Kinetics

By

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Factors affecting the stability of drugs and their metabolites in biological matrices
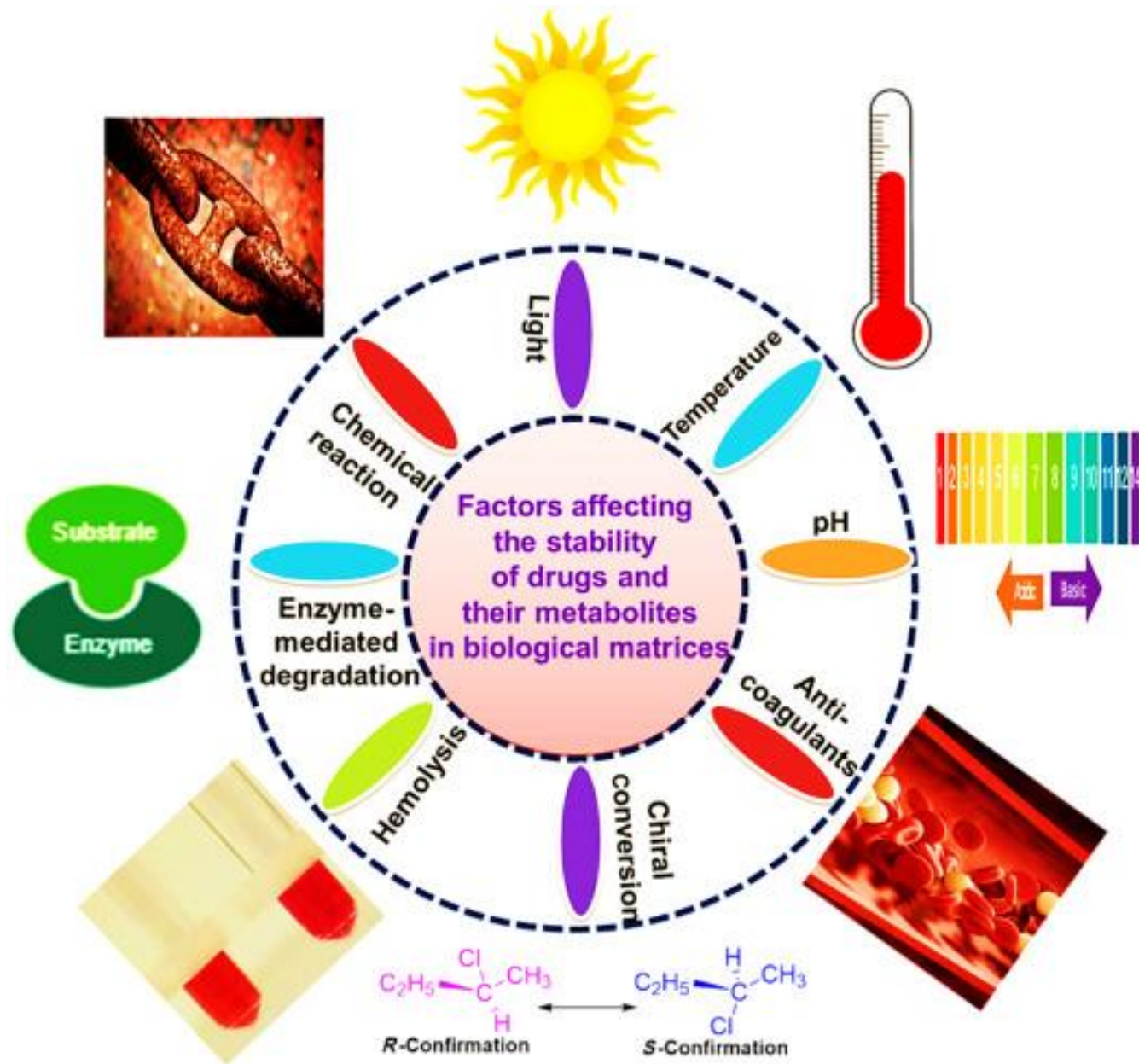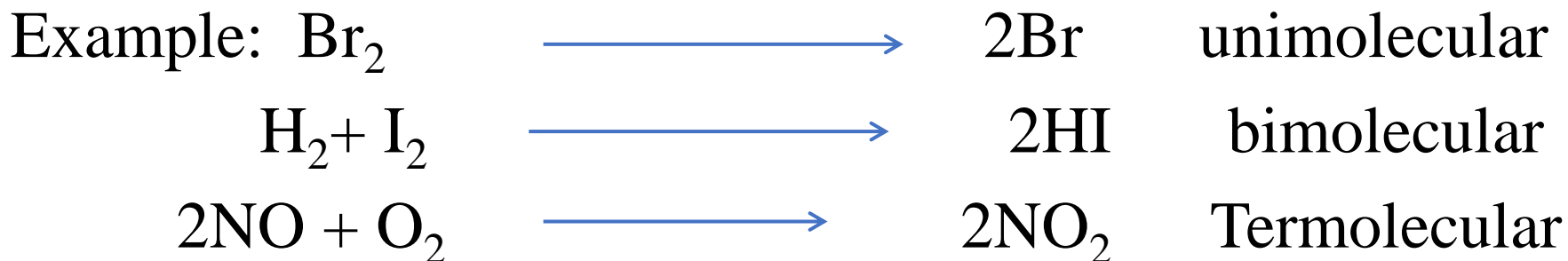
CHEMICAL KINETICS AND STABILITY

- The stability of drug product with time is important in determination of shelf life and expired date.

- The stability affected by factors, such as temperature, humidity, and light.

- This chapter studies the rates and mechanisms of reactions specially the decomposition and stabilization of drug products.

- For example, thiamine hydrochloride is most stable at a pH of 2 to 3 and is unstable above pH 6, so in preparation, the pharmacist should select the buffered vehicle that prevents the degradation.

- Applications of chemical kinetics in pharmacy result in the production of more-stable drug preparations.

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

Molecularity

Molecularity is the number of molecules, atoms, or ions reacting in an elementary process. molecularity classify the reaction into unimolecular, bimolecular, and Termolecular.   molecularity cannot gives complete detail about order of reaction specially those of several steps while kinetic study gives details.

Example: Br_2 $\longrightarrow$ $2Br$ unimolecular

$H_2 + I_2$ $\longrightarrow$ $2HI$ bimolecular

$2NO + O_2$ $\longrightarrow$ $2NO_2$ Termolecular

While the real detail mechanism revealed by kinetic study as follows:

$$2NO \longrightarrow N_2O_2 \quad \text{(fast)}$$
$$N_2O_2 + O_2 \longrightarrow 2NO_2 \quad \text{(slow)}$$
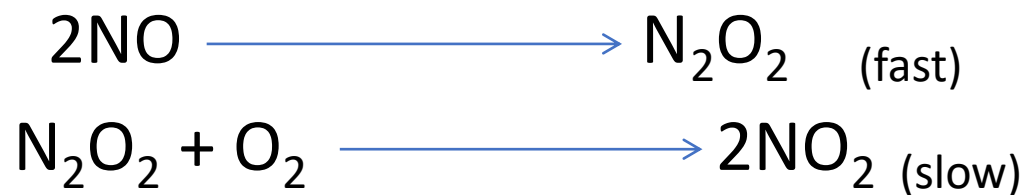
The rate of the reaction is given by the slow step.

