LIVERSIDGE LECTURE*

Recent Advances in the Study of Kinetic Hydrogen Isotope Effects

By R. P. Bell
UNIVERSITY OF STIRLING, STIRLING FK9 4LA, SCOTLAND

In recent years several hundred papers have been published annually on the subject of hydrogen isotope effects, and this review is therefore restricted to certain aspects of the subject. No reference is made to the qualitative or semi-quantitative use of isotope effects in elucidating the broad outlines of reaction mechanisms, though such applications now enter into the everyday practice of the organic chemist. Nor will any attempt be made to deal with secondary or solvent isotope effects. In the latter category intensive work has continued on reactions in H_2O–D_2O mixtures which in principle offer intriguing possibilities for unravelling both the nature of the species involved in equilibria in solution, and the intimate nature of transition states.[1] In practice, however, the results of such studies have been slightly disappointing, partly because the distinction between different possibilities usually demands very accurate measurements, and partly because the interpretation of very small differences places some strain on the simplifying assumptions which have to be made in the theoretical treatment.

The present review attempts to estimate how far the available experimental material on *primary kinetic hydrogen isotope effects*, especially in solution, can be accounted for by a theoretical treatment. Particular attention will be given to reactions of the type

$$\begin{aligned} \mathrm{XH} + \mathrm{Y} &\xrightarrow{k^{\mathrm{H}}} \mathrm{X} + \mathrm{HY} \qquad (1) \\ \mathrm{XD} + \mathrm{Y} &\xrightarrow{k^{\mathrm{D}}} \mathrm{X} + \mathrm{DY} \end{aligned}$$

(and the corresponding reaction involving tritium), where X and Y are either atoms or groups, and the primary isotope effect is defined as the ratio $k^{\mathrm{H}}/k^{\mathrm{D}}$. As it stands, equation (1) describes the transfer of a hydrogen atom, but by putting appropriate charges on X and Y it can be made to represent a proton transfer (*i.e.* an acid–base reaction), or the transfer of a hydride ion H^-, and therefore embraces a very large number of reactions. The theories described below are generally applicable to all three types of transfer, examples being drawn from each.

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*Delivered in London on 1st November 1973, and subsequently in Newcastle, Hull, Sheffield, Lancaster, Cardiff, and Bangor.

[1] For a review, see V. Gold, *Adv. Phys. Org. Chem.*, 1969, **7**, 259.

Two isotopes of the same element, or compounds derived from them, were originally believed to have identical chemical and physical properties (except of course for a few physical properties such as density or molecular velocity which depend directly upon molecular mass). The first isotopes available separately were those of heavy elements involved in radioactive series, notably lead, so that this belief appeared to have a good experimental foundation, since any isotopic differences are extremely small. Moreover, it gradually became evident that all interatomic and intermolecular forces depended essentially upon nuclear charges and electronic structures, and only to a very minor extent upon nuclear masses, thus providing a theoretical basis for the almost identical properties of isotopic species.

The experimental position was drastically changed by the discovery of deuterium in 1931, since it was soon found that the replacement of hydrogen by deuterium frequently has a major effect on the equilibrium and particularly on the velocity of a reaction in which bonds involving these isotopes are made or broken.* A further stimulus to the experimental and theoretical study of isotope effects arose during the second world war from the need to separate the isotopes of heavy elements, especially uranium, in connection with the atomic bomb. In particular, the theory of isotope effects was developed during this period, initially by Urey[3] and by Bigeleisen and Mayer,[4] and subsequently for rate processes by Bigeleisen.[5] Although refinements, especially in methods of computation, have been added, the three papers just quoted contain in essence the theory which is generally accepted today.

We shall first outline the physical principles which underlie the existence of kinetic isotope effects. In view of our imperfect theoretical understanding of the absolute rates of even the simplest reactions, it might appear an impossible task to derive expressions for the effect of isotope substitution, but in fact this turns out to be a relatively simple problem because a large proportion of the unknown factors cancel out when we are comparing two isotopic species. This principle of cancellation of unknowns is widely used in chemistry, for example in interpreting the effect of chemical substitution on physical or chemical properties, but whereas in general it often represents not much more than a pious hope, in the case of isotopic substitution it has a firm basis in theory. The principle involved is that *potential energy curves or surfaces are unaffected by isotopic substitution*, and this follows directly from the fact that interatomic and intermolecular forces depend upon attractions or repulsions between the charges on electrons and nuclei, and not upon nuclear masses. This statement is true to the extent that the motions of electrons and nuclei can be treated separately, *i.e.* to

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* It is interesting to recall that, at a Royal Society Discussion in 1932,[2] F. Soddy, who introduced the term 'isotope' in 1913, was reluctant to admit that deuterium could be an isotope of hydrogen, on the grounds that they differed too widely in properties.

[2] F. Soddy, *Proc. Roy. Soc.*, 1933, **A144**, 11.

[3] H. C. Urey, *J. Chem. Soc.*, 1947, 569. (Liversidge Lecture).

[4] J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, 1947, **15**, 261.

[5] J. Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.

within the Born–Oppenheimer approximation, which may be regarded as exact for most practical purposes.

The simplest application of this principle is to the dissociation (homolytic or heterolytic) of the two bonds X–H and X–D, for which the dependence of energy on internuclear distance will be identical, as shown in Figure 1. In particular, it appears that these two bonds will have the same dissociation energy Q_0, which for a simple dissociation process can be equated to the activation energy. The rates of dissociation of X—H and X—D should therefore differ only in virtue of their different vibration frequencies, which cannot differ by a factor of more than $2^{\frac{1}{2}}$. In fact the isotope effect k^H/k^D is usually greater than this, and frequently much greater, so that some other factor must be involved. This is primarily the *zero-point energy, i.e.* the fact that the lowest level of any oscillator is not at the bottom of the potential energy curve, but above it by an amount $\epsilon_0 = \frac{1}{2}h\nu$, where ν is the oscillator frequency. Since this frequency depends upon the isotopic mass, so does the zero-point energy, and the dissociation energy is therefore different for X—H and X—D, as shown by Q_H and Q_D in Figure 1.

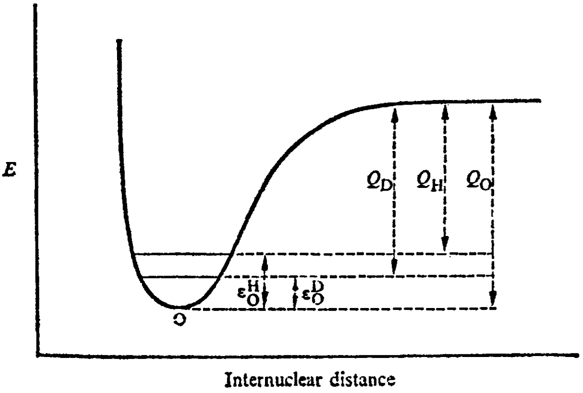

Figure 1 *Effect of zero-point energy in the dissociation of the bonds* X—H *and* X—D (Reproduced by permission from 'Acid and Bases', Methuen, London, 1969)

The existence and magnitude of zero-point energy does of course follow from any quantum-theoretical treatment of the oscillator, but in view of other quantum effects considered later in this article it is useful to note its relation to the *uncertainty principle.* If the system really did exist in the motionless state represented by the lowest point of the curve in Figure 1 both its position and its momentum would be exactly defined, thus contravening the uncertainty principle. On the other hand, the quantum-mechanical description of the zero-point level yields only probability distributions for the position and the momentum (though a definite value for the energy), and the principle is satisfied.

It is easily seen that the isotopic differences in zero-point energy are of the right order of magnitude to account for the large kinetic isotope effects observed for hydrogen. In the expression $4\pi^2\nu^2 = f/\mu$ for the frequency of a harmonic oscillator, the force constant f is the same for XH and XD, since the potential energy curves are identical, while the ratio of reduced masses μ_H/μ_D is *ca.* $\frac{1}{2}$, since hydrogen is always bound to a much heavier atom. However, the observed value of ν^D/ν^H is always somewhat greater than $2^{-\frac{1}{2}}$ (= 0.707), partly because the reduced masses are slightly higher than m_H and m_D, and partly because of anharmonicity. An average value is $\nu^D/\nu^H = 0.741$, giving for the difference in zero-point energies (per mol)

$$E_0{}^H - E_0{}^D = \tfrac{1}{2}N\mathbf{h}\nu_H[1 - 0.741] = 0.130N\mathbf{h}\nu_H \qquad (2)$$

and the corresponding expression for tritium is $E_0{}^H - E_0{}^T = 0.185N\mathbf{h}\nu_H$. The differences in zero-point energy for other pairs of isotopes are much smaller, for two reasons. In the first place the numerical factor in equation (2) is much reduced, *e.g.* 0.0286 for ^{16}O and ^{18}O, and in the second place the numerical value of ν is also smaller because of the increased reduced mass.

If this difference in activation energies is reflected in the kinetic isotope effect, the value of k^H/k^D is given by

$$k^H/k^D = \exp\{(E_0{}^H - E_0{}^D)/\mathbf{R}T\} \qquad (3)$$

and Table 1 gives the numerical values at 298 K for four common types of X—H bond.* The predicted effects are large, and are of the approximate magnitude observed experimentally. Because of the exponential dependence of the isotope effect upon ΔE_0 the predicted effects are much smaller for isotopes of elements other than hydrogen, *e.g.*, *ca.* 1.07 for ^{16}O and ^{18}O bound to a heavier atom.

Table 1 *Zero-point energies for* X—H *bonds*

Bond	ν/cm^{-1}	ΔE_0/cal mol^{-1}	exp($\Delta E_0/\mathbf{R}T$) *at* 298 K
C—H	2900	1080	6.2
N—H	3100	1150	7.0
O—H	3300	1220	7.9
S—H	2500	930	4.8

The above considerations apply to the simple dissociation of an X—L bond, where L represents H, D, or T. In the more common type of reaction represented by (1) it is also necessary to take into account the zero-point energies of vibrations of the transition state X---L---Y, some of which will depend upon the mass of L. This is illustrated in Figure 2, where the activation energies are now E_H and E_D. It is clear that the effect of allowing for the zero-point energy of the transition state is to decrease the difference in activation energies for the two isotopes, and hence the magnitude of the isotope effect, which is now given by

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* The stretching frequencies given represent average values, but vary only slightly for a given type of bond in different species.

$$k^H/k^D = \exp(\Delta E_0/\mathbf{R}T), \quad \Delta E_0 = (E_0{}^H - E_0{}^D)_{XL} - (E_0{}^H - E_0{}^D)^{\ddagger} \quad (4)$$

in which $\ddagger$ as usual refers to the transition state. Equation (3) and the numerical values in Table 1 should thus represent *maximum values* for k^H/k^D in reactions involving transfers of protons, hydrogen atoms, or hydride ions, and this is in general accord with experience, since values less than those in Table 1 are often observed. In principle, it would be possible for ΔE_0 to become negative, giving $k^H/k^D < 1$, but this is unlikely, since the formation of a transition state involves a loosening of bonds and hence a decrease of frequencies and zero-point energies: no values of $k^H/k^D < 1$ have been reported for single-stage reactions of the type XL + Y, though they may occur in reactions involving free hydrogen atoms, such as L + XY, in which there is no isotopically sensitive zero-point energy in the initial state. Apart from zero-point energy in the transition state, there are other reasons why k^H/k^D may fall below the maximum values in Table 1 for reactions involving more than one stage: two examples may be quoted. The first relates to *electrophilic aromatic substitution*,[6] for which the mechanism is given in equation (5), where B is a base.

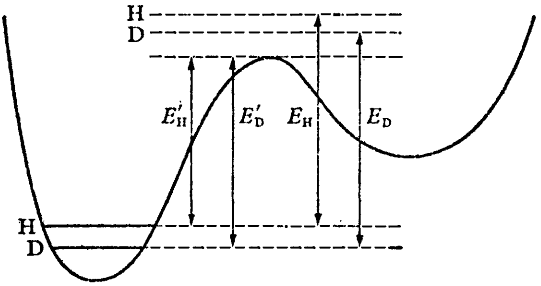

Figure 2 *Zero-point energies and hydrogen isotope effect for a proton-transfer reaction* (Reproduced by permission from 'The Proton in Chemistry', 2nd edn., Chapman and Hall, London, 1974)

$$\mathrm{ArH} + \mathrm{X}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{XArH}^+ \qquad (5)$$

$$\mathrm{XArH}^+ + \mathrm{B} \xrightarrow{k_2} \mathrm{ArX} + \mathrm{BH}^+$$

According to this scheme, the observed velocity constant k is given by

$$k = k_1k_2[\mathrm{B}]/(k_{-1} + k_2[\mathrm{B}]) \qquad (6)$$

Since of the three velocity constants only k_2 will exhibit any considerable hydrogen isotope effect, there are three possibilities for the observed value of k^H/k^D: (i) if $k_{-1} \ll k_2[\mathrm{B}]$, $k^H/k^D = 1$, no isotope effect; (ii) if $k_{-1} \gg k_2[\mathrm{B}]$, $k^H/k^D = k_2{}^H/k_2{}^D$: normal isotope effect; (iii) if $k_{-1} \approx k_2[\mathrm{B}]$, k^H/k^D will be abnormally

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[6] For a review, see H. Zollinger, *Adv. Phys. Org. Chem.*, 1964, **2**, 253.

low, and will depend upon the nature and concentration of B. All these possibilities have been observed in practice. The second example is connected with *internal return* in proton-transfer reactions occurring in media of low dielectric constant. Thus in the isotopic exchange of Ph_3CD or Ph_3CT with cyclohexylamine, catalysed by cyclohexylamide ion,[7] the observed isotope effects have been shown to be smaller than those relating to the single proton-transfer steps: however, this complication is unlikely to arise for reactions in water or other solvents of high dielectric constant.

Returning to single-stage reactions, the simple treatment outlined above, and represented by equations (3) or (4), is of course over-simplified, since it fails to take into account the effect of isotopic substitution on translational and rotational motion and on all vibrational states above the lowest. This is most easily remedied by the use of *transition state theory*, in which the velocity constant is expressed in terms of the partition functions of the reactants and of the transition state. It might be thought that this would yield a very intractable expression for the isotope effect, but in fact the result is relatively simple because of two simplifying factors. The first is the cancellation in the final expression of the partition functions for types of motion which are not appreciably affected by the isotopic substitution, or which remain essentially unchanged on passing from the initial to the transition state: this applies particularly to vibrations of bonds or parts of the system removed from the reactive site. In the second place, classical mechanics provides some very useful *product rules* (used for many years by spectroscopists) which relate the effects of isotopic substitution on molecular mass, moments of inertia, and vibrational frequencies, and hence on translational, rotational, and vibrational partition functions. These rules serve to eliminate both molecular masses and moments of inertia from the expression for isotope effects, leaving only the isotopic masses and the vibration frequencies: this simplification was first introduced by Urey[3] and by Bigeleisen and Mayer[4] for equilibrium effects, and by Bigeleisen[5] for kinetic effects.

The resulting expression can be written in several different ways. For reactions of the type XL + Y the most convenient is

$$\frac{k^{\mathrm{H}}}{k^{\mathrm{D}}} = \left(\frac{m^{\ddagger\mathrm{D}}}{m^{\ddagger\mathrm{H}}}\right)^{\frac{1}{2}} \prod_{\ddagger} \frac{u_i^{\mathrm{H}} \operatorname{cosech} \frac{1}{2}u_i^{\mathrm{H}}}{u_i^{\mathrm{D}} \operatorname{cosech} \frac{1}{2}u_i^{\mathrm{D}}} \Big/ \prod_{\mathrm{XL}} \frac{u_i^{\mathrm{H}} \operatorname{cosech} \frac{1}{2}u_i^{\mathrm{H}}}{u_i^{\mathrm{D}} \operatorname{cosech} \frac{1}{2}u_i^{\mathrm{D}}} \tag{7}$$

with a corresponding expression for the tritium isotope effect. In this equation $u_i = \mathbf{h}\nu_i/\mathbf{k}T$, and $m^{\ddagger}$ is the reduced mass for motion along the reaction coordinate; if X and Y are considerably heavier than L the ratio $m^{\ddagger\mathrm{D}}/m^{\ddagger\mathrm{H}}$ will be close to the ratio of isotopic masses. The first product is taken over all vibration frequencies in the transition state, and the second over all vibration frequencies in XL, although, as already mentioned, it is only necessary to include those frequencies which are appreciably changed both by isotopic substitution and on passing from the initial to the transition state.

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[7] A. Streitwieser, P. H. Owens, G. Sonnicksen, W. K. Smith, G. R. Ziegler, H. M. Niemeyer, and T. L. Kruger, *J. Amer. Chem. Soc.*, 1973, **95**, 4254.

Equation (7) should be of very general validity, since its deduction involves only the following assumptions: (i) the vibrations are simple harmonic; (ii) the translational and rotational partition functions have their limiting high-temperature values; (iii) the general assumptions of transition-state theory are valid. Of these the first two will certainly be satisfied for the temperature range usually investigated, while the third is commonly taken for granted for reactions in solution, though we shall see later that some additional considerations may be necessary. For hydrogen isotope effects equation (7) leads to the same semi-quantitative predictions as equation (6), but it is difficult to make any more quantitative tests or predictions. The relevant vibration frequencies of the initial state can usually be derived from spectroscopic observations, or estimated with some confidence, but equation (7) (unlike the corresponding expression for isotope effects on equilibria) also contains vibration frequencies of the transition state. These are not accessible from any independent experimental source, and although in principle they could be calculated from quantum theory, these calculations have proved very difficult even for the simplest reactions: in fact, the measurement of kinetic isotope effects seems at present the most promising method of obtaining such information.

Nevertheless, some valuable generalizations have been arrived at by applying equation (7) to *models of the transition state*, in which assumptions are made about its geometry and force constants. Although it is not possible to determine which detailed model is appropriate for a given reaction, modern computing techniques make it a relatively simple matter to calculate isotope effects for a wide range of models covering all eventualities which seem at all likely, and also over a wide range of temperatures. This kind of *computer experiment* has been pursued particularly by Wolfsberg, Stern, and their collaborators,[8–13] and some of their conclusions are listed below.

(1) No appreciable errors are involved in omitting from the calculations parts of molecules separated by more than two bonds from positions of isotopic substitution at which force-constant changes occur on passing from the initial state to the transition state. This justifies the so-called *cut-off procedure*, in which a simple model is applied to reactions between complicated species.

(2) For large primary effects, which in practice includes most primary kinetic hydrogen isotope effects, *zero-point energy effects are dominant*, which means that under suitable conditions the simple equation (4) will be a good approximation to equation (7).

(3) Again for large primary effects, predictions were made about the isotope effect on the *Arrhenius parameters*, which are operationally defined by the equations

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[8] M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, 1964, **8**, 225, 325.

[9] M. J. Stern and M. Wolfsberg, *J. Chem. Phys.*, 1963, 39, 2776; 1966, **45**, 2618; *J. Pharm. Sci.*, 1965, **54**, 849.

[10] M. J. Stern, M. E. Schneider, and P. C. Vogel, *J. Chem. Phys.*, 1971, **55**, 4286.

[11] P. C. Vogel and M. J. Stern, *J. Chem. Phys.*, 1971, **54**, 779.

[12] M. J. Stern and P. C. Vogel, *J. Amer. Chem. Soc.*, 1971, 93, 4664.

[13] M. E. Schneider and M. J. Stern, *J. Amer. Chem. Soc.*, 1972, 94, 1517.

$$E_A = \mathbf{R}T^2\mathrm{d}\ln k/\mathrm{d}T, \quad \ln A_A = \ln k + E_A/\mathbf{R}T \qquad (8)$$

If zero-point energy effects are dominant, it seems intuitively likely that $E_A{}^D - E_A{}^H$ will be close to the zero-point energy difference ΔE_0 in equation (4), and hence cannot exceed the difference $(E_0{}^H - E_0{}^D)_{XL}$ in the initial state, and also that the ratio $A_A{}^D/A_A{}^H$ will be close to unity. These expectations are borne out by the detailed calculations. Thus Schneider and Stern[13] found, for several reaction types, a wide variation of force constants and a temperature range 20—2000 K, that $A_A{}^D/A_A{}^H$ was always between 0.6 and 1.4, being usually much closer to unity.

No exact quantitative significance attaches to the term 'large' primary effect, which limits the last two conclusions, but they were found to be valid when k^H/k^D at 300 K is greater than *ca.* 2.7, thus including a large proportion of observed primary hydrogen effects. It should be stressed, however, that the position is quite different for secondary effects, equilibrium effects, and especially for heavy atom isotope effects. Zero-point energy effects are no longer dominant, and the calculated curves relating isotope effect to temperature may show maxima, minima, inflections, and one or more cross-overs from values greater than unity to values less than unity.[14] However, this type of behaviour has been found experimentally in only a very few cases.

The treatment outlined so far represents the generally accepted approach to hydrogen isotope effects. We shall refer to it as the *semi-classical* treatment, and distinguish its predictions by the subscript *s*, since although quantum theory is of course involved in the concept of zero-point energy and the formulation of partition functions, it will appear later that a further type of quantum correction is important for hydrogen isotope effects. As already indicated, the magnitude of these effects is usually consistent with the semi-classical treatment, though a quantitative comparison is not possible since the frequencies in the transition state can only be guessed at. Moreover, the generalizations about Arrhenius parameters described in the last paragraph have been confirmed for a number of reactions, though there are comparatively few investigations in which the temperature variation of the isotope effect has been studied with sufficient accuracy. However, the past ten to fifteen years have revealed an increasing number of experimental results which appear to be inconsistent with the semi-classical treatment: the remainder of this review will deal with these anomalies and their possible explanation, beginning with solution reactions.

Anomalously high isotope effects. According to Table 1, the maximum value expected for $(k^H/k^D)_s$ at 298 K for a reaction involving cleavage of a C—H bond is 6.2. This prediction takes into account the zero-point energy of stretching vibrations, and may need modifying if bending vibrations are also allowed for: these show much larger frequency variations than do stretching vibrations, ν_{CH} (bending) varying from *ca.* 750 to 1450 cm^{-1} in different compounds. However,

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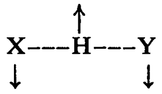
[14] M. J. Stern, W. Spindel, and E. V. Monse, *J. Chem. Phys.*, 1968, **48**, 2908; E. V. Monse, W. Spindel, and M. J. Stern, *Adv. Chem. Ser.*, 1969, **89**, 148.

since the transition state possesses only one fewer real vibration than the reactants (corresponding to the appearance of a translation along the reaction co-ordinate), it is certainly unrealistic to suppose that the formation of the transition state can involve the complete loss of zero-point energy associated both with a C—H stretch and also with one or more C—H bending modes.* Nor is it necessarily correct to assume that bending frequencies in the transition state are lower than in the initial state: thus in the (doubly degenerate) vibration



$$\underset{\downarrow}{X}{-}{-}{-}\overset{\uparrow}{H}{-}{-}{-}\underset{\downarrow}{Y}$$

although X---H and H---Y are longer than normal bonds, the hydrogen is now constrained on both sides and there is a finite bending force constant even when only central forces between the atoms are involved (*i.e.*, in the absence of any preferred valency directions).[15] Moreover, it is found[16] that the bending frequency of the symmetrical ion HF_2^- is 1225 cm^{-1}, while calculated energy surfaces for systems such as H---H---H,[17] H---H---CH_3,[18] and F_3C---H---CH_3,[19] as well as electrostatic models for proton-transfer reactions,[20,21] all give bending frequencies in the range 750—1500 cm^{-1}. It is thus likely that the zero-point energies of the bending vibrations of the initial and transition states are approximately equal, in which case the figures in Table 1 can still be regarded as maximum values for $(k^H/k^D)_S$. Experimental support for this cancellation comes from observations on the acid-catalysed hydrolysis of ethyl vinyl ether, which is known to involve a rate-determining proton transfer from the acid to carbon. Kresge and Chiang[22] found, for catalysis by formic acid, $k^H/k^D = 6.8$ at 298 K, which is close to the maximum value 7.9 predicted for O—H stretching alone. On the other hand, catalysis by hydrofluoric acid (an acid of similar strength, but devoid of bending vibrations) gave $k^H/k^D = 3.3$: this is only *ca.* $\frac{1}{4}$ of the maximum value of 13.3 predicted from the stretching frequency $\nu_{HF} = 4141$ cm^{-1}, and the difference could be accounted for if both transition states and formic acid have two bending frequencies of *ca.* 1100 cm^{-1}, in agreement with the above estimates.

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* Strictly speaking one should not speak of the loss or gain of zero-point energies associated with individual types of vibration, but only of the overall change of zero-point energy. This is because the individual vibrational modes in general represent a combination of stretching and bending, and there is not necessarily a one-to-one correlation between vibrations in the initial and the transition states. However, the description given here is sufficiently accurate for present purposes.

[15] H. C. Longuet-Higgins, *Phil. Mag.*, 1955, **46**, 98; C. J. S. M. Simpson, *J. Chem. Phys.*, 1956, **24**, 1108; R. G. Pearson, *J. Chem. Phys.*, 1959, **30**, 1537.

[16] G. L. Coté and H. W. Thompson, *Proc. Roy. Soc.*, 1951, **A210**, 206.

[17] See *e.g.* W. A. Van Hook, in 'Isotope Effects in Chemical Reactions', ed. C. J. Collins and N. S. Bowman, A. C. S. Monograph 167, New York, 1970, Table 1.13.

[18] J. S. Shapiro and R. E. Weston, *J. Phys. Chem.*, 1972, **76**, 1669.

[19] T. E. Sharp and H. S. Johnston, *J. Chem. Phys.*, 1962, **37**, 1541.

[20] R. P. Bell, *Trans. Faraday Soc.*, 1961, **57**, 961.

[21] R. P. Bell, W. H. Sachs, and R. L. Tranter, *Trans. Faraday Soc.*, 1971, **67**, 1995.

[22] A. J. Kresge and Y. Chiang, *J. Chem. Soc.* (*B*), 1967, 58; *J. Amer. Chem. Soc.*, 1969, **91**, 1025.

However, in the present context we wish to identify isotope effects which are definitely too high to be accounted for by the semi-classical treatment, and we shall therefore revise the values in Table 1 by including the assumption that the sum of the isotopically dependent bending frequencies in the initial state may decrease by up to 750 cm^{-1} on forming the transition state: this almost certainly exaggerates the possible effect of the bending vibrations. The results, rounded off to the nearest unit, are given in Table 2. The temperatures have been chosen to correspond with the experimental results which follow.

Table 3 collects together experimentally observed isotope effects which are markedly greater than the predicted maximum values in Table 2. Their probable errors are sometimes difficult to assess, but are throughout considerably smaller than the discrepancies with the values in Table 2.

Anomalous isotope effects upon Arrhenius parameters. Further discrepancies with the semi-classical treatment arise when we consider the quantities $E_A{}^D - E_A{}^H$ and $A_A{}^D/A_A{}^H$, derived by means of equation (8) from experimental measurements over a range of temperatures. We have already seen that $(E_A{}^D - E_A{}^H)_s$ should be less than the difference of zero-point energies in the initial state. Almost all the available data relate to the breaking of C—H bonds, for which Table 2 gives $E_0{}^H - E_0{}^D = 1.4$ kcal mol^{-1}, with some allowance for bending vibrations: the corresponding figure for tritium is $E_0{}^H - E_0{}^T = 1.9$ kcal mol^{-1}. We have also seen that theory predicts $0.6 < (A_A{}^D/A_A{}^H)_s < 1.4$, with values closer to unity being more probable; the corresponding limits for $(A_A{}^T/A_A{}^H)_s$ will be *ca.* 0.5 – 1.6.

Table 4 contains examples of reported Arrhenius parameters which fall well outside the above limits. Their accuracy varies considerably, since in some instances they are based on measurements over only a limited range of temperatures, but in most cases the discrepancy with the semi-classical predictions appears to exceed considerably the probable experimental error.

The evidence collected in Tables 3 and 4 forces us to the conclusion that, at least for the systems concerned, the semi-classical expression (7) for the hydrogen isotope effect is erroneous or incomplete. It might of course be suggested that the inadequacy lies in the fundamental assumptions of transition-state theory, on which the whole of the usual treatment of kinetic isotope effects is based, and in particular in the assumption that there is an equilibrium distribution of energy between the various degrees of freedom in the transition state. While this assumption is admittedly an approximation, which may cause appreciable errors if applied to fast gas reactions involving simple species, it is reasonable to suppose that for relatively slow reactions in solution the ubiquitous solvent molecules will act as an efficient thermostat to bring about equilibration between different degrees of freedom. Moreover, although a quantitative treatment of the non-equilibrium problem is far from easy, it is difficult to envisage any way in which departures from equilibrium could produce the large increases in isotope effects illustrated in Tables 3 and 4.

Table 2 *Maximum semi-classical isotope effects with allowance for bending vibrations. At each temperature the first entry represents* $(k^{\mathrm{H}}/k^{\mathrm{D}})_{\mathrm{s}}$ *and the second* $(k^{\mathrm{H}}/k^{\mathrm{T}})_{\mathrm{s}}$.

Bond	ΔE_0/cal mol^{-1}	T/K	221	243	263	298	323	363
C—H	1354		22, 85	17, 57	13, 42	10, 27	8, 21	6, 15
N—H	1428		26, 109	20, 73	15, 52	11, 33	9, 25	7, 18
O—H	1503		31, 140	23, 91	18, 64	13, 39	10, 29	8, 20
S—H	1206		16, 53	12, 37	10, 28	8, 19	7, 15	5, 11

Table 3 *Anomalously large hydrogen isotope effects in solution reactions* (L = H, D, or T).

Reaction	*T*/K	k^H/k^D	k^H/k^T	*Ref.*
Proton transfers				
Me_2CLNO_2 + 2,6-lutidine in water	298	19	—	*a*
Me_2CLNO_2 + 2,6-lutidine in Bu^tOH/H_2O	298	24	—	*b*
Me_2CLNO_2 + 2,4,6-collidine in Bu^tOH/H_2O	298	23	79	*b, c*
$CH_3(CH_2)_2CLNO_2CO_2Me$ + 2,4,6-collidine in water	303	27	—	*d*
$Ph_3C.CLMeCN + Bu^tO^-$ in Bu^tOD	298	15	—	*e*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in toluene	298	45	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in mesitylene	298	31	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in cyclohexene	298	33	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in Bu_2O	298	41	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in PhCl	298	50	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in THF	298	13	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in CH_2Cl_2	298	11*	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + (NMe_2)_2C{=}NH$ in MeCN	298	12*	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + Bu_3N$ in toluene	298	14	—	*f*
$4\text{-}NO_2C_6H_4CLNO_2 + Bu_3N$ in MeCN	298	2.2*	—	*f*
Hydride ion transfers				
$PhCL(CF_3)OH + MnO_4^-$ in water	298	16	57	*g, c*
$CF_3CL(OH)O^- + MnO_4^-$ in water	298	14	—	*h*
$3,5\text{-}(NO_2)_2C_6H_3CL(CF_3)OH + CrO_3$ in $AcOH\text{–}H_2O$	298	13	—	*i*
$PhCL_2OH + MnO_2$ (heterogeneous)	†	14-18	—	*j*
Hydrogen atom transfers				
CH_3CL_2OH + H in water	†	17	—	*k*
CL_3OH + H in water	†	20	—	*l*
$CL_3CO_2^-$ + H in water	†	22	—	*l*

Reaction	*T*/K	$k^{\mathrm{H}}/k^{\mathrm{D}}$	$k^{\mathrm{H}}/k^{\mathrm{T}}$	*Ref.*
C_6H_5OL + styrylperoxy radical in styrene	338	>15	—	*m*
2,6-di-$Bu^tC_6H_3OL$ + styrylperoxy radical in PhCl	303	30	—	*m*
Cumyl-O_2L + tetralylperoxy radical in PhCl	303	17	—	*m*
2,3,4,6-Me_4C_6HOL + polyvinylacetate radical in vinyl acetate	318	16	—	*m*
1,2,3,-$C_6H_3(OL)_3$ + polyvinyl acetate radical in vinyl acetate	323	19	—	*m*
2,4,6-tri-$Bu^tC_6H_2OL$ + $\dot{C}H_3$ in heptane	363	—	50	*n*
$C_{14}L_{12}$ (dihydrophenanthrene) + O_2 in octane	263	64	—	*o*
	242	95	—	*o*
	221	*ca.* 250	—	*o*
Disproportionation of $CL_2(CH_2)_2CL_2NO\cdot$ in benzene	298	13	—	*p*
Disproportionation of $(MeCL_2)_2NO\cdot$ in CF_2Cl_2	298	14	—	*p*
2,2,6,6-Tetramethylpiperidyl + $C_6L_5CL_3$ (solvent)	263	24	—	*q*
2,2,6,6-Tetramethylpiperidyl + C_6L_{12} (solvent)	295	16	—	*q*

*These values are not markedly abnormal, but are included to illustrate the solvent dependence of the isotope effect. †Temperature not stated, but probably near room temperature.

[a] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A294**, 273. [b] E. S. Lewis and L. Funderburk, *J. Amer. Chem. Soc.*, 1964, **86**, 2531; 1967, **89**, 2322. [c] E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 2322. [d] H. Wilson, J. D. Caldwell, and E. S. Lewis, *J. Org. Chem.*, 1973, **38**, 564. [e] S. M. Wong, H. F. Fischer, and D. J. Cram, *J. Amer. Chem. Soc.*, 1971, **93**, 2235. [f] E. F. Caldin and S. Mateo, *J.C.S. Chem. Comm.*, 1973, 854; S. Mateo, Ph.D. Thesis, University of Kent, 1974. [g] R. Stewart and R. van der Linden, *Discuss. Faraday Soc.*, 1960, **29**, 211. [h] R. Stewart and M. M. Mocek, *Canad. J. Chem.*, 1963, **41**, 1161. [i] R. Stewart and D. G. Lee, *Canad. J. Chem.*, 1964, **42**, 439. [j] I. M. Goldman, *J. Org. Chem.*, 1969, **34**, 3489. [k] C. Lifshitz and G. Stein, *J. Chem. Soc.*, 1962, 3706. [l] M. Anbar and D. Meyerstein, *J. Phys. Chem.*, 1964, **68**, 3184. [m] M. Simonyi and F. Tüdös, *Adv. Phys. Org. Chem.*, 1970, 9, 127. [n] L. N. Shishkina and I. V. Berezin, *Zhur. fiz. Khim.*, 1965, 39, 2547. [o] A. Bromberg, K. A. Muszkat, and E. Fischer, *Chem. Comm.*, 1968, 1352; A. Bromberg and K. A. Muszkat, *J. Amer. Chem. Soc.*, 1969, **91**, 2860; A. Bromberg, K. A. Muszkat, E. Fischer, and F. S. Klein, *J.C.S. Perkin II*, 1972, **588**. [p] D. F. Bowman, T. Gillan, and K. U. Ingold, *J. Amer. Chem. Soc.*, 1971, **93**, 6555. [q] R. J. Roberts and K. U. Ingold, *J. Amer. Chem. Soc.*, 1973, **95**, 3228.

Table 4 *Anomalous hydrogen isotope effects on Arrhenius parameters for solution reactions* (L = H, D, *or* T)

Reaction	$E_A^D - E_A^H$ /kcal mol^{-1}	$E_A^T - E_A^H$ /kcal mol^{-1}	A_A^D/A_A^H	A_A^T/A_A^H	*Ref.*
Proton transfers					
$(CH_2)_3COCLCO_2Et + CH_2ClCO_2^-$ in D_2O	1.5	3.3	2.9	25	*a, b*
$(CH_2)_3COCLCO_2Et + F^-$ in D_2O	2.4	2.7	24	50	*a, b*
$PhMeCLCH_2Br + EtO^-$ in EtOH	1.8	3.2	2.5	3.0	*c, d*
$2\text{-}MeC_6H_4COCH_2L + OH^-$ in H_2O	—	3.6	—	30	*e*
$4\text{-}MeOC_6H_4COCH_2L + OH^-$ in H_2O	—	3.3	—	13	*e*
$CH_3CL_2NO_2$ + 2-Bu^t-pyridine in EtOH–H_2O	2.8	—	11	—	*f*
Me_2CLNO_2 + 2,6-lutidine in EtOH–H_2O	2.9	—	14*	—	*f*
Me_2CLNO_2 + 2,4,6-collidine in BuOH–H_2O	3.0	—	7	—	*g*
$PhCL_2NO_2 + OH^-$ in H_2O	1.7	—	2.4	—	*h*
$PhCL_2NO_2$ + morpholine in H_2O	2.6	—	10	—	*h*
$PhCL_2NO_2$ + imidazole in H_2O	1.8	—	2.1	—	*h*
$PhCL_2NO_2 + HPO^{2-}$ in H_2O	2.3	—	5.2	—	*h*
$4\text{-}NO_2C_6H_4CL_2CN + EtO^-$ in EtOH–Et_2O	1.9	—	5	—	*i*
$4\text{-}NO_2C_6H_4CL_2NO_2 + Et_3N$ in MeCN	1.0	—	1.8	—	*j*
$4\text{-}NO_2C_6H_4CL_2NO_2 + Bu_3^tN$ in MeCN	0.8	—	1.7	—	*j*
$4\text{-}NO_2C_6H_4CL_2NO_2 + Et_3N$ in toluene	2.2	—	3.9	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in cyclohexene	5.4	—	260	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in mesitylene	4.7	—	87	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in toluene	4.3	—	32	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in Bu_2O	4.2	—	32	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in PhCl	3.7	—	11	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in THF	1.8	—	1.6	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in CH_2Cl_2	1.9	—	1.2	—	*k*
$4\text{-}NO_2C_6H_4CL_2NO_2 + (NMe_2)_2C{=}NH$ in MeCN	1.5	—	1.0	—	*k*

Reaction	$E_A^D - E_A^H$	$E_A^T - E_A^H$	A_A^D/A_A^H	A_A^T/A_A^H	*Ref.*
	/kcal mol^{-1}				
4-MeOCL_2CH_2SMe_2^+ + OH^- in Me_2SO–H_2O	2.3	—	8	—	*l*
4-MeOCL_2CH_2Br + OH^- in Me_2SO–H_2O	2.3	—	7	—	*l*
Hydride ion transfers					
PhCL(CF_3)OH + MnO_4^- in H_2O	2.3	—	3.0	—	*m*
CF_3CL(OH)O^- + MnO_4^- in H_2O	1.9	—	2.3	—	*n*
(4-Me_2NC_6H_4)$_3$CL + chloranil in MeCN	3.4	—	24	—	*o*
Hydrogen atom transfers					
n-C_7H_{15}L + $\dot{C}H_3$ in heptane	—	3.4	—	5.0	*p*
PhSL + $Ph_3C\cdot$ in toluene	—	2.6	—	5.3	*q*
Me_2CLOH + H in 6M-H_2SO_4	1.9†	—	2.4	—	*r*
L-migration in methylcyclopentadiene in CCl_4	2.4	—	10	—	*s*

*The authors give $A_A^D/A_A^H = 7$ for this reaction: the value 14 given in the Table is calculated from their reported values of k^H/k^D. † The authors report a different value for the difference in activation energies, which was defined by $\Delta E = RT\ln(k^H/k^D)$, *i.e.* assuming that $A^H = A^D$, and was not derived from the temperature coefficient of k^H/k^D.

[a] R. P. Bell, J. A. Fendley, and J. R. Hulett, *Proc. Roy. Soc.*, 1956, **A235**, 453. [b] J. R. Jones, *Trans. Faraday Soc.*, 1969, **65**, 2430. [c] V. J. Shiner and M. L. Smith, *J. Amer. Chem. Soc.*, 1961, **83**, 593. [d] V. J. Shiner and B. Martin, *Pure Appl. Chem.*, 1964, **8**, 371. [e] J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 993. [f] E. S. Lewis and J. D. Allen, *J. Amer. Chem. Soc.*, 1964, **86**, 2022. [g] E. S. Lewis and L. Funderburk, *J. Amer. Chem. Soc.*, 1967, **89**, 2322. [h] J. R. Keeffe and N. H. Munderloh, *J.C.S. Chem. Comm.*, 1974, 17. [i] E. F. Caldin and G. Tomalin, *Trans. Faraday Soc.*, 1968, **64**, 2814. [j] E. F. Caldin, A. Jarcewski, and K. T. Leffek, *Trans. Faraday Soc.*, 1967, **63**, 110. [k] E. F. Caldin and S. Mateo, *J.C.S. Chem. Comm.*, 1973, 854; S. Mateo, Ph.D. Thesis, University of Kent, 1974. [l] L. F. Blackwell and J. L. Woodhead, *J.C.S. Perkin. II*, 1974, in the press. [m] R. Stewart and R. van der Linden, *Discuss. Faraday Soc.*, 1960, **29**, 211. [n] R. Stewart and M. M. Mocek, *Canad. J. Chem.*, 1963, **41**, 1161. [o] E. S. Lewis, J. M. Perry, and R. H. Grinstein, *J. Amer. Chem. Soc.*, 1970, **92**, 899. [p] V. L. Antonovskii and I. V. Berezin, *Zhur. fiz. Khim*, 1960, **34**, 1286. [q] E. S. Lewis and M. M. Butler, *J. Org. Chem.*, 1971, **36**, 2582. [r] K. Vacek and C. von Sonntag, *J.C.S. Chem. Comm.*, 1969, 1256. [s] S. McLean, C. J. Webster, and R. J. D. Rutherford, *Canad. J. Chem.*, 1969, **47**, 1555.

It seems likely that the neglected factor is the *transmission coefficient*, which usually appears in the early stages of transition-state derivations. Thus a common formulation is

$$k = \frac{\kappa \mathbf{k} T}{\mathbf{h}} K^{\ddagger} \tag{9}$$

where κ is such a transmission coefficient. However, κ has usually disappeared by the time that practical applications of equation (9) are reached, usually on the grounds that it is close to unity; in any case, it is commonly cancelled out, either explicitly or implicitly, when considering ratios such as $k^{\mathrm{H}}/k^{\mathrm{D}}$, and therefore does not appear in equation (7).

There are two ways in which transmission coefficients differing from unity can arise. The first depends upon the form of the potential energy surface characterizing the reaction, and expresses the fact that not all systems possessing energies greater than that of the transition state will actually react: expressed in another way, the mass-point whose translation represents the motion leading to reaction may be reflected back into the valley representing reactants, even when its energy is higher than that of the col which leads to the valley representing products. This is the type of transmission coefficient usually denoted by **k**: it will always be less than unity, and should not be affected by isotopic substitution.*

The second type of transmission coefficient has quite a different origin, and is commonly referred to as the *quantum-mechanical tunnel effect*, being usually denoted by Γ. It depends upon the fact that, according to quantum theory, the probability of a particle crossing an energy barrier is a continuous function of the energy of the particle W: in particular this probability is non-zero even when W is less than the energy E at the highest point of the barrier. This is in contrast with the classical picture of particle motion (implicitly adopted in the usual transition state treatment), according to which this probability $G(W)$ is zero when $W < E$, and unity when $W > E$. It turns out that G, and hence Γ, depends upon the mass of the particle, so that the expression (7) for $k^{\mathrm{H}}/k^{\mathrm{D}}$, or the simplified version (4), should be multiplied by a factor $\Gamma^{\mathrm{H}}/\Gamma^{\mathrm{D}}$.

The theory and applications of the tunnel effect have been the subject of several recent reviews[24-27] and only some of its principles and consequences

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* This statement is not strictly correct, since although the energy is the same function of nuclear positions for isotopes of different masses, the correct method for constructing the energy surface does depend upon these masses.[23] However, it seems likely that only small isotope effects will arise from this cause.

[23] S. Glasstone, K. J. Laidler, and H. Eyring, 'The Theory of Rate Processes', McGraw-Hill, New York, 1941, pp. 100—107.

[24] E. F. Caldin, *Chem. Rev.*, 1969, 69, 135.

[25] C. B. Duke, 'Tunneling in Solids', Academic Press, New York, 1969.

[26] M. D. Harmony, *Chem. Soc. Rev.*, 1972, 1, 211.

[27] R. P. Bell, 'The Proton in Chemistry', Chapman and Hall, London, 1973, 2nd edn., Chapter 12.

will be described here. The tunnel effect arises in a very direct way from the fundamental tenets of quantum theory, as expressed by the *uncertainty principle* or the *wave-particle duality of matter*. These are represented respectively by equations (10a) and (10b), in which v_x is the velocity in the x-direction, Δx and $\Delta(mv_x)$ the uncertainties, and λ_x the effective wavelength of the particle in this direction.

$$\Delta x . \Delta(mv_x) \approx \mathbf{h}/2\pi \qquad (10a)$$

$$\lambda_x = \mathbf{h}/mv_x \qquad (10b)$$

If the uncertainty Δx (or, what comes to the same thing, the effective wavelength λ_x) is small compared with the dimensions of the barrier, the motion of the particle can be treated by classical mechanics, and this is usually the case for nuclei heavier than H, D, or T. By contrast, in virtue of its low mass the electron has a large effective wavelength, and we are of course quite accustomed to describing its behaviour in terms of wave mechanics, and to abandoning any attempt to localize it on a molecular scale. In fact, one of the earliest quantitative applications of the tunnel effect was to the emission of electrons from metals in strong electric fields [28]* and more recently the tunnelling of electrons at junctions between insulators, conductors, semi-conductors, and super-conductors has received much attention.[30] The hydrogen isotopes occupy an intermediate position, in that under normal conditions their effective wavelengths have the order of magnitude 10^{-9}—10^{-8} cm, which is comparable with the distances through which these nuclei move in chemical reactions. It has therefore been suggested many times during the past fifty years that the tunnel effect should be taken into account in any quantitative treatment of the kinetics of such reactions, especially in considering isotope effects, though it is only comparatively recently that this view has received any substantial experimental support.

Two general points emerge from our discussion of equation (10). In the first place the dependence of the tunnel effect on isotopic mass is clear, since the lighter isotope will always have the larger wavelength and hence the greater departure from classical behaviour. In the second place the close relation between the uncertainty principle and the tunnel effect shows that this effect has the same logical status as zero-point energy, the existence of which also follows directly from the uncertainty principle, as we have seen. It is therefore strictly

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* The other early application of tunnelling theory was the treatment by Gamow[29] of the emission of α-particles from radioactive nuclei. Although the mass of the α-particle is much greater than that of the electron, corresponding to a shorter wavelength, the energy barrier surrounding the nucleus is a very narrow one (*ca.* 10^{-12} cm), so that the problem is essentially a non-classical one.

[28] R. H. Fowler and L. Nordheim, *Proc. Roy. Soc.*, 1928, **A119**, 173; L. Nordheim, *Proc. Roy. Soc.*, 1928, **A121**, 626.

[29] See *e.g.* G. Gamow, 'Structure of Atomic Nuclei and Nuclear Transformations', Clarendon Press, Oxford, 1937, Chapter 5.

[30] See *e.g.* J. M. Ziman, 'Principles of the Theory of Solids', Cambridge University Press, 1972, 2nd edn., Chapters 6 and 11; L. Solymar, 'Superconductive Tunnelling and Applications', Chapman and Hall, London, 1972.

illogical to use equations such as (7) and (4) which allow for isotopic differences in zero-point energy but ignore the tunnel effect, though of course the relative importance of these two factors cannot be decided without further calculation or experiment. The well-established term 'tunnel effect' is in fact a somewhat misleading one, since it seems to suggest a separate and special effect outside the standard framework of quantum theory, and from this point of view 'tunnel correction' would be a happier description.

Provided that passage of the system through the transition state can be described by the motion of a particle of constant mass along a single separable co-ordinate, there is no difficulty in principle in calculating the reaction probability (or permeability) $G(W)$ in terms of the one-dimensional energy barrier thus defined. Chemical reactions normally involve a Boltzmann distribution over a range of energies, and it is therefore usual to evaluate the transmission coefficient or tunnel correction Γ by integration:

$$\Gamma = (\mathbf{k}T)^{-1} \exp(E/\mathbf{k}T) \int_0^\infty \exp(-W/\mathbf{k}T)G(W)dW \tag{11}$$

It is not usually possible to obtain explicit expressions for $G(W)$ or Γ, though numerical methods are available[31] for evaluating them for a one-dimensional barrier of arbitrary form. However, if the relevant part of the barrier can be approximated by a parabola, which will be the case near the top of any barrier of finite curvature, then a particularly simple result is obtained: this is analogous to the assumption of simple harmonic motion in simplifying the solution of vibrational problems, an assumption which is made in most transition-state treatments, including the derivation of equation (7) for the isotope effect. If the potential energy $V(x)$ near the top of the barrier is represented by the parabola (12).

$$E - V(x) = \tfrac{1}{2}Fx^2 \tag{12}$$

it is convenient to introduce a *barrier frequency* ν_t defined by

$$4\pi^2\nu_t^2 = F/m \tag{13}$$

$i\nu_t$ is often termed the *imaginary frequency* corresponding to motion along the reaction co-ordinate.* For tunnel corrections of moderate magnitude, the isotopic ratio of tunnel corrections is found to be[32]

$$\Gamma^{\mathrm{H}}/\Gamma^{\mathrm{D}} = u_t^{\mathrm{H}} \operatorname{cosec} \tfrac{1}{2}u_t^{\mathrm{H}}/u_t^{\mathrm{D}} \operatorname{cosec} \tfrac{1}{2}u_t^{\mathrm{D}} \tag{14}$$

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* ν_t is actually the frequency with which a particle of mass m would vibrate in a parabolic potential well having the same curvature as the barrier. The term 'imaginary frequency' arises in the following way. In treating the vibrations of a stable polyatomic molecule we end up with the so-called secular equation, having a number of positive roots λ, each of which is related to the (real) frequency of a normal vibration by $\lambda = 4\pi^2\nu^2$. When the same treatment is applied to a transition state, one of the roots, corresponding to motion along the reaction co-ordinate, turns out to be negative, and for this root we can write $\lambda_t = 4\pi^2(i\nu_t)^2$, where ν_t is the real frequency introduced in (13).

[31] R. J. Le Roy, K. A. Quickert, and D. J. Le Roy, *Trans. Faraday Soc.*, 1970, **66**, 2997; R. J. Le Roy, E. D. Sprague, and F. Williams, *J. Phys. Chem.*, 1972, **76**, 546.

[32] R. P. Bell, *Trans. Faraday Soc.*, 1959, **55**, 1.

where $u_t = \mathbf{h}\nu_t/\mathbf{k}T$. This bears a remarkable resemblance to equation (7), which expresses k^H/k^D in terms of factors of the form u cosech $\frac{1}{2}u$, where $u = \mathbf{h}\nu/\mathbf{k}T$, and ν is a real frequency. In fact, since cosech x = i cosec ix, instead of introducing the tunnel correction by multiplying equation (7) by Γ^H/Γ^D, we need only include the imaginary frequency iν_t in the product $\underset{\ddagger}{\Pi}$ over the frequencies of the transition state.* The parallelism between the two types of quantum correction is further illustrated by the expansions (15) and (16) which are valid when $u < 2\pi$.

$$\tfrac{1}{2}u \operatorname{cosech} \tfrac{1}{2}u = 1 - \frac{u^2}{24} + \frac{7u^4}{5760} - \ldots. \tag{15}$$

$$\tfrac{1}{2}u \operatorname{cosec} \tfrac{1}{2}u = 1 + \frac{u^2}{24} + \frac{7u^4}{5760} + \ldots. \tag{16}$$

These show that, for small values of u, the corrections arising from a real frequency ν and an imaginary frequency iν are of similar magnitudes, but opposite in direction.

We shall now consider how the inclusion of a tunnel correction will modify the predictions of the semi-classical treatment, the latter being distinguished as before by the subscript s. The following conclusions are easily derived from equation (14), valid for a parabolic barrier, but they are equally true for a barrier of any shape provided that the corrections for tunnelling do not become too large. Subject to this limitation, all the effects are predicted to become more marked as the temperature decreases. The conclusions are stated in terms of H/D isotope effects; the corresponding statements for tritium should be obvious.

(*a*) $k^H/k^D > (k^H/k^D)_s$. This follows from the fact that Γ^H/Γ^D is always greater than unity (greater tunnelling by the lighter particle), and obviously provides a possible explanation for the unexpectedly large isotope effects recorded in Table 3.

(*b*) $(E_A{}^D - E_A{}^H)$ will be greater than $(E_A{}^D - E_A{}^H)_s$, and may exceed the difference in zero-point energies $(E_0{}^H - E_0{}^D)$. This is because in reactions involving appreciable tunnelling the average energy of the reacting systems falls below the top of the barrier by an amount which is greater for the lighter isotope. This prediction is consistent with the abnormal differences in observed activation energies quoted in Table 4.

(*c*) $A_A{}^D/A_A{}^H > (A_A{}^D/A_A{}^H)_s$. At first sight this prediction might appear to be in the wrong direction, since it implies that the effect of a significant tunnel correction is to *decrease* the apparent pre-exponential factor. The qualitative reason for this should be clear from Figure 3, which shows schematically the Arrhenius plots for k^H and k^D over a wide range of temperature. The straight

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* There is of course no imaginary frequency in the initial state, since this is a stable species. The same applies to the final state, showing that the tunnel effect plays no part in equilibrium isotope effects, but only in kinetic ones.

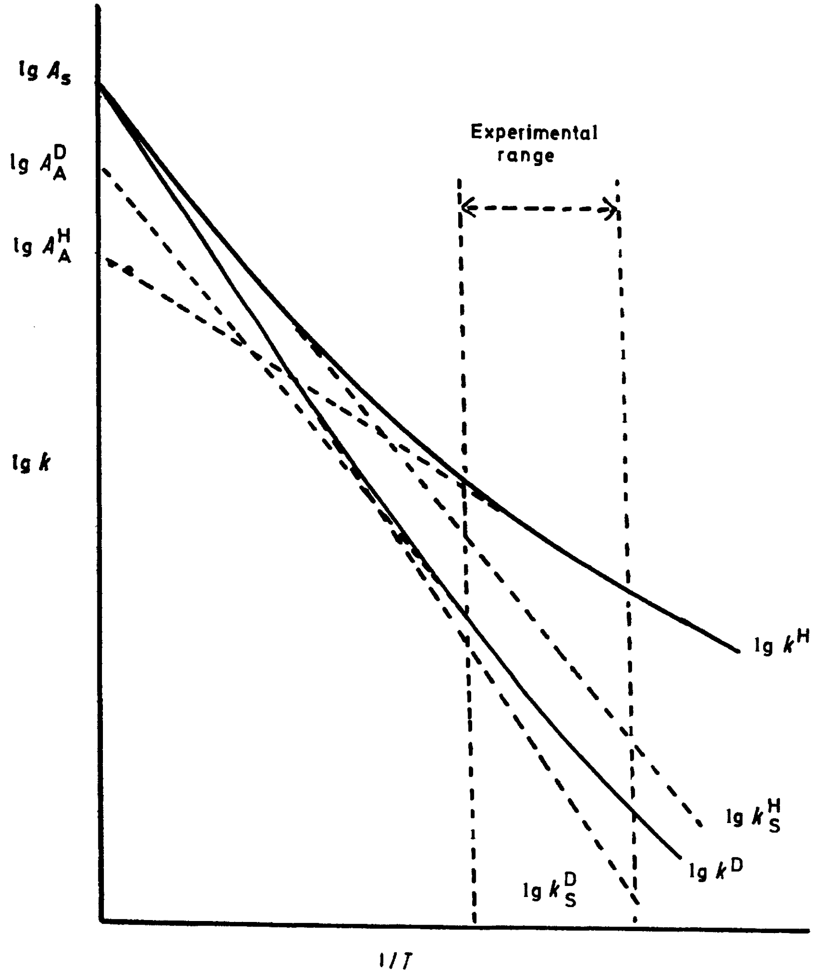

Figure 3 *Effect of tunnel correction on Arrhenius parameters*

lines correspond to the semi-classical theory, and extrapolate to a common values of $\lg(A_A)_s$ at $T = \infty$. The curved lines include the tunnel corrections, and deviate from the semi-classical values by an amount which increases with decreasing temperature and is greater for hydrogen than for deuterium at the same temperature. The procedure involved in calculating A_A from equation (8) amounts to fitting the experimental results to a straight line over a limited temperature range (indicated by vertical lines in Figure 3), and then extrapolating these straight lines to $T = \infty$. The Figure shows that these extrapolated values are both less than $(A_A)_s$, but that $A_A^D > A_A^H$, as stated above. This criterion for the existence of appreciable tunnel corrections is particularly valuable, since we have already seen that there are good theoretical reasons for supposing that $A_A{}^D/A_A{}^H)_s$ is a close to unity. The large values of $A_A{}^D/A_A{}^H$ reported in Table 4 are therefore highly significant in this context. A reaction which involves a considerable tunnel correction may in fact have $A_A{}^D/A_A{}^H \gg 1$, and yet exhibit 'normal' values of k^H/k^D and $E_A{}^D - E_A{}^H$, since the effect of tunnelling in increasing the latter may be compensated by the reduction caused by zero-point energy in the transition state.

(*d*) $E_A{}^H$ and $E_A{}^D$ will both decrease with decreasing temperature, but this effect will be greater for the lighter isotope, as illustrated in Figure 3. Appreciable deviations from the simple Arrhenius equation are anticipated only at low temperatures, and accurate measurements over a large temperature range are needed to detect them with certainty. There are few investigations of reactions in solution involving hydrogen which satisfy these conditions, and even fewer in which more than two isotopes have been studied. Most of these are due to Caldin and his collaborators: thus the reaction of the 2,4,6-trinitrobenzyl anion with acetic acid and with hydrogen fluoride in ethanol shows deviations in the expected sense below 183 and 263 K, respectively,[33] and the same is true for the reaction of 4-nitrobenzyl cyanide with ethoxide ions in ethanol—ether below 173 K.[34] The deviations from the simple Arrhenius law amounted to 50—100%, and were thus well outside the experimental error, but only for the last reaction was it shown that the deviations are considerably less for the deuterium compound. In general the study of Arrhenius deviations for reactions of a single isotopic species does not constitute a very useful criterion for appreciable tunnel corrections,[35] especially since such deviations may arise from quite different causes,[36] while if temperature coefficients have been measured for more than one isotope a comparison of Arrhenius parameters is more rewarding.

So far we have considered only the qualitative effect of tunnel corrections upon isotope effects. A quantitative treatment is much more difficult, since although we can usually make a good estimate of the height of the energy barrier, its shape and dimensions cannot be obtained experimentally, and any theoretical calculations must at present be based upon grossly simplified models. It is, however, possible to calculate the barrier characteristics which are necessary to account for the observed effects, in particular the values of $E_A{}^D - E_A{}^H$ and $A_A{}^D/A_A{}^H$, and then to judge whether these are reasonable in terms of what we know about molecular dimensions. This has been done particularly by Caldin,[24,37,38] and some of his results for proton-transfer reactions are given in Table 5. Since the shape of the barrier is unknown, and often also the enthalpy change in the reaction, calculations were made on the basis of equation 14, valid

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[33] E. F. Caldin and E. Harbron, *J. Chem. Soc.*, 1962, 3454; E. F. Caldin and M. Kasparian, *Discuss. Faraday Soc.*, 1965, 39, 25.
[34] E. F. Caldin, M. Kasparian, and G. Tomalin, *Trans. Faraday Soc.*, 1968, **64**, 2823.
[35] For a detailed analysis, see M. J. Stern and R. E. Weston, *J. Chem. Phys.*, 1974, **60**, 2803.
[36] J. R. Hulett, *Quart. Rev.*, 1964, **18**, 227.
[37] E. F. Caldin and G. Tomalin, *Trans. Faraday Soc.*, 1968, **64**, 2814, 2823.
[38] Ref. *k* of Table 4.

Table 5 *Barrier dimensions for proton-transfer reactions calculated from isotope effects* (*Values at* 298 K *unless otherwise stated*)

Reaction	$2a$/pm	ν_t^{H}/cm^{-1}	$(E^{\mathrm{D}} - E^{\mathrm{H}})$/kcal mol^{-1}	$\Gamma^{\mathrm{H}}/\Gamma^{\mathrm{D}}$	$E_{\mathrm{A}}^{\mathrm{H}}/E^{\mathrm{H}}$
I	117	924	0.42	1.79	0.88
II	117	1106	0.6	2.45	0.81
III	122	1001	1.2[a]	2.46[a]	0.87
IV	127	908	1.4[a]	1.92[a]	0.84
V	114	965	1.3	2.76	0.88
VI[b]	159	908	0.9	1.74	0.95
VII[c,d]	163	600	1.0	1.89	0.89
VIII (i)	82	1563	1.3	22	0.41
(ii)	80	1540	1.3	13	0.43
(iii)[d]	79	1420	1.2	6.5	0.49
(iv)	78	1408	1.0	6.0	0.50
(v)	79	1388	0.66	5.8	0.49
(vi)	90	988	0.73	1.75	0.88
(vii)	95	936	1.2	1.64	0.85
(viii)	96	890	0.57	1.53	0.80

[a] Values for tritium rather than deuterium. [b] Values for tritium yield identical barrier dimensions for this reaction. [c] Values at 183 K. [d] Low-temperature deviations from the Arrhenius equation yield barrier dimensions agreeing with those in the Table.

Key to reactions (references as in Table 4)

I $(\mathrm{CH_2})_3\mathrm{CO\overset{|}{C}LCO_2Et} + \mathrm{CH_2ClCO_2}^-$ in $\mathrm{D_2O}$
II $(\mathrm{CH_2})_3\mathrm{CO\overset{|}{C}LCO_2Et} + \mathrm{F}^-$ in $\mathrm{D_2O}$
III $2\text{-}\mathrm{MeOC_6H_4COCH_2L} + \mathrm{OH}^-$ in $\mathrm{H_2O}$
IV $2\text{-}\mathrm{MeC_6H_4COCH_2L} + \mathrm{OH}^-$ in $\mathrm{H_2O}$
V $\mathrm{Me_2CLNO_2}$ + 2,4,6-collidine in BuOH—$\mathrm{H_2O}$
VI $\mathrm{PhMeCLCH_2Br} + \mathrm{EtO}^-$ in EtOH
VII $4\text{-}\mathrm{NO_2C_6H_4CL_2CN} + \mathrm{EtO}^-$ in EtOH—$\mathrm{Et_2O}$
VIII $4\text{-}\mathrm{NO_2C_6H_4CLNO_2} + (\mathrm{NMe_2})_2\mathrm{C{=}NH}$ in (i) cyclohexene, (ii) mesitylene, (iii) toluene, (iv) dibutyl ether, (v) chlorobenzene, (vi) THF, (vii) dichloromethane, (viii) acetonitrile.

for moderate tunnelling through a symmetrical parabolic barrier. The calculations yield E^{H} and E^{D}, the true barrier heights (differing slightly because of the different zero-point energies) and also the barrier frequencies ν_t^{H}. In place of these frequencies we can specify the curvature (or negative force constant) F, as defined in equations (12) and (13), and a quantity which is easier to visualize is $2a$, the width of the barrier at its base, which is related to ν_t and F by*

$$a^2 = 2E/F = E/2\pi^2 m\nu_t^2 \tag{17}$$

Several points of interest emerge from Table 5. Most of the barrier widths $2a$ lie between 90 and 160 pm, and thus approximate to bond lengths. The difference between the true barrier heights, $E^{\mathrm{D}} - E^{\mathrm{H}}$, is now always less than $E_0{}^{\mathrm{H}} - E_0{}^{\mathrm{D}}$, the difference between the zero-point energies in the initial state, as it should be. However, not too much quantitative weight should be attached to these barrier parameters, since they are derived on the arbitrary assumption of a symmetrical parabolic barrier. In particular, since this barrier certainly underestimates the width at low energies, $2a$ will underestimate the distance through which the proton moves. The values obtained for ν_t^{H} are close to those predicted by various models for proton-transfer reactions,[20,21,39] and they are numerically similar to the real frequencies of bending vibrations for stable species or transition states. In view of equations (15) and (16), this means that it would be inconsistent to include bending vibrations in calculting isotope effects, but to omit tunnel corrections. Finally, it is satisfactory that for one of the reactions in Table 5 the same barrier dimensions can account for the results for all three isotopes, while for three other reactions low-temperature deviations from the Arrhenius equation yield the same dimensions as do the H/D isotope effects: clearly further cross-checks of this kind would be desirable.

The quantity $E_{\mathrm{A}}{}^{\mathrm{H}}$ is a measure of the average excess energy of the systems which react, and Table 5 shows that for most systems it amounts to 80—95% of E^{H}, the true barrier height. This implies that the semi-classical picture of proton-transfer reactions at ordinary temperatures is not usually radically modified by the inclusion of tunnel corrections: in particular, the qualitative use of hydrogen isotope effects for elucidating reaction mechanisms remains valid. On the other hand, the effect of tunnel corrections upon $k^{\mathrm{H}}/k^{\mathrm{D}}$ can be considerable, since

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* In some instances the tunnel correction is large enough to require the inclusion of some additional terms in equation (4). For a few of the systems studied, notably in ref. *k* of Table 4, the overall energy change in the reaction is known, and calculations can therefore be made with the appropriate unsymmetrical barrier. This affects the values derived for the barrier parameters, but the general conclusions are essentially the same as when a symmetrical barrier is assumed. The method of calculation employed by Caldin contains a minor inconsistency, in that he assumes identical values of $2a$ for the two isotopes, and hence arrives at slightly different values of the curvature F. Since it is a basic assumption of the theory that the potential energy surface is unaffected by isotopic substitution, it would be more logical to assume identical values for F, which, because of the difference in zero-point energies, would lead to slightly different values for $2a^{\mathrm{H}}$ and $2a^{\mathrm{D}}$. However, it is clear that this revision would have no appreciable effect on the results of the calculations.

[39] R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc.* (*B*), 1967, 985; R. A. More O'Ferrall, *ibid.*, 1970, 785.

for the same reactions the values of Γ^H/Γ^D vary between 1.5 and 2.5. Moreover, for the reaction of 4-nitrophenylnitromethane with tetramethylguanidine in the less polar solvents [reactions VIII (i) to VIII (v)] $E_A{}^H$ is only 40—50% of E^H, and Γ^H/Γ^D varies between 6 and 22, so that for these systems even the qualitative picture of the proton passing over the barrier can be misleading.

Similar conclusions are reached by treating the results for other proton-transfer reactions, and for transfer of hydrogen atoms or hydride ions (Table 4). It therefore seems a reasonable inference that the tunnel correction makes an appreciable contribution to the isotope effect for most reactions involving hydrogen transfer, even when the experimental information currently available does not reveal any discrepancies with the semi-classical treatment. We have seen that the value of $A_A{}^D/A_A{}^H$ is the most significant criterion in this context, and there are in fact very few well-established examples of $A_A{}^D/A_A{}^H \leqslant 1$. Exceptions in this respect are the oxidation of $LCOO^-$ by $MnO_4{}^-$, $A_A{}^D/A_A{}^H = 0.8$,[40] the reaction of $PhCL_2NO_2$ with piperidine,[41a] $A_A{}^D/A_A{}^H = 0.3$, and of $(4\text{-}NO_2C_6H_4)_2CL_2$ with Bu^tO^-,[42] $A_A{}^D/A_A{}^H = 0.3$ and the elimination reaction of $Ph_2CLCH_2OSO_2Ph$ in presence of MeO^-,[41b] $A_A{}^D/A_A{}^H = 0.9$. The next paragraph shows that these values could be consistent with an appreciable tunnel correction, but the question must at present remain open.

Conclusions (*b*) and (*c*) (p. 531) need modification if the tunnel correction becomes large, as will always be the case when the temperature is sufficiently low. This becomes physically apparent if we consider the limiting case when the temperature is so low that thermal activation is inappreciable, and reactions can only occur in an exothermic direction. Reaction for both isotopic species will then take place by tunnelling from the zero-point levels: both $E_A{}^H$ and $E_A{}^D$ will tend to zero, and the difference $E_A{}^D - E_A{}^H$ will be much *less* than $E_0{}^H - E_0{}^D$. Similarly, the ratio $A_A{}^D/A_A{}^H$ (now equal to k^D/k^H) is just the ratio of barrier permeabilities from the zero-point levels, and this will certainly be much *less* than unity, because of both the lower mass and the higher energy level of the lighter isotope. Detailed calculations have been carried out for an extended form of equation (14)[32,27,43] and also for other types of barrier,[44,45] giving the following result for the temperature variation of $A_A{}^D/A_A{}^H$ for a given reaction. Starting at unity at high temperatures, as the temperature is lowered it increases, passes through a maximum ($\gg 1$), decreases, and finally becomes much less than unity at very low temperatures. There is thus an intermediate temperature range in which $A_A{}^D/A_A{}^H$ (and also $E_A{}^D - E_A{}^H$) is close to its semi-classical value, although the tunnel correction is large. This behaviour is not often encountered in practice, although it probably explains the fact that in the oxidation of dihydrophenanthrene[46] $A_A{}^D/A_A{}^H$ has the almost 'normal' value of 1.6, although

[40] R. P. Bell and D. P. Onwood, *J. Chem. Soc. (B)*, 1967, 150.

[41] (*a*) Ref. *k* of Table 4; (*b*) A. V. Willi, *J. Phys. Chem.*, 1966, **70**, 2705.

[42] J. H. Kim and K. T. Leffek, *Canad. J. Chem.*, 1974, **52**, 592.

[43] R. P. Bell and R. L. Tranter, unpublished calculations.

[44] A. Bromberg, K. A. Muszkat, and A. Warshel, *J. Chem. Phys.*, 1970, **52**, 5952.

[45] M. J. Stern and R. E. Weston, *J. Chem. Phys.*, 1974, **60**, 2808.

[46] Ref. *o* of Table 3.

k^H/k^D is *ca.* 100 at 242 K, suggesting a tunnel correction Γ^H/Γ^D of *ca.* 10. In any event the message of these calculations is clear: deviations of A_A^D/A_A^H from the semi-classical limits provide good evidence for a considerable degree of tunnelling, but the absence of such deviations does not exclude the presence of significant tunnelling.

Equation (14) indicates that the tunnel correction to the isotope effect is determined only by the shape of the barrier near the top, and is independent of the overall enthalpy or free-energy change of the reaction: the same is true for barriers of any form provided that the tunnel correction does not become too large. This is physically reasonable, since for moderate tunnel corrections almost all the reacting systems have energies close to the top of the barrier, as shown in the last column of Table 5. However, if the tunnel corrections become large, so that systems of lower energy are involved, the value of Γ^H/Γ^D should depend upon the overall ΔH or ΔG, and in particular should have a maximum value when ΔH or ΔG is zero, *i.e.* for a symmetrical barrier. This is shown by detailed calculation,[21] and its physical basis is apparent from Figure 4: only that part of the barrier which lies above both the initial and the final states is available for tunnelling, and the extent of this region is at a maximum for a symmetrical barrier.

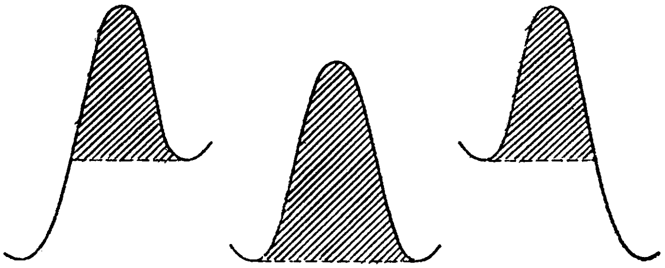

Figure 4 *Tunnelling regions (shaded areas) as a function of barrier symmetry* (Reproduced by permission from 'The Proton in Chemistry', 2nd edn., Chapman and Hall, London, 1974)

It has been known for some time that k^H/k^D frequently varies considerably with ΔG, which for proton transfers is proportional to $\Delta pK = pK_1 - pK_2$, where 1 and 2 represent the two acid–base systems involved, and in some instances there is evidence for a maximum in k^H/k^D in the neighbourhood of $\Delta pK = 0$. The variations in pK are commonly effected by introducing substituents into one or both of the reactants, and studies have been made of proton-abstraction by bases from carbonyl compounds[47] and nitroalkanes,[48] and of base-catalysed

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[47] F. A. Long and D. Watson, *J. Chem. Soc.*, 1958, 2019; R. P. Bell and J. E. Crooks, *Proc. Roy. Soc.*, 1965, **A286**, 285; D. J. Barnes and R. P. Bell, *ibid.*, 1970, **A318**, 421.

[48] O. Reitz, *Z. Phys. Chem. (A)*, 1936, **176**, 363; R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A294**, 273; J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 905; R. P. Bell and R. L. Tranter, *Proc. Roy. Soc.*, 1974, **A337**, 517.

elimination reactions.[49] In other investigations ΔpK for a given reaction has been changed by varying the composition of mixtures of dimethylsulphoxide with water or alcohols. This procedure has been applied to the inversion of (−)-menthone[50] and the ionization of nitroethane,[51] both in presence of hydroxide ions, the base-catalysed isotope exchange of diphenylmethane,[52] and the base-catalysed elimination reaction of $PhCH_2CH_2\overset{+}{N}Me_3$.[53] For hydrogen atom transfers there is less evidence for the dependence of k^H/k^D upon ΔH or ΔG, though such an effect is apparent in a study of 17 reactions between free radicals and thiols.[54]* A particularly striking example of this kind appears in a study of the oxidation of dihydrophenanthrene by molecular oxygen.[55] This is a chain reaction with two stages,

Initiation $PH_2 + O_2 \rightarrow \dot{P}H + H\dot{O}_2$

Propagation $PH_2 + H\dot{O}_2 \rightarrow \dot{P}H + H_2O_2$

of which the first is almost thermoneutral, while the second is strongly exothermic ($\Delta H \simeq -40$ kcal mol^{-1}). Correspondingly, at 263 K it is found that k^H/k^D is 64 for the initiation reaction, but only 7.2 for propagation. Finally, a close parallel to these results for chemical processes is to be found in isotopic separation in the cathodic discharge of hydrogen, in which the rate-determining process is believed to be the passage of a proton across an energy barrier from the hydronium ion to the cathode. The height and position of the barrier can be varied by varying the potential applied to the cathode, and this is in fact found to have a considerable effect on the isotopic separation factor. For example, in the electrolysis of strong acids at a mercury cathode[56] k^H/k^D changes linearly from 3.4 to 9.0 as the cathode potential is varied from −0.7 to 1.3 V, corresponding to a variation of 14 kcal mol^{-1} in ΔG for the electrochemical reaction.

In the present context it is natural to attribute all these variations in isotope effect to the variations in the tunnel correction Γ^H/Γ^D already discussed. There is, however, an alternative explanation which has been generally accepted,

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* The authors claim that there is a maximum in the plot of k^H/k^D against ΔH, but the evidence for this is slight, since it depends upon the values for only two reactions, one of which appears to have been mis-plotted on the diagram. However, there is no doubt that k^H/k^D does vary considerably with ΔH.

[49] J. F. Bunnett, *Angew. Chem. Internat. Edn.*, 1962, **1**, 225; D. Cook, R. E. J. Hutchinson, J. K. Macleod, and A. J. Parker, *J. Org. Chem.*, 1974, **39**, 534; D. J. McLennan and R. J. Wong, *J.C.S. Perkin II*, 1974, 526.

[50] R. P. Bell and B. G. Cox, *J. Chem. Soc. (B)*, 1970, 194.

[51] R. P. Bell and B. G. Cox, *J. Chem. Soc. (B)*, 1971, 783.

[52] F. S. Yakushin, U. I. Ranneva, V. V. Marchenko, I. A. Romanskii, and A. I. Shatenshtein, *Kinetika i Kataliz*, 1971, **12**, 591.

[53] A. F. Cockerill, *J. Chem. Soc. (B)*, 1967, 967.

[54] W. A. Pryor and K. G. Kneipp, *J. Amer. Chem. Soc.*, 1971, **93**, 5584.

[55] Ref. *o* of Table 3.

[56] J. O'M. Bockris and D. B. Matthews, *Electrochim. Acta*, 1966, **11**, 43; *J. Chem. Phys.*, 1966, **44**, 298.

originally due to Westheimer[57] and later elaborated by other authors.[58] This explanation depends upon the existence in the transition state of a hydrogen-transfer reaction of two types of stretching motion

$$\text{(a)}\quad \overset{\leftarrow}{\mathrm{X}}{-}{-}{-}\overset{\rightarrow}{\mathrm{H}}{-}{-}{-}\overset{\leftarrow}{\mathrm{Y}} \qquad\qquad \text{(b)}\quad \overset{\leftarrow}{\mathrm{X}}{-}{-}{-}\overset{(?)}{\mathrm{H}}{-}{-}{-}\overset{\rightarrow}{\mathrm{Y}}$$

Of these (a) is the motion leading to reaction, and may be assigned an imaginary frequency. On the other hand, (b) (the so-called 'symmetrical' vibration) is a real vibration and will possess a zero-point energy. In a completely symmetrical transition state the central hydrogen will remain stationary in this vibration which will therefore contribute nothing to the isotope effect, but in a less symmetrical situation the frequency and zero-point energy will be somewhat dependent on the mass of the hydrogen isotope. The effect of this is to decrease the observed isotope effect (*cf.* Figure 2 and equation 4), so that this picture predicts that in a series of similar reactions the isotope effect should have a maximum value when the transition state is symmetrical, falling to lower values for reactant-like or product-like transition states. Since the value of ΔH or ΔG is a reasonable measure of how far the transition state departs from symmetry, this prediction is in qualitative accord with the observed variations in $k^{\mathrm{H}}/k^{\mathrm{D}}$.

There are thus available two quite different alternative explanations for these variations, and experiment does not help in choosing between them. Some guidance may be sought by model calculations, and so far these have suggested that the tunnel correction has much more influence than the symmetrical vibration of the transition state. Thus a treatment based on bond orders[59] and the Westheimer picture predicts only a small variation in $k^{\mathrm{H}}/k^{\mathrm{D}}$ (7.0 to 7.3) for a series of proton abstractions from carbon acids for which the observed values range from 3.5 to 10.3, and a fairly realistic electrostatic model[21] yields the same result: on the other hand, when the tunnel correction was included the last model predicted variations close to those observed.* Similarly, calculations based on semi-empirical energy surfaces for the initiation and propagation steps in the oxidation of dihydrophenanthrene[60] indicate that the very large difference between the isotope effects for these two reactions originates in the tunnel corrections and not in any real vibrations of the transition state, while the same conclusion is reached in a theoretical treatment of the effect of polarization potential upon electrolytic H/T separation.[56] Further work is clearly required, but it may be noted that both explanations relate the isotope effect to the *symmetry of the transition state* or the *degree of proton transfer*, though the quantitative meaning

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* The opposite conclusion was reached in another set of model bond-order calculations,[39] but this is because the authors calculated tunnel corrections from the first few terms of equation (16), which is not permissible for the values of u involved.

[57] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

[58] J. Bigeleisen, *Pure Appl. Chem.*, 1964, **8**, 217; A. V. Willi and M. Wolfsberg, *Chem. and Ind.*, 1964, 2097; W. J. Albery, *Trans. Faraday Soc.*, 1967, **63**, 200.

[59] A. V. Willi, *Helv. Chim. Acta*, 1971, **54**, 1220.

[60] A. Warshel and A. Bromberg, *J. Chem. Phys.*, 1970, **52**, 1262; A. Bromberg, K. A. Muszkat, and A. Warshel, *ibid.*, p. 5952.

of these terms is different in the two cases. Thus if a reaction is modified by introducing substituents, the sign of $\delta(k^{\mathrm{H}}/k^{\mathrm{D}})/(\delta(\Delta G)$ should still serve to discriminate between reactant-like transition states (positive sign) and product-like ones (negative sign).

It now seems certain that the *variation of isotope effects with solvent* cannot be attributed solely to the effect of the solvent on ΔG, as was at first supposed.[50–53] This is shown most clearly by the results of Caldin and Mateo[61] for the reaction of 4-nitrophenylnitromethane with tetramethylguanidine in eight aprotic solvents (see Tables 3—5). Although $k^{\mathrm{H}}/k^{\mathrm{D}}$ at 298 K varies between 11 and 50, it bears no relation to the rather small variations in ΔG (*ca.* 3 kcal mol^{-1}). It is, however, noticeable that the very high isotope effects found in non-polar solvents are much reduced on passing to polar solvents such as dichloromethane and acetonitrile, and this suggests an explanation in terms of the *involvement of solvent molecules* with the polar transition state: moreover, since the magnitude of the isotope effect on the rates and on the Arrhenius parameters is evidence for a considerable tunnel correction in the less polar solvents, it may be this correction which is affected. It has so far been assumed that the mass m in equations (10) and (13) is close to the mass of the appropriate hydrogen isotope, but if the proton transfer involves the simultaneous rotation or translation of one or more solvent molecules, the *effective mass* for passage across the energy barrier will be greater than this, and the tunnel correction correspondingly reduced.* In the less polar solvents the interaction of the solvent with the transition state will involve only electron polarization, and hence no increase in effective mass. Calculation shows[61] that the observed effects could be accounted for by increases in the effective masses of the proton and deuteron to 1.2—1.3 and 2.2—2.3, respectively, in the more polar solvents. Two other findings lend some support to this explanation. Firstly, Tables 3—5 show that large tunnel corrections are frequently found for sterically hindered systems, and this has been attributed to a higher and steeper energy barrier:[62] according to the present view the role of the hindering groups is to exclude solvent molecules and thus preserve a low effective mass for the proton. Secondly, in the racemization of $\mathrm{Ph_3C.CLMeCN}$ by potassium t-butoxide in t-butyl alcohol[63] $k^{\mathrm{H}}/k^{\mathrm{D}} = 15$ at 298 K, but is reduced to 5 on the addition of crown ether: this can be explained by supposing that in the former case the potassium ion forms a contact ion-pair with the transition state, thus effectively excluding solvent from the already crowded system, while the addition of crown ether removes the potassium ion and permits the approach of a solvent molecule, thus increasing the effective mass of the proton. Further studies of the solvent-dependence of hydrogen

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* An increase in effective mass will of course also affect the contribution of real vibrations of the transition state, but we have seen that this effect is likely to be small, and it would in fact *increase* the isotope effect.

[61] Ref. *f* of Table 3. A similar lack of correlation has been observed in the reactions of several carbon acids with bases in mixed aqueous-organic solvents (B. G. Cox and A. Gibson, to be published).

[62] Ref. *b* of Table 3.

[63] Ref. *e* of Table 3.

isotope effects may prove a valuable method of investigating the extent of solvent participation in proton-transfer reactions. Such dependence should be small in hydrogen-atom transfers, but no evidence on this point is yet available.

A number of criticisms can be levelled against the procedure outlined here of multiplying the semi-classical transition state expression by a tunnel correction calculated for a one-dimensional barrier, since in any fully quantum-mechanical treatment the tunnel correction would not appear separately. Motion along the reaction path constitutes a separable co-ordinate only when the barrier is parabolic (which gives an additional reason for choosing barriers of this form), and then only in the immediate neighbourhood of the energy maximum: in general, therefore, the tunnelling situation should strictly be formulated in terms of an energy surface involving at least two spatial co-ordinates, which presents a much more difficult problem than the one-dimensional barrier. It appears, therefore, that the usual procedure is strictly justifiable only when the quantum corrections are small[64] (*i.e.* given by the first term of equation 16). However, in spite of much work on the subject there appears to be no agreement as to whether the one-dimensional treatment over- or under-estimates the tunnel corrections when these become large. Further, since the detailed shape of the energy surface is unknown for solution reactions, it seems reasonable to adhere to the present formulation, especially since a single co-ordinate is a good approximate representation of the motion of a light particle between two heavy centres. Finally, the use of equation (11) can be criticized, since it assumes a continuous energy distribution in the reactants, in place of quantized vibrational levels. However, since in most reactions the energies of interest are those near the top of the barriers, the vibrational levels become close together. Moreover, one component of the energy W will be the relative translational motion of the reactants, which is not quantized, and since further in solution each vibrational level will be broadened by interactions with the solvent the assumption of a continuous energy distribution probably causes little error. It has been claimed[56] that the absence of any sudden changes of slope in the Tafel relation for the electrolytic H/T separation demonstrates that discrete vibrational levels in the hydronium ion are not involved. In our present state of knowledge it seems justifiable to retain the simple treatment outlined in this review.

Much experimental and theoretical work has been carried out on *hydrogen isotope effects in gas reactions*, mainly involving hydrogen atom transfer. Only a brief review will be given here, since the position is in some respects more confused than for solution reactions. This is largely because attempts at theoretical interpretation have been more ambitious, in that *ab initio* or empirical energy surfaces have been used to predict not only isotope effects, but also absolute values of velocity constants, especially for reactions involving hydrogen atoms and molecules, or simple radicals such as CH_3 and CF_3. Moreover, when several light atoms are moving simultaneously the reaction co-ordinate will be a complicated function of atomic positions, and the effective mass for tunnelling will

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[64] E. Wigner, *Z. phys. Chem.* (*B*), 1932, **19**, 203.

vary along this co-ordinate. It should also be remembered that measured velocity constants for elementary gas reactions are frequently of relatively low accuracy, and rarely extend to lower temperatures, at which comparison between theory and experiment is most informative. In particular, it is usually unprofitable to look for large qualitative anomalies such as those illustrated in Tables 3 and 4. Most authors have used the transition-state theory expression (7) multiplied by some form of tunnel correction. Even for reactions involving only three atoms it is rarely possible to derive a sufficiently accurate energy surface from first principles,* and it is usual to employ some form of semi-empirical surface involving constants which are adjusted to fit an experimental quantity such as the observed activation energy. The general conclusion[67] is that the observed isotope effects can be reproduced by such a procedure, but only if a substantial tunnel correction is included. For example, when a completely empirical energy surface was fitted to the results for $Cl + H_2$ (HD, D_2), omission of tunnelling or inclusion of only the first term of equation (16) led to unrealistically small bending force constants for the transition state.[68]

Many modern theories of simple gas reactions (not specifically concerned with isotope effects) abandon transition-state theory in favour of the more fundamental approach of considering individual trajectories connecting specified rotational and vibrational states of reactants and products, various combinations of classical and quantum mechanics being used in the calculations.[69] The calculated rates of these individual processes can in some instances be compared directly with the results of molecular beam experiments, while the reaction rate observed in ordinary kinetic experiments is obtained by averaging over all possible trajectories and states. Comparisons with the transition-state treatment (including tunnel corrections) for a few simple systems suggests that while this treatment may give erroneous results for the interconversion of specified quantum states, the averaged reaction rate is predicted fairly accurately, except at low temperatures. This result is a comforting one for many chemists, since it is by no means self-evident that the transition-state approach will remain valid in the absence of solvent molecules to maintain an equilibrium energy distribution.

During the past few years interesting observations have been reported on *hydrogen isotope effects in solid state reactions*. These systems have the advantage that they can be studied down to very low temperatures, while the presence of a fixed framework may help to define the reaction co-ordinate in a simple manner and to justify a one-dimensional tunnelling treatment. Most of the experimental

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* The most accurate *ab initio* calculation for three hydrogen atoms[65] is restricted to linear configurations, and a very recent report[66] states that 'for the first time the non-empirical calculation of reaction surfaces for chemically important processes seems to be within reach'.

[65] B. Liu, *J. Chem. Phys.*, 1973, **58**, 1925.

[66] 'Computational Chemistry and Physics', Science Research Council, London, 1974, p. 5.

[67] For references see Ref. 27, p. 289.

[68] M. J. Stern, A. Persky, and F. S. Klein, *J. Chem. Phys.*, 1973, **58**, 5697.

[69] For a recent review with many references see J. N. L. Connor, *Ann. Reports (A)*, 1973, **70**, p. 5.

work relates to crystals or glasses of methyl cyanide,[70] methyl isocyanide,[71] and methanol[72] in all of which methyl radicals can be generated by irradiation. The subsequent hydrogen-abstraction process

$$\dot{C}H_3 + CH_3X \rightarrow CH_4 + \dot{C}H_2X$$

is then followed by e.s.r. observations at temperatures between 67 and 125 K. The observed velocity constants give strongly curved Arrhenius plots, with apparent activation energies which are a small fraction of those observed for the same reactions in the gas phase at much higher temperatures (300 to 600 K), and pre-exponential factors which are lower by many powers of ten than the vibration frequency of the C—H bond. This behaviour is indicative of tunnelling, and a quantitative treatment[73] gives a complete description of the experimental facts for the reaction in solid acetonitrile. The tunnel 'corrections' are extremely large at these low temperatures, ranging from *ca.* 10^5 to 10^{15}, and it is reasonable to describe the reaction as taking place entirely by a tunnelling mechanism. Very large hydrogen isotope effects would be expected, and in fact the abstraction of deuterons from the species CD_3X is too slow to be detectable, though CD_3-radicals disappear very slowly to give products other than $\dot{C}D_2X$.* Even in the absence of tunnelling the effects of zero-point energy would lead to large values of k^H/k^D at these low temperatures, and experiment can only give lower limits for this quantity, for example, $k^H/k^D > 2 \times 10^3$ for acetonitrile at 87 K, and $k^H/k^D > 1.1 \times 10^3$ for methyl isocyanide at 110 K. These limits are, respectively, about three and six times the maximum values expected from zero-point energy effects alone, though still far below the values of 10^5—10^7 predicted by the tunnelling model.[73]

Similar effects may be involved in irradiated solid hydroxyurea[74] and its deuteriated analogue, where the conversion of pairs of neighbouring $NH_2CONH\dot{O}$ radicals into separated radicals has been followed by e.s.r. observations between 253 and 268 K. The process shows a large isotope effect ($k^H/k^D \simeq 17$), and is believed to involve the transfer of hydrogen atoms from a hydroxyurea molecule to an adjacent radical. The reported Arrhenius parameters show large anomalies characteristic of tunnelling processes, but the accuracy is admittedly low and further evidence would be desirable. Another type of anomalous effect appears in the diffusion of the hydrogen isotopes in palladium,[75] where the order of rates is D > H > T, the activation energies being in the reverse order. This has been explained in terms of a tunnelling process from individual vibrational levels of the three isotopes in the octahedral sites. A similar

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* This behaviour has led to the term 'all-or-nothing' isotope effects,[71] since under the same conditions the reactions of CH_3X and CD_3X lead predominantly to quite different products, a fact which might even have preparative applications.

[70] E. D. Sprague and F. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 787.

[71] J.-T. Wang and F. Williams, *J. Amer. Chem. Soc.*, 1972, **94**, 2930.

[72] A. Campion and F. Williams, *J. Amer. Chem. Soc.*, 1972, **94**, 7633.

[73] R. J. Le Roy, E. D. Sprague, and F. Williams, *J. Phys. Chem.*, 1972, **76**, 546.

[74] Y. Haven, R. C. Williams, P. J. Hamrick, and H. Shields, *J. Chem. Phys.*, 1974, **60**, 127.

[75] For a review see G. Sicking, *Ber. Bunsengesellschaft phys. Chem.*, 1972, **76**, 790.

explanation has been given for the large H/D isotope effect for diffusion in several other metals at low temperatures.[76]

There are many interesting possibilities in the investigation of hydrogen isotope effects in solid-state processes, especially at low temperatures, but the experimental techniques are frequently difficult. Some of the advantages of localized systems might be retained by studying intramolecular transfers of protons or hydrogen atoms in rigid molecules, or between species adsorbed strongly on a surface: little has been done in this direction. In conclusion, attention is drawn to two intriguing (though not strictly relevant) recent reports. The first[77] describes an e.s.r. study of the reaction of hydrogen atoms with thin films of poly(isobutene) and poly(ethylene oxide) between 99 and 145 K. The activation energies vary with temperature and are less than one third of values estimated for the corresponding gas reaction. The results are interpreted in terms of a tunnelling mechanism, but no isotope effects were measured. The second[78] reports calorimetric estimations of the average time τ required to add a formaldehyde molecule to a growing polymer chain in films of solid formaldehyde between 4.2 and 150 K: it thus relates to the reaction $CH_2\text{-}\dot{O} + CH_2O \rightarrow CH_2\text{-}O\text{-}CH_2\text{-}\dot{O}$. The Arrhenius equation is obeyed between 150 and 80 K, with $E_A \bumpeq 2.5$ kcal mol^{-1}: at 80 K $\tau \bumpeq 10^{-5}$s. Below 80 K, E_A decreases towards zero, and in the range 10—4.2 K τ approaches a limiting value $\bumpeq 10^{-2}$s; by contrast, the values extrapolated from the linear Arrhenius plot above 80 K are $\tau \bumpeq 10^{30}$ years at 10 K and 10^{100} years at 4.2 K. No deuterium isotope effect could be detected, and it is concluded that the reaction involves tunnelling of CH_2O molecules as a whole. Calculation shows that, in spite of the large mass of this species, such a mechanism is feasible at the very low temperatures involved.

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[76] For diffusion in tantalum, and references to measurements in vanadium, niobium, and palladium, see J. M. Gill, D. O. Hayward, and N. Taylor, *Proc. Roy. Soc.*, 1973, **A335**, 141.

[77] A. M. Dubinskaya and P. Yu. Butyagin, *Doklady Akad. Nauk S.S.S.R.*, 1973, **211**, 141.

[78] V. I. Goldanskii, M. D. Frank-Kamenetskii, and I. M. Barkalov, *Doklady Akad. Nauk S.S.S.R.*, 1973, **211**, 133.