

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

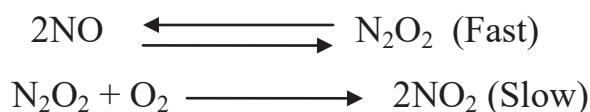
Molecularity is the number of molecules, atoms, or ions reacting in an elementary process. molecularity classify the reaction into unimolecular, bimolecular, and Termolecular. molecularity cannot gives complete detail about order of reaction specially those of several steps while kinetic study gives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

Example: $\text{Br}_2 \longrightarrow 2\text{Br}$ unimolecular

$\text{H}_2 + \text{I}_2 \longrightarrow 2\text{HI}$ bimolecular

$2\text{NO} + \text{O}_2 \longrightarrow 2\text{NO}_2$ Termolecular

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



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



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

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

The shelf-life 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., $0.9C$).

Table 14.6.1 Common Types of Elementary Reactions and Their Rate Laws

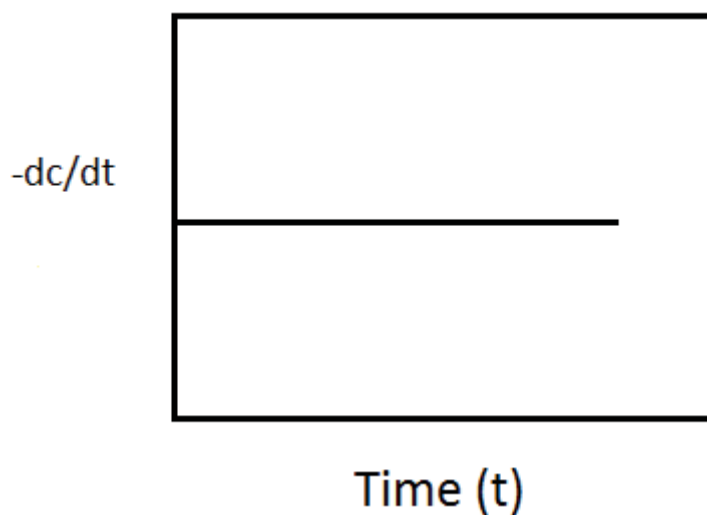
Elementary Reaction	Molecularity	Rate Law	Reaction Order
$A \rightarrow \text{products}$	unimolecular	$\text{rate} = k[A]$	first
$2A \rightarrow \text{products}$	bimolecular	$\text{rate} = k[A]^2$	second
$A + B \rightarrow \text{products}$	bimolecular	$\text{rate} = k[A][B]$	second
$2A + B \rightarrow \text{products}$	termolecular	$\text{rate} = k[A]^2[B]$	third
$A + B + C \rightarrow \text{products}$	termolecular	$\text{rate} = k[A][B][C]$	third

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

$$-\frac{dC}{dt} = k_0$$

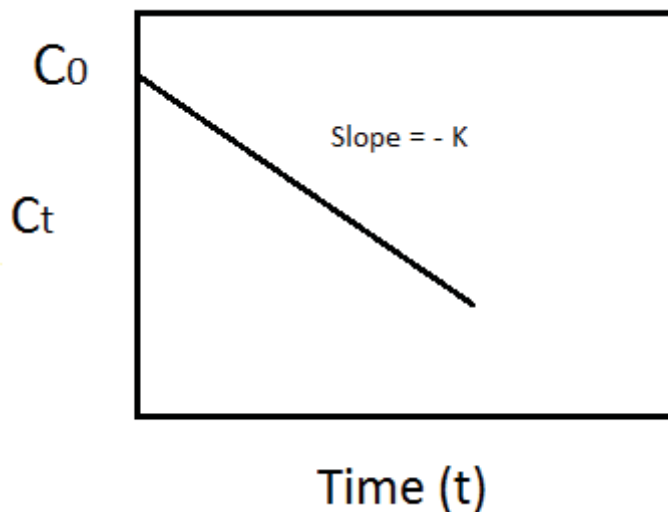
It means that the rate of reaction not depend on concentration of reactant, it is constant with time.



