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A Carbon-14 Isotope Effect Study of the Dieckmann Condensation of Diethyl Phenylenediacetate[1,2]

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The principle of locating the rate-determining step in a reaction by successively labeling different positions in a molecule and determining whether or not there is an isotope effect in the reaction has been applied to the Dieckmann condensation of diethyl phenylenediacetate. An intramolecular isotope effect of 5.6% is observed with diethyl phenylenediacetate-1-C^{14} and an intermolecular isotope effect of about 8.5% is observed with both diethyl phenylenediacetate-1-C^{14} and diethyl phenylenediacetate-2-C^{14} when the reaction is carried out in alcohol solution using sodium ethoxide as the condensing agent. The only step in the Dieckmann condensation which involves both labeled positions is carbon–carbon bond formation, so it is concluded that this is the rate-determining step of the reaction. The theoretical implications of this interpretation are discussed briefly. When the reaction with diethyl phenylenediacetate-1-C^{14} is carried out in toluene solution using metallic sodium as the condensing agent an intramolecular isotope effect of 1.6% is observed. The low value in this case probably is due to product selection in an irreversible step not involving the isotopic center prior to the rate-determining step.

Introduction

The gross features of the Claisen condensation, of which the Dieckmann condensation is a special case involving intramolecular condensation of an ester of a dibasic acid to produce a cyclic β-ketoester, are well established.[4] However, no rate studies of the reaction have been made, and the rate-determining step of the reaction has not been identified.

The development of the theory of the effect of isotopic substitution on the rate of chemical reactions[5] during recent years has made available a powerful new tool for locating the rate-determining step of a reaction. In general, if the isotopic element enters into bond formation or rupture in an essentially irreversible rate-determining step, there will be a difference in the rate of reaction of the labeled and unlabeled molecules, with the molecule containing the heavier isotope usually reacting more slowly. For carbon tracer work this isotope effect is usually expressed as a ratio of rate constants, $k_{C^{12}}/k_{C^*}$, or as percentage isotope effect, $(k_{C^{12}}/k_{C^*} - 1)100$. Numerous examples are known in which the presence[6] or absence[7] of a carbon, nitrogen or oxygen isotope effect has led to conclusions concerning the rate-determining step of a reaction. The principle has been used for many years in studying reactions involving hydrogen isotopes, with which the effects are often very large.

Frequently a reaction sequence is such that either bond formation or bond rupture of a different bond at the labeled position might be rate-determining, and a simple isotope effect experiment would not distinguish adequately between the various possibilities. Since either bond formation or bond rupture involves two atoms, further information can be obtained by observing whether or not there is an isotope effect in the reaction of the same compound but with the other suspected position labeled. Thus, if large isotope effects are observed with the same compound in *both* of two experiments which differ only in the position of labeling, the actual rate-controlling step must involve *both* of these labeled positions. Hence, it can only be bond formation or rupture between the atoms at the labeled positions. Whether it is bond formation or bond rupture is, of course, obvious from the structure of the product. Also, from theoretical considerations, one would expect smaller isotope effects in bond formation than in bond rupture.[7d,8,9] The situation is complicated further by the fact that bond formation and bond rupture are to some extent concerted in many reactions. Bigeleisen and Wolfsberg have discussed this in some detail from a theoretical point of view.[10]

Data already are available for the application of this principle to the decarboxylation of malonic acid. That rupture of the carbon–carbon bond is the central action in the rate-determining step in the decarboxylation of malonic acid is shown by the fact that large isotope effects have been observed in the decarboxylation of *both* malonic-1-C^{14} acid[11] and malonic-2-C^{14} acid.[12] Rupture of the carbon–carbon bond is the only step in the reaction sequence which involves both of the labeled positions.

The present research was undertaken in an attempt to apply this principle to a study of the mechanism of the Dieckmann condensation of diethyl phenylenediacetate, where carbon–carbon bond formation was suspected of being the rate-determining step. Isotope effect experiments were carried out in which the diethyl phenylenediacetate was labeled with carbon-14 successively in the carbonyl carbon and in the methylene group adjacent to the ring.

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(3) Pan-American Refining Corporation Fellow, 1953–1954.

(4) E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 185.

(5) For a review of these developments and other isotope effect work, see G. A. Ropp, *Nucleonics*, **10**, No. 10, 22 (1952).

(6) (a) A. Fry and M. Calvin, *J. Phys. Chem.*, **56**, 897 (1952); (b) J. A. Schmitt, A. L. Myerson and F. Daniels, *ibid.*, **56**, 917 (1952); (c) F. W. Stacey, J. G. Lindsay and A. N. Bourns, *Can. J. Chem.*, **30**, 135 (1952); (d) J. Bigeleisen, *ibid.*, **30**, 443 (1952); (e) A. E. Cahill and H. Taube, THIS JOURNAL, **74**, 2312 (1952); (f) G. A. Ropp and V. F. Raaen, *J. Chem. Phys.*, **22**, 1223 (1954); (g) C. C. Lee and J. W. T. Spinks, *Can. J. Chem.*, **32**, 327 (1954); and others.

(7) (a) J. Bigeleisen, A. A. Bothner-By and L. Friedman, THIS JOURNAL, **75**, 2908 (1953); (b) W. H. Stevens, J. M. Pepper and M. Lounsbury, *Can. J. Chem.*, **30**, 529 (1952); and others.

(8) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

(9) W. A. Shepard, R. F. W. Bader and A. N. Bourns, *Can. J. Chem.*, **32**, 345 (1954).

(10) J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 1972 (1953); **22**, 1264 (1954).

(11) P. E. Yankwich and M. Calvin, *ibid.*, **17**, 109 (1949).

(12) G. A. Ropp and V. F. Raaen, THIS JOURNAL, **74**, 4992 (1952).

