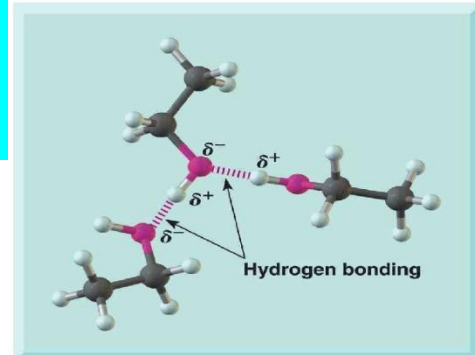


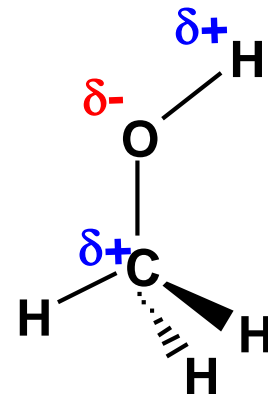
Reactions of Alcohols

The hydroxyl group has two reactive covalent bonds, the C–O bond and the O–H bond.

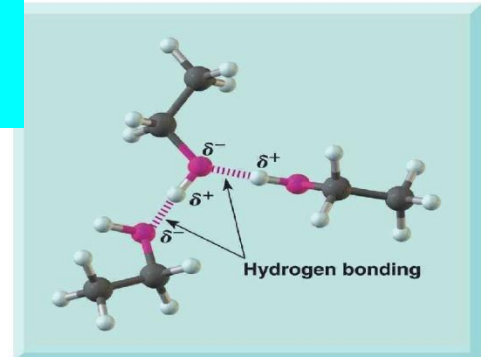


Important reaction:

- Reaction with Metals
- Substitution of the Hydroxyl Hydrogen
- Nucleophilic Substitution of the Hydroxyl Group
- Elimination Reactions of Alcohols
- Oxidation to aldehyde, ketone



Reaction with HX



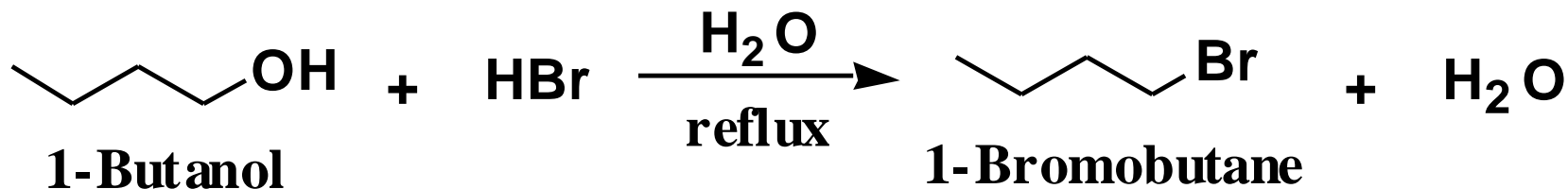
- 3° alcohols react very rapidly with HCl, HBr, and HI



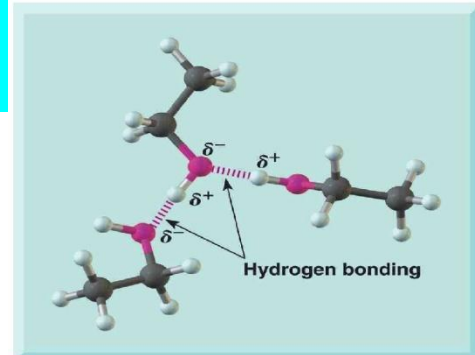
2-Methyl-2-propanol

2-Chloro-2-methylpropane

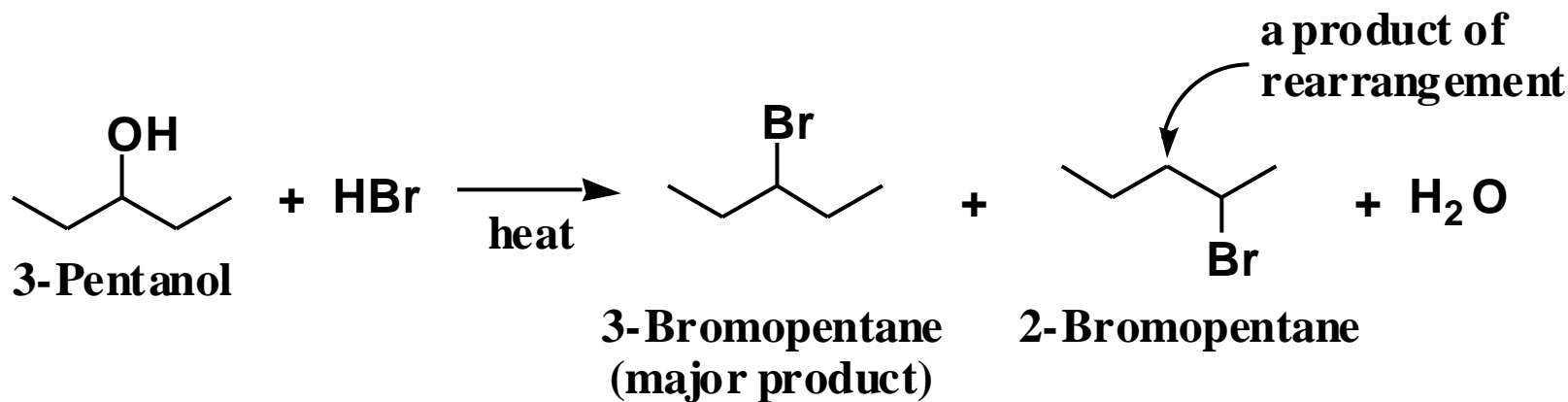
- low-molecular-weight 1° and 2° alcohols are unreactive under these conditions
- 1° and 2° alcohols require concentrated HBr and HI to form alkyl bromides and iodides



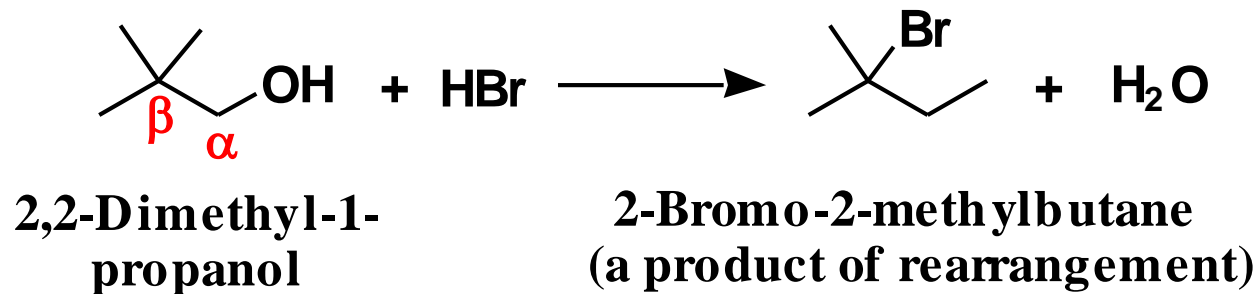
Reaction with HX



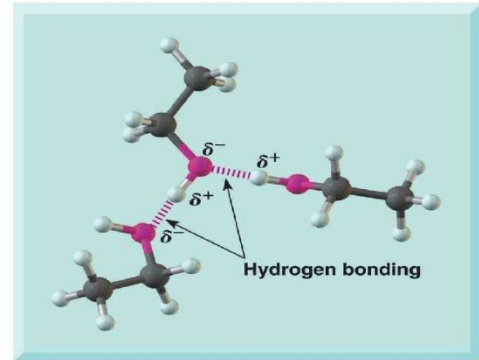
- with HBr and HI, 2° alcohols generally give some rearranged product



- 1° alcohols with extensive β -branching give large amounts of rearranged product



Reaction with HX



◆ Based on

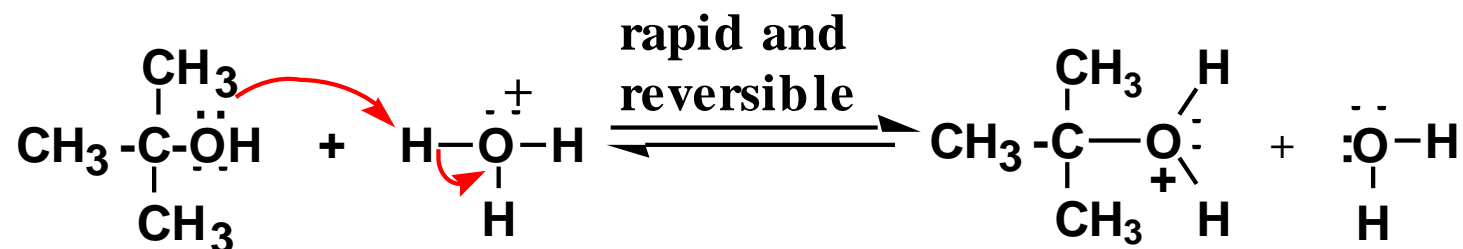
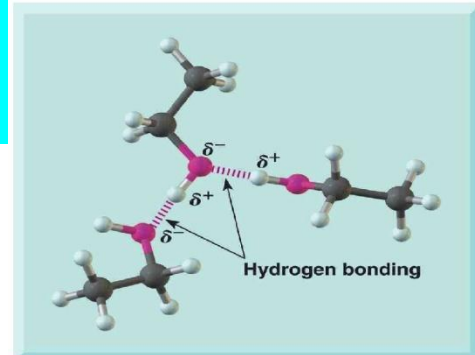
- the relative ease of reaction of alcohols with HX ($3^\circ > 2^\circ > 1^\circ$) and

◆ Reaction of 2° and 3° alcohols with HX

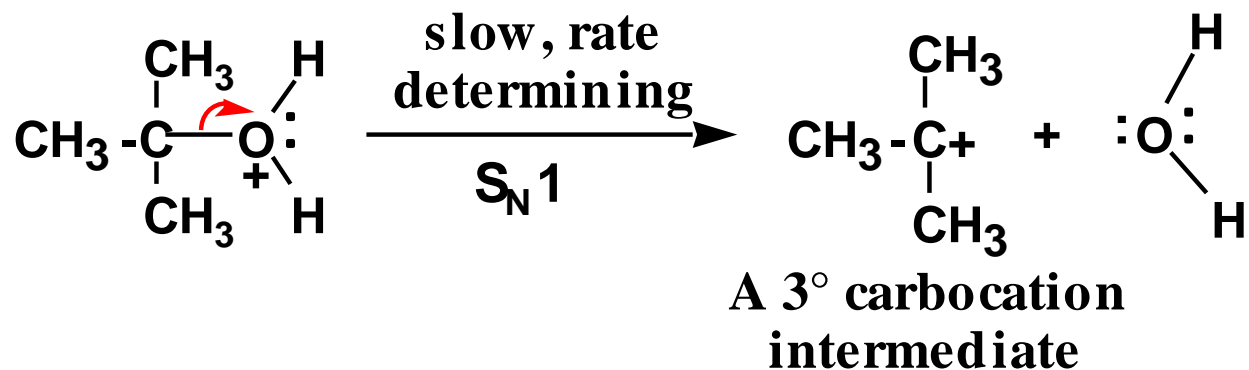
- occurs by an S_N1 mechanism, and
- involves a carbocation intermediate
- Rearrangements occur

Reaction with HX - S_N1

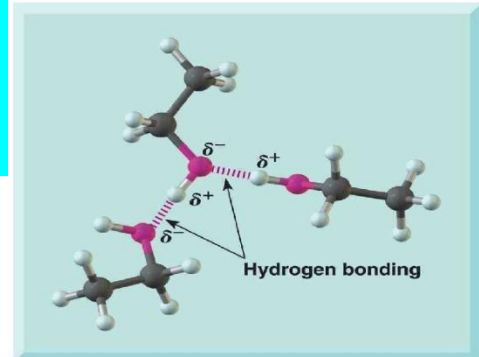
Step 1: proton transfer to the OH group gives an oxonium ion



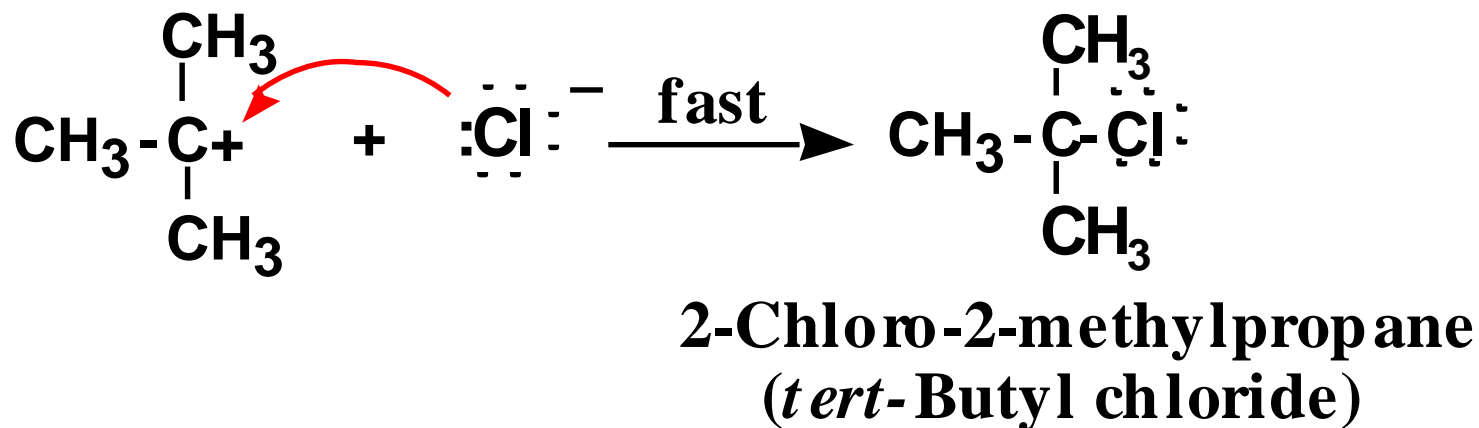
Step 2: loss of H₂O gives a carbocation intermediate



