Teacher: DR. SUBHANKAR SARDAR
Class : Semester-2
Paper: C4T: Organic Chemistry
Topic : Substitution and Elimination Reaction

Comments: Read whole the notes thoroughly. This part is very important for final examination.

References:

1) Organic Chemistry by T.W. Graham Solomons, Craig B. Fryhle
2) A Guide book of mechanism in Organic Chemistry by Peter Sykes

temperature and 1 atm pressure.

2) Ethyl bromide (bp 38 °C) and ethyl iodide (bp 72 °C) are both liquids, but ethyl chloride (bp 13 °C) is a gas.

3) The propyl chlorides, propyl bromides, and propyl iodides are all liquids.

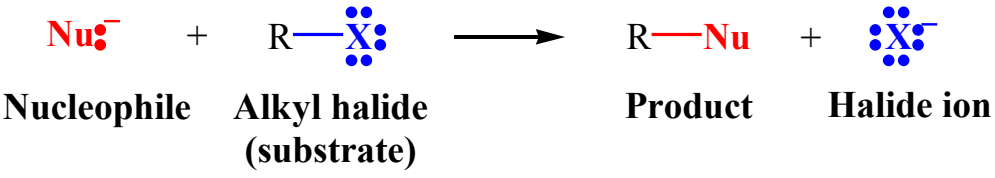
4) In general, higher alkyl chlorides, bromides, and iodides are all liquids and tend to have boiling points near those of alkanes of similar molecular weights.

5) **Polyfluoroalkanes** tend to have **unusually low boiling points**.

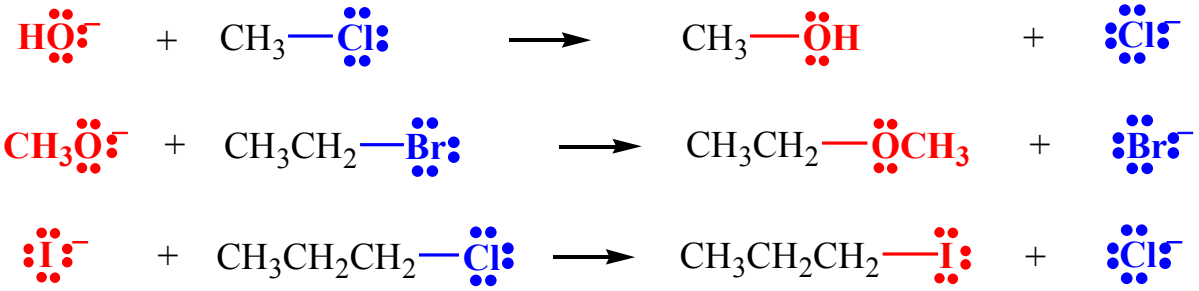
i) Hexafluoroethane boils at −79 °C, even though its molecular weight (MW = 138) is near that of decane (MW = 144; bp 174 °C).

6.3 NUCLEOPHILIC SUBSTITUTION REACTIONS

1. **Nucleophilic Substitution Reactions:**



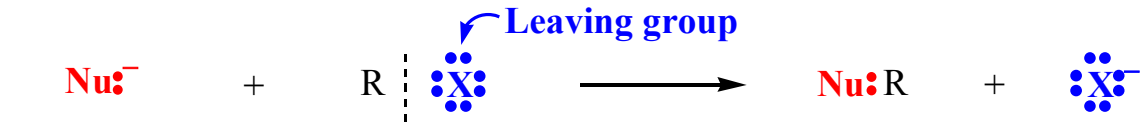
***Examples*:**



2. A **nucleophile**, a species with an **unshared electron pair** (**lone-pair electrons**), reacts with an **alkyl halide** (**substrate**) by replacing the halogen substituent (**leaving group**).

3. In nucleophilic substitution reactions, the C–X bond of the substrate undergoes ***heterolysis***, and the lone-pair electrons of the nucleophile is used to form a new

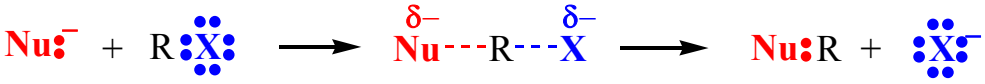
bond to the carbon atom:



Nucleophile **Heterolysis occurs here**

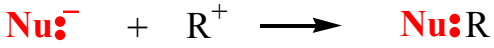
4. **When does the C–X bond break?**

1) Does it break at the same time that the new bond between the nucleophile and the carbon forms?



2) Does the C–X bond break first?

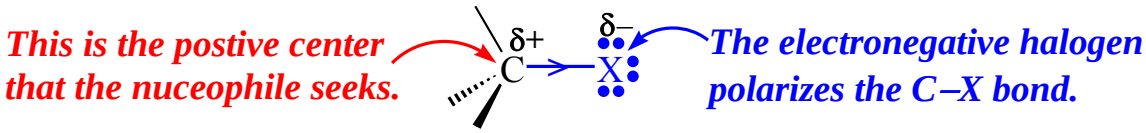
And then



6.4 NUCLEOPHILES

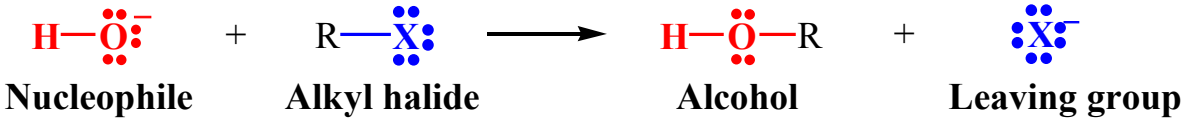
1. A **nucleophile** is a reagent that seeks **positive center**.

1) The word nucleophile comes from ***nucleus***, the positive part of an atom, plus -***phile*** from Greek word ***philos*** meaning to **love**.

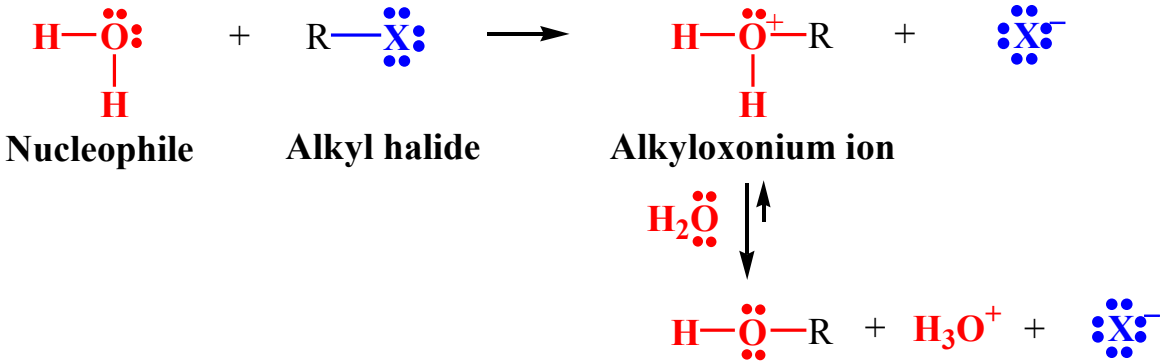


2. A **nucleophile** is any **negative ion** or any **neutral molecule** that has at least **one unshared electron pair**.

1) ***General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion***



2) ***General Reaction for Nucleophilic Substitution of an Alkyl Halide by Water***



i) The first product is an alkyloxonium ion (protonated alcohol) which then loses a proton to a water molecule to form an alcohol.

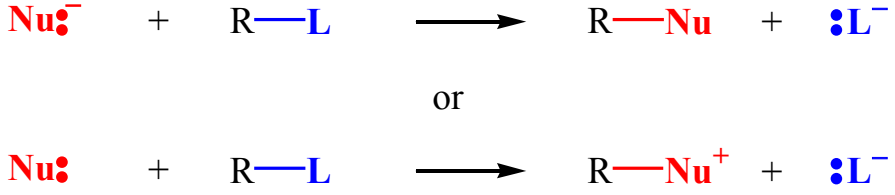
6.5 LEAVING GROUPS

1. ***To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.***

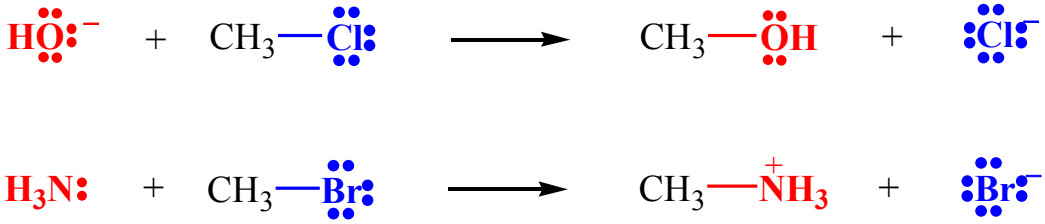
1) In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.

i) Because halide ions are relatively stable and very weak bases, they are good leaving groups.

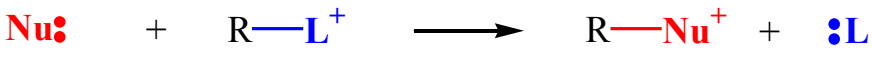
2. ***General equations for nucleophilic substitution reactions*:**



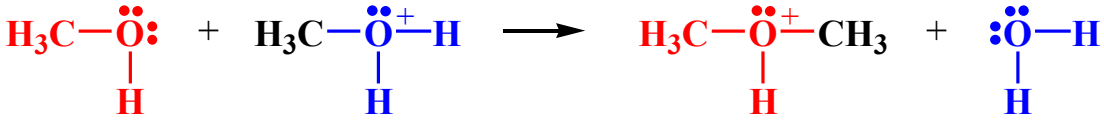
***Specific Examples*:**



3. ***Nucleophilic substitution reactions where the substarte bears a formal positive charge*:**



***Specific Example*:**



6.6 KINETICS OF A NUCLEOPHILIC SUBSTITUTION REACTION: AN S_N2 REACTION

1. **Kinetics:** the relationship between reaction rate and reagent concentration
2. The reaction between methyl chloride and hydroxide ion in aqueous solution:

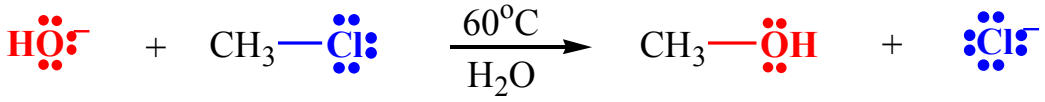


Table 6.3 Rate Study of Reaction of $CHCl_3$ with OH^- at 60 °C

Experimental Number	Initial $[CH_3Cl]$	Initial $[OH^-]$	Initial (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

1) The rate of the reaction can be determined experimentally by measuring the rate at which **methyl chloride** or **hydroxide ion** ***disappears*** from the solution, or the

rate at which **methanol** or **chloride ion** ***appears*** in the solution.

2) The ***initial rate*** of the reaction is measured.

2. The rate of the reaction depends on the concentration of **methyl chloride** and the concentration of **hydroxide ion**.

1) **Rate equation:** Rate $\propto$ $[CH_3Cl]$ $[OH^-]$ $\Rightarrow$ Rate = k $[CH_3Cl]$ $[OH^-]$

i) k is the rate constant.

2) Rate = k $[A]^a$ $[B]^b$

i) The overall order of a reaction is equal to the sum of the exponents a and b.

ii) For example: Rate = k $[A]^2$ $[B]$

The reaction is second order with respect to [A], first order wirth respect to [B], and third order overall.

3. **Reaction order:**

1) The reaction is **second order overall**.

2) The reaction is **first order** with respect to **methyl chloride** and **first order** with respect to **hydroxide ion**.

4. For the reaction to take place a **hydroxide ion** and **methyl chloride** molecule **must collide**.

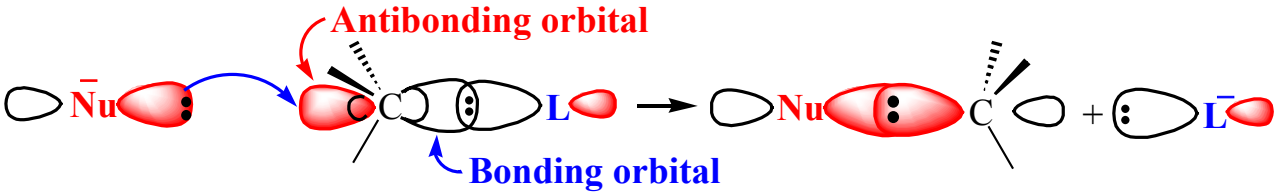
1) The reaction is **bimolecular** — two species are involved in the **rate-determining step**.

3) The **S_N2 reaction: Substitution, Nucleophilic, bimolecular**.

6.7 A MECHANISM FOR THE S_N2 REACTION

1. The **mechanism** for **S_N2 reaction:**

1) Proposed by Edward D. Hughes and Sir Christopher Ingold (the University College, London) in 1937.



2) The **nucleophile** attacks the carbon bearing the **leaving group** from the **back side**.

i) The orbital that contains the **electron pair** of the **nucleophile** begins to **overlap** with an **empty** (**antibonding**) **orbital** of the carbon bearing the **leaving group**.

ii) The bond between the **nucleophile** and the carbon atom is **forming**, and the bond between the carbon atom and the **leaving group** is **breaking**.

iii) The formation of the bond between the **nucleophile** and the carbon atom provides most of the energy necessary to break the bond between the carbon atom and the **leaving group**.

2. **Walden inversion:**

1) The **configuration** of the carbon atom becomes **inverted** during S_N2 reaction.

2) The first observation of such an inversion was made by the Latvian chemist Paul Walden in 1896.

3. **Transition state:**

1) The **transition state** is a fleeting arrangement of the atoms in which the nucleophile and the leaving group are both bonded to the carbon atom undergoing attack.

2) Because the **transition state** involves both the nucleophile and the substrate, it accounts for the observed second-order reaction rate.

3) Because bond formation and bond breaking occur simultaneously in a single transition state, the S_N2 reaction is a ***concerted reaction***.

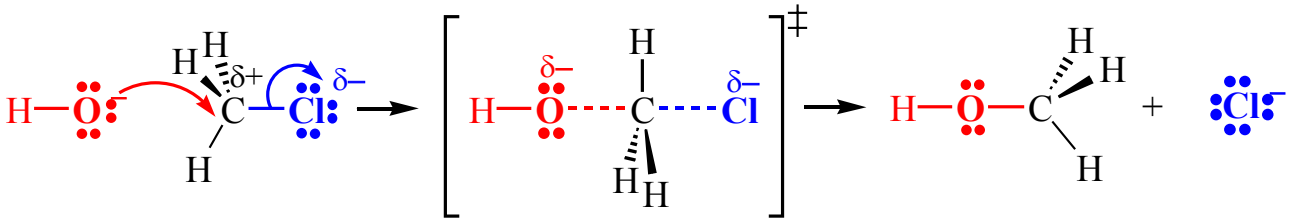
4) Transition state lasts only as long as the time required for one molecular vibration, about 10^{-12} s.

A Mechanism for the S_N2 Reaction

Reaction:

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^-$$

Mechanism:



Transtion state

The negative hydroxide ion pushes a pair of electrons into the partially positive carbon from the back side. The chlorine begins to move away with the pair of electrons that have bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride has departed. The configuration of the carbon has inverted.

6.8 TRANSIITION STATE THEORY: FREE-ENERGY DIAGRAMS

1. **Exergonic** and **endergonic**:
   1) A reaction that proceeds with a **negative free-energy change** is **exergonic**.
   2) A reaction that proceeds with a **positive free-energy change** is **endergonic**.

2. The reaction between CH_3Cl and HO^- in aqueous solution is highly **exergonic**.
   1) At 60 °C (333 K), $\Delta G° = -100$ kJ mol^{-1} (–23.9 Kcal mol^{-1}).
   2) The reaction is also **exothermic**, $\Delta H° = -75$ kJ mol^{-1}.

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^- \qquad \Delta G° = -100 \text{ kJ mol}^{-1}$$

3. The **equilibrium constant** for the reaction is extremely large:

$$\Delta G^\circ = -2.303\ RT \log K_{eq} \Rightarrow \log K_{eq} = \frac{-\Delta G^o}{2.303\ RT}$$

$$\log K_{eq} = \frac{-\Delta G^o}{2.303\ RT} = \frac{-(-100\ \text{kJ mol}^{-1})}{2.303 \times 0.00831\ \text{kJ K}^{-1}\ \text{mol}^{-1} \times 333\ \text{K}} = 15.7$$

$$K_{eq} = 5.0 \times 10^{15}$$

$$R = 0.08206\ \text{L atm mol}^{-1}\ \text{K}^{-1} = 8.3143\ \text{j mol}^{-1}\ \text{K}^{-1}$$

1) A reaction goes to **completion** with such a large equilibrium constant.
2) The energy of the reaction goes **downhill**.

4. If **covalent bonds are broken** in a reaction, the **reactants must go up an energy hill first**, before they can go downhill.
   1) **A free-energy diagram:** a plotting of the **free energy** of the reacting particles against the **reaction coordinate**.

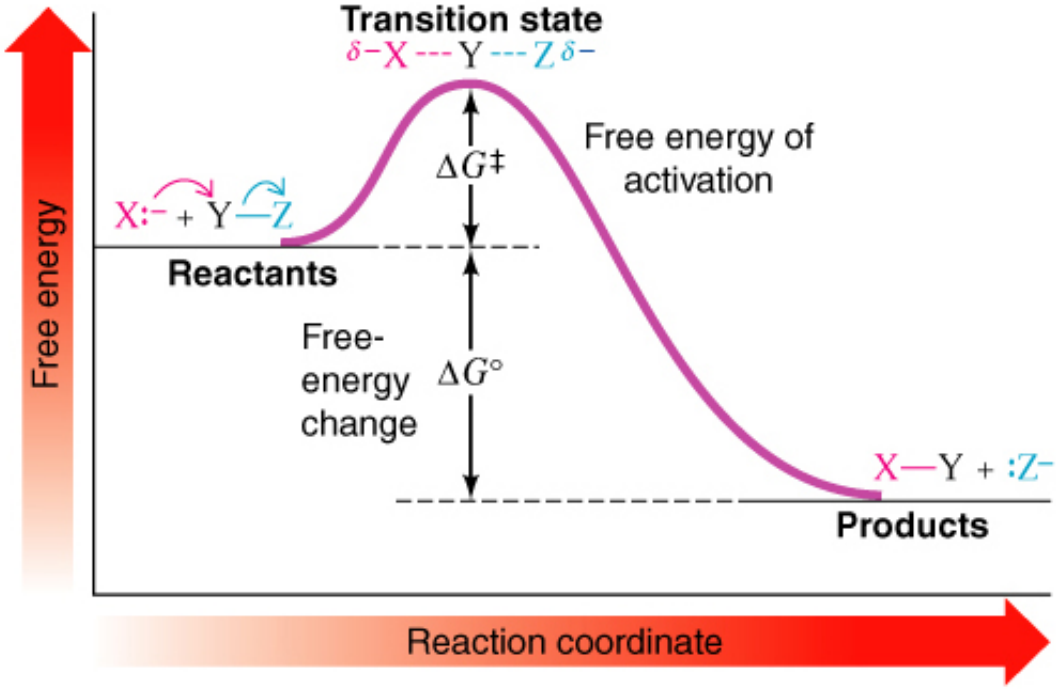


Figure 6.1 **A free-energy diagram for a hypothetical S_N2 reaction that takes place with a negative ΔG°.**

   2) The reaction coordinate measures the progress of the reaction. It represents the

changes in bond orders and bond distances that must take place as the reactants are converted to products.

5. **Free energy of activation, $\Delta G^{\ddagger}$:**
   1) The height of the **energy barrier** between the reactants and products is called the **free energy of activation**.

6. **Transition state:**
   1) The top of the energy hill corresponds to the transition state.
   2) *The difference in free energy between the reactants and the transition state is the* ***free energy of activation***, $\Delta G^{\ddagger}$.
   3) *The difference in free energy between the reactants and the products is the* ***free energy change*** *for the reaction*, $\Delta G°$.

7. A free-energy diagram for an endergonic reaction:

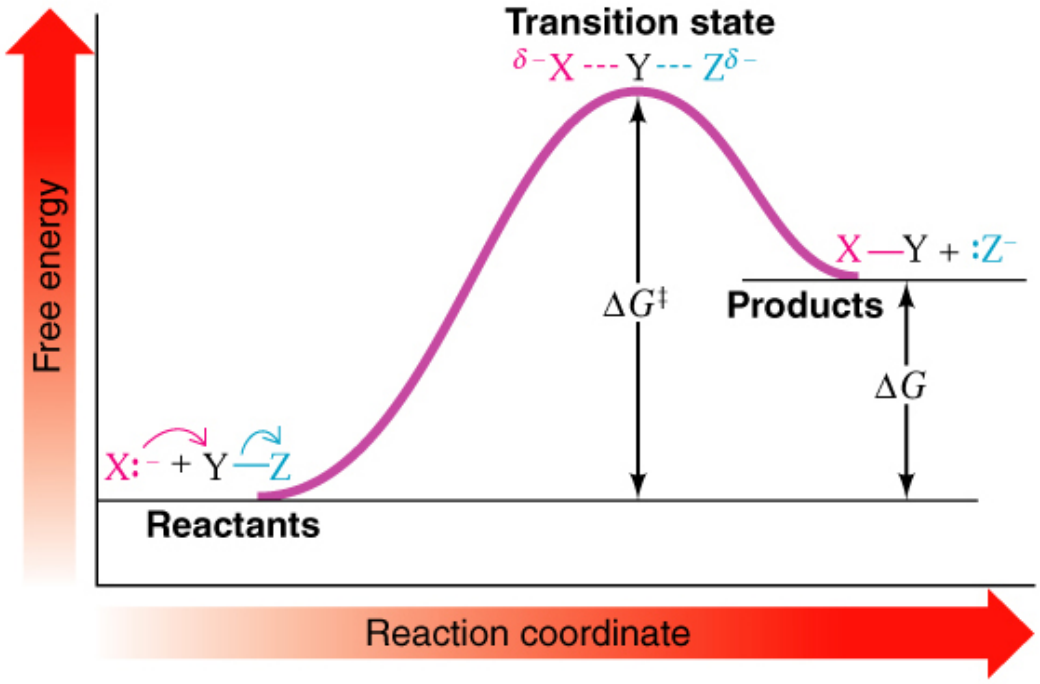


Figure 6.2 **A free-energy diagram for a hypothetical reaction with a positive free-energy change.**

   1) The energy of the reaction goes **uphill**.
   2) $\Delta G^{\ddagger}$ will be larger than $\Delta G°$.

8. **Enthalpy of activation** ($\Delta H^{\ddagger}$) and **entropy of activation** ($\Delta S^{\ddagger}$)**:**

$$\Delta G^{\circ} = \Delta H^{\circ} - \Delta S^{\circ} \quad \Rightarrow \quad \Delta G^{\ddagger} = \Delta H^{\ddagger} - \Delta S^{\ddagger}$$

1) $\Delta H^{\ddagger}$ is the difference in bond energies between the reactants and the transition state.
   i) It is the energy necessary to bring the reactants close together and to bring about the partial breaking of bonds that must happen in the transition state.
   ii) Some of this energy may be furnished by the bonds that are partially formed.

2) $\Delta S^{\ddagger}$ is the difference in entropy between the reactants and the transition state.
   i) Most reactions require the reactants to come together with a particular orientation.
   ii) This requirement for a particular orientation means that the transition state must be more ordered than the reactants and that $\Delta S^{\ddagger}$ will be negative.
   iii) The more highly ordered the transition state,the more negative $\Delta S^{\ddagger}$ will be.
   iv) **A three-dimensional plot of free energy versus the reaction coordinate:**

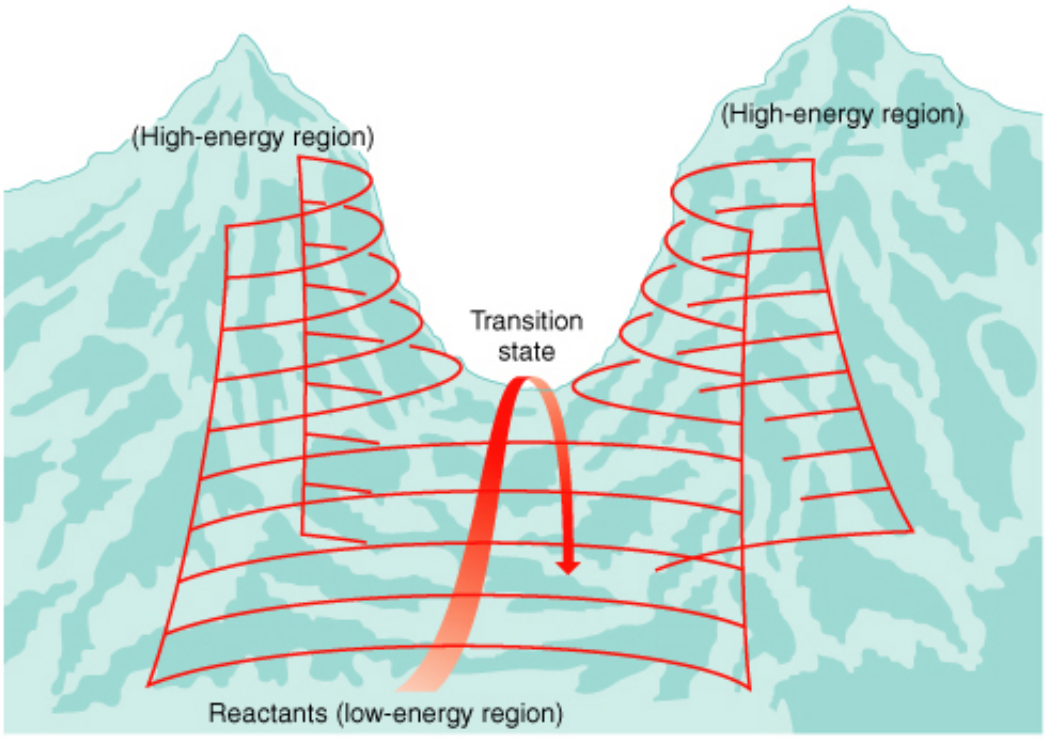


Figure 6.3 **Mountain pass or col analogy for the transition state.**

v) The transition state resembles a mountain pass rather than the top of an energy hill.

vi) The reactants and products appear to be separated by an energy barrier resembling a mountain range.

vii) Transition state lies at the top of the route that requires the lowest energy climb. Whether the pass is a wide or narrow one depends on $\Delta S^{\ddagger}$.

viii) A wide pass means that there is a relatively large number of orientations of reactants that allow a reaction to take place.

9. Reaction rate versus temperature:

1) Most chemical reactions occur much more rapidly at higher temperatures ⇒ For many **reactions taking place near room temperature, a *10 °C increase* in temperature will cause the reaction rate to *double***.

i) This dramatic increase in reaction rate results from a large increase in the number of collisions between reactants that together have sufficient energy to surmont the barrier ($\Delta G^{\ddagger}$) at higher temperature.

2) Maxwell-Boltzmann speed distribution:

i) The average **kinetic energy** of gas particles depends on the absolute temperature.

$$KE_{av} = 3/2\ kT$$

k: Boltzmann's constant = $R/N_0 = 1.38 \times 10^{-23}$ J K^{-1}

R = universal gas constant

N_0 = Avogadro's number

ii) In a sample of gas, there is a distribution of velocities, and hence there is a distribution of **kinetic energies**.

iii) As the temperature is increased, the average velocity (and kinetic energy) of the collection of particles increases.

iv) The kinetic energies of molecules at a given temperature are not all the same ⇒ **Maxwell-Boltzmann speed distribution:**

$$F(v) = 4\pi \left(\frac{m}{2\pi k_B T}\right)^{3/2} v^2 e^{-mv^2/2k_B T} = 4\pi (m/2\pi k_B T)^{3/2} v^2 \exp(-mv^2/2k_B T)$$

k: Boltzmann's constant = $R/N_0 = 1.38 \times 10^{-23}$ J K^{-1}

e is 2.718, the base of natural logarithms

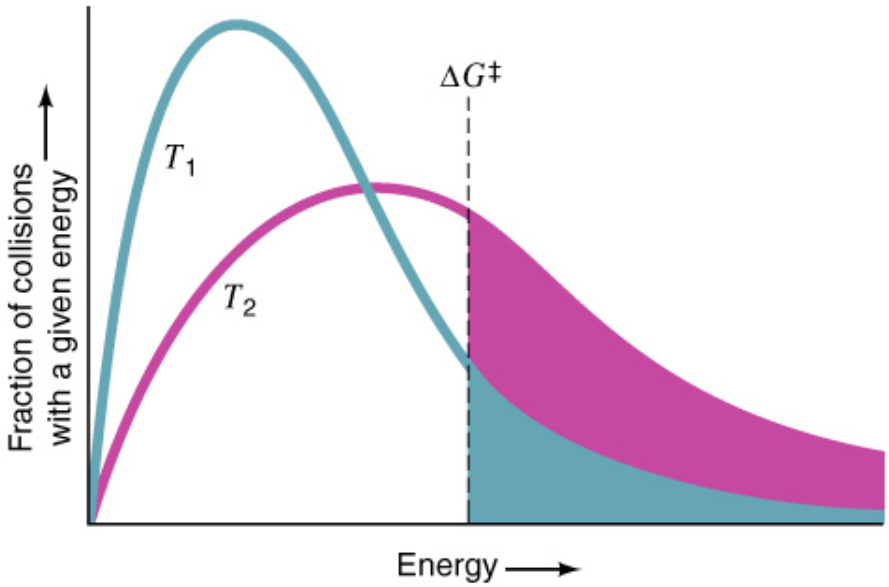


Figure 6.4 **The distribution of energies at two temperatures, T_1 and T_2 ($T_1 > T_2$). The number of collisions with energies greater than the free energy of activation is indicated by the appropriately shaded area under each curve.**

3) Because of the way energies are distributed at different temperature, increasing the temperature by only a small amount causes a large increase in the number of collisions with larger energies.

10. The relationship between the rate constant (k) and $\Delta G^{\ddagger}$:

$$k = k_0 e^{-\Delta G^{\ddagger}/RT}$$

1) k_0 is the absolute rate constant, which equals the rate at which all transition states proceed to products. At 25 °C, $k_0 = 6.2 \times 10^{12}$ s^{-1}.
2) **A reaction with a lower free energy of activation will occur very much faster than a reaction with a higher one**.

11. If a reaction has a $\Delta G^{\ddagger}$ less than 84 kJ mol^{-1} (20 kcal mol^{-1}), it will take place readily at room temperature or below. If $\Delta G^{\ddagger}$ is greater than 84 kJ mol^{-1}, heating

will be required to cause the reaction to occur at a reasonable rate.

