Chap. 6 Methods of Studying Organic Rxns

Determining Reaction Mechanisms

1. Identification of reaction products
2. Determination of Intermediates

→ Determining no. of steps
  ( a one step reaction, with reaction $\rightarrow$ T.S. $\rightarrow$ product, is an elementary reaction )
  
  if more than one elementary steps, an intermediate is involved
  
  $\text{reactant} \xrightarrow{k_1} \text{intermediate} \xrightarrow{k_2} \text{product}$
  
  depending on the magnitude of $k_1$, $k_2$, the concentration of intermediate can be high or low

→ Isolating intermediate
  quench the reaction ( by cooling, by diluting, by removing catalyst,…..)

→ Spectroscopic characterization
  UV-VIS, IR, NMR, ESR…….

If not isolable, not spectroscopically observable,
→ trap the intermediate by a trapping agent
→ Disprove an intermediate
    synthesize a proposed intermediate and compare the reaction properties…

→ Crossover Experiment
    To differentiate intra-molecular or inter-molecular
    \( \text{(inter fragmental)} \)
→ **Isotope labeling**  
the least perturbation to a system is by isotope replacement 

\[
\begin{align*}
\text{O} & \quad \text{H} \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 & (S) \\
\text{CH}_3\text{CH}_2 & \quad \text{CH}_3\text{CH}_2 & \quad \text{Br} \\
\text{CH}_3\text{CH}_2 & \quad \text{CH}_3\text{CH}_2 & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{CH}_3 & \quad \text{H} \\
\text{CH}_2\text{CH}_3 & \quad \text{CH}_2\text{CH}_3 & (R)
\end{align*}
\]

suggest inversion of reaction center

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{CH}_3 & \quad \text{H} \\
\text{CH}_2\text{CH}_3 & \quad \text{CH}_2\text{CH}_3 & (R) \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} & \quad \text{H}_2\text{O}
\end{align*}
\]

suggest an achiral reaction center

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

rule out

→ **Stereochemical Studies**
→ **Solvent Effect**

Solvent affects reaction rate through relative stabilization of reactants / transition → deduce T.S. structure

e.g

$S_{N1}$  
\[ (\text{CH}_3)_3\text{C}-\text{Cl} \rightarrow (\text{CH}_3)_3\text{C} \cdot \cdot \text{Cl} \rightarrow (\text{CH}_3)_3\text{C}-\text{Nu} + \text{X}^- \]

the rate increases with increasing solvent polarity.

→ more ionic character in T.S. than the reactant

$S_{N2}$  
\[ \text{OH}^- + \text{CH}_3\text{-Br} \rightarrow [ \text{HO} \cdot \cdot \text{CH}_3 \cdot \cdot \text{Br} ] \rightarrow \text{CH}_3\text{OH} + \text{Br}^- \]

The rate decreases with increasing solvent polarity

→ less ionic character in T.S. than starting material

**Measurement of solvent polarity :**

\[ \mu : \text{dipole moment (a molecular property)} \]

\[ +e -e \]

\[ \mu = e \cdot r = 4.8 \times 10^{-18} \text{ esu} \cdot \text{cm} \]

\[ = 4.8 \text{ D} \]

\[ \varepsilon : \text{dielectric constant, effect of substance on the E-field between an capacitor, relating to polarity and polarizability} \]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\varepsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>1.89</td>
</tr>
<tr>
<td>CCl$_4$</td>
<td>2.23</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>4.8</td>
</tr>
<tr>
<td>H$_2$O</td>
<td>78.4</td>
</tr>
<tr>
<td>MeOH</td>
<td>32.7</td>
</tr>
<tr>
<td>EtOH</td>
<td>24.5</td>
</tr>
<tr>
<td>$n$-PrOH</td>
<td>20.4</td>
</tr>
</tbody>
</table>

$Z : \text{Kosower scale}$

<table>
<thead>
<tr>
<th>$\text{CO}_2\text{CH}_3$</th>
<th>$\text{CH}_2\text{CH}_3$</th>
<th>$\text{CO}_2\text{CH}_3$</th>
<th>$\text{CH}_2\text{CH}_3$</th>
</tr>
</thead>
</table>

the charge-transfer band is sensitive to solvent

the transition energy : $Z=E_T$
$E_T(30)$

charge-transfer band

$\alpha$: acidity as H-bonding Donor (the ability of the solvent to donate a proton in solvent-solute H-bond)

