SUPPORTING INFORMATION

Lithium Diisopropylamide: Nonequilibrium Kinetics and Lessons Learned About Rate Limitation

Russell F. Algera, Lekha Gupta, Alexander C. Hoepker, Jun Liang, Yun Ma, Kanwal J. Singh, and David B. Collum*

Department of Chemistry and Chemical Biology
Baker Laboratory, Cornell University
Ithaca, New York 14853–1301
E-mail: dbc6@cornell.edu

I. Simulation Protocols

Generic Scheme.

Assuming the generic scheme

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2[\mathrm{C}]} \text{product}$$

an expression for [B] at a steady state follows.

$$[\mathrm{B}] = \frac{k_1[\mathrm{A}]}{k_{-1} + k_2[\mathrm{C}]}$$

From this expression one readily obtains the rate law for consumption of C.

$$-\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = \frac{k_1 k_2[\mathrm{A}][\mathrm{C}]}{k_{-1} + k_2[\mathrm{C}]}$$

II. Simulations

All figures were generated in Igor Pro® using simulated data from Wolfram Mathematica®. Following each figure is a chemical scheme and demarcated Mathematica code that can be copied and directly executed to recreate the plots. The figure numbers correspond to those in the manuscript.

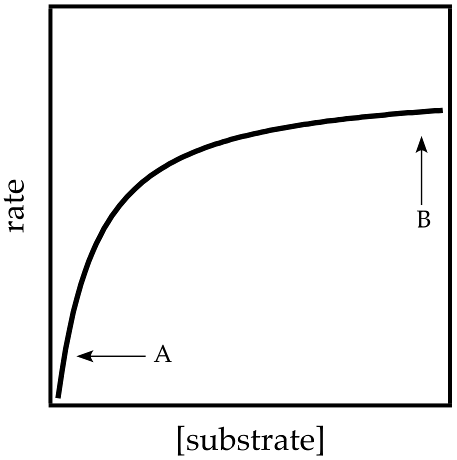
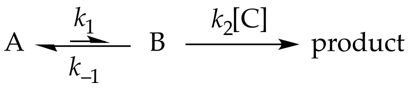


Figure 2. Saturation kinetics. A and B correspond to regions of substrate-concentration-dependent and substrate-concentration-independent regions.



$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B]$$

$$\frac{d[B]}{dt} = k_1[A] - k_{-1}[B] - k_2[B][C]$$

$$\frac{d[C]}{dt} = -k_2[B][C]$$

```
sol[k1_, kn1_, k2_, a0_, c0_] :=  NDSolve[{a'[t] == -k1*a[t] + kn1*b[t],     b'[t] == k1*a[t] -
kn1*b[t] - k2*b[t]*c[t], c'[t] == -k2*b[t]*c[t],     a[0] == (a0 kn1)/(k1 + kn1), b[0] == (a0
k1)/(k1 + kn1),     c[0] == c0}, {a, b, c}, {t, 0, 1000}]

Manipulate[{Plot[-c'[10] /. sol[k1, kn1, k2, a0, c0], {c0, 0, 0.1},     PlotRange -> {0,
0.0001}]}, {{k1, 0.001, "k1"}, 0,    10}, {{kn1, 1, "kn1"}, 0, 10}, {{k2, 1000, "k2"}, 0,
10}, {{a0, 0.1, "a0"}, 0, 10}, {{c0, 0.01, "c0"}, 0, 0.1}]

Export["table.xls",   Table[-c'[10] /. sol[0.001, 1, 100, 0.1, x], {x, 0, 0.1, 0.001}]]
```

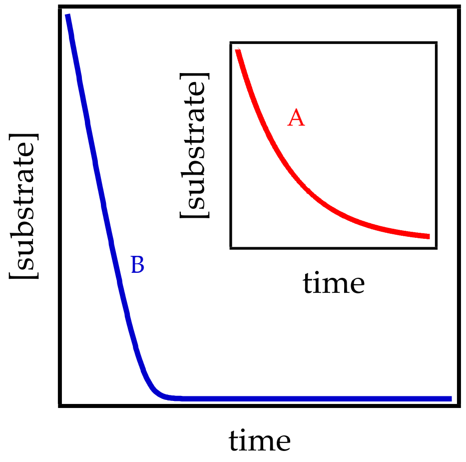


Figure 4. Decays of substrate ArH according to eqs 5 and 6 assuming rate-limiting proton transfer (k_2[ArH]/k_{-1} = 0.1; curve A) and rate-limiting deaggregation (k_2[ArH]/k_{-1} = 10; curve B).

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2[\mathrm{C}]} \text{product}$$

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k_1[\mathrm{A}] + k_{-1}[\mathrm{B}]$$

$$\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = k_1[\mathrm{A}] - k_{-1}[\mathrm{B}] - k_2[\mathrm{B}][\mathrm{C}]$$

$$\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = -k_2[\mathrm{B}][\mathrm{C}]$$

```
sol[k1_, kn1_, k2_, a0_, c0_] :=   NDSolve[{a'[t] == -k1*a[t] + kn1*b[t],     b'[t] == k1*a[t] -
kn1*b[t] - k2*b[t]*c[t], c'[t] == -k2*b[t]*c[t],     a[0] == (a0 kn1)/(k1 + kn1), b[0] == (a0
k1)/(k1 + kn1),     c[0] == c0}, {a, b, c}, {t, 0, 10000}]

Export["table.xls", {Table[    Evaluate[c[t] /. sol[0.0001, 1, 10, 0.1, 0.01]], {t, 0, 50000,
10}], Table[    Evaluate[c[t] /. sol[0.0001, 1, 1000, 0.1, 0.01]], {t, 0, 5000,      1}]}]
```

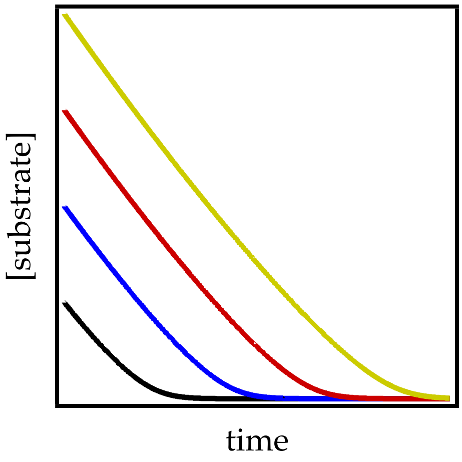
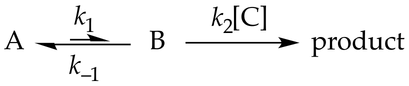


Figure 5. Zeroth-order decays at various initial starting concentrations of ArH showing parallel decays and the onset of rate-limiting proton transfer (curvatures) at low ArH concentration.



