Organic Chemistry I

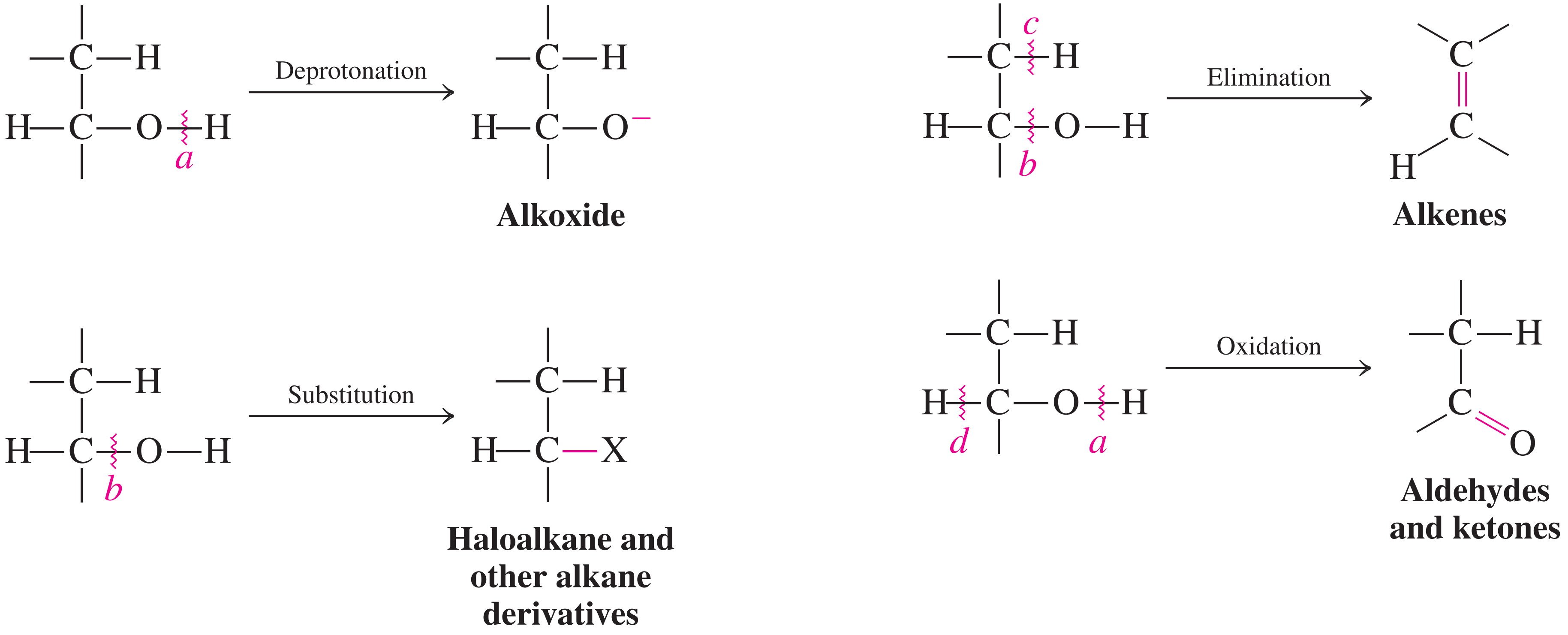
Mohammad Jafarzadeh
Faculty of Chemistry, Razi University

Organic Chemistry, *Structure and Function* **(7th edition)**

By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

9. Further Reactions of Alcohols and the Chemistry of Ethers

A variety of reaction modes available to alcohols. Usually at least one of the four bonds marked *a*, *b*, *c*, or *d* is cleaved.



9.1 REACTIONS OF ALCOHOLS WITH BASE: PREPARATION OF ALKOXIDES

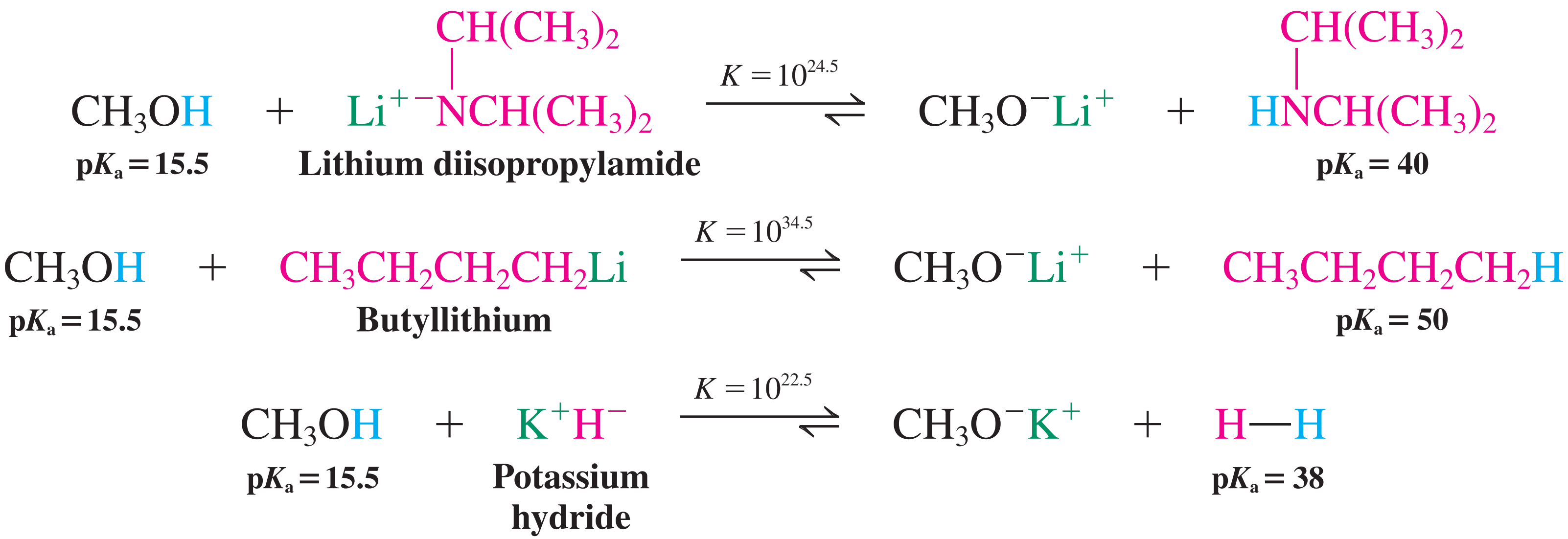
The hydroxy group of alcohols is deprotonated to furnish their conjugate bases, the alkoxides.

