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1. Learning Outcomes

After studying this module, you shall be able to

- What are S_E2 reactions
- Learn mechanism of S_E2 reactions
- Identify type of S_E2 reactions based on stereochemistry of products
- Evaluate conditions favoring S_E2 reactions
- Analyze importance of organomercury compounds in S_E2 mechanism

2. Introduction

Electrophilic aliphatic substitution reactions are chemical reactions in which an electrophile (an electron deficient species) removes a functional group in a compound. The electrophilic substitution bimolecular mechanisms are termed S_E2 mechanisms. Analogues to S_N2 reactions these reactions follow bimolecular rate kinetics, where the reaction rate is first order in substrate and first order in the electrophile when both reactants are in dilute solutions.

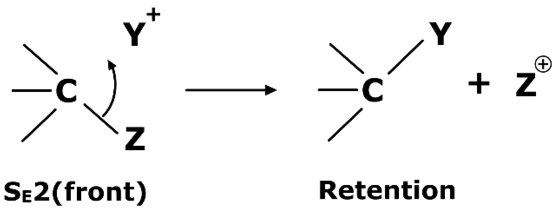
3. S_E2 reactions

The S_E2 reactions involve a substrate with good leaving group and an electron deficient electrophile. Good leaving groups for electrophilic substitution are those which have outer shell that is deficient in a pair of electrons. The proton is a common leaving group in aliphatic systems, especially acidic protons such as protons at α-position to a carbonyl group or at an alkynyl position. Organometallic compounds are especially susceptible to electrophilic substitution.

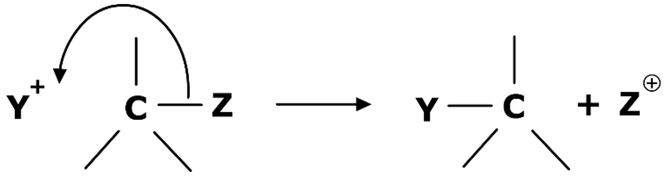
3.1 Mechanism of S_E2 reactions

The S_E2 reaction mechanism proceeds via a single transition state where the old bonds and the newly formed bonds are both present simultaneously. Unlike S_N2 substitution, which always results in inversion of configuration of reaction centre, for S_E2 reactions there are two possible ways of electrophile attack to the reaction centre.

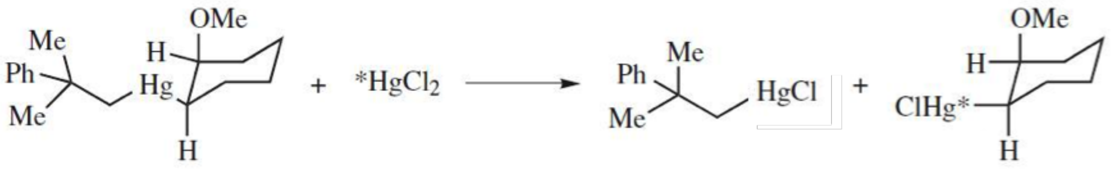
- The first one is attack from the front, which is called S_E2 (front) that results in retention of configuration.



- The second option is attack of the electrophile from the rear, which is called S_E2 (back) that leads to inversion of configuration.



Majority of second-order electrophilic substitutions proceed via retention of configuration implicating front side attack resulting from S_E2 (front) mechanism. For example, when compound 1 was treated with labeled mercuric chloride*, the product 2 produced with 100% retention of configuration, thereby confirming S_E2 (front) mechanism.



1 2

*labelled mercury

For an electrophilic substitution reaction evidences for front attack are second-order kinetics along with stereo chemical retention of configuration.

S_E2 (front) reactions are possible and easy at bridgehead carbons. Further, even bulky substrates such as neopentyl systems undergo electrophilic substitution although S_N2 reactions at neopentyl and bridgehead positions are extremely slow, because attack from the rear is blocked and the transition state for the reaction lies very high in energy.

