placed over the room ever since. In fact, the guard is there not to keep the lecturer in but to keep intruders out. Most if not all lecturers value this quiet time to have a last run over their material and get their minds into the right mood. In particular, if members of the press realized the state of mind of one about to give a lecture, which is much like that of an athlete about to run a race, I am sure they would refrain from tackling him just before the lecture starts, to get, for instance, his views on the atomic bomb. After the lecture he should be at their service and oblige them in any way he can, because he is free to switch his mind off his lecture.

I have emphasized the difference between the spoken and written word. To prepare a talk, and to write an account of it, are two separate tasks and the latter may be much the heavier. I think, therefore, that, when a man is invited to speak, it should be made clear at the same time whether he is to write as well. I know to my cost what a difficult position one is placed in if one discovers, after agreeing to talk, that the heavy labor of writing up the material is also expected. I am sure the task is often imposed unwittingly, under the idea that if a man is talking he will have written what he wants to say, but you will have realized from my remarks about reading that I feel this ought not to be assumed. The most embarrassing thing is to be told that a tape recording will be made, and asked if one would please correct it. It is embarrassing to see a verbatim report with all the remarks recorded literally, and it is generally far less trouble to write it from the beginning than to try to patch the record.

In conclusion, I hope you will realize that the last thing I want is to seem to lay down the law about lecturing. I have spoken so feelingly about the pitfalls because I have so often fallen into them myself. One has to be constantly watchful if they are to be avoided, and even then one does not escape. It is most dangerous to be complacent about a lecture, to think that it will be all right because one knows the stuff and has given a similar talk elsewhere. Every lecture must be approached as if it were a new problem. No pains are too great in the attempt to make a talk a success, and I believe that, given the right treatment, any subject can be made fascinating to any audience.

Kinetic Isotope Effects and Organic Reaction Mechanisms

A fruitful application of quantum theory to organic chemistry has now been strengthened.

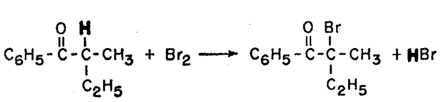
M. J. Goldstein

The replacement of any atom in a molecule by one of its isotopes is surely the smallest and most trivial of all the possible structural perturbations in chemistry. Yet the addition of one judiciously placed neutron can often depress the rate of chemical reaction tenfold. This kinetic isotope effect has long been better understood than almost any other rate phenomenon. It has provided the organic chemist with a unique and often indispensable tool with which to pry open the secrets of reaction mechanisms.

In part because the technique proved to be so very useful, a curious development has ensued. The theoretical foundations were slowly refashioned, through the achievements based on them, into simpler guides, which soon became working rules. More recently, the limitations of such rules have become apparent, and the need for their revision has become increasingly obvious. Here I am concerned with the development of this problem and of its resolution, and also with the stimulus which both provided toward a newer, perhaps more fruitful, application of a phenomenon that was well understood long ago.

Elucidation of Reaction Mechanisms

To illustrate how a technique can be distorted by its application, I have chosen to describe the reactions of molecular bromine with four different organic molecules. The first of these reactions, that of molecular bromine with the ketone, **1**



$$C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{H}{|}}{C}}-CH_3 + Br_2 \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{Br}{|}}{C}}-CH_3 + HBr$$

1

will serve to demonstrate the kinds of questions that were asked, and often quite adequately answered, without the use of kinetic isotope effects at all (*1*).

This reaction is strongly catalyzed, for example by acetate ions, and so it must in fact represent the sum of several simpler reactions or steps. In the first of these, acetate is consumed as it reacts with **1**. In some later step acetate will have to be regenerated in order that it cancel out when all the steps are added together. Every molecule encounters these steps in a fixed sequence. Each step is limited by the availability of some precursor which it alone must consume. The first step is here also the rate-limiting one, the bottleneck that controls the velocity of those that follow. These things are known from kinetic experiments. If the concentration of either **1** or of acetate is changed, the reaction rate changes proportionately. Doubling the concentration of either doubles the rate; doubling the concentration of both quadruples the rate. But a change in bromine concentration has no effect whatever! Since it is surely a reactant, bromine must be kinetically impotent only

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because it is waiting for a transient intermediate, one that has been produced in a prior, more difficult, step.

