There are only two important things in chemistry, kinetics and thermodynamics. And, \( \exp(-\Delta G/RT) = k_1/k_{-1} \), so there’s really only one thing.

Kinetics provides information about the transition state of a reaction.

We'll use a simple example to learn the basic tools, then look at more applications to catalysis.

\[
\text{NaCN} + I \xrightleftharpoons[k_{-1}][k_1] \text{CN} \quad \Delta G \sim 60 \text{ kcal/mol} \\
\text{i.e. } k_1 \gg k_{-1}
\]

Rate:

\[
\frac{d[\text{EtCN}]}{dt} = \frac{-d[\text{NaCN}]}{dt} = \frac{-d[\text{EtI}]}{dt} = k[\text{NaCN}][\text{EtI}]
\]

1st step: measure change in concentration over time under known conditions.

Common techniques:
- GC
- UV/Vis
- NMR
- IR
- HPLC

Note: data for EtCN are hypothetical
An aside on reaction deceleration

Crude Data

\[ [\text{EtI}] = [\text{NaCN}] \]

![Graph showing concentration over time with a deceleration phase starting at time 3.](image-url)
Data can be plotted to determine reaction’s overall order:

0\textsuperscript{th}: \(-\frac{d[A]}{dt} = k \rightarrow [A] = kt\)

1\textsuperscript{st}: \(-\frac{d[A]}{dt} = k[A] \rightarrow [A] = \exp(kt)\)  
\[\ln[A] = kt\]

2\textsuperscript{nd}: \(-\frac{d[A]}{dt} = k[A]^2 \rightarrow 1/[A] = kt\)  
(also for \(k[A][B]\) if \([A] = [B]\)
2 common methods to determine order in individual components. **Pseudo 1\textsuperscript{st}-order:** one component in huge excess (its concentration \(\sim\) constant) Collect data at various excessive concentrations

\[
\text{Rate} = k[\text{NaCN}][\text{EtI}] \sim k[\text{NaCN}]_0[\text{EtI}] = k_{\text{obs}}[\text{EtI}]
\]

Note \([\text{EtI}] = 1 \rightarrow 0\), but \([\text{NaCN}] = 10 \rightarrow 9\) up to 200 \(\rightarrow\) 199
Replot data in 1st order coordinates
Slope of line = $k_{obs}$

Rxn is 1st order in NaCN!!
But...is 10-200 equiv NaCN really representative??
An alternative is the method of ‘initial rates’
Keep one component constant (EtI) and vary the other (NaCN), but keep close to synthetic conditions

Look at the first 10% of the reaction. Assume concentrations don’t change much at low conversion. i.e. \( v = k[EtI][NaCN] \sim k[EtI]_0[NaCN]_0(c = 0 \rightarrow 10\%) \)
Notes

Need more data points/time for initial rate

Data looks pretty linear for first 10%

Slope of best-fit line is $k_{obs}$

$K_{obs} = k[\text{NaCN}][\text{EtI}]$ and $[\text{EtI}]$ was constant

Again, the rxn is first order in $[\text{NaCN}]$

But...we ignored 90% of the reaction.
Case Study 1: Bergman, JACS, 1981, 7028

Confusion: Huge solvent effects on rate and (in related systems) stereochemistry

What's the mechanism??

concerted attack/migration mechanism:

pre-migration mechanism

notes: you should be able to derive these equations. Why not consider an associative mechanism?
Case Study 1: Bergman, JACS, 1981, 7028

Actual data

Rxn in THF and 3-MeTHF look like superposition of concerted attack and pre-migration

\[
\text{rate} = \frac{k_1 k_2[1][PR_3]}{k_2[PR_3] + k_{-1}} + k_3[1][PR_3]
\]

Rxn in 2,5 Me₂THF only shows concerted attack. How to explain? Solvent assistance.

\[
\text{rate} = \frac{k_1 k_2[1][PR_3][S]}{k_2[PR_3] + k_{-1}}
\]

but [S] is constant, so kinetically invisible

Figure 1. Dependence of the pseudo-first-order rate constant \(k_{\text{obsd}}\), for conversion of 1 to 2 in excess PMePh₂, upon phosphine concentration in the following solvents: (●) THF; (■) 3-MeTHF; (▲) 2-MeTHF; (♦) 2,5-Me₂THF.
Case Study 1: Bergman, JACS, 1981, 7028

Mechanism predicts 1st order dependence on THF. Do expt in 2,5-Me₂THF, add THF (note only minor change in dipole)

