ACCOUNTS OF CHEMICAL RESEARCH

VOLUME 5 NUMBER 7 JULY, 1972

Theoretical Evaluation of Experimentally Observed Isotope Effects

MAX WOLFSBERG

Department of Chemistry, University of California, Irvine, California 92664†

Received April 26, 1971

The basic principle which underlies most theoretical considerations of isotope effects is the Born–Oppenheimer (BO) approximation. This approximation states that one can separate the quantum mechanics of molecules into a problem of electronic motion with the nuclei in fixed positions and a separate problem of nuclear motion.

In the electronic motion problem, the only property of nuclei which appears is their charge. The potential energy for the nuclear motion problem is the electronic energy (including the repulsion between nuclei) as a function of nuclear configuration; this potential energy is then independent of the isotopic masses of the nuclei. The kinetic energy expression of the nuclear motion problem does, of course, contain the masses of the nuclei. Thus, the study of isotope effects on molecular properties is a study of how different masses of nuclei affect motion on the same potential surface. Clearly, study of effects of isotopic substitution must be an important tool for giving information about the potential energy surfaces on which molecules move.

In the past four decades, a large number of studies on isotope effects has been carried out. The studies have involved a strong interplay between experiment and theory and the participation of many distinguished scientists. While a few historic publications may be noted, no attempt is made here to summarize the extensive literature.

In this Account, it will not be possible to review all the areas of chemistry where isotope effects have been studied. The use of isotope effects in deducing the force constants, which characterize the potential energy surfaces on which molecules move, from observed vibrational spectra is a clear example of how isotope effects can be employed. Much interest in isotope effects has involved effects on gas-phase equilibrium constants. The appropriate theory will be developed. This theory may be used to interpret experimental results in order to obtain information about the energy levels corresponding to the potential energy surfaces on which molecules move. This theory may also be applied to the consideration of isotope effects on the vapor pressures of condensed phases and of isotope effects on reaction rates. It will be shown that the theoretical evaluation of experimentally observed effects enables one to obtain detailed information about the potential energy surfaces corresponding to the condensed phase and to the reaction transition state.

In the theoretical study of isotope effects, as in many theoretical endeavors, it is often necessary to make use of simplifying assumptions or simplifying models. (The BO approximation is one such assumption.) It is often possible, in a given study, both to test the validity of the model and to obtain detailed information about the model.

Professor Wolfsberg's main research interests are in the area of isotope effects, energy transfer, and the electronic structure of molecules. He has been pursuing these interests actively since the receipt of his Ph.D. from Washington University, St. Louis, in 1951. From 1951 to 1969 he was at Brookhaven National Laboratory, and from 1966 to 1969 he was also Professor at the State University of New York at Stony Brook. Since 1969 he has been at University of California, Irvine.

Isotope Effects in Vibrational Spectroscopy

For small displacements of the nuclei in a molecule from the equilibrium internuclear separation, the potential energy for nuclear motion is often approximated as a quadratic function in the internal displacement coordinates (*i.e.*, bond stretches, bond angles, etc.). In this harmonic approximation, vibrations are described in terms of normal mode frequencies ν_i.[1]

Spectroscopists try to correct observed fundamental frequencies to harmonic frequencies by methods based on the theory of anharmonic vibrations, *vide infra*. From the observed harmonic frequencies, one tries to obtain the coefficients in the quadratic potential function—the harmonic force constants. For a diatomic molecule with potential function

$$V = (1/2)k(r - r_0)^2 \tag{1}$$

where $r - r_0$ or Δr is the displacement of the internuclear distance from its equilibrium value and k is the force constant, the harmonic frequency is given by

$$\nu = (1/2\pi)\sqrt{k/\mu} \tag{2}$$

---

† Work supported by the U. S. Atomic Energy Commission under Contract AT(04-3)-34, Project Agreement No. 188.

[1] E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill, New York, N. Y., 1955.

μ is the reduced mass of the diatomic molecule AB ($\mu = m_A m_B/(m_A + m_B)$). Observation of isotopic frequencies of H_2, HD, and D_2 tests the above expression and whether the frequencies have been properly corrected for anharmonicity, but basically one frequency determines k. The fact that this is what is found in practice to a good degree of accuracy confirms a prediction of the BO approximation.

For a bent triatomic molecule like H_2O, the most general quadratic force field has the form

$$V = (1/2)k_{rr}(\Delta r_1^2 + \Delta r_2^2) + (1/2)k_{\delta\delta}\Delta\delta^2 + k_{rr'}\Delta r_1\Delta r_2 + k_{r\delta}(\Delta r_1\Delta\delta + \Delta r_2\Delta\delta) \quad (3)$$

Here Δr and $\Delta\delta$ refer to bond stretch displacement and bond angle displacement, respectively. The experimental observation of the three harmonic frequencies of H_2O cannot suffice to obtain all four potential constants. If, however, data for D_2O and HDO are also available, all four constants can be obtained. In fact, one not only obtains the constants but one tests at the same time whether the observed (corrected) frequencies correspond truly to the harmonic frequencies and also whether the BO approximation is valid. The frequencies of isotopically substituted molecules are connected through some relationships independent of potential constants (the Teller–Redlich product rule and the so-called sum rules[1]) so that the maximum number of force constants that could be determined by having data available for several isotopically substituted molecules is not equal to the number of frequencies available. The extensive literature on harmonic force constant determinations attests to the importance of isotope effects in such studies.

Recently, there has been much interest in obtaining cubic and quartic force constants in the potential energy expressions[2] (the coefficients of terms cubic and quartic in the displacements, *i.e.*, $k_{rrr}(\Delta r_1^3 + \Delta r_2^3)$, $k_{rrrr}(\Delta r_1^4 + \Delta r_2^4)$, etc.). The experimental data here are obtained from the anharmonicity corrections found when comparing observed fundamentals, overtones, and combination bands. By making use of isotopic substitution, one obtains additional data about the same force field. For calculations on specific systems, reference should be made to the literature, *e.g.*, water[3] (H_2O, D_2O, HDO), ammonia[4] (NH_3, ND_3).