$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{B} \xrightarrow{k_2[\mathrm{C}]} \text{product}$$

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k_1[\mathrm{A}] + k_{-1}[\mathrm{B}]$$

$$\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = k_1[\mathrm{A}] - k_{-1}[\mathrm{B}] - k_2[\mathrm{B}][\mathrm{C}]$$

$$\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = -k_2[\mathrm{B}][\mathrm{C}]$$

```
sol[k1_, kn1_, k2_, a0_, c0_] :=   NDSolve[{a'[t] == -k1*a[t] + kn1*b[t],     b'[t] == k1*a[t] -
kn1*b[t] - k2*b[t]*c[t], c'[t] == -k2*b[t]*c[t],     a[0] == (a0 kn1)/(k1 + kn1), b[0] == (a0
k1)/(k1 + kn1),     c[0] == c0}, {a, b, c}, {t, 0, 10000}]

Export["table.xls",  { Table[Evaluate[c[t] /. sol[0.00001, 0.1, 1000, 0.1, 0.001]], {t, 0,
5000, 1}], Table[Evaluate[c[t] /. sol[0.00001, 0.1, 1000, 0.1, 0.002]], {t, 0,     5000, 1}],
Table[Evaluate[c[t] /. sol[0.00001, 0.1, 1000, 0.1, 0.003]], {t, 0,     5000, 1}]}]
```

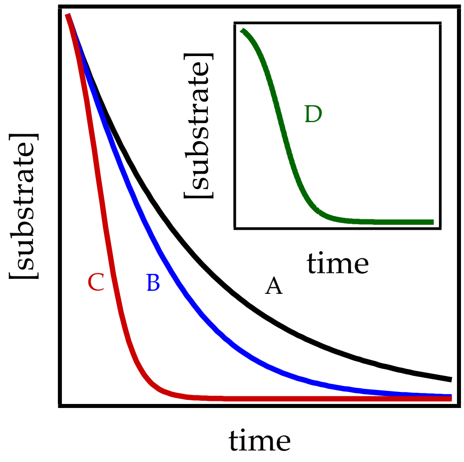


Figure 8. Varying degrees of autocatalysis superimposed on first-order decays: curve A, none; curve B, mild; curve C, medium; curve D, strong.

$$\mathrm{A} \xrightarrow{k_1} \mathrm{B}$$

$$\mathrm{A} \xrightarrow{k_2[\mathrm{B}]} \mathrm{B}$$

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k_1[\mathrm{A}] - k_2[\mathrm{A}][\mathrm{B}]$$

$$\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} = k_1[\mathrm{A}] + k_2[\mathrm{A}][\mathrm{B}]$$

```
sol[k1_, k2_, a0_] :=   NDSolve[{a'[t] == -k1*a[t] - k2*a[t]*b[t],     b'[t] == k1*a[t] +
k2*a[t]*b[t], a[0] == a0, b[0] == 0}, {a,     b}, {t, 0, 1000}]

Export["table.xls",   {Table[Evaluate[a[t] /. sol[0.1, 0, 0.1]], {t, 0, 60, 0.3}],
Table[Evaluate[a[t] /. sol[0.1, 1, 0.1]], {t, 0, 60, 0.3}], Table[Evaluate[a[t] /. sol[0.1, 5, 0.1]],
{t, 0, 60, 0.3}]}]
```

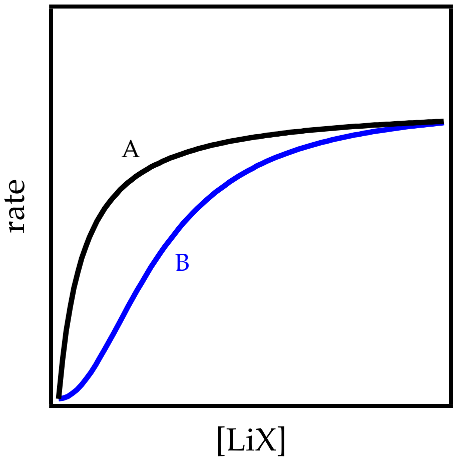


Figure 9. Simulation of catalysis showing first-order (curve A) and second-order (curve B) saturation kinetics.

$$\text{rate} = \frac{ax^n}{1 + ax^n}$$

```
Export["table.xls", {Table[1*x^1/(1 + 1*x^1), {x, 0, 10, 0.1}], Table[0.2*x^2/(1 + 0.2*x^2),
{x, 0, 10, 0.1}]}]
```

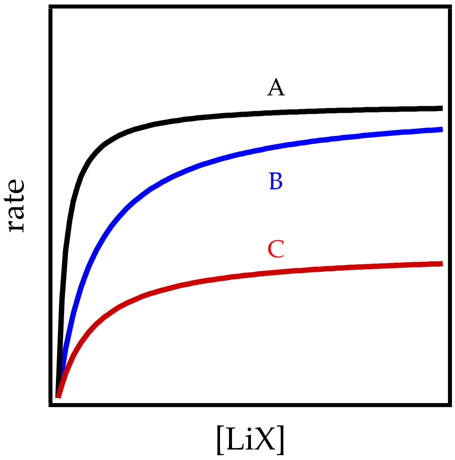


Figure 10. Saturation behavior for LiX catalysts. Curve A is a strong catalyst, curve B is a weak catalyst, and curve C corresponds to catalysis with a different deaggregation step than those of curves A and B.

$$\text{rate} = \frac{ax^n}{1 + ax^n}$$

```
Export["table.xls", {Table[5*x^1/(1 + 5*x^1), {x, 0, 10, 0.1}], Table[0.2*x^1/(1 + 0.2*x^1),
{x, 0, 10, 0.1}], Table[0.5*x^1/(1 + 1*x^1), {x, 0, 10, 0.1}]}]
```

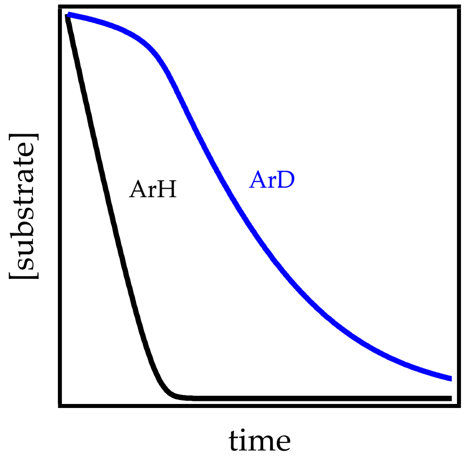
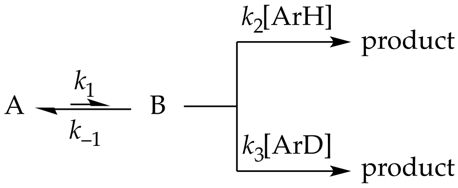


Figure 11. Plot showing preferential metalation of ArH over ArD corresponding to $k_H/k_D = 24$.



