UCRL-1564 Rev.

UNCLASSIFIED

UNIVERSITY OF CALIFORNIA — BERKELEY

TWO-WEEK LOAN COPY

This is a Library Circulating Copy which may be borrowed for two weeks. For a personal retention copy, call Tech. Info. Division, Ext. 5545

RADIATION LABORATORY

UCRL-1564 Revised
Unclassified-Chemistry Distribution

UNCLASSIFIED

UNIVERSITY OF CALIFORNIA

Radiation Laboratory

Contract No. W-7405-eng-48

THE C^{14} ISOTOPE EFFECT IN THE DECARBOXYLATION OF α-NAPTHYL AND PHENYLMALONIC ACIDS

Arthur Fry and Melvin Calvin

July 3, 1952

Berkeley, California

THE C^{14} ISOTOPE EFFECT IN THE DECARBOXYLATION OF α-NAPHTHYL AND PHENYLMALONIC ACIDS[1,2]

by

Arthur Fry[3] and Melvin Calvin

Radiation Laboratory and Department of Chemistry, University of California, Berkeley

ABSTRACT

The isotope effects in the decarboxylation of α-naphthylmalonic acid-1-C^{14} and phenylmalonic acid-1-C^{14} have been measured, both in solution and on the liquid acids near their melting points. The carboxyl group containing C^{12} is lost as carbon dioxide about 10% more frequently than is the C^{14}-containing carboxyl group. Theoretical calculations give values in reasonable agreement with experiment.

For publication in Journal of Physical Chemistry

---

(1) The work described in this paper was sponsored by the U.S. Atomic Energy Commission.

(2) This paper was abstracted from the thesis submitted by Arthur Fry to the Graduate Division of the University of California in partial fulfillment of the requirements for the Ph.D. degree, June 1951.

(3) Present address: Department of Chemistry, University of Arkansas, Fayetteville, Arkansas.

THE C^{14} ISOTOPE EFFECT IN THE DECARBOXYLATION OF α-NAPHTHYL AND PHENYLMALONIC ACIDS[1,2]

Arthur Fry[3] and Melvin Calvin

Radiation Laboratory and Department of Chemistry,
University of California, Berkeley

Introduction

In recent years the question of the effect of the substitution of isotopic carbon on the rate of chemical reactions has received considerable attention. A considerable portion of this attention has been directed toward determining the isotope effect in the decarboxylation of malonic acids. Yankwich and Calvin[4] studied the decarboxylation of malonic acid-1-C^{14} and bromomalonic acid-1-C^{14}, and found rupture ratios for C^{12}-C^{12} bonds to C^{14}-C^{12} bonds of 1.12 ± 0.03 and 1.41 ± 0.08, respectively. The value for bromomalonic acid was the result of only one experiment and the bromomalonic acid used was admittedly of doubtful purity so there is doubt as to the validity of the result.

---

(1) The work described in this paper was sponsored by the U.S. Atomic Energy Commission.

(2) This paper was abstracted from the thesis submitted by Arthur Fry to the Graduate Division of the University of California in partial fulfillment of the requirements for the Ph.D. degree, June 1951.

(3) Present address: Department of Chemistry, University of Arkansas, Fayetteville, Arkansas.

(4) P. E. Yankwich and M. Calvin, J. Chem. Phys., 17, 109 (1949).

This work, and the earlier work of Beeck, Otvos, Stevenson and Wagner[5] on the C^{13} isotope effect in the electron impact and thermal cracking of propane, led Bigeleisen[6,7] to report the results of theoretical calculations of these isotope effects. In all cases, the theoretical calculations gave much smaller values for the isotope effects than those calculated from the observed data. Bigeleisen expressed his results as ratios of rate constants for the various processes involved. The decarboxylation of a malonic acid may be represented by the following equations, where C^* represents C^{13} or C^{14}:

$$RCH(COO)_2 \xrightarrow{k_1} CO_2 + RCH_2COOH \qquad (I)$$

$$RCH\begin{matrix} C^*OOH \\ COOH \end{matrix} \xrightarrow{k_2} C^*O_2 + RCH_2COOH \qquad (II)$$

$$RCH\begin{matrix} C^*OOH \\ COOH \end{matrix} \xrightarrow{k_3} CO_2 + RCH_2C^*OOH \qquad (III)$$

For the labeled malonic acid molecule the rupture ratio C^{12}-C^{12}/C^{14}-C^{12} is given by the ratio k_2/k_3. Using these equations, Bigeleisen[7] calculated values for $k_2/2k_2$ and $k_1/2k_3$ fpr malonic and bromomalonic acids. From these values the

---

(5) O. Beeck, J.W. Otvos, D.P. Stevenson and C.D. Wagner, J. Chem. Phys., 16, 255, 993 (1948).

(6) J. Bigeleisen, J. Chem. Phys., 17, 345 (1949).

(7) J. Bigeleisen, J. Chem. Phys., 17, 425 (1949).

ratio k_3/k_2 can be calculated as 1.038 for both acids at 400°K., as compared to the values of 1.12 and 1.41 observed by Yankwich and Calvin[4] for malonic and bromomalonic acids, respectively.[8]

In order to check this large discrepancy between the observed and calculated values for the isotope effect, Bigeleisen and Friedman[9] studied the C^{13} isotope effect in the decarboxylation of malonic acid of normal isotopic composition. The observed value corresponding to k_3/k_2 above was found to be 1.020, while the calculated value was 1.0198. The agreement in the C^{13} case thus is excellent, and would seem to add support to the theoretical calculations in the C^{14} case. However, that the theoretical calculations are not entirely adequate is shown by the discrepancy between the observed and calculated value corresponding to $k_1/2k_2$ above. The calculated value is 1.021, while the observed value is 1.037.

