

Factors effects on stability

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

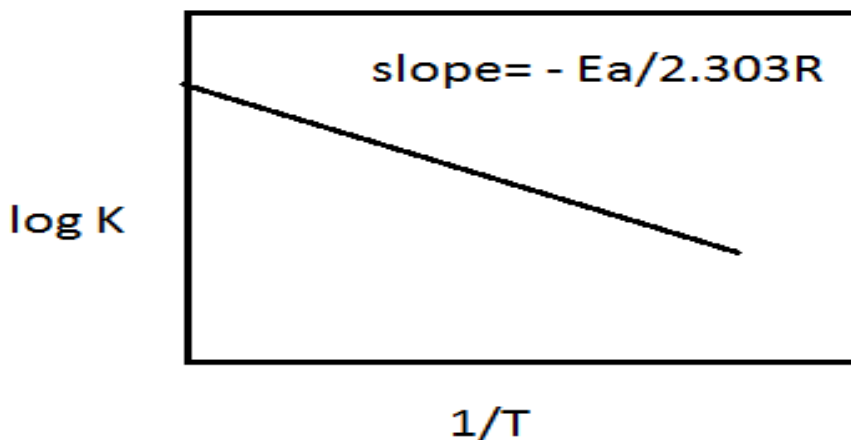
1. Temperature effect**Collision Theory**

- 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,

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

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

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

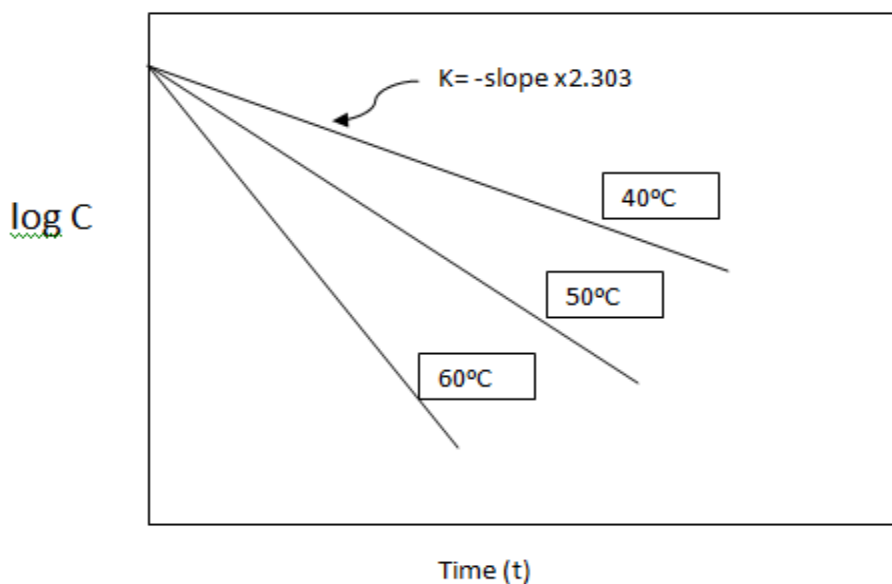


- In case at 2 temperatures t_1 and t_2 , the equation becomes:

