ANDERSON SERANGOON JUNIOR COLLEGE

2025 H3 CHEMISTRY

FURTHER ORGANIC MECHANISMS

Learning Outcomes

Nucleophilic Substitution

Students should be able to:

(a) explain how the relative rate of nucleophilic substitution is affected by the nature of the
  (i) nucleophile
  (ii) leaving group
  (iii) substituents

(b) describe and compare the mechanisms and kinetics of S_N1 and S_N2 reactions, in terms of
  (i) the energy profile and rate law, including steady state approximation in S_N1 [mathematical treatment of steady state is **not** required]
  (ii) stereochemistry, including ion pair interactions in S_N1
  (iii) substituents effects

(c) explain the factors affecting competition between S_N1 and S_N2 mechanisms [solvent effects are **not** required]

Elimination

Students should be able to:

(a) understand and apply the following concepts to the study of elimination reactions:
  (i) *syn*– and *anti*– elimination; and its effect on stereoselectivity
  (ii) regioselectivity: Zaitsev (thermodynamic) and Hofmann (kinetic) product(s)

(b) describe and compare the mechanisms and kinetics of E1 and E2 reactions, in terms of
  (i) the energy profile and rate law
  (ii) regioselectivity

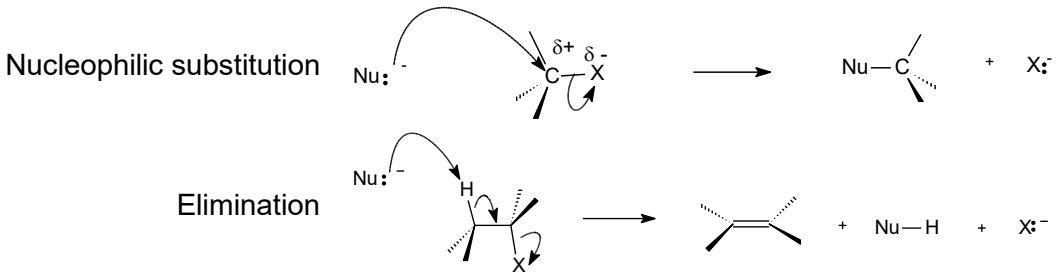
(c) explain the E2/S_N2 competition, in terms of
  (i) substrate effects
  (ii) base effects

References

1. Organic Chemistry, 7th edition, McMurry J (2008)
2. Organic Chemistry, J Clayden
3. Organic Chemistry as a Second Language, David R. Klein
4. *ChemgaPedia*

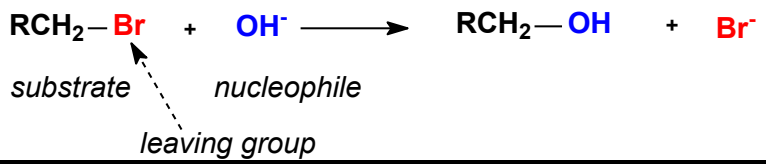
1. Nucleophilic substitution of halogenoalkanes

$C^{\delta+}–X^{\delta-}$ covalent bond is polar in halogenoalkane, thus the carbon is electron–deficient and attracts nucleophiles to undergo two main types of reactions: either **substitution** of the halogen or undergo base–induced **elimination** to yield an alkene.



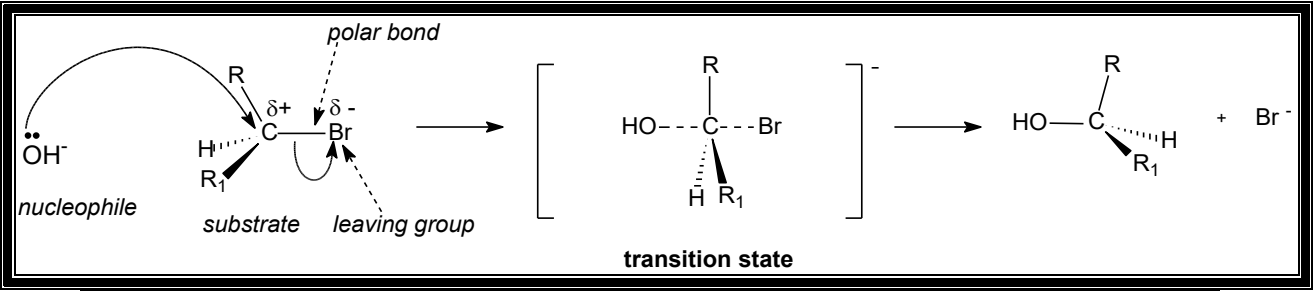
Depending on the substrates and conditions used, a mixture of both substitution and elimination products can form.

Reagents and conditions: **NaOH(aq)**, heat under reflux

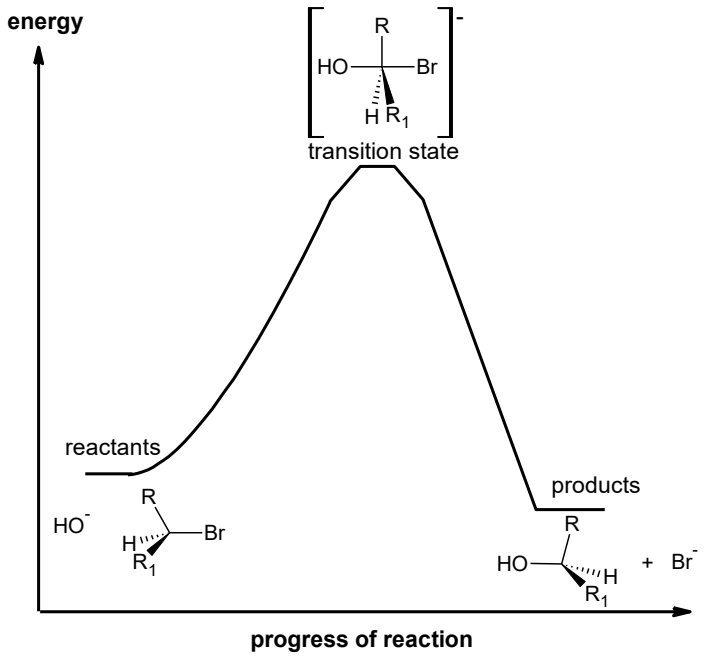


1.1 S_N2 mechanism

This is a **one–step** reaction mechanism. The nucleophile, $OH^–$, approaches the substrate, RCH_2CH_2Br, from a direction **opposite the leaving group**, in this case Br. The C–O bond is partially formed and the C–Br bond is partially broken in the transition state. The transition state contains a pentavalent carbon atom.



A **transition state** is an unstable species that has very short lifetime and thus cannot be isolated. It lies in an energy maximum.

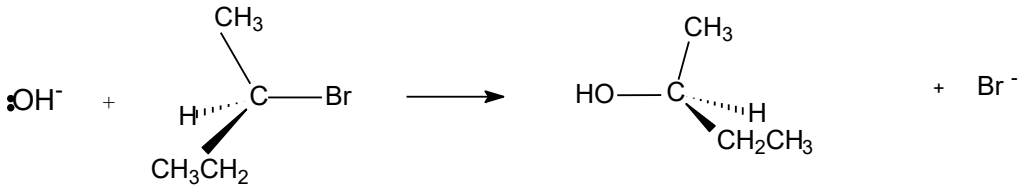


Since it is a bimolecular, **one–step** reaction, one nucleophile (OH^- ion) and one substrate molecule (RCH_2Br) are involved in the **rate–determining step**. Thus the rate equation is:

rate = k [Nu][substrate]

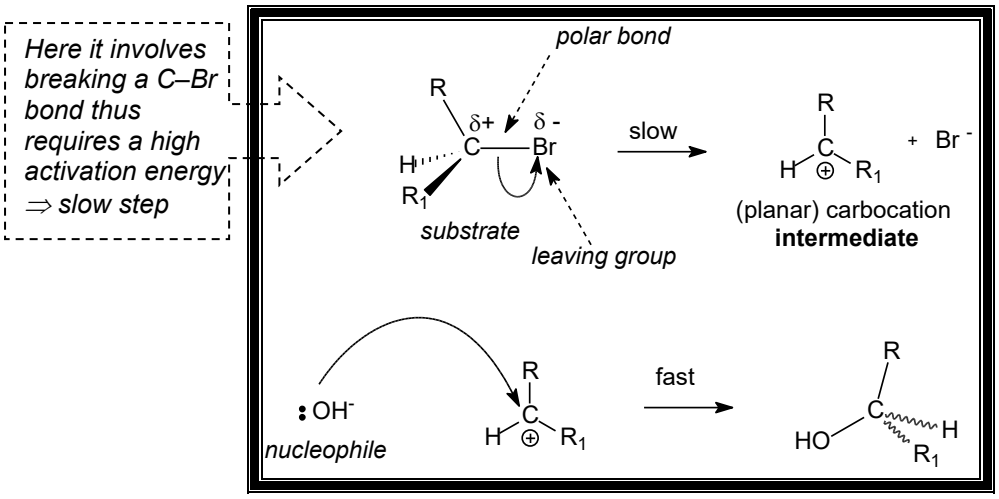
This nucleophilic substitution is known as **S_N2** (Bimolecular Nucleophilic substitution).

Should the bromoalkane be an enantiopure sample, say *R* isomer only, the product formed will be the *S* isomer or vice versa. In other words, there will be **an inversion of configuration**. Thus from the products, we can also deduce whether this is a S_N2 reaction.



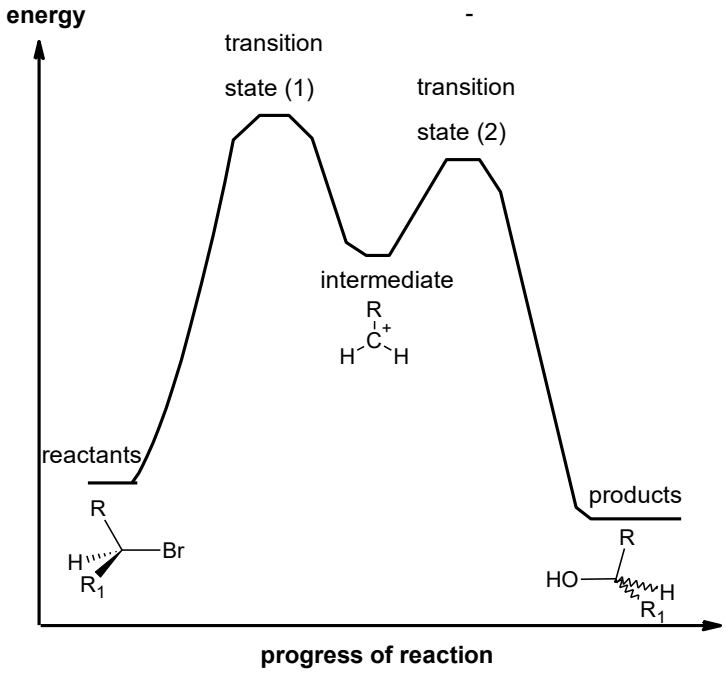
(R)-2-bromobutane **(S)**-butan-2-ol

1.2 S_N1 mechanism



This is a **two–step** reaction mechanism with a carbocation **intermediate** formed.