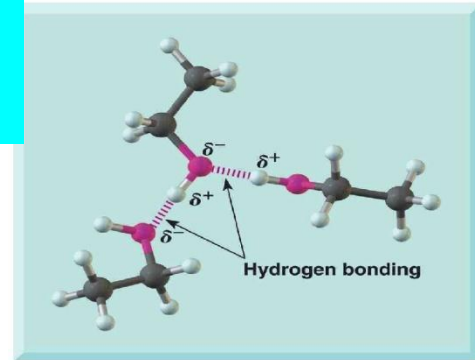
Reaction with HX - S_N1



Step 3: reaction of the carbocation intermediate (an electrophile) with halide ion (a nucleophile) gives the product

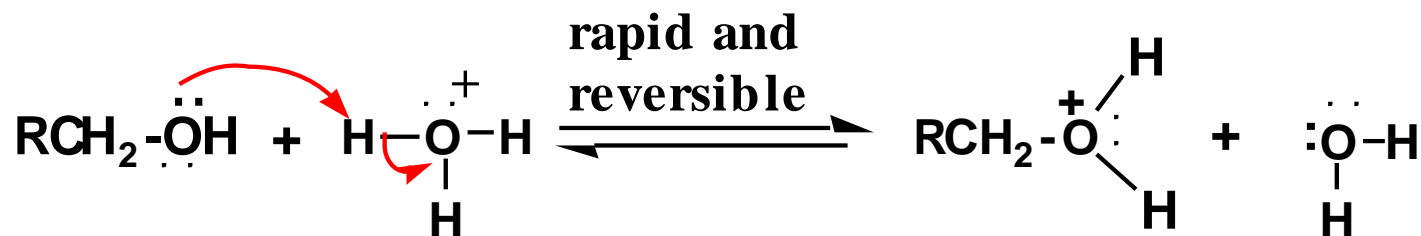


Reaction with HX - S_N2

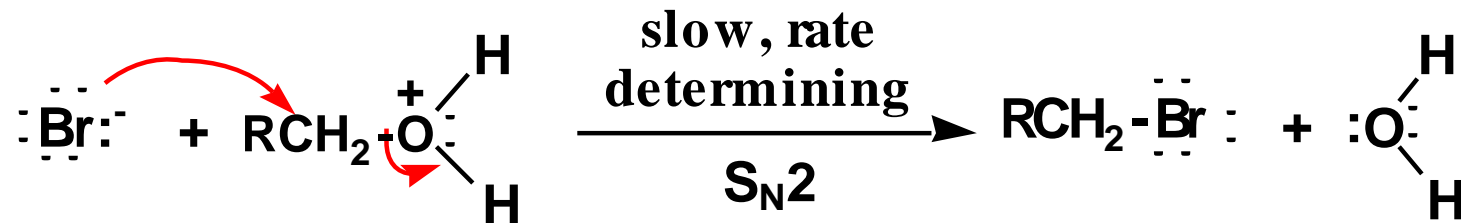


- ◆ 1° alcohols react with HX by an S_N2 mechanism

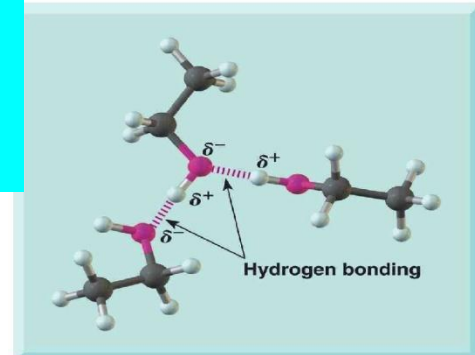
Step 1: rapid and reversible proton transfer



Step 2: displacement of HOH by halide ion

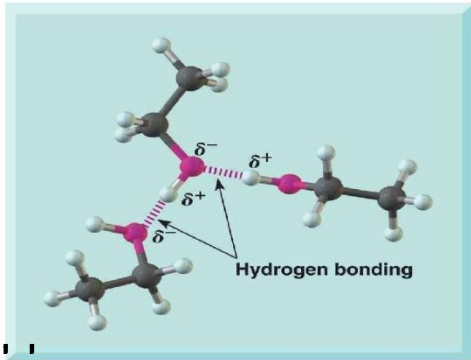


Reaction with HX

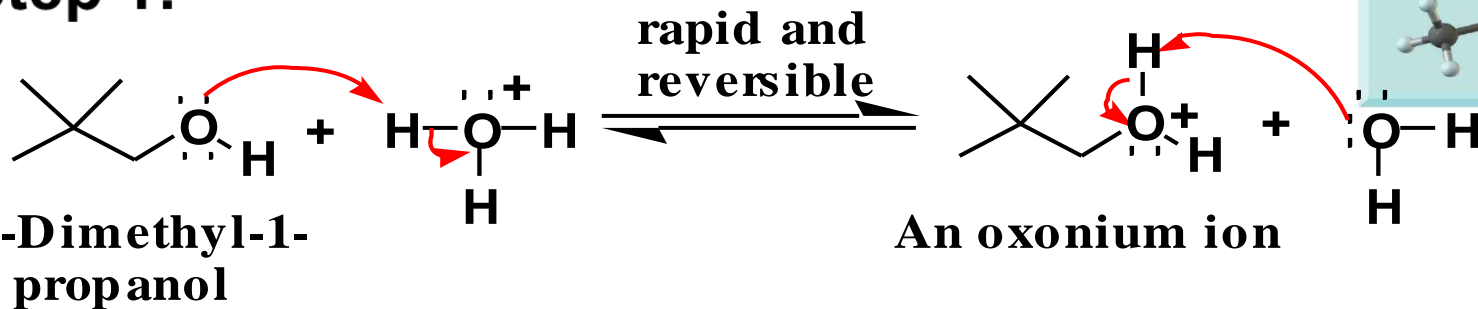


- ◆ For 1° alcohols with extensive β -branching
 - S_N1 is not possible because this pathway would require a 1° carbocation
 - S_N2 is not possible because of steric hindrance created by the β -branching
- ◆ These alcohols react by a concerted loss of HOH and migration of an alkyl group

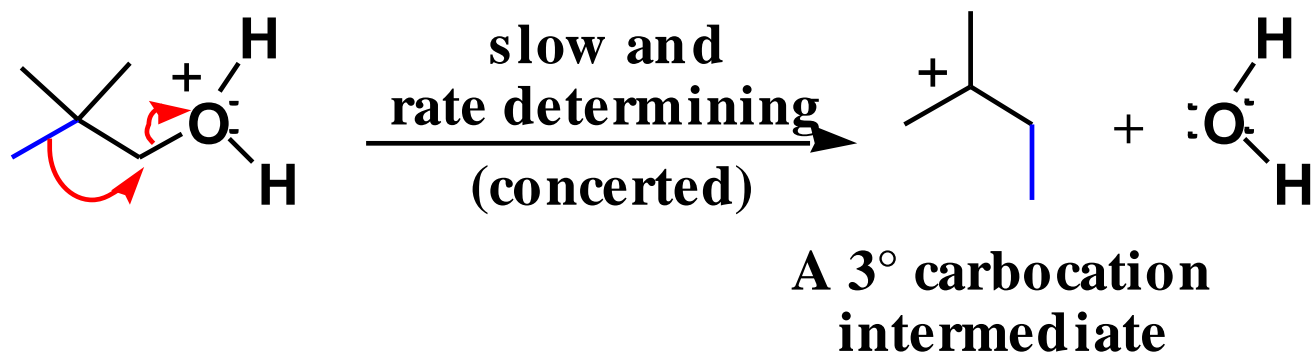
Reaction with HX



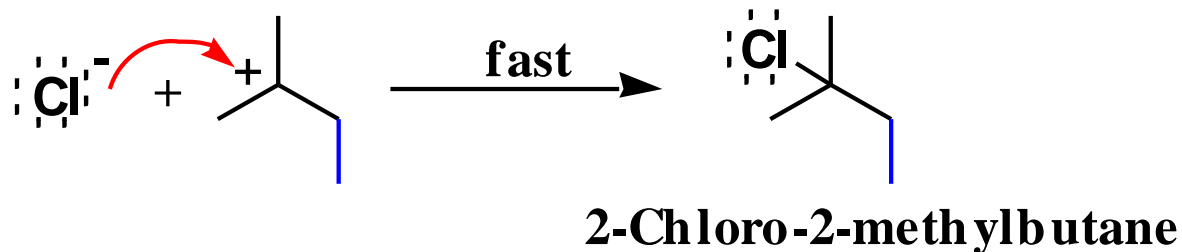
Step 1:



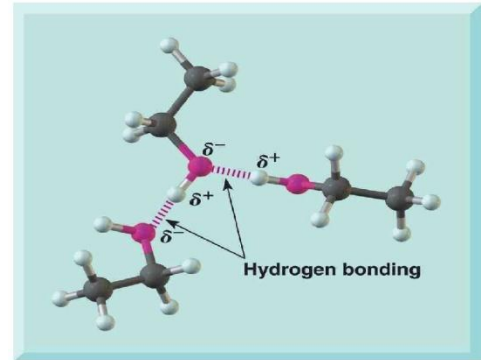
Step 2: concerted elimination of HOH and migration of a methyl group gives a 3° carbocation



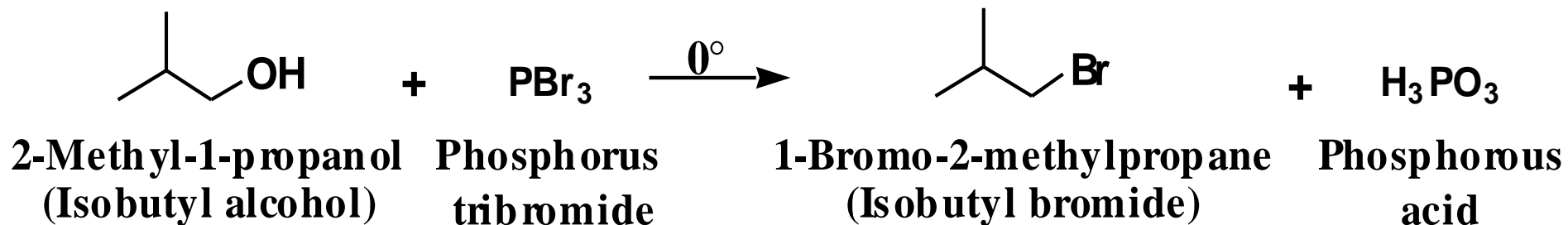
Step 3:



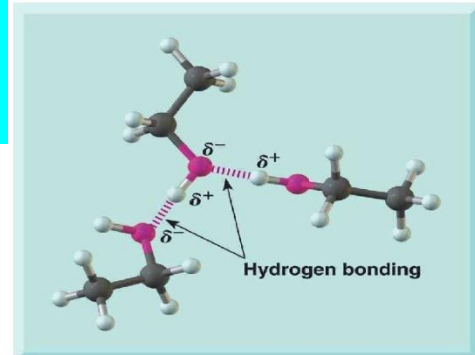
Reaction with PBr₃



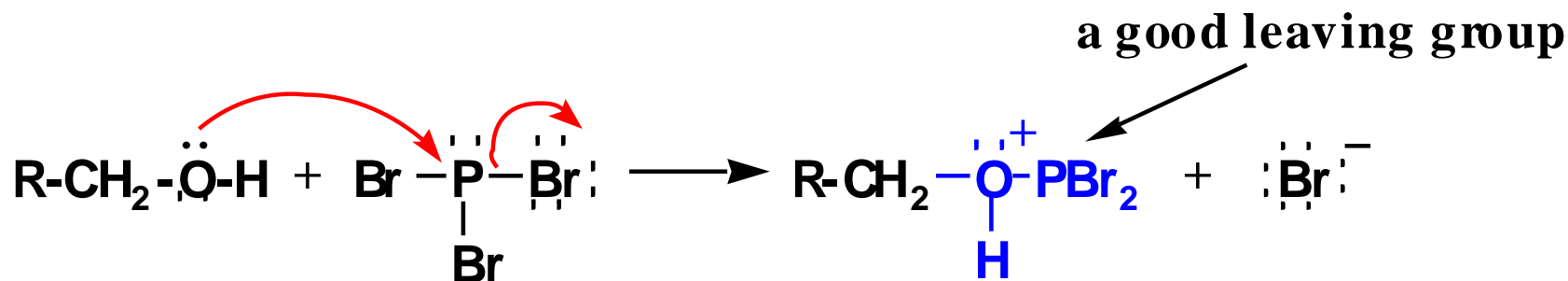
- ◆ An alternative method for the synthesis of 1° and 2° bromoalkanes is reaction of an alcohol with phosphorus tribromide.
- ◆ this method gives less rearrangement than with HBr.



