

Isotope Effects as Tools for the Elucidation of Reaction Mechanisms

Predictions from Model Calculations

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Model calculations, based on the statistical-mechanical formulation of isotope effects, have been used to predict how analyses of experimentally measured isotope effects may be used to gain information concerning the differences between the reactants and the transition state in a rate process or between the reactants and the products in an equilibrium process. It is shown that while isotope effects cannot be used generally to obtain reliable information about geometry differences, they can be used to determine or set limits on force constant differences and possibly to gain insight into the nature of reaction coordinates. Information of this type can be useful in the elucidation of reaction mechanisms. A method by which isotope effects for large molecular systems may be studied theoretically by working with smaller model molecules is presented.

RECENTLY, pharmaceutical chemists have been much interested in using reaction kinetics for the elucidation of mechanisms of reaction. In "determining" a mechanism, one usually postulates a model for the reaction and sees if the kinetic data are consistent with values predicted by the model. It is then possible to eliminate certain models and, with the use of chemical knowledge and intuition, to choose between the remaining reasonable models.

Usually, several reasonable models are consistent with the experimental data, and one must look for additional methods for choosing between the possibilities. The measurement of relative rates is a step in this direction, since many unknown or poorly known factors will cancel in the rate ratio. One means of measuring relative rates is the introduction of chemical substituents somewhat removed from the reaction center. The drawback of such a procedure is that chemical substituents are often sufficiently different to cause a change in mechanism.

Another means of measuring relative rates is the introduction of *isotopic* substituents. Since, within the framework of the Born-Oppenheimer approximation, interatomic electronic forces¹ are

independent of the nuclear masses, the potential-energy surface describing the motions of the nuclei is independent of isotopic substitution. Thus, the mechanism of reaction remains the same when an isotopic substitution is made even at the reaction center. The rates of isotopic reactions, however, will differ, the magnitude and direction of the difference depending for the most part on the changes in interatomic electronic forces occurring as the reaction proceeds.²

In this presentation, the authors will not try to give a general review³ of all the work done in this field, but rather will present a brief discussion of the nature of isotope effects and some predictions from model calculations concerning how one would interpret experimentally observed effects.

It must be emphasized that the calculations presented in this paper are for arbitrary models. While the models may represent particular types of reactions, no effort has been made to reproduce any experimental result or to predict results for specific systems. Rather, the philosophy of these calculations has been to try to find out exactly what does influence an isotope effect, for it is only these things that we can hope to learn about from experiments. We also try to determine how much about these influencing factors can be extracted from actual experimental isotope-effect data, either directly or by comparison with model calculations. Since mechanistic descriptions, such as nonbonded interactions, hyperconjugation, inductive effects,

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¹ When the displacement of a molecule from its nonvibrating (equilibrium) internuclear configuration is not too large, these forces can be well-approximated in terms of harmonic force constants, which are second derivatives of the potential energy with respect to the particular internuclear motions involved. Thus, for a particular coordinate q_i (q_i might be a change in a bond distance, a change in the angle between two bonds, etc.), the force constant f_i is given by $f_i = (\partial^2 V / \partial q_i^2)_0$, where V is the potential energy, and the subscript 0 indicates that the derivative is taken at the equilibrium position. In this paper, specific force constants will be given subscripts indicating the coordinates involved; e.g., f_{O-X} indicates the force constant, f_i , where q_i is a CX-stretching coordinate. It is also possible to define force constants for interactions between the motions described by two different coordinates, viz., $f_{ij} = (\partial^2 V / \partial q_i \partial q_j)_0$.

² It is possible to imagine a situation in which two alternative mechanisms exist, the first favoring one isotopic reactant and the second favoring the other isotopic reactant. It is conceivable that in such a situation, the two isotopic reactions will proceed by different alternatives. This rather unusual situation must be distinguished from the case of an actual change in mechanism caused by the introduction of a chemical substituent.

³ Reviews of the theoretical and experimental progress in isotope effects can be found in the literature [e.g., (1) and (2)]. These reviews contain references to the work by Bigeleisen which is not specifically acknowledged in this paper.

etc., can be translated into descriptions of force constant changes, it is of particular interest to see if such force constant changes can be identified.

While the force constants used in the model calculations are reasonable, they were chosen somewhat arbitrarily. In fact, at times different force constants were used for the same molecule to show that the general conclusions do not depend in some way on a particular choice of force constants. Thus, no real significance should be given to the numerical values presented in the tables other than the fact that they represent the "exact" values which correspond to particular hypothetical models.⁴ The details of many of the calculations presented in this paper and of similar calculations can be found in the literature (3-6).

THEORETICAL EXPRESSIONS FOR ISOTOPE EFFECTS

In the following discussions several assumptions will be made. Rates will be discussed in the framework of the transition-state theory (7). While this theory has some inadequacies, such inadequacies tend to cancel in the isotopic rate ratio so that reasonable answers result. The vibrational degrees of freedom of molecules will be considered as quantum-mechanical harmonic oscillators. Translational and rotational degrees of freedom will be considered classical. As will be seen, isotope effects on rates, except for a usually small temperature-independent contribution, are quantum-mechanical effects. For the present, isotope effects on transmission coefficients and on quantum-mechanical tunneling (passage through, rather than over, a potential barrier) will generally be ignored. For simplicity, cases in which only one reactant is isotopically substituted will be considered.

In the transition-state formulation, a *single* reaction step (we will consider only the rate-determining step) can be represented as



where R is the reactant(s), $[T]^\ddagger$ is the transition state (the symbol \ddagger will be used to denote transition-state quantities), and P is the product(s). The transition state can be thought of as the highest (least stable) point along the easiest (least expenditure of energy) pathway from reactant(s) to product(s) on the potential-energy surface representing a reaction. The rate constant, k_r , for this reaction step is given by

$$k_r = \frac{kT}{h} K^\ddagger \quad (\text{Eq. 2})$$

where k is Boltzmann's constant, h is Planck's constant, T is the absolute temperature, and K^\ddagger is the equilibrium constant for the assumed equilibrium between reactant(s) and transition state after omis-

sion of the degree of freedom corresponding to the decomposition motion (also referred to as the reaction coordinate) in the transition state. Thus, the statistical-mechanical expression for K^\ddagger contains all $3N$ degrees of freedom for each reactant (N = number of atoms in a molecule) but only $3N^\ddagger - 1$ degrees of freedom for the transition state.

