

Subject	Chemistry
Paper No and Title	5; Organic Chemistry-II
Module No and Title	16; Neighbouring group participation in SN reactions and Anchimeric assistance
Module Tag	CHE_P5_M16

Principal Investigator		Co- Principal Investigator and Technical Coordinator
Prof A.K.Bakhshi Sir Shankar Lal Professor, Department of Chemistry University of Delhi		Dr Vimal Rarh Deputy Director, Centre for e- Learning and Assistant Professor, Department of Chemistry, SGTB Khalsa College, University of Delhi <i>Specialised in : e-Learning and Educational Technologies</i>
Paper Coordinator	Content Writer	Reviewer
Prof. Diwan S. Rawat Department of Chemistry, University of Delhi	Prof. Diwan S. Rawat Department of Chemistry, University of Delhi Dr. Mukesh C. Joshi Assistant Prof. Department of Chemistry, Motilal Nehru College, South campus, University of Delhi,	Prof. H.G.Krishnamurthy Emeritus Professor Department of Chemistry, University of Delhi
Anchor Institute : SGTB Khalsa College, University of Delhi		

CHEMISTRY
PAPER 5; Organic Chemistry-II
MODULE 16; Neighbouring group participation in SN reactions and Anchimeric assistance

TABLE OF CONTENTS

1. Learning Outcomes
2. Introduction
3. Mechanism of anchimeric assistance
4. Examples of reactions where anchimeric assistance is operative
 - 4.1 Reactions with oxygen as neighbouring group donor
 - 4.2 Reactions with sulphur as neighbouring group donor
 - 4.3 Reactions with nitrogen as neighbouring group donor
 - 4.4 Double bond donors and rearrangements
5. Summary

1. Learning Outcomes

After studying this module, you shall be able to

- Know what is anchimeric assistance
- Learn mechanism of anchimeric assistance
- Identify functional groups taking part in anchimeric assistance
- Evaluate outcomes of anchimeric assistance for various reactions
- Analyze how to know if anchimeric assistance is operational

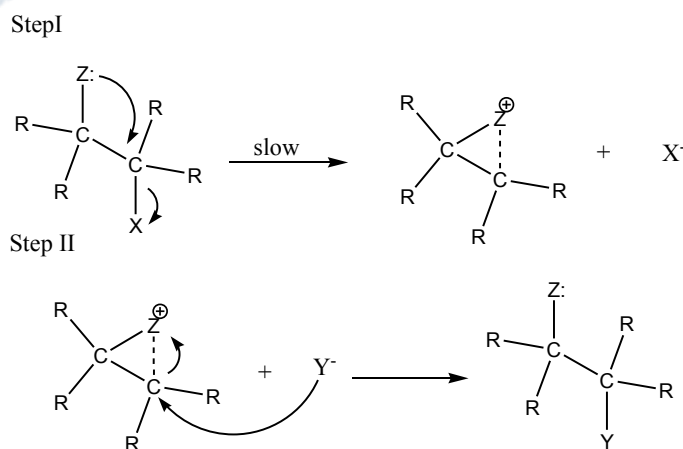
2. Introduction

When a catalytic functional group or atom is part of the reacting molecule, the catalysis is called intra-molecular catalysis. **Anchimeric assistance** (anchimeric in Greek means “adjacent parts”) is a case of intra-molecular catalysis where a suitably placed intra-molecular nucleophile assists in a substitution reaction by enhancing rate of reaction.

3. Mechanism of anchimeric assistance

The bimolecular mechanisms for nucleophilic substitution are termed S_N2 reactions. S_N2 reactions follow second order rate kinetics. The geometric alignment of transition state for S_N2 mechanism is such that the nucleophile attacks from the rear of the leaving group, leading to inversion of configuration.

However, there are some examples of retention of configuration in S_N2 reactions, where an atom or group (Z) close to the carbon undergoing substitution assist in the reaction with its available pair of electrons. Such a group is called a neighbouring group (NG) and the assistance provided is termed neighbouring group participation (NGP). If such participation leads to an enhanced reaction rate, the group is said to provide **anchimeric assistance**.