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

$$C_t = C_0 - k_0 t$$

$$t = \frac{C_0 - C_t}{k_0}$$



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 $1/2C_0$.

$$t_{1/2} = \frac{C_0 - 1/2C_0}{k_0}$$

$$t_{1/2} = \frac{1/2C_0}{k_0}$$

For shelf life
$$t_{90\%} = \frac{C_0 - 0.9C_0}{k_0} = \frac{0.1C_0}{K_0}$$

- The unit of zero order rate constant is:

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

First-Order Reactions

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

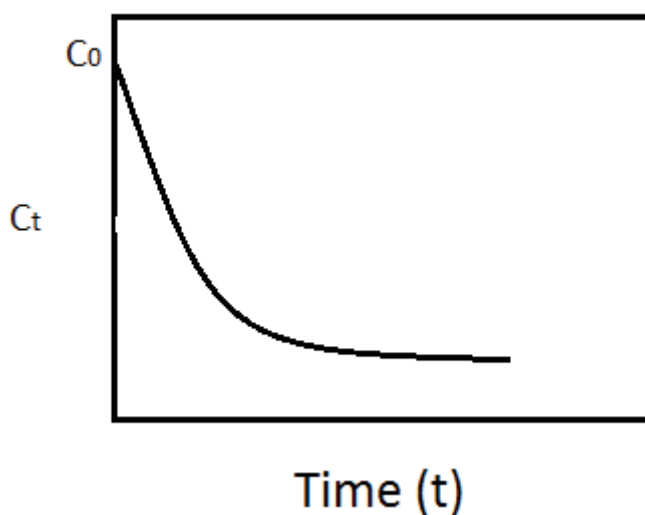


Although two molecules of hydrogen peroxide appear in the equation, the reaction was found to be first order.

The rate equation is written

$$-\frac{dC}{dt} = k C$$

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



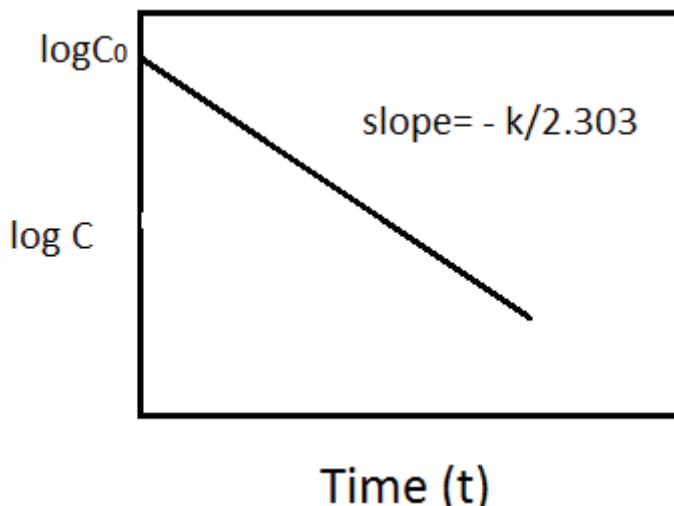
The half-life for a first-order reaction is 32 s. What was the original concentration if, after 2.0 minutes, ? the reactant concentration is 0.062 M

- a) 0.84 M)
- b) 0.069 M)
- c) 0.091 M)
- d) 0.075 M)
- e) 0.13 M)

Integrating above equation, we have

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

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



For calculation of half life of reaction follows first order;

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

at half life; $t = t_{1/2}$, $C_t = \frac{1}{2} C_0$

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

$$t_{1/2} = 0.693/k$$

For shelf life t_{90} ;

$$\log \frac{C_0}{0.9 C_0} = \frac{K t_{10\%}}{2.303}, \quad t_{90} = 0.105/k$$

- The unit of first order rate constant is:

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

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 $\log(\text{concentration})$ versus t yields a straight line, and it is second-order if $1/(\text{concentration})$ 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 ;

$t_{1/2}$ for a second-order reaction, in which $a = b$, is proportional to $1/a$.

[For a reaction $2A + B \rightleftharpoons 2C$, with the rate equation: $\text{Rate} = k[A]^2[B]$

- . a) the order with respect to A is 1 and the order overall is 1)
- . b) the order with respect to A is 2 and the order overall is 2)
- . c) the order with respect to A is 2 and the order overall is 3)
- . d) the order with respect to B is 2 and the order overall is 2)
- . e) the order with respect to B is 2 and the order overall is 3)

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

$$-d[C]/dt = k_f[C] \quad \text{where } c = \text{concentration of drug in solution} \\ = \text{solubility}$$

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

$$K_f [C] = K_0 \quad \text{where } K_0 = \text{zero order rate constant of suspension}$$

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

$$-d[C]/dt = K_0$$

Second-Order Reactions

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



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 are 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

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

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:

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

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



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

K is constant and [A] is constant

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

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**

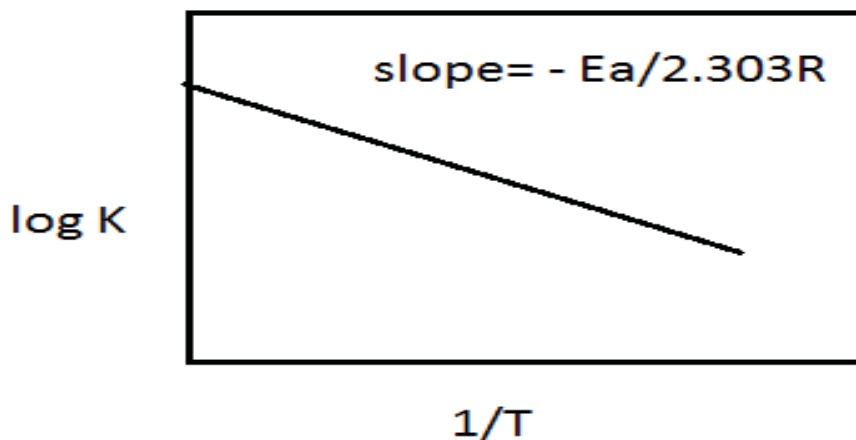
Reaction rates are expected to be proportional to the number of collisions per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature.

The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius,

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

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

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.

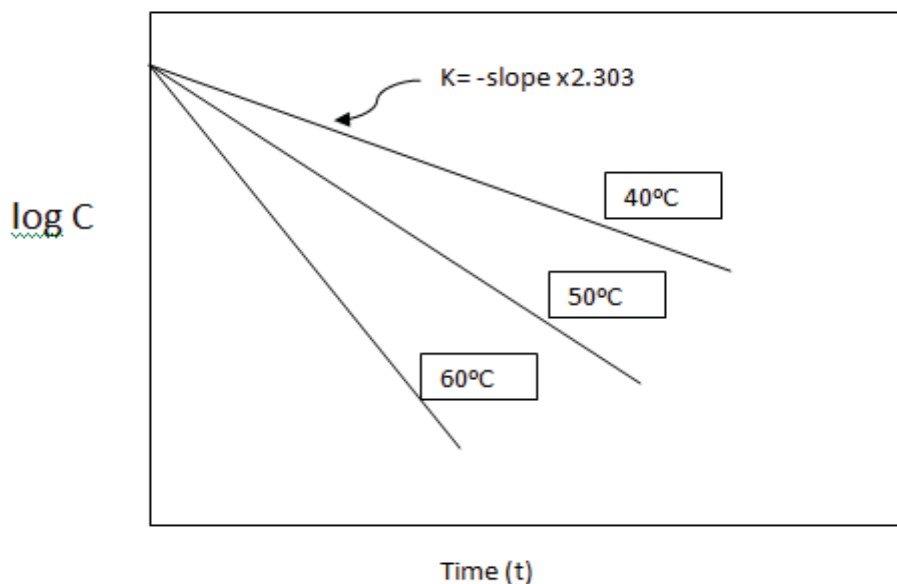


In case at 2 temperatures t_1 and t_2 , the equation becomes:

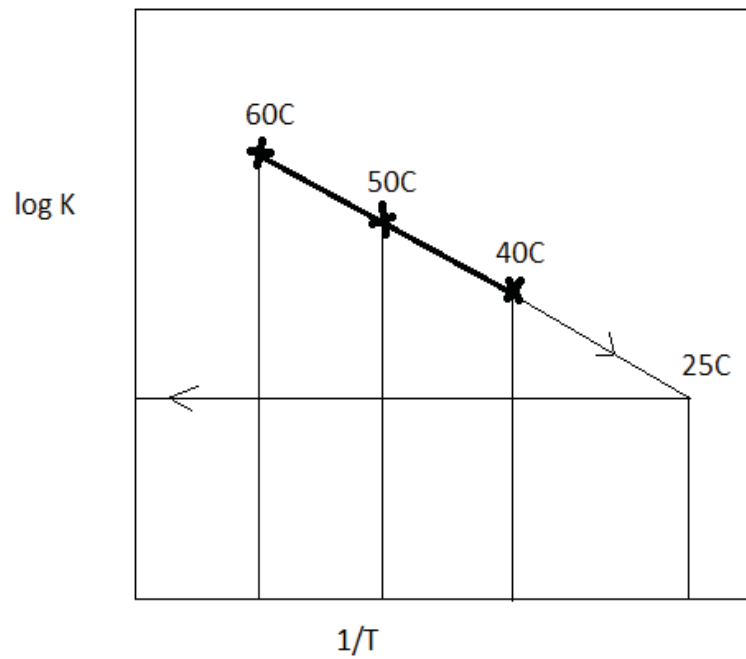
$$\log \frac{K_2}{K_1} = \frac{Ea}{2.303R} \left(\frac{T_2 - T_1}{T_2 T_1} \right)$$

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 $K_{25}^{\circ}\text{C}$ as shown in this figure:



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

$$t_{90\%} = 0.105 / K_{25^{\circ}\text{C}}$$

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.