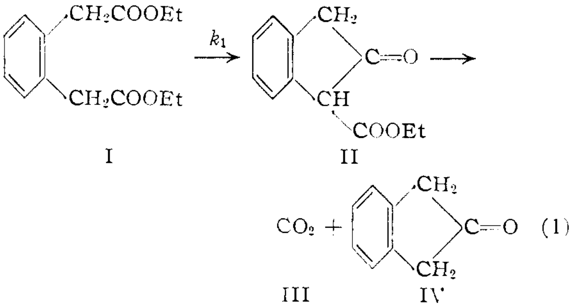
To bring about the condensation, two general sets of reaction conditions were employed. In the first case, the ester was treated with powdered sodium in toluene at 100°.[13] In the second case, the ester was treated with sodium ethoxide in absolute alcohol at 80°.[14] The intramolecular isotope effect was measured with diethyl phenylenediacetate-1-C^{14} under both sets of reaction conditions, and the intermolecular[15] isotope effect was measured with both diethyl phenylenediacetate-1-C^{14} and diethyl phenylenediacetate-2-C^{14} in alcohol solution.

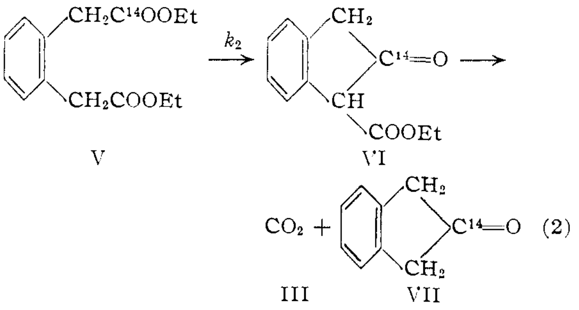
The intramolecular effect was obtained by comparing the molar activity of the carbon dioxide with that of the 2-hydrindone obtained by hydrolysis and decarboxylation of the ethyl 2-hydrindone-1-carboxylate formed at complete reaction.

The intermolecular values were obtained by comparing the molar activity of the ethyl 2-hydrindone-1-carboxylate at 9% reaction with its molar activity at 100% reaction or with the molar activity of the diethyl phenylenediacetate used.

Calculations and Results

Since the carbon-14 is present in only tracer amounts, the condensing ester consists of both labeled and unlabeled molecules, and three reaction products are possible from each experiment. With diethyl phenylenediacetate-1-C^{14} these three reaction products are II, VI and VII, whereas with diethyl phenylenediacetate-2-C^{14} they are II, XI and XII.


I II III IV (1)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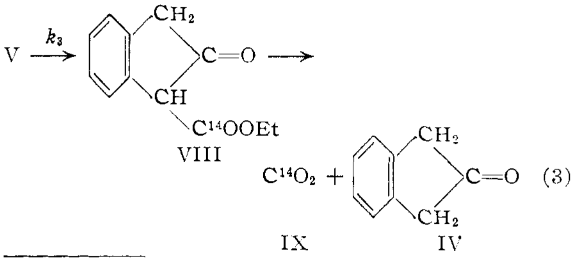
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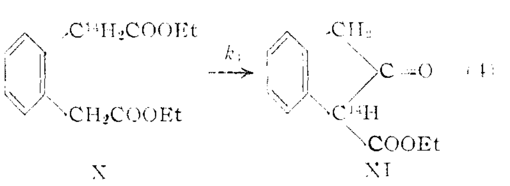
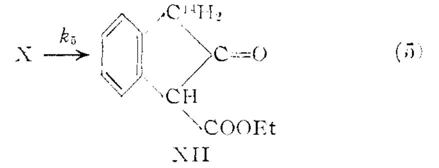

X XI (4)


XII (5)

The intramolecular isotope effect for diethyl phenylenediacetate-1-C^{14} is given by the ratio k_3/k_2. The intermolecular isotope effect is given by the ratio $k_1/2k_2$ for diethyl phenylenediacetate-1-C^{14} and by the ratio $k_1/2k_4$ for diethyl phenylenediacetate-2-C^{14}.

Parentheses indicate concn., *i.e.*, concn. of I = (I), etc., and at time = 0, we let (I) = (I_0), (V) = (V_0) and (X) = (X_0). Since hydrolysis and decarboxylation of ethyl 2-hydrindone-1-carboxylate (II, VI and VII) is quantitative, as shown by collection of the carbon dioxide evolved, for the experiments with diethyl phenylenediacetate-1-C^{14}, the molar activity of the carbon dioxide, (IX)/[(IX) + (III)], is equal to the molar activity of the carboxyl group of ethyl 2-hydrindone-1-carboxylate, and the molar activity of the hydrindone, (VII)/[(VII) + (IV)], is equal to that of the carbonyl group of the same ester.

In the intramolecular experiments, it is then easy to show that the ratio of rate constants is related to the molar activities of the carbon dioxide and hydrindone by equation 6.

$$\frac{k_3}{k_2} = \frac{(\mathrm{IX})}{(\mathrm{III}) + (\mathrm{IX})} \Big/ \frac{(\mathrm{VII})}{(\mathrm{IV}) + (\mathrm{VII})} \qquad (6)$$

For the intermolecular experiments with diethyl phenylenediacetate-1-C^{14}, the molar activity of the ethyl 2-hydrindone-1-carboxylate is given by equation 7.

$$\frac{(\mathrm{VI}) + (\mathrm{VIII})}{(\mathrm{II}) + (\mathrm{VI}) + (\mathrm{VIII})} = \frac{(\mathrm{V})_0(1 - e^{-(k_2+k_3)t})}{(\mathrm{V}_0)(1 - e^{-(k_2+k_3)t}) + (\mathrm{I}_0)(1 - e^{-k_1t})} \qquad (7)$$

If we stop the reaction when only a negligibly small fraction of the starting ester has reacted, we may expand the exponential terms in power series and neglect squared and higher terms. This gives equation 8.

$$\frac{(\mathrm{VI}) + (\mathrm{VIII})}{(\mathrm{II}) + (\mathrm{VI}) + (\mathrm{VIII})} \cong \frac{(\mathrm{V}_0)(k_2 + k_3)}{(\mathrm{V}_0)(k_2 + k_3) + (\mathrm{I}_0)k_1} \qquad (8)$$

Since this is a tracer experiment, the labeled molecules are present in very small concentration and we may assume that (II) + (VI) + (VIII) ≅ (II) and that $(\mathrm{V}_0)(k_2 + k_3) + (\mathrm{I}_0)k_1 \cong (\mathrm{I}_0)k_1$. We also may assume that the unlabeled center in the labeled molecule reacts at the same rate as the corresponding center in an unlabeled molecule so that $k_3 \cong$

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(13) W. H. Perkin, Jr., and A. F. Titley, *J. Chem. Soc.*, **121**, 1562 (1922).

