9

Kinetics of drug stability

The routes of decomposition of drugs, and the steps taken to prevent them, were considered in Chapter 8. In this chapter the rates of decomposition will be studied and useful information, such as shelf-life, will be predicted. Calculations of this type are important as there is little merit in producing the latest wonder drug designed to cure all ills only to watch it fall apart on the dispensary shelf as a result of decomposition.

Rate, order and molecularity

The underlying principle on which all of the science of kinetics is built is the law of mass action introduced in Chapter 1. This states that the rate of a chemical reaction (i.e. the speed of the reaction or, simply, how fast it is) is proportional to the active masses of the reacting substances. Active mass is a complicated term to measure, but, fortunately, if the solutions in question are dilute, the active mass may be replaced by concentration, which is much easier to handle. If the concentration of a solute is greater than about 0.1 mol L^{-1}, significant interactions arise between the solute molecules or ions. In cases like this, effective and measured concentrations are not the same and use must be made of *activity* instead of concentration.

The *rate* of a chemical reaction is, in a dilute solution, proportional to the concentrations of the various reactants each raised to the power of the number of moles of the reactant in the balanced chemical equation. This sounds too easy, and in fact it is. In practice, the rate of a chemical reaction depends only on a small number of concentration terms, and the sum of the powers to which these concentrations are raised is termed the *order* of the reaction. This is because chemical reactions occur in a number of steps, or stages (called a *mechanism*) and the rate of the overall reaction is often governed by the rate of the slowest step (called, not surprisingly, the *rate-determining step*). Even if every other stage of a chemical reaction occurs essentially instantaneously, the rate of the reaction as a whole cannot exceed that of the slowest stage.

For example, if the rate of a chemical reaction depended only on the concentration of compound A, this could be written as

$$\text{Rate} \propto [A]$$

and the reaction would be *first order*, e.g.

$$C_2H_6 \rightleftharpoons C_2H_4 + H_2$$

If the rate of the reaction depended on the concentrations of A and B, or on the concentration of A squared, this could be written as

$$\text{Rate} \propto [A][B] \qquad \text{or} \qquad \text{Rate} \propto [A]^2$$

and the reaction would be *second order*, e.g.

$$CH_3COOC_2H_5 + NaOH \rightleftharpoons C_2H_5OH + CH_3COONa$$

To further complicate matters, the order of a chemical reaction cannot be predicted from the chemical equation, even if it has been balanced. The order of a reaction is determined *experimentally* from accurate measurements of the rate under different conditions. It is possible for reactions to be third order, zero order (often found in solid-state reactions such as the release of drug from pharmaceutical suspensions) or even of a fractional order.

The third term to be considered in this section is *molecularity*. The molecularity of a reaction is the total number of molecules taking part in the slowest of the elementary reaction steps. In most chemical reactions, two molecules collide and react; the molecularity is 2 and the reaction is said to be *bimolecular*. Reactions in which only one molecule is involved (*unimolecular*) are known, but usually occur in the gas phase. Reactions with a molecularity higher than 2 are very rare, since this would require three or more reactants all encountering each other at the same time.

Rate equations and first-order reactions

Differential rate equations like these are not much use to the practising chemist, so it is usual to integrate the differential form of the rate equation, shown above, to obtain more useful expressions. This can be carried out as follows for a first-order reaction. In this reaction, compound A reacts to form products. At the start of the reaction (time 0) the concentration of A is equal to a mol L^{-1}, while the concentration of products will be zero (since the reaction has not started). At some later time, t, the concentration of products has increased to x mol L^{-1} and as a result the concentration of A has fallen to $(a - x)$ mol L^{-1}. This can be represented mathematically as

$$A \longrightarrow \text{products}$$

At time = 0,

$$[\mathrm{A}] = a, \quad [\text{products}] = 0$$

At time = t,

$$[\mathrm{A}] = (a - x), \quad [\text{products}] = x$$

From the law of mass action, the rate of reaction is proportional to [A]. If we rewrite 'rate' as $\mathrm{d}x/\mathrm{d}t$, i.e. the rate of production of x with respect to t, and substitute $(a - x)$ for [A], then

$$\frac{\mathrm{d}x}{\mathrm{d}t} \propto (a - x)$$

and so

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k(a - x)$$

where k is the constant of proportionality. This expression can be integrated to give

$$\int \frac{\mathrm{d}x}{(a - x)} = \int k \, \mathrm{d}t = k \int \mathrm{d}t$$
$$-\ln(a - x) + c = kt$$

where ln represents the natural (base e) logarithm. To find c, recall that at $t = 0$, $x = 0$; therefore,

$$-\ln a + c = 0$$

and so

$$c = \ln a$$

so that

$$-\ln(a - x) + \ln a = kt$$

or

$$\ln \frac{a}{(a - x)} = kt \tag{9.1}$$

which is equivalent to

$$\ln(a - x) = \ln a - kt \tag{9.2}$$

If a plot of equation (9.1) is made, with t on the horizontal axis and $\ln[a/(a - x)]$ on the vertical axis, a straight line passing through the origin will be obtained for a reaction obeying first-order kinetics. The slope of this straight line will be equal to k, the *rate constant* for the reaction (see Figure 9.1).

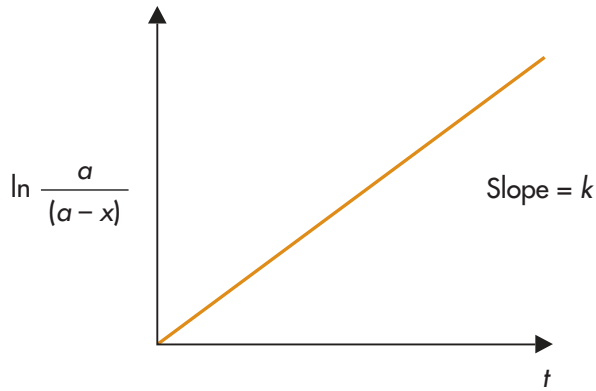

Figure 9.1 Graph of $\ln[a/(a - x)]$ vs t.

For equation (9.2), a plot of $\ln(a - x)$ vs t will yield a straight line the slope of which is negative and equal to $-k$, and the intercept with the vertical axis equal to $\ln a$ (see Figure 9.2).

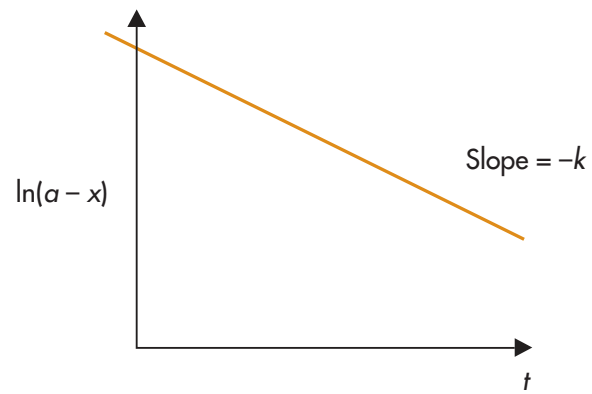

Figure 9.2 Graph of $\ln(a - x)$ vs t.

The rate constant, k, is a very important measure of a reaction rate and has the dimension of time^{-1} for a first-order process. This can be shown

from equation (9.1), where cancelling terms on the left-hand side of the equation results in no units. The right-hand side of the equation must also have no units if the equation is to be valid. The term t has the dimension of 'time', so k must have the dimension of time^{-1}. Units of 'inverse time' are hard to comprehend, but it means that k, the rate constant, gives us a measure of how much of the reaction occurs *per unit of time*, i.e. *per second*, or *per hour*, or *per day*, etc.

On a practical point, the fact that the units of concentration cancel out for a first-order reaction means that *any* physical quantity that is *proportional* to the concentration may be used in the equation in place of concentration, e.g. light absorbance or titration volume. This is very useful, since it means data measured in the laboratory can be inserted directly into the integrated rate equation.

Half-life

The half-life ($t_{\frac{1}{2}}$) of a reaction is an important term that may be derived from equation (9.1). The half-life is defined as the time taken for the concentration of reactant to fall to half its original value:

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

$$\ln \frac{a}{(a-\frac{1}{2}a)} = kt_{\frac{1}{2}}$$

$$\ln 2 = kt_{\frac{1}{2}}$$

$$t_{\frac{1}{2}} = \frac{0.693}{k} \qquad (9.3)$$

For first-order reactions (only), $t_{\frac{1}{2}}$ is independent of concentration. This means that the time taken for the reactant concentration to fall from 1 M to 0.5 M will be the same as the time taken to fall from 0.5 M to 0.25 M. This is *not* true for higher orders of reaction and occasionally this fact is used to infer that a reaction is first order.

Shelf-life

The shelf life (t_{90}) of a pharmaceutical product is the length of time the product may safely be stored on the dispensary shelf before significant decomposition occurs. This is important since, at best, drugs may

decompose to inactive products; in the worst case the decomposition may yield toxic compounds. The shelf-life is often taken to be the time for decomposition of 10% of the active drug to occur, leaving 90% of the activity. A similar expression to equation (9.3) can be obtained by substituting ln(100/90) in place of ln 2 to give

$$t_{90} = \frac{0.105}{k} \tag{9.4}$$

from which the shelf-life can easily be calculated once k, the reaction rate constant, has been determined.

Second-order reactions

For reactions of the type

$$2A \longrightarrow \text{products} \quad \text{or} \quad A + B \longrightarrow \text{products}$$

the rate of the reaction will be first order with respect to each reactant and hence second order overall. A useful integrated rate equation may be obtained by a similar process to the derivation of equation (9.1) as follows:

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

Therefore,

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

Hence,

$$\frac{1}{(a - x)} + c = kt$$

At $t = 0$, $x = 0$, therefore $1/a + c = 0$ and $c = -1/a$ to give

$$\frac{1}{(a - x)} - \frac{1}{a} = kt \tag{9.5}$$

Equation (9.5) is the equation of a straight line of the type $y - c = mx$, so that a plot of $1/(a - x)$ against t yields a straight line of slope k, with an intercept on the vertical axis of $1/a$.

Equation (9.5) is valid for second-order reactions in which the concentrations of the reactants are equal. A general second-order equation may also be derived that will apply to reactions of the type A + B $\longrightarrow$ products when [A] does not equal [B], but this is outside the scope of this book. In most cases it is possible to arrange for the concentrations of the reactants to be equal and equation (9.5) may be used.

The term k is, again, the rate constant for the reaction, but in a second-order process k has dimensions of concentration^{-1} time^{-1}. The relationship between the half-life and the second-order rate constant, k, for initial equal concentrations of reactant can be found by substituting $t = t_{\frac{1}{2}}$ into equation (9.5) as follows:

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

$$\frac{1}{(a-\frac{1}{2}a)} - \frac{1}{a} = kt_{\frac{1}{2}}$$

$$\frac{1}{\frac{1}{2}a} - \frac{1}{a} = kt_{\frac{1}{2}}$$

$$\frac{1}{a} = kt_{\frac{1}{2}}$$

$$t_{\frac{1}{2}} = \frac{\mathbf{1}}{\boldsymbol{ak}} \qquad (9.6)$$

Since k is a constant, the half-life of a second-order reaction where the initial reactant concentrations are equal is inversely proportional to a, the initial reactant concentration.

In some second-order reactions the concentration of one of the reactants is many times more than the concentration of the other, so large in fact as to be considered constant throughout the reaction. In these cases, the reaction appears to follow first-order kinetics, even though, strictly speaking, it is still a second-order process. Reactions such as these are termed *pseudo first-order* reactions. A good example is the acid- or base-catalysed hydrolysis of an ester, in which the concentration of water is so large compared to the concentration of ester as to be considered constant. The rate of the hydrolysis appears to vary only with the concentration of the ester.

Zero-order reactions

There are some reactions in which the rate of the reaction is independent of the concentration of the reactants but does depend on some other factor, such as the amount of catalyst present. These reactions are termed *zero-order* reactions, and rate equations can be derived as follows:

$$\frac{dx}{dt} = k[A]^0$$

Therefore,

$$\int dx = \int k\, dt$$

which gives

$$\boldsymbol{x = kt + c} \tag{9.7}$$

In zero-order reactions the amount of product formed varies with time so that the amount of product formed after 20 minutes will be twice that formed after 10 minutes. Reactions that follow zero-order kinetics are quite rare, but they do occur in solid-phase reactions such as release of drug from a pharmaceutical suspension.

Reaction rates and temperature

For most chemical reactions an increase in temperature will bring about an associated increase in reaction rate, which can be measured by an increase in k, the reaction rate constant. As a very rough guide, if the temperature of a reaction increases by 10°C the reaction rate will approximately double.

The Swedish chemist Arrhenius first expressed mathematically the relationship between reaction rate and temperature, namely,

$$\boldsymbol{k = Ae^{-E/RT}} \tag{9.8}$$

where A is a constant known as the *frequency factor* and is a measure of the number of collisions taking place between reactants; $e^{-E/RT}$ is the small fraction of the total number of collisions that result in a successful reaction; E is the activation energy for the reaction, i.e. the energy required to force the reactants to collide with enough energy to form a product; R is the universal gas constant ($R = 8.314\ \text{J K}^{-1}\ \text{mol}^{-1}$), which seems to crop up in almost every physical chemistry equation; and T is the temperature in kelvin.

Taking logarithms of equation (9.8) gives

$$\ln k = \ln A - \frac{E}{RT} \tag{9.9}$$

which is instantly recognisable as the equation of a straight line ($y = c - mx$). This means that if the reaction rate, k, is determined at a number of temperatures, a graph of $\ln k$ against $1/T$ (T in kelvin) will yield a straight line of slope $-E/R$ that intersects the vertical axis at $\ln A$. The activation energy, E, for the reaction may be determined from data like these.

Even more usefully, if the reaction rate k_1 is determined at a temperature T_1, and the rate k_2 is determined at a temperature T_2, then the two forms of equation (9.9) may be subtracted to give

$$\ln \frac{k_2}{k_1} = -\frac{E}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \tag{9.10}$$

This useful equation may be used to predict the reaction rate at any temperature once k_1 and E are known for temperature T_1. This type of calculation is extremely important in pharmaceutical science since it is used to predict shelf-life for medicines. Once a medicine has been manufactured, it is stored under high-stress conditions (e.g. at elevated temperature, high humidity, under strong lighting, etc.), the rates of decomposition are measured and the activation energy is calculated. From these data, the value of k may be predicted and the likely shelf-life for the medicine can be calculated for room temperature (25°C) or refrigerator temperature (4°C). Another useful point to notice is that since k enters into the graphs as $\ln k$, and into the equations as a ratio, any physical quantity that is proportional to k, such as the actual reaction rates at fixed concentrations of reactants, may be used in the equation instead of k.

Calculations using *Arrhenius plots*, such as those described above, are carried out in the pharmaceutical industry every day. It should be made clear, however, that they involve a number of assumptions. It is assumed that the linearity of the graph obtained from equation (9.9) extends to room temperature, or, mathematically, that A and E are independent of temperature. If the line cannot be extrapolated to room temperature, shelf-life predictions are invalid. Second, it is assumed that the same chemical reaction is occurring with decomposition at high temperature as at low temperature. This is usually the case, but until proven it remains an assumption in most calculations.

Tutorial example

Q *1 The reaction between aspirin and gastric acid may be followed by titrating the liberated salicylic and acetic acids with sodium hydroxide. In an experiment using equimolar amounts of reactants, the following data were obtained:*

Time (s)	*0*	*89*	*208*	*375*	*625*	*803*
[Aspirin] (mol L^{-1})	*1.6*	*1.4*	*1.2*	*1.0*	*0.8*	*0.7*

Determine the order of the reaction and determine the rate constant.

A 1 The order of a chemical reaction cannot be determined by inspection, it must be determined experimentally. In practice, this means measuring the decomposition of the compound under controlled conditions and applying each of the rate equations in turn to see which type of equation fits the data and gives the best straight line. This is what scientists term an empirical method, and what the man in the street calls 'trial and error'!

In the case of the hydrolysis of aspirin, it would be sensible to try the second-order rate equation first (especially since the question stresses that the reactant concentrations are equal). For a second-order process, equation (9.5) is valid, i.e.

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

where $(a - x)$ is the concentration of each reactant at time t, and a plot of $1/(a - x)$ vs t should yield a straight line of slope k.

This plot was carried out and a straight line was obtained with a slope of 1.0×10^{-3}. This proves that the reaction is second order with a rate constant, $k = 1.0 \times 10^{-3}$ (mol $L^{-1})^{-1}$ s^{-1}.

Problems

Q9.1 Determine the first-order rate constant for the hydrolysis of acetyl-β-methylcholine at 85°C from the information given below.

Drug] (mg mL^{-1})	9.35	7.45	4.52	3.46	1.26	0.90
t (days)	0.08	0.75	1.96	2.96	5.75	6.75

Q9.2 (a) Hydrogen peroxide solutions are normally stable, but when metal ions are added, hydrogen peroxide decomposes:

$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

In a solution containing $FeCl_3$, the concentration of H_2O_2 varied as follows:

Time (s)	0	0 27	52	86	121	160	218
$[H_2O_2]$ (M)	0.80	0.72	0.64	0.56	0.48	0.40	0.32

Using these data, determine the order of the reaction with respect to peroxide, and the value of the rate constant (include appropriate units).

(b) Discuss how you would use kinetic data obtained from monitoring the degradation of a drug to construct an Arrhenius plot. How could you use this plot to determine the frequency factor and activation energy for the reaction?

(c) For a first-order reaction, deduce the units for the frequency factor and activation energy.

(Answers to problems can be found on p. 266.)