Strong bases are needed to deprotonate alcohols completely

To remove a proton from the OH group of an alcohol, a base stronger than the alkoxide is used, including lithium diisopropylamide, butyllithium, and alkali metal hydrides (e.g., potassium hydride, KH).

Such hydrides are particularly useful because the only by-product of the reaction is hydrogen gas.

Three Ways of Making Methoxide from Methanol



$$\underset{\mathbf{p}K_a = \mathbf{15.5}}{CH_3OH} + \underset{\textbf{Lithium diisopropylamide}}{Li^{+-}\overset{CH(CH_3)_2}{\overset{|}{N}}CH(CH_3)_2} \xrightleftharpoons{K = 10^{24.5}} CH_3O^-Li^+ + \underset{\mathbf{p}K_a = \mathbf{40}}{H\overset{CH(CH_3)_2}{\overset{|}{N}}CH(CH_3)_2}$$

$$\underset{\mathbf{p}K_a = \mathbf{15.5}}{CH_3OH} + \underset{\textbf{Butyllithium}}{CH_3CH_2CH_2CH_2Li} \xrightleftharpoons{K = 10^{34.5}} CH_3O^-Li^+ + \underset{\mathbf{p}K_a = \mathbf{50}}{CH_3CH_2CH_2CH_2H}$$

$$\underset{\mathbf{p}K_a = \mathbf{15.5}}{CH_3OH} + \underset{\textbf{Potassium hydride}}{K^+H^-} \xrightleftharpoons{K = 10^{22.5}} CH_3O^-K^+ + \underset{\mathbf{p}K_a = \mathbf{38}}{H{-}H}$$

Alkali metals also deprotonate alcohols—but by reduction of H^+

Another common way of obtaining alkoxides is by the reaction of alcohols with alkali metals, such as lithium. Such metals reduce water—in some cases, violently—to yield alkali metal hydroxides and hydrogen gas.

When the more reactive metals (sodium, potassium, and cesium) are exposed to water in air, the hydrogen generated can ignite spontaneously or even detonate.

$$2\,\mathrm{H{-}OH} \quad + \quad 2\,\mathrm{M}\ (\mathrm{Li, Na, K, Cs}) \quad \longrightarrow \quad 2\,\mathrm{M^{+}\,{}^{-}OH} \quad + \quad \mathrm{H_2}$$

The alkali metals act similarly on the alcohols to give alkoxides, but the transformation is less vigorous.

Alkoxides from Alcohols and Alkali Metals

$$2\,\mathrm{CH_3CH_2OH} \quad + \quad 2\,\mathrm{Na} \quad \longrightarrow \quad 2\,\mathrm{CH_3CH_2O^{-}Na^{+}} \quad + \quad \mathrm{H_2}$$

$$2\,\mathrm{(CH_3)_3COH} \quad + \quad 2\,\mathrm{K} \quad \longrightarrow \quad 2\,\mathrm{(CH_3)_3CO^{-}K^{+}} \quad + \quad \mathrm{H_2}$$

The reactivity of the alcohols used in this process decreases with increasing substitution, methanol being most reactive and tertiary alcohols least reactive.

Relative Reactivity of ROH with Alkali Metals

$$R = CH_3 > \text{primary} > \text{secondary} > \text{tertiary}$$

Decreasing reactivity →

2-Methyl-2-propanol reacts so slowly that it can be used to safely destroy potassium residues in the laboratory.

Alkoxides can be useful reagents in organic synthesis. For example, the reaction of hindered alkoxides with haloalkanes gives elimination. Less branched alkoxides attack primary haloalkanes by the S_N2 reaction to give ethers.

$$CH_3CH_2CH_2CH_2Br \xrightarrow[E2]{(CH_3)_3CO^-K^+,\ (CH_3)_3COH} CH_3CH_2CH{=}CH_2 + (CH_3)_3COH + K^+Br^-$$

9.2 REACTIONS OF ALCOHOLS WITH STRONG ACIDS: ALKYLOXONIUM IONS IN SUBSTITUTION AND ELIMINATION REACTIONS OF ALCOHOLS

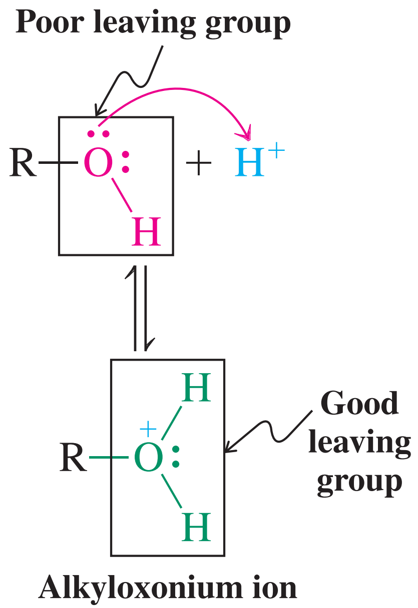
The heterolytic cleavage of the O–H bond in alcohols is readily achieved with strong bases. To break the C–O linkage, an acid is needed.

