Alkylhalides

These are compounds that have the general formula $R - X$ (where $X = F, Cl, Br$ or $I$), $R$ can be simple alkyl (CH$_3$, ethyl propyl) or substituted alkyl gp. In other word the halogen attached saturated, SP$^3$ hyberdized carbon.

Other classes like aromatic halide or vinylic halide also exist but their chemistry is quite different from alkylhalide
Organohalides compounds are used extensively in modern society. Some are used as solvents (chloroform $\text{CHCl}_3$ and dichloromethane $\text{CH}_2\text{ClCH}_2\text{Cl}$), some as insecticides (DDT), some as intermediates in the synthesis of other organic compounds.
Nomenclature:

- The simple alkylhalides are generally given common names. The name of the alkyl gp is followed by the name of the halogen e.g.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \text{n-hexyl bromide}
\]

\[
\text{H}_3\text{C} \quad \text{CH}_3
\]

\[
\text{H}_3\text{C} \quad \text{CH} \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I} \quad \text{Isohexyl iodide}
\]

\[
\text{H}_3\text{C} \quad \text{C} \quad \text{CH}_3
\]

\[
\text{t-butyl chloride}
\]

\[
\text{CH}_2\text{Cl}
\]

\[
\text{Benzyl chloride}
\]

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In systemic naming according to the IUPAC system, the appropriate prefix, fluoro, chloro, bromo or iodo and the position number are added to the parent name of hydrocarbon to indicate the presence of the halogen.

If the parent chain can be properly numbered from either end, then begin at the end near the substituent that has alphabetical priority.

4-bromo-2,3-dimethylheptane

2-bromo-5,6-dimethylheptane
Preparation of alkylhalides:

- Organic halides are rarely found in nature (thyroxine (3,5,3',5'-tetraiodothyronine) “hence must be prepared when needed” the following are example of alkylhalides preparation that been covered before:

1) \( R-H + X_2 \rightarrow R-X + HX \) (\( X = \text{Cl, Br} \))

2) \( R_1-C=C-R_2 + HX \rightarrow R_2-C-C-R_3 \)

3) \( HC=CH + X_2 \rightarrow R-C-C-R' \)

4) \( R-C≡C-R' + 2X_2 \rightarrow R-C-C-R' \)

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Preparation from alcohol:

- The most valuable method for preparation of alkylhalides involve the replacement of the hydroxyl gp of an alcohol by a halide.

- The simplest, but least useful, method for converting an alcohol to alkylhalide involve treating alcohol with halogen acid HCl, HBr or HI. This reaction work best with allylic, benzylic then with tertiary alcohol.

- Primary and secondary alcohols reacts much slower and at higher energy or catalyst may needed.

\[ R\text{-OH} + \text{HX} \rightarrow R\text{-X} + \text{H}_2\text{O} \]

\[ \text{H}_3\text{C}(-\text{CH}_3)(-\text{CH}_3)\text{C}(-\text{CH}_3)\text{OH} + \text{HCl conc} \rightarrow \text{H}_3\text{C}(-\text{CH}_3)(-\text{CH}_3)\text{C}(-\text{CH}_3)\text{Cl} \]
- Reactivity order of alcohols with halogen acids towards the formation of alkyl halide follows this sequence:

  - Allylic
  - Benzylic

\[
\begin{align*}
3^\circ \text{ alcohol} & \rightarrow R-C-OH \\
2^\circ \text{ alcohol} & \rightarrow R-CH-R \\
1^\circ \text{ alcohol} & \rightarrow R-C-OH
\end{align*}
\]

- With 1\text{ry} and 2\text{ry} alcohol ZnCl as catalyst may be required.

- The reactivity of halogen acids sequence as follow:

\[
\begin{align*}
\text{HI} & \rightarrow \text{HBr} \\
\text{HBr} & \rightarrow \text{HCl}
\end{align*}
\]
Mechanism of the reaction of alcohols with halogen acids

Step I

\[ R-\text{OH} + HX \rightarrow R-\text{OH}_2 + X^- \]

Step 2

\[ R-\text{OH}_2 \rightarrow R^+ + H_2O \]

\[ \text{Carbocation} \]

Step 3

\[ R^+ + X^- \rightarrow R-X \]

Step 1 & 2 are the same initial steps presented in the catalyzed dehydration of alcohols to give alkenes. Here the carbocation instead of loosing proton to give alkene, it reacts with halide ion to give alkylhalide.

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If the carbocations are formed during the rxn of alcohols with HX as suggested by the mechanism, then rearrangement of the intermediate carbocation would occur if this will give a more stable carbocation.

