STEREOCHEMISTRY

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Part-1: Nucleophilic Substitution Reactions

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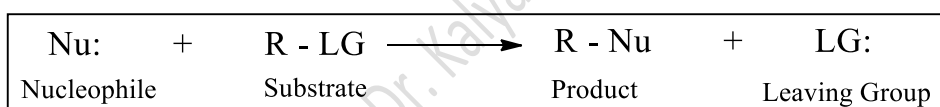
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- *General Features of Nucleophilic Substitution Reaction*

- *Nucleophiles*

- *Mechanisms for Nucleophilic Substitution*

3. *Substitution Nucleophilic Bimolecular*

4. *Substitution Nucleophilic Unimolecular*

- *Stereochemistry of the S_N2 Reaction*

Nucleophilic Substitution Reaction

A substitution reaction is a chemical reaction during which an atom or one functional group in a chemical compound is replaced by another atom or functional group. In organic chemistry, nucleophilic substitution is a class of reactions in which a leaving group (LG) is replaced by an electron rich species (nucleophile). The whole molecular entity of which the electrophile and the leaving group are part is usually called the substrate. The most general form of substitution reaction may be given as the following:

$$
\text{Nu:} \quad + \quad \text{R - LG} \quad \longrightarrow \quad \text{R - Nu} \quad + \quad \text{LG:}
$$

Nu:	R - LG	R - Nu	LG:
Nucleophile	Substrate	Product	Leaving Group

The electron pair from the nucleophile (**Nu:**) attacks the substrate (**R-LG**) forming a new bond, while the leaving group (**LG:**) departs with an electron pair. The principal product in this case is R-Nu.

General Features of Nucleophilic Substitution Reactions

The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged.

$$
\text{Nu}^- \quad + \quad \text{R - X} \quad \longrightarrow \quad \text{R - Nu} \quad + \quad \text{X}^-
$$

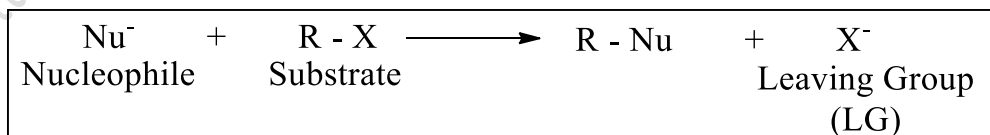| Nu^-	R - X	R - Nu	X^-
Nucleophile	Substrate		Leaving Group (LG)

Figure 1: General form of nucleophilic substitution reaction

Three components are necessary in any nucleophilic substitution reactions as abbreviated in its general form (**Figure 1**):

1. **R- in R-X**: An alkyl group R containing an **sp³** hybridized carbon atom bonded to X in the substrate, R-X.

2. **X- in R-X**: An atom (or group of atoms) called a leaving group, which is capable of accepting the electron density in the C-X bond.

3. **Nu: or Nu⁻**: A nucleophile is an electron rich (a neutral or an anion) species that tends to attack the substrate at a position of low electron density.

As these substitution reactions involve electron rich species, i.e., nucleophiles, they are called nucleophilic substitution reactions. Nucleophilic substitutions are Lewis acid-base reactions. The nucleophile (Lewis base) donates its electron pair, the alkyl halide (Lewis acid) accepts it, and the C-X bond is heterolytically cleaved. Nucleophilic substitution reactions can be broadly categorised as taking place at a saturated aliphatic carbon or at (less often) an aromatic or other unsaturated carbon centre. Nucleophilic substitution reactions occur when an electron rich species, the nucleophile, reacts at an electrophilic saturated carbon atom attached to an electronegative group, the leaving group, that can be displaced as shown in the general scheme in **Figure 1**.

