating heteroatoms can strongly affect selectivity. Therefore, reagent-controlled steps should be placed where protecting groups and chemoselectivity issues are manageable.

Mode 3: auxiliary control (attach chirality temporarily)

A **chiral auxiliary** is a chiral group covalently attached to the substrate to create a diastereomeric environment for a key step; after the stereochemistry is set, the auxiliary is removed.

Strategic advantages

- Auxiliaries often deliver high and reliable selectivity because the stereochemical information is built into the substrate (diastereoselective control).
- They can be predictable and scalable.

Strategic disadvantages

- Installation and removal add steps (step economy penalty).
- The auxiliary must be recoverable or inexpensive.

Auxiliary strategies are typically chosen when:

- high enantioselectivity is essential,
- catalytic enantioselective options are unreliable or incompatible,
- the stereochemical decision point is pivotal and worth the extra steps.

14.4.4 Diastereoselective C–C bond formation: aldol reactions as a central case

Among bond-forming reactions, aldol additions are a cornerstone because they:

- form a new C–C bond,
- create up to two new stereocenters (the β -hydroxy carbon and possibly the α -carbon),
- produce functionalized products that can be elaborated (FGI) into alkenes, carbonyls, or polyol motifs.

Although detailed transition-state drawings are beyond the minimal requirements here, a key planning idea is that aldol stereochemistry is often controlled by a **chair-like transition state** (Zimmerman–Traxler logic). Even without drawing the full model, synthesis planners use these qualitative rules:

- Choose the enolate geometry (E vs. Z) to bias syn vs. anti relationships in the aldol product.
- Use a cyclic, chair-like transition state to rationalize which substituents prefer pseudo-equatorial positions.
- Select reaction conditions and enolate generation methods that preserve the chosen enolate geometry.

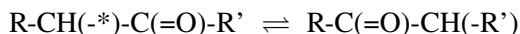
Strategic translation: stereochemical control in aldol chemistry is not an afterthought; it is built into how the nucleophile is generated and how the electrophile is presented.

14.4.5 Stereochemical “fragility”: when stereocenters are lost

Synthesis planning must also anticipate steps that can *erase* stereochemistry. The most common mechanisms are:

Epimerization via enolization

Any stereocenter α to a carbonyl is at risk under acidic or basic conditions that permit enol/enolate formation:



(where * indicates a stereocenter). Even brief exposure to base can lead to partial racemization/epimerization.

Planning response:

- Avoid strong base after establishing α -stereocenters unless conditions are carefully controlled (temperature, time, base strength).
- Consider installing α -stereocenters late, or using transformations that do not proceed through enolates.

Stereochemical scrambling at carbocations (SN1)

If a step proceeds through a planar carbocation intermediate (SN1-like), stereochemical information at that center may be lost, leading to racemization. Thus, when a stereocenter must be preserved, favor stereospecific pathways (often SN2) or alternative bond constructions that avoid carbocation character.

14.4.6 Convergent synthesis and stereochemistry: preserving optical purity

Convergent synthesis is attractive for step economy, but it introduces a stereochemical requirement: **each fragment must be prepared with the correct stereochemical integrity** before coupling.

Stereo-integrity checkpoints

In a convergent plan, include explicit checkpoints:

- Ensure each fragment contains the correct enantiomer/diastereomer (or a manageable mixture) *before* coupling.
- Verify that coupling conditions do not epimerize sensitive stereocenters (especially α to carbonyls).
- Prefer couplings that are stereospecific when stereochemical information must be transferred across a bond-forming step.

Why late-stage resolution is usually a poor strategy

Separating enantiomers or diastereomers at the end is often inefficient because:

- you may discard half (or more) of the material,
- purification becomes harder as molecules become more complex,
- downstream transformations can amplify small stereochemical impurities into major complications.

Therefore, stereochemical control should be designed into the route at earlier, simpler stages whenever feasible.

14.4.7 Double asymmetric induction: when substrate and reagent both influence selectivity

A sophisticated but practically important scenario is **double asymmetric induction**: a chiral substrate reacts with a chiral reagent/catalyst. The selectivity depends on whether the two chiral influences reinforce each other (*matched*) or oppose each other (*mismatched*).

Strategic lesson

If you already have strong substrate control, introducing a chiral reagent may not improve outcomes and can even reduce selectivity if mismatched. Conversely, if substrate control is weak or gives the wrong diastereomer, reagent control can override it.

In planning terms:

Do not assume chirality always adds. Evaluate whether existing stereocenters help, hurt, or are irrelevant for the next stereochemical decision point.