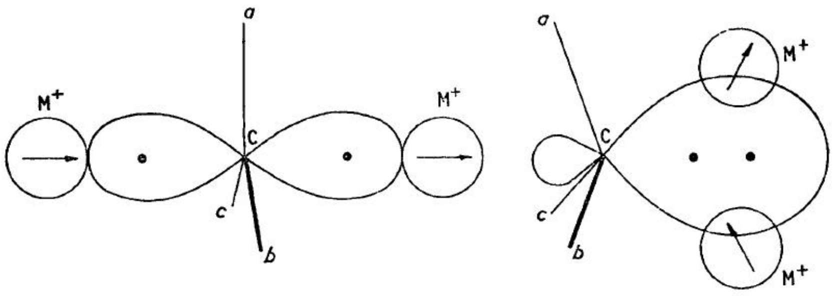
S_E2 (back) reactions proceeds with inversion of configuration. The reaction of optically active sec-butyl tri neopentyltin with bromine gives inverted sec-butyl bromide.

$$\text{sec-BuSnR}_3 + \text{Br}_2 \longrightarrow \text{sec-BuBr} \quad \text{where R= neopentyl}$$

3.2 Stereochemistry of S_E2 reactions

In S_E2 mechanism, in the transition state, the two electrons of the carbon-metal bond occupy the central orbital. It was proposed by Ingold et al that the electronic distribution giving rise to different stereochemistry of products depend on the degree of bond extension, and the degree of bond ionicity of intermediate in the transition state.

For S_E2 (back) reactions, it was shown that the transition state has good bond extension potential and high ionicity, thus the carbon orbital spreads comparably on both sides of the atom, leading to inversion of configuration. In contrast, when the transition state has little bond extension and low ionicity the electrons of the original metal bond remain nearly where they were resulting into retention of configuration, through a transition state such as S_E2 (front).



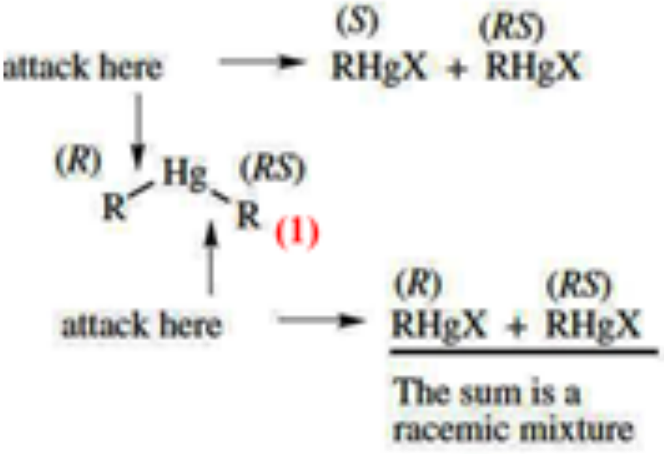
S_E2 (Inv.) S_E2 (Ret.)

Electronic distributions determining stereochemistry in S_E2 reactions

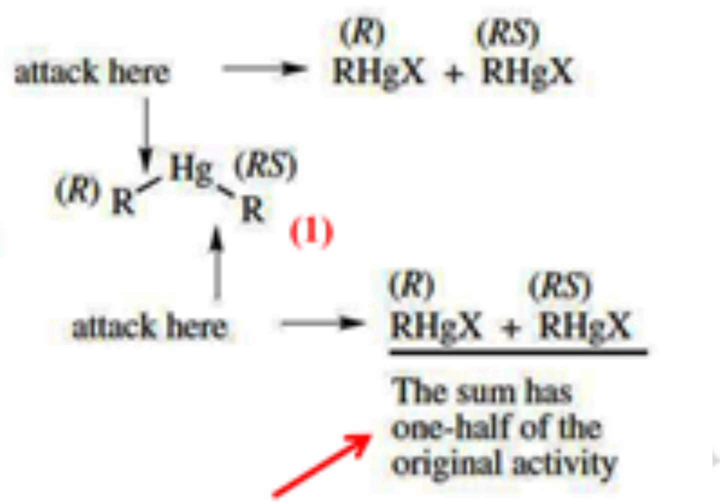
In a classical experiment to determine the stereochemistry of S_E2 mechanism sec-butylmercuric bromide was reacted with racemic sec-butylmagnesium bromide leading to the optically active product di-sec-butylmercury having one sec-butyl group optically active and the other with a racemic centre (1). The di-secbutyl compound was then treated with mercuric bromide to give 2 equivalent of sec-butylmercuric bromide. The steric course of the reaction was predicted assuming that the bonds between the mercury and each carbon have a 50% chance of breaking.