(14) W. Dieckmann, *Ber.*, **55**, 2470 (1922).

(15) The intramolecular effect is a measure of the relative rates of reaction of the labeled and unlabeled center in the same molecule. The intermolecular effect is a measure of the relative rate of reaction of the labeled center in the labeled molecule and the unlabeled molecule.

$k_1/2$. Applying these assumptions to equation 8 we obtain equation 9

$$\frac{k_1}{2k_2} \cong \frac{(\mathrm{V_0})/(\mathrm{I_0})}{2\,\dfrac{(\mathrm{VI}) + (\mathrm{VIII})}{(\mathrm{II})} - \dfrac{(\mathrm{V_0})}{(\mathrm{I_0})}} \tag{9}$$

where $(\mathrm{V_0})/(\mathrm{I_0}) \cong$ molar activity of diethyl phenylenediacetate-1-C^{14} = molar activity of ethyl 2-hydrindone-1-carboxylate, and $[(\mathrm{VI}) + (\mathrm{VIII})]/(\mathrm{II}) \cong$ molar activity of ethyl 2-hydrindone-1-carboxylate at a negligibly small fraction of complete reaction.

By applying the same procedure to the intermolecular experiments with diethyl phenylenediacetate-2-C^{14}, we obtain equation 10

$$\frac{k_1}{2k_4} \cong \frac{(\mathrm{X_0})/(\mathrm{I_0})}{2\,\dfrac{(\mathrm{XI}) + (\mathrm{XII})}{(\mathrm{II})} - \dfrac{(\mathrm{X_0})}{(\mathrm{I_0})}} \tag{10}$$

where $(\mathrm{X_0})/(\mathrm{I_0}) \cong$ molar activity of diethyl phenylenediacetate-2-C^{14} = molar activity of ethyl 2-hydrindone-1-carboxylate at complete reaction, and $[(\mathrm{XI}) + (\mathrm{XII})]/(\mathrm{II}) \cong$ molar activity of ethyl 2-hydrindone-1-carboxylate at a negligibly small fraction of complete reaction.

We have applied these equations to the case where the reaction was stopped at 9% of complete reaction. The error involved in assuming that this is a negligibly small fraction of complete reaction is small.[16] The assumption that the unlabeled center in the labeled molecule reacts at the same rate as the corresponding center in an unlabeled molecule probably involves only a small error, as has been shown to be the case for the decarboxylation of malonic acid.[17]

Table I gives the molar activities of the compounds for all the intramolecular experiments and the isotope effect values calculated from them using equation 6. The fact that the sum of the molar activities of the carbon dioxide and hydrindone is essentially equal to the molar activity of ethyl 2-hydrindone-1-carboxylate serves as a suitable check on the experimental procedure and counting accuracy. The molar activity balance is accurate within the experimental error of approximately 0.5%. Samples 20 and 21 afford another check on the procedure. In these experiments the molar activity of diethyl phenylenediacetate-2-C^{14}, ethyl 2-hydrindone-1-carboxylate and hydrindone are all equal within a small experimental error, as they should be, and no activity was found in the carbon dioxide. Two sets of reaction conditions in toluene solution and three sets of reaction conditions in alcoholic solution are represented. In view of the errors involved, the differences between the two sets of conditions in toluene are probably not significant, and the differences between the three sets of conditions in alcohol solution are certainly not significant. The over-all average of all the values is 1.6 ± 0.5% for the experiments in toluene, and 5.6 ± 0.7% for all the experiments in alcohol.

Table II gives the molar activities of the compounds for the intermolecular 9% condensation experiments and the isotope effect values calculated from them using equations 9 and 10. It

TABLE I

INTRAMOLECULAR ISOTOPE EFFECT IN THE CYCLIZATION OF DIETHYL PHENYLENEDIACETATE-1-C^{14}

Run	Reaction conditions[a] Diethyl phenylene-diacetate-1-C^{14} with	Carbon dioxide	2-Hydrindone[b]	Ethyl 2-hydrindone-1-carboxylate[b]	CO_2 + 2-hydrindone	Isotope effect, % $100[(k_3/k_2) - 1)]$ (using eq. 6)
1	Sodium in toluene	7.82	7.64	15.84	15.46	2.3
2	for 2 hours at	7.93	7.80	15.73	15.70	1.7
3	100°	7.97	7.79	15.80	15.76	2.3
4		7.89	7.74	15.43	15.63	1.9
					Average	2.1 ± 0.3
5	Sodium in toluene	14.01	14.09	28.49	28.10	−0.6
6[c]	for 15 min. at	13.19	12.90	26.06	26.10	2.2
7[c]	100°	13.06	12.92	25.97	25.98	1.1
					Average	0.9 ± 1.0
8	Sodium ethoxide	14.50	13.73	27.85	28.23	5.6
9	in absolute al-	14.49	13.73	28.42	28.22	5.5
10	cohol for 15	14.49	13.73	28.06	28.22	5.5
11	min. at 80°	14.33	13.79	28.13	28.12	3.9
					Average	5.1 ± 0.6
12	Sodium ethoxide	14.25	13.48	27.85	27.73	5.7
13[c]	in alcohol for	13.39	12.83	26.26	26.22	4.4
14[c]	1.5 hr. at 80°	13.34	12.64	26.26	25.98	5.5
15[c]		13.55	12.65	26.39	26.20	7.1
					Average	5.7 ± 0.7
16	100% excess so-	12.14	11.33	23.66	23.47	7.1
17	dium ethoxide	11.77	11.23		23.00	4.8
18	in alcohol for 2	12.02	11.23	23.21	23.25	7.0
19	hr. at 80°	11.90	11.29	23.21	23.19	5.4
					Average	6.1 ± 0.9
	Diethyl phenylene diacetate-2-C14 with					
20[d]	Sodium ethoxide	0.00	18.69	18.77	18.69	
21[d]	in alcohol 15 min. at 80°	0.00	18.78	19.01	18.78	

[a] A relative drift rate of one volt per minute in this counting system is approximately equal to 6 microcuries per mole. [b] Obtained by multiplying the measured carbon dioxide value by 12 or 14, the number of carbon atoms in the molecule. [c] Molar activity of the diethyl phenylenediacetate-1-C^{14} = 26.12 volts/min. [d] Molar activity of the diethyl phenylenediacetate-2-C^{14} = 18.70 volts/min.

