Outline: Isotope effects

- see section 8.1 of A&D
  - experimental approach
  - primary isotope effect
  - secondary isotope effect
  - equilibrium isotope effect
  - solvent isotope effect
  - heavy atom isotope effects
Measurement of an isotope effect

- performed to determine if a bond changes in a certain way during the rate-limiting step
- expressed as a ratio whose numerator is the rate constant measured for the naturally abundant isotope and the denominator is the rate constant measured for the varied isotope
  - e.g. $k_H/k_D$

Types of isotope effects

- **kinetic isotope effects** (kie): result from a change in the rate constant of a reaction:
  - **normal** effect: ratio > 1
  - **inverse** effect: ratio < 1
  - **primary** isotope effect: when the isotopically substituted bond is cleaved during the rate-limiting step
  - **secondary** isotope effect: attributable to a change of hybridation state, not cleavage of bonds

- **equilibrium** isotope effects: result from displacement of an equilibrium
Origin of isotope effects

- the origin of all isotope effects is a difference in the frequency of vibrational modes of a substituted molecule with respect to an unsubstituted molecule.

- it is these vibrational modes that principally affect the shape of the potential energy well on an energy surface.

Zero point energy

- zero point energy (ZPE) is the energy level of the vibrational ground state for most molecules at ambient temperature.

- the vibrational frequencies of C-D bonds are lower than those of C-H bonds, due to a the mass difference.
  - therefore, a C-D bond is stronger and more difficult to cleave.
Primary isotope effects

- in general, bonds involving heavier isotopes are more stable and more difficult to break

- the cleavage of a C-D bond can be several fold slower than the cleavage of a C-H bond

- the degree of cleavage of the bond at the transition state is given by the ratio:

\[
\frac{k_H}{k_D}
\]

Values of primary isotope effects

- the magnitude depends on the relative mass difference between the two isotopes
  - e.g. H vs D, $^{12}$C vs $^{13}$C, $^{14}$N vs $^{15}$N, etc

- maximum normal values at 25 °C :
  - H vs D : 6.4 (typically 2-7)
  - H vs T : 13
  - $^{12}$C vs $^{13}$C : 1.04
  - $^{14}$N vs $^{15}$N : 1.03

- the value observed experimentally is related to the degree and the linearity of cleavage realised at the TS of the rds
  - 50% transfer, at 180°, gives the maximum effect
**Energy surfaces and isotope effects**

- a transition state is found at the *col* of an energy surface
- the *shape* of the col is determined by the *potential energy wells*
  - these, in turn, are determined by the *vibrational states*

**Differences of ZPE**

- the magnitude of a primary isotope effect is related to the difference in activation energy of the two reactants
  - this difference is based on the relative difference of the ZPEs of the reactants and the activated complexes:

\[
\Delta \Delta G^\ddagger_{\text{CH/CD}} = \Delta ZPE_{\text{reactant}} - \Delta ZPE_{\text{TS}}
\]
**Vibrational modes**

- one particular vibrational mode determines the reaction coordinate for the transfer of a proton:

```
A   H   B
```

- whereas other vibrational modes have little to do with the isotope effect:

```
A   H   B
```

- and one mode is characteristic of the activated complex:

```
A   H   B
```

**Exothermicity and endothermicity**

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an exothermic equilibrium, the transition state resembles the reactant, A-H
  - little cleavage is achieved at the TS, so little difference of $\Delta G^\ddagger$

[Diagram of potential energy vs. reaction coordinate showing $\Delta G^\ddagger_{TS}$, $\Delta G^\ddagger_{C-H}$, $\Delta G^\ddagger_{C-D}$, $\Delta ZPE_{reactant}$, and $\Delta ZPE_{TS}$]
Exothermicity and endothermicity

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an exothermic equilibrium, the transition state resembles the product, B-H
  - B-H almost completely formed, little difference in ΔG‡

Exothermicity and endothermicity

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an isothermal equilibrium, the transition state resembles the reactant as little as it resembles the product
  - little difference in ZPE_TS, so large ΔΔG_C/HCD

Symmetric stretching does not involve movement of H/D, so little ΔZPE at TS

Potential energy

ΔG_C-D

ΔZPE_TS

ΔG_C-H

ΔZPE_reactant

Rxn. co-ord.
Non-linear transition states

• for non-linear proton transfers, the bending vibrational modes are more important and even symmetrical stretching implies movement of H/D:

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

• therefore, there will be as much $\Delta ZPE$ at the TS as in the reactant, and little $\Delta \Delta G^\ddagger_{\text{CH/CD}}$

Secondary isotope effects

• result from the cleavage of bonds *adjacent* to the substituted atoms
• caused by a change in *hybridation* of the atom bearing the isotope, rather than the cleavage of its bond
  – the change of hybridation of carbon from $sp^3$ to $sp^2$ is 14 % slower for every deuterium it bears, compared to hydrogen
Vibrations and 2° isotope effects

