TRITIUM AND NITROGEN-15 ISOTOPE EFFECTS IN THE DECOMPOSITION OF *p*-NITROPHENETHYLTRI-METHYLAMMONIUM IODIDE

by

JOHN JOSEPH SPARAPANY

Bachelor of Science
Buena Vista College
Storm Lake, Iowa
1951

Master of Science
North Dakota State Agricultural College
Fargo, North Dakota
1953

Submitted to the faculty of the Graduate School of
the Oklahoma State University in partial
fulfillment of the requirements
for the degree of
DOCTOR OF PHILOSOPHY

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Thesis Approved:

Ernest M. Hodnett
Thesis Adviser

Henry P. Johnston

Tom E. Moore

Clarence M. Cunningham

Robert T. MacVicar
Dean of the Graduate School

ACKNOWLEDGMENT

Grateful acknowledgment is made to Dr. E. M. Hodnett, thesis adviser, for his assistance and guidance throughout this work.

Acknowledgment is also made for financial support by the Department of Chemistry in the form of a Teaching Assistantship and a Research Fellowship, the latter sponsored by the Atomic Energy Commission under Contract No. AT (11-1)-71, No. 5; the investigation described in this thesis was done as part of the above contract.

This work was conducted in the facilities of the Radioisotopes and Radiations Laboratory.

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INTRODUCTION

The object of this work was to contribute to our knowledge of the mechanism of the decomposition of quaternary ammonium salts by the Hofmann elimination. In addition, the effect of various attacking reagents on the observed isotope effect was also examined in an effort to gain some insight as to the sensitivity of the isotope effect toward the activated complex molecules.

More specifically the problem has been, first, to study the reaction kinetics of the decomposition of p-nitrophenethyltrimethylammonium iodide in aqueous and non-aqueous solutions, since the order of reaction is related to the mechanism; second, to prepare the salt labeled with tritium on the carbon β to the ammonium group; and third, to determine the tritium and nitrogen-15 isotope effects in the decomposition of the salt. Comparison of the observed isotope effects for reactions involving different attacking reagents gives some insight as to the sensitivity of the observed isotope effect to the activated complex molecules and observation of an isotope effect in the decomposition of the salt allows a more accurate decomposition path to be chosen for the mechanism of the reaction.

HISTORICAL

The Kinetic Isotope Effect

It is known that isotopic molecules do not react at identical rates if the bond to the isotopic atom is broken during the reaction. This difference in reaction rates is called the isotope effect. A theoretical treatment of the isotope effect has been prepared by Roginsky (23).

The relation between the mechanism of a reaction and the magnitude of the isotope effect has been developed by Eyring (13) on the basis of the absolute reaction rate theory. The ratio of reaction rate constants for two isotopic molecules undergoing reaction in the same vessel may be expressed as:

$$\frac{k_1}{k_2} = \frac{K_1}{K_2} \left(\frac{m_2^*}{m_1^*}\right)^{1/2} \frac{Q_{A_2}}{Q_{A_1}} \; \frac{Q_1^*}{Q_2^*} \; \frac{\delta_2}{\delta_1}$$

where:

k = rate constant.

K = transmission coefficient.

m^* = effective mass of the activated complex along the coordinate of decomposition, usually calculated from the reduced mass ($m_1 \; m_2/m_1 + m_2$) of the atoms involved in the bond being broken in the rate-controlling step of the reaction.

Q_A = complete partition function of the reactant molecule.

Q^* = complete partition function of the activated complex molecule.

δ = length of the top of the potential energy barrier.

Wiberg (29) has developed an equation, in which the ratio of the rate constants is expressed as a function of the effective masses of the activated complexes and the vibrational frequencies of the isotopic molecules.

Eyring's equation may be expressed in the form:

$$k = K \frac{C_A^*}{C_A C_B} \left(\frac{k'T}{2\pi m^*} \right)^{1/2}$$

where:

k = rate constant

K = transmission coefficient

C* = concentration of the activated complex molecules

C_B and C_A = concentration of the reactants

k' = Boltzman constant

m* = effective mass of the activated complex in the direction of the reaction

For a reaction in which two isotopic species are present, it is possible to write two such equations, one equation for each isotopic species. Assuming the subscript 1 to denote the lighter species, and the subscript 2 to denote the heavier species, these equations take the form:

$$k_1 = K_1 \frac{C_{A_1}^*}{C_{A1} C_{A2}} \left(\frac{k'T}{2\pi m_1^*} \right)^{1/2}$$

$$k_2 = K_2 \frac{C_{A_2}^*}{C_{A_1} C_{A_2}} \left(\frac{K\ T}{2\pi m^*} \right)^{1/2}$$

The quotient of these two equations is the ratio of the rate constants for the reaction.

$$\frac{k_1}{k_2} = \frac{K_1\, C^*_{A_1}\, C_{A_2}}{K_2\, C^*_{A_2}\, C_{A_1}} \left(\frac{m^*_2}{m^*_1} \right)^{1/2}$$

Wiberg substituted a free-energy term for the ratio of the concentrations, and also assumed that the transmission coefficients were the same for the isotopic species. The equation then reduced to:

$$\frac{k_1}{k_2} = \frac{f}{f^*} \left(\frac{m^*_2}{m^*_1} \right)^{1/2}$$

where:

$$f = \frac{\sigma 1}{\sigma 2} \prod^{3N-6} \frac{u_i}{u_i + \Delta u_i} \quad \frac{(1 - e^{-(u_i + \Delta u_i)})}{(1 - e^{-u_i})} \quad \exp\left(\Delta u_i/2\right)$$

σ = symmetry number

u_i = $h\nu/kT$

h = Planck constant

ν = vibrational frequency of the bond being broken

k = Boltzman constant

T = absolute temperature

Δu_i = $h(\nu_{i1} - \nu_{i2})/kT$

Unless it is possible to determine the shape of the potential energy surface, it is not possible to evaluate f*. If a value for f* cannot be estimated, the above equation can be used only to determine the maximum isotope effect for the reaction. This involves the assumption that there is no bonding in the transition state: that is, f* = 1. Wiberg therefore arrived at the following equation for the maximum isotope effect for a given reaction:

$$\frac{k_1}{k_2} = \left(\frac{m^*_2}{m^*_1}\right)^{1/2} \frac{h\nu_2}{h\nu_1} \left(\frac{1 - e^{-h\nu_1/RT}}{1 - e^{-h\nu_2/RT}}\right) \exp \frac{h\nu_1 - h\nu_2}{2RT}$$

where $h\nu$ is expressed in calories per mole. However, the last term of the equation is approximately equal to one up to about 400-500° (29), and at temperatures below this the above equation reduces to:

$$\frac{k_1}{k_2} = \left(\frac{m_2^*}{m_1^*}\right)^{1/2} \frac{h\nu_2}{h\nu_1} \exp (h\nu_1 - h\nu_2)/2RT$$

Bigeleisen and Mayer (3) have also shown that it is possible to express the ratio of the reaction rates of isotopic molecules as a function of the vibrational frequencies of the molecules. Bigeleisen (1) obtained the following equation for the ratio of the reaction rates of isotopic molecules; however, the equation is a good approximation only for small positive values of Δu.

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

$G(u) = 1/2 - 1/u + 1/(e^u - 1)$

$u = h\nu/kT$ and $\Delta u = h(\nu_1 - \nu_2)/kT$

h = Planck constant

k = Boltzman constant

T = absolute temperature

N = number of vibrational degrees of freedom

ν = fundamental vibrational frequency

This equation assumes that the transmission coefficients for the isotopic molecules are the same $(K_1 = K_2)$ and that the length of the top of the potential barrier for the isotopic molecules is the same $(\delta_1 = \delta_2)$.

It is to be expected that the lighter isotopic molecule will have the greater reaction rate, since the heavier isotopic molecule will require the greater activation energy. The term $(m_2^*/m_1^*)^{1/2}$ is greater than unity, if it is assumed that the subscript 1 refers to the lighter molecule. In bond cleavage the isotopic atoms in the reactant molecules are usually more "tightly" bonded than the isotopic atoms in the activated complex molecules, hence

$$\sum_{i}^{3N-6} G(u_i)\,\Delta u_i > \sum_{i}^{3N'-6} G(u_i^*)\,\Delta u_i^*$$

As is evident from Bigeleisen's equation, the maximum isotope effect will be observed when the isotopic atoms are essentially free from bonding in the activated complex so that

$$\sum_{i}^{3N'-6} G(u_i^*)\,\Delta u_i^* = 0$$

When the observed isotope effect is less than the maximum value calculated from Bigeleisen's equation, it indicates the occurrence of a three-center reaction in which a new bond is being formed while the old bond is being broken. Then, the zero-point energy of the activated complex tends to offset the zero-point energy of the reactant molecules. If the bonding in the activated complex molecules is as strong as the bonding of the reactant molecules, then

$$\sum_{i}^{3N-6} G(u_i)\Delta u_i = \sum_{i}^{3N'-6} G(u_i^*)\Delta u_i^*$$

and Bigeleisen's equation reduced to

$$\frac{k_1}{k_2} = \left(\frac{m_2^*}{m_1^*}\right)^{1/2}$$

In order to calculate the theoretical isotope effect for a particular reaction it is necessary to evaluate the function $G(u_i)\Delta u_i$ for the reactant molecules and for the activated complex. This calculation however requires a full knowledge of the vibrational frequencies affected by isotopic substitution in the reactant molecule and the activated complex. This information is often not available even for the reactant molecule, and hence the best that can be accomplished at present from a theoretical viewpoint is to make approximate calculations.

The term $(m_2^*/m_1^*)^{1/2}$ can be neither directly measured nor calculated exactly, since m* represents the effective mass of the activated complex along the reaction coordinate. However, Slater (25) has shown in an extensive investigation that the effective mass can, in certain cases, coincide with the reduced mass of the two atoms between which the chemical bond is broken in the decomposition of the intermediate complex.

Therefore:

$$m^* \approx \mu i = \frac{m_1 m_2}{m_1 + m_2}$$

In the application of Eyring's theory m* is often taken to be identical with the mass of the whole intermediate complex, and subsequently the vibration of the intermediate complex at one of the bonds was replaced by translation motion. In this case, instead of 3N-6, 3N-7 factors remained in the vibrational sum for the intermediate complex, and a translational factor appeared for the transition coordinate. Bigeleisen's equation also does not take into consideration the tunneling effect, which for most isotopes is negligable except in the case of hydrogen isotopes.

Bigeleisen and Wolfsburg (4) (5) have extended the isotope effect equation to include the reduced mass factor for an isotopic three-centered reaction.

In the case of three-center reactions of the type

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

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

$$X_L = \alpha \left| r_B - r_C \right| - \beta \left| r_B - r_A \right|$$

where $\left| r_B - r_C \right|$ and $\left| r_B - r_A \right|$ are the separation of B-C and B-A respectively, and β / α determines the relative amount of bond formation between A-B to bond extension between B-C in the activated complex. In considering this type of three-center reaction the isotope effect equation for simultaneous bond rupture and bond formation takes the form

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

where $p = \beta^2 / \alpha^2$ and m_x = mass of atom x

When p is equal to zero, the above equation reduces to the simple case of bond rupture; when 1/p is equal to zero it becomes the combination of two atoms, molecules or radicals. Since the use of the Bigeleisen equation requires a thorough knowledge of all the fundamental vibrational frequencies in both the normal molecule and the activated complex its use is restricted to either the calculation of the maximum theoretical isotope effect in which

$$G(u_i^*)\Delta u_i^* = 0$$

or to the few reactions in which the shape of the potential energy surface is known. A much simpler method of calculating the maximum theoretical isotope effect is available through application of the equation derived by Eyring and Cagle (9). This equation takes the form

$$\alpha = \frac{k_1}{k_2} \approx \frac{\sinh\,(h\nu_1/2kT)}{\sinh\,(h\nu_2/2kT)}$$

where:

α = maximum theoretical isotope effect

h = Planck constant

k = Boltzman constant

T = absolute temperature

ν = fundamental vibrational frequency

k_x = rate constant of the reaction involving the isotopic atom x.

The major assumption used in the derivation of this equation is that the potential barriers for analogous reactions of molecules differing only in isotopic composition are identical in form and height.

Isotope Effect of Tritium.

The mass ratio of tritium to protium is 3:1, the largest ratio exhibited by any pair of isotopes. Tritium has proven extremely useful in the elucidation of mechanisms of organic reactions, since it is easily prepared in an atomic pile by the bombardment of lithium with neutrons. However, due to the low energy of the radiation of tritium, some difficulty was encountered in obtaining accurate measurements of the activity. A method for tritium assay was developed by Wilzbach. Van Dyken, Kaplan, and Brown, in which the tritium in the combined state is converted to tritium gas and tritiated methane by reduction at 600° with zinc (27). The gas is introduced into an ionization chamber and the activity determined by measurement of the radiation-induced ionization of the gas with a vibrating reed electrometer (28).

Theoretical calculations for the isotope effect of tritium cannot be made through the use of Bigeleisen's equation, since the difference in the vibrational frequencies (Δ u) is too great for the approximations made by Bigeleisen. However, Wiberg's equation is suitable for the calculation of the maximum tritium isotope effect although the calculations are somewhat more difficult, and as in Bigeleisen's equation, no correction for the tunneling effect of tritium is applied. Roginsky (23) states that the tunneling effects of hydrogen and its isotopes are sometimes quite large, and unless this effect is corrected for, a correspondingly large error is introduced in the theoretical calculation of the isotope effect.

The Tunneling Effect of Tritium.

According to classical mechanics, in order for a particle to overcome a potential energy barrier, the particle should have energy equal to or greater than the height of the barrier. However, according to wave mechanics, the motion of a particle is analogous to the motion of a radiation wave, and waves at least partially penetrate into any barrier and, depending on its thickness, some part of the radiation passes through the barrier. In a similar way the particles leak through the energy barriers at energies insufficient to surmount them; this is called the tunneling effect or tunnel transfer. The probability of tunnel leakage of a particle falls sharply with increasing width of the potential barrier and increasing particle mass. According to Wigner (30) a correction factor of $(1-u_i^2/24)$ must be applied for hydrogen and its isotopes. Again, $u_i = hc\omega_i/kT$, where ω_i is the stretching frequency along the transition coordinate. Therefor the Wiberg equation should be multiplied by a factor of

$$\left[1 + (u_{i2}^2 - u_{i1}^2)/24 \right]$$

in order to correct for the tunneling effect.

