

KINETIC ISOTOPE EFFECTS IN THE DECARBOXYLATION  
OF SOME SUBSTITUTED BENZOIC ACIDS

by  
John Buccini

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DEDICATED  
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## ABSTRACT OF M.Sc. THESIS

submitted by John Buccini

Kinetic Isotope Effects in the Decarboxylation of Some Substituted Benzoic Acids.

(A) The carboxyl- $C^{13}$  kinetic isotope effects were measured for the decarboxylations of 4-methylsalicylic acid in solutions of quinoline and of .02 M quinoline in nitrobenzene. The observed isotope effects at  $195^{\circ}C$  were  $0.7 \pm .1 \%$  and  $2.2 \pm .1 \%$ , for the quinoline-nitrobenzene and pure quinoline solutions, respectively. These results indicate that the mechanism of this reaction involves the equilibrium formation of ion pairs, followed by the formation of a reaction intermediate which can decompose to either products, or an ion pair.

(B) The carboxyl- $C^{13}$  kinetic isotope effects were measured for the decarboxylation of 4-methoxyanthranilic acid in aqueous solutions of different pH and constant ionic strength (0.5). The isotope effects observed at  $60^{\circ}C$  were  $4.2 \pm .1\%$ ,  $1.4 \pm .1\%$  and 0 for solutions of pH = -.3, 1.3, and 4.0, respectively. These results are interpreted in terms of a mechanism in which the acid (HA), the acid anion ( $A^{-}$ ) and zwitterion (Z) are all protonated to form non-Bjerrum intermediates, ( $H_2A^*$ ,  $HA^*$  and  $HZ^*$ , respectively) of which only  $HA^*$  can decarboxylate.

TABLE OF CONTENTS

	PAGE
INTRODUCTION . . . . .	1
THE THEORETICAL PREDICTION OF ISOTOPE EFFECTS . . . . .	3
Temperature Dependence of the Isotope Effect . . . . .	12
EXPERIMENTAL EVALUATION OF THE KINETIC ISOTOPE EFFECT . . . . .	14
The Method of Absolute Rates . . . . .	14
The Method of Competitive Rates . . . . .	14
The Isotopic Competitive Method at a Tracer Concentration of $A_0^*$ . . . . .	19
Intermolecular and Intramolecular Isotope Effects . . . . .	21
HISTORICAL REVIEW . . . . .	22
PURPOSES OF THE PRESENT INVESTIGATION . . . . .	35
(A) The Decarboxylation of 4-Methylsalicylic Acid in Quinoline . . . . .	35
(B) The Decarboxylation of 4-Methoxyanthranilic Acid in Aqueous Solutions . . . . .	41
EXPERIMENTAL . . . . .	48
Materials . . . . .	48
Quinoline . . . . .	48
Nitrobenzene . . . . .	48
4-Methylsalicylic Acid . . . . .	48
4-Methoxyanthranilic Acid . . . . .	48
Buffer Solutions . . . . .	48
Apparatus . . . . .	49
Apparatus Used in the Decarboxylations of 4-Methylsalicylic Acid . . . . .	49
Apparatus Used in the Decarboxylations of 4-Methoxyanthranilic Acid . . . . .	49
The High Vacuum System . . . . .	53

TABLE OF CONTENTS (cont'd)

	PAGE
Procedure . . . . .	55
Collection and Purification of CO <sub>2</sub> . . . . .	55
Measurement of the Amount of CO <sub>2</sub> . . . . .	58
RESULTS . . . . .	62
DISCUSSION . . . . .	67
BIBLIOGRAPHY . . . . .	68

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## INTRODUCTION

In order to predict the effects of isotopic substitution on reaction rates, one must first have a theory of chemical reactions. The most successful theory to date has been the theory of absolute reaction rates as put forward by Eyring (13), Polanyi (12) and others (15). This theory assumes that a chemical reaction can be represented by a three dimensional surface, the shape of which is determined by the reaction coordinate, and the potential energy of the reacting system. Such a surface is called a potential energy surface. It is assumed that there is but one potential energy surface along which a reaction takes place. On this surface, one part of coordinate space represents the reactants, and another, the products. Separating these two regions there is an energy barrier. In order for a chemical reaction to occur, the reactants must approach one another and pass over the energy barrier. The molecular species corresponding to the top of the energy barrier, for the energetically easiest path from reactants to products, is called the "activated complex". It is proposed that there is always a concentration of activated complex in equilibrium with the reactants, and that the rate of reaction is determined by the rate of decomposition of the complex.

