CARBON-14 ISOTOPE EFFECTS IN THE DECARBOXYLATION OF 2-BENZOYLPROPIONIC ACID

by

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for the degree of
DOCTOR OF PHILOSOPHY
May, 1959

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ACKNOWLEDGMENT

Grateful acknowledgment is made to Dr. E. M. Hodnett, thesis adviser, for his assistance and guidance throughout this work, to J. J. Sparapany for invaluable assistance in the construction of apparatus, and to others at the Radioisotope and Radiations Laboratory for stimulating discussions and suggestions.

Acknowledgment is also made for financial support by the Department of Chemistry and by a grant from the Dow Chemical Company through the Research Foundation.

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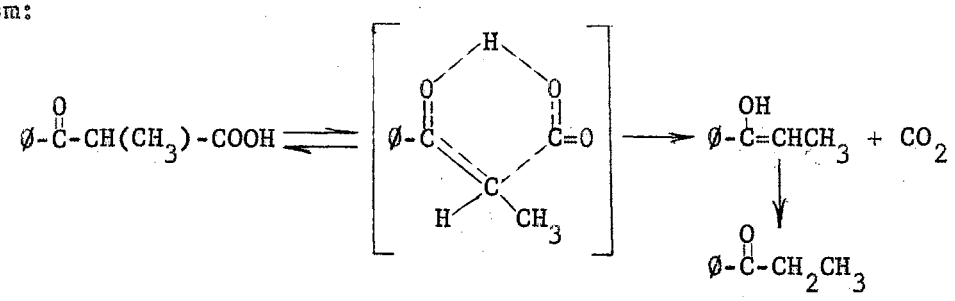
INTRODUCTION

The object of this work was to contribute to our understanding of the tendency of β-keto acids to split off carbon dioxide, a process which purportedly takes place by the following cyclic concerted mechanism:



In addition, it was hoped that the experimental results might lend credence to our present theories of isotope effects.

More specifically, the problem has been, first, to prepare a β-keto acid--namely, 2-benzoylpropionic acid--with certain desirable properties and to study the kinetics of its decarboxylation, since the order of the reaction is related to the reaction mechanism; second, to label the acid with carbon-14 in the 1-, 2- and carbonyl-positions, successively; and, third, to determine the isotope effects for the decarboxylation of the labeled compounds under several different conditions. By comparing the observed isotope effects with various values which have been calculated from theoretical considerations, it was hoped that a better insight into the transition state for the reaction under consideration could be obtained.

HISTORICAL

The Kinetic Isotope Effect

The effect of substituting one isotope of an atom for another in a molecule should manifest itself whenever a property of that molecule is influenced by the mass of the particular atom in question. It would be expected that such properties as vapor pressure, diffusion rate, absorption, thermodynamic functions, chemical equilibria and reaction rates could be affected. It has been amply demonstrated experimentally that this is indeed the case.

The effect of isotopic substitution on reaction rates was first demonstrated by Washburn and Urey (64) in 1932 when they showed that deuterium is enriched in the liquid phase in the electrolysis of water. Eyring (26) explained this phenomenon on the basis of a zero-point energy difference between isotopic molecules. Subsequently, the deuterium isotope effect became a useful and powerful tool in the study of reaction mechanisms and in the development of the theories of rate processes.

In the past 15 years a variety of radioisotopes and enriched stable isotopes have become readily available, and a myriad of tracer experiments have been conducted using them. It was at first felt that no appreciable rate effects resulted on isotopic substitution of the heavier atoms such as carbon, and no corrections were necessary in quantitative tracer studies. This assumption was shown to be in error by the work of Beeck, Otvos, Stevenson, and Wagner (4), who obtained a

significant isotope effect in the rupture of carbon-carbon bonds in propane-1-C^{13} by electron impact. Since that time many papers have been published showing quantitatively as well as qualitatively the effect of carbon-13, carbon-14, nitrogen-15, and oxygen-18 isotopes on both organic and inorganic reaction rates.

Isotope effects have been expressed quantitatively in a variety of ways. From the standpoint of correlation of theory and experiment, the simplest expressions are k*/k and k/k*, where k and k* refer to the specific reaction rate constants for the normal and the labeled molecules, respectively. The ratio k/k* is convenient in that it is a number larger than one. Both expressions will appear in this thesis.

The differences in the physical and physiochemical properties of isotopes decrease with decreasing differences in the masses of the corresponding isotopes. The greatest effect, then, should occur in the case of hydrogen (H^1) versus tritium (H^3), where the mass of the latter exceeds that of the former by 200%. On the other hand, the mass of carbon-14 exceeds that of carbon-12 by only 16.7%, and a much smaller isotope effect should be expected.

Maximum values for the ratio k/k* have been calculated by Bigeleisen (8) for the isotopes of a number of the elements. Several of these are listed below for purposes of comparison.

Stable Isotope	Tracer Isotope	k/k*
H^1	H^3	60
H^1	H^2	18
C^{12}	C^{14}	1.5
C^{12}	C^{13}	1.25

Much lower values are actually encountered experimentally. The more common ranges are listed below.

Stable Isotope	Tracer Isotope	k/k*
H^1	H^3	1 - 15
H^1	H^2	1 - 10
C^{12}	C^{14}	1.00 - 1.12
C^{12}	C^{13}	1.00 - 1.06

The determination of isotope effects is important in that it can be used to further elucidate reaction mechanisms. It is now generally agreed that isotopic fractionation is evident in a reaction when a bond to the isotopic atom is broken or formed in the rate-determining step. Wiberg (66) has pointed out that this is not necessarily true. Nevertheless, many papers have been published based on this supposition. This technique was used as early as 1935 (62).

Precise quantitative determinations of isotope effects have become increasingly important as the theory has evolved. The relation between the mechanism of a reaction and the magnitude of the isotope effect has been treated theoretically and is based on the equations of statistical thermodynamics for isotopic equilibria (24) and the theory of absolute reaction rates (31). Calculations are based on comparisons of the expressions for the rate constants of the same reaction for molecules of different isotopic composition; that is,

$$\frac{k_1}{k_2} = \frac{K_1}{K_2} \frac{\delta_2}{\delta_1} \left[\frac{\bar{m}_2}{\bar{m}_1}\right]^{1/2} \frac{Q_2}{Q_1} \frac{Q_1^*}{Q_2^*} \qquad (1)$$

where: k = the rate constant
K = the transmission coefficient
δ = the length of the top of the potential barrier
$\bar{m}$ = the effective mass of the activated complex along the coordinate of decomposition, usually calculated as the reduced mass $mm_1/m + m_1$ of the two atoms involved in the bond being broken or formed in the rate-controlling step of the reaction
Q = the complete partition function

The subscripts 1 and 2 refer to the normal and labeled molecules, respectively, and the symbol * refers to the activated complex.

Bigeleisen and Goeppert-Mayer (11) have demonstrated that the ratio of the partition functions of two isotopic molecules can be expressed as a simple function of the vibrational frequencies of the two molecules. Bigeleisen (7) was thus able to obtain the following equation for the ratio of reaction rates of isotopic molecules:

$$\frac{k_1 s_2 s_1^*}{k_2 s_1 s_2^*} = \left(\frac{\bar{m}_2}{\bar{m}_1}\right)^{1/2} \left[1 + \sum_i^{3N-6} G(u_i)\Delta u_i - \sum_i^{3N'-6} G(u_i^*)\Delta u_i^*\right] \qquad (2)$$

where: $G(u) = 1/2 - 1/u + 1/(e^u - 1)$
$u = h\nu_1/kT$
$\Delta u = h(\nu_1 - \nu_2)/kT$
h = Planck constant
k = Boltzmann constant
T = the absolute temperature
ν = the fundamental vibrational frequencies of the normal and isotopic molecules
s = symmetry numbers, the ratio of which is generally unity
3N-6 = the number of vibrational modes in a molecule containing N atoms

Tables of G(u) as a function of u are available (11).

A number of assumptions have been made in order to arrive at equation 2. Since the potential energy surfaces for isotopic molecules are nearly the same, $\mathcal{J}_1 = \mathcal{J}_2$. Also, it was assumed that $\kappa_1 = \kappa_2$. The value of u_i was taken to be small. The "tunnel effect" was neglected, so that the equation is inapplicable in the case of hydrogen. Other approximations are less obvious.

Equation 2 states that there are two principal ways in which a variation in the isotopic mass changes the reaction rate:
(1) The "reduced-mass effect," expressed by $(\bar{m}_2/\bar{m}_1)^{1/2}$, which evaluates

the ratio of the rupture frequencies of the critical bonds within the two isotopic activated complexes.

(2) The "zero-point energy effect," given by $1 + \sum G(u)\Delta u - \sum G(u^*)\Delta u^*$, which expresses the effect of mass on the equilibrium between the reactants and the activated complex.

There are several ways to evaluate the effective mass factor, all leading to different results. In order to evaluate the free-energy term, a detailed knowledge of the vibrational frequencies of both isotopically-substituted molecules and the activated complex are necessary.

Equation 2 permits some general predictions to be made about isotope effects. If the subscripts 1 and 2 refer to light and heavy molecules, respectively, the reduced mass factor will be greater than unity. For normal reactions involving bond rupture, the force constants of the reactants are greater than those of the activated complex; that is,

$$\sum G(u)\Delta u \; > \; \sum G(u^*)\Delta u^*$$

Hence the reaction rate of the lighter molecule will be greater than that for the heavier molecule, or $k_1/k_2 > 1$. The maximum isotope effect would be obtained if the isotopic atoms were free from bonding in the activated complex; that is, when

$$\sum G(u^*)\Delta u^* = 0$$

It also follows from the theory that the isotope effect should diminish as the temperature increases, tending to the ratio of the effective masses. This has been demonstrated experimentally many times (15) and is now an active area of investigation.

In the case where the isotopic reactants are atoms, $\sum G(u)\Delta u$ is

zero and k_1/k_2 may become less than unity. Stranks (60) has pointed out that this may also be true in the case of ring closure. Cases in which the lighter isotope reacts more slowly than the heavier one are known as "inverse isotope effects." A number of these effects have been reported, but most have been discredited on the basis of new experimental data (49).

In the case of hydrogen, where isotopic mass differences are so great, it is possible to have "secondary isotope effects." Secondary isotope effects occur when the isotopic atoms are not directly involved in a bond-breaking or bond-forming step of a reaction. In this case, $(\bar{m}_2/\bar{m}_1)^{1/2} = 1$. These effects have been experimentally demonstrated (54) and find their place in mechanism studies. They are insignificant in the case of carbon-14 versus carbon-12.

Equation 2 is applicable when there is competition between molecules differing in isotopic composition. The isotope effect is therefore an intermolecular one. If compound A'BA' decomposes to form A'B and A', as in the case of malonic acid, then the decomposition of ABA' into AB and A' or into A'B and A will show an intramolecular isotopic competition, or an intramolecular isotope effect. In this case equation 2 can be readily simplified. Since the original molecules are isotopically identical,

$$\sum \underline{G}(u)\Delta u = 0$$

The activated complexes are completely analogous structurally, so that

$$\sum \underline{G}(u^*)\Delta u^* \approx 0$$

Equation 2 reduces simply to the reduced mass factor. The intramolecular isotope effect should be smaller than the intermolecular isotope effect

and should be temperature-independent. A comparison of the available data (47) substantiates the former conclusion, but repudiates the latter. The intramolecular case is of no importance in this paper owing to the nature of the compounds involved.

It may be noted that kinetic isotope effects should be equal for the forward and reverse reactions. Their magnitude should be the same irrespective of whether chemical bonds are broken or formed (9).

The influence of activation energy on the magnitude of the isotope effect has been of considerable interest. Wiberg (66) has said that, in general, in any series of related reactions, the reaction with the lowest activation energy will have the lowest isotope effect. Although this cannot be predicted from simple theory, there is a good deal of experimental evidence to back it up (19).

Bigeleisen (15) has recently derived another equation for theoretically calculating isotope effects; namely,

$$\frac{k_1 s_2 s_1^*}{k_2 s_1 s_2^*} = \frac{\nu_{1L}^*}{\nu_{2L}^*} \left[1 + \frac{\bar{\gamma}}{24} \frac{\hbar c}{kT} \sum_i^{3N-6} \left(\frac{1}{m_{1i}} - \frac{1}{m_{2i}} \right) \left(a_{ii} - a_{ii}^* \right) \right]^2 \quad (3)$$

where: (ν_{1L}^*/ν_{2L}^*) = the ratio of the frequencies along the path of decomposition (imaginary frequencies in the transition state)

$\bar{\gamma}$ = a function of u_i

$\hbar$ = $h/2\pi$

m_i = the mass of one of the atoms involved in the critical bond

a_{ii} = the diagonal force constant

The advantages of equation 3 over equation 2 have yet to be demonstrated.

In the case of simple bond rupture or formation, the simpler equation of Eyring and Cagle (27) is approximately as accurate as equation 2.

$$\frac{k_1}{k_2} = \frac{\sinh\ (h\nu_1/2kT)}{\sinh\ (h\nu_2/2kT)} \qquad (4)$$

where: sinh = the hyperbolic sine
$\nu_{1,2}$ = the frequencies of the hypothetical diatomic molecules of the isotope and the other atom involved in the bond to be broken

The other symbols have the same significance as in equation 2. This expression is actually a special case of the more general Bigeleisen equation, valid for certain limiting conditions.

In equation 2 the reduced mass factor $(\bar{m}_2/\bar{m}_1)^{1/2}$ for a given reaction is evaluated as a simple bond rupture or formation. Since many reactions--for example, S_N2--involve simultaneous bond rupture and formation, Bigeleisen and Wolfsberg (12) (14) have extended the theory to include such three-center reactions.

In a three-center reaction of the type

$$A + B\text{-}C \longrightarrow [A\text{--}B\text{--}C] \longrightarrow A\text{-}B + C$$

the reaction coordinate, x_L, in the transition state may be expressed as

$$x_L = \alpha|r_B - r_C| \quad - \beta|r_B - r_A|$$

where $r_B - r_C$ and $r_B - r_A$ are the separation of B and C and B and A, respectively, and β/α determines the relative amount of bond formation between A and B to bond extension between B and C in the activated complex.

From these considerations, the isotope effect equation becomes

$$\frac{k_1}{k_2} = \left[\frac{\left(\frac{1}{m_{B_1}} + \frac{1}{m_{C_1}}\right) + p\left(\frac{1}{m_{B_1}} + \frac{1}{m_{A_1}}\right) - \frac{2p^{1/2}}{m_{B_1}} \cos ABC}{\left(\frac{1}{m_{B_2}} + \frac{1}{m_{C_2}}\right) + p\left(\frac{1}{m_{B_2}} + \frac{1}{m_{A_2}}\right) - \frac{2p^{1/2}}{m_{B_2}} \cos ABC}\right] \left[1 + \sum_{i}^{3N-6} G(u_i)\Delta u_i - \sum_{i}^{3N'-6} G(u_i^*)\Delta u_i^*\right] \quad (5)$$

where: $p = \beta^2/\alpha^2$

m_x = the mass of atom x (or fragment x)

ABC = the angle between A, B and C in the activated complex

When p = 0, equation 5 reduced to the simple case of bond rupture, while, when 1/p = 0, it becomes the combination of two atoms, molecules or radicals.

Other quantum-mechanical approaches to the reaction rate problem have been made [for example, that of Bauer and Wu (2)], but no isotope effects have been calculated based on them. It will be interesting to see how the results of the different approaches compare.

The difficulties in the a priori calculation of relative reaction rates or the interpretation of experimental data by means of the equations presented above are those which are inherent in the Eyring method for calculations of absolute reaction rates. However, these equations reduce to a minimum the number of properties of the activated complex which have to be evaluated. In many cases it is possible to get a priori qualitative answers about the relative rates and information about the reaction mechanism and the nature of the activated complex from experimentally determined relative rates.

Kinetic isotope effects have been the subject of a number of reviews.