- the most important vibrational mode is the out of plane bending:

\[ sp^3 \quad \text{v.s.} \quad sp^2 \]

- there is less steric hindrance for out of plane bending on a \( sp^2 \) carbon

- this vibrational mode is therefore subject to a secondary isotope effect

Change of hybridation

- a change of hybridation from \( sp^3 \) to \( sp^2 \) manifests itself as a normal secondary isotope effect:
**Change of hybridation**

- a change of hybridation from $sp^2$ to $sp^3$ manifests itself as an *inverse* secondary isotope effect:

$$
\Delta G^\circ_{C-H} < \Delta G^\circ_{C-D}; \text{ reactants favoured more for deuterated compound}
$$

**Equilibrium isotope effects**

- an equilibrium involving a change of hybridation or bond strength can show a secondary isotope effect, depending on differences in $ZPE$:
Equilibrium isotope effects

• an equilibrium involving a change of hybridation or bond strength can show a secondary isotope effect, depending on differences in $ZPE$:

\[
\Delta G^\circ_{C-H} > \Delta G^\circ_{C-D}; \quad \text{products favoured more for deuterated compound}
\]

Solvent isotope effects

• measured by comparing the rate of a reaction in $H_2O$ with that of the same reaction in $D_2O$
• result from proton transfers between electronegative atoms that accompany the formation and/or cleavage of bonds at the rds
  – especially if a water molecule is involved in the mechanism!
  – also include primary isotope effects of molecules that exchange protons
**Fractionation factors**

- the exchange of protons/deuterons can be subject to an equilibrium isotope effect
  - often observed when donor and acceptor atoms are different
  - e.g. N-H vs O-H
- a **fractionation factor**, \( \phi \), is measured to determine which atom prefers the H or D:
  - consider the solvent exchange equilibrium:
    \[
    X^\text{H}_i + S^\text{D}_j \rightleftharpoons X^\text{D}_j + S^\text{H}_i
    \]
    \[
    K_{eq} = \phi = \frac{[S^\text{D}_j X^\text{H}_i]}{[S^\text{H}_i X^\text{D}_j]} = \frac{[X^\text{D}_j]}{[X^\text{H}_i]} \]
    for \( \phi > 1 \), D prefers X
    for \( \phi < 1 \), D prefers solvent

**Values of \( \phi \)**

<table>
<thead>
<tr>
<th>Bond</th>
<th>( \phi )</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO-L</td>
<td>1.0</td>
</tr>
<tr>
<td>LO^-</td>
<td>0.5</td>
</tr>
<tr>
<td>RO-L_2^+</td>
<td>0.69</td>
</tr>
<tr>
<td>R_2C-L</td>
<td>0.69</td>
</tr>
<tr>
<td>R_2N-L</td>
<td>0.92</td>
</tr>
<tr>
<td>R_3N-L^-</td>
<td>0.97</td>
</tr>
<tr>
<td>RS-L</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- note:
  - L = H or D
  - typically, alcohols do not have a preference for H or D
  - however, bonds with C, N and S prefer H

- fractionation factors can be used to predict solvent isotope effects...

...either equilibrium:

\[
\frac{K_{\text{H}_2\text{O}}}{K_{\text{D}_2\text{O}}} = \prod_{i} \frac{\phi_{\text{prod}}^{\text{H}_2\text{O}}}{\phi_{\text{prod}}^{\text{D}_2\text{O}}}
\]

or kinetic:

\[
\frac{k_{\text{D}_2\text{O}}}{k_{\text{H}_2\text{O}}} = \prod_{i} \frac{\phi_{\text{react}}^{\text{H}_2\text{O}}}{\phi_{\text{react}}^{\text{D}_2\text{O}}}
\]
Proton inventory

- if a rate constant is measured as a function of the molar fraction \( n \) of \( \text{D}_2\text{O} \) in \( \text{H}_2\text{O} \), the number of protons "in flight" at the TS can be determined
  - i.e.:
    \[
    k_n = k_{\text{H}_2\text{O}}(1 - n) + k_{\text{D}_2\text{O}}(n) = k_{\text{D}_2\text{O}}(1 - n) + \phi k_{\text{H}_2\text{O}}(n) = k_{\text{H}_2\text{O}}(1 - n + n \phi)
    \]

SO
\[
\frac{k_n}{k_{\text{H}_2\text{O}}} = \prod_{i}^{'} (1 - n + n \phi_i^{'} \phi_i) \quad \text{often } \phi = 1, \text{ for N-L and O-L}
\]

therefore
\[
\frac{k_n}{k_{\text{H}_2\text{O}}} = (1 - n + n \phi_1') (1 - n + n \phi_2') (1 - n + n \phi_3') ...
\]

where each \( \phi \) represents a fractionation factor for a proton in flight at the TS