An **intermediate** can be a molecule, ion or free radical that is formed in one step of a reaction mechanism and consumed in a subsequent step.
Like transition states, intermediates are unstable. However, intermediates can be observed with special instruments. An intermediate is more stable than a transition states and thus lies in a shallow "trough" between two transition states, a local energy minima.

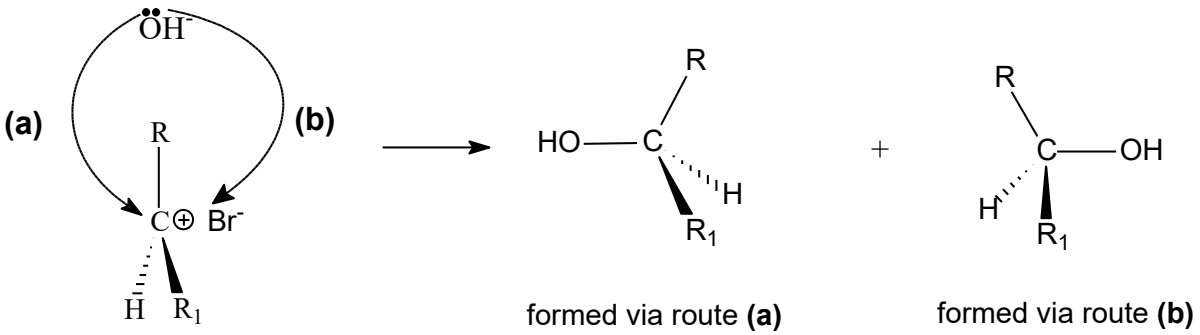


Only one RCH_2Br substrate molecule is involved in the **rate–determining step**.

Thus, the rate equation is:
rate = k [substrate]

This nucleophilic substitution is known as **S_N1** (Unimolecular Nucleophilic substitution).

Since a **planar carbocation** is formed in the intermediate, there are two possible approaches the nucleophile can "attack", forming two stereochemically different isomers.



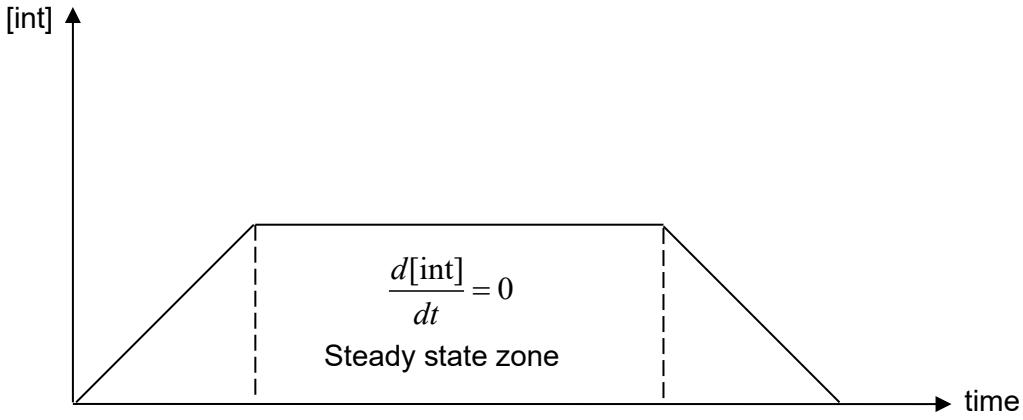
Should the bromoalkane be an enantiopure sample, say *R* isomer only, the product formed will be a mixture of both *R* and *S* isomers.

Steady State Approximation

What is Steady Sate Approximation?

One or more intermediates can be formed in multi–step reaction. An intermediate does not appear in the rate equation, as its concentration cannot be measured. Hence, it is necessary to express the concentration of intermediates in terms of concentration of species that can be measured.

If the concentrations of the intermediates is a lot smaller than that of the reactants, the rate of change of concentration of the intermediates will also be very small, and that can be assumed to be zero. In other words, the concentration of an intermediate remains low (but not zero) and constant for most of the reaction as shown by the following graph:



Steady State Approximation in S_N1

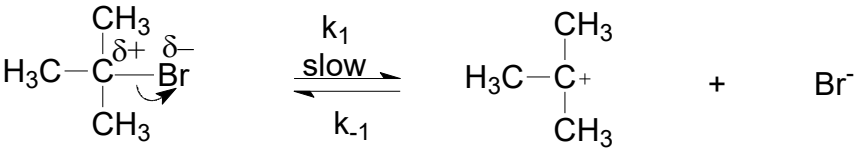
The steady state approximation can be applied to S_N1 mechanism. The carbocation concentration is low because it is consumed in the second step as quickly as it is generated.

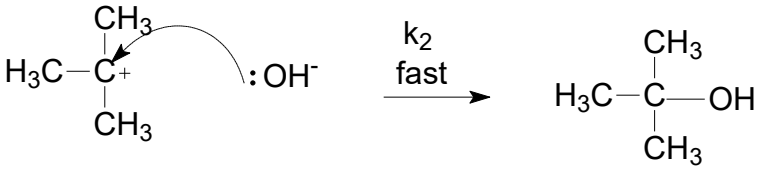
The first step in S_N1 is the slow step with a high activation energy. The second step has a lower activation energy as it involves the collision of two oppositely charged particles. The nucleophile (OH^-) is also in a much higher concentration than the carbocation and hence it is able to react immediately with the carbocation formed.

It is also assumed that the rate of the backward reaction in Step 1 is a lot slower than that between the carbocation and OH^- as
(1) OH^- is a better nucleophile
(2) $[OH^-] >> [Br^-]$

Energetically, the C–Br bond broken is also weaker than the C–O bond formed.

S_N1 Mechanism:





Applying steady state approximation,

$$\frac{d[carbocation]}{dt} = 0$$

$$k_1[RX] - k_2[carbocation][OH^-] - k_{-1}[carbocation][Br^-] = 0$$

Rearranging,

$$k_1[RX] = k_2[carbocation][OH^-] + k_{-1}[carbocation][Br^-]$$

$$[carbocation] = \frac{k_1[RX]}{k_2[OH^-] + k_{-1}[Br^-]}$$

Assuming that $k_2[OH^-] >> k_{-1}[Br^-]$

$$[carbocation] = \frac{k_1[RX]}{k_2[OH^-]}$$

$$\text{Rate of formation of product}$$

$$= k_2[carbocation][OH^-]$$

$$= k_2 \frac{k_1[RX]}{k_2[OH^-]}[OH^-]$$

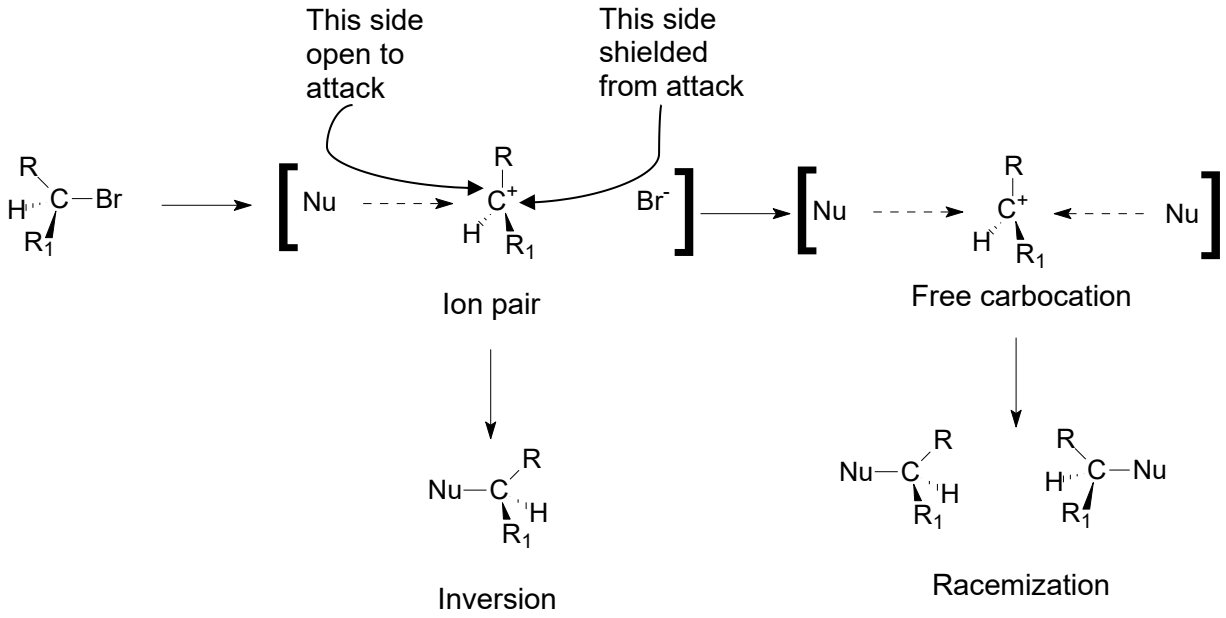
$$= k_1[RX]$$

For your information

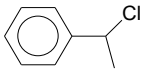
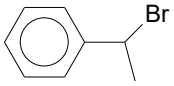
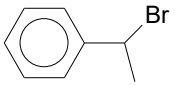
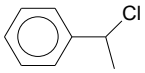
Ion Pair Interactions in S_N1

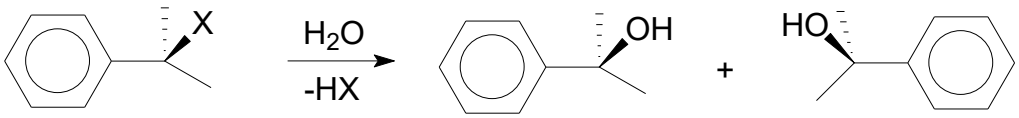
The predication that S_N1 reactions on enantiomerically pure substrates should lead to racemic products is exactly what is observed. Surprisingly, though, few S_N1 occur with complete racemization. Most give a minor excess of inversion.

The reason for the lack of complete racemization is due to **ion pairs interactions**. Dissociation of the substrate occurs to give a structure in which the two ions are still loosely associated and in which the carbocation is effectively shielded from nucleophilic attack on one side by the departing anion. Hence, if a certain amount of substitution occurs before the two ions fully diffuse apart, then a net inversion of configuration will be observed.



Example:

In the hydrolysis of  vs  , a racemic mixture is formed when  reacts but inversion is favored for  .



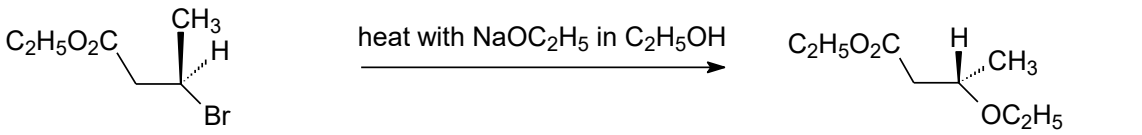
If X = Br	50%	50%
If X = Cl	41%	59%

Chloride is a comparatively weaker leaving group than bromide. The higher charge density of chloride ion causes it to be attracted to the carbocation even after cleavage, especially in non–polar solvents which prevent complete solvation and separation of ions. This causes steric hindrance on one face, favouring 'back–side' attack. Furthermore, the C–Cl bond is stronger than the C–Br bond and requires more energy to break. The nucleophile can attack from the back–side before the C–Cl bond is completely broken.

