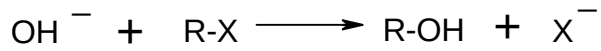
SUBSTITUTION AND ELIMINATION REACTIONS

Nucleophilic Substitution at sp^3 Carbon

Substitution is the replacement of one group by another. The conversion of an alkyl halide into an alcohol is one of the most widely studied substitution reactions.



OH^- is called nucleophile and X^- is called leaving group. A nucleophile is a reagent that brings an electron pair. Kinetic measurements on the reactions of alkyl halides with a number of different nucleophile show two extreme types. In the one type,

$$\text{Rate} = k_1[\text{R-X}] \qquad (1)$$

And in the second type $\text{Rate} = k_2[\text{R-X}][\text{Nu:}]$ (2)

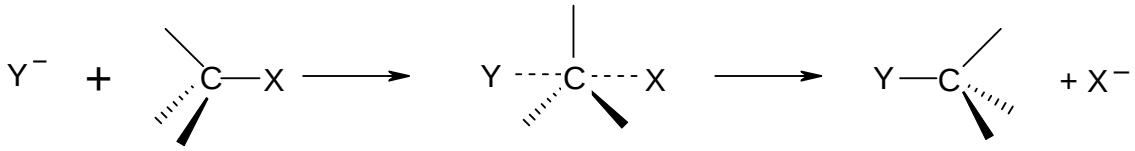
In some cases the rate equations are found to be mixed or are complicated due to other reasons.

Mechanisms

The most common mechanisms of substitution reactions are S_N1 and S_N2 mechanisms. S_N1 mechanism follows rate equation (1), i.e. first order kinetics while S_N2 mechanism follows rate equation (2), i.e. second order kinetics.

The S_N2 Mechanism

S_N2 stands for *substitution nucleophilic bimolecular.* In this mechanism the nucleophile approaches the substrate from a position 180º away from the leaving group (backside attack). The reaction is a one step process with no intermediate.

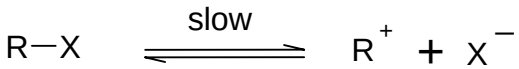


The C-Y bond is formed as the C-X bond is broken. The energy required to break the C-X bond is supplied by the simultaneous formation of the C-Y bond. During the formation of the transition state the hybridization of the carbon atom changes from sp^3 to sp^2 with an approximately perpendicular p-orbital. One lobe of the p-orbital overlaps with the nucleophile and the other lobe overlaps with the leaving group. Because of this, a front side S_N2 mechanism is not possible. During the transition state the carbon atom and the three non reacting substituents are approximately coplanar. Since both the substrate and the nucleophile are involved in the rate determining step, the mechanism follows a second order kinetics. If the solvent (i.e. if the nucleophile is present in large excess) acts as nucleophile, the mechanism will be bimolecular, but the kinetics will be first order (i.e. rate depends on the concentration of substrate only, a pseudo first order kinetics).

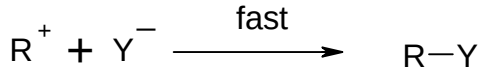
The S_N1 Mechanism

S_N1 stands for *substitution nucleophilic unimolecular*. S_N1 mechanism consists of two steps.

Step 1



Step 2

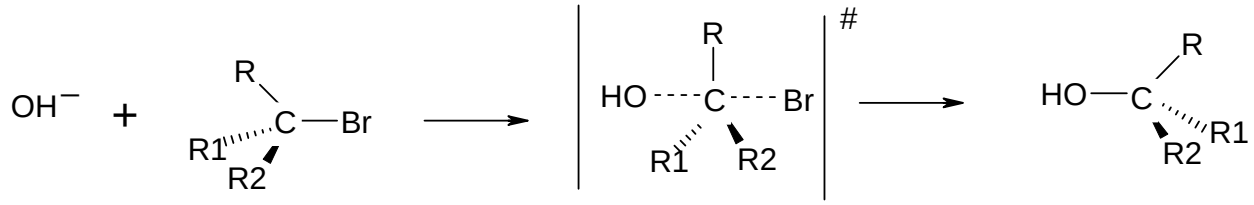


The first step is the slow ionization of the substrate and is the rate determining step. The second step is a rapid reaction between the intermediate carbocation and the nucleophile. The ionization is always assisted by solvent. The energy necessary to break the bond is largely recovered by solvation of R^+ and X^-. In this mechanism the slow step involves only the concentration of substrate. Even though solvent is required to assist ionization, it does not enter the rate expression. Therefore during S_N1 mechanism first order kinetics is followed.

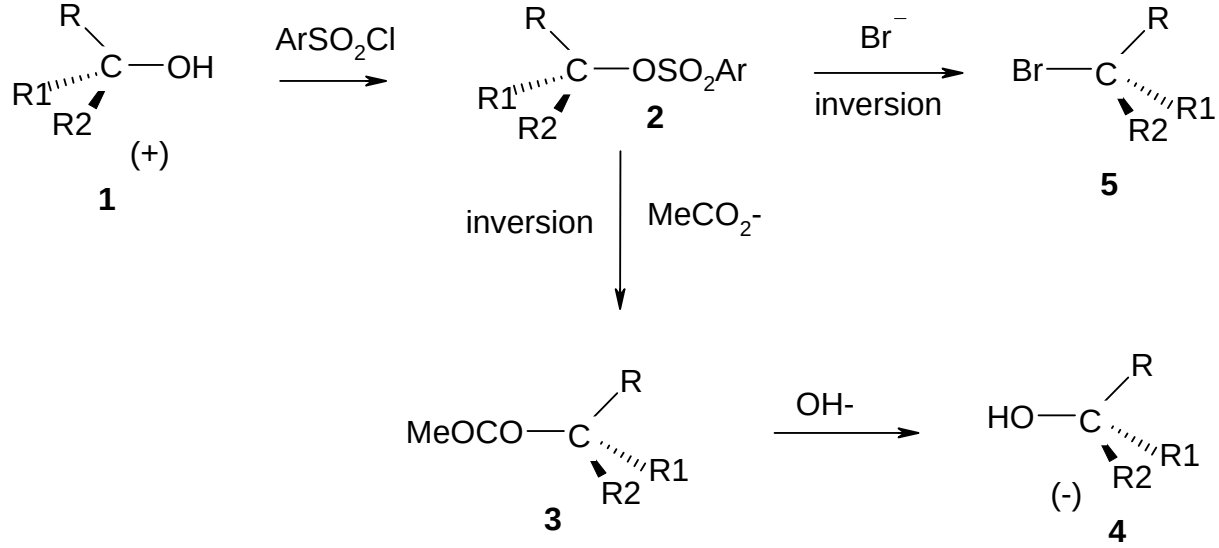
Stereochemical Aspects of Substitution Reactions

S_N2 Mechanism: Inversion of Configuration

S_N2 Mechanism is accompanied by inversion of configuration. Consider the hydrolysis of an optically active halide,



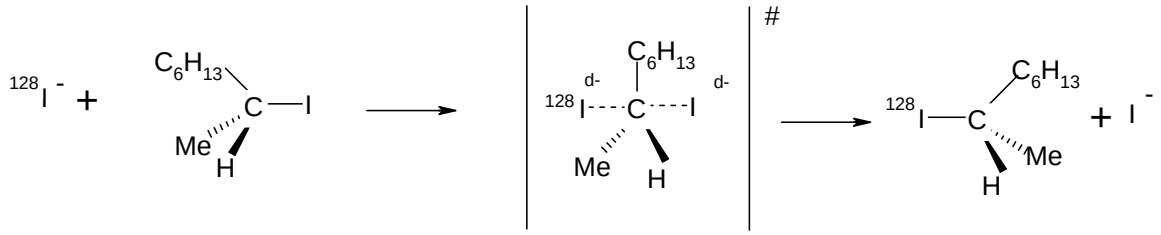
Here inversion of configuration has taken place at the chiral centre. Since the starting material and the product are different, we cannot tell whether inversion of configuration has taken place just by measuring optical rotation. Compounds, other than mirror images, which have opposite configuration do not necessarily exhibit opposite directions of optical rotation. There are methods to determine the relative configuaration. For example consider the following reactions of an optically active alcohol,



Where R = $PhCH_2$, R1 = Me, R2 = H and Ar = *p*-MeC_6H_4 (*p*-tolyl)

The tosylate (**2**) has the same configuration as the alcohol (**1**), because the C-O bond is not broken during this step. The conversion of **2** to **3** is an S_N2 reaction, $MeCO_2^-$ displaces $ArSO_3^-$. Therefore the conversion of **2** to **3** involves inversion of configuration. During the hydrolysis of the acetate, the C-O bond is not broken. Therefore **4** has the same configuration as **3**. In fact **4** is found to be the mirror image of **1**. This result proves that inversion of configuration has taken place during the conversion of **2** to **3** or in other words the results prove that S_N2 mechanism takes place with inversion of configuration.

The occurrence of inversion of configuration during S_N2 mechanism is established by the reaction between optically active (+)2-iodooctane and radio active iodide ions.

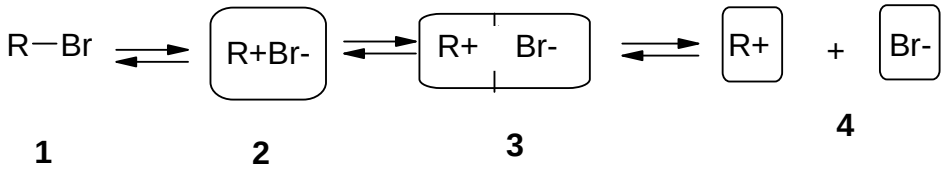


The reaction was minitored by observing the distribution of ^{128}I between sodium iodide and 2-iodooctane and the rate of the reaction was calculated. Also the reaction was monitored polarimetrically and the rate of racemisation was determined. Rate of reaction is equal to rate of inversion. Rate of inversion is half the rate of racemisation because one inversion will gives rise to a (-)-isomer which will pair off with a molecule of the (+)-isomer. Thus the rate of reaction was obtained polarimetrically. The two rates were found to be identical within the experimental errors. This result also shows that S_N2 reactions are attended by inversion of configuration.

S_N1 Mechanism: Racemisation

S_N1 mechanism involves a planar carbocation intermediate. Since the carbocation is planar attack of the nucleophile can take place from either side with equal probability. This if the starting material is optically active, S_N1 mechanism will lead to racemisation, i.e. an optically inactive (±) product.

But in practice S_N1 mechanism is always accompanied by some degree of inversion. The relative proportions of racemisation and inversion were found to depend on (i) the stability of carbication and (b) the solvent. The more stable the carbocation, the greater is the proportion of racemisation. The more nucleophilic the solvent, the greater is the proportion of inversion. The S_N1 ionisation follows sequence,



Here **2** is an intimate ion pair, in which there are no solvent molecules between the ions. **3** is a solvent separated ion pair and **4** is a completely separated (completely solvated) pair of ions. If the nucleophile (even if it is the solvent) attacks the intimate ion pair, inversion will take place because the front side is blocked from attack by Br^-. The attack on **3** and **4** will lead to racemisation. If the carbocation is stable, its lifetime will be more and hence the proportion of racemisation will be more. The solvolysis of (+)C_6H_5MeCl, leads to 98% racemisation while (+)$C_6H_{13}CHMeCl$, leads only to 34% racemisation. (+)C_6H_5MeCl can form stable benzyl type carbocation while (+)$C_6H_{13}CHMeCl$ forms a less stable cabocation.