Nucleophilic Substitution Reaction

A common example of nucleophilic substitution reaction is the alkaline hydrolysis of an alkyl halide, e.g., R-Br to the corresponding alcohol (R-OH), where the attacking nucleophile is the OH⁻ and the leaving group is Br⁻.

$$R\text{-}Br + OH^- \rightarrow R\text{-}OH + Br^-$$
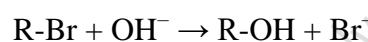
Kinetic measurement on reactions in which alkyl halides (R-X) react with a variety of different nucleophiles, Nu:, have revealed two essentially extreme types: one in which, rate of the reaction is dependent of [Nu:],

$$\text{Rate} = k_2[\text{R-X}][\text{Nu:}] \qquad \text{------------- I}$$

and another in which, the rate is independent of [Nu:],

$$\text{Rate} = k_1[\text{R-X}] \qquad \text{------------------------II}$$

Nucleophiles

Nucleophile means "*nucleus loving*" which describes the tendency of an electron rich species to be attracted to the positive nuclear charge of an electron poor species, the *electrophile*. A nucleophile is, therefore, a chemical species that donates an electron pair to form a chemical bond in relation to a reaction. All molecules or ions with a free pair of electrons or at least one π bond can act as nucleophiles. Since nucleophiles donate electrons, they are by definition Lewis bases. The term 'Nucleophilic' describes the affinity of a nucleophile to the nuclei.

Possible Mechanisms for Nucleophilic Substitution

Overall, a nucleophilic substitution can be represented as follows:
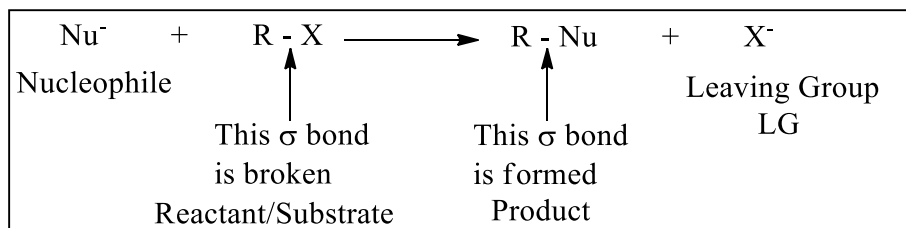
There are two fundamental events in a nucleophilic substitution reaction:

1. breaking of the **σ** bond to the leaving group

2. formation of the new **σ** bond to the nucleophile

Nucleophilic substitution at an **sp³** hybridised carbon, therefore, involves two **σ** bonds: the bond to the leaving group, which is broken, and the bond to the nucleophile, which is formed.

Two Mechanisms for Nucleophilic Substitution

1. The **S$_N$2** mechanism (substitution nucleophilic bimolecular), illustrated by the reaction in Figure **2**.

2. The **S$_N$1** mechanism (substitution nucleophilic unimolecular), illustrated by the reaction in Figure **3**.

The numbers **1** and **2** in the names **S$_N$1** and **S$_N$2** refer to the kinetic order of the reactions. It may also indicate the molecularity of the reaction. For example, **S$_N$2** means that the kinetics are second order. The number **2** does not refer to the number of steps in the mechanism. **S$_N$2** reaction is a single-step process whereas **S$_N$1** reaction is a two-step process.

Mechanisms for Nucleophilic Substitution Bimolecular Reactions (S$_N$2)

Bond breaking and bond formation occur at the same time.

Figure 2: Mechanism of S$_N$2 reaction
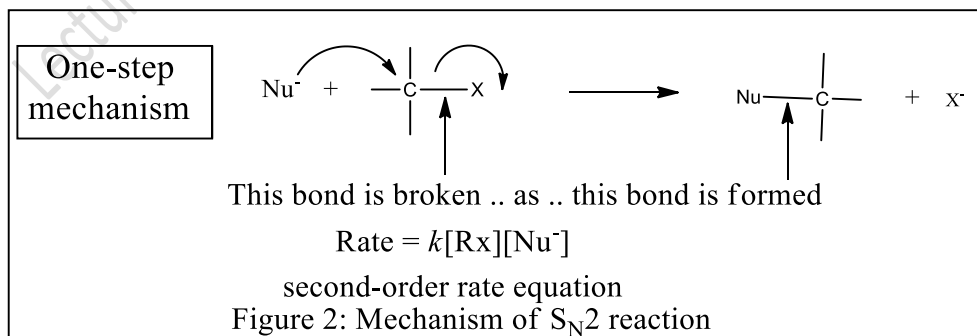
Here, the C-X bond is broken as the C-Nu bond is formed, the mechanism has one-step. The rate of such a bimolecular reaction depends on the concentration of both the reactants; that is, the rate equation is second order. Reaction of methyl bromide (CH_3Br) with the nucleophile acetate ($CH_3CO_2^-$) affords the substitution product methyl acetate ($CH_3CO_2CH_3$) with loss of Br^- as the leaving group. The rate of reaction depends on the concentration of both reactants; that is, the rate equation is *second order*. This bimolecular reaction involves a one-step mechanism in which the C-X bond is broken as the C-Nu bond formed.

