

MUNI PHARM

Kinetics.

Rates and orders of reactions.

Influence of temperature and other factors on reaction rates.

The importance of kinetics in formulation and development of pharmaceuticals

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DRUG KINETICS

- the **rate** of a reaction is given by the expression dc/dt
 - where dc is the increase or decrease of concentration over an infinitesimal time interval dt .
- in pharmacy:
 - **drug stability** – describing the process of a drug inactivation by its conversion to a less favorable physical or chemical form.
 - **dissolution** – concern on the rapidity with which a solid medical form is converted to a molecular solution of the drug
 - **absorption, distribution, metabolism, and elimination process** – drug pharmacokinetics in the body
 - **drug action at the molecular level** – a rate of process is important for a drug action

Rates, Order, and Molecularity of Reactions

- Reactions:

- Homogeneous
- Heterogeneous - at the contact of two phases
- Isolated – for studying of fundamental relationships
- Simultaneous - reversible, lateral, consequential (chain)

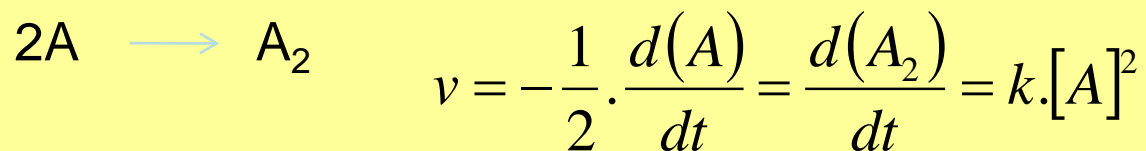
- Rate of reaction (instantaneous): $v = -\frac{dc_{\text{reactant}}}{dt}$ or $v = \frac{dc_{\text{product}}}{dt}$

- Molecularity of reaction:

- the number of molecules, atoms, or ions reacting in an elementary process

- unimolecular: $A \longrightarrow \text{product(s)}$ (isomerization, decomposition, ...)

- bimolecular (2 types):
 $A + B \longrightarrow C + D$ $v = -\frac{d(A)}{dt} = k \cdot [A] \cdot [B]$ $k = \text{rate constant}$



- reactions of higher molecularity are seldom

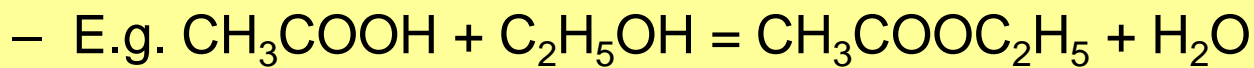
Rates, Order, and Molecularity of Reactions

- **generally**: the **rate** of a chemical reaction is **proportional** to the product of the **molar concentration** of the reactants each **raised** to a power usually equal to the **number of molecules** undergoing reaction



$$v = -\frac{1}{a} \cdot \frac{d(A)}{dt} = -\frac{1}{b} \cdot \frac{d(B)}{dt} = \dots = k \cdot [A]^a \cdot [B]^b \cdot [C]^c \dots$$

- $a + b + c + \dots$ (the sum of the exponents) = **order of a reaction**



- second-order reaction

- **when acetic acid** is used as **solvent**, ethyl alcohol is changed appreciably from its original concentration, whereas the concentration of acetic acid is **essentially unchanged because it is present in great excess**. In this case, the contribution of the acetic acid to the rate expression is considered **constant**. The reaction is then said to be a **pseudo-first-order** reaction because it depends only on the first power of the concentration of ethyl alcohol

ZERO-ORDER REACTIONS

- rate of reaction is independent of the concentration of the reactants



$$v = -\frac{d(A)}{dt} = k_0$$

$$\int_{A_0}^{A_t} dA = -k_0 \cdot \int_0^t dt$$

$$A_t - A_0 = -k_0 \cdot t$$

A_0 = the initial concentration at $t = 0$

$$A_t = A_0 - k_0 \cdot t$$

A_t = the concentration after time t

$$t_{1/2} = \frac{A_0}{2 \cdot k_0}$$

$t_{1/2}$ = the *half-life* is the time required for one-half of the material to disappear

FIRST-ORDER REACTIONS

- the concentration decreases exponentially with time:
 - eg. $\text{H}_2\text{O}_2 \longrightarrow 2\text{H}_2\text{O} + \text{O}_2$

$$v = -\frac{d(A)}{dt} = k_1 \cdot [A]$$

... Integrating equation between concentration c_0 at time $t = 0$ and concentration c at some later time, t , we have:

$$\int_{A_0}^{A_t} \frac{dA}{A} = -k_1 \cdot \int_0^t dt$$

$$\ln A_t - \ln A_0 = -k_1 \cdot t \qquad \ln \frac{A_t}{A_0} = -k_1 \cdot t \qquad t_{1/2} = \frac{\ln 2}{k_1}$$