If the solvent is more nucleophilic, then the proportion of inversion will be more. For example, solvolysis of (+)C_6H_5MeCl in 80% acetone/ 20% water leads to 98% racemisation, but in water alone, only 80% racemisation is observed. This is because water is more nucleophilic than acetone.

Effect of Solvent

Increase in polarity of the solvent (i.e. increase in dielectric constant, ε) increases the rate of S_N1 reaction. The rate of solvolysis of Me_3CBr is 3×10^4 times faster in 50% aqueous ethanol than in

ethanol alone. This occurs because in the S_N1 reaction charge is developed and concentrated in the transition state compared with the starting material.

$$R\text{-}X \rightarrow [R^{\delta+}\cdots\cdots X^{\delta-}]^{\#} \rightarrow R^{+} + X^{-}$$

The energy required for the ionization is decreased with increase in dielectric constant (ε). Also the ion pair is stabilized by solvation in a solvent with high polarity. The importance of solvation in S_N1 reaction is borne out by the fact that S_N1 reactions are extremely uncommon in the gas phase.

In S_N2 reactions solvent polarity has a much less marked effect. The reaction rate slightly decreases with increase in polarity of the solvent. This is because in S_N2 reactions new charge is not developed and existing charge is dispersed in the transition state compared with the starting material.

$$Nu^{-} + R\text{-}X \rightarrow [Nu^{\delta-}\cdots\cdots R\cdots\cdots X^{\delta-}]^{\#} \rightarrow Nu\text{-}R + X^{-}$$

The solvation of the transition state is less effective than that of the nucleophile. Thus there will be a slight decrease in rate. But if the solvent is changed from a polar hydroxylic one to a polar non-hydroxylic solvent, the rate of S_N2 reaction will be greatly enhanced. The rate of reaction of MeI with N_3^- at 0ºC is 4.5×10^4 times greater in N,N-dimethyl formamide (DMF) (ε = 37) than that in methanol (ε = 33). In methanol the nucleophile (N_3^-) is highly solvated through hydrogen bonding. In DMF, the nucleophile is very less strongly solvated and it is not by hydrogen bonding. Unsolvated N_3^- ion is a much powerful nucleophile than the solvated one. Therefore the reaction rate is much higher in DMF than that in methanol. Also the rate of S_N2 reaction is about 10^9 times higher in dimethyl sulphoxide (DMSO) than in methanol due to the same reason.

A change in solvent can change the mechanism of the reaction from S_N1 to S_N2 or vice versa. Increase in solvent polarity and ion solvating ability may change the mechanism from S_N2 to S_N1. Change of solvent from hydroxylic to polar, non-protic solvents often changes the reaction mode from S_N1 to S_N2.

Effect of Substrate Structure

Consider following compounds

CH_3-Cl	$MeCH_2$-Cl	Me_2CH-Cl	Me_3C-Cl
1	**2**	**3**	**4**

Among these **1** and **4** undergo hydrolysis readily. **2** and **3** are more resistant towards hydrolysis compared to **1** and **4**. Bromomethane and bromoethane undergo S_N2 reaction, 2-bromopropane undergoes a mixed S_N1 and S_N2 mechanism (the relative proportion of the two mechanisms depends on the concentration of the nucleophile, OH^-) and 2-bromo-2-methylpropane follows S_N1 mechanism.

Steric factors play an important role in S_N2 reactions. In S_N2 transition state; there are five groups around the central carbon atom. Thus there is an increase in crowding during the formation of the transition state. The crowding in the transition state will increase with increase in the size of the substituents. A more crowded transition state is less stable and its formation will be very slow. The relative rate of S_N2 reaction in the above series can be given as,

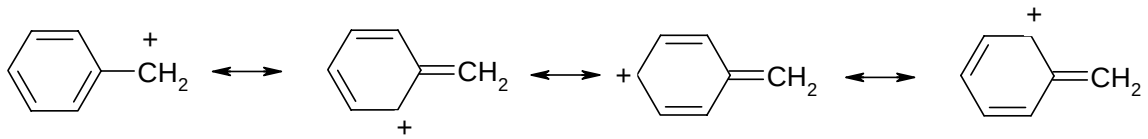
Relative	CH_3-Cl	$MeCH_2$-Cl	Me_2CH-Cl	Me_3C-Cl
S_N2 rate	1	2.7×10^{-2}	4.9×10^{-4}	2.2×10^{-5}

For S_N1 reactions the rate of reaction depends on the stability of carbo cation. Stability increases the rate of S_N1 reactions. Stability of carbo cation depends on inductive effects of the substituents, hyperconjugation and steric factors. Substituents with +I effect increase the stability of carbo cations. Hyper conjugation also increases the stability of carbo cations. In the above series the

numbers of hyperconjugative hydrogen atoms in the intermediate carbo cations are 0, 3, 6 and 9 respectively. The stability of carbo cations will be in the order, tertiary>secondary>primary>methyl. Thus in the above series the rate of S_N1 reaction will be in the order, **4**>**3**>**2**>**1**. If steric factors are considered, there will be a relief in crowding when the carbo cation is formed. The relief in crowding will be more pronounced in the case of the reactant with bulky groups. Thus, steric factors also favor the formation of a tertiary carbo cation compared to secondary and primary carbo cations.

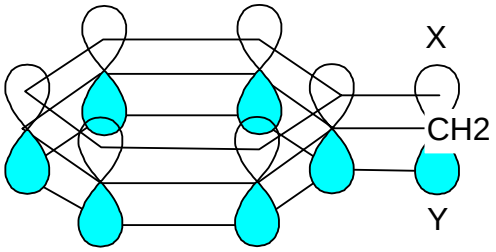
Thus the rate of S_N2 reaction decreases in the above order of alkyl halides while the rate of S_N1 reaction increases in the above order.

Hydrolysis of benzyl chloride in 50% aqueous acetone follows a mixed S_N1 and SN2 mechanism. But in water only S_N1 mechanism is observed. Also the rate of reaction of benzyl chloride is much higher compared to methyl chloride. This is due to the resonance stabilization of the intermediate benzylic carbo cation.



Diphenylchloromethane ($(C_6H_5)_2CH$-Cl) during hydrolysis undergoes only S_N1 mechanism with increased rate. Triphenylcholomthane ($(C_6H_5)_3C$-Cl) readily undergoes ionization. In these three examples there is successive increase in resonance stabilization of the carbo cation.

In the case of benzyl chloride the rate of S_N2 reaction is also slightly increased. This is due to the overlap of the *p*-orbital of the carbon atom in the transition state with the π-*p*-orbitals of the carbon atoms in the benzene ring.



In allyl halides also the rate of S_N1 reaction is greatly enhanced due to resonance stabilization of the carbo cation similar to benzyl halides. S_N2 reaction rate is also more compared to alkyl halides due to the overlap of the *p*-orbital of the carbon atom with the π-cloud of allyl group in the transition state. The relative proportion of S_N1 and S_N2 mechanisms depends on the conditions of the reaction.

Vinyl halides (eg: Chloroethene) and halogenobenzenes are very unreactive towards nucleophilic substitution. In these cases the halogen is attached to sp^2 hybridised carbon atom. Due to the greater electro negativity of the sp^2 hybridised carbon, C-X bond is more stable and less easily broken. Also the π-electrons of the double bond inhibit the close approach of the nucleophile. The double bond does not stabilize the S_N2 transition state and the S_N1 carbo cation intermediate.

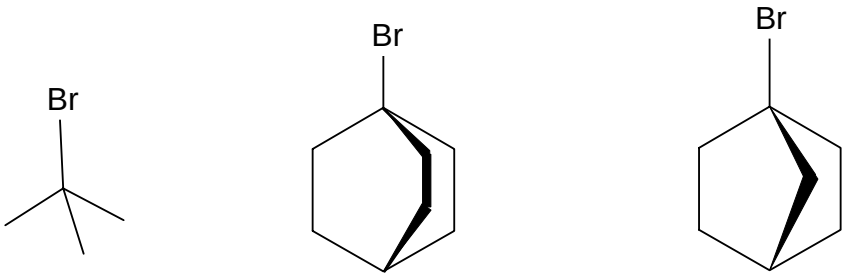
If bulky substituents are present in β-position, then also S_N2 reaction is inhibited by steric factors. The relative rates of S_N2 reaction for a series of compounds with EtO^- in EtOH are given below.

CH_3-CH_2-Br	$MeCH_2$-CH_2-Br	Me_2CH- CH_2-Br	Me_3C- CH_2-Br
(a) 1.0	(b) 2.8×10^{-1}	(c) 3×10^{-2}	(d) 4.2×10^{-6}

The decrease in reaction rate in the above order is due to the increased difficulty of EtO^- to approach from the back side of the carbon containing Br. In (d) (neopentyl bromide) the nucleophile interefere

with methyl groups only. But in (b) and (c) at least in one conformation, the nucleophile can approach along the side of hydrogen atom. This is the reason why the rate of substitution is much lower for (d) compared to (c).

If the leaving group is attached to the bridgehead of a bicyclic system, the the rate of substitution will be very low. Consider the rates of solvolysis of the following compounds in 80% aqueous ethanol at 25ºC.



(i) (ii) (iii)

1 10^{-6} 10^{-14}

Since all are tertiary halides, the rate of S_N2 reaction will be very low. The attack of the nucleophile from the back side of the carbon containing bromine is prevented in (ii) and (iii) because of their cage like structure. Also it is impossible for the bridgehead system to achieve the S_N2 transition state. Thus the rate of S_N2 reaction will be very very low for (ii) and (iii). Also the rate of S_N1 reaction will be very low for (ii) and (iii). It is impossible for (ii) and (iii) to form a planar carbo cation intermediate because of their rigid cage like structure. The carbo cations formed will not be planar and will have very high energy and therefore are formed very slowly. (iii) is more rigid compared to (ii) and therefore the rate of substitution is much lower for (iii) compared to (ii).

Effect of Nucleophile (Entering Group)

The nature of the nucleophile does not alter the rate of S_N1 reaction, because the nucleophile does not take part in the rate determining step. But in the case of S_N2 reaction stronger nucleophiles increase the rate of reaction. Soft bases are good nucleophiles. Soft base is one in which the donor atom is of low electronegativity, high polarisibility and is easy to oxidize. RS^-, I^-, SCN^- etc. are examples. If the attacking atom is the same, then basicity can be correlated with nucleophilicity. Thus basicity and hence nucleophilicity of some oxygen containing nucleophiles follows the order,

$$EtO^- > PhO^- > MeCO_2^- > NO_3^-$$

Nucleophiles with large sizes are found to be stronger. Nucleophilicity follows the order,

$$I^- > Br^- > Cl^- \qquad RS^- > RO^-$$

For large atoms, the hold of nucleus on the peripheral electrons will be less and hence they are readily polarisable. Thus large atoms can initiate binding at large nuclear separations. Also large nucleophiles are less solvated. A less solvated nucleophile is a stronger nucleophile than a more solvated one. Large, highly polarisable and weakly solvated, I^- is a very much stronger nucleophile than small, less polarisable and highly solvated F^-.