Effects in inorganic chemistry (60), with isotopes of hydrogen (66) and with carbon (49) (70) have been summarized. A general and comprehensive treatise has been prepared by Roginsky (47). An excellent general review has been published by Bigeleisen and Wolfsberg (15).

The Mechanism of β-Keto Acid Decarboxylation

Although ordinary acids decarboxylate by several different mechanisms [see Brown's review (18)], depending on the experimental conditions, the usual mechanism is

$$R\text{-}COOH \rightleftharpoons R\text{-}COO^- + H^+$$

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}\ddot{O}^- \longrightarrow R^- + CO_2$$

$$R^- + H^+ \longrightarrow RH$$

In other words, these acids decompose by a first order reaction of their anions. Acids containing electron-attracting groups so located that relatively stable carbanions result, such as trichloroacetic and nitroacetic acids, readily lose carbon dioxide according to this mechanism.

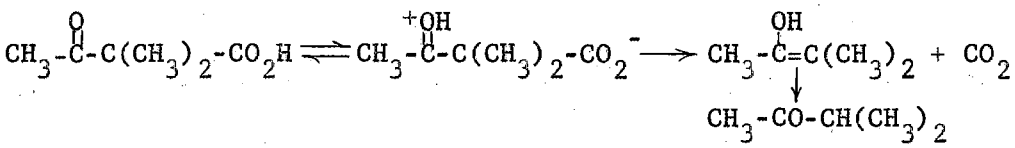
On the other hand, anions of ordinary β-keto acids are relatively stable. Widmark (67) found, for example, that the kinetic expression for the decomposition of acetoacetic acid in aqueous solutions of varying hydrogen ion concentration is

$$v = k[CH_3COCH_2COO_2H] + k'[CH_3COCH_2CO_2^-]$$

where k/k' is about 50. Other β-keto acids behave similarly (18).

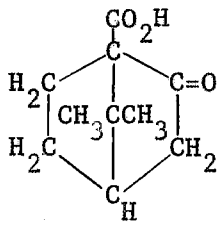
For several years after this discovery it was not known which form decomposes--the keto form or the enol form. Pedersen (43) solved this problem by using α,α-dimethylacetoacetic acid, which cannot enolize,

and found a behavior analogous to that of acetoacetic acid. Since the reaction rate constants were of the same order of magnitude, he concluded that both reactions involve the keto form of the acid. Subsequently Pedersen (44) (45) carried out the kinetic experiments on α,α-dimethylacetoacetic acid in the presence of bromine and found that it had no effect on the reaction rate and was taken up as fast as the acid decomposed. The ketone product could not be halogenated under the reaction conditions. This work suggested that the enol form of the ketone was the first product of the decarboxylation. With these facts in mind and with his previous experience with ordinary acid decompositions, Pedersen (44) suggested the following mechanism:



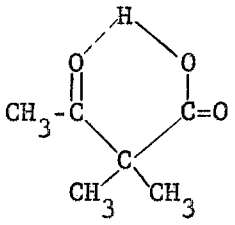
It was proposed, then, that the ordinary form of the acid is stable. The acid anion decomposes very slowly. Owing to the weakly basic properties of the keto group, it will to some extent take up hydrogen ions. The attraction of the positive charge then leads to a more rapid decomposition than that of the simple anion.

That the enol is formed is evident also from the fact that acids which are incapable of yielding stable enol products owing to steric restrictions are quite stable. For example, ketopinic acid, is quite

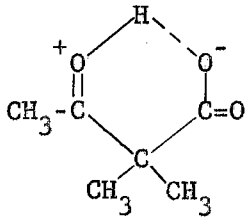


stable and has a sharp melting point above 200° (17).

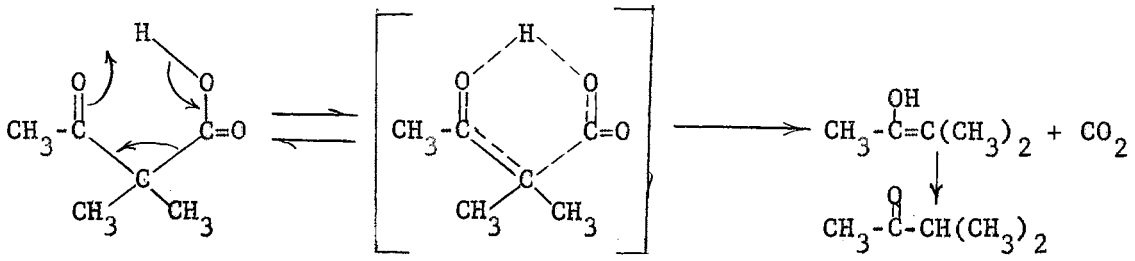
Westheimer and Jones (65) argued that the fraction of the dipolar ion present should decrease with a decrease in the dielectric constant of the solvent. Since they found that changes in the solvent had little effect on the rate of reaction, they proposed a chelate intermediate in preference to the zwitterion.



However, Hine (33) points out that although the relative concentration of the dipolar ion should decrease with the ion-solvating power of the solvent, its specific rate constant should increase, because the reaction involves charge destruction in the transition state. Coulombic attraction within the dipolar ion should still lead to a cyclic intermediate.



Schenkel (52) proposed a cyclic intermediate which differs slightly from that of Pedersen and Hine.



This cyclic, concerted mechanism is now generally accepted.

The behavior of β-keto acids containing other functional groups can usually be rationalized by the above mechanism, although the details have yet to be worked out. Acetonedicarboxylic acid has been studied (68), and it was found that, although it behaves as a β-keto acid (its decarboxylation is catalyzed by primary amines), its univalent ion is more unstable than the undissociated acid.

Steinberger and Westheimer (57) found that with dimethyloxaloacetic acid the monoanion and dianion decompose, but the undissociated acid is stable. They were even able to detect the enolate anion in the reaction product by a spectroscopic technique. The decarboxylation of this class of compounds is subject to heavy-metal cation catalysis, which is not true for simple β-keto acids.

Although not a β-keto acid, malonic acid is similar in structure and behavior, and an analogous decomposition mechanism has been suggested (35). The effect of structure is evident when one considers that malonic acid decomposes ten times as fast as its univalent anion (32) (the divalent anion is stable), whereas it is the univalent anion of dibromomalonic acid that is unstable (40).

Isotope Effects in the Decarboxylation of β-Keto Acids

Apparently, simple β-keto acids have not been studied from the

standpoint of isotope effects resulting from their decarboxylation. There has been some work done on ketodicarboxylic acids labeled in the carboxyl group, but the interest here has been in the metal-catalyzed reactions, probably because of their biological implications. An interesting example is afforded by the work of Gelles and Reed (29), who found the following carbon-13 isotope effects:

	Oxaloacetic acid	Yttrium (III) Oxaloacetate	Dysprosium (III) Oxaloacetate
k/k^*	1.06	1.05	1.10

These results indicate a definite "magnetic" isotope effect.

In contrast to simple β-keto acids, probably no compound has received more isotopic study than malonic acid and its substituted analogues. The literature is so extensive that no specific work will be mentioned at this point. Bigeleisen (15) has summarized most of the data and has discussed the results critically. Despite the large amount of effort, the status of the experimental work leaves much to be desired. There is considerable discrepancy between results of workers. There are even surprising deviations within the same laboratories. Little has been contributed toward an understanding of the reaction mechanism, although the work has made possible a great deal of theoretical maneuvering.

INTRODUCTION TO EXPERIMENTAL WORK

The purpose of this section is to present an over-all picture of the experimental work involved in this project. A succinct discussion of all of the syntheses that were carried out will be given. Details of those reactions which proved to be vital to the problem will be presented in a later section. Mathematical expressions pertinent to the various experiments will also be included in this section.

To be suitable for an isotope effect study, the β-keto acid to be used should have certain properties. It should be a solid in order to facilitate the radioactivity assays. It should be stable at room temperature, yet decompose at a convenient rate as close to room temperature as possible. It should be easily purified and decompose cleanly. Finally, it should be obtainable by a reasonable route of synthesis. 2-Benzoylpropionic acid was chosen for this work because it met these requirements.

Syntheses of Compounds

Most β-keto acids that are known to date have been prepared by hydrolysis of the corresponding esters. 2-Benzoylpropionic acid, for example, has been prepared in no other way (34). It was decided to follow this path, at least to the point where some of the acid would be available for testing. The routes were selected, however, on the basis of whether or not they could be used to label the molecule with carbon-14, starting with the latter in the form of barium carbonate.

2-Benzoylpropionic Acid by Ester Hydrolysis: An attempt was made to prepare ethyl 2-benzoylpropionate by the following reaction according to the method of Wallingford (63), who obtained the ester in 37% yield:

$$\text{ØCOCH}_2\text{CH}_3 + (\text{CH}_3\text{CH}_2\text{O})_2\text{CO} \xrightarrow{\text{NaOCH}_2\text{CH}_3} \text{ØCOC(CH}_3\text{)COOCH}_2\text{CH}_3 + 2\text{CH}_3\text{CH}_2\text{OH}$$

$$\text{ØCOC(CH}_3\text{)COOCH}_2\text{CH}_3 \xrightarrow{\text{H}^+} \text{ØCOCH(CH}_3\text{)COOCH}_2\text{CH}_3$$

On distillation no sharp fraction was obtained. A cut which should have included the ester (b.p. 180-190° at 45 mm. pressure) was hydrolyzed by the method of Hope and Perkin (34), but only benzoic acid was obtained.

Ethyl 2-benzoylpropionate has been prepared by the Blaise reaction in a 40% yield (23).

$$\text{ØCN} + \text{BrCH(CH}_3\text{)COOCH}_2\text{CH}_3 \xrightarrow[(2)\text{H}_2\text{O},\text{H}^+]{(1)\text{Zn},\text{CuBr}_2} \text{ØCOCH(CH}_3\text{)COOCH}_2\text{CH}_3 + \text{ZnBrOH} + \text{NH}_4^+$$

By this procedure, a 58% yield of product (b.p. 230-240° at 105 mm.) was obtained.

Hydrolysis of this material gave only a 10% yield of 2-benzoylpropionic acid, m.p. 77-78° with decomposition. Hope and Perkin (34) reported 82-83° as the melting point.

The starting materials for the Blaise reaction were not immediately available, so they were synthesized. Benzonitrile was prepared by several methods as indicated below:

a) $$\text{ØCONH}_2 \xrightarrow[\triangle]{\text{NaCl}\cdot\text{AlCl}_3} \text{ØCN} + \text{H}_2\text{O}$$

Norris and Klemka (42) report 97% yields by their method. On repeating their work, only a 40% yield of impure benzonitrile was obtained.

b) $$\text{ØCONH}_2 \xrightarrow[200°]{\text{H}_2\text{NSO}_3\text{NH}_4} \text{ØCN} + \text{NH}_4\text{HSO}_4$$

Boivin (16) has obtained the nitrile in nearly quantitative yields by dehydrating benzamide in this manner. This procedure and variations of it were tried, but no more than 56% of contaminated benzonitrile could be obtained.

c) $$\text{ØCONH}_2 \xrightarrow[\triangle]{\text{POCl}_3} \text{ØCN}$$

This common method gave an 82% yield of the nitrile, which in turn was used in the Blaise reaction.

The ethyl 2-bromopropionate was prepared in 68% yield by the Hell-Vohlhard-Zelinsky reaction using Zelinsky's original method (72).

$$\text{CH}_3\text{CH}_2\text{COOH} + \text{Br}_2 \xrightarrow{\text{P}} \text{CH}_3\text{CHBrCOBr} \xrightarrow{\text{CH}_3\text{CH}_2\text{OH}} \text{CH}_3\text{CHBrCOOCH}_2\text{CH}_3$$

2-Benzoylpropionic Acid from Propiophenone, Sodium and Carbon Dioxide: Since Beckmann and Paul (3) had obtained benzoylacetic acid by carbonation of the anion of acetophenone, it was thought that a similar technique might be used for 2-benzoylpropionic acid.

$$\text{ØCOCH}_2\text{CH}_3 \xrightarrow{\text{Na}} \text{ØCOCHCH}_3 \xrightarrow[-\text{Na}^+]{\text{CO}_2} \text{ØCOCH(CH}_3\text{)COO}^- \xrightarrow{\text{H}_2\text{O, H}^+} \text{ØCOCH(CH}_3\text{)COOH}$$

Equimolar amounts of sodium sand and propiophenone in dry ether were stirred together for 2 hours. After separation of the remaining sodium, dry-ice was added to the solution. The mixture was decomposed with water, and the aqueous phase was extracted with ether, acidified and again extracted. The ether extract was evaporated, and the residual oil was dissolved in a petroleum ether-benzene solution. On cooling, a 5% yield of the acid was obtained, m.p. 76-77°.

Obviously, none of these procedures were satisfactory. It was then discovered that an excellent method was available for preparing β-keto acids.

2-Benzoylpropionic Acid from Propiophenone, Sodium Amide and Carbon Dioxide: The best method to date for preparing β-keto acids is that of Levine and Hauser (38) in which sodium amide in liquid ammonia serves as a base which can remove an α-hydrogen from a ketone. The ketone anion can then be carbonated.

$$\text{ØCOCH}_2\text{CH}_3 + \text{NaNH}_2 \xrightarrow{\text{NH}_3} [\text{ØCOCHCH}_3]^- \text{Na}^+ + \text{NH}_3$$

$$[\text{ØCOCHCH}_3]^- \text{Na}^+ \xrightarrow[(2)\ \text{H}^+]{(1)\ \text{CO}_2} \text{ØCOCH(CH}_3\text{)COOH}$$

In general, yields of 50-70% should be expected using this technique. However, in this case only a 25% yield was obtained. The low yield is offset by the high purity of the product and the fact that most of the unreacted propiophenone can be recovered if desired. It was later found that potassium amide is twice as effective as sodium amide, and use of the latter was abandoned altogether. The best technique devised, and all of the syntheses which follow, will be described in detail later.

Each step of the syntheses was carried out at least once using

"dead" materials before attempting to use labeled compounds. The "hot" runs were similar to the "dead" runs except that corresponding "dead" compounds were added as scavengers during various extractions and transfer operations. These scavenger operations served to recover small amounts of "hot" materials which would ordinarily be lost in these operations.

Preparation of 2-Benzoylpropionic Acid-1-C^{14}: A one-step procedure making use of the reaction just discussed was used. Using apparatus D shown in the Appendix, carbon-14 dioxide was liberated from barium carbonate by the use of sulfuric acid and condensed by means of liquid nitrogen in a tube containing a solution of the enolate of propiophenone. The tube was sealed and the carbonation occurred upon warming to room temperature. Based on barium carbonate, a 56% yield was obtained.

Preparation of 2-Benzoylpropionic Acid-Carbonyl-C^{14}: This acid was prepared by the following series of steps:

$$BaC^{*}O_3 \xrightarrow{H_2SO_4} C^{*}O_2 \xrightarrow{\text{ØMgBr}} \text{ØC*OOH}$$

$$\text{ØC*OOH} \xrightarrow{SOCl_2} \text{ØC*OCl}$$

$$\text{ØC*OCl} \xrightarrow{(C_2H_5)_2Cd} \text{ØC*OCH}_2\text{CH}_3$$

$$\text{ØC*OCH}_2\text{CH}_3 \xrightarrow[(2)\ CO_2]{(1)\ KNH_2} \text{ØC*OCH(CH}_3\text{)COOH}$$

Benzoic acid was prepared in 90% yield by carbonation of phenylmagnesium bromide in apparatus D just as described for the carboxyl-labeled acid.

"Hot" acids such as benzoic and acetic have been prepared by many investigators using all kinds of equipment, most of which have been rather elaborate. The relatively simple technique used here gives essentially the same yields.

The benzoic acid was converted to benzoyl chloride in 91% yield by refluxing with excess thionyl chloride and distilling.

The benzoyl chloride was mixed with an excess of diethylcadmium in benzene, prepared by adding cadmium chloride to a solution of phenylmagnesium bromide. After working up the mixture and fractionating, a 72% yield of propiophenone was obtained.

