NUCLEOPHILIC SUBSTITUTION REACTIONS

SEM-2, CC-3
PART-12, PPT-26

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Nucleophilic Substitution Reactions
Part-12

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Formation, Stability and Reactions of Allylic Carbocations

- The effective stabilization in allyl cation is provided by conjugation of \( \pi \) electrons of the double bond with the carbocation carbon atom. The allyl cation has a filled (bonding) orbital containing two electrons delocalized over all three atoms and an empty orbital with coefficients on the terminal atoms only, illustrated in **Figure 1**. It’s this orbital that is attacked by nucleophiles and so it’s the end carbon atoms that are attacked by nucleophiles.

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**Figure 1: \( \pi \)-Molecular orbitals of allyl cation**

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Formation, Stability and Reactions of Allylic Carbocations

• A symmetrical allyl cation can give one product only by the $S_N 1$ reaction. The two delocalized structures of the cyclohexenyl cation are identical and the $\pi$ bond is shared equally among the three carbon atoms as shown in Figure 2.

![Illustration of delocalized $\pi$ bond in cyclohexenyl cation]

Figure 2: Delocalized $\pi$ bond in cyclohexenyl cation

• Treatment of cyclohexenol with HBr gives the corresponding allylic bromide. Only one compound is formed because attack at either end of the allylic cation gives the same product (Figure 3).

• However, when the allylic cation is unsymmetrical, then a mixture of products may be formed. It doesn’t matter which of the two butenols are treated with HBr, the same cation is obtained (Figure 4).

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**Figure 3:** Cyclohex-2-enol gives one product with HBr

**Figure 4:** Formation of a delocalized allyl cation

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• When delocalized allylic cation reacts with Br\(^{-}\), about 80% goes to one end and 20% to the other, giving a mixture of butenyl bromides, shown in Figure 5. The regioselectivity (where the nucleophile attacks) is determined by steric hindrance: attack is faster at the less hindered end of the allylic system.

\[
\begin{align*}
\text{Br} & \quad \text{Br}^- \\
\text{3-Bromobut-1-ene} & \quad \text{delocalized allyl cation} & \quad \text{(E)-1-Bromobut-2-ene} \\
20\% & \quad 80\%
\end{align*}
\]

Figure 5: Reaction in an unsymmetrical allyl cation

• The tertiary allylic alcohol 2-methylbut-3-en-2-ol reacts well by the \(S_N 1\) mechanism because it is both tertiary and allylic. The allylic carbocation intermediate is unsymmetrical and reacts only at the less substituted end to give ‘prenyl bromide’ (Figure 6).

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- The benzyl cation (Ph-CH$_2^+$) is about as stable as the allyl cation but lacks its ambiguity of reaction. Though the positive charge is delocalized around the benzene ring, the benzyl cation almost always reacts on the side chain.

**Figure 6: Preparation of prenyl bromide**

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Allylic Rearrangement

• An allylic rearrangement or allylic shift is an organic reaction in which the double bond in an allylic compound shifts to the next carbon atom. It is encountered in nucleophilic substitution.

• In reaction conditions that favour a $S_{N}1$ reaction mechanism, the intermediate is a carbocation for which several resonance structures are possible. This explains the product distribution (or product spread) after recombination with nucleophile. This type of process is called an $S_{N}1'$ substitution.

• Alternatively, it is possible for nucleophile to attack directly at the allylic position, displacing the leaving group in a single step, in a process referred to as $S_{N}2'$ substitution. This is likely in cases when the allylic compound is unhindered, and a strong nucleophile is used. The products will be similar to those seen with $S_{N}1'$ substitution.

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Allylic Rearrangement

• Thus reaction of 1-chloro-2-butene with sodium hydroxide gives a mixture of but-2-en-1-ol and but-3-en-2-ol. Nevertheless, the product in which the OH group is on the primary atom is minor.

\[ \text{(E)-1-Chlorobut-2-ene (B)} \xrightarrow{\text{NaOH}} \text{(E)-But-2-en-1-ol Minor} + \text{But-3-en-2-ol (Major)} \]

Figure 7: Alkaline hydrolysis of 1-chlorobut-2-ene

• In the substitution of 1-chloro-3-methylbut-2-ene, the secondary 2-methylbut-3-en-2-ol is produced in a yield of 85%, while that for the primary 3-methylbut-2-en-1-ol is 15%.

\[ \text{1-Chloro-3-methylbut-2-ene (A)} \xrightarrow{\text{NaOH}} \text{3-Methylbut-2-en-1-ol (B) 15\%} + \text{2-Methylbut-3-en-2-ol (C); 85\%} \]

Figure 8: Alkaline hydrolysis of 1-chloro-3-methylbut-2-ene

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Allylic Rearrangement

• In one reaction mechanism the nucleophile attacks not directly at the electrophilic site but in a conjugate addition over the double bond as shown in Figure 9.