Mechanism:

H₃C─CH─C─CH₃ + HCl → H₃C─CH─C─CH₃ Only product

2-chloro-2,3-dimethylbutane

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Problem: Give the product of the reaction of

\[
\text{H}_3\text{C} - \text{CH} - \text{C} - \text{CH}_3 + \text{HCl} \rightarrow \text{H}_3\text{C} - \text{CH} - \text{C} - \text{CH}_3
\]

1° and 2° alcohols are best converted into their corresponding chloride or bromide by treatment with thionyl chloride (SOCl₂) or phosphorous trichloride and tribromide respectively.

\[
\text{H}_3\text{C} - \text{CH}_2 - \text{C} - \text{CH}_3 + \text{SOCl}_2 \rightarrow \text{H}_3\text{C} - \text{CH}_2 - \text{C} - \text{CH}_3 + \text{SO}_2 + \text{HCl}
\]

\[
3 \text{H}_3\text{C} - \text{CH}_2 - \text{C} - \text{CH}_2\text{OH} \rightarrow 3 \text{H}_3\text{C} - \text{CH}_2 - \text{C} - \text{CH}_2\text{Cl} + \text{H}_3\text{PO}_3
\]

Phosphorus acid

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In the reaction of SOCl$_2$ with alcohols, the inorganic byproducts SO$_2$ & HCl are gases and can be absorbed in alkaline soln. and facilitate the isolation of alkylhalide.

SOCl$_2$ and PX$_3$ are less acidic than HCl, hence the reaction does not involve the formation of carbocation, therefore there is no rearrangement for the carbon skeleton as in the case of the reaction with HX.
Reactions of alkylhalides

Nucleophilic substitution:

The electronegative halogen pulls the electron from the carbon resulting in an electropositive carbon and electronegative halogen i.e the halogen-carbon bond in alkylhalides is polar bond.

On the other hand halide ion is extremely weak base therefore can be displaced by strong Bases. These bases possess an unshared pair of electrons and seeking a relatively +ve site i.e seeking a nuclous with which to share their pair of electrons therefore they are nucleophiles.

Saturated $Sp^3$

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Basic, electron rich reagents are called nucleophilic reagent (nucleus loving). Therefore the typical reaction of alkylhalides is nucleophilic substitution or nucleophilic displacement.

\[ R-X + Y \rightarrow R-Y + X \]

The halide ion acts as a leaving group to be displaced by the nucleophile (electron rich reagent).

The nucleophile may be either an organic or inorganic anion or it may be a neutral molecule having an unshared electron i.e. they acts as Lewis base.
Examples of nucleophilic substitution

- Alkane: \( R \rightarrow R' \)
- Thioether: \( R \rightarrow S \rightarrow R' \)
- 1° Amine: \( R \rightarrow NH_2 \)
- Alkyne: \( R \rightarrow C \equiv C \rightarrow R' \)
- Alcohol: \( R \rightarrow OH \)
- Nitrile: \( R \rightarrow CN \)
- Ether: \( R \rightarrow O \rightarrow R' \)
- Thiol: \( R \rightarrow SH \)
- Ester: \( R \rightarrow COOR' \)
- Malonic ester ion: \( HOOC \rightarrow COOEt \)

For Dr. Elrashied Ali Elobaid
The wide and different varieties of compounds that can be made by the use of alkylhalides indicate the extreme importance of nucleophilic substn rxn in synthesis.

2) **Dehydrohalogenation:**

\[
\text{C} \quad \text{X} \\
\text{H} \\
\text{C} \quad \text{C} \\
\text{KOH (Alc)} \xrightarrow{} \text{C}=\text{C} + \text{H}_2\text{O} + \text{KX} \\
\text{Alkene}
\]

3) **Preparation of Grignard reagents:** an organo magnesium halide (RMgX)

\[
\text{R} \quad \text{X} + \text{Mg} \xrightarrow{\text{dry ether}} \text{R-MgX} \xrightarrow{\text{H}_2\text{O}} \text{R-H} + \text{Mg}\text{X} \quad \text{OH}
\]

4) **Reduction:**

\[
\text{R} \quad \text{X} + \text{H}_2 \xrightarrow{\text{Ni}} \text{R-H} + \text{HX}
\]

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Kinetics of nucleophilic aliphatic substn: Second order and first order kinetics

- To study this kinetics let us take the rxn of methylbromide with hydroxide ion to yield methanol as example.

\[
\text{H}_3\text{C}--\text{Br} + \text{OH}^- \rightarrow \text{H}_3\text{C}--\text{OH} + \text{Br}^-
\]

