This chapter focuses on the reactions of alcohols and thiols. Like alkyl halides, alcohols undergo substitution and elimination reactions. However, unlike alkyl halides, alcohols and thiols undergo oxidation reactions. This chapter explains how to recognize oxidations, and it presents some of the ways that oxidations of alcohols and thiols are carried out in the laboratory. A consideration of alcohol oxidation in nature leads to a discussion of the stereochemical relationships of groups within molecules. Finally, the strategy used in planning organic syntheses is introduced.

10.1 DEHYDRATION OF ALCOHOLS

Strong acids such as $\text{H}_2\text{SO}_4$ and $\text{H}_3\text{PO}_4$ catalyze a $\beta$-elimination reaction in which water is lost from a secondary or tertiary alcohol to give an alkene. The conversion of cyclohexanol into cyclohexene is typical:

$$\text{cyclohexanol} \xrightarrow{\text{H}_3\text{PO}_4} \text{cyclohexene} + \text{H}_2\text{O} \quad (10.1)$$

A reaction such as this, in which the elements of water are lost from the starting material, is called a dehydration. Thus, in Eq. 10.1, cyclohexanol is said to be dehydrated to cyclohexene. Heat and Lewis acids such as alumina (aluminum oxide, $\text{Al}_2\text{O}_3$) can also be used to catalyze or promote dehydration reactions.

Most acid-catalyzed dehydrations of alcohols are reversible reactions. However, these reactions can easily be driven toward the alkene products by applying Le Châtelier’s principle (Sec. 4.9B). For example, in Eq. 10.1, the equilibrium is driven toward the alkene product because the water produced as a by-product forms a strong complex with the catalyzing acid
H$_3$PO$_4$, and the cyclohexene product is distilled from the reaction mixture. (Alkenes can be removed by distillation because they have considerably lower boiling points than alcohols with the same carbon skeleton.) The dehydration of alcohols to alkenes is easily carried out in the laboratory and is an important procedure for the preparation of some alkenes.

Alcohol dehydration superficially resembles the E2 reaction of alkyl halides, which is also a $\beta$-elimination. We might ask whether we could apply the same strongly basic reaction conditions to alcohol dehydration that we use for the E2 reaction.

\[
\text{E}_2 \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{NaOH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{Br}^- + \text{H}_2\text{O}
\]

As Eq. 10.2b shows, alcohol dehydration is not promoted by strong bases. One reason is that a strong base will remove the O—H proton, which is far more acidic than a C—H $\beta$-proton. The second and major reason is that the OH group is a very poor leaving group because it is a relatively strong base. Recall from Secs. 9.4F and 9.5C that good leaving groups are weak bases.

As Eq. 10.1 illustrates, alcohol dehydration is acid-catalyzed. The role of the acid is to convert the $\text{—OH}$ group, a poor leaving group, into the $\text{—OH}_2$ group, a good leaving group (because H$_2$O is a weak base). The use of Bronsted or Lewis acids to activate the $\text{—OH}$ group as a leaving group will prove to be a central theme in alcohol chemistry.

Alcohol dehydration occurs by a three-step mechanism that consists entirely of acid–base steps and involves a carbocation intermediate. In the first mechanistic step, the $\text{—OH}$ group is activated as a leaving group by acting as a Bronsted base (Sec. 8.7) to accept a proton from the catalyzing acid:

\[
\text{Brønsted acid–base reaction}
\]

Thus, the basicity of alcohols (Sec. 8.7) is important to the success of the dehydration reaction. Next, the carbon–oxygen bond of the alcohol breaks in a Lewis acid–base dissociation to give water and a carbocation:
Finally, water, the conjugate base of the catalyzing acid H$_2$O$^+$, removes a $\beta$-proton from the carbocation in another Brønsted acid–base reaction:

This step generates the alkene product and regenerates the catalyzing acid H$_2$O$^+$.