---

(8) There is a mathematical error in the equation in the paper by Bigeleisen[7]. The unlabeled carbon dioxide evolved from the labeled malonic acid molecule has been neglected. The corrected general equation, using Bigeleisen's symbols, is:

$$\frac{CO_2}{C^*O_2} = \frac{(k_2 + k_3)\ Mo(1-e^{-k_1 t}) + k_3 Mo^*(1-e^{-(k_2 + k_3)t})}{k_2 Mo^*(1-e^{-(k_2 + k_3)t})}$$

which, at small time becomes

$$\frac{CO_2}{C^*O_2} = \frac{Mok_1}{Mo^*k_2} + \frac{k_3}{k_2}$$

and at infinite time becomes

$$\frac{CO_2}{C^*O_2} = \frac{Mo}{Mo^*}\ \frac{(k_2 + k_3)}{k_2} + \frac{k_3}{k_2}$$

However, this error is not important at the tracer level, and undoubtedly would not affect the calculated values.

(9) J. Bigeleisen and L. Friedman, J. Chem. Phys., 17, 998 (1949).

A short time later Pitzer[10] also calculated the theoretically expected C^{14} isotope effect in the decarboxylation of malonic acid. He used essentially the same mathematical approach as did Bigeleisen, but used a different model for the reaction, thus requiring a different choice of vibrational frequencies in making the calculation. Pitzer calculates that the C^{12}-C^{12}/C^{14}-C^{12} rupture ratio (k_3/k_2) may be as high as 1.14, as compared to Yankwich and Calvin's observed value of 1.12 and Bigeleisen's calculated value of 1.038. This model thus leads to very satisfactory agreement with the observed C^{14} results, but it would also presumably lead to a value of approximately 1.07 for the C^{13} case. Here the agreement with Bigeleisen and Friedman's[9] observed result of 1.020 is quite poor while Bigeleisen's calculation of 1.0198 is in excellent agreement. Pitzer's calculations would lead to no great difference between the malonic and bromomalonic acid cases, and hence the observed rupture ratio of 1.41 for bromomalonic acid is not in accord with any of the calculations.

Some support has recently been given to Bigeleisen's theoretical calculations by the investigations of Lindsay, Bourns and Thode[11] and of Roe and Hellmann[12].

In a much more thorough investigation of the C^{13} isotope effect in the decarboxylation of malonic acid of normal isotopic composition, Lindsay, Bourns and Thode[11] report values of 1.021 and 1.026 for k_3/k_2 for two different samples of malonic acid. They investigated the distribution of C^{13} among the three carbon atoms of the molecule and found that there was no appreciable difference. They

---

(10) K. S. Pitzer, J. Chem. Phys., 17, 1341 (1949).

(11) J. G. Lindsay, A. N. Bourns and H. G. Thode, Can. J. Chem., 29, 192 (1951).

(12) A. Roe and M. Hellmann, J. Chem. Phys., 19, 660 (1951).

also obtained a value of 1.046 for the value corresponding to $k_1/2k_2$. Bigeleisen and Friedman's calculated value for this ratio is 1.021 while their observed value is 1.037.

Roe and Hellmann[12] checked the isotope effect in the decarboxylation of malonic acid-1-C^{14} using a somewhat different technique than that used by Yankwich and Calvin[4]. They obtained a value of 1.06 ± 0.02 for k_3/k_2 in comparison to Yankwich and Calvin's[4] value of 1.12 ± 0.03 and Bigeleisen's[7] calculated value of 1.038.

The inconsistencies among the various observed and calculated values for the isotope effects in the decarboxylation of malonic acids leave a great deal to be desired. It would seem that additional careful experimental work should be done, and that the various models and vibrational frequency selectsions for the theoretical calculations should be reconsidered. The bromomalonic acid case is of special interest since it is the case with the largest reported isotope effect, and also it is least satisfactorily explained by theory. However, the difficulties in preparation and purification of this acid are such that the reliability of any measurements made with this acid might be open to question.

A different approach to the problem is to inquire into possible reasons for the abnormally high value of the isotope effect in the bromomalonic acid case. One obvious difference between malonic acid and bromomalonic acid is the presence of the large negative bromine in the latter case. Another is the fact that bromomalonic acid decarboxylates at a lower temperature than malonic acid, and from zero point energy considerations it might be expected that larger isotope effects would be obtained at lower temperatures.

Another very desirable characteristic for a suitable malonic acid would be ease of purification of the malonic acid itself and of the substituted malonic acid itself and of the substituted acetic acid derived from it.

Blicke and Feldkamp[13] have prepared a series of α-naphthylalkyl acetic acids by hydrolysis and decarboxylation of the corresponding α-naphthylalkyl malonic esters. They state that addition of acid to an aqueous solution of the potassium salt of the malonic acid at room temperature results in the precipitation of the malonic acid as an oil which spontaneously loses carbon dioxide, forming the corresponding acetic acid.

Such acids would be nearly ideally suited to a study of the isotope effect in the decarboxylation of the malonic acid. A large group is present such as bromomalonic acid; the acids apparently decarboxylate at room temperature; the substituted acetic acids produced are stable and readily purified.

On investigation of the alkaline hydrolysis of α-naphthylmalonic ester it soon became apparent that the carbon dioxide evolution upon addition of acid was not due to decarboxylation of the malonic acid, but rather to carbonate caused by basic cleavage of the ester.[14]

The free α-naphthylmalonic acid, however, did decarboxylate in solution at relatively low temperatures, so it was decided to carry out isotope effect experiments using it. Later the isotope effect in the decarboxylation of phenylmalonic acid was also studied.

---

(13) F. F. Blicke and R. F. Feldkamp, J. Am. Chem. Soc., 66, 1087 (1944).

