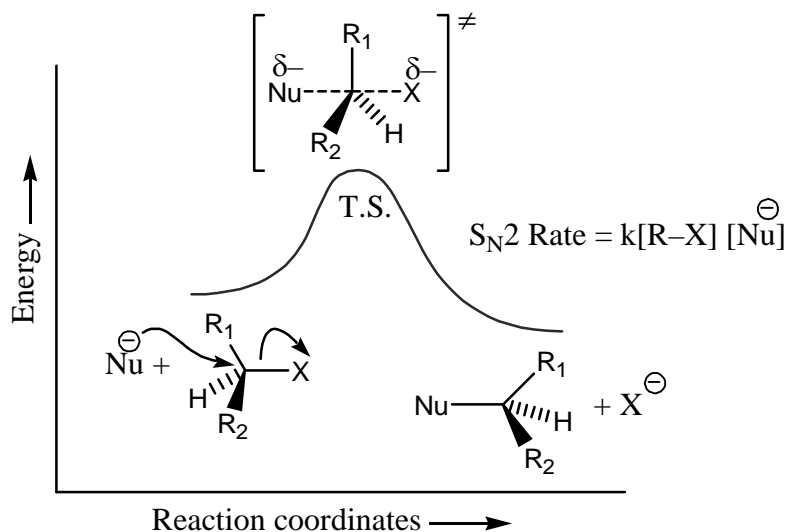


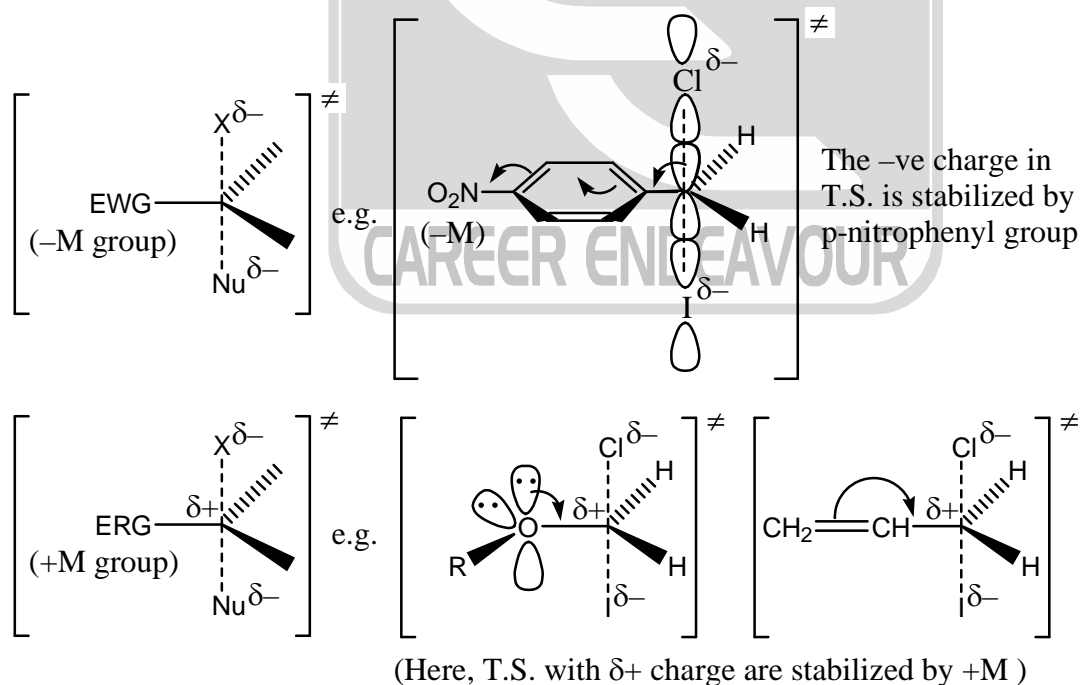
5.2 Nucleophilic substitution

Types of Nucleophilic Substitution reactions:

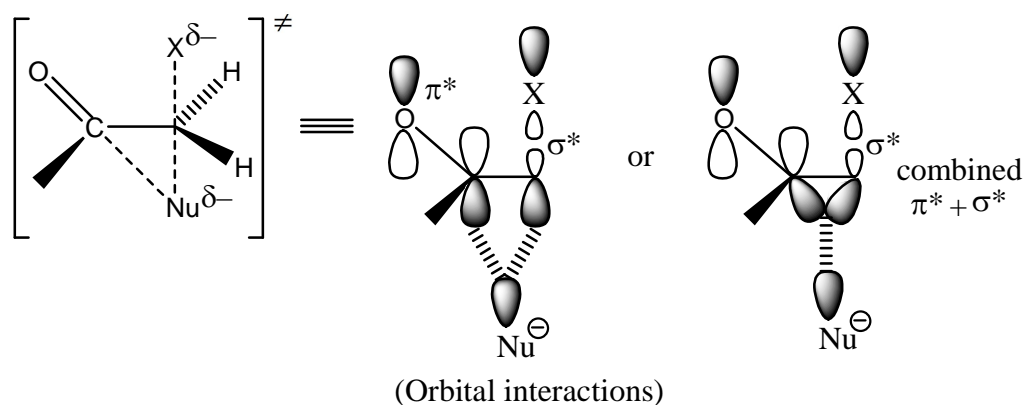
(i) The S_N2 Mechanism: Potential energy diagram for S_N2 reaction



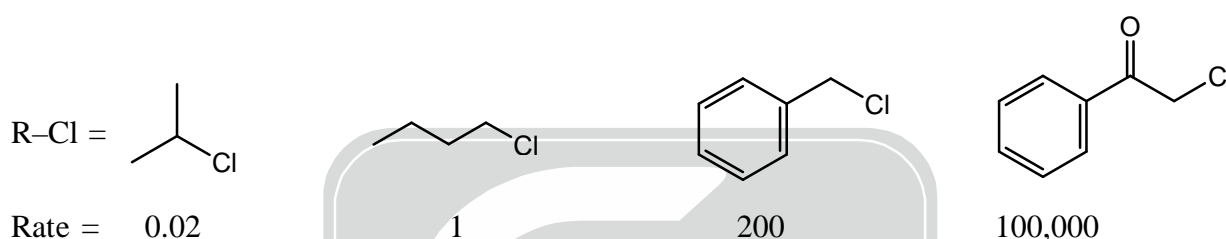
- S_N2 reaction mechanism involves the **back-side** approach of the Nu^- filled orbital to the σ^* antibonding orbital of the C-X bond.
- Lesser the crowding around the reactive centre, faster or better the S_N2 reaction.
So, reactivity for different R-X shows order $3^\circ < 2^\circ < 1^\circ < CH_3-X$
- Stable the transition state, faster the reaction (Both +M and -M groups can increase the S_N2 rate).
Possible T.S. are



- In α -halocarbonyl compounds, the C=O moiety assists nucleophilic approach/attack at the reaction centre via π^* antibonding interaction and makes these substrate the most reactive in S_N2 reactions.



Relative S_N2 rates of different R-Cl with KI in acetone:

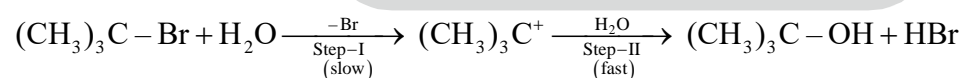


- S_N2 reactions are more favoured in Aprotic solvents (acetone, DMF, DMSO, acetonitrile etc.) because non-solvated free nucleophile shows better and faster reaction/attack. In protic solvent e.g. alcohol/water the nucleophilicity of nucleophile decreases due to solvation or H-bonding.
- Better the leaving group, faster the S_N reactions (Both S_N2 and S_N1). Leaving tendency order is:

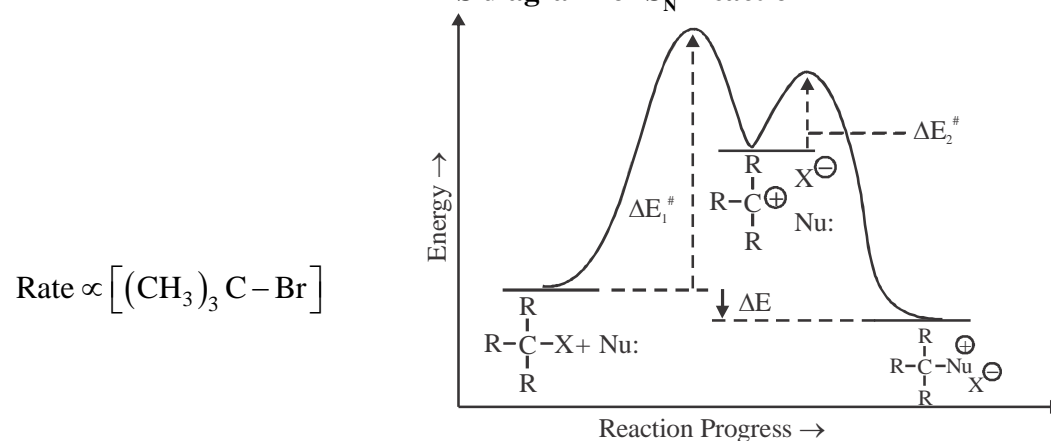
$$\ominus \text{NH}_2 < \ominus \text{OH} < \text{AcO}^\ominus \leq \text{F}^\ominus < \text{Cl}^\ominus < \text{CF}_3\text{COO}^\ominus < \text{Br}^\ominus < \text{I}^\ominus < \text{OMs}^\ominus < \text{OTs}^\ominus < \text{ONs}^\ominus < \text{OTf}^\ominus$$
- Stronger the nucleophile, faster the S_N2 reaction
- S_N2 reaction at chiral centre gives mostly inversion product due to Back-side attack of nucleophile.

(ii) The S_N1 Mechanism:

It not only shows first order kinetics, but the chiral 3° -alkyl bromide reactant undergoes substitution by the modest nucleophile water with extensive racemization.



PES diagram for S_N1 reaction

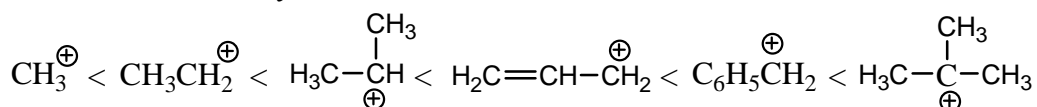


The first order kinetics of these reactions suggest a two-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide. In this mechanism, a carbocation is formed as a high-energy intermediate, and this form bonds immediately to nearby nucleophiles.

Various features for S_N1 :