When a mechanism is proposed for a particular reaction, we are, at present, usually satisfied if we have a general idea of the structure of the activated complex. One way in which information may be gained about the activated complex is from the studies of isotopic substitution. As most reactions involve only a small part of a given reactant molecule, we may learn the fate of a particular atom in this part of the molecule by conducting "tracer" studies; i.e. we can substitute an isotope  $b^*$  for a given atom  $b$  in the reactive part of the molecule, and then locate the isotope  $b^*$  in the reaction products. Such experiments



will lead to the conclusion that certain bonds are broken, made or unaffected. These results will enable us to postulate one, or more, possible activated complexes. These models can then be experimentally tested to see if they are correct.

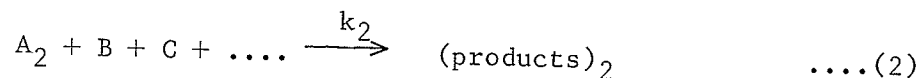
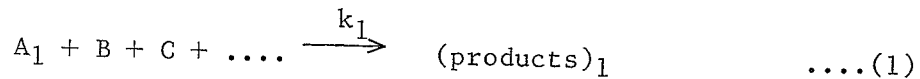
One way of testing a possible complex involves isotopic substitution within the reaction center, and the measurement of the relative rates of reaction of the two isotopic isomers. If the two rates are different, there is said to be a kinetic isotope effect.

Often, there is more than one possible activated complex. However, these different complexes frequently give rise to different predictions as to the existence of a kinetic isotope effect. Thus the determination of the kinetic isotope effect can be used as a powerful diagnostic tool.

In some cases, a measurable kinetic isotope effect can be observed when the labelled atom is not at the actual reaction site. This is referred to as a secondary isotope effect. The following discussion will be limited to primary kinetic isotope effects, i.e. those cases in which the labelled atom is at the actual reaction site.

THE THEORETICAL PREDICTION OF ISOTOPE EFFECTS

When an atom b of a molecule is replaced by its isotope b\*, a number of relatively small effects come into play, all of which must be taken into consideration in order to understand the over-all effect. Using the theory of absolute reaction rates, Bigeleisen (3) has arrived at an expression for predicting the kinetic isotope effect in the following type of reaction.



A<sub>1</sub> and A<sub>2</sub> are isotopic isomers.

k<sub>1</sub> and k<sub>2</sub> are the specific rate constants for the reactions expressed by equations (1) and (2), respectively.

B, C, etc. may or may not be present; if they are present, they may be other A molecules, or different species.

The subscripts (1) and (2) usually refer to the light and heavy isotopes, respectively.

For reactions involving the isotopes of carbon and heavier elements, Bigeleisen (3) proposes the following equation for the theoretical calculation of the kinetic isotope effect.

$$(s_2/s_1)(s_1^\ddagger/s_2^\ddagger)(k_1/k_2) = (K_1/K_2)(\nu_{L1}^\ddagger/\nu_{L2}^\ddagger) \left[ 1 + \sum_i^{3n-6} G(u_{i2}^\ddagger)\Delta u_i - \sum_i^{3n^\ddagger-7} G(u_{i2}^\ddagger)\Delta u_i^\ddagger \right] (1 + \Delta|u_L^\ddagger|^2/24) \quad \dots(3)$$

The various symbols and terms in equation (3) will now be defined and discussed.

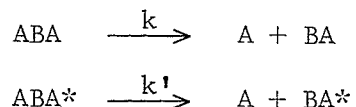
In any term, the superscript (‡) refers to a property of the activated complex, and the subscripts (1) and (2) refer to the light and heavy isotopes, respectively.

The ratio k<sub>1</sub>/k<sub>2</sub> gives the relative rate of reaction of the two isotopic isomers, A<sub>1</sub> and A<sub>2</sub>. This ratio is thus a measure of the kinetic

isotope effect in a particular reaction.

The classical symmetry number ( $s$ ) is the number of indistinguishable positions that a molecule (or activated complex) can take in space. In effect, the symmetry numbers convert the calculated ratio of rates of reaction to the ratio of rates per equivalent position in the reactant molecule.

For example, if ABA and ABA\* are isotopic isomers which decompose according to the following reactions,



then, in calculating  $k/k'$  we must account for the fact that even if there is no kinetic isotope effect due to the substitution of A\* for A, the value of  $k'$  will be one half that of  $k$ . This occurs because the probability of the rupture of the A-B bond in ABA is twice that in ABA\*. Thus, for the above reactions, assuming an activated complex of the form A---B-A, we will have  $s_1 = 2$ ,  $s_2 = 1$ ,  $s_1^\ddagger = 1$ , and  $s_2^\ddagger = 1$ . Therefore the left hand side of equation (3) would become  $k/2k'$ .