The mechanism for anchimeric assistance is a two step mechanism where two consecutive S_N2 reaction leads to retention of configuration. In the first step, the neighbouring group (Z) acts as a nucleophile, attacking the substitution centre and expelling out the leaving group. In the next step, the external nucleophile (Y) attack from backside displacing the neighbouring group and retaining the overall configuration. Since the first step is slow and is rate determining, the reaction follows first order kinetics and there is no effect of concentration of Y^- on rate of reaction.

Anchimeric assistance enhances rate of reactions by several order of magnitudes. This is because step I is the rate determining step and the neighbouring group Z which is readily available within the substrate makes the attack much faster as compared to attack by any external nucleophile Y for which, to react, the substrate has to collide with Y^- . Since, Z is readily available by virtue of its position its attack is much faster.

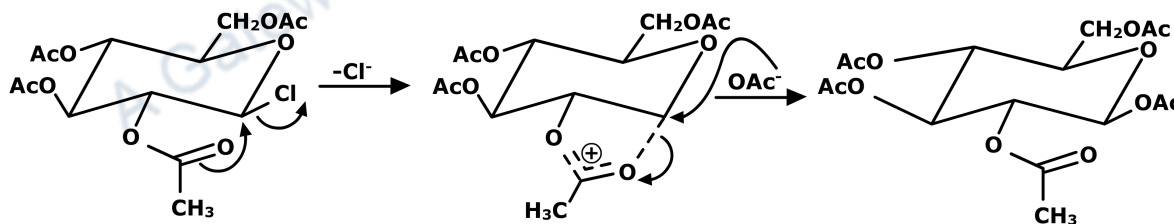
Thermodynamically also, anchimeric assistance is favoured as the reaction between the substrate and Y^- involves a large decrease in entropy of activation (ΔS^\ddagger), as the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of entropy.

Important atoms and groups that can act as neighbouring groups are COO^- , $COOR$, $COAr$, $OCOR$, OR , OH , O^- , NH_2 , NHR , NR_2 , $NHCOR$, SH , SR , S^- , SO_2Ph , I , Br , and Cl . The effectiveness of halogens as neighbouring groups decreases in the order $I > Br > Cl$. The chloride is a very weak neighbouring group and can be shown to act in this way only when the solvent does not interfere.

4. Examples of reaction where anchimeric assistance is operative

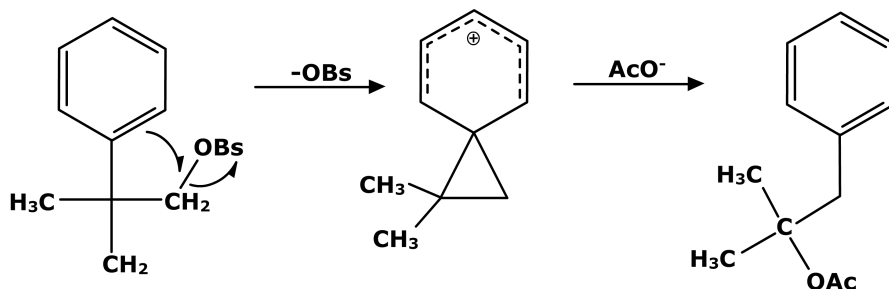
NGP takes place by internal attack of a nucleophile leading to formation of a ring. Upon attack of the external nucleophile the ring can have three different fates:

- (1) Ring opening at the same point where the ring closure took place,



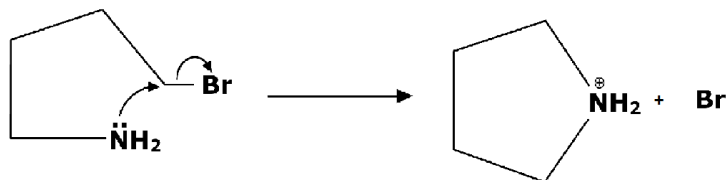
Such reactions lead to an un-rearranged product with the same configuration as the starting material