There were three possible outcomes from the reaction namely (A), (B) and (C) as depicted below;

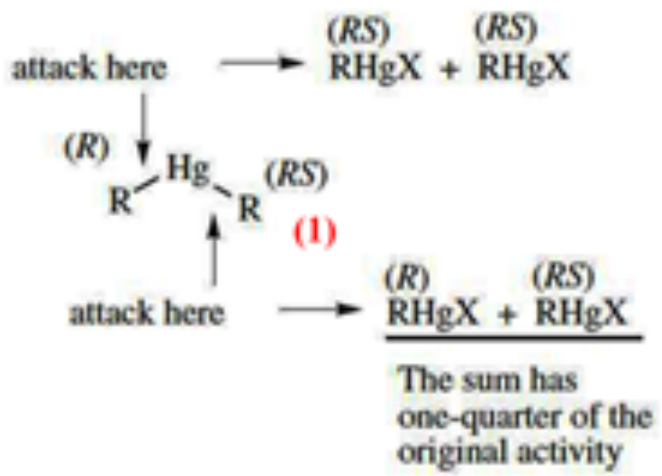
(A) If inversion:



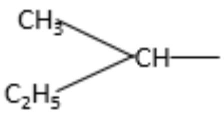
(B) If retention:



(C) If racemization



Where R =



The reaction resulted in product with one-half of the original optical activity (pathway B), therefore demonstrating retention of configuration under several different sets of conditions. Thus retention of configuration suggested S_E2 (front) mechanism to be operative for the reaction.

3.3 Factors influencing S_E2 reactions

3.3.1 Substrate

For the S_E2 (back) mechanism, the reactivity of alkyl groups is

$$Me > Et > Pr > iPr > neopentyl$$

As is expected, since the backside attack is significantly affected by steric hindrance.

There are strong effects of substrate structure on kinetics of S_E2 (front) mechanism. For the following reaction catalyzed by bromide ion;

$$RHgBr + Br_2 \longrightarrow RBr + HgBr_2$$

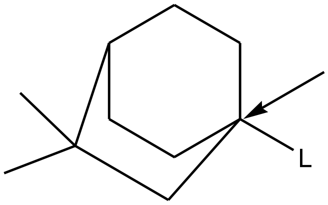
The following substrate gave relative rate data as tabulated below;

R	**Relative rate**
$-CH_3$	1
$-CH_2CH_3$	10.8
$-CH(CH_3)_2$	780
$-C(CH_3)_3$	3370
$-CH_2CH(CH_3)_2$	1.24
$-CH_2C(CH_3)_3$	0.173

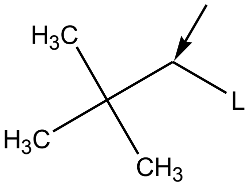
As can be seen from the table, the branching at α-carbon increased rate of reaction due to electron donating inductive effect of R- groups that stabilize the electron deficient transition state in S_E2 front mechanism. On the other hand, branching at β-carbon decreased the rate of reaction significantly due to stearic hindrance.

In contrast, for some organotin substrates the rates of second-order substitutions were found to increase with increasing electron withdrawal by substituents. This was explained based on associated ion pair to an S_E2 mechanism, analogous to Sneen's ion-pair mechanism for nucleophilic substitution.

S_E2 (front) reactions are possible at sterically crowded positions such as a bridgehead carbon or neopentyl system owning to the orientation of incoming electrophile.



bicyclo [2.2.2] octane derivative



Neopentyl chloride

3.3.2 Leaving group

Electrophilic substitution requires an electropositive leaving group attached to alkyl group substrate. In aliphatic organic chemistry, most of the functional groups are electro negative therefore, due to lack of substrates the number of electrophile substitution reactions is less as

compared to nucleophilic substitution reactions. Generally, S_E2 reactions proceed with alkyl groups attached to metals as leaving group. Organomercury compounds have been most extensively studied for S_E2 reactions as they are stable but sufficiently reactive, easily prepared, purified, and identified. For the substrate R-HgX, the more electronegative group X decreases the polarity of C-Hg bond and results in less stable HgX^+, therefore the leaving tendency of HgX decreases with increasing electro negativity of X. Thus, HgR (from RHgR) is a better leaving group than HgCl (from RHgCl).