12. A free-energy diagram for the reaction of methyl chloride with hydroxide ion:

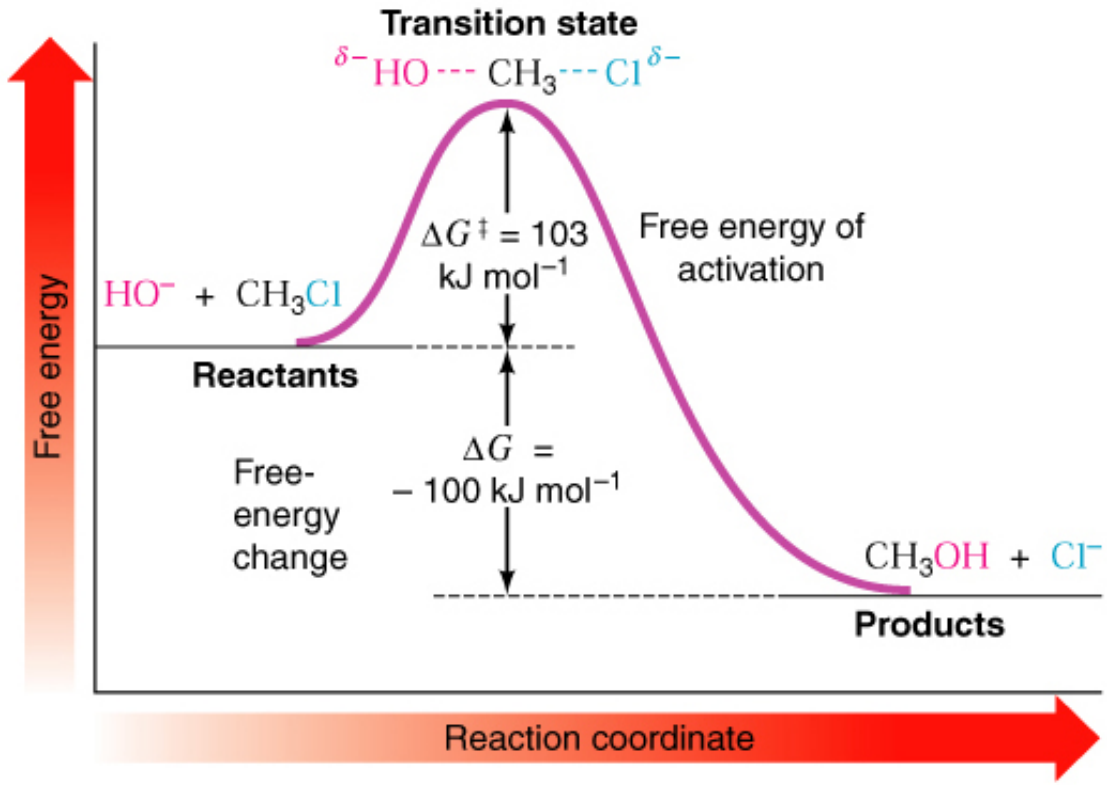
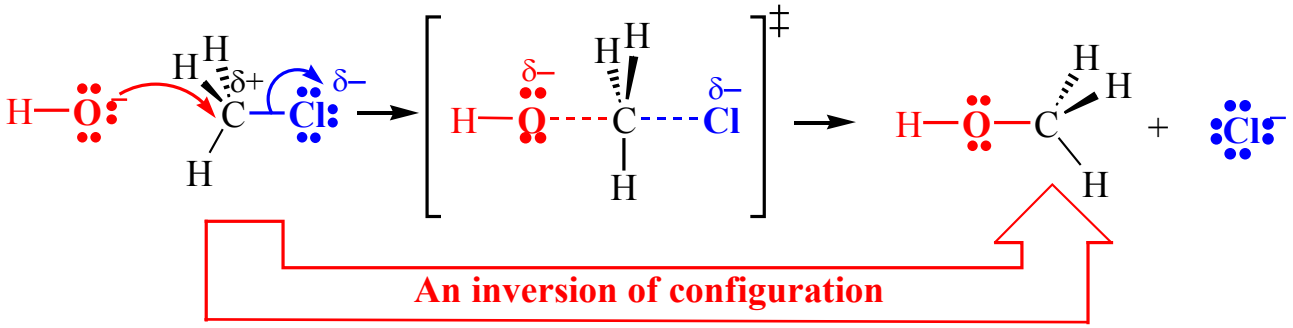


Figure 6.5 **A free-energy diagram for the reaction of methyl chloride with hydroxide ion at 60 °C.**

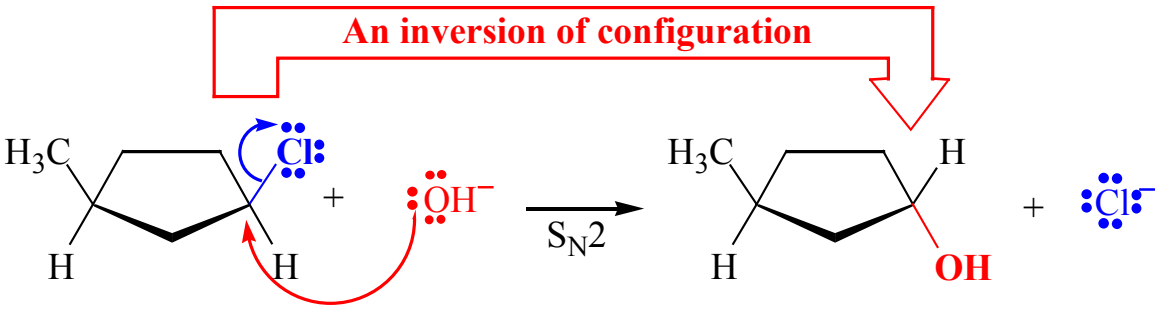
1) At 60 °C, $\Delta G^{\ddagger}$ = 103 kJ mol^{-1} (24.6 kcal mol^{-1}) ⇒ the reaction reaches completion in a matter of a few hours at this temperature.

6.9 THE STEREOCHEMISTRY OF S_N2 REACTIONS

1. In an S_N2 reaction, **the nucleophile attacks from the back side**, that is, **from the side directly opposite the leaving group**.
   1) This attack causes **a change in the configuration** (**inversion of configuration**) of the carbon atom that is the target of nucleophilic attack.

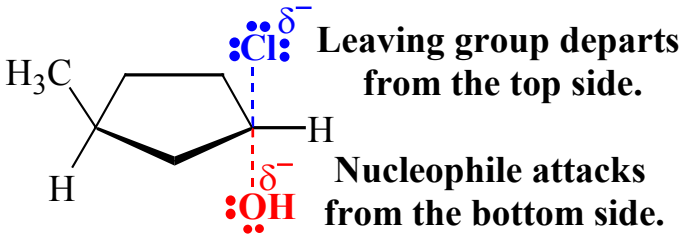


2. **Inversion of configuration** can be observed when hydroxide ion reacts with *cis*-1-chloro-3-methylcyclopentane in an S_N2 reaction:

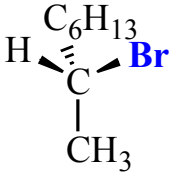


***cis*-1-Chloro-3-methylcyclopentane** ***trans*-3-methylcyclopentanol**

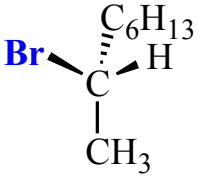
1) The transition state is likely to be:



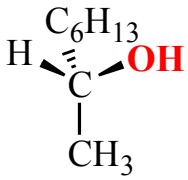
3. **Inversion of configuration** can be also observed when the S_N2 reaction takes place at a **stereocenter** (with ***complete*** inversion of stereochemistry at the chiral carbon center):



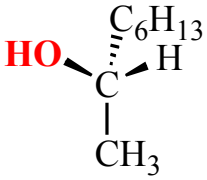
(*R*)-(–)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$



(*S*)-(+)-2-Bromooctane
$[\alpha]_D^{25} = +34.25°$



(*R*)-(–)-2-Octanol
$[\alpha]_D^{25}$ **= –9.90°**



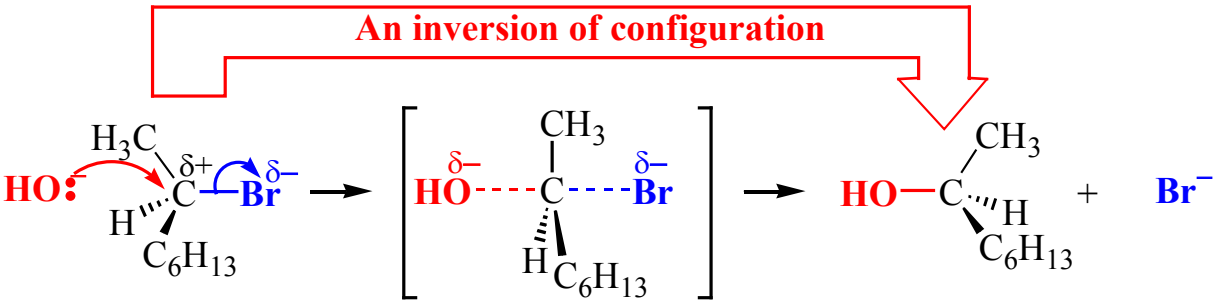
(*S*)-(+)-2-Octanol
$[\alpha]_D^{25}$ **= +9.90°**

1) The (*R*)-(–)-2-bromooctane reacts with sodium hydroxide to afford only (*S*)-(+)-2-octanol.

2) **S_N2 reactions always lead to inversion of configuration.**

The Stereochemistry of an S_N2 Reaction

S_N2 Reaction takes place with complete inversion of configuration:



(*R*)-(–)-2-Bromooctane
$[\alpha]_D^{25}$ **= –34.25°**
Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol
$[\alpha]_D^{25}$ **= +9.90°**
Enantiomeric purity = 100%

6.10 THE REACTION OF *TERT*-BUTYL CHLORIDE WITH HYDROXIDE ION: AN S_N1 REACTION

1. When *tert*-butyl chloride with sodium hydroxide in a mixture of water and acetone, the rate of formation of *tert*-butyl alcohol is dependent on the concentration of *tert*-butyl chloride, but is ***independent of the concentration of hydroxide ion***.

1) *tert*-Butyl chloride reacts by substitution at virtually the **same rate** in **pure water** (where the hydroxide ion is 10^{-7} *M*) as it does in **0.05 *M* aqueous sodium hydroxide** (where the hydroxide ion concentration is **500,000 times larger**).
2) The rate equation for this substitution reaction is **first order respect to *tert*-butyl chloride** and ***first order overall***.

$$(CH_3)_3C{-}Cl + OH^- \xrightarrow[H_2O]{\text{acetone}} (CH_3)_3C{-}OH + Cl^-$$

$$\text{Rate} \propto [(CH_3)_3CCl] \Rightarrow \text{Rate} = k\,[(CH_3)_3CCl]$$

2. ***Hydroxide ions*** do not participate in the transition state of the step that controls the rate of the reaction.

1) The reaction is **unimolecular** ⇒ **S_N1** reaction (**Substitution**, **Nucleophilic**, **Unimolecular**).

6.10A MULTISTEP REACTIONS AND THE RATE-DETERMINING STEP

1. The **rate-determining step** or the **rate-limiting step** of a multistep reaction:

Step 1 Reactant $\xrightarrow{\text{slow}}$ Intermediate 1 ⇒ Rate = k_1 [reactant]

Step 2 Intermediate 1 $\xrightarrow{\text{fast}}$ Intermediate 2 ⇒ Rate = k_2 [intermediate 1]

Step 3 Intermediate 2 $\xrightarrow{\text{fast}}$ Product ⇒ Rate = k_3 [intermediate 2]

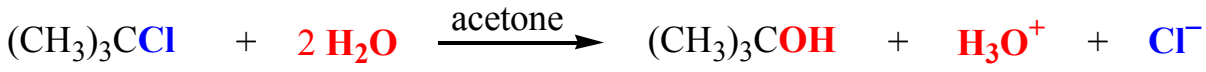
$$k_1 << k_2 \text{ or } k_3$$

1) The concentration of the intermediates are always very small because of the slowness of step 1, and steps 2 and 3 actuallu occur at the same rate as step 1.
2) Step 1 is the **rate-determining step**.

6.11 A MECHANISM FOR THE S_N1 REACTION

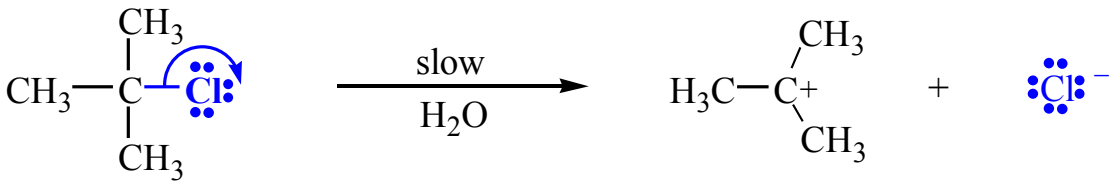
A Mechanism for the S_N1 Reaction

Reaction:



Mechanism:

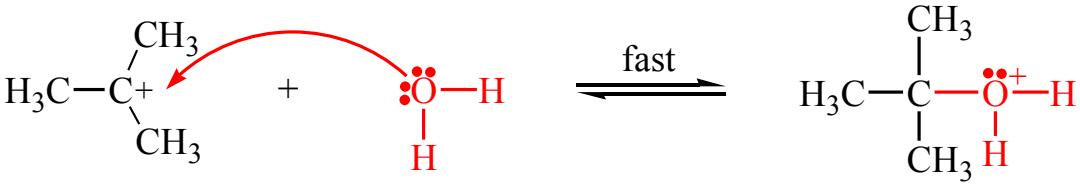
Step 1



Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. Although not shown here, the ions are slovated (and stabilized) by water molecules.

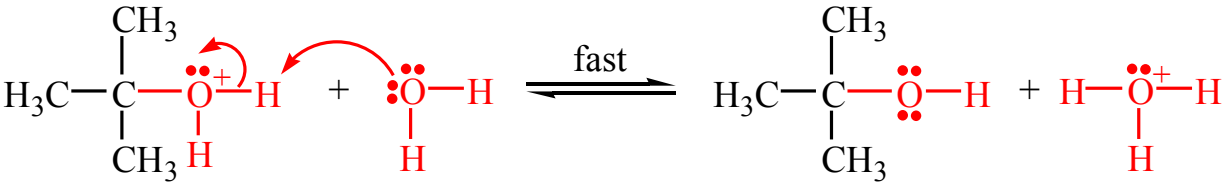
Step 2



A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.

1. The first step is **highly endothermic** and has **high free energy of activation**.
   1) It involves heterolytic cleavage of the C–Cl bond and there is no other bonds are formed in this step.
   2) The free energy of activation is about 630 kJ mol^{-1} (150.6 kcal mol^{-1}) in the gas phase; the free energy of activation is much lower in aqueous solution — about 84 kJ mol^{-1} (20 kcal mol^{-1}).

2. A free-energy diagram for the S_N1 reaction of *tert*-butyl chloride with water:

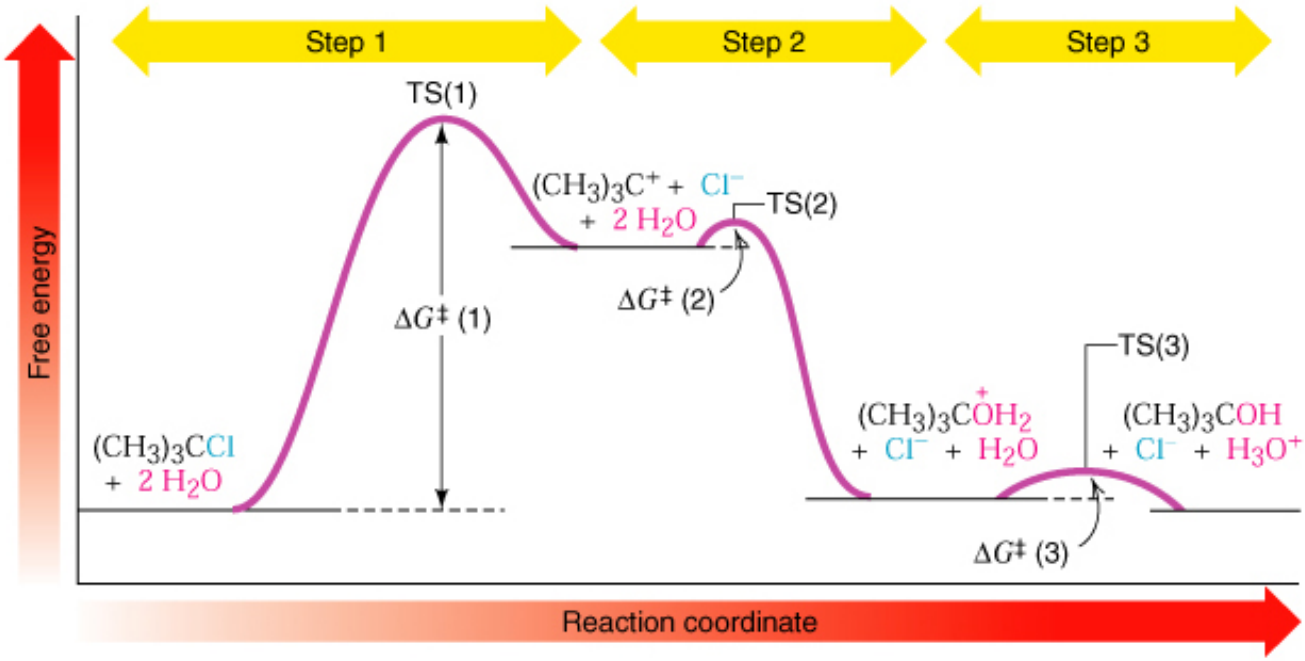
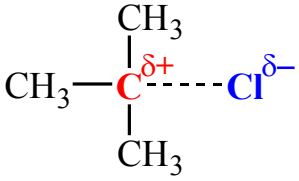


Figure 6.7 **A free-energy diagram for the S_N1 reaction of *tert*-butyl chloride with water. The free energy of activation for the first step, $\Delta G^‡(1)$, is much larger than $\Delta G^‡(2)$ or $\Delta G^‡(3)$. TS(1) represents transition state (1), and so on.**

3. The C–Cl bond of *tert*-butyl chloride is largely broken and ions are beginning to develop in the transition state of the rate-determining step:



6.12 CARBOCATIONS

1. In 1962, George A. Olah (Nobel Laureate in chemistry in 1994; now at the University of Southern California) and co-workers published the first of a series of papers describing experiments in which alkyl cations were prepared in an environment in which they were reasonably stable and in which they could be observed by a number of spectroscopic techniques.

6.12A THE STRUCTURE OF CARBOCATIONS

1. The structure of **carbocations** is **trigonal planar**.

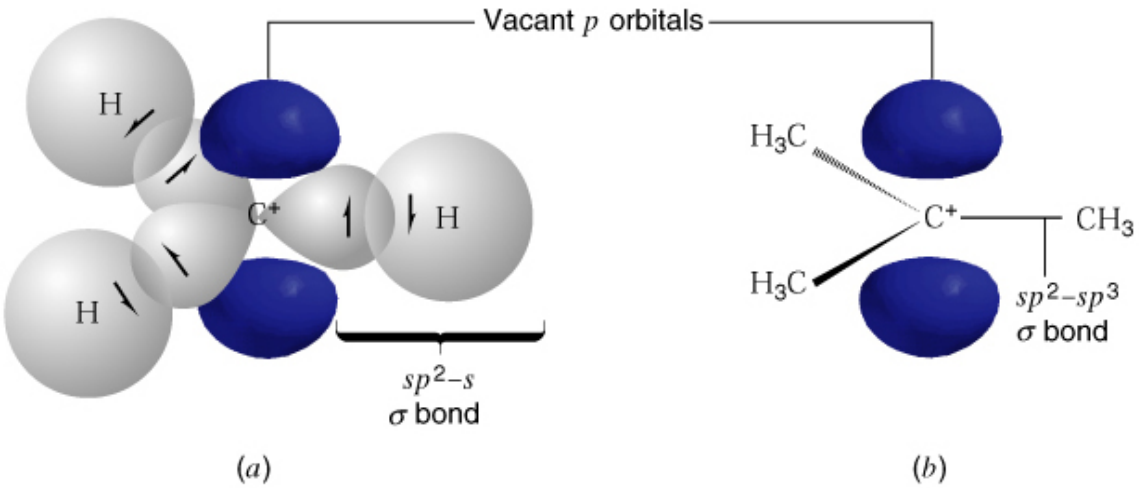
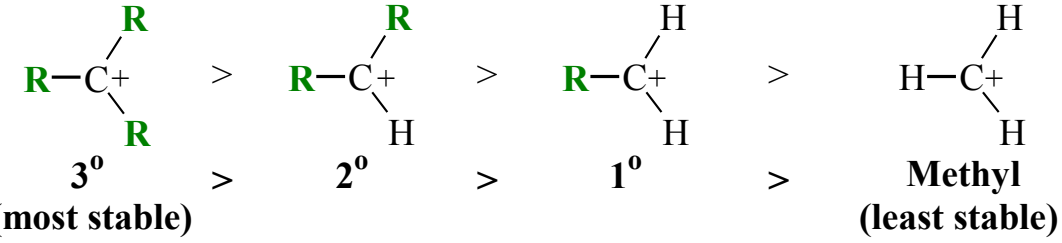


Figure 6.8 **(a) A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with 1s orbitals of the hydrogen atoms. The *p* orbital is vacant. (b) A dashed line-wedge representation of the *tert*-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl group with sp^2 orbitals of the central carbon atom.**

6.12B THE RELATIVE STABILITIES OF CARBOCATIONS

1. **The order of stabilities of carbocations:**



1) **A charged system is stabilized when the charge is dispersed or delocalized**.

2) **Alkyl groups**, when compared to **hydrogen atoms**, are **electron releasing**.

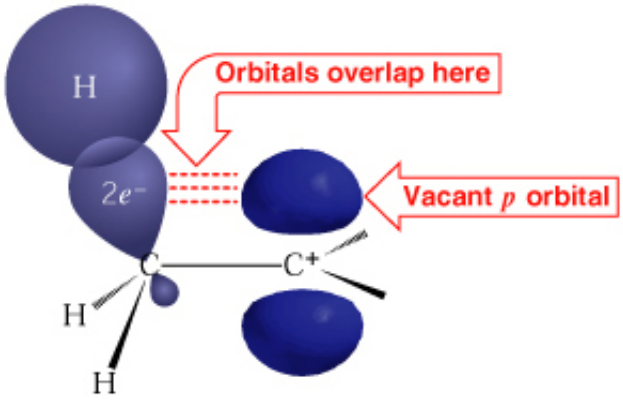
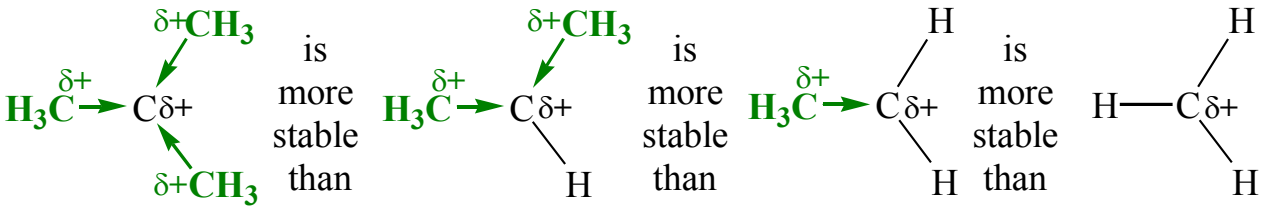


Figure 6.9 ***How a methyl group helps stabilize the positive charge of a carbocation.*** **Electron density from one of the carbon-hydrogen sigma bonds of the methyl group flows into the vacant *p* orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2-hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability. This interaction of a bond orbital with a *p* orbital is called hyperconjugation.**

2. **The delocalization of charge and the order of stability of carbocations parallel the number of attached methyl groups.**



***tert*-Butyl cation (3°) (most stable)** | **Isopropyl cation (2°)** | **Ethyl cation (1°)** | **Methyl cation (least stable)**

3. **The relative stabilities of carbocations is 3° > 2° > 1° > methyl**.

4. **The electrostatic potential maps for carbocations:**

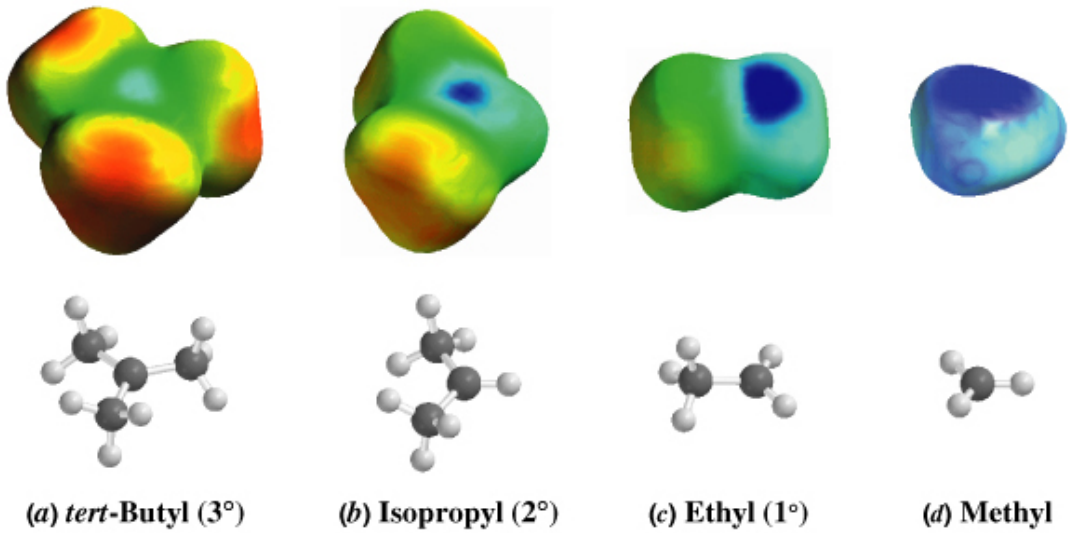
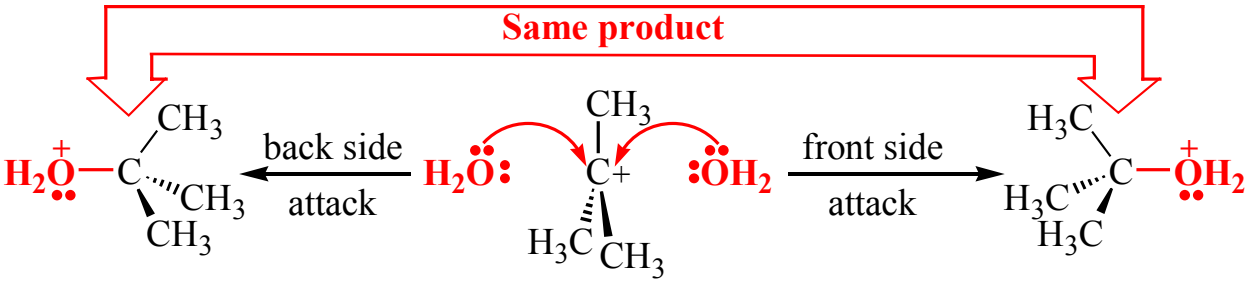


Figure 6.10 **Electrostatic potential maps for (a) *tert*-butyl (3°), (b) isopropyl (2°), (c) ethyl (1°), and (d) methyl carbocations show the trend from greater to lesser delocalization (stabilization) of the positive charge. (The structures are mapped on the same scale of electrostatic potential to allow direct comparison.)**

6.13 THE STEREOCHEMISTRY OF S_N1 REACTIONS

1. The carbocation has a **trigonal planar structure** ⇒ It may react with a **nucleophile** from either the **front side** or the **back side**:



1) With the *tert*-butyl cation it makes no difference.

2) With some cations, **different products** arise from the two reaction possibilities.

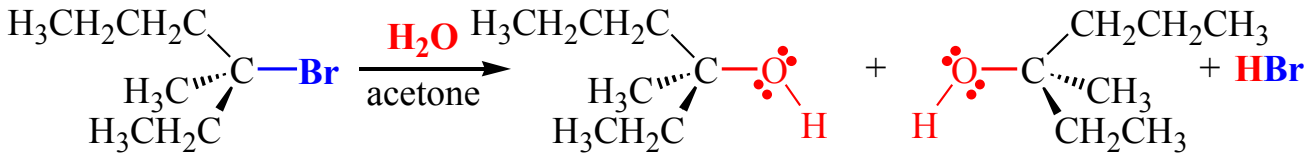
6.13A REACTIONS THAT INVOLVE RACEMIZATION

1. **Racemization:** a reaction that transforms an optically active compound into a racemic form.

1) **Complete racemization** and **partial racemization**:

2) **Racemization** takes place **whenever the reaction causes chiral molecules to be converted to an achiral intermediate**.

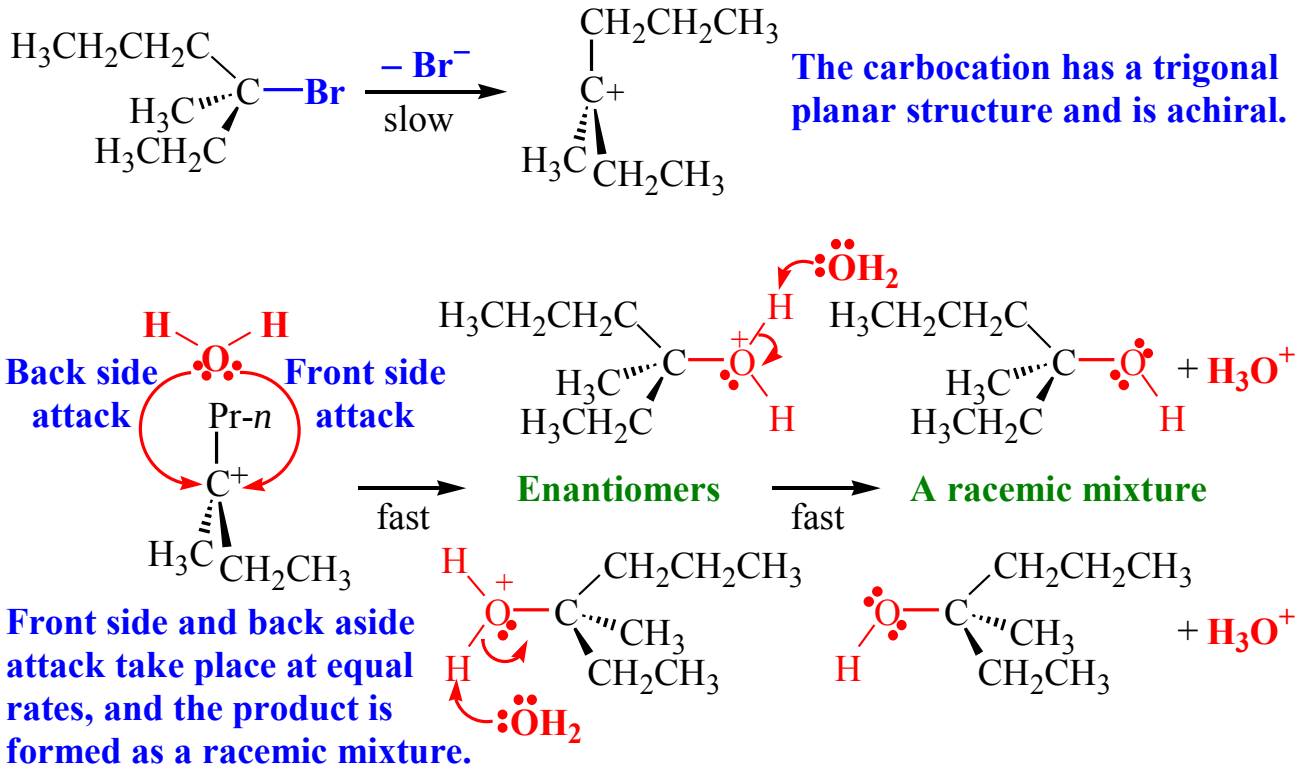
2. Heating optically active (*S*)-3-bromo-3-methylhexane with aqueous acetone results in the formation of racemic 3-methyl-3-hexanol.



