CARBON-14 ISOTOPE EFFECTS IN THE REACTION OF BENZYL BROMIDE AND OF p-NITROBENZYL BROMIDE WITH SILVER NITRITE

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INTRODUCTION

The object of this research was to gain a better understanding of the mechanism by which the two isomeric products are formed in the reaction of alkyl halides with silver nitrite in a hetrogeneous system.

Specifically the purpose was to test the hypothesis of Kornblum (23) that the two products are derived through a common transition state rather than through two separate and competing reaction paths.

$$\text{R-X} + \text{AgNO}_2 \longrightarrow (\text{common transition state}) \begin{cases} \xrightarrow{k_1} \text{R-ONO} + \text{AgX} \\ \xrightarrow{k_2} \text{R-NO}_2 + \text{AgX} \end{cases}$$

or

$$\text{R-X} + \text{AgNO}_2 \begin{cases} \longrightarrow (\text{transition state \#1}) \xrightarrow{k_1} \text{R-ONO} + \text{AgX} \\ \longrightarrow (\text{transition state \#2}) \xrightarrow{k_2} \text{R-NO}_2 + \text{AgX} \end{cases}$$

According to existing theory the kinetic isotope effect is due to difference in activation energy or difference in energy required to reach the transition state between normal and isotopically labeled molecules. This effect might be utilized to differentiate between pathways having common and separate transition states.

The procedure used was: (1) to determine whether the products are formed by reactions of equal kinetic order, (2) to synthesize benzyl bromide and p-nitrobenzyl bromide in which the α-carbon atoms are labeled with tracer amounts of carbon-14, and (3) to determine the kinetic isotope effect in the formation of each product from the reaction of these

compounds with silver nitrite in anhydrous ether solution. If the isotope effects in the formation of each product are found to be equal, the two products may have come through a common transition state. If the kinetic isotope effects are not equal, our present concept of kinetic isotope effects would require the assumption of separate transition states in the formation of the two products.

HISTORICAL PART

The Victor Meyer Reaction

In 1872 Victor Meyer and O. Stuber (29) reported that amyl iodide reacted with silver nitrite to yield both the nitrite and the nitro derivative. The reaction, however, has not been widely used as a preparative method.

In recent years the reaction has been investigated extensively by Nathan Kornblum and others because it is typical of reactions in which an anion can undergo bond formation at more than one site. In the Victor Meyer reaction both carbon-oxygen and carbon-nitrogen bonds are formed.

Primary and secondary alkyl chlorides have been found to be unreactive with silver nitrite, but tertiary chlorides react readily. Primary alkyl bromides and iodides also react readily with silver nitrite giving the nitro derivative as the principal product. When the beta carbon of the primary halide has one or more alkyl groups, the reactivity of the alkyl halide is greatly reduced (25). Neopentyl bromide has been shown to be extremely unreactive even when dimethylformamide is used as the solvent in which case a homogeneous reaction mixture is obtained (25). This lack of reactivity indicates that the reaction does not have a simple S_N1 type mechanism in which the rate-determining step would be the formation of a carbonium ion. However, for the reaction of silver nitrite with 1-bromobutane, 2-bromobutane, and tert-butyl bromide, the relative reaction rates are in the ratio of 1:4:1500 (23). In the case

of the para substituted benzyl bromides where the steric effect should be constant, p-methylbenzyl bromide was found to react sixteen times as fast as benzyl bromide and one hundred and eighty times as fast as p-nitrobenzyl bromide (23). These are relative reactivity ratios which would be expected for an S_N1 reaction. The tertiary aliphatic halides yield several products other than the expected nitro and nitrite derivatives (24). The nitrite is the principal derivative, but generally an appreciable amount of dehydrohalogenation takes place to yield the alkene.

Kornblum (22) has investigated the stereochemistry of the reaction using optically active 2-bromooctane and α-phenylethyl chloride. The reaction of the optically active 2-bromooctane with silver nitrite in anhydrous ether was found to produce both the nitrite and nitro derivatives with inversion of structure and little, if any, retention of configuration.

The reaction of optically active α-phenylethyl chloride with silver nitrite was found to produce the nitro derivative with inversion of configuration and the nitrite ester with retention of configuration. However, during the course of the reaction much racemization had taken place, and just how much of this was due to the reaction of the alkyl halide with the silver nitrite was not certain because optically active α-phenylethyl chloride was found to lose its activity on contact with silver chloride under these conditions. The inversion of both products from the 2-bromooctane would suggest that both products were formed by an S_N2 reaction; however, in the reaction of α-phenylethyl chloride the difference in configuration of the products would suggest separate reaction paths.

That the reaction of an alkyl halide with silver nitrite is strictly

heterogeneous when carried out in anhydrous ether is borne out by the fact that the solubility of silver nitrite in ether is too small to be detected either gravimetrically or by evaporation of 200 ml. of ether which had stood over silver nitrite (23).

No noticeable amounts of decomposition products from the nitro compound are detected in the reaction of primary aliphatic bromides and iodides with silver nitrite in ether solution. However, it is known that when both the nitro compound and nitrite ester are present in a dimethylformamide solution of sodium nitrite, considerable decomposition of the nitro derivative takes place if the α-carbon atom of the primary nitro derivative has hydrogen atoms available (21).

The reaction of primary and secondary alkyl halides with sodium nitrite in dimethylformamide has been shown to be second order; it is first order in alkyl halide and first order in sodium nitrite (23). This kinetic order would be indicative of an S_N2 reaction; however both the nitro compound and the nitrite ester are obtained.

The lack of clear-cut evidence for either type of reaction and studies of other reactions of this same general type has led Kornblum to postulate that the two products of the reaction are derived through a common transition state possessing both S_N1 and S_N2 character (23). The postulated common transition state is achieved through a concerted mechanism in which a silver ion exerts a pull on the halide atom and at the same time there is a nucleophilic displacement by the nitrite ion. With this model he is able to explain the fact that those molecules which would be expected to form carbonium ions more readily give the greatest yields of nitrite ester, by reasoning that the incoming nitrite ion would have its greatest concentration of negative charge on the oxygen atoms;

therefore those transition states which possessed more carbonium ion character would have a greater tendency to undergo oxygen alkylation, while those transition states which possessed less carbonium ion character would tend to undergo nitrogen alkylation.

The Kinetic Isotope Effect

Any property of an atom or molecule which is a function of mass should be affected by isotopic substitution. Some of the more important of these properties are nuclear stability, rates of diffusion, chemical equilibrium, chemical reaction rates, and vibrational frequencies.

When Giauque and Johnston (14) in 1929 discovered that ordinary oxygen contains appreciable amounts of oxygen-17 and oxygen-18, the physical scale of atomic weights was established; and the fact that many other elements were also aggregates of several isotopes was readily apparent.

The isotopes of hydrogen with their large relative mass differences were logically the first isotopes by which the kinetic isotope effect was demonstrated. In 1932 Washburn and Urey (36) found that during the electrolysis of water there was an enrichment of the liquid phase in deuterium. In 1933 Lewis and McDonald (27) reported the isolation of a small amount of heavy water, D_2O. Once the existence of deuterium had been experimentally confirmed, both Cremer and Polanyi (9) and Eyring (13) predicted that hydrogen and deuterium would react at different rates because of differences in zero-point vibrational energies. In the year 1934 alone approximately 200 papers were published dealing with the uses, properties, and isolation of deuterium.

For a number of years the assumption was made that the heavier

elements would not show significant differences in kinetic reaction rate on isotopic substitution. In 1948 Beeck, Otvos, Stevenson, and Wagoner (2) published a paper indicating a significant kinetic isotope effect in the rupture of the carbon-carbon bonds of propane-1-C^{13} by electron impact. Since that time the kinetic isotope effect of carbon has been experimentally demonstrated many times and has become a useful tool in the study of reaction mechanisms.

Primary kinetic isotope effects are dependent on an isotopic bond being broken or formed in the rate-determining step of a reaction. Carbon isotope effects have been used in this manner to discover the rate-controlling steps of reactions.

Secondary kinetic isotope effects, i.e. effects which occur when the isotopic bond is not involved in the reaction, are known for the hydrogen isotopes (26,35); however they are too small to be important for such heavier elements as carbon, nitrogen, and oxygen.

Isotope effects are generally expressed as k*/k or as k/k*, where k is the rate constant for the reaction involving the molecule containing the lighter isotope and k* indicates the rate constant for the reaction involving the molecule containing the heavier atom. The molecule containing the lighter isotope characteristically reacts faster than the molecule containing the heavy isotope. However, several reverse isotope effects have been reported for reactions in which the molecule containing the heavy isotope reacted faster (32). The magnitudes of the experimentally determined isotope effects k/k* of carbon-14 have varied from 1.00 to 1.14. However, isotope effects as high as 9.6 have been reported for deuterium (8).

Several people have investigated the effect of difference in

activation energies on the kinetic isotope effect for a series of related reactions. Ropp and Raaen (34) investigated the isotope effect of saponification in 90% ethanol solution of a series of ethyl esters of substituted benzoic acids labeled with carbon-14 in the α-position, and the results (Table I) indicate an increase in isotope effect with increasing activation energy.

TABLE I

ISOTOPE EFFECTS IN THE SAPONIFICATION OF CARBOXYL-C^{14} ESTERS AT 25° IN 90% ETHANOL 0.32M SOLUTIONS

	k_{12}/k_{14}
Ethyl benzoate	1.080
Ethyl p-methoxybenzoate	1.092
Ethyl p-chlorobenzoate	1.081
Ethyl p-methylbenzoate	1.078
Ethyl m-chlorobenzoate	1.072
Ethyl m-nitrobenzoate	1.067

Since this time other work has produced similar results, which have been compiled and discussed in a recent publication by Buist and Bender (7). The evidence available indicates a linear relationship between activation energy and kinetic isotope effect for a reaction within a series of closely related compounds.

With the development of statistical thermodynamics and the absolute rate theory of Eyring and others (16), it has become possible to develop equations by which crude theoretical calculations of the isotope effects can be made. Several other equations for the calculation of reaction

rates have been derived (1,17). However, the equations of Bigeleisen (5), which are based on the absolute rate theory of Eyring, have been the most extensively used for the calculation of kinetic isotope effects.