Proton inventory

- the plot of \( k_n/k_{\text{H}_2\text{O}} \) vs \( n \) reveals the number of protons in flight
  - i.e., 1 = linear, 2 = quadratic, 3 = cubic
Heavy atom isotope effects

- typically very small (little relative mass difference) and difficult to measure
  - often, one measures, by NMR or MS, the proportion of an isotope in the product or in remaining reactant
  - e.g. $^{12}\text{C}/^{13}\text{C}$, $^{15}\text{N}/^{14}\text{N}$, $^{35}\text{Cl}/^{37}\text{Cl}$, etc

\[
\text{N}=\text{C}^- + \text{Cl}^+ \xrightarrow{\text{TS}} \text{N}=\text{C}^- + \text{Cl}^- + \frac{k_{\text{Cl}}}{k_{\text{Cl}}} = 1.0057
\]

Exercise #1: KIE of elimination

- KIEs were measured for the following elimination reaction:

\[
\text{EtO}^- + \text{EtN}^+ \xrightarrow{\text{ET}} \text{EtN}^+ + \text{Et}^- \quad (\text{TS1 or TS2})
\]

\[
\text{EtO}^- + \text{EtN}^+ \xrightarrow{\text{ET}} \text{EtN}^+ + \text{Et}^- \quad (\text{TS2 or TS3})
\]

- Which TS is most consistent with these data?
Exercice #2: KIE of elimination

- KIE was measured for the following elimination reaction:

\[
\frac{k_H}{k_D} = 1.1
\]

(too small for TS1 or TS2)

- Which TS is most consistent with these data?

Outline: Origins of substituent effects

- see section 8.2 of A&D
  - field / dipole effects
  - inductive effects
  - resonance effects
  - polarisability effects
  - steric effects
  - solvation effects
Substituent effects

• variation of the reactivity of a molecule upon variation of a substituent group, normally remote from the site of reactivity

• provide information regarding the activated complex of the rate-limiting TS

• allow a mechanism to be elucidated in detail
  – HOWEVER, caution is required, considering this approach involves the study of many different molecules

Linear Free Energy Relationships (LFERs)

• every characteristic of a reactant that stabilises a TS (and thereby favours formation of the activated complex) of the rls will result in the acceleration of the reaction
  – especially the delocalisation of charge (+ve or -ve) developed at the TS of the rls

• these correlations can be quantified by using different scales based on the electronic or steric nature of the reactants

• these relationships are often linear and referred to as Linear Free Energy Relationships, LFERs
A useful approximation

- quantity of free energy necessary to change $K$ by one order of magnitude:

\[ \Delta G = -RT \ln K \]
\[ \Delta G = -2.303 \times RT \log K \]
\[ \Delta G = 2.303 \times RT \times pK \]
\[ \Delta G = 1.4 \text{kcal/mol} \times pK \text{ (at 298 K)} \]

- this is equally valid for $\Delta G_{\text{rxn}} (K_{\text{eq}})$ as for $\Delta G^\ddagger (K^\ddagger, k_{\text{obs}})$

Field effects

- the variation of a substituent can change the magnitude or even the direction of a dipole moment

- a field effect results from the effect of this change, transmitted through space, on the site of reactivity

- weaker than an inductive effect
- much weaker than a resonance effect
**Inductive effect**

- the electron donating or withdrawing ability of a given substituent, on the site of reactivity
- depends on the electronegativity of the substituent

![Inductive effect diagram](image)

\[ R = pK_a \]

- transmitted via the electron density of connecting $\sigma$ bonds
- decreases over distance

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>4.76</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>4.87</td>
</tr>
<tr>
<td>Br</td>
<td>2.90</td>
</tr>
<tr>
<td>Cl</td>
<td>2.86</td>
</tr>
<tr>
<td>F</td>
<td>2.59</td>
</tr>
</tbody>
</table>

**Resonance effect**

- ability of a substituent to withdraw or donate electron density through $\pi$ bonds
- important model for explanation of delocalisation of electron density in conjugated systems

![Resonance effect diagram](image)
Polarisability effect

- the ability of a cloud of electron density to deform can affect its reactivity

- a centre that strongly retains its electron density is said to be “hard” whereas a centre whose electron density is more diffuse is said to be “soft”
  - e.g. a thiolate (RS-) of comparable basicity to an alkoxide (R'O-) is nevertheless more nucleophilic AND a better leaving group, owing to its greater polarisability

Nucleophilicity

- nucleophilic substitution on a carbonyl or on a phosphate ester (“hard” centres) typically leads to formation of an intermediate
  - TS involves bond formation
  - rate depends simply on the strength (basicity) of the (hard) nucleophile

- nucleophilic substitution on a saturated carbon (a “soft” centre) does not involve an intermediate
  - rather, there are five bonds around the carbon at the TS
  - large, polarisable (soft) nucleophiles react more quickly
**Nucleofugality**

- the ease of expulsion of a leaving group (its *nucleofugality*) depends strongly on its electronic nature, affected by its protonation state and its basicity.