TABLE II

INTERMOLECULAR ISOTOPE EFFECT IN THE CYCLIZATION OF DIETHYL PHENYLENEDIACETATE-1-C^{14} AND DIETHYL PHENYLENEDIACETATE-2-C^{14}

	Relative molar activities, drift rate, v./min.[a]			Isotope effect, % $100[(k_1/2k_4) - 1)]$ (using eq. 10)	
		Ethyl 2-hydrindone-1-, carboxylate[b]			
Run	Diethyl phenylene-diacetate[b]	9% reaction	100% reaction	From col. 2 and 3	From col. 3 and
22[c]	5.81	5.57	5.76	9.0	7.1
23[c]	5.78	5.57	5.76	7.8	7.1
24[c]	5.75	5.52	5.72	8.6	7.5
25[c]	5.75	5.52	5.78	8.6	9.9
26[c]	5.70	5.49	5.77	8.0	11.0
			Average	8.4 ± 0.4	8.5 ± 1.5
				$100[(k_1/2k_2) - 1)]$ (using eq. 9)	
27[d]	23.27	22.10	23.30	11.1	6.3
28[d]	23.07	22.39	23.30	7.2	11.4
29[d]	23.17	22.39	23.28	8.5	8.3
			Average	8.9 ± 1.4	8.7 ± 1.8

[a] A relative drift rate of one volt per minute in this counting system is approximately equal to 6 microcuries per mole. [b] Obtained by multiplying the measured carbon dioxide value by 12 or 14, the number of carbon atoms in the molecule. [c] Diethyl phenylenediacetate-2-C^{14} used. [d] Diethyl phenylenediacetate-1-C^{14} used.

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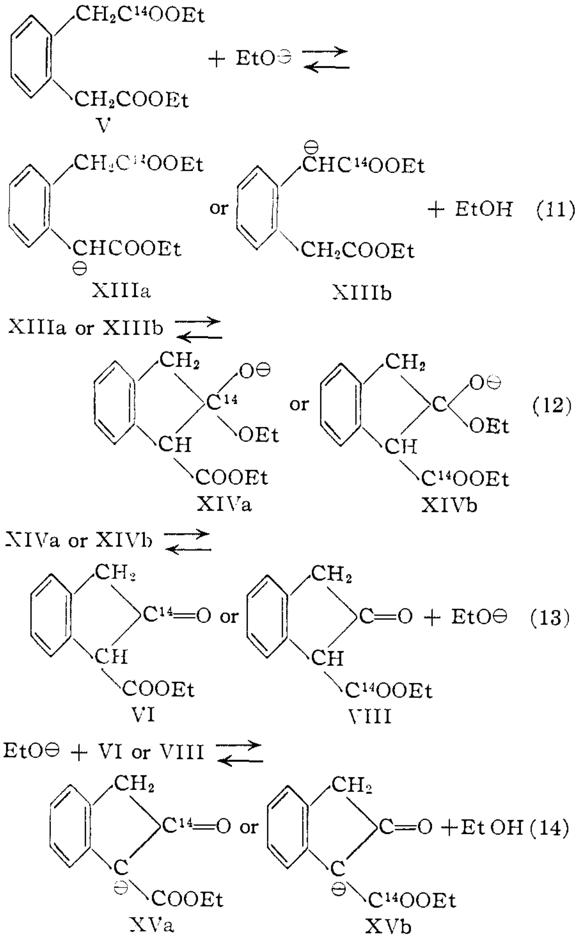
(16) J. Bigeleisen, *Science*, **110**, 14 (1949).

(17) J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 2120 (1952).

should be noted that the molar activity of diethyl phenylenediacetate is essentially equal to the molar activity of ethyl 2-hydrindone-1-carboxylate at complete reaction. This indicates quite conclusively that the compounds are not contaminated by other radioactive compounds. The results are somewhat less reliable than those obtained in the intramolecular case, but the isotope effect values are clearly larger.

Discussion

The generally accepted mechanism of the sodium ethylate catalyzed Claisen condensation as applied to the reaction of diethyl phenylenediacetate-1-C^{14} is shown below. A similar reaction sequence could be written for diethyl phenylenediacetate-2-C^{14}, differing only in the position of the labeled atom.



The Claisen condensation has been shown to be reversible.[18] However, by using excess base, the reaction can be made effectively irreversible by essentially quantitative conversion of the β-keto ester to the enolate salt, equation 14. The fact that the isotope effect values are the same whether the reaction is carried out for 15 minutes or 1.5 hours indicates that the reaction is not reversible under these conditions. The experiments in toluene solution will be discussed later.

In the experiments in alcohol solution the presence of a large isotope effect when diethyl phenylenediacetate-1-C^{14} is used is good evidence that neither equation 11 nor equation 14 represents the rate-determining step, since the isotopic center is not involved in either of these two steps. Insofar as the ester with the label in this position is concerned, either equation 12 or 13 could represent the rate-controlling step, since bond formation or rupture at a carbonyl carbon occurs in each. Equation 12 represents carbon–carbon bond formation, and equation 13 represents carbon–oxygen bond rupture. However, since a large isotope effect also is observed in the reaction of diethyl phenylenediacetate-2-C^{14}, equation 13 could not represent the rate-controlling step because this step does not involve the isotopic center in this case. The only step which involves the isotopic center with *both* labeled esters is represented by equation 12; hence, this must be the rate-determining step of the reaction.