From the absolute rate theory, the ratio of rate constants for two isotopic molecules would be as follows:

$$\frac{k_1}{k_2} = \frac{K_1}{K_2} \frac{\delta_2}{\delta_1} \left[\frac{m_2}{m_1}\right]^{1/2} \frac{Q_2}{Q_1} \frac{Q_1^*}{Q_2^*}$$

where: k = the rate constant

K = the transmission coefficient

S = the length of the top of the potential barrier

m = the effective mass of the activated complex along the coordinate of reaction

Q = the complete partition function

Q^* = the partition function for the activated complex

Bigeleisen and Mayer (4) pointed out that when the value of $h\upsilon/kT$ is small, the ratio of the partition functions can be closely approximated by a function of the vibrational frequencies of the two molecules. The equation by which they approximated the ratio of the partition function is:

$$\frac{Q_2}{Q_1} = \frac{S_1}{S_2} \left[1 + \sum_{i}^{3N-6} G(\mu_i)\, \Delta\mu_i\right]$$

where: $G(\mu) = 1/2 - 1/\mu + 1/(e^{\mu} - 1)$

$\mu = h\upsilon/kT$

h = Planck's constant

k = Boltzmann's constant

T = absolute temperature

υ = fundamental vibrational frequency

S = symmetry numbers, the ratio of which is generally unity

3N-6 = the number of vibrational modes in a molecule containing N atoms

Substituting the right-hand member of this equation for the ratio of partition functions in the first equation and assuming that the transmission coefficients are equal and that the lengths of the tops of the potential energy barriers are equal gives the following equation.

$$\frac{k_1 S_2 S_1^*}{k_2 S_1 S_2^*} = \left(\frac{m_2}{m_1}\right)^{1/2} \left[1 + \sum_{i}^{3N-6} G(\mu_i)\Delta\mu_i - \sum_{i}^{3N'-6} G(\mu_i^*)\Delta\mu_i^* \right]$$

where: * indicates the activation comples and the symbols 1 and 2 refer to the normal and the labeled molecules, respectively.

The equation is thus divided into two parts, one of which is temperature dependent and one of which is temperature independent.

The reduced mass factor, or temperature-independent factor, is usually calculated as $m_1\ m_2/(m_1 + m_2)$ where m_1 and m_2 represent either the reacting isotopic fragments or the isotopic atoms involved in bond formation.

This factor has been expanded by Bigeleisen and Wolfsberg (6) to include three-centered reactions having concerted mechanisms. The temperature-independent factor then takes the form:

$$\left[\frac{\left(\frac{1}{m_{B_1}} + \frac{1}{m_{C_1}}\right) + p\left(\frac{1}{m_{B_1}} + \frac{1}{m_{A_1}}\right) - \frac{2p^{1/2}}{m_{B_1}}}{\left(\frac{1}{m_{B_2}} + \frac{1}{m_{C_2}}\right) + p\left(\frac{1}{m_{B_2}} + \frac{1}{m_{A_2}}\right) - \frac{2p^{1/2}}{m_{B_2}}} \right]$$

where: p is a function of the ratio of bond formation to bond rupture in the transition state

> The subscript A represents the atom or group with which the new bond is being formed and subscript C represents the atom or group undergoing bond rupture.

Theoretical treatment of the isotope effect has been expanded to cover a four-centered reaction by Yankwich (37).

Calculation of the temperature-dependent factor requires a knowledge of the fundamental vibrational frequencies of the reacting species and the change in frequency upon isotopic substitution. The latter is often approximated by using Hooke's law. In addition a configuration and vibrational frequencies for the transition state must be assumed.

Since μ and consequently $G(\mu)$ are functions of temperature, it is apparent that temperature should affect the magnitude of the isotope effect. Ropp and Raaen found this to be true of the saponification in 90% ethanol of ethyl benzoate-α-C^{14} (34). The isotope effect varied as follows:

Temp., °C	Concn. of Ester, M	k_{12}/k_{14}
0	0.32	1.090
25	0.32	1.077
78.5	0.32	1.065

This decrease in isotope effect with an increase in temperature has also been reported by other investigators (7).

Comprehensive compilations of available information on isotope effects have been made by Roginsky (33) and by Melander (28).

INTRODUCTION TO EXPERIMENTAL PART

Kinetics of the Reaction

The reaction of silver nitrite with an alkyl halide in ether solution is heterogeneous; the reaction rate is therefore a function of the available surface of the silver nitrite crystals as well as of the concentration of alkyl halide.

Since the initial surface of silver nitrite and the variation of the surface during the course of the reaction are not readily measurable, the rate constant and the reaction rate order have not been determined. However it is possible to determine whether both derivatives are produced by reactions of equal kinetic order by varying the concentration of alkyl halide and the amount of silver nitrite at the start of the reaction and determining the ratio of the two products which are formed. This argument is as follows for the reaction:

$$A + B \xrightarrow{k_1} C + E$$
$$A + B \xrightarrow{k_2} D + E$$

If the two isomeric products are derived through reactions of different rate orders,

$$\frac{dC}{dt} = k_1 A^a B^b \qquad \text{and} \qquad \frac{dD}{dt} = k_2 A^{a'} B^{b'}.$$

The reaction is of the competitive type and the ratio of the rates of formation of C and D becomes

$$\frac{dC}{dD} = \frac{k_1 A^a B^b}{k_2 A^{a'} B^{b'}}$$

Changing the concentration of either reactant would change the ratio of products formed if they are produced by reactions of different orders with respect to the reactant that is varied in concentration. If the two isomeric products are derived through reactions of the same kinetic rate order,

$$\frac{dC}{dt} = k_1 A^a B^b \qquad \text{and} \qquad \frac{dD}{dt} = k_2 A^a B^b$$

$$\frac{dC}{dD} = \frac{k_1 A^a B^b}{k_2 A^a B^b} = \frac{k_1}{k_2}$$

In this case changing the concentrations of the reactants could not affect the ratio of the products.

As has been mentioned previously, the over-all reaction rate order was not obtainable. However, theoretically the order with respect to the alkyl halide could be obtained by using such a large excess of silver nitrite that its effective exposed surface would remain essentially constant during the reaction. An attempt was made to do this during this investigation.

Separation of the Products and Reactants

In the separation of the products and reactants, no appreciable amount of side reaction could be tolerated owing to the possibility of an isotope effect in the side reaction which would lead to an error in the determination of the isotope effect in the reaction being studied. This made the separations particularly difficult because the compounds

involved were both thermally unstable and capable of undergoing a variety of reactions under the conditions normally used in separations of this type. For this reason the reaction was carried out at 0° to prevent appreciable decomposition of the alkyl nitrite and in the dark to prevent decomposition of the silver nitrite. Both the nitrites and nitro compounds derived from the benzyl bromides were found to be too unstable for distillation even at reduced pressure without some decomposition. The nitrite esters decompose very readily at elevated temperatures to approximately equal amounts of alcohol and aldehyde, presumably by a free-radical mechanism. p-Nitrobenzyl nitrite has been found to give appreciable amounts of the acetal (18). Extractions involving water cannot be used because of the possibility of hydrolysis of the nitrites and bromides. In aqueous solutions of strong mineral acids both the normal and aci forms of the nitro derivatives are decomposed. When the aci form of the nitro derivative, which forms in the presence of a base, is treated with a strong acid solution, an aldehyde and nitrous oxide are produced. The nitro derivative could also be subject to attack by nitrous acid, from hydrolysis of the nitrite, to form nitrolic acids.

Column chromatography using silica and alumina columns was investigated for the separation of benzyl bromide and its derivatives. A variety of organic eluants were tried and the ultraviolet spectra of the eluted fractions was examined with Beckman Recording Spectrophotometer. Benzyl bromide was found to be cleanly separated from its derivatives with an alumina column and other eluants; however a good separation of the two isomeric derivatives was not obtained.

Since a fast, efficient method of separating the nitrite and the nitro derivative was not achieved, it was necessary to convert the

thermally unstable nitrite quickly and quantitatively to a stable compound before attempting the separation.

Alkaline hydrolysis of the nitrite was found to be so slow at low temperatures that thermal decomposition was feared as a competitive reaction. Acid hydrolysis of the nitrite is very rapid even in dilute solution; however the reverse reaction is so fast that equilibrium prevents the use of this method. The nitro derivative is also subject to side reactions under these conditions. Attempts were made to make the hydrolysis in dilute acid irreversible by adding such reagents as urea and methylamine hydrochloride to react with the nitrous acid as it was formed; however this was not effective as had been hoped.

When carbon dioxide was bubbled through a methanol solution of benzyl nitrite and α-nitrotoluene, the nitrite was quantitatively removed as methyl nitrite in 30 minutes; methyl nitrite boils at -17°. The α-nitrotoluene and the benzyl alcohol which is derived from the nitrite ester can then be separated by the alkali solubility of the nitro compound.

Determination of the Kinetic Isotope Effect

The reaction produces two isomeric products which may come through a common transition state or through two separate transition states. Both products have been found to be derived through reactions of the same reaction rate order. Therefore, the ratio of products will be equal to the ratio of rate constants for their formation, k_1/k_2. This means that if benzyl-α-C^{14} bromides react completely with silver nitrite, the ratio of the molar radioactivities of the products will be $(k_1^*/k_1)/(k_2^*/k_2)$. If both products are derived through a common transition state, k_1^*/k_1

should be equal to k_2^*/k_2 and the molar radioactivities of the two products would therefore be equal. Since the rate constants are for reactions of equal kinetic order, they can be added and the total or over-all isotope effect, k_t^*/k_t, can be determined. Here $k_t^*/k_t = (k_1^* + k_2^*)/(k_1 + k_2)$.

This total isotope effect could be determined by several methods (5). The most convenient method available was to measure the molar radioactivity of the unreacted alkyl halide after a known percent of reaction had taken place. With this molar radioactivity and with a knowledge of the molar radioactivity of the original starting material, the kinetic isotope effect can be determined by the equation (11):

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

where: k^*/k = the ratio of the rate constant for the labeled molecule to that of the normal molecule

A_f = the specific activity of unreacted substrate after f extent of reaction

A_o = specific activity of original reactant

f = the fraction reacted

This equation has been shown to be applicable to a reaction of any kinetic order when the competitive method with tracer level labeling is used (5).

Radioactivity Assay of Carbon-14 Labeled Compounds

The samples of the carbon-14 labeled material to be assayed were weighed on a micro-balance and oxidized in hot Van Slyke solution using the apparatus shown in Figure 5 of the Appendix. The compounds which contained no halogen were assayed without the use of the U-tube

containing stannous chloride, and the samples which contained no nitrogen were assayed without the use of the heated tube containing the lead peroxide. The carbon dioxide was collected in an ionization chamber and the radioactivity of the collected gas was measured by means of a vibrating reed electrometer (Applied Physics Corporation, Model 30).