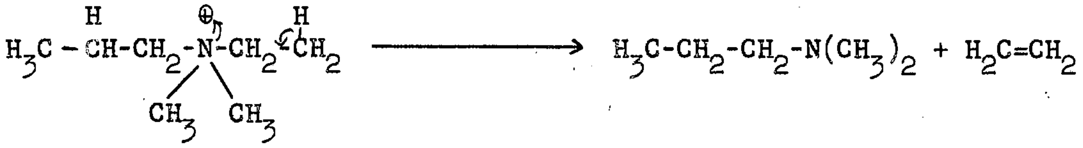
Isotope Effect of Nitrogen-15.

Although there are several radioactive isotopes of nitrogen (11) the half lives are too short to be of much practical use as tracers in the elucidation of mechanisms of organic reactions. However, the non-radioactive nitrogen-15 has been used extensively for the determination of isotope effects, and theoretical evaluation of the nitrogen isotope effect in organic reactions is possible through the use of Bigeleisen's equation, providing enough information concerning the vibrational frequencies is available.

Experimental evaluation of the nitrogen-15 isotope effect is made through the use of mass spectrographic analysis, which necessitates isolation and purification of the nitrogen in the sample as nitrogen gas.

Mechanisms of Elimination.

The Hofmann rule in elimination reaction was the first to have its underlying mechanism identified: in 1927 Hanhart and Ingold (14) recognized this rule as a consequence of the inductive effect. A heterolytic elimination always involves a strongly electron-attracting group, which, by inducing a positive charge on all the surrounding atoms, loosens the protons. A sufficient loosening of a β-proton would thereby permit elimination by an E2 mechanism. A group which, by releasing electrons, tends to neutralize the induced positive charge on the β-carbon atom, and thus strengthen its hold on the β-protons, will inhibit reaction. The terminal methyl group of the n-propyl group acts in this way, and so determines that, in accordance with Hofmann's rule, the n-propyl group will show relatively little tendency to engage in an olefin-forming process if an ethyl group is available to do so:

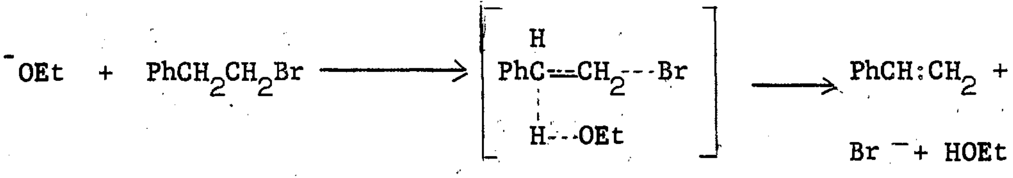


$$H_3C-\overset{H}{C}H-CH_2-\overset{\oplus}{N}(CH_3)_2-CH_2-\overset{H}{C}H_2 \longrightarrow H_3C-CH_2-CH_2-N(CH_3)_2 + H_2C{=}CH_2$$

Skell and Hauser (23) used an isotopic method to distinguish between the bimolecular and unimolecular eliminations. In studying the mechanism of the reaction of phenethyl bromide with ethoxide ion to give styrene, these investigators demonstrated that the reaction proceeds by a bimolecular mechanism. The reaction may proceed by either of the two following mechanisms:

1. $$^{-}OEt + PhCH_2CH_2Br \longrightarrow HOEt + Ph\bar{C}HCH_2Br$$

$$Ph\bar{C}HCH_2Br \longrightarrow PhCH{:}CH_2 + Br^{-}$$

2. 

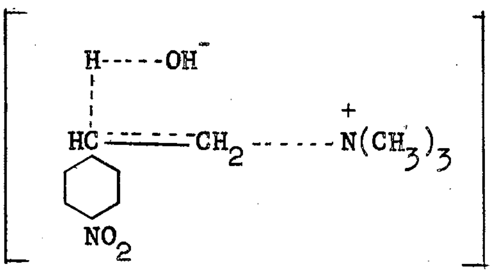
$$^{-}OEt + PhCH_2CH_2Br \longrightarrow \left[\begin{matrix} H \\ PhC{=}{=}CH_2{-}{-}Br \\ \vdots \\ H{-}{-}OEt \end{matrix}\right] \longrightarrow PhCH{:}CH_2 + Br^{-} + HOEt$$

Skell and Hauser stated that the first step in mechanism 1 must be reversible, and by using deuterated alcohol as the solvent, the recovered reactant should contain deuterium. They found the recovered phenethyl bromide to be free of deuterium, indicating the concerted mechanism to be correct.

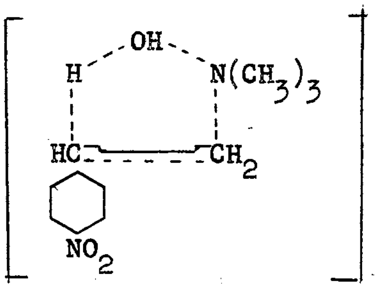
In 1933 Hughes and Ingold (18) studied the olefin-forming elimination reaction of p-nitrophenethyltrimethylammonium iodide in neutral and basic solutions at 100°. These authors found the reaction to be second order in basic solution and first order in neutral solution. The mechanism proposed in both cases was the removal of a hydrogen atom from the carbon atom beta to the ammonium group, followed by an immediate elimination of trimethylamine to form the olefin. They suggested that the hydroxide ion was the attacking reagent in basic solution and that the water molecule was the reagent in neutral solution. However, the first-order kinetics observed by Hughes and Ingold may also be explained by either of two mechanisms. It can be explained by the use of the general unimolecular mechanism (14) in which the trimethylamine splits off in a slow ionizing step followed by the loss of a beta proton in a fast step to form the olefin. Since the neutral solutions were buffered with silver oxide, the mechanism may also be explained as pseudo-first order in which the reagent is the hydroxide ion. The hydroxide ion consumed in the reaction can be regenerated by the reaction of more silver oxide with a water molecule, or by the reaction of the eliminated trimethylamine with water to form a trimethylammonium ion and a hydroxide ion.

Hughes and Ingold (18) observed the rate constant for this decomposition to be 4.0×10^{-5} sec.^{-1}

Hodnett and Flynn (17) investigated the mechanism of this elimination using the iodide salt labeled with tritium on the carbon atom beta to the ammonium group. These authors distinguished between the unimolecular and bimolecular mechanism. In their method the unreacted iodide was precipitated as the picrate and assayed for radioactivity. The p-nitrostyrene formed in the decomposition was also recovered, derivitized, and assayed with the picrates. They found an appreciable isotope effect in the decomposition which indicated that the rate-determining step of the reaction was the breaking of the carbon-hydrogen bond, showing the bimolecular mechanism to be correct. However, this did not determine whether a concerted mechanism is involved in the rate-determining step. It is possible that the carbon-nitrogen bond is broken at the same time as the carbon-hydrogen bond, leading to a transition state which may be represented as



or



Hodnett and Flynn found the value of the intermolecular isotope effect to be 2.03 ± 0.11, the intramolecular isotope effect to be 7.4 ± 2.8, and the secondary isotope effect to be 0.868 ± 0.04.

INTRODUCTION TO EXPERIMENTAL WORK

Synthesis of p-Nitrophenethyltrimethylammonium Iodide.

Phenethylamine was nitrated with fuming nitric acid by the method of Hanhart and Ingold (14). After neutralization of the excess acid with sodium hydroxide, the nitrated amine was extracted with ether and then extracted from the ethereal solution with hydrochloric acid. The amine hydrochloride was then obtained by evaporating the hydrochloric acid over a steam bath, and drying in a vacuum desiccator. The amine hydrochloride was treated with sodium hydroxide solution and the free amine extracted with ether. The free amine was then methylated by the same procedure used by Hughes and Ingold (18).

Synthesis of p-Nitrophenethyl-2-t-trimethylammonium Iodide.

Several methods for the synthesis of the labeled compound were attempted with varying degrees of success. The methods used were as follows:

1. Phenylacetic acid was allowed to exchange with tritiated water which was prepared by the method of Hodnett, Feldman, and Flynn (16). The water was distilled and the labeled phenylacetic acid reduced with lithium aluminum hydride by the method of Nystrom and Brown (22). The complex was hydrolyzed with dilute hydrochloric acid, and the tritiated phenethyl alcohol recovered. The alcohol was refluxed

with 48 per cent hydrobromic acid to convert it to the bromide. The bromide was nitrated by the method of Foreman and McElvain (10). The p-nitrophenethyl bromide was sealed in a flask containing an alcoholic solution of trimethylamine and solid potassium iodide and allowed to react for several days in the cold. The quaternary ammonium salt precipitated from the solution.

2. The labeled salt was also prepared by dissolving p-nitrophenylacetic acid in a solution of dioxan-tritiated water containing a catalytic amount of sodium hydroxide (21). After the exchange was allowed to proceed for several days, the dioxan-water solution was distilled and the labeled acid purified. The p-nitrophenylacetic acid was refluxed with thionyl chloride to prepared the acid chloride, which was then reduced with lithium borohydride. The metal complex obtained was hydrolyzed with dilute hydrochloric acid to yield the labeled p-nitrophenethyl alcohol. The alcohol was refluxed with 49 per cent hydrobromic acid and the resulting p-nitrophenethyl bromide allowed to react with trimethylamine in the presence of potassium iodide and methyl alcohol. The quaternary ammonium compound which precipitated from solution was then purified.

Synthesis of Phenethyltrimethylammonium Iodide.

Phenylacetic acid was reduced with lithium aluminum hydride by the method of Nystrom and Brown (22). The resulting phenethyl alcohol was refluxed with hydriodic acid for several hours to prepare the phenethyl iodide. The iodide was extracted with ether and the ether evaporated. The phenethyl iodide was added to a solution of 25 per cent trimethylamine in methanol and allowed to react for several days at room temperature. The product which crystallized was filtered and recrystallized from 95 per cent ethanol.

Purification of Formamide.

Eastman Kodak formamide was purified by distillation under vacuum. The fraction which distilled at 70° at 1 mm. of mercury pressure (20) was collected and the purity determined from the freezing point.

Reaction Kinetics.

In order to determine which nucleophilic reagent or reagents were responsible for the decomposition of the iodide salt in water solutions, several kinetic runs were made using the non-radioactive compound. The main objects of these runs were to determine the order of reaction with respect to each reactant, and to determine the rate constant of the reaction.

Two runs were performed using the same hydroxide ion concentration and different initial concentrations of the iodide salt to determine the order of the reaction with respect to the iodide salt. Several other runs were performed using the same initial concentrations of the iodide salt, and different hydroxide ion concentrations, and a method was developed for determining the order of reaction with respect to the hydroxide ion from these data.

The kinetic runs were performed as follows: A weighed portion of the iodide salt was dissolved in 50 ml. of buffer solution, and 5 ml.-aliquots placed in separate vials. The vials were sealed and placed in an oil bath at 98.30 ± 0.05°. The vials were removed from the bath at various times and the unreacted salt precipitated as the picrate. The picrates were filtered and weighed to determine the extent of reaction, and plots were made of the logarithm of the fraction unreacted versus time.

For the kinetic runs in which alcohol was used as the solvent and formamide and N,N-dimethylformamide used as the reagents, samples of the iodide salt were weighed into separate vials, and the appropriate amount of the solution pipetted into each vial. The vials were sealed and placed in an oil bath. The samples were then treated in the same manner as those in aqueous solutions.

Determination of the Isotope Effect with Tritium.

The decomposition of the iodide salt labeled with tritium on the carbon atom beta to the ammonium group was conducted in water solutions at two hydroxide ion concentrations to determine whether the rate of the reaction had any effect on the magnitude of the isotope effect. According to the theoretical equations used to calculate the isotope effect, the isotope effect should have no dependancy on the concentration of the reactants. However, there is some experimental evidence to support the idea that the more rapid the reaction, the less selective the reaction becomes.

The decomposition of the salt was also conducted in alcoholic solutions of formamide and N,N-dimethylformamide to determine if a difference in the attacking reagent would produce a measurable difference in the magnitude of the isotope effect. According to the Wiberg and Bigeleisen equations, the magnitude of the isotope effect is dependent in part upon the vibrational frequencies of the activated complex. By using a different reagent the vibrational frequencies of the activated complex could be expected to be somewhat different, but whether the difference is large enough to cause a measurable difference in the isotope effect is not known. Also, these equations utilize the reduced mass in lieu of the effective mass of the activated complex along the reaction coordinate. This may also be somewhat in error and may be discernable by using different nucleophilic reagents.

The samples used for radioactive assay were prepared in a similar manner as those used for the kinetic studies, and the activity of the picrates determined using a vibrating reed electrometer. A large sample of the iodide salt was allowed to react until approximately 5 to 10 per cent of the salt had decomposed, and the *p*-nitrostyrene formed by the decomposition of the salt was converted to the dibromide and assayed along with the picrates for radioactivity.

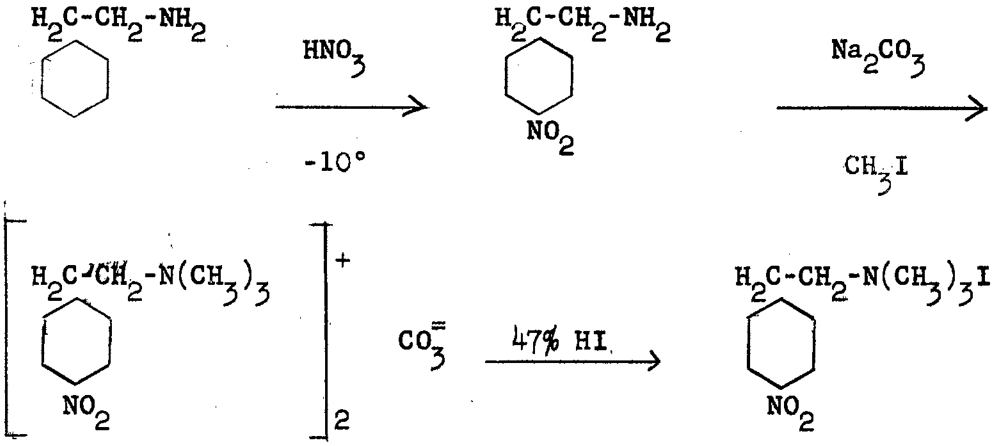
Determination of the Isotope Effect with Nitrogen-15.