- weak bases (whose conjugate acids have $pK_a$ values below $\sim 8.0$) are typically very easily expelled.

---

**Steric effects**

- may strongly affect the probability, and therefore the rate, of a given reaction.

- voluminous substituents may prevent a certain angle of a collision, rendering it non-productive.

- note that even if steric effects are often treated separately from electronic effects, steric hindrance itself is also the result of the repulsion between clouds of *electron* density.
**Solvation effects**

- a change of solvent may affect the reactivity of a reactant, depending on the nature of this interaction
  - may involve any of the effects described above
  - e.g. change of relative nucleophilicity:
    - in aprotic solvents: \( F^- > Cl^- > Br^- > I^- \)
    - in protic solvents: \( I^- > Br^- > Cl^- > F^- \)

**Outline: Hammett plots**

- see section 8.3 of A&D
  - substituent parameter, \( \sigma \)
  - reaction constant, \( \rho \)
  - elucidation of mechanisms
  - deviations from linearity
  - other substituent parameters
Hammett

- **Louis Hammett** (1894-1987)
  - American physical chemist (Columbia)
  - studied the correlation of structure and function
  - credited with inventing the expression “physical organic chemistry”
  - laureate of awards from the National Academy of Science, two Norris Awards, Priestley Medal

Hammett Relation

- Hammett noted that the acidity constants of substituted benzoic acids varied according to the ability of the substituent to donate or withdraw electron density
  - he measured the empirical value corresponding to this capacity (substituent constant, $\sigma$)
    \[
    (pK_a)_X = (pK_a)_H - \sigma_X
    \]
- the rate constants of other reactions may be affected in the same way as the acidity reaction
  - a second parameter can therefore be used for each reaction (reaction constant, $\rho$)
    \[
    \log k_X = \log k_H + \rho \sigma_X
    \]
    \[
    \log \left( \frac{k_X}{k_H} \right) = \rho \sigma_X
    \]
Substituent constants, $\sigma^0$

- Constants averaged over several different reactions give a better correlation than those originally observed by Hammett.

- These constants can be determined even more distinctly for meta vs para substituents.
  - For certain substituents, these values may vary significantly.
    - E.g., for NO$_2$, $\sigma^0_m = 0.71$, whereas $\sigma^0_p = 0.81$.
    - For F, $\sigma^0_m = 0.34$, whereas $\sigma^0_p = 0.15$.
    - For OMe, $\sigma^0_m = 0.1$, whereas $\sigma^0_p = -0.12$.

Table of substituent constants

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma^0_m$</th>
<th>$\sigma^0_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe$_2$</td>
<td>-0.10</td>
<td>-0.32</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>-0.09</td>
<td>-0.30</td>
</tr>
<tr>
<td>OH</td>
<td>0.02</td>
<td>-0.22</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>0.1</td>
<td>-0.12</td>
</tr>
<tr>
<td>CH$_4$</td>
<td>-0.06</td>
<td>-0.14</td>
</tr>
<tr>
<td>H</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ph</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>F</td>
<td>0.34</td>
<td>0.15</td>
</tr>
<tr>
<td>Br</td>
<td>0.37</td>
<td>0.26</td>
</tr>
<tr>
<td>I</td>
<td>0.34</td>
<td>0.28</td>
</tr>
<tr>
<td>Cl</td>
<td>0.37</td>
<td>0.34</td>
</tr>
<tr>
<td>OCOCH$_3$</td>
<td>0.39</td>
<td>0.31</td>
</tr>
<tr>
<td>CO$_2$R</td>
<td>0.35</td>
<td>0.44</td>
</tr>
<tr>
<td>COCH$_3$</td>
<td>0.36</td>
<td>0.47</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>0.46</td>
<td>0.53</td>
</tr>
<tr>
<td>CN</td>
<td>0.62</td>
<td>0.71</td>
</tr>
<tr>
<td>SO$_2$CH$_3$</td>
<td>0.64</td>
<td>0.73</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>0.71</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Note: $\sigma^0_m$ and $\sigma^0_p$ represent the substituent constants for meta and para positions, respectively.

