CHAPTER 6

Aliphatic Nucleophilic Substitution

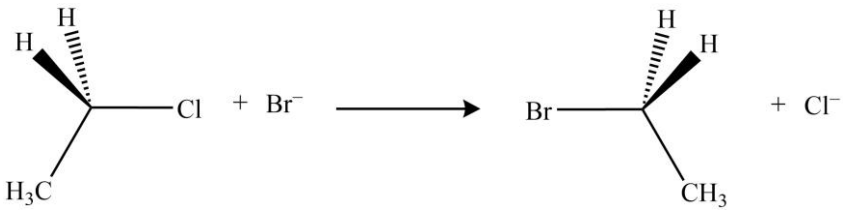
❖ The SN_2, SN_1, Mixed SN_1 and SN_2, SN_i, SN_1', SN_2', SN_i' and SET Mechanisms

Although the number of mechanisms by which the nucleophilic substitutions proceed is very large, certain patterns can still be used to profile them for more systematic and simplistic analysis. Some of the prominent types of aliphatic nucleophilic substitutions are given below.

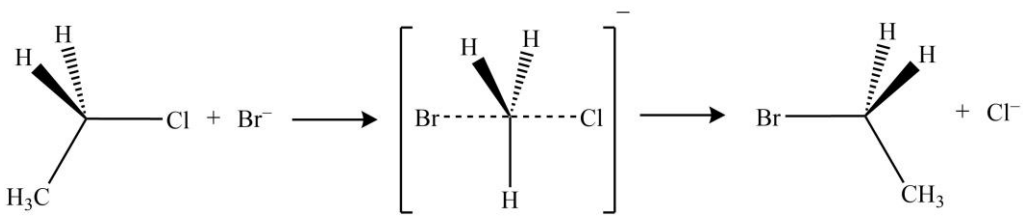
➢ *SN_2 (Substitution Nucleophilic Bimolecular) Mechanism*

In SN_2 reactions, the "SN" stands for "nucleophilic substitution", and "2" means that the rate-determining step is bimolecular. In other words, a stronger nucleophile displaces a weaker one via the formation of a transition state.

Illustrative reaction: One of the most common examples of the SN_2 reaction is the attack of Br^- on ethyl chloride results in ethyl bromide, with chloride ejected as the leaving group.



Mechanism involved: The proposed mechanism for the reaction given above involves a single step which must be discussed before we give the salient features of the same. The process occurs most often at the sp^3 hybridized carbon with a stable electronegative leaving group attached to it (usually halide X^-).



The breaking of the carbon–halogen bond and the formation of the new covalent bond takes place simultaneously via a transition state in which the carbon under nucleophilic attack is in 5-coordination with probable sp^2 hybridization. The nucleophilic attack at the carbon takes place at 180° w.r.t the leaving group to provides a good overlap between the nucleophile's lone pair and the antibonding orbital (σ*) C–X bond. The leaving group is then detached from the opposite side and the product is formed with inversion of the tetrahedral geometry at the central carbon atom if the substrate is chiral.

Salient Features: The main features of the mechanism involved in nucleophilic substitution bimolecular or SN_2 type reactions are given below.

i) SN_2 reactions follow second-order kinetics with the rate law

$$Rate = k[RX][Nu]$$

Where k is the rate constant. The symbol $[RX]$ and $[Nu]$ represent the molar concentration of the substrate and attacking nucleophiles, respectively.

ii) If the alkyl halide is chiral, then this often leads to an inversion of configuration, called the Walden inversion.

iii) The rate of the substitution becomes independent of the concentration of the attacking reagent if its concentration is extremely high in comparison to the substrate.

iv) The rate of the substitution increases as the steric bulk around the carbon center decreases.

v) The SN_2 reactions are favored in polar aprotic solvents.

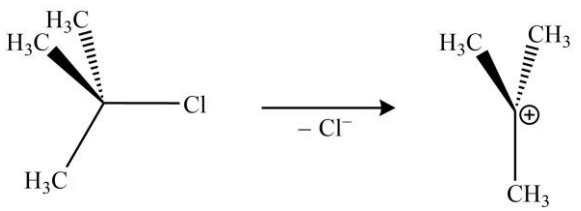
- ***SN_1 (Substitution Nucleophilic Unimolecular) Mechanism***

In SN_1 reactions, the word "SN" stands for "nucleophilic substitution", and "1" means that the rate-determining step is unimolecular in nature. In other words, a stronger nucleophile displaces a weaker one via the formation of an intermediate.

