**Elementary reactions**

stoichiometry = mechanism \((\text{Cl}^- + \text{H}_2 \rightarrow \text{HCl} + \text{H}^+)\)

- monomolecular reactions (decay: \(\text{N}_2\text{O}_4 \rightarrow 2\text{NO}_2\); radioactive decay; some isomerisations)

- bimolecular reactions (collision; most common)

\[
\text{ClCH}_3 + \text{CN}^- \rightarrow \text{Cl}^- + \text{CH}_3\text{CN}
\]

- trimolecular reactions

\[
\text{O} + \text{O}_2 + \text{N}_2 \rightarrow \text{O}_3 + \text{N}_2
\]

\((\text{N}_2\text{ carries out the surplus energy})\)
A (general) reaction is a sequence of elementary reactions = reaction mechanism.

**Example:** \(2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}\)

- \(\text{H}_2 + \text{O}_2 \rightarrow \text{HO}_2^+ + \text{H}^+\)
- \(\text{HO}_2^+ + \text{H}_2 \rightarrow \text{H}_2\text{O} + \text{OH}^+\)
- \(\text{H}^+ + \text{O}_2 \rightarrow \text{O}^+ + \text{OH}^+\)
- \(\text{H}_2 + \text{OH}^+ \rightarrow \text{H}_2\text{O} + \text{H}^+\)
- \(\text{H}_2 + \text{O}^+ \rightarrow \text{H}^+ + \text{OH}^+\)

**radical A^+**

**activated molecule A^* (energy-rich, local energy minimum)**

**activated complex (transition state) AB‡, AB# (saddle point)**
We need to get rid of unstable (unknown) intermediates.

- rate-determining step
  - fastest (parallel reactions)
  - slowest (consecutive reactions)

- Bodenstein principle of (quasi)stationary state
  intermediates fast reach (almost) constant concentrations

  e.g.: \( A \rightleftharpoons A^* \rightarrow B \)
  \[ \frac{dc_{A^*}}{d\tau} \approx 0 \]

- pre-equilibrium
  reversible reaction part of chain

  e.g.: \( \ldots \rightarrow A + B \rightleftharpoons C + D \rightarrow \ldots \)
  \[ \frac{c_C c_D}{c_A c_B} \approx K \]

  can be derived from the above principle (for \( \gamma = 1 \))
Lindemann(-Hinshelwood) mechanism

\[ A(g) \rightarrow B(g) \]

Inelastic collisions in the gas phase activate molecules:

\[ A + A \xleftrightarrow{k_1} A + A^* \]
\[ A^* \xrightarrow{k_2} B \]

\( c_{A^*} \ll c_A \) \Rightarrow stationary state \( \frac{dc_{A^*}}{d\tau} = 0 \) \Rightarrow

\[ -\frac{dc_A}{d\tau} = \frac{dc_B}{d\tau} = k_2 \frac{k_1 c_A^2}{k_2 + k_{-1} c_A} \]

- \( k_{-1} c_A \gg k_2 \) (ambient pressures): \( \frac{dc_B}{d\tau} = \frac{k_2 k_1}{k_{-1}} c_A \) \hspace{1cm} 1st order

- \( k_{-1} c_A \ll k_2 \) (low pressures): \( \frac{dc_B}{d\tau} = k_1 c_A^2 \) \hspace{1cm} 2nd order

E.g.: cyclopropane \( \rightarrow \) propene, \( N_2O_5 \rightarrow NO_2 + NO_3^* \),
dimethyldiazene (azomethane) \( CH_3-N\equivN-CH_3 \rightarrow C_2H_6 + N_2 \)
Chain reactions

- initiation (typically free radicals are produced)
  - heat
  - chemical (peroxides)
  - light (UV)

- propagation (cyclic reaction with radical recovery)
  - chain transfer (no branching)
  - chain branching

