Lecture No.1/ Ch.3 ...*By Prof. Dawood Salim Abid*

Substrate + Reagent ⟶ [Intermediate(s)] / [Transition state(s)] ⟶ Products
⟶ By-products

Starting material $\underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}}$ Intermediate(s) $\underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}}$ Product(s)

$$K_{eq} = \frac{[products]}{[reactants]}$$
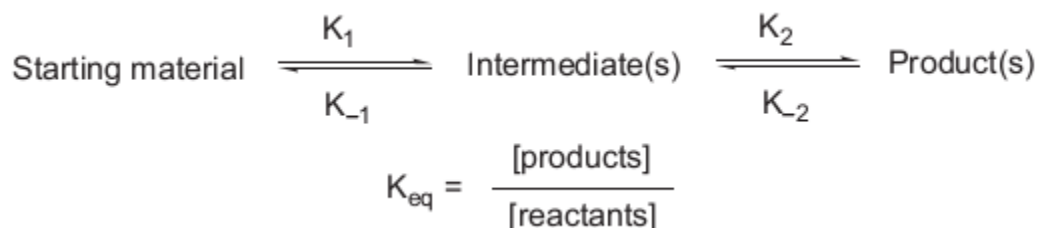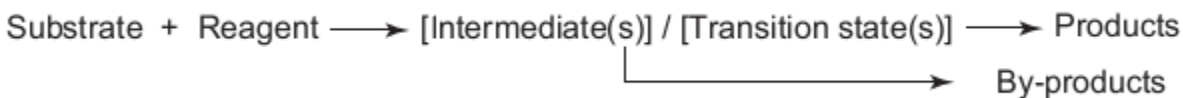
The rate of a reaction is dependent on the following three factors:

1) The number of effective collisions taking place between the reacting molecules in a given period of time. The greater the number of collisions, the faster the reaction.
2) The fraction of collisions that occur with sufficient energy to get the reacting molecules over the energy barrier (not all collisions between molecules lead to chemical change).
3) The fraction of collisions that occur with the proper orientation.

There are two ways of speeding reactions up: (i) we can heat the reactants so that a higher proportion of them have the activation energy on collision; (ii) we can add a suitable catalyst to the reaction mixture.

The rate of a chemical reaction can be defined as the number of reactant molecules converted into products in a given time.

As the reactants change into products, they pass through an unstable state of maximum free energy, called the *transition state* or *activated complex* that is not stable, having transient existence, and cannot be isolated.

Intermediates are molecule or ion that represent a localized energy minimum having fully formed bonds and existing for some finite length of time with some stability. The transition state has a higher energy than either the reactants or products. The energy required to reach the transition state from the reactant energy

minimum is defined as the *activation energy*. This activation energy, also called the *energy barrier* for a reaction, is the minimum energy molecules must have if they are to react. A reaction coordinate diagram describes the energy changes that take place in each of the steps (Figure 1.1).
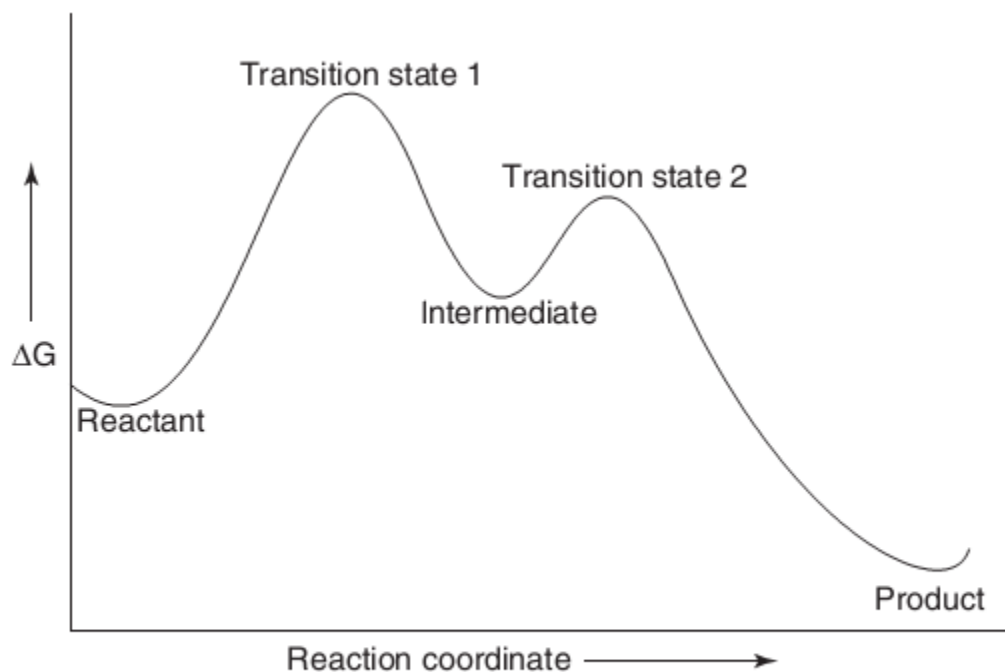

Figure 1.1 Reaction profile showing the reaction intermediate where $k_2 > k_{-1}$.
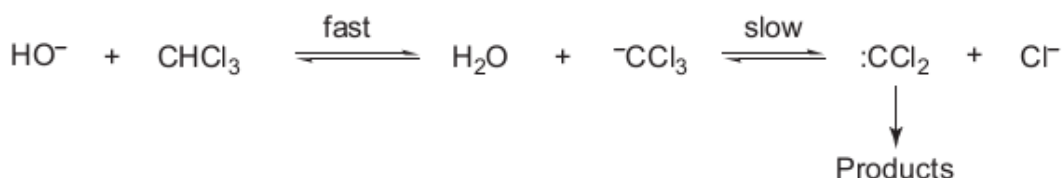
Many of the reactive intermediates of organic chemistry are charged species, such as **carbocations** (carbenium and carbonium ions) and **carbanions**, but there is an important subgroup of formally neutral electron-deficient reactive intermediates. For example, a carbon-containing reactive center can be either trivalent, with a single nonbonding electron, that is, a carbon centered **radical**, or divalent with two nonbonding electrons, that is, a **carbene**. Neutral reactive intermediates such as radicals, carbenes, nitrenes, and arynes

Table 1.2 Common reactive intermediates and their relationships.

