

Unit 1: Basic Aspects of Organic Chemistry

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Advanced Organic Chemistry I, subject code MPC102T, is a core Semester 1 subject of M.Pharm Pharmaceutical Chemistry. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject is the mechanistic foundation of drug synthesis. It begins with the short lived reactive intermediates, carbocations, carbanions, free radicals, carbenes and nitrenes, whose behaviour decides which products a reaction can give, and with the experimental methods by which mechanisms are proved rather than guessed. The same unit then works through the four great reaction families, substitution, addition, elimination and rearrangement, with their mechanisms, relative reactivity and orientation, and closes with the chemistry of enolates. Unit 2 studies the named reactions in depth, from the Mannich and Sandmeyer reactions to the Sharpless epoxidation and the Suzuki coupling, because these are the bond forming tools medicinal chemists actually use. Unit 3 covers the standard synthetic reagents, aluminium isopropoxide to the BOP coupling reagent, and the protecting group strategy that makes multi step synthesis possible. Unit 4 applies named ring forming reactions to the heterocyclic nuclei found in real drugs: imidazole antifungals, pyrazole analgesics, pyrimidine antibacterials, quinoline antimalarials, acridine anticancer agents, phenothiazine antipsychotics and purine drugs. Unit 5 reverses the whole way of thinking: the synthon approach and retrosynthesis, in which a target molecule is dissected backwards into purchasable starting materials. A student who completes this subject should be able to propose a mechanism for an unfamiliar reaction, choose reagents and protecting groups for a planned transformation, and dissect a small drug molecule into a workable synthetic route.

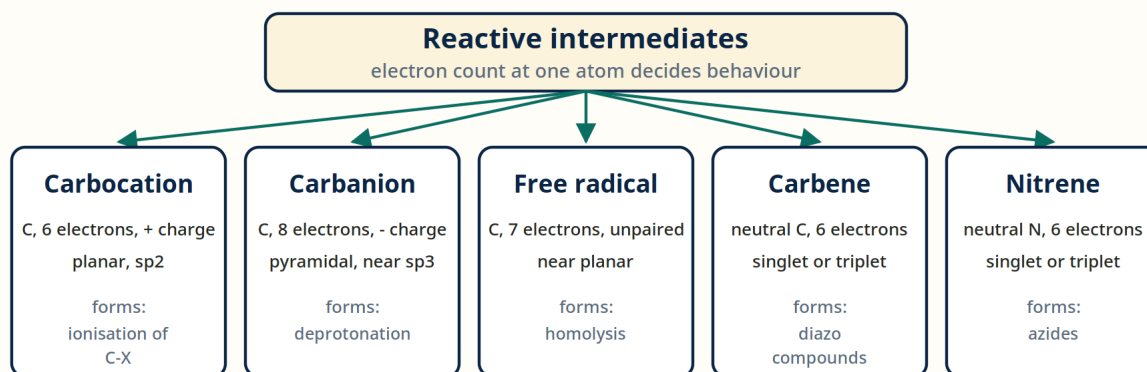
1.1 Reactive intermediates: the idea behind the mechanisms

Most organic reactions do not jump from starting material to product in one step. Between the two there is at least one **intermediate**: a real chemical species, formed in one step and consumed in the next, sitting in an energy valley between two transition states. Intermediates are usually too reactive to isolate, but they can often be detected spectroscopically, trapped with a suitable reagent, or inferred from their products. Five families dominate organic mechanism: carbocations, carbanions, free radicals, carbenes and nitrenes. Each is defined by the electron count at one key atom, and that electron count decides its structure, its stability order and the reactions it will undergo. A sixth species, benzyne, is covered later in this unit with aromatic substitution, where it belongs mechanistically.

Intermediate	Key atom and electrons	Geometry at the key atom	Typical character
Carbocation	Carbon with 6 electrons, positive charge, empty p orbital	Planar, sp ²	Electrophile, attacked by nucleophiles
Carbanion	Carbon with 8 electrons, negative charge, lone pair	Pyramidal, close to sp ³ (planar when conjugated)	Nucleophile and strong base
Free radical	Carbon with 7 electrons, one unpaired electron	Planar or shallow pyramid, near sp ²	Adds to pi bonds, abstracts hydrogen atoms
Carbene	Neutral carbon with 6 electrons, two non-bonding electrons	Singlet: sp ² with lone pair; triplet: two singly occupied orbitals	Adds to alkenes, inserts into bonds
Nitrene	Neutral nitrogen with 6 electrons, nitrogen analogue of a carbene	Singlet or triplet, like carbenes	Inserts into C-H bonds, adds to alkenes

The working rule of this unit is simple: whichever intermediate a reaction passes through, the conditions that stabilise that intermediate will speed the reaction up, and the products will be the ones that intermediate naturally gives. Nearly every selectivity question in Units 1 and 2 reduces to that rule.