In order to characterize this intermediate, we need a different kind of experiment. The bromine is omitted entirely and the solvent H_2O is replaced by D_2O. The deuterium atoms (here used only as labels) will then soon begin to accumulate in **1**, but only at the position where the bromine atom would have gone, and at precisely the same rate. This tells us several things: the same intermediate must be responsible for both kinds of observations—deuterium exchange and bromination; the intermediate must lack the unique reactive **H** (see *2*) of **1**; and the intermediate still retains the electron pair which had held this hydrogen in place. For just as acetate is a base, at least in the sense that it can pluck off **H** only as a proton while leaving the bonding pair of electrons behind, so too, under these conditions, water is an acid that can donate **H** (or **D**) as a proton (or deuteron) to just such an electron pair.

To learn still more about this intermediate, we turn now to a rather different kind of labeling experiment. This one demands of us the ability to recognize that the drawing of **1** given above is, in fact, an ambiguously flat projection of either of two real molecules, **1a** or **1b** of Fig. 1. These are related, one to the other, as the object and the image of a mirror reflection are. With some effort, either can be isolated from a mixture containing both. Now if only one kind of molecule, say **1a**, is treated with acetate in water, it is soon transformed into a 50–50 mixture of the two. And, once again, this occurs at the same rate at which bromine would have been introduced had it been present. It must then follow that our reactive intermediate contains the unique plane of symmetry through which molecules **1a** or **1b** must be interconverted. This, too, is shown in Fig. 1.

Let us now elaborate from this example the two important goals of a classical mechanistic study: (i) the discovery of the rate-limiting step (and, from this, of all other steps) and (ii) the formulation of a detailed structural description of the reactive intermediates in every such step. Each goal requires its own technique. The first requires reaction kinetics; the second, structural labeling, as by the use of isotopes or of symmetry properties.

Use of the Kinetic Isotope Effect

It is always easier to change a technique than it is to change the ends toward which this technique is directed. And so it was that, when the kinetic isotope effect was first introduced, it was regarded as merely a substitute or a supplement for the older methods, the application of which too often could be frustrated by experimental perversity.

This use began in 1949 (*3*), fully 17 years after the kinetic isotope effect had been discovered (*4*). By this time, the originally formulated rule (*5*) that "heavier isotopes are slightly more inert" than lighter ones had been sharpened. Theory and experiment convinced each other that it was both adequate and useful to assume that kinetic isotope effects must possess certain intrinsic magnitudes (variously described as a "normal," "maximum," or "theoretical" isotope effect). If, as was believed, it were dependent only on the ratio of isotopic masses and on the temperature, this effect would amount to a sixfold to eightfold retardation of the rate of reaction at room temperature if hydrogen were replaced by deuterium. At higher temperatures this factor should be lower (*6*).

I examine below, more critically, both this assumption and the quantitative approach that it encouraged. More important than either, however, was this added condition: the full magnitude of any such intrinsic value should be observable only if a covalent bond to the isotopically substituted atom were broken in the rate-limiting step. To the degree that such a step might be less than rate-limiting, the observed value would be less than the intrinsic one. In the extreme, it would often be undetectable (*7*).

The substitution of deuterium for the **H** of ethanol in Fig. 2 illustrates a typical application of these rules. The rate of this reaction, a brominative oxidation, varies directly with bromine concentration. For this and other reasons, one had been left to choose between two mechanistic hypotheses which differ principally with respect to their first, rate-limiting steps. In the first of these mechanisms, the rate-limiting