Illustrative reaction: The most common example of an SN_1 reaction is the formation of alcohols from alkyl halides as shown below.

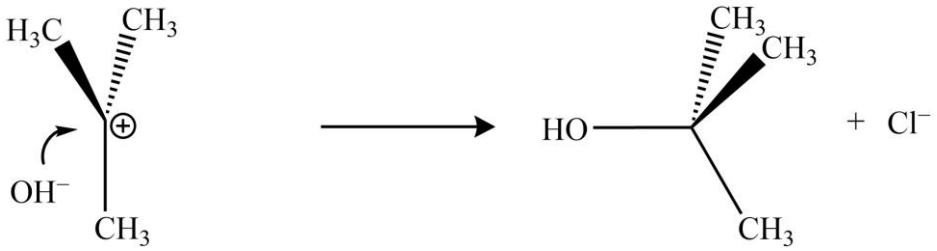
Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same.

i) Formation of intermediate:



The carbocation formed during this step is trigonal planar in geometry and is open for attack from both sides. Now since the carbocations are electron-deficient species and very reactive, The OH^- will attack from either side to give the same product, which will be the second step of the reaction.

ii) Attack by the Nucleophile:



Now since the faces of the carbocations formed are homotopic, the OH^- can attack from either side to give the same product.

Salient Features: The main features of the mechanism involved in nucleophilic substitution unimolecular or SN_1 type reactions are given below.

i) SN_1 reactions follow first-order kinetics with the rate law

$$Rate = k[RX]$$

Where k is the rate constant and $[RX]$ represents the molar concentration of the substrate (tert-butyl halide in this case).

ii) If the alkyl halide has one or more asymmetric carbons, two stereoisomers (diastereomers or enantiomers) will be formed.

iii) The rate of the nucleophilic substitution unimolecular is almost independent of the concentration of the attacking reagent.

iv) The rate of the substitution increases as the steric bulk around the carbon center increase.

v) Since an unstable intermediate carbocation is formed in course of the SN_1 reactions (rate-determining step), any factor that can support this will boost up the rate. Normal solvents of choice are both protic (to hydrolyze the leaving group in particular) and polar (to simply stabilize ionic intermediates). Archetypal polar protic solvents include alcohol and water, which are also capable of acting as nucleophiles (i.e. support solvolysis). Therefore, we can conclude that the SN_1 reactions are favored in polar and protic solvents.

vi) Since the intermediate formed is carbocation, the possibility of rearrangement to form more stable carbocation and yielding different products is also there.

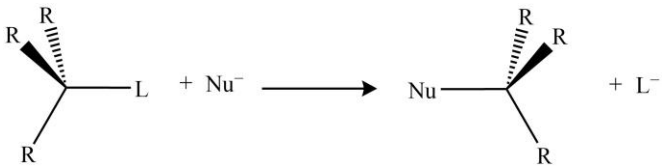
vii) The substitution at bridgehead carbon is either absent or takes place very slowly because the carbocation in such cases cannot attain planar geometry.

viii) In asymmetric alkyl halides, racemization does not take place fully all the time because the nucleophile attacks even before the complete detachment of leaving group. This leads to some inversion also causing unequal racemic mixture.

➢ ***Mixed SN_1 and SN_2 Mechanism***

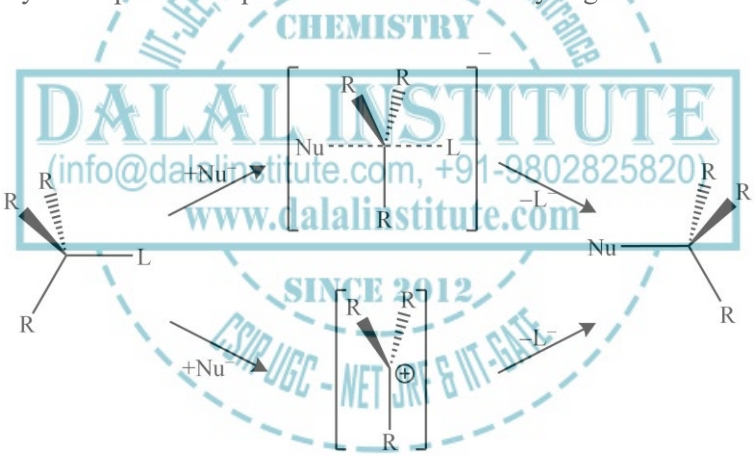
Most of the organic reactions are either SN_1 or SN_2 over a vast range of experimental conditions. However, some reactions show both types of characteristic features under certain conditions indicating that they are neither SN_1 nor SN_2 but a mixture of two. In other words, some nucleophilic substitution reactions proceed via mixed SN_1 and SN_2 mechanisms.