Five Reactive Intermediates at a Glance



Stabilise the intermediate and you speed the reaction: the working rule of Units 1 and 2.

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Figure: The five reactive intermediates. Electron count at the key atom decides structure, stability and reaction type.

1.2 Carbocations

A **carbocation** is a species with a positively charged carbon atom that has only six electrons in its valence shell and an empty p orbital. The charged carbon is sp² hybridised and planar, which is why nucleophiles can attack it from either face and why S_N1 reactions give racemisation.

Formation of carbocations:

- **Ionisation of a C-X bond:** an alkyl halide, alcohol (after protonation) or sulfonate ester breaks heterolytically in a polar solvent, the leaving group taking the electron pair. This is the slow step of S_N1 and E1.
- **Protonation of an alkene or alcohol:** addition of a proton to a pi bond, or loss of water from a protonated alcohol, as in acid catalysed dehydration.
- **From diazonium and diazo compounds:** loss of nitrogen gas from an alkyldiazonium ion or protonation of a diazo compound.
- **Electrophilic attack on an aromatic ring:** the sigma complex (arenium ion) of electrophilic aromatic substitution is a carbocation delocalised around the ring.

Stability of carbocations. The charge is stabilised by anything that donates electrons towards the empty p orbital:

- **Hyperconjugation and inductive effect:** alkyl groups donate, so the order is tertiary > secondary > primary > methyl. A tert-butyl cation has nine alpha C-H bonds that can hyperconjugate; a methyl cation has none.
- **Resonance:** allyl and benzyl cations, in which the charge is shared over a pi system, are far more stable than simple primary cations. Triphenylmethyl (trityl) cations are stable enough to exist as isolable salts.
- **Adjacent heteroatoms:** a neighbouring oxygen or nitrogen lone pair stabilises strongly (oxocarbenium and iminium ions), which is why acetals hydrolyse through such cations.

Reactions of carbocations are the synthetic applications the syllabus asks for:

- **Capture by a nucleophile:** the SN1 substitution step, and the termination of Friedel-Crafts alkylation.
- **Loss of a proton:** gives an alkene, the E1 pathway.
- **Rearrangement:** a 1,2-hydride or 1,2-alkyl shift converts a less stable cation into a more stable one whenever the shift produces a more substituted or resonance stabilised cation. This Wagner-Meerwein type shift explains rearranged products in SN1 reactions and in pinacol type chemistry (section 1.13).
- **Addition to pi bonds:** a cation adds to an alkene to give a new, larger cation, the basis of cationic polymerisation and of many terpene cyclisations in nature.

The classical versus non-classical carbocation question (whether the 2-norbornyl cation is a pair of rapidly equilibrating classical ions or one bridged, delocalised ion) is the famous historical example of carbocation structure being settled by experiment; the bridged description is now accepted for that system.

1.3 Carbanions

A **carbanion** is a species with a negatively charged carbon carrying a lone pair: eight electrons at carbon. Simple alkyl carbanions are pyramidal and are among the strongest bases in common use. When the charge can be delocalised into an adjacent pi system, as in enolates and benzyl anions, the carbon flattens towards planar.

Formation of carbanions:

- **Deprotonation of a C-H bond of measurable acidity:** a base removes a proton alpha to a carbonyl, nitrile, sulfone or nitro group. The guide is the pKa of the conjugate acid: the weaker the acid (higher pKa of the C-H), the stronger the base needed.
- **From organometallic compounds:** Grignard reagents, organolithiums and acetylides behave as carbanion equivalents in most of their reactions.
- **Decarboxylation:** beta-keto acids and malonic acid derivatives lose carbon dioxide on heating through a cyclic transition state, leaving an enolate that is protonated on work up.
- **Addition of a nucleophile to an activated alkene** or reduction of certain pi systems with metals.

Stability of carbanions runs opposite to carbocations in one respect: electron withdrawing groups stabilise the charge.

- **Resonance delocalisation:** enolates of 1,3-dicarbonyl compounds (ethyl acetoacetate, malonic ester) are the most useful stabilised carbanions; their conjugate acids have pKa values near 9 to 13, so even alkoxide bases generate them fully.
- **Inductive withdrawal:** groups such as nitro, cyano and sulfonyl stabilise strongly; the nitro group makes nitromethane (pKa about 10) a practical carbon acid.
- **s Character of the orbital holding the pair:** acidity runs terminal alkyne (sp, pKa about 25) > alkene (sp², about 44) > alkane (sp³, about 50), because more s character holds the pair closer to the nucleus.
- Alkyl groups destabilise simple carbanions, so the order methyl > primary > secondary > tertiary holds for unstabilised anions, the reverse of the carbocation order.