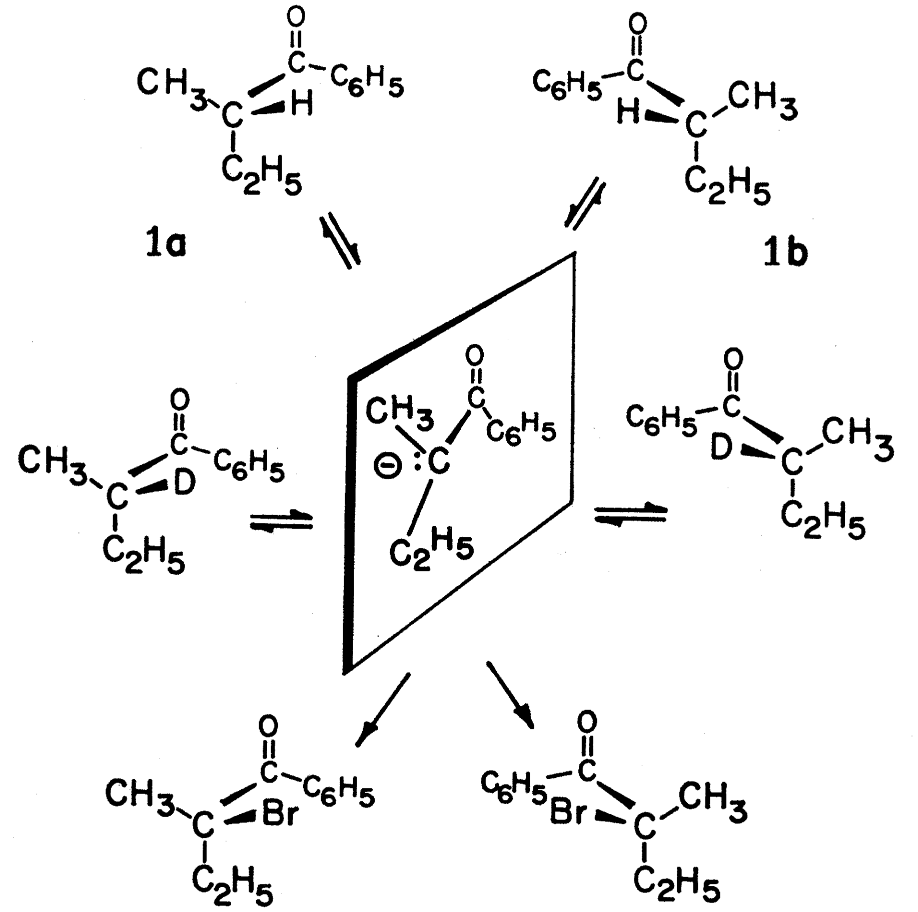


Fig. 1. The common mechanism of acetate-catalyzed bromination, deuterium exchange, and racemization.

$CH_3\mathbf{CH_2}OH + 2Br_2 + H_2O \rightarrow CH_3CO_2H + 4HBr$

2

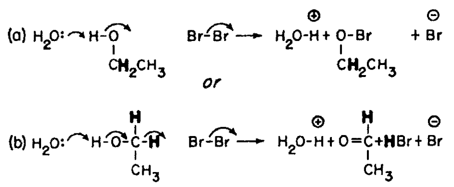


Fig. 2. The brominative oxidation of ethanol to acetic acid.

step would be the transformation of **2** to CH_3CH_2OBr (Fig. 2, reaction a). (The curved arrows are a convenient formalism, a "bookkeeping" device for representing pairs of electrons. They should, of course, never be literally interpreted as representing a realistic path for the motion of electrons.) In subsequent, more rapid steps (not shown in Fig. 2), CH_3CH_2OBr would be converted to CH_3CHO and this, in turn, would be oxidized still further to CH_3CO_2H by bromine. Since the cleavage of C–**H** bonds would thus occur only after the rate-limiting step, deuterium substitution at this position should have no effect.

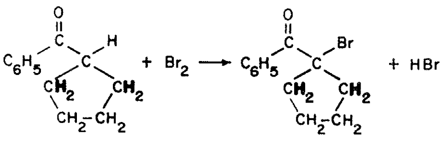
In a reasonable alternative mechanism, the rate-limiting step would be a direct oxidation of **2** to CH_3CHO (Fig. 2, reaction b). As in the first mechanism, CH_3CHO would then be further oxidized to CH_3CO_2H. Unlike the first mechanism, however, this one would permit detection of a kinetic isotope effect. The observation (*8*) that $k_H/k_D = 4.3$ at 25°C thus sufficed to exclude the first hypothesis.

Kinetic effects provided by isotopes of elements other than hydrogen are considerably smaller and much more difficult to measure, and so they have been measured less often. Nonetheless, their range of application is surely greater. A particularly elegant illustration of their use is provided by the brominative decarboxylation reaction summarized in Fig. 3.

It had been apparent from other evidence that the decarboxylation of **4** (Fig. 3, reaction c) would somehow have to be included in the reaction mechanism. It was less clear how this intermediate might be produced. It might result from the attack either of molecular bromine, as in reaction a, or of the much more reactive brominating agent H_2OBr^+, as in reaction b. (Such an ion, which need never be present in very high concentration, can easily be derived from a prior reaction of bromine with water.) It was not known which of the three steps might be the rate-limiting one.

When C^{13} was substituted for C^{12} at **C**, no kinetic isotope effect was detected ($k_{12}/k_{13} = 1.002 \pm 0.003$ at 20°C). But when a large excess of HBr was added beforehand, the isotope effect rose to a "normal" value (1.047 ± 0.001) (*9*). This value would appear to implicate reaction c. But, then, how could the HBr have transformed this, an otherwise facile step, into the most difficult of all? It could have done this only if it depressed the available concentration of **4**. This it could do if both **4** and HBr were products of a prior, reversible reaction. Clearly, therefore, reaction a, not b, must precede c, and so, presumably, reaction a should also be chosen as the rate-limiting step in the absence of added HBr.