(14) This basic carbonate cleavage reaction was studied in some detail, and the results are to be published elsewhere.

Procedure and Results

The substituted malonic esters were prepared by condensation of diethyl oxalate with the substituted acetic ester, and decarboxylation of the resulting glyoxylate. The most satisfactory hydrolysis procedure was found to be trans-esterification of the malonic ester with acetic acid catalyzed by hydrochloric acid.[15]

Alpha-naphthylmalonic acid and phenylmalonic acids were decarboxylated in the liquid state near the melting points, and in dioxane-1 N hydrochloric acid solution at 72.8°C and at 87.5°C. The carbon dioxide evolved was collected as barium carbonate. The α-naphthyl and phenylacetic acids were purified, and samples of them and of the starting malonic acids were oxidized by a wet combustion method, and the resulting carbon dioxide collected as barium carbonate.

The C^{14} activity measurements were made using an ionization chamber and a vibrating reed electrometer connected to a Brown recorder. The ionization chambers were filled to a standard pressure with carbon dioxide generated in a vacuum system from the barium carbonate samples with concentrated sulfuric acid. The samples from each run were measured in the same ionization chamber and on the same instrument in as rapid succession as possible in order to minimize any variations in the procedure and instruments. At least two independent activity measurements were made on each sample.

The specific activities of the various samples are shown in Table I. The values given are averages of two or more activity determinations, and the indicated errors are average deviations of these measurements.

---

(15) This procedure was kindly suggested by Professor James Cason.

Table I

Specific Activities of α-Naphthylmalonic Acid-1-C^{14}, Phenylmalonic Acid-1-C^{14} and Their Decarboxylation Products

Run. No.	Temp. °C	Carbon Dioxide	Relative Specific Activity Drift Rate, Volts/min. x 10^2				
			α-Naphthylacetic Acid		α-Naphthylmalonic Acid		CO_2 + 12 x α-Naphthylacetic Acid
			Observed	x 12*	Observed	x 13*	
Liquid							
1	163.0	1567±3	140.0±1.4	1680±17	250.0±0.3	3250±4	3247
2	163.0	1601±15	144.0±0.4	1728±5	255.4±0.5	3320±6	3329
Solution							
3	100.5**	1543±3	141.7±0.1	1700±1	251.0±1.8	3263±23	3243
4	72.8	1561±13	143.0±1.0	1716±12	251.0±2.4	3263±31	3277
5	72.8	1150±1	105.0±0.4	1260±5	184.2±2.0	2395±26	2410
6	87.5	1149±1	104.6±0.0	1255±0	184.3±1.9	2396±25	2404
7	87.5	1543±24	141.2±1.2	1694±14	250.0±2.4	3250±31	3237
			Phenylacetic Acid		Phenylmalonic Acid		CO_2 + 8 x Phenylacetic Acid
			Observed	x 8*	Observed	x 9*	
Liquid							
1	163.0	1527±9	205.3±0.1	1642±1	368.6±2.0	3173±18	3169
2	163.0	1492±1	205.3±0.0	1642±0	351.4±2.0	3163±18	3134
Solution							
3	72.8	1465±14	209.1±1.1	1673±9	350.2±2.4	3152±22	3138
4	72.8	1468±10	206.1±2.1	1649±17	350.2±2.7	3152±24	3117

* Factor to convert to specific activity of the single labeled carbon atom.

** Bath temperature, actual decomposition temperature unknown, ~85-95°C

The final two columns in Table I show the activity balance between the substituted malonic acid and its decarboxylation products. The activity balance is well within the error of the activity measurements for all of the runs on α-naphthylmalonic acid, and is only 1.1% off in the most widely deviating case with the phenylmalonic acid. The average deviation of the activity balance from 100% is 0.46% for all runs.

Discussion

The decarboxylation of phenylmalonic acid in solution has been shown to be first order with respect to malonic acid.[16] For malonic acid itself the decarboxylation has been shown to be first order, both in the pure liquid and in solution.[17]. The kinetics of decarboxylation of several other substituted malonic acids in solution has also been studied,[16,18] and in each case found to be first order in respect to the malonic acid. It therefore seems reasonable to assume that we are dealing with first order reactions here, and if so the specific activities of the products and reactants may be related to the specific rate constants of equations (I), (II) and (III) by the following equations, where $RCH(COOH)_2 = M = M_o$ at $t = 0$,

$$RCH\begin{matrix} C^*OOH \\ COOH \end{matrix} = M^*_m = M^*_o \text{ at } t = 0,$$

(16) A.L. Bernoulli and W. Wege, Helv. Chim. Acta, 2, 522 (1919).

(17) (a) C.N. Hinshelwood, J. Chem. Soc., 117, 156 (1920);
(b) J. Laskin, Tran. Siberian Acad. Agr. Forestry, 6, No. 1, 7 (1926);
(c) G.A. Hall, Jr., J. Am. Chem. Soc., 71, 2691 (1949).

(18) A.L. Bernoulli and H. Jakubowicz, Helv. Chim. Acta, 4, 1018 (1921).