Figure 2. Dependence upon [THF] of $k_1$ for reaction of 1 with PMePh₂, determined in studies using 0.01 M 1 and varying excess concentrations of phosphine in THF/2,5-Me₂THF mixtures.
Previous work (JACS 1993, 12226) had shown 1st order in OsO4-L, zero order in Fe(III)
Case Study 2: Corey, JACS, 1996, 319

These are saturation kinetics!!. Same as many enzymes and Lewis-Acid cat Rxns

Proposed structure of L*OsO₄(olefin) for allyl benzoate

\[
V = \frac{k_{\text{cat}}[\text{Os}]_{\text{M}}[\text{olefin}]}{1 + K_{\text{M}}[\text{olefin}]} = \frac{k_{\text{cat}}[\text{Os}]_{\text{M}}[\text{olefin}]}{K_m + [\text{olefin}]}
\]
Case Study 2: Corey, JACS, 1996, 319

Binding appears correlated to selectivity in asymmetric dihydroxylation
Poor correlation between rate and selectivity

Table 1. Comparison of the Michaelis–Menten parameters $K_m$ and $V_{max}$ and Observed Enantioselectivity in the Catalytic Asymmetric Dihydroxylation of Olefins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chiral (formula no.)</th>
<th>$K_m$</th>
<th>$V_{max}$</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(2)</td>
<td>0.017M</td>
<td>1.1 x 10^{-4}</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>(4)</td>
<td>0.009M</td>
<td>5.5 x 10^{-4}</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>(7)</td>
<td>0.017M</td>
<td>1.3 x 10^{-4}</td>
<td>28%</td>
</tr>
<tr>
<td>4</td>
<td>(8)</td>
<td>0.0085M</td>
<td>5.5 x 10^{-4}</td>
<td>57%</td>
</tr>
<tr>
<td>5</td>
<td>(4)</td>
<td>0.0086M</td>
<td>1.3 x 10^{-4}</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>(10)</td>
<td>0.001M</td>
<td>3.0 x 10^{-4}</td>
<td>79%</td>
</tr>
<tr>
<td>7</td>
<td>(11)</td>
<td>0.0006M</td>
<td>1.7 x 10^{-4}</td>
<td>96%</td>
</tr>
<tr>
<td>8</td>
<td>(7)</td>
<td>0.16M</td>
<td>0.6 x 10^{-4}</td>
<td>40%</td>
</tr>
<tr>
<td>9</td>
<td>(7)</td>
<td>0.16M</td>
<td>0.6 x 10^{-4}</td>
<td>40%</td>
</tr>
</tbody>
</table>

DHQD-PYDZ-OMe ligand (13)

1 This reaction was performed using 0.3 mM DHQD-PYDZ ligand and 0.25 mM K$_2$O$_2$CO$_2$K.

2 Unless otherwise indicated, all reactions were performed at 0°C in 1:1 tert-butyl alcohol–water using the (DHQD)$_2$PYDZ ligand (1 mM) and K$_2$O$_2$CO$_2$H$_2$O (0.5 mM).

Kinetic Investigations Provide Additional Evidence That an Enzyme-like Binding Pocket Is Crucial for High Enantioselectivity in the Bis-Cinchona Alkaloid Catalyzed Asymmetric Dihydroxylation of Olefins

E. J. Corey* and Mark C. Noe
Case Study 3: Jacobsen, JACS, 1996, 10924

The reaction

\[
\text{Y + TMSN}_3 \xrightarrow{\text{Et}_2\text{O or TBME}} \text{TMSO} \quad \text{N}_3
\]

where \( Y = \text{CH}_2, \text{CHR, CH}_2\text{CH}_2, \text{CH=CH, N-R, O, C=O} \)

The data:

\[
\begin{align*}
 k_{\text{obs}} & \quad (\text{M} \cdot \text{s}^{-1}) \\
 [1\text{b}]^2 & \quad (\text{M}^2)
\end{align*}
\]
Rate = $k[(\text{salen})\text{Cr}]^2[\text{epoxide}]^{-1}[\text{Azide}]^0$

2 Cr's involved in RDS  
Epoxide inhibits rxn!!  
Azide either (a) involved after RDS or (b) present in ground state
Case Study 4: Jacobsen, JACS 1999, 6086 and unpublished work

The rxn:

$$\text{HNu} + (\pm)2 \xrightleftharpoons{(R,R)} 3 \rightarrow \text{Nu} + (R,R)4$$