Type	C	N	O
-Onium ion	R_5C^+ carbonium ion	R_4N^+ ammonium ion	R_3O^+ oxonium ion
Neutral molecule	R_4C	R_3N	R_2O
Anion	R_3C^- carbanion	R_2N^- amide anion	RO^- alkoxide
Radical	$R_3C^{\bullet}$ carbon radical	$R_2N^{\bullet}$ aminyl radical	$RO^{\bullet}$ oxyl radical
-Enium ion	R_3C^+ carbenium ion	R_2N^+ nitrenium ion	RO^+ oxenium ion
-Ene	$R_2C:$ carbene	$RN:$ nitrene	$:O:$ oxene

A classic example of the combined uses of kinetic and product-trapping studies is that of Hine and coworkers in their work on the hydrolysis of chloroform under basic conditions. The observation that chloroform undergoes deuterium for hydrogen exchange (in D_2O) faster than hydrolysis and further that the rate

of hydrolysis is retarded by addition of chloride ion is strong evidence in favor of the mechanism shown. Further circumstantial evidence for dichlorocarbene formation is provided by trapping experiments, for example, with alkenes, giving 1,1-dichlorocyclopropanes as products (Scheme 1.1).

$$HO^- + CHCl_3 \underset{fast}{\rightleftharpoons} H_2O + {}^-CCl_3 \underset{slow}{\rightleftharpoons} :CCl_2 + Cl^-$$
$$\downarrow$$
$$Products$$

Scheme 1.1
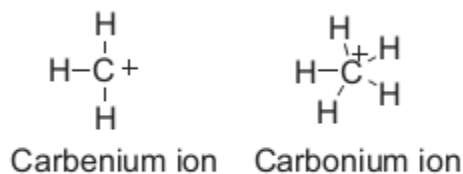
Carbocations

Carbenium ion   Carbonium ion

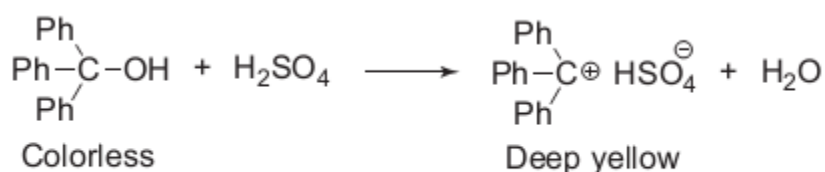**Figure 2.1** Carbenium and carbonium ions.

The history of carbocations dates back to 1891 when G. Merling reported that he added bromine to tropylidene (cycloheptatriene) and then heated the product to obtain a crystalline, water-soluble material, C_7H_7Br.

Doering and Knox convincingly showed that it was tropylium (cycloheptatrienylium) bromide (Figure 2.2). This ion is predicted to be aromatic by the Hückel rule.
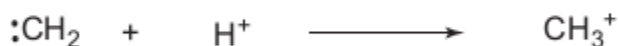

Figure 2.2 Tropylium bromide.

In 1902 Norris and Kehrman independently discovered that colorless triphenyl-methanol gave deep yellow solutions in concentrated sulfuric acid (Scheme 2.1).

Scheme 2.1 Reaction of triphenylmethanol with conc. H_2SO_4.

Carbonium Ions and Carbenium Ions

$$R_4\overset{+}{N} \qquad R_4\overset{+}{P} \qquad R_3\overset{+}{O} \qquad R_3\overset{+}{S}$$

Ammonium   Phosphonium   Oxonium   Sulfonium

$$:CH_2 \ + \ H^+ \longrightarrow CH_3^+$$

Scheme 2.2 Hypervalent and hypovalent cations.
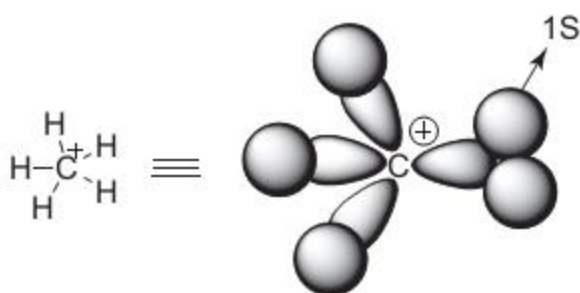
$$CH_4 + H^+ \longrightarrow CH_5^+ \xrightarrow{-H_2} \ ^+CH_3$$

Figure 2.3 Representation of the structure of CH_5^+.

Table 2.1 Relationship between hypovalent and hypervalent carbocations.

Property	CH_3^+	CH_5^+
Number of bonds to C^+	3	5
Electrons in outer shell	6	8
Empty orbital	Yes, a p orbital	No
Electron-deficient	Yes	No

Olah was able to make carbocations from alcohols. He treated *tert*-butanol with SbF_5 and HF in liquid SO_2 (Scheme 2.3).
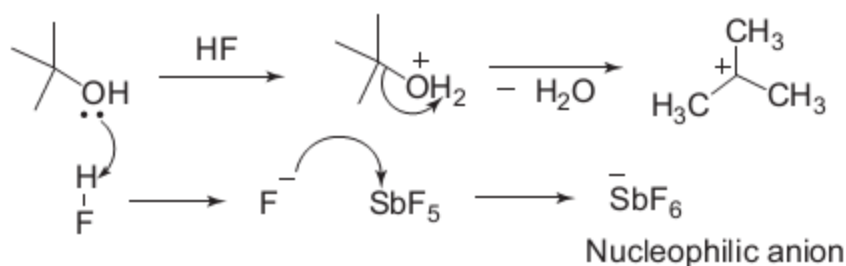
Scheme 2.3   Generation of *tert*. butyl cation.

Structures and Geometry of Carbocations

Carbocations are electron-deficient species that are the most important intermediates in several kinds of reactions. A common model for carbocation structure is a planar species exhibiting sp^2 hybridization, as shown in Figure 2.4 for methyl cation. The p-orbital that is not utilized in the hybrids is empty and is often shown bearing the positive charge since it represents the orbital available to accept electrons. There is a vacant p orbital perpendicular to the plane of the molecule;
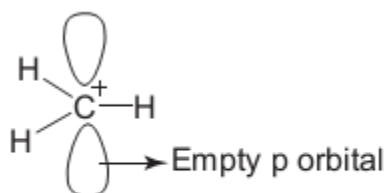

Figure 2.4   Methyl cation.

The ΔH for heterolytic dissociation of alkanes in the gas phase varies with the alkyl groups as follows: methyl > ethyl > *iso*-propyl > *tert*-butyl, which is consistent with the generalization that the ease of formation of carbocations is $3° > 2° > 1°$.

We may also explain the electron-donating ability of a methyl or other alkyl group in terms of *hyperconjugation* (σ conjugation into empty p orbital), a lowering of the energy of a system by delocalization of electrons through π bonds involving sp^3-

hybridized carbon atoms adjacent to the carbocation center. In molecular orbital terms, hyperconjugation is the overlap of the filled sigma orbitals of the C–H bonds adjacent to the carbocation with the empty "p" orbital on the positively charged carbon atom (Scheme 2.5a).