- This reaction result from collision between a hydroxide ion and methyl bromide molecule.
- There is a direct relation between the reaction rate and the concentration of both reactant. If we doubled the conc of [OH] or [CH₃Br] the reaction rate is doubled and vice versa if we half the concentration the rxn rate is halved.
The reaction rate is depend upon the conc of both [OH] and [CH₃Br] and expressed by the following equation:

\[
\text{Reaction rate} = k [\text{OH}] [\text{CH}_3\text{Br}]
\]

where \( k \) is the rate constant

- Such reaction is said to be second order reaction and represented as \( S_{N2} \) (substitution, nucleophilic, bimolecular) i.e the two molecules take part in the step kinetically measured.
Now let us look at the corresponding rxn between t-butylchloride and hydroxide ion to yield t-butyl alcohol.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{C} & \quad \text{Cl} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{OH} \\
\text{H}_3\text{C} & \quad \text{OH} \\
\text{Cl} & \\
\end{align*}
\]

- In this reaction if we doubled the conc of t-butylchloride the reaction rate is doubled.
- Where as if doubled the conc of the hydroxide ion there is no change in the reaction rate.
- Therefore the reaction rate is said to be depend upon the conc of t-butylchloride but independent on the hydroxide ion conc.
- The reaction rate expressed by \( \text{rate} = k [\text{t-butylchloride}] \) it’s 1\text{st order} rxn as only one reactant take part in kinetically measured step \( S_{N1} \) i.e unimolecular reaction.

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To account for such difference in the kinetic of the reaction rates between the two previous examples of reaction, it has been proposed that nucleophilic substn can proceed by two different mechanism.

1) **The mechanism of reaction of CH₃Br and OH:**

The OH ion approach the methyl bromide from the site opposite to the bromide, the OH ion used its lone pair of es and made a bond with the carbon 180° away from the bromide ion.

\[
\begin{array}{c}
\text{OH} \\
\text{H}\\n\text{C} \\
\text{H}\\n\text{H}\\n\text{Br} \\
\end{array} \quad \rightarrow \quad \left[ \begin{array}{c}
\text{H} \\
\text{C} \\
\text{H}\\n\text{Br} \\
\end{array} \right] \quad \rightarrow \quad \begin{array}{c}
\text{HO} \\
\text{C} \\
\text{H}\\n\text{H} \\
\end{array} + \quad \begin{array}{c}
\text{Br} \\
\end{array}
\]

**Transition state**

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The transition state with a partial formed C-OH bond and a partial broken C-Br bond formation is the stage before leaving of the bromo gp as bromide ion.

- This reaction is said to be $S_{N2}$.
- It’s a single step reaction no intermediate only transition state.
- The reaction proceed with inversion of the configuration, as a result the OH ion attacks from the back site of the leaving gp (Br).
Application to $S_N2$:

1) The $S_N2$ reaction is applicable in some reaction to synthesized the inverted isomer from the other one which is difficult to be directly synthesized.

\[
\begin{align*}
\text{(+)-1-phenyl-2-propanol} & \quad \text{TosCl} \quad \text{pyridine} \quad \text{(-)-1-phenyl-2-propanol} \\
& \quad \text{H}_2\text{O} / \text{OH} \qquad \text{H}_3\text{C-}-\text{CO}: \quad \text{OH}
\end{align*}
\]
2) German chemist **Paul Walden** he found (+) and (-) malic acid could be interconverted through a series of simple substitution reaction.

\[
\begin{align*}
(-) - \text{Malic acid} & \quad \xrightarrow{\text{PCl}_5, \text{Ether}} \quad (+) - \text{Chlorosuccinic acid} \\
(-) - \text{Chlorosuccinic acid} & \quad \xleftarrow{\text{Ag}_2\text{O}, \text{H}_2\text{O}} \quad (+) - \text{Malic acid}
\end{align*}
\]
2) Mechanism of reaction of t-butyldichloride with OH ion

- The reaction of t-butyldichloride with the OH to yield t-butanol follow 1st order kinetics i.e the rate depends upon the con. of only one reactant, the 3°-butylchloride.

\[
\text{\begin{align*}
\text{CH}_3&\text{CH}_3 \\
\text{H}_3\text{C} & -\text{Cl} \\
\text{H}_3\text{C}
\end{align*}} + \text{\underline{OH}} \rightarrow \text{\begin{align*}
\text{CH}_3&\text{CH}_3 \\
\text{H}_3\text{C} & -\text{OH} \\
\text{H}_3\text{C}
\end{align*}} + \text{\underline{Cl}}
\]

- To understand that the rate is independent of the [OH] and only depend upon the t-butyldichlorde let us see the mechanism:
1) \[ \text{t-butyl chloride} \rightarrow \text{t-butyl carbocation} + \text{chloride ion} \] slow

2) \[ \text{t-butyl carbocation} + \text{OH} \rightarrow \text{t-butyl alcohol} \] Fast

**t-butyl chloride** slowly dissociates (step 1) into t-butyl carbocation and chloride ion.

The carbocation then rapidly (step 2) combines with the OH ion to yield t-butylalcohol.