The latter synthesis was reported (22) to be one of the best general methods for preparing ketones. After making numerous runs under a variety of conditions, it has been concluded that the procedure leaves much to be desired. The yields were generally lower than 72%. In addition, the ketone was contaminated with ethyl benzoate which subsequently turned up in the acid as benzamide.

The propiophenone was converted to 2-benzoylpropionic acid in 60% yield by the use of potassium amide in liquid ammonia and dry-ice.

The over-all yield was 35%, based on barium carbonate.

Preparation of 2-Benzoylpropionic Acid-2-C^{14}: The following synthesis scheme was used:

$$BaC^*O_3 \xrightarrow{H_2SO_4} C^*O_2 \xrightarrow{CH_3MgI} CH_3C^*OOH$$

$$CH_3C^*OONa \xrightarrow{(C_2H_5O)_3PO} CH_3C^*OOC_2H_5$$

$$CH_3C^*OOC_2H_5 \xrightarrow{LiAlH_4} (CH_3C^*H_2O)_4LiAl \xrightarrow[H_2SO_4]{48\%\ HBr} CH_3C^*H_2Br$$

$$CH_3C^*H_2Br \xrightarrow[(2)\ CO_2]{(1)\ Mg} CH_3C^*H_2COOH$$

$$CH_3C^*H_2COONa \xrightarrow[\text{ØH}]{AlCl_3} \text{ØCOC}^*H_2CH_3$$

$$\text{ØCOC}^*H_2CH_3 \xrightarrow[(2)\ CO_2]{(1)\ KNH_2} \text{ØCOC}^*H(CH_3)COOH$$

Acetic acid was prepared by carbonation of methylmagnesium iodide as previously described for benzoic acid, and was finally obtained in 90% yield in the form of its sodium salt.

For the conversion of sodium acetate to ethyl acetate in 95% yield, ethyl phosphate was preferred over ethyl sulfate, which was tried in a "dead" run, because of its greater stability and higher boiling point.

Until recently, labeled bromoethane has been prepared by synthesizing and isolating ethanol, which was then converted to the bromide. The procedure followed here eliminates this rather tedious intermediate step. Ethyl acetate was reduced with lithium aluminum hydride in the usual manner. The organometallic complex was dried and decomposed with hydrobromic acid, giving a 92% yield of pure bromoethane.

The bromoethane was converted to propionic acid in 91% yield by the common technique of pouring a Grignard solution onto dry-ice. The acid was recovered as sodium propionate.

The latter was converted to propiophenone by means of a Friedel-Crafts reaction. Fractionation of the products gave the ketone in 86% yield.

The ketone was converted to 2-benzoylpropionic acid in 61% yield using potassium amide and dry-ice as previously mentioned.

In retrospect, it is apparent that 2-benzoylpropionic acid-carbonyl-C^{14} could have been prepared best by utilizing the last three steps of the synthesis just discussed. The better of the paths could not be ascertained a priori, so the dialkylcadmium path to the ketone was chosen in order to become familiar with this important technique.

The over-all activity yields were excellent in all of these syntheses.

Kinetics of the Decarboxylation of 2-Benzoylpropionic Acid

Since one of the eventual goals of the project was to correlate the experimental findings with the cyclic, concerted mechanism of β-keto acid decarboxylation, which is kinetically first order, it seemed desirable to study the kinetics of the reaction under the same conditions that were to be used in the isotope effect work.

The decomposition was carried out, in duplicate or triplicate, under different conditions, varying the temperature, solvent and stirring.

Initially a pressure-measuring technique was used to follow the course of the reaction. This was soon abandoned in favor of a simpler volume-measuring method, using either apparatus A or B, illustrated in the Appendix.

If the reaction is first order, then

$$\frac{dC_{CO_2}}{dt} = kC_A$$

where: t = the time in minutes
C_{CO_2} = the concentration of CO_2 in mmoles/ml. of solution
C_A = the concentration of the acid at any time

If C_o = the original acid concentration,

so that $C_A = C_o - C_{CO_2}$,

then $$\frac{dC_{CO_2}}{dt} = k(C_o - C_{CO_2})$$

which on integration yields

$$\log (C_o - C_{CO_2}) = - \frac{k}{2.3} t + C \qquad (6)$$

A plot of log C_A versus time should give a straight line, the slope of which could be used to evaluate the rate constant, k.

C_{CO_2} may be found from the measured volume of carbon dioxide and the ideal gas law; that is,

$$C_{CO_2} = \frac{PV}{RTv_1} \qquad (7)$$

where: P = the pressure of the carbon dioxide in mm.
V = the volume of gas in ml., measured at time t
R = 62.4 mm.-ml./mmole-°K
T = the absolute temperature
v_1 = the volume of the liquid in ml.

In actual practice the volume of liquid was considered constant, which was essentially the case, and the quantity of residual acid (as millimoles) was plotted, thus saving an additional calculation. Primed quantities, such as C_o', will be used to indicate simply mmoles.

The half-life, τ, is perhaps a more meaningful term than k. It may be determined directly from the graphs of log C_A' versus time. The specific rate constant may then be determined from the expression

$$k = \frac{2.3 \log 2}{\tau} \qquad (8)$$

Radioactivity Assay of Carbon-14-Labeled Compounds

Acid samples were assayed by the wet combustion method. The material was oxidized with Van Slyke solution in the apparatus shown in the Appendix. The "hot" carbon dioxide was collected in an ionization chamber and the activity determined on an Applied Physics Corporation Vibrating Reed Electrometer, Model 30. Internal counting is desirable in the case of carbon-14 because it is only a weak β emitter [0.155 Mev.; half-life, 5720 yrs. (37)].

Determination of the Observed Isotope Effect

One of the three following isotopic competitive methods is generally used to determine isotope effects: (a) The method of continuous isotopic analysis of the product (51) or of successive product fractions (53), (b) isotopic analysis of the product after a known amount of reaction (58), and (c) isotopic analysis of the original reactant after a known amount of reaction (25). Method (c) is ideal for this study because of the ease of recovery and purification of 2-benzoylpropionic acid.

If one of the isotopic species in a reaction is present in tracer amounts, which is generally the case in experiments of this type, then the isotope effect may be calculated from the following equation (25):

$$\frac{k^*}{k} = 1 + \frac{\log (A_f/A_o)}{\log (1 - f)} \qquad (9)$$

where: k^*/k = the ratio of the reaction rate constant of the labeled (tracer) molecule to that of the ordinary molecule
A_f = the specific activity of the unreacted substrate after the reaction has proceeded to the extent of f.
A_o = the specific activity of the original substrate
f = the fraction reacted

This equation has been derived from mathematical manipulations of the ordinary rate expressions for the two isotopic molecules. It is not limited to first order reactions.

In the present problem known amounts of labeled 2-benzoylpropionic acid were decomposed to various extents of reaction as determined by the volume of carbon dioxide liberated. The acid remaining was recovered and assayed along with samples of the original acid. From these quantities the isotope effects were calculated using equation 9.

EXPERIMENTAL PROCEDURES

Synthesis of "Dead" 2-Benzoylpropionic Acid

This is essentially the method of Levine and Hauser (38), modified in that potassium amide replaces sodium amide. It represents the best of the procedures tried.

In a 200-ml. 3-neck flask equipped with a magnetic stirrer, dropping funnel and dry-ice condenser with a soda-lime tube attached was placed about 100 ml. of liquid ammonia and a crystal or two of ferric nitrate (catalyst). To the stirred liquid was added, a small piece at a time, 3.9 g. (100 mmoles) of metallic potassium. After the intense blue color disappeared, 12.2 g. (90 mmoles) of propiophenone in 25 ml. of absolute ether was added over a period of 5 minutes. The dry-ice condenser was replaced by a water reflux condenser, and the flask, containing the potassium derivative of the ketone, was placed on a steam bath. The ammonia was evaporated as rapidly as possible, sufficient ether being added to maintain the volume at approximately 90 ml. As soon as the ether began to reflux, the mixture was poured into a flask containing a large excess of dry-ice. After the reaction mixture had come to room temperature, ether and a minimum of water were added until two homogeneous layers were present. The aqueous phase was filtered and extracted with ether to remove the by-products. (From these extracts about 3 ml. of impure propiophenone was recovered.) After cooling to 0°, the aqueous solution was acidified with cold sulfuric acid (4 ml. of acid in 25 ml. of water), and the liberated β-keto acid (an oil or crystals at this

point) was extracted with ether. Five extractions were carried out. The ether was evaporated in a stream of nitrogen. The residual acid was dissolved in a minimum of benzene at room temperature and an equal volume of petroleum ether (usually of low boiling range, although not a requirement) was added. Crystallization occurred either spontaneously or upon stirring with a rod. More petroleum ether was added until there was a 2 to 3-volume excess. After cooling on dry-ice, the supernatent liquid was poured off, and the crystals were dried under vacuum. Drying removed small amounts of water, permitting better control of the crystallization. The acid crystals were dissolved in a minimum of benzene at 35°, and an equal volume of petroleum ether was added quickly and without stirring. If at this point the solution was left undisturbed, large crystals could be obtained. Stirring resulted in the rapid formation of fine crystals. Two additional volumes of petroleum ether were added, and crystallization was completed in a refrigerator. After the mother liquor was poured off and the solid was dried, 9.7 g. (54.5 mmoles) of 2-benzoylpropionic acid was obtained, m.p. 77-78°; yield 61%.

Synthesis of 2-Benzoylpropionic Acid-1-C^{14}

A solution of the sodium derivative of propiophenone was prepared as described in the previous synthesis using 150 ml. of liquid ammonia, 12.2 g. (90 mmoles) of ketone, 2.16 g. (93 mmoles) of metallic sodium and 90 ml. of dry ether. In the meantime, apparatus D was assembled and evacuated for 2 hours. The dropping funnel contained 90 ml. of concentrated sulfuric acid. The generating flask contained 12.21 g. (63 mmoles) of oven-dried barium carbonate, 136 mg. of which was "hot" (490 μc.), on top of which was packed a wad of glass wool to prevent spattering. The

system was filled with dry nitrogen and the enolate solution was transferred to the reaction vessel by means of a drawn-down tube. After reassembly, the reaction tube was cooled in liquid nitrogen, and the apparatus was again evacuated. Sulfuric acid was introduced over a period of 2 hours, after which the mixture was heated for 15 minutes. The carbonation tube was then sealed off, removed from the liquid nitrogen, wrapped in a towel and shaken for 45 minutes to complete the carbonation.

The tip of the tube was broken off and the contents was decomposed with a small amount of water. The ether layer was washed twice with water and the combined aqueous solutions were extracted 3 times with ether. After cooling to 0°, the aqueous phase was acidified with 6 ml. of concentrated sulfuric acid in 40 ml. of cold water. The acid thus liberated was recovered and recrystallized once as previously described for the "dead" acid. The 6.32 g. (35.5 mmoles) of acid represented a yield of 56%, based on barium carbonate. Activity: 8 μc./mmole.

Synthesis of 2-Benzoylpropionic Acid-Carbonyl-C^{14}

Preparation of Benzoic Acid-1-C^{14}: This technique was decided upon after considering many of the methods that have been reported in the literature.

A solution of phenylmagnesium bromide was prepared under nitrogen from 2.1 ml. (20 mmoles) of bromobenzene in 25 ml. of ether and 0.50 g. (21 mmoles) of magnesium turnings, using magnetic stirring. After dilution with 20 ml. of ether, this solution had a normality of 0.434 as determined by titration (30).

Twenty ml. (8.68 mmoles, 20% excess) of the Grignard solution was

placed in the reaction tube of apparatus D. The 65-ml. conical generating flask contained 1.40 g. (7.1 mmoles) of barium carbonate, 0.0545 g. of which contained 2 mc. of activity. Carbon dioxide was generated and condensed as described in the last synthesis. The reaction tube was sealed off and brought slowly to -20°, where it was held for 15 minutes to complete the carbonation. The tube was frequently shaken.

The tube was opened and its contents acidified with 10 ml. of 2N hydrochloric acid. The aqueous layer was continuously extracted with ether for 14 hours. The ether layer was evaporated in the presence of an excess of sodium carbonate solution, and the ether extracts were added and evaporated. This basic solution was extracted with ether for 6 hours. The aqueous phase was acidified with dilute hydrochloric acid and cooled. The crystals of benzoic acid were filtered off, washed and dried. Additional acid was obtained from the mother liquor, giving a total of 0.76 g. (6.3 mmoles) of benzoic acid, m.p. 122-123°, Yield: 88%. Activity: 340 μc./mmole.

Preparation of Benzoyl-1-C^{14} Chloride: This is a personal adaptation of a common preparative reaction.

In a small pear-shaped flask 4.88 g. (40 mmoles) of benzoic acid, 0.323 g. (900 μc.) of which was from the above preparation, was heated under reflux for 1 1/2 hours with 6 ml. of thionyl chloride (100% excess). Most of the excess thionyl chloride was distilled off through a short Metroware column. Distillation was continued after addition of 10 ml. of petroleum ether (66-75°). Heating was stopped after all the low-boiling components had distilled and benzoyl chloride was refluxing in the column. The latter was distilled directly into a cooled, vertical receiver constructed from a 15-ml. centrifuge tube having a stopcock

at the bottom. There was collected in 91% yield 5.12 g. (36.5 mmoles) of product, b.p. 190-193°. Two portions of "dead" benzoyl chloride were distilled through the apparatus, giving finally 8.2 ml. of material.

Preparation of Propiophenone-1-C^{14}: A modification of the method of Cason (21) was used.

In a 300-ml., 3-neck flask equipped with a condenser, dropping funnel and Hershberg stirrer, a Grignard reagent was prepared over a period of one hour using 3.35 g. (140 mmoles) of magnesium turnings and excess (13 ml.) bromoethane in 70 ml. of sodium-dried ether. To the stirred, ice-cold solution was added over a 5-minute period 13.7 g. (75 mmoles) of powdered cadmium chloride, previously dried at 120°. The mixture was heated under reflux for 30 minutes. Forty ml. of ether was distilled off, 65 ml. of benzene was added and an additional 35 ml. of distillate was collected. After adding 50 ml. of benzene and cooling, the 8.2 ml. of benzoyl-1-C^{14} chloride from the previous preparation in 15 ml. of benzene was added over a period of 2 minutes. The temperature was allowed to rise to 40° and was maintained at 35-40° for 3 hours. Stirring was difficult because of the thickness of the suspension.

The mixture was decomposed with sulfuric acid and ice. The aqueous layer was washed twice with ether. The benzene layer plus ether extracts was washed successively with water, 5% sodium carbonate solution, water and a saturated sodium chloride solution. Most of the ether was evaporated in a nitrogen stream. Much of the remaining solvent was removed through a fractionating column. The residue was vacuum-fractionated using a semimicro column. After collecting 1.0 ml. of forerun, 6.6 g. (50 mmoles) of product, b.p. 100-102° at 15.5 mm., was obtained, representing a 72% yield. Scavenger ketone was added to the distilling

flask and distilled, giving finally 12.0 g. of propiophenone-1-C^{14}.

Preparation of 2-Benzoylpropionic Acid-Carbonyl-C^{14}: The acid was prepared from the propiophenone-1-C^{14} exactly as described for the "dead" acid. After two crystallizations, 9.6 g. (54 mmoles, 60% yield) of product was obtained.

The presence of benzamide was suspected in the product. The acid was dissolved in excess 1N potassium hydroxide and extracted overnight with ether. On evaporation of the ether, 0.25 g. of benzamide remained. The aqueous phase was acidified and extracted with ether. The ether was evaporated and the residue was crystallized twice.

On drying, the acid consisted of "flowing" crystals; that is, they appeared wet. The melting point was a little low--76°. A mixture of 5.14 g. of this labeled acid and 2 g. of pure "dead" acid was dissolved in 30 ml. of benzene. Ten ml. of petroleum ether was added and crystallization was allowed to proceed without disturbance. A total of 60 ml. of petroleum ether was added. No cooling was employed. The large crystals were dried, powdered and dried again under vacuum. This material gave every indication of being pure. Activity: 7.2 μc./mmole.