(a)

(b)
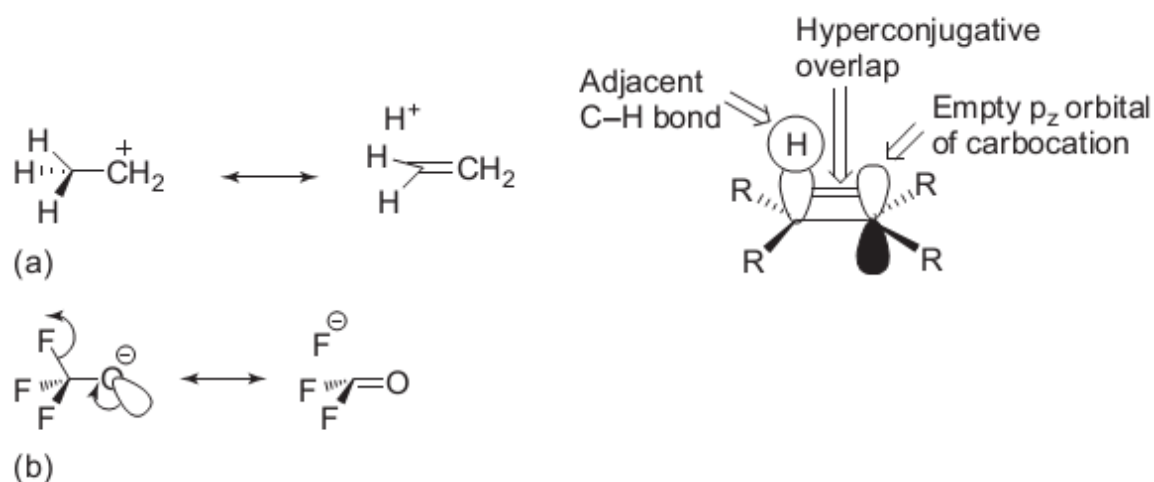
Scheme 2.5 (a) Stabilization of carbocation by hyperconjugation with an adjacent methyl group; (b) negative hyperconjugation.
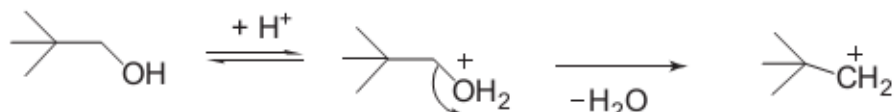
Generation of Carbocation

From a Halide

$$MeCOF + BF_3 \rightleftharpoons MeCO^+BF_4^-$$
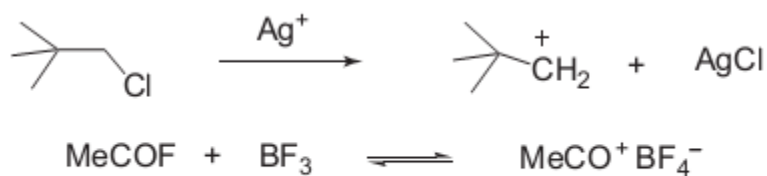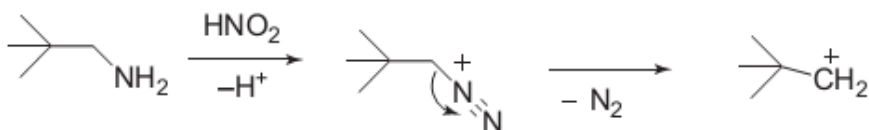
Scheme 2.6

From an Alcohol

By treatment with acid, protonation of lone-pair electrons occurs, resulting in conversion into a better leaving group that promotes heterolysis (Scheme 2.7). Solvolysis reactions are promoted by polar solvents such as dimethyl sulfoxide (DMSO), DMF (dimethylformamide), THF (tetrahydrofuran), and so on. These solvents stabilize the transition state as well as the ions formed.
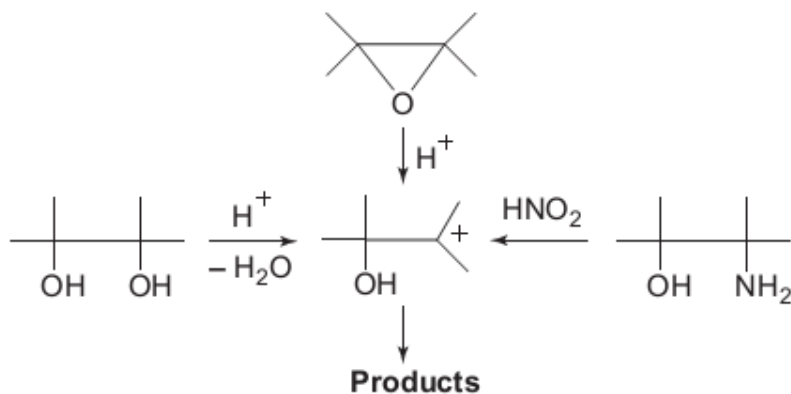

Scheme 2.7

From an Amine

Amines are treated with nitrous acid to give diazonium ion that loses molecular nitrogen to form a carbenium ion (Scheme 2.8).
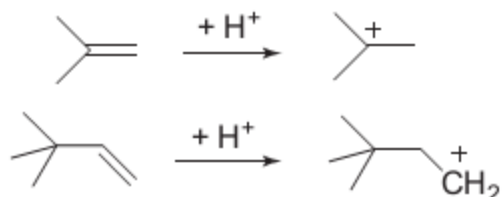

Scheme 2.8

Note that there could be more than one route for the generation of a given carbocation (Scheme 2.9).
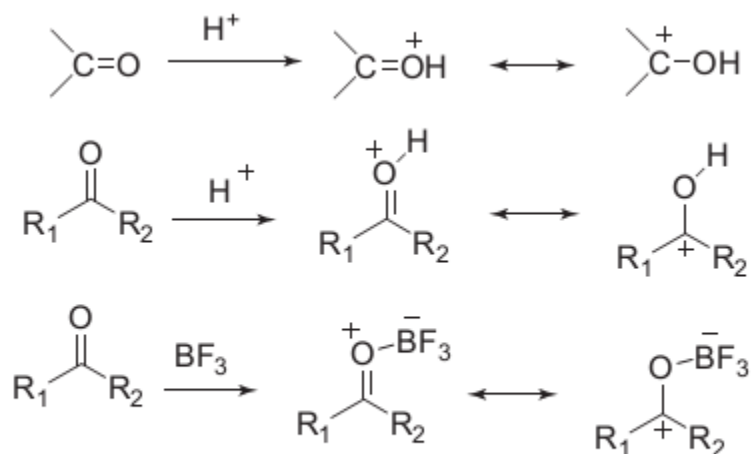

Scheme 2.9

From an Alkene

Carbocations may also be formed from alkenes by protonation (Scheme 2.10).