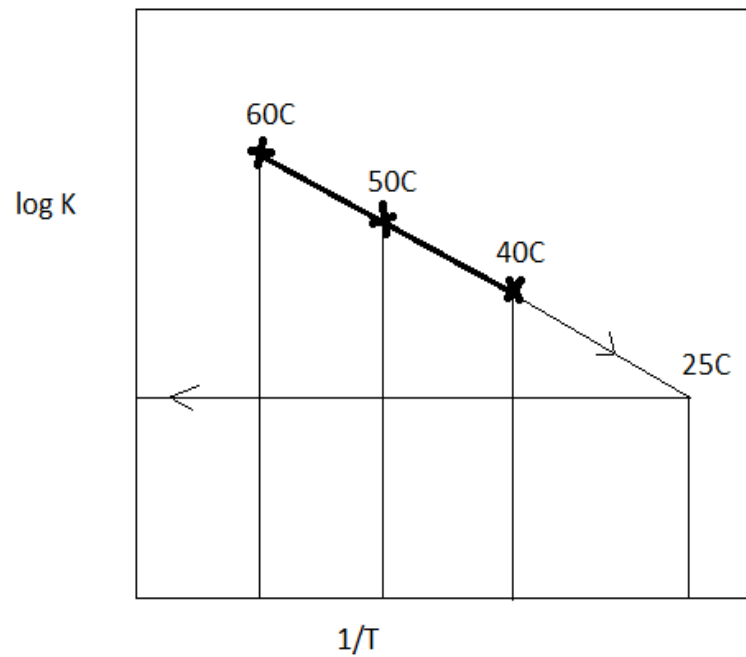
$$\log \frac{K_2}{K_1} = \frac{Ea}{2.303R} \left(\frac{T_2 - T_1}{T_2 T_1} \right)$$

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

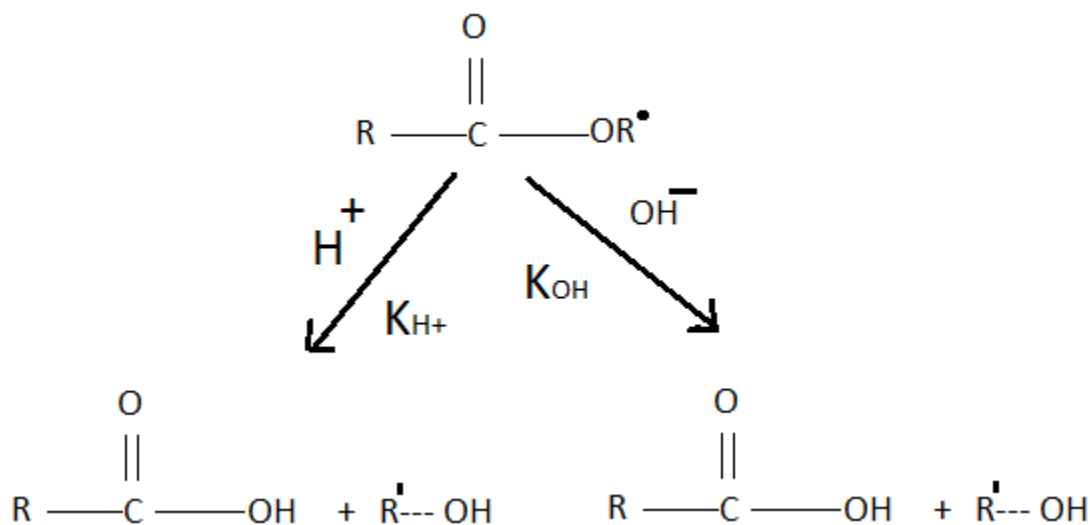
- For ionic compound, the ionic strength affects the rate of reaction while for neutral molecule, the rate of reaction independent on ionic strength.

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.

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^- 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

