ISOTOPE EFFECTS IN DISPLACEMENT REACTIONS

CARBON-13 ISOTOPE EFFECTS IN NUCLEOPHILIC ALIPHATIC DISPLACEMENT REACTIONS

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by

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SCOPE AND CONTENTS:

Carbon-13 isotope effects have been measured for the solvolysis reactions of 1-bromo-1-phenylethane in methanol and ethanol and for the bimolecular reaction of this halide and benzyl bromide with alkoxide ion. For the unimolecular displacements, the rate constant ratio, k10/k13, has been found to be 1.006, which corresponds to an isotope effect of 0.6 per cent. Rate constant ratios, k12/k13, of 1.003 and 1.053 have been observed for the reaction of 1-bromo-1-phenylethane with ethoxide ion and of benzyl bromide with methoxide ion, respectively. Extensive tests have been performed to establish that the reactions were unidirectional under the conditions used and that the experimental procedures were uncomplicated by exchange, rearrangement, or isotopic fractionation. The results have been discussed in terms of the Bigeleisen expression for the theoretical calculation of isotope effects.

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GENERAL INTRODUCTION

Since 1948, when the first observation of carbon isotope effects in unidirectional processes was reported (1), the study of isotope effects for elements of higher atomic number than hydrogen has attracted the interest of many workers. Most of the attention, however, has been directed towards the measurement of isotope effects in simple bond rupture processes. Such reactions as the pyrolysis of hydrocarbons (2), and the decarboxylation of carboxylic acids (3,4,5) serve as examples of the type of process examined. To a lesser extent, studies of isotope effects in pure bond formation reactions have been reported (6,7,3).

Until the work for this thesis was practically complete, however, no results had been published for isotope effect studies in three-centre displacement reactions, i.e., reactions in which bond formation and bond rupture proceed simultaneously. Such displacement reactions are very commonly encountered in aliphatic organic chemistry. Indeed, an example of this process was used by London in the first treatment of chemical reactions by the application of absolute rate theory.

Mechanistic studies of these reactions have established that these processes may occur by either of two mechanisms. One, the so-called S_N^1 mechanism, is thought to proceed via an unimolecular path involving a simple bond rupture in the rate-determining step; while the second, the S_M^2 mechanism, is considered to be a bimolecular, or three-centre, displacement. The mechanism that is operative in a particular case is governed by the structure of the reactant and the reaction conditions. In general, primary compounds react by the S_M^2 mechanism and tertiary by the S_N^1 ; secondary compounds form an intermediate group which may react by either mechanism depending on the reaction conditions.

The study of reactions of compounds belonging to this intermediate type should provide information on the magnitude of carbon isotope effects for three-centre displacements and pure bond rupture processes in closely related systems. This was the main purpose of the work reported in this thesis. In addition, however, the possibility existed that isotope effect studies of this kind might provide a new criterion of mechanism for displacement reactions in aliphatic systems.

Two approaches are possible in a carbon isotope effect study, namely the use of either carbon-13 or carbon-14 as the rarer isotope. No synthesis of labelled compounds is required with the former, since advantage can be taken of the fact that

the natural abundance of carbon-13 is about one per cent. In other words, the label is already present in the compound. Carbon-14 studies have the advantage that isolation of the reacting carbon, free from all other carbon atoms in the molecule, is unnecessary, and hence no degradation problems arise. The major disadvantages in its use arise from the relatively low accuracy of the analytical methods for radicisotopes and the danger of contamination of labelled compounds with material of natural isotopic abundance. In Carbon-13 studies, on the other hand, the measurements of relative isotopic abundances using the mass spectrometer are considerably more accurate and contamination is much less serious since both the compound and possible impurities would have approximately the same isotopic abundance. Certain restrictions are imposed on the system chosen, however, since the carbon at the reacting centre must be isolated and converted into a form suitable for mass spectrometric analysis. In the present investigation, the advantages of the use of carbon-13 appeared to be of primary importance as small differences in isotopic fractionations were expected and the higher accuracy of measurement was desirable.

The first reaction system chosen for this study was the alcoholysis of 1-bromo-1-phenylethane, with and without added base in the form of alkoxide ion. As a consequence of the results obtained in this system, the study was extended

to the methanolysis of benzyl bromide in dilute base.

Compounds containing the 1-phenylethyl group have been studied (9,10,11,12) in a variety of reactions by both kinetic and stereochemical means. These time-honored mechanistic criteria show that this group is definitely of the intermediate type. Also, since the reacting carbon atom is in a position alpha to the benzene ring, a 'handle' is provided by the phenyl group whereby the reacting centre may be isolated from the rest of the molecule by degradative means. For these two reasons, the 1-phenylethyl system suited the original aims of this study admirably, and the results with this system indicated the logical extension of the study to the benzyl system.

HISTORICAL INTRODUCTION

A - Isotope Effects

Early History of Isotope Effects

Discovery

Following the discovery of isotopes (13), there was considerable speculation concerning the possibility of differences in the chemical reactivity of various isotopic species. Early attempts (14) to demonstrate these differences proved abortive owing to the very small differences sought in the systems studied. The discovery of deuterium (15) in 1932, along with the discovery of the heavy isotopes of carbon (16), nitrogen (17), and oxygen (18) in the period 1928-30, allowed the investigation of systems in which there is a large percentage mass difference. Urey predicted, from calculations by methods of statistical mechanics, a large difference in vapor pressure for H₂ and HD, and realized their separation by fractional distillation (15).

Exchange Isotope Effects

Extending his calculations to exchange reactions of hydrogen and deuterium, as well as their halides, Urey

predicted (20) equilibrium constants for some typical reactions. An example of the type of system is:

$$H_2 + D_2 \rightleftharpoons 2HD \tag{I}$$

Calculations yielded an equilibrium constant of 3.28 at 25°C. Experimentally, the value at this temperature was found to be 3.28 (21). Similar agreement between calculated and experimental values was found for other systems involving hydrogen and douterium (22). Further calculations of equilibrium constants for typical exchanges involving other light isotopes, such as lithium, carbon, and nitrogen, resulted in the prediction of a series of constants all differing slightly from unity (23). These differences are known as exchange isotope effects. An example of the type of system considered is:

$$1/2 \operatorname{CO}_2^{16} + \operatorname{H}_2^{018} \Longrightarrow 1/2 \operatorname{CO}_2^{18} + \operatorname{H}_2^{016}$$
 (II)

Calculations yielded an equilibrium constant of 1.044 at 0° C. Experimentally, the measured value was found to be 1.046 at this temperature (24).

As the experimental methods of measuring isotope abundances were improved, many more exchange reactions were studied with results consistently agreeing with theory.

Kinetic Isotope Effects

Since an exchange process involves two opposing unidirectional reactions, the observation of exchange isotope effects showed that isotopic molecules may react at different rates. Isotope effects in unidirectional processes arising from a difference in reaction rates of isotopic species are referred to as kinetic isotope effects and were observed for isotopes of hydrogen shortly after the discovery of deuterium (19). Carbon isotope effects in an unidirectional process were not observed, however, until 1948, when the first report was published by Stevenson and co-workers (1). These authors found that the dissociation of propane-1- C^{13} , caused by electron bombardment in a mass spectrometer, favored rupture of the C^{12} - C^{12} bond over the C^{12} - C^{13} bond. In a propane molecule containing the natural abundances of carbon isotopes, it was found that rupture of a C12 - C12 bond occurred 12 per cent more frequently than that of a $C^{12} - C^{13}$ bond. This study was extended to the pyrolysis of propane, in which an 8 per cent more frequent $C^{12} - C^{12}$ bond rupture was observed (2).

Carbon isotope effects then attracted the interest of many workers; and, in this early work, a controversy soon arose. In studies of the decarboxylation of malonic acid, labelled in the carboxyl group with carbon-14, Yankwich and Calvin (3) found that for the molecule, $HOOC12 - C^{12}H_2 - C^{14}OOH$

there is a 12 per cent more frequent rupture of a C^{12} - C^{12} bond than a C^{12} - C^{14} bond. This is an intramolecular isotope effect of 12 per cent. Two other groups, Bigeleisen and Friedman (4), and Lindsay, Bourns, and Thode (5), carried out a carbon-13 isotope effect study with malonic acid containing the natural abundance of carbon isotopes and, using the mass spectrometer for measurement of the isotopic ratios, observed an intramolecular carbon-13 effect of 2.0 and 2.5 per cent, respectively. These carbon-13 results are to be compared with a theoretical value of 2.0 per cent calculated by Bigeleisen (25) from fundamental vibrational frequency data. (See next section.) On the other hand, theory predicts that the carbon-14 effect should be very close to twice the carbon-13 value (26), whereas the value reported by Yankwich and Calvin was very much higher. Considerable controversy developed over this disagreement between experimental results and theoretical predictions for carbon-14 isotope effects for this reaction and others (27, 28).

The carbon-14 effects usually are measured using counting techniques in which, for the early work at least, a reproducibility of one to two per cent is considered good. Carbon-13 effects, on the other hand, are measured using the mass spectrometer with which a precision of 0.1 per cent or better is readily obtainable. Recently, the malonic acid

decomposition has been re-examined by Yankwich, Promislow, and Nystrom (29) using malonic acid containing one per cent carbon-14 as well as carbon-13, and measuring the isotopic ratios mass spectrometrically. They reported isotope effects of 5.5 and 2.9 per cent for carbon-14 and carbon-13, respectively. The ratio of these effects is 1.91, which is in good agreement with the theoretical prediction of 2.0. This would appear to settle the controversy. The malonic acid case, however, does serve to point up the dangers associated with carbon isotope effect studies using labelled compounds.

Since an isotope effect in an unidirectional process will be observed only if the rate-determining step involves some change in the bonding of the element in question, the study of such fractionations has important application in the field of reaction mechanisms. Further, since the size of the effect is governed, in part, by the nature of the activated complex, an isotope effect study should yield information on the nature of this complex. Over the past nine years, the interest in kinetic isotope effects has increased for these reasons. Several authors have reviewed kinetic isotope effects recently (27,28,30,31).

The development of the general theory of isotope effects in unidirectional processes is outlined in the following section. In this thesis, it is not intended to develop the theory in detailed terms, but rather to show the

lines of reasoning upon which it is based.

General Theory of Isotope Effects

According to classical statistical mechanics, kinetic energy follows the equipartition law and spatial distribution of the molecules is given by the Boltzman equation. No isotope effects, therefore, would be predicted for equilibrium processes. Very small isotope effects, however, would be predicted from classical considerations for unidirectional reactions of higher order than one, since collision numbers for molecules are dependent on their masses. As has already been indicated, sizable isotope effects of both types have been observed, and, hence, these effects must be quantum phenomena.

The total energy of a molecule is a sum of the translational energy and the internal energy, which is, itself, a sum of the electronic, rotational, and vibrational energies. According to quantum mechanics all of these are quantized. The source of isotope effects, therefore, must be one of these energies.

The energy levels of translation are so closely spaced that they may be considered as continuous and, hence, classical. For most chemical reactions, the electrons are all in their respective ground states and, since the electronic ground states for isotopic molecules are almost identical,

electronic energy differences cannot be considered as a source of isotope effects. Further, since the product of the absolute temperature and the Boltzman constant is large, except for very low temperatures and for hydrogen compounds, the rotational energy level distribution can be considered as classical.

The one type remaining, the vibrational energy levels, are relatively far apart and transitions may occur at moderate temperatures. This is the only type of molecular energy seriously affected by quantum considerations. Therefore, differences in the vibrational energy levels for isotopic molecules must be the source of chemical isotope effects.

Bigeleisen (32) has developed the theory of chemical isotope effects in unidirectional processes using only the hypotheses of the absolute rate theory. On the basis of this theory, for reactions in which A_1 , B, C,... react to give P_1 and A_2 , B, C,... give P_2 , where A_1 and A_2 are isotopic molecules, one can express the rate constants as follows:

$$k_{1} = \kappa_{1} \frac{C_{1}^{+}}{C_{A1} C_{B} \cdots} \left(\frac{kT}{2 m_{1}^{+}}\right)^{1/2} \frac{1}{61}$$
(1)

$$k_2 = K_2 \frac{C_2^+}{C_{A2} C_{B} \cdots} \left(\frac{kT}{2 m_2^+}\right) \frac{1/2}{\delta 2}$$
 (2)

where K1 and K2 are transmission coefficients, +indicates

the activated complex, m[±] is the effective mass of the complex moving along the reaction coordinate, and δ is the length of the top of the potential energy barrier of the reaction coordinate. Since the potential energy surfaces are the same, as an approximation, for two isotopic molecules, $\delta_1 = \delta_2$. Combination of 1 and 2 therefore gives:

$$\frac{k_{1}}{k_{2}} = \frac{K_{1}}{K_{2}} \cdot \frac{C_{A2} C_{1}}{C_{A1} C_{2}^{\ddagger}} \cdot \left(\frac{m_{2}^{\ddagger}}{m_{1}^{\ddagger}}\right)^{1/2}$$
(3)

The ratios of the concentrations of the various molecular species in equation 3 may be replaced by the complete partition function, Q, and thus:

$$\frac{k_{1}}{k_{2}} = \frac{K_{1}}{K_{2}} \cdot \frac{Q_{A2} Q_{C1}}{Q_{A1} Q_{C2}^{*}} \cdot \left(\frac{m_{2}^{*}}{m_{1}^{*}}\right)^{1/2}$$
(4)

Although the calculation of a complete partition function is difficult, if not impossible, the treatment of isotope effects requires that only partition function ratios for isotopic molecules be considered. Furthermore, for reasons outlined above, these ratios can be expressed in terms of the partition functions of the vibrational energy levels only.

Bigeleisen and Mayer (33) have shown that the ratio of vibrational partition functions for isotopic molecules may be expressed as:

$$\frac{Q_2}{Q_1} = \frac{\sigma_1}{\sigma_2} \left[1 + \sum_{i=1}^{n} \frac{1}{u_i} + \frac{1}{e^{u_i} - 1} \right]^{\Delta u_i}$$
(5)

where $u = h \sqrt{kT}$, in which $\sqrt{2}$ = the fundamental vibrational frequency, and G represents a symmetry number. The function:

$$\left(\frac{1}{2} - \frac{1}{u_i} + \frac{1}{e^{u_i} - 1}\right)$$

has been termed the free energy function (33) and is represented by $G(u_i)$. Bigeleisen and Mayer have tabulated values of this function for various u values from 0 to 25.

Equation 5 allows one to calculate the ratios for the partition functions from a knowledge of the vibrational frequencies of the molecule alone. Although the vibrational frequencies of the molecule containing the common isotope are usually available from spectroscopic studies, this is not the case for the rare isotope. In practice, one calculates the vibrational frequencies of the rare molecule using the 'normal vibration' equation and the known vibrational frequency of the normal molecule (34).

To continue the development of the theory of isotope effects, one can substitute in equation 4 for the ratio of the partition functions Q_{A2}/Q_{A1} and Q_{C1}/Q_{C2}^{*} and, using the abbreviated form of equation 5, obtain an expression of the following form:

 $\frac{k_{1}}{k_{2}} = \frac{K_{1}}{K_{2}} \frac{\sigma_{1}\sigma_{2}^{*}}{\sigma_{1}\sigma_{2}} \left(\frac{m_{2}^{*}}{m_{1}^{*}}\right)^{1/2} \left[1 + \sum_{i}^{3n-b} G(u_{i}) \Delta u_{i} - \sum_{i}^{3n-b} G(u_{i}) \Delta u_{i}^{*}\right]$ (6)

In all cases, except for hydrogen, one assumes the ratio of the transmission coefficients to be unity. Also, the symmetry numbers are assumed to be the same for isotopic molecules. The quantity in the square brackets is referred to as the free energy factor since it provides a quantitative measure of the energy differences in the initial and transition states. If all molecules were in their ground states, the first summation in this factor would express the zero point energy differences for the two isotopic species in their initial states, the second the corresponding zero point differences in the transition state. The quantity $(m_2^*/m_1^*)^{1/2}$ is called the effective mass factor and arises from the effect of isotopic mass upon the rate with which a reacting molecule passes over the energy barrier. An important feature of the Bigeleisen approach is that these two factors, upon which the relative rates of reaction of isotopic molecules depend, are set out so clearly. The subsequent discussion for kinetic isotope effects is based on a contribution of each of these factors in various unidirectional processes.