$RCH_2COOH = A$

and $RCH_2C^*OOH = A^*$.

$$\frac{C^*O_2}{C^*O_2 + CO_2} = \frac{k_2}{k_2 + k_3} \quad \frac{M_o^*(1 - e^{-(k_2 + k_3)t})}{M_o(1 - e^{-k_1 t}) + M_o^*(1 - e^{-(k_2 + k_3)t})} \qquad \text{(IV)}$$

$$\frac{A^*}{A^* + A} = \frac{k_3}{k_2 + k_3} \quad \frac{M_o^* (1 - e^{-(k_2 + k_3)t})}{M_o (1 - e^{-k_1 t}) + M_o^* (1 - e^{-(k_2 + k_3)t})} \qquad \text{(V)}$$

When the reaction is complete, t = , and equations (IV) and (V) become, after rearrangement,

$$\frac{k_3}{k_2} = \frac{\dfrac{C^*O_2 + CO_2}{C^*O_2} \qquad \dfrac{M_o + M_o^*}{M_o^*}}{\dfrac{M_o + M_o^*}{M_o^*}} \qquad \text{(VI)}$$

and

$$\frac{k_2}{k_3} = \frac{\dfrac{M_o + M_o^*}{M_o^*}}{\dfrac{A^* + A}{A^*} \quad \dfrac{M_o + M_o^*}{M_o^*}} \qquad \text{(VII)}$$

By combining equations (IV) and (V) <u>at any time whether the reaction is complete or not</u>, we obtain equation (VIII).

$$\frac{k_3}{k_2} = \frac{\dfrac{A^*}{A^* + A}}{\dfrac{C^*O_2}{C^*O_2 + CO_2}} \qquad \text{(VIII)}$$

The values $\dfrac{C^*O_2}{CO_2 + C^*O_2}$, $\dfrac{A^*}{A^* + A}$ and $\dfrac{M_o^*}{M_o^* + M_o}$ are the molar specific activities of the carbon dioxide, the substituted acetic acid and the substituted malonic acid, respectively. These are the values given in Table I.

For ease of tabulation and convenience of reference, the percentage isotope effect may be defined as 100 $(k_2/k_3 - 1)$. The percentage isotope effect values may then be calculated from the data in Table I using equations (VI), (VII), and (VIII) with the results shown in Table II. The agreement among the calculations by three different equations furnishes a measure of the internal consistency of the data.

The C^{14} isotope effects in the decarboxylation of liquid α-naphthylmalonic acid-1-C^{14} and phenylmalonic acid-1-C^{14} at 163.0°C are thus seen to be 7.6± 0.4 and 8.8 ±1.5 percent. The corresponding values in solution between 72.8 and ~95°C are 9.7±0.8 and 13.2±1.5 percent. The precision of the measurements is not great enough to show a significant temperature coefficient of the isotope effect in the solution experiments. However, there is a significant difference in the isotope effect between the liquid acid at 163.0°C and the acid in solution at 72.8 to 95°C, and this may well be chiefly due to a temperature effect.

Table II

C^{14} Isotope Effect in the Decarboxylation of α-Naphthylmalonic Acid-1-C^{14} and Phenylmalonic Acid-1-C^{14}

Run. No.	Temp. °C	Percent Isotope Effect, $100(k_2/k_3-1)$			
		CO_2 and Diacid, Equation VI	Monoacid and Diacid, Equation VII	CO_2 and Monoacid, Equation VIII	Average
		α-Naphthylmalonic Acid-1-C^{14}			
Liquid					
1	163.0	7.4	7.0	7.2	7.2±0.1
2	163.0	7.4	8.5	7.9	7.9±0.5
Average	163.0				7.6±0.4
Solution					
3	100.5*	11.5	8.8	10.2	10.2±0.9
4	72.8	9.0	10.9	9.9	9.9±0.6
5	72.8	8.3	11.0	9.6	9.6±0.9
Average	72.8				9.8±0.8
6	87.5	8.5	10.0	9.2	9.2±0.5
7	87.5	10.6	8.9	9.8	9.8±0.6
Average	87.5				9.5±0.6
Average all soln. runs					9.7±0.8
		Phenylmalonic-Acid-1-C^{14}			
Liquid					
1	163.0	7.8	7.3	7.5	7.5±0.3
2	163.0	12.0	8.0	10.1	10.0±2.0
Average	163.0				8.8±1.5
Solution					
3	72.8	15.1	13.2	14.2	14.2±1.0
4	72.8	14.7	9.8	12.3	12.3±2.4
Average	72.8				13.2±1.5

* Bath temperature, actual decomposition temperature unknown, ~85-95°C

These values compare to the values obtained for malonic acid itself of 12 ± 3 percent obtained by Yankwich and Calvin[4] and of 6 ± 2 percent obtained by Roe and Hellman[12]. Regardless of which value is more nearly correct for malonic acid itself, none of the data so far obtained with C^{14} is consistent with the theoretical value calculated by Bigeleisen[7]. The closest value, 6 percent, is still 58 percent higher than the upper limit of 3.8 percent calculated by Bigeleisen[7]. Even the value of 4 percent taken at the extreme low end of the error interval indicated by Roe and Hellman[12] is slightly higher than the calculated upper limit. The C^{14} isotope effect values on substituted malonic acid reported here are all much larger than this, with the lowest value being exactly twice the calculated value.

The C^{13} experimental data seem to be in considerably better agreement with the calculated values, although even here the experimental values are all higher than the calculated upper limit, in one case[11] by 24 percent. All the experimental data using C^{13} thus far reported has been on malonic acid itself, and if we assume Roe and Hellman's[12] data on malonic acid is correct, it would be expected that the C^{13} isotope effect values for substituted malonic acids would be considerably larger than the calculated value of 1.98 percent in view of the larger C^{14} values reported for these substituted acids in this work.

Pitzer's calculations[10] have recently been criticized by Bothner-By and Bigeleisen[19]. Pitzer makes use of equation IX which was derived by Bigeleisen[20].

(19) A. A. Bothnery-By and J. Bigeleisen, J. Chem. Phys., 19, 755 (1951).

(20) J. Biteleisen, J. Chem. Phys., 17, 675 (1949).