Carbon-14 decays by emission of a weak β particle (0.155 Mev.) and has a half-life of 5720 years. Because of the long half-life of carbon-14 no correction for decay during the time interval required to run the experiments was necessary.

Theoretical Basis for the Possibility of Different Isotope Effects in the Formation of the Two Products

When different mechanisms are assumed for the formation of each product, the calculated isotope effects for their formation can be quite different. The three-center equation of Bigeleisen can be used to calculate the isotope effect in the formation of each of the two products.

The following development is not intended as a quantitative calculation of the kinetic isotope effect or to imply that the mechanisms chosen are the actual processes by which the products are formed. The purpose of the development is to illustrate that if sufficiently different reaction models are assumed, appreciably different isotope effects in the formation of each product are calculated from Bigeleisen's three-center equation (6).

If the nitrite ester is assumed to be formed by an S_N1 reaction in which a carbonium ion reacts with the nitrite ion to cause alkylation at the oxygen atom of the nitrite ion and the nitro derivative is assumed to be formed by a nucleophilic displacement of the bromine atom

by the incoming nitrite ion, the values for the isotope effects may be calculated as follows, using the temperature-independent factor of Bigeleisen and Wolfsberg (6) for a three-center reaction.

$$\left[\frac{\frac{1}{m_b}+\frac{1}{m_c}+p\left(\frac{1}{m_b}+\frac{1}{m_a}\right)+\frac{2p^{\frac{1}{2}}}{m_b}}{\frac{1}{m_b^*}+\frac{1}{m_c^*}+p\left(\frac{1}{m_b^*}+\frac{1}{m_a^*}\right)+\frac{2p^{\frac{1}{2}}}{m_b^*}}\right]^{1/2}$$

If atomic masses are used and the subscript a designates the incoming atom and the subscript c the outgoing atom, then the calculated values for the temperature-independent factor at different values of p are

p = 1	nitrite	1.062
	nitro	1.060
p = 0	nitrite	1.069
	nitro	1.069

When p is equal to zero a pure S_N1 process is assumed and when p is equal to unity, a pure S_N2 process. This factor alone produces only small differences in the calculated isotope effects. Bender and Buist (3) also predict very little change in the calculated isotope effect with change in the value of p.

The temperature-dependent factor of the Bigeleisen equation is

$$1 + \sum_{i}^{3N-6} G(\mu_i)\Delta\mu_i - \sum_{i}^{3N'-6} G(\mu_i^{\ddagger})\Delta\mu_i^{\ddagger}$$

With the assumption mentioned above that the nitrite derivative is formed by an S_N1 process and that the nitro derivative is formed by an S_N2 process the calculation of the temperature-dependent factor may be

made on the following basis. The carbon-bromine bond is assumed to be completely broken in the transition state and the fundamental vibrational frequency for the bond before rupture has been found from the infrared spectrum of the benzyl bromide to be 550 cm^{-1} (30). The $\Delta\mu_i$ value for the heavier atom is calculated by using Hooke's law and the reduced masses of the atoms involved in the reacting bond. The value for the temperature-dependent factor calculated in this manner is 1.039. The magnitude of the isotope effect for formation of the nitrite is

$$k/k^* = 1.039 \times 1.069 = 1.111$$

When the nitro derivative and consequently a carbon-nitrogen bond is formed in the reaction, the following transition state model and vibrational frequencies are used. The transition state is assumed to correspond to an S_N2 reaction in which there is partial bonding to both the bromine atom and the incoming nitrogen atom. The vibrational frequencies for the partial bonds are calculated using Hooke's law, on the assumption that the force constants are one-half those of the normal bonds. The frequencies used for the normal bonds are: carbon-bromine, 550 cm^{-1} and carbon-nitrogen, 875 cm^{-1}. The $\Delta\mu_i$ values are calculated as before. The temperature-dependent factor calculated for this model is 0.989 and the isotope effect is

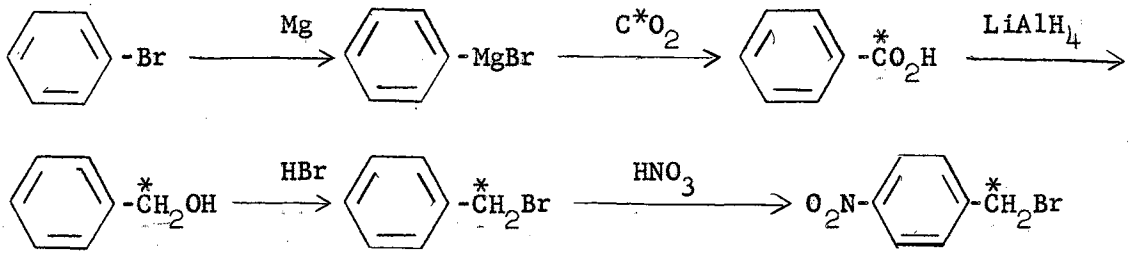
$$k/k^* = 0.989 \times 1.060 = 1.048$$

This value is significantly different from the calculated isotope effect in the formation of the nitrite derivative using the different reaction model.

EXPERIMENTAL

General Procedures

The benzyl-α-C^{14} bromides which were used in this research were prepared by the following scheme:



The silver nitrite used in this work was prepared by the method described by Kornblum (25). The silver nitrite was prepared in a dark room by mixing solutions containing equimolar quantities of sodium nitrite and silver nitrate and filtering off the silver nitrite which precipitated. The solid was then washed three times with distilled water and dried in a vacuum desiccator.

Mallincrodt anhydrous ether was used in all of the reactions. It was generally kept over calcium hydride.

The reactions were carried out in a thermostatically controlled cold bath which was kept in a dark refrigerated room.

Preparation of Phenylmagnesium Bromide

A 100-ml. three-neck flask was fitted with a condenser, a 50-ml. dropping funnel and a glass stopper. To this flask was added 0.63 g.

of magnesium turnings; the flask and contents were dried overnight in a 110° oven.

The Grignard reagent was prepared in the usual manner using 2.6 ml. (3.9 g.) of bromobenzene in a total of 50 ml. of diethyl ether which had previously been dried over calcium hydride.

The contents of the reaction flask were stirred with a magnetic stirrer. After the addition of the ether solution of bromobenzene was complete, the flask was heated gently by means of an infrared lamp and the contents stirred for an additional three hours. The flask was allowed to cool and a 5-ml. sample of the Grignard reagent was removed by pipette and hydrolyzed in a mixture of water and methanol. An excess of standard hydrochloric acid solution was then added and the mixture was back-titrated with a standard sodium hydroxide solution (15). The Grignard reagent, which was found to be 0.46 N, was then used in the following preparation of benzoic-α-C^{14} acid.

Preparation of Benzoic-α-C^{14} Acid

A system consisting of a 50-ml. pear-shape flask attached to a 50-ml. pressure-equalized dropping funnel, connected to a vial through a U-tube, was prepared as shown in Figure 2 of the Appendix. Twenty milliliters of the 0.46 N phenylmagnesium bromide solution was placed in the vial by means of a pipette. Then 0.0216 g. (2.74 millicuries) of barium carbonate-C^{14} and 1.4296 g. of normal barium carbonate were placed in the pear-shape flask and covered with glass wool. Fifty milliliters of concentrated sulfuric acid was added to the dropping funnel. The Grignard reagent was frozen by means of a liquid nitrogen bath and the system evacuated. The sulfuric acid was added dropwise

to the barium carbonate as the liberated carbon dioxide condensed in the vial containing the Grignard reagent. After the addition of the sulphuric acid was complete and the pear-shape flask had been heated briefly, the vial containing the frozen Grignard reagent and carbon dioxide was sealed off with a torch. The vial was allowed to warm to approximately -30° and was maintained at that temperature for three hours. When the vial warmed to room temperature it was opened and the contents were poured on 30 g. of cracked ice and dilute hydrochloric acid. After being stirred for several minutes, the solution was made alkaline with 15 ml. of 20% sodium hydroxide solution and the ether layer was removed. The aqueous layer was acidified with 10 ml. of concentrated hydrochloric acid and extracted with three 20-ml. portions of diethyl ether. The ether layers were combined and the ether was evaporated. The benzoic acid was then recrystallized from 30 ml. of water; 0.854 g. of benzoic acid was obtained (95% yield).

Then 1.0 g. of unlabeled benzoic acid was dissolved in and recrystallized from the mother liquor. This solid was combined with the original crystals to give a total of 1.8104 g. of benzoic acid which was used in the following preparation of benzyl bromide.

Preparation of Benzyl-α-C^{14} Bromide

A 300-ml. three-neck flask was fitted with a condenser, a closed 50-ml. dropping funnel, a magentic stirrer and a stopper. One hundred milliliters of diethyl ether which had been dried over calcium hydride was placed in the flask and the system flushed with dry nitrogen. Then 3.3 g. of powdered lithium aluminum hydride was added to the flask and stirred for 20 minutes with a magnetic stirrer. The benzoic-α-C^{14} acid

(1.81 g.) from the previous preparation, plus enough unlabeled benzoic acid to give a total of 10 g. was dissolved in 50 ml. of dry diethyl ether. This solution was added dropwise by means of the dropping funnel to the flask while the system was being stirred and continually flushed with dry nitrogen. The reaction mixture was stirred and heated with an infrared lamp for an additional three hours. The reaction flask was placed in an ice bath and 50 ml. of distilled water was added dropwise while nitrogen was passed through the system. Then 20 ml. of 10% hydrobromic acid solution was added to the flask. The contents of the flask were transferred to a separatory funnel and the ether layer was removed. The aqueous layer was then extracted twice with 20-ml. portions of diethyl ether. The aqueous layer was then made alkaline with a 20% solution of sodium hydroxide and extracted again with 20 ml. of ether. The ether extracts were combined in a 300-ml. distilling flask. The ether was distilled off and 40 ml. of 48% hydrobromic acid solution was added to the flask. The flask was fitted with a reflux condenser and heated to reflux for six hours. It was then stoppered and allowed to stand overnight.

The flask was then cooled to -10° with an ice-acetone bath and 15 ml. of phosphorus tribromide was added to it dropwise with stirring. The sub-zero temperature was maintained for two hours and the flask was then placed in a cold room at 6° for an additional 24 hours. The organic layer was separated and the aqueous layer extracted twice with 30-ml. portions of diethyl ether. The organic layers were then combined and dried overnight with calcium chloride. The mixture was placed in a 100-ml. distilling flask and the ether was distilled at atmospheric pressure. The benzyl bromide was distilled at reduced pressure in a

small vacuum-jacketed fractionating column packed with a Nichrome wire coil. The pressure was maintained at 13 mm. of mercury; 9.77 g. of material was obtained at 81°.

Approximately 12 g. of unlabeled benzyl bromide was added to the residue in the distilling flask. The material which distilled over at 81° and 13 mm. pressure was added to the original distillate to give a total of 21.67 g. of benzyl bromide. The radioactivity of the benzyl-α-C^{14} bromide was determined to be 13.64 μc./mmole for a total of 1.74 millicuries of carbon-14. Over-all activity yield based on the radioactivity of the original barium carbonate was 63.5%.

Preparation of p-Nitrobenzyl-α-C^{14} Bromide

A 100-ml. three-neck flask was fitted with a stirrer, a 50-ml. dropping funnel and a thermometer. The flask was placed in a 0° bath. After 20 g. of acetic anhydride and 12 g. of glacial acetic acid were placed in the flask and allowed to cool 12.6 g. of fuming nitric acid was added and the mixture allowed to cool to the bath temperature. With vigorous stirring 16.1 g. (0.714 millicuries) of benzyl-α-C^{14} bromide was added dropwise through the separatory funnel over a period of forty-five minutes. The temperature of the flask continued to rise after the addition was complete to a maximum of 7°. The reaction was allowed to proceed in the cold bath with stirring for ten hours. At the end of this period the pale yellow solid which formed in the flask was broken up with a spatula. The contents of the flask were placed in a beaker with 100 ml. of cold water and vigorously stirred for several minutes. The solid material was then separated by means of a fritted glass funnel and dissolved in 60 ml. of hot methanol. The crystals which formed on cooling were

removed by filtration. Then 2 g. of unlabeled p-nitrobenzyl bromide, which had previously been prepared in this same manner, was dissolved in and recrystallized from the mother liquor. These crystals were combined with those from the original filtration. The combined crystals were recrystallized from 60 ml. of anhydrous methanol. The yield was 11.41 g. of light cream-colored, needle-shaped crystals melting at 100° (lit. 98.5-99.5°) (23). The radioactivity yield was 44.4% based on benzyl-α-C^{14} bromide. This material was used directly in the isotope effect determinations.

100% Reaction of Benzyl-α-C^{14} Bromide with Silver Nitrite:

Run Number One

All operations in the following experiment which involved silver salts were carried out with a minimum of exposure to light.

Into a dry three-neck 100-ml. flask fitted with a ground-glass sealed stirrer and two glass stoppers was placed 2.27 g. of silver nitrite (approximately 50% excess) and 0.1 g. of calcium hydride. The flask was sealed and placed in a cold bath (-0.2° ± 0.2°). One milliliter of benzyl bromide (1.44 g.) was dissolved in 25 ml. of dry ether and the solution was cooled in the cold bath temperature. This solution was then added to the reaction flask and the reaction was allowed to proceed with stirring for 28 hours.

One milliliter of the solution was then removed and placed in a solution of methanol and water which was saturated with silver nitrate. The absence of turbidity indicated complete reaction of the benzyl bromide.

The reaction flask was removed from the cold bath and the silver salts were filtered from the solution by means of a fritted glass filter. The ether was evaporated under reduced pressure. The liquid residue was immediately dissolved in methanol and placed in a filter funnel containing a fine glass frit while carbon dioxide was being passed continuously up through the frit.

In a previous experiment it was found that no nitrite could be detected with sulfanilic acid and 1-naphthylamide after passing carbon dioxide through a similar sample for forty-five minutes. In the present experiment the carbon dioxide was bubbled through the system vigorously for sixty minutes. The solution was then transferred to a 20-ml. distilling flask and the methanol was distilled on the vacuum line.

Ten milliliters of 20% sodium hydroxide solution was added to the flask and the solution shaken intermittently for one hour. Then 7 ml. of a 1:1 solution of isopentane and diethyl ether was added and the solution placed in a screw-capped bottle. This mixture was placed on a mechanical shaker for one hour. The organic layer was separated from the aqueous layer and the extraction repeated with another 7-ml. portion of the isopentane-ether solvent. Then 2 ml. of 20% sodium hydroxide solution was added to the combined organic extracts and this mixture was placed on the shaker for an hour. This aqueous layer was separated and added to the original aqueous portion. The organic layer was dried with anhydrous calcium sulphate for eight hours and the solvent distilled under reduced pressure. The liquid residue was transferred to a microdistillation apparatus (Figure 3) by means of a capillary pipette and distilled on the vacuum line. The yield was 147 mg. of colorless benzyl alcohol with a refractive index at 20° of 1.5353 (lit. 1.5404) (20).

The aqueous alkaline layer was made acidic (pH 5) by the addition of 35 ml. of a 40% solution of hydroxylamine hydrochloride (23) and the nitro derivative was extracted by adding 15 ml. of the isopentane-ether mixture and shaking for one hour. The organic layer was removed and the process repeated with another 15-ml. portion of the organic solvent. The aqueous layer was allowed to stand at room temperature overnight and the process was repeated a third time.

The organic layers were combined and dried for 12 hours with calcium chloride. The solution was separated from the drying agent and the solvent was distilled under reduced pressure. The liquid residue was distilled in the same manner as the benzyl alcohol. The yield was 0.6584 g. of nearly colorless α-nitrotoluene with a refractive index at 20° C. of 1.5316 (lit. 1.5315) (23).

Oxidation of Products

A. Benzyl Alcohol

The benzyl-α-C^{14} alcohol was placed in a tared vial by means of a capillary dropper and the vial and contents were weighed again. Enough potassium permanganate to give a 3% excess of permanganate was weighed out and added to the flask with 5 ml. of 5% sodium hydroxide solution and 3 ml. of distilled water. The vial was then sealed off with a torch and agitated by hand with cooling for ten minutes. It was shaken mechanically for 18 hours at room temperature.

At the end of this period the permanganate color could no longer be detected. The vial was opened and the contents transferred quantitatively by washing with distilled water into an apparatus for continuous

ether extraction. The solution was made acidic with 6 ml. of concentrated hydrochloric acid and the benzoic acid was extracted by continuous ether extraction for six hours. The ether was evaporated by passing nitrogen over the solution. The benzoic acid residue was dried for 36 hours in a desiccator over calcium chloride and sodium hydroxide.

The flask was then removed, water was added and the benzoic acid residue was titrated to a phenolphthalein end point using a standard sodium hydroxide solution. The yield of benzoic acid was calculated by its base equivalence. The benzoic acid was reprecipitated by the addition of 5 ml. of concentrated hydrochloric acid and extracted with two 15-ml. portions of diethyl ether. The ether was evaporated and the benzoic acid was recrystallized from distilled water. The benzoic acid was then dried in a desiccator and was found to have a melting point of 123°. This material was used in making the radioactivity determinations reported in Table III.

B. Oxidation of α-Nitrotoluene

The α-nitrotoluene-α-C^{14} from the 100% reaction was oxidized by the same procedure used for the benzyl alcohol except that 7 ml. of 5% sodium hydroxide solution was used instead of 5 ml. of this material. The vial was shaken for forty-eight hours and two drops of formaldehyde solution was used to destroy the remaining permanganate. The yield of benzoic acid was determined as before and the acid was purified in the same manner as the acid from the benzyl alcohol. The melting point of the final material was 123°; the yield and radioactivity of the benzoic acid are given in Table III.

C. Oxidation of the Initial Benzyl Bromide

A 0.3620-g. sample of the initial benzyl-α-C^{14} bromide was oxidized in the same manner as the benzyl alcohol except that 10 ml. of 5% sodium hydroxide solution was used and the reaction time on the mechanical shaker was extended to seventy-two hours. The determination of yield and the purification of the benzoic acid was carried out in the same manner as in the previous cases. The final product had a melting point of 123°. The yield and the radioactivity are given in Table III.

100% Reaction of Benzyl-α-C^{14} Bromide with Silver Nitrite

Run Number Two

The complete experiment described above was repeated starting with one milliliter of benzyl-α-C^{14} bromide which reacted completely. The separation and oxidation to benzoic acid were carried out using the same general procedure as in the first experiment. The yields of benzoic acid from the three sources and their radioactivities are given in Table III, under the heading "Run Two".

Partial Reaction of Benzyl-α-C^{14} Bromide

Into a 50-ml. volumetric flask was weighed 3.1811 g. of the benzyl-α-C^{14} bromide. The flask was placed in a 0° bath and filled to volume with diethyl ether which had been dried over calcium hydride. Into a three-neck flask which was fitted with a glass-sealed stirrer and two stoppers were placed 2.0025 g. (enough for 70% of complete reaction) of silver nitrite and 0.2 g. of calcium hydride. This flask was placed in a cold bath and 25 ml. of ether cooled to 0° was added by pipette.

The contents of the volumetric flask were transferred quantitatively to the three-neck flask by washing with an additional 25 ml. of dry ether cooled to 0°. The reaction was allowed to proceed with stirring in the dark for thirty-seven hours. Then 10 ml. of the solution was removed by means of a cold pipette and added to a solution containing a large excess of silver nitrate. After this solution had reacted in the dark the silver bromide which precipitated was removed, dried and weighed. The reaction was found to have reached 69.9% of completion when the sample was taken.

The reaction flask was removed from the bath and the silver salts were separated from the solution by filtration and most of the ether was distilled under reduced pressure. The unreacted benzyl bromide was separated from the products by means of a chromatographic column using neutral activated alumina and anhydrous ether as elutant.

Previous experiments using the ultraviolet absorption spectrum to identify the compounds in the eluted fractions had indicated that the benzyl bromide was cleanly separated from the two products and was the first compound to be eluted.

The separation of products in the present experiment was followed by means of an Abbe refractometer. The ether solution of the unreacted benzyl-α-C^{14} bromide was then distilled under reduced pressure. When the ether had distilled, the liquid residue was distilled under reduced pressure on the vacuum line with a micro-distillation apparatus (Figure 3). The yield was 0.55 g. of colorless benzyl bromide which was oxidized to benzoic acid by the process described previously. The yield of benzoic acid and the radioactivity are given in Table V.

100% Reaction of p-Nitrobenzyl-α-C^{14} Bromide

A 300-ml. three-neck flask was fitted with a glass-sealed stirrer and two stoppers. Then 2.16 g. of the p-nitrobenzyl-α-C^{14} bromide was placed in the flask with 200 ml. of anhydrous ether which had been passed over molecular sieve (Linde #5A). The flask was stoppered and placed in a cold bath (0° ± 0.2°) in a dark room for two hours.

