19.8 REDUCTION OF ALDEHYDES AND KETONES TO ALCOHOLS

Aldehydes and ketones are reduced to alcohols with either lithium aluminum hydride, LiAlH₄, or sodium borohydride, NaBH₄. These reactions result in the net addition of the elements of H₂ across the C=O bond.

\[
\text{Cyclobutanone} + \text{LiAlH}_4 \rightarrow \text{Cyclobutanol} + \text{H}_2\text{O}^+ + \text{Li}^+ + \text{Al}^{3+} \text{ salts}
\]

(19.22)

As these examples illustrate, reduction of an aldehyde gives a primary alcohol, and reduction of a ketone gives a secondary alcohol.

Lithium aluminum hydride is one of the most useful reducing agents in organic chemistry. It serves generally as a source of H·⁻, the hydride ion. Because hydrogen is more electronegative than aluminum (Table 1.1), the Al–H bonds of the \(\text{AlH}_4^–\) ion carry a substantial fraction of the negative charge. In other words,

\[
\text{H—Al—H} \quad \text{reacts as if it were} \quad \text{H—Al—H}^–
\]

(19.24)

The hydride ion in LiAlH₄ is very basic. For this reason, LiAlH₄ reacts violently with water and therefore must be used in dry solvents such as anhydrous ether and THF.

\[
\text{Li}^+ + \text{H—Al—H} + \text{OH} \rightarrow \text{H—Al—H} + \text{H}^+ + \text{Li}^+ + \text{HOH}
\]

(19.25)

Like many other strong bases, the hydride ion in LiAlH₄ is a good nucleophile, and LiAlH₄ contains its own “built-in” Lewis acid, the lithium ion. The reaction of LiAlH₄ with aldehydes and ketones involves the nucleophilic reaction of hydride (delivered from \(\text{AlH}_4^–\)) at the carbonyl carbon. The lithium ion acts as a Lewis acid catalyst by coordinating to the carbonyl oxygen.
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The addition product, an alkoxide salt, can react with AlH$_3$, and the resulting product can also serve as a source of hydride.

![Diagram](19.26a)

$$\text{Li}^+ \overset{\text{O}^-}{\longrightarrow} \text{AlH}_3 \quad \rightarrow \quad \text{Li}^+ \overset{\text{O}^-}{\longrightarrow} \text{AlH}_3$$

(19.26a)

Similar processes occur at each stage of the reduction until all of the hydrides are consumed. Hence, as shown in the stoichiometry of Eq. 19.22, all four hydrides of LiAlH$_4$ are active in the reduction. In other words, it takes one-fourth of a mole of LiAlH$_4$ to reduce a mole of aldehyde or ketone.

After the reduction is complete, the alcohol product exists as an alkoxide addition compound with the aluminum. This is converted by protonation in a separate step into the alcohol product. The proton source can be an aqueous HCl solution or even an aqueous solution of a weak acid such as ammonium chloride.

![Diagram](19.26b)

$$\text{R} - \text{C} - \text{R}_\text{H} \quad \rightarrow \quad \text{R} - \text{C} - \text{R} \quad + \quad \text{AlH}_3$$

(19.26b)

The reaction of sodium borohydride with aldehydes and ketones is conceptually similar to that of LiAlH$_4$. The sodium ion is a much weaker Lewis acid than the lithium ion. For this reason, NaBH$_4$ reductions are carried out in protic solvents such as alcohols. Hydrogen bonding between the alcohol solvent and the carbonyl group serves as a weak acid catalysis that activates the carbonyl group. Unlike LiAlH$_4$, NaBH$_4$ reacts only slowly with alcohols and can even be used in water if the solution is not acidic.