3.3.3 Solvent

There are considerable effects of nature of solvent on S_E2 reactions. When competing S_E1 and S_E2 reactions may run parallel than polar solvents favor S_E1 mechanism while less polar solvents favor S_E2 mechanism.

Comparison between S_E1 and S_E2 mechanism based on reactivity

S_E1 mechanisms are favored in comparison to S_E2 reactions if;

(i) Strong electron withdrawing (–I) groups are present on substrate alkyl group.

(ii) Polar protic solvents are used for the reaction.

4. Examples of S_E2 reactions

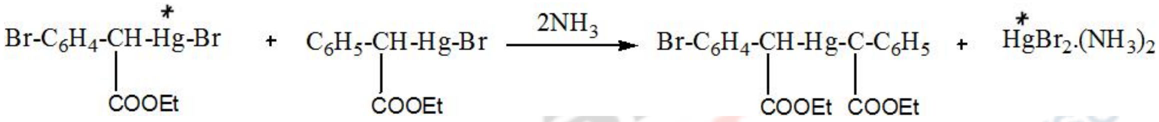
4.1 Alkyl exchange

The rate of the following alkyl exchange reaction with alkyl mercury substrate and labeled* mercury halide was found to follow second order kinetics with retention of configuration therefore implicating S_E2 mechanism.

$$RHgX + \overset{*}{Hg}X_2 \xrightarrow{EtOH} R\overset{*}{Hg}X + HgX_2$$

Further support for S_E2 mechanism was provided by the rate coefficients that increased in the order of X= Br<I<<OAc<<NO_3 which should be the order if the reaction follows S_E2 (front) mechanism.

In another example by use of radioactive mercury (^{203}Hg) it was shown that a mercury atom from the original molecule preferentially transfers into the complex $HgBr_2.(NH_3)_2$.



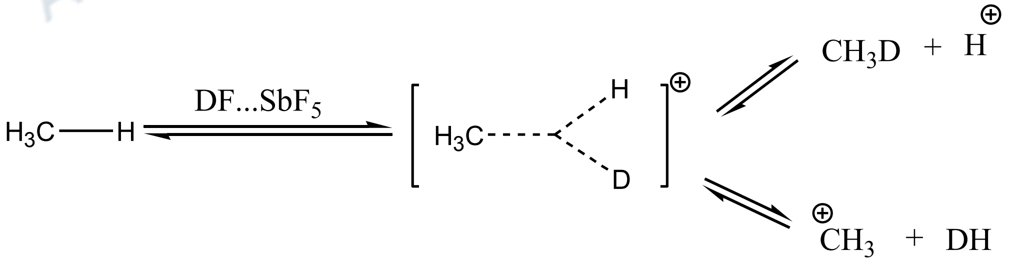
$$\underset{\displaystyle COOEt}{Br\text{-}C_6H_4\text{-}CH}\text{-}\overset{*}{Hg}\text{-}Br + \underset{\displaystyle COOEt}{C_6H_5\text{-}CH}\text{-}Hg\text{-}Br \xrightarrow{2NH_3} \underset{\displaystyle COOEt}{Br\text{-}C_6H_4\text{-}CH}\text{-}Hg\text{-}\underset{\displaystyle COOEt}{C}\text{-}C_6H_5 + \overset{*}{Hg}Br_2.(NH_3)_2$$

4.2 Deuteration

Deuteration reactions are important from the mechanistic point of view. Such reactions with alkanes are accomplished by treatment with super acids (HSO_3-F or HF-SbF_5) as strong acids can only remove slightly acidic protons.