By definition, the constants for H, Ph, and OMe are set to 0 by definition.
**σ\textsubscript{meta} VS σ\textsubscript{para}**

- from this table we note that σ\textsubscript{para} > σ\textsubscript{meta} for several substituents
  - this tendency is especially pronounced for oxygenated substituents such as OH and OR
- in the *para* position, substituents can have very strong resonance effects
  - for oxygenated substituents these resonance effects are often in *competition* with inductive effects:

  \[
  \sigma_{\text{para}} < 0; \text{donator; resonance effect predominates}
  \]
  \[
  \sigma_{\text{meta}} > 0; \text{withdrawer; inductive effect predominates}
  \]

**Reaction constant, ρ**

- measure of the sensitivity of a given reaction to electronic perturbation, on passing from reactants to the TS of the rls
  - ρ = 1 for the ionisation of benzoic acid, by definition
  - ρ > 0 for reactions accelerated by electron withdrawing groups
    - increase of negative charge at TS
  - ρ < 0 for reactions accelerated by electron donating groups
    - increase of positive charge at TS
**Hammett: aryl acetate hydrolysis**

\[
\text{HO}^- + \text{H}_2\text{C} = \text{OAr} \rightarrow \text{H}_2\text{C} = \text{OH} + \text{OAr}^-
\]

Leaving groups

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

\[\sigma\]

Graphique de Hammett

Groupes partants

Pente \(\rho = 0.8\)

\([-0.4, -0.2, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4]\)

\([-0.4, -0.2, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4]\)

- \(\delta^-\)
- \(\delta^+\)

Resembles reactants more \((\rho = 0.8, \text{not } \sim 2)\)

**Hammett: ethyl benzoate hydrolysis**

\[
\text{HO}^- + \text{X} = \text{COEt} \rightarrow \text{X} = \text{COH} + \text{EtOH}
\]

Electrophile

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

\[\sigma\]

Graphique de Hammett

Groupes partants

Pente \(\rho = 2.5\)

\([-0.4, -0.2, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4]\)

\([-0.4, -0.2, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4]\)

- \(\delta^-\)
- \(\delta^+\)

TS stabilised by EWGs \((\rho > 0)\)
Hammett: methyl benzoate hydrolysis

- two mechanisms are consistent with the observed value of \( \rho = 2.23 \):
  - attack on the methyl group:
    
    ![Reaction 1](image1)

  - or attack on the acyl group:
    
    ![Reaction 2](image2)

- so the Hammett plot (alone) does not allow us to distinguish between these mechanisms

Hammett: nucleophilic substitution

- only one mechanism is consistent with the observed value of \( \rho = -5.09 \):
  - consider attack on central carbon in \( \text{rls} \) (\( \text{S}_\text{N}2 \)):
    
    ![Reaction 3](image3)

  - compared to departure of chloride in \( \text{rls} \) (first step of \( \text{S}_\text{N}1 \)):
    
    ![Reaction 4](image4)

- in this case, the Hammett plot allows the distinction between these two mechanisms
Deviation from linearity of Hammett eqn

• for certain reactants, the lowest energy reaction pathway may change upon variation of the substituent
  – especially true if two pathways have similar degrees of electronic dependence, but in opposite directions

• this manifests itself as an upward curvature of the Hammett plot

Example: Upward curving Hammett plot

\[ \text{EDG} \quad \text{EWG} \]
Example: Upward curving Hammett plot

![Diagram showing a Hammett plot with upward curving](image)

Deviation from linearity of Hammett eqn

- for certain other reactions, the rate-limiting step can change upon variation of the substituent
  - this is especially true if two reaction steps have TS that are similar in energy
- this manifests itself as a downward curving Hammett plot
Example: Downward curving Hammett plot

Other substituent parameters

- many other chemists have proposed other complementary substituent parameters

- some of these alternative parameters may be more appropriate for a certain kind of reaction of for a certain type of substituent

- for example:
  - $\sigma_I$ for isolated inductive effects
  - $\sigma_R$ isolated resonance effects
  - $\sigma_*$ for reactions that involved the stabilisation of negative charge by resonance
    - based on the ionisation of phenols
  - $\sigma_+^*$ for reactions that involve the stabilisation of positive charge by resonance
    - based on the formation of a benzylic cation
Outline: Other “LFERs”

- see section 8.4 of A&D
  - Taft parameters
  - nucleophilicity and nucleofugality
  - Swain-Scott parameters

Taft

- Robert W. Taft (1922 – 1996)
  - American professor of physical organic chemistry
  - one of the founders of the University of California, Irvine (UCI) in 1965
  - studied substituent effects, acidity and basicity
Taft Parameters

• the parameters developed by Hammett take account of:
  – field effects
  – inductive effects
  – resonance effects
  – but NOT steric effects

• in response, Taft developed different parameters that take account of the polar nature of a substituent (inductive effects and field effects) and of its steric nature
  – $\sigma^*$ = Taft’s polar substituent parameter
  – $E_s$ = Taft’s steric parameter

Taft Parameters

• reference reaction is the hydrolysis of methyl acetate de ($R = CH_3$):

\[
\begin{align*}
\text{ROMe} + H_2O & \rightarrow \text{ROH} + \text{MeOH} \\
\log\left(\frac{k_A}{k_{CH_3}}\right) &= E_s \\
\sigma^* &= \frac{1}{2.48}\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]
\end{align*}
\]