The function G(u) is defined by Bigeleisen and Mayer[21] who have tabulated values of

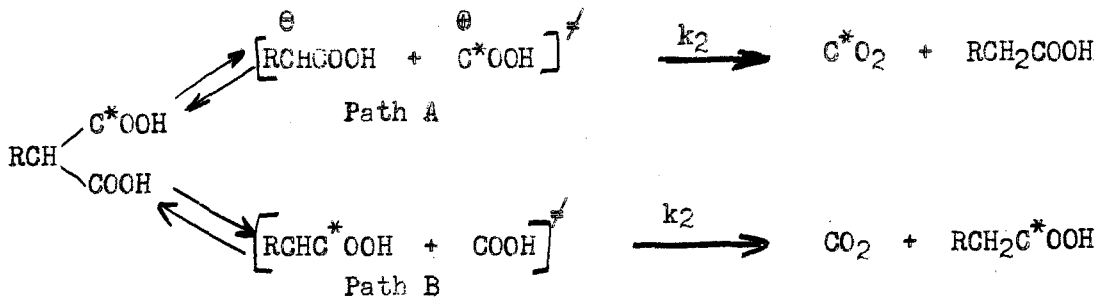
(21) J. Bigeleisen and M. G. Mayer, J. Chem. Phys., 15, 261 (1947).

$$\frac{k_3}{k_2} = \left(\frac{\mu_2}{\mu_3}\right)^{1/2} \left[1 + \sum_i^{3n-6} G(u_i)\Delta u_i - \sum_i^{3n-7} G(u_i^{\neq})\Delta u_i^{\neq}\right] \quad \text{(IX)}$$

G(u) as a function of u. The reaction coordinate reduced mass μ, is assumed to be the reduced mass of the atoms forming the bond being broken. The symbol $\neq$ refers to the activated complex. Bothner-By and Bigeleisen[19] point out that the term $\sum_i^{3n-6} G(u_i)\Delta u_i$ refers to the normal molecule, and since k_2 and k_3 both refer to the same molecule in this case, all the terms Δu_i are identically zero. They state that in Pitzer's model these vibrations of the normal molecule contribute the major effect to the calculated difference in rates.

While it is not entirely clear how Pitzer's calculations should be interpreted, we shall show below that Pitzer's answer can be obtained using Pitzer's numerical data and a somewhat modified model using equation (IX), granting that $\sum_i^{3n-6} G(u_i)\Delta u_i$ is identically zero.

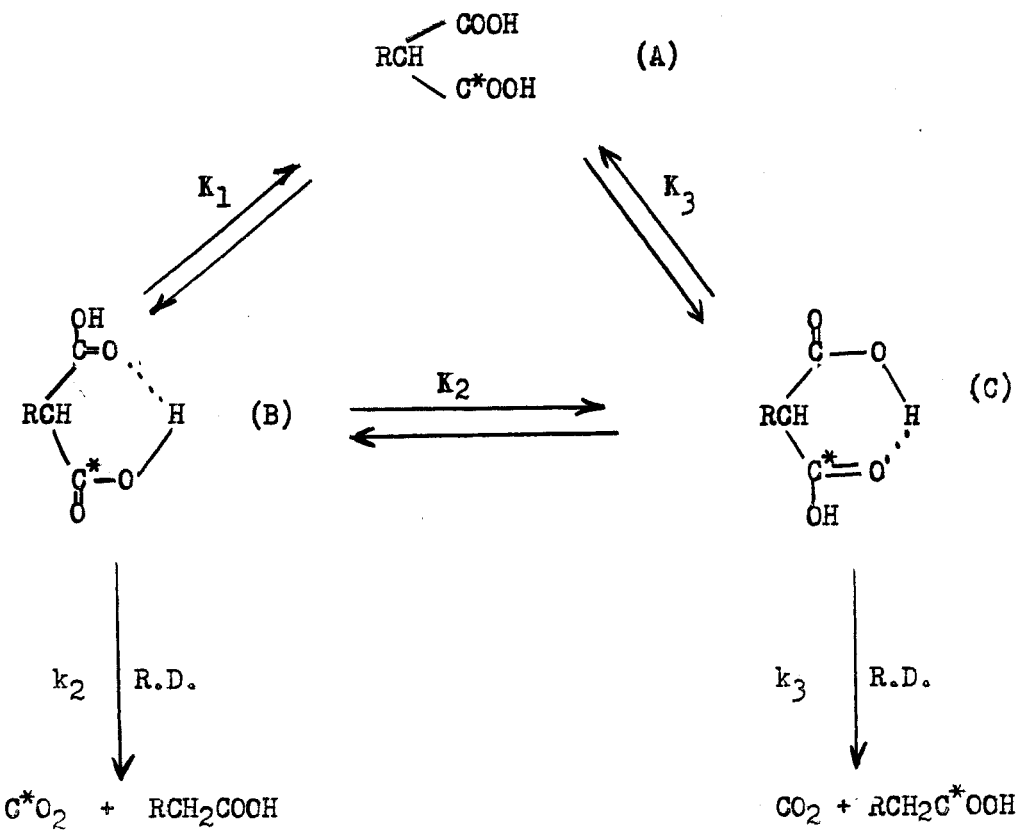
We may rewrite equations II and III to show an activated complex in which the carboxyl group which will eventually become carbon dioxide is no longer bonded to the molecule.



