BP204T · B.PHARM THEORY

BP204T Pharmaceutical Organic Chemistry

Unit III — Alkyl Halides

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From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit III (12 hours).

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UNIT III — ALKYL HALIDES: SUBSTITUTION AND ELIMINATION

Chapter 9 — Alkyl Halides: What They Are, How They Are Classified, and the Key Terms

Learning objectives

- Define alkyl halides and name them using the IUPAC system.
- Classify alkyl halides as primary, secondary, or tertiary.
- Define: nucleophile, electrophile, leaving group, carbocation, nucleophilic substitution, elimination.
- Explain why the carbon–halogen bond is the reactive centre of the molecule.
- Predict, in simple terms, which alkyl halides react faster in substitution reactions.

9.1 Definitions

- **Alkyl halide:** A compound formed when one hydrogen atom of an alkane is replaced by a halogen atom (F, Cl, Br, or I). General formula: R–X, where R is an alkyl group and X is a halogen.
- **Alkyl group (R):** A part of a molecule containing only carbon and hydrogen atoms, attached to the rest of the molecule at one point — e.g., CH_3– (methyl), CH_3–CH_2– (ethyl).
- **Nomenclature:** In IUPAC naming, the halogen is named as a prefix: fluoro, chloro, bromo, iodo. Example: CH_3–Cl is called chloromethane; CH_3–CH_2–Br is called bromoethane.
- **Bond polarity:** The C–X bond is polar because halogens pull electrons more strongly than carbon. The carbon becomes slightly positive (written δ^+) and the halogen slightly negative (δ^-). This slight positive charge on carbon is what makes alkyl halides reactive — it attracts electron-rich species.

9.2 Terminology alert — learn these first

- **Nucleophile ("nucleus-lover"):** A species rich in electrons that donates a pair of electrons to form a new bond. Examples: OH^-, CN^-, I^-, NH_3. Think of it as an "electron giver".
- **Electrophile ("electron-lover"):** A species that accepts a pair of electrons because it is electron-poor. The δ^+ carbon of an alkyl halide is an electrophile.
- **Leaving group:** The atom or group that leaves the molecule with the bonding electron pair during a reaction. In alkyl halides, the halide ion (Cl^-, Br^-, I^-) is the leaving group. A good leaving group is a weak base — iodide (I^-) is the best leaving group among halides, fluoride (F^-) the worst.
- **Carbocation:** A carbon atom carrying a positive charge, formed when the C–X bond breaks and the halogen takes both electrons. General form: R_3C^+. It has only six electrons and is electron-hungry, so it is very reactive and short-lived.
- **Substitution reaction:** A reaction in which one atom or group in a molecule is replaced by another. In nucleophilic substitution, the leaving group X^- is replaced by a nucleophile.
- **Elimination reaction:** A reaction in which atoms are removed from a molecule (typically H and X from adjacent carbons), forming a double bond (an alkene).
- **Rate-determining step:** The slowest step of a multi-step reaction. The overall speed of the reaction is decided by this step alone, like the slowest person decides the speed of a walking group.

9.3 Classification of alkyl halides

Look at the carbon atom attached to the halogen — count how many *other carbon atoms* are attached to it:

- **Primary (1°) alkyl halide:** The halogen-bearing carbon is attached to only ONE other carbon. Example: $CH_3–CH_2–Br$ (bromoethane).
- **Secondary (2°) alkyl halide:** The halogen-bearing carbon is attached to TWO other carbons. Example: $CH_3–CHBr–CH_3$ (2-bromopropane).
- **Tertiary (3°) alkyl halide:** The halogen-bearing carbon is attached to THREE other carbons. Example: $(CH_3)_3C–Br$ (2-bromo-2-methylpropane, commonly called tert-butyl bromide).

> **Worked example:** Classify $CH_3–CH_2–CH_2–Cl$. Step 1: Find the carbon carrying Cl — it is the first carbon. Step 2: Count carbons attached to it — only one (the second carbon). Step 3: Answer: primary (1°) alkyl halide, 1-chloropropane.

Key takeaway: The class of an alkyl halide (1°, 2°, 3°) decides which reaction mechanism it follows — this is the single most important fact in Chapters 10 and 11.

