Physical Pharmacy II

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- **CONTENTS:**

✓ CHEMICAL KINETICS AND STABILITY
✓ INTERFACIAL PHENOMENA
✓ COLLOIDAL DISPERSIONS
✓ COARSE DISPERSIONS
✓ RHEOLOGY

CHEMICAL KINETICS AND STABILITY

This chapter introduces the rates and mechanisms of reactions with particular emphasis on decomposition and stabilization of drug products.

The purpose of stability testing is:

1) Provide evidence on how the **quality** of a drug substance or drug product **varies** with time under the influence of a variety of environmental factors, such as temperature, humidity, and light

2) Establish a **retest** period for the drug substance or a **shelf life** for the drug product and recommended storage conditions

3) It is essential for pharmacists and pharmaceutical scientists to study, understand, and interpret conditions of **instability** of pharmaceutical products as well as to be able to **offer solutions** for the stabilization of these products.

If a community pharmacist is asked to compound a prescription product, there are many factors that he or she must consider:

- The pharmacist must recognize that **alterations in stability** may occur when a drug is combined with other ingredients.
  - For example, if thiamine hydrochloride, which is **most stable at a pH of 2 to 3** and is **unstable above pH 6**, is combined with a buffered vehicle of, say, pH 8 or 9, the vitamin is rapidly inactivated

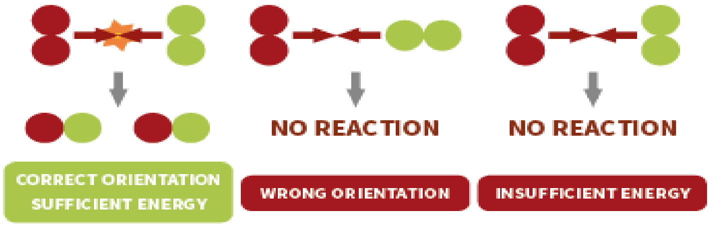
- patients may store these products in a bathroom medicine cabinet where the humidity and temperature are higher than the typical storage place for medications.

- **How does this affect the shelf life of the product?**
- A community pharmacy practitioner should be able to understand this and advise patients on these matters.
- the pharmacist is able to assist the physician and patient regarding the proper storage and use of medicinal agents.

MAKING CHEMICAL REACTIONS HAPPEN FASTER

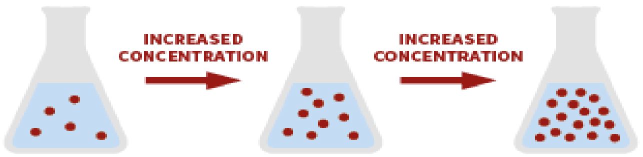
There are a number of different things that we can change to make a chemical reaction faster. Here, we explain the concept of collision theory, and how it can be used to explain the effects of five different factors on the rate of a chemical reaction.

COLLISION THEORY



Collision theory states that, for a reaction to occur, particles must collide with the correct orientation and with sufficient energy for a reaction to occur. Different factors affect the rate of the reaction by affecting the frequency of particle collisions, and/or the proportion of collisions that have enough energy to react.

INCREASE CONCENTRATION OF REACTANTS

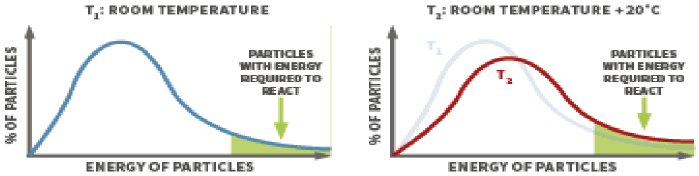


↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the concentration of reactants in solution increases the rate of reaction as there are a greater number of particles available to react. This increases the frequency of collisions between particles.

INCREASE TEMPERATURE OF REACTION



↑ FREQUENCY OF COLLISIONS

↑ % SUCCESSFUL COLLISIONS

Increasing the temperature increases the kinetic energy of particles. This increases the frequency of particle collisions, and a greater proportion of collisions will have the energy required to react.

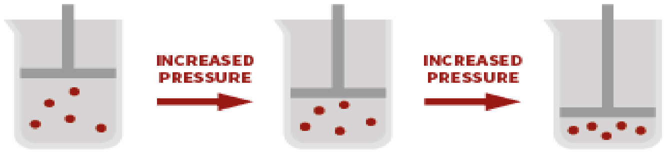
INCREASE SURFACE AREA OF REACTANTS

↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the surface area of solid reactants increases the number of particles that are exposed and available to react, and as a consequence this increases the frequency of particle collisions, increasing rate.

INCREASE PRESSURE OF REACTION

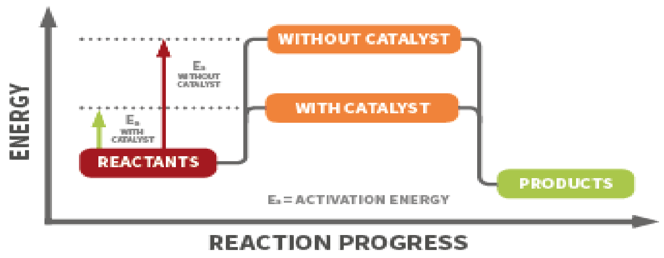


↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the pressure of a reaction involving gases forces the gas particles closer together. This will increase the frequency of particle collisions, and therefore increase the rate of reaction.

USE A CATALYST IN THE REACTION



A catalyst provides an alternative route for the reaction, with a lower activation energy. This means that particle collisions need less energy in order for a reaction to occur, increasing the rate of the reaction.

FUNDAMENTALS AND CONCENTRATION EFFECTS

Rates, Order, and Molecularity of Reactions

A- 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.*

- 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, a and b, of the substances A and B, respectively.
- *In the reaction:* $aA + bB + \cdots = \text{Products}$
- *the rate of the reaction is:*

$$\text{Rate} = \frac{1}{a}\frac{d[A]}{dt} = \frac{1}{b}\frac{d[B]}{dt} = \cdots k[A]^a[B]^b \cdots$$

where k is the rate constant.

$$\text{Rate} = k[A]^a[B]^b$$

- **B- Order of a process**
- The overall order of a reaction is the sum of the exponents of the concentration terms, A and B.
- The order with respect to one of the reactants, A or B, is the exponent a or b of that particular concentration term.
- For example: In the reaction of **ethyl acetate** with **sodium hydroxide** in aqueous solution,

$$\mathrm{CH_3COOC_2H_5} + \mathrm{NaOH_{soln}} \rightarrow \mathrm{CH_3COONa} + \mathrm{C_2H_5OH}$$

- the rate expression is:

$$\text{Rate} = -\frac{d[\mathrm{CH_3COOC_2H_5}]}{dt}$$

$$= -\frac{d[\mathrm{NaOH}]}{dt} = k[\mathrm{CH_3COOC_2H_5}]^1\ [\mathrm{NaOH}]^1$$

- ✓ The reaction is **first** order (a=1) with respect to ethyl acetate and first order (b = 1) with respect to sodium hydroxide solution
- ✓ overall the reaction is **second** order (a + b = 2).

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- ✓ The reaction is **first** order (a=1) with respect to ethyl acetate and first order (b = 1) with respect to sodium hydroxide solution
- ✓ overall the reaction is **second** order (a + b = 2).

- Suppose that in this reaction, sodium hydroxide as well as water was in great excess and ethyl acetate was in a relatively low concentration.
- As the reaction proceeded, ethyl acetate would change appreciably from its original concentration, whereas the concentrations of NaOH and water would remain essentially unchanged because they are present in great excess.
- In this case, the contribution of sodium hydroxide to the rate expression is considered constant and the reaction rate can be written as

$$\boxed{\frac{d[\mathrm{CH_3COOC_2H_5}]}{dt} = k'[\mathrm{CH_3COOC_2H_5}]}$$

$$k' = k[\mathrm{NaOH}].$$

- The reaction is then said to be a **pseudo– first-order reaction** because it depends only on the first power (a=1) of the concentration of ethyl acetate.
- In general, when one of the reactants is present in such great excess that its concentration may be considered constant or nearly so, the reaction is said to be of **pseudo-order.**
- **EXAMPLE**
- In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water, $(CH_3CO)_2O + 2C_2H_5OH \rightarrow 2CH_3CO_2C_2H_5 + H_2O$
- the rate of reaction is

$$\text{Rate} = -\frac{d[(CH_3CO)_2O]}{dt} = k[(CH_3CO)_2O]\,[C_2H_5OH]^2$$

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. its concentration remains essentially constant, and the rate expression can be written as

$$-\frac{d[(CH_3CO)_2O]}{dt} = k'[(CH_3CO)_2O]$$

- Kinetically the reaction is therefore a **pseudo–first-order reaction**

C- Molecularity

- A reaction whose overall order is measured can be considered to occur through several steps or elementary reactions.
- Each of the elementary reactions has a stoichiometry giving the number of molecules taking part in that step.
- **The molecularity is the number of molecules, atoms, or ions reacting in an elementary reaction.**
- order and molecularity are ordinarily identical only for elementary reactions.
- In the reaction: $Br_2 \rightarrow 2Br$
- The process is unimolecular because the single molecule, decomposes to form two bromine atoms

- In the single step reaction, $H_2 + I_2 \rightarrow 2HI$
- The process is bimolecular because two molecules, one of H_2 and one of I_2 must come together to form the product HI.

- However, bimolecular reactions may or may not be second order
- Termolecular reactions, that is, processes in which three molecules must come together simultaneously, are rare.

- Chemical reactions that proceed through more than one step are known as complex reactions.
- The overall order determined kinetically may not be identical with the molecularity because the reaction consists of several steps, each with its own molecularity.

- For the overall reaction $2NO + O_2 \rightarrow 2NO_2$
- the order has been found experimentally to be 2.
- The reaction is not termolecular, in which two molecules of NO would collide simultaneously with one molecule of O2.
- Instead, the mechanism is postulated to consist of two elementary steps, each being bimolecular:

$$2NO \rightarrow N_2O_2$$

$$N_2O_2 + O_2 \rightarrow 2NO_2$$

Rate Constants, Half-Life, Shelf Life, and Apparent or Pseudo-order

$$\boxed{dY/dt = KY^n}$$

$$\frac{-dY}{dt} = K_0Y^0$$

$$Y^0 = 1$$

$$\frac{-dY}{dt} = K_0$$

$$\frac{-dY}{dt} = KY^1$$

$$Y^1 = Y,$$

$$\frac{-dY}{dt} = KY$$

k

Rate Constants, Half-Life, Shelf Life, and Apparent or Pseudo-order

A- 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.
- Any change in the conditions of the reaction, for example, in temperature or solvent, or a slight change in one of the reacting species, will lead to a rate law having a different value for the specific rate constant.

k

- Variations in the specific rate constant are of great physical significance because a change in this constant necessarily represents a change at the molecular level as a result of a variation in the reaction conditions.

- Rate constants derived from reactions consisting of a number of steps of different molecularity are functions of the specific rate constants for the various steps.

- Any change in the nature of a step due to a modification in the reaction conditions or in the properties of the molecules taking part in this step could lead to a change in the value of the overall rate constant.

B- Units of the Basic Rate Constants

- To arrive at units for the rate constants appearing in zero-, first-, and second-order rate laws, the equation expressing the law is rearranged to have the constant expressed in terms of the variables of the equation.
- Thus, for a zero-order reaction,

A is the molar concentration of the reactant

$$k = -\frac{dA}{dt} = \frac{\text{moles/liter}}{\text{second}}$$

$$= \frac{\text{moles}}{\text{liter second}} = \boxed{\text{moles liter}^{-1}\ \text{second}^{-1}}$$

- for a first-order reaction,

$$k = -\frac{dA}{dt}\frac{1}{A} = \frac{\text{moles/liter}}{\text{second-moles/liter}}$$

$$= \frac{1}{\text{second}} = \boxed{\text{second}^{-1}}$$

- and for a second-order reaction,

$$k = \frac{dA}{dt}\frac{1}{A^2} = \frac{\text{moles/liter}}{\text{second }(\text{moles/liter})^2}$$

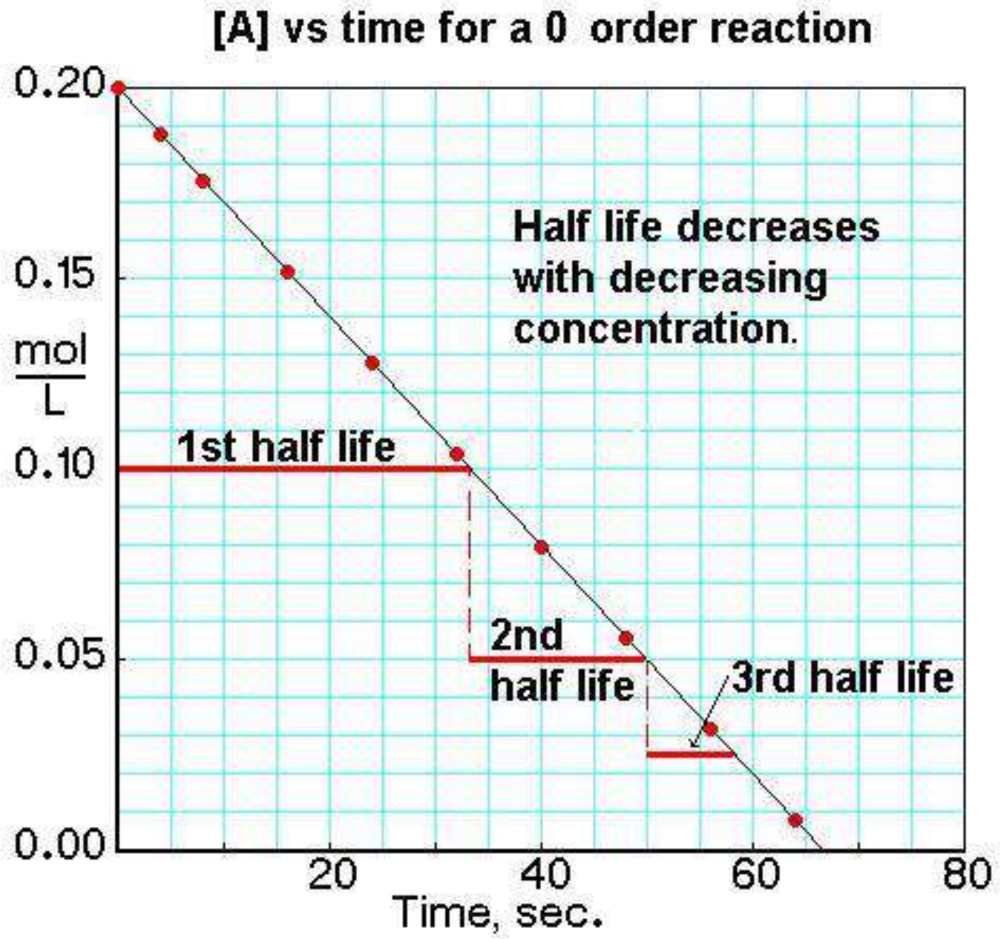
$$= \frac{\text{liter}}{\text{moles-second}} = \text{liter second}^{-1}\ \text{mole}^{-1}$$

C- “Apparent” or “pseudo”-order

- describes a situation where one of the reactants is present in large excess or does not effect the overall reaction and can be held constant.
- **For example,** many hydrolysis decomposition reactions of drug molecules are second order.
- Usually the amount of water present is in excess of what is needed for the reaction to proceed.
- In other words, the concentration of water is essentially constant throughout the reaction.
- In this case, the second-order reaction behaves like a first-order reaction and is called an apparent or pseudo–first order reaction.

D- The half-life

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



E- Shelf life

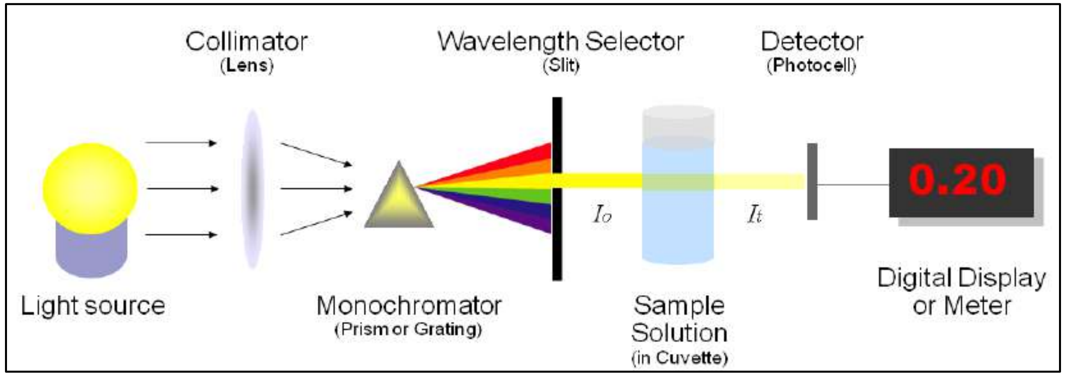
- (also referred to as the expiration dating period)
- is the time period during which a drug product is expected to remain within the approved specification for use, provided that it is stored under the conditions defined on the container label.
- The shelf life is the time required for 10% of the material to disappear; it is the time at which A has decreased to 90% of its original concentration

- **Expiration date** is the date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used.