Isotope Effects on Chemical Equilibria in the Gas Phase

The effect of isotopic substitution on equilibrium constants has long[5] been the subject of experimental and theoretical investigations. There are two types of isotope effects on equilibrium constants. Thus for reactions 4 the deviation of K_1/K_2 from unity is the isotope effect on the equilibrium constant (often, also

$$\begin{aligned} CH_3Cl + HBr &\overset{K_1}{\rightleftharpoons} CH_3Br + HCl \\ CD_3Cl + HBr &\overset{K_2}{\rightleftharpoons} CD_3Br + HCl \end{aligned} \quad (4)$$

in this Account, one refers to K_1/K_2 as the isotope effect). Similarly the deviation of the equilibrium constant K_3 from unity (or, sloppily, K_3) is the isotope effect for the isotopic exchange equilibrium 5. Obviously,

$$CH_3Cl + CD_3Br \overset{K_3}{\rightleftharpoons} CH_3Br + CD_3Cl \quad (5)$$

here, $K_3 = K_1/K_2$. K_3 at room temperature has been calculated[6] to be 1.13. The isotope effect is comparatively small for a H/D effect since the methyl group, where the isotopic substitution occurs, is preserved in all relevant species; the effect is called a secondary effect. For reaction 6, Bigeleisen, *et al.*,[7] have determined

$$NH_3 + HD \overset{K_4}{\rightleftharpoons} NH_2D + H_2 \quad (6)$$

$K_4 = 5.3$ at 295°K. Here the deviation of K_4 from $^3/_2$ is important; there are statistically three ways of forming NH_2D relative to NH_3 and two ways of forming HD relative to H_2, so that if H and D were randomly distributed K would be $^3/_2$. Similarly for equilibrium 7

$$H_2O + D_2O \overset{K_5}{\rightleftharpoons} 2HDO \quad (7)$$

the deviation of K_5 from 4 is important. There are statistically two ways of forming HDO relative to H_2O or to D_2O. Thus, in the absence of isotope effects, the equilibrium constant is equal to 4.

When one expresses these equilibrium constants theoretically, one replaces the concentrations in the K expression by molecular partition functions[8] Q. Isotope

$$K_3 = \frac{Q_{CD_3Cl}/Q_{CH_3Cl}}{Q_{CD_3Br}/Q_{CH_3Br}} \quad (8)$$

effects can be expressed in terms of ratios of partition functions of isotopic molecules; these ratios will be taken here, when possible, as heavy molecule over light molecule, a convenient convention established by Bigeleisen and Mayer.[9]

If classical mechanics is employed, it is straightforward to show that the isotopic ratio of partition functions is equal to the ratio of the isotopically substituted masses raised to the power $^3/_2$ times the inverse ratio of the symmetry numbers s. The symmetry number s of a molecule is defined[8] as the number of different values of rotational coordinates which correspond to one orientation of the molecule, remembering that identical atoms are indistinguishable. Thus, $s_{NH_3} = 3$, $s_{H_2} = s_{H_2O} = s_{D_2O} = 2$, $s_{HD} = s_{HDO} = s_{NH_2D} = 1$. Then

$$\frac{Q_{CD_3Cl}}{Q_{CH_3Cl}}\frac{s_{CD_3Cl}}{s_{CH_3Cl}} = \frac{Q_{CD_3Br}}{Q_{CH_3Br}}\frac{s_{CD_3Br}}{s_{CH_3Br}} = \left[\left(\frac{m_D}{m_H}\right)^{3/2}\right]^3 \quad (9)$$

---

(2) J. Overend, *Annu. Rev. Phys. Chem.*, **21**, 265 (1970).

(3) D. Papousek and J. Pliva, *Collect. Czech. Chem. Commun.*, **29**, 1973 (1964).

(4) Y. Morino, K. Kuchitsu, and S. Yamamoto, *Spectrochim. Acta, Part A*, **24**, 335 (1968).

(5) See, for instance, H. C. Urey and D. Rittenberg, *J. Chem. Phys.*, **1**, 137 (1933).

(6) V. J. Shiner, Jr., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *J. Amer. Chem. Soc.*, **90**, 7171 (1968); E. A. Halevi and M. Wolfsberg, unpublished calculations.

(7) M. Perlman, J. Bigeleisen, and N. Elliott, *J. Chem. Phys.*, **21**, 70 (1953).

(8) See, for instance, J. E. Mayer and M. G. Mayer, "Statistical Mechanics," Wiley, New York, N. Y., 1940.

(9) J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, **15**, 261 (1947).

Thus K_3 equals unity since all s values in (9) are equal to 3. Since the inverse ratio of the symmetry numbers of two isotopic molecules just equals the ratio of the relative number of ways of forming the two molecules, and since the atomic mass factors always cancel, the classical situation always corresponds to a random distribution of isotopes—*i.e.*, classically there is no isotope effect. The values $^3/_2$ and 4 for K_4 and K_5, respectively, follow directly from the symmetry number factors. Classical mechanics is adequate when the spacing between energy levels is small compared to $\mathbf{k}T$ (where $\mathbf{k}$ is the Boltzmann constant and T the absolute temperature), so that isotope effects will vanish at high temperatures. An isotope effect is a manifestation of quantization of energy levels.

The formula for the molecular partition function Q is

$$Q = \sum_i e^{-\epsilon_i/\mathbf{k}T} \tag{10}$$

where the summation is over the energy levels ϵ_i of the molecule. In evaluating partition functions only the ground electronic state is taken into account (the spacing of excited electronic states is generally such so that they do not contribute to Q). For the evaluation of isotopic partition function ratios, the zero of energy is taken to be the nonrotating, nonvibrating molecule; this zero of energy is the same for both of the isotopic molecules within the framework of the BO approximation. It also follows from the BO approximation that ΔE of the reaction from the zero of energy of reactants to the zero of energy of products does not enter into the calculations here since this quantity cancels in the evaluation of the isotope effect. Thus Q only involves the energy of nuclear motion. To evaluate partition functions of molecules one must know the energy levels. The translational motion of the center of mass can be separated. It is usually adequate to consider the rotational and vibrational motions separately. For the translational–rotational motions, the spacing between energy levels is sufficiently small so that classical mechanics may usually be employed at room temperature and above. Therefore the origin of isotope effects is in the quantization of vibrational energy levels. To a good approximation, the vibrations may be taken to be harmonic.