Perhaps the first hint that something might be awry was provided by the repeated detection of kinetic isotope effects where none were expected. For example, the acetate-catalyzed bromination of the ketone, **5**



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(like that of **1**, which it closely resembles) is significantly retarded if we replace the single reacting hydrogen atom by deuterium; k_H/k_D is here 6.17 at 27°C (*10*). Such an isotope effect, which we have come to expect, has been classified as "primary." The reaction is also retarded, though considerably less so, when the four adjacent nonreacting **H** hydrogens are replaced by deuterium; under otherwise identical conditions, k_H/k_D is then 1.24.

Many of these latter "secondary" hydrogen isotope effects have now been measured (*11*). Often they are greater than this one, but, often too, enough smaller so that the deuterated compound can become the more reactive. This suggests a pair of dilemmas: if a secondary isotope is unusually large or a primary one unusually small, the two may be confused; if the secondary effect is less than 1, it may cancel out a primary one. Fortunately some very recent experiments have taught us how to factor out a primary effect (*12, 13*), but these do not concern us here.

Much more important has been the discovery that the intrinsic magnitude of a primary hydrogen-isotope effect can often depend upon a great deal more than just temperature. Whenever the reacting hydrogen of a ketone, such as that of either **1** or **5**, is removed by a base, it is always the more reactive base that produces the larger isotope effect. In other reactions, however, the more reactive reagent produces the smaller effect. In at least one case, both patterns have been observed; k_H/k_D increases with an increase in reagent reactivity up to a maximum; further increase in reactivity then causes it to diminish (*13, 14*). Clearly the magnitude of the kinetic isotope effect must contain more information than we had anticipated. This will, however, be best appreciated if we first examine some of the more fundamental origins of all isotope effects.

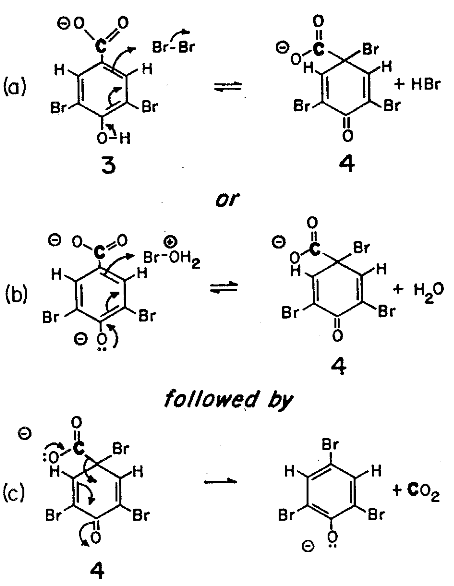


Fig. 3. The bromodecarboxylation of 3,5-dibromo-4-hydroxybenzoic acid.

Origins

We know from our experience that the mass of any object can be detected only if it moves. This is as true for the mass of an atomic nucleus, oscillating as it does within its molecular framework, as it is for our own mass as we compress the spring of a bathroom scale. But the nucleus, because its mass is so much smaller than ours, is much more sensitive to the restrictions of quantum theory. In particular, its oscillations can be allotted only certain discrete values of average kinetic energy. And these can never be removed, not even at the temperature of absolute zero.

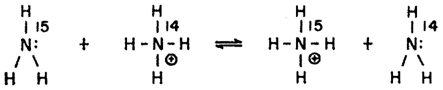
Because this irrevocable increment of internal energy is a quantum phenomenon, its magnitude must surely

Table 1. Vibrational frequencies (waves per centimeter) of ammonia and the ammonium ion (*15*). Numerals in parentheses denote the number of independent modes which possess the same frequency.

Frequency designation	$N^{14}H_3$	$N^{15}H_3$	$N^{14}H_4^+$	$N^{15}H_4^+$
ν_1	3337	3334	3040	3040
ν_2	950	945	1725(2)	1725(2)
ν_3	3414(2)	3404(2)	3142(3)	3130(3)
ν_4	1628(2)	1625(2)	1411(3)	1406(3)

increase as the nuclear mass decreases. It increases, also, as the restraints which limit such motion increase. These restraints, conventionally measured as restoring force constants, have been set by the attractions and the repulsions of negative electrons and positive nuclei. But, most important, they depend not at all upon atomic mass. As a result, it is *always* true that molecules which contain the heavier of two isotopes require less of this "zero-point" energy. And this advantage increases as the restraints about the isotopically substituted atom increase.

