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Chemistry 04 lessons and exercises with solutions

Realized by:

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General introduction

1. The Science of Carbon Compounds

Organic chemistry is one of the most dynamic and expansive branches of modern science. In its broadest sense, it is the study of compounds that contain carbon, a deceptively simple definition that encompasses well over twenty million known substances, with thousands of new ones being synthesised or discovered every year. From the simplest hydrocarbon methane (CH_4) to the double-helix of deoxyribonucleic acid (DNA), from the aspirin tablet on a pharmacist's shelf to the polymers woven into athletic clothing, organic molecules pervade every dimension of our lives.

The central role of carbon in this vast chemistry stems from a unique combination of properties. Carbon is a second-row element of group IVA, possessing four valence electrons and therefore the capacity to form four covalent bonds simultaneously. Unlike most other elements, carbon forms strong, stable bonds with itself, giving rise to chains, branched structures, rings, and three-dimensional cages of arbitrary complexity. This property «called catenation» is unmatched in the periodic table. Combined with carbon's ability to bond to hydrogen, oxygen, nitrogen, sulfur, phosphorus, and the halogens, catenation generates an essentially boundless chemical space.

2. Historical Perspective and the Demise of Vitalism

For much of the eighteenth century, chemists divided matter into two irreconcilable domains: inorganic substances, derived from the mineral world, and organic substances, obtained exclusively from living organisms. The prevailing doctrine «vitalism» held that organic compounds owed their existence to a mysterious 'vital force' inherent to life, and that they could therefore never be prepared in a laboratory from purely mineral starting materials.

This dogma was overturned in 1828 when the German chemist Friedrich Wöhler inadvertently synthesised urea ($H_2N–CO–NH_2$), a compound found in mammalian urine, by simply heating ammonium cyanate «an inorganic salt» in aqueous solution. Wöhler's experiment demonstrated conclusively that organic molecules

obey the same chemical laws as inorganic ones and require no special vital force. In a letter to his mentor Jöns Jacob Berzelius, he famously wrote that he could make urea 'without the use of kidneys, either of man or dog'.

In the decades that followed, the systematic synthesis of organic natural products accelerated rapidly. August Kekulé proposed the tetravalence of carbon and the cyclic structure of benzene (1865). Jacobus Henricus van 't Hoff and Joseph-Achille Le Bel independently explained optical activity through the concept of the tetrahedral carbon atom (1874). Emil Fischer deciphered the stereochemistry of sugars (1891). These milestones laid the theoretical foundations of modern organic chemistry.

3. Importance and Scope of Organic Chemistry

Today, organic chemistry stands at the crossroads of virtually every applied science and technology:

Pharmaceuticals and medicine: the design and synthesis of drugs, from analgesics and antibiotics to anticancer agents and antivirals is fundamentally an exercise in organic chemistry. Understanding how a molecule interacts with a biological receptor requires knowledge of its three-dimensional shape, electronic distribution, and functional group chemistry.

Materials science and engineering: polymers (plastics, rubbers, fibres, resins), adhesives, coatings, and semiconducting organic materials are all products of applied organic synthesis. The properties of these materials, mechanical strength, thermal stability, electrical conductivity, are engineered at the molecular level through deliberate choice of functional groups and connectivity.

Energy: petroleum refining, petrochemical production, biofuels, and the development of organic photovoltaic cells all depend on a deep understanding of carbon-based molecules and their reactivity.

Agriculture and food science: pesticides, herbicides, fertilisers, flavourings, preservatives, and vitamins are organic molecules whose properties and safety profiles are analysed through the tools of organic chemistry.

Biochemistry and molecular biology: the molecules of life, amino acids, proteins, nucleotides, nucleic acids, lipids, carbohydrates, enzyme cofactors, hormones, are all organic compounds. The central dogma of molecular biology (DNA → RNA → protein) is, at its most fundamental level, a sequence of organic chemical transformations.

4. Why Organic Chemistry Matters to Engineers

For students of engineering, organic chemistry is not merely a prerequisite to be endured. It is a fundamental tool. Process engineers designing a chemical plant must understand reaction mechanisms to optimise yield, minimise by-products, and ensure safety. Civil and materials engineers must know why certain polymers degrade under UV irradiation and why others resist solvents or extreme temperatures. Biomedical engineers designing drug-delivery systems or tissue scaffolds must understand how functional groups govern solubility, biocompatibility, and degradation rate. Environmental engineers assessing the fate of a pollutant in soil or groundwater must be able to predict its reactivity and persistence.

The preparatory cycle of engineering schools provides the theoretical bedrock on which these applied skills will later be built. This course covers four essential pillars of organic chemistry, each of which recurs throughout the engineering curriculum and professional practice:

Nomenclature: a precise, universal language for naming and communicating the identity of organic molecules. Without it, no two chemists, or engineers, can be certain they are discussing the same compound.

Isomerism and Stereochemistry: the recognition that identical molecular formulas can correspond to profoundly different molecules with different physical properties, biological activities, and reactivities. Many pharmaceutical disasters (e.g., thalidomide) have resulted from neglect of stereochemistry.

Electronic Effects: the understanding of how electron distribution within a molecule influences its stability, acidity, basicity, and reactivity. These concepts explain why one molecule reacts readily while a structurally similar one is inert.

Reaction Mechanisms: a step-by-step account of bond-breaking and bond-forming events. Mechanisms provide the predictive framework that distinguishes scientific chemistry from mere empirical formula following.

Organic chemistry rewards patience and systematic thinking. Rather than memorising isolated facts, seek to understand the underlying principles "electronegativity, orbital overlap, thermodynamic stability, kinetic accessibility" and the facts will follow naturally. A student who understands why the SN2 reaction proceeds with inversion needs no separate rule for each substrate; the mechanism itself provides the answer.

The Author

CHAPTER 1: Nomenclature of Organic Compounds

1. Definitions and General Concepts

1.1 Organic Chemistry

Organic chemistry is the branch of chemistry devoted to the study of carbon-containing compounds. With very few exceptions (CO, CO_2, carbonates, cyanides), virtually all compounds containing carbon are classified as organic. Carbon's unique ability to form four stable covalent bonds, with itself and with hydrogen, oxygen, nitrogen, sulfur, and halogens gives rise to millions of distinct molecules ranging from simple methane (CH_4) to complex biopolymers.

1.2 Molecular Formulas of Organic Compounds

1.2.1 Gross (Molecular) Formula

The gross formula, also called the molecular formula, gives the total number of each type of atom in a molecule without conveying any structural information. It is obtained by summing all atoms of each element.

Example: Hexane (C_6H_{14}) six carbon atoms and fourteen hydrogen atoms, but no indication of connectivity.

1.2.2 Developed and Semi-Developed Formulas

The developed (or fully expanded) formula shows every bond explicitly. The semi-developed formula (also called the condensed structural formula) groups hydrogen atoms next to the carbon they are bonded to, while still displaying carbon-to-carbon bonds.

Example: Propane developed — $H_3C–CH_2–CH_3$ (semi-developed); each C–H and C–C bond drawn explicitly in the full version.

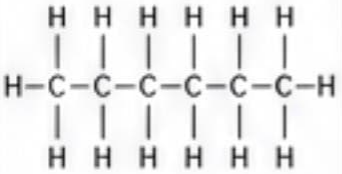
Molecular formula (gross formula)	Semi-developed formula	Developed (full) formula	Skeletal (line-angle) formula
C_6H_{14}	$CH_3–CH_2–CH_2–CH_2–CH_2–CH_3$		

Figure 1. Different representations of organic molecules: molecular formula, semi-developed structure, fully developed structure, and skeletal formula.

1.2.3 Geometric Representations

Three-dimensional information is conveyed through several conventions: line-angle (skeletal) formulas represent each vertex or end of a line as a carbon atom with implicit hydrogens; wedge-dash notation uses solid wedges for bonds projecting toward the viewer and dashed wedges for bonds going away. These representations are discussed in detail in Chapter 2 (Stereochemistry).

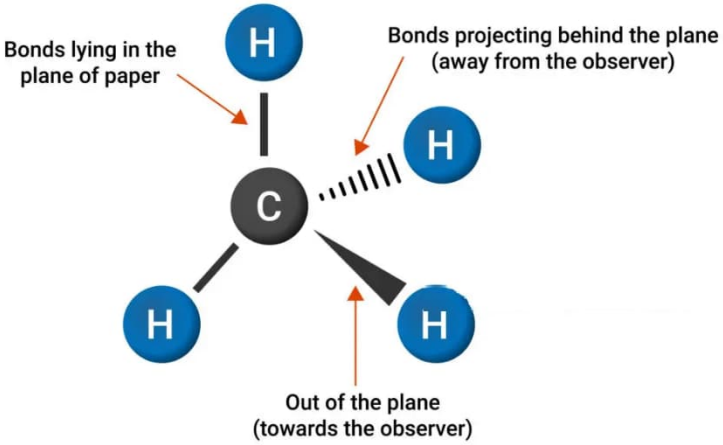


Figure 2: Three dimentionnal molecular representation

1.3 Classification of Carbon Atoms

Carbon atoms in organic molecules are classified according to the number of other carbon atoms directly bonded to them:

Primary carbon (1°): bonded to exactly one other carbon atom. Example: the terminal carbons in propane.

Secondary carbon (2°): bonded to exactly two other carbon atoms. Example: the middle carbon in propane.

Tertiary carbon (3°): bonded to three other carbon atoms. Example: the central

carbon in isobutane.

Quaternary carbon (4°): bonded to four other carbon atoms. Example: the central carbon in neopentane (2,2-dimethylpropane).

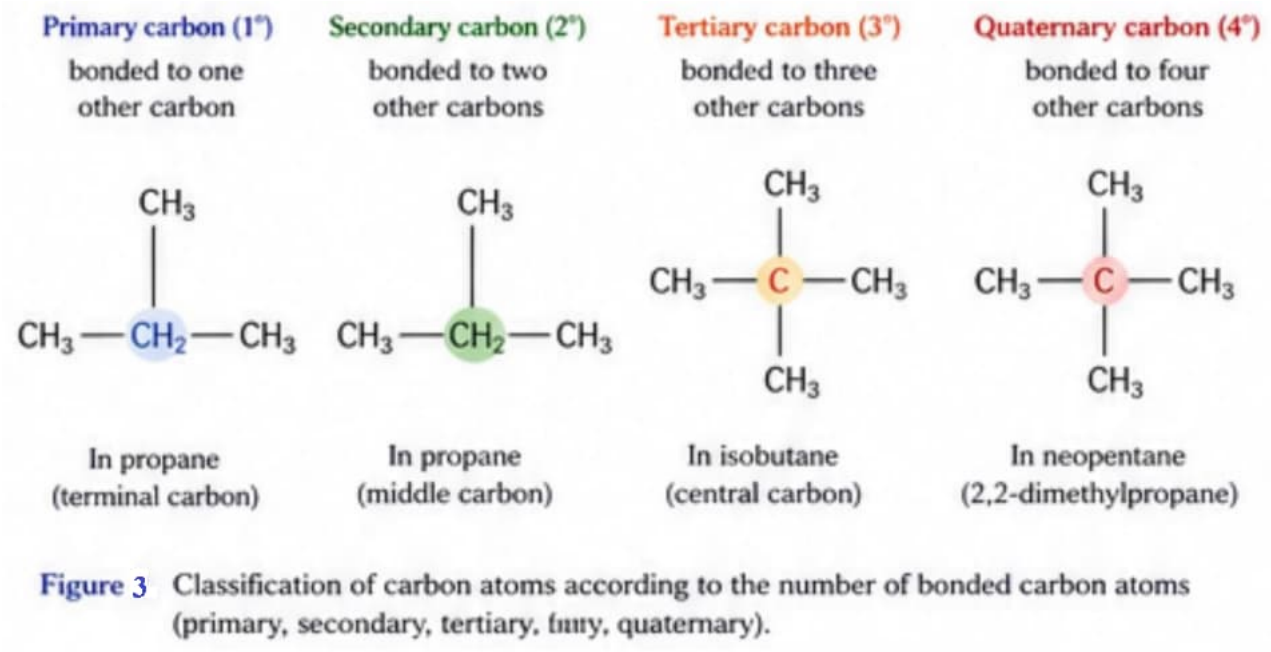


Figure 3 Classification of carbon atoms according to the number of bonded carbon atoms (primary, secondary, tertiary, and quaternary).

1.4 Chemical Functions and Functional Groups

A functional group is an atom or a group of atoms responsible for the characteristic chemical reactions of a molecule. The same functional group reacts in a similar way regardless of the rest of the molecule. Understanding functional groups is the cornerstone of systematic organic chemistry.

Functional Group	Class of Compound	General Formula
–OH	Alcohol	R–OH
–COOH	Carboxylic acid	R–COOH
–CHO	Aldehyde	R–CHO
C=O (internal)	Ketone	R–CO–R'
$–NH_2$	Primary amine	$R–NH_2$
–X (F, Cl, Br, I)	Alkyl halide	R–X
–COO–	Ester	R–COO–R'
$–CONH_2$	Amide	$R–CONH_2$
–C≡N	Nitrile	R–CN
–O– (between two R)	Ether	R–O–R'

Functional group	Class of compound	General formula	Example
–OH	Alcohol	R–OH	$CH_3–CH_2–OH$ Ethanol
–COOH	Carboxylic acid	R–COOH	$CH_3–COOH$ Acetic acid
–C(=O)–H	Aldehyde	R–CHO	$CH_3–CHO$ Acetaldehyde
–C(=O)– (internal)	Ketone	R–CO–R'	$CH_3–CO–CH_3$ Acetone
$–NH_2$	Primary amine	$R–NH_2$	$CH_3–CH_2–NH_2$ Ethylamine
–X (F, Cl, Br, I)	Alkyl halide	R–X	$CH_3–CH_2–Cl$ Chloroethane
–C(=O)–COO–	Ester	R–COO–R'	$CH_3–COO–CH_3$ Methyl acetate
–C(=O)–$CONH_2$	Amide	$R–CONH_2$	$CH_3–CONH_2$ Acetamide
–C≡N	Nitrile	R–CN	$CH_3–CN$ Acetonitrile
–O– (between two R)	Ether	R–O–R'	$CH_3–O–CH_3$ Dimethyl ether

Figure 4. Common functional groups in organic chemistry with their general formulas.

1.5 Groups and Radicals

An organic radical (or substituent) is a fragment derived from a parent compound by removing one or more hydrogen atoms. When named as substituents, alkane-derived radicals are called alkyl groups and are denoted by the letter R.

Methyl: $–CH_3$ (from methane)

Ethyl: $–CH_2CH_3$ (from ethane)

Propyl / isopropyl: $–CH_2CH_2CH_3$ / $–CH(CH_3)_2$

Butyl, isobutyl, sec-butyl, tert-butyl: four constitutional isomers of $C_4H_9–$

2. Systematic Nomenclature (IUPAC Rules)

2.1 General Naming Rules

The International Union of Pure and Applied Chemistry (IUPAC) established a systematic set of nomenclature rules that allow any organic compound to be given a unique, unambiguous name. The name is built from three components:

Prefix(es): describe substituents and their positions on the principal chain.

Root (stem): reflects the length of the principal carbon chain (meth-, eth-, prop-, but-, pent-, hex-, hept-, oct-, non-, dec-...).

Suffix: indicates the principal functional group (if any) and the degree of unsaturation.

2.2 Alkanes

Alkanes are saturated hydrocarbons with the general formula C_nH_{2n+2} for acyclic (open-chain) compounds.

2.2.1 Unbranched (Straight-Chain) Alkanes

The first ten unbranched alkanes are named using Greek/Latin prefixes combined with the suffix -ane:

n	Molecular Formula	IUPAC Name	Boiling Point (°C)
1	CH_4	Methane	−161.5
2	C_2H_6	Ethane	−88.6
3	C_3H_8	Propane	−42.1
4	C_4H_{10}	Butane	−0.5
5	C_5H_{12}	Pentane	36.1
6	C_6H_{14}	Hexane	68.7
7	C_7H_{16}	Heptane	98.4
8	C_8H_{18}	Octane	125.7
9	C_9H_{20}	Nonane	150.8
10	$C_{10}H_{22}$	Decane	174.1

2.2.2 Branched-Chain Alkanes

To name a branched alkane:

- Identify the longest continuous carbon chain, this is the principal chain, which gives the root name.
- Number the chain from the end closest to the first branch point.
- Name each branch (substituent) as an alkyl group and assign its locant.

Alphabetise substituents (ignoring multiplying prefixes di-, tri-, etc.).

If two or more identical substituents are present, use di-, tri-, tetra- prefixes.

Example: 2-methylpentane

Longest chain: 5 carbons (pentane). A methyl group at C-2. Full name: 2-methylpentane. Formula: $CH_3CH(CH_3)CH_2CH_2CH_3$.

Example: 2,3-dimethylbutane

Longest chain: 4 carbons (butane). Two methyl groups at C-2 and C-3. Full name: 2,3-dimethylbutane.

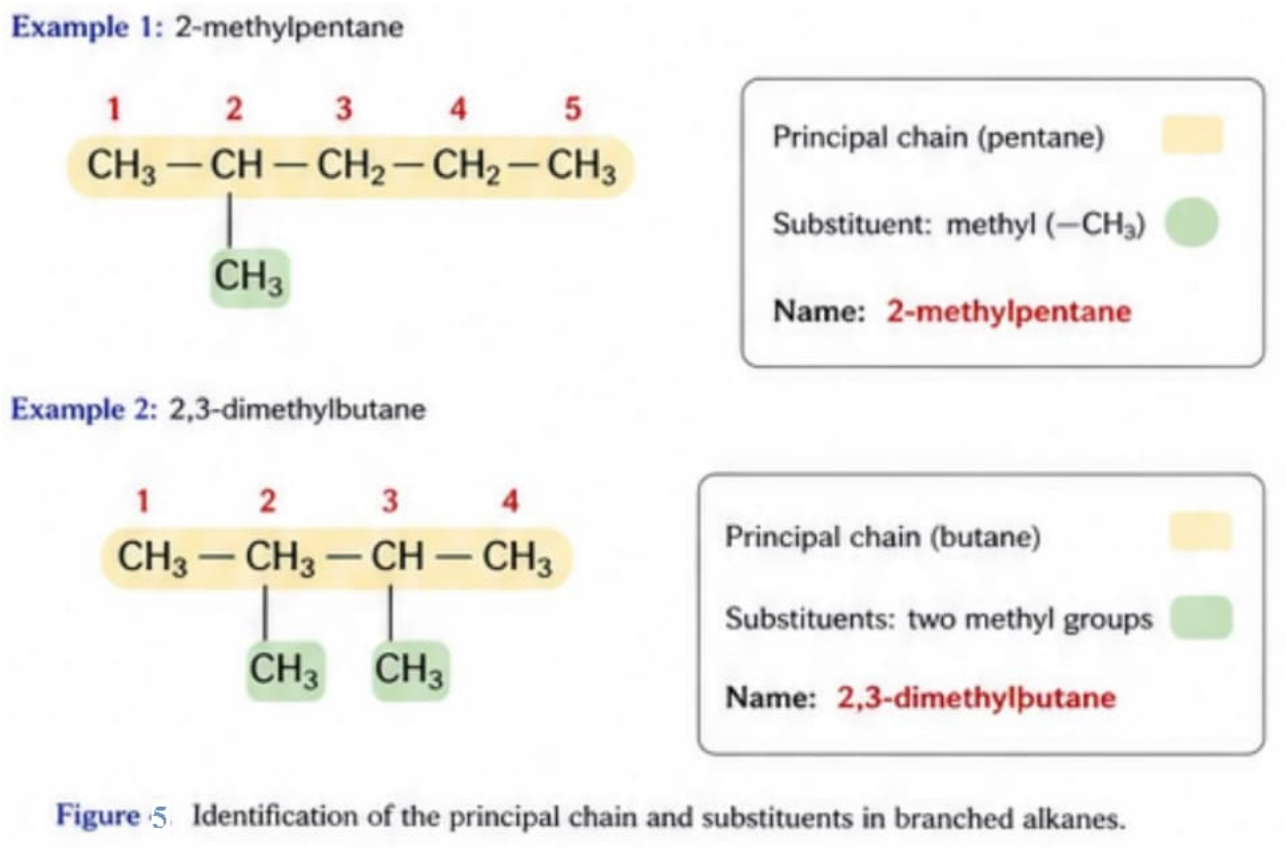


Figure 5 Identification of the principal chain and substituents in branched alkanes.

2.3 Alkenes

Alkenes contain at least one carbon-carbon double bond (C=C). The suffix changes from -ane to -ene. The general formula for a monoene is CnH_2n.

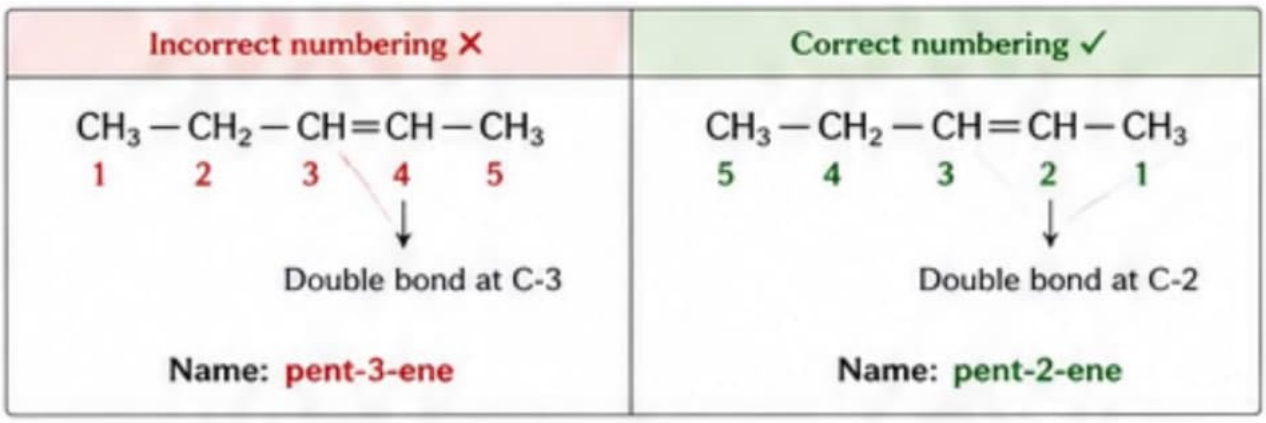


Figure 6. Numbering of carbon chains in alkenes to give the double bond the lowest locant.

2.3.1 Alkenes with One Double Bond

The name is obtained by folowing:

- Choose the longest chain containing the double bond.
- Number from the end that gives the double bond the lower locant.
- Insert the locant of the first doubly bonded carbon before -ene.

Example: 1-butene : CH_2=CH–CH_2–CH_3: four-carbon chain, double bond starting at C-1.

Example: 2-butene: CH_3–CH=CH–CH_3: double bond starting at C-2.

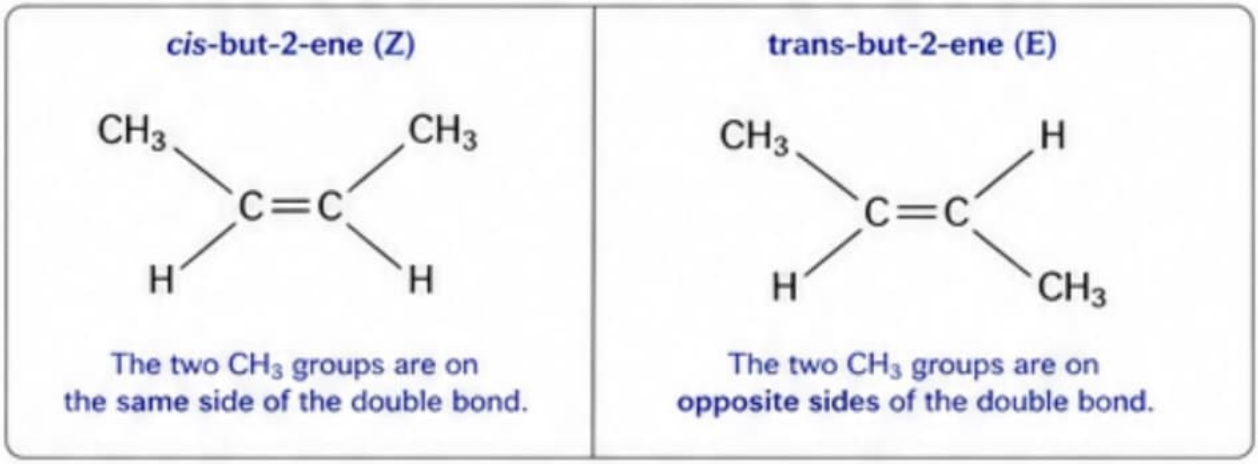


Figure 7. Geometric isomerism: *cis* and trans configurations in alkenes (but-2-ene).

2.3.2 Alkenes with Multiple Double Bonds

When two or more double bonds are present the suffixes -adiene, -atriene, etc. are used. Each double bond is assigned a locant.

Example: 1,3-butadiene — CH_2=CH–CH=CH_2: two conjugated double bonds at C-1 and C-3.

2.4 Alkynes

Alkynes contain at least one carbon-carbon triple bond (C≡C). The suffix is -yne. The general formula for a monoyne is C_nH_{2n-2}. Numbering follows the same rules as for alkenes, giving the triple bond the lowest possible locant.

Example: 1-butyne — HC≡C–CH_2–CH_3

Example: 2-butyne — CH_3–C≡C–CH_3

2.5 Combined Alkenes and Alkynes

When a chain contains both double and triple bonds the stem ends with -en-yne (or -enyne). Both multiple bonds receive locants; double bonds are named before triple bonds in the suffix sequence (e.g., pent-1-en-4-yne).

2.6 Cyclic Hydrocarbons

Cycloalkanes and cycloalkenes are named by adding the prefix cyclo- to the corresponding acyclic name. Substituents are numbered to give the lowest locant set. Benzene, cyclohexane, and cyclopentane are the most frequently encountered rings.

Example: Cyclopentane — A five-membered saturated ring: C_5H_{10}.

Example: 1,3-cyclohexadiene — A six-membered ring with conjugated double bonds at C-1 and C-3.

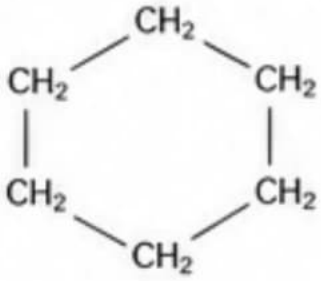
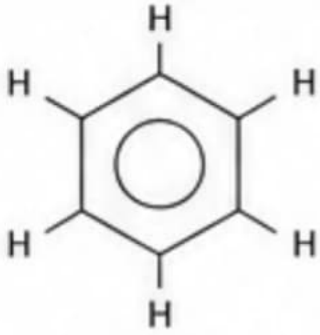
Cyclohexane (C_6H_{12})	Benzene (C_6H_6)
	
Saturated six-membered ring (no double bonds).	Aromatic six-membered ring with delocalized π-electrons.

Figure 8 Representation of cyclic hydrocarbons: cyclohexane and benzene.

3. Naming Compounds with Functional Groups

3.1 Priority of Functional Groups (Suffix vs. Prefix)

When a molecule contains a functional group that appears as a suffix in the IUPAC name, the principal chain must contain that group, and it receives the lowest possible locant. The IUPAC priority order (highest → lowest as suffix): carboxylic acids > anhydrides > esters > acyl halides > amides > nitriles > aldehydes > ketones > alcohols > amines.

Highest priority (as suffix)

Lowest priority (as suffix)

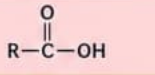
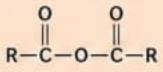
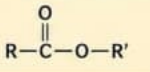
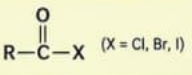
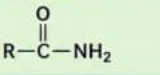
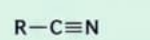
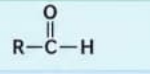
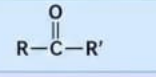
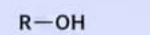
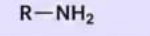
Order	Functional group	Structure (general formula)	Example (name)	Suffix / Prefix
1	Carboxylic acids		Ethanoic acid (CH_3COOH)	Suffix: -oic acid
2	Anhydrides		Ethanoic anhydride $(CH_3CO)_2O$	Suffix: -anhydride
3	Esters		Ethyl ethanoate ($CH_3COOCH_2CH_3$)	Suffix: -oate
4	Acyl halides		Ethanoic chloride (CH_3COCl)	Suffix: -oyl halide
5	Amides		Ethanamide (CH_3CONH_2)	Suffix: -amide
6	Nitriles		Ethanenitrile (CH_3CN)	Suffix: -nitrile
7	Aldehydes		Ethanal (CH_3CHO)	Suffix: -al
8	Ketones		Propanone (CH_3COCH_3)	Suffix: -one
9	Alcohols		Ethanol (CH_3CH_2OH)	Prefix: hydroxy-
10	Amines		Ethanamine ($CH_3CH_2NH_2$)	Prefix: amino-

Figure 9. priority of functional groups

3.2 Ethers and Thioethers

Simple ethers (R–O–R') are named as alkoxy derivatives of an alkane (systematic) or as 'alkyl alkyl ether' (common). Thioethers (R–S–R') replace 'oxy' with 'thio'.

Example: Methoxymethane — $CH_3–O–CH_3$ (dimethyl ether, common name).

Example: 2-ethoxybutane — $C_2H_5–O–CH(CH_3)CH_2CH_3$.

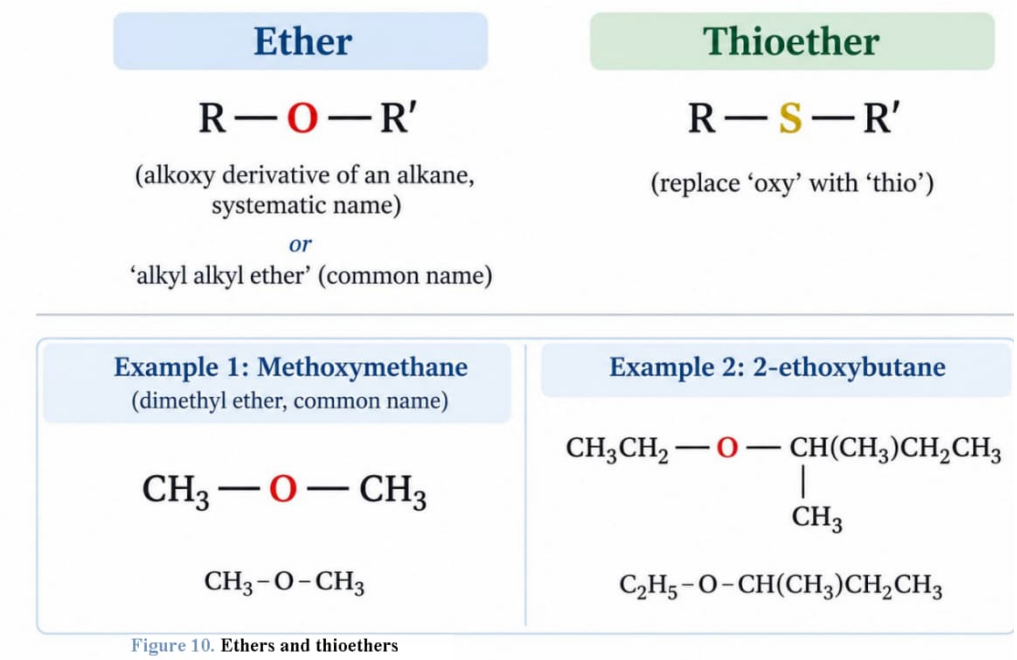


Figure 10. **Ethers and thioethers**

3.3 Alcohols and Thiols

Alcohols (R–OH) are named by replacing the terminal -e of the alkane name with -ol. Thiols (R–SH) use the suffix -thiol.

Example: Propan-1-ol — $CH_3CH_2CH_2OH$ — OH at C-1.

Example: Propan-2-ol — $CH_3CH(OH)CH_3$ — OH at C-2 (isopropanol).

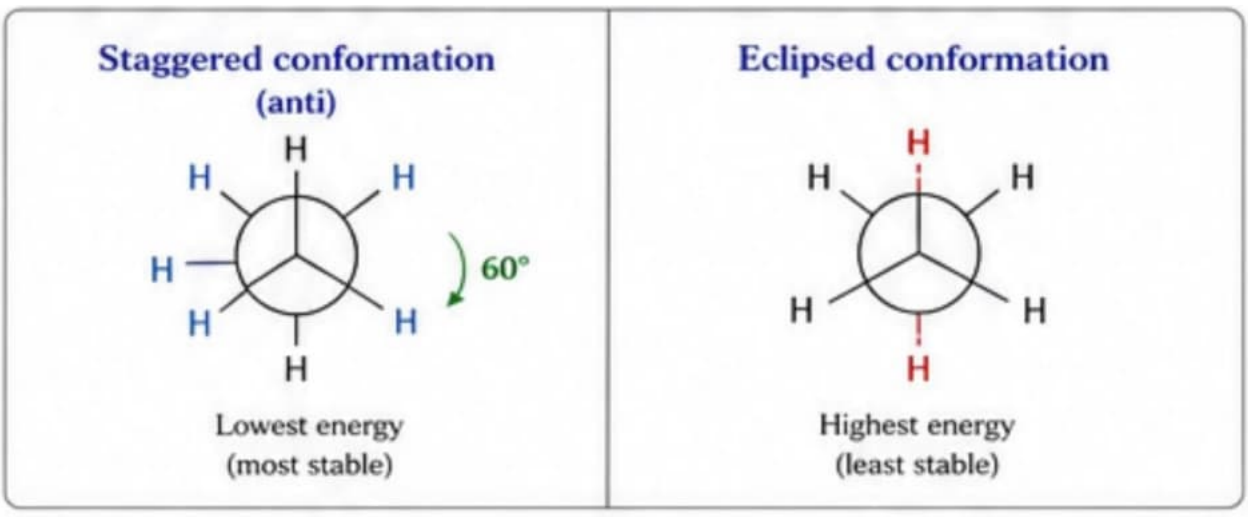


Figure11 Newman projection showing staggered and eclipsed conformations of ethane.