- termination
  - recombination (of radicals)
  - reaction (low-reactive radical—inhibition)
  - deactivation at walls
Example (not in detail)

\[
H_2 + Cl_2 \rightarrow 2 HCl
\]

initiation: \[ Cl_2 \xrightarrow{k_1} 2 Cl^* \]

propagation: \[
\begin{align*}
Cl^* + H_2 & \xrightarrow{k_2} HCl + H^* \\
H^* + Cl_2 & \xrightarrow{k_3} HCl + Cl^*
\end{align*}
\]

cycle (up to \[10^6\])

termination: \[ 2Cl^* \xrightarrow{k_4} Cl_2 \]

\[
\frac{dc_{HCl}}{d\tau} = k_2 c_{Cl^*} c_{H_2} + k_3 c_{H^*} c_{Cl_2} \quad \text{steady state} \quad 2k_2 \sqrt{\frac{k_1}{k_4} c_{Cl_2} c_{H_2}}\]
Enzyme catalysis: Michaelis–Menten kinetics

Mechanism of Michaelis and Menten (Enzyme, Substrate, Product):

\[
E + S \xrightleftharpoons[k_1]{k_2} ES \xrightarrow{k_-1} E + P
\]

stationary state (because \(c_E, c_{ES} \ll c_S\)):

\[
\frac{dc_{ES}}{d\tau} = k_1c_Ec_S - (k_-1 + k_2)c_{ES} = 0
\]

balance: \(c_E + c_{ES} = c_{E0}\)

Eliminating \(c_E\) (\(\Rightarrow c_{ES}\)) from \(\frac{dc_P}{d\tau}\):

\[
\frac{dc_P}{d\tau} = k_2c_{ES} = k_2 \frac{c_{E0}}{K_M/c_S + 1} = v_{\text{max}} \frac{c_S}{K_M + c_S}
\]

where \(K_M = \frac{k_2 + k_-1}{k_1} = \text{Michaelis constant}\) a \(v_{\text{max}} = k_2c_{E0}\)

\(c_S \gg K_M \Rightarrow \frac{dc_S}{d\tau} = -v_{\text{max}}\) (zeroth order, most of E is saturated, ES)

\(c_S \ll K_M \Rightarrow \frac{dc_S}{d\tau} = -\frac{v_{\text{max}}}{K_M}c_S\) (first order, most of E is free, E)
Experimentally available: $K_M$ and $v_{\text{max}} = k_2 c_{E_0}$ (often not both $c_{E_0}$ and $k_2$ simultaneously)

$$\frac{dc_S}{d\tau} = -v_{\text{max}} \frac{1}{K_M/c_S + 1}$$

Integrated form

$$K_M \ln \frac{c_{S_0}}{c_S} + c_{S_0} - c_S = v_{\text{max}} \tau$$

😊 cannot solve for $c_S(\tau)$ (using elem. functions) ⇒ numerical solution
**Metabolism of alcohols**

Alcohol dehydrogenase, various types human:
In liver and the lining of the stomach
Further oxidation to acids and $H_2O + CO_2$

\[
\begin{align*}
CH_3\ CH_2OH & \rightarrow \ CH_3\ CHO \ \text{hangover} \\
CH_2OH\ CH_2OH & \rightarrow \ldots \rightarrow (COOH)_2 \ (\text{kidney stones}) \\
CH_3OH & \rightarrow \ HCHO \ (\text{□}) \rightarrow \ HCOOH \ (\text{□})
\end{align*}
\]

**Example.** Calculate the time needed to metabolize $c_{S0} = 1$ wt. % of ethanol to $c_S = 0.1$ %.

Data: $v_{\text{max}} = 0.12 \text{ g L}^{-1} \text{ hod}^{-1}$, $K_M = 0.06 \text{ g L}^{-1}$.

$\rho_{\text{blood}} = 1.06 \text{ g cm}^{-3} \Rightarrow 1$ wt. % = $1.06 \text{ g L}^{-1}$

0th order: $\tau = \frac{c_{S0} - c_S}{v_{\text{max}}} = \frac{(1 - 0.1) \times 1.06}{0.12} \text{ h} = 7.7 \text{ h}$

More accurate: $\tau = \frac{K_M \ln \frac{c_{S0}}{c_S} + c_{S0} - c_S}{v_{\text{max}}} = 9.2 \text{ h}$

Other data: $K_M = 0.02$–$0.05 \text{ g L}^{-1}$, include absorption of ethanol in the body, …
Michaelis–Menten kinetics III