$$R\text{—}H + D^{\oplus} \rightleftharpoons R\text{—}D + H^{\oplus}$$

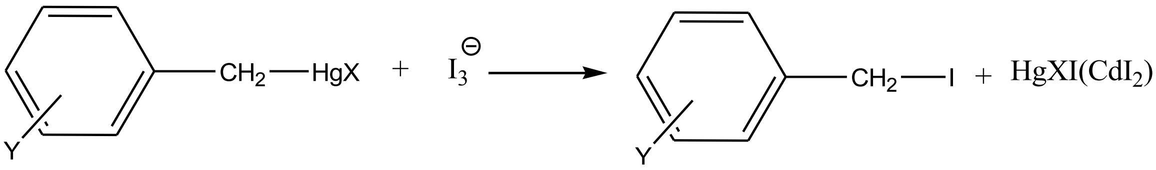
The mechanism of the exchange involve attack of H^+ or D^+ on the C–H bond to give the penta-valent methanonium ion, when the reaction is carried out on methane.



These reactions are S_E2 reactions as both the entering group and leaving group are electrophilic in nature and in the transition state the electron pair of the breaking bond remains with the substrate.

4.3 Halo-demercuration

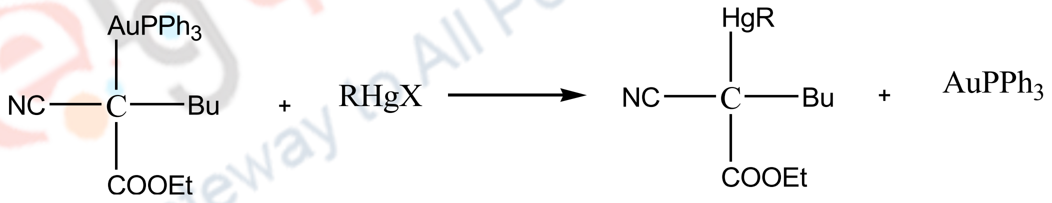
The reaction of benzylmercury halides with iodine in the presence of an excess of cadmium iodide was found to be second order overall (first with respect to each of the components) in various solvents such as methanol, ethanol, and dimethylformamide.



4.4 Proto-demercuration

The reaction of benzylmercury chloride with hydrogen chloride in alcohol and dioxane was found to follow S_E2 mechanism.

The substitution of 1-Cyano-1-carbethoxypentyl-(triphenylphosphine)-Gold(I) by alkyl mercuric salts was found to follow S_E2 mechanism.



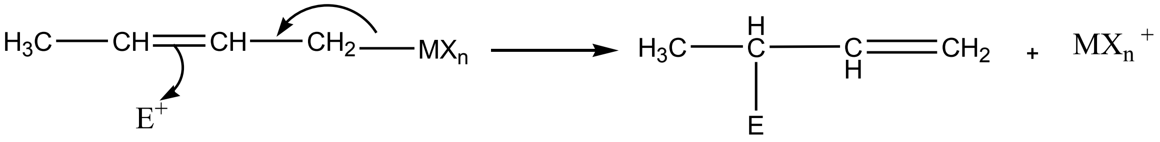
The following reaction under dioxane was found to follow a second order kinetics with respect to both the reactants.

$$R_4Sn + HgX_2 \longrightarrow RHgX + R_3SnX$$

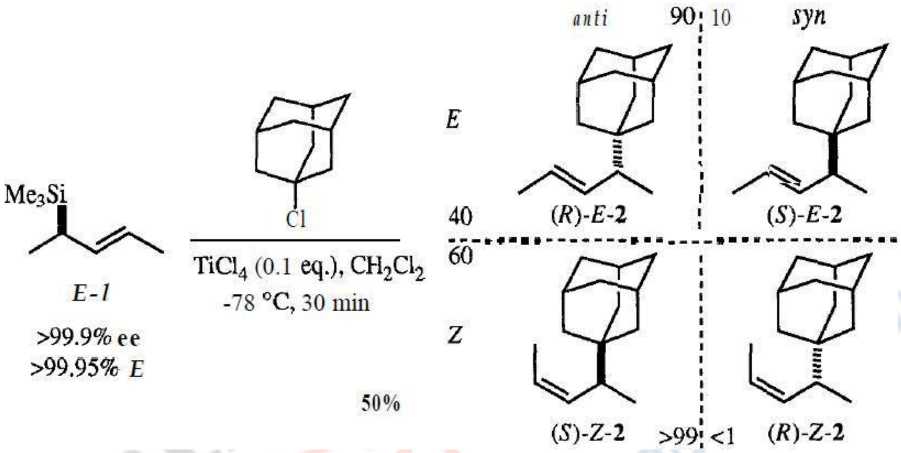
4.5 Bimolecular allylic rearrangement (S_E2') reactions

Allylic organometallic compounds may undergo electrophilic substitution reaction at the □ or γ carbon atom. If the attack is on the γ carbon atom then the reaction is called S_E2' i.e bimolecular electrophilic substitution reaction with rearrangement.