$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B]$$

$$\frac{d[B]}{dt} = k_1[A] - k_{-1}[B] - k_2[B][ArH] - k_3[B][ArD]$$

$$\frac{d[ArH]}{dt} = -k_2[B][ArH]$$

$$\frac{d[ArD]}{dt} = -k_3[B][ArD]$$

```
sol[k1_, kn1_, k2_, k3_, a0_, h0_, d0_] :=  NDSolve[{a'[t] == -k1*a[t] + kn1*b[t],    b'[t] ==
k1*a[t] - kn1*b[t] - k2*b[t]*h[t] - k3*b[t]*d[t],    h'[t] == -k2*b[t]*h[t], d'[t] == -
k3*b[t]*d[t],    a[0] == (a0 kn1)/(k1 + kn1), b[0] == (a0 k1)/(k1 + kn1),    h[0] == h0, d[0]
== d0}, {a, b, h, d}, {t, 0, 10000}]

Manipulate[ Plot[Evaluate[{h[t], d[t]} /. sol[k1, kn1, k2, k3, a0, h0, d0]], {t,    0, 1000}],
{{k1, 0.0001, "k1"}, 0, 1}, {{kn1, 1, "kn1"}, 0,    1}, {{k2, 24000, "k2"}, 0, 1}, {{k3, 1000,
"k3"}, 0,    1}, {{a0, 0.1, "a0"}, 0, 1}, {{h0, 0.001, "h0"}, 0,    1}, {{d0, 0.001, "d0"}, 0, 1}]

Export["table.xls",   Flatten[Table[   Evaluate[{h[t], d[t]} /.     sol[0.0001, 1, 24000, 1000,
0.1, 0.001, 0.001]], {t, 0, 2000,     1}], 1]]
```

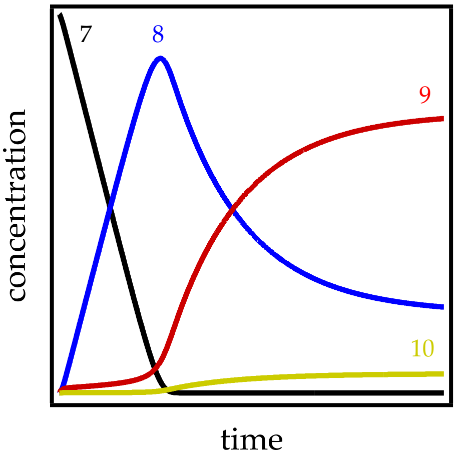


Figure 17. Simulated plots of concentration versus time for the reaction of **7** (black trace) with lithium diisopropylamide in tetrahydrofuran at –78 °C. The functions derive from a mathematical model based on Scheme 6. xxno label on yellow

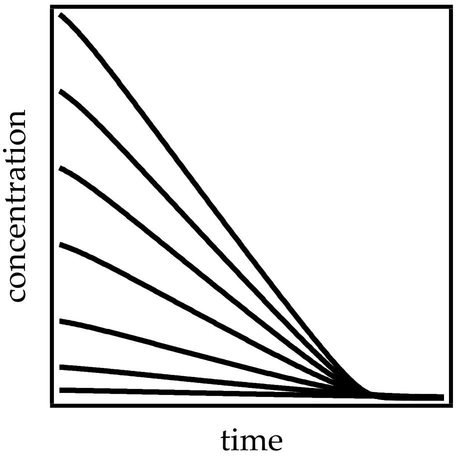


Figure 18. Simulations of plots showing concentration versus time for various initial concentrations of carbamate **7**. The original manuscript simply displayed independent linear fits.

$$\frac{\mathrm{d}[\mathrm{ArH}]}{\mathrm{d}t} = -k_1[\mathrm{ArH}][\mathrm{A}_2] - k_3[\mathrm{A{\cdot}ArLi}^*][\mathrm{ArH}]$$

$$\frac{\mathrm{d}[\mathrm{ArLi}]}{\mathrm{d}t} = -k_4[\mathrm{ArLi}][\mathrm{A}_2] + k_{-4}[\mathrm{A{\cdot}ArLi}][\mathrm{A}_2]^{0.5} + 2k_3[\mathrm{A{\cdot}ArLi}^*][\mathrm{ArH}]$$

$$\frac{\mathrm{d}[\mathrm{A{\cdot}ArLi}]}{\mathrm{d}t} = k_1[\mathrm{ArH}][\mathrm{A}_2] - k_2[\mathrm{A{\cdot}ArLi}] + k_{-2}[\mathrm{A{\cdot}ArLi}^*] + k_4[\mathrm{ArLi}][\mathrm{A}_2] - k_{-4}[\mathrm{A{\cdot}ArLi}][\mathrm{A}_2]^{0.5}$$

$$\frac{\mathrm{d}[\mathrm{A{\cdot}ArLi}^*]}{\mathrm{d}t} = k_2[\mathrm{A{\cdot}ArLi}] - k_{-2}[\mathrm{A{\cdot}ArLi}^*] - k_3[\mathrm{A{\cdot}ArLi}^*][\mathrm{ArH}]$$

$$[\mathrm{A}_2] = \frac{[\mathrm{A}]_0 - [\mathrm{ArLi}]}{2} - [\mathrm{A{\cdot}ArLi}] - [\mathrm{A{\cdot}ArLi}^*]$$

```
sys[k1_, k2_, kn2_, k3_, k4_, kn4_, a0_, s0_] :=   NDSolve[{arh'[t] == -k1*arh[t]*a2[t] -
k3*aarlis[t]*arh[t],     arli'[t] == -k4*arli[t]*a2[t] + kn4*aarli[t]*a2[t]^0.5 +       2
k3*aarlis[t]*arh[t],     aarli'[t] ==       k1*arh[t]*a2[t] - k2*aarli[t] + kn2*aarlis[t] +
k4*arli[t]*a2[t] -      kn4*aarli[t]*a2[t]^0.5,     aarlis'[t] == k2*aarli[t] - kn2*aarlis[t] -
k3*aarlis[t]*arh[t],     a2[t] == a0/2 - 0.5*arli[t] - aarli[t] - aarlis[t], arh[0] == s0,     arli[0] ==
aarli[0] == aarlis[0] == 0}, {arh, arli, aarli, aarlis,     a2}, {t, 0, 2000}]

Manipulate[  Flatten[Table[    Evaluate[{arh[t], arli[t], aarli[t], aarlis[t]} /.       sys[k1, k2,
kn2, k3, k4, kn4, a0, s0]], {t, 0, 2000, 1}],    1], {{k1, 0.020495, "k1"}, 0, 1}, {{k2, 0.09695,
"k2"}, 0,    1}, {{kn2, 1.4131, "kn2"}, 0, 1}, {{k3, 828.12, "k3"}, 0,    1}, {{k4, 0.0461,
"k4"}, 0, 1}, {{kn4, 0.0027294, "k1"}, 0,    1}, {{a0, 0.1, "a0"}, 0, 1}, {{s0, 0.0074, "s0"}, 0,
1}]

Export["carbamate.xls",«insert table from above»]

Manipulate[{Flatten[    Table[Evaluate[      arh[t] /. sys[k1, k2, kn2, k3, k4, kn4, a0, 0.001]],
{t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[      arh[t] /. sys[k1, k2, kn2, k3, k4, kn4, a0,
0.004]], {t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[      arh[t] /. sys[k1, k2, kn2, k3, k4,
kn4, a0, 0.01]], {t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[      arh[t] /. sys[k1, k2, kn2,
k3, k4, kn4, a0, 0.02]], {t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[      arh[t] /. sys[k1,
k2, kn2, k3, k4, kn4, a0, 0.03]], {t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[      arh[t] /.
sys[k1, k2, kn2, k3, k4, kn4, a0, 0.04]], {t, 0, 200,       0.5}]], Flatten[    Table[Evaluate[
arh[t] /. sys[k1, k2, kn2, k3, k4, kn4, a0, 0.05]], {t, 0, 200,       0.5}]]}, {{k1, 0.020495,
"k1"}, 0, 1}, {{k2, 0.09695, "k2"}, 0,    1}, {{kn2, 1.4131, "kn2"}, 0, 1}, {{k3, 828.12,
"k3"}, 0,    1}, {{k4, 0.0461, "k4"}, 0, 1}, {{kn4, 0.0027294, "k1"}, 0,    1}, {{a0, 0.5, "a0"},
0, 1}, {{s0, 0.0074, "s0"}, 0, 1}]

Export["carbamate.xls",«insert table from above»]
```

