Topic 12: Addition to $\pi^*$

Tetrahedral intermediates

Read:
I. Fleming Molecular Orbitals and Organic Chemical Reactions, 5.1.3.1, 5.1.4, 5.2.1
Addition of Nucleophiles to Simple C=C Bonds is Not Common

- Addition to C=C much slower than addition to C=O

- Directed addition: 5-membered T.S. confers an entropic advantage

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Addition of Nucleophiles to C=O

■ The C=O bond is polarized

\[
\text{Dipole Moment: } \mu = \Delta q \times \text{dist.} = 2.7 \text{ D} \\
\text{suggests } \pm 0.23 \text{ charges}
\]

■ Electronegative atoms distort the HOMO and LUMO

■ "Coefficients" describe the relative size of p orbitals in \( \pi \) and \( \pi^* \)

■ The coefficient is bigger on carbon in \( \pi^*_{\text{C=O}} \)

■ The Bürgi-Dunitz Angle = Preferred Nu—C — O angle = 109°

(Crystal structures confirm attack trajectory)

The Felkin-Anh Analysis

- Chiral centers adjacent to carbonyls control the stereoselectivity of Nu addition
  (The selectivity is usually modest.)

\[
\begin{align*}
\text{Me} & \quad \text{Et}_2\text{O} \\
\text{Me} & \quad 35 \, ^\circ\text{C} \\
\text{Ph} & \quad \text{LiAlH}_4 \\
\text{Nu} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph}
\end{align*}
\]

- Strong nucleophiles = early, reactant-like transition states (= Felkin,Cram)
- Nucleophiles attack opposite side of large groups (= Dauben)
- Attack from Bürgi-Dunitz angle (= Anh)
- Forming bond eclipses small rather than medium group

\[
\begin{align*}
\text{BIG} & \quad \text{Med} \\
\text{R} & \quad \text{S} \\
\text{Nu} & \quad \text{S} \\
\text{Me} & \quad \text{O}
\end{align*}
\]

Cost = 5.5 kcal/mol

- Nucleophile attacks on the opposite side of electronegative groups

\[
\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{S} & \quad \text{Nu}
\end{align*}
\]

\[
\begin{align*}
\text{Nu} & \quad \alpha^* \\
\text{OMe} & \quad \text{Med} \\
\text{R} & \quad \text{O}^-
\end{align*}
\]


*His last name is Nguyễn, not Anh
Chelation Control and Lewis Acids

■ Gives opposite of Felkin-Anh (= Cram's chelate model)

![Chemical structures and reactions]

■ Siloxy groups are poor for chelation: \( RO >> R_3SiO \)

■ Good chelating metals: \( TiX_4, ZnX_2, MgX_2, LiX \)

■ Bad solvents for chelation control: DMSO, DMF, ROH, DME, THF
(-compete with substrate for chelation to metal)

■ Lewis Acids: Increase \( \delta^+ \) and lower LUMO, thus chelated form is more reactive than un-chelated.

■ Lewis Acidity Scales

<table>
<thead>
<tr>
<th>L.A.</th>
<th>( \Delta H )</th>
<th>( \Delta \delta(H-3) )</th>
<th>LUMO lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCl_3</td>
<td>-6.6</td>
<td>1.35</td>
<td>1.00</td>
</tr>
<tr>
<td>AlCl_3</td>
<td>-25.6</td>
<td>1.23</td>
<td>0.91</td>
</tr>
<tr>
<td>BF_3</td>
<td>+4.1</td>
<td>1.17</td>
<td>0.76</td>
</tr>
<tr>
<td>AlEt_3</td>
<td>-10.1</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>SnCl_4</td>
<td>+10.0</td>
<td>0.87</td>
<td>0.61</td>
</tr>
</tbody>
</table>

