EXPERIMENT #5: SODIUM BOROHYDRIDE REDUCTION OF VANILLIN

EXPERIMENTS IN ORGANIC CHEMISTRY
From Microscale to Macroscale

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SECTION 24

Hydride Reductions

Overview

If you carried out the catalytic hydrogenation in Experiment 16.1, you have already used sodium borohydride (NaBH₄) as a source of hydride ions. In that experiment the hydride served two purposes: to reduce Pt⁴⁺ to Pt⁰ in the reaction

\[
\text{Pt}^{4+} + 4\text{H}^- \rightarrow \text{Pt}^{0} + 2\text{H}_2(g)
\]

and to generate hydrogen gas in the presence of acid, according to the equation

\[
\text{H}^+ + \text{H}^- \rightarrow \text{H}_2(g)
\]

Hydride ion also functions as a good nucleophile because of its negative charge. It can attack a positive center such as the carbon of a carbonyl group or a carbon with a halogen or other good leaving group on it:

\[
\begin{align*}
\text{O}^– \quad \text{R} – \text{C} – \text{R}’ + \text{H}^- & \rightarrow \text{R} – \text{C} – \text{R}’^- \\
\text{O}^– & \\
\text{R} – \text{C} – \text{R}’ + \text{H}^- & \rightarrow \text{R} – \text{CH}_3 + \text{X}^- \\
\text{H}^- & \\
\end{align*}
\]

In the first example, where hydride ion attacks a carbonyl group, if the final product is acidified (in other words, H⁺ is added), the alkoxide anion is protonated to give an alcohol:

\[
\begin{align*}
\text{O}^– & \\
\text{R} – \text{C} – \text{R}’ + \text{H}^- & \rightarrow \text{R} – \text{C} – \text{R}’^- & \text{(1 NaBH₄)} \\
\text{O}^– & \\
\text{R} – \text{C} – \text{R}’ + \text{H}^- & \rightarrow \text{R} – \text{C} – \text{R}’^- & \text{(2 H⁺)} \\
\text{OH} & \\
\end{align*}
\]

This reaction works equally well on aldehydes:

\[
\begin{align*}
\text{O}^– & \\
\text{R} – \text{C} – \text{H} + \text{H}^- + \text{NaBH₄} & \rightarrow \text{R} – \text{CH}_2\text{OH} & \text{(1 H⁺)} \\
\text{O}^– & \\
\end{align*}
\]

The acid must, of course, be added in a second step after the hydride addition because if a hydride and acid are mixed, they react with each other to form hydrogen gas.

\[
\text{H}^- + \text{H}^+ \rightarrow \text{H}_2
\]

This reaction would destroy any hydride present, making it attack on the carbonyl impossible.

There are many hydride reagents available today. The development of various selective hydride reagents by Herbert C. Brown and others since the late 1940s represents a fascinating saga in the history of organic chemistry. You will use sodium borohydride because it is an inexpensive and effective reagent for converting ketones and aldehydes to alcohols.

Lithium aluminium hydride (LiAlH₄, sometimes abbreviated LAH) is a stronger reducing agent than NaBH₄. In addition to the foregoing reactions, LiAlH₄ can, for example, reduce esters to alcohols in a two-step attack:

\[
\begin{align*}
\text{O}^– & \\
\text{R} – \text{C} – \text{O} – \text{R’} + \text{H}^- + \text{LiAlH}_4 & \rightarrow \text{R} – \text{C} – \text{O} – \text{R’}^- & \text{ion from LiAlH}_4 \\
\text{O}^– & \\
\text{R} – \text{C} – \text{H} + \text{H}^- & \rightarrow \text{R} – \text{CH}_3 & \text{(acidity from attack)} \\
\text{O}^– & \\
\text{R} – \text{C} – \text{H} + \text{H}^- & \rightarrow \text{R} – \text{C} – \text{H}^- & \text{(second attack)} \\
\text{O}^– & \\
\end{align*}
\]

Actually, two alcohols are produced from an ester, since the alkoxide eliminated after the first hydride attack (R'O⁻) will be protonated during the second acidification step to give R'O⁻.

There are many hydride reagents that have been “fine-tuned” to a certain strength so that they can carry out a particular reduction without reducing other functional groups present. These reagents are very useful for syntheses of complex molecules containing numerous functional groups.

Many of these reagents have organic groups on them, such as lithium aluminium tri-tert-butoxyhydride [LiAlH₄(Ot-Bu)₃]. Compared with plain LiAlH₄, adding an electron-rich group such as an alkoxide group on the aluminium decreases the positive charge on the Al and therefore decreases the strength of the hydride ion. As the difference in electronegativity between the Al and H is decreased, the negative character of the H⁻ is decreased.
EXPERIMENT #5: SODIUM BOROHYDRIDE REDUCTION OF VANILLIN

Hydride Reductions

So this particular reagent, LiAlH₄(Or-Bu)₃, with three oxygens on the aluminum, is a fairly weak hydride source and will only reduce the most easily reduced groups.

A few common hydride reagents and the groups they can reduce appear in Table 24-1. This table shows that LiAlH₄, a strong reducing agent, will reduce many functional groups, whereas the much weaker NaBH₄ will only react with a few.

TABLE 24-1  SOME COMMON HYDRIE REDUCING AGENTS

<table>
<thead>
<tr>
<th></th>
<th>NaBH₄</th>
<th>LiAlH₄(Or-Bu)₃</th>
<th>LiBH₄</th>
<th>BH₃</th>
<th>AlH₃</th>
<th>LiAlH₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easiest to reduce</td>
<td>Aldehyde</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Ketone</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Acid chloride</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Ester</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Carboxylic acid</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Nitrile</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td></td>
<td>Nitro</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Hardest to reduce</td>
<td>Alkene</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

*× indicates complete reduction in 1 hour.

The products of hydride reductions of acid chlorides, esters, carboxylic acids, nitriles, nitro groups, and alkynes are shown in the following reactions:

\[
\begin{align*}
\text{O} & \xrightarrow{RC\text{Cl}} \text{RCH}_2\text{OH} + \text{Cl}^- \\
\text{O} & \xrightarrow{RC\text{OR'}} \text{RCH}_2\text{OH} + \text{R'OH} \\
\text{O} & \xrightarrow{RC\text{OH}} \text{RCH}_2\text{OH} \\
\text{R} - \text{C} &= \text{N} & \text{R} - \text{CH}_2\text{NH}_2 \\
\text{R} - \text{NO}_2 & \rightarrow \text{R} - \text{NH}_2 \\
\text{R} - \text{CH} &= \text{CH} - \text{R} & \text{R} - \text{CH}_2\text{CH}_2 - \text{R}
\end{align*}
\]

Note that many of these reactions involve attack of two equivalents of hydride on a somewhat positive center such as a carbonyl, nitrile carbon, or the nitrogen of a nitro group.

The reaction in Experiment 24.1 is reduction of a ketone, cyclohexanone.

Overall reaction:

\[
\begin{align*}
\text{O} & \xrightarrow{(1) \text{NaBH}_4} \text{OH} \\
\text{O} & \xrightarrow{(2) \text{H}^+} \text{H}_2\text{O}
\end{align*}
\]

The mechanism is very simple: attack of the hydride ion on the carbonyl carbon to form the alkoxyde followed by protonation to form the alcohol.

Cyclohexanone

MW 98, bp 155°C

dens. 0.95 g/mL

Alkoxide intermediate

Cyclohexanol

MW 106, bp 161°C

dens. 0.96 g/mL

In Experiment 24.2 an aldehyde is reduced to a primary alcohol.

Vanillin

MW 162, mp 81–82°C

(m, 4-hydroxy-3-methoxybenzene)

Vanillyl alcohol

4-tert-Butylocyclohexanol

MW 154, mp 115°C

Experiment 24.3 illustrates the stereochemical requirements of NaBH₄ by looking at the ratios of the cis and trans products formed in the reaction with 4-tert-butylocyclohexanone. This molecule is “locked” in a chair conformation, and equatorial attack is less hindered than axial attack.

4-tert-Butylocyclohexanol

MW 154, mp 47–50°C

Trans and/or cis

4-tert-Butylocyclohexanol

MW 156

By examining the ratios of products formed we can see how selective NaBH₄ is.

Biochemically, hydride ion is often stored as NADH (nicotinamide adenine dinucleotide hydride) or NADPH (a phosphorylated version):
EXPERIMENT #5: SODIUM BOROHYDRITE REDUCTION OF VANILLIN

When butanoic acid is treated with sodium borohydride, 1-butanol is not obtained. There are, however, definite signs of reaction (bubbling, heat). What might the reaction be?

QUESTIONS

1. What is a hydride ion in terms of protons, neutrons, and electrons? Is it electrophilic or nucleophilic, and why?
2. Considering the electronegativities of boron and hydrogen, why is the hydrogen in NaBH₄ considered a hydride?

3. Besides reductions of ketones, give specific examples of two other types of reactions that can be conducted using hydride ions.
4. Supply the missing product or reagents for each of the following reactions.

(a) [Diagram]
(b) [Diagram]
(c) [Diagram]
(d) [Diagram]
(e) [Diagram]

5. What reagent could you use to reduce an ester in the presence of a nitrile group, for example in the transformation?

6. How is NaBH₄ made?

REFERENCE


7. When butanoic acid is treated with sodium borohydride, 1-butanol is not obtained. There are, however, definite signs of reaction (bubbling, heat). What might the reaction be?
EXPERIMENT 24.2 REDUCTION OF VANILLIN USING NaBH₄

Estimated Time: 2.0 hours

Prelab

1. Calculate the millimoles in 0.13 g of NaBH₄ and the theoretical yield of vanillyl alcohol.

Special Hazards

NaBH₄ is flammable and corrosive. Avoid contact of the irritating NaBH₄ powder with skin or eyes and flush with a lot of water if contact occurs.

Procedure

In a 50-mL beaker, dissolve vanillin (8.0 mmol, 1.8 g) in 1 M aqueous NaOH (7 mL). Add NaBH₄ (0.13 g, ______ mmol) and swirl the flask occasionally for the next 20–30 minutes. Cook the solution in an ice bath, and add 7 mL of 5% aqueous HCl to reprotonate the phenol group and drive the product out of solution. If necessary, scratch with a stirring rod to induce precipitation. Collect the product by suction filtration, wash with water, and air dry. Recrystallize the vanillyl alcohol from ethyl acetate, using a ratio of 5 mL per gram.

TLC analysis. (If necessary, reread Section 4 for general procedures involving TLC.) Obtain three TLC slides (Caution: handle only by the edges!) and on each mark three dots lightly in pencil about 1 cm from the end, as shown in Figure 46-2. Be sure not to disturb the surfaces of the slides. In pencil label the central spot on each slide M (for mixture) and the outer spots with the sample times, as shown. On the middle dot (M) of each slide spot the authentic vanillin–vanillyl alcohol mixture your instructor has prepared. Be sure to keep the spots small and sharp, using either a filled-flute metal syringe needle or a fine glass capillary drawn out in a flame for spotting. It is best to touch the tip of the spotter two or three times to the spot to ensure adequate sample without having a spot that is too large in diameter.

Develop the slides in 1:1 ethyl acetate–toluene in a covered jar. Allow the solvent to rise about two-thirds to three-fourths of the way up the slides before removing them and marking the solvent fronts quickly (before the solvent evaporates) in pencil. After the slides have dried for a couple of minutes, observe them under a UV light and mark any spots visible. (Caution: Never look directly at a UV light or shine it on your skin.) Next, place the slides in an iodine chamber for a few minutes, and mark the spots observed. Tape the slides directly into your lab book or make an accurate sketch of them.