Water has a high pK_a (15.7), is a weak acid. Hydroxide, its conjugate base, is an exceedingly poor leaving group. *For alcohols to undergo substitution or elimination reactions, the OH must first be converted into a better leaving group.*

Haloalkanes from primary alcohols and HX: Water can be a leaving group in S_N2 reactions

The simplest way of turning the hydroxy substituent in alcohols into a good leaving group is to protonate the oxygen to form an alkyloxonium ion.

Protonation changes OH from a bad leaving group into neutral water, a good leaving group.



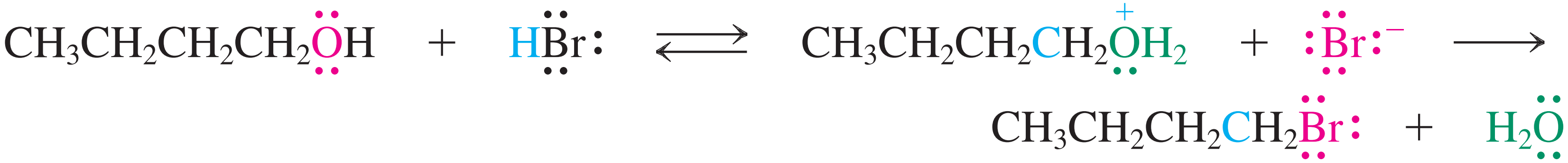
This reaction is reversible and, under normal conditions, the equilibrium lies on the side of unprotonated alcohol. However, this is immaterial if a nucleophile is present in the mixture that is capable of trapping the oxonium species.

For example, alkyloxonium ions derived from primary alcohols are subject to such nucleophilic attack. Thus, the butyloxonium ion resulting from the treatment of 1-butanol with concentrated HBr undergoes displacement by bromide to form 1-bromobutane.

The originally nucleophilic (red) oxygen is protonated by the electrophilic proton (blue) to give the alkyloxonium ion, containing an electrophilic (blue) carbon and H_2O as a leaving group (green).

In the subsequent S_N2 reaction, bromide acts as a nucleophile.

Primary Bromoalkane Synthesis from an Alcohol



$$CH_3CH_2CH_2CH_2\ddot{\underset{\cdot\cdot}{O}}H + H\ddot{\underset{\cdot\cdot}{Br}}: \rightleftharpoons CH_3CH_2CH_2CH_2\overset{+}{\underset{\cdot\cdot}{O}}H_2 + :\ddot{\underset{\cdot\cdot}{Br}}:^- \longrightarrow$$

$$CH_3CH_2CH_2CH_2\ddot{\underset{\cdot\cdot}{Br}}: + H_2\ddot{\underset{\cdot\cdot}{O}}$$

The reaction of primary alcohols with concentrated HI proceeds in similar fashion to furnish primary iodoalkanes.

Concentrated HCl is sluggish in turning primary alcohols into the corresponding chloroalkanes, because chloride ion is a relatively weak nucleophile under protic conditions. Therefore, this conversion, while possible, is usually carried out by other reagents.

In general, the acid-catalyzed S_N2 reaction of *primary* alcohols with HBr or HI is a good way of preparing simple *primary* haloalkanes.

Iodoalkane Synthesis

$HO(CH_2)_6OH + 2\ HI$

1,6-Hexanediol

$$\downarrow$$

$I(CH_2)_6I + 2\ H_2O$

85%

1,6-Diiodo-hexane

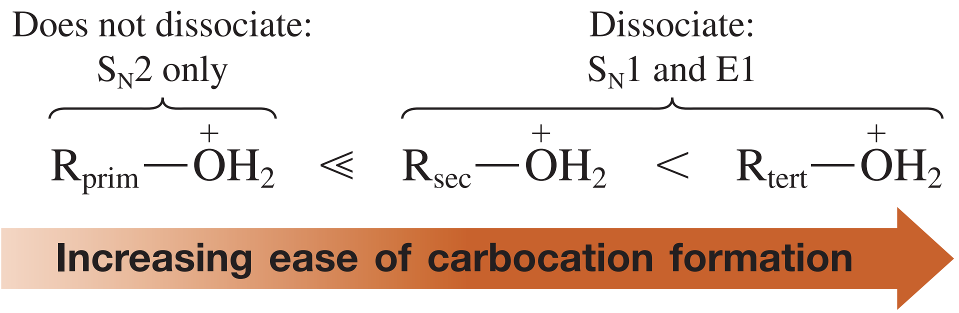
Secondary and tertiary alcohols and HX: Water can be a leaving group to form carbocations in S_N1 and E1 reactions

Alkyloxonium ions derived from secondary and tertiary alcohols, in contrast with their primary counterparts, lose water with increasing ease to give the corresponding carbocations. The reason for this difference in behavior is the difference in carbocation stability.

Primary carbocations are too high in energy to be accessible under ordinary laboratory conditions, whereas secondary and tertiary carbocations are generated with increasing ease.

Thus, primary alkyloxonium ions undergo only S_N2 reactions, whereas their secondary and tertiary relatives enter into S_N1 and E1 processes. When good nucleophiles are present, we observe S_N1 products.

