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Subject	Chemistry
Paper No and Title	**05, ORGANIC CHEMISTRY-II (REACTION MECHANISM-I)**
Module No and Title	**15, The Neighbouring Mechanism, Neighbouring Group Participation by π and σ Bonds**
Module Tag	**CHE_P5_M15**

TABLE OF CONTENTS

1. Learning Outcomes

After studying this module, you shall be able to

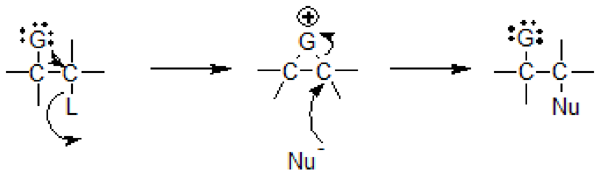
- Know about NGP reaction
- Learn reaction mechanism of NGP reaction
- Identify stereochemistry of NGP reaction
- Evaluate the factors affecting the NGP reaction
- Analyse Phenonium ion, NGP by alkene, and NGP by heteroatom.

2. Introduction

The reaction centre (carbenium centre) has direct interaction with a lone pair of electrons of an atom or with the electrons of s- or p-bond present within the parent molecule but these are not in conjugation with the reaction centre. A distinction is sometimes made between n, s and p-participation. An increase in rate due to Neighbouring Group Participation (NGP) is known as "anchimeric assistance". "Synartetic acceleration" happens to be the special case of anchimeric assistance and applies to participation by electrons binding a substituent to a carbon atom in a β-position relative to the leaving group attached to the α-carbon atom. In accordance with the underlying model, these electrons then provide for a three-centre bond (or bridge)", "fastening together" (as the word "synartetic" is means to suggest) the α and β-carbon atoms between whichthe charge is divided in the intermediate bridge ion form (and in the transition state preceding its formation).

3. NGP Participation

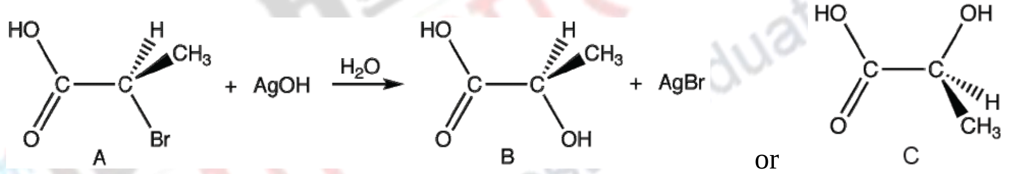
NGP is often seen in nucleophilic substitution reactions, wherein a neighbouring group aids in the removal of the leaving group to form a reactive intermediate that leads to product formation. The increase of reaction rate and unexpected stereo chemical outcomes are associated in reactions involving NGP. An atom having an unshared pair of electrons and is present on the β – positon to the leaving group can act as a neighbouring group. Also, NGP is most often observed in solvolysis reactions where the solvent acts as the nucleophile. For example:



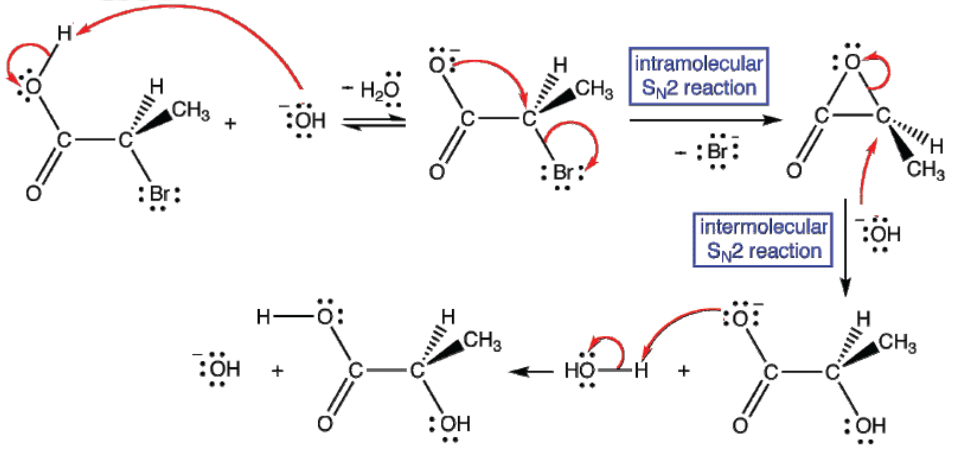
During NGP, the neighbouring group (G) attacks the electrophilic centre to eliminate the leaving group (L). A cyclic intermediate, is thus formed, which is very reactive. The nucleophile (Nu^-)