If formation of the carbon–carbon bond and elimination of ethoxide ion were concerted (effectively a displacement reaction), one would expect little or no isotope effect with diethyl phenylenediacetate-1-C^{14}. This is the type of behavior found by Bigeleisen, Bothner-By and Friedman[7a] in the somewhat similar pyrolysis of barium adipate. Even if the reaction had been concerted in this manner, an intermolecular isotope effect would still be expected in the case of diethyl phenylenediacetate-2-C^{14}. It seems likely that an intermolecular isotope effect would be found in the pyrolysis of barium adipate-2-C^{14}.

While the central action in the rate-determining step of this reaction is certainly carbon–carbon bond formation, the observed isotope effect values are considerably higher than would be expected for a simple reaction of this type. Bigeleisen[8] has treated the effect of isotopic substitution on the rates of chemical reactions theoretically and has derived equation 15 relating the rate constants to vibrational frequencies of the bonds.

$$\frac{k}{k^*} = \left(\frac{\mu^*}{\mu}\right)^{1/2}\left[1 + \sum_i^{3n-6} G(u_i)\Delta u_i - \sum_i^{3n-6} G(u_i^{\neq})\Delta u_i^{\neq}\right] \quad (15)$$

The function $G(u)$ is defined by Bigeleisen and Mayer[19] who tabulated values of $G(u)$ as a function of u. The reaction coördinate effective mass, μ, is usually assumed to be the reduced mass of the atoms forming the bond which is being formed or broken. The symbol $\neq$ refers to the activated complex, and * refers to the heavy molecule. The first term under the summation sign refers to the ground state, and the second to the transition state. In general, the heavy molecule reacts slower, so k/k^* is usually greater than one.

For an intramolecular reaction, the term $\sum_i^{3n-6} G(u_i)\Delta u_i$ is zero because the ground state is the same molecule, regardless of whether the light or heavy atom is undergoing reaction.

In his original treatment of intramolecular isotope effects, Bigeleisen[20] assumed a model for the

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[18] C. R. Hauser and W. B. Renfrow, Jr., THIS JOURNAL, **59**, 1823 (1937).

[19] J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, **15**, 261 (1947).

[20] J. Bigeleisen, *ibid.*, **17**, 344 (1949).

activated complex in which all the atoms in the molecule are unbonded. Hence, the term $\sum_{i}^{3n-6} G(u_i)^{\neq} \cdot \Delta u_i^{\neq}$ was also zero and the isotope effect was equal to the reduced mass term. He stated that this model led to an upper limit for the effect. However, Fry and Calvin[21] pointed out that a different model could be assumed in the malonic acid case in which the activated complex for reaction involving the heavy atom was different from that involving the light atom. This leads to a value of $\sum_{i}^{3n-6} \Delta G(u_i)^{\neq} u_i^{\neq}$ different from zero, and, hence, to values for the isotope effect either greater than or less than the reduced mass term.

A similar model with results similar to the malonic acid case may be chosen here, but calculations are rather meaningless in such a complicated system as this, especially since no spectroscopic information is available. It does seem significant that the observed value of 5.6% is considerably higher than Bigeleisen's calculated upper limit of 3.8% for a case of simple carbon–carbon bond formation.

In an intermolecular isotope effect study the rate of reaction of the labeled and unlabeled molecule is compared, and in this case the ground states of the two molecules are different. Therefore, in this case we must consider the vibrational frequencies of all bonds in the ground state as well as those in the transition state. In simple bond rupture reactions, the transition state has one less bond involving the isotopic center than the ground state and, hence, the term in brackets in equation 15 is >1. In simple bond formation reactions the transition state has one more bond involving the isotopic center than the ground state, and hence the term in brackets is <1. Therefore, in this case, if simple bond formation were involved, we would expect an intermolecular isotope effect somewhat smaller than the reduced mass term, 3.8%.

While no claim is made that the observed intermolecular isotope effect values of about 8.5% are very precise numbers, it is clear that errors in the assumptions involved in the calculations could not reduce the values to the 3.8% figure. It may be that the further data will show that this theory should not be applied in this way to bond formation studies. Obviously this is not a *simple* bond formation case, and perhaps if complete partition functions were known, there would be no discrepancy between experiment and this theory.[22]

The experiments using metallic sodium as the condensing agent and toluene as the reaction medium were not as extensive as those in alcohol solution, and there is considerable uncertainty in the isotope effect values reported. However, there is no question but that the results are different from those obtained in alcohol solution, indicating a difference in the mechanism of the reaction.

The most obvious difference between the two sets of reaction conditions is that formation of the ions XIIIa and XIIIb is probably not completely reversible due to precipitation of the sodium salts in the non-polar medium. If formation of XIIIa and XIIIb is not reversible, the position of the label in the product will be determined when the carbanion is formed even if the over-all rate-determining step is carbon–carbon bond formation. As mentioned above, carbanion formation would not be expected to take place with an isotope effect since the labeled position is not involved.

That there is any isotope effect at all in these experiments probably is due to some amount of reversibility in the formation of XIIIa and XIIIb.

Experimental

Preparation of Sodium Cyanide-C^{14}.—Sodium cyanide-C^{14} was prepared by the method of Adamson[23] as modified by Aronoff and Racusen.[24] Two grams of sodium azide were placed in the bottom of a 6-inch Pyrex test-tube. A slow stream of nitrogen was passed into the tube to exclude oxygen while the azide was decomposed by heating with a small flame. The degradation product was cooled and 100 mg. of barium carbonate-C^{14} was mixed with it. Nitrogen was passed through the tube while it was heated to redness for 15–20 minutes. After the tube was cooled, water was added carefully. The tube and contents were pulverized in a mortar and the entire mass was transferred to a distillation apparatus. The solution was acidified with sulfuric acid and the hydrogen cyanide was distilled into sodium hydroxide solution. Duplicate experiments with inactive barium carbonate gave yields of about 75%, as determined by silver nitrate titration.

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(21) A. Fry and M. Calvin, *J. Phys. Chem.*, **56**, 901 (1952).