- (2) Ring opening at a different point from which the ring closure took place



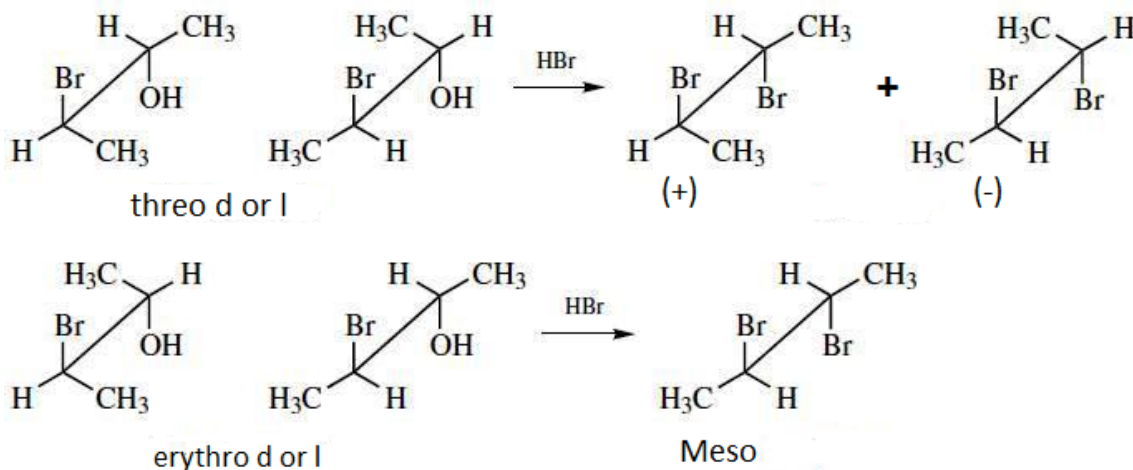
Such reactions lead to a rearranged product.

(3) No ring opening so the overall reaction is a Cyclization.

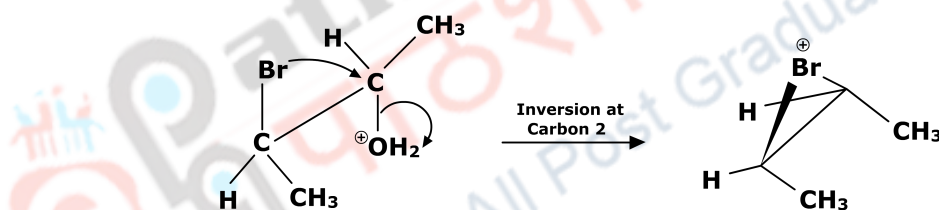


At times the cyclic intermediate may undergo ring opening at two points competitively so that some of the product is rearranged and some remains un-rearranged.

The initial existence of the phenomena of anchimeric assistance was observed for the reaction where, dl pair of 3-bromo-2-butanol when treated with HBr to give dl-2,3-dibromobutane, while the erythro pair gave the meso isomer.



Interestingly, either of the two threo isomers alone also gave dl pair. This is explained by the presence of a common bromonium ion intermediate formed as a result of attack by the neighbouring bromine atom.

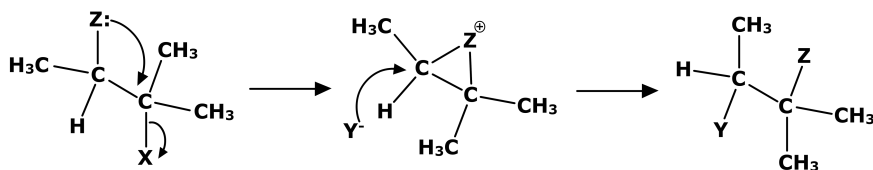


This symmetrical intermediate gives equal opportunity to the incoming nucleophile Br^- to attack both carbon atoms equally.