Let us now apply these principles, in a qualitative manner, to the reversible transfer of a proton between the two molecules $N^{14}H_3$ and $N^{15}H_3$.



$$\mathrm{H_2\overset{H}{N}{}^{15}\!:} + \mathrm{H{-}\overset{H}{\underset{H}{N}}{}^{14}_{\oplus}{-}H} \rightleftharpoons \mathrm{H{-}\overset{H}{\underset{H}{N}}{}^{15}_{\oplus}{-}H} + \mathrm{H_2\overset{H}{N}{}^{14}\!:}$$

We need concern ourselves only with the nitrogen atoms and with the N–H covalent bonds which provide the principal restraint to their internal motion. Since none of the bonds in NH_4^+ differs appreciably from those in NH_3, it is clear that, because of their greater number, the nitrogen should be held more firmly. As a consequence, the "zero-point" energy content of $N^{15}H_4^+$ is less than that of $N^{14}H_4^+$ by an amount greater than the amount by which the "zero-point" energy content of $N^{15}H_3$ is less than that of $N^{14}H_3$. In sum, less energy is required to supply the species on the right of the reaction symbol than to supply those on the left. With energy always in limited supply, many more of the species on the right can therefore be accommodated. In conventional terms, we would then predict $N^{15}H_3$ to be a stronger base than $N^{14}H_3$, or, alternatively, $N^{14}H_4^+$ to be a stronger acid than $N^{15}H_4^+$. More generally, the problem of energy distribution should always be resolved so as to favor locating the heavier of two isotopes in those species whose structure holds the substituted atom most firmly.

Matters become significantly more complicated if we want also to predict the magnitude of this equilibrium isotope effect. For there is rarely any *direct* way to measure the force constants about a single atom. We can, however, measure the restraints on *all the atoms* by using spectroscopic data. However numerous and complicated the nuclear vibrations may be, they can always be resolved into a much smaller number of mutually independent vibrational modes. Although these are rarely simple, each has the unique advantage of being associated with a characteristic, and experimentally accessible, vibrational frequency (ν). As indicated in Table 1, the magnitudes of such frequencies are lower in the heavier molecule and ion, except for those (less common) modes which require no displacement of the substituted atom. In those the frequencies remain unchanged. The distribution of average kinetic energy among the various modes in all four species—$N^{15}H_3$, $N^{14}H_4^+$, $N^{15}H_4^+$, and $N^{14}H_3$—is governed only by these frequencies and by the temperature. As a result, Table 1 provides all the data we need to compute the ratio

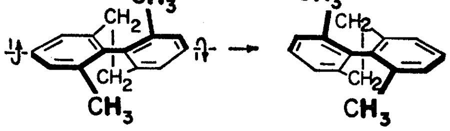
$$K = (N^{15}H_4^+)\ (N^{14}H_3)/(N^{15}H_3)\ (N^{14}H_4^+)$$

The answer, 1.035 at 25°C, is within the experimental uncertainty of the value observed, 1.034 (*15, 16*).

Before we consider the peculiar attributes of rate processes, it might perhaps be instructive to compare $N^{15}H_4^+$ with $CH_3N^{14}H_3^+$. This, too, is a weaker acid than $N^{14}H_4^+$, but by a greater factor (24.9) and for quite different reasons. The lowered acidity of $CH_3N^{14}H_3^+$ can be traced to the rather different attractions and repulsions which the added atoms provide, and, in addition, to the altered manifold of possible kinetic energies which such new forces require. These matters can now no longer be deduced from simple considerations of atomic restraint. A qualitative understanding is, in part, provided by the older generalization that a CH_3 group is always a more effective electron donor than a hydrogen atom is. A quantitative prediction would here require the use of thermochemical as well as spectroscopic data. Each kind of substitution—N^{15} for N^{14} or CH_3 for H—can thus be understood only within its own external frame of reference.

Very little need be added to extend our more qualitative considerations to kinetic isotope effects. The rate of a chemical reaction will, again, be determined by the relative abilities of different species to accommodate the least possible energy. But this time the reactants will have to be compared with something quite different—a transition state. By "transition state" one means that molecular configuration which is most difficult to attain along the path between the reactants and the products, a path that was chosen because (and insofar as) it entailed the least formidable transition state of all the possible paths to the products. Necessarily, this transition state is encountered during the most rate-limiting of all the steps in this journey. Both by analogy and by more critical analysis, one can expect that the magnitude of a kinetic isotope effect will be principally determined by the changing restraints which the isotopically substituted atom experiences as it rises from the reactant to the transition state (*17*). The breaking of a covalent bond to this atom is surely the most effective way to release many of its restraints. Such a transition state can never benefit from the presence of the heavier of two isotopes quite so much as the reactant could. An isotopically heavy reactant will therefore react more slowly than a lighter one.