Rate

The rate, velocity, or speed 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 the reaction

$$\text{Reactant} \longrightarrow \text{Products}$$

$$\text{Rate} = - \frac{d[Reactant]}{dt} = K[product]^a$$

where k is the rate constant and exponent a represent the order of reaction.

Specific Rate Constant

The constant, k, appearing in the rate law associated with a single-step (elementary) reaction is called the specific rate constant for that reaction.

The <u>half-life</u> is the time required for one-half of the material to disappear; the time at which C has decreased to 1/2 C.

The <u>shelf-life</u> is the time required for 10% of the material to disappear; it is the time at which C has decreased to 90% of its original concentration (i.e., 0.9C).

Kinetic study

Zero-Order Reactions

Garrett found that the loss in color of a multisulfa product followed a zero-order rate. The rate expression for the change of concentration, C, with time is therefore
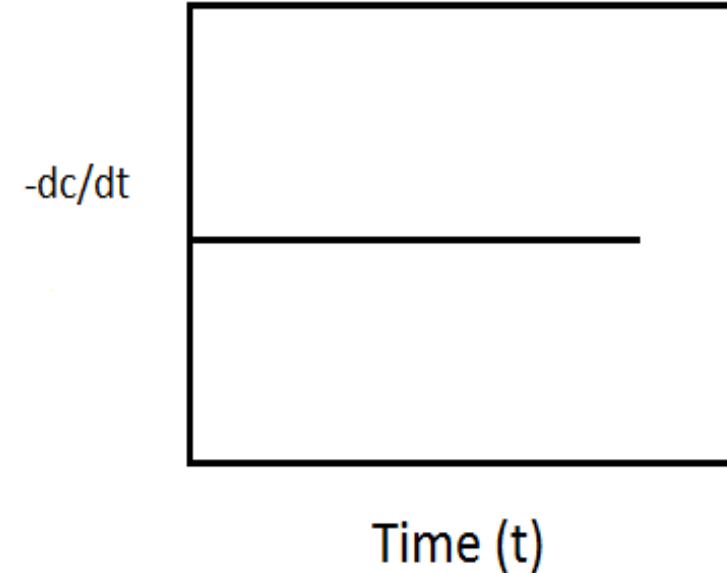
$$- \, dc/dt \quad = k_0$$

It means that the rate of reaction not depend on concentration of reactant, it is constant with time.

The rate equation can be integrated between the initial concentration, C_0, at t = 0, and C_t, the absorbance after time (t):

$$\mathbf{C_t = C_o - k_o t}$$

$$t = \frac{Co - Ct}{ko}$$

-dc/dt

Time (t)

Because the half-life is the time required for one-half of the material to disappear, in the present case, after one half, the concentration becomes $1/2C_o$.
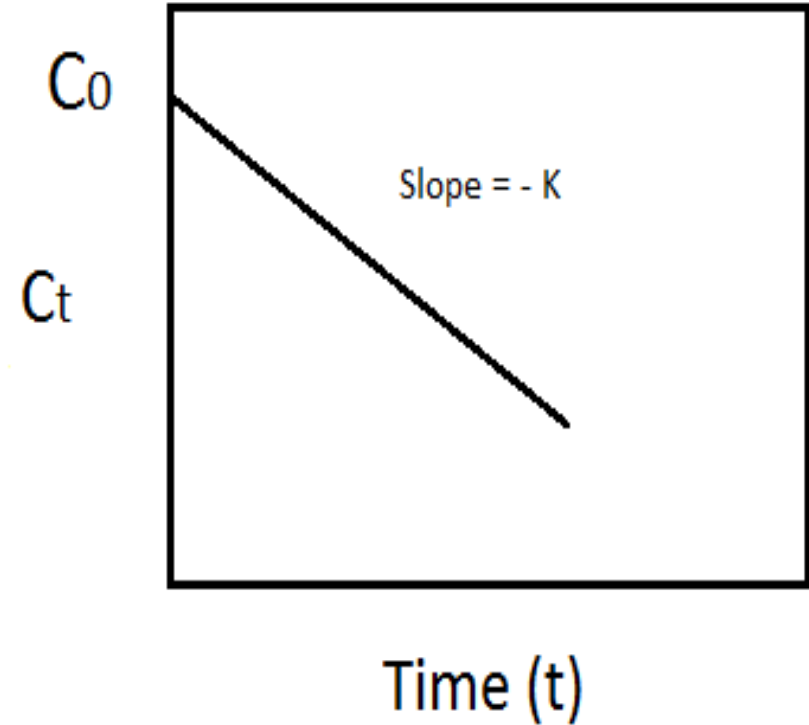
$$t_{1/2} = \frac{Co - 1/2Co}{ko}$$

$$Co$$

$$Ct$$

Slope = - K

$$t_{1/2} = \frac{\frac{1}{2}Co}{ko}$$

For shelf life

$$t_{10\%} = \frac{Co - 0.9Co}{ko} = \frac{0.1C0}{K0}$$

Time (t)

- The unit of zero order rate constant is:

$$k_0 = -\frac{dC}{dt} = \frac{mole/liter}{second} = \frac{mole}{liter\ second} = \text{mole liter}^{-1}\text{second}^{-1}$$
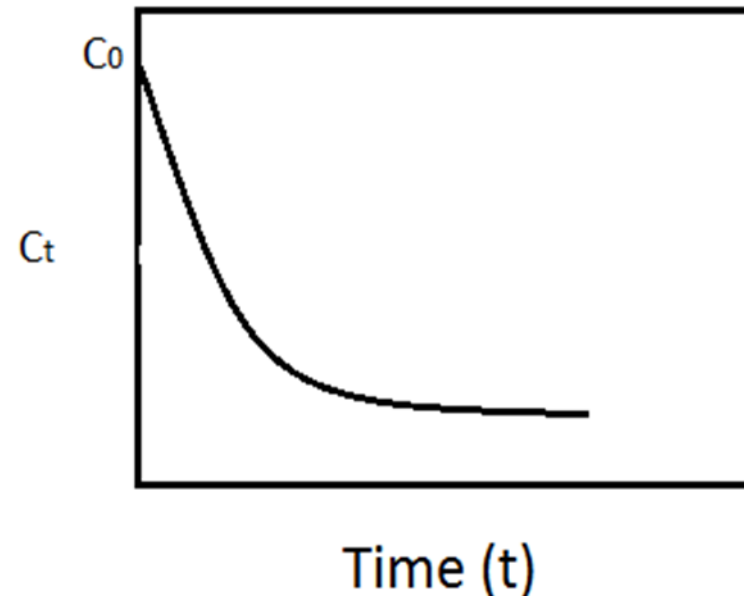
First-Order Reactions

Harried showed that the <u>decomposition rate</u> of hydrogen peroxide catalyzed by 0.02 M KI was <u>proportional</u> to the <u>concentration</u> of hydrogen peroxide remaining in the reaction mixture at any time. The data for the reaction

$$2H_2O_2 = 2H_2O + O_2$$

Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be first order.