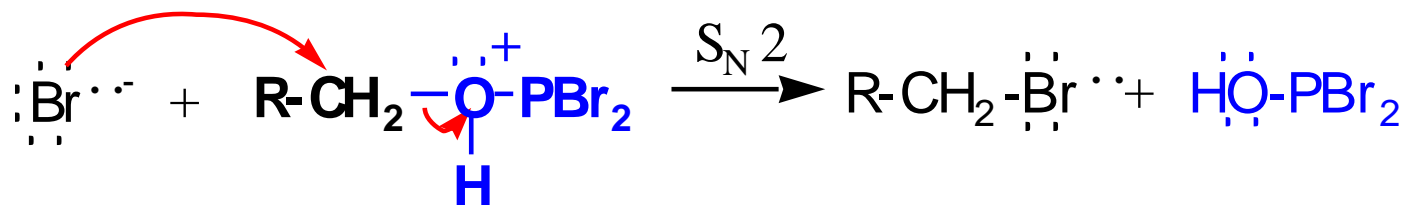
Reaction with PBr₃



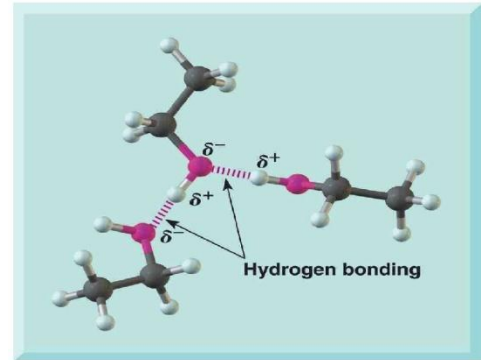
Step 1: formation of a protonated dibromophosphite converts H₂O, a poor leaving group, to a good leaving group



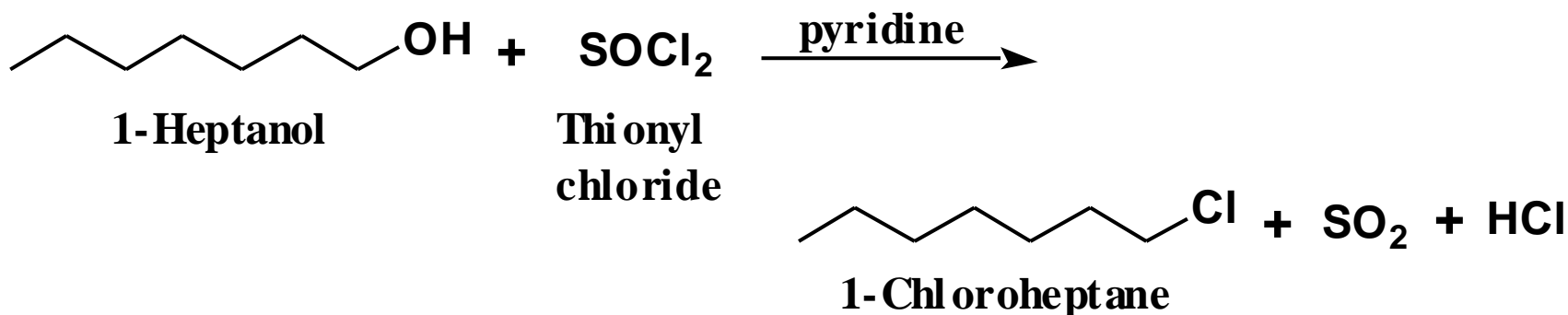
Step 2: displacement by bromide ion gives the alkyl bromide



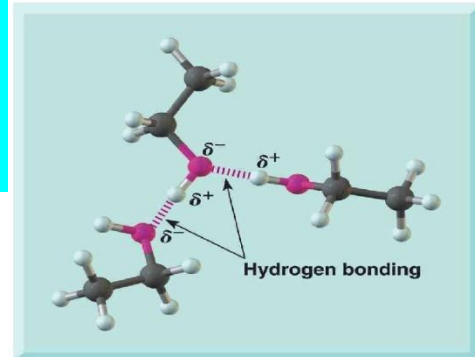
Reaction with SOCl_2



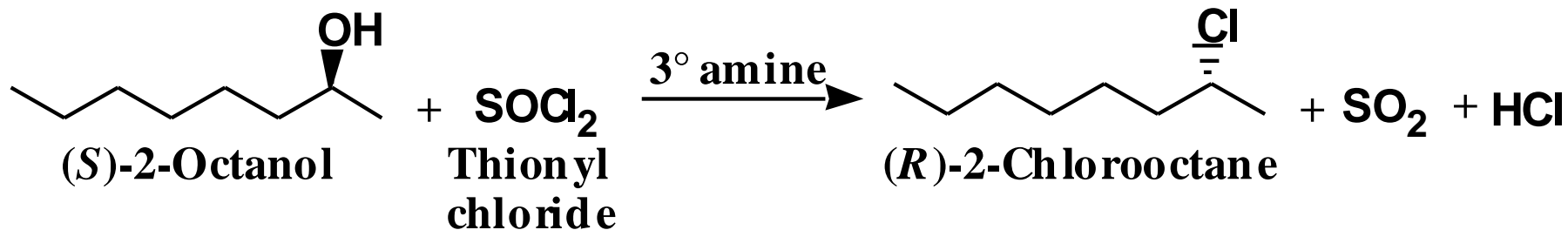
- ◆ Thionyl chloride is the most widely used reagent for the conversion of 1° and 2° alcohols to alkyl chlorides
- ◆ a base, pyridine or triethylamine, is added to catalyze the reaction and to neutralize the HCl



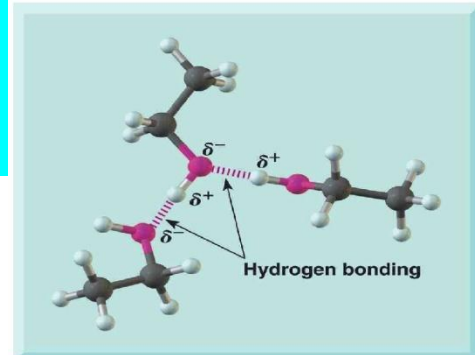
Reaction with SOCl_2



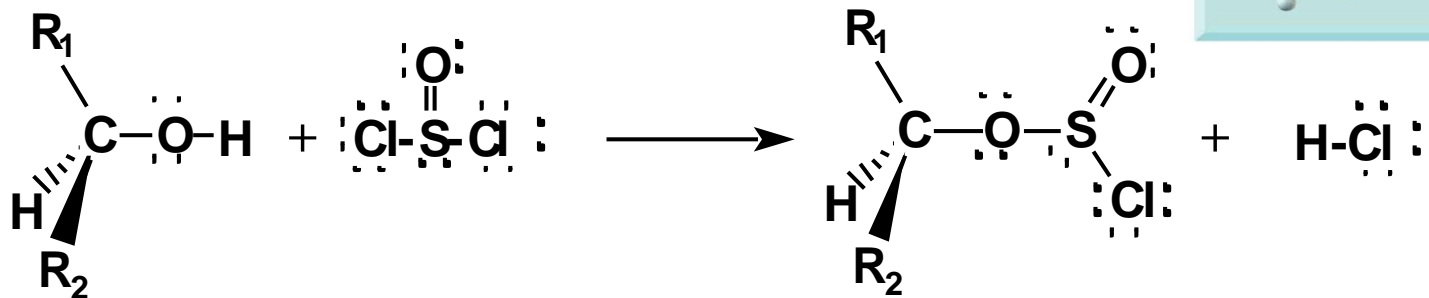
- ◆ Reaction of an alcohol with SOCl_2 in the presence of a 3° amine is stereoselective.
- ◆ It occurs with inversion of configuration.



Reaction with SOCl_2

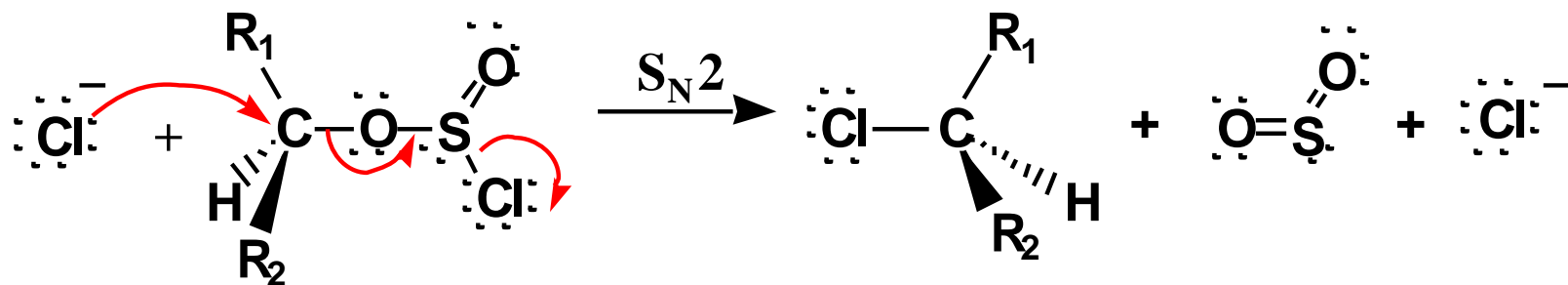


Step 1: formation of an alkyl chlorosulfite

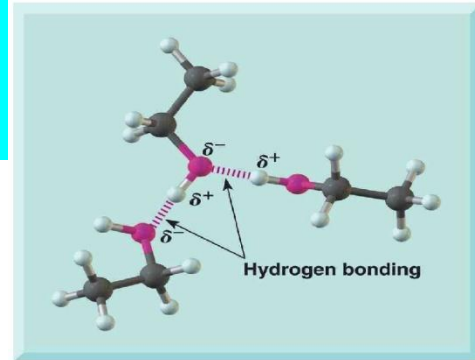


An alkyl
chlorosulfite

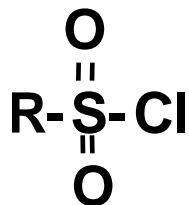
Step 2: nucleophilic displacement of this leaving group
by chloride ion gives the chloroalkane



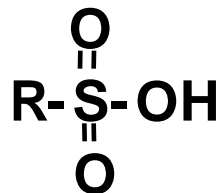
Alkyl Sulfonates



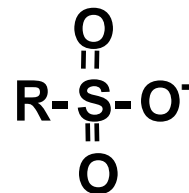
- ◆ **Sulfonyl chlorides are derived from sulfonic acids**
- ◆ **sulfonic acids, like sulfuric acid, are strong acids**



**A sulfonyl
chloride**

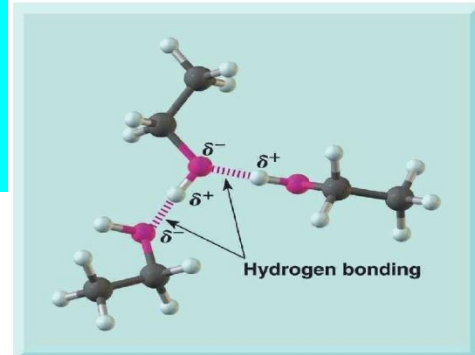


**A sulfonic acid
(a very strong acid)**

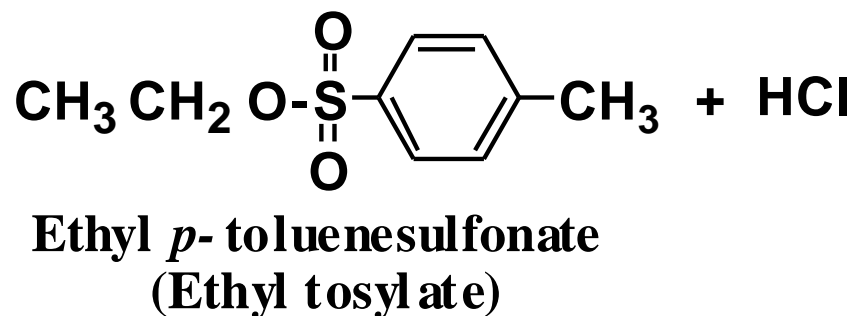
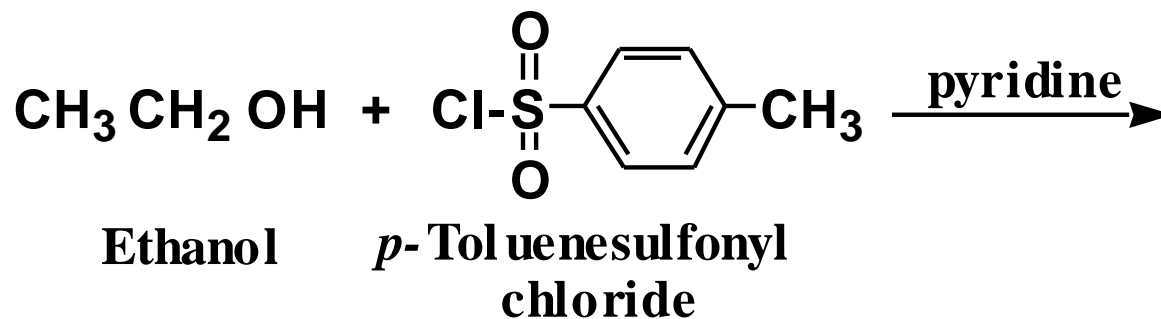


**A sulfonate anion
(a very weak base and
stable anion; a very
good leaving group)**

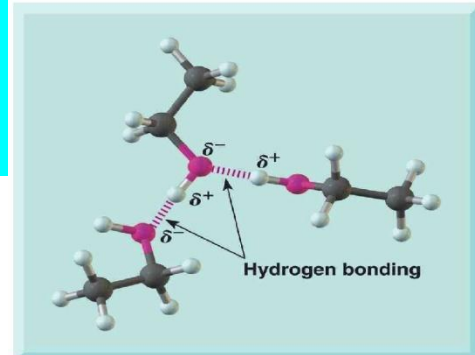
Alkyl Sulfonates



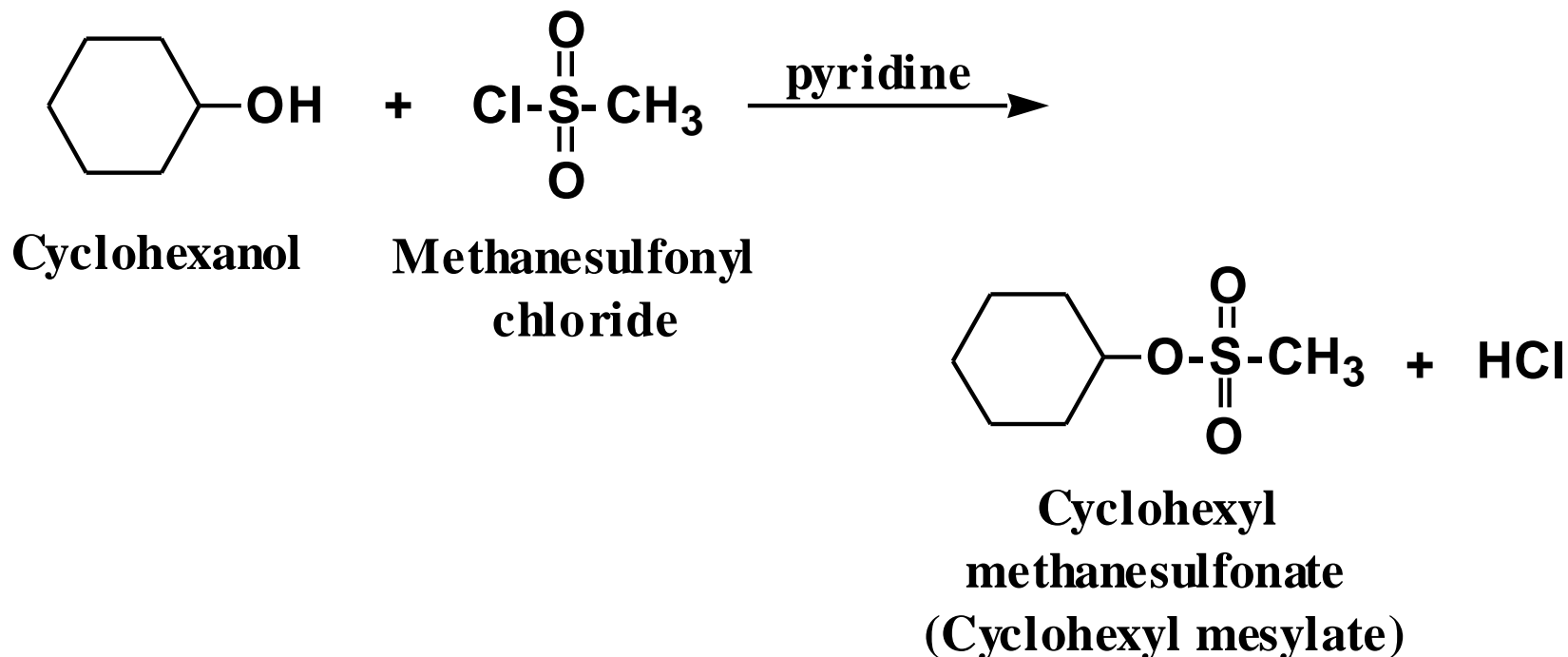
- Commonly used sulfonyl chloride is *p*-toluenesulfonyl chloride (Ts-Cl)