It is often convenient to calculate the reduced partition function ratio $(s_2/s_1)f$ of Bigeleisen and Mayer[9] (eq 11) where m_i refers to atomic mass and the product

$$\frac{s_2}{s_1}f = \frac{Q_2}{Q_1}\bigg/\left(\frac{Q_2}{Q_1}\right)_{\text{classical}} = \prod_i \left(\frac{m_{i1}}{m_{i2}}\right)^{3/2} \frac{s_2}{s_1}\frac{Q_2}{Q_1} \tag{11}$$

is over all isotopically substituted atoms. If the relevant $(s_2/s_1)f$'s equal unity, the relevant K or ratios of K's will equal the symmetry number factor, *i.e.*, no isotope effect. Isotope effects can be written in terms of $(s_2/s_1)f$'s rather than Q's. Thus

$$K_4 = \frac{f_{\mathrm{NH_2D}}}{f_{\mathrm{HD}}} = \frac{s_{\mathrm{NH_3}}}{s_{\mathrm{NH_2D}}}\frac{s_{\mathrm{HD}}}{s_{\mathrm{H_2}}}\frac{[(s_2/s_1)f]_{\mathrm{NH_2D}}}{[(s_2/s_1)f]_{\mathrm{HD}}} = \frac{3}{2}\frac{[(s_2/s_1)f]_{\mathrm{NH_2D}}}{[(s_2/s_1)f]_{\mathrm{HD}}} \tag{12}$$

A difference in $(s_2/s_1)f$ from unity represents a quantum effect.

Within the approximations for energy levels discussed above, $(s_2/s_1)f$ can be expressed in the form[9]

$$\frac{s_2}{s_1}f = \prod_i \frac{u_{2i}}{u_{1i}}\frac{1 - e^{-u_{1i}}}{1 - e^{-u_{2i}}}e^{(u_{1i}-u_{2i})/2} \tag{13}$$

where $u_i = (h\nu_i/\mathbf{k}T) = 1.43 \times$ normal mode vibrational frequency in cm^{-1}/T, and h is Planck's constant. The product extends over all the normal mode vibrational frequencies of the molecule. The subscripts 1 and 2 refer to two isotopic molecules, with 2 referring to the heavier molecule, as previously mentioned. Equation 13 follows from eq 11. Since the translations and rotations are taken to be classical, molecular mass and moment of inertia terms cancel. When the vibrational spacing becomes small compared to $\mathbf{k}T$, *i.e.*, when u_i goes to zero, $(s_2/s_1)f$ goes to unity, as expected. The ratio of u_i's term in the above expression arises from the classical vibrational partition functions. The ratio of $(1 - e^{-u_i})$'s term arises from the vibrational excitation while the last term arises from the vibrational zero-point energy. With the above 1, 2 convention, $\nu_{1i} \geq \nu_{2i}$, and, consequently, $u_{1i} \geq u_{2i}$. The zero-point energy difference term is therefore equal to or larger than unity. The vibrational zero-point energy difference is the only energy difference between two isotopic molecules in their ground states. Also, in the consideration of isotope effects on equilibria, the only quantities which arise from the isotope effect on the differences of the ground-state energies of products and reactants are the vibrational zero-point energies in the form in which they are included in eq 12 and 13. Since frequencies tend to be higher in molecules with larger force constants ("tighter" binding), the zero-point energy and consequently also the isotope effect on the zero-point energy will tend to be larger in those molecules with tighter binding. Since at room temperature, with u_i fairly large, there tends to be little vibrational excitation, the zero-point energy factor is often the leading factor in the above expression. These considerations (these are equivalent to just considering the isotope effect on the energy change of the reaction with all molecules in their respective ground states (ΔE_0)) lead to the frequently made statement that the heavy isotope tends to concentrate (relative to the light isotope) in that species where it is more tightly bound.

For small u_i's the expression for f can be expressed in a power series in $(h/T)^2$. The first nonvanishing term past the first one (the classical one) is often referred to as the first quantum correction. Thus

$$\frac{s_2}{s_1}f = 1 + \frac{1}{24}\sum_i (u_{1i}^2 - u_{2i}^2) = 1 + \frac{1}{24}\left(\frac{h}{\mathbf{k}T}\right)^2 \times \sum_i (\nu_{1i}^2 - \nu_{2i}^2) = 1 + \frac{1}{24}\left(\frac{h}{2\pi\mathbf{k}T}\right)^2 \times \sum_j (a_{jj}^{xx} + a_{jj}^{yy} + a_{jj}^{zz})\left(\frac{1}{m_{1j}} - \frac{1}{m_{2j}}\right) \tag{14}$$

The difference between the sums of the squares of the frequencies has been expressed by means of the first-order sum rule[1] in terms of the three per atom diagonal force constants for cartesian coordinate displacements (a_{jj}^{xx}, a_{jj}^{yy}, a_{jj}^{zz}) and the atomic masses (m_j). The sum in the last expression need only extend over isotopically substituted atoms. The above two terms represent the first two terms in a series which converges if all u_i are smaller than 2π. Bigeleisen and Ishida[10] have carried out extensive work on such series (actually expansion of ln $[(s_2/s_1)f]$) and have extended the radius of convergence of this series by introduction of modulating factors. The terms, and in particular the first terms, look very similar to the above expression. Such developments are especially important if one wants to study in detail how isotope effects depend on force constants because the higher order correction terms, just like the first quantum correction, can be directly expressed in terms of force constants, geometry, and atomic masses.

Equation 14 is very useful for looking at isotope effects. The expression predicts that the deviation of $(s_2/s_1)f$ from unity increases with increasing force constants at the position of isotopic substitution. For an equilibrium, it again predicts that the heavy atom should concentrate in that species in which that atom is subject to the largest force constants.

An isotope effect involving a position not directly involved in the bond breaking or bond making of a reaction is called a secondary effect. Equation 14 leads to the prediction that such effects should vanish in the absence of force constant changes at the position of isotopic substitution. This has been affirmed[11] (within limits) by carrying out calculations of equilibria using the exact expressions. Thus, the observation[12] of an isotope effect ($K_H/K_D = 0.98$ at 25°C) on the equilibrium

$$\begin{aligned}&\text{triphenylcarbinol} + H^+ = \text{triphenyl cation} + H_2O\\&\text{tri(phenyl}p\text{-}d\text{)carbinol} + H^+ = \text{triphenyl cation} + H_2O\end{aligned} \qquad (15)$$

is indicative of a change of force constant between reactant and product at the position of isotopic substitution. Note that, both here and in the case of eq 18, liquid phase equilibria are regarded in terms of gas phase theory (see the following section).