3.4 Carboxylic Acids, Salts, and Anhydrides

Carboxylic acids (–COOH) are named with the suffix -oic acid (or -carboxylic acid if the COOH carbon is not part of the principal chain). The carboxyl carbon always receives the number 1.

Example: Ethanoic acid (acetic acid) — CH_3COOH — two carbons including the COOH.

Example: Butanedioic acid (succinic acid) — $HOOCCH_2CH_2COOH$.

Carboxylate salts are named [cation] [stem]-oate. Anhydrides carry the suffix -oic anhydride or -ic anhydride (common).

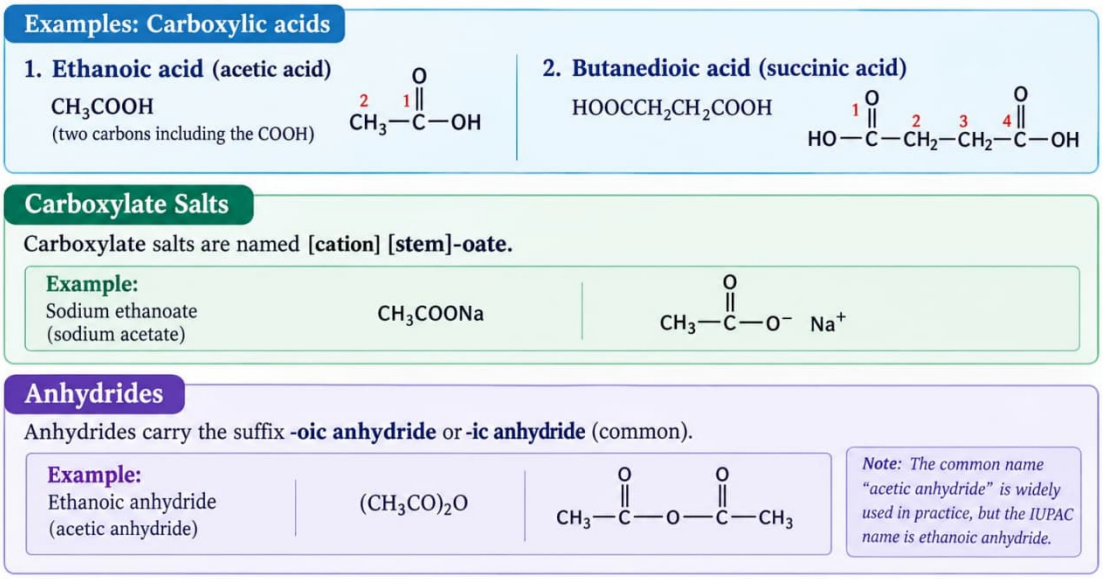


Figure 12. carboxylic acids derivatives

3.5 Esters

Esters (R–COO–R') are named [alkyl] [acid stem]-oate. The alkyl part names the –OR' group; the acid part names the acyl portion.

Example: Ethyl ethanoate — $CH_3COOC_2H_5$ (ethyl acetate). The acid is ethanoic acid; the alkyl group is ethyl.

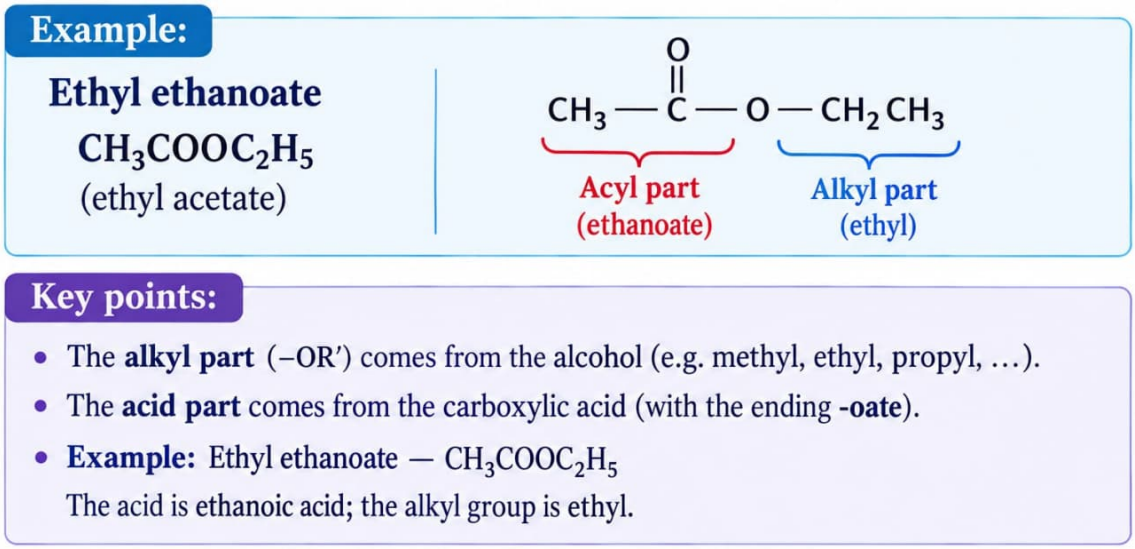


Figure 13. Esters

3.6 Acid Halides (Acyl Halides)

Formed by replacing –OH of a carboxylic acid with a halide. Suffix: -oyl halide (systematic) or -yl halide (common). Example: ethanoyl chloride (CH_3COCl), also called acetyl chloride.

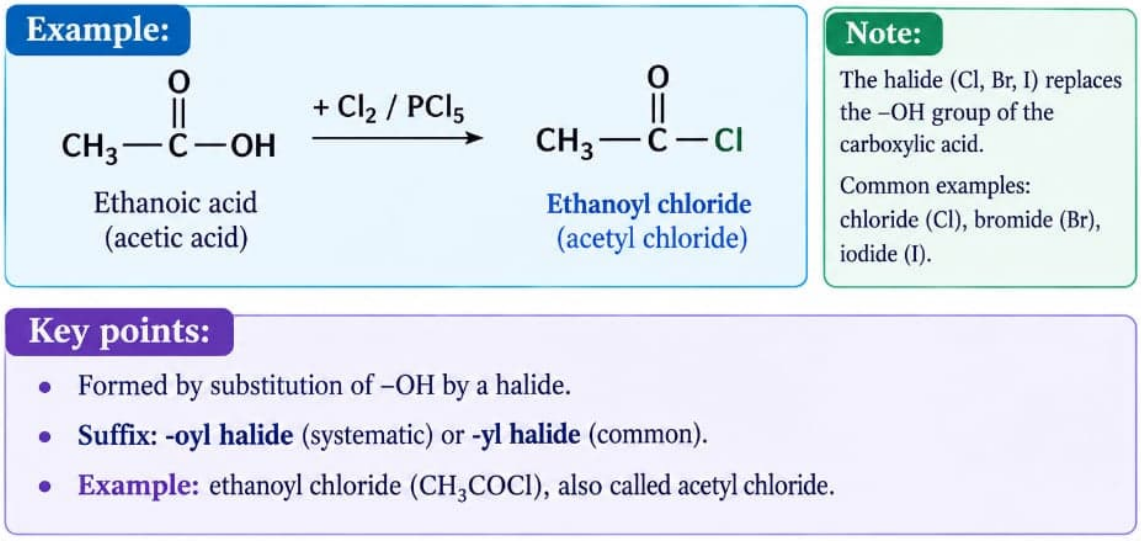


Figure 13. Acids Halides

3.7 Amides

Amides ($R–CONH_2$) use the suffix -amide. N-substituted amides carry the letter N before the substituent name: N-methylpropanamide.

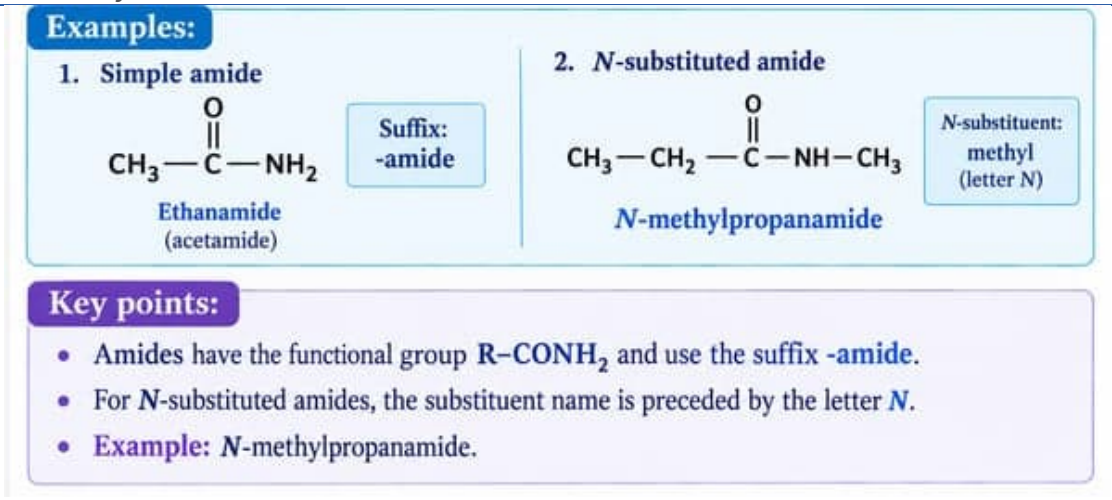


Figure 14. Amides

3.8 Nitriles

Nitriles (R–C≡N) are named with the suffix -nitrile (systematic) or -onitrile when the CN carbon is part of the chain count. Example: ethanenitrile (CH_3CN), commonly called acetonitrile.

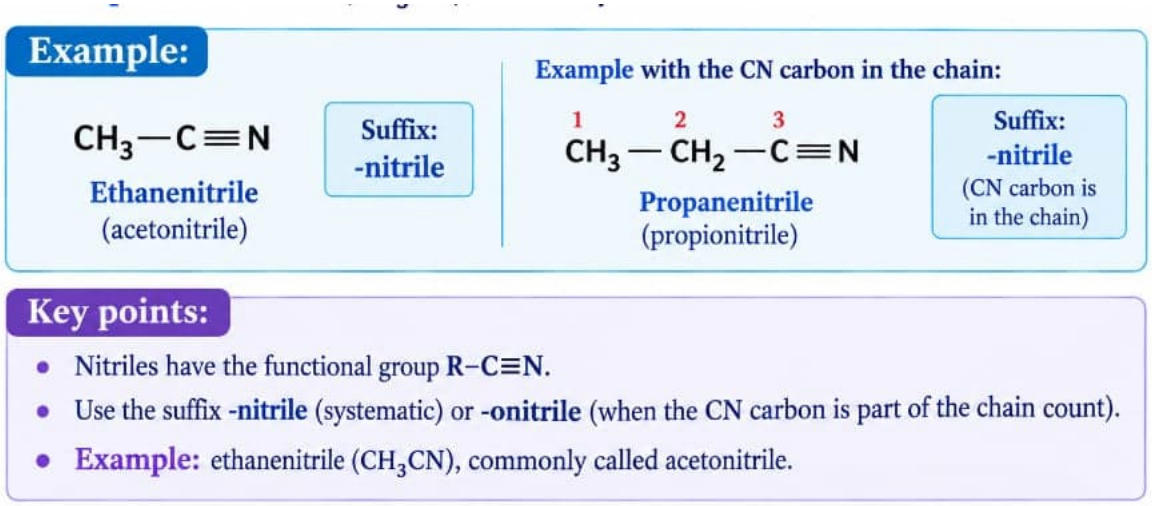


Figure 15. Nitriles

3.9 Aldehydes and Ketones

Aldehydes (R–CHO) use the suffix -al; the carbonyl carbon is always C-1. Ketones (R–CO–R') use the suffix -one, with the carbonyl carbon given the lowest available number.

Example: Propanal CH_3CH_2CHO.

Example: Propan-2-one CH_3COCH_3 (acetone, the simplest ketone).

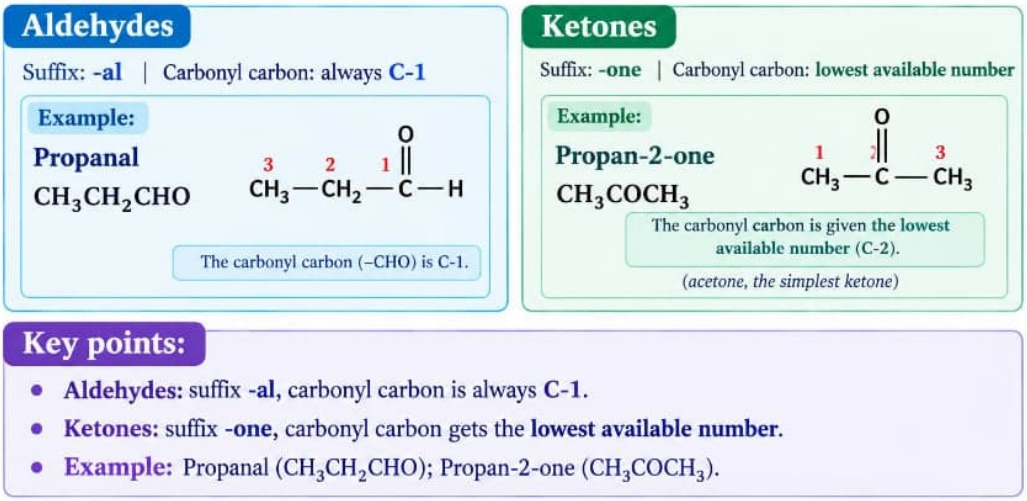


Figure 16. Aldehydes and Ketones

3.10 Amines

Primary amines ($R–NH_2$) are named by replacing the terminal -e with -amine, or by naming the chain as an alkylamino substituent. Secondary (R_2NH) and tertiary (R_3N) amines are named N,N-dialkyl… or listed alphabetically with N- prefixes.

Example: Propan-1-amine — $CH_3CH_2CH_2NH_2$.

Example: N,N-dimethylpropan-1-amine — $(CH_3)_2N–CH_2CH_2CH_3$.

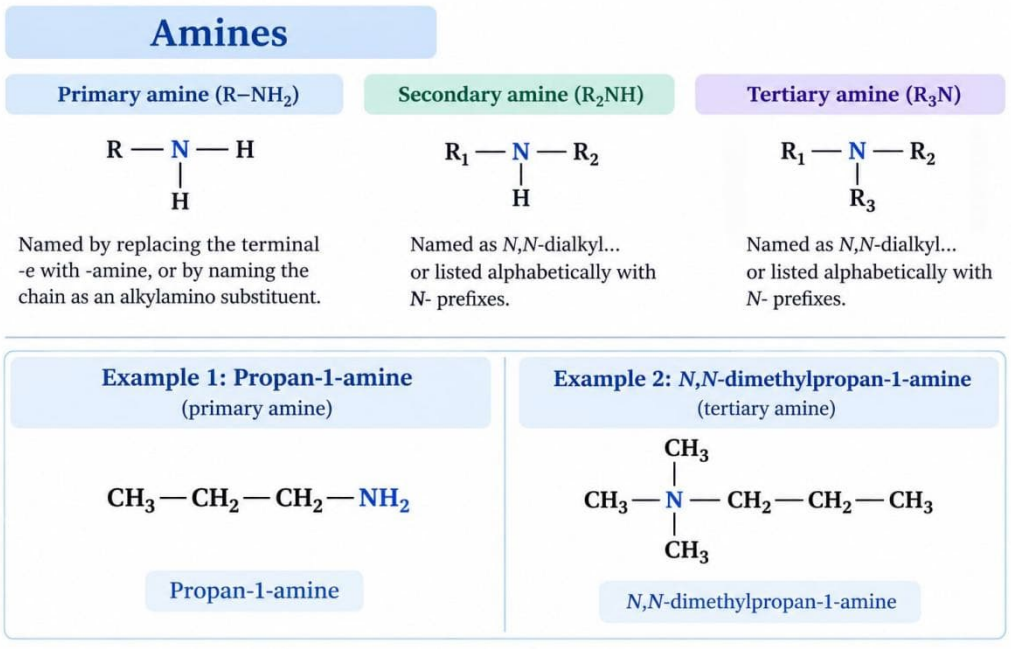


Figure 17. Amines

3.11 Epoxides

Epoxides (three-membered cyclic ethers) are named as oxacyclopropane derivatives (oxirane parent) or, in common nomenclature, as [alkyl] oxide.

Systematic: 2-methyloxirane (propylene oxide).

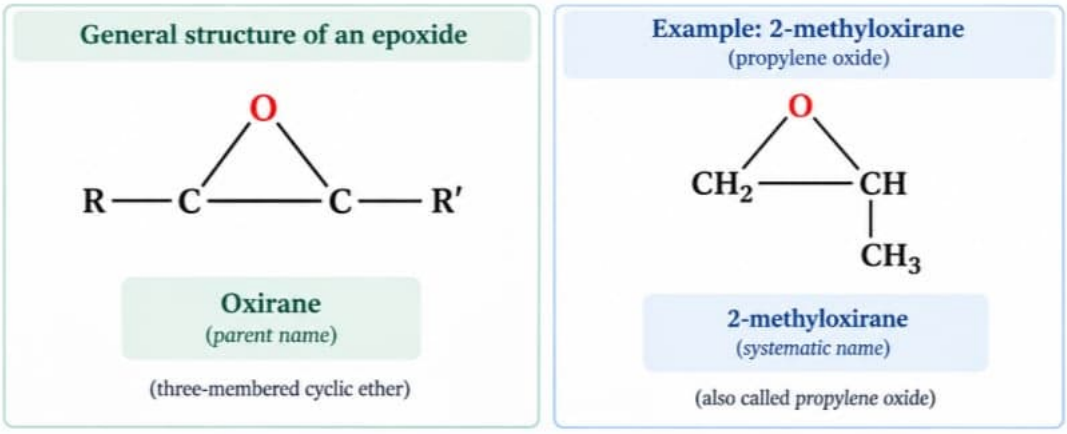


Figure 18. Epoxides

3.12 Compounds with Halogens and Nitro Groups

Halogens appear as prefixes: fluoro-, chloro-, bromo-, iodo-. Nitro (–NO_2) is also a prefix. Their locants are assigned so as to minimise the complete set.

Example: 2-chloropropane $CH_3CHClCH_3$.

Example: 1-bromo-2-nitrobenzene a benzene ring with Br at C-1 and NO_2 at C-2.

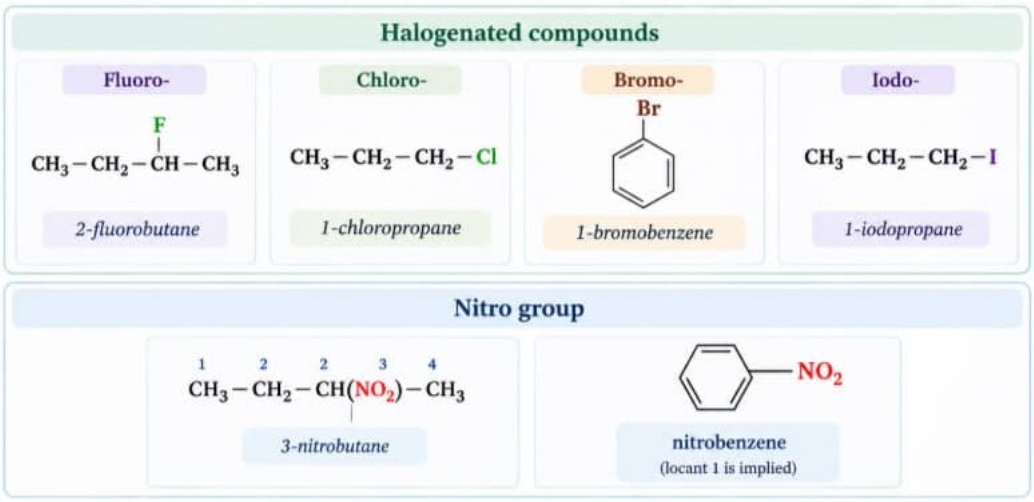


Figure 19. Halogens and Nitro groups

4. Aromatic Compounds

4.1 Benzene and Aromaticity

Benzene (C_6H_6) is the archetypal aromatic compound. Its six π electrons are delocalised over the ring, satisfying Hückel's rule (4n + 2 electrons, n = 1). It is represented by a hexagon with an inscribed circle. Fused-ring aromatic systems

(naphthalene, anthracene) extend this delocalization.

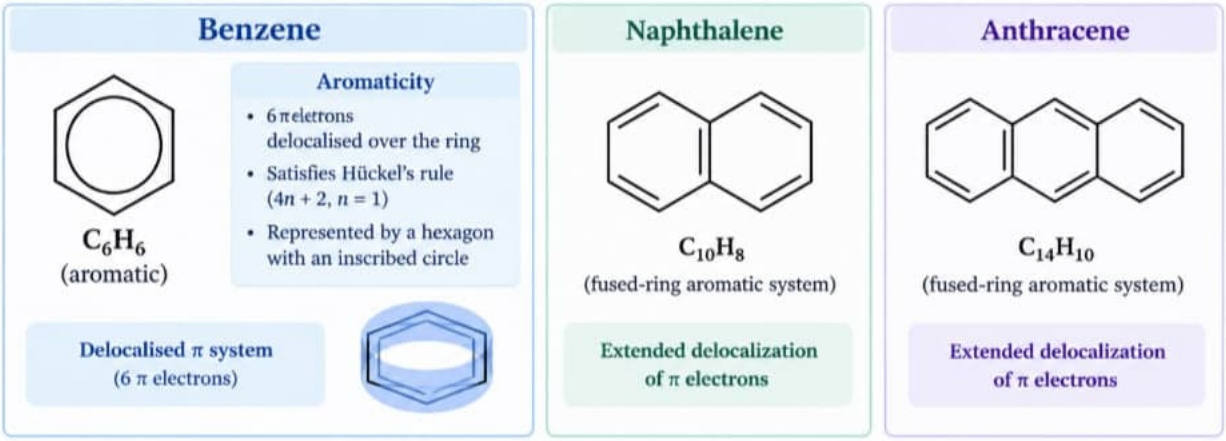


Figure 20. Aromatic Compounds

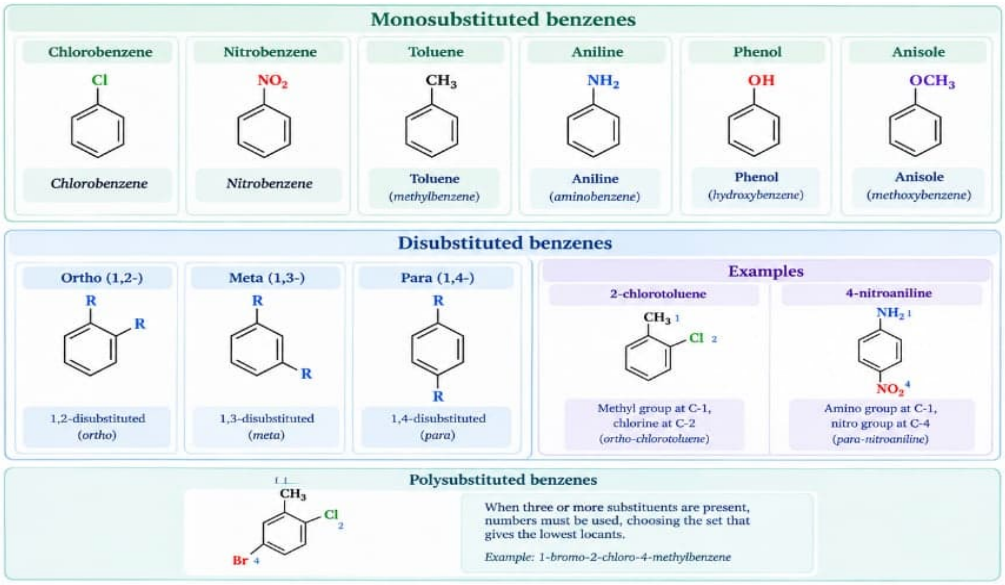
4.2 Naming Substituted Benzenes

Monosubstituted benzenes are named as [substituent]benzene (e.g., chlorobenzene, nitrobenzene). Many common names survive in IUPAC recommendations: toluene (methylbenzene), aniline (aminobenzene), phenol (hydroxybenzene), anisole (methoxybenzene).

For disubstituted benzenes, positions are indicated by ortho (1,2-), meta (1,3-), and para (1,4-) or by numbers. For three or more substituents, numbers must be used, choosing the set that gives the lowest locants.

Example: 2-chlorotoluene; Methyl group at C-1, chlorine at C-2 (ortho-chlorotoluene).

Example: 4-nitroaniline; Amino group at C-1, nitro group at C-4 (para-nitroaniline).



5. Nomenclature of Polyfunctional Compounds

5.1 Order of Priority of the Principal Functional Groups

Many organic molecules of practical interest (drugs, natural products, monomers) carry two or more different functional groups. IUPAC rules require that only one group, the principal characteristic group, be expressed as a suffix. All the other groups are cited as prefixes, in alphabetical order, together with the alkyl substituents. The choice of the principal group is made according to a fixed order of seniority, summarised in the table below (from the most senior to the least senior).

Class	Suffix (principal group)	Prefix (secondary group)
Carboxylic acid	-oic acid / -carboxylic acid	carboxy-
Anhydride	-oic anhydride	—
Ester	alkyl -oate / -carboxylate	alkoxycarbonyl-
Acid halide	-oyl halide	halocarbonyl-
Amide	-amide / -carboxamide	carbamoyl-
Nitrile	-nitrile / -carbonitrile	cyano-
Aldehyde	-al / -carbaldehyde	formyl- (oxo-)
Ketone	-one	oxo-
Alcohol	-ol	hydroxy-
Thiol	-thiol	sulfanyl-
Amine	-amine	amino-
Ether	—	alkoxy-
Halide, nitro	—	halo-, nitro-

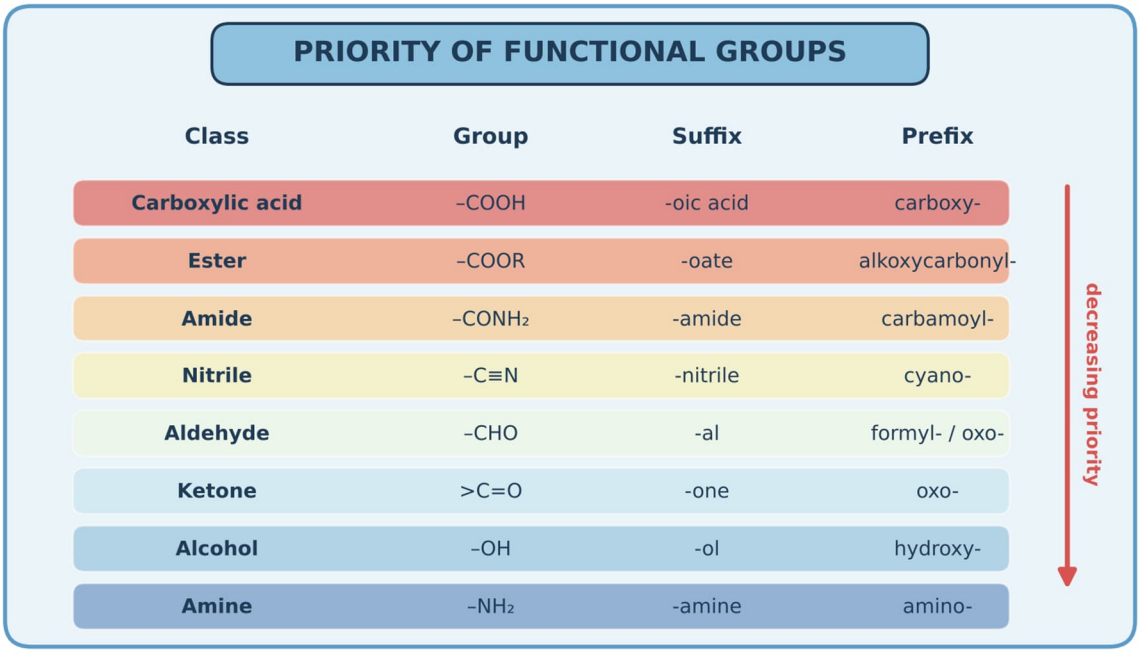


Figure 21. Decreasing seniority of the principal functional groups (suffix) and their prefix names

Note: halogens (fluoro-, chloro-, bromo-, iodo-), the nitro group (nitro-), the alkoxy group (methoxy-, ethoxy-) and alkyl groups are never expressed as suffixes. They are always prefixes, whatever the other groups present in the molecule.

5.2 Systematic Procedure for Naming a Polyfunctional Compound

The following algorithm can be applied to any open-chain compound. It is the method recommended to students because it avoids the most common errors.

Step 1 – Identify all the functional groups present and determine the principal group using the order of seniority.

Step 2 – Choose the principal chain. According to the IUPAC 2013 recommendations, the principal chain is the one that (i) contains the maximum number of principal groups; then (ii) is the longest; then (iii) contains the maximum number of multiple bonds; then (iv) carries the maximum number of substituents.

Step 3 – Number the principal chain so as to give the lowest possible locants, successively, to: (i) the principal group(s); (ii) the multiple bonds considered together (ene and yne); (iii) the double bonds; (iv) the prefixes taken together; (v) the prefix cited first in alphabetical order.

Step 4 – Name and number all the substituents (prefixes), arrange them alphabetically, and use multiplying prefixes (di-, tri-, tetra-) where needed.

Multiplying prefixes are ignored in the alphabetical order, but iso- and neo- are taken into account.

Step 5 – Assemble the name: prefixes + stem (chain length) + unsaturation infix (-an-, -en-, -yn-) + suffix of the principal group. The terminal "e" of the stem is elided before a suffix beginning with a vowel (propan-1-ol, but propane-1,2-diol).

Step 6 – Add stereodescriptors (E/Z, R/S, cis/trans) in front of the complete name, in parentheses, preceded by their locants.

5.3 Worked Examples

Example 1: HO–CH_2–CH_2–CHO. Principal group: aldehyde (–CHO), so the suffix is -al and the CHO carbon is C-1. The OH group on C-3 is cited as a prefix: 3-hydroxypropanal.

Example 2: CH_3–CO–CH_2–COOH. Principal group: carboxylic acid (C-1). The ketone becomes the prefix oxo- on C-3: 3-oxobutanoic acid (acetoacetic acid).

Example 3: H_2N–CH_2–CH_2–OH. The alcohol is senior to the amine: the OH carbon is C-1 and the amine is cited as a prefix: 2-aminoethan-1-ol (ethanolamine).

Example 4: CH_2=CH–CH_2–CH(OH)–CH_3. Principal group: alcohol. Numbering must give the lowest locant to the OH first: from the right, OH is on C-2 and the double bond on C-4: pent-4-en-2-ol (and not pent-1-en-4-ol).

Example 5: NC–CH_2–CH_2–$COOCH_3$. The ester is senior to the nitrile, so the ester carbon is C-1. When the nitrile is expressed as the prefix cyano-, its carbon is not counted in the principal chain: the chain is C(=O)–CH_2–CH_2 (three carbons, propanoate) with a cyano group on C-3. Name: methyl 3-cyanopropanoate.

Example 6: CH_3–CH(Cl)–CH_2–CO–CH_3. Principal group: ketone. Numbering from the end nearer to C=O gives the carbonyl the locant 2 and Cl the locant 4: 4-chloropentan-2-one.

Example 7: HOOC–CH_2–CH(NH_2)–COOH. Two carboxylic acid groups are both on the principal chain: butanedioic acid. The amino group is at C-2: 2-aminobutanedioic acid (aspartic acid).

Example 8: CH_3–CH(OH)–CH(CH_3)–CHO. Principal group: aldehyde (C-1); OH on C-3; methyl on C-2. Alphabetical order: hydroxy before methyl: 3-hydroxy-2-

methylbutanal.

Note: in Example 5 the carbon of the –C≡N group belongs to the prefix cyano- and is therefore not part of the principal chain. A frequent student error is to write "methyl 3-cyanobutanoate", which counts the CN carbon twice. Always check the total number of carbons of your name against the molecular formula.

6. Nomenclature of Substituted and Polycyclic Ring Systems

6.1 Substituted Cycloalkanes

A cycloalkane bearing a single substituent needs no locant: methylcyclohexane, chlorocyclopentane. When several substituents are present, the ring is numbered so as to give the lowest set of locants; if there is still a choice, the substituent cited first in alphabetical order receives locant 1.

Example: 1-ethyl-3-methylcyclohexane (and not 1-methyl-3-ethylcyclohexane): the locant set {1,3} is the same in both directions, so the alphabetical rule decides.

Example: 1,1,3-trimethylcyclopentane: the set {1,1,3} is lower than {1,3,3}.

When the ring carries the principal functional group, the carbon bearing this group is C-1 and the locant "1" is often omitted: cyclohexanol, cyclohexanone, cyclopentanecarboxylic acid (the COOH carbon is not part of the ring, hence the suffix -carboxylic acid).

Example: 3-methylcyclohexan-1-ol: the OH carbon is C-1; numbering continues in the direction giving the lowest locant to the methyl group.

Example: cyclohex-2-en-1-one: the C=O carbon is C-1 and the double bond is between C-2 and C-3.

6.2 Ring or Chain: Which One Is the Parent?

When a molecule contains both a ring and a chain, the parent hydride is the one that bears the principal characteristic group. If there is no principal group (hydrocarbons), current IUPAC recommendations (2013) choose the ring as the parent hydride; older rules chose the component with the greater number of carbon atoms. Both styles are still found in textbooks.

Example: $C_6H_{11}–CH_2–CH_2–OH$ is 2-cyclohexylethan-1-ol: the OH is on the chain, so the chain is the parent.

Example: $C_6H_5–CH_2–CH_2–CH_3$ is propylbenzene: the ring is the parent.

6.3 Bicyclic Compounds (von Baeyer Nomenclature)

Bridged bicyclic alkanes contain two rings sharing two bridgehead carbon atoms. They are named with the prefix bicyclo, followed in square brackets by the number of carbon atoms in each of the three bridges, in decreasing order and separated by full stops, and then by the name of the alkane containing the total number of carbon atoms.