Illustrative reaction: The common depictive example of SN_1-SN_2 mixed-mechanism is shown below.

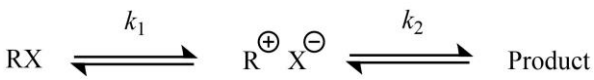


Mechanism involved: There are two theories that are typically used to rationalize the borderline nucleophilic substitution mechanism as given below.

i) Simultaneity of SN_1 and SN_2: As the name suggests, this theory says that the reaction proceeds simultaneously via SN_1 and SN_2 pathways. The pictorial representation of this theory is given below.



ii) Intermediatory mechanism: This theory assumes that the reaction takes place via the formation of an intermediary ion-pair as shown below.



When the formation of ion-pair is the rate-determining step, the reaction becomes SN_1; whereas, if the conversion of ion-pair into the product is the rate-determining step, the reaction becomes SN_2; if $k_1 = k_2$, we get a borderline case.

Salient Features: The main features of the mixed SN_1 and SN_2 mechanism are given below.

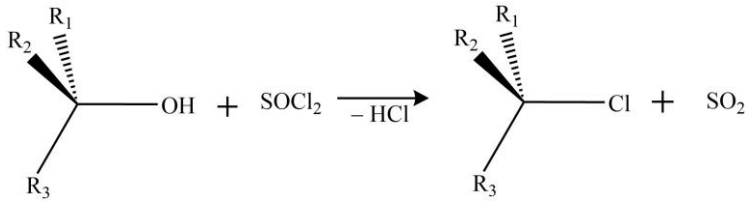
i) SN_1 pathway competes with the SN_2 route to dominate the products' ratio for asymmetric reactants.

ii) The ion-pair theory can be applied to both SN_1 and SN_2 as well.

➢ *SNi (Substitution Nucleophilic Internal) Mechanism*

In SN_i reactions, the "SN" stands for "nucleophilic substitution", and the "*i*" means that the substitution takes place internally in the molecule.

Illustrative reaction: One of the most common examples of the SN_i reaction is the displacement of OH^- of alcohols by Cl^- in the presence of $SOCl_2$.



Mechanism involved: The $SOCl_2$ first reacts with the alcohol to give rise to an alkyl chloro sulfite (i.e. intimate ion pair). The next step is concerted and involves the loss of an SO_2 molecule and its displacement by its own chloride group.

The major point of difference between SN_i and SN_1 is actually that the ion pair is not completely separate, and therefore, no actual carbocation is generated (otherwise we would have got racemized product).

Salient Features: The main features of the mechanism involved in nucleophilic substitution internal or SN_i type reactions are given below.

i) SN_i reactions follow second-order kinetics with the rate law

$$Rate = k[ROH][SOCl_2]$$

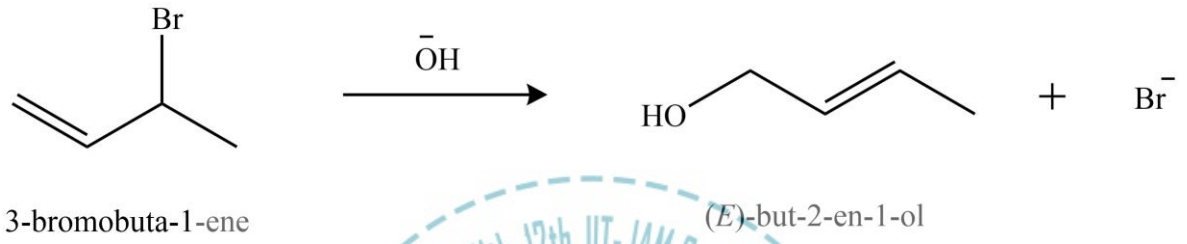
Where *k* is the rate constant. The symbol $[ROH]$ and $[SOCl_2]$ represent the molar concentration of the substrate and species with attacking nucleophiles, respectively.

ii) If the alcohol is chiral, then this leads to the retention of configuration.