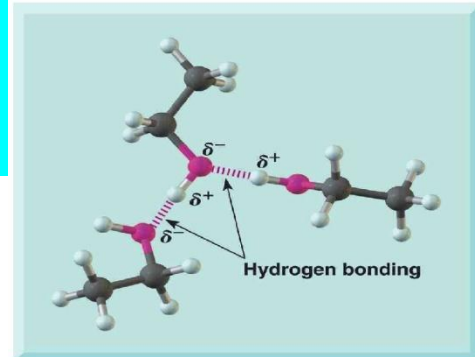
Alkyl Sulfonates



- ◆ Another commonly used sulfonyl chloride is methanesulfonyl chloride (Ms-Cl)

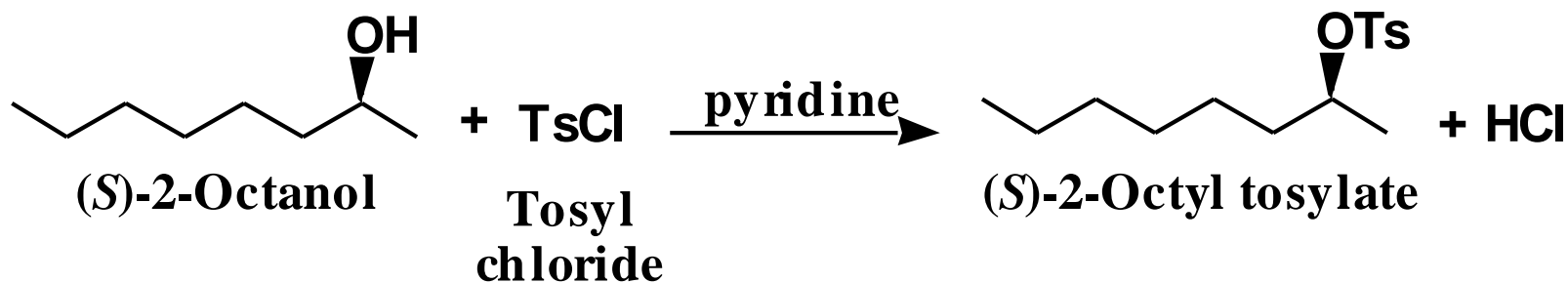


Alkyl Sulfonates

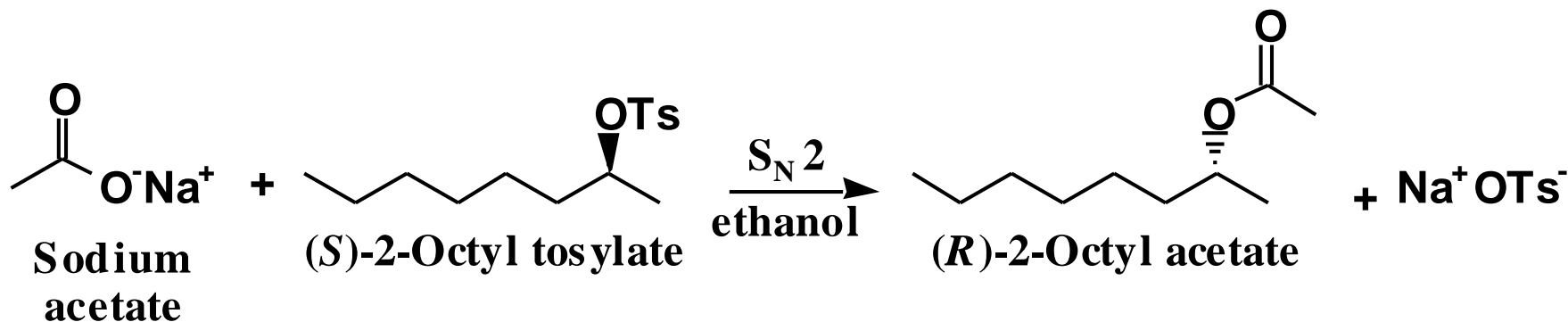


- ◆ This two-step procedure converts (*S*)-2-octanol to (*R*)-2-octyl acetate

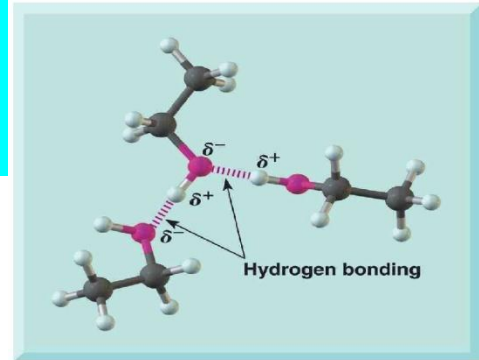
Step 1: formation of a *p*-toluenesulfonate (Ts) ester



Step 2: nucleophilic displacement of tosylate

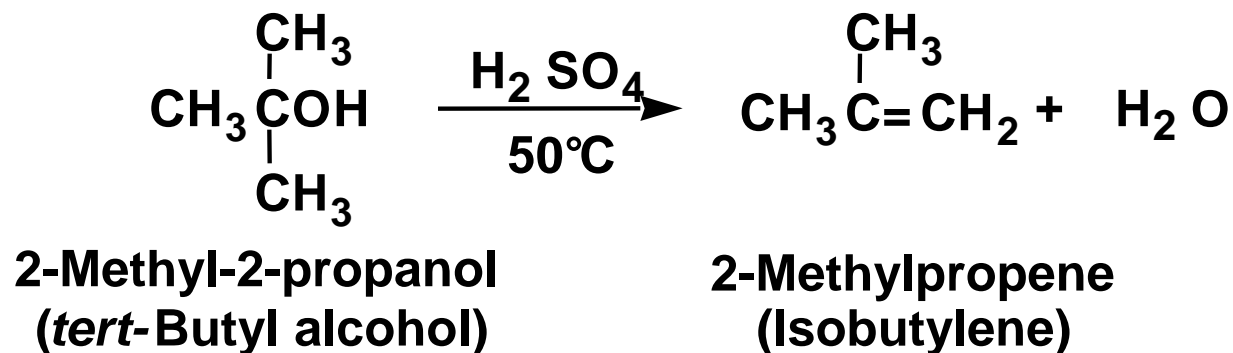
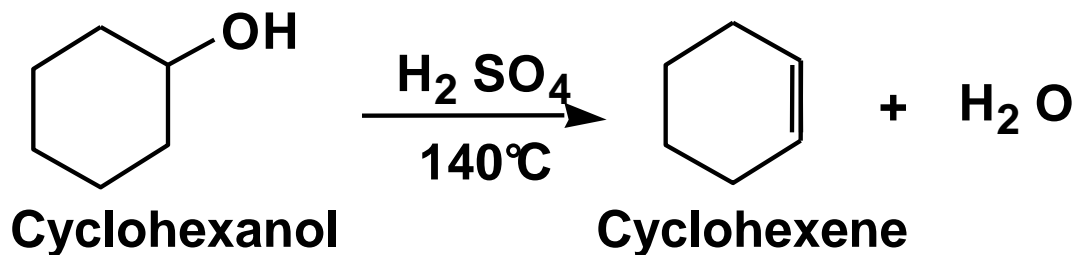
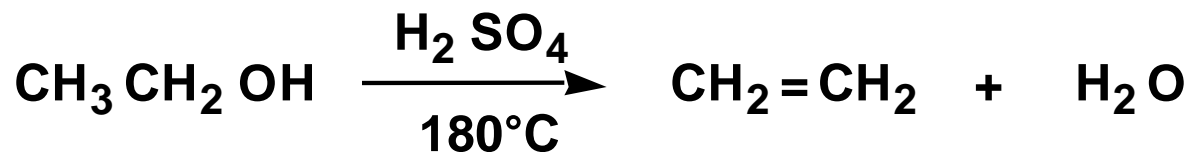
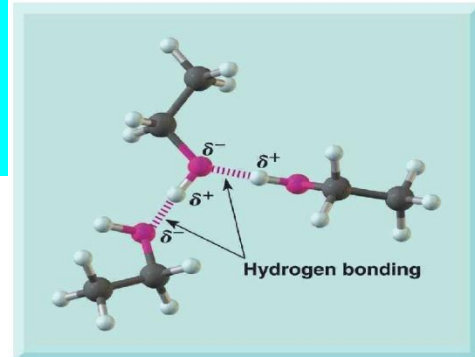


Dehydration of ROH

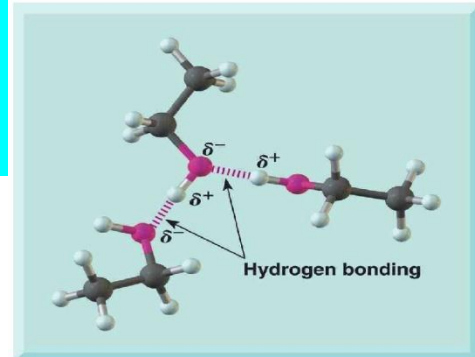


- ◆ An alcohol can be converted to an alkene by acid-catalyzed dehydration (a type of β -elimination)
 - 1° alcohols must be heated at high temperature in the presence of an acid catalyst, such as H_2SO_4 or H_3PO_4
 - 2° alcohols undergo dehydration at somewhat lower temperatures
 - 3° alcohols often require temperatures at or slightly above room temperature

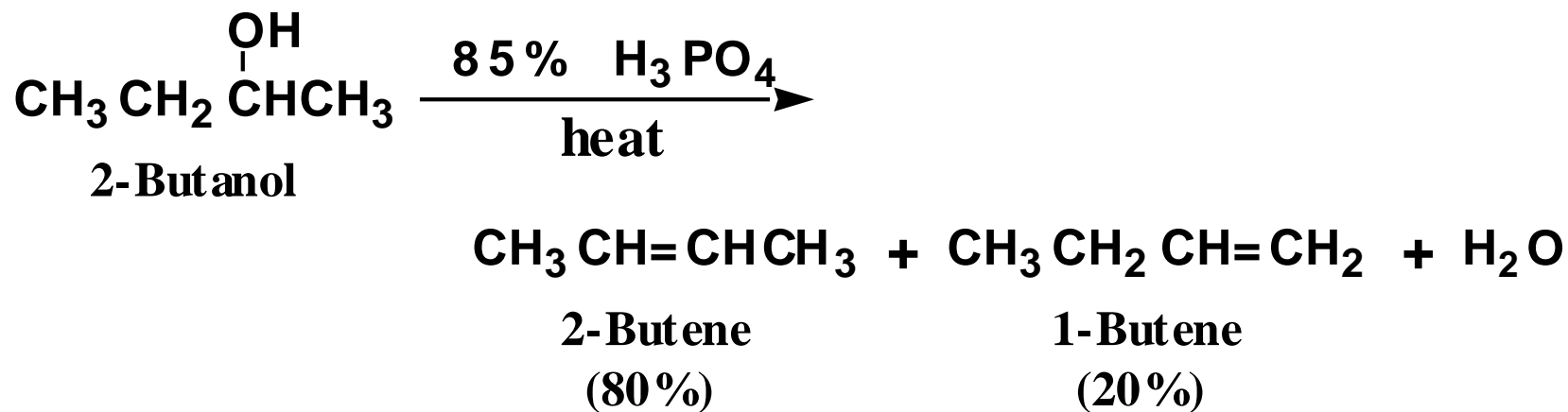
Dehydration of ROH



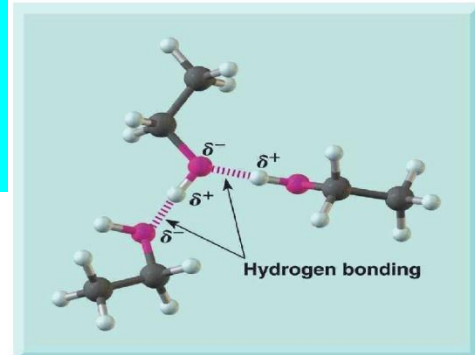
Dehydration of ROH



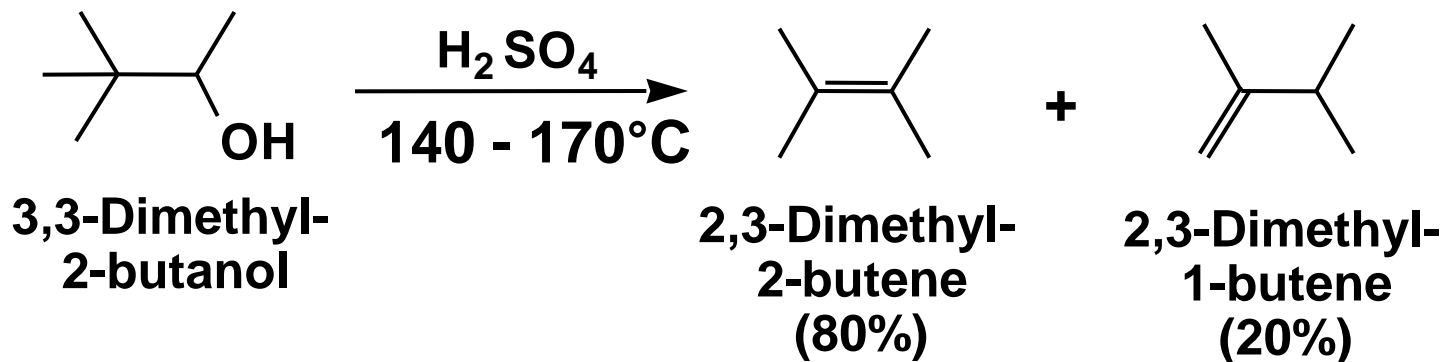
- where isomeric alkenes are possible, the alkene having the greater number of substituents on the double bond (the more stable alkene) usually predominates (Zaitsev rule)