Reactivity of Oxonium Ions



$$\overbrace{R_{prim}—\overset{+}{O}H_2}^{\text{Does not dissociate: } S_N2 \text{ only}} \ll \overbrace{R_{sec}—\overset{+}{O}H_2 < R_{tert}—\overset{+}{O}H_2}^{\text{Dissociate: } S_N1 \text{ and E1}}$$

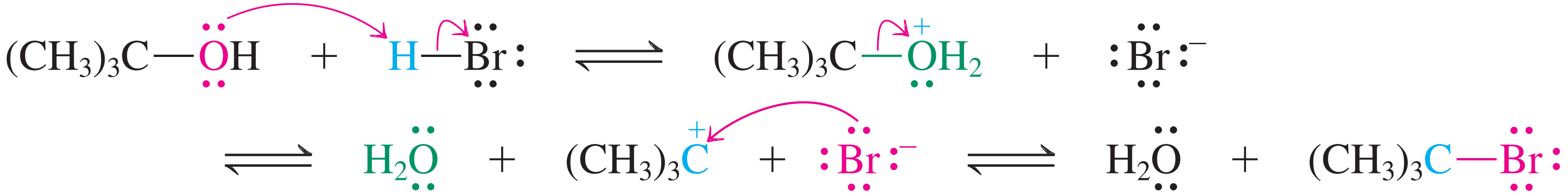
Increasing ease of carbocation formation

Synthetically, this fact is exploited in the preparation of *tertiary* haloalkanes from *tertiary* alcohols in the presence of excess concentrated aqueous hydrogen halide. The product forms in minutes at room temperature. The **mechanism** is precisely the **reverse** of that of **solvolysis**.

Conversion of 2-Methyl-2-propanol into 2-Bromo-2-methylpropane

$$(CH_3)_3COH + \underset{\textbf{Excess}}{HBr} \rightleftharpoons (CH_3)_3CBr + H_2O$$

Mechanism of the S_N1 Reaction of Tertiary Alcohols with Hydrogen Halides



The reason for the success of this process is that relatively low temperatures are sufficient to generate the tertiary carbocation, thus largely preventing competing E1 reactions.

At higher temperatures (or in the absence of good nucleophiles), elimination becomes dominant.

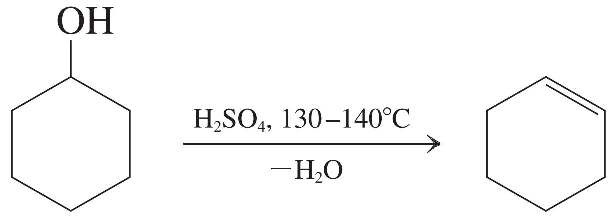
This explains why protonated *secondary* alcohols show the most complex behavior in the presence of HX, following S_N2, S_N1, and E1 pathways:

They are relatively hindered, compared with their primary counterparts (thus reduced S_N2 reactivity), and relatively slow in forming carbocations, compared with their tertiary counterparts (e.g., retarded S_N1 reactivity).

The E1 reaction, here called **dehydration**, because it results in the loss of a molecule of water, is one of the methods for the synthesis of alkenes. Rather than the “nucleophilic” acids HBr and HI (called because the conjugate base is a good nucleophile), “nonnucleophilic” acids, such as H_3PO_4 or H_2SO_4, are employed.

In the example, the conjugate base of the acid is the poor nucleophile HSO_4^-, and proton loss from the intermediate carbocation is observed. Dehydration of tertiary alcohols is even easier, often occurring at slightly above room temperature.