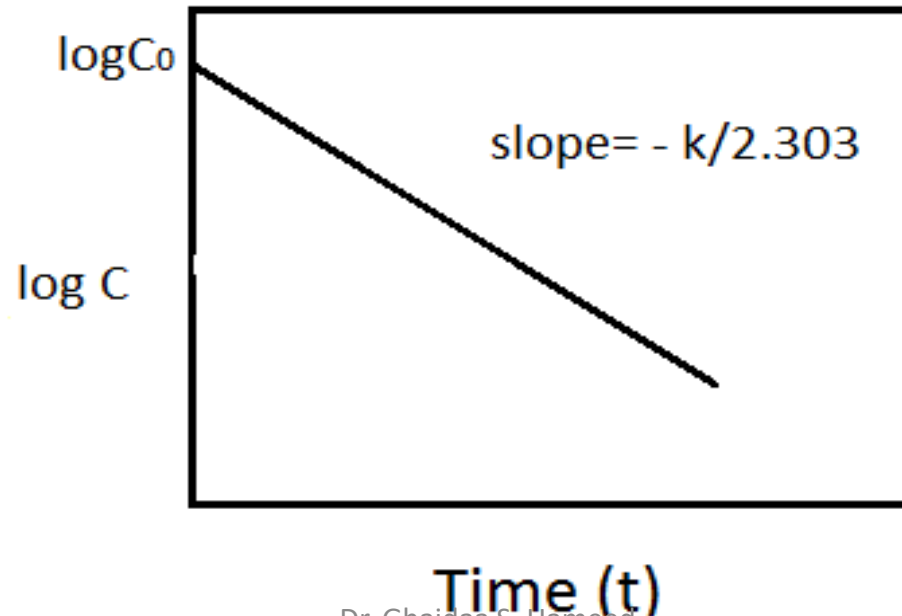The rate equation is written $- dc/dt = k\,C$

where c is the concentration of hydrogen peroxide remaining undecomposed at time t and k is the first-order rate constant.

Integrating above equation, we have

$$\ln C = \ln C_0 - Kt$$

(Common logarithm) $\quad \log C = \log C_0 - \dfrac{k}{2.303}\, t$

logCo

slope= - k/2.303

log C

Time (t)

For calculation of half life of reaction follows first order;

$$\log \frac{C_0}{C_t} = \frac{K\,t}{2.303}$$

at half life; t= t1/2, Ct= ½ C$_0$

$$\log \frac{C_0}{\frac{1}{2}\,C_0} = \frac{K\,t1/2}{2.303}$$

$$t\,\tfrac{1}{2} = 0.693/k$$

- The unit of first order rate constant is:

$$k = -\frac{dC}{dt}\frac{1}{C} = \frac{mole/liter}{second.mole/liter} = \frac{1}{second} = second^{-1}$$

For shelf life t$_{90}$;

$$\log \frac{C_0}{0.9\,C_0} = \frac{K\,t10\%}{2.303} \quad , \qquad t_{90} = 0.105/k$$

Determination of Order

The order of a reaction can be determined by several methods.

1. **Substitution Method**. The data from kinetic study can be substituted in the equations for each order. When the calculated k values remain constant for different Ct, the reaction is considered to be of that order.

2. **Graphic Method**. A plot of the data in the form of a graph can also be used to ascertain the order.

If a straight line results when concentration is plotted against t, the reaction is zero order.

The reaction is first order if log (concentration) versus t yields a straight line,

and it is second-order if 1/(concentration) versus t gives a straight line.

3. **Half-Life Method**. In a zero-order reaction, the half-life is proportional to the initial concentration, a, as observed in Table 15-2. The half-life of a first-order reaction is independent of initial concentration a;

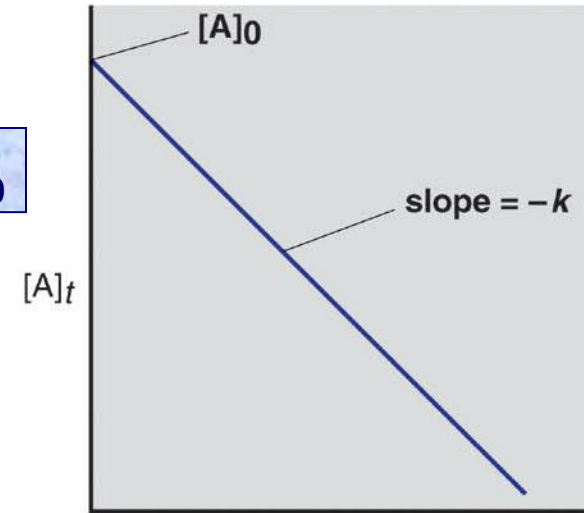t1/2 for a second-order reaction, in which a = b, is proportional to 1 /a.
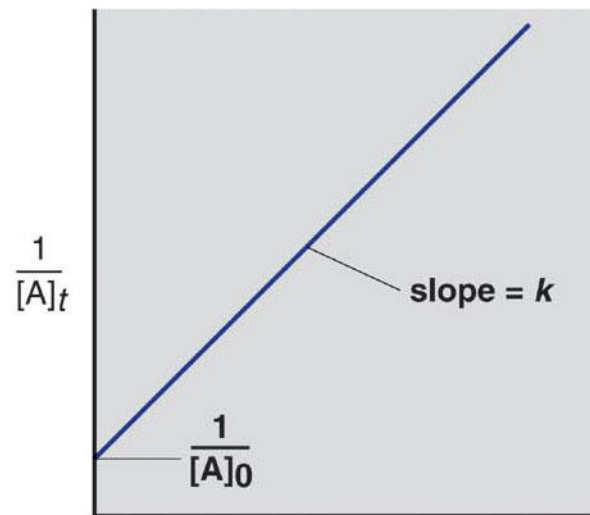
Graphical method to determine reaction order
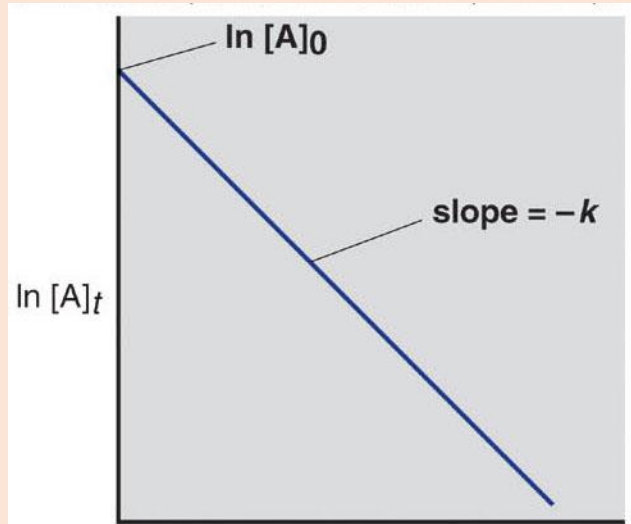
$$[A]_t = -kt + [A]_0$$