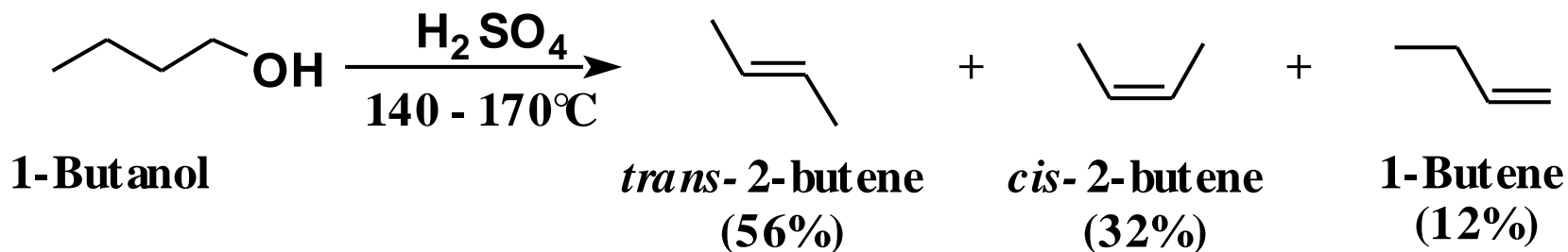
Dehydration of ROH



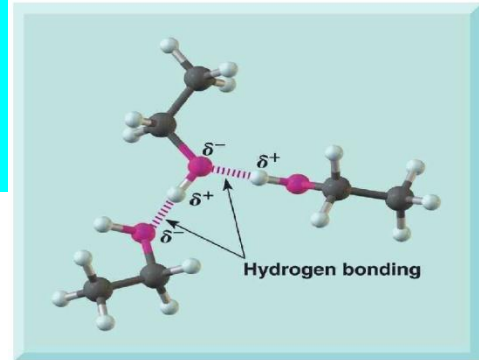
- Dehydration of 1° and 2° alcohols is often accompanied by rearrangement



- acid-catalyzed dehydration of 1-butanol gives a mixture of three alkenes

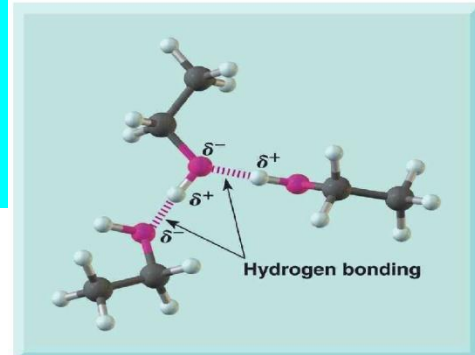


Dehydration of ROH

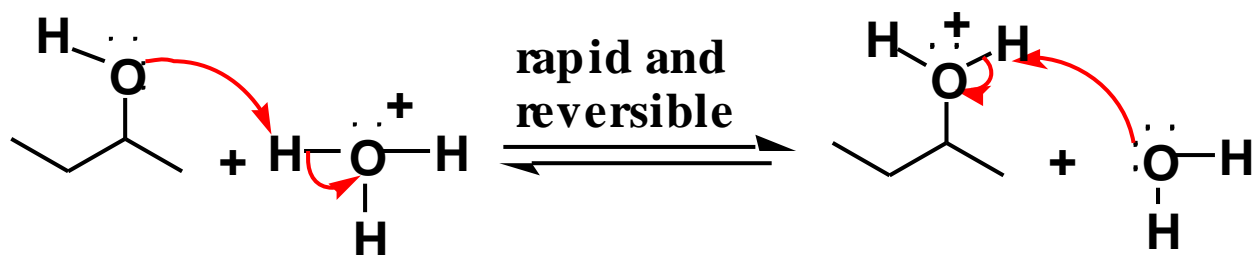


- ◆ Based on evidence of
 - ease of dehydration ($3^\circ > 2^\circ > 1^\circ$)
 - prevalence of rearrangements
- ◆ Chemists propose a three-step mechanism for the dehydration of 2° and 3° alcohols
 - because this mechanism involves formation of a carbocation intermediate in the rate-determining step, it is classified as E1

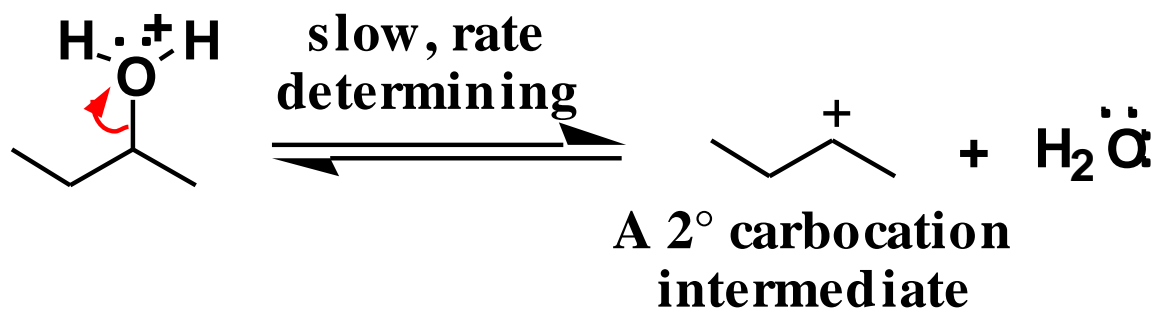
Dehydration of ROH



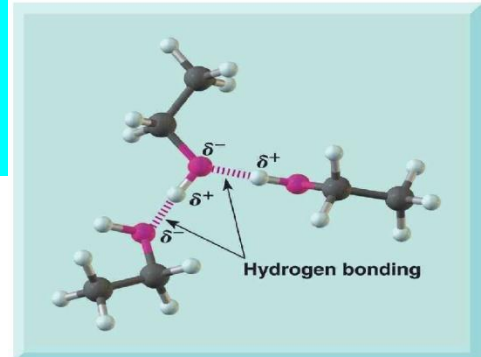
Step 1: proton transfer to the -OH group gives an oxonium ion



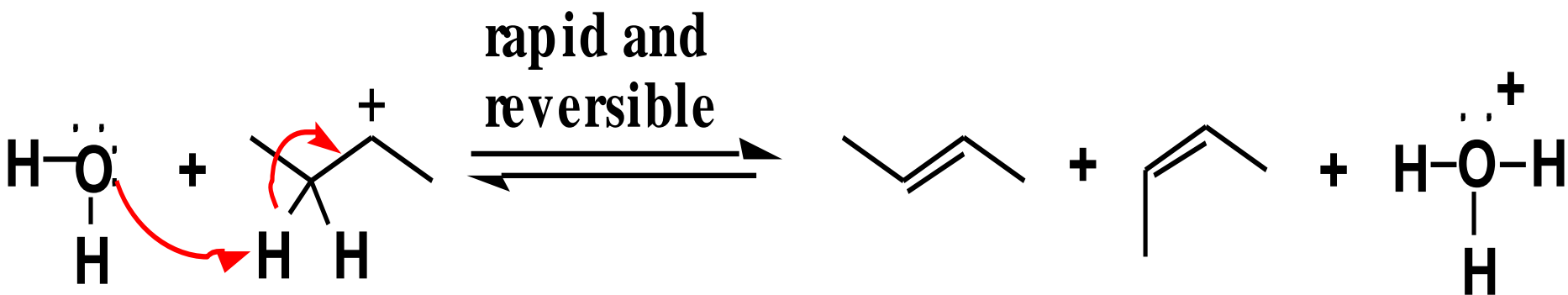
Step 2: loss of H₂O gives a carbocation intermediate



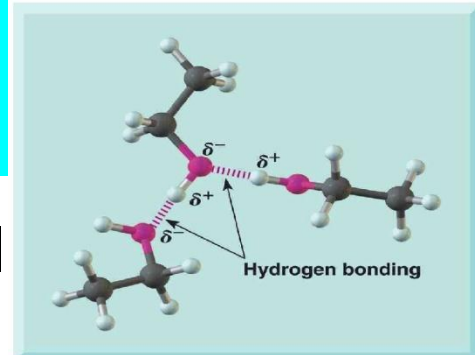
Dehydration of ROH



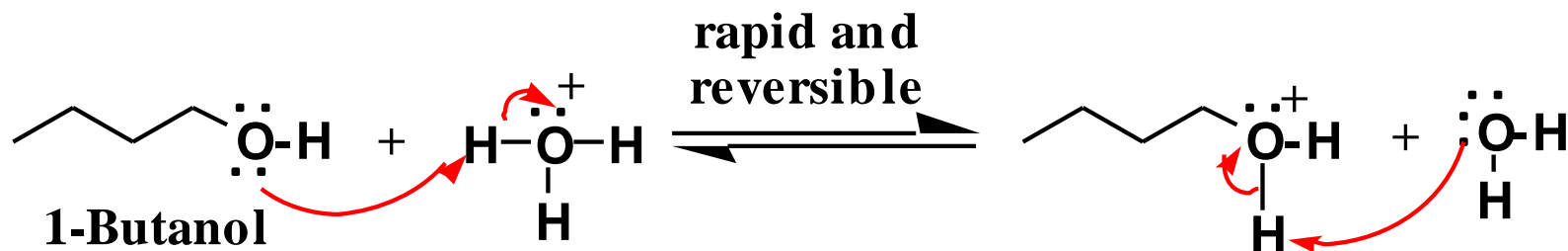
Step 3: proton transfer from a carbon adjacent to the positively charged carbon to water; the sigma electrons of the C-H bond become the pi electrons of the carbon-carbon double bond



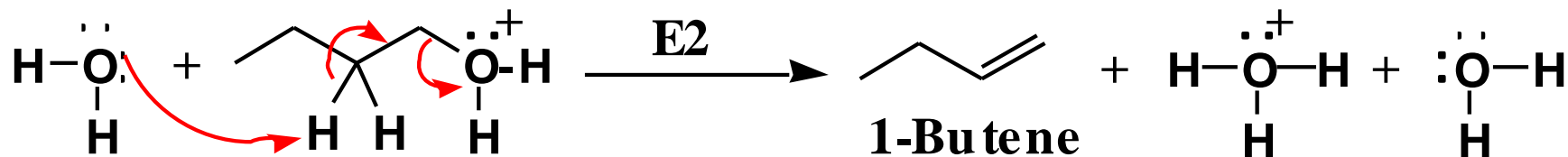
Dehydration of ROH



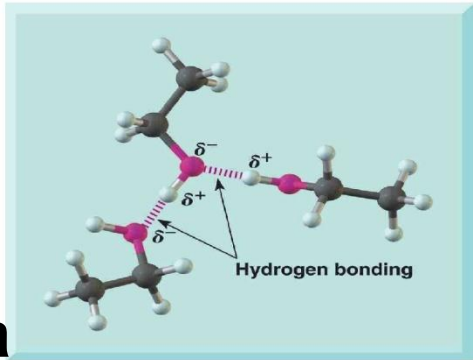
- ◆ 1° alcohols with little β-branching give terminal alkenes and rearranged alkenes
 - Step 1: proton transfer to OH gives an oxonium ion



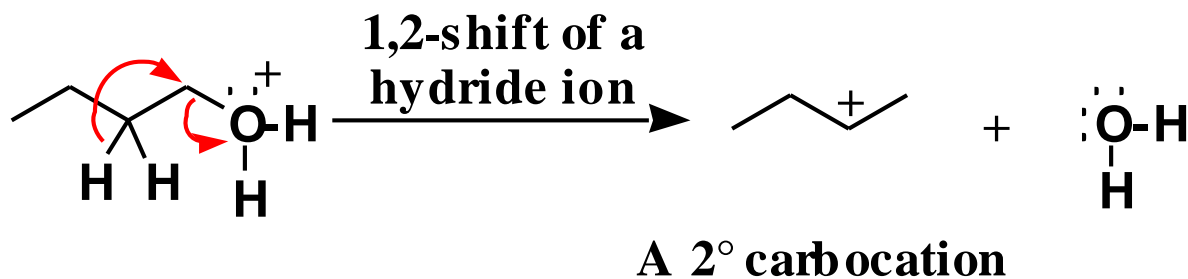
Step 2: loss of H from the β-carbon and H₂O from the α-carbon gives the terminal alkene



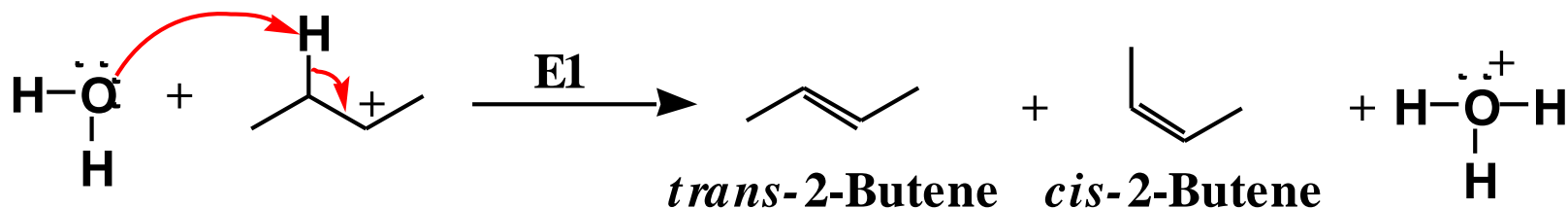
Dehydration of ROH



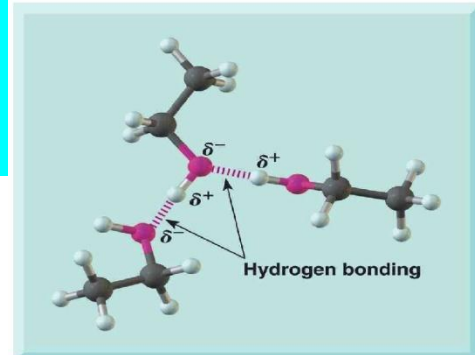
Step 3: shift of a hydride ion from β -carbon and loss of H_2O from the α -carbon gives a carbocation