Equation 14 states than an isotope effect depends on a change in $a_{jj}^{xx} + a_{jj}^{yy} + a_{jj}^{zz}$ at the isotopically substituted position. One does not usually think in terms of cartesian force constants but in terms of valence force constants (*i.e.*, force constants for stretches, bends, etc.) Equation 14 can be recast in a form appropriate for such force constants, but then the equation involves not only the valence force constants but also the geometry in the vicinity of the position of the isotopic substitution. Since, however, geometry changes will generally be accompanied by force constant changes, it is still proper to say that the first-order correction leads to the conclusion that sizable isotope effects will occur only if there are force constant changes at the position of isotopic substitution.

Equation 14 contains only the first quantum correction. While eq 14 serves to give qualitative insights into the nature of isotope effects, it does not ordinarily yield quantitative accuracy except at high temperature. For routine exact calculations, digital computer programs are available which enable one to calculate normal vibrational frequencies from force constants, atomic masses, and geometry, and subsequently to calculate equilibrium isotope effects through the use of eq 12 and 13. Alternatively one could employ the expansions of Bigeleisen and Ishida.

An interesting conclusion from eq 14 is that the quantum effect on K_5 (eq 7) vanishes. Thus the symmetry factor, 4, is expected for K_5 while the exactly calculated value in the harmonic approximation is $4(0.96) = 3.85$. In the next order of approximation in the eq 14 type of series, one finds that the deviation from the classical value arises from the HOH bending force constant and, if one carries out exact calculations, one finds that $K = 4$ when the bending force constant equals 0.[13] One also finds that the difference between K for water and the corresponding K's for H_2S and H_2Se directly reflects the magnitudes of the bending force constants.

At very low temperatures, the temperature dependence of the isotope effect will be of the form

$$K_1/K_2 = Ae^{B/T} \qquad (16)$$

where B is the appropriate zero-point energy difference and A reflects products of ratios of frequencies or molecular masses and moments of inertia (Teller–Redlich product rule). This equation is correct if all the frequencies which are affected by isotopic substitution correspond to u_i's much larger than unity. Many quantitative misinterpretations of isotope effects have occurred from the assumption that this form is always valid. When it is valid, zero-point energy differences between isotopic molecules may be deduced from experiment. Thus from observation of the equilibrium 6 and from the known zero-point energies of H_2 and HD and the molecular geometries, Bigeleisen, *et al.*,[7] deduced the zero-point energy difference between NH_3 and NH_2D. In this way, isotope effects may be used to supplement data available from spectroscopy in order to obtain force constants of molecules.

At very high temperatures, where eq 14 is quantitatively valid, the isotope effect will have the form (omitting a possible symmetry number factor)

$$K_1/K_2 = 1 + (C/T^2) \qquad (17)$$

where C contains information about the changes of the

---

[10] J. Bigeleisen and T. Ishida, *J. Chem. Phys.*, **48,** 1311 (1968); T. Ishida, W. Spindel, and J. Bigeleisen, *Advan. Chem. Ser.*, **No. 89,** 192 (1969).

[11] M. J. Stern and M. Wolfsberg, *J. Chem. Phys.*, **45,** 2618 (1966).

[12] A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, **89,** 5510 (1967).

[13] M. Wolfsberg, A. A. Massa, and J. W. Pyper, *J. Chem. Phys.*, **53,** 3138 (1970).

cartesian force constants between reactant and product at the position of isotopic substitution. The transition from the low-temperature form to the high-temperature form is not always a regular one. It is possible for the equilibrium constant ratio to invert from larger than unity to smaller than unity and back again in the intermediate temperature region. Such effects and others have been studied recently by Stern, Spindel, and Monse.[14] Such effects occur especially if some valence force constants at the position of isotopic substitution increase in going from reactant to product, while others decrease.

Sometimes isotope effects are discussed in the same terms used to discuss chemical substituent effects. Thus, an isotope effect results because hydrogen has a higher electronegativity than deuterium or because hydrogen has larger steric requirements than deuterium. It will be shown by an example how such statements fit into the theoretical framework discussed here.

When one says that H is more electronegative than D, one is talking about an isotope effect as a substituent effect and one is discussing the effect of the substituent on the variation of ΔE_0 of the reaction. In an isotope effect, the variation of the ΔE_0 of the reaction refers to the change in the zero-point energy difference between product(s) and reactant(s) so that, when one considers an isotope effect to be a substituent effect, one is taking the effect to reside in the zero-point energy factor. K_6/K_7 for the equilibria

$$\begin{gathered} \mathrm{HCOOH} \overset{K_6}{\rightleftharpoons} \mathrm{HCOO^-} + \mathrm{H^+} \\ \mathrm{DCOOH} \overset{K_7}{\rightleftharpoons} \mathrm{DCOO^-} + \mathrm{H^+} \end{gathered} \qquad (18)$$

has been described in terms of the greater electron withdrawing power of H compared to D: at 25°C $K_6/K_7 = 1.06–1.12$.[15] This isotope effect indicates that the force constants at the isotopic position are smaller in the ion than in the undissociated acid. This effect has been theoretically studied by Bell and Crooks[16] through eq 13 by using observed frequencies for all molecular species, and $K_6/K_7 = 1.09$ was obtained.

It will be shown that, if one considers the origin of the decrease in the force constants at the isotopically substituted position in going from the undissociated acid to the ion as an inductive effect, one obtains the picture that H is more electron withdrawing than D. In the following, the symbols H and D will be used to refer to the particular isotopes while hydrogen refers to either isotope. Suppose for the point of this argument that the force constant which is decreasing is the carbon–hydrogen stretching force constant (one knows[16] that, while there is a net decrease in force constant at the hydrogen position, the situation is not as simple as this). This decrease means that it is easier to stretch the bond in the ion than in the acid. If one assigns this easing as an inductive effect, one must say that, when the carbon–hydrogen bond is shifted from its equilibrium internuclear separation (taken to be the same in the acid and the ion), the hydrogen becomes more electron withdrawing so that the energy of the ionization process decreases. H carries out vibrations with larger amplitudes than D in the respective zero-point vibrational states. Thus, on the average, the H in the C–H bond would tend to be more electron withdrawing than the D in the C–D bond. Thus, one sees that, if one assigns a force constant change to a particular type of effect, one can assign the resultant isotope effect as that same type of effect. If a force constant change arises from nonbonded (steric) interactions, then the corresponding isotope effect may be termed steric.