Figure 3: S_N2 reaction
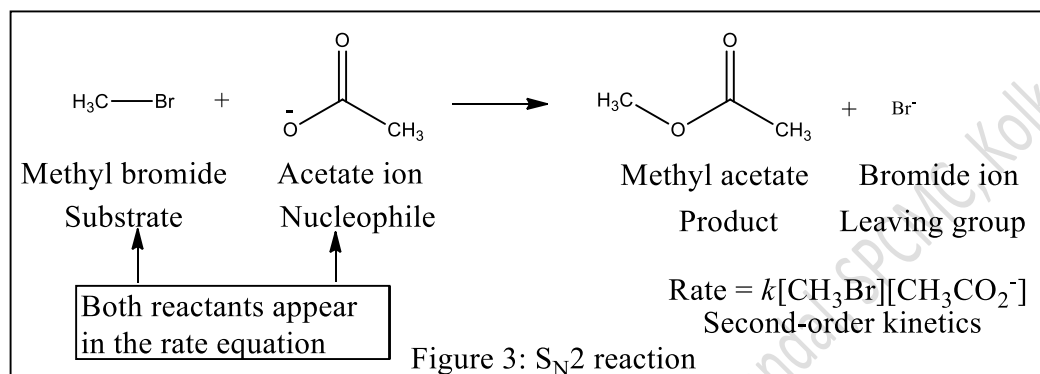
Hydrolysis of the primary halide bromoethane (ethyl bromide) in aqueous base has been shown to proceed according to **Equation 1** as shown in **Figure 4**, and has been interpreted as involving participation of both alkyl halide and hydroxyl ion in the *rate-determining* (i.e., *slowest*) *step* of the reaction.


$$CH_3CH_2Br + OH^- \xrightarrow{H_2O} CH_3CH_2OH + Br^-$$
Rate = $k[CH_3CH_2Br][OH^-]$--------Equation 1
Figure 4: Alkaline hydrolysis of ethyl bromide
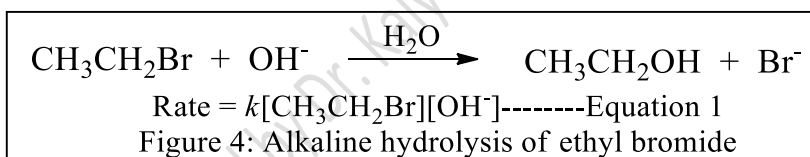
In this S_N2 reaction, the attack of OH^- (the nucleophile) on an ethyl bromide (the electrophile) results in ethyl alcohol, with bromide ejected as the leaving group. Ingold has suggested a *transition state* in which the attacking hydroxyl ion becomes partially bonded to the reacting carbon atom before the incipient bromide ion has become wholly detached from it.

The S_N2 Mechanism

Therefore, the breaking of the C–Br bond and the formation of the new bond (C–OH) occur simultaneously through a transition state in which a carbon under nucleophilic attack is pentacoordinate, and approximately sp^2 hybridized.

The transition state of a chemical reaction is defined as the state corresponding to the highest potential energy along this reaction coordinate, and often marked with the double dagger ‡ symbol. As an example, the transition state shown in **Figure 5** occurs during the S_N2 reaction of bromoethane with a hydroxyl anion. The energy necessary to break the C-Br bond is supplied by simultaneous formation of the C-OH bond.

Figure 5: Mechanism of an S_N2 reaction
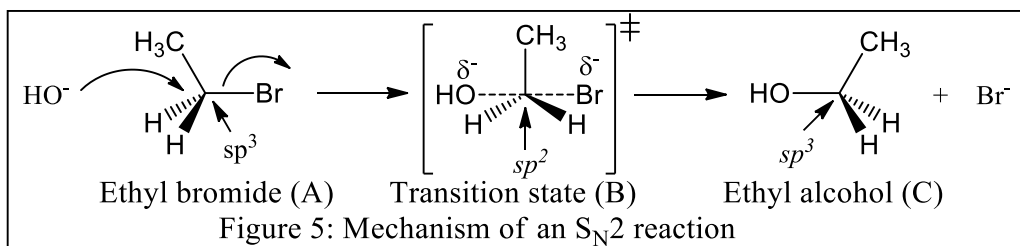
Stereochemistry of the S_N2 Reaction

In **backside attack**, the nucleophile approaches from the opposite side to the leaving group of the substrate **(A)**, forming **B**. In this example, the leaving group was drawn on the right, so the nucleophile attacks from the left. Because the nucleophile and leaving group are in the opposite position relative to the other three groups on carbon, **backside attack** results in *inversion* of configuration around the stereogenic centre. **Figure 6** illustrates the nucleophilic approach.