➢ ***SN_1' (Substitution Nucleophilic Unimolecular Prime) Mechanism***

In SN_1' reactions, the word "SN" stands for "nucleophilic substitution", "1" means that the rate-determining step is unimolecular in nature, and prime indicates that there is a double bond in the vicinity of leaving group. In other words, a stronger nucleophile displaces a weaker one via the formation of an intermediate that has a delocalization of π-electron density.

Illustrative reaction: The most common example of SN_1' reaction is the formation of but-2-ene-1-ol from 3-bromobuta-1-ene as shown below.



3-bromobuta-1-ene (*E*)-but-2-en-1-ol

Mechanism involved: The proposed mechanism for the reaction given above involves two steps which must be discussed before we give salient features of the same. At first, the detachment of bromide ion gives rise to an allylic carbocation system in which the positive charge is distributed at 1st and 3rd carbon atoms. Now since the terminal carbon is primary but 3rd carbon is secondary, the first carbon is more electron deficient, and therefore, will become the first choice for attacking nucleophile to yield our product.

3-bromobuta-1-ene (*E*)-but-2-en-1-ol

One more reason that why the nucleophile did not attack at the 3rd carbon to give normal SN_1 is that there is more steric hindrance at the 3rd carbon than what it is at 1st.

Salient Features: Almost all of the features of SN_1' prime are similar to the SN_1 mechanism with some exceptions as given below.

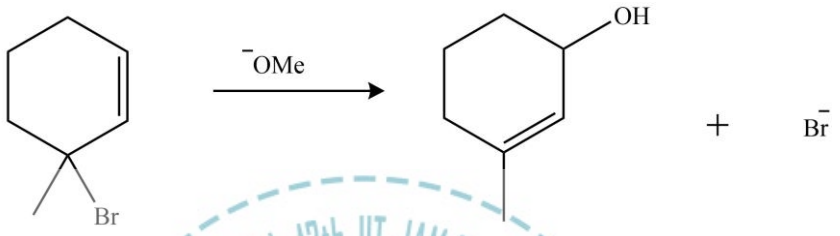
i) The carbonation formed in SN_1 was simple but rearrangeable in the case of allylic systems.

ii) The nucleophile attack on γ-carbon rather than the α- one.

➢ ***SN_2' (Substitution Nucleophilic Bimolecular Prime) Mechanism***

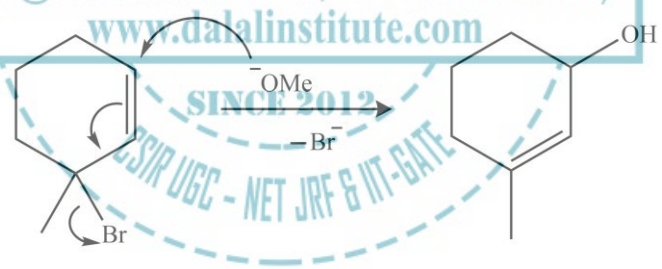
In SN_2' reactions, the "SN" stands for "nucleophilic substitution", "2" means that the rate-determining step is bimolecular, and prime indicates that there is a double bond in the vicinity of leaving group. In other words, a stronger nucleophile displaces a weaker one via the formation of a transition state; though the attachment and detachment are at different carbons.

Illustrative reaction: One of the most common examples of the SN_2' reaction is the conversion of 3-bromo-3-methylcyclohex-1-ene into 3-methylcyclohex-2-en-1-ol, with bromide ejected as the leaving group.



3-bromo-3-methylcyclohex-1-ene 3-methylcyclohex-2-en-1-ol

Mechanism involved: The proposed mechanism for the reaction given above involves the use of a double bond as a relay system of electron density. Instead of attacking at the 3rd carbon in the cycle (would have yield normal SN_2 product), the incoming nucleophile attacks at 1st carbon due to its greater electron deficiency than the 3rd one which is obviously caused by electrons' relay from first carbon to bromine.



3-bromo-3-methylcyclohex-1-ene 3-methylcyclohex-2-en-1-ol

One more reason that why the methoxide ion did not attack at the 3rd carbon to give normal SN_2 is that there is more steric hindrance at the 3rd carbon than what it is at 1st. In other words, the greater electron deficiency and a less steric hindrance at first carbon make it a better site for nucleophilic attack.