The transmission coefficient ( $K$ ) is the fraction of the activated complexes which decomposes in the direction corresponding to the completed reaction. Thus, the transmission coefficient accounts for the activated complexes which decompose to reactants rather than to products. In order to be able to calculate  $K$ , the potential energy surface for a reaction must be known, and even then a rigorous calculation is not necessarily possible. Because the potential energy surface is not generally known,  $K$  cannot be evaluated. However, some theoretical calculations (20) have shown that in cases of experimental interest above room temperature, the ratio of the transmission coefficients can be taken as unity. It should be noted that this assumption is one of the weakest

points in the theory. It would be most desirable to be able to calculate the values of the two transmission coefficients.

The frequency  $\nu_L^\ddagger$  corresponds to the stretching vibration along the coordinate of decomposition for the bond in the activated complex which is about to be broken. This frequency is an imaginary number. It has been shown (6) that the ratio  $\nu_{L1}^\ddagger/\nu_{L2}^\ddagger$  can be replaced by  $(m_2^*/m_1^*)^{1/2}$ , where  $m^*$  is the effective (or reduced) mass of the activated complex along the coordinate of decomposition. In the earlier literature,  $m^*$  was assumed to be the reduced mass of the two atoms which form the bond about to be broken. Now, however,  $m^*$  is usually taken to be the reduced mass of the two molecular fragments created by the cleavage of the bond(+). If  $M'$  and  $M''$  are the two separating molecular fragments, then

$$\frac{\nu_{L1}^\ddagger}{\nu_{L2}^\ddagger} = \left(\frac{m_2^*}{m_1^*}\right)^{1/2} = \left(\frac{1/M_1' + 1/M_1''}{1/M_2' + 1/M_2''}\right)^{1/2} \quad \dots(4)$$

Thus, the term  $\nu_{L1}^\ddagger/\nu_{L2}^\ddagger$  is dependent only on the reduced masses of the sets of molecular fragments formed by the two isotopic isomers. For this reason, this term is called the reduced mass factor, or the temperature independent factor.

In the last term of equation (3),

$$\Delta |u_L^\ddagger|^2 = |u_{L1}^\ddagger|^2 - |u_{L2}^\ddagger|^2$$

and 
$$u_L^\ddagger = h\nu_L^\ddagger/kT$$

where  $h$  is Planck's constant,  $k$  is the Boltzmann constant and  $T$  is the absolute temperature of the reaction.

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(+) In fact, this value is correct "only if the centers of mass of the two fragments lie on the extensions of the line corresponding to the broken bond". Otherwise the mass fragment value is only an approximation (40).

The last term of equation (3) gives the correction for the effect of quantum mechanical "tunneling" on the rate of reaction. Quantum mechanically there is a possibility that reactants can pass into products without passing over the usual energy barrier. This is accomplished by "tunneling", or leakage through the energy barrier. The net effect is a slight increase in the rate of reaction. A calculation of the tunnel effect would require a thorough knowledge of the potential energy surface for the reaction. As this is generally unknown, the effect of tunneling on the rate of a reaction cannot be calculated. However, from general experience it is found that the tunnel correction is negligible for the isotopes of carbon and the heavier elements. It is therefore assumed that the correction is negligible in the consideration of isotope effects.

Thus, omitting the symmetry numbers, and neglecting the ratio of the transmission coefficients and the tunnel correction, equation (3) reduces to equation (5).

$$(k_1/k_2) = (\nu_{L1}^\ddagger/\nu_{L2}^\ddagger) \left[ 1 + \sum_i^{3n-6} G(u_{i2})_{\Delta u_i} - \sum_i^{3n^\ddagger-7} G(u_{i2}^\ddagger)_{\Delta u_i^\ddagger} \right] \dots(5)$$

The reduced mass (or temperature independent) term and the other remaining term (which will be referred to as the zero-point energy term) are the two factors which will determine whether or not there will be a kinetic isotope effect. While both terms are necessary for a quantitative theoretical prediction, the zero-point energy term alone can be employed in a very useful qualitative discussion of the prediction of kinetic isotope effects.

In the theory of the electronic structure of the hydrogen atom, the nuclear mass (M) enters the calculations only in the form of the reduced mass of the system ( $\mu$ ). If m is the mass of the electron, then  $1/\mu = 1/m + 1/M$ . As the minimum value of M is about 1850m, a change in

M from unity to infinity will not noticeably affect the value of  $\mu$ . Thus, a change in the nuclear mass of the hydrogen atom will have a negligible effect on the electronic structure of the atom. Extending this idea to the heavier elements, the electronic structures of two isotopes should be the same to a very high degree of approximation.