A theorem due to Slater (35) has shown that, in an unimolecular process, the effective mass may be calculated from the imaginary diatomic molecule composed of the atoms which form the bond undergoing change in the rate-controlling step. The m_1^*/m_2^* ratio is then taken as the ratio of the reduced mass for the two isotopic diatomic molecules. This

theorem has often been considered as unrealistic. Indeed, it does not seem altogether reasonable to assume that, for a decomposition of one bond in a polyatomic molecule, the reaction coordinate necessarily involves only motion of the atoms of this bond. In a forthcoming publication (36), Bigeleisen suggests that a more realistic assumption would be that a simple bond rupture proceeds by a coordinate that tears the decomposition fragments apart. Then, roughly, the mass term would be:

$$\left(\frac{m_{2}^{*}}{m_{1}^{*}}\right)^{1/2} = \left(\left[\frac{1}{M_{A1}} + \frac{1}{M_{B1}}\right] / \left[\frac{1}{M_{A2}} + \frac{1}{M_{B2}}\right]\right)^{1/2}$$
(7)

where the M's refer to the mass of each fragment, A and B. For the case of a diatomic molecule, it is evident that equation 7 is identical to the mass term based on the Slater theorem. For polyatomic molecules, however, equation 7 affords values which are lower than those found using the Slater hypothesis. For example, the calculation of the mass factor for a reaction of a $C^{12} - Br^{79}$ bond and a $C^{13} - Br^{79}$ bond leads to a value of 1.035 using the Slater method; whereas equation 7 affords a value of 1.002 for the same bond in the 1-bromo-1-phenylethane molecule.

In the following sections, a discussion of the application of equation 6 to various unidirectional processes is presented.

Isotope Effects in Bond Rupture Processes

Unidirectional reactions in which the rate determining step is a simple bond rupture process are discussed in this section. Isotopic fractionations in these processes are of two types, termed the intermolecular and the intramolecular (5). An example of these two modes of reaction is shown by the following reaction equations for the decomposition of malonic acid:

In such a system, the ratio k_3/k_2 is a measure of the socalled intramolecular isotope effect, while the ratio, $k_1/2k_2$ gives the intermolecular effect. The latter will be discussed first.

A model must be chosen in order to apply the Bigeleisen expression to a kinetic isotope effect in an unidirectional process of bond rupture. The first assumption, which is usually made, is that all bonds in the molecule other than the bond undergoing fission remain unchanged throughout the course of the reaction. A second assumption is that the transition state is very much like the products of the reaction and, hence, the bond undergoing reaction may be considered as being completely broken in this state. The

free energy term for the transition state, $G(u_i^{\dagger}) \Delta u_i^{\dagger}$, then becomes equal to zero. A knowledge of the vibrational frequency of the bond broken allows one to determine the value of the $G(u_1) A u_1$ term for the initial state. Since Au, is positive, the free energy factor in equation 6 for an intermolecular isotope effect will be greater than unity. For the case of malonic acid, using a $C^{12} - C^{12}$ vibrational frequency of 900 cm.⁻¹ (34) and a temperature of 140° C., the free energy factor becomes equal to 1.015. Assuming the Slater hypothesis, the effective mass term, calculated as the square root of the ratio of the reduced masses of C^{13} - C^{12} bond to the $C^{12} - C^{12}$ bond, has a value of 1.020. Combination of the two factors gives a value for $k_1/2k_2$ of 1.035, in other words, an isotope effect of 3.5 per cent. This will also be the theoretical isotope effect for any decarboxylation of a carboxylic acid proceeding by a ratedetermining carbon-carbon bond rupture.

Table I summarizes some measurements of carbon-13 isotope effects in a number of decarboxylation reactions. The agreement between theory and experiment may be considered good considering the assumptions that have been made in applying the Bigeleisen expression.

TABLE I

CARBOXYL-C¹³ INTERMOLECULAR ISOTOPE EFFECTS IN DECARBOXYLATION REACTIONS

Acid Studied	T (^o C.)	k _l /nk Experimental	² Calc.	Reference
сн ₂ .(соон) ₂	138 137 149 173 196	1.037 ± 0.002 1.034 1.041 1.034 1.036	1.035 1.031	4 37 37 37 37
CH3-CH3 CH3-COOH	61.2 92	1.037 ± 0.003 1.038 ± 0.001 1.032	1.041 1.038	38 39 38
c1 ₃ c.cco ⁻	70.4	1.0338 ± 0.000	7 1.040	40

In extending the discussion to the intramolecular isotope effect, k_3/k_2 , for the malonic acid case, one finds that equation 6 may reduce to a very simple form. Since the initial states are exactly the same for the two modes of reaction, $u_{4_i} = u_{3_i}$. This means that the free energy term for the initial state becomes equal to zero. Equation 6 then reduces to the following:

$$k_{3}/k_{2} = (m_{2}^{\#}/m_{1}^{\#})^{1/2} \left[1 - \sum_{i}^{3n-6} G(u_{i}) \Delta u_{i}^{\#}\right]$$
(8)

In the early work on intramolecular isotope effects, the contribution of the transition state term in the free energy factor was neglected on the following grounds. If one considers the first row elements in the periodic table, one finds the free energy term for isotopes differing by one mass unit to be in the range 0.1 and 0.2 at room temperature, and even less at higher temperatures. These differences result from large changes in the chemical bonding of the element, i.e. the difference between the bonding in a chemical compound and the uncombined gaseous atoms. Since the $G(u_i^{\dagger}) \Delta u_i^{\dagger}$ free energy term corresponds to a pair of isotopic isomers in the transition state where bonding is very much weaker, it seems reasonable to neglect it. Thus, equation 8 reduces to the following form:

$$k_3/k_2 = (m_2^*/m_1^*)^{1/2}$$
 (9)

Applying the Slater hypothesis for the evaluation of the effective mass factor, the rate constant ratio for $C^{12} - C^{12}$ and $C^{12} - C^{13}$ bonds assumes a value of 1.020, corresponding to an intramolecular isotope effect of 2.0 per cent. The fragment theory for the mass term gives a k_3/k_2 ratio which is very much lower, namely 1.004.

Although a great deal of work has been reported on the intramolecular effect for the malonic acid system, probably the most reliable experimental figure for the ratio, k_3/k_2 , is 1.029 at 140°C. obtained by Yankwich (29). This value is significantly larger than the 1.020 predicted by the Slater hypothesis and almost an order of magnitude greater than that given by the fragment theory. The much closer agreement between experiment and theory using the Slater theorem might be considered as providing support for this method of evaluating the effective mass factor.

It should be noted that equation 9 predicts that the intramolecular effect should be temperature independent. Careful experiments have shown, however, the existence of a definite temperature coefficient (41). It can only be concluded, therefore, that the free energy function must make a definite contribution to the overall effect. This is perhaps to be expected. An examination of the possible structure of the transition state shows that, in this rather special case of an intramolecular effect, there are isotopic bonds which are not broken and for which the energy difference should be as great as in an initial state. The transition states may be represented as:

 $c^{12} - c^{12} - - - c^{13}$ and $c^{13} - c^{12} - - - c^{12}$ Of the two transition states, that in which the c^{13} bond is not broken will have the lower energy. Thus, in the $G(u_i^{\dagger}) \Delta u_i^{\dagger}$ term, Δu_i^{\dagger} will be negative, for this special case. As a result, the overall free energy factor will be greater than unity. Thus, one would expect an isotope effect greater than the mass term and with a temperature dependence. In a qualitative way, the value reported by Yankwich seems reasonable.

In summary, then, it can be seen that at the present stage in the development of theory, precise calculations of

isotope effects in bond rupture processes are not possible. Useful qualitative predictions, however, can be made with confidence. Thus, for intermolecular effects, where the free energy term is greater for the initial state than for the transition state, the overall free energy factor will always be greater than unity. Since the magnitude of the isotope effect is determined by the product of the effective mass factor and the free energy factor, the isotope effect will favor the lighter isotope. Also, the intermolecular isotope effect would be expected to be always greater than the intramolecular effect. These conclusions are supported by the experimental results reported to date. Since information about the transition state is very limited, one is unable to calculate any value other than an upper limit for intermolecular effects and a lower limit for intramolecular effects.

Isotope Effects in Bond Formation Processes

•

X

A reaction in which the rate-determining step is the formation of a new bond is the type of unidirectional process considered in this section. Such a reaction for two isotopic species could be expressed by the equations:

$$B - R + A_1 \xrightarrow{K_1} A_1 - B - R \tag{V}$$

$$B - R + A_2 \xrightarrow{k_2} A_2 - B - R \tag{VI}$$

where k_1/k_2 is the fractionation factor of the bond formation.

Some simplifying assumptions must again be made in order to apply the Bigeleisen expression to a typical reaction. Since there is no bond in the initial state, the $G(u_i) \triangle u_i$ term for equation 6 may be taken as zero. This is equivalent to considering the reaction as the formation of a diatomic molecule from the separated atoms. Thus, equation 6 becomes:

$$k_{1}/k_{2} = (m_{2}^{*}/m_{1}^{*})^{1/2} \left[1 - \sum_{c}^{5n-6} G(u_{1}^{*}) \Delta u_{1}^{*}\right]$$
(10)

The effective mass factor may be calculated as the square root of the ratio of the reduced masses of the hypothetical diatomic molecules formed by the atoms between which bond formation is taking place, assuming the Slater hypothesis, or as the square root of the ratio of the 'reduced masses' of the whole reacting molecules, assuming the fragment theory (equation 7). Whichever mass term is the more appropriate for a bond rupture process will, of course, be more appropriate for a reaction of bond formation. In either case, however, a value greater than unity is obtained for this factor. The free energy factor, on the other hand, will assume a value less than unity, since Δu_i^{\pm} has a positive value. Thus, since the two factors operate in opposite directions, the overall k1/k2 ratio should be small and might even be less than unity, in which case formation of the heavier isotopic bond would be favored. This would give rise to a

reverse isotope effect. Table II summarizes the few experimental results available for pure bond formation studies.

TABLE II

EXPERIMENTAL ISOTOPE EFFECTS IN BOND FORMATION PROCESSES

		ĸ	L ^K H	
Re	action	Туре	Range of Values	Reference
HSO3	+ RCOR *	s ³⁴	0.998 - 1.003	6
RI	+ NR [®] 3	N15	1.001 - 1.003	7
CN ⁻	+ C ₆ H ₅ .CH ₂ C1	C^{14}_{CN} of	1.010 ± 0.005	8

In the bisulphite addition reaction, the ratio, k_{32}/k_{34} , was very close to unity for all systems studied and there was a definite indication of a small reverse effect with 2-heptanone. The authors attempted to evaluate this effect for the addition reaction from equation 10, assuming that the mass term is given by the simple diatomic model and that the new bond is completely formed in the transition state. The value for k_{32}/k_{34} of 1.001 so obtained is in very close agreement with the experimental result. Only a slightly lower value, namely, 1.000, is obtained using the mass fragment expression, equation 7, for the effective mass factor. There would seem to be justification, therefore, for concluding that, in the bisulphite addition reaction, the transition state is very much like the product. The third example given in Table II concerns the isotope effect of a bond formation reaction in an overall three-centre displacement. Although the observed isotope effect is not so accurate as the other examples shown, the tendency for a small effect is evident in this bond formation process. Also, it should be noted that this result is from a preliminary study in which the experimental techniques have not been fully perfected.

Isotope Effects in Three-Centre Displacement Processes

The majority of chemical reactions involving aliphatic organic compounds fall into this category. These processes involve simultaneous bond formation and rupture and may be represented as follows, for two isotopic molecules:

$$A + B_1 - C \xrightarrow{k_1} [A - B_1 - C] \xrightarrow{k_2} A - B_1 + C \quad (VII)$$

$$A + B_2 - C \xrightarrow{k_2} [A - B_2 - C] \xrightarrow{k_2} A - B_2 + C \quad (VIII)$$

As pointed out previously, the Bigeleisen equation, 6, consists of two factors, the mass and the free energy factors. Each of these factors will be discussed in turn in the following paragraphs.

Some theoretical work has been reported by Bigeleisen (42,43) for the temperature independent factor, the mass term.

In a consideration of three atoms A, B, C, involved in a chemical reaction which breaks a bond between B and C and forms an A - B bond, the reaction coordinate, x_L , which increases as the reaction proceeds, may be written as follows, after the method developed by Slater (35) for simple bond rupture:

$$x_{\rm L} = \alpha \left| \mathbf{r}_{\rm B} - \mathbf{r}_{\rm C} \right| - \mathcal{Q} \left| \mathbf{r}_{\rm B} - \mathbf{r}_{\rm A} \right| \tag{11}$$

where $r_B - r_C$ and $r_B - r_A$ are the separation of B and C and B and A, respectively, and $\mathcal{Q}_{\mathcal{A}}$ determines the relative amount of bond formation between A and B and bond extension between B and C. The reaction coordinate, x_L , leads then to a frequency, \mathcal{Q}_L , which is dependent only on the masses of the atoms involved:

$$O_{L} \ll \left[2(m_{B}^{-1} + m_{C}^{-1}) + Q^{2}(m_{B}^{-1} + m_{A}^{-1}) + 2 \times Q m_{B}^{-1} \right]^{1/2}$$
(12)

For simultaneous bond rupture and bond formation, equation 6, substituting for mass term, becomes:

$$\frac{k_{1}}{k_{2}} = \frac{K_{1}}{K_{2}} \left[\frac{\left(m_{B1}^{-1} + m_{C1}^{-1}\right) + p\left(m_{B1}^{-1} + m_{A1}^{-1}\right) + 2p^{1/2}m_{B1}^{-1}}{\left(m_{B2}^{-1} + m_{C2}^{-1}\right) + p\left(m_{B2}^{-1} + m_{A2}^{-1}\right) + 2p^{1/2}m_{B2}^{-1}} \right]^{\frac{1}{2}}{\left[m_{B2}^{-1} + m_{C2}^{-1}\right] + p\left(m_{B2}^{-1} + m_{A2}^{-1}\right) + 2p^{1/2}m_{B2}^{-1}} \right]^{\frac{1}{2}}}$$
where $p = \left(\frac{3^{2}}{\sigma^{2}}\right)^{\frac{1}{2}} \left[1 + \sum_{i}^{3k-6} G(u_{i}) \Delta u_{i} - \sum_{i}^{3k-6} G(u_{i}) \Delta u_{i}^{\frac{1}{2}}\right]$ (13)

In the case of complete bond rupture in the transition state, p = 0 and the mass term reduces to that given by the

Slater theorem. For bond formation processes, where p is infinite, the mass term expression in equation 13 becomes the square root of the ratio of reduced masses of the isotopic bond formed, namely, $M_{\Delta} - M_{B}$. In a typical threecentre displacement, however, p will be equal or close to unity and so the masses of the three atoms involved must be considered. Table III gives the value of the mass term for various p values in some three-centre systems. At p = 1, for a symmetrical system such as the first, the mass term is considerably greater than that given by the Slater treatment for simple bond rupture or bond formation. In the three unsymmetrical systems, however, the mass term for p = 1 is quite close to that given by the Slater theorem for bond rupture, i.e. at p = 0, although the magnitude of the mass of the departing group determines whether it is greater or smaller.

TABLE III

VALUES FOR THE MASS TERM FOR VARIOUS 3-CENTRE DISPLACEMENTS

	System				Vari	Various p Va					
А	В	С	0	0.5	1	2	\sim				
c ¹²	C ¹² or 14	c ¹²	1.0400	1.0535	1.0541	1.0535	1.0400				
c ¹²	C ¹² or 14	c1 ³⁵	1.0578	1.0605	1.0582	1.0552	1.0378				
N ¹⁴	C ¹² or 13	1 ¹²⁷	1.0371	1.0352	1.0326	1.0307	1.0214				
0 ¹⁶	C ¹² or 13	Br ⁷⁹	1.0350	1.0348	1.0329	1.0314	1.0227				

A consideration of the free energy factor is virtually impossible with the present assumptions and the models used. In the previously discussed processes, a basic simplification of the model was that no other bonds change as the activated complex proceeds along the reaction coordinate. This is definitely not true in any three-centre displacement. Thus, only qualitative predictions may be made for the free energy term in such processes. Since a bond is being formed in the transition state the $G(u_i) \Delta u_i$ term assumes some value. In the case of a reaction in which p = 1, the extent of bond rupture is the same as the extent of bond formation. One might therefore conclude that the $G(u_i) \ge u_i$ and the $G(u_i^{\pm}) \ge u_i^{\pm}$ terms would be approximately equal and that the isotope effect would be given by the mass term In the case where bond formation has proceeded to a alone. very much greater extent than bond rupture, on the other hand, the $G(u_i) \ge u_i^{\dagger}$ term would be greater than the $G(u_i) \ge u_i^{\dagger}$ term and the overall free energy factor would assume a value less than unity. A small isotope effect would be expected approaching the value for pure bond formation as a limit. Finally, in the case where p is small, an isotope effect approaching that of pure bond rupture would be observed.