Synthetic applications: carbanions and their equivalents are carbon nucleophiles, so they build carbon skeletons. Enolate alkylation and acylation, the aldol and Claisen condensations, the Michael addition (Unit 2), acetylide additions to carbonyl compounds and the reactions of Grignard and organolithium reagents all run through carbanion character at carbon. Section 1.14 treats enolates, the most important family, in detail.

1.4 Free radicals

A **free radical** is a species with an unpaired electron. Carbon radicals have seven electrons at the radical centre and are close to planar. They are electrically neutral, which makes their chemistry different from ionic chemistry: radicals react well in non-polar media, are barely affected by solvent polarity, and react in chains.

Formation of free radicals:

- **Homolysis of weak bonds:** peroxides, azo compounds and N-bromosuccinimide break on heating or irradiation to give radicals that start chains. Bond weakness is the guide: the O-O bond of a peroxide breaks far more easily than a C-C bond.
- **Photolysis:** light cleaves halogens and ketones (the Norrish reactions) into radical pairs.
- **Single electron transfer:** metals such as sodium, iron(II) and samarium(II) iodide donate one electron to a substrate, giving radical anions or radicals.
- **Hydrogen atom abstraction:** a reactive radical removes a hydrogen atom from a substrate, leaving a new radical at that carbon.

Stability of radicals follows the same broad order as carbocations, because both are electron deficient: tertiary > secondary > primary > methyl, and resonance stabilised allyl and benzyl radicals are especially stable. The bond dissociation energy of the C-H bond broken is the quantitative guide: the weaker the bond, the more stable the radical left behind. Allylic and benzylic C-H bonds are weak precisely because the radicals are delocalised.

Reactions and synthetic applications:

- **Chain halogenation of alkanes:** initiation, propagation (abstraction, then halogen capture) and termination steps. Selectivity follows radical stability, and bromine is far more selective than chlorine because its abstraction step is endothermic and has a later, more product like transition state.
- **Allylic and benzylic bromination with NBS** (Unit 3), which keeps the bromine concentration low so that substitution at the activated position beats addition to the double bond.
- **Addition to alkenes:** the peroxide effect in HBr addition (anti-Markovnikov product) works because a bromine radical adds first to give the more stable carbon radical.
- **Radical cyclisations and reductions:** tributyltin hydride chemistry, now increasingly replaced by less toxic alternatives, closes rings by radical addition and reduces halides by hydrogen atom transfer.
- **Polymerisation:** most commodity plastics are made by radical chain growth.

Radical inhibitors such as hydroquinone and hindered phenols (BHT) break chains by donating a hydrogen atom to give a radical too stable to continue the chain, which is why they are added to monomers and to formulations as antioxidants.

1.5 Carbenes

A **carbene** is a neutral species with a divalent carbon carrying two non-bonding electrons: $R_2C:$. The two electrons can be paired in one orbital (**singlet carbene**, bent, sp^2 like, with an empty p orbital, so it behaves as electrophile and nucleophile at once) or unpaired in two orbitals (**triplet carbene**, which behaves like a diradical and reacts stepwise).

Formation of carbenes:

- **From diazo compounds:** diazomethane and ethyl diazoacetate lose nitrogen on heating, irradiation or metal catalysis (copper, rhodium) to give carbenes or metal carbenoids.
- **Alpha elimination:** chloroform with strong base loses HCl to give dichlorocarbene, the classic example.

- **From diazirines and tosylhydrazones** (the Bamford-Stevens route to diazo compounds).

Reactions and synthetic applications:

- **Cyclopropanation:** singlet carbenes add to alkenes in one concerted step, so the alkene geometry is preserved in the cyclopropane (stereospecific syn addition); triplet carbenes add stepwise and the stereochemistry is scrambled. This difference is a standard experimental test for carbene spin state. The Simmons-Smith reagent (ICH_2ZnI) transfers a methylene equivalent without free carbene and is the practical laboratory method.
- **Insertion into C-H and X-H bonds:** metal carbenoids insert into C-H bonds, a reaction now used for late stage functionalisation.
- **The Reimer-Tiemann reaction:** dichlorocarbene adds to a phenoxide ring and hydrolysis of the dichloromethyl product gives an ortho formyl phenol (salicylaldehyde from phenol).
- **Rearrangement:** the Wolff rearrangement of α -diazoketones passes through a carbene like intermediate (Unit 1, section 1.13).

