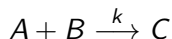


Mathematical models of chemical reactions

The Law of Mass Action

Chemical A and B react to produce chemical C:



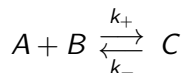
The rate constant k determines the rate of the reaction. It can be interpreted as the probability that a collision between the reactants produces the end results.

If we model the probability of a collision with the product $[A][B]$ we get the law of mass action:

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

A two way reaction

The reverse reaction may also take place:



The production rate is then:

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

At equilibrium when $d[C]/dt = 0$ we have:

$$k_-[C] = k_+[A][B] \quad (1)$$

If $A + B \xrightarrow{k} C$ is the only reaction involving A and C then

$$d[A]/dt = -d[C]/dt$$

so that

$$[A] + [C] = A_0 \quad (2)$$

Substituting (2) into (1) yields:

$$[C] = A_0 \frac{[B]}{K_{eq} + [B]}$$

where $K_{eq} = k_-/k_+$.

Notice that

$$[B] = K_{eq} \implies [C] = A_0/2$$

and

$$[B] \rightarrow \infty \implies [C] \rightarrow A_0$$

Gibbs free energy

Molecules have different chemical potential energy, quantified by *Gibbs free energy*

$$G = G^0 + RT \ln(c)$$

where c is the concentration of the molecule, T is the temperature, R the gas constant.

G^0 is the energy at $c = 1\text{M}$, called the *standard free energy*.

Gibbs free energy

Can be used to compare two states:



Change in free energy after this reaction:

$$\begin{aligned}\Delta G &= G_B - G_A \\ &= (G_B^0 + RT \ln(B)) - (G_A^0 + RT \ln(A)) \\ &= (G_B^0 - G_A^0) + (RT \ln(B) - RT \ln(A)) \\ &= \Delta G^0 + RT \ln(B/A)\end{aligned}$$

If $\Delta G < 0$, i.e. there is less free energy after the reaction, then B is the preferred state.

Gibbs free energy at equilibrium

At equilibrium neither states are favoured and $\Delta G = 0$:

$$\Delta G = \Delta G^0 + RT \ln(B/A) = 0$$

Given G^0 , the concentrations at equilibrium must satisfy:

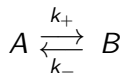
$$\ln(B_{eq}/A_{eq}) = -\Delta G^0/RT$$

or

$$\frac{B_{eq}}{A_{eq}} = e^{-\Delta G^0/RT}$$

Gibbs free energy and rate constants

The reaction



is governed by

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

and at equilibrium $\frac{d[A]}{dt} = 0$, so

$$k_-[B] - k_+[A] = 0, \text{ or } A/B = k_-/k_+ = K_{eq}$$

Comparing with the Gibbs free energy we find:

$$K_{eq} = e^{\Delta G^0/RT}$$

Note:

$$\Delta G^0 < 0 \implies K_{eq} < 1 \implies B_{eq} > A_{eq}$$

Gibbs free energy with several reactants

The reaction



has the following change in free energy:

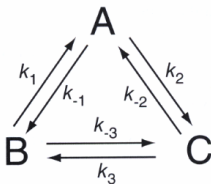
$$\begin{aligned}\Delta G &= \gamma G_C + \delta G_D - \alpha G_A - \beta G_B \\ &= \gamma G_C^0 + \delta G_D^0 - \alpha G_A^0 - \beta G_B^0 \\ &\quad + \gamma RT \ln([C]) + \delta RT \ln([D]) - \alpha RT \ln([A]) - \beta RT \ln([B]) \\ &= \Delta G^0 + RT \ln\left(\frac{[C]^\gamma [D]^\delta}{[A]^\alpha [B]^\beta}\right)\end{aligned}$$

At equilibrium with $\Delta G = 0$:

$$\Delta G^0 = RT \ln\left(\frac{[A]_{eq}^\alpha [B]_{eq}^\beta}{[C]_{eq}^\gamma [D]_{eq}^\delta}\right)$$

Detailed balance

Consider the cyclic reaction:



In equilibrium all states must have the same energy:

$$G_A = G_B = G_C$$

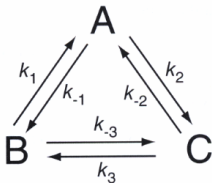
All transitions must be in equilibrium:

$$k_1[B] = k_{-1}[A], \quad k_2[A] = k_{-2}[C], \quad k_3[C] = k_{-3}[B]$$

Which yields:

$$k_1[B] \cdot k_2[A] \cdot k_3[C] = k_{-1}[A] \cdot k_{-2}[C] \cdot k_{-3}[B]$$

Detailed balance



cont.

$$k_1[B] \cdot k_2[A] \cdot k_3[C] = k_{-1}[A] \cdot k_{-2}[C] \cdot k_{-3}[B]$$

so

$$k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$$

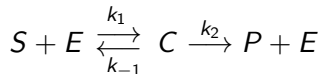
This last condition is independent of the actual concentrations and must hold in general. Thus only 5 free parameters in the reaction.