1: Nu = OAr

(R,R)-3a: M = Co
(R,R)-3b: M = Co(OAc)(H_2O)
(R,R)-3c: M = Co(OAc)(CF_3SO_3)(H_2O)
(R,R)-3d: M = Co(OAc)(HOAr)
[ArOH = 3,5-C_6H_4F_2OH]

Data:

$$\text{Rate} = k_{\text{obs}}[\text{Co}]^2$$

**log log plot**

$$y = 2.0577x + 3.8479$$
$$R^2 = 0.9947$$

$$V = k[A]^n$$
$$\log(V) = \log(k[A]^n) = n \log(k[A])$$
Case Study 4: Jacobsen, JACS 1999, 6086 and unpublished work

Saturation kinetics with epoxide

Inhibition by PhOH
Case Study 4: Jacobsen, JACS 1999, 6086 and unpublished work

rate = \frac{k_{cat}[Co]_t^2[Epox]}{K_d[ArOH]+[Epox]}
Case Study 5: Stahl, JACS 2002, 766

The rxn

\[
\begin{array}{c}
\text{MeO} \\
\text{OH} \\
\text{OMe}
\end{array}
\xrightarrow{5\% \text{Pd(OAc)}_2, \text{O}_2, \text{DMSO, 80 °C}}
\begin{array}{c}
\text{MeO} \\
\text{O}
\end{array}
\]

(2)

The data: DMSO critical, but is not reduced (O2 required) or oxidized (no dimethyl sulfone is formed)

\[2 \text{ formed:O}_2 \text{ consumed} = 2 \ (\text{O}_2 \text{ is a 4 e- oxidant here})\]

Under the rxn conditions, disproportionation observed (sometimes referred to as ‘catalase activity’)

\[
\begin{array}{c}
\text{H}_2\text{O}_2
\end{array}
\xrightarrow{[^{\text{Pd}}]}\n\begin{array}{c}
\text{H}_2\text{O} + 1/2 \text{O}_2
\end{array}
\]

(5)

Pd black (precipitated Pd metal) observed during course of reaction
Case Study 5: Stahl, JACS 2002, 766

Also: Pd black correlates with rate decrease
Rate independent of [ROH]

Conclude oxidation of Pd is rate limiting

Predicts rate = k[O2][Pd] (i.e. linear increase in rate with [Pd])

Propose catalyst decomposition is time-dependent. Decomposition is bimolecular; more pronounced at higher [Pd]
Described by \( k_{\text{dec}} \) competitive with \( k_{\text{cat}} \)
Eq 7 models data in trace B

\[
\frac{d (pO_2)}{dt} = k_{\text{cat}}[Pd]_t \cdot pO_2; \quad [Pd]_t = \frac{[Pd]_0}{1 + [Pd]_0(k_{\text{dec}} \cdot t)}
\]
Integrated form models experimental data

Proposed mechanism

\[ (pO_2)_t = (pO_2)_0 \left(1 + k_{\text{dec}} [Pd]_0 \cdot t \right)^{k_{\text{dec}}} \]

\[ k_{\text{cat}} = 1.25 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1} \]

\[ k_{\text{dec}} = 1.7 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1} \]
The reaction:

$$\text{ArCl} + \text{Ni(PPh}_3)_4 \rightarrow \text{ArNiCl(PPh}_3)_2$$

The data:

1st order in [ArCl]

$$k_{obs} \times 10^4$$ vs [ArCl]

$R^2 = 0.9946$

Non-linear inhibition by PPh3

$$k_{obs} \times 10^4$$ vs [PPh3]

Proposed mechanism

\[ \begin{align*}
\text{Ni(PPh}_3\text{)}_4 & \quad \underset{K' > 10}{\longrightarrow} \quad \text{Ni(PPh}_3\text{)}_3 + \text{PPh}_3 \\
\text{Ni(PPh}_3\text{)}_3 & \quad \underset{K < 10^{-6}}{\longrightarrow} \quad \text{Ni(PPh}_3\text{)}_2 + \text{PPh}_3 \\
\text{Ni(PPh}_3\text{)}_3 + \text{ArCl} & \quad \overset{k_1}{\longrightarrow} \quad (\text{PPh}_3\text{)}_2\text{NiAr}(X) + \text{PPh}_3 \\
\text{Ni(PPh}_3\text{)}_2 + \text{ArCl} & \quad \overset{k_2}{\longrightarrow} \quad (\text{PPh}_3\text{)}_2\text{NiAr}(X)
\end{align*} \]