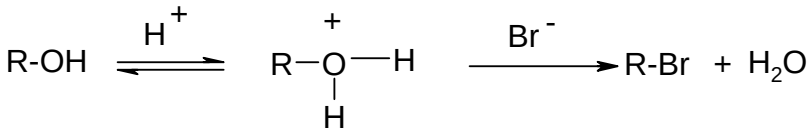
Efect of Leaving Group

Changing the leaving group will alter the rate of both S_N1 and S_N2 reaction. Leaving ability of a group is influenced by the following factors, (a) Strength of R-X bond, (b) polarisability of R-X bond and (c) stability of X^-. For halides the reactivity will be in the order,

R-I > R-Br > R-Cl > R-F

If the basicity of X^- is low it will be a better leaving group. Anions of strong acids such as tosylate (p-$MeC_6H_4SO_3^-$), triflate ($CF_3SO_3^-$), brosylate (p-$BrC_6H_4SO_3^-$) etc. are very good leaving groups. High polarisability makes I^- both a good nucleophile and a good leaving group. I^- is often used as a catalyst to promote slow displacement reactions.

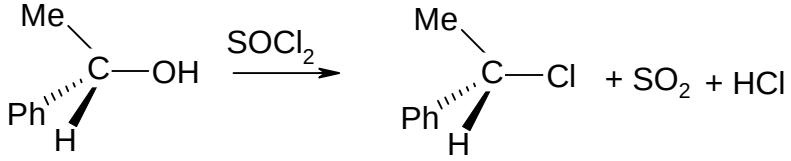
Hard bases are weak leaving groups. Thus groups such as OH^-, OR^-, NH_2^- etc. cannot be displaced normally. Difficult displacements can be accomplished by modification of the leaving group. OH^- cannot be displaced by Br^- normally, but can be displaced if protonated first.



There are two reasons for the occurrence of this reaction, (a) Br^- is now attacking a positively charged species and (b) weakly basic H_2O is a better leaving group than strongly basic OH^-. Similarly ethers can be cleaved using HI.

S_Ni Mechanism: Retention of Configuration

The replacement of OH by Cl by using thionyl chloride, $SOCl_2$, takes place with retention of configuration.

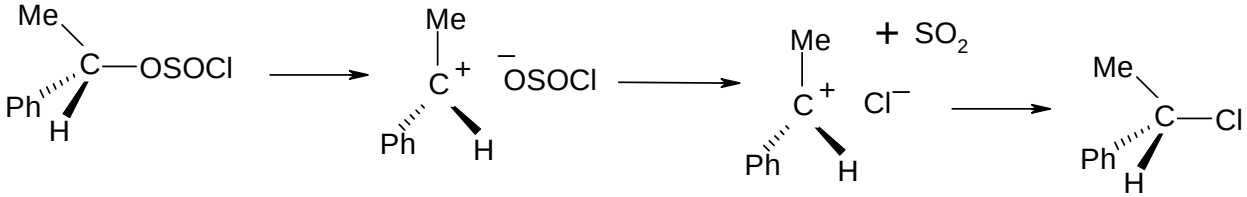


(a) (b)

The reaction follows second order rate equation.

Rate = k[ROH][$SOCl_2$]

The reaction does not proceed through an S_N2 mechanism, otherwise an inversion of configuration would have been observed. The actual intermediate in such reactions is an alkyl chlorosulphite (ROSOCl). During the formation of alkyl chlorosulphite, the R-O bond is not broken and hence proceeds by retention of configuration. The ion pair R^+ $^-$OSOCl is involved in the reaction. Since the ion pair is involved the chlorine atom of the chlorosulphite ion should attack from the front side. Since chlorine atom is part of the chlorosulphite ion it cannot go to the back side of the carbon atom. The mechanism of this reaction is known as S_Ni (*substitution nucleophilic internal*) mechanism.

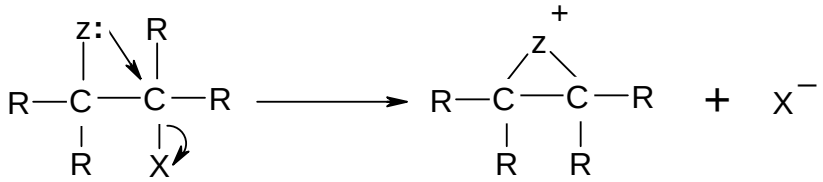


If the chlorination is carried out in the presence of pyridine, the reaction takes place with inversion configuration. This occurs because the HCl liberated during the reaction combines with pyridine to form pyridinium hydrogen chloride ($C_5H_5NH^+Cl^-$). The chloride ion of pyridinium hydrogen chloride is an effective nucleophile which attacks from the backside of the carbon atom in a normal S_N2 mode leading to inversion of configuration.

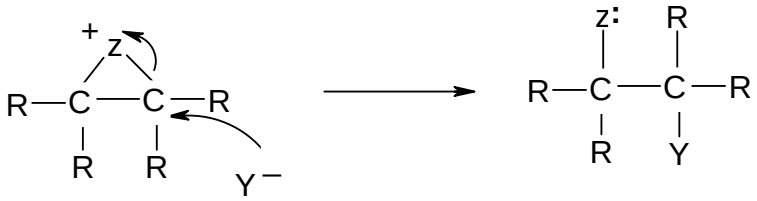
Neighbouring Group Participation (NGP): Retention of Configuration

In the case of certain substrates the rate of substitution reaction is greater than expected and the configuration at the chiral carbon is retained. No racemisation or inversion has been observed in such cases. In these cases there is usually a group with unshared paired of electrons β to the leaving group. The mechanism of such reactions is called *neighbouring group participation.* Neighbouring group mechanism consists of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration. In the first step of the reaction neighbouring group acts as a nucleophile, pushing out the leaving group. In the second step the external nucleophile displaces the neighbouring group by back side attack and the neighbouring group regains its initial position.

Step 1

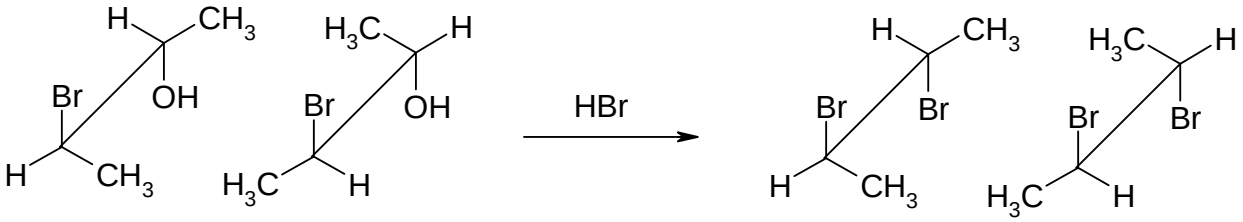


Step 2



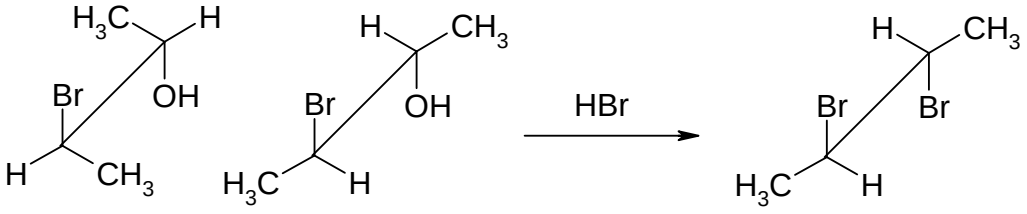
Since the rate of reaction is much faster than the direct reaction between the substrate and Y^-, the neighbouring group Z is said to be lending anchimeric assistance. Neighbouring group mechanism follows a first order rate equation, since Y^- does not take part in the rate determining step. The attack of the neighbouring group is faster than that of the external nucleophile because the neighbouring group is more available. Participation of a neighbouring group can be reduced or eliminated if a strong outside nucleophile is present. In such cases the reaction proceeds through a normal S_N2 pathway. Neighbouring group participation can also be reduced if the stability of the carbocation is increased and the reaction will follow an S_N1 pathway. Some of the examples of neighbouring group participation are described below.

1. It was observed that the threo dl-pair of 3-bromo-2-butanol when treated with HBr gave dl-2,3-dibromobutane while the erythro pair gave the meso isomer.



threo dl pair

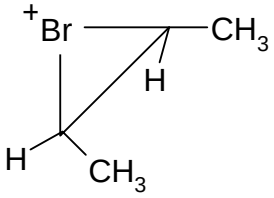
dl pair



erythro dl pair

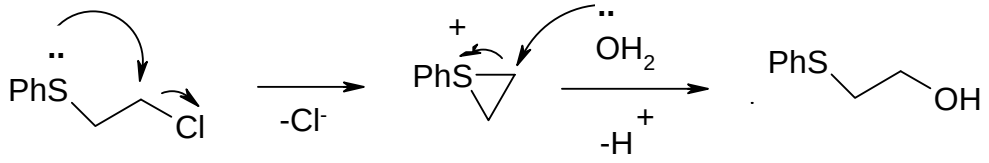
meso

The results show that retention of configuration has taken place. Even if the reaction is carried out with any of the threo isomer, the same dl pair of 2,3-dibromobutane is obtained. This is because the intermediate present is symmetrical, and hence the attack of nucleophile can take place at any of the two carbons leading to d and l isomers.

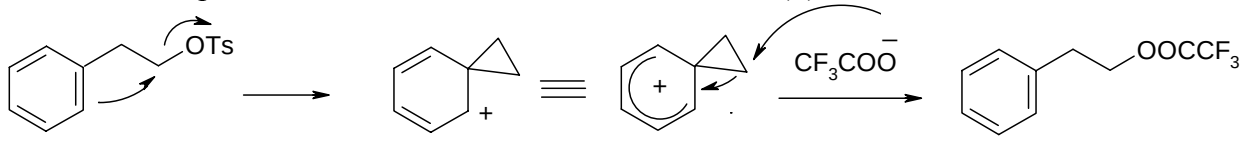


Bromonium ion intermediate

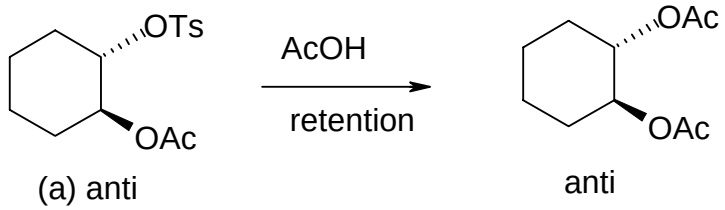
2. PhS-CH_2-CH_2-Cl (a) reacts with water 600 times faster than CH_3-CH_2-CH_2-Cl (b). This is due to the neighboring group participation of sulphur atom in (a). Neighboring group participation is not possible in (b).



