**Nucleophilic Addition To Carbonyls**

Lewis basic site-reacts with electrophiles

![Lewis basic site](image1)

Electron-deficient carbon-reacts with nucleophiles

![Electron-deficient carbon](image2)

Overall reaction:

![Overall reaction](image3)

This can occur by either of three mechanisms:

1. **Simultaneous**
   
   ![Simultaneous mechanism](image4)

2. **Electrophilic attack**
   
   ![Electrophilic attack](image5)

3. **Nucleophilic attack**
   
   ![Nucleophilic attack](image6)

Which mechanism is operative will depend on electrophilicity of $E^+$, and nucleophilicity of Nuc:

**General rule:** when $E^+$ is $H^+$ or strong Lewis acid, Nuc is neutral

$\Rightarrow$ choose mechanism #2

- when $E^+$ = $Li^+$, $Na^+$, $K^+$; Nuc is anionic $\Rightarrow$ mechanism #1
- when $E^+$ = $R_4N^+$; Nuc is anionic $\Rightarrow$ mechanism #3
**Case study - hydration of carbonyls:**

\[ R\overset{\text{O}}{R'} + H_2O \rightleftharpoons HO\overset{\text{OH}}{R\overset{\text{OH}}{R'}} \]

normally \( K_{eq} \) (ketones < \( 10^{-5} \)) (aldehydes \( 10^{-3} \) to \( 10^{3} \))

Ex:

\[ \overset{\text{O}}{\text{CCl}_3}H + H_2O \rightleftharpoons \overset{\text{OH}}{\text{Cl}_3\overset{\text{H}}{C}}H \]

\( K_{eq} = 3 \times 10^4 \)

**Why do EWG’s favor hydrates?**

**Kinetics of hydration**

\[ R\overset{\text{H}}{\text{H}} \rightleftharpoons \overset{\text{HO}}{R\overset{\text{OH}}{\text{H}}} \] \( \overset{\text{(+H}_2\text{O)}}{(+\text{H}_2\text{O})} \) \( \overset{(-\text{H}_2\text{O})}{(-\text{H}_2\text{O})} \) \( k_1 \)

**How to measure \( k_1 \)? Look at carbonyls with \( K_{eq} \ll 1 \)**

look at oxygen isotope exchange rate:

\[ H_2O^* + \overset{\text{O}}{\text{R}_1\text{R}_2} \rightleftharpoons \overset{\text{HO}}{\text{H}_1\text{R}_2} \]

so, since \( k_1 \ll k_{-1} \),

\[ \frac{d}{dt} \left[ \overset{\text{O}}{\text{R}_1\text{R}_2} \right] \approx \frac{d}{dt} \left[ \overset{\text{HO}}{\text{R}_1\text{R}_2} \right] \]
look at effect of pH on rate:

What's going on here?
rate increases with increasing [H⁺], [OH⁻]

Implication: 2 different mechanisms, one in acid, one in base

acid catalysis- 2 choices

specific acid catalysis - protonation occurs before R.D.S.:

\[
\begin{align*}
H^+ + R_1R_2O & \quad \text{fast} \quad \rightarrow \quad R_1R_2OH + H_2O \\
R_1R_2OH + H_2O & \quad \text{slow} \quad \rightarrow \quad k_2 R_1R_2O + H^+
\end{align*}
\]

\[v = k_2[H_2O] \left[ R_1R_2 \right] \sim k_1[ R_1R_2 ]\]

alternative #2 - general acid catalysis

\[
\begin{align*}
R_1R_2O + H^-A & \quad \text{fast} \quad \rightarrow \quad R_1R_2OH + H_2O \\
R_1R_2OH + H_2O & \quad \text{slow} \quad \rightarrow \quad + H^+
\end{align*}
\]