9.4 Why the C–X bond breaks

The carbon–halogen bond breaks in a way where the halogen takes both shared electrons (this is called heterolysis, "hetero" = different, "lysis" = breaking — the electrons go to one side only):

$R–X \rightarrow R^+ + X^-$

The ease of breaking follows: C–I > C–Br > C–Cl > C–F. So alkyl iodides react fastest and alkyl fluorides slowest.

9.5 Pharmacy relevance

Many drug molecules contain halogen atoms — for example, the sedative chloral ($CCl_3–CHO$, Chapter 18) is a halogenated carbonyl compound, and several anaesthetics and antiseptics are alkyl halides or their close relatives. Understanding how C–X bonds break is the foundation for understanding how such drugs react and are made.

9.6 India context

India's pharmaceutical industry is one of the largest producers of generic medicines in the world. Many active pharmaceutical ingredients (APIs) made in Indian plants are built using alkyl halides as starting materials, because the C–X bond is easy to replace with other useful groups. A B.Pharm student in India will meet alkyl halide chemistry in almost every medicinal chemistry and synthesis topic later in the course.

9.7 Common confusions

1. **Alkyl halide vs aryl halide:** An alkyl halide has the halogen on a saturated carbon chain (e.g., $CH_3–CH_2–Br$); an aryl halide has it directly on a benzene ring (e.g., $C_6H_5–Br$). Their reactivity is very different — do not mix them up.
2. **Nucleophile vs base:** The same species (e.g., OH^-) can act as a nucleophile (donating electrons to carbon → substitution) or as a base (pulling off a proton → elimination). Which role it plays depends on conditions (Chapter 11).
3. **Carbocation vs carbanion:** A carbocation (R_3C^+) is positively charged and electron-poor; a carbanion (R_3C^-) is negatively charged and electron-rich. They are opposites.

9.8 Common mistakes

1. Counting the halogen-bearing carbon itself when classifying 1°, 2°, 3° — count only the *other* carbons attached to it.
2. Writing the leaving group as X^+ — the halogen always leaves as X^- (it takes the electron pair).
3. Forgetting that bond breaking is shown with the arrow pointing from the bond toward the halogen (electrons move to X).

9.9 Mnemonic

- **"No Exit Left Cold"** — Nucleophile, Electrophile, Leaving group, Carbocation: the four actors in every substitution/elimination reaction. If you can name all four in a reaction, you understand it.

9.10 One-minute revision

- Alkyl halide = R–X; halogen named as prefix (chloro, bromo…).
- C–X bond is polar: $C(\delta^+)$–$X(\delta^-)$; carbon is the electrophile.
- Nucleophile = electron giver; electrophile = electron taker.
- Leaving group leaves as X^-; I^- is the best halide leaving group.
- Carbocation = R_3C^+, electron-hungry, short-lived.
- Substitution = replacement; elimination = removal forming a double bond.
- Classify by carbons attached to the C–X carbon: 1 (primary), 2 (secondary), 3 (tertiary).
- Reactivity of bond breaking: C–I > C–Br > C–Cl > C–F.
- Rate-determining step = slowest step, decides overall speed.

9.11 Practice questions

MCQs (answer key at the end of the chapter)

1. Which of the following is a tertiary alkyl halide?

a) CH_3–CH_2–Br b) CH_3–CHBr–CH_3 c) $(CH_3)_3$C–Cl d) CH_3–I

2. In an alkyl halide, the carbon attached to the halogen is:

a) δ^- b) δ^+ c) neutral d) negatively charged

3. Which halide ion is the best leaving group?

a) F^- b) Cl^- c) Br^- d) I^-

4. A nucleophile is best described as:

a) an electron-pair acceptor b) an electron-pair donor c) a proton donor d) a free radical

5. Which C–X bond breaks most easily?

a) C–F b) C–Cl c) C–Br d) C–I

Short-answer

1. Define alkyl halide and give two examples with IUPAC names.
2. What is a carbocation? Why is it highly reactive?
3. Classify the following as 1°, 2°, or 3°: (i) CH_3–CH_2–CH_2–CH_2–I, (ii) $(CH_3)_2$CH–Cl, (iii) $(CH_3)_3$C–Br.

Long-answer

1. Explain, using bond polarity, why the carbon atom of an alkyl halide is attacked by nucleophiles. Illustrate with the heterolysis of the C–X bond.