Consider now the replacement of an atom in a complex molecule by one of its isotopes. The interatomic forces will not be affected by the change in nuclear mass, as these forces are determined by the electronic structure. Thus, isotopic isomers should have the same interatomic distances, vibrational force constants and also the same potential energy surface for any reaction, to a very high degree of approximation.

When the translational motion of an atom is considered, it is the total mass,  $m + M$ , and therefore  $M$  which is of importance. The translational energy of an atom is then governed by the nuclear mass. Isotopic substitution should, therefore, affect the vibrational frequencies of the bonds to the labelled atom, as these vibrations involve acceleration of the nuclear mass. In fact, it is found that the substitution of the heavier isotope reduces the frequency of vibration associated with a particular bond to the labelled atom.

In the zero-point energy term,  $n$  is the number of atoms in a particular species, and

$$G(u_i) = 1/2 - 1/u_i + 1/(e^{u_i} - 1)$$

also,  $\Delta u_i = u_{i1} - u_{i2}$

where  $u_i = h\nu_i/kT$

and  $\nu_i$  is the vibrational frequency associated with the  $i^{\text{th}}$  normal mode of vibration. In the reactant, there are  $3n-6$  normal modes of vibration,

while there are only  $3n^{\ddagger}-7$  normal modes in the activated complex. The missing mode of vibration in the activated complex corresponds to  $\nu_L^{\ddagger}$ , and has already been taken into consideration in the reduced mass factor.

When all the oscillators in a molecule are in their lowest energy states, the total vibrational energy of the molecule is not zero, but a minimum value ( $V_0$ ), called the zero-point energy. If the minimum in the potential energy curve for the normal molecule is taken as the energy origin, then it is easily shown (25) that

$$V_0 = \sum_i^{3n-6} \frac{1}{2} h \nu_i$$

As previously stated, the substitution of a heavier isotope in a molecule will result in a decrease in the vibrational frequencies of the bonds to the labelled atom. Assuming that the vibrational frequencies of the bonds to other atoms are not appreciably affected, one would expect the molecule with the heavier isotope to have a lower zero-point energy than the one with the light isotope, i.e. we would expect

$$\sum_i^{3n-6} \frac{1}{2} h \nu_{i1} > \sum_i^{3n-6} \frac{1}{2} h \nu_{i2}$$

or,  $V_{01} > V_{02}$

If the top of the energy barrier is taken as the energy origin for the activated complex, a similar argument shows that the zero-point energy ( $V_0^{\ddagger}$ ) is given by

$$V_0^{\ddagger} = \sum_i^{3n^{\ddagger}-7} \frac{1}{2} h \nu_i^{\ddagger}$$

It follows, therefore, that

$$\sum_i^{3n^{\ddagger}-7} \frac{1}{2} h \nu_{i1}^{\ddagger} > \sum_i^{3n^{\ddagger}-7} \frac{1}{2} h \nu_{i2}^{\ddagger}$$

or,  $V_{01}^{\ddagger} > V_{02}^{\ddagger}$

This situation is shown graphically in Figure 1.

$$\text{Let } \Delta V = V_{o1} - V_{o2}$$

$$\text{and } \Delta V^\ddagger = V_{o1}^\ddagger - V_{o2}^\ddagger$$

The summation  $\sum_i^{3n-6} G(u_{i2})\Delta u_i$  is related to  $\Delta V$ , the difference

between the zero-point energies of the isotopic reactants. The summation

$\sum_i^{3n^\ddagger-7} G(u_{i2}^\ddagger)\Delta u_i^\ddagger$  is related to  $\Delta V^\ddagger$ , the difference between the zero-point

energies of the isotopic activated complexes. From equation (5), it

is seen that the ratio  $k_1/k_2$  is proportional to

$$\sum_i^{3n-6} G(u_{i2})\Delta u_i - \sum_i^{3n^\ddagger-7} G(u_{i2}^\ddagger)\Delta u_i^\ddagger$$

Thus the kinetic isotope effect will be proportional to the quantity  $(\Delta V - \Delta V^\ddagger)$ . It is interesting to note that the kinetic isotope effect is not dependent upon the activation energy of the reaction (i.e. the difference in energy level between the reactants and the activated complexes).