Hydrogen bonded complex

\[v = k_3 [ R_1R_2 ] [HA] [H_2O] \sim k_2 [ R_1R_2 ] [HA] \]

in this case, proton transfer occurs in R.D.S.
in basic solution, we can change nucleophiles:

\[
\begin{align*}
\text{OH} & \quad \text{slow} \quad R_1 & \quad R_2 \quad \text{fast} \quad \text{OH} \\
\text{HO}^{-} & \quad + \quad \text{H}_2\text{O} & \quad \text{H} \quad + \quad \text{OH}^{-}
\end{align*}
\]

\[\nu = k_2[R_1 \quad R_2 \quad ][-\text{OH}]\]

base-catalyzed hydration (nucleophilic catalysis)
can also be viewed as:

\[
\begin{align*}
\text{OH} & \quad \text{Na}^+ \\
\text{HO}^{-} & \quad + \quad \text{H}_2\text{O} & \quad \text{H} \quad + \quad \text{Na}^+\text{OH}^{-}
\end{align*}
\]

these really represent examples of specific base & general base catalysis
so, which mechanisms are operative? It will depend on nature of acid, base, and/or carbonyl; all mechanisms have been observed in carbonyl hydration
see Jencks, JACS, 1978, 100, 5444
McClelland, JACS, 1983, 105, 2718

Case Study #2 - Cyanohydrin Formation

\[
\begin{align*}
\text{RCHO} & \quad + \quad \text{HCN} \\
\text{RCHO} & \quad \text{CN} \\
\end{align*}
\]

kinetics of this reaction were studied by Lapworth; he found that rate was not \( \propto [\text{HCN}] \), but rather:

\[\nu = k [\text{RCHO}] [\text{CN}^-]\] (Lapworth, JCS, 1903, 83, 998)

so, mechanism is:

\[
\begin{align*}
\text{CN}^- & \quad \text{slow} \quad \text{R}_1 & \quad \text{H} & \quad \text{fast} \quad \text{R}_1 & \quad \text{CN} \\
\text{NC}^- & \quad + \quad \text{H} \quad + \quad \text{HCN} & \quad \text{NC}^- & \quad \text{OH}
\end{align*}
\]
tertiary amines were also shown to catalyze reaction:

\[
\text{RCHO} + \text{HCN} + \text{R}_3\text{N} \rightleftharpoons \text{HO\,CN} + \text{R}_3\text{N}
\]

Does it just increase [CN\,]^\text{-}? No . . . look at kinetics:

\[
\nu = k_4 [\text{RCHO}] [\text{HCN}] [\text{R}_3\text{N}]^2 \leftarrow \text{bimolecular in amine}
\]

Why?

\[
\text{HCN} + \text{R}_3\text{N} \rightleftharpoons \text{R}_3\text{NH\,CN}
\]

this is an example of general acid catalysis


**Scope of Nucleophilic Addition**

nucleophiles that add readily: C\,-, H\,-, :NR\,\text{3} (R=H, alkyl)

nucleophiles that add under acid catalysis: ROH, RSH, HNR\,\text{2}

**Addition of Carbon Nucleophiles**

While all carbanions are nucleophilic enough to add to carbonyls, they are also basic enough to deprotonate carbonyl α-protons; thus, we will often observe competing modes of reaction

Common carbanion nucleophiles: R-CC\,-, CN, R-Li, R-MgBr

Mechanism usually involves a 4-center transition state:

because of the compact nature of the transition state, reaction rate will be very sensitive to steric factors
Chemoselectivity of Grignard Additions

![Chemoselectivity of Grignard Additions](image)

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>1,2 addition</th>
<th>reduction</th>
<th>enolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Br</td>
<td>80</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>n-Pr</td>
<td>Cl</td>
<td>51</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>n-Pr</td>
<td>Br</td>
<td>35</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>n-Pr</td>
<td>I</td>
<td>30</td>
<td>69</td>
<td>1</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Cl</td>
<td>0</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Br</td>
<td>0</td>
<td>65</td>
<td>29</td>
</tr>
<tr>
<td>i-Pr</td>
<td>I</td>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

Mosher, JOC, 1962, 27, 1

Where does product #2 come from? β - hydride transfer

![Chemoselectivity of Grignard Additions](image)

- this is related to the Meerwein - Pondorf - Verley reaction

**Conclusion:** only CH₃, 1°, sp², & sp Grignards add cleanly to ketones
(but all Grignards, RLi add to aldehydes)

Typically, small M⁺ (Li⁺, Ce³⁺) promote 1,2 addition to carbonyls
Addition of Enolates to Carbonyls - The Aldol Reaction

original version:

- this reaction is made irreversible only by the final $\beta$-elimination

the use of irreversible deprotonation using strong bases created a new version

- we stop at $\beta$-hydroxy carbonyl compounds; diastereoisomers possible
Observations:

1) Z - enolates give mainly syn aldol products

2) E - enolates give mainly anti aldol

3) Stereoselectivity (for syn) of Z - enolates is better than that of E (for anti)

4) Stereoselectivity is better for both when R' is large

5) Stereoselectivity is better for both when when R'' is large (mostly when M = boron)

6) Correlation reversed when R is large

How to explain? **Zimmerman-Traxler model**  
*JACS, 1957, 79, 1920*

Z - enolate:
**E - enolate:**

\[ \text{R''CHO} + \text{R'OMR} \xrightarrow{\text{aldol}} \text{anti} \text{favored} \]

\[ \text{R''CHO} + \text{R'OMR} \xrightarrow{\text{aldol}} \text{syn} \text{disfavored} \]

- now return to observations: 1,3-diaxial interaction between R' & R'' controls stereochem.

so large R' & R'' increases stereoselectivity

-favored/disfavored difference not as great

for E-enolate (1,3-diaxial vs. gauche)

When R is large, anti T.S. for Z looks better

"syn" T.S. for E ""

**Allyl Nucleophilic Addition**

\[ \text{M} + \text{H} \xrightarrow{\text{anti}} \text{OM} \]

\[ \text{M} + \text{H} \xrightarrow{\text{syn}} \text{OM} \]

this looks simple, but there are 2 possibilities:

\[ \gamma \alpha \]

\[ 4 - \text{center T.S.} \]

\[ \gamma \alpha \]

\[ 6 - \text{center T.S.} \]
which mechanism prevails depends on M:

6 - center: $M = \text{B, Cr, SiX}_3$

4 - center: $M = \text{BaCl}$

both: $M = \text{Li, MgX}$

neither: $M = \text{SnR}_3$

$\Rightarrow$ 6 - center transition state looks like Zimmerman - Traxler:

```
E
Hoffman, JOC 1981, 46, 1309

also:
```
Addition/Elimination Mechanism

Variant #1 - Addition of Nitrogen Nucleophiles to Aldehydes & Ketones

\[
\begin{align*}
& \text{R}^1 \text{R}^2 \text{O} \quad \text{H}_2\text{N-Z} \\
\xrightarrow{\text{H}^+} & \text{R}^1 \text{R}^2 \text{N}^=\text{Z} \xrightarrow{-\text{H}^+} \text{R}^1 \text{R}^2 \text{ON}^=\text{Z} \\
\rightarrow & \text{R}^1 \text{R}^2 \text{N}^=\text{Z} \xrightarrow{+\text{H}^+} \text{R}^1 \text{R}^2 \text{N} = \text{Z}
\end{align*}
\]

\(Z = \text{R, OR, NR}_2\)

- this process is typically reversible; equilibrium can favor either s.m. or product, depending on choice of conditions

look at pH - rate profile of

\[
\begin{align*}
\text{O} + \text{H}_2\text{NOH} & \rightarrow \text{NOH} + \text{H}_2\text{O}
\end{align*}
\]

Why a bell - shaped pH rate profile?
look at kinetics

\[
\begin{align*}
\text{v}_{\text{max}} \text{ at pH 4.8}
\end{align*}
\]

formulate reaction as

\[
\text{O} + \text{H}_2\text{NOH} \overset{\text{fast}}{\underset{\text{k}_1}{\rightarrow}} \text{OH} \overset{\text{k}_2}{\underset{\text{H}^+}{\rightarrow}} \text{NOH} + \text{H}_2\text{O}
\]

\[
\text{v} = k_2 \frac{k_1}{k_{-1}} [\text{O}] [\text{H}_2\text{NOH}] [\text{H}^+]
\]

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but since we have a second equilibrium: \[ H + H_2NOH \rightleftharpoons H_3NOH \]

\[ \Rightarrow \quad v = \frac{k_2 k_1}{k_{-1}} \left( [H_2NOH] + [H_3NOH] \right) \left( [H^+] \right) \] when \([H^+] \ll K_a\)

\[ v = \frac{k_2 k_1}{k_{-1}} \left( [H_2NOH] + [H_3NOH] \right) K_a \left( [H^+] \right) \] when \([H^+] \gg K_a\)

so this gives the following pH - rate profile:

```
<table>
<thead>
<tr>
<th>pH</th>
<th>k_obs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

something's wrong here . . . what is it?

What about \[ \text{slow} \quad \text{fast} \] \[ \text{slow} \quad \text{fast} \]