The rate of the overall reaction is determined by the slow breaking of the C-Cl bond to form the carbocation.
• Once the carbocation formed it rapidly react with \textbf{OH} ion to yield the $t$-butylalcohol.
• therefore rate determining step is the formation of the carbocation, this why is $S_{N1}$ reaction it’s a unimolecular reaction rate determined by only one molecule.
The stereochemistry of $S_{N2}$ Rxn

- In $S_{N2}$ rxns of an alkylhalide the nucleophile does not take the position previously occupied by the halogen, but it takes the opposite position, this result from the back attack of the nucleophile.
methylalcohol

Methylbromide
It follows that an optically active substrate should give an optically active product.
As the **OH** ion taken a position opposite to that of the **halogen**, this reaction is said to proceed with the **inversion** of the **configuration**.

The configuration of alcohol is opposite to that of the starting alkylhalide.

Hence **$S_{N_2}$** reaction proceed with complete inversion of the configuration, the inversion exactly similar to the umbrella when turn inside out by the effect of the strong wind.
In $\text{S}_\text{N}2$ reactions the reactivity of alkylhalides is as follows: $\text{CH}_3\text{X} > 1^\circ > 2^\circ > \text{Neopentyl} > 3^\circ$

- $\text{CH}_3\text{Cl}$ is the most reactive alkylhalide by $\text{S}_\text{N}2$ followed by 1ry alkylhalides e.g (ethyl propyl).
- Branching next to the leaving group greatly slows the reaction as in 2ry alkylhalide e.g isopropyl.
- Further branching as in the case of 3ry butyl halides stop the reaction by SN2, even if the branching one carbon away from the leaving group as in the case of neopentyl halides.

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Stereochemistry of the $\text{S}_\text{N}1$ reaction

- When one carries an $\text{S}_\text{N}1$ reaction starting with a pure optically active isomer, the product is usually a racemic mixture of both optical isomers with a slight predominance of the isomer that corresponds to inversion

(R)-6-chloro-2,6-dimethyloctane

60% inversion

40% retention
Planar carbocation

50% inversion

50% retention

dissociation

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\( \text{SN}_1 \) rxns proceeds via a carbocation, this carbocation is a flat planar molecule, then the nu attack the carbocation at either site equal which result in a racemic mixture, with sometimes slight predomination to inversion.

Inversion of the configuration

Retention

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The predomination of the inversion is due to the hindrance that caused by leaving gp, which while leaving doesn’t allow the nucleophile to attack at its site then the back attack leads to more inverted isomer.

When the carbocation is highly stable then racemisation occurs.

High temp increase racemisation as it enhance the leaving of the halogen.

Reactivity of alkylhalides by SN1 is:

Allylic & benzylic > 3° > 2° > 1° > CH₃X
Cis-1-chloro-3-methylcyclopentane → trans-3-methylcyclopentanol

Transition state
Rearrangement in $S_N1$

- Since SN2 involve no carbocation, hence there is no rearrangement of the product. However, since SN1 involve a carbocation rearrangement do occur if this will give a more stable carbocation.

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Factors determining which mechanism in nucleophilic substn

1. Steric effect:

   As the attack of the nucleophile on the alkylhalide occur at the back of the molecule, it follows that bulky gp attached to the carbon bearing the halogen will shield that carbon and hence retard the $S_{N2}$ rxn compared to a carbon carrying smaller gp (see slide 31).

   The reactivity of alkylhalide towards $S_{N2}$ rxns is $CH_3X > 1^\circ > 2^\circ > Neopentyl >> 3^\circ$
2) The attacking nucleophile and its concentration:
The nature of the nucleophile play major role in $S_{N2}$ rxns, this why $S_{N2}$ rxns are favoured by powerful nucleophiles in high concentration. $S_{N1}$ does not affected by nucleophile because in the rate limiting step the added nucleophile has no part.