Zero-Order Reactions

- the loss in color of a multisulfa product (as measured by the decrease of spectrophotometric absorbance at a wavelength of 500 nm) followed a zero-order rate.

$$\frac{-dY}{dt} = K_0 Y^0$$



- where K_0 is the zero-order rate constant and the minus sign shows negative change over time.
- Since $Y^0 = 1 \longrightarrow$ $$\frac{-dY}{dt} = K_0$$

- The rate expression for the change of absorbance, A, with time is therefore

$$\boxed{-\frac{dA}{dt} = k_0}$$

where the minus sign signifies that the absorbance is decreasing (i.e., the color is fading).

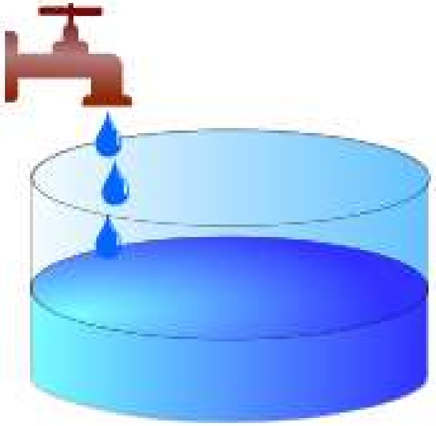
- The velocity of fading is seen to be constant and independent of the concentration of the colorant used.
- The rate equation can be integrated between the initial absorbance, A_0, corresponding to the original color of the preparation at t = 0, and A_t , the absorbance after t hours:

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

$$A_t - A_0 = -k_0 t$$

$$A_t = A_0 - k_0 t$$

Tap and Tank

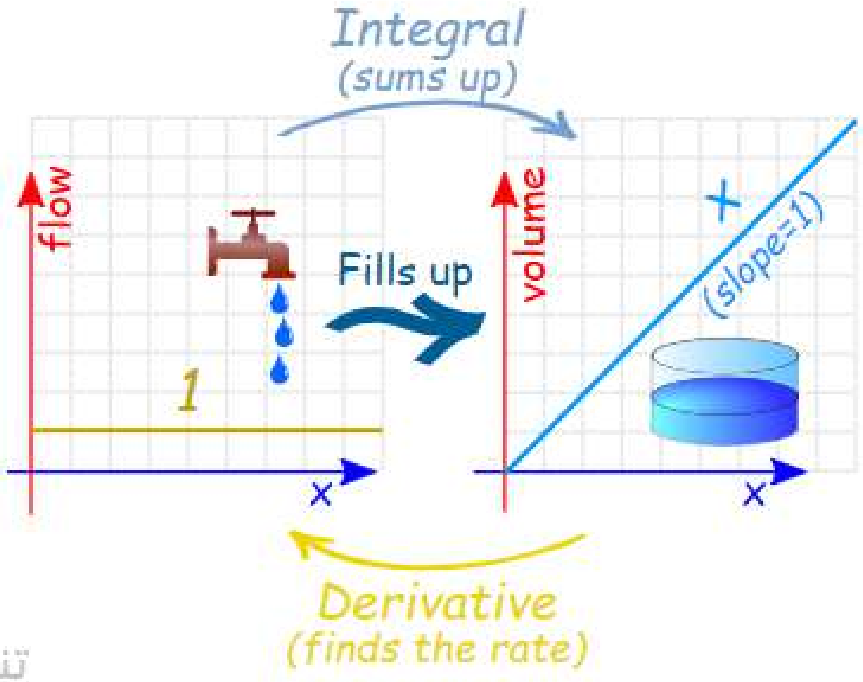


Integration is like filling a tank from a tap.

The input (before integration) is the **flow rate** from the tap.

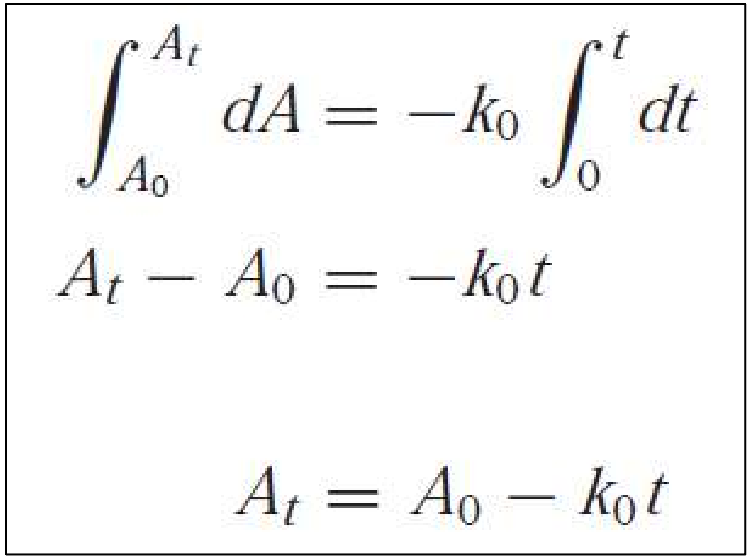
Integrating the flow (adding up all the little bits of water) gives us the **volume of water** in the tank.

Simple Example: Constant Flow Rate



Integration: With a flow rate of **1**, the tank volume increases by **x**

Derivative: If the tank volume increases by **x**, then the flow rate is **1**



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

$$A_t - A_0 = -k_0 t$$

$$A_t = A_0 - k_0 t$$

- When this linear equation is plotted with c on the vertical axis against t on the horizontal axis, the slope of the line is equal to $-k_0$.

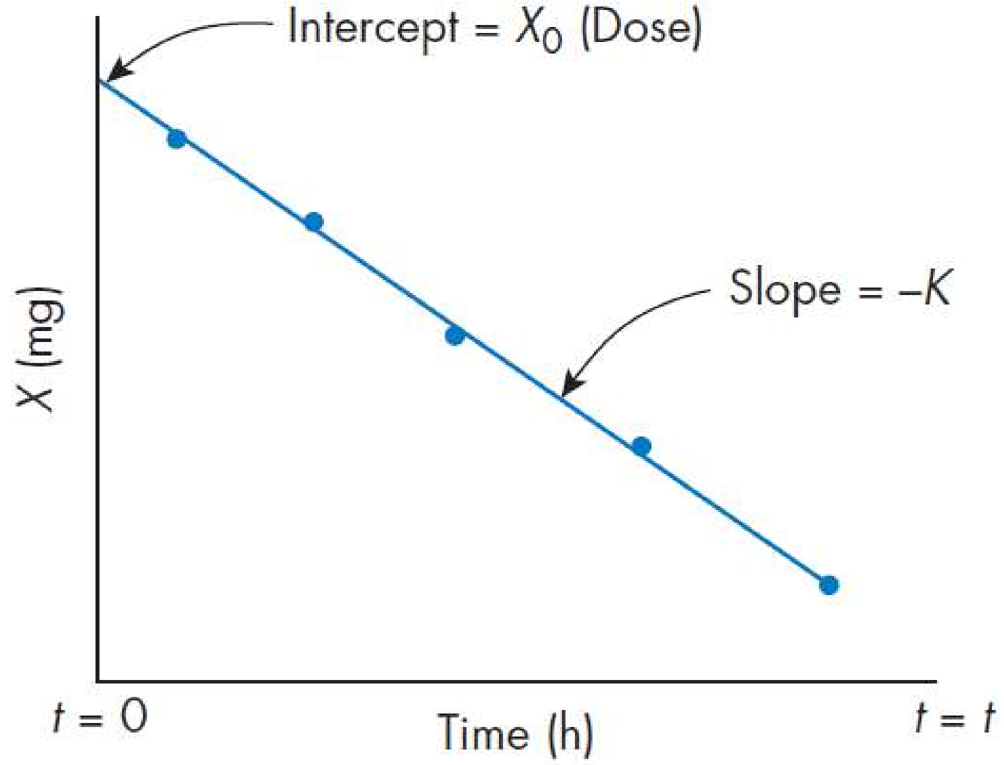
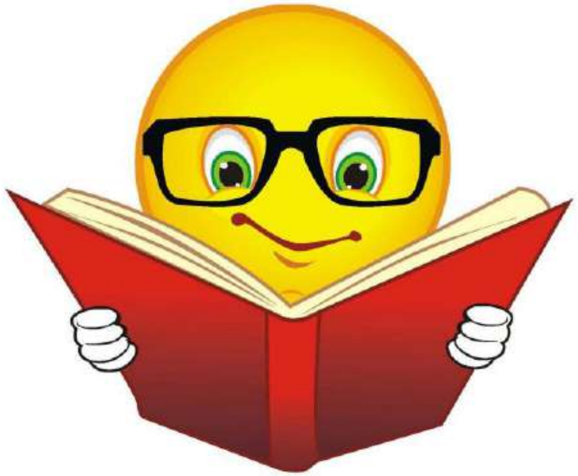


Figure 1.15 Rectilinear graph (R.L.) of zero-order process. *X*, concentration of drug; *K*, rate constant.

- **Applications of zero-order processes:**
  1) administration of a drug as an intravenous infusion,
  2) administration of drugs through transdermal drug delivery systems.
  3) administration of controlled release dosage forms



$$A_t = A_0 - k_0 t$$

- the **half-life** is the time required for one-half of the material to disappear

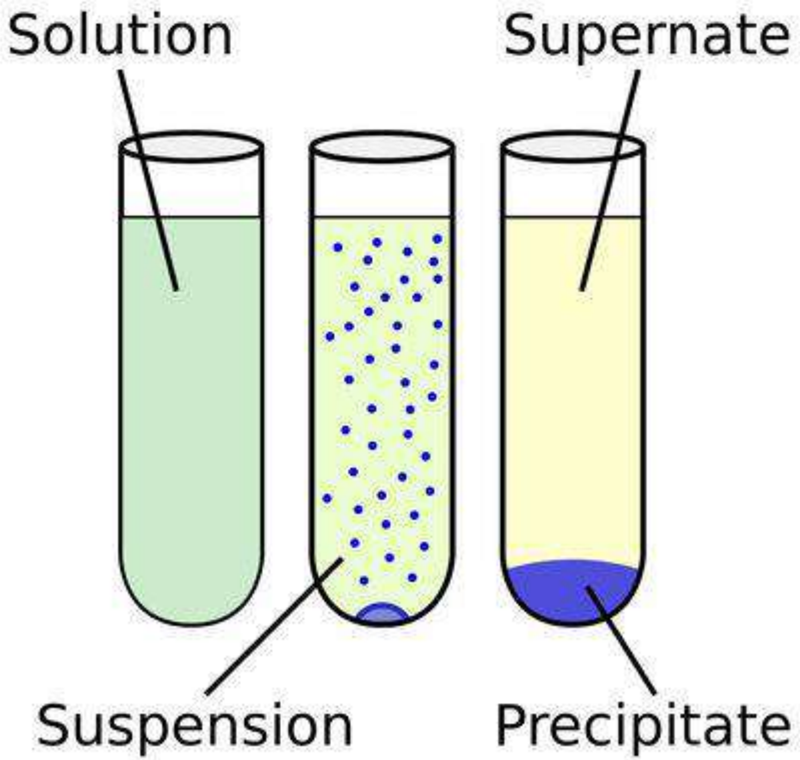
$$t_{1/2} = \frac{\frac{1}{2} A_0}{k_0}$$

- The **shelf life** is the time at which A has decreased to 90% of its original concentration

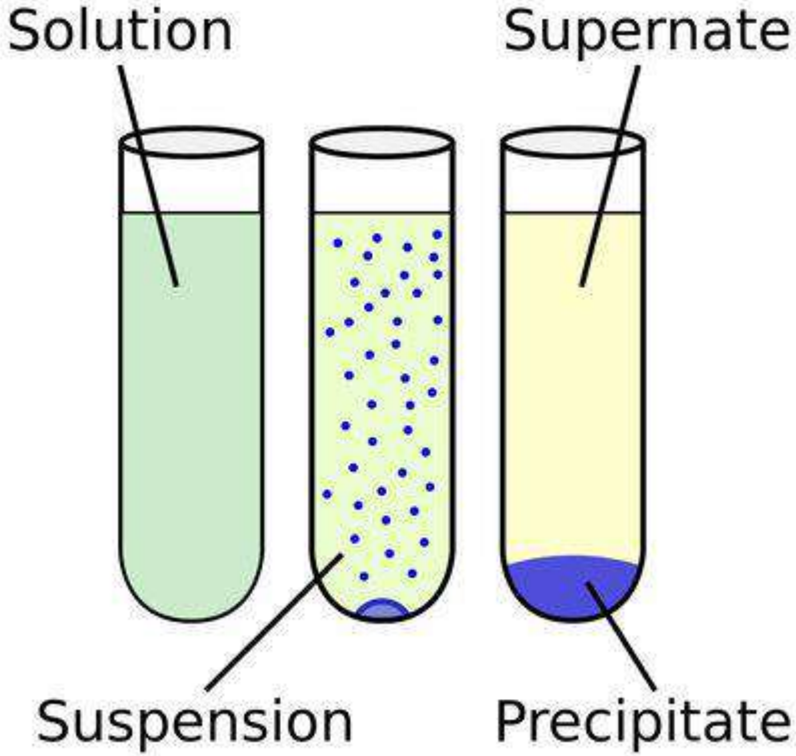
$$t_{90} = \frac{0.10[A]_0}{k_0}$$

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.
- This concentration is, of course, the drug's equilibrium solubility in a particular solvent at a particular temperature.



- The important point is that the amount of drug in solution remains constant despite its decomposition with time.
- The reservoir of solid drug in suspension is responsible for this constancy.



- The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

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

- where [A] is the concentration of drug remaining undecomposed at time t, and k is known as a first-order rate constant.
- When the concentration [A] is rendered constant, as in the case of a suspension, we can write

$$k[A] = k_0$$

- so that the first-order rate law becomes

$$-\frac{d[A]}{dt} = k_0$$

- The equation obviously is a zero-order equation.

- It is referred to as an apparent zero-order equation, being zero order only because of the suspended drug reservoir, which ensures constant concentration.

- Once all the suspended particles have been converted into drug in solution, the system changes to a first-order reaction.

- *EXAMPLE*

- 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.

- The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation

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

- where [A] is the concentration of drug remaining undecomposed at time t, and k is known as a first-order rate constant.
- When the concentration [A] is rendered constant, as in the case of a suspension, we can write

$$k[A] = k_0$$

- so that the first-order rate law becomes

$$-\frac{d[A]}{dt} = k_0$$

- ***Answer:***
- k_0 = k ×[Aspirin in solution]
- Thus,

$$k_0 = (4.5 \times 10^{-6}\,\text{sec}^{-1}) \times (0.33\ \text{g}/100\ \text{mL})$$

$$k_0 = 1.5 \times 10^{-6}\ \text{g}/100\ \text{mL}\ \ \text{sec}^{-1}$$

$$t_{90} = \frac{0.10[A]_0}{k_0} = \frac{(0.10)(6.5\ \text{g}/100\ \text{mL})}{(1.5 \times 10^{-6}\ \text{g}/100\ \text{mL sec}^{-1})}$$

$$= 4.3 \times 10^{5}\ \text{sec} = 5.0\ \text{days}$$

- In the equation $dY/dt = KY^n$, the numerical value (n) of the exponent of the substance (Y) undergoing the change is the order of the process.
- Typical orders and types of process encountered in science include:
  - zero order
  - first order
  - second order
  - third order

First-order reactions

$$\frac{-dY}{dt} = KY^1$$

- where Y is again the mass of a substance undergoing a change or a transfer, and K is the first order elimination rate constant.

- Since

$$Y^1 = Y, \longrightarrow \frac{-dY}{dt} = KY$$

- Example: the decomposition rate of **hydrogen peroxide** catalyzed by 0.02M**KI** was proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time.

