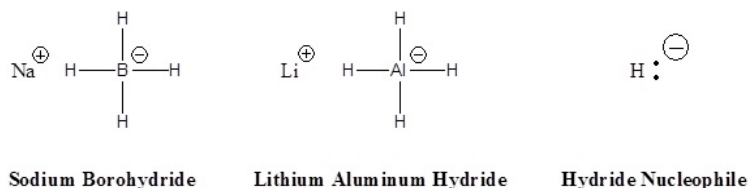


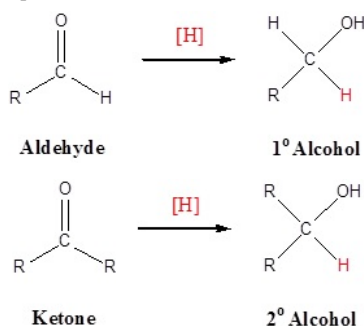
## 13.7: REDUCTION OF THE CARBONYL GROUP - SYNTHESIS OF 1° AND 2° ALCOHOLS

### REDUCTION OF ALDEHYDES AND KETONES

The most common sources of the hydride nucleophile are lithium aluminum hydride ( $\text{LiAlH}_4$ ) and sodium borohydride ( $\text{NaBH}_4$ ). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in  $\text{LiAlH}_4$  is more polar, thereby, making  $\text{LiAlH}_4$  a stronger reducing agent.



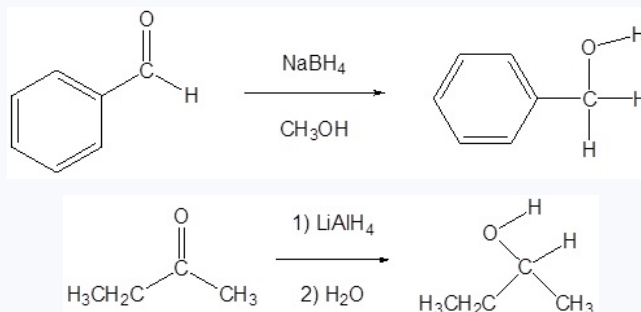
Addition of a hydride anion ( $\text{H}^-$ ) to an aldehyde or ketone gives an alkoxide anion, which upon protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols.



In metal hydrides reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note!  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  are both capable of reducing aldehydes and ketones to the corresponding alcohol.

Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. A carbonyl (aldehyde or ketone) plus two electrons and two protons becomes an alcohol.

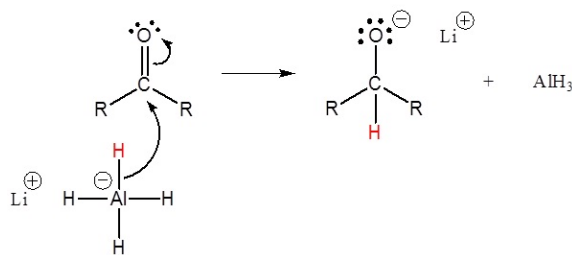
#### Example 1



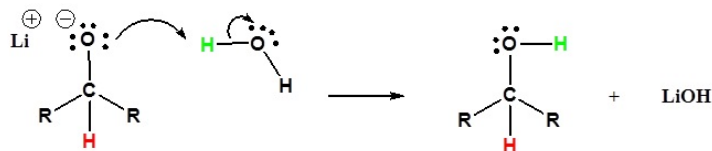
### MECHANISM

This mechanism is for a  $\text{LiAlH}_4$  reduction. The mechanism for a  $\text{NaBH}_4$  reduction is the same except methanol is the proton source used in the second step.

- 1) Nucleophilic hydride anion reacts with the electrophilic carbonyl carbon forcing the pi electrons onto the electronegative oxygen atom.

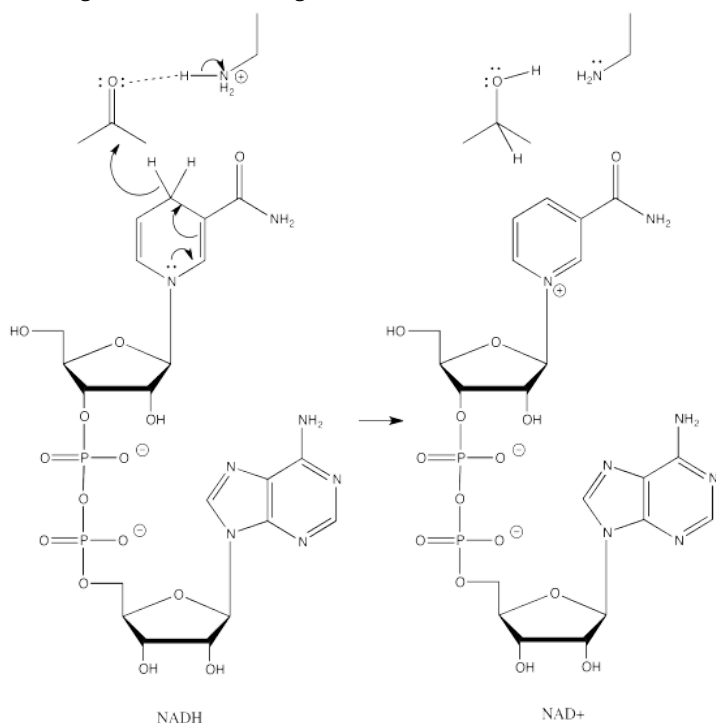


2) The alkoxide is protonated.



