SUPPORTING INFORMATION

Lithium Diisopropylamide: Nonequilibrium Kinetics and Lessons Learned About Rate Limitation

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I. Simulation Protocols

Generic Scheme.

Assuming the generic scheme

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2[C]} \text{product}$$
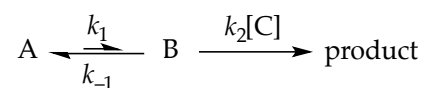
an expression for [B] at a steady state follows.

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

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

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

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.
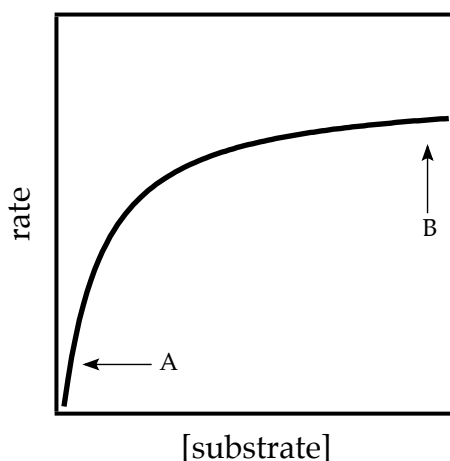
Figure S1. (Figure 2 in manuscript) Saturation kinetics. A and B correspond to regions of substrate-concentration-dependent and substrate-concentration-independent regions.
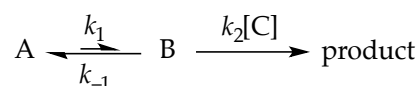
$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2[C]} product$$

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

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

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

```
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}]]
```
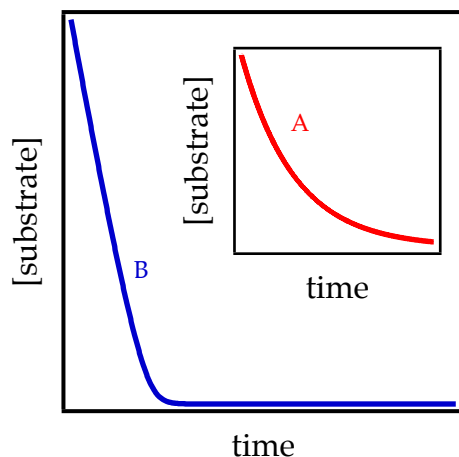
Figure S2.   (Figure 4 in manuscript) Decays of substrate ArH according to eqs 5 and 6 assuming rate-limiting proton transfer (k_2[ArH]/k_{-1} = 0.1; curve A) and rate-limiting deaggregation (k_2[ArH]/k_{-1} = 10; curve B).
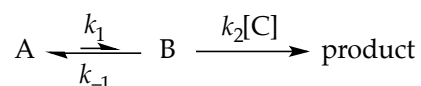
$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2[C]} product$$

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

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

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

```
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, 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}]}]
```
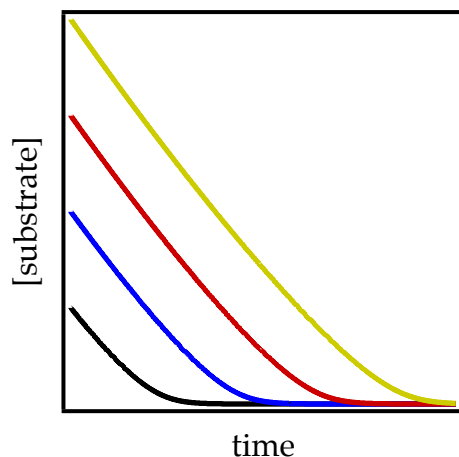
Figure S3.   (Figure 5 in manuscript) Zeroth-order decays at various initial starting concentrations of ArH showing parallel decays and the onset of rate-limiting proton transfer (curvatures) at low ArH concentration.
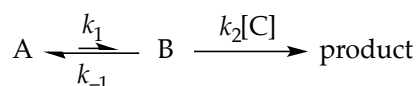
$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2[C]} \text{product}$$