(22) One possible way of fitting these results into this theory would be to assume that there is some contribution to the isotope effect from bond rupture at both the methylene and carbonyl carbons. The carbanion formed by abstraction of a proton from the methylene carbon of diethyl phenylenediacetate is a typical enolate anion, and as such has considerable double bond character. This enolate anion formation is undoubtedly rapid and reversible (see W. G. Brown and K. Eberly, THIS JOURNAL, **62**, 113 (1940)), and little or no isotope effect would be expected in its formation. In going from this ion to the condensation product, the π-electrons of the double bond would have to be localized on the methylene carbon in the transition state. This, in effect, breaks part of a carbon–carbon double bond leading to an over-all increased isotope effect. A similar situation would prevail at the carbonyl carbon. It seems likely that in the transition state for formation of a new bond, the carbonyl group is polarized, leaving the π-electrons localized on the oxygen and leaving a vacant orbital at the carbon. This polarization is permanent and is essentially rupture of part of the carbon–oxygen double bond, leading to an increased isotope effect. The rate-determining step of the reaction would thus involve formation of the carbon–carbon bond, but in the transition state this would be concerted with localization of the π-electrons of the carbonyl group on the oxygen. A similar polarized carbonyl model also may be used to account for the 6–10% isotope effects observed by Ropp and Raaen[6f] in the saponification of carbon-14 labeled substituted ethyl benzoates. If carbon–oxygen bond formation is rate-determining as assumed by Ropp and Raaen, the isotope effect may be increased above the reduced mass term by polarization of the carbonyl group. This is essentially rupture of part of the carbon–oxygen double bond and destruction of the resonance interaction between the ring and carbonyl carbon. Since this interaction is greatest with ethyl anisate and least with ethyl *m*-nitrobenzoate, a greater isotope effect would be expected with the former than with the latter, as was observed. This interpretation is very similar to that given by Ropp and Raaen. Actually, a similar situation should exist in almost all carbonyl addition and condensation reactions, since in most cases addition to the carbonyl group is thought to be rate-controlling. The isotope effect observed by Lee and Spinks[6g] in the reaction between 4-hydroxycoumarin and formaldehyde-C^{14} was interpreted as being one of bond rupture, since the isotope effect value observed was larger than that predicted for simple carbon–carbon bond formation. It appears that carbon–carbon bond formation might be rate-determining if this step were accompanied by polarization of the carbonyl group of the formaldehyde in the manner described above. If carbon–carbon bond formation is rate-determining, as seems likely, an isotope effect also should be observed if the reaction were carried out with 4-hydroxycoumarin-3-C^{14} and inactive formaldehyde. No isotope effect would be predicted with these compounds if dehydration of the original adduct were rate-controlling.

(23) A. W. Adamson, THIS JOURNAL, **69**, 2564 (1947).

(24) S. Aronoff, private communication.

Preparation of Diethyl Phenylenediacetate-1-C^{14}.—Xylylene bromide, prepared by the method of Perkin,[14] was converted to phenylenediacetonitrile-1-C^{14} by reaction with the sodium cyanide-C^{14} according to the method of Moore and Thorpe.[25] Although sodium cyanide-C^{14} reacted with both of the halogen atoms in the xylylene bromide, the actual concentration of labeled cyanide ion was so low that the number of double-labeled phenylenediacetonitrile molecules was statistically insignificant. The nitrile was hydrolyzed to phenylenediacetic-1-C^{14} acid by heating with concd. hydrochloric acid.[26] The acid was exhaustively purified by partition between ether and sodium hydroxide solution, by activated charcoal treatments, and by repeated recrystallizations alternately from water and from ether-petroleum ether mixture. The pure phenylenediacetic-1-C^{14} acid melted at 150–151°; the reported m.p. is 150°.[26] The acid was esterified by refluxing it for 3 hours in absolute alcohol which had been saturated with dry, gaseous, hydrogen chloride. The solution then was concentrated to about one-third the original volume under reduced pressure, poured into cold water, and the ester extracted into ether. The ether solution was washed with water, 10% sodium bicarbonate solution, and then with water again. After a final drying with potassium carbonate, the ether was evaporated under reduced pressure and the ester fractionated; b.p. 193–194° at 15 mm. pressure, reported b.p. 173–174° at 10 mm.

Preparation of Diethyl Phenylenediacetate-2-C^{14}.—*o*-Toluic acid-1-C^{14} was prepared in 62% yield by carbonation of *o*-tolylmagnesium bromide with carbon-14 dioxide in a sweep system. The acid was converted to *o*-methylbenzyl alcohol-1-C^{14} by reduction with lithium aluminum hydride. A 2-liter three-neck flask was fitted with a condenser, a mechanical stirrer and a dropping funnel. To the flask was added 300 ml. of anhydrous ether and 10 g. (0.263 mole) of lithium aluminum hydride. The stirrer was started and 28 g. (0.206 mole) of *o*-toluic acid-1-C^{14} in 300 ml. of anhydrous ether was added dropwise over a period of one hour. The solution was heated at reflux temperature for 45 minutes after all the *o*-toluic acid had been added. After cooling the flask, 75 ml. of ice-water was added slowly, followed by a cold solution of 50 ml. of concentrated sulfuric acid in 800 ml. of water. The ether layer was separated, washed with 10% sodium bicarbonate solution and then with water. After drying with anhydrous magnesium sulfate and evaporating the ether, the *o*-methylbenzyl alcohol-1-C^{14} distilled as a clear oil, b.p. 210–217° at 730 mm., reported b.p. 217°.[27] The yield was 20.1 g., 80%.

The alcohol was converted to *o*-methylbenzyl-1-C^{14} bromide in 69% yield by treatment with phosphorus tribromide. The *o*-methyl benzyl-1-C^{14} bromide (25 g., 0.143 mole) was brominated with bromine (23 g., 0.143 mole) by the same procedure described above for the bromination of *o*-xylene. The *o*-xylylene-1-C^{14} bromide was recrystallized once from a small amount of chloroform. The yield was 25 g., 70%, m.p. 90–92°, reported m.p. 93°.[28] Diethyl phenylenediacetate-2-C^{14} was prepared from *o*-xylylene-1-C^{14} bromide by the reaction sequence previously described for diethyl phenylenediacetate-1-C^{14}.