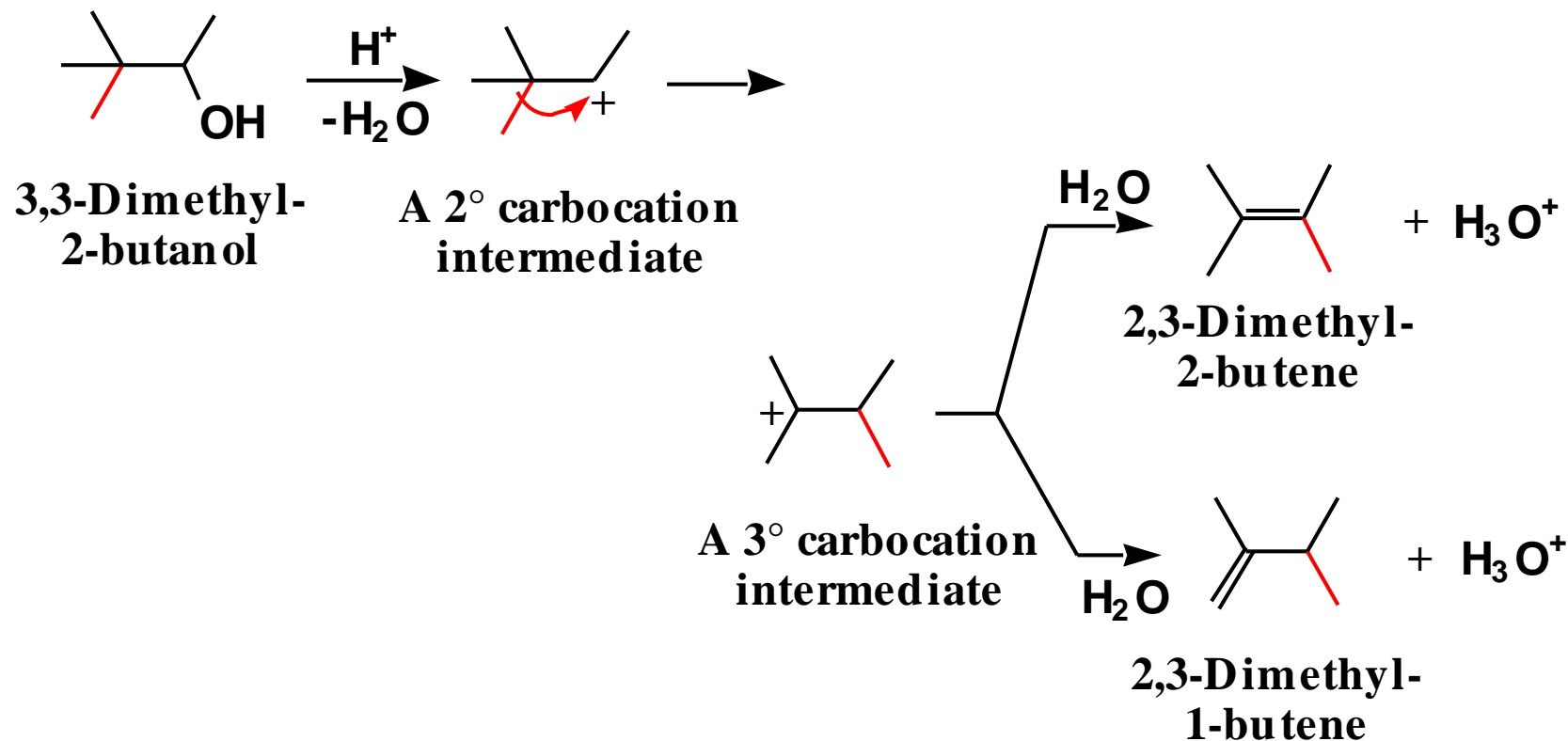
Step 4: proton transfer to solvent gives the alkene



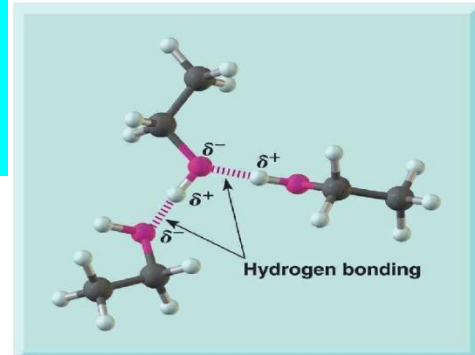
Dehydration of ROH



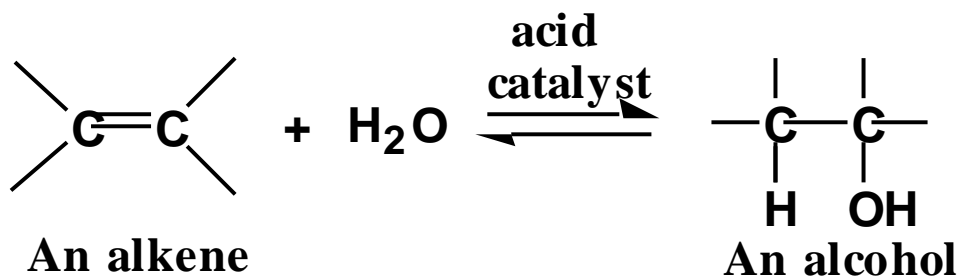
- Dehydration with rearrangement occurs by a carbocation rearrangement



Dehydration of ROH

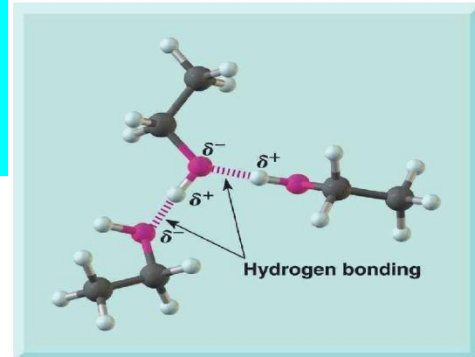


Acid-catalyzed alcohol dehydration and alkene hydration are competing processes

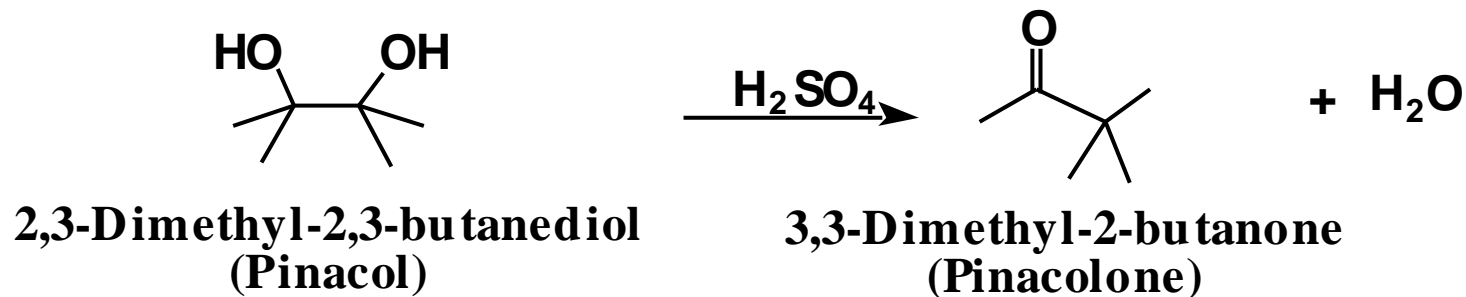


Principle of microscopic reversibility: the sequence of transition states and reactive intermediates in the mechanism of a reversible reaction must be the same, but in reverse order, for the reverse reaction as for the forward reaction

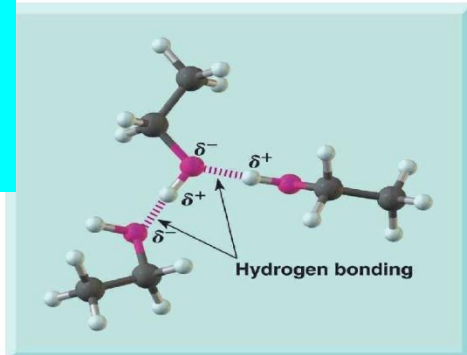
Pinacol Rearrangement



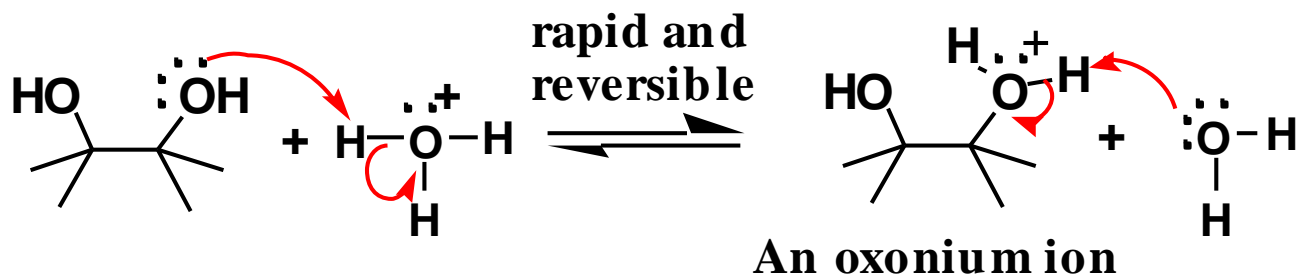
- ◆ The products of acid-catalyzed dehydration of a glycol are different from those of alcohols



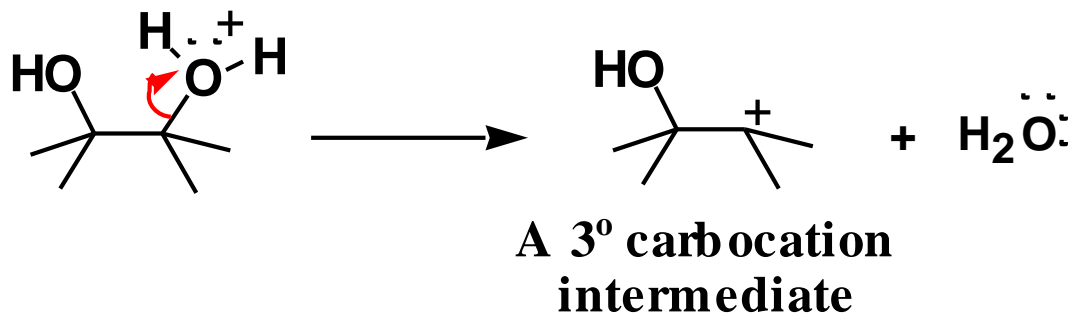
Pinacol Rearrangement



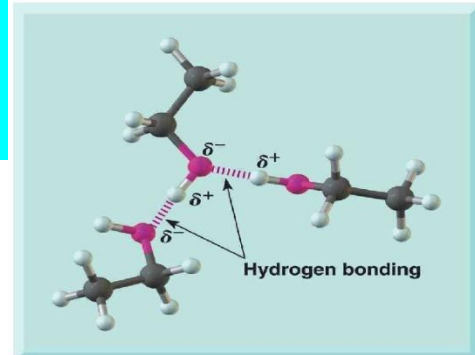
Step 1: proton transfer to OH gives an oxonium ion



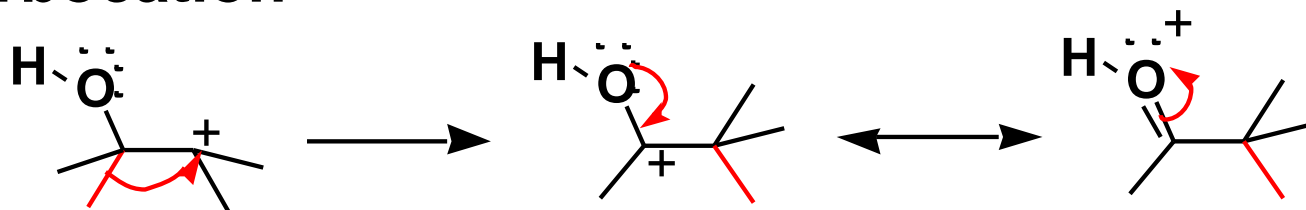
Step 2: loss of water gives a carbocation intermediate



Pinacol Rearrangement

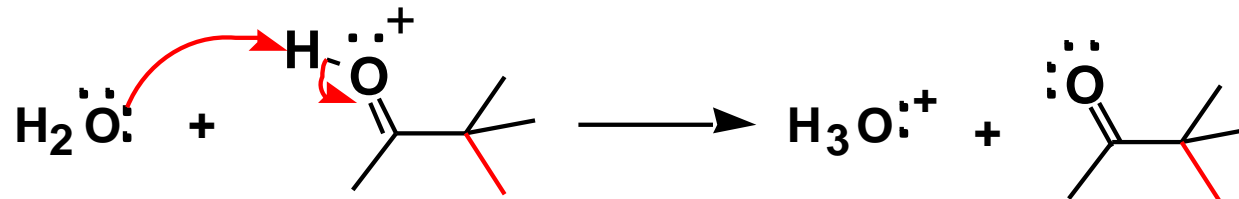


Step 3: a 1,2- shift of methyl gives a more stable carbocation

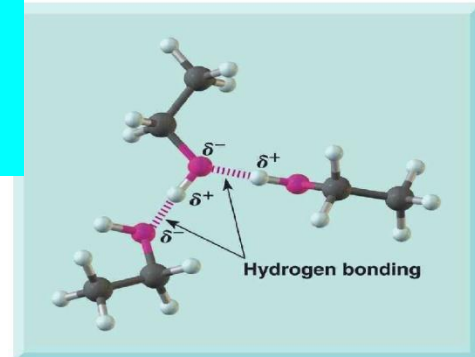


A resonance-stabilized cation intermediate

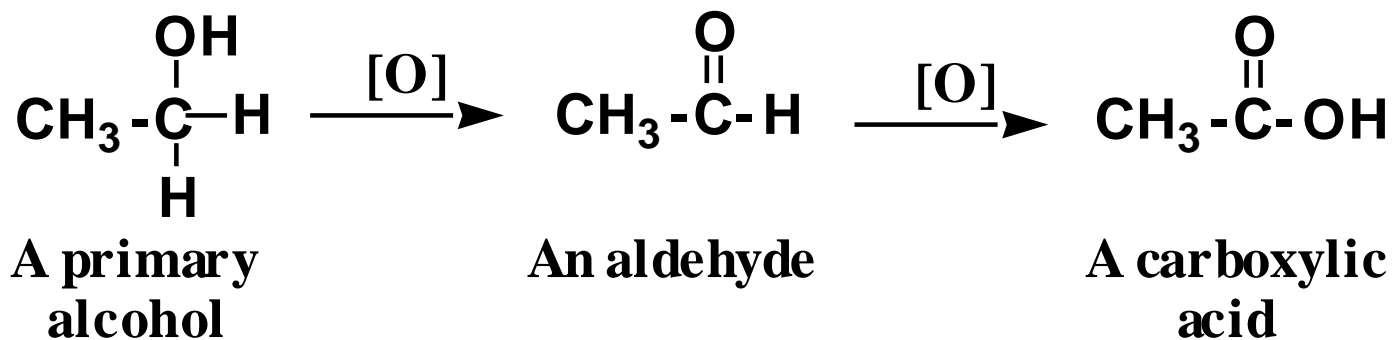
Step 4: proton transfer to solvent completes the reaction