![Diagram](19.26c)

$$\text{H} - \text{C} - \text{O} - \text{R} \quad \overset{\text{AlH}_3}{\longrightarrow} \quad 4 \text{H} - \text{C} - \text{O} - \text{H} + \text{H}_2\text{O} + \text{Li}^+, \text{Al}^{3+} \text{salts}$$

(19.26c)

As Eq. 19.23 shows, all four hydride equivalents of NaBH$_4$ are active in the reduction.
Because LiAlH$_4$ and NaBH$_4$ are hydride donors, reductions by these and related reagents are generally referred to as hydride reductions. The important mechanistic point about these reactions is that they are further examples of nucleophilic addition. Hydride ion from LiAlH$_4$ or NaBH$_4$ is the nucleophile, and the proton is delivered from acid added in a separate step (in the case of LiAlH$_4$ reductions) or solvent (in the case of NaBH$_4$ reductions).

Unlike the additions discussed in Sec. 19.7, hydride reductions are not reversible. Reversal of carbonyl addition would require the original nucleophilic group, in this case, H$_3$_, to be expelled as a leaving group. As in $S_N1$ or $S_N2$ reactions, the best leaving groups are the weakest bases. Hydride ion is such a strong base that it is not easily expelled as a leaving group. Hence, hydride reductions of all aldehydes and ketones are irreversible—they go to completion.

Both LiAlH$_4$ and NaBH$_4$ are highly useful in the reduction of aldehydes and ketones. Lithium aluminum hydride is, however, a much more reactive agent than sodium borohydride. A significant number of functional groups react with LiAlH$_4$ but not with NaBH$_4$; among such groups are alkyl halides, alkyl tosylates, and nitro groups. Sodium borohydride can be used as a reducing agent in the presence of these groups.

Sodium borohydride is also a much less hazardous reagent than lithium aluminum hydride. The greater selectivity and safety of NaBH$_4$ make it the preferred reagent in many applications, but either reagent can be used for the reduction of simple aldehydes and ketones. Both are very important in organic chemistry.

**Discovery of NaBH$_4$ Reductions**

The discovery of NaBH$_4$ reductions illustrates that interesting research findings are sometimes serendipitous (obtained by accident). In the early 1940s, the U.S. Army Signal Corps became interested in methods for generating hydrogen gas in the field. NaBH$_4$ was proposed as a relatively safe, portable source of hydrogen: addition of acidified water to NaBH$_4$ results in the evolution of hydrogen gas at a safe, moderate rate. To supply the required quantities of NaBH$_4$, a large-scale synthesis was necessary. The following reaction appeared to be suitable for this purpose.

$$4\text{NaH} + 3\text{B(OCH}_3)_3 \rightarrow \text{NaBH}_4 + 3\text{NaOCH}_3 \quad (19.30)$$
The problem with this process was that the sodium borohydride had to be separated from the sodium methoxide by-product. Several solvents were tried in the hope that a significant difference in solubilities could be found. In the course of this investigation, acetone was tried as a recrystallization solvent, and it was found to react with the NaBH₄ to yield isopropyl alcohol. Thus was born the use of NaBH₄ as a reducing agent for carbonyl compounds.

These investigations, carried out by Herbert C. Brown (1912–2004) at Purdue University, were part of what was to become a major research program in the boron hydrides, shortly thereafter leading to the discovery of hydroboration (Sec. 5.4B). Brown even described his interest in the field of boron chemistry as something of an accident, because it sprung from his reading a book about boron and silicon hydrides that was given to him by his girlfriend (who later became his wife) as a graduation present. Mrs. Brown observed that the choice of this particular book was dictated by the fact that it was among the least expensive chemical titles in the bookstore; in the depression era, students had to be careful how they spent their money! For his work in organic chemistry, Brown shared the Nobel Prize in Chemistry in 1979 with Georg Wittig (Sec. 19.13).

Aldehydes and ketones can also be reduced to alcohols by catalytic hydrogenation. This reaction is analogous to the catalytic hydrogenation of alkenes (Sec. 4.9A).

\[
\text{cycloheptanone} + \text{H}_2 \xrightarrow{\text{Ni catalyst}\ 102\ \text{atm}\ 120\ ^\circ\text{C}} \text{cycloheptanol} \quad (19.31)
\]

Catalytic hydrogenation is less important for the reduction of carbonyl groups than it once was because of the modern use of hydride reagents.

It is usually possible to use catalytic hydrogenation for the selective reduction of an alkene double bond in the presence of a carbonyl group. Palladium catalysts are particularly effective for this purpose.

PROBLEMS

19.20 From what aldehyde or ketone could each of the following be synthesized by reduction with either LiAlH₄ or NaBH₄?

(a) \[\text{CH}_2\text{OH}\]

(b) \[\text{OH} \quad \text{CH}_3\text{CHCH}_2\text{CH}_3\]

(c) \[\text{OH} \quad \text{OH} \quad \text{OH}\]
19.21 Which of the following alcohols could not be synthesized by a hydride reduction of an aldehyde or ketone? Explain.

\[ \text{H}_3\text{C} \quad \text{OH} \]

A

\[ \text{H}_3\text{C} \quad \text{CH}_3 \text{OH} \]

B

\[ \text{H}_3\text{C} \quad \text{CH}_3 \text{CH}_3 \text{OH} \]

C

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19.9 REACTIONS OF ALDEHYDES AND KETONES WITH GRIGNARD AND RELATED REAGENTS

Grignard reagents were introduced in Sec. 8.8. The reaction of Grignard reagents with carbonyl groups is the most important application of the Grignard reagent in organic chemistry. Addition of Grignard reagents to aldehydes and ketones in an ether solvent, followed by protonolysis, gives alcohols.

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{CHCH}_3 + \text{BrMgCH}_2\text{CH}_3 & \rightarrow \text{ether} \rightarrow \text{H}_2\text{O}^+ \rightarrow \text{(CH}_3\text{)}_2\text{CHCH}_2\text{CH}_3 \\
\text{2-methylpropanal} & \quad \text{ethylmagnesium bromide} & \quad \text{2-methyl-3-pentanol} \\
\text{H}_3\text{C} = \text{C} - \text{CH}_3 + \text{CH}_3\text{CH}_2\text{CH}_2\text{MgBr} & \rightarrow \text{ether} \rightarrow \text{H}_2\text{O}^+ \rightarrow \text{H}_3\text{C} = \text{C} - \text{CH}_3 \\
\text{acetone} & \quad \text{propylmagnesium bromide} & \quad \text{2-methyl-2-pentanol}
\end{align*}
\]

(19.33)

(68% yield)

(19.34)

(68% yield)

The reaction of Grignard reagents with aldehydes and ketones is another example of carbonyl addition. In this reaction, the magnesium of the Grignard reagent, a Lewis acid, bonds to the carbonyl oxygen. This bonding, much like protonation in acid-catalyzed hydration, makes the carbonyl carbon more electrophilic (that is, makes it more reactive toward nucleophiles) by making the carbonyl oxygen a better acceptor of electrons. The carbon group of the Grignard reagent reacts as a nucleophile at the carbonyl carbon. Recall that this group is a strong base that behaves much like a carbanion (Secs. 8.8B and 11.4C).

\[
\begin{align*}
\text{BrMg}^+ :\ddot{\text{O}}: - \text{MgBr} & \rightarrow \text{R} - \text{C} = \text{R} - \delta^+ \\
\text{R} \quad \text{R} & \quad \text{R} \quad \text{R}
\end{align*}
\]

(19.35a)

a bromomagnesium alkoxide

The product of this addition, a bromomagnesium alkoxide, is essentially the magnesium salt of an alcohol. Addition of dilute acid to the reaction mixture gives an alcohol.

\[
\begin{align*}
\text{BrMg}^+ :\ddot{\text{O}}: - \text{H}_2\text{O}^+ & \rightarrow \text{R} - \text{C} = \text{R}' + \text{H}_2\ddot{\text{O}}^- + \text{Br}^- + \text{Mg}^{2+} \\
\text{R} \quad \text{R} & \quad \text{R} \quad \text{R}
\end{align*}
\]

(19.35b)