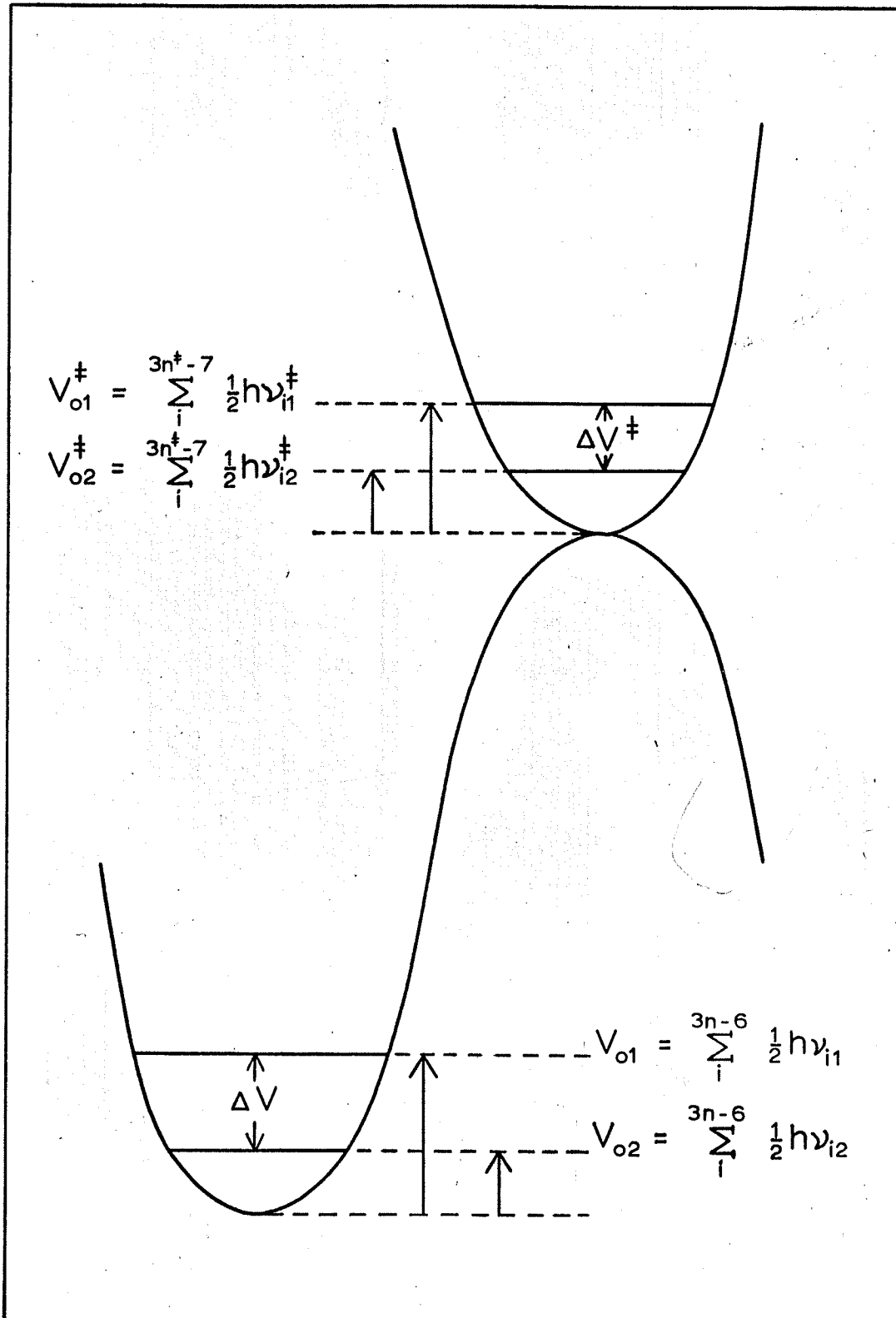
The problem of predicting a kinetic isotope effect has now been reduced to one of evaluating the vibrational frequencies of the normal modes of oscillation of the reactants and the activated complexes. While these frequencies in the reactants can be evaluated from infra red spectra, generally they have been found only for very simple molecules. In the last few years the use of computers has enabled some theoreticians to obtain the vibrational frequencies of some rather complex molecules, and some exact calculations of  $k_1/k_2$  for various models of the activated complex have been carried out (17). In the case of activated complexes, the vibrational frequencies would have to be estimated on the basis of known frequencies for the stable compounds and would, of course, depend



FIGURE 1: The potential energy profile showing the relation between the zero-point energies of the isotopic reactants and of the isotopic activated complexes.