then attacks this intermediate to form the product. If the attack takes place on the carbon that was having the leaving group then the configuration will be retained because the configuration on that carbon will be inverted twice. The examples of groups, like, halides, hydroxides, ethers, thio ethers, amino groups, carboxylates, phenyl group, π-bonds etc., have been identified to act as neighbouring groups in many reactions.

Thus, according to the IUPAC, interaction of a reaction centre with a lone pair of electrons in an atom or electrons present in σ-bond or π-bond in organic chemistry is known as NGP. When NGP operates, increase in the reaction of rate is normal. It is also possible for neighbouring groups to influence many reactions in organic chemistry. For nucleophilic substitution reactions, NGP can be defined as the introduction of a new reaction intermediate by a substituent that bonds to the reaction centre. For such substitutions, NGP occurs primarily occurs in the form of intra-molecular nucleophilic attack, followed by inter-molecular substitution. Some nucleophilic aliphatic substitution reactions that are in totality intermolecular in nature observably begin with a nucleophilic atom in the substrate which reacts intra-molecularly with the carbon atom which bears the leaving group and finally expelling the leaving group. The resultant intermediate latter reacts with the external nucleophile giving the observed substitution product, which happens to be an intermolecular nucleophilic substitution. **For example:**



The role of the nucleophilic atom present in the substrate in the overall reaction is known as neighbouring group participation or anchimeric assistance. The net reaction is thus a nucleophilic substitution in which **A** is the substrate and **B,** the substitution product. If the reaction was to take place via S_N1 mechanism, it would yield **B**, as substitution product and resulting in retention of configuration at the chiral centre, and its enantiomer (**C**), resulting in inversion of configuration.

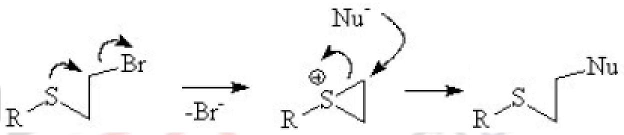


If the reaction was to take place via S_N2 mechanism, it would happen with inversion of configuration at the chiral centre, yielding **C** as the only substitution product. The formation of **B** as the only substitution product proves to great extent in favour of the fact that the reaction is not a simple intermolecular nucleophilic aliphatic substitution that follows either S_N1 or S_N2 path. Neighbouring group participation is invoked to explain the course of the reaction. There are some conditions for NGP reactions when it in operation:

1. It is normal for the reaction of rate to be increased.
2. There is a strong possibility for the stereochemistry of the reaction to be abnormal (or unexpected) as compared with a normal reaction.

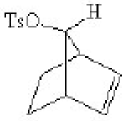
3.1 NGP by Heteroatom Lone Pairs

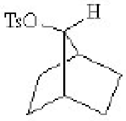
A fine example of NGP is when reaction of a sulphur or nitrogen mustard occurs with a nucleophile, the rate of reaction happens to be much higher for the sulphur mustard and a nucleophile than it would be for a primary alkyl chloride not having a heteroatom.



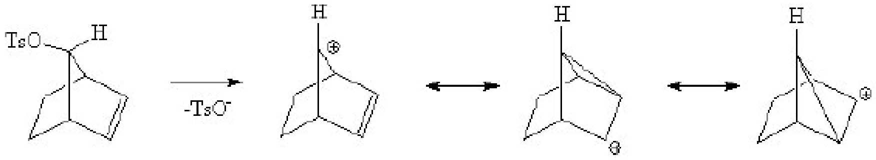
3.2 NGP by Alkene

The π orbitals of an alkene are able to stabilize a transition state by helping to delocalize the positive charge of the carbocation. For instance the unsaturated tosylate will react more quickly (1011 times faster for aqueous solvolysis) with a nucleophile than the saturated tosylate.