Cyclopropane rings appear in real drugs (ciprofloxacin carries one), which is why carbene transfer chemistry matters to pharmaceutical chemists.

1.6 Nitrenes

A **nitrene** is the nitrogen analogue of a carbene: a neutral, monovalent nitrogen species R-N: with six electrons at nitrogen, existing in singlet and triplet states. Nitrenes are generated and consumed in situ; they are never bottled.

Formation of nitrenes:

- **From azides:** alkyl and acyl azides lose nitrogen on heating or irradiation. Acyl azides are the key intermediate of the Curtius rearrangement (section 1.13).
- **From N-halo compounds and hydroxylamine derivatives** under basic or metal catalysed conditions.

Reactions and synthetic applications:

- **Insertion into C-H bonds:** singlet nitrenes insert concertedly; triplet nitrenes abstract hydrogen and recombine, like radicals.
- **Addition to alkenes:** gives aziridines, the nitrogen analogues of cyclopropanes, which are themselves reactive intermediates and occur in mitomycin class antibiotics.
- **Rearrangement:** acyl nitrenes rearrange to isocyanates (Curtius), and the closely related Hofmann rearrangement of amides passes through an electron deficient nitrogen of the same family. Both convert a carboxylic acid derivative into an amine with one carbon fewer, a standard move in drug synthesis.

1.7 Benzyne (aryne)

Benzyne is a benzene ring containing a formal triple bond: 1,2-didehydrobenzene. The extra π bond lies in the plane of the ring, made from sp^2 orbitals that overlap poorly, so benzyne is extraordinarily reactive and exists only as a fleeting intermediate. It is generated by removing two ortho substituents from a benzene ring: classically, a strong base such as sodium amide removes the proton ortho to a halogen and the halide then leaves (the elimination half of the elimination-addition mechanism), or an ortho silyl triflate is treated with fluoride, the modern clean method.

The evidence for benzyne is a model of mechanism proof (section 1.8): when chlorobenzene labelled with carbon-14 at the carbon bearing chlorine is treated with potassium amide, the aniline product has the amino

group split almost equally between the labelled carbon and its neighbour, which is only possible if a symmetrical intermediate, benzyne, is attacked at either end. Benzyne is trapped by dienes in Diels-Alder reactions and is attacked by nucleophiles, and this addition chemistry is its main synthetic use: it installs substituents at positions that ordinary aromatic substitution cannot reach, including the ipso and cine substitution patterns seen when an amino group ends up adjacent to where the leaving group was.

1.8 Types of mechanisms and how mechanisms are determined

A mechanism is a step by step account of bond breaking and bond making, written with curly arrows: a full headed arrow moves an electron pair (ionic steps), a single headed fishhook arrow moves one electron (radical steps). Mechanisms are classified by what happens overall (substitution, addition, elimination, rearrangement), by the intermediate involved, and by molecularity (unimolecular or bimolecular rate determining step). A mechanism is a hypothesis, and the syllabus expects the experimental methods used to test one:

- **Product analysis:** the products, including minor ones and their ratios, must all fit the proposed steps. Rearranged products point to carbocations; scrambled stereochemistry points to planar intermediates.
- **Kinetics:** the rate law gives the composition of the rate determining transition state. First order in substrate alone supports SN1; first order in both substrate and nucleophile supports SN2.
- **Isolation and detection of intermediates:** stable examples are isolated (trityl salts), reactive ones are seen spectroscopically at low temperature, and carbocations have been observed directly in superacid media by NMR.
- **Trapping:** a reagent that reacts characteristically with the suspected intermediate diverts the reaction: dienes trap benzyne and carbenes, TEMPO captures radicals, azide ion captures carbocations.
- **Crossover experiments:** if a rearrangement run on a mixture of two differently labelled substrates gives no mixed label products, the migrating group never leaves the molecule: the reaction is intramolecular.
- **Kinetic isotope effect:** replacing a hydrogen broken in the rate determining step with deuterium slows the reaction several fold (kH/kD commonly 2 to 7). A large primary isotope effect proves C-H cleavage is rate determining, as in E2; its absence excludes it, as in E1.
- **Stereochemical evidence:** inversion proves backside attack (SN2); racemisation proves a planar intermediate (SN1); syn versus anti addition distinguishes concerted from stepwise carbene addition.
- **Isotopic labelling:** labelled atoms are followed into the products, as in the carbon-14 benzyne experiment of section 1.7 and oxygen-18 studies of ester hydrolysis that show which bond breaks.
- **Substituent effects:** the Hammett equation relates rate or equilibrium to substituent constants; the sign and size of rho show how much charge builds up in the transition state and where.

