Course Code: BSC202
Course Name: Chemistry-I (Concepts in chemistry for engineering)

(Organic reactions and synthesis of a drug molecule)

(Lecture-Part 2)

For
B.Tech. CSE
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By

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Nucleophilic Substitution Reaction

- ➢Incoming **nucleophile** (meaning nucleus loving; the nucleo- part of the name comes from nucleus, the positive center of an atom) replaces the existing group (leaving group).
- ➢ A nucleophile is a Lewis base that seeks a positive center replaces the existing group.

$$\mathrm{Nu}{:}^{-} \quad + \quad \mathrm{R{-}LG} \longrightarrow \mathrm{R{-}Nu} \quad + \quad {:}\mathrm{LG}^{-}$$

$\mathrm{Nu}{:}^{-}$	$\mathrm{R{-}LG}$	$\mathrm{R{-}Nu}$	${:}\mathrm{LG}^{-}$
The nucleophile donates an electron pair to the substrate.	The bond between the carbon and the leaving group breaks, giving both electrons from the bond to the leaving group.	The nucleophile uses its electron pair to form a new covalent bond with the substrate carbon.	The leaving group gains the pair of electrons that originally bonded it in the substrate.

- ➢ In this type of reaction a **nucleophile (Nu:) replaces a leaving group (LG) in the molecule** that undergoes substitution (called the **substrate).**

- ➢**The nucleophile is always a Lewis base**, and it may be negatively charged or neutral.

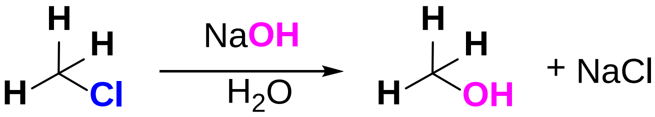
- ➢ The **leaving group** is always a species that takes a pair of electrons with it when it departs.

Nucelophilic Substitution Reactions at saturated Carbon atoms

- *Generally Nucelophilic Substitution reaction could be classified in two types depending on their kinetics (rate)of reaction.*

(a) S_N2 reaction: **Substitution, Nucleophilic, Bimolecular** (Overall order of reaction = 2)

For example, the reaction that takes place between chloromethane and hydroxide ion in aqueous solution is an example of **S_N2 reaction (Scheme 1).**



(CH_3Cl) (CH_3OH)

Scheme 1: Example of Substitution Reaction

- Experimentally it was observed that the rate depends on the concentration of both the reacting species i.e. chloromethane and on the concentration of hydroxide ion.

$$\text{Rate} \propto [CH_3Cl][OH^-]$$

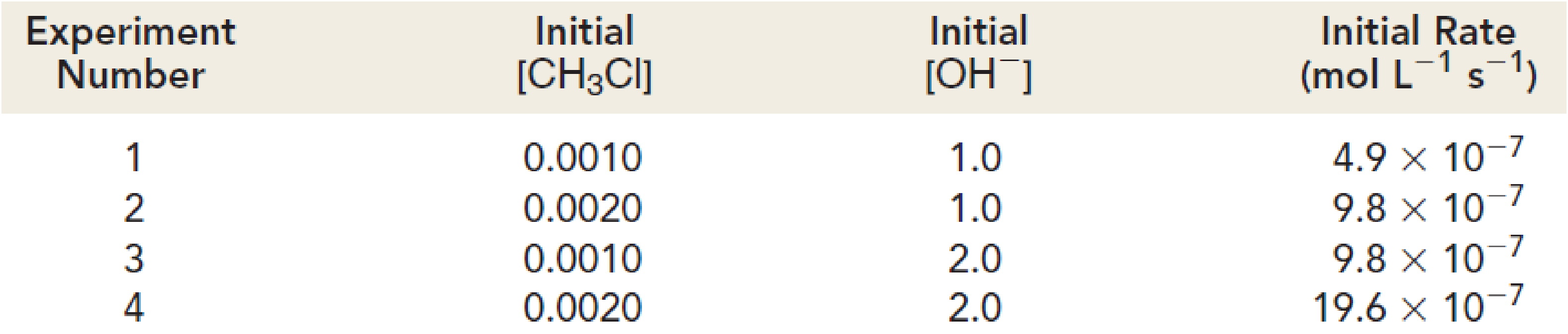
$$\text{Rate} = k[CH_3Cl][OH^-]$$

k is known as rate constant

Experimental Evidence To Support The Reaction Mechanism

- *Kinetic studies were performed and order of reaction was determined by studying the effect of variation in the concentration of both the species on the rate constant of the reaction. The data has been shown below:*