The decomposition of the iodide salt labeled with nitrogen-15 was conducted in an aqueous solution buffered at a pH of 6.0. Samples of nitrogen were obtained for mass spectrographic analysis from the unreacted iodide salt by allowing the unreacted salt to precipitate from solution, and collecting the nitrogen contained in the unreacted salt by a modified Dumas method.

EXPERIMENTAL PROCEDURES

Synthesis of p-Nitrophenethyltrimethylammonium Iodide

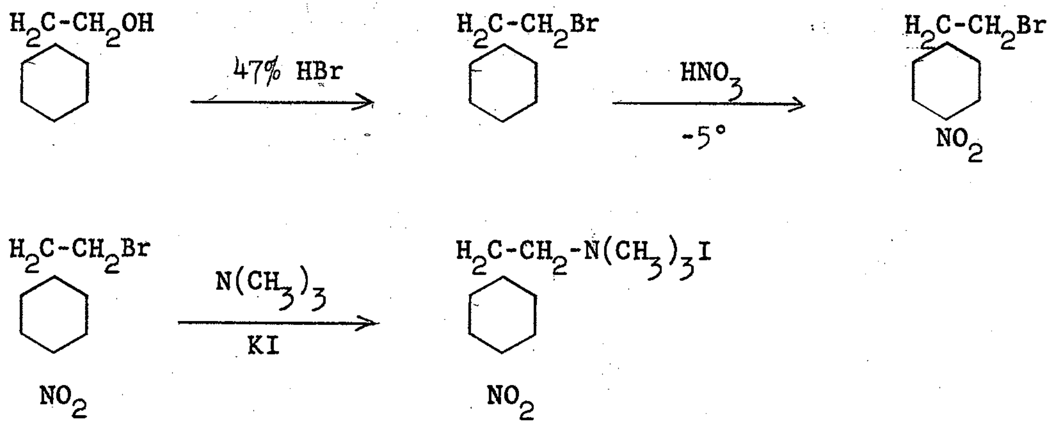
The compound was initially prepared according to the following scheme:



Twenty grams of phenethylamine was added in the course of 1.5 hours to 100 ml. of fuming nitric acid (sp. gr. 1.49-1.50) at -10°. Nitration appeared to follow almost immediately with the evolution of heat. Upon completion of the addition of the nitric acid, the solution was allowed to warm to 0° and was then made basic by the addition of solid sodium hydroxide. The product was extracted with ether, and re-extracted from the ethereal solution with hydrochloric acid. The product was recovered as the hydrochloride salt by evaporation of the solvent over a steam bath. Recrystallization of the p-nitrophenethylamine hydrochloride from 95 per cent alcohol gave 24.6 g. of almost colorless plates which melted at 209-210°; lit. (14) 210°.

The p-nitrophenethylamine hydrochloride was neutralized with 6 N sodium hydroxide and the amine extracted with ether. Upon evaporation of the ether, 37 g. of sodium carbonate and 37 ml. of absolute ethyl alcohol were added to the free amine. With care, 52 ml. of methyl iodide was added to the solution. The methylation took place with the evolution of heat and was completed by refluxing the solution over a steam bath. The carbonates were removed by filtration, washed with ether, and neutralized with 47 per cent hydriodic acid. The quaternary ammonium iodide was filtered, washed with acetone and ethyl ether, and crystallized from 95 per cent ethyl alcohol. Fifteen grams of yellow leaflets were obtained which melted at 203-204°; lit (18) 199°. The over-all yield based on the β-phenethylamine was 26.8 per cent.

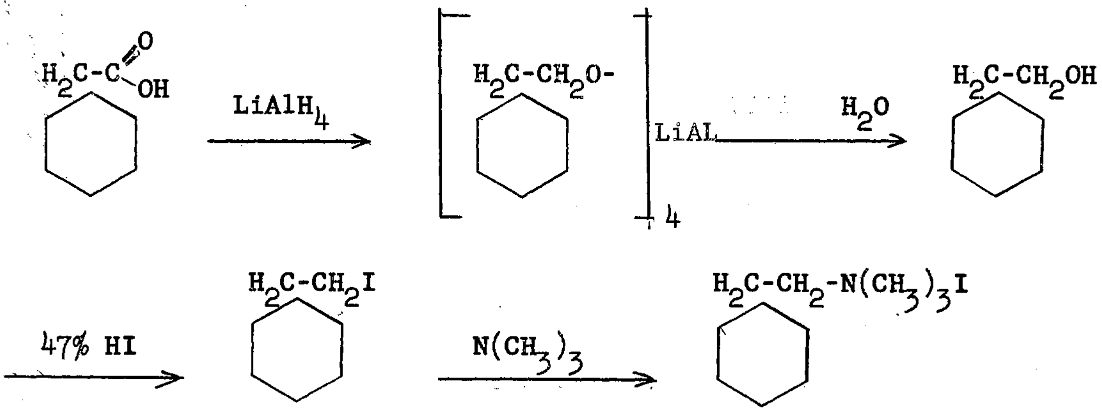
The synthesis of the p-nitrophenethyltrimethylammonium iodide was also accomplished according to the following scheme:



Phenethyl alcohol (4.5 g.) was refluxed for 18 hours with 17 g. of 47 per cent hydrobromic acid containing 2.6 g. of concentrated sulfuric acid. The solution was diluted with water and the phenethyl bromide extracted with ether. The p-nitrophenethyl bromide was prepared by the method of Foreman and McElvain (10) by cautiously adding the phenethyl bromide to a solution of acetic acid-acetic anhydride containing a slight excess of fuming nitric acid. Upon completion of the addition of the phenethyl bromide, the solution was allowed to react for an additional two hours with constant stirring. The reaction mixture was poured into 100 ml. of water containing 15 g. of sodium carbonate. The yellow product which separated was taken up in benzene and the benzene evaporated over a steam bath. The product was placed in a glass-stoppered Erlenmeyer flask with 5 g. of solid potassium iodide and 20 ml. of a solution of 25 per cent trimethylamine in methanol. The mixture was allowed to react for several days at room temperature. The yellow crystals which separated were filtered from the solution, washed with a minimum of slightly acidified water to remove the potassium iodide, and the quaternary ammonium salt crystallized from 95 per cent ethyl alcohol. The melting point of the product was observed to be 204-207°.

Synthesis of Phenethyltrimethylammonium Iodide

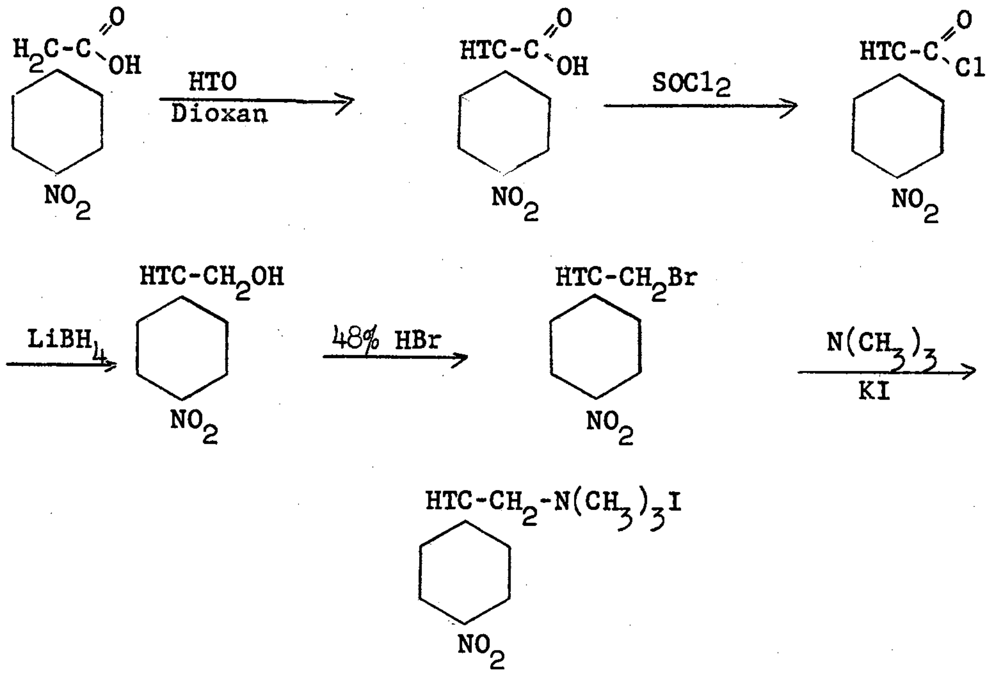
Phenethyltrimethylammonium iodide was prepared in excellent yields according to the following scheme:



Twenty grams of phenylacetic acid was dissolved in ether and reduced with lithium aluminum hydride according to the method of Nystrom and Brown (22). The excess hydride and the hydride complex were removed by the addition of dilute hydrochloric acid. The phenethyl alcohol which formed was extracted from the mixture with several portions of ether, and the ether evaporated. Seventy milliliters of 47 per cent hydriodic acid was added to the phenethyl alcohol and the solution refluxed for 12 hours. The solution was neutralized with sodium carbonate and the phenethyl iodide extracted with ether. Thirty milliliters of a solution containing 25 per cent trimethylamine in methanol was added to the phenethyl iodide and the mixture allowed to react at room temperature for several days. The crystals which formed were filtered, washed with ether, and dried in a vacuum desiccator. The melting point of the product was observed to be 227-231°; lit. (19) 227-230°.

Synthesis of p-Nitrophenethyl-2-t-trimethylammonium Iodide

The labeled salt was prepared according to the following scheme:



Ten grams of p-nitrophenylacetic acid was dissolved in a solution of 1 ml. of tritiated water (92 mc./g.), 10 ml. of dioxan and a trace of sodium hydroxide (21). The exchange was allowed to take place for three days at 98°. The water-dioxan solution was distilled on a vacuum line, and collected in a flask cooled in a dry ice-alcohol solution. The acid was recrystallized by dissolving it in boiling water and then adding concentrated hydrochloric acid. The tritiated acid was refluxed with thionyl chloride (10 ml.) until fuming ceased. The excess thionyl chloride was removed by vacuum distillation until the acid chloride crystallized. Five milliliters of benzene was added to the acid chloride and then distilled under vacuum to remove the last traces of thionyl chloride. The acid chloride was then reduced with an ethereal solution of lithium borohydride. After purification, the resulting p-nitrophenethyl alcohol was refluxed with 47 per cent hydrobromic acid (30 ml.) for several hours, and diluted with water to crystallize the bromide. The p-nitrophenethyl bromide was recrystallized from petroleum ether (boiling range 61-75°). The melting point of the product was observed to be 66-68°; lit. (10) 68°.

Six and one-half grams of the bromide was placed in an Erlenmeyer flask with 6 g. of potassium iodide and 16 ml. of trimethylamine solution. The mixture was allowed to react at 2° for several days, and the product which crystallized was filtered. The solid was washed with dilute hydrochloric acid to remove the potassium iodide. The p-nitrophenethyltrimethylammonium iodide was recrystallized from 95 per cent ethanol and dried in vacuo. The melting point of the iodide salt was observed to be 200-203°; lit. (18) 199°.

The salt was assayed on a vibrating reed electrometer for radioactivity by the method of Wilzbach, Kaplan and Brown (28). The activity of the salt was found to be 34.16 µc./mmole. Approximately 3 g. of the labeled salt was diluted with 15 g. of non-radioactive salt and then recrystallized from 95 per cent ethanol to effect homogeneity. The diluted salt was assayed and the activity was found to be 6.04 µc./mmole.

Purification of Formamide

Approximately 0.8 g. of calcium oxide was added to 250 ml. of Eastman Kodak formamide and the mixture vacuum distilled. The formamide which distilled at 70° at a pressure of 1 mm. of mercury was collected and the purity determined by the freezing point (20). The pressure during the distillation was maintained by the use of a Todd manostat (26) and measured with a Zimmerli gage. The freezing point of the purified formamide was 2.45-2.50°; lit. (15) 2.55°.

Kinetic Studies in Aqueous Solutions

The kinetics of the decomposition of the quaternary ammonium salt were studied in water solutions buffered at pH values of 4.60, 5.30, 6.00, 6.20, 6.60, and 7.00. The buffer solutions were prepared according to Clark and Lubs (6).

Approximately 2.4 g. of the quaternary ammonium salt was dissolved in enough buffer solution to bring the total volume to 50 ml. Five-milliliter aliquots were pipetted into several vials and the vials sealed and placed in a constant-temperature bath maintained at 98°. At various times the samples were removed from the bath, the vials broken, and the unreacted salt precipitated as the picrate. The picrates were filtered and weighed to determine the extent of reaction. A plot was then made of the logarithm of the fraction unreacted versus time, and the rate constant determined from the slope of the line.

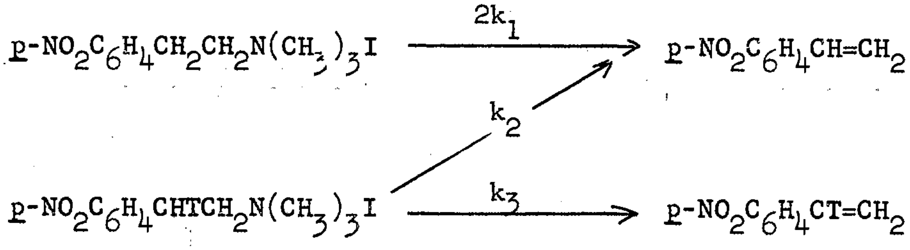
Kinetic Studies in Non-Aqueous Solutions

The kinetics of the decomposition of the quaternary ammonium salt were also studied in alcohol, alcohol-formamide, and alcohol-N,N-dimethylformamide solutions.

Approximately 0.240 g. of the iodide salt was weighed into separate vials, and 5 ml. of solution pipetted into each vial. The contents of the vials were cooled to prevent combustion of the vapors during the sealing of the vials. After the vials were sealed, they were placed in a constant-temperature bath maintained at 98°. The samples were removed at various intervals, and the unreacted salt precipitated as the picrate. The picrate was filtered and weighed to determine the extent of reaction. A correction factor had to be applied to the weight of the picrate due to its solubility in the solution. The rate constants for the decomposition were determined from the slope of the line obtained by plotting the logarithm of the fraction unreacted versus time.