How do we know if anchimeric assistance is involved in a reaction mechanism? Experimentally to demonstrate the involvement of anchimeric assistance in a reaction, following methods are employed;

- Comparing the rate of the NGP reaction with the rate expected in the absence of participation. The reactions where participation takes place, these reactions go much faster.
- To compare the rate constant for the intra-molecular reaction with that of the analogous intermolecular one. This method is limited to those systems where corresponding analogous intermolecular reactions may occur. Here the rate of intra-molecular reactions is much faster as compared to inter-molecular reactions.
- Examination of stereochemistry of products formed. Unusual stereochemistry might be observed such as retention of configuration in $\text{S}_{\text{N}}2$ mechanism.

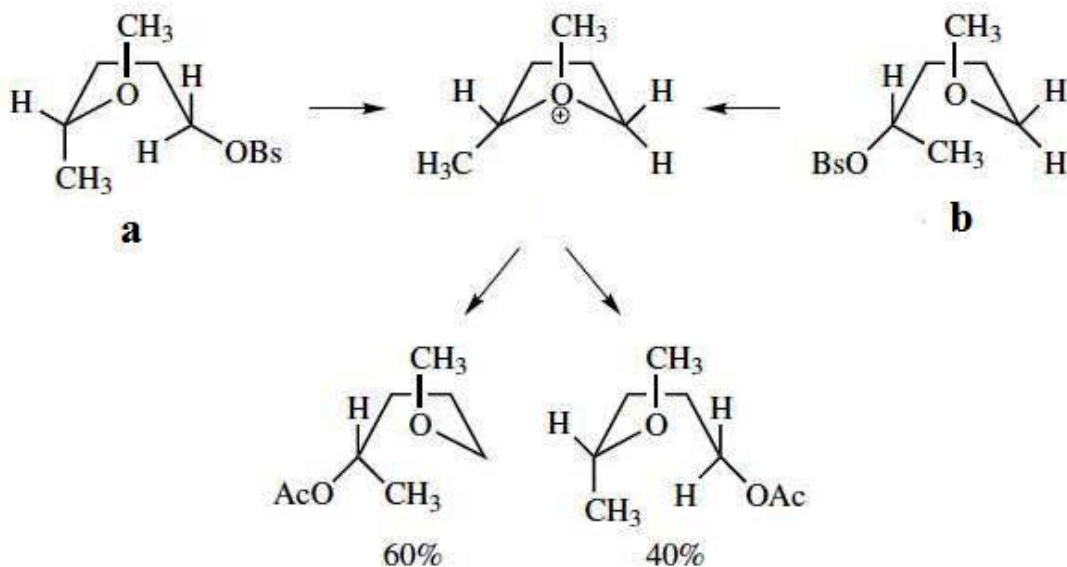
Here reactions with rearranged products due to anchimeric assistance through a cyclic intermediate have been observed. The cyclic intermediate gives the external nucleophile with equal potential to attack any of the carbon atoms, and based on polar and steric conditions the more stable product would predominate as follows;



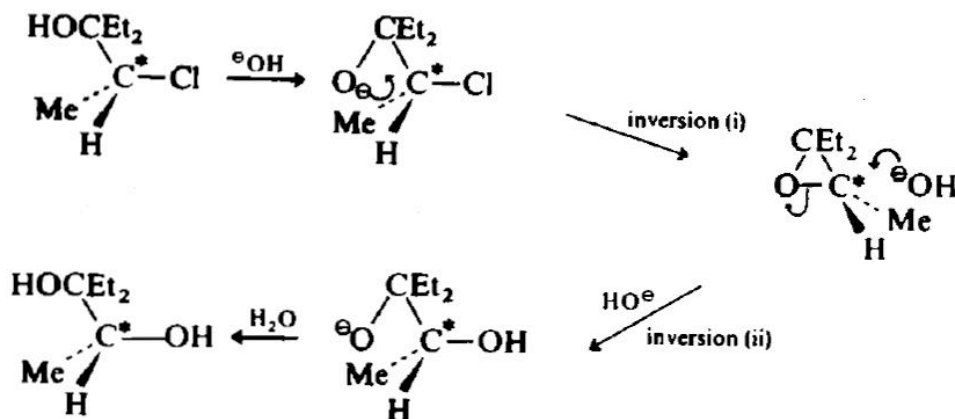
In such cases, substitution and rearrangement products are often formed together.