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

- The rate equation is written as

$$-\frac{dc}{dt} = kc$$

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

- Integrating equation between concentration C_0 at time t = 0 and concentration c at some later time, t, we have

$$\int_{c_0}^{c} \frac{dc}{c} = -k \int_{0}^{t} dt$$

$$\ln c - \ln c_0 = -k(t - 0)$$

$$\ln c = \ln c_0 - kt$$

$$\log c = \log c_0 - kt/2.303$$

(Common Log) $\log N = x \longleftrightarrow N = 10^x$

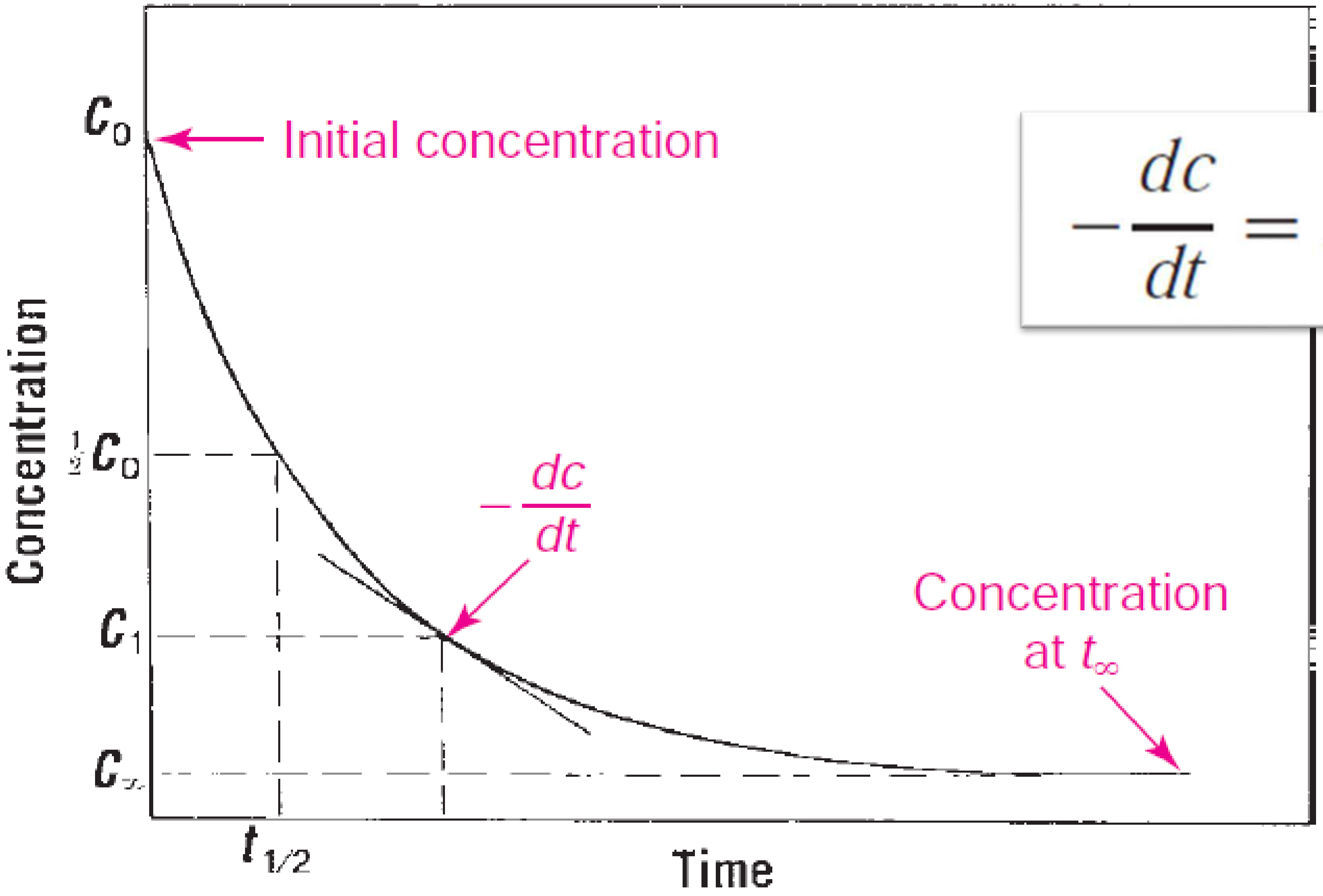
(Natural Log) $\ln N = x \longleftrightarrow N = e^x$

$$\log a = \frac{\ln a}{2.303}$$

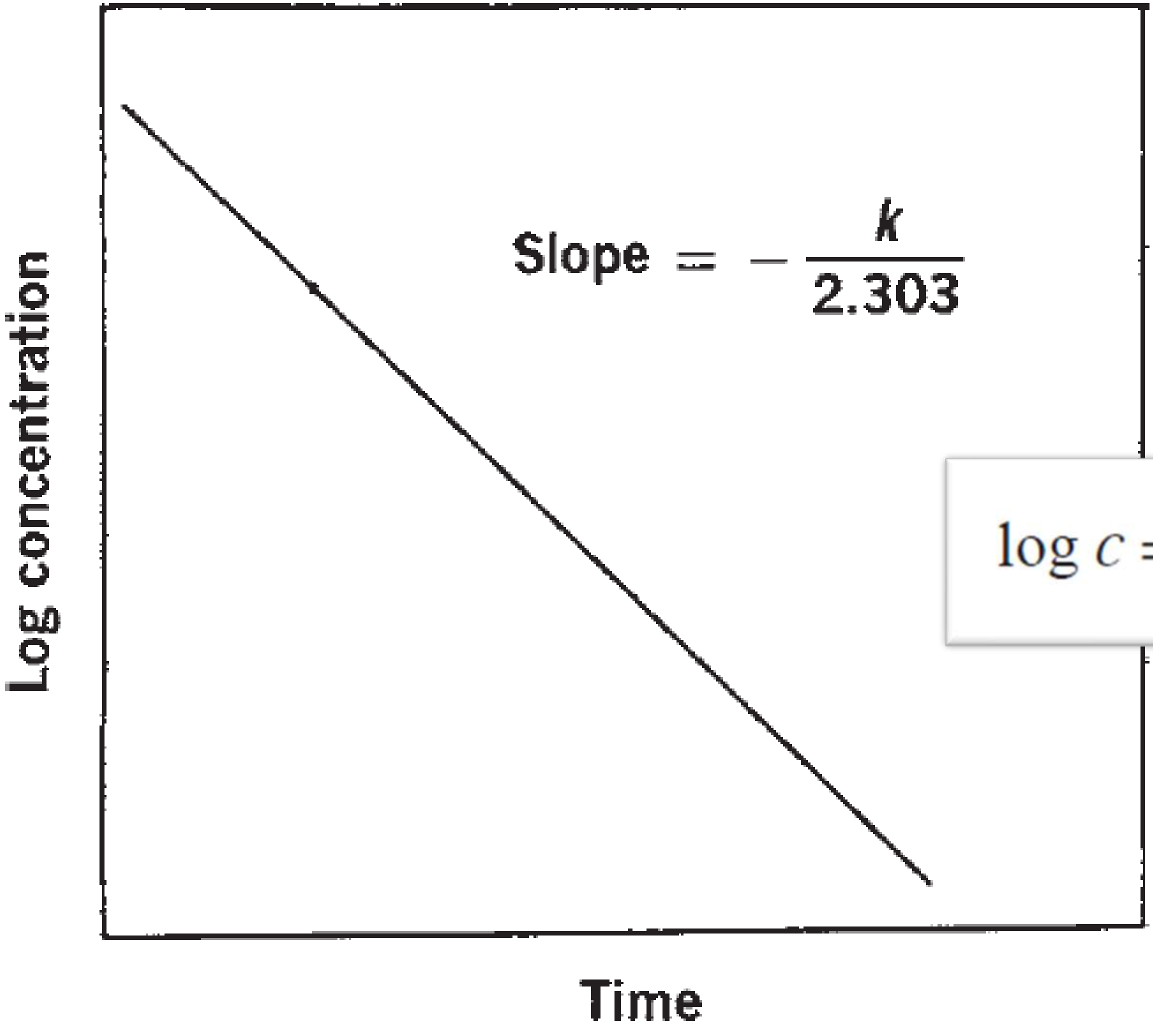
- In exponential form

$$c = c_0 e^{-kt} \qquad c = c_0 10^{-kt/2.303}$$

$$\ln(e) = 1$$


C_0
Initial concentration
Concentration
$\frac{1}{2}C_0$
$-\frac{dc}{dt}$
C_1
Concentration at t_∞
C_∞
$t_{1/2}$
Time

$$-\frac{dc}{dt} = kc$$



$$\log c = \log c_0 - kt/2.303$$

A linear plot of log *C* versus time for a first-order reaction.

$$\log c = \log c_0 - kt/2.303$$

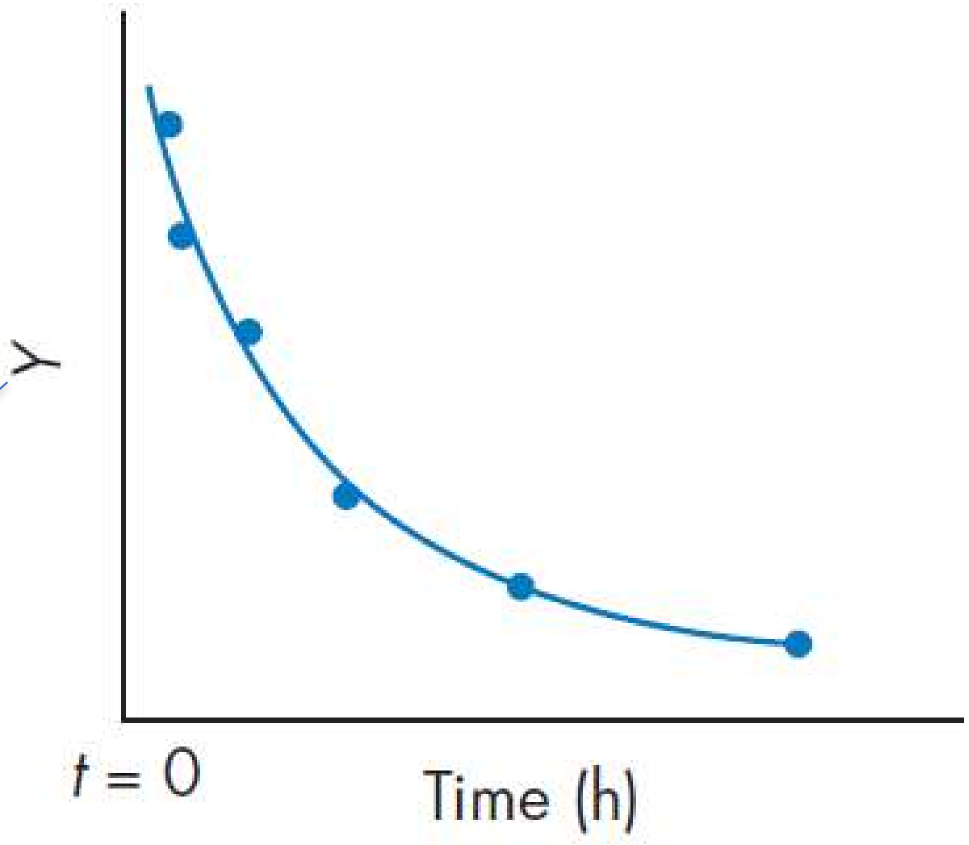
$$t_{1/2} = \frac{2.303}{k} \log \frac{500}{250} = \frac{2.303}{k} \log 2$$

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

Table 1.3 Values for parameters over time in zero- and first-order processes

Time (h)	Zero order $\frac{-dY}{dt} = K_0$		First order $\frac{-dY}{dt} = KY$	
	X (mg)	dX/dt (mg h^{-1})	X (mg)	dX/dt (mg h^{-1})
0	100	–	100	–
1	90	10	90	10
2	80	10	81	9
3	70	10	72.9	8.10
4	60	10	65.61	7.29
5	50	10	59.05	6.56
6	40	10	53.14	5.91
7	30	10	47.82	5.32
8	20	10	43.04	4.78
9	10	10	38.74	4.30

- **Applications**
- First-order elimination is extremely important in pharmacokinetics since the majority of therapeutic drugs are eliminated by this process.



mass of drug in the body (X), or concentration of drug in plasma

EXAMPLE

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

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

$$k = \frac{2.303}{65} \log \frac{57.90}{9.60} = 0.0277 \text{ min}^{-1}$$

$$0.0277 = \frac{2.303}{25} \log \frac{57.90}{c}; c = 29.01$$

EXAMPLE

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?

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

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

Second-Order Reactions

The rates of bimolecular reactions, which occur when two molecules come together,

$$A + B \rightarrow \text{ Products}$$

are frequently described by the second-order equation.

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 written as

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

- where dx/dt is the rate of reaction and a – x and b – x are the concentrations of A and B, respectively, remaining at time t.

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

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

- integrated, using the conditions that x = 0 at t = 0 and x = x at t = t.

$$\int_0^x \frac{dx}{(a-x)^2} = k\int_0^t dt$$

$$\left(\frac{1}{a-x}\right) - \left(\frac{1}{a-0}\right) = kt$$

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

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

- When $x/a(a-x)$ is plotted against t, a straight line results if the reaction is second order. The slope of the line is k.

- When, in the general case, A and B are not present in equal concentrations, integration of equation yields

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

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

- The half-life of a second-order reaction is

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

EXAMPLE

the saponification of ethyl acetate at 25◦C:

$$CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH$$

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

$$k = \frac{1}{0.01 \times 20} \frac{0.00566}{0.00434} = 6.52 \text{ liter mole}^{-1} \text{ min}^{-1}$$

(b) $$t_{1/2} = \frac{1}{ak}$$

$$t_{1/2} = \frac{1}{0.01 \times 6.52} = 15.3\,\mathrm{min}$$

Determination of Order

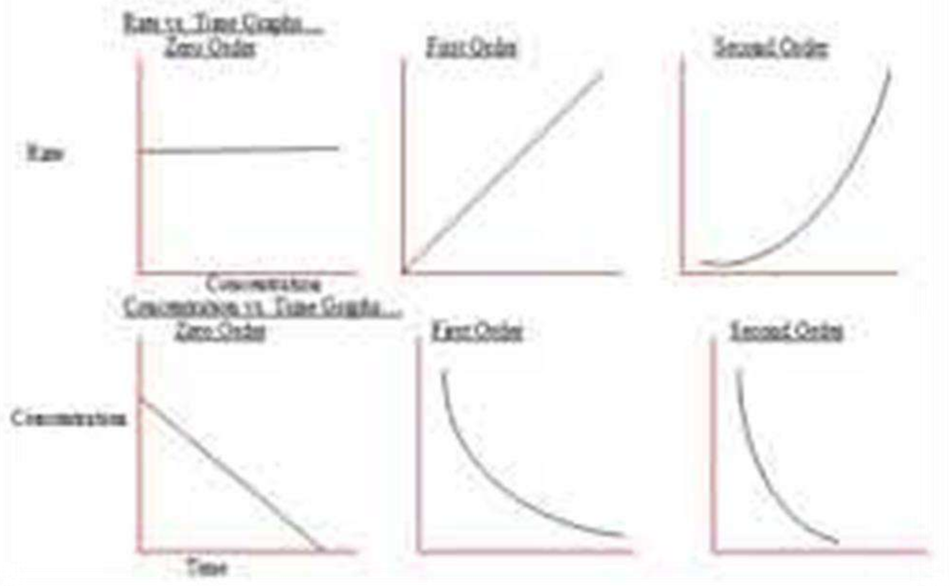
- The order of a reaction can be determined by several methods.

A) Substitution Method:

- The data accumulated in a kinetic study can be substituted in the integrated form of the equations that describe the various orders.
- 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.

