SINCE 2013

NAAS SCORE : 4.32 (2017 to 2020)

SJIF 2020 = 6.618, 2021: 6.95, 2022: 7.128

IPI Value 2019: 1.90

2020: 1.90; 2021: 2.53; 2022-23: 2.59.

CiteFactor Impact Factor 2020-21:0.57

Academic Resource Index 2020:10

Received on:

8th May 2024

Revised on:

18th June 2024

Accepted on:

20th June 2024

Published on:

1st July 2024

Volume No.

Online & Print

43

Page No.

17 to 37

IRJC is an international open access print & online journal, peer reviewed, worldwide abstract listed, published quarterly with ISSN, Free-membership, downloads and access.

ALIPHATIC NUCLEOPHILIC SUBSTITUTION REACTION

MANINDRA KUMAR YADAV AND DR. MUKTA JAIN

S.S. JAIN SUBODH P.G.(AUTONOMOUS) COLEGE RAMBAGH, JAIPUR.

E-mail: *drmuktajain1@gmail.com*

ABSTRACT:

Nucleophilic substitution reactions (SN1 and SN2) are fundamental processes in organic chemistry, wherein a nucleophile replaces a leaving group in a molecule. The SN1 mechanism involves a two-step process, where the leaving group departs first, generating a carbocation intermediate, which is then attacked by the nucleophile. This mechanism proceeds via a carbocation intermediate and is fevered in polar protic solvents and with tertiary substrates. Conversely, the SN2 mechanism involves a concerted, one-step process where the nucleophile attacks the substrate while the leaving group departs simultaneously. SN2 reactions are fevered in polar aprotic solvents and with primary substrates due to their concerted nature. Both mechanisms play crucial roles in synthetic chemistry, providing access to a wide range of organic compounds with diverse functionalities. Understanding the factors governing these reactions is essential for predicting reaction outcomes and designing efficient synthetic routes.

KKEYWORDS: *Nucleophilic Reaction, SN1, SN2, Anions, Carbon-Hydrogen Bond etc.*

INTRODUCTION:

Nucleophilic substitution reactions, categorized into SN1 (substitution nucleophilic unimolecular) and SN2 (substitution nucleophilic bimolecular), are among the most fundamental transformations in organic chemistry [1]. These reactions involve the replacement of a leaving group in a molecule by a nucleophile, resulting in the formation of a new chemical

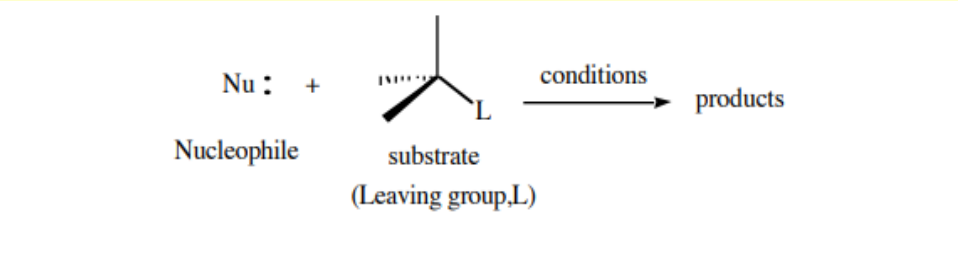
compound. The mechanisms of SN1 and SN2 reactions differ significantly, impacting their kinetics, stereochemistry, and substrate preferences [2-5].

In SN1 reactions, the process occurs in two distinct steps: the departure of the leaving group to form a carbocation intermediate, followed by the attack of the nucleophile on the carbocation [6]. This mechanism is characterized by its unimolecular nature, where the rate-determining step depends solely on the concentration of the substrate. Conversely, SN2 reactions proceed via a concerted mechanism, where the nucleophile attacks the substrate while the leaving group is departing, leading to inversion of stereochemistry at the reaction centre [7,8]. These reactions are bimolecular, with the rate depending on both the concentration of the substrate and the nucleophile.[9]

Understanding the factors influencing the choice between SN1 and SN2 mechanisms, such as substrate structure, solvent polarity, and nucleophile strength, is crucial for predicting reaction outcomes and designing synthetic routes in organic chemistry. Moreover, the versatility of nucleophilic substitution reactions makes them indispensable tools for the synthesis of complex organic molecules in both academic and industrial settings. This introduction sets the stage for exploring the intricacies of SN1 and SN2 reactions and their significance in organic synthesis.

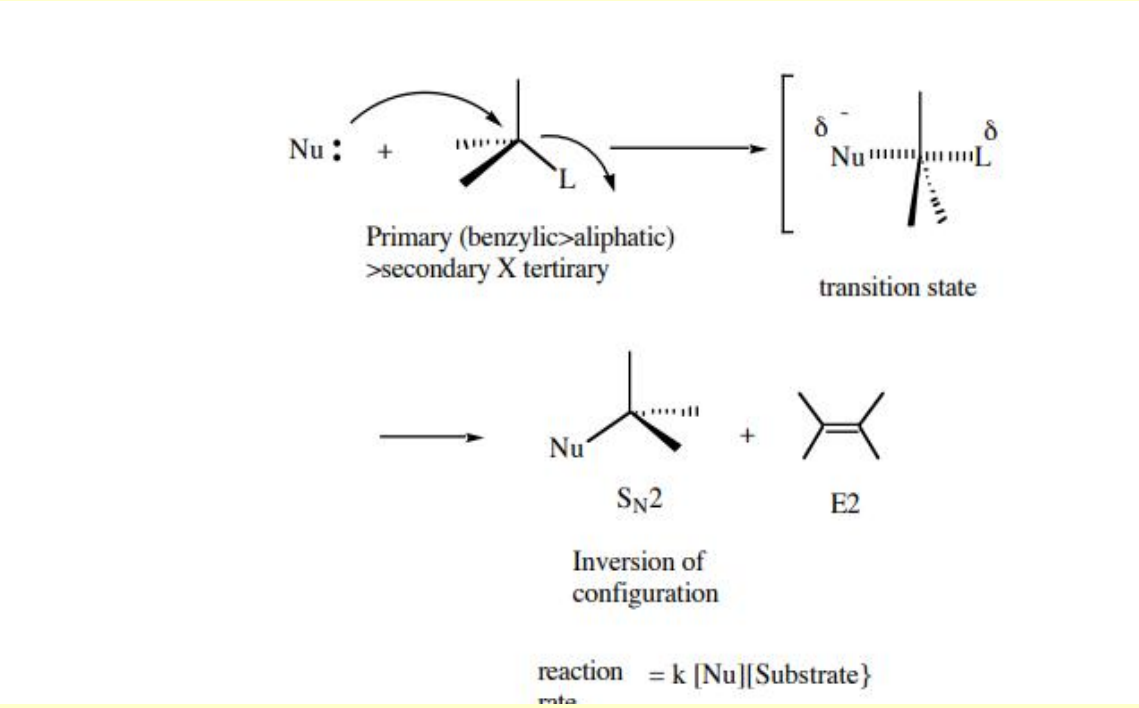
Review of literature:

Aliphatic Nucleophilic Substitution



Chemical species known as nucleophiles react with centres that have a positive ionic character. The process is known as aliphatic nucleophilic substitution when the centre is an aliphatic carbon. These kinds of chemical reactions are crucial for both the synthesis of new compounds and the comprehension of organic chemistry's mechanisms. Although there may be multiple reaction courses in all nucleophilic substitution reactions, they all start out looking the same. A nucleophile (Nu), which carries two electrons as an anion or a neutral compound, is the attacking species in all reactions. The leaving group (L), which is lost during the reaction, is present in the organic compound referred to as the substrate. Its structure has a significant impact on the reaction's result.[10] The reaction's environment, particularly the temperature and solvent, plays a significant role in the process. The reaction is examined from a mechanistic perspective in order to

comprehend the end products and their formation. The Second-Order Nucleophilic Substitution Reaction (SN2).[11]



When a nucleophile attacks a primary substrate and occasionally a secondary substrate the SN2 reaction takes place. A secondary substrate's reaction is influenced by both the leaving group and the nucleophile. The SN2 mechanism does not cause reactions in tertiary substrates.[12]