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

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

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

```
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, 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}]}]
```
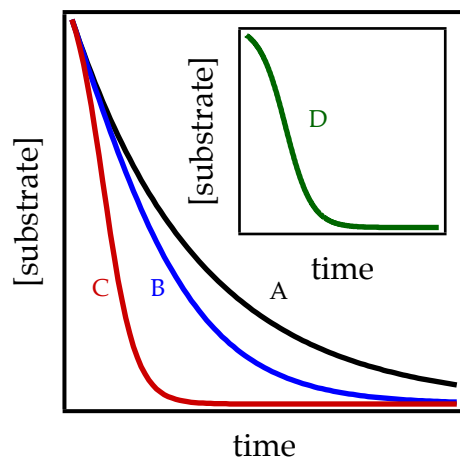
Figure S4. (Figure 8 in manuscript) Varying degrees of autocatalysis superimposed on first-order decays: curve A, none; curve B, mild; curve C, medium; curve D, strong.

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

$$A \xrightarrow{\quad k_2[B] \quad} B$$
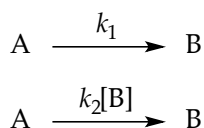
$$\frac{d[A]}{dt} = -k_1[A] - k_2[A][B]$$

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

```
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}]}]
```
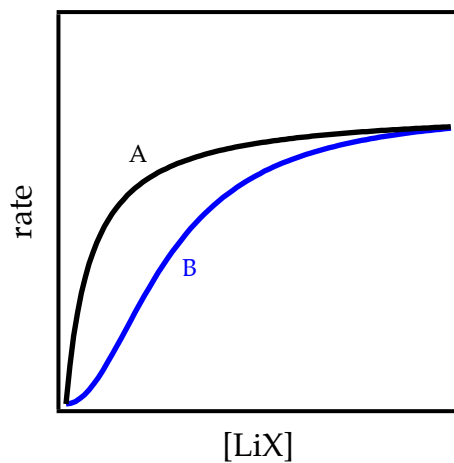
Figure S5. (Figure 9 in manuscript)Simulation of catalysis showing first-order (curve A) and second-order (curve B) saturation kinetics.

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

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}]}]
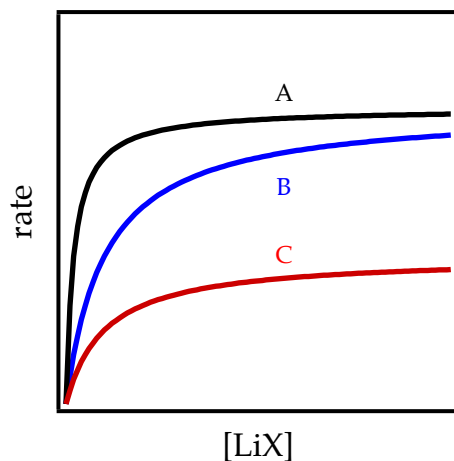
Figure S6. (Figure 10 in manuscript) Saturation behavior for LiX catalysts. Curve A is a strong catalyst, curve B is a weak catalyst, and curve C corresponds to catalysis with a different deaggregation step than those of curves A and B.

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

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}]}]
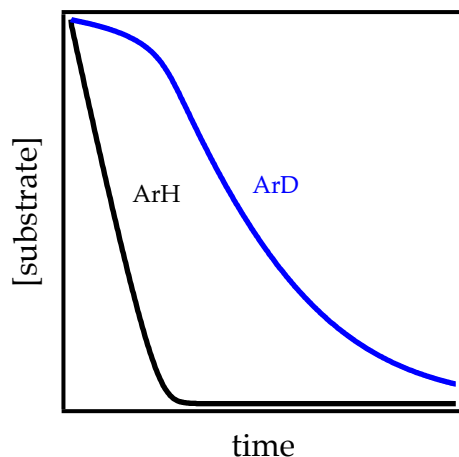
Figure S7. (Figure 11 in manuscript) Plot showing preferential metalation of ArH over ArD corresponding to $k_H/k = 24$.
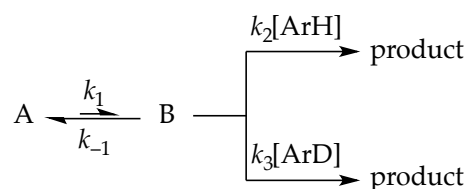
$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B]$$

