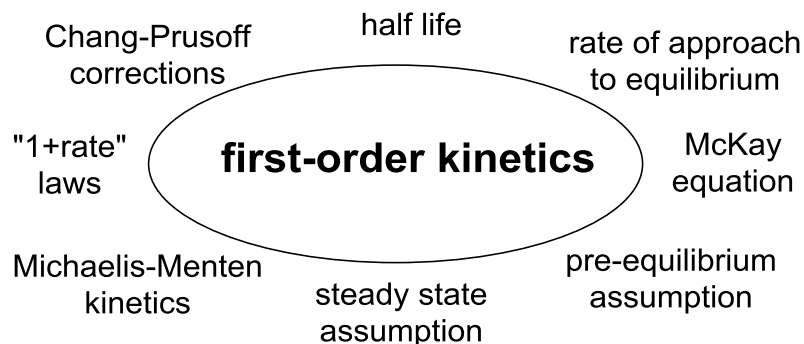# First-Order Kinetics

Eugene E. Kwan

$$[A]_t = [A]_0 \exp(-kt)$$

Scope of Lecture

Chang-Prusoff corrections

half life

rate of approach to equilibrium

"1+rate" laws

first-order kinetics

McKay equation

Michaelis-Menten kinetics

steady state assumption

pre-equilibrium assumption

Helpful References

1. "Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions." Blackmond, D.G. *ACIE*, **2005**, *44*, 4302-4320.

2. "Asymmetric Hydrogenation." Knowles, J.S. *Acc. Chem. Res.* **1983**, *16*, 106-112.

3. "Asymmetric Hydrogenation...Kinetics, Mechanism, and Origin of Enantioselection." Landis, C.R.; Halpern, J. *JACS* **1987**, *109*, 1746-1754.

4. "Reevaluation of the Mechanism of the Amination of Aryl..." Hartwig, Blackmond, Buchwald, et al. *JACS* **2006**, *128*, 3584.

5. "Investgations of Pd-Catalyzed ArX Coupling Reactions..." Blackmond, D.G. et al. *JOC*, **2006**, *71*, 4711-4722.

Key Questions:
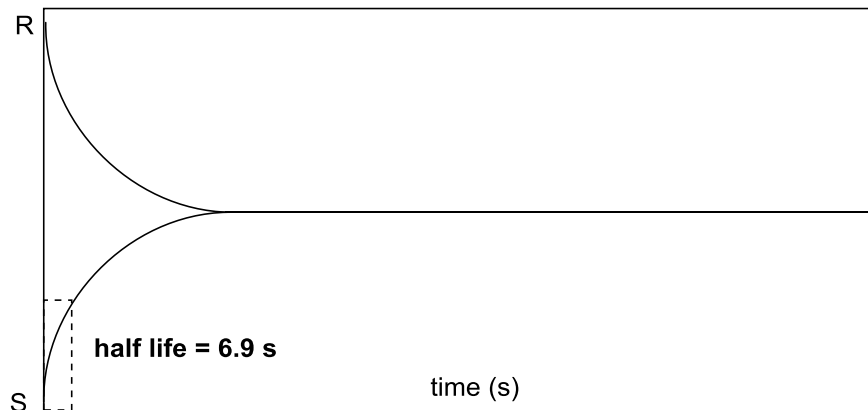
half life = 6.9 s

If the half life of this process is 6.9 s, what is the value of k_f? 0.1 s^{-1}? 10 s^{-1} 0.05 s^{-1}?
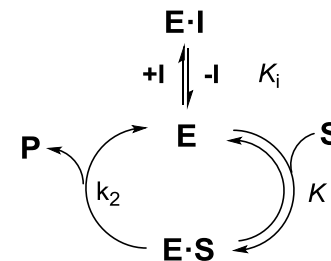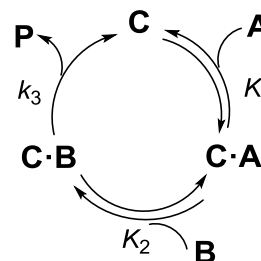
Rate laws for these catalytic cycles?

Kinetics and Mechanism

In the next few lectures, we will address the issue of how kinetic data can inform us about mechanism. Though you may currently regard this as an esoteric topic, suited only for experts, I hope to show you that this can be extremely powerful tool that any chemist can use. In general, we use kinetics to assess:

(1) transition state stoichiometry
   If we know the ground state stoichiometry, then the kinetic order in the reagents will tell us the transition state stoichiometry.

**(2) on- vs. off-cycle nature of intermediates**
   Which intermediates lie on the catalytic cycle? Which are simply dead ends? Is there catalyst deactivation? Why is there an induction period?

(3) whether mechanism A or mechanism B is more plausible
   Ultimately, we want to know what the mechanism is. Often, kinetics will allow us to rule some possibilities out. We might also want to know whether a mechanism changes from one substrate to the next (this happens a lot, sadly).

First-Order Kinetics

For any particular kinetic scenario, one can write down a set of differential equations. The simplest possible case is the irreversible conversion of A to B:

$$A \xrightarrow{k} B$$
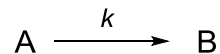
By convention, lowercase k refer to rate constants, while uppercase K refer to equilibrium constants (only the former is present in this example). The rate equation is:

$$r = \frac{d[B]}{dt} = -\frac{d[A]}{dt} = k[A]$$

Ultimately, we would like to know how long the reaction will take. More precisely, we would like to *integrate* d[A]/dt so we can get an expression for [A] in terms of time:

$$\frac{d[A]}{[A]} = -k \, dt$$

$$\int_0^t \frac{d[A]}{[A]} = \int_0^t -k \, dt$$

$$\ln[A]\big|_0^t = -kt$$

$$\ln[A]_t - \ln[A]_0 = -kt$$

$$\ln[A]_t = \ln[A]_0 - kt$$

$$[A]_t = [A]_0 \exp(-kt)$$

First order reactions always have an exponential decay behavior. To find out the half life, we ask what t will give a concentration of [A] that is half of the original, $[A]_0$:

$$[A]_0 / 2 = [A]_0 \exp(-kt_{1/2})$$

$$\ln(1/2) = -kt_{1/2}$$

$$-0.693 = -kt_{1/2}$$

$$t_{1/2} = 0.693 / k$$

This is the **half life** of the reaction. The unique feature of first-order kinetic scenarios is that the half life is concentration-independent. (For second-order reactions, the half life will depend on concentration.)