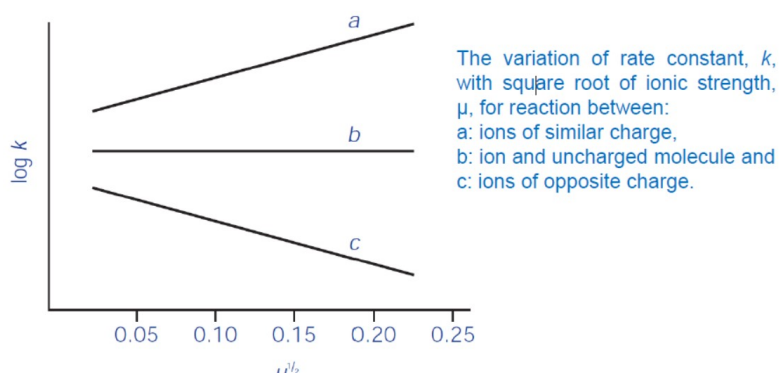
b. Effect of the ionic strength

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 opposite sign, an increase in dielectric constant of the solvent results in a decrease in the rate constant. For ions of like charge, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.

Ionic Strength



3. Catalysis effect: Specific Acid-Base Catalysis Effects

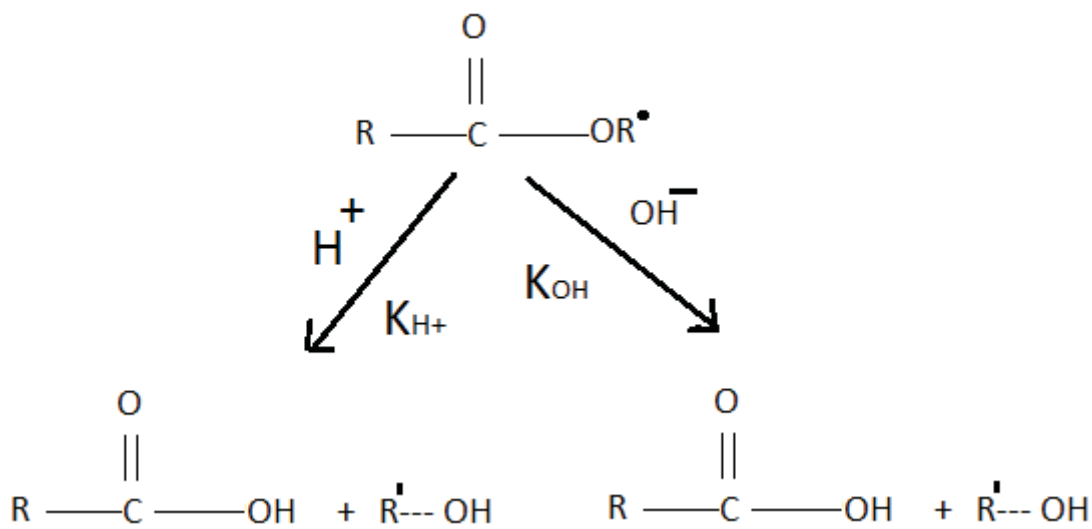
The rate of a reaction is frequently influenced by the presence of a catalyst.

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.