Determination of the Isotope Effect with Tritium

The decomposition of p-nitrophenethyl-2-t-trimethylammonium iodide may occur in one of three ways:



Samples of the iodide salt were weighed into vials and the solvent to be used was added to each vial (approximately 1 ml. per 0.1 g. of salt). The vials were sealed and placed in an oil bath at 98°. Samples were removed at various times corresponding approximately to 5, 40, 50, 60, and 80 per cent reaction and the unreacted iodide salt was precipitated with saturated picric acid. The picrates were filtered, weighed and assayed according to the method of Wilzbach, Van Dyken, Kaplan, and Brown, (27, 28). Two samples were removed from the bath at approximately 5 per cent reaction, one in which the unreacted salt was treated as previously mentioned and the second in which the p-nitrostyrene formed by the decomposition was extracted with carbon tetrachloride and treated with bromine to form the dibromo derivative of the p-nitrostyrene. The p-nitrostyrene dibromide was then recrystallized from a methanol-water solution, dried, weighed, and assayed for tritium. The isotope effect was then calculated from these data by the following equations (2):

$$(k_2 + k_3)/2k_1 = 1 + \frac{\log N_1/N_2}{\log (1-f)}$$

$$k_3/2k_1 = N_3/N_2 \quad (\text{as } f \longrightarrow 0)$$

where:

f = fraction reacted

N_1 = molar activity of reactant at time corresponding to f

N_2 = molar activity of initial reactant

N_3 = molar activity of product

It is evident from the above equations that in order to determine $k_3/2k_1$, it is necessary to measure the extent of reaction and to isolate and measure the activity of the product at one or more low extents of reaction. It is also evident from the above equations that in order to determine $(k_2 + k_3)/2k_1$ it is necessary to measure the extent of reaction and measure the activity of the reactant at one or more higher extents of reaction.

The picrates were assayed on a vibrating reed electrometer and the readings obtained in millivolts. These readings were converted to microcuries/millimole (μc./mmole) with the aid of the following constants:

3.09×10^{-17}	coulombs/disintegration of tritium in methane
3.70×10^{10}	disintegrations/second for one curie.
1.0×10^{12}	ohms (resistance of electrometer)

Determination of the Isotope Effect with Nitrogen-15

The decomposition of the iodide salt containing nitrogen-15 was conducted in an aqueous solution buffered at a pH of 6.0. The salt was not enriched with nitrogen-15, since the amount of nitrogen-15 occurring naturally was sufficient. The nitrogen samples used for mass spectrographic analysis were obtained from the unreacted iodide salt by a modified Dumas method.

Approximately 0.5 g. of the iodide salt was weighed into each of three reaction vials, and 10 ml. of buffer solution pipetted into each vial. The vials were sealed and placed in a constant temperature bath maintained at 98°. The samples were removed from the bath after 84 hours, corresponding to 80 per cent reaction. The unreacted salt which precipitated on cooling of the solution was filtered and dried in a vacuum desiccator overnight. The filtrate was added to 30 ml. of saturated picric acid solution but no precipitate appeared, indicating that the amount of iodide salt remaining in solution was less than the solubility of the picrate. The dried salt was weighed into a porcelain boat, and the salt pyrolysed in the apparatus shown in Figure 1. The apparatus was swept with carbon dioxide until all the air was expelled and the bubbles passing through the mercury dissolved in the potassium hydroxide. The level of the potassium hydroxide solution was brought up to stopcock A, and the stopcock closed. Stopcock B was opened to the vacuum and the nitrogen ampule and drying tube evacuated. When the pressure in the nitrogen ampule and drying tube was approximately 0.1 micron, the boat containing the iodide salt was moved into the heater by means of a magnet and a steel ball bearing. The temperature of the heater was maintained at 620°. A steady stream of carbon dioxide swept the combustion gases through the copper oxide and copper gauze, and the nitrogen collected in the gas collector. Upon completion of the combustion, stopcock A was opened, and the nitrogen allowed to expand into the drying tube and nitrogen ampule. The ampule was then sealed at point C, and marked for identification.

The results of the first mass spectrograph analysis indicated several impurities in the nitrogen and the remaining nitrogen samples were purified by cycling several times through the apparatus shown in Figure 2. The system was evacuated to a pressure of 0.1 micron and stopcocks adjusted to permit cycling of the sample in the direction indicated by the arrows. The temperature of the heater was maintained at 482° and the break-off tip in the sample holder broken. From 10 to 12 complete cycles of the Toepler pump were made and the trap immersed in liquid nitrogen. Several additional cycles of the pump were made in order to remove the condensables from the system. Stopcock B was then adjusted to permit pumping of the gas into the sample collector. After several complete cycles of the pump, the mercury in the pump was allowed to rise into joint E, and the sample collector sealed at point D.

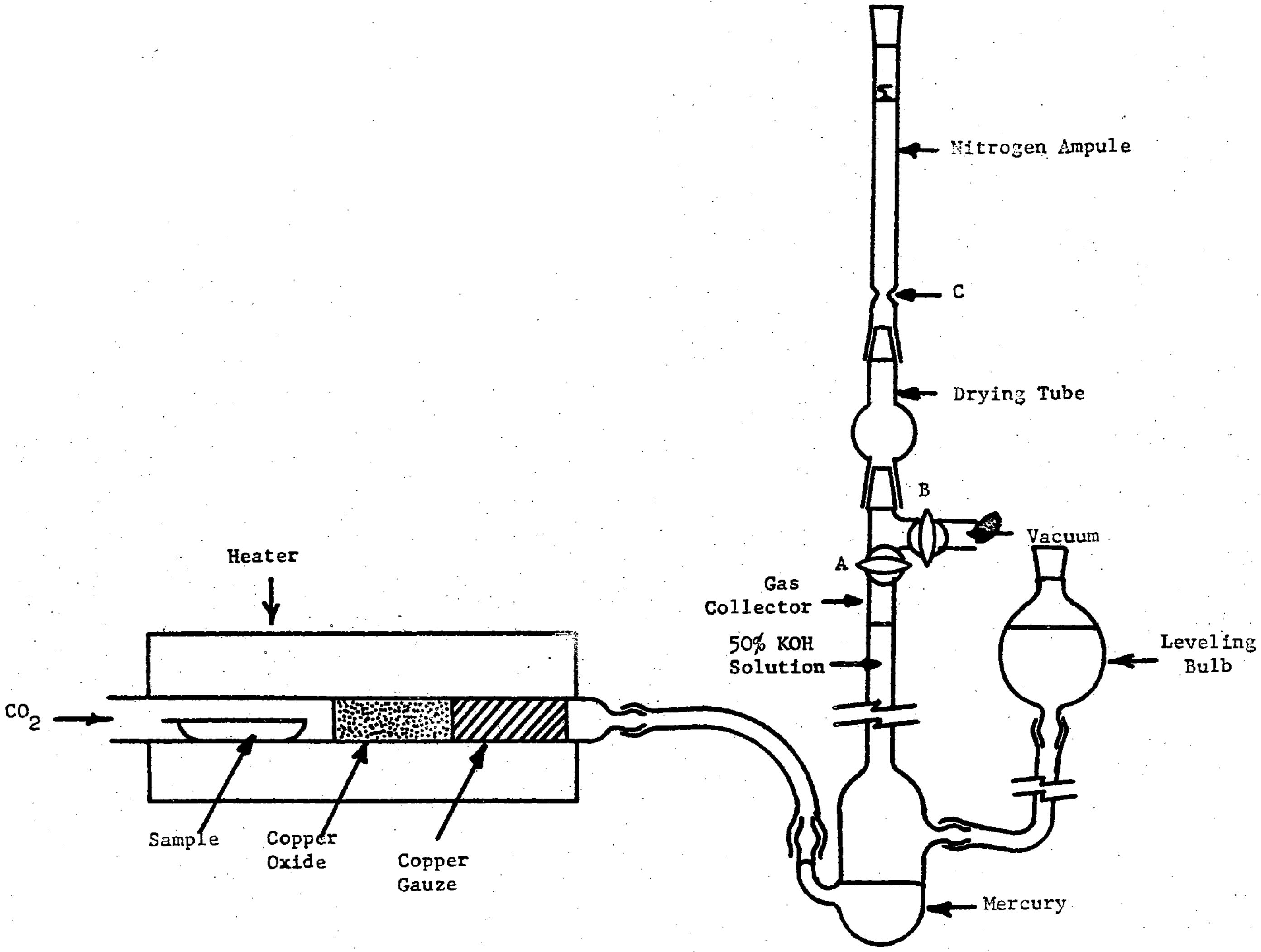


Figure 1. Combustion Apparatus for Collecting Nitrogen for Mass Spectrographic Analysis

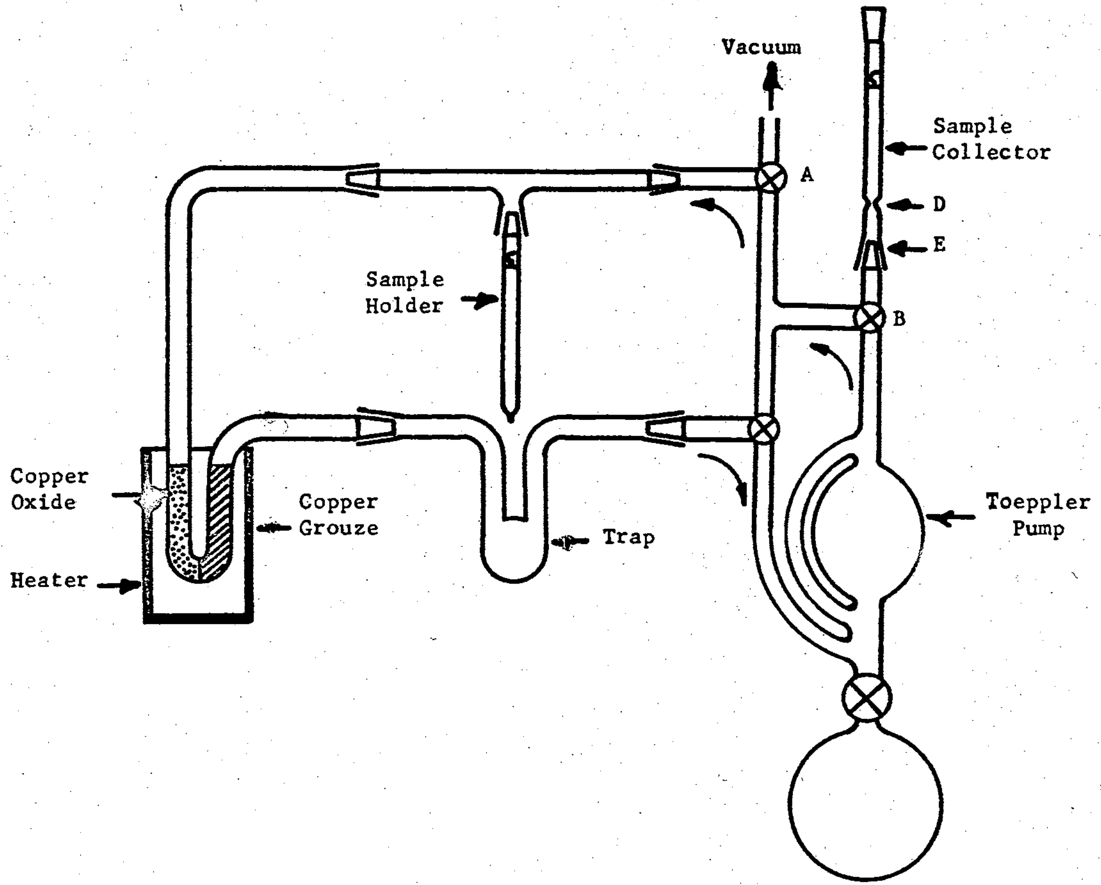


Figure 2. Apparatus for Purification of Nitrogen Samples

RESULTS

Determination of Order of Reaction with Respect to the Iodide Salt

Two methods were utilized for the determination of the order of the reaction with respect to the iodide salt. The method of half lives as outlined by Frost and Pearson (12) was the first method applied to the reaction.

Two consecutive decompositions were conducted using the same hydroxide ion concentration but different initial concentrations of the iodide salt. A plot of the concentration of the iodide salt versus time gave reaction curves from which the half life of the reaction could be determined. However, some interference of the p-nitrostyrene with the picrate was experienced, and the fraction of unreacted salt could not be determined with any degree of accuracy above 20 per cent reaction. It was therefore necessary to extrapolate to 50 per cent reaction to determine the half life of the reaction. These curves are represented in Figure 3. Since extrapolation over a relatively large per cent reaction was necessary, the order of the reaction with respect to the iodide salt was also determined by the fractional life period method. This method is closely related to the method of half lives. By use of the equation

$$\frac{\left(\frac{\Delta X_1}{\Delta T}\right)}{\left(\frac{\Delta X_2}{\Delta T}\right)} = \left(\frac{X_1}{X_2}\right)^m$$