Alcohol Dehydration by the E1 Mechanism

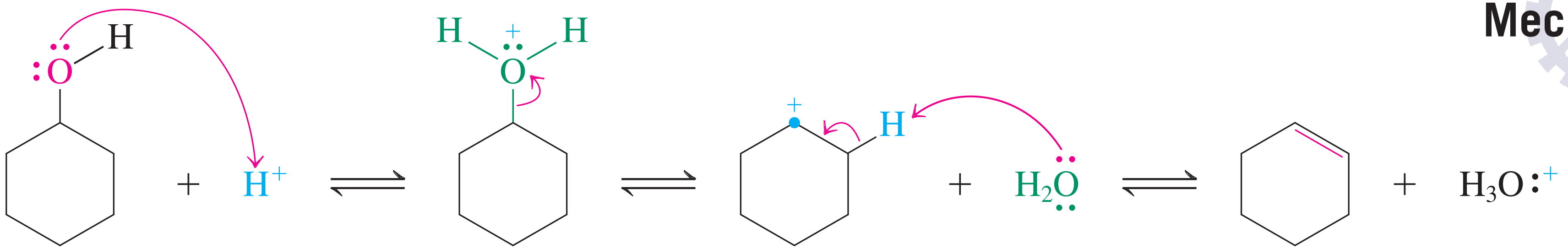


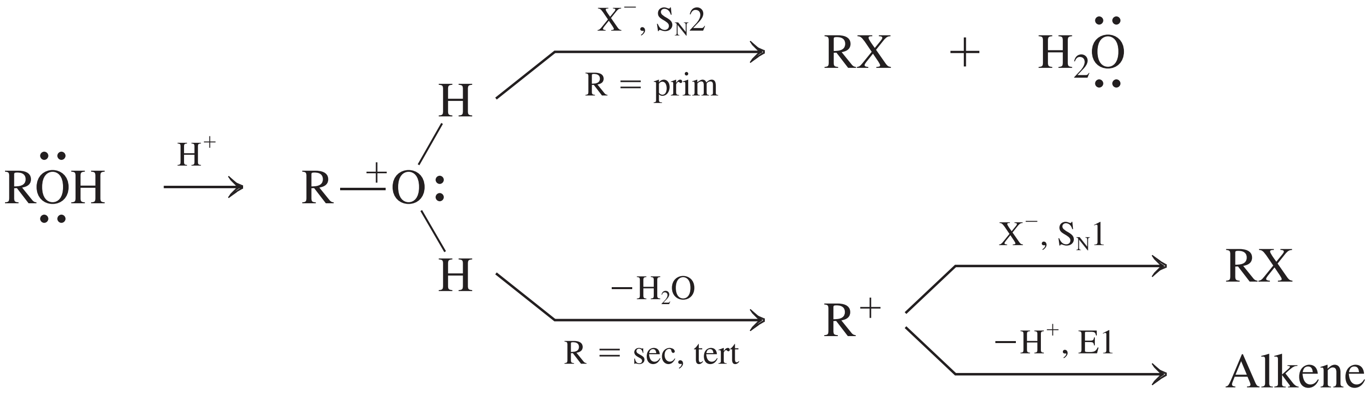
87%

Cyclohexanol **Cyclohexene**

Mechanism of the Dehydration of Cyclohexanol

Mechanism





9.3 CARBOCATION REARRANGEMENTS

When alcohols are transformed into carbocations, the carbocations themselves are subject to rearrangements. The two rearrangements, known as **hydride shifts** and **alkyl shifts**, can occur with most types of carbocations.

The rearranged molecules can then undergo further S_N1 or E1 reactions.

The result is likely to be a complex mixture, unless we can establish a thermodynamic driving force toward one specific product.

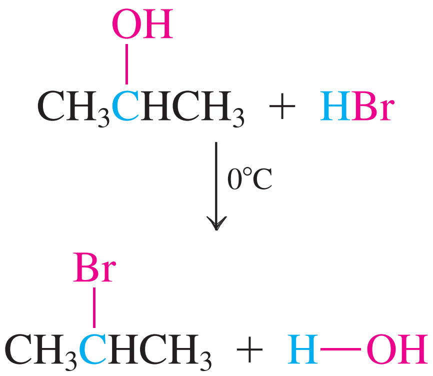
Hydride shifts give new S_N1 products

Treatment of 2-propanol with concentrated hydrogen bromide gives 2-bromopropane, as expected.

Exposure of the more highly substituted secondary alcohol 3-methyl-2-butanol to the same reaction conditions produces a surprising result.

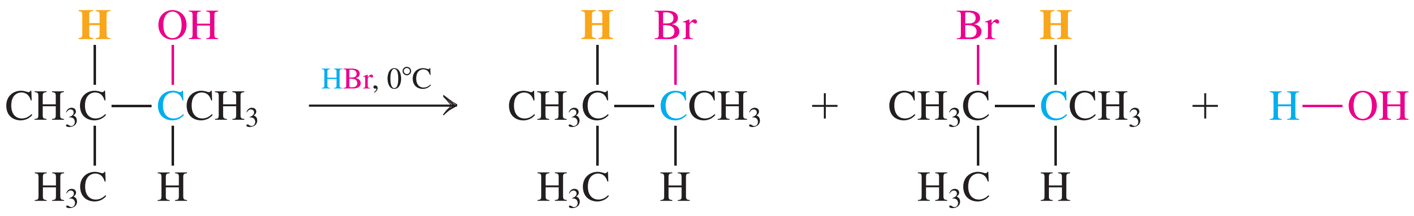
The expected S_N1 product (2-bromo-3-methylbutane) is only a minor component of the reaction mixture, while the major product is 2-bromo-2-methylbutane.

Normal S_N1 Reaction of an Alcohol (No Rearrangement)



$$CH_3\overset{OH}{\overset{|}{C}}HCH_3 + HBr \xrightarrow{0°C} CH_3\overset{Br}{\overset{|}{C}}HCH_3 + H{-}OH$$

Hydride Shift in the S_N1 Reaction of an Alcohol with HBr



$$CH_3\underset{H_3C}{\overset{H}{C}}{-}\underset{H}{\overset{OH}{C}}CH_3 \xrightarrow{HBr,\ 0°C} CH_3\underset{H_3C}{\overset{H}{C}}{-}\underset{H}{\overset{Br}{C}}CH_3 + CH_3\underset{H_3C}{\overset{Br}{C}}{-}\underset{H}{\overset{H}{C}}CH_3 + H{-}OH$$