B) Graphic Method:

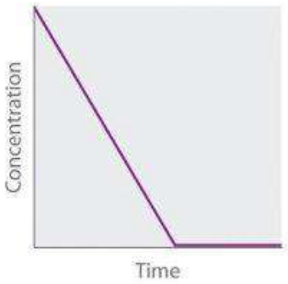
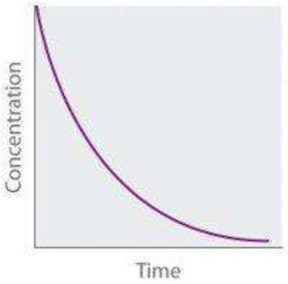
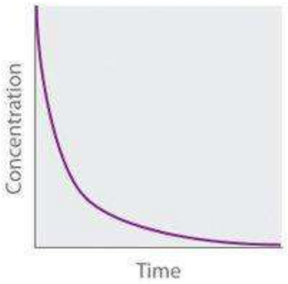
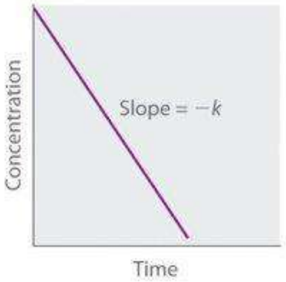
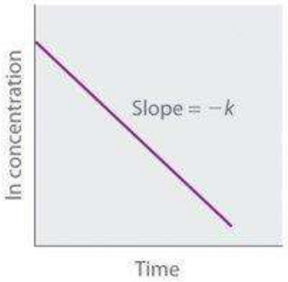
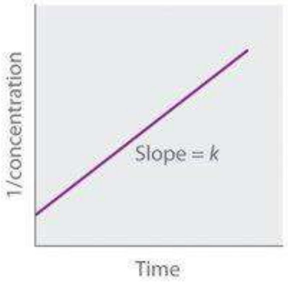
A plot of the data in the form of a graph can also be used to ascertain the order.



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

b) First order if log (a – x) versus t yields a straight line

c) Second order if 1/(a – x) versus t gives a straight line (in the case in which the initial concentrations are equal).

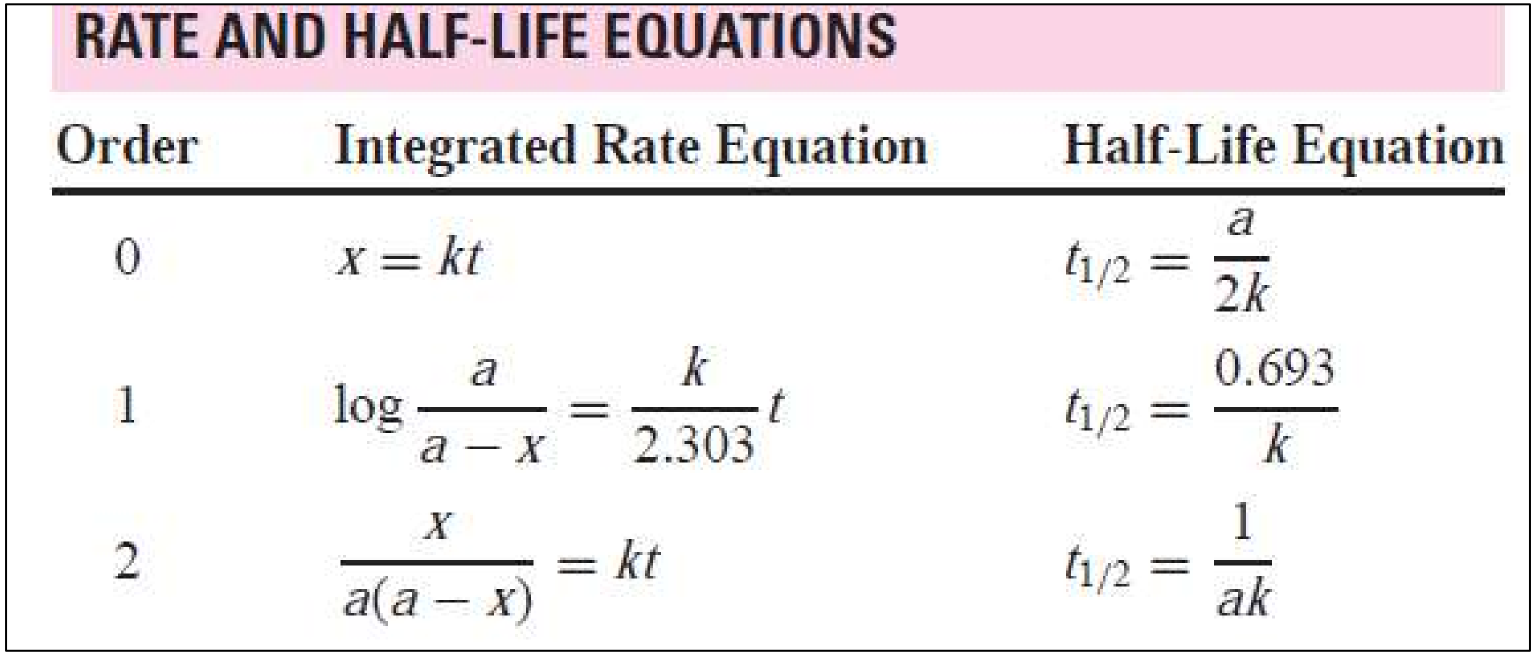
	Zeroth Order	**First Order**	**Second Order**
Differential rate law	$\text{Rate} = -\frac{\Delta[A]}{\Delta t} = k$	$\text{Rate} = -\frac{\Delta[A]}{\Delta t} = k[A]$	$\text{Rate} = -\frac{\Delta[A]}{\Delta t} = k[A]^2$
Concentration vs. time			
Integrated rate law	$[A] = [A]_0 - kt$	$[A] = [A]_0 e^{-kt}$ or $1n[A] = 1n[A]_0 - kt$	$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$
Straight-line plot to determine rate constant			
Relative rate vs. concentration	[A], *M* — Rate, M/s 1 — 1 2 — 1 3 — 1	[A], *M* — Rate, M/s 1 — 1 2 — 2 3 — 3	[A], *M* — Rate, M/s 1 — 1 2 — 4 3 — 9
Half-life	$t_{1/2} = \frac{[A]_0}{2k}$	$t_{1/2} = \frac{0.693}{k}$	$t_{1/2} = \frac{1}{k[A]_0}$
Units of *k*, rate constant	M/s	1/s	$M^{-1} \cdot s^{-1}$

C) Half-Life Method:

a) In a **zero-order** reaction, the half-life is proportional to the initial concentration, a

b) The half-life of a **first-order** reaction is independent of a;

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



RATE AND HALF-LIFE EQUATIONS

Order	Integrated Rate Equation	Half-Life Equation
0	$x = kt$	$t_{1/2} = \frac{a}{2k}$
1	$\log \frac{a}{a-x} = \frac{k}{2.303}t$	$t_{1/2} = \frac{0.693}{k}$
2	$\frac{x}{a(a-x)} = kt$	$t_{1/2} = \frac{1}{ak}$

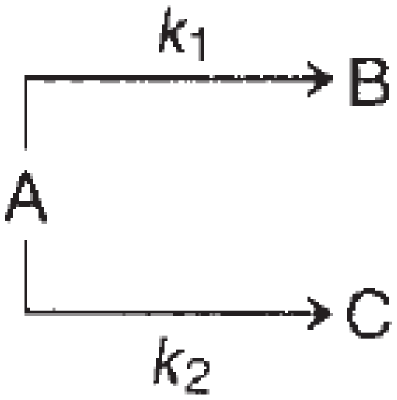
Complex Reactions

- Many reactions involve more than one-step or elementary reactions and accordingly are known as complex reactions.

- These processes include:

(a) Reversible reaction, (b) Parallel or side reactions, (c) Series or consecutive reactions

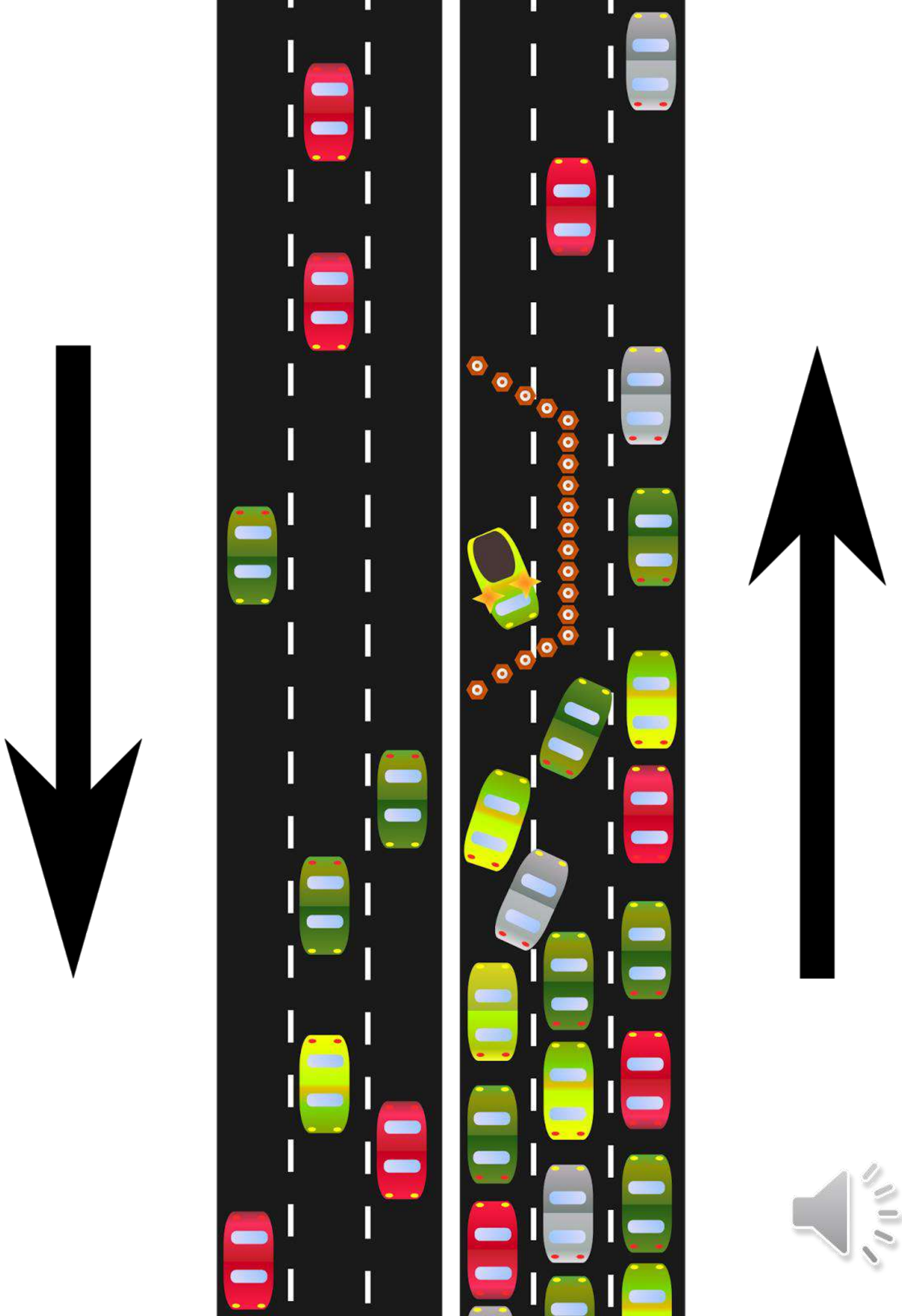
$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C + D$$



$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Rate-Determining Step

- In a reaction sequence in which one step is much slower than all the subsequent steps leading to the product, the rate at which the product is formed may depend on the rates of all the steps **preceding** the slow step but does not depend on any of the steps following.
- The slowest step in a reaction sequence is called **the rate-determining step of the reaction.**



- Consider the mechanistic pathway

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \quad \text{(step 1 and step 2)}$$

$$B + C \xrightarrow{k_3} D \quad \text{(step 3)}$$

$$D \xrightarrow{k_4} P \quad \text{(step 4)}$$

- which can be postulated for the observed overall reaction

$$A + C \rightarrow P$$

- Thus, we see that reactions may exhibit a simple first- or second-order behaviour, yet the detailed mechanism for these reactions may be quite complex.

TEMPERATURE EFFECTS

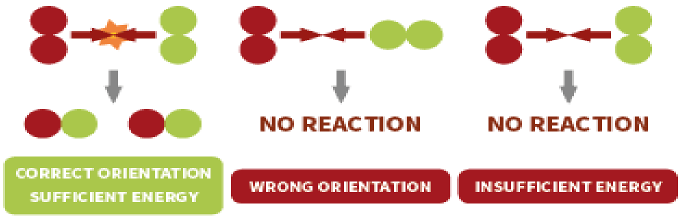
A number of factors other than concentration may affect the **reaction velocity.**

Among these are **temperature**, **solvents**, **catalysts**, and **light**. This section discusses the effect of temperature covered.

MAKING CHEMICAL REACTIONS HAPPEN FASTER

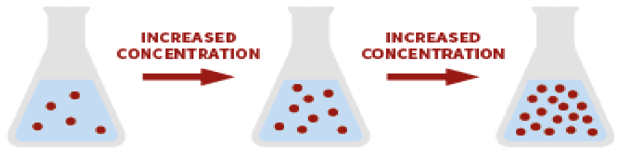
There are a number of different things that we can change to make a chemical reaction faster. Here, we explain the concept of collision theory, and how it can be used to explain the effects of five different factors on the rate of a chemical reaction.

COLLISION THEORY



Collision theory states that, for a reaction to occur, particles must collide with the correct orientation and with sufficient energy for a reaction to occur. Different factors affect the rate of the reaction by affecting the frequency of particle collisions, and/or the proportion of collisions that have enough energy to react.

INCREASE CONCENTRATION OF REACTANTS

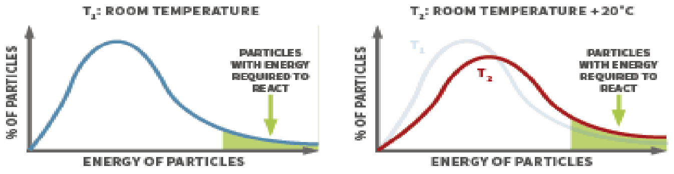


↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the concentration of reactants in solution increases the rate of reaction as there are a greater number of particles available to react. This increases the frequency of collisions between particles.

INCREASE TEMPERATURE OF REACTION

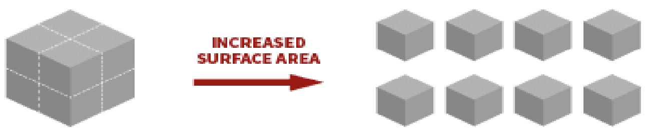


↑ FREQUENCY OF COLLISIONS

↑ % SUCCESSFUL COLLISIONS

Increasing the temperature increases the kinetic energy of particles. This increases the frequency of particle collisions, and a greater proportion of collisions will have the energy required to react.

INCREASE SURFACE AREA OF REACTANTS

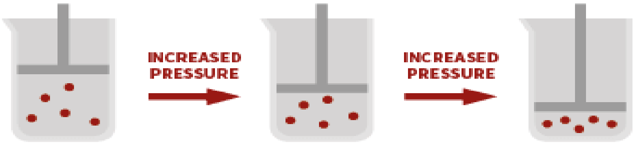


↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the surface area of solid reactants increases the number of particles that are exposed and available to react, and as a consequence this increases the frequency of particle collisions, increasing rate.

INCREASE PRESSURE OF REACTION

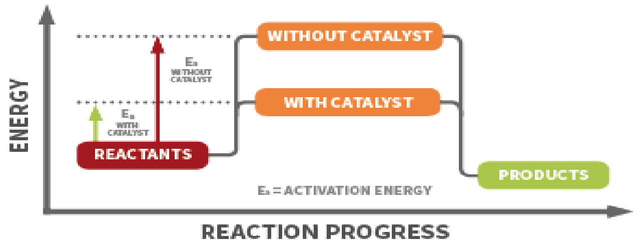


↑ FREQUENCY OF COLLISIONS

– % SUCCESSFUL COLLISIONS

Increasing the pressure of a reaction involving gases forces the gas particles closer together. This will increase the frequency of particle collisions, and therefore increase the rate of reaction.