Then 7.75 g. of silver nitrite and 0.2 g. of calcium hydride were weighed in a dark room with a red-filtered lamp for illumination. These were added to the reaction flask with a minimum of exposure to light. The reaction was allowed to proceed in the dark with stirring for forty hours. One milliliter of the reaction mixture was removed by means of a pipette fitted with a small fritted glass filter. This sample of the reaction mixture was added to 1 ml. of a saturated solution of silver nitrate in 75% methanol and 25% water. Since no turbidity could be detected after one hour, the reaction was considered to be complete.

The reaction flask was then removed from the bath and the silver salts were removed from the solution by filtration. The solution was quickly concentrated to approximately 50 ml. by passing a stream of dry nitrogen over the ether solution. Most of the α,p-dinitrotoluene precipitated upon concentration of the solution and was removed by filtration. This solid was set aside for further purification. The remaining ether in the solution was quickly evaporated by a stream of dry nitrogen gas. The solid residue was immediately dissolved in 12 ml. of methanol and 0.2 ml. of 5N-hydrochloric acid. This solution was placed in a fine fritted-glass funnel and carbon dioxide was bubbled through it.

Before the solution was submitted to the carbon-dioxide wash, one

drop of the solution was removed and added to three drops of a mixture of sulfuric acid and diphenylamine (38). A dark blue color immediately formed. This test for nitrite was made periodically during the treatment with carbon dioxide and after forty-five minutes no color was visible. This bubbling however was continued for an additional fifteen minutes.

The mixture was transferred to a 250-ml. Erlenmeyer flask and the methanol was evaporated under a stream of nitrogen. The residue was dissolved in 80 ml. of distilled water by heating and then allowed to cool overnight in a room at 6°.

The crystals which had formed on standing in the cold room were filtered off and discarded. The aqueous solution was extracted twice with 30-ml. portions of diethyl ether. The ether was evaporated and the residue was dissolved in 40 ml. of n-heptane by heating. The crystals which had formed were removed by filtration. The yield was 0.18 g.; the melting point of the crystals was 91-92°. They gave a negative test for nitrite when treated with the sulfuric acid-diphenylamine reagent.

These crystals were recrystallized from another 40-ml. portion of n-heptane giving 0.13 g. of white, flaky crystals of p-nitrobenzyl alcohol with a melting point of 93° (lit. 93°) (31). This material was kept in the dark and was used directly for the radioactivity determinations.

The α,p-dinitrotoluene which had separated when the original ether solution was concentrated was purified by two recrystallizations from 80-ml. portions of n-heptane to give 0.55 g. of white, needlelike crystals with a melting point of 90° (lit. 89-90°) (23). No blue color was detected when this material was treated with the sulfuric acid-diphenylamine

reagent. This material was used directly for the radioactivity determinations.

Partial Reaction of p-Nitrobenzyl-α-C^{14} Bromide

A 300-ml. three-neck flask was fitted with a glass-sealed stirrer and two glass stoppers; 2.9988 g. of p-nitrobenzyl-α-C^{14} bromide was weighed into the flask which was placed in a bath at 0° ± 0.2° in a dark room maintained at 3°. Then 200 ml. of anhydrous diethyl ether at 0° was added to the flask by means of a cold dry pipette. This procedure was found in a separate experiment to give a total volume of 200.9 ml. when the p-nitrobenzyl bromide had dissolved.

After the p-nitrobenzyl bromide had dissolved with stirring, 2.14 g. of silver nitrite and 0.2 g. of calcium hydride were weighed in a dark room and added to the flask. The reaction was allowed to proceed with stirring in the dark for thirty-six hours. Then 25 ml. of the reaction mixture was removed by means of a cool pipette fitted with a very small fritted glass filter. The sample was added to a saturated 1:1 methanol-water solution of silver nitrate. This mixture was placed in a dark room for forty-eight hours to react.

The reaction flask was removed from the cold bath and the silver salts removed by filtration. The ether was then evaporated under a stream of dry nitrogen gas and the residue was dissolved in 200 ml. of warm n-heptane. The solution was allowed to cool to room temperature and the crystals which formed were removed by filtration and discarded. The n-heptane solution was then further cooled to approximately -30° with dry ice in an acetone bath. The temperature was maintained at that level for about one hour and the crystals which formed were filtered off.

After these crystals were recrystallized from 5 ml. of dry methanol and from 3 ml. of methanol, the melting point was found to be 94-96°. These crystals were then recrystallized two times from 2-ml. portions of dry methanol. The final product was 0.10 g. of needle-like crystals of p-nitrobenzyl bromide with a melting point of 99° (Lit. 98.5-99.5) (23). This material was used in the radioactivity assays.

Determination of the Extent of Reaction

After forty-eight hours the solution containing the silver nitrate and the 25 ml. of the original reaction mixture from the experiment above was filtered by means of a previously weighed fritted-glass filter funnel. The silver salts in the funnel were washed with distilled water and acetone to remove silver nitrate and organic residues. The filter and silver bromide were then dried in a vacuum desiccator in a dark room. A yield of 0.876 g. of silver bromide was obtained. Calculation showed that 29.8% of the initial p-nitrobenzyl bromide had not reacted when the flask was removed from the bath and filtered. This extent of reaction was used in the calculation of the isotope effect.

The Effect of Varying the Amount of Silver Nitrite and the Concentration of Benzyl Bromide on the Ratio of Products

The following general procedure was used several times with different concentrations of benzyl bromide and amounts of silver nitrite.

A three-neck flask was fitted with a glass-sealed stirrer and two stoppers. Two grams of silver nitrite was weighed in a dark room and placed in the dry flask with 0.1 g. of calcium hydride. The flask was then placed in a 0° bath in a refrigerated dark room. Thirty milliliters

of anhydrous ether at 0° was added to the flask with a cold dry pipette. Then 20 ml. of a 0.6329N solution of benzyl bromide in diethyl ether at 0° was added with a cold pipette to the reaction flask with stirring. After twenty-four hours a 1-ml. sample of the solution was withdrawn from the reaction flask and treated with silver nitrate solution; no turbidity was detected.

Two 15-ml. samples of the reaction mixture were withdrawn using a cool pipette fitted with a small, detachable fritted-glass filter. The two samples were treated separately as follows:

1. Determination of the Nitro Derivative by Titration - One of the 15-ml. samples was added to a solution of 10 ml. of distilled water and 40 ml. of methanol. This solution was immediately titrated with a standard sodium hydroxide solution to a phenolphthalein end-point and the yield of nitro derivative calculated from the base used. The yield of nitrite derivative was then calculated by difference. The results of this experiment and others using this procedure are recorded in Table II.

2. Direct Determination of the Yield of Benzyl Nitrite - The other 15-ml. sample of the reaction mixture was placed in a small distilling flask and the ether was removed under reduced pressure. Then 5 ml. of methanol was placed on top of the fine glass frit shown in the apparatus in Figure 4. The system including the Dumas nitrogen determination apparatus was washed with carbon dioxide. The residue from the reaction mixture which was left in the flask after the other was removed was washed into the separatory funnel above the glass frit with two 5-ml. portions of methanol. While carbon dioxide was being passed continuously through the system, this solution was forced down into the methanol which was already in the chamber, air being carefully excluded. The separatory

funnel was then washed with a small amount of methanol which was also forced into the chamber.

Carbon dioxide was bubbled through the methanol solution and through the Dumas nitrogen determination apparatus. The carbon dioxide was bubbled through the solution for one hour at the end of which time the collection of nitrogen appeared to be complete. Ice water was used in the condenser above the methanol solution during the passage of carbon dioxide through the solution.

The nitrogen collected was assumed to be from methyl nitrite through exchange of methanol with benzyl nitrite. The yield of nitrite was calculated from the volume of gas collected and is given in parentheses in Table II.

The Effect of Varying the Amount of Silver Nitrite on the Ratio of Products Formed in the Reaction of p-Nitrobenzyl Bromide with Silver Nitrite

The reactions were carried out in the same manner as the reactions of benzyl bromide. In this case however, only the amount of silver nitrite was varied. The methods of determining the product yields differed from the methods used in the case of benzyl bromide.

(A) Yield of Nitro Derivative - In the titration of the nitro derivative colorimetric detection of the end-point could not be used owing to the fact that the salt of the nitro compound is colored. For this reason a pH meter and glass electrode were used to determine the equivalence point. When the volume of standard sodium hydroxide was plotted against pH, an inflection point was obtained at a pH of about 8.45 which was considered to be the equivalence point. The yield of nitrite derivative was calculated by difference. The results and the conditions of the reactions

are given in Table II.

(B) Yield of Nitrite Derivative - The procedure was the same as that for determination of benzyl nitrite except that 0.2 ml. of 5N hydrochloric acid solution was added to the reaction mixture after admission of the sample to the carbon dioxide washing chamber. The results are in parentheses in Table II.

Attempted Determination of Reaction Rate Order with Respect to p-Nitrobenzyl Bromide

A dry 300-ml. three-neck flask was fitted with a glass-sealed stirrer and two stoppers. Then 2.965 g. of p-nitrobenzyl bromide was added to the flask and the flask was placed in a bath at -2.0° ± 0.2° in a dark, refrigerated room. Then 200 ml. of ether which had been dried over an activated adsorbent, Linde #5A Molecular Sieve, was added to the flask and the contents stirred for thirty minutes in the cold bath. Then a 20-ml. sample was removed by pipette and added to 50 ml. of a saturated solution of silver nitrate in a 3:1 solution of methanol and water. This mixture was placed in a dark room to react. Then 22.20 g. of silver nitrite (more than eleven times the required amount) was added to the reaction flask and the contents were stirred for thirty minutes. A 20-ml. sample was removed from the flask and treated in the same manner as the original sample with silver nitrate. Sixty minutes after the addition of the silver nitrite another 20-ml. sample was removed and treated in the same way.

Another reaction was carried out in the same manner using the same amounts of reagents and the same conditions. In this case a 20-ml. sample was removed before the addition of silver nitrite and samples

were removed at two hours and at four hours after the addition of the silver nitrite. These samples received the same treatment as the previous samples.

A third reaction was carried out using the same procedure and amounts of reactants with 20-ml. samples withdrawn before the addition of silver nitrite and at three hours and five hours after the addition of silver nitrite. These samples were also treated in the same manner as the previous ones.

After the withdrawn samples had been allowed to react at least twenty-four hours with the silver nitrate solution, the silver bromide which had precipitated was filtered from the solution with previously weighed fritted-glass funnels. The precipitates were washed with distilled water and then with acetone. They were dried in a vacuum desiccator and weighed. The extent of reaction for each time interval was calculated from the amount of silver bromide produced in the reaction with silver nitrate. These data are plotted in Figure 1.

RESULTS

That there is no variation in product ratio with variation in the effective concentration of reactants is demonstrated by data in Table II. The differences shown in the data are felt to be within the experimental errors which could be expected with the method used in the analysis.

TABLE II

YIELDS OF NITRITE AND NITRO DERIVATIVES IN THE REACTION OF SILVER NITRITE AND BENZYL HALIDES AT 0°

Compound	Halide, M	Silver Nitrite g./100 ml.	Yield	
			Nitro-Compd. %	Nitrite, %
Benzyl Bromide	0.072	1.3	68.3	31.7
	0.072	25.0	67.4	32.6
	0.253	4.0	68.5	31.5 (27.4)
	0.253	20.0	67.6	32.4
p-Nitrobenzyl bromide	0.093	4.3	74.9	25.1 (22.1)
	0.093	20.0	73.0	27.0

Each group of radioactivity determinations in Tables III-VI was made in one day to minimize variation in the absolute reading obtained from the electrometer.

TABLE III

100% REACTIONS OF BENZYL-α-C^{14} BROMIDE

Source	Yield of Benzoic Acid, %	Activity, μc./mmole	Average Activity, μc./mmole
RUN 1			
Benzyl bromide	98.4	4.20 4.12 4.13	4.15
α-Nitrotoluene	101.9	4.16 4.15 4.11	4.14
Benzyl alcohol	95.7	4.22 4.12 4.16	4.17
RUN 2			
Benzyl bromide	98.6	4.04 4.04 4.06 4.08	4.06
α-Nitrotoluene	96.6	4.04 4.07 4.02	4.04
Benzyl alcohol	97.9	4.03 4.05	4.04

TABLE IV

100% REACTION OF p-NITROBENZYL-α-C^{14} BROMIDE

Compound	Activity, μc./mmole	Average Activity, μc./mmole
	FIRST ASSAY GROUP	
p-Nitrobenzyl bromide	6.04 5.96 5.98	5.99
α,p-Dinitrotoluene	5.99 5.97	5.98
p-Nitrobenzyl alcohol	5.98 5.96	5.97
	SECOND ASSAY GROUP	
p-Nitrobenzyl bromide	5.99 5.95 5.89	5.94
α,p-Dinitrotoluene	5.93 6.01 5.95	5.96
p-Nitrobenzyl alcohol	5.93 5.94 5.90	5.92

TABLE V

70% REACTION OF BENZYL-α-C^{14} BROMIDE

Source	Yield of Benzoic Acid, %	Activity, μc./mmole	Average Activity, μc./mmole	Total Isotope Effect k_t^*/k_t
		FIRST ASSAY GROUP		
0% REACTION				
Benzyl bromide	98.4	4.03 4.09 4.11	4.08	0.960
AFTER 70% REACTION				
Benzyl bromide	102	4.29 4.29 4.25	4.28	
		SECOND ASSAY GROUP		
0% REACTION				
Benzyl bromide	98.4	3.94 3.95 3.91	3.93	0.954
AFTER 70% REACTION				
Benzyl bromide	102	4.21 4.13 4.14	4.16	

TABLE VI

70% REACTION OF p-NITROBENZYL-α-C^{14} BROMIDE

Source	Activity, μc./mmole	Average Activity, μc./mmole	Total Isotope Effect, k_t^*/k_t
	FIRST ASSAY GROUP		
0% Reaction	5.91 5.92 5.87	5.90	
			0.894
70% Reaction	6.57 6.74 6.80	6.70	
	SECOND ASSAY GROUP		
0% Reaction	5.95 5.97 6.02	5.98	
			0.892
	6.85 6.77 6.84	6.82	

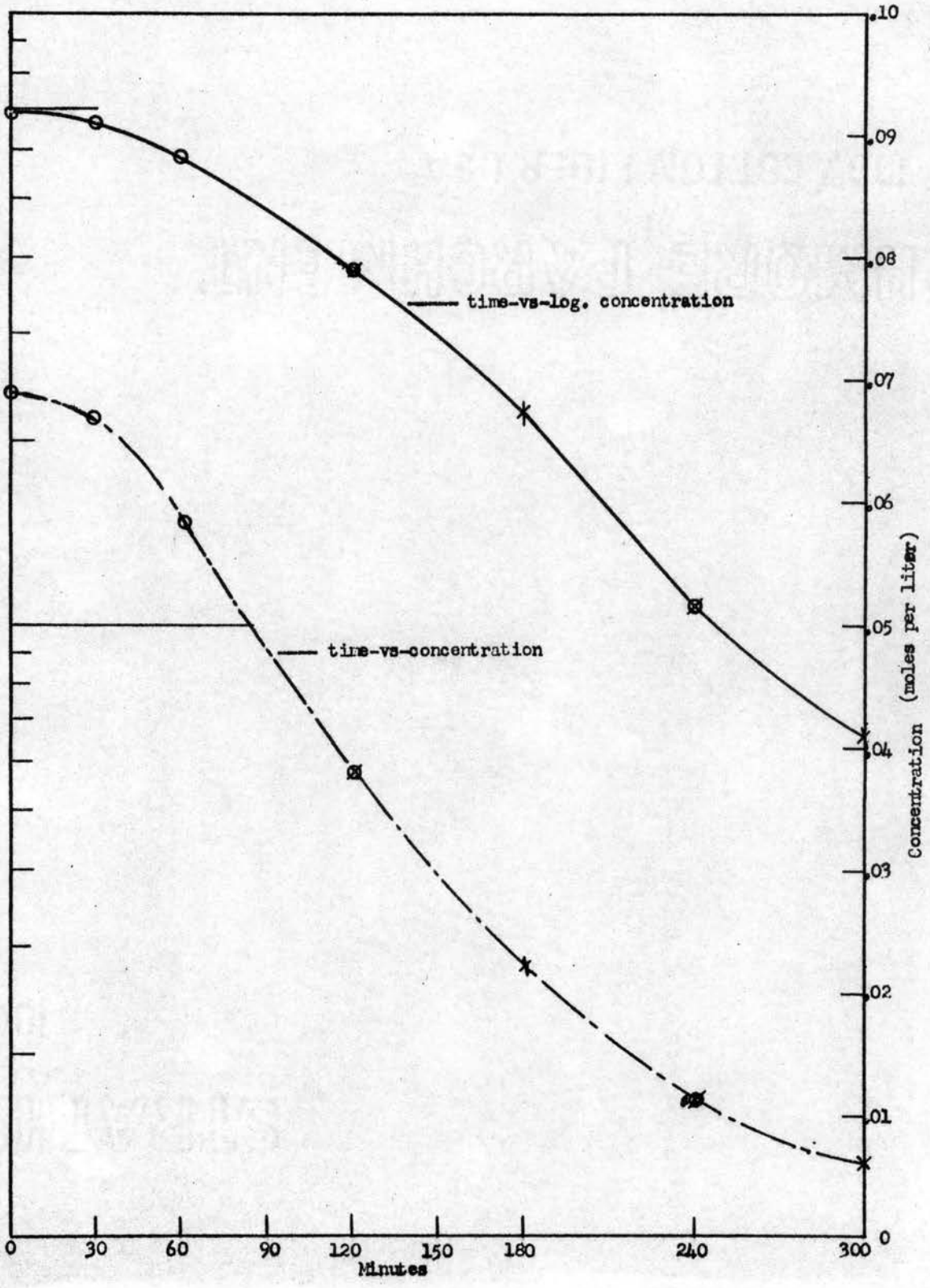


Figure 1. Rate of Reaction of p-Nitrobenzyl Bromide with Large Excess of Silver Nitrite.

DISCUSSION OF RESULTS

Statistical Analysis of Results

The results from both the 100% reactions with benzyl-α-C^{14} bromide (Table III) were subjected to an analysis of variation using an F distribution (10). The hypothesis that the benzoic acid from all three sources had equal radioactivities was found to pass the test in both runs for all significance levels from 0.500 to 0.001. A significance level of 0.500 means that even a correct hypothesis would be rejected 50% of the time using these limits. At a significance level of 0.001 a correct hypothesis would be rejected only 0.1% of the time.

The results from both assay groups for the three compounds in the 100% reaction with p-nitrobenzyl-α-C^{14} bromide were subjected to the same analysis as the data for the reaction with benzyl bromide. The hypothesis that all three compounds had equal molar radioactivities was also found to pass the test at all significance levels from 0.500 to 0.001.

These results indicate that no detectable difference in the molar radioactivities of the products or starting material was found in either of the reactions studied.

The 95% confidence limits for the difference of the mean molar radioactivities of the starting material compared to the remaining substrate after 70% reaction was determined for both reactions (12). The assumption was made that the variance in activity determinations

for both the starting material and the unreacted substrate was equal. The assumption was also made that the universe of individual activity determinations would follow a normal distribution. A two tail test was employed. The results are as follows:

70% Reaction of Benzyl-α-C^{14} Bromide

Source of Data	Mean Radioactivity Difference (95% confidence level) μc./mmole
Assay Group 1 (Table V)	0.20 ± 0.077
Assay Group 2 (Table V)	0.23 ± 0.078

70% Reaction of p-Nitrobenzyl-α-C^{14} Bromide

Assay Group 1 (Table VI)	0.80 ± 0.211
Assay Group 2 (Table VI)	0.84 ± 0.091

100% Reaction of Benzyl-α-C^{14} Bromide

The results listed in Table III are for samples from two completely separate experiments except that both experiments were carried out in essentially the same manner. It is essential that the yield of benzoic acid be near 100% to avoid any appreciable isotope effect in the oxidation. The effect of small amounts of impurities in the material before oxidation would not affect the true activity of the benzoic acid unless the impurity was itself oxidized to benzoic acid. Even in this eventuality the effect would be minimized if the impurity which was oxidized to benzoic acid had nearly the same molar radioactivity as the material for which the assay was being made. Since the only known possible contaminants which would oxidize to benzoic acid would be of nearly

equal radioactivity, the effects of small amounts of impurities in the materials before oxidation are not as important as would otherwise be the case.

The results indicate that any difference in the molar radioactivities of the benzoic acid derived from the three different sources, if any difference does exist, is too small to be detected with the precision achieved in this work.