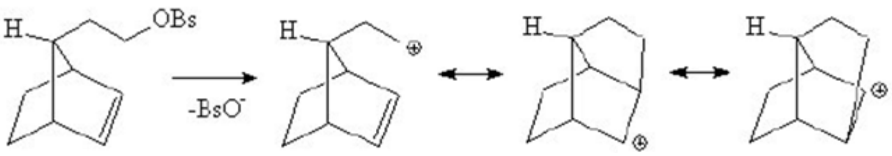




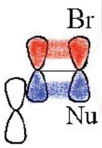
The carbocationic intermediate produced will be stabilized by resonance when the positive charge spreads over several atoms. This is shown in the diagram below:



Even, if the alkene is far off from the reacting centre, even then the alkene can still act in this manner. For instance, while forming alkyl benzenesulfonate, the alkene is still able to delocalise the carbocation.



Also an increase in the rate of the S_N2 reaction of allyl bromide with a nucleophile as compared with the reaction of *n*-propyl bromide, is due to the fact that the orbitals of the π-bond overlap with those of the transition state. In the allyl system the alkene orbitals overlap with the orbitals of a S_N2 transition state.

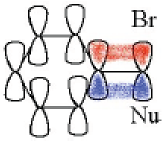


3.3 NGP by Cyclopropane, Cyclobutane or a homoallyl group

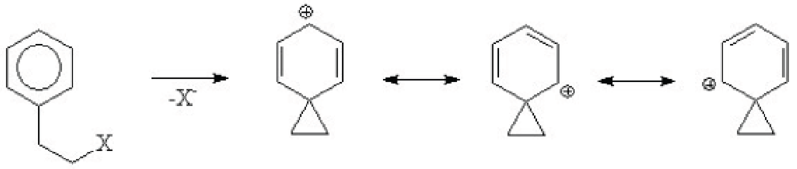
If Cyclopropylmethyl chloride is made to react with ethanol and water, then a mixture of 48% cyclopropylmethyl alcohol, 47% cyclobutanol and 5% homoallyl alcohol (but-3-enol) is formed. This is due to the fact that the carbocationic intermidate is delocalised onto many different carbons through a reversible ring opening.

3.4 NGP through an Aromatic Ring

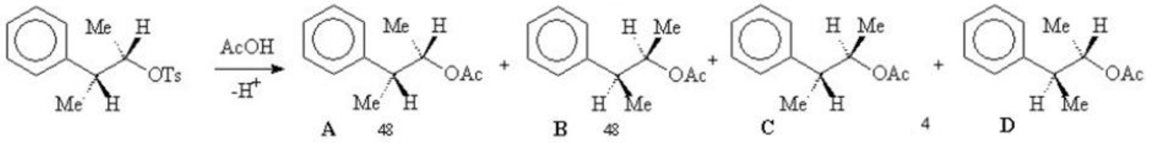
Consider the case in which the reactivity of benzyl halide is higher because the S_N2 transition state enjoys a similar overlap effect to that in the allyl system.



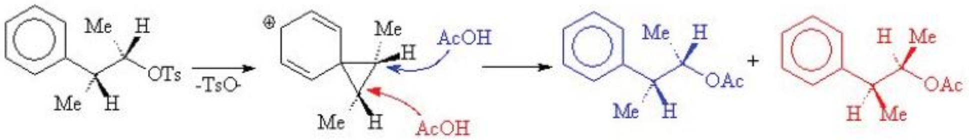
An aromatic ring can aid in the formation of a carbocationic intermediate called a phenonium ion by delocalisation of the positive charge.



Example: When the tosylate tends to react with acetic acid in solvolysis then, instead of a simple S_N2 reaction forming B, a 48:48:4 mixture of A, B and (C+D) was obtained.

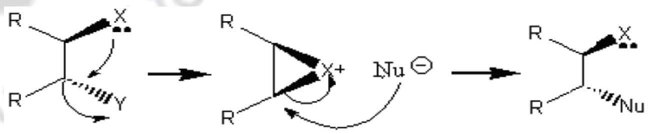


The mechanism which forms A and B is depicted below.



