ural barrier to the passage of ions. However, the hydrocarbon surface of nonactin allows it to enter readily into, and pass through, membranes. Because nonactin binds and thus transports ions, the ion balance crucial to proper cell function is upset, and the cell dies.

**Ion Channels** Ion channels, or “ion gates,” provide passageways for ions into and out of cells. (Recall that ions are not soluble in membrane phospholipids.) The flow of ions is essential for the transmission of nerve impulses and for other biological processes. A typical channel is a large protein molecule imbedded in a cell membrane. Through various mechanisms, ion channels can be opened or closed to regulate the concentration of ions in the interior of the cell. Ions do not diffuse passively through an open channel; rather, an open channel contains regions that bind a specific ion. Such an ion is bound specifically within the channel at one side of the membrane and is somehow expelled from the channel on the other side. Remarkably, the structures of the ion-binding regions of these channels have much in common with the structures of ionophores such as nonactin. The first X-ray crystal structure of a potassium-ion channel was determined in 1998 by a team of scientists at Rockefeller University led by Prof. Roderick MacKinnon (b. 1956), who shared the 2003 Nobel Prize in Chemistry for this work. The interior of the channel contains binding sites for two potassium ions; these sites are oxygen-rich, much like the interior of nonactin. The oxygens in each site are situated so that they just “fit” a potassium ion and are too far apart to interact effectively with a sodium ion. The exterior of the channel molecule contains many groups that “solubilize” or “anchor” it within the phospholipid bilayer of the cell membrane. When two potassium ions bind into the channel, the repulsion between the two ions balances the ion-binding forces, and one of the ions can then leave the channel; this is postulated to be the mechanism of ionic conduction.

**PROBLEM 8.23** The crown ether [18]-crown-6 (structure on p. 352) has a strong affinity for the methylammonium ion, CH₃NH₃⁺. Propose a structure for the complex between [18]-crown-6 and this ion. (Although the crown ether is bowl-shaped, you can draw a planar structure for purposes of this problem.) Show the important interactions between the crown ether and the ion.

## 8.6 ACIDITY OF ALCOHOLS AND THIOLS

Alcohols and thiols are weak acids. In view of the similarity between the structures of water and alcohols, it may come as no surprise that their acidities are about the same.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{O}^- & :\text{Na}^+ & \text{common: sodium ethoxide} \\
\text{CH}_3\text{CH}_2\text{SH} & :\text{H}^+ & \text{substitutive: sodium ethanolate}
\end{align*}
\]

The conjugate bases of alcohols are generally called alkoxides. The common name of an alkoxide is constructed by deleting the final \(yl\) from the name of the alkyl group and adding the suffix \(oxide\). In substitutive nomenclature, the suffix \(ate\) is simply added to the name of the alcohol.

The relative acidities of alcohols and thiols are a reflection of the element effect described in Sec. 3.6A. Thiols, with \(pK_a\) values near 10, are substantially more acidic than alcohols. For example, the \(pK_a\) of ethanethiol, \(\text{CH}_3\text{CH}_2\text{SH}\), is 10.5.
The conjugate bases of thiols are called *mercaptides* in common nomenclature and *thiolates* in substitutive nomenclature.

\[ \text{CH}_3\text{S}^- \quad \text{common: sodium methyl mercaptide} \]

\[ \text{CH}_3\text{S}^- \quad \text{substitutive: sodium methanethiolate} \]

### PROBLEMS

8.24 Give the structure of each of the following compounds.

(a) sodium isopropoxide  
(b) potassium tert-butoxide  
(c) magnesium 2,2-dimethyl-1-butanolate

8.25 Name the following compounds.

(a) Ca(OCH\(_3\))\(_2\)  
(b) Cu\(\text{SCH}_3\)CH\(_3\)
The rate of this reaction depends strongly on the alcohol. The reactions of sodium with anhydrous (water-free) ethanol and methanol are vigorous, but not violent. However, the reactions of sodium with some alcohols, such as tert-butyl alcohol, are rather slow. The alkoxides of such alcohols can be formed more rapidly with the more reactive potassium metal.

Because thiols are much more acidic than water or alcohols, they, unlike alcohols, can be converted completely into their conjugate-base mercaptide anions by reaction with one equivalent of hydroxide or alkoxide. In fact, a common method of forming alkali-metal mercaptides is to dissolve them in ethanol containing one equivalent of sodium ethoxide:

\[
C_2H_5SH + C_2H_5O^– \rightleftharpoons C_2H_5O^– + C_2H_5OH \quad (8.13)
\]

Because the equilibrium constant for this reaction is \(>10^5\) (Sec. 3.4E), the reaction goes essentially to completion.

Although alkali-metal mercaptides are soluble in water and alcohols, thiols form insoluble mercaptides with many heavy-metal ions, such as \(\text{Hg}^{2+}\), \(\text{Cu}^{2+}\), and \(\text{Pb}^{2+}\).

\[
2\text{CH}_3(\text{CH}_2)_9\text{SH} + \text{PbCl}_2 \xrightarrow{\text{C}_2\text{H}_5\text{OH}} [\text{CH}_3(\text{CH}_2)_8\text{S}]_2\text{Pb} + 2\text{HCl} \quad (8.14)
\]

\[
2\text{PhSH} + \text{HgCl}_2 \rightarrow (\text{PhS})_2\text{Hg} + 2\text{HCl} \quad (8.15)
\]

The insolubility of heavy-metal mercaptides is analogous to the insolubility of heavy-metal sulfides (for example, lead(II) sulfide, \(\text{PbS}\)), which are among the most insoluble inorganic compounds known. One reason for the toxicity of lead salts is that the lead forms very strong (stable) mercaptide complexes with the thiol groups of important biomolecules.