The term $\sum_{i}^{3n-6} G(u_i)\Delta u_i$ is identically zero, since for both Path A and Path B the ground state is the same molecule. In calculating the ratio k_3/k_2 Δu_i is defined by the equation $\Delta u_i = u_i$ Path B——u_i Path A. In the activated complexes there are two sets of corresponding vibrational frequencies, one referring to $RCHC^*OOH^{\ominus}$ and $RCHCOOH^{\ominus}$ and the other referring to $COOH^{\oplus}$ and $C^*OOH^{\oplus}$. For the first set, all Δu_i will be negative since the vibrational frequencies of $RCHC^*OOH$ are less than those of RCHCOOH, while in the second set, all Δu_i will be positive. If we examine Pitzer's calculations we see that he has calculated $G(u_i)\Delta u_i$ for very nearly these same two sets of intermediates. His calculations for the "normal acid molecule" serve as an adequate calculation for the negative of the contribution of the $RCHCOOH^{\ominus}$ term to our activated complex. His calculations for the "activated complex" give the contribution of the $COOH^{\oplus}$ term to our activated complex. The algebraic sum of these two terms is then $\sum_{i}^{3n-7} G(u_i^{\neq})\Delta u_i^{\neq}$, and is negative. But the whole term is substracted from one in equation IX, so the overall effect is to multiply the square root of the reduced mass ratio by a number greater than one. The value of k_3/k_2 calculated in this manner is 1.14. This is in quite reasonable agreement with all the data available on the decarboxylation of C^{14} substituted malonic acids. It is quite possible that for individual compounds, better agreement with theory could be obtained by using experimentally determined vibrational frequencies. At any rate, in the case of a molecule like malonic acid, setting $\sum_{i}^{3n-6} (u_i^{\neq})\Delta u_i^{\neq}$ equal to zero <u>does not give an upper limit to the isotope effect as has been claimed</u>.[7]

Another factor which must be considered in determining the overall isotope effect in a reaction is the possibility of an isotope effect in an equilibrium prior to the rate determining step and multiplying an isotope effect in the latter. Such a situation would be expected to be the rule rather than the exception, since most reactions do involve pre-equilibria of one sort or another.

We may take as a simple model of such an equilibrium in the case of malonic acid the equilibrium between the two different hydrogen bonded internal rings, thus:



Then, $K_1 = (B)/(A)$ and $K_2 = (C)/(B)$ and the general equations X and XI may be derived in the same manner as equations IV and V where $\beta = \dfrac{k_2 + k_3K_2}{1 + K_2 + 1/K_1}$.

$$\frac{C^*O_2}{C^*O_2 + CO_2} = \frac{k_2 M_o^* (1 - e^{-\beta t})}{(k_2 + k_3 K_2) M_o (1 - e^{-k_1 t}) + M_o^* (1 - e^{-\beta t})} \qquad (X)$$

$$\frac{A^*}{A^* + A} = \frac{k_3 K_2 M_o^* (1 - e^{-\beta t})}{(k_2 + k_3 K_2) M_o (1 - e^{-k_1 t}) + M_o^* (1 - e^{-\beta t})} \qquad (XI)$$

By combining equations X and XI at any time we obtain equation XII.

$$\frac{\dfrac{A^*}{A^* + A}}{\dfrac{C^*O_2}{C^*O_2 + CO_2}} = \frac{k_3 K_2}{k_2} \qquad (XII)$$

Thus it is seen that the isotope effect on the rate of the reaction is multiplied by the equilibrium constant, and it is actually this product that is measured experimentally.

If the reaction involves a pre-equilibrium of this sort, the ratio of rate constants must be recalculated using the different "normal molecules" (B) and (C), but to a first approximation the same calculation we have made above applies since all the terms which are different between (B) and (C) in the ground state are also different, but in the opposite sense between (B) and (C) in the activated state. However, recognition that such pre-equilibria exist should aid in establishing more exact models for the reaction and hence to make possible more exact calculations.

We may make a crude calculation of the equilibrium constant, K_2, according to the method of Urey[22] or Bigeleisen and Mayer[21]. This involves choosing appropriate

(22) H. C. Urey, J. Chem. Soc., 562 (1947).

vibrational frequencies for the molecules (B) and (C). For lack of more exact knowledge, the free carbonyl and free hydroxyl frequencies are chosen as those of monomeric acetic acid, while the hydrogen-bonded carbonyl and hydroxyl are assigned the corresponding frequencies of acetic acid dimer. All other frequencies are assumed to be the same for the two molecules. Although there seems to be some question in the literature as to which frequencies should be assigned to the above vibrations, for this calculation we take the assignments of Davies and Sutherland[23]. The effect of C^{14} substitution was

(23) M. M. Davies and G.B.B.M. Sutherland, J. Chem. Phys., 6, 755 (1938).

calculated using the assumption of simple harmonic vibration. The frequencies assigned by Davies and Sutherland are shown in Table III, along with the calculated values for C^{14} substitution.

Table III

Frequencies for Normal and Hydrogen Bonded Acetic Acid Carboxyl Group Vibrations

Bond	Frequency, cm^{-1} Monomer	Dimer
$C^{12}=O$	1768	1701
$C^{14}=O$	1694	1630
$C^{12}-O$	1393	1435
$C^{14}-O$	1335	1375

Using these frequencies, the equilibrium constant is calculated to be 0.991 at 350°K.[24]. When combined with the ratio k_3/k_2 calculated above, this gives an over-

(24) Dr. P. E. Yankwich kindly pointed out an error in sign in the calculation of this constant in an earlier draft of this paper.

Aside from these theoretical calculations, the effect of the substituent on the isotope effect in the decarboxylation of substituted malonic acids is of considerable interest. There is a fairly large difference between the two acids studied in this work, and between them and malonic acid itself, regardless of which value is chosen for the isotope effect in the latter case. It seems possible that resonance stabilization of the incipient intermediate ion in the transition state may have an effect on the isotope effect, in which case we should be able to increase or decrease the effect by appropriate substitution of the aromatic ring.