With the introduction of the subscripts 1 and 2 to represent the light and heavy isotopic species, respectively, the isotopic rate-constant ratio, k_1/k_2 , is given by

$$\frac{k_1}{k_2} = \frac{K_1^\ddagger}{K_2^\ddagger} \quad (\text{Eq. 3})$$

$$\frac{k_1}{k_2} = \frac{Q_2}{Q_1} \frac{Q_2^\ddagger}{Q_1^\ddagger} \quad (\text{Eq. 4})$$

where Q_i is the complete statistical-mechanical partition function for the reactant (only the isotopically substituted reactant need be included since for the other reactants, $Q_1 = Q_2$), and Q_i^\ddagger is the transition-state partition function after omission of the contribution of the degree of freedom corresponding to the decomposition motion. Substitution of the expressions for the translational, rotational, and vibrational partition function contributions gives (1, 2)

$$\frac{k_1}{k_2} = \frac{\left(\frac{M_2}{M_1}\right)^{3/2} \left[\frac{I_{A_2} I_{B_2} I_{C_2}}{I_{A_1} I_{B_1} I_{C_1}}\right]^{1/2}}{\left(\frac{M_2^\ddagger}{M_1^\ddagger}\right)^{3/2} \left[\frac{I_{A_2^\ddagger} I_{B_2^\ddagger} I_{C_2^\ddagger}}{I_{A_1^\ddagger} I_{B_1^\ddagger} I_{C_1^\ddagger}}\right]^{1/2}} \times \frac{\prod_i^{3N-6} \frac{[1 - \exp(-u_{1i})]}{[1 - \exp(-u_{2i})]}}{\prod_i^{3N^\ddagger-7} \frac{[1 - \exp(-u_{1i}^\ddagger)]}{[1 - \exp(-u_{2i}^\ddagger)]}} \times \frac{\exp\left[\sum_i^{3N-6} (u_{1i} - u_{2i})/2\right]}{\exp\left[\sum_i^{3N^\ddagger-7} (u_{1i}^\ddagger - u_{2i}^\ddagger)/2\right]} \quad (\text{Eq. 5})$$

or

$$\frac{k_1}{k_2} = \frac{\nu_{1L}^\ddagger}{\nu_{2L}^\ddagger} \times \frac{\prod_i^{3N-6} \frac{u_{2i}}{u_{1i}}}{\prod_i^{3N^\ddagger-7} \frac{u_{2i}^\ddagger}{u_{1i}^\ddagger}} \times \frac{\prod_i^{3N-6} \frac{[1 - \exp(-u_{1i})]}{[1 - \exp(-u_{2i})]}}{\prod_i^{3N^\ddagger-7} \frac{[1 - \exp(-u_{1i}^\ddagger)]}{[1 - \exp(-u_{2i}^\ddagger)]}} \times \frac{\exp\left[\sum_i^{3N-6} (u_{1i} - u_{2i})/2\right]}{\exp\left[\sum_i^{3N^\ddagger-7} (u_{1i}^\ddagger - u_{2i}^\ddagger)/2\right]}$$

$$\frac{k_1}{k_2} = (\nu_{1L}^\ddagger/\nu_{2L}^\ddagger) \times (VP) \times (EXC) \times (ZPE) \quad (\text{Eq. 6})$$

The numerators refer to isotopically substituted reactant and the denominators to transition state. The first term in Eq. 5, which contains molecular masses (M) and principal moments of inertia (I),

⁴ There is always a danger, of course, in drawing conclusions from model calculations. Even if one considers a large number of cases, a chance exists that for some reactions, actual or model, a particular conclusion will not be valid.

arises from the classical translational and rotational partition functions and is designated as *MMI*. The second term, designated *EXC*, contains vibrational frequencies ($u = h\nu/kT$; ν = normal mode vibrational frequency) and arises from the thermal excitation of vibrations. The last term, designated *ZPE*, arises from the difference between reactant and transition state of the isotopic shifts in vibrational zero-point energy. Equations 5 and 6 are completely equivalent, and one may be derived from the other with the Teller-Redlich product rule (1, 2). In Eq. 6, *MMI* has been replaced by $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, the isotopic ratio of the zero or imaginary frequencies of the transition state,⁶ times *VP*, a vibrational-product term. The products and sums in both equations are taken over only the real (genuine) normal vibrational frequencies, *i.e.*, $3N - 6$ real frequencies for reactant molecules and $3N^\ddagger - 7$ real frequencies for transition states.⁶ Both equations apply to chemical equilibria as well as to rates. In the case of an equilibrium, k_1/k_2 is replaced by K_1/K_2 , the ratio of the isotopic equilibrium constants; the denominator terms are replaced by corresponding terms for the isotopically substituted reaction product with the vibrational terms taken over all $3N - 6$ frequencies; and the factor $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ in Eq. 6 is omitted. Everything in the following discussions about rates, except for material dealing specifically with $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, applies to equilibria as well.

Equation 6, which is usually called Bigeleisen's formulation, is useful for the examination of the behavior of isotope effects at infinite temperature. As T increases, *ZPE* $\rightarrow 1$ and *EXC* $\rightarrow 1/VP$, so that at infinite temperature, $k_1/k_2 = \nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. This result is just the equation obtained if the classical rather than quantum-mechanical vibrational partition functions are used. It is clear then that any kinetic isotope effect other than $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ is a quantum-mechanical effect. In the case of an equilibrium, of course, the classical (infinite-temperature) limit is unity.

We will consider Eqs. 5 and 6 as primary expressions and assume that they correctly describe an isotope effect. These equations apply both to primary and secondary isotope effects. A primary isotope effect can be defined as one in which the isotopically substituted atom(s) is involved in the bond-breaking or bond-making of the reaction, while a secondary isotope effect is one in which the isotopic atom(s) is not so involved. Equations 5 and 6 are actually gas-phase formulations, and the specific effects of solvents, etc., are only taken into account inasmuch as solvent, etc., molecules are included in the models used for the calculations. To extrapolate to the liquid phase (or solution), one would have to take into account effects due to condensation (or to nonspecific solvent interactions), but these

⁶ The solution of the equations for the internal motions of a transition state gives rise to normal vibrational frequencies plus one imaginary (or in its limit, zero) frequency, ν_{1L}^\ddagger , which corresponds to nongenuine "vibration" along the decomposition path. The value of ν_{1L}^\ddagger is an imaginary number. ν_{1L}^\ddagger can be thought of as the "frequency" of an oscillator with a negative restoring force. $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ often is referred to as the ratio of the frequencies of decomposition. It should be remembered, however, that this factor enters into the equations through the Teller-Redlich product rule and that transition-state theory actually deals with the decomposition as a classical translation.

⁷ For a linear molecule (or transition state), there are $3N - 5$ ($3N^\ddagger - 6$) real vibrational frequencies and only two rotational degrees of freedom.

should be small, since vapor-pressure isotope effects are generally quite small (8).

METHOD OF CALCULATION AND MODEL SYSTEMS CONSIDERED

To utilize either Eq. 5 or Eq. 6, one must know or be able to calculate all of the normal vibrational frequencies of all of the isotopic reactants and transition states. Complete vibrational analyses (determinations of force constants from measured frequencies) have been carried out for some molecules. The experimental techniques are not yet sufficiently well developed to permit complete analyses of complicated molecules. Obviously, an experimental determination of the vibrational frequencies of a transition state cannot be performed. As shall become evident, the primary quantitative use of kinetic isotope effects is the determination of the force constant *changes* as the reactant "passes over" into the transition state. Therefore, one is forced to make educated guesses concerning the force constants of the reactant and transition state assumed to be involved in the reaction. Force constants for particular internuclear motions are more or less transferable between molecules (9), and are, of course, independent of isotopic substitution. We assume that the electronic forces in a transition state are analogous to those in stable molecules.