To compare accurate experimental isotope effects with theoretical calculations in a case where spectroscopic data are available (so that force constants may be deduced), it is necessary to correct the previously discussed theory to obtain high accuracy. The corrections include such factors as quantum mechanical rotation, rotation–vibration interaction, centrifugal distortion. Usually, however, the chief correction factor arises from the anharmonicity of the vibrations and the main effect of this anharmonicity is to change the zero-point energy factor. The equilibrium constant K_5 (eq 7) has recently been determined[17] by mass spectroscopic methods to be 3.75 at 298°K. A harmonic calculation yields the value 3.85, in fair agreement with experiment. The anharmonicity correction had been evaluated prior to the carrying out of the experiment. This evaluation was carried out with the vibrational energy formula for water

$$E(n_1, n_2, n_3)/hc = \sum_{i=1}^{3} \omega_i(n_i + {}^1/_2) + \sum_{i \leq j} x_{ij}(n_i + {}^1/_2)(n_j + {}^1/_2) \qquad (19)$$

where n_i refers to vibrational quantum number, ω_i refers to normal mode vibrational frequency in cm^{-1}, and the x_{ij}'s are anharmonicity coefficients. The x_{ij}'s for the three water species had been obtained previously both experimentally and theoretically. The anharmonicity correction obtained led to a lowering of the theoretically evaluated equilibrium constant to 3.4. The dilemma resulting from the disagreement of this number with the experimentally observed value gave rise to a reexamination[18] of the theory and led to the rediscovery that the vibrational energy of the molecule is not correctly expressed by (19) but that a constant term, G_0, must be added to (19). The constant term, G_0, depends on the masses of the atoms and the anharmonicity of the potential. It has been well known, but has been ignored by spectroscopists because it does not contribute to the difference in energy between levels (in

---

[14] M. J. Stern, W. Spindel, and E. U. Monse, *J. Chem. Phys.*, **48**, 2908 (1968).

[15] E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).

[16] R. P. Bell and J. E. Crooks, *Trans. Faraday. Soc.*, **58**, 1409 (1962).

[17] (a) L. Friedman and V. J. Shiner, Jr., *J. Chem. Phys.*, **44**, 4639 (1966); (b) J. W. Pyper, R. S. Newbury, and G. W. Barton, Jr., *ibid.*, **46**, 2253 (1967).

[18] (a) M. Wolfsberg, *Advan. Chem. Ser.*, **No. 89**, 185 (1969); (b) J. R. Hulston, *J. Chem. Phys.*, **50**, 1483 (1969); (c) M. Wolfsberg, *ibid.*, **50**, 1484 (1969).

the same electronic state). When G_0 is taken into account in the evaluation of K_5 for reaction 7, the anharmonicity correction vanishes. Thus the correct theoretical value of K_5 is very close to 3.85. The experimental value is about 3% lower. This small difference may be due to experimental error. If such error is ruled out, however, this difference may lead to further corrections in the theory.

The above discussion shows how isotope effects may be used to gain insight into theory. The point has been made that isotope effects can be used to give information about force fields. Thus the measured K_4 (eq 6) has been used to obtain the zero-point energy difference between NH_3 and NH_2D. It must be conceded, however, that in general direct spectroscopy is a better method for determining the force fields of gas-phase molecules than is the measurement of isotope effects on gas-phase equilibrium constants. Isotope effects on vapor pressure (*vide infra*) are isotope effects on phase equilibria, and from these one can obtain information about condensed-phase force fields; this information is often difficult to obtain by spectroscopy.

Vapor Pressure Isotope Effects

The vapor pressure can be considered to be the equilibrium constant for the equilibrium between the gas phase and the condensed phase (solid or liquid). The ratio of the vapor pressures of isotopic substances may then be expressed in terms of isotopic ratios of gas-phase and condensed-phase partition functions. These concepts have been formally derived, together with appropriate correction factors, by Bigeleisen.[19]

In the case of monatomic substances, the rare gases, the only degrees of freedom in the gas phase are the translations. In the condensed phase these translations become bound. One expects and finds that the vapor pressure of the light isotope will be larger than that of the corresponding heavy isotope. From the magnitude of the isotope effect and also from its temperature coefficient, one can deduce information about the binding in the condensed phase.[20,21]

For molecules the situation is more complicated. Not only do both translational and rotational degrees of freedom have to be considered but also the internal vibrational degrees of freedom. The binding of the translational and rotational degrees of freedom will tend toward a normal isotope effect, *i.e.*, light species has higher vapor pressure than heavy species. On the other hand if the force constants for the internal vibrations of the molecule are smaller (larger) in the condensed phase than in the vapor phase, this effect will tend toward an inverse (normal) isotope effect. One knows from vibrational spectroscopy that in many cases internal vibrational frequencies of molecules shift toward lower frequencies (smaller force constants) in going from the gas phase to the condensed phase. In molecular systems where this happens one therefore has the effect of the translations and the rotations tending toward a normal isotope effect while the effect of the internal vibrations tends toward an inverse effect. The temperature dependence of the effects due to these different degrees of freedom is different. The result often is that one has a normal effect over a certain temperature range and an inverse effect over another, accompanied by the so-called "crossover" phenomenon.

A theoretical model often used in the study of vapor pressure isotope effects is the harmonic cell model of the condensed phase.[19,22] In this model, each condensed phase molecule possesses $3N$ (N equals the number of atoms) degrees of freedom, assumed to be harmonic vibrations. One can then try to fit observed gas–condensed-phase frequency shifts and the vapor-pressure isotope effect data to obtain information about the force constants in the condensed phase. The situation is somewhat more complicated than has been indicated; there are interactions between the rotational, translational, and vibrational degrees of freedom in the condensed phase. Among the molecules which have been considered within the framework of this model are: ethylene,[22,23] methane,[24] and ethane.[25] The theoretical consideration of the vapor pressures of the methanes and their temperature dependences gives evidence about the hindering of the rotational degrees of freedom in the condensed phase. The most precise data available on the isotopic ethylenes[23] show that the simple harmonic cell model does need corrections, such as consideration of anharmonicity.

Isotope effects on chemical equilibria in the gas phase can be corrected to the liquid phase by adding terms involving ratios of isotopic vapor pressure ratios. Thus for the equilibria of eq 4

$$(K_1/K_2)_{\text{liquid}} = (K_1/K_2)_{\text{gas}}[(p_{CD_3Br}/p_{CH_3Br})/(p_{CD_3Cl}/p_{CH_3Cl})] \quad (20)$$

Generally, unless there are specific solvent effects, the deviation of an isotopic vapor pressure ratio from unity is much less than the deviation of the corresponding $(s_2/s_1)f$ from unity and any cancellation occurring in taking ratios of f's will be even more complete in taking ratios of isotopic vapor pressure ratios. Thus, at 250°K, $p_{CD_3Br}/p_{CH_3Br} = p_{CD_3Cl}/p_{CH_3Cl} = 1.03$.[26] Thus the value of the equilibrium constant isotope effect is usually not strongly phase dependent. The same argument applies when reaction rates are considered within the transition-state-theory framework in the following section.