Experimental

Preparation of diethyl α-naphthylmalonate-1-C^{14}. - Diethyl α-naphthylmalonate-1-C^{14} was prepared according to the procedure of Blicke and Feldkamp[13]. Ethyl α-naphthylacetate was prepared by treating 41.03 g. of α-naphthylacetic acid with 100 cc. of absolute alcohol and 5 cc. concentrated sulfuric acid for 16 hrs. The solution was poured onto ice, extracted into ether, washed with sodium carbonate solution, washed with water and dried. The ether was evaporated and the residue heated *in vacuo* to remove any traces of water. From the sodium carbonate solution 2.03 g. of α-naphthylacetic acid was recovered. A solution of sodium ethoxide was prepared by dissolving 4.82 g. of freshly cut sodium in 100 cc. of magnesium dried absolute alcohol, and to this was added

30.60 g. of freshly distilled diethyl oxalate-1-2-C_2^{14}, followed by the ethyl α-naphthylacetate prepared above. The solution was heated to reflux for a few minutes with stirring, and upon cooling the entire contents of the flask solidified. The mixture was filtered with the aid of ether, and the precipitate suspended in water. The suspension was acidified and ether extracted. The ether solution was dried, the ether evaporated, and the glyoxalate heated at 175-185°C at 15 mm. for one hour in the presence of 20 g. of ground glass. Most of the carbon monoxide came off in the first few minutes. The residual oil was dissolved in alcohol, filtered and allowed to cool in the refrigerator overnight. The diethyl α-naphthylmalonate weighed 39.49 g., 67.4% yield, m.p. 59-59.5°C. Recrystallization from alcohol gave a product of m.p. 62-62.5°C, reported, m.p. 62°C[13]. Alcohol is a much more satisfactory solvent for recrystallization than the petroleum ether used by Blicke and Feldkamp.

Preparation of diethyl oxalate-1,2-C_2^{14}. - Diethyl oxalate-1,2-C_2^{14} was prepared by dissolving 3.15 g. of anhydrous oxalic acid-1,2-C^{14}, prepared by the reaction of $C^{14}O_2$ with potassium on sand at 360°C and 47.85 g. of commercial anhydrous oxalic acid in 100 cc. of absolute alcohol saturated with hydrogen chloride gas. The solution was allowed to stand overnight and the alcohol and water were removed by vacuum distillation. Another 100 cc. of absolute alcohol saturated with hydrogen chloride, along with 96.7 g. of commercial diethyl oxalate was added to the residue. After standing overnight the solution was vacuum distilled and the fraction boiling at 89-94°C at 24 mm. was collected, wt. = 147.4 g., 82.1% yield based on total oxalate used.

Transesterification of diethyl α-naphthylmalonate-1-C^{14}.- A solution of 5.26 g. of diethyl α-naphthylmalonate-1-C^{14} in 25 cc. of glacial acetic acid and 2 cc. of concentrated hydrochloric acid was left standing at room tempera-

ture for 1-1/2 months. At the end of this time the acetic acid, ethyl acetate, water and hydrochloric acid were blown off at room temperature by a stream of air. The yellow crystalline residue was stirred up with benzene and filtered, giving 2.92 g., 69.4% yield, of white prisms of α-naphthylmalonic acid-1-C^{14}, m.p. 156-162° d. The benzene filtrate contains the unhydrolyzed mono- and di-esters along with any α-naphthylacetic acid. The α-naphthylmalonic-1-C^{14} acid was further purified by solution in base, extraction of the solution with ether, decolorization of the basic solution with charcoal, acidification and extraction into ether. Most of the ether was evaporated, the solution was filtered, and a large excess of benzene was added. Upon standing the α-naphthylmalonic acid-1-C^{14} crystallized as fine white prisms, m.p. 162-5° d. Ivanov and Pshenichnii[24] reported the melting point as "toward 151°d." The equivalent weight was determined on an inactive sample prepared in a similar manner. A sample of 34.3 mg. required 2.97 cc. of 0.1000 N sodium hydroxide, giving an equivalent weight of 115.5, calculated, 115.1. Additional recrystallizations of the labeled acid failed to change the melting point (which depended somewhat on the rate of heating) but were carried out in order to insure complete radioactive purity.

Phenylmalonic acid-1-C^{14}, m.p. 162-5°, was prepared in a similar manner from phenylacetic acid and diethyl oxalate-1,2-C_3^{14}.

Decarboxylation experiments. - The decarboxylation experiments were carried out in the apparatus shown in Figure 1.

In a typical experiment, 0.4306 g. of α-naphthylmalonic acid-1-C^{14} was placed in the decarboxylation chamber, B, the condenser was affixed using high vacuum silicone stopcock grease to grease the joints, and the system was flushed with dry carbon dioxide-free nitrogen for one hour. The outlet gas was led from the top of the condenser through a spiral trap cooled by a dry ice-isopropyl

(24) D. Ivanov and G. Pshenichnii, Ann. Univ. Sofia, II, Faculte phys-math, Livre 2, 33, 177-202 (in French, 203-11) (1937); C.A. 32, 3356[9].

alcohol bath to remove any solvent or entrained solid, and then through a spiral bubbler. After thorough flushing, the spiral bubbler was filled with carbonate-free 1 N sodium hydroxide, and the solvent in the lower flask, A, was heated to reflux, thus heating the decarboxylation chamber to the boiling point of the solvent. For this experiment the solvent used was mesitylene, giving a decomposition temperature of 163.0°C. After a few minutes at 163°, the solid α-naphthalenemalonic acid gradually began to melt and simultaneously decarboxylate. The "melting" became progressively faster as more α-naphthaleneacetic acid "impurity" was formed. Within about 5 minutesof the time the heating was first started all visible reaction had ceased, leaving a clear light yellow liquid. The nitrogen sweep was continued for an additional 1-1/2 hours to insure complete recovery of the carbon dioxide. The contents of the sodium hydroxide bubbler were washed into an equal volume of 1 N ammonium nitrate, and excess barium chloride was added. The barium carbonate formed, when collected and dried, weighed 0.3708 g., 100.5% yield. The α-naphthylacetic acid-1-C^{14} was washed from the decarboxylation chamber with the aid of alcohol, and was titrated with 1.000 N sodium hydroxide, 1.87 cc. being required for neutralization. Assuming complete reaction, this gives a yield of 100.0%. The basic solution from the titration was evaporated to dryness, dissolved in water and extracted with ether. The aqueous phase was acidified, decolorized with charcoal and the hot solution filtered. Upon cooling the α-naphthaleneacetic acid crystallized out, sometimes in needles and sometimes in plates. The crude acid was recrystallized twice more from boiling water. The final product melted at 128-30°C.