The above is an *analytic* solution where we can write the integrated rate law in terms of elementary functions. In more complicated scenarios, the math becomes very challenging and it is much more efficient to use numerical integration methods. One popular computer program is called COPASI.
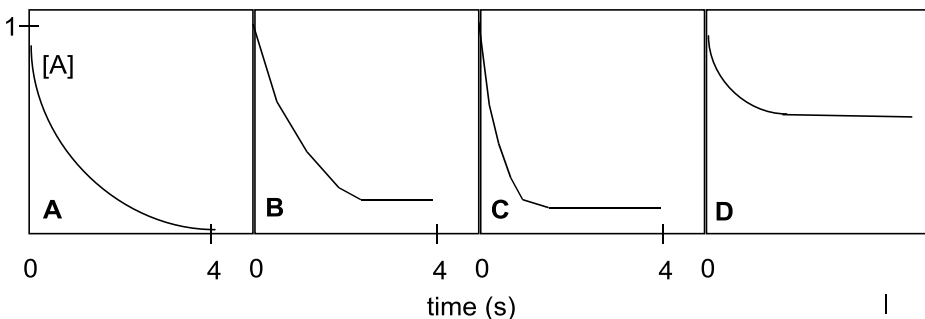
Approach to Equilibrium

Life becomes slightly more interesting if A and B can interconvert *reversibly*:

$$A \xrightarrow{\ k\ } B \qquad \text{- - - ->} \qquad A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$$

irreversible   **reversible**
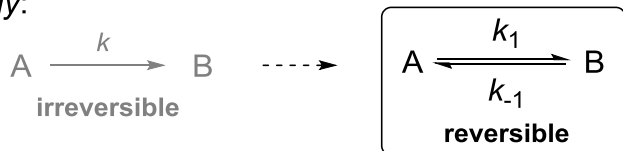
Consider just such a scenario in which:

$k_1 = 1 \text{ s}^{-1}$ $k_{-1} = 0.1 \text{ s}^{-1}$
$[A]_0 = 1.0$ M (concentration of A at time 0)
$[B]_0 = 0.001$ M (concentration of B at time 0).

Which of the following curves is most likely?

To understand this problem, we have to recognize two things.[4] The first is to understand that the equilibrium ratio of [A] and [B] is $K = k_1/k_{-1} = 1/0.1 = 10$. The total mass balance is 1.001 M, which places the final equilbrium ratio at about 91% B and 9% A. (If you wanted to know exactly, you could set up a high school-style equilibrium problem.) This rules out **A** and **D**.

To distinguish between **B** and **C**, we need to know how fast equilibrium is approached. In **B**, equilibrium is approached in about 3 seconds; in **C**, equilibrium is approached within 1 sec (the figures are all very approximate). Intuitively, we expect that rate of approach to equilibrium will be approached *slower* than the forward rate itself because of the reverse rate.

As it turns out, **B** is correct. Let's use some math to see why. The mass balance is:

$$[A]_0 + [B]_0 = [A] + [B] = [A]_{eq} + [B]_{eq}$$

$$[B] = [A]_{eq} + [B]_{eq} - [A]$$

By definition, the rate going forwards and the rate going backwards at equilibrium will be equal:

$$k_1[A]_{eq} = k_{-1}[B]_{eq} \qquad \text{substitute}$$

$$[B] = [A]_{eq} + \frac{k_1}{k_{-1}}[A]_{eq} - [A]$$

The flux in A is the rate of stuff creating A minus the rate of stuff destroying A:

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

$$\frac{d[A]}{dt} = k_{-1}\left([A]_{eq} + \frac{k_1}{k_{-1}}[A]_{eq} - [A]\right) - k_1[A]$$

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

$$\frac{d[A]}{dt} = (k_1 + k_{-1})([A]_{eq} - [A])$$

As before, we separate variables and integrate. Note that the subscript of "eq" means the concentration value at t=infinity.

Approach to Equilibrium

$$\int_0^t \frac{d[A]}{[A]_{eq}-[A]} = \int_0^t dt$$

$$-\ln\left[\frac{[A]_t-[A]_{eq}}{[A]_0-[A]_{eq}}\right] = (k_1+k_{-1})t$$

$$[A]_t = [A]_{eq} + \left([A]_0-[A]_{eq}\right)$$

$$\exp\left[-(k_1+k_{-1})t\right]$$

This is the desired result. As t goes to infinity, the exponential goes to zero, and $[A]_t$ becomes its equilibrium value. The characteristic "natural rate constant" k_1+k_{-1} is **larger** than k_1, but the rate of approach to equilibrium is **smaller** than the forward rate. In the example before, it would be 1.1 s^{-1}, which is a half life of 0.63 s. Assuming five half lives for full conversion, the expected time to equilibrium is about 3 seconds.

Here is another question. One might think about monitoring the optical rotation of a racemization process over time:

half life = 6.9 s

time (s)
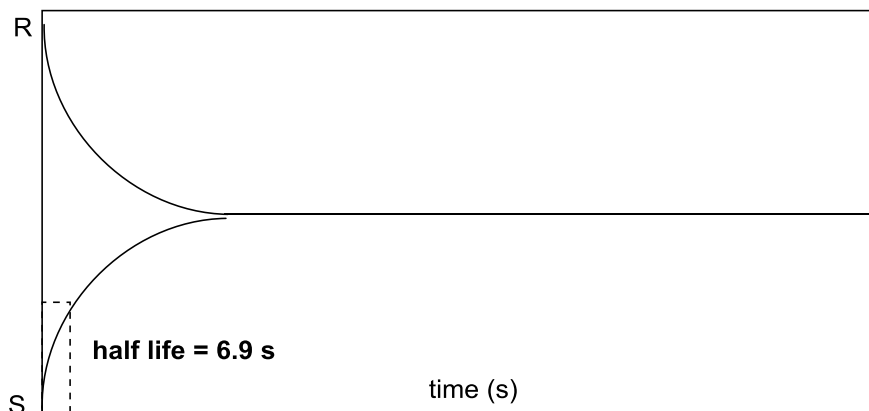
If the half life of this process is 6.9 s, what is the value of k_f?
0.1 s^{-1}?   10 s^{-1} 0.05 s^{-1}?

A half life of 6.9 seconds means a total rate constant of 0.1 s^{-1}, which means a forward rate of half that: 0.05 s^{-1}.
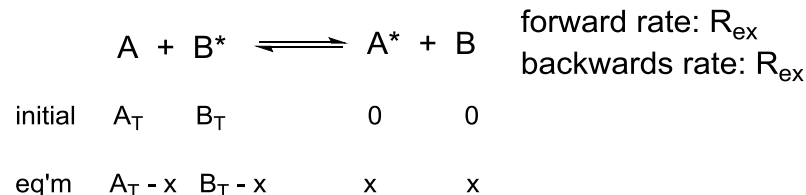
Exchange Kinetics: The McKay Equation

To turn the question around in a somewhat surprising way, what about the kinetics of a system *already* at chemical equilibrium? For example, we can imagine this equilibrium:
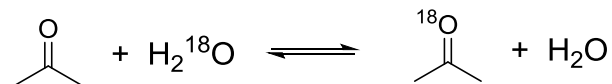
Let us assume the driving force is entirely due to the entropy of mixing. That means the equilibrium constant is 1 for this reaction, with a free energy of reaction of R ln 2. One can monitor the approach to equilibrium by NMR or isotope ratio mass spectrometery. Remarkably, just as in the previous examples, the approach is a first-order process, regardless of the actual mechanism of the exchange!

Q: What is the rate of this exchange, R_{ex}?

Let us consider this generic scheme:

					forward rate: R_{ex}
	A + B* $\rightleftharpoons$ A* + B				backwards rate: R_{ex}
initial	A_T	B_T	0	0	
eq'm	A_T - x	B_T - x	x	x	

What are the concentrations at equilibrium? Let the initial concentrations be A_T and B_T, such that:

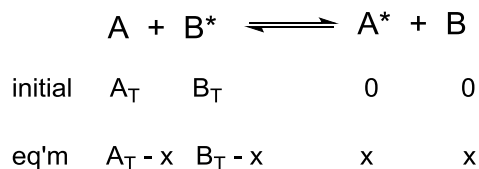$$K = \frac{x^2}{\left([A_T]-x\right)\left([B_T]-x\right)} = 1$$

We now solve the equation to get the final concentrations of $[A^*]$ and $[B^*]$:

$$x^2 = [A_T][B_T] - ([A_T]+[B_T])x + x^2$$

$$([A_T]+[B_T])x = [A_T][B_T]$$

$$x = \frac{[A_T][B_T]}{[A_T]+[B_T]}$$

The final concentrations are:

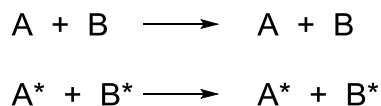$$A + B^* \; \rightleftharpoons \; A^* + B$$

initial	A_T	B_T	0	0
eq'm	$A_T - x$	$B_T - x$	x	x

$$[A^*]_{eq} = \frac{[A_T][B_T]}{[A_T]+[B_T]} = [*]_T \left(\frac{[A]_T}{[A]_T+[B]_t} \right)$$

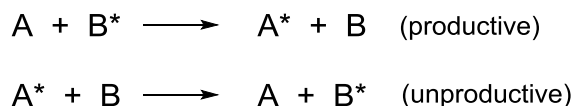Note that the total amount of label $[*]_T$ is the same as $[B]_T$:

$$[B^*]_{eq} = [B]_T - \frac{[A_T][B_T]}{[A_T]+[B_T]}$$

$$[B^*]_{eq} = \frac{[B]_T^2}{[A_T]+[B_T]} = [*]_T \left(\frac{[B]_T}{[A]_T+[B]_t} \right)$$

As the system approaches equilibrium, some exchanges will be unproductive, because they will be of the form:

$$A + B \longrightarrow A + B$$

$$A^* + B^* \longrightarrow A^* + B^*$$

Productive exchanges are countered by unproductive ones:

$$A + B^* \longrightarrow A^* + B \quad \text{(productive)}$$

$$A^* + B \longrightarrow A + B^* \quad \text{(unproductive)}$$

The total rate of exchange will be constant at $R_{ex}[A]_T[B]_T$. We can partition this into productive and unproductive terms:

$$\frac{d[A^*]}{dt} = R_{ex}(productive) - R_{ex}(unproductive)$$

$$\frac{d[A^*]}{dt} = R_{ex} \left(\frac{[A][B^*]-[A^*][B]}{[A_T][B_T]} \right)$$

Substituting to express everything in terms of constants and $[A^*]$ gives:

$$\frac{d[A^*]}{dt} = R_{ex} \left(\frac{([A^*]_{eq}-[A^*])([A_T]+[B_T])}{[A_T][B_T]} \right)$$

Integration gives the McKay equation:

$$\ln\left(1 - \frac{[A^*]_t}{[A^*]_{eq}}\right) = -R_{ex} \left(\frac{[A_T]+[B_T]}{[A_T][B_T]} \right) t$$

Note that $[A^*]_t/[A^*]_{eq}$ is a ratio from 0 to 1 that tells you how much exchange has occurred. This also means that regardless of how the exchange itself happens, equilibrium will be reached in a first-order process. For details, see Duffield, *JACS* **1946**, *68*, 557.

Multistep Reactions

One of the simplest models for a multistep reaction is this:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \overset{k_2}{\longrightarrow} C$$
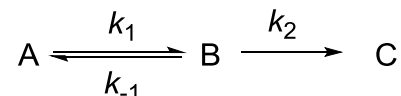
(1) What does it mean for A and B to be in pre-equilibrium?
(2) What does it mean for B to be in a steady state?
(3) What is the definition of a rate-determining step?

The differential equations have an analytic solution, but it looks awful. Instead, I will use COPASI to numerically integrate.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \overset{k_2}{\longrightarrow} C$$
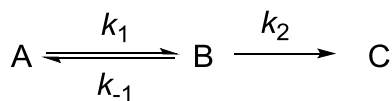
(For all of these cases, assume the reaction is sufficiently exo-ergic to make the final step irreversible.) One limiting scenario is that of a **pre-equilibrium**.

For an initial condition of A=1.0 M, k_1=10, k_{-1}=100, k_2=0.1, we get the following behavior:
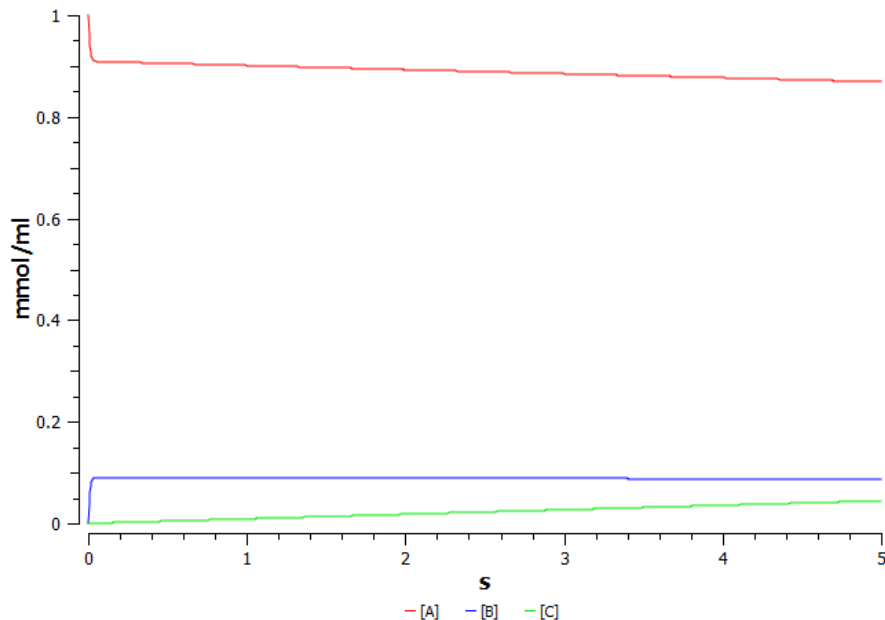
This means that after a brief induction period where B builds up to its equilibrium concentration, a ca. 9:1 ratio of A to B is maintained at all times. Over time, the product C trickles in.