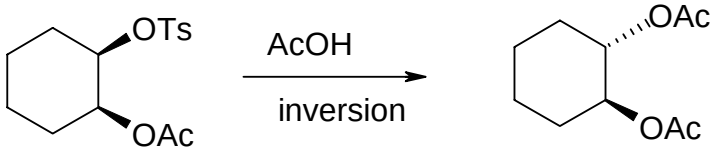
(3) Ph-CH_2-CH_2-OTs (i) reacts with CF_3COOH 3000 times faster than CH_3-CH_2-OTs (ii). (i) reacts much faster than (ii) because of the neighboring group participation of the phenyl group. The reaction involves a phenonium ion intermediate. The reaction of (ii) is a normal substitution reaction.



(4) Consider the following two reactions,

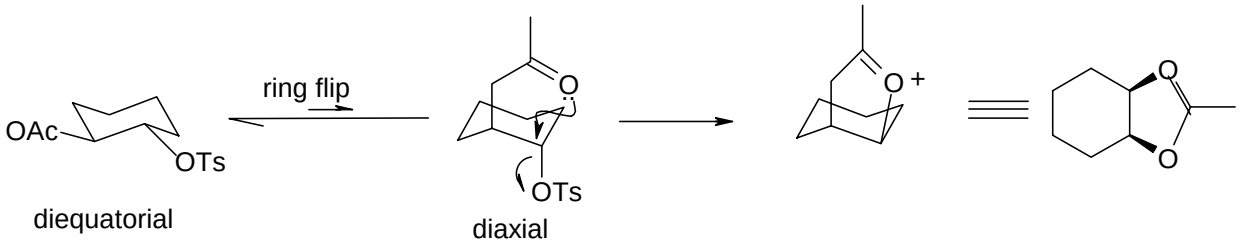


(a) anti anti

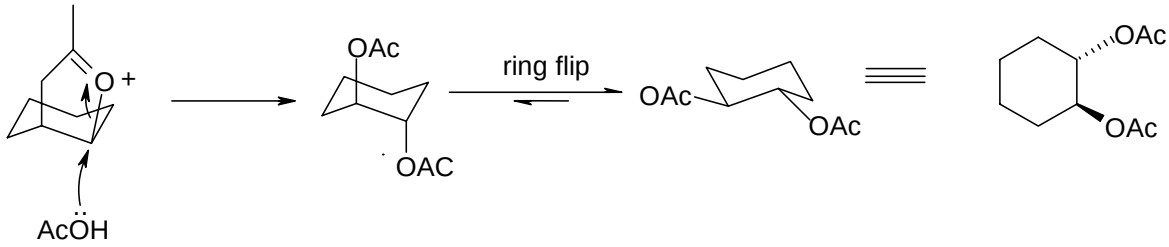


(b) syn anti

In these cases (a), the anti isomer reacts 670 times faster than (b) with acetic acid. Also both isomers give the same product. The reaction of the anti isomer takes place with retention of configuration and the reaction of syn isomer takes place with inversion of configuration. Now consider the reaction of the anti isomer. In the anti isomer both substituents are equatorial.

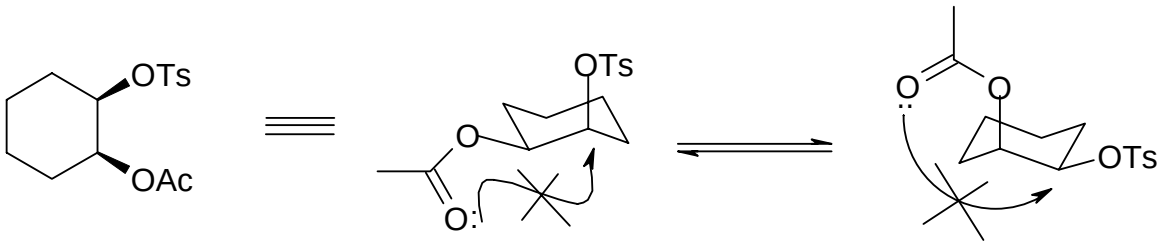


diequatorial diaxial

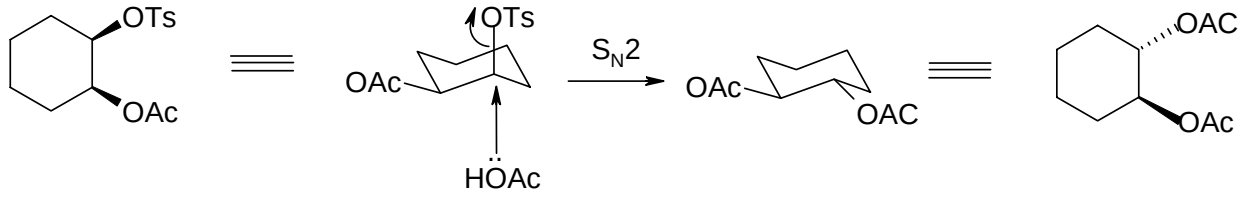


In this case ring flip gives the diaxial isomer. In the diaxial isomer, the acetate group is properly placed for neighbouring group participation. The first S_N2 reaction (attack of oxygen atom of acetyl group) gives a syn product, which is attacked by acetic acid by a second S_N2 reaction giving anti product.

In the syn diastereomer (b), the acetyl group is not properly placed for neighbouring group participation. The reaction is a normal S_N2 reaction (only one S_N2 reaction) leading to inversion.

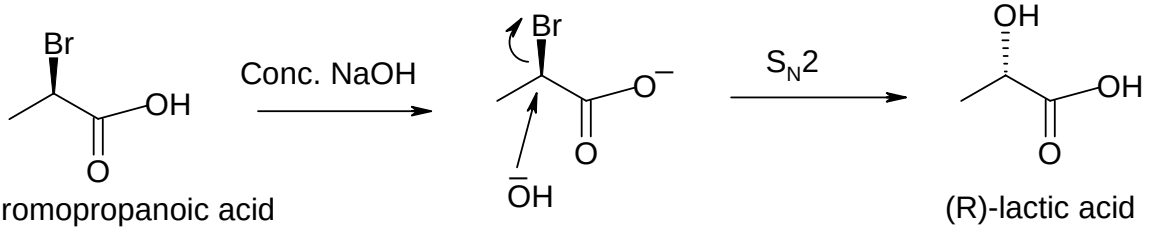


NGP is impossible in both conformations



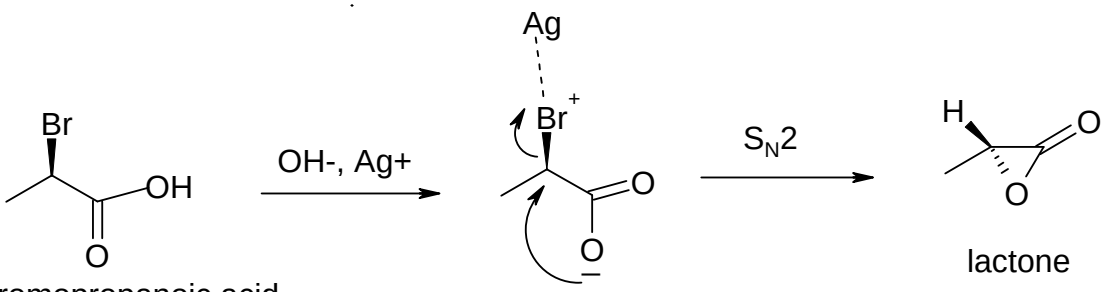
(5) The reaction between (S)-2-bromopropanoic acid and concentrated NaOH gives (R)-Lactic acid with inversion of configuration. But if the reaction is carried out using Ag_2O and a low concentration of NaOH, (S)-lactic acid is obtained, i.e. with retention of configuration. When the reaction is carried out with conc. NaOH, it proceeds through a normal S_N2 pathway because the nucleophile (OH^-) and the leaving group (Br^-) both are good. But in the second case, the concentration of OH^- is low and hence water acts as nucleophile. Also the silver ions of Ag_2O get attached to bromine atoms and the leaving group is AgBr instead of Br^-. AgBr is an even better leaving group compared to Br^-. So in the second case, the leaving group is very good but the nucleophile is not so good. These conditions favour an S_N1 reaction. But in this case S_N1 reaction is very difficult, because the cation formed will be unstable since it is adjacent to a carbonyl group. Here the carboxylate participates in the departure of Br^- forming a lactone. The lactone is attacked by water to form the final product and two successive S_N2 reactions (two successive inversions) lead to retention of configuration.

(a) <u>Reaction with Conc. NaOH</u>

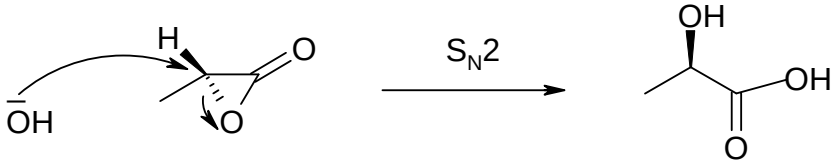


(S)-2-bromopropanoic acid (R)-lactic acid

(b) <u>Reaction with dilute NaOH and Ag_2O</u>



(S)-2-bromopropanoic acid

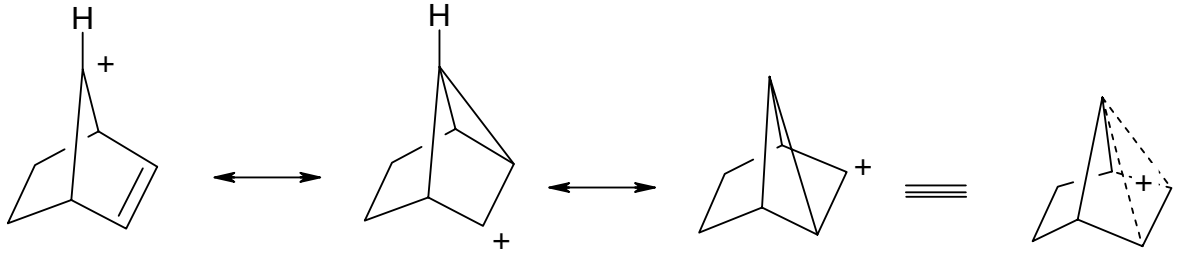


(S)-lactic acid

Two successive inversions lead to retention of configuration

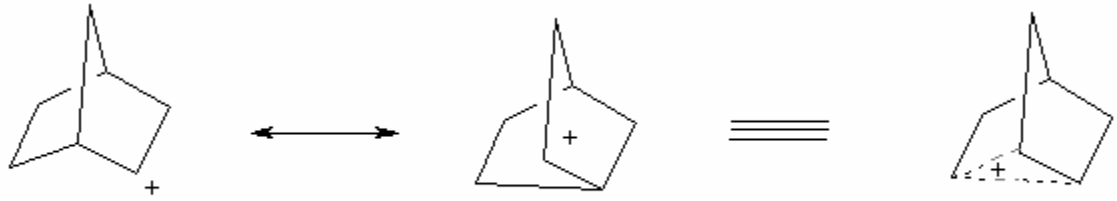
Non-Classical Carbocations

A classical carbocation is one in which the positive charge is localized on one carbon atom or delocalized through resonance involving an unshared pair of electrons or by a double bond or triple bond in allylic position. In a non-classical carbocation the positive charge is delocalised by a double bond or triple bond which is not in allylic position or by a single bond. 7-norbornenyl cation, norbornyl cation, cyclopropylmethyl cation etc. are examples.