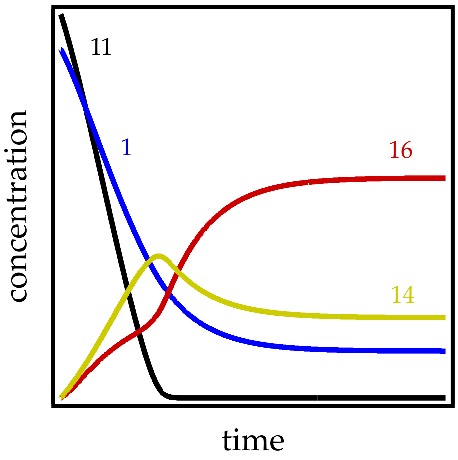


Figure 19. Simulated time-dependent concentrations of ester **11**, lithium diisopropylamide dimer **1**, enolate homodimer **14**, and mixed dimer **16**. The functions are from the model described in Scheme 7.

$$\frac{d[\text{ester}]}{dt} = -k_2[\text{A}][\text{ester}]$$

$$\frac{d[\text{A}_2]}{dt} = -k_1[\text{A}_2] + k_{-1}[\text{A}]^2 - k_3[\text{A}_2][\text{E}] + k_{-3}[\text{A}_2][\text{AE}]$$

$$\frac{d[\text{A}]}{dt} = 2k_1[\text{A}_2] - 2k_{-1}[\text{A}]^2 - k_2[\text{A}][\text{ester}] + k_3[\text{A}_2][\text{E}] - k_{-3}[\text{A}][\text{AE}] - k_4[\text{A}][\text{E}] + k_{-4}[\text{AE}]$$

$$\frac{d[\text{AE}]}{dt} = k_3[\text{A}_2][\text{E}] - k_{-3}[\text{A}][\text{AE}] + k_4[\text{A}][\text{E}] - k_{-4}[\text{AE}]$$

$$\frac{d[\text{E}]}{dt} = k_2[\text{A}][\text{ester}] - k_3[\text{A}_2][\text{E}] + k_{-3}[\text{A}][\text{AE}] - k_4[\text{A}][\text{E}] + k_{-4}[\text{AE}] - 2k_5[\text{E}]^2 + 2k_{-5}[\text{E}_2]$$

$$\frac{d[\text{E}_2]}{dt} = k_5[\text{E}]^2 - k_{-5}[\text{E}_2]$$

```
sol[k1_, kn1_, k2_, k3_, kn3_, k4_, kn4_, k5_, kn5_, a0_, s0_] := NDSolve[{est'[t] == -
k2*a[t]*est[t], a2'[t] == -k1*a2[t] + kn1*a[t]^2 - k3*a2[t]*e[t] + kn3*a[t]*ae[t], a'[t] ==
2 k1*a2[t] - 2 kn1*a[t]^2 - k2*a[t]*est[t] + k3*a2[t]*e[t] - kn3*a[t]*ae[t] - k4*a[t]*e[t] +
kn4*ae[t], ae'[t] == k3*a2[t]*e[t] - kn3*a[t]*ae[t] + k4*a[t]*e[t] - kn4*ae[t], e'[t] ==
k2*a[t]*est[t] - k3*a2[t]*e[t] + kn3*a[t]*ae[t] - k4*a[t]*e[t] + kn4*ae[t] - 2 k5*e[t]^2 + 2
kn5*e2[t], e2'[t] == k5*e[t]^2 - kn5*e2[t], a2[0] == a0/2, est[0] == s0, a[0] == ae[0] ==
e[0] == e2[0] == 0}, {est, a2, a, ae, e, e2}, {t, 0, 20000}]

Manipulate[ Flatten[Table[ Evaluate[{est[t], a2[t], ae[t], e2[t]} /. sol[k1, kn1, k2, k3,
kn3, k4, kn4, k5, kn5, a0, s0]], {t, 0, 20000, 10}], 1], {{k1, 0.000070944, "k1"}, 0, 1},
{{kn1, 267.46, "kn1"}, 0, 1}, {{k2, 223.44, "k2"}, 0, 1}, {{k3, 0.33594, "k3"}, 0, 1},
{{kn3, 0.84648, "kn3"}, 0, 1}, {{k4, 910.74, "k4"}, 0, 1}, {{kn4, 0.00051948, "k1"}, 0,
1}, {{k5, 451.57, "k5"}, 0, 1}, {{kn5, 0.0080254, "kn5"}, 0, 1}, {{a0, 0.1, "a0"}, 0, 1},
{{s0, 0.055, "s0"}, 0, 1}]

Export["ester.xls",«insert table from above»]
```

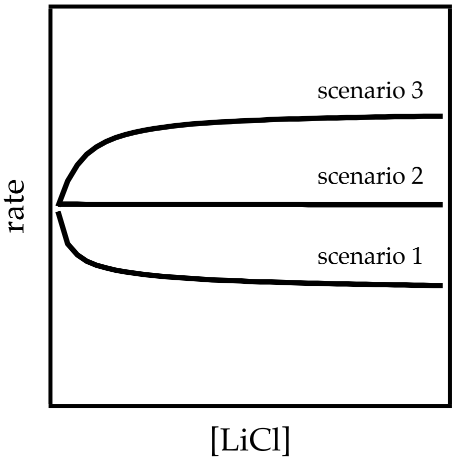


Figure 22. Plot of initial rate versus LiCl concentration showing catalyzed inhibition (scenario 1), no change in rate (scenario 2), and catalyzed acceleration (scenario 3).

$$\frac{\mathrm{d}[\mathrm{A}_2]}{\mathrm{d}t}=-k_1[\mathrm{A}_2]+k_{-1}[\mathrm{A}_2^*]-(k_2+k_5[\mathrm{LiX}])[\mathrm{A}_2]+\left(k_{-2}+\frac{k_5k_{-2}}{k_2}[\mathrm{LiX}]\right)[\mathrm{A}]^2$$