Bender and Hoeg (44) have reported the first isotope effect investigation of a three-centre displacement. Their system was:

$$CH_{3}I + (C_{2}H_{5})_{3}N \longrightarrow (C_{2}H_{5})_{3}N^{\dagger}CH_{3}I^{-}$$
(IX)

These authors studied the carbon-14 isotope effect at 25°C. using C¹⁴-methyl iodide and obtained a value of 10.2 per In order to calculate a theoretical value for this cent. isotope effect, Bender applied the three-centre mass term of equation 13, assuming p = 1, for the three reacting centres, carbon, nitrogen and iodine. As seen from Table III, at p = 1, the mass term is 1.065. (Carbon-14 effects are twice those of carbon-13.) In evaluating the free energy factor, Bender assumed that bond rupture is the only important consideration, and thus arrived at a value for this term corresponding to that for a pure bond rupture process. There is an obvious inconsistency in the models chosen for the calculation of the two terms of the Bigeleisen expression; nevertheless, this approach yields a k_{12}/k_{14} ratio of 1.0962 which is in rather close agreement with the experimental result. The agreement, however, between their experimental result and the value calculated using equation 6 and the Slater theorem is even better if one uses a pure bond rupture model for evaluation of both terms of the expression. This situation serves to show that the calculation of the temperature dependent factor in the three-centre model suffers because of the lack of detailed information on the transition state.
Some preliminary, but yet unpublished, experiments have been carried out by Fry (8) on the carbon-14 isotope effect in the following reaction:

$$CN^{-} + C_6H_5.CH_2^{14}C1 \longrightarrow C_6H_5.CH_2CN + C1^{-}$$
 (X)

Although pure second-order kinetics were not observed, this reaction was considered to be largely bimolecular. An effect of five per cent was obtained for the benzyl carbon atom labelled with carbon-14. This isotope effect corresponds to a k_{12}/k_{14} ratio of 1.05. The data in Table II show that for this case the mass term is 1.058 for the typical S_N^2 process, at p = 1. Therefore, the experimental result suggested that there is greater contribution by the $G(u_1) \Delta u_1$ term. This is to say that bond formation has proceeded to a greater extent than bond rupture in the transition state, if the process is a typical S_N^2 reaction.

In summary, one can conclude that the present theory does not allow a satisfactory examination of three-centre displacements. One cannot, however, overlook the scarcity of experimental data upon which a better theoretical approach might be based.

B - Nucleophilic Aliphatic Substitutions

In general, the reactions under consideration may be represented by the equation

$$Y^{*} + Alk - X \longrightarrow Alk - Y + X^{*}$$
 (XI)

in which a new bond is formed by coordination and another bond broken by heterolysis. There is an electron transfer from Y to the substitution centre, Alk-, and from it to X; thus, after substitution, Y becomes one electron unit more positive and X one unit more negative. Apart from this, there is no restriction on the charge of any of the species involved.

The scope of this reaction was not generally recognized until mechanistic studies showed a common pattern for many, seemingly different, processes. Some examples of this substitution reaction are the Finkelstein and Menschutkin reactions, various forms of the Hofmann degradation, and the hydrolysis and alcoholysis of alkyl halides.

Various postulates for the mechanisms of these reactions were advanced from 1911 onwards by several different authors (45,46). In the period 1927-1930, C. K. Ingold and co-workers (47,48,49) began to apply two of these postulates, one, a synchronous substitution and the second, a ratedetermining dissociation, to organic systems. Starting from

1933, Hughes and Ingold, in a brilliant series of investigations, showed a common pattern for all nucleophilic substitutions (50,51,52). The fundamental idea is that these two reaction mechanisms differ in the number of stages. Firstly, there is a single-stage process in which two reacting species undergo covalency changes simultaneously. This is a synchronous substitution and is called the bimolecular mechanism or the S_N^2 . It may be represented by the equation:

Y' Alk-X
$$\xrightarrow{k_2}$$
 [Y----Alk----X] \longrightarrow Y-Alk X' (XII)

in which the transition state is shown in the square brackets. Secondly, there is a two-stage process in which the first step is a slow heterolysis and the second a rapid coordination between a carbonium ion and the substituting agent. This is the prior dissociation mechanism and is called unimolecular or S_N l. The following reaction equations demonstrate the process:

$$Alk-X \xrightarrow{k_1}_{k_2} Alk^+ + X^- \qquad (XIII)$$

$$Alk^{+} + Y^{-} \xrightarrow{k_{3}} Alk - Y \qquad (XIV)$$

Since the slow step is the first, there is only one molecule undergoing covalency changes in the stage which determines the overall rate.

It should be noted, and emphasized, that, in

accordance with the Ingold designation of these mechanisms, the numerals in the S_N^2 and S_N^1 abbreviations indicate the number of molecular species undergoing covalency changes in the rate-determining stage.

This idea of a duality of mechanism for nucleophilic substitution reactions is not universally accepted. Some writers believe that the above mechanisms are extremes of a single substitution process, sometimes called a termolecular mechanism. Indeed, it seems reasonable that this is so. On the basis of the usual criteria of mechanism, however, examples of these extremes are numerous. It is in these extremes that the interest of this thesis lies.

In general, primary compounds demonstrate bimolecular behavior and tertiary compounds show unimolecular behavior. Secondary compounds form an intermediate group which shows no definite mechanistic pattern, since the reaction conditions dictate the mechanism followed in individual cases.

The various criteria upon which the development of this mechanism study depends have been treated thoroughly by numerous authors (53,54); hence, a detailed discussion of this subject will be omitted in this thesis. A brief description will be given, however, of the kinetic and stereochemical criteria, since it is on these that conclusions concerning the mechanism of reaction for the systems investigated in the present research have been based. The rate of a typical bimolecular reaction, in which the reacting species are in small and controllable concentrations, will be governed by a second-order kinetic expression of the form:

$$rate = k_2 [Y] [Alk-X]$$
(14)

For the case in which the substituting agent is in large excess, however, the rate expression will exclude the [Y] term. The following equation is, therefore, a limiting expression for the rate of a $S_N 2$ process:

$$rate = k_2 [Alk-X]$$
(15)

The general rate expression for a reaction proceeding by the unimolecular mechanism is as follows:

rate =
$$k_1 \left[Alk - X \right] \left[1 + k_2 / k_3 [X] / [Y] \right]^{-1}$$
 (16)

where the rate constants are those indicated in the reaction equations XIII and XIV. For the case in which the rate of reversal of the heterolysis, k_2 , is small relative to the rate of reaction of the carbonium ion with Y⁻, i.e. when $k_2 \langle \langle k_3 \rangle$, the rate expression reduces to the simple firstorder form:

$$rate = k_1 [Alk-X]$$
(17)

When the rate of reversal of the first step is large in comparison to the rate of the second, another limiting form arises, namely:

rate =
$$\frac{k_1 k_3}{k_2} \begin{bmatrix} Alk - X \end{bmatrix} \begin{bmatrix} Y \\ X \end{bmatrix}$$
 (18)

If at the same time, X is in large excess the rate expression reduces to that of a typical S_N^2 process:

$$rate = k^{1} [Alk - X] [Y]$$
(19)

With the exception of the reaction of compounds yielding relatively stable carbonium ions, e.g. that of p, p[']dimethylbenzhydryl halides, solvolytic processes proceeding by the unimolecular mechanism show first-order kinetics.

It is apparent from the foregoing discussion that the determination of kinetic order fails as a criterion of mechanism when the substituting agent is solvent. Another kinetic criterion, which has frequently proved useful in such cases, has been the determination of the sensitivity of the reaction rate to the addition of some reagent which is much more powerfully nucleophilic than solvent molecules, e.g. the addition of ethoxide ion to the reaction system of an alkyl halide in ethanol. Thus, if the reaction with solvent is proceeding by the bimolecular mechanism, the rate will be enhanced by the presence of the stronger reagent. On the other hand, if the rate-determining step does not involve molecules of solvent as nucleophilic species, then the addition of small amounts of the stronger reagent will be without effect on the rate. Of course, in the presence of large concentrations, the bimolecular reaction of the reagent with halide molecules will start to compete with the unimolecular process and rate enhancement will be observed. This criterion has proved useful in the reaction systems with which this thesis is concerned.

Stereochemical studies, where they can be applied, have proved very useful in mechanistic investigation. In a typical S_N^2 process, a new bond is formed as the old bond is broken and, on the basis of quantum mechanical considerations, a back-side attack is favored because the bond overlap allowed in this configuration is a maximum. Thus, if an optically active compound undergoes bimolecular substitution at the centre of asymmetry, the stereochemical result will be inversion of configuration at this centre.

Isotope exchange experiments in conjunction with stereochemical studies have further substantiated the detailed mechanism of the S_N^2 process. For example, the reaction of an optically active halide with a radioactive isotope of the departing group may be followed by the rate of pickup of tracer in the organic molecule. For a typical S_N^2 process, the overall rate of tracer pickup is found to be identical with the rate of inversion of the starting compound, thus clearly demonstrating that every individual act of bimolecular substitution proceeds with inversion at

the reaction centre.

In the case of the unimolecular substitution, the carbonium ion, formed by heterolysis, may assume a planar configuration and as such will be open to attack from either side. A typical S_N^1 reaction of an optically active compound, therefore, should lead to a racemized product. Total racemization, however, is rarely observed; instead, there is obtained a predominance of the inverted product. This has been attributed to a shielding effect of the departing group, making the rear side of the reacting carbon more accessible for attack by the displacing reagent (53). Recently, Winstein and his co-workers (55) have visualized the formation of the carbonium ion as proceeding through a series of steps as follows:

 $R-X \xrightarrow{R^{\dagger}} R^{\dagger} X \xrightarrow{R^{\dagger}} R^{\dagger} / X \xrightarrow{R^{\dagger}} R^{\dagger} + X \xrightarrow{R^{\dagger}} free \qquad (XV)$ ion pair ion pair carbonium ion

where the solvated ion pair represents a situation in which the ions are separated by only a few solvent molecules. A reaction leading to racemization must proceed through the free carbonium ion. In addition, however, some reaction may occur with the other ionic species by a back-side attack leading to an inverted product. The relative extent to which the two processes occur will be related to the stability of the free carbonium ion.

Many workers have studied nucleophilic aliphatic substitution reactions for systems in which the alkyl substituent is 1-phenylethyl (9,10,11,12). These studies have shown that compounds of this type definitely belong to the so-called intermediate class and that either pure unimolecular or pure bimolecular behavior may be observed depending upon the reaction conditions.

The methanolysis of 1-chloro-1-phenylethane in absolute methanol has been shown to follow a first-order rate law (10). As previously discussed, this observation, by itself, does not permit one to conclude that the reaction is proceeding by an unimolecular mechanism. The addition of methoxide ion in small concentrations, however, was without effect upon the reaction rate, and, indeed, even with methoxide concentrations as high as 3.5 M., kinetic analysis showed that 39 per cent of the reaction was still first-order. One therefore would appear to be justified in concluding that the reaction in pure solvent proceeds by an unimolecular mechanism. This conclusion is further supported by the observation that the product of methanolysis of the optically active chloride was largely racemic (10). Although analogous studies have not been made for the methanolysis of 1-bromo-1-phenylethane, this halide would undoubtedly exhibit similar behavior.

Because of the lower ionizing power of ethanol, the

rate of ethanolysis of 1-phenylethyl halides was much more sensitive to the addition of alkoxide ion (11). Thus, although very small concentrations of ethoxide ion were without significant effect on the ethanolysis rate of 1bromo-1-phenylethane, at base concentrations of 0.05 M. as much as 25 per cent of the reaction was second-order. Pure second-order kinetics were observed for the reaction of the bromide using ethoxide concentrations of 1.5 M. or higher.

Stereochemical studies have been made on the reaction of 1-chloro-1-phenylethane in ethanol (10). In the absence of added base, the product is racemic, while with ethoxide concentrations of 2.8 M., a product of high optical purity, but with an inverted configuration, was obtained.

From these results, it may be concluded that alcoholysis of 1-phenylethyl halides in pure methanol and ethanol proceeds by the unimolecular mechanism. The tendency for reaction by this mechanism is so great in methanol that a pure bimolecular reaction cannot be achieved even at very high concentrations of added methoxide ion. On the other hand, because of the lower ionizing power of ethanol, a bimolecular reaction, with the virtual exclusion of the unimolecular process, may be achieved in this solvent if ethoxide concentrations as high as 2 M. are used.

In the present investigation, the bromide was used rather than the chloride since its boiling point is such as

to permit easier separation of starting compound and the alcoholysis product. Isotope effect measurements were made for both methanolysis and ethanolysis in pure solvent and for the reaction of ethoxide ion (concentration ca. 2 M.) in ethanol.

For systems in which the alkyl substituent is the benzyl group, S_N^2 or bimolecular behavior has been clearly demonstrated (56). Indeed, this is the normal displacement mechanism since the alkyl group is primary. Although first-order kinetic results have been obtained for solvolysis reactions of benzyl halides, no definite conclusions can be drawn concerning the mechanism operative in such cases. It is to be noted, however, that the rates are extremely sensitive to the presence of added alkali. This result does not preclude an unimolecular mechanism in pure solvent but certainly it does nothing to support it.

Winstein, on the basis of his extensive studies on the correlation of solvolysis rates, assigns the reactions of benzyl compounds in hydroxylic solvents to his nucleophilic category (57). It is possible that something approaching an unimolecular mechanism could be achieved with benzyl compounds in solvents of very high ionizing power, e.g. formic acid, but isotope effect studies in such systems were beyond the scope of the work of this thesis. Isotope effect measurements have been made, however, for the bimolecular

reaction of methoxide ion with benzyl bromide in methanol solvent.

It is evident, on the basis of the foregoing discussion, that a study of the 1-phenylethyl system can provide information on the magnitude of isotope effects for both the unimolecular and bimolecular mechanism of substitution. This was the main purpose of the work to be reported in this thesis. In order to compare the effects for two different systems reacting by the bimolecular mechanism, the investigation was extended briefly to the benzyl system.

EXPERIMENTAL

General Discussion

The experimental work of this investigation developed in the following way. Firstly, the starting materials were prepared and the rates of reaction measured for those processes for which an isotope effect study was to be made. Next, a method of separation which allowed the isolation of a small amount of product from a large amount of starting compound was developed. Thirdly, a method of degradation was perfected whereby the carbon atom at the centre of reaction was isolated in a form suitable for mass spectrometric analysis, i.e. carbon dioxide. This degradation was necessary because the small differences between the C^{12}/C^{13} ratios at the centre of substitution for the starting compound and the product of a partial reaction would be lost if the whole molecule was converted to carbon dioxide. This degradation consisted of two stages: the first was an oxidation of the compounds to benzoic acid and the second a decarboxylation of the benzoic acid. The mass spectrometric analysis of the carbon dioxide was the next phase of this study. Finally, some extensive experiments were carried out to test the reliability of the various degradation and

separation procedures.

This experimental section is arranged in such a way that these main topics are discussed in the above order. Those phases of the investigation in which the 1-phenylethyl system and benzyl system nocessitated different approaches are sub-divided. The remaining headings, not so sub-divided, are applicable to both systems.