Example: bicyclo[2.2.1]heptane (norbornane): bridges of 2, 2 and 1 carbon atoms + 2 bridgeheads = 7 carbons.

Example: bicyclo[4.4.0]decane (decalin): two fused six-membered rings; the bridge between the bridgeheads contains 0 carbons.

Numbering starts at one bridgehead, proceeds around the largest bridge to the second bridgehead, continues around the next largest bridge back to the first bridgehead, and finishes with the smallest bridge.

6.4 Spiro Compounds

In spiro compounds two rings share one single carbon atom (the spiro atom). The name uses the prefix spiro followed, in square brackets, by the number of carbons in each ring excluding the spiro atom, in increasing order: spiro[4.5]decane contains a five-membered ring and a six-membered ring sharing one carbon (4 + 5 + 1 = 10 carbons). Numbering begins in the smaller ring at the atom adjacent to the spiro atom.

7. Trivial Names Retained by IUPAC

Many compounds were named long before systematic nomenclature existed. A number of these trivial names are so widely used that IUPAC retains them, either as preferred names or for general use. An engineer will encounter them constantly in industry, safety data sheets and catalogues.

Trivial name	Systematic name	Formula
Formaldehyde	methanal	$HCHO$
Acetaldehyde	ethanal	CH_3CHO
Acetone	propan-2-one	CH_3COCH_3

Trivial name	Systematic name	Formula
Formic acid	methanoic acid	HCOOH
Acetic acid	ethanoic acid	CH_3COOH
Oxalic acid	ethanedioic acid	HOOC–COOH
Glycerol	propane-1,2,3-triol	$HOCH_2CH(OH)CH_2OH$
Ethylene glycol	ethane-1,2-diol	$HOCH_2CH_2OH$
Toluene	methylbenzene	$C_6H_5CH_3$
Phenol	benzenol	C_6H_5OH
Aniline	benzenamine	$C_6H_5NH_2$
Styrene	ethenylbenzene	$C_6H_5CH=CH_2$
Acetylene	ethyne	$HC\equiv CH$
Ethylene	ethene	$CH_2=CH_2$
Chloroform	trichloromethane	$CHCl_3$

Common names of alkyl groups are also retained: isopropyl (propan-2-yl), isobutyl (2-methylpropyl), sec-butyl (butan-2-yl), tert-butyl (2-methylpropan-2-yl), vinyl (ethenyl), allyl (prop-2-en-1-yl), phenyl (C_6H_5–) and benzyl ($C_6H_5CH_2$–).

In functional class nomenclature (radicofunctional nomenclature), the compound is named as the alkyl group followed by the class name: ethyl alcohol (ethanol), methyl chloride (chloromethane), diethyl ether (ethoxyethane), ethyl methyl ketone (butan-2-one). This system is still widely used for simple molecules.

8. Degree of Unsaturation (Double Bond Equivalent)

8.1 Definition and Formula

The degree of unsaturation (DU), also called the double bond equivalent (DBE) or index of hydrogen deficiency, gives the total number of rings plus π bonds in a molecule. It is calculated directly from the molecular formula and is an extremely useful first step when proposing structures compatible with a formula.

For a compound of formula CcHhNnOoXx (X = halogen):

$DU = (2c + 2 + n – h – x) / 2$

Oxygen and sulfur (divalent atoms) do not appear in the formula. A halogen counts as a hydrogen, and each nitrogen adds one hydrogen to the saturated reference formula.

8.2 Interpretation

DU = 0: saturated, acyclic compound (alkane, alcohol, ether, amine…).

DU = 1: one double bond (C=C or C=O) or one ring.

DU = 2: one triple bond, two double bonds, two rings, or one ring plus one double bond.

DU ≥ 4: often indicates an aromatic (benzene) ring, which accounts for 4 units (one ring + three C=C).

Example: C_4H_8: DU = (8 + 2 – 8)/2 = 1 → but-1-ene, but-2-ene, 2-methylpropene, cyclobutane or methylcyclopropane.

Example: C_6H_6: DU = (12 + 2 – 6)/2 = 4 → benzene (1 ring + 3 C=C).

Example: C_3H_6O: DU = (6 + 2 – 6)/2 = 1 → propanal, propan-2-one, prop-2-en-1-ol, methoxyethene, oxetane…

Example: C_2H_3N: DU = (4 + 2 + 1 – 3)/2 = 2 → acetonitrile $CH_3–C{\equiv}N$ (one triple bond).

Example: C_7H_7Cl: DU = (14 + 2 – 7 – 1)/2 = 4 → chlorotoluene or benzyl chloride (aromatic ring).

9. Common Errors in Nomenclature

The following mistakes are the most frequently encountered in examination papers. Learning to recognise them is the best way to avoid them.

Not choosing the longest chain: $CH_3–CH(C_2H_5)–CH_2–CH_3$ is not "2-ethylbutane" but 3-methylpentane, because the longest chain contains five carbons.

Numbering from the wrong end: $CH_3–CH_2–CH_2–CH(CH_3)–CH_3$ is 2-methylpentane and not 4-methylpentane.

Forgetting the alphabetical order: write 3-ethyl-2-methylhexane, not 2-methyl-3-ethylhexane.

Counting multiplying prefixes in the alphabetical order: 4-ethyl-2,2-dimethylhexane (e before m; "di" is ignored).

Giving a locant to a group that can only be at the end of the chain: write propanoic acid and propanal, not "propan-1-oic acid" or "propan-1-al", because a carboxylic

acid or an aldehyde group is necessarily at C-1.

Choosing a principal group that is not the most senior: HO–CH_2–CH_2–COOH is 3-hydroxypropanoic acid, not "3-carboxypropan-1-ol".

Forgetting to elide or keep the final "e": propan-2-ol (elided before a vowel) but propane-1,2-diol and butanenitrile (kept before a consonant).

Writing separate words incorrectly: methyl ethanoate (two words for an ester), but chloroethane (one word for a substituted hydrocarbon).

Exercises: Chapter 1

Exercise 1.1: Give the IUPAC name for each of the following compounds: (a) $CH_3CH_2CH(CH_3)CH_2CH_3$ (b) $(CH_3)_3CCH_2CH_3$ (c) $CH_3CH{=}CHCH_2CH_3$ (d) $HC{\equiv}CCH_2CH_2OH$

Solution: (a) 3-methylpentane — longest chain: 5C; methyl at C-3 (gives 3, not 4).

(b) 2,2-dimethylbutane — longest chain: 4C; two methyls at C-2.

(c) pent-2-ene — longest chain containing the double bond: 5C; double bond at C-2.

(d) pent-4-yn-1-ol — chain: 5C; triple bond at C-4; OH (suffix) at C-1.

Exercise 1.2: Draw the semi-developed structural formula corresponding to each name: (a) 3-ethyl-2-methylhexane (b) 2,4-dimethylpent-1-ene (c) 4-chlorobutan-2-ol

Solution: (a) $CH_3–CH(CH_3)–CH(C_2H_5)–CH_2–CH_2–CH_3$

(b) $CH_2{=}C(CH_3)–CH_2–CH(CH_3)–CH_3$

(c) $ClCH_2–CH_2–CH(OH)–CH_3$

Exercise 1.3: Classify each carbon in 2-methylbutane as primary, secondary, or tertiary.

Solution: Structure: $CH_3–CH(CH_3)–CH_2–CH_3$

C-1 ($CH_3–$): primary (bonded to 1 other carbon).

C-2 ($–CH(CH_3)–$): tertiary (bonded to 3 carbons: C-1, C-3, the branch CH_3).

Branch CH_3 off C-2: primary.

C-3 ($–CH_2–$): secondary (bonded to C-2 and C-4).

C-4 ($–CH_3$): primary.

Exercise 1.4: Name the following oxygenated compounds: (a) CH_3CH_2OH (b) CH_3COCH_3 (c) CH_3CH_2COOH (d) $CH_3COOC_2H_5$ (e) HCHO

Solution: (a) Ethanol — two carbons, OH suffix.

(b) Propan-2-one (acetone) — three carbons, ketone at C-2.

(c) Propanoic acid — three carbons including the COOH carbon.

(d) Ethyl ethanoate — acid part: ethanoate ($CH_3COO–$); alkyl part: ethyl (C_2H_5).

(e) Methanal (formaldehyde) — one carbon, aldehyde.

Exercise 1.5: Arrange the following by priority order of functional group (highest suffix priority first): aldehyde, ester, ketone, carboxylic acid, alcohol, nitrile.

Solution: Carboxylic acid > ester > nitrile > aldehyde > ketone > alcohol.

Exercise 1.6: Name the disubstituted benzene ring with: a methyl group at C-1 and a nitro group at C-3.

Solution: 1-methyl-3-nitrobenzene (or 3-nitrotoluene using the retained name toluene). It is a meta relationship.

Exercise 1.7: Give the IUPAC name of the following polyfunctional compounds: (a) $HOCH_2–CH_2–COOH$ (b) $CH_3–CO–CH_2–CHO$ (c) $H_2N–CH_2–CH_2–CH_2–COOH$ (d) $CH_3–CH(OH)–CH_2–CO–CH_3$

Solution: (a) 3-hydroxypropanoic acid: the acid is the principal group (C-1); OH is cited as a prefix on C-3.

(b) 3-oxobutanal: the aldehyde is senior to the ketone, so CHO is C-1 and the ketone becomes oxo- on C-3.

(c) 4-aminobutanoic acid (GABA, an important neurotransmitter): COOH is C-1, NH_2 on C-4.

(d) 4-hydroxypentan-2-one: the ketone is senior to the alcohol; numbering from the end closer to C=O gives C=O the locant 2 and OH the locant 4.

Exercise 1.8: Write the semi-developed formula of: (a) 2-methylbut-3-en-2-ol (b) 4-chlorobutanenitrile (c) ethyl 3-oxobutanoate (d) N-methylpropanamide (e) 3-ethylpent-1-yne.

Solution: (a) $CH_2=CH–C(OH)(CH_3)–CH_3$

(b) $Cl–CH_2–CH_2–CH_2–C\equiv N$ (the nitrile carbon is C-1).

(c) $CH_3–CO–CH_2–COO–CH_2–CH_3$ (ethyl acetoacetate).

(d) $CH_3–CH_2–CO–NH–CH_3$

(e) $HC\equiv C–CH(C_2H_5)–CH_2–CH_3$

Exercise 1.9: Calculate the degree of unsaturation of the following formulas and

propose one possible structure for each: (a) C_5H_{10} (b) C_4H_6 (c) $C_3H_4O_2$ (d) C_8H_{10} (e) C_4H_9N.

Solution: (a) DU = (10 + 2 – 10)/2 = 1: pent-1-ene or cyclopentane.

(b) DU = (8 + 2 – 6)/2 = 2: but-1-yne, buta-1,3-diene or cyclobutene.

(c) DU = (6 + 2 – 4)/2 = 2: prop-2-enoic acid (acrylic acid) CH_2=CH–COOH (one C=C + one C=O).

(d) DU = (16 + 2 – 10)/2 = 4: ethylbenzene or one of the three xylenes (dimethylbenzenes).

(e) DU = (8 + 2 + 1 – 9)/2 = 1: pyrrolidine (a saturated five-membered ring containing N) or but-3-en-1-amine.

Exercise 1.10: The following names are incorrect. Explain the error and give the correct name: (a) 2-ethylpropane (b) 4-methylhexane (c) 2-methyl-3-ethylpentane (d) 1,2-dimethylcyclohexan-3-ol (e) 3-pentanone-1-ol.

Solution: (a) The longest chain contains 4 carbons: CH_3–CH(CH_3)–CH_2–CH_3 is 2-methylbutane.

(b) Numbering must start from the end nearer the branch: 3-methylhexane.

(c) Substituents must be in alphabetical order: 3-ethyl-2-methylpentane.

(d) The OH carbon of a cyclohexanol must be C-1: 2,3-dimethylcyclohexan-1-ol.

(e) The ketone is senior to the alcohol and the locant precedes the suffix: 1-hydroxypentan-3-one.

Exercise 1.11: Name the following cyclic and bicyclic compounds: (a) a cyclohexane ring bearing a methyl and an isopropyl group in positions 1 and 4 (b) a cyclopentane ring with two chlorine atoms on adjacent carbons (c) a bicyclic alkane C_8H_{14} with bridges of 3, 3 and 0 carbon atoms (d) two cyclohexane rings sharing one carbon atom.

Solution: (a) 1-isopropyl-4-methylcyclohexane (alphabetical order: i before m), also called 1-methyl-4-(propan-2-yl)cyclohexane in current IUPAC style (m before p).

(b) 1,2-dichlorocyclopentane (two stereoisomeric forms, cis and trans, exist).

(c) bicyclo[3.3.0]octane: 3 + 3 + 0 + 2 bridgeheads = 8 carbons.

(d) spiro[5.5]undecane: 5 + 5 + 1 = 11 carbons.

Exercise 1.12: Give the systematic name corresponding to each trivial name and write its formula: (a) glycerol (b) acetic anhydride (c) acrylonitrile (d) isobutyl alcohol (e) p-xylene.

Solution: (a) propane-1,2,3-triol: $HOCH_2–CH(OH)–CH_2OH$.

(b) ethanoic anhydride: $CH_3–CO–O–CO–CH_3$.

(c) prop-2-enenitrile: $CH_2=CH–C\equiv N$ (monomer of polyacrylonitrile fibres).

(d) 2-methylpropan-1-ol: $(CH_3)_2CH–CH_2–OH$.

(e) 1,4-dimethylbenzene: $CH_3–C_6H_4–CH_3$ (para isomer).

Exercise 1.13: Classify every carbon atom (1°, 2°, 3°, 4°) of 2,2,4-trimethylpentane (isooctane, the reference compound of the octane scale) and count the hydrogen atoms of each type.

Solution: Structure: $(CH_3)_3C–CH_2–CH(CH_3)–CH_3$.

Primary carbons: the five CH_3 groups (three on C-2, C-1 included, and two at the other end: C-5 and the methyl on C-4). They carry 15 primary H.

Secondary carbon: C-3 (CH_2), bonded to C-2 and C-4; 2 secondary H.

Tertiary carbon: C-4 (CH), bonded to three carbons; 1 tertiary H.

Quaternary carbon: C-2, bonded to four carbons; no H. Total: 8 C and 18 H (C_8H_{18}).

Exercise 1.14: Name the following aromatic compounds: (a) $C_6H_5–CH_2OH$ (b) $C_6H_5–COOH$ (c) $C_6H_5–CO–CH_3$ (d) a benzene ring carrying OH at C-1 and NO_2 at C-4 (e) a benzene ring carrying three methyl groups at positions 1, 3 and 5.

Solution: (a) phenylmethanol (benzyl alcohol).

(b) benzoic acid (benzenecarboxylic acid).

(c) 1-phenylethan-1-one (acetophenone).

(d) 4-nitrophenol (p-nitrophenol): the OH group defines C-1.

(e) 1,3,5-trimethylbenzene (mesitylene).

Exercise 1.15: An industrial solvent has the molecular formula C_4H_8O. It does not react with Tollens' reagent (no aldehyde) and its carbon chain is unbranched. Its IR spectrum shows a C=O band. Identify it and give two isomers having another functional group.

Solution: DU = (8 + 2 – 8)/2 = 1: one C=O bond. No aldehyde and unbranched chain → butan-2-one (methyl ethyl ketone, MEK), $CH_3–CO–CH_2–CH_3$.

Isomers with other functional groups: butanal (aldehyde, $CH_3CH_2CH_2CHO$), but-3-en-1-ol (alcohol with C=C), ethoxyethene (enol ether), tetrahydrofuran (cyclic ether).

Exercise 1.16: Draw the structure of each compound and indicate its principal function: (a) 2-amino-3-hydroxypropanoic acid (serine) (b) 4-hydroxy-3-methoxybenzaldehyde (vanillin) (c) 2-hydroxybenzoic acid (salicylic acid).

Solution: (a) $HO–CH_2–CH(NH_2)–COOH$: principal function carboxylic acid; prefixes amino (C-2) and hydroxy (C-3).

(b) A benzene ring carrying CHO at C-1, OCH_3 at C-3 and OH at C-4: principal function aldehyde (suffix -carbaldehyde, here the retained name benzaldehyde).

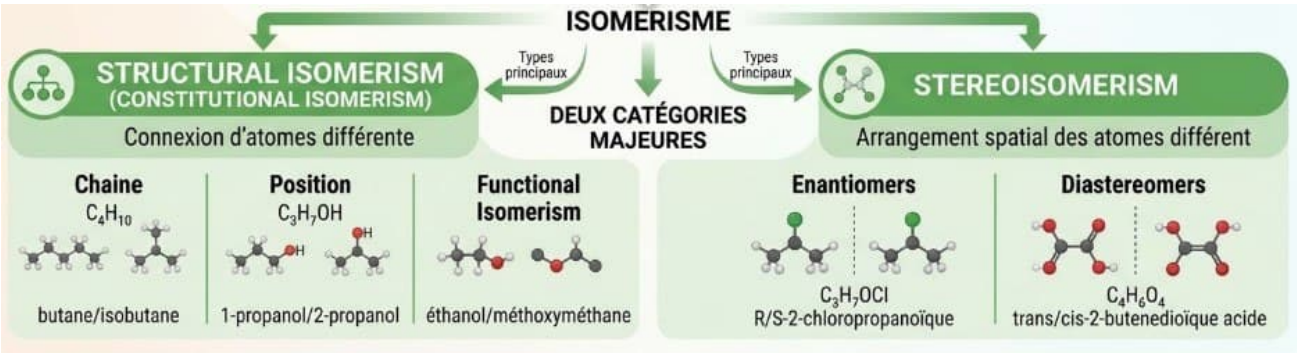
(c) A benzene ring carrying COOH at C-1 and OH at C-2 (ortho position): principal function carboxylic acid; it is the precursor of aspirin (acetylsalicylic acid).

CHAPTER 2: Isomerism and Stereochemistry

1. Isomerism in Organic Compounds

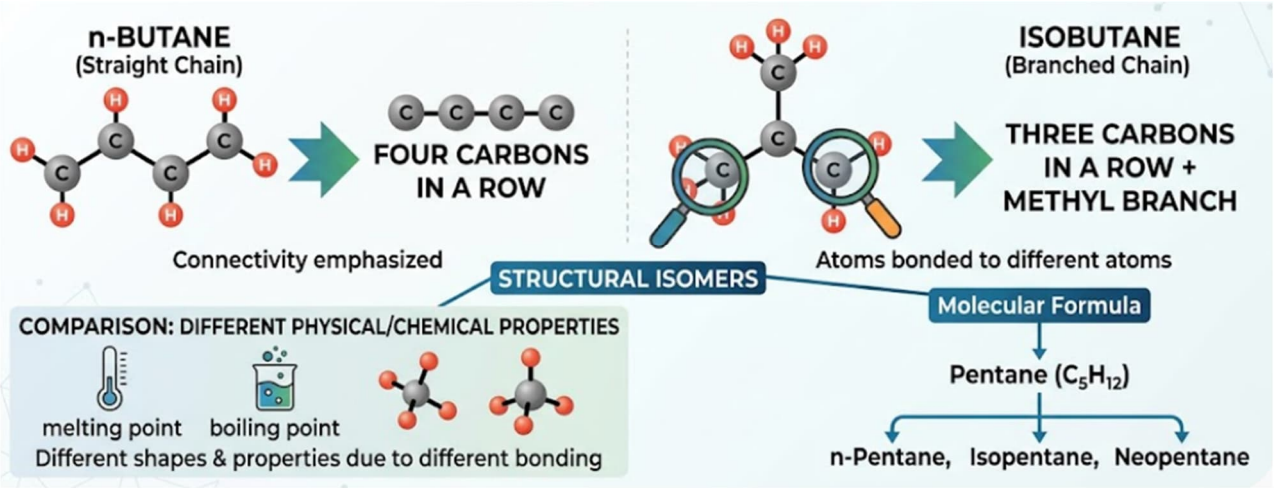
1.1 Definition

Two or more compounds sharing the same molecular formula but differing in the arrangement of atoms are called isomers. Isomerism is subdivided into two major categories: structural (constitutional) isomerism and stereoisomerism.



2. Structural (Constitutional) Isomerism

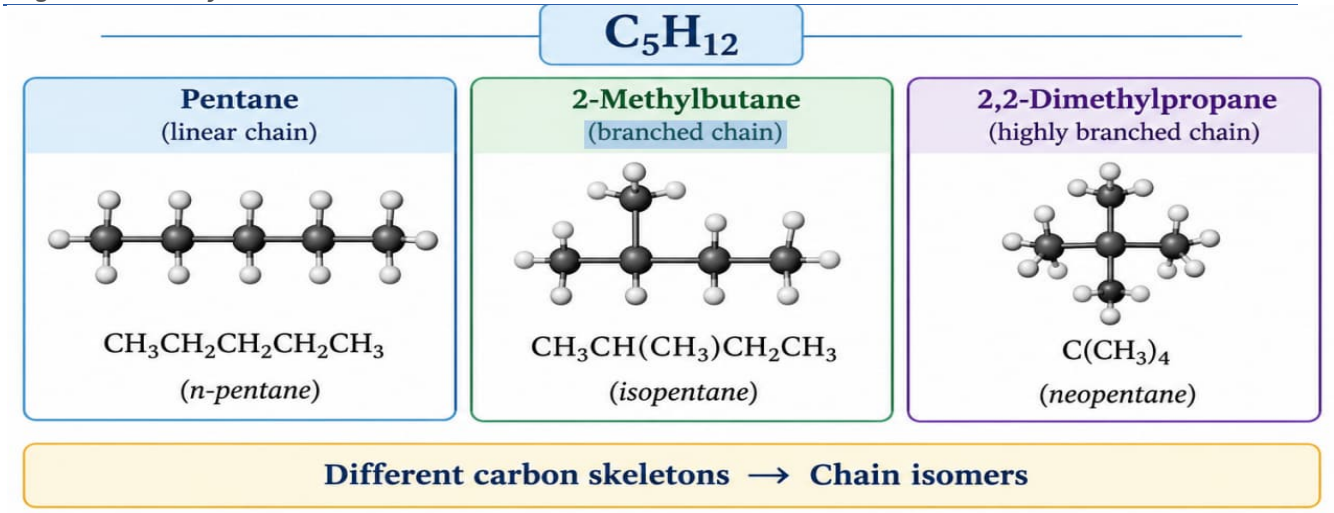
Structural isomers have the same molecular formula but differ in the connectivity of their atoms i.e., in which atoms are bonded to which other atoms.



2.1.1 Chain Isomerism

Chain isomers differ in the arrangement of the carbon skeleton. The principal chain has a different length.

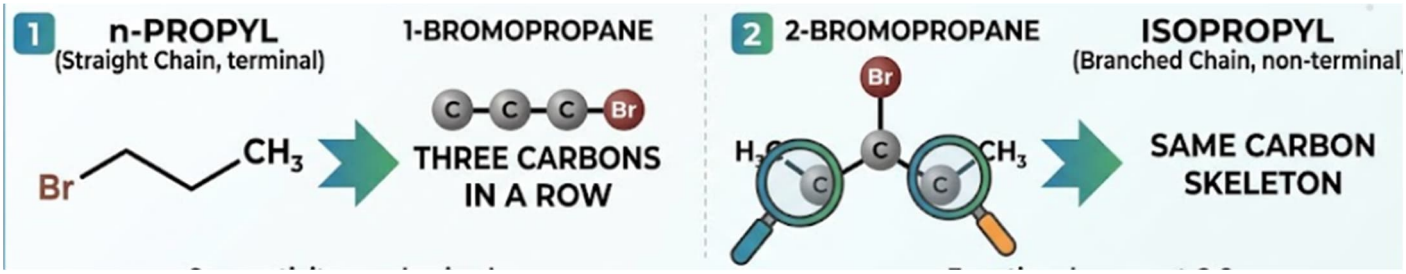
Example: C_5H_{12}; Pentane ($CH_3CH_2CH_2CH_2CH_3$), 2-methylbutane ($CH_3CH(CH_3)CH_2CH_3$), and 2,2-dimethylpropane (neopentane) are three chain isomers.



2.1.2 Position Isomerism

Position isomers have the same carbon skeleton and the same functional group, but the group is attached at a different position on the chain.

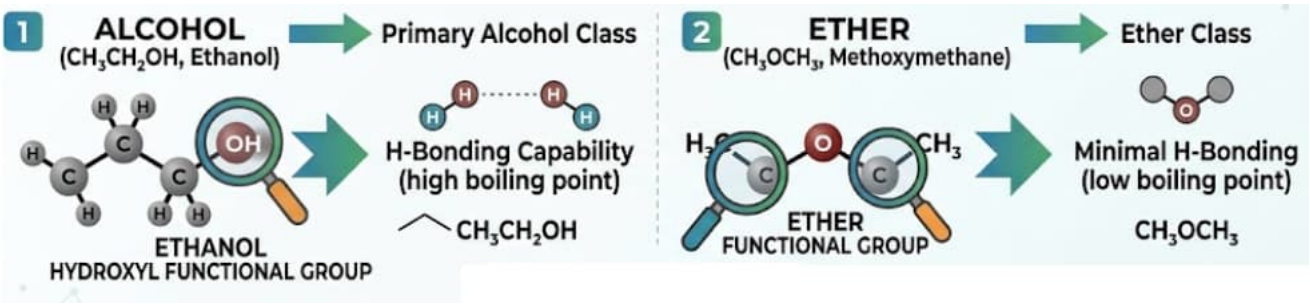
Example: C_3H_7Br; 1-bromopropane ($BrCH_2CH_2CH_3$) and 2-bromopropane ($CH_3CHBrCH_3$).



2.1.3 Functional Group Isomerism

Functional group isomers have the same molecular formula but belong to different compound classes because they contain different functional groups.

Example: C_2H_6O — Ethanol (CH_3CH_2OH, an alcohol) and methoxymethane (CH_3OCH_3, an ether).

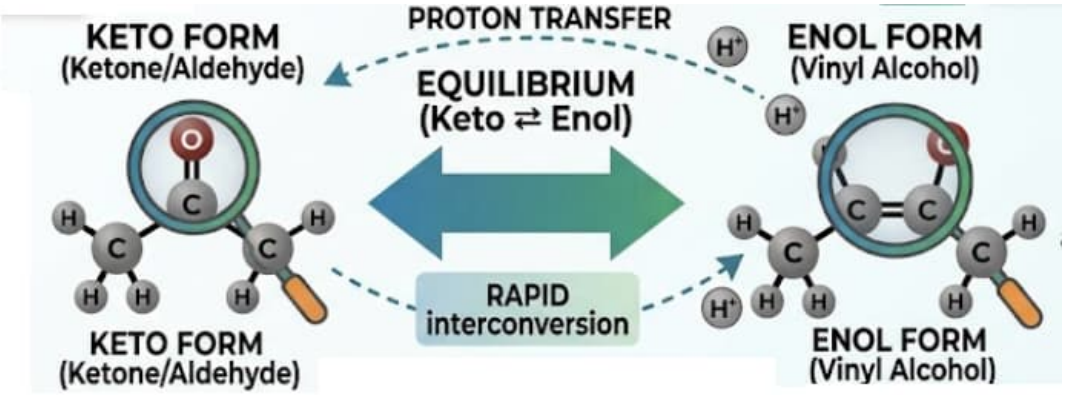


Example: C_3H_6O — Propanal (CH_3CH_2CHO, aldehyde) and propan-2-one (CH_3COCH_3, ketone).

2.1.4 Tautomerism

Tautomers are constitutional isomers that interconvert rapidly through proton transfer. The most important case is keto-enol tautomerism, where a ketone (or aldehyde) is in equilibrium with its enol form (a vinyl alcohol). The keto form is generally favoured.

Example: Propan-2-one ⇌ prop-1-en-2-ol ; $CH_3–CO–CH_3$ ⇌ $CH_3–C(OH)=CH_2$ (keto form ≫ enol form, ~99.9 : 0.1).

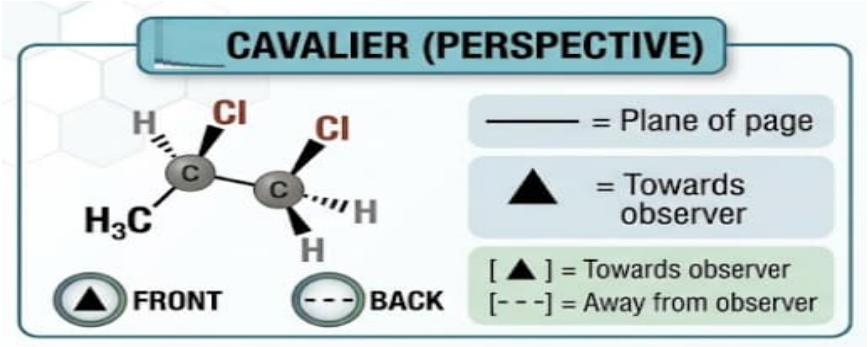


3. Plane Representations of Three-Dimensional Molecules

Because organic molecules are three-dimensional objects, several two-dimensional conventions have been developed to convey spatial information on a flat page.

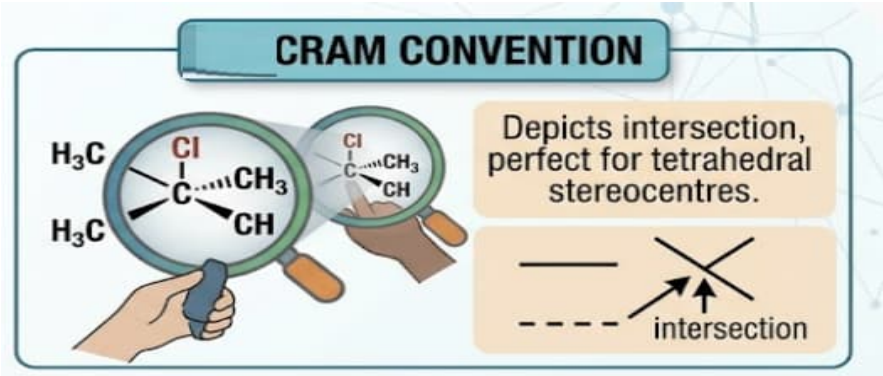
3.1 Cavalier (Perspective) Representation

Bonds in the plane of the page are drawn as ordinary lines –. Bonds projecting toward the observer are drawn as solid bold wedges (▲). Bonds projecting away are drawn as dashed wedges or hatched bonds (------). This is the most intuitive method and closely resembles what we 'see' in 3D.



3.2 Cram Convention

In the Cram (or wedge-dash) projection, the same symbolism as Cavalier is used but the molecule is depicted with the central atom at the intersection of the bonds. The convention is especially useful for tetrahedral stereocentres.



3.3 Newman Projection

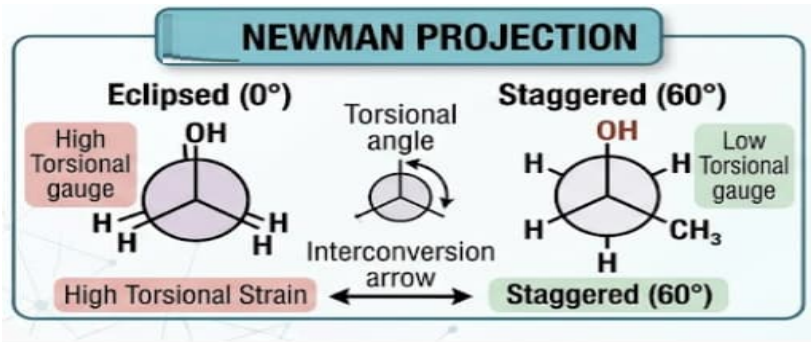
A Newman projection looks along a specific C–C bond axis. The front carbon is represented by a dot (or a small circle) and the back carbon by a large circle. The three bonds of the front carbon radiate from the centre; those of the back carbon emerge from behind the circle. Newman projections are ideal for analysing conformational isomers.

Eclipsed conformation: front and back substituents are directly aligned (dihedral angle = 0°). Maximum torsional strain.

Staggered conformation: front and back substituents are offset by 60°. Minimum torsional strain; most stable.

Gauche conformation: a staggered arrangement where two large groups are 60° apart.

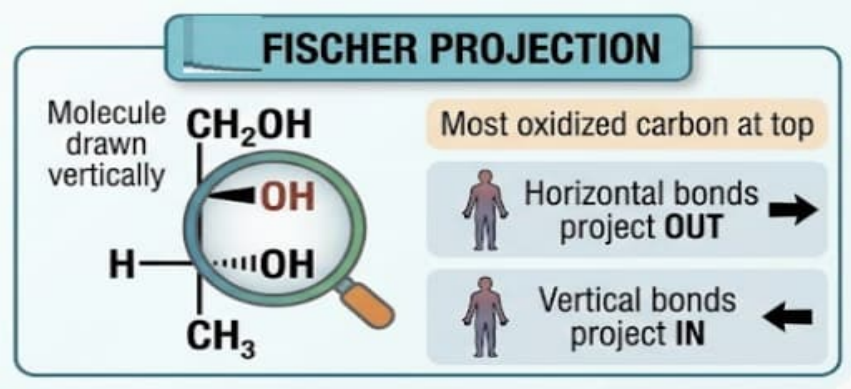
Anti conformation: a staggered arrangement where two large groups are 180° apart. Most stable for butane.



3.4 Fischer Projection

A Fischer projection is used especially for open-chain sugars and amino acids. The molecule is drawn vertically with the most oxidised carbon at the top. The horizontal bonds at each carbon project toward the viewer; the vertical bonds project away.