A First order

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

C Zero order

B Second order

$$1/[A]_t = kt + 1/[A]_0$$

Figure 16.7

Suspensions, Apparent Zero-Order Kinetics

Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles, so that the concentration remains constant. The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

$$-d[C]/dt = k_f[C]$$ where c= concentration of drug in solution

$$= \text{solubility}$$

K_f= first order rate constant of solution

When the concentration [C] is rendered constant, as in the case of a suspension, we can write

$K_f [C] = K_0$ where K_0= zero order rate constant of suspension

Thus, $K_0 = K_f \ x \ \text{Solubility}$

Second-Order Reactions

The rates of bimolecular reactions, which occur when two molecules come together, are frequently described by the second-order equation.

$$A + B \longrightarrow Products$$
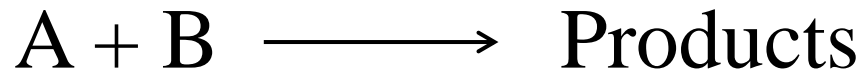
When the speed of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

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

If a and b is the initial concentrations of A and B respectively, and x is the concentration of each species reacting in time t, the rate law can be integrated and written according to 3 possibilities:

1. When, in the simplest case, both A and B are present in the same concentration so that a = b,

$$\frac{x}{a(a-x)} = Kt$$

The rate constant, k, in a second-order reaction therefore has the dimensions liter/ (mole sec) or liter mole^{-1} sec^{-1}.
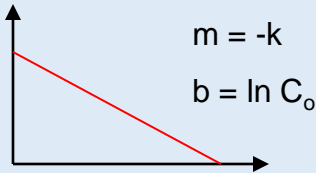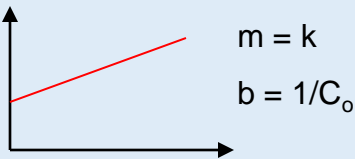
The half-life of a second-order reaction is

t1/2= 1/ak

2. When, in the general case, A and B are not present in equal concentrations but the difference in concentration is not big, integration of equation yields:

$$\frac{2.303}{a-b} \log \frac{b(a-x)}{a(b-x)} = Kt$$

Summary of Rate Laws to One-Component

	First-Order	Second-Order	Zeroth-Order
differential rate law (-dC/dt)	kC	kC^2	k
Equation	$\ln C = \ln C_o - kt$	$1/C = kt + 1/C_o$	$C_t = C_o - k_0 t$
Shelf life	$0.105/k$		$0.1C°/k_0$
Linear Plot	m = -k b = ln C_o	m = k b = 1/C_o	m = -k b = C_o
Half-Life	$0.693/k$	$1/kC_o$	$C_o/2k_0$
Units on k	$time^{-1}$	$M^{-1}\ time^{-1}$	$M\ time^{-1}$

?

?

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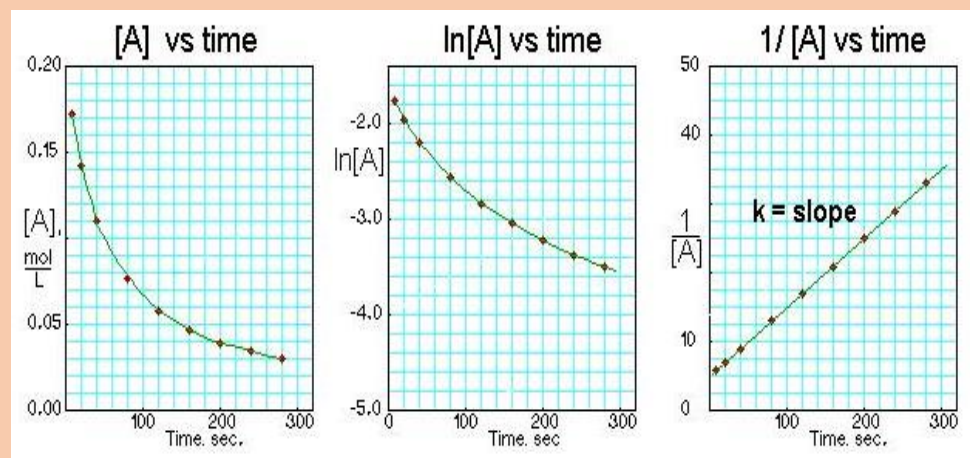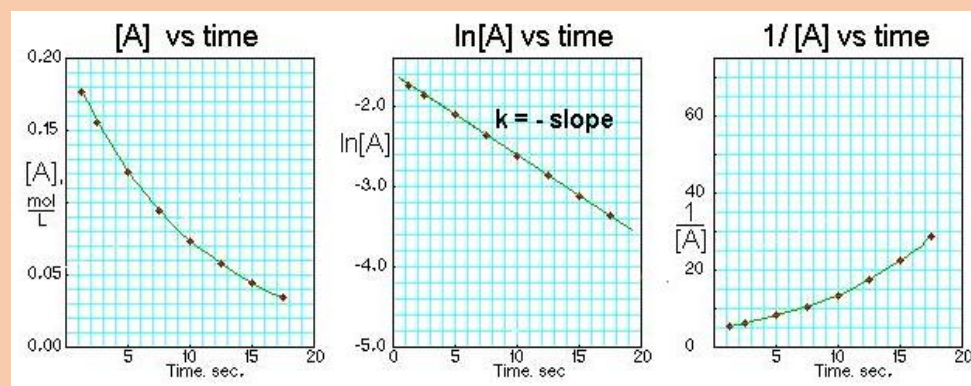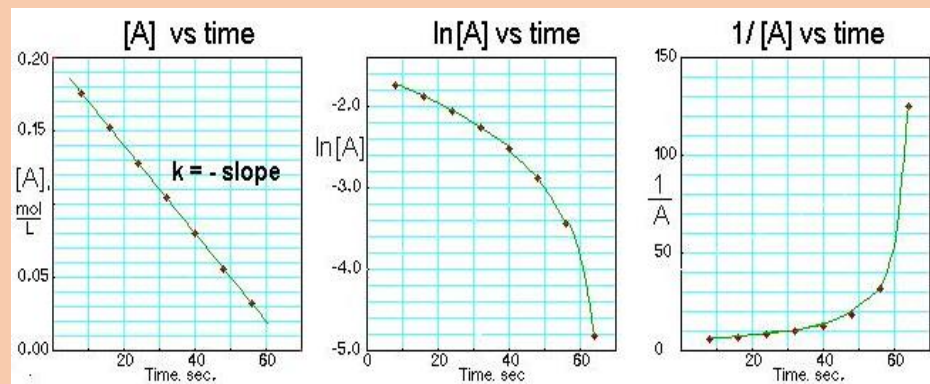
H.W

Thus the gradient of a plot of $1/c$ against t gives the rate constant, k.

Units of k from Eqn 7.9 are:

$$\frac{dc}{c^2 dt} = -k \qquad (7.13)$$

i.e. $\text{conc}^{-1}\ \text{time}^{-1}$ and typical units are $L\ \text{mole}^{-1}\ s^{-1}$ or similar.

Example 7.2

Consider the following decomposition data.

t (days)	0	30	60	90	120	150
c (mmole L^{-1})	100	2.17	1.10	0.74	0.56	0.44

From Figure 7.2, it can be seen that the rate constant is $0.015\ L\ \text{mmole}^{-1}\ \text{day}^{-1}$.