- Any species, either neutral or -vely charged can act as a nucleophile as long as it has an unshared pair of electrons i.e a Lewis base.
- Generally strong nucleophilic reagent are good electron donars i.e are good Lewis bases.
- Nucleophilicity always related to basicity.
• Charged nucleophiles are stronger than neutral e.g. \( \text{\textit{\text{\texttt{OH}}} \) stronger than \( \text{\textit{\text{\texttt{H}}}2\text{\textit{\text{\texttt{O}}}}} \)), \( \text{\textit{\text{\texttt{OR}}} \) stronger than \( \text{\textit{\text{\texttt{ROH}}} \).}
• In a group of nucleophiles in which the nucleophilic atom is the same nucleophilicity parallel basicity.

Nucleophilic reagent having N with unshared pair of es

\[
\begin{align*}
\text{NH}_2 & \\
\text{R} & \text{NH} \\
\text{R} & \text{NH}_2 \\
\text{NH}_3
\end{align*}
\]

Decrease in nucleophilicity

Nucleophilic reagent having O with unshared pair of es

\[
\begin{align*}
\text{OC}_2\text{H}_5 & \\
\text{\textit{\text{\texttt{OH}}} & \text{O} \\
\text{\textit{\text{\texttt{H}}}3\text{\textit{\text{\texttt{C}}} & \text{\textit{\text{\texttt{C}}} & \text{\textit{\text{\texttt{O}}} \\
\text{\textit{\text{\texttt{H}}}2\text{\textit{\text{\texttt{O}}} & \text{\textit{\text{\texttt{R}}} \text{\textit{\text{\texttt{OH}}}
\end{align*}
\]
• Nucleophilicity usually increases going down a column of periodic table. Thus, HS\(^-\) is nucleophilic than OH\(^-\), and halide reactivity order I\(^-\) >Br\(^-\) > Cl\(^-\).

• Nucleophilicity in gp of nucleophile having different nucleophilic atoms is not parallel to basicity

Pattern of increase nucleophilicity:
H\(_2\)O < CH\(_3\)CO\(_2\)^- < NH\(_3\) < Cl\(^-\) < OH\(^-\) < CH\(_3\)O\(^-\) < I\(^-\) < CN\(^-\) < HS\(^-\)

• Generally nucleophilicity is rough stimation it depend on the substrate, the solvent and even the reactant conc
3) The leaving group:

In $S_N^2$ rxn, the leaving gp is expelled with a pair of es and it’s a negatively charged, hence the best leaving gp is that best stabilize the $-ve$ charge. Groups that best stabilize $-ve$ charge are also weak bases.

Thus weak bases such as $\text{Cl}^-$, $\text{Br}^-$, and tosylate ion make good leaving grp, while strong base such as $\text{OH}^-$ and $\text{NH}_2^-$ made poor leaving group.

Relative reactivity:

\[
\begin{align*}
\text{OH}^- & \quad \text{NH}_2^- & \quad \text{OR}^- & \quad \text{F}^- & \quad \text{Cl}^- & \quad \text{Br}^- & \quad \text{I}^- & \quad \text{TosO}^- \\
<< 1 & \quad 1 & \quad 200 & \quad 10,000 & \quad 30,000 & \quad 60,000
\end{align*}
\]

$SN_2$ reaction favoured by presence a less good leaving
The solvent effect:

Polar solvent increases the rate of an SN2 reaction of an alkyl halide when the nucleophile is a neutral molecule.

\[
\begin{align*}
\text{Nu} + R\text{X} &\longrightarrow \text{Nu}^{-}\cdots R\text{X}\cdots^{-}\text{Nu} \longrightarrow \text{Nu} \longrightarrow R + \text{X}
\end{align*}
\]

Solvation stabilizes the transition state with its developing electrical charge more than it does the Reactant.

On the other hand, if the nucleophile is charged, the use of a polar solvent decreases the rate of an SN2 reaction.

\[
\begin{align*}
\text{Nu}^{-} + R\text{X} &\longrightarrow \text{Nu}^{-}\cdots R\text{X}\cdots^{-}\text{Nu} \longrightarrow \text{Nu} \longrightarrow R + \text{X}
\end{align*}
\]
Negatively charged nucleophile is surrounded by cage of solvent hence stabilized it and reduce its energy of reactivity.

Solvent polarity is indicated by a quantity called dielectric constant which is a measure of the solvent ability to insulate opposite charges.