– steric parameter is measured for the acid hydrolysis reaction, where the polarity of the substituent does not influence the rate

– polarity parameter is measured for the difference between the acid (A) and base (B) hydrolysis reactions

adjustment factor to make $\sigma^*$ the same magnitude as the Hammett $\sigma$ value
**Taft Equation**

- takes account of the sensitivity of a given reaction to polar effects ($\rho^*$) and steric effects ($\delta$):

\[
\log\left(\frac{k_s}{k_{CH_3}}\right) = \rho^* \sigma^* + \delta E_s
\]

<table>
<thead>
<tr>
<th>R Group</th>
<th>$E_s$</th>
<th>$\sigma^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1.24</td>
<td>0.49</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Et</td>
<td>-0.07</td>
<td>-0.10</td>
</tr>
<tr>
<td>iPr</td>
<td>-0.47</td>
<td>-0.19</td>
</tr>
<tr>
<td>t-Bu</td>
<td>-1.54</td>
<td>-0.30</td>
</tr>
<tr>
<td>CH$_2$Ph</td>
<td>-0.38</td>
<td>0.22</td>
</tr>
<tr>
<td>Ph</td>
<td>-2.55</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Nucleophilicity et nucleofugality**

- nucleophilicity and basicity involve the donation of electron density to an electrophile
  - good bases are often good nucleophiles

- nucleofugality and acidity involve acceptance of electron density from a substrate
  - good leaving groups (nucleofuges) are often the conjugate bases of good acids

- good nucleophiles are often poor leaving groups and vice versa
  - BUT there are exceptions!
**Solvation**

- solvation masks a nucleophile and decreases its reactivity
  - nucleophiles are typically more reactive in solvents that are polar, but *aprotic*
- nucleophiles having an adjacent electronegative atom can be orders of magnitude more reactive (known as the *a effect*)
  - partially related to ground state destabilisation
  - partially related to a decrease in reactant solvation

**Polarisability, basicity and solvation**

- in general, nucleophilicity increases on descending a column of the periodic table
  - this tendency is due to polarisability
- HOWEVER, in polar *aprotic* solvents, anions are not well solvated, such that nucleophilicity increases with basicity on ascending a column of the periodic table
Shape of a nucleophile

- steric hindrance decreases nucleophilicity
- linear nucleophiles are typically better than expected on the basis of their basicity
  - e.g.: $\text{NC}^-$, $\text{N}_3^-$

Swain

- **C. Gardner Swain** (1917–1988)
  - Professor of Chemistry, MIT
  - studied physical organic chemistry and reactions mechanisms
  - focused on nucleophilic reactivities, solvent effects, substituent effects, isotope effects
  - developed nucleophilicity scale (in 1953) with graduate student, Carleton Scott
### Swain-Scott Parameters

- developed to create a LFER of nucleophilicity
- current reference reactions:

  \[
  \begin{align*}
  H_3C-\text{I} + \text{Nuc}_x & \xrightarrow{k_{\text{CH}_3-\text{I}, \text{Nuc}_x}} H_3C-\text{Nuc} \\
  H_3C-\text{I} + H_2O & \xrightarrow{k_{\text{CH}_3-\text{I}, \text{H}_2O}} H_3C-\text{OH}
  \end{align*}
  \]

- for a reaction of interest:

  \[
  \begin{align*}
  R-GP + \text{Nuc}_x & \xrightarrow{k_{R-GP, \text{Nuc}_x}} R-\text{Nuc} \\
  R-GP + H_2O & \xrightarrow{k_{R-GP, \text{H}_2O}} R-\text{OH}
  \end{align*}
  \]

\[
\log \left( \frac{k_{\text{CH}_3-\text{I}, \text{Nuc}_x}}{k_{\text{CH}_3-\text{I}, \text{H}_2O}} \right) = n_x
\]

\[
\log \left( \frac{k_{R-GP, \text{Nuc}_x}}{k_{R-GP, \text{H}_2O}} \right) = SN_x
\]

### Values of \( n_x \)

- index of effective nucleophilicity, relative to water
  - NB: note log scale!