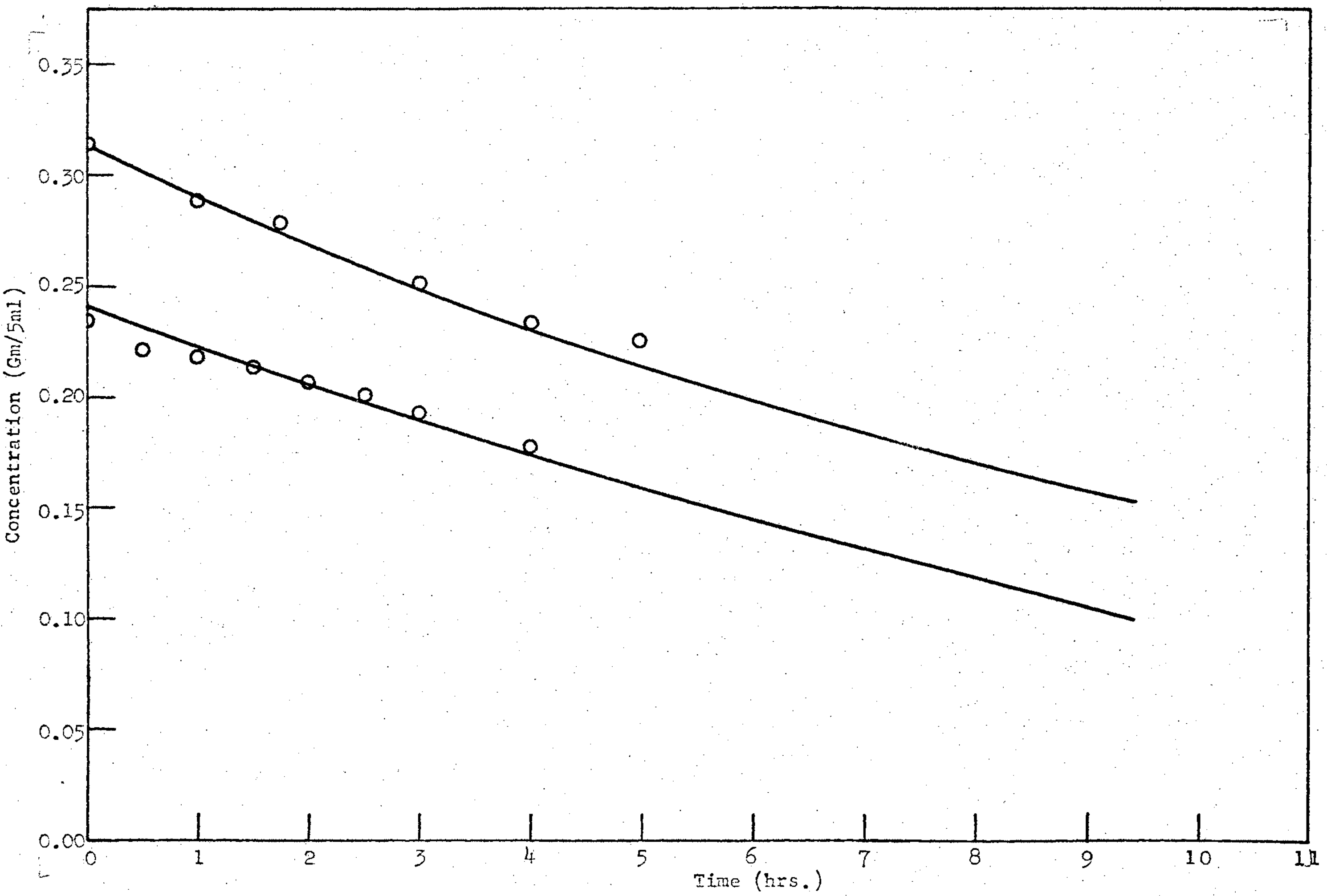


Figure 3. Determination of Order of Reaction by Half-Lives

where:

X_1 = initial concentration of the salt for run 1

X_2 = initial concentration of the salt for run 2

n = order of reaction with respect to the iodide salt

T = time

Values obtained for the order of reaction with respect to the iodide salt are listed in Table I.

TABLE I

ORDER OF THE REACTION WITH RESPECT TO THE IODIDE SALT

Time, T, Hours	Change in Concentration*		Order, n
	ΔX_1	ΔX_2	
0			
	0.3025	0.2290	0.94
0.5			
	0.2925	0.2220	0.93
1.0			
	0.2820	0.2137	0.94
1.5			
	0.2720	0.2070	0.92
2.0			
	0.2520	0.1915	0.93
3.0			

*Values for ΔX_1 and ΔX_2 refer to corresponding ΔT and not to total elapsed time.

Determination of Rate Constants for the Reaction in Aqueous Solutions

Several decompositions were conducted at various hydroxide ion concentrations of the solvent. The various hydrogen ion concentrations of the solution ranged from pH of 4.6 to pH of 7.0 inclusive. For each run conducted at a single hydroxide ion concentration of the solution, a plot was made of 2.303 log A/A_o versus time, where A_o represents the initial concentration of the iodide salt, and A represents the concentration of the iodide salt at time t. The resulting curves are shown in Figures 4, 5, and 6. Since the solutions were buffered, the value of the slope of the lines obtained from these plots must be divided by the corresponding hydroxide ion concentration to obtain the rate constant for the reaction. The rate constants obtained by this method are listed in Table II.

TABLE II

RATE CONSTANTS AS A FUNCTION OF HYDROXIDE ION CONCENTRATION

pH	Slope, hr^{-1}	Hydroxide Ion Concentration, moles/liter	Reaction Rate Constant, liters/mole sec.
4.60	0.000857	3.98×10^{-10}	597 ± 21
5.30	0.00421	2.00×10^{-9}	586 ± 61
6.00	0.0218	1.00×10^{-8}	606 ± 51
6.20	0.0316	1.59×10^{-8}	553 ± 63
6.60	0.0774	3.98×10^{-8}	542 ± 39
7.00	0.151	1×10^{-7}	447 ± 28

Determination of Rate Constants for the Reaction in Non-Aqueous Solutions

The decomposition of the iodide salt was determined in absolute ethanol, however no reaction was detected over a period of 120 hours. Due to the inertness of the alcohol as a reagent, alcohol was used as a solvent in subsequent non-aqueous studies. A solution containing 6.01 per cent by weight of formamide in absolute ethanol was used to study the decomposition of the salt. The results of this decomposition are illustrated in Figure 7. The rate constant, obtained by dividing the slope of the line (0.0711) in Figure 5 by the concentration of