FIGURE 1

POTENTIAL ENERGY



REACTION COORDINATE

upon the model chosen for the complex. However, in more complex molecules, the reaction center comprises only a small portion of the molecule, and, if all the vibrational frequencies cannot be evaluated, it is usually assumed that the vibrational frequencies of the bonds removed from the reaction site are unchanged in going from the initial state to the activated state, i.e.  $\nu_j = \nu_j^\ddagger$  for those bonds removed from the reaction site. This results in the cancellation of such pairs of terms as  $G(u_{j2})\Delta u_j$  and  $G(u_{j2}^\ddagger)\Delta u_j^\ddagger$ . If, however, within the reaction center there is one bond to the labelled atom that is considerably weakened, or completely broken in the activated complex, the pair of terms corresponding to this vibrational mode will not vanish. For the limiting case in which the bond is completely broken in the activated complex,  $\nu_i^\ddagger = \nu_L^\ddagger$ , and the term for the activated state vanishes. Thus, assuming all other frequencies unchanged, the maximum zero-point energy contribution to the kinetic isotope effect would be  $1 + G(u_{i2})\Delta u_i$ .

If the bond to the labelled atom is only weakened, then the contribution to the kinetic isotope effect is less by the amount  $G(u_{i2}^\ddagger)\Delta u_i^\ddagger$ . The zero-point energy contribution would be, therefore,

$$1 + G(u_{i2})\Delta u_i - G(u_{i2}^\ddagger)\Delta u_i^\ddagger$$

As  $\Delta u$  is always positive, and  $G(u)$  is also always positive and increases with  $u$  (2), if the bond to the labelled atom is weakened or broken in the activated state,  $k_1/k_2 > 1$ , and the rate of reaction will be greater for the lighter isotope.

If a bond to the labelled atom had actually strengthened in the activated complex, then  $G(u_{i2})\Delta u_i < G(u_{i2}^\ddagger)\Delta u_i^\ddagger$  and  $k_1/k_2 < 1$ . This is referred to as a reverse isotope effect. It is much less common than the previous case.

In general, then, if a bond to a labelled atom is appreciably changed (weakened or strengthened) in the activated complex, an isotope effect will occur.

At this point it should be noted that the zero-point energy contribution is the most important term for those cases involving the isotopes of hydrogen. For the isotopes of carbon and heavier elements, the reduced mass factor must also be taken into consideration.

### Temperature Dependence of the Isotope Effect

The magnitude of  $k_1/k_2$  will be determined by two factors, i.e. the reduced mass factor and the zero-point energy factor. As the former is temperature independent its contribution will be the same at all temperatures. Therefore any effect of temperature on the value of  $k_1/k_2$  can be attributed to the zero-point energy term, unless the transmission coefficients and/or the tunnel correction come into play.

The zero-point energy term involves the energy difference  $\Delta V - \Delta V^\ddagger$ . As the temperature is decreased, this energy difference will become more and more important, and in the limit as the temperature approaches the absolute zero, the ratio  $k_1/k_2$  will approach infinity for the usual case in which  $k_1/k_2 > 1$ . For the less common case of the reverse isotope effect,  $k_1/k_2$  will approach zero.

We have defined  $\Delta u_i$  as follows;

$$\Delta u_i = u_{i1} - u_{i2} = h(\nu_{i1} - \nu_{i2})/kT$$

In the high temperature limit, as the temperature approaches infinity, the  $\Delta u$  terms in the zero-point energy term approach zero. Therefore, both  $G(u)\Delta u$  terms vanish and the zero-point energy term reduces to unity. Thus the high temperature limit is

$$k_1/k_2 = \nu_{L1}^\ddagger / \nu_{L2}^\ddagger$$

for both the common and reverse isotope effects.

The temperature variation of  $k_1/k_2$  is usually quite noticeable over temperature ranges of about 60°C. Yankwich and Belford (46) have studied the temperature dependence of the intermolecular kinetic isotope effect in the decarboxylation of malonic acid in quinoline solutions. They used acid labelled with carbon-13 in the -COOH group, and compared the rates of decarboxylation of malonic-1-C<sup>12</sup> and malonic-1-C<sup>13</sup> acids. The value of  $k_{12}/k_{13}$  varied from 1.0567 at 34°C to 1.0379 at 118°C.

EXPERIMENTAL EVALUATION OF THE KINETIC ISOTOPE EFFECT (+)

The magnitude of the ratio  $k/k^*$  may be experimentally evaluated by two methods.

I - The Method of Absolute Rates

In this method, the rate of reaction for each of the isotopic species is measured directly, and the ratio  $k/k^*$  is calculated. Except for a few special cases, the accuracy of the measurements is not better than a few per cent. However, for isotopes of the elements heavier than hydrogen, the ratio of rate constants differs from unity by only a few per cent. Thus an error of a few per cent in each of  $k$  and  $k^*$  would mean that a small isotope effect might not be detected. For this reason, this method is limited to the isotopes of hydrogen, where  $k$  is usually greater than  $k^*$  by several orders of magnitude.