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>( n_x )</th>
<th>( pK_a ) conj. acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhS(^{-})</td>
<td>9.92</td>
<td>6.52</td>
</tr>
<tr>
<td>I(^{-})</td>
<td>7.42</td>
<td>-10.7</td>
</tr>
<tr>
<td>NC(^{-})</td>
<td>6.70</td>
<td>9.3</td>
</tr>
<tr>
<td>Et(_3\text{N})</td>
<td>6.66</td>
<td>10.7</td>
</tr>
<tr>
<td>CH(_2\text{O})</td>
<td>6.29</td>
<td>15.7</td>
</tr>
<tr>
<td>Br(^{-})</td>
<td>5.79</td>
<td>-7.77</td>
</tr>
<tr>
<td>N(_3)^{-}</td>
<td>5.78</td>
<td>4.74</td>
</tr>
<tr>
<td>PhO(^{-})</td>
<td>5.75</td>
<td>9.89</td>
</tr>
<tr>
<td>Aniline</td>
<td>5.70</td>
<td>4.58</td>
</tr>
<tr>
<td>PhSH</td>
<td>5.70</td>
<td>-</td>
</tr>
<tr>
<td>Pyridine</td>
<td>5.23</td>
<td>5.23</td>
</tr>
<tr>
<td>Cl(^{-})</td>
<td>4.37</td>
<td>-5.7</td>
</tr>
<tr>
<td>CH(<em>3\text{CO}</em>{2})^{-}</td>
<td>4.3</td>
<td>4.75</td>
</tr>
<tr>
<td>F(^{-})</td>
<td>2.7</td>
<td>3.45</td>
</tr>
<tr>
<td>H(_2\text{O})</td>
<td>0.0</td>
<td>-1.7</td>
</tr>
<tr>
<td>CH(_3\text{OH})</td>
<td>-0.0</td>
<td>-1.7</td>
</tr>
</tbody>
</table>
Example of Swain-Scott parameters

- the following reaction was studied for its dependence on nucleophilicity and nucleofugality:

\[
\begin{align*}
\text{Ar} & \text{OPNP} \quad \text{Nuc}^2 \quad \text{Nuc}^2 \\
\text{Ar} & \text{OPNP} \\
\text{Ar} & \text{Nuc}
\end{align*}
\]

- slope of Swain-Scott plot, \( s = 0.18 \)

Outline: Brønsted Relationships

- see section 8.5 of A&D
  - \( \beta_{\text{nuc}} \)
  - \( \beta_{\text{LG}} \)
  - acid-base catalysis
Brønsted

- **Johannes Brønsted** (1879-1947)
  - Danish physical chemist (Copenhagen)
  - studied protonic theory of acid-base reactions (as did Lowry)
  - acid-base catalysis

Brønsted catalysis law

- Brønsted noted that the rate constants for reactions catalysed by a general acid (having a proton in flight in the rate limiting transition state) are proportional to the acidity constants of the general acids:
  
  $k_{obs} \propto K_a^\alpha$

  \[ \log k_{obs} = \alpha \cdot \log K_a = -\alpha \cdot pK_a \]

  and for general bases:

  $k_{obs} \propto K_b^\beta$

  \[ \log k_{obs} = \beta \cdot \log K_b = -\beta \cdot pK_b \]

- Brønsted plots (log $k$ vs $pK$) have slopes between 0 and 1:
  - slope of 0: no proton transfer in rds
  - slope of 1: proton already transferred before rds
  - intermediate slope: proportional with charge developed at TS of rds
**Brønsted-type plots**

- correlation of rate constants with the acidity of *parent compounds* of different fragments of reactants:
  - $pK_a$ of conjugate acids of nucleophiles
    - slope $\beta_{\text{nuc}}$
  - $pK_a$ of conjugate acids of leaving groups
    - slope $\beta_{\text{lg}}$

$\beta_{\text{nuc}}$

- for the reaction of a series of nucleophiles having similar electronic and steric structure, the rate constant can be related to the basicity of the nucleophile:

$$
\log(k) = \beta_{\text{nuc}} \log(K_b) + \log(C)
$$

$$
\log(k) = \beta_{\text{nuc}} pK_a + \log(C')
$$

- $\beta_{\text{nuc}}$ is a measure of the sensitivity of the reaction to the basicity (nucleophilicity) of the nucleophile
- $\beta_{\text{nuc}}$ is thus related to the *charge developed on the nucleophile* at the TS and therefore to the *degree of bond formation*
\( \beta_{lg} \)

- for the reaction of a series of substrates having similar electronic and steric structure, the rate constant can be related to the acidity of the conjugate acid of the leaving group:

\[
\log(k) = \beta_{lg} pK_a + \log(C)
\]

- \( \beta_{lg} \) is a measure of the sensitivity of the reaction to the acidity of the conjugate acid (nucleofugality) of the leaving group
- \( \beta_{lg} \) is thus related to the charge developed on the leaving group at the TS and therefore to the degree of bond cleavage

---

**Slopes of Brønsted-type plots**

- the value of the slope of a Brønsted-type plot can only very rarely be directly related to the degree of bond formation or cleavage
  - the slope \( \beta \) must also be known for the equilibrium constant of the reaction as well as for the rate constant
  - the effective relative charge, \( \varepsilon \), must also be known for the reactants and the products

\[
\beta_{lg} = -0.3 \quad \beta_{nuc} = +0.6
\]