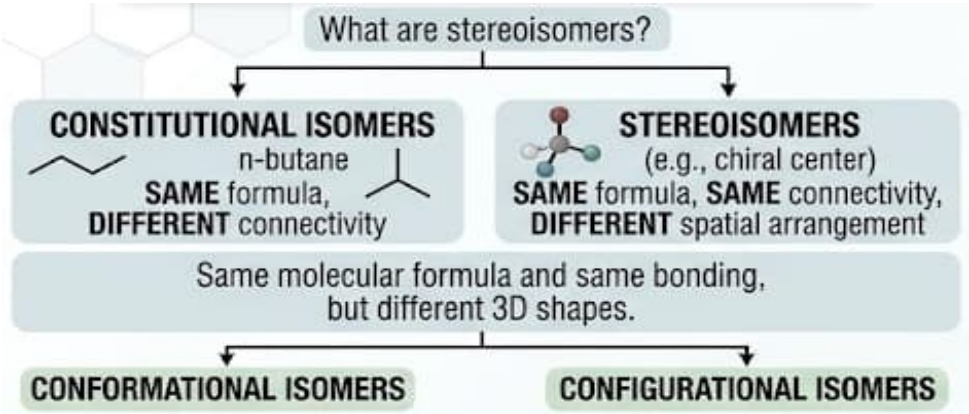
Note: Remember: in a Fischer projection, horizontal bonds come OUT of the page; vertical bonds go INTO the page.



4. Stereoisomerism

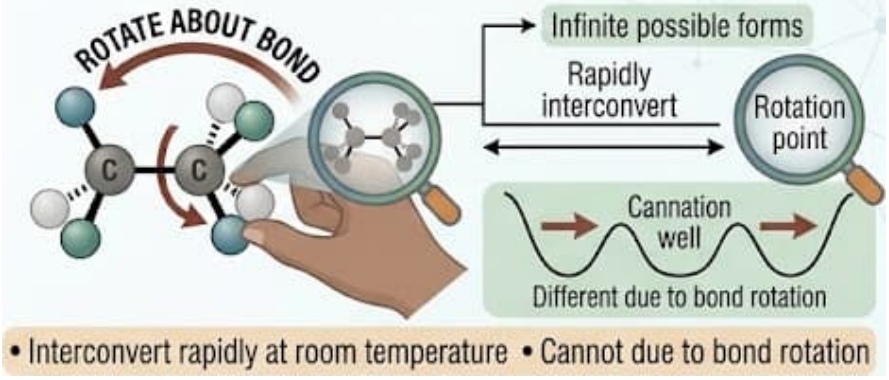
4.1 Definition

Stereoisomers have identical molecular formulas and identical connectivity (they are not constitutional isomers), but differ in the spatial arrangement of their atoms. Stereoisomerism is divided into conformational isomerism and configurational isomerism.



4.2 Conformational Isomerism

Conformational isomers (conformers) differ only in the rotation about one or more single bonds. They interconvert freely at room temperature and cannot be isolated.

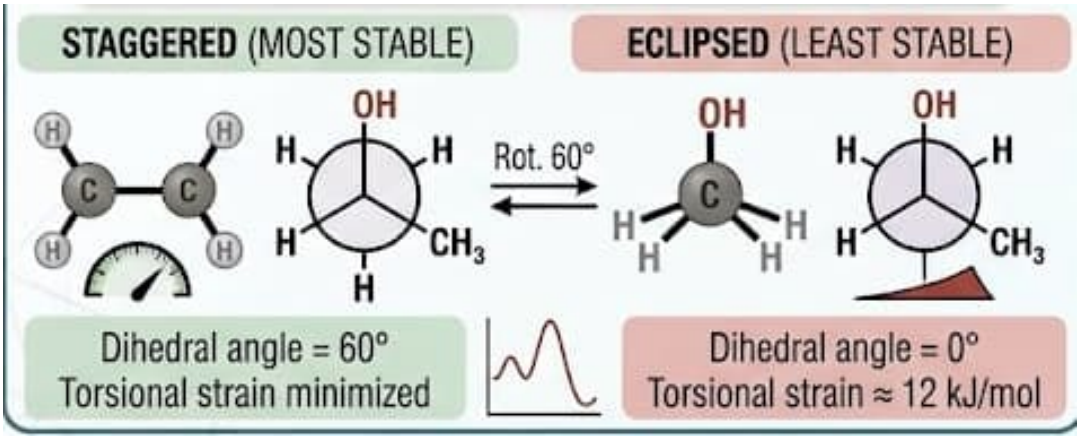


4.2.1 Conformations of Ethane

In ethane (CH_3–CH_3), rotation about the C–C bond gives rise to an infinite number of conformations. Two limiting cases are:

Staggered (most stable): dihedral angle H–C–C–H = 60°; torsional strain minimised.

Eclipsed (least stable): dihedral angle H–C–C–H = 0°; torsional strain ≈ 12 kJ/mol.



4.2.2 Conformations of Butane

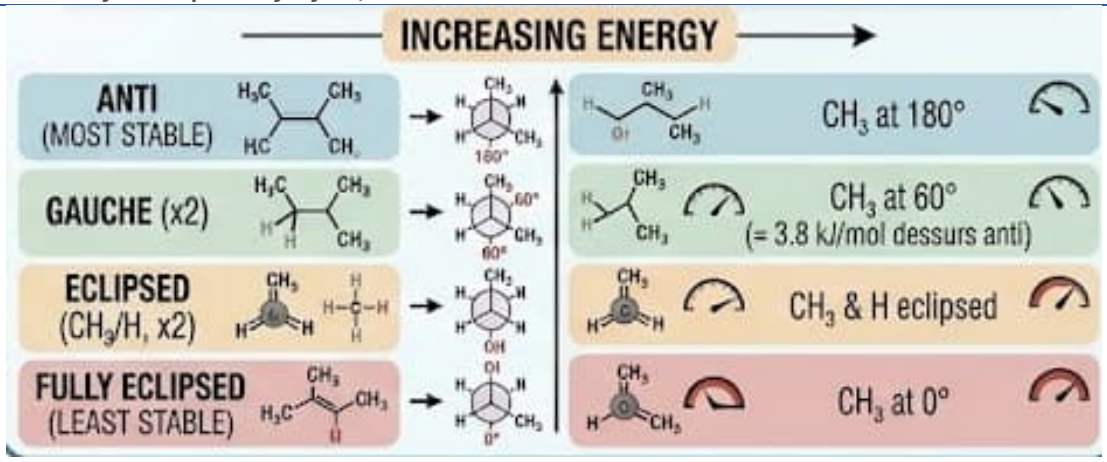
For butane ($CH_3CH_2CH_2CH_3$), rotation about the central C_2–C_3 bond gives four distinct conformers of interest. Arranged by increasing energy:

Anti (CH_3 groups 180° apart): most stable; no gauche interactions.

Gauche (two conformers, CH_3 groups 60° apart): each has one gauche interaction (≈ 3.8 kJ/mol above anti).

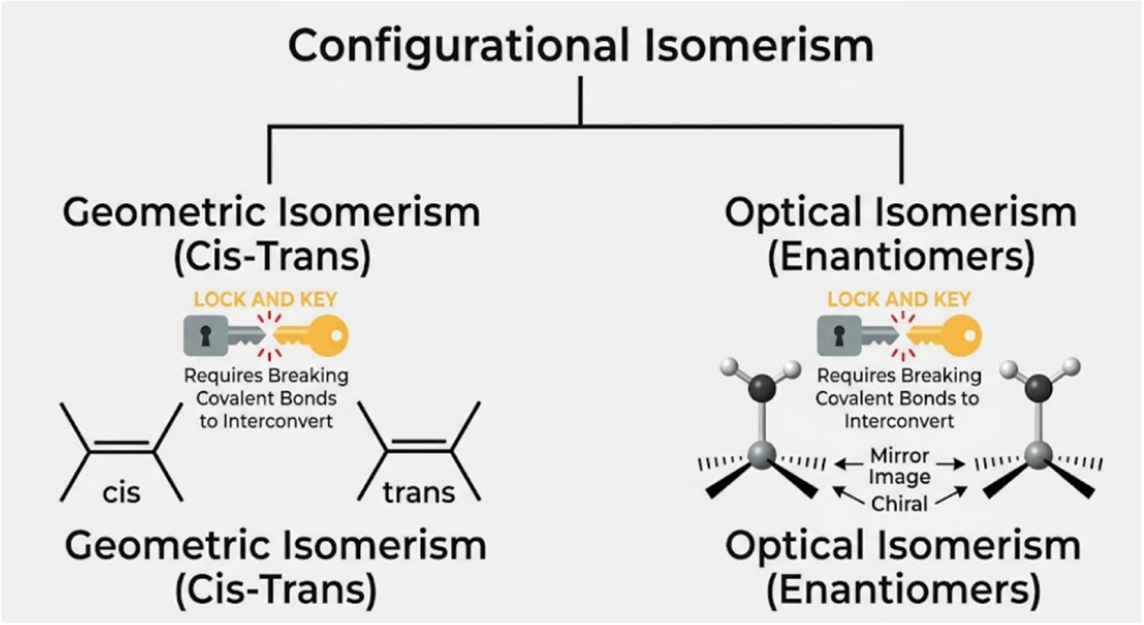
Eclipsed (CH_3/H, two conformers, 120° between CH_3): moderate strain.

Fully eclipsed (CH_3 groups 0° apart): least stable; maximum strain (≈ 19 kJ/mol above anti).



5. Configurational Isomerism

Configurational isomers cannot interconvert without breaking covalent bonds. They are divided into geometric (cis-trans) isomers and optical (enantiomeric) isomers.



5.1 Geometric (Cis-Trans) Isomerism

5.1.1 Definition and Conditions

Geometric isomerism arises from restricted rotation — most commonly around a C=C double bond or within a ring. It requires that each doubly bonded (or ring) carbon bears two different substituents.

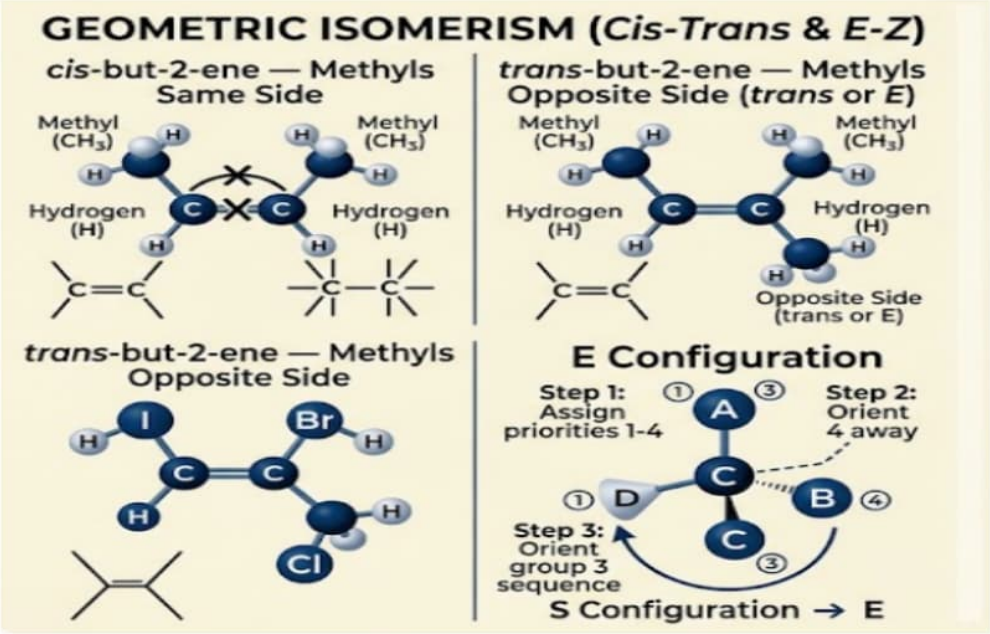
5.1.2 Cis-Trans Notation

When two identical (or similar) groups are on the same side of the double bond (or ring), the isomer is called cis (Z in the E-Z system). When they are on opposite sides

it is called trans (E).

Example: cis-but-2-ene; Both methyl groups on the same side of the C=C: cis or (Z).

Example: trans-but-2-ene; Methyl groups on opposite sides: trans or (E).



5.1.3 E-Z Notation (Cahn-Ingold-Prelog, CIP Rules)

When simple cis/trans notation is ambiguous (i.e., when all four substituents are different), the CIP priority system is used:

Assign priorities 1 (highest) and 2 (lowest) to the two groups on each doubly bonded carbon, based on atomic number (higher atomic number = higher priority). In case of a tie, compare the next atom outward.

If the two high-priority groups (one from each carbon) are on the same side of the double bond: (Z); from German zusammen, 'together'.

If they are on opposite sides: (E); from German entgegen, 'opposite'.

Note: Common priority pairs: I > Br > Cl > F > O > N > C > H.

5.2 Optical Isomerism — Enantiomers

5.2.1 Stereogenic (Chiral) Centre

A stereogenic centre (chiral centre) is a carbon atom bonded to four different substituents. Such a carbon is tetrahedral and can exist in two non-superimposable mirror-image configurations. The two forms are called enantiomers.

A molecule with exactly one stereocentre is chiral: it lacks an internal mirror plane (plane of symmetry) and rotates the plane of polarised light. The enantiomers are

designated (+) or (–) based on the direction of optical rotation, or R and S based on their absolute configuration.

5.2.2 R-S Nomenclature (CIP Rules)

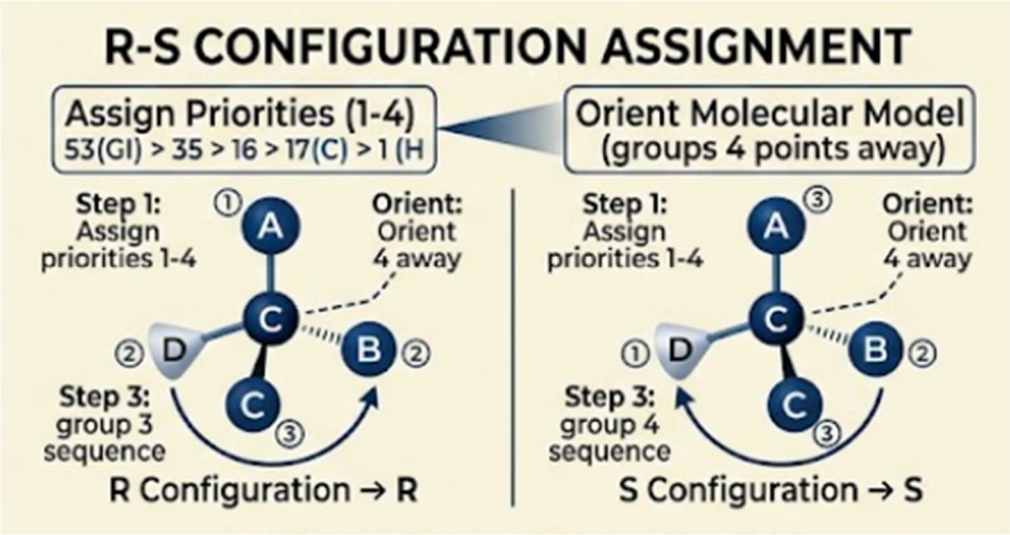
Assign CIP priorities 1–4 to the four substituents on the stereocentre.

Orient the molecule so that the lowest-priority group (4) points away from you.

Read groups 1→2→3:

Clockwise: configuration is R (from Latin rectus, 'right').

Counterclockwise: configuration is S (from Latin sinister, 'left').

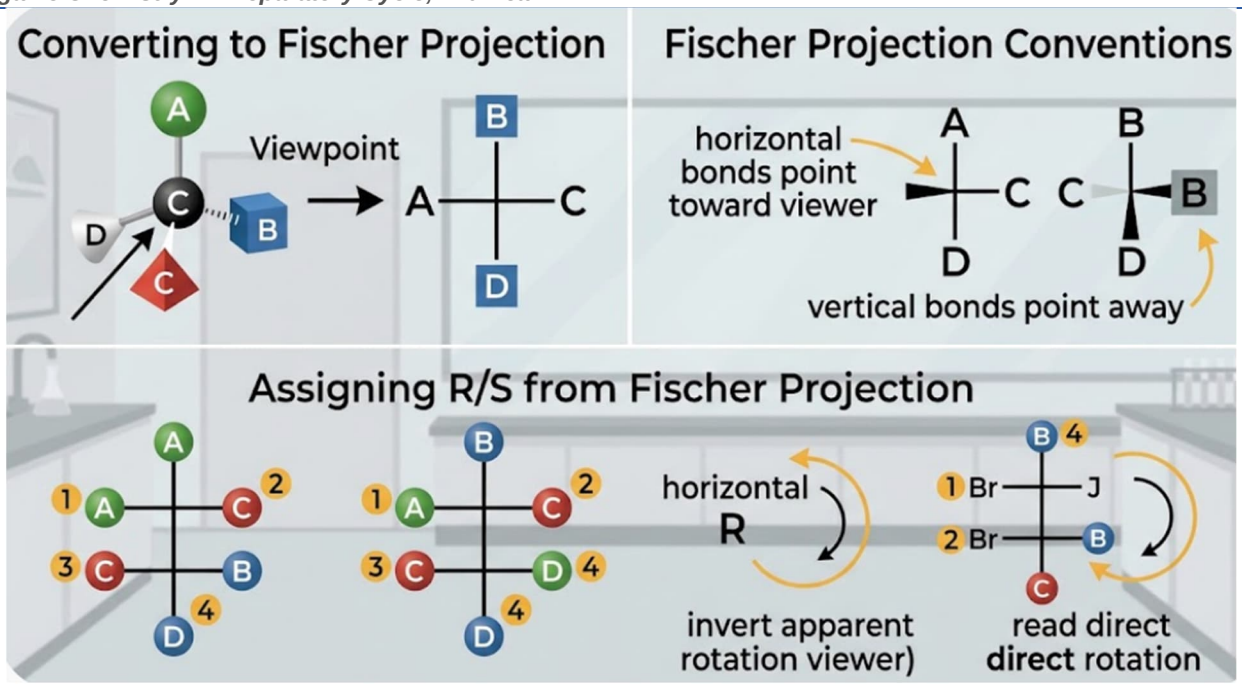


5.2.3 Fischer Projection and Configuration

In a Fischer projection, the chiral centre has horizontal bonds pointing toward the viewer. To assign R/S directly from a Fischer projection:

Identify the lowest-priority group. If it is on a horizontal bond (pointing toward viewer), assign the apparent rotation sense, then invert R↔S.

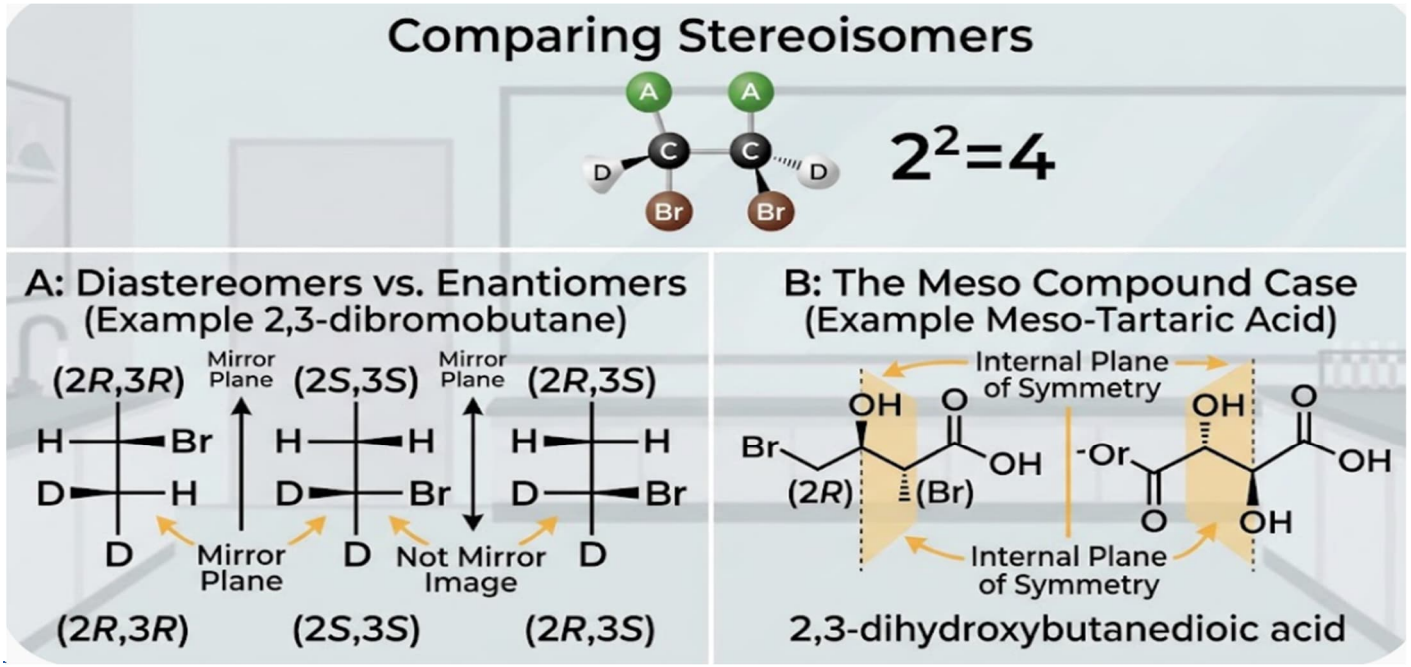
If the lowest-priority group is on a vertical bond (pointing away from viewer), read the rotation directly.



5.2.4 Diastereomers

When a molecule has two or more stereocentres, the maximum number of stereoisomers is 2^n (n = number of stereocentres). Stereoisomers that are not mirror images of each other are called diastereomers. Diastereomers have different physical and chemical properties.

A special case: a meso compound has two or more stereocentres but possesses an internal plane of symmetry, making the molecule achiral (it is identical to its mirror image). Example: meso-tartaric acid has two stereocentres of opposite configuration.



6. Conformations of Cyclic Compounds

6.1 Ring Strain in Cycloalkanes

If cycloalkanes were planar, their internal C–C–C angles would be 60° (cyclopropane), 90° (cyclobutane), 108° (cyclopentane) and 120° (cyclohexane), whereas an sp^3 carbon prefers 109.5°. The deviation from the ideal tetrahedral angle produces angle strain (Baeyer strain). Eclipsing interactions between adjacent C–H bonds add torsional strain (Pitzer strain), and close contacts between non-bonded atoms add steric strain.

Experimental heats of combustion per CH_2 group show that cyclopropane (strain ≈ 115 kJ/mol) and cyclobutane (≈ 110 kJ/mol) are highly strained, cyclopentane is slightly strained (≈ 26 kJ/mol), whereas cyclohexane is practically strain-free. This is because cyclohexane is not planar: it adopts a puckered chair conformation in which all bond angles are close to 109.5° and all C–H bonds are staggered.

Cycloalkane	Planar angle	Total strain (kJ/mol)	Preferred shape
Cyclopropane	60°	≈ 115	planar
Cyclobutane	90°	≈ 110	folded ("butterfly")
Cyclopentane	108°	≈ 26	envelope
Cyclohexane	120°	≈ 0	chair

6.2 Chair and Boat Conformations of Cyclohexane

The chair conformation is the most stable conformation of cyclohexane. In the chair, every C–C bond is in a staggered arrangement (as can be checked with a Newman projection along any C–C bond), and the C–C–C angles are about 111°.

The boat conformation is about 29 kJ/mol less stable than the chair. Four of its C–C bonds are eclipsed, and the two "flagpole" hydrogens point toward each other, creating steric repulsion. A slightly twisted boat (the twist-boat) relieves part of this strain and lies about 23 kJ/mol above the chair. The half-chair is the highest-energy point (≈ 45 kJ/mol) on the path connecting the chair to the twist-boat.

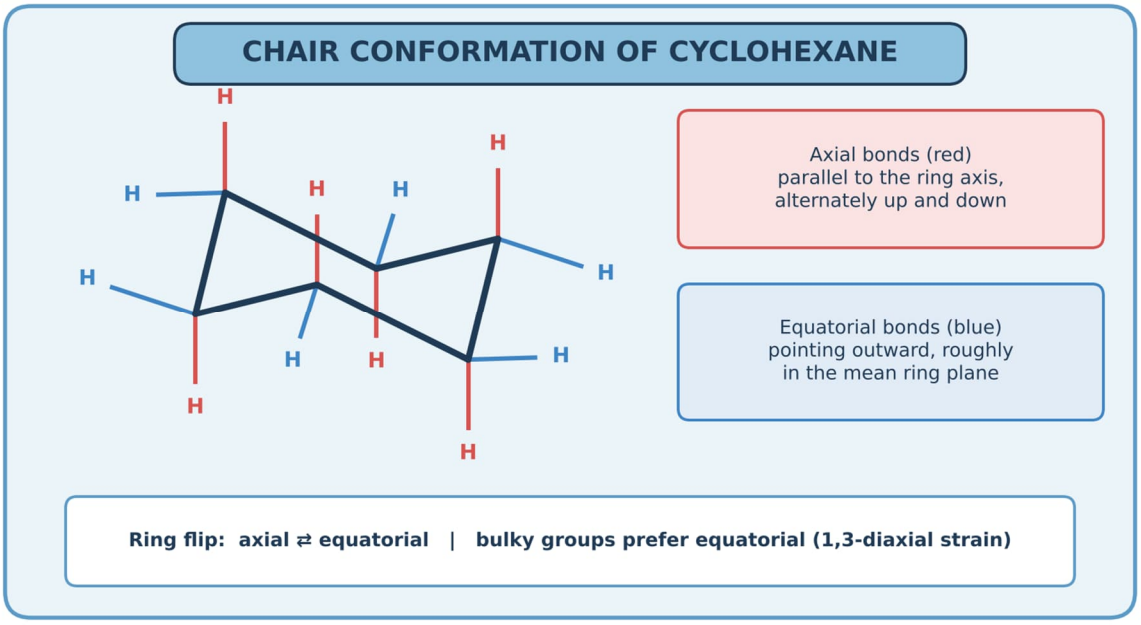


Figure 22. Chair conformation of cyclohexane: axial (red) and equatorial (blue) hydrogens

6.3 Axial and Equatorial Positions

Each carbon of the chair carries two hydrogens in two different types of positions:

Axial positions: six bonds parallel to the vertical axis of the ring, alternately pointing up and down.

Equatorial positions: six bonds pointing outward, roughly along the "equator" of the ring, alternately slightly up and slightly down.

At room temperature the ring flips rapidly (about 10^5 times per second) between two chair conformations. During this ring inversion every axial bond becomes equatorial and vice versa, but an "up" substituent remains "up".

6.4 Monosubstituted Cyclohexanes and A-Values

In a monosubstituted cyclohexane the two chairs are no longer equivalent. When the substituent is axial, it suffers steric repulsion with the two axial hydrogens located on the same side of the ring at C-3 and C-5: these are called 1,3-diaxial interactions. Each 1,3-diaxial interaction between a CH_3 and an H is equivalent to a gauche-butane interaction (≈ 3.8 kJ/mol). The equatorial conformer is therefore more stable.

The free-energy difference between the axial and equatorial conformers is called the A-value. The larger the A-value, the stronger the preference for the equatorial position.

Substituent	A-value (kJ/mol)	% equatorial at 25 °C
–F	1.0	≈ 60
–Cl	2.2	≈ 70
–OH	3.9	≈ 83
$–CH_3$	7.3	≈ 95
$–CH_2CH_3$	7.5	≈ 95
$–CH(CH_3)_2$	9.2	≈ 97
$–C(CH_3)_3$	> 20	> 99.9
$–C_6H_5$	12.6	≈ 99

The equilibrium constant is related to the A-value by $\Delta G° = –RT \ln K$. For methylcyclohexane, $K = \exp(7300 / (8.314 \times 298)) \approx 19$, i.e. 95% equatorial and 5% axial. The tert-butyl group is so bulky that it practically "locks" the ring in the conformation where it is equatorial.

6.5 Disubstituted Cyclohexanes

For disubstituted cyclohexanes, cis/trans isomerism (configurational) and axial/equatorial preferences (conformational) must be considered together.

1,2-disubstituted: trans = (e,e) or (a,a); cis = (a,e) or (e,a).

1,3-disubstituted: cis = (e,e) or (a,a); trans = (a,e) or (e,a).

1,4-disubstituted: trans = (e,e) or (a,a); cis = (a,e) or (e,a).

Example: trans-1,4-dimethylcyclohexane exists almost entirely in the diequatorial chair and is therefore more stable than cis-1,4-dimethylcyclohexane, in which one methyl group must always be axial.

Example: cis-1-tert-butyl-4-methylcyclohexane: the tert-butyl group is equatorial, which forces the methyl group to be axial.

7. Optical Activity and Polarimetry

7.1 Plane-Polarised Light and Optical Rotation

Ordinary light consists of waves vibrating in all planes perpendicular to the direction of propagation. After passing through a polariser, only the waves vibrating in one plane are transmitted: the light is plane-polarised. When plane-polarised light passes through a solution of a chiral compound, the plane of polarisation is rotated by an angle α. Compounds that cause such a rotation are

said to be optically active.

Dextrorotatory (+ or d): rotation to the right (clockwise, as seen by the observer facing the light source).

Levorotatory (– or l): rotation to the left (anticlockwise).

Two enantiomers rotate the plane of polarised light by the same angle but in opposite directions. Note that the sign of rotation (+/–) is an experimental quantity and has no simple relation with the R/S descriptor: (R)-glyceraldehyde is dextrorotatory, whereas (R)-lactic acid is levorotatory.

7.2 Specific Rotation

The observed rotation α depends on the concentration, the path length, the wavelength, the temperature and the solvent. To compare compounds, the specific rotation $[\alpha]$ is defined by Biot's law:

$$[\alpha]^{T}\lambda = \alpha \,/\, (l \times c)$$

where α is the observed rotation (degrees), l the path length of the cell in decimetres (dm), and c the concentration in g/mL. The measurement is usually made at 20 or 25 °C with the sodium D line (λ = 589 nm).

Example: A solution of 2.0 g of sucrose in 10.0 mL of water placed in a 1.0 dm tube gives α = +13.3°. Then c = 0.20 g/mL and $[\alpha] = 13.3 \,/\, (1.0 \times 0.20) = +66.5°$, which is the tabulated value for sucrose.

7.3 Racemic Mixtures and Enantiomeric Excess

A racemic mixture (racemate) contains equal amounts of two enantiomers. It is optically inactive because the rotations of the two enantiomers cancel out. It is denoted (±) or rac-. A racemate is obtained whenever a chiral compound is formed from achiral reagents without any chiral influence (for example, an SN1 reaction via a planar carbocation, or the addition of HBr to an alkene).

The optical purity of a mixture of enantiomers is expressed by the enantiomeric excess (ee):

$$\text{ee}\,(\%) = |\%\ \text{major} - \%\ \text{minor}| = ([\alpha]_{\text{observed}} \,/\, [\alpha]_{\text{pure enantiomer}}) \times 100$$

Example: A sample of 2-butanol has $[\alpha] = +6.76°$, whereas pure (S)-(+)-2-butanol has $[\alpha] = +13.52°$. ee = 6.76/13.52 × 100 = 50%. The mixture contains 75% (S) and

25% (R).

Separating the two enantiomers of a racemate is called resolution. It is usually carried out by reaction with an enantiomerically pure reagent (for instance a chiral acid or base) to form two diastereomeric salts. Unlike enantiomers, diastereomers have different physical properties (solubility, melting point) and can be separated by crystallisation; the pure enantiomers are then regenerated.

8. Interconversion Between Stereochemical Representations

8.1 Rules for Manipulating Fischer Projections

Fischer projections are powerful but must be manipulated with care. The following operations either preserve or invert the configuration:

A rotation of 180° in the plane of the paper preserves the configuration (horizontal bonds remain toward the viewer).

A rotation of 90° in the plane of the paper inverts the configuration (it is forbidden if one wants to keep the same molecule).

Exchanging any two substituents inverts the configuration; two successive exchanges restore it.

Keeping one substituent fixed and rotating the other three clockwise or anticlockwise preserves the configuration.

8.2 From a Cram Representation to a Fischer Projection

Orient the molecule so that the main carbon chain is vertical, with both vertical bonds pointing away from the observer (behind the plane) and both horizontal bonds pointing toward the observer. Then flatten the molecule onto the paper: the stereocentre becomes the intersection of a cross.

For molecules with two adjacent stereocentres (for example 2,3-dihydroxybutanoic acid or the sugars), the Fischer projection corresponds to an eclipsed conformation of the main chain, viewed from the side where horizontal substituents point toward the observer.

8.3 From a Newman Projection to a Fischer Projection

Start from the eclipsed conformation in which the two carbon atoms of the main chain (the groups that will be vertical in the Fischer projection) are eclipsed. If the

Newman projection is staggered, first rotate the rear carbon by 60° (or 180°) to obtain this eclipsed conformation. Then read the substituents: the front carbon becomes the upper stereocentre and the rear carbon the lower stereocentre (or vice versa), keeping the left/right positions of the substituents.

8.4 Erythro and Threo Nomenclature

For molecules with two adjacent stereocentres carrying similar substituents, the older erythro/threo descriptors (derived from the sugars erythrose and threose) are still used:

Erythro: in the Fischer projection, the two identical (or similar) substituents are on the same side of the vertical chain.

Threo: they are on opposite sides.

In the corresponding eclipsed Newman projection, the erythro isomer has the similar groups eclipsed with each other, whereas in the threo isomer they are not.

9. Configurational Nomenclature of Natural Molecules

9.1 The D/L System

Before the R/S system existed, Emil Fischer introduced the D/L system, which is still used for sugars and amino acids. The reference compound is glyceraldehyde (2,3-dihydroxypropanal). In the Fischer projection with the CHO group at the top and the CH_2OH group at the bottom:

D-glyceraldehyde: the OH on the stereocentre is on the right; this is (R)-glyceraldehyde.

L-glyceraldehyde: the OH is on the left; this is (S)-glyceraldehyde.

For a sugar, the configuration is defined by the stereocentre farthest from the carbonyl group (the penultimate carbon). Almost all natural sugars belong to the D series (D-glucose, D-fructose, D-ribose).

For an α-amino acid, the Fischer projection is drawn with COOH at the top and the side chain R at the bottom; the amino acid is L if the NH_2 group is on the left. All the amino acids found in proteins belong to the L series. Most of them have the (S) configuration; L-cysteine is (R) because the CH_2SH group has a higher CIP priority than COOH.