4.1 Reactions with oxygen as neighbouring group donor

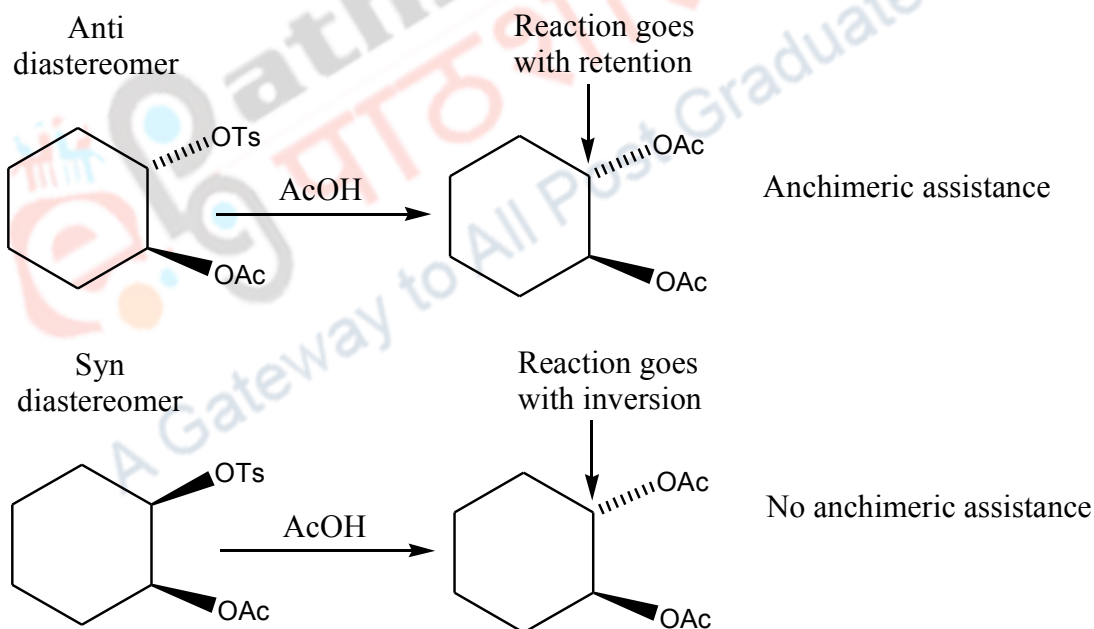
The acetolysis of two different substrates (a) 4-methoxy-1-pentyl brosylate and, (b) 5-methoxy-2-pentyl brosylate, with a common intermediate structure gave the same mixture of products which further confirmed participation by neighbouring group leading to a common intermediate.



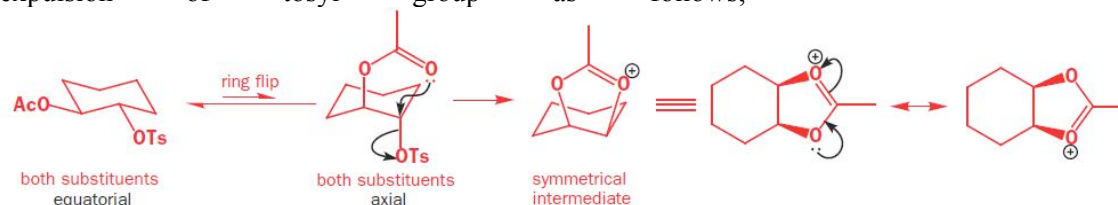
The hydrolysis of 1,2-dichlorohydrin under alkaline conditions was found to yield 1,2-diol with retention of configuration following S_N2 mechanism. Here formation of a cyclic intermediate takes place as a result of anchimeric assistance.



Another example of anchimeric assistance in cyclic system with oxygen donor is the following reaction where one starting material has syn and the other has anti stereochemistry, however the products have the same (anti) stereochemistry.