Table 1: Rate Study of Reaction of ***CH_3Cl with OH^- at 60°C***



Experiment Number	Initial $[CH_3Cl]$	Initial $[OH^-]$	Initial Rate (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}

- The experiments show that the rate depends on the concentration of chloromethane *and on the concentration of hydroxide ion. When the concentration* of chloromethane in experiment 2 was *doubled* , the rate *doubled. When we doubled the concentration* of hydroxide ion in experiment 3, the rate *doubled. When we doubled both* concentrations in experiment 4, the rate increased by a factor of *four.*

- *Therefore rate could be represented as* **Rate = $k[CH_3Cl][OH^-]$.**

Continued…..

Mechanism for the S_N2 Reaction

- *Based on this experiment and the rate law, this reaction is said to be **second order overall.** Since both the species are involved in the step whose rate is being measured therefore this types of reaction is also considered as **biomolecular**. And that is why we call this type of reaction **S_N2 reaction, meaning substitution, nucleophilic, bimolecular.***

$$\textbf{Rate} = k[CH_3Cl][OH^-].$$

- *The orbital that contains the electron pair of the nucleophile (its highest occupied molecular orbital, or HOMO) begins to overlap with an empty orbital (the lowest unoccupied molecular orbital, or LUMO) of the carbon atom bearing the leaving group (Figure 2).*

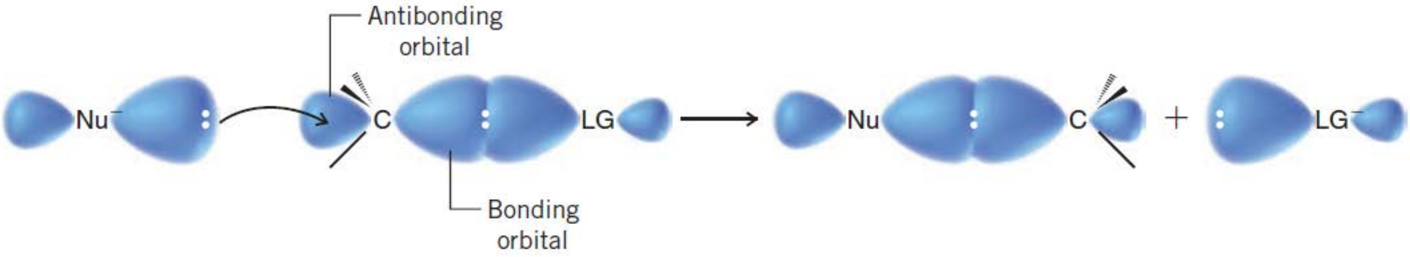


Figure 2: Schematic representation of orbitals involved in an S_N2 reaction

- *As the reaction progresses, the bond between the nucleophile and the carbon atom strengthens, and the bond between the carbon atom and the leaving group weakens.*

Continued….

Mechanism for the S_N2 Reaction

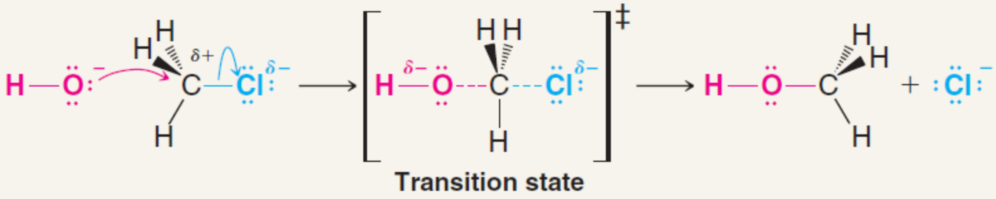
- *According to this mechanism: The nucleophile approaches the carbon bearing the leaving group from the **back side, that is, from the side directly opposite the leaving group.***

- *As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes **inversion—its tetrahedral bonding configuration is turned inside out**.*

REACTION

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

MECHANISM



The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that 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 atom begins to invert.

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

Figure 3: Reaction Mechanism for the nucleophilic substitution reaction between chloromethane and hydroxide ion.

Continued….