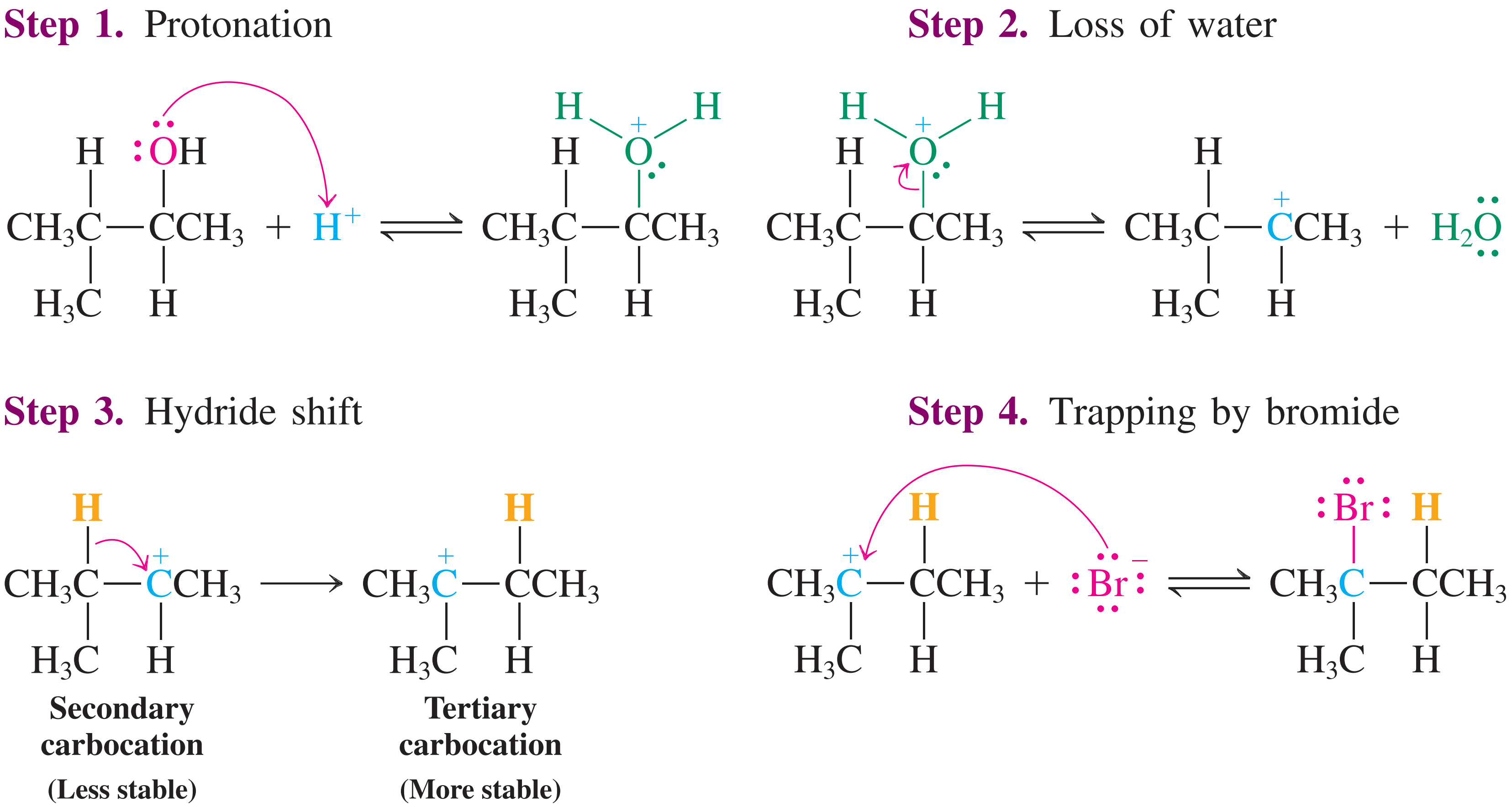
3-Methyl-2-butanol

Minor product
2-Bromo-3-methylbutane
(Normal product)

Major product
2-Bromo-2-methylbutane
(Rearranged product)

The mechanism of this transformation: *carbocations can undergo rearrangement* by **hydride shifts,** in which the hydrogen (yellow) moves *with both electrons* from its original position to the neighboring carbon atom. A shift of the tertiary hydrogen to the electron-deficient neighbor then generates a tertiary cation, *which is more stable.*