Mathematically, we can say that the rate is:

$$v = k_2[B] = k_2 K[A]$$

where we have used the pre-equilibrium assumption that we can treat the first step as an equilibrium with $K=k_1/k_{-1}$. What is the rate-determining step? Here is the corresponding diagram:
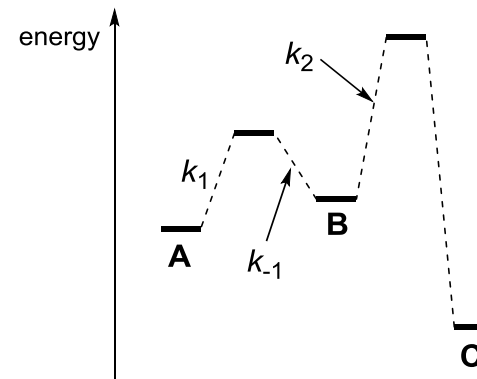
One can immediately see that even in this simple case, the identity of the rate-determining step is a bit nebulous. (For a full treatment, see "The Rate Determining Step is Dead..." Kozuch, S.; Martin, J.M.L. *ChemPhysChem*, **2011**, *12*, 1413.)

(1) Mathematically, we can't just say that k_2 is rate-determining, since altering the k_1/k_{-1} ratio will change the rate, too. The Laidler "control factor" looks at the change in the overall rate with respect to changes in the individual rate constants:

$$CF_i = \left(\frac{\partial \ln(rate)}{\partial \ln(k_i)} \right)_{K_{j \neq i}, k_{j \neq i}}$$

(The logs are a kind of normalization.) Indeed, one finds that 2 s into the reaction, the control factors are:

0.9 (k_1), -0.9 (k_{-1}), 1.0 (k_2)

The second control factor is negative, because speeding up the rate at which B goes back to A will slow down the reaction.

(2) In another sense, the unreacted materials spend most of their time as A (the "resting state"). From there, the highest point they must traverse is the k_2 transition state. So we really have a "rate-determining zone" between the resting state and the highest energy transition state after it. No one step is rate-determining.

$$A \xrightleftharpoons[k_{-1}]{k_1} B \xrightarrow{k_2} C$$
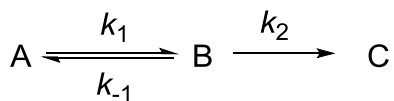
Another scenario is that of a **steady state** in B. One assumes that B is getting produced as fast as it is being used up.

For an initial condition of A=1.0 M, k_1=1, k_{-1}=0.01, k_2=100, we get the following behavior:
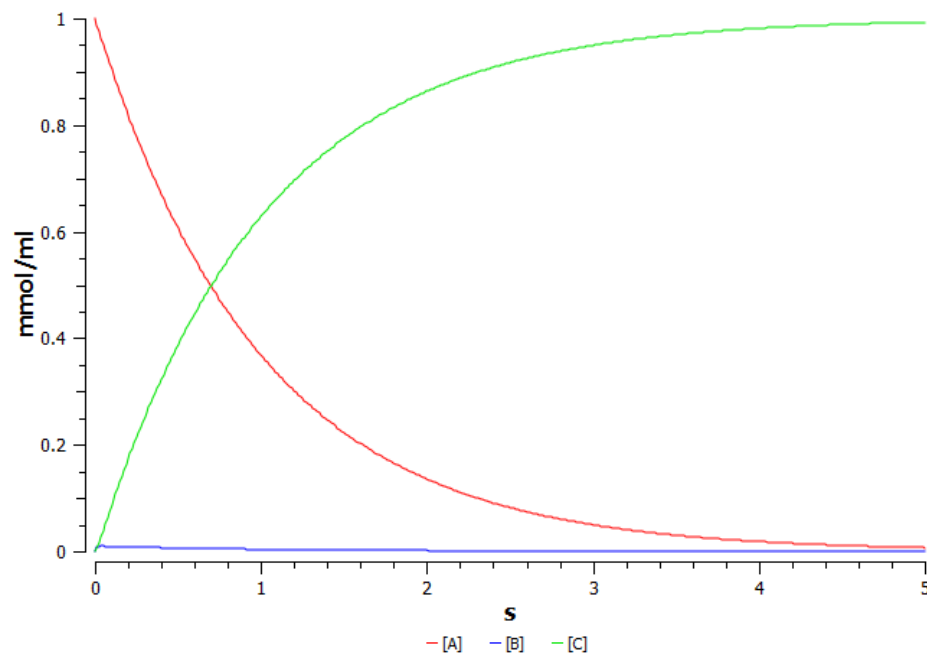
Now, as soon as B is formed, it reacts to form C. Only a small amount of B is ever present. Mathematically, the SS condition is:

$$\frac{\partial[B]}{dt} = 0 = k_1[A] - k_{-1}[B] - k_2[B]$$

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

Note that [B] is not constant over the course of the reaction! In fact, it builds up to a maximum very quickly, and then slowly decays over the course of the reaction. Zooming in on the graph reveals this:
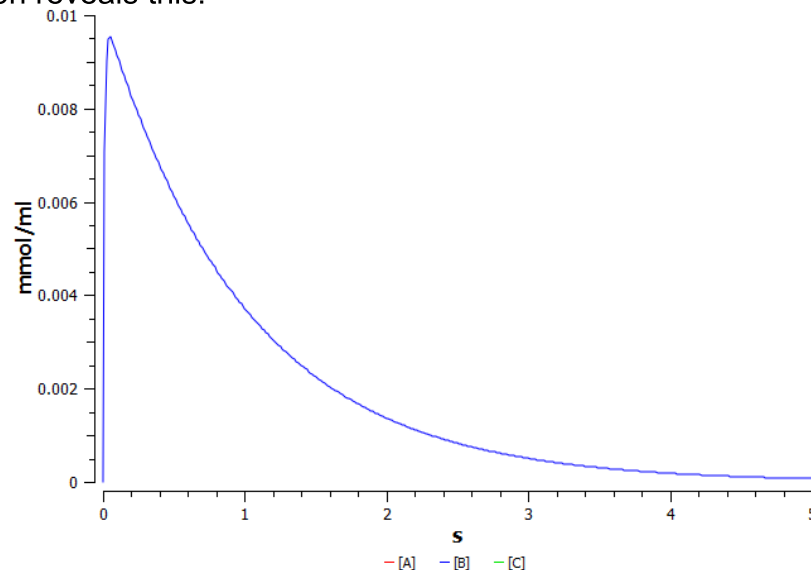
Mathematically, if d[B]/dt were *actually* zero, then d[A]/dt would also have to be zero, and the overall rate would have to be zero. Overall, the steady state approximation is good when:

(1) [B] decays slowly over most of the course of the reaction
(2) [B] is relatively small compared to [A]
(3) the instantaneous rates of [A] and [B] decay are correlated, but $|\Delta[B]/\Delta t| << |\Delta[A]/\Delta t|$.