Mechanism-writing

1. Show, using curved arrows in words (describe electron movement), how R–X breaks to give R^+ and X^-. State which species is the electrophile and which is the leaving group.

Application-based

1. A student has two bottles labelled "C–F compound" and "C–I compound" and wants the one that reacts faster with OH^-. Which should she choose, and why?

Viva

1. What is the difference between a nucleophile and an electrophile?
2. Why is iodide a better leaving group than fluoride?

Answer key (MCQs): 1-c, 2-b, 3-d, 4-b, 5-d.

Chapter 10 — Nucleophilic Substitution: SN1 and SN2

Learning objectives

- State the order of reaction (kinetics) for SN1 and SN2.
- Describe the SN2 mechanism step by step: one-step, backside attack, inversion of configuration (Walden inversion).
- Describe the SN1 mechanism step by step: two-step, carbocation intermediate, racemisation, rearrangements.
- Compare substrate reactivity orders (1° > 2° > 3° for SN2; 3° > 2° > 1° for SN1).
- Explain the effect of solvent: polar aprotic favours SN2; polar protic favours SN1.
- Predict which mechanism a given alkyl halide will follow.

10.1 Definitions

- **Order of reaction:** The total power to which concentration terms are raised in the rate equation. It is found by experiment, not by looking at the equation.
- **Rate equation (rate law):** A mathematical expression showing how reaction speed depends on concentrations, e.g., rate = k[RX][Nu^-].
- **Concerted (one-step) reaction:** A reaction in which bond breaking and bond forming happen at the same time, in a single step — no intermediate is formed.
- **Inversion of configuration:** The three-dimensional arrangement at a carbon atom flips like an umbrella turning inside-out during backside attack (called Walden inversion).
- **Racemisation:** Formation of equal amounts of two mirror-image forms (enantiomers), giving an optically inactive mixture (a racemic mixture).
- **Rearrangement:** A hydride ion (H^-) or methyl group (CH_3^-) shifts from an adjacent carbon to the carbocation centre, forming a more stable carbocation.

10.2 Terminology alert — learn these first

- **Backside attack:** The nucleophile approaches the carbon from the side opposite to the leaving group (180° away), because the leaving group blocks the front side.
- **Polar aprotic solvent:** A solvent with a significant dipole but NO O–H or N–H bonds (cannot donate hydrogen bonds) — e.g., DMSO, DMF, acetone, acetonitrile. It dissolves ions but does not "wrap up" anions.
- **Polar protic solvent:** A solvent WITH O–H or N–H bonds (can donate hydrogen bonds) — e.g., water, ethanol, methanol. It wraps (solvates) both cations and anions strongly.
- **Stereochemistry:** The study of the three-dimensional arrangement of atoms in molecules.
- **Carbocation stability order:** 3° > 2° > 1° > methyl. More alkyl groups push electrons toward the positive carbon and stabilise it (hyperconjugation and inductive effect — electron-donating effects of neighbouring C–H and C–C bonds).

10.3 SN2 — the one-step substitution

Concept. SN2 means "Substitution, Nucleophilic, 2nd order (bimolecular)". The nucleophile attacks and the leaving group leaves in one single step.

Reaction equation with conditions: $CH_3–CH_2–Br + OH^- \rightarrow CH_3–CH_2–OH + Br^-$ Conditions: typically aqueous acetone or a polar aprotic solvent; primary alkyl halide; good nucleophile.

Kinetics: rate = k[RX][Nu^-] — second order overall (first order in each). Both the alkyl halide and the nucleophile appear in the rate equation because both are present in the single slow step.

Mechanism in step-by-step words:

1. The nucleophile (OH^-) approaches the δ^+ carbon from the back side, directly opposite the C–Br bond.
2. As the new C–O bond starts forming, the C–Br bond starts breaking — both happen simultaneously.
3. The reaction passes through a single transition state in which the carbon is partially bonded to both OH and Br (five groups crowded around carbon for an instant).
4. The bromide ion (Br^-) leaves, and the product alcohol is formed with inverted configuration — the three other groups have flipped like an umbrella in the wind (Walden inversion).

Substrate order: 1° > 2° > 3°. Reason: in the crowded transition state, bulky groups around the carbon block the nucleophile's approach. Methyl halides react fastest; tertiary halides hardly react by SN2 at all.