Exercise 1

Suggest explanations for the observed stereochemistries of the following reactions based on different reaction mechanisms.

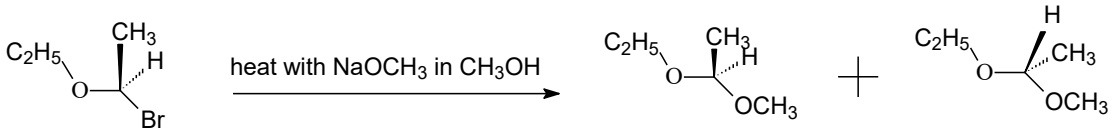
(a)



Ethyl (R)-2-bromopropanoate

Ethyl (S)-2-ethoxypropanoate
(100%)

(b)

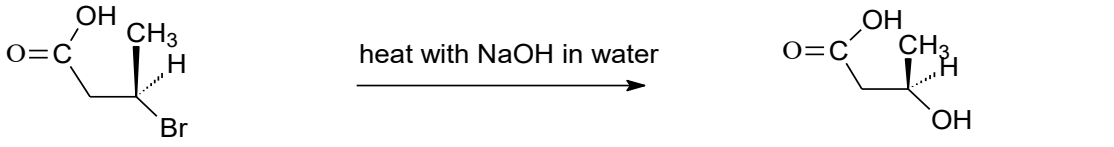


(R)-1-bromo-1-ethoxyethane

(50%)

(50%)

(c)



(R)-2-bromopropanoic acid

(R)-2-hydroxypropanoic acid
(100%)

[Hint: How many inversions do you think the molecule has undergone?]

2 Factors affecting rate of nucleophilic substitution

2.1 Nature of nucleophiles

A **nucleophile** must be a *Lewis base* in that it must have at least **one unshared (lone) pair of electrons** which can "attack" an electron–deficient carbon. It can be a neutral species like H_2O or a negatively charged species like CN^-, OH^- etc.

A **strong nucleophile** has a **high tendency to share an electron pair** to form a covalent bond with carbon, thus increases the rate of S_N2 reactions.

The strength of nucleophiles depends on many factors, including **basicity** and **sterics**.

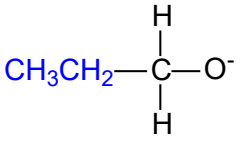
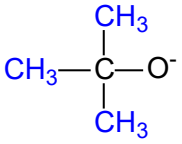
(a) Basicity

A stronger base has a higher tendency to share an electron pair to form a covalent bond with a proton. As such, nucleophilicity parallels basicity. The conjugate bases of weak acids are generally better nucleophiles.

Stronger base (stronger nucleophile)	Weaker conjugate acid (weaker nucleophile)
NH_2^-	NH_3
OH^-	H_2O
F^-	HF

(b) Steric effects of substituents in nucleophile

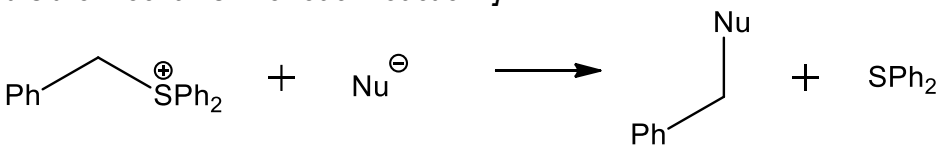
A small (less bulky) nucleophile is able to approach the substrate more easily, resulting in a faster reaction.

Stronger nucleophile	Weaker nucleophile
	

Exercise 2

The rates of a series of nucleophilic substitution reactions were determined experimentally. Suggest an explanation for the observations.

[Hint: What is the mechanism for each reaction?]



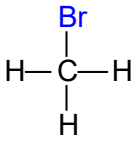
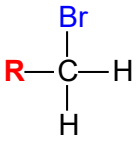
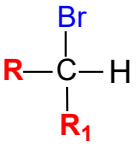
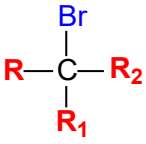
Nu^-	CH_3COO^-	Cl^-	PhO^-	^-OH	PhS^-
Rel rate	3.9	4.0	3.8	74	107

Note:
The nature of the attacking nucleophile plays a major role in S_N2 reaction but not in S_N1 reaction. S_N1 reaction occur through a rate–limiting step in which the added nucleophile has no kinetics role.

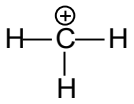
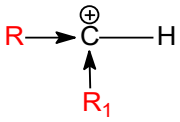
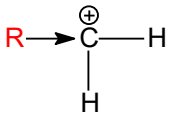
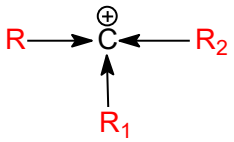
2.2 Inductive effect

In S_N1: Rate increases if there are electron–donating groups attached to the electron deficient ($\delta+$) carbon.

Types of bromoalkanes:

Methyl	Primary	Secondary	Tertiary
			
Relative rate of **S_N1** reaction	*1 (slowest)*	*26*	6×10^{7} *(fastest)*

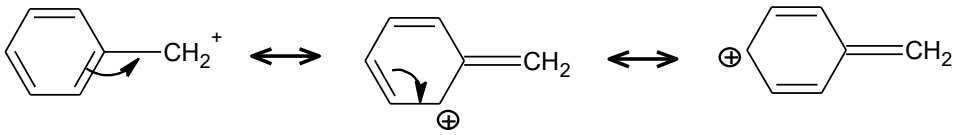
Reason:
It will yield the most stable carbocation.

Least stable carbocation ⟶ Most stable carbocation			
Methyl	Primary	Secondary	Tertiary
			

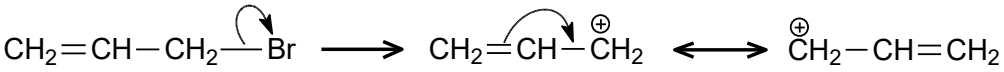
The more highly substituted the carbocation (i.e. the more alkyl groups there are), the **more electron–donating inductive effect** (*through sigma bonds*) to help **disperse the positive charge** of the carbocation intermediate.

FYI only
The same is true for donation of π electrons into the empty p–orbitals on carbocations, creating **resonance–stabilised allylic and benzyl carbocations**. Any spreading of the positive charge stabilises the carbocation.

Benzyl carbocation:

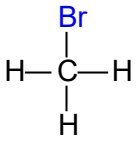
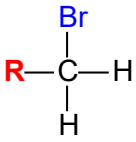
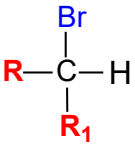
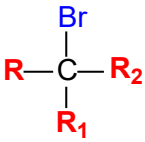


Allylic carbocation:



2.3 *Steric effect*

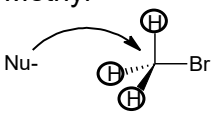
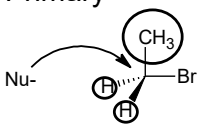
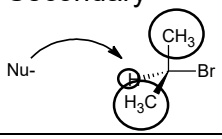
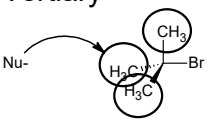
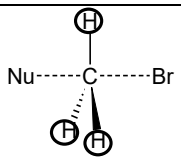
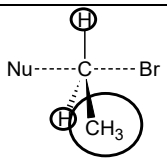
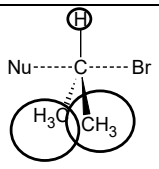
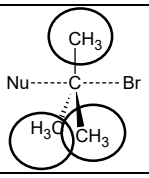
In S_N2: Rate decreases if substrate has big bulky substituents attached to the electron deficient (δ+) carbon.

Methyl	Primary	Secondary	Tertiary
			
Relative rate of **S_N2** reaction	*1 (fastest)*	1×10^{-2}	1×10^{-3} *(slowest)*

Reasons:

1 The bulky substituents shield the δ+ carbon from the attacking nucleophile. This is known as **steric hindrance**.

2 The transition state is more "crowded" and higher in energy. This leads to higher activation energy, thus slowing down the reaction.

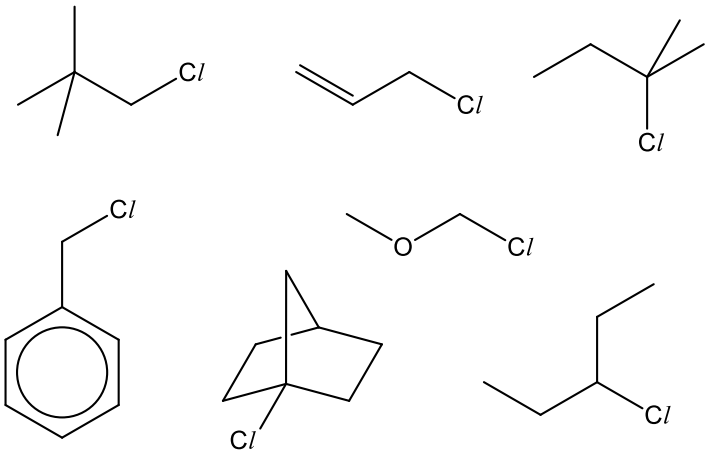
Least hindered substrate ⟶ Most hindered substrate			
Methyl	Primary	Secondary	Tertiary
			
Least "crowded" transition state		Most "crowded" transition state	
			

In summary,

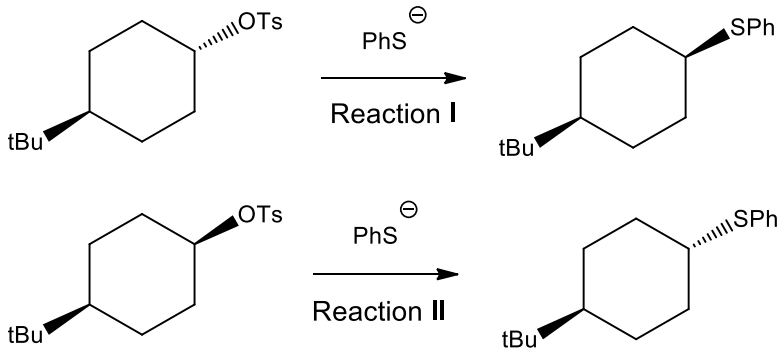
Steric effects of substituents on substrate on rate of:	
S_N1	**S_N2**
• **Rate increases** if the substrates have big bulky substituents on the δ+ carbon • Depends on stability of carbocation formed	• **Rate decreases** if substrate has big bulky substituents on the δ+ carbon • Depends on extent of steric hindrance

Exercise 3

(a) Rank the 7 compounds in order of S_N1 reactivity. Explain your reasoning.



(b) It is found that reaction **I** occurs 31 times slower than reaction **II**. With reference to the lowest–energy conformations of both reactants, suggest an explanation for the observations.

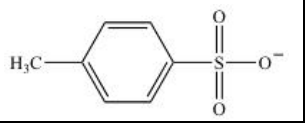


2.4 Nature of leaving group

A good leaving group has little tendency to share an electron pair to form a covalent bond with carbon or it **can stabilise the extra electron density** it receives as it leaves the δ+ carbon.