This all means that $k_1 << k_{-1} + k_2$: the rate of product formation is equal to the rate of starting material consumption.

$$\frac{\partial[A]}{dt} = -k_1[A] + k_{-1}[B]_{SS} = \frac{k_1 k_2[A]}{k_{-1} + k_2}$$

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

What is the rate-determining step here? The energy diagram corresponding to these rates is:
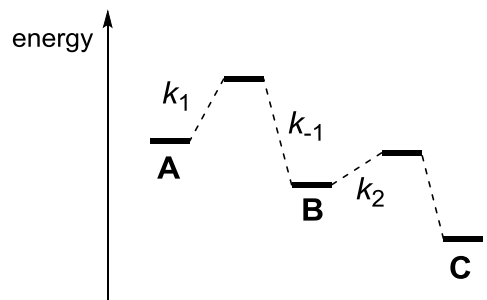
In this case, it is clear the rate-determining step corresponds to k_1. As soon as B is formed, it is much more likely to go towards C than A. The sensitivity factors for d[C]/dt are (2 seconds in):

-0.99 (k_1), 0.00 (k_{-1}), -0.01 (k_2)

This also agrees with our rule that we go from the resting state, A, to the highest barrier, which is associated with k_1. (B is not the resting state; the previous graphs show that it is only transiently occupied by things passing to product.)

An interesting question is whether reversible means fast and irreversible means slow, or whether "the" rate-determining transition state is always the one that is highest in energy. Consider this energy diagram:
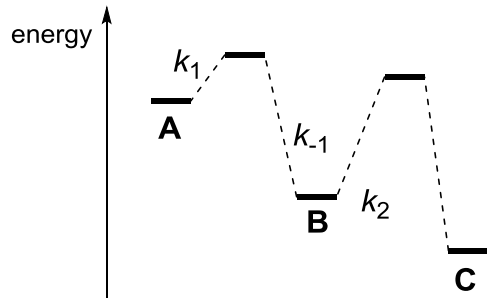
In this case, A immediately becomes B, which then trickles out to C. The rate-determining step is k_2, even though its transition state is not the highest in energy! However, this still hews to

our notion that the rate-determining step (or steps) correspond to the biggest gap between the resting state (B here) and the next transition state that is highest in energy.

One could argue that here, the "pre-equilibrium" from A to B is fast, but then the irreversible step to C is slow. However, this is misleading, because an equilibrium between A and B will never be established here. Some numbers that correspond to this scenario are: A=1.0 M, k_1=100, k_{-1}=1, k_2=10:
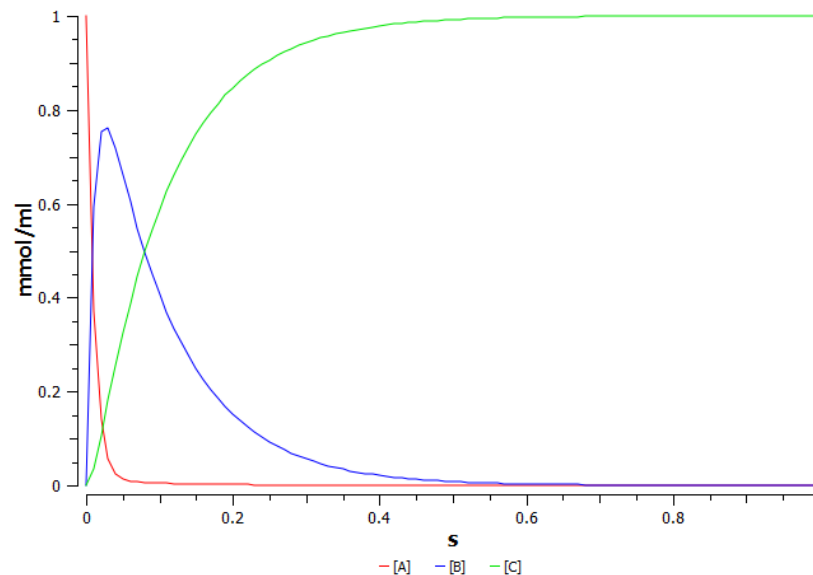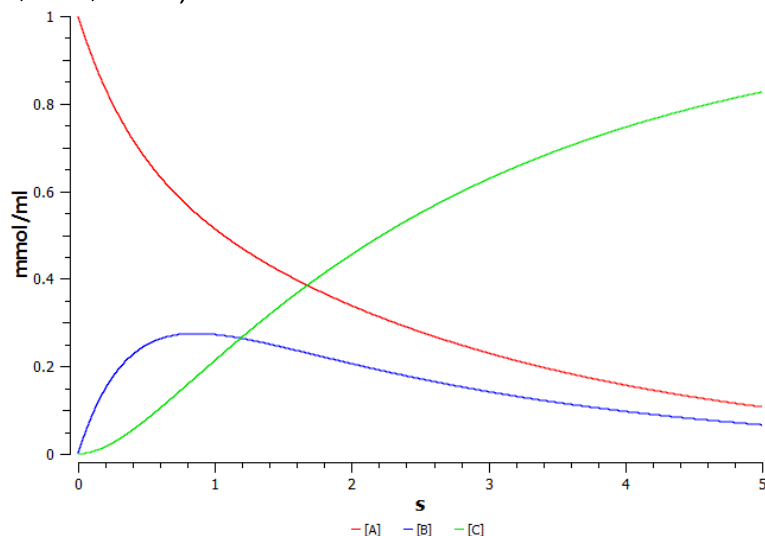

This is clearly a steady state, not pre-equilibrium scenario!

What if the barrier heights are very similar?
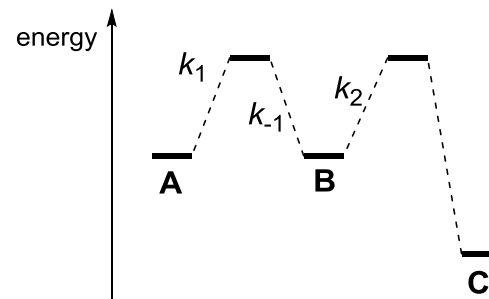
Setting all the rates to 1 gives some weird behavior (see *JACS* **2010**, *132*, 6276):