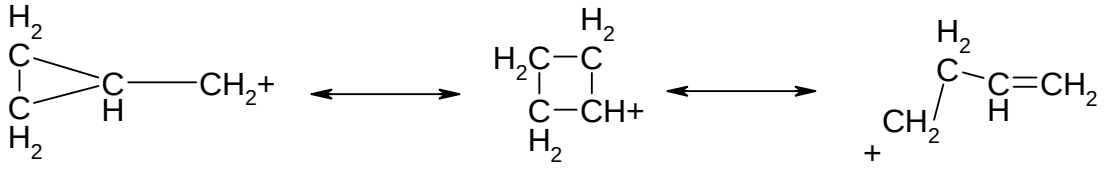


7-Norbornenyl cation

7-Norbornenyl cation is also called a homoallylic carbocation, because in this cation there is a carbon atom between the positively charged carbon and the double bond.



Norbornyl cation:- Positive charge is delocalised by single bond



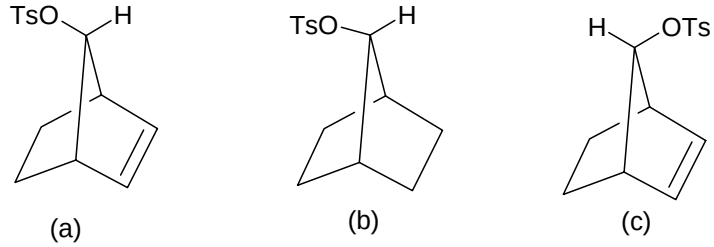
Cyclopropylmethyl cation

Neighbouring Group Participation by π and σ Bonds

There are several examples where carbon-carbon double bonds or single bonds participate in the departure of the leaving group through the formation of a carbocation. Many of these reactions involve the formation of a non-classical carbocation. Some examples are described below.

(1) C=C as a neighbouring group

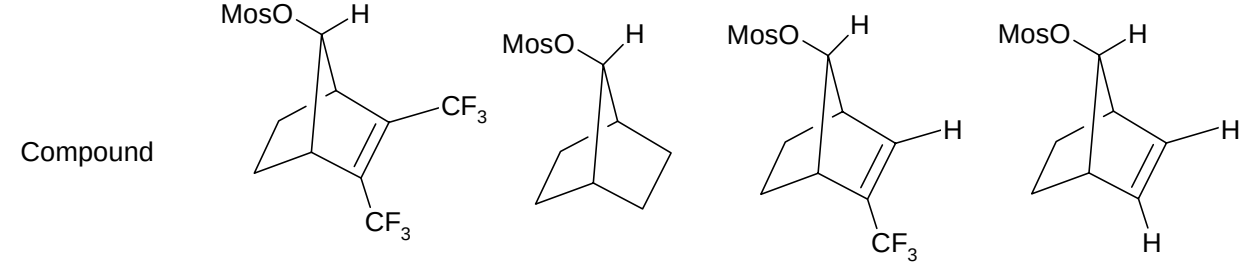
The acetolysis of (a) is 10^{11} times faster than that of (b). Also the acetolysis of (c) is much slower than that of (a).



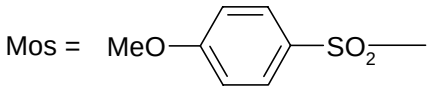
(a) (b) (c)

The acetolysis of (a) involves the formation of a non-classical carbocation (7-norbornenyl cation) by the participation of the double bond. In (b) neighbouring group participation is not possible. In (c) the double bond is not properly placed to participate in the removal of the leaving group.

Strong electron withdrawing groups attached to the double bond lower the ability of the double bond to act as a neighbouring group. In the following example a CF_3 group attached to the double bond decreases the solvolysis rate by a factor of 10^6. A second CF_3 group has an equally strong effect. In fact the solvolysis rate of the substrate with two CF_3 groups is lower than that of the saturated substrate. Two CF_3 groups completely removes the ability of the C=C bond to act as a neighbouring group by electron withdrawal.

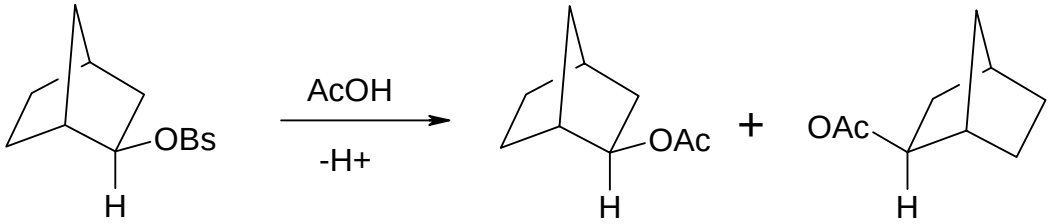


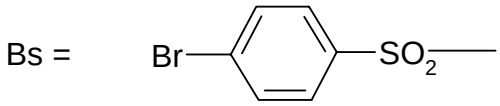
Compound				
Relative rate of solvolysis	1	17	1.5 X 10^6	1.4 X 10^{12}



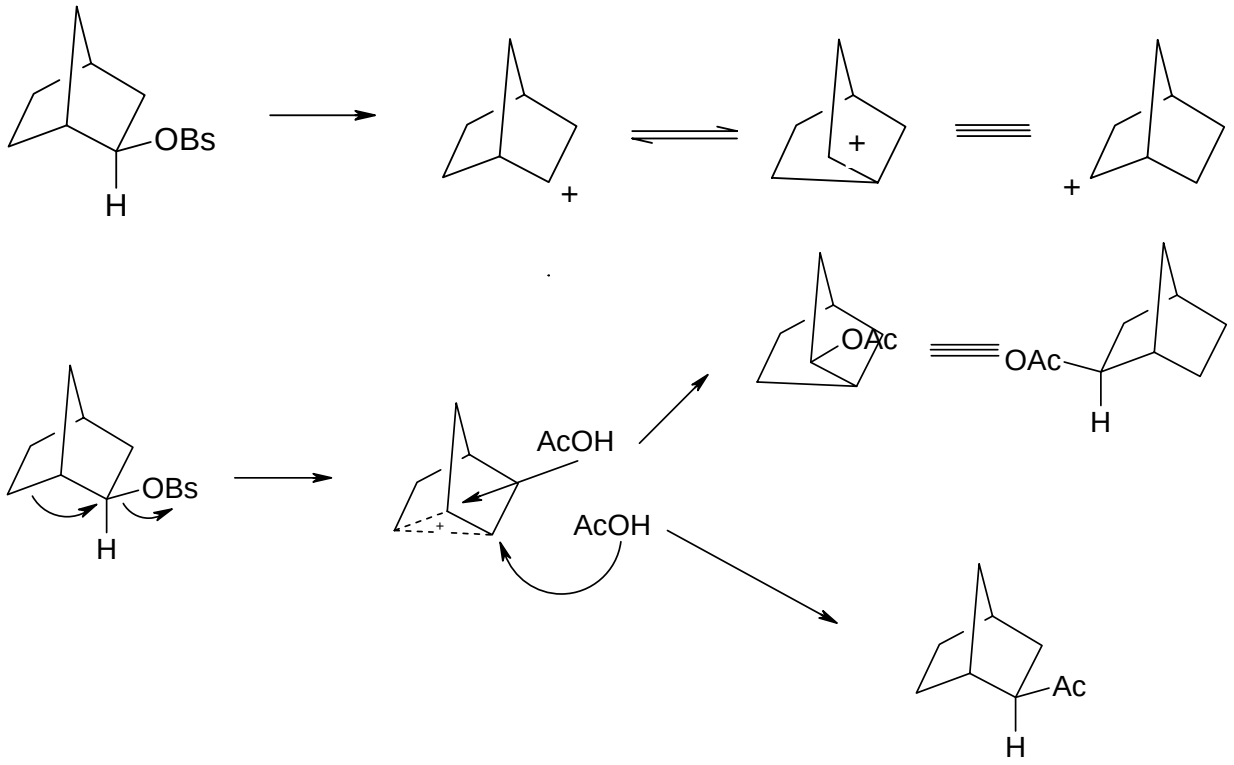
Carbon-Carbon Single Bond as a Neighbouring Group

(1) Exo-2-norbornyl brosylate reacts with acetic acid 350 times faster than the endo-isomer. Also optically active exo-2-norbornyl brosylate gave a racemic mixture of two exo acetates, no endo product was isolated.

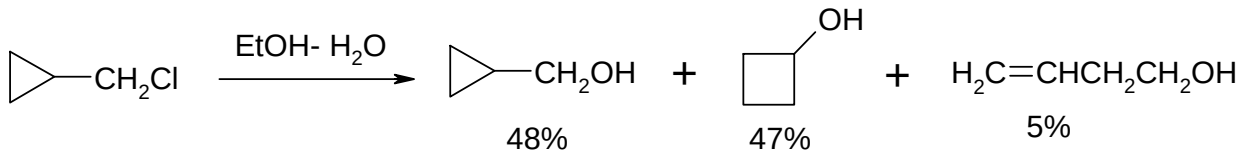


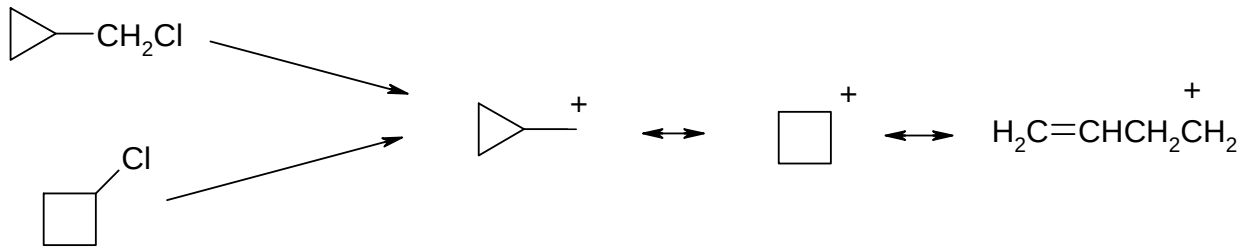


This reaction of the exo isomer involves the neighbouring group participation of C-C single bond and subsequent formation of a non-classical carbocation. In the endo isomer the single bond is not properly placed to effect the removal of the leaving group.



(2) Cyclopropylmethyl substrates undergo substitution reactions very rapidly. The product is always a mixture which contains cyclopropylmethyl, cyclobutyl and homoallylic compounds. Also cyclobutyl substrates give the same mixture of products and undergo substitution reactions very rapidly. Both substrates form the same intermediate non-classical carbocation.





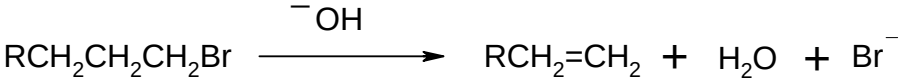
There are evidences for the neighbouring group participation of methyl group and even hydrogen in nucleophilic substitution reactions.

ELIMINATION REACTIONS

Elimination reactions involve the removal of two atoms or groups from a molecule and they are not replaced by other atoms or groups. The most common type of elimination reaction is 1,2-elimination (αβ-elimination or simply β-elimination), in which two groups are removed from adjacent atoms. In most of the cases one group is a proton and the other one is a nucleophile. 1,2-elimination results in the formation of a multiple bond.