Isotope Effects on Reactions

Isotope effects on reaction rate constants of elementary steps have usually been considered within the

---

(19) J. Bigeleisen, *J. Chem. Phys.*, **34**, 1485 (1961).

(20) J. Bigeleisen and E. Roth, *ibid.*, **35**, 68 (1961).

(21) M. W. Lee, S. Fuks, and J. Bigeleisen, *ibid.*, **53**, 4077 (1970).

(22) M. J. Stern, W. A. Van Hook, and M. Wolfsberg, *ibid.*, **38**, 497 (1963).

(23) J. Bigeleisen and T. Ishida, *ibid.*, **49**, 5498 (1968).

(24) J. Bigeleisen, C. B. Cragg, and M. Jeevanandam, *ibid.*, **47**, 4335 (1967).

(25) W. A. Van Hook, *ibid.*, **46**, 1907 (1967).

(26) I. Kiss, L. Matus, and I. Opauszky, *J. Chim. Phys. Physicochim. Biol.*, **60**, 52 (1963). These numbers were taken from a graph; they may not be exactly correct.

framework of transition-state theory. For the reaction step 21 the rate constant k is given by eq 22, where **k**

$$\mathrm{A} + \mathrm{B} + \ldots \longrightarrow [\mathrm{T}]^{\ddagger} \longrightarrow \text{products} \qquad (21)$$

$$k = (\mathbf{k}T/h)(Q_{\mathrm{T}}'^{\ddagger}/Q_{\mathrm{A}}Q_{\mathrm{B}}\ldots) \qquad (22)$$

is the Boltzmann constant. $Q_{\mathrm{T}}'^{\ddagger}$ is the partition function of the transition state with the degree of freedom corresponding to the reaction coordinate omitted.

One then obtains for the isotopic ratio of rate constants

$$\frac{k_1}{k_2} = \left(\frac{Q_2}{Q_1}\right)_{\mathrm{A}} \left(\frac{Q_2}{Q_1}\right)_{\mathrm{B}} \cdots \Big/ \left(\frac{Q_2'^{\ddagger}}{Q_1'^{\ddagger}}\right)_{T} \qquad (23)$$

The rate constant ratio has been expressed, just like the equilibrium constant ratio, in terms of partition function ratios, 2 over 1 (heavy over light). The expression for k_1/k_2 looks just like the corresponding expression for the equilibrium constant ratio with reaction reactants (transition state) replacing the equilibrium reactants (products).

With the use of reduced partition function ratios $(s_2/s_1)f$ of reactants and transition state, eq 23 becomes[27]

$$\frac{k_1}{k_2} = \left[\left(\frac{s_1}{s_2}\right)_{\mathrm{A}} \left(\frac{s_1}{s_2}\right)_{\mathrm{B}} \left(\frac{s_2}{s_1}\right)^{\ddagger}\right] \left(\frac{\nu_{1\mathrm{L}}^{\ddagger}}{\nu_{2\mathrm{L}}^{\ddagger}}\right) \times \frac{[(s_2/s_1)f]_{\mathrm{A}}[(s_2/s_1)f]_{\mathrm{B}}\ \ldots}{[(s_2/s_1)f]^{\ddagger}} \left[\left(1 + \frac{1}{24}\frac{h^2|\nu_{1\mathrm{L}}^{\ddagger}|^2}{(\mathbf{k}T)^2}\right) \Big/ \left(1 + \frac{1}{24}\frac{h^2|\nu_{2\mathrm{L}}^{\ddagger}|^2}{(\mathbf{k}T)^2}\right)\right] \qquad (24)$$

where $\nu_{\mathrm{L}}^{\ddagger}$ is the imaginary or zero frequency of the transition state which is omitted in calculating $Q'^{\ddagger}$. $f^{\ddagger}$ has the same form as f, eq 13, except that the product is only over the $3N^{\ddagger} - 7$ real frequencies of the transition state. $(s_2^{\ddagger}/s_1^{\ddagger})f^{\ddagger}$, just like $(s_2/s_1)f$, goes to unity in the limit of very high temperature so that the high temperature or classical limit of the isotope effect is $\nu_{1\mathrm{L}}^{\ddagger}/\nu_{2\mathrm{L}}^{\ddagger}$ (the deviation from the first bracket symmetry number factor is again the isotope effect). The last term in brackets (not present in eq 23) is the Wigner tunnelling correction, which depends on the magnitudes of the imaginary frequencies and the temperature. It is assumed here that vibrations are harmonic; anharmonicity corrections for both reactant and transition-state species have, to the author's best knowledge, been undertaken in only one case.[28]

If one focuses on the zero-point energy contributions from the f's or the Q's, one reaches a conclusion similar to that reached for equilibrium isotope effects. The light isotope will tend to concentrate in that species, reactant or transition state, in which its binding is the lesser. If the light isotope concentrates in the transition state, then it will react more rapidly than the heavy isotope and $k_1/k_2 > 1$. Since transition states tend to be less tightly bound than reactants, this case is referred to as a normal effect. Just as in the case of equilibrium effects, one can again expand f for low vibrational frequencies or high temperatures to obtain the first quantum correction expression (including Wigner tunnelling, but omitting symmetry number factors)

$$\frac{k_1}{k_2} = \frac{\nu_{1\mathrm{L}}^{\ddagger}}{\nu_{2\mathrm{L}}^{\ddagger}}\left[1 + \frac{1}{24}\left(\frac{h}{2\pi\mathbf{k}T}\right)^2 (\Delta a^{xx} + \Delta a^{yy} + \Delta a^{zz}) \times \left(\frac{1}{m_1} - \frac{1}{m_2}\right)\right] \qquad (25)$$

It has been assumed here that there is only one isotopically substituted atom, isotopic masses m_1 and m_2. Δa^{xx} refers to the cartesian force constant change (reactant minus transition state) at the position of isotopic substitution.

