Chapter 14 Aldehydes and Ketones: Addition Reactions at Electrophilic Carbons

Overview of Chapter 14
1. Structures of aldehydes and ketones

<table>
<thead>
<tr>
<th>( \text{electrophilic C} )</th>
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</thead>
<tbody>
<tr>
<td>( \text{R, R'} = \text{alkyl, aryl: ketones} )</td>
</tr>
<tr>
<td>( \text{R} = \text{alkyl, aryl; R'} = \text{H: aldehydes} )</td>
</tr>
<tr>
<td>lone pair: more basic than C=O ( \pi )</td>
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Aldehyde C=O carbons are less sterically hindered and more electrophilic compared with the corresponding ketone carbons (i.e., with the same \( R \)).

2. Reactions of aldehydes and ketones with an electrophile and a nucleophile

\( \sigma \)-framework
all of these sigma-bonds and lone pairs on the same plane

\( \pi \)-bonding

Two lone pairs: Highest occupied molecular orbitals (HOMOs) of the C=O group

Lowest unoccupied molecular orbital (LUMO)

between sp\(^2\) and sp\(^3\); on its way to sp\(^3\)

3. Activation of RR'\( \text{C}=\text{Z} \) (\( Z = \text{O and N} \)) with H-A or a Lewis acid

\[ \text{activates C}=\text{O toward a nucleophilic addition} \]

becomes even more \( \delta^+ \); i.e., more electrophilic

or

(if M\(^+\) is used)
Chapter 14: Overview (continued)

4. Four categories of nucleophilic addition reactions

Two classes of nucleophiles: reversible and irreversible

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I. Nucleophilic Addition Reactions of RR’C=Z (Z: electronegative atom)

I-1. Irreversible nucleophiles [\(H^-\) - Type 1; \(R^-\) - Type 2]

1. Sodium borohydride (NaBH₄)
   - mild reducing agent
   - relatively stable reagent (against moisture, air)
   
   \[
   \text{Na}^+ \quad \overset{\text{B-H}}{\text{H}} \quad \text{H}
   \]

2. Lithium aluminum hydride (LiAlH₄)
   - more polarized, more \(\sigma\) on the \(H\) → a stronger \(H^-\) donor
   - Also, the larger size difference between Al-H than B-H makes dissociation of Al-H much easier.

   \[
   \begin{array}{c}
   \text{Li}^+ \quad \overset{\text{H}}{\text{Al}} \quad \overset{\text{H}}{\text{H}} \\
   \end{array}
   \]

In addition, the difference in the coordination power of Na⁺ and Li⁺ (stronger) on the C=O oxygen further contributes to make the reactivity of LiAlH₄ stronger. **Reduction with LiAlH₄ requires an aqueous (usually acidic) workup.**

3. Sodium cyanoborohydride [Na(CN)BH₃] (much weaker hydride reagent; often used to selectively reduce imines under acidic conditions, e.g., in acetic acid)

4. Diisobutylaluminum hydride (DIBAL or DIBAL-H) - powerful red. agent
   --reaction needs to be carried out in anhydrous conditions (e.g., anhyd THF or ether).
I-1 (1) Hydride reducing agents (cont’d)

Reduction with LiAlH₄:

\[
\text{O}^* \xrightarrow{\text{LiAlH}_4 \text{ (anhyd. aprotic solvent e.g., THF)}} \text{O-Al-H}^{\oplus} \xrightarrow{\text{H}_2\text{O}^\ominus \text{ hydrolysis}}} \text{OH} + \text{LiOH} + \text{Al(OH)}_3
\]

All of these three Hs could be used in the reduction of a ketone.

Note: O-Al bond stronger than O-Li

*This acid-hydrolysis step may be quite complex, depending upon the stoichiometry between a ketone and LiAlH₄. However, all of those hydrolysis step should involve

Reduction with NaBH₄:

\[
\text{O}^* \xrightarrow{\text{NaBH}_4 \text{ (usually in a protic solvent e.g., ethanol)}} \text{OH}
\]

\[
\text{O}^* \xrightarrow{\text{Na}^+ \text{ OR}} \text{OR} \xrightarrow{\text{BH}_3} \text{ reacts with the solvent 3 x RO-H to form B(OR)}_3 \text{ and 3 x H}_2
\]