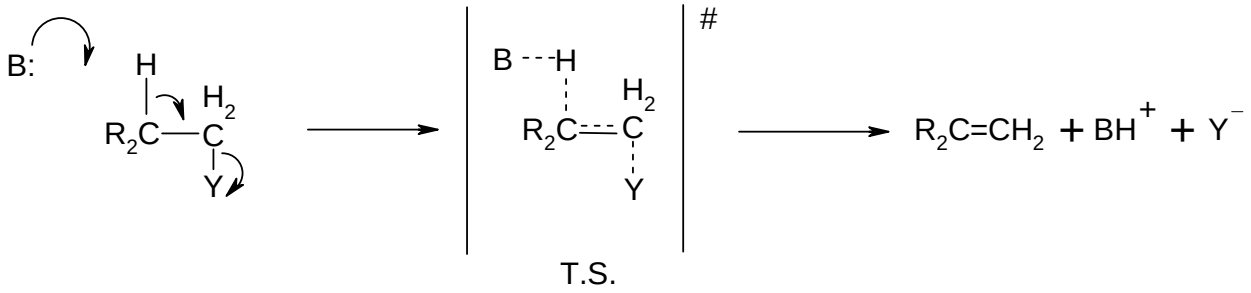
1,2-Elimination

In 1,2-eliminations, the carbon atom from which nucleophile is removed is the 1-(α-) carbon and the carbon atom from which proton is removed is the 2-(β-) carbon. The most common elimination reaction is the base induced removal of hydrogen halide from alkyl halides.



There are three simple mechanisms associated with 1,2-eliminations.

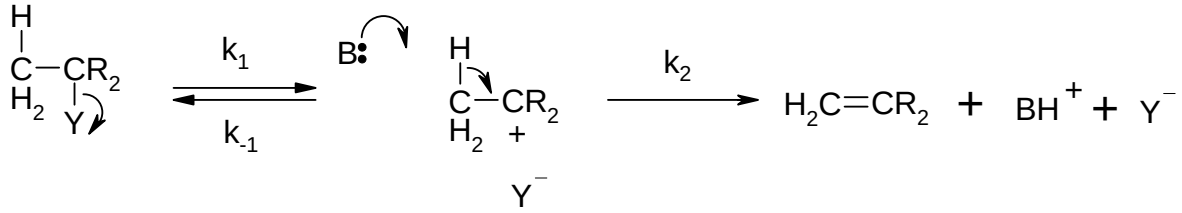
(i) <u>E2 Mechanism</u>: - This is a concerted (one step) process. The breaking of the C-H and C-Y bond takes place at the same time and proceeds through a transition state.



E2 (Elimination bimolecular) mechanism follows second order kinetics. The rate of the reaction depends on the concentration of the base and the substrate.

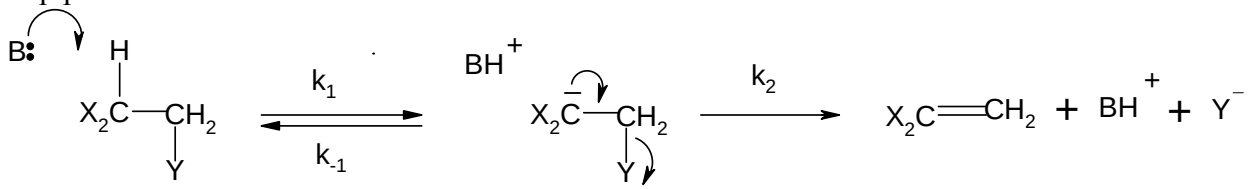
Rate = k[substrate][base]

E1 Mechanism: - If the C-Y bond is broken first during elimination, a carbocation intermediate will be formed. This is a two step process and follows first order kinetics.



In E1 (Elimination Unimolecular) mechanism, formation of the carbocation is the rate limiting step, i.e. $k_2 >> k_{-1}$. Rate depends only on the concentration of the substrate.

E1cB (*Elimination*, *unimolecular*, *conjugate base*) Mechanism: - In this mechanism, first step is the abstraction of proton by base leading to the formation of a carbanion. This is a two step process and follows second order kinetics.

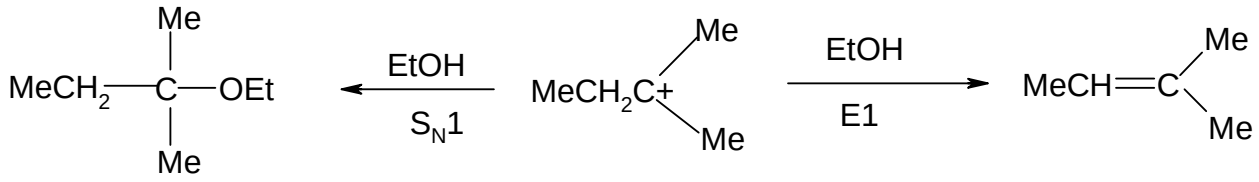


Rate of E1cB depends on the concentration of the substrate and the base. Among the three mechanisms E2 is the most common and E1cB is the least common.

E1 Mechanism

Consider the E1 elimination reaction of the bromide, $MeCH_2CMe_2Br$ in EtOH. The reaction follows a first order kinetics. First step is the formation of carbocation, which is slow and rate limiting. In the second step, a proton is removed from the carbocation by a base. In this case, the solvent acts as the base. Thus the E1 rate equation is indistinguishable from E2 rate equation. If the solvent itself is the base, then E2 rate equation also will follow a pseudo first order kinetics. But these two mechanisms can be distinguished by adding a small amount of the conjugate base of the solvent. E1 reactions are unaffected by the concentration and nature of the base. Increase in concentration of the base increases the rate of E2 mechanism. Also E2 is faster with strong bases than with weak bases.

Since a carbocation intermediate is involved, there will be always competition between S_N1 (substitution) and E1 (elimination). In a solvent with high dielectric constant, the ratio of substitution to elimination products is independent of the leaving group. For example, in 80% aq. ethanol t-butyl iodide solvolyses about 100 times faster than t-butyl chloride, but the ratio of elimination to substitution products is the same for the chloride and the iodide. This shows that, S_N1 and E1 have the same rate determining step, i.e. they proceed through the same carbocation intermediate. Formation of carbocation is followed by either addition of a nucleophile (S_N1) or removal of a proton (E1). Consider the reaction of $MeCH_2CMe_2Br$ in EtOH. First step is the formation of carbocation, followed either by addition of a solvent molecule (S_N1) or removal of a proton (E1).

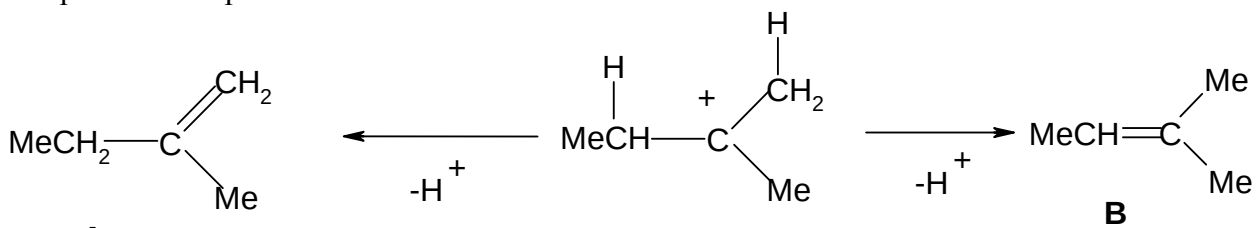


In solvents of low ionizing power, the ratio of substitution to elimination depends on the nature of the leaving group. This is because in such solvents formation of ion-pairs will take place and the leaving group itself acts as the base.

Factors favouring S_N1, also favours E1. An alkyl group in the substrate that can give rise to a relatively stable carbocation and a good ionizing, ion solvating medium promote E1. The reactivity of alkyl halides under E1 conditions will be the order,

tertiary > secondary > primary

Branching at β-carbon atom also favours E1 mechanism. Branching at β-carbon leads to the formation of more heavily substituted and hence more thermodynamically stable alkene during E1 elimination. If there is the possibility of formation of two different alkenes, the more substituted alkene will be the predominant product. During E1 elimination of MeCH2CMe2Br, two products are possible.



A

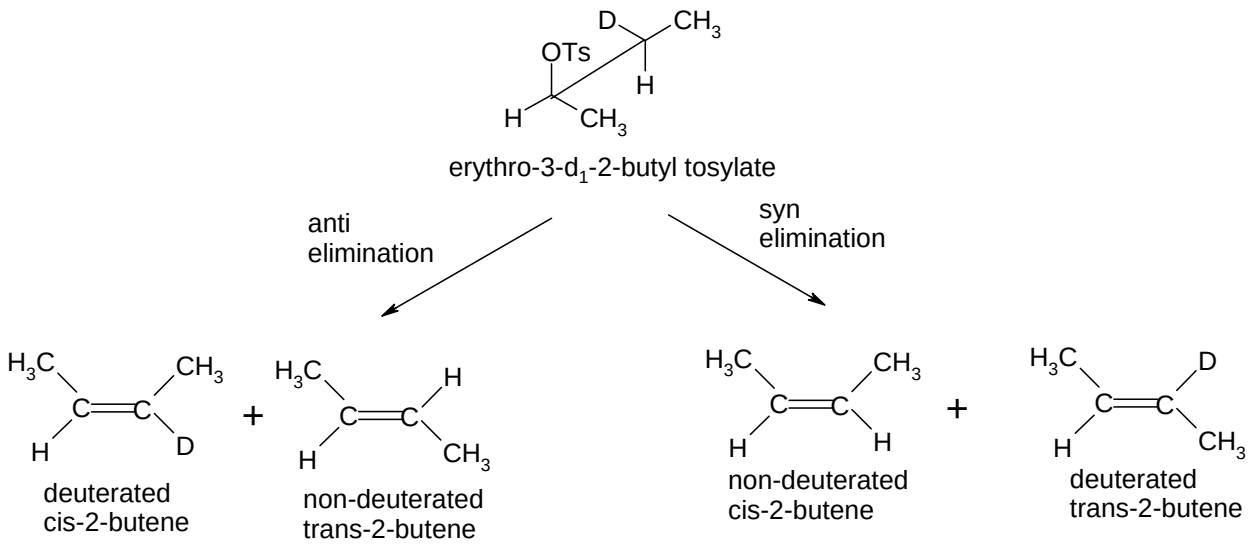
18%

B

82%

In this reaction B is the major product. E1 may lead to unusual products due to the rearrangement of the initial carbocation formed.

In E1 mechanism, stereo selectivity of elimination depends on the ionizing power of the solvent. In highly polar solvents, the attack of the base (usually the solvent) can take place from either side of the carbocation and lead to a mixture of anti and syn elimination products. But in solvents with low ionizing power, ion pairs are involved and the leaving group will act as the base (the leaving group is the better base compared to solvent). In such cases syn elimination takes place. For example, consider the syn and anti elimination in erythro-3-d_1-2-butyl tosylate. Syn-elimination gives a mixture of non-deuterated cis-2-butene and deuterated tran-2-butene. Anti- elimination gives a mixture of deuterated cis-2-butene and non-deuterated trans-2-butene. In nitromethane (poorly ionizing solvent), the product is that of syn elimination. In this case tosylate acts as base and removes a proton or deuteron from the same side of it (the side from which it is leaving). In aqueous ethanol a mixture of syn and anti elimination products (a mixture of four products) was obtained.