Preparation of Materials

1-Bromo-1-phenylethane

There are several published preparations of 1-bromol-phenylethane. Walling, Kharasch, and Mayo (58) have reported yields up to 85 per cent for the addition of hydrogen bromide to styrene at room temperature. Phenyl methyl carbinol has been converted to the bromide in good yields using 48 per cent hydrobromic acid (59) and Conant and Blatt (60) have obtained a 74 per cent yield from the carbinol using dry hydrogen bromide at 0° C. The latter procedure was used in all preparations for this study and, although only a slight change was made in the published procedure, the yields were consistently better than 85 per cent.

Dry hydrogen bromide, prepared by the action of bromine on tetralin (61), was bubbled through the carbinol, maintained at 0°C. in an ice-bath, until the reaction was complete. The organic layer was separated, placed in an open beaker over fused sodium sulphate and freed of excess hydrogen bromide under reduced pressure using a vacuum desiccator containing potassium hydroxide pellets. The drying agent was separated and washed well with anhydrous ether. Removal of the ether from the combined washings and the crude product left a residue which was fractionally distilled under reduced pressure. This procedure afforded 85-93 per cent yields of 1-bromo-1-phenylethane with the following physical constants: b.p. $83-4^{\circ}C./10 \text{ mm., n}_{D}^{25}$ 1.5592; lit. (62): b.p. $86-8^{\circ}C./14 \text{ mm., n}_{D}^{25.2}$ 1.5594.

1-Methoxy and 1-Ethoxy-1-phenylethane

In order to develop degradation procedures for both the starting material and the products, as described later, it was necessary to prepare samples of the products for each reaction to be studied. In the 1-phenylethyl system, these were 1-methoxy and 1-ethoxy-phenylethane. The preparations employed for each of these ethers consisted of a straightforward solvolysis of 1-bromo-1-phenylethane in the appropriate anhydrous alcohol. In each case, a twentyfour hour reflux period, and an isolation by ether extraction gave a 75 per cent yield of product. The physical constants found were as follows:

1-Ethoxy-1-phenylethane: b.p. 65-6°C./11 mm., n_D²⁵ 1.4821; lit. (63): b.p. 66-7°C./11 mm., n_D²⁰ 1.4848. l-Methoxy-l-phenylethane: b.p. 55-6°C./10 mm., n_D²⁵ 1.4900; lit. (64): b.p. 54-7°C./11 mm., n_D²⁰ 1.4918.

Benzyl Bromide and Benzyl Methyl Ether

Benzyl bromide and benzyl methyl ether, obtained from Eastman Kodak Co., Rochester, N.Y., were carefully fractionated to give materials with the following physical constants:

Benzyl bromide: b.p. 73-4°C./10 mm., n_D²⁵ 1.5728; lit. (65): b.p. 198°C./760 mm. Benzyl methyl ether: b.p. 57-3°C./14 mm., n_D²⁵ 1.5000; lit. (66): b.p. 170°C./760 mm., n_D²⁰ 1.5022.

Solvents

Absolute methanol and ethanol were prepared from the commercial 'absolute' materials by treatment with magnesium (61). In all other cases in which anhydrous solvents were required, standard methods of drying were employed. All solvents were distilled through a twentyinch Vigreux column before use.

Kinetics

Solvolysis Reactions of 1-Bromo-1-phenylethane

The rates of solvolysis of 1-bromo-1-phenylethane in absolute methanol and ethanol were followed by measuring the rate of formation of hydrogen bromide using an acid-base titration. A reaction temperature was chosen such that, on the basis of published work or rough preliminary runs, there would be approximately five per cent reaction in fifteen minutes. This was a convenient rate for the partial reactions in the subsequent isotope effect experiments.

A weighed sample of the bromide was added to the appropriate solvent, which had been previously thermostatted, and the resulting solution was maintained at the desired reaction temperature to within $\pm 0.02^{\circ}$ C. At various time intervals, accurately measured aliquots were removed from the reaction vessel and pipetted into a mixture of benzene and cold water. This served to effectively quench the reaction. The resulting mixture was immediately titrated with standard sodium hydroxide solution using a phenolphthalein indicator. The results of the kinetic measurements in absolute alcohol are summarized in Table IV. The value of the rate constant k_1 , for each kinetic run, was obtained by a plot of time against the logarithm of bromide concentration applying the method of least squares.

TABLE IV

KINETIC RESULTS FOR SOLVOLYSES OF 1-BROMO-1-PHENYLETHANE

Solvents	(°C.)	Conc. of RBr (M.)	$10^{3}k_{1} (min.^{-1})$
Abs olut e ethan o l	44.98	0.486 0.525 0.512	3.52 3.64 3.64
Absolute methanol	25.00	0.112 0.114 0.303	Avg. 3.61 3.42 3.43 3.34
			<u>Avg. 3.40</u>

Reaction of 1-Bromo-1-phenylethane and Benzyl Bromide with Alkoxide Ion

In the reaction of 1-bromo-1-phenylethane with ethoxide ion in ethanol and of benzyl bromide with methoxide in methanol, the rate was measured by following the rate of bromide ion formation. Again, reaction temperatures were chosen such as to give approximately five per cent reaction in fifteen minutes.

The reagent, absolute ethanol or methanol containing the desired concentration of the corresponding alkoxide ion, was prepared and equilibrated to the temperature of reaction. A weighed sample of organic bromide was added and, after thorough shaking, aliquots of the reaction mixture were placed in separate tubes which were then sealed and placed in a constant temperature bath. As before, the temperature of the bath was maintained within $\pm 0.02^{\circ}$ C. of the desired reaction temperature. After varying periods of time, a tube was removed from the bath, opened, and quickly poured into a cold benzene-water mixture containing sufficient nitric acid to neutralize the unreacted base. After extracting the aqueous layer with benzene, the benzene was washed once with cold water and the combined water layers titrated for bromide ion using the modified Volhard method described by Diehl and Smith (67). The value of k_2 , the rate constant, was obtained by plotting time against log a(b - x)/b(a - x), applying the method of least squares. The results of the kinetic measurements for the reaction of 1-bromo-1-phenylethane are shown in Table V and for that of benzyl bromide in Table VI.

TABLE V

KINETIC RESULTS FOR THE REACTION OF 1-BROMO-1-PHENYLETHANE WITH ETHOXIDE ION

Solvent	Temp. (°C.)	Conc. of RBr (M.)	$C_{2}^{\text{Conc.of}}$ (M.)	10 ³ k ₂	(1./mole- min.)
Absolute ethanol	25.00	0.470 0.483 0.498	2.175 2.160 1.848	3.16 3.24 3.28	
					Avg. 3.23

TABLE VI

KINETIC RESULTS FOR THE REACTION WITH METHOXIDE ION OF BENZYL BROMIDE

Solvent	Temp.	Conc. of	Conc. of	10 ³ k ₂ (1./mole-
	(°C.)	RBr (M.)	CH ₃ 0 (M.)	min.)
Absolute methanol	0.00	0.537 0.424 0.519	1.108 1.122 0.911	5.33 5.29 5.31 <u>Avg. 5.31</u>

Isotope Effect Reactions and Product Separations

The difference in the isotopic ratios in reactant and product for the atom at the reaction centre is a function of the extent of reaction, it being a maximum initially and decreasing to zero for complete conversion to product. For an infinitesimally small extent of reaction, the isotope effect is given directly by the quotient of the isotopic ratio for the atom in question in the product and in the reactant. In practice, however, the reaction is allowed to proceed to some known extent of reaction, five to ten per cent in this study, and the isotope effect calculated using an expression developed in a later section.

The isotope effect reactions were carried out in the following way. For the unimolecular solvolyses, one litre of the appropriate solvent was equilibrated to the temperature of reaction and a weighed sample of 1-bromo-1-phenylethane added. This solution (approximately 0.5 M. in bromide) was placed in the constant temperature bath for a short time (ca. 15 minutes) after which the reaction mixture was poured into a cold mixture of 3-4 litres of water and 600 ml. benzene. After vigorous shaking, the layers were separated and the aqueous layer extracted three more times with benzene, using about 300 ml. per extraction. The combined benzene extracts were thoroughly washed with cold water and then dried over calcium chloride for one to two hours. After the benzene had been removed by distillation under reduced pressure, the residue was ready for the separation of the product from the unreacted starting material.

For the reaction with alkoxide ion, a solution of the sodium alkoxide in the corresponding anhydrous alcohol (approximately 2 M. for ethoxide ion and 1 M. for methoxide ion) was prepared and thermostatted to the desired temperature of reaction. A procedure similar to that used for the unimolecular solvolyses was then followed. For these reactions, however, the quenching mixture contained sufficient nitric acid to neutralize the unreacted base present in the reaction mixture.

The separation of the mixture of solvolysis product and unreacted starting material obtained by the above extraction was accomplished by fractional distillation. This fractionation, however, was complicated by the following considerations: (1) a small quantity of product was present relative to the amount of starting material, (2) the boiling

point differences for the various alkoxy derivatives and the corresponding halides were in the range of ten to twenty degrees at 10 mm. pressure, and (3) prolonged heating of 1bromo-1-phenylethane caused decomposition to hydrogen bromide and styrene. This decomposition is catalyzed by metal packings commonly used in fractionating columns. Therefore, an efficient column, having an unreactive packing, low holdup, and high throughput was required. For this purpose, a column with a tantalum metal spiral-type packing was constructed (68).

With this column only one distillation was necessary to separate the methyl ethers from the corresponding halides. Two distillations, however, were required to separate 1ethoxy-1-phenylethane from 1-bromo-1-phenylethane.

Degradation of Compounds to Benzoic Acid

1-Phenylethyl System

Since the C^{12}/C^{13} ratios of the carbon atom at the centre of reaction in the reactant and in the product obtained after a small extent of reaction must be intercompared, this atom must be removed from the rest of the molecule and converted to carbon dioxide for mass spectrometric analysis. Furthermore, the yields for the various steps in the degradation must be as high as possible to avoid extraneous isotopic fractionation. The 1-bromo-1-phenylethane

molecule has a benzene ring attached directly to the reacting carbon atom. This group may serve as a 'handle' to remove the desired carbon atom from the rest of the molecule. Since a benzene ring is relatively stable to oxidation, the obvious approach was to oxidize the side-chain completely to form benzoic acid which then may be readily decarboxylated.

Attempts to convert the bromide and the two ether products to benzoic acid in a single-stage oxidation resulted in low yields because of a tendency for benzene ring degradation. After a considerable investigation of reagents and reaction conditions, it was found that the best overall yields of the acid could be obtained using a two-stage oxidation procedure. In the first stage, the compounds were oxidized with alkaline potassium permanganate in a pyridinewater solvent to give a mixture of benzoic and benzoylformic acids. This acid mixture, after isolation, was further oxidized with hydrogen peroxide, whereby the benzoylformic acid was quantitatively converted to benzoic acid (69).

Oxidation Procedure

The detailed procedure for the oxidation is presented in the following paragraphs.

1-Bromo-1-phenylethane (1.651 g., 0.00843 mole) was dissolved in pyridine (50 ml.) and water (100 ml.) and the solution placed in a 500 ml. three-necked flask fitted with

a reflux condenser and a glass-chain stirrer. Potassium hydroxide (5 g., 0.0841 mole) was added and the solution heated under reflux for fifteen minutes with vigorous stirring. Without removing the heater, solid potassium permanganate (8 g., 0.0506 mole) was added slowly through the condenser. This addition of the oxidizing agent required about fifteen minutes. Any potassium permanganate adhering to the inside of the condenser was washed into the reaction flask with a minimum of water. The reaction mixture was then heated under reflux for an additional thirty minutes with vigorous stirring.

The reaction mixture was cooled to about 50°C. and the excess potassium permanganate was then destroyed by the addition of 95 per cent ethanol. The reaction mixture was filtered through a 10 cm. diameter, medium porosity, sinteredglass funnel, and the inorganic solids thoroughly washed with about 250 ml. of hot water added in small portions. The filtrate was cooled with ice and acidified with concentrated hydrochloric acid. When definitely acid, the filtrate was extracted four times with ether using approximately 300 ml. for each extraction. The combined ether extracts were concentrated by distillation, and the final traces of ether removed at a water aspirator.

The organic residue, contained in a 100 ml. roundbottomed flask, was treated with about five ml. of 30 per

cent hydrogen peroxide and 30 ml. of water. This mixture was stirred vigorously for two to three hours and was allowed to stand overnight.

The crude benzoic acid-water mixture was heated under reflux to dissolve the benzoic acid. More water was added, as necessary, to obtain a solution. After a reflux period of a few minutes to destroy the excess hydrogen peroxide, the solution was allowed to cool and the benzoic acid collected and dried; the yield was 0.808 g. (74.2%). Additional benzoic acid was recovered by ether extraction of the supernatant liquid and ether washing of all apparatus used in the first recrystallization. The ether was removed by distillation and the residue recrystallized to yield a second crop of acid (0.101 g.). The total yield of benzoic acid, thus obtained, was 0.909 g. or 85.2%. Physical constants for this product were: m.p. 121.5 - 121.8°C. (corr.), N.E. 122.2 \pm 1.

A similar procedure, using, however, one and one half times as much oxidizing agent, was followed for 1methoxy-1-phenylethane and the corresponding ethoxy compound. Oxidations of approximately 1 g. samples gave yields of benzoic acid which were generally slightly higher than those obtained from the bromide.

Benzyl System

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For this system, the degradation problems were less

difficult. Since the carbon atom at which substitution occurs is attached to the benzene ring only, benzoic acid is the only possible acid product from the oxidation of the side chain and no rearrangements can occur.

Yields of benzoic acid obtained by direct oxidation of benzyl bromide with alkaline permanganate in aqueous pyridine solution were considerably lower than those obtained from 1-bromo-1-phenylethane. The oxidation of benzyl methyl ether, however, afforded yields of approximately 90 per cent. For this reason, the benzyl bromide was first converted to methyl ether by the action of sodium methoxide in methanol, and the ether was then oxidized to benzoic acid using the standard procedure. In this way, benzyl bromide was converted to acid in an overall yield of 85 per cent or better.

The procedure employed for the degradation of benzyl bromide was as follows. Benzyl bromide (1.603 g., 0.00939 mole) was heated under reflux with 1 M. sodium methoxide solution (25 ml.) for two hours, the solution then was cooled and poured into ice water. After ether extraction and concentration, the organic residue was oxidized using potassium hydroxide (5 g.), pyridine (50 ml.), water (100 ml.), and potassium permanganate (10 g., 0.0633 mole) following the procedure previously described for the 1-phenylethyl compounds. The oxidation product, worked up in the usual way, but omitting the hydrogen peroxide treatment, gave pure benzoic acid in a yield of 85.7%. Direct oxidation of benzyl methyl ether (0.949 g., 0.00778 mole) gave benzoic acid in 93.1% yield.

Decarboxylation of Benzoic Acid

Benzoic acid may be decarboxylated in a number of ways, namely, thermally (70), catalytically (71), by the Hunsdiecker (72) or the Schmidt reaction (73,74). Previous work in this laboratory indicated that the Schmidt reaction, in which benzoic acid is treated with hydrazoic acid to give carbon dioxide and aniline, was the best approach for this investigation. The carbon dioxide evolved was collected by precipitation as barium carbonate using a method described by Calvin (75).

Great care was taken in all stages of the procedure to avoid carbonate contamination. All solutions were freshly prepared for each set of samples using water which had been deionized by means of the ion exchange resins, Amberlite IRA 400 and Amberlite IR 120, and had been boiled to remove dissolved carbon dioxide. Blank runs, in which the whole procedure was carried out in the absence of benzoic acid, gave less than 0.2 mg. of barium carbonate, compared with 180-250 mg. in a typical decarboxylation.

The decarboxylations were carried out in an apparatus

consisting of a series of traps which allowed the reaction flask to be swept with nitrogen gas in order to remove the evolved carbon dioxide. A cylinder of purified nitrogen. fitted with a needle valve, was attached to a fritted-disc type, gas-washing bottle containing about 150 ml. of Feiser's solution, prepared by the method of Vogel (61). From this scrubber, the nitrogen was led into a 50 ml. test tube, the reaction flask, by means of a glass tube extending almost to the bottom of the tube. The gas stream was then passed into a second scrubber, containing approximately 150 ml. of 3 per cent potassium permanganate in 5 per cent sulphuric acid. This bubbler served to trap sulphur dioxide, formed by the reduction of sulphuric acid by hydrazoic acid, which might be carried over from the reaction flask. Finally, the gas stream was led through approximately 50 ml. of 0.2 M. carbonate-free alkali, made up from a 1 M. stock solution of sodium hydroxide prepared from sodium by the method described by Calvin (76).