## BIOLOGICAL REDUCTION

Addition to a carbonyl by a **semi-anionic** hydride, such as  $\text{NaBH}_4$ , results in conversion of the carbonyl compound to an alcohol. The hydride from the  $\text{BH}_4^-$  anion acts as a nucleophile, adding  $\text{H}^-$  to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.

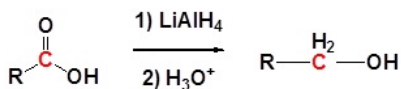


Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

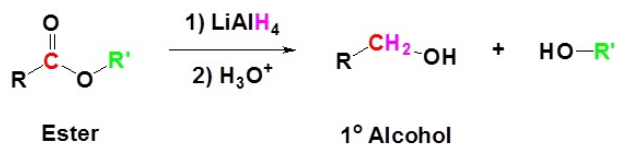
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation,  $\text{NAD}^+$ . However,  $\text{NAD}^+$  is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

## REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids can be converted to  $1^\circ$  alcohols using Lithium aluminum hydride ( $\text{LiAlH}_4$ ). Note that  $\text{NaBH}_4$  is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



Esters can be converted to 1° alcohols using  $\text{LiAlH}_4$ , while sodium borohydride ( $\text{NaBH}_4$ ) is not a strong enough reducing agent to perform this reaction.



## REDUCTION REACTION SUMMARY

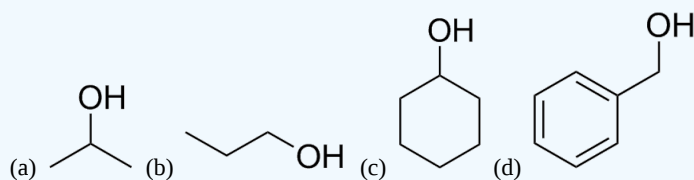
The table below summarizes the reduction reactions covered so far in our text. It is important to distinguish between functional group reactivity as we add more multiple-step synthetic pathways.

Reactant	Reduction Product with Specified Reagents		
	$\text{H}_2$ with Pt, Pd or Ni	1) $\text{NaBH}_4$ 2) $\text{H}_3\text{O}^+$	1) $\text{LiAlH}_4$ 2) $\text{H}_3\text{O}^+$
$\text{R}-\overset{\text{O}}{\text{C}}-\text{Cl}$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$
$\text{R}-\overset{\text{O}}{\text{C}}-\text{H}$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$
$\text{R}-\overset{\text{O}}{\text{C}}-\text{R}'$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$	$\text{RCH}_2-\text{OH}$
$\text{R}-\overset{\text{O}}{\text{C}}-\text{OR}'$	no rxn	no rxn	$\text{RCH}_2-\text{OH}$
$\text{C}=\text{C}$	no rxn	no rxn	$\begin{array}{c}   \quad   \\ \text{---C---C---} \\   \quad   \\ \text{H} \quad \text{H} \end{array}$

### Exercise

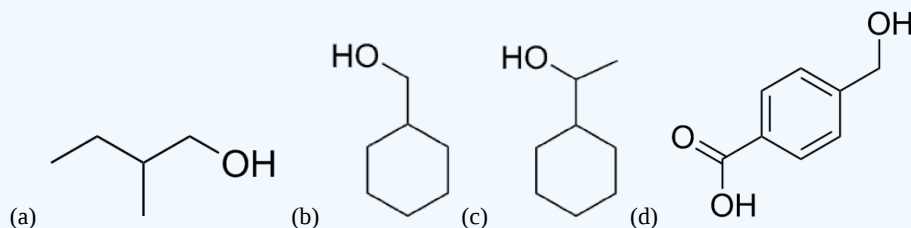
11.

Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.



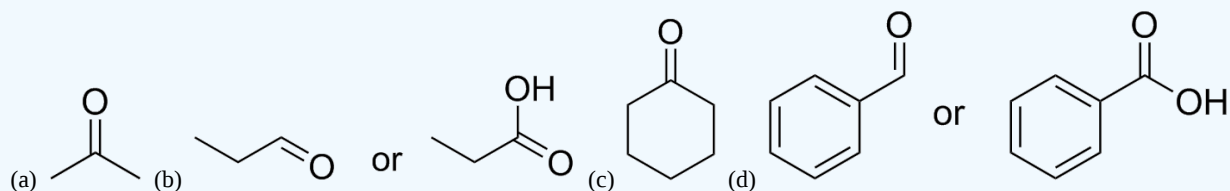
12.

Given the following alcohol, draw the structure from which it could be derived using only  $\text{NaBH}_4$



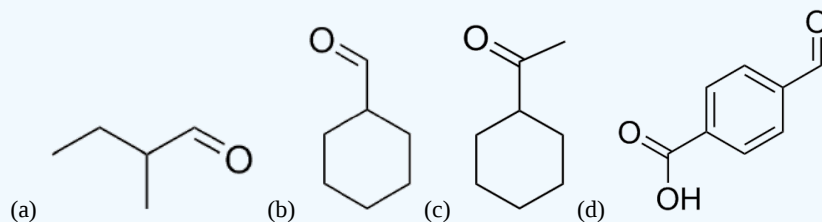
## Answer

11.



12.

Note,  $\text{NaBH}_4$  is only a strong enough reducing agent to reduce ketones and aldehydes.



## CONTRIBUTORS AND ATTRIBUTIONS

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- Prof. Steven Farmer ([Sonoma State University](#))
- Chris P Schaller, Ph.D., ([College of Saint Benedict / Saint John's University](#))

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