Synthesis of 2-Benzoylpropionic Acid-2-C^{14}

Preparation of Sodium Acetate-1-C^{14}: This is principally the method of Lamprecht and Rehberg (36) with the recovery technique of Murray (39) and is similar to the benzoic acid synthesis.

Into the carbonation tube of apparatus D was placed 20 ml. of an ether solution of methylmagnesium iodide (15 mmoles), prepared in the usual manner. Twenty-five ml. of concentrated sulfuric acid was added slowly to the 35 ml. flask containing 0.985 g. (5 mmoles) of barium

carbonate, 17.6 mg. of which represented 1.42 mc. of activity. The sealed reaction tube was allowed to warm slowly until the ether started to melt. It was then wrapped in a towel and shaken for 1/2 hour.

The contents of the tube was transferred to a 10-ml. flask, cooled, and 20 ml. of water slowly added. The ether was evaporated in a nitrogen stream after adding 10 ml. of 20% sodium hydroxide solution. After adding 3.06 g. (about 7% excess) of silver sulfate, the mixture was heated to near-boiling, then cooled to near-freezing, and 10 ml. of cold 50% sulfuric acid was added. The mixture was subjected to steam distillation using superheated steam. Almost all of the acetic acid came over in the first 150 ml. of distillate, although another 100 ml. was collected. The distillate was titrated to an end-point of pH 8.0 using a pH meter, and required 21.7 ml. of 0.208N sodium hydroxide, corresponding to 4.50 mmoles (90% yield) of acetic acid.

Part of this solution was lost. The remainder was evaporated to a small volume, transferred to a 50-ml. pear-shaped flask (with thermometer well) and evaporated to dryness at 140°. The final amount of sodium acetate-1-C^{14} was 0.337 g.

Preparation of Ethyl Acetate-1-C^{14}: This is a simplified version of Ropp's method (48).

The labeled sodium acetate from the above synthesis was diluted with dry "dead" salt to 2.40 g. (29 mmoles), and 10 ml. of freshly-distilled ethyl phosphate was added, along with some boiling chips. The flask was placed on one end of the yoke portion of apparatus D, a small receiving flask placed at the other, and the joint to the vacuum line was stoppered. The system was not evacuated. The reaction flask was heated slowly to 190-200° while the receiver was cooled in liquid

nitrogen. Most of the ester came over between 160-190° over a period of 10 minutes. After 15 minutes at 200°, the flask was cooled and 1 ml. of "dead" ester added and distilled. The product was distilled once on the vacuum line into a graduated receiver. If complete recovery of the scavenger is assumed, 2.43 g. (27.5 mmoles) of ethyl acetate-1-C^{14} was recovered. Yield: 95%.

Preparation of Bromoethane-1-C^{14}: The 3.33 g. of "hot" ethyl acetate, diluted to 3.6 g. (41 mmoles) was mixed with 20 ml. of sodium-dried ether and added dropwise to a magnetically-stirred mixture of 0.91 g. (24 mmoles) of lithium aluminum hydride and 30 ml. of ether contained in a 100-ml. 2-neck flask. After reduction was complete, the ether was removed as completely as possible on the vacuum line.

The flask was then equipped with a dropping funnel, having a nitrogen inlet attached, and a short reflux condenser. The top of the condenser was designed so that it could be cooled with dry-ice and was connected in series to a soda-lime tube heated to 40° and a receiver containing phosphorus pentoxide, which in turn led to a mercury valve. The flask was cooled in liquid nitrogen and its contents was thoroughly wetted with 15 ml. of cold 48% hydrobromic acid. A cold mixture consisting of 16 ml. of concentrated sulfuric acid and 30 ml. of 48% hydrobromic acid was added all at once. With no nitrogen coming in, the flask was heated to 100° while the top of the condenser was cooled with dry-ice. Under these conditions no bromoethane could distill over. After 15-30 minutes the dry-ice was removed, nitrogen was led in, and the temperature was slowly raised to 160°. After no more bromoethane appeared to come over, the material in the receiver was distilled on the vacuum line through a tube containing Drierite and phosphorus pentoxide into another

receiver containing calcium oxide. The product was distilled from the calcium oxide through a similar tube into a graduated receiver. The 5.8 ml. (8.30 g., 75 mmoles) of pure bromoethane represented a 92% yield (95% on "dead" runs).

Preparation of Sodium Propionate-2-C^{14}: A Grignard reagent was started using 0.8 ml. of "dead" bromoethane in 15 ml. of dry ether and 2.2 g. (92 mmoles) of magnesium turnings. The 5.8 ml. of "hot" bromoethane in 145 ml. of ether was then added slowly. After stirring for 1/2 hour, the solution was poured onto an excess of dry-ice.

The acid was recovered as described for acetic acid. The 900 ml. of distillate collected required 79.2 ml. of 1.003N sodium hydroxide solution to titrate it to a pH 7.7 end-point. About 500 ml. of water was distilled off. The residual liquid was treated with Norite, filtered and evaporated at 130-140° to a constant weight of 7.60 g. The yield (79.3 mmoles by titration; 79.2, by weight) was 92%.

Preparation of Propiophenone-2-C^{14}: The method of Speer and Jeanes (56) was employed. For detailed directions see reference 52, p. 662.

A mixture of 8.49 g. (88.3 mmoles) of sodium propionate, (7.60 g. of which was "hot"), 48.5 g. (335 mmoles) of anyhdrous aluminum chloride and 45 ml. (39.5 g., 507 mmoles) of dry benzene was stirred magnetically and heated under reflux for 15 hours. The dark-brown solution was poured carefully onto cracked ice and acidified with hydrochloric acid. The aqueous layer was washed three times with ether. The combined organic portions were washed with 50 ml. of 0.2N sodium hydroxide and dried for 2 hours over anhydrous magnesium sulfate. Most of the solvent was removed in a nitrogen stream. The remainder was distilled off through

a semimicro column. The residue gave no forerun and very little residue on fractionation; yield 10.15 g. (86%), b.p. 98-100° at 14 mm. A single scavenger operation gave finally 12.43 g. of ketone.

Preparation of 2-Benzoylpropionic Acid-2-C^{14}: This was carried out exactly as described for the "dead" acid using the 12.43 g. of labeled propiophenone. After two crystallizations, 10.1 g. (57 mmoles, 61% yield) of acid was obtained. Activity: 8.0 μc./ mmole.

Properties of 2-Benzoylpropionic Acid

The melting point of the acid has been reported (34) to be 82-83°. The melting points of such unstable compounds depend, of course, on the rate of heating. However, all of the purified acids used in this work gave an apparent melting point of 77-78° in a Fisher-Johns (hot stage) melting point apparatus. Decomposition is rapid at this temperature.

The high degree of purity of the acids was shown in a number of ways. The molecular weight of the "dead" acid was determined by titration of 0.1 g. samples with 0.05N sodium hydroxide solution using a 3:1 thymol blue-cresyl red indicator. The molecular weight was calculated to be 178.8±0.2 compared to the actual value of 178.2.

On complete decarboxylation, the acids gave volumes of carbon dioxide within 1% of the theoretical amount.

The ultraviolet spectra of all of the acids were run on a Beckman DK spectrophotometer, covering the range of 220-360 mμ. The absolute ethanol solutions were all of the same concentration. The curves obtained were essentially identical in form and height, exhibiting one maximum at about 242 mμ.

Kinetics of the Decarboxylation of 2-Benzoylpropionic Acid

These studies were carried out principally at two different temperatures--68 and 78°. One run was made at 58° using acid only, but the reaction reached nearly 60% completion before a homogeneous solution was obtained. It could have been run in a solvent, but this seemed to be unnecessary in view of sufficient data at the other two temperatures. This run will not be discussed further except to say that it appeared to be consistent with the results of the other runs.

The constant-temperature bath was controlled to within ±0.02° using a mercury-expanding vapor-type thermoregulator. At 78° the vaporizing liquid was ethanol; at 68°, isopropyl ether.

Apparatus B (see Appendix) was used exclusively for the kinetic runs reported here. Apparatus A was used in the beginning when pure solid was to be decomposed with no stirring. The results were essentially the same with both pieces of equipment.

To make a run, a sample of acid was weighed in the reaction tube, and solvent was added if called for. The mercury was adjusted in the gas-measuring tube (this was a section of a 100-ml. burette) to a height which experience had shown would give a known "zero volume" reading at the temperature to be used, and the reaction tube was put in place. Time was recorded from the moment the apparatus was immersed in the constant-temperature bath. The pressure inside the apparatus was maintained close to atmospheric by following the volume change with the mercury leveling bulb. Volume readings were recorded periodically.

To illustrate the kind of data that were necessary, all the information pertinent to Series III, Run 1, has been given below:

Run #1: acid + stirring + 1 ml. of 1,1-diphenylethane

Temperature: 78° Weight of tube + sample 13.0279
Barometric pressure: 737 mm. Weight of tube 12.8944
Pressure of CO_2: 732 mm. Weight of sample 0.1335 g.

C_o = 0.749 mmole Volume correction: 0.6 ml. - 0.9 ml. = -0.3 ml.

$Y = 3.34 \times 10^{-2}$ ml./mmole

Time	Volume Reading, ml.	Corrected Volume, ml.	C'_{CO_2}, mmoles	C'_A, mmoles
12:50	start			
54	7.5	7.2	0.240	0.509
55	9.2	8.9	0.297	0.452
56	10.7	10.4	0.348	0.401
57	12.0	11.7	0.391	0.358
58	13.1	12.8	0.428	0.321
59	14.1-	13.8-	0.460	0.289
1:00	14.9	14.6	0.487	0.262
02	16.3	16.0	0.534	0.215
04	17.35	17.05	0.570	0.179
06	18.25	17.95	0.600	0.149
08	18.9	18.6	0.621	0.128
10	19.45	19.15	0.640	0.109
12	19.95	19.65	0.657	0.092
14	20.3	20.0	0.670	0.079
20	21.15	20.85	0.697	0.052

The barometric pressure was, of course, necessary. This was not, however, the pressure of the carbon dioxide. Although the vapor pressure of the 1,1-diphenylethane was negligible, that of the propiophenone formed was not, amounting to 5 mm. at 78°, 3 mm. at 68° and 1 mm. at 58°. The appropriate value was subtracted from atmospheric pressure to give the partial pressure of the carbon dioxide. C'_o, as previously defined, is the initial quantity of acid. The volume correction, to be subtracted from the volume readings, consists of two terms, the solubility correction and the "zero volume" reading.

The correction for carbon dioxide solubility was determined using

both 1,1-diphenylethane and propiophenone saturated with carbon dioxide at 68 and 78° under both stirring and nonstirring conditions. In addition, at the end of two runs (the above example was one of them) the amount of gas in the residual liquid was determined. This was done using a Van Slyke blood gas analyzer. The liquids from the two sources gave somewhat different results. A value of 0.6 ml. of gas/ml. of liquid was selected as the best value for both solvents at both temperatures. This is the largest source of error whenever solvents were used.

"Y" is simply the factor P/RT which converts milliliters of carbon dioxide to millimoles. C_A' is the difference, $C_o' - C_{CO_2}'$. This quantity, when plotted on semi-log paper against time, should give a straight line if the reaction is first order.

As will be seen later, the plot of C_A' against time invariably gives a smooth curve, the major error in which is not due to the randomness of the points. Therefore, rather than record all of the mass of data for all of the runs, only the conditions--temperature, sample size, and so on--will be given (Table I). By the use of the graphs in the RESULTS section, which are really a summary of the data, any unknown quantities can be found by back-calculation.

Radioactivity Assay of Carbon-14-Labeled Compounds

Assays were made by the wet combustion procedure (41) using the wet combustion apparatus illustrated in the Appendix. Five to ten mg. samples were weighed out on a microbalance in platinum boats, which were placed in the combustion tube, C, along with a pinch of potassium iodate. When the combustion tube was not in place, "dead" carbon dioxide continually passed through the apparatus. With the tube in place and D full of Van

TABLE I

EXPERIMENTAL CONDITIONS FOR THE KINETIC STUDIES

Solvent: A= 1,1-diphenylethane, B = propiophenone

Series	Run	Temperature °C	CO_2 Pressure mm.	C_o' mmoles	Volume Correction ml.	Stirring	Solvent
I	1	78	745	0.562	0.8	no	none
	2		732	0.752	0.8	no	none
	3		732	0.752	0.9	yes	none
	4		732	0.582	0.9	yes	none
II	1	68	739	0.745	0.5	no	none
	2		739	0.525	0.5	no	none
	3		741	0.508	0.6	yes	none
	4		744	0.711	0.6	yes	none
III	1	78	732	0.749	0.3	yes	1.0 ml. A
	2		732	0.518	0.3	yes	1.0 ml. A
	3		738	0.541	-0.2	yes	2.0 ml. A
IV	1	68	750	0.749	0.0	yes	1.0 ml. A
	2		750	0.509	0.0	yes	1.0 ml. A
V	1	78	734	0.570	1.0	yes	0.3 ml. B
	2		734	0.566	1.0	yes	0.5 ml. B

Slyke solution, an evacuated ionization chamber (evacuated, or flushed with carbon dioxide at F) was moved to G and opened after stopcock H was moved from "flush" to "straight through." The combustion tube was half-filled with Van Slyke solution, heated for 1 minute, filled completely and again heated for a minute. "Dead" carbon dioxide was let in through I until the pressure inside the chamber reached atmospheric. Counting was done on the vibrating reed electrometer. The U-tube, E, contained coarse crystals of stannous chloride.

Generally, the Van Slyke solution was made as follows: To a mixture of 2.5 g. of potassium iodate, 12.5 g. of chromium trioxide and 50 ml. of 85% phosphoric acid was added slowly 166 ml. of 20% fuming sulfuric acid. However, in order to get consistent readings with 2-benzoylpropionic acid-2-C^{14}, it was necessary to switch to a preparation consisting of 5 g. of potassium iodate, 25 g. of chromium trioxide, 167 ml. of 85% phosphoric acid to which phosphoric pentoxide was added to bring it to about 100%, and 333 ml. of 25% fuming sulfuric acid (20). This solution also proved to be much more stable than the former.

The vibrating reed electrometer gives readings in terms of millivolts, which may be converted to microcuries with the aid of the following constants:

1.39×10^{-6}	coulombs/disintegration (for carbon-14 in carbon dioxide)
3.7×10^{10}	disintegrations/second for one curie
1.0×10^{10}	ohms (resistance of the #3 resistor)

From these constants the conversion factor 0.01945 μc./mv. can be obtained.

Determination of the Isotope Effects

Isotope effects were calculated using the equation

$$\frac{k^*}{k} = 1 + \frac{\log (A_f/A_o)}{\log (1 - f)}$$

previously discussed on page 25. The fractional extent of reaction, f, was determined from the volume of carbon dioxide given off (taking the solubility into account) and the final theoretical volume of gas. The latter could be used satisfactorily, because it was shown a number of times that the final volume of carbon dioxide at complete decarboxylation was very close to theoretical (within 1%).

The reactions were carried out in apparatus A, C, or C modified with a top portion analogous to B, which simply replaced the stopper. Apparatus A was used for 0.2500-g. samples; C, for 0.5000-g. samples; modified C, for decarboxylations in 1,1-diphenylethane.

A reaction was stopped by removing the apparatus from the bath and adding an excess of 0.2N sodium hydroxide to the sample tube. The two phases were poured into a 15-ml. centrifuge tube and "whipped" with a microspatula to insure that all of the acid was converted to its sodium salt. The sample tube was rinsed with more base and finally a little water. The final volume was about 5 ml. The propiophenone was extracted three times with ether, again using the whipping technique and drawing off the ether with a dropper. The aqueous solution was cooled, acidified with cold, dilute sulfuric acid and extracted five times with ether. The ether extracts were placed in another 15-ml. centrifuge tube, and the ether was evaporated in a nitrogen stream. About 0.5 ml. of benzene was added, and the acid was crystallized by addition of 2 ml. of petroleum ether. The acid was recrystallized using 0.5-1.0 ml. of benzene and

1.5-3.0 ml. of petroleum ether. The mother liquor was poured off, and, after rinsing with a little mixed solvent, the crystals were dried under vacuum in the centrifuge tube. The recovered acid was then ready to be assayed, along with samples of the original acid, to give values of A_f and A_o. A sample of the original acid was also put through this recovery treatment for purposes of control.