(*S*)-3-bromo-3-methylhexane (optically active) **(*S*)-3-methyl-3-hexanol (optically inactive, a racemic form)** **(*R*)-3-methyl-3-hexanol**

i) The S_N1 reaction proceeds through the formation of an ***achiral*** trigonal planar carbocation intemediate.

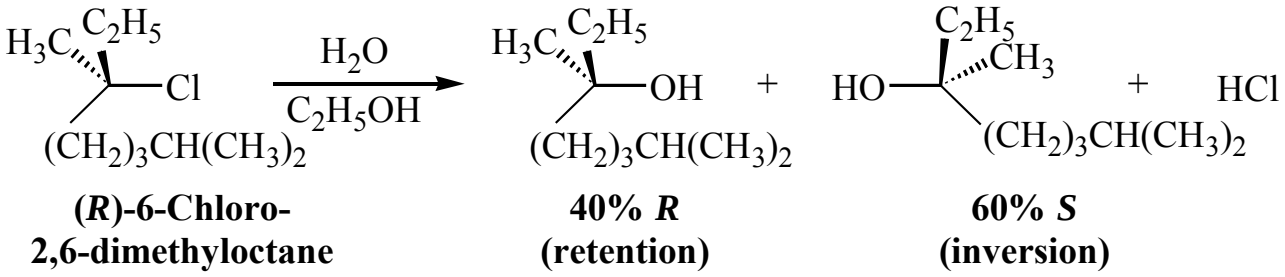
The stereochemistry of an S_N1 Reaction



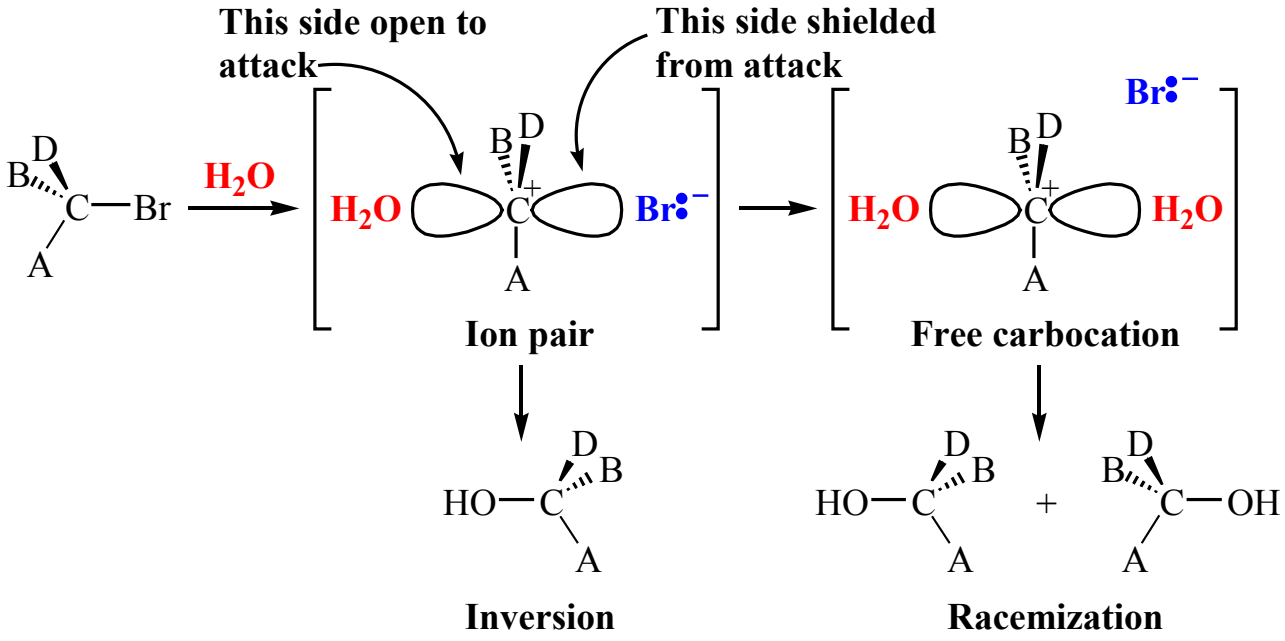
The S_N1 reaction of (*S*)-3-bromo-3-methylhexane proceeds with racemization because the intermediate carbocation is achiral and attacked by the nucleophile can occur from either side.

3. **Few S_N1 displacements occur with complete racemization**. Most give a minor

(0 ~ 20 %) amount of inversion.



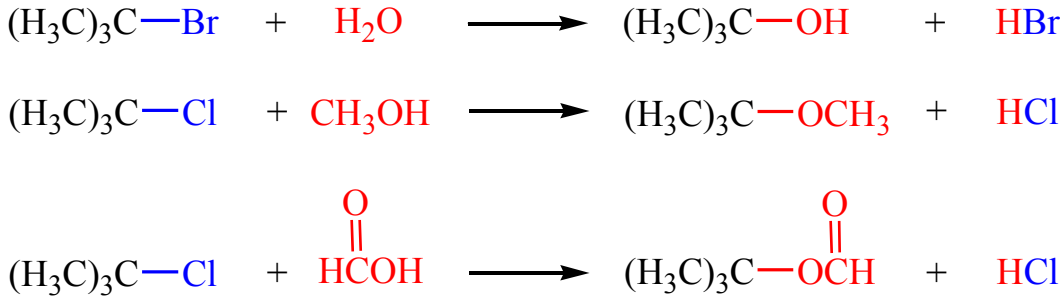
(*R*)-6-Chloro-2,6-dimethyloctane | **40% *R* (retention)** | **60% *S* (inversion)**



6.13B SOLVOLYSIS

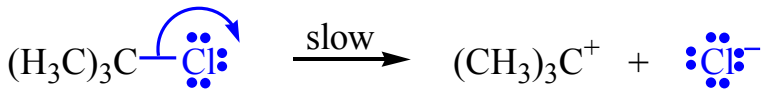
1. **Solvolysis** is a nucleophilic substitution in which **the nucleophile is a molecule of the solvent** (**solvent + *lysis***: cleavage by the solvent).
   1) **Hydrolysis**: when the solvent is water.
   2) **Alcoholysis**: when the solvent is an alcohol (e.g. **methanolysis**).

Examples of Solvolysis

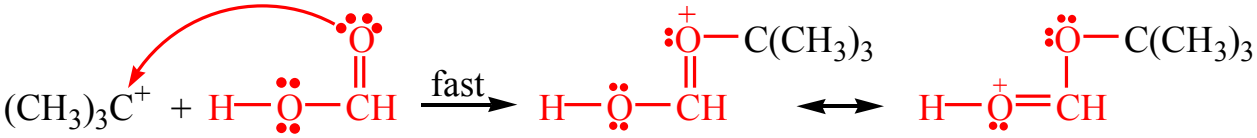


2. Solvolysis involves the initial formation of a carbocation and the subsequent reaction of that cation with a molecule of the solvent:

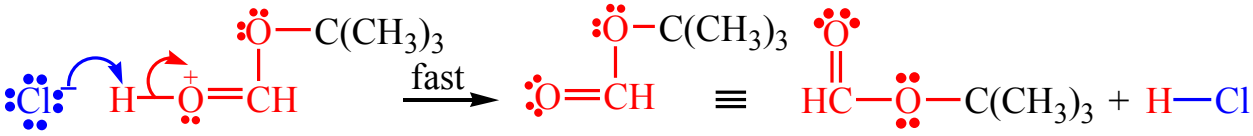
Step 1



Step 2



Step 3



6.14 FACTORS AFFECTING THE RATES OF S_N1 AND S_N2 REACTIONS

1. Factors Influencing the rates of S_N1 and S_N2 reactions:
   1) The **structure** of the **substrate**.
   2) The **concentration** and **reactivity** of the **nucleophile** (for bimolecular reactions).
   3) The **effect** of the **solvent**.
   4) The **nature** of the **leaving group**.

6.14A THE EFFECT OF THE STRUCTURE OF THE SUBSTRATE

1. S_N2 Reactions:

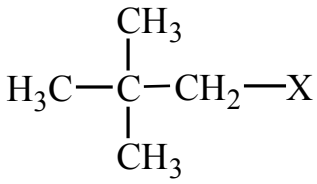
1) Simple alkyl halides show the following general order of reactivity in S_N2 reactions:

methyl > 1° > 2° >> 3° (unreactive)

Table 6.4 Relative Rates of Reactions of Alkyl Halides in S_N2 Reactions

Substituent	Compound	Relative Rate
Methyl	**CH_3X**	30
1°	**CH_3CH_2X**	1
2°	**$(CH_3)_2CHX$**	0.02
Neopentyl	**$(CH_3)_3CCH_2X$**	0.00001
3°	**$(CH_3)_3CX$**	~0

i) Neopentyl halids are primary halides but are **very unreactive**.



A neopentyl halide

2) **Steric effect:**

i) A **steric effect** is an effect on relative rates caused by the **space-filling properties** of those parts of a molecule **attached at or near** the **reacting site**.

ii) **Steric hindrance:** the spatial arrangement of the atoms or groups at or near the reacting site of a molecule **hinders or retards** a reaction.

iii) Although most molecules are reasonably flexible, very large and bulky groups can often hinder the formation of the required transition state.

3) An S_N2 reaction requires an approach by the nucleophile to a distance within bonding range of the carbon atom bearing the leaving group.

i) Substituents on or near the reacting carbon have a **dramatic inhibiting effect**.

ii) Substituents cause the free energy of the required transition state to be increased and, consequently, they increase the free energy of activation for the reaction.

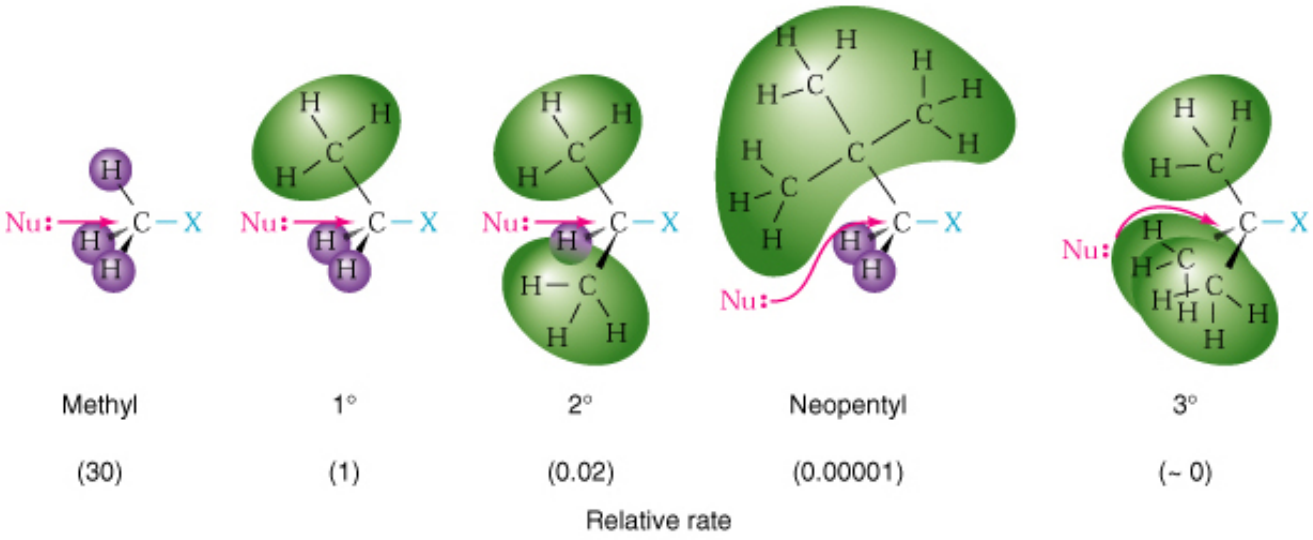
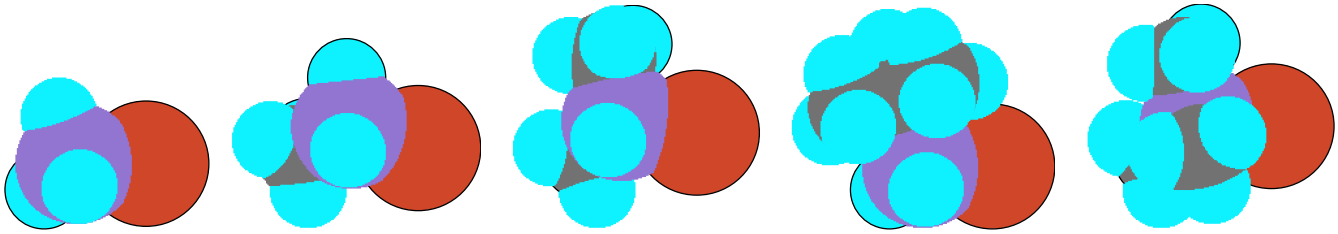


Figure 6.11 **Steric effects in the S_N2 reaction.**



CH_3–Br **CH_3CH_2–Br** **$(CH_3)_2CH$–Br** **$(CH_3)_3CCH_2$–Br** **$(CH_3)_3C$–Br**

2. S_N1 Reactions:

1) **The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed.**

Table 6A **Relative rates of reaction of some alkyl halides with water:**

Alkyl halide	Type	Product	Relative rate of reaction
CH_3Br	Methyl	CH_3OH	1.0
CH_3CH_2Br	1°	CH_3CH_2OH	1.0
$(CH_3)_2CHBr$	2°	$(CH_3)_2CHOH$	12
$(CH_3)_3CBr$	3°	$(CH_3)_3COH$	1,200,000

2) Organic compounds that **are capable of forming relatively stable carbocation** can undergo S_N1 reaction at a reasonable rate.

i) Only **tertiary halides** react by an S_N1 mechanism for **simple alkyl halides**.

ii) ***Allylic halides*** and ***benzylic halides***: A ***primary*** allylic or benzylic carbocation is approximately as stable as a ***secondary*** alkyl carbocation (2° allylic or benzylic carbocation is about as stable as a 3° alkyl carbocation).

iii) The stability of allylic and benzylic carbocations: **delocalization**.

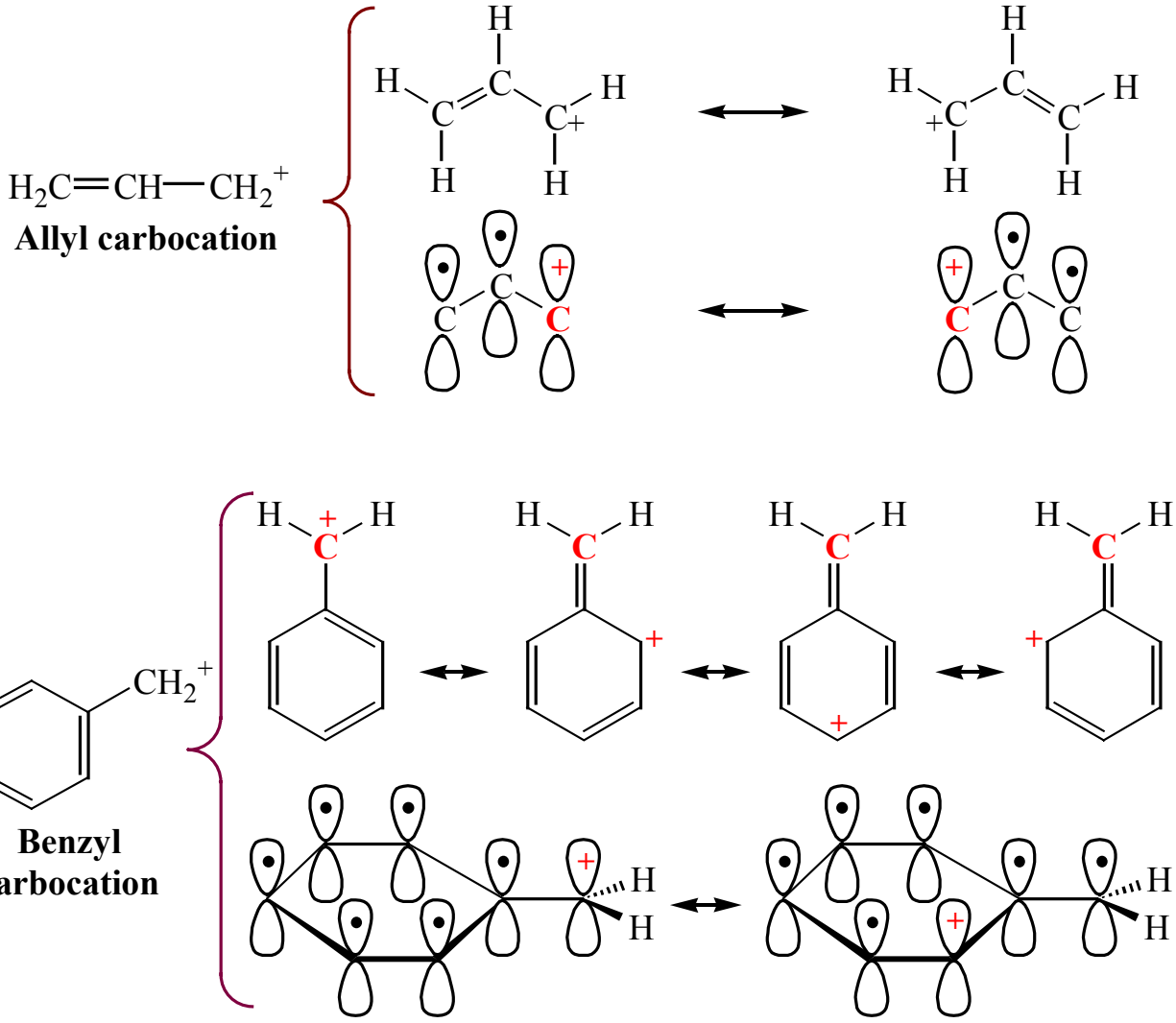


Table 10B **Relative rates of reaction of some alkyl tosylates with ethanol at 25 °C**

Alkyl tosylate	*Product*	*Relative rate*
CH_3CH_2OTos	$CH_3CH_2OCH_2CH_3$	1
$(CH_3)_2CHOTos$	$(CH_3)_2CHOCH_2CH_3$	3
$H_2C{=}CHCH_2OTos$	$H_2C{=}CHCH_2OCH_2CH_3$	35
$C_6H_5CH_2OTos$	$C_6H_5CH_2OCH_2CH_3$	400
$(C_6H_5)_2CHOTos$	$(C_6H_5)_2CHOCH_2CH_3$	10^5
$(C_6H_5)_3COTos$	$(C_6H_5)_3COCH_2CH_3$	10^{10}

4) The stability order of carbocations is exactly the order of S_N1 reactivity for alkyl halides and tosylates.

5) **The order of stability of carbocations:**

3°	>	**2°**	≈	**Allyl**	≈	**Benzyl**	>>	**1°**	>	**Methyl**
R_3C^+	>	**R_2CH^+**	≈	**$H_2C{=}CH{-}CH_2^+$**	≈	**$C_6H_5{-}CH_2$**	>>	**RCH_2^+**	>	**CH_3^+**

6) Formation of **a relatively stable carbocation is important in an S_N1 reaction** ⇒ **low free energy of activation** ($\Delta G^{\ddagger}$) for the slow step of the reaction.

i) The $\Delta G°$ for the first step is positive (***uphill in terms of free energy***) ⇒ the first step is ***endothermic*** ($\Delta H°$ is positive; ***uphill in terms of enthalpy***).

7) The **Hammond-Leffler postulate**:

i) ***The structure of a transition state resembles the stable species that is nearest it in free energy*** ⇒ Any factor that stabilize a high-energy intermediate should also stabilize the transition state leading to that intermediate.

ii) The transition state of a highly **endergonic** step lies close to the products in free energy ⇒ **it resembles the products of that step in structure**.

iii) The transition state of a highly **exergonic** step lies close to the reactants in free energy ⇒ **it resembles the reactants of that step in structure**.

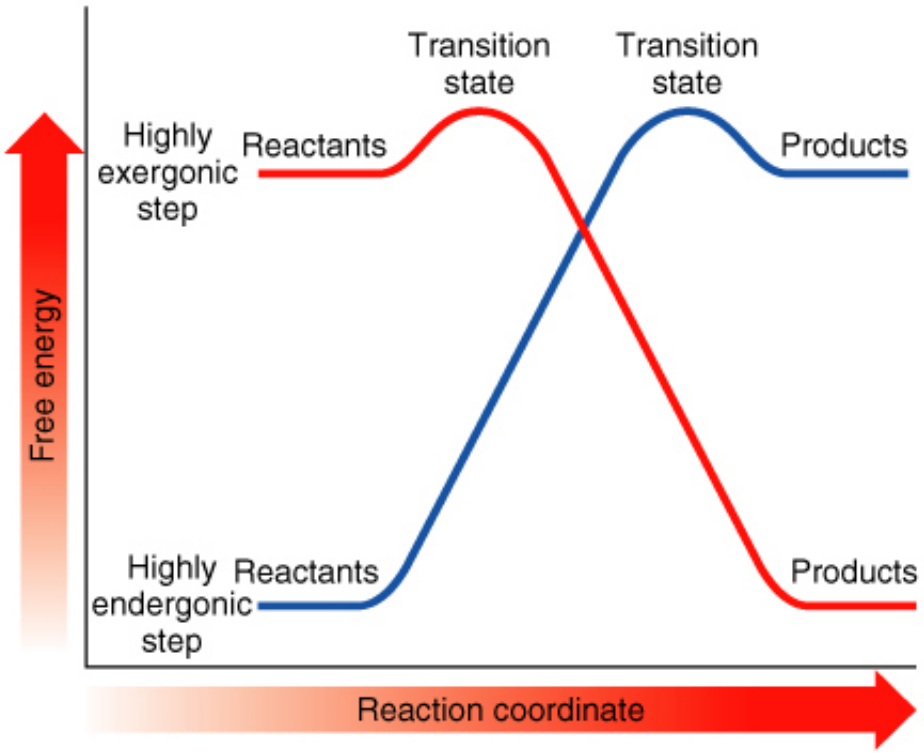
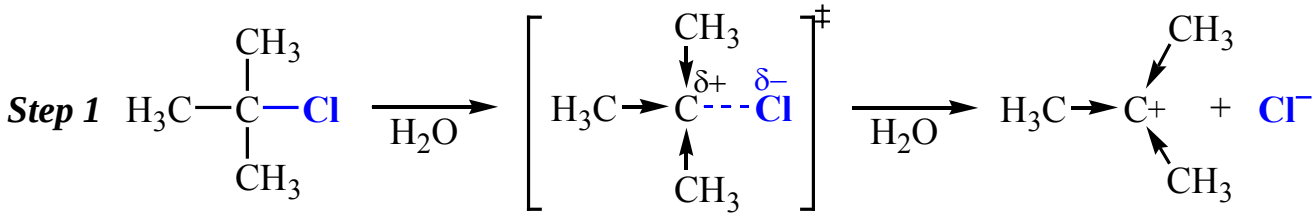


Figure 6.12 **Energy diagrams for highly exergonic and highly endergonic steps of reactions.**

7) The transition state of the first step in an S_N1 reaction resembles to the product of that step:



Reactant | **Transition state** *Resembles product of step Because ΔG° is positive* | **Product of step** *stabilized by three electron-releasing groups*

i) Any factor that stabilizes the carbocation —— such as delocalization of the positive charge by electron-releasing groups —— should also stabilize the transition state in which the positive charge is developing.

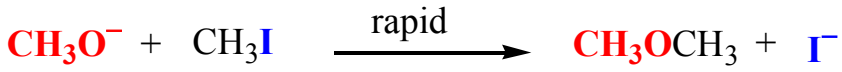
8) The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide is so large that, for all practical purposes, an S_N1 reaction does not compete with the corresponding S_N2 reaction.

6.14B THE EFFECT OF THE CONCENTRATION AND STRENGTH OF THE NUCLEOPHILE

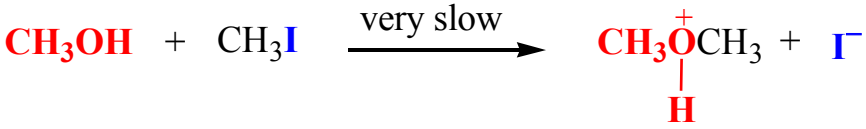
1. Neither the concentration nor the structure of the nucleophile affects the rates of S_N1 reactions since the nucleophile does not participate in the rate-determining step.

2. The rates of S_N2 reactions depend on both the concentration and the structure of the nucleophile.

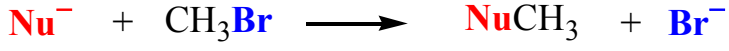
3. **Nucleophilicity:** the ability for a species for a **C** atom in the S_N2 reaction.
   1) It depends on **the nature of the substrate** and **the identity of the solvent**.
   2) Relative nucleophilicity (on a ***single*** substrate in a ***single*** solvent system):
   3) Methoxide ion is a good nucleophile (reacts rapidly with a given substrate):



   4) Methanol is a poor nucleophile (reacts slowly with the same substrate under the same reaction conditions):



   5) The S_N2 reactions of bromomethane with nucleophiles in aqueous ethanol:



Nu =	HS^-	CN^-	I^-	CH_3O^-	HO^-	Cl^-	NH_3	H_2O
Relative reactivity	125,000	125,000	100,000	25,000	16,000	1,000	700	1

4. **Trends in nucleophilicity:**
   1) Nucleophiles that have the **same attacking atom**: **nucleophilicity roughly parallels basicity**.

i) A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid ⇒ HO^- is a better nucleophile than H_2O; RO^- is a better nucleophile than ROH.

ii) In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities:

$$\mathbf{RO^- > HO^- >> RCO_2^- > ROH > H_2O}$$

2) Correlation between electrophilicity-nucleophilicity and Lewis acidity-basicity:

i) "**Nucleophilicity**" measures the affinity (or how rapidly) of a Lewis base for a carbon atom in the S_N2 reaction (relative rates of the reaction).

ii) "**Basicity**", as expressed by pK_a, measures the affinity of a base for a proton (or the position of an acid-base equilibrium).

Correlation between Basicity and Nucleophilicity

Nucleophile	CH_3O^-	HO^-	$CH_3CO_2^-$	H_2O
Rates of S_N2 reaction with CH_3Br	25	16	0.3	0.001
pK_a of conjugate acid	15.5	15.7	4.7	–1.7

iii) A HO^- (pK_a of H_2O is 15.7) is a stronger base than a CN^- (pK_a of HCN is ~10) but CN^- is a stronger nucleophile than HO^-.

3) Nucleophilicity usually increases in going down a column of the periodic table.

i) HS^- is more nucleophilic than HO^-.

ii) The halide reactivity order is: $I^- > Br^- > Cl^-$

iii) Larger atoms are more **polarizable** (their electrons are more easily distorted) ⇒ a larger nucleophilic atom can donate a greater degree of electron density to the substrate than a smaller nucleophile whose electrons are more tightly held.

6.14C Solvent Effects on S_N2 Reactions: Protic and Aprotic Solvents

1. **Protic Solvents:** ***hydroxylic solvents*** such as **alcohols** and **water**

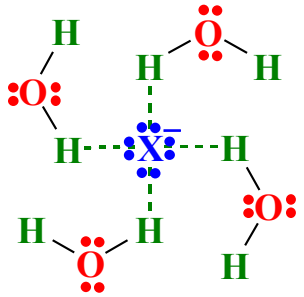
1) The solvent molecule has **a hydrogen atom attached to an atom of a strongly electronegative element**.

2) In protic solvents, the nucleophile with **larger nucleophilic atom** is **better**.

   i) Thiols (**R–SH**) are stronger nucleophiles than alcohols (**R–OH**); **RS**$^-$ ions are more nucleophilic than **RO**$^-$ ions.

   ii) The order of reactivity of halide ions: $I^- > Br^- > Cl^- > F^-$

3) Molecules of protic solvents form **hydrogen bonds nucleophiles**:



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.

   i) A small nucleophile, such fluoride ion, because its charge is more concentrated, is strongly solvated than a larger one.

4) ***Relative Nucleophilicity in Protic Solvents:***

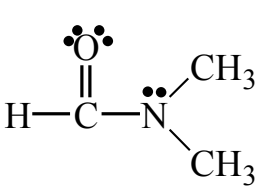
$$SH^- > CN^- > I^- > HO^- > N_3^- > Br^- \; CH_3CO_2^- > Cl^- > F^- > H_2O$$

2. Polar Aprotic Solvent:

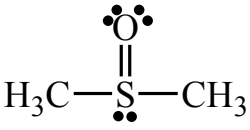
1) **Aprotic solvents** are those solvents whose molecules do not have **a hydrogen atom attached to an atom of a strongly electronegative element**.

   i) Most aprotic solvents (benzene, the alkanes, *etc*.) are relatively nonpolar, and they do not dissolve most ionic compounds.

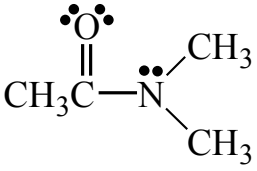
   ii) Polar aprotic solvents are ***especially useful*** in S_N2 reactions:



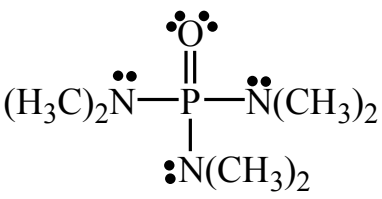
***N,N*-Dimethylformamide**



Dimethyl sulfoxide



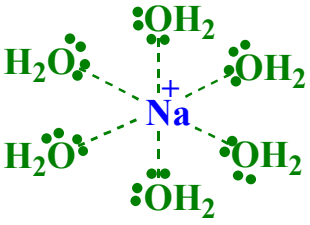
Dimethylacetamide



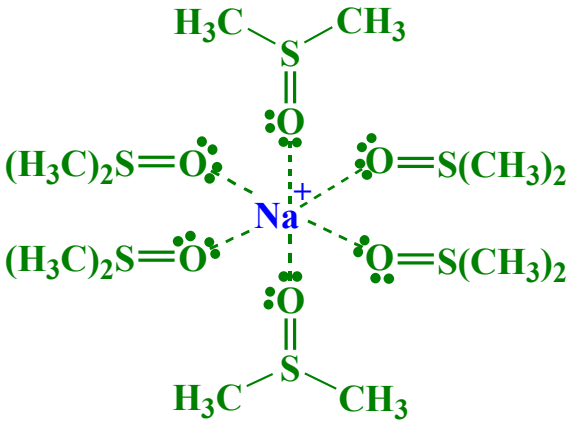
Hexamethylphosphoramide

(DMF) **(DMSO)** **(DMA)** **(HMPA)**

1) **Polar aprotic solvents** dissolve ionic compounds, and they **solvate cations** very well.