$$A_t = A_0 \cdot e^{-k_1 \cdot t}$$

the half-life is a constant,
independent of the concentration

SECOND-ORDER REACTIONS

- $A + B \longrightarrow$ products (the rates of bimolecular reactions, which occur when two molecules come together)
- When the rate of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B , and both are proportional to the product of the concentrations of the reactants:

$$v = -\frac{d(A)}{dt} = -\frac{d(B)}{dt} = k_2 \cdot [A] \cdot [B]$$

- If a and b are the initial concentrations of A and B , respectively, and x is the concentration of each species reacting in time t :

$$\frac{dx}{dt} = k_2 \cdot (a - x) \cdot (b - x)$$

- When A and B are present in the same concentration so that $a = b$:

$$\frac{dx}{dt} = k_2 \cdot (a - x)^2$$

$$\int_0^x \frac{dx}{(a-x)^2} = k_2 \int_0^t dt \rightarrow \left(\frac{1}{a-x}\right) - \left(\frac{1}{a-0}\right) = k_2 \cdot t \rightarrow t_{1/2} = \frac{1}{a \cdot k_2}$$

The half-life of a second-order reaction

SECOND-ORDER REACTIONS



- When, in the general case, A and B are not present in equal concentrations:

when $a \neq b$, then
$$\frac{dx}{dt} = k.(a - x).(b - x)$$

$$\frac{2,303}{a - b} \cdot \log \frac{b.(a - x)}{a.(b - x)} = k_2.t$$

Determination of Order

1. *Substitution method*: the data are substituted in the integrated form of the equations that describe the various orders: $v = k \cdot c^n$

When the equation is found in which the calculated k values remain constant within the limits of experimental variation, the reaction is considered to be of that order.

2. *Half-Life Method*:

$t_{1/2}$ is proportional to $1/a^{n-1}$

3. *Graphic Method*

- $c = f(t)$...0. order
- $\log c = f(t)$...1. order
- $1/c = f(t)$...2. order

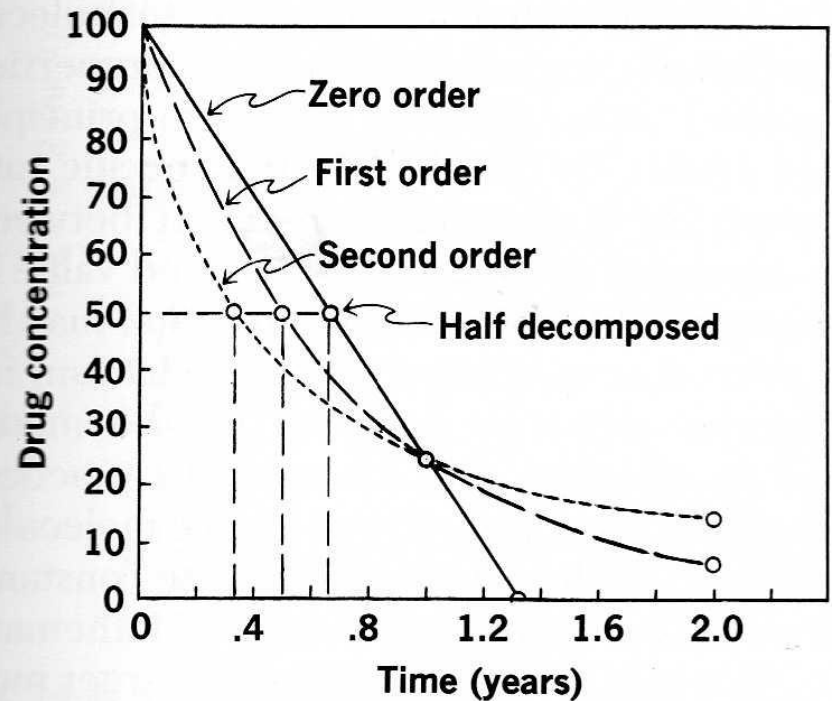


FIG. 14-6. Comparison of zero-(—), first-(— —) and second-(-----) order reactions.

EFFECT OF TEMPERATURE AND OTHER FACTORS ON THE RATE OF REACTION

- A number of factors other than concentration may affect the rate of reaction: temperature, solvents, catalysts, light...

- temperature:

- The **Arrhenius equation** (empirical relation): $k = A.e^{-E_a/R.T}$

A = the *frequency factor*, E_a = the *energy of activation* (only molecules having sufficient kinetic energy to overcome energy barriers can react)

- **from kinetic theory of gases:** for molecules with $E > E_a$ the fraction of the molecules having a given kinetic energy can be expressed by the *Boltzmann distribution law* :

$f_i = \frac{N_i}{N_{total}} = e^{-E_i/R.T}$

$k_2 = P \cdot z \cdot f$, k_2 = rate constant of bimolecular reaction, z = collision factor (number of collisions per second per cubic centimeter), P = steric or probability factor (probability that a collision between molecules will lead to product) $\longrightarrow A = z \cdot P$

EFFECT OF TEMPERATURE AND OTHER FACTORS ON THE RATE OF REACTION

- effect of the solvent:

- nonelectrolytes: reaction is related to internal pressures or solubility parameters of the solvent and the solute
- ionic reactions: reaction is related also to ionic strength and dielectric constant of the solvent

For bimolecular reaction (nonideal solution): $A + B \rightleftharpoons (A...B)^* \longrightarrow$ products
 thermodynamic equilibrium constant should be written in terms of activities:

$$k^* = \frac{a^*}{a_A \cdot a_B} = \frac{c^*}{c_A \cdot c_B} \cdot \frac{\gamma^*}{\gamma_A \cdot \gamma_B}$$

$$v = f \left(\begin{array}{l} \text{frequency with which an activated complex goes} \\ \text{to product} \end{array} \right) \cdot c^*$$

$$v = f \cdot k^* \cdot c_A \cdot c_B \cdot \frac{\gamma_A \cdot \gamma_B}{\gamma^*}, \quad \text{also} \quad v = k_2 \cdot c_A \cdot c_B$$

$$k_2 = f \cdot k^* \cdot \frac{\gamma_A \cdot \gamma_B}{\gamma^*} = k_0 \cdot \frac{\gamma_A \cdot \gamma_B}{\gamma^*} \quad k_0 = \text{rate constant in infinitely dilute solution}$$

EFFECT OF TEMPERATURE AND OTHER FACTORS ON THE RATE OF REACTION

- effect of the solvent:

$$k_2 = k_0 \cdot \frac{\gamma_A \cdot \gamma_B}{\gamma^*} \quad \wedge \quad \log \gamma_2 = \frac{V_2 \cdot \Phi_1^2}{2,303 \cdot R \cdot T} \cdot (\delta_1 - \delta_2)^2$$

$$\log k_2 = \log k_0 + \log \gamma_A + \log \gamma_B - \log \gamma^*$$

$$\log k_2 = \log k_0 +$$

$$+ \frac{V_A \cdot \Phi_1^2}{2,303 \cdot R \cdot T} \cdot (\delta_1 - \delta_A)^2 + \frac{V_B \cdot \Phi_1^2}{2,303 \cdot R \cdot T} \cdot (\delta_1 - \delta_B)^2 - \frac{V^* \cdot \Phi_1^2}{2,303 \cdot R \cdot T} \cdot (\delta_1 - \delta^*)^2$$

is valid : $V_A \approx V_B \approx V^* \approx V$

$$\log k_2 = \log k_0 + \frac{V \cdot \Phi_1^2}{2,303 \cdot R \cdot T} \cdot (\Delta\delta_A^2 + \Delta\delta_B^2 - \Delta\delta^{*2})$$

- when $\Delta\delta^* \sim 0$ a $\Delta\delta_A > 0$, $\Delta\delta_B > 0$, then $k > k_0$... solvation of activated complex
- when $\Delta\delta^* > 0$ a $\Delta\delta_A \sim 0$, $\Delta\delta_B \sim 0$, then $k < k_0$... solvation of reactants

EFFECT OF TEMPERATURE AND OTHER FACTORS ON THE RATE OF REACTION

- effect of the solvent:
- influence of ionic strength:
 - $A^{z_A} + B^{z_B} \rightleftharpoons (A\dots B)^{(z_A+z_B)} \longrightarrow \text{products}$
 - the activity coefficient γ_i of an ion in a dilute aqueous solution (<0.01 M) at 25 °C is given by the Debye-Hückel equation:

$$\log \gamma_i = -0.51 \cdot z_i^2 \cdot \sqrt{\mu}$$

then

$$\log k = \log k_0 + 1.02 \cdot z_A \cdot z_B \cdot \sqrt{\mu} \quad \mu = \text{ionic strength}$$

- if one of the reactants is a **neutral molecule** - the rate constant is **independent** of the ionic strength
- reacting ions of the **same sign**: the rate of reaction with the ionic strength **increases**
- reacting ions of **opposite sign**: the rate of reaction with the ionic strength **decreases**

EFFECT OF TEMPERATURE AND OTHER FACTORS ON THE RATE OF REACTION

- effect of the solvent:
- influence of dielectric constant:
 - material constant that indicates how many times the electrical power decreases when the bodies with power charge are placed instead of in a vacuum environment in medium
 - in infinitely dilute solution, where ionic strength $\mu = 0$:

$$\ln k = \ln k_{\epsilon=\infty} - \frac{N \cdot z_A \cdot z_B \cdot e^2}{R \cdot T \cdot r^*} \cdot \frac{1}{\epsilon}$$

- $k_{\epsilon=\infty}$ = rate constant in a medium of infinite dielectric constant
- ϵ = dielectric constant of the solution (equal approximately to the dielectric constant of the solvent in dilute solutions),
- N = Avogadro's number, z_A (z_B) = charges on the two ions,
- e = unit of electric charge, r^* = distance between ions in the activated complex
- reacting ions of the **same sign**: the rate of reaction with the dielectric constant **increases**
- reacting ions of **opposite sign**: the rate of reaction with the dielectric constant **decreases**