As for equilibria, the first quantum correction expression has limited quantitative validity. It is, however, a very valuable qualitative tool. It leads to k_1/k_2 larger than unity if the force constants at the position of isotopic substitution are lower in the transition state than in the reactant. If one forgets the classical factor $\nu_{1\mathrm{L}}^{\ddagger}/\nu_{2\mathrm{L}}^{\ddagger}$, eq 25 emphasizes that isotope effects on rates yield information about force constant changes between reactant and transition state. It is to be expected that the larger the force constant change the larger will be the isotope effect.

Computer programs are available which, using as input the geometry and force constants of reactants and transition states, enable one to calculate isotopic rate constant ratios based on the exact (transition-state theory) isotopic rate constant ratio. As for equilibria, these programs have been extensively used to verify the prediction of eq 25 that, in the absence of force constant changes between reactant and transition state at the position of isotopic substitution, there will be substantially no isotope effects aside from the factor $\nu_{1\mathrm{L}}^{\ddagger}/\nu_{2\mathrm{L}}^{\ddagger}$.

A general review of kinetic isotope effects will not be attempted, nor does space permit a direct demonstration of the use of isotope effects in the elucidation of reaction mechanism. Instead the origin of a few isotope effects will be discussed in very simple terms.

$$\mathrm{H} + \mathrm{H_2} \longrightarrow \mathrm{H_2} + \mathrm{H}$$

$$\mathrm{H} + \mathrm{D_2} \longrightarrow \mathrm{HD} + \mathrm{D}$$

$$k_{\mathrm{H}}/k_{\mathrm{D}} = 4.0\text{[29]}\ (T = 400^{\circ}\mathrm{K}) \qquad (26)$$

The large effect is explainable in terms of $\nu_{1\mathrm{L}}^{\ddagger}/\nu_{2\mathrm{L}}^{\ddagger}$ (which for deuterium substitution must be between 1 and $2^{1/2}$) and a large quantum mechanical factor arising from the fact that the force constants at the position of isotopic substitution are lower in the transition state than in the reactant. The force constant which corresponds to H–H stretch in the reactant must decrease in going from reactant to transition state sufficiently to more than compensate for the new force constants present in the transition state $\mathrm{H_3}^{\ddagger}$ species. Tunnelling probably contributes to the effect.

---

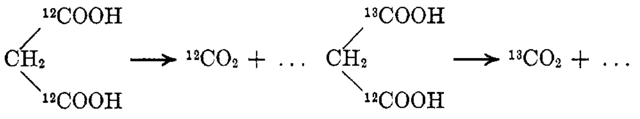
(27) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

(28) R. E. Weston, *ibid.*, **31**, 892 (1959).

(29) D. J. Le Roy, B. A. Ridley, and K. A. Quickert, *Discuss. Faraday Soc.*, **44**, 92 (1967).

$$\mathrm{H} + \mathrm{H}_2 \longrightarrow \mathrm{H}_2 + \mathrm{H}$$
$$\mathrm{D} + \mathrm{H}_2 \longrightarrow \mathrm{DH} + \mathrm{H}$$
$$k_\mathrm{H}/k_\mathrm{D} = 0.6^{29}\ (T = 400°\mathrm{K}) \tag{27}$$

The isotopically substituted reactant is an atom, with reduced partition function ratio unity. In the transition state the isotopically substituted atom is subject to some binding; therefore the quantum mechanical effect will lead to $k_\mathrm{H}/k_\mathrm{D}$ less than unity. While $\nu_{1\mathrm{L}}{}^{\ddagger}/\nu_{2\mathrm{L}}{}^{\ddagger}$ is larger than unity, the quantum mechanical effect more than compensates for the classical effect and an inverse effect is observed.



$$\frac{k_{^{12}\mathrm{C}}}{2k_{^{13}\mathrm{C}}} = 1.045^{30}\ (T = 329°\mathrm{K}) \tag{28}$$

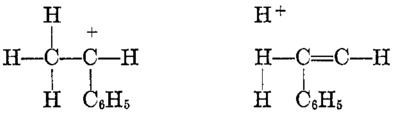
Carbon isotope effects have been most frequently studied in decarboxylation reactions. It is supposed that the elementary step which is rate determining involves breaking the C–C bond involving the $\mathrm{CO_2}$ carbon. One expects then an isotope effect in which the light species reacts more rapidly than the heavy species, as observed. The carbon isotope effect is much smaller than hydrogen isotope effects. This is to be expected from the first quantum correction equation (eq 25) since the quantum mechanical effect depends, for equal force constant changes between reactant and transition state, on $\Delta m/m_1m_2$, where $\Delta m = m_2 - m_1$.

$$\mathrm{C_6H_5CH(CH_3)Cl} \longrightarrow \text{solvolysis}$$
$$\mathrm{C_6H_5CD(CH_3)Cl} \longrightarrow \text{solvolysis}$$
$$k_\mathrm{H}/k_\mathrm{D} = 1.15^{31}\ (T = 298°\mathrm{K}) \tag{29}$$

The examples so far discussed all involve primary isotope effects. This example is a kinetic α secondary effect (of a type first observed by Streitwieser and coworkers[32]). Primary hydrogen isotope effects are as a rule much larger than secondary ones. Small as they are, these secondary effects are significant since it has been shown by calculations that the quantum mechanical contribution to the secondary effect would be very small in the absence of changes in force constant at the position of isotopic substitution between reactant and transition state. The classical factor $\nu_{1\mathrm{L}}{}^{\ddagger}/\nu_{2\mathrm{L}}{}^{\ddagger}$ is expected to be quite close to unity for most secondary effects. The rate-determining step in the above solvolysis is of the SN1 type (*i.e.*, unimolecular decomposition of the chloride reactant to yield carbonium ion), and it is the author's belief that the normal isotope effect reflects largely the lowering of the Cl–C–H bending force constant in going from reactant to transition state.

$$\mathrm{C_6H_5CH(CH_3)Cl} \longrightarrow \text{solvolysis}$$
$$\mathrm{C_6H_5CH(CD_3)Cl} \longrightarrow \text{solvolysis}$$
$$k_\mathrm{H}/k_\mathrm{D} = 1.22^{31}\ (T = 298°\mathrm{K}) \tag{30}$$

This is a β secondary isotope effect (of a type first observed by Shiner[33] and Lewis[34]). On a per deuterium basis this β effect is smaller than the corresponding α effect. The normal isotope effect is taken as evidence of the lowering of the hydrogen force constants in the methyl group in the transition state relative to reactant. The transition state is carbonium ion like; the force constant lowering is usually taken as evidence for hyperconjugation in the transition state (eq 31).