$\beta$: basicity as H-bonded Acceptor

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$\epsilon$</th>
<th>$\mu$ (D)</th>
<th>$Z$</th>
<th>$E_T(30)$</th>
<th>$\pi$</th>
<th>$\beta$</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formamide</td>
<td>111.0</td>
<td>3.37</td>
<td>83.3</td>
<td>56.5</td>
<td>0.97</td>
<td>0.48</td>
<td>0.71</td>
</tr>
<tr>
<td>Water</td>
<td>78.4</td>
<td>1.8</td>
<td>94.6</td>
<td>63.1</td>
<td>1.09</td>
<td>0.47</td>
<td>1.17</td>
</tr>
<tr>
<td>Formic acid</td>
<td>58.5</td>
<td>1.82</td>
<td>54.3</td>
<td>65.3</td>
<td>0.65</td>
<td>0.38</td>
<td>1.23</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>46.5</td>
<td>4.06</td>
<td>71.1</td>
<td>45.1</td>
<td>1.00</td>
<td>0.76</td>
<td>0.00</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>36.7</td>
<td>3.24</td>
<td>68.5</td>
<td>43.5</td>
<td>1.00</td>
<td>0.76</td>
<td>0.00</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>35.9</td>
<td>3.56</td>
<td>71.3</td>
<td>45.6</td>
<td>0.75</td>
<td>0.40</td>
<td>0.22</td>
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<tr>
<td>Acetonitrile</td>
<td>35.9</td>
<td>3.53</td>
<td>71.3</td>
<td>45.6</td>
<td>0.75</td>
<td>0.40</td>
<td>0.22</td>
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<tr>
<td>Methanol</td>
<td>32.7</td>
<td>2.37</td>
<td>83.6</td>
<td>55.4</td>
<td>0.60</td>
<td>0.66</td>
<td>0.93</td>
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<tr>
<td>Hexamethylphosphoramide</td>
<td>29.3</td>
<td>4.31</td>
<td>62.8</td>
<td>40.9</td>
<td>0.87</td>
<td>1.05</td>
<td>0.00</td>
</tr>
<tr>
<td>Ethanol</td>
<td>24.5</td>
<td>1.66</td>
<td>79.6</td>
<td>51.9</td>
<td>0.54</td>
<td>0.75</td>
<td>0.83</td>
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<tr>
<td>1-Propanol</td>
<td>20.4</td>
<td>3.09</td>
<td>78.3</td>
<td>50.7</td>
<td>0.52</td>
<td>0.90</td>
<td>0.84</td>
</tr>
<tr>
<td>1-Butanol</td>
<td>17.5</td>
<td>1.75</td>
<td>77.7</td>
<td>50.2</td>
<td>0.47</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>Acetone</td>
<td>20.6</td>
<td>2.69</td>
<td>65.7</td>
<td>42.2</td>
<td>0.71</td>
<td>0.43</td>
<td>0.08</td>
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<tr>
<td>2-Propanol</td>
<td>19.9</td>
<td>1.66</td>
<td>76.3</td>
<td>48.4</td>
<td>0.48</td>
<td>0.48</td>
<td>0.76</td>
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<tr>
<td>Pyridine</td>
<td>12.9</td>
<td>2.37</td>
<td>64.0</td>
<td>40.5</td>
<td>0.87</td>
<td>0.64</td>
<td>0.00</td>
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<tr>
<td>t-Butyl alcohol</td>
<td>12.5</td>
<td>1.66</td>
<td>71.3</td>
<td>43.3</td>
<td>0.41</td>
<td>0.93</td>
<td>0.42</td>
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<tr>
<td>Methylene chloride</td>
<td>8.9</td>
<td>1.14</td>
<td>64.2</td>
<td>40.7</td>
<td>0.82</td>
<td>0.10</td>
<td>0.13</td>
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<tr>
<td>Tetrahydrofuran</td>
<td>7.58</td>
<td>1.75</td>
<td>37.4</td>
<td>0.58</td>
<td>0.55</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1,2-Dimethoxyethane</td>
<td>7.20</td>
<td>1.71</td>
<td>62.1</td>
<td>38.2</td>
<td>0.53</td>
<td>0.41</td>
<td>0.00</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>6.17</td>
<td>1.68</td>
<td>79.2</td>
<td>51.7</td>
<td>0.64</td>
<td>0.45</td>
<td>1.12</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>6.02</td>
<td>1.82</td>
<td>38.1</td>
<td>0.55</td>
<td>0.45</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Chloroform</td>
<td>4.80</td>
<td>1.15</td>
<td>63.2</td>
<td>39.1</td>
<td>0.58</td>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>4.2</td>
<td>1.15</td>
<td>34.5</td>
<td>0.27</td>
<td>0.47</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.27</td>
<td>0</td>
<td>54.0</td>
<td>34.3</td>
<td>0.59</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>2.23</td>
<td>0</td>
<td>32.4</td>
<td>0.28</td>
<td>0.10</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>n-Hexane</td>
<td>1.89</td>
<td>0.085</td>
<td>31.0</td>
<td>0</td>
<td>-0.04</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Data from the compilation in reference 34. *Data from reference 38. *Data from the compilation in reference 39, pp. 365–371. *Data from the compilation in reference 35, p. 301. *0.13 M EtOH. *Values for $\pi$, $\beta$, and $\alpha$ from reference 40. *Data from the compilation in reference 42.
§ Application of Kinetics in Studying Rxn Mechanism

**reaction rate** : rate of change of concentration of reactant or product

For a reaction

\[ n_A A + n_B B + n_C C \rightarrow n_P P \]

rate \[= \frac{1}{n_A} \frac{dA}{dt} = \frac{1}{n_B} \frac{dB}{dt} = \frac{1}{n_C} \frac{dC}{dt} = \frac{1}{n_P} \frac{dP}{dt} \]

\[= k_r [A]^a [B]^b [C]^c \]

overall reaction order = \( a + b + c \). ← determined by experiment not by stoichiometry

(For elementary reaction

the order of the reaction = the no. of reacting molecule

= molecularity)

**Pseudo order** : if one reactant doesn't change its concentration significantly, e.g. \([C] = \text{const}\)

rate \(= k'[A]^a [B]^b\), reaction order = \( a + b \)

e.g. ROTs \(\xrightarrow{\text{aq EtOH}}\) R-OEt pseudo first order

**zero order**

\[ A \xrightarrow{k} \text{product} \]

rate \(= -\frac{dA}{dt} = k \int -dA = \int kdt \)

Differential rate equation

\[ A - A_0 = -kt \]
Integration rate equation

e.g. Saturation reaction on the surface of a metal

half life \( t^{1/2} = \) the time for \( A = \frac{A_0}{2} \)

\[ \frac{A_0}{2} - A_0 = -kt^{1/2}, \quad t^{1/2} = \frac{A_0}{2k} \]
First order reaction

\[ A \xrightarrow{k} P \]

\[ -\frac{d[A]}{dt} = k[A], \quad \int \frac{d[A]}{[A]} = -\int k dt \]

\[ ln \left( \frac{[A]}{[A]_0} \right) = -kt, \quad [A] = [A]_0 e^{-kt}, \quad t_{1/2} = \frac{ln2}{k} = \frac{0.693}{k} \]

plot \( ln[A] \) v.s \( t \) → straight line, \( \text{slope} = -k \)

Second order reaction

type 1

\[ 2A \xrightarrow{k} P \]

\[ \frac{d[P]}{dt} = -\frac{d[A]}{2dt} = k[A]^2, \]

\[ \frac{d[A]}{2[A]^2} = -k dt, \quad \int \frac{d[A]}{[A]^2} = -\int 2k dt, \quad \frac{1}{[A]} - \frac{1}{[A]_0} = 2kt \]

plot \( \frac{1}{[A]} \) v.s \( t \) → straight line \( \text{slope} = 2k \)

\[ t_{1/2} : \quad \frac{2}{[A]_0} - \frac{1}{[A]_0} = 2kt_{1/2} \quad t_{1/2} = \frac{1}{2k[A]_0} \]

type 2

\[ A + B \xrightarrow{k_2} P \]

\[ -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_2[A][B], \]

\[ ln \left( \frac{[A]}{[B]} \right) + ln \left( \frac{[B]_0}{[A]_0} \right) = ([A]_0 - [B]_0)k_2 t, \]

plot \( ln[A] \) v.s \( t \) → straight line \( \text{slope} = ([A]_0 - [B]_0)k_2 \)
Reversible reaction

\[ \text{A} \xleftrightarrow{k_1} \text{B} \]

\[- \frac{dA}{dt} = \frac{dB}{dt} = k_1 A - k_{-1} B \quad , \quad A_0 + B_0 = A + B \]

\[- \frac{dA}{dt} = k_1 - k_{-1} (A_0 + B_0 - A) \]

\[ k_1 A - k_{-1} (A_0 + B_0) = (k_1 + k_{-1}) A - k_{-1} (A_0 + B_0) \]

\[ \int \frac{dA}{(k_1 + k_{-1}) A - k_{-1} (A_0 + B_0)} \quad = \int -dt \quad \vdots \quad \int \frac{dx}{a + bx} = \frac{1}{b} \ln(a + bx) \]

\[ \frac{1}{k_1 + k_{-1}} \ln[(k_1 + k_{-1}) A - k_{-1} (A_0 + B_0)] = -t + \text{const.} \]

at \( t = 0 \)
\[ \text{const.} = \frac{1}{k_1 + k_{-1}} \ln[(k_1 + k_{-1}) A_0 - k_{-1} (A_0 + B_0)] \]

subst. into above eq.

\[ \ln \left( \frac{(k_1 + k_{-1}) A_0 + k_{-1} (A_0 + B_0)}{(k_1 + k_{-1}) A - k_{-1} (A_0 + B_0)} \right) = (k_1 + k_{-1}) t \]

\[ \ln \left( \frac{k_1 A_0 + k_{-1} B_0}{k_1 A + k_{-1} A_0 - k_{-1} B_0} \right) = (k_1 + k_{-1}) t \]

at \( t = \infty \)
\[ A = A_\infty \quad , \quad B = B_\infty \quad \quad k_{eq} = \frac{B_\infty}{A_\infty} = \frac{k_1}{k_{-1}} \quad k_1 = k_{-1} \frac{B_\infty}{A_\infty} \]

\[ \ln \left( \frac{A_0}{k_{-1} A_\infty} \right) = (k_1 + k_{-1}) t \]

\[ \ln \left( \frac{B_\infty}{k_{-1} A_\infty} \right) = (k_1 + k_{-1}) t \]

\[ \ln \left( \frac{A_0 B_\infty - A_\infty B_0}{B_\infty A - B A_\infty} \right) = (k_1 + k_{-1}) t \]

plot left hand side v.s. \( t \) \rightarrow slop = k_1 + k_{-1}

\[ \rightarrow k_1, k_{-1} \text{ from } k_1 = k_{-1} \frac{B_\infty}{A_\infty} \]
more common simplification: Pseudo first order

\[ A + B \rightarrow P \quad \text{let} \ [B] \gg [A] \quad \text{so that} \ [B] \ \text{is relatively constant} \]

\[-\frac{d[A]}{dt} = k'[A] \quad \text{where} \ k' = k_2[B] \]

\[ \Rightarrow \ln \left( \frac{[A]}{[A_0]} \right) = -k't \]

**third order reaction**

\[ 3A \rightarrow \text{product} \]

\[ \text{rate} = -\frac{d[A]}{3dt} = k[A]^3 \]

\[ 2A + B \rightarrow \text{product} \]

\[ \text{rate} = -\frac{1}{2} \frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A]^2[B] \]

\[ A + B + C \xrightarrow{k} \text{product} \]

\[ \text{rate} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = -\frac{d[C]}{dt} = k[A][B][C] \]

For consecutive and irreversible reaction

\[ A \xrightarrow{k_1} B \xrightarrow{k_2} C \]

\[ \text{rate} = \frac{d[C]}{dt} = k_2[B] \]

\[ \frac{d[B]}{dt} = k_1[A] - k_2[B], \quad -\frac{d[A]}{dt} = k_1[A], \quad [A] = [A_0]e^{-k_1t} \]

\[ \Rightarrow C = A_0 - A_0e^{-k_1t} - \frac{k_1A_0}{k_2 - k_1}(e^{-k_1t} - e^{-k_2t}) \]
Figure 6.15
Variation of [A], [B], and [C] with time for $k_1/k_2 = 3.0$.

Figure 6.16
Variation of [A], [B], and [C] with time for $k_1/k_2 = 0.33$.

Figure 6.17
Variation of [A], [B], and [C] with time for $k_1/k_2 = 0.033$. 
Apply steady state approximation to [B] in the case \( k_2 >> k_1 \)

\[
\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0
\]

i.e. the first step is slower

\[
k_1[A] = k_2[B]
\]

\[
\text{rate} = \frac{d[C]}{dt} = k_2[B] = k_1[B]
\]

the s.s.a. is more accurate if \( k_1/k_2 << 1 \)

For \( A + B \xrightarrow{k_1} C \xrightarrow{k_2} D \)

\[
\text{rate} = \frac{d[D]}{dt} = k_2[C]
\]

applying steady state approximation

\[
\frac{d[C]}{dt} = k_1[A][B] - k_2[C] - k_{-1}[C] = 0
\]

\[
[C] = \frac{k_1[A][B]}{k_2 + k_{-1}}
\]

\[
\text{rate} = \frac{d[D]}{dt} = \frac{k_1k_2[A][B]}{k_2 + k_{-1}}
\]

if \( k_2 << k_{-1} \), \( k_2 + k_{-1} \approx k_{-1} \) (the reverse reaction is fast)

\[
\text{rate} = k_2\left(\frac{k_1}{k_{-1}}\right)[A][B] = k_2 K[A][B]
\]

if \( k_2 >> k_{-1} \)

\[
\text{rate} = k_1[A][B]
\]

Pre-equilibrium const.
e.g. $E_{1cb}$ rxn

$$
\begin{align*}
Z \text{CH}_2\text{CH}_2\text{X} + B & \xrightarrow{k_1} \text{ZCHCH}_2\text{X} + \text{BH}^+ \\
& \xleftarrow{k_{-1}} \Theta
\end{align*}
$$

electron-withdrawing

$$
\begin{align*}
\Theta \text{ZCHCH}_2\text{X} & \xrightarrow{k_2} \text{ZCH}=\text{CH}_2 + \text{X}^-
\end{align*}
$$

s.s.a. 

$$
\frac{d[\Theta \text{ZCHCH}_2\text{X}]}{dt} = 0 = k_1[\text{ZCH}_2\text{CH}_2\text{X}][B] \\
- k_{-1}[\Theta \text{ZCHCH}_2\text{X}][\text{BH}^+] \\
- k_2[\Theta \text{ZCHCH}_2\text{X}]
$$

$$
[\Theta \text{ZCHCH}_2\text{X}] = \frac{k_1[\text{ZCH}_2\text{CH}_2\text{X}][B]}{k_{-1}[\text{BH}^+] + k_2}
$$

rate = $\frac{d[\text{ZCH}\equiv\text{CH}_2]}{dt} = \frac{k_2 \cdot k_1[\text{ZCH}_2\text{CH}_2\text{X}][B]}{k_{-1}[\text{BH}^+] + k_2}$

(1) assume $k_2 >> k_{-1}[\text{BH}^+]$ (formation of carbanion is slow, destruction is fast)

$$
\text{rate} = k_1[\text{ZCH}_2\text{CH}_2\text{X}][B]
$$

(2) assume $k_{-1}[\text{BH}^+] >> k_2$ (the destruction of anion is slow)

$$
\text{rate} = \frac{k_2 \cdot k_1[\text{ZCH}_2\text{CH}_2\text{X}][B]}{k_{-1}[\text{BH}^+]} 
$$

To distinguish between (1) or (2), one can use a buffer.
Experimental methods for determination of reaction orders

(1) method of integration
\[ -\frac{dA}{dt} = k[A]^a[B]^b[C]^c \] evaluation of a, b, c by integration plot

(2) method of half life
\[ t_{1/2} \propto A_0^{-1-n}, \quad n \text{ is the order} \]
determine the relationship between \( t_{1/2} \) and \( A_0 \) \( \Rightarrow \) order

(3) method of isolation \quad \text{--------Pseudo orders}
\[ -\frac{dA}{dt} = k[A]^a[B]^b[C]^c \]
make the concentration of B and C extremely large
so that they don’t change with progress of rxn.

(4) Differential method

\[ \text{monitor the conc. of A v.s. t} \]
\[ if \quad -\frac{dA}{dt} = kA^n, \quad \log(-\frac{dA}{dt}) = \log k + n \log A \]
determine several \( -\frac{dA}{dt} \), plot \( \log(-\frac{dA}{dt}) \) v.s. \( \log A \)
the slope is the order of A

no matter what the order is,
\[ \log(-\frac{dA}{dt}) \text{ v.s. } \log A \text{ is always a straight line, with slope } n \]
Arrhenius Theory & Transition State Theory

rate constant is a function of temperature activation energy

Arrhenius equation: \( k = A \exp\left(-\frac{E_a}{RT}\right) \)

\( \ln k = -\frac{E_a}{RT} + \ln A \)

\( \text{Ea} : \) activation energy
\( A : \) pre exponential factor

\( \ln k \) relate to probability

Transition state Theory

The starting material is in equilibrium with activated complex

treat the TS as a species, rate = \([AB]^\dagger \times \text{frequency of T.S}\)

\( k_r = \left(\frac{\kappa k T}{h}\right) e\left(-\frac{\Delta G^\dagger}{RT}\right) = \left(\frac{\kappa k T}{h}\right) e\left(\Delta S^\dagger / R\right) e\left(-\frac{\Delta H^\dagger}{RT}\right) \)

transmission coefficient, to account for probability of reactant to product

for \( \Delta G^\dagger = \Delta H^\dagger - T \Delta S^\dagger \) \( (\text{Ea} = \Delta H^\dagger + RT) \)

\( \ln \left(\frac{k_r}{T}\right) = \ln \left(\frac{\kappa k}{h}\right) + \frac{\Delta S^\dagger}{R} - \frac{\Delta H^\dagger}{RT} \)

\( \text{plot} \quad \ln \left(\frac{k_r}{T}\right) \quad v.s. \quad \frac{1}{T} \rightarrow \Delta H^\dagger, \quad \text{then} \quad \Delta S^\dagger \) from slope
\( \Delta S^i \) reflects the change in the order of the system from reactants to activated complex (T.S.)

\[(CH_3)_3\text{C-O-O-C(CH}_3)_3 \rightarrow [(CH_3)_3\text{-C-O} \cdots \text{O-C(CH}_3)_3]^t \rightarrow 2 (CH_3)_3\text{CO}·\]

\( \Delta S^i = 13.8 \text{ eu} \) one molecule becomes two

\( \Delta S^r = -11.7 \text{ eu} \) two fragments connected together

\( 2 \text{C} \rightarrow [\cdots]^r \rightarrow \text{C} \)

\( \Delta S^r = -26 \text{ eu} \) two molecules combine to one

For competing reaction

If irreversible, the product ratio is the rate constant ratio.

\[
\frac{k_B}{k_C} = \frac{[B]}{[C]} = e^{\Delta G^+/RT}
\]

<table>
<thead>
<tr>
<th>([B]/[C])</th>
<th>(\Delta G^+ (\text{kcal/mol}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>2.73</td>
</tr>
<tr>
<td>1000</td>
<td>4.09</td>
</tr>
<tr>
<td>10000</td>
<td>5.45</td>
</tr>
</tbody>
</table>
Different product ratio for diff. reaction time (or temperature) for reversible reaction

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{O} & \quad + \quad \text{NH}_2\text{NH}-\text{CNH}_2 & \quad \overset{20 \text{ sec}}{\leftrightarrow} & \quad \text{CNH}_2\text{NH} \quad + \quad \text{O} \\
\text{1} & \quad : \quad 1 & \quad : \quad 1 & \quad 2.5 \text{ hr} & \quad \text{CNH}_2\text{NH} \\
\text{Cl} & \quad + \quad \text{Cl} & \quad \text{hours} & \quad \text{Cl} & \quad \text{Cl} \\
\text{a week} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

different prod. ratio at diff. temperature

**Figure 6.26**
Temperature effects on the reaction of 44 with water.
Both time effect and temperature effect are of same origin → the time required to reach the equilibrium.

Kinetic enolate v.s Thermodynamic enolate

If a bulky base used, non-hydroxylic solvent used, low temperature used → less substituted enolate dominates (Kinetic enolate)

If hydroxylic solvent used, or higher temperature equilibrium reached → more substituted enolate dominates (Thermodynamic enolate)
Curtin-Hammet Principle

For two equilibrium conformational isomer, each leading to different product, the product ratio is determined by the activation energy difference, not by the population of the isomer.

\[
B \rightleftharpoons A \quad K_c = \frac{[A]}{[B]}
\]

rate of Product \( P_A = \frac{dP_A}{dt} = k_a[A] = k_aK_c[B] \)

Product \( P_B = \frac{dP_B}{dt} = k_b[B] \)

Product ratio \( \frac{dP_A}{dt} / \frac{dP_B}{dt} = \frac{k_aK_c[B]}{k_b[B]} = \frac{k_aK_c}{k_b} \)

\[
k_r = \frac{\kappa kT}{h} e^{-\Delta G_r^*/RT}
\]

\[
K_c = e^{-(\Delta G/RT)}
\]

product ratio \( \frac{(\kappa kT / h)e^{-\Delta G_r^*/RT}}{(\kappa kT / h)e^{-\Delta G_a^*/RT}} = e^{(\Delta G_r^*/RT + \Delta G_b^*/RT + \Delta G_c^*/RT)} = e^{\Delta G_r^*/RT} = e^{\Delta G^*/RT} \)
Kinetic Isotope Effect

The KIE results from the zero point energy difference for H- or D-substituted species

\[ E_0 = \frac{1}{2} h \nu_0 \]

due to anharmonicity

\[ \nu_0 = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \]

E.g. for a C-H bond, \( \nu_{C-H} \sim 3000 \text{cm}^{-1} \)

replaced by D, \( \nu_{C-D} \sim 2100 \text{cm}^{-1} \)

In ground state, the zero point energy differs by \( \Delta E_0 \), in transition state, zpe differs by \( \Delta E_0^\ddagger \), (usually \( \Delta E_0^\ddagger < \Delta E_0 \))

depend on the extent of C-H bond breakage, \( k_H/k_D \) may vary.

\[ k_H/k_D = \exp \left\{ \frac{(\Delta E_0 - \Delta E_0^\ddagger)}{RT} \right\} \]

For C-H, \( k_H/k_D \) maximum value at room temp. \( \sim 7 \) for primary KIE

depend on the ext. of bond cleavage, \( 1 < k_H/k_D < 7 \)

Information provided by primary KIE:

1. \( k_H/k_D > 2 \) → strong evidence that the C-H bond is broken in T.S.
2. the magnitude of \( k_H/k_D \) provides qualitative indication of where the T.S. lies relative to S.M. or Product

\[ \begin{array}{ccc}
C - H \cdots A & C \cdots H \cdots A & C \cdots H - A \\
\text{symmetric} & \text{large} & \text{small}
\end{array} \]

\[ k_H/k_D \quad \text{small} \quad \text{large} \quad \text{small} \]
early transition state

\[ k_{H}/k_{D} \sim 1 \]

C-H (or C-D) bond is slightly broken in the T.S.

late transition state

\[ k_{H}/k_{D} \sim 1 \text{ (small)} \]

C-H (or C-D) is nearly fully broken away from S.M., but nearly fully from in product.

Symmetric T.S
C-H (or C-D) is half-broken \( \frac{k_{H}}{k_{D}} \) large

\[ \frac{k_{H}}{k_{D}} \sim 1 \text{ (small)} \]

[ Transition State Theory Description : ]

\[ \rightarrow \quad B \cdots H \cdots A \rightarrow \quad B \cdots H \cdots A \quad \text{symmetric stretching} \]

( reaction coordinate )

\[ \uparrow \quad \uparrow \quad \uparrow \quad \uparrow \quad \uparrow \quad \uparrow \quad \uparrow \quad \uparrow \]

\[ \rightarrow \quad B \cdots H \cdots A \rightarrow \quad B \cdots H \cdots A \quad \text{asymmetric stretching} \]

\[ \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \quad \downarrow \]

in plane bending out-of-plane bending

of low energy & cancel similar bending in S.M.

e.g. \[ \phi \text{CH}_2\text{CH}_2\text{-X} \overset{\text{EtO-}}{\text{EtOH, } 30^\circ} \rightarrow \phi \text{CH=CH}_2 \]

\[ X = \text{Br O}^{\text{Ts}} \text{SMe}_2 ^{\text{NMe}}_3 \]

\[ k_{H}/k_{D} = 7.11 \quad 5.67 \quad 5.07 \quad 2.98 \]

\[ \sim 7 \]

\[ \text{50% H-transfer} \]

for non-linear T.S. KIE is also smaller
usual range of Primary Kinetic Isotope Effects  5~8
Some KIE are much larger than expected maximum
Because oversimplifications :
1. C-H bending vibration (~48 if considered)
2. Tunneling of H will increase $k_H/k_D$

Tunneling Effect

by Classical mechanical Theory
the probability of finding $m$ in the other side is zero.

by Quantum mechanical Theory
There is finite probability on the other side of the barrier

Intra molecular KIE :

if $R \cdot = Cl$ \hspace{1cm} $k_H/k_D = 1.3$
$R \cdot = Br$ \hspace{1cm} $k_H/k_D = 4.6$ Transition State lies to the right (occurs later)
Secondary Isotope Effect

The effect of isotope substitution at a bond not broken in the transition state. → result from zero-point-energy difference due to change of force constant in a vibration in going from reactant to T.S. (α-, β- 2° KIE)

\[ \frac{k_H}{k_D} > 1 \]  (normal secondary isotope effect).

For \( sp^2 \rightarrow sp^3 \)

\[ \frac{k_H}{k_D} < 1 \approx \frac{1}{1.41} = 0.71 \]  (Inverse IE)
\( \alpha \) -isotope effect

\( \beta \) -secondary isotope effect: the isotope bond to a position next to reaction center

The hyperconjugation weakens \( \beta \) -H (or \( \beta \) -D) bond, thus a small ZPE contribution. \( \rightarrow \) faster for H- species (C-H > C-D)
Isotope effect on Acidity (Not Kinetic IE, but equilibrium IE)

\[
\begin{align*}
\text{C}_6\text{D}_5\text{OH} & \quad \rightarrow \quad \text{C}_6\text{D}_5\text{O}^- + \text{H}^+ & \text{Ka(H)/Ka(D)} = 1.12 \\
\text{C}_6\text{D}_5\text{COOH} & \quad \rightarrow \quad \text{C}_6\text{D}_5\text{C}^- + \text{H}^+ & 1.02 \\
\text{C}_6\text{D}_5\text{CD}_2\text{COOH} & \quad \rightarrow \quad \text{C}_6\text{D}_5\text{CD}_2\text{COO}^- + \text{H}^+ & 1.12 \\
\text{DCOOH} & \quad \rightarrow \quad \text{DCOO}^- + \text{H}^+ & 1.06 \\
\text{CD}_3\text{COOH} & \quad \rightarrow \quad \text{CD}_3\text{COO}^- + \text{H}^+ & 1.033
\end{align*}
\]

The C-D bond is shorter than C-H by 0.009Å, the electron-density is closer to C, equivalent to a e⁻-donating group. (+I effect, C-D > C-H)

Path A: nucleophilic addition
Path B: electron transfer followed by combination of radicals
\[k_H/k_D = 0.84\], implying rehybridization
Substituent Effect and Linear Free Energy Relationship

A substituent can influence a reaction rate, equilibrium or property via inductive, resonance, steric effect.

Resonance Effect: Polarization of charge density through $\pi$-bond formation (or $\pi$-system) in a structure

\[
\begin{align*}
\text{F} & \quad \text{F}^+ \\
\text{OMe} & \quad \text{OMe}^+ \\
\text{CN} & \quad \text{CN}^-
\end{align*}
\]

+ R: e-donating: halogen, OR, NR$_2$, alkyl
- R: e-withdrawing: -NO$_2$, -CN, -CO$_2$R, -C$_6$H$_5$

Inductive Effect: Due to polarization of a $\sigma$-bond, the bond dipole, transmit through bonds by successive polarization. Short range, electrostatic in nature

Field Effect: Through space electrostatic interaction

+ I: alky
- I: halogen, $^+\text{NR}_3$, $^+\text{SR}_2$, $-\text{CX}_3$
higher acidity for 2-fluoroethanol

![Diagram showing stabilization by inductive withdrawal through bond and through space field effect.]

**The importance of through space effect**

![Chemical structures showing the effect of different substituents on pKa values.]

For X on acidity on the two type cpd., Field effect outweighs distance.
Transmission of electronic properties through $\sigma$-framework?

Thus field effect seems to be important.

Stabilization

similar stabilization with or without $\sigma$ bond

Linear Free Energy Relationship

\[
\begin{align*}
\text{COOH} & \rightleftharpoons \text{COO}^- + H^+ & K_a_1 \\
\text{COOH} & \rightleftharpoons \text{COO}^- + H^+ & K_a_2 > K_a_1 \\
\text{COOCH}_3 + \text{OH}^- & \rightarrow \text{COO}^- + \text{CH}_3\text{OH} & k_1 \\
\text{COOCH}_3 + \text{OH}^- & \rightarrow \text{COO}^- + \text{CH}_3\text{OH} & k_2 > k_1
\end{align*}
\]

$\Delta \Delta G^\circ \propto \Delta \Delta G^\ddagger$

the free energy change of the rxn by the structure change

the free energy change of the T.S by the structure change

from $\Delta G \triangleq -RT\ln K$, $\Delta G^\ddagger = -RT\ln k$

\[
\log k = \rho \log K + A
\]

with no substituent $\log k_0 = \rho \log K_i^\circ + A$

\[
\log \frac{k}{k_0} = \rho \log \frac{K}{K_i^\circ}
\]

let \( \log \frac{K}{K_i^\circ} = \sigma \)

then $\log \frac{k}{k_0} = \rho \sigma \Rightarrow$ Hammet equation
\[ \sigma : \text{substituent constant} = \log \frac{K_i}{K_i^\circ} \]

A measure of the electronic effect of the substituent S at a particular position.

at 25°C in H₂O

\[ \rho : \text{reaction constant} \]

A measure of sensitivity of the reaction to the electronic effect of a substituent

\( \rho = 1 \) for ionization of benzoic acid

( the reference system )

\( \rho : + \) for reaction favored by e⁻-withdrawing

\( - \) for reaction favored by e⁻-donating

\[ \sigma : + \] for e⁻-withdrawing

\[ - \] for e⁻-donating

<table>
<thead>
<tr>
<th>Substituted Benzoic acid</th>
<th>( \sigma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-NH₂</td>
<td>-0.66</td>
</tr>
<tr>
<td>P-CH₃</td>
<td>-0.17</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
</tr>
<tr>
<td>P-Cl</td>
<td>0.23</td>
</tr>
<tr>
<td>P-CN</td>
<td>0.66</td>
</tr>
<tr>
<td>P-NO₂</td>
<td>0.78</td>
</tr>
</tbody>
</table>
For a particular rxn, plot rates v.s $\sigma$, if a linear curve is obtained, a linear free energy relationship exists.

\[
\text{e.g.} \quad \text{CHO} + \text{H}_2\text{NNHCONH}_2 \quad \rightarrow \quad \text{CH=NNHCONH}_2
\]

semi carbazide

\[
\rho = 0.91 \quad \text{means there is negative charge developed in the T.S.}
\]

at pH 1.75, the first step is rate-determining

\[
\rho = 0.91 \quad \rho = 0.91
\]

\[
\sigma
\]

\[
0.1 \quad 0.2 \quad 0.3 \quad 0.4 \quad 0.5 \quad 0.6 \quad 0.7 \quad 0.8
\]

\[
\text{XXX}
\]

decrease in $\rho$ reflect lower sensitivity not different charge formation

magnitude of $\sigma \rightarrow$ sensitivity to the substituent $\rightarrow$ extent of charge development? (not necessary)

\[
\text{e.g.} \quad \text{COOH} \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{COO}^- + \text{H}^+
\]

\[
\rho = 1.0
\]

\[
\text{COOH} \quad 40\% \text{EtOH-H}_2\text{O} \quad \rightarrow \quad \text{COO}^- + \text{H}^+
\]

\[
\rho = 1.71
\]

\[
\text{CH}_2\text{COOH} \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{CH}_2\text{COO}^- + \text{H}^+
\]

\[
\rho = 0.49
\]

\[
\text{CH}_2\text{CH}_2\text{COOH} \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{CH}_2\text{CH}_2\text{COO}^- + \text{H}^+
\]

\[
\rho = 0.212
\]
Inferring mechanism from Hammet $\rho$ value

$$\text{C}_\text{O} \text{CH}_3 + \text{OH}^- \rightarrow \text{C}_\text{O} \text{CH}_3$$

$\rho = 2.2$

typical $S_N2$ reaction has low $\rho$ values

e.g.

$$\text{CH}_2\text{Cl} + \text{OH}^- \rightarrow \text{H}_2\text{O} \rightarrow \text{CH}_2\text{Cl}$$

$\rho = -0.3$

> bond breaking

$$\text{CH}_2\text{Cl} + \text{I}^- \rightarrow \text{CH}_2\text{I}$$

$\rho = 0.8$

> bond formation

the large value of 2.2 for ester hydrolysis rules out a $S_N2$ mechanism

However

$$\text{EtOHO}^- + \text{O} \rightarrow \text{EtO} \text{CH}_2\text{CH}_2\text{OH}$$

$\rho = -0.95$

$$\text{S} \text{O}^- + \text{CH}_3\text{CH}_2\text{I} \rightarrow \text{S} \text{O} \text{CH}_2\text{CH}_3$$

$\rho = -1.0$

$$\text{S} \text{NH}_2 + \text{C} \text{O} \text{Cl} \rightarrow \text{S} \text{C} \text{NH}$$

$\rho = -2.8$
Nonlinear Hammet Correlation

If not due to expt’l error, if not due to impurity, if not due to side reactions. → may due to change of mechanism or change of rate determining step.

\[
\begin{align*}
S-C-H + H_2NNHCNH_2 & \xrightarrow{k_1} S-C-HNHNNHCNH_2 \\
S & \xrightarrow{k_{-1}} S-CH=NNHCNH_2 + H_2O
\end{align*}
\]

Favored by e-withdrawing gps.

Favored by e-donating gps.

For neutral pH:

\[
\log K_{eq} (\log k_1/k_{-1})
\]

\[
\log k_{overall}
\]

\[
\log k_{dehyd}
\]

at Neutral pH, the observed rate is the resultant of two → insensitive to \( \sigma \)

at pH = 3.9

2nd step became r.d.s.

the first step is r.d.s.
**Substituent Constants**

$\sigma$: defined with respect to

\[ \begin{align*}
\text{Substituent} & \quad \sigma_p & \quad \sigma_m \\
\text{F} & \quad .06 & \quad .34 \\
\text{NMe}_3^+ & \quad .82 & \quad .88 \\
\text{NH}_2 & \quad -.66 & \quad -.16 \\
\text{COCH}_3 & \quad .50 & \quad .38 \\
\text{OCH}_3 & \quad -.27 & \quad .12
\end{align*} \]

\( \sigma_m > \sigma_p \) - the inductive effect (and field effect) are distance-dependent. The closer, the stronger.

\[ |\sigma_p| > |\sigma_m| \]

The newer interaction due to resonance, the stronger interaction. The resonance did not bring the stronger interaction.

\[ \sigma^+ \text{ defined with respect to} \]

\[ \begin{align*}
\text{direct resonance interaction with reaction center.} \\
\text{more sensitive for those can interact through resonance}
\end{align*} \]

\[ \text{correlate well with } \sigma \]
\( \sigma^- \): defined with respect to

\[
\begin{array}{c}
\text{S-} \quad \text{OH} \\
\text{S-} \quad \text{O}^- \\
\text{S-} \quad \text{O}
\end{array}
\]

Which sets of \( \sigma^- \)'s correlate better will depend on the nature of the reaction center.

**Yukawa-Tsuno equation**

\[
\log \frac{K}{K_0} = \rho \sigma + \rho r (\sigma^+ - \sigma^-)
\]

A term to correct for the additional contribution from resonance

depend on rxn, large \( r \rightarrow \) large resonance contribution

\( r \rightarrow 0 \), original Hammet eq.

**Swain-Lupton**

\[
\log \frac{k_x}{k_0} = f F + r R
\]

Field effect

(Polar)

for ortho-substituents, steric effect may involve.

\( \sigma^* \): a measure of polar effect of alkyl substituent in aliphatic system.

\[
\sigma^* = \frac{1}{2.48} \left[ (\log \frac{k_x}{k_0})_B - (\log \frac{k_x}{k_0})_A \right]
\]

**Taft equation**

\[
\log \frac{k_x}{k_0} = \rho^* \sigma^* - S E_S
\]

Steric substituent constant

\( E_S = \log \left( \frac{k}{k_0} \right)_A \)

Acid-hydrolysis of aliphatic ester \( \text{RCO}_2\text{R'} \), only related to steric effect