Rate = \[ \frac{k_1[\text{PPh}_3] + k_2K}{[\text{PPh}_3]} \frac{[\text{Ni}]_T[\text{ArCl}]}{[\text{ArCl}]} = k_{\text{obs}}[\text{Ni}]_T \]

\[ k' = \frac{k_{\text{obs}}}{[\text{ArCl}]} = \frac{k_1[\text{PPh}_3] + k_2K}{[\text{PPh}_3]} \]

\[ k'[\text{PPh}_3] = k_1[\text{PPh}_3] + k_2K \]

plot \( k'[\text{PPh}_3] \) vs. \( [\text{PPh}_3] \)

\[ \begin{align*}
\text{For p-Cl}_2\text{Ph:} & \\
k_1 &= 1 \times 10^{-4} \\
Kk_2 &= 1.1 \times 10^{-5} \\
k_2 &= 10
\end{align*} \]

So \( \text{Ni}[\text{PPh}_3]_2 \) 10^5x more reactive than \( \text{Ni}[\text{PPh}_3]_3 \), but much less prevalent.
High yields for terminal and internal epoxides; stereospecific:

<table>
<thead>
<tr>
<th>anhydride</th>
<th>yield (%)$^b$</th>
<th>ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-7</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>(S)-7</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>(R)-11</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>(S)-21</td>
<td>96 ($^{(e)}$97)</td>
<td>97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>epoxide</th>
<th>epoxide/1</th>
<th>anhydride</th>
<th>yield (%)$^b$</th>
<th>trans:cis$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td>40</td>
<td>100</td>
<td>41</td>
<td>95</td>
<td>1:20</td>
</tr>
<tr>
<td>2</td>
<td>±42</td>
<td>200</td>
<td>±43</td>
<td>99</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>3</td>
<td>±44</td>
<td>75</td>
<td>±45</td>
<td>99</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>4</td>
<td>±46</td>
<td>100</td>
<td>±47</td>
<td>99</td>
<td>&gt;100:1</td>
</tr>
</tbody>
</table>

Ar = 4-Cl phenyl
Anhydride formation displays induction period; no anhydride formed until epoxide consumed. Independent rxns similar in rate; show first order dependence on catalyst.
Ready; Catalysis

Kinetics-case study 7

$$\text{Rate (lactone)} = k[\text{epox}]^0[\text{CO}]^0[\text{catalyst}]^1[\text{Solvent}]^1$$

$$\text{Rate (anhydride)} = k[\text{lactone}]^1[\text{CO}]^0[\text{catalyst}]^1[\text{Solvent}]^{-1}$$

Epoxide (and solvent) inhibit lactone $\rightarrow$ anhydride

Coates, JACS, 2007, 4948
Scheme 2. Proposed Catalytic Cycle of Double Carbonylation

Resting state in presence of epoxide (no open LA sites)

Resting state, no epoxide

Scheme 3. Proposed Rate-Determining Step of Propylene Oxide Carbonylation (RDS\(_1\))

S = Lewis basic solvent

Scheme 4. Proposed Rate-Determining Step of \(\beta\)-Butyrolactone Carbonylation (RDS\(_2\))

S = Lewis basic solvent

Coates, JACS, 2007, 4948
Recall: $\Delta G = -RT\ln(K)$ and $\Delta G = \Delta H - T\Delta S$

Merging and rearranging gives the **Van’t Hoff Equation**: $\ln(K) = (-\Delta H/R)(1/T) + (\Delta S/R)$

$\ln(K)$ vs. $1/T$ gives $\Delta H$ and $\Delta S$

Hartwig, *JACS*, 2006, 9306

n.b. increasing temperature decreases contribution of $\Delta H$
The Eyring equation: determination of $\Delta H^\ddagger$ and $\Delta S^\ddagger$.

$$\ln \frac{k}{T} = -\frac{\Delta H^\ddagger}{R} \cdot \frac{1}{T} + \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R}$$

$$y = mx + b$$

Table 2. Activation Parameters for Degenerate Olefin Exchange between (bo)Pd(ns$^X$) and ns$^X$.