Now we get an early phase where B builds up, and then a late phase where it exits to C. So this is *neither* pre-equilibrium *nor* steady-state. Even the concept of "rate" is nebulous: is it d[A]/dt or d[C]/dt? They are no longer equal in magnitude!
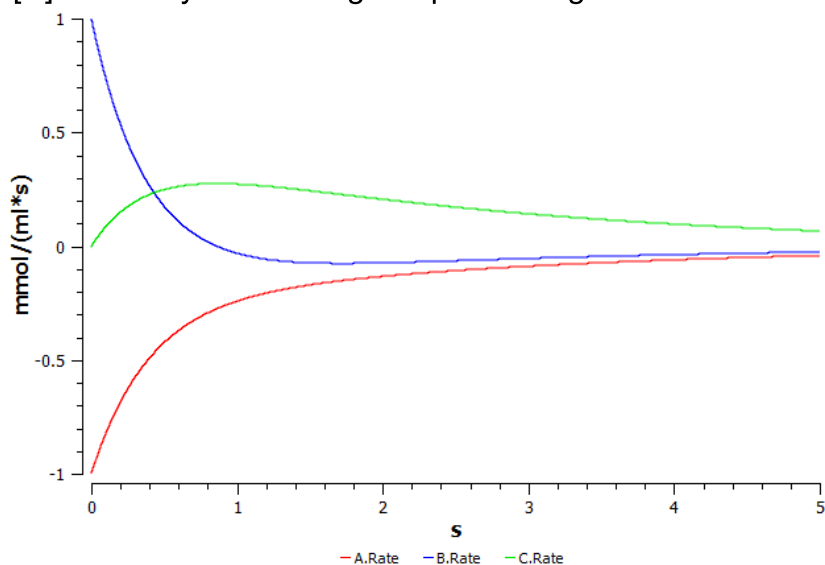
Michaelis-Menten Kinetics

The Michaelis-Menten system is the simplest possible catalytic cycle. A substrate binds to the enzyme, undergoes a reaction, and is then immediately released:
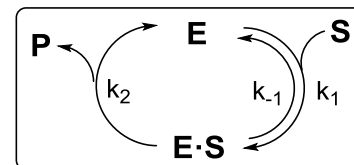
Under the pre-equilibrium assumption:

$$K = \frac{[E \cdot S]}{[E][S]}$$

which is true if $k_2 \ll k_{-1}$

We can then write v, the rate of product formation d[P]/dt:

$$v = k_2 [E \cdot S]$$
$$v = k_2 K [E][S]$$

pre-equilibrium

$$v = \frac{k_2 K [S] E_T}{1 + K[S]}$$

write as total enzyme concentration

The last substitution is necessary because [E] is not really easy to measure, whereas [S] is (since [E]<<[S]). The math behind the substitution is:

$$E_T = [E]+[E \cdot S]$$
$$= [E]+K[E][S]$$

Therefore, $[E]=E_T/(1+K[S])$.

Note that the fraction $1/1+K[S]$ is always less than one, which reflects the fact that some of the enzyme is tied up in the enzyme-substrate complex. Also, an implicit **free substrate assumption** has been made here; that is, one assumes that there is no need to write $[S_T]$ for the total substrate

concentration. It turns out this is valid as long as $[S] \ll 1/K_m$, where K_m is the Michaelis constant ($1/K$) in this case. If this isn't true, the much more complicated "Morrison equation" will be required (*Biochim. et Biophys. Acta - Enzymology* **1969**, *185*, 269).

If one applies the **steady state approximation** ("Briggs-Haldane"), we guess that [E·S] is constant:

$$(k_2 + k_{-1})[E \cdot S] = k_1[E][S]$$

This says the rate of enzyme substrate complex formation is equal to the rate of its breakdown.

$$[E \cdot S] = \frac{k_2 k_1 [E][S]}{k_2 + k_{-1}}$$

We can now apply the same trick as before to write:

$$v = k_2 [E \cdot S]$$

We are just substituting in the previous equation here.

$$v = \frac{k_2 k_1 [E][S]}{k_2 + k_{-1}}$$

Now, we replace [E] with $E_T / (1 + K[S])$ as before.

$$v = \frac{k_2 k_1 [S]}{k_2 + k_{-1}} \left(\frac{E_T}{1 + K[S]} \right)$$

Regardless of which assumption we make, we have arrived at the **Michaelis-Menten Equation**, which takes the form:

$$v = \frac{V_{max}[S]}{K_m + [S]}$$

where V_{max} and K_m are constants that are chosen to reproduce the kinetic data. Thus, from the fit of the data alone, we can't tell which assumption is justified.

In the steady-state approximation $K_m = (k_{-1} + k_2) / k_1$ and $V_{max} = k_2 E_T$. But the decomposition of these terms cannot be done from one set of kinetic data. (For more complicated systems, the pre-equilibrium and steady state assumptions will give different expressions.)

"1+rate" Laws

As you might imagine, such derivations get complicated very quickly with more complex kinetic schemes. But note the form of the expression for the pre-equilibrium rate law:

$$v = \frac{k_2 K [S] E_T}{1 + K[S]}$$
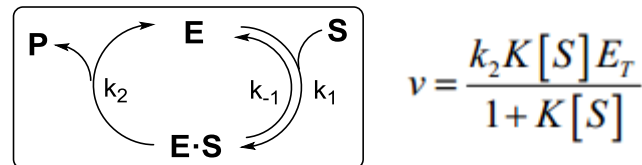
numerator: terms moving towards product

product: forms of the enzyme

Numerator: What are the things we need to do a reaction? We need an enzyme and a substrate, which are represented by E_T and [S]. Moving from E to P, we collect the pre-equilibrium constant (K) and rate constant (k_2).

Denominator: But not all of the enzyme is necessarily available to do the reaction (i.e., exists as E·S); in fact, a lot of it is free (E). So, the terms in the numerator represent all the states of the enzyme. The "1" term represents free enzyme, while the $K[S]$ term represents enzyme-substrate complex.

This works very well in general for pre-equilibrium scenarios (and only those!). We can learn a lot about the rate law by thinking about what happens when certain terms are large and when certain terms are small. For example:

Q: What happens when [S] is small?

The denominator becomes 1, meaning the reaction becomes first order in substrate. By contrast, if substrate is the dominant term, then the $K[S]$ terms in the numerator and denominator will cancel, meaning that the reaction is zero order in substrate.

Now we can tackle some more complicated scenarios.

Consider this pre-equilibrium system, which can be considered to be a model of the Heck reaction:
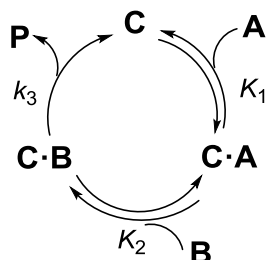
You can work out the rate law for this manually (please do this!) by writing $C_T = [C] + [C·A] + [C·B] = [C] + K_1[A][C] + K_2[B][C·A]$. This simplifies to $C_T = [C] + K_1[A][C] + K_2[B]K_1[A][C]$, which can be solved for [C] to give $[C] = C_T / (1 + K_1[A] + K_1K_2[A][B])$.

