The steady state approximation is a method used to estimate the overall reaction rate of a multi-step reaction. It assumes that the rate of change of intermediate concentration in a multi-step reaction are constant. This method can only be applied when the first step of the reaction is significantly slower than subsequent step in an intermediate-forming consecutive reaction.

**Introduction**

Before discussing the steady state approximation, it must be understood that the approximation is derived to simplify the kinetic expression for product concentration, \( [\text{product}] \). Consider the following sequential reaction:

\[
[A \xrightarrow{k_1} B \xrightarrow{k_2} C]
\]

Calculating the \([\text{product}]\) depends on all the rate constants in each step. For example, if the kinetic method was used to find the concentration of \( C \), \([C]\), at time \( t \) in the above reaction, the expression would be

\[
[C] = [A]_0 \left(1+ \frac{k_2e^{-k_1t}-k_1e^{-k_2t})}{k_1 - k_2}\right) \label{1}
\]

With a more complicated mechanisms, the kinetic expression becomes harder to derive. To simplify this calculation, we often use one of two approximations for determining the overall reaction rates of consecutive reactions: the steady state approximation and the **pre-equilibrium approximation**. This article concerns the steady state approximation.

**Steady State Approximation**

The steady state approximation is applies to a consecutive reaction with a slow first step and a fast second step (\( k_1 \ll k_2 \)). If the first step is very slow in comparison to the second step, there is no accumulation of intermediate product, such as product \( B \) in the above example.

\[
\frac{d[B]}{dt} = 0 = k_1[A] - k_2[B] \tag{2} \]

Thus

\[
[B] = \frac{k_1[A]}{k_2} \tag{3}
\]

From the mechanism:

\[
\frac{d[C]}{dt} = k_2[B] = \frac{k_2k_1[A]}{k_2} = k_1[A] \tag{4}
\]

Solving for \([C]\):

\[
[C] = [A]_0 (1- e^{-(k_1t)}) \tag{5}
\]

Equation \(\ref{5}\) is much simpler to derive than Equation \(\ref{1}\), especially with a more complicated multi-step reaction mechanisms.

Example \(\PageIndex{1}\)
Consider the reaction:

\[ A + 2B \xrightarrow{k_{-1}} C \]

a. What is the expected rate law according to the following proposed multi-step mechanism under the steady state approximation with \( k_2 \gg k_{-1} \) for the following mechanism:

\[ \text{[A + B \ce{<=>[k_1][k_{-1}]} I \tag{Slow}] I + B \xrightarrow{k_2} C \tag{Fast}] \]

b. If \( x \) is the order of the reaction with respect to \( A \), \( y \) is the order of the reaction with respect to \( B \), and \( n \) is the overall reaction order. What are the values of \( x \), \( y \), and \( n \)?

**Solution**

a. First we use the Steady State Approximation for the intermediate (i.e., Equation \ref{2})

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

then we solve for the (steady-state) concentration of the intermediate

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

Because the second step is much faster than the first step, then \( k_2 \gg k_{-1} \) then \( k_{-1} \approx 0 \) for this approximation and the above equation can be simplified to

\[
[I] = \frac{k_1[A][B]}{k_2}
\]

The rate law for the production of \( [C] \) can be constructed directly from the second step and when the steady-state concentration of \([I]\) is added, the final rate law expression is derived.

\[
\begin{align*}
\frac{d[C]}{dt} &= k_2[I][B] \\
&= \frac{k_1k_2[A][B]}{k_2} \\
&= k_1[A][B]
\end{align*}
\]

b. Direct inspection of the final rate law derived above gives these parameters:

- \( x = 1 \)
- \( y = 1 \)
- \( n = 2 \)

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**Use of the Steady-State Approximation in Enzyme Kinetics**

In 1925, George E. Briggs and John B. S. Haldane applied the steady state approximation method to determine the rate law of the enzyme-catalyzed reaction (Figure 1). The following assumptions were made:

1. The rate constant of the first step must be slower than the rate constant of the second step (\( k_1 \ll k_2 \)), hence \( \frac{d[ES]}{dt} = 0 \)
2. Enzyme concentration must be significantly lower than the substrate concentration to keep the first step slower than the second step.
Figure 1: Steady state dynamics in enzymes

This gives the following:

\[
\frac{d[P]}{dt} = k_2[ES] \label{6}
\]

where

\[
\frac{d[ES]}{dt} = 0 = k_1[E][S] - k_{-1}[ES] - k_2[ES] \label{7}
\]

Because

\[
[S] \gg [E] \label{8}
\]

Using the second assumption and the fact that enzyme concentration equals the initial concentration of enzyme minus the concentration of the enzyme-substrate intermediate,

\[
[E] = [E]_o - [ES] \label{9}
\]

The following equation is obtained:

\[
k_1[E]_o[S] = k_{-1}[ES] + k_2[ES] + k_1[ES][S] \label{10}
\]

From this equation, the concentration of the ES intermediate can be found:

\[
[ES] = \frac{k_1[E]_o[S]}{(k_{-1} + k_2) + k_1[S]} \label{11}
\]

Substitute this into Equation \(\ref{6}\) gives,

\[
\frac{d[P]}{dt} = \frac{k_2[E]_o[S]}{(k_{-1} + k_2) + [S]} = \frac{k_2[E]_o[S]}{K_M + [S]} \label{12}
\]
\[ K_M = \frac{k_{-1} + k_{2}}{k_1} \]

Because in most of the cases, only the initial \( d[P]/dt \) is measured to determine the rate of product formation, Equation \ref{12} can be rewritten as:

\[ v_o = \frac{d[P]_0}{dt} = \frac{k_2[E]_0[S]}{K_M + [S]} \]

Because \( [E]_o = \frac{v_{max}}{k_2} \). Equation \ref{14} becomes the following:

\[
\begin{align}
  v_0 &= \frac{d[P]_o}{dt} \\
  &= \frac{(k_2/k_2)v_{max}[S]}{K_M + [S]} \label{15} \\
  &= \frac{v_{max}[S]}{K_M + [S]} \label{16}
\end{align}
\]

This equation is a useful tool to in calculating \( v_{max} \) and \( K_M \) (the Michaelis constant) of an enzyme by using the Lineweaver-Burk plot \( (1/[S] \text{ vs. } 1/v_0) \) or the Eadie-Hofstee plot \( (v_0/[S] \text{ vs. } v_0) \).

**Problems**

Given the reaction \( A \xrightarrow{k_1} B \xrightarrow{k_2} C \)

where \( k_1 = 0.2 \text{ M}^{-1} \text{s}^{-1} \), \( k_2 = 2000 \text{ s}^{-1} \)

1. Write the reaction rates for A, B, and C.
2. Is this a steady-state reaction?
3. Write the expression for \( d[C]/dt \) using the Steady State Approximation
4. Calculate \( d[C]/dt \) if \( [A] = 1 \text{M} \)
5. Calculate \( [C] \) at \( t = 3 \text{s} \) and \( [A]_0 = 2 \text{M} \)

**Solutions**

1) \( d[A]/dt = -k_1[A]; \ d[B]/dt = k_1[A] - k_2[B]; \ d[C]/dt = k_2[B] \)

2) Because \( k_1 \) is much larger than \( k_2 \), this is a steady state reaction.

3) \( d[C]/dt = k_2[B] \)

where \( d[B]/dt = k_1[A] - k_2[B] = 0 \)

so, \( [B] = \frac{k_1[A]}{k_2} \)

Substitute this into \( d[C]/dt \)

\( d[C]/dt = k_1[A] \)
4) \( \frac{d[C]}{dt} = 0.2 \text{M}^{-1} \text{s}^{-1} (1 \text{M}) = 0.2 \text{ s}^{-1} \)

5) \([C] = [A]_0 (1-e^{-kt}) = 2 \text{M}(1-e^{-0.2(3)}) = 0.9 \text{ M}\)

References:


Contributors and Attributions

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