$$\frac{\mathrm{d}[\mathrm{A}_2^*]}{\mathrm{d}t}=k_1[\mathrm{A}_2]-k_{-1}[\mathrm{A}_2^*]-k_3[\mathrm{A}_2^*][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t}=2(k_2+k_5[\mathrm{LiX}])[\mathrm{A}_2]-2\left(k_{-2}+\frac{k_5k_{-2}}{k_2}[\mathrm{LiX}]\right)[\mathrm{A}]^2-k_4[\mathrm{A}][\mathrm{S}]+k_3[\mathrm{A}_2^*][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t}=-k_3[\mathrm{A}_2^*][\mathrm{S}]-k_4[\mathrm{A}][\mathrm{S}]$$

```
sol[k1_, kn1_, k2_, kn2_, k3_, k4_, k5_, a0_, s0_, c_] :=  NDSolve[{a2'[     t] == -(k1) a2[t]
+ (kn1) a2s[t] - (k2 + k5*c) a2[       t] + (kn2 + k5*kn2/k2*c) a[t]^2,     a2s'[t] == (k1) a2[t] -
(kn1) a2s[t] - k3*a2s[t]*s[t],     a'[t] ==       2 (k2 + k5*c) a2[t] - 2 (kn2 + k5*kn2/k2*c) a[t]^2
-       k4*a[t]*s[t] + k3*a2s[t]*s[t],     s'[t] == -k3*a2s[t]*s[t] - k4*a[t]*s[t],     a2[0] == (     4
a0 kn1 + (k2 kn1^2)/(k1 kn2 + kn1 kn2) - (       Sqrt[k2] kn1^(3/2) Sqrt[k2 kn1 + 8 a0 k1 kn2
+ 8 a0 kn1 kn2])/(       k1 kn2 + kn1 kn2))/(8 (k1 + kn1)),      a2s[0] == (     4 a0 k1 + (k1 k2
kn1)/(k1 kn2 + kn1 kn2) - (       k1 Sqrt[k2] Sqrt[kn1] Sqrt[       k2 kn1 + 8 a0 k1 kn2 + 8 a0
kn1 kn2])/(k1 kn2 + kn1 kn2))/(     8 (k1 + kn1)),     a[0] == (-k2 kn1 +       Sqrt[k2] Sqrt[kn1]
Sqrt[k2 kn1 + 8 a0 k1 kn2 + 8 a0 kn1 kn2])/(      4 (k1 kn2 + kn1 kn2)), s[0] == s0}, {a2, a2s,
a, s}, {t, 0,      10000}]

Manipulate[ Table[-D[Fit[       Table[Evaluate[          Flatten[{t, s[t]} /.            sol[k1, kn1, k2,
kn2, k3, k4, k5, a0, s0, c]]], {t, ti, tf,          10}], {1, x, x^2}, x], x] /. x -> 0, {a0, 0, 0.3,
0.001}], {{k1, 0.0005, "k1"}, 0, 10}, {{kn1, 0.5, "kn1"}, 0,    10}, {{k2, 1.*^-10, "k2"}, 0,
10}, {{kn2, 0.1, "kn2"}, 0,    10}, {{k3, 5, "k3"}, 0, 10}, {{k4, 33, "k4"}, 0,    10}, {{k5,
0.05, "k5"}, 0, 10}, {{a0, 0.3, "a0"}, 0,    1}, {{s0, 0.005, "s0"}, 0, 10}, {{c, 0, "c"}, 0,
0.01}, {{ti, 10, "ti"}, 0, 1000}, {{tf, 200, "tf"}, 0, 1000}]
```

III. Parallel versus Serial Barrier Order Dependence

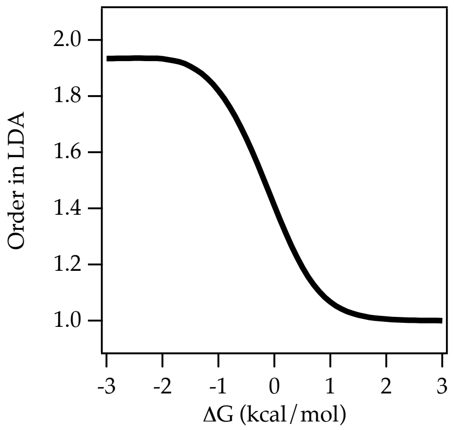
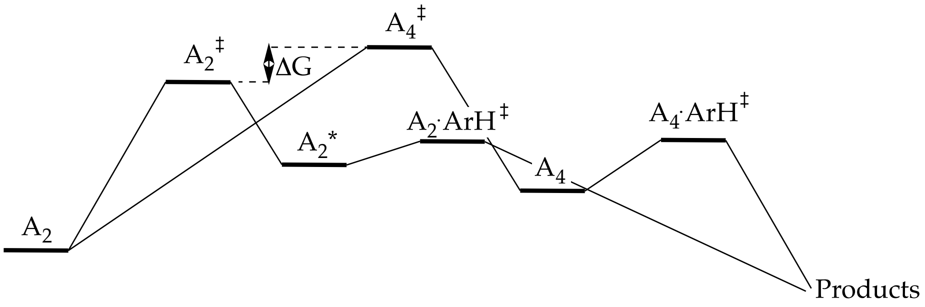


Figure A. Order in LDA versus ΔG (parallel)



$$\frac{\mathrm{d}[\mathrm{A}_2]}{\mathrm{d}t} = -k_1[\mathrm{A}_2] + k_{-1}[\mathrm{A}_2^*] - 2k_1k_2[\mathrm{A}_2]^2 + 2\frac{k_1k_2}{K}[\mathrm{A}_4] + \frac{k_3}{2}[\mathrm{A}_2^*][\mathrm{S}] + \frac{3k_4}{2}[\mathrm{A}_4][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{A}_2^*]}{\mathrm{d}t} = k_1[\mathrm{A}_2] - k_{-1}[\mathrm{A}_2^*] - k_3[\mathrm{A}_2^*][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{A}_4]}{\mathrm{d}t} = k_1k_2[\mathrm{A}_2]^2 - \frac{k_1k_2}{K}[\mathrm{A}_4] - k_4[\mathrm{A}_4][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -k_3[\mathrm{A}_2^*][\mathrm{S}] - k_4[\mathrm{A}_4][\mathrm{S}]$$

```
Solve[{-k1*a2 + kn1*a2s == 0, -2 k2*k1*a2^2 + 2*k2*k1*a4/Keq == 0,    2 a2 + 2 a2s + 4
a4 == a0}, {a2, a2s, a4}]

sol2[k1_, kn1_, k2_, Keq_, k3_, k4_, a0_, s0_] :=   NDSolve[{a2'[t] == -k1*a2[t] +
kn1*a2s[t] - 2 k2*k1*a2[t]^2 +       2*k2*k1*a4[t]/Keq + 1/2 k3*a2s[t]*s[t] +
3/2*k4*a4[t]*s[t],     a2s'[t] == k1*a2[t] - kn1*a2s[t] - k3*a2s[t]*s[t],     a4'[t] ==
k2*k1*a2[t]^2 - k2*k1*a4[t]/Keq - k4*a4[t]*s[t],     s'[t] == -k3*a2s[t]*s[t] - k4*a4[t]*s[t],
a2[0] == (-k1 - kn1 + Sqrt[      k1^2 + 2 k1 kn1 + kn1^2 + 4 a0 Keq kn1^2])/(4 Keq kn1),
a2s[0] == (-(k1/Keq) - k1^2/(Keq kn1) + (      k1 Sqrt[k1^2 + 2 k1 kn1 + kn1^2 + 4 a0 Keq
kn1^2])/(Keq kn1))/(     4 kn1), a4[0] == ((2 k1)/Keq + k1^2/(Keq kn1) + 2 a0 kn1 + kn1/
Keq - Sqrt[k1^2 + 2 k1 kn1 + kn1^2 + 4 a0 Keq kn1^2]/Keq - (      k1 Sqrt[k1^2 + 2 k1 kn1 +
kn1^2 + 4 a0 Keq kn1^2])/(Keq kn1))/(     8 kn1), s[0] == s0}, {a2, a2s, a4, s}, {t, 0, 10000}]

Manipulate[{Plot[-s'[1] /.      sol2[k1, kn1, Exp[-4186.8 g/(8.314*195.13)], keq1, k3, k4, a0,
s0], {a0, 0, 10}],    Plot[Evaluate[{s[t]} /.       sol2[k1, kn1, Exp[-4186.8 g/(8.314*195.13)],
keq1, k3, k4, a0,       s0]], {t, 0, 1000}, PlotRange -> {0, 0.01}]}, {{k1, 0.00001,     "k1"}, 0,
10}, {{kn1, 10, "kn1"}, 0, 1000}, {{g, 0, "g"}, -10,    10}, {{keq1, 1.`*^-12, "Keq1"}, 0,
1000}, {{k3, 10000, "k3"}, 0,    1000}, {{k4, 1000000000, "k4"}, 0, 1000}, {{a0, 0.1, "a0"},
0,    1}, {{s0, 0.01, "s0"}, 0, 1}]

Flatten[Table[{g, a} /.     FindFit[Flatten[      Table[{10^a0, Log[-s'[0.1]]} /.
sol2[0.000001, 1, Exp[-4186.8 g/(8.314*195.13)], 1.`*^-12,         10000, 1000000000,
10^(a0), 0.01], {a0, -1, 1, 0.01}]],     a*Log[x] + b, {a, b}, x], {g, -3, 3, 1}], 0]
```