4. Neighbouring Group Participation on S_N2 reactions

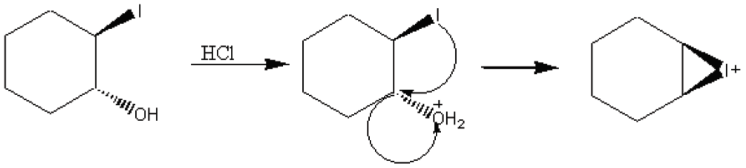
For nucleophilic substitution reactions, neighbouring group participation is defined as the introduction of a new reaction intermediate by a substituent that bonds to the reaction centre. For such substitutions, neighbouring group participation occurs primarily in the form of intra-molecular nucleophilic attack, followed by inter-molecular substitution.



NGP in bimolecular nucleophilic substitution

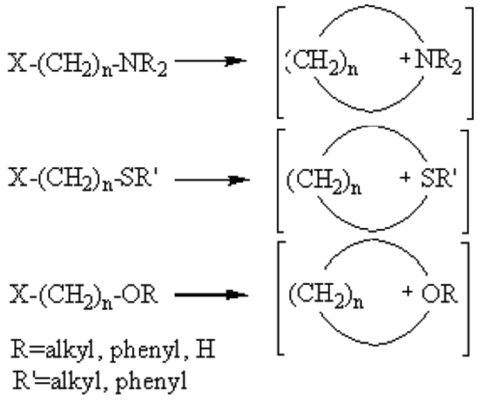
The result of this participation is the formation of a substituted product with retention of configuration by opposing the inversion of configuration, which is typically associated with the S_N2 mechanism. Hence, the mechanism of the reaction is changed. In addition to this neighboring groups can also affect the stereochemical outcome of a reaction. If a neighbouring group affects a reaction in such a way that the rate of the reaction is increased, then that neighbouring group is said to provide anchimeric assistance. The background reaction is used to determine if the neighbouring group is rate enhancing. It is usually the analogous reaction in the absence of the neighbouring group. NGP has been observed for a wide variety of substituents.

β-Halogens (one carbon removed from the leaving group) are a very basic example of NGP, forming cyclic halonium ions with the reacting centre. Ions of this type are known for chlorine, bromine, and iodine. Cyclic ions of this type are formed stereospecifically with inversion of configuration.



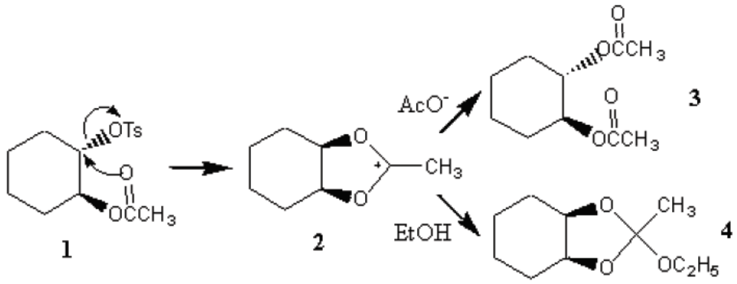
Formation of a cyclic iodonium intermediate

Similarly, sulfides, amines, alcohols, and ethers can be effective NGP's. Like the halogens, these groups add stereospecificity to the reaction centre. Unlike halogens, these groups do not have to be in the β-position in order to act as a neighbouring group, and can therefore form cyclic intermediates of rings of varying sizes. These groups mostly provide anchimeric assistance, in addition to the aforementioned retention of configuration of the products.



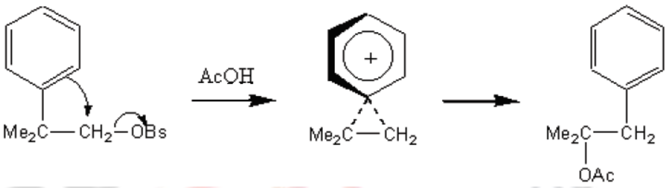
Amines, sulfides, ethers, and alcohols as participating neighbouring groups X=leaving group

β-Acetoxy substituents are also known to be neighbouring participants, forming 5-membered cyclic species by bonding through the carbonyl carbon. The existence of the acetoxonium ion (**2**) has been supported by trapping experiments in ethanol to give **4**. These trapping experiments were important in showing that the reaction was not proceeding by a classical S_N1 mechanism. The reaction produce **3** proceeds with the inversion of configuration, once again yielding an overall retention of configuration.