Dieckmann Condensation of Diethyl Phenylenediacetate Using Metallic Sodium as Condensing Agent.[13]—Metallic sodium (1.02 g., 0.044 mole) was granulated under 30 ml. of toluene at 100°, and 5 g. (0.02 mole) of diethyl phenylenediacetate-1-C^{14} dissolved in 20 ml. of toluene was added. Reaction began at once with the formation of a bulky, gelatinous, sodium derivative. Heating was continued for 2 hours in some cases, but there was little change in appearance after the first 10 minutes. After cooling the flask, 100 ml. of ice-water and powdered ice were added and the mixture shaken until the sodium derivative had dissolved. The aqueous layer was separated from the toluene, extracted with ether, and freed of dissolved ether by bubbling a stream of air through the solution. It was then cooled in an ice-bath and acidified with dilute hydrochloric acid. A yellow oil separated, which soon became solid and was removed by filtration. This crude ethyl 2-hydrindone-1-carboxylate was a flaky, yellow solid, which could be purified by recrystallization from alcohol, m.p. 65–66°, reported m.p. 65°.[13] The yield of crude material was 3.5 g., 70%.

Dieckmann Condensation of Diethyl Phenylenediacetate Using Sodium Ethoxide as Condensing Agent.[13]—A solution of sodium ethoxide was made by dissolving 0.42 g. (0.018 mole) of sodium in 15 ml. of absolute alcohol. To this was added 4.5 g. (0.018 mole) of diethyl phenylenediacetate dissolved in 15 ml. of absolute alcohol. The resulting solution was refluxed for 15 minutes, cooled under the water tap, diluted with 60–70 ml. of cold water, and finally acidified with dilute hydrochloric acid. A pale yellow precipitate of ethyl 2-hydrindone-1-carboxylate formed and was removed by filtration. The precipitate was washed several times with water while still on the funnel, and then recrystallized from alcohol, giving 2.58 g., 70% yield, of pure ester, m.p. 65°, reported m.p. 65°.[13]

Dieckmann Condensation at 9% of Complete Reaction.—A solution of sodium ethoxide was prepared by dissolving 140 mg. (0.0061 mole, 9% of the amount required for complete reaction) of sodium in 50 ml. of absolute alcohol. Diethyl phenylenediacetate (17 g., 0.068 mole) was added in one portion and the solution was heated at reflux temperature for 15 minutes. After cooling, the solution was diluted with 100 ml. of ice-water, and unreacted diethyl phenylenediacetate was removed by ether extraction. The aqueous solution was acidified with dilute sulfuric acid and extracted with ether. The ether was evaporated giving 0.9 g. of ethyl 2-hydrindone-1-carboxylate. This is 72% yield based on sodium and 6.5% yield based on diethyl phenylenediacetate.

Decarboxylation of Ethyl 2-Hydrindone-1-carboxylate.—The decarboxylation of ethyl 2-hydrindone-1-carboxylate was carried out in a sweep system consisting of a gas purification train, a decarboxylation flask fitted with a pressure equalizing dropping funnel through which the sweep gas entered and a reflux condenser, a trap cooled by a Dry Ice–isopropyl alcohol-bath, and a spiral bubbler for absorbing the carbon dioxide.

In a typical run, 1.043 g. of labeled ethyl 2-hydrindone-1-carboxylate was placed in the flask and 10 ml. of 20% sulfuric acid was run into the dropping funnel. The system was swept with nitrogen gas for about 30 minutes to remove any carbon dioxide present. Then the spiral bubbler was filled with sodium hydroxide solution, the acid was allowed to flow into the flask, and the flask was heated on the steam-bath for 5 hours. During the heating, the system was swept with a stream of nitrogen to carry the carbon dioxide evolved into the sodium hydroxide trap. At the end of the reaction, the contents of the sodium hydroxide bubbler were washed into an equal volume of 1 *N* ammonium chloride, and excess barium chloride was added. The barium carbonate formed, when collected and dried, weighed 1.005 g. This represents a yield of 100.1%, based on quantitative decarboxylation.

After decarboxylation of the ester, the condenser and walls of the flask were rinsed with 10 ml. of alcohol. The resulting solution, including the reaction solvent, was heated until all the hydrindone dissolved. A small amount of hydrindone (less than 10%) condensed to anhydro-bis-2-hydrindone, m.p. 170–175°, reported m.p. 170°,[29] under the decarboxylation conditions, and this product was removed by cooling the solution to 50°. At this temperature the dimer precipitated. The suspension was filtered and upon cooling the filtrate at 10°, hydrindone crystallized in long white needles, m.p. 57°, reported m.p. 60°.[13]

Combustion of Compounds.—All compounds were oxidized to carbon dioxide by a Van Slyke–Folch wet combustion method.[30] The oxidation was essentially quantitative in all cases. From 0.130 g. of ethyl 2-hydrindone-1-carboxylate, 1.5220 g., 100.2% yield, of barium carbonate was obtained. From 0.2115 g. of 2-hydrindone, 2.874 g., 101% yield, of barium carbonate was obtained. From 0.2300 g. of diethyl phenylenediacetate, 2.564 g., 101%-yield, of barium carbonate was obtained. The blank correction was approximately 2 mg.

Isotopic Composition Measurements.—The C^{14}-activity measurements were made by a rate of charge method using an ionization chamber and vibrating reed electrometer connected to a Brown recorder. For all activity determinations, the ionization chamber was filled with the same weight of car-

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(25) C. W. Moore and J. F. Thorpe, *J. Chem. Soc.*, **93**, 175 (1908).

(26) J. V. Braun, O. Kruber and E. Danziger, *Ber.*, **49**, 2642 (1916).

(27) A. Colson, *Ann. chim.*, **36**, 117 (1885).

(28) W. H. Perkin, *J. Chem. Soc.*, **53**, 5 (1888).