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

$$OH^- \text{ is } -\frac{dc}{dt} = K_{\text{observed}} [\text{ester}]$$

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

K_{observed} = total rate constant of the system

K_{H^+} = rate constant for acid catalysis reaction

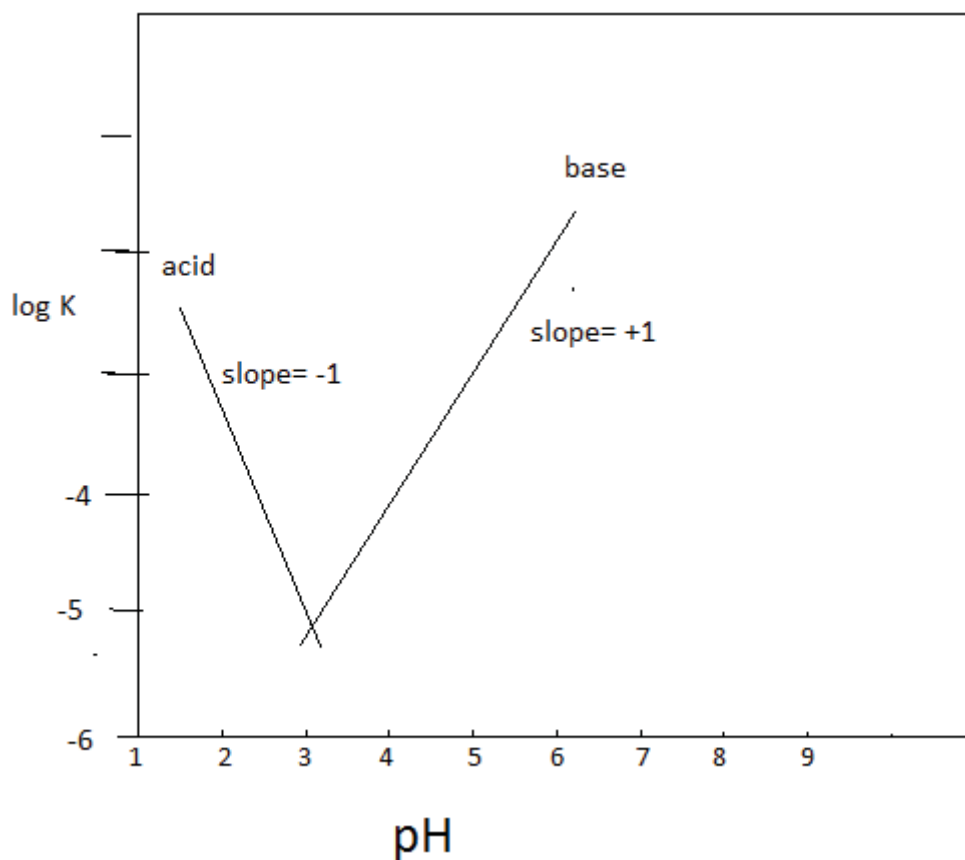
K_{OH^-} = rate constant for base catalysis reaction

$[H^+]$ = 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

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

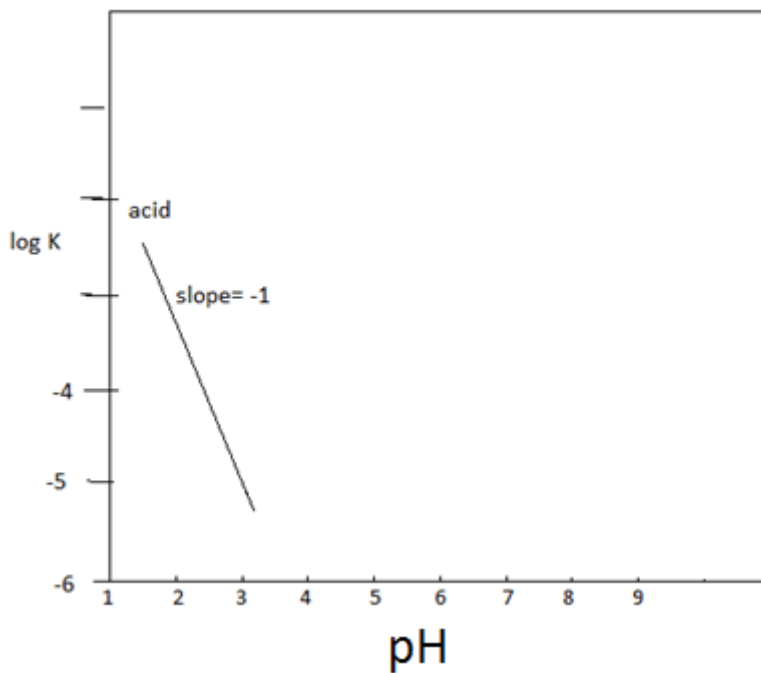
Since $[\text{OH}^-]$ concentration value is very low, thus the part $(K_{\text{OH}^-} [\text{OH}^-])$ is neglected from equation at low pH.

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

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

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

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



2. at high PH

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

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

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

$$K_w = [\text{H}^+] [\text{OH}^-] \longrightarrow [\text{OH}^-] = K_w / [\text{H}^+]$$

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

$$K_{\text{observed}} = K_{\text{OH}^-} \frac{k_w}{[\text{H}^+]}$$

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

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

$$\log K_{\text{observed}} = (\log K_{\text{OH}^-} + \log k_w) + 1 \times \text{pH}$$