II - The Method of Competitive Rates

There are two types of competitive methods which may be used; the chemical competitive method and the isotopic competitive method. For several reasons (6) the former method is limited to the isotopes of hydrogen, and will not be discussed here.

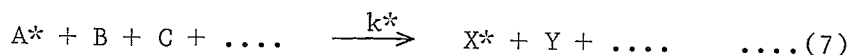
In the isotopic competitive method, the isotopic reactants,  $A$  and  $A^*$ , are present in a mixture and either undergo unimolecular decomposition, or react with other chemical species,  $B$ ,  $C$ , etc., where these latter species may be other  $A$  molecules. This method is especially simple when applied to systems in which  $A^*$  is present to the extent of 1 % or less. As the natural abundances of  $C^{13}$ ,  $N^{15}$  and  $O^{18}$  are of the order of 1 % or less, this method can conveniently

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(+) In the previous discussion,  $k_1$  and  $k_2$  represented the specific rate constants for the reactions of the species containing the light and heavy isotopes, respectively. In the following discussion, as a matter of convenience,  $k_1$  and  $k_2$  are replaced by  $k$  and  $k^*$ , respectively.

be used in those cases requiring carbon, nitrogen or oxygen labelling in A\*, as in these cases natural samples of a reactant can be used to achieve the mixture of isotopic reactants. The necessity for isotopic enrichment of the reactant mixture is thus avoided. Also, systems employing A\* at tracer concentrations (much less than 1 %) can be treated by this method. This method is not, however, limited to those cases for which  $A^*/A \leq .01$ .

Consider the case in which the rate of reaction is of first order with respect to the concentration of A or A\*, and of some arbitrary order b with respect to the concentration of B, c with respect to the concentration of C, etc. . The reactions can be written as follows, where X and X\* are the isotopic products.



If  $k \neq k^*$ , the difference in the reaction rates will result in a continual change in the isotopic content of both the reactant and the product. The value of  $k/k^*$  can be evaluated by measuring the fractional amounts of conversion of A and A\* and the isotopic content of either the remaining reactant or the product.

(1) Analysis of the isotopic content of the remaining reactant after a known amount of reaction

If  $A_0, A_0^*, B_0, C_0$ , etc. represent the initial amounts of the reactants, and A, A\*, B, C, etc. represent the amounts of the reactants remaining after a time t, and extent of reaction f, then the rates of reactions (6) and (7) at time t can be expressed as follows.

$$- dA/dt = k(A)(B)^b(C)^c \text{-----}$$

$$- dA^*/dt = k^*(A^*)(B)^b(C)^c \text{-----}$$

It follows from these two equations that.....

$$\frac{dA}{dA^*} = \frac{k(A)}{k^*(A^*)}$$

and therefore  $d \ln(A) = (k/k^*) d \ln(A^*)$

Integrating this equation between the limits  $A_0$  and  $A$  for the left hand side, and  $A_0^*$  and  $A^*$  for the right hand side, we get, after converting to logarithms to base 10,

$$\frac{k}{k^*} = \frac{\log(A/A_0)}{\log(A^*/A_0^*)} \quad \dots(8)$$

The measured fractional conversion,  $f$ , is given by

$$(1 - f) = \frac{(A + A^*)}{(A_0 + A_0^*)}$$

By setting  $R_0 = A_0^*/A_0$  (i.e. the ratio of labelled to unlabelled molecules in the initial reactant) and  $R_{af} = A^*/A$  (i.e. the ratio of labelled to unlabelled molecules in the reactant remaining after an amount of reaction,  $f$ ) expressions (9) and (10) can be derived for  $A/A_0$  and  $A^*/A_0^*$ , respectively.

$$(1 - f) = \frac{A(1 + A^*/A)}{A_0(1 + A_0^*/A_0)} = \frac{A(1 + R_{af})}{A_0(1 + R_0)}$$

$$\frac{A}{A_0} = \frac{(1 - f)(1 + R_0)}{(1 + R_{af})} \quad \dots(9)$$

$$(1 - f) = \frac{A^*(1 + A/A^*)}{A_0^*(1 + A_0/A_0^*)} = \frac{A^*(1 + 1/R_{af})}{A_0^*(1 + 1/R_0)}$$

$$\frac{A^*}{A_0^*} = \frac{(1 - f)(1 + R_0)R_{af}}{(1 + R_{af})R_0} \quad \dots(10)$$

Substituting equations (9) and (10) into equation (8) gives

$$\frac{k}{k^*} = \frac{\log \left[ \frac{(1 - f)(1 + R_0)}{(1 + R_{af})} \right]}{\log \left[ \frac{(1 - f)(1 + R_0)R_{af}}{(1 + R_{af})R_0} \right]} \quad \dots(11)$$

If we let  $\theta = (k/k^* - 1)$ , then the deviation of  $\theta$  from zero will be a measure of the kinetic isotope effect. A positive value



of  $\theta$  will correspond to the normal isotope effect ( $k > k^*$ ); a negative value of  $\theta$ , to the reverse isotope effect. For elements heavier than hydrogen, and showing a normal isotope effect, the value of  $\theta$  is usually between zero and + 0.1 .

