
Chapter 1

Basic Principles of Chemical Kinetics

1.1 Symbols, terminology and abbreviations

This book follows as far as possible the recommendations of the International Union of Biochemistry and Molecular Biology. However, as these allow some latitude and in any case do not cover all of the cases that we shall need, it is useful to begin by noting some points that apply generally in the book. First of all, it is important to recognize that a chemical substance and its concentration are two different entities and need to be represented by different symbols. The recommendations allow square brackets around the chemical name to be used without definition for its concentration, so [glucose] is the concentration of glucose, $[A]$ is the concentration of a substance A , and so on. In this book I shall use this convention for names that consist of more than a single letter, but it has the disadvantage that the profusion of square brackets can lead to forbiddingly complicated equations in enzyme kinetics (see some of the equations in Chapter 8, for example, and imagine how they would look with square brackets). Two simple alternatives are possible: one is just to put the name in italics, so the concentration of A is A , for example, and this accords well with the standard convention that chemical names are written in roman (upright) type and algebraic symbols are written in italics. However, experience

International Union of Biochemistry (1982) "Symbolism and terminology in enzyme kinetics" *European Journal of Biochemistry* **128**, 281–291

Chapter 8, pages 189–226

shows that many readers barely notice whether a particular symbol is roman or italic, and so it discriminates less well than one would hope between the two kinds of entity. For this reason I shall use the lower-case italic letter that corresponds to the symbol for the chemical entity, so a is the concentration of A, for example. If the chemical symbol has any subscripts, these apply unchanged to the concentration symbol, so a_0 is the concentration of A_0 , for example. Both of these systems (and others) are permitted by the recommendations as long as each symbol is defined when first used. This provision is satisfied in this book, and it is good to follow it in general, because almost nothing that authors consider obvious is perceived as obvious by all their readers. In the problems at the ends of the chapters, incidentally, the symbols may not be the same as those used in the corresponding chapters: this is intentional, because in the real world one cannot always expect the questions that one has to answer to be presented in familiar terms.

As we shall see, an enzyme-catalyzed reaction virtually always consists of two or more steps, and as we shall need symbols to refer to the different steps it is necessary to have some convenient indexing system to show which symbol refers to which step. The recommendations do not impose any particular system, but, most important, they do require the system in use to be stated. Because of the different ways in which, for example, the symbol k_2 has been used in the biochemical literature one should never assume in the absence of a clear definition what is intended. In this book I use the system preferred by the recommendations: for a reaction of n steps, these are numbered 1, 2 ... n ; lower-case italic k with a positive subscript refers to the kinetic properties of the forward step corresponding to the subscript, for example, k_2 refers to the forward direction of the second step; the same with a negative subscript refers to the corresponding reverse reaction, for example, k_{-2} for the second step; a capital italic K with a subscript refers to the thermodynamic (equilibrium) properties of the whole step and is typically the ratio of the two kinetic constants, for example, $K_2 = k_2/k_{-2}$.

The policy regarding the use of abbreviations in this book can be stated very simply: *there are no abbreviations in this book* (other than in verbatim quotations and the index, which needs to include the entries readers expect to find). Much of the modern literature is rendered virtually unintelligible to nonspecialist readers by a profusion of unnecessary abbreviations. They save little space, and little work (because with

modern word-processing equipment it takes no more than a few seconds to expand all of the abbreviations that one may have found it convenient to use during preparation), but the barrier to comprehension that they represent is formidable. A few apparent exceptions (like “ATP”) are better regarded as standardized symbols than as abbreviations, especially because they are more easily understood by most biochemists than the words they stand for.

1.2 Order of a reaction

1.2.1 Order and molecularity

Chemical kinetics as a science began in the middle of the 19th century, when Wilhelmy was apparently the first to recognize that the rate at which a chemical reaction proceeds follows definite laws, but although his work paved the way for the law of mass action of Waage and Guldberg, it attracted little attention until it was taken up by Ostwald towards the end of the century, as discussed by Laidler. Wilhelmy realized that chemical rates depended on the concentrations of the reactants, but before considering some examples we need to examine how chemical reactions can be classified.

One way is according to the *molecularity*, which defines the number of molecules that are altered in a reaction: a reaction $A \rightarrow P$ is *unimolecular* (sometimes called *monomolecular*), and a reaction $A + B \rightarrow P$ is *bimolecular*. One-step reactions of higher molecularity are extremely rare, if they occur at all, but a reaction $A + B + C \rightarrow P$ would be *trimolecular* (or *termolecular*). Alternatively one can classify a reaction according to its *order*, a description of its kinetics that defines how many concentration terms must be multiplied together to get an expression for the rate of reaction. Hence, in a *first-order reaction* the rate is proportional to one concentration; in a *second-order reaction* it is proportional to the product of two concentrations or to the square of one concentration; and so on.

For a simple reaction that consists of a single step, or for each step in a complex reaction, the order is usually the same as the molecularity (though this may not be apparent if one concentration, for example that of the solvent if it is also a reactant, is so large that it is effectively constant). However, many reactions consist of sequences of unimolecular and bimolecular steps, and the molecularity of the complete reaction need not be the same as its order. Indeed, a complex reaction often has no meaningful order, as the overall rate often cannot

L. F. Wilhelmy (1850) “Über das Gesetz, nach welchem die Einwirkung der Säuren auf Rohrzucker stattfindet” *Poggendorff's Annalen der Physik und Chemie* **81**, 413–433, 499–526

P. Waage and C. M. Guldberg (1864) “Studier over Affiniteten” *Forhandlinger: Videnskabs-Selskabet i Christiania*, 35–40, 111–120. There is an English translation by H. I. Abrash at <http://tinyurl.com/3levsg1>

K. J. Laidler (1993) *The World of Physical Chemistry*, pages 232–289, Oxford University Press, Oxford

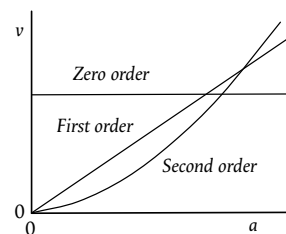


Figure 1.1. Order of reaction. When a reaction is of first order with respect to a reactant A the rate is proportional to its concentration a . If it is of second order the rate is proportional to a^2 ; if it is of zero order it does not vary with a .

be expressed as a product of concentration terms. As we shall see in later chapters, this is almost universal in enzyme kinetics, where not even the simplest enzyme-catalyzed reactions have simple orders. Nonetheless, the individual steps in enzyme-catalyzed reactions nearly always do have simple orders, usually first or second order, and the concept of order is important for understanding enzyme kinetics. The binding of a substrate molecule to an enzyme molecule is a typical example of a second-order bimolecular reaction in enzyme kinetics, whereas conversion of an enzyme–substrate complex into products or into another intermediate is a typical example of a first-order unimolecular reaction.

1.2.2 First-order kinetics

The rate v of a first-order reaction $A \rightarrow P$ can be expressed as

$$v = \frac{dp}{dt} = -\frac{da}{dt} = ka = k(a_0 - p) \quad (1.1)$$

in which a and p are the concentrations of A and P respectively at any time t , k is a *first-order rate constant* and a_0 is a constant. As we shall see throughout this book, the idea of a *rate constant*¹ is fundamental in all varieties of chemical kinetics. The first two equality signs in the equation represent alternative definitions of the rate v : because every molecule of A that is consumed becomes a molecule of P, it makes no difference to the mathematics whether the rate is defined in terms of the appearance of product or disappearance of reactant. It may make a difference experimentally, however, because experiments are not done with perfect accuracy, and in the early stages of a reaction the relative changes in p are much larger than those in a (Figure 1.2). For this reason it will usually be more accurate to measure increases in p than decreases in a .

The third equality sign in the equation is the one that specifies that this is a first-order reaction, because it states that the rate is proportional to the concentration of reactant A.