In the solution experiments the solid α-naphthylmalonic acid-1-C^{14} was placed in the decarboxylation chamber and dissolved in 3 cc. of dioxane which had been purified by distillation over hydrochloric acid and then over sodium. Nine cc. of

1 N hydrochloric acid was added, and the flushing procedure carried out as described above. In this case the gas inlet tube served to stir the solution in the decarboxylation chamber. The solvents used for the constant temperature bath in the solution experiments were technical ethyl acetate, b.p. 72.8°C, technical dioxane, b.p. 100.5°C, and the dioxane-water azeotrope, b.p. 87.5°C, containing 18% water. In these experiments the reaction was considerably slower, and the reactions were allowed to run overnight. Visible bubbles were no longer apparent after about 2 hours, and the initially clear solution had become turbid. A short time later several drops of yellow oil had collected in the bottom of the decarboxylation chamber. Apparently the α-naphthylacetic acid was less soluble than malonic acid. Blank runs on the procedure, omitting only the α-naphthalenemalonic acid, gave 0.1-0.5 mg. of barium carbonate.

Combustion of α-naphthylmalonic and α-naphthylacetic acids. - Samples of the α-naphthylmalonic acid-1-C^{14} and of the α-naphthylacetic acid-1-C^{14} were oxidized to carbon dioxide by a modified Van Slyke-Folch wet combustion. From 0.1077 g. of α-naphthylmalonic acid-1-C^{14}, 1.2173 g., 101.4% yield, of barium carbonate was obtained, and from 0.1068 g. of α-naphthaleneacetic-acid-1-C^{14}, 1.1516 g., 101.4%, yield was obtained. All the barium carbonate yields reported are high by about 1.2% due to coprecipitated barium carbonate. This correction was determined by comparing the pressure of carbon dioxide volved from the barium carbonate samples in a constant volume system with the corresponding pressure from a sample of pure barium carbonate.

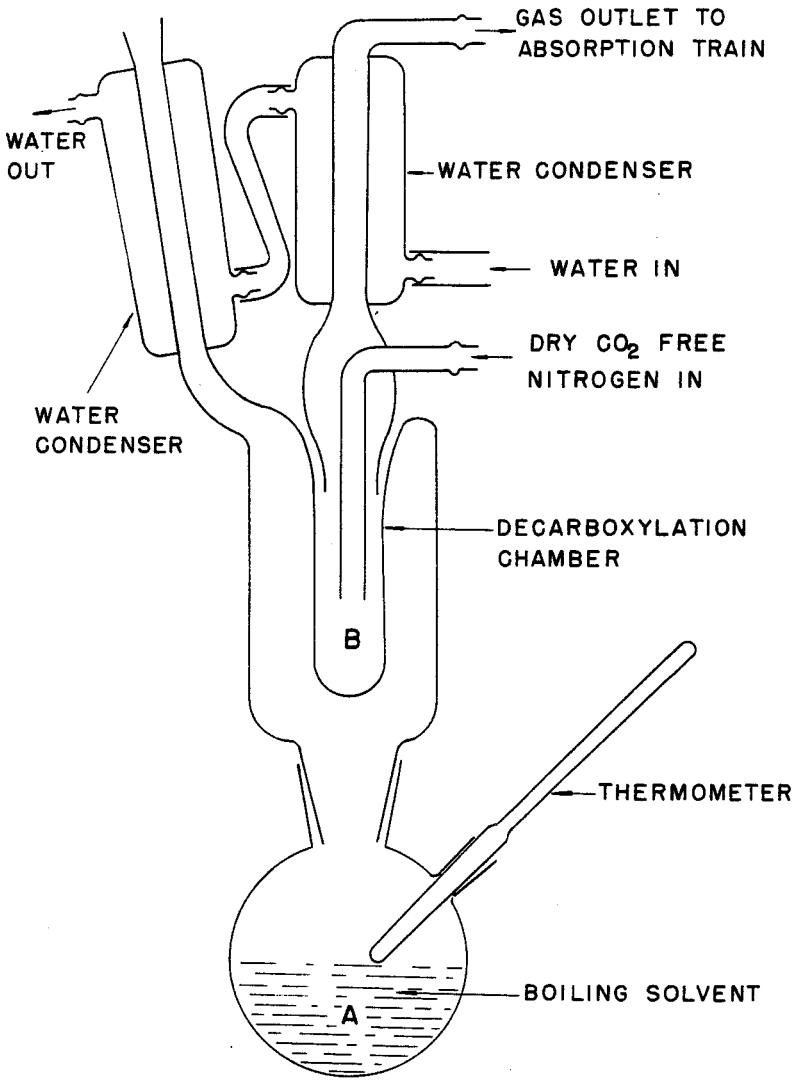


FIG. I APPARATUS FOR CONSTANT TEMPERATURE DECARBOXYLATION OF MALONIC ACIDS

MU 2749