While the line was thoroughly swept with nitrogen with an empty test tube in place, another reaction flask containing an accurately weighed sample, approximately one millimole, of benzoic acid dissolved in 3-4 ml. of concentrated sulphuric acid was cooled to 0°C. Approximately 80 mg. of sodium azide was added to the cold solution and the flask quickly placed on the line, replacing the empty test tube.

A water bath, maintained at about 40°C., was placed around the reaction flask and the nitrogen stream adjusted to give a gentle flow of bubbles through the alkali trap. After two hours, the heating was stopped and the alkali trap removed.

The contents of the alkali trap were quickly poured into a 125 ml. Erlenmeyer flask, and 10 ml. of ammonium chloride solution (ca. 1 M.) was added, followed by 20 ml. of barium chloride solution (ca. 1 M.). The flask was stoppered, shaken vigorously and allowed to stand for at least fifteen minutes. At the end of this time, the contents of the flask, containing the precipitated barium carbonate, were filtered through a weighed, medium porosity, sintered-glass funnel. Extraneous carbon dioxide pick-up was avoided by placing a watch glass over the funnel during the filtration. The solids collected on the funnel were washed well with boiling, carbonate-free water to remove the last traces of barium chloride. The funnel was then dried in an oven at 110°C. for at least an hour, cooled, and weighed again. Some typical results for this procedure were: 0.121 g. benzoic acid yielded 0.177 g. BaCO, (90.6%); 0.169 g. benzoic acid to 0.248 g. BaCO, (90.8%); 0.115 g. benzoic acid gave 0.178 g. BaCO₂ (93.2%).

Preparation of Carbon Dioxide Samples for Mass Spectrometric Analysis

The carbon dioxide samples were prepared using the

high-vacuum system illustrated in Figure 1.

The high-vacuum line, with stopcocks S7 and S3 closed, was pumped down to about 10^{-6} mm. Hg. Approximately 70 mg. of barium carbonate was placed in flask A which was then attached to the line. To flask B was added ten ml. of concentrated sulphuric acid, which had been heated to 170° C. for an hour and stored in a desiccator over potassium hydroxide pellets, and the flask placed in position B1 (indicated by dotted lines in Figure 1.). Stopcocks S2 and S1 were closed to bypass the oil diffusion pump, P2, and S3 and S7 were opened in order to evacuate the entire system with the mechanical pump, P1. After the initial surge of air was removed, S2 and S1 were opened to readmit the diffusion pump and S3 closed. This allowed the line to be pumped down fairly rapidly to about 10^{-5} mm. Hg.

The acid in flask B was frozen, using a liquid air bath, and then allowed to thaw. This procedure was repeated three times to remove the air from the acid. Then, with S6 closed and the U-tube, Ul, surrounded with a liquid air bath, the sulphuric acid was poured into flask A by slowly rotating B to position B2. When the initial rush of carbon dioxide had ceased, a water bath at 60° C. was placed around flask A to ensure complete reaction. The evolved carbon dioxide was thus trapped in Ul. Stopcock S7 was closed and the noncondensed gases in the trap were removed by opening S6 for



thirty seconds. This stopcock was then closed. The liquid air bath was removed from Ul and replaced with a slurry of carbon dioxide in acetone. Stopcocks S4 and S5 were adjusted so as to connect traps Ul and U2 with the sample tube, T2, while at the same time isolating the system from the manifold. A liquid air bath was placed around T2, stopcock S6 opened, and the carbon dioxide allowed to distill through an anhydrone drying tube, U2, and condense in the sample tube. One minute was allowed for this distillation. Then, S6 was closed and Ul allowed to warm up to room temperature. The cold trap of carbon dioxide and acetone was again placed on Ul, S6 opened, and another distillation to the sample tube was carried out. After thirty seconds, the sample tube was sealed off and the sample was then ready for analysis.

Mass Spectrometry

General Discussion

The relative abundances of the carbon isotopes were measured using a 180 degree, directional focussing mass spectrometer of the Nier type equipped with an automatic recorder.

The C^{12}/C^{13} ratios were determined by measuring the ion currents due to the CO_2^+ species. The isotopic ratio in each sample may be determined from the mass spectrometer mass

ratio for the 44 and 45 peaks, after allowing for the contribution of $C^{12}O^{16}O^{17}$ to the 45 peak.

The 44/45 mass ratio may be equated as follows:

$$\frac{44}{45} = \frac{c^{12} c^{16} c^{16}}{c^{13} c^{16} c^{16} + c^{12} c^{16} c^{17}}$$

Now the probability of occurrence of $C^{13}O^{16}O^{16}$ as compared with that of $C^{12}O^{16}O^{16}$ is given simply by the C^{13}/C^{12} ratio. Since there are two atoms of oxygen in a molecule of carbon dioxide, the $C^{12}O^{16}O^{17}/C^{12}O^{16}O^{16}$ ratio is twice the O^{17}/O^{16} ratio. Therefore, with the occurrence of all the species taken as relative to the $C^{12}O^{16}O^{16}$, the 44/45 ratio may be expressed as:

$$\frac{44}{45} = \frac{1}{c^{13}/c^{12} + 2 \ o^{17}/o^{16}}$$

Hence,

$$c^{12}/c^{13} = \frac{1}{44/45 - 2 0^{17}/0^{16}}$$

The $0^{17}/0^{16}$ ratio has been determined by Thode (77) for tank oxygen and was found to be 0.00039.

A sample consisting of carbon dioxide derived from the reactant used in a series of runs was chosen as a standard for each isotope effect study. The procedure employed was to analyze the standard, then another sample, and the standard again, all in the shortest possible time.

A single analysis consisted of a series of at least six double spectrograms where each double spectrogram was a scan of the 44 and 45 mass peaks in the order: 44,45,45,44. The 44/45 ratio for each double spectrogram was measured and the average ratio for the series calculated. If the mean deviation of this ratio was less than 0.1 per cent the analysis was accepted. The value of the average 44/45 ratio for an unknown sample was accepted, if the 44/45 ratio of the standard, before and after the unknown, agreed to within 0.1 per cent. All the C^{12}/C^{13} ratios reported in this thesis are based on a standard having a 44/45 ratio of 85.00 and are judged to be accurate to + 0.1 percent. These ratios, however, are not absolute values because of the $0^{17}/0^{16}$ ratio employed and the choice of an arbitrary value for the 44/45 ratio for the standard. Owing to day-to-day fluctuations in the electronics of the instrument, the C^{12}/C^{13} ratios reported for various series cannot be intercompared. Such an intercomparison is, of course, not required in the evaluation of isotope effects.

Calculation of Isotope Effects in Unidirectional Reactions

The following data are required for the calculation of an isotope effect in an unidirectional reaction:

> The isotopic ratios for the reactant and the product.

2. The extent of the reaction.

An equation due to Stevens (78) using this data may be formulated in the following way.

Consider any general unidirectional reaction.

$$A + B + \dots \qquad \stackrel{k_{L}}{\longrightarrow} M + N + \dots \qquad (20)$$

$$A_1 + B + \dots + \underbrace{k_H}_{M_1} + N + \dots$$
 (21)

where A represents the light and A_1 the heavy isotope. Let a, a_1 , b, be the initial concentrations of the reactants and x, x_1 , and y be the amounts reacted in time t. Therefore, after time t has passed, the reactant concentrations will be $(a - x), (a_1 - x_1), \ldots$ etc. The rates of the isotopic reaction may then be expressed as:

$$dx/dt = k_{L} (a - x)(b - y) \dots$$
 (22)

$$dx_1/dt = k_H (a_1 - x_1)(b - y) \dots$$
 (23)

Therefore,

1.00

$$dx/dt/dx_1/dt = k_1/k_H \frac{(a - x)}{(a_1 - x_1)}$$
 (24)

which upon integration gives:

$$k_{\rm L}/k_{\rm H} = \ln \frac{a}{(a-x)} / \ln \frac{a_{\rm I}}{(a_{\rm I}-x_{\rm I})}$$
 (25)

This equation holds regardless of the overall order of the reaction, as long as the reaction is first order with respect to A. Now let a_1/a equal s, x_1/x equal s_1 , and s_1/s equal r. Then, a_1 equals sa, x_1 equals s_1x which equals rsx. If the reaction proceeds until x/a equals f, and if af is substituted for x, sraf for x_1 , and sa for a_1 , equation 19 becomes:

$$k_{\rm L}/k_{\rm H} = \frac{\ln \frac{a}{(a-af)}}{\ln \frac{sa}{(sa-sarf)}} = \frac{\ln \frac{1}{(1-f)}}{\ln \frac{1}{(1-rf)}}$$
(26)

or,

$$k_{\rm L}/k_{\rm H} = \frac{\ln(1-\hat{z})}{\ln(1-x\hat{z})}$$
(27)

The C^{12}/C^{13} ratios obtained from mass spectrometric analysis of the carbon dioxide formed from reactant and product correspond to the quantities a/a_1 and x/x_1 , respectively. The r in equation 27 may, therefore, be equated as follows in terms of measured mass ratios.

$$r = s_1/s = x_1/x/a_1/a = C^{12}/C^{13}$$
 react. C^{12}/C^{13} prod.

The factor f may be expressed in terms of the extent of reaction as,

$$f = x/a = \%$$
 reaction 100

An example for such a calculation follows. The data for the reaction of 1-bromo-1-phenylethane in absolute methanol, Run No. 4, are $a/a_1 = 91.00$, $x/x_1 = 91.60$,
f = 0.048. The apparent fractionation factor, C^{12}/C^{13} product C^{12}/C^{13} reactant, is 1.0066. Applying equation 27, k_{12}/k_{13} is found to be 1.0068, a value which differs from the apparent fractionation factor by less than the error in the measurements of the isotopic ratios. For larger isotope effects, however, this correction is greater. For example, in the reaction of benzyl bromide with methoxide ion, Run No. 1, for which the isotopic ratios are $a/a_1 =$ 91.00, $x/x_1 =$ 95.65 at f = 0.0712, the apparent fractionation factor is 1.0511, while the k_{12}/k_{13} ratio is 1.0531, calculated using equation 27.

Validity of Experimental Methods

General Discussion

In a study of isotope effects for unidirectional processes, there are certain complications which could lead to spurious results. Firstly, the reaction should show no significant tendency for reversal under the conditions used in the isotope effect study. Otherwise, the fractionation will be that corresponding to an equilibrium process (isotope exchange reaction) rather than to an unidirectional process and, hence, will be in no way related to reaction mechanism. Secondly, there can be no other unidirectional process operative, especially in the isolation procedure, which could change the isotopic ratio for the atom at the

reaction centre. Thirdly, the molecular species analyzed mass spectrometrically must arise from, and only from, samples of the reactant and product. Fourthly, each degradation step should be free of fractionation. This means, in the ideal case, quantitative conversion in each step. This situation, however, is unusual in organic systems, although very high yields can frequently be obtained. Finally, the degradation step must be free of rearrangement so that the carbon ultimately analyzed mass spectrometrically is the atom at the centre of reaction only. It is evident that these complications may arise in one or other of the three distinct stages of each isotope effect study, viz. the reaction itself, the isolation of the product and the degradation of the product and the reactant. Although the difficulties inherent in the reaction itself were resolved on the basis of earlier investigations, extensive experimental work was done, in the 1-phenylethyl system, to determine the validity of the isolation techniques and the degradation methods employed. In the benzyl system, isotope exchange between halide and ether would be most unlikely under the bimolecular reaction conditions used, rearrangements would not be possible during the degradation, and decomposition or exchange during the separation procedure would be much less likely to occur than in the more labile 1-phenylethyl system.

The Reaction

Although, as mentioned previously, a significant reversal of the processes, assumed to be unidirectional, could invalidate all of the results reported, the following considerations rule out this complication. The bimolecular reactions, all of which were carried out in the presence of excess alkoxide ion, were strictly unidirectional since there would be no tendency for cleavage of unprotonated ethers by attack of bromide ion. The constancy of the value of k, for reactions in pure solvent up to 70 to 80 per cent reaction# shows that there was no great tendency for the reverse reaction to occur even under solvolysis conditions. Furthermore, since all unimolecular isotope effect experiments were carried out to only about five per cent completion, the reverse reaction, if it occurs at all, would be of no significance. This conclusion was further substantiated by the observation that the unimolecular isotope effect was the same for methanolysis whether hydrogen bromide was allowed to build up as the reaction proceeded or was continuously neutralized by addition of methoxide ion. (See RESULTS.)

The bimolecular reaction is complicated by a concurrent elimination process which constituted about 30 per

"The decrease in rate constant for reactions proceeding almost to completion has been attributed to the reaction of hydrogen bromide with solvent (11,12).

cent of the total reaction. Again, since the isotope effect runs were carried out to only small extents of reaction, less than ten per cent, no significant change in the C^{12}/C^{13} ratio of the reactant would result by virtue of this side reaction. Furthermore, the ether product was freed of all styrene before degradation and, therefore, its C^{12}/C^{13} ratio would be unaffected by the elimination process. There is no tendency for the elimination reaction to occur under the unimolecular conditions.

Tests of the Separation Methods

In the separation procedure, there were two possible complications for isotope effect measurements. Firstly, an exchange reaction between product and reactant, for the reasons previously mentioned, could affect an isotopic fractionation subsequently measured. Secondly, any loss of product by an unidirectional decomposition having an isotope effect could also change the C^{12}/C^{13} ratio of the product and so invalidate any isotope effects based on it. Each of these possibilities was examined.

Exchange

The kinetic studies demonstrated that the reaction was successfully stopped by pouring the reaction solution into a water-benzene mixture. After the benzene extraction, however, the benzene solution was allowed to stand over

calcium chloride for an hour or more. There was, therefore, a remote possibility that, during this time, the product and reactant could exchange substituent groups, i.e. bromide for alkoxy group. Furthermore, following the removal of the benzene the two compounds were in close contact at an elevated temperature until the fractional distillation was completed. Now, 1-bromo-1-phenylethane is known to decompose under prolonged heating to give hydrogen bromide. The possibility, therefore, existed that some of the ether was reconverted back to bromide and methanol by ether cleavage, and then, perhaps, ether reformed by the action of the methanol on unreacted bromide. An exchange reaction of this sort would very likely tend to lower the observed isotope effect since little or no isotopic discrimination between bromide and ether would be expected in such a process.

In order to test the possibility of any exchange occurring during the separation procedure, a trial separation using a sample of 1-ethoxy-1-phenylethane-1-C¹³ and normal 1-bromo-1-phenylethane was carried out. A synthetic mixture of the labelled ether and normal bromide, in a ratio corresponding to that present in a reaction mixture at the end of a typical isotope effect experiment, was prepared, cooled, and added quickly to a cold solution of absolute ethanol and sodium ethoxide. The standard procedure for separation of ether and bromide was then carried out

immediately. A sample of the ether was degraded in the usual way to give carbon dioxide, whose isotopic abundance was then compared to that of the carbon dioxide prepared from the original labelled ether. The results of this analysis appear in Table VII.

TABLE VII

MASS SPECTROM	ETRIC RESULTS OF EXCHANGE	STUDY
Sample	C ¹² /C ¹³ Ratios	Average
Original Ether	20.49 ; 20.77	20.63
Ether after isolation	22.86 ; 23.13	23.00

In this tracer experiment the mole ratio of 1-bromo-1-phenylethane to 1-ethoxy-1-phenylethane-1- C^{13} was 14.74 : 1. Since the isotopic abundance of the bromide was normal, the C^{12}/C^{13} ratio for its alpha carbon would be about 90. Therefore, in the case of a complete exchange, the final C^{12}/C^{13} ratio for the alpha carbon of the ether would be 85.59 compared to 20.63 for the original labelled ether; in other words, there would be a change in ratios before and after such an equilibrium of 64.96. Since the measured change was 2.37, only a very small exchange could have occurred, i.e. less than four per cent. Indeed, this small change in isotopic ratios could be entirely due to a slight contamination of the final ether sample with some normal abundance bromide. In any case, the observed isotope effect would not be significantly reduced.