Important: D/L describes a relative configuration with respect to glyceraldehyde and does not correspond to the sign of rotation. D-fructose is levorotatory; D-glucose is dextrorotatory.

9.2 Meso Compounds: the Example of Tartaric Acid

Tartaric acid (2,3-dihydroxybutanedioic acid, HOOC–CH(OH)–CH(OH)–COOH) has two stereocentres bearing the same four substituents. Instead of $2^2 = 4$ stereoisomers, only three exist:

(2R,3R)-tartaric acid: dextrorotatory, natural tartaric acid found in grapes.

(2S,3S)-tartaric acid: levorotatory, the enantiomer of the former.

(2R,3S)-tartaric acid: meso-tartaric acid, which possesses an internal plane of symmetry and is therefore achiral and optically inactive. (2R,3S) and (2S,3R) describe the same molecule.

Property	(R,R)	(S,S)	meso	racemic (±)
Melting point (°C)	170	170	146	206
[α]D (water)	+12°	–12°	0°	0°
Solubility (g/100 mL)	139	139	125	21

The table shows that enantiomers have identical physical properties except for the sign of rotation, whereas diastereomers (R,R and meso) have different properties. The racemate behaves as a distinct crystalline compound.

9.3 Chirality Without a Stereogenic Carbon

Chirality is a property of the whole molecule. A molecule can be chiral without any stereogenic carbon atom if it lacks a plane and a centre of symmetry. Examples include allenes of the type RCH=C=CHR (axial chirality: the substituents at both ends lie in perpendicular planes), biphenyls with bulky ortho substituents whose rotation around the central bond is blocked (atropisomers), and helicenes. Conversely, a molecule with stereocentres can be achiral (meso compounds).

10. Importance of Stereochemistry in Biology and Pharmacy

Biological receptors and enzymes are built from L-amino acids and D-sugars: they are themselves chiral. They therefore interact differently with the two enantiomers of a chiral molecule, in the same way that a right hand fits only into a

right glove. As a consequence, two enantiomers can have very different odours, tastes, or pharmacological effects.

Compound	(R) or first enantiomer	(S) or second enantiomer
Carvone	(R): spearmint odour	(S): caraway odour
Limonene	(R): orange odour	(S): lemon/turpentine odour
Ibuprofen	(R): inactive (slowly converted in vivo)	(S): anti-inflammatory
Thalidomide	(R): sedative	(S): teratogenic
Asparagine	L: bitter taste	D: sweet taste

The thalidomide tragedy (1957–1961) is the most famous example: the drug was sold as a racemate to treat morning sickness and caused severe birth defects in more than 10,000 children. It was later shown that the two enantiomers interconvert in the body, so even the pure (R) form would not have been safe. Since then, regulatory agencies require that the biological activity of each enantiomer of a new chiral drug be studied separately, and many drugs are now marketed as single enantiomers (for example esomeprazole, escitalopram, levofloxacin).

For the engineer, this means that asymmetric synthesis and chiral separation (chiral chromatography, enzymatic resolution) are major industrial processes. The 2001 Nobel Prize in Chemistry (Knowles, Noyori, Sharpless) rewarded the development of chiral catalysts able to produce one enantiomer selectively.

Exercises : Chapter 2

Exercise 2.1: How many structural isomers exist for C_4H_{10}? Draw and name them.

Solution: There are 2 structural (chain) isomers of C_4H_{10}:

(1) Butane: $CH_3–CH_2–CH_2–CH_3$ (unbranched, n-butane).

(2) 2-Methylpropane (isobutane): $(CH_3)_3CH$ — one branch at C-2.

Exercise 2.2: Explain why cis-trans isomerism exists for but-2-ene but not for but-1-ene.

Solution: In but-2-ene ($CH_3–CH=CH–CH_3$), each doubly bonded carbon carries two different groups (CH_3 and H), so two distinct spatial arrangements (cis and trans) exist.

In but-1-ene ($CH_2=CH–CH_2–CH_3$), the terminal doubly bonded carbon (C-1) carries two identical hydrogen atoms, so there is no possibility of cis/trans isomerism.

Exercise 2.3: Assign E or Z to: (a) $CH_3CH=CHBr$ (b) $(CH_3)(C_2H_5)C=C(Cl)(F)$

Solution: (a) On C-1: groups are CH_3 and H; priority: CH_3 (C) > H. On C-2: groups are Br and H; priority: Br > H. CH_3 and Br are on opposite sides $\Longrightarrow$ (E).

(b) On C-1: CH_3 vs C_2H_5; C_2H_5 > CH_3. On C-2: Cl vs F; Cl (Z=17) > F (Z=9). C_2H_5 and Cl on the same side $\Longrightarrow$ (Z).

Exercise 2.4: Assign R or S to: (a) (S)-2-bromobutane given that it has a negative optical rotation (b) lactic acid (2-hydroxypropanoic acid) in the L-configuration.

Solution: (a) The question states S configuration; (S)-2-bromobutane has groups: Br (1) > CH_2CH_3 (2) > CH_3 (3) > H (4). Placing H away from viewer, the sequence 1→2→3 is counterclockwise $\Longrightarrow$ S.

(b) L-lactic acid corresponds to the (S) enantiomer (same convention as L-amino acids). Groups at the stereocentre: OH (1) > COOH (2) > CH_3 (3) > H (4). Counterclockwise 1→2→3 with H away $\Longrightarrow$ S.

Exercise 2.5: A compound of formula $C_4H_8Br_2$ has two stereocentres. How many stereoisomers are possible? Is a meso form possible?

Solution: Maximum stereoisomers = 2^2 = 4: (R,R), (S,S), (R,S), and (S,R).

(R,S) and (S,R) are mirror images; if the two stereocentres are identical (i.e., the

molecule has a potential internal mirror plane), they represent the same meso compound.

For 2,3-dibromobutane: (R,R) and (S,S) are enantiomers; (R,S) is the meso compound (identical to its mirror image). So there are 3 distinct stereoisomers.

Exercise 2.6: Draw the Newman projection of (a) the anti conformer and (b) the most stable gauche conformer of butane, viewed along the C2–C3 bond.

Solution: (a) Anti: front carbon bears CH_3 (top), H (bottom-left), H (bottom-right). Back carbon bears CH_3 (bottom, 180° from front CH_3), H (top-left), H (top-right). The two CH_3 groups are 180° apart — maximum separation.

(b) Gauche: same atoms, but back CH_3 is rotated 60° relative to front CH_3 (60° dihedral). One gauche interaction (≈ 3.8 kJ/mol above anti).

Exercise 2.7: Draw and name all the isomers (structural and stereoisomers) of formula C_4H_8.

Solution: DU = 1: one double bond or one ring.

Alkenes: but-1-ene CH_2=CH–CH_2–CH_3; but-2-ene CH_3–CH=CH–CH_3, which exists as two geometric isomers, (Z)-but-2-ene (cis) and (E)-but-2-ene (trans); 2-methylpropene CH_2=C$(CH_3)_2$.

Cycloalkanes: cyclobutane and methylcyclopropane.

Total: 6 isomers (5 constitutional isomers, one of which exists as a pair of E/Z diastereomers).

Exercise 2.8: Methylcyclohexane: (a) Draw the two chair conformations. (b) Which one is more stable and why? (c) Using the A-value (7.3 kJ/mol), calculate the percentage of each conformer at 25 °C.

Solution: (a) In one chair the CH_3 group is axial; after ring flip it becomes equatorial.

(b) The equatorial conformer is more stable: an axial methyl suffers two 1,3-diaxial interactions with the axial H atoms on C-3 and C-5 (2 × 3.8 ≈ 7.6 kJ/mol).

(c) K = [eq]/[ax] = exp(ΔG°/RT) = exp(7300 / (8.314 × 298)) = exp(2.95) ≈ 19.

Hence % equatorial = 19/20 = 95% and % axial = 5%.

Exercise 2.9: Indicate, for each compound, whether the most stable chair has both substituents equatorial: (a) cis-1,2-dimethylcyclohexane (b) trans-1,2-dimethylcyclohexane (c) cis-1,3-dimethylcyclohexane (d) trans-1,4-di-tert-butylcyclohexane.

Solution: (a) No: cis-1,2 is (a,e) in both chairs; the two chairs have the same energy.

(b) Yes: trans-1,2 can adopt the (e,e) chair, which is strongly favoured over (a,a).

(c) Yes: cis-1,3 can adopt the (e,e) chair.

(d) Yes: trans-1,4 is (e,e); with two tert-butyl groups the ring is effectively locked.

Exercise 2.10: A solution of 0.50 g of a pure enantiomer in 25 mL of ethanol, placed in a 20 cm polarimeter tube, rotates the plane of polarised light by –1.30°. (a) Calculate its specific rotation. (b) What would be the observed rotation of its enantiomer under the same conditions? (c) And that of the racemic mixture?

Solution: (a) c = 0.50/25 = 0.020 g/mL; l = 20 cm = 2.0 dm. $[\alpha] = \alpha/(l \times c) = -1.30/(2.0 \times 0.020) = -32.5°$.

(b) +1.30° (same magnitude, opposite sign).

(c) 0° (the racemate is optically inactive).

Exercise 2.11: A synthetic sample of (S)-ibuprofen has $[\alpha] = +45.0°$, whereas the pure (S) enantiomer has $[\alpha] = +57.0°$. Calculate the enantiomeric excess and the percentage of each enantiomer.

Solution: ee = 45.0/57.0 × 100 = 79%. Let x be the fraction of (S): x – (1 – x) = 0.79, so x = 0.895. The sample contains 89.5% (S) and 10.5% (R).

Exercise 2.12: Assign the R or S configuration to the stereocentre of each molecule: (a) but-3-en-2-ol, $CH_3–CH(OH)–CH=CH_2$, drawn with C-2 in the centre, CH_3 in the plane on the left, $CH=CH_2$ in the plane on the right, OH on a wedge pointing up and H on a dash pointing down (b) 2-chlorobutane in Fischer

projection with CH_3 at the top, C_2H_5 at the bottom, Cl on the right and H on the left (c) L-alanine.

Solution: (a) Priorities: OH (1) > $CH{=}CH_2$ (2) > CH_3 (3) > H (4). The vinyl carbon is treated as (C,C,H) because the double bond is duplicated, which is higher than CH_3 (H,H,H). H points away from the viewer (dash). The sequence OH (top) → vinyl (right) → CH_3 (left) runs clockwise: the configuration is (R).

(b) Priorities: Cl (1) > C_2H_5 (2) > CH_3 (3) > H (4). H is on a horizontal bond (toward the viewer). The path Cl (right) → C_2H_5 (bottom) → CH_3 (top) runs clockwise; since H is horizontal, the configuration is reversed: (S).

(c) L-alanine (NH_2 on the left, COOH at the top, CH_3 at the bottom, H on the right). Priorities: NH_2 > COOH > CH_3 > H. The path NH_2 (left) → COOH (top) → CH_3 (bottom) is clockwise; H is horizontal, so the configuration is reversed: (S)-alanine.

Exercise 2.13: 2,3-Dibromobutane: (a) How many stereoisomers exist? (b) Draw them in Fischer projection. (c) Identify the enantiomers, the diastereomers and the meso compound. (d) Which of them is optically active?

Solution: (a) The two stereocentres carry the same set of substituents (H, Br, CH_3, $CHBrCH_3$), so there are only 3 stereoisomers instead of 4.

(b) (2R,3R): Br on the right at C-2 and on the left at C-3; (2S,3S): the mirror image; meso (2R,3S): both Br on the same side.

(c) (2R,3R) and (2S,3S) are enantiomers. Each of them is a diastereomer of the meso form. (2R,3S) and (2S,3R) are the same compound (meso), which has an internal mirror plane.

(d) Only (2R,3R) and (2S,3S) are optically active. The meso form is inactive.

Exercise 2.14: Convert the following Newman projection into a Fischer projection: front carbon C-2 carries CH_3 (top), OH (bottom right) and H (bottom left); rear carbon C-3 carries CH_3 (bottom), OH (top left) and H (top right) of butane-2,3-diol. Assign R/S to each stereocentre and say whether the molecule is chiral.

Solution: The given conformation is staggered (anti CH_3 groups). Rotate the rear

carbon by 180° to eclipse the two CH_3 groups: the rear carbon then carries CH_3 (top), OH (bottom right) and H (bottom left). In the eclipsed form the two OH groups are on the same side and the two H on the same side.

In Fischer projection (CH_3 at top and bottom), both OH groups are on the same side: this is the erythro, i.e. meso, isomer (2R,3S)-butane-2,3-diol. It possesses a mirror plane and is achiral.

Exercise 2.15: Explain why trans-cyclooctene exists but trans-cyclohexene does not, and why buta-1,2-diene ($CH_2=C=CH–CH_3$) is achiral whereas penta-2,3-diene ($CH_3–CH=C=CH–CH_3$) is chiral.

Solution: A trans double bond requires the ring to span the opposite sides of the C=C plane; at least eight carbons are needed to do so without excessive strain. In cyclohexene the ring is too short: a trans arrangement would twist the π bond and break it.

In allenes, the substituents at the two ends lie in perpendicular planes. Buta-1,2-diene has two identical H atoms on C-1, which creates a plane of symmetry: it is achiral. In penta-2,3-diene each terminal carbon carries two different groups (H and CH_3), so the molecule has no plane of symmetry and is chiral (axial chirality), without any stereogenic carbon atom.

Exercise 2.16: Draw the Newman projections along the C-2–C-3 bond of 2-methylbutane, and rank the staggered conformations by stability.

Solution: C-2 carries H and two CH_3 groups; C-3 carries two H and one CH_3 (C-4).

Staggered conformation A: the C-4 methyl is anti to H of C-2 and gauche to both methyls of C-2 → two gauche interactions (≈ 7.6 kJ/mol).

Staggered conformations B and C (equivalent): the C-4 methyl is anti to one methyl of C-2 and gauche to the other → one gauche interaction (≈ 3.8 kJ/mol).

Stability: B = C > A. The eclipsed conformations are all less stable, the worst being the one where CH_3 eclipses CH_3.

CHAPTER 3: Electronic Effects in Organic Molecules

1. Introduction

The reactivity and physical properties of an organic molecule depend not only on its functional group(s) but also on how electrons are distributed throughout the molecule. Electronic effects describe the way in which electrons are redistributed through the molecular framework in response to the presence of electronegative atoms, π systems, or geometric constraints. The three major electronic effects studied in this chapter are: the inductive effect, the mesomeric (resonance) effect, and hyperconjugation. A fourth factor « the steric effect» is also introduced.

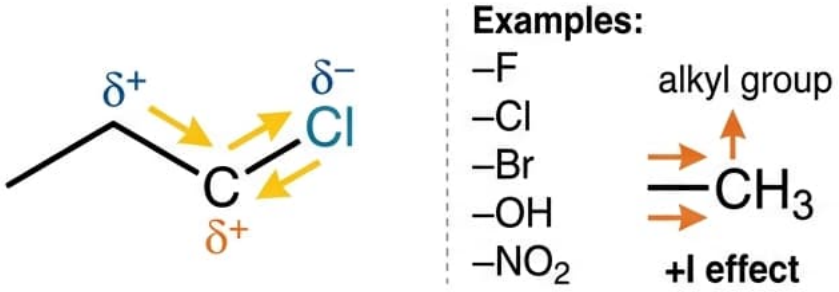
2. The Inductive Effect

2.1 Definition and Mechanism

The inductive effect (I effect) is the permanent polarisation of a covalent bond arising from a difference in electronegativity between two bonded atoms. It operates through the σ-bond framework and decreases rapidly with distance (roughly by a factor of three for each additional carbon atom in the chain).

–I effect (electron-withdrawing inductive effect): electropositive atoms or groups withdraw electron density through the σ bonds. Examples: –F, –Cl, –Br, –I, –OH, –OR, $–NO_2$, $–NR_3^+$, –C=O, –CN.

+I effect (electron-donating inductive effect): groups that push electron density toward the chain. Examples: alkyl groups ($–CH_3$, $–C_2H_5$, etc.) donate slightly by hyperconjugation (see Section 4) and induction.



2.2 Factors affecting the Inductive Effect

Electronegativity of the substituent: the greater the electronegativity difference, the stronger the –I effect.

Distance from the reaction site: the effect diminishes rapidly along the chain; it is essentially negligible beyond three bonds.

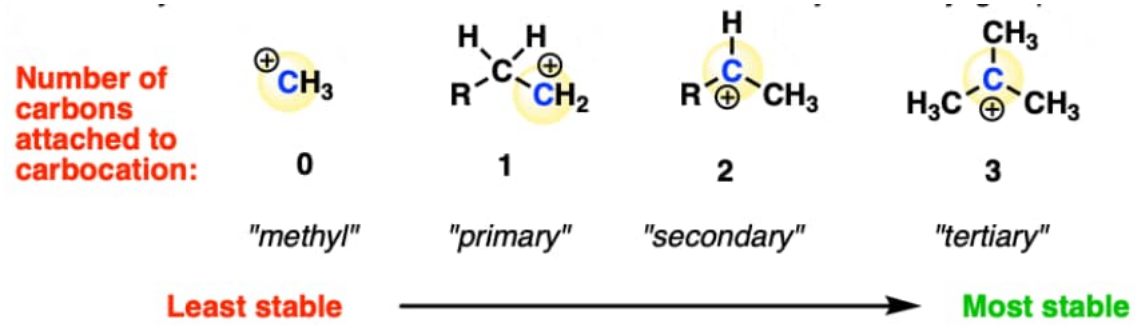
Number of electronegative groups: multiple electronegative substituents on the same carbon produce additive –I effects.

2.3 Inductive Effect and Carbocation Stability

Alkyl groups stabilise carbocations (R^+) by donating electron density toward the positive centre (hyperconjugation and +I). This explains the stability order:

3° carbocation > 2° carbocation > 1° carbocation > methyl cation

A tertiary carbocation is stabilised by three alkyl groups donating electrons, while a methyl cation has none. This order is crucial for predicting the course of SN1 and E1 reactions.

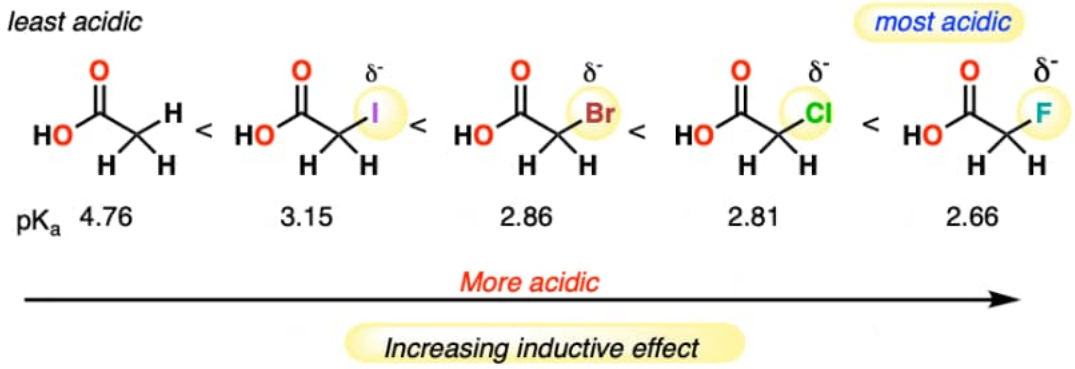


2.4 Inductive Effect and Acidity

For carboxylic acids RCOOH, strong electron-withdrawing groups (–I) increase acidity by stabilising the carboxylate anion ($RCOO^-$) through delocalisation of the negative charge. The more stable the conjugate base, the stronger the acid.

Example: Chloroacetic acid vs. acetic acid — $ClCH_2COOH$ ($pK_a \approx 2.86$) is about 100 times more acidic than CH_3COOH ($pK_a \approx 4.76$) because the –Cl withdraws electrons and stabilises $–COO^-$.

Example: Trichloroacetic acid — Cl_3CCOOH ($pK_a \approx 0.65$) is far stronger: three chlorines accumulate their –I effects.

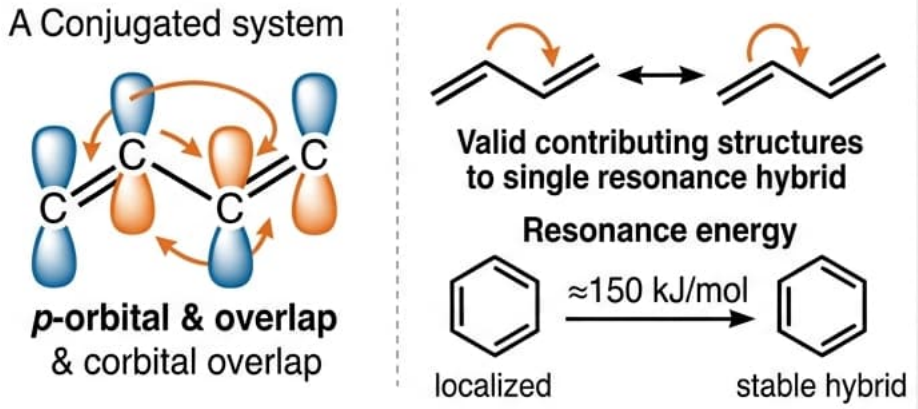


3. The Mesomeric (Resonance) Effect

3.1 Conjugated Systems

A conjugated system is one in which alternating single and double (or triple) bonds allow the p-orbitals on adjacent atoms to overlap continuously, forming an extended π system. π electrons are delocalised over the entire conjugated framework.

Example: 1,3-butadiene — CH_2=CH–CH=CH_2: four sp^2 carbons with overlapping p-orbitals form a delocalised π system over four centres.



3.2. Resonance Structures

Resonance structures (also called canonical structures or contributing structures) are different Lewis structures of the same molecule that differ only in the position of π electrons and lone pairs — never in the position of atomic nuclei. The actual molecule is a resonance hybrid, an average of all contributing structures.

Note: Resonance structures do NOT represent different molecules interconverting. The molecule has a single, time-averaged electronic structure; the hybrid.

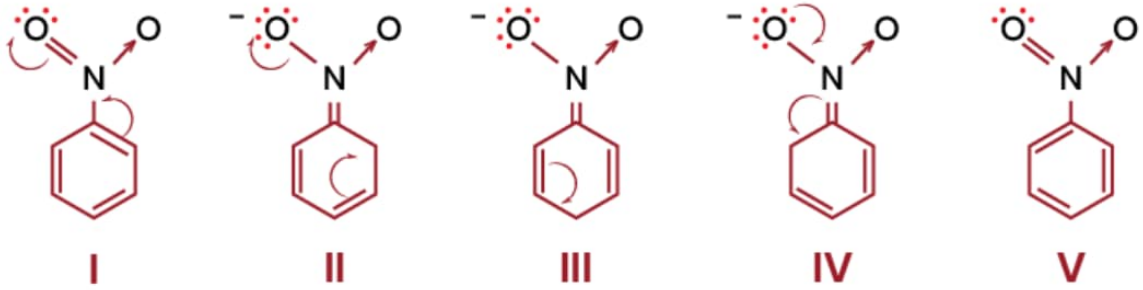
Rules for drawing valid resonance structures:

Only electron pairs (π bonds and lone pairs) may be moved; atoms must not be relocated.

The number of unpaired electrons must remain constant.

Structures with complete valence octets and minimal formal charges are more important contributors.

Negative formal charge should reside on the more electronegative atom.



3.2 Resonance Energy (Delocalisation Energy)

The resonance energy is the difference between the actual energy of the resonance hybrid and the energy of the most stable contributing structure. It represents the stabilisation arising from electron delocalisation. Benzene has a resonance energy of approximately 150 kJ/mol relative to a hypothetical cyclohexatriene with localised double bonds.

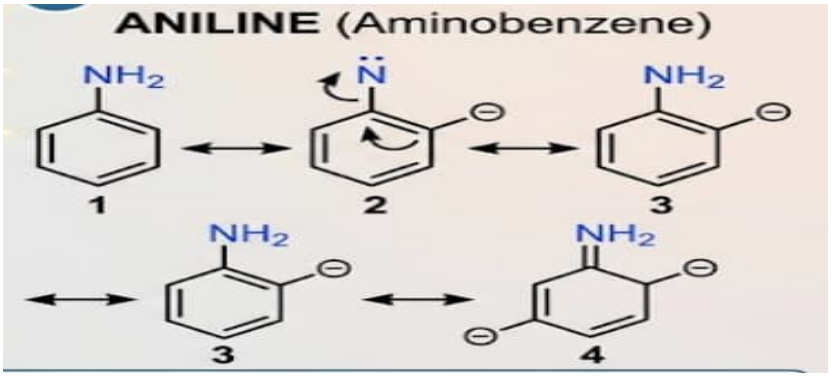
3.3 Positive Resonance Effect (+M or +R Effect)

A group exhibits a +M effect (electron-donating by resonance) when it possesses a lone pair on an atom adjacent to the π system, and donates that lone pair into the π framework, increasing electron density on the conjugated system.

Examples of +M groups: –OR, –OH, $–NR_2$, $–NH_2$, –SR, –X (halogens weak +M, strong –I).

Example: Aniline (aminobenzene) — The lone pair on N is delocalised into the ring, increasing electron density especially at ortho and para positions. This activates the

ring toward electrophilic aromatic substitution and directs substituents to ortho/para.



3.4 Negative Resonance Effect (–M or –R Effect)

A group exhibits a –M effect (electron-withdrawing by resonance) when it possesses an electron-deficient π bond adjacent to the conjugated system. It withdraws electron density from the ring/system.

Examples of –M groups: $–NO_2$, –CHO, –COR, –COOH, –COOR, –CN, $–SO_3H$.

Example: Nitrobenzene The nitro group ($–NO_2$) withdraws π electrons from the ring. Electron density is reduced, particularly at ortho and para positions. The ring is deactivated toward electrophilic attack and directing to meta.

3.5 Application: Electrophilic Aromatic Substitution Orientation

Electronic effects determine both the rate and the regioselectivity (position of substitution) of electrophilic aromatic substitution (EAS):

Substituent type	M effect	I effect	Ring reactivity	Directing effect
$–NH_2$, –OH, –OR	+M (dominant)	–I	Activated (faster)	ortho/para
–X (F, Cl, Br, I)	+M	–I (dominant)	Slightly deactivated	ortho/para
$–NO_2$, –CHO, –CN	–M	–I	Strongly deactivated	meta
Alkyl (–R)	+I (hyperconj.)	—	Slightly activated	ortho/para

4. Hyperconjugation

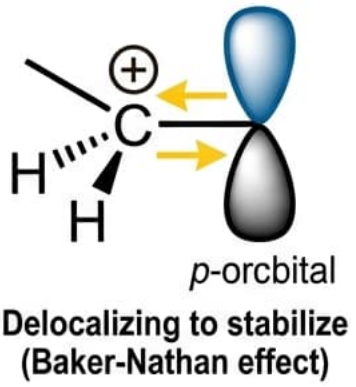
Hyperconjugation is the delocalisation of electrons from a σ bond (typically C–H or C–C) into an adjacent empty or partially filled p orbital or antibonding π* orbital. It is sometimes called 'σ-conjugation' or the Baker-Nathan effect.

Hyperconjugation explains:

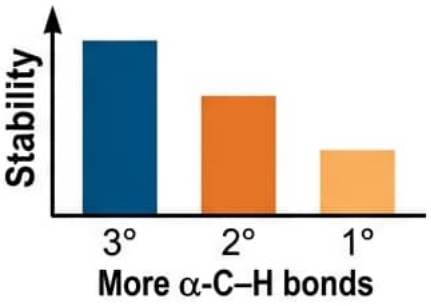
Stability of carbocations: more α-C–H bonds ⟹ greater hyperconjugation ⟹ greater stabilisation. Tertiary carbocations (9 α-H) are more stable than secondary (6 α-H) or primary (3 α-H).

Stability of free radicals: same argument applies.

Slightly shortened C–C bonds adjacent to C=C or C=O (partial double-bond character due to σ→π* delocalisation).



Delocalizing to stabilize
(Baker-Nathan effect)



More α-C–H bonds

Stability of free radicals,
Partal character in C-C bonds

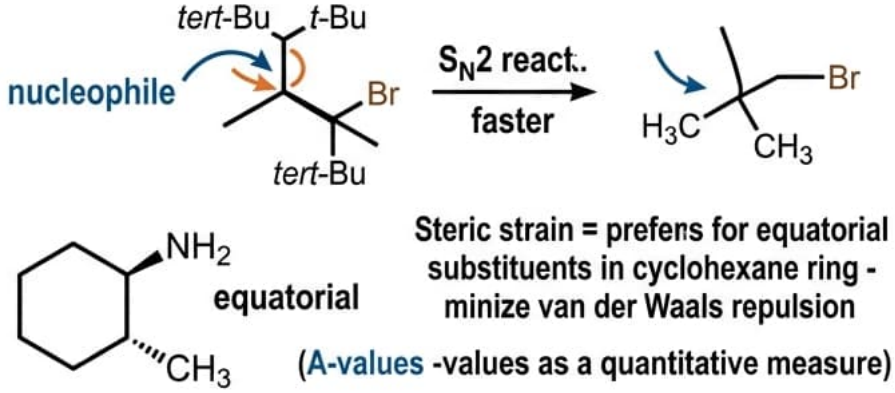
5. Steric Effect

The steric effect is a purely spatial (non-electronic) influence on reactivity arising from the size and shape of substituents. Large groups physically block the approach of reagents to a reaction centre.

Steric hindrance: bulky groups around a reactive site reduce reaction rate by obstructing the transition state. Example: t-butyl bromide reacts much more slowly by SN2 than methyl bromide.

Steric strain (van der Waals strain): non-bonded atoms forced into proximity experience repulsion. This contributes to the preference for equatorial substituents in cyclohexane.

A-values: quantitative measure of the steric preference for equatorial vs. axial positions in cyclohexane rings.



6. Acidity and Basicity of Organic Compounds

6.1 Brønsted and Lewis Definitions

According to Brønsted and Lowry, an acid is a proton (H^+) donor and a base is a proton acceptor. Every acid HA has a conjugate base A^-, and the stronger the acid, the weaker its conjugate base. According to Lewis, an acid is an electron-pair acceptor (BF_3, $AlCl_3$, H^+, carbocations) and a base is an electron-pair donor (NH_3, H_2O, $R–O^-$). The Lewis definition is broader and is the one used to describe most organic reaction mechanisms.

6.2 The pKa Scale

In water, the strength of an acid is measured by its acidity constant:

$HA + H_2O \rightleftharpoons A^- + H_3O^+$ $\quad Ka = [A^-][H_3O^+] / [HA] \quad pKa = –\log Ka$

The lower the pKa, the stronger the acid. A difference of one pKa unit corresponds to a factor of ten in acidity. An acid–base equilibrium always lies on the side of the weaker acid and the weaker base: a base can deprotonate significantly any acid whose pKa is lower than that of its own conjugate acid.

Compound	Conjugate base	Approximate pKa
HCl	Cl^-	–7
CF_3COOH	CF_3COO^-	0.5
CH_3COOH	CH_3COO^-	4.8
C_6H_5OH (phenol)	$C_6H_5O^-$	10.0
H_2O	HO^-	15.7
CH_3CH_2OH	$CH_3CH_2O^-$	16
CH_3COCH_3 (α-H)	$CH_2=C(O^-)CH_3$	19
$HC≡CH$	$HC≡C^-$	25
NH_3	NH_2^-	36

Compound	Conjugate base	Approximate pKa
$CH_2=CH_2$	$CH_2=CH^-$	44
CH_4	CH_3^-	≈ 50

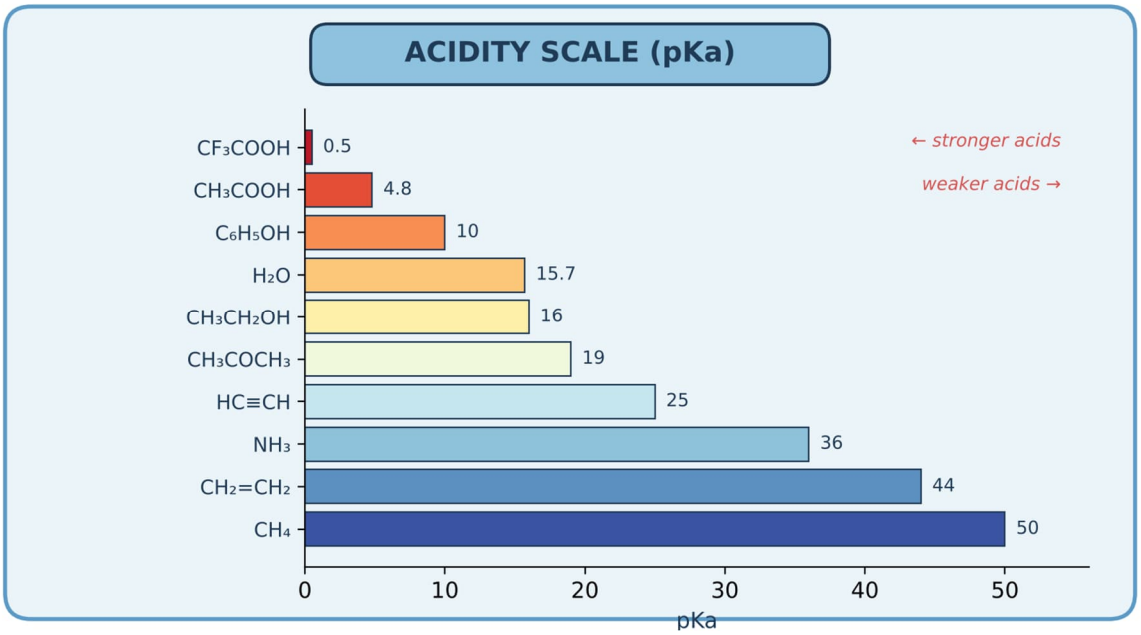


Figure 23. pKa values of representative organic and inorganic acids (lower pKa = stronger acid)

6.3 Structural Factors Governing Acidity

The acidity of HA depends essentially on the stability of the conjugate base A^-: everything that stabilises the negative charge increases the acidity. Five factors are classically considered, in approximate order of importance.