Solvent effect: Favoured by **polar aprotic solvents** (DMSO, DMF, acetone). These solvents dissolve the ionic nucleophile but do not form hydrogen bonds to it, so the nucleophile stays "free" and reactive. Polar protic solvents wrap the nucleophile in hydrogen bonds and slow it down.

Stereochemistry: Complete inversion of configuration — a single mirror-image starting material gives a single mirror-image product (the opposite one).

> **Worked example:** (S)-2-bromobutane + I^- → (R)-2-iodobutane + Br^-. The iodide attacks from the back side; the product has the opposite configuration (S becomes R). Only one product, no mixture.

Key takeaway: SN2 = one step, second order, backside attack, inversion, fastest with 1° substrates and polar aprotic solvents.

10.4 SN1 — the two-step substitution

Concept. SN1 means "Substitution, Nucleophilic, 1st order (unimolecular)". The leaving group leaves first, forming a carbocation; then the nucleophile attacks.

Reaction equation with conditions: $(CH_3)_3C–Br + H_2O \rightarrow (CH_3)_3C–OH + HBr$ Conditions: typically aqueous ethanol (polar protic solvent); tertiary alkyl halide; often with heating.

Kinetics: rate = k[RX] — first order. Only the alkyl halide concentration matters, because the slow step involves only the alkyl halide breaking apart. The nucleophile attacks after the slow step, so its concentration does not affect the rate.

Mechanism in step-by-step words:

1. **Step 1 (slow, rate-determining):** The C–Br bond breaks on its own; Br^- leaves with the electron pair, leaving a planar carbocation, $(CH_3)_3C^+$. This step is slow because breaking a bond without help needs energy.
2. **Step 2 (fast):** The nucleophile (water) attacks the flat carbocation from either the top face or the bottom face with equal probability.
3. A final quick proton loss gives the alcohol product.

Substrate order: 3° > 2° > 1°. Reason: the slow step forms a carbocation, and more stable carbocations form faster. Tertiary carbocations are the most stable, so tertiary halides react fastest by SN1.

Rearrangements: Because a carbocation is formed, a hydride (H^-) or methyl shift from a neighbouring carbon can occur to give a MORE stable carbocation before the nucleophile attacks. Example: $CH_3–CH_2–CH_2–CH_2–Cl$ (1°) can rearrange via hydride shift to a 2° carbocation, giving a mixture including the 2° product. This never happens in SN2 (no carbocation is formed).

Solvent effect: Favoured by **polar protic solvents** (water, ethanol). These stabilise both the carbocation and the leaving anion through solvation, helping the C–X bond break in step 1.

Stereochemistry: Racemisation. The carbocation is flat (planar), so the nucleophile attacks from both faces equally, giving a 50:50 mixture of both enantiomers (a racemic mixture), which is optically inactive.

> **Worked example:** (S)-3-bromo-3-methyl? — simpler: (R)-2-bromobutane by SN1 gives a racemic mixture of (R)- and (S)-butan-2-ol. The planar $CH_3–CH^+–CH_2–CH_3$ carbocation is attacked from above and below equally.

Key takeaway: SN1 = two steps, first order, carbocation intermediate, racemisation, rearrangements possible, fastest with 3° substrates and polar protic solvents.

10.5 Comparison table: SN1 vs SN2

Feature	SN1	SN2
Steps	Two (via carbocation)	One (concerted)
Kinetics	First order: rate = k[RX]	Second order: rate = k[RX][Nu^-]
Substrate order	3° > 2° > 1°	1° > 2° > 3°
Stereochemistry	Racemisation (both enantiomers)	Complete inversion (Walden inversion)
Rearrangements	Possible (hydride/methyl shifts)	Never
Favoured solvent	Polar protic (water, ethanol)	Polar aprotic (DMSO, DMF, acetone)
Typical substrate	Tertiary alkyl halides	Primary alkyl halides
Rate-determining step	C–X bond breaking (ionisation)	Single step: attack + leaving together

10.6 How to predict: a simple decision path

1. Is the substrate 3°? → SN1 (stable carbocation).
2. Is the substrate 1°? → SN2 (no crowding for backside attack).
3. Is the substrate 2°? → Mixture; strong nucleophile + polar aprotic solvent pushes SN2; weak nucleophile + polar protic solvent + heat pushes SN1.