Reduction with DIBAL (Al in DIBAL quite Lewis acidic):

\[
\text{O}^* \xrightarrow{\text{DIBAL (anhyd. aprotic solvent e.g., THF)}} \text{O-Al-H}^{\oplus} \xrightarrow{\text{H}_2\text{O}^\ominus \text{ hydrolysis}}} \text{OH} + \text{Al(OH)}_3 + 2 (\text{H}_2\text{C})_3\text{CH}
\]
I-1. Irreversible nucleophiles (cont’d)

(b) $R^\ominus$ nucleophiles: Type 2

Could be $sp^3$, $sp^2$, $sp$ carbanions
Grignard reagents ($R\text{-MgX}$)
alkyllithium ($R$-$Li$) or sodium ($R$-$Na$)
alkenyl lithium ($C$-$CHLi$)
aldehyl lithuum/sodium or lithium/sodium acetylide ($C\equiv C$-$Li$; $C\equiv C$-$Na$)

Grignard reagents: $R$-$MgX$ ($X$ is usually $Br$ or $I$, sometimes $X=Cl$)

Preparation of Grignard reagents:
(i) Alkyl Grignard reagents from $R$-$X$

Preparation of Grignard reagents: $R$-$MgX$

Formally equivalent to:

Preparation of Grignard reagents:
(ii) Alkynyl Grignard reagents:

Preparation of Grignard reagents:
(iii) Alkenyl and aryl grignard reagents from their halide precursors

Cyanide carbanion - often reversible nucleophile
Chapter 14  I-1. Irreversible nucleophiles

(b) R⊙M⊙ (Type 2; organometallic reagents) (cont’d)

Note: Reactions with epoxides

\[ \text{H} \xrightarrow{\text{PhMgBr}} \text{H} \]

\[ \text{H} \xrightarrow{\text{PhMgBr}} \text{H} \]

*NH₄Cl: weakly acidic; pKa ~9.7; commonly used for the work-up of organometallic reactions; the only exception is the work-up of a carboxylate product (you need to acidity the solution to pH~1-2).

I-2. Reversible nucleophiles

**Type 3:** Divalent nucleophiles (ROH & RSH); requires an acid catalyst

**Type 4:** Trivalent nucleophiles (R-NH₂ & RR'NH); w/o activation by an acid

(a) ROH (alcohols)

```
ketone | ROH, H⁺ or L.A. \rightarrow \text{hemi-ketal} \rightarrow ROH, H⁺ or L.A. \rightarrow \text{ketal}
        | ROH, H⁺ or L.A. \rightarrow \text{hemi-acetal} \rightarrow ROH, H⁺ or L.A. \rightarrow \text{acetal}
```

(b) RSH (thiols or mercaptans)

```
ketone | RSH, H⁺ or L.A. \rightarrow \text{hemithioketal} \rightarrow RSH, H⁺ or L.A. \rightarrow \text{thioketal}
        | RSH, H⁺ or L.A. \rightarrow \text{hemithioacetal} \rightarrow RSH, H⁺ or L.A. \rightarrow \text{thioacetal}
```
Chapter 14: I-2. Reversible nucleophiles (cont’d)

(c) Mechanism (similar for both ROH and RSH nucleophile additions)

Since ROH and RSH are not nucleophilic enough to add to a C=O, the C=O has to be activated by the use of H+ or a Lewis acid. Incidentally, their conjugate bases, RO⁻/RS⁻ can add (quite easily as being highly nucleophilic) to the C=O, but the adducts are less stable than the original C=O, thus reverse back to the C=O and RO⁻/RS⁻.

Mechanism using H-B for the acid catalyst, p-TsOH:

\[ \text{BF}_3\cdot \text{O(CH}_2\text{CH}_3)_2^{**} \]

(catalytic)
Chapter 14: I-2. Reversible nucleophiles: Mechanism (cont’d)

Comments:
1. The ketalization and acetalization reactions from ketone and aldehyde, respectively, under acid-catalyzed conditions are reversible. High yields of ketals and acetals can be achieved by the use of excess alcohols and/or continuous removal of the resulting water (using, e.g., a Dean-Stark apparatus).
2. Conversely, if a ketone or aldehyde is desired from its corresponding ketal or acetal, a large excess of water needs to be added to the solution of ketal or acetal in the presence of an acid catalyst.
3. Throughout the mechanism for the acid-catalyzed ketalization and acetalization, DO NOT involve negatively-charged intermediates. The only negatively charged species allowed is the conjugate base (\(\text{BH}^-\)) of a strong acid catalyst.