The labelled compound, 1-ethoxy-1-phenylethane-1- C^{13} , was prepared by the following sequence of reactions:

$$\begin{array}{c} C \neq 0_{2} \xrightarrow{CH_{3}MgI} CH_{3}C \neq 00Na \xrightarrow{p-TosCl} (CH_{3}C \neq 0)_{2}0 \xrightarrow{C_{6}H_{6}} C_{6}H_{5}C \neq 0CH_{3} \\ \downarrow LiAlH_{4} \\ C_{6}H_{5}C \neq HOC_{2}H_{5}CH_{3} \xrightarrow{C_{2}H_{5}OH} C_{6}H_{5}C \neq HBrCH_{3} \xrightarrow{HBr} C_{6}H_{5}C \neq HOHCH_{3} \end{array}$$

The first steps of this synthesis, leading to acetophenone, have become standard methods for the preparation of labelled materials. Following the reduction with lithium aluminum hydride, the final steps were similar to those previously described, although adapted to a semi-micro scale. The overall yield for the synthesis was 35 per cent.

Sodium acetate- $1-C^{13}$:- This compound was prepared by a Grignard synthesis following the method of Sakami, Evans, and Gurin (79). The apparatus consisted of a 2-1. roundbottomed flask fitted with a dropping funnel and two sidearms each of which was equipped with stopcocks. One sidearm was connected to a mechanical pump; the other was attached, through a calcium chloride drying tube, to a gas generator. The latter consisted of a 2-necked, 100 ml., round-bottomed flask fitted with a dropping funnel. An ethereal solution of methyl magnesium iodide was prepared by the addition of

methyl iodide (14 g., 0.0985 mole) in 20 ml. of dry ether to a mixture of magnesium (1.4 g., 0.0583 mole), dry ether (25 ml.), and a crystal of iodine. This solution was placed in the dropping funnel attached to the large reaction flask. Barium carbonate-C¹³ (5.060 g., 0.0257 mole; C¹³ content 61.8%), supplied by Eastman Kodak Co., was placed in the gas generator flask, the whole apparatus evacuated and the system was then isolated from the pump. Carbon dioxide-C13 was generated by the dropwise addition of 40 per cent perchloric acid solution onto the solid carbonate and was allowed to pass into the large reaction flask. After closing the second stopcock, the gas generator was removed and the reaction flask, with the attached dropping funnel containing the Grignard reagent, was cooled to -20°C. The Grignard reagent was introduced slowly and the flask was constantly shaken until the reaction mixture had congealed. The mixture was then allowed to stand at -20°C. overnight. Hydrolysis of the product with 20 per cent sulphuric acid was followed by a continuous liquid-liquid extraction with ether for 24 hours. The ether extract was concentrated, the residue taken up in water, and, after separation of a small quantity of insoluble liquid, the aqueous solution was carefully adjusted to a pH of 6 by the addition of dilute sodium hydroxide. The aqueous solution was then evaporated to dryness and the sodium acetate-C¹³ dried at 140°C. under

vacuum. The yield was 1.828 g., 86.8%.

Acetophenone-l- C^{13} :- This compound was prepared following the method of Shantz and Rittenberg (80). The dry labelled sodium acetate was first intimately mixed with dry unlabelled sodium acetate (22.968 g., 0.292 mole) and p-toluene sulphonyl chloride (58 g.; 0.305 mole), purified by the method of Vogel (61), was added. The mixture of acid chloride and salt was heated slowly and the acetic anhydride so formed collected as distillate.

Without further purification, the acetic anhydride was added to a mixture of dry benzene (150 ml.) and anhydrous aluminum chloride (38 g.). This mixture was heated under reflux until the evolution of hydrogen chloride had ceased, then poured into ice water, and extracted with ether. The ether extracts were washed with dilute alkali, water and then dried over magnesium sulphate.

The ether was removed by distillation and the residue distilled under reduced pressure. Acetophenone-l- C^{13} , b.p. 78-80°C./10 mm., n_D^{22} 1.5320, was obtained in good yield (8.558 g.). These constants are to be compared with b.p. 78-79°C./10 mm., n_D^{22} 1.5322 found for a sample of reagent grade acetophenone.

<u>l-phenylethanol-l- C^{13} </u>:- The acetophenone-l- C^{13} (8.557 g.) was reduced to the carbinol using lithium aluminum

hydride (2.0 g.; 0.0529 mole) in anhydrous ether (50 ml.) following the usual procedure (81). The excess lithium aluminum hydride was destroyed by the cautious addition of water followed by the addition of 20 per cent sulphuric acid (80 ml.). The crude product, after ether extraction and drying over magnesium sulphate, was isolated by the evaporation of the ether. No further purification was attempted.

<u>1-Bromo-1-phenylethane-1-C¹³</u>:- A slight modification of the bromination procedure was applied here, because of the small quantities involved. The crude carbinol was dissolved in carbon tetrachloride (25 ml.) and treated with dry hydrogen bromide until the reaction was complete. The reaction mixture was poured into water and extracted with carbon tetrachloride. The combined extracts were dried over magnesium sulphate and concentrated to yield crude 1bromo-1-phenylethane-1-C¹³. This product was used directly in the synthesis of 1-ethoxy-1-phenylethane-1-C¹³.

<u>l-Ethoxy-l-phenylethane-l-C¹³</u>:- The crude bromide was dissolved in absolute ethanol (100 ml.) and heated under reflux for twenty-four hours. Periodically, small amounts of a solution of sodium ethoxide in absolute ethanol were added to neutralize the hydrogen bromide formed. This was done to force the reaction to completion. At the end of the reflux period, the reaction mixture was cooled, poured into

a mixture of ice and water and extracted with ether. The combined extracts were dried over magnesium sulphate and then concentrated. The residue was fractionally distilled to give 1-ethoxy-1-phenylethane-1- C^{13} . The main fraction (5.980 g.) had a boiling point of 64.5°C./10 mm., n_D^{25} 1.4820, while a secondary fraction (1.102 g.), collected before and after the main fraction, boiled in the range 64-5°C./10 mm., n_D^{25} 1.4828.

Recovery

In a study such as this, it is important that there be no serious loss of product during the isolation. In the event of a fairly large loss of ether through some decomposition process involving isotopic fractionation with respect to the carbon atom at the seat of substitution, the isotopic ratio of this carbon atom in the product finally isolated would not correspond to that of product originally formed in the displacement process under investigation. Such a situation would arise if, for example, hydrogen bromide formed by the thermal decomposition of unreacted bromide brought about a non-reversible cleavage of the ether product to bromide and methanol. (The possibility of this process occurring and then being followed by formation of new ether by reaction of the bromide with methanol has been eliminated by the results of the exchange studies reported in the

previous section.)

In order to establish that the isolation procedures did not involve any serious loss of the ether formed during the partial reactions in the isotope effect experiments, some synthetic mixtures of 1-bromo-1-phenylethane and 1ethoxy-1-phenylethane were prepared and immediately subjected to the usual separation procedure. After the fractional distillation, the various fractions were analyzed for their ether content using the Zeisel determination for ethoxy groups (82). The results for two such trials are given in Table VIII.

TABLE VIII

RECOVERY OF 1-ETHOXY-1-FHENYLETHANE FROM A SYNTHETIC REACTION MIXTURE

Weight of Ether in Reaction Mixture	Weight of Bromide in Reaction Mixture	Ethe Weight	er Found Per Cent
4.299	95.0010	3.925	91.4 <u>+</u> 0.7
4.470	80.3154	4.248	95.3 ± 0.7

The small loss of product probably can be attributed to mechanical loss throughout the operation. Since the benzene must be removed by distillation under reduced pressure, undoubtedly some of the ether would be carried over with this solvent. Even if all of the 5-9 per cent loss were to result from some decomposition process in which there was isotopic fractionation, this would not significantly affect the isotopic ratio of the remaining ether.

The second consideration is the purity of the samples of product subjected to degradation to benzoic acid. Again, the Zeisel method for ethoxy group determination was applied to some typical samples of 1-ethoxy-1-phenylethane taken through the usual separation procedure. In all cases, the ether samples were found to be from 93-95 per cent pure. The styrene content for each of these samples was found to be less than one per cent. The rest of the impurity probably was mainly 1-bromo-1-phenylethane although phenyl methyl carbinol formed by hydrolysis in the separation procedure might be present. In any event, this small contamination of the product with less than 10 per cent impurity, whose isotopic abundance would differ by one to two per cent at the most from that of the pure ether, would not significantly affect the isotopic ratio of the carbon dioxide formed by the degradation. This fact serves to illustrate the advantage of doing isotope effect studies with natural abundance materials. Such an impurity, using labelled compounds, could give rise to an entirely spurious effect.

Tests of Degradation Methods Tests for Rearrangements

There is the possibility that rearrangement could occur in the potassium permanganate oxidation of either the

product or reactant to the mixture of benzoic and benzoylformic acids with the result that the carbon atom ultimately found in the carboxyl group of the benzoic acid would not be the carbon atom originally alpha to the benzene ring in the ether or the bromide. Such a rearrangement would completely eliminate any isotopic difference originally present at this centre. No rearrangement would be expected in the hydrogen peroxide oxidation of benzoylformic acid to benzoic acid (83,84).*

To test the possibility of rearrangement in the alkaline permanganate oxidation, an acid degradation scheme was developed. This scheme consisted of two stages: first, an oxidation of the ether to acetophenone with acidic chromic anhydride, and, second, a haloform reaction on acetophenone (85) to yield benzoic acid. This method was applied to a sample of 1-ethoxy-1-phenylethane-1- C^{13} . The benzoic acid so obtained was decarboxylated in the usual fashion to yield a carbon dioxide sample for analysis. This sample was compared mass spectrometrically with another carbon dioxide sample, prepared from the labelled ether using the standard

^{*}In the early stages of this degradation study, the mixture of benzoylformic and benzoic acid was converted to pure benzoic acid using sulphuric acid. The question arose as to which of the two possible carbon atoms of benzoylformic acid, the carbonyl or the carboxyl carbon, was lost from the molecule using this reagent. Since previous mechanistic studies failed to establish this point, a carbon-14 tracer study of the reaction was therefore undertaken and is presented in detail as an appendix to this thesis.

alkaline permanganate oxidation. The results of this intercomparison are given in Table IX.

TABLE IX

INTERCOMPAR	ISON OF CO, SAMPLES FROM LA	BELLED
	ETHER DEGRADATIONS	
Degradation	C^{12}/C^{13} Ratios Found	Average
Alkaline	20.22 ; 20.22	20.22 ± 0.2
Acidic	20.13 ; 20.22	20,18 + 0,2

It is highly unlikely that the step-wise degradation through acetophenone would involve rearrangement of the carbon chain. Still more unlikely would be a result in which exactly the same amount of rearrangement occurred in the two degradation procedures since acid and alkaline oxidations would be expected to proceed by entirely different mechanisms. The possibility that both mechanisms proceed with complete rearrangement is eliminated since the amount of C¹³ found in the carbon dioxide was about what would be expected on the basis of the C¹³ content of the barium carbonate used in the synthesis of the labelled ether. It can, therefore, be concluded that the procedure for the degradation of the ether products to benzoic acid involved no rearrangement. Since the oxidation of the bromide proceeds through the carbinol whose mechanism of oxidation can be expected to correspond to that of the ether, it can be assumed that the bromide also is converted to carbon dioxide

without rearrangement.

Acidic Degradation Method:- A few preliminary trials with nitric acid, sodium dichromate in sulphuric acid, and acid potassium permanganate with and without prior cleavage of the ether with hydrobromic acid were not too promising. Attention was then turned to a chromic anhydride oxidation followed by a haloform reaction on the resulting acetophenone. Again, a few trials under different conditions were required to accomplish the conversion to acetophenone in fair yield. The haloform reaction was performed following the method of VanArendonk and Cupery (85) giving an 85 per cent yield of benzoic acid from acetophenone.

To a solution of chromic anhydride (2.5 g.; 0.025 mole), water (3 ml.), acetic acid (28 ml.), and sulphuric acid (2 ml.) at -10° C., was added 1-ethoxy-1-phenylethane- $1-C^{13}$ (0.664 g.; 0.00462 mole) in small portions. The temperature rose immediately, but was maintained below 30° C. for thirty minutes. After the reaction mixture was vigor-ously stirred at room temperature for one hour, it was poured into ice water and extracted thoroughly with ether. The combined extracts were washed twice with dilute alkali and once with water. This served to remove any trace of acidic products that might have been formed by further oxidation of acetophenone. The ether was then removed by distillation.

The crude product was dissolved in methanol (25 ml.) and a 20 per cent solution of sodium hydroxide (25 ml.) added. Chlorine was bubbled into the reaction mixture, which was vigorously stirred. No attempt was made to cool the reaction mixture and the cloudy suspension cleared as the temperature rose to 80°C. An additional 25 ml. of 20 per cent sodium hydroxide solution was added in small portions. When an excess of chlorine was detected by adding a drop of the reaction mixture to potassium iodide solution, the introduction of chlorine gas was stopped and the stirring continued for another fifteen minutes. The excess halogen was destroyed by the addition of a few drops of acetone and the solution cooled to room temperature. The reaction mixture was then acidified and ether extracted. The extracts were concentrated and the residue recrystallized to yield benzoic acid (0.251 g., 46.5% yield), m.p. 121.5-121.8°C. (corr.).

Carbon dioxide samples were prepared from this acid in the usual way.

Tests for Isotopic Fractionations in the Degradation Steps

As mentioned previously, quantitative yields for interconversions of organic molecules are rare. Although the yields in each of the degradation stages were high, the possibility remained that isotopic frationation during the conversion of ether or bromide to carbon dioxide might affect, to a measurable extent, the isotopic abundance of this gas. This, depending upon its direction, might either augment or diminish the experimentally observed isotope effect.

To test for this possibility, the following interconversions were carried out: (1) methyl phenyl carbinol to 1-bromo-1-phenylethane, in duplicate, using dry hydrogen bromide, (2) samples of the bromides prepared in (1) to 1methoxy-1-phenylethane, using absolute methanol, and (3) a sample of the methyl phenyl carbinol used in (1) to 1methoxy-1-phenylethane using methyl sulphate. Since preparation (3) involved no change in the bonding of the carbon atom alpha to the benzene ring, this atom in the ether would be expected to have the same isotopic abundance as in the carbinol even though the reaction was considerably less than quantitative. Furthermore, since (1) takes place in high yield, the carbon atom alpha to the ring of the halide should have the same C^{12}/C^{13} ratio as that of the carbinol. At least one sample of each of these materials, including the carbinol, was degraded to benzoic acid in the usual way so that eight different benzoic acid samples were obtained.

The benzoic acid samples were decarboxylated by the Schmidt reaction and the evolved carbon dioxide precipitated as barium carbonate. Duplicate or triplicate decarboxylations

were carried out for some of the acid samples. All of the barium carbonate samples, a total of fourteen, were decomposed and the carbon dioxide analyzed mass spectrometrically.

In Figure 2, the interconversions and the degradation routes employed, together with the final C^{12}/C^{13} ratios found for the carbon dioxide samples, are shown diagramatically. The yields for the interconversions are given in brackets. It is to be noted that the C^{12}/C^{13} ratios given for the carbon dioxide samples correspond to separate Schmidt reactions. An examination of the data in Figure 2 shows that all the C^{12}/C^{13} ratios are the same within the limits of analysis, viz. 90.93 ± 0.1. These results definitely establish that either there was no fractionation in the degradation reactions or that any small fractionation that did occur was identical for degradation of the ether and the In either event, the degradations were entirely bromide. suitable for the isotope effect studies in which a comparison was being made of the isotopic ratios in the initial bromide and the product of partial reaction.

Summary

The above experiments establish (1) that there was no appreciable exchange between starting compound and ether product, or decomposition of this product, during the separation procedure, (2) that the product from which carbon dioxide samples were prepared was of satisfactory purity,

Figure 2

STUDY OF FRACTIONATION IN DEGRADATIONS



(3) that no rearrangement of the carbon chain accompanied the oxidation reactions, and (4) that either no measurable isotopic fractionation occurred during the conversion of reactant and product to carbon dioxide or it was the same for each compound. It may be concluded, therefore, that an intercomparison of the isotopic ratios for the carbon dioxide prepared from the reactant and from the product of a small extent of reaction provided a true measure of the isotope effect in the reactions studied.