1. Nature of the atom carrying the charge. Along a period, acidity increases with electronegativity: CH_4 (pKa ≈ 50) < NH_3 (36) < H_2O (15.7) < HF (3.2). Down a group, acidity increases with atomic size, because the charge is spread over a larger volume: HF < HCl < HBr < HI, and ROH (pKa ≈ 16) < RSH (pKa ≈ 10).

2. Hybridisation. An sp orbital has 50% s character, holds electrons closer to the nucleus and stabilises a negative charge better than sp^2 (33%) or sp^3 (25%): HC≡CH (pKa 25) > $CH_2=CH_2$ (44) > $CH_3–CH_3$ (50). This is why terminal alkynes can be deprotonated by $NaNH_2$.

3. Resonance. Delocalisation of the negative charge over several atoms strongly stabilises the anion. The carboxylate ion distributes its charge equally over two oxygen atoms, which explains why acetic acid (pKa 4.8) is about 10^{11} times more acidic than ethanol (pKa 16). In the phenoxide ion, the charge is delocalised into the aromatic ring (ortho and para positions), which makes phenol (pKa 10) much

more acidic than cyclohexanol (pKa 18).

4. Inductive effect. –I groups near the acidic site stabilise the anion; +I groups destabilise it. The effect decreases quickly with distance (see Section 2 of this chapter).

5. Solvation. In water, small, compact anions are strongly stabilised by hydrogen bonding. For instance, the order of alcohol acidity in water, $CH_3OH > CH_3CH_2OH > (CH_3)_2CHOH > (CH_3)_3COH$, is mainly due to the poorer solvation of bulky alkoxides; in the gas phase the order is reversed.

6.4 Effect of Substituents on the Acidity of Phenols and Benzoic Acids

Substituents on an aromatic ring modify acidity through both inductive and mesomeric effects. Electron-withdrawing groups ($–NO_2$, –CN, –CHO, halogens) increase acidity; electron-donating groups ($–CH_3$, $–OCH_3$, $–NH_2$) decrease it. Groups with a –M effect are particularly efficient in the ortho and para positions, where they can delocalise the negative charge of the phenoxide ion directly.

Phenol	pKa	Benzoic acid	pKa
Phenol	10.0	Benzoic acid	4.20
4-methylphenol	10.3	4-methylbenzoic acid	4.37
4-chlorophenol	9.4	4-chlorobenzoic acid	3.98
3-nitrophenol	8.4	3-nitrobenzoic acid	3.45
4-nitrophenol	7.2	4-nitrobenzoic acid	3.44
2,4,6-trinitrophenol	0.4	4-methoxybenzoic acid	4.47

2,4,6-Trinitrophenol (picric acid) is as strong as many mineral acids: its anion is stabilised by three nitro groups located ortho and para to the oxygen.

6.5 Basicity of Amines

The basicity of a nitrogen compound depends on the availability of the nitrogen lone pair. It is conveniently expressed by the pKa of the conjugate acid (the ammonium ion, pKaH): the higher the pKaH, the stronger the base.

Base	Conjugate acid	pKaH
NH_3	NH_4^+	9.25
CH_3NH_2	$CH_3NH_3^+$	10.6

Base	Conjugate acid	pKaH
$(CH_3)_2NH$	$(CH_3)_2NH_2^+$	10.7
$(CH_3)_3N$	$(CH_3)_3NH^+$	9.8
$C_6H_5NH_2$ (aniline)	$C_6H_5NH_3^+$	4.6
Pyridine	$C_5H_5NH^+$	5.2
CH_3CONH_2 (amide)	$CH_3C(OH)=NH_2^+$	≈ –0.5

Aliphatic amines are more basic than ammonia because alkyl groups (+I) increase the electron density on nitrogen and stabilise the ammonium ion. In water the order is secondary ≈ primary > tertiary > NH_3: the tertiary ammonium ion carries only one N–H bond and is less well solvated by hydrogen bonding.

Aniline is about one million times less basic than methylamine, because the nitrogen lone pair is delocalised into the aromatic ring (+M effect) and is less available for protonation.

Amides are practically not basic: the lone pair of nitrogen is strongly delocalised toward the carbonyl oxygen (N–C=O ↔ N^+=C–O^-). Protonation, when it occurs, takes place on oxygen.

Pyridine is a weaker base than aliphatic amines because its lone pair occupies an sp^2 orbital, with more s character than the sp^3 lone pair of an amine.

7. Stability of Reactive Intermediates

Most organic reactions proceed through short-lived, high-energy species: carbocations, carbanions and radicals. Their relative stabilities, governed by the electronic effects studied in this chapter, determine the rate and the regioselectivity of many reactions (Markovnikov rule, SN1 versus SN2, Zaitsev rule).

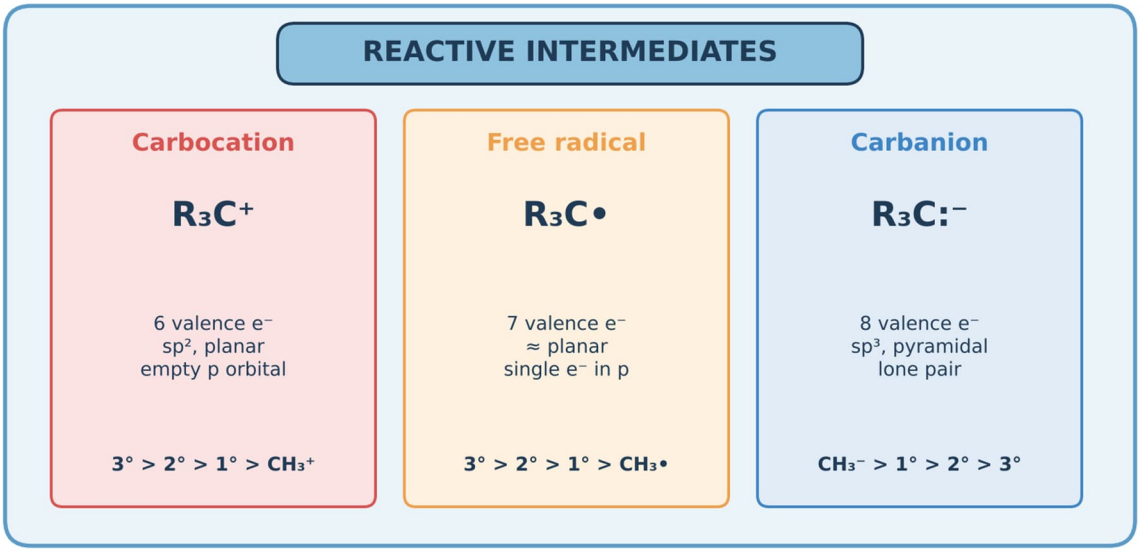


Figure 24. Structure and hybridisation of the three main carbon-centred reactive intermediates

7.1 Carbocations

A carbocation is a trivalent carbon carrying a positive charge and only six valence electrons. It is sp^2 hybridised and planar, with an empty p orbital perpendicular to the plane. Carbocations are stabilised by electron donation toward this empty orbital:

By +I effect and hyperconjugation of alkyl groups: $(CH_3)_3C^+ > (CH_3)_2CH^+ > CH_3CH_2^+ > CH_3^+$.

By resonance (+M) with an adjacent π system or lone pair: allyl ($CH_2{=}CH{-}CH_2^+$) and benzyl ($C_6H_5{-}CH_2^+$) cations are about as stable as secondary alkyl cations, and much more stable than primary ones. An adjacent oxygen atom with a lone pair ($CH_3{-}O{-}CH_2^+ \leftrightarrow CH_3{-}O^+{=}CH_2$) is a very powerful stabilising group.

Overall order: benzyl, allyl, tertiary > secondary > primary > methyl. Vinyl ($CH_2{=}CH^+$) and phenyl ($C_6H_5^+$) cations are very unstable, because the positive charge is in an sp orbital (or sp^2 for phenyl) that cannot overlap with the π system.

Because carbocations are electron deficient, they readily undergo rearrangements (1,2-hydride or 1,2-methyl shifts) whenever a more stable cation can be formed. This point is discussed in Chapter 4.

7.2 Carbanions

A carbanion carries a negative charge and an unshared electron pair on carbon (eight valence electrons). Simple alkyl carbanions are sp^3 hybridised and pyramidal. Their stability order is the reverse of that of carbocations, because alkyl

groups (+I) increase the negative charge:

CH_3^- > primary > secondary > tertiary.

Carbanions are strongly stabilised by –M groups that delocalise the negative charge: enolate ions (adjacent C=O), the anion of nitromethane ($CH_2{=}NO_2^-$), and the anion of malonic esters. They are also stabilised by greater s character (acetylide ions $HC{\equiv}C^-$). Carbanions are key intermediates in carbon–carbon bond formation (Grignard reagents behave as carbanion equivalents).

7.3 Free Radicals

A free radical carries an unpaired electron (seven valence electrons on carbon). Alkyl radicals are nearly planar (sp^2) with the single electron in a p orbital. Like carbocations, radicals are electron deficient and are stabilised by alkyl groups (hyperconjugation) and by resonance:

Benzyl ≈ allyl > tertiary > secondary > primary > methyl.

This order is reflected in the C–H bond dissociation energies (BDE): CH_3–H 439 kJ/mol, CH_3CH_2–H 421, $(CH_3)_2CH$–H 413, $(CH_3)_3C$–H 404, $CH_2{=}CHCH_2$–H 369, $C_6H_5CH_2$–H 377 kJ/mol. The weaker the C–H bond, the more stable the radical formed.

Intermediate	Electrons on C	Geometry	Stability order
Carbocation R_3C^+	6	planar (sp^2)	3° > 2° > 1° > CH_3^+
Radical $R_3C\bullet$	7	almost planar	3° > 2° > 1° > $CH_3\bullet$
Carbanion R_3C^-	8	pyramidal (sp^3)	CH_3^- > 1° > 2° > 3°
Carbene R_2C:	6 (neutral)	bent	very reactive

8. Aromaticity and Hückel's Rule

8.1 Criteria for Aromaticity

Benzene is much more stable than expected for a cyclic triene (resonance energy ≈ 150 kJ/mol) and does not undergo the addition reactions typical of alkenes. This special stability, called aromaticity, is not limited to benzene. A molecule (or ion) is aromatic if it satisfies all of the following conditions:

It is cyclic.

It is planar (or nearly planar).

It is fully conjugated: every atom of the ring has a p orbital (sp^2 or sp hybridised), so that the π electrons form a continuous cyclic cloud.

It contains (4n + 2) π electrons, where n = 0, 1, 2, … (Hückel's rule): 2, 6, 10, 14… π electrons.

A cyclic, planar, fully conjugated system with 4n π electrons (4, 8, …) is antiaromatic and particularly unstable. Molecules that avoid planarity to escape this destabilisation (such as cyclooctatetraene, which adopts a tub shape) are simply non-aromatic.

8.2 Examples

Species	π electrons	Classification
Benzene C_6H_6	6	aromatic (n = 1)
Cyclopentadienyl anion $C_5H_5^-$	6	aromatic
Cycloheptatrienyl (tropylium) cation $C_7H_7^+$	6	aromatic
Cyclopropenyl cation $C_3H_3^+$	2	aromatic (n = 0)
Cyclobutadiene C_4H_4	4	antiaromatic
Cyclooctatetraene C_8H_8	8	non-aromatic (tub-shaped)
Naphthalene $C_{10}H_8$	10	aromatic (n = 2)
Cyclopentadiene C_5H_6	4 (one sp^3 C)	non-aromatic

The remarkable acidity of cyclopentadiene (pKa ≈ 16, compared with ≈ 50 for alkanes) is explained by the aromaticity of its conjugate base, the cyclopentadienyl anion.

8.3 Aromatic Heterocycles

Heteroatoms (N, O, S) can be part of an aromatic ring. The key question is whether the heteroatom lone pair belongs to the π system:

Pyridine (C_5H_5N): the nitrogen is sp^2 and contributes one electron to the π system, like a CH. Its lone pair lies in the plane of the ring (sp^2 orbital) and is not part of the aromatic sextet; it remains available for protonation (pyridine is basic, pKaH = 5.2).

Pyrrole (C_4H_4NH): the nitrogen lone pair is in a p orbital and is part of the aromatic sextet (4 electrons from two C=C + 2 from N). Protonating it would

destroy aromaticity: pyrrole is practically not basic (pKaH ≈ –3.8).

Furan and thiophene: oxygen and sulfur contribute one lone pair to the aromatic sextet; their second lone pair lies in the plane of the ring.

These heterocycles are found in many biomolecules and drugs: pyridine in vitamin B_3 (nicotinamide), pyrrole in haemoglobin and chlorophyll (porphyrins), imidazole in histidine, purine and pyrimidine bases in DNA.

9. Electronic Effects and Physical Properties

9.1 Dipole Moments

When a bond connects two atoms of different electronegativity, the electron density is displaced toward the more electronegative atom, creating partial charges $\delta+$ and $\delta-$. The bond dipole moment is $\mu = q \times d$ (expressed in debye, 1 D = 3.336×10^{-30} C·m). The molecular dipole moment is the vector sum of the bond moments: it depends on both bond polarity and molecular geometry.

Example: CO_2 (linear) and CCl_4 (tetrahedral) have polar bonds but $\mu = 0$ because the bond moments cancel. CH_3Cl has $\mu = 1.87$ D; H_2O has $\mu = 1.85$ D.

Example: cis-1,2-dichloroethene ($\mu = 1.9$ D) is polar, whereas trans-1,2-dichloroethene ($\mu = 0$) is not; this explains why the cis isomer has a higher boiling point (60 °C versus 48 °C).

9.2 Intermolecular Forces and Boiling Points

The physical properties of organic compounds (boiling point, melting point, solubility) are governed by intermolecular forces, which themselves depend on the electronic structure of the molecules:

London dispersion forces: present in all molecules; they increase with molecular size and surface area. Linear alkanes boil higher than their branched isomers: pentane (36 °C) > 2-methylbutane (28 °C) > 2,2-dimethylpropane (10 °C).

Dipole–dipole interactions: between polar molecules (aldehydes, ketones, halogenoalkanes).

Hydrogen bonds: between an H bonded to N, O or F and a lone pair on N, O or F. They are the strongest intermolecular interactions (10–40 kJ/mol).

Compound	Main interaction	Boiling point (°C)
Butane	dispersion	–0.5
Methoxyethane	dipole–dipole	7
Propanal	dipole–dipole	49
Propan-1-ol	hydrogen bonds	97
Acetic acid	H-bonds (dimers)	118

Hydrogen bonding also explains the water solubility of small alcohols, amines and carboxylic acids. As the hydrocarbon part becomes longer, the hydrophobic character dominates: methanol, ethanol and propanol are completely miscible with water, whereas hexan-1-ol is only slightly soluble (≈ 6 g/L).

Exercises: Chapter 3

Exercise 3.1: Rank the following carboxylic acids in order of decreasing acidity (strongest acid first): acetic acid (CH_3COOH), fluoroacetic acid (FCH_2COOH), difluoroacetic acid ($F_2CHCOOH$), trifluoroacetic acid (CF_3COOH).

Solution: Decreasing acidity: CF_3COOH ($pK_a \approx 0.5$) > $F_2CHCOOH$ ($pK_a \approx 1.3$) > FCH_2COOH ($pK_a \approx 2.6$) > CH_3COOH ($pK_a \approx 4.8$).

More fluorine atoms = stronger cumulative –I effect = better stabilisation of the conjugate base (carboxylate anion) = stronger acid.

Exercise 3.2: Explain why the –OH group in phenol (C_6H_5OH) activates the ring toward electrophilic aromatic substitution and directs incoming electrophiles to the ortho and para positions.

Solution: Oxygen possesses two lone pairs. The lone pair in the plane of the ring (σ lone pair) participates in the –I effect (withdrawing). The out-of-plane lone pair overlaps with the ring π system (+M effect), donating electron density to the ring.
Resonance structures show increased electron density at ortho (C-2, C-6) and para (C-4) positions, while C-1 and C-3 and C-5 carry less. Electrophiles (E^+) attack where electron density is highest $\Longrightarrow$ ortho/para substitution.
Since +M > –I for –OH, the net effect is ring activation (phenol reacts 10^6 times faster than benzene in bromination).
Exercise 3.3: Write all resonance structures for the allyl cation ($CH_2=CH–CH_2^+$) and identify which carbon(s) bear the positive charge.

Solution: Two resonance contributors: $^+CH_2–CH=CH_2 \leftrightarrow CH_2=CH–CH_2^+$.
The positive charge is delocalised equally between C-1 and C-3 (the two terminal carbons). C-2 is not charged in any structure.
The resonance hybrid has partial positive charge on both terminal carbons. This delocalisation makes the allyl cation far more stable than a primary carbocation.

Exercise 3.4: Which carbocation is more stable: $(CH_3)_3C^+$ or $(CH_3)_2CH^+$? Justify using both inductive and hyperconjugative arguments.

Solution: $(CH_3)_3C^+$ (tertiary) is more stable than $(CH_3)_2CH^+$ (secondary).

Inductive: three alkyl (methyl) groups each donate electron density (+I) toward the electron-deficient carbon, partially dispersing the positive charge.

Hyperconjugation: the tertiary cation has 9 α-C–H bonds participating in σ→p(empty) overlap, vs. 6 in the secondary. More hyperconjugation = more stabilisation.

Exercise 3.5: Explain the effect of the nitro group ($–NO_2$) on the acidity of benzoic acid when placed at the para position.

Solution: Para-nitrobenzoic acid is more acidic than benzoic acid (lower pK_a).

The nitro group at the para position exerts both –I (weak, through sigma bonds) and –M effects (strong, through π resonance): it withdraws electron density from the ring and especially from the para carbon.

This stabilises the carboxylate anion ($p\text{-}O_2N–C_6H_4–COO^-$) by delocalising the negative charge across the ring and onto the nitro group oxygen atoms.

Greater anion stability ⟹ weaker O–H bond in the acid ⟹ stronger acid. pK_a(4-nitrobenzoic acid) ≈ 3.44 vs. pK_a(benzoic acid) ≈ 4.20.

Exercise 3.6: Classify the following compounds in order of increasing acidity and justify: ethanol, phenol, acetic acid, water, 4-nitrophenol, ethyne.

Solution: Increasing acidity (decreasing pKa): ethyne (25) < ethanol (16) < water (15.7) < phenol (10.0) < 4-nitrophenol (7.2) < acetic acid (4.8).

Ethyne: the negative charge is localised on carbon (low electronegativity) despite sp hybridisation.

Ethanol is slightly less acidic than water in solution: the ethyl group (+I) destabilises the alkoxide, which is also less well solvated.

Phenol: the phenoxide charge is delocalised over the ring (ortho and para carbons).

4-Nitrophenol: the –M and –I effects of NO_2 in the para position delocalise the charge onto the nitro oxygens.

Acetic acid: the charge of the carboxylate is shared equally by two electronegative oxygen atoms.

Exercise 3.7: Rank the following bases from the strongest to the weakest: ammonia, aniline, ethylamine, acetamide, diethylamine, 4-nitroaniline. Explain.

Solution: Diethylamine (pKaH ≈ 11.0) > ethylamine (10.7) > ammonia (9.25) > aniline (4.6) > 4-nitroaniline (1.0) > acetamide (≈ –0.5).

Alkyl groups (+I) increase the electron density on N (aliphatic amines more basic than NH_3). In aniline the lone pair is delocalised into the ring (+M), and the –M effect of the para nitro group reinforces this delocalisation (push–pull system). In acetamide the lone pair is conjugated with C=O and is practically unavailable.

Exercise 3.8: Write the equation of the reaction between ethyne and sodium amide ($NaNH_2$). Is the equilibrium displaced to the right? Would sodium hydroxide be suitable? (pKa: HC≡CH 25; NH_3 36; H_2O 15.7)

Solution: $HC{\equiv}CH + NH_2^- \rightleftharpoons HC{\equiv}C^- + NH_3$. The equilibrium lies on the side of the weaker acid: NH_3 (pKa 36) is much weaker than ethyne (pKa 25). K = 10^(36 – 25) = 10^{11}: the reaction is complete.

With HO^-: $HC{\equiv}CH + HO^- \rightleftharpoons HC{\equiv}C^- + H_2O$; K = 10^(15.7 – 25) ≈ 10^{-9}. The equilibrium lies far to the left: NaOH is not a strong enough base to deprotonate a terminal alkyne.

Exercise 3.9: Arrange the following carbocations in order of decreasing stability and justify: CH_3^+, $(CH_3)_3C^+$, $CH_2{=}CH{-}CH_2^+$, $CH_3{-}CH_2^+$, $C_6H_5{-}CH_2^+$, $(CH_3)_2CH^+$, $CH_2{=}CH^+$.

Solution: Decreasing stability: $C_6H_5CH_2^+ \approx (CH_3)_3C^+ > CH_2{=}CHCH_2^+ \approx (CH_3)_2CH^+ > CH_3CH_2^+ > CH_3^+ \approx CH_2{=}CH^+$.

Benzyl and allyl cations are stabilised by resonance (the positive charge is shared by the two terminal carbons of the allyl cation, and by the CH_2 carbon and the

ortho and para carbons of the benzyl cation). Alkyl cations are stabilised by +I and hyperconjugation, proportionally to the number of alkyl groups. The vinyl cation is very unstable because its empty orbital is an sp orbital that cannot be stabilised by the adjacent π bond.

Exercise 3.10: Explain the following order of bond dissociation energies: $(CH_3)_3C–H$ (404 kJ/mol) < $(CH_3)_2CH–H$ (413) < $CH_3CH_2–H$ (421) < $CH_3–H$ (439). Predict the major monobromination product of 2-methylpropane under radical conditions.

Solution: Breaking a C–H bond homolytically gives a radical; the more stable the radical, the weaker the bond. Tertiary radicals are stabilised by hyperconjugation with 9 C–H bonds (versus 6, 3 and 0 for the others).

Bromine radicals are very selective (the hydrogen abstraction step is endothermic and has a late, product-like transition state, according to Hammond's postulate). The tertiary H is abstracted preferentially: the major product is 2-bromo-2-methylpropane, $(CH_3)_3CBr$ (> 99%).

Exercise 3.11: Use Hückel's rule to determine whether each species is aromatic, antiaromatic or non-aromatic: (a) cyclopropenyl anion $C_3H_3^-$ (b) tropylium cation $C_7H_7^+$ (c) cyclopentadienyl cation $C_5H_5^+$ (d) pyrimidine (e) cyclohepta-1,3,5-triene.

Solution: (a) 4 π electrons, cyclic, planar, conjugated: antiaromatic.

(b) 6 π electrons (n = 1): aromatic. This explains why tropylium salts are stable and can be isolated.

(c) 4 π electrons: antiaromatic (very unstable).

(d) Pyrimidine (a six-membered ring with two N atoms, like pyridine): 6 π electrons, each N contributes one electron and keeps its lone pair in the plane: aromatic.

(e) Cycloheptatriene contains one sp^3 CH_2 group that breaks the cyclic conjugation: non-aromatic.

Exercise 3.12: Which nitrogen atom of imidazole (a five-membered aromatic ring containing an N–H nitrogen and a pyridine-like nitrogen) is protonated first?

Justify.

Solution: Imidazole contains 6 π electrons: 2 from each C=C/C=N double bond (4) and 2 from the lone pair of the N–H nitrogen (pyrrole-like). The second nitrogen (pyridine-like, =N–) has its lone pair in an sp^2 orbital in the ring plane, not involved in the aromatic sextet. Protonation therefore takes place on this pyridine-like nitrogen, without loss of aromaticity. The resulting cation is symmetrical and resonance stabilised, which makes imidazole a relatively strong base (pKaH ≈ 7.0), as observed in the amino acid histidine.

Exercise 3.13: Explain why: (a) trans-1,2-dichloroethene has no dipole moment; (b) propan-1-ol boils at 97 °C whereas its isomer methoxyethane boils at 7 °C; (c) 2,2-dimethylpropane boils at a lower temperature than pentane.

Solution: (a) The two C–Cl bond moments are equal and point in opposite directions in the trans isomer: their vector sum is zero.

(b) Propan-1-ol molecules form intermolecular hydrogen bonds O–H···O. Methoxyethane has no O–H bond: only dipole–dipole and dispersion forces exist between its molecules.

(c) 2,2-Dimethylpropane is almost spherical: its contact surface, and therefore the dispersion forces, are smaller than for linear pentane.

Exercise 3.14: Draw the resonance structures of the enolate ion of acetone and of the phenoxide ion. On which atoms is the negative charge located?

Solution: Enolate: $^{-}CH_2–CO–CH_3 \leftrightarrow CH_2=C(O^{-})–CH_3$. The charge is shared between the α-carbon and the oxygen; the oxygen form is the major contributor (negative charge on the more electronegative atom).

Phenoxide: four principal structures. One with the charge on oxygen (aromatic ring intact) and three with the charge on the ortho (2 structures) and para (1 structure) carbons, the oxygen being doubly bonded to the ring. This explains why electrophiles attack phenols and phenoxides at the ortho and para positions.

Exercise 3.15: Compare the acidity of the following pairs and justify: (a)

CH_3CH_2COOH and $CH_3CHClCOOH$; (b) $CH_3CHClCOOH$ and $ClCH_2CH_2COOH$; (c) $ClCH_2COOH$ and FCH_2COOH; (d) HCOOH and CH_3COOH.

Solution: (a) $CH_3CHClCOOH$ (pKa ≈ 2.8) is more acidic than propanoic acid (4.87): the –I effect of chlorine stabilises the carboxylate.

(b) 2-chloropropanoic acid (2.8) is more acidic than 3-chloropropanoic acid (4.0): the inductive effect decreases with distance.

(c) FCH_2COOH (2.6) is more acidic than $ClCH_2COOH$ (2.86): fluorine is more electronegative (stronger –I).

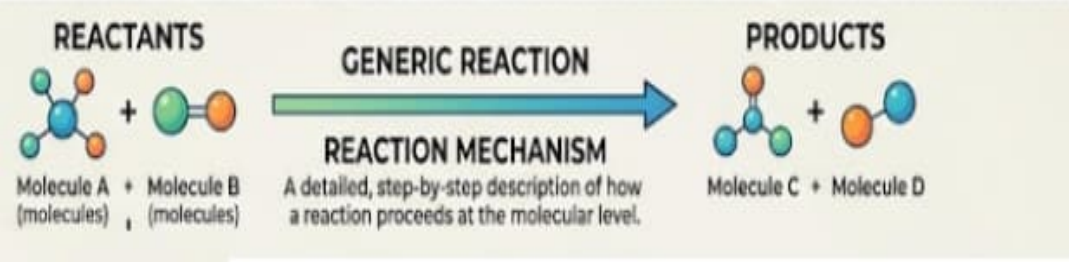
(d) HCOOH (3.75) is more acidic than CH_3COOH (4.76): the methyl group exerts a +I effect that destabilises the carboxylate anion.

CHAPTER 4: Reaction Mechanisms in Organic Chemistry

1. General Concepts

1.1 Organic Reactions and Reaction Mechanisms

A reaction mechanism is a detailed, step-by-step description of how a chemical reaction proceeds at the molecular level. It identifies each species formed along the pathway, the bonds broken and formed at each step, the geometry of the transition states, and the energy changes involved. Mechanisms allow chemists to predict products, explain selectivity, and design new reactions.



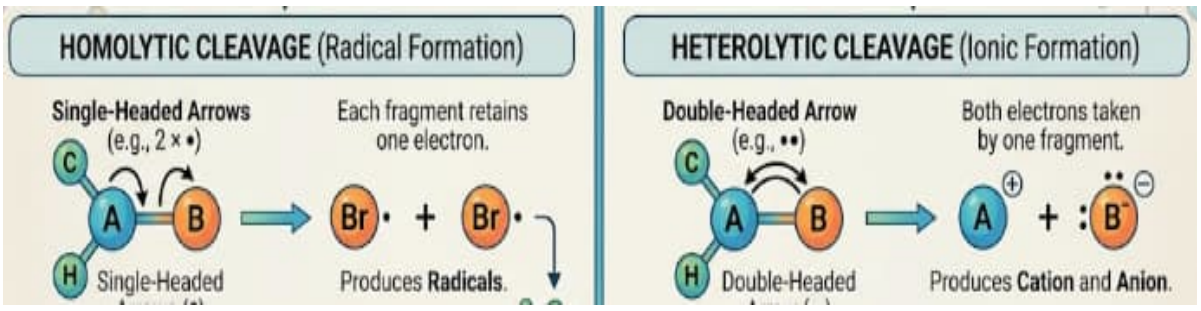
1.2 Bond Breaking and Formation

1.2.1 Bond Breaking

When a covalent bond breaks, the electrons in the bond must be distributed between the two fragments. Two modes exist:

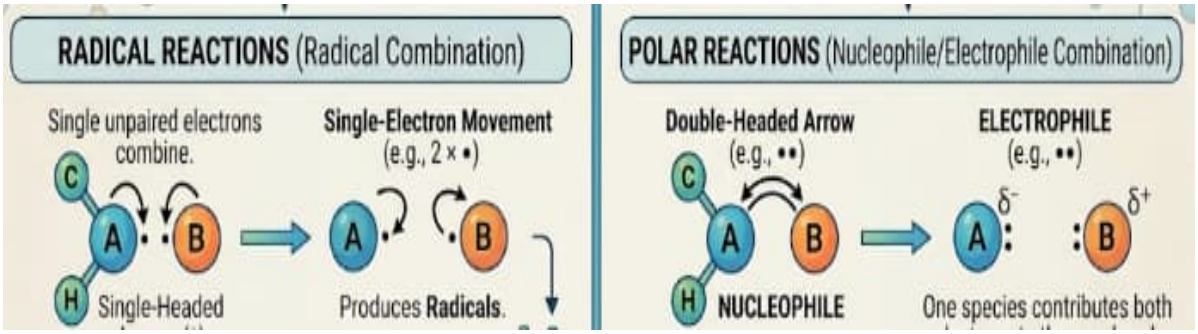
Homolytic cleavage: each fragment retains one electron of the bonding pair. This produces two radicals (species with unpaired electrons). Promoted by UV light or radical initiators. A–B → A• + B•

Heterolytic cleavage: both electrons of the bonding pair are taken by one fragment. This produces a cation and an anion (ionic species). A:B → A^+ + $:B^-$ (or $A:^-$ + B^+).



1.2.2 Bond Formation

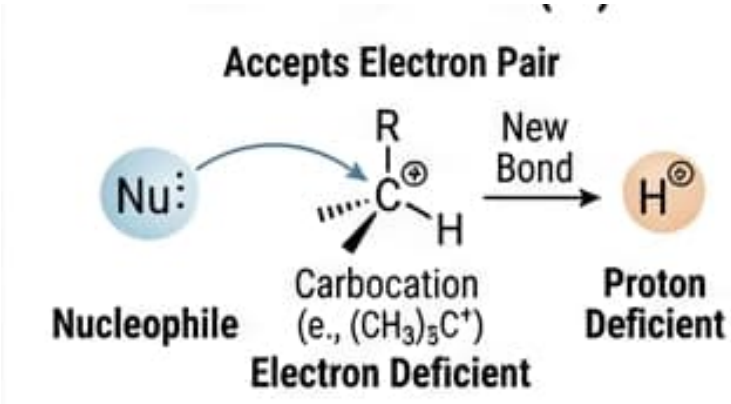
Bond formation is the reverse: two electrons (one from each species in radical reactions; both from one species in polar reactions) combine to form a new covalent bond.



1.3 Reactive Intermediates

1.3.1 Electrophiles

An electrophile (E^+) is an electron-deficient species that seeks electrons. It accepts an electron pair from a nucleophile to form a new bond. Common electrophiles include: carbocations (R^+), protons (H^+), Lewis acids (BF_3, $AlCl_3$), halogen molecules (Br_2, Cl_2), and halonium ions.

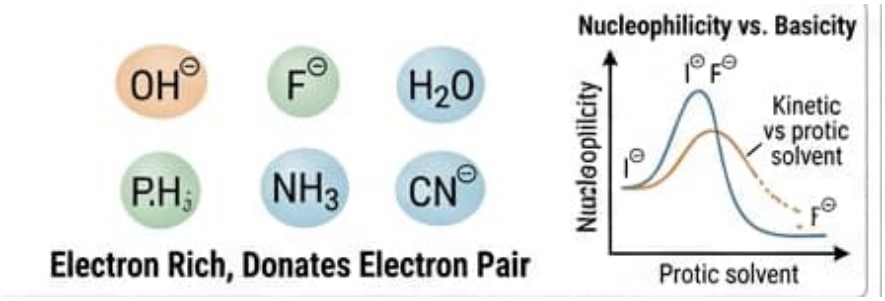


1.3.2 Nucleophiles

A nucleophile (Nu:) is an electron-rich species that donates an electron pair to an electrophile. Common nucleophiles: halide ions (F^-, Cl^-, Br^-, I^-), hydroxide (OH^-), water (H_2O), alcohols (ROH), amines (RNH_2), cyanide (CN^-), and carbanions.

Note: Nucleophilicity and basicity are related but distinct. Nucleophilicity is kinetic (how fast a species attacks); basicity is thermodynamic (how much it binds to H^+).

In protic solvents, larger, more polarisable atoms are better nucleophiles even if they are weaker bases.



2. Classification of Organic Reactions

2.1 Nucleophilic Substitution Reactions

In a substitution reaction, an atom or group in a molecule is replaced by another. Nucleophilic substitution (SN) involves a nucleophile replacing a leaving group.

2.1.1 SN2 Bimolecular Nucleophilic Substitution

The SN2 reaction proceeds by a single concerted step: the nucleophile attacks the back face of the carbon bearing the leaving group (180° Walden inversion), and simultaneously the leaving group departs. The transition state involves a pentacoordinate carbon.

Rate = k [substrate][nucleophile] (second-order kinetics).