Oxidation: 1° ROH



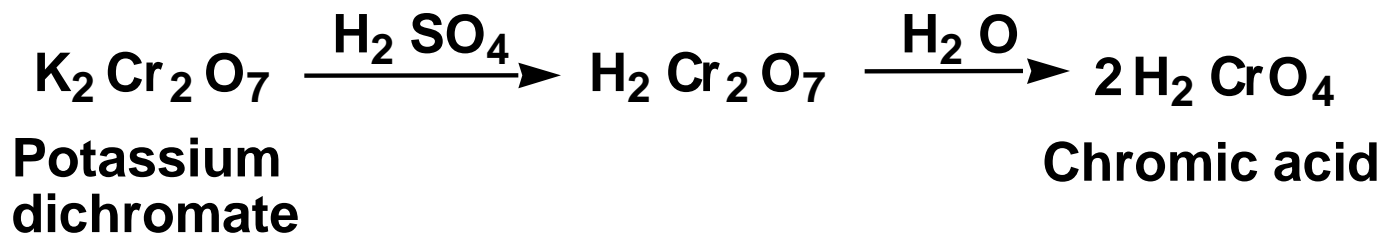
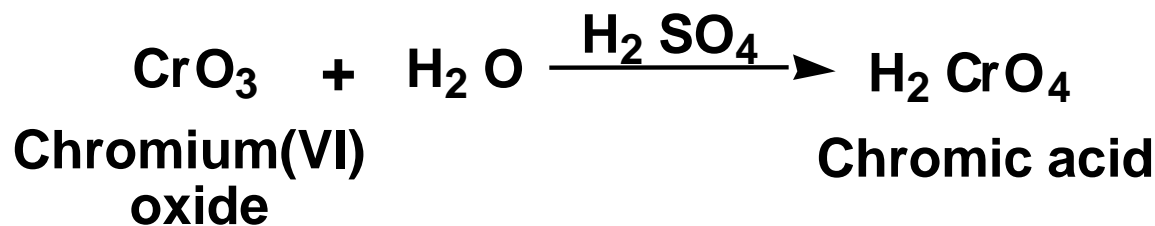
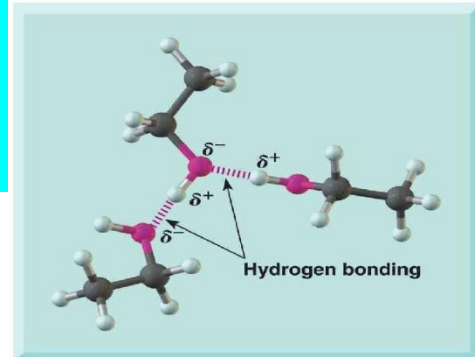
- ◆ Oxidation of a primary alcohol gives an aldehyde or a carboxylic acid, depending on the experimental conditions



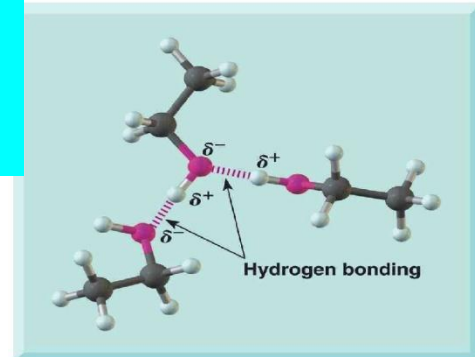
- to an aldehyde is a two-electron oxidation
- to a carboxylic acid is a four-electron oxidation

Oxidation of ROH

- ◆ A common oxidizing agent for this purpose is chromic acid, prepared by dissolving chromium(VI) oxide or potassium dichromate in aqueous sulfuric acid

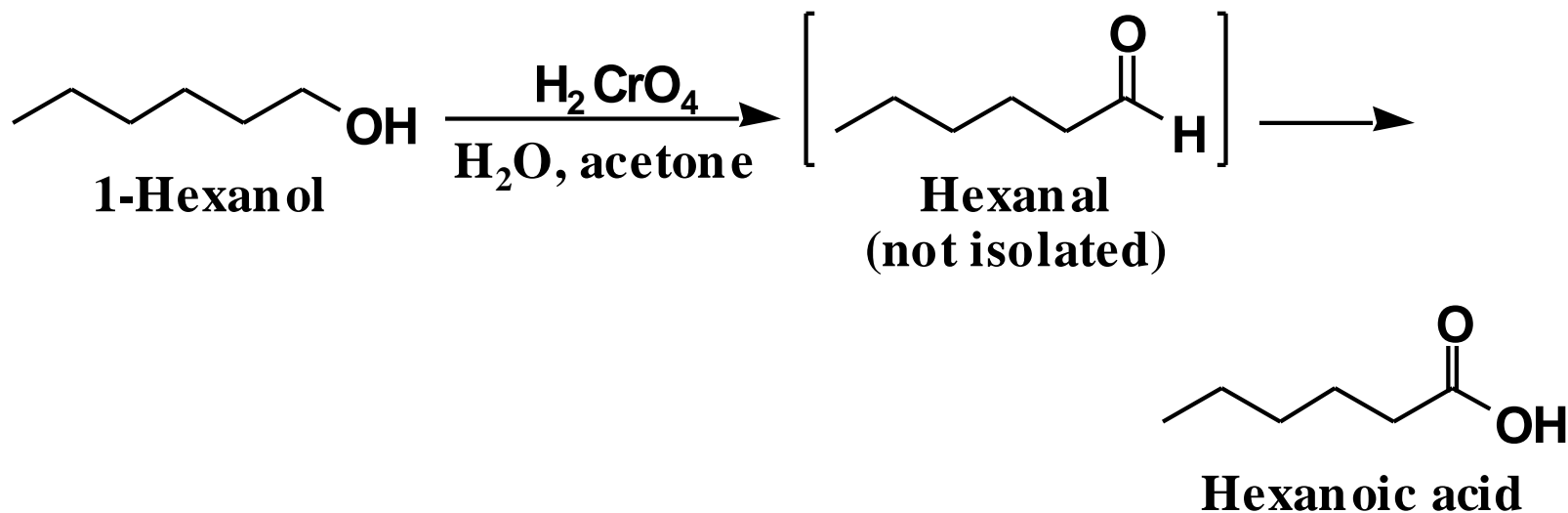


Oxidation: 1° ROH

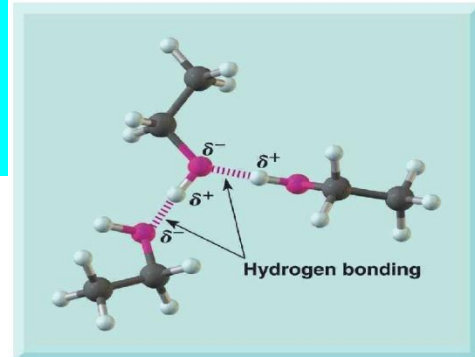


◆ Oxidation of 1-octanol gives octanoic acid

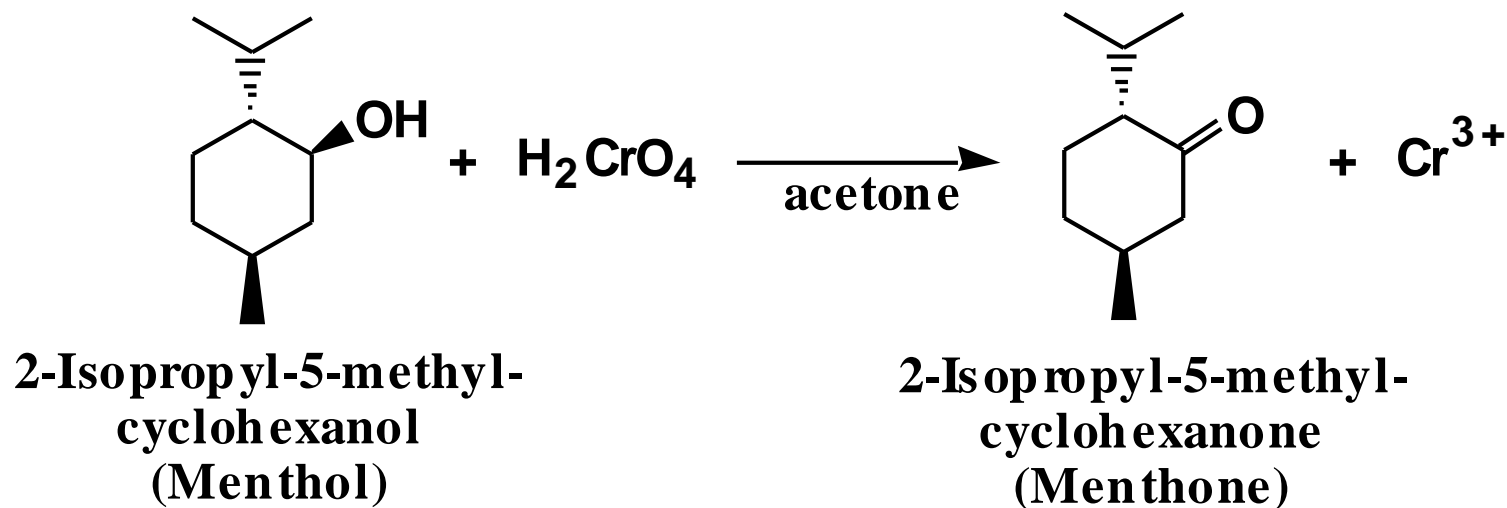
- the aldehyde intermediate is not isolated



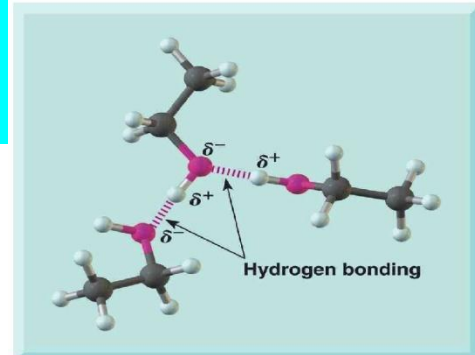
Oxidation: 2° ROH



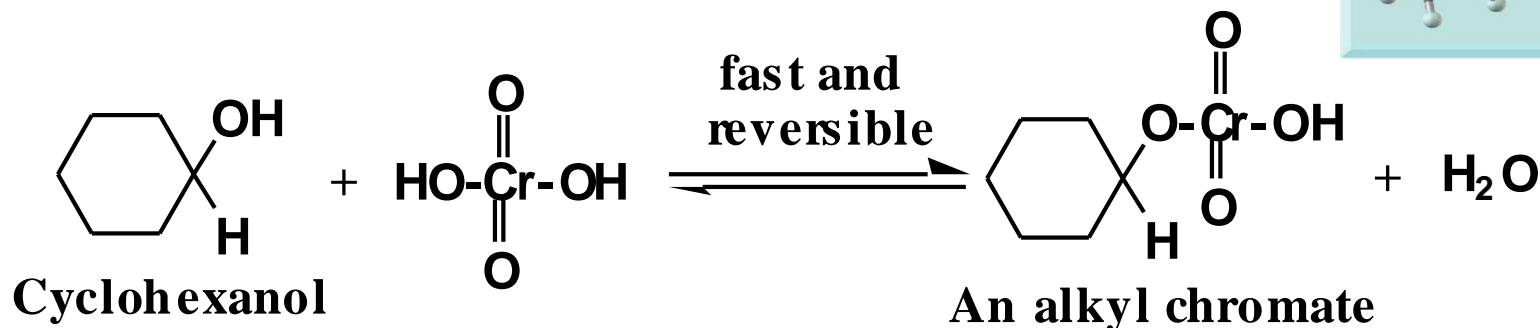
- ◆ 2° alcohols are oxidized to ketones by chromic acid