Using the "1+rate law" mnemonic, or the full derivation, one finds that:

$$v = \frac{k_3 K_1 K_2 [A][B] C_T}{1 + K_1[A] + K_1 K_2 [A][B]}$$

Competitive Inhibition

In drug discovery, we often talk about IC_{50} values, which is how much drug you need to cut the activity of an enzyme in half. One can also speak of K_i values, which have to do with how tightly the inhibitor binds to the enzyme. It is defined as a dissociation constant:

$$E·I \underset{+I}{\overset{-I}{\rightleftharpoons}} E \qquad K_i = \frac{[E][I]}{[E·I]}$$

Therefore, it has units of molarity, and smaller values mean tighter binding. Practically, K_i is harder to measure than IC_{50}. To find K_i, one must measure the rates of the enzymatic reaction while independently varying [inhibitor] and [substrate]. By contrast, IC_{50} just requires the rates for various [inhibitor] at a fixed [substrate], which is a lot less work.

"An Intuitive Look at the Relationship of K_i and IC_{50}..." Burlingham, B.T.; Widlanski, T.S. *J. Chem. Ed.* **2003** *80* 214-8.

Q: Are K_i and IC_{50} values directly comparable?

For example, three different inhibitors of the protease NS3 (hepatitis C) have reported inhibitory potencies of:

- compound 1: K_i of 0.6 μM
- compound 2: IC_{50} = 6.4 μM
- compound 3: IC_{50} = 28 μM

Which is the best inhibitor? We need more information. Whether the numbers are comparable or not depends on exactly how the inhibitor works. The most common case is *competitive inhibition*, where the inhibitor binds unproductively:

$$v = \frac{K k_2 [S] E_T}{1 + K[S] + K_i^{-1}[I]}$$
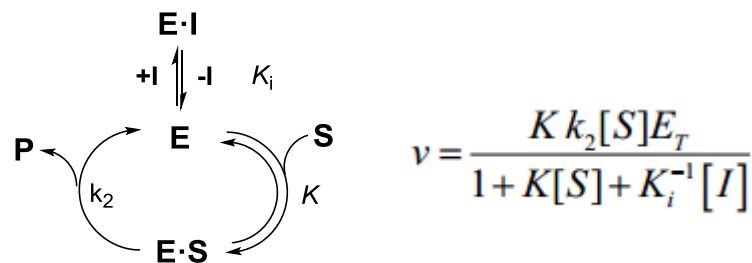
(The inverse power is a consequence of the definition of K_i as mentioned above.) As usual, the first term in the denominator represent free enzyme, the second, enzyme-substrate complex, and the third, enzyme-inhibitor complex.

To find the IC_{50}, we ask: what does [I] have to be in order to halve the rate v?) When the substrate concentration is low, the concentration of enzyme-substrate complex is low, and the rate simplifies to:

$$v = \frac{K k_2 [S] E_T}{1 + K_i^{-1}[I]}$$

In the absence of inhibitor, [I]=0, and the rate is just the numerator. To halve the rate, the denominator must change from 1 to 2. Thus, we must solve:

$$1 + K_i^{-1}[I] = 2$$

Thus, $[I] = IC_{50} = K_i$.

What does this look like for an arbitrary substrate concentration? Note that substituting in $IC_{50} = K_i$ no longer works. Now, the denominator becomes:

$$1 + K[S] + K_i^{-1}[I] = 2 + K[S]$$

This number is bigger than 2, which means the rate reduction is *less* than half. So the same amount of inhibitor that was effective at low concentrations is no longer quite as effective.

Now, we must solve:

$$1 + K[S] + K_i^{-1}[I] = 2(1 + K[S])$$

$$K_i^{-1}[I] = 1 + K[S]$$

$$[I] = K_i(1 + K[S]) = K_i\left(1 + \frac{[S]}{K_m}\right)$$

This says that the IC_{50} value must make the denominator twice as big.

$K_m = (k_{-1} + k_2) / k_1$, which simplifies to $K_m = 1/K$.

This last equation is the **Chang-Prusoff correction** we have been looking for--it says the IC_{50} value has to be larger when there is more substrate present.
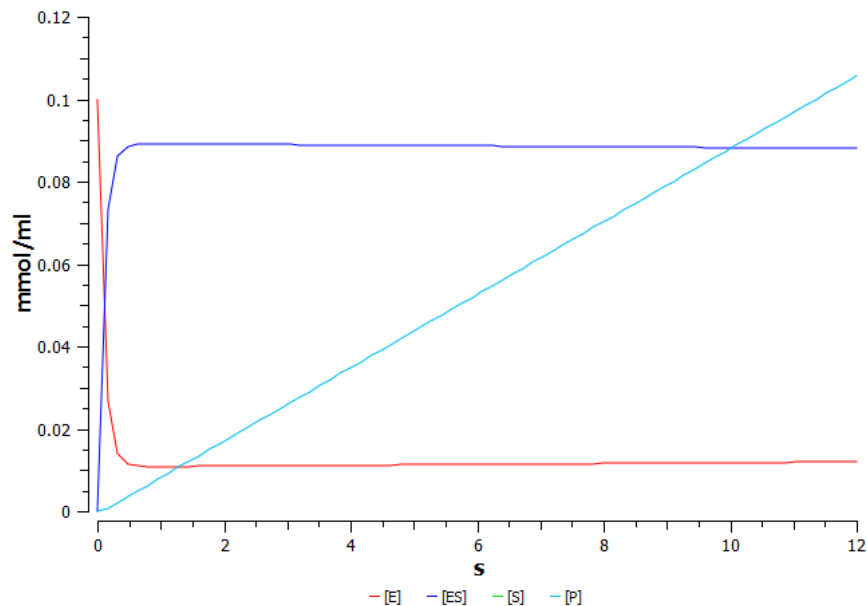
COPASI and Resting States

Let's return to the Michaelis-Menten system and look at some numbers. What if $k_1 = 10$, $k_{-1} = 1$, $k_2 = 0.1$?
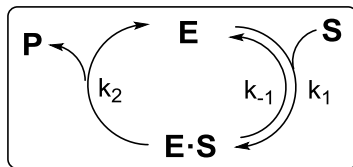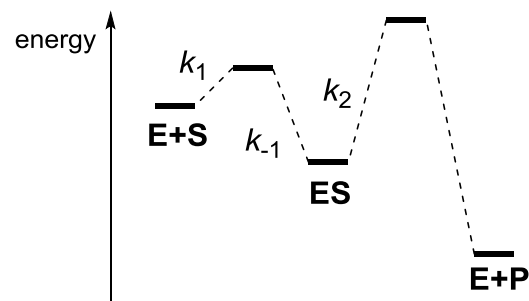
This is pre-equilibrium.