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

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

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

```
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]]
```
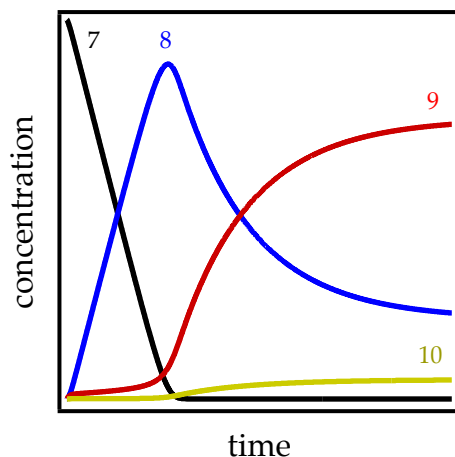
Figure S8.   (Figure 17 in manuscript) Simulated plots of concentration versus time for the reaction of 7 (black trace) with lithium diisopropylamide in tetrahydrofuran at − 78 °C. The functions derive from a mathematical model based on Scheme 6.
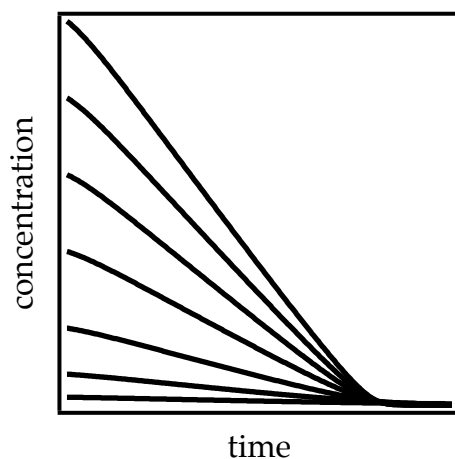
Figure S9. (Figure 18 in manuscript) Simulations of plots showing concentration versus time for various initial concentrations of carbamate **7**. The original manuscript simply displayed independent linear fits.

$$\frac{d[\text{ArH}]}{dt} = -k_1[\text{ArH}][\text{A}_2] - k_3[\text{A·ArLi}^*][\text{ArH}]$$

$$\frac{d[\text{ArLi}]}{dt} = -k_4[\text{ArLi}][\text{A}_2] + k_{-4}[\text{A·ArLi}][\text{A}_2]^{0.5} + 2k_3[\text{A·ArLi}^*][\text{ArH}]$$

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

$$\frac{d[\text{A·ArLi}^*]}{dt} = k_2[\text{A·ArLi}] - k_{-2}[\text{A·ArLi}^*] - k_3[\text{A·ArLi}^*][\text{ArH}]$$

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

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»]
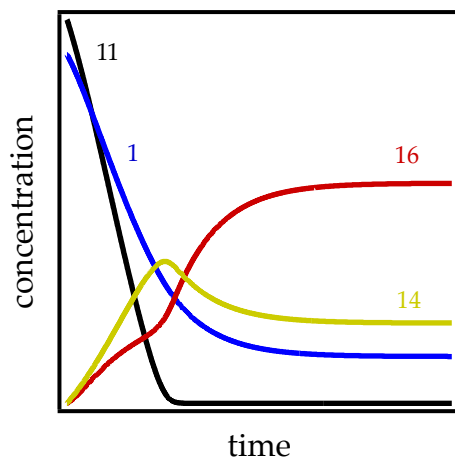
Figure S10. (Figure 19 in manuscript) Simulated time-dependent concentrations of ester **11**, lithium diisopropylamide dimer **1**, enolate homodimer **14**, and mixed dimer **16**. The functions are from the model described in Scheme 7.

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

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

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

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

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

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

```
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»]
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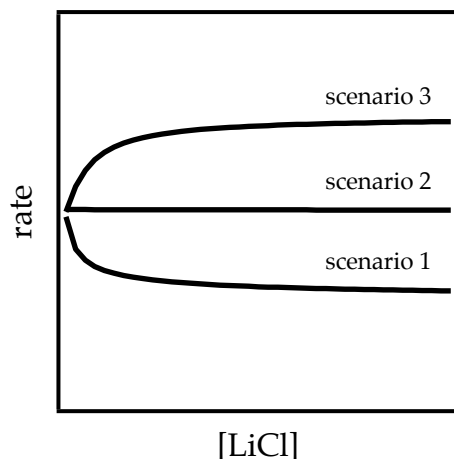**Figure S11**. (Figure 22 in manuscript) Plot of initial rate versus LiCl concentration showing catalyzed inhibition (scenario 1), no change in rate (scenario 2), and catalyzed acceleration (scenario 3).

$$\frac{d[A_2]}{dt} = -k_1[A_2] + k_{-1}[A_2^*] - (k_2 + k_5[LiX])[A_2] + \left(k_{-2} + \frac{k_5 k_{-2}}{k_2}[LiX]\right)[A]^2$$

$$\frac{d[A_2^*]}{dt} = k_1[A_2] - k_{-1}[A_2^*] - k_3[A_2^*][S]$$

$$\frac{d[A]}{dt} = 2(k_2 + k_5[LiX])[A_2] - 2\left(k_{-2} + \frac{k_5 k_{-2}}{k_2}[LiX]\right)[A]^2 - k_4[A][S] + k_3[A_2^*][S]$$

$$\frac{d[S]}{dt} = -k_3[A_2^*][S] - k_4[A][S]$$