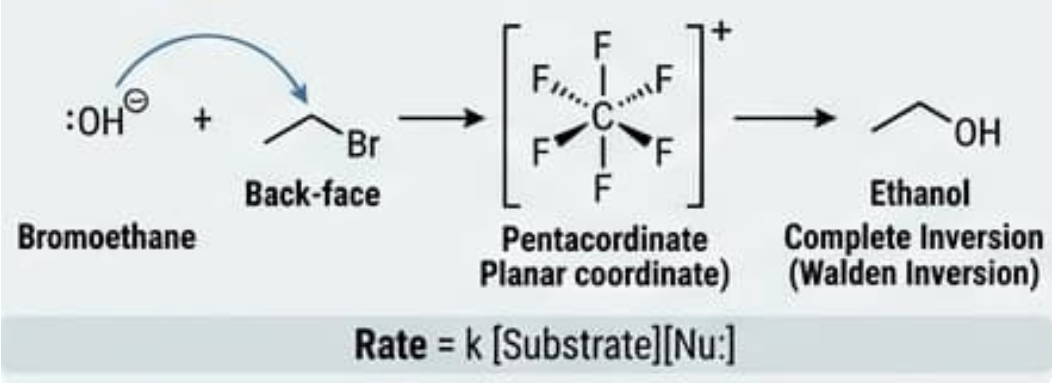
Stereochemistry: complete inversion of configuration (Walden inversion).

Substrate reactivity order: methyl > 1° > 2° ≫ 3° (steric effects dominate).

Best leaving groups: $I^- > Br^- > Cl^- > F^- > OH^-$ (weaker base = better leaving group).

Favoured by: primary substrates, strong nucleophiles, polar aprotic solvents (DMSO, acetone, acetonitrile).

Example: SN2 of bromoethane $CH_3CH_2Br + OH^- \rightarrow CH_3CH_2OH + Br^-$. One step, rate depends on both concentrations.



2.1.2 SN1 Unimolecular Nucleophilic Substitution

The SN1 reaction proceeds in two steps: (1) ionisation of the leaving group to form a carbocation intermediate, and (2) rapid capture of the carbocation by the nucleophile. The rate-determining step is step 1.

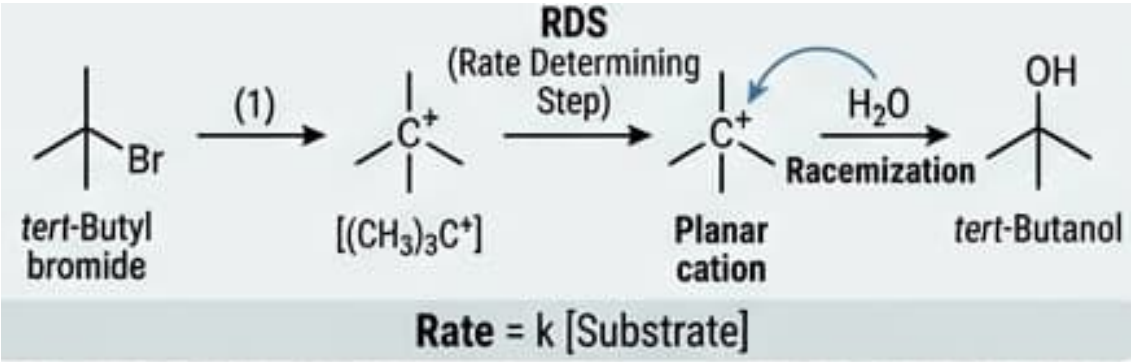
Rate = k [substrate] (first-order; the nucleophile does not appear in the rate law).

Stereochemistry: racemisation (the planar carbocation can be attacked from either face), often with slight excess of inversion.

Substrate reactivity order: 3° ≫ 2° > 1° (stabilised carbocation required).

Favoured by: tertiary or benzylic/allylic substrates, weak nucleophiles, polar protic solvents (water, alcohols) that stabilise ions.

Example: SN1 of tert-butyl bromide — $(CH_3)_3CBr + H_2O \rightarrow [(CH_3)_3C^+] \rightarrow (CH_3)_3COH + HBr$. Two steps; rate = $k[(CH_3)_3CBr]$.

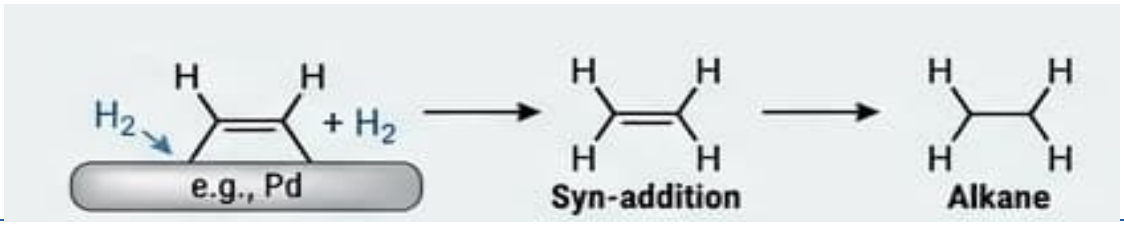


2.2 Addition Reactions

Addition reactions occur across multiple bonds (C=C, C=O, C≡C). A molecule AB adds across the π bond to give a product where A is bonded to one carbon and B to the other.

2.2.1 Hydrogenation (H_2 addition)

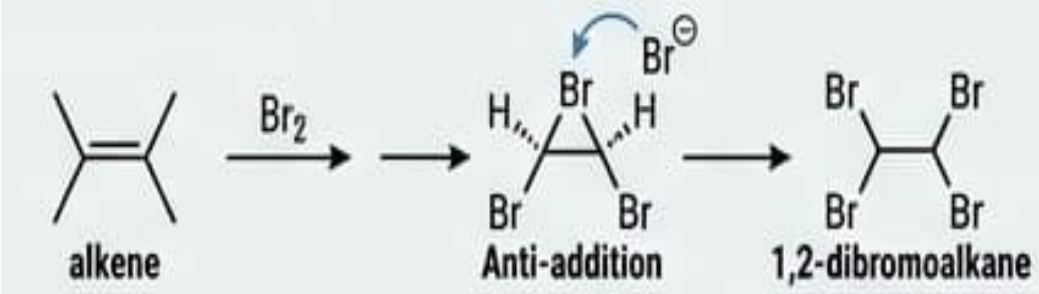
Catalytic hydrogenation (H_2/Pd, Pt, or Ni) converts alkenes and alkynes to alkanes. The reaction is syn-addition (both H atoms added to the same face of the double bond). It is exothermic and irreversible.



2.2.2 Halogenation (X_2 addition)

Bromine or chlorine adds across alkene double bonds via a bromonium (or chloronium) ion intermediate, giving anti-addition (the two halogens add to opposite faces).

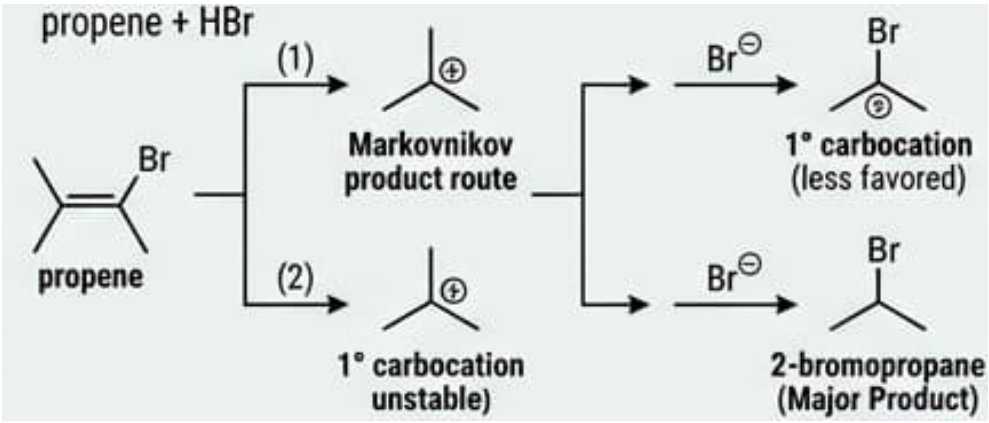
Example: Bromine addition to ethene — $CH_2=CH_2 + Br_2 \rightarrow BrCH_2–CH_2Br$ (1,2-dibromoethane); anti addition proved by the trans product from cyclopentene.



2.2.3 Hydrohalogenation (Markovnikov's Rule)

Adding HX (HBr, HCl, HI) to an unsymmetrical alkene: the proton (H^+) adds to the carbon bearing more hydrogens (less substituted), and the halide adds to the carbon bearing fewer hydrogens (more substituted). This reflects carbocation stability — the more stable carbocation forms preferentially.

Example: Propene + HBr — $CH_3–CH=CH_2 + HBr \rightarrow CH_3–CHBr–CH_3$ (2-bromopropane, major, Markovnikov) + $CH_3–CH_2–CH_2Br$ (1-bromopropane, minor, anti-Markovnikov).



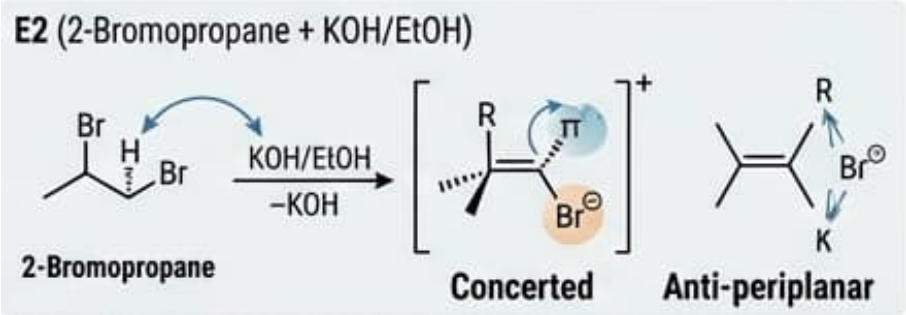
2.2.4 Hydration (H_2O addition)

Water adds across alkenes under acid catalysis (H_3O^+ or H_2SO_4). The mechanism is electrophilic: H^+ adds first to give the more stable carbocation, then water attacks. Product: alcohol (Markovnikov selectivity).

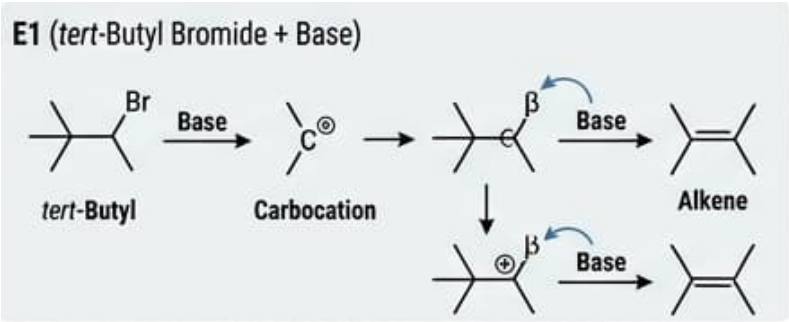
2.3 Elimination Reactions

In elimination reactions, atoms or groups on adjacent carbons are removed to form a new π bond (double bond). Elimination is the reverse of addition and competes with substitution.

E2 (Bimolecular elimination): concerted, single step. Base abstracts a β-H simultaneously as the leaving group departs. Requires anti-periplanar geometry (H and LG must be 180° apart). Rate = k[substrate][base]. Gives the more substituted alkene preferentially (Zaitsev rule).



E1 (Unimolecular elimination): two steps; carbocation intermediate forms first (same as SN1 step 1), then base removes a β-H. Rate = k[substrate]. Also gives Zaitsev product.



Example: E2 of 2-bromopropane; $(CH_3)_2CHBr$ + KOH/EtOH → $CH_3CH{=}CH_2$ (propene) + KBr + H_2O.

2.4 Radical Reactions

Radical (or free-radical) reactions involve homolytic bond cleavage. The mechanism follows three stages:

Initiation: homolytic cleavage of a weak bond (e.g., Cl_2 → 2 Cl•) by heat or UV light.

Propagation: the radical reacts with a molecule to give a product and a new radical, which continues the chain. Each step produces a new radical.

Termination: two radicals combine to give a stable molecule, ending the chain.

Example: Radical halogenation of methane:

Initiation: $Cl_2 \rightarrow 2\ Cl\bullet$

Propagation: $Cl\bullet + CH_4 \rightarrow HCl + CH_3\bullet$; then $CH_3\bullet + Cl_2 \rightarrow CH_3Cl + Cl\bullet$

Termination: $Cl\bullet + Cl\bullet \rightarrow Cl_2$; $CH_3\bullet + Cl\bullet \rightarrow CH_3Cl$; $CH_3\bullet + CH_3\bullet \rightarrow C_2H_6$

Reactivity of radicals toward H abstraction: 3° > 2° > 1° > CH_4 (same trend as carbocations). Radical bromination (Br•) is more selective than chlorination (Cl•).

2.5 Rearrangement Reactions

2.5.1 General Concepts

In a rearrangement, the carbon skeleton or substituent arrangement changes during the reaction. Rearrangements typically occur via carbocation intermediates and involve 1,2-shifts: a hydride (H^-) or an alkyl group migrates from a carbon adjacent to the carbocation to the cationic centre.

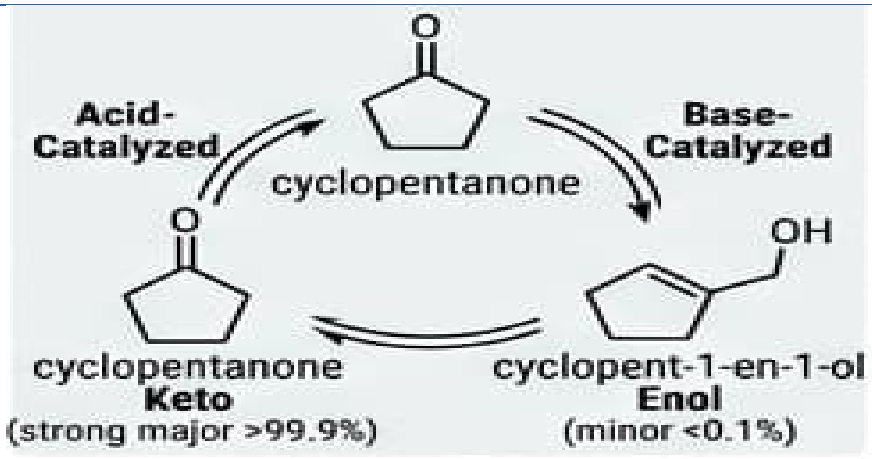
2.5.2 Keto-Enol Tautomerism

Keto-enol tautomerism is the most common example of acid- or base-catalysed rearrangement. A proton migrates from the α-carbon to the oxygen (or vice versa) through a six-membered (cyclic) or stepwise transition state.

Acid-catalysed mechanism: protonation of the carbonyl oxygen → enol → deprotonation at α-C → keto form.

Base-catalysed mechanism: deprotonation at α-C by base → enolate anion → protonation of oxygen → enol → equilibrium.

Example: Cyclopentanone ⇌ cyclopent-1-en-1-ol — Both forms coexist in equilibrium; keto form (>99.9%) strongly favoured by thermodynamics.


Acid-
Catalyzed
cyclopentanone
Base-
Catalyzed
OH
cyclopentanone
Keto
(strong major >99.9%)
cyclopent-1-en-1-ol
Enol
(minor <0.1%)

3. Energetics and Kinetics of Organic Reactions

3.1 Thermodynamics: Enthalpy, Entropy and Free Energy

Whether a reaction can occur is determined by the change in Gibbs free energy: $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. A reaction is thermodynamically favourable (exergonic) when $\Delta G^\circ < 0$. The equilibrium constant is related to ΔG° by $\Delta G^\circ = -RT \ln K$: at 25 °C, a ΔG° of –5.7 kJ/mol corresponds to $K = 10$, and –17 kJ/mol to $K \approx 1000$.

The enthalpy change can be estimated from bond dissociation energies: $\Delta H^\circ \approx \Sigma$ (energies of bonds broken) $- \Sigma$ (energies of bonds formed). The entropy term is significant when the number of molecules changes: additions (two molecules → one) have $\Delta S^\circ < 0$, eliminations (one → two) have $\Delta S^\circ > 0$. This is why high temperatures favour elimination over substitution and addition.

3.2 Kinetics: Rate Laws and Activation Energy

A favourable ΔG° does not mean that a reaction is fast. The rate depends on the activation energy Ea (or free energy of activation $\Delta G^\ddagger$), i.e. the energy difference between the reactants and the transition state. According to the Arrhenius equation, $k = A \cdot \exp(-Ea/RT)$: a lower activation energy or a higher temperature gives a larger rate constant. As a rule of thumb, the rate of many organic reactions roughly doubles for each 10 °C increase in temperature.

The rate law is determined experimentally and gives information on the mechanism: it involves only the species that participate in the rate-determining step (the slowest step).

3.3 Energy Diagrams: Transition States and Intermediates

The progress of a reaction is represented by a reaction-coordinate diagram (energy profile), in which the potential energy is plotted against the reaction coordinate.

A transition state (‡) is a maximum on the energy curve. It has partially formed and partially broken bonds, a lifetime of the order of a molecular vibration ($\approx 10^{-13}$ s), and cannot be isolated.

A reaction intermediate is a local minimum between two transition states (carbocation, carbanion, radical). It has a finite lifetime and can sometimes be

detected or trapped.

A one-step (concerted) reaction such as SN2 or E2 shows a single maximum; a two-step reaction such as SN1 or E1 shows two maxima separated by the intermediate. The highest transition state corresponds to the rate-determining step.

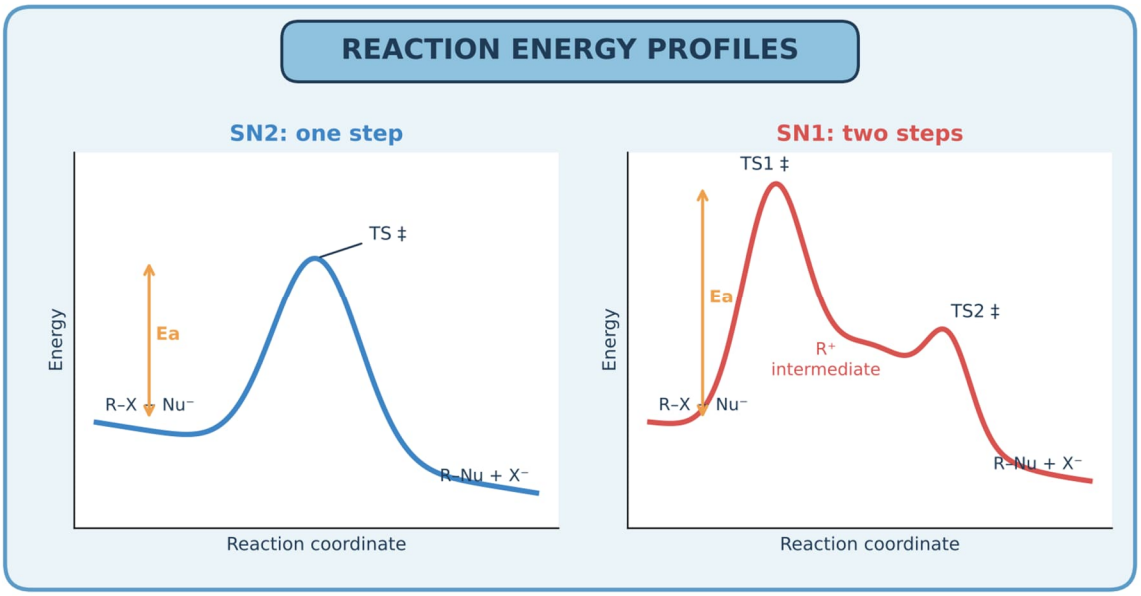


Figure 25. Energy profiles of a one-step reaction (SN2) and of a two-step reaction (SN1)

3.4 Hammond's Postulate

The structure of a transition state resembles the species (reactant, intermediate or product) to which it is closest in energy. In an endothermic step, the transition state is "late" and resembles the products; in an exothermic step, it is "early" and resembles the reactants.

Consequence: in the rate-determining ionisation step of SN1 or E1 reactions (strongly endothermic), the transition state resembles the carbocation. Anything that stabilises the carbocation (tertiary substrate, resonance) also stabilises the transition state and increases the rate. This is the basis of the Markovnikov rule and of the reactivity order 3° > 2° > 1° in SN1 reactions.

3.5 Kinetic Versus Thermodynamic Control

When a reaction can give two different products, the product ratio may depend on the conditions:

Kinetic control (low temperature, short reaction time, irreversible conditions): the major product is the one formed fastest, i.e. via the lowest-energy transition state.

Thermodynamic control (high temperature, long time, reversible conditions): the products equilibrate and the major product is the most stable one.

Example: Addition of HBr to buta-1,3-diene gives two products via the same allylic cation: 3-bromobut-1-ene (1,2-addition) and 1-bromobut-2-ene (1,4-addition). At –80 °C the 1,2-adduct predominates (≈ 80%, kinetic product); at 40 °C the 1,4-adduct predominates (≈ 80%, thermodynamic product, more substituted double bond).

3.6 Catalysis

A catalyst increases the rate of a reaction by providing an alternative pathway with a lower activation energy, without being consumed and without changing the position of equilibrium (it accelerates the forward and the reverse reactions equally). Acid catalysts (H_2SO_4, H_3PO_4, zeolites) act by protonating the substrate; metal catalysts (Pd, Pt, Ni) activate H_2 on their surface; enzymes are highly selective biological catalysts. In industry, more than 80% of chemical processes use at least one catalytic step.

4. Competition Between Substitution and Elimination

4.1 The Four Mechanisms Compared

Alkyl halides (and alcohols activated as sulfonates or protonated alcohols) react with nucleophiles/bases according to four main mechanisms. The outcome depends on five factors: the structure of the substrate, the nature of the nucleophile or base, the leaving group, the solvent and the temperature.

Criterion	SN2	SN1	E2	E1
Number of steps	1 (concerted)	2 (carbocation)	1 (concerted)	2 (carbocation)
Rate law	k[RX][Nu]	k[RX]	k[RX][B]	k[RX]
Best substrates	CH_3 > 1° > 2°	3°, allyl, benzyl	3° > 2° > 1°	3° > 2°
Reagent	good nucleophile	weak nucleophile	strong base	weak base
Solvent	polar aprotic	polar protic	variable	polar protic
Stereochemistry	inversion (Walden)	racemisation	anti-periplanar	not stereospecific
Rearrangement	no	possible	no	possible

4.2 Nature of the Nucleophile and of the Base

Nucleophilicity (a kinetic property: rate of attack on carbon) and basicity (a thermodynamic property: affinity for H^+) usually vary in parallel, but there are important exceptions:

Within a group of the periodic table in protic solvents, nucleophilicity increases downward: $I^- > Br^- > Cl^- > F^-$ and $RS^- > RO^-$, whereas basicity decreases. Large, polarisable atoms are less solvated and more nucleophilic.

Bulky bases such as tert-butoxide ($(CH_3)_3CO^-$), LDA or DBU are strong bases but poor nucleophiles: they favour elimination.

Good nucleophiles that are weak bases (I^-, Br^-, RS^-, N_3^-, CN^-) favour SN2.

4.3 Effect of the Solvent

Polar protic solvents (H_2O, ROH, RCOOH) solvate both cations and anions efficiently by hydrogen bonding. They stabilise carbocations and leaving groups and therefore favour SN1 and E1; by solvating the nucleophile, they reduce its reactivity in SN2.

Polar aprotic solvents (acetone, DMSO, DMF, acetonitrile) solvate cations well but leave anions "naked" and highly reactive. They strongly accelerate SN2 reactions (rate increases of 10^3 to 10^6 are common).

4.4 Leaving Group Ability

A good leaving group is a weak base, able to stabilise the negative charge it takes with it. The order is: TsO^- (tosylate) $\approx I^- > Br^- > H_2O > Cl^- \gg F^- > HO^-, RO^-, NH_2^-$. The OH group of an alcohol is a poor leaving group; it must be activated by protonation (H_2O leaves) or by conversion into a tosylate or a chloride ($SOCl_2$, PCl_5).

4.5 Regioselectivity of Elimination: Zaitsev and Hofmann

When several β-hydrogens are available, elimination usually gives the more substituted (more stable) alkene: this is Zaitsev's rule. With a bulky base, or with poor leaving groups such as $-N^+R_3$, the less substituted alkene is formed predominantly: this is the Hofmann product, resulting from the easier access of the base to the less hindered primary hydrogens.

Example: 2-bromobutane + $CH_3CH_2O^-Na^+$ → but-2-ene (≈ 80%, Zaitsev, mainly E) + but-1-ene (≈ 20%).

Example: 2-bromo-2-methylbutane + $(CH_3)_3CO^-K^+$ → 2-methylbut-1-ene (≈ 70%, Hofmann) + 2-methylbut-2-ene (≈ 30%).

4.6 Practical Decision Guide

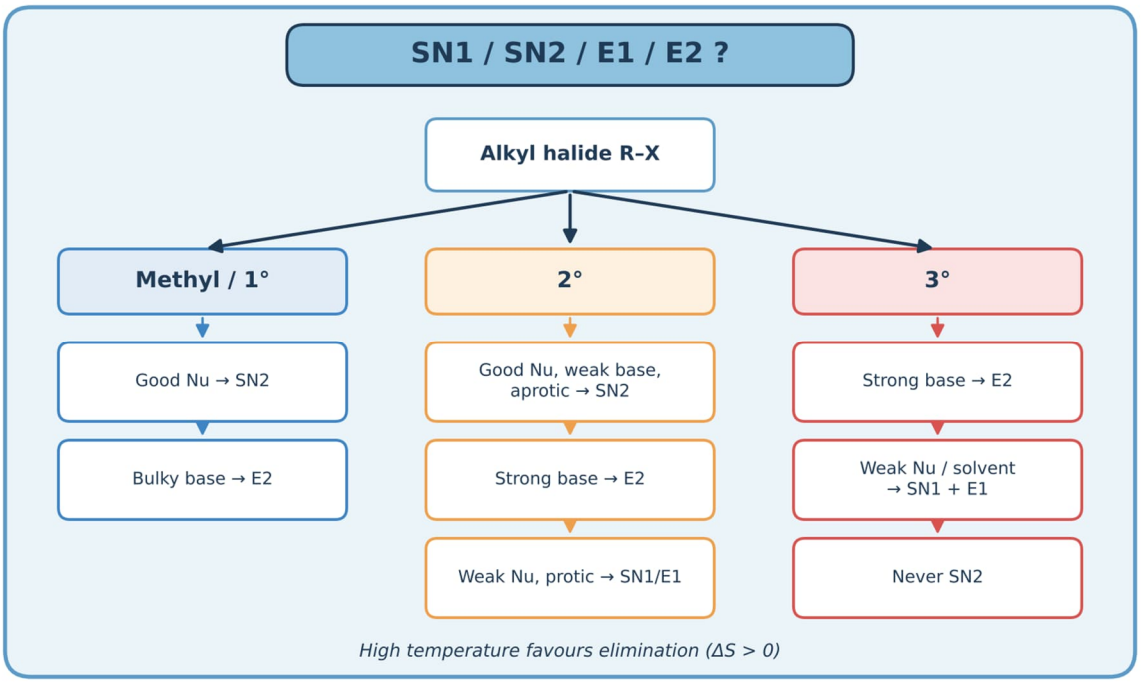


Figure 26. Decision chart for predicting the dominant mechanism of an alkyl halide reaction

Methyl and primary substrates: SN2 with almost all nucleophiles; E2 only with bulky strong bases (t-BuOK).

Secondary substrates: SN2 with good nucleophiles that are weak bases in aprotic solvents; E2 with strong bases (HO^-, RO^-), especially on heating; SN1/E1 in protic solvents with weak nucleophiles.

Tertiary substrates: never SN2. E2 with strong bases; SN1 + E1 with weak nucleophiles/bases (solvolysis), elimination increasing with temperature.

5. Carbocation Rearrangements

5.1 1,2-Hydride and 1,2-Alkyl Shifts

Whenever a carbocation is formed (SN1, E1, addition of HX to alkenes, dehydration of alcohols), it may rearrange into a more stable carbocation by migration of a neighbouring group with its bonding electron pair. The most common rearrangements are:

1,2-hydride shift: a hydrogen atom moves with its electron pair (as H^-) from the adjacent carbon to the cationic centre.

1,2-methyl (alkyl) shift: a methyl group migrates in the same way.

The driving force is the formation of a more stable carbocation (secondary → tertiary, primary → secondary or tertiary, or a cation stabilised by resonance).

Example: 3-methylbutan-2-ol + HBr → 2-bromo-2-methylbutane (major product). Protonation and loss of water give a secondary carbocation $(CH_3)_2CH–CH^+–CH_3$; a 1,2-hydride shift converts it into the tertiary cation $(CH_3)_2C^+–CH_2–CH_3$, which is then captured by Br^-.

Example: 3,3-dimethylbutan-2-ol + H_2SO_4 (heat) → 2,3-dimethylbut-2-ene (major). The secondary cation undergoes a 1,2-methyl shift to give the tertiary cation $(CH_3)_2C^+–CH(CH_3)_2$, which loses a proton to form the tetrasubstituted alkene (Zaitsev).

Note: rearrangements are a signature of a carbocation intermediate. They never occur in SN2 or E2 reactions, which are concerted.

5.2 Dehydration of Alcohols

Heating an alcohol with a concentrated acid (H_2SO_4 or H_3PO_4, 140–180 °C) produces an alkene. For secondary and tertiary alcohols the mechanism is E1: (1) protonation of OH; (2) loss of water to form the carbocation (rate-determining step); (3) loss of a β-proton. The ease of dehydration follows carbocation stability: tertiary (≈ 25–80 °C) > secondary (≈ 100–140 °C) > primary (≈ 170–180 °C). The most substituted alkene is the major product (Zaitsev).

6. Additional Reactions of Alkenes and Alkynes

6.1 Anti-Markovnikov Addition of HBr (Peroxide Effect)

In the presence of peroxides (ROOR) or light, HBr adds to alkenes according to a radical chain mechanism. The bromine radical adds first to the less substituted carbon to produce the more stable (more substituted) carbon radical, which then abstracts H from HBr. The bromine therefore ends up on the less substituted carbon: anti-Markovnikov orientation. This effect, discovered by Kharasch (1933), is observed only with HBr, not with HCl or HI.

Example: $CH_3–CH=CH_2$ + HBr (ROOR) → $CH_3–CH_2–CH_2Br$ (1-bromopropane), whereas without peroxide 2-bromopropane is obtained.

6.2 Hydroboration–Oxidation

Borane (BH_3, as BH_3·THF) adds to alkenes in a concerted, four-centre syn addition: boron attaches to the less hindered carbon and hydrogen to the more substituted carbon. Subsequent oxidation with H_2O_2/NaOH replaces boron by OH with retention of configuration. The overall result is the anti-Markovnikov, syn addition of water, without carbocation rearrangement.

Example: 2-methylpropene → (1) BH_3·THF; (2) H_2O_2, NaOH → 2-methylpropan-1-ol, whereas acid-catalysed hydration gives 2-methylpropan-2-ol.

6.3 Oxidation of Alkenes

Epoxidation: peroxyacids such as mCPBA (meta-chloroperoxybenzoic acid) transfer an oxygen atom to the double bond in a concerted syn addition, giving an epoxide. Acid hydrolysis of the epoxide gives a trans-1,2-diol (anti dihydroxylation).

Syn dihydroxylation: cold, dilute, basic $KMnO_4$ or OsO_4 gives a cis-1,2-diol (syn addition) via a cyclic intermediate.

Oxidative cleavage: ozone (O_3) cleaves the double bond. After a reductive work-up (Zn/H_3O^+ or $(CH_3)_2S$), each carbon of the former double bond becomes a carbonyl group (aldehyde or ketone). Hot concentrated $KMnO_4$ also cleaves the double bond but oxidises aldehydes further to carboxylic acids (and $=CH_2$ to CO_2).

Example: $(CH_3)_2C=CH–CH_3$ + O_3, then Zn/H_3O^+ → $(CH_3)_2C=O$ (acetone) + CH_3CHO (ethanal). Ozonolysis is used to locate the position of a double bond in an unknown alkene.

6.4 Halohydrin Formation

When an alkene reacts with Br_2 or Cl_2 in water, the cyclic halonium ion is opened by water (present in large excess) instead of halide. The product is a halohydrin: the OH group is attached to the more substituted carbon (Markovnikov-type orientation, because this carbon carries the greater partial positive charge) and the addition is anti.

Example: propene + Br_2/H_2O → 1-bromopropan-2-ol, $CH_3–CH(OH)–CH_2Br$.

6.5 Reactions of Alkynes

Hydrogenation: H_2/Pd (or Pt, Ni) reduces an alkyne completely to the alkane. With Lindlar's catalyst (Pd poisoned with Pb and quinoline), the reaction stops at the cis (Z) alkene. Reduction by sodium in liquid ammonia gives the trans (E) alkene.

Hydration: in the presence of H_2SO_4 and $HgSO_4$, water adds to an alkyne (Markovnikov) to give an enol that tautomerises to a ketone. Terminal alkynes give methyl ketones: propyne → propan-2-one.

Acidity: terminal alkynes (pKa 25) are deprotonated by $NaNH_2$ to give acetylide ions, excellent nucleophiles that react with primary alkyl halides (SN2) to form new C–C bonds: $HC{\equiv}C^-\ Na^+ + CH_3CH_2Br \rightarrow HC{\equiv}C–CH_2CH_3 + NaBr$.

7. Electrophilic Aromatic Substitution

7.1 General Mechanism

Because of its aromatic stability, benzene does not undergo addition reactions with electrophiles. Instead, it undergoes substitution, which preserves the aromatic ring. The mechanism (SEAr) has two steps:

Step 1 (slow, rate-determining): the π electrons of the ring attack the electrophile E^+ to give a resonance-stabilised carbocation called the arenium ion (σ complex or Wheland intermediate). Aromaticity is temporarily lost.

Step 2 (fast): a base removes the proton from the sp^3 carbon bearing E, and aromaticity is restored.