There is a fast induction period, followed by a slower conversion of ES to P:

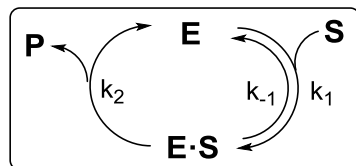What is the energy diagram for this? Traditionally, one would write something like:

This is for *one* turnover of the catalytic cycle. The **resting state** is ES, and the turnover-limiting step is k_2. Looking at the 1+rate law,

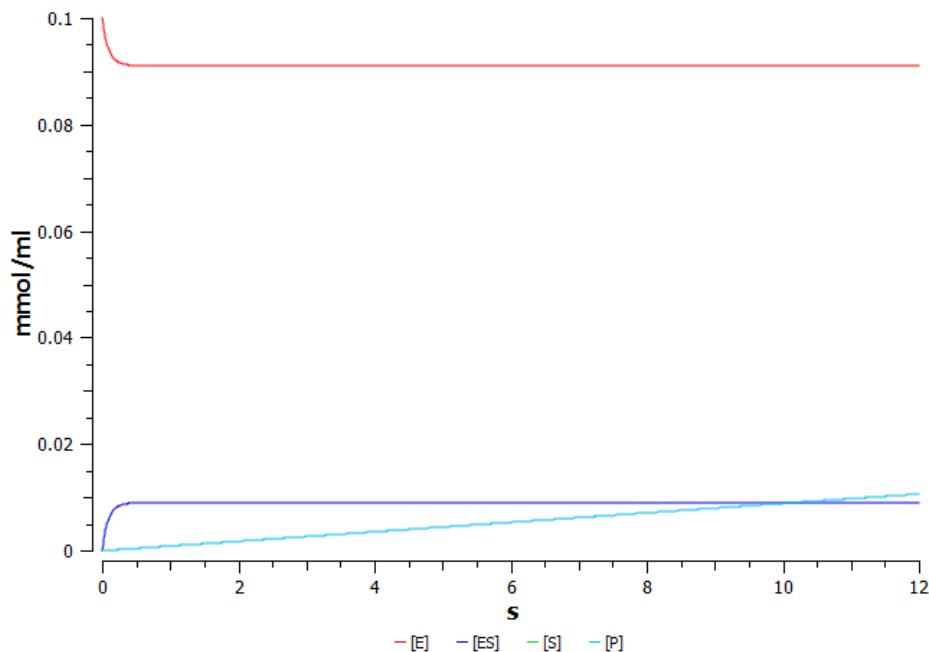$$v = \frac{k_2 K[S] E_T}{1 + K[S]} \approx \frac{k_2 K[S] E_T}{K[S]} = k_2 E_T$$

Alternatively, one may consider a system like:
$k_1=1$, $k_{-1}=10$, $k_2=0.1$?

This is also pre-equilibrium, but now E is favored over ES.

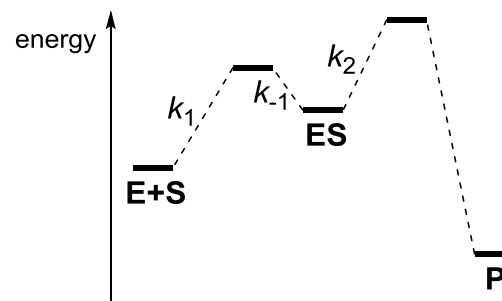There is a fast induction period to form ES, and then slow product formation:

Note that the red line, which represents [E] is much higher than the blue line, which is [ES]. Mathematically, we have:
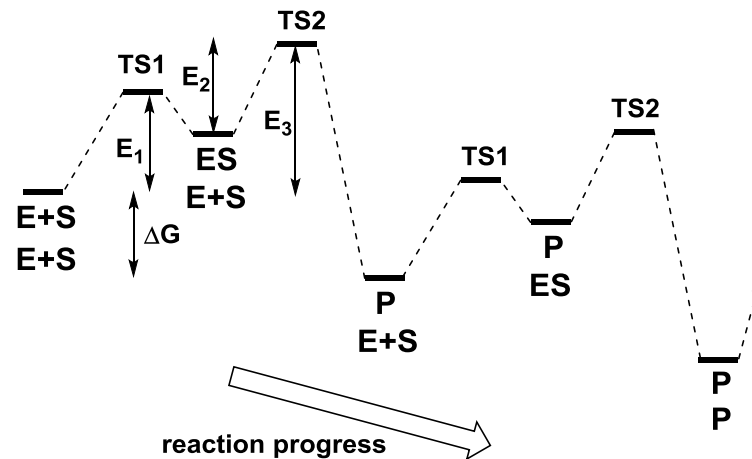
$$v = \frac{k_2 K[S]E_T}{1+K[S]} \approx k_2 K[S]E_T$$

Once again, there is no one turnover limiting step. Moving the equilibrium right will help; so will increasing k_2.

What is the energy diagram for this?

If we want to consider the energy diagram for the *ensemble*, however, we can double up the diagram as the free energy drops from turnover to turnover:

Thedrop between cycles represents the free energy lost in one turnover. **What is the turnover-limiting step?**

The recipe is to consider the possible energetic spans in the forward direction. Here, we have a span of E_1 from E+S to TS1, a span of E_3 from E+S to TS2, and a span of E_2 from ES to TS2. Since E_3 is the largest span, the resting state is E+S, and the turnover-limiting transition state is TS2. Overall, the rate of reaction will depend on E_3.

This helps for thinking about more complicated scenarios. What is the turnover-limiting step here?
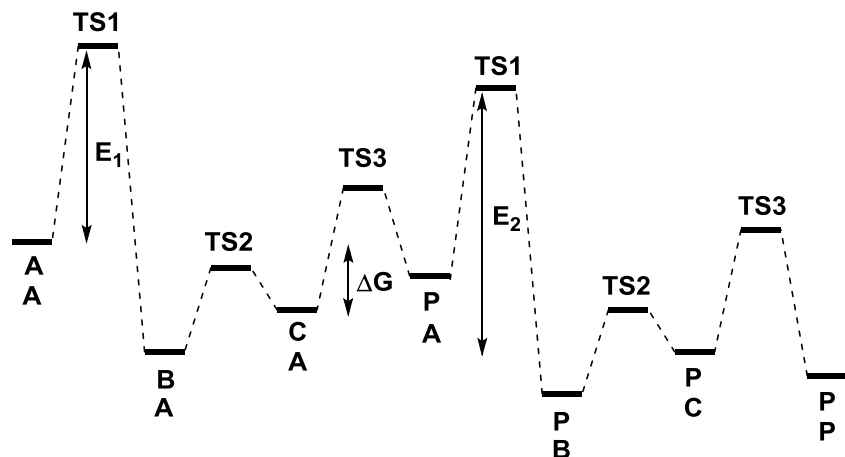
Even though you might think the reaction is controlled by the gap E_1, it is actually controlled by the larger gap E_2. The resting state of the catalytic system is B. On each turn of the cycle, the largest gap it must surmount is E_2, so that's what controls the rate of reaciton. Because TS1 appears *before* the resting state in the cycle, ΔG must be added to E_1 to get the effective barrier to reaction.

Whether you decide this recipe is a hackneyed attempt to make something simple very complicated, or a good way to think about things, it's important to decide what the resting state is for every catalytic cycle. In reality, the rate-determining and selectivity-determing steps can change depending on the reaction conditions. If different energetic gaps become similar, then it's possible for these terms to become meaningless...