```
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
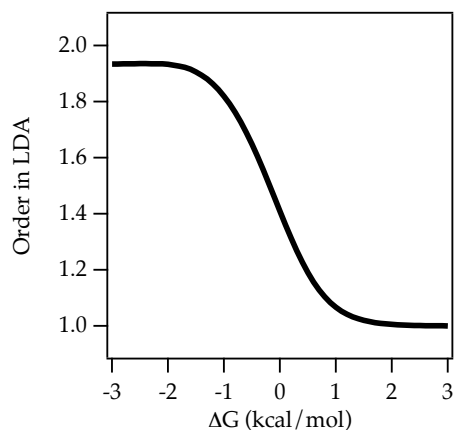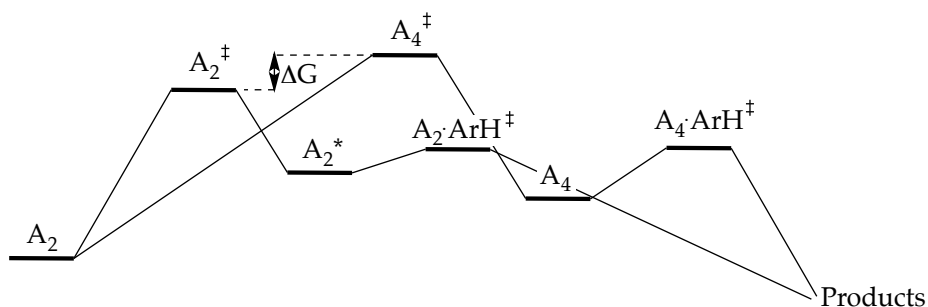

Figure S12. Order in LDA versus ΔG (parallel)

$$\frac{d[A_2]}{dt} = -k_1[A_2] + k_{-1}[A_2^*] - 2k_1k_2[A_2]^2 + 2\frac{k_1k_2}{K}[A_4] + \frac{k_3}{2}[A_2^*][S] + \frac{3k_4}{2}[A_4][S]$$

$$\frac{d[A_2^*]}{dt} = k_1[A_2] - k_{-1}[A_2^*] - k_3[A_2^*][S]$$

$$\frac{d[A_4]}{dt} = k_1k_2[A_2]^2 - \frac{k_1k_2}{K}[A_4] - k_4[A_4][S]$$

$$\frac{d[S]}{dt} = -k_3[A_2^*][S] - k_4[A_4][S]$$

```
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]
```

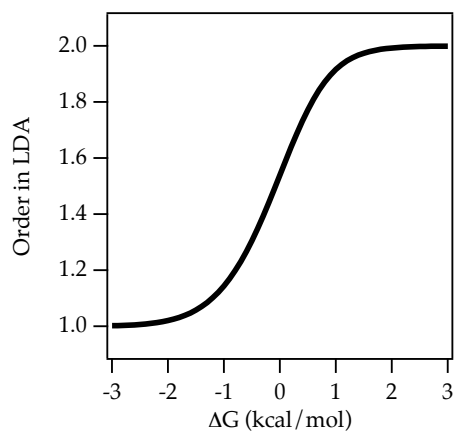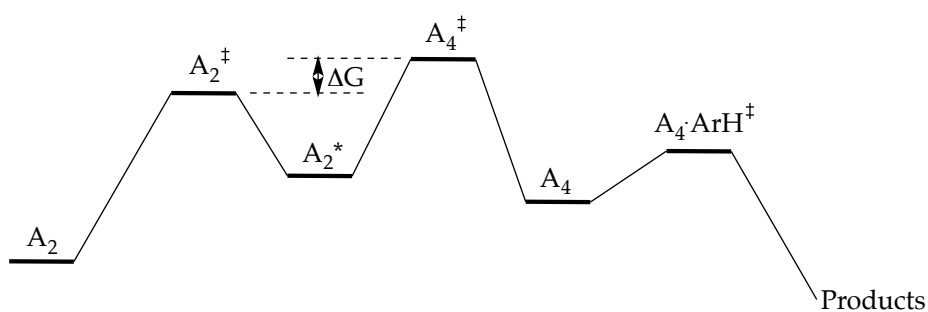**Figure S13**. Order in LDA versus ΔG (series)