**Curing a Disease with Mercaptides**

A relatively rare inherited disease of copper metabolism, Wilson's disease, can be treated by using the tendency of thiols to form complexes with copper ions. Accumulation of toxic levels of copper in the brain and liver causes the disease. Penicillamine is administered to form a complex with the \(\text{Cu}^{2+}\) ions:

\[
\text{SH} + \text{NH}_3 \xrightarrow{\text{Cu}} \text{O} \quad \text{O} \quad \text{O} \\
\text{C–O–C} \quad \text{C–O–C} \\
(\text{CH}_2)_2\text{C} \quad (\text{CH}_2)_2\text{C} \\
\text{O} \\
\text{penicillamine} \\
\text{ionized carboxylic acid}
\]

The penicillamine-copper complex, unlike ordinary cupric thilates, is relatively soluble in water because of the ionized carboxylic acid groups, and its solubility allows it to be excreted by the kidneys.
B. Polar Effects on Alcohol Acidity

Substituted alcohols and thiols show the same type of polar effect on acidity as do substituted carboxylic acids (Sec. 3.6C). For example, alcohols containing electronegative substituent groups have enhanced acidity. Thus, 2,2,2-trifluoroethanol is more than three $pK_a$ units more acidic than ethanol itself.

Relative acidity:

$$
\begin{align*}
\text{H}_3\text{C}—\text{CH}_2—\text{OH} & < \text{F}_3\text{C}—\text{CH}_2—\text{OH} \\
pK_a & \quad 15.9 \quad 12.4
\end{align*}
$$

The polar effects of electronegative groups are more important when the groups are closer to the $—\text{OH}$ group:

Relative acidity:

$$
\begin{align*}
\text{F}_3\text{C}—\text{CH}_2—\text{CH}_2—\text{CH}_2—\text{OH} & < \text{F}_3\text{C}—\text{CH}_2—\text{CH}_2—\text{OH} < \text{F}_3\text{C}—\text{CH}_2—\text{OH} \\
pK_a & \quad 15.4 \quad 14.6 \quad 12.4
\end{align*}
$$

Notice that the fluorines have a negligible effect on acidity when they are separated from the $—\text{OH}$ group by four or more carbons.

C. Role of the Solvent in Alcohol Acidity

Primary, secondary, and tertiary alcohols differ significantly in acidity; some relevant $pK_a$ values are shown in Table 8.3. The data in this table show that the acidities of alcohols are in the order methyl $>$ primary $>$ secondary $>$ tertiary. For many years chemists thought that this order was due to some sort of polar effect (Sec. 3.6C) of the alkyl groups around the alcohol oxygen. However, chemists were fascinated when they learned that in the gas phase—in the absence of solvent—the order of acidity of alcohols is exactly reversed.

Relative gas-phase acidity:

$$
(CH)_3\text{COH} > (CH)_2\text{CHOH} > CH_3\text{CH}_2\text{OH} > CH_3\text{OH}
$$

### Table 8.3

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>$pK_a$</th>
<th>Alcohol</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$OH</td>
<td>15.1</td>
<td>(CH)$_3$CHOH</td>
<td>17.1</td>
</tr>
<tr>
<td>CH$_3$CH$_2$OH</td>
<td>15.9</td>
<td>(CH)$_2$COH</td>
<td>19.2</td>
</tr>
</tbody>
</table>
Notice carefully what is being stated here. The relative order of acidity of different types of alcohols is reversed in the gas phase compared with the relative order of acidity in solution. It is not true that alcohols are more acidic in the gas phase than they are in solution; rather, all alcohols are much more acidic in solution than they are in the gas phase.

Branched alcohols are more acidic than unbranched ones in the gas phase because \( \alpha \)-alkyl substituents stabilize alkoxide ions more effectively than hydrogens. (Recall that stabilization of a conjugate-base anion increases acidity; Fig. 3.2, p. 113). This stabilization occurs by a polarization mechanism. That is, the electron clouds of each alkyl group distort so that electron density moves away from the negative charge on the alkoxide oxygen, leaving a partial positive charge on the central carbon. The anion is stabilized by its favorable electrostatic interaction with this partial positive charge.

Because a tertiary alcohol has more \( \alpha \)-alkyl substituents than a primary alcohol, a tertiary alkoxide is stabilized by this polarization effect more than a primary alkoxide. Consequently, tertiary alcohols are more acidic in the gas phase.

The same polarization effect is present in solution, but the different acidity order in solution shows that another, more important, effect is operating as well. The acidity order in solution is due to the effectiveness with which alcohol molecules solvate their conjugate-base anions. Recall from Sec. 8.4B that anions are solvated, or stabilized in solution, by hydrogen bonding with the solvent. Such hydrogen bonding is nonexistent in the gas phase. It is thought that the alkyl groups of a tertiary alkoxide somehow adversely affect the solvation of the alkoxide oxygen, although a precise description of the mechanism is unclear. (It is known not to be a simple steric effect.) Reducing the solvation of the tertiary alkoxide increases its energy and therefore increases its basicity. Because primary alkoxides do not have so many alkyl branches, the solvation of primary alkoxides is more effective. Consequently, their solution basicities are lower. To summarize: tertiary alkoxides are more basic in solution than primary alkoxides. An equivalent statement is that primary alcohols are more acidic in solution than tertiary alcohols.

The essential point of this discussion is that the solvent is not an idle bystander in the acid–base reaction; rather, it takes an active role in stabilizing the molecules involved, especially the charged species.

Just as water can accept a proton to form the hydronium ion, alcohols, ethers, thiols, and sulfides can also be protonated to form positively charged conjugate acids. Alcohols and ethers do not differ greatly from water in their basicities; thiols and sulfides, however, are much less basic.

Further Exploration 8.2
Salvation of Tertiary Alkoxides