Lastly, 

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{O} \\
\text{O} \quad \text{H}
\end{array} \quad \begin{array}{c}
\text{H}_3\text{COCH}_3
\end{array}
\]

\text{Does not involve an } S_N^2 \text{ step!}

Representative reactions:
(1) cyclic acetal formation

\[
\text{CH}_3\text{CHO} + \text{H}_2\text{O} \xrightarrow{p-\text{TsOH} \ (\text{catalytic})} \text{CH}_3\text{OCH}_3 + \text{H}_2\text{O}
\]

(2) cyclic thioacetal formation

\[
\text{CH}_3\text{CHO} + \text{H}_2\text{O} \xrightarrow{p-\text{TsOH} \ (\text{catalytic})} \text{CH}_3\text{SCH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

(3) cyclic ketal formation from diols: acetonide formation

\[
\text{CH}_3\text{CHO} + \text{H}_2\text{O} \xrightarrow{p-\text{TsOH} \ (\text{catalytic})} \text{CH}_3\text{OCH}_3 + \text{H}_2\text{O}
\]

called (5-membered) acetonide (i.e., acetonel adduct)
Chapter 14: I-2 reversible nucleophiles-ROH/RSH Representative reactions (cont’d)

(4) Transketalization reaction: Spiroketal formation

![Chemical structure](image)

Mechanism for the spiroketalization step:

![Mechanism diagram](image)

(5) Hydrolysis of ketals and acetals - Acid-catalyzed ketal-acetal formation reactions from, respectively, ketones and aldehydes are reversible. Therefore, treatment of ketals or acetals with an acid and excess water should produce their corresponding carbonyl compounds. This process is called “hydrolysis.” Mechanism of the reaction is exactly the same as the formation of ketals and acetals except going to the opposite direction.

![Hydrolysis reaction](image)

Mechanism for the hydrolysis shown on the next page.
Chapter 14: I-2 reversible nucleophiles-ROH/RSH Representative reactions (cont’d)

(5) Hydrolysis of ketals and acetals:

Mechanism:

\[
\begin{align*}
\text{ROH/RSH} & \rightarrow \text{ROH/RSH}^{-} + \text{H}^+ \\
\text{H-B} & \rightarrow \text{H-B}^+ \\
\text{lone pair-assisted ionization!} & \\
\text{SN1!} & \\
\text{SN2!} & \\ \\
\text{Not an SN2!!} & \\
\end{align*}
\]

The “take-home message:”

Lone pair-assisted ionization!
Chapter 14  I-2. Reversible nucleophiles (cont’d)

Type 4 nucleophiles: Trivalent nucleophiles

Amines are sufficiently nucleophilic enough to add to ketone and aldehyde C=O carbons without activation of the C=O oxygen atom by an acid. However, the last dehydration step from the aminol intermediates requires an activation of the hydroxyl oxygen atom (by H+ or L.A.).

(1) Imine formation [from a ketone/aldehyde and a 1°-amine]

\[
\text{aldehyde} + \text{H}_2\text{N}-\text{CH}_3 \xrightarrow{\Delta \text{ or } H^+} \text{imine} + \text{H}_2\text{O}
\]

Mechanism:

Those RR’C=N-Z formation reactions from RR’C=Os have the optimum rate at around pH = 4.7. If the conditions are too acidic, the formation of such derivatives becomes slow, presumably due to the exclusive protonation of an amine, thus depriving the nucleophilicity of an amine. Although the protonation is required for the dehydration from the aminol intermediate, the formation of these RR’C=N-Z compounds can be achieved even without adding an acid catalyst, especially when the reaction involves an aldehyde (often heating is required to complete the reaction, though). Amazingly, the formation of hydrazones (RR’C=NNH\textsubscript{2}) can be achieved under basic conditions with strong heating.
Chapter 14  I-2. Reversible nucleophiles: Type 4 nucleophiles (trivalent nucleophiles) (cont’d)

(2) Oxime formation

$$\text{R} = \text{H}_2\text{N}-\text{OH} \quad \Delta \text{ or } \Delta, \text{H}^+ \rightarrow \text{R} = \text{N} = \text{OH} + \text{H}_2\text{O}$$

oxime

(3) Hydrazone formation

$$\text{R} = \text{H}_2\text{N} = \text{NH}_2 \quad \Delta \text{ or } \Delta, \text{H}^+ \rightarrow \text{R} = \text{N} = \text{NH}_2 + \text{H}_2\text{O}$$

hydrazone

Application: Wolff-Kishner reduction

Reduction of RR’C=O to RR’CH₂

An alternative method for the formation of a methylene group from a C=O:

Reduction of thioacetal/thioketal derivatives with Raney Ni.