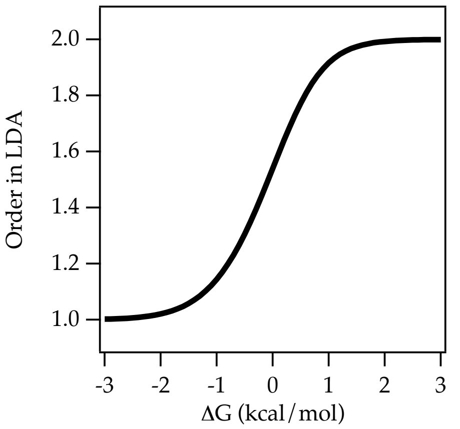
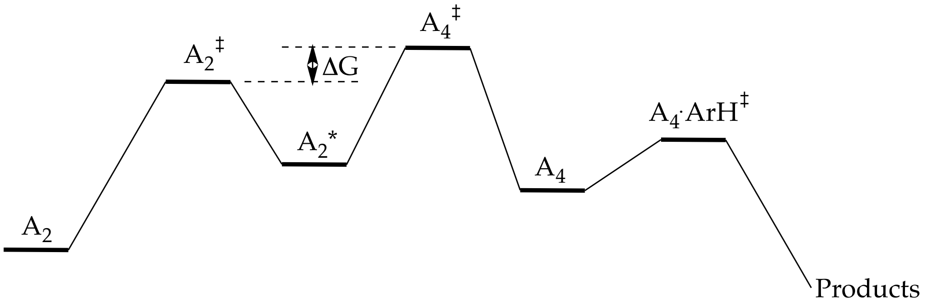


Figure B. Order in LDA versus ΔG (series)



$$\frac{\mathrm{d}[\mathrm{A}_2]}{\mathrm{d}t} = -k_1[\mathrm{A}_2] + k_{-1}[\mathrm{A}_2^*] - k_{-1}k_2[\mathrm{A}_2][\mathrm{A}_2^*] + \frac{k_{-1}k_2}{K}[\mathrm{A}_4] + \frac{3k_3}{2}[\mathrm{A}_4][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{A}_2^*]}{\mathrm{d}t} = k_1[\mathrm{A}_2] - k_{-1}[\mathrm{A}_2^*] - k_{-1}k_2[\mathrm{A}_2][\mathrm{A}_2^*] + \frac{k_{-1}k_2}{K}[\mathrm{A}_4]$$

$$\frac{\mathrm{d}[\mathrm{A}_4]}{\mathrm{d}t} = k_{-1}k_2[\mathrm{A}_2][\mathrm{A}_2^*] - \frac{k_{-1}k_2}{K}[\mathrm{A}_4] - k_3[\mathrm{A}_4][\mathrm{S}]$$

$$\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = -k_3[\mathrm{A}_4][\mathrm{S}]$$

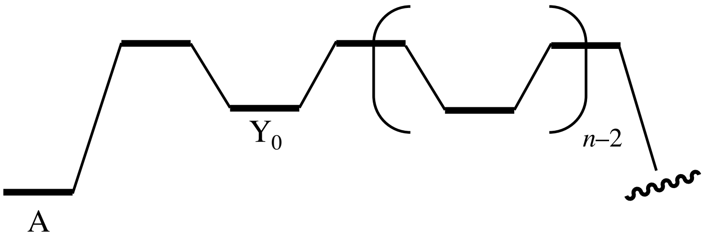
```
Solve[{k1*a2 - kn1*a2s == 0, -k2*kn1*a2*a2s + k2*kn1/Keq1*a4 == 0,    2 a2 + 2 a2s + 4
a4 == a0}, {a2, a2s, a4}]

sol[k1_, kn1_, k2_, Keq1_, k3_, a0_, s0_] :=   NDSolve[{a2'[t] == -k1*a2[t] + kn1*a2s[t] -
k2*kn1*a2[t]*a2s[t] +       k2*kn1/Keq1*a4[t] + 3/2*k3*a4[t]*s[t],     a2s'[t] ==       k1*a2[t] -
kn1*a2s[t] - k2*kn1*a2[t]*a2s[t] + k2*kn1/Keq1*a4[t],     a4'[t] == k2*kn1*a2[t]*a2s[t] -
k2*kn1/Keq1*a4[t] - k3*a4[t]*s[t],     s'[t] == -k3*a4[t]*s[t],     a2[0] == (-k1 - kn1 + Sqrt[
k1^2 + 2 k1 kn1 + 4 a0 k1 Keq1 kn1 + kn1^2])/(4 k1 Keq1),     a2s[0] == (-(k1/Keq1) -
kn1/Keq1 + Sqrt[      k1^2 + 2 k1 kn1 + 4 a0 k1 Keq1 kn1 + kn1^2]/Keq1)/(4 kn1),     a4[0]
==      1/(8 kn1) (k1/Keq1 + 2 a0 kn1 + (2 kn1)/Keq1 + kn1^2/(k1 Keq1) -       Sqrt[k1^2 + 2
k1 kn1 + 4 a0 k1 Keq1 kn1 + kn1^2]/Keq1 - (        kn1 Sqrt[k1^2 + 2 k1 kn1 + 4 a0 k1 Keq1
kn1 + kn1^2])/(        k1 Keq1)), s[0] == s0}, {a2, a2s, a4, s}, {t, 0, 10000}]

Manipulate[{Plot[-s'[1] /.     sol[k1, kn1, Exp[-4186.8 g/(8.314*195.13)], keq1, k3, a0,
s0], {a0, 0, 10}],    Plot[Evaluate[{s[t]} /.       sol[k1, kn1, Exp[-4186.8 g/(8.314*195.13)],
keq1, k3, a0,       s0]], {t, 0, 1000}, PlotRange -> {0, 0.01}],    Flatten[Table[{g, a} /.
FindFit[Flatten[       Table[Log[-s'[1]] /.          sol[k1, kn1, Exp[-4186.8 g/(8.314*195.13)],
keq1, k3, a0,            s0], {a0, 0.01, 10, 0.01}]], a*Log[x] + b, {a, b},       x], {g, -3, 3, 1}],
0]}, {{k1, 0.001, "k1"}, 0,    10}, {{kn1, 1000, "kn1"}, 0, 1000}, {{keq1, 1, "Keq1"}, 0,
1000}, {{k3, 1000000000, "k3"}, 0, 1000}, {{a0, 0.1, "a0"}, 0,    1}, {{g, 0, "g"}, -3, 3},
{{s0, 0.01, "s0"}, 0, 1}]

Flatten[Table[{g, a} /.    FindFit[Flatten[      Table[Log[-s'[1]] /.        sol[0.001, 1000, Exp[-
4186.8 g/(8.314*195.13)], 1, 1000000000,          a0, 0.01], {a0, 0.01, 10, 0.01}]], a*Log[x] +
b, {a, b},      x], {g, -3, 3, 0.1}], 0]
```