Because of the difficulty in calculating vibrational frequencies from known or assumed force fields by hand or with a desk calculator, calculations in the past have been carried out only for very small molecules.⁷ Modern digital computers, however, now allow one to calculate frequencies corresponding exactly to given (known or assumed) force constants and geometries for large molecules. Dr. J. H. Schachtschneider, Shell Development Co., has written machine programs for calculating the normal harmonic vibrational frequencies of molecules. These programs, which use the *FG*-matrix method of Wilson (10), now make it feasible to calculate frequencies for molecules containing as many as 30 (or more) atoms. We have modified these programs so that the isotope effect on a rate (or on an equilibrium) is calculated automatically according to Eqs. 5 and 6. Each individual factor (*MMI*, *EXC*, etc.) as well as k_1/k_2 is evaluated. In cases where $\nu_{1L}^\ddagger = \nu_{2L}^\ddagger = 0$ (this is a limiting case representing a very flat potential barrier at the transition state), the ratio $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ is evaluated by calculating $(MMI)/(VP)$. For an equilibrium, $(MMI)/(VP) = 1$.

The model reactions presented here can be classified into four categories: (a) $RX \rightarrow [R \cdots X]^\ddagger$ (S_N1 -type reaction), (b) $RX + X \rightarrow \left[\begin{array}{c} \cdots X \\ R \cdots \\ \cdots X \end{array} \right]^\ddagger$ (S_N2 -type reaction), (c) $RCOOH \rightarrow [R \cdots COOH]^\ddagger$ (decarboxylation-type reaction), and (d) $RH + R' \rightarrow [R \cdots H \cdots R']^\ddagger$ (proton-transfer-type reaction). R is a polyatomic organic group, usually an alkyl group, and X has a mass of 80. X might be a bromine atom, but no particular significance should

⁷ The calculation of the normal-vibrational-mode frequencies of a molecule is a problem in classical mechanics. The methods are described in textbooks such as that by Wilson *et al.* (10). Unless there is considerable symmetry in the molecule, the solution of the equations of motion for a molecule containing as few as five atoms is extremely tedious, if carried out by hand or with a desk calculator.

be attached to its mass, except that it is much heavier than a hydrogen atom. As will be seen later, X might even be thought of as a polyatomic organic group. The force constants used to characterize these models are those for bond stretching, bond-angle bending, torsional motion, and out-of-plane wagging. In some calculations, force constants for interactions between these motions were included in the force fields.

The geometry of the S_N1 -type transition state usually was kept the same as that of the reactant, although sometimes the bond to be broken was lengthened. As will be explicitly pointed out later, the exact choice of geometry does not change our general conclusions. A zero or imaginary frequency, ν_L^\ddagger , corresponding to CX bond break, was produced by setting the relevant CX-stretching force constant (f_{CX}^\ddagger) equal to zero or to a negative value, respectively.⁸ In the S_N2 -type transition state, the geometry about the reaction-center carbon atom was a trigonal bipyramid with XCX angle = 180°, XCH (or XCC) angles = 90°, and HCH (or HCC or CCC) angles = 120°. The CX bond lengths were generally larger than in the reactant. A zero (or imaginary) ν_L^\ddagger was produced either by setting one CX-stretching force constant equal to zero (or negative) and the other CX-stretching force constant greater than zero, or by setting the two f_{CX}^\ddagger 's equal to each other with an equal (or larger) interaction force constant.⁹ The latter condition corresponds to a decomposition motion in which one CX distance is increasing while the other is decreasing. In the decarboxylation-type reaction, the geometry of the transition state generally was kept the same as in the reactant, although sometimes the CC bond to be broken was elongated. A zero or imaginary ν_L^\ddagger was produced by setting the relevant $f_{CC}^\ddagger \leq 0$. In the proton-transfer-type transition state, the geometry of R and R' was the same as in the reactant. The CHC angle at the bridged hydrogen was linear. A zero or imaginary ν_L^\ddagger was produced by setting $f_{C_1H}^\ddagger f_{C_2H}^\ddagger - f_{interact.}^\ddagger \leq 0$, which corresponds to a decomposition motion in which one CH distance is increasing while the other is decreasing.

In the following discussions, no further details of the force fields or geometries will be described explicitly, except when pertinent to the immediate argument. The details of how the changes in force constants and geometry between reactant and transition state come about will not be considered, nor will these changes be rationalized. Some of these changes may not even have reasonable physical bases. By starting with assumed force field and geometry changes and calculating isotope effects "exactly" with the primary expressions, we have, in effect, a perfect "theoretical experiment" in that the calculated isotope effects correspond exactly (in the framework of the primary expressions) to our imposed force constant and geometry changes. If, then, we treat the exactly calculated isotope effects as if they were experimental values, we can subject

TABLE I.—APPARENT VALUES OF *MMI* FROM ARRHENIUS-TYPE PLOTS (300–325°K)

Model Reaction ^a	k_1/k_2 , 300°K	<i>MMI</i>	
		Apparent	Exact
$\{ \text{CD}_3\text{X} \rightarrow [\text{CD}_3 \cdots \text{X}]^\ddagger$	1.502	0.94	1.000
$\{ \text{CD}_3\text{X} \rightarrow [\text{CD}_3 \cdots \text{X}]^\ddagger$	1.376	1.06	1.000
$\left\{ \begin{array}{l} \text{CD}_2\text{X} + \text{X} \rightarrow \\ \left[\text{CD}_2 \cdots \text{X}_2 \right]^\ddagger \end{array} \right.$	0.855	1.17	1.271
$\left\{ \begin{array}{l} \text{CD}_2\text{X} + \text{X} \rightarrow \\ \left[\text{CD}_3 \cdots \text{X}_2 \right]^\ddagger \end{array} \right.$	0.791	1.09	1.271
$\text{CF}_3\text{D} + \cdot\text{CH}_3 \rightarrow$ $[\text{F}_3\text{C} \cdots \text{D} \cdots \text{CH}_3]^\ddagger$	3.627	1.08	1.038

^a Cases within brackets differ in the imposed force constant changes between reactant and transition state.

them to the same analyses that one might apply to real experimental values. Comparison of the results obtained from the analyses with the input (force constants, etc.) to the exact calculations should make it possible to determine how much about the input parameters can be extracted from the calculated isotope effects. It is hoped that such conclusions based on model calculations will carry over into real systems.

All of the machine calculations were carried out with an IBM 7094 computer.

DETERMINATION OF GEOMETRIES OF TRANSITION STATES FROM ISOTOPE EFFECT MEASUREMENTS

For large u (low temperatures or high frequencies) $EXC \rightarrow 1$. The low-temperature approximation is then

$$k_1/k_2 = (MMI)(ZPE) \quad (\text{Eq. 7})$$

It has been shown (4) that this approximation is a fairly good one for many reactions, even at room temperature. According to Eq. 7, the isotope effect can be expressed by an Arrhenius-type equation

$$\ln(k_1/k_2) = \ln A + B/T \quad (\text{Eq. 8})$$

where $A = MMI$ and B is the difference between reactant and transition state of the isotopic shifts in zero-point energy. However, the fact that Eq. 7 yields reasonable fits to the exact values of k_1/k_2 is not in itself sufficient evidence that a semilog plot, according to Eq. 8, will yield accurate values of MMI .¹⁰ Table I lists some apparent values of MMI obtained from the infinite-temperature intercepts of Arrhenius-type plots of isotope effects in the vicinity of room temperature. A straight line was drawn through the points at 300°K and 325°K. As with actual experimental values, there was no difficulty in fitting the data for a limited temperature range to a $1/T$ plot, even though, unless the excitation terms are truly negligible, the actual temperature dependence is more complex. Thus, the point at 400°K is usually fit quite well by the line drawn through the 300°K and 325°K points.