If the reaction is between two different species, A and B, it is unlikely that their starting concentrations will be

H.W

$= k_2[\%O_2]^2$, where k_2
here are two concen-
wn as *second order*.
e detail below.

$\ln \alpha A = \ln$

hence
$$\ln A = \ln A_o - kt \qquad (7.8)$$

Thus, although the intercept of the graph will alter, the gradient remains the same.

Example 7.1

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ions during storage
ody compartment to
into blood, follow
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ivided by the corre-

(7.1)

Consider the following example. A tritiated cardiac stimulant is administered by i.v. injection. Blood samples have the following radioactivity counts per second (cps).

t (min)	0	30	60	90	120	150
cps		59.7	24.3	9.87	4.01	1.63	0.67
ln (cps)	4.09	3.19	2.29	1.39	0.49	-0.41

From Figure 7.1, it can be seen that the rate constant for absorption from the blood is 0.03 min^{-1}.

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3. When A and B are not present in equal concentrations and the difference in concentration is very big

(*Pseudo-first-order reaction*):

Suppose that in this reaction, A was in great excess and B was in a relatively low concentration.

As the reaction proceeded, B would change appreciably from its original concentration, whereas the concentrations of A would remain essentially unchanged because they are present in great excess. In this case the contribution of A to the rate expression is considered constant and the reaction rate can be written as

$$A + B \longrightarrow Products$$
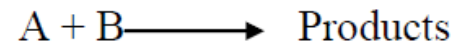
$$-\frac{d[B]}{dt} = K\,[A][B]$$

K is constant and [A] is constant

$$-\frac{d[B]}{dt} = K'\,[B]$$

where K'= K [A], K'= Pseudo-first-order constant

Factors effects on stability

A number of factors other than concentration may affect the reaction velocity. Among these are temperature, solvents, catalysts, and light.

1. Temperature effect

Collision Theory

Reaction rates are expected to be proportional to the number of collisions per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.
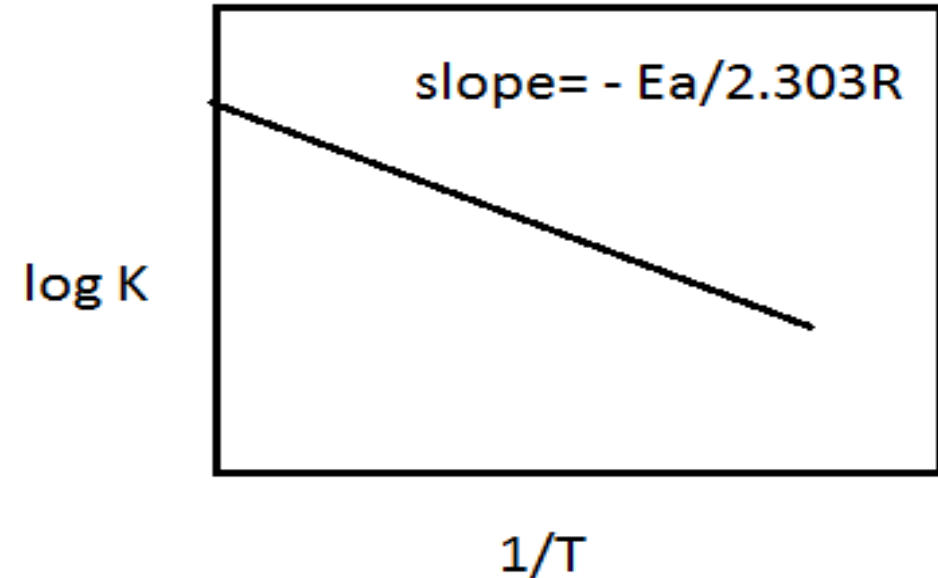
The effect of temperature on reaction rate is given by the equation, first

suggested by Arrhenius,

$$k = Ae^{-Ea/RT}$$

or $\quad \log K = \log A - \dfrac{Ea}{2.303R} \dfrac{1}{T}$

where k is the specific reaction rate, A is a constant known as the Arrhenius factor or the frequency factor, *Ea* is the energy of activation. R is the gas constant, 1.987 calories/deg mole, and T is the absolute temperature.
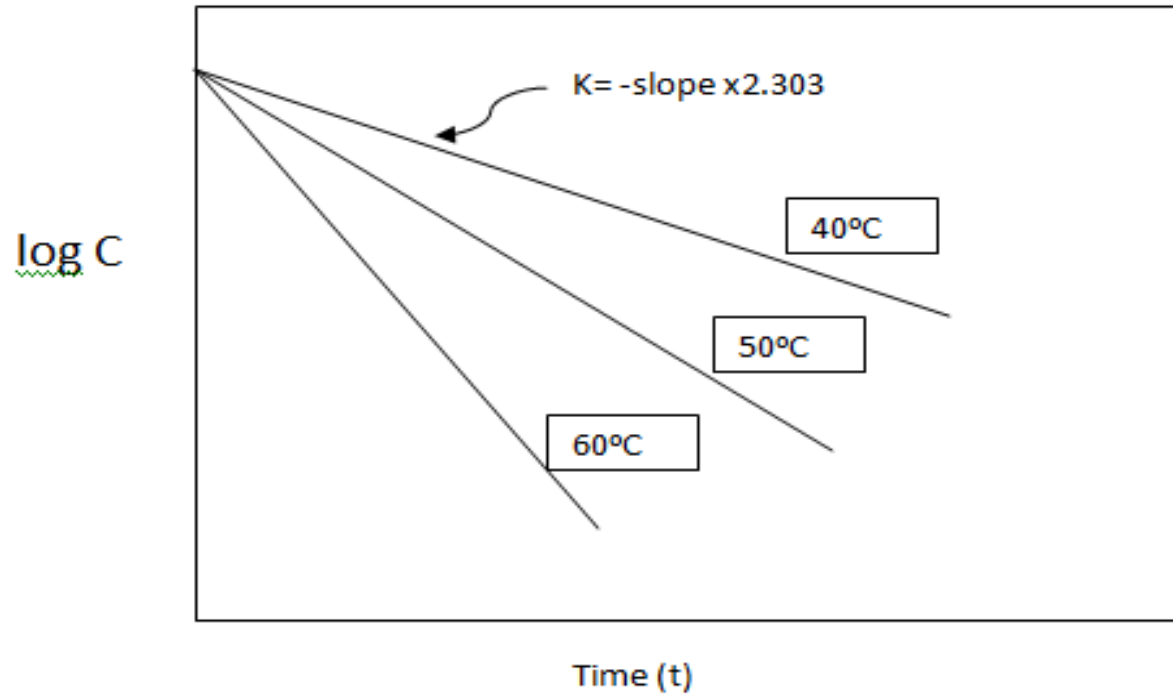
slope= - Ea/2.303R

log K

1/T

In case at 2 temperatures t1 and t2, the equation becomes:

$$\text{Log}\frac{K2}{K1} = \frac{Ea}{2.303R}(\frac{T2-T1}{T2T1})$$

Accelerated stability testing

The k values for the decomposition of drug at various elevated temperatures are obtained by plotting log of concentration against time as shown in this figure:

- Then the logarithm of rate constants (k) at various temperatures are plotted against reciprocal of absolute temperature and the resulting line extrapolated to the room temperature to get $K_{25}°C$ as shown in this figure:

The shelf life $t_{90\%}$ can be calculated from equation

$$t_{90\%} = 0.105/ K_{25\,°C}$$
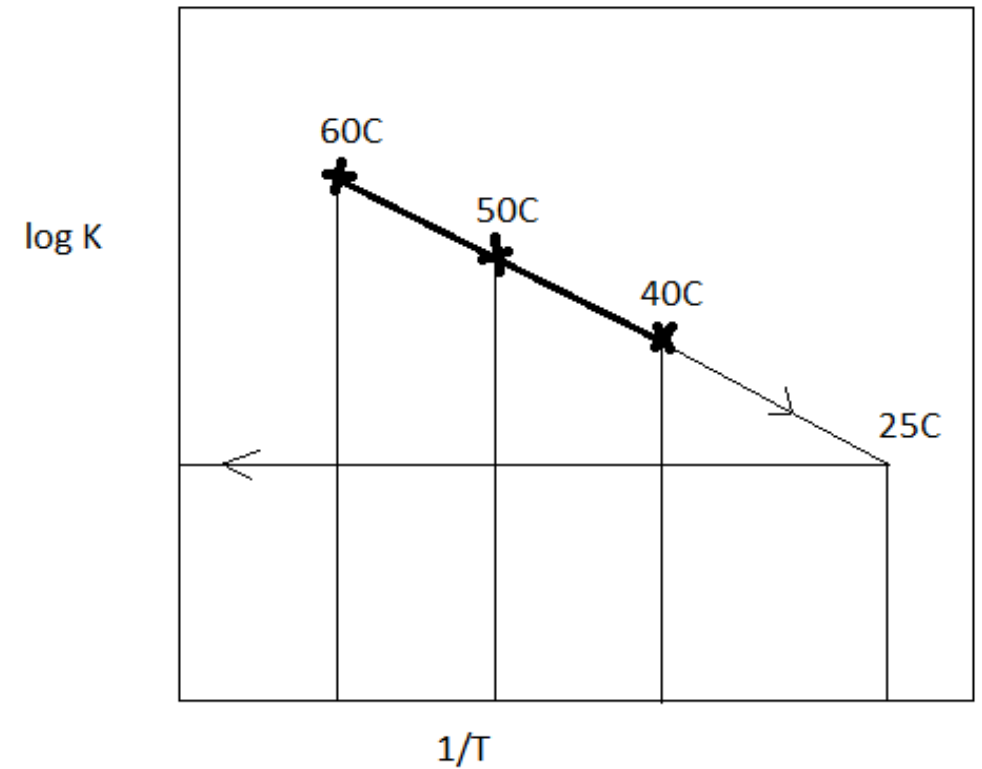
2. Medium Effects: Solvent, Ionic Strength, Dielectric Constant

a. Effect of the Solvent

In summary, it can be said that the polarity of solvents affect the rate of reactions depending on the polarity of reactant.

b. Effect of the ionic strength

For ionic compound, the ionic strength affects the rate of reaction while for neutral molecule, the rate of reaction independent on ionic strength.

c. Effect of the Dielectric Constant

The dielectric constant affects the rate constant of an ionic reaction. For a reaction between ions of <u>opposite sign</u>, an increase in dielectric constant of the solvent results in a decrease in the rate constant. For ions of <u>like charge</u>, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.
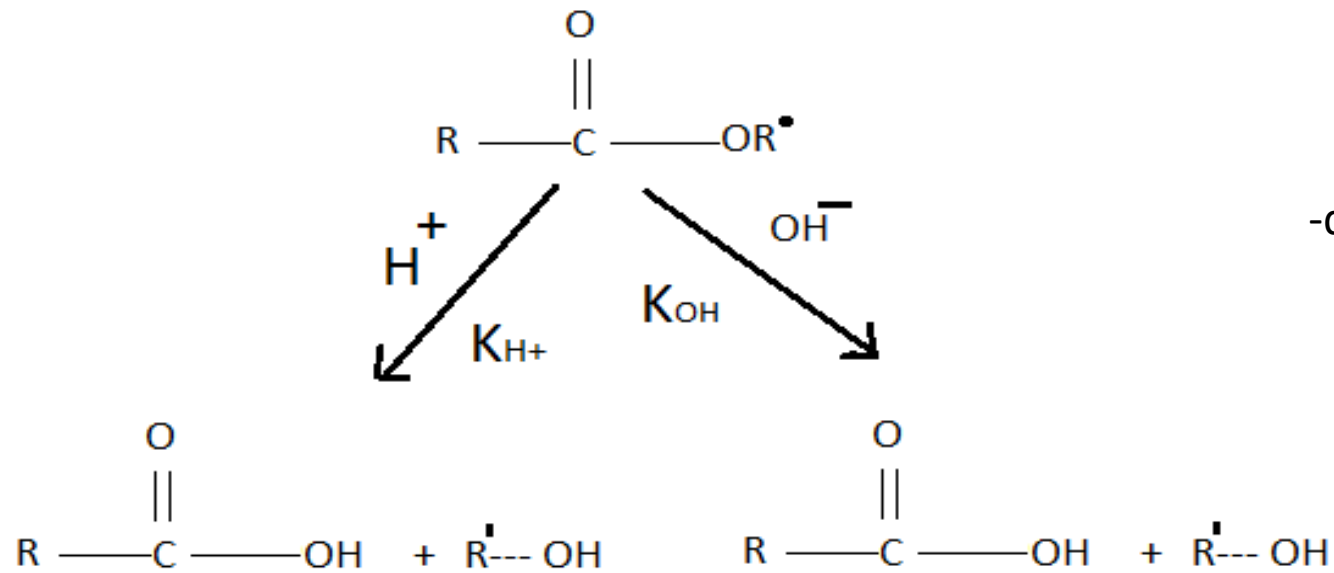
3. Catalysis effect: Specific Acid-Base Catalysis Effects

The rate of a reaction is frequently influenced by the presence of a catalyst.

A catalyst is defined as a substance that influences the speed of a reaction without itself being altered chemically.

Solutions of a number of drugs undergo accelerated decomposition on the addition of acids or bases.

If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base, so that the reaction can be considered to be catalyzed by hydrogen or hydroxyl ions. Best example of specific acid-base catalysis, is the hydrolysis of esters.