The energy profile ties these methods together. Each step has a transition state at an energy maximum and any intermediate sits in the valley between two maxima. The highest transition state relative to the starting material is rate determining, and by the Hammond postulate its structure resembles whichever stable species, reactant, intermediate or product, is closer to it in energy.

How evidence is matched to a mechanism question

Question: is an intermediate involved, and which one?

-> trap it, detect it spectroscopically, or find its rearranged products

Question: which step is rate determining?

-> measure the rate law and the kinetic isotope effect

Question: does a group migrate within the molecule or between molecules?

-> run a crossover experiment with two labelled substrates

Question: what happens at the reacting carbon?

-> follow the stereochemistry of a single enantiomer substrate

Question: how much charge develops in the transition state?

-> measure rates for ring substituted substrates, apply the Hammett equation

1.9 Nucleophilic substitution at saturated carbon: SN1, SN2 and SNi

SN2 (substitution, nucleophilic, bimolecular). The nucleophile attacks carbon from the side opposite the leaving group as the C-X bond breaks: one step, no intermediate, rate = $k[\text{RX}][\text{Nu}]$. The carbon passes through a planar pentacoordinate transition state and the configuration inverts (Walden inversion). Methyl and primary substrates react fastest; tertiary substrates essentially never react this way because the backside is blocked. Strong, compact nucleophiles, polar aprotic solvents (DMSO, DMF, acetone) that leave the nucleophile unsolvated, and good leaving groups (iodide, tosylate) accelerate SN2.

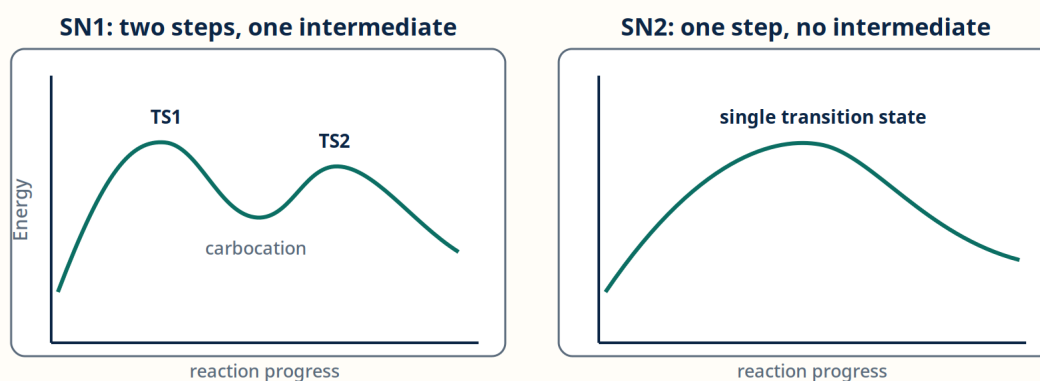
SN1 (substitution, nucleophilic, unimolecular). The C-X bond ionises first, slowly, to a planar carbocation; the nucleophile then attacks either face, giving racemisation (often with some net inversion, because the leaving group shields one face as an ion pair). Rate = $k[\text{RX}]$ only. Tertiary, benzylic and allylic substrates, polar protic solvents that stabilise ions, and weak nucleophiles favour SN1. Rearranged products are diagnostic.

SNi (substitution, nucleophilic, internal). In a few reactions the leaving group itself delivers the nucleophile from the same face: classically, an alcohol with thionyl chloride without base forms a chlorosulfite that collapses internally, giving retention of configuration. Adding pyridine flips the outcome to inversion, because free chloride then attacks from the back in an ordinary SN2 step: a neat proof that mechanism, not the reagent name, decides stereochemistry.

Feature	SN1	SN2
Steps	Two, via a carbocation	One, concerted
Rate law	$k[\text{RX}]$	$k[\text{RX}][\text{Nu}]$
Substrate order	Tertiary > secondary > primary	Methyl > primary > secondary
Stereochemistry	Racemisation, some inversion	Complete inversion
Rearrangements	Common	Absent
Solvent that helps	Polar protic	Polar aprotic
Nucleophile strength	Matters little	Matters greatly

Secondary substrates sit on the borderline and can react by either pathway, which is why they are the standard examination battleground: the winner is decided by nucleophile strength, solvent and temperature (higher temperature and a good leaving group also open the competing E1 door).

Energy Profiles: SN1 Two Steps, SN2 One Step



SN1 rate is set by the first hump alone; SN2 cannot rearrange and inverts cleanly.

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Figure: Energy profiles for SN1 and SN2. Only SN1 has an intermediate, so only SN1 can rearrange or racemise.