¹⁰ It has been shown (4) that good estimates of ZPE can be obtained from the slopes of such plots.

⁸ All of the calculations explicitly presented in this paper were carried out using a zero value of ν_L^\ddagger . Other calculations have been carried out with ν_L^\ddagger imaginary. The latter do not change any of the conclusions which will be presented.

⁹ A condition that produces a zero frequency is $f_{ij} f_{ij} = f_i f_j^2$, where f_{ij} is the interaction force constant. No other interaction force constants involving the coordinates q_i and q_j may appear if this condition is to be rigorous. For an imaginary frequency, the condition is $f_{ij} f_j < f_{ij}^2$.

As the values in Table I indicate, the apparent values of MMI determined from Arrhenius plots in the vicinity of room temperature do not give reliable information about the exact MMI . (It will be shown later that the Arrhenius pre-exponential factor appears to bear some relation to the types of force constant changes occurring during the reaction.) MMI is dependent only on geometry, atomic masses, and isotopic positions. However, it does vary rather slowly with geometry changes so that to derive useful information about geometry from Arrhenius-type plots, very good estimates of MMI would have to be obtained. While the values shown in Table I are not good estimates, it is possible that Arrhenius-type plots at very low temperatures (very high u), where Eq. 7 is almost exact, might provide apparent values of MMI of the necessary accuracy.

In several calculations that we have carried out (5), we have found that different choices of geometries, within fairly broad limits, lead either to negligible differences in the calculated isotope effects or to differences that can be canceled with small changes in force constant assignments.

It appears that actual geometries and geometry changes cannot be determined directly from measured isotope effects in the room-temperature region. Thus, in analyzing experimental isotope effect data, one should be interested primarily in determining force constant changes. In many cases it may be possible to correlate force constant changes with geometry changes.

ISOTOPE EFFECTS IN THE ABSENCE OF FORCE CONSTANT CHANGES

For small u (high temperature or low frequencies), Eq. 6 can be expanded in powers of $1/T$. Consideration of only the first term in the expansion yields (1)¹¹

$$\ln \left(\frac{k_1}{k_2} \right) = \ln \left(\frac{\nu_{1L}^\ddagger}{\nu_{2L}^\ddagger} \right) + \frac{1}{24} \left(\frac{h}{2\pi kT} \right)^2 \times \left[\sum_{\substack{i,j \\ \text{reactant}}} f_{ij}(g_{1,ij} - g_{2,ij}) - \sum_{\substack{i,j \\ \ddagger}} f_{ij}^\ddagger(g_{1,ij} - g_{2,ij})^\ddagger \right] \quad (\text{Eq. 9})$$

In Eq. 9, f_{ij} refers to the force constant involving the internal coordinates q_i and q_j . (When $i = j$, the force constant is just what has been defined as f_i in Footnote 1.) The g_{ij} 's are the corresponding G -matrix (kinetic-energy) elements of Wilson (10) which can be evaluated from a knowledge (or assumption) of molecular geometry and atomic masses.

For Cartesian displacement coordinates, Eq. 9 becomes

$$\ln \left(\frac{k_1}{k_2} \right) = \ln \left(\frac{\nu_{1L}^\ddagger}{\nu_{2L}^\ddagger} \right) + \frac{1}{24} \left(\frac{h}{2\pi kT} \right)^2 \times \sum_i (a_{ii} - a_{ii}^\ddagger) \left(\frac{1}{m_{1i}} - \frac{1}{m_{2i}} \right) \quad (\text{Eq. 10})$$

¹¹ Equation 9 implicitly contains the Wigner quantum-mechanical tunneling correction. For cases where $\nu_{L}^\ddagger = 0$, as in the calculations explicitly presented in this paper, there is no tunneling so that the value of the tunneling correction is identically unity.

TABLE II.—CALCULATION WITH NO FORCE CONSTANT CHANGES AT ISOTOPIC POSITIONS

$$\text{CD}_3\text{CH}_2\text{X} + \text{X} \rightarrow [\text{CD}_3\text{CH}_2 \cdots \text{X}_2]^\ddagger, \quad \nu_{1L}^\ddagger/\nu_{2L}^\ddagger = 1.039$$

T, °K	MMI	EXC	ZPE	$\frac{k_1/k_2}{\nu_{1L}^\ddagger/\nu_{2L}^\ddagger}$
100	1.131	0.957	0.957	0.997
300	1.131	0.932	0.985	1.000
2000	1.131	0.920	0.998	1.000

where $a_{ii} - a_{ii}^\ddagger$ is the difference, between reactant and transition state, in the sums of the three diagonal (not interaction) Cartesian force constants of the isotopically substituted atom i , and m_{1i} and m_{2i} are the isotopic atomic masses of atom i . Only isotopically substituted atoms need be included in the sum, since for the other atoms, $1/m_1 - 1/m_2 = 0$. Equations 9 and 10 are referred to as the high-temperature approximation. It has been shown (3, 4) that this approximation generally does not predict isotope effects very well at room temperature. Yet, these equations give physical insight into isotope effects and are starting points for investigating the nature and causes of such effects.

For example, Eq. 10 states that if there is no force constant or geometry change (a geometry change in the absence of a force constant change is unreasonable) between reactant and transition state at the isotopic position(s), there will be no isotope effect other than the classical limit, $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. This consideration, of course, applies only to secondary isotope effects since, by definition, a primary isotope effect must involve force constant changes. The question then arises as to whether this prediction is true in the vicinity of room temperature (it is obviously true at sufficiently high temperatures) or if the perturbation of the coupling of vibrational motions could cause a secondary isotope effect in the room-temperature region, even in the absence of force constant changes involving the isotopic atoms.

We have calculated (5, 6) isotope effects for a large number of model reactions under the conditions that there be no force constant or geometry changes at the isotopic positions. Under these conditions, isotope effects at room temperature, aside from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, are found to be, for reasonable values of the force constants, less than $\sim 1\%$ per α -deuterium, less than $\sim 0.2\%$ per β -deuterium, and even less per γ - and δ -deuterium substitution.^{12,13}

Table II shows the results for a typical calculation, a β -D₃ effect in an S_N2 -type reaction. At 2000°K, as expected, the zero-point energy contribution is negligible and $(MMI)(EXC) \cong \nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. At 300°K, this relation is no longer true, but ZPE has changed sufficiently so that there is still no effect other than $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. Even at 100°K, the cancellation occurs, so that an effect other than

¹² Hydrogen atoms covalently bonded to a carbon atom directly involved in the bond-making or bond-breaking of a reaction will be designated as α -atoms. Hydrogen atoms covalently bonded to a carbon atom one bond removed from a reaction-center carbon will be designated as β -atoms, etc. The limits given in the statement in the text refer to cases in which only force constants involving the reaction center were permitted to change.

¹³ Some α -deuterium secondary effects under these conditions have been found to be somewhat larger if a hydrogen atom, bonded to the same carbon atom that the isotopic atom is bonded to, is involved in the reaction coordinate. This effect will be discussed elsewhere (8).