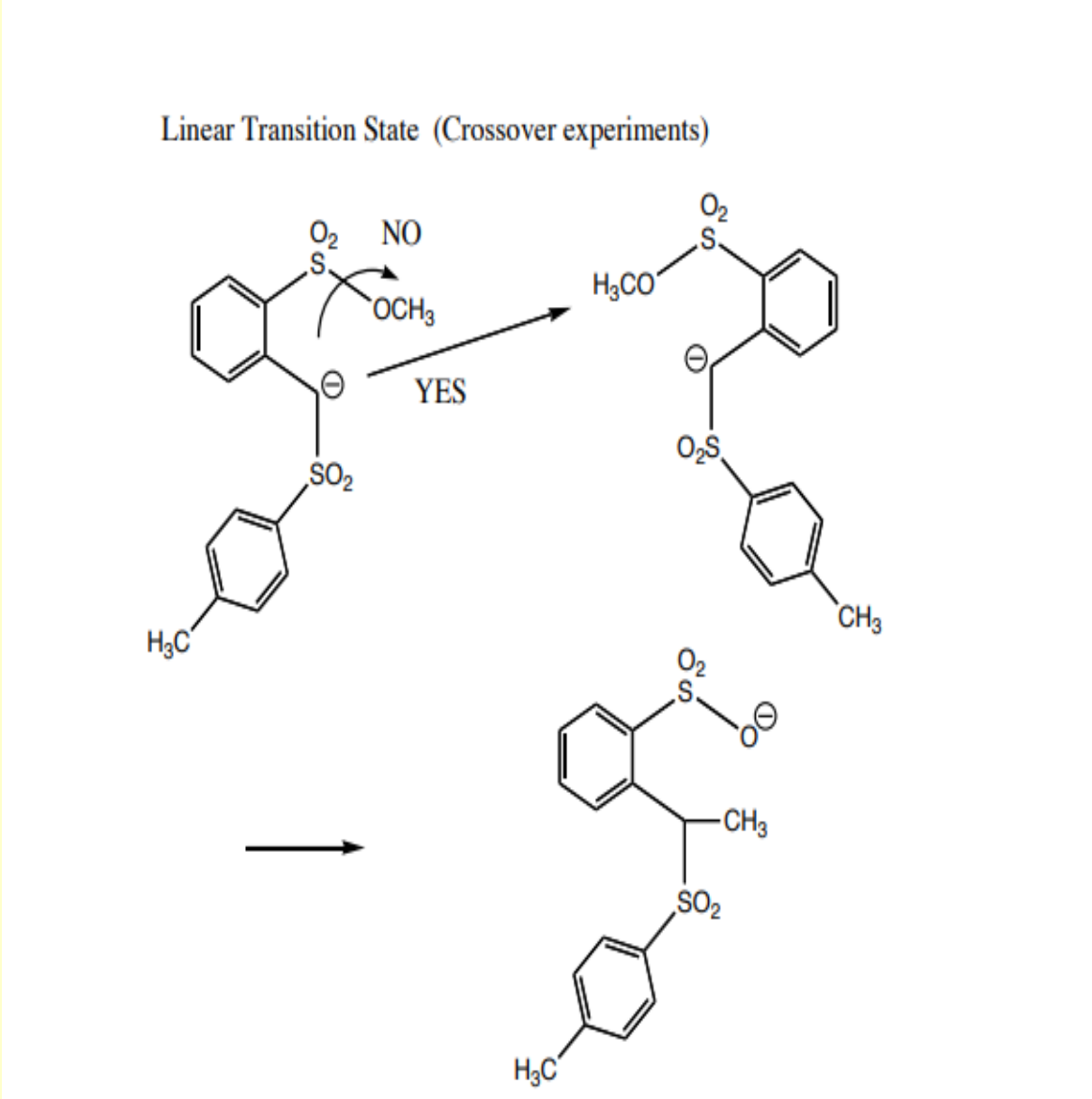
The reaction is referred to as second-order because the total rate is dependent on both the nucleophile and substrate concentrations. To produce a pentavalent transition state , the process necessitates that the nucleophile approach the substrate from the leaving group's backside. The configuration of the organic substituents is reversed; a S enantiomer would become a R enantiomer. The Walden inversion is another name for the procedure.

Alkene can also occur sometimes when the nucleophile exhibits very basic properties, such as alkoxides. The E2 process, sometimes referred to as the Elimination Second-order reaction, produces this product. The responses below demonstrate that the transition state has to be linear. Because an internal linear assault is not conceivable, the carbanion must attach a methyl from another molecule, not internally.

Here are a few properties of leaving groups, substrates, and nucleophiles.

The SN2 mechanism needs a backside assault. The response is extremely sensitive to the presence of groups that prevent the backside assault. Thus, primary substrates are the best since they provide

the least resistance to the nucleophile's backside assault. Neopentyl bromide, with a relative rate of 10-7, is a main substrate with poor reactivity since the only substituent is a bulky tert-butyl group [13].

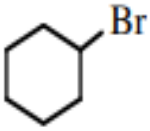
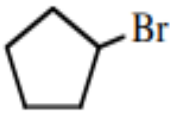


Some properties of nucleophiles are given by the Swain-Scott equation

Substrate Reactivity

1^{o}-benzylic $> CH_3 >$ 1^{0}-aliphatic $>> 2^{0}$ not at all 3^{0}
1^{o}-allylic

relative reactivity of several aliphatic bromides

CH_3Br	1		.001
CH_3CH_2Br	.01		
$CH_3CHBrCH_3$	.001		.01
$CH_3CBr(CH_3)_2$	10^{-5}	$CH_2=CHCH_2Br$	2.3
		$PhCH_2Br$	4.0
$CH_3C(CH_3)_2CH_2Br$	10^{-7}		

Groups that leave are crucial to the SN2 process. Easily made from alcohols and sulfonyl anhydride or sulfonyl chloride, esters of sulfonic acids make up some of the best leaving groups; these are not halogens. When other reactions are competing, using a triflate or tosylate with a secondary substrate can effectively increase the quantity of SN2 reaction.[14]

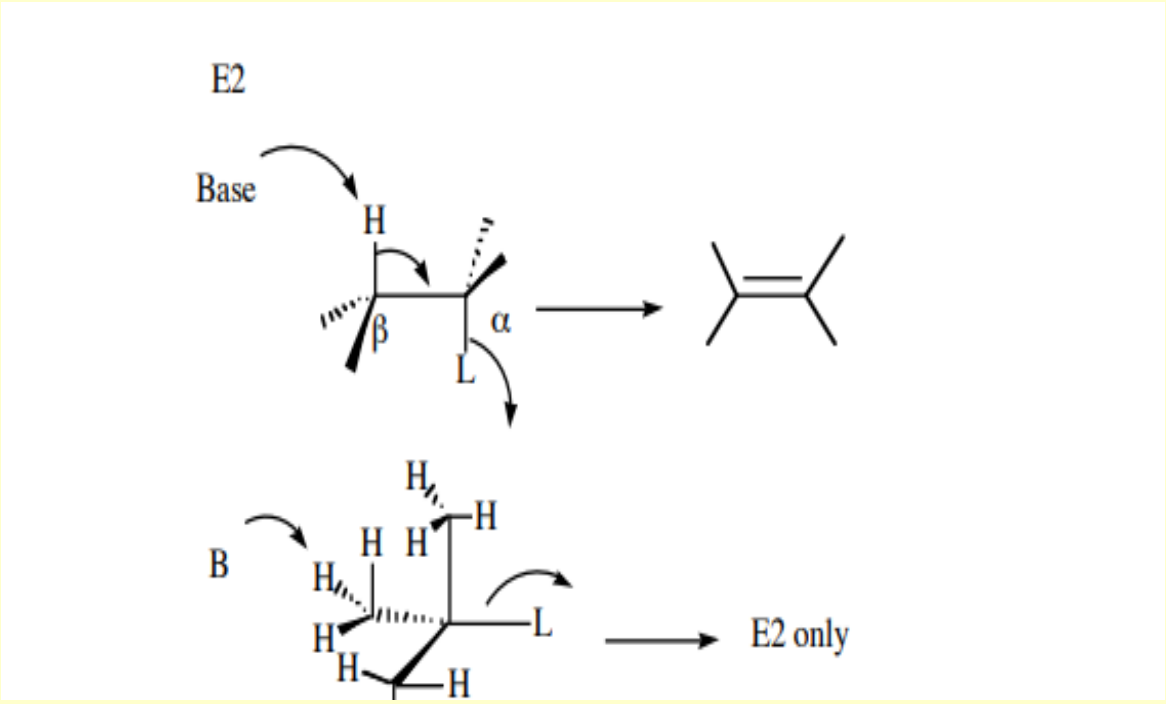
Nucleophiles

$$n_{CH_3I} = \log(k_{nu} / k_{CH_3OH})$$

n = nucleophilicity constant. Compares nucleophiles in with methyl iodide. The standard nucleophile is water.