1.10 Nucleophilic aromatic substitution and electrophilic aromatic substitution

SNAr (addition-elimination). A nucleophile can displace a leaving group from an aromatic ring only if the ring carries strong electron withdrawing groups (nitro groups above all) ortho or para to the leaving group. The nucleophile adds first, giving an anionic sigma complex (a Meisenheimer complex) whose charge is delocalised onto the nitro groups; the leaving group then departs and aromaticity returns. Because bond formation, not bond breaking, is rate determining, the leaving group order is unusual: fluoride is the best leaving group, $F > Cl > Br > I$, the reverse of aliphatic substitution. The 2,4-dinitrochlorobenzene reaction with amines is the standard example, and the Smiles rearrangement (Unit 4) is an intramolecular version. Where no activating group exists, strong base can still force substitution through the benzyne mechanism of section 1.7, and the label ends up at two positions: cine substitution.

Electrophilic aromatic substitution and orientation. The syllabus requires relative reactivity and orientation across the reaction families, and aromatic substitution is where orientation is most examined. An electrophile adds to the ring to give a sigma complex; loss of the ring proton restores aromaticity. Substituents already on the ring decide both speed and position:

- **Activating, ortho/para directing groups** (OH, OR, NH₂, alkyl) donate electrons and stabilise the sigma complex for ortho and para attack.
- **Deactivating, meta directing groups** (NO₂, CN, carbonyl, SO₃H) withdraw electrons; meta attack avoids placing positive charge next to the withdrawing group.
- **Halogens are the exception:** deactivating by induction yet ortho/para directing by resonance donation of a lone pair.

The same directing logic controls polysubstituted rings in drug intermediates, where the order in which groups are introduced is planned around it: nitrate first while the ring is still reactive, and never attempt a Friedel-Crafts step on a strongly deactivated ring.

1.11 Elimination reactions: E1, E2 and E1cB

Elimination removes two groups from adjacent carbons and forms a double bond. Three mechanisms cover the spectrum:

E2 (bimolecular). A base removes a beta hydrogen at the same moment as the leaving group departs: one step, rate = $k[RX][base]$. The breaking C-H and C-X bonds must lie in the same plane, and the

anti-periplanar arrangement (dihedral angle 180 degrees) is strongly preferred because the orbitals align best; in cyclohexane rings this means both groups must be axial, which can force the less substituted alkene. E2 is the default mechanism with strong bases.

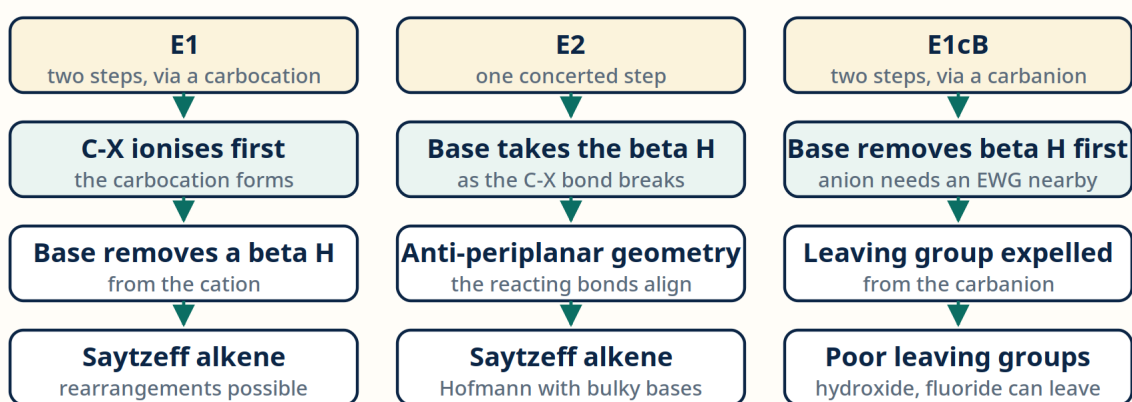
E1 (unimolecular). Ionisation gives the carbocation of the SN1 reaction, and a weak base or solvent then removes a beta proton. E1 therefore competes with SN1 under the same conditions and shares its rearrangements and solvent preferences; substitution usually dominates unless heat favours elimination.

E1cB (unimolecular, conjugate base). The base removes the proton first, giving a carbanion (the conjugate base of the substrate), which then expels the leaving group. This pathway needs an acidic beta hydrogen (flanked by a carbonyl, nitro or similar group) and a poor leaving group such as hydroxide or fluoride that will not leave from the neutral molecule: the aldol dehydration and the behaviour of 2-halo carboxylates are examples. A primary kinetic isotope effect is small or absent for the second step, and hydrogen exchange into recovered starting material is the classic test.

Saytzeff and Hofmann orientation. When two different beta carbons carry hydrogens, two alkenes can form. With small bases the more substituted, more stable alkene dominates (**Saytzeff product**), because the transition state shares the stability of the alkene being formed. With bulky bases (potassium tert-butoxide), with charged substrates such as quaternary ammonium hydroxides in the Hofmann elimination, or where a conjugated or statistically favoured product intervenes, the less substituted alkene dominates (**Hofmann product**) because the least hindered proton is removed fastest. Examination answers should state the rule and then the reason: alkene stability in the transition state against steric access to the proton.

Feature	E1	E2	E1cB
Intermediate	Carbocation	None	Carbanion
Rate law	$k[RX]$	$k[RX][base]$	$k[RX][base]$, with prior equilibrium
Needs	Ionising solvent, weak base	Strong base	Acidic beta H, poor leaving group
Stereochemistry	Not specific	Anti-periplanar preferred	Not specific
Rearrangements	Possible	No	No

Three Elimination Pathways: E1, E2 and E1cB



Same overall result, loss of HX: the order of the two bond events is the whole difference.

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Figure: E1, E2 and E1cB compared. The three mechanisms differ only in the order in which the two bonds break.

1.12 Addition reactions in outline

Electrophilic addition to alkenes. A proton or other electrophile adds to give the more stable carbocation, and the nucleophile captures it: the **Markovnikov rule** (the electrophile adds to the carbon that leaves the more stable cation). HBr with peroxides reverses the orientation by switching to a radical chain in which bromine adds first. Acid catalysed hydration gives Markovnikov alcohols; hydroboration-oxidation gives the anti-Markovnikov alcohol by a concerted, sterically controlled addition.

Addition to alkynes follows the same cation logic through vinyl cations; hydration gives enols that tautomerise to carbonyl compounds.

Nucleophilic addition to carbonyl compounds is driven by the polarised C=O bond: the nucleophile attacks carbon, the pi electrons move to oxygen, and protonation gives the product. Cyanide, Grignard reagents, hydride donors, water, alcohols and amines all follow this pattern, and its reversibility with weak nucleophiles is what makes acetal chemistry and protecting groups (Unit 3) work. Conjugate (Michael) addition is the special case treated in Unit 2.

Orientation across these additions is always read the same way: identify the intermediate of the first step and put the first bond where it leaves the most stable intermediate.

1.13 Rearrangement reactions

A rearrangement moves a group or a bond within a molecule to give a skeletal isomer. The syllabus grouping is by the atom to which the key group migrates.

Carbon to carbon migrations:

- **Wagner-Meerwein rearrangement:** a 1,2-alkyl shift to an adjacent carbocation. The migrating group moves with its bonding electron pair into the empty p orbital, which must align with the C-C bond. It rationalises ring expansions and contractions in terpene chemistry and the behaviour of bicyclic systems such as camphene and isoborneol.
- **Pinacol rearrangement:** a vicinal diol in acid loses water from one carbon and the group on the neighbouring carbon shifts as the carbonyl forms. The group that migrates is the one best able to support positive charge in the transition state (aryl migrates well), and the carbon that loses water is the one giving the more stable cation. Pinacol itself gives pinacolone.
- **Wolff rearrangement:** an alpha-diazoketone loses nitrogen on heating, irradiation or silver oxide catalysis and the alkyl group shifts to the electron deficient carbon, giving a ketene, which water, alcohols or amines capture as the one carbon homologated acid, ester or amide. This is the last step of the Arndt-Eistert homologation (with diazomethane, Unit 3).

Carbon to nitrogen migrations (through electron deficient nitrogen):

- **Hofmann rearrangement:** a primary amide with bromine and alkali gives an amine with one carbon fewer. The N-bromoamide anion rearranges as the alkyl group migrates to nitrogen and bromide leaves, giving an isocyanate, which hydrolyses to the amine. Migration occurs with retention at the migrating carbon, and crossover experiments show it is intramolecular.
- **Curtius rearrangement:** an acyl azide on heating loses nitrogen and rearranges to the isocyanate through an acyl nitrene like transition state (section 1.6). Because the acid is converted to the azide through its chloride, the sequence acid to amine with loss of the carbonyl carbon is a standard, mild route to amino drug intermediates. The Lossen rearrangement of hydroxamic acids and the Schmidt reaction of acids with hydrazoic acid are the same family.

Carbon to oxygen migration:

- **Baeyer-Villiger oxidation:** a peracid converts a ketone into an ester by inserting oxygen beside the carbonyl; the group that migrates to oxygen is the one better able to bear partial positive charge (tertiary > secondary > aryl > primary > methyl). It is treated in full in Unit 2.
- **Dakin oxidation:** the phenolic variant, in which an ortho or para hydroxy aryl ketone is converted by alkaline peroxide into a catechol or quinol derivative, showing the same migration to oxygen.

Rearrangements are proved intramolecular by crossover experiments (section 1.8) and their synthetic value is that they rebuild skeletons that direct bond formation cannot reach: ring expansions, contracted amines and homologated acids.

1.14 Chemistry of enolates

An **enolate** is the conjugate base of a carbonyl compound formed by removing an alpha proton: the negative charge is shared between the alpha carbon and the carbonyl oxygen, and the two resonance forms explain why enolates can react at carbon or at oxygen. Carbon attack is the synthetically important mode with most electrophiles.

Formation. The alpha protons of simple ketones and esters have pKa values around 20 to 25, so a base must be chosen with care:

- **Strong, hindered bases** such as lithium diisopropylamide (LDA) in THF at low temperature remove the proton completely and irreversibly, giving the kinetic enolate: deprotonation at the less substituted alpha carbon, because that proton is removed fastest.
- **Weaker bases or protic conditions** give only a small equilibrium concentration of enolate, but that is enough when the enolate is trapped productively, as in the aldol reaction; equilibration then favours the more substituted, thermodynamic enolate.
- **1,3-Dicarbonyl compounds** (pKa about 9 to 13) form enolates fully with alkoxides, which is why ethyl acetoacetate and diethyl malonate are the classic alkylating nucleophiles of the acetoacetic ester and malonic ester syntheses, closed by hydrolysis and decarboxylation.

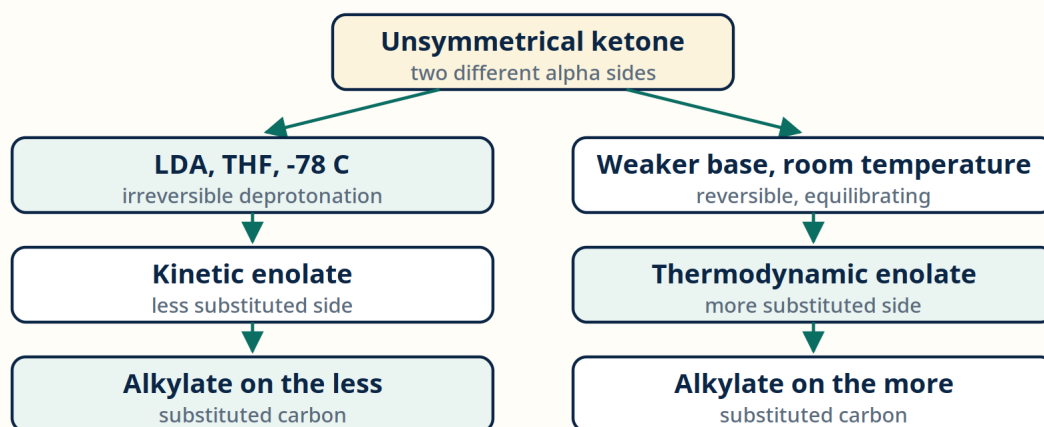
Regio and stereochemistry. Unsymmetrical ketones can give two enolates; low temperature and LDA give the kinetic (less substituted) enolate, while conditions allowing equilibration give the thermodynamic (more substituted) one. Enolate geometry (E or Z, set by the base, solvent and metal) carries through into aldol diastereoselectivity, the basis of boron enolate methodology.

Reactions of enolates:

- **Alkylation:** SN2 attack on methyl, primary and allylic halides. Limitations: secondary halides invite elimination, and O-alkylation can intrude with very reactive electrophiles.
- **Acylation and the Claisen condensation:** an ester enolate attacks another ester carbonyl; the Dieckmann variant is intramolecular (Unit 2).
- **Aldol addition and condensation:** an enolate attacks an aldehyde or ketone carbonyl, giving beta-hydroxy carbonyl compounds that dehydrate to enones.
- **Michael addition:** enolates add conjugately to alpha,beta-unsaturated carbonyl compounds (Unit 2).
- **Halogenation:** enols and enolates react with halogens at the alpha position; under basic conditions polyhalogenation follows, ending in the haloform reaction for methyl ketones.

Enolates are the thread joining this subject: they are the nucleophile in the Mannich, Dieckmann and Michael reactions of Unit 2, they are protected and unmasked in Unit 3 strategies, and in Unit 5 the disconnection of a 1,3-difunctional compound is read directly as an enolate bond construction.

Kinetic vs Thermodynamic Enolate Control



Same ketone, two products: base and temperature decide which enolate forms.

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Figure: Kinetic versus thermodynamic enolate control. Base strength and temperature choose the enolate, and the enolate chooses the product.

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