TABLE III.—CALCULATIONS WITH NO FORCE CONSTANT CHANGES AT ISOTOPIC POSITIONS

Model Reaction	k_1/k_2 , 300°K	$\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CD}_2\text{X} \rightarrow [\text{CH}_3\text{CH}_2\text{CH}_2\text{CD}_2\cdots\text{X}]^\ddagger$	1.0343	1.0276
$\text{CH}_3\text{CD}_2\text{CH}_2\text{CH}_2\text{X} \rightarrow [\text{CH}_3\text{CD}_2\text{CH}_2\text{CH}_2\cdots\text{X}]^\ddagger$	1.0060	1.0060
$\text{CH}_3\text{C}^{14}\text{H}_2\text{CH}_2\text{X} \rightarrow [\text{CH}_3\text{C}^{14}\text{H}_2\text{CH}_2\cdots\text{X}]^\ddagger$	1.0145	1.0143
$\text{HOOC}^{13}\text{CH}_2\text{COOH} \rightarrow [\text{HOOC}^{13}\text{CH}_2\cdots\text{COOH}]^\ddagger$	1.0036	1.0034
$\text{CH}_3\text{CH}_2\text{CD}_2\text{CH}_2\text{X} + \text{X} \rightarrow [\text{CH}_3\text{CH}_2\text{CD}_2\text{CH}_2\cdots\text{X}_2]^\ddagger$	1.0023	1.0120

^a Very large force constants used. All stretching force constants equal 10 mdynes/Å. All bending and torsional force constants equal 5 mdynes-Å. All normally important interaction force constants equal 1 unit. The interaction force constant between the two CX stretches in the transition state equals 10 mdynes/Å.

$\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ of only $\sim 0.1\%$ per deuterium is exhibited. Such cancellation is but one of the many indications we have obtained that the interplay between the individual factors in the primary equations makes consideration of the complete equation(s) imperative. Table III presents results at 300°K for a few more calculations of this type. At lower temperatures, the deviations from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ increase. The secondary carbon-isotope effects in the third and fourth cases indicate that, in the absence of force constant changes, heavy-atom isotopes behave in a similar manner to hydrogen isotopes. The last entry in Table III is representative of a number of calculations that we have made in which very large force constants (as indicated in Footnote a, Table III) were used. With such force constants, the molecules are quite "stiff" so that discrepancies from the high-temperature-approximation behavior would be expected to be larger. While the deviations from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ in such cases are somewhat larger than in the previous cases, the magnitudes are still quite small. As expected, the deviations decrease as the temperature increases.

We conclude from these calculations that secondary isotope effects around room temperature appreciably different from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ do not arise just from the coupling of vibrational motions but must reflect a force constant change occurring at the isotopic position. Isotope effects, therefore, may be used as probes for force constant changes. Thus, the presence or absence of an isotope effect (in addition to $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$) at a particular atomic position is evidence for or against a change of bonding of the atom at that position between reactant and rate-determining transition state (or between reactant and product in an equilibrium). (As shown in the following section, secondary heavy-atom isotope effects, even in the presence of force constant changes, may be sufficiently small so that deviations from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ cannot be detected. On the other hand, the contribution to secondary hydrogen isotope effects from relatively small force constant changes at the isotopic position tends to be large compared to $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$.) Similar considerations should apply to biological activity. The introduction of isotopic substitution in various positions in a biologically active compound should help to determine which parts of the molecule are actually responsible for the activity and thus give information regarding the mechanism of action. In the case of a mechanism of action involving an equilibrium process, the presence or absence of an isotope effect on the activity is evidence for or against the participation of the isotopic position. In the case of a mechanism of action involving a rate process, the isotope effect generally

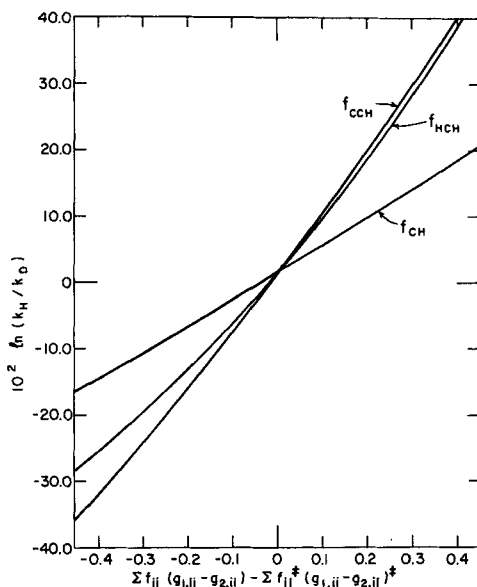


Fig. 1.—Isotope effect at 300°K for a model reaction $\text{CH}_3\text{CD}_2\text{CH}_2\text{X} \rightarrow [\text{CH}_3\text{CD}_2\text{CH}_2\cdots\text{X}]^\ddagger$ as a function of force constant change. The labels indicate the types of force constants changed at the isotopic positions. The units of the abscissa are mdynes Å.⁻¹(a.m.u.)⁻¹.

will give information regarding only the rate-determining step.

ISOTOPE EFFECTS AND FORCE CONSTANT CHANGES

In the preceding section, it was pointed out that the high-temperature approximation predicts that there will be an isotope effect in addition to $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ if there is a difference between reactant and transition state in the force constants at the isotopic positions. This effect will, according to Eqs. 9 and 10, be proportional to the magnitude of the force constant difference but independent of the actual values of the force constants. If, on balance, the force constants decrease in going from reactant to transition state, the isotope effect will be normal ($k_{\text{light}}/k_{\text{heavy}} = k_1/k_2 > 1$); if the force constants increase, the effect will tend¹⁴ to be inverse ($k_1/k_2 < 1$).

¹⁴ $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ is always ≥ 1 . If the force constant increase is very small or if the temperature is sufficiently high, the classical contribution will be the major one, and the isotope effect will be normal.

As mentioned previously, mechanistic descriptions can be translated into descriptions of force constant changes. It is, therefore, of great interest to see if such force constant changes can be characterized by comparing experimental isotope effects with calculated effects. Indeed, if the force constant changes occurring during a reaction can be identified, the rationalization of proposed mechanisms will be enhanced. However, it is not the purpose of this discussion to correlate mechanisms with force constant changes but rather to examine the feasibility of determining the force constant changes.

Figure 1 shows the calculated isotope effect, at 300°K, for a β -D₂ substitution in an S_N1-type reaction in which the effect was produced by independently changing three different force constants at the isotopic positions, as indicated. The isotope effects are plotted as functions of the force constant changes. The abscissa is such that, if the high-temperature approximation had applied rigorously at 300°K, three superimposed straight lines would have resulted. When no force constant changes at the isotopic positions are made (abscissa = 0), k_1/k_2 is just about $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, as expected from the preceding section. When a force constant change is made, the direction of the isotope effect is that predicted by the high-temperature approximation (*i.e.*, a lowering of a force constant from reactant to transition state causes a normal effect, etc.). It is obvious from Fig. 1 that an observed effect at a single temperature could have been caused by any one force constant change (or combination of force constant changes).