$$\frac{d[A_2]}{dt} = -k_1[A_2] + k_{-1}[A_2^*] - k_{-1}k_2[A_2][A_2^*] + \frac{k_{-1}k_2}{K}[A_4] + \frac{3k_3}{2}[A_4][S]$$

$$\frac{d[A_2^*]}{dt} = k_1[A_2] - k_{-1}[A_2^*] - k_{-1}k_2[A_2][A_2^*] + \frac{k_{-1}k_2}{K}[A_4]$$

$$\frac{d[A_4]}{dt} = k_{-1}k_2[A_2][A_2^*] - \frac{k_{-1}k_2}{K}[A_4] - k_3[A_4][S]$$

$$\frac{d[S]}{dt} = -k_3[A_4][S]$$

```
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
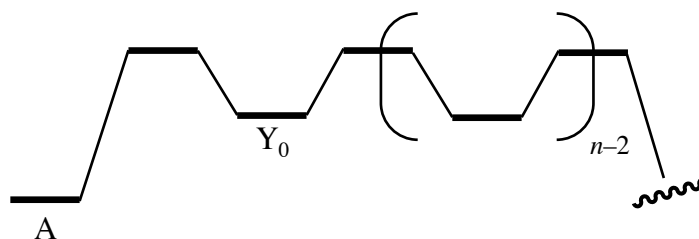
Assume the forward rate constant for conversion of A to Y_0 is k_1 and the reverse rate constant is k_{-1}. All intermediates Y_i are of the same energy; otherwise stated, they are pairwise interconverted with rate constant k_{-1}. The time-varying concentration of Y_i is:

$$\frac{d[Y_i]}{dt} = k_{-1}[Y_{i-1}] - 2k_{-1}[Y_i] + k_{-1}[Y_{i+1}]$$

Assuming a steady state has been reached $\frac{d[Y_i]}{dt} = 0$, and

$$[Y_{i-1}] = 2[Y_i] - [Y_{i+1}] \tag{1a}$$

On shifting the index,

$$[Y_i] = 2[Y_{i+1}] - [Y_{i+2}] \tag{1b}$$

From equation 1b, it follows that $[Y_{m-1}] = 2[Y_m]$ and generally that

$$[Y_{m-x}] = (x+1)[Y_m] \tag{2}$$

The time-varying concentration of Y_0 is

$$\frac{d[Y_0]}{dt} = k_1[A] - 2k_{-1}[Y_0] + k_{-1}[Y_1]$$

Applying the steady state approximation to the former expression gives

$$[Y_0] = \frac{k_1[A] + k_{-1}[Y_1]}{2k_{-1}} \tag{3}$$

Using equation 1b for $[Y_0]$ we find $[Y_0] = 2[Y_1] - [Y_2]$. Given that $\frac{[Y_2]}{[Y_1]} = \frac{m-1}{m}$ from equation 2, $[Y_0] = 2[Y_1] - \frac{m-1}{m}[Y_1] = \left(2 - \frac{m-1}{m}\right)[Y_1]$. Therefore,

$$[Y_1] = \frac{[Y_0]}{\left(2 - \dfrac{m-1}{m}\right)} \tag{4}$$

On combining equations 3 and 4,

$$[Y_0] = \frac{k_1[A] + k_{-1}\left(\dfrac{[Y_0]}{\left(2 - \dfrac{m-1}{m}\right)}\right)}{2k_{-1}}$$

Simplification of the above gives

$$[Y_0] = \frac{k_1[A]}{k_{-1}}\left(\frac{1}{2 - \dfrac{1}{2 - \dfrac{m-1}{m}}}\right)$$

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

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:

$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[Y_0]$$

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

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

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

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

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

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 $[Y_{m-x}] = (x+1)[Y_m]$, so we provisionally assume that $[Y_{m-x}] = (x+1)[Y_m]$ and $[Y_{m-(x-1)}] = x[Y_m]$ are true. From equation 1a, we know that $[Y_{i-1}] = 2[Y_i] - [Y_{i+1}]$, so $[Y_{m-(x+1)}] = 2[Y_{m-x}] - [Y_{m-(x-1)}] = 2(x+1)[Y_m] - x[Y_m] = (x+2)[Y_m]$ and the proof is complete.

V. Arbitrary Height Barriers in Series

We want to derive a general expression for 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.

$$C \xrightleftharpoons[k_{-1}]{k_1} I_1 \xrightleftharpoons[k_{-2}]{k_2} \ldots \xrightleftharpoons[k_{-n}]{k_n} P$$
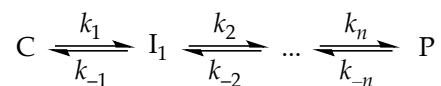