Scheme 2.10

From Carbonyl Compounds

The reaction of aldehydes and ketones with an acid catalyst gives the corresponding oxygen-stabilized cation. Protonation of carbonyl compounds also gives carbocations (Scheme 2.11). Here, note that carbocations are positively charged species. They are much more likely to be formed in acidic than in basic media; in fact, carbocations are never seen under conditions that are strongly basic.
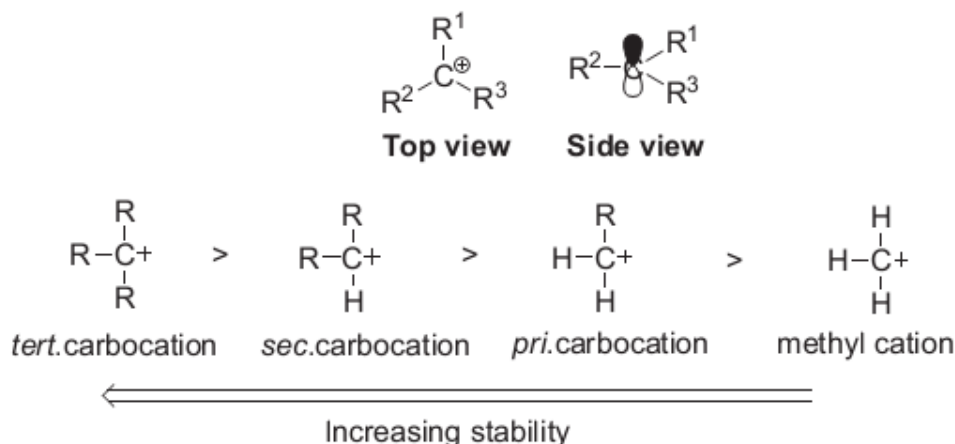

Scheme 2.11

Carbocation Stability

- nucleophilic substitution (S_N1) and elimination (E1) reactions;
- additions of electrophiles to double and triple bonds;
- electrophilic aromatic substitution;
- additions to carbonyl compounds and enolate chemistry (albeit in masked form).

Three main structural factors help to stabilize carbocations:

1) neighboring carbon atoms;
2) neighboring carbon–carbon multiple bonds;
3) neighboring atoms with lone pairs.

The greater the number of alkyl substituents bonded to the positively charged carbon, the more stable the carbocation will be. The order of relative stability of carbocations is: tertiary ~ benzylic > allylic ~ secondary > primary ~ vinyl > phenyl. The nature of electron release by alkyl groups is not very clear. It may be an inductive effect, a resonance effect (hyperconjugation), or a combination of the two. When we refer to the inductive effect of the alkyl groups, it should be clear that this might well include a contribution from hyperconjugation.
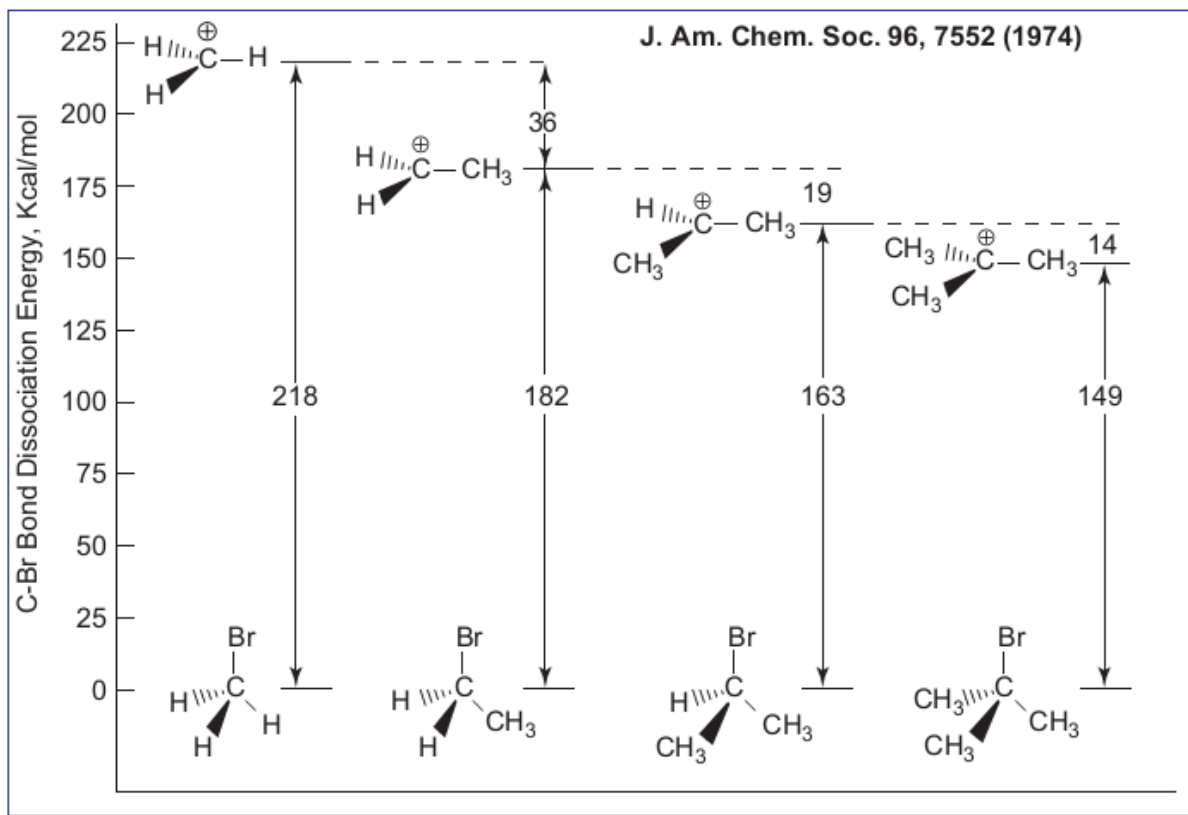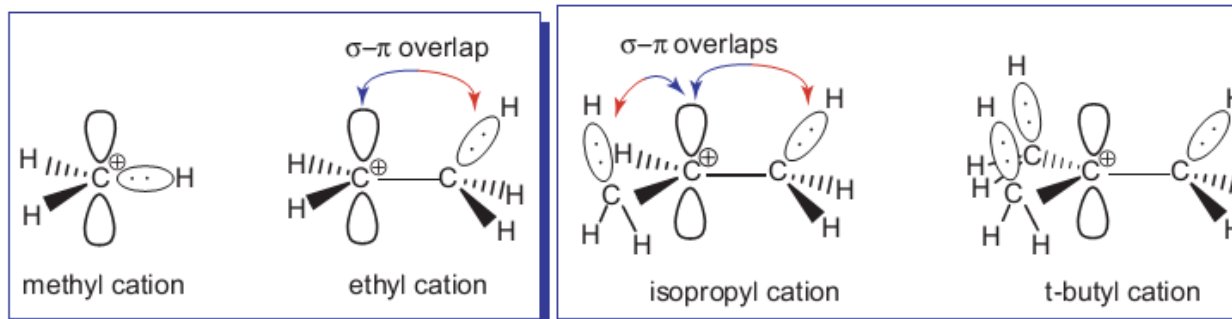

Top view   **Side view**

tert.carbocation   *sec*.carbocation   *pri*.carbocation   methyl cation

Increasing stability

σ–π overlap

methyl cation   ethyl cation

σ–π overlaps

isopropyl cation   t-butyl cation

J. Am. Chem. Soc. 96, 7552 (1974)

C-Br Bond Dissociation Energy, Kcal/mol

225 —

200 —

175 —

150 —

125 —

100 —

75 —

50 —

25 —

0 —

36

19

14

218   182   163   149

Figure 2.6   Relative stabilities of carbocations in quantitative terms.

it is formed. The energy difference between 1°, 2°, and 3° cations is approximately $11-15$ kcal mol^{-1}.