RESULTS

The results for the isotope effect study of the unimolecular solvolysis of 1-bromo-1-phenylethane in absolute methanol are presented in Table X. For each individual experiment, the bromide was dissolved in the solvent, which had been equilibrated to the desired reaction temperature. The solvolysis was allowed to continue for a definite period of time, such that there was about five per cent reaction. Then the reaction was stopped and the carbon atom at the seat of substitution isolated as carbon dioxide from samples of the product and the starting material.* From the results of the mass spectrometric analysis of the two carbon dioxide samples, a (C^{12}/C^{13}) $product)/(C^{12}/C^{13} reactant)$ ratio was calculated and averaged for a series of experiments. The rate constant ratio, k_{12}/k_{13} , was then calculated, using equation 27, from this average and the average extent of reaction. The precision of the k_{12}/k_{13} ratio has been arbitrarily expressed as twice the standard deviation of the mean.

^{*}Since unchanged bromide recovered from one experiment was frequently purified and added to the stock quantity of this starting material for use in the next experiment, the $C^{12}/Cl3$ ratio of the starting material was not the same for all experiments.

TABLE X

SOLVOLYSIS OF 1-BROMO-1-PHENYLETHANE IN ABSOLUTE METHANOL

 $(Temperature = 25.00 \pm 0.02^{\circ}C.)$

Compound Degraded	Per Cent Reaction	Conc. ^a RBr (M.)	C^{12}/C^{13} Ratios	$\frac{C^{12}/C^{13}}{C^{12}/C^{13}}$ React.
ROCH	5.1	0.409	91.72	
RBr			91.16	1.0061
ROCH	5.1	0.477	91.75	
RBr			91.13	1.0068
ROCH	4.7	0.563	91.49	
RBr			90.95	1.0059
ROCH	4.8	0.423	91.60	
RBr			91.00	1.0066
ROCH	4.8	0.497	91.56	
RBr			90.94	1.0068
ROCH	4.7	0.555	91.54	
RBr			90.87	1.0074
				1.0066
	4.9			+ 0.0005 b
	Compound Degraded ROCH ₃ RBr ROCH ₃ RBr ROCH ₃ RBr ROCH ₃ RBr ROCH ₃ RBr ROCH ₃ RBr ROCH ₃ RBr	Compound DegradedPer Cent ReactionROCH3 RBr5.1ROCH3 RBr5.1ROCH3 RBr4.7ROCH3 RBr4.8ROCH3 RBr4.8ROCH3 RBr4.8ROCH3 RBr4.7A.OCH3 RBr4.7A.OCH3 RBr4.7	Compound DegradedPer Cent ReactionConc. RBr (M.)ROCH3 RBr5.10.409ROCH3 RBr5.10.477ROCH3 RBr4.70.563ROCH3 RBr4.80.423ROCH3 RBr4.80.497ROCH3 RBr4.70.555ROCH3 RBr4.70.555	Compound DegradedPer Cent ReactionConc.a RBr (M.) C^{12}/C^{13} RatiosROCH3 RBr5.10.40991.72 91.16ROCH3 RBr5.10.47791.75 91.13ROCH3 RBr4.70.56391.49 90.95ROCH3 RBr4.80.42391.60 91.00ROCH3 RBr4.80.49791.56 90.94ROCH3 RBr4.70.55591.54 90.87

 $k_{12}/k_{13} = 1.0068 \pm 0.001$

a = initial concentration

b = standard deviation of the mean

Although previous kinetic studies (10,11,12) have shown that there is only a small tendency for reversal of the solvolysis reaction, nevertheless, it was considered desirable to establish that this was not a complicating factor in the isotope effect study in methanol. Since methanolysis rates are quite insensitive to the addition of small amounts of methoxide ion (11), two experiments were carried out in which sufficient base was present to neutralize the hydrogen bromide produced in the partial reaction. The results of these experiments are given in Table XI. It is seen that the isotope effect values were not significantly different from those obtained using the usual solvolytic reaction conditions.

The results for the isotope effect experiments on the solvolysis of 1-bromo-1-phenylethane in absolute ethanol are presented in Table XII. In this system, it was not possible to carry out a test for reversibility, since the addition of base, even in very small amounts, is known to bring about a significant contribution of the second-order process to the overall rate (10). On the basis of the observed lack of sensitivity of the isotope effect in methanolysis to hydrogen bromide build-up during reaction, it was assumed that reversibility was not a complication in the ethanolysis system as well.

TABLE XI

SOLVOLYSIS OF 1-BROMO-1-PHENYLETHANE IN ABSOLUTE METHANOL CONTAINING SMALL AMOUNTS OF METHOXIDE ION Methoxide ion conc. = 0.023 M. Temperature = $25.00 \pm 0.02^{\circ}$ C. C¹²/C¹³ Ratios c^{12}/c^{13} Compound Per Cent Conc.^a Degraded Reaction RBr (M.) Expt. c12/c13 No. ROCH3 1 5.0 0.452 91.54 91.07 RBr 1.0052 ROCH3 2 0.475 5.0 91.52 RBr 90.99 1.0058 5.0 Avg. 1.0055

 $k_{12}/k_{13} = 1.0056 \pm 0.001$

a = initial concentration

TABLE XII

SOLVOLYSIS OF 1-BROMO-1-PHENYLETHANE IN ABSOLUTE ETHANOL

 $(Temperature = 44.98 \pm 0.02^{\circ}C.)$

Expt. No.	Compound Degraded	Per Cent Reaction	Conc. ^a RBr (M.)	C ¹² /C ¹³ Ratios	$\frac{c^{12}/c^{13}}{c^{12}/c^{13}}$ React.
1	ROCH	4.9	0.501	91.45	
	RBr			90.86	1.0065
2	ROC ₂ H ₅	4.9	0.513	91.35	
	RBr			90.88	1.0052
3	ROC ₂ H ₅	5.8	0.509	91.59	
	RBr			90.97	1.0065
4	ROC ₂ H ₅	5.6	0.512	91.59	
	RBr			91.02	1.0063
Avg.		5.3			1.0061 ± 0.0005 ^b

 $k_{12}/k_{13} = 1.0063 \pm 0.001$

a = initial concentration

2

b = standard deviation of the mean

The data for the bimolecular reaction of 1-bromo-1phenylethane with ethoxide ion are given in Table XIII. A procedure similar to that used for the unimolecular solvolyses was employed. A solution of anhydrous alcohol and sodium alkoxide, at the proper concentration, was equilibrated to the temperature of reaction. The bromo compound was then dissolved in this solution, and the reaction allowed to proceed for a definite period of time. The isolation, degradation and analysis of the carbon dioxide samples for the product and starting material were carried out as described previously.

The isotope effect of the bimolecular reaction of 1bromo-1-phenylethane with ethoxide ion in ethanol was found to be 0.3 ± 0.1 per cent which is significantly different from that of the solvolysis of this halide in absolute ethanol or methanol, viz., 0.6 ± 0.1 per cent. (It is of interest to note that experiments 6 and 7 in Table XIII were carried out some nine months after the first five runs. This fact gives added confidence in the reproducibility of the measurements.)

The isotope effect for the reaction of benzyl bromide with methoxide ion was found to be 5.3 ± 0.1 per cent. The data for this study appear in Table XIV. Although this isotope effect is more than an order of magnitude larger than that found for the bimolecular reaction in the 1-phenyl-

TABLE XIII

REACTION OF 1-BROMO-1-PHENYLETHANE WITH ETHOXIDE ION IN ETHANOL

Ethoxide ion conc. ca. 2 M. Temperature = $25.00 \pm 0.02^{\circ}C$.

Expt. No.	Compound Degraded	Per Cent Reaction	Conc. ^a RBr (M.)	C^{12}/C^{13} Ratios	$\frac{C^{12}/C^{13} \text{ Prod.}}{C^{12}/C^{13} \text{ React.}}$
1	ROCOH	4.8	0.498	91.42	
	RBr			91.16	1.0029
2	ROC,H5	4.9	0.515	91.01	
	RBr			90.74	1.0030
3	ROC ₂ H ₅	7.4	0.501	91.74	
	RBr			91.52	1.0024
4	ROC ₂ H ₅	7.5	0.508	93.47	
	RBr			93.15	1.0034
5	ROC_H	7.9	0.508	91.28	
	RBr			91.07	1.0023
6	ROC2H5	8.9	0.504	91.49	
	RBr			91.16	1.0036
7	ROC2H5	7.6	0.513	91.47	
	RBr			91.16	1.0034
Avg.		7.0			1.0030 b
					± 0.0005

 $k_{12}/k_{13} = 1.0031 \pm 0.001$

a = initial concentrationb = standard deviation of the mean

TABLE XIV

REACTION OF BENZYL BROMIDE WITH METHOXIDE ION IN ABSOLUTE METHANOL

Methoxide ion conc. ca. 1 M. Temperature = 0.00 ± 0.02°C.

Expt. No.	Comp ound Degraded	Per Cent Reaction	Conc. ^a RBr (M.)	C ¹² /C ¹³ Ratios	$\frac{C^{12}/C^{13} \text{ Prod.}}{C^{12}/C^{13} \text{ React.}}$
1	ROCH	7.1	0.473	95.65	
	RBr			91.00	1.0511
2	ROCH	6.2	0.485	95.65	
	RBr			90.98	1.0513
3	ROCH	8.6	0.491	95.67	
	RBr			91.07	1.0505
4	ROCH	7.0	0.489	95.82	
	RBr			91.11	1.0517
5	ROCH	8.3	0.488	95.63	
	RBr			90.98	1.0511
Avg.		7.4			1.0511
					± 0.0004 ^b

 $k_{12}/k_{13} = 1.0531 \pm 0.0008$

a = initial concentration

b = standard deviation of the mean

ethyl system, it is interesting to note that the precision of this determination was the best of all the isotope effect studies undertaken.

DISCUSSION

Unimolecular Solvolysis of 1-Bromo-1-phenylethane

Present theory for the S_N^1 mechanism of displacement proposes that the rate-controlling step is a bond fission to form a free carbonium ion, although recent refinements of this theory, as described previously, suggest that the bond rupture proceeds through a series of increasingly solvated ion-pairs (55). Recent work on the 1-phenylethyl system has shown that the main pathway for substitution by the unimolecular mechanism involves reaction of the solvent with the intimate ion-pair rather than the free carbonium ion (86). The formation of this ion-pair, however, involves covalent bond break at the seat of substitution, and, hence, should be analogous to any bond rupture process insofar as isotope effects are concerned.

Although the ionic species formed in unimolecular displacements are heavily solvated, it may be assumed that the long-range electrostatic forces of solvation do not lead to isotopic fractionations of the same order of magnitude as covalent binding forces. Support for this assumption is provided by the observation (87) that no measurable isotopic fractionation results when a solid substance is equilibrated

with a saturated solution of that substance. Since no fractionation, within the limits of measurement, occurs in a crystallization process, no isotope effect would be expected in a process involving interaction of solvent molecules with solute.

Ion-pair formation would, of course, be a readily reversible process. It seems fairly well established, however, that bond formation leads to a very small isotope effect (6,7). Therefore, it may be safely concluded that the isotope effect in the equilibrium process of ion-pair formation is essentially an isotope effect for the forward reaction of bond rupture.

The rate constant ratio, k_{12}/k_{13} , of 1.006 \pm 0.001 observed for the solvolysis of 1-bromo-1-phenylethane in absolute methanol and ethanol is very much lower than that predicted by the Bigeleisen expression, equation 6, using the model of complete bond rupture in the transition state. As was discussed in the Historical Introduction, for the calculation of the isotope effect in a simple bond rupture process, a model is usually chosen for the transition state such that the bond undergoing fission is considered completely broken, while the vibrational frequencies of all other bonds remain unchanged. The free energy factor of equation 6 thus reduces to $1 + \sum_{i=1}^{3n-6} G(u_i) a u_i$. The vibrational stretching frequency of the C-Br bond has been given by Mortimer, Blodgett and Daniels (88) for various organic bromides and a value of 549 cm.⁻¹ for the vibrational stretching frequency of a secondary C-Br bond may be used. Thus, a value of u_i equal to 2.5868 at 25°C. may be calculated for the initial state and a $G(u_i)$ value of 0.1948 may be found in the Bigeleisen table (33). For a comparison of a C^{12} -Br to a C^{13} -Br bond, the free energy term for the initial state becomes 0.0177 and the free energy factor 1.0177 at 25°C. In a similar way the free energy factor of 1.0145 may be found for the same system at $45^{\circ}C$.

The mass factor for equation 6 may be determined using the Slater theorem which affords a value of 1.035 for the effective mass term for a C^{12} or 13 -Br bond. The product of the mass factor and the free energy factor gives the k_{12}/k_{13} ratio for the rate-determining rupture of a C^{12} or 13 -Br bond. This ratio is found to be 1.053 at 25°C. and 1.051 at 45°C. An alternative prediction may be made if the mass term is considered as the reduced mass of the two molecular fragments formed by the rate-determining heterolysis. (See page 15.) This calculation gives a mass factor of 1.002, which, when combined with the free energy factor, gives k_{12}/k_{13} ratios of 1.020 and 1.018 at 25°C. and 45°C., respectively.

It is profitable to use the experimental value for k_{12}/k_{13} to calculate the free energy contribution to the

isotope effect, since it is apparent that, regardless of the assumptions made for evaluation of the mass term, the free energy factor calculated on the assumption of a zero contribution from the transition state is much too large. This calculation may be done by evaluating the following expression:

$$\begin{bmatrix} G(u_{i}) \diamond u_{i} - G(u_{i}) \diamond u_{i}^{*} \end{bmatrix} = \begin{bmatrix} \frac{k_{12}/k_{13} \text{ (observed)}}{(m_{2}^{*}/m_{1}^{*})^{\frac{1}{2}}} \end{bmatrix} - 1 \quad (29)$$

where m_2^*/m_1^* is the mass term evaluated either from the Slater or the molecular fragment hypothesis. Assuming the Slater hypothesis, the free energy contribution would have to be - 0.028 to afford the observed k_{12}/k_{13} ratio; whereas, the fragment mass term requires a free energy contribution of + 0.004. These values are to be compared to the free energy term of 0.01766 calculated previously, using a diatomic model with complete bond rupture in the transition state, i.e., $G(u_i^*) \simeq u_i^* = 0$.

It is evident that with either mass formulation there must be a considerable contribution by the free energy term of the transition state, $G(u_i^{\dagger}) \triangle u_i^{\dagger}$, to the overall free energy factor.* That this should be the case in the ionization of 1-bromo-1-phenylethane is perhaps not surprising,

It is interesting to note that, using the Slater model for the effective mass term, the observed k_{12}/k_{13} ratio requires a $G(u_1^) \circ u_1^*$ term larger than the $G(u_1) \circ u_1$ term, while the fragment theory does not.

since the transition state leading to the carbonium ion has a benzene ring adjacent to the developing positive centre. The stabilizing effect of a benzene ring on such centres is well-known (89,90). This stabilization, due to conjugative mesomerism or internal conjugation, causes a dispersal of charge over the entire ring so that the C-C bond of the C^+ - phenyl bonding is strengthened. This could be represented as:



Thus, the transition state will possess a bond that is strengthened relative to the same bond in the initial state and, since an increased bond strength leads to an increased vibrational frequency, the $G(u_i^{\dagger}) \rightarrow u_i^{\dagger}$ term can no longer be considered to be negligible. A further bond strengthening is possible in the transition state owing to the presence of the methyl group. A stabilization, due to hyperconjugation, could tend to strengthen the C-CH₃ bond. If this is so, a further increase in the $G(u_i^{\dagger}) \rightarrow u_i^{\dagger}$ term is to be expected.

It is therefore proposed that a stabilization of the transition state by internal conjugation and hyperconjugation allows a significant contribution by the $G(u_i^{\dagger}) \ge u_i^{\dagger}$ term to the overall free energy factor and that this is responsible for the very small isotope effect observed for unimolecular solvolyses in the 1-phenylethyl system.