	n	pKa
CH_3COO^-	4.3	4.8
N_3^-	5.8	4.7
CH_3O^-	6.3	16
NH_2OH	6.6	5.8
^-CN	6.7	9.3
t-BuO^-	4.0	20
Ph_3P	8.7	8.7
H_2O	0.0	7

$$RS^- > ArS^- > S_2O_3^- > I^- > CN^- > SCN^- > OH^- > N_3^- > ArC$$



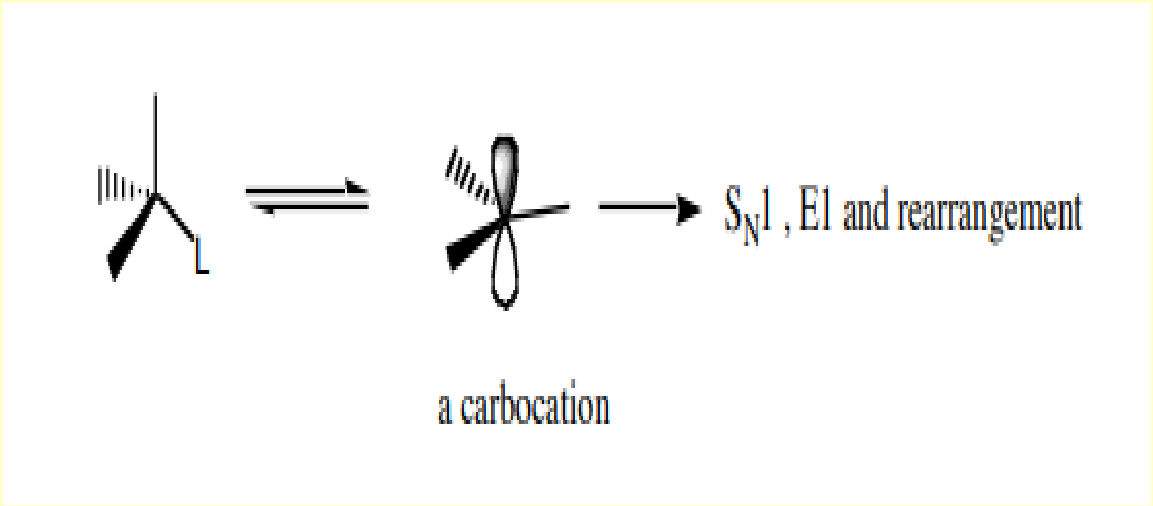
Alkoxides and nitrogen anions are good bases for the reaction. Elimination rises with secondary substrates and is the lone result of a tertiary substrate with a base when there are more beta

hydrogens present. Because carbon-hydrogen bonds are stronger than those of carbon-leaving group, higher temperatures facilitate the removal of [15]

Substitution Nucleophilic First-order (SN1)

A first-order reaction is another reaction involving organic substrates and leaving groups. This indicates that the concentration of the substrate alone determines the rate of the reaction, not the concentration of nucleophiles. Though elimination and rearrangement are frequently present, substitution may be the reaction's ultimate result.

Sometimes SN1 reactions are referred to as solvolysis reactions, which denotes a solvent-induced reaction. In order to interact with the ionic leaving group and stabilize the polar carbocation intermediate, the majority of solvents are polar. The chemistry of carbocations and the parameters affecting their stability are the main subjects of research for the SN1 process [16



Solvents in Solvolysis

The substrate creates a somewhat stable carbocation in the presence of the solvent, which is the reason for the reactions in this section. As a result, the name "solvolysis" suggests a carbocation process and refers to a reaction with the solvent. First order refers to the fact that the rate of a solvolysis reaction, or Sn1 reaction, is independent of any nucleophile's concentration in the substrate. Solvolysis rate = k [RX].[17]

Important conclusions about solvent character that is, a solvent's capacity to induce a substrate to produce a carbocation have been drawn from several investigations of these reactions in various solvents. Grunwald and Wainstein created an early scale in 1940 that is still in use. The ionizing power of a solvent is represented by the specified value Y in the equation below. The rate constant for t-butyl chloride ionization in 80% ethanol and 20% water is found experimentally. The rate

constant for t-butyl chloride ionization in different solvents is then calculated, and the results are entered into the equation [18].

$$Y = \ln\left(\frac{k(\text{solvent})}{k(80\%\ \text{EtOH-}20\%\ \text{water})}\right)$$

for t-butyl chloride as substrate

Some values of Y for several solvents are listed below. Thus, formation of carbocations by solvolysis occurs better in solvents with higher Y values.

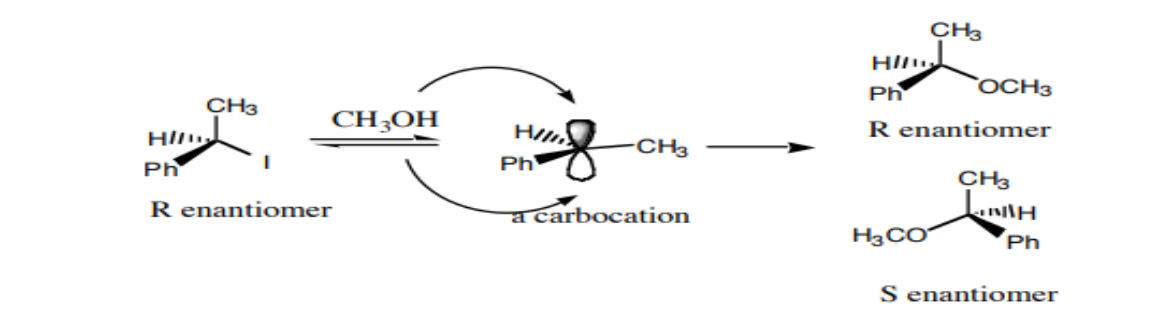
Solvent	Y
CF_3COOH	1.84
H_2O	3.49
80% EtOH	0.0
HCOOH	2.05
20% EtOH	3.05
EtOH	-2.03

Another substrate, adamantyl tosylate, was used to refine the Y scale into a Y (OTs) scale. The new substrate is a better indicator of pure ionizing capacity since it prevented any solvent from attacking the cation site from the backside [19].

The Y values for CF3COOH (4.57) and CF3CH2OH (1.8) have been updated. When t-butyl chloride is the substrate, there is some backside help, as evidenced by the greater value of trifluoroacetic acid with the adamantyl system. In 1972, Bently and Schleyer developed a technique to ascertain a solvent's nucleoplicity (N). The following solvents have their N listed: 20% EtOH (-.09), CF3COOH (-5.6), HCOOH (-3.0), and H2O (-.41). Greater solvent nucleophilicity is indicated by larger values [20]. 20% EtOH is the best in this case.

Stereochemistry and Ion Pairs

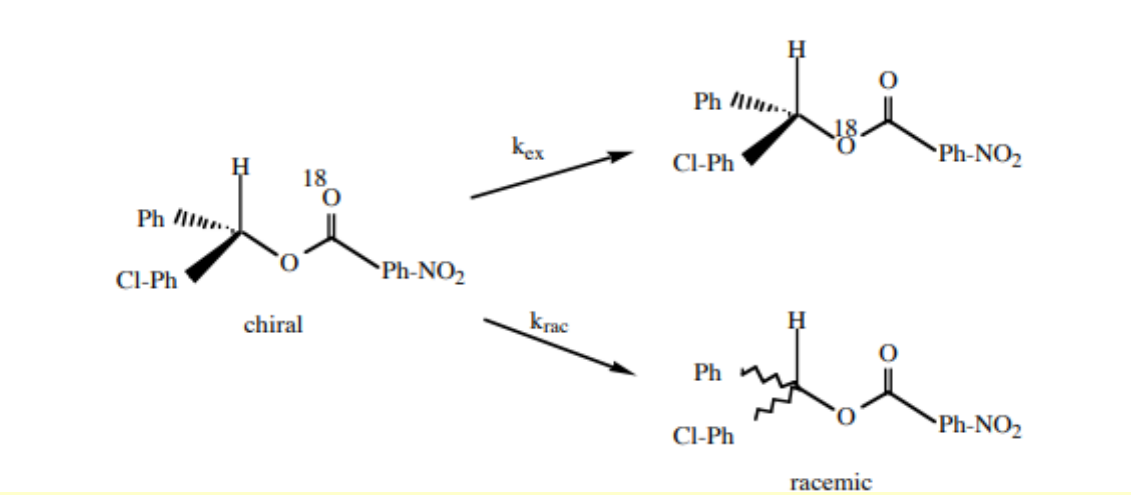
With an empty p orbital, the carbocation intermediate is a flat sp2 hybrid. It is possible for nucleophiles to bind to the polymer equally from the top or bottom. The predicted result, as indicated below, would be racemic if a chiral substrate were employed. A secondary substrate with a R configuration is shown in the example, producing a planar carbocation that is attacked by the solvent and yields the R and S product mixture (after proton loss) [21].