Delocalized π bond

Is more stable than

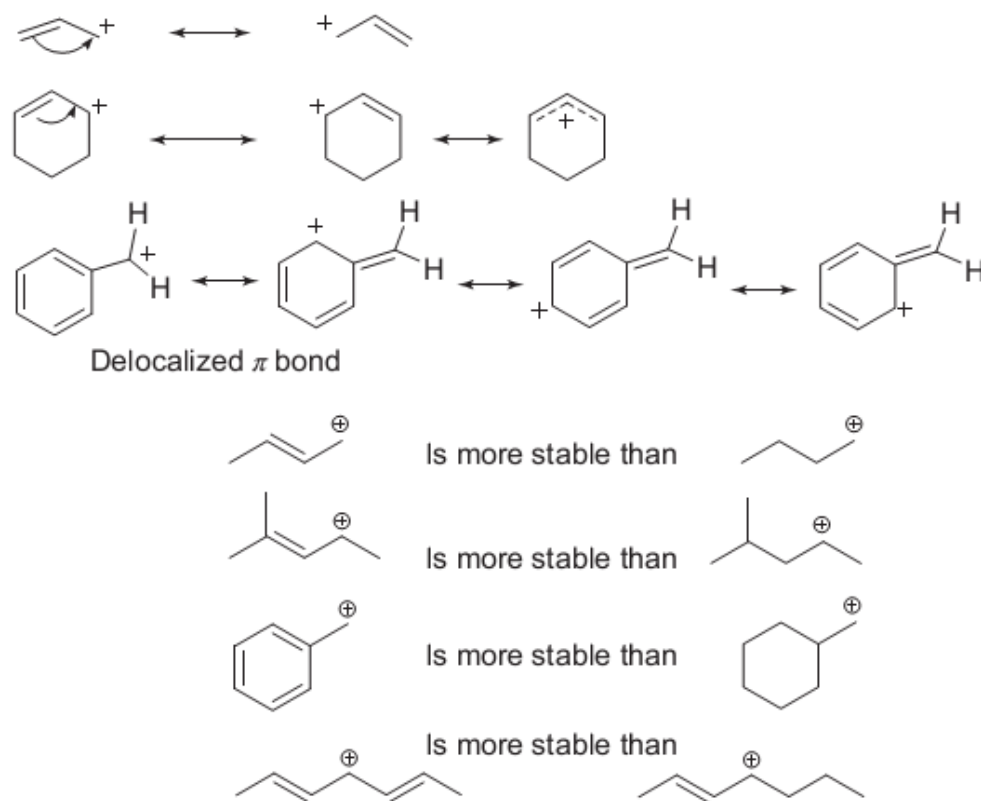Is more stable than

Is more stable than

Is more stable than

Figure 2.7 Effect on carbocation stability of resonance stabilization by conjugation with pi bonds.

There are basically two types of carbocations: (i) those that are *not* stabilized by resonance effects (simple alkyl carbocations) and (ii) those that *are* stabilized by resonance, which usually occurs either through lone pair (nonbonding) electrons on adjacent atoms or through conjugated π-bonding electrons (e.g., **allylic** and the **benzylic** carbocations, Figure 2.7).
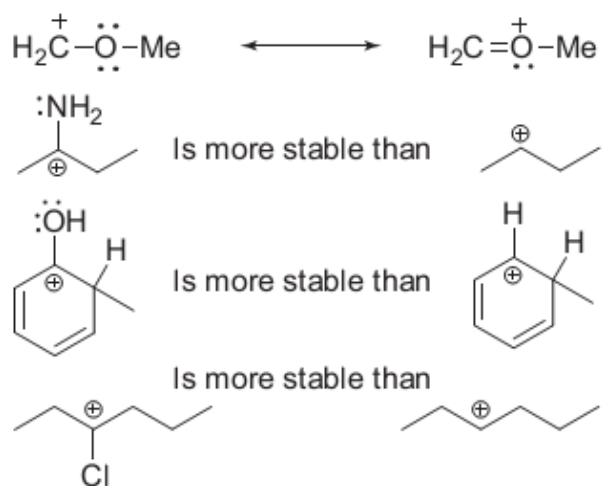
Figure 2.8 Effect on carbocation stability of resonance stabilization through lone pair (non-bonding) electrons.
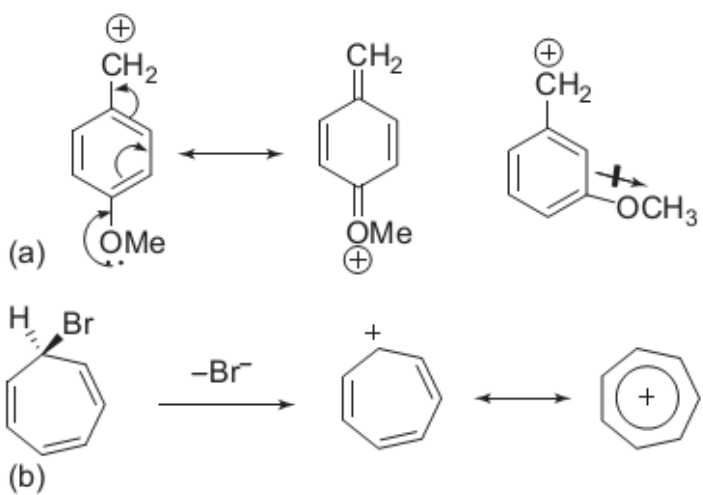

Figure 2.9 Carbocation charge stabilization through (a) conjugation and (b) aromatization.
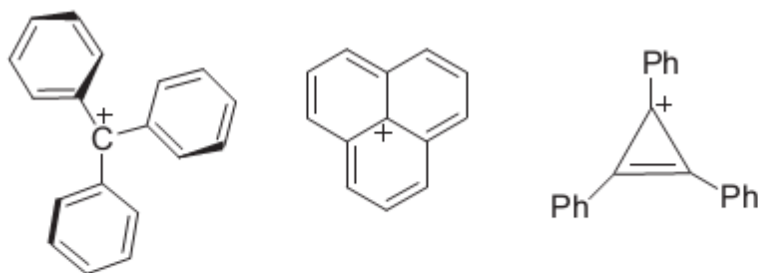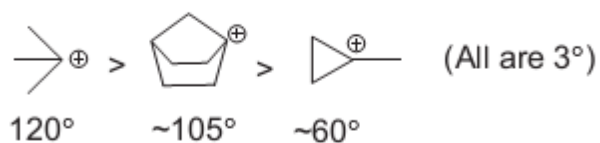
Figure 2.10 Examples of long-lived carbenium ions.

$120°$ $\sim105°$ $\sim60°$

Figure 2.11 Preference of carbocations for planar geometry (120° inter-bond angles).