"Secondary" kinetic isotope effects are hardly more mysterious. These teach us merely that the local restraints about an atom can be altered in the transition state even if no covalent bond to that atom is broken. As might be expected, such kinetic isotope effects are most often detected only if the isotopically substituted atom is no more than one or two bonds removed from the reaction site. A particularly simple and instructive example is provided by a reaction that requires the breaking of no covalent bond at all.



Here the barrier to reaction is in part supplied by the mutual opposition of the two $\mathbf{CH_3}$ groups. As the two twisting hexagonal rings (indicated by curved arrows) transform the reactant into its mirror image, the two CH_3 groups are squeezed far closer to each other than their electron clouds would normally tolerate. Surely the displacement of at least two of their six hydrogens will then become more difficult in the transition state. This unusual situation thus implies an enhanced advantage of deuterated CH_3 groups in the transition state. Indeed, when six deuterium atoms were introduced at the positions indicated, the rate was actually increased: $k_H/k_D = 0.86$ at 22°C (*18*).

It is perhaps unfortunate that so many theoretical treatments have been preoccupied with primary hydrogen kinetic isotope effects. In spite of the great number of experimental studies, hardly ever is a covalent bond to hydrogen found to be broken unless a second one is concurrently being formed. As a result, these rather common transition states always require an increase in the *formal* covalency of hydrogen from 1 to 2. Of itself, this should result in increased restraints (as in the conversion of NH_3 to NH_4^+) were it not that both such "bonds" are exceedingly weak. Any reliable *a priori* analysis is therefore extremely difficult.

In retrospect, of course, one can survey the mass of accumulated data and extract from it a pattern that is both simple and rational in its symmetry. A reagent that is best at plucking a hydrogen off the periphery of an organic molecule is also one that demands only minimum weakening of the original bond to hydrogen (*19*). A reagent that is exceedingly poor at this task will require the new bond to be almost fully formed in the transition state. In either event, the hydrogen atom in transit finds itself almost as restrained as it was in the reactant. It would be still more restrained were it not that no such atom can ever be held by more than one full covalent bond. Only when the attacking reagent is of intermediate power does the transferred hydrogen achieve an appreciable measure of vibrational freedom. Only then does it propagate a large primary isotope effect. It has now been demonstrated in several ways that the necessary condition for maximum freedom of longitudinal motion (that is, motion from the reactant residue toward the attacking reagent) in the transition state is the condition that the stretching force constant between the hydrogen atom and its original partner be indentical to that between the hydrogen atom and its new partner (*20*).

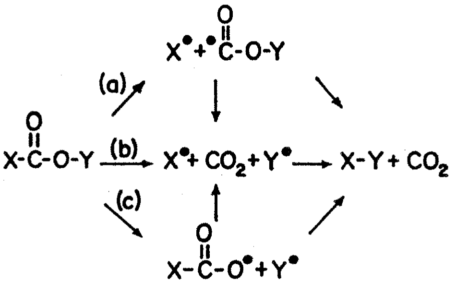


Fig. 4. Possible mechanism of uncatalyzed thermal decarboxylation.

Kinetic isotope effects thus provide a sensitive probe for measuring force-constant changes at preselected atoms as these enter the transition state. They provide, indeed, the *only* means of measuring any unambiguously defined local properties of a complicated transition state. As such, they fill a vital gap in the development of a structural theory of chemical reactivity. We know that the rates of chemical reactions are decided by energetic differences between reactants and transition states. The history of organic chemistry has been largely the story of an increased success and efficiency in elucidating the structures of our reactants and products. It has, however, told us very little about the structures of transition states. Those that are "known" are those which can reliably be deduced by interpolation. And even these are rarely more than hybrids of those structures which have been established for the immediate precursors and products of such transition states.

The only questions that now remain are those of precision and of accuracy. How quantitatively will kinetic isotope effects permit us to specify the structures of transition states?

A Quantitative Approach

It is now clear that this question, and the qualitative insight which suggested it, were too long obscured by several attempts at a quantitative approach that were altogether premature. The most common artifice, the "single frequency approximation" (*21*), will serve as an example.