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R} \!-\!\!\text{C}\!-\!\!\text{OR}^\bullet \end{array}$$

-dc/dt =K observed [ester]

K_{H+} K_{OH}

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}\!-\!\!\text{C}\!-\!\!\text{OH} \end{array} + \text{R}^\bullet\text{---OH} \qquad \begin{array}{c} \text{O} \\ \parallel \\ \text{R}\!-\!\!\text{C}\!-\!\!\text{OH} \end{array} + \text{R}^\bullet\text{---OH}$$

The general formula for hydrolysis of ester which affected by both H^+ and OH^- is

$$K_{observed} = K_{H^+}[H^+] + K_{OH^-}[OH^-]$$

$K_{observed}$ = total rate constant of the system
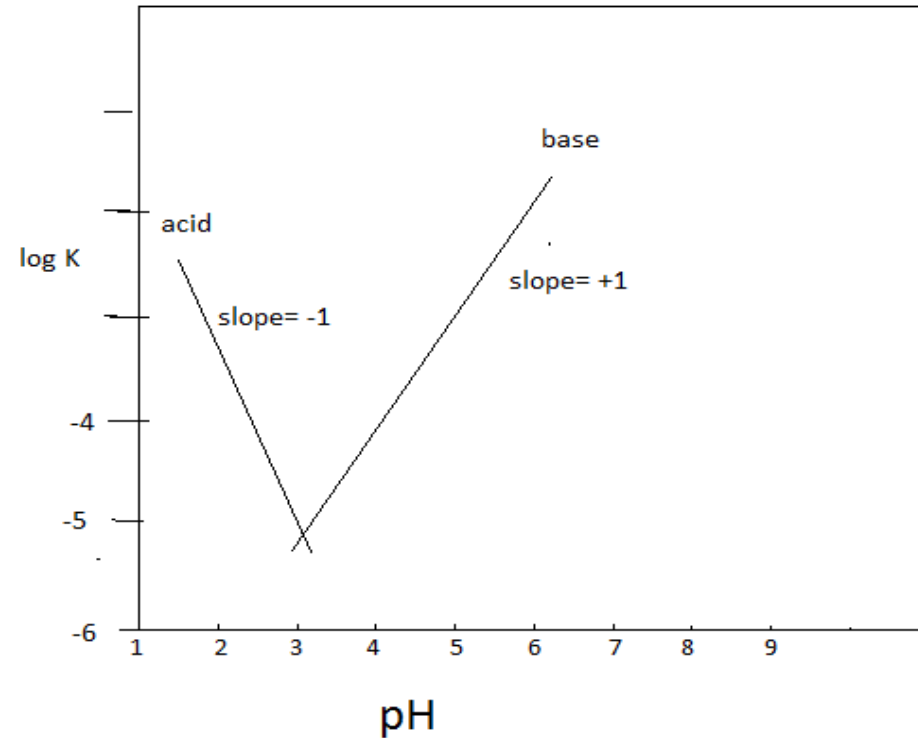
K_{H^+} = rate constant for acid catalysis reaction

K_{OH^-} = rate constant for base catalysis reaction

$[H^+]$ = hydrogen ion concentration

$[OH^-]$ = hydroxide ion concentration

Note: K_{H^+} and K_{OH^-} are second order rate constants.

The pH- Rate profile for the specific acid-base-catalyzed hydrolysis of ester as shown in this figure:

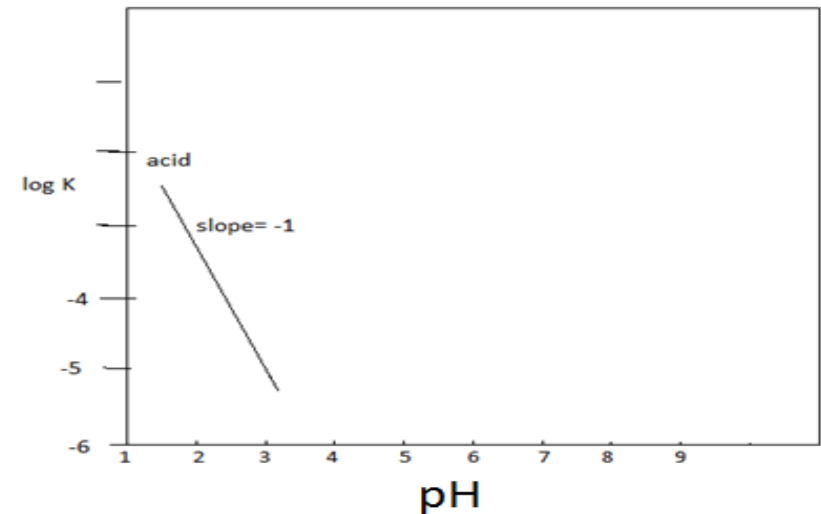Explanation of pH- Rate profile

1. at low PH

$$K_{observed} = K_{H^+} [H^+] + K_{OH^-}[OH^-]$$

Since $[OH^-]$ concentration value is very low, thus the part $(K_{OH^-}[OH^-])$ is neglected from equation at low pH.

So, $K_{observed} = K_{H^+} [H^+]$

$\log K_{observed} = \log K_{H^+} + \log [H^+]$

$\log K_{observed} = \log K_{H^+} - pH$

$\log K_{observed} = \log K_{H^+} \mathbf{-1} \times pH$

2. at high PH

$$K_{observed} = K_H^+ [H^+] + K_{OH}^-[OH^-]$$

Since $[H^+]$ concentration value is very low, thus the part
$(K_H^+ [H^+])$ is neglected from equation at high pH.

So, $K_{observed} = K_{OH}^-[OH^-]$

$Kw = [H^+] [OH^-]$ $\qquad\qquad$ $[OH^-] = Kw/ [H^+]$

$K_{observed} = K_{OH}^-[OH^-]$

$K_{observed} = K_{OH}^- \ Kw/[H+]$

$\log K_{observed} = \log K_{OH}^- + \log kw - \log [H^+]$

$\log K_{observed} = \log K_{OH}^- + \log kw + pH$

$\log K_{observed} = (\log K_{OH}^- + \log kw) \mathbf{+1} x \ pH$
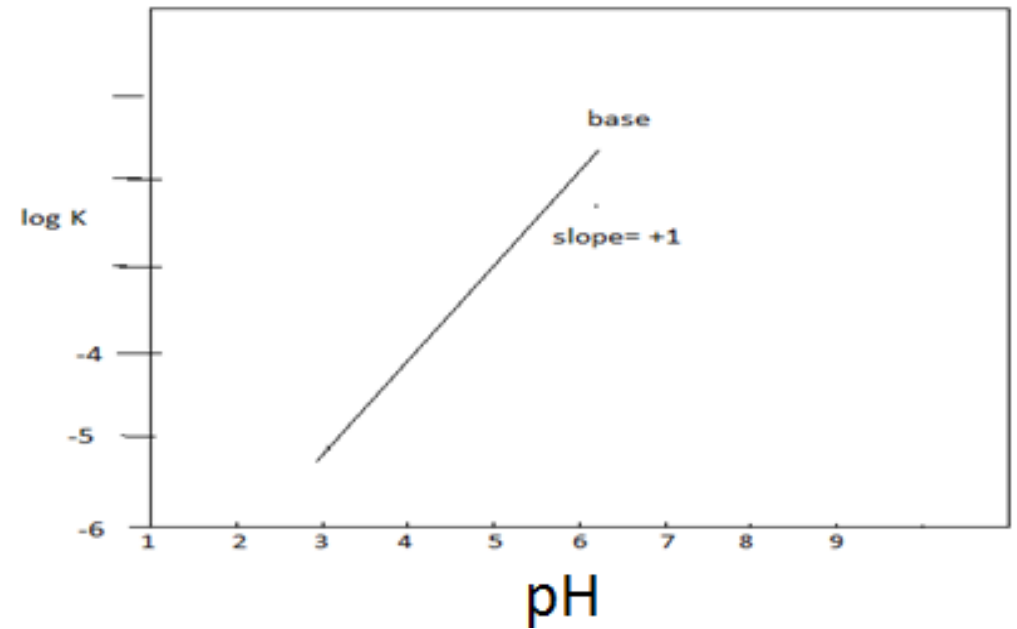
STABILITY OF PHARMACEUTICALS

Decomposition and Stabilization of Medicinal Agents

Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis, and these processes may affect the stability of drugs in liquid, solid, and semisolid products.