A sodium ion solvated by molecules of the protic solvent water



A sodium ion solvated by molecules of the aprotic solvent dimethyl sulfoxide

2) **Polar aprotic solvents do not solvate anions to any appreciable extent** because they **cannot form hydrogen bonds** and because **their positive centers are well shielded from any interaction with anions**.

i) **"Naked" anions are highly reactive both as bases and nucleophiles**.

ii) The relative order of reactivity of halide ions is the same as their relative basicity in DMSO:

$$F^- > Cl^- > Br^- > I^-$$

iii) The relative order of reactivity of halide ions in alcohols or water:

$$I^- > Br^- > Cl^- > F^-$$

3) **The rates of S_N2 reactions generally are vastly increased when they are carried out in polar aprotic solvents.**

4) **Solvent effects on the S_N2 reaction of azide ion with 1-bromobutane:**

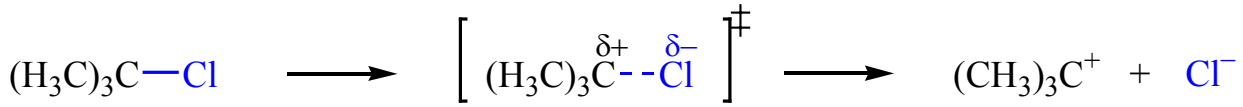
$$N_3^- + CH_3CH_2CH_2CH_2Br \xrightarrow{\text{Solvent}} CH_3CH_2CH_2CH_2N_3 + Br^-$$

Solvent	HMPA	CH_3CN	DMF	DMSO	H_2O	CH_3OH

Relative reactivity	**200,000**	**5,000**	**2,800**	**1,300**	**6.6**	**1**

6.14D SOLVENT EFFECTS ON S_N1 REACTIONS: THE IONIZING ABILITY OF THE SOLVENTS

1. **Polar protic solvent** will greatly increase the rate of ionization of an alkyl halide ***in any S_N1 reaction***.
   1) Polar protic solvents **solvate cations** and **anions effecttively**.
   2) Solvation **stabilizes the transition state** leading to the intermediate carbocation and **halide ion** more it does the **reactants** ⇒ the **free energy of activation** is **lower**.
   3) The transition state for the ionization of organohalide resembles the product carbocation.



Reactant **Transition state** **Products**

Separated charges are developing

2. **Dielectric constant:** a measure of a solvent's ability to insulate opposite charges from each other.

Table 6.5 Dielectric Constants of Some Common Solvents

Name	Structure	Dielectric constant, ε
APROTIC (NONHYDROXYLIC) SOLVENTS		
Hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	1.9
Benzene	C_6H_6	2.3
Diethyl ether	$CH_3CH_2–O–CH_2CH_3$	4.3
Chloroform	$CHCl_3$	4.8
Ethyl acetate	$CH_3C(O)OC_2H_5$	6.0
Acetone	$(CH_3)_2CO$	20.7
Hexamethylphosphoramide (HMPA)	$[(CH_3)_2N]_3PO$	30
Acetonitrile	CH_3CN	36
Dimethylformamide (DMF)	$(CH_3)_2NCHO$	38
Dimethyl sulfoxide (DMSO)	$(CH_3)_2SO$	48
PROTIC (HYDROXYLIC) SOLVENTS		
Acetic acid	$CH_3C(O)OH$	6.2
tert-Butyl alcohol	$(CH_3)_3COH$	10.9
Ethanol	CH_3CH_2OH	24.3
Methanol	CH_3OH	33.6
Formic acid	$HC(O)OH$	58.0
Water	H_2O	80.4

1) Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water.
2) Methanol-water and ethanol-water are commonmixed solvents for nucleophilic substitution reactions.

Table 6C **Relative rates for the reaction of 2-chloro-2-methylpropane with different solvents**

Solvent	Relative rate
Ethanol	1
Acetic acid	2
Aqueous ethanol (40%)	100
Aqueous ethanol (80%)	14,000
Water	105

6.14E THE NATURE OF THE LEAVING GROUP

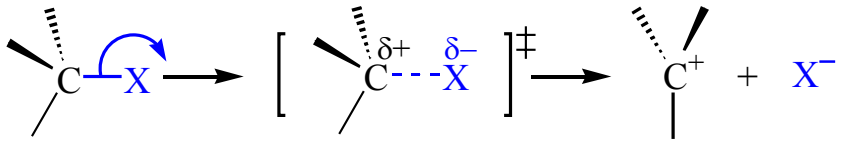
1. **Good Leaving Group:**

   1) The **best leaving groups** are those that become the **most stable ions** after they depart.

   2) Most leaving groups leave as a negative ion ⇒ the best leaving groups are those ions that stabilize a negative charge most effectively ⇒ the best leaving groups are weak bases.

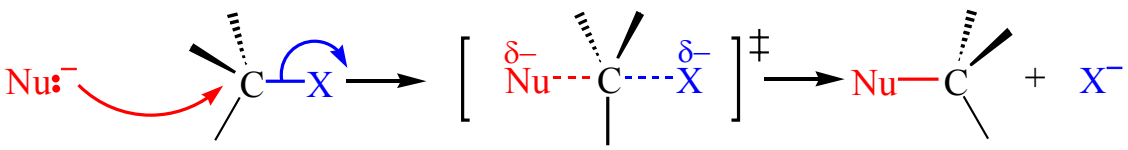
2. **The leaving group** begins to acquire a negative charge as the transition state is reached in either an S_N1 or S_N2 reaction.

S_N1 Reaction (rate-limiting step)



Transition state

S_N2 Reaction



Transition state

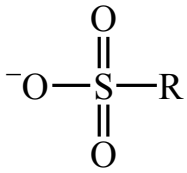
1) Stabilization of the developing negative charge at the leaving group stabilizes

the transition state (lowers its free energy) ⇒ lowers the free energy of activation ⇒ increases the rate of the reaction.

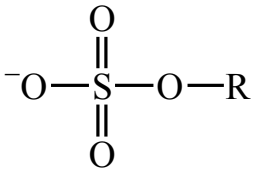
3. **Relative reactivity of some leaving groups:**

Leaving group	**$TosO^-$**	**I^-**	**Br^-**	**Cl^-**	**F^-**	**HO^-, H_2N^-, RO^-**
Relative reactivity	**60,000**	**30,000**	**10,000**	**200**	**1**	**~0**

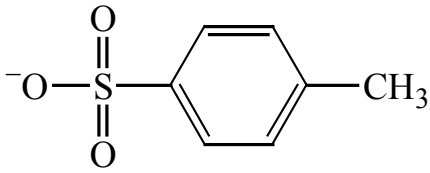
4. **Other good leaving groups:**



An alkanesulfonate ion



An alkyl sulfate ion

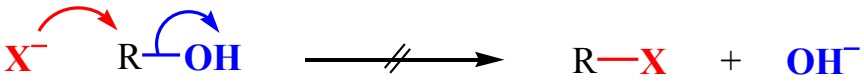


***p*-Toluenesulfonate ion**

1) These anions are all the conjugate bases of very strong acids.
2) The trifluoromethanesulfonate ion ($CF_3SO_3^-$, **triflate ion**) is one of the best leaving group known to chemists.
   i) It is the anion of CF_3SO_3H, an exceedingly strong acid — one that is much stronger than sulfuric acid.

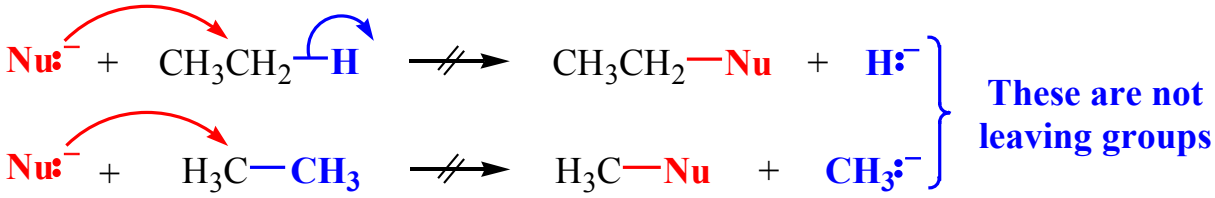
$CF_3SO_3^-$, **triflate ion**
(a "super" leaving group)

5. **Strongly basic ions rarely act as leaving groups**.

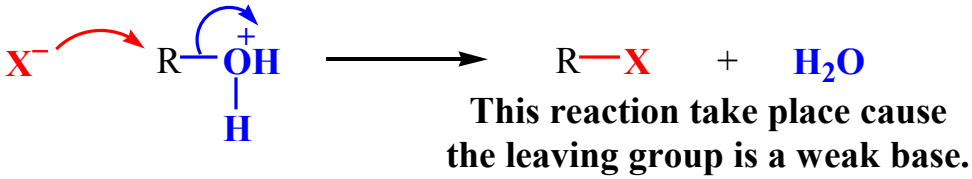


This reaction doesn't take place because the leaving group is a strongly basic hydroxide ion.

1) Very powerful bases such as hydride ions (**H:**$^-$) and alkanide ions (**R:**$^-$) virtually never act as leaving groups.



6. **Protonation** of an alcohol with a strong acid turns its poor OH^- leaving group (strongly basic) into a **good leaving group** (**neutral water molecule**).



6.14F SUMMARY: S_N1 VERSUS S_N2

1. Reactions of alkyl halides by an S_N1 mechanism are favored by the use of:
   1) substrates that can form relatively stable carbocations.
   2) weak nucleophiles.
   3) highly ionizing solvent.

2. Reactions of alkyl halides by an S_N2 mechanism are favored by the use of:
   1) relatively unhindered alkyl halides.
   2) strong nucleophiles.
   3) polar aprotic solvents.
   4) high concentration of nucleophiles.

3. The effect of the leaving group is the same in both S_N1 and S_N2:

R–I > R–Br > R–Cl S_N1 or S_N2

Table 6.6 Factors Favoring S_N1 versus S_N2 Reactions

Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g. alcohols, water)	Polar aprotic (e.g. DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after departs, the better the leaving group)	

6.15 ORGANIC SYNTHESIS: FUNCTIONAL GROUP TRANSFORMATIONS USING S_N2 REACTIONS

1. **Functional group transformation (interconversion): (Figure 6.13)**

2. Alkyl chlorides and bromides are easily converted to alkyl iodide by S_N2 reaction

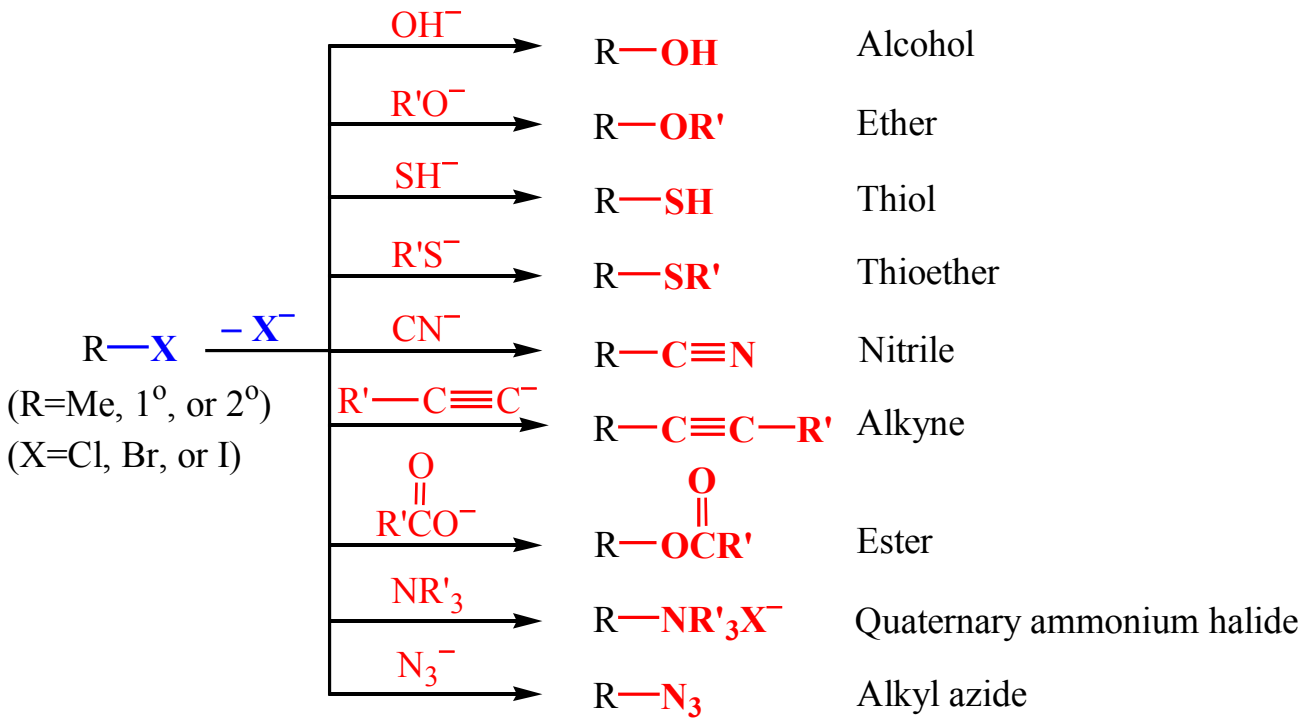
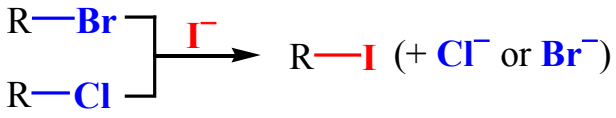
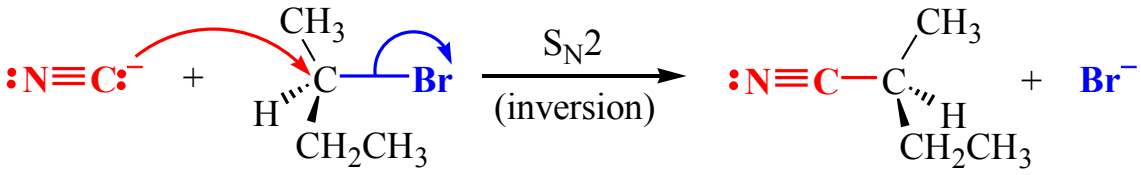


Figure 6.13 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.



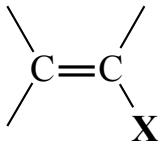
3. **Inversion of configuration** in **S_N2 reactions**:



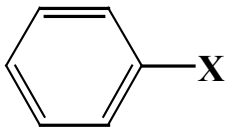
(*R*)-2-Bromobutane **(*S*)-2-Methylbutanenitrile**

6.15A THE UNREACTIVITY OF VINYLIC AND PHENYL HALIDES

1. Vinylic halides and phenyl halides are generally unreactive in S_N1 or S_N1 reactions.
   1) Vinylic and phenyl cations are highly unstable and do not form readily.
   2) The C–X bond of a vinylic or phenyl halide is stronger than that of an alkyl halide and the electrons of the double bond or benzene ring repel the approach of a nucleophile from the back side.



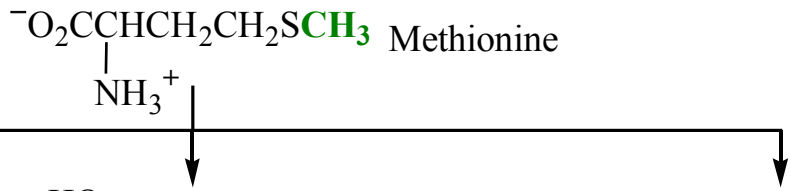
A vinylic halide

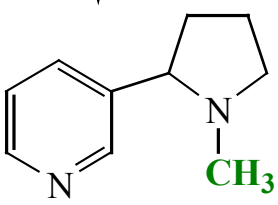


Phenyl halide

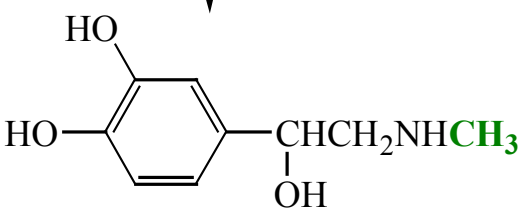
The Chemistry of….

Biological Methylation: A Biological Nucleophilic Substitution Reaction

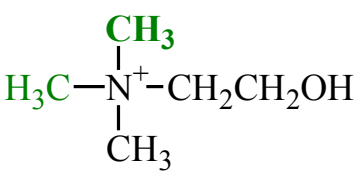




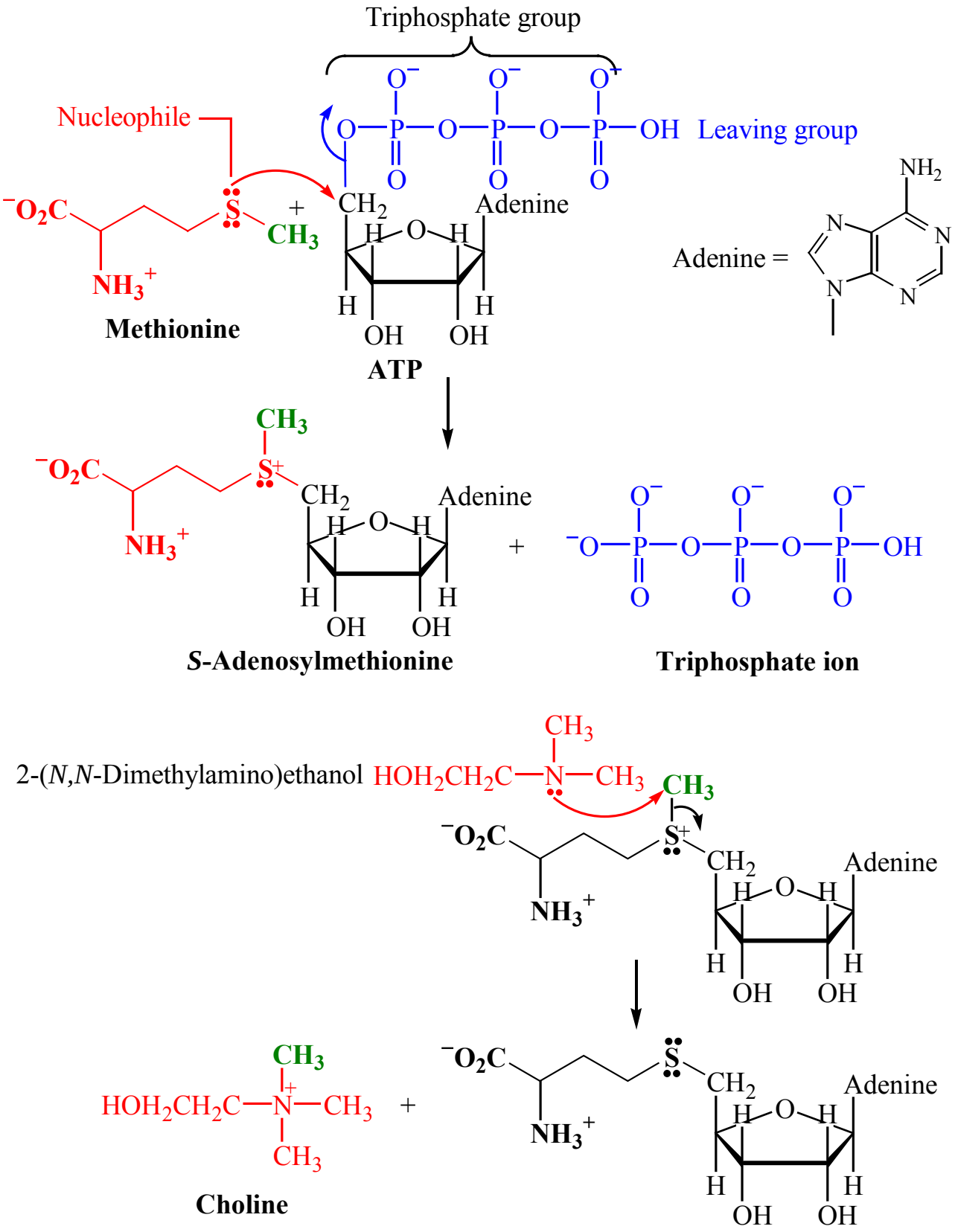
Nicotine



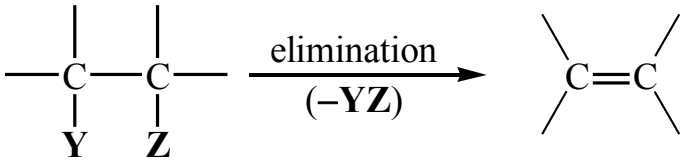
Adrenaline



Choline

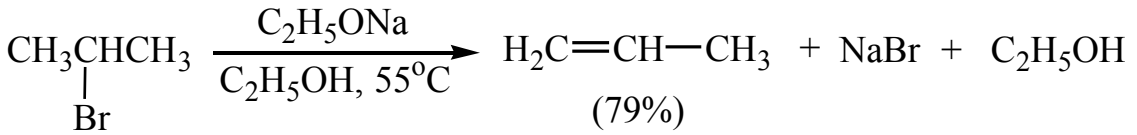

Triphosphate group
Nucleophile
Leaving group
Adenine
Adenine =
Methionine
ATP
S-Adenosylmethionine
Triphosphate ion
2-(N,N-Dimethylamino)ethanol
Choline

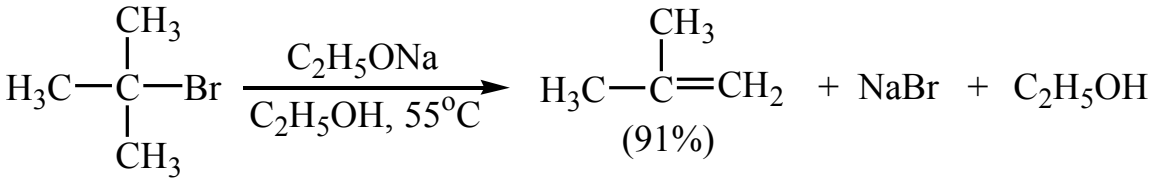
6.16 ELIMINATION REACTIONS OF ALKYL HALIDES



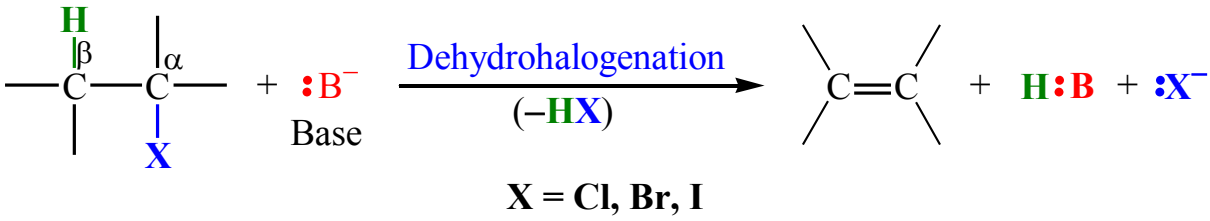
6.16A DEHYDROHALOGENATION

1. Heating an alkyl halide with a strong base causes elimination to happen:





2. **Dehydrohalogenation:**



1) alpha (α) carbon atom:

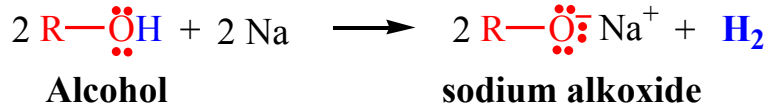
2) beta (β) hydrogen atom:

3) β-elimination (1,2-elimination):

6.16B BASES USED IN DEHYDROHALOGENATION

1. Potassium hydroxide dissolved in ethanol and the sodium salts of alcohols (such as sodium ethoxide) are often used as the base for dehydrohalogenation.

1) The sodium salt of an alcohol (a sodium alkoxide) can be prepared by treating an alcohol with sodium metal:

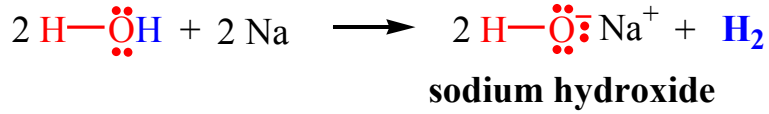


Alcohol **sodium alkoxide**

i) This is an **oxidation-reduction reaction**.

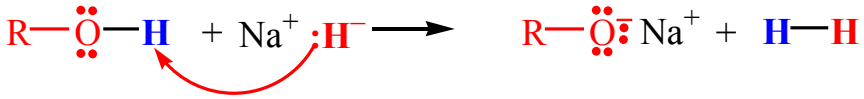
ii) Na is a very powerful reducing agent.

iii) Na reacts vigorously (at times explosively) with water:



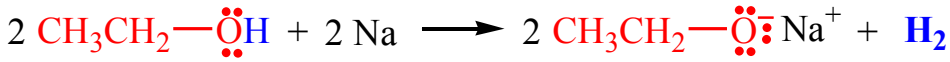
sodium hydroxide

2) Sodium alkoxides can also be prepared by reacting an alcohol with sodium hydride ($H:^-$):



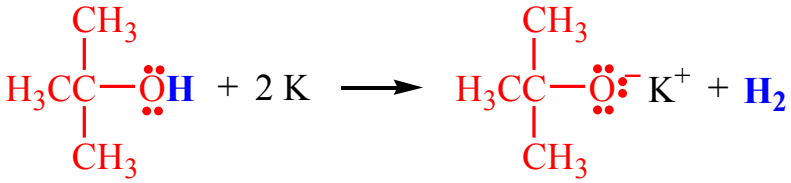
2. Sodium (and potassium) alkoxides are usually prepared by using excess of alcohol, and the excess alcohol becomes the solvent for the reaction.

1) Sodium ethoxide:



Ethanol (excess) **sodium ethoxide**

2) Potassium *tert*-butoxide:



***tert*-Butyl alcohol (excess)** **Potassium *tert*-butoxide**

6.16C MECHANISMS OF DEHYDROHALOGENATIONS

1. **E2 reaction**
2. **E1 reaction**

6.17 THE E2 REACTION

1. Rate equation

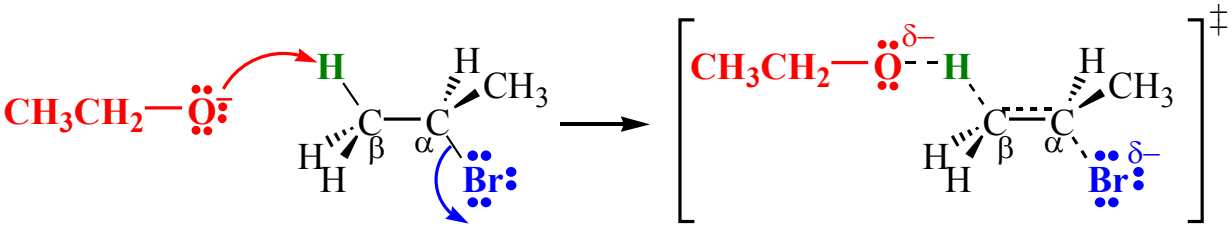
$$\text{Rate} = k\,[CH_3CHBrCH_3]\,[C_2H_5O^-]$$

A Mechanism for the E2 Reaction

Reaction:

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

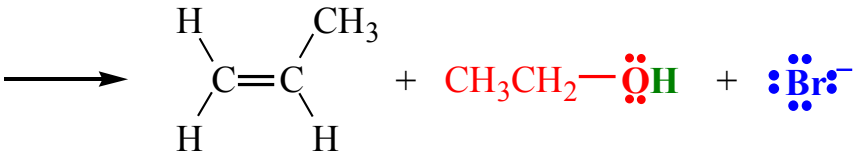
Mechanism:



The basic ethoxide ion begins to remove a proton from the β-carbon using its electron pair to form a bond to it. At the same tim, the electron pair of the β C–H bond begins to move in to become the π bond of a double bond, and the bromide begins to depart with the electrons that bonded it to the α carbon.

Transition state

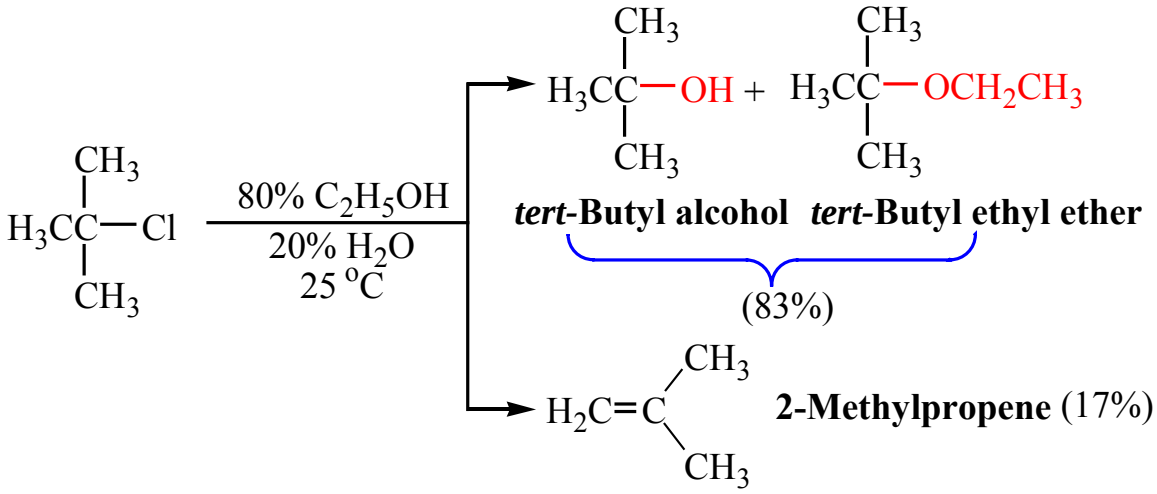
Partial bonds now exist between the oxygen and the β hydrogen and between the α carbonand the bromine. The carbon-carbon bond is developing double bond character.



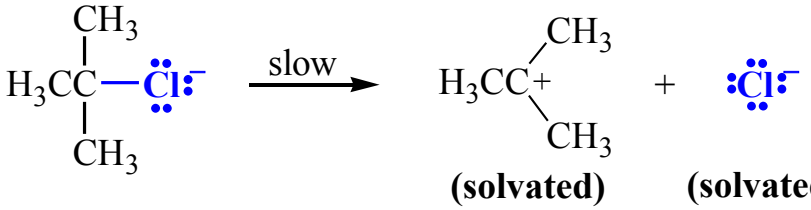
Now the double bond of the alkene is fully formed and the alkene has a trigonal plannar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

6.18 THE E1 REACTION

1. Treating *tert*-butyl chloride with 80% aqueous ethanol at 25°C gives ***substitution products*** in 83% yield and an ***elimination product*** in 17% yield.

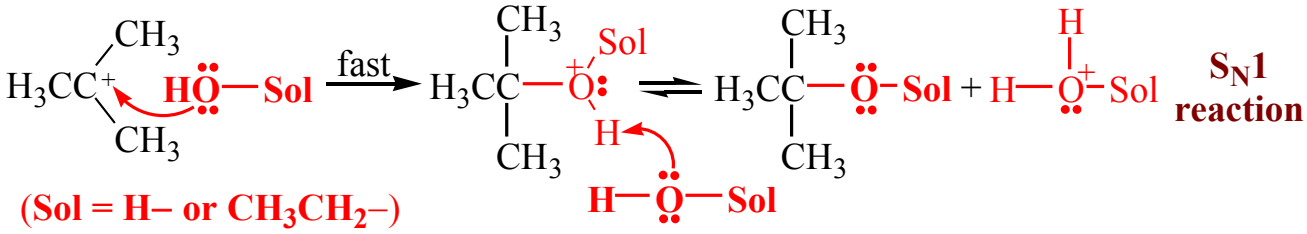


1) The initial step for reactions is the formation of a *tert*-butyl cation.