14.4.8 A practical planning checklist for stereochemical control

Before finalizing a multistep route, audit it stereochemically:

- **Locate stereochemical decision points:** which steps create or set stereocenters?
- **Assign the control mode:** substrate, reagent/catalyst, or auxiliary for each decision point.
- **Check for fragility:** are any stereocenters at risk of epimerization or racemization in later steps?
- **Plan the order accordingly:** install fragile stereocenters late, or avoid conditions that scramble them.
- **Minimize stereochemical “repairs”:** avoid plans that require late-stage separations or corrections.

14.4.9 Summary: stereochemistry as an integrated design constraint

Stereochemical control is not an isolated topic; it is interwoven with retrosynthesis, FGI, and chemoselectivity. A successful route:

- uses retrosynthetic logic to place key bond constructions at points where stereochemical control is achievable,
- chooses functional group interconversions that *enable* selective reactions rather than undermine stereochemical integrity,
- uses chemoselective reagents and protecting groups to keep the reaction focused on the intended site,
- deploys substrate control, reagent/catalyst control, and auxiliary strategies deliberately at the stereochemical decision points.

In multistep synthesis, stereochemistry is best treated as a resource: once established with high fidelity, it can guide subsequent transformations—but only if the route is designed to preserve it.

14.5 Problems

14.5.1 Problem 1: Retrosynthetic tree for a substituted aryl ketone (EAS vs. acylation strategy)

Design a synthesis of **4-methoxyacetophenone** from **benzene** and any needed inorganic reagents.

- Draw a full retrosynthetic analysis using at least **two distinct disconnections** that lead to plausible starting materials.
- Propose a forward synthesis (3–5 steps) including reagents and conditions.
- Your route must address **regiochemical control** (para vs. ortho) and justify why the major product is 4-substituted.
- Identify at least one plausible side reaction and a strategy to minimize it.

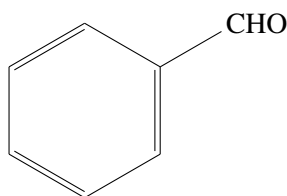
14.5.2 Problem 2: Alcohol-to-leaving-group FGI and selective SN2 substitution

Synthesize **2-phenoxyethanol** $\text{PhO}-\text{CH}_2-\text{CH}_2-\text{OH}$ from **phenol** and **ethylene glycol** $\text{HO}-\text{CH}_2-\text{CH}_2-\text{OH}$.

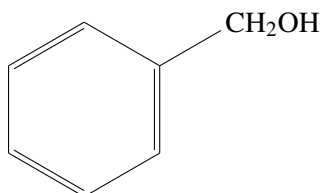
- Provide a retrosynthetic analysis that identifies the key **C–O bond formation** step.
- Propose a forward synthesis and explicitly include the **FGI** used to create a suitable electrophile.
- Specify how you will control **mono-substitution** vs. di-substitution (formation of $\text{PhO}-\text{CH}_2-\text{CH}_2-\text{OPh}$).
- State whether your key substitution is SN1 or SN2 and justify mechanistically.

14.5.3 Problem 3: Chemoselective reduction in a multifunctional substrate

You are given the substrate **methyl 4-formylbenzoate** (a para-substituted aromatic bearing both an aldehyde and an ester):



Design a synthesis of **methyl 4-(hydroxymethyl)benzoate**:



- Propose conditions for a **chemoselective reduction** of the aldehyde without reducing the ester.
- Provide a mechanistic rationale for the selectivity (reactivity hierarchy, kinetics, or reagent choice).
- Identify at least one competing pathway (over-reduction, transesterification, etc.) and propose how to avoid it.

14.5.4 Problem 4: Protecting-group logic for an amino alcohol (orthogonality requirement)

Design a synthesis of **3-aminopropyl methyl ether** $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OCH}_3$ from **3-aminopropan-1-ol** $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$.

- Explain why a “naive” methylation strategy can lead to mixtures (identify the competing nucleophiles).
- Propose a route that uses an **amine protecting group** to ensure **selective O-alkylation**.
- Your protecting group strategy must be **orthogonal** to the O-alkylation conditions: explicitly state why the protection survives, and how it is removed.
- Provide the complete forward synthesis with reagents and conditions.

14.5.5 Problem 5: Retrosynthesis via aldol disconnection with diastereoselectivity analysis

Target molecule:



(4-hydroxy-2-hexanone; the relative configuration at the alcohol-bearing carbon is unspecified.)