Examples of Martin physical pharmacy text book

Example 1 In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$$
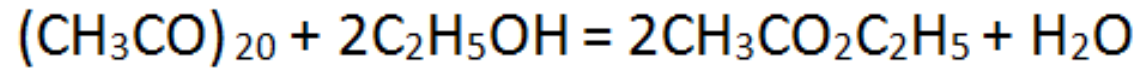
The rate of reaction is

$$Rate = -\frac{d[(CH3CO)2O]}{dt}$$

$$= k\ [(CH_3CO)_2O]\ [C_2H_5OH]^2$$

What is the order of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction?

If the alcohol, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer: The reaction appears to be first order with respect to acetic anhydride, second order with respect to ethyl alcohol, and overall third order. However, because alcohol is the solvent, its concentration remains essentially constant, and the rate expression can be written

$-d [(CH_3CO)_2O]/dt = k'[(CH_3CO)_2O]$

Kinetically the reaction is therefore a pseudo-first-order reaction.

Example .2

Shelf Life of an Aspirin Suspension-

A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25°C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is 4.5×10^{-6} sec^{-1}. Calculate the zero-order rate constant. Determine the shelf life, t_{90}, for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25°C.

Answer: $k_o = k \times$ [Aspirin in solution], from equation (k [A] $= k_0$). Thus,

$k_o = (4.5 \times 10^{-6}$ sec$^{-1}) \times (0.33$ g/100 mL)

$k_o = 1.5 \times 10^{-6}$ g/100 mL sec^{-1}

$t_{90} = 0.10$[A]$_o$ /k_0 =

[(0.10X6.5 g/100 mL)]/ [(1.5 x 10^{-6} g/100 mLsec^{-1})]

$= 4.3 \times 10^5$ sec $= 5.0$ days

EXAMPLE .3

Decomposition of Hydrogen Peroxide

The catalytic decomposition of hydrogen peroxide can be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(a)   Calculate k using equation ($k= \dfrac{2.303}{t} \log \dfrac{C_0}{C}$).

(b) How much hydrogen peroxide remained undecomposed after 25 min?

(a)

$$k = \frac{2.303}{t} \log \frac{C_0}{C}$$

$$k = \frac{2.303}{t} \log \frac{57.90}{9.60} = 0.0277 \text{ min}^{-1}$$

(b)

$$0.0277 = \frac{2.303}{25} \log \frac{57.90}{C}$$

$$c = 29.01$$

EXAMPLE .4

First-Order Half-Life

A solution of a drug contained 500 units/mL when prepared. It was analyzed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to one-half of its original concentration?
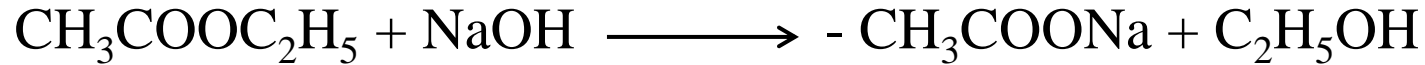
We have

$$k = \frac{2.303}{40} \log \frac{500}{300} = 0.0128 \text{ day}^{-1}$$

$$t = \frac{2.303}{0.0128} \log \frac{500}{250} = 54.3 \text{ days}$$

Example .5

Saponification of Ethyl Acetate

Walker investigated the saponification of ethyl acetate at 25°C:

$$CH_3COOC_2H_5 + NaOH \longrightarrow - CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 M. The change in concentration, x, of alkali during 20 min was 0.000566 mole/liter, therefore, (a - x) = 0.01000 - 0.00566 = 0.00434.

Compute (a) the rate constant and (b) the half-life of the reaction.

(a) Using equation

$$\frac{x}{a(a-x)} = Kt$$

or

$$k = \frac{1}{at} \left(\frac{x}{a-x} \right)$$

, we obtain

$$k = \frac{1}{0.01 \times 20} \left(\frac{0.00566}{0.00434} \right)$$

$$k = 6.52 \text{ liter mole}^{-1} \text{ min}^{-1}$$

(b) The half-life of a second-order reaction is

$t_{1/2} = 1/ak$

It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t1/2 = \frac{1}{0.01 x 6.52} = 15.3 \text{ min}$$

Example .6

The rate constant k_1 for the decomposition of 5-HMF (5-hydroxymethylfurfural) at 120°C (393 K) is 1.173 hr^{-1} or

3.258 x 10^{-4} sec^{-1}, and k_2 at 140°C (413 K) is 4.860 hr^{-1}. What is the activation energy, Ea, in kcal/mole and the frequency factor, A, in sec^{-1} for the breakdown of 5-HMF within this temperature range?

We have

$$\text{Log}\frac{K2}{K1} = \frac{Ea}{2.303R}\left(\frac{T2-T1}{T2T1}\right)$$

$$\text{Log}\frac{4.860}{1.173} = \frac{Ea}{2.303x1.987}\left(\frac{413-393}{413 \text{ x } 393}\right)$$

Ea = 23 kcal/mole

At 120°C, using equation

$$\text{Log K} = \text{log A} - \frac{Ea}{2.303R}\frac{1}{T}$$

, we obtain

$$\text{Log }(3.258 \text{ x } 10^{-4} \text{ sec}^{-1}) = \text{log A} - \frac{23,000 \text{ cal}}{2.303x1.987}\frac{1}{393}$$

A = 2 x 10⁹ sec⁻¹

Example .7

Increased Shelf Life of Aspirin

Aspirin is most stable at pH 2.5. At this pH the apparent fist-order rate constant is 5×10^{-7} sec^{-1} at 25°C. The shelf life of aspirin in solution under these conditions can be calculated as follows:

t_{90} = $0.105/(5 \times 10^{-7})$ = 2.1×10^5 sec

= 2 days

As one can see, aspirin is very unstable in aqueous solution.

Would making a suspension increase the shelf life of aspirin?

The solubility of aspirin is 0.33g/100mL. At pH 2.5, the apparent zero- order rate constant for an aspirin suspension is

$$k_o = 5 \times 10^{-7} \text{ sec}^{-1} \times 0.33 \text{ g}/100 \text{ mL} = 1.65 \times 10^{-7} \text{ g/mL} \cdot \text{sec}$$

If one dose of aspirin at 650 mg per teaspoonful is administered, then one has 650 mg/5 mL = 13 g/100 mL. For this aspirin suspension,

$$t_{90} = [(0.1)(13)]/[1.65 \times 10^{-7}] = 7.9 \times 10^6 \text{ sec} = 91 \text{ days}$$

The increase in the shelf-life of suspensions as compared to solutions is a result of the interplay between the solubility and the stability of the drug. In the case of aspirin, the solid form of the drug is stable, whereas when aspirin is in solution it is unstable. As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.