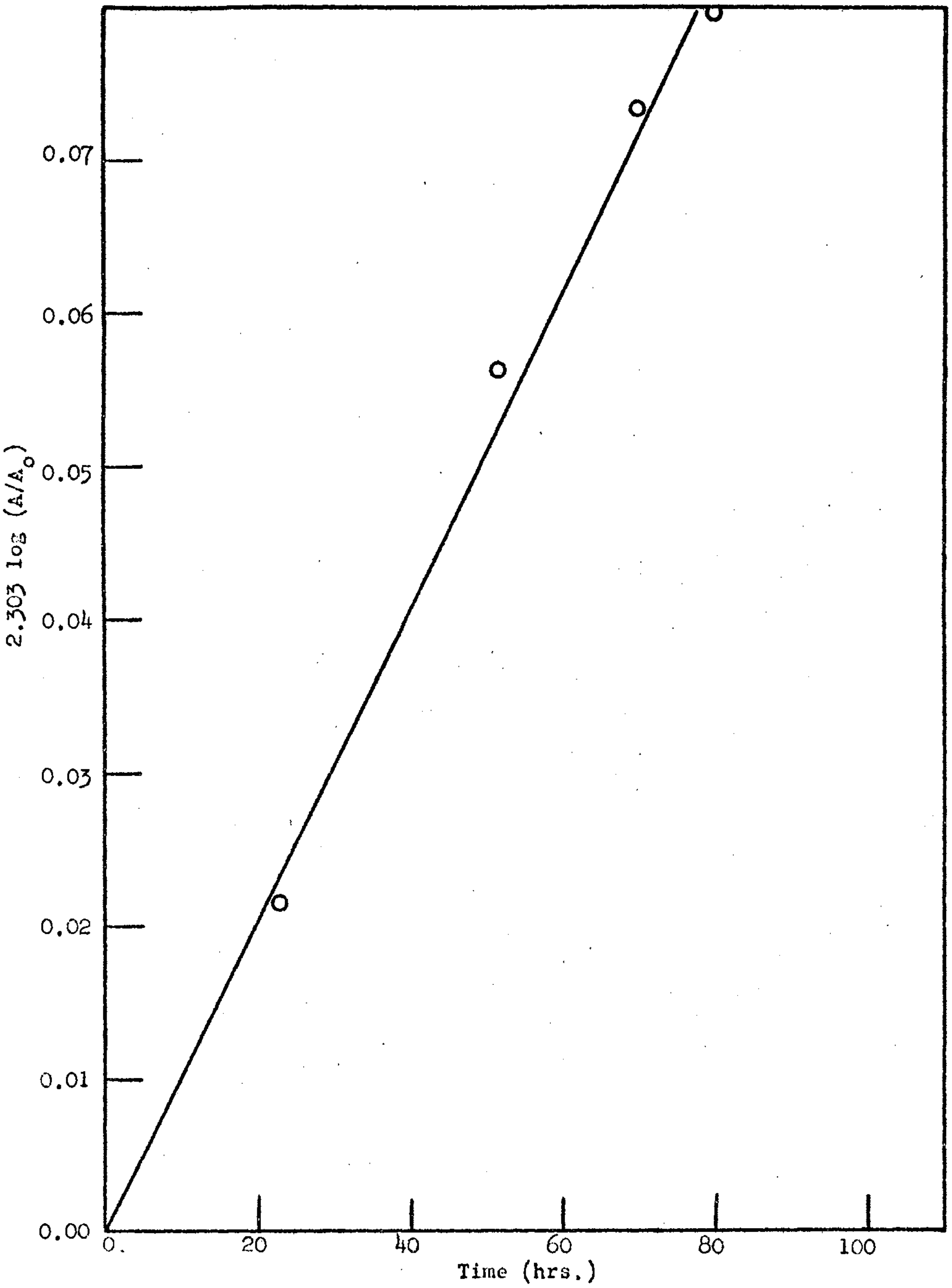


Figure 4. Decomposition of Iodide Salt at pH of 4.60

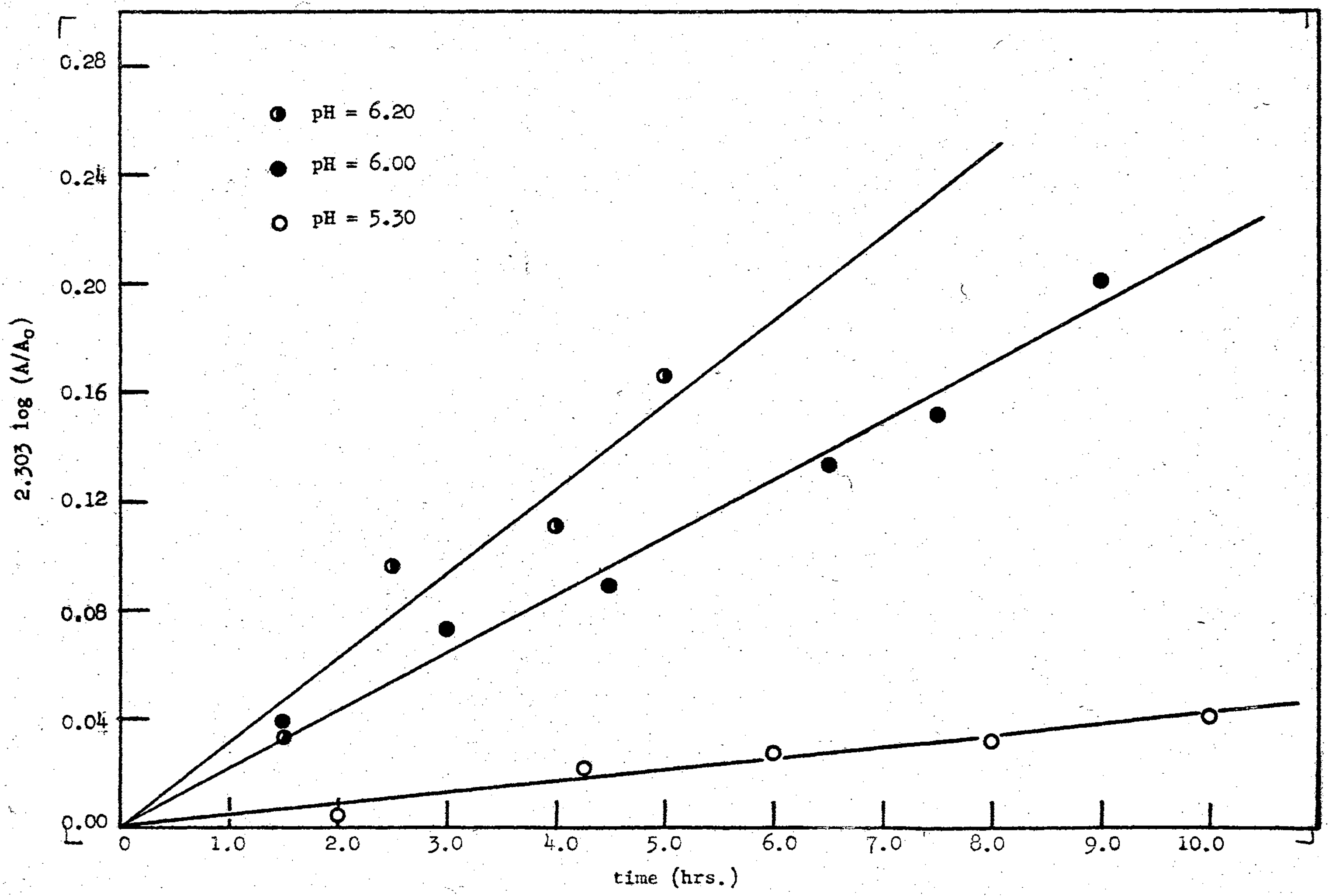


Figure 5. Decomposition of Iodide Salt at pH of 5.30, 6.00, and 6.20

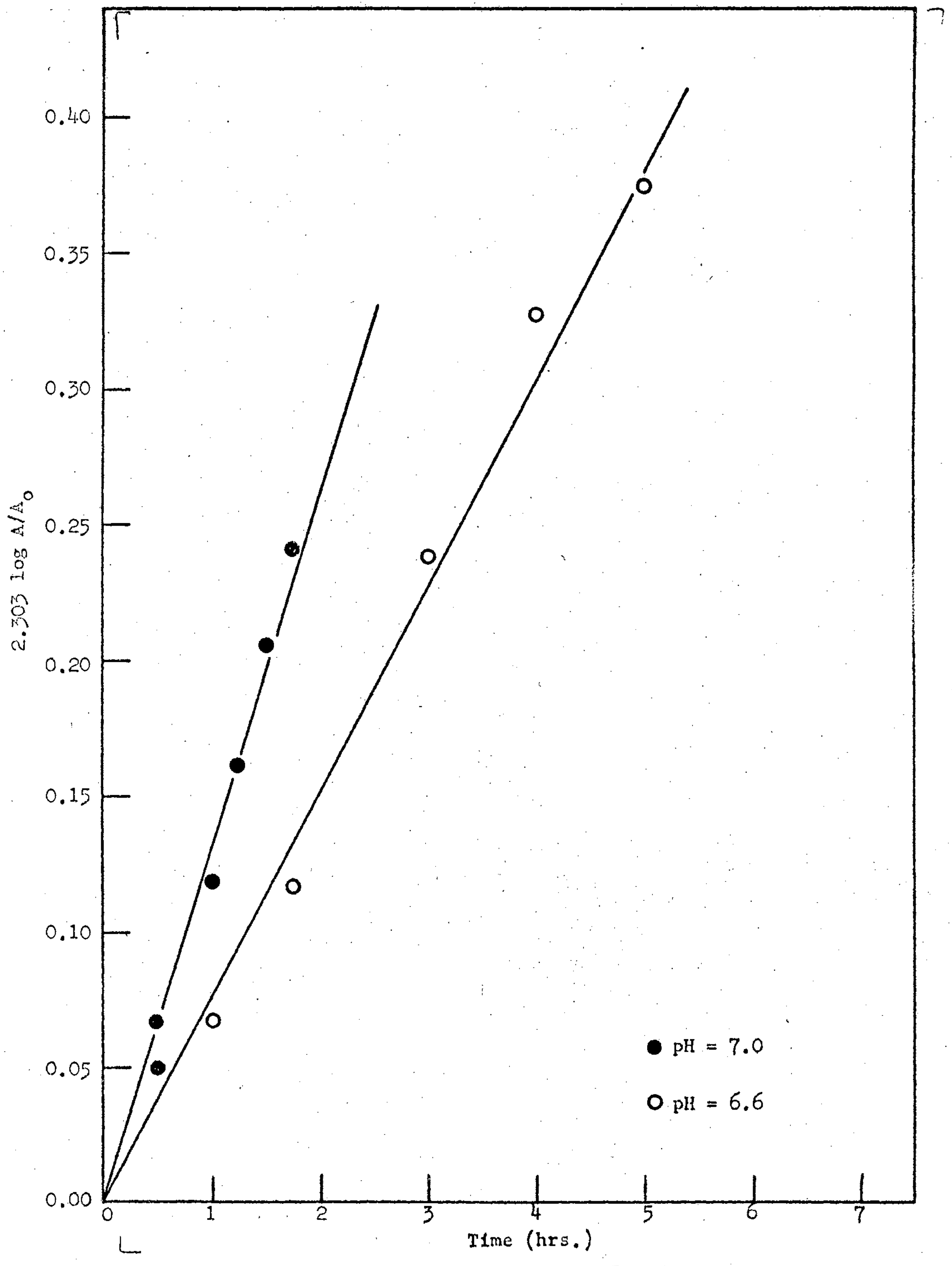


Figure 6. Decomposition of Iodide Salt at pH of 6.60 and 7.00

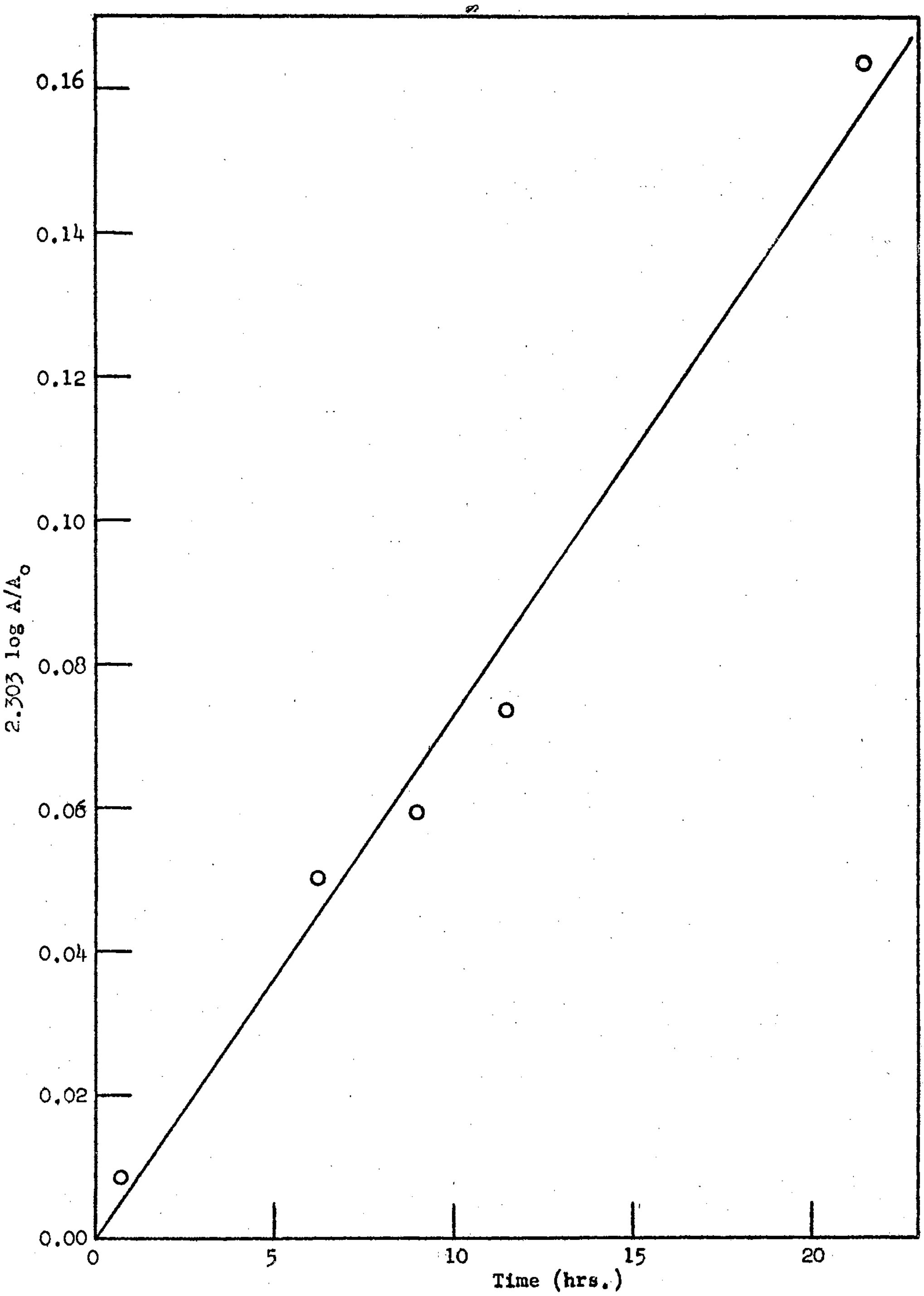


Figure 7. Decomposition of Iodide Salt in 6.01% Formamide

formamide (1.006 moles/liter), was found to be 1.97 ± 0.18 x 10^{-5} liters/mole sec.

Figure 8 represents the decomposition of the iodide salt in N,N-dimethylformamide-alcohol solution. A solution containing 5.97 per cent by weight of N,N-dimethylformamide in absolute alcohol was prepared from distilled Eastman Kodak N,N-dimethylformamide. The rate constant for the decomposition, obtained by dividing the slope of the line (0.0372) by the concentration of N,N-dimethylformamide (0.515 moles/liter), was found to be 2.01 ± 0.05 x 10^{-5} liters/mole sec.

Determination of Order of Reaction with Respect to the Hydroxide Ion Concentration

For determination of the order of reaction with respect to the hydroxide ion in buffered solutions, it is necessary to have two or more sets of data at different hydroxide ion concentrations. For this case, it is possible to write two rate equations as follows:

$$2.303 \log A/A_o = k\ (B)^n t$$

and

$$2.303 \log A'/A_o' = k\ (B')^n t'$$

where B and B' represent the hydroxide ion concentrations at different values of the pH, and n is the order of the reaction with respect to the hydroxide ion concentration. By taking the quotient of the above equations the following equation is obtained.

$$\frac{\log A/A_o}{\log A'/A_o'} = \left(\frac{B}{B'}\right)^n \frac{t}{t'}$$

However, if $\log A/A_o$ is chosen equal to the $\log A'/A_o'$ this equation reduces to:

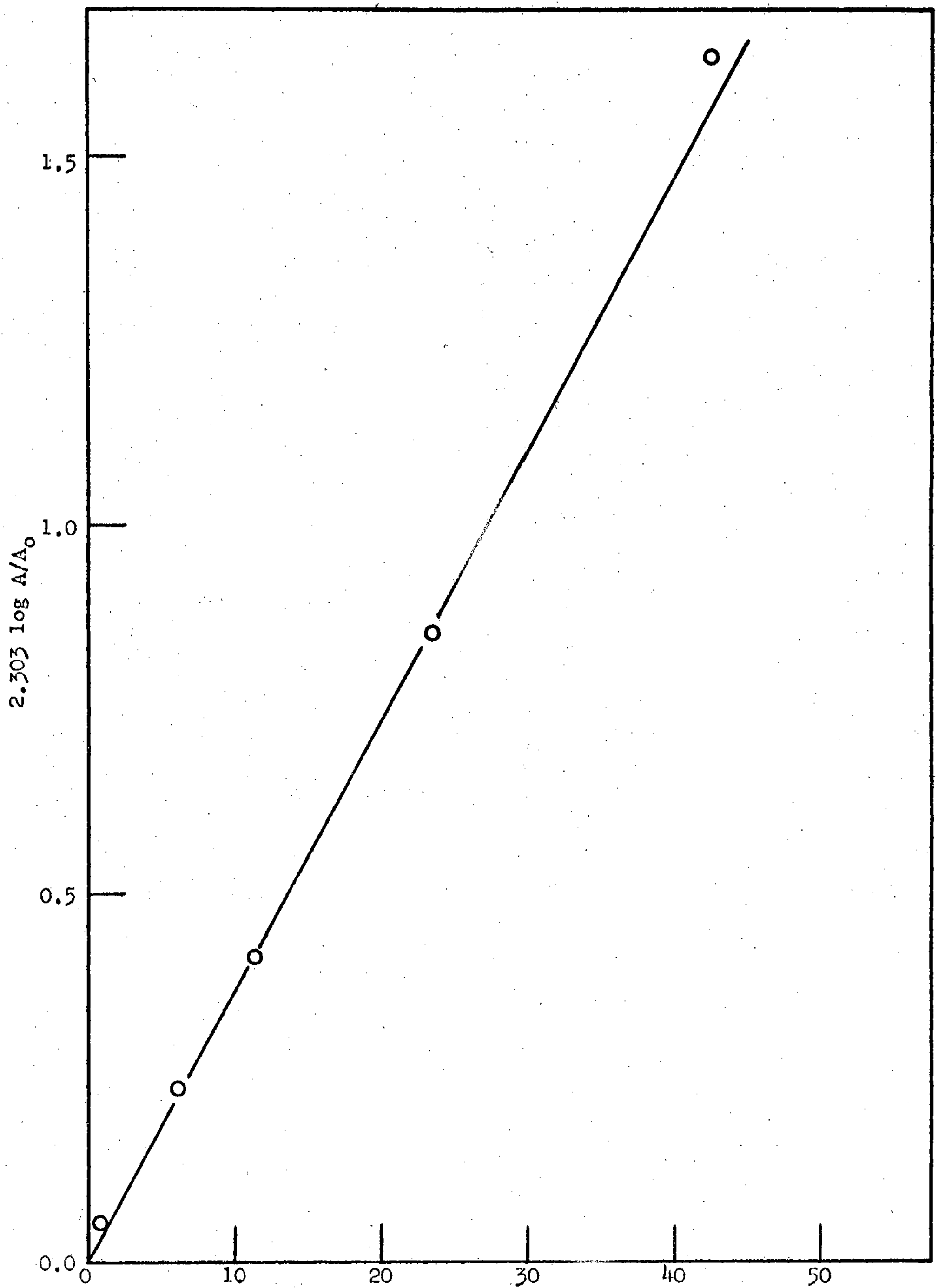


Figure 8. Decomposition of Iodide Salt in 5.97% N,N-Dimethylformamide

$$\left(\frac{B}{B'}\right)^n = \frac{t'}{t}$$

which may be written as

$$n = \frac{\log \frac{t'}{t}}{\log B/B'}$$

It is evident from this equation, that in order to evaluate n, it is necessary to know the concentration of hydroxide ion at two different strengths, and the ratio of the time (t'/t) in which the log A/A_o is equal to log A'/A_o'. The values of n obtained from this equation are listed in Table III.

TABLE III

ORDER OF REACTION WITH RESPECT TO HYDROXIDE ION

pH	$\log \frac{t'}{t}$	log B/B'	n
6.00 6.20	0.16137	0.20140	0.801
6.20 6.60	0.38917	0.39794	0.977
5.30 6.00	0.71517	0.69897	1.02
5.30 6.60	1.25720	1.29667	0.969

Determination of Kinetic Isotope Effects with Tritium

The radioactivity assays were made on a vibrating reed electrometer. Readings were obtained in millivolts, which were converted to microcuries/millimole (μc./mmole) with the aid of the following constants:

3.09×10^{-17} coulombs/disintegration of tritium in methane

3.70×10^{10} disintegrations/second for one curie

1.0×10^{12} ohms (resistance of electrometer)

From these constants a value of 8.747×10^{-4} μc./millivolt is obtained.

In most cases the activities used in the calculations of the isotope effect for a particular run were averages of 10 to 15 assays of the picrate of the unreacted iodide salt and 3 to 6 assays of the dibromo derivitive of the p-nitrostyrene. When the isotope effect for a particular decomposition was to be determined, it was found that the best results were obtained when the individual assays of the samples were mixed chronologically. This intermixing of samples tended to minimize errors caused by slow drifts in the vibrating reed electrometer.

The individual activity measurements given below are averages of 10-20 converted millivolt readings as obtained from the strip chart of the recording apparatus. The specific activities were averaged for each per cent reaction and the average deviation determined.

Tritium Isotope Effects in Aqueous Solutions

The isotope effects were obtained in aqueous solutions for two different hydroxide ion concentrations. Determinations included two decomposition studies, one study at a pH of 6.0 and one at a pH of 6.6. The isotope effects were calculated from the following equations:

$$(k_2 + k_3)/2k_1 = 1 + \frac{\log N_1/N_2}{\log (1 - F)}$$

$$k_3/2k_1 = N_3/N_2 \quad (\text{as } F \longrightarrow 0)$$

The results of the decomposition studies at a pH of 6.0 are listed in Table IV, and the results of the studies at a pH of 6.6 are listed in Table V.