![Figure 9: Conjugate addition of nucleophiles in allylic system](image)

• This is usual in allylic compounds which have a bulky leaving group in $S_N2$ conditions or bulky non-leaving substituent which give rise to significant steric hindrance (consequently prevents nucleophilic attack), thereby increasing the conjugate substitution.

• This kind of reaction is termed $S_N1'$ ($S_N1$ type reaction with rearrangement) or $S_N2'$ ($S_N2$ type reaction with rearrangement), depending on whether the reaction follows $S_N1$-like mechanism or $S_N2$-like mechanism.

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Allylic Rearrangement

- When treated with hydrogen bromide, crottyl alcohol produces a mixture of crottyl bromide and 3-bromobut-1-ene (Figure 10).

![Reaction of crottyl alcohol with HBr](image)

- The formation of the rearranged product is an example of anionotropy, and constitutes a three-carbon system, i.e., the allylic system. Nucleophilic substitution reactions of allylic halides may occur by the $S_N2$ mechanism, and when this is operating, substitution proceeds normally. When, however, nucleophilic substitution reactions are carried out under conditions which favour the unimolecular mechanism, then the product may be a mixture of two isomers, the rearranged product being an example of the allylic rearrangement.

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Allylic Rearrangement

- The mechanism by which this rearrangement occurs is known as $S_N1'$, and is believed to occur via a resonance hybrid (ambident) cation as shown in Figure 11.

![Figure 11: Reaction between crotyl alcohol with HBr](image)

- The evidence to support this $S_N1'$ mechanism is obtained by studying the conversion of $\alpha$-methylallyl and crotyl chloride into $\alpha$-methylallyl and crotyl ether by reaction with ethanolic sodium ethoxide. The concentration of the sodium ethoxide was made so small as to give first-order kinetics, or so large to give second-order kinetics. The results were shown in Figure 12.

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Allylic Rearrangement

With second order substitution, each chloride gives its own rearranged ether (thus the $S_N2$ mechanism). With first order substitution, however, each chloride gives the same mixture of isomeric ethers.

Figure 12: Evidence to support $S_N1'$ mechanism

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Allylic Rearrangement

• This latter result may be explained by assuming that two mechanisms are operating, $S_{N1}$ (without derangement) and $S_{N1}'$ (with rearrangement), both proceeding through a common intermediate ambident cation.

• In addition to the $S_{N1}'$ mechanism, there is also the $S_{N2}'$, i.e., a bimolecular nucleophilic substitution with allylic rearrangement. A good example of it has been provided which suppressed the $S_{N2}$ reaction by steric factors and reduced the $S_{N1}$ reaction by means of a reagent of high nucleophilic activity and a solvent of low ionizing power.

• It is found that the reaction between $\alpha,\alpha$-dimethylallyl chloride and sodium thiophenoxide in ethanol gives 62% of rearranged product by a second order reaction (i.e., $S_{N2}'$) as shown in Figure 13.
Ion pair formation occurs in the allylic rearrangement. α,α-Dimethylallyl chloride in acetic acid undergoes acetolysis accompanied by rearrangement to γ,γ-dimethylallyl chloride (Figure 14).

The rate of isomerization was shown to be proportional to the concentration of the starting chloride only. Thus a possible mechanism is the $S_{N}1'$. If this were so, then the rate of isomerization would be affected by addition of chloride ions (since the first step is ionization).

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Allylic Rearrangement

Experiment showed that the rate was unaffected by added chloride ions, and it was also shown that when an excess of radioactive chloride ion was added, the rate of isomerization was far greater than the incorporation of Cl\(^{-}\).

It thus appears that the chloride ion is set free during the isomerization and is mainly the ‘first ion’ to recombine, even though the solution contains excess of Cl\(^{-}\) ions.

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Allylic Rearrangement

- This result can be explained by assuming that the starting chloride undergoes ionization to form an ion-pair, and this is followed by internal return as shown in **Figure 15**.

![Diagram of Allylic Rearrangement](image)

- Nevertheless, some ion pairs escape from the solvent cage, and these ‘free’ carbocations are capable of undergoing acetolysis and combination with Cl\(^-\).