The leaving group is expelled with a negative charge in most nucleophilic substitution reactions, hence the **best leaving groups** are those that **best stabilize the negative charge**. Furthermore, because the **stability of an anion is inversely related to its basicity**, the best leaving groups should be the **weakest bases**.

The greater the extent of charge stabilisation by the leaving group, the more stable the transition state, the faster the reaction. The weaker the basicity, the better the leaving group.

Weaker base (good leaving group)	**Stronger bases (poor leaving groups)**
I^- Br^- TsO^- ("tosylate") 	Cl^- F^- NH_2^- OH^- OR^-

In both S_N1 and S_N2: Rate increases if leaving group is stabilised.

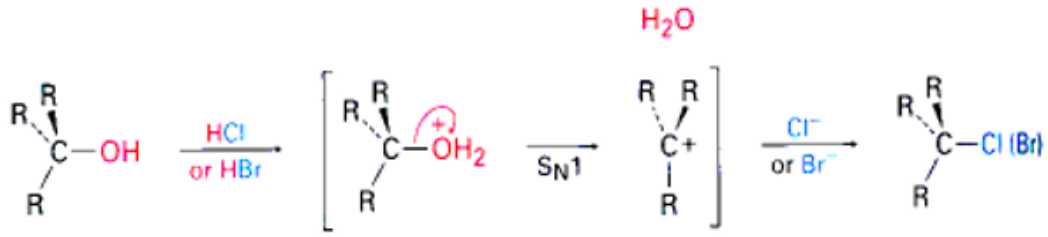
Exercise 4

Which is a better leaving group, NH_3 or H_2O?

S_N1 is usually carried out under acidic conditions:
One of the common ways to convert a poor leaving group into better leaving group is by **protonation**, i.e. decreasing electron density.

E.g. In the reaction of alcohol with HBr (acidic) to yield halogenoalkane, water can act as a leaving group.

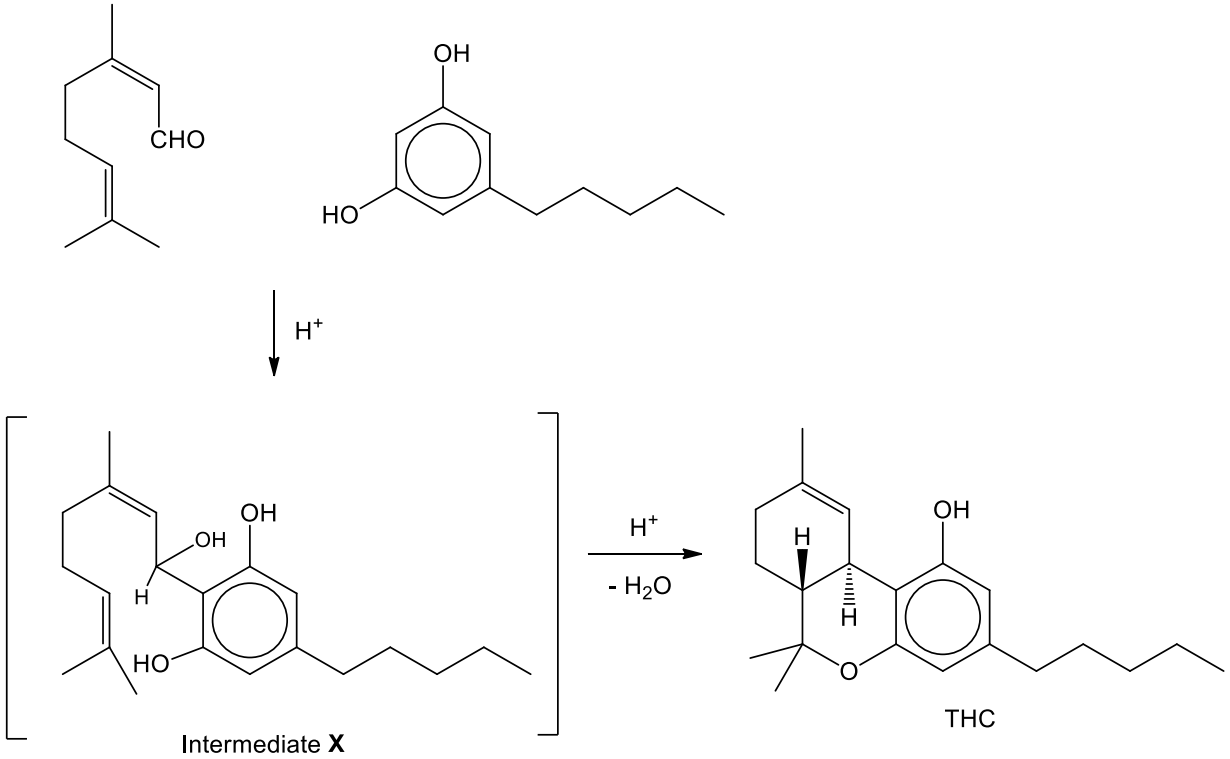
In the acidic medium, the –OH group in alcohol can be protonated and then loses a water molecule to generate a carbocation. Reaction of the carbocation then yields the alkyl halide.



3˚ alcohol | carbocation | alkyl chloride or bromide

Exercise 5 [N10/6(c)]

Tetrahydrocannabinol, THC, is a major ingredient of marijuana. The last step in the synthesis of THC is given below.



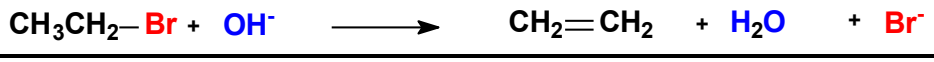
(i) Intermediate **X** is protonated and then loses water to form a carbocation. Suggest a structure for this carbocation, and hence suggest a mechanism for the production of THC from **X**. [3]

(ii) Explain why this synthesis produces a mixture of the two enantiomers of THC. [1]

3 Elimination of HX from halogenoalkane

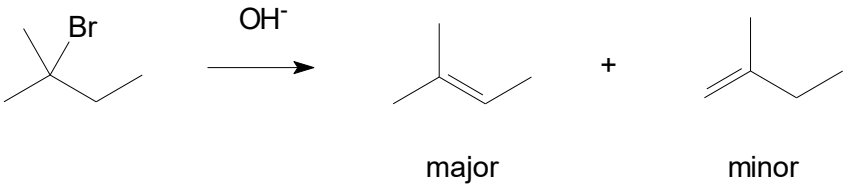
3.1 Introduction

Reagents and conditions: **KOH in ethanol**, heat under reflux
Example:



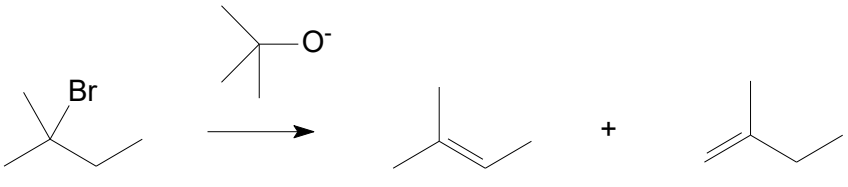
Elimination reactions are more complex than substitution reactions. There is, for example, the problem of *regiochemistry**. *What products result by loss of HX from an unsymmetrical halide?* In fact, most elimination reactions almost always yield a mixture of products.

According to **Zaitsev's rule** (or **Saytzeff's rule**), base–induced elimination reactions generally form larger amount of the **more highly substituted alkene products** (or alkenes with more alkyl substituents on the C=C double bond carbons), which are more **stable** (i.e. *thermodynamic control* products).



The major **Zaitsev** product is stabilised by the interaction between the empty π^* orbitals of the C=C double bond with the filled orbitals of parallel C–H and C–C bonds of substituent groups. An increase in substitution increases the C–H and C–C bonds, thereby increasing the stability of the product.

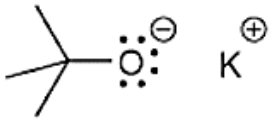
However, there are exceptions in which the Zaitsev product (the more highly substituted alkene) is not the major product. For example, if the reaction above is performed with a **sterically hindered base** (rather than using OH^- as the base), then the major product will be the less highly substituted alkene (i.e. *kinetic control* products).



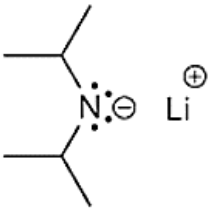
In this case, the **Hofmann** product is the major product when a sterically hindered base is used. This case illustrates an important concept: *The regiochemical outcome of an E2 reaction can often be controlled by carefully choosing the base.*

*Regioselective: Any process that favours bond formation at a particular atom over other possible atoms. The description of a reaction's regioselectivity (or the absence of regioselectivity) is called the reaction's regiochemistry.

Below are two examples of sterically hindered bases.



potassium *tert*–butoxide
(*t*–BuOK)



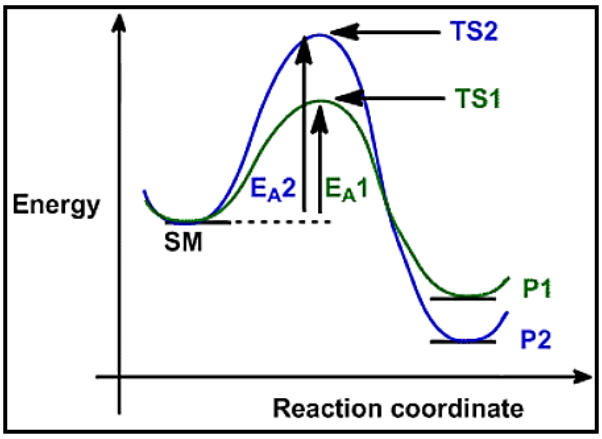
lithium diisopropylamide
(LDA)

3.2 Kinetic and Thermodynamic Control

The potential outcome of a reaction is usually influenced by two factors:

1. the relative stability of the products (i.e. thermodynamic factors)
2. the rate of product formation (i.e. kinetic factors)

The following simple reaction coordinate diagram provides a basis for the key issues about kinetic and thermodynamic control:



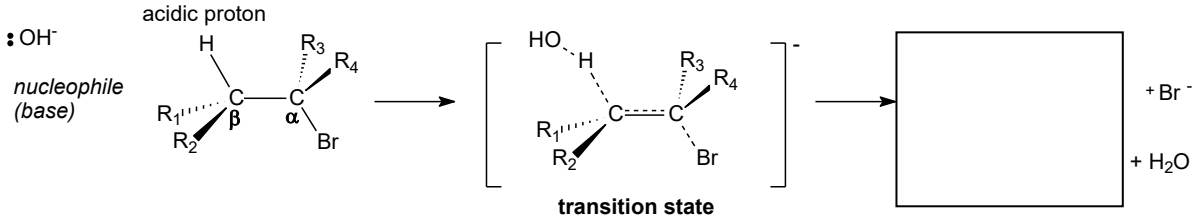
Consider the case where a starting material (SM) can react in a similar manner to give two different products, P1 and P2 via different pathways represented by green and blue curves.