**Donor Effects on C=O Reactivity**

- Donation slows addition of nucleophiles

\[
\begin{align*}
\text{OH} & \quad \text{OH}^- \\
\text{CHO} & \quad \text{CHO}^- \\
\text{CH}_3\text{CO} & \quad \text{CH}_3\text{CO}^- \\
\end{align*}
\]

- Rates of HO\(^{-}\) addition to C=O

\[
k_{rel} (\text{OH}^-) \quad 10^{11} \quad 10^9 \quad 10^7 \quad 10^4 \quad 1 \quad <1
\]


- Evidence for Donation = Rotational Barriers

\[
\begin{align*}
\text{MeO} & \quad \text{MeOH} \quad \text{MeO}^- \\
\text{Me} & \quad \text{Me}^- \\
\end{align*}
\]

Costs ~12 kcal/mol to twist

\[
\begin{align*}
\text{O} & \quad \text{O}^- \\
\text{O} & \quad \text{O}^+ \\
\end{align*}
\]

\(p_O \rightarrow \pi^*\)

Overall Hydrolysis Rates:

\[
\begin{align*}
\text{Cl} & \quad \ggg & \text{OR} & \quad \ggg & \text{NR}_2 & \quad \ggg & \text{O}^- \\
10^{11} & \quad 10^0 & \quad 10^{-2} & \quad ??
\end{align*}
\]

\(p_N\) is more nucleophilic than \(p_O\)

Costs ~20 kcal/mol to twist
Effects of Ring Size on C=O Reactivity

■ Electronic and strain effects

$$\begin{align*}
\text{H}_2\text{O} + \text{R}^+\text{R}^- & \xrightarrow{\text{e- deficient}} \text{OH} + \text{H} \\
\text{H}_3\text{C} = \text{CH}_3 + \text{Me} & \xrightarrow{\text{Me}} \text{CH}_3 = \text{CH}_2 + \text{Me} \\
\text{CH}_3 = \text{CH}_2 & \xrightarrow{\text{H}} \text{Me} + \text{Me}
\end{align*}$$

\[ K_{eq} = \begin{array}{c}
0.008 \\
0.6 \\
1 \\
2300 \\
1,200,000
\end{array} \]

\[ \sigma_{\text{C-H}} = \text{donor} \]

C&S A, 5th Ed. Table 7.4

■ Relative rates for carbonyl addition

NaBH\textsubscript{4} in \textit{i}-PrOH

\[ k_{rel} = \begin{array}{c}
12,400 \\
20 \\
10 \\
1 \\
0.5
\end{array} \]

Proposed model: \textit{pyramidalization relieves eclipsing}

- lubiprostone
- cyclopropanone
- cyclopropanone hydrate
- commercially available

- Wants 120° instead of 60°

- best conf. = 2 eclipse
- many confs. always ≥1 eclipse
- no eclipse
- many confs. always ≥1 eclipse
Effects of Charge and Electronegativity

■ Formal charge is more important than electronegativity

\[ \text{N} \quad < \quad \text{O} \quad < \quad \text{N}^+ \quad < \quad + \text{O} \quad < \quad + \text{N}^- \]

reacts w/ 

\[ \text{B} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{B} \quad \text{C} \quad \text{N} \quad \text{E} \quad \text{t} \quad \text{Si} \quad \text{E} \quad \text{t} \]

\[ \pi^*_{\text{C} = \text{N}} \]

\[ \text{E} \quad \pi^*_{\text{C} = \text{N}^+} \]

■ Borch reductive amination


\[ \text{RNH}_2 + \text{O} \xrightarrow{\text{NaCNBH}_3} \text{aq. MeOH} \quad \text{pH 5} \quad \text{NHR} \]

\[ 5 \text{ fast elementary steps} \]

\[ \text{H}_2\text{O} + \text{HNR} \]

\[ \text{fast} \]

\[ \text{NC} \quad \text{B} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

\[ \text{slow} \]

\[ \text{HN} \quad \text{R} \quad \text{B} \quad \text{CN} \quad \text{H} \quad \text{H} \quad \text{H} \]
Substitution through Addition-Elimination

- Easier to add to $\pi^*$ than $\sigma^*$

- Unstable Tetrahedral Intermediate (TIM)

- Stable TIM with Weinreb's amide

Why Are Acid Chlorides Reactive?