In undergraduate organic chemistry classes, the aforementioned example is frequently given as the last tale. However, a lot of carbocation reactions involving chiral substrates result in products that occasionally retain configuration during the reaction and sometimes exhibit some degree of configuration inversion. A more thorough explanation of the carbocation intermediate's existence as a sequence of ion pairs results from these data. The substrate solvates into tight pairs, solvated pairs, and the free carbocation in order of sequence. The racemization reaction is exclusively produced by the free carbocation, as seen above. Depending on the reaction conditions, the ion pairs need distinct stereochemical outcomes, and several SN1 reactions arise from the ion pairs prior to the formation of the free ion [22].

1. The rate of the reaction rises when LiCLO4 is introduced. This occurs as a result of the perchlorate's weak nucleophilicity, which delays substitution while also entering the solvent-separated ion and stabilizing it by polar contact.

2. The substrate below provides the internal return's initial product. While the racemization takes place in the free ion, the O-18 exchanges take place in the tight ion-pair to yield the rearranged product with maintained configuration.



3. The addition of NaN3 give an amide product with inverted configuration. This occurs from backside attack on the solvent separated ion-pai [23]

The Chemistry of Carbocations

Carbocation intermediates are involved in reactions that occur via SN1 or E1 processes. Understanding the variables affecting the stability (or instability) of the intermediate is a key component of studying carbocation intermediates. In certain situations, this becomes fascinating from an intellectual standpoint as one learns about response processes, and in other situations, useful synthetic techniques emerge.

Substituent Effects on Carbocation

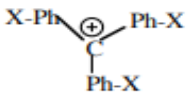
The positive charge of a carbocation can be stabilized by substituents that can donate electrons, thereby reducing the localized charge. Substituents or functional groups containing non-bonding pi electrons can effectively stabilize a carbocation. For instance, a fluorine atom positioned alpha to a carbocation centre provides stabilization. The six non-bonding electrons of fluorine are in 2p orbitals, matching the size to overlap with the 2p cationic site. This stabilizing effect is primarily observed as a directing effect rather than a rate-enhancing one.

However, fluorine atoms situated beta to a carbocation centre exert strong destabilization, preventing the formation of simple beta fluoroalkyl carbocations. Fluorine atoms located further away from the cationic centre, especially in the beta position, are highly destabilizing. This destabilizing effect is evident in systems like triphenyl cations and slows down the solvolysis of benzylic toluates.[24]

Nevertheless, examples of alpha stabilization are well-documented and are utilized to control certain carbocation reactions effectively.

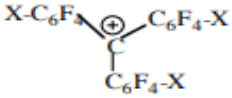
Cyclopropyl Carbinyl Cation

The following illustrates how fluorine affects the cyclopropyl carbinyl system. The early research on classical vs non-classical carbocations often focused on the cyclopropyl carbinyl system. Recent research on a difluoro derivative reveals



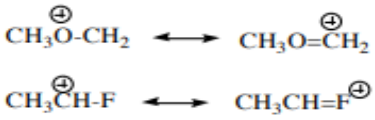
X	pK_R
H	-6.6
CH_3	-3.6
NO_2	-16.2
OCH_3	+0.8
$(CH_3)_2N$	+9.4
$PhCH_2^+$	-20
Ph_2CH^+	-13.3
F	-17.7
CF_3	-26

larger positive pK_R is more stable cation

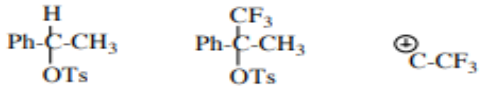


benzylic
allylic $> 3^0 > 2^0 > Ph^+ \quad C=C^+ \quad XX \quad 1^0 > CH_3^+$

$NH_2 > CH_3O > OH > Ph > CH_3 >> F ; CN > C=O >> NO_2$

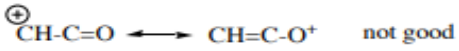


Fluorine alpha to a carbocation stabilized the carbocation in a manner similar to oxygen stabilization.



rel rate 10^5 rel rate 1

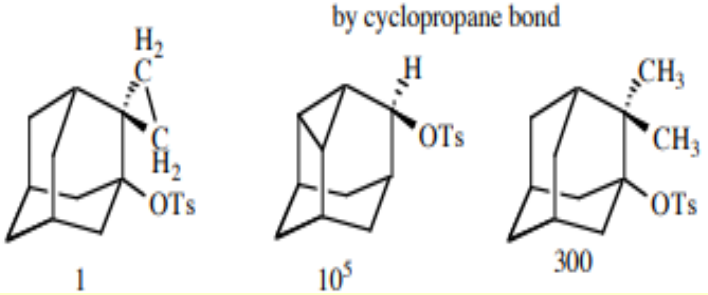
unfavorable β influence of fluorine atoms



not good

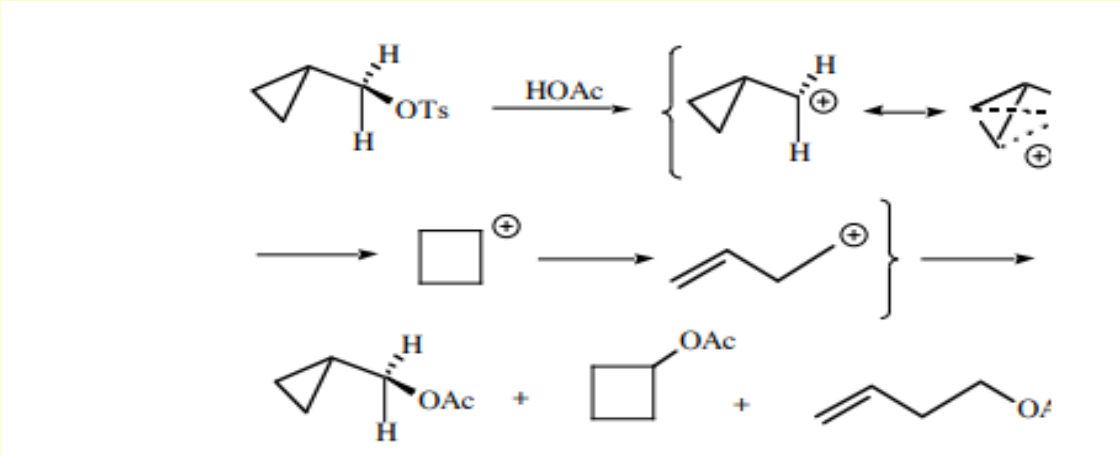
perpindicular bisected

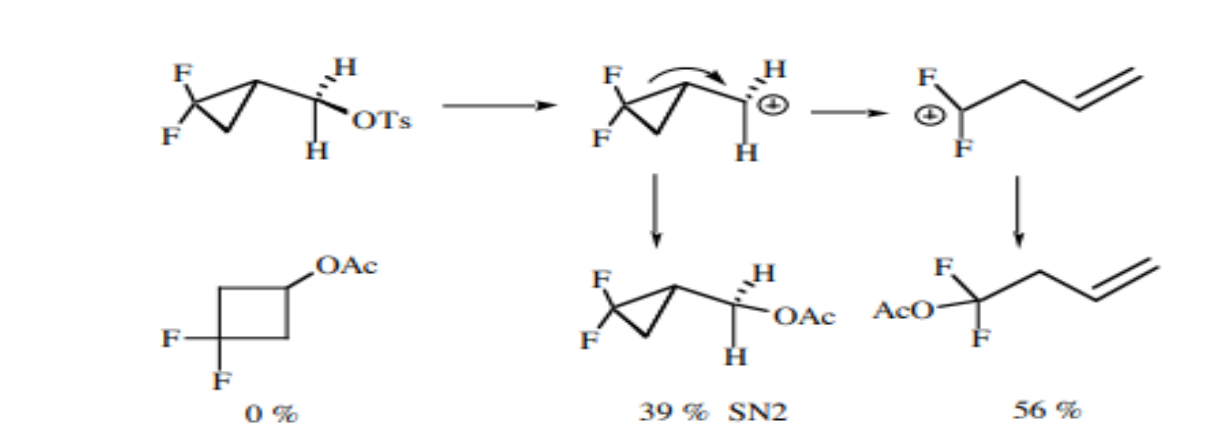
good overlap and stabilization by cyclopropane bond