The experimental conditions important in the decarboxylations have been tabulated below. The volume of carbon dioxide has been corrected for solubility.

TABLE II

EXPERIMENTAL CONDITIONS FOR THE DECARBOXYLATION OF LABELED ACIDS.

Sample weight: A = 0.5000 g., B = 0.2500 g.

Compound	Temperature, °C	Sample Weight	Pressure of CO_2, mm.	Volume of CO_2, ml.
2-Benzoylpropionic Acid-1-C^{14}	58	A	742	70.0
		A	739	65.0
		A	739	67.5
	78	A	734	69.8
		A	734	64.8
		B	734	25.3
2-Benzoylpropionic Acid-Carbonyl-C^{14}	78	B	738	26.3
		A	738	65.0
		A	738	70.8
2-Benzoylpropionic Acid-2-C^{14}	78	B	745	24.3
		A	745	71.0
		A	745	63.8
2-Benzoylpropionic Acid-2-C^{14} + 5 ml. of 1,1-diphenylethane	78	A	734	73.6
		A	742	67.6

RESULTS

Kinetics of the Decarboxylation of 2-Benzoylpropionic Acid

Results of the kinetic studies have been summarized in the form of five graphs, shown on the following pages. Only for Run 1 of Series III have all of the experimental points been plotted. This is enough to illustrate the smoothness of the curves.

No readings were made until after the reaction had proceeded for 5 minutes (30 minutes for pure solid at 68°). By this time temperature equilibrium had been reached, and the reaction mixture had become one phase. The reaction rate was quite low until liquid began to form, and increased until the mixture was homogeneous.

Various extents of reaction have been indicated on the graphs. These usually range from 20-90% decomposition.

A vertical line represents the error in the value of C_A' at whatever point it crosses a curve. These have been determined from the errors in the carbon dioxide volumes, which in turn have been estimated on the basis of the errors involved in the "zero volume" reading and in the solubility correction. These are all estimated errors and do not represent statistical treatment of any of the data.

The half-life, τ, for each of the runs has been determined directly from the graphs. Since the curves are, in general, not straight, τ for both the initial and the final portion of the curves has been estimated. From the average values of τ for the initial part of the reaction, the