10.7 Pharmacy relevance

The SN1/SN2 logic is used in drug synthesis whenever a halogen is replaced by another group — e.g., replacing –Cl with –CN, –OH, or an amino group to build drug molecules. Many antihistamines, local anaesthetics, and other drugs are assembled through nucleophilic substitution steps in the factory.

10.8 India context

Indian API manufacturers routinely use SN2 reactions (e.g., alkylation with alkyl halides in DMF or acetone) to attach side chains to drug cores. Knowing that polar aprotic solvents speed up SN2 helps a production chemist choose the right solvent on the plant floor.

10.9 Common confusions

1. **"SN1 because one step"** — wrong. The "1" in SN1 refers to first-order kinetics (one molecule in the slow step), not one step. SN1 has TWO steps.
2. **Order vs molecularity:** Order is measured experimentally; do not assume the balanced equation tells you the order.
3. **Racemisation vs inversion:** SN1 gives a mixture of both mirror images (racemisation); SN2 gives a single product with flipped geometry (inversion). They are not the same.
4. **Strong nucleophile ≠ strong base:** I^- is a great nucleophile but a weak base; it gives substitution, not elimination. (More in Chapter 11.)

10.10 Common mistakes

1. Drawing a carbocation in an SN2 mechanism — SN2 has no intermediate at all.
2. Forgetting that in SN1 the nucleophile concentration does not appear in the rate law.
3. Predicting rearrangement in SN2 reactions.
4. Saying "polar solvent favours SN2" without specifying aprotic — polar *protic* solvents slow SN2 down.

10.11 Mnemonics

- **"1-2-3, 3-2-1":** SN1 substrate order is 3° > 2° > 1°; SN2 is the reverse, 1° > 2° > 3°.
- **"Protic for plus":** polar *protic* solvents favour the *plus* (carbocation) pathway, SN1. **"Aprotic attacks":** polar *aprotic* solvents keep the nucleophile free to *attack* in SN2.

10.12 One-minute revision

- SN2: one step, rate = k[RX][Nu^-], backside attack, inversion (Walden), 1° > 2° > 3°, polar aprotic solvent, no rearrangement.
- SN1: two steps, rate = k[RX], carbocation intermediate, racemisation, 3° > 2° > 1°, polar protic solvent, rearrangements possible.
- Slow step of SN1 = C–X bond breaking (ionisation); nucleophile attacks after.
- Backside attack happens because the leaving group blocks the front.
- Planar carbocation → attack from both faces → racemic mixture.
- 2° substrates give mixtures; conditions decide.
- I^- is a good nucleophile but weak base → substitution.
- "Protic for plus, aprotic attacks."
- Never draw a carbocation in SN2; never draw a one-step SN1.

10.13 Practice questions

MCQs

1. The rate law for an SN2 reaction is:

a) rate = k[RX] b) rate = k[RX][Nu^-] c) rate = k[Nu^-] d) rate = k[RX]^2

2. Which substrate reacts fastest by SN2?

a) $(CH_3)_3C–Br$ b) $CH_3–CHBr–CH_3$ c) $CH_3–CH_2–Br$ d) $CH_3–Br$

3. SN1 reactions give:

a) complete inversion b) a racemic mixture c) retention only d) no product

4. Which solvent favours SN1?

a) DMSO b) DMF c) acetone d) ethanol

5. Carbocation rearrangement is possible in:

a) SN2 only b) SN1 only c) both SN1 and SN2 d) neither

Short-answer

1. Write the rate laws for SN1 and SN2 and explain why the nucleophile appears in only one of them.
2. Why do tertiary alkyl halides prefer SN1 while primary alkyl halides prefer SN2?
3. What is Walden inversion? In which mechanism does it occur?

Long-answer

1. Compare SN1 and SN2 mechanisms with respect to kinetics, steps, stereochemistry, substrate structure, and solvent effects. Give one example reaction for each.
2. Explain why polar protic solvents favour SN1 but slow down SN2.

Mechanism-writing

1. Write the complete step-by-step mechanism for the reaction: $(CH_3)_3C–Br + H_2O \rightarrow (CH_3)_3C–OH + HBr$. Label the rate-determining step and show the stereochemical outcome if the starting material were chiral.