TABLE IV

DECOMPOSITION OF THE IODIDE SALT AT A pH OF 6.0

Extent of Reaction, %	Activity of Picrate, μc./mmole	Activity of p-Nitrostyrene Dibromide, μc./mmole	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
0	5.95			
	5.93			
	5.93			
4.43	6.21	2.55	0.419	
	6.23	2.61	0.429	
48.7	7.44			0.662
	7.42			0.667
	7.48			0.655
53.6	7.75			0.657
75.9	8.90			0.716
	8.97			0.715
	9.70			0.656
0	4.08			
	4.05			
	4.04			
7.69	4.33	1.67	0.413	
	4.33	1.72	0.399	
	4.31	1.73	0.411	
48.7	5.17			0.639
	5.23			0.621
	5.23			0.621
	5.26			0.612
55.7	5.51			0.625
	5.56			0.614
	5.52			0.622
	5.52			0.622
72.7	5.97			0.704
	6.01			0.698
	6.02			0.697
0	4.06			
	4.02			
	4.04			
	4.06			
2.00	4.14	1.70	0.415	
	4.15	1.70	0.415	
	4.16	1.71	0.417	
	4.13	1.71	0.417	

Averages: $k_3/2k_1 = 0.415 \pm 0.005$

$(k_2 + k_3)/2k_1 = 0.656 \pm 0.030$

TABLE V

DECOMPOSITION OF THE IODIDE SALT AT A pH OF 6.6

Extent of Reaction, %	Activity of Picrate, µc./mmole	Activity of p-Nitrostyrene Dibromide, µc./mmole	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
0	4.03			
	3.96			
	3.95			
	3.91			
9.31	4.28	1.71	0.416	
	4.29	1.75	0.426	
	4.29	1.68	0.409	
	4.26	1.71	0.416	
44.2	4.88			0.633
	4.87			0.637
	4.82			0.655
54.5	5.35			0.612
	5.33			0.616
	5.40			0.600
74.2	6.17			0.669
	6.15			0.671

Averages: $k_3/2k_1 = 0.417 \pm 0.005$

$(k_2 + k_3)/2k_1 = 0.637 \pm 0.021$

Tritium Isotope Effects in Non-Aqueous Solutions

Non-aqueous isotope effect studies were made using absolute ethanol as the solvent and formamide and N,N-dimethylformamide as the reagents.

The results of these studies are tabulated in Tables VI and VII.

Determination of the Kinetic Isotope Effect with Nitrogen-15

The isotope effect of nitrogen-15 was obtained in an aqueous solution buffered at a pH of 6.0. Calculations of the theoretical isotope effect for this reaction cannot be correlated with the observed isotope effect since no attempt was made to determine the amount of carbon-13 in the position alpha to the ammonium group, and no attempt was made to determine the amount of nitrogen-15 in the ammonium group.

Assays of the nitrogen obtained from the unreacted salt were made by mass spectrographic analysis at the Argonne National Laboratory, Lemont, Illinois, through the courtesy of Dr. Benjamin D. Holt. The results of this mass spectrographic analysis are tabulated in Table VIII.

TABLE VI

DECOMPOSITION OF THE IODIDE SALT BY 6.01% FORMAMIDE IN ABSOLUTE ETHANOL

Extent of Reaction, %	Activity of Picrate, μc./mmole	Activity of p-Nitrostyrene Dibromide, μc./mmole	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
0	4.18			
	4.18			
	4.19			
	3.98			
7.74		2.23	0.532	
		2.19	0.522	
		2.14	0.510	
		2.10	0.502	
39.41	4.79			0.732
	4.80			0.728
	4.79			0.732
44.61	4.96			0.716
	4.96			0.716
	4.94			0.723
	4.93			0.724
52.03	5.01			0.758
	5.01			0.758
	4.95			0.772
	5.02			0.753
80.24	6.39			0.741
	6.39			0.741
	6.40			0.740
	6.40			0.740
0	4.23			
	4.25			
	4.27			
	4.28			
7.50		2.19	0.514	
		2.20	0.516	
		2.20	0.516	
		2.18	0.512	

Averages: $k_3/2k_1 = 0.516 \pm 0.008$

$(k_2 + k_3)/2k_1 = 0.738 \pm 0.013$

TABLE VII

DECOMPOSITION OF THE IODIDE SALT BY 5.97% N,N-DIMETHYLFORMAMIDE IN ABSOLUTE ETHANOL

Extent of Reaction, %	Activity of Picrate, μc./mmole	Activity of p-Nitrostyrene Dibromide, μc./mmole	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
0	3.99			
	4.01			
	4.02			
	4.01			
10.0		2.07	0.516	
		2.09	0.521	
		2.06	0.514	
21.15	4.31			0.696
	4.33			0.676
	4.30			0.707
34.14	4.36			0.800
	4.36			0.800
	4.37			0.794
57.44	4.96			0.751
	4.96			0.751
	4.92			0.761
80.53	6.04			0.750
	6.06			0.748
	6.02			0.752

Averages: $k_3/2k_1 = 0.517 \pm 0.003$

$(k_2 + k_3)/2k_1 = 0.749 \pm 0.028$

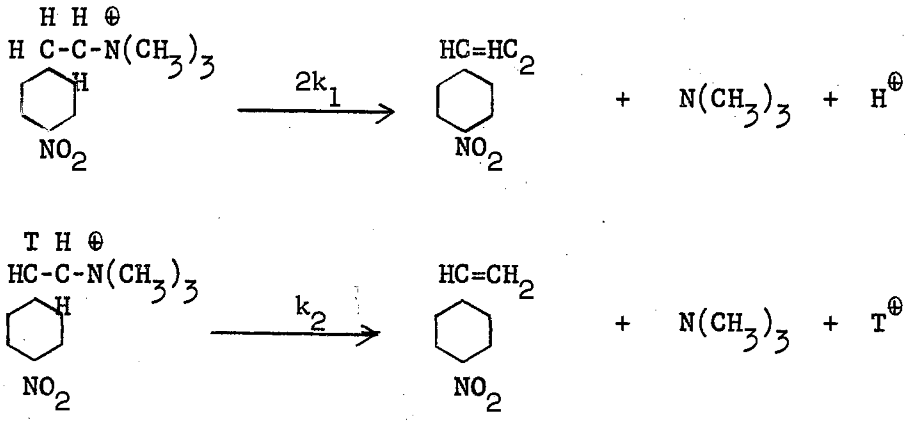
TABLE VIII

DECOMPOSITION OF IODIDE SALT AT A pH OF 6.0

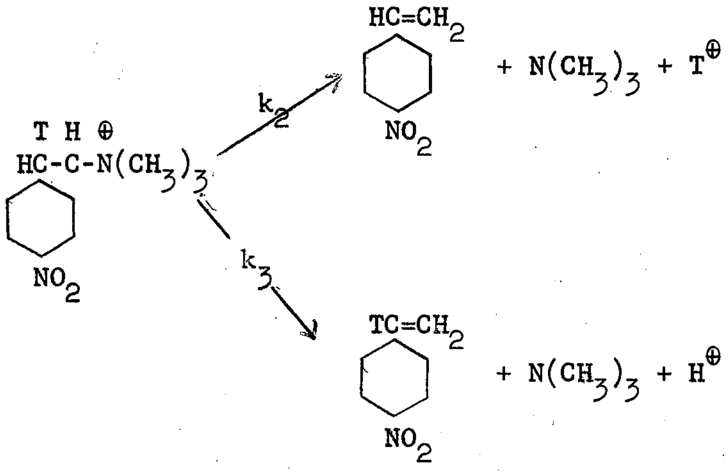
Extent of Reaction, %	Sample Designation	Per Cent N-15			Per Cent N-15 Average
0	0-1	0.358	0.357	0.357	0.357 ± 0.001
	0-2	0.358	0.356	0.359	
	0-3	0.359	0.355	0.358	
80	3-1	0.362	0.363	0.363	0.364 ± 0.001
	3-3	0.365	0.362	0.362	
	4-1	0.363	0.368	0.365	
	4-2	0.365	0.364	0.365	

Calculation of the Tritium Isotope Effect from Experimental Data

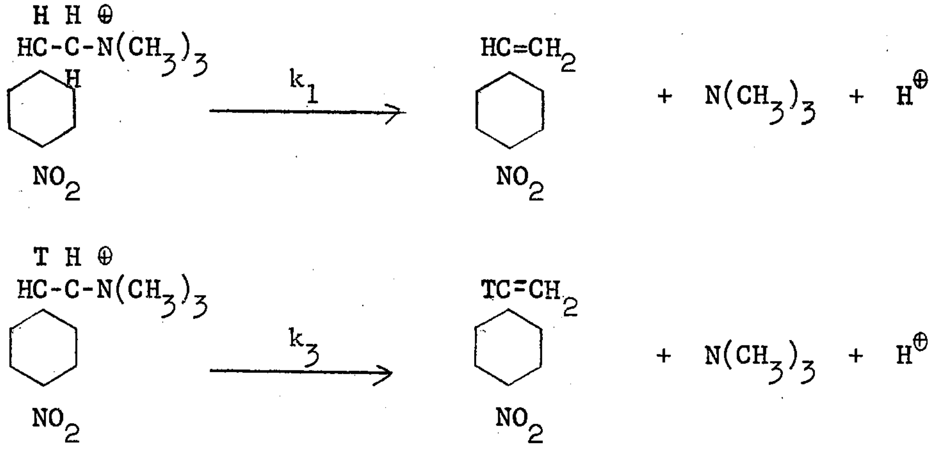
From the experimental values obtained for $k_3/2k_1$ and $\frac{k_2 + k_3}{2k_1}$ it is possible to obtain the value for the intermolecular isotope effect (k_1/k_2), the intramolecular isotope effect (k_3/k_2) and the secondary isotope effect (k_1/k_3). The intermolecular isotope effect is the ratio of the reaction rates for the labeled and unlabeled molecule to form the unlabeled product. This may be represented for this decomposition by the following reactions:



The intramolecular isotope effect is exhibited when a labeled molecule has two paths of decomposition, one to give a labeled product, and the other to give an unlabeled product. This may be represented as follows:



The secondary isotope effect is the effect on the rate of reaction due to an isotopic atom in the vicinity of the reaction site. This may be represented as follows:



The deviation of the value of k_3 from the value of k_1 may be attributed directly to the effect of the tritium atom on the lability of the hydrogen atom undergoing reaction.

The values obtained for the inter-, intra- and secondary isotope effects are listed in Table IX.

TABLE IX

INTER-, INTRA-, AND SECONDARY ISOTOPE EFFECTS

Solvent	$k_3/2k_1$	$(k_2 + k_3)2k_1$	k_1/k_2	k_3/k_2	k_1/k_3
Water, pH = 6.0	0.415 ± 0.005	0.656 ± 0.030	2.12 ± 0.31	1.76 ± 0.28	1.20_5 ± 0.015
Water, pH = 6.6	0.417 ± 0.005	0.637 ± 0.021	2.47 ± 0.12	1.99 ± 0.31	1.20_0 ± 0.015
6.01% formamide	0.516 ± 0.008	0.738 ± 0.013	2.28 ± 0.22	2.35 ± 0.25	0.97 ± 0.02
5.97% N,N-dimethylformamide	0.517 ± 0.003	0.749 ± 0.028	2.20 ± 0.30	2.27 ± 0.31	0.97 ± 0.01

Calculations of the Nitrogen Isotope Effect from Experimental Data

From the experimental values obtained for the per cent nitrogen-15 in the unreacted salt it is possible to calculate the nitrogen isotope effect from the following equation (8),

$$k^*/k = 1 + \frac{\log (N^{15}/N^{14})/(N_o^{15}/N_o^{14})}{\log (1 - f)}$$

where f is the fraction reacted, (N^{15}/N^{14}) is the ratio at the fraction reacted corresponding to f, and (N_o^{15}/N_o^{14}) is the ratio determined at f=0.

However, since the salt molecule contains two nitrogen atoms, but only one of which is involved in the reaction, the observed difference in the per cent nitrogen-15 at 80 per cent reaction is approximately one-half of the difference due to the isotope effect. It is impossible to calculate the ratio of nitrogen-15 in the nitro group and the ammonium group due to the method of preparation used for the quaternary ammonium salt. It is highly probable that an isotope effect is involved in the reaction of the trimethylamine with *p*-nitrophenethyl bromide and that the ammonium group of the iodide salt is somewhat deficient in nitrogen-15 as compared to the nitrogen-15 present in the nitro group. However, this deficiency is small and will be neglected in the calculation of the observed isotope effect. The value of the nitrogen isotope effect then calculates to be 1.024 ± 0.004.

DISCUSSION OF RESULTS

Kinetics of the Decomposition of p-Nitrophenethyltrimethylammonium Iodide

Kinetic studies of the decomposition of the iodide salt were made for two reasons: first, to determine the nature of the attacking reagent in neutral and acid solutions, and second, to determine the order of reaction with respect to each reactant. Hughes and Ingold (18) reported that the reaction was pseudo first order in neutral solutions, in which the water molecule was the attacking reagent and that the reaction was retarded by the addition of acids. However, dependency of the rate on the hydroxide ion concentration was observed in the pH range of 4.60 to 7.00 and discrepancies in the rate constants may be explained on the basis of different ionic strengths of the buffer solutions used, since no attempts were made to correct for salt effects.

It is apparent from the data in Tables I and III that the reaction is first order with respect to the iodide salt and with respect to the hydroxide ion. A second-order rate constant of 447 ± 28 liters per mole second was obtained from the kinetic studies in neutral aqueous solutions. The rate constant obtained by Hughes and Ingold (18) on the assumption that the decomposition was first order is 0.146 ± 0.010 hour^{-1}. However, assuming the pH of the solution to be 7.0, the second order rate constant for the reaction studied by Hughes and Ingold calculates to be 406 ± 28 liters per mole second, in fair agreement with the value obtained in this study.

The seemingly excessive scattering of the experimental points in Figures 2 and 3 may be accounted for in two ways. The picrate of the iodide salt is somewhat soluble in water and corrections were made in an attempt to account for the solubility in both the reaction solution and the water used to wash the picrates. The difference in contact time between the wash water and the picrates would give rise to errors in the solubility correction factor and thereby lead to such scattering. In some instances, the p-nitrostyrene formed in the decomposition of the salt could be removed as a hard, glassy lump, and washed to remove any unreacted salt from its surface, however this was at most times extremely difficult and sometimes impossible. Any p-nitrosytrene remaining in the picrate or the removal of some of the unreacted salt in an attempt to remove the p-nitrostyrene would be reflected as an error in the fraction of salt unreacted.

In the kinetic studies made in non-aqueous solutions, rate constants of 2.04×10^{-5} and 2.00×10^{-5} liters per mole second were found for the formamide and N,N-dimethylformamide solutions respectively. Although N,N-dimethylformamide is a much stronger base than formamide and one might expect the rate of decomposition of the salt in dimethylformamide solution to be greater, the approach of the nitrogen atom of the dimethylformamide molecule to the labile hydrogen atom in the salt is somewhat more sterically hindered than that of the formamide molecule, giving rise to fewer effective collisions and tending to offset the difference in basicity.