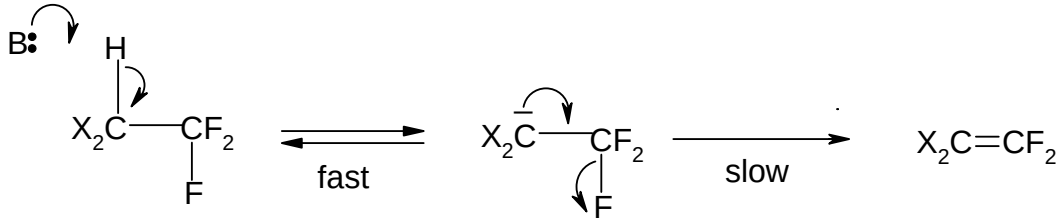


E1cB Mechanism

E1cB follows the rate equation,

$$\text{Rate} = k[\text{substrate}][\text{base}]$$

It is kinetically indistinguishable from E2 mechanism. But these two mechanisms can be distinguished by isotopic labeling. In E1cB mechanism, the first step is the formation of carbanion. But reactions proceeding by this pathway are very rare. This is due to the fact that activation energy for E2 is generally more favourable than that for E1cB. One example for E1cB mechanism is the elimination reaction of X_2CHCF_3 (where X = halogen).



In this reaction, halogen atoms on β-carbon atom make the β-hydrogen more acidic. Electron withdrawal from the negatively charged carbon by halogen atoms and CF_3 group makes the carbanion stable. Also F^- is a very poor leaving group. All these factors favour E1cB mechanism.

There are three limiting cases for E1cB mechanism. (i) The carbanion returns to starting material faster than it forms product, i.e. step 1 is reversible while step 2 is slow. This mechanism is designated as $(E1cB)_R$. (ii) Step 1 is slower and formation of the product from carbanion is faster. Step 1 is irreversible and this mechanism is represented as $(E1cB)_I$ or $(E1cB)_{irr}$. (iii) Step 1 is faster and formation of the product from carbanion is slow and step 1 is irreversible. This is possible only if the carbanion is exceptionally stable. This mechanism is designated as $(E1cB)_{anion}$. (i) and (ii) are second order and difficult to distinguish from E2 mechanism. Carbanion mechanisms may give either syn or anti elimination.

Elimination versus Substitution

E1 reactions are often accompanied by S_N1. Also E2 reactions are often accompanied by S_N2, even though they do not have a common transition state. The ratio of products of elimination to those of substitution is affected by several factors.

(a) Basicity and Size of the Nucleophile: - Attack of the nucleophile on carbon atom leads to substitution while attack on hydrogen leads to elimination. Since bases attack protons, more basic nucleophile favours elimination over substitution. If the size of the nucleophile is large, the elimination is favoured. For a large nuclophile it is often difficult to approach a carbon atom because of the presence of substituents. But it is easier to approach a hydrogen atom which is always less hindered. Therefore bulky bases like t-butoxide favour elimination.

(b) Substrate structure: - Elimination reactions will become more favourable in the order, primary < secondary < tertiary. An increase in number of substituents will favour the transition state leading to the formation of alkene. Bulky substrate favour elimination due to the relief from steric strain. Double bonds or aryl groups present in the substrate which can stabilize the developing double bond through conjugation also favours elimination.

(c) Nature of Leaving group: - The ratio of E1 to S_N1 is unaffected by the nature of the leaving group. But nature of leaving group affects E2 to S_N2 ratio. But in both these cases C-Y bond breaking is involved and hence correlation is difficult.

(d) Temperature: - During elimination two molecules react to give three molecules while in substitution, two molecules give two molecules. Therefore entropy change is favourable for elimination. According to the equation $\Delta G = \Delta H - T\Delta S$, for elimination with increase in temperature, the term $-T\Delta S$ will become more and more negative and hence ΔG will become more and more negative. Thus high temperatures favour elimination.

E2 Mechanism

In E2 elimination, proton abstraction and leaving group elimination are concerted. This process need not be exactly synchronous, i.e. C-H bond breaking may be ahead of or behind C-Y bond breaking. E2 reactions are far more common compared to E1 and E1cB. This is surprising because two bond reactions have higher activation barrier than one bond reactions. A reaction follows E2 pathway only when it is forced to do so. In many cases the activation barrier for the destruction of the intermediate is zero, i.e. the intermediate has no life time. Thus as the intermediate becomes more and more unstable to exist, elimination is forced into a concerted and finally to a synchronous E2 mechanism.

E2 reactions are affected by the strength of the base. The stronger the base, the more favourable an E2 reaction will be. Thus the rate of E2 in the following bases will be in the order $^-NH2 > ^-OR > ^-OH$. If the solvent is changed from polar-hydroxylic to polar aprotic, the strength of the base is greatly enhanced. In polar aprotic solvents, there is no envelope of hydrogen bonded solvent molecules around the base and it will be a more powerful base. Better leaving groups also favour E2 mechanism. Anions of strong oxy-acids (e.g.:- tosylate) act as good leaving groups and favour E2 mechanism. Among halide ions the relative rates of E2 will be in the order, $I^- > Br^- > Cl^- > F^-$. Structural features of the substrate also play an important role in E2 reactions. Structural features that stabilize the product alkene or the transition state increase the rate of elimination. Thus alkyl substitution at both α- and β-carbon atoms and introduction of a phenyl ring that can conjugate with the developing double bond increase the rate of elimination.

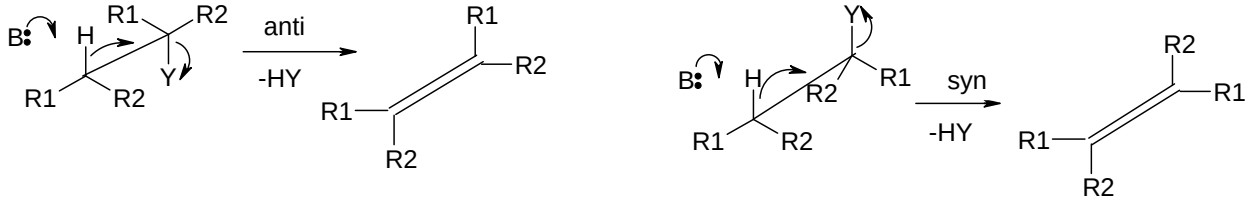
There are evidences for the existence of E2 eliminations. The reaction displays proper second order kinetics. When the hydrogen is replaced by deuterium there is isotope effect, which shows that breaking of C-H (or C-D) bond is involved in the rate determining step. But these two evidences are not enough to prove E2 mechanism. The most important evidence for E2 mechanism is that it can be stereospecific.

Stereoselectivity in E2

In E2 mechanism the five atoms involved in the transition state should be in one plane. If H, C^{α}, C^{β} and Y lie in one plane in the transition state, the *p*-orbitals of the developing double bond will be parallel to one another and maximum overlap is possible. It will be energetically favourable for the base to lie in this common plane. Thus E2 elimination will always takes place with a planar transition sate. There are two possibilities for this elimination. (A) H and Y may be trans to one another, i.e. the dihedral angle is 180º. (B) H and Y may be cis to one another, i.e. the dihedral angle is 0º.

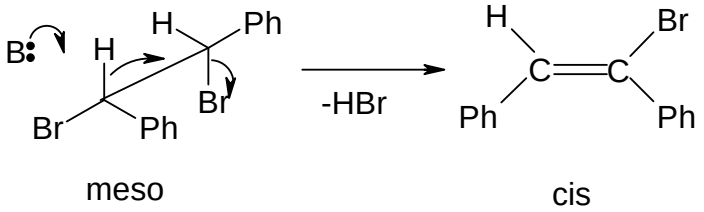
(**A**) (**B**)

Conformation (A) is called *anti-periplanar*. Elimination from this conformation in which H and Y depart in opposite directions is called anti elimination. Conformation (B) is *syn-periplanar*. Elimination from this conformation in which H and Y depart in the same direction is called syn elimination. In the absence of special features anti elimination is favoured over syn elimination. The possible reasons for this are (a) In anti elimination lower energy staggered conformation is involved while in syn elimination higher energy eclipsed conformation is involved. (b) In anti elimination, the base and the leaving group are as far apart as possible. (c) During double bond formation, the electron pair of the C-H bond is attacking the α-carbon atom from the opposite side of C-Y bond in anti elimination. This is similar to the backside attack in S_N2 mechanism. If both C^{α} and C^{β} are chiral, syn elimination and anti elimination will lead to different products.

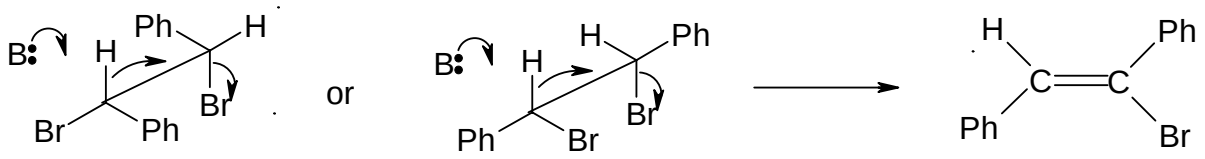


Some examples for the predominant anti elimination is given below.

(1)Elimination of HBr from meso-1,2-dibromo-1,2-diphenylethane gave cis-2-bromostilbene. The (+) or (-) isomer gave the trans olefin. In this case elimination is exclusively anti.

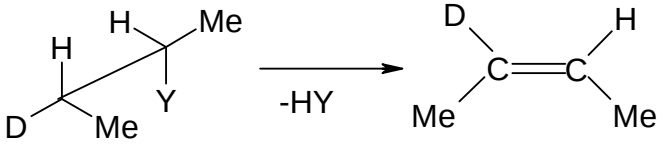


meso cis

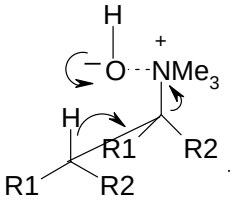


dl pair trans

(2) For the substrate HDMeC-CYHMe, where Y = Br, OTs or NMe_3^+ elimination was 100% stereoselectively anti.

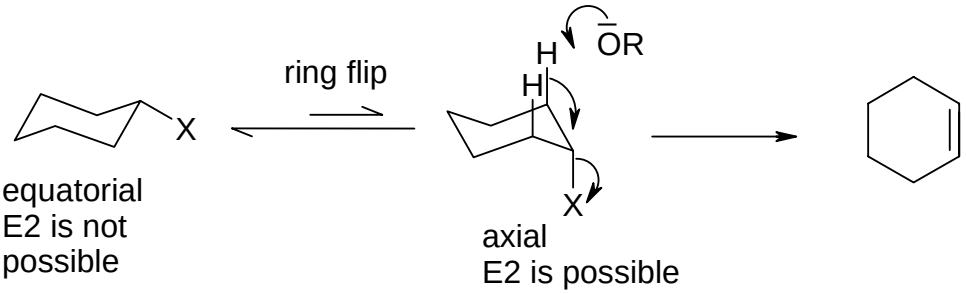


However with longer chain NR_3^+ compounds some amount of syn elimination is also observed. Such cases involve the formation of quaternary ammonium hydroxide ion pair and the leaving group acts as the base. The transition state is cyclic which favours the syn elimination of hydrogen.