1 10^5 300

There are only two products seen in the difluoro system, and the one with the intact cyclopropane ring is mostly the result of SN2 assault on the fundamental carbon. Although the difluoro alkene has a substantial fluorine atom-directed influence on the carbocation, the first order rate constant for solvolysis is around 2 x 10 -5 sec-1, a factor of 105 less than that of the parent hydrogen system. Strong instability of the fluoine atoms on the beta or gamma carbocation is indicated by the lack of the cyclobutyl product [25].





The solvolytic ring opening exhibits rivalry between the production of the difluoro cation and the alkyl cation as methyl groups are added next to the difluoro function. The ring opening was dominated by the tertiary alkyl cation system, which has two methyl groups. However, cyclobutyl cations are still not seen.

A diene is produced when the chlorofluoro cyclopropane is ionized, releasing a fluoroallylic cation that removes a proton. In this instance, the fluorine atom is close to the cationic site, but it appears to have little effect since proton loss occurs quickly.

NUCLEOPHILIC SUBSTITUTION REACTION AN SN2 REACTION

MECHANISM FOR THE SN2 REACTION

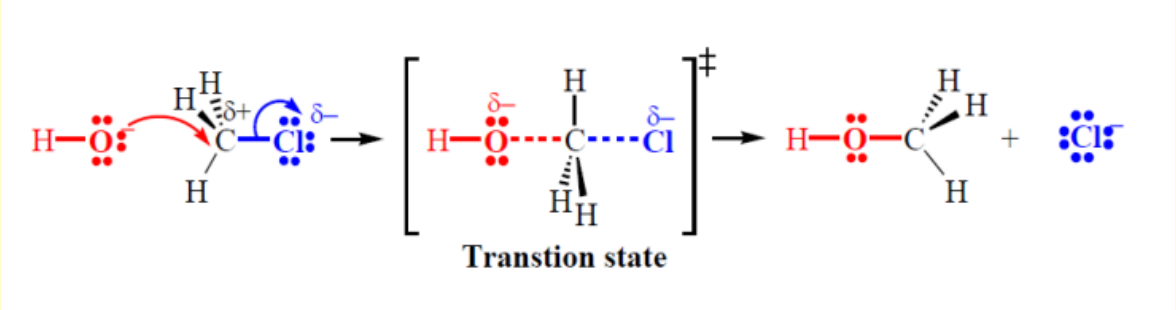
. The nucleophile attacks the carbon bearing the leaving group from the back side

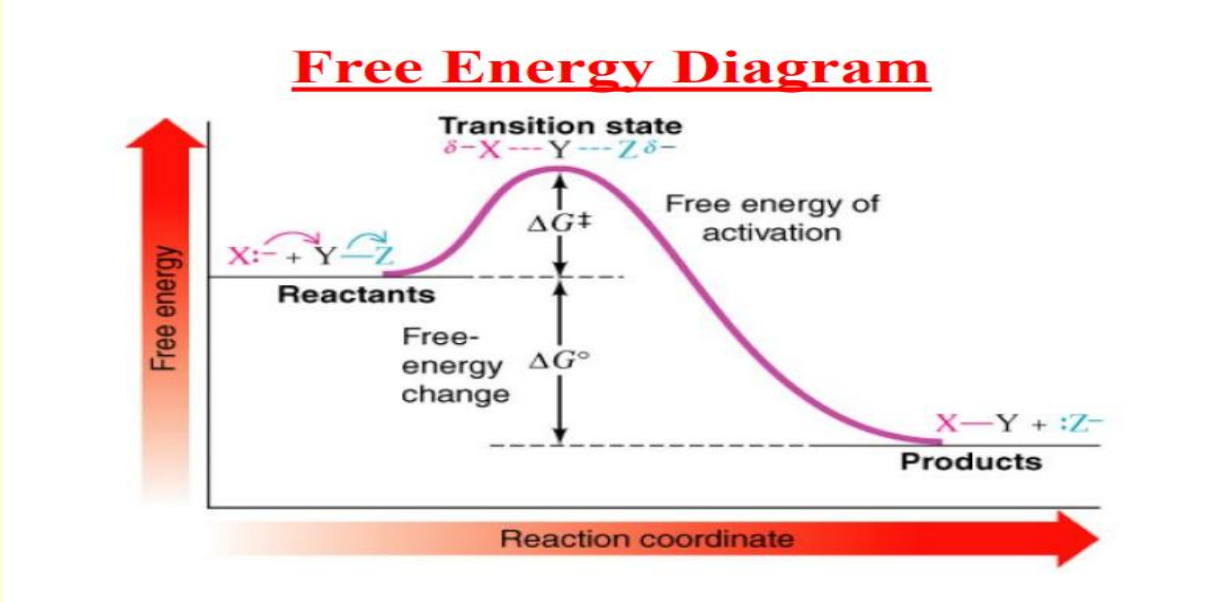
• The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.

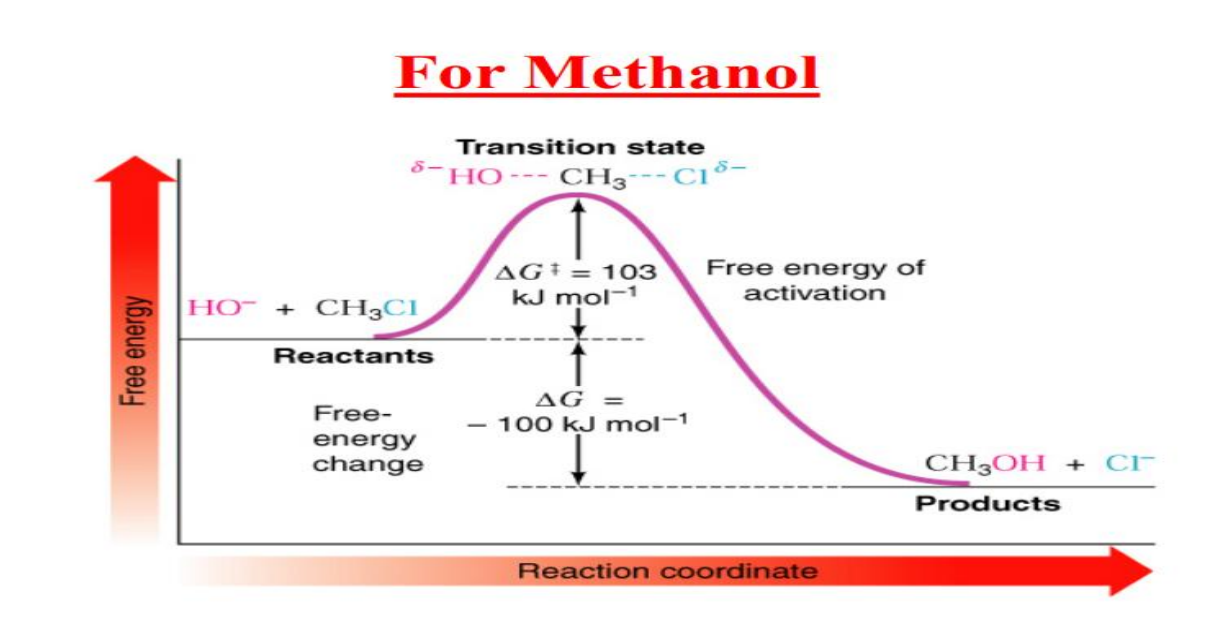
• The configuration of the carbon atom becomes inverted during SN2 reaction

• Because bond formation and bond breaking occur simultaneously in a single transition state, the SN2 reaction is a concerted reaction.