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Substitution Nucleophilic Internal

$S_{Ni}$ Mechanism: Retention of Configuration

- Most of the displacement reactions lead to inversion of configuration, to racemization, or to a mixture of both. However, a number of cases are known, though relatively rare, of reactions that proceed with actual retention of configuration, i.e., in which the starting material and the 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, $\text{SOCl}_2$, starting from a benzylic alcohol, in particular (Figure 16).

\[
\begin{align*}
\text{(R)-1-phenylethanol} & \quad \xrightarrow{\text{SOCl}_2} \quad \text{(R)-}\alpha\text{-phenyl-ethanol chloride} \\
\text{Cl} + \text{SO}_2 + \text{HCl} &
\end{align*}
\]

Figure 16: Reaction of an benzylic alcohol with $\text{SOCl}_2$: $S_{Ni}$ reaction

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**S_Ni Mechanism: Retention of Configuration**

- This reaction has been shown to follow a *second order* rate equation, \( \text{rate} = \frac{k[\text{ROH}][\text{SOCl}_2]}{} \), but the reaction does not proceed by the simple S_N2 mode for this would lead to *inversion of configuration* in the product, which is not observed here.

- Carrying out the reaction under milder conditions allows of the isolation of an alkyl chlorosulphite, ROCl (B; Figure 17), and this can be shown to be a true intermediate. The chlorosulphite (B) is formed with *retention of configuration*. This is because the R-O bond is not being broken during the course of the reaction.

- The rate at which the alkyl chlorosulphite intermediate (B) breaks down to the product, RCl (E), is found to increase with increasing polarity of the solvent, and also with increasing stability of the resultant carbocation R⁺.
S\textsubscript{N}i Mechanism: Retention of Configuration

- The latter fact indicates the involvement of an ion pair, R\textsuperscript{+}·OSOCl \textsubscript{(C)} in the reaction. In the S\textsubscript{N}i mechanism part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process.

- **Mechanism of S\textsubscript{N}i reaction:** The first step in the mechanism of S\textsubscript{N}i reaction is the same as the very fast step of the S\textsubscript{N}1 mechanism - dissociation into an intimate ion pair. But in the second step part of the leaving group attacks, necessarily from the front side since it is unable to get to the rear side. This results in retention of configuration of the product.

- Alkyl chlorosulphite, ROSOCl \textsubscript{(B)}, formed (ROH + SOCl\textsubscript{2}→ ROSOCl + HCl) in the first step ionizes slowly to give an ion pair (C) which collapse into an intimate ion pair (D) within a solvent cage. This then recombines to give product, RCl.

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**S_Ni Mechanism: Retention of Configuration**

- During formation of product, attack by Cl\(^{-}\) is likely to occur on the same side of R\(^{+}\) from which \(\text{-OSOCl}\) departed, to give the corresponding alkyl chloride with *retention of configuration*. Figure 17 illustrates the mechanism of the reaction.

![Figure 17: Mechanism of \(S_{Ni}\) reaction](image)

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Evidence for the $S_{Ni}$ Mechanism

- It is to be noted that if the SOCl$_2$ reaction on ROH [here, \((R)-\alpha-\)phenylethanol; A; Figure 18] is carried out in the presence of pyridine, the product RCl is found now to have undergone inversion of configuration [C; \((S)-\alpha-\)phenylethyl chloride].

- This occurs because the HCl produced during the formation of ROSOCl (A) from ROH and SOCl$_2$ is converted by pyridine into C$_5$H$_5$NH$^+Cl^-$ and Cl$^-$, being an effective nucleophile, attacks (A) ‘from the back’ in a normal $S_{N2}$ reaction to give the corresponding halide (C) with inversion of configuration (Route I).

- In an alternative pathway (Route II), pyridine reacts with ROSOCl (A) to give ROSON$^+C_5H_5$ (D) before anything further can take place. The Cl$^-$ freed in this process now attacks from the rear in an $S_{N2}$ reaction to give product (C) with inversion of configuration.

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Evidence for the $S_{Ni}$ Mechanism

- The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.

Figure 18: Reaction of an alcohol with SOCl$_2$ in presence of pyridine: $S_{N2}$ reaction

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Solve the Problems

1. 4-Chlorobut-1-ene is less reactive than 1-chlorobut-2-ene towards alcoholic silver nitrate. Justify the statement.

2. Allyl chloride gives white precipitate with silver nitrate solution whereas vinyl chloride does not. Explain.

3. 1-Chlorobut-2-ene may yield a mixture of isomeric products with alcoholic potassium cyanide. Explain.

4. If the reaction of an alcohol with thionyl chloride and pyridine follows an $S_N2$ mechanism, what is the stereochemistry of the alkyl chloride formed from (S)-2-butanol? Explain with plausible mechanism.

5. Draw the product formed when (R)-2-pentanol is treated each of the following reagent and justify their formation:
   (a) $\text{SOCl}_2$, pyridine;  (b) $\text{H}_2\text{SO}_4$;  (c) $\text{PBr}_3$, then NaCN  
   (d) $\text{TsCl}$, Pyridine;  (d) HBr;  (f) $\text{POCl}_3$, pyridine