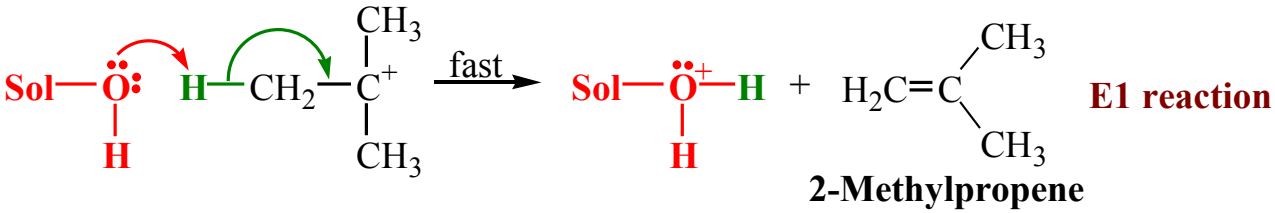


2) Whether substitution or elimination takes place depends on the next step (the fast step).

i) The S_N1 reaction:



ii) The E1 reaction:



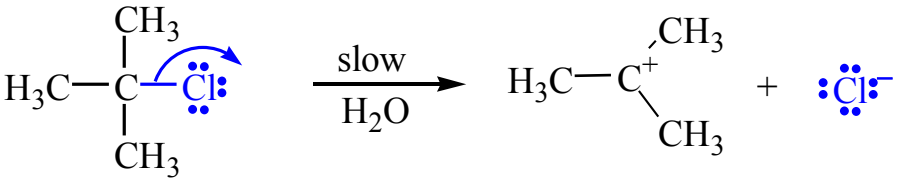
iii) The E1 reaction almost always accompany S_N1 reactions.

A Mechanism for the E1 Reaction

Reaction:

Mechanism:

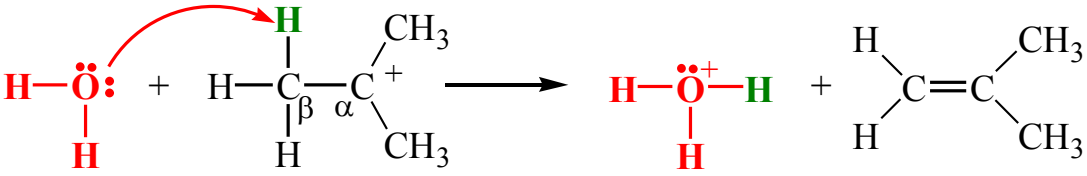
Step 1



Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocatoin and a chloride ion. The ions are solvated(and stabilized) by surrounding water molecules.

Step 2



A molecule of water removes one of the hydrogens from the β carbon of the carbocation. An electron pair moves in to form a double bond between the α and β carbon atoms.

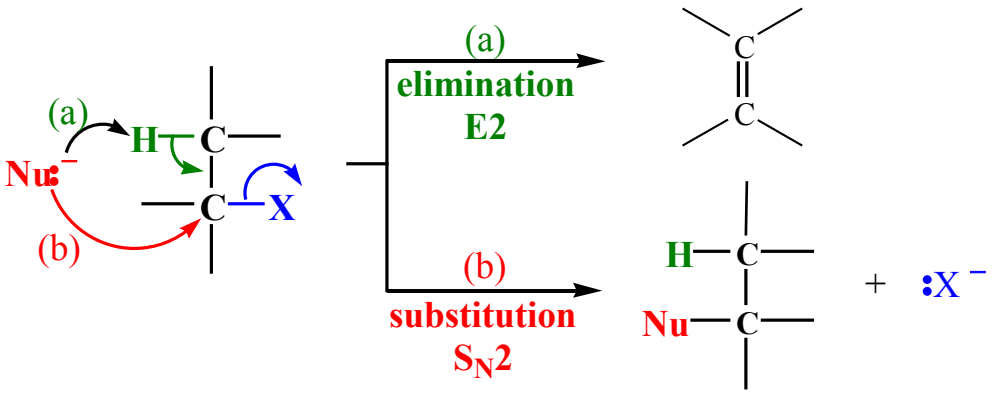
This step produces the alkene and a hydronium ion

6.19 SUBSTITUTION VERSUS ELIMINATION

1. Because the reactive part of a nucleophile or a base is an unshared electron pair, all nucleophiles are potential bases and all bases are potential nucleophiles.
2. Nucleophileic substitution reactions and elimination reactions often compete with each other.

6.19A S_N2 VERSUS E2

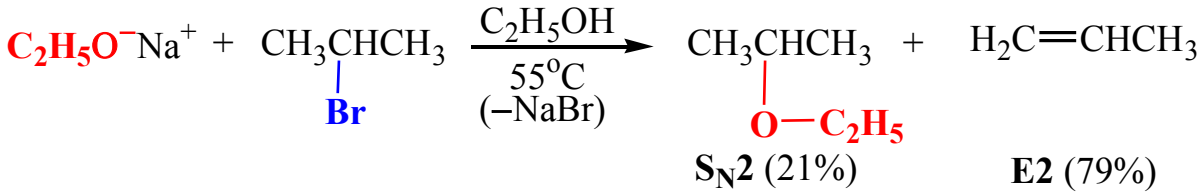
1. Since eliminations occur best by an E2 path when carried out with a high concentration of a strong base (and thus a high concentration of a strong nucleophile), substitution reactions by an S_N2 path often compete with the elimination reaction.
   1) When the nucleophile (base) attacks a β carbon atom, elimination occurs.
   2) When the nucleophile (base) attacks the carbon atom bearing the leaving group, substitution results.



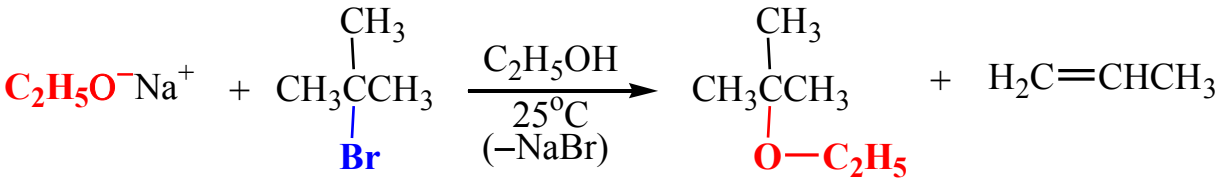
2. ***Primary*** halides and ethoxide: **substitution is favored**

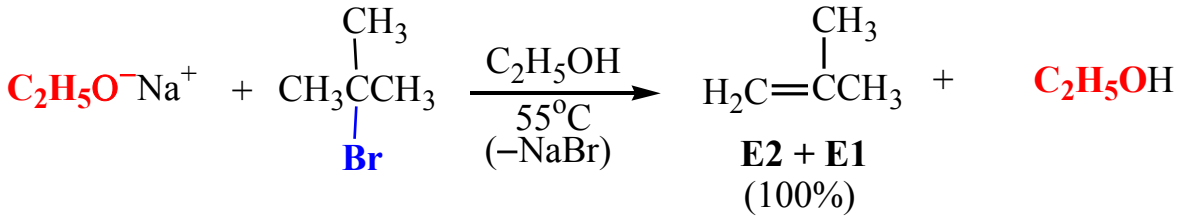
$$CH_3CH_2O^-Na^+ + CH_3CH_2Br \xrightarrow[55^oC]{C_2H_5OH} CH_3CH_2OCH_2CH_3 + H_2C{=}CH_2$$
$$(-NaBr)$$

3. ***Secondary*** halides: **elimination is favored**



4. ***Tertiary*** halides: **no S_N2 reaction, elimination reaction is highly favored**





1) Elimination is favored when the reaction is carried out at higher temperature.
   i) Eliminations have higher free energies of activation than substitutions because eliminations have a greater change in bonding (more bonds are broken and formed).
   ii) Eliminations have higher entropies than substitutions because eliminations have a greater number of products formed than that of starting compounds).

2) Any substitution that occurs must take place through an S_N1 mechanism.

6.19B TERTIARY HALIDES: S_N1 VERSUS E1

1. E1 reactions are favored:
   1) with substrates that can form stable carbocations.
   2) by the use of poor nucleophiles (weak bases).
   3) by the use of polar solvents (high dielectric constant).

2. It is usually difficult to influence the relative position between S_N1 and E1 products.

3. S_N1 reaction is favored over E1 reaction in most unimolecular reactions.

1) In general, substitution reactions of tertiary halides do not find wide use as synthetic methods.
2) Increasing the temperature of the reaction favors reaction by the E1 mechanism at the expense of the S_N1 mechanism.
3) **If elimination product is desired, it is more convenient to add a strong base and force an E2 reaction to take place**.

6.20 OVERALL SUMMARY

Table 6.7 Overall Summary of S_N1, S_N2, E1 and E2 Reactions

CH_3X	RCH_2X	RR'CHX	RR'R"CX
Methyl	**1°**	**2°**	**3°**
	Bimolecular reactions	**only**	**S_N1/E1 or E2**
Gives S_N2 reactions	Gives mainly S_N2 except with a hindered strong base [e.g., $(CH_3)_3CO^-$] and then gives mainly E2	Gives mainly S_N2 with weak bases (e.g., I^-, CN^-, RCO_2^-) and mainly E2 with strong bases (e.g., RO^-)	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used E2 predominates

Table 6D Reactivity of alkyl halides toward substitution and elimination

Halide type	*S_N1*	*S_N2*	*E1*	*E2*
Primary halide	Does not occur	**Highly favored**	Does not occur	Occurs when strong, hindered bases are used
Secondary halide	Can occur under solvolysis conditions in polar solvents	**Favored by good nucleophiles in polar aprotic solvents**	Can occur under solvolysis conditions in polar solvents	**Favored when strong bases are used**
Tertiary halide	**Favored by nonbasic nucleophiles in polar solvents**	Does not occur	Occurs under solvolysis conditions	**Highly favored when bases are used**

Table 6E Effects of reaction variables on substitution and elimination reactions

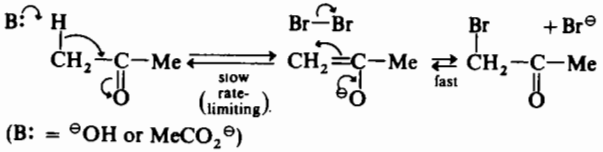
Reaction	*Solvent*	*Nucleophile/base*	Leaving group	Substrate structure
S_N1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by good nucleophile/weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
S_N2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by good nucleophile/ weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 1°, allylic, and benzylic substrates
E1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
E2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by poor nucleophile/ strong base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3° substrates

By analogy with acids above, specific basic catalysis is found to be characteristic of reactions in which there is rapid, reversible proton-removal from the substrate *before* the slow, rate-limiting step.

In *general base catalysis*, bases other than $^{\ominus}OH$ are involved. Thus in the base catalysed bromination of acetone (*cf.* p. 295) in an acetate buffer it is found that,

$$\text{Rate} = k_{\ominus OH}[^{\ominus}OH][\text{MeCOMe}] + k_{MeCO_2^{\ominus}}[MeCO_2^{\ominus}][\text{MeCOMe}]$$

and the reaction is believed to proceed:



(B: = $^{\ominus}OH$ or $MeCO_2^{\ominus}$)

Again by analogy with acids above, general base catalysis is found to be characteristic of reactions in which removal of proton from the substrate is slow, i.e. rate-limiting, and is followed by rapid conversion of the intermediate into products.

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4

Nucleophilic substitution at a saturated carbon atom

A type of reaction that has probably received more detailed study than any other—largely due to the monumental work of Ingold and his school—is nucleophilic substitution at a saturated carbon atom: the classical displacement reaction exemplified by the conversion of an alkyl halide into an alcohol by the action of aqueous base:

$$HO^{\ominus} + R{-}Hal \rightarrow HO{-}R + Hal^{\ominus}$$

Kinetic measurements on reactions in which alkyl halides are attacked by a wide variety of different nucleophiles, Nu:, have revealed two, essentially extreme, types: one in which,

$$\text{Rate} = k_2[\text{RHal}][\text{Nu:}] \qquad [1]$$

and another in which,

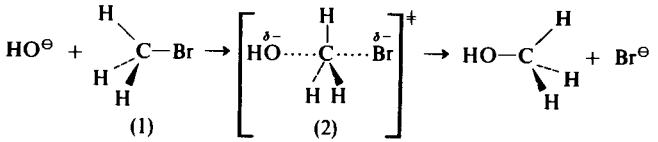
$$\text{Rate} = k_1[\text{RHal}] \qquad [2]$$

i.e. the rate is independent of [Nu:]. In some cases the rate equations are found to be 'mixed' or are otherwise complicated, but examples are known which exactly follow the simple relations above.

4.1 RELATION OF KINETICS TO MECHANISM

Hydrolysis of the primary halide bromomethane (methyl bromide) in aqueous base has been shown to proceed according to equation [1]

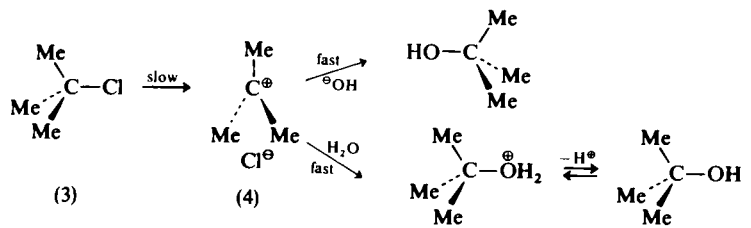
above, and this has been interpreted as involving the participation of both alkyl halide and hydroxyl ion in the rate-limiting (i.e. slowest) step of the reaction. Ingold has suggested a transition state in which the attacking hydroxyl ion becomes partially bonded to the reacting carbon atom before the incipient bromide ion has become wholly detached from it; thus part of the energy necessary to effect the breaking of the C—Br bond is then supplied by that produced in forming the HO—C bond. Quantum mechanical calculation shows that an approach by the hydroxyl ion along the line of centres of the carbon and bromine atoms is that of lowest energy requirement. This can be represented:



(1) (2) Transition state

The negative charge is spread in the transition state in the course of being transferred from hydroxyl to bromine, and the hydrogen atoms attached to the carbon atom attacked pass through a position in which they all lie in one plane (at right angles to the plane of the paper as drawn above). The initially sp^3 hybridised carbon atom becomes sp^2 hybridised in the transition state, the HO and Br being associated with the two lobes of the unhybridised *p* orbital that is thereby made available. This type of mechanism has been designated by Ingold as S_N2: Substitution Nucleophilic bimolecular.

By contrast, hydrolysis of the tertiary halide 2-chloro-2-methylpropane (3,*t*-butyl chloride) in base is found kinetically to follow equation [2], i.e. as the rate is independent of [$^{\ominus}$OH], this can play no part in the rate-limiting step. This has been interpreted as indicating that the halide undergoes slow ionisation (in fact, completion of the R→Cl polarisation that has already been shown to be present in such a molecule) as the rate-limiting step to yield the ion pair $R^{\oplus}Cl^{\ominus}$ (4); followed by rapid, non rate-limiting attack by $^{\ominus}$OH or, if that is suitable, by solvent, the latter often predominating because of its very high concentration:



(3) (4)

This type of mechanism has been designated S_N1: Substitution Nucleophilic unimolecular. The energy necessary to effect the initial ionisation is largely recovered from the energy evolved through solvation of the resultant ion pair. The entropy of activation, $\Delta S^{\ddagger}$, for such a dissociative process (*cf.* p. 39) is also advantageous; thus $\Delta S^{\ddagger}$ for the hydrolysis of Me_3CCl is found to be $+51\ J\ K^{-1}\ mol^{-1}$, compared with $-17\ J\ K^{-1}\ mol^{-1}$ for hydrolysis of CH_3Cl. The cation in the ion pair (4), in which the central carbon atom carries the +ve charge, is of course a carbocation intermediate, and during its formation the initially sp^3 hybridised carbon atom collapses to a more stable planar (sp^2) state, in which the three methyl groups are as far apart from each other as they can get. Attack by $^{\ominus}$OH or solvent (e.g. H_2O:) can then take place from either side of this planar intermediate. If attainment of this planar state is inhibited by steric or other factors (*cf.* p. 87), the carbocation intermediate will be formed only with difficulty, if at all; i.e. ionisation, and hence reaction by the S_N1 pathway, may then not take place.

Thus the salient difference between reaction by the S_N2 and S_N1 pathways is that S_N2 proceeds in one step only, *via* a transition state; while S_N1 proceeds in two steps, *via* an actual (carbocation) intermediate.

A certain element of confusion is to be met with both in textbooks, and in the literature, over the use and meaning of the terms *order* (*cf.* p. 39) and *molecularity* as applied to reactions. The order is an experimentally determined quantity, the overall order of a reaction being the sum of the powers of the concentration terms that appear in the rate equation:

Rate = k_3[A][B][C]	Third order overall
Rate = k_3[A]^2[B]	Third order overall
Rate = k_2[A]^2	Second order overall

Generally, however, it is the order with respect to a particular reactant (or reactants) that is of more interest and significance than the overall order, i.e. that the above reactions are first order, second order, and second order, respectively, with respect to A. Examples of both zero order, and non-integral orders, with respect to a particular reactant are also known.

The molecularity refers to the number of species (molecules, ions, etc.) that are undergoing bond-breaking and/or bond-making in one step of the reaction, usually in the rate-limiting step. It is important to realise that the molecularity is not an experimentally determined quantity, and has significance only in the light of the particular mechanism chosen for the reaction: it is an integral part of the mechanistic interpretation of the reaction and is susceptible to re-

evaluation, in the light of additional experimental information about the reaction, in a way that the order cannot be. The molecularity of the reaction as a whole only has meaning if the reaction proceeds in a single step (an *elementary* reaction), as is believed to be the case with the hydrolysis of bromomethane above (p. 78); order and molecularity then coincide, the reaction being second order overall (first order in each reactant) and bimolecular. Order and molecularity do not always, or necessarily, have the same value, however.

Simple kinetic measurements can, however, be an inadequate guide to which of the above two mechanisms, S_N1 or S_N2, is actually operating in, for example, the hydrolysis of a halide. Thus, as we have seen (p. 45), where the solvent can act as a nucleophile (*solvolysis*), e.g. H_2O, we would expect for an S_N2 type reaction,

$$\text{Rate} = k_2[\text{RHal}][\text{H}_2\text{O}]$$

but as $[H_2O]$ remains effectively constant the rate equation actually observed will be,

$$\text{Rate} = k_{obs}[\text{RHal}]$$

and simple kinetic measurements in aqueous solution will thus suggest, erroneously, that the reaction is of the S_N1 type.

A kinetic distinction between the operation of the S_N1 and S_N2 modes can often be made by observing the effect on the overall reaction rate of adding a competing nucleophile, e.g. azide anion, $N_3^{\ominus}$. The total nucleophile concentration is thus increased, and for the S_N2 mode where [Nu:] appears in the rate equation, this will result in an increased reaction rate due to the increased [Nu:]. By contrast, for the S_N1 mode [Nu:] does not appear in the rate equation, i.e. is not involved in the rate-limiting step, and addition of $N_3^{\ominus}$ will thus be without significant effect on the observed reaction rate, though it will naturally influence the composition of the product.

4.2 EFFECT OF SOLVENT

Changing the solvent in which a reaction is carried out often exerts a profound effect on its rate and may, indeed, even result in a change in its mechanistic pathway. Thus for a halide that undergoes hydrolysis by the S_N1 mode, increase in the polarity of the solvent (i.e. increase in ϵ, the dielectric constant) and/or its ion-solvating ability is found to result in a very marked increase in reaction rate. Thus the rate of solvolysis of the tertiary halide, Me_3CBr, is found to be 3×10^4 times faster in 50% aqueous ethanol than in ethanol alone. This occurs because, in the S_N1 mode, charge is developed and concentrated in

the T.S. compared with the starting material:

$$\text{R—Hal} \rightarrow \left[\overset{\delta+}{\text{R}} \cdots \overset{\delta-}{\text{Hal}}\right]^{\ddagger} \rightarrow \text{R}^{\oplus}\text{Hal}^{\ominus}$$

The energy required to effect such a process decreases as ϵ rises; the process is also facilitated by increasing solvation, and consequent stabilisation, of the developing ion pair compared with the starting material. That such effects, particularly solvation, are of prime importance is borne out by the fact that S_N1 type reactions are extremely uncommon in the gas phase.

For the S_N2 mode, however, increasing solvent polarity is found to have a much less marked effect, resulting in a slight decrease in reaction rate. This occurs because in this particular example new charge is not developed, and existing charge is dispersed, in the T.S. compared with the starting materials;

$$\text{Nu}^{\ominus} + \text{R—Hal} \rightarrow \left[\overset{\delta-}{\text{Nu}} \cdots \text{R} \cdots \overset{\delta-}{\text{Hal}}\right]^{\ddagger} \rightarrow \text{Nu—R} + \text{Hal}^{\ominus}$$

thus, solvation of the T.S. is likely to be somewhat less effective than that of the initial nucleophile—hence the slight decrease. This differing behaviour of S_N1 and S_N2 modes to changes of solvent can be used to some extent diagnostically.

A very marked effect on the rate of S_N2 reactions is, however, effected on transferring them from polar hydroxylic solvents to polar non-hydroxylic solvents. Thus the reaction rate of the primary halide, MeI, with $N_3^{\ominus}$ at 0° increased $4{\cdot}5 \times 10^4$-fold on transfer from methanol ($\epsilon = 33$) to N,N-dimethylmethanamide(dimethyl formamide, DMF), $HCONMe_2$, with very much the same polarity ($\epsilon = 37$). This very large rate difference stems from the fact that the attacking nucleophile, $N_3^{\ominus}$, is highly solvated through hydrogen-bonding in MeOH (*cf.* p. 57) whereas it is very much less strongly solvated—and not by hydrogen-bonding—in $HCONMe_2$. The largely unsolvated $N_3^{\ominus}$ anion (in $HCONMe_2$) is a very much more powerful nucleophile than when surrounded (as in MeOH) by a very much less nucleophilic solvation envelope, hence the rise in reaction rate. Rate increases of as much as 10^9-fold have been observed on transferring S_N2 reactions from, e.g. MeOH, to another polar non-protic solvent, dimethyl sulphoxide (DMSO), Me_2SO ($\epsilon = 46$).

So far as actual changes of mechanistic pathway with change of solvent are concerned, increase in solvent polarity and ion-solvating ability may (but not necessarily will) change the reaction mode from $S_N2 \rightarrow S_N1$. Transfer from hydroxylic to polar, non-protic solvents (e.g. DMSO) can, and often do, change the reaction mode from $S_N1 \rightarrow S_N2$ by enormously increasing the effectiveness of the nucleophile in the system.

4.3 EFFECT OF STRUCTURE

An interesting sequence is provided by the reaction with base of the series of halides:

CH_3-Br	$MeCH_2-Br$	Me_2CH-Br	Me_3C-Br
(5)	(6)	(7)	(8)

The first and last members are described in the literature as undergoing ready hydrolysis, the two intermediate members being more resistant. Measurement of their rates of hydrolysis with dilute, aqueous ethanolic sodium hydroxide solution gives the plot* (Fig. 4.1),

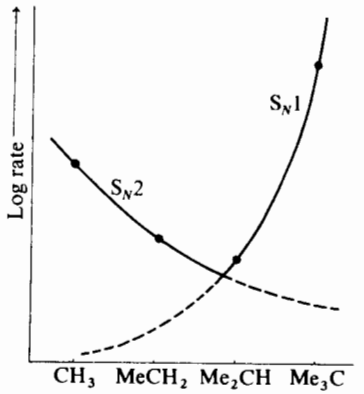


Fig. 4.1

and further kinetic investigation reveals a change in order of reaction, and hence presumably, of mechanism, as the series is traversed. Thus bromomethane (5) and bromoethane (6) are found to follow a second order rate equation, 2-bromopropane (7) a mixed second and first order equation, the relative proportion of the two depending on the initial [$^{\ominus}$OH] (the higher the initial concentration the greater the second order proportion) and the total rate here being a minimum for the series, while 2-bromo-2-methylpropane (8) is found to follow a first order rate equation.

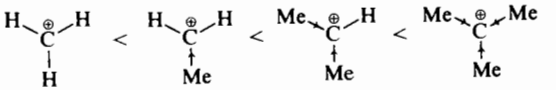
In seeking an explanation for the implied changeover in mechanistic pathway we need to consider, in each case, the effect on the transition state of both electronic and steric factors. For S_N2 attack, the enhanced inductive effect of an increasing number of methyl groups, as we go across the series, might be expected to make the carbon atom that

* Based on Ingold, *Structure and Mechanism in Organic Chemistry*, by permission of Cornell University Press.

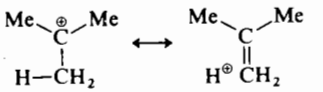
bears the bromine progressively less positively polarised, and hence less readily attacked by $^{\ominus}$OH. This effect is probably small, and steric factors are of more importance; thus $^{\ominus}$OH will find it progressively more difficult to attack the bromine-carrying carbon as the latter becomes more heavily substituted. More significantly, the resultant S_N2 transition state will have *five* groups around this carbon atom (compared with only *four* in the initial halide), there will thus be an increase in crowding on going from the initial halide to the transition state, and this relative crowding will increase as the size of the original substituents increases (H $\longrightarrow$ Me). The more crowded the T.S. relative to the starting materials, the higher its energy will be, and the slower therefore will it be formed. We would thus expect the purely S_N2 reaction rate to decrease as the above series is traversed. It is in fact possible to effect nucleophilic substitution ($Br^{\ominus}$ + R—Cl) on a series of halides analogous to those in Fig. 4.1 (p. 82), under conditions such that a strictly second order rate equation (S_N2 pathway) is followed throughout. We then observe:

Relative S_N2 rate:	CH_3Cl	$MeCH_2Cl$	Me_2CHCl	Me_3CCl
	1	$2{\cdot}7\times10^{-2}$	$4{\cdot}9\times10^{-4}$	$2{\cdot}2\times10^{-5}$

For S_N1 attack, considerable charge separation has taken place in the T.S. (*cf.* p. 81), and the ion pair intermediate to which it gives rise is therefore often taken as a model for it. As the above halide series is traversed, there is increasing stabilisation of the carbocation moiety of the ion pair, i.e. increasing rate of formation of the T.S. This increasing stabilisation arises from the operation of both an inductive effect,



and hyperconjugation (p. 25), e.g.



via the hydrogen atoms attached to the α-carbons, the above series of carbocations having 0, 3, 6 and 9 such hydrogen atoms, respectively.

Support for such an interaction of the H—C bonds with the carbon atom carrying the positive charge is provided by substituting H by D in the original halide, the rate of formation of the ion pair is then found to be slowed down by ≈10% per deuterium atom incorporated: a result compatible only with the H—C bonds being involved in the ionisation. This is known as a *secondary kinetic isotope effect*, secondary

because it is a bond other than that carrying the isotopic label that is being broken (*cf.* p. 46). The relative contributions of hyperconjugation and inductive effects to the stabilisation of carbocations is open to debate, but it is significant that a number of carbocations will only form at all if they can take up a planar arrangement, the state in which hyperconjugation will operate most effectively (*cf.* p. 104).

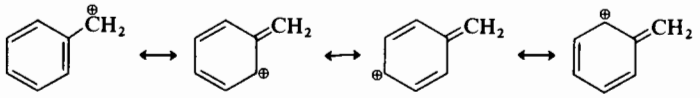
In steric terms there is a relief of crowding on going from the initial halide, with a tetrahedral disposition of four substituents about the sp^3 hybridised carbon atom, to the carbocation, with a planar disposition of only *three* substituents (*cf. five* for the S_N2 T.S.) about the now sp^2 hybridised carbon atom. The three substituents are as far apart from each other as they can get in the planar carbocation, and the relative relief of crowding (halide → carbocation) will increase as the substituents increase in size (H → Me → Me_3C). The S_N1 reaction rate would thus be expected to increase markedly (on both electronic and steric grounds) as the series of halides is traversed. It has not, however, proved possible to confirm this experimentally by setting up conditions such that the four halides of Fig. 4.1 (p. 82) all react *via* the S_N1 pathway.

Thus, as the S_N2 rate is expected to *decrease*, and the S_N1 rate to *increase*, across the series in Fig. 4.1, the reason for the observed pattern of reaction rates, and changeover in reaction pathway, becomes apparent.

A similar mechanistic changeover is observed, though considerably sooner, in traversing the series:

CH_3-Cl	$C_6H_5CH_2-Cl$	$(C_6H_5)_2CH-Cl$	$(C_6H_5)_3C-Cl$
(9)	(10)	(11)	(12)

Thus for hydrolysis in 50% aqueous acetone, a mixed second and first order rate equation is observed for phenylchloromethane (benzyl chloride, 10)—moving over almost completely to the S_N1 mode in water alone. Diphenylchloromethane (11) is found to follow a first order rate equation, with a very large increase in total rate, while with triphenylchloromethane (trityl chloride, 12) the ionisation is so pronounced that the compound exhibits electrical conductivity when dissolved in liquid SO_2. The main reason for the greater promotion of ionisation—with consequent earlier changeover to the S_N1 pathway in this series—is the considerable stabilisation of the carbocation, by delocalisation of its positive charge, that is now possible:



This is a classical example of an ion stabilised by charge delocalisation *via* the agency of the delocalised π orbitals of the benzene nucleus (*cf.* the negatively charged phenoxide ion, p. 23). The effect will become progressively more pronounced, and S_N1 attack further facilitated, with $(C_6H_5)_2CHCl$(11) and $(C_6H_5)_3CCl$(12), as the possibilities for delocalising the positive charge are increased in the carbocations to which these latter halides give rise.

S_N2 attack on the CH_2 in (10) is found to proceed at very much the same rate as on that in $MeCH_2Cl$, suggesting that any adverse steric crowding in the T.S. by the bulky C_6H_5 group is compensated by a small electronic (inductive?) effect promoting reaction.

Similar carbocation stabilisation can also occur in the hydrolysis of allyl halides, e.g. 3-chloropropene:

$$CH_2{=}CH{-}CH_2Cl \rightarrow [CH_2{=}CH{-}\overset{\oplus}{C}H_2 \leftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2]\ Cl^{\ominus}$$

S_N1 attack is thus promoted and allyl, like benzyl, halides are normally more reactive than species, e.g. $CH_3CH_2CH_2Cl$ and $C_6H_5CH_2CH_2CH_2Cl$, in which such carbocation stabilisation cannot take place. S_N2 attack is also speeded up, compared with $CH_3CH_2CH_2Cl$, presumably because any electronic effect of the double bond—promoting reaction—is not here nullified by an adverse steric effect, as with the bulky C_6H_5 group in $C_6H_5CH_2Cl$ (*cf.* above). The proportion of the total reaction proceeding by each of the two pathways is found to depend on the conditions: more powerful nucleophiles promoting the S_N2 mode (*cf.* p. 96).

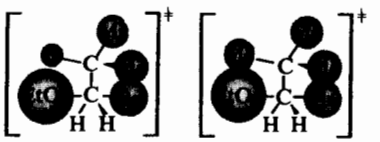
By contrast, vinyl halides such as chloroethene, $CH_2{=}CHCl$, and halogenobenzenes are very unreactive towards nucleophiles. This stems from the fact that the halogen atom is now bonded to an sp^2 hybridised carbon, with the result that the electron pair of the C—Cl bond is drawn closer to carbon than in the bond to an sp^3 hybridised carbon. The C—Cl is found to be stronger, and thus less easily broken, than in, for example, CH_3CH_2Cl, and the C—Cl dipole is smaller; there is thus less tendency to ionisation (S_N1) and a less positive carbon for $^{\ominus}OH$ to attack (S_N2); the π electrons of the double bond also inhibit the close approach of an attacking nucleophile. The double bond would not help to stabilise either the S_N2 transition state or the carbocation involved in the S_N1 pathway. Very much the same considerations apply to halogenobenzenes, with their sp^2 hybridised carbons and the π orbital system of the benzene nucleus; their reactions, which though often bimolecular are not in fact simply S_N2 in nature, are discussed further below (p. 170).