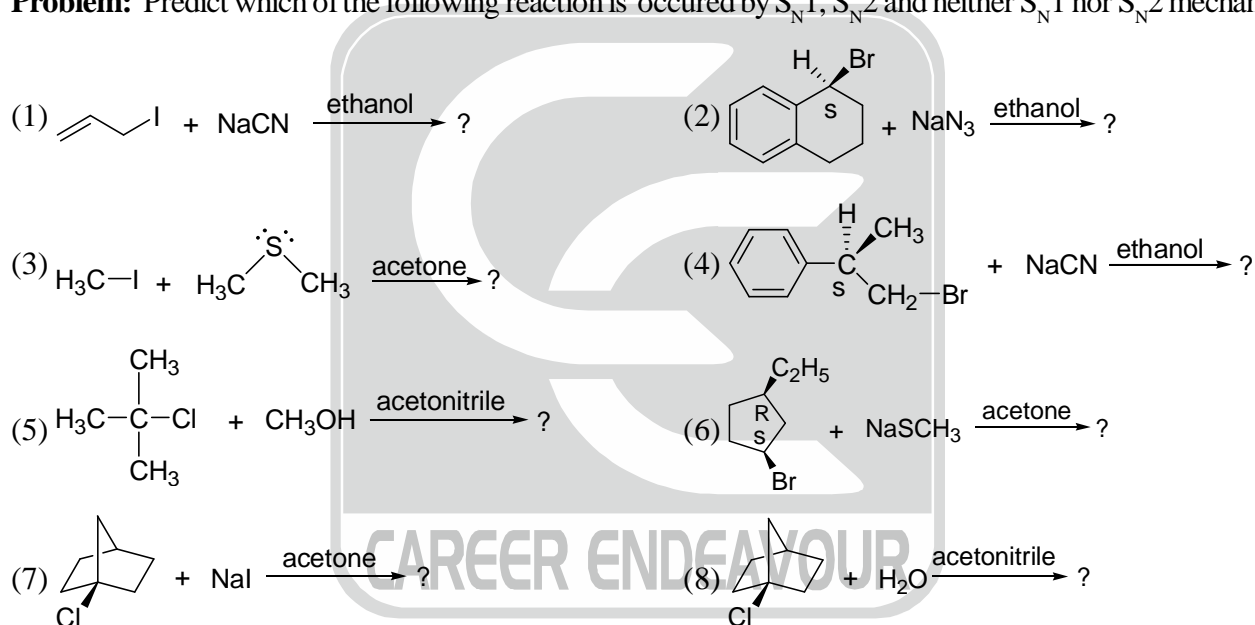
- (i) The reactant having the tendency to form stable carbon cation, we expect the S_N1 mechanism.
- (ii) Since nucleophiles only participate in the fast second step, recombination of the halide anion with the carbocation intermediate simply reforms the starting compound.
- (iii) The Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate.

Carbocation Stability:



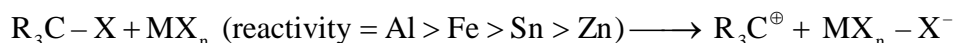
- (iv) The stereospecificity of these reactions may vary. The positively-charged carbon atom of a carbocation has a trigonal (flat) configuration (it prefers to be sp^2 hybridized), and can bond to a nucleophile equally well from either face.

Problem: Predict which of the following reaction is occurred by S_N1 , S_N2 and neither S_N1 nor S_N2 mechanism.

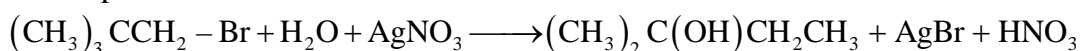


Activation by electrophilic cations:

Heterolytic cleavage of the carbon-halogen bond of alkyl halides may be facilitated by the presence of certain metal cations. In the extreme, carbocations may be generated as shown in the following equation, where R is alkyl or hydrogen, and M = Al (n=3) or Fe (n=3) or Sn (n=4) or Zn (n=2).

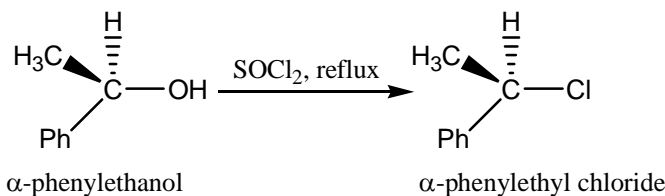


In aqueous or alcoholic solution it promotes ionization of the alkyl halide and the formation of S_N1 products. When silver nitrate is used with 1° or 2° -alkyl halides, rearrangement may occur before the product formation stage. For example:

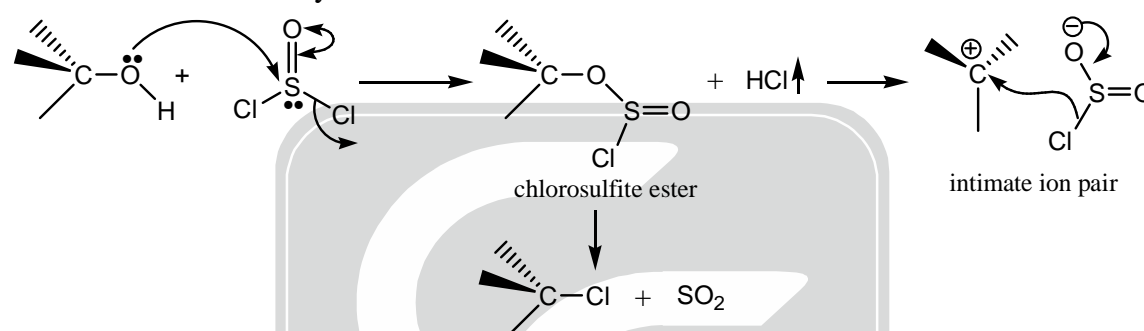


Thionyl Chloride Reaction on Alcohol: S_N1 Mechanism: Retention in Configuration

In the previous discussion regarding the stereochemical outcome of nucleophilic substitution reactions we have seen that these reactions may proceed with either inversion of configuration, to racemization, or to a mixture of both. However, few cases are known where substitution proceeds with complete retention of configuration. For example, the chlorination of alcohols with thionyl chloride is very important from stereochemical point of view. When a chiral alcohol is treated with thionyl chloride only, we get the product with retention of configuration.

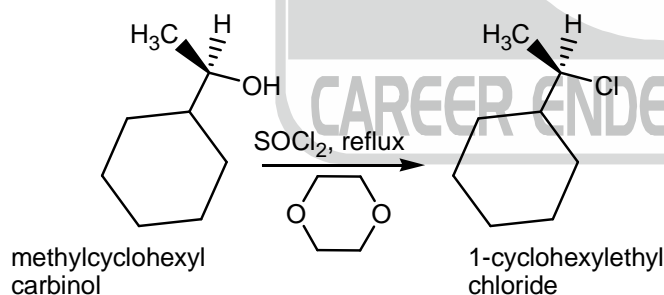


The reaction has been shown to follow a second order rate equation, rate = $k[\text{ROH}][\text{SOCl}_2]$. The reaction is believed to proceed via the S_Ni (Substitution Nucleophilic internal) pathway as shown below via the intermediate formation of alkyl chlorosulfite:

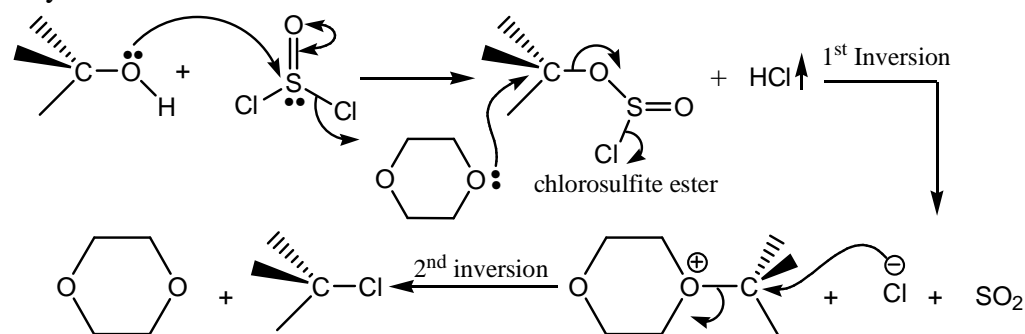


Here alkyl chlorosulfite breaks down to the product directly through a nucleophilic attack of chloride ion on the same side of alkyl group from where the leaving group departs. An alternative description involves the formation of an ion pair from the alkyl chlorosulfite, which then collapses to product through a nucleophilic attack of chloride ion from the same side as before.

Similar retention of configuration is also observed when the reaction is carried out in dioxane solvent.



The reaction is believed to proceed via a double inversion via participation of the solvent in the following ways:



However, when the reaction is carried out in presence of pyridine, we get the product with inversion of configuration; for example: