Linear Free Energy Relationships

**Idea:** understand new behavior by comparing it to old behavior

**Examples:**
- Hammett (electronic effects on rate)
- Bronsted (acidity on rate)
- Taft (sterics on rate)

**Definition:** a linear log-log correlation between the rate/equilibrium constants in one series of reactions with the rate/equilibrium constants in another series of reaction

\[
\Delta G_2 = m\Delta G_1 + b
\]

m = slope, the strength of the effect
b = intercept, the rate of the reference reaction

**In general:**
- rates (kinetics) are related to equilibria (thermodynamics)
- these correlations only hold within a series of closely related compounds
The linear correlation between \( \log K \) and \( \log k \) implies a linear correlation between the free energies:

\[
\log K = \frac{-\Delta G_0}{2.3RT}
\]

\[
\log k = \frac{-\Delta G^\ddagger}{2.3RT} + \log \left( \frac{k_B T}{h} \right)
\]

The second equation is the Eyring relation.
Hammett Equation

\[
\begin{align*}
\text{H} & \quad \text{OH} + \text{H}_2\text{O} \quad \stackrel{K}{\rightleftharpoons} \quad \text{H}_2\text{O} + \text{H}_3\text{O}^+ \\
\text{X} & \\
\text{H} & \quad \text{OCH}_3 + \text{NMe}_3 \quad \stackrel{k}{\rightleftharpoons} \quad \text{OCH}_3 + \text{NMe}_4^+ \\
\text{X} & \\
\end{align*}
\]

Why is there a correlation?

(1) The position of the ground state acid-base equilibrium is primarily determined by the stability of the benzoate anion.

(2) The rate of the hydrolysis reaction depends on the stability of the transition state. If nucleophilic attack is rate limiting, then the benzoate and the transition state are similar in structure. Therefore, substituents will have a similar effect on both.

(3) The correlation is commonly interpreted as a measure of electronic effects. (For a more detailed analysis of benzoic acid acidity, please see *J. Chem. Ed.* 1971 48 338.)
Hammett Equation

Traditionally, the Hammett LFER is written as:

$$\log \left( \frac{k_X}{k_H} \right) = \rho \sigma$$

$k_X$ – rate of reaction with substituent X

$k_H$ – rate of reaction with no substituent (hydrogen)

$\sigma$ – substituent constant, relative $pK_a$ of $X$-substituted benzoic acid vs. benzoic acid:

$$\sigma \equiv \log \frac{K_X}{K_H} = pK_a(\text{PhCO}_2\text{H}) - pK_a(X-\text{PhCO}_2\text{H})$$

$\rho$ – reaction constant, the slope of the correlation

*note*: capital letters $K$ represent equilibrium constants, lowercase letters $k$ are rates
Hammett Substituent Constants ($\sigma$)

\[
\sigma \equiv \log \frac{K_X}{K_H} = pK_a \left( \text{PhCO}_2\text{H} \right) - pK_a \left( X-\text{PhCO}_2\text{H} \right)
\]

<table>
<thead>
<tr>
<th>$X^-$</th>
<th>$\sigma_{\text{para}}$</th>
<th>$\sigma_{\text{meta}}$</th>
<th>positive = electron withdrawing</th>
<th>negative = electron donating</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$C(=O)O$-$</td>
<td>0.45</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$C(=O)$-$</td>
<td>0.50</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH$_2^-$</td>
<td>-0.66</td>
<td>-0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br$^-$</td>
<td>0.23</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-Bu$^-$</td>
<td>-0.20</td>
<td>-0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOC(=O)$-$</td>
<td>0.45</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>0.23</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC$^-$</td>
<td>0.66</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F$^-$</td>
<td>0.06</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H$^-$</td>
<td>0</td>
<td>0</td>
<td>(by definition)</td>
<td></td>
</tr>
<tr>
<td>HO$^-$</td>
<td>-0.37</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$O$-$</td>
<td>-0.27</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3^-$</td>
<td>-0.17</td>
<td>-0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO$_2^-$</td>
<td>0.78</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph$^-$</td>
<td>0.01</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF$_3^-$</td>
<td>0.54</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ortho not used because of steric effects
- meta is a measure of pure induction
- para is induction and resonance

OR groups are $e^-$ donating as para substituents, but $e^-$ withdrawing as meta substituents

Hansch, Leo, Taft  *Chem Rev* 1991 91 165
Hammett Reaction Constants

benzaldehyde + semicarbazide (pH 1.75):

\[
\log \left( \frac{k_X}{k_H} \right) = \rho \sigma
\]

- \(\rho\) measures the relative sensitivity of the reaction to electronic effects
- "relative" means transition vs. ground state

- \(|\rho| > 1\): more sensitive than benzoic acid dissociation
- \(|\rho| < 1\): less sensitive than benzoic acid dissociation
- \(\rho > 0\): electron withdrawing groups speed up the reaction (same direction as the benzoic acid dissociation)
- \(\rho < 0\): electron donating groups speed up the reaction
Some examples:

\[ X-C-\text{Cl} + \text{H}_2\text{O} \rightarrow X-C-\text{OH} + \text{HCl} \]

\[ r = -4.48 \]
(prototypical \( S_N1 \))

late transition state \( \rightarrow \) large \( \delta^+ \) on C

\[ X-C-\text{Cl} + \text{H}_2\text{O} \rightarrow X-C-\text{OH} + \text{HCl} \]

\[ r = -1.31 \]
(prototypical \( S_N2 \))

little positive charge build up in the transition state
\[
\begin{align*}
X-\text{OH} + H_2O & \rightleftharpoons X-\text{O}^- + H_3O^+ \\
\rho &= +2.26 \\
X-\text{CH}_2\text{NH}_2 + H_3O^+ & \rightleftharpoons X-\text{CH}_2\text{NH}_3^+ + H_2O \\
\rho &= -1.05 \\
X-\text{NH}_2 + H_3O^+ & \rightleftharpoons X-\text{NH}_3^+ + H_2O \\
\rho &= -3.19
\end{align*}
\]
Non-Linear Hammett Plots

**Concave down curvature** indicates a change in rate-determining step:

\[ \text{OHH}_X + n\text{-BuNH}_2 \rightleftharpoons \text{OHNH}_X \text{N} - \text{BuNH}_2 \text{O} \rightarrow \text{le9} \]

- **Left hand portion**
  - rds is addition, which is sped up by EWGs (slope is positive)

- **Right hand portion**
  - rds is elimination, which is sped up by EDGs (slope is negative)
Non-Linear Hammett Plots

**Concave up curvature** indicates a change in mechanism:

- reactions are performed in 99.9% $\text{H}_2\text{SO}_4$

- methyl ester hydrolysis is accelerated by electron donating groups

- EDGs assist the departure of methanol and stabilize the acylium ion

- this corresponds to an $A_{Ac1}$ mechanism (unimolecular acyl-carbon cleavage in acid)
Non-Linear Hammett Plots

**Concave up curvature** indicates a change in mechanism:

- with ethyl esters and electron withdrawing groups, a new mechanism becomes available

- this mechanism is accelerated by electron withdrawing groups

- EWGs assist the departure of benzoic acid

- this corresponds to an $A_{\text{AL}}1$ mechanism (alkyl-oxygen cleavage)

- ethyl cation is metastable in superacid media
Non-Linear Hammett Plots

Curved plots can indicate a gradual change in mechanism:

\[
\text{PhH, 100 °C} \quad \text{acetone, 20 °C}
\]

\[
\begin{array}{c}
\text{Cl} \quad \text{NPhH, 100 °C} \quad \text{Br} \\
\text{X} \quad \text{X} \quad \text{X} \\
\end{array}
\]

\[
\begin{array}{c}
\text{S_N1-like, large slope} \\
\text{S_N2-like, small slope} \\
\end{array}
\]

Meta and para substituents are on separate lines because para substituents are able to stabilize positive charge through resonance as well as induction.
Changing the Reference

In some cases, the correlation with Hammett constants may be poor. For example, substituted phenol and benzoic acid $pK_a$ values are not well correlated for strongly electron donating or withdrawing substituents:
Changing the Reference

Benzoate is stabilized by resonance to a far smaller degree than is phenolate:

Which reference is best will depend on the reaction. We can define a modified substituent constant using the phenol reference:

\[
\log\left(\frac{k_X}{k_H}\right) = \rho^{-}\sigma^{-}
\]

\[
\sigma^{-} \equiv \log\frac{K_X}{K_H} = pK_a(\text{PhOH}) - pK_a(\text{X-PhOH})
\]
Changing the Reference

For example, the hydrolysis of phosphate dianions involves expulsion of phenolate:

\[
\begin{align*}
\text{PO}_3^{2-} &\rightarrow \text{PO}_2^- + \text{X}^+ \\
\end{align*}
\]

The slope is 2.6 and the rate is highly correlated with leaving group pKa, suggesting bond-breaking is highly advanced in the transition state.

Kirby JACS 1967 89 415
Changing the Reference

For reactions involving resonance-stabilized carbocations, the canonical reference is the solvolysis rate of cumyl chlorides:

Brown showed that this is a much better reference for many electrophilic aromatic substitution reactions. This is benzhydryl chloride ethanolation:

Changing the Reference

In the solvolysis of benzyl tosylates in aqueous acetone, Brown proposes a change in mechanism from $S_{N1}$ (electron donating) to $S_{N2}$ (electron withdrawing):

The clear break in this plot was used to argue that $S_{N1}$ and $S_{N2}$ are in fact, distinct mechanisms, rather than extremes along a continuum.

Brown and Okamoto *JACS* 1957 79 1913, *JOC* 1957 22 486
Steric Effects: Taft Equation

In ortho-substituted or aliphatic systems, no single reference, however chosen, is sufficient because of steric effects. Following a suggestion by Ingold, Taft attempted to separate electronic and steric effects by studying ester hydrolysis:

**basic conditions**

\[
\begin{align*}
\text{neutral} & \quad \text{anionic} & \quad \text{acidic conditions} \\
R_{O}O_{\cdot}R' & \quad R_{O}O_{\cdot}R' & \quad R_{O}O_{\cdot}R'
\end{align*}
\]

\[
\begin{align*}
\text{R}_{O}O_{\cdot}R' & \quad \text{H}_{2}O & \quad \text{H}_{2}O \\
\text{cationic} & \quad \text{cationic} & \quad \text{cationic}
\end{align*}
\]

Taft proposed that under basic conditions, the substrate becomes anionic, so the rate is affected by both steric and electronic effects.

add reference to review by Shorter (1970)
Steric Effects: Taft Equation

Under acidic conditions, the substrate remains cationic, so presumably the reaction rate is dominated by steric effects.

*acidic conditions*

\[
\begin{align*}
\text{H}^+ & \text{O}^- \quad \text{R} \quad \text{O}^\cdot \quad \text{R}' \\
\text{H}_2\text{O} & \text{cationic} \quad \text{cationic} \\
\text{OH}^- & \text{R} \quad \text{OH} \quad \text{R}^\cdot \\
\end{align*}
\]

This is supported by the Hammett rho values for benzoate ester hydrolysis:

basic conditions: +2.2 to +2.8, acidic conditions: −0.2 to +0.5

Taft defined a new polar substituent constant:

\[
\sigma^* \equiv \left[ \log \left( \frac{k}{k_0} \right)_B - \log \left( \frac{k}{k_0} \right)_A \right] / 2.48
\]

- \(k\) is the rate for the hydrolysis of \(\text{R-CO}_2\text{R}'\)
- \(k_0\) is the rate for the hydrolysis of \(\text{Me-CO}_2\text{R}'\)
- B and A mean basic and acidic conditions, respectively
- 2.48 roughly equalizes the magnitude with that of the Hammett constants
Steric Effects: Taft Equation

$$
\sigma^* \equiv \left[ \log \left( \frac{k}{k_0} \right)_B - \log \left( \frac{k}{k_0} \right)_A \right] / 2.48
$$

The ratios normalize the effect against a standard acetate.

The first term contains steric and electronic effects, while the second term contains only steric effects. This means the result should only contain electronic effects.

Taft called the second term the steric substituent constant:

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

Thus, the Taft–Ingold LFER is:

$$
\log \left( \frac{k}{k_0} \right) = \rho^* \sigma^* + \delta E_S
$$

where each reaction now has two sensitivity factors, one for electronic and one for sterics.
Steric Effects: Charton and Sterimol Values

Charton showed the Taft steric constants are highly correlated to van der Waals radii, indicating that they are a true measure of steric effects. Charton modified the Taft constants so that they could be used with van der Waals parameters directly.

The Verloop Sterimol parameters take this a step further by considering the fact that substituents are non-spherical.

<table>
<thead>
<tr>
<th>substituent</th>
<th>$-E_s$ (Taft)</th>
<th>$v$ (Charton)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>-1.24</td>
<td>0</td>
</tr>
<tr>
<td>Me</td>
<td>0</td>
<td>0.52</td>
</tr>
<tr>
<td>Et</td>
<td>0.07</td>
<td>0.56</td>
</tr>
<tr>
<td>$^3$Pr</td>
<td>0.36</td>
<td>0.68</td>
</tr>
<tr>
<td>$^3$Bu</td>
<td>0.39</td>
<td>0.68</td>
</tr>
<tr>
<td>$^1$Pr</td>
<td>0.47</td>
<td>0.76</td>
</tr>
<tr>
<td>$^5$C$<em>8$H$</em>{11}$</td>
<td>0.79</td>
<td>0.87</td>
</tr>
<tr>
<td>PhCH$_2$</td>
<td>0.38</td>
<td>0.7</td>
</tr>
<tr>
<td>$^3$Bu</td>
<td>1.54</td>
<td>1.24</td>
</tr>
<tr>
<td>1-adamantyl</td>
<td></td>
<td>1.33</td>
</tr>
<tr>
<td>Ph</td>
<td>2.54</td>
<td>0.57 and 1.66</td>
</tr>
<tr>
<td>CH($^3$Pr)$_2$</td>
<td></td>
<td>1.54</td>
</tr>
<tr>
<td>CH($^3$Pr)$_2$</td>
<td></td>
<td>1.70</td>
</tr>
<tr>
<td>CEt$_3$</td>
<td></td>
<td>2.38</td>
</tr>
</tbody>
</table>
Sigman has shown that the enantioselectivity of NHK allylations can be studied with Charton parameters.

The breaks in the graph might suggest a change in the catalyst structure or mechanism. Sigman instead proposes that the Charton parameters are flawed because they consider the minimum radius of rotation about the primary substituent axis. Effectively, substituents are considered spherical!

The Charton values of these groups is the same:

\[ n-\text{Pr}, \, n-\text{Bu}, \, i-\text{Bu}: \, \nu = 0.68 \]
Applications to Asymmetric Catalysis

Re-analysis of the same NHK allylation data with the Sterimol parameters shows a much better fit. Other systems have been analyzed with good results.
Synergistic Electronic and Steric Effects

Regardless of the size of X and Y, the oxazoline-proline catalysts are poorly selective:

This is simply a two-dimensional free energy relationship:

\[
\Delta \Delta G^\dagger = -1.87 + 1.34X + 3.03Y - 0.99Y^2 - 1.19XY + 0.62XY^2 - 0.73YX^2
\]

Note that this is a quadratic, rather than, linear function. This is called a response surface. The presence of linear and quadratic cross-terms indicates an interaction between X and Y.
Synergistic Electronic and Steric Effects

The quinoline-proline scaffold is much more selective. A similar response surface was fitted to the data:

$$\Delta\Delta G^\ddagger = -1.20 + 1.22E + 2.84S - 0.85S^2 - 3.79ES + 1.25ES^2$$

This equation describes the data very well:

Sigman Science 2011 333 1875, JACS 2013 130 2482
Electronic and steric factors interact strongly. Electron poor ligands are poorly sensitive to stercics, while electron rich ligands are improved greatly by larger substituents. This argues for optimizing variables together, rather than one at a time.

Sigman Science 2011 333 1875, JACS 2013 130 2482