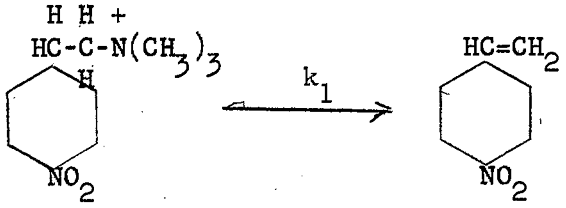
Theoretical Evaluation of the Isotope Effect

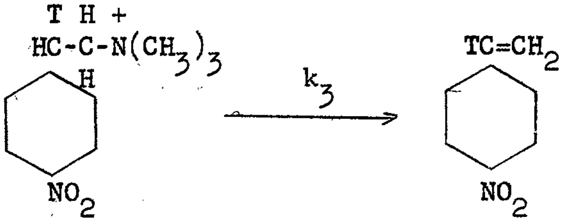
The following qualitative relations may be obtained from the observed isotope effects:

(1) No significant difference in the tritium isotope effect is observed due to differences of the rate of reaction. The isotope effect observed in aqueous solution buffered at a pH of 6.0 agrees well with that observed in aqueous solution buffered at a pH of 6.6. This is the expected result since the difference in the heights of the potential energy barriers for the breaking of the carbon-hydrogen and carbon-tritium bonds is not dependent upon the rate of the reaction.

(2) No significant difference in the tritium isotope effect is observed due to differences in basicity of the attacking reagent. The isotopic effect observed in the non-aqueous solutions using formamide and N,N-dimethylformamide as the reagent are in good agreement with each other, indicating that the nature of the attacking reagent has little effect on the observed isotope effect. This view is also supported by the fact that the observed isotope effects for aqueous and non-aqueous solutions are also in good agreement. Since the isotope effect is dependent on the vibrational frequencies of the activated complex as well as those for the normal molecule, it is apparent that the vibrational frequencies of the activated complex are not seriously affected by the nature of the reagent.

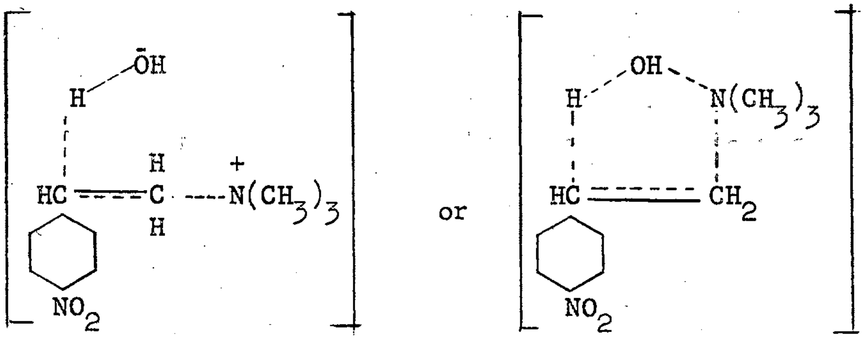
(3) The substitution of a tritium atom on the carbon beta to the ammonium group decreases the reactivity of the hydrogen atom attached to the same carbon. The reactions which are represented by the rate constants k_1 and k_3 are





The experimental value obtained for the ratio k_1/k_3 is approximately 1.25 indicating that the hydrogen atoms on the carbon beta to the ammonium group in the dead molecule are 25 per cent more reactive than the corresponding hydrogen atoms in the labeled molecule. However, this secondary isotope effect appeared only in the aqueous solution.

(4) The mechanism by which the salt decomposes is a concerted mechanism, since both tritium and nitrogen-15 isotope effects were observed, indicating that the carbon-hydrogen and carbon-nitrogen bonds are broken simultaneously in the rate-controlling step of the reaction. The transition state may then be represented as



Theoretical Evaluation of the Maximum Tritium Isotope Effect

The theoretical evaluation of the tritium isotope effect may be made through the use of Wiberg equation (19), in which

$$\frac{k_1}{k_2} = \frac{f}{f*} \left(\frac{m_2^*}{m_1^*} \right)^{1/2}$$

where:

k = rate constant

$m*$ = effective mass of the activated complex along the coordinate of decomposition, usually calculated from the reduced mass $(m_1 m_2/m_1 + m_2)$ of the atoms involved in the bond being broken in the rate-controlling step of the reaction

f = free energy term

The function f is given by

$$f = \frac{\sigma 1}{\sigma 2} \prod_{i}^{3n-6} \frac{u_i}{u_i + \Delta u_i} \quad \frac{(1-e^{-(u_i + \Delta u_i)})}{(1 - e^{-u_i})} \exp \Delta u_i/2$$

where:

σ = symmetry number

u_i = $h\nu/kT$

h = Planck constant

ν = vibrational frequency

k = Boltzman constant

T = absolute temperature

Δu_i = $h(\nu_{i_1} - \nu_{i_2})/kT$

A similar expression may be written for f*, but since a detailed knowledge of the potential energy surface at the energy barrier is not available there is no way to evaluate the vibrational frequencies in the transition state and hence no way to evaluate f*. However, it is possible to calculate the maximum isotope effect which corresponds to no bonding to the hydrogen or tritium in the activated complex. In this case f* becomes equal to 1 and the equation may be written

$$\frac{k_H}{k_T} = \left(\frac{m_T^*}{m_H^*}\right)^{1/2} \quad \frac{h\nu_T}{h\nu_H} \quad \exp h(\nu_H - \nu_T)/2RT \left(\frac{1 - e^{-h\nu_H/RT}}{1 - e^{-h\nu_T/RT}}\right)$$

where $h\nu$ is expressed in calories per mole (2.86 times the value in cm^{-1}).

The last term of this equation is approximately equal to 1 for the the temperature used for the decomposition of the iodide salt, and can therefore be omitted, and the maximum isotope effect calculated from

$$\frac{k_H}{k_T} = \left(\frac{m_T^*}{m_H^*}\right)^{1/2} \quad \frac{h\nu_T}{h\nu_H} \quad \exp h(\nu_H - \nu_T)/2RT$$

The fundamental vibrational frequency for the carbon-tritium bond has not been determined, but it may be approximated from the frequency of the corresponding carbon-hydrogen bond by application of the following equation (9).

$$\nu_T = \nu_H \left(\frac{m_H^*}{m_T^*}\right)^{1/2}$$

where:

ν = vibrational frequency

m* = reduced mass

In order to further simplify the calculation, it is usually assumes that the non-reacting bonds of the molecule are not affected during reaction, and it is therefore necessary to consider only the stretching frequency of the bond undergoing reaction.

The various constants used in the calculation of the maximum isotope effect are tabulated below.

$\nu_H = 2926\ \mathrm{cm}^{-1}$
$\nu_T = 1817\ \mathrm{cm}^{-1}$
$m_H^* = 0.9299$
$m_T^* = 2.411$
$R = 1.987$ cal/mole
$T = 371°$ K.

The maximum value of k_H/k_T then calculates to be 8.58. Since the observed isotope effect is considerably lower than the calculated isotope effect, one is lead to conclude that the carbon-hydrogen bond being broken is still quite strong in the activated complex.

Theoretical Evaluation of the Maximum Nitrogen Isotope Effect

The theoretical evaluation of the nitrogen isotope effect may be made through the use of the Eyring-Cagle equation (9) or the Bigeleisen equation (1). The Eyring-Cagle equation is expressed as

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

and the Bigeleisen equation may be expressed as

$$\frac{k_1}{k_2} = \left(\frac{m_2^*}{m_1^*}\right)^{1/2} \left[1 + \sum G(u_i)\,\Delta u_i - \sum G(u_i^*)\,\Delta u_i^*\right]$$

where:

$$u_i = hc\omega/kT \text{ and } \Delta u_i = hc/kT(\omega_2 - \omega_1)$$

$$G(u) = 1/2 - 1/u + 1/e^u - 1$$

In the evaluation of the theoretical isotope effect for the decomposition of the salt, four separate bond ruptures must be considered since the salt was not enriched in nitrogen-15. The bonds ruptured are:

$C^{12} - N^{14}$
$C^{13} - N^{14}$
$C^{12} - N^{15}$
$C^{13} - N^{15}$

The amount of $C^{13} - N^{15}$ linkages occurring in the salt due to natural abundance of both isotopes in extremely small, and can be neglected in the calculations. The amount of N^{14} remaining in the unreacted salt due to the isotope effect in breaking the $C^{13} - C^{14}$ bond as compared to the per cent N^{14} in the sample is also very small, and will be neglected in the calculations although a slight error is introduced in the value of the maximum theoretical isotope effect. However, this tends to increase the per cent N^{14} remaining in salt over that which would be present had all of the bonds been either $C^{12} - N^{14}$ or $C^{12} - N^{15}$, thereby decreasing slightly the maximum theoretical isotope effect.

The various constants used in the calculation of the maximum isotope effect are tabulated below.

$\nu_{N^{14}} = 1335 \text{ cm}^{-1}$

$\nu_{N^{15}} = 1314 \text{ cm}^{-1}$

$m^*_{N^{14}C^{12}}$ = 6.464 g./mole

$m^*_{N^{15}C^{12}}$ = 6.669 g./mole

k = 1.38×10^{-16} erg/deg.

T = 371°

h = 6.62×10^{-27} erg sec.

The values of the maximum theoretical isotope effect are listed below along with the measured values of the isotope effect.

Bigeleisen equation	1.0408
Eyring-Cagle equation	1.0413
Observed isotope effect	1.024 ± 0.004

CONCLUSIONS

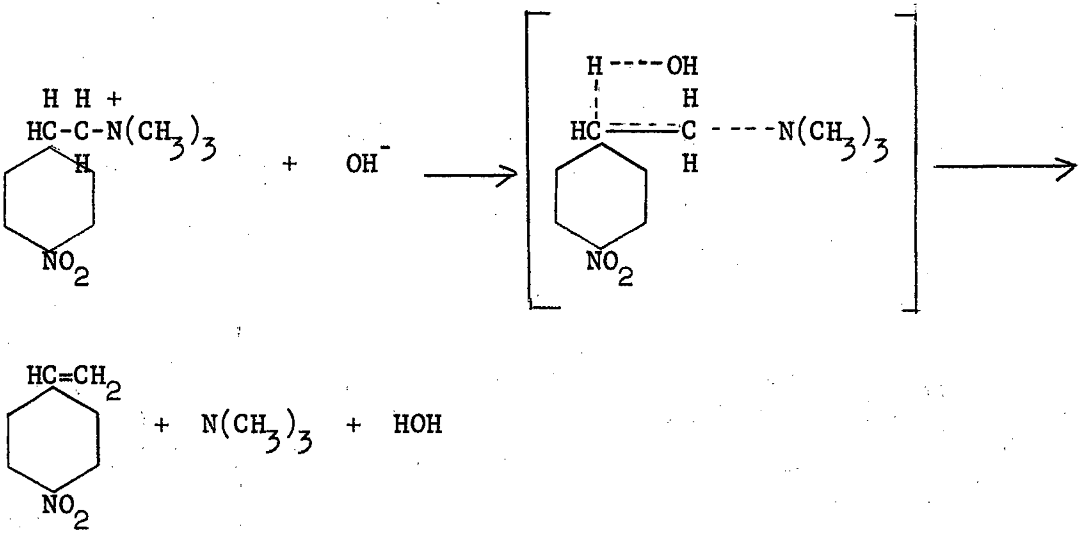
The theory of the kinetic isotope effect predicts that for two isotopic molecules undergoing reaction in the same vessel, the lighter molecule will have a greater rate constant if the isotopic center is involved in the rate-determining step of the reaction. The magnitude of this difference in reaction rate constants is determined by the ratio of the masses of the isotopic species and the nature of the activated complex of the system. In this work, the decomposition of p-nitrophenethyltrimethylammonium iodide was studied in both aqueous and non-aqueous solutions. The following conclusions were formed from the comparison of experimentally obtained isotope effects with theoretical considerations.

(1) The tritium isotope effect involved in the decomposition of the iodide salt is independent of the rate of the reaction. This is indicated by the fact that there is no difference in the observed isotope effect in aqueous solutions buffered at a pH of 6.0 and 6.6.

(2) The variation of the tritium isotope effect due to different attacking reagents is well within the limits of experimental errors. One may conclude from this that the nature of the attacking reagent has little effect on the isotope effect and that the hydrogen is still quite strongly bonded to the carbon in the activated complex. This conclusion is further supported by the fact that the isotope effects in aqueous and non-aqueous solutions are in good agreement. Still another fact in support

of this conclusion is that the observed tritium isotope effect is much lower than the maximum theoretical isotope effect, the maximum theoretical isotope effect being calculated on the basis of no bonding in the activated complex.

(3) The decomposition of the salt takes place by a concerted mechanism. Since both tritium and nitrogen isotope effects were observed in the decomposition of the salt indicating that both the carbon-hydrogen and carbon-nitrogen bonds are broken in the rate determining step of the reaction, the reaction must then proceed by a mechanism similar to



(4) Correlation of the observed and theoretical isotope effects is impossible. Since there is no way to determine the extent of bonding in the activated complex, and therefore no way of obtaining the vibrational frequencies of the activated complex, the "zero point energy effect", which expresses the effect of mass change on the equilibrium between reactant molecules and the activated complexes is incalculable. Furthermore, the "reduced mass effect", which expresses the effect of mass on the

frequency of breaking or forming bonds in the activated complex, has been expanded to include three-center reactions, and it is evident from the above conclusion concerning the activated complex of the decomposition of the salt, that a five-center term is needed to adequately describe the system.

(5) The substitution of a tritium on the carbon beta to the ammonium group has a marked influence in aqueous solutions on the reactivity of the hydrogen atom attached to the same carbon atom. The reactivity of this hydrogen atom is decreased by approximately 25 per cent as indicated by the value of the secondary isotope effect.

SUMMARY

The salt, p-nitrophenethyltrimethylammonium iodide, was prepared and the kinetics of its decomposition studied under various conditions. The salt was shown to decompose bimolecularly and to follow first-order kinetics in buffered aqueous solutions. The decomposition was also observed to be first order in hydroxide ion in aqueous solutions, and that in nonaqueous solutions the decomposition could be initiated by formamide and N,N-dimethylformamide.

Isotope effect studies showed the decomposition