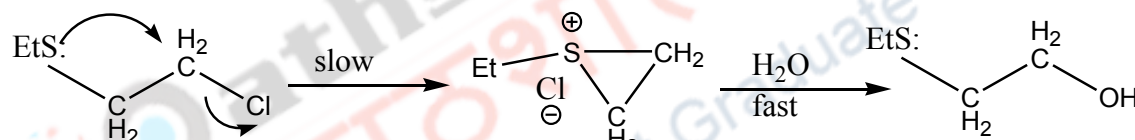
The mechanism involves participation of acetyl group in expulsion of tosyl group as follows;



Thus only when both the substituents are in axial position there is a greater chance of anchimeric assistance and faster kinetics is observed. For the syn diastereomer NGP is impossible, and substitution goes simply by intermolecular displacement of OTs by AcOH. Therefore just one S_N2 step leads to overall inversion of configuration, and a slower reaction rate.

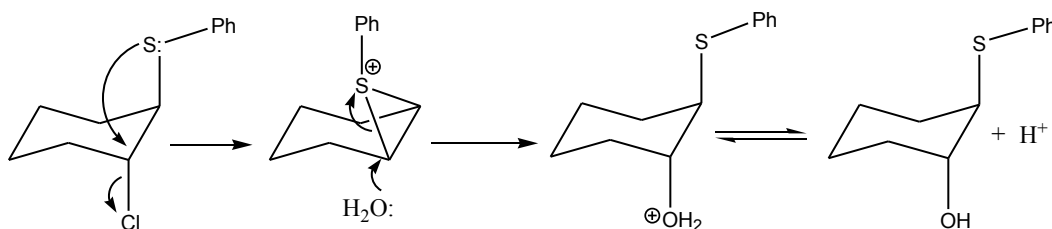
4.2 Reactions with sulphur as neighbouring group donor

The hydrolysis of $\text{EtSCH}_2\text{CH}_2\text{Cl}$ was found to be 10^4 times faster than $\text{EtOCH}_2\text{CH}_2\text{Cl}$ under comparable conditions owing to the sulfonium ion intermediate mediated anchimeric assistance as shown below;



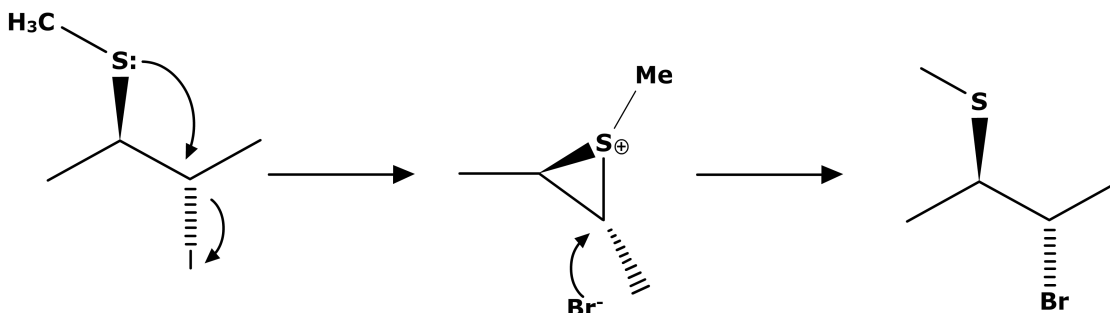
In comparison, for $\text{EtOCH}_2\text{CH}_2\text{Cl}$ substrate the electronegative oxygen atom provides no internal assistance and thus the reaction proceeds with simple S_N2 mechanism. For substrates of the type $\text{RSCH}_2\text{CH}_2\text{X}$ the NGP occurs so readily that ordinary S_N2 reactions are hard to observe.

Trans 2-thio-substituted chloro cyclohexane undergoes reaction with aqueous solution of ethanol 70000 times faster than the unsubstituted compound. However, the cis 2-thio-substituted compound reacts a little more slowly than the unsubstituted compound. These experimental observations have been ascribed to anchimeric assistance provided by sulphur atom present in correct stereochemistry to assist expulsion of the leaving group.