The influence of steric factors on the reaction pathway is particularly observed when substitution takes place at the β-position. Thus for the

series,

CH_3-CH_2-Br	$MeCH_2-CH_2-Br$	Me_2CH-CH_2-Br	Me_3C-CH_2-Br
(6) 1·0	(13) $2{\cdot}8 \times 10^{-1}$	(14) $3{\cdot}0 \times 10^{-2}$	(15) $4{\cdot}2 \times 10^{-6}$

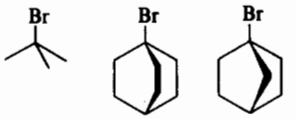
the figures quoted are relative rates of reaction (S_N2 throughout) with $EtO^{\ominus}$ in EtOH at 55°. Any differences in electronic effect of the Me groups through two saturated carbon atoms would be very small, and the reason for the rate differences is steric: increased difficulty of approach of $EtO^{\ominus}$ 'from the back' of the carbon atom carrying Br, and increased crowding in the resultant T.S. The reason for the particularly large drop in rate between 1-bromo-2-methylpropane (14) and 1-bromo-2,2-dimethylpropane(neopentyl bromide, 15) is that the T.S. for the former, though somewhat crowded, can, by rotation about the $C_\alpha-C_\beta$ bond, adopt one conformation (14*a*) in which the attacking $EtO^{\ominus}$ is interfered with only by H, while no such relief of crowding is open in the T.S. (15*a*) for the latter (but see also, p. 110):



(14*a*) (15*a*)

The T.S. (15*a*) will thus be at a much higher energy level, ΔG^{*} (p. 38) will be larger and the reaction rate correspondingly lower.

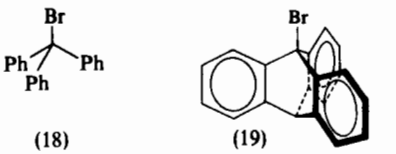
The effect of structure on relative reactivity may be seen particularly clearly when a halogen atom is located at the bridgehead of a bicyclic system. Thus the following rates were observed for solvolysis in 80% aqueous ethanol at 25°:



(8)	(16)	(17)
1	$\approx 10^{-6}$	$\approx 10^{-14}$

All are tertiary halides so that attack by the S_N2 mode would not be expected to occur on (16) or (17) any more than it did on (8) (*cf.* p. 82). S_N2 attack 'from the back' on the carbon atom carrying Br would in any case be prevented in (16) and (17) both sterically by their cage-like structure, and also by the impossibility of forcing their fairly rigid framework through transition states with the required planar distribution of bonds to the bridgehead carbon atom (*cf.* p. 84). Solvolysis *via* rate-limiting formation of the ion pair (S_N1), as happens with (8) is also inhibited because the resultant carbocations from (16) and (17) would be unable, because of their rigid frameworks, to stabilise themselves by collapsing to the stable planar state. These carbocation intermediates are thus of very much higher energy level than usual, and therefore are formed only slowly and with reluctance. The very greatly reduced solvolysis rate of (17) compared with (16) reflects the greater rigidity about the bridgehead (cationic) carbon with a one-carbon (17), than with a two-carbon (16), bridge.

This rigidity is carried even further in 1-bromotriptycene (19),



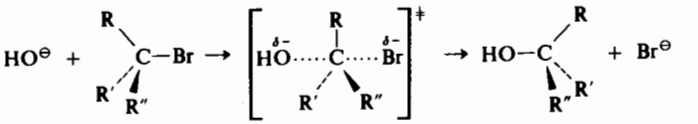
(18)	(19)
1	10^{-23}

in which the bromine atom is found to be virtually inert to nucleophiles. Despite the formal resemblance in the environment of the bromine atom in (19) to that in (18), they are found to differ in their rate of reaction under parallel conditions by a factor of $\approx 10^{-23}:1$! This is because stabilisation of the carbocation from (18) can occur by delocalisation of its charge through the π orbital systems of the three benzene rings; whereas the extremely rigid structure of (19) will hold the cation's empty orbital (from loss of $Br^{\ominus}$) all but at right angles to these π orbital systems, thus preventing such delocalisation.

4.4 STEREOCHEMICAL IMPLICATIONS OF MECHANISM

Hydrolysis of an optically active form of a *chiral** halide presents some interesting stereochemical features. Thus considering each pathway in turn:

4.4.1 S_N2 mechanism: inversion of configuration



(+) (?)

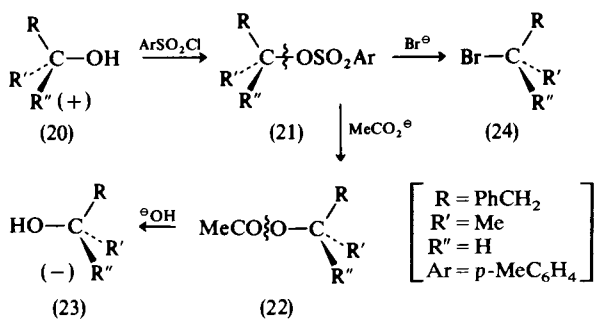
* A *chiral* compound is one that is not superimposable on its mirror image.

It will be seen that the spatial arrangement of the three residual groups attached to the carbon atom attacked has been effectively turned inside out. The carbon atom is said to have undergone *inversion* of its *configuration* (the arrangement in space of the groups attached to it). Indeed, if the product could be the bromide, instead of, as here, the corresponding alcohol, it would be found to rotate the plane of polarisation of plane polarised light in the opposite direction, i.e. (−), to the starting material, (+), for it would, of course, be its mirror image (*cf.* p. 89). The actual product is the alcohol, however, and we are unfortunately not able to tell, merely by observing its direction of optical rotation, whether it has the same or the opposite configuration to the bromide from which it was derived: compounds, other than mirror images, that have opposite configurations do not necessarily exhibit opposite directions of optical rotation, while compounds that have the same configuration do not necessarily exhibit the same direction of optical rotation. Thus in order to confirm that the above S_N2 reaction is, in practice, attended by an inversion of configuration, as theory requires, it is necessary to have an independent method for relating the configuration of starting material and product, e.g. the bromide and corresponding alcohol above.

4.4.2 Determination of relative configuration

This turns essentially on the fact that if a chiral compound undergoes a reaction in which a bond joining one of the groups to the chiral centre is broken, then the centre may—though it need not of necessity—undergo inversion of configuration; while if the compound undergoes reaction in which no such bond is broken then the chiral centre will preserve its configuration intact.

Thus in the series of reactions on the optically active(+) alcohol (20),

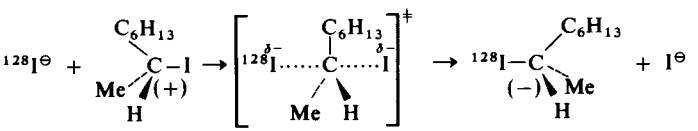


(20) (21) (24) (23) (22)

formation of an ester with 4-methylbenzenesulphonyl(tosyl) chloride

is known not to break the C—O bond of the alcohol,* hence the tosylate (21) must have the same configuration as the original alcohol. Reaction of this ester (21) with $MeCO_2^{\ominus}$ is known to be a displacement in which $ArSO_3^{\ominus}$ (Ar = *p*-MeC_6H_4) is expelled and $MeCO_2^{\ominus}$ introduced,* hence the C—O bond *is* broken in this reaction, and inversion of configuration can thus take place in forming the acetate (22). Alkaline hydrolysis of the acetate (22 → 23) can be shown not to involve fission of the alkyl-oxygen C—O linkage,† so the alcohol (23) must have the same configuration as the acetate (22). As (23) is found to be the mirror image of the starting material (20)—opposite direction of optical rotation—an inversion of configuration must have taken place during the series of reactions, and can have occurred only during reaction of $MeCO_2^{\ominus}$ with the tosylate (21). Reaction of this tosylate (21) with a number of nucleophiles showed that inversion of configuration occurred in each case: it may thus be concluded with some confidence that it occurs on reaction with $Br^{\ominus}$ to yield the bromide (24), i.e. that the bromide (24), like the acetate (22), has the opposite configuration to the original alcohol (20).

The general principle—that bimolecular (S_N2) displacement reactions are attended by inversion of configuration—was established in an elegant and highly ingenious experiment, in which an optically active alkyl halide undergoes displacement by the same—though isotopically labelled—halide ion as nucleophile, e.g. radioactive $^{128}I^{\ominus}$ on (+)2-iodooctane (25):



The displacement was monitored by observing the changing distribution of radioactive ^{128}I between the inorganic (sodium) iodide and 2-iodooctane, and it was found, under these conditions, to be second order overall (first order with respect to $^{128}I^{\ominus}$ and to 2-iodooctane) with $k_2 = 3{\cdot}00 \pm 0{\cdot}25 \times 10^{-5}$ (at 30°).

If *inversion* takes place, as S_N2 requires, the optical activity of the solution will decline to zero, i.e. *racemisation* will occur. This will happen because inversion of the configuration of a molecule of (+) (25) results in formation of a molecule of its mirror image (−)

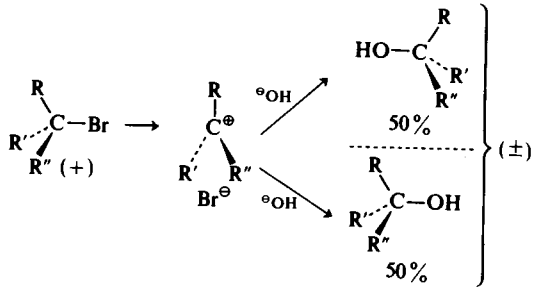
* That such is the case may be shown by using an alcohol labelled with ^{18}O in its OH group, and demonstrating that this atom is not eliminated on forming the tosylate; it is, however, eliminated when the tosylate is reacted with $MeCO_2^{\ominus}$.

† Hydrolysis of an acetate in which the alcohol-oxygen atom is ^{18}O labelled fails to result in the latter's replacement, thus showing that the alkyl-oxygen bond of the acetate is not broken during its hydrolysis (*cf.* p. 47).

(25*a*), which 'pairs off' with a second molecule of (+) (25) to form a (±) racemate: the observed rate of *racemisation* will thus be twice the rate of inversion. The reaction was monitored polarimetrically, the rate of racemisation measured thereby, and the rate of inversion calculated from it: it was found to have $k = 2{\cdot}88 \pm 0{\cdot}03 \times 10^{-5}$ (at 30°).

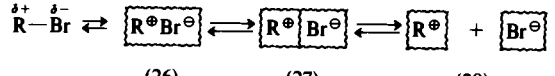
The rate of displacement and of inversion are thus identical within the limits of experimental error, and it thus follows that each act of bimolecular displacement must thus proceed with inversion of configuration. Having shown that S_N2 reactions are attended by inversion of configuration, independent demonstration that a particular reaction occurs *via* the S_N2 mode is often used to correlate the configuration of product and starting material in the reaction.

4.4.3 S_N1 mechanism: racemisation?



As the carbocation formed in the slow, rate-limiting step of the reaction is planar, it might be expected that subsequent attack by a nucleophile such as $^{\ominus}OH$, or the solvent (H_2O:), would take place with equal readiness from either side of this planar carbocation; leading to a 50/50 mixture of species having the same, and the opposite, configuration as the starting material, i.e. that *racemisation* would take place yielding an optically inactive (±) product.

In practice, however, the expected racemisation—and nothing but racemisation—is rarely observed, it is almost always accompanied by some degree of inversion. The relative proportions of the two are found to depend on: (*a*) the structure of the halide, in particular the relative stability of the carbocation to which it can give rise; and (*b*) the solvent, in particular on its ability as a nucleophile. The more stable the carbocation, the greater is the proportion of racemisation; the more nucleophilic the solvent, the greater is the proportion of inversion. These observations become understandable if the rate-limiting S_N1 ionisation follows the sequence:



(26) (27) (28)

Here (26) is an *intimate* ion pair in which the jointly solvated gegenions are in very close association with no solvent molecules between them, (27) is a *solvent-separated* ion pair, and (28) represents the now dissociated, and separately solvated, pair of ions.

In a solvolysis reaction, attack on $R^{\oplus}$ by a solvent molecule, e.g. H_2O:, in (26) is likely to lead to inversion, as attack can take place (by the solvent envelope) on the 'back' side of $R^{\oplus}$, but not on the 'front' side where there are no solvent molecules, and which is shielded by the $Br^{\ominus}$ gegen ion. Attack in (27) is more likely to lead to attack from either side, leading to racemisation, while attack on (28) can clearly happen with equal facility from either side. Thus the longer the life of $R^{\oplus}$, i.e. the longer it escapes nucleophilic attack, the greater the proportion of racemisation that we should expect to occur. The life of $R^{\oplus}$ is likely to be longer the more stable it is—(*a*) above—but the shorter the more powerfully nucleophilic the solvent—(*b*) above.

Thus solvolysis of (+)$C_6H_5CHMeCl$, which can form a stabilised benzyl type carbocation (*cf.* p. 84), leads to 98% racemisation while (+)$C_6H_{13}CHMeCl$, where no comparable stabilisation can occur, leads to only 34% racemisation. Solvolysis of (+)$C_6H_5CHMeCl$ in 80% acetone/20% water leads to 98% racemisation (above), but in the more nucleophilic water alone to only 80% racemisation. The same general considerations apply to nucleophilic displacement reactions by Nu: as to solvolysis, except that $R^{\oplus}$ may persist a little further along the sequence because part at least of the solvent envelope has to be stripped away before Nu: can get at $R^{\oplus}$. It is important to notice that racemisation is clearly very much less of a stereochemical requirement for S_N1 reactions than inversion was for S_N2.

4.4.4 The mechanistic borderline

Reference has already been made (p. 82) to the fact that the reactions of some substrates, e.g. secondary halides, may follow a mixed first/second order rate equation. The question then arises whether such a reaction is proceeding *via* both S_N2 and S_N1 pathways simultaneously (their relative proportions depending on the solvent, etc.) or whether it is proceeding *via* some specific, 'in between' mechanistic pathway.

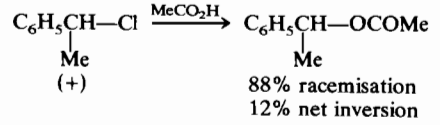
In solvolytic reactions like those we have just been considering, where the solvent itself is the nucleophile, such mixed kinetics may not be detectable, irrespective of what is actually happening, as both S_N1 and S_N2 pathways are likely to follow a rate equation of the form:

$$\text{Rate} = k[\text{R—X}]$$

This is so because in the S_N2 pathway the concentration of nucleophile will remain essentially constant throughout the reaction as—being also the solvent—it is present in very large, unchanging

excess. This raises the question whether the mixture of racemisation/inversion observed in such cases stems from the simultaneous operation of S_N1 and S_N2 pathways for solvolysis, rather than *via* the relatively elaborate, variable ion pair hypothesis advanced above.

In some cases at least it is possible to demonstrate that a 'mixed' S_N1+S_N2 pathway is *not* operating. Thus solvolysis of the halide, $(+)C_6H_5CHMeCl$, mentioned above, but this time in $MeCO_2H$,

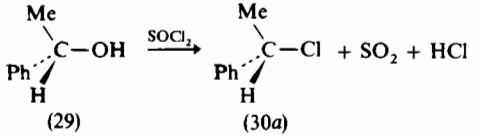


was found to lead to 88% racemisation, and 12% net inversion. Adding the much more powerfully nucleophilic $MeCO_2^{\ominus}$ (as $MeCO_2^{\ominus}Na^{\oplus}$) to the reaction mixture was found to result in: (*a*) no increase in the overall reaction rate, and (*b*) no increase in the proportion of net inversion. This strongly suggests that the inversion that is observed does *not* stem from part of the overall reaction proceeding *via* an S_N2 pathway simultaneously with the (major) S_N1 mode. If it did, we would expect the change to a much more powerful nucleophile ($MeCO_2H \rightarrow MeCO_2^{\ominus}$) to lead to marked increases in both (*a*) and (*b*) above.

A good deal of interest, and controversy, has centred on whether in the last analysis there is perhaps a continuous spectrum of mechanistic pathways intermediate between S_N2 and S_N1: these imperceptibly shading into each other *via* gradually varying transition states from the pure S_N2 side, and *via* gradually varying ion pair/solvent combinations from the pure S_N1 side. It is an area in which theory has shaded over into semantics if, indeed, not even into theology!

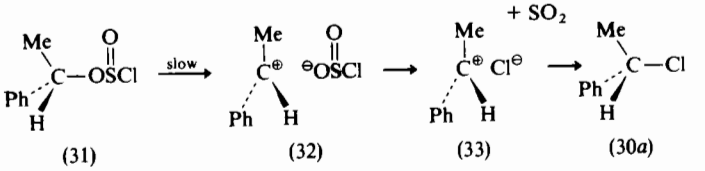
4.4.5 S_Ni mechanism: retention of configuration

Despite what has been said above about displacement reactions leading to inversion of configuration, to racemisation, or to a mixture of both, a number of cases are known of reactions that proceed with actual retention of configuration, i.e. in which the starting material and product have the same configuration. One reaction in which this has been shown to occur is in the replacement of OH by Cl through the use of thionyl chloride, $SOCl_2$:



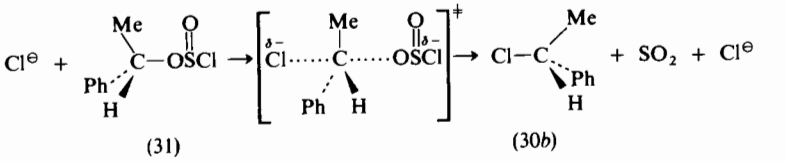
The reaction has been shown to follow a second order rate equation, rate $= k_2[ROH][SOCl_2]$, but clearly cannot proceed by the simple S_N2 mode for this would lead to inversion of configuration (p. 87) in the product, which is not observed.

Carrying out the reaction under milder conditions allows of the isolation of an alkyl chlorosulphite, ROSOCl (31), and this can be shown to be a true intermediate. The chlorosulphite is formed with retention of configuration, the R—O bond not being broken during the reaction. The rate at which the alkyl chlorosulphite intermediate (31) breaks down to the product, RCl (30*a*), is found to increase with increasing polarity of the solvent, and also with increasing stability of the carbocation $R^{\oplus}$: an ion pair, $R^{\oplus\ominus}OSOCl$ (32), is almost certainly involved. Provided collapse of the ion pair to products then occurs rapidly, i.e. in the intimate ion pair (33) within a solvent cage (*cf.* p. 90), then attack by $Cl^{\ominus}$ is likely to occur on the same side of $R^{\oplus}$ from which $^{\ominus}OSOCl$ departed, i.e. with retention of configuration:



Whether the breaking of the C—O and the S—Cl bonds occurs simultaneously, or whether the former occurs first, is still a matter of debate.

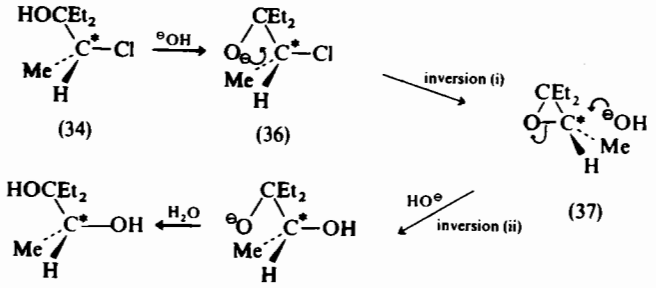
It is interesting that if the $SOCl_2$ reaction on ROH (29) is carried out in the presence of pyridine, the product RCl is found now to have undergone inversion of configuration (30*b*). This occurs because the HCl produced during the formation of (31) from ROH and $SOCl_2$ is converted by pyridine into $C_5H_5NH^{\oplus}Cl^{\ominus}$ and $Cl^{\ominus}$, being an effective nucleophile, attacks (31) 'from the back' in a normal S_N2 reaction with inversion of configuration:



4.4.6 Neighbouring group participation: 'retention'

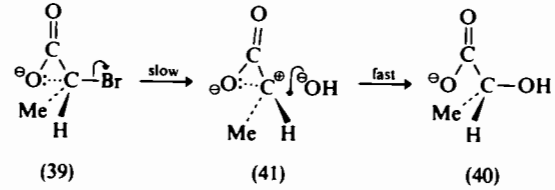
There are also some examples of retention of configuration in nucleophilic displacement reactions where the common feature is an atom or group—close to the carbon undergoing attack—which has an electron

pair available. This *neighbouring group* can use its electron pair to interact with the 'backside' of the carbon atom undergoing substitution, thus preventing attack by the nucleophilic reagent; attack can thus take place only 'from the frontside', leading to retention of configuration. Thus base hydrolysis of the 1,2-chlorohydrin (34) is found to yield the 1,2-diol (35) with the same configuration (retention):



Initial attack by base on (34) yields the alkoxide anion (36), *internal* attack by this $RO^{\ominus}$ then yields the epoxide (37) with inversion of configuration at C* (these cyclic intermediates can actually be isolated in many cases); this carbon atom†, in turn, undergoes ordinary S_N2 attack by $^{\ominus}OH$, with a second inversion of configuration at C*. Finally, this second alkoxide anion (38) abstracts a proton from the solvent to yield the product 1,2-diol (35) with the same configuration as the starting material (34). This *apparent* retention of configuration has, however, been brought about by two successive inversions.

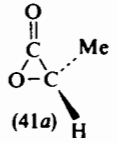
Another example of oxygen as a neighbouring group occurs in the hydrolysis of the 2-bromopropanoate anion (39) at low $[^{\ominus}OH]$, which is also found to proceed with retention of configuration (40). The rate is found to be independent of $[^{\ominus}OH]$, and the reaction is believed to proceed:



Whether the intermediate (41) is a zwitterion as shown or a highly

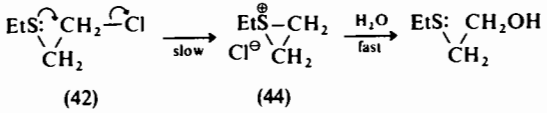
† Preferential attack takes place on this, rather than the other, carbon of the three-membered ring as it will be the more positive of the two, carrying as it does only one electron-donating alkyl group.

labile α-lactone (41*a*)

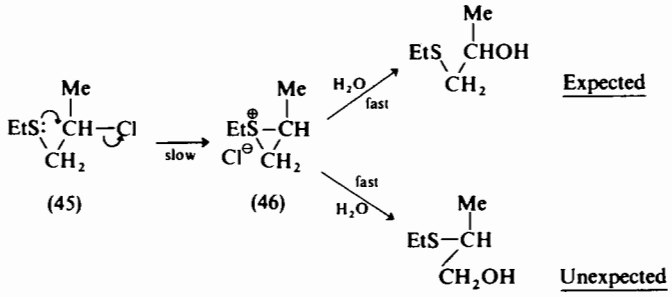


has not been clearly established. As the concentration of nucleophile, $[^{\ominus}OH]$, is increased an increasing proportion of normal S_N2 'attack from the back', with inversion of configuration, is observed.

Neighbouring group effects have also been observed with atoms other than oxygen, e.g. sulphur and nitrogen, and in situations where, though no stereochemical point is at issue, unexpectedly rapid rates suggest a change in reaction pathway. Thus $EtSCH_2CH_2Cl$ (42) is found to undergo hydrolysis 10^4 times faster than $EtOCH_2CH_2Cl$ (43) under comparable conditions, and this has been interpreted as involving S: acting as a neighbouring group:



By contrast, O: in (43) is sufficiently electronegative not to donate an electron pair (unlike $O^{\ominus}$ in $RO^{\ominus}$ and $RCO_2{}^{\ominus}$ above), and hydrolysis of $EtOCH_2CH_2Cl$ thus proceeds *via* ordinary S_N2 attack by an external nucleophile—which is likely to be very much slower than the *internal* nucleophilic attack in (42) → (44). That a cyclic sulphonium salt such as (44) is involved is demonstrated by the hydrolysis of the analogue (45), which yields two alcohols (the unexpected one in greater yield) indicating the participation of the unsymmetrical intermediate (46):



N: can act as a neighbouring group in similar circumstances, e.g. the hydrolysis of $Me_2NCH_2CH_2Cl$, but the rate is markedly slower,

under comparable conditions, than that for (42) above, because of the greater stability of the cyclic immonium ion intermediate corresponding to (44). Such cyclic species are formed during the hydrolysis of mustard gas, $S(CH_2CH_2Cl)_2$ and the related nitrogen mustards, such as $MeN(CH_2CH_2Cl)_2$: the cyclic immonium salts derived from the latter are also powerful neurotoxins. The π orbital system of the benzene ring can also act as a neighbouring group (*cf.* pp. 105, 376).

4.5 EFFECT OF ENTERING AND LEAVING GROUPS

4.5.1 The entering group

Changing the nucleophilic reagent employed, i.e. the *entering group*, will not directly alter the rate of an S_N1 displacement reaction for this reagent does not take part in the rate-limiting step of the overall reaction. In an S_N2 displacement, however, the more strongly nucleophilic the reagent the more the reaction will be promoted. The *nucleophilicity* of a reagent might perhaps be expected to correlate with its basicity, as both involve the availability of electron pairs and the ease with which they are donated. The parallel is by no means exact, however, in that basicity involves electron pair donation to hydrogen, whereas nucleophilicity involves electron pair donation to another atom, very often carbon; basicity involves an equilibrium (thermodynamic), i.e. $\Delta G^{\ominus}$, situation, whereas nucleophilicity usually involves a kinetic, i.e. $\Delta G^{\ddagger}$, one; basicity is likely to be little affected by steric influences, whereas nucleophilicity may be markedly affected.

This distinction follows to some extent the recently introduced one between *hard* and *soft bases*: a hard base is one in which the donor atom is of high electronegativity, low polarisability, and is hard to oxidise, i.e. $^{\ominus}OH$, $^{\ominus}OR$, R_3N:; while a soft base is one in which the donor atom is of low electronegativity, high polarisability, and is easy to oxidise, e.g. $RS^{\ominus}$, $I^{\ominus}$, $SCN^{\ominus}$; for a given degree of basicity, softness promotes nucleophilicity. Basicity data are often the more readily available, however, and can be used as a guide to nucleophilicity provided like is being compared with like. Thus if the attacking atom is the same (*cf.* electronegativity above), then the two run reasonably in parallel, and we find the stronger the base the more powerful the nucleophile:

$$EtO^{\ominus} > PhO^{\ominus} > MeCO_2^{\ominus} > NO_3^{\ominus}$$

A shift in mechanistic type can also occur with change of nucleophile, thus a displacement that is S_N1 with, for example, H_2O:, $HCO_3^{\ominus}$, $MeCO_2^{\ominus}$, etc., may become S_N2 with $^{\ominus}OH$ or $EtO^{\ominus}$.

Nucleophilicity is found to be very much affected by the *size* of the attacking atom in the nucleophile, at least for comparisons within the same group or sub-group of the periodic table; thus we find:

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus} \qquad RS^{\ominus} > RO^{\ominus}$$

Size as well as electronegativity, governs polarisability (*cf.* soft bases, above): as the atom increases in size the hold the nucleus has on the peripheral electrons decreases, with the result that they become more readily polarisable, leading to the initiation of bonding at increasing nuclear separations. Also the larger the nucleophilic ion or group the less its solvation energy, i.e. the more readily is it converted into the effective, largely non-solvated, nucleophile; thus heats of hydration of $I^{\ominus}$ and $F^{\ominus}$ are 284 and 490 kJ mol^{-1}, respectively. This combination of factors makes the large, highly polarisable, weakly solvated iodide ion, $I^{\ominus}$, a very much better nucleophile than the small, difficulty polarisable, strongly solvated (H-bonding with a hydroxylic solvent) fluoride ion, $F^{\ominus}$. We should, on this basis, expect the increase in reaction rate on transfer from a hydroxylic to a polar non-protic solvent (*cf.* p. 81) to be much less for $I^{\ominus}$ than, for example, for $Br^{\ominus}$ or $Cl^{\ominus}$: as is indeed found to be the case ($Br^{\ominus}$ is a better nucleophile than $I^{\ominus}$ in Me_2CO).

A further interesting point arises with nucleophiles which have more than one—generally two—suitable atoms through which they can attack the substrate, *ambident* nucleophiles:

$$[^{\ominus}X{=}Y \leftrightarrow X{=}Y^{\ominus}]$$

It is found in practice that in (highly polar) S_N1 reactions attack takes place on the carbocationic intermediate, $R^{\oplus}$, through the atom in the nucleophile on which *electron density* is the higher. With, for example, halides that do not readily undergo S_N1 attack this can be promoted by use of the silver salt of the anion, e.g. AgCN, as $Ag^{\oplus}$ promotes $R^{\oplus}$ formation by precipitation of AgHal (*cf.* p. 102):

$$[^{\ominus}\underset{\cdot\cdot}{C}{\equiv}\dot{N} \leftrightarrow \underset{\cdot\cdot}{C}{=}\dot{\underset{\cdot\cdot}{N}}^{\ominus}]$$

$$R{-}Br + Ag^{\oplus}[CN]^{\ominus} \xrightarrow[slow]{} AgBr\downarrow + R^{\oplus} + [CN]^{\ominus} \xrightarrow[fast]{} R{-}\overset{\oplus}{N}{\equiv}C^{\ominus}$$

In the absence of such promotion by $Ag^{\oplus}$, e.g. with $Na^{\oplus}[CN]^{\ominus}$, the resulting S_N2 reaction is found to proceed with preferential attack on the atom in the nucleophile which is the more *polarisable*:

$$NC^{\ominus} + R{-}Br \rightarrow \left[\overset{\delta-}{N}C \cdots R \cdots \overset{\delta-}{Br}\right]^{\ddagger} \rightarrow N{\equiv}C{-}R + Br^{\ominus}$$

T.S.

This is understandable as, unlike S_N1, bond formation is now taking place in the T.S. for the rate-limiting step, for which ready polarisability of the bonding atom of the nucleophile is clearly important—the

beginning of bonding at as great an internuclear separation as possible (*cf.* above). This AgCN/NaCN dichotomy has long been exploited preparatively. Similarly, nitrite ion $[NO_2]^{\ominus}$ is found to result in the formation of alkyl nitrites, R—O—N=O, under S_N1 conditions (O is the atom of higher electron density) and nitroalkanes, $R—NO_2$, under S_N2 conditions (N is the more readily polarisable atom).

4.5.2 The leaving group

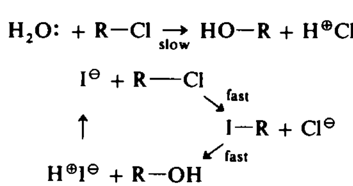
Changing the *leaving group* will clearly alter the rate of both S_N1 and S_N2 reactions, as breaking the bond to the leaving group is involved in the slow, rate-limiting step of both. We might expect the relative ability of Y as a leaving group, in R—Y, to be influenced by: (*a*) the strength of the R—Y bond; (*b*) the polarisability of this bond; (*c*) the stability of $Y^{\ominus}$; and (related to the latter) (*d*) the degree of stabilisation, through solvation, of the forming $Y^{\ominus}$ in the T.S. for either S_N1 or S_N2.