USE A CATALYST IN THE REACTION

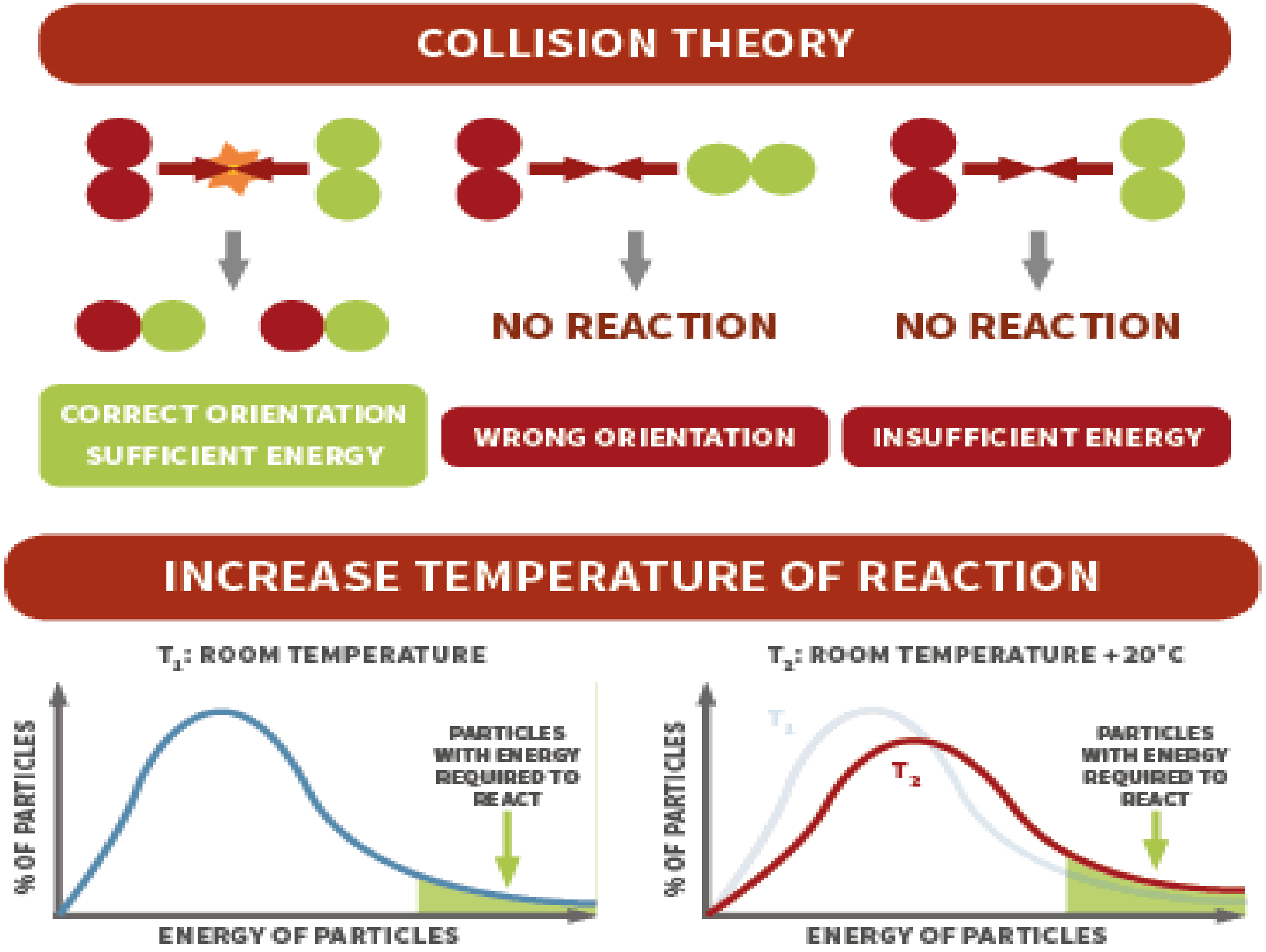


A catalyst provides an alternative route for the reaction, with a lower activation energy. This means that particle collisions need less energy in order for a reaction to occur, increasing the rate of the reaction.

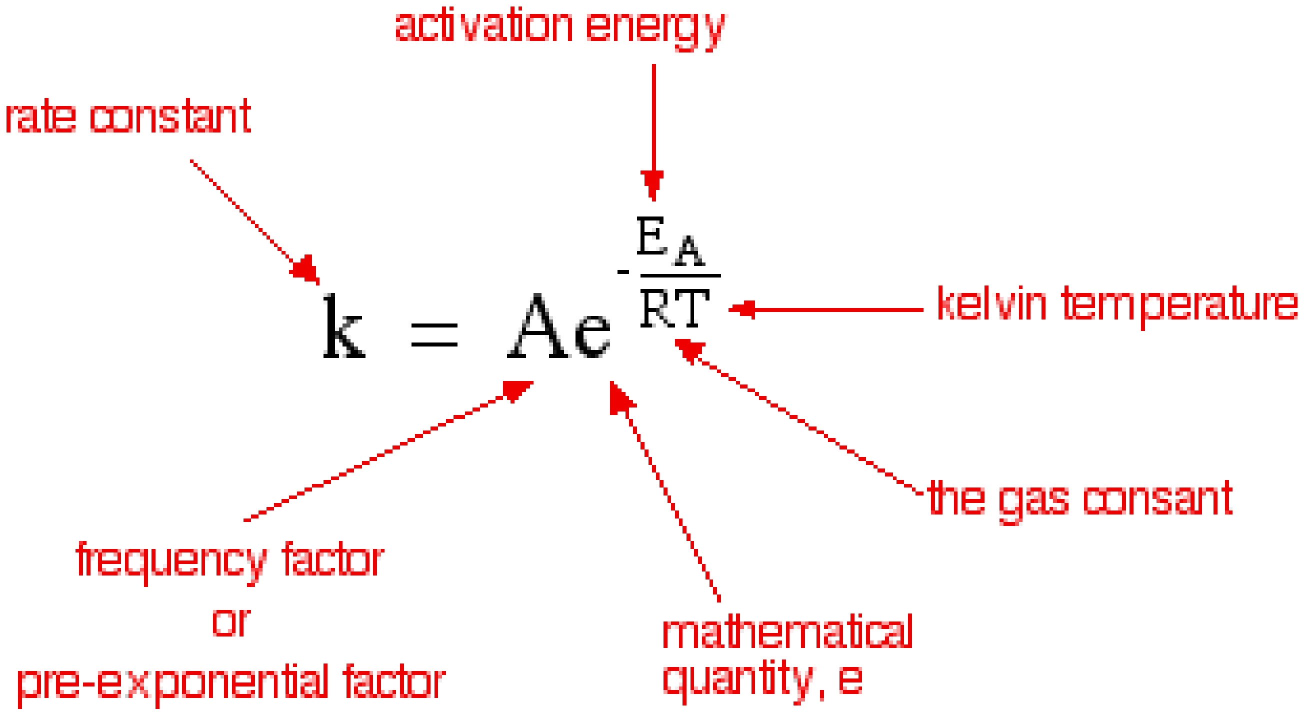
Collision Theory

- 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.
- As a reaction proceeds from reactants to products, the system must pass through a **state whose energy is greater than that of the initial reactants.**
- This “barrier” is what prevents the reactants from immediately becoming products.
- The activation energy, **Ea**, is a measure of this barrier.

- speed of many reactions increases about two to three times with each 10◦ rise in temperature.



- The effect of temperature on reaction rate is given by **Arrhenius equation,,**



$$k = Ae^{-\frac{E_A}{RT}}$$

activation energy

rate constant

kelvin temperature

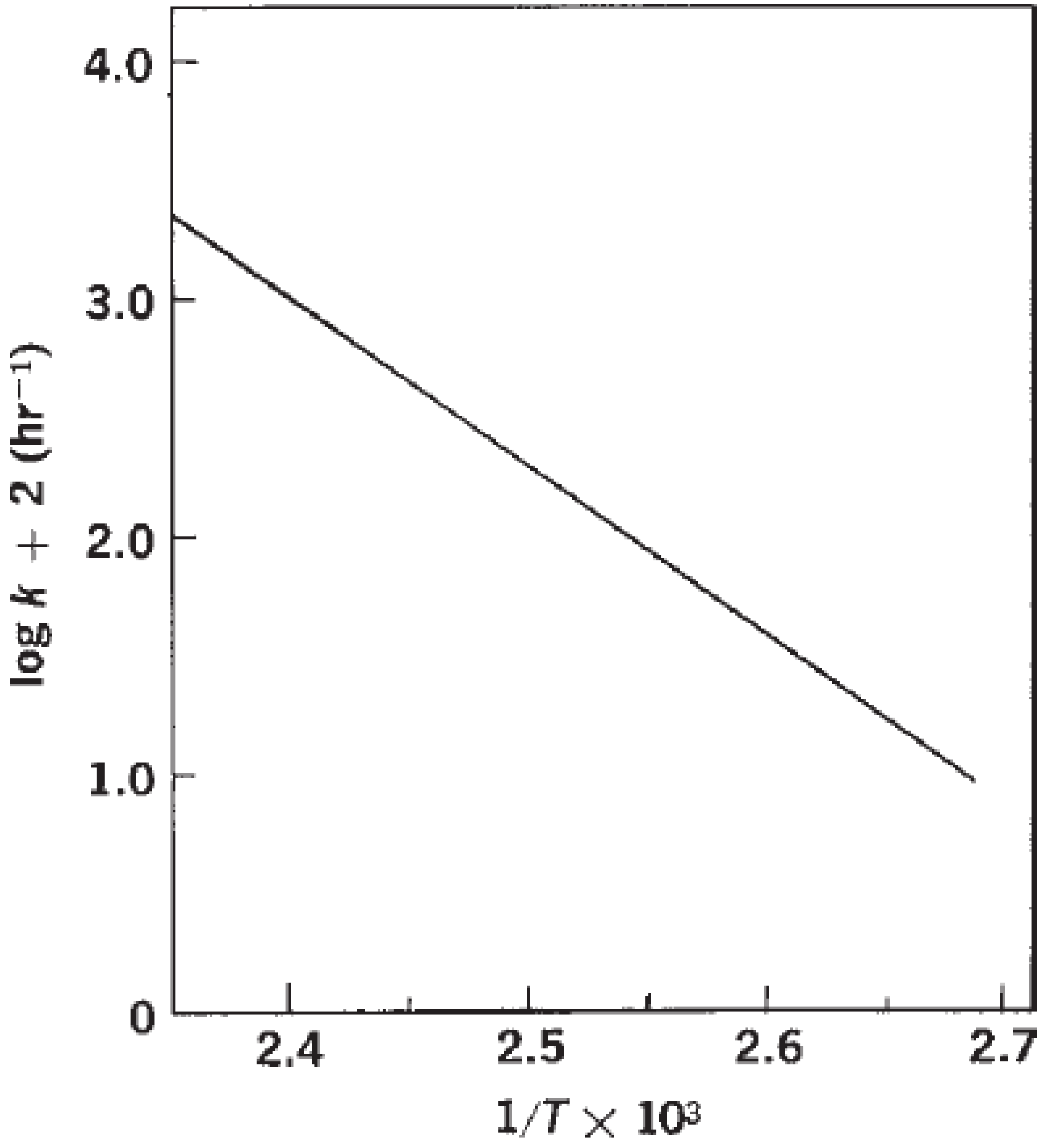
the gas consant

frequency factor
or
pre-exponential factor

mathematical
quantity, e

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT}$$

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT}$$



- The constants A and Ea can be evaluated by determining k at several temperatures and plotting 1/T against log k.
- The slope of the line so obtained is –Ea/2.303 R, and the intercept on the vertical axis is log A, from which Ea and A can be obtained.
- It should be observed that because the reciprocal of the absolute temperature is plotted along the horizontal axis, the temperature is actually decreasing from left to right across the graph

- Plot log $t_{1/2}$ instead of log k on the vertical axis.
- The half-life for a **first-order** reaction is related to k by equation **$t_{1/2}$ = 0.693/k**, and in logarithmic form

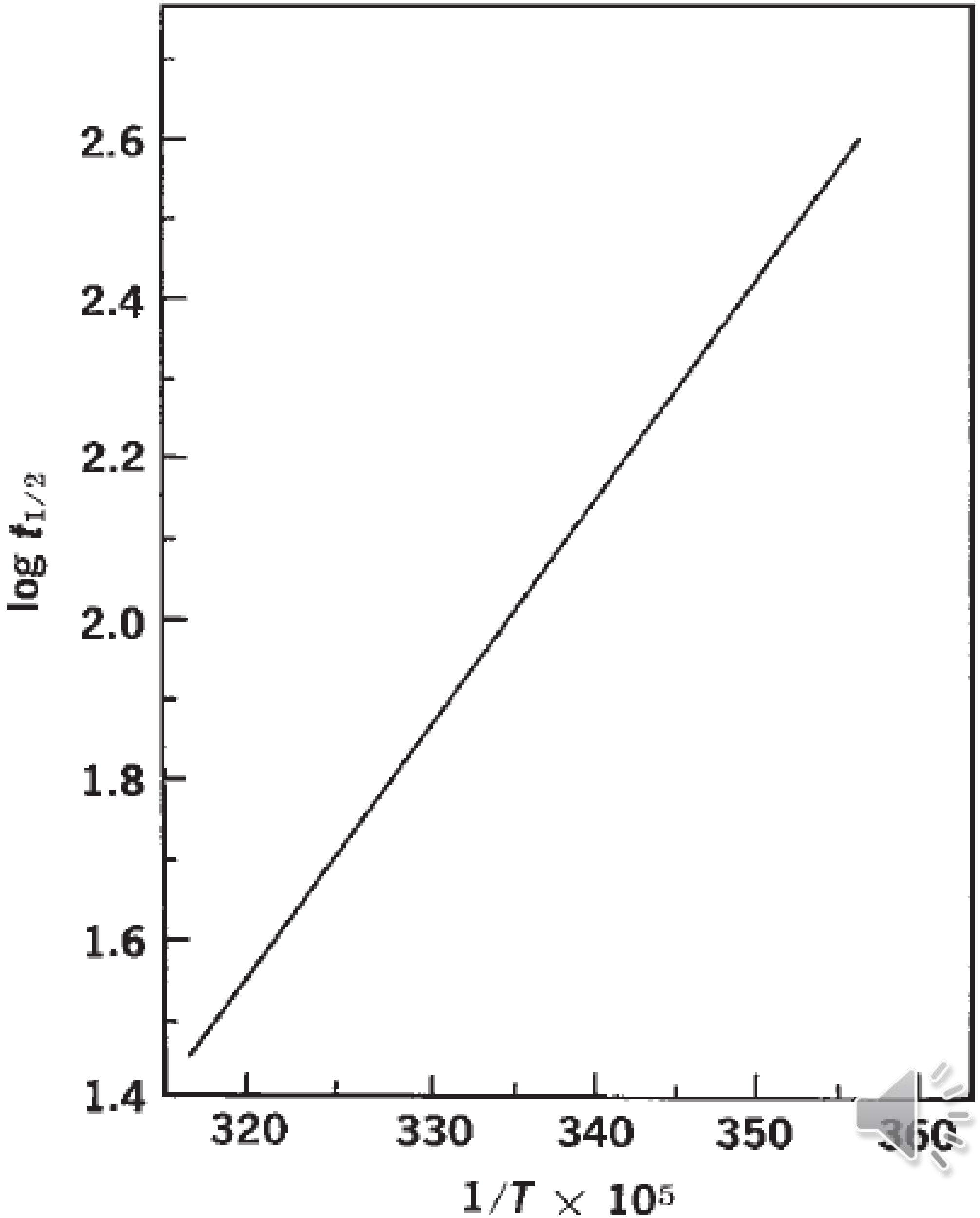
$$\log k = \log 0.693 - \log t_{1/2}$$

- Substituting equation into logarithmic form of Arrhenius equation gives:

$$\log t_{1/2} = \log 0.693 - \log A + \frac{E_a}{2.303R}\frac{1}{T}$$

- $E_a/2.303R$ is obtained as the slope of the line resulting from plotting log $t_{1/2}$ against 1/T.

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT}$$



- Arrhenius equation at a temperature T₂ can be written as:

$$\log k_2 = \log A - \frac{E_a}{2.303\,R}\frac{1}{T_2}$$

- and for another temperature T₁ as

$$\log k_1 = \log A - \frac{E_a}{2.303\,R}\frac{1}{T_1}$$

- Subtracting these two expressions yields

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303\,R}\left(\frac{T_2 - T_1}{T_2\,T_1}\right)$$

EXAMPLE

- The rate constant k_1 for the decomposition of 5 hydroxymethylfurfural at 120◦C (393 K) is 1.173 hr−1 or 3.258 × 10−4 sec−1 and k2 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?

$$\log \frac{4.860}{1.173} = \frac{E_a}{2.303 \times 1.987} \frac{413 - 393}{413 \times 393}$$

$$E_a = 23\,\text{kcal/mole}$$

- At 120◦C, using Arrhinius equation

$$\log (3.258 \times 10^{-4}\ \text{sec}^{-1}) = \log A - \frac{23{,}000\,\text{cal}}{2.303 \times 1.987} \frac{1}{393}$$

$$A = 2 \times 10^{9}\ \text{sec}^{-1}$$

OTHER FACTORS—A MOLECULAR VIEWPOINT

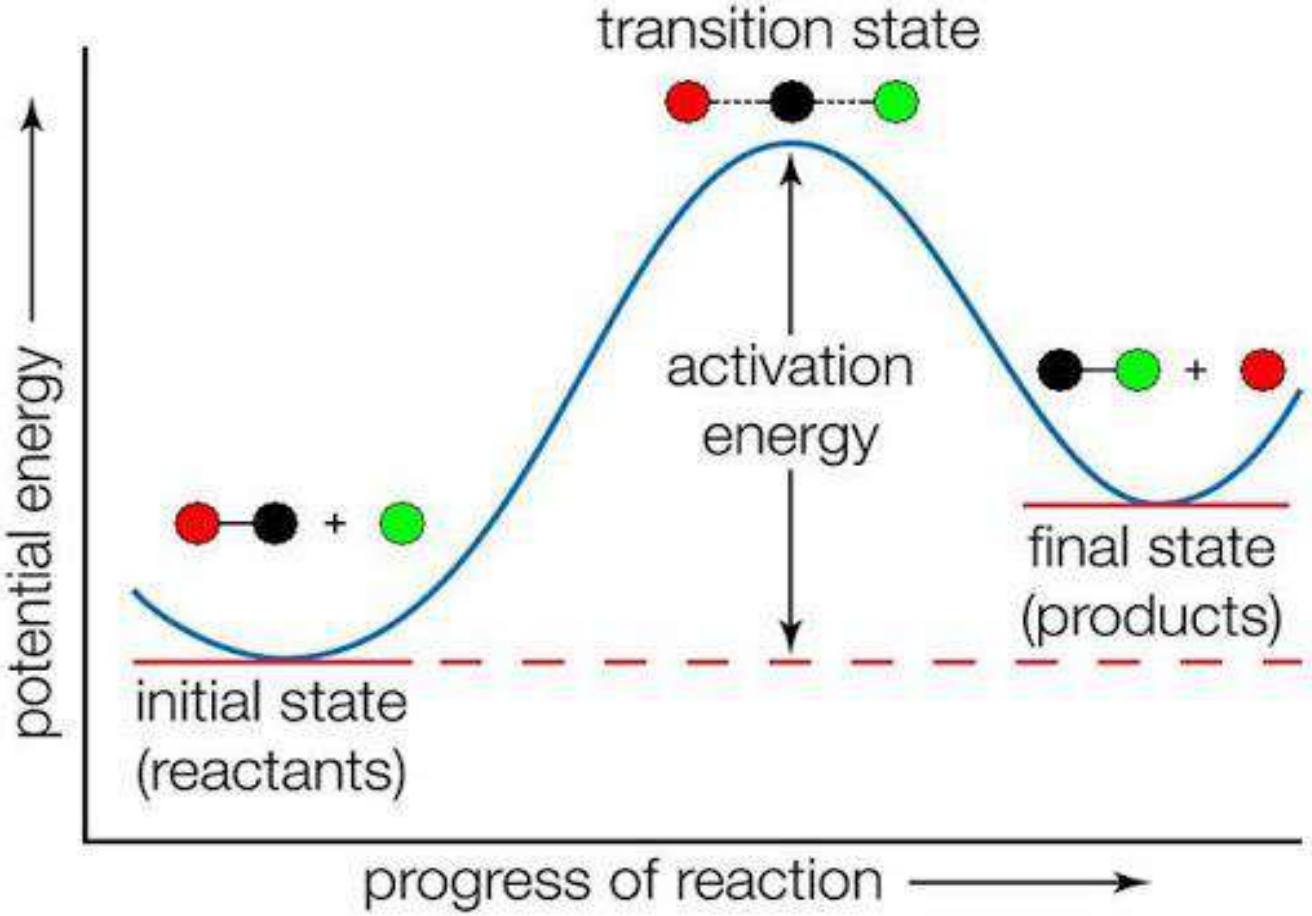
Transition-State Theory

- An alternative to the collision theory is the transition-state theory or absolute rate theory, according to which an equilibrium is considered to exist between the **normal reactant molecules** and an **activated complex of these molecules.**
- Decomposition of the activated complex leads to product.
- For an elementary bimolecular process, the reaction can be written as

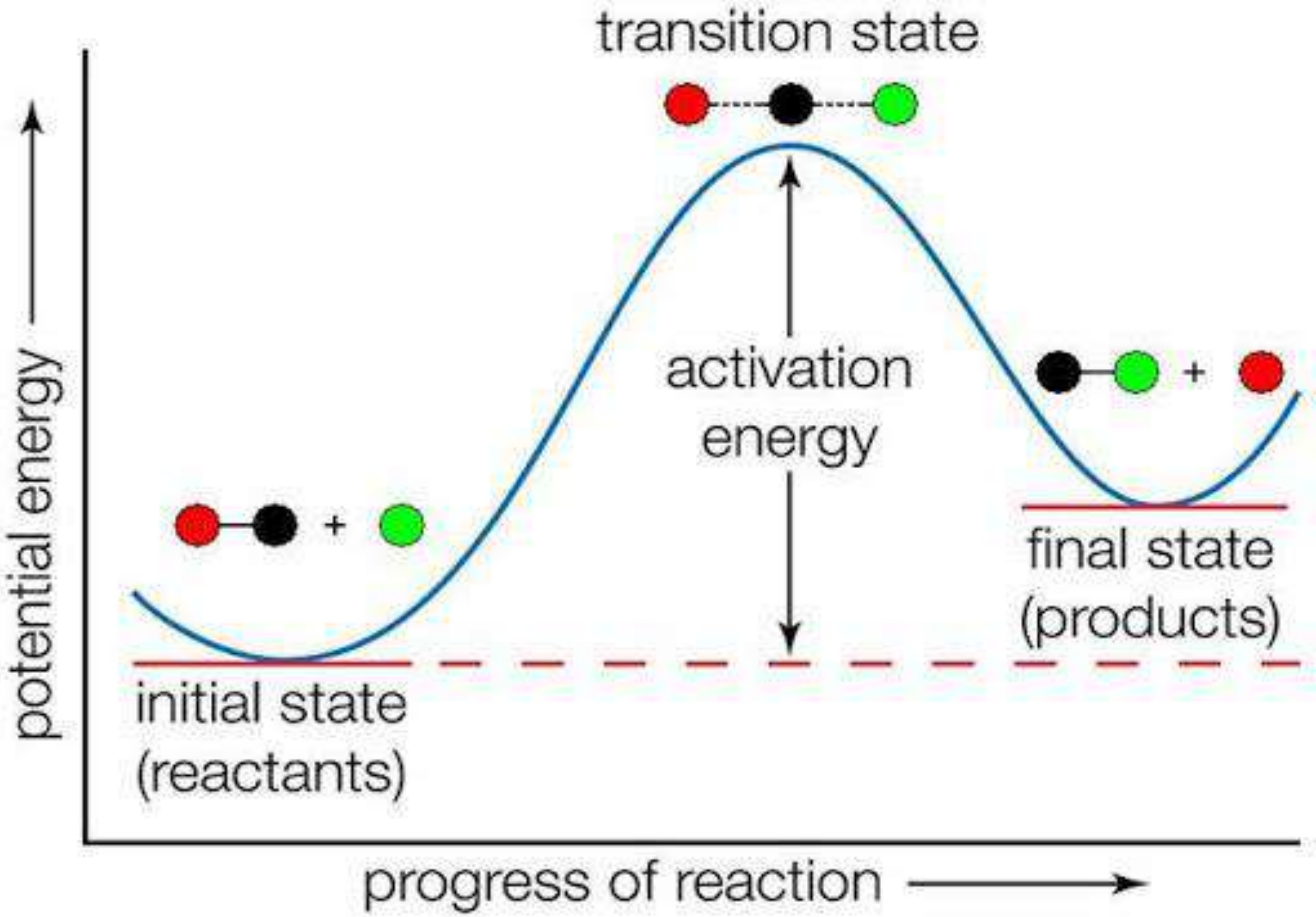
$$\underset{\substack{\text{Normal reactant}\\ \text{molecules}}}{A + B} \rightleftharpoons \underset{\substack{\text{Activated}\\ \text{molecules in the}\\ \text{transition state}\\ \text{(activated complex)}}}{[A \cdots B]^{\ddagger}} \rightarrow \underset{\substack{\text{Product}\\ \text{molecules}}}{P}$$

- A double dagger is used to designate the activated state,

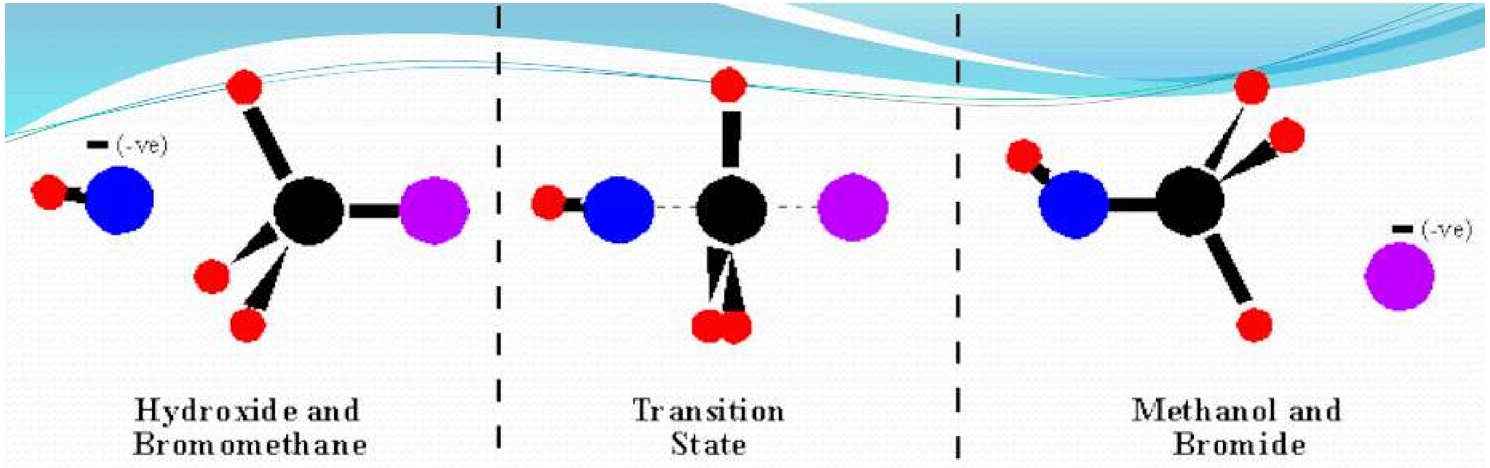
- The transition state theory assumes that simply a collision between the reactant molecules does not really causes a reaction.
- During the collision, the reactant molecules form a transition state or activated complex which decomposes to give the products.
- The **activated complex** (or **transition state**) is a temporary intermediate, of a high energy and unstable arrangement of atoms that may form products or may break apart to reform the reactants



- According to TST, between the state where molecules are reactants and the state where molecules are products, there is a state known as the transition state.
- In the transition state, the reactants are combined in a species called the activated complex.



- The theory suggests that there are three major factors that determine whether a reaction will occur:
  a) The concentration of the activated complex
  b) The rate at which the activated complex breaks apart
  c) The way in which the activated complex breaks apart:
     1) whether it breaks apart to reform the reactants, or
     2) whether it breaks apart to form a new complex, the products.



reactants **activated complex**

- The example reaction shown above involves the reactants, **hydroxide** and **bromomethane**, forming the products, **methanol** and **bromide.**
- The activated complex is clearly different than the reactants or the products.
- A successful collision and reaction have clearly occurred because in the third part of the image products (methanol and bromide) are formed that are different than the reactants (hydroxide and bromomethane)

Medium Effects: Solvent, Ionic Strength

Effect of the Solvent

- The influence of the solvent on the rate of decomposition of drugs is a topic of great importance to the pharmacist.
- The reaction of **nonelectrolytes** is related to the relative **internal pressures** or **solubility** parameters of the solvent and the solute.
- The **polar** solvents, those with high internal pressures, tend to accelerate reactions that form products having higher internal pressures than the reactants. (a polar solvent tends to increase the rate of those reactions in which product formed is more polar than reactants).
- If, on the other hand, the products are less polar than the reactants, they are accelerated by solvents of low polarity or internal pressure and retarded by solvents of high internal pressure.

- To illustrate this principle, we can use the reaction between ethyl alcohol and acetic anhydride:

$$C_2H_5OH + (CH_3CO)_2O \rightarrow CH_3COOC_2H_5 + CH_3COOH$$

- The activated complex, resembling ethyl acetate, is less polar than the reactants, and, accordingly, the reaction should be favoured in a solvent having a relatively low solubility parameter.

- The rate constants for the reaction in various solvents are given in the following table together with the solubility parameters of the solvents.

- The reaction slows down in the more polar solvents as predicted.

INFLUENCE OF SOLVENTS ON RATE CONSTANTS

Solvent	Solubility Parameter, δ	k at 50°C
Hexane	7.3	0.0119
Carbon tetrachloride	8.6	0.0113
Chlorobenzene	9.5	0.0053
Benzene	9.2	0.0046
Chloroform	9.3	0.0040
Nitrobenzene	10.0	0.0024

Influence of Ionic Strength

- In a reaction between ions, the reactants A and B have charges zA and zB, respectively, and the activated complex (A ··· B)‡ has a charge of zA + zB.
- A reaction involving ions can be represented as

$$A^{z_A} + B^{z_B} \rightleftharpoons [A \cdots B]^{\ddagger(z_A+z_B)} \rightarrow \text{Products}$$

- The rate equation at 25°C is :

$$\log k = \log k_0 + 1.02 z_A z_B \sqrt{\mu}$$

- where k**0** is the rate constant in an infinitely dilute solution in which μ= 0.
- It follows from equation that a plot of log k against √μ should give a straight line with a slope of 1.02zAzB.

$$\log k = \log k_0 + 1.02 z_A z_B \sqrt{\mu}$$

- Increased ionic strength would be expected to decrease the rate of reaction between oppositely charged ions and increase the rate of reaction between similarly charged ions

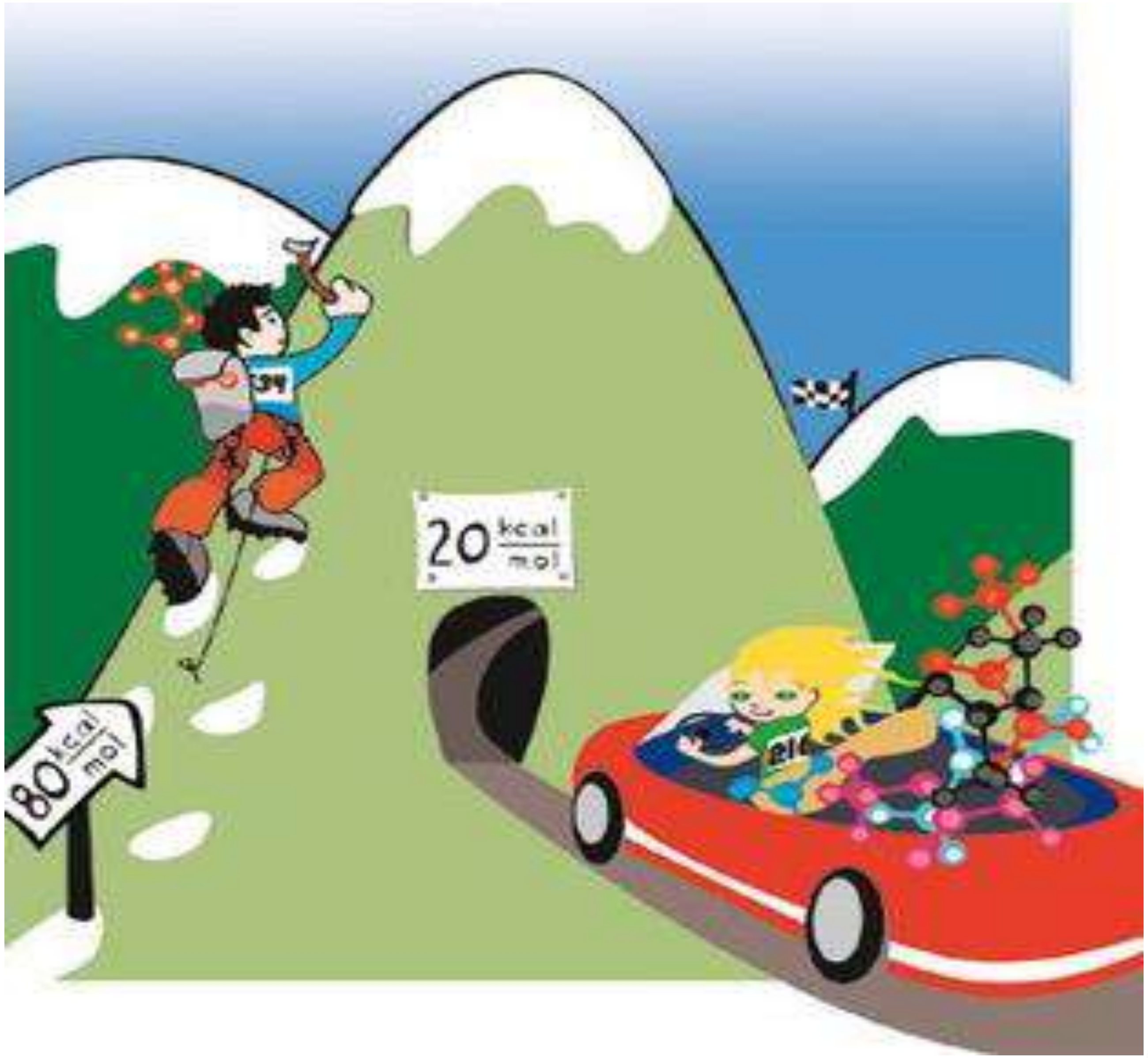
- If one of the reactants is a neutral molecule, zAzB = 0, and the rate constant, should then be independent of the ionic strength in dilute solutions.

