Mythodology in Organic Chemistry:
A kinetic analysis
**Myth** [from Greek]

A fiction or half-truth, especially one that forms part of an ideology.


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**Myths in Organic Chemistry**

1. The reactivity-selectivity principle  
   (incl. Leffler-Hammond-postulate)

2. Charge and orbital control of ambident reactivity  
   (Principle of hard and soft acids and bases, HSAB)

3. Gibbs' energy profiles for $S_{N1}$-solvolyses
1. The Reactivity-Selectivity Principle
The Reactivity Selectivity Principle

Highly reactive: Unselective

Unreactive: Highly selective
The Reactivity-Selectivity Principle

The higher selectivity of brominations can be explained by the homolytic bond dissociation energies (in kJ mol⁻¹):
Stability Selectivity ($\text{N}_3^- / \text{H}_2\text{O}$) Plot for Carbocations Derived from Solvolysis of Alkyl Chlorides

\[
\begin{align*}
R-\text{Cl} & \quad \text{R} + \text{Cl}^- \\
\text{R-N}_3 & \quad \text{R-OH}
\end{align*}
\]

in 80 % aq acetone, 25 °C

Constant Selectivity Relationships for the Reactions of Carbenium Ions with Nucleophiles

\[ \log k = \log k_{H_2O} + N_+ \]

Additions of Carbanions to Quinone Methides Follow Linear Reactivity-Selectivity Relationships

R. Lucius, H. Mayr,
*Angew. Chem.* 2000, 112, 2086-2089;

R. Lucius, R. Loos, H. Mayr,
*Angew. Chem.* 2002, 114, 97-102;
Reactivity-Selectivity Relationships

Reactivity-Selectivity Relationships

log $k$ (-70 °C) vs. $E$

Reactivity-Selectivity Relationships

diffusion control $(2 - 4) \times 10^9 \text{ M}^{-1} \text{s}^{-1}$

Reactivity-Selectivity Relationships

diffusion control $(2 - 4) \times 10^9$ M$^{-1}$ s$^{-1}$

Reactivity-Selectivity Relationships

Try to Formulate the Reactivity-Selectivity Principle!

Try to Formulate the Reactivity-Selectivity Principle!

- $\text{diffusion control (2 - 4) } \times 10^9 \text{ M}^{-1}\text{ s}^{-1}$

- $\log k$ (-70 °C)

- More reactive $R^+$ less reactive $R^+$

- $\text{SiMe}_3$, $\text{SiMe}_2\text{Cl}$
Try to Formulate the Reactivity-Selectivity Principle!

- diffusion control (2 - 4) \times 10^9 \text{ M}^{-1} \text{s}^{-1}
- log \( k \) (-70 °C)
- less reactive \( R^+ \) particle
- more reactive \( R^+ \) particle
- Reactivity
Try to Formulate the Reactivity-Selectivity Principle!

diffusion control $(2 - 4) \times 10^9 \text{ M}^{-1} \text{s}^{-1}$
Try to Formulate the Reactivity-Selectivity Principle!

diffusion control \((2 - 4) \times 10^9 \text{ M}^{-1} \text{s}^{-1}\)

\[
\log k \quad (-70 \, ^\circ\text{C})
\]

more reactive \(R^+\) less reactive \(R^+\)

particle

Reactivity

AB
The Reactivity Selectivity Principle

Highly reactive:
Unselective

Unreactive:
Highly selective
The Bell-Evans-Polanyi Principle

$$B_i + HX \rightarrow B_i H^+ + X^-$$

Hammond-Leffler’s $\alpha$ as a Measure for the Position of the Transition State

$\alpha = 0$  Reactant-like transition state  $\alpha = 1$  Product-like transition state

$\delta \Delta G^\ddagger = \alpha \delta \Delta G^\circ$

A is more reactive and less selective than B.
Why $\alpha$ Cannot Be a Measure for the Position of the Transition State

- Nitroalkane Anomaly

\[
\begin{array}{c}
\text{O}_2\text{N} \quad \text{O}_2\text{N} \\
\text{X} \quad \text{X} \\
\end{array}
\]

\[
\text{Cl} + + \text{Cl}^{-} \quad \leftrightarrow \quad \text{Cl}^{-} + \text{Cl} \\
\]

\[
\alpha = \frac{\delta \Delta G^\ddagger}{\delta \Delta G^\circ} = 1.54
\]

Acceptors groups stabilize the transition state of deprotonation more than the resulting carbanion.

Acceptors groups accelerate C-protonation of carbanions.

- Identity Reactions
1. The Reactivity-Selectivity Principle

Conclusions:

• A decrease of selectivity with increasing reactivity can only be expected in reactions which are close to diffusion control.

• In activation-controlled reactions selectivity can decrease, increase or remain constant when reactivity is altered.

• The Leffler-Hammond postulate, which was used as a basis to derive the reactivity-selectivity principle, neglects the role of intrinsic barriers and, therefore, may lead to erroneous conclusions.
3. Free Energy Profiles of $S_{N1}$ Reactions
Gibbs energy diagram

Contrary to statements in many text books, the highest point on a Gibbs energy diagram does not necessarily correspond to the transition state of the rate-limiting step. For example, in a stepwise reaction consisting of two reaction steps

\[
\begin{align*}
(1) & \quad A + B & \rightarrow & \quad C \\
(2) & \quad C + D & \rightarrow & \quad E
\end{align*}
\]

one of the transition states of the two reaction steps must (in general) have a higher standard Gibbs energy than the other, whatever the concentration of D in the system. However, the value of that concentration will determine which of the reaction steps is rate-limiting. If the particular concentrations of interest, which may vary, are chosen as the standard state, then the rate-limiting step is the one of highest Gibbs energy.