Figure 6: Mechanism of S_N2 reaction
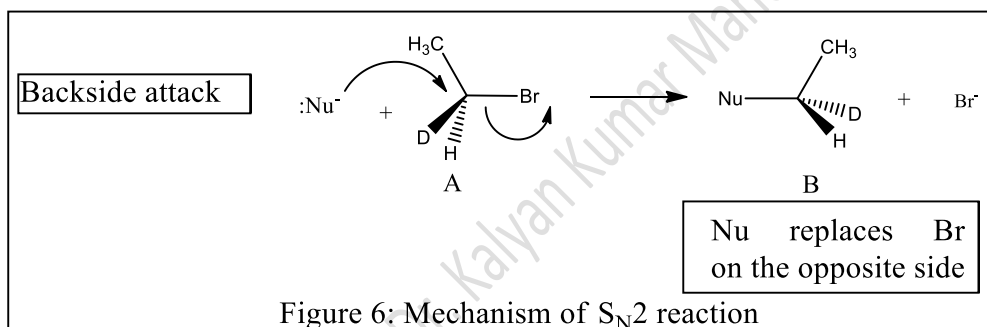
The Identity of the R Group

The rate of an S_N2 reaction change as the alkyl group in the substrate alkyl halide changes from $CH_3 \rightarrow 1° \rightarrow 2° \rightarrow 3°$. As the number of **R** groups on the carbon with the leaving group increases, the rate of an S_N2 reaction decreases.

CH_3-X	RCH_2-X	R_2CH-X	R_3C-X
Methyl	1°	2°	3°
Increasing rate of an S_N2 reaction			

- Methyl and 1° alkyl halides undergo S_N2 reactions with ease.

- 2° Alkyl halides react more slowly.

- 3° alkyl halides do not undergo S_N2 reactions.

This order of reactivity can be explained by steric effects. As small **H** atoms are replaced by larger alkyl groups, steric hindrance caused by bulky **R** groups makes nucleophilic attack from the *backside* more difficult, slowing the reaction rate. **Figure 7** illustrates the effect of

increasing steric hindrance around the carbon bearing the leaving group in a series of alkyl halides.


Figure 7: Effect of steric crowding in S_N2 reaction
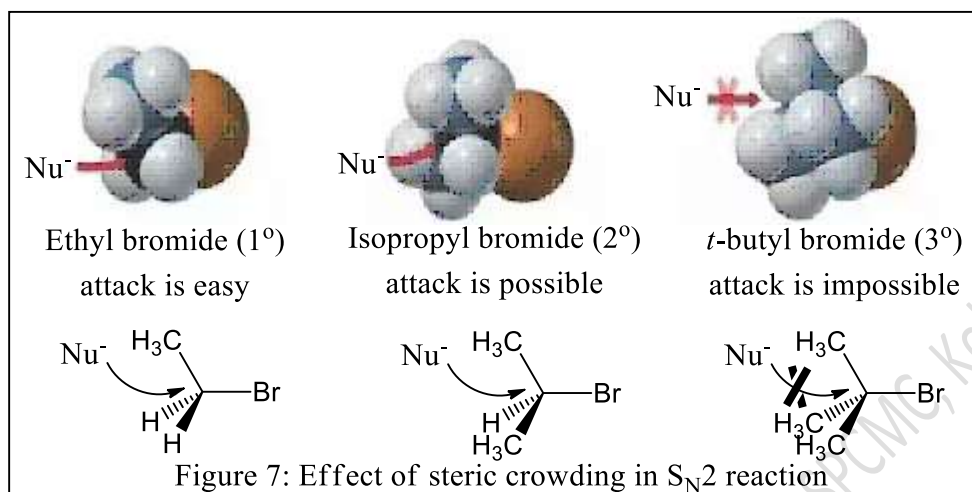
The *transition state* of each S_N2 reaction consists of five groups around the central carbon atom-three bonds to either **H** or **R** groups and the two partial bonds to the leaving group and the nucleophile.