Application-based

1. A chemist wants to convert 1-bromopropane to propan-1-ol quickly. Which solvent should she choose — water or DMSO — and which mechanism will operate? Justify your answer.

Viva

1. Why does the rate of an SN1 reaction not depend on the nucleophile concentration?
2. What is a racemic mixture, and why does SN1 produce one?

Answer key (MCQs): 1-b, 2-d, 3-b, 4-d, 5-b.

Chapter 11 — Elimination: E1 and E2, Saytzeff's Rule, Substitution vs Elimination

Learning objectives

- Define elimination and identify the atoms removed.
- Describe the E2 mechanism: one-step, second order, anti-periplanar geometry.
- Describe the E1 mechanism: two-step via carbocation, first order.
- State Saytzeff's (Zaitsev's) rule and apply it to predict the major alkene.
- Explain the Hofmann product formed with bulky bases.
- Compare substitution vs elimination and choose conditions favouring each.

11.1 Definitions

- **Elimination reaction:** A reaction in which two atoms or groups are removed from adjacent carbons, forming a carbon–carbon double bond (alkene). The most common type is dehydrohalogenation: removal of H and X.
- **Dehydrohalogenation:** Elimination of hydrogen and halogen: –CH–CX– → –C=C– + HX. Typically done with alcoholic KOH (heat).
- **Alkene:** A hydrocarbon containing a C=C double bond.
- **Saytzeff's (Zaitsev's) rule:** In elimination, the major product is the MORE substituted alkene — the double bond forms preferentially toward the more substituted carbon (the one that had more alkyl groups).
- **Hofmann product:** The LESS substituted alkene, formed as the major product when a bulky base is used.

11.2 Terminology alert — learn these first

- **Anti-periplanar:** The H and the leaving group (X) must lie in the same plane but on opposite sides (180° apart, "anti") at the moment of elimination. This geometry lets the forming p-orbitals overlap to make the π bond. Think of two people pulling a rope in opposite directions while standing in line.
- **β-carbon / β-hydrogen:** The carbon next to the C–X carbon is the α-carbon's neighbour — it is called the β-carbon, and its hydrogens are β-hydrogens. Elimination removes a β-hydrogen.
- **Regioselectivity:** Preference for forming one structural isomer over another (e.g., which alkene forms when two are possible).
- **Bulky base:** A large base, e.g., potassium tert-butoxide, $(CH_3)_3CO^-K^+$, which has difficulty reaching crowded hydrogens and so removes the most accessible (least hindered) hydrogen instead.

11.3 E2 — the one-step elimination

Concept. E2 = "Elimination, 2nd order (bimolecular)". The base pulls off a β-hydrogen while the leaving group leaves, all in one step.

Reaction equation with conditions: $CH_3–CH_2–CH_2–Br + KOH$ (alcoholic, heat) → $CH_3–CH=CH_2 + KBr + H_2O$ (Propene is the product; with 2-bromobutane two alkenes are possible — see Saytzeff below.)

Kinetics: rate = k[RX][base] — second order. Both the alkyl halide and the base are involved in the single slow step.

Mechanism in step-by-step words:

1. The base (OH^-) approaches a β-hydrogen that is anti-periplanar to the C–Br bond.
2. In one concerted step: the base pulls the hydrogen off (forming water), the C–H electrons form the C=C double bond, and Br^- leaves — all simultaneously.
3. No intermediate is formed; there is a single transition state.

Substrate order: 3° > 2° > 1° (more substituted substrates eliminate faster, because the transition state has partial double-bond character, and more substituted double bonds are more stable).

Stereochemistry: Must be anti-periplanar — H and X opposite each other in the same plane. This requirement decides which stereoisomer of alkene forms.

> **Worked example:** 2-bromobutane, $CH_3–CHBr–CH_2–CH_3$, with alcoholic KOH gives two alkenes: but-2-ene ($CH_3–CH=CH–CH_3$, more substituted) as the MAJOR product and but-1-ene ($CH_2=CH–CH_2–CH_3$, less substituted) as the minor product — following Saytzeff's rule.

Key takeaway: E2 = one step, second order, anti-periplanar, no intermediate, Saytzeff product predominates.