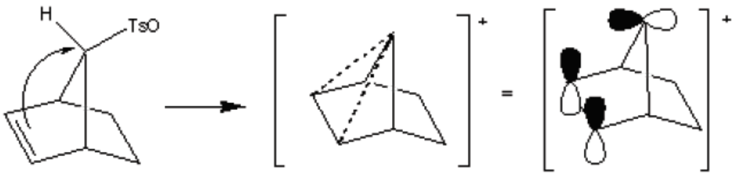
Acetoxy group as a NGP

In addition to substituents with lone pairs of electrons, p-bonded systems have been shown to be participating neighbouring groups. β-Phenyl groups form phenonium ions by donation of p-electrons. The phenonium ion intermediate has been supported by the stereochemistry of the final substitution products as an inverted configuration.



Phenyl group as a neighbouring group

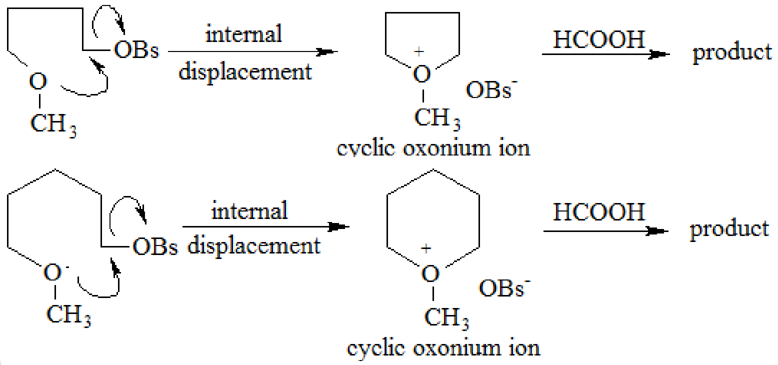
NGP has also been demonstrated for non-conjugated p-systems. Perhaps the most famous example of p-bond neighbouring group participation is that of *anti*-7-norbornenyl derivatives. These derivatives were believed to participate via a p-orbital interaction. Though this interaction invokes a molecular orbital explanation (as opposed to the nucleophilic nature of the neighbouring groups), still the retention of configuration is observed in substitution products as seen with previous examples. In other words, one observed only *anti*-substitution with respect to the double bond.



Stabilization of the norbornenyl cation through p-orbital interaction

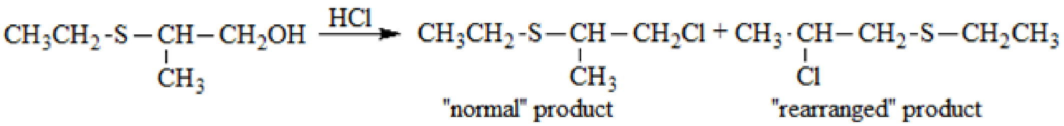
Supporting evidence was provided for this type of cation versus a rapidly equilibrating structure by Gassman et al., who substituted one methyl group onto the double bond and showed a significant rate increase (13.3 times greater than the unsubstituted reaction) for a similar substitution reaction. When they substituted a second methyl group onto the double bond, the rate increase was similar to that in the first substitution (148 times greater than the unsubstituted reaction). Hence, the stabilization of the carbocation is dependent on both carbons in the double bond. If the structure of the carbocation were rapidly equilibrating between the two double bonded carbons, then we would have shown no rate increase by adding the second methyl group.

Thus, the S_N2 pathway is a more favourable pathway in which displacement of brosylate is possible for compounds like $H_3COCH_2CH_2CH_2CH_2OBs$ and $H_3COCH_2CH_2CH_2\ CH_2CH_2OBs$. The internal displacement pathway lead to the formation of relatively stable 5- & 6-membered cyclic oxonium salts. As the chain length increases, the likelihood of cyclic oxonium ion formation diminishes, and rates approach to that of the reference case where only S_N2 attack by HCOOH is possible.