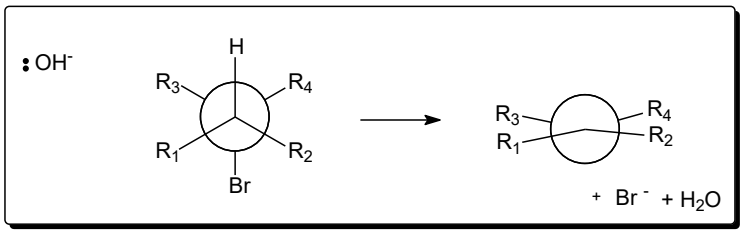
Reaction 1 via pathway 1 (green) generates product 1 (P1) via transition state 1 (TS1). This will be the faster reaction since it has a lower energy (more stable) transition state, and therefore a lower activation energy (E_A1). Therefore, product 1, P1 is the kinetic product (the product that forms the fastest).

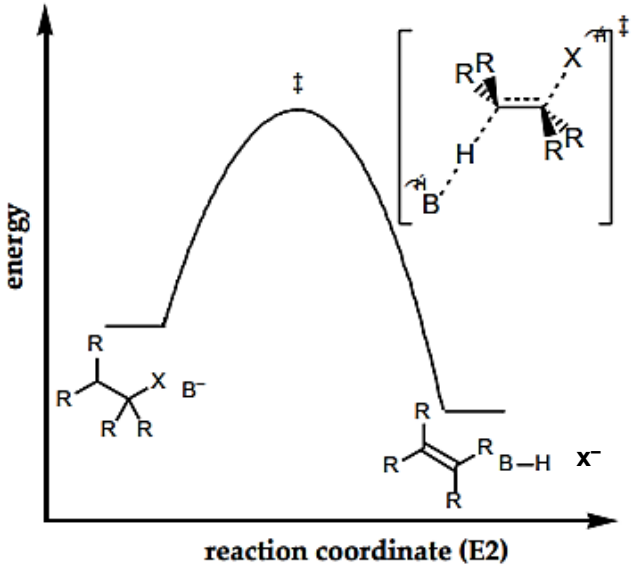
Reaction 2 via pathway 2 (blue) generates product 2 (P2) via transition state 2 (TS2). P2 is the more stable product since P2 is at a lower energy than P1. Therefore, P2 is the thermodynamic product (the more stable product).

3.3 *E2 mechanism*

Like S_N2, it is a one–step reaction. The base abstracts a H atom (proton) on the adjacent carbon (β–carbon). At the same time, an alkene double bond begins to form and Br begins to leave in the transition state. Once the C–H bond is broken, the products are formed.







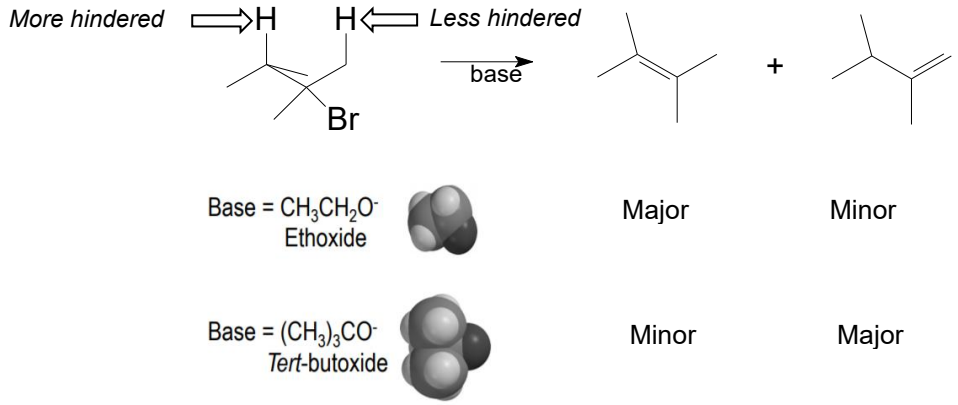
Since it is bimolecular, **one–step** reaction, it implies one nucleophile (OH^- ion) and one substrate molecule are involved in the **one and only rate–determining step**. Thus, the rate equation is:

rate = ____

3.4 The Regiochemical Outcome of an E2 Reaction

Zaitsev elimination: Major E2 product is **more highly substituted** alkene.

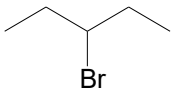
Hofmann elimination: Major E2 product is **less highly substituted** alkene **if a sterically hindered base is used**.



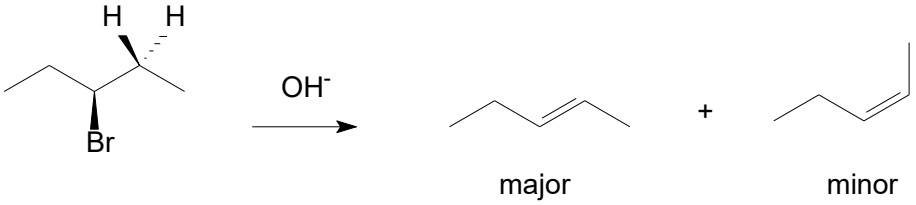
A sterically hindered base abstracts a "less hindered" H atom (proton), leading towards the less highly substituted, kinetically controlled alkene.

3.5 The Stereochemical Outcome of an E2 Reaction

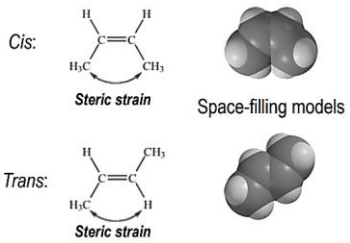
The examples on page 16 focused on *regiochemistry*. We will now focus our attention on *stereochemistry*. For example, consider performing an E2 reaction with the following substrate:



The elimination of HBr produces the same result and so regiochemistry is not an issue in this case. In this case, stereochemistry is relevant as two stereoisomeric alkenes are possible:

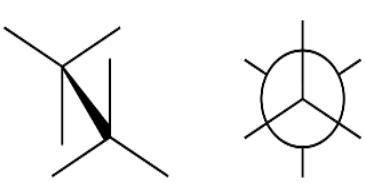


Notice that the adjacent carbon (β–carbon) has two "different" H atoms (protons). In such a case, both stereoisomers (*cis* and *trans*) are produced, but the *trans* product predominates.
General rule: *Trans* alkene isomer is more stable than *cis* alkene isomer due to less steric strain.

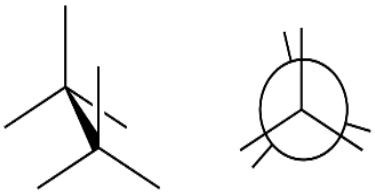


This specific example is said to be *stereoselective*, because the substrate produces two stereoisomers in *unequal* amounts.

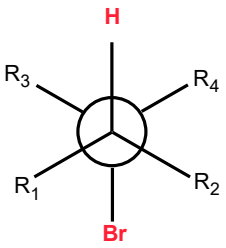
Now, let us consider a case when the adjacent carbon (β–carbon) contains only one H atom (proton). In such a case, only one product is formed. The reaction is said to be *stereospecific* (rather than stereoselective. In other words, E2 elimination of a HX always occurs in an **anti–periplanar geometry**. *Periplanar* means the four reacting atoms (H, 2C, Br) lie in the same plane and *anti* means **H and Br are on opposite sides of the molecule** to adopt a more stable **staggered conformation** (as compared to eclipsed conformation).



Staggered conformation



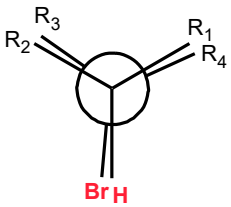
Eclipsed conformation



anti-periplanar geometry:

H, Br on **opposite** sides of molecule

Staggered conformation (more stable)

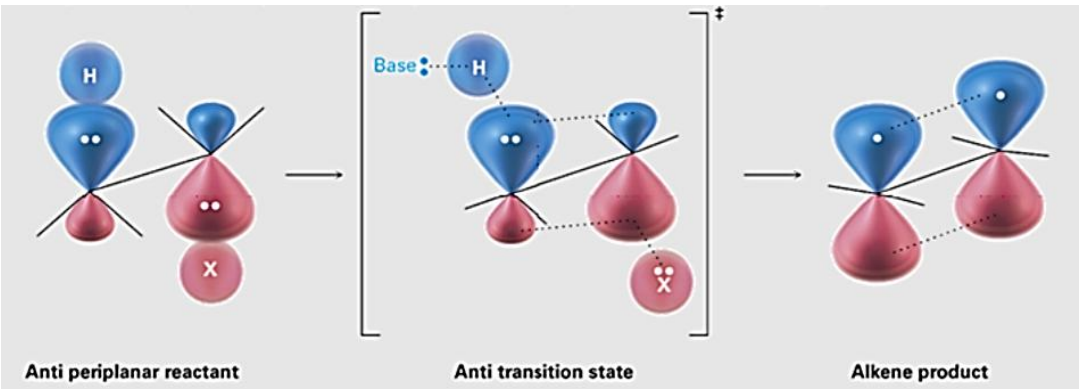


syn-periplanar geometry:

H, Br on **same** sides of molecule

Eclipsed conformation (less stable)

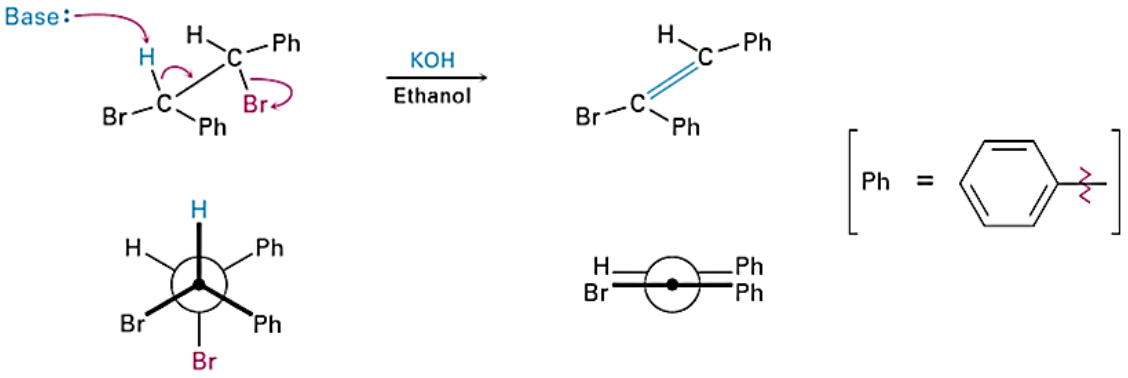
The sp^3 σ orbitals in the reactant C–H and C–X bonds must overlap and become *p* π orbitals in the alkene product; there must also be some overlap in the transition state. This can occur most easily if all the orbitals are in the same plane to begin with, i.e. if they are periplanar.



Similar to S_N2 reactions with 180° geometry, where an electron pair from the incoming nucleophile pushes out the leaving group on the **opposite** side of the molecule. In an E2 reaction, an electron pair from a neighboring C–H bond pushes out the leaving group on the **opposite** side of the molecule.

S_N2 reaction (backside attack) **E2 reaction (anti periplanar)**

Example: *meso*–1,2–dibromo–1,2–diphenylethane undergoes E2 elimination on treatment with a base to give only the *E* alkene. None of the isomeric *Z* alkene is formed because the transition state leading to the *Z* alkene would have to have syn–periplanar geometry and would thus be higher in energy (less stable).