The isotope effect appears to be equal in the formation of each of the products.

100% Reaction of p-Nitrobenzyl-α-C^{14} Bromide

The two assay groups shown in Table IV are simply two sets of radioactivity evaluations from the same materials. They are listed in separate groups because the two groups of determinations were made at different times and the absolute reading on the electrometer has been found to change over a period of time. The results indicate that if there is a difference in radioactivity between the two products or between the starting material and the products, it is too small to be demonstrated with the precision that was attained in this experiment. No difference in kinetic isotope effect was detected in the formation of the products of either this reaction or the reaction of silver nitrite with benzyl bromide. The fact that in both cases the starting materials had the same radioactivities as the products can be taken as additional evidence that no appreciable errors were introduced by possible side reactions such as thermal decomposition of the nitrite derivatives.

70% Reaction of Benzyl Bromide

Both assay groups in Table V are for assays of the same material. As in the other instance they are separate because there was a time lapse between the groups of activity determinations. As can be seen, the values for the isotope effect differ by 0.6%. This difference is not large enough to alter the conclusion that a definite isotope effect exists in the reaction. This isotope effect however is not large by comparison to other carbon-14 isotope effects which are usually 10-12%.

70% Reaction of p-Nitrobenzyl Bromide

The two assay groups listed in Table VI are for the same materials. The values for the isotope effect in this case are in fairly good agreement. The large isotope effect, as compared to the isotope effect with benzyl bromide, is probably due to a difference in activation energy since benzyl bromide has been reported to react approximately eleven times as fast as p-nitrobenzyl bromide with silver nitrite (23).

The Ratios of Yields of Products

The values given in Table II for the yields of nitro and nitrite derivatives were obtained by titration of the nitro derivative and then calculating the yield of nitrite by difference. The values for the nitrite yields in parenthesis in the table were obtained by use of a Dumas nitrogen determination on methyl nitrite which was liberated through exchange of methyl alcohol with the benzyl nitrite as was explained in the experimental section. These values for the nitrite yield are probably not as reliable as those obtained by the titration since

some of the nitrite derivatives may have been lost in the process of distilling the ether away from the sample before the determination. In the process of handling the material before the determination other small losses may have occurred. Finally, any dissolved atmospheric nitrogen in the sample would produce an error. However the agreement between the two methods is fairly good. The method shows the efficiency of the benzyl nitrite to methyl nitrite transesterification.

The small differences found in the yields of products probably are due to experimental error. The system of analysis could easily have given variances as large as one or two percent. In any case, if the two derivatives are produced by reactions of different orders, the effect of varying the reactants as much as they were in these experiments should lead to a more striking change in product ratios. The conclusion that the products are derived through reactions of equal kinetic order is also consistent with Kornblum's common transition state concept of the reaction.

Reaction Rate Order With Respect to p-Nitrobenzyl Bromide

The attempt to determine the reaction rate order with respect to p-nitrobenzyl bromide by carrying out a series of reactions for different times in a large excess of silver nitrite gave results which were not characteristic of any of the classical kinetic rate orders. The results are plotted on both zero-order and first-order coordinates in Figure 1. Three of the points on the curve are subject to some error in that after the removal of the first sample, the relative proportion of solution to silver nitrite is reduced by as much as 10%. This however was partially compensated by the fact that although over ten times

the required amount of silver nitrite was used, its available surface was decreasing slightly during the reaction. These errors should not be great enough to seriously affect the shape of the curves.

The low initial rate (15.5% complete at one hour and 44.8% complete in two hours) which was observed in this experiment is not without precedent in other reactions. In the heterogeneous reaction of an alkyl halide with magnesium turnings to give a Grignard reagent this low initial rate or induction period, presumably due to an inactive coating on the magnesium, is often observed. This phenomenon would also be expected of an auto-catalytic reaction where one of the products of the reaction acts as a catalyst for further reaction.

Induction periods are also commonly encountered in reactions at solid-gas interfaces (19). In these cases the reaction has been found to start at reactive sites on the crystal surface and spread as the reaction progresses.

CONCLUSIONS

No difference in the molar radioactivity was found between the two isomeric products and the starting material in the complete reaction of benzyl-α-C^{14} bromide with silver nitrite. The same results were obtained in the reaction of p-nitrobenzyl-α-C^{14} bromide with silver nitrite.

An appreciable over-all isotope effect is present in both reactions. Therefore, the conclusion is drawn that the kinetic isotope effect in the formation of each of the products in both reactions must be equal or so nearly equal that no difference could be detected with the precision attained in this work. This fact coupled with evidence that both products appear to arise by reactions of equal reaction rate order argues strongly against separate reaction paths with appreciably different mechanisms for the formation of the two isomeric products.

The fact that the over-all kinetic isotope effect in the reaction of silver nitrite with p-nitrobenzyl-α-C^{14} bromide was over ten percent is fortunate since an isotope effect of this magnitude should increase the sensitivity for detection of a difference in the kinetic isotope effects for the formation of the two products.

The findings of this work are consistent with the results which would be expected from a common transition state and must be considered as additional evidence for such a reaction path in the formation of the two isomeric products.

SUMMARY

Benzyl bromide and p-nitrobenzyl bromide were prepared with the alpha carbon atom of each compound labeled at the tracer level with carbon-14. These compounds are known to react with silver nitrite in diethyl ether to yield both a nitrite and a nitro derivative.

The over-all kinetic isotope effect in this reaction was determined for each of these benzyl bromides by measuring the radioactivity of the starting material and that of the remaining substrate after a known percent of reaction had occurred. From this information the experimental isotope effect was determined.

The isotope effects in the formation of each of the products were found to be equal in each of the reactions studied. This was done by carrying out 100% reactions and comparing the molar radioactivities of both the products and the starting material. The molar radioactivities of the products and starting materials were found to be equal within the limitations of experimental precision.

Both derivatives were produced by reactions of equal rate order since varying the effective concentrations of both reactants caused no change in the ratio of compounds produced.

Since no difference in the activities of the products was observed in either of the reactions studied, the isotope effect in the formation of each of the two products of the reaction must be equal. These results argue against radically different reaction paths for the formation of the

two isomeric products. However, the results are consistent with a common transition state for the formation of each of the products as was postulated by Kornblum (23).

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APPENDIX

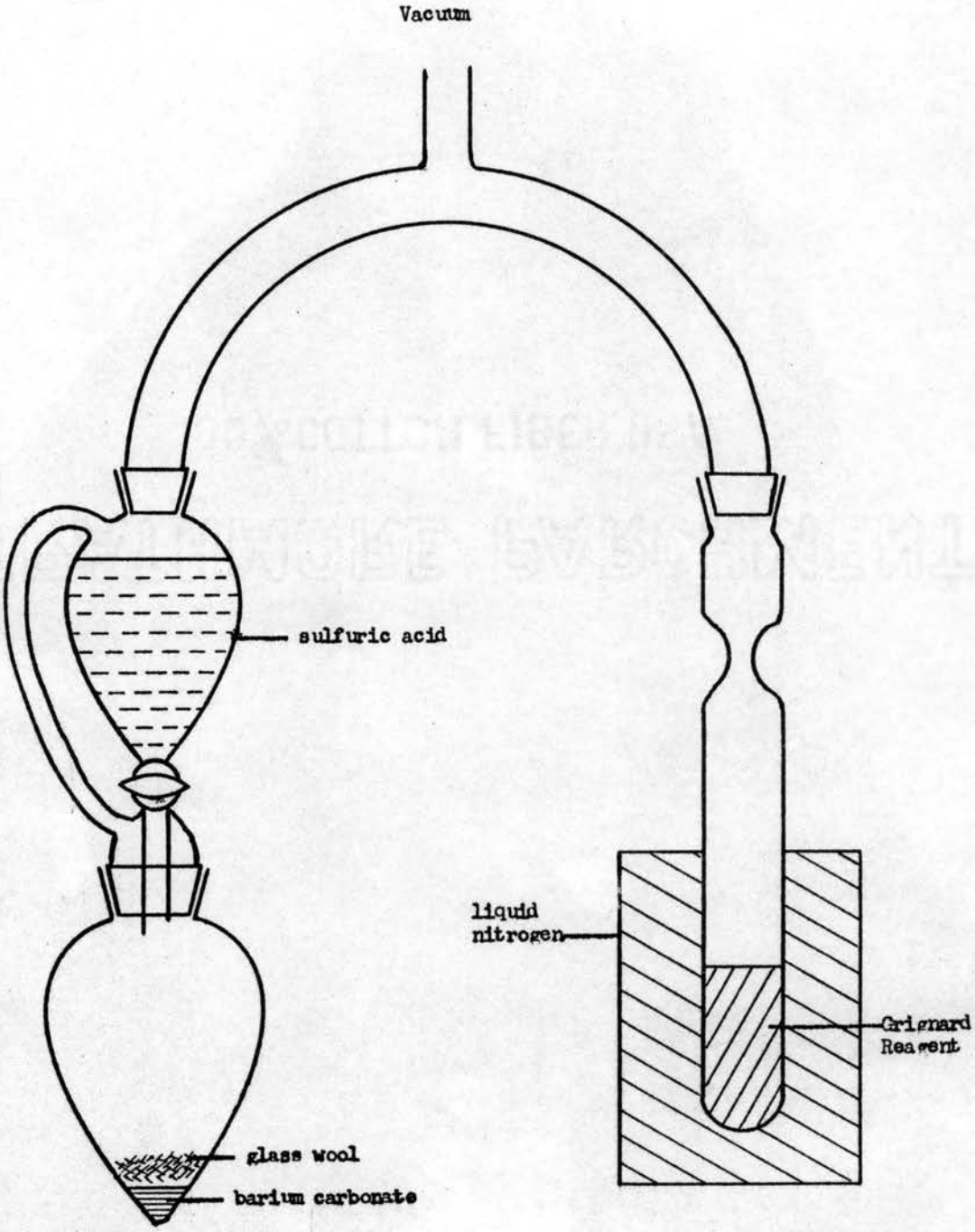

Figure 2. Apparatus for Preparation of Benzoic-α-C^{14} Acid.