Some support for this interpretation is found in a recent study by Magee and Daniels (91) of the carbon-13 isotope effects in the unimolecular decomposition of some substituted ureas. The observed rate constant ratios, k_{12}/k_{13} , are given in the second column of Table XV. From this table it is evident that the isotope effect decreases as phenyl substitution increases in the reactant.

TABLE XV

UNIMOLECULAR DECOMPOSITION OF SOME SUBSTITUTED UREAS

Reactant	^k 12 ^{/k} 13	$\left[\left(\frac{k_{12}}{k_{13}} \right) / \left(\frac{m_2}{m_1} \right)^{\frac{1}{2}} \right] - 1$		
		Slater model	Fragment model	
sym-Dimethylurea	1.026 ₉ ± 0.001	+ 0.006	÷ 0.0242	
Phenylurea	1.016 ± 0.004	- 0.005	+ 0.0155	
sym-Diphenylurea	1.007 ₆ ± 0.001	- 0.013	+ 0.0058	
3,3' -Dimethyl- carbanilide	1.007 ₁ ± 0.003	- 0.014	+ 0.0054	

In the last two columns of Table XV, the free energy contribution to the observed k_{12}/k_{13} ratio for each compound is listed for the two alternative mass factors. These values, evaluated by means of expression 28, are to be
compared with the free energy term of 0.018 found for a C-N bond rupture, assuming the usual model for the transition state. It is to be noted that, with either mass formulation, the free energy contribution decreases with increased phenyl substitution. Therefore, the $G(u_i^{\ddagger}) \simeq u_i^{\ddagger}$ term is of increasing significance for the reaction of the more highly substituted ureas.

These authors have proposed the following mechanism for this process,

$$\begin{array}{ccc} R-NH-C-NH-R^{*} & \longrightarrow & R-N=C-NH-R^{*} & \longrightarrow & Products & (XVI) \\ 0 & 0H & 0- \\ (I) & (II) & (III) & (III) \end{array}$$

in which the decomposition of (III) may be considered as the rate-determining step. The effect of phenyl substitution on the magnitude of the isotope effect was attributed to a resonance stabilization of the transition state. This can be shown as follows:



such a stabilization would tend to increase the $G(u_i) \ge u_i^{\ddagger}$ in the free energy factor and, hence, would lower the overall isotope effect in a way similar to that proposed for the 1-phenylethyl system.

Some unpublished work by Bender (92) has shown a carbon-14 isotope effect of about five per cent for the unimolecular hydrolysis of 2-chloro-2-methylpropane. This would correspond to a k_{12}/k_{13} ratio of 1.025. The Slater theorem for the mass factor of a C-Cl bond rupture is 1.029, while the fragment theory provides a value of 1.0066 for this reactant. Again, using equation 28, the free energy contribution can be calculated and is found to be - 0.0039 for the Slater mass factor and + 0.0183 for the molecular fragment mass factor. These values are to be compared with a value of + 0.0224 found by assuming the usual model for the transition state of a bond rupture process. It therefore must be concluded that, in this system also the transition state term, $G(u_i^{\dagger}) \land u_i^{\dagger}$, must make a significant contribution to the overall free energy factor. This is to be expected since the text. butyl carbonium ion has three methyl groups adjacent to the positive centre and each of these groups would tend to stabilize the positive centre by hyperconjugation. Thus, the overall k12/k13 ratio would be expected to be lower than the value calculated using the usual model for the transition state of a bond rupture process.

Bimolecular Reaction of 1-Bromo-1-phenylethane with Ethoxide Ion and of Benzyl Bromide with Methoxide Ion

The k_{12}/k_{13} ratio for the bimolecular reaction of 1-bromo-1-phenylethane with ethoxide ion was found to be 1.003 ± 0.001 at 25°C., a value which is slightly lower than the k_{12}/k_{13} ratio of 1.006 ± 0.001 observed for the unimolecular solvolysis of this halide at the same temperature. The k_{12}/k_{13} ratio for the reaction of benzyl bromide with methoxide ion, on the other hand, was 1.053 ± 0.001 at 0°C. It is clear that there is a large difference in the isotope effect for the two bimolecular processes studied.

Bigeleisen (42,43) has developed an effective mass factor for three-centre displacements which considers the three atoms undergoing covalency changes in the transition This factor, shown in equation 13, expresses the state. masses of the three atoms as a function of p, the relative extent of bond formation to bond rupture in the transition state. For the bimolecular processes involved in this study, there is C-O bond formation and C-Br bond fission and, for this system, the magnitude of the mass factor at various p values is given in Table III, page 26. From this table, it is evident that the mass factor changes slightly from 1.035, at p = 0, to 1.033, at p = 1, i.e., from a transition state with complete bond rupture to one in which bond formation and bond fission have proceeded to the same extent. This

factor, then, might be responsible, in part, for the slightly higher isotope effect in unimolecular solvolysis compared to the bimolecular reaction in the 1-phenylethyl system. It cannot, however, account for the very large difference in effects for the two bimolecular reactions.

Turning to the free energy factor, it will be recalled that, for the unimolecular reactions discussed previously, it was necessary to assume that internal conjugation was very important in determining the magnitude of the contribution of the $G(u_i^{\pm}) = u_i^{\pm}$ term to the overall free energy factor. In a similar way, a partial explanation for the bimolecular isotope effects may be found by an examination of the transition states in the two systems, i.e., the l-phenylethyl and the benzyl.

In the 1-phenylethyl system, kinetic studies have shown that this substituent tends strongly to promote unimolecular reactions (89). Therefore, it may be concluded that the transition state of any second-order process involving this group would have considerable carbonium ion character. In other words, the carbon atom at the seat of displacement would be electron deficient and, hence, conjugated with the adjacent benzene ring. Furthermore, owing to steric factors, close approach of the attacking group would be hindered. Therefore, the transition state for the bimolecular reaction would be one in which bond fission has

proceeded much further than bond formation, and, also, one which would be stabilized by internal conjugation. In other words, the $G(u_1^{\ddagger})au_1^{\ddagger}$ term for this bimolecular reaction may not be too greatly different from the same term in the unimolecular case.

In the benzyl system, there is strong kinetic evidence (56,93,94) that a balance exists in the transition state between bond rupture and bond formation, i.e., the relative extents of each are the same. In this situation, the carbon atom at the seat of displacement bears about the same charge in the transition state as in the initial state. Therefore, there will be less internal conjugation.

It is in this respect, i.e., internal conjugation in the transition state, that the bimolecular reactions of 1-bromo-1-phenylethane and of benzyl bromide differ, and it is suggested that it is this difference which is responsible, at least in part, for the markedly different isotope effects associated with these systems. In the unimolecular reactions of 1-bromo-1-phenylethane, the low isotope effect was attributed to internal conjugation in the transition state resulting in a large $G(u_i^{\dagger}) \Delta u_i^{\dagger}$ term and, hence, a low isotope effect. If the transition state for the bimolecular reaction of this compound is not too greatly different from that of the unimolecular reaction, a corresponding low effect might be expected. In the bimolecular reaction of

benzyl bromide, on the other hand, where less conjugation is possible in the transition state, the free energy term for this state might be expected to be very much smaller and the isotope effect correspondingly larger.

This explanation for the observed isotope effects, however, is not without difficulty. Firstly, one would expect the $G(u_1^{\ddagger}) a u_1^{\ddagger}$ term for the 1-phenylethyl system to be smaller in the bimolecular case than in the unimolecular case, since internal conjugation would certainly be less in the bimolecular transition state. The resulting increase in the overall free energy term would not be entirely compensated for by a slightly lower mass term corresponding to some value of p between 0 and 1. Therefore, one would not predict a smaller isotope effect for the bimolecular process relative to that for an unimolecular, as appears to be the case, although one might not expect a very large difference between the two.

Furthermore, one certainly would not have expected such a very great difference in the isotope effects for the two bimolecular systems. That this difference is real, the writer believes there is no question, and, therefore, it must be concluded that isotope effects provide a very sensitive measure of the nature of the transition state. Clearly, much more experimental work is required to adequately interpret the full significance of these results.

An obvious test for this interpretation of the effect of internal conjugation on isotope effects would be a study of a truly unimolecular reaction of a benzyl compound. This is not easy to accomplish since solvolyses of benzyl compounds in alcohol or water solvents, in all probability, proceed by a bimolecular mechanism. Preliminary experiments on the formolysis of benzyl bromide proved unsuccessful because of the tendency for a reversal of the displacement reaction. Examination of the literature indicated that solvolysis of benzyl tosylates in a highly ionizing medium might prove successful. Since such an investigation would involve entirely different experimental procedures it was beyond the scope of this thesis. It is suggested, however, that this should be the next step in attempting to relate isotope effects in nucleophilic displacement processes to the nature of the transition state.

APPENDIX

<u>A Carbon-14 Tracer Study of the Decarbonylation</u> <u>Reaction of Benzoylformic Acid with</u> <u>Sulphuric Acid</u>

The reaction of benzoylformic acid with concentrated sulphuric acid to yield benzoic acid has been studied kinetically by Elliot and Hammick (95). From the results of this study, it was concluded that either of the two following mechanisms were consistent with the observed kinetic data:

Mechanism I:



Mechanism II:

These authors concluded that mechanism I was the most probable because of the work of Calvin and Lemmon (96) in which the thermal decomposition of ethyl pyruvate was examined. This decomposition was shown, by means of a tracer study, to proceed without rearrangement of the carbon skeleton.

It is to be noted that the proposed mechanisms differ in that I involves no phenyl migration, whereas II proceeds with migration, and, therefore, a tracer study would allow a distinction between the two possibilities. A study of the decarbonylation of carbon-14 labelled benzoylformic acid, $^{14}_{6}C_{6}H_{5}COCCOH$, was carried out and a result consistent with mechanism I was obtained.

Shortly after the completion of this investigation, Baumholzer and Schmid (84) reported a similar tracer study, using benzoylformic acid-carboxyl- C^{14} . These authors have obtained the same result and have discussed its mechanistic implications in detail.

The labelled material was obtained by the following reaction sequence:

Benzoic acid-carboxyl-C¹⁴, obtained from the Nuclear Instrument and Chemical Corp., Chicago, Ill., was converted to benzoyl chloride with thionyl chloride by a standard method (97); the acid chloride, without purification, was treated with cuprous cyanide to yield benzoyl cyanide (98), which was purified by distillation. Owing to inefficient recovery of the cyanide by small scale distillation, inactive carrier material was added to ensure a maximum recovery of the active compound. The twice-distilled benzoyl cyanide was then hydrolyzed to benzoylformic acid-carbonyl-C¹⁴ (93).

The labelled benzoylformic acid was treated with concentrated sulphuric acid in the usual fashion (95) to yield benzoic acid. Since this material was found to have the same activity, on a molar basis, as the benzoylformic acid, no phenyl group migration could have occurred during the decarbonylation, provided that there was no rearrangement in the hydrolysis step of the synthesis. Phenyl group migration in the synthesis followed by a corresponding migration in the decarbonylation would, of course, lead to the same experimental result. To show that no rearrangement accompanied the hydrolysis reaction, a sample of benzoylformic acid was decarboxylated using hydrogen peroxide (69), a reagent which could be expected to produce benzoic acid without rearrangement (83,84). The benzoic acid, obtained in this way, had the same activity on a molar basis as the starting material. Hence, it can be concluded that the sulphuric acid decarbonylation proceeded without phenyl migration.

The results of this tracer study are given in Table XVI.

TABLE XVI

RESULTS FROM BENZOYLFORMIC ACID DECOMPOSITION STUDY



Experimental

Carbonyl-labelled benzoyl cyanide:- Benzoic acidcarboxy1-C¹⁴ (1.98 g., 0.0162 mole) was heated under reflux with thionyl chloride (17 g.,) for one hour. The reaction mixture was cooled and most of the excess thionyl chloride removed under reduced pressure. Dry benzene (4 ml.) was added and then removed by distillation under reduced pressure. The benzene distillation procedure was repeated four times. Cuprous cyanide (2.0 g.,) was added and the mixture heated to 145°C. The temperature was then allowed to rise to 200°C. over a period of two hours during which time the reaction mixture was frequently shaken. Crude benzoyl cyanide was isolated from the reaction mixture by distillation under reduced pressure. When most of the cyanide had been collected, the distillation was interrupted, inactive benzoyl cyanide (0.512 g.) added and the distillation completed. The product was distilled a second time, again using inactive carrier (0.559 g.) to ensure good recovery of active material.

The distillate, recrystallized from light petroleum ether, gave benzoyl cyanide: m.p. 33.5-34°C.; activity (from benzene solution) 2.20 mc./mole.

Carbonyl-labelled benzovlformic acid:- Concentrated hydrochloric acid (12 ml.) was added to benzoyl cyanidecarbonyl-C¹⁴ (1.32 g., 0.0101 mole) and the solution allowed to stand at room temperature for five days. The solution was then diluted with water, extracted with ether, and the combined ether extracts were dried over magnesium sulphate. The solvent was removed by distillation and the residue was recrystallized from low-boiling petroleum ether to give 0.929 g. (61.2% yield) of benzoylformic acid-carbonyl-C¹⁴: m.p. 63.5-64°C.; activity (from water solution) 2.19 mc./ mole.

Benzoic acid (via Hydrogen Peroxide):- To a mixture of labelled benzoylformic acid (0.106 g., 0.00071 mole) and water (10 ml.) was added 30 per cent hydrogen peroxide solution (0.5 ml.). The reaction mixture was allowed to stand overnight and then was diluted with water and extracted with ether. Removal of the ether gave benzoic acid (0.085 g., 99.9% yield). This product was recrystallized twice from water before the radioactivity assays were performed. Radioactivity assay (from water solution): 2.20 mc./mole. Benzoic acid (via Sulphuric acid):- Concentrated sulphuric acid (10 ml.) was added to labelled benzoylformic acid (0.154 g., 0.00102 mole) and the resulting solution allowed to stand at room temperature for three hours during which time the reaction mixture was vigorously stirred. Then, the solution was warmed to 50°C., allowed to cool, poured into ice-water, and ether extracted. Benzoic acid (0.122 g., 99.4% yield) was obtained on removal of the solvent and was recrystallized twice from water before radioactivity assay. Radioactivity assay (from water solution): 2.19 mc./mole.

<u>Radioactivity Assays</u>:- The radioactivity of the various products obtained in this study was determined by ionization chamber measurements on the carbon dioxide produced by Van Slyke oxidation.

A solution of the material to be assayed was prepared using an appropriate solvent. Aliquots of this solution were taken, and the solvent carefully evaporated. (For all measurements of acid samples, a crystal of sodium hydroxide was added before removal of the solvent.) The solid residue was then oxidized completely by wet oxidation (99), and the evolved carbon dioxide was swept into an ionization chamber with inactive carbon dioxide. The activity of each sample was measured by the rate of drift method described by Raaen and Ropp (100). A calibration curve was prepared from the rates of drift for samples of benzoic acid of known activity. This plot allowed the direct conversion of a rate of drift measurement to an activity figure.

SUMMARY

1. The carbon-13 isotope effects have been measured for the unimolecular solvolysis of 1-bromo-1-phenylethane. In absolute methanol, the effect was found to be 0.6 \pm 0.1 per cent at 25°C., and, in absolute ethanol, the effect was 0.6 \pm 0.1 per cent at 45°C.

2. A carbon-13 isotope effect of 0.3 \pm 0.1 per cent was found for the reaction of 1-bromo-1-phenylethane with ethoxide ion at 25°C.

3. A carbon-13 isotope effect of 5.3 \pm 0.1 per cent was obtained for the reaction of benzyl bromide with methoxide ion at 0^oC.

4. Extensive tests have been carried out to definitely establish (a) that the reactions were unidirectional under the conditions employed, and (b) that the separation, purification and degradation methods were uncomplicated by exchange, rearrangement, or spurious isotopic fractionation. 5. This work constitutes the first study of carbon-13 isotope effects in unimolecular and bimolecular nucleophilic displacement reactions and is of special interest in that it allows a comparison of effects for the two displacement mechanisms using the same substrate, viz.,

1-bromo-1-phenylethane.

6. The results have been discussed in terms of the Bigeleisen theory of isotope effects and an interpretation, based on the effect of internal conjugation on the free energy difference for isotopic transition states, has been proposed.

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