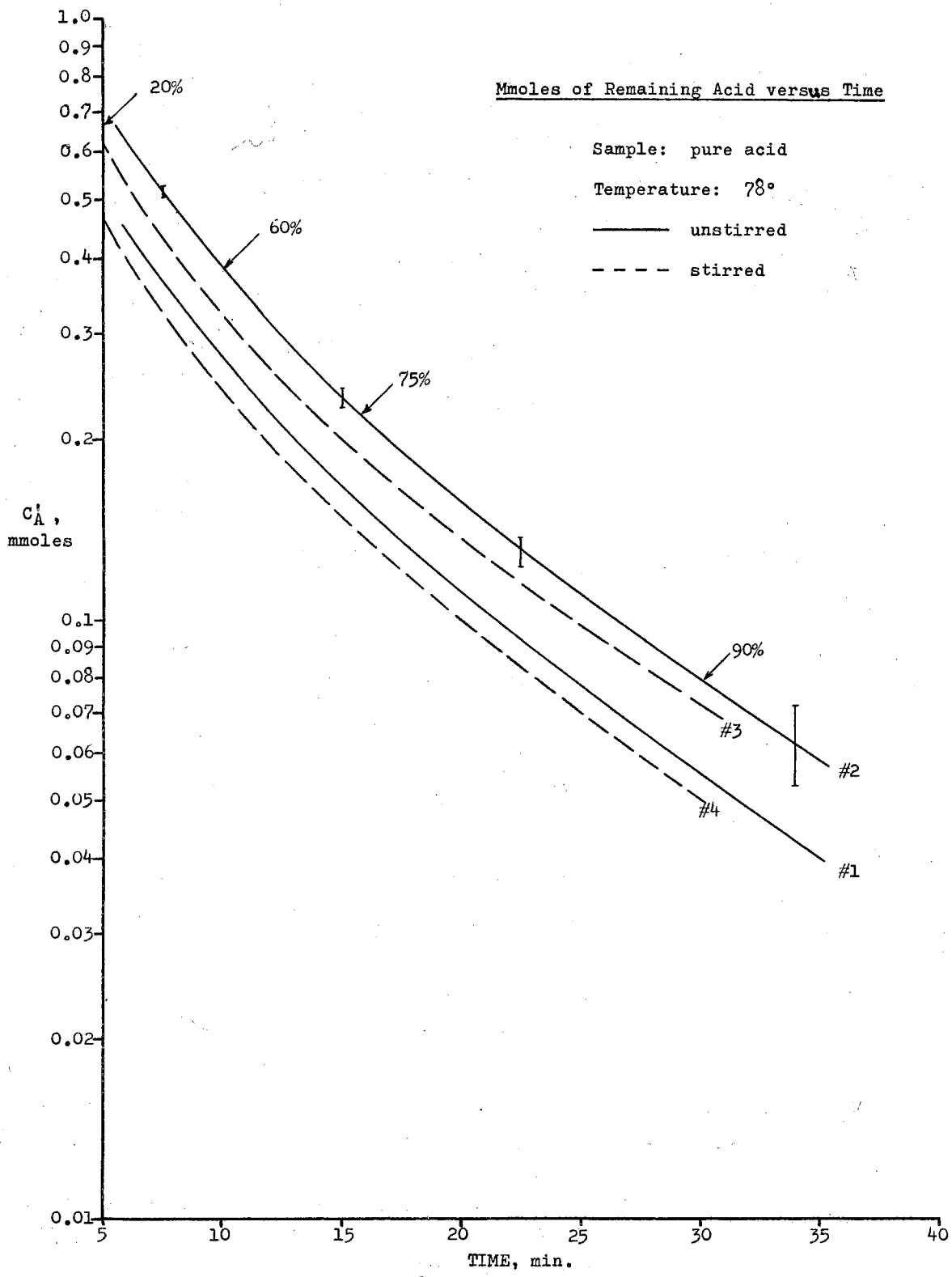


Figure 1. Decomposition of 2-Benzoylpropionic Acid: Series I

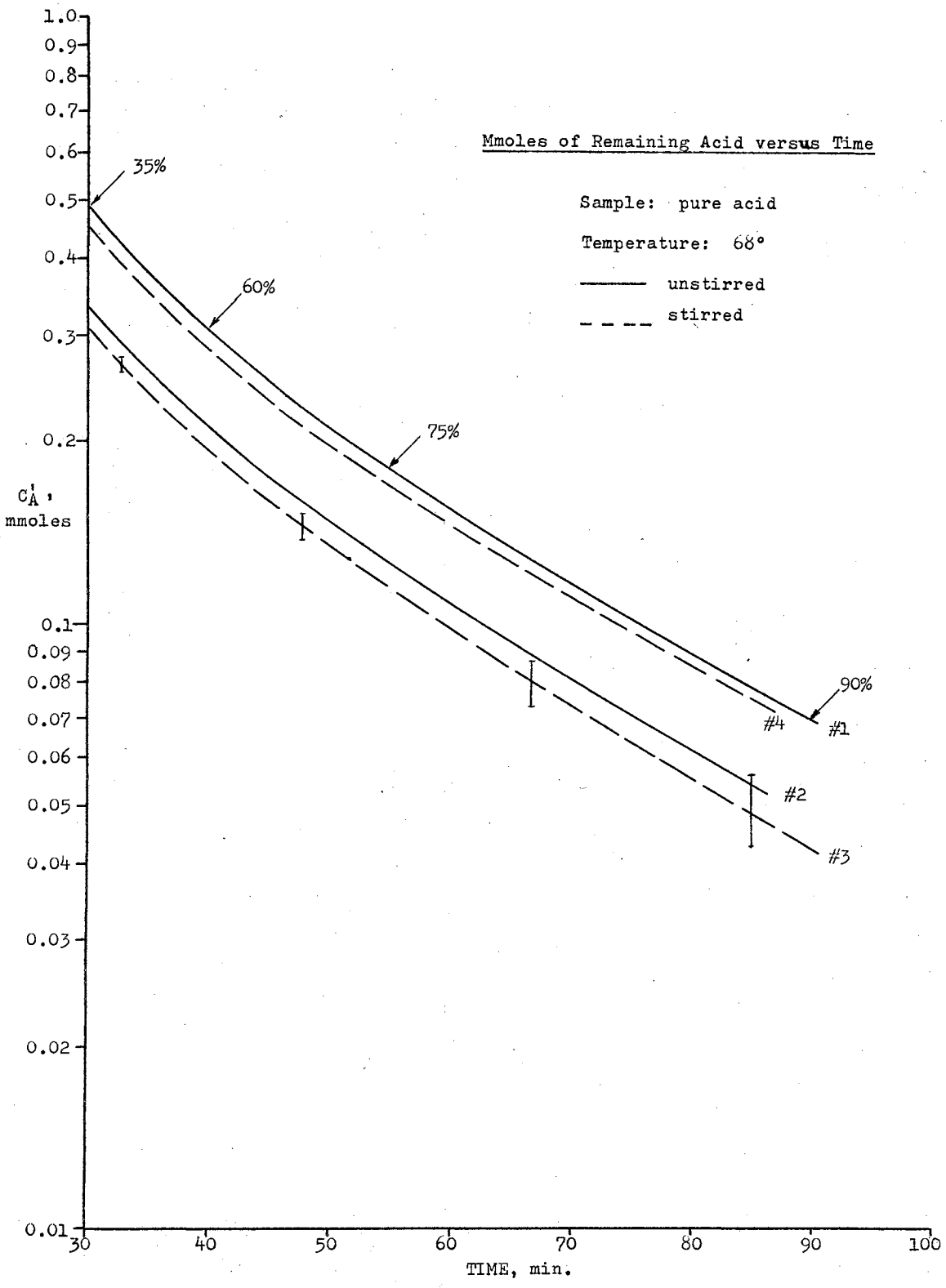


Figure 2. Decomposition of 2-Benzoylpropionic Acid: Series II

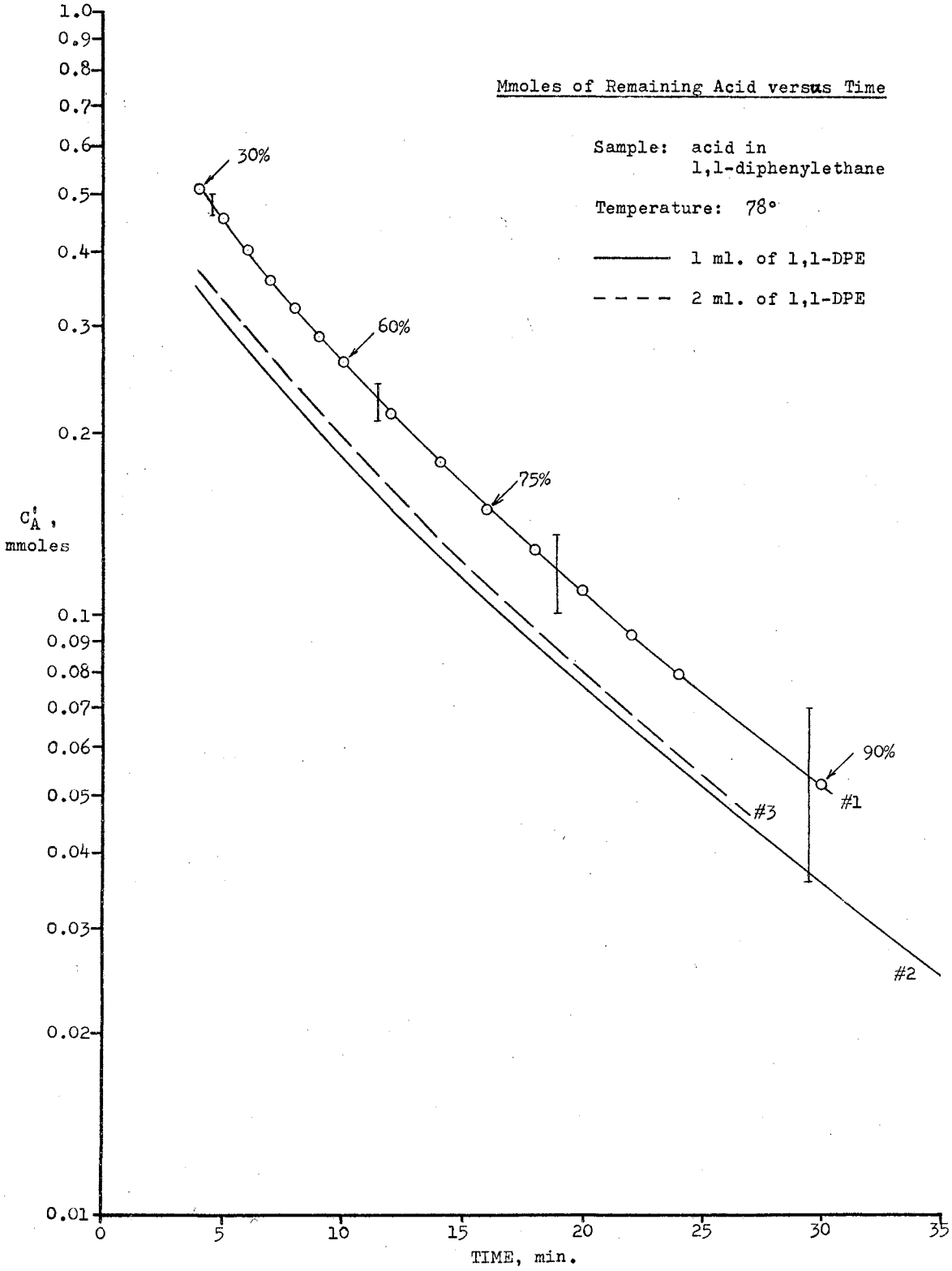


Figure 3. Decomposition of 2-Benzoylpropionic Acid: Series III

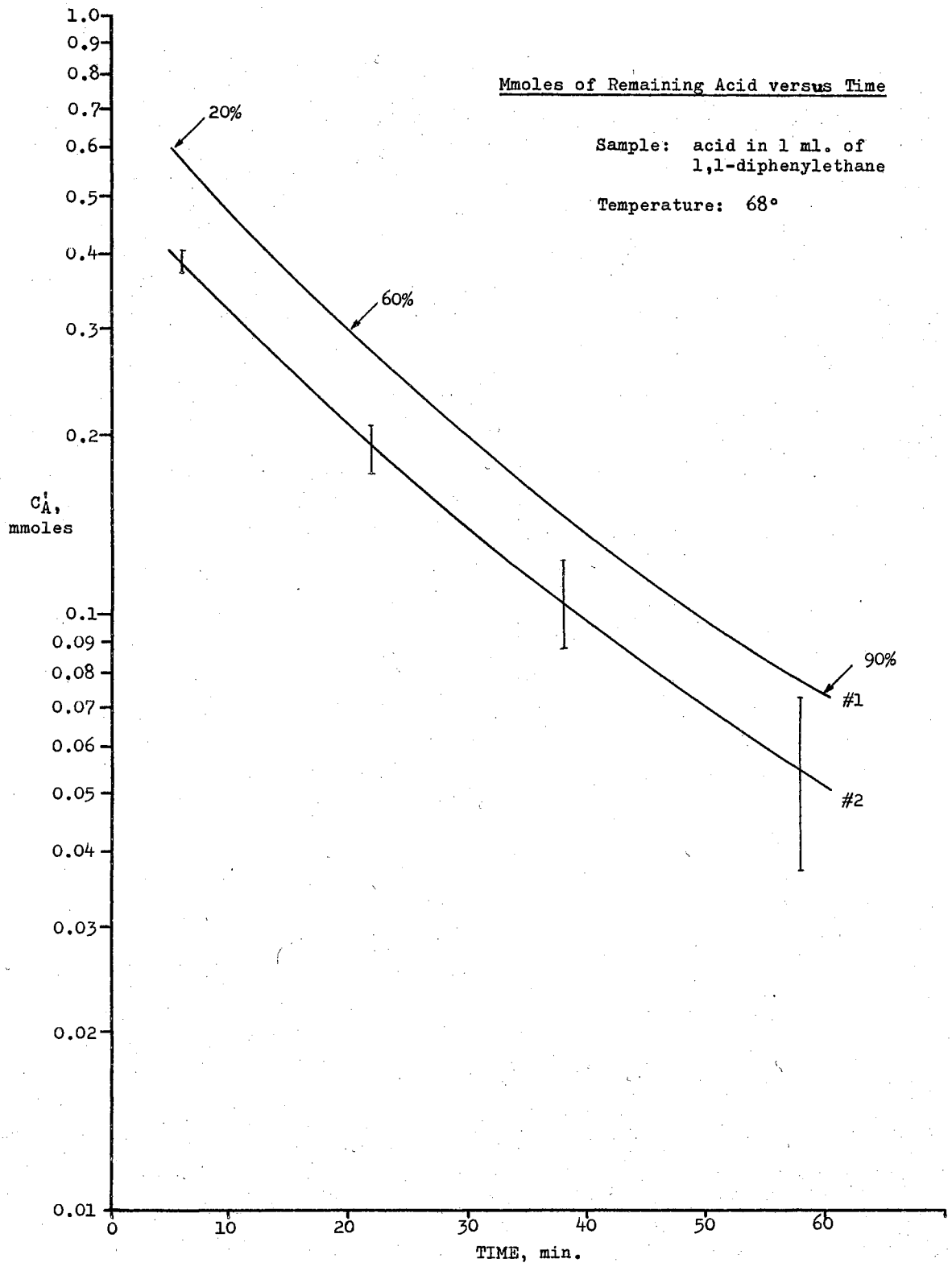


Figure 4. Decomposition of 2-Benzoylpropionic Acid: Series IV

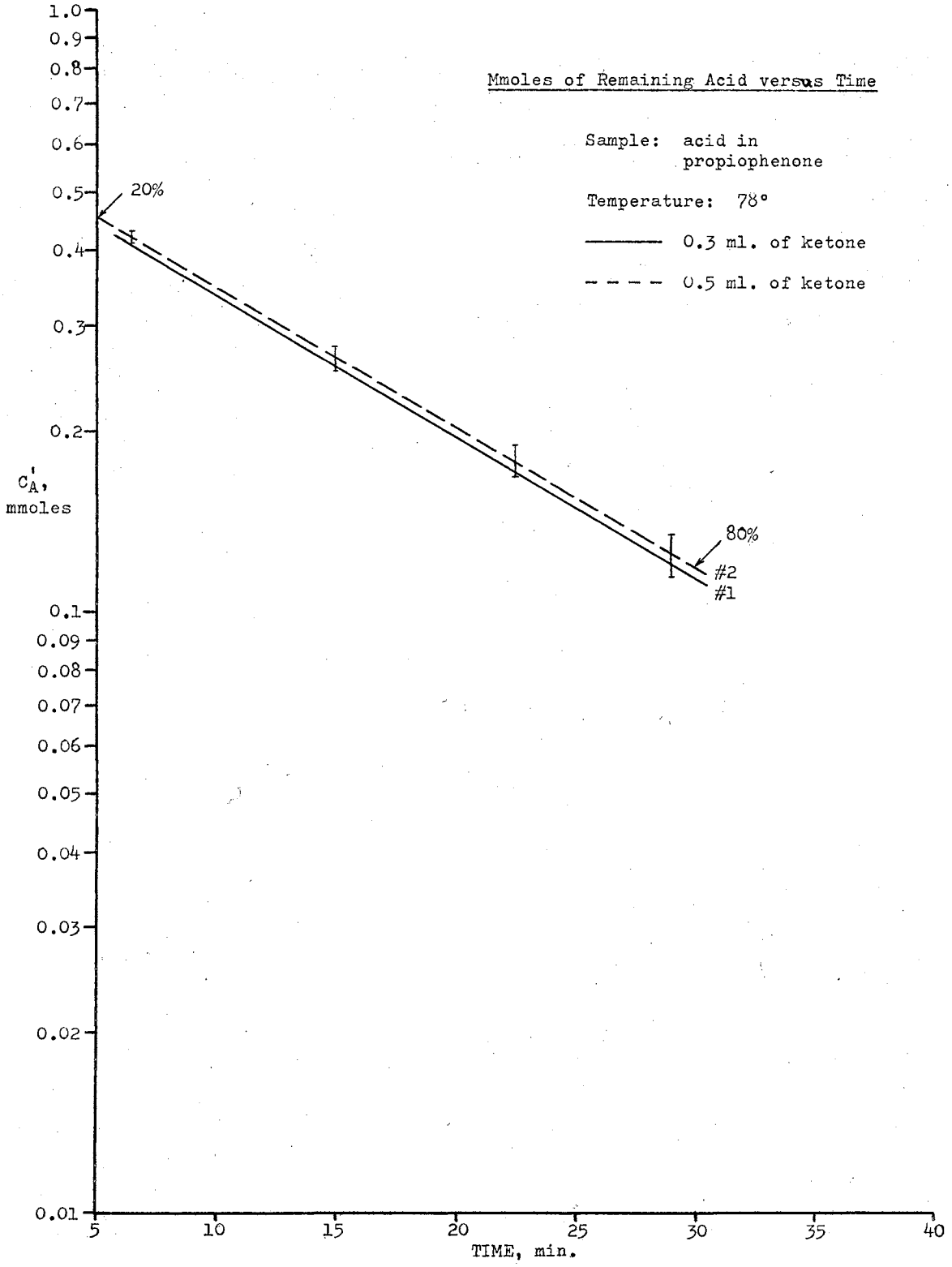


Figure 5. Decomposition of 2-Benzoylpropionic Acid: Series V

reaction rate constants have been determined from the relation

$$k = \frac{2.3 \log 2}{\tau}$$

Only the average deviation of the mean has been given as a measure of the precision.

TABLE III

HALF-LIVES AND SPECIFIC REACTION RATE CONSTANTS FOR THE DECARBOXYLATION OF 2-BENZOYLPROPIONIC ACID UNDER VARIOUS CONDITIONS

1,1-DPE = 1,1-diphenylethane

Figure	Reaction Conditions	Half-Lives, min.		Initial Specific Rate Constants, $sec.^{-1} \times 10^3$
		Initial	Final	
1	78°, pure solid	5.6±0.15	10.6±0.50	2.07 ±0.055
2	68°, pure solid	14.0±0.25	26.1±0.50	0.834±0.015
3	78°, in 1,1-DPE	6.2±0.23	9.3±0.37	1.870±0.068
4	68°, in 1,1-DPE	14.8±0.65	22.5±1.5	0.784±0.035
5	78°, in propiophenone	12.7±0.25	12.7±0.25	0.918±0.018

The Observed Kinetic Isotope Effect

The activities of all of the acid samples assayed have been included in Table IV along with other pertinent information. The individual activity measurements are averages of ten converted millivolt readings as obtained from the strip chart of the recording apparatus of the electrometer. The specific activities were averaged for each sample, and 95% confidence levels were determined using the Student-t-distribution (71).

Table V gives the observed isotope effects obtained with the aid of equation 6 and the data from Table IV. Again 95% confidence levels have been determined for the average isotope effect values.

Table VI deserves a word of explanation. When differences between average values of certain quantities are found, it is important to know if the difference is real, or if it merely occurred by chance. The table gives the probability of the occurrence of the observed differences between various averages, assuming that the true values are identical. The values to be compared have come from Tables IV and V, and have been designated A, B and so on.

As an example, consider the comparison of I and J. The table shows that there is one chance in three that the difference between the isotope effect at 58° and that at 78° would occur under the experimental conditions used; therefore, there is no significant difference between the averages. If the probability were < 0.05, one could say that the difference might be significant; if < 0.01, definitely significant.

This comparison has been made using the "t" test (71).

TABLE IV

ACTIVITIES OF LABELED COMPOUNDS

Compound: 2-BPA = 2-benzoylpropionic acid.
Type of Sample: 0 = original acid; C = control; R = recovered acid

Compound	Temperature, °C	Type of Sample	% Reaction	Activity, μc./mmole	Average Activity	Standard Deviation	95% Confidence Limits	Designation
2-BPA-1-C^{14} (before dilution)	58	0	0.0	8.46 8.26 8.40 8.31	8.358	0.090	0.143	A
		C	0.0	8.21 8.27 8.18	8.220	0.052	0.098	B
		R	89.6	9.70 9.77 9.69	9.720	0.044	0.108	none
2-BPA-1-C^{14} (after dilution)		0	0.0	6.67 6.73 6.64 6.71	6.688	0.040	0.064	C
		C	82.9	6.80 6.70 6.78 6.65	6.732	0.070	0.112	D

(Continued)

Compound	Temperature, °C	Type of Sample	% Reaction	Activity, μc./mmole	Average Activity	Standard Deviation	95% Confidence Limits	Designation
		R		7.69 7.64 7.69 7.64	7.665	0.029	0.047	none
	78	R	86.1	7.62 7.73 7.71	7.687	0.059	0.146	none
		0	0.0	6.84 6.84 6.80	6.827	0.024	0.058	E
		C	0.0	6.76 6.75 6.82	6.777	0.037	0.095	F
		R	83.4	7.80 7.75 7.80	7.783	0.029	0.073	none
		R	77.4	7.56 7.54 7.53	7.543	0.016	0.039	none
		R	60.5	7.25 7.28 7.26	7.263	0.016	0.039	none

(Continued)

Compound	Temperature, °C	Type of Sample	% Reaction	Activity, μc./mmole	Average Activity	Standard Deviation	95% Confidence Limits	Designation
2-BPA-carbonyl-C^{14}	78	0	0.0	7.27 7.24 7.25 7.32 7.31	7.278	0.036	0.041	G
		C	0.0	7.30 7.25	7.275	0.036	0.324	none
		R	63.1	7.27 7.24 7.29	7.267	0.025	0.063	none
		R	78.0	7.32 7.27 7.32	7.287	0.059	0.147	none
		R	85.0	7.30 7.32 7.26	7.293	0.031	0.077	H
2-BPA-2-C^{14}	78	0	0.0	8.11 8.08 8.01 8.14 8.06	8.080	0.049	0.061	none
		C	0.0	8.08 8.09	8.085	0.010	0.090	none

(Continued)

Compound	Temperature, °C	Type of Sample	% Reaction	Activity, μc./mmole	Average Activity	Standard Deviation	95% Confidence Limits	Designation
		R	59.0	8.47 8.44	8.455	0.022	0.201	none
		R	86.2	8.91 8.93 8.92	8.920	0.010	0.025	none
		0	77.4	8.63 8.64	8.635	0.010	0.090	none
2-BPA-2-C^{14} (in 5 ml. of 1,1-diphenylethane)	78		0.0	8.05 8.04 8.05 8.08 8.06	8.056	0.019	0.024	none
		R	87.8	8.95 8.93 8.94	8.940	0.010	0.025	none
		R	81.3	8.78 8.79 8.75 8.77	8.77	0.017	0.028	none

TABLE V

OBSERVED ISOTOPE EFFECTS

Abbreviations are same as in Tables III and IV

Compound	Temperature °C	% Reaction	Isotope Effect, k/k*	Average k/k*	Standard Deviation	95% Confidence Limits	Designation
2-BPA-1-C^{14}	58	89.6	1.071				
		82.9	1.084	1.077	0.0056	0.0139	I
		86.1	1.076				
	78	83.4	1.079				
		77.4	1.072	1.074	0.0044	0.0109	U
		60.5	1.071				
2-BPA-carbonyl-C^{14}	78	63.1	0.998				
		78.0	1.001	1.000	0.0017	0.0043	none
		85.0	1.001				
2-BPA-2-C^{14}	78	59.8	1.053				
		86.2	1.053	1.051	0.0035	0.0086	K
		77.4	1.047				
2-BPA-2-C^{14} in 1,1-DPE	78	87.8	1.052	1.053	0.0014	0.0127	L
		81.3	1.054				

TABLE VI

PROBABILITY OF DIFFERENCES WITHIN PAIRS OF AVERAGE ACTIVITIES AND ISOTOPE EFFECTS

Comparison of Averages of X and Y		Probability of the Difference Occurring Due to Chance
X	Y	
A	B	0.07
C	D	0.32
E	F	0.13
G	H	0.55
I	J	0.33
K	L	0.50
J	K	0.01

DISCUSSION OF RESULTS

Kinetics of the Decarboxylation of 2-Benzoylpropionic Acid

The main objective of the kinetic studies was to determine that the decomposition was first order under the same conditions that were to be used for the isotope effect determinations. If this were not the case, a new reaction mechanism would have to be proposed before any theoretical treatment of the isotope effects could be considered.

The graphs included in the previous section hold the solution to this problem. Consider first Series I and II. If no volume change is assumed, the plots of C_A' versus time should give straight lines if the decomposition is first order. However, all of the lines are curved. If anything, the volume of the solution should decrease with time, which would lead to even greater curvature if concentrations were plotted. The fact that the curves are parallel reflects only the comparative precision of the various runs, since the concentration of acid in ketone at any particular time is roughly the same for all of the runs at any one temperature.

That the curvature is real is shown by the magnitude of the experimental errors which have been indicated on the graphs. These are probably maxima. The same decrease in the slope was found in numerous other runs using different acid samples and two different pieces of apparatus.

If 2-benzoylpropionic acid decomposes by a cyclic, concerted mechanism, one would expect this extraordinary decrease in rate. The

carbonyl oxygen of the propiophenone formed in the reaction can form hydrogen bonds with the carboxyl hydrogen of the acid. As the decomposition proceeds, and the relative amounts of ketone increases, more and more acid molecules find it difficult to attain a cyclic configuration. The specific rate constant should therefore decrease, which is the case.

Series III, IV and V represent attempts to prove this hypothesis. The acid was decomposed in 1,1-diphenylethane not only because its vapor pressure was low, but primarily because it cannot show hydrogen bonding as exhibited by the ketone. The curves of Series III and IV still show a decrease in slope, but it is not as large as the decrease exhibited by the acid-ketone system. Dilution would be expected to give such a result.

With reference to Series III and IV, there are two important observations to be made: first, the initial slopes of the curves are very close to those for Series I and II. In other words, 1,1-diphenylethane molecules have little influence on the 2-benzoylpropionic acid. Second, the curves are essentially parallel. In this case the concentrations of the acid in the solvent at any given time vary considerably from one run to another, with a maximum difference of nearly 3 to 1 for Runs 1 and 3. In other words, the half-life of the reaction is independent of the initial reactant concentration.

For any reaction

$$\tau \propto \frac{1}{a^{n-1}} \qquad (10)$$

where a is the initial concentration of reactant and n is the order (28). It is evident that only for a first order reaction is the

half-life dependent of the initial concentration of the reactant. Thus, the decomposition of 2-benzoylpropionic acid has been shown to be first order with respect to the acid, although the specific rate constant varies as the environment of the acid changes.

Series V further demonstrates the influence of propiophenone on the specific reaction rate. The curves in this case are straight because the change in the acid-to-ketone ratio is relatively small. The rate constant calculated from these curves is close to that found for Series I near the end of the runs, which is to be expected. Again the curves are parallel, indicating a first order reaction, but the initial concentrations only differ by a factor of two in this case.