11.4 E1 — the two-step elimination

Concept. E1 = "Elimination, 1st order (unimolecular)". Like SN1, the leaving group leaves first to form a carbocation; then a (weak) base removes a β-proton.

Reaction equation with conditions: $(CH_3)_3C–Br$ → (with heat, weak base / polar protic solvent) → $(CH_3)_2C=CH_2$ + HBr (2-methylpropene, the more substituted alkene.)

Kinetics: rate = k[RX] — first order. The slow step is carbocation formation; the base acts after it.

Mechanism in step-by-step words:

1. **Step 1 (slow, rate-determining):** The C–X bond breaks; X^- leaves, forming a carbocation. (Identical to step 1 of SN1.)
2. **Step 2 (fast):** A weak base (often the solvent itself) removes a β-hydrogen; the C–H electrons form the double bond.

Rearrangements: Possible, exactly as in SN1 — a hydride or methyl shift can give a more stable carbocation before proton loss.

Solvent: Favoured by polar protic solvents and weak bases, plus heat — the same conditions as SN1, and indeed SN1 and E1 often compete (substitution vs elimination mixtures).

Stereochemistry: No anti-periplanar requirement in the strict sense — the planar carbocation can lose a proton from either face; the more stable (Saytzeff) alkene predominates.

> **Worked example:** $(CH_3)_3C–Cl$ heated in ethanol gives mainly $(CH_3)_2C=CH_2$ (2-methylpropene) plus some substitution product (tert-butyl ethyl ether / tert-butanol) — SN1 and E1 occur together.

Key takeaway: E1 = two steps via carbocation, first order, Saytzeff product, rearrangements possible; always competes with SN1.

11.5 Saytzeff's rule with examples

Rule: The major alkene is the more substituted one (more alkyl groups on the double-bond carbons), because more substituted alkenes are more stable.

Example 1: 2-bromobutane + alcoholic KOH → but-2-ene (major, disubstituted) + but-1-ene (minor, monosubstituted). $CH_3–CHBr–CH_2–CH_3$ → $CH_3–CH=CH–CH_3$ (major) + $CH_2=CH–CH_2–CH_3$ (minor)

Example 2: 2-bromo-2-methylbutane → 2-methylbut-2-ene (trisubstituted, major) + 2-methylbut-1-ene (disubstituted, minor).

Hofmann exception: With a bulky base like potassium tert-butoxide, $(CH_3)_3CO^-K^+$, the base cannot easily reach the crowded β-hydrogens, so it removes the most exposed hydrogen — giving the LESS substituted alkene (Hofmann product) as major.

Key takeaway: Normal bases → Saytzeff (more substituted alkene); bulky bases → Hofmann (less substituted alkene).

11.6 Comparison table: E1 vs E2

Feature	E1	E2
Steps	Two (via carbocation)	One (concerted)
Kinetics	First order: rate = k[RX]	Second order: rate = k[RX][base]
Intermediate	Carbocation	None
Rearrangements	Possible	Never
Geometry requirement	None strict	Anti-periplanar H and X
Substrate order	3° > 2° > 1°	3° > 2° > 1°
Base	Weak base (often solvent)	Strong base needed
Solvent	Polar protic	Varies; heat helps
Major product	Saytzeff alkene	Saytzeff alkene (Hofmann with bulky base)

11.7 Substitution vs elimination — how to choose

Condition	Favours
Good nucleophile, weak base (I^-, Br^-, CN^-)	Substitution (SN1/SN2)
Strong, bulky base (tert-butoxide)	Elimination (E2)
Primary substrate	SN2 (substitution)
Tertiary substrate	SN1/E1 (mixture)
Secondary substrate	Mixture — conditions decide
Low temperature	Substitution
High temperature (heat)	Elimination
Polar aprotic solvent + strong nucleophile	SN2
Polar protic solvent + weak base + heat	SN1/E1

Memory logic: Substitution needs a good electron-giver attacking carbon; elimination needs a good proton-puller. Strong bulky bases are good proton-pullers but poor attackers (too big to reach carbon) → elimination wins.

Worked example: $CH_3–CH_2–Br$ + aqueous KOH (low temp) → $CH_3–CH_2–OH$ (substitution, SN2). $CH_3–CH_2–Br$ + alcoholic KOH (heat) → $CH_2=CH_2$ (elimination, E2). Same reagents' atoms, different solvent and temperature — different product. (Aqueous vs alcoholic KOH is the classic textbook distinction.)