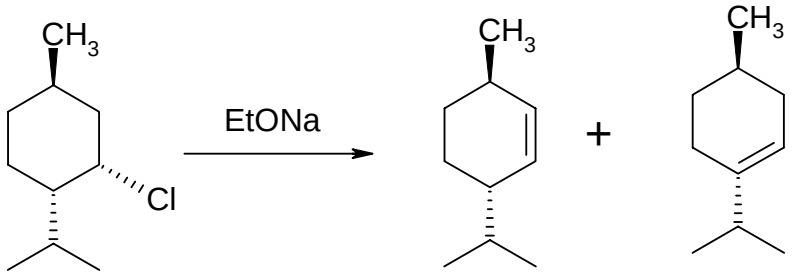


(3) Anti elimination also occurs in the formation of triple bonds. Elimination from cis- and trans-HOOC-CH=CCl-COOH give the same product, HOOCC≡CCOOH. The trans isomer reacts about 50 times faster than the cis-isomer.

(4) In the case of cyclohexyl substrates both the leaving group and hydrogen should be at axial positions. Only in this arrangement C-H bond is anti-periplanar to C-Y bond. Syn elimination is not at all possible with cyclohexyl systems. For monosubstituted cyclohexyl substrates, axial conformer is less stable. But a considerable amount of this conformer will be present and elimination will takes place from this conformer. The equatorial conformer is antiperiplanar only to C-C bonds and elimination from this conformer is not possible.

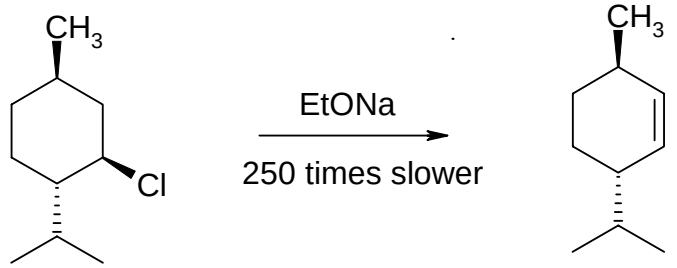


Consider the following two diastereomeric cyclohexyl derivatives. On reaction with sodium ethoxide both eliminate HCl, but (A) reacts rapidly and gives a mixture of products while (B) gives a single product slowly.



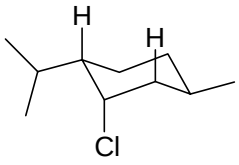
(**A**)

ratio 1:3



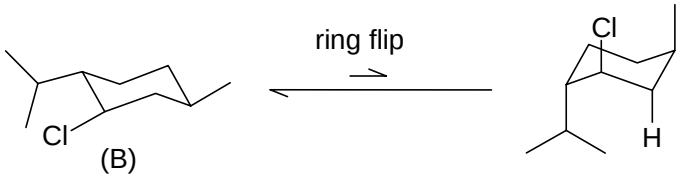
(**B**)

Both (A) and (B) will adopt chair conformations. Normally the largest substituent is in equatorial position. In this case the largest substituent is isopropyl group. In (A) isopropyl group is equatorial which means that methyl group is also equatorial. The Cl should be axial. Thus in the most favoured conformation of (A) chlorine atom is in axial position and have two axial hydrogen atoms on adjacent carbon atoms. Since the conditions required for E2 elimination is already present in the preferred conformation (A) undergoes elimination readily. Because of the presence of two hydrogen atoms in axial positions on adjacent carbon atoms two products are formed. In (B) again isopropyl group and hence methyl group are in equatorial position. But in this case chlorine atom should be in equatorial position. From this conformer elimination is not possible since there are no anti-periplanar protons. Therefore it should undergo ring flip first. Ring flip gives a conformer in which all three substituents are in axial positions which is very much less stable. This is the reason for the slow reaction of (B). Also in this conformer (i.e. with three axial groups) only one anti-periplanar proton is present and hence only one product is formed.



(A)

Favoured conformation. Cl is axial and two axial hydrogens present on adjacent carbons. Reaction is fast and gives a mixture of two products.



(B)

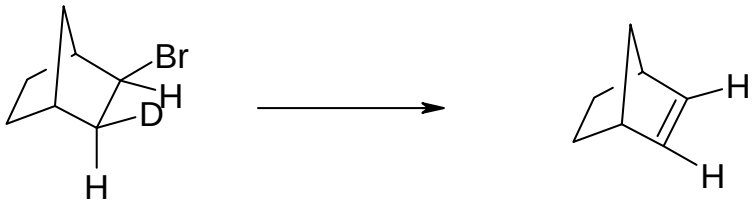
Favoured conformation. Since Cl is equatorial E2 is not possible.

disfavoured. Reaction is slow. Gives only one product.

Syn Elimination

In some cases there are special structural features favouring syn elimination in E2 mechanism. An example is given below.

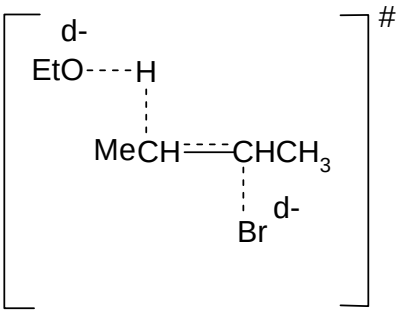
The deuterated norbornylbromide gave 94% of the product not containing deuterium during elimination. In this case the exo bromine atom cannot achieve anti-periplanar conformation with the β-hydrogen atom because of rigidity of molecule. Thus syn elimination is preferred and deuterium which is syn to Br is eliminated.



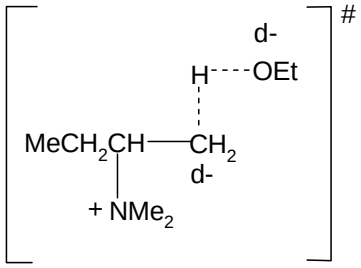
Orientation in E2: Saytzev Versus Hofmann

In many E2 reactions two (or three) β-hydrogen atoms are available. In such cases there are two possible products; the most substituted alkene and the least substituted alkene. In order to predict the orientation two empirical rules have been proposed. Hofmann stated that the predominant product will be the alkene with least number of alkyl substituents on the double bond carbon atoms. Saytzev proposed that the predominant product will be the alkene with most substituents on double bond carbon atoms. It was found that in some cases, the predominant product is the Hofmann product, while in some other cases Saytzev product is the predominant product. The composition of the alkene mixture obtained was found to depend on the nature of the leaving group.

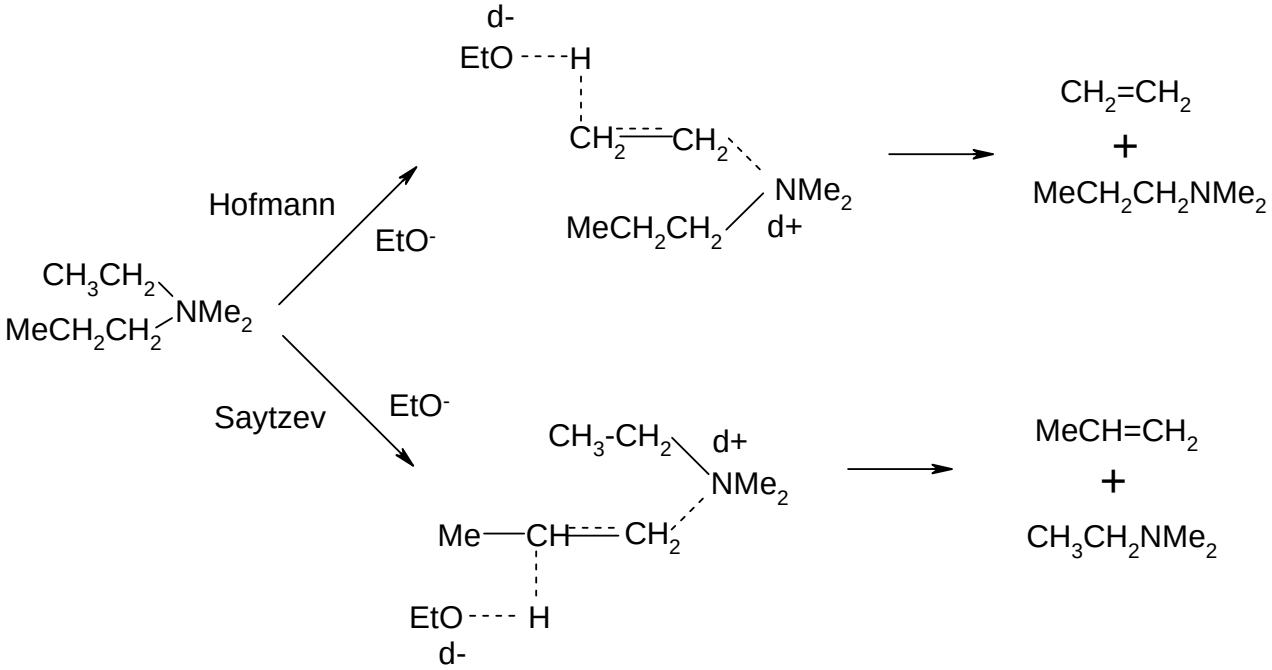
If the leaving group is neutral (when it is attached to the carbon atom), the predominant product is the Saytzev product. Thus when Y = Br, OTs etc, the predominant product is the more stable, more heavily substituted alkene. In such cases, the transition state is more alkene like. If the number of alkyl substituents is more, the T.S. will be more stable. Therefore, the more substituted alkene will be the predominant product. An example is the elimination reaction of MeCH2CHBrMe.



If Y is positively charged (i.e. groups like Me_3N^+, Me_2S^+ etc), the predominant product is the Hofmann product. Groups like $^+NMe_3$ will exert powerful –I effect/field effect on both β-carbon atoms. Thus the hydrogens attached to the β-carbon atoms will be highly acidic and the removal of such hydrogen atoms will be enhanced. In other words, positively charged leaving groups enhance the formation of carbanion. These groups also stabilize the carbanion by electron withdrawal. Therefore, whenever groups like $^+NMe_3$ is involved, the transition sate is more carbanion like (E1cB like transition state). A carbanion like transition sate is stable with the least number of alkyl substituents. Thus Hofmann product is favoured.



An example is shown below.



In this example Hofmann product will be predominating. Transition state for Hofmann elimination is more favourable. Since the transition state has carbanion character, the transition

state with the least number of alkyl substituents is favoured. Hence the predominant product is the least substituted alkene.

If Fluorine is the leaving group, even though it is not positively charged, Hofmann product will be the predominant product. The reason is that F is an extremely powerful electron withdrawing group and it is an extremely poor leaving group. Thus the C-F bond breaking is delayed and the transition state will be more carbanion like.

Steric factors may also important in elimination reactions. Normally positively charged leaving groups are larger than neutral leaving groups. Since the positively charged leaving groups are large enough to hinder the attack of base on protons, the base will attack the least hindered proton leading to Hofmann elimination. Also bulky substrates favour Hofmann elimination. Bulky bases prefer Hofmann elimination, while small bases prefer Saytzev elimination.