The values for the specific rate constants given in Table III, p. 50, were determined from the earliest possible data because this is the most accurate portion, and because the influence of the propiophenone is at a minimum.

The effect of temperature on the specific reaction rate is reflected in the experimental activation energy, E_a, which is easily obtained from the equation

$$\log k_2/k_1 = \frac{E_a(T_2 - T_1)}{2.3RT_2T_1} \qquad (11)$$

This equation is an integrated form of the Arrhenius equation [see (28) p. 23]. Here k_2 and k_1 are the respective rate constants at temperatures T_2 and T_1. If the values at 78 and 68° for k_2 and k_1 are taken to be 2.07×10^{-3} and 0.834×10^{-3} sec.$^{-1}$, respectively, E_a has a value of 21.8 kcal./mole.

The arguments presented so far have not ruled out Pedersen's

zwitterion as a possible intermediate in β-keto acid decomposition. However, the kinetic data contain the answer to this problem. If a compound breaks down unimolecularly in a linear fashion, as in the case of an acid by the carbanion mechanism, the entropy of activation, $\triangle S^*$, will be zero or positive, since the activated complex is less "ordered" than the reactant molecule. For example, it can be calculated from available data (61) that $\triangle S^*$ for the decarboxylation of the trichloroacetate ion is 23 e.u. On the other hand, if a cyclic intermediate is formed from a non-cyclic reactant, $\triangle S^*$ will be negative, because internal rotations in the reactant become vibrations in the activated complex with a loss in entropy [(28), p. 106].

The equation [(28), p. 96] which relates $\triangle S^*$ to other quantities which are available from experiment is

$$k_r = (kT/h)e^{\triangle S^*/R} \cdot e^{-\triangle H^*/RT} \qquad (12)$$

For a reaction in solution

$$\triangle H^* = E_a - RT \qquad (13)$$

Substituting $E_a - RT$ for $\triangle H^*$ in equation 12, rearranging and taking logarithms of both sides results in the expression

$$2.3R \log \frac{k_r h}{kT} = -\frac{(E_a - RT)}{T} + \triangle S^* \qquad (14)$$

where: k_r = the specific rate constant at temperature T
E_a = the empirical activation energy
h = Planck's constant
k = Boltzmann's constant

All of the quantities in equation 14 that are necessary for the

determination of ΔS^* for 2-benzoylpropionic acid decarboxylation are known. Using the values E_a = 21.8 kcal./mole, $k_r = 2.07 \times 10^{-3}$ sec.$^{-1}$ (from Table III) and T = 351°K, ΔS^* is found to be -11 e.u. The same result is obtained using the value for k_r at 341°K. Thus, the cyclic activated complex is favored over any other type.

Comparison of the Observed Isotope Effects with Those Found by Other Investigators

Because of the lack of data, no comparison can be made of the observed isotope effects with those for the decarboxylation of other simple β-keto acids. Isotope effects found in other acid decarboxylations may be considered, however.

The values of 1.077 and 1.051 for the 1- and 2-labeled 2-benzoylpropionic acids are not unexpected nor abnormal isotope effects as far as magnitude is concerned. Acids which decarboxylate with considerable ease frequently show isotope effects in this range, whatever the mechanism. For example, the decomposition of the trichloroacetate ion at 70° would lead to an isotope effect of about 1.07 if we assume that carbon-14 substitution leads roughly to twice the carbon-13 isotope effects (10). Mesitoic acid shows a higher effect--1.10 (59). These acids decarboxylate by the carbanion mechanism.

Malonic acid, which probably loses carbon dioxide by a cyclic mechanism, gives carbon-14 isotope effects in the same region--1.064 and 1.076 at 154° when labeled in the 1- and 2-positions, respectively (50). This is comparable to the present findings, as far as carboxyl-labeling is concerned. On the other hand, with 2-benzoylpropionic acid-2-C^{14} a lower isotope effect was observed. This was in

contrast to the higher effect found by Ropp and Raaen for malonic acid-2-C^{14}. It is felt that the lower effect observed in this study is real, and is substantiated by statistical treatment of the data. Theoretically, little or no difference should be observed for an acid labeled successively in two adjacent positions (13).

It was previously mentioned (p. 15) that a carbon-13 isotope effect of 1.06 was found for oxaloacetic acid. If this compound behaves as a simple β-keto acid, a value of about 1.12 should be expected if carbon-14 were used. This seems abnormally high, but might be partially explained on the basis of a high activation energy, since the undissociated acid is probably fairly stable (recall that this is true of dimethyloxaloacetic acid).

These comparisons serve to demonstrate that, irrespective of the mechanism, acids upon decarboxylation tend to exhibit carbon-14 isotope effects in the range 1.06-1.12.

The lack of any isotope effect when 2-benzoylpropionic acid-carbonyl-C^{14} decomposes cannot be compared to other findings, since such studies apparently have not been reported in the literature.

The small temperature dependence of the isotope effect observed in the decarboxylation of 2-benzoylpropionic acid-1-C^{14} at 58° and 78° is in keeping with the work of other investigators and, as will be seen below, with theory. It was pointed out on p. 57 that the magnitude of the difference observed in the present case has no actual significance.

Theoretical Evaluation of the Kinetic Isotope Effect

An attempt has been made to evaluate theoretically the isotope

effects for the 2-benzoylpropionic acid decompositions making use of equations 4 and 5, pages 9 and 10. For an accurate calculation one would need the fundamental vibrational frequencies of the molecule and the transition state, for both isotopic species. As this information is often not available even for the normal molecule, the best that can be done theoretically is to make approximate calculations based on models of the transition state. Since the fundamental vibrational frequencies involving carbon-14 bonds have not been determined, they are approximated from the frequencies of the corresponding carbon-12 bonds by application of the harmonic oscillator approximation for the diatomic molecules [(24), p. 165], thus:

$$\frac{w_2}{w_1} = \left(\frac{m_1}{m_2}\right)^{1/2} \qquad (15)$$

where: w = the vibrational frequency in $cm.^{-1}$
m = the reduced mass of the two atoms involved in the bond

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

The stretching frequencies are considered the most important in bond breakage and have been used exclusively in the calculations which follow. Since no vibrational frequencies for simple β-keto acids were available, they were approximated on the basis of compounds which have structurally similar parts. Thus, by using these known frequencies, calculating the corresponding frequencies for carbon-14 bonds, and finally assuming certain frequencies in the transition state, it was possible to approximate the free energy factor in Bigeleisen's equation.

Since a cyclic, concerted reaction may be looked upon as a three-center reaction, equation 5 has been used for evaluating the isotope

effects. The effective mass term in this equation is usually evaluated using the masses of the atoms involved in bond rupture and formation, following the method of Slater (55). However, Bigeleisen [(15), p. 30] has suggested that perhaps a more reasonable a priori formulation would involve the masses of the fragments A, B and C in the reaction

$$A + B\text{-}C \longrightarrow [A\text{--}B\text{--}C] \longrightarrow A\text{-}B + C$$

Both methods have been used here.

Use of the Eyring-Cagle Equation

This equation

$$\frac{k_1}{k_2} = \frac{\sinh\ (hcw_1/2kT)}{\sinh\ (hcw_2/2kT)}$$

is useful in the case of simple bond rupture. It is assumed that the bond in question is completely broken in the transition state (that is, one vibrational mode is completely lost) and that all other bonds remain the same.

Consider first the decompositon of 2-benzoylpropionic acid-1-C^{14}. Taking

$h = 6.62 \times 10^{-27}$ erg sec./molecule
$k = 1.38 \times 10^{-16}$ erg/deg. molecule
$c = 3.00 \times 10^{10}$ cm./sec.
$T = 351°K$
$w_1 = 1176$ cm.$^{-1}$ [C^{12}-C^{12} frequency in acetic acid (46)]
$w_2 = 1134$ cm.$^{-1}$ (calculated using equation 15)

then, $k_1/k_2 = 1.097$

If T = 331°K, then

$k_1/k_2 = 1.102$

which points out the small temperature dependence of isotope effects.

Note that in the case of the 2-labeled acid, the same calculations apply, since it is the same bond being broken. Thus the simple theory predicts that no difference in isotope effects should be expected for molecules in which the two atoms involved in bond rupture are successively labeled.

The values calculated above are higher than experimental, which suggests that the reaction has some three-center character.

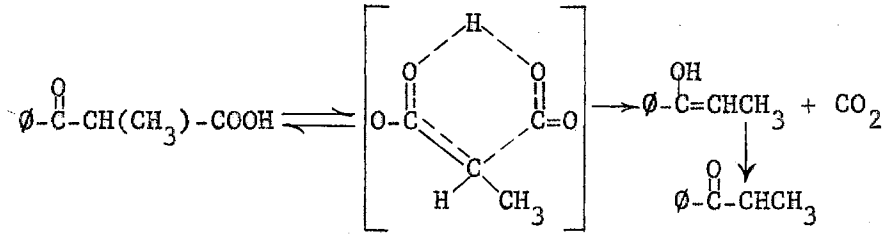
The Eyring-Cagle equation cannot be applied in the case of the carbonyl-labeled acid, for no bond is completely broken in the transition state.

Use of the Bigeleisen Three-Center Equation

The equation

$$\frac{k_1}{k_2} = \left[\frac{\left(\frac{1}{m_{B_1}} + \frac{1}{m_{C_1}}\right) + p\left(\frac{1}{m_{B_1}} + \frac{1}{m_{A_1}}\right) - \frac{2p^{1/2}}{m_{B_1}}\cos ABC}{\left(\frac{1}{m_{B_2}} + \frac{1}{m_{C_2}}\right) + p\left(\frac{1}{m_{B_2}} + \frac{1}{m_{A_2}}\right) - \frac{2p^{1/2}}{m_{B_2}}\cos ABC}\right]^{1/2} \left[\frac{1 + \sum_{i}^{3N-6} G(u_i)\Delta u_i}{1 + \sum_{i}^{3N'-6} G(u_i^*)\Delta u_i^*}\right]$$

will be applied to the reaction



which will be considered to be analogous to the general reaction

$$A + B\text{-}C \longrightarrow [A\text{--}B\text{--}C] \longrightarrow A\text{-}B + C$$

where B is (or contains) the carbon-12 or carbon-14 atom.

The Temperature-Independent Factor: In all of these calculations the effective mass term (the temperature-independent factor, abbreviated TIF) has been estimated in two ways, both for p = 0 and p = 1: 1) on the basis of atomic masses, and 2) on the basis of molecular fragment masses. The particle masses have been given in terms of A_1, B_2 and so on, ignoring the "m" notation. The carboxyl hydrogen has been ignored in determining the fragment masses. Cosine ABC has been taken to be cos 120°, or -1/2. On substituting the appropriate values for the various quantities in the temperature-independent factor, the following results were obtained:

TABLE VII

TEMPERATURE-INDEPENDENT FACTORS IN BIGELEISEN'S THREE-CENTER EQUATION

Sample: 2-BPA = 2-benzoylpropionic acid
Type of Mass: A = atomic; B = fragment

Sample	p	Type of Mass	Particle Masses A_1	A_2	B_1	B_2	C_1	C_2	TIF
2-BPA-1-C^{14}	0	A			12	14	12	12	1.038
		F			28	30	133	133	1.028
	1	A	16	16	12	14	12	12	1.050
		F	16	16	28	30	133	133	1.022
2-BPA-2-C^{14}	0	A			12	14	12	12	1.038
		F			28	30	44	44	1.022
	1	A	12	12	12	14	12	12	1.047
		F	105	105	28	30	44	44	1.027

In the case of the carbonyl-labeled compound, in which the carbon-oxygen bond is considered to be weakened as the carbon-carbon bond is strengthened, it seems unlikely that the temperature-independent factor could be calculated in the above manner, since it would imply that complete cleavage of the carbon-oxygen bond resulted from the decomposition. A better <u>a priori</u> method is to take for $\bar{m}_2$ and $\bar{m}_1$ in $(\bar{m}_2/\bar{m}_1)^{1/2}$ the masses of the whole intermediate complexes, which is in accordance with Eyring's original concept. Thus, TIF = $(180.2/178.2)^{1/2}$ = 1.005.

<u>The Temperature-Dependent Factor</u>: The free energy term (the temperature-dependent factor, abbreviated TDF) in Bigeleisen's equation has been calculated using different sets of assumptions. The main assumption to note is that for the calculation of vibrational frequencies in the transition state when p = 1, the bond order has been taken to be 0.5 if a single bond is being broken, and 1.5 if a double bond is being broken or formed.

The various quantities necessary for the evaluation of the temperature-dependent factors for all of the decarboxylation reactions have been tabulated on the following page. This table requires considerable explanation in order that the method of calculation will be clearly understood.

The bonds involved are:

1) For 2-benzoylpropionic acid-1-C^{14}

$$\underset{\text{Bond:}}{\overset{\quad 1\ \ 2}{C\text{-}C^*\text{-}O}} \longrightarrow \underset{\quad 1\quad 2}{[C\text{---}C^*\underline{\text{---}}O]} \longrightarrow \underset{1}{C} + \underset{\quad 1\quad 2}{C^*\!=\!O}$$

2) For 2-benzoylpropionic acid-2-C^{14}

$$\underset{\text{Bond:}}{\overset{\quad 2\ \ 1}{C\text{-}C^*\text{-}C}} \longrightarrow \underset{\quad 2\quad 1}{[C\underline{\text{---}}C^*\text{---}C]} \longrightarrow \underset{\quad 2\quad 1}{C\!=\!C^*} + \underset{1}{C}$$

TABLE VIII

QUANTITIES NECESSARY FOR THE EVALUATION OF THE TEMPERATURE-DEPENDENT FACTORS

Compound	Molecular Species	Bond	Order	k_f	Frequencies, $cm.^{-1}$ carbon-12	carbon-14	$G(u_i)\Delta u_i$	$G(u_i^*)\Delta u_i^*$
2-BPA-1-C^{14}	R	1	1.0	4.9	1176	1134	0.0518	
	P		0.0	0.0	0			
	C		0.5	2.45	836	806		0.0298
	R	2	1.0	6.86	1300	1246	0.0703	
	P		2.0	22.7	2380			
	C		1.5	14.8	1920	1840		0.01207
2-BPA-2-C^{14}	R	1	1.0	4.9	1176	1134	0.0518	
	P		0.0	0.0	0			
	C		0.5	2.45	836	806		0.0298
	R	2	1.0	4.02	1070	1032	0.0443	
	P		2.0	9.28	1625			
	C		1.5	6.65	1377	1327		0.0669
2-BPA-carbonyl-C^{14}	R	1	2.0	11.7	1710	1638	0.1057	
	P		1.0	4.18	1020			
	C		1.5	8.0	1508		0.0872	
	R	2	1.0	4.02	1070	1032	0.0443	
	P		2.0	9.28	1625			
	C		1.5	6.65	1377	1327		0.0669

3) For 2-benzoylpropionic acid-carbonyl-C^{14}

$$\underset{\text{Bond:}}{\overset{}{}} \quad \underset{1\ \ 2}{O{=}C^{*}{-}C} \longrightarrow \left[\underset{1}{O}\cdots\underset{2}{C^{*}}\cdots C\right] \longrightarrow \underset{1\ \ 2}{O{-}C^{*}{=}C}$$

In every case bond 1 is being broken and bond 2 is being formed.

The molecular species refers to the reactant (R), the activated complex (C) or the product (P). k_f is the force constant for the bond under consideration. It can be calculated for normal molecules from the relation (1)

$$w = 1307(k_f/\mu)^{1/2} \tag{16}$$

where: w = the vibrational frequency in $cm.^{-1}$, obtained from infrared spectra data
μ = the reduced mass of the atoms forming the bond

If a bond order in the activated complex was taken to be 0.5, then k_f was taken to be 0.5 the k_f value for the single bond. If the order was taken to be 1.5, the corresponding k_f was obtained by taking a value half-way between the values for the k_f's for the corresponding bond in the reactant and product. The frequencies in the intermediate complex were then calculated from equation 16.