Let’s focus briefly on the acid–base reaction in the last step of the mechanism (Eq. 10.3c), in which H$_2$O is the base. A common error in thinking about the mechanism is to use hydroxide ion (OH$^-$) as the base; after all, hydroxide is a stronger base than water. However, hydroxide cannot be the base, because the reaction is carried out in strongly acidic solution; hydroxide cannot survive in strong acid because it protonates instantaneously to form water. Nor is hydroxide necessary as a base, because the carbocation is a very strong acid; the p$K_a$ of a carbocation $\beta$-proton is $-8$ to $-10$. Water is perfectly adequate as a base to remove such an acidic proton because the conjugate acid of water has a p$K_a$ of $-1.74$. (See Sec. 3.4E.) When a reaction is carried out in H$_2$O$^+$, H$_2$O is typically used as the base. On the other hand, we’ll see numerous examples of different reactions that take place in strongly basic solution. For these reactions, strong acids are not involved. A reaction that requires a base such as OH$^-$ would involve the conjugate acid of OH$^-$, namely H$_2$O, as the acid, not H$_2$O$^+$. To summarize: An acid and its conjugate base always act in tandem in a mechanism. (If necessary, reread the discussion of amphoteric compounds on pp. 104–105, Sec. 3.4E.).

Let’s now return to the dehydration mechanism shown in Eqs. 10.3a–c. We’ve discussed a mechanism like this twice before. First, alcohol dehydration is an E1 reaction (Sec. 9.6). Once the —OH group of the alcohol is protonated, it becomes a very good leaving group (water). Like a halide leaving group in the E1 reaction, the protonated —OH departs to give a carbocation, which then loses a $\beta$-proton to H$_2$O to give an alkene.

Alcohol dehydration: E1 reaction of an alkyl halide:
Second, the dehydration of alcohols is the reverse of the hydration of alkenes (Sec. 4.9B). Hydration of alkenes and dehydration of alcohols are the forward and reverse of the same reaction.

Recall from the principle of microscopic reversibility (Sec. 4.9B) that the forward and reverse of the same reaction must have the same intermediates and the same rate-limiting transition states. Thus, because protonation of the alkene is the rate-limiting step in alkene hydration, the reverse of this step—loss of the proton from the carbocation intermediate (Eq. 10.3)—is rate-limiting in alcohol dehydration. This principle also requires that if a catalyst accelerates a reaction in one direction, it also accelerates the reaction in the reverse direction. Thus, both the hydration of alkenes to alcohols and the dehydration of alcohols to alkenes are catalyzed by acids.

The involvement of carbocation intermediates explains several experimental facts about alcohol dehydration. First, the relative rates of alcohol dehydration are in the order tertiary > secondary >> primary. Application of Hammond’s postulate (Sec. 4.8C) suggests that the rate-limiting transition state of a dehydration reaction should closely resemble the corresponding carbocation intermediate. Because tertiary carbocations are the most stable carbocations, dehydration reactions involving tertiary carbocations should be faster than those involving either secondary or primary carbocations, as observed. In fact, the dehydration of primary alcohols is generally not a useful laboratory procedure for the preparation of alkenes. (Primary alcohols react in other ways with H₂SO₄; see Problem 10.60, p. 481.)

Second, if the alcohol has more than one type of β-hydrogen, then a mixture of alkene products can be expected. As in the E1 reaction of alkyl halides, the most stable alkene—the one with the greatest number of branches at the double bond—is the alkene formed in greatest amount:

$$
\begin{align*}
\text{H}_3\text{C} &= \text{C} = \text{CH}_2\text{CH}_3 & \text{H}_2\text{O} + \text{H}_2\text{SO}_4 \\
\text{H}_3\text{C} &= \text{C} = \text{CH} \rightarrow \text{CH}_3 & \text{H}_2\text{C} = \text{C} = \text{CH}_2\text{CH}_3 + \text{H}_2\text{O} \\
\text{2-methyl-2-butanol} & \rightarrow \text{2-methyl-2-butene} & \text{2-methyl-1-butene}
\end{align*}
$$