To see if it is possible to distinguish between different force constant changes by examining the temperature dependence of an isotope effect, we changed the three force constants in Fig. 1 independently by amounts sufficient to produce a 15% effect at 300°K (about the magnitude of observed β -D₂ secondary effects) and calculated the isotope effects at several temperatures. The results are shown in Table IV. While the temperature dependences for the three cases are fairly similar, the pre-exponential factors, A, from Arrhenius-type plots around 300°K are somewhat different. Table V shows results for similar calculations. The first two cases here again represent model reactions in which about the same isotope effect at 300°K was produced by changing different force constants. As in the cases in Table IV, the bending force constant change produced a lower A than did the stretching force constant change. While not enough calculations have been carried out to formulate any general rules concerning the magnitudes and directions (from unity) of the A factors, it appears that comparison of A factors obtained from experimental secondary isotope effect data and A factors obtained from model calculations may help to determine, or to put some limits on, the

types of force constant changes occurring during a reaction.

When several types of force constants change at the same time, rather strange temperature dependences may occur. In such cases, model calculations can be extremely useful for the rationalization of the effects.

Another method available for bracketing the force constant changes occurring during a reaction is that of making isotopic substitutions of different atomic positions in the same reactant molecule. Since the force constants are independent of isotopic substitution, this method provides several "sighting points" to "look at" the same set of force constant changes. Any model proposed for a reaction must reproduce, with the same force constant changes, all isotopic-substitution effects. For example, a model which predicts the correct (observed) secondary deuterium effect but the wrong primary carbon-isotope effect must be revised.

To investigate whether secondary carbon-isotope effects could be helpful in distinguishing between different force constant changes, we calculated the β -C¹⁴ effects for the same reaction and same force fields used to produce the secondary deuterium effects shown in Table IV. (β -C¹⁴ refers here to CH₂C¹⁴H₂CH₂X; some would call such effects α -secondary effects.) The C¹⁴ effects at room temperature and above were found to be only slightly greater than $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, even though the force constant changes were sufficiently large to produce normal-magnitude secondary deuterium effects. At 300°K, the β -C¹⁴ effects (k_1/k_2) for the force constant changes shown in Table IV (in descending order) are 1.0170, 1.0178, and 1.0193. The value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for these cases is 1.0143. It would be extremely difficult to distinguish experimentally between the three isotope effects. In fact, due to the uncertainty in the determination of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from experimental data (as discussed in the following section), it would be, at least presently, almost impossible to distinguish between the measured isotope effects and $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. In other secondary isotope effect calculations in which "reasonable" force constant changes at the carbon-isotope position have been made, similar results were obtained. It appears that secondary isotope effects of heavy atoms (C, O, etc.) cannot be used generally to gain useful information about force constant changes.

DETERMINATION OF $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ FROM EXPERIMENTAL DATA

In the preceding sections, much of what has been said referred to $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$, *i.e.*, the part of the isotope effect aside from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, the classical or infinite-temperature limit. The problem of the determination of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from experimental measurements in the vicinity of room temperature is of

TABLE IV.—TEMPERATURE DEPENDENCE OF ISOTOPE EFFECTS PRODUCED BY DIFFERENT FORCE CONSTANT CHANGES AT ISOTOPIC POSITIONS



Force Constant Change	k_1/k_2				A ^a
	200°K	300°K	400°K	500°K	
f_{CH} , 4.5 → 4.2 mdynes/Å.	1.229	1.152	1.115	1.094	1.01
f_{HCH} , 0.53 → 0.35 mdynes-Å.	1.238	1.153	1.109	1.083	0.99
f_{CCH} , 0.68 → 0.60 mdynes-Å.	1.241	1.150	1.105	1.079	0.98

^a Pre-exponential factor from Arrhenius-type plot (300–325°K).

TABLE V.—PRE-EXPONENTIAL FACTORS A FROM ARRHENIUS-TYPE PLOTS (300–325°K) FOR SOME MODEL REACTIONS

Reaction ^a	Force Constant Change at Isotopic Positions	k_1/k_2 , 300°K	A
$CD_3X \rightarrow [CD_3 \cdots X]^\ddagger$	f_{HCX} , 0.62 \rightarrow 0.37 mdynes-Å.	1.50	0.94
$CD_3X \rightarrow [CD_3 \cdots X]^\ddagger$	f_{CH} , 5.1 \rightarrow 4.56 mdynes/Å.	1.50	1.06
$CD_3X + X \rightarrow [CD_3 \cdots X_2]^\ddagger$	f_{HCX} , 0.62 \rightarrow 0.41 mdynes-Å. ^b	0.86	1.17
$CD_3CH_2X + X \rightarrow [CD_3CH_2 \cdots X_2]^\ddagger$	f_{HCH} , 0.53 \rightarrow 0.40 mdynes-Å.	1.37	0.98

^a The first and third cases are identical to the first and third cases, respectively, of Table I. ^b In this case, there is a net increase (from reactant to transition state) in the force constants at the isotopic positions since each hydrogen (deuterium) is involved in one HCX-bonding coordinate in the reactant but in two HCX-bonding coordinates in the transition state. As expected, the isotope effect is inverse.

TABLE VI.—CUT-OFF CALCULATIONS FOR $CH_3CD_2CH_2X + X \rightarrow [CH_3CD_2CH_2 \cdots X_2]^\ddagger$

T, °K	$CH_3CD_2CH_2X$ ^b	$C-CD_2CH_2X$ ^c	$C-CD_2-C$ ^d	CD_2 ^e
		Values of Isotope Effect k_1/k_2		
50	1.8763	1.8669	2.0190	2.1224
100	1.4008	1.3990	1.4209	1.4568
200	1.1920	1.1918	1.1917	1.2061
300	1.1244	1.1244	1.1222	1.1296
500	1.0689	1.0690	1.0661	1.0683
∞ ^f	1.0027	1.0028	1.0000	1.0000
		Decomposition of Isotope Effect at 300°K		
MMI	1.0725	1.0756	1.0000	1.0000
EXC	0.9547	0.9533	0.9982	0.9965
ZPE	1.0982	1.0966	1.1242	1.1336

^a In each case, the isotope effect was produced by lowering f_{CD} from 4.5 mdynes/Å. in the reactant to 4.36 mdynes/Å. in the transition state and lowering f_{DCD} from 0.53 mdynes-Å. to 0.445 mdynes-Å. ^b Complete model $CH_3CD_2CH_2X + X \rightarrow [CH_3CD_2CH_2 \cdots X_2]^\ddagger$. ^c $C-CD_2CH_2X + X \rightarrow [C-CD_2CH_2 \cdots X_2]^\ddagger$. ^d Equilibrium $C-CD_2-C \rightleftharpoons C-CD_2-C$, with indicated force constant changes at isotopic positions. ^e Equilibrium $CD_2 \rightleftharpoons CD_2$, with indicated force constant changes at isotopic positions. ^f For the reactions, the infinite temperature value of k_1/k_2 is $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. For the equilibria, the effective value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ (in Eq. 6) is unity.