Overall Features of the S_N2 Reaction

- *The S_N2 reaction proceeds in a single step (**without any intermediates**) through an unstable arrangement of atoms called the **transition state.***

- *The S_N2 reaction is said to be a **concerted** reaction, because bond forming and bond breaking occur in concert (simultaneously) through a single transition state.*

Stereochemistry of S_N2 Reactions

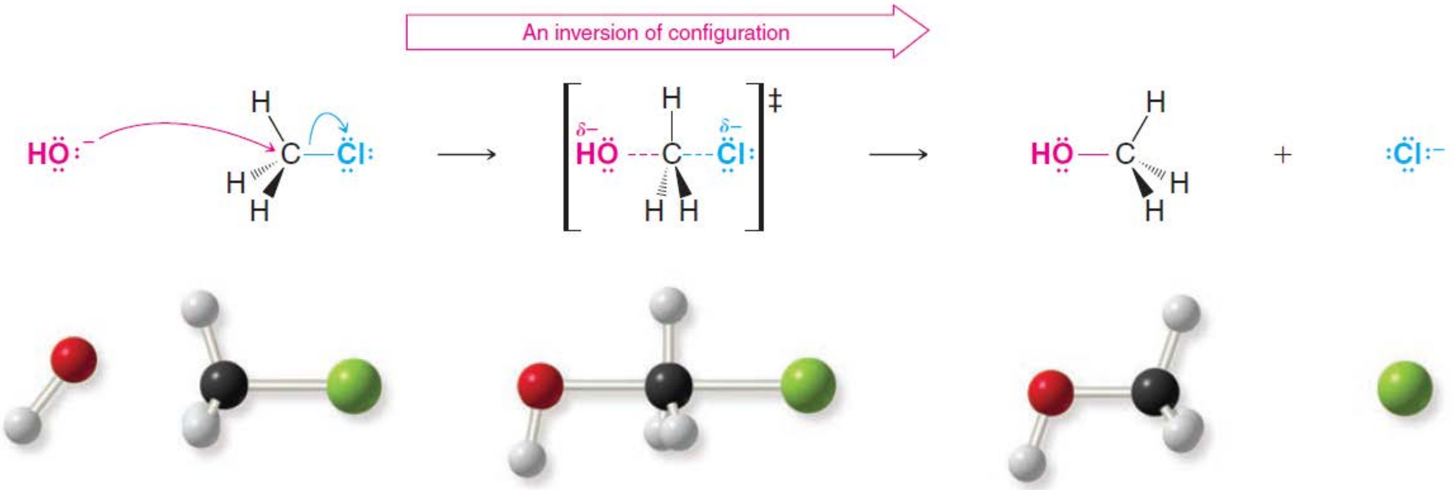


***Figure 4**: Inversion during S_N2 Reactions*

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Stereochemistry of S_N2 Reactions

- *The nucleophile approaches the substrate carbon from the back side with respect to the leaving group.*

- *In other words, **the bond to the nucleophile that is forming is opposite (at 180°) to the bond to the leaving group that is breaking**.*

- *Nucleophilic displacement of the leaving group in an S_N2 reaction causes **inversion** of configuration at the substrate carbon.*

- *For example, when **cis-1-chloro-3-methylcyclopentane reacts with hydroxide ion in an S_N2 reaction, the product** is **trans-3-methylcyclopentanol**. The hydroxide ion ends up being bonded on the opposite side of the ring from the chlorine it replaces.*