<table>
<thead>
<tr>
<th>entry</th>
<th>olefin</th>
<th>temp range (K)</th>
<th>$k$ (M$^{-1}$s$^{-1}$) at 25°C</th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>$\Delta S^\ddagger$ (cal/mol·K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nsCF$_3$</td>
<td>224–286</td>
<td>749</td>
<td>7.3</td>
<td>-24</td>
</tr>
<tr>
<td>2</td>
<td>nsBr</td>
<td>253–284</td>
<td>492</td>
<td>8.8</td>
<td>-30</td>
</tr>
<tr>
<td>3</td>
<td>nsCH$_3$</td>
<td>264–295</td>
<td>284</td>
<td>7.2</td>
<td>-24</td>
</tr>
<tr>
<td>4</td>
<td>nsOCH$_3$</td>
<td>254–294</td>
<td>257</td>
<td>8.2</td>
<td>-27</td>
</tr>
</tbody>
</table>

Supports associative mechanism (usually associative approx -30eu Dissociative +10-20eu)

Stahl, JACS, 2004, 14832
Potential mechanisms:

Small entropy of activation inconsistent with mechanism a. (Labeling studies ruled out mechanism b).

Bergman, 1995, 6382
Use in asymmetric catalysis

$$\ln(\text{e.r}) = \frac{\Delta \Delta H^\ddagger}{R}(1/T) - \frac{\Delta \Delta S^\ddagger}{R}$$

$$\Delta \Delta H^\ddagger = \Delta H^\ddagger_{\text{minor}} - \Delta H^\ddagger_{\text{major}}$$

$$\Delta \Delta S^\ddagger = \Delta S^\ddagger_{\text{minor}} - \Delta S^\ddagger_{\text{major}}$$

**Table 2.** Relative Activation Parameters for the Formation of Indene Oxide Enantiomers Catalyzed by Complexes 2a–c, e–g

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>substituent</th>
<th>$\Delta \Delta H^\ddagger$ (kcal mol$^{-1}$)</th>
<th>$\Delta \Delta S^\ddagger$ (cal mol$^{-1}$ K$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2g</td>
<td>OSi(Pr)$_3$</td>
<td>1.70 ± 0.08</td>
<td>-0.69 ± 0.35</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>OCH$_3$</td>
<td>1.40 ± 0.16</td>
<td>-0.07 ± 0.76</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>CH$_3$</td>
<td>0.66 ± 0.05</td>
<td>2.90 ± 0.21</td>
</tr>
<tr>
<td>4</td>
<td>2c</td>
<td>H</td>
<td>0.29 ± 0.10</td>
<td>3.80 ± 0.44</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>Br</td>
<td>0.11 ± 0.09</td>
<td>3.60 ± 0.40</td>
</tr>
<tr>
<td>6</td>
<td>2e</td>
<td>NO$_2$</td>
<td>-0.28 ± 0.02</td>
<td>2.50 ± 0.10</td>
</tr>
</tbody>
</table>

Biggest change in selectivity with temperature when $\Delta \Delta H^\ddagger$ dominates.

Note with 2e, ee decrease with decreasing T

Practice problem: oxidative addition of ArX to Pd(0). Hartwig, JACS, 2005, 6944

Kinetics studied for ArCl, ArBr and ArI

Your job: derive rate laws for each path; determine which one(s) is(are) consistent with data.

Scheme 1. Possible Mechanisms and Rate Expressions for the Oxidative Addition of ArX to 2

Path A
ArX \[ k_1 \]

Path B
L-Pd-(ArX) + L \[ k_2 \]

Path C
ArX \[ k_1 \]

Path D
L-Pd + L \[ k_2 \]

Path E

\[ w/\text{PhI} \]

\[ w/\text{PhBr} \]: rate = [ArBr][L]^{0.5}
Small $\Delta S^\ddagger$; same rate with sub. ArBr’s

‘Lineweaver-Burk Plot’

\[ w/\text{ArCl} \]

Figure 1. Plots of $k_{obs}$ vs [PhI] and $k_{obs}$ vs [Q-phos-tol] ([PhI] = 0.95 M) for the oxidative addition of PhI to 2 at 30 °C in THF.

Figure 2. Plots of $1/k_{obs}$ vs 1/[PhCl] ([Q-phos-tol] = 0.08 M) and $1/k_{obs}$ vs [Q-phos-tol] ([PhCl] = 6.56 M) for the oxidative addition of PhCl to 2 at 60 °C in THF.
Data:
Rxn with ND₃ showed no D incorporation into ligand
Figure S2. Plot of $k_{\text{obs}}$ for the oxidative addition of ammonia and the ratio of the concentrations of pentene and ammonia that includes all data points.