- Perform an aldol retrosynthetic disconnection to identify plausible carbonyl fragments.
- Propose a forward aldol synthesis (including enolate generation conditions).
- Predict whether the product will be formed as a mixture of diastereomers or with a preference; justify your answer using transition-state/conformational reasoning.
- Propose one modification (choice of enolate type, temperature, order of addition, or auxiliary) aimed at improving diastereoselectivity.

14.5.6 Problem 6: Convergent fragment coupling using organometallic addition and FGI

Synthesize **1-phenyl-2-propanol** $\text{Ph}-\text{CH}(\text{OH})-\text{CH}_3$ from **benzene** and **ethanol** as the only organic feedstocks (inorganic reagents allowed).

- Provide a convergent retrosynthesis that identifies the key **C–C bond formation**.
- Translate synthons into realistic **synthetic equivalents** (e.g., organometallic nucleophile and carbonyl electrophile).
- Include at least one necessary **FGI** to reach the required oxidation level for the electrophile.
- Discuss whether the product is formed as a racemate or in enantioenriched form, and why.

14.5.7 Problem 7: Managing regioselectivity and functional group compatibility in aromatic synthesis

Design a synthesis of **3-bromobenzoic acid** from **toluene**.

- Provide a retrosynthetic analysis that addresses the meta relationship between Br and CO₂H.
- Propose a forward synthesis that uses directing effects strategically (installation order matters).
- Identify at least one step where **FGI** is essential and justify its placement (early vs. late).
- Explain how you will avoid forming significant amounts of the ortho and para brominated isomers.

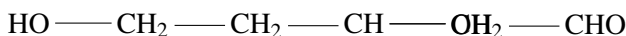
14.5.8 Problem 8: Stereochemical control by substrate vs. reagent (design choice)

Target: **(R)-1-phenylethanol** Ph—CH(OH)—CH₃ in **high enantiomeric excess**.

- Propose **two different strategies**: (a) substrate-controlled approach starting from an enantiopure chiral pool precursor (you may choose an appropriate chiral starting material); (b) reagent-controlled approach starting from an achiral precursor (e.g., acetophenone) using an enantioselective reduction.
- For each strategy, give a retrosynthetic plan and a forward synthesis.
- Compare the two routes in terms of step count, robustness, and potential stereochemical failure modes (racemization, poor ee, etc.).

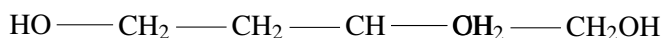
14.5.9 Problem 9: Protecting group selection in the presence of acid/base-sensitive functionality

Target molecule:



(a hydroxy-substituted aldehyde)

Starting material:



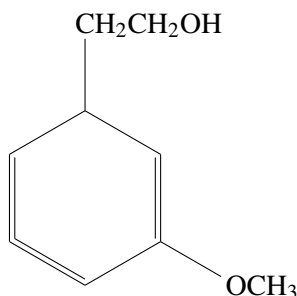
(the corresponding triol)

Design a synthesis converting the terminal primary alcohol into the aldehyde *without* oxidizing the other alcohols.

- Identify why direct oxidation is problematic (chemoselectivity).
- Propose a protecting group plan for the alcohols that should remain unchanged.
- Your plan must include a clear **order**: protection $\rightarrow$ selective oxidation $\rightarrow$ deprotection.
- State at least one condition incompatibility you considered (acid-labile vs. base-labile protecting groups).

14.5.10 Problem 10: “Final boss” retrosynthesis integrating disconnections, FGIs, chemoselectivity, and stereocontrol

Target molecule (mid-complexity, multiple functional groups, one stereocenter):



(A trisubstituted anisole bearing a benzylic secondary alcohol side chain and a primary alcohol side chain; relative positions as drawn.)

- Draw a full retrosynthetic tree that includes: (i) at least **two alternative disconnections** for forming the benzylic C–C bond; (ii) at least **one FGI-based disconnection** (oxidation level manipulation).
- For your preferred route, write a forward synthesis that specifies: (i) reagents/conditions for each step; (ii) at least one deliberate chemoselectivity choice (why one functional group reacts and another does not); (iii) at least one protecting-group decision (even if you argue none are needed, justify that claim).

- Provide a stereochemical plan for the secondary alcohol: indicate whether you will make a racemate or an enantioenriched product; if enantioenriched, specify whether control is substrate-, reagent-, or auxiliary-based and identify the stereochemical decision point.
- Identify the **highest-risk step** in your sequence and propose one backup strategy (alternate reagents, different order, different disconnection).