IV. Standard Steady State Treatment of Multiple Barriers in Series



Assume the forward rate constant for conversion of A to Y$_0$ is k_1 and the reverse rate constant is k_{-1}. All intermediates Y$_i$ are of the same energy; otherwise stated, they are pairwise interconverted with rate constant k_{-1}. The time-varying concentration of Y$_i$ is:

$$\frac{\mathrm{d}[\mathrm{Y}_i]}{\mathrm{d}t} = k_{-1}[\mathrm{Y}_{i-1}] - 2k_{-1}[\mathrm{Y}_i] + k_{-1}[\mathrm{Y}_{i+1}]$$

Assuming a steady state has been reached $\frac{\mathrm{d}[\mathrm{Y}_i]}{\mathrm{d}t} = 0$, and

$$[\mathrm{Y}_{i-1}] = 2[\mathrm{Y}_i] - [\mathrm{Y}_{i+1}] \tag{1a}$$

On shifting the index,

$$[\mathrm{Y}_i] = 2[\mathrm{Y}_{i+1}] - [\mathrm{Y}_{i+2}] \tag{1b}$$

From equation 1b, it follows that $[\mathrm{Y}_{m-1}] = 2[\mathrm{Y}_m]$ and generally that

$$[\mathrm{Y}_{m-x}] = (x+1)[\mathrm{Y}_m] \tag{2}$$

The time-varying concentration of Y$_0$ is

$$\frac{\mathrm{d}[\mathrm{Y}_0]}{\mathrm{d}t} = k_1[\mathrm{A}] - 2k_{-1}[\mathrm{Y}_0] + k_{-1}[\mathrm{Y}_1]$$

Applying the steady state approximation to the former expression gives

$$[\mathrm{Y}_0] = \frac{k_1[\mathrm{A}] + k_{-1}[\mathrm{Y}_1]}{2k_{-1}} \tag{3}$$

Using equation 1b for [Y$_0$] we find $[\mathrm{Y}_0] = 2[\mathrm{Y}_1] - [\mathrm{Y}_2]$. Given that $\frac{[\mathrm{Y}_2]}{[\mathrm{Y}_1]} = \frac{m-1}{m}$ from equation 2, $[\mathrm{Y}_0] = 2[\mathrm{Y}_1] - \frac{m-1}{m}[\mathrm{Y}_1] = \left(2 - \frac{m-1}{m}\right)[\mathrm{Y}_1]$. Therefore,

$$[\mathrm{Y}_1] = \frac{[\mathrm{Y}_0]}{\left(2 - \frac{m-1}{m}\right)} \tag{4}$$

On combining equations 3 and 4,

$$[\mathrm{Y}_0] = \frac{k_1[\mathrm{A}] + k_{-1}\left(\frac{[\mathrm{Y}_0]}{\left(2 - \frac{m-1}{m}\right)}\right)}{2k_{-1}}$$

Simplification of the above gives

$$\begin{aligned}
[\mathrm{Y}_0] &= \frac{k_1[\mathrm{A}]}{k_{-1}}\left(\frac{1}{2 - \frac{1}{2 - \frac{m-1}{m}}}\right) \\
&= \frac{k_1[\mathrm{A}]}{k_{-1}}\left(\frac{m+1}{m+2}\right)
\end{aligned}$$

To obtain an expression for the rate of consumption of [A] as a function of relevant rate constants and the number of barriers begin with the rate law for A and employ the preceding result:

$$\begin{aligned}
\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} &= -k_1[\mathrm{A}] + k_{-1}[\mathrm{Y}_0] \\
&= -k_1[\mathrm{A}] + k_{-1}\left(\frac{k_1[\mathrm{A}]}{k_{-1}}\left(\frac{m+1}{m+2}\right)\right) \\
&= -k_1\left(1 - \frac{m+1}{m+2}\right)[\mathrm{A}] \\
&= -k_1\left(\frac{1}{m+2}\right)[\mathrm{A}]
\end{aligned}$$

Notice that the number of barriers is $m+2$, so we define $n = m+2$, and the above expression becomes

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -\frac{k_1}{n}[\mathrm{A}] \tag{5}$$

Therefore, the rate of a process that proceeds through *n* barriers of equal activation energy relative to the ground state attenuates the rate associated with reactivity through a single such barrier by a factor of *n*.

Proof of equation 2:

We want to show that $[\mathrm{Y}_{m-x}]=(x+1)[\mathrm{Y}_m]$, so we provisionally assume that $[\mathrm{Y}_{m-x}]=(x+1)[\mathrm{Y}_m]$ and $[\mathrm{Y}_{m-(x-1)}]=x[\mathrm{Y}_m]$ are true. From equation 1a, we know that $[\mathrm{Y}_{i-1}]=2[\mathrm{Y}_i]-[\mathrm{Y}_{i+1}]$, so $[\mathrm{Y}_{m-(x+1)}]=2[\mathrm{Y}_{m-x}]-[\mathrm{Y}_{m-(x-1)}]=2(x+1)[\mathrm{Y}_m]-x[\mathrm{Y}_m]=(x+2)[\mathrm{Y}_m]$, and the proof is complete.