The greater the dielectric constant, the greater is the solvent ability to solvate ions.
### Polar protic solvent decrease rate of SN₂ when nu is charged due to H-bonding

<table>
<thead>
<tr>
<th>Polar protic solvent</th>
<th>Dielectric constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-H</td>
<td>80</td>
</tr>
<tr>
<td>CH₃-OH</td>
<td>33</td>
</tr>
<tr>
<td>C₂H₅-OH</td>
<td>24</td>
</tr>
<tr>
<td>HO-CO-CH₃</td>
<td>6</td>
</tr>
</tbody>
</table>

These polar protic solvent decrease rate of SN₂ when nu is charged due to H-bonding.
Polar aprotic solvents solvate cations more than anions (nucleophile) then preferable in $S_{N2}$ even charged nu such as:

**Dimethylsulphoxide**

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S} \quad \text{O} \\
\text{H}_3\text{C} &
\end{align*}
\]

Dielectric constant: **45**

**Dimethylformamide**

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{H}_3\text{C} &
\end{align*}
\]

Dielectric constant: **37**

**Hexamethylphosphoramide (HMPA)**

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{P} \quad \text{N} \\
\text{H}_3\text{C} & \quad \text{O} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \quad \text{H}_3\text{C}
\end{align*}
\]

Dielectric constant: **30**
Factors favour $S_{N1}$:

- **Sterric effect**: alkylhalide that contain groups that hinder attacks of nucleophile from back and contains gps that can stabilize the carbocation are favoured substitution by $S_{N1}$.

- **Leaving gp**: presence of good leaving gp like bromo iodo alkylhalide rather than chloride.

- **Solvent**: a highly polar solvent to help ionization of alkylhalide and stabilized the resultant ions by solvation.

- **Nucleophile**: weak nucleophile and present in dilute solution.
Elimination reaction of Alkylhalides

- This is a dehydrohalogenation rxn (elimination of HX)

- Bases used in dehydrohalogenation:
  - KOH / Alco
  - ROH / Na (Na alkoside = RO⁻ Na⁺)

\[
\text{R-OH} + \text{Na}^+ : \text{H}^- \rightarrow \text{R} - \text{O}^- \text{Na}^+ + \text{H}_2
\]

- K-tertiary butoxide

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Mechanism of dehydrohalogination (elimination)

- Two mechanisms are important in dehydrohalogenation, these are E₂ and E₁ Rxns.

The E₂ Rxn:
The E₂ rxns are favoured by the use of strong base e.g. OH⁻ or OR⁻ and high temp.
When isopropyl bromide is heated with KOH alcoholic to form propene the reaction rate depends on the concentration of both reactants.

\[ \text{H}_3\text{C} - \text{C} - \text{CH}_3 \xrightarrow{\text{KOH / alco}} \Delta \xrightarrow{\Delta} \text{H}_3\text{C} - \text{C} = \text{CH}_2 \]
Rate = $k \left[ \text{H}_3\text{C} = \text{C} - \text{CH}_3 \right][\text{OH}]

E2 single step reaction no intermediate the mechanism of the reaction as follow:

This mechanism indicate that the rate limiting step must involve the collision between the base and alkylhalide. It is a single step process without an intermediate. The base attack abstract a proton from a carbon next to the carbon bearing the leaving gp, accordingly C=C bond start to form, the halogen begins to depart taking with it the electron pair.
• E2 is a bimolecular rxn in which HX is eliminated from alkylhalide in the presence of strong base.
• The proton abstracted by the base is antiperiplanar geometry (geometry in which the hydrogen and the halogen in opposite site)

Anti

syn

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Anti-elimination study by Deuterium isotope

- About 1.2 Kcal/mol more energy is required for breaking a C-D bond than for a C-H. Thus replacing the β-hydrogen in an alkyl halide with deuterium should reduce the rate of formation of the alkene, this confirmed that the hydrogen abstracted from alkylhalide anti to the halogen.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{D} & \quad \text{H} & \quad \text{Br}
\end{align*}
\]
The $E_1$ Rxn

- Elimination may different way than that mentioned in the case of $E_2$.
- When t-butyl chloride is treated with 80% aqueous ethanol at 25˚C, for example, one obtains substn product in 83% and an elimination product in 17% yield.
E1 elimination begins with the same unimolecular dissociation shown in SN1, whether substitution or elimination depends on the next step.

If the solvent molecule reacts as a nucleophile and attacks the +ve charge carbon, then substitution will occur and the product is t-butyralcohol or t-butylethylether and the reaction is SN1.
• E₁ the dissociation is followed by the loss of \( H^+ \) from the adjacent carbon rather than substitution.
• In fact, E₁ and SN₁ reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a non basic nucleophile.
• The best E₁ substrates are also the best SN₁ substrate, and a mixture of substitution and elimination products are usually obtained.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{Cl} \\
\text{CH}_3 & \quad \text{C} \quad \text{OH} \quad + \quad \text{CH}_2 \\
\text{H}_3\text{C} & \quad \text{C} \quad \text{CH}_3 \\
\end{align*}
\]