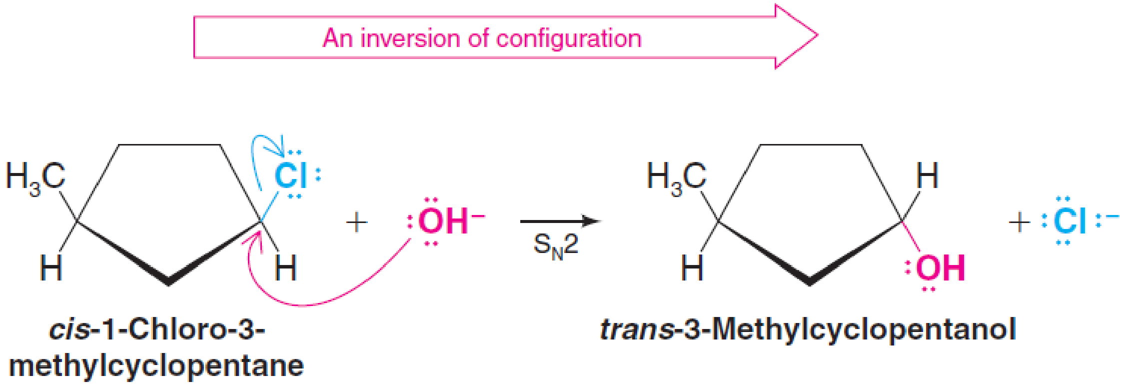
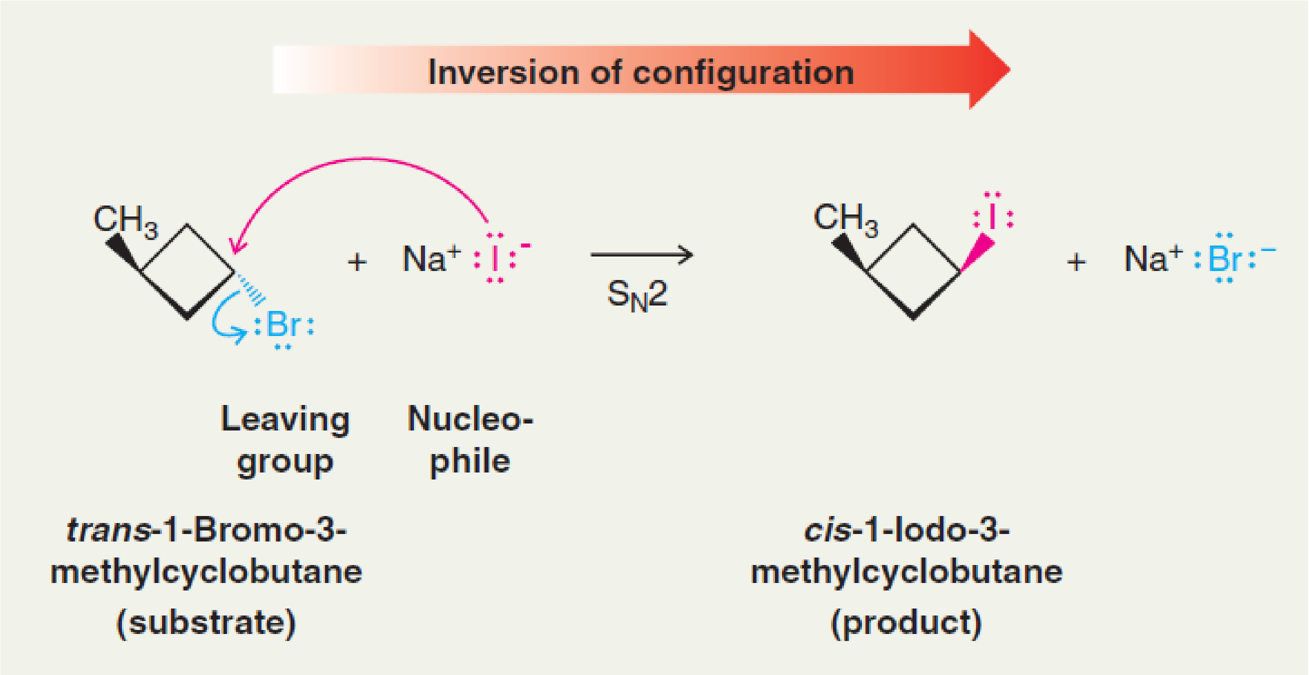


Figure 5: Reaction between cis-1-chloro-3-methylcyclopentane reacts with hydroxide ion

Examples of S_N2 Reactions

Question 1: Give the structure of the product that would be formed when *trans-1-bromo-3-methylcyclobutane undergoes an* S_N2 reaction with NaI.

Answer: As reaction mechanism has already been specified which is S_N2 so one thing is very clear that we will end up with *cis* isomer sincer the starting material is *trans*.



Problems based on S_N2 Reactions

Question 2*: Using chair conformational structures, show the nucleophilic substitution reaction that would take place when* ***trans-1-bromo-4-tert-butylcyclohexane (Figure 7)*** *reacts with iodide ion. (Show the most stable conformation of the reactant and the product.)*

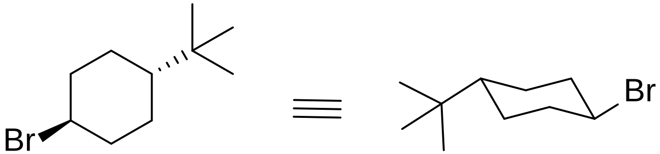


Figure 7: Structure of trans-1-bromo-4-tert-butylcyclohexane

Question 3*: When optically pure (+)-2-chlorobutane is allowed to react with potassium iodide in acetone in an S_N2 reaction, the 2-iodobutane that is produced has a minus rotation. What is the configuration of (-)-2-iodobutane? Of (+)-2-iodobutane?*

References

- *Information regarding the source of this study material:*

Chapter No. 06; Book: Organic Chemistry, Publisher: John Wiley & Sons, Inc.; 10th edition; Authors: T. W. G. Solomons and C. B. Fryhle.

- ***Rest of the topics of this unit will be discussed in next part of the lecture.***

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