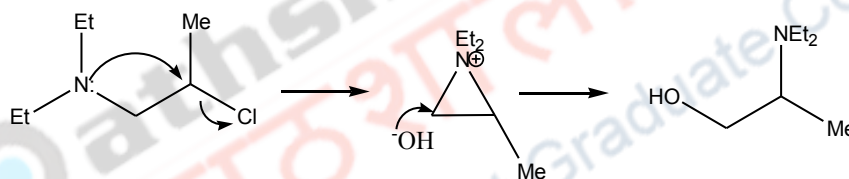
As shown above the thio substituent displaces the chloro group by attacking the back side of the carbon to which the chloro group is attached. Since back-side attack requires both substituents to be in axial positions thus only the trans isomer which has both of its substituents in axial positions reacts faster. Subsequent attack by water or ethanol on the sulfonium ion is further facilitated as

the positively charged sulphur is an excellent leaving group and breaking the three-member ring releases strain.



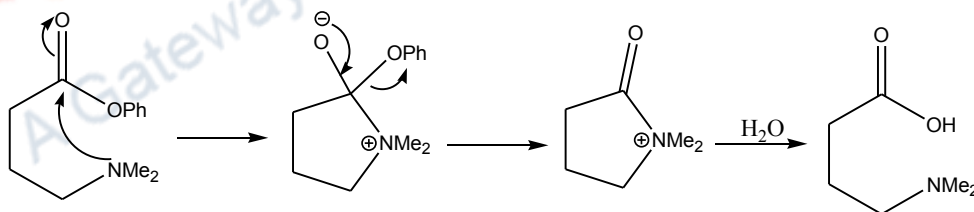
4.3 Reactions with nitrogen as neighbouring group donor

Amines as lone pair donor for anchimeric assistance

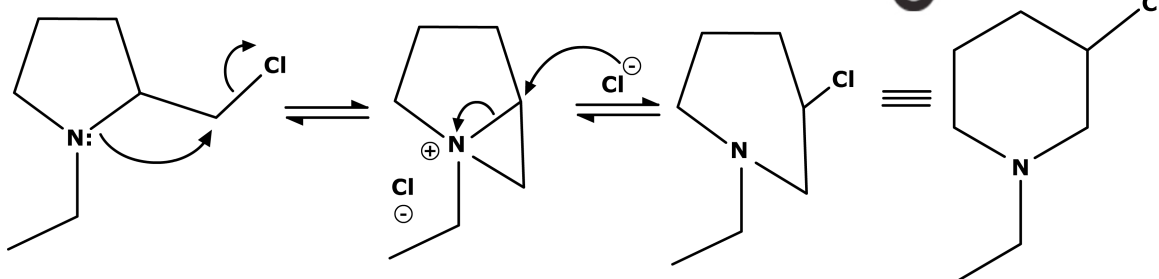


In the above reaction the substrate is a secondary alkyl chloride. Notice that the product alcohol is a rearranged product.

In the following, the -NMe_2 is providing anchimeric assistance for hydrolysis of ester.

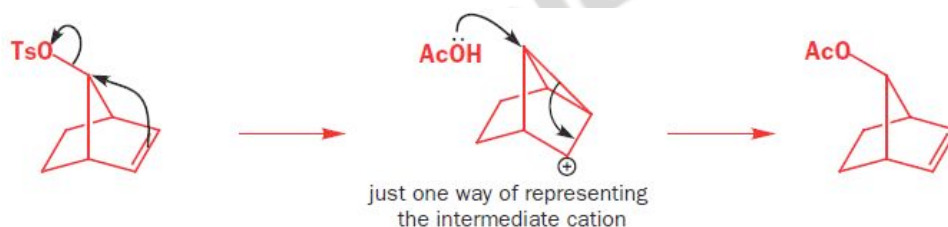


A ring expansion reaction involving anchimeric assistance is as follows;



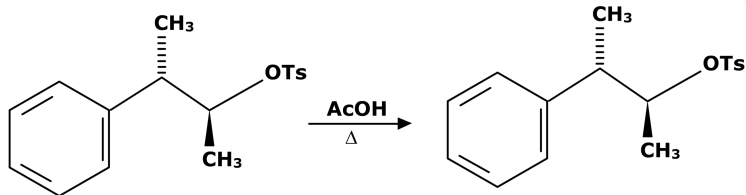
4.4 Double bond participation and rearrangements