The observed reactivity (S_N2 or S_N1) sequence for *halides*

$$R—I > R—Br > R—Cl > R—F$$

suggests that here (*a*) and (*b*) above are probably more important than (*c*) and (*d*). For a wider range of potential leaving groups, involvement of (*c*) would suggest that the weaker $Y^{\ominus}$ is as a base (or the stronger H—Y is as an acid) the better a leaving group it will be. This is borne out to some extent over a series of leaving groups in which the atom in Y through which it is attached to R remains the same. Thus the anions of strong 'oxygen acids' such as p-$MeC_6H_4SO_3^{\ominus}$ (tosylate, *cf.* p. 88), $CF_3SO_3^{\ominus}$ (triflate) are good leaving groups (as indeed are halide anions); with such O-leaving groups, (*c*) and (*d*) above are of increased importance. Relative leaving group ability may however vary with change of solvent, reflecting the influence of (*d*). This variation in relative ability can be particularly marked on changing from a hydroxylic solvent to a bipolar, non-protic one (e.g. Me_2SO, $HCONMe_2$, etc.) as initial (*c*)/(*d*) domination may then shift to (*a*)/(*b*) control.

High polarisability makes $I^{\ominus}$ both a good entering and a good leaving group, it can thus often be used as a catalyst to promote an otherwise slow displacement reaction, e.g.:



This is known as *nucleophilic catalysis*. The stronger, and harder, as a base a leaving group is, the less readily can it be displaced; thus groups such as $^{\ominus}OH$, $^{\ominus}OR$, $^{\ominus}NH_2$ bonded to carbon by small, highly electronegative atoms of low polarisability (*cf.* hard bases, above) cannot normally be displaced directly by other nucleophiles.

Displacements that are otherwise difficult, or even impossible, to accomplish directly may sometimes be effected by modification of the potential leaving group—often through protonation—so as to make it weaker, and/or softer, as a base. Thus $^{\ominus}OH$ cannot be displaced directly by $Br^{\ominus}$, but is displaced readily if protonated first:

$$Br^{\ominus} + R—\ddot{O}H \not\rightarrow Br—R + {}^{\ominus}OH$$

$$\downarrow\uparrow H^{\oplus}$$

$$Br^{\ominus} + R—\overset{\oplus}{O}H(H) \rightarrow Br—R + H_2O$$

There are two main reasons for this: (*a*) $Br^{\ominus}$ is now attacking a positively charged, as opposed to a neutral, species, and (*b*) the very weakly basic H_2O is a very much better leaving group than the strongly basic $^{\ominus}OH$. The well known use of HI to cleave ethers results from $I^{\ominus}$ being about the most nucleophilic species that can be generated in the strongly acid solution required for the initial protonation:

$$R—\ddot{O}Ph \overset{H^{\oplus}}{\rightleftarrows} R—\overset{\oplus}{O}Ph(H) \xrightarrow{I^{\ominus}} RI + PhOH$$

4.6 OTHER NUCLEOPHILIC DISPLACEMENTS

In this discussion of nucleophilic displacement at a saturated carbon atom, interest has tended to centre on attack by nucleophilic anions $Nu:^{\ominus}$, especially $^{\ominus}OH$, on polarised neutral species, especially alkyl halides, $^{\delta+}R—Hal^{\delta-}$. In fact this general type of displacement is extremely common involving, in addition to the above, attack by non-charged nucleophiles Nu: on polarised neutral species,

$$Me_3N: + Et—Br \rightarrow Me_3\overset{\oplus}{N}Et + Br^{\ominus}$$

$$Et_2S: + Me—Br \rightarrow Et_2\overset{\oplus}{S}Me + Br^{\ominus}$$

nucleophilic anions on positively charged species,

$$I^{\ominus} + C_6H_{13}—\overset{\oplus}{O}H(H) \rightarrow C_6H_{13}—I + H_2O:$$

$$Br^{\ominus} + Me—\overset{\oplus}{N}Me_3 \rightarrow Me—Br + :NMe_3$$

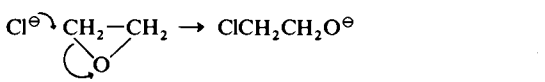
and non-charged nucleophiles on positively charged species (N_2 is probably the best leaving group there is):

$$H_2O: + PhN_2^{\oplus} \longrightarrow PhOH + N_2 + H^{\oplus}$$

We have also seen good leaving groups other than halide ion, e.g. tosylate anion (*cf.* p. 88),

$$MeCO_2^{\ominus} + ROSO_2C_6H_4Me\text{-}p \rightarrow MeCO_2R + p\text{-}MeC_6H_4SO_3^{\ominus}$$

and 'internal' leaving groups (*cf.* p. 94):



There are also nucleophilic displacement reactions, of considerable synthetic importance, in which the attacking atom in the nucleophile is carbon in either a carbanion (p. 288) or a source of negatively polarised carbon (*cf.* p. 221); new carbon–carbon bonds are thus formed:

$$HC{\equiv}CH \overset{^{\ominus}NH_2}{\rightleftarrows} HC{\equiv}C^{\ominus} + Pr{-}Br \longrightarrow HC{\equiv}C{-}Pr + Br^{\ominus}$$

$$CH_2(CO_2Et)_2 \overset{EtO^{\ominus}}{\rightleftarrows} (EtO_2C)_2CH^{\ominus} + PhCH_2{-}Br \longrightarrow (EtO_2C)_2CH{-}CH_2Ph + Br^{\ominus}$$

$$\overset{\delta+\ \delta-}{BrMgPh} + C_6H_{13}{-}Br \longrightarrow MgBr_2 + Ph{-}C_6H_{13}$$

It should be remembered that in the above examples what is nucleophilic attack from the viewpoint of one participant is electrophilic attack from the viewpoint of the other. Any designation of the process as a whole tends therefore to be somewhat arbitrary, reflecting as it does our preconceptions about what constitutes a reagent as opposed to a substrate (*cf.* p. 30).

Hardly surprisingly, not all nucleophilic displacement reactions proceed so as to give 100% yields of the desired products! Here, as elsewhere, side-reactions occur yielding unexpected, and in preparative terms unwanted, products. A major side-reaction is *elimination* to yield unsaturated compounds: this is discussed in detail below (p. 246).

5

Carbocations, electron-deficient N and O atoms and their reactions

Reference has already been made in the last chapter to the generation of carbocations, in ion pairs, as intermediates in some displacement reactions at a saturated carbon atom, e.g. the solvolysis of an alkyl halide *via* the S_N1 mechanism. Carbocations are, however, fairly widespread in occurrence and, although their existence is often only transient, they are of considerable importance in a wide variety of chemical reactions.

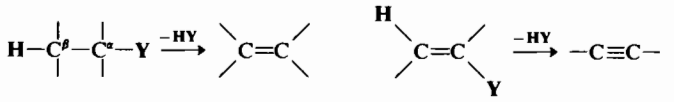
5.1 METHODS OF FORMING CARBOCATIONS

5.1.1 Heterolytic fission of neutral species

The obvious example is simple *ionisation*, the group attached to carbon departing with its bonding electrons to form an ion pair, $R^{\oplus}Y^{\ominus}$:

9
Elimination reactions

Elimination reactions involve the removal from a molecule of two atoms or groups, without their being replaced by other atoms or groups. In the great majority of such reactions the atoms or groups are lost from adjacent carbon atoms, one of them very often being a proton and the other a nucleophile, Y: or $Y^{\ominus}$, resulting in the formation of a multiple bond, a 1,2-(or αβ-) elimination:



Eliminations from atoms other than carbon are also known;

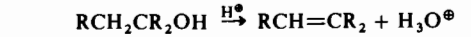
as are eliminations both from the same atom, 1,1-(α-) eliminations (*cf.* p. 266), and from atoms further apart than 1,2-, i.e. reversal of 1,4-addition (*cf.* p. 195), also 1,5- and 1,6-eliminations leading to cyclisation. 1,2-Eliminations are by far the most common and important, however, and most of our discussion will be concerned with them.

9.1 1,2-(β-)ELIMINATION

In 1,2-eliminations involving carbon atoms (i.e. most), the atom from which Y is lost is usually designated as the 1-(α-) carbon and that losing (usually) H as the 2-(β-) carbon; in the older αβ-terminology, the α- is commonly omitted, and the reactions are referred to as β-eliminations. Among the most familiar examples are base-induced elimination of hydrogen halide from alkyl halides—this almost certainly the most common elimination of all—particularly from bromides (1);

(1)

acid-catalysed dehydration of alcohols (2);



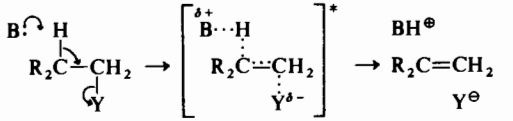
(2)

and Hofmann degradation of quaternary alkylammonium hydroxides (3):

(3)

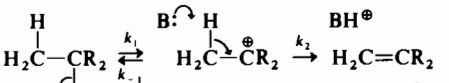
Many other leaving groups are known, however, e.g. SR_2, SO_2R, OSO_2Ar, etc. 1,2-Eliminations are, of course, the major route to alkenes.

Three different, simple mechanisms can be envisaged for 1,2-eliminations, differing from each other in the timing of H—C and C—Y bond-breaking. This could (*a*) be concerted,



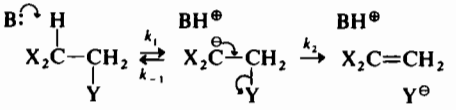
(4)

i.e. a one-step process, passing through a single T.S. (4); this is referred to as the E2 mechanism (*Elimination*, *bimolecular*) and is somewhat reminiscent of S_N2 (*cf.* p. 78). Alternatively, the H—C and C—Y bonds can be broken separately in two-step processes. If the C—Y bond is broken first, (*b*), a carbocationic intermediate (5) is involved;



(5)

this is referred to as the E1 mechanism (*Elimination, unimolecular*). It is reminiscent of S_N1 (*cf.* p. 79), and the carbocationic intermediates for S_N1 and E1 are, of course, identical. Finally, the H—C bond could be broken first, (*c*), involving a carbanion intermediate (6);



(6)

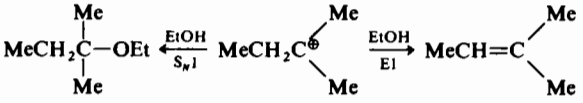
this is referred to as the E1cB mechanism [*Elimination*, from *conjugate Base*, i.e. (6)]. Examples of reactions proceeding by all three mechanisms are known: E1cB is the least, and E2 probably the most, common. The three mechanisms will now be considered in turn, but it should be realised that they are only limiting cases (*cf.* S_N1/S_N2), and that in fact a continuous mechanistic spectrum, in the relative time of breaking of the two bonds, is available and is indeed observed in practice.

9.2 E1 MECHANISM

If, as is normally the case, carbocation, e.g. (5), formation is slow and rate-limiting (i.e. $k_2 > k_{-1}$), then the rate law observed with, for example, the bromide $MeCH_2CMe_2Br$ is;

$$\text{Rate} = k[MeCH_2CMe_2Br]$$

the overall elimination is then completed (7) by rapid, non rate-limiting removal of a proton from (8) usually by a solvent molecule, in this case EtOH:



(9) (8) (7)

It could be claimed that such an E1 solvolytic elimination would be indistinguishable kinetically from a bimolecular (E2) elimination, in which EtOH was acting as base, because the [EtOH] term in the E2 rate law,

$$\text{Rate} = k[MeCH_2CMe_2Br][EtOH]$$

would remain constant. The two can often be distinguished, however, by adding a little of the conjugate base of the solvent, i.e. $^{\ominus}OEt$ in this case. If no significant change in rate is observed, an E2 mechanism cannot be operating, for if $^{\ominus}OEt$ is not participating as a base the much weaker EtOH certainly cannot be.

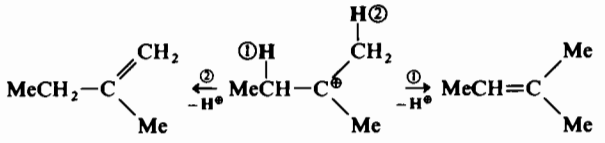
The carbocation (8) is identical with that from S_N1 solvolysis

(p. 79), and the latter reaction to yield the substitution product (9) is commonly a competitor with E1 elimination. Some evidence that the two processes do have a common intermediate is provided by the fact that the $E1/S_N1$ ratio is reasonably constant for a given alkyl group irrespective of the leaving group, $Y^{\ominus}$. The two processes do, however, proceed from (8) to products—(7) and (9), respectively—*via* different T.S.s, and the factors that influence elimination *v.* substitution are discussed subsequently (p. 260).

The factors that promote unimolecular, as opposed to bimolecular (E2), elimination are very much the same as those that promote S_N1 with respect to S_N2, namely: (*a*) an alkyl group in the substrate that can give rise to a relatively stable carbocation, and (*b*) a good ionising, ion-solvating medium. Thus (*a*) is reflected in the fact that with halides, increasing E1 elimination occurs along the series,

primary < secondary < tertiary

reflecting the relative stability of the resultant carbocations; primary halides hardly ever undergo E1 elimination. Branching at the β-carbon atom also favours E1 elimination; thus $MeCH_2CMe_2Cl$ is found to yield only 34% of alkene, while Me_2CHCMe_2Cl yields 62%. This is probably related to the fact that Me_2CHCMe_2Cl can lead to a more heavily substituted, and hence thermodynamically more stable (*cf.* p. 26), alkene than the first. This is, with E1 reactions, also the major controlling factor (Saytzeff elimination, p. 256) in orientation of elimination, where more than one alkene can be derived by loss of different β-protons from a carbocationic intermediate (8):



(10) (8) (7)

Thus in the above case the elimination product is found to contain 82% of (7). Unexpected alkenes may arise, however, from rearrangement of the initial carbocationic intermediate before loss of proton. E1 elimination reactions have been shown as involving a dissociated carbocation; they may in fact often involve ion pairs, of varying degrees of intimacy depending on the nature of the solvent (*cf.* S_N1, p. 90).

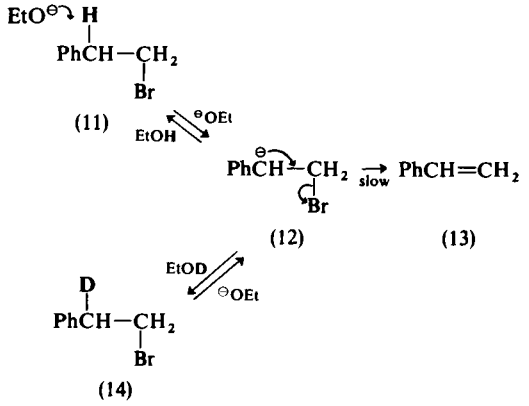
9.3 E1cB MECHANISM

If, as might be expected for this pathway, formation of the carbanion intermediate (6) is fast and reversible, while subsequent loss of the

leaving group, $Y^{\ominus}$, is slow and rate-limiting, i.e. $k_{-1} > k_2$, then this reaction will follow the rate law,

$$\text{Rate} = k[RY][B]$$

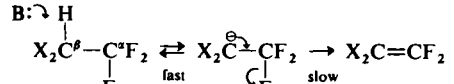
and will be kinetically indistinguishable from the concerted (E2) pathway. It should be possible to distinguish between them, however, by observing exchange of isotopic label, between as yet unchanged substrate and solvent, arising during fast, reversible carbanion (6) formation—something that clearly could not happen in the one-step, concerted (E2) pathway. A good example to test would be $PhCH_2$-CH_2Br (11), as the Ph group on the β-carbon would be expected to promote acidity in the β-H atoms, and also to stabilise the resultant carbanion (12) by delocalisation:



(11) (12) (13) (14)

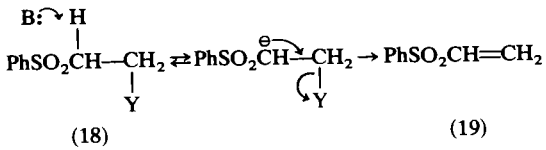
The reaction was carried out with $^{\ominus}OEt$ in EtOD, and (11) re-isolated after ≈ half-conversion to (13): it was found to contain no deuterium, i.e. no (14); nor did the alkene (13) contain any deuterium, as might have been expected by elimination from any (14) formed. This potentially favourable case thus does not proceed by an E1cB pathway of the form described above; though we have not ruled out the case where $k_2 \gg k_{-1}$, i.e. essentially irreversible carbanion formation.

In fact reactions proceeding by this carbanion pathway are exceedingly rare; this is not altogether surprising as calculations suggest that the energy of activation for E2 is generally more favourable than that for E1cB, in most cases by ≈30–60 kJ (7–14 kcal) mol^{-1} (the reverse of step 2 would require addition of $Y^{\ominus}$ to C=C, which certainly doesn't happen at all easily). One example that almost certainly involves the latter pathway, however, is X_2CHCF_3 (15, X = Hal):



(15) (16) (17)

This has all the right attributes in the substrate: (*a*) electronegative halogen atoms on the β-carbon to make the β-H more acid, (*b*) stabilisation of the carbanion (16) through electron-withdrawal by the halogen atoms on the carbanion carbon atom, and (*c*) a poor leaving group in F. An attempt has been made to correlate the relative leaving group ability of a series of different Y groups in the ElcB reaction:

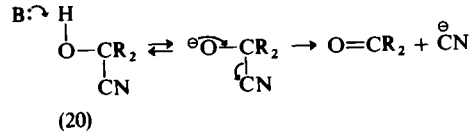


(18) (19)

Y: PhSe > PhO > PhS ≈ $PhSO_2$ > PhSO > MeO ≫ CN

The observed order of ability did not, however, correlate with the pK_a of YH, with the strength of the C—Y bond, or with the polar effect of Y! Clearly, leaving group ability even in this simple reaction is a highly complex attribute.

Other examples of the E1cB pathway are benzyne formation from C_6H_5F (*cf.* p. 174), reversal of simple nucleophilic addition to C=O, e.g. base-induced elimination of HCN from cyanohydrins (20; *cf.* p. 212),



(20)

and base-induced dehydration of aldols to $\alpha\beta$-unsaturated carbonyl compounds (*cf.* p. 225).

9.4 E2 MECHANISM

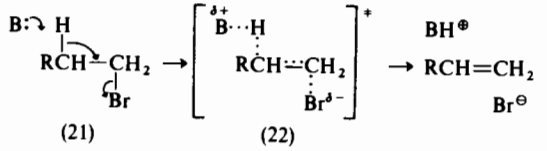
By far the commonest elimination mechanism is the one-step concerted (E2) pathway exhibiting, e.g. for the base-induced elimination of HBr from the halide RCH_2CH_2Br (21), the rate law:

$$\text{Rate} = k[RCH_2CH_2Br][B]$$

As B is often a nucleophile as well as a base, elimination is frequently accompanied by one-step, concerted (S_N2) nucleophilic substitution

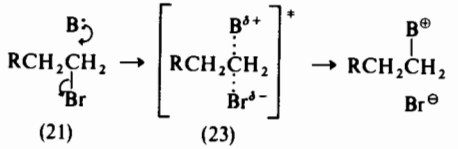
(*cf.* p. 78):

E2:



(21) (22)

S_N2:



(21) (23)

The factors that influence elimination *v.* substitution are discussed subsequently (p. 260). Evidence for the involvement of C—H bond fission in the rate-limiting step—as a concerted pathway requires—is provided by the observation of a primary kinetic isotope effect (*cf.* p. 46) when H is replaced by D on the *β*-carbon.

One of the factors that affects the rate of E2 reactions is, hardly surprisingly, the strength of the base employed; thus we find:

$$^{\ominus}NH_2 > {}^{\ominus}OR > {}^{\ominus}OH$$

Some studies have been made with bases of the type $ArO^{\ominus}$, as this allows study of the effects of variation in basic strength (by introduction of *p*-substituents in $C_6H_5O^{\ominus}$) without concomitant change in the steric requirements of the base. With a given base, transfer from a hydroxylic solvent, e.g. H_2O or EtOH, to a bipolar aprotic one, e.g. $HCONMe_2$ (DMF) or $Me_2S^{\oplus}—O^{\ominus}$ (DMSO), can have a very pronounced effect as the strength of the base, e.g. $^{\ominus}OH$, $^{\ominus}OR$, is enormously increased thereby. This arises because the base has, in the latter solvents, no envelope of hydrogen-bonded solvent molecules that have to be stripped away before it can act as a base (*cf.* effect on nucleophilicity in S_N2, p. 81). Such change of solvent may result in a shift of mechanistic pathway from E1 to E2 for some substrate/base pairs.

To explain the effect change of Y may have on the rate of reaction of R—Y (in which R remains the same) we need to consider: (*a*) any effect Y may have on C—H bond-breaking (E2 is a *concerted* reaction), (*b*) the strength of the C—Y bond, and (*c*) the stability of $Y^{\ominus}$, as reflected in the pK_a of H—Y. It thus comes as no surprise to find that forecasting the relative ability of Y as a leaving group is far from easy! If the atom in Y that is directly bonded to C in R—Y (and to H in H—Y) remains the same, e.g. oxygen, then the rate of reaction of R—Y may correlate not too badly with the *inverse* of the pK_a of H—Y: the stronger the oxy-acid, the better is

its oxy-anion as a leaving group. Thus $p\text{-}MeC_6H_4SO_3^{\ominus}$ ('tosylate', Ts) is a very much better leaving group than $^{\ominus}OH$, reflecting $p\text{-}MeC_6H_4SO_3H$ being a very much stronger acid (lower pK_a value) than H_2O. Where the atom through which Y is bonded to C in R—Y does not stay the same, however, this inverse correlation with pK_a often breaks down. Thus the importance of the strength of the C—Y bond (rather than the pK_a of H—Y) is borne out by the relative rate sequence observed for $PhCH_2CH_2Hal$ with $^{\ominus}OEt$/EtOH:

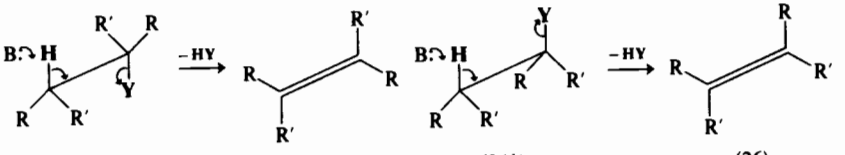
	$PhCH_2CH_2F$	$PhCH_2CH_2Cl$	$PhCH_2CH_2Br$	$PhCH_2CH_2I$
Rel. rate:	1	70	$4{\cdot}2 \times 10^3$	$2{\cdot}7 \times 10^4$

Incipient solvation of the developing $Y^{\ominus}$ in the transition state (e.g. 22), through hydrogen-bonding or other means, can also play its part in determining relative leaving group ability, and this may or may not follow the same general sequence as acid strength of HY and/or C—Y bond strength. Change of solvent thus can, and does, change the sequence of relative leaving group ability in a series of different $Y^{\ominus}$s.

Finally, the major structural features in the substrate promoting E2 elimination are those that serve to stabilise the resultant alkene or, more particularly, the T.S. that precedes it. Such features include increasing alkyl substitution at both *α*- and *β*-carbon atoms (leading to alkenes of increasing thermodynamic stability), or introduction of a phenyl group that can become conjugated with the developing double bond.

9.4.1 Stereoselectivity in E2

With acylic molecules elimination could be envisaged as taking place from one or other of two limiting conformations—the *anti-periplanar* (24*a*) or the *syn-periplanar* (24*b*):



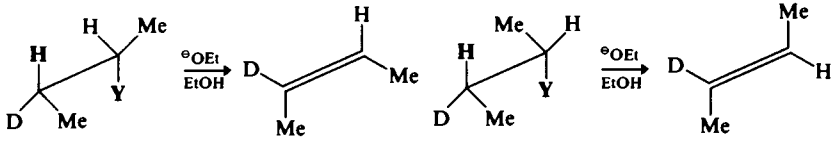
(24*a*) (25) (24*b*) (26)

There is an obvious advantage in elimination taking place from a conformation in which H, C^{β}, C^{α} and Y are in the same plane as the *p* orbitals that are developing on C^{β} and C^{α}, as $H^{\oplus}$ and $Y^{\ominus}$ are departing, will then be parallel to each other, and thus capable of maximum overlap in the forming *π* bond. It will be energetically advantageous for the attacking atom of the base B to lie in this common plane also.

Having established the desirability of elimination taking place from a planar conformation, there remains the question of whether either (24*a*) or (24*b*) is preferred over the other.

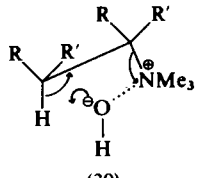
Three possible grounds can be stated for favouring elimination from the anti-periplanar conformation (24*a*): (*a*) elimination would then be taking place from the lower energy 'staggered' conformation (24*a*), rather than from the higher energy 'eclipsed' conformation (24*b*; *cf.* p. 7), and this energy differential is likely to be reflected in the corresponding transition states; (*b*) the attacking base, B:, and the departing leaving group, $Y^{\ominus}$, would be as far apart from each other as possible in the T.S.; and (*c*) the electron pair developing from the initial C—H bond would be attacking the α-carbon atom from the side opposite to that from which the electron pair of the initial C—Y bond will be departing (*cf.* the favoured 'backside' attack in the S_N2 pathway, p. 78). It seems likely that (*a*) will be the most significant of these features, however. We would thus forecast a preference for ANTI ('opposite side') elimination of H and Y (from 24*a*), rather than SYN ('same side') elimination (from 24*b*).

Where, as with (24) above, both C^{β} and C^{α} are chiral, elimination from the two conformations will lead to different products—the *trans*-alkene (25) from (24*a*) and the *cis*-alkene (26) from (24*b*). Thus knowing the configuration of the original diastereoisomer (e.g. 24), and establishing the configuration of the geometrical isomeride(s) that is formed, enables us to establish the degree of stereoselectivity of the elimination process. In most simple acyclic cases, ANTI elimination is found to be very much preferred, e.g. in about the simplest system, (26) and (27), that permits of stereochemical distinction:



(26) (28) (27) (29)

For Y = Br, Ts or $\overset{\oplus}{N}Me_3$, elimination was essentially 100% stereoselectively ANTI—only (28) was obtained from (26), and only (29) was obtained from (27). There are, however, numerous exceptions with longer chain $\overset{\oplus}{N}R_3$ compounds, perhaps because of some SYN elimination of the β-H *via* a cyclic transition state involving the quaternary ammonium hydroxide ion pair (30):



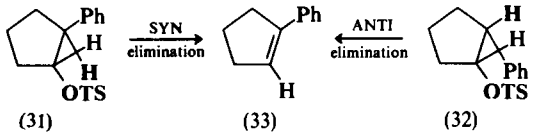
(30)

The degree of stereoselectivity may be influenced to some extent by the polarity and ion-solvating ability of the solvent.

In cyclic compounds the conformation from which elimination can take place may to a considerable extent be enforced by the relative rigidity of the ring structure. Thus for a series of eliminations from different sized rings, the following degrees of stereoselectivity were observed for HY elimination from the cyclic compounds $(CH_2)_nCHY$:

Ring size	%SYN elimination
Cyclobutyl	90
Cyclopentyl	46
Cyclohexyl	4
Cycloheptyl	37

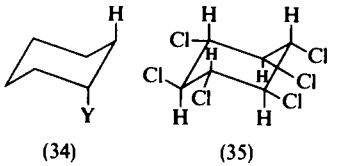
The relative lack of stereoselectivity with cyclopentyl compounds is reflected in the behaviour of the *trans*- and *cis*-isomerides, (31) and (32). Each, if it eliminates by E2 at all, will be converted into the same alkene (33)—(31) *via* SYN elimination, and (32) *via* ANTI elimination:



(31) (33) (32)

ANTI elimination [(32) → (33)] was found to proceed only 14 times faster than SYN elimination [(31) → (33)] reflecting the fact that the energy needed to distort the ring, so that (32) can assume an approximately anti-periplanar conformation, almost outweighs the normal energetic advantage of the staggered conformation over the, syn-periplanar, eclipsed one, i.e. (31).

The marked ANTI stereoselectivity observed with cyclohexyl systems (see above) reflects the ability to achieve, and the very marked preference to eliminate from, the so-called *trans*-diaxial conformation (34):

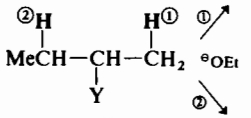


(34) (35)

Thus of the geometrical isomers of hexachlorocyclohexane, $C_6H_6Cl_6$, one is found to undergo elimination of HCl at a rate slower, by a factor of 7–24 × 10^3, than any of the others: it is found to be the one (35) that cannot assume the above *trans*-diaxial conformation.

9.4.2 Orientation in E2: Saytzev *v.* Hofmann

In substrates which have alternative β-hydrogen atoms available, it is possible to obtain more than one alkene on elimination, e.g. (36) where there are two possibilities:

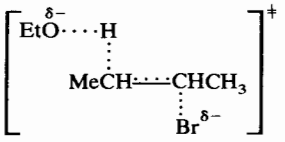


(36)

	Y = Br	$^{\oplus}SMe_2$	$^{\oplus}NMe_3$
$MeCH_2CH{=}CH_2$ (37)	19%	74%	95%
$MeCH{=}CHCH_3$ (38)	81%	26%	5%

To help in forecasting which alkene is the more likely to be produced there have long been two empirical rules that can be summarised as follows: (*a*) Hofmann (1851; working on $R^{\oplus}NMe_3$ compounds, i.e. $Y = {}^{\oplus}NMe_3$) stated 'that alkene will predominate which has least alkyl substituents on the double bond carbons', i.e. (37) above; (*b*) Saytzev (1875; working on RBr compounds, i.e. Y = Br) stated 'that alkene will predominate which has most alkyl substituents on the double bond carbons', i.e. (38) above. Both generalisations are valid as the figures quoted above indicate. It is thus clear that the composition of the alkene mixture obtained on elimination is influenced by Y, the nature of the leaving group, and an explanation is required about how this influence may be exerted.

Saytzev elimination, which appears to occur when Y is neutral (e.g. with Y = OTs, etc., as well as Br), leads to the more stable (i.e. more heavily substituted, *cf.* p. 26) alkene. It seems reasonable to suppose, therefore, that reaction here proceeds *via* a T.S. in which a not inconsiderable degree of 'alkene character' has already been developed; the alkyl substituents thereby being able to begin exerting their stabilising (energy lowering) effect quite early in the single step of the E2 pathway, e.g. (38*a*):

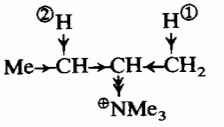


(38*a*)

The preference for Saytzev elimination in the E1 pathway has already been referred to (p. 249).

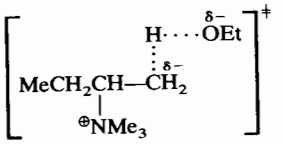
This appears to be wholly logical—just what we would have

expected from an E2 pathway—so the real question is why a +vely charged Y should prompt a divergence from this apparent norm? A Y group such as $^{\oplus}NMe_3$ will exert a powerful, electron-withdrawing, inductive/field effect on both the β-carbon atoms, and thus on the H atoms attached to them,



(36*a*)

thus making these hydrogens markedly more acidic. They will thus be much more readily removed by base than when Y was Br, and the powerful electron-withdrawal by $^{\oplus}NMe_3$ will also stabilise the incipient carbanion forming as either H is being removed. This effect will, in the case of ^{②}H, be reduced to some extent through electron-donation by the Me substituent on this β-carbon; such an acid-weakening effect does not occur with ^{①}H, which is thus more acidic than ^{②}H, and hence the proton that is more easily removed by base. This effect of $^{\oplus}NMe_3$ is apparently sufficient to make relative proton acidity, rather than potential alkene stabilisation, the controlling factor. The reaction now proceeds through a T.S. (37*a*)

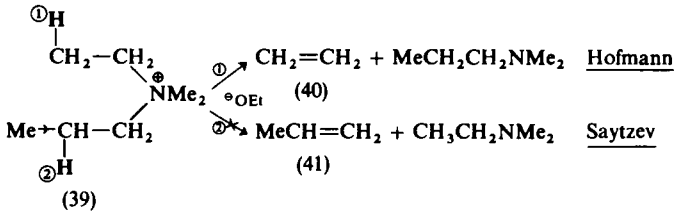


(37*a*)

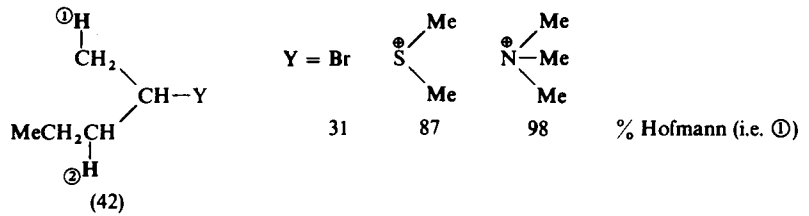
possessing some degree of 'carbanion character', but in which little or no 'alkene character' has yet developed. E2 eliminations can thus involve transition states along a whole spectrum of 'character', whose nature is determined in considerable part by Y.