(29) F. Heusler and H. Schieffer, *Ber.*, **32**, 32 (1899).

(30) A. Fry, B. M. Tolbert and M. Calvin, *Trans. Faraday Soc.*, **49**, 1444 (1953).

bon dioxide, which was generated in a vacuum system from 1.4000 g. of barium carbonate with sulfuric acid.

The same ionization chamber was used for all activity determinations. All samples were counted for 1.5 hours and a background correction was made. All three of the activity determinations for each set were made in close succession, in order to minimize variations in the instruments. The average counting error with samples run in close succession was approximately 0.5%. Many of the activity determinations were repeated one or more times.

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[CONTRIBUTION FROM ROHM AND HAAS COMPANY, REDSTONE ARSENAL RESEARCH DIVISION]

Alkaline Nitration. I. The Nitration of Amines with Cyanohydrin Nitrates[1]

BY WILLIAM D. EMMONS AND JEREMIAH P. FREEMAN

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Acetone cyanohydrin nitrate (I) has been found to be a unique reagent for effecting nitration under alkaline conditions. By means of this reagent primary and secondary amines may be converted to the corresponding nitramines. Other cyanohydrin nitrates that were studied in this connection are discussed.

The introduction of a nitro group into an organic molecule almost always requires the use of a highly acidic reagent. This requirement limits the number and type of compounds that can be nitrated because of the sensitivity of some compounds to acids. A reagent which could effect nitration under neutral or alkaline conditions would be highly desirable. As a starting point in the search for such a reagent, the synthesis of nitramines[2] from amines has been examined.

Several attempts to convert amines to nitramines by the action of a nitrate ester in the presence of added base are recorded in the literature.[3] Thus, Bamberger isolated phenylnitramine in poor yield from the reaction of aniline, ethyl nitrate and sodium ethoxide.[4] This method has not been useful, however, as the predominant reaction is one of alkylation. For instance, pyridine is converted to a quaternary nitrate by the action of alkyl nitrates,[5] and piperidine is alkylated to form tertiary amines.[6] The predominance of this latter reaction suggests that nitrate esters behave more like alkyl halides or tosylates than like carboxylic esters. This view finds support in the work of Baker and Easty[7] who studied the solvolysis of nitrate esters. They interpreted their data on the basis that no reaction involving attack on nitrogen occurred. It has recently been shown,[8] however, that the hydrolysis of nitrate esters must occur by cleavage of the oxygen–nitrogen bond since a nitrate ester labeled with O^{18} yields an alcohol containing O^{18}. It has also been postulated that oxygen–nitrogen bond cleavage occurs during the reaction of hydrazine with certain nitrate esters.[9]

Efforts to effect the nitration of amines with simple alkyl nitrates appeared to be predestined to failure regardless of the strength of the added base because of the competition from side reactions. It was decided therefore to alter the structure of the nitrate ester with a view to weakening the oxygen–nitrogen bond so that nucleophilic attack on the molecule would occur on nitrogen. Efforts in this direction led to the synthesis of trichloroethyl nitrate whose reaction with secondary amines has been reported.[10] In this case the amine attacked the α-hydrogen atoms instead of the nitro group. Significantly, however, no alkylation was noted.

$$Cl_3CCH_2ONO_2 + R_2NH \longrightarrow R_2\overset{\oplus}{N}H_2\overset{\ominus}{N}O_2 + Cl_3CCHO$$

This preliminary study led to the imposition of certain restrictions on the structure of the nitrate ester to be used for alkaline nitrations.

First of all, the nitrate ester should possess no α-hydrogen atoms. Secondly, it should contain bulky groups around the α-carbon atom to hinder bimolecular displacement reactions. Lastly, it should contain an electronegative group to weaken the oxygen–nitrogen bond. The latter requirement is also desirable because it prevents the facile unimolecular solvolysis characteristic of most tertiary nitrate esters.[11] In the search for a molecule which possessed all these structural features, attention was focused on the heretofore unknown nitrate esters of ketone cyanohydrins. The nitration of the readily available acetone cyanohydrin was attempted first. The synthesis of acetone cyanohydrin nitrate (I) was accomplished smoothly by nitration of the cyanohydrin with fuming nitric acid in acetic anhydride. By this method the nitrate ester I was obtained consistently in yields of 65–70%. It proved to be a colorless liquid which could be

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(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) At present there are three good methods for the preparation of secondary nitramines, and all involve strongly acidic conditions. They are: (a) the oxidation of nitrosamines with peroxytrifluoroacetic acid [W. D. Emmons, THIS JOURNAL, **76**, 3468 (1954)]; (b) the chloride ion-catalyzed direct nitration of amines [W. J. Chute, K. G. Herring, L. E. Toombs and G. F Wright, *Can. J. Research*, **26B**, 89 (1948)]; and (c) the nitrolysis of dialkylamides with nitric acid [A. H. Lamberton, *Quart. Revs.*, **5**, 75 (1951)]. Only the second of these methods is applicable to the synthesis of primary nitramines.

(3) H. J. Backer, *Sammlung Chem. und Chem. Tech. Vorträge*, **18**, 365 (1912).

(4) E. Bamberger, *Ber.*, **53**, 2321 (1920).

(5) E. S. Lane, *J. Chem. Soc.*, 1172 (1953).

(6) D. T. Gibson and A. K. Macbeth, *ibid.*, 438 (1921).

(7) J. Baker and D. Easty, *ibid.*, 1193, 1207 (1952).

(8) M. Anbar, I. Dostrovsky, D. Samuel and A. D. Yoffe, *ibid.*, 3603 (1954).

(9) R. T. Merrow and R. W. VanDolah, THIS JOURNAL, **76**, 4522 (1954).

(10) W. D. Emmons, K. S. McCallum and J. P. Freeman, *J. Org. Chem.*, **19**, 1472 (1954).

(11) For instance, G. R. Lucas and L. P. Hammett [THIS JOURNAL, **64**, 1928 (1942)] have demonstrated that *t*-butyl nitrate undergoes unimolecular solvolysis in aqueous ethanol at a rate similar to that of *t*-butyl chloride.