- If the reacting molecules are uncharged in a solution having a reasonable ionic strength, the rate expression is

$$\log k = \log k_0 + b\mu$$

where *b* is a constant obtained from experimental data.

Catalysis



- **Catalysis:**
- The rate of a reaction is frequently influenced by the presence of a catalyst.
- The hydrolysis of sucrose in the presence of water at room temperature proceeds with a decrease in free energy, the reaction is so slow as to be negligible.
- When the hydrogen ion concentration is increased by adding a small amount of acid, however, inversion proceeds at a measurable rate.

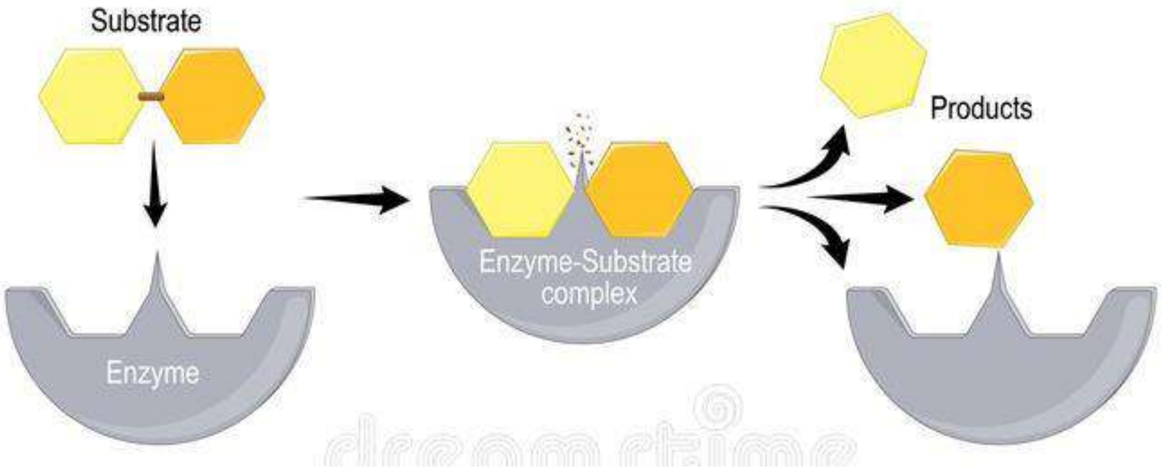
- **A catalyst** is therefore defined as a substance that influences the speed of a reaction without itself being altered chemically.

- When a catalyst decreases the velocity of a reaction, it is called a **negative catalyst.**
- Actually, negative catalysts often may be changed permanently during a reaction and should be called **inhibitors** rather than catalysts.

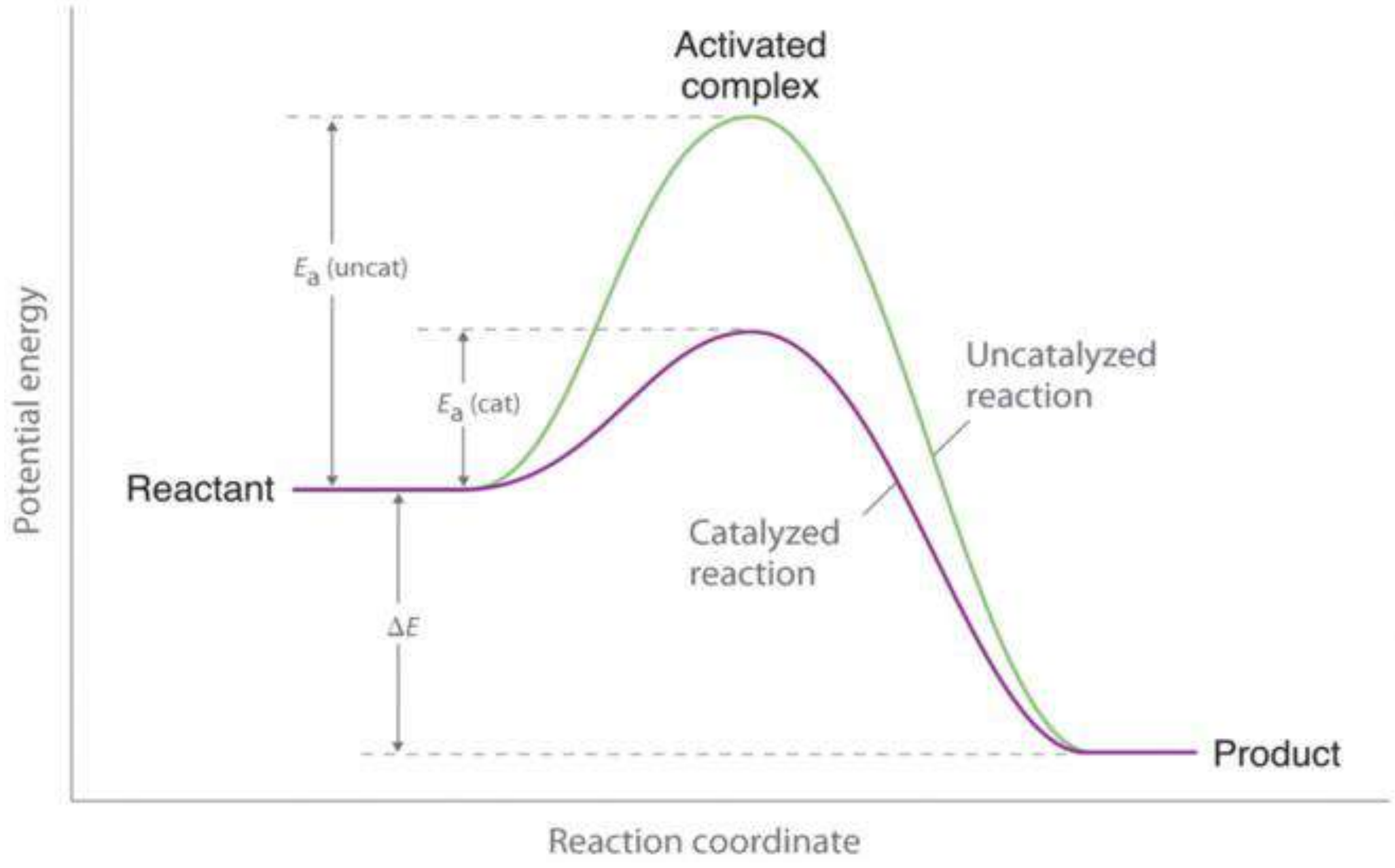
- The catalyst **increases the velocity** of the reverse reaction to the same extent as the forward reaction so that although the **equilibrium** is reached more quickly in the presence of the catalyst, the **equilibrium constant**, remains the same and the product yield is not changed.

$$K = k_{\text{forward}} / k_{\text{reverse}}$$

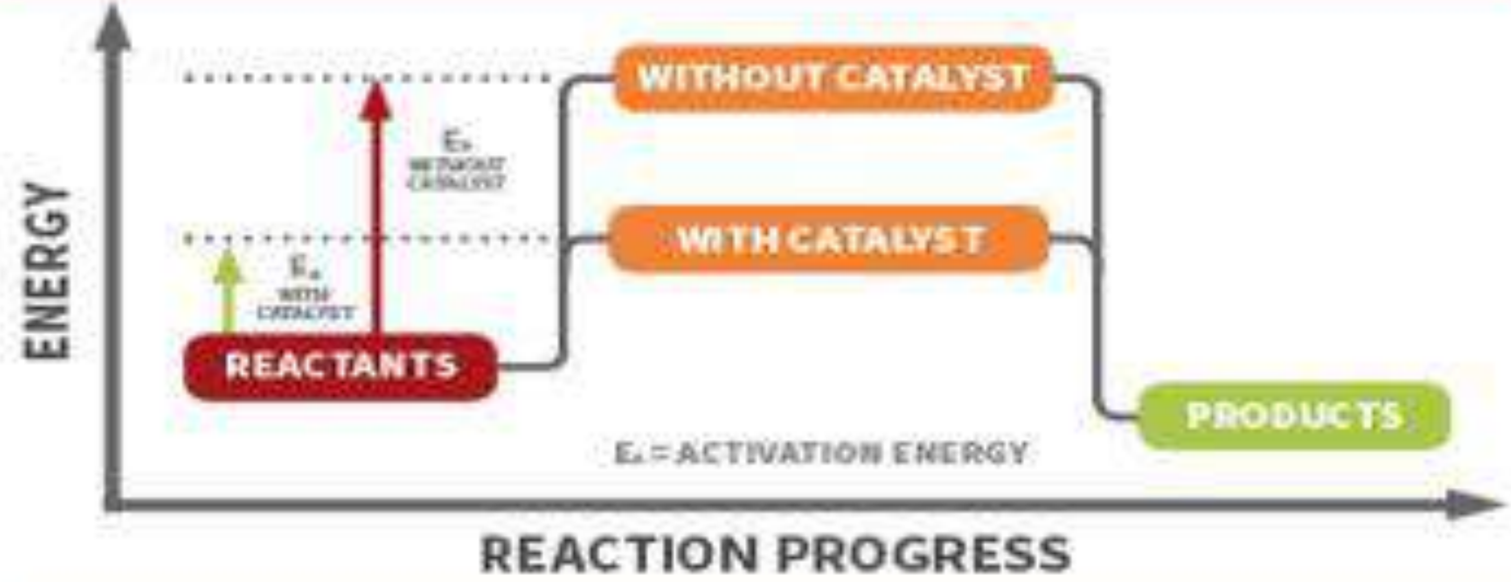
- Catalysis is considered to operate in the following way (mechanism):



A. The catalyst combines with the reactant (substrate) and forms an intermediate known as a complex, which then decomposes to regenerate the catalyst and yield the products.
    - In this way, the catalyst decreases the energy of activation by changing the mechanism of the process, and the rate is accordingly increased


Activated complex
E_a (uncat)
E_a (cat)
Uncatalyzed reaction
Reactant
Catalyzed reaction
ΔE
Product
Potential energy
Reaction coordinate

USE A CATALYST IN THE REACTION



A catalyst provides an alternative route for the reaction, with a lower activation energy. This means that particle collisions need less energy in order for a reaction to occur, increasing the rate of the reaction.

B. Alternatively, a catalyst may act by producing free radicals such as H_3, which bring about fast chain reactions.

- **Chain reactions** are reactions consisting of a series of steps involving free atoms or radicals that act as intermediates.
- The chain reaction is begun by an initiating step and stopped by a chain-breaking or terminating step.
- Negative catalysts, or inhibitors, frequently serve as chain breakers in such reactions.

- *Catalytic action may be homogeneous or heterogeneous and may occur in either the gaseous or the liquid state.*

A- Homogeneous catalysis: occurs when the catalyst and the reactants are in the same phase.

- Acid–base catalysis, the most important type of homogeneous catalysis in the liquid phase.
- Example

Acid catalysed hydrolysis of sucrose

$$\underset{\text{Sugar}}{C_{12}H_{22}O_{11}} + \underset{\text{water}}{H_2O} \xrightarrow[50\text{-}60^{\circ}C]{\text{dil.HCl}} \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Fructose}}{C_6H_{12}O_6}$$

B- Heterogeneous catalysis: occurs when the catalyst and the reactants form separate phases in the mixture. Example:

$$2SO_2(g) \xrightarrow{Pt(s)} 2SO_3(g)$$

- The catalyst may be a **finely divided solid** such as platinum or it may be the **walls of the container.**

- The catalysis occurs at the surface of the solid and is therefore sometimes known as **contact catalysis.**

- The reactant molecules are adsorbed at various points or active centres on the rough surface of the catalyst

- The adsorption weakens the bonds of the reactant molecules and lowers the activation energy.

- The activated molecules then can react, and the products diffuse away from the surface.

- Other substances, known as **promoters**, are found to increase the activity of a catalyst. For example, cupric ions promote the catalytic action of ferric ions in the decomposition of hydrogen peroxide.

- The exact mechanism of promoter action is not understood, although the promoter is thought to change the properties of the surface so as to **enhance the adsorption of the reactants** and thus increase the catalytic activity

STABILITY OF PHARMACEUTICALS

The Federal Food, Drug, and Cosmetic Act requires that manufacturers establish controls for the manufacture, processing, packing, and holding of drug products to ensure their safety, identity, strength, quality, and purity .

Requirements for these controls, also known as current good manufacturing practices, are established and monitored by the Food and Drug Administration (FDA).

- Stability of a pharmaceutical preparation is the capability of a formulation in a specific container-closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.

- Stability testing is used to:
  a) Provide evidence as to how the **quality** of the drug product varies with time.
  b) Establish **shelf life** for the drug product.
  c) Determine recommended **storage conditions.**
  d) Determine **container closure** system suitability.

- The testing should cover, as appropriate,
    - the physical,
    - chemical,
    - biologic, and microbiologic attributes,
    - preservative content (e.g., antioxidant, antimicrobial preservative),
    - functionality tests (e.g., for a dose delivery system).

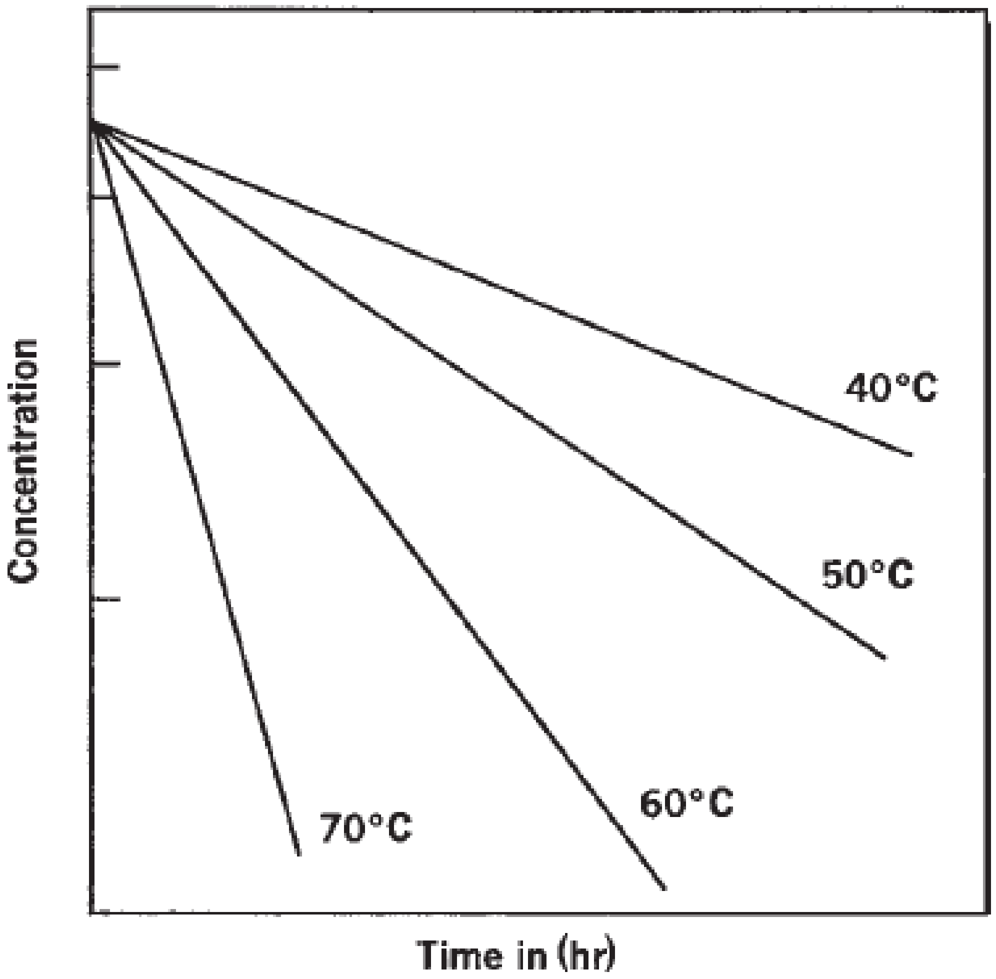
- The stability of drug products needs to be evaluated over time in the same container-closure system in which the drug product is marketed.
- When a manufacturer changes the packaging of a drug product (e.g., from a bottle to unit dose), stability testing must be performed on the product in its new packaging, and expiration dating must reflect the results of the new stability testing

Accelerated Stability and Stress Testing

- Accelerated stability studies are designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.
- Stability study to predict the shelf life of the product, by accelerating the rate of decomposition, preferably by increasing the temperature of reaction conditions.
- Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping.

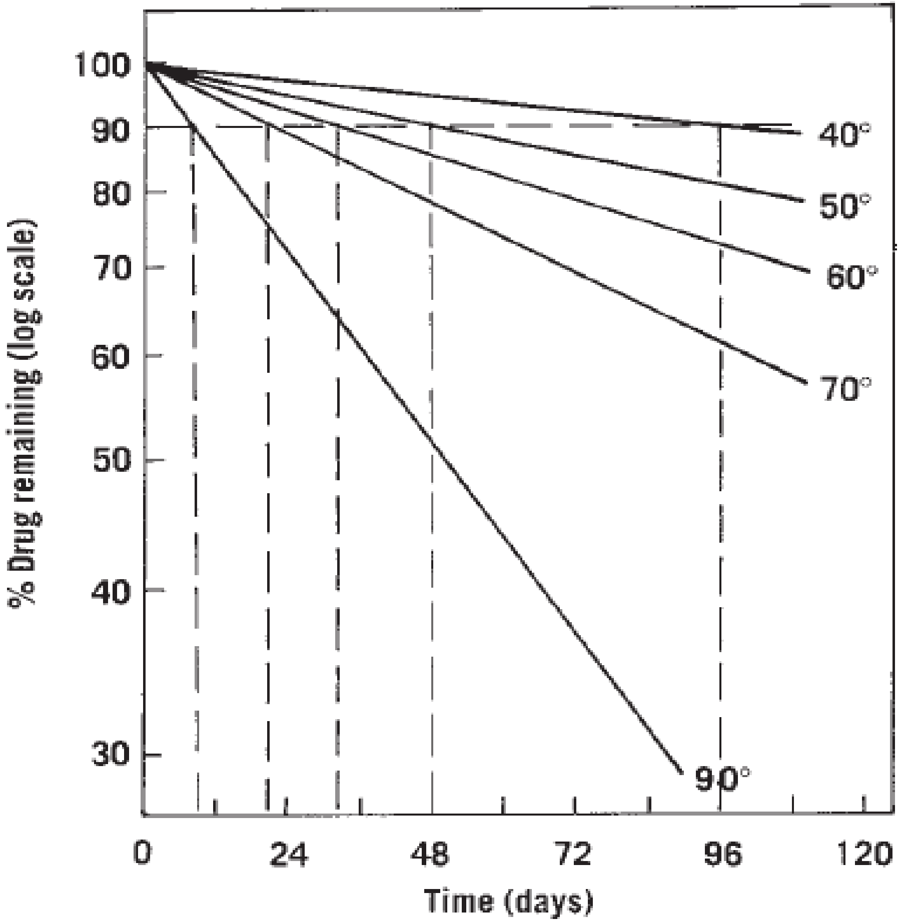
- The method of accelerated testing of pharmaceutical products based on determination of the **k values** for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some function of **concentration against time**
- The logarithms of the specific rates of decomposition are then plotted against the reciprocals of the absolute temperatures, and the resulting line is extrapolated to room temperature.
- The k_{25} is used to obtain a measure of the stability of the drug under ordinary shelf conditions.

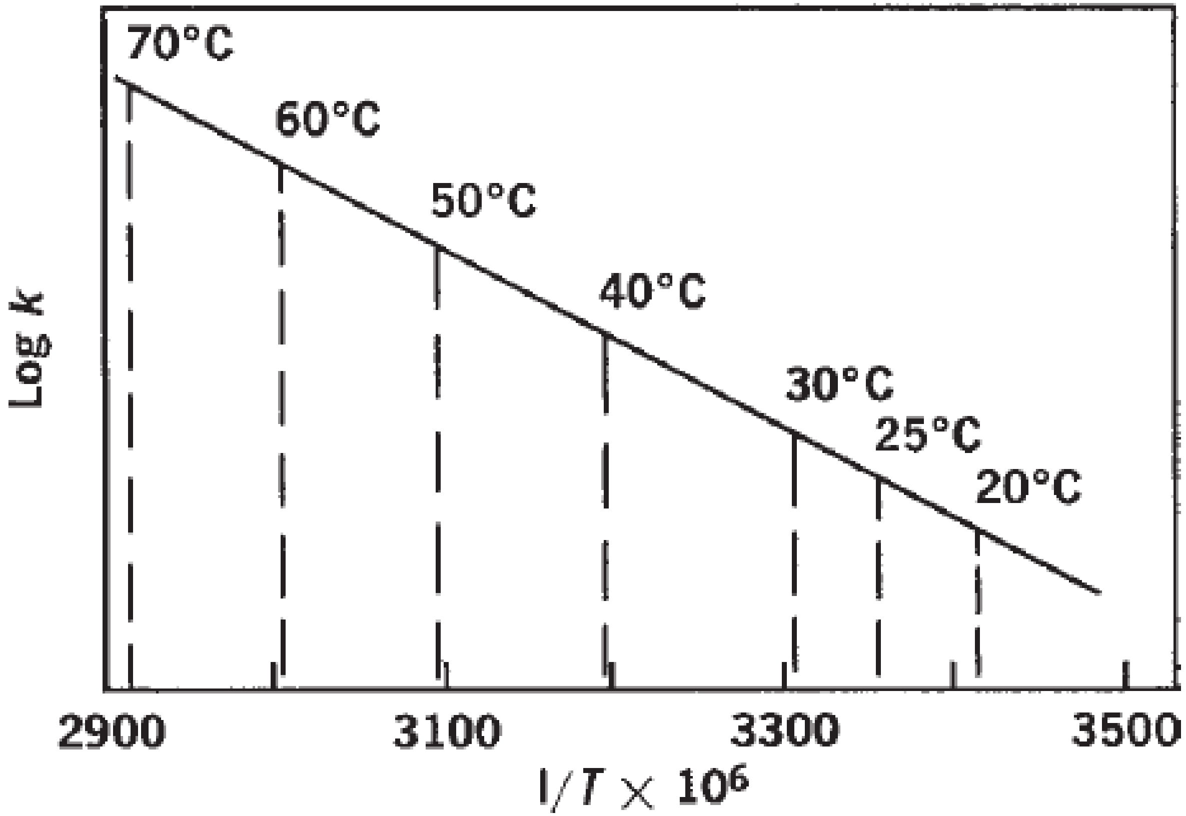
Accelerated breakdown of a drug in aqueous solution at elevated temperature.



Time in days required for drug potency to fall to 90% of original value.

Arrhenius plot for predicting drug stability at room temperatures

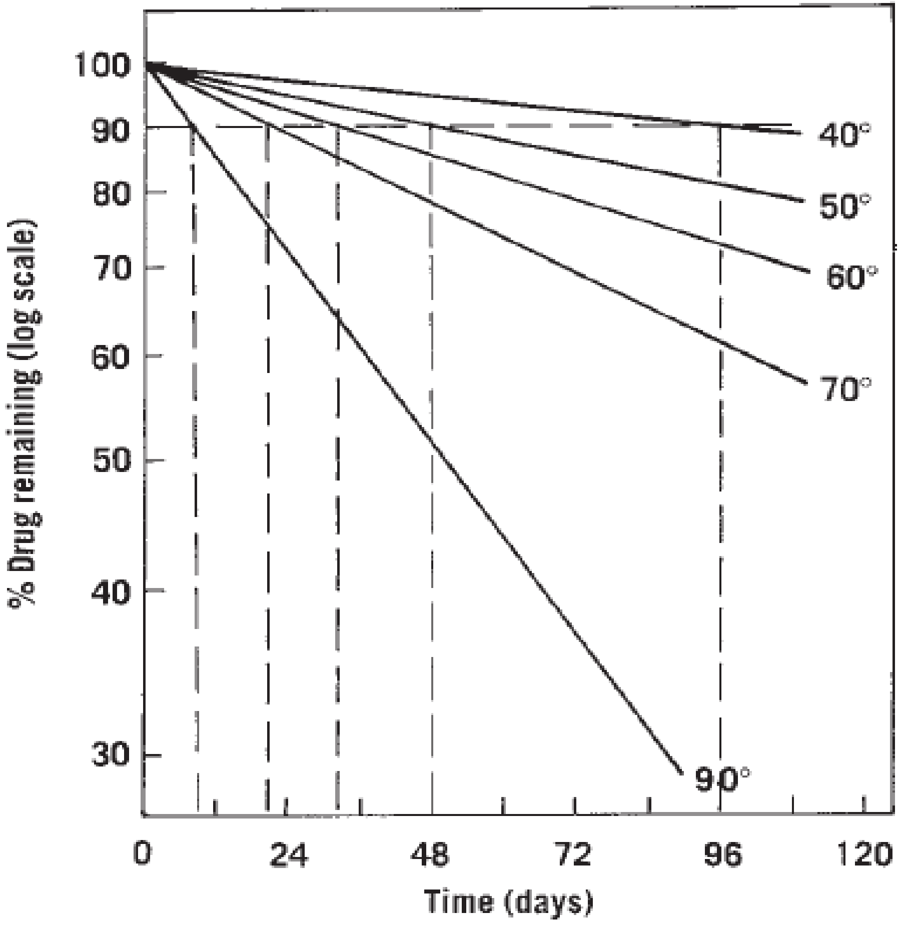




$$\log c = \log c_0 - kt/2.303$$

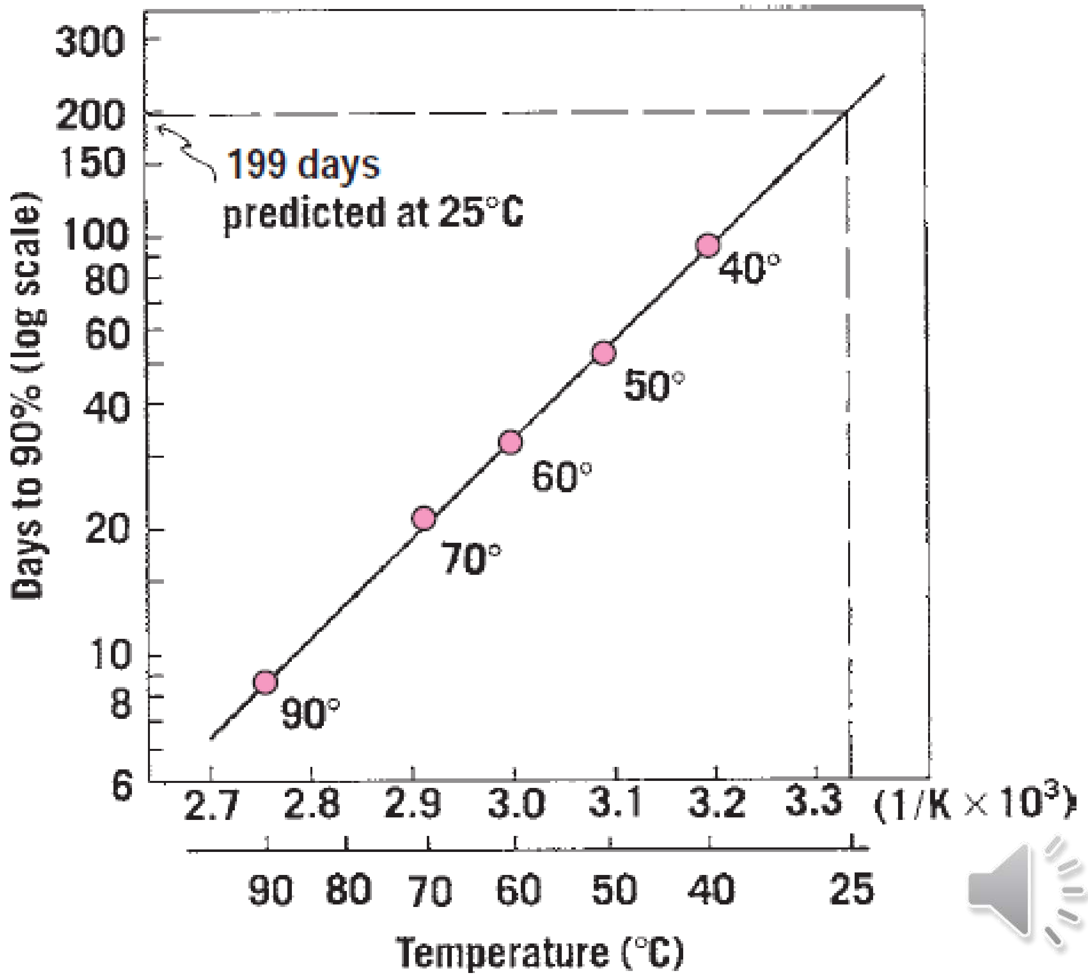
$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT}$$

Time in days required for drug potency to fall to 90% of original value.



$$\log c = \log c_0 - kt/2.303$$

A log plot of t_{90} (i.e., time to 90% potency) on the vertical axis against reciprocal temperature (both Kelvin and centigrade scales are shown) on the horizontal axis.



- The fractional life period is plotted against reciprocal temperatures and the time in days required for the drug to decompose to some fraction of its original potency at room temperature is obtained.

- As observed in the figure, the log percent of drug remaining is plotted against time in days, and the time for the potency to fall to 90% of the original value (i.e.,t_{90}) is read from the graph

- The log time to 90% is then plote against 1/T, and the time at 25°C gives the shelf life of the product in days.
- The decomposition data result in a t_{90} value of 199 days

Example: Expiration Dating

- The initial concentration of a drug decomposing according to first-order kinetics is 94 units/mL. The specific decomposition rate, k, obtained from an Arrhenius plot is 2.09 × 10-5 hr-1 at room temperature, 25°C. Previous experimentation has shown that when the concentration of the drug falls below 45 units/mL it is not sufficiently potent for use and should be removed from the market. **What expiration date should be assigned to this product?**

$$\log c = \log c_0 - kt/2.303 \qquad t = \frac{2.303}{k} \log \frac{c_0}{c}$$

$$t = \frac{2.303}{2.09 \times 10^{-5}} \log \frac{94}{45} = 3.5 \times 10^4 \text{ hr} \cong 4 \text{ years}$$

Stress Testing

- assess the effect of severe conditions on the drug product.
- to elucidate the intrinsic stability of the drug substance is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

- The testing typically includes the effects of temperature [in 10°C increments (e.g., 50°C–60°C) above that for accelerated testing], humidity (e.g., 75% relative humidity or greater)

- Such studies include **photostability testing** and specific testing of **certain products** (e.g., metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid).

long Term Testing

- long term testing is normally performed for longer duration of the test period in order to allow significant product degradation under recommended storage conditions.

- Pharmaceutical companies store a drug at room temperature, under natural light, and expected levels of humidity in the areas where the drug will be sold. These tests often run for years.