Properly placed π -electrons of a C=C double bond in a substrate can also function as NG and lend anchimeric assistance

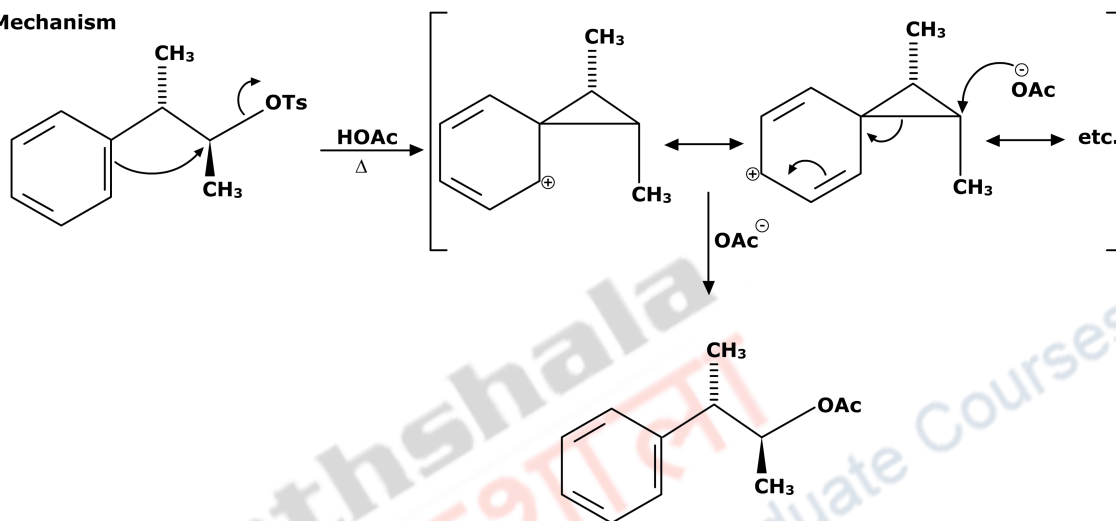


For the above reaction the product showed retention of stereochemistry and extremely fast reaction kinetics, i.e. 10^{11} times faster than that of the saturated substrate. The ability of a carbon-carbon double bond to serve as a neighbouring group depends strongly on its electron density. Therefore, when the electron-withdrawing CF_3 groups are present in the substrate, the solvolysis rate is lowered severely.

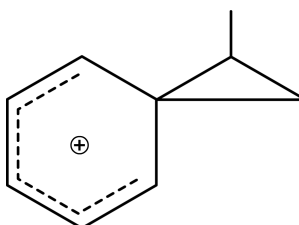
Aryl groups are a suitable NG in substitution reactions. One example has already been mentioned, another example is as follows.



Mechanism



There is retention of configuration in the product acetate. This clearly indicates the participation of phenyl group. The π electrons of the ring assist and stabilize the developing positive charge. The intermediates, for the sake of book keeping, can be shown as the delocalized phenonium ion.



Phenonium ion

5. Summary

- Anchimeric assistance is a case of intra molecular catalysis where NGP leads to enhancement of rate of reaction.
- Anchimeric assistance involves two steps where first step is rate determining leading to overall first order kinetics
- For reactions that may go by S_N2 mechanism, if anchimeric assistance is involved, the reactions proceed with retention of configuration.
- Various functional groups may participate in NGP including COO^- , $COOR$, $COAr$, $OCOR$, OR , OH , O^- , NH_2 , NHR , NR_2 , $NHCOR$, SH , SR , S^- , SO_2Ph , I , Br , and Cl .
- Neighbouring groups with electron releasing property are more efficient.
- In NGP the intermediate has a cyclic structure which may lead to normal, rearranged or cyclic product.
- For NGP to occur proper orientation of functional groups is a necessary requirement.
- Double bond and phenyl ring can also function as NGs in S_N reactions.