***meso*-1,2-Dibromo-1,2-diphenylethane (anti periplanar geometry)** **(*E*)-1-Bromo-1,2-diphenylethylene**

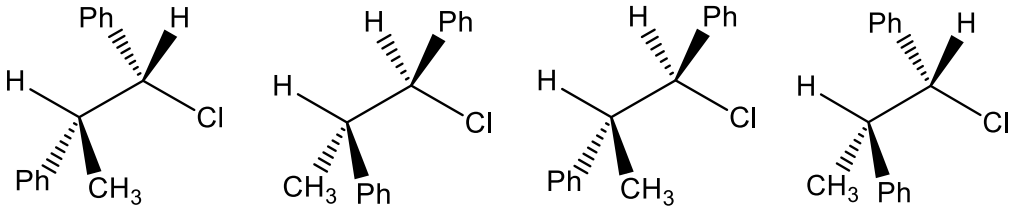
Exercise 6

The molecule of 1–chloro–1,2–diphenylpropane contains two chiral centres. Draw the Newman projections of possible stereoisomers of the above molecule.

When separate mixtures of the two racemates (i.e. [RS + SR] and [RR + SS]) are treated with base sodium ethoxide in ethanol, a pure sample of *E*–1–methyl–1,2–diphenylethene is produced from one racemate and pure *Z*–1–methyl–1,2–diphenylethene is formed from the other racemate.

$$C_6H_5CH(CH_3)—CHClC_6H_5 \xrightarrow{C_2H_5ONa} C_6H_5C(CH_3)=CHC_6H_5 \quad (+C_2H_5OH + NaCl)$$

By drawing out the mechanism using your Newman projection formulae, explain which racemate gives which alkene isomer.

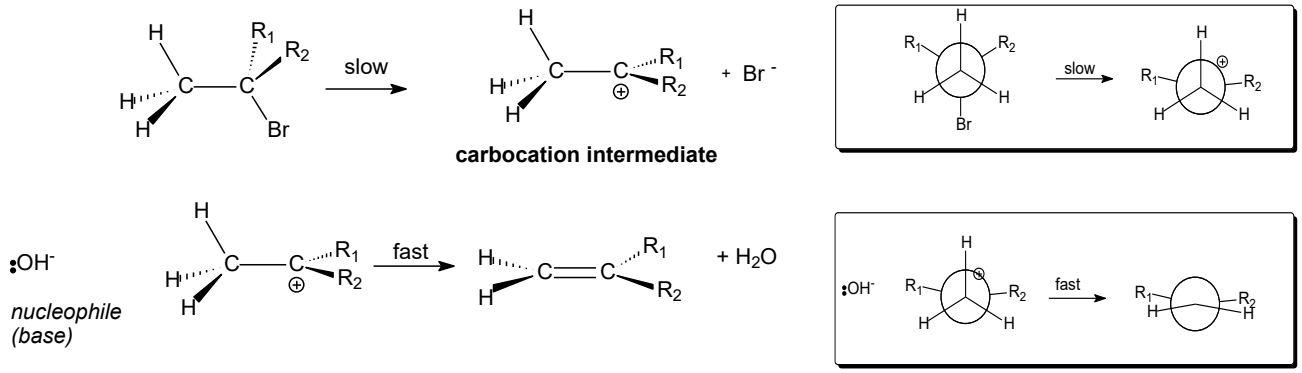


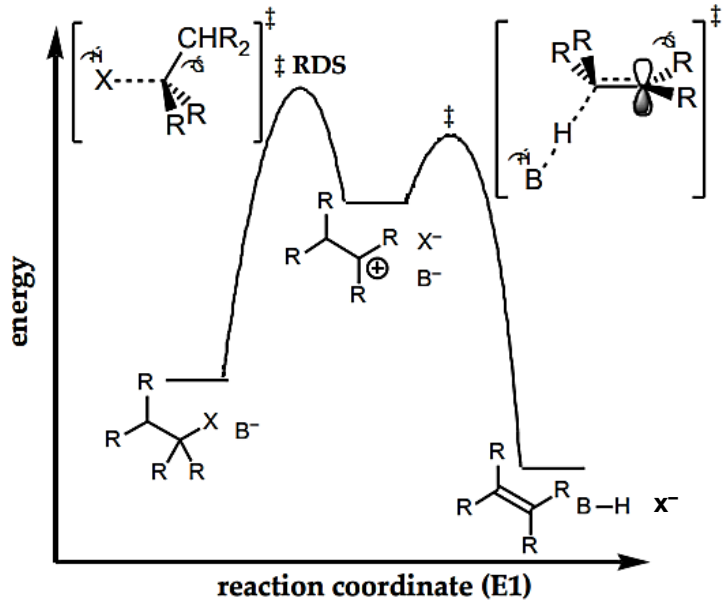
RR SS RS SR

Note: enantiomers give one isomeric alkene, while the diastereomers give the other isomeric alkene.

3.6 E1 mechanism

Like S_N1, this is a **two–step** reaction mechanism with a carbocation **intermediate** formed, with the dissociation of the C–X bond. The dissociation requires high activation energy and thus it is a slow step.





Since only the substrate molecule is involved in the **rate–determining step**, the rate equation is:

rate = ____

3.7 The Regiochemical Outcome of an E1 Reaction

When two regio–isomers can be formed, the major product is the more thermodynamically stable product (i.e. Zaitsev product).

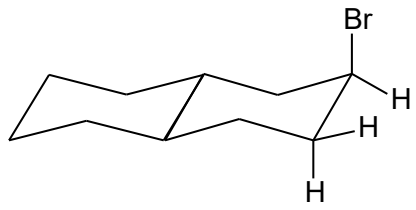
3.8 The Stereochemical Outcome of an E1 Reaction

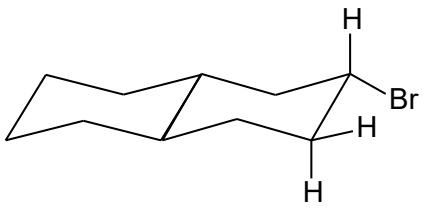
Unlike E2 reactions, E1 reactions are not stereospecific. That is, they do not require anti–periplanarity in order for the reaction to occur, as the halide and the H atom are lost in separate steps. Nevertheless, E1 reactions are stereoselective. In other words, when *cis* and *trans* products are possible, we generally observe a preference for formation of the *trans* stereoisomer.

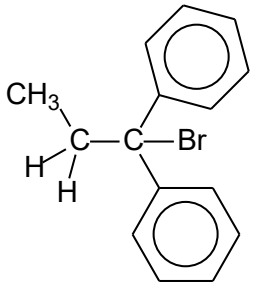
When both the *E*– and *Z*– isomers can be formed, the stereoselectivity of the product can be predicted based on the relatively stability of the transition state and the alkene formed.

Exercise 7

Predict whether the following compounds will eliminate HBr by an E1 or an E2 mechanism. Give reasons for your answers.
Hint: ring-flip is not possible for the 2nd compound







E2 versus E1

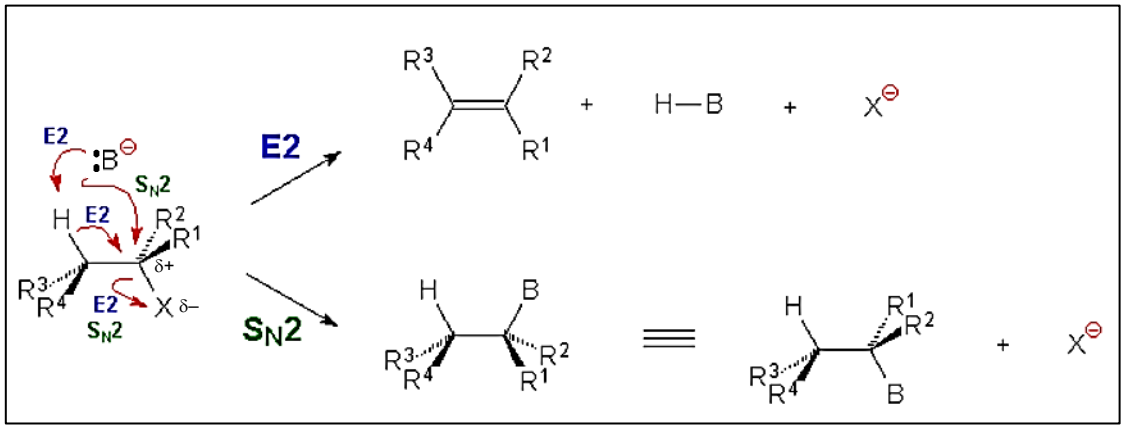
	E2	E1
Mechanism:	Concerted (One–step)	Two–step
Rate Equation:	Rate = *k* [RX][Base]	Rate = *k* [RX]
Stereochemistry:	Stereospecific (anti–periplanar TS)	Not stereospecific
Product Ratio:	Zaitsev Product: The most highly substituted alkene usually predominates. Hofmann Product: Use of a sterically hindered base will result in formation of the least substituted alkene.	

3.9 E2/S_N2 Competition

In E2/S_N2 competition, the issue of which mechanism outdoes the other is dependent upon the **rates** of the competing reactions. The product ratio (E2/S_N2) is dependent on the quotient of the reaction rates of the two mechanistic alternatives. When a reaction is to be controlled in order for a specific mechanism to be followed, the quotient must be as large or as small as possible, respectively. Due to this, the energy of the desired mechanism's transition state should be minimised as much as possible without lowering the energy of the transition state of the competing mechanism, as well. This is because the reaction rate is directly correlated with the energy of the transition state.

The energies of the transition states of E2 and S_N2 reactions are influenced by several parameters. The most significant of these in the E2/S_N2 competition are:

- structure of the substrate
- type of base used



Source: ChemgaPedia

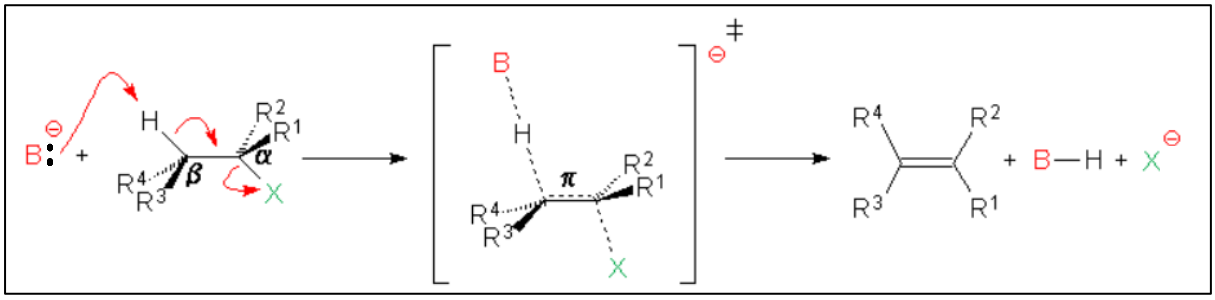
The Role of the Substrate Structure in the E2/S_N2 Competition

The structure of the substrate is one important parameter in E2/S_N2 competition. Depending on the number, size, and the degree of branching of alkyl substituents at the δ+ carbon atom (α–carbon), the reaction rates of E2 and S_N2 reactions are considerably differently influenced by various factors.

The reaction rate of the E2 reaction increases greatly in the order of primary, secondary, tertiary halogenoalkanes, while the reaction rate of S_N2 reactions decreases in the same order.

In an E2 reaction, the base abstracts a proton from the periphery and not from inside the substrate molecule. Therefore, in an E2 reaction, the base and the substrate molecule do not need to approach each other as closely as they would have to in an S_N2 reaction. Steric interactions thus do not influence the reaction rate of E2 reaction very much. In contrast to S_N2 reactions, E2 reactions are even more rapid with an increasing number of alkyl substituents at the δ+ carbon (α–carbon).

In the transition state of the E2 reaction, the bonds of the β hydrogen atom and the halogen atom have already been partially cleaved. In addition, a new π bond between the α–carbon and β–carbon atom has been partially formed. The partially formed double bond in the transition state of the E2 reaction is also stabilised by alkyl substituents. Therefore, the activation energy of the E2 reaction with tertiary halogenoalkanes is much lower than it is with secondary or primary halogenoalkanes. As a result, E2 reactions proceed most rapidly with tertiary halogenoalkanes, while they run slowest with primary halogenoalkanes.



Source: ChemgaPedia

The Role of the Type of Base Used in the E2/S_N2 Competition

The reactants of an E2 reaction are a halogenoalkane with a hydrogen atom in β position and a base. The hydrogen in β position is abstracted as a proton by the base and the halogen (X) leaves the molecule as an anion. Characteristic of the base is a lone electron pair, which may accept a proton. However, due to this lone electron pair, the base is, in addition, a nucleophile. Instead of the abstraction of the hydrogen in β position, in principle a nucleophilic attack by the base on the δ+ carbon may therefore occur. This is the basic prerequisite of the existence of E/SN competition.

In an S_N2 reaction, the nucleophile attacks the δ+ carbon atom inside the molecule. In contrast, the base in an E2 elimination abstracts a proton that is located closer to the periphery of the molecule. **S_N2 reactions are** therefore **influenced by steric limitations to a considerably greater degree than E2 reactions**.

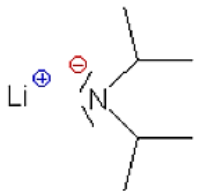
The nucleophilicity of a base in an S_N2 reaction is reduced to a large degree when the base contains massive, sterically demanding substituents. In this case, the reaction rate of the S_N2 reaction is decreased, as the energy of the transition state is increased (hence higher E_a) by

the interactions of the sterically demanding nucleophile (base) and the substrate molecule. In contrast, the energy of the transition state of the E2 reaction is influenced by bulky substituents of the base to a noticeably lesser degree.

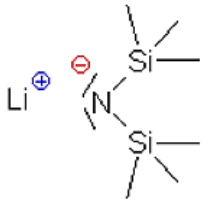
Thus, for the purpose of controlling the E2/S_N2 competition, the following consequences pertaining to the type of base applied result:

Favouring the E2 mechanism

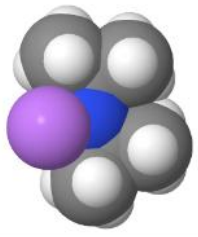
- **In favour of the E2 reaction, as strong as possible, non–nucleophilic bases* with bulky, sterically–demanding substituents are usually used.**
- Some examples of particularly strong, non–nucleophilic bases are the lithium dialkylamides LDA (lithium diisopropylamide) and LHMDS (lithium hexamethyldisilazide).
- When LDA or LHMDS are used, even E2 reactions with primary and secondary halogenoalkanes may be achieved. This is exceptional, as in these cases the S_N2 reaction is normally preferred over the E2 reaction.

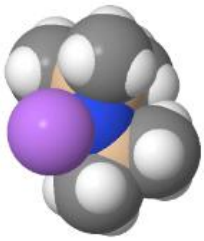


LDA



LHMDS

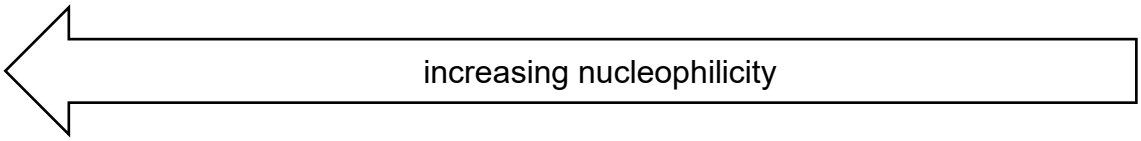




Favouring the S_N2 mechanism

- In order to favour the S_N2 reaction and largely prevent the E2 reaction, the base used must not be too strong. As basicity increases, nucleophilicity generally increases, as well. This is due to the fact that these two properties are both correlated with the availability of lone, non–bonding electron pairs. However, the basicity usually increases to a higher degree than the nucleophilicity does – that is, with increasing basicity the E2 reaction continuously exceeds the S_N2 reaction more and more. This effect is observed even the base is not bulky and sterically demanding. However, it is larger in connection with such a base.
- S_N2 reactions without any considerable E2 reactions as side reactions can, therefore, only be obtained with good nucleophiles that show a basicity that is as low as possible. Such bases are, for example, anions such as hydrogensulphide (HS^-), alkyl sulphides (RS^-), iodide (I^-), and cyanide (CN^-).

**As the name suggests, a non–nucleophilic base is a sterically hindered organic base that is a poor nucleophile.*



$HS^- > RS^- > ArS^- > I^- > CN^- > OH^- > N_3^- > Br^- > ArO^- > Cl^- > AcO^- > H_2O$

Nucleophilicity of several weak and moderately strongly basic nucleophiles in S_N2 reactions

General rule: Nucleophiles with a lower basicity than that of the hydroxide anion, OH^-, tend to react with primary and secondary halogenoalkanes, for instance, in an S_N2 reaction, while nucleophiles with a higher basicity than that of the OH^- tend to react in an E2 reaction.

Nucleophilicity trends (compared with basicity)

1. Across a row in the periodic table nucleophilicity (lone pair donation) $C^- > N^- > O^- > F^-$ since increasing electronegativity decreases the lone pair availability. This is the **same order** as for basicity.

2. If one is comparing the same central atom, higher electron density will increase the nucleophilicity,
   e.g. an anion will be a better Nu (lone pair donor) than a neutral atom such as $HO^- > H_2O$. This is the **same order** as for basicity.

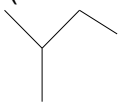
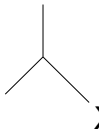
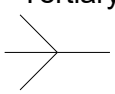
3. Within a group in the periodic table, increasing **polarisation** of the nucleophile as you go down a group enhances the ability to form the new C-X bond and increases the nucleophilicity, so $I^- > Br^- > Cl^- > F^-$. The electron density of larger atoms is more readily distorted *i.e.* polarised, since the electrons are further from the nucleus.
   Note that is the **opposite order** to basicity (acidity increases down a group) where polarisability is much less important for bond formation to the very small proton.

4 Summaries

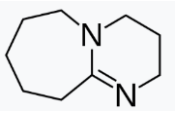
Factors favouring	S_N1	S_N2	E1	E2
Overall kinetics	1st order	2nd order	1st order	2nd order
Substrate	One that forms the most stable carbocation (3°)	Methyl>1°>2° (preferably less sterically hindered)	One that forms the most stable carbocation (3°)	Methyl<1°<2°<3°
Nucleophile/Base	–	Strong, not bulky nucleophile	–	Strong base
Leaving group	A good leaving group			
Stereochemistry of products	Racemisation	Inversion of configuration	Mixture of *cis*/*trans* (or *E*/*Z*) isomers	Either *cis* or *trans*; *either E or Z* isomer predominates

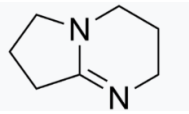
Type of halogenoalkane (substrate)	S_N1	S_N2	E1	E2
Primary halides	Does not occur	Highly favoured	Does not occur	Occurs when strong bases are used
Secondary halides	Particularly with benzylic and allylic halides if weakly basic nucleophiles are used	Occurs in competition with E2 reactions. Predominates if weakly basic or nonbasic nucleophiles are used	Particularly with benzylic and allylic halides if weakly basic nucleophiles are used	Occurs in competition with S_N2 reactions. Predominates if strong bases are used
Tertiary halides	Occurs in competition with E1 reactions	Does not occur	Occurs in competition with S_N1 reactions	Favoured when strong bases are used

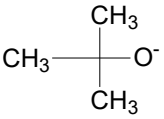
General pattern of reactivity expected from various classes of alkyl halides in reaction with a representative range of nucleophiles (which may behave as bases)

	Poor nucleophile (e.g. H_2O, ROH)	Weakly basic nucleophile (e.g. I^-, RS^-)	Strongly basic, unhindered nucleophile (e.g. RO^-)	Strongly basic, hindered nucleophile (e.g. DBU, DBN, *t*-BuO^-)
Primary (unhindered) 	No reaction	S_N2	S_N2	E2
Primary (hindered) 	No reaction	S_N2	E2	E2
Secondary 	S_N1, E1(slow)	S_N2	E2	E2
Tertiary 	S_N1 or E1	S_N1 or E1	E2	E2

DBU: DBN: *t*-BuO^-:



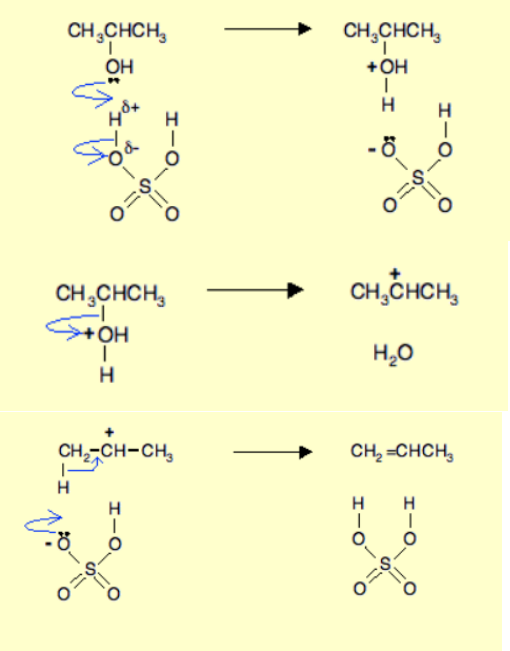




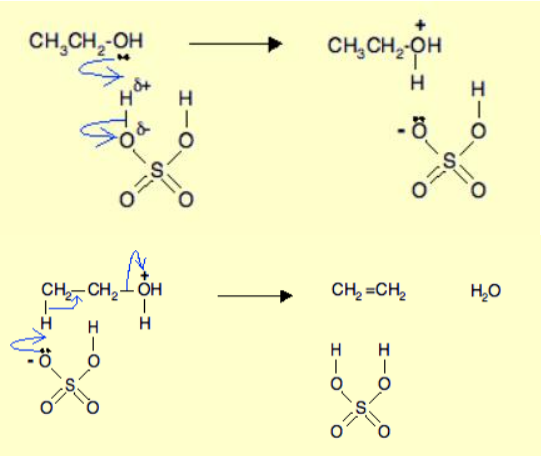
For your information:

The following shows the elimination mechanism for alcohols:

E1:



E2:



Exercise 8 [N12/4(a)]

There are two main routes by which nucleophilic substitution reactions take place, the S_N1 and the S_N2 mechanisms.

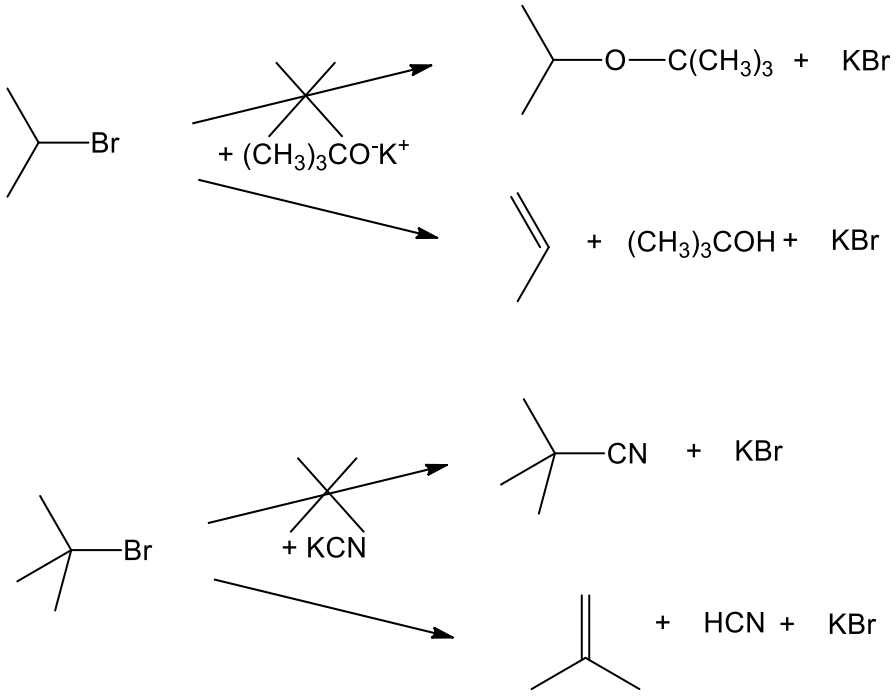
(i) Using bromo–compounds as examples, describe and explain the features of a molecule that would favour the S_N1 mechanism over the S_N2 mechanism. [2]

Features that favour S_N1 over the S_N2

Any two of the following:

- Larger number of electron donating alkyl substituents. These alkyl bromides can form more stable carbocations.
- Allylic or benzylic bromides. These can form resonance-stabilised carbocations.
- Large and bulky substituents surrounding the electron deficient carbon that hinders formation of pentavalent transition state.

(ii) Some reagents that would be expected to undergo nucleophilic substitution reactions cause elimination reactions instead.

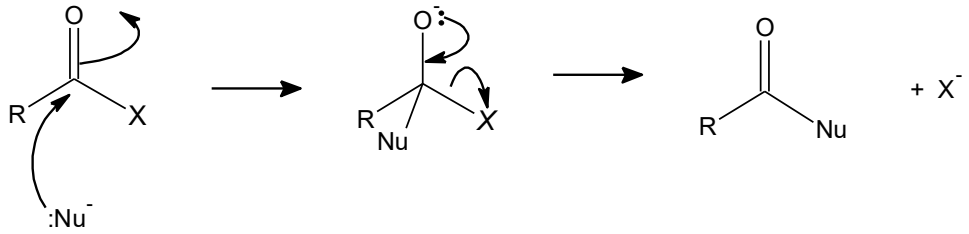


Suggest reasons why the reactions occur in the way shown. [2]

5 Addition-elimination (acid/base-catalysed hydrolysis)

Hydrolysis is a very important reaction in syntheses. Esters and amides undergo both acid- and base- catalysed hydrolysis. Each reaction proceeds via an **addition-elimination mechanism**. It is similar to nucleophilic addition. Esters and amides contain a good leaving group, which will depart with the reformation of the π bond.

Addition-elimination mechanism



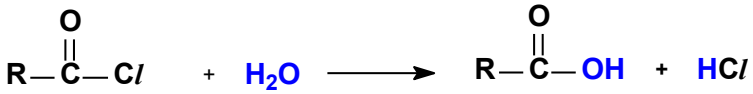
where X is a good leaving group

Acyl chlorides being a reactive compound can be hydrolysed by water. Esters and amides require the presence of acids and bases to catalyse the hydrolysis process.

5.1 Hydrolysis of acyl chlorides

Acyl chlorides

Reagents and conditions : H_2O, room temperature



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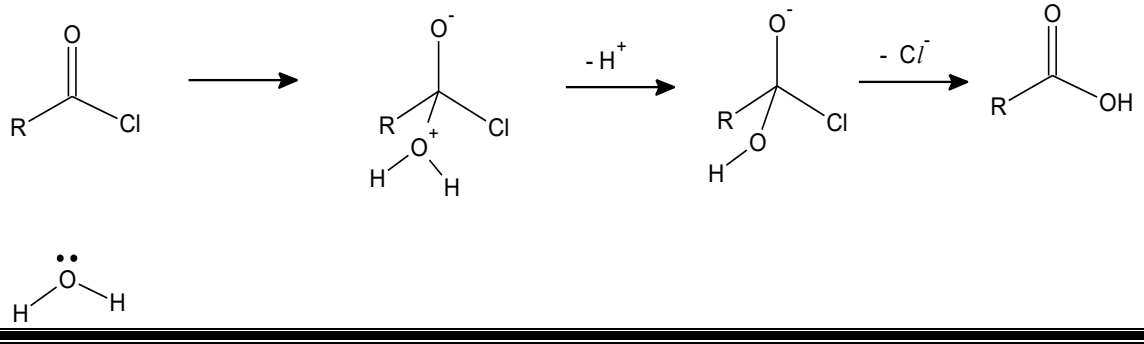
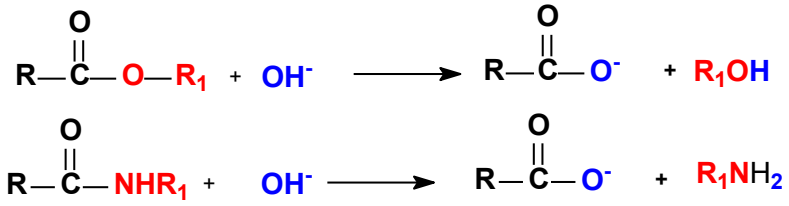


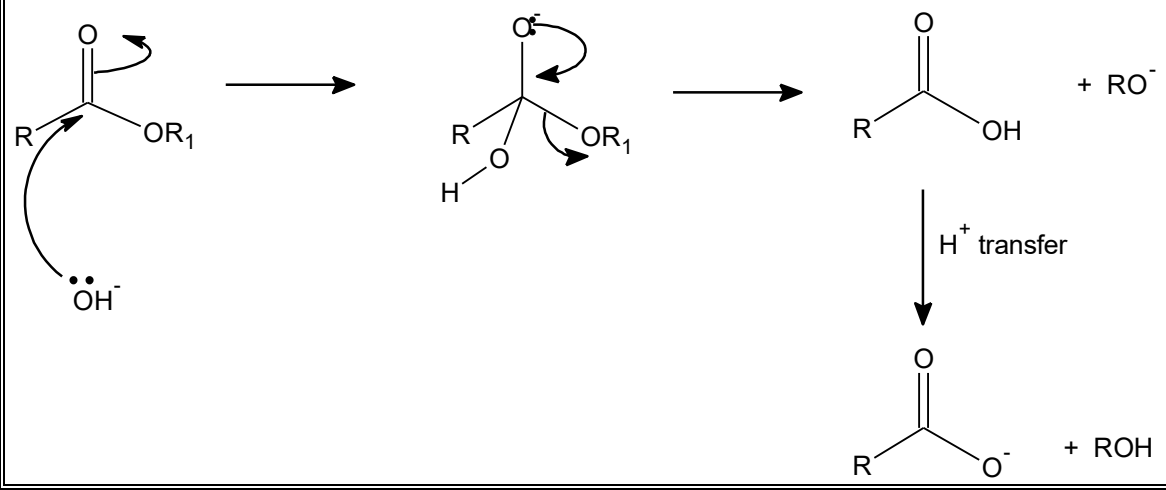
5.2 *Base-catalysed hydrolysis of esters & amides*

Esters & amides

Reagents and conditions: aqueous NaOH, heat



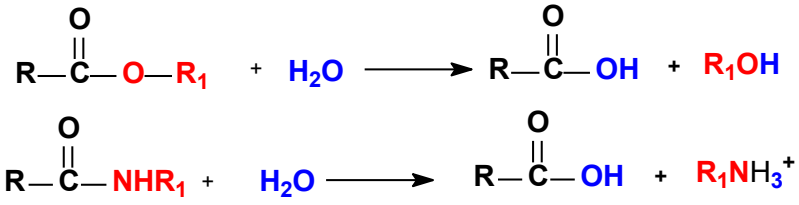
Hydrolysis of esters by aqueous alkali



5.3 *Acid-catalysed hydrolysis of esters & amides*

Esters & amides

Reagents and conditions: aqueous HC*l*, heat

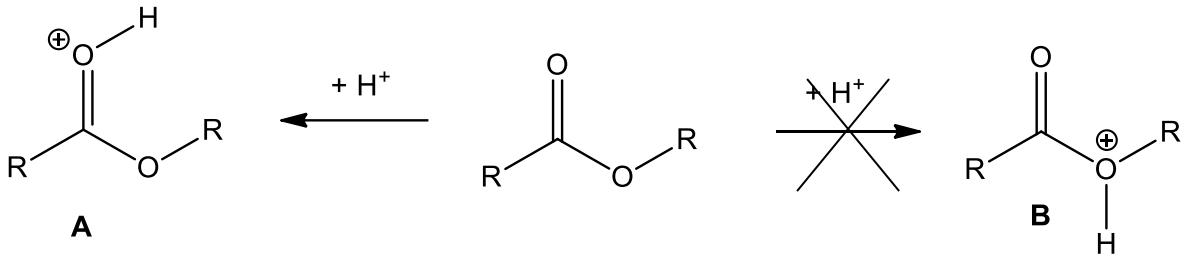


Exercise 9 [N07/4(a)]

Both esters and amides undergo acid-catalysed hydrolysis. The mechanism for the hydrolysis of either functional group involves the following four steps:

- protonation;
- nucleophilic addition of water;
- proton transfer;
- elimination of an alcohol or an amine molecule.

For esters, the protonation that occurs during the first step produces the more stable cation **A** rather than cation **B**.



(i) Suggest why cation **A** is more stable than cation **B**. [1]

(ii) Use the information given above to suggest a mechanism for the following reaction.

$$CH_3CONHCH_3 + H_2O + H^+ \rightarrow CH_3COOH + CH_3NH_3^+$$

[3]