Finally, alcohols that react to give rearrangement-prone carbocation intermediates yield rearranged alkenes:

$$
\begin{align*}
\text{H}_3\text{C} &= \text{C} = \text{CH} \rightarrow \text{CH}_3 & \text{H}_3\text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \\
\text{H}_3\text{C} &= \text{C} = \text{CH} \rightarrow \text{CH}_3 & \text{H}_3\text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \\
\text{3,3-dimethyl-2-butanol} & \rightarrow \text{2,3-dimethyl-1-butene} & \text{2,3-dimethyl-2-butene}
\end{align*}
$$

$$
\begin{align*}
\text{H}_3\text{C} &= \text{C} = \text{CH} \rightarrow \text{CH}_3 & \text{H}_3\text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \\
\text{H}_3\text{C} &= \text{C} = \text{CH} \rightarrow \text{CH}_3 & \text{H}_3\text{C} = \text{C} = \text{CH}_3 + \text{H}_2\text{O} \\
\text{1-cyclobutylethanol} & \rightarrow \text{1-methylcyclopentene}
\end{align*}
$$
10.1 What alkene(s) are formed in the acid-catalyzed dehydration of each of the following alcohols?
   (a) 3-methyl-3-heptanol
   (b) \( \text{PhCHCH}_2\text{Ph} \)

10.2 Give the curved-arrow mechanism for the reaction in Problem 10.1a. In each step, identify all Brønsted acids and bases, all electrophiles and nucleophiles, and all leaving groups.

10.3 Identify the major alkene product(s) in part (a) of Problem 10.1.

10.4 Give the structure of the carbocation intermediate involved in the acid-catalyzed dehydration of 3-ethyl-3-pentanol.

10.5 Give the structures of two alcohols, one secondary and one tertiary, that could give each of the following alkenes as a major acid-catalyzed dehydration product. In each case, which alcohol would dehydrate most rapidly?
   (a) 1-methylcyclohexene
   (b) 3-methyl-2-pentene

10.6 (a) Give a curved-arrow mechanism for the reaction in Eq. 10.6.
   (b) After reading Study Guide Link 10.2, explain why the rearrangement in Eq. 10.7 is favorable even though both of the carbocation intermediates involved are secondary.

10.7 A certain reaction is carried out in methanol with \( \text{H}_2\text{SO}_4 \) as a catalyst.
   (a) What Brønsted acid is present in highest concentration in such a solution? (Hint: \( \text{H}_2\text{SO}_4 \) is completely dissociated in methanol, just as it is in water.)
   (b) If a base is involved in the reaction mechanism, what is the basic species?

10.2 REACTIONS OF ALCOHOLS WITH HYDROGEN HALIDES

Alcohols react with hydrogen halides to give alkyl halides:

\[
\begin{align*}
(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH} + \text{HBr} & \xrightarrow{\text{H}_2\text{SO}_4, \text{heat, 5–6 h}} (\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Br} + \text{H}_2\text{O} & (10.8) \\
3\text{-methyl-1-butanol} & & 1\text{-bromo-3-methylbutane} \\
(\text{CH}_3)_2\text{C} \xrightarrow{25^\circ\text{C}, 20 \text{ min}} \text{H}_2\text{O} & (\text{CH}_3)_2\text{C} \xrightarrow{} \text{H}_2\text{O} & (10.9) \\
\text{tert-butyl alcohol} & & \text{tert-butyl chloride} & (\text{almost quantitative})
\end{align*}
\]

The equilibrium constant for the formation of alkyl halides from alcohols is not large; hence, the successful preparation of alkyl halides from alcohols, like the dehydration of alcohols to alkenes, usually depends on the application of Le Châtelier’s principle (Sec. 4.9B). For example, in both Eqs. 10.8 and 10.9, the reactant alcohols are soluble in the reaction solvent, which is an aqueous acid, but the product alkyl halides are not. Separation of the alkyl halide products from the reaction mixture as water-insoluble layers drives both reactions to completion. For alcohols that are not water-soluble, a large excess of gaseous HBr can be used to drive the reaction to completion.

The mechanism of alkyl halide formation depends on the type of alcohol used as the starting material. In the reactions of tertiary alcohols, protonation of the alcohol oxygen is followed by carbocation formation. The carbocation reacts with the halide ion, which is formed by ionization of strong acid HCl, and which is present in great excess: