CEE 690K  
ENVIRONMENTAL REACTION KINETICS

Lecture #18

Prediction Methods:  QSAR, LFERs
Brezonik, pp.553-578

Kinetic Prediction Methods

- Types
  - Based on properties
    - QPAR: Quantitative Property-Activity Relationships
      - e.g., predicting bioaccumulation from $K_{ow}$
    - QPPR: Quantitative Property-Property Relationships
      - e.g., predicting $K_{ow}$ from chromatographic retention time ($k'$)
  - Based on structure
    - QSAR: Quantitative Structure-Activity Relationships
      - e.g., rate constants from ring substituents
    - QSPR: Quantitative Structure-Property Relationships
      - e.g., solubility from ionic radius
N-chloro-organics

- Reactions of chlorine with organic amines
  - Primary amines
    \[ R - NH_2 + HOCl \rightarrow R - NHCl + HOCl \rightarrow R - NCl_2 \]
  - Secondary amines
    \[ R_2 - NH + HOCl \rightarrow R_2 - NCl \]
- Inorganic chloramines can transfer their active chlorine in a similar fashion

LFERs

- Linear Free Energy Relationships
  - Theoretical Basis
    - Kinetics are correlated to thermodynamics for a given "type" of reaction
      \[ \frac{\Delta G^\circ}{\Delta G} \approx \text{const.} \]
  - Types
    - Bronsted: acid/base catalyzed reactions
    - Hammett: aromatic and alkene reactions
    - Taft: aliphatic reactions
    - Marcus: metal redox reactions
Hammett Equation

- Developed in 1930s to explain substituent effects on rates of meta and para substituted benzene compounds
- Reaction rates depend on substituent and position and effect is similar from one reaction to another

\[
\log \left( \frac{k_i}{k_o} \right) = \rho \log \left( \frac{K_i}{K_o} \right)
\]

- And \( \sigma_i = \log \left( \frac{K_i}{K_o} \right) \)
- So: \( \log \left( \frac{k_i}{k_o} \right) = \rho \sigma \)

Because the ion recombinations (benzoate + proton) are diffusion controlled, they all occur at about the same rate. This makes \( k_f \) directly proportional to \( K \), and results in \( \rho = 1.0 \) for benzoic acid dissociation.

Hammett Equation II

- Use
  - Meaning
    - Substituent constants are a measure of changes in electron density at the reactive site as a result of the presence of the substituent
      - As \( \sigma \) ↑, e⁻ density ↓
  - Source of Constants
    - Table 7-3A for substituent constants (\( \sigma \))
    - Table 7-3B for reaction constants (\( \rho \))
  - Effects of meta and para substituents are additive
  - Not applicable to ortho substituents due to large steric affects
  - Reactions which Hammett Equation applies
    - Hydrolysis
    - Aromatic substitution
    - Oxidation
    - Enzyme catalyzed reactions
Substituent Constants

Values
- from Table 7-3 (pg. 563)
- $\sigma > 0$
  - Electron withdrawing
- $\sigma < 0$
  - Electron donating

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma_m$</th>
<th>$\sigma_p$</th>
<th>$\sigma^*_m$</th>
<th>$\sigma^*_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{-NH}_2$</td>
<td>-0.66</td>
<td>-0.15</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>$\text{-OH}$</td>
<td>-0.26</td>
<td>0.08</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>$\text{-OCH}_3$</td>
<td>-0.16</td>
<td>-0.07</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>$\text{-CH}_3$</td>
<td>-0.01</td>
<td>0.06</td>
<td>-0.18</td>
<td>0.11</td>
</tr>
<tr>
<td>$\text{H}$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\text{F}$</td>
<td>0.08</td>
<td>0.35</td>
<td>0.35</td>
<td>0.52</td>
</tr>
<tr>
<td>$\text{Cl}$</td>
<td>0.23</td>
<td>0.37</td>
<td>0.11</td>
<td>0.47</td>
</tr>
<tr>
<td>$\text{Br}$</td>
<td>0.23</td>
<td>0.38</td>
<td>0.15</td>
<td>0.43</td>
</tr>
<tr>
<td>$\text{I}$</td>
<td>0.29</td>
<td>0.54</td>
<td>0.14</td>
<td>0.39</td>
</tr>
<tr>
<td>$\text{-CN}$</td>
<td>0.68</td>
<td>0.62</td>
<td>0.56</td>
<td>0.56</td>
</tr>
<tr>
<td>$\text{-CH}_3\text{SO}_2$</td>
<td>0.71</td>
<td>0.68</td>
<td>0.59</td>
<td>0.59</td>
</tr>
</tbody>
</table>

$\log \left( \frac{k_i}{k_o} \right) = \rho \sigma$

Reaction Constants

Values
- from Table 7-3 (pg. 563)

Meaning
- $\rho > 0$
  - Nucleophilic reaction
  - Hindered by high electron density
- $\rho < 0$
  - Electrophilic reaction
  - Accelerated by high electron density

<table>
<thead>
<tr>
<th>Reactions</th>
<th>$\rho$</th>
<th>$\rho^*$</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionization of benzoic acids</td>
<td>1.45</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\text{pH}$-catalyzed hydrolysis of ethylbenzoates</td>
<td>0.73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylation of benzoic acids</td>
<td>0.35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ionization of carboxylic acids</td>
<td>1.72</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkaline hydrolysis of $\text{CeI}_3\text{H}_2\text{O}_2\text{CR}^+\text{H}^+$ in water</td>
<td>0.79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Catalysis of nitramide decomposition by $\text{RCOO}^-$</td>
<td>-1.43</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acid hydrolysis of formic acid, $\text{CH}_2\text{O}$</td>
<td>-4.17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkaline hydrolysis of primary amides</td>
<td>1.60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ionization of orthobenzoic acids</td>
<td>1.79</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hydrolysis of bromoethanes</td>
<td>-11.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acid dissociation constants of aldehyde-esters</td>
<td>-1.25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkaline hydrolysis of diphthalate esters</td>
<td>4.69</td>
<td>1.53</td>
<td>-</td>
</tr>
<tr>
<td>Acid hydrolysis of orthobenzamides</td>
<td>-0.81</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acid hydrolysis of ethylbenzoates</td>
<td>1.32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkyl iodide reaction with alkylpyridines</td>
<td>2.03</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$\log \left( \frac{k_i}{k_o} \right) = \rho \sigma$
Hammett Relationship

- **Mono-substituted aromatics and HOCl**
  - Assumed $\sigma^\prime_\text{ortho} = \sigma^\prime_\text{para}$
  - second-order rate constants for the reaction of phenoxide ion, phenol, anisole and butylphenylether with HOCl versus the estimated Hammett constants of the substituents on benzene ($O^-$, OH, OCH3 and COC4H9) ($T$ 22–25 °C).

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

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Hammett Relationship

- **Poly-substituted aromatics and HOCl**
  - Cross-linear correlation between the second-order rate constants for the reactions of substituted phenoxide ions (PhO$^-$) and 1,3-dihydroxybenzene anions (BOH$^-$ and BO$_2$$^–$) with HOCl and the Hammett constants ($T$ 22–25 °C).
  - Assumed $\sigma^\prime_\text{ortho} = \sigma^\prime_\text{para}$

Large negative slope (-3.6 to -3.9) indicates electrophilic nature of this reaction.

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Calculation of sigma

Example of $\sum \sigma_{o,p,m}$ calculation for the corrected Hammett-type correlation

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Combined Hammett plot

Corrected Hammett-type correlation of log $k$ versus $\sum \sigma_{o,p,m}$ (determined from substituent position to the most probable chlorine reactive site) for the reaction of HOCl with phenoxide ions (PhO$^-$), 1,3-dihydroxybenzene anions (BOHO$^-$ and BO$_2$$^-$) [T 22–25 °C]

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Components

Composition

- Resonance (R)
- Field (F) or Inductive

Relationship

\[ \sigma_p \approx R + F \]
\[ \sigma_m \approx 0.3R + 1.1F - 0.03 \]

Other types of reactions

- Reactions involving carbonium ions or carbanion intermediates
  - Need to use \( \sigma^+ \) values (\( \sigma^+_p, \sigma^+_m \))
  - These were determined from hydrolysis of m- and p-substituted 2-chloro-phenylpropanones
Taft relationship

- Includes electronic and steric effects
- Applied mostly to aliphatics
  - Therefore resonance isn't important

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Taft Substituent Constants

- From Schwarzenbach et al., 1993
- Environmental Organic Chemistry

### Table 12.4 Examples of Taft Polar and Steric Substituent Constant for Aliphatic Systems

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma^*$</th>
<th>$E_s$</th>
<th>Substituent</th>
<th>$\sigma^*$</th>
<th>$E_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.89</td>
<td>1.24</td>
<td>-CH$_3$H$_2$</td>
<td>0.92</td>
<td>2.31</td>
</tr>
<tr>
<td>C$_2$H$_5$</td>
<td>-0.10</td>
<td>0.07</td>
<td>-CH$_2$F</td>
<td>1.30</td>
<td>0.34</td>
</tr>
<tr>
<td>n-C$_3$H$_7$</td>
<td>-0.12</td>
<td>0.36</td>
<td>-CH$_2$Cl</td>
<td>2.05</td>
<td>0.67</td>
</tr>
<tr>
<td>i-C$_3$H$_7$</td>
<td>-0.19</td>
<td>0.47</td>
<td>-CH$_2$Br</td>
<td>1.03</td>
<td>0.24</td>
</tr>
<tr>
<td>n-C$_4$H$_9$</td>
<td>-0.13</td>
<td>0.39</td>
<td>-CH$_3$C$_2$H$_4$</td>
<td>1.94</td>
<td>1.54</td>
</tr>
<tr>
<td>i-C$_4$H$_9$</td>
<td>-0.12</td>
<td>0.93</td>
<td>-CH$_3$C$_3$H$_7$</td>
<td>2.65</td>
<td>2.66</td>
</tr>
<tr>
<td>s-C$_5$H$_11$</td>
<td>-0.21</td>
<td>1.13</td>
<td>-CH$_3$C$_4$H$_10$</td>
<td>0.99</td>
<td>0.90</td>
</tr>
<tr>
<td>t-C$_5$H$_11$</td>
<td>0.30</td>
<td>1.54</td>
<td>CH$_3$Br</td>
<td>1.00</td>
<td>0.27</td>
</tr>
<tr>
<td>cyc-C$_5$H$_11$</td>
<td>-0.15</td>
<td>0.79</td>
<td>-CH$_2$Br$_2$</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td>CH$_2$CH$_2$-C$_6$H$_14$</td>
<td>-0.06</td>
<td>0.98</td>
<td>-CH$_2$Br$_3$</td>
<td>2.43</td>
<td></td>
</tr>
<tr>
<td>CH$_2$OHCH$_2$H$_2$</td>
<td>-0.54</td>
<td>1.83</td>
<td>-CH$_3$OC$_2$H$_5$</td>
<td>0.82</td>
<td>0.19</td>
</tr>
<tr>
<td>C$_6$H$_5$(phenyl)</td>
<td>0.66</td>
<td>2.55</td>
<td>-CH$_2$OC$_2$H$_5$</td>
<td>0.85</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Data taken from a more comprehensive data set given by Williams (1993).

Adding a steric term, it is postulated that:

$$\log \left( \frac{k}{k_0} \right) = \alpha \sigma^* + \delta E_s$$  \hspace{1cm} (12-29)
**Taft Plot**

- **Formation of organic chloramines**

Taft's correlation for chlorination of basic aliphatic amines at 25 °C. Full symbols (●) represent rate constant values used by Abia et al. (1998) and were used for calculation of correlation coefficients and Taft's plot equations; open circles (○) represent other rate constants reported in literature.

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

**Interpretation**

- **Reaction schemes proposed by Abia et al. (1998) for the chlorination of organic aliphatic amines:** (a) primary and secondary amines; (b) tertiary amines.

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Degradation of Organic Chloramines

<table>
<thead>
<tr>
<th>Parent Amine</th>
<th>$k_{obs}$ (s$^{-1}$)</th>
<th>$t_\frac{1}{2}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>1.3E-04</td>
<td>86</td>
</tr>
<tr>
<td>Glycine</td>
<td>1.4E-06</td>
<td>8400</td>
</tr>
<tr>
<td>Histidine</td>
<td>2.7E-04</td>
<td>43</td>
</tr>
<tr>
<td>Leucine</td>
<td>1.6E-04</td>
<td>72</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>2.2E-04</td>
<td>52</td>
</tr>
<tr>
<td>Serine</td>
<td>2.4E-04</td>
<td>49</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.5E-06</td>
<td>3300</td>
</tr>
<tr>
<td>Glycine N acetyl</td>
<td>6.0E-07</td>
<td>19000</td>
</tr>
<tr>
<td>Glycine ethyl ester</td>
<td>2.3E-04</td>
<td>50</td>
</tr>
<tr>
<td>Glycylglycine</td>
<td>1.0E-05</td>
<td>1100</td>
</tr>
<tr>
<td>Sarcosine</td>
<td>5.3E-05</td>
<td>210</td>
</tr>
</tbody>
</table>

QSPRs

Relationship between basicity and 2nd order rate constants for reaction of HOCl with N-compounds

Data Sources: Friend, 1956; Hussain et al., 1972; Isaac et al., 1983; Armesto et al., 1993; Armesto et al., 1994; Antelo et al., 1995; Abia et al., 1998
QPAR

- Rate constants vs nucleophilicity

Swain–Scott plot of log \( k \) for the reaction of HOCl with \( \mathrm{Cl}^- \), \( \mathrm{Br}^- \), \( \mathrm{I}^- \), \( \mathrm{SO}_3^- \), and \( \mathrm{CN}^- \) versus the nucleophilicity (\( N \)) of the anions at 25 °C. Adapted from Gerritsen and Margerum (1990).

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

QAAR

- Linear correlation between the log \( k_{\text{HOCl}} \) and log \( k_{\text{O}_3} \) for selected aromatic compounds (mostly phenols) for which electrophilic chlorine and ozone attack is expected.

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Figure 8-2. The rate constant, \( k \), for metal-catalyzed decarboxylation of malonic acid ([pyridinedicarboxylic acid] is correlated with \( K_{\text{eq}} \), the dissociation constant for the corresponding metal-organic complex — a linear free-energy relationship.

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

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Nonylphenol

- Non-ionic detergent metabolite

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Steroids

[Chemical structure of a steroidal compound]

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

triclosan

[Chemical structure of triclosan]

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
atenolol

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Nadolol

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Ciprofloxacin

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

Flumequine

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
□ Naproxen

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

□ Ketoprofen

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]
Trimethoprim

Sulfa--

From: Deborde & von Gunten, 2008 [Wat. Res. 42(1)13]

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Table 4.1. Mechanisms of Acid-Base Catalysis

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Rate expression</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Specific $H^+$</td>
<td>$S + H_2O$</td>
<td>$P = k[H_2S] + k[H_2S] + k[H_2S]$</td>
<td>For protolytic case, expression applies when $k_H \ll k_A$ or $k_H$ or $k_H$. For $H_2O$ formation, initial $H^-$ transfer is from $H_2O$ or $H_2S$ or $H_2S$.</td>
</tr>
<tr>
<td>II. General acid</td>
<td>$S + HA$</td>
<td>$P = k[H_A] + k[H_2S] + k[H_2S]$</td>
<td>Expression applies when $k_A \ll k_H$. Rate controlling step is formation of $S$. $P$ written for presence of several Bronsted acids in system.</td>
</tr>
<tr>
<td>III. General acid</td>
<td>$SH + HA$</td>
<td>$P = k[H_A] + k[H_2S] + k[H_A]$</td>
<td>Protonic mechanism yields general acid catalysis regardless of relative sizes of $k_A$ and $k_H$.</td>
</tr>
<tr>
<td>IV. Specific $OH$</td>
<td>$HS + B$</td>
<td>$P = k[H_A] + k[H_2S] + k[H_2S]$</td>
<td>For protolytic case, expression applies when $k_A \ll k_H$. Regardless of nature of proton acceptor in first step.</td>
</tr>
<tr>
<td>V. General base</td>
<td>$HS + H_2O$</td>
<td>$P = k[H_A] + k[H_2S] + k[H_A]$</td>
<td>Expression applies when $k_B \ll k_H$. Rate controlling step is formation of $S$. $P$ written for presence of several Bronsted bases.</td>
</tr>
<tr>
<td>VI. General base</td>
<td>$HS + B$</td>
<td>$P = k[H_A] + k[H_2S] + k[H_A]$</td>
<td>Protolytic case yields general base catalysis regardless of relative sizes of $k_A$ and $k_B$.</td>
</tr>
</tbody>
</table>

Mechanisms 3

- Metal ion assisted hydrolysis of a methyl imidazolide

- Ester hydrolysis by metal ion stabilization of transition state

- 2-oxo-2-methyl hydrogen phosphate

Mechanisms 4

- Cyst(e) assisted hydrolysis of paracetamol

- Deamination of coxalidase

- Metal ion catalyzed hydrolysis of ATP
☐ To next lecture