Rate:

\[ v = - \frac{dc_S}{d\tau} = v_{\text{max}} \frac{1}{K_M/c_S + 1} \]

Linear in \((1/c_S, 1/v)\)
(Lineweaver & Burk):

\[ \frac{1}{v} = \frac{K_M}{v_{\text{max}} c_S} + \frac{1}{v_{\text{max}}} \]
Example—carbonic anhydrase

$$\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{HCO}_3^- + \text{H}^+$$

<table>
<thead>
<tr>
<th>[CO$_2$]/mmol dm$^{-3}$</th>
<th>$v$/mol dm$^{-3}$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>$2.78 \times 10^{-5}$</td>
</tr>
<tr>
<td>2.5</td>
<td>$5.00 \times 10^{-5}$</td>
</tr>
<tr>
<td>5.0</td>
<td>$8.33 \times 10^{-5}$</td>
</tr>
<tr>
<td>20.0</td>
<td>$16.7 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

$K_M = 0.01$ mol dm$^{-3}$

[according to DeVoe, Kistiakowski, JACS 83, 274 (1961)]
Babel of units

Enzyme activity unit (amount of substance / time)

- SI: mol s\(^{-1}\) (katal)
- more common: \(\mu\text{mol/min}\) ("enzyme unit", U)

**Specific activity** (per kg of enzyme)

- SI: mol s\(^{-1}\) kg\(^{-1}\)
- \(\mu\text{mol min}^{-1} \text{ mg}^{-1}\)

**Turnover number** (per mole),

- SI: mol s\(^{-1}\) mol\(^{-1}\) = s\(^{-1}\)
- often min\(^{-1}\) etc.

**Molar mass**: g mol\(^{-1}\) = Da (dalton)

or \(1 \text{ g mol}^{-1}/N_A = \frac{1}{12} \text{ m}^{(12}\text{C}) = 1 \text{ u} = 1.660539 \times 10^{-27} \text{ kg} = 1 \text{ Da}\)

**Example**: 1 \(\mu\text{g}\) of enzyme \((M = 40\text{ kDa})\) in the excess of substrate provides the reaction rate of 6 \(\mu\text{mol}\) of substrate/min. What is the turnover number (in s\(^{-1}\))?

### Deprecated units:

- \(1 \text{ M} = 1 \text{ mol dm}^{-3}\)
- \(1 \text{ m} = 1 \text{ mol kg}^{-3}\)

\((1 \text{ mol dm}^{-3})\)

- \(1 \text{ Da} = 1 \text{ g mol}^{-1}\)
- \(1 \text{ bar} = 10^5 \text{ Pa}\)
- \(1 \text{ Å} = 10^{-10} \text{ m}\)
- \(1 \text{ cal}_{\text{th}} = 4.184 \text{ J}\) (thermochemical)
- \(1 \text{ cal}_{\text{IT}} = 4.1868 \text{ J}\) (intl./IAPWS)
- \(1 \text{ cal}_{\text{IUNS}} = 4.182 \text{ J}\) (food)
Inhibition

- reversible
- irreversible

**reversible inhibition**: the inhibitor is bound non-covalently (H-bonds, etc.), decreases the turnover

\[
E + S \xrightleftharpoons[k_{-1}]{k_1} ES \xrightarrow[k_2]{k_i} E + P
\]

\[
E + S \xrightleftharpoons[k_{-1}]{k_1} EI \xrightarrow[k_2]{k_i} E + P
\]

**irreversible inhibition**: “catalyst poisoning”, usually covalently bound \(\Rightarrow\) inactive complex \(EI^*\)
Competitive reversible inhibition

\[
E + S \xrightleftharpoons[k_1 \rightleftharpoons k_{-1}]{k_2} ES \rightarrow E + P + I
\]

\[
k_i \downarrow \uparrow k_{i-1}
\]

EI

The inhibitor binds to the same site as the substrate ("competes" with the substrate)
The inhibitor binds to the enzyme-substrate complex

Also anti-competitive

often partial (slows down the reaction)
Mixed (non-competitive) reversible inhibition