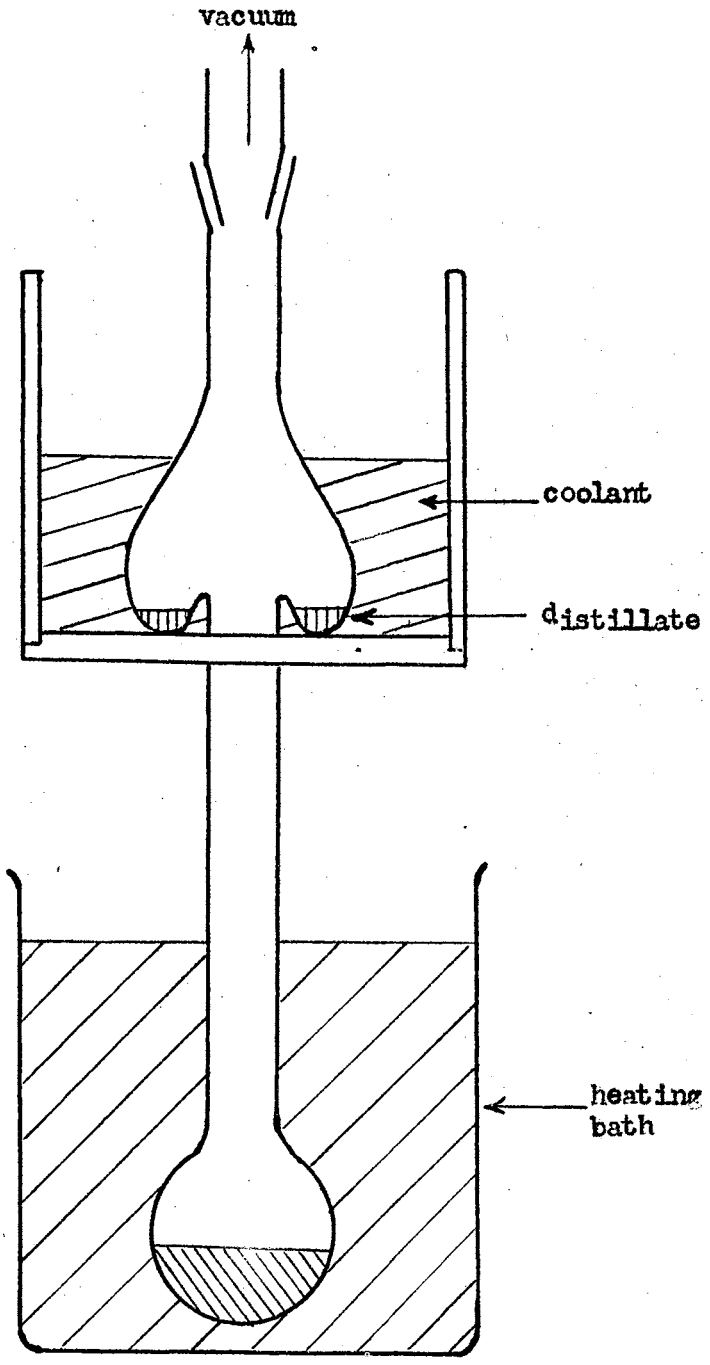

Figure 3. Micro Distillation Apparatus

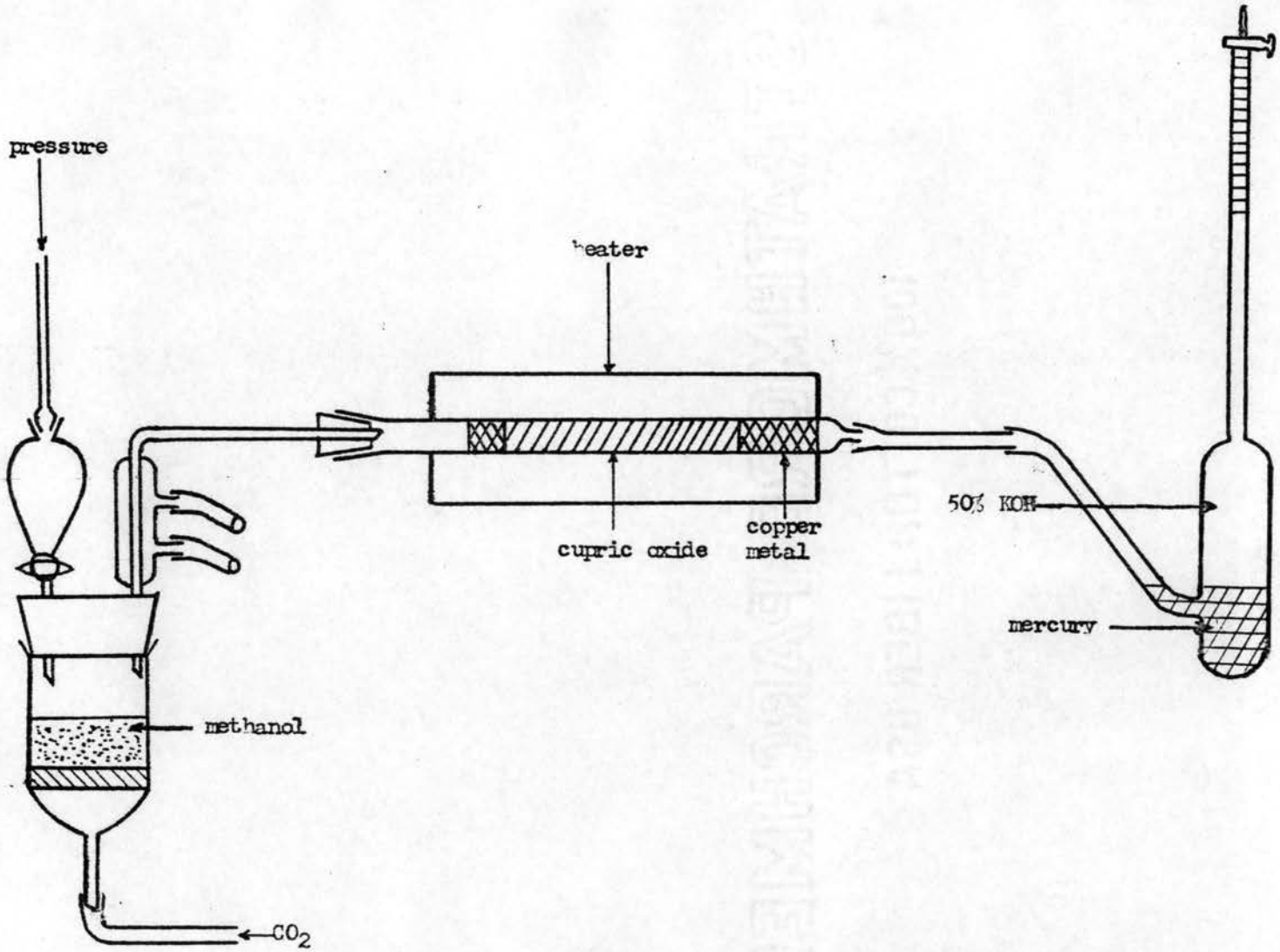

Figure 4. Nitrogen Determination Apparatus

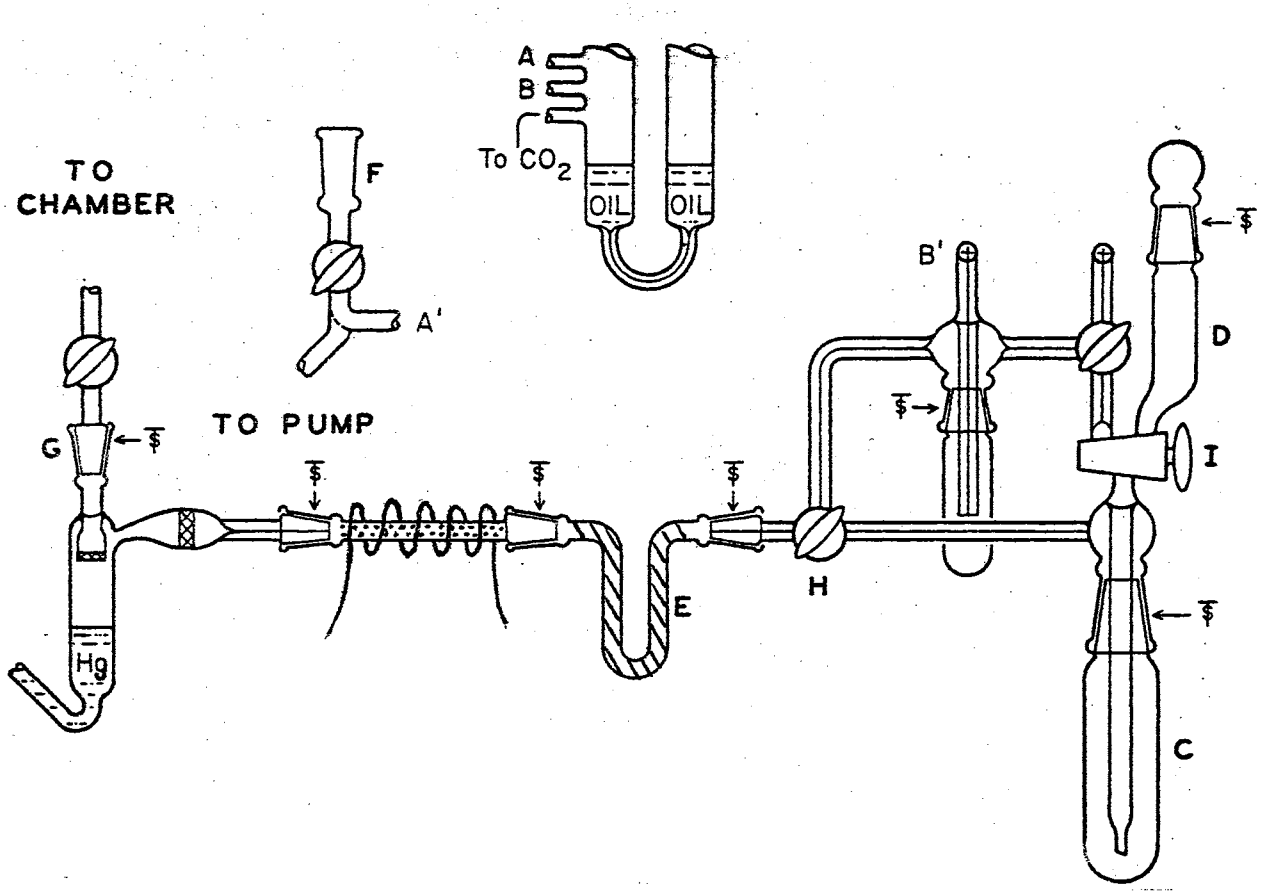

Figure 5. Wet Combustion Apparatus for the Oxidation of Radiocarbon Compounds for $C^{14}O_2$ Counting.

VITA

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