From the frequencies thus available the corresponding frequencies for the C^{14}-labeled molecules and intermediate complexes were calculated from equation 15.

The fundamental vibrational frequencies for the 2-benzoylpropionic acid molecule were assumed to be the same as those found in molecules having structurally similar parts. The frequencies for the various bonds under consideration are as follows:

Bond	Compound	Frequency, $cm.^{-1}$	Reference
C-C	acetic acid	1176	46
C-O	acids	1300	5, p. 162
C=O	carbon dioxide	2380	46, p. 89
C-C	acetone	1070	46, p. 58
C=C	aromatic-conj.	1625	5, p. 34
C=O	acetophenone	1710	5, p. 137
C-O	alcohols	1020	5, p. 109

$G(u_i)\Delta u_i$ and $G(u_i^*)\ \Delta u_i^*$ were calculated knowing that

$$u = hcw_1/kT \qquad \text{and} \qquad \Delta u = hc(w_1 - w_2)/kT$$

where the subscripts 1 and 2 refer to the carbon-12 and carbon-14-labeled molecules, respectively. G(u) was obtained from available tables (11). The quantity hc/kT has a value of 0.0041 at 351°K.

$G(u_i)\Delta u_i$ was also calculated at 331°K for 2-benzoylpropionic acid-1-C^{14} and has a value of 0.0567, which may be compared to 0.0518 at 351°K. This reflects the small temperature dependence of the isotope effect, which was also evident from the Eyring-Cagle equation. Further calculations at 331° seemed unnecessary.

Theoretical Isotope Effects from Combinations of Temperature-Independent and Temperature-Dependent Factors: Making various assumptions about the transition state, it is possible to combine the appropriate TIF and TDF values from Tables VII and VIII to give theoretical isotope effects which may be compared with the experimental values; that is

Isotope Effect = TIF X TDF

A. 2-Benzoylpropionic Acid-1-C^{14}

1. Assume complete bond cleavage in the transition state and all other bonds the same. p = 0

a) Atomic masses

TIF = 1.038
TDF = 1.0518

I. E. = 1.092

b) Fragment masses

TIF = 1.028
TDF = 1.0518

I. E. = 1.082

2. Same assumptions as 1, but p = 1.

a) Atomic masses

TIF = 1.050
TDF = 1.0518

I. E. = 1.105

b) Fragment masses

TIF = 1.022
TDF = 1.0518

I. E. = 1.075

3. Assume a concerted mechanism and p = 1

a) Atomic masses

TIF = 1.050
TDF = 1 + (0.0518 + 0.0703) - (0.0298 + 0.1207) = 0.9716

I. E. = 1.020

b) Fragment masses

TIF = 1.022
TDF = 0.9716

I. E. = 0.995

B. 2-Benzoylpropionic Acid-2-C^{14}

1. Assume complete bond cleavage in the transition state and all other bonds the same. p = 0

a) Atomic masses

TIF = 1.038
TDF = 1.0518

I. E. = 1.092

b) Fragment masses

TIF = 1.028
TDF = 1.0518

I. E. = 1.082

2. Same assumptions as 1, but p = 1.

a) Atomic masses

TIF = 1.047
TDF = 1.0518

I. E. = 1.101

b) Fragment masses

TIF = 1.027
TDF = 1.0518

I. E. = 1.080

3. Assume a concerted mechanism and p = 1.

a) Atomic masses

TIF = 1.047
TDF = 1 + (0.0518 + 0.0443) - (0.0298 + 0.0669) = 1.00

I. E. = 1.047

b) Fragment masses

TIF = 1.027
TDF = 1.00

I. E. = 1.027

C. 2-Benzoylpropionic Acid-Carbonyl-C^{14}

TIF = 1.005
TDF = 1 + (0.0443 + 0.1057) - (0.0669 + 0.0872) = 0.9959

I. E. = 1.001

In the case of the carboxyl-labeled acid, the experimental results seem to be reproduced best by a simple bond-cleavage model, for the values for the concerted mechanism are far too low. This could be due to an unwise choice of the vibrational frequency for carbon dioxide. On the other hand, with carbon-14 in the 2-position, the concerted mechanism is somewhat favored. This simply means that little faith can be put in the theoretical calculations. The calculations merely suggest that at least some emphasis should be placed on the concerted scheme.

It was hoped that the lower isotope effect found for the 2-labeled acid as compared to the 1-labeled could be predicted from

theory. However, there is apparently no way of doing this on a rational basis. If the decomposition of the acid proceeds by way of a cyclic intermediate, the number of degrees of rotational freedom will be decreased. It has been suggested (69) that this could influence the magnitude of the isotope effects, and might explain the difference observed for the 1 and 2-labeled acids. Unfortunately, there is no way of evaluating these rotational effects.

The theoretical isotope effect for the carbonyl-labeled acid fortuitously agreed very well with the experimental value. The lack of any effect is due to the fact that there is very little difference in the energy of the carbon-oxygen double-bond being broken and the carbon-carbon double-bond being formed.

The difficulties involved in trying to theoretically reproduce empirical isotope effects are now apparent and bear emphasis. In the first place, there are several ways in which the effective mass factor may be calculated, all leading to different results. For example, Table VII shows that in one case a difference of 3% was obtained between TIF values calculated on the basis of atomic and fragment masses, respectively. Unfortunately, there is no <u>a priori</u> way of deciding which type of mass to use.

In the second place, the frequencies to be used in the reactant molecules are uncertain. The frequencies to be used in the activated complex are even more nebulous. Since the free energy factor is rather sensitive to frequency changes, its value is obviously quite uncertain.

Finally, it should be noted that it is frequently pointless to assign or to calculate values of p and thereby draw conclusions. This

is due to the fact that the effective mass factor is far too insensitive to changes in p, which is evident from a consideration of Table VII. Other uncertainties are so great that, in most cases, p-values become meaningless.

It is evident, then, that great care should be exercised when one attempts to draw conclusions from isotope effects calculated by theoretical means.

CONCLUSIONS

The observed isotope effects have shown, first of all, that when 2-benzoylpropionic acid decomposes, the bond between carbons 1 and 2 is broken in the rate-determining step. This observation may seem obvious and trite, but note that no isotope effect was found when o-aminobenzoic acid-α-C^{14} was decarboxylated (49).

If an isotope effect had been found in the case of the carbonyl-labeled acid, the cyclic, concerted mechanism would have been further substantiated. The absence of an observed effect, however, has not ruled out this mechanism, for it has been shown that little or no effect should be expected, whatever the mechanism.

Attempts to correlate the observed isotope effects with theory proved to be unfruitful, which was undoubtedly due to the many uncertainties involved in the theoretical calculations. Accurate reproduction of the observed effects and an explanation of the difference in effects observed with the 1- and 2-labeled acids must await further refinements of the theory.

Theoretical calculations suggest that not too much emphasis should be placed on the three-center character of the decarboxylation. However, other evidence--in particular, the negative entropy of activation--strongly suggests that the cyclic, concerted mechanism is essentially correct. If we assume that this is true, perhaps the most important conclusion to be reached is that isotope effects resulting from reactions which proceed by cyclic, concerted mechanisms are essentially the

same as those found in other types of reactions. In other words, the magnitude of isotope effects cannot be used to distinguish this type of mechanism from any other type. This is essentially what has come to be realized in the case of S_N1 and S_N2 reactions (6).

SUMMARY

A representative β-keto acid, 2-benzoylpropionic acid, was prepared and the kinetics of its decarboxylation was studied under a variety of conditions. The acid was shown to decarboxylate unimolecularly under the same conditions as those used in the isotope effect work. From the kinetic data the entropy of activation was determined and found to be negative, which further supports the cyclic, concerted mechanism proposed for β-keto acid decomposition.

With barium carbonate-C^{14} as the source of carbon-14, 2-benzoylpropionic acid was synthesized with the tagged atom in the 1-, 2- and carbonyl-positions, successively. The isotope effect associated with the decarboxylation of each of these compounds was determined by radioactivity assay of the original acid and the unreacted acid recovered after a known percent decomposition. The magnitudes of the observed isotope effects are given below.

Compound	Temperature °C	Isotope Effect, k/k*
2-benzoylpropionic acid-1-C^{14}	58	1.077
	78	1.074
2-benzoylpropionic acid-2-C^{14}	78	1.051
Same, in 1,1-diphenylethane	78	1.053
2-benzoylpropionic acid-carbonyl-C^{14}	78	1.000

Isotope effects for these reactions were calculated from theoretical considerations. Because of the many uncertainties in such

calculations, little correlation with the experimentally determined isotope effects could be obtained.

The most important observation was that the isotope effects in β-keto acid decarboxylations fall in the range of those observed for reactions which are similar in nature, but which differ in mechanism. Therefore, it is unlikely that the magnitude of isotope effects can be used to demonstrate the existence of cyclic, concerted mechanisms.

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APPENDIX

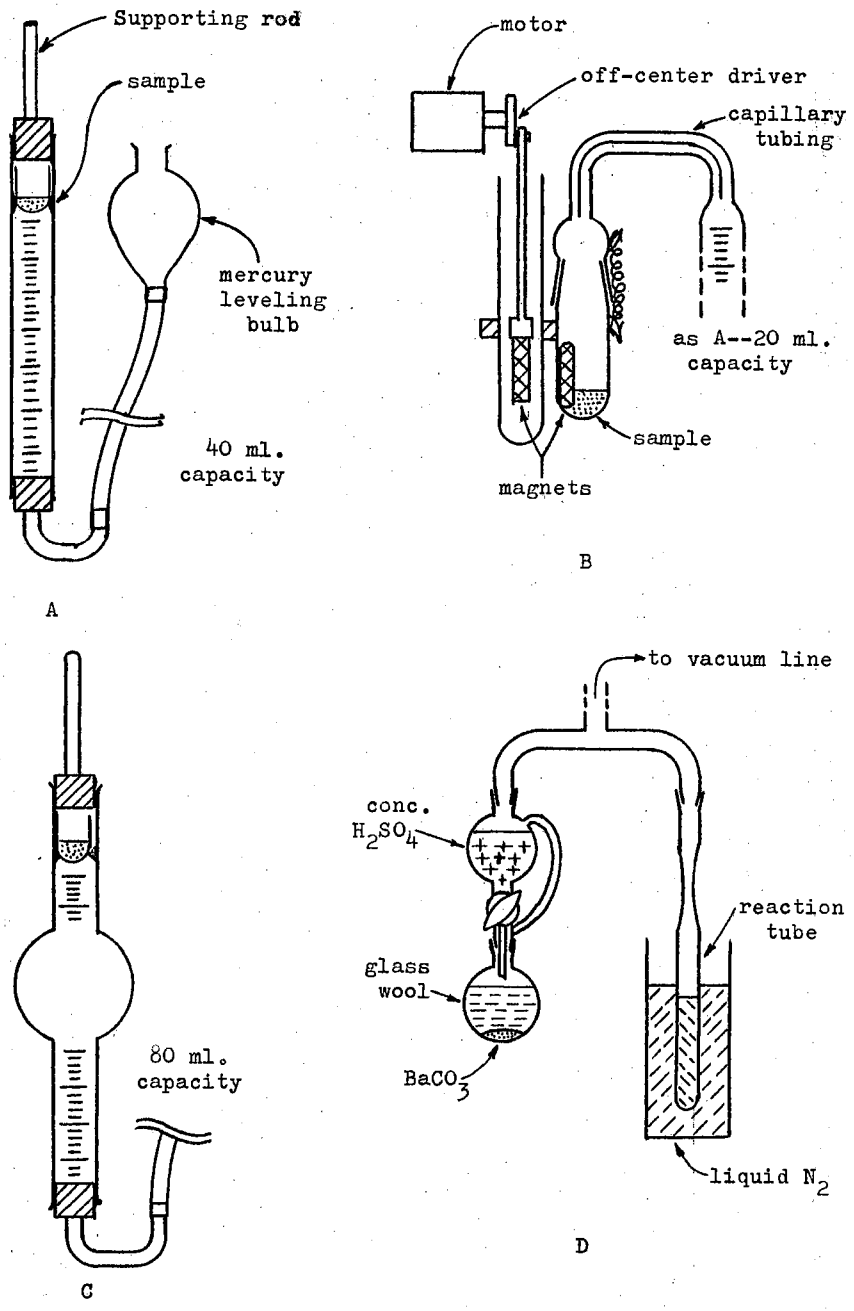

Fig. 6. Illustrations of Apparatus

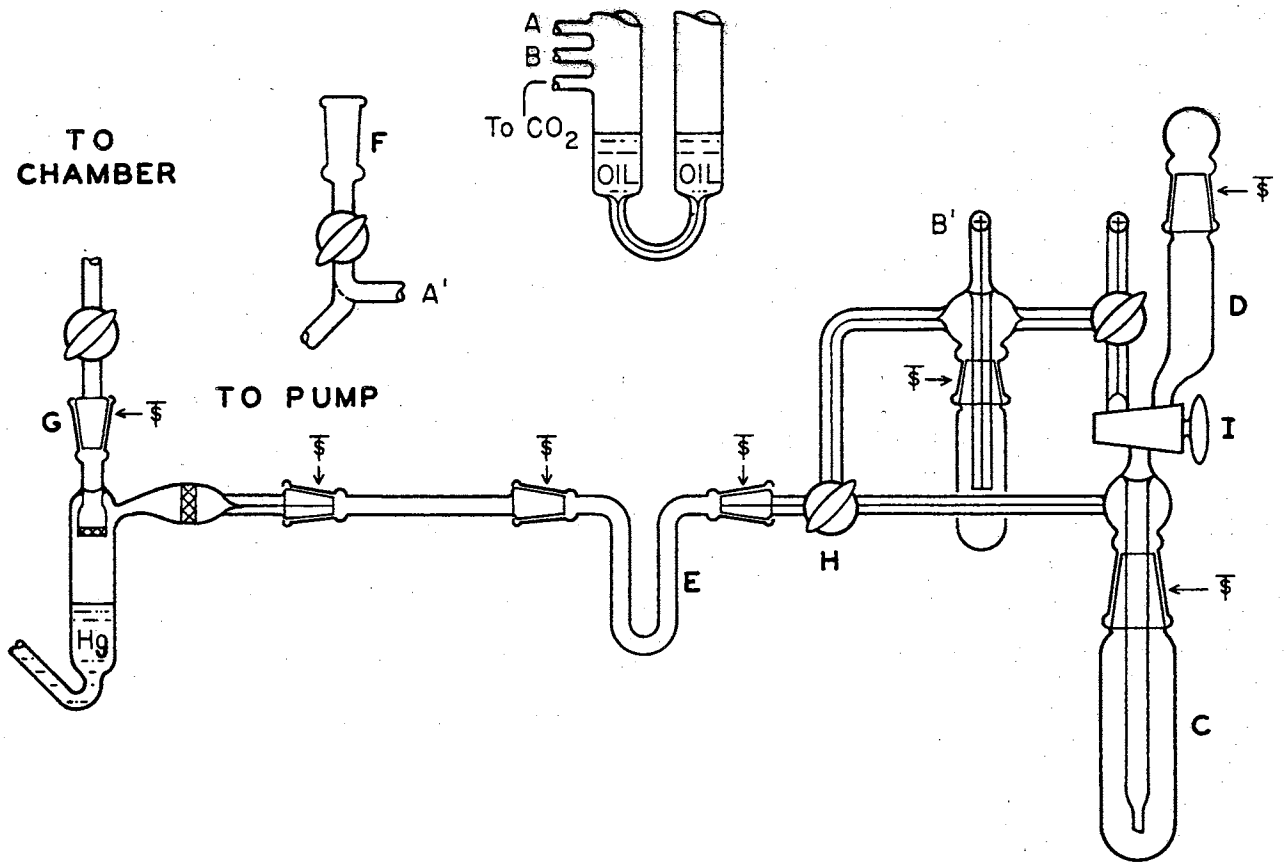

Fig. 7. Wet combustion apparatus for the oxidation of radiocarbon compounds for $C^{14}O_2$ counting.

VITA

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