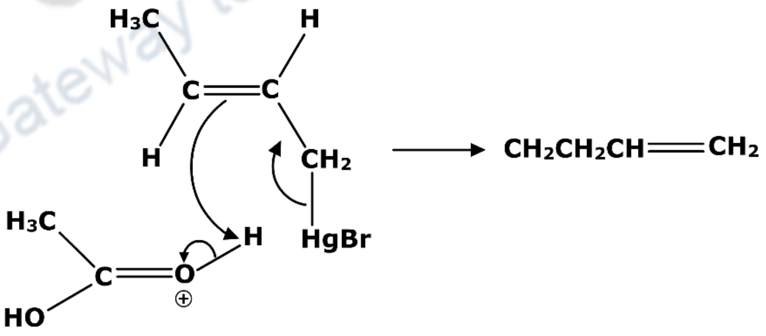
The general scheme for rearrangement is shown below;



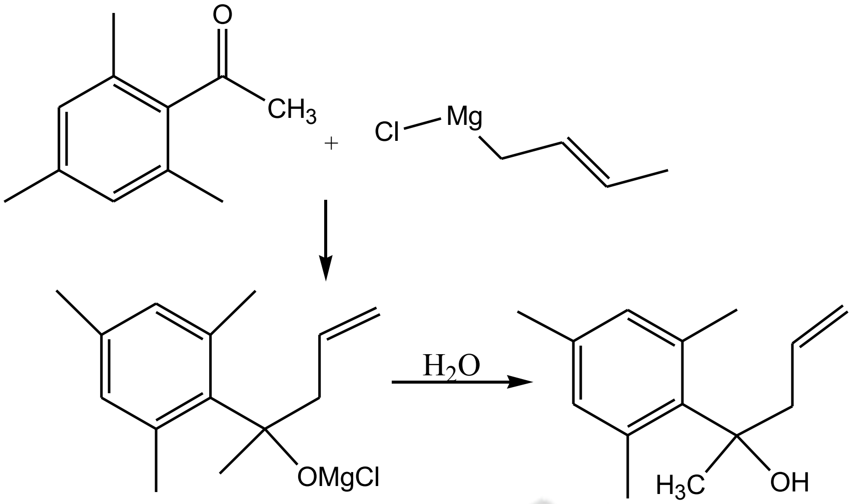
For allyl silanes, the following reaction proceeds even when the allylic group has a bulky substituent attached to it. The product of rearrangement has been shown to have anti conformation for allylsilanes with a very high degree of stereo specificity (95%).



Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups. An example of a reaction proceeding with acetic acid/perchloric acid functional by an S_E2' mechanism is as follows;



Another example for S_E2' reaction with allyl magnesium substrate giving rise to rearranged product is shown in the following reaction.



5. Summary

- Electrophilic substitutions bimolecular (S_E2) are reactions where an electrophile (electron deficient species) replaces another group in substrate.
- S_E2 reactions proceed via a single transition state where concerted bond formation and bond breaking takes place.
- S_E2 reactions are divided as S_E2 (front) and S_E2 (back) based on the direction of incoming electrophile which decides the stereochemistry of products.
- For S_E2 (front) mechanism, reactions proceed with retention of configuration, whereas for S_E2 (back) mechanism generally racemic mixtures are obtained.
- S_E2 mechanisms are rare due to the requirement of an electrophilic leaving group which is rare in aliphatic organic compounds.
- S_E2 mechanisms are favored by less polar solvents.
- S_E2 mechanisms may take place at bridgehead carbon and bulky neopentyl groups.