Mixed inhibition: the inhibitor bound both to E and ES

(Pure) non-competitive inhibition: inhibitor affects a different part of the enzyme, $k_i = k_i'$, $k_{i-1} = k_{i-1}'$
Reversible inhibition: some math

\[ \begin{align*}
E + S & \xrightleftharpoons{k_1}{k_{-1}} ES \\
+ I & \xrightleftharpoons{k_i}{k_{i-1}} EI \\
& \xrightleftharpoons{k_i'}{k_{i-1}'} ESI
\end{align*} \]

**Stationary state:**

\[
\frac{dc_{ES}}{d\tau} = k_1c_Ec_S - (k_{-1} + k_2)c_{ES} - k_i'c_Ic_{ES} + k_{i-1}'c_{ESI} = 0
\]

**Pre-equilibrium:**

\[
c_{EI} = \frac{k_i}{k_{i-1}}c_Ec_I, \quad c_{ESI} = \frac{k_i'}{k_{i-1}'}c_{ES}c_I
\]

**Balance:**

\[
c_E + c_{ES} + c_{EI} + c_{ESI} = c_{E0}
\]

we assume \( c_I \gg c_E \), \( \Rightarrow c_I \approx c_{I0} \) is known (no balance of I needed)
Reversible inhibition: Lineweaver–Burk

\[
\frac{1}{v} = \frac{\alpha K_M}{v_{max}} \frac{1}{c_S} + \frac{\alpha'}{v_{max}}, \quad \alpha = 1 + \frac{k_i}{k_i - 1} c_I, \quad \alpha' = 1 + \frac{k_i'}{k_i' - 1} c_I
\]
Reversible inhibition

**time vs. substrate conc.**

- $\alpha = 1 \ \alpha' = 1$ (no inhibition)
- $\alpha = 2 \ \alpha' = 1$ (competitive)
- $\alpha = 1 \ \alpha' = 2$ (uncompetitive)
- $\alpha = 2 \ \alpha' = 2$ (non-competitive)

**Lineweaver–Burk**

- $\alpha = 1 \ \alpha' = 1$ (no inhibition)
- $\alpha = 2 \ \alpha' = 1$ (competitive)
- $\alpha = 1 \ \alpha' = 2$ (uncompetitive)
- $\alpha = 2 \ \alpha' = 2$ (non-competitive)
Reversible inhibition – summary

\[
\frac{1}{v} = \frac{\alpha K_M}{v_{\text{max}} c_S} + \frac{\alpha'}{v_{\text{max}}}, \quad \alpha = 1 + \frac{k_i}{k_i^{-1} c_I}, \quad \alpha' = 1 + \frac{k_i'}{k_i'^{-1} c_I}
\]

No inhibition:
\[\alpha = \alpha' = 1\]

Competitive:
\[\alpha > 1\]
inhibitor binds to the free enzyme in the L-B diagram:
greater \( K_M \)
the same \( v_{\text{max}} \)

Uncompetitive:
\[\alpha' > 1\]
inhibitor binds to the enzyme-substrate complex in the L-B diagram:
smaller \( K_M \)
smaller \( v_{\text{max}} \)

Mixed (non-competitive):
\[\alpha, \alpha' > 1\]
inhibitor binds to both the free enzyme and enzyme-substrate complex in the L-B diagram:
the same \( K_M \)
smaller \( v_{\text{max}} \)
Photon energy = \( h\nu \) = energy source for the reaction

Planck constant: \( h = 6.62607 \times 10^{-34} \) J s

Frequency \( \nu \), wave number \( \tilde{\nu} = 1/\lambda \), wave length \( \lambda \). It holds: \( c = \lambda \nu \).

**Quantum yield**

\[
\Phi = \frac{\text{# of molecules transformed/decomposed/...}}{\text{# of photons absorbed}}
\]

Chain reactions: \( \Phi > 1 \). Example:

\[
2 \text{HI} \rightarrow \text{H}_2 + \text{I}_2
\]

\[
\text{HI} + h\nu \rightarrow \text{H}^+ + \text{I}^-
\]

\[
\text{H}^+ + \text{HI} \rightarrow \text{H}_2 + \text{I}^-
\]

\[
2\text{I}^- \rightarrow \text{I}_2
\]

\[
\Phi = 2
\]

**Example:** How much HI decomposes by absorbing energy of 100 J in the form of light of wave length 254 nm?

0.42 mmol