- Increasing the number of **R** groups on the carbon with the leaving group increases crowding in the transition state, decreasing the rate of an S_N2 reaction.

- The S_N2 reaction is fastest with unhindered halides.

Table 1: Characteristics of the S_N2 Mechanism	
Characteristic	Result
Kinetics	Second-order kinetics
Rate	$k[RX][Nu^-]$
Mechanism	One-step
Stereochemistry	*Backside* attack of the nucleophile *Inversion of configuration* at a *stereogenic* centre
Identity of R	Unhindered halides react fastest Rate: $CH_3X > RCH_2X > R_2CHX > R_3CX$

Mechanisms for Nucleophilic Substitution Unimolecular Reactions (S$_N$1)

Bond breaking occurs before bond formation.
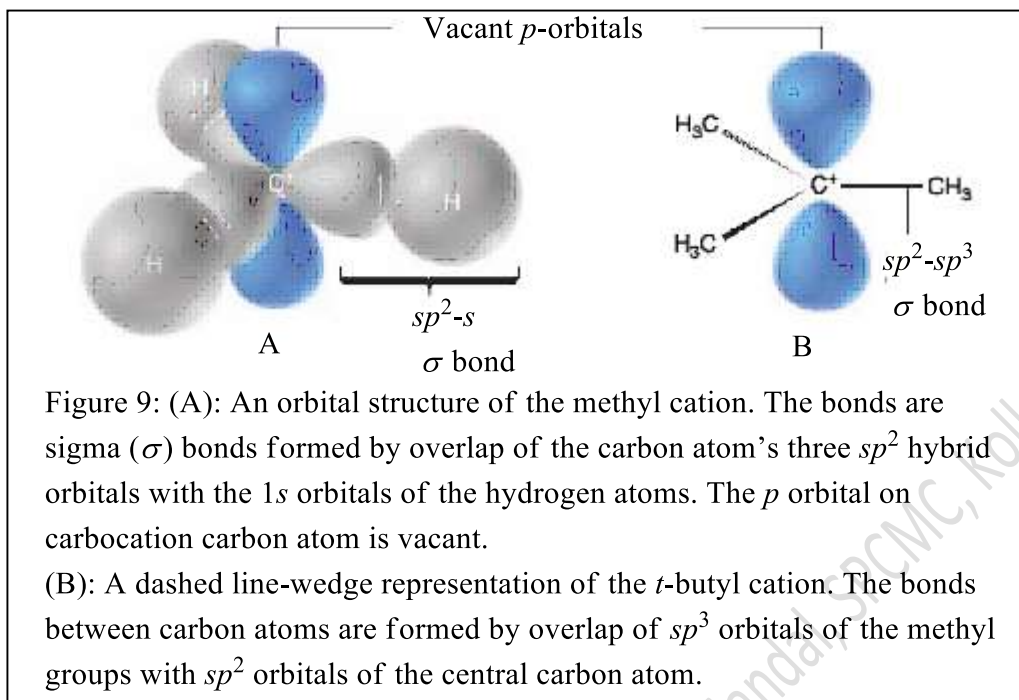

Figure 5: Mechanism of S$_N$1 reaction
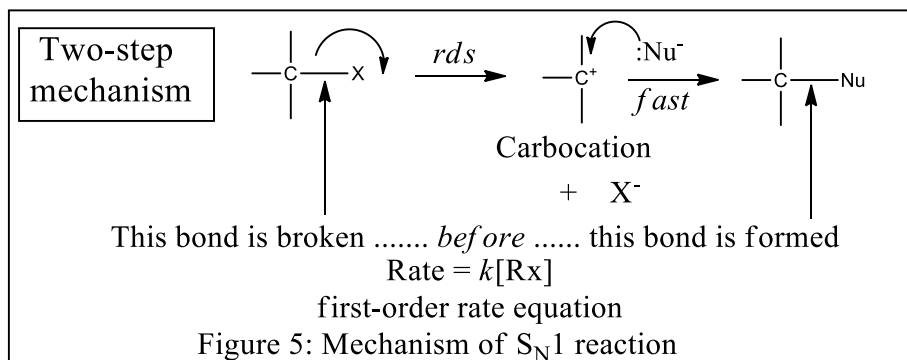
Here, the C-X bond is broken first and then the C-Nu bond is formed, the mechanism has two-steps and a carbocation is formed as a reactive intermediate. The first step is rate-determining, and the rate of such a unimolecular reaction depends on the concentration of RX only; therefore, the rate equation is first order. **Figure 6** illustrates a similar nucleophilic substitution reaction with *t*-butyl bromide [(CH$_3$)$_3$CBr], which also leads to substitution of Br$^-$ by CH$_3$CO$_2^-$. Kinetic data show that this reaction rate depends on the concentration of only one reactant, the alkyl halide; that is, the rate equation is *first order*. This suggests a two-step mechanism in which the rate-determining step involves the alkyl halide only.