\( \varepsilon = +0.7 \quad \varepsilon = +0.4 \)
Brønsted-type plot

$$\text{Et} \quad \text{LG} + \quad \underbrace{\text{Nuc}}_{\beta_{\text{nuc}} = 0.5} \quad \rightarrow \quad \text{Et-Nuc} + \quad \underbrace{\text{LG}}_{\beta_{\text{lg}} = -0.5}$$

- isoenergetic and symmetric

$\log k_2$ vs. $pK_a$ of conjugate acids

$\delta_{-\text{Nuc}} \quad \delta_{\text{Me}} \quad \delta_{\text{H}} \quad \delta_{\text{LG}}$

Brønsted-type plot

$$\text{Et} \quad \text{LG} + \quad \underbrace{\text{Nuc}}_{\beta_{\text{nuc}} = 0.5} \quad \rightarrow \quad \text{Et-Nuc} + \quad \underbrace{\text{LG}}_{\beta_{\text{lg}} = -0.2}$$

- better

$\log k_2$ vs. $pK_a$ of conjugate acids

$\delta_{-\text{Nuc}} \quad \delta_{\text{Me}} \quad \delta_{\text{H}} \quad \delta_{\text{GP}}$
Brønsted-type plot

\[ \text{Et- LG}^- + \overset{\text{Nuc}}{\text{C}} \rightarrow \text{Et-Nuc} + \overset{\text{LG}}{\text{C}} \]

\[ \text{better} \]

\[ \log k_2 \]

\[ pK_a \text{ of conjugate acids} \]

\[ \beta_{\text{nuc}} = 0.2 \]

\[ \beta_{\text{lg}} = -0.5 \]

\[ \text{less C-Nuc formation} \]

\[ \text{worse} \]

\[ \beta_{\text{nuc}} = 0.5 \]

\[ \beta_{\text{lg}} = -0.8 \]

\[ \text{more C-GP cleavage} \]
**Brønsted-type plot**

![Brønsted-type plot diagram](image)

- 

**Brønsted-type plot**

![Brønsted-type plot diagram](image)

**Thermodynamics and kinetics**
Outline: “LFERs”

- see section 8.6 of A&D
  - mathematical considerations
  - thermodynamic considerations
  - enthalpy/entropy compensation
Mathematics of LFERs

- the relative influence of a substituent is fairly constant, from one reactin
to another
  - but... why???
- consider the effect of a substituent on $\Delta G_{\text{rxn}}$:
  $$\Delta G_{\text{ref}} = -2.303RT \log(K_{\text{ref}}) \quad \text{and} \quad \Delta G_X = -2.303RT \log(K_X)$$
  so $\Delta G_{\text{ref}} - \Delta G_X = 2.303RT \log(K_X / K_{\text{ref}})$
  and $C_X = \log(K_X / K_{\text{ref}})$
- we then measure its effect for a new, but similar reaction:
  $$C'_X = \log(K'_X / K'_{\text{ref}})$$
  and the ratio $Q = C'_X / C_X$ tells us the sensitivity of this reaction
- whence the general equation:
  $$\log(K'_X / K'_{\text{ref}}) = QC_X$$
  and by analogy, $\log(k'_X / k'_{\text{ref}}) = QC_X$

Thermodynamic considerations

- empirically, we find that these relations are often linear, for similar reactions
- under these conditions, where $\Delta \Delta G' = Q \Delta \Delta G$, one could also write:
  $$(\Delta \Delta H' - T \Delta \Delta S') = Q (\Delta \Delta H - T \Delta \Delta S)$$
- for this relationship to be linear, one of the following must be true:
  1. $\Delta \Delta H' = \Delta \Delta H$, by coincidence, and the values of $\Delta \Delta S$ and $\Delta \Delta S'$ are linearly proportional, OR
  2. $\Delta \Delta S' = \Delta \Delta S$, by coincidence, and the values of $\Delta \Delta H$ and $\Delta \Delta H'$ are linearly proportional, OR
  3. the values of $\Delta H$ and $\Delta S$ are linearly proportional for the two reactions
- this last condition is in fact the most common
  - represents entropy/enthalpy compensation
**Enthalpy/entropy compensation**

- this phenomenon is easily explained on considering examples of steric effects and solvation effects:
  - **steric effect:**
    - for a reaction involving nucleophilic attack, a substrate having more steric hindrance at the TS will have a higher $\Delta H^\ddagger$
    - but since the nucleophile and solvent molecules will be more distant and bound less tightly at the transition state, $\Delta S^\ddagger$ will be less negative
  - **solvation effect:**
    - for an $S_n^2$ reaction, the polar activated complex is stabilised in a polar solvent, so $\Delta H^\ddagger$ is smaller
    - but since the development of charge at the TS will lead to solvent molecules being bound more tightly, $\Delta S^\ddagger$ is equally more negative

---

**Summary of LFERs**

- Table 8.6, A&D