Salient Features: Almost all of the features of SN_2' prime are similar to the SN_2 mechanism with some exceptions as given below.

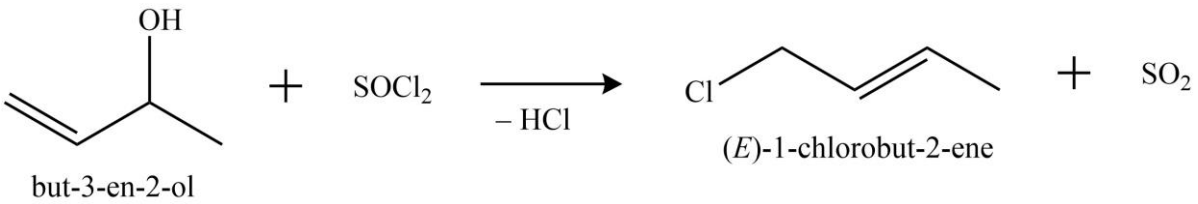
i) The nucleophilic attack and the detachment of leaving group takes place at different carbon atoms.

ii) The double bond is used as an electrons' relay system.

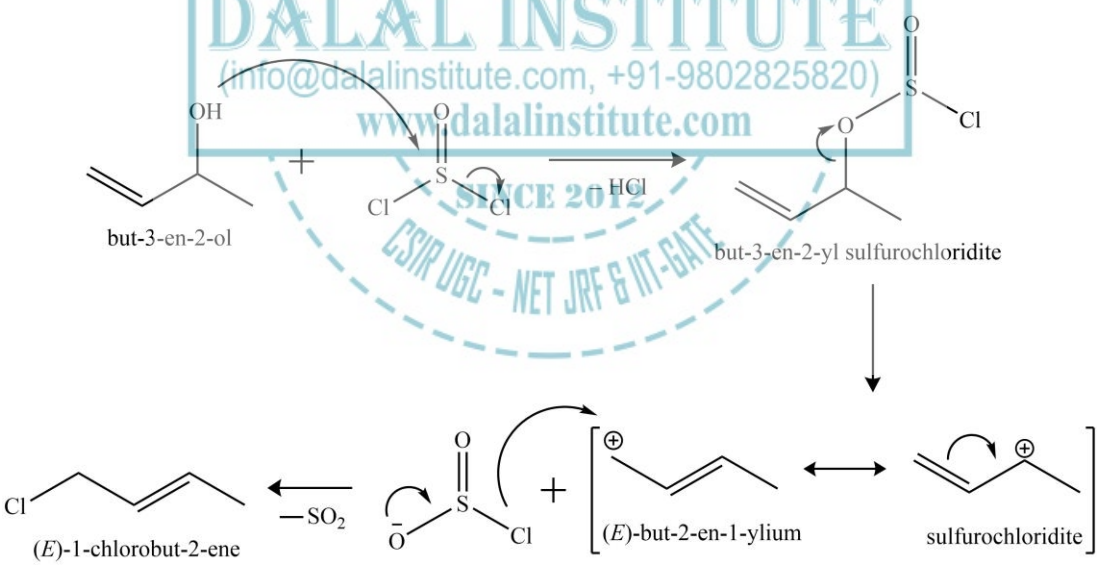
- ***SN_i' (Substitution Nucleophilic Internal Prime) Mechanism***

In SN_i' reactions, the "SN" stands for "nucleophilic substitution", the "*i*" means that the substitution takes place internally in the molecule, and prime indicates that there is a double bond in the vicinity of leaving group.

Illustrative reaction: One of the most common examples of the SN_i' reaction is the displacement of OH of in but-3-en-2-ol by Cl in the presence of $SOCl_2$.



Mechanism involved: The proposed mechanism for the reaction given above initially proceed normally like SN_i; however, the detachment of sulfurochloridite ion gives rise to an allylic carbocation system in which the positive charge is distributed at 1st and 3rd carbon atoms. Now since the terminal carbon is primary but 3rd carbon is secondary, the first carbon is more electron deficient, and therefore, will become the first choice for attacking nucleophile to yield our product.



One more reason that why the nucleophile did not attack at the 2nd carbon to give normal SN_i is that there is more steric hindrance at the 2nd carbon than what it is at 4th.