In this approach it was assumed (or, better, hoped) that a transition state might keep all of the vibrational frequencies of the reactant save one. And, in fact, if one judiciously selected reactant mode were destroyed, one could derive the intrinsic kinetic isotope effects referred to earlier, which quite often agreed with the effects observed. Discrepancies, as they arose, could then easily be attributed to more trivial changes in other frequencies. Such a theoretical approach was never seriously believed useful for much more than *post hoc* rationalization. Nor was there any doubt but that it must be restricted to unimolecular reactions. (Bimolecular transition states, such as those most often encountered in hydrogen transfer reactions, possess *five more* legitimate vibrational modes than the reactants do.)

It was less clear that any prediction of a kinetic isotope effect would depend critically on a prior choice of transition state structure or, at the very least, on a choice of that part of the structure which distinguishes the transition state from the reactant. For, as we have seen, the reactions of large organic molecules are almost always very local phenomena, involving only a few intimately linked covalent bonds. If the vibrational modes of a transition state are anything at all like those of a stable molecule, they surely require the concurrent displacement of a great many atoms, quite often scattered throughout the entire structure.

Much of our increased understanding can be traced to a single investigation—the analysis of the carbon kinetic isotope effect in the reaction

$$NO_2 + CO \rightarrow NO + CO_2$$

achieved by Johnston, Bonner, and Wilson in 1956 (*22*). This analysis was distinguished from earlier, and no less rigorous, attempts principally by its use of valence force constants as structural parameters. These, together with atomic masses and configuration, fix the structure of the transition state. They determine its vibrational frequencies and so set the magnitude of the kinetic isotope effect it demands. Because force constants are rational and unambiguous properties of covalent bonds, they simplify the construction of a series of *possible* transition states. Each such possibility, when specified in abundant detail, requires its own characteristic kinetic isotope effect. And so each can be judged against values actually observed.

In practice, this technique could be applied to the study of transition states that were large enough to pose serious problems of organic reaction mechanism only after high-speed digital computers had become available. The computational labor would otherwise have been a crushing burden. To illustrate, my co-workers and I have had to use some 18 hours of computer time (with a CDC 1604 computer) to evaluate 23 hypotheses for a 16-atom transition state (*23*). Although every transition state must include an impressive list of structural parameters, very few of these have any important influence on kinetic isotope effects. It must then be equally true that an experimental kinetic isotope effect should be used to judge only those parameters that have such an influence. As expected, these are found to be very largely the force constants in the immediate vicinity of the isotopically substituted atom.

We have been principally stimulated by a problem that is almost classical in its simplicity (see Fig. 4): To what degree will a choice among the paths a, b, and c be altered as we vary the structure of the polyatomic fragments *X* and *Y*? Each such path includes an untold number of quantitative variations. And so it often occurs that a single experimental value will accommodate several transition states, often appropriate to more than one of these paths. For this reason we have always had to measure both carbon and oxygen kinetic isotope effects. Two nuclear probes are obviously better than one. We have quite recently encountered at least one example which required us to use still a third probe (at *X*, fortunately a carbon atom) in order to distinguish one variant of b from one of c. Although more such difficulties are to be expected, so too are the techniques for their solution.

We now have the means with which to formulate the structures of transition states and to exclude a great number of possibilities through the measurement of kinetic isotope effects. It is still much too early to judge, in general, how many more possibilities might then remain. We can only hope that, in the end, these will differ so trivially that their differences then reflect only the uncertainties in experimental data. Surely we cannot ask for more than this.