11.8 Pharmacy relevance

Elimination reactions are used to introduce double bonds into drug intermediates, and the Saytzeff/Hofmann logic controls which isomer forms — important because different alkene isomers can have different biological activity. Dehydrohalogenation is also a standard step in preparing unsaturated building blocks for vitamins and steroids.

11.9 India context

Indian fine-chemical manufacturers use elimination steps when making unsaturated intermediates for drugs and agrochemicals. Choosing alcoholic KOH with heat versus aqueous KOH at room temperature is a routine plant-level decision that directly follows the substitution-vs-elimination rules in section 11.7.

11.10 Common confusions

1. **E1 vs SN1:** Same first step (carbocation), different second step — SN1 adds a nucleophile to carbon; E1 removes a proton from the β-carbon. They compete with each other.
2. **Saytzeff vs Hofmann:** Saytzeff = more substituted alkene (normal); Hofmann = less substituted (bulky base). Do not swap them.
3. **Aqueous KOH vs alcoholic KOH:** Aqueous KOH (low temperature) gives substitution (alcohol); alcoholic KOH (heat) gives elimination (alkene). This is a favourite exam question.

11.11 Common mistakes

1. Applying Saytzeff's rule to the substrate instead of the possible alkene products — count substituents on the double bond of the PRODUCTS.
2. Forgetting the anti-periplanar requirement in E2 stereochemistry questions.
3. Predicting rearrangement in E2 — E2 has no carbocation, so no rearrangement.
4. Writing the Hofmann product as major with a small base like OH^-.

11.12 Mnemonics

- **"Saytzeff Says More":** Saytzeff's rule — the MORE substituted alkene wins.
- **"Big Base, Bare Bond":** a bulky (big) base grabs the most bare (least hindered) hydrogen → Hofmann product.

11.13 One-minute revision

- E2: one step, rate = k[RX][base], anti-periplanar, no intermediate, no rearrangement.
- E1: two steps via carbocation, rate = k[RX], rearrangements possible, competes with SN1.
- Saytzeff: more substituted alkene is major.
- Hofmann: bulky base → less substituted alkene is major.
- Weak-base good nucleophiles → substitution; strong bulky bases → elimination.
- Heat favours elimination; low temperature favours substitution.
- 1° → SN2; 3° → SN1/E1; 2° → mixture.
- Aqueous KOH (cold) → alcohol; alcoholic KOH (heat) → alkene.

11.14 Practice questions

MCQs

1. The major product of 2-bromobutane with alcoholic KOH is:

a) but-1-ene b) but-2-ene c) butane d) butan-2-ol

2. E2 reactions require the H and X to be:

a) syn-periplanar b) anti-periplanar c) gauche d) any arrangement

3. Which base gives the Hofmann product as major?

a) OH^- b) $(CH_3)_3CO^-$ c) I^- d) CN^-

4. Rearrangement is possible in:

a) E2 only b) E1 only c) both d) neither

5. Heating an alkyl halide with alcoholic KOH gives mainly:

a) alcohol b) alkene c) ether d) alkane

Short-answer

1. State Saytzeff's rule and illustrate with the elimination of 2-bromobutane.
2. What is the Hofmann product? When does it become the major product?
3. Distinguish between E1 and E2 with respect to kinetics and intermediates.

Long-answer

1. Compare substitution and elimination reactions. How do the nature of the reagent, substrate structure, solvent, and temperature decide which pathway dominates? Give examples.
2. Explain the E1 and E2 mechanisms stepwise, including stereochemical requirements.

Mechanism-writing

1. Write the E2 mechanism for $CH_3–CHBr–CH_2–CH_3$ + OH^- (alcoholic, heat), showing the anti-periplanar arrangement in words and identifying the major and minor alkenes.

Application-based

1. A student treats 2-bromo-2-methylbutane with potassium tert-butoxide and gets a different major product than her friend who used KOH. Explain the difference.

Viva

1. Why does heat favour elimination over substitution?
2. What is the difference between the first step of SN1 and the first step of E1?

Answer key (MCQs): 1-b, 2-b, 3-b, 4-b, 5-b.

References

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