Figure 6: S$_N$1 reaction
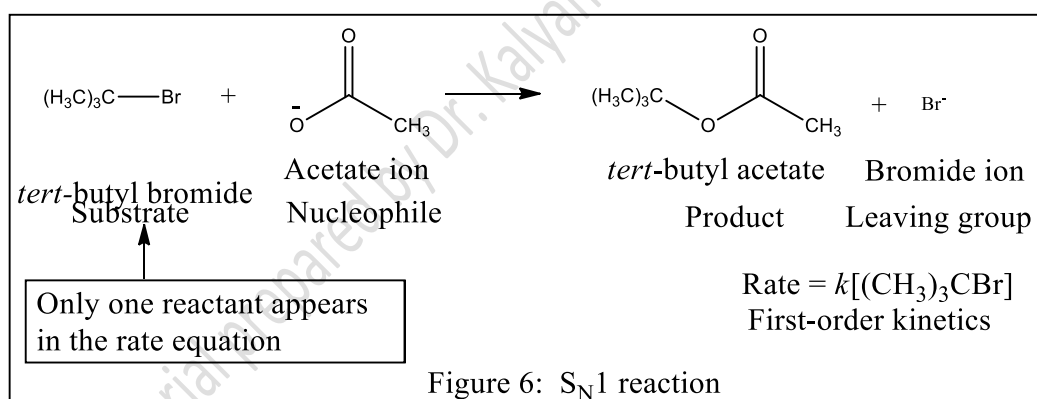
The Structure of Intermediate Carbocations

- Carbocations are trigonal planar. Trigonal planar structure of a carbocation of the type R^{1}R^{2}R^{3}C$^+$ can be accounted for on the basis of *sp^2* hybridization (**Figure 9**).

Figure 9: (A): An orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 hybrid orbitals with the $1s$ orbitals of the hydrogen atoms. The p orbital on carbocation carbon atom is vacant.

(B): A dashed line-wedge representation of the t-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl groups with sp^2 orbitals of the central carbon atom.

The central carbon atom in a carbocation is electron deficient; it has only six electrons in its valence shell: In the given structure (**Figure 9**), these six electrons are used to form three sigma covalent bonds to hydrogen atoms or alkyl groups. The p orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction.

The Relative Stabilities of Carbocations

The relative stabilities of carbocations are related to the number of alkyl groups attached to the positively charged trivalent carbon. Tertiary carbocations are the most stable, and the methyl carbocation is the least stable. The overall order of stability is as follows (**Figure 10**).

The Relative Stabilities of Carbocations

Figure 10: Relative stabilities of simple carbocations
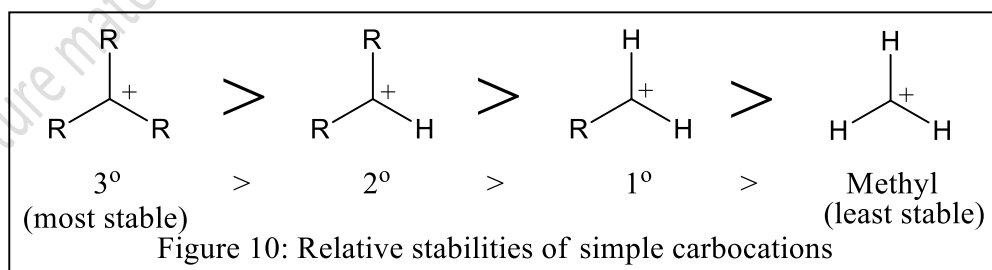
This order of carbocation stability can be explained on the basis of hyperconjugation. **Hyperconjugation (Figure 11)** involves electron delocalization (via partial orbital overlap) from a filled bonding orbital to an adjacent unfilled orbital.