\( \text{H}_2\text{O}, \text{Ethanol}, \text{65°C} \)
- E₁ always accompany SN₁ rxn.
- As E₁ proceed via carbocation rearrangement is possible if it will give stable carbocation
**$S_N1$ Versus $E1$:**

- Since $E1$ like $SN1$ proceed through the formation of a carbocation, they respond similarly to the same factor:
  1. $E1$ rxns are favoured with substrate that can form stable carbocation.
  2. They are also favoured by weak nucleophile (bases).
  3. Are generally favoured by polar solvent.
  4. In most unimolecular rxn $SN1$ rxn is favoured over $E1$. Increasing temp, however, favours the $E1$ at the expense of the $SN1$ rxn.

- If the elimination product is desired however, it is more convenient to add a strong base and favour an $E2$ rxn to place.

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**S

N

2 versus E2:** Since elimination occur best by an E2 path, when carried out with a high conc of strong base (and thus a high conc of a strong nucleophile). Then substitution rxns by SN2 path often compete with the elimination rxn, when the nucleophile (base) attacks a β-hydrogen, elimination occurs, when the nucleophile attacks the carbon bearing the leaving gp, substn results.
• When the alkylhalide substrate is 1ry and the base is ethoxide ion, substitution is highly favoured.

\[
\text{H}_3\text{C} \equiv \text{CH}_2\text{Br} + \text{C}_2\text{H}_5\text{O}^- \text{Na}^- \xrightarrow{\text{Ethanol}} 55 \, ^\circ\text{C} \quad \text{H}_3\text{C} \equiv \text{CH}_2\text{OC}_2\text{H}_5 + \text{H}_2\text{C} \equiv \text{CH}_2
\]

90% \[\text{SN}_2\]

10% \[\text{E}_2\]

• With the 2ry alkylhalides, however the elimination is favoured.

\[
\text{H}_3\text{C} \equiv \text{C} \equiv \text{CH}_3 + \text{C}_2\text{H}_5\text{O}^- \text{Na}^- \xrightarrow{\text{Ethanol}} 55 \, ^\circ\text{C} \quad \text{H}_3\text{C} \equiv \text{C} \equiv \text{CH}_3 + \text{H}_2\text{C} \equiv \text{C} \equiv \text{CH}_3
\]

21% \[\text{SN}_2\]

79% \[\text{E}_2\]

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With 3\textsuperscript{ry} alkylhalide an \( S_{\text{N}2} \) can not take place and thus elimination is highly favoured, especially when the rxn is carried at higher temp. Any substn that occurs probably occurs by \( S_{\text{N}1} \) mechanism.
Increasing the rxn temp is only one way of increasing elimination product.

Another way to increase elimination is to use a strong, sterically hindered base such as tertiary butoxide.

Then the size of the bulky tertiary butoxide ion appear to inhibit its rxn by substn and hence elimination predominates.

\[
\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_3\text{O}^-\text{Na}^+ \rightarrow \text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{C}=(\text{CH}_2)\text{CH}_2\text{OCH}_3
\]

1% E2  
99% SN2
\[
\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{C}^{-}-\text{CH}_2\text{Br} + \text{H}_3\text{C}^{-}\text{C}^{-}\text{ONa} \rightarrow \\
\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{C}^{-}-\text{CH}_2\text{O}^{-}\text{C}^{-}\text{CH}_3
\]

15% \text{ SN2}

\[
\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{C}^{-}-\text{CH}_2\text{O}^{-}\text{C}^{-}\text{CH}_3
\]

85% \text{ E2}
Tertiary Halides: $S_{N1}$ versus E2

- $SN_2$ rxn donot take place with 3ry alkylhalide.
- Suppose we want to prepare t-butylethylether from t-butyl bromide.

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{OC}_2H_5 \\
\text{Br}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{Br} \\
\text{CH}_3
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{OC}_2H_5 \\
\text{Br}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{Br} \\
\text{CH}_3
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{OC}_2H_5 \\
\text{Br}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
H_3C \quad & \quad \text{CH}_3 \\
\begin{array}{c}
\text{Br} \\
\text{CH}_3
\end{array} \\
\end{align*}
\]

- At higher temp the yield of alkene resulting from elimination is even increase.
- The best choice is an $SN_1$ rxn but the nucleophile is not ethoxide ion, but weak nucleophile ethanol and temp low.
- Ethanolysis should be carry

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\[
\text{CH}_3 \text{C} - \text{C} - \text{Br} + \text{C}_2\text{H}_5\text{OH} \quad \xrightarrow{25 \, ^\circ \text{C}} \quad \text{CH}_3 \text{C} - \text{C} - \text{OC}_2\text{H}_5
\]

81%  
\text{SN}_1

9%  
\text{E}_1
Aryl halides and Vinylhalide

- Aryl halides are cpds having a halogen atom directly attached to benzene ring.