Thus, in this method, the problem of evaluating the magnitude of the kinetic isotope effect has been reduced to one of measuring the extent of reaction,  $f$ , and the two ratios,  $R_0$  and  $R_{af}$  . The values of the isotopic ratios can be determined with a precision of 0.1 % or better by mass spectrometric analysis. If radioactive isotope is used, a precision of about 0.2 % can be obtained by measurements of radioactivity. The error in the value of  $f$  is usually about 0.5 % . If a precision of a few per cent in  $\theta$  is required, then it can be shown (6) that the extent of reaction must be greater than 0.5 . For  $f > 0.5$  , the precision in  $\theta$  increases with increasing extent of reaction, until  $f > 0.9$  , at which point the error in the determination of  $f$  increases, and the precision in  $\theta$  again decreases.

(2) Analysis of the isotopic content of the product after a known amount of reaction

If  $X$  and  $X^*$  are the amounts of isotopic products produced up to time  $t$  and extent of reaction  $f$ , then, in the previous notation,  $A = A_0 - X$  and  $A^* = A_0^* - X^*$  . At any time  $t$ , the rates of reactions (6) and (7) can now be written as follows.

$$\begin{aligned} dX/dt &= k(A_0 - X)(B)^b(C)^c \text{-----} \\ dX^*/dt &= k^*(A_0^* - X^*)(B)^b(C)^c \text{-----} \end{aligned}$$

It follows from these two equations that

$$\frac{dX}{dX^*} = \frac{k(A_0 - X)}{k^*(A_0^* - X^*)}$$

and therefore  $d \ln(A_0 - X) = (k/k^*) d \ln(A_0^* - X^*)$

Integrating this equation between the limits zero and  $X$  for

the left hand side, and zero and  $X^*$  for the right hand side, we get, after converting to logarithms to base 10,

$$\frac{k}{k^*} = \frac{\log(1 - X/A_0)}{\log(1 - X^*/A_0^*)} \quad \dots(12)$$

The measured fractional conversion,  $f$ , is given by

$$f = \frac{(X + X^*)}{(A_0 + A_0^*)}$$

By setting  $R_0 = A_0^*/A_0$  (as before) and  $R_{xf} = X^*/X$  (i.e. the ratio of labelled to unlabelled molecules in the product collected after a measured extent of reaction,  $f$ ) expressions (13) and (14) can be derived for  $X/A_0$  and  $X^*/A_0^*$ , respectively.

$$f = \frac{X(1 + X^*/X)}{A_0(1 + A_0^*/A_0)} = \frac{X(1 + R_{xf})}{A_0(1 + R_0)}$$

$$\frac{X}{A_0} = \frac{f(1 + R_0)}{(1 + R_{xf})} \quad \dots(13)$$

$$f = \frac{X^*(1 + X/X^*)}{A_0^*(1 + A_0/A_0^*)} = \frac{X^*(1 + 1/R_{xf})}{A_0^*(1 + 1/R_0)}$$

$$\frac{X^*}{A_0^*} = \frac{f(1 + R_0)R_{xf}}{(1 + R_{xf})R_0} \quad \dots(14)$$

Substituting equations (13) and (14) into equation (12) gives

$$\frac{k}{k^*} = \frac{\log \left[ \frac{1 - f(1 + R_0)}{(1 + R_{xf})} \right]}{\log \left[ \frac{1 - f(1 + R_0)R_{xf}}{(1 + R_{xf})R_0} \right]} \quad \dots(15)$$

Thus in this method, the problem of evaluating the magnitude of the kinetic isotope effect has been reduced to one of measuring the extent of reaction,  $f$ , and the two ratios,  $R_0$  and  $R_{xf}$ .

Bigeleisen and Allen (5) have reported a study of the errors involved in evaluating the quantity  $(k^*/k - 1)$  by this method. They calculated the per cent error in this quantity as a function of the extent of reaction, assuming

$$(i) \quad (k^*/k - 1) = -.1 ,$$