Figure 11: Hyperconguation in between a sigma bonding orbital and an adjacent carbocation *p* orbital.
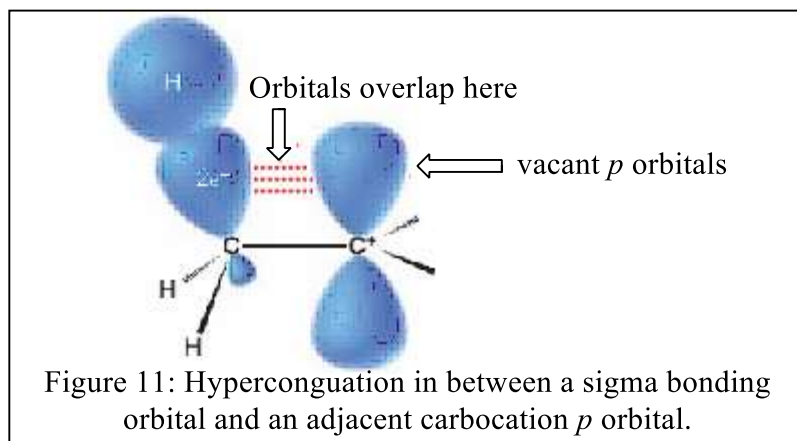
A methyl group attached to the carbocation carbon atom helps to stabilize the positive charge of a carbocation. Electron density from one of the carbon-hydrogen σ bonds of the methyl group flows into the vacant *p* orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2-hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability of the carbocation. This interaction of a bond orbital with a *p* orbital is called hyperconjugation.

In the case of a carbocation, the unfilled orbital is the vacant *p* orbital of the carbocation, and the filled orbitals are C-H or C-C σ bonds at the carbons *adjacent* to the *p* orbital of the carbocation. Sharing of electron density from adjacent C-H or C-C sigma bonds with the carbocation *p* orbital delocalizes the positive charge. Any time a charge can be dispersed or delocalized by hyperconjugation, inductive effects, or resonance, a system will be stabilized.

Figure 11 shows a representation of hyperconjugation between a σ bonding orbital and an adjacent carbocation *p* orbital. Tertiary carbocations have three carbons with C-H bonds (or, depending on the specific example, C-C bonds instead of C-H) adjacent to the carbocation that can overlap partially with the vacant *p* orbital. Secondary carbocations have only two adjacent carbons with C-H or C-C bonds to overlap with the carbocation; hence, the possibility for hyperconjugation is less and the secondary carbocation is less stable than the tertiary carbocation.

Primary carbocations have only one adjacent carbon from which to derive hyperconjugative stabilization, and so they are even less stable. A methyl carbocation has no possibility for hyperconjugation, and it is the least stable of all in this series. **Figure 12** illustrates the stability order of simple carbocations:
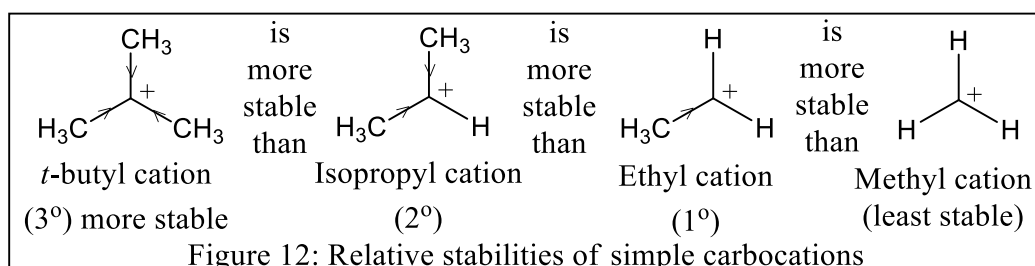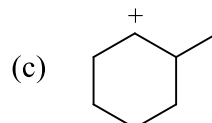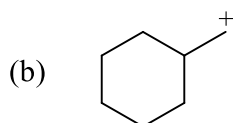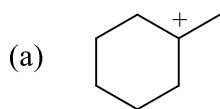

Figure 12: Relative stabilities of simple carbocations

In summary:

- **The relative stability of carbocations is 3° > 2° > 1° > methyl.**

Problem: Rank the following carbocations in order of increasing stability:

(a)   (b)   (c)