$$\mathrm{H}{-}\overset{\mathrm{H}}{\underset{\mathrm{H}}{\mathrm{C}}}{-}\overset{+}{\underset{\mathrm{C_6H_5}}{\mathrm{C}}}{-}\mathrm{H} \qquad \mathrm{H}{-}\overset{\mathrm{H^+}}{\underset{\mathrm{H}}{\mathrm{C}}}{=}\underset{\mathrm{C_6H_5}}{\mathrm{C}}{-}\mathrm{H} \tag{31}$$

$$\mathrm{CH_3I} + \mathrm{I}^{*-} \longrightarrow \mathrm{CH_3I}^{*} + \mathrm{I}^{-}$$
$$\mathrm{CD_3I} + \mathrm{I}^{*-} \longrightarrow \mathrm{CD_3I}^{*} + \mathrm{I}^{-}$$
$$k_\mathrm{H}/k_\mathrm{D} = 1.10^{35}\ (T = 293°\mathrm{K}) \tag{32}$$

This is another α secondary effect. I* refers to radioactive tracer and the isotope effect on the exchange reaction is studied. On a per deuterium basis, this α effect is considerably smaller than the α effect of eq 29. The rate-determining step involves the reactant combining with I^{*-} to form a hexatomic transition state (SN2 reaction). While the HCI bending force constants are probably lower in the transition state than in reactant, overall there is much less decrease in bending force constant at the position of isotopic substitution between reactant and transition state than in the case of eq 29 because there are six such constants in the transition state while there are only three in the reactant.

For each of these examples, one could carry out a calculation making use of the programs which incorporate eq 24. Geometries of reactant and transition state would have to be supplied, as well as the force constants of both species. It has been implied how the force constants change at the position of isotopic substitution but often the force constant which changes is not wholly determined (*e.g.*, it is a stretching force constant or a bending force constant).

Detailed theoretical studies of the isotope effect of eq 32, as well as of other SN2 reactions of methyl iodide, have been carried out by Willi.[36,37] In these studies the lowering of the HCH bending force constants and the raising of the C–H stretching force constants (by analogy to stable molecules with sp^3 and sp^2 hybridization) in going from reactant to transition state were considered in addition to the effects arising from the H–C– leaving group and from the H–C– entering group bending force constants. Additionally, different ways of

---

(30) P. E. Yankwich, R. L. Belford, and G. Fraenkel, *J. Amer. Chem. Soc.*, **75**, 832 (1953).

(31) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *ibid.*, **90**, 418 (1968).

(32) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *ibid.*, **80**, 2326 (1958).

(33) V. J. Shiner, Jr., *ibid.*, **75**, 2925 (1953); **76**, 1603 (1954).

(34) E. S. Lewis and C. E. Boozer, *ibid.*, **76**, 791 (1954).

(35) S. Seltzer and A. A. Zavitsas, *Can. J. Chem.*, **45**, 2023 (1967).

(36) A. V. Willi and C. M. Won, *J. Amer. Chem. Soc.*, **90**, 5999 (1968).

(37) A. V. Willi, *Can. J. Chem.*, **44**, 1889 (1966).

postulating the force constants in the transition state to obtain the zero or imaginary frequency $\nu_L^{\ddagger}$ were explored by Willi and the isotope effect was found to have some sensitivity to these ways. Generally, given an isotope effect at one temperature, one can always set up a transition-state model which reproduces the isotope effect. However, this transition-state model will not be unique. It has been emphasized that those force constants which do not involve the isotopic position do usually affect the isotope effect either very little or not at all (except possibly through $\nu_{1L}^{\ddagger}/\nu_{2L}^{\ddagger}$). One can ascertain whether a certain *a priori* model can account for the observed isotope effect. If the isotope effect data are available as a function of temperature, these data can rule out certain postulated transition states. As in the case of equilibria, the temperature dependence of isotope effects on rate constants need not follow a simple exponential law. Data for more than one isotope of an atom (*e.g.*, obtaining data for H, D, and T) may also sharpen the model of the transition state. This course has been used[38] in the case of the hydrogen–chlorine reaction ($H_2 + Cl$) where data have been obtained for HD, D_2, HT, DT. If isotope effects are obtained for isotopic substitution in various positions of the reactants, one can try to "tie down" the force field in the transition state at these various positions. For simple reactions semiempirical methods have been developed for obtaining the properties of the transition state.[39] Isotope effects calculated in this way are then compared with experiment. Johnston[39] has reviewed much of this work. Often good agreement is obtained; sometimes the agreement is not so good, and this is taken by the workers who use this approach to mean that transition-state theory fails.

In the calculations mentioned at the end of the last paragraph, tunnelling is usually taken into account. It is usually handled in a manner more sophisticated than the method of the Wigner correction. In reactions in organic systems, tunnelling is usually tested by a method developed by Bell[40] which involves the temperature dependence of the isotope effect. Bell[41] and others[42] believe that they have obtained data for reactions where the isotope effect indicates tunnelling.

This discussion of rate constants has been based on transition-state theory. A number of classical trajectory calculations of rate constants have now been carried out. In these calculations, the reactant molecules are assumed to be initially in a distribution of quantum states. The motion of the atoms is then calculated classically starting from these initial states, without further quantum considerations. Isotope effects result. Little work has been done in the calculation of dynamic isotope effects by purely quantum mechanical methods. Much interesting work will be forthcoming on dynamical calculations of isotope effects and on comparison with the results both of experiments and of transition-state theory calculations.

Conclusions

A number of areas in the theoretical interpretation of isotope effects have been reviewed. The object of most of this work has been to obtain information about the derivatives with respect to internuclear coordinates (*i.e.*, the force constants) of the potential function on which nuclei move. The usefulness of isotope effects as a tool for obtaining such information rests largely (1) on the validity of the Born–Oppenheimer approximation and (2) on the fact that, given a theoretical model for a certain phenomenon, it is usually fairly easy to develop a theory for the corresponding isotope effect.

---

(38) A. Persky and F. S. Klein, *J. Chem. Phys.*, **44**, 3617 (1966).

(39) H. S. Johnston, "Gas Phase Reaction Rate Theory," Ronald Press, New York, N. Y., 1966.

(40) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 205–214.

(41) R. P. Bell, J. A. Fendley, and J. R. Hulett, *Proc. Roy. Soc., Ser. A*, **235**, 453 (1956).

(42) See, for instance, E. F. Caldin and G. Tomalin, *Trans. Faraday Soc.*, **64**, 2823 (1968).