5. Neighbouring Group Participation on S_N1 reactions

The S_N1 pathway leading to a primary carbocation intermediate is not as favourable as an NGP (internal displacement) pathway leading to an episulfonium ion intermediate.

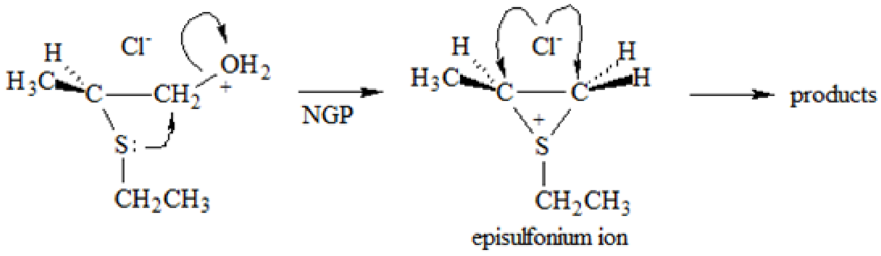


$$CH_3CH_2\text{-}S-\underset{CH_3}{CH}-CH_2OH \xrightarrow{HCl} CH_3CH_2\text{-}S-\underset{CH_3}{CH}-CH_2Cl + CH_3\cdot\underset{Cl}{CH}-CH_2\text{-}S-CH_2CH_3$$

"normal" product

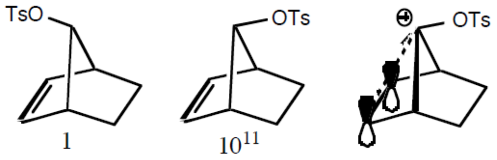
"rearranged" product

Rationale:

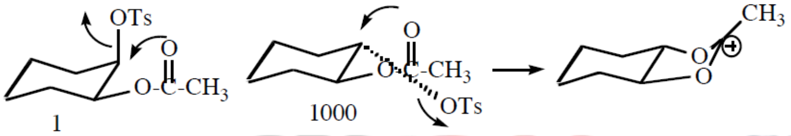


6. Neighbouring groups and Rearrangements

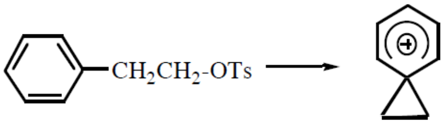
Case 1. The exo bicyclic tosylate undergoes solvolysis 1011 times faster than the endo isomer. This happens because the pi bond assists the formation of the carbocation and the assistance is much better from the backside of the tosyl group.



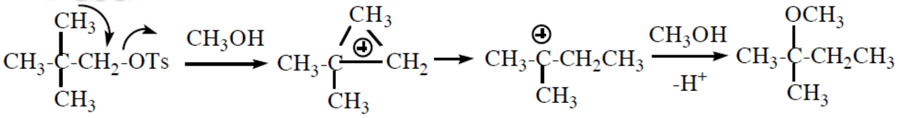
Case 2. The *trans*-tosylate undergoes solvolysis 1000 times faster than the *cis* isomer. The non bonding electrons of the carbonyl group assist the formation of the developing charge, and again the assistance is much better from the backside of the leaving group.



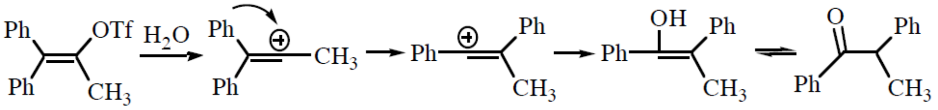
Case 3. Although 1º cations are not formed in solvolysis reactions, neighboring groups can assist the solvolysis of a primary substrate in a synchronous step to form a stable carbocation. Rearrangement occurs in β-pheny substrates because the phenyl group donates electrons, from the backside, to give a stable cyclic phenonium ion.



Case 4. The neopentyl system, another primary substrate, rearranges rapidly to give the product. CH_3 group assists the formation of a charge in a cyclic ion to give the more stable 3º carbocation.