TABLE VII.—CUT-OFF CALCULATIONS FOR $HOOCCH_2C^{13}OOH \rightarrow [HOOCCH_2 \cdots C^{13}OOH]^\ddagger$

T, °K	$HOOCCH_2-C^{13}OOH$ ^b	$C-CH_2-C^{13}OOH$ ^c	$X^{46}-CH_2-C^{13}OOH$ ^d	$C-C^{13}OOH$ ^e	$X^{59}-C^{13}OOH$ ^f	$C-C^{13O}$ ^g
		Values of $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$ ^h				
50	1.1847	1.1826	1.1860	1.1730	1.2133	1.3393
100	1.0859	1.0854	1.0862	1.0818	1.0981	1.1460
200	1.0398	1.0396	1.0397	1.0386	1.0443	1.0601
300	1.0245	1.0244	1.0244	1.0241	1.0265	1.0334
500	1.0121	1.0120	1.0120	1.0120	1.0126	1.0144
		Values of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$				
	1.0054	1.0038	1.0056	1.0023	1.0063	1.0198

^a In each case, $f_{CC}(f_{CX}^{59}$ in the $X^{59}-COOH$ calculation) for the bond at the isotopic carbon was lowered from 4.4 mdynes/Å. in the reactant to 0.0 in the transition state. ^b Complete model $HOOCCH_2C^{13}OOH \rightarrow [HOOCCH_2 \cdots C^{13}OOH]^\ddagger$. ^c $C-CH_2C^{13}OOH \rightarrow [C-CH_2 \cdots C^{13}OOH]^\ddagger$. ^d $X^{46}-CH_2C^{13}OOH \rightarrow [X^{46}-CH_2 \cdots C^{13}OOH]^\ddagger$. ^e X^{46} is an atom with mass of 45 a.m.u., representing COOH. The bond lengths, bond angles, and force constants for this case were the same as in the $C-CH_2C^{13}OOH$ case. ^f $C-C^{13}OOH \rightarrow [C \cdots C^{13}OOH]^\ddagger$. ^g $X^{59}-C^{13}OOH \rightarrow [X^{59} \cdots C^{13}OOH]^\ddagger$. ^h X^{59} is an atom with mass of 59 a.m.u., representing $HOOCCH_2$. The bond lengths, bond angles, and force constants for this case were the same as in the $C-C^{13}OOH$ case. ⁱ $C-C^{13} \rightarrow [C \cdots C^{13}]^\ddagger$. ^j The rate ratio for this particular isotopic substitution in the decarboxylation of malonic acid is usually referred to as $k_1/2k_2$.

much interest, since for some applications of the considerations of the previous sections, the approximate magnitude of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ would have to be known or guessed. Another important reason for wanting to be able to determine $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from experimental data is that the value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ depends on the nature of the reaction coordinate.¹⁶ Comparison of an experimentally measured $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ and values

obtained (or just reasoned) from model calculations should be useful in determining the nature of the transition state. For cases of isotope effects on equilibria, of course, the problem of the experimental determination of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ never arises.

The secondary C^{14} effects discussed under *Isotope Effects and Force Constant Changes* suggest a method for directly measuring $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ —the measurement of secondary carbon-isotope effects. From our model calculations, it appears that secondary heavy-atom effects at room temperature and above should be quite close to $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, even when

¹⁶ The value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ could conceivably be as large as the square root of the isotopic atomic mass ratio. Such a value would correspond to a reaction coordinate in which only the isotopic atom is moving. Except for some primary isotope effects, a situation of this sort is unrealistic.

"reasonably large" force constant changes at the isotopic position are occurring. A model consistent with the estimated $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for the carbon-isotope substitution can provide information regarding $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for other isotopic substitutions. The danger in such a procedure is that two (or more) models may predict the same value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for the secondary carbon substitution but differing values for other isotopic substitutions.

Of more direct utility would be methods of obtaining $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from the experimentally measured isotope effects corresponding to any particular isotopic substitution. Four methods (11, 12) used in the past for determining or setting limits on $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from experimental measurements in the vicinity of room temperature were evaluated (4) with the aid of model calculations. The conclusion was drawn that none of these methods is *generally* valid and that their application requires, at least, some assumptions about the nature of the transition state. The most promising method seems to be the so-called "gamma-bar" method (12). In this method, $\ln(k_1/k_2)$ is plotted against $\bar{\gamma}/T^2$, and the infinite-temperature intercept is taken as $\ln(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$. $\bar{\gamma}$ is a temperature-dependent function defined (operationally) as (1, 12)

$$\bar{\gamma} = \frac{12}{\bar{u}} \left(\frac{1}{2} - \frac{1}{\bar{u}} + \frac{1}{\exp(\bar{u}) - 1} \right) \quad (\text{Eq. 11})$$

where $\bar{u} = h\bar{\nu}/kT$; $\bar{\nu}$ is an average frequency considered to be characteristic of the reaction. The rationale for this method can be seen from examination of the gamma-bar equation, which is Eq. 9 or Eq. 10 with the coefficient $1/24$ replaced by $\bar{\gamma}/24$.¹⁶ This modified high-temperature equation has been found to fit many model-calculation results; cases have been devised, however, where no such fit is possible (4). The problem in using this method for the determination of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ from experimental data is that there is presently no reliable *a priori* method for the prediction of the characteristic frequency. It is possible that, by varying the characteristic frequency in such a way that a plot of $\ln(k_1/k_2)$ versus $\bar{\gamma}/T^2$ yields the best straight line, reasonable estimates of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ might be obtained. Obviously, more investigation along these lines is necessary.

LARGE MOLECULES

It appears from the previous discussions that there is much to be learned from comparison of experimental and calculated isotope effects. However, when one is dealing with molecules containing more than about 20 atoms, even the machine calculations become quite cumbersome and use large amounts of computer time. (The time required for the solution of the equations of motion is approximately proportional to the number of atoms raised to the third power.) Pharmaceutical chemistry is, for the most part, concerned with large molecules, the detailed structures, etc., of some of which are not known.

In the following discussion, we will consider the possibility of carrying out calculations on smaller model molecules and of still obtaining the same answers that would have been obtained had the complete larger molecules been considered. Such calculations have been termed "cut-off" calculations (4, 6).

The high-temperature approximation (Eq. 9) predicts that if one wants to calculate an isotope effect for a particular model system, one need only include those parts of the molecule containing the isotopic positions and atoms involved in coordinates coupling them to the isotopic positions. Of the latter atoms, only those involved in coordinates with force constant changes need be included. This prediction, of course, applies only to the isotope effect aside from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. Therefore, if $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ in the complete calculation and in the cut-off calculation differed, a correction (multiply by ratio of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$'s) would have to be made. In the calculations discussed below, the validity of the above prediction and the extent to which it can be applied are examined.

Table VI presents results for a model reaction

$$\text{CH}_3\text{CD}_2\text{CH}_2\text{X} + \text{X} \rightarrow \left[\text{CH}_3\text{CD}_2\text{CH}_2 \cdots \text{X}_2 \right]^\ddagger$$

The geometry and force constants of each reactant and transition state in the cut-off models are the same as the corresponding geometry and force constants in the complete model. Thus, at very high temperatures, where Eq. 9 is "exact," the isotope effects (aside from $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$) for all the cases must be identical. If the condition that the complete calculation and a cut-off calculation give the same $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$ in the high-temperature approximation is not fulfilled, any agreement or disagreement between the two calculations is found to be a function of the particular choice of force constants used. Agreement in the high-temperature equation is, therefore, a primary condition for application of the cut-off procedure.