```
\[ v = k_1 \left( [H_2NOH] + [H_3NOH] \right) \left( [H^+] \right) \]

\[ 1 + \frac{[H^+]}{K_a} \]
```

so, now combine the two curves

```
<table>
<thead>
<tr>
<th>pH</th>
<th>k_obs</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
```

```
pH - rate behavior indicates a change in rate - determining step at pH ~ 5```

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Variant #2 - Addition to Carboxylic Acid Derivatives

\[ \text{tetrahedral intermediate} \]

- this is sometimes referred to as nucleophilic acyl substitution, but more properly thought of as addition/elimination

alternate version:

\[ Y = \text{OR, } O_2\text{CR, } NR_2, \text{ Cl, Br, F, SR} \]

order of reactivity:

\[ \text{RCHO} > \sim > \text{ROR'} > \text{RRO'} > \text{ROR'} > \text{RNR}_2 \]

(based on electronegativity and π - donation of Y)

Mechanism #1 - saponification
Mechanism #2 - Fischer esterification

\[
\begin{align*}
R\text{COOH} & \quad \text{HCl} \quad \text{MeOH} \\
\quad & \quad \rightarrow \\
R\text{COOMe} & \quad \text{MeOH} \\
\end{align*}
\]

an alternative mode of catalysis - nucleophilic catalysis

\[
\begin{align*}
\text{phenyl} & \quad \text{pyridine} \\
\text{very slow reaction (} & \quad t_{1/2} > 24h) \\
\text{phenyl} & \quad \text{cyclohexanol} \\
\text{very slow reaction (} & \quad t_{1/2} \sim 1h) \\
\end{align*}
\]

Why does pyridine accelerate the reaction?

it’s not going to deprotonate cyclohexanol \( K_{eq} = 10^{5-17} = 10^{-12} \)

So, look at alternative mechanisms:
So why is this any faster?
reason 1: pyridine is a far better nucleophile than an alcohol

reason 2: acyl pyridinium ion $\text{A}$ is far more reactive than the acyl chloride (Why? better leaving group)

$\Rightarrow$ combine better nucleophilicity with better leaving group ability & you have **nucleophilic catalysis**

better nucleophilic catalysts than pyridine: $\text{NMe}_2$ (DMAP), $\text{PBU}_3$ (NE$_3$ also used)

**Conjugate (1,4) Addition**

$\alpha,\beta$ - unsaturated carbonyl compounds have 2 sites of attack by nucleophiles: C-2 or C-4 (C $\beta$)

Addition to C$\beta$ is referred to as 1,4-addition (conjugate addition):

What factors govern 1,2- vs. 1,4 - addition?

enolate (more stable) thermodynamic product

alkoxide (less stable) kinetic product
Why is 1,2-adduct the kinetic product? Look at transition states

unless there is a high concentration of E*, 1,4-addition is slower in general

Examples of 1,4-additions:

Why 1,4-addition?

no longer a cyclic transition state, so 1,2 & 1,4 are kinetically similar
One major category of 1,4-additions is the addition of organocuprate reagents to α, β-unsaturated carbonyl compounds:

![Reagent](attachment:reagent.png)

How does this work & why does it give 1,4-addition?

- all organocopper reagents are Cu species - free radicals so, probably the mechanism involves free radical intermediates:

\[ \text{JACS, 1994, 116, 2902-2913} \]

### 1,2 vs. 1,4 Addition

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>M</th>
<th>1,2 addition</th>
<th>1,4 addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>Me</td>
<td>MgCl</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>MgCl</td>
<td>67</td>
<td>33</td>
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<tr>
<td>i-Pr</td>
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<td>t-Bu</td>
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<td>MgCl</td>
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<td>67</td>
</tr>
<tr>
<td>t-Bu</td>
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<td>Li</td>
<td>85</td>
<td>15</td>
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</table>