It is interesting in this respect that when Y is F, despite this not being +vely charged, there is a marked tendency towards the Hofmann product: thus $EtCH_2CH(F)CH_3$ leads to no less than 85% of $EtCH_2CH{=}CH_2$. This 'unexpected' result stems from the extremely powerful electron-withdrawing effect of F (*cf.* $^{\oplus}NMe_3$); and also that $F^{\ominus}$ is an extremely poor leaving group, thereby delaying C—F bond-breaking in the T.S. 'spectrum'. Support for the importance of proton acidity, and the development of 'carbanion character' in the T.S., for Hofmann elimination is provided by the observation that increase in the strength of the base attacking RY (whether Y is +vely charged or not) also leads to increasing formation of the Hofmann product. β-Substituents that would help stabilise a developing −ve charge promote formation of the Hofmann product,

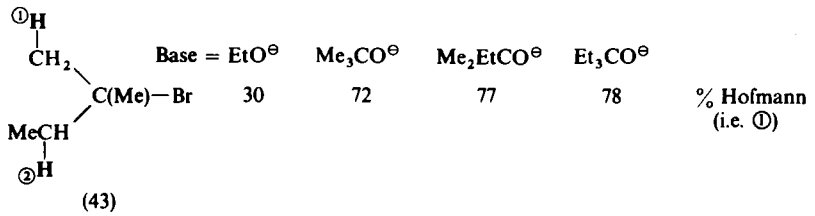
but substituents such as Ph, C=C, etc., promote formation of whichever alkene has its double bond conjugated with them. Another manifestation of Hofmann elimination is that where, as in (39), there are alternative potential $RNMe_2$ leaving groups, the least substituted alkene is always formed preferentially, i.e. (40) rather than (41):



The effect of Y on the mode of elimination may also involve a steric element. Thus it is found that increase in the size of Y and, more particularly branching in it, leads to an increasing proportion of Hofmann elimination with the same alkyl group, e.g. with (42):

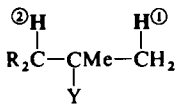


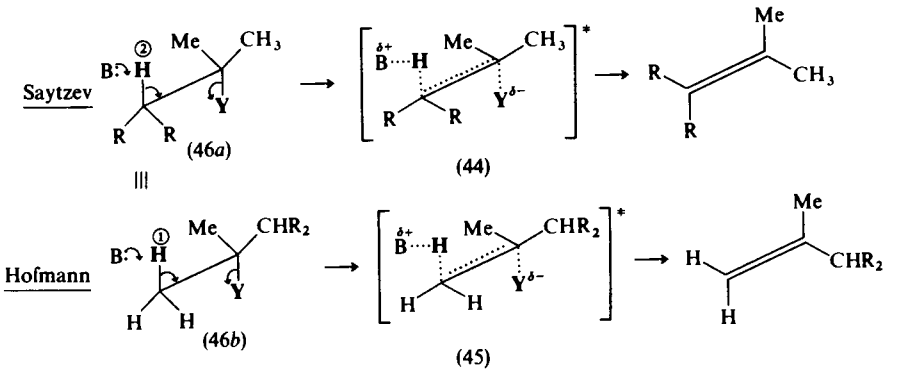
The proportion of Hofmann elimination is also found to increase with increasing branching in the alkyl group of the substrate (constant Y and base), and with increasing branching in the base, e.g. with (43), a bromide where preferential Saytzev elimination would normally be expected:



It may be mentioned in passing that the volume, and quantitative precision, of data available in this field owes much to the use of gas/liquid chromatography for the rapid, and accurate, quantitative analysis of alkene mixtures.

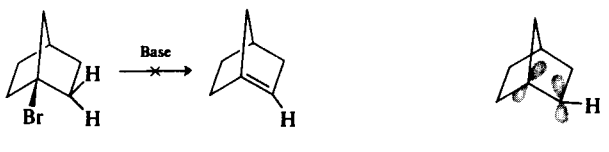
These several steric effects are explainable on the basis that any crowding, irrespective of its origin, will make the T.S. (44) that involves the removal of proton ② from (46*a*)—Saytzev elimination—relatively more crowded than the T.S. (45) that involves removal of proton ① from (46*b*)—Hofmann elimination. The differential will increase as the crowding increases (in R, Y or B), and Hofmann elimination will thus be progressively favoured over Saytzev:



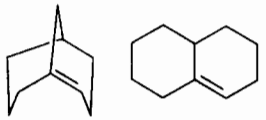


In many cases it is all but impossible to distinguish, separately, the operation of electronic and steric effects, as they often both operate towards the same end result. Except where crowding becomes extreme, however, it seems likely that the electronic effects are commonly in control.

In cyclic systems, the usual simple requirements of Saytzev or Hofmann rules may be overridden by other special requirements of the system, e.g. the preference for elimination from the *trans*-diaxial conformation in cyclohexane derivatives (*cf.* p. 255). Another such limitation is that it is not normally possible to effect an elimination so as to introduce a double bond on a bridgehead carbon atom in a fused ring system (Bredt's rule), e.g. (47) ⇸ (48):



This is presumably the case because the developing *p* orbitals in an E2 reaction, far from being coplanar (*cf.* p. 253), would be virtually at right angles to each other (49), and so could not overlap significantly to allow development of a double bond. The relatively small ring system is rigid enough to make the distortion required for effective *p* orbital overlap energetically unattainable; there seems no reason why an E1 or E1cB pathway would be any more successful: the bicycloheptene (48) has, indeed, never been prepared. With bigger rings, e.g. the bicyclononene (50), or a more flexible system (51), sufficient distortion is now possible to allow the introduction of a double bond by an elimination reaction:



(50) (51)

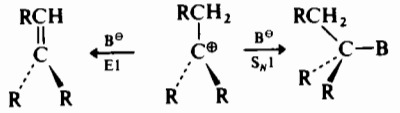
9.5 ELIMINATION *v.* SUBSTITUTION

E1 elimination reactions are normally accompanied by S_N1 substitution, as both have a common—carbocationic—intermediate; though this is converted into *either* elimination *or* substitution products *via* different T.S.s in a fast, non rate-limiting step. Similarly, E2 elimination is often accompanied by S_N2 substitution, though in this case the parallel, concerted processes involve entirely separate pathways throughout. Thus considering elimination *v.* substitution there are really three main issues: (*a*) factors influencing $E1/S_N1$ product ratios, (*b*) factors influencing $E2/S_N2$ product ratios, and (*c*) factors influencing change of pathway, i.e. $E1/S_N1 \rightarrow E2/S_N2$ (or *vice versa*), as such a shift often changes the proportion of elimination to substitution.

The last of these, (*c*), may well be the most potent. Thus $E1/S_N1$ solvolysis of Me_3CBr, and of $EtMe_2CBr$, in EtOH (at 25°) was found to yield 19% and 36%, respectively, of alkene; while introduction of 2M $EtO^{\ominus}$—which shifts the mechanism in part at least to $E2/S_N2$—resulted in the alkene yields rising to 93% and 99%, respectively. It is indeed found generally, for a given substrate, that the $E2/S_N2$ ratio is substantially higher than the $E1/S_N1$ ratio. A point that is worth bearing in mind when contemplating preparative, synthetic operations is the use of a less polar solvent (the $E1/S_N1$ process is favoured by polar, ion-solvating media)—the classical alcoholic, rather than aqueous, potash for elimination of HBr from alkyl bromides. A shift in mechanism may also be induced by increasing the concentration of the base employed, e.g. $^{\ominus}OH$; hence the classical use of concentrated, rather than dilute, potash for elimination.

In either (*a*) or (*b*), the carbon structure of the substrate is of considerable importance, the proportion of elimination rising on going: primary < secondary < tertiary. In electronic terms this stems from increasing relative stabilisation of the T.S. for elimination as the number of alkyl groups on the carbon atoms of the developing double bond increases (*cf.* p. 256). Thus with $EtO^{\ominus}$ in EtOH on alkyl bromides, we find: primary → *ca.* 10% alkene, secondary → *ca.* 60%, and tertiary → >90%. This stems not only from an increasing rate of elimination, but also from a decreasing rate of substitution. Similarly, substituents such as C=C and Ar that can stabilise the developing double bond through conjugation (*cf.* p. 253) also strongly favour elimination: under comparable conditions, CH_3CH_2Br yielded ≈1% alkene, while $PhCH_2CH_2Br$ yielded ≈99%.

In $E1/S_N1$ increasing branching in R—Y leads to an increase in the proportion of elimination. This arises from increasing stability of the progressively more highly substituted alkene product and, more importantly, of the T.S. leading to it from the carbocation intermediate. A steric factor may also operate to favour elimination in that the sp^2 hybridised carbon atom in the carbocation (52) remains sp^2 hybridised (≈120° bond angles) on elimination (53), but becomes sp^3 hybridised (≈109° bond angles) on substitution (54):



(53) (52) (54)

Crowding strain is thus re-introduced in the T.S. for substitution, but much less so, if at all, in the T.S. for elimination, and the differential between them will become greater—increasingly favouring elimination—as the size and degree of branching in the R groups increases; but only becoming significant when larger/more branched than Me_3C—Y. A related, but slightly different, point is that the peripheral H will be much more accessible than the relatively hindered carbocationic carbon; we should thus expect the proportion of elimination to rise as the size of the attacking base/nucleophile increases: as is indeed observed, i.e. $Me_3CO^{\ominus}$ is usually better than $EtO^{\ominus}$ for carrying out elimination reactions with. This discussion has tended to centre on the $E1/S_N1$ case, but essentially analogous steric effects are involved in the differential stabilisation of the T.S. for E2 with respect to the T.S. for S_N2.

The $E1/S_N1$ ratio is, of course, substantially independent of the leaving group Y, but this is not the case with $E2/S_N2$, where breaking of the C—Y bond is involved in each alternative T.S. The following rough sequence, in order of increasing promotion of elimination, is

observed:

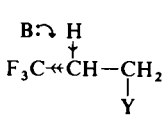
$$\text{Tosylate} < Br < \overset{\oplus}{S}Me_2 < \overset{\oplus}{N}Me_3$$

The attacking base/nucleophile is obviously of importance also; we require, ideally, a species that is a strong base but a poor nucleophile. Preparatively, tertiary amines, e.g. Et_3N, pyridine, are often used to promote elimination. Though these are not particularly strong bases, they are poor nucleophiles because of steric effects, e.g. branching in Et_3N, impeding nucleophilic attack on carbon, but not basic attack on a peripheral hydrogen. The use of a base of relatively high b.p. is also advantageous (see below).

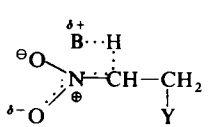
Finally, elimination—whether E1 or E2—is favoured with respect to substitution by rise in temperature. This is probably due to elimination leading to an increase in the number of particles, whereas substitution does not. Elimination thus has a more +ve entropy term (*cf.* p. 241), and because this ($\Delta S^{\ddagger}$) is multiplied by T in the relation for the free energy of activation, $\Delta G^{\ddagger}$ ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, *cf.* p. 38), it will increasingly outweigh a less favourable $\Delta H^{\ddagger}$ term as the temperature rises.

9.6 EFFECT OF ACTIVATING GROUPS

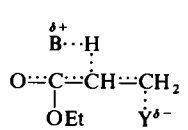
We have to date considered the effect of alkyl substituents in promoting elimination reactions in suitable substrates, and also, in passing, that of Ar and C=C. Elimination is, in general, promoted by most electron-withdrawing substituents, e.g. CF_3, NO_2, $ArSO_2$, CN, C=O, CO_2Et, etc. Their effect can be exerted: (*a*) through making the β-H atoms more acidic (55), and hence more easily removable by a base, (*b*) through stabilisation of a developing carbanion by electron-withdrawal (56), or in some cases, (*c*) through stabilisation of the developing double bond by conjugation with it (57):



(55)



(56)

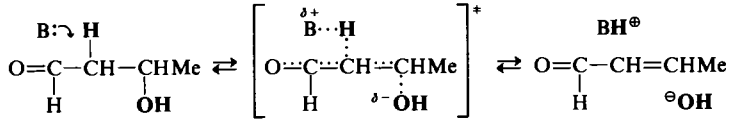


(57)

The more powerfully electron-withdrawing the substituent the greater the chance that the T.S. in an E2 elimination will be 'carbanion-like' (*cf.* p. 257), or even that the reaction pathway may be shifted to the E1cB mode (*cf.* p. 249), e.g. possibly with NO_2 or $ArSO_2$, especially if the leaving group, Y, is a poor one.

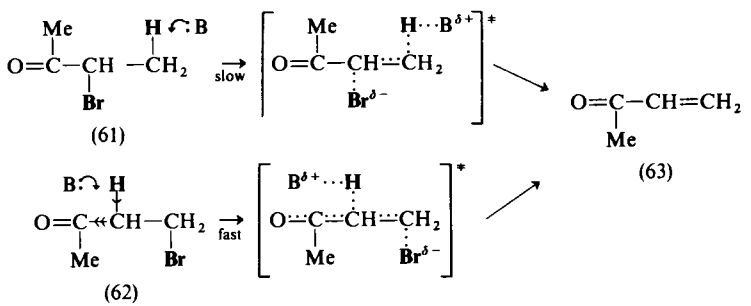
A good example of elimination promotion is by the CHO group in aldol (58) making possible a base-catalysed dehydration to an

$\alpha\beta$-unsaturated aldehyde (59, *cf.* p. 225):



(58) (60) (59)

Dehydrations are normally acid-catalysed (protonation of OH turning it into $^{\oplus}OH_2$, H_2O being a better leaving group than $^{\ominus}OH$), and a base-catalysed elimination is here made possible by the CHO group making the β-H atoms more acidic, and stabilising the resultant carbanion, i.e. (*a*)/(*b*) on p. 262. Stabilisation, by conjugation, of the developing double bond [(*c*) above] has been included in the T.S. (60) above, but how large a part this plays is not wholly clear. It is, however, significant that electron-withdrawing substituents are usually very much more effective in promoting elimination when they are on the β-, rather than the α-, carbon atom: they could conjugate with a developing double bond equally well from either position, but can only increase acidity of β-H, and stabilise a carbanion from the β-position. This is clearly seen in base-induced elimination of HBr from 1- and 2-bromoketones, (61) and (62), respectively,



(61) (63) (62)

where both give the same $\alpha\beta$-unsaturated (i.e. conjugated) ketone (63), but (62) is found to eliminate HBr very much faster than (61), under analogous conditions. Such β-substituents are often effective enough to promote loss of more unusual—and poor—leaving groups such as OR, NH_2, etc. (OH above).

9.7 OTHER 1,2-ELIMINATIONS

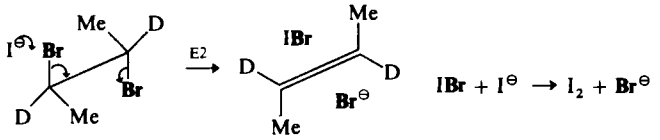
Attention has to-date been devoted almost entirely to eliminations in which it has been H that has been lost, as a proton, from the β-carbon atom. These are certainly the most important eliminations, but examples are known that involve the departure of an atom or group other than

H from C^{β}, the commonest probably being 1,2-dehalogenations and, in particular, 1,2-debromination. This can be induced by a number of different species including iodide ion, $I^{\ominus}$, metals such as zinc, and some metal ions, e.g. $Fe^{2\oplus}$. The reaction with $I^{\ominus}$ in acetone is found to follow the rate law (after allowance has been made for the $I^{\ominus}$ complexed by the I_2 produced in the reaction),

$$\text{Rate} = k[\text{1,2-dibromide}][I^{\ominus}]$$

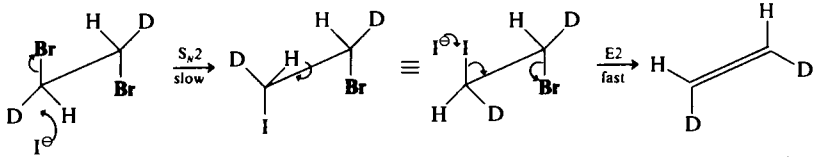
which would be compatible with a simple E2 pathway.

This is borne out by the high degree of ANTI stereoselectivity that is observed in acyclic examples (*cf.* p. 254), when either or both the bromine atoms are attached to secondary or tertiary carbon atoms, e.g. (64):



(64) (65)

only the *trans*-alkene (65) is obtained. When either or both the bromine atoms are attached to primary carbon atoms, e.g. (66), however, the overall reaction is found to proceed stereoselectively SYN, i.e. the *cis*-alkene (67) is the only product. This somewhat surprising result is believed not to represent a stereochemical change in the elimination itself, but to result from a composite S_N2/E2 mechanism; in which S_N2 displacement of Br by $I^{\ominus}$, with inversion of configuration (68), is followed by a stereoselective ANTI elimination on the 1-iodo-2-bromide (68) to yield (67)—the overall reaction being an apparent SYN elimination [(66) → (67)]:

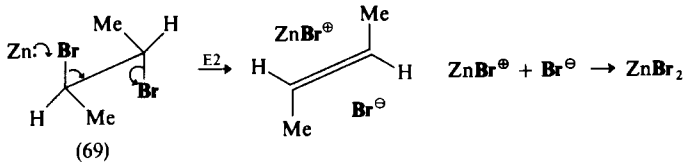


(66) (68) (68) (67)

Support for the actual elimination step, in each case, being E2 is provided by the fact that changing the alkyl substituents on C^{α} and C^{β} results in reaction rates that, in general, increase with the relative thermodynamic stability of the product alkene.

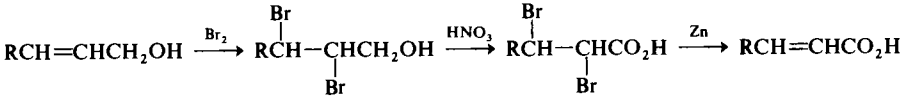
$Br^{\ominus}$ and $Cl^{\ominus}$ are much less effective at inducing 1,2-dehalogenation than $I^{\ominus}$, but metals—particularly Zn—have long been used. Reaction takes place heterogeneously at the surface of the metal, the solvent

renewing the active surface by removing the metal halide that is formed there. With simple examples, like those above, e.g. (69), there is a high degree of ANTI stereoselectivity, and the reaction pathway is probably simple E2, though the metal surface is certainly involved.



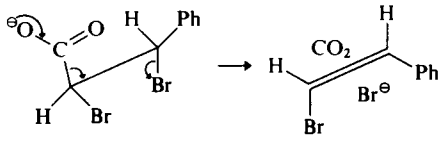
(69)

Strict ANTI stereoselectivity is, however, departed from with longer chain 1,2-dibromides, i.e. above C_4. The reaction may also be induced by Mg, hence the impossibility of making Grignard reagents from simple 1,2-dibromides. Metal cations have also been used to induce dehalogenation, the reaction then has the advantage over that with metals of occurring homogeneously. Debromination is rarely a preparatively useful reaction as the 1,2-dibromide starting material has usually been prepared by adding bromine to the product alkene! Bromination/debromination is, however, sometimes used for 'protecting' double bonds, e.g. in the oxidation of (70) → (71), which could not be carried out directly because the double bond would be attacked oxidatively at the same time.



(70) (71)

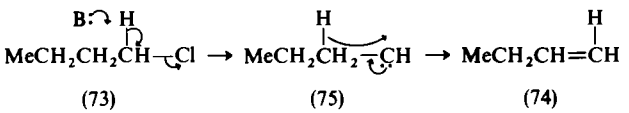
Eliminations have also been carried out on a number of compounds of the form $HalCH_2CH_2Y$, where Y = OH, OR, OCOR, NH_2, etc.; these eliminations normally require conditions more drastic than for 1,2-dihalides, and metals or metal cations are found to be more effective than $I^{\ominus}$. These eliminations are often found to be somewhat indiscriminate in their stereochemistry. The elimination of $CO_2/Br^{\ominus}$ from the diastereoisomer (72) of 2,3-dibromo-3-phenylpropanoate in Me_2CO is, however, found to proceed 100% ANTI, and under extremely mild conditions:



(72)

9.8 1,1-(α-)ELIMINATION

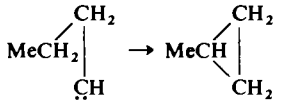
A relatively small number of examples are known of 1,1-eliminations in which both H and the leaving group, Y, are lost from the same (α-) carbon atom, e.g. (73) → (74). They tend to be favoured: (*a*) by powerfully electron-withdrawing Y groups—these increase the acidity of the α-H atoms, and stabilise a developing -ve charge on the α-carbon atom, (*b*) by using very strong bases, B, and (*c*) by the absence of β-H atoms—though this is not a requirement (*cf.* 73):



(73) (75) (74)

In some, though not necessarily all, cases loss of $H^{\oplus}$ and $Cl^{\ominus}$ is thought to be concerted, leading directly to the *carbene* (*cf.* p. 50) intermediate (75); formation of the product alkene from (75) then requires migration of H, with its electron pair, from the β-carbon atom. A 1,1-elimination (Eα) will be indistinguishable kinetically from 1,2-(E2), and evidence for its occurrence rests on isotopic labelling, and on inferential evidence for the formation of carbenes, e.g. (75).

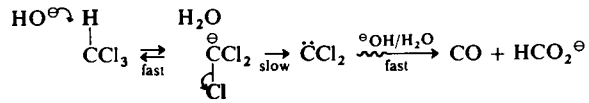
Thus introduction of 2D atoms at the α-position in (73) is found to result in one of them being lost in going to (74)—both would be retained in E2; while introduction of 2D at the β-position in (73) results in both being still present in (74), though one is now on the terminal (α- in 73) carbon atom—one would have been lost in E2. From such isotopic labelling data it is possible to determine how much of a given elimination proceeds by the 1,1-, and how much by the 1,2-pathway. Use of $C_6H_5{}^{\ominus}Na^{\oplus}$—an enormously strong base—in decane solution is found to result in 94% 1,1-elimination from (73), while $Na^{\oplus}NH_2{}^{\ominus}$ caused much less, and $Na^{\oplus}OMe^{\ominus}$ hardly any at all, i.e. the operation of factor (*b*) above. It was also found that, for a given base, alkyl bromides and iodides underwent much less 1,1-elimination than the corresponding chlorides, i.e. operation of factor (*a*), above. Inferential evidence for the formation of the carbene intermediate (75) is provided by the isolation from the reaction mixture of the cyclopropane (76),



(75) (76)

such intramolecular 'insertions' to form cyclopropanes being a common reaction of suitable carbenes; it is an example of 'internal trapping' (*cf.* p. 50). Only 4% of (76) was isolated from the reaction of (73), but no less than 32% of (76) was isolated from the 1,1-elimination of the isomeric chloride, $MeCH(Cl)CH_2CH_3$.

The most familiar, and most studied, example of 1,1-elimination occurs where no β-H atoms are available—the operation of factor (*c*) above—in the hydrolysis of haloforms, e.g. $CHCl_3$ (77), with strong bases. This involves an initial 1,1-elimination, probably *via* a two-step, i.e. 1,1-E1cB, pathway, to yield a dichlorocarbene intermediate (78);

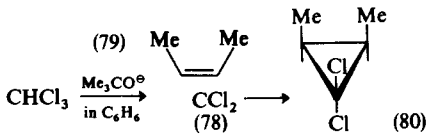


(77) (78)

The hydrolysis, as expected, follows the rate law,

$$\text{Rate} = k[CHCl_3][{}^{\ominus}OH]$$

and the fast, reversible first step is supported by the fact that deuterated chloroform, $CDCl_3$, is found to undergo base-catalysed exchange with H_2O (loss of D) much faster than it undergoes hydrolysis. Further support for the above mechanism comes from the observation that $HCCl_3$ is relatively inert towards $PhS^{\ominus}$ alone; but will, if ${}^{\ominus}OH$ is added, then react very rapidly to form $HC(SPh)_3$, i.e. $PhS^{\ominus}$ while not nucleophilic enough to attack $HCCl_3$ will attack the highly reactive CCl_2. This dichlorocarbene is a highly electron-deficient species and (if generated in a non-protic solvent) will add to the double bond of (electron-rich) alkenes, e.g. *cis* 2-butene (79), to form cyclopropanes, e.g. (80), a 'trapping' reaction (*cf.* p. 50):



Under suitable conditions, this can be a useful preparative method for cyclopropanes; another preparative 'trapping' reaction of CCl_2 is its electrophilic attack on phenols in the Reimer–Tiemann reaction (p. 290).

It should however, be emphasised that in protic solvents, with the common bases, and with substrates containing β-H atoms 1,1-elimination occurs to only a small extent if at all.

9.9 PYROLYTIC SYN ELIMINATION

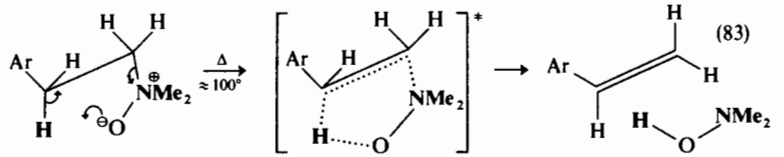
There are a number of organic compounds including esters—especially acetates, xanthates (see below)—amine oxides, and halides that undergo

pyrolytic elimination of HY, in the absence of added reagents, either in inert solvents or in the absence of solvent—in some cases in the gas phase. In general these eliminations follow the rate law,

$$\text{Rate} = k[\text{substrate}]$$

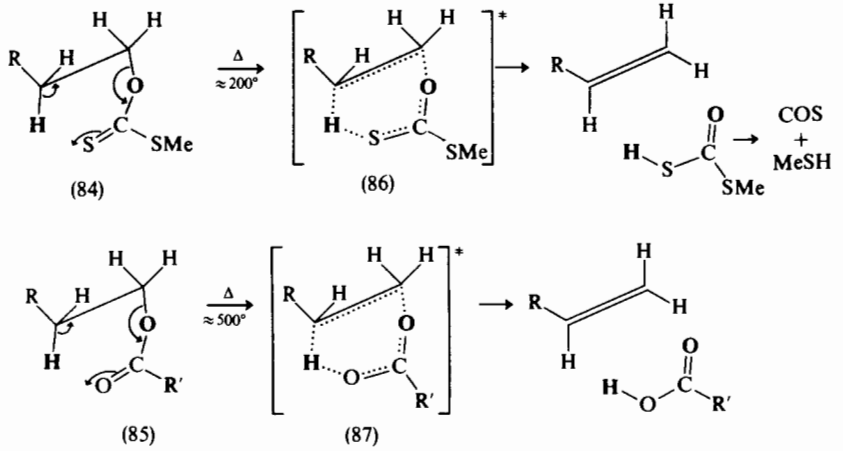
but are usually distinguishable from E1 eliminations (that follow the same rate law) by the degree of SYN stereoselectivity that they exhibit. They are sometimes referred to as E*i* eliminations (*elimination, intramolecular*), and the degree of SYN stereoselectivity reflects the extent to which they proceed *via* cyclic transition states, e.g. (81) below, that would dictate a SYN pathway.

The reaction that is perhaps of the greatest synthetic utility—because it proceeds at relatively low temperatures—is the Cope reaction of tertiary amine oxides, e.g. (82):



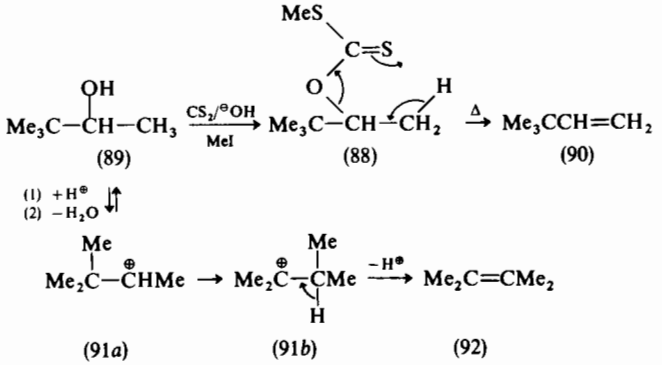
The leaving groups, H and NMe_2O, must assume a syn-periplanar conformation, with respect to each other, to be close enough together to permit the development of the O···H bond in the T.S. (81); the products are the alkene (83) and N,N-dimethylhydroxylamine. The Cope reaction, proceeding *via* this tight, essentially planar five-membered T.S., exhibits the greatest degree of SYN stereoselectivity of any of these reactions.

The pyrolysis of xanthates (84)—the Chugaev reaction—and of carboxylic esters (85) differ from the above in proceeding *via* six-membered, cyclic transition states, e.g. (86) and (87), respectively:



The six-membered rings in these T.S.s are more flexible than the five-membered T.S.—(81) above—and need not be planar (*cf.* cyclohexanes *v.* cyclopentanes). Elimination may thus proceed, in part at least, from conformations other than the syn-periplanar, with the result that the degree of SYN stereoselectivity in these eliminations may sometimes be lower than that observed in the Cope reaction. Both reactions require higher temperatures than for the Cope reaction, carboxylic esters particularly so.

One of the major advantages of this group of elimination reactions, as a preparative method for alkenes, is that the conditions are relatively mild, in particular any acidity/basicity is low. This means that it is possible to synthesise alkenes that are labile, i.e. which isomerise during the course of alternative methods of synthesis through bond migration (into conjugation with others), or molecular rearrangement. Thus pyrolysis of the xanthate (88) of the alcohol (89) results in the formation of the unrearranged terminal alkene (90), whereas the more usual acid-catalysed dehydration of (89) results in rearrangement in the carbocationic intermediate (91, *cf.* p. 111), and thus in formation of the thermodynamically more stable, rearranged alkene (92):



Pyrolysis of alkyl chlorides and bromides (alkyl fluorides are too stable; alkyl iodides lead to some alkane, as well as alkene, through reduction by the eliminated HI) also results in the formation of alkenes, but temperatures up to 600° are required, and the elimination is seldom of preparative use; paradoxically it is the type that has received the most detailed study. A wholly concerted 1,2-elimination of hydrogen halide would involve a highly strained, four-membered T.S. It seems not unlikely therefore that a good deal of C—Hal bond-breaking takes place in advance of the C—H bond-breaking: a high degree of 'carbocationic character' thereby being developed at the C—Hal carbon atom. It thus comes as no surprise to find that eliminations of HHal are observed to exhibit less SYN stereoselectivity than the others. Further mention will be made of E*i* concerted eliminations, and of other reactions involving cyclic T.S.s, subsequently (p. 340).