In the last two cases (C—CD₂—C and CD₂) in Table VI, there is no actual reaction taking place. For these cases, the values listed as k_1/k_2 are the isotope effects on the equilibria between cut-off "molecules" with the same force constant changes at the isotopic positions as in the complete model (*i.e.*, the reactant "molecule" has the same force constants where applicable as the reactant in the complete model, and the product "molecule" has the same force constants where applicable as the transition state in the complete model). The effective value of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ in the equilibrium cases is unity.

The C—CD₂CH₂X and C—CD₂—C calculations give values of k_1/k_2 , at room temperature and above, which are related to the k_1/k_2 values for the complete model by the ratios of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$. Even the most extreme case (CD₂) gives reasonable results, but this case probably carries the cut-off procedure too far for comfort. The deviations between the cut-off and complete models increase as the temperature is decreased so that, below $\sim 100^\circ\text{K}$, the deviations for the C—CD₂—C model become nonnegligible.

Examination of the individual factors (*MMI*, etc.) for the different cases in Table VI indicates again that only the complete expression (*MMI*) \times (*EXC*) \times (*ZPE*) should be considered. It is interesting that the frequency shifts $[(\nu_{1L} - \nu_{2L}) - (\nu_{1L}^\ddagger - \nu_{2L}^\ddagger)]$ for a complete calculation and for a

¹⁶ One can think of $\bar{\gamma}$ as a factor which introduces the dependence of the isotope effect on the actual magnitudes of the force constants into the high-temperature approximation. The value of $\bar{\gamma}$, however, varies rather slowly with vibrational frequency (or force constant) (1) so that, except at very low temperatures and/or in reactions involving changes in very large force constants, the isotope effect would still be largely dependent only on the force constant changes.

cut-off calculation that gives the same $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$ are generally quite different and occur over different frequency ranges. This fact certainly indicates that it is better for considerations of isotope effects to discuss force constant changes than to discuss individual frequency shifts.

Table VII presents the results of cut-off calculations for a primary C^{13} -effect in a decarboxylation reaction. The isotope effect results from the vanishing in the transition state of a CC-stretching force constant. The values listed are $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$ so that no further correction is necessary for purposes of comparison. Comparison of the results for $C-CH_2C^{13}OOH$ and $X^{45}-CH_2C^{13}OOH$ indicates that substitution of a point-mass atom (45 a.m.u., representing COOH) instead of a carbon atom (12 a.m.u.) has, in this case, little influence on $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$. That such substitution has little effect has been found to be generally true, if the substitution is made at positions at least two bonds removed from the isotopic position(s). The point-mass-atom calculation does, however, reproduce the $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ of the complete calculation better than does the carbon-atom calculation. In comparing the $C-C^{18}OOH$ and $X^{69}-C^{18}OOH$ calculations, it can be seen that the point-mass-atom (59 a.m.u., representing $HOOCCH_2$) calculation does not reproduce $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$ for the complete calculation as well as does the carbon-atom calculation but does reproduce $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ better. The extreme cut-off in the last case ($C-C^{13}$) of Table VII is a quite poor approximation to the complete case, even at room temperature and somewhat above.

We have carried out cut-off calculations for a primary hydrogen-isotope effect in a proton-transfer reaction. For the complete reaction $CF_3CF_2CF_2D + CH_3CH_2CH_2 \cdot \rightarrow [CF_3CF_2CF_2 \cdots D \cdots CH_2CH_2CH_3]^\ddagger$, k_1/k_2 at 300°K was 8.236. For the cut-off reaction $X^{119}-CF_2D + X^{29}-CH_2 \cdot \rightarrow [X^{119}-CF_2 \cdots D \cdots CH_2-X^{29}]^\ddagger$ with the same force constant changes, k_1/k_2 at 300°K was 8.241. $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for both the complete calculation and the cut-off calculation was $1.411 \approx \sqrt{2}$, since in both cases the reaction coordinate involves the hydrogen (deuterium) atom moving between two heavy groups. The computer time used for the cut-off calculation was about a factor of 20 lower than that necessary for the complete calculation. Cut-off closer to the reaction center in reactions of this type caused appreciable deviations from the complete-reaction results.

The indication from these calculations is that isotope effects for very large molecular systems may be studied theoretically by using smaller molecules in the calculations. It appears that large changes in, or even complete omission of, all parts of the molecules more than two bonds removed¹⁷ from the isotopic position(s) will not affect appreciably the

calculated values of $(k_1/k_2)/(\nu_{1L}^\ddagger/\nu_{2L}^\ddagger)$. In some cases, this cut-off procedure may be carried one bond closer, but only with considerable caution.

SUMMARY

The transition-state theory of rate processes shows that experimentally determined isotope effects can provide useful information about force constant changes between reactants and transition states. Such information should be extremely useful for the elucidation of reaction mechanisms. Isotope effects on equilibria can, in a similar manner, be used to investigate force constant differences between reactants and products.

In this presentation, we have tried to investigate a few of the predictions of the theory and show how comparison of experimental and calculated effects can yield the desired information regarding force constant changes. The increasing availability of modern digital computers should increase greatly the use of these methods.

Some of the important conclusions of this presentation are: (a) Generally reliable information about geometry changes occurring in a reaction cannot be determined directly from room-temperature-region isotope effects. (b) Isotope effects, other than $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, at room temperature and above are extremely small unless there is a force constant change at the isotopic position. Isotope effects, therefore, may be used as probes for such changes and thus for participation in reaction mechanisms. (c) Measurement of the temperature dependence of an isotope effect and the use of different isotopic substitutions in the same molecule may help determine or place limits on the particular force constant changes occurring between reactants and transition state. (d) Secondary heavy-atom isotope effects may give information about the decomposition motion in a transition state. (e) Isotope effects for very large molecular systems may be studied theoretically by working with smaller model molecules. This latter conclusion should be of particular interest to the pharmaceutical chemist.

It is hoped that the methods described in this paper will be applied to problems of pharmaceutical interest.

REFERENCES

- (1) Bigeleisen, J., and Wolfsberg, M., *Adv. Chem. Phys.* **1**, 15(1958).
- (2) Melander, L., "Isotope Effects on Reaction Rates," The Ronald Press, New York, N. Y., 1960.
- (3) Stern, M. J., and Wolfsberg, M., *J. Chem. Phys.*, **39**, 2776(1963).
- (4) Wolfsberg, M., and Stern, M. J., *Pure Appl. Chem.*, **8**, 225(1964).
- (5) *Ibid.*, **8**, 325(1964).
- (6) Stern, M. J., and Wolfsberg, M., unpublished data.
- (7) Glasstone, S., Laidler, K. J., and Eyring, H., "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.
- (8) Bigeleisen, J., *J. Chim. Phys.*, **60**, 35(1963).
- (9) Schachtschneider, J. H., and Snyder, R. G., *Spectrochim. Acta*, **19**, 117(1963).
- (10) Wilson, E. B., Decius, J. C., and Cross, P. C., "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955.
- (11) Yankwich, P. E., and Ikeda, R. M., *J. Am. Chem. Soc.*, **81**, 1532(1959).
- (12) Bigeleisen, J., et al., *ibid.*, **84**, 1813(1962).

¹⁷ An exception would be a case in which a torsional coordinate involving the isotopic position as a terminal atom undergoes a force constant change. This change, which contributes to the isotope effect even in the high-temperature approximation, could not be included in a calculation in which all atoms more than two bonds removed from the isotopic position were cut off.