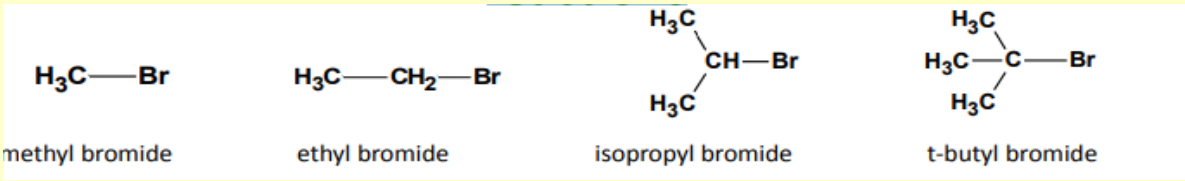
Mechanism

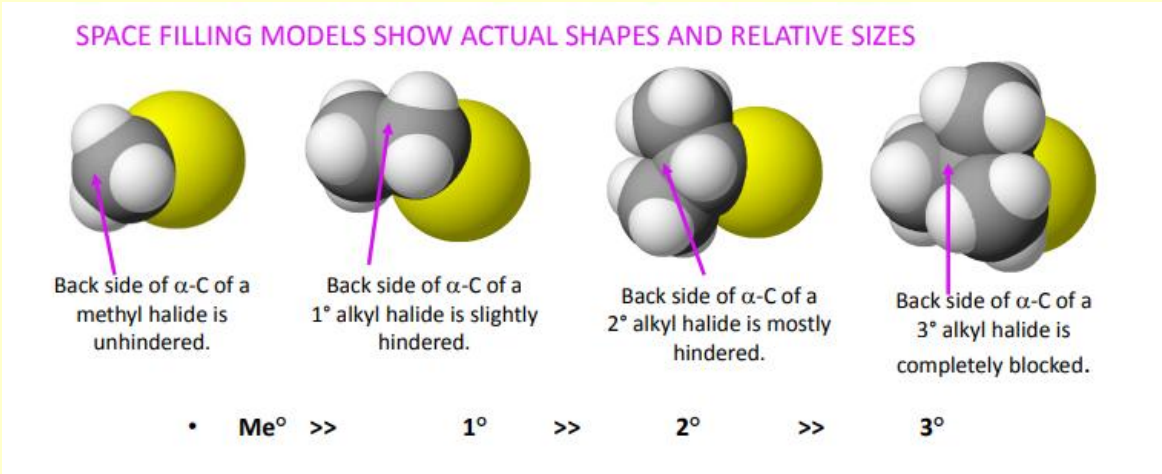






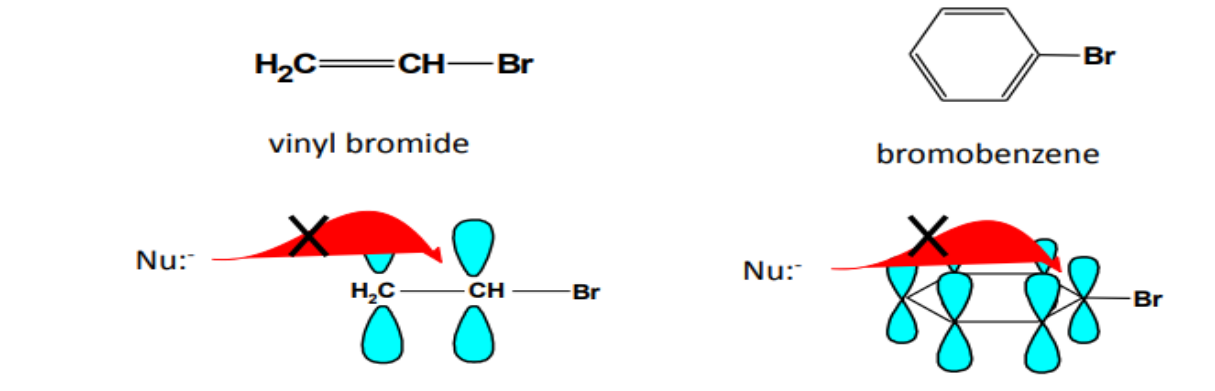
Effect of nature of substrate on rate of SN2 reactions





Effect of the nucleophile on rate of SN2 reactions

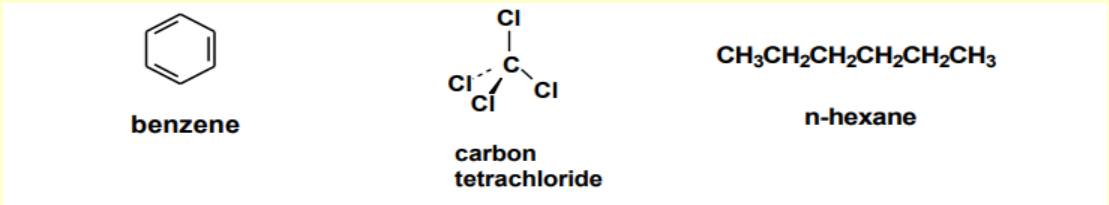
•The α-carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and thesealkyl halides do not undergo SN 2 reactions[26].



The overlapping p-orbitals that form the p-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon

Effect of the solvent on rate of SN2 reactions

Nucleophiles are not stabilized or solvated by non-polar solvents such as hexane, benzene, or carbon tetrachloride. Similar to protic solvents, SN 2 reactions in non-polar solvents proceed quite slowly.

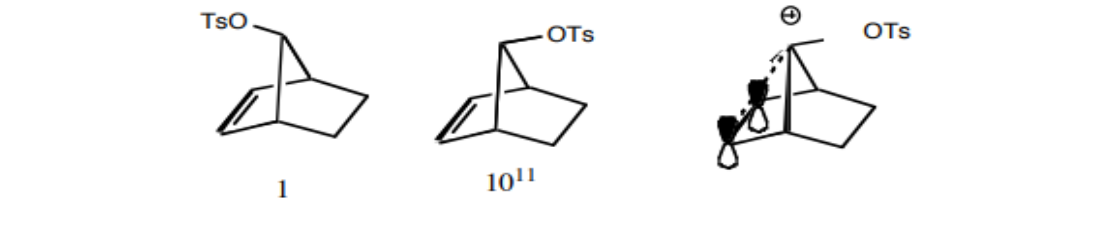


SN2 Conditions Summary.

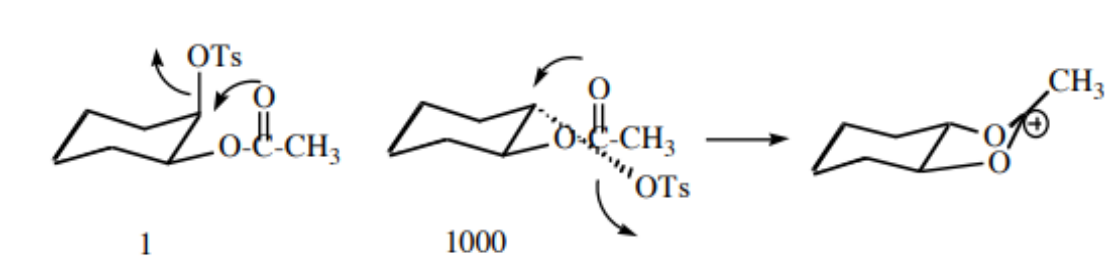
1) Substrate (methyl > primary > secondary >> tertiary
2) Nucleophile (negative charge > neutral)
3) leaving group (Y) (Y stabilizes a negative charge)
4) solvent (needs to be polar and aprotic)

Neighboring groups and Rearrangements

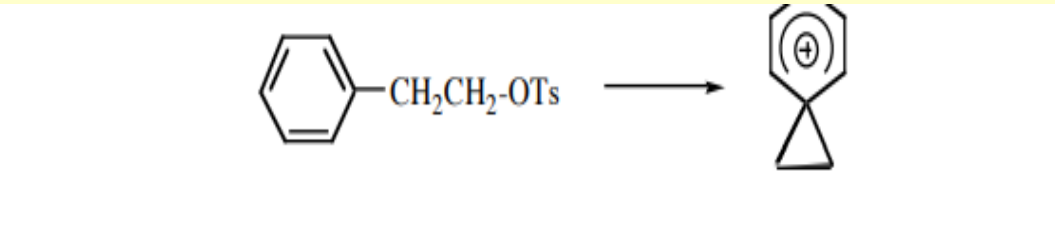
Case 1: Compared to the endo isomer, the exon bicyclic toluate undergoes solvolysis 1011 times quicker. This occurs as a result of the pi bond aiding in the carbocation's development. The support from the tosyl group's rear is far superior.