P. Müller,
Glossary of Terms Used in Physical Organic Chemistry, IUPAC Recommendations 1994,
Conventional Energy Profile for $S_N1$ Reactions

\[ R-X + \text{SolvOH} \xrightarrow{\Delta G^\ddagger} R^+ + X^- + \text{SolvOH} \]

\[ R^-\text{O}\text{Solv} + HX \]

\[ R-X \xrightarrow{k_1} R^+ + X^- \xrightarrow{k_2} R^-\text{O}\text{Solv} + HX \]

\[ k_{-1} \]

Reaction coordinate

Energy
Rate Constants \( \log k_1 \) (20 °C) for the Decay of Benzhydrylium Ions in Several Solvents Plotted vs the Electrophilicity \( E \)

Solvent Nucleophilicities $N_1$

MeOH (M)  
80M20AN

EtOH (E)  
80E20AN

EtOH (E)  
80E20W

20M80AN

20E80AN  
20E80W

Water (W)  
20T80W

Water (W)  
20W80AN

80T20W

log $k_1 = s(N_1 + E)$

$E$ = empirical electrophilicity parameter
$s, N_1$ = nucleophile-specific parameters

AN = acetonitrile

Determination of Halide Nucleophilicities

Reactions of Ar₂CH⁺ with Chloride Ions

in H₂O/CH₃CN = 80/20 (20 °C)

\[ k_{1\psi} = 1.51 \times 10^7 \left[ \text{Cl}^- \right] + 9.37 \times 10^4 \]

\( r^2 = 0.9957 \)

in H₂O/CH₃CN = 1/1 (20 °C)

\[ k_{\text{solv}} \]

Nucleophilicities of Cl⁻ and Br⁻ in Different Solvents

\[
\log k = s(N + E)
\]

Solvent Ionizing Power \( Y_{\text{Cl}} \) of different solvents


Quantitative Energy Profiles for Benzhydryl Solvolysis Reactions

in 80 % aq EtOH (20 °C)

Ar₂CHCl

X = H

X = Me

X = OMe

X = OMe

Ar₂CHO(Solv)

\[ \Delta G \]

Energies in kJ mol⁻¹

S. Minegishi, R. Loos, S. Kobayashi, H. Mayr,
Quantitative Energy Profiles for Benzhydryl Solvolysis Reactions

in 100 % CF₃CH₂OH (20 °C)

Energies in kJ mol⁻¹

Comparison of Chloride and Solvent Nucleophilicities:

- Graph showing the comparison of chloride and solvent nucleophilicities with log $k$ on the y-axis and electrophilicity $E$ on the x-axis.

- Equations:
  - $k_{obs} = k_1 \frac{k_2}{k_2 + k_{-1}[X^-]} = \frac{k_1}{1 + \alpha[X^-]}$ with $\alpha = k_{-1}/k_2$
  - $k_1$ and $k_{-1}$ represent the forward and reverse rate constants for the reaction $R-X \rightleftharpoons R^+ + X^-$
  - $k_2$ represents the rate constant for the reaction $R^+ + X^- \rightarrow R-OSolv + HX$

- References:
Comparison of Chloride and Solvent Nucleophilicities: When Can Common Ion Effects be Expected?

When Can Common Ion Effects be Expected?

\[ R-X \quad k_1 \quad R^+ + X^- \quad k_2 \quad \text{R-OSolv} + \text{HX} \]

in solvolysis: \[ k_{\text{obs}} = \frac{k_2}{k_1} \times \frac{1}{1 + \alpha[X^-]} \]

with \( \alpha = \frac{k_{-1}}{k_2} \)

substrate | \( E \) | solvent | \( \alpha / \text{M}^{-1} \)
--- | --- | --- | ---
(ani)\(_2\)CHCl | 0 | 15W85A | 3700
(ani)(tol)CHCl | 1.48 | 15W85A | 1500
(ani)PhCHCl | 2.11 | 15W85A | 700
(PhOC\(_6\)H\(_4\))PhCHCl | 2.90 | 15W85A | 140
(tol)\(_2\)CHCl | 3.63 | 20W80A | 74
(tol)PhCHCl | 4.59 | 20W80A | 32
Ph\(_2\)CHCl | 5.90 | 20W80A | 11.5
| 30W70A | 2.08
(4-NO\(_2\)C\(_6\)H\(_4\))PhCHCl | 9 | 30W70A | 0.71
(CH\(_3\))\(_3\)CBr | 8.5–9 | 10W90A | \( \approx 1 \)

diffusion limit

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\( a \) C. Ingold et al., S. Winstein et al., G. Kohnstam et al., 1940-1969.
3. Free Energy Profiles of $S_n1$ Reactions

Conclusion:

$R-X + \text{SolvOH} \rightarrow R^+ + X^- + \text{SolvOH}$

$R-\text{OSolv} + X^- \rightarrow R-\text{OSolv}$

$R^+ + X^- + \text{SolvOH} \rightarrow R-\text{OSolv} + X^-$
1/2 Examination of some concepts of Organic Chemistry with quantitative methods: Reactivity-Selectivity-Principle; HSAB principle for explaining ambident reactivity; Energy profiles of S_N1 solvolyses.


5/6 Ion stabilities in gas phase and solution (Acidity functions).

7/8 Stability scales for carbocations: Lewis and Brønsted acidities; isodesmic reactions.

9/10 Hammett and Hammett-Brown equation.

11/12 Curtin-Hammett principle and applications to acid- and base-catalyzed reactions.

13/14 Scales of Electrophilicity and Nucleophilicity (Swain-Scott, Ritchie, Patz-Mayr, and future developments).