Enzyme Kinetics

Characteristics of enzymes:

- Made of proteins
- Acts as catalysts for biochemical reactions
- Speeds up reactions by a factor $> 10^7$
- Highly specific
- Often part of a complex regulation system

Reaction model of enzymatic reaction



with

S: Substrate

E: Enzyme

C: Complex

P: Product

Mathematical model of enzymatic reaction

Applying the law of mass action to each compound yields:

$$\begin{aligned}\frac{d[S]}{dt} &= k_{-1}[C] - k_1[S][E] + J_S \\ \frac{d[E]}{dt} &= (k_{-1} + k_2)[C] - k_1[S][E] \\ \frac{d[C]}{dt} &= k_1[S][E] - (k_2 + k_{-1})[C] \\ \frac{d[P]}{dt} &= k_2[C] - J_P\end{aligned}$$

Here we also supply the substrate at rate J_S and the product is removed at rate J_P .

Equilibrium

Note that In equilibrium

$$d[S]/dt = d[E]/dt = d[C]/dt = d[P]/dt = 0$$

it follows that that $J_S = J_P$.

Production rate:

$$J = J_P = k_2[C]$$

In equilibrium we have

$$\frac{d[E]}{dt} = 0$$

that is

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

Since the amount of enzyme is constant we have

$$[E] = E_0 - [C]$$

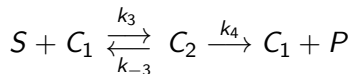
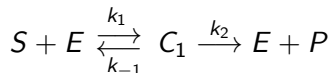
This yields

$$[C] = \frac{E_0[S]}{K_m + [S]}$$

with $K_m = \frac{k_{-1} + k_2}{k_1}$ and E_0 is the total enzyme concentration.

Production rate: $\frac{d[P]}{dt} = k_2[C] = V_{max} \frac{[S]}{K_m + [S]}$, where $V_{max} = k_2 E_0$.

Cooperativity, 1.4.4



with

- S: Substrate
- E: Enzyme
- C1: Complex with one S
- C1: Complex with two S
- P: Product

Mathematical model of cooperativ reaction

Applying the law of mass action to each compound yields:

$$\begin{aligned}\frac{ds}{dt} &= -k_1se + k_{-1}c_1 - k_3sc_1 + k_{-3}c_2 \\ \frac{dc_1}{dt} &= k_1se - (k_{-1} + k_2)c_1 - k_3sc_1 + (k_4 + k_{-3})c_2 \\ \frac{dc_2}{dt} &= k_3sc_1 - (k_4 + k_{-3})c_2\end{aligned}$$

Equilibrium

Set $\frac{dc_1}{dt} = \frac{dc_2}{dt} = 0$, and use $e_0 = e + c_1 + c_2$,

$$c_1 = \frac{K_2 e_0 s}{K_1 K_2 + K_2 s + s^2}$$
$$c_2 = \frac{e_0 s^2}{K_1 K_2 + K_2 s + s^2}$$

where $K_1 = \frac{k_{-1} + k_2}{k_1}$, $K_2 = \frac{k_4 + k_{-3}}{k_3}$

Reaction speed:

$$V = k_2 c_1 + k_4 c_2 = \frac{(k_2 K_2 + k_4 s) e_0 s}{K_1 K_2 + K_2 s + s^2}$$

Case 1: No cooperation

The binding sites operate independently, with the same rates k_+ and k_- . k_1 , k_{-3} and k_4 are associated with events that can happen in two ways, thus:

$$k_1 = 2k_3 = 2k_+$$

$$k_{-3} = 2k_{-1} = 2k_-$$

$$k_4 = 2k_2$$

So:

$$K_1 = \frac{k_{-1} + k_2}{k_1} = \frac{k_- + k_2}{2k_+} = K/2$$

$$K_2 = \frac{k_{-3} + k_4}{k_3} = \frac{2k_- + 2k_2}{k_+} = 2K$$

where

$$K = \frac{k_- + k_2}{k_+}$$

Which gives this reaction speed:

$$\begin{aligned}V &= \frac{(k_2K_2 + k_4s)e_0s}{K_1K_2 + K_2s + s^2} \\ &= \frac{(2k_2K + 2k_2s)e_0s}{K^2 + 2Ks + s^2} \\ &= \frac{2k_2(K + s)e_0s}{(K + s)^2} = \frac{2k_2e_0s}{(K + s)}\end{aligned}$$

Note that this is the same as the reaction speed for twice the amount of an enzyme with a single binding site.

Case 2: Strong cooperation

The first binding is unlikely, but the next is highly likely, i.e. k_1 is small, and k_3 is large. We go to the limit:

$$k_1 \rightarrow 0, k_3 \rightarrow \infty, k_1 k_3 = \text{const}$$

so

$$K_2 \rightarrow 0, K_1 \rightarrow \infty, K_1 K_2 = \text{const}$$

In this case the reaction speed becomes:

$$V = \frac{k_4 e_0 s^2}{K_m^2 + s^2} = V_{\max} \frac{s^2}{K_m^2 + s^2}$$

with $K_m^2 = K_1 K_2$, and $V_{\max} = k_4 e_0$

The Hill equation

In general with n binding sites, the reaction rate in the limit will be:

$$V = V_{\max} \frac{s^n}{K_m^n + s^n}$$

This model is often used when the intermediate steps are unknown, but cooperativity suspected. The parameters V_{\max} , K_m and n are usually determined experimentally.