Mechanism of Carbocation Rearrangement



Step 1. Protonation

Step 2. Loss of water

Step 3. Hydride shift

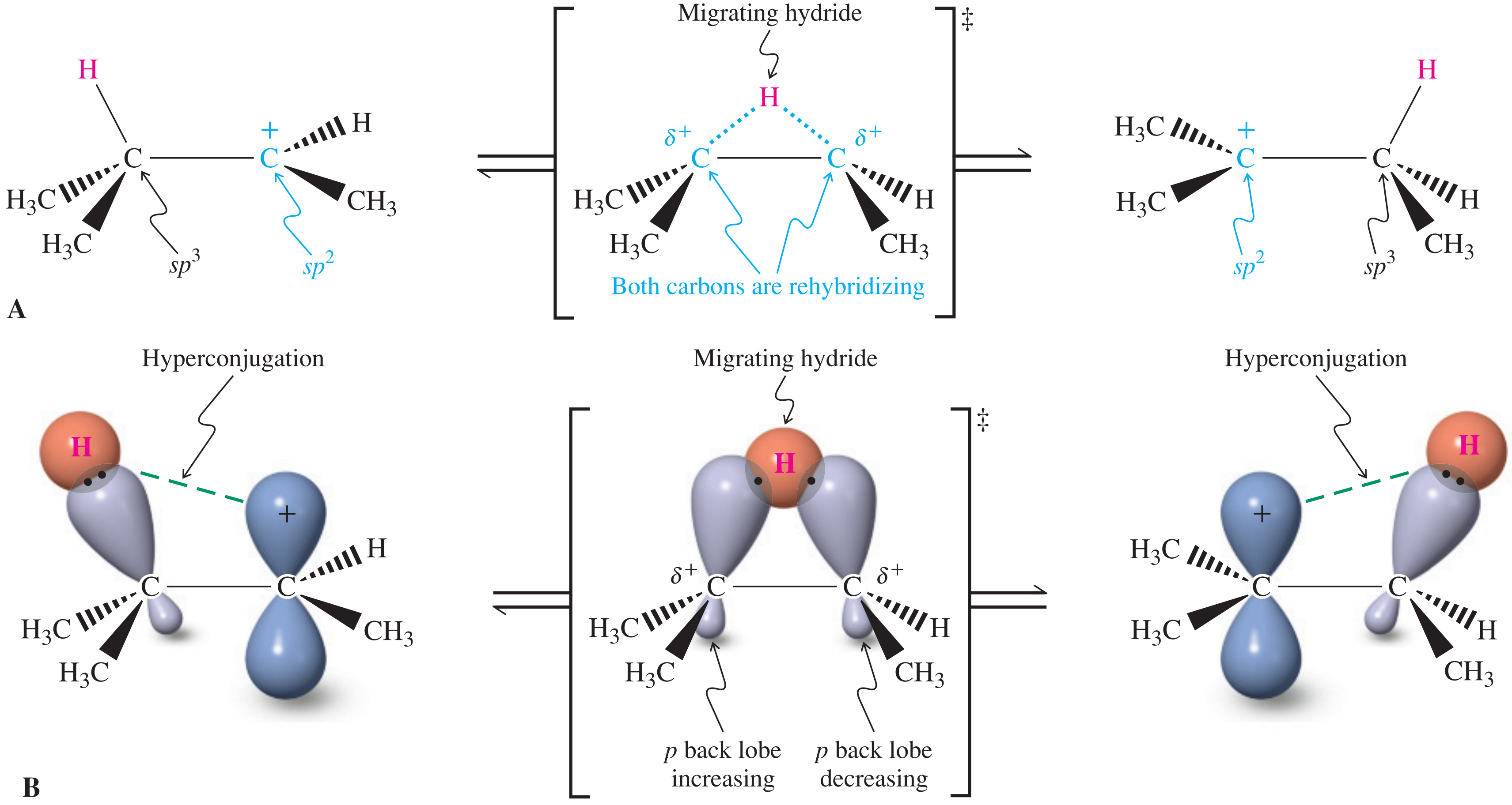
Step 4. Trapping by bromide

Secondary carbocation
(Less stable)

Tertiary carbocation
(More stable)

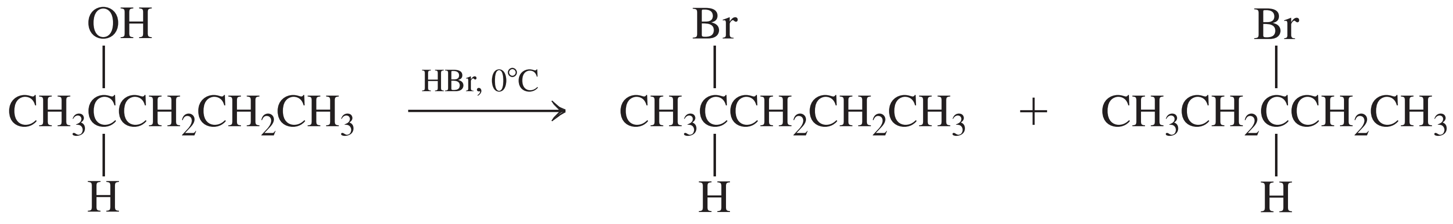
The hydrogen and the positive charge formally exchange places between the two neighboring carbon atoms participating in the reaction.

Hydride shifts of carbocations are generally very fast—faster than S_N1 or E1 reactions. This rapidity is due to hyperconjugation, which weakens the C–H bond.



Primary carbocations are too unstable to be formed by rearrangement.

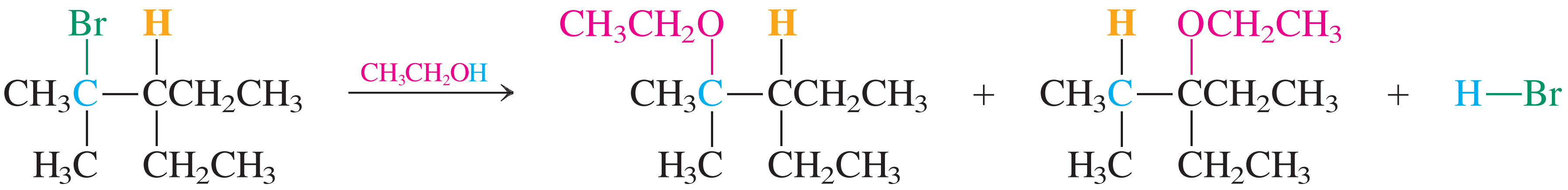
Carbocations of comparable stability, for example, the pairs secondary–secondary or tertiary–tertiary, equilibrate readily. Any added nucleophile will trap all carbocations present, furnishing mixtures of products.



$$CH_3\underset{H}{\overset{OH}{C}}CH_2CH_2CH_3 \xrightarrow{HBr,\ 0^\circ C} CH_3\underset{H}{\overset{Br}{C}}CH_2CH_2CH_3 + CH_3CH_2\underset{H}{\overset{Br}{C}}CH_2CH_3$$

Carbocation rearrangements take place regardless of the nature of the precursor to the carbocation: alcohols, haloalkanes, and alkyl sulfonates.

Rearrangement in Solvolysis of a Haloalkane



$$CH_3\underset{H_3C}{\overset{Br}{C}}-\underset{CH_2CH_3}{\overset{H}{C}}CH_2CH_3 \xrightarrow{CH_3CH_2OH} CH_3\underset{H_3C}{\overset{CH_3CH_2O}{C}}-\underset{CH_2CH_3}{\overset{H}{C}}CH_2CH_3 + CH_3\underset{H_3C}{\overset{H}{C}}-\underset{CH_2CH_3}{\overset{OCH_2CH_3}{C}}CH_2CH_3 + H-Br$$

2-Bromo-3-ethyl-2-methylpentane

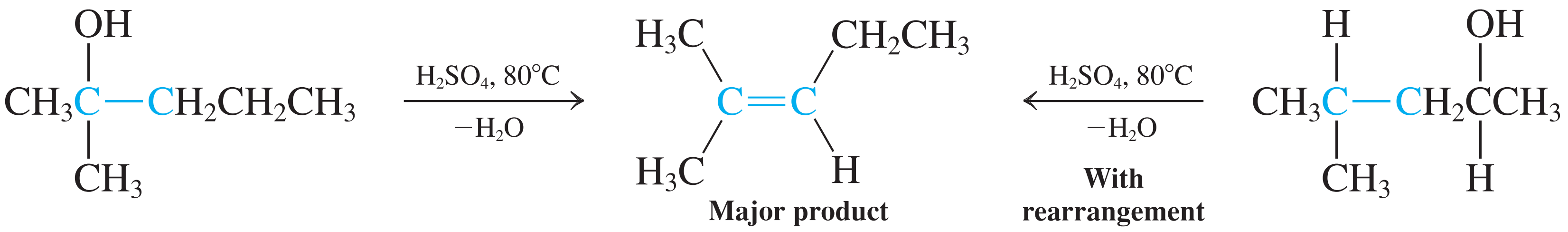
2-Ethoxy-3-ethyl-2-methylpentane (Normal product)