Salient Features: Almost all of the features of SN_i' prime are similar to the SN_i mechanism with some exceptions as given below.

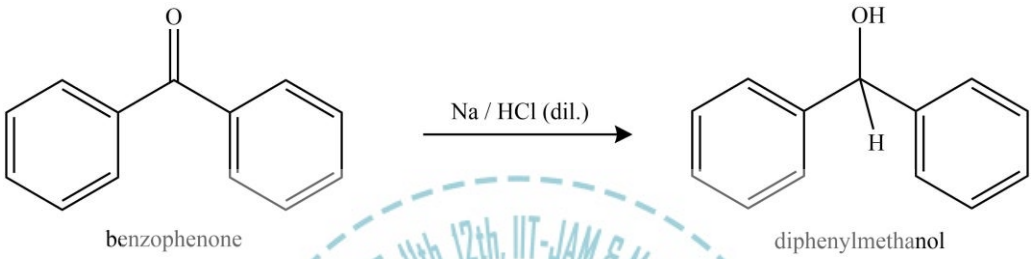
i) The carbonation formed in SN_i was simple but rearrangeable in the case of allylic systems.

ii) The nucleophile attack on the 1st carbon rather than the 3rd one.

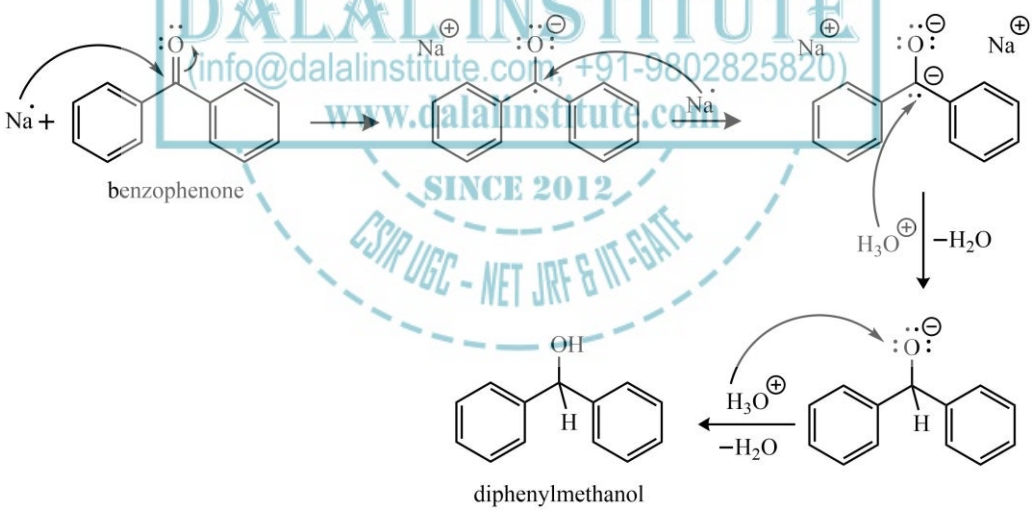
➢ ***SET (Single-Electron Transfer) Mechanism***

SET (single electron transfer) reactions may simply be defined as the organic reaction mechanism in which an electron-rich molecule gives away one of its electrons to an electron-poor molecule to form radical cation and radical anion, respectively. Furthermore, these radical anions and cations can bind to give new bonds or may react in some other way to yield strange products.

Illustrative reaction: One of the most common examples of the SET reactions is the transformation of benzophenone into 1,1-diphenylmethanol in the presence of metallic sodium.



Mechanism involved: The proposed mechanism for the reaction given above involves four steps which must be discussed before we give salient features of the same. The process occurs most often via the formation of benzophenone anion and dianion as given below.



At this stage, some protons are added in the form of very weak (NH_4Cl) or strong acid (HCl). The protonation of benzophenone dianion would yield 1,1-diphenylmethanol.

Salient Features: The main features of the mechanism involved in simple electric transfer or SET type reactions are given below.

i) The electron transfer results in radical cation and radical cation.

ii) The SET mechanisms can be distinguished from polar mechanisms by careful analysis of end products.

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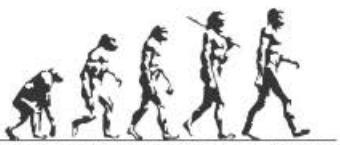

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