- **Relative reactivity** toward Nu:
  
  \[
  \begin{align*}
  \text{O}_\text{Br} & > \text{O}_\text{Cl} & > & > & \text{O}_\text{F} \\
  \end{align*}
  \]

- The order is not because of electronegativity: \( \text{Br} (3.0) < \text{Cl} (3.2) < \text{F} (4.0) \)

- **C-X bond lengths:**
  
  \[
  \begin{align*}
  \text{O}_\text{Br} & > 1.88 \, \text{Å} & \text{O}_\text{Cl} & > 1.73 \, \text{Å} & \text{O}_\text{F} & > 1.34 \, \text{Å} \\
  \end{align*}
  \]

- Long bonds = poor overlap \( n_X \rightarrow \pi^* \)

- **Cation stability:**
  
  \[
  \begin{align*}
  \text{H}_3^+\text{CF}_3 & > \text{H}_3^+\text{F} > \text{H}_3^+ > \text{H}_3^+ \text{F}_3 & > & > & > & > & > \\
  \end{align*}
  \]

**Conclusion:** acid chlorides are reactive b/c of poor l.p donation
Nucleophilic Acyl Transfer Catalysis

- 4-DMAP catalyzes acyl transfer

\[ \text{O} \text{O} + \text{HO} \rightarrow \text{O} \text{O} \]

*Used in conjunction w/ stoichiometric bases.*

10 mol% DMAP leads to $10^4$ rate acceleration in the acylation of $3^\circ$ alcohols.

- The key residue in the ribosome looks like DMAP, but is just a base.

- Rebek “three-phase test” distinguishes nucleophilic catalysis from base catalysis.

"…grinding the polymer-bound acylating agent and polymer-bound amine in a mortar, with or without solvent, failed to induce direct reaction between the solid phases."

**LUMO Lowering Catalysis**

- **Knoevenagel Condensation** – It looks like addition of an enolate to a C=O, but not the use of a 2° amine.

  \[ RCH_2CHO + \text{AcOEt} \xrightarrow{\text{AcOH}} \text{acetoacetic ester} \]

  Jones *Org. React.* (1967), 204
  Crowell & Peck *JACS* (1953), 1075

- **Organocatalytic D-A**
  *(rapid equilibrium for iminium ion formation)*

  \[ \text{OEtO} + \text{NH} + \text{AcOH} \xrightarrow{\text{fast D-A}} \]

  \[ \text{NH}_2\text{Me}_{12} \]

  up to 93% e.e.

Conjugate Addition Reactions

**Effects of conjugation and E.N. on LUMO**

LUMO coefficients predict 1,4

- **LUMO coefficients predict 1,4**
  - LUMO coefficients: +0.62, -0.43, +0.53, +0.60
  - HF/STO-3G coeff.

- **Charge predicts 1,2**
  - Best for 1,2 C=O addition
  - Worst Nu for 1,4 addition
  - High, localized charge
  - Best Nu for 1,4 addition
  - F⁻ or Cs⁺ -OR

- **Charge predicts 1,2**
  - 6x higher

**LUMO coefficients predict 1,4**

- **LUMO coefficients predict 1,4**
  - LUMO coeff. 0.62 -0.42 -0.53 0.60
  - \( c^2 \propto e^{-}\)pop. 0.38 0.17 0.28 0.36

**Charge predicts 1,2**

- **Charge predicts 1,2**
  - +1.25
  - +0.21

**Effects of conjugation and E.N. on LUMO**

- **Effects of conjugation and E.N. on LUMO**
  - 2000 Nobel prize
  - Conjugation →

**Charge predicts 1,2**

- **Charge predicts 1,2**
  - +0.21