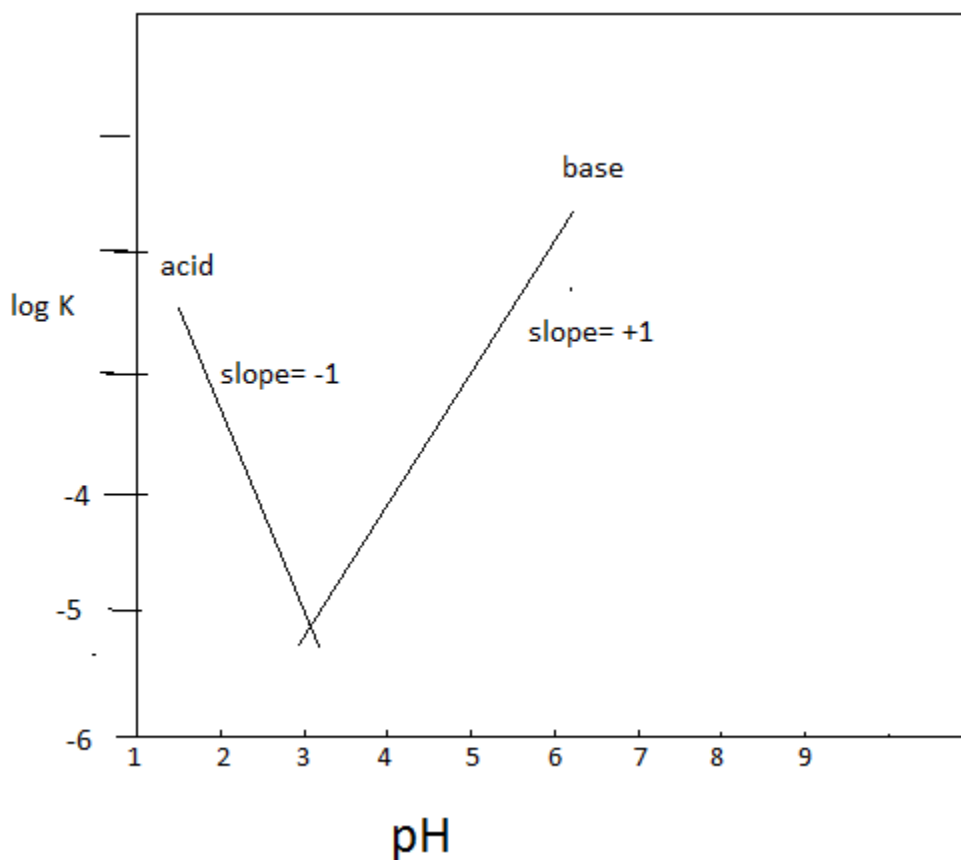
K_{H^+} = rate constant for acid catalysis reaction

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

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

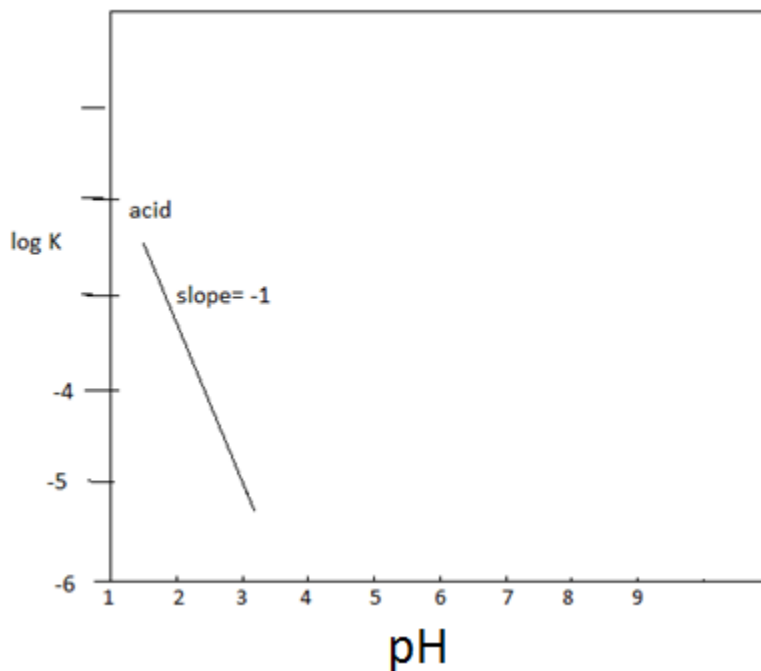
Since $[\text{OH}^-]$ concentration value is very low, thus the part $(K_{\text{OH}^-} [\text{OH}^-])$ is neglected from equation at low pH.

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.

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

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

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

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

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

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

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