3-Ethoxy-3-ethyl-2-methylpentane (Rearranged product)

Carbocation rearrangements also give new E1 products

At elevated temperatures and in relatively nonnucleophilic media, rearranged carbocations yield alkenes by the E1 mechanism.

Rearrangement in E1 Elimination

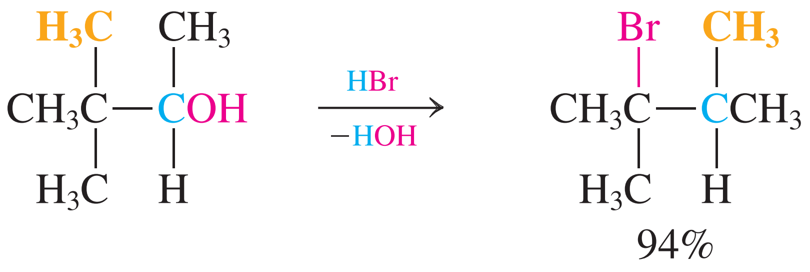


2-Methyl-2-pentanol **2-Methyl-2-pentene** **4-Methyl-2-pentanol**

Other carbocation rearrangements are due to alkyl shifts

Carbocations, particularly when lacking suitable (secondary and tertiary) hydrogens next to the positively charged carbon, can undergo another mode of rearrangement, known as **alkyl group migration** or **alkyl shift.**

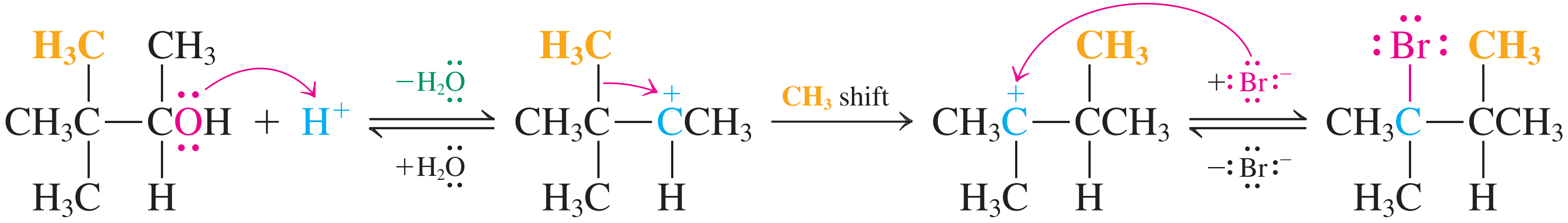
Rearrangement by Alkyl Shift in S_N1 Reaction



3,3-Dimethyl-2-butanol **2-Bromo-2,3-dimethylbutane**

As in the hydride shift, the migrating group takes its electron pair with it to form a bond to the neighboring positively charged carbon. *The moving alkyl group and the positive charge formally exchange places.*

Mechanism of Alkyl Shift



The rates of alkyl and hydride shifts are comparable when leading to carbocations of similar stability.

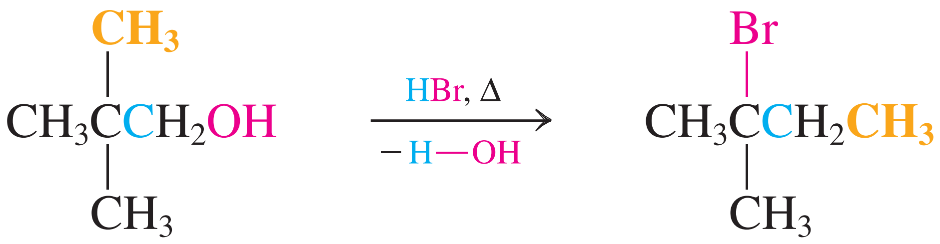
Either type of migration is faster when furnishing tertiary carbocations relative to those ending in their secondary counterparts.

Primary alcohols may undergo rearrangement

Treatment of a primary alcohol with HBr or HI normally produces the corresponding haloalkane through S_N2 reaction of the alkyloxonium ion.

It is possible in some cases to observe alkyl and hydride shifts to primary carbons bearing leaving groups, even though primary carbocations are not formed in solution.

Rearrangement in a Primary Substrate



$$\mathrm{CH_3\overset{CH_3}{\underset{CH_3}{C}}CH_2OH} \xrightarrow[-\mathrm{H{-}OH}]{\mathrm{HBr},\ \Delta} \mathrm{CH_3\overset{Br}{\underset{CH_3}{C}}CH_2CH_3}$$

2,2-Dimethyl-1-propanol
(Neopentyl alcohol)

2-Bromo-2-methylbutane

In this case, after protonation to form the alkyloxonium ion, steric hindrance interferes with direct displacement by bromide.

Instead, water leaves *at the same time* as a methyl group migrates from the neighboring carbon, thus bypassing formation of a primary carbocation.

Rearrangements of primary substrates are relatively difficult processes, usually requiring elevated temperatures and long reaction times.

Mechanism of Concerted Alkyl Shift