V. Arbitrary Height Barriers in Series

We want to derive a general expression for the overall rate in terms of the microscopic rate constants and do so paralleling Wagner, C. *Advances in Catalysis*, **1970**, *21*, 323. Consider the scheme depicted below.

$$\mathrm{C} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{I}_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \cdots \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} \mathrm{P}$$

At each step, denote $K_i = k_i/k_{-i}$. Assume that a single rate-limiting step exists at position m, for which all preceding and subsequent steps are at equilibrium. By mass balance,

$$\left[\mathrm{I}_{m-1}\right]^* = \left[\mathrm{C}\right]\prod_{i=1}^{m-1} K_i$$

$$\left[\mathrm{I}_m\right]^* = \left[\mathrm{P}\right]\prod_{i=m+1}^{n} K_i^{-1}$$

Given that $K_{\mathrm{eq}} = \prod_{i=1}^{n} K_i$, a rate expression assuming exclusive rate-limitation at position m follows.

$$\begin{aligned} v_m^* &= k_m\left(\left[\mathrm{I}_{m-1}\right]^* - \frac{\left[\mathrm{I}_{m-1}\right]^*}{K_m}\right) \\ &= k_m\left(\left[\mathrm{C}\right]\prod_{i=1}^{m-1} K_i - \frac{\left[\mathrm{P}\right]\prod_{i=m+1}^{n} K_i^{-1}}{K_m}\right) \\ &= k_m\prod_{i=1}^{m-1} K_i\left(\left[\mathrm{C}\right] - \left[\mathrm{P}\right]\prod_{i=1}^{n} K_i^{-1}\right) \\ &= k_m\prod_{i=1}^{m-1} K_i\left(\left[\mathrm{C}\right] - \frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}\right) \end{aligned}$$

The overall rate at steady state is given by

$$v = v_m = k_m\left(\left[\mathrm{I}_{m-1}\right] - \frac{\left[\mathrm{I}_{m-1}\right]}{K_m}\right)$$

We are now in a position to relate v to the various v^*. Begin by finding the ratio $\frac{v_m}{v_m^*}$.

$$
\begin{aligned}
\frac{v_m}{v_m^*} &= \frac{k_m\left(\left[\mathrm{I}_{m-1}\right]-\frac{\left[\mathrm{I}_m\right]}{K_m}\right)}{k_m\prod_{i=1}^{m-1}K_i\left(\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}\right)} \\
&= \frac{\prod_{i=1}^{m-1}K_i^{-1}\left(\left[\mathrm{I}_{m-1}\right]-\frac{\left[\mathrm{I}_m\right]}{K_m}\right)}{\left(\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}\right)}
\end{aligned}
$$

Sum over all $\frac{v_m}{v_m^*}$.

$$
\begin{aligned}
\sum_{m=1}^{n}\frac{v_m}{v_m^*} &= \sum_{m=1}^{n}\frac{\prod_{i=1}^{m-1}K_i^{-1}\left(\left[\mathrm{I}_{m-1}\right]-\frac{\left[\mathrm{I}_m\right]}{K_m}\right)}{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}} \\
&= \frac{1}{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}}\left(\sum_{m=1}^{n}\prod_{i=1}^{m-1}K_i^{-1}\left[\mathrm{I}_{m-1}\right]-\sum_{m=1}^{n}\prod_{i=1}^{m}K_i^{-1}\left[\mathrm{I}_m\right]\right) \\
&\text{note that } \left[\mathrm{I}_0\right] \text{ is } \left[\mathrm{C}\right] \text{ and } \left[\mathrm{I}_n\right] \text{ is } \left[\mathrm{P}\right] \\
&= \frac{1}{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}}\left(\left[\mathrm{C}\right]+\sum_{m=2}^{n}\prod_{i=1}^{m-1}K_i^{-1}\left[\mathrm{I}_{m-1}\right]-\sum_{m=1}^{n-1}\prod_{i=1}^{m}K_i^{-1}\left[\mathrm{I}_m\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}\right) \\
&= \frac{1}{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}}\left(\left[\mathrm{C}\right]+\sum_{m=1}^{n-1}\prod_{i=1}^{m}K_i^{-1}\left[\mathrm{I}_m\right]-\sum_{m=1}^{n-1}\prod_{i=1}^{m}K_i^{-1}\left[\mathrm{I}_m\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}\right) \\
&= \frac{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}}{\left[\mathrm{C}\right]-\frac{\left[\mathrm{P}\right]}{K_{\mathrm{eq}}}} \\
&= 1
\end{aligned}
$$

With this trivial identity, proceed to find the overall reaction rate.

$$
\sum_{m=1}^{n}\frac{v_m}{v_m^*} = \sum_{m=1}^{n}\frac{v}{v_m^*} = v\sum_{m=1}^{n}\frac{1}{v_m^*} = 1
$$

Therefore,

$$v = \frac{1}{\sum_{m=1}^{n} \frac{1}{v_m^*}}$$

$$= \frac{1}{\sum_{m=1}^{n} \frac{1}{k_m \prod_{i=1}^{m-1} K_i \left([\mathrm{C}] - \frac{[\mathrm{P}]}{K_{\mathrm{eq}}} \right)}}$$

$$= \frac{[\mathrm{C}] - \frac{[\mathrm{P}]}{K_{\mathrm{eq}}}}{\sum_{m=1}^{n} \frac{1}{k_m \prod_{i=1}^{m-1} K_i}}$$

Under initial rate conditions, assume [P] ≈ 0 to give the expression below (equation 32 in the manuscript)

$$-\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = \frac{[\mathrm{C}]_0}{\sum_{m=1}^{n} \frac{1}{k_m \prod_{i=1}^{m-1} K_i}}$$

Particular Cases.

1) *Equivalent–Energy Intermediates*

We examine the case where all intermediates in the conversion of C to P are of equal energy. This means $1 = K_2 = K_3 = \ldots = K_{n-1}$. Therefore,

$$-\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = \frac{[\mathrm{C}]_0}{\frac{1}{k_1} + \sum_{m=2}^{n} \frac{1}{k_m K_1}}$$

$$= \frac{k_1 [\mathrm{C}]_0}{1 + \frac{k_1}{K_1} \sum_{m=2}^{n} \frac{1}{k_m}}$$

$$= \frac{k_1 [\mathrm{C}]_0}{1 + k_{-1} \sum_{m=2}^{n} \frac{1}{k_m}}$$

2) *Equivalent–Energy Intermediates and Barriers of Equal Height*

$$
\begin{aligned}
-\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} &= \frac{k_1[\mathrm{C}]_0}{1+k_{-1}\sum_{m=2}^{n}\frac{1}{k_{-1}}} \\
&= \frac{k_1[\mathrm{C}]_0}{1+\sum_{m=2}^{n}1} \\
&= \frac{k_1[\mathrm{C}]_0}{n}
\end{aligned}
$$

3) *Differing Molecularity — Two Barrier Case*

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{I} \underset{k_{-2}}{\overset{k_2[\mathrm{S}]}{\rightleftharpoons}} \text{product}$$

Following the equation described in the previous section,

$$
\begin{aligned}
\frac{\mathrm{d}[\mathrm{product}]}{\mathrm{d}t} &= \frac{[\mathrm{A}]_0}{\sum_{m=1}^{n}\frac{1}{k_m\prod_{i=1}^{m-1}K_i}} \\
&= \frac{[\mathrm{A}]_0}{\frac{1}{k_1}+\frac{1}{k_2[\mathrm{S}]\left(\frac{k_1}{k_{-1}}\right)}} \\
&= \frac{k_1k_2[\mathrm{A}]_0[\mathrm{S}]}{k_{-1}+k_2[\mathrm{S}]}
\end{aligned}
$$

as expected from a standard steady state treatment.

VI. Full reference 17.

Gaussian 03, Revision B.04, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.;Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.;

Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.