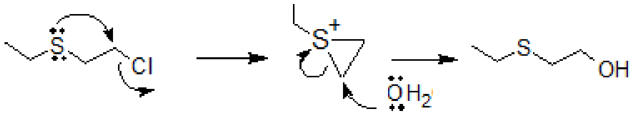


Case 5. This shows the uncommon case of a vinyl cation that can be formed by solvolysis because of the good leaving group triflate. The phenyl group migrates to give a more stable benzylic-type ion.



7. Examples

1.



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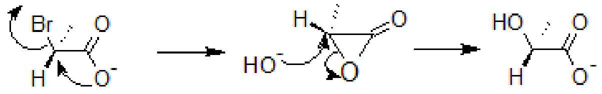
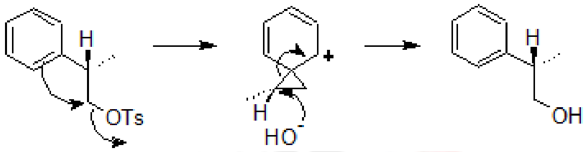
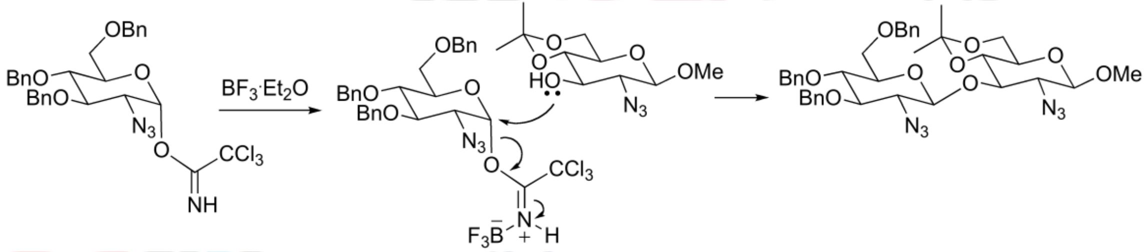


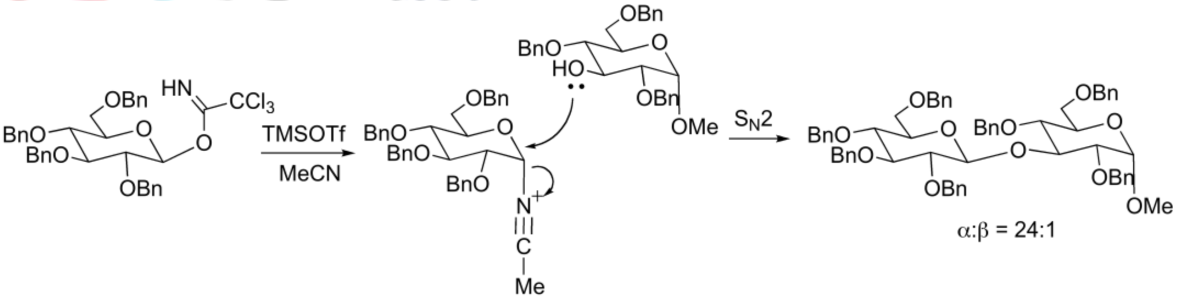
3.



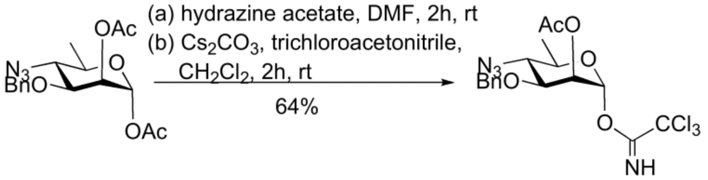
4. S_N2 type reaction: Inversion of configuration (non-NGP reaction)



5.



6. NGP - S_N1 reaction



8. Summary

- NGP is a useful tool for synthetic chemists. In S_N2 reactions, retention of configuration of the reaction centre can be obtained instead of the expected inversion of configuration.
- Also, if the neighbouring group helps stabilize the intermediate produced in the rate determining step, rate acceleration occurs.
- In the case study, the effects of solvent polarity on the competition between NGP and S_N2 direct substitution were addressed. It was observed that polar solvents increased NGP. Use of polar solvents seemed to help stabilize the cyclic cation intermediate.
- Also, the strength of the nucleophile was found to affect the reaction outcome. When strong nucleophiles were used, only direct substitution was observed.