References and Notes

1. The description which follows distorts, because of its brevity, the outstanding contributions of many who have followed the pioneering discovery and analysis of Arthur Lapworth, *J. Chem. Soc.* **85**, 30 (1904). A more complete review may be found in J. Hine, *Physical Organic Chemistry* (McGraw-Hill, New York, ed. 2, 1962), pp. 108 ff, 233 ff.
2. In this article, bold-face type is used to identify particular atoms of the molecule.
3. F. H. Westheimer and N. Nicolaides, *J. Amer. Chem. Soc.* **71**, 25 (1949); L. Melander, *Nature* **163**, 599 (1949).
4. H. E. R. Washburn and H. C. Urey, *Proc. Nat. Acad. Sci. U.S.* **18**, 496 (1932).
5. H. Eyring, *ibid.* **19**, 78 (1933).
6. Here and subsequently I have chosen to define the magnitude of a kinetic isotope effect as the ratio of two specific rate constants (k). The one pertaining to the isotopically light molecule is always the numerator; that pertaining to the heavier is the denominator. A significant number of chemists, though hardly a majority, prefer to define the isotope effect in just the inverse sense. A ratio of unity is described as the absence of a kinetic isotope effect according to either usage.
7. An important exception is observed under quite restricted but well-understood circumstances. Should a substituted hydrogen be involved in prototropic equilibria prior to the rate-limiting step, the intrinsic kinetic isotope effect (if any) expected from the rate-limiting step will often be distorted by an equilibrium isotope effect of unusual magnitude. See V. Gold and M. A. Kessick, *J. Chem. Soc.* **1965**, 6718 (1965), and references cited therein.
8. L. Kaplan, *J. Amer. Chem. Soc.* **80**, 2639 (1958).
9. E. Grovenstein, Jr., and G. A. Ropp, *ibid.* **78**, 2560 (1956).
10. W. D. Emmons and M. F. Hawthorne, *ibid.*, p. 5593.
11. E. A. Halevi, in *Progress in Physical Organic Chemistry*, S. G. Cohen, A. Streitwieser, Jr., R. W. Taft, Eds. (Wiley, New York, 1963), vol. 1, p. 109.
12. R. E. Davis, R. E. Kenson, C. L. Kibby, H. H. Lloyd, *Chem. Commun. No. 2* (1965), p. 593; M. J. Goldstein and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.* **87**, 2293 (1965); A. J. Kresge, *ibid.* **86**, 5014 (1964); M. M. Kreevoy, P. J. Steinward, W. V. Kayser, *ibid.* **88**, 124 (1966).
13. V. Gold and M. A. Kessick, *J. Chem. Soc.* **1965**, 6718 (1965).
14. A. J. Kresge, *Pure Appl. Chem.* **8**, 517 (196[illegible] R. P. Bell and J. E. Crooks, *Proc. Roy. Soc. London, Ser. A* **286**, 285 (1965).
15. H. C. Urey, *J. Chem. Soc.* **1947**, 562 (1947).
16. A particularly lucid survey of some applications of equilibrium isotope effects has been provided by J. Bigeleisen, *Science* **147**, 463 (1965).
17. J. Bigeleisen and M. Wolfsberg, in *Advances in Chemical Physics*, I. Prigogine, Ed. (Interscience, New York, 1958), vol. 1, p. 15.
18. K. Mislow, R. Graeve, A. J. Gordon, G. H. Wahl, Jr., *J. Amer. Chem. Soc.* **86**, 1733 (1964).
19. This discussion illustrates an approach most clearly advocated by G. S. Hammond, *ibid.* **77**, 334 (1955).
20. F. H. Westheimer, *Chem. Rev.* **61**, 265 (1961); J. Bigeleisen, *Pure Appl. Chem.* **8**, 217 (1964).
21. L. Melander, *Isotope Effects on Reaction Rates* (Ronald, New York, 1960), p. 16 ff.
22. H. S. Johnston, W. A. Bonner, D. J. Wilson, *J. Chem. Phys.* **26**, 1002 (1957).
23. M. J. Goldstein and G. L. Thayer, Jr., *J. Amer. Chem. Soc.* **87**, 1925, 1933 (1965); M. J. Goldstein, *Tetrahedron Letters* **1964**, 1601 (1964); ——— and M. Yoshida, in "Abstracts of Papers, 149th National Meeting, American Chemical Society, April 1965," p. 55P.
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The Search for Good Wine

Two of the oldest industries in the world are in the midst of biochemical and technological change.

Maynard A. Amerine

Among the glories of the Neolithic Revolution were the domestication of grapes, the discovery of fermentation as a food process, and the subsequent development of the wine industry. At a very early stage the industry acquired regional and varietal wine types, presses, crude filters, at least one by-product (vinegar), a host of legends, heroes (Noah), and widespread acceptance by consumers. Although Greek and Roman wines were probably better than those of Egypt or the Fertile Crescent countries, they were undoubtedly crude by modern standards (*1*). The pitch-lined clay amphora, at best, was a poor container for wine, although more aesthetic than animal skins as storage vessels. Toward the end of the Roman period, introduction of the wooden barrel improved storage and facilitated transportation. Some time during the Middle Ages sulfur dioxide, as an antiseptic agent, was introduced into wine-making; international trade in wines continued throughout this period for the consumption of the nobility and the wealthy, and particularly for ecclesiastic use. The monastic system also helped to maintain a certain degree of sophistication in grape-growing and wine-making; in fact, it was responsible for the development of several of the best wine regions of Europe.

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