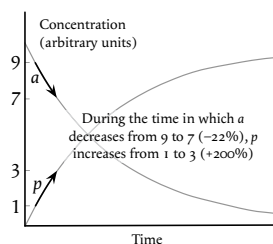


Figure 1.2. Relative changes in concentration. For a stoichiometric reaction $A \rightarrow P$, any change in a is matched by an opposite change in p . However, in the early stages of a reaction the *relative* increases in p are much larger than the relative changes in a .

¹Some authors, especially those with a strong background in physics, object to the term “rate constant” (preferring “rate coefficient”) for quantities like k in equation 1.1 and for many similar quantities that will occur in this book, on the perfectly valid grounds that they are not constant, because they vary with temperature and with many other conditions. However, the use of the word “constant” to refer to quantities that are constant only under highly restricted conditions is virtually universal in biochemical kinetics (and far from unknown in chemical kinetics), and it is hardly practical to abandon this usage in this book. See also the discussion at the end of Section 10.4.3.

Finally, if the time zero is defined in such a way that $a = a_0$ and $p = 0$ when $t = 0$, the stoichiometry allows the values of a and p at any time to be related according to the equation $a + p = a_0$, thereby allowing the last equality in the equation.

Equation 1.1 can readily be integrated by separating the two variables p and t , bringing all terms in p to the left-hand side and all terms in t to the right-hand side:

$$\int \frac{dp}{a_0 - p} = \int k dt$$

therefore

$$-\ln(a_0 - p) = kt + \alpha$$

in which α , the constant of integration, can be evaluated by noting that there is no product at the start of the reaction, so $p = 0$ when $t = 0$. Then $\alpha = -\ln(a_0)$, and so

$$\ln\left(\frac{a_0 - p}{a_0}\right) = -kt \quad (1.2)$$

Taking exponentials of both sides we have

$$\frac{a_0 - p}{a_0} = e^{-kt}$$

which can be rearranged to give

$$p = a_0(1 - e^{-kt}) \quad (1.3)$$

Notice that the constant of integration α was included in this derivation, evaluated and found to be nonzero. Constants of integration must always be included and evaluated when integrating kinetic equations; they are rarely found to be zero.

Inserting $p = 0.5a_0$ into equation 1.3 at a time $t = t_{0.5}$ known as the *half-time* allows us to calculate $kt_{0.5} = \ln 2 = 0.693$, so $t_{0.5} = 0.693/k$. This value is independent of the value of a_0 , so the time required for the concentration of reactant to decrease by half is a constant, for a first-order process, as illustrated in Figure 1.3. The half-time is not a constant for other orders of reaction.

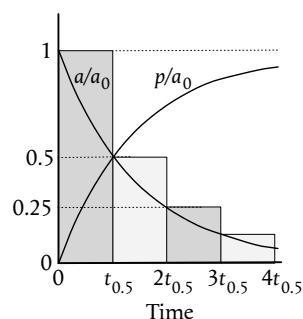


Figure 1.3. First-order decay. The *half-time* $t_{0.5}$ is the time taken for the reactant concentration to decrease by half from any starting point. For a first-order reaction, but not for other orders of reaction, it remains constant as the reaction proceeds.

1.2.3 Second-order kinetics

The commonest type of bimolecular reaction is one of the form $A + B \rightarrow P + Q$, in which two different kinds of molecule

A and B react to give products. In this example the rate is likely to be given by a second-order expression of the form

$$v = \frac{dp}{dt} = kab = k(a_0 - p)(b_0 - p)$$

in which k is now a *second-order rate constant*.² Again, integration is readily achieved by separating the two variables p and t :

$$\int \frac{dp}{(a_0 - p)(b_0 - p)} = \int k dt$$

For readers with limited mathematical experience, the simplest and most reliable method for integrating the left-hand side of this equation is to look it up in a standard table of integrals.³ It may also be done by multiplying both sides of the equation by $(b_0 - a_0)$ and separating the left-hand side into two simple integrals:

$$\int \frac{dp}{a_0 - p} - \int \frac{dp}{b_0 - p} = \int (b_0 - a_0)k dt$$

Hence

$$-\ln(a_0 - p) + \ln(b_0 - p) = (b_0 - a_0)kt + \alpha$$

Putting $p = 0$ when $t = 0$ we find $\alpha = \ln(b_0/a_0)$, and so

$$\ln \left[\frac{a_0(b_0 - p)}{b_0(a_0 - p)} \right] = (b_0 - a_0)kt$$

or

$$\frac{a_0(b_0 - p)}{b_0(a_0 - p)} = e^{(b_0 - a_0)kt} \quad (1.4)$$

A special case of this result is important: if a_0 is negligible compared with b_0 , then $(b_0 - a_0) \approx b_0$; p can never exceed a_0 , on account of the stoichiometry of the reaction, and so $(b_0 - p) \approx b_0$. Introducing both approximations, equation 1.4 can be simplified as follows:

$$\frac{a_0}{b_0(a_0 - p)} = e^{kb_0t}$$

²Conventional symbolism does not indicate the order of a rate constant. For example, it is common practice to illustrate simple enzyme kinetics with a mechanism in which k_1 is a second-order rate constant and k_2 is a first-order rate constant: there is no way to know this from the symbols alone, it is important to define each rate constant when it is first used.

³The integrals listed in Table 1.1 are sufficient for the purposes of this chapter (and the last one will not be needed until Chapter 7).

Table 1.1. Standard integrals

$\int a dx = ax$
$\int a \cdot f(x) dx =$ $a \int f(x) dx$
$\int x dx = \frac{1}{2}x^2$
$\int x^2 dx = \frac{1}{3}x^3$
$\int x^n dx = \frac{x^{n+1}}{n+1}$ for $n \neq -1$
$\int \frac{1}{x} dx = \ln x$
$\int e^x dx = e^x$
$\int \frac{dx}{a + bx} = \frac{1}{b} \ln(a + bx)$
$\int \frac{x dx}{a + bx} =$ $\frac{a + bx - a \ln(a + bx)}{b^2}$

1. In all examples, x is variable; a , b and n are constants and $f(x)$ is a function of x .

2. Standard tables usually omit the constant of integration (assuming that users know that it must be added).

3. Tables intended primarily for the use of mathematicians often write $\log x$ where a biochemist would expect $\ln x$.

and, remembering that $1/e^{kb_0t} \equiv e^{-kb_0t}$, this can be rearranged to read

$$p = a_0(1 - e^{-kb_0t})$$

which has exactly the same form as equation 1.3, the equation for a first-order reaction. This type of reaction is known as a *pseudo-first-order reaction*, and kb_0 is a *pseudo-first-order rate constant*. Pseudo-first-order conditions occur naturally when one of the reactants is the solvent, as in most hydrolysis reactions, but it is also advantageous to create them deliberately, to simplify evaluation of the rate constant (Section 1.5).

§ 1.5, pages 11–13

1.2.4 Third-order kinetics

A trimolecular reaction, such as $A + B + C \rightarrow P + \dots$, does not normally consist of a single trimolecular step involving a three-body collision, which would be inherently unlikely; consequently it is not usually third-order. Instead it is likely to consist of two or more *elementary steps*, such as $A + B \rightleftharpoons X$ followed by $X + C \rightarrow P$. In some reactions the kinetic behavior as a whole is largely determined by the rate constant of the step with the smaller rate constant, accordingly known as the *rate-limiting step* (or, more objectionably, as the *rate-determining step*).⁴ When there is no clearly defined rate-limiting step the rate equation is typically complex, with no integral order. Some trimolecular reactions do display third-order kinetics, however, with $v = kabc$, where k is now a *third-order rate constant*, but it is not necessary to assume a three-body collision to account for third-order kinetics. Instead, we can assume a two-step mechanism, as before but with the first step rapidly reversible, so that the concentration of X is given by $x = Kab$, where K is the equilibrium constant for binding of A to B, the association constant of X (Figure 1.4). The rate of reaction is then the rate of the slow second step:

$$v = k'xc = k'Kab c$$

where k' is the second-order rate constant for the second step. Hence the observed third-order rate constant is actually the product of a second-order rate constant and an equilibrium constant.

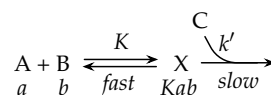


Figure 1.4. Third-order kinetics. A reaction can be third-order overall without requiring any third-order step in the mechanism, if a rapid equilibrium maintains an intermediate X at a concentration Kab and this reacts slowly with the third reactant C in a second-order reaction with rate constant k' .

⁴These terms are widespread in chemistry, but they involve some conceptual confusion, as discussed in Section 14.1.3, and as far as possible are best avoided.

§ 14.1.3, pages 383–385

1.2.5 Zero-order kinetics

Some reactions are observed to be of *zero order*, with a constant rate, independent of the concentration of reactant. If a reaction is zero order with respect to only one reactant, this may simply mean that the reactant enters the reaction after the rate-limiting step. However, some reactions are zero-order overall, which means that they are independent of all reactant concentrations. These are invariably catalyzed reactions and occur if every reactant is present in such large excess that the full potential of the catalyst is realized. Enzyme-catalyzed reactions commonly approach zero-order kinetics at very high reactant concentrations.

1.2.6 Determination of the order of a reaction

The simplest means of determining the order of a reaction is to measure the rate v at different concentrations a of the reactants. A plot of $\ln v$ against $\ln a$ is then a straight line with slope equal to the order. As well as the *overall order* it is useful to know the order with respect to each reactant, which can be found by altering the concentration of each reactant separately, keeping the other concentrations constant. The slope of the line is then equal to the order with respect to the variable reactant. For example, if the reaction is second-order in A and first-order in B,

$$v = ka^2b$$

then

$$\ln v = \ln k + 2 \ln a + \ln b$$

Hence a plot of $\ln v$ against $\ln a$ (with b held constant) has a slope of 2 (Figure 1.5), and a plot of $\ln v$ against $\ln b$ (with a held constant) has a slope of 1 (Figure 1.6). If the plots are drawn with the slopes measured from the *progress curve* (a plot of concentration against time), the concentrations of all the reactants change with time. Therefore, if valid results are to be obtained, either the initial concentrations of the reactants must be in stoichiometric ratio, in which event the overall order is found, or (more usually) the “constant” reactants must be in large excess at the start of the reaction, so that the changes in their concentrations are insignificant. If neither of these alternatives is possible or convenient, the rates must be obtained from a set of measurements of the slope at zero time, that is to say measurements of initial rates. This method

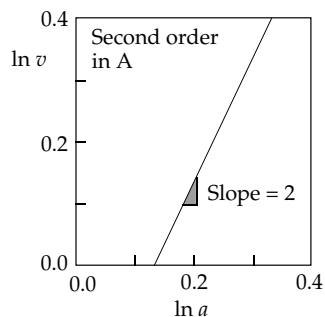


Figure 1.5. Determination of the order of reaction. The line is drawn for a reaction that is second-order in a reactant A (and first-order in another reactant B, but this is not evident from the plot) so the slope of the line is 2. The appearance of the plot (though not the numerical values) would be the same if logarithms to base 10 or any other base were used instead of natural logarithms, provided that the same changes were made in both coordinates.

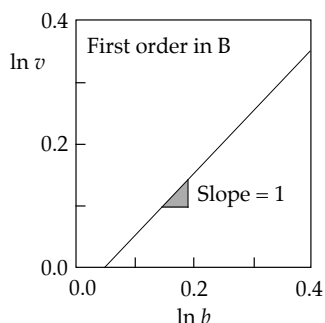


Figure 1.6. Determination of the order of reaction for a reaction that is first-order in a reactant B. The slope of the line is 1.

is usually preferable for kinetic measurements of enzyme-catalyzed reactions, because the progress curves of enzyme-catalyzed reactions often do not rigorously obey simple rate equations for extended periods of time. The progress curve of an enzyme-catalyzed reaction (Section 2.9) often requires a more complicated equation than the integrated form of the rate equation derived for the initial rate, because of progressive loss of enzyme activity, inhibition by accumulating products and other effects.

§2.9, pages 63–71

1.3 Dimensions of rate constants

Dimensional analysis provides a quick and versatile technique for detecting algebraic mistakes and checking results. It depends on the existence of a few simple rules governing the permissible ways of combining quantities of different dimensions, and on the frequency with which algebraic errors result in dimensionally inconsistent expressions. Concentrations can be expressed in M (or $\text{mol} \cdot \text{l}^{-1}$), and reaction rates in $M \cdot \text{s}^{-1}$. In an equation that expresses a rate v in terms of a concentration a as $v = ka$, therefore, the rate constant k must be expressed in s^{-1} if the left- and right-hand sides of the equation are to have the same dimensions. All first-order rate constants have the dimensions of time^{-1} , and by a similar argument second-order rate constants have the dimensions of $\text{concentration}^{-1} \times \text{time}^{-1}$ (Figure 1.7), third-order rate constants have the dimensions of $\text{concentration}^{-2} \times \text{time}^{-1}$, and zero-order rate constants have the dimensions of $\text{concentration} \times \text{time}^{-1}$.

Knowledge of the dimensions of rate constants allows the correctness of derived equations to be checked easily: the left- and right-hand sides of any equation (or inequality) must have the same dimensions, and all terms in a summation must have the same dimensions. For example, if $(1 + t)$ occurs in an equation, where t has the dimensions of time, then the equation is incorrect, even if the “1” is intended to represent a time that happens to have the numerical value of 1. Rather than mixing dimensioned constants and variables in an expression in this way it is better to write the unit after the number, $(1 \text{ s} + t)$ for example, or to give the constant a symbol, $(t_0 + t)$ for example, with a note in the text defining t_0 as 1 s. Although both alternatives appear more clumsy than just writing $(1 + t)$ they avoid confusion. Section 9.6.1 contains an example, equation 9.12, where clarity requires inclusion of units inside an equation.

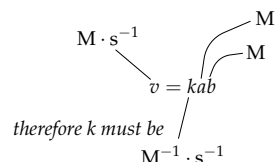


Figure 1.7. Units of rate constants. If a rate $v = kab$ is measured in $M \cdot \text{s}^{-1}$ and the two concentrations a and b are measured in M , then the left- and right-hand sides of the equation can only have the same units if the second-order rate constant k is measured in $M^{-1} \cdot \text{s}^{-1}$.

§9.6.1, pages 242–244

$$\frac{k_{1H}}{k_{2H}} = e^{4.8 \text{ kJ mol}^{-1} / RT}$$

To include the value of a dimensioned quantity in an equation (4.8 kJ/mol in this example, which is simplified from equation 9.12 on page 243) one must include the units explicitly in the equation, or else introduce an algebraic symbol defined as having the value concerned.

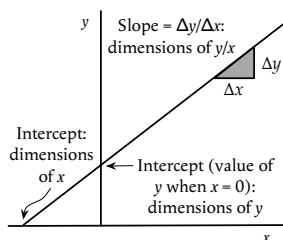


Figure 1.8. Application of dimensional analysis to graphs. The intercept on the ordinate is the value of y when $x = 0$, and has the same dimensions as y ; The intercept on the abscissa is the value of x when $y = 0$, and has the same dimensions as x . The slope is an increment in y divided by the corresponding increment in x , and has the dimensions of y/x .

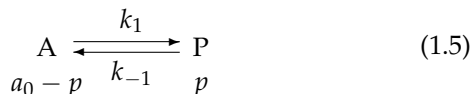
Quantities of different dimensions can be multiplied or divided, but must not be added or subtracted. Thus, if k_1 is a first-order rate constant and k_2 is a second-order rate constant, a statement such as $k_1 \gg k_2$ is meaningless, just as $5 \text{ g} \gg 25^\circ \text{C}$ is meaningless. However, a pseudo-first-order rate constant such as $k_2 a$ has the dimensions of concentration $^{-1} \times \text{time}^{-1} \times \text{concentration}$, which simplifies to time^{-1} ; it therefore has the dimensions of a first-order rate constant, and *can* be compared with other first-order rate constants.

Another major principle of dimensional analysis is that one must not use a dimensioned quantity as an exponent or take its logarithm. For example, e^{-kt} is permissible, if k is a first-order rate constant, but e^{-t} is not. An apparent exception is that it is often convenient to take the logarithm of what appears to be a concentration, for example when pH is defined as $-\log[\text{H}^+]$. The explanation is that the definition is not strictly accurate and to be dimensionally correct one should define pH as $-\log[\text{H}^+]/[\text{H}^+]_0$, where $[\text{H}^+]_0$ is the value of $[\text{H}^+]$ in the standard state, corresponding to $\text{pH} = 0$. As $[\text{H}^+]_0$ has a numerical value of 1 it is usually omitted from the definition. Whenever one takes the logarithm of a dimensioned quantity in this way, a standard state is implied whether stated explicitly or not.

Dimensional analysis is particularly useful as an aid to remembering the slopes and intercepts of commonly used plots, and the rules are simple: any intercept must have the same dimensions as whatever variable is plotted along the corresponding axis, and a slope must have the dimensions of the ordinate (y) divided by those of the abscissa (x). These rules are illustrated in Figure 1.8.

1.4 Reversible reactions

All chemical reactions are reversible in principle, and for many the reverse reaction is readily observable in practice as well, and must be allowed for in the rate equation:



In this case,

$$v = \frac{dp}{dt} = k_1(a_0 - p) - k_{-1}p = k_1 a_0 - (k_1 + k_{-1})p$$

This differential equation is of exactly the same form as equation 1.1, and can be solved in the same way:

$$\int \frac{dp}{k_1 a_0 - (k_1 + k_{-1})p} = \int dt$$

Therefore

$$\frac{\ln[k_1 a_0 - (k_1 + k_{-1})p]}{-(k_1 + k_{-1})} = t + \alpha$$

Setting $p = 0$ when $t = 0$ gives $\alpha = -\ln(k_1 a_0)/(k_1 + k_{-1})$, and so

$$\ln \left[\frac{k_1 a_0 - (k_1 + k_{-1})p}{k_1 a_0} \right] = -(k_1 + k_{-1})t$$

Taking exponentials of both sides, we have

$$\frac{k_1 a_0 - (k_1 + k_{-1})p}{k_1 a_0} = e^{-(k_1 + k_{-1})t}$$

which can be rearranged to give

$$p = \frac{k_1 a_0 [1 - e^{-(k_1 + k_{-1})t}]}{k_1 + k_{-1}} = p_\infty [1 - e^{-(k_1 + k_{-1})t}] \quad (1.6)$$

where $p_\infty = k_1 a_0 / (k_1 + k_{-1})$. This is the value of p after infinite time, because the exponential term approaches zero as t becomes large. The expected behavior is illustrated in Figure 1.9.

1.5 Determination of first-order rate constants

It is common for a reaction to be first-order in every reactant, and it is then often possible to carry it out under pseudo-first-order conditions overall by keeping every reactant except one in large excess. In many practical situations, therefore, the problem of determining a rate constant can be reduced to the problem of determining a first-order rate constant. We have seen in equation 1.3 that for a simple first-order reaction,

$$p = a_0(1 - e^{-kt})$$

and in the more general case of a reversible reaction, equation 1.6:

$$p = p_\infty [1 - e^{-(k_1 + k_{-1})t}]$$

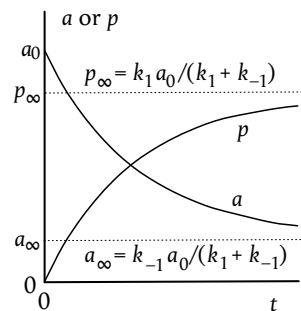


Figure 1.9. First-order decay for a reversible reaction

So

$$p_{\infty} - p = p_{\infty} e^{-(k_1 + k_{-1})t} \quad (1.7)$$

Therefore,

$$\ln(p_{\infty} - p) = \ln p_{\infty} - (k_1 + k_{-1})t$$

Thus a plot of $\ln(p_{\infty} - p)$ against t gives a straight line of slope $-(k_1 + k_{-1})$ (Figure 1.10). Before pocket calculators became universally available this was usually expressed in terms of logarithms to base 10:

$$\log(p_{\infty} - p) = \log p_{\infty} - \frac{(k_1 + k_{-1})t}{2.303}$$

so that a plot of $\log(p_{\infty} - p)$ against t gives a straight line of slope $-(k_1 + k_{-1})/2.303$. However, it is nowadays just as convenient to retain the form in terms of natural logarithms.⁵

Guggenheim pointed out a major objection to this plot: it depends heavily on an accurate value of p_{∞} . In the general case of a reversible reaction with p_{∞} different from a_0 an accurate value of p_{∞} is difficult to obtain, and even in the special case of an irreversible reaction with p_{∞} identical to a_0 the instantaneous concentration of A at zero time may be difficult to measure accurately. Guggenheim suggested measuring two sets of values p_i and p'_i at times t_i and t'_i , such that every $t'_i = t_i + \tau$, where τ is a constant. Then, from equation 1.7,

$$p_{\infty} - p_i = p_{\infty} e^{-(k_1 + k_{-1})t_i} \quad (1.8)$$

$$p_{\infty} - p'_i = p_{\infty} e^{-(k_1 + k_{-1})(t_i + \tau)} \quad (1.9)$$

By subtraction,

$$p'_i - p_i = p_{\infty} [1 - e^{-(k_1 + k_{-1})\tau}] e^{-(k_1 + k_{-1})t_i}$$

Taking logarithms,

$$\ln(p'_i - p_i) = \ln p_{\infty} + \ln[1 - e^{-(k_1 + k_{-1})\tau}] - (k_1 + k_{-1})t_i$$

⁵An argument could be made for dispensing with common logarithms (to base 10) altogether in modern science, as they are now virtually never used as an aid to arithmetic. However, this will hardly be practical as long as the pH scale continues to be used, and in historical references, such as that in the legend of Figure 2.3, it would be incorrect to imply that natural logarithms were used if they were not. Finally, when graphs need to span several orders of magnitude (as in Figure 2.13) it is much easier for the reader to interpret a scale marked in decades than in powers of e . Otherwise, however, there usually is no good reason to use common logarithms, and then, as in Figures 1.5 and 6, they are replaced with natural logarithms.

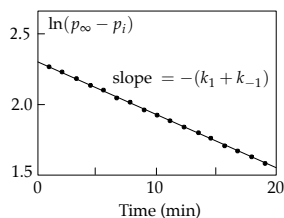


Figure 1.10. Naive approach to determining a first-order rate constant. This plot is unsatisfactory, because it depends too much on an accurate value of p_{∞} , the concentration of product after infinite time.

E. A. Guggenheim (1926) "On the determination of the velocity constant of a unimolecular reaction" *Philosophical Magazine, Series VII* **2**, 538–543

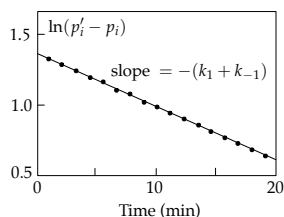


Figure 1.11. The Guggenheim plot. This plot allows a first-order rate constant to be determined without requiring an accurate value for the degree of reaction at equilibrium. Symbols are as follows: p , p' , concentrations of product at times t and $t + \tau$ respectively, where τ is a constant.

This has the form

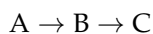
$$\ln(p'_i - p_i) = \text{constant} - (k_1 + k_{-1})t_i$$

So a plot of $\ln(p'_i - p_i)$ against t_i gives a straight line of slope $-(k_1 + k_{-1})$, as illustrated in Figure 1.11. It is known as a *Guggenheim plot*, and does not require an estimate of p_∞ . As k_1/k_{-1} is equal to the equilibrium constant, which can be estimated independently, the values of the individual rate constants k_1 and k_{-1} can be calculated from the two combinations.

The Guggenheim plot is insensitive to deviations from first-order kinetics: it can give an apparently good straight line even if first-order kinetics are not accurately obeyed. For this reason it should not be used to determine the order of reaction, which should be established independently. The same comment applies to the related Kézdy–Swinbourne plot, the subject of Problem 1.3 at the end of this chapter.

1.6 The steady state

All of the chemical processes considered to this point have been single-step reactions, but reality is not so simple, and this is particularly important for considering enzyme-catalyzed reactions, because these are essentially never single-step reactions. A reaction of more than one step, such as



usually does not have simple first-order kinetics, even if it is unimolecular overall (as this one is), and similar considerations apply to reactions that are bimolecular overall, and to reactions with more than two steps.

Nonetheless, in conditions where the concentration of intermediate is always very small the behavior can be simple. In such conditions a reaction may reach a state in which the concentration of intermediate does not change perceptibly during significant periods of time. The general idea is quite familiar from everyday observation of the flow of water in a basin when the outlet is left open. Initially (Figure 1.12) the level of water in the basin is too small to bring the pressure at the outlet to a value sufficient to drive the water out as fast as it enters, so the level must rise. Once the necessary pressure is reached the water flows out as fast as it enters (Figure 1.13) and the level remains constant as long as the

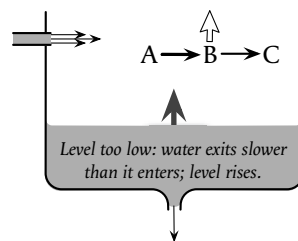


Figure 1.12. Approach to a steady state. In a reaction $A \rightarrow B \rightarrow C$, the concentration of the intermediate B rises if $A \rightarrow B$ proceeds faster than $B \rightarrow C$. However, as the rate of the second reaction increases with the concentration of B it increases in these conditions. The same can be observed in a tank when water flows in faster than it flows out.

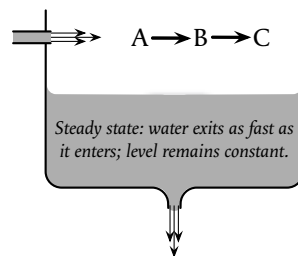


Figure 1.13. Steady state. Once the concentration of B is sufficient to drive the reaction $B \rightarrow C$ as fast as $A \rightarrow B$ it will remain constant, and the system will be in a *steady state*.

D. L. Chapman and L. K. Underhill (1913) "The interaction of chlorine and hydrogen: the influence of mass" *Journal of the Chemical Society (Transactions)* **103**, 496–508

M. Bodenstein (1913) "Eine Theorie der photochemischen Reaktionsgeschwindigkeiten" *Zeitschrift für Physikalische Chemie* **85**, 329–397

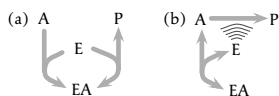
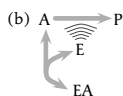


Figure 1.14. (a) Fulhame supposed that a catalyst E would first react with a reactant A to produce a complex EA that would regenerate the original catalyst E at the same time as releasing product P . This is essentially the modern view of catalysis, but (b) Henri also examined the possibility that despite forming a complex the catalytic effect was due to action of the free catalyst on the reaction.



ELIZABETH FULHAME. Almost all that is known of Elizabeth Fulhame is derived from her book *An Essay on Combustion*, which she published privately in 1794. She appears to have been the wife of Dr Thomas Fulhame, a physician who obtained his doctorate from the University of Edinburgh on the basis of a study of puerperal fever. The interest of her work for enzymology lies not only in her description of catalysis, a generation before Berzelius, but also in the emphasis that she placed on the role of water and in the fact that she was possibly the first to realize that a chemical reaction might require more than one step. She was a pioneer in the study of the effect of light on silver salts, and her discovery of photo-reduction marks a first step for developing photography.

J. J. Berzelius (1836) "Quelques idées sur une nouvelle force agissant dans les combinaisons des corps organiques" *Annales de Chimie et de Physique* **61**, 146–151

W. P. Jencks (1969) *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York

external conditions remain constant. Notice that this is *not* an equilibrium, because there is continuous unidirectional flow through the system; instead it is a *steady state*. If you are not convinced you can readily verify that a basin of water will behave as described.

Although we have assumed here that the steady state is reached from below—either a low concentration of intermediate or a low level of water—it is also possible, though less likely in simple reactions, for the initial concentration of intermediate to be higher than the steady-state value, and in this case it will decrease until the same steady state is reached.

The idea of a steady state was introduced by Chapman and Underhill, and developed by Bodenstein in particular. As we shall see in later chapters, it is absolutely crucial in the analysis of enzyme catalysis, because enzyme-catalyzed reactions are very often studied in conditions where the enzyme concentration is very small compared with the concentrations of the reactants, and this implies that the concentrations of all intermediates in the process are also very small.

1.7 Catalysis

To this point we have discussed the dependence of reaction rates on concentrations as if the only concentrations that needed to be considered were those of the reactants, but this is obviously too simple: more than two centuries ago Fulhame noted that many reactions would not proceed at a detectable rate unless the mixture contained certain necessary nonreactant components (most notably water). In a major insight that did not become generally adopted in chemistry until many years later, she realized that her observation was most easily interpreted by supposing that such components were consumed in the early stages of the reaction and regenerated at the end.

Fulhame's work was largely forgotten by the time that Berzelius introduced the term *catalysis* for this sort of behavior. He considered it to be an "only rarely observed force", unlike Fulhame, who had come to the opposite conclusion that water was necessary for virtually all reactions. Both points of view are extreme, of course, but at least in enzyme chemistry the overwhelming majority of known reactions do require water. To a considerable degree the study of enzyme catalysis is the study of catalysis in aqueous solution, and as the relevant terminology will be introduced later in the book

when we need it, there is little to add here, beyond remarking that despite its age the classic book by Jencks remains an excellent source of general information on catalysis in chemistry and biochemistry, for readers who need more emphasis on chemical mechanisms than is found in the present book.

Fulhame's view that a catalyst reacts in a cyclic fashion, consumed in one step of reaction, and regenerated in a later one (Figure 1.14a), is now generally accepted as an explanation of catalysis, but even at the beginning of the 20th century this was not fully understood, and Henri discussed the possibility that an enzyme might form a complex with its substrate but that this complex was not part of the reaction cycle; instead, the free enzyme might act on the substrate, perhaps by emitting some sort of radiation, as suggested by Barendrecht, and shown in Figure 1.14b. These ideas are completely obsolete, though they are still occasionally discussed, for example by Schnell and co-workers, but they led Henri to enunciate a principle, now called *homeomorphism*, that remains vital for kinetic analysis: the fact that a particular equation generates an equation consistent with experimental observations does not demonstrate that the equation is correct, because two or more mechanisms may lead to indistinguishable kinetic equations.

1.8 The influence of temperature and pressure on rate constants

1.8.1 The Arrhenius equation

From the earliest studies of reaction rates, it has been evident that they are profoundly influenced by temperature. The most elementary consequence of this is that the temperature must always be controlled if meaningful results are to be obtained from kinetic experiments. However, with care, one can use temperature much more positively and, by carrying out measurements at several temperatures, deduce important information about reaction mechanisms.

The studies of van 't Hoff and Arrhenius form the starting point for all modern theories of the temperature dependence of rate constants. Harcourt had earlier noted that the rates of many reactions approximately doubled for each 10°C rise in temperature, but van 't Hoff and Arrhenius attempted to find a more exact relationship by comparing kinetic observations with the known properties of equilibrium constants. Any

V. Henri (1903) *Lois Générales de l'Action des Diastases*, Hermann, Paris

H. P. Barendrecht (1913) "Enzyme action, facts and theory" *Biochemical Journal* 7, 549–561

S. Schnell, M. J. Chappell, N. O. Evans and M. R. Roussel (2006) "The mechanism indistinguishability problem in enzyme kinetics: the single-enzyme single-substrate reaction as a case study" *Comptes rendus Biologies* 329, 51–61

S VANTE AUGUST ARRHENIUS (1859–1927) was born in Vik, in an agricultural district of Sweden, but his family moved to Uppsala when he was very young. He was educated at Uppsala but became Professor of Physics at Stockholm's Högskola, and later Rector. In the context of this book he is mainly known for the equation that bears his name, but his primary interest was the properties of ions in solution. A man of broad interests, he wrote books of popular science devoted to such topics as the evolution of stars and the treatment of smallpox.

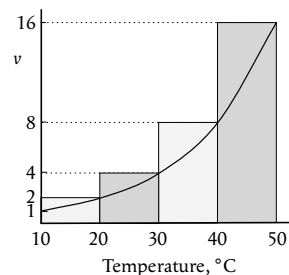


Figure 1.15. In the absence of complications rates of reaction typically increase by a factor of about 2 with each 10 °C increase in temperature.

equilibrium constant K varies with the absolute temperature T in accordance with the van 't Hoff equation,

$$\frac{d \ln K}{dT} = \frac{\Delta H^0}{RT^2}$$

where R is the gas constant and ΔH^0 is the standard enthalpy change in the reaction. But K can be regarded as the ratio k_1/k_{-1} of the rate constants k_1 and k_{-1} for the forward and reverse reactions (because the net rate of any reaction is zero at equilibrium). So we can write

$$\frac{d \ln(k_1/k_{-1})}{dT} = \frac{d \ln k_1}{dT} - \frac{d \ln k_{-1}}{dT} = \frac{\Delta H^0}{RT^2}$$

This equation can be partitioned as follows to give separate expressions for k_1 and k_{-1} :

$$\frac{d \ln k_1}{dT} = \frac{\Delta H_1^0}{RT^2} + \lambda$$

$$\frac{d \ln k_{-1}}{dT} = \frac{\Delta H_{-1}^0}{RT^2} + \lambda$$

where λ is a quantity about which nothing can be said *a priori* except that it must be the same in both equations (because otherwise it would not vanish when one equation is subtracted from the other). Thus far this derivation follows from thermodynamic considerations and involves no assumptions. However, it proved difficult or impossible to show experimentally that the term λ in these equations was necessary. So Arrhenius postulated that its value was in fact zero, and that the temperature dependence of any rate constant k could be expressed by an equation of the form

$$\frac{d \ln k}{dT} = \frac{E_a}{RT^2} \quad (1.10)$$

where E_a is the activation energy and corresponds to the standard enthalpy of reaction ΔH^0 in the van 't Hoff equation. Integration with respect to T gives

$$\ln k = \ln A - \frac{E_a}{RT} \quad (1.11)$$

where $\ln A$ is a constant of integration. It may be written as an expression for k by taking exponentials:

$$k = Ae^{-E_a/RT} \quad (1.12)$$

J. H. van 't Hoff (1884) *Études de Dynamique Chimique*, pages 114–118, Muller, Amsterdam

A. V. Harcourt (1867) "On the observation of the course of chemical change" *Journal of the Chemical Society* **20**, 460–492

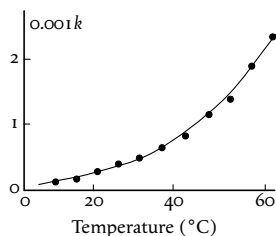


Figure 1.16. Temperature dependence of a rate constant according to the Arrhenius equation.

However, the version in equation 1.11 is more convenient for graphical purposes, as it shows that a plot of $\ln k$ against $1/T$ is a straight line of slope $-E_a/R$, or, if $\log k$ is plotted against $1/T$, the slope is $-E_a/2.303R$. This plot, illustrated in Figure 1.17, is known as an *Arrhenius plot*, and provides a simple method of evaluating $-E_a$.

1.8.2 Elementary collision theory

It is instructive to relate the rates of reactions in the gas phase with the frequencies of collisions between the reactant molecules. According to the Maxwell-Boltzmann distribution of energies among molecules, the number of molecules in a mixture that have energies in excess of $-E_a$ is proportional to $e^{-E_a/RT}$. We can therefore interpret the Arrhenius equation to mean that molecules can take part in a reaction only if their energy exceeds some threshold value, the *activation energy*. In this interpretation, the constant A ought to be equal to the frequency of collisions, Z , at least for bimolecular reactions, and it certainly follows from equation 1.12 that A is the value the rate constant would have if infinite temperature, with $1/T = 0$, could be attained. For some simple reactions in the gas phase, such as the decomposition of hydrogen iodide, A is indeed equal to Z , but in general it is necessary to introduce a factor P ,

$$k = PZe^{-E_a/RT} \quad (1.13)$$

and to assume that, in addition to colliding with sufficient energy, molecules must also be correctly oriented if they are to react. The factor P is then taken to be a measure of the probability that the correct orientation will be adopted spontaneously, so we modify the interpretation above to say that at infinite temperature every collision is productive if the orientation is correct.

With this interpretation of the factor P , equation 1.13 accords reasonably well with modern theories of reaction rates in the gas phase. However, virtually all of the reactions that interest biochemists concern complicated molecules in the liquid phase, and collision frequencies have little relevance for these. Thus we need a theory that explains the experimental observations in a way that is as appropriate in aqueous solution as it is in the gas phase.

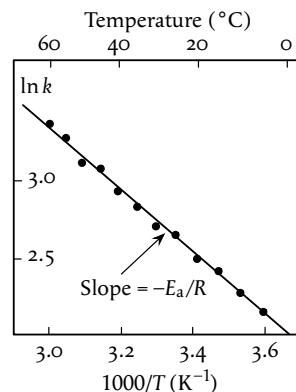


Figure 1.17. Arrhenius plot for the data in Figure 1.16. The activation energy E_a is calculated from the slope. Notice that the zero on the abscissa scale (corresponding to infinite temperature) is located far to the left of the region shown. The practical importance of this is discussed in Section 11.5 (pages 278–279).

HENRY EYRING (1901–1981) was born in Colonia Juárez to parents who had moved to Mexico during a period of perceived persecution of Mormons in the USA. Later his family were forced by the turmoil that followed the Mexican revolution of 1910 to return to the USA, but despite this troubled childhood he was able to win a scholarship to the University of Arizona, and later obtained his doctorate at the University of California, Berkeley, for work on ionization provoked by α particles. He developed his ground-breaking work on the theory of reaction rates at Princeton, and later worked at the University of Utah, Salt Lake City. The Royal Swedish Academy of Sciences awarded him the Berzelius Medal in 1977, apparently as partial compensation for its earlier failure to recognize the importance of this work.

1.8.3 Transition-state theory

The *transition-state theory* (sometimes called the *theory of absolute reaction rates*) is derived largely from the work of Eyring, and was fully developed in the book by Glasstone and co-workers. It is so called because it relates the rates of chemical reactions to the thermodynamic properties of a particular high-energy state of the reacting molecules, known as the *transition state*. (The term *activated complex* is also sometimes used, but it is best avoided in discussions of enzyme reactions, in which the word *complex* is often used with a different meaning). As a reacting system passes along a notional “reaction coordinate”, it must pass through a continuum of energy states, as illustrated in Figure 1.18, and at some stage it must pass through a state of maximum energy. This maximum energy state is the transition state, and should be clearly distinguished from an *intermediate*, which represents not a maximum but a metastable minimum on the reaction profile. No intermediates occur in the reaction profile shown in Figure 1.18, but a two-step example is shown in Figure 1.19 with one intermediate and two transition states. A bimolecular reaction can be represented as

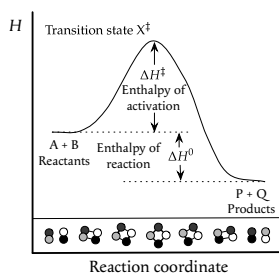


Figure 1.18. Reaction profile according to transition-state theory. The diagrams below the abscissa axis indicate the meaning of the reaction coordinate for a simple bimolecular reaction, but they should not be interpreted too exactly.

where $X^\ddagger$ is the transition state. It is assumed to be in *quasi-equilibrium* with A and B: this means that it is an imaginary state in which the entire system (including products P and Q) is at equilibrium just before the products are abruptly swept away. For fuller discussion of what this means see the discussion in the book by Laidler and co-workers; the important point is that the sudden absence of P and Q has no effect on the concentration of $X^\ddagger$, which is related to those of A and B by an ordinary equilibrium expression:

$$[X^\ddagger] = K^\ddagger[A][B]$$

where $K^\ddagger$ is given by

$$\Delta G^\ddagger = -RT \ln K^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

and $\Delta G^\ddagger$, $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are the Gibbs energy, enthalpy and entropy of formation, respectively, of the transition state from

H. Eyring (1935) “The activated complex in chemical reactions” *Journal of Physical Chemistry* **3**, 107–115

S. Glasstone, K. J. Laidler and H. Eyring (1940) *Theory of rate processes*, McGraw–Hill, New York

K. J. Laidler, J. H. Meiser and B. C. Sanctuary (2002) *Physical Chemistry*, 4th edition, pages 819–826, Houghton Mifflin, Boston

the reactants.⁶ The concentration of $X^\ddagger$ is therefore given by

$$[X^\ddagger] = [A][B]e^{\Delta S^\ddagger/R}e^{-\Delta H^\ddagger/RT} \quad (1.16)$$

Given the way the quasi-equilibrium was described, the transition-state species in equilibrium with A and B are ones that in the immediate past were molecules of A and B. Because of this the first step in equation 1.15 must be written with an irreversible arrow: it is a mistake, found in many accounts of the theory, including those in the first and second editions of this book,⁷ to represent this as a reversible reaction. The practical importance of this is that molecules that reach $X^\ddagger$ from the left in equation 1.15 are like bodies propelled up a slope towards a col: any that reach it are virtually certain to continue down the slope on the other side.

As written, equation 1.16 contains no information about time, like any true thermodynamic equation. We can introduce time by taking account of the natural vibrations that the transition state can undergo. For all but one of the vibration modes the transition state is in no way special: most chemical bonds vibrate in the same way as they would in an ordinary molecule. The exception is the bond that becomes broken in the reaction: its vibration frequency can be calculated from the same quantum-mechanical principles that underlie other vibrations, but it is assumed to have no restoring force, so once the bond starts to break it continues to break. Figure 1.20 illustrates curves for the dependence of energy on bond length in a breaking C—H bond. Notice that for short bond lengths the curves are of similar shape, but for stretched bonds they are quite different: the curve for the ground state has a minimum and that for the transition state does not. We shall again consider molecular vibrations in Section 9.6, because they are important for understanding the effects of isotopic substitution on reaction rates.

It follows from considerations of this kind (for more detail, see the book by Laidler and co-workers mentioned above) that equation 1.16 allows calculation of the concentration of the transition state, and vibration frequency for the breaking bond allows the rate constant for the breakdown of $X^\ddagger$ to be calculated as RT/Nh , where N is the Avogadro constant and h is Planck's constant.⁸ The second-order rate constant for the

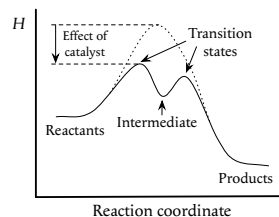


Figure 1.19. Distinction between transition states and intermediates. The reaction consists of more than one step, with multiple maxima and hence multiple transition states. In such examples states of minimum energy along the reaction profile are called *intermediates*. In catalysis, the major subject of this book, the existence of an intermediate causes the maximum energy barrier to the reaction to be lowered.

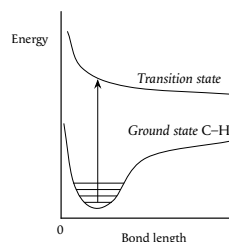


Figure 1.20. Breaking a C—H bond. In the ground state the vibrational levels are quantized, but in the transition state the corresponding vibrational mode is missing. At ordinary temperatures virtually all molecules are in the lowest vibrational state. The figure is simplified from Figure 9.14 (page 243).

§9.6, pages 242–246

⁶They are not real thermodynamic quantities, however, and are usually called the Gibbs energy, enthalpy and entropy of *activation*.

⁷I am grateful to the late Keith Laidler for explaining this to me.

⁸The numerical value of RT/Nh is about $6.25 \times 10^{12} \text{ s}^{-1}$ at 300 K.

complete reaction is therefore

$$k = \frac{RT}{Nh} e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/RT} \quad (1.17)$$

Taking logarithms, we obtain

$$\ln k = \ln \left(\frac{RT}{Nh} \right) + \frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT}$$

and differentiating,

$$\frac{d \ln k}{dT} = \frac{\Delta H^\ddagger + RT}{RT^2} \quad (1.18)$$

Comparison of this with equation 1.10, the Arrhenius equation, shows that the activation energy E_a is not equal to $\Delta H^\ddagger$, but to $\Delta H^\ddagger + RT$. Moreover, E_a is not strictly independent of temperature, so the Arrhenius plot ought to be curved (not only because of the obvious variation of RT with temperature, but also because $\Delta H^\ddagger$ is not strictly temperature-independent). However, the expected curvature is so slight that one would not normally expect to detect it (and the curvature one does often detect in Arrhenius plots is usually attributable to other causes); the variation in k that results from the factor T in equation 1.18 is trivial in comparison with variation in the exponential term.

As both A and E_a in equation 1.11 can readily be determined in practice from an Arrhenius plot, both $\Delta H^\ddagger$ and $\Delta S^\ddagger$ can be calculated, from

$$\Delta H^\ddagger = E_a - RT \quad (1.19)$$

$$\Delta S^\ddagger = R \ln \left(\frac{ANh}{RT} \right) - R \quad (1.20)$$

The enthalpy and entropy of activation of a chemical reaction provide valuable information about the nature of the transition state, and hence about the reaction mechanism. A large enthalpy of activation indicates that a large amount of stretching, squeezing or even breaking of chemical bonds is necessary for the formation of the transition state.

The entropy of activation gives a measure of the inherent probability of the transition state, apart from energetic considerations. If $\Delta S^\ddagger$ is large and negative, the formation of the transition state requires the reacting molecules to adopt precise conformations and approach one another at a precise

KEITH JAMES LAIDLER (1916–2003) was born in Liverpool, but he spent most of his working life in Canada, at the University of Ottawa. He studied with Cyril Hinshelwood at Oxford and obtained his doctorate under Henry Eyring at Princeton, and with both of these distinguished teachers he participated in laying the foundations of chemical kinetics. After such a beginning one might have expected him to build his career in physical chemistry, but he became increasingly interested in the interface between physical chemistry and enzyme kinetics. His book *The Chemical Kinetics of Enzyme Action* (1958) was for a long time unrivaled as a model of how the subject should be presented.

angle. As molecules vary widely in their conformational stability, that is to say in their rigidity, and in their complexity, one might expect the values of $\Delta S^\ddagger$ to vary widely between different reactions. They do, though establishing the variation with certainty is difficult for the sort of reactions that interest biochemists because of the restricted temperature range over which they can usually be studied (Section 11.4). The molecules that are important in metabolic processes are mostly large and flexible, and so uncatalyzed reactions between them are inherently unlikely, which means that $-\Delta S^\ddagger$ is usually large.

Equation 1.17 shows that a catalyst can increase the rate of a reaction either by increasing $\Delta S^\ddagger$ (in practice this usually means decreasing the positive quantity $-\Delta S^\ddagger$) or by decreasing $\Delta H^\ddagger$, or both. It is likely that both effects are important in enzyme catalysis, though definite evidence of this cannot usually be obtained because the uncatalyzed reactions are too slow for their values of $\Delta S^\ddagger$ and $\Delta H^\ddagger$ to be measured.

In all of this it must not be forgotten that the solvent, normally water in enzyme-catalyzed reactions, is a part of the system and that entropy effects in the solvent can contribute greatly to entropies of activation. It is an error, therefore, and possibly a serious one, to try to interpret their magnitudes entirely in terms of ordering or disordering of the reactants themselves. Solvent effects can be of major importance in reactions involving ionic or polar species.

1.8.4 Effects of hydrostatic pressure

I shall not discuss pressure effects extensively in this book (for more detail, see the book by Laidler and Bunting, as well as more recent reviews by Northrop and by Masson and Balny), but it is convenient to mention them briefly, both because their treatment has some similarities with that of temperature, and because they can provide valuable information about the mechanistic details of chemical reactions.

The major difference between temperature and pressure effects on reactions in liquid solution is that whereas it is easy to change the rate of a reaction by increasing the temperature, an increase of a few degrees being usually sufficient to produce an easily measurable change, large increases in pressure, typically much more than 100 bar, are necessary to produce comparable results. This difference results from the very low compressibility of water and other liquids: to produce a chemical effect the increase in pressure must alter

K. J. Laidler and P. S. Bunting (1973) *The Chemical Kinetics of Enzyme Action*, 2nd edition, pages 220–232, Clarendon Press, Oxford

D. B. Northrop (2002) "Effects of high pressure on enzymatic activity" *Biochimica et Biophysica Acta* **1595**, 71–79

P. Masson and C. Balny (2005) "Linear and non-linear pressure dependence of enzyme catalytic parameters" *Biochimica et Biophysica Acta* **1724**, 440–450

the volume occupied by the reacting molecules—something easy to achieve for reactions in the gas phase, but much more difficult in the liquid phase.

Another difference is that although enthalpies of activation are always positive, so all rate constants increase with temperature, volumes of activation can be either positive or (more commonly) negative, and so rate constants may change in either direction with increasing pressure. Forming the transition state for any reaction often implies bringing the reacting molecules into closer proximity than they would be in a stable system, especially if the reacting groups are ions of the same sign, but it can also imply bringing them further apart, especially if they are oppositely charged. These possibilities can be distinguished experimentally by examining the effect of pressure: increasing the pressure favors formation of a transition state that occupies a smaller volume than the ground state, so the reaction should be accelerated by increased pressure and has a negative *volume of activation*, which is defined in analogy to the entropy and enthalpy of activation as the molar volume change that accompanies formation of the transition state. Conversely, if the transition state occupies a larger volume than the ground state its formation will be retarded by increased pressure, and the reaction will show a positive volume of activation.

Effects on the solvent molecules can make the major contribution to the magnitudes of volumes of activation, just as they can for those of entropies of activation, and in chemical reactions the values of the two parameters are often highly correlated, as discussed by Laidler and Bunting in their book. The same may well apply to enzyme reactions, though it is made more difficult to establish experimentally by the difficulty of studying an enzyme-catalyzed reaction over a wide enough temperature range to allow accurate estimation of the entropy of activation, as we shall see in detail in Section 11.5.

§11.5, pages 278–279

Summary of Chapter 1

§1.2, pages 3–9

- The **order** of a reaction is the number of concentrations multiplied together in the expression for its rate; the **molecularity** is the number of molecules that participate in a step. For simple reactions the order may be the same as the molecularity, but that is not true in general; in particular, it is virtually never true for enzyme-catalyzed reactions.

- **Dimensional analysis** allows a rapid (but not infallible) check on the correctness of equations. §1.3, pages 9–10
- Simple-minded approaches to the determination of rate constants are vulnerable to inaccuracies in knowledge of the final state of the system. §1.5, pages 11–13
- A reaction that proceeds in two or more steps can reach a **steady state** in which the intermediate concentrations remain essentially constant, if conditions are such that these concentrations are very small. §1.6, pages 13–14
- A **catalyst** is a reactant that participates in a reaction but is regenerated at the end of a cycle of steps. §1.7, pages 14–15
- The temperature dependence of a reaction can be understood in terms of the availability of energy for the reactants to reach a **transition state** from which the products can be formed. §1.8, pages 15–21

Problems

Solutions and notes are on pages 459–460.

- 1.1 The data in the table were obtained for the rate of a reaction with stoichiometry $A + B \rightleftharpoons P$ at various concentrations of A and B. Determine the order with respect to A and B and suggest an explanation for the order with respect to A.
- 1.2 Check the following statements for dimensional consistency, assuming that t represents time (units s), v and V represent rates (units $M \cdot s^{-1}$ or $\text{mol} \cdot \text{l}^{-1} \cdot s^{-1}$), and a , p , s and K_m represent concentrations (units M):
- In a plot of v against v/s , the slope is $-1/K_m$ and the intercept on the v/s axis is K_m/V .
 - In a bimolecular reaction $2A \rightleftharpoons P$, with rate constant k , the concentration of P at time t is given by $p = a_0^2 kt / (1 + 2a_0 kt)$.
 - A plot of $t / \ln(s_0/s)$ against $(s_0 - s) / \ln(s_0/s)$ for an enzyme-catalyzed reaction gives a straight line of slope $1/V$ and ordinate intercept V/K_m .

[A] mM	[B] mM	v $\mu\text{M} \cdot \text{s}^{-1}$
10	10	0.6
20	10	1.0
50	10	1.4
100	10	1.9
10	20	1.3
20	20	2.0
50	20	3.9
100	20	2.9
10	50	3.2
20	50	4.4
50	50	7.3
100	50	9.8
10	100	6.3
20	100	8.9
50	100	14.4
100	100	20.3

F. J. Kézdy, J. Jaz and A. Bruylants (1958) "Cinétique de l'action de l'acide nitreux sur les amides. I. Méthode générale" *Bulletin de la Société Chimique de Belgique* **67**, 687–706

E. S. Swinbourne (1960) "Method for obtaining the rate coefficient and final concentration of a first-order reaction" *Journal of the Chemical Society* 2371–2372

§ 1.8.1, pages 15–17

§ 1.8.3, pages 18–21

- 1.3 Kézdy and co-workers on the one hand, and Swinbourne on the other, independently suggested an alternative to the Guggenheim plot. First obtain an expression for $(p_\infty - p_i)/(p_\infty - p'_i)$ by dividing the expression for $p_\infty - p_i$ in equation 1.8 by that for $p_\infty - p'_i$ in equation 1.9. Show that the resulting expression can be rearranged to show that a plot of p'_i against p_i gives a straight line. What is the slope of this line? If several plots of the same data are made with different values of t , what are the coordinates of the point of intersection of the lines?
- 1.4 Many reactions display an approximate doubling of rate when the temperature is raised from 25 °C to 35 °C (Figure 1.15). What does this imply about their enthalpies of activation? ($R = 8.31 \text{ J mol}^{-1} \text{ K}^{-1}$, $0^\circ\text{C} = 273 \text{ K}$, $\ln 2 = 0.693$)
- 1.5 In the derivation of the Arrhenius equation (Section 1.8.1) a term λ was introduced and subsequently assumed to be zero. In the light of the transition-state theory (Section 1.8.3), and assuming (not strictly accurately) that the enthalpy of activation does not change with temperature, what would you expect the value of λ to be at 300 K (27 °C)?
- 1.6 Some simple reactions involving nitric oxide (NO) have two unusual kinetic features: they follow third-order kinetics, so that, for example, the reaction with molecular oxygen has a rate proportional to $[\text{NO}]^2[\text{O}_2]$, and their rates decrease with increasing temperature. Suggest a simple way to explain these observations without requiring a trimolecular step and without contradicting the generalization that all elementary rate constants increase with temperature.