Reaction with a Nucleophile

The carbocation may react with an electron-rich species (neutral or anionic), that is, with a nucleophile (known as S_N1) to give the stable compound. The carbon–halogen bond breaks heterolytically without any assistance from the nucleophile, forming a carbocation. The carbocation then reacts with the nucleophile to form the substitution product, that is, an ionization mechanism (Scheme 2.12).

Treatment of an alkene with formaldehyde in the presence of an acid gives a 1,3-diol together with an α,β-unsaturated alcohol or cyclic acetal (**Prins reaction**) (Scheme 2.13).

(I) $R-I$ + $\overset{\ominus}{OH}$ $\longrightarrow$ $R-OH$ + $I^{\ominus}$

CH_3CHCH_2CN $\overset{NaI}{\underset{acetone}{\longrightarrow}}$ CH_3CHCH_2CN
$|$ $|$
Br I

 CH_2OTs $\overset{LiBr}{\underset{acetone}{\longrightarrow}}$ CH_2Br

$CH_3CH(CH_2)_5CH_3$ + PhS^- $\overset{ethanol}{\longrightarrow}$ $CH_3CH(CH_2)_5CH_3$
$|$ $|$
OTs SPh

(II) $R-I$ + NMe_3 $\longrightarrow$ $R-\overset{+}{N}Me_3$ $I^{\ominus}$

CH_3CH_2I + $(CH_3CH_2CH_2CH_2)_3P$ $\longrightarrow$ $(CH_3CH_2CH_2CH_2)_3\overset{+}{P}CH_2CH_3\ I^-$

$PhC(CH_3)_2Cl$ + CH_3CH_2OH $\longrightarrow$ $PhC(CH_3)_2\overset{+}{\underset{H}{O}}CH_2CH_3$ $\overset{}{\underset{-H^+}{\longrightarrow}}$ $PhC(CH_3)_2OCH_2CH_3$

$CH_3CHCH_2CH_3$ + H_2O $\overset{acetone}{\longrightarrow}$ $CH_3CHCH_2CH_3$ $\overset{}{\underset{-H^+}{\longrightarrow}}$ $CH_3CHCH_2CH_3$
$|$ $|$ $|$
OTs $+OH_2$ OH
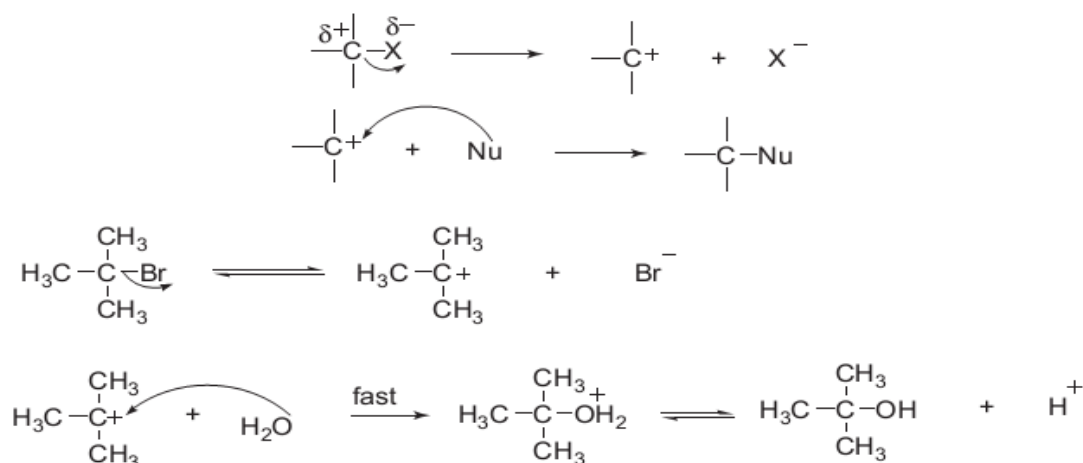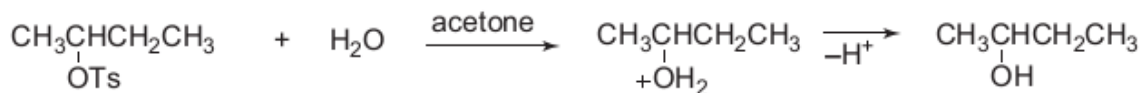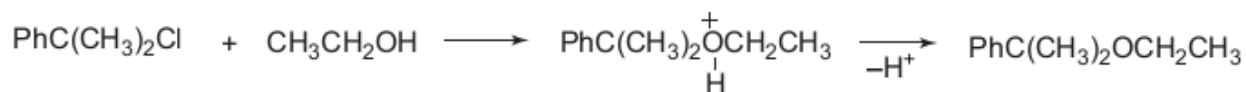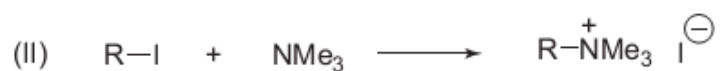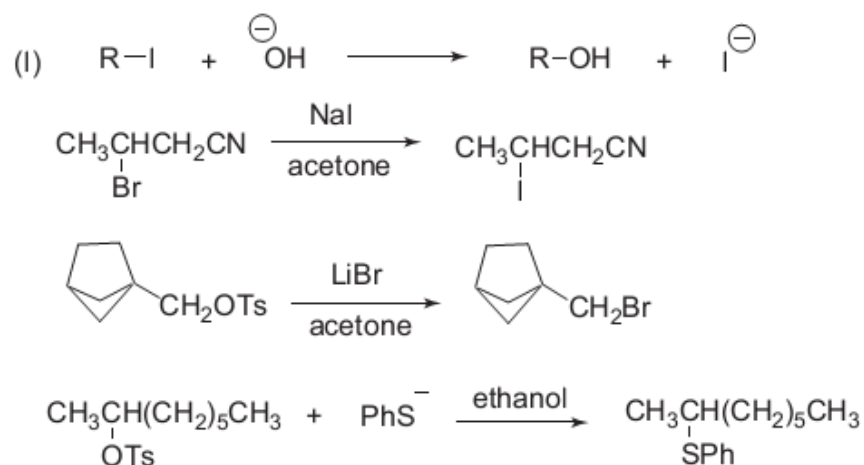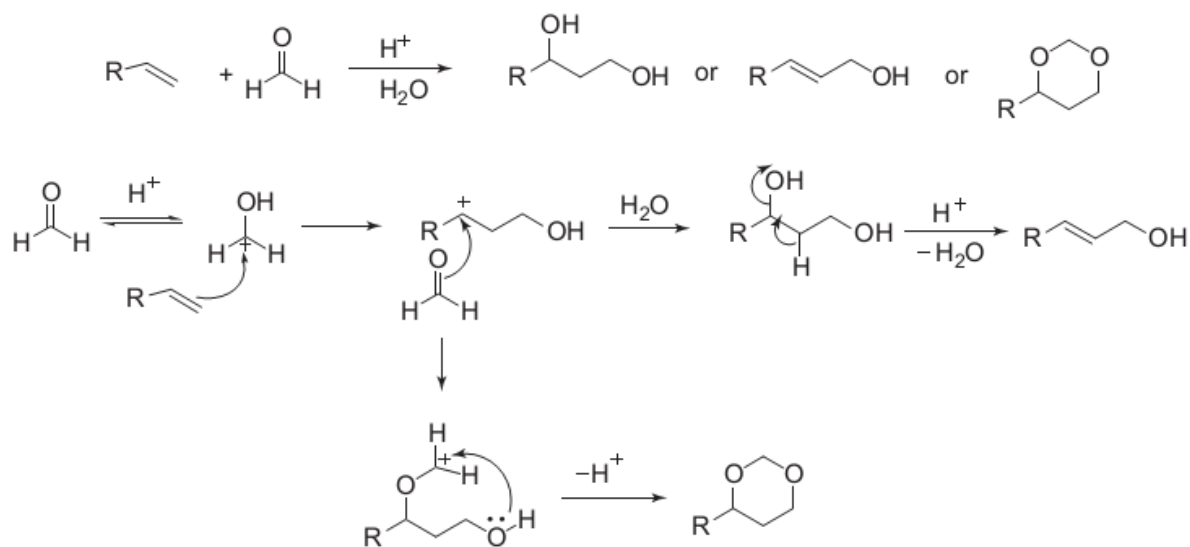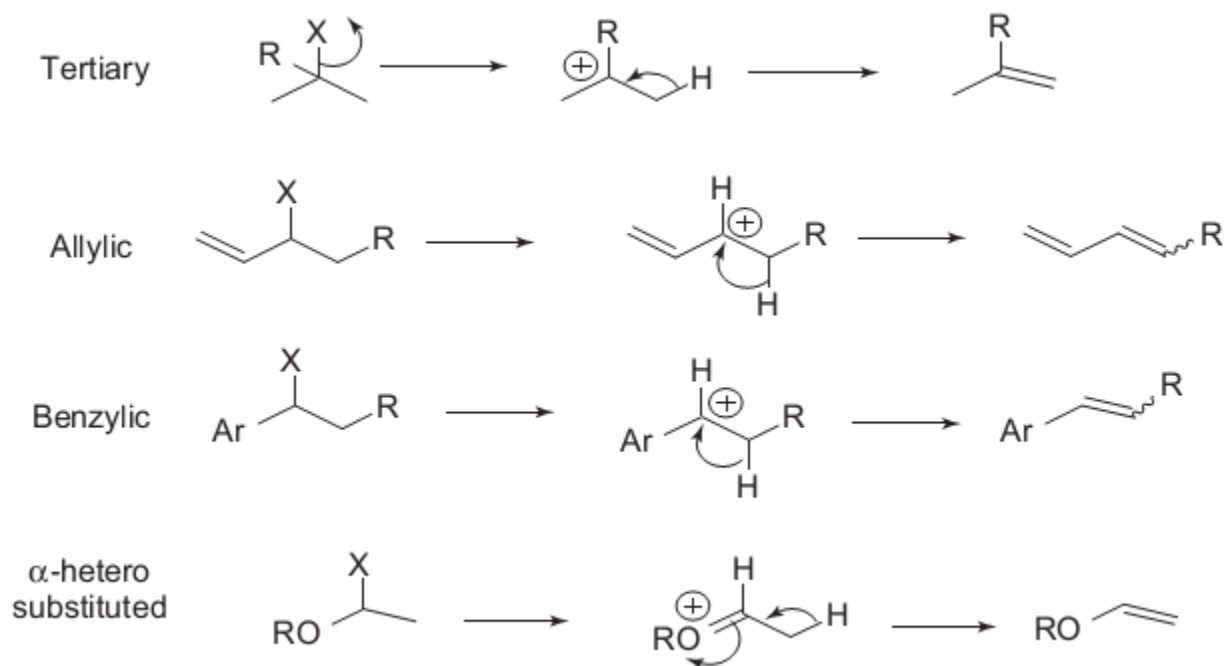
Scheme 2.12