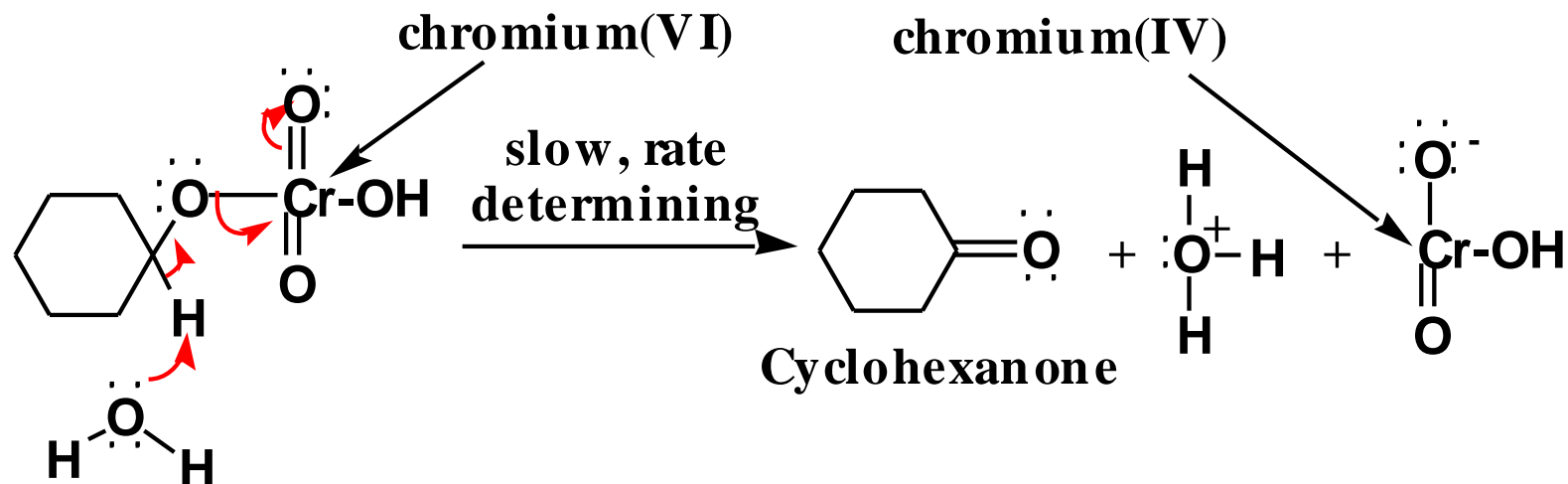
Chromic Acid Oxidation of ROH



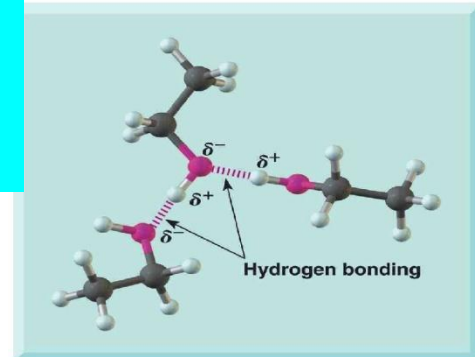
- Step 1: formation of a chromate ester



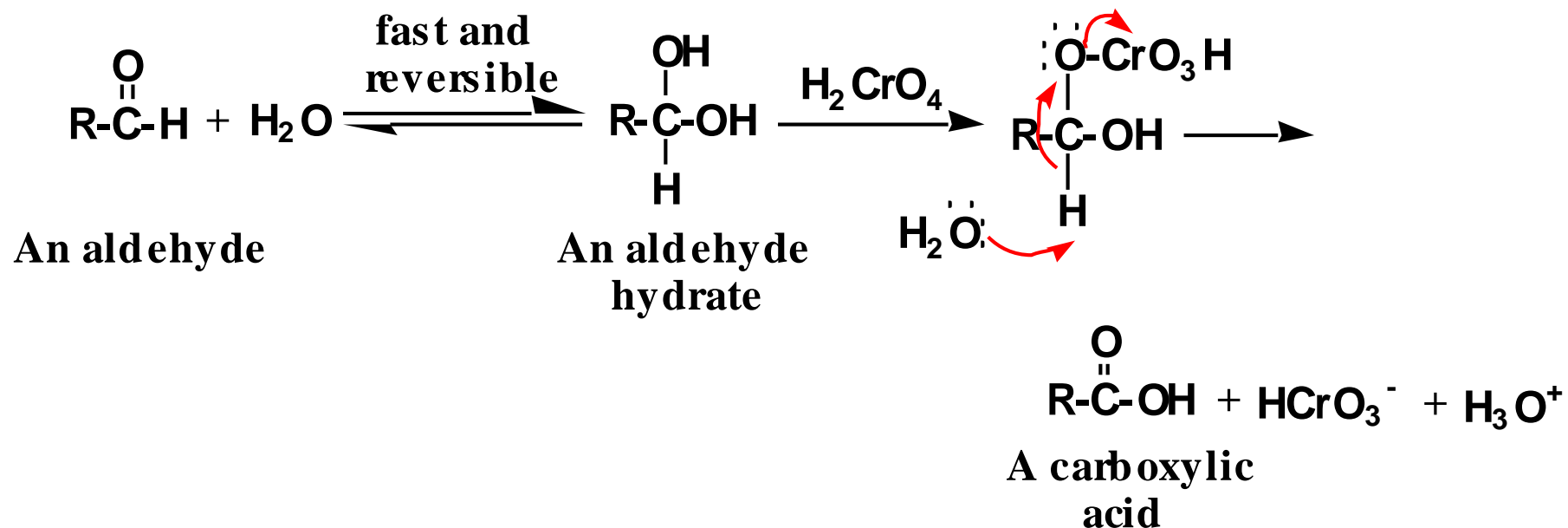
- Step 2: reaction of the chromate ester with a base, here shown as H₂O



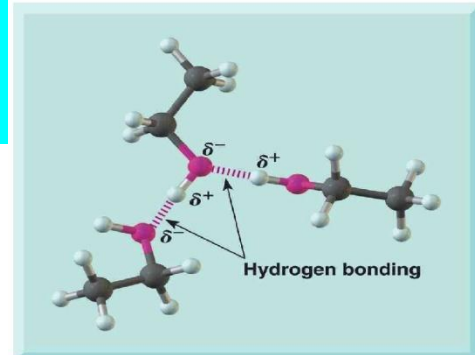
Chromic Acid Oxidation of RCHO



- chromic acid oxidizes a 1° alcohol first to an aldehyde and then to a carboxylic acid
- in the second step, it is not the aldehyde per se that is oxidized but rather the aldehyde hydrate

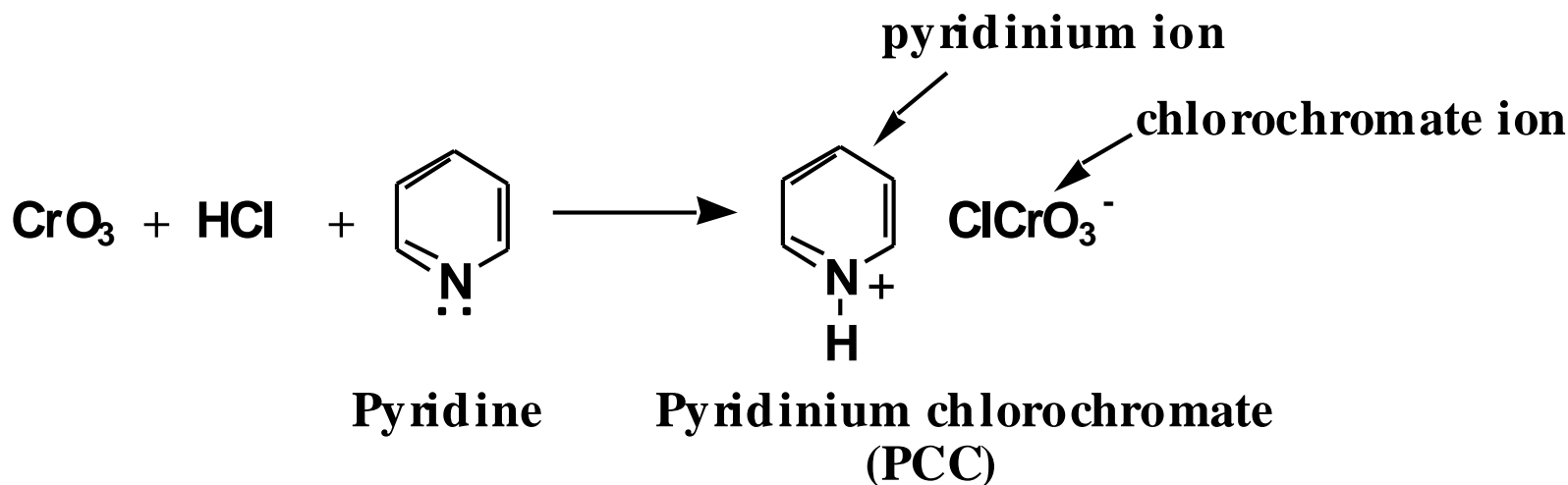


Oxidation: 1° ROH to RCHO



◆ Pyridinium chlorochromate (PCC):

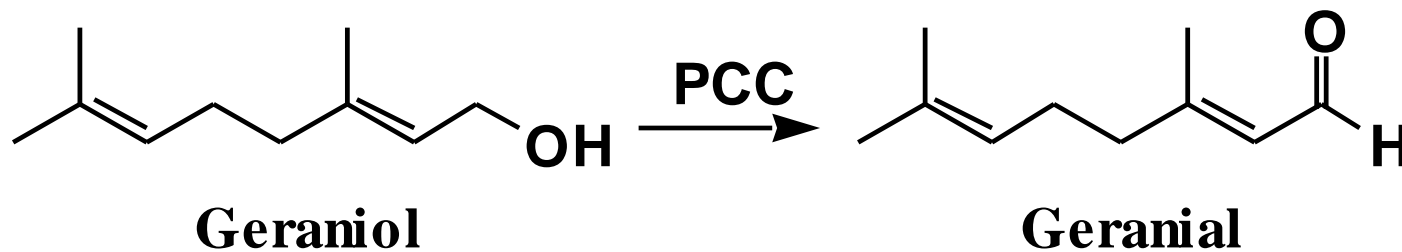
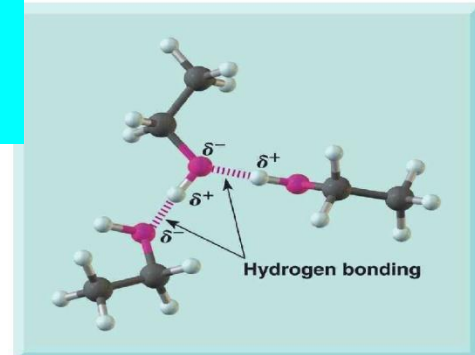
a form of Cr(VI) prepared by dissolving CrO₃ in aqueous HCl and adding pyridine to precipitate PCC as a solid



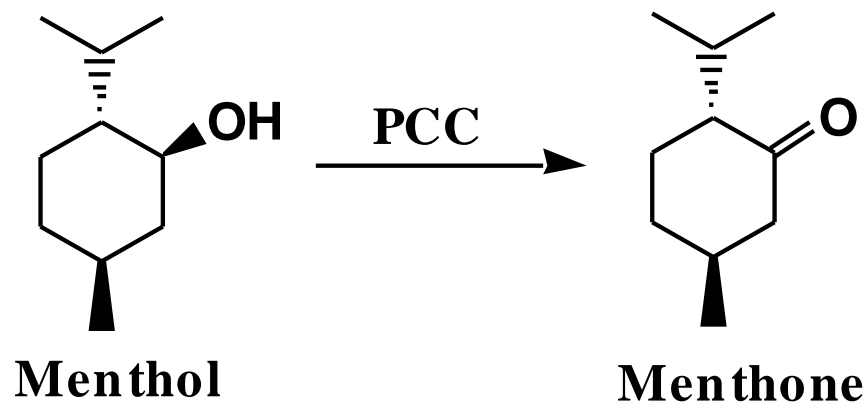
■ PCC is selective for the oxidation of 1° alcohols to aldehydes; it does not oxidize aldehydes further to carboxylic acids

Oxidation: 1° ROH

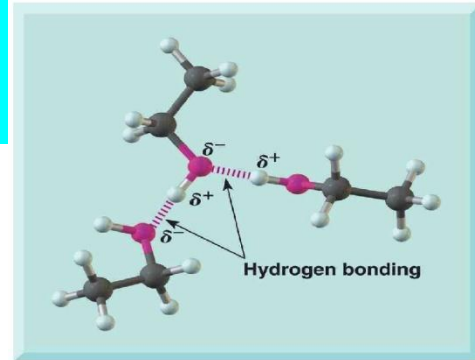
- PCC oxidizes a 1° alcohol to an aldehyde



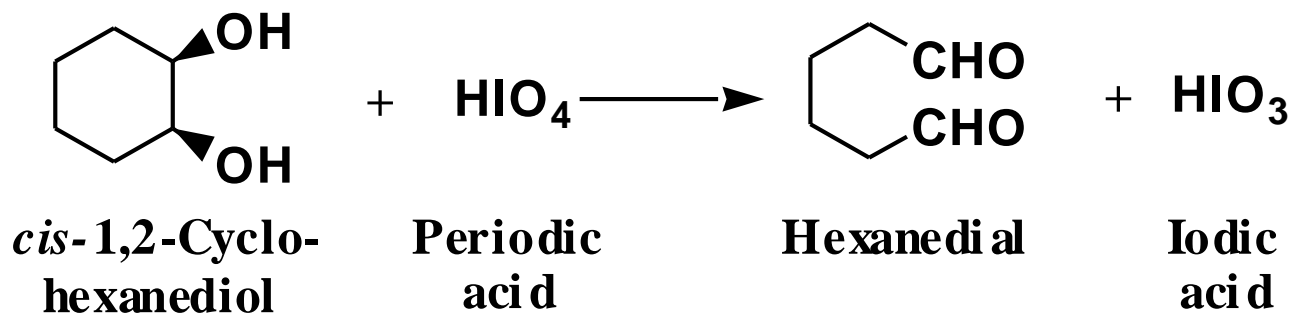
- PCC also oxidizes a 2° alcohol to a ketone



Oxidation of Glycols

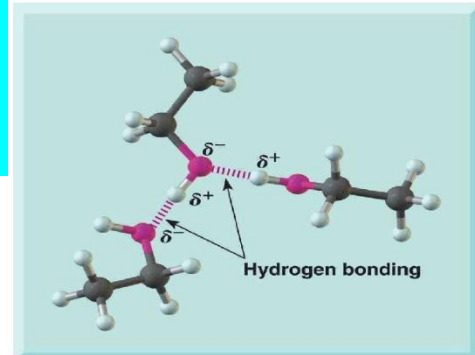


- ◆ Glycols are cleaved by oxidation with periodic acid, HIO_4

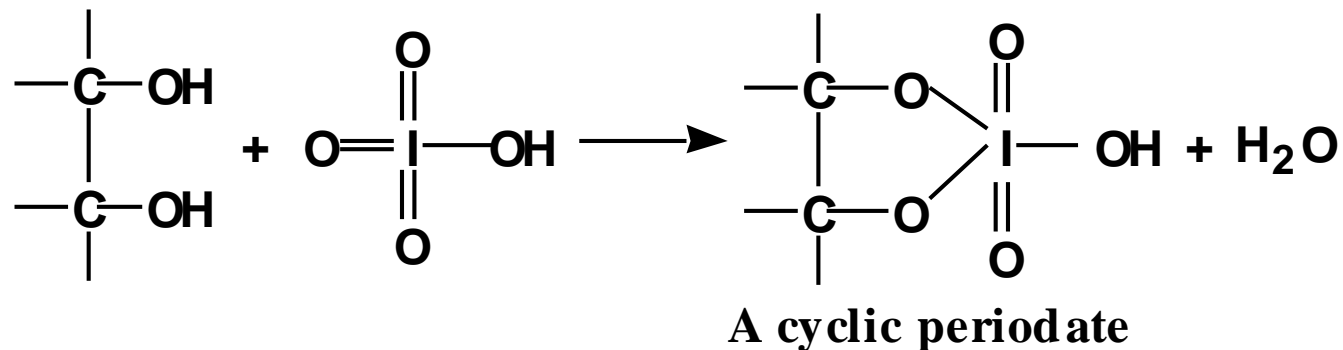


Oxidation of Glycols

- ◆ The mechanism of periodic acid oxidation of a glycol is divided into two steps



Step 1: formation of a cyclic periodate



Step 2: redistribution of electrons within the five-membered ring