At each step, denote $K_i = k_i/k_{-i}$. Assume that a single rate-limiting step exists at position m, for which all preceding and subsequent steps are at equilibrium. By mass balance,

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

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

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

$$v_m^* = k_m\left(\left[I_{m-1}\right]^* - \frac{\left[I_{m-1}\right]^*}{K_m}\right)$$

$$= k_m\left([C]\prod_{i=1}^{m-1} K_i - \frac{[P]\prod_{i=m+1}^{n} K_i^{-1}}{K_m}\right)$$

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

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

The overall rate at steady state is given by

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

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

$$\frac{v_m}{v_m^*} = \frac{k_m\left([I_{m-1}] - \dfrac{[I_m]}{K_m}\right)}{k_m\displaystyle\prod_{i=1}^{m-1} K_i\left([C] - \dfrac{[P]}{K_{eq}}\right)}$$

$$= \frac{\displaystyle\prod_{i=1}^{m-1} K_i^{-1}\left([I_{m-1}] - \dfrac{[I_m]}{K_m}\right)}{\left([C] - \dfrac{[P]}{K_{eq}}\right)}$$

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

$$\sum_{m=1}^{n}\frac{v_m}{v_m^*} = \sum_{m=1}^{n}\frac{\displaystyle\prod_{i=1}^{m-1} K_i^{-1}\left([I_{m-1}] - \dfrac{[I_m]}{K_m}\right)}{[C] - \dfrac{[P]}{K_{eq}}}$$

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

note that $[I_0]$ is $[C]$ and $[I_n]$ is $[P]$

$$= \frac{1}{[C] - \dfrac{[P]}{K_{eq}}}\left([C] + \sum_{m=2}^{n}\prod_{i=1}^{m-1} K_i^{-1}[I_{m-1}] - \sum_{m=1}^{n-1}\prod_{i=1}^{m} K_i^{-1}[I_m] - \frac{[P]}{K_{eq}}\right)$$

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

$$= \frac{[C] - \dfrac{[P]}{K_{eq}}}{[C] - \dfrac{[P]}{K_{eq}}}$$

$$= 1$$

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,

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

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

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

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

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

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,

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

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

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

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

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

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

$$= \frac{k_1[C]_0}{n}$$

3) *Differing Molecularity — Two Barrier Case*

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \underset{k_{-2}}{\overset{k_2[S]}{\rightleftharpoons}} \text{product}$$
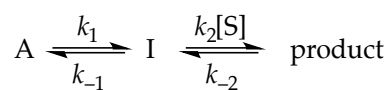
Following the equation described in the previous section,

$$\frac{d[\text{product}]}{dt} = \frac{[A]_0}{\sum_{m=1}^{n} \frac{1}{k_m \prod_{i=1}^{m-1} K_i}}$$

$$= \frac{[A]_0}{\frac{1}{k_1} + \frac{1}{k_2[S]\left(\frac{k_1}{k_{-1}}\right)}}$$

$$= \frac{k_1 k_2 [A]_0 [S]}{k_{-1} + k_2 [S]}$$

As expected from a standard steady state treatment.

VI. Complete Reference 18

Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.