Scheme 2.13

Elimination of a Proton

Substrates that readily eliminate by E1

Tertiary

Allylic

Benzylic

α-hetero
substituted

Scheme 2.14

HO⁻   H   Br   ⟶   HOH   +   [isobutylene structure]   Br⁻

$$Me-CH=CMe_2 \quad + \quad H_2O$$
Elimination

$$\overset{H}{\underset{Br}{Me-CH-CMe_2}} \quad \xrightarrow{\text{Slow}} \quad \overset{H}{Me-CH-\overset{+}{C}Me_2} \quad \xrightarrow{\overline{OH}}$$

E1

Br⁻

$$\xrightarrow{S_N1}$$

$$\overset{-}{OH} \quad Me-\overset{H}{CH}-\underset{OH}{CMe_2} \quad + \quad Br^-$$
Substitution

$$H_2SO_4 \rightleftharpoons H^+ \quad + \quad HO-\overset{O}{\underset{O}{S}}-O^-$$

[(CH₃)₃C-OH] $\xrightarrow{H^+}$ [(CH₃)₃C-OH₂⁺] $\xrightarrow{\text{Slow}}$ [carbocation] $\xrightarrow{\text{Fast}}$ [isobutylene]

Scheme 2.15

Only one alkene possible

[t-BuOH] OH H⁺ ⟶ [isobutylene]

Ph
OH
[cyclohexanol with Ph] $\xrightarrow{H^+}$ [Ph-cyclohexene]

Ph

Two regioisomeric alkenes possible

OH
[1-methylcyclohexanol] $\xrightarrow{H^+}$ [1-methylcyclohexene] + [methylenecyclohexane]

Two stereoisomeric alkenes possible

OH
[Ph-CH(OH)-CH₂-CH₃] $\xrightarrow{H^+}$ Ph—[trans-alkene] + Ph—[cis-alkene]
Ph   95%   5%