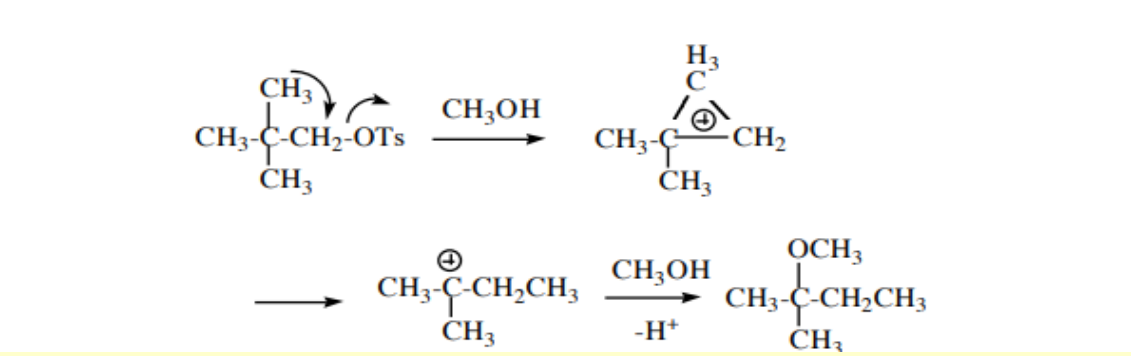
Case 2: Compared to the cis isomer, the trans tosylate undergoes solvolysis 1000 times quicker. Once more, the support from the departing group's back is superior to that of the carbonyl group's non-bonding electrons in aiding the development of the growing charge.



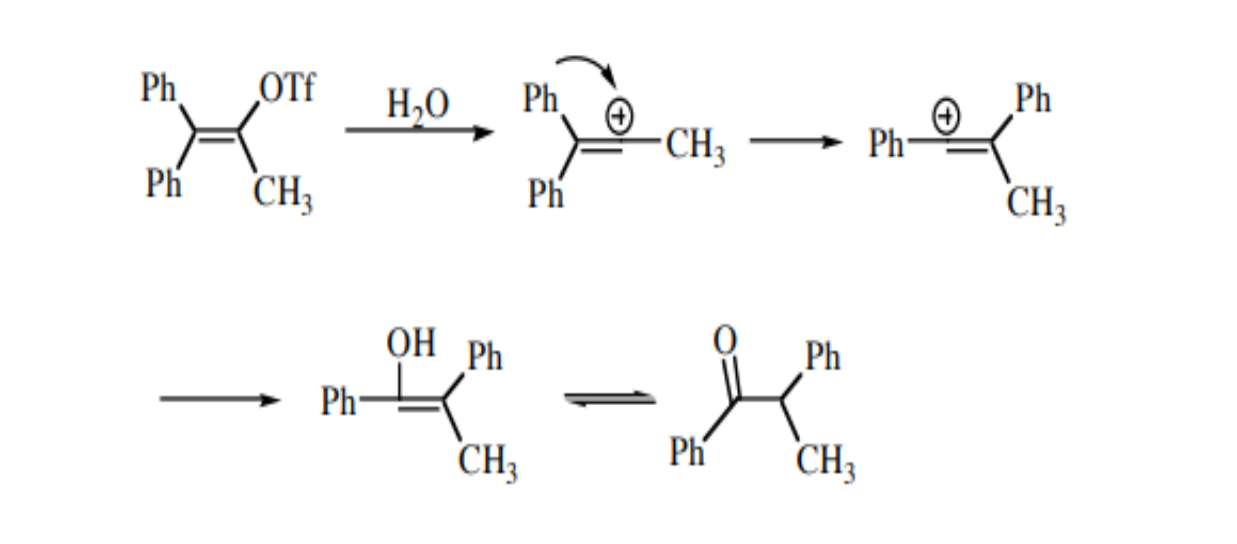
Case 3: Neighboring groups can help solvolyze a primary substrate in a synchronous step to generate a stable carbocation, even though primary cations are not formed in solvolysis processes. Because the phenyl group gives electrons from the back to produce a stable cyclic phenonium ion, rearrangement happens in beta pheny substrates.



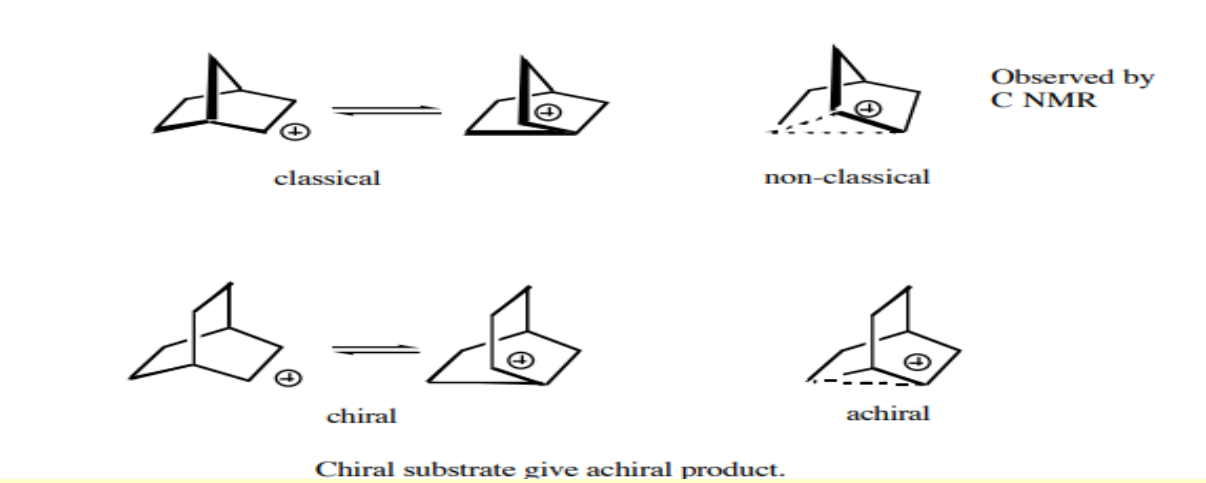
Case 4: The result displayed is the quick rearrangement of the neopentyl system, another major substrate. The more stable tertiary carbocation is produced when a cyclic ion's charge is formed with the help of the methyl group.



Case 5. Thus 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.