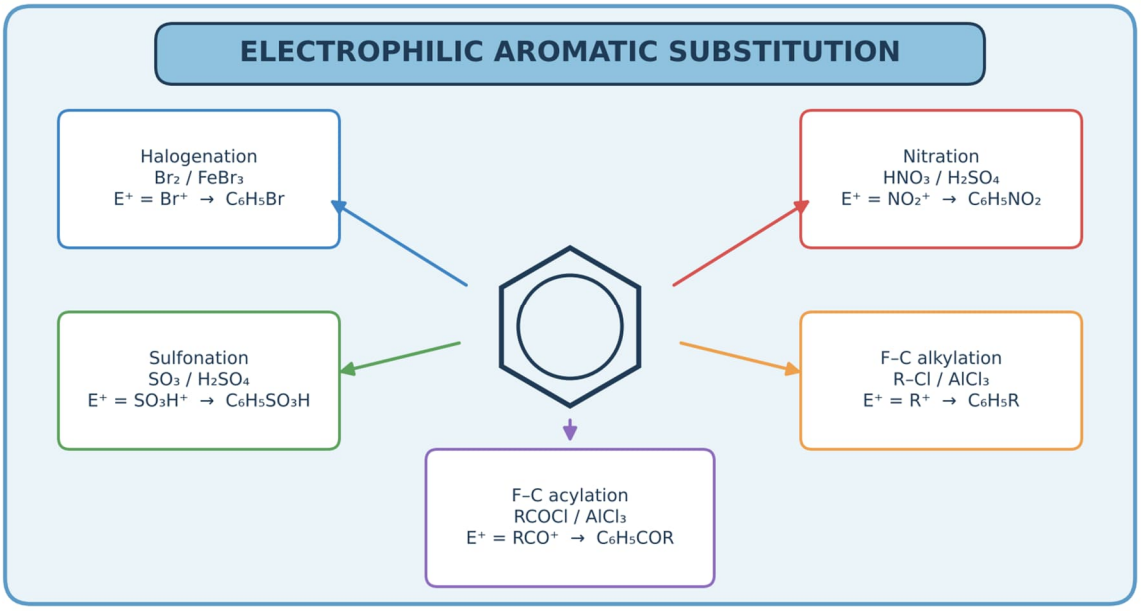


Figure 27. The five classical electrophilic aromatic substitutions of benzene and their electrophiles

7.2 The Main Reactions

Reaction	Reagents	Electrophile	Product
Halogenation	Br_2 / $FeBr_3$ (or $Cl_2/AlCl_3$)	Br^+ (Br–Br–$FeBr_3$)	bromobenzene
Nitration	HNO_3 / H_2SO_4	NO_2^+ (nitronium)	nitrobenzene
Sulfonation	SO_3 / H_2SO_4 (oleum)	SO_3 or HSO_3^+	benzenesulfonic acid
Friedel–Crafts alkylation	R–Cl / $AlCl_3$	R^+	alkylbenzene
Friedel–Crafts acylation	RCOCl / $AlCl_3$	$RC{\equiv}O^+$ (acylium)	aryl ketone

Friedel–Crafts alkylation has three limitations: the carbocation can rearrange (1-chloropropane gives mainly isopropylbenzene); the product, being more activated than benzene, undergoes polyalkylation; and the reaction fails on strongly deactivated rings (nitrobenzene). Acylation avoids rearrangements and polysubstitution, because the acylium ion is resonance stabilised and the ketone formed deactivates the ring. The ketone can then be reduced to an alkyl group (Clemmensen: Zn(Hg)/HCl; Wolff–Kishner: $H_2N–NH_2$/KOH).

7.3 Second Substitution: Activating and Directing Effects

The substituent already present on the ring determines both the rate and the position of a second substitution, through its inductive and mesomeric effects (Chapter 3):

Activating, ortho/para-directing groups (+M or +I): $–NH_2$, –NHR, –OH, –OR, –NHCOR, alkyl groups, phenyl. They stabilise the arenium ion when the attack takes place in the ortho or para position (a resonance structure places the positive charge on the carbon bearing the substituent).

Deactivating, ortho/para-directing groups: halogens (–F, –Cl, –Br, –I). Their –I effect lowers the rate, but their +M effect still directs ortho/para.

Deactivating, meta-directing groups (–M and/or –I): $–NO_2$, –CN, $–SO_3H$, –CHO, –COR, –COOH, –COOR, $–N^+R_3$, $–CF_3$. Ortho and para attack would place the positive charge next to the electron-withdrawing group; the meta arenium ion is the least destabilised.

Example: nitration of toluene gives mainly 2-nitrotoluene (≈ 60%) and 4-nitrotoluene (≈ 37%), with only ≈ 3% of 3-nitrotoluene; toluene reacts about 25 times faster than benzene.

Example: nitration of nitrobenzene (more forcing conditions, ≈ 100 °C) gives mainly 1,3-dinitrobenzene (≈ 93%).

Synthetic planning: the order of introduction of substituents matters. To prepare 3-bromonitrobenzene, nitrate first (NO_2 directs meta) and then brominate; to prepare 4-bromonitrobenzene, brominate first (Br directs para) and then nitrate.

8. Nucleophilic Addition to Carbonyl Compounds

8.1 Reactivity of the Carbonyl Group

The C=O bond is strongly polarised (Cδ+–Oδ–) and the carbonyl carbon is sp^2 hybridised and planar. It is therefore attacked by nucleophiles, perpendicular to the plane of the carbonyl group, to give a tetrahedral alkoxide intermediate, which is subsequently protonated. Aldehydes are more reactive than ketones for two reasons: electronic (one alkyl group (+I) instead of two, so a larger δ+ on carbon) and steric (less hindered approach of the nucleophile). Attack on either face of a planar carbonyl gives a racemic product when a new stereocentre is created.

Under acid catalysis, protonation of the carbonyl oxygen makes the carbon even more electrophilic, which allows attack by weak nucleophiles (water, alcohols).

8.2 Main Nucleophilic Additions

Hydration: $R_2C{=}O + H_2O \rightleftharpoons R_2C(OH)_2$ (gem-diol). The equilibrium favours the hydrate for methanal (99.9%) but the carbonyl compound for acetone (0.1% hydrate).

Cyanohydrin formation: $R_2C{=}O + HCN$ (catalysed by CN^-) → $R_2C(OH)CN$. This reaction lengthens the carbon chain by one carbon; it is the first step of the industrial synthesis of methyl methacrylate (Plexiglas).

Hemiacetals and acetals: R–CHO + R'OH ⇌ R–CH(OH)OR' (hemiacetal); with a second molecule of alcohol and acid catalysis, the acetal $R–CH(OR')_2$ is formed and water is eliminated. Acetals are stable in basic medium and are used to protect carbonyl groups. The cyclic forms of sugars (glucose) are intramolecular hemiacetals.

Reduction by hydrides: $NaBH_4$ (in methanol or ethanol) and $LiAlH_4$ (in dry ether) deliver a hydride ion H^- to the carbonyl carbon. Aldehydes give primary alcohols; ketones give secondary alcohols. $LiAlH_4$ also reduces esters and carboxylic acids to primary alcohols, whereas $NaBH_4$ does not.

Grignard reagents: organomagnesium compounds R–MgX (prepared from R–X and Mg in dry ether) behave as carbanions R^-. They add to carbonyl groups to create a new C–C bond: methanal gives primary alcohols, other aldehydes give secondary alcohols, and ketones give tertiary alcohols, after acid hydrolysis. With CO_2 they give carboxylic acids.

Example: $CH_3MgBr + CH_3CH_2CHO$ → (after H_3O^+) $CH_3CH_2CH(OH)CH_3$ (butan-2-ol).

Example: $C_6H_5MgBr + CH_3COCH_3$ → (after H_3O^+) $C_6H_5C(OH)(CH_3)_2$ (2-phenylpropan-2-ol).

Addition–elimination with nitrogen nucleophiles: primary amines RNH_2 add to aldehydes and ketones and then lose water to give imines ($R_2C{=}NR'$, Schiff bases). With hydroxylamine (NH_2OH) oximes are formed, and with 2,4-dinitrophenylhydrazine (2,4-DNPH) coloured, crystalline hydrazones are formed; the latter reaction is a classical test for aldehydes and ketones (orange-yellow precipitate).

8.3 Distinguishing Aldehydes from Ketones

Aldehydes are easily oxidised to carboxylic acids, whereas ketones resist mild oxidation. This difference is the basis of several qualitative tests:

Tollens' reagent ($[Ag(NH_3)_2]^+$): an aldehyde reduces silver(I) to metallic silver (silver mirror).

Fehling's solution (Cu^{2+} tartrate complex, basic): an aldehyde gives a brick-red precipitate of Cu_2O on heating.

Potassium dichromate ($K_2Cr_2O_7/H_2SO_4$): the orange solution turns green (Cr^{3+}) with aldehydes, primary and secondary alcohols.

Exercises : Chapter 4

Exercise 4.1: Predict the product(s) and mechanism (SN1 or SN2) for:

(a) 1-bromopropane + NaI in acetone

(b) 2-bromo-2-methylpropane + H_2O at 25°C

Solution: (a) SN2: 1-Bromopropane is primary; NaI is a strong nucleophile; acetone is a polar aprotic solvent.

Product: 1-iodopropane ($CH_3CH_2CH_2I$) + NaBr. Inversion of configuration (but here the carbon is achiral).

Rate = $k[CH_3CH_2CH_2Br][NaI]$.

(b)SN1: $(CH_3)_3CBr$ is tertiary; H_2O is a weak nucleophile and polar protic solvent.

Step 1: ionisation → $(CH_3)_3C^+ + Br^-$.

Step 2: water attacks → $(CH_3)_3COH_2^+ \rightarrow (CH_3)_3COH + H^+$.

Product: 2-methylpropan-2-ol. Expect racemisation.

Exercise 4.2: A student treats (R)-2-bromobutane with NaOH in DMSO.

Predict the product's stereochemistry. What would happen if H_2O were used instead of DMSO?

Solution: In DMSO (polar aprotic): SN2 mechanism. The nucleophile (OH^-) attacks the back of the C–Br bond. Complete inversion: (R)-2-bromobutane gives (S)-butan-2-ol.

In H_2O (polar protic): SN1 also becomes competitive for a secondary substrate. The carbocation intermediate is planar; OH^- can attack from both faces. Product: a racemic mixture of (R) and (S)-butan-2-ol (or slight excess of inversion product if SN2 still dominates partially).

Exercise 4.3: Write the propagation steps for the radical monochlorination of ethane. Calculate the enthalpy change using bond energies: C–H = 413 kJ/mol, Cl–Cl = 243 kJ/mol, H–Cl = 432 kJ/mol, C–Cl = 339 kJ/mol.

Solution: Propagation step 1: $Cl\bullet + CH_3CH_3 \rightarrow HCl + CH_3CH_2\bullet$

ΔH_1 = bonds broken – bonds formed = (C–H) – (H–Cl) = 413 – 432 = –19 kJ/mol

(exothermic).

Propagation step 2: $CH_3CH_2\bullet + Cl_2 \rightarrow CH_3CH_2Cl + Cl\bullet$

ΔH_2 = (Cl–Cl) – (C–Cl) = 243 – 339 = –96 kJ/mol (exothermic).

Overall chain $\Delta H = \Delta H_1 + \Delta H_2 = -19 + (-96) = -115$ kJ/mol.

Exercise 4.4: Predict the major organic product(s) of the following reactions:

(a) 1-methylcyclohexene + HBr

(b) 2-methylbut-2-ene + Br_2 in CCl_4

(c) propene + H_2O/ H_2SO_4

Solution: (a) HBr adds to 1-methylcyclohexene (Markovnikov). H^+ protonates the double bond at the less substituted carbon (C_2) to form the more stable 3° carbocation at C_1. Br^- attacks C_1.

Major product: 1-bromo-1-methylcyclohexane.

(b) Br_2 adds across the double bond via a bromonium ion; anti addition.

Product: (2R,3S)- and (2S,3R)-2,3-dibromo-2-methylbutane (a racemic mixture); anti addition.

(c) H_2SO_4 protonates propene to give the 2° carbocation ($CH_3–CH^+–CH_3$, Markovnikov); water attacks.

Major product: propan-2-ol (2-propanol).

Exercise 4.5: Explain why the E_2 elimination of (1R,2R)-1-bromo-2-methylcyclohexane gives exclusively the (E)-alkene while the (1R,2S) isomer gives the (Z)-alkene.

Solution: E2 requires strict anti-periplanar geometry: the leaving group (Br) and the β-H must be 180° apart (trans diaxial in a cyclohexane).

(1R,2R)-isomer: when Br is axial, the trans-diaxial β-H at C_2 is on the opposite side ⟹ the two methyl groups end up on the same side in the ring transition state ⟹ (E)-alkene.

(1R,2S)-isomer: when Br is axial, the trans-diaxial β-H at C_2 is now positioned so that upon elimination, the methyl groups end up on opposite sides ⟹ (Z)-alkene.

This demonstrates the stereochemical rigidity of E2 and the power of conformational analysis.

Exercise 4.6: Predict the major product and the dominant mechanism (SN1, SN2, E1, E2) of each reaction: (a) 1-bromobutane + NaCN in DMSO (b) 2-bromo-2-methylpropane + CH_3CH_2ONa in ethanol, 70 °C (c) 2-bromo-2-methylpropane in ethanol, 25 °C (d) 1-bromobutane + $(CH_3)_3COK$ (e) (R)-2-iodooctane + NaN_3 in acetone.

Solution: (a) SN2 (primary substrate, good nucleophile, polar aprotic solvent): $CH_3CH_2CH_2CH_2CN$ (pentanenitrile).

(b) E2 (tertiary substrate, strong base, heat): 2-methylpropene $(CH_3)_2C=CH_2$.

(c) SN1 (solvolysis, weak nucleophile, protic solvent, tertiary substrate): 2-ethoxy-2-methylpropane, $(CH_3)_3C–O–CH_2CH_3$, with some 2-methylpropene (E1).

(d) E2 (bulky strong base, even with a primary substrate): but-1-ene.

(e) SN2 with inversion of configuration: (S)-2-azidooctane.

Exercise 4.7: Draw the energy profile of the SN1 hydrolysis of 2-chloro-2-methylpropane. Indicate the transition states, the intermediate, the rate-determining step and the activation energy. Write the rate law.

Solution: The profile shows two maxima. The first (higher) transition state TS1 corresponds to the heterolysis of the C–Cl bond; it leads to the tertiary carbocation $(CH_3)_3C^+$, a local minimum (the intermediate). The second, lower maximum TS2 corresponds to the attack of water on the carbocation, giving $(CH_3)_3C–OH_2^+$, which then loses a proton to give 2-methylpropan-2-ol.

The rate-determining step is the ionisation (step 1, highest TS). The activation energy is the difference between the energy of TS1 and that of the reactants. Rate law: $v = k[(CH_3)_3CCl]$ (first order, independent of the nucleophile concentration).

Exercise 4.8: Explain why the reaction of 3-methylbutan-2-ol with concentrated HCl gives mainly 2-chloro-2-methylbutane and not 2-chloro-3-methylbutane. Write the complete mechanism.

Solution: Step 1: protonation of the OH group: $(CH_3)_2CH–CH(OH_2^+)–CH_3$.

Step 2: loss of water gives a secondary carbocation $(CH_3)_2CH–CH^+–CH_3$.

Step 3: 1,2-hydride shift from C-3 to C-2 gives the more stable tertiary carbocation $(CH_3)_2C^+–CH_2–CH_3$.

Step 4: $Cl^–$ attacks the tertiary carbocation: $(CH_3)_2CCl–CH_2–CH_3$, 2-chloro-2-methylbutane. The rearrangement proves that the reaction goes through a carbocation (SN1).

Exercise 4.9: Give the product(s) of the reaction of 1-methylcyclohexene with: (a) HBr (b) HBr, peroxides (c) H_2O/H_2SO_4 (d) BH_3·THF, then $H_2O_2/NaOH$ (e) O_3, then Zn/H_3O^+ (f) Br_2/H_2O.

Solution: (a) 1-bromo-1-methylcyclohexane (Markovnikov, via the tertiary carbocation).

(b) 1-bromo-2-methylcyclohexane (anti-Markovnikov, radical mechanism; mixture of cis and trans).

(c) 1-methylcyclohexan-1-ol (Markovnikov).

(d) trans-2-methylcyclohexan-1-ol (anti-Markovnikov, syn addition of H and OH; obtained as a racemate).

(e) Ring opening: 6-oxoheptanal, $CH_3–CO–(CH_2)_4–CHO$ (a ketoaldehyde with 7 carbons).

(f) trans-2-bromo-1-methylcyclohexan-1-ol (OH on the more substituted carbon, anti addition).

Exercise 4.10: An alkene of formula C_6H_{12} gives, after ozonolysis followed by a reductive work-up, only one product: propan-2-one. Identify the alkene. What product would be obtained with an alkene giving propanal and ethanal?

Solution: Each half of the alkene gives $(CH_3)_2C=O$, so the alkene is $(CH_3)_2C=C(CH_3)_2$: 2,3-dimethylbut-2-ene.

If the products are CH_3CH_2CHO and CH_3CHO, the alkene is $CH_3CH_2–CH=CH–CH_3$: pent-2-ene (C_5H_{10}), whose E or Z configuration cannot be determined by ozonolysis.

Exercise 4.11: Give the main product(s) of the mononitration (HNO_3/H_2SO_4) of:

(a) anisole (methoxybenzene) (b) benzoic acid (c) chlorobenzene (d) acetanilide ($C_6H_5NHCOCH_3$). Indicate in each case whether the reaction is faster or slower than with benzene.

Solution: (a) 2- and 4-nitroanisole (mainly para); faster than benzene (–OCH_3: +M > –I, activating, o/p).

(b) 3-nitrobenzoic acid; slower (–COOH: –M, –I, deactivating, meta).

(c) 1-chloro-2-nitrobenzene and 1-chloro-4-nitrobenzene (mainly para); slower (halogen: deactivating but o/p director).

(d) mainly 4-nitroacetanilide (para, because the $NHCOCH_3$ group is bulky); faster than benzene (activating, though less than –NH_2 because the nitrogen lone pair is partly delocalised on the C=O).

Exercise 4.12: Propose a synthesis of: (a) 1-(4-bromophenyl)ethan-1-one from benzene (b) 3-bromobenzoic acid from toluene (c) propylbenzene from benzene, avoiding carbocation rearrangement.

Solution: (a) Benzene + $Br_2/FeBr_3$ → bromobenzene; then $CH_3COCl/AlCl_3$ → 4-bromoacetophenone (Br directs para; the bulky acylium ion favours para).

(b) Toluene + $KMnO_4$ (hot) → benzoic acid; then $Br_2/FeBr_3$ → 3-bromobenzoic acid (COOH directs meta). Brominating first would give the ortho/para isomers.

(c) Benzene + $CH_3CH_2COCl/AlCl_3$ → propiophenone $C_6H_5COCH_2CH_3$ (no rearrangement of the acylium ion); then Clemmensen reduction (Zn(Hg)/HCl) → propylbenzene. Direct alkylation with 1-chloropropane would give mainly isopropylbenzene.

Exercise 4.13: Write the products of the reactions of ethanal (CH_3CHO) with: (a) $NaBH_4$ then H_2O (b) CH_3CH_2MgBr then H_3O^+ (c) HCN/CN^- (d) excess methanol, H^+ (e) Tollens' reagent.

Solution: (a) ethanol CH_3CH_2OH (reduction of an aldehyde → primary alcohol).

(b) butan-2-ol $CH_3CH(OH)CH_2CH_3$ (Grignard + aldehyde → secondary alcohol; racemic).

(c) 2-hydroxypropanenitrile $CH_3CH(OH)CN$ (lactonitrile, a cyanohydrin).

(d) 1,1-dimethoxyethane $CH_3CH(OCH_3)_2$ (an acetal) + H_2O.

(e) ethanoate ion CH_3COO^- (acetic acid after acidification) + metallic silver (silver mirror).

Exercise 4.14: Using the Grignard reaction, propose two different syntheses of 2-methylbutan-2-ol, $(CH_3)_2C(OH)CH_2CH_3$, starting from a ketone in each case.

Solution: Disconnection at the C–OH carbon:

Route 1: propan-2-one (CH_3COCH_3) + CH_3CH_2MgBr, then H_3O^+.

Route 2: butan-2-one ($CH_3COCH_2CH_3$) + CH_3MgBr, then H_3O^+.

Both routes give the tertiary alcohol. Anhydrous conditions are essential, because Grignard reagents are destroyed by water (R–MgX + H_2O → R–H + Mg(OH)X).

Exercise 4.15: Using the bond dissociation energies below, calculate ΔH° for the addition of HBr to ethene and say whether it is exothermic. Data (kJ/mol): C=C 611; C–C 347; H–Br 366; C–H 413; C–Br 285.

Solution: Bonds broken: C=C (611) + H–Br (366) = 977 kJ/mol.

Bonds formed: C–C (347) + C–H (413) + C–Br (285) = 1045 kJ/mol.

ΔH° = 977 – 1045 = –68 kJ/mol: the reaction is exothermic. Since ΔS° < 0 (two molecules give one), the reaction becomes less favourable at high temperature, where the reverse elimination can take over.

Exercise 4.16: Compare the reactivity of the following pairs in SN2 and justify: (a) CH_3CH_2Br and $(CH_3)_2CHBr$; (b) CH_3CH_2Cl and CH_3CH_2I; (c) CH_3O^- and CH_3S^- as nucleophiles toward CH_3I in methanol; (d) the reaction of CH_3CH_2Br with CN^- in ethanol and in DMSO.

Solution: (a) CH_3CH_2Br reacts faster: the secondary carbon is more hindered for backside attack.

(b) CH_3CH_2I reacts faster: I^- is a better leaving group (weaker base, weaker C–I bond).

(c) CH_3S^- is the better nucleophile in a protic solvent: sulfur is larger, more polarisable and less solvated than oxygen, although CH_3O^- is the stronger base.

(d) The reaction is much faster in DMSO (polar aprotic): CN^- is not solvated by hydrogen bonds and is therefore more reactive.

APPENDIX A: Summary Sheets

A.1 Nomenclature at a Glance

Naming procedure: (1) identify the principal group; (2) choose the principal chain (maximum number of principal groups, then longest); (3) number for lowest locants: principal group, then multiple bonds, then prefixes; (4) list prefixes alphabetically; (5) assemble prefixes + stem + unsaturation + suffix.

Number of C	Stem	Alkyl group	Number of C	Stem
1	meth-	methyl	6	hex-
2	eth-	ethyl	7	hept-
3	prop-	propyl	8	oct-
4	but-	butyl	9	non-
5	pent-	pentyl	10	dec-

Seniority of principal groups: acid > anhydride > ester > acid halide > amide > nitrile > aldehyde > ketone > alcohol > thiol > amine. Always prefixes: halo-, nitro-, alkoxy-, alkyl-.

Degree of unsaturation: DU = (2C + 2 + N – H – X) / 2. One ring or one double bond = 1; one triple bond = 2; a benzene ring = 4.

A.2 Stereochemistry at a Glance

CIP priorities: higher atomic number first; at the first point of difference compare the sets of atoms; multiple bonds are counted by duplicating atoms (C=O counts as C bonded to O, O).

R/S: place the lowest priority group (4) at the back and read 1 → 2 → 3. Clockwise = R; anticlockwise = S. In a Fischer projection, if group 4 is on a horizontal bond, invert the result.

E/Z: compare the higher-priority group on each carbon of the double bond. Same side = Z; opposite sides = E.

Number of stereoisomers: at most 2^n for n stereogenic elements; fewer when meso forms exist.

Relationship	Same connectivity?	Mirror images?	Same physical properties?

Relationship	Same connectivity?	Mirror images?	Same physical properties?
Constitutional isomers	no	no	no
Enantiomers	yes	yes	yes (except sign of α)
Diastereomers	yes	no	no
Conformers	yes	—	interconvert rapidly

A.3 Electronic Effects at a Glance

Group	Inductive effect	Mesomeric effect	Effect on aromatic ring
–NH_2, –OH, –OR	–I	+M (dominant)	activating, o/p
–CH_3, alkyl	+I	— (hyperconjugation)	activating, o/p
–F, –Cl, –Br, –I	–I (dominant)	+M	deactivating, o/p
–CHO, –COR, –COOH	–I	–M	deactivating, meta
–NO_2, –CN, –SO_3H	–I	–M	strongly deactivating, meta
–N^+R_3, –CF_3	–I	—	strongly deactivating, meta

Acidity increases with: electronegativity and size of the atom carrying the charge, s character, resonance delocalisation of the anion, nearby –I groups. Basicity of amines decreases with delocalisation of the nitrogen lone pair (aniline, amides).

Stability: carbocations and radicals 3° > 2° > 1° > methyl (allyl and benzyl strongly stabilised); carbanions methyl > 1° > 2° > 3°.

A.4 Reaction Mechanisms at a Glance

Reaction type	Typical reagents	Key feature
SN2	Nu^-, 1° RX, aprotic solvent	inversion, one step
SN1	H_2O/ROH, 3° RX	carbocation, racemisation
E2	strong base, heat	anti-periplanar, Zaitsev
E1	acid, heat, 3° ROH	carbocation, Zaitsev
Electrophilic addition	HX, H_2O/H^+, X_2	Markovnikov; X_2 anti
Radical addition	HBr / ROOR	anti-Markovnikov
Hydroboration–oxidation	BH_3; H_2O_2/HO^-	anti-Markovnikov, syn

Reaction type	Typical reagents	Key feature
Radical substitution	X_2, hν	3° H > 2° H > 1° H
SEAr	E^+ + Lewis acid	arenium ion, substitution
Nucleophilic addition	$NaBH_4$, RMgX, HCN	attack on C=O carbon

APPENDIX B: Model Examinations with Detailed Solutions

Model Examination 1 (Duration: 1 h 30 min)

Question 1 (5 points): (a) Give the IUPAC name of: (i) $CH_3–CH(CH_3)–CH_2–CH(C_2H_5)–CH_2–CH_3$ (ii) $HOOC–CH_2–CH(OH)–CH_3$ (iii) $CH_2=CH–CO–CH_3$ (iv) $CH_3–CH(NH_2)–CH_2–OH$. (b) Write the formula of: (i) 2,2,4-trimethylpentane (ii) ethyl propanoate (iii) 4-methylpent-3-en-2-one.

Solution: (a) (i) Two chains of six carbons exist (the second passes through the ethyl group); both carry the same two substituents. Numbering from the end closer to the first branch gives the locant set {2,4}, lower than {3,5}. Name: 4-ethyl-2-methylhexane (alphabetical order: ethyl before methyl).

(ii) 3-hydroxybutanoic acid. (iii) but-3-en-2-one (methyl vinyl ketone). (iv) 2-aminopropan-1-ol (the alcohol is senior to the amine).

(b) (i) $(CH_3)_3C–CH_2–CH(CH_3)_2$ (ii) $CH_3CH_2–COO–CH_2CH_3$ (iii) $(CH_3)_2C=CH–CO–CH_3$ (mesityl oxide).

Question 2 (5 points): Consider 3-chlorobut-1-ene, $CH_2=CH–CHCl–CH_3$. (a) Does it have a stereocentre? Assign the CIP priorities of its substituents. (b) Draw the (R) enantiomer in Cram and Fischer representations. (c) Does this compound show geometric isomerism? Same question for 1-chlorobut-2-ene.

Solution: (a) C-3 carries four different groups (Cl, $CH=CH_2$, CH_3, H): it is a stereocentre. Priorities: Cl (1) > $CH=CH_2$ (2) > CH_3 (3) > H (4).

(b) Cram: C-3 in the centre, CH_3 in the plane on the left, $CH=CH_2$ in the plane on the right, Cl on a wedge pointing up and H on a dash. With H at the back, Cl (top) → vinyl (right) → CH_3 (left) runs clockwise: (R). Fischer: $CH=CH_2$ at the top, CH_3 at the bottom, Cl on the right and H on the left. The path Cl (right) → vinyl (top) → CH_3 (bottom) is anticlockwise (apparent S); since H is on a horizontal bond the result is inverted: (R).

(c) 3-Chlorobut-1-ene: no, C-1 carries two identical H atoms. 1-Chlorobut-2-ene, $ClCH_2–CH=CH–CH_3$: yes, each carbon of the double bond carries two different groups; (E) and (Z) isomers exist.

Question 3 (5 points): (a) Rank in order of increasing acidity: CH_3COOH, $ClCH_2COOH$, $Cl_2CHCOOH$, CH_3CH_2OH, C_6H_5OH. (b) Explain why aniline is a weaker base than cyclohexylamine. (c) Draw the resonance structures of the nitrobenzene molecule and deduce the effect of the NO_2 group on electrophilic substitution.

Solution: (a) CH_3CH_2OH (16) < C_6H_5OH (10) < CH_3COOH (4.76) < $ClCH_2COOH$ (2.86) < $Cl_2CHCOOH$ (1.29).

(b) In aniline, the nitrogen lone pair is delocalised into the aromatic ring (+M effect) and is less available to bind H^+; protonation would destroy this stabilising conjugation. In cyclohexylamine the lone pair is localised on an sp^3 nitrogen bonded to an alkyl group (+I). pKaH: 4.6 versus 10.6.

(c) NO_2 withdraws electrons from the ring by –M effect: resonance structures place positive charges at the ortho and para carbons. The ring is deactivated, and electrophiles attack the meta position, which is the least electron-poor.

Question 4 (5 points): (a) Complete the following reactions and name the mechanism: (i) $(CH_3)_3C–Br + H_2O \rightarrow$ (ii) $CH_3CH_2CH_2Br + CH_3O^-$ (in DMSO) $\rightarrow$ (iii) $CH_3–CH=CH_2 + HCl \rightarrow$ (iv) $CH_4 + Cl_2$ (hν) $\rightarrow$. (b) For reaction (ii), write the rate law and explain what happens to the rate if the concentration of CH_3O^- is doubled.

Solution: (a) (i) $(CH_3)_3C–OH$ + HBr: SN1. (ii) $CH_3CH_2CH_2–O–CH_3 + Br^-$ (1-methoxypropane): SN2. (iii) $CH_3–CHCl–CH_3$ (2-chloropropane): electrophilic addition, Markovnikov. (iv) CH_3Cl + HCl: radical substitution (chain reaction: initiation, propagation, termination).

(b) $v = k[CH_3CH_2CH_2Br][CH_3O^-]$. The reaction is first order in each reactant: doubling $[CH_3O^-]$ doubles the rate.

Model Examination 2 (Duration: 1 h 30 min)

Question 1 (4 points): A compound A of formula $C_5H_{10}O$ is a ketone with a branched chain. (a) Calculate its degree of unsaturation. (b) Give all possible structures and names of A. (c) Which of them is chiral?

Solution: (a) DU = (10 + 2 – 10) / 2 = 1 (the C=O bond).

(b) Ketones $C_5H_{10}O$: pentan-2-one, pentan-3-one (unbranched) and 3-

methylbutan-2-one, $(CH_3)_2CH–CO–CH_3$ (branched). A is 3-methylbutan-2-one.

(c) None: 3-methylbutan-2-one has no stereocentre (C-3 carries two identical CH_3 groups).

Question 2 (6 points): 2,3-Dichlorobutane: (a) How many stereoisomers does it have? (b) Draw them in Fischer projection and assign R/S configurations. (c) Indicate the relationships between them. (d) Draw the most stable conformation of the meso isomer in Newman projection along the C-2–C-3 bond.

Solution: (a) Three stereoisomers: (2R,3R), (2S,3S) and the meso form (2R,3S).

(b) In Fischer projection (CH_3 top and bottom): Cl on the same side at C-2 and C-3 → meso (2R,3S); Cl on opposite sides → (2R,3R) or (2S,3S) depending on the side.

(c) (2R,3R) and (2S,3S) are enantiomers; each is a diastereomer of the meso form.

(d) Meso isomer, staggered conformation with the two CH_3 groups anti: then the two Cl atoms are also anti (and the two H anti). This conformation, with all large groups anti, has a centre of symmetry and is the most stable.

Question 3 (5 points): (a) Classify the following radicals in order of stability and justify: $CH_3•$, $(CH_3)_2CH•$, $(CH_3)_3C•$, $CH_2=CH–CH_2•$. (b) Write the mechanism of the monochlorination of propane under light, and predict the products, given that a secondary H reacts 3.8 times faster than a primary H with Cl•.

Solution: (a) $CH_3• < (CH_3)_2CH• < (CH_3)_3C• < CH_2=CH–CH_2•$. Alkyl radicals are stabilised by hyperconjugation (number of α C–H bonds); the allyl radical is further stabilised by resonance.

(b) Initiation: $Cl_2 \rightarrow 2\ Cl•$ ($h\nu$). Propagation: $Cl• + C_3H_8 \rightarrow HCl + C_3H_7•$; $C_3H_7• + Cl_2 \rightarrow C_3H_7Cl + Cl•$. Termination: combination of two radicals.

Propane has 6 primary H and 2 secondary H. Relative amounts: 1-chloropropane $\propto 6 \times 1 = 6$; 2-chloropropane $\propto 2 \times 3.8 = 7.6$. Percentages: 1-chloropropane = 6/13.6 = 44%; 2-chloropropane = 7.6/13.6 = 56%.

Question 4 (5 points): Starting from but-1-ene and any inorganic reagents, indicate how to prepare: (a) butan-2-ol (b) butan-1-ol (c) 1,2-dibromobutane (d)

propanal (e) but-1-yne.

Solution: (a) H_2O/H_2SO_4 (Markovnikov hydration).

(b) BH_3·THF, then H_2O_2/NaOH (anti-Markovnikov hydration).

(c) Br_2 in CCl_4 (anti addition via a bromonium ion).

(d) O_3, then Zn/H_3O^+: CH_3CH_2CHO + HCHO.

(e) Br_2 (gives 1,2-dibromobutane), then excess $NaNH_2$ (double E2 elimination): $CH_3CH_2C{\equiv}CH$.

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The content of this tutorial has been developed from multiple independent academic sources. The following representative texts are recommended for further study:

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