Scheme 2.16

Rearrangements of Carbocations

1,2-Hydride shift

$$CH_3CH_2\overset{+}{C}HCH_2 \longrightarrow CH_3CH_2\overset{+}{C}HCH_3$$

pri.carbocation → *sec*.carbocation

1,2-Hydride shift

sec.carbocation → *tert*.carbocation

1,2-methyl shift

sec.carbocation → *tert*.carbocation

Scheme 2.17

1,3-hydride shift

Does not work

1,4-alkyl shift

Does not work
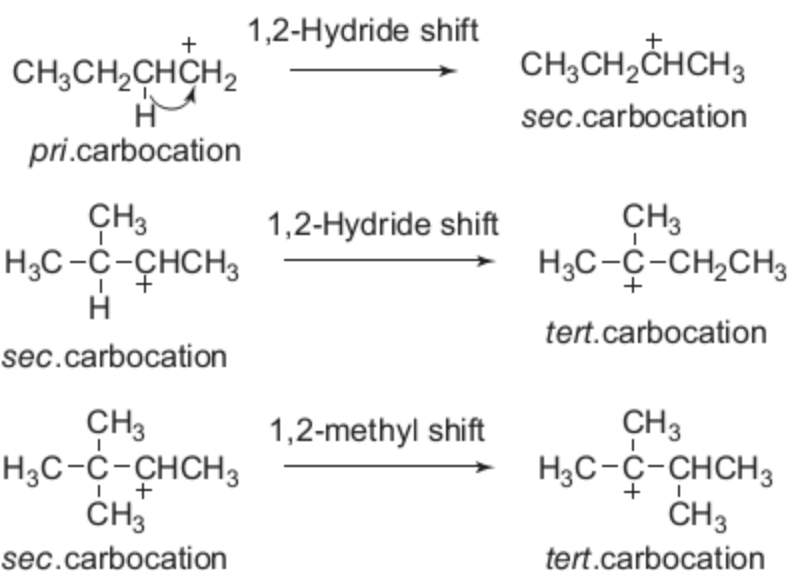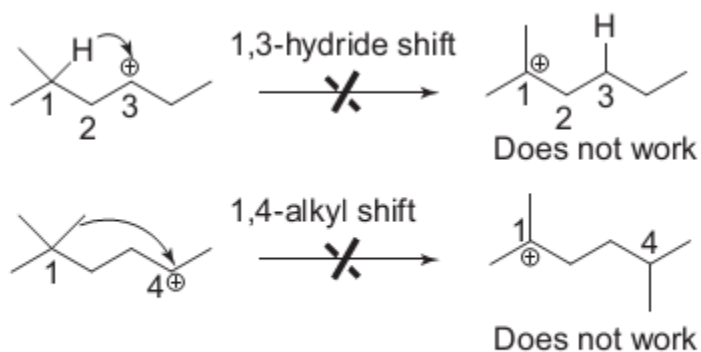
Scheme 2.18

In the absence of special electronic effects, alkyl groups show a clear dependence on the size of the migrating group. In general, smaller groups migrate before larger ones:
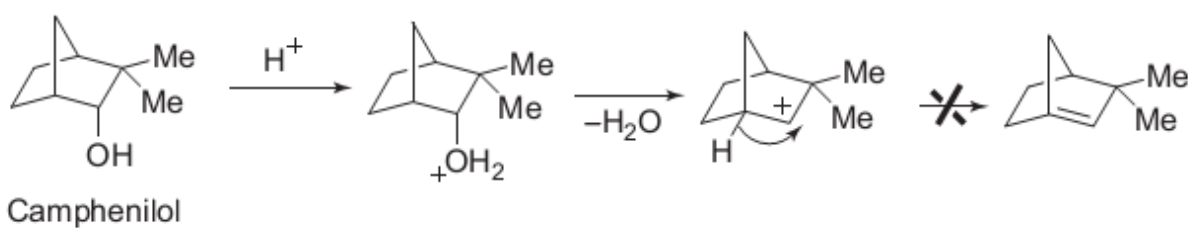
$$H > Me > CHMe_2 > CMe_3$$

It is difficult to give an absolute scale for migratory aptitude, however, since migratory aptitude is inevitably linked to the stability of the cation being formed.
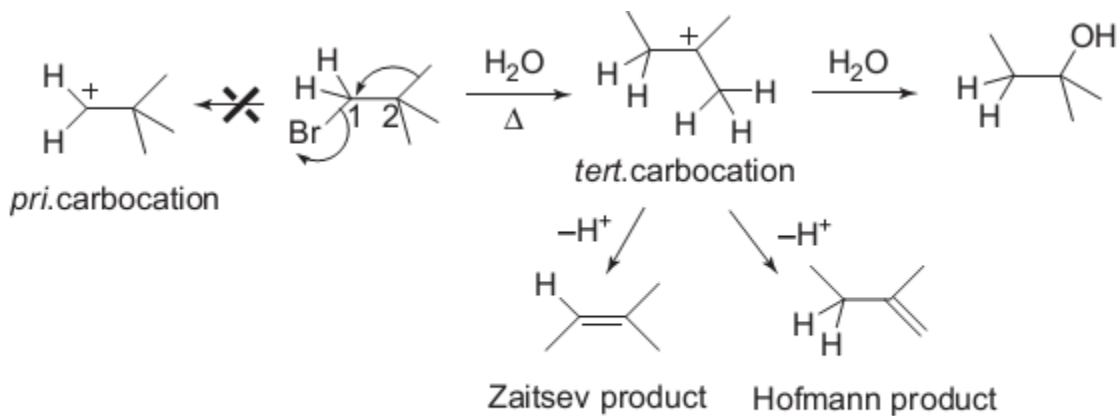
Carbocation rearrangements also can occur by ring expansion, which is another type of 1,2-shift (Scheme 2.19).
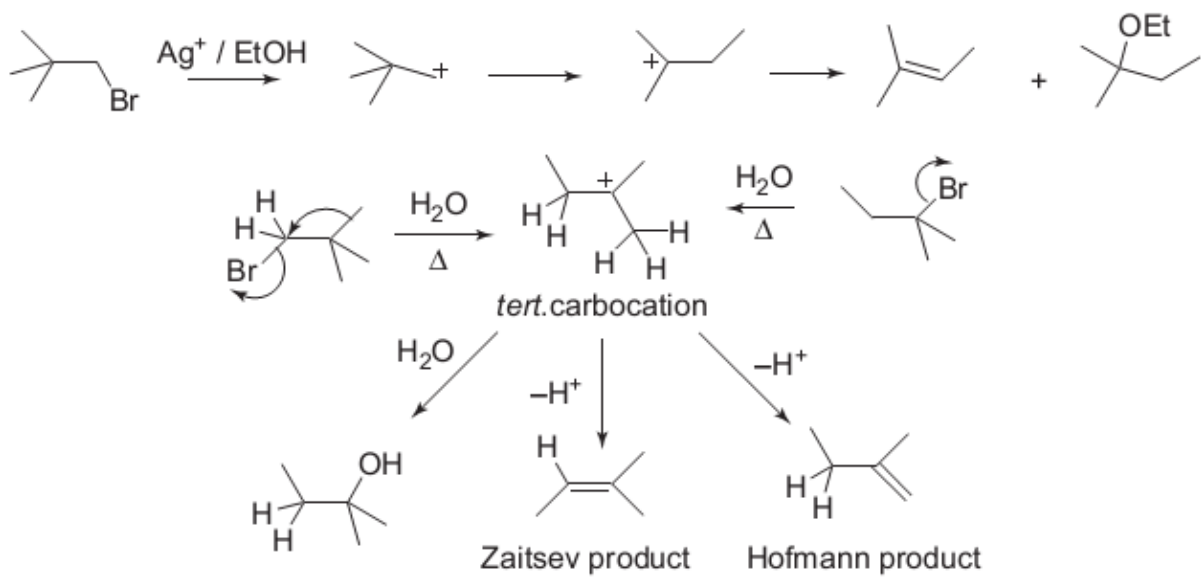

Scheme 2.19

Camphenilol

Scheme 2.20

pri.carbocation

tert.carbocation

Zaitsev product   Hofmann product

Scheme 2.22

Scheme 2.23