Norbornyl Systems

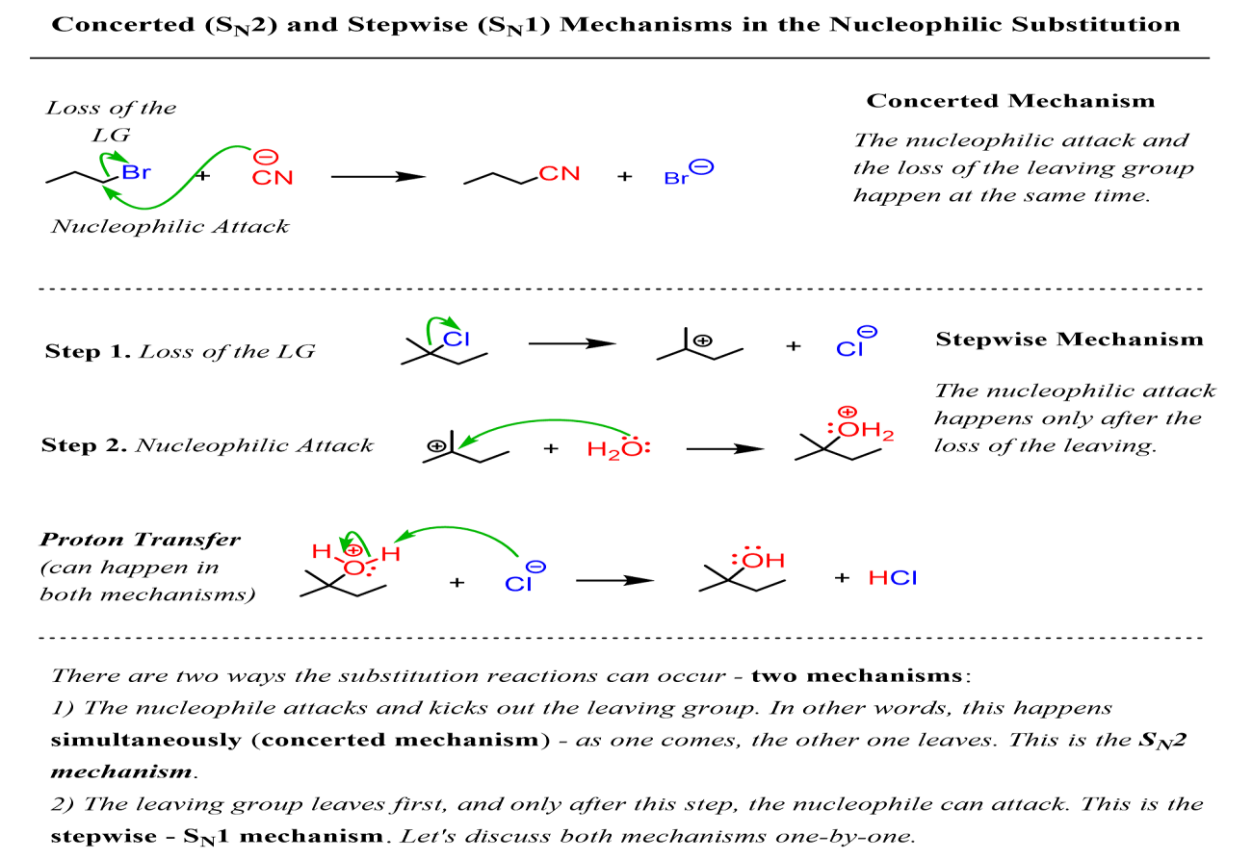


The fluorinated norbornyl system underwent an ionic treatment with Br2, resulting in a rearrangement. The 49% yield product demonstrates how the exocyclic difluoro ethylene function's fluorine atoms impact the result by giving up their pi electrons to form a fluorine-stabilized carbocation that combines with the bromide ion. (JOC, 831; Smart, 1974).

Applications of Aliphatic Nucleophilic Substitution Reactions.

In the production of medicines, aliphatic nucleophilic substitution reactions are often employed.

The production of complex organic compounds and the alteration of natural products both depend on these processes. Comprehending the workings of these reactions is essential to creating effective synthetic pathways.



CONCLUSION:

In conclusion, aliphatic nucleophilic substitution reactions play a fundamental role in organic chemistry, encompassing a wide range of important transformations. These reactions involve the substitution of a nucleophile for a leaving group on an aliphatic carbon atom, resulting in the formation of a new organic compound. The most common mechanisms for these reactions include SN1 and SN2, each with its own set of characteristics and influencing factors.

Throughout the study of aliphatic nucleophilic substitution reactions, we have explored the various factors that affect reaction rates and selectivity, such as the nature of the nucleophile and leaving group, solvent polarity, steric hindrance, and the structure of the substrate. Understanding these factors allows chemists to predict reaction outcomes and design synthetic routes with precision.

Moreover, aliphatic nucleophilic substitution reactions find wide applications in the synthesis of pharmaceuticals, agrochemicals, and various other organic compounds essential to daily life. They

provide versatile tools for organic chemists to construct complex molecules efficiently and selectively.

Continued research in this field aims to expand our understanding of reaction mechanisms, develop new catalytic systems, and discover novel synthetic methodologies. By harnessing the principles of aliphatic nucleophilic substitution, researchers strive to address pressing challenges in drug discovery, materials science, and beyond, ultimately driving innovation and advancement in the field of organic chemistry.

Funding

Nill

Conflict of interests

The authors declare that they have no conflict of interest.

REFERENCES:

1. March J. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. John Wiley & Sons; 2013.
2. Smith MB, March J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. John Wiley & Sons; 2007.
3. Carey FA, Sundberg RJ. Advanced Organic Chemistry: Part A: Structure and Mechanisms. Springer Science & Business Media; 2007.
4. Clayden J, Greeves N, Warren S. Organic Chemistry. Oxford University Press; 2012.
5. Solomons TWG, Fryhle CB, Snyder SA. Organic Chemistry. John Wiley & Sons; 2013.
6. Brown WH, Iverson BL, Anslyn EV, Foote CS. Organic Chemistry. Cengage Learning; 2008.
7. Loudon GM. Organic Chemistry. Roberts and Company Publishers; 2015.
8. Vollhardt KPC, Schore NE. Organic Chemistry: Structure and Function. WH Freeman; 2007.
9. Katritzky AR, Musumarra G. New insights into aliphatic nucleophilic substitution reactions from the use of pyridines as leaving groups. Chem Soc Rev. 1984;13(1):47-68.
10. Rossi RA, Pierini AB, Pene Nory AB. Nucleophilic substitution reactions by electron transfer. Chem Rev. 2003;103(1):71-168.
11. Nelson JD. Aliphatic nucleophilic substitution. In: Practical Synthetic Organic Chemistry: Reactions, Principles, and Techniques. 2020:1-63.
12. Jaiswal AK, Prasad PK, Young RD. Nucleophilic substitution of aliphatic fluorides via pseudohalide intermediates. Chem Euro J. 2019;25(25):6290-6294.
13. Katritzky AR, Brycki BE. The mechanisms of nucleophilic substitution in aliphatic compounds. Chem Soc Rev. 1990;19(2):83-105.
14. Gillespie PD, Ugi I. A Re-examination of the Limiting Mechanisms of Aliphatic Nucleophilic Substitution. Agnew Chem Int Ed Engl. 1971;10(7):503-506.

15. Loch AR, Lippa KA, Carlson DL, Chin YP, Traina SJ, Roberts AL. Nucleophilic aliphatic substitution reactions of pyrochlore, alachlor, and metolachlor with bisulfide (HS-) and polysulfides (Sn2-). Environ Sci Technol. 2002;36(19):4065-4073.
16. Burnett JF, Zahler RE. Aromatic Nucleophilic Substitution Reactions. Chem Rev. 1951;49(2):273-412.
17. Lee I, Sung DD. Nucleophilic Aliphatic Substitution. In: Organic Reaction Mechanisms· 2004: An Annual Survey Covering the Literature Dated January to December 2004. 2008:249-283.
18. Moloney JG, Moloney MG. Nucleophilic Aliphatic Substitution. In: Organic Reaction Mechanisms· 2017: An annual survey covering the literature dated January to December 2017. 2020:317-341.
19. Lanke V, Marek I. Nucleophilic substitution at quaternary carbon stereo enters. J Am Chem Soc. 2020;142(12):5543-5548.
20. Jasch H, Hofling SB, Heinrich MR. Nucleophilic substitutions and radical reactions of J Org Chem. 2012;77(3):1520-1532.
21. Castro EA, Ugarte D, Rojas MF, Pavez P, Santos JG. Nucleophilic substitution reactions of diethyl 4-nitrophenyl phosphate trimester: Kinetics and mechanism. Int J Chem Kinet. 2011;43(12):708-714.
22. Beleskey IP, Drozd VN. A New Mechanism of Nucleophilic Substitution. Russ Chem Rev. 1979;48(5):431.
23. Park KH, Kyong JB, Kevil DN. Nucleophilic substitution reactions of p-nitro benzyl chloroformate. Bull Korean Chem Soc. 2000;21(12):1267-1270.
24. Brutschy B, Eggert J, Janes C, Baumgarten H. Nucleophilic substitution reactions in molecular clusters following photoionization. J Phys Chem. 1991;95(13):5041-5050.
25. Moloney JG, Moloney MG. Nucleophilic Aliphatic Substitution 2018. In: Organic Reaction Mechanisms 2018: An annual survey covering the literature dated January to December 2018. 2021:247-276.
26. Hamlin TA, Swart M, Bickelhaupt FM. Nucleophilic substitution (SN2): dependence on nucleophile, leaving group, central atom, substituents, and solvent. Chem Phys Chem. 2018;19(11):1315-1330.