Chlorobenzene  Bromobenzene  m-bromochlorobenzene

Vinyl halide

\[ \text{H}_2\text{C} \equiv \text{CHCl} \]

Vinyl chloride

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• Preparation of aryl halide is by EAS (Electrophilic aromatic substitution)
• Unlike alkyl halides, aryl halides undergo nucleophilic substitution with extreme difficulty.
• They don’t react for example with OH\(^{-}\), CN\(^{-}\) or NH\(_{3}\) under mild conditions required for aliphatic halides.

\[
\text{Cl} - \text{C}_6\text{H}_{11}\text{Cl} + \text{aq NaOH} \rightarrow \text{C}_6\text{H}_{11}\text{OH}
\]

chlorocyclohexane \(\rightarrow\) cyclohexanol

\[
\text{Cl} - \text{C}_6\text{H}_5\text{Cl} + \text{aq NaOH} \rightarrow \text{No rxn}
\]

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• Aryl halide e.g chloro benzene is a resonance hybrid structures

Structure 2,3 & 4 halogen carries a +ve charge and this prevents its departure as Cl\(^-\) required in nucleophilic substitution.

• The C-Cl bond in aryl halide is stronger and shorter due to double bond character.

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They don’t undergo SN2 because the halo-substituted carbon of the aromatic ring is sterically shielded from backside approach.

Backside displacement is sterically Blocked therefore no SN2

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They don’t undergo SN1 because dissociation of the aryl halide is energetically unfavoured due to the instability of the aryl cation.

The presence of certain gps like NO2 and CN at position ortho or para or both to the halogen markedly activate aromatic nucleophilic substitution.

In meta position these gps has no effect.
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Nucleophilic substitution in aryl halide proceed by a mechanism in which the nucleophile first added to the electron-deficient-aryl halide, forming a resonance-stabilized negatively charge intermediate, its addition elimination mechanism.

Stable carbanion

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The resonance stabilized hybrids shows that –ve charge ion is at ortho or para position to the halo gp therefore presence of a strong electron withdrawing gp at these position stabilize this ion.

No effect when these gp at met position.

Note the differences between the electrophilic aromatic substn reaction which occur readily in the presence of electron donating gp that stabilized the carbocation intermediate whereas nucleophilic aromatic subst occurs more readily in presence of es withdrawing gps that stabilize the carbanion intermediate.

es withdrawing gp deactivate EAS whereas activate NAS
Nucleophilic Aromatic Subst: The benzyne

- Halobenzene without electron withdrawing substituent don’t react with nucleophiles under most condition. At high temp and pressure however chloro benzene can be force to react.
- Chemists at Dow company discovered at 1928 that phenol can be formed from chloro benzene in large scale by treat it with dil NaOH at 350° and 170 atm pressure.

\[
\text{Cl} \quad 1) \text{NaOH, 350°, 170 atm} \quad \text{OH} \\
\]
This reaction and other reactions in which the ary halides treated with strong base are quite different from the other nucleophilic substn just studied. The reaction here proceed by an elimination addition mechanism.

Cl

\[ \text{H} \rightarrow \text{OH} \rightarrow \text{benzyne} \rightarrow \text{H}_2\text{O} \rightarrow \text{Addition product} \]

Elimination product
A similar reaction occurs with strong bases, if bromobenzene is treated with sodamine (NaNH₂) in liquid ammonia (NH₃) it will give aniline.
• Evidence to support the benzyne mechanism, if radioactive $^{14}$C labelled bromobenzene was treated sodamide in liq ammonia.

• Another fact is that comps containing two gps ortho to halogen do not react at all.
Vinylic halides

- Vinylic halides are generally unreactive in SN1 or SN2 vinylic cation are highly unstable, this explain their unreactivity in SN1 rxns.
- They are also unreactive in SN2 rxns because the C-X has double bond character and shorter and stronger to break.

Also the \( \pi \) electrons of the double bond repels an approaching nucleophile.

\[
\text{\begin{align*}
\text{C} &= \text{C} \\
\text{Cl} &\quad \rightarrow \\
\text{C} &= \text{C} \quad \\
\text{Cl} &
\end{align*}}
\]

\[
\text{C} &= \text{C} + \text{AgNO}_3 \quad \text{alc} \quad \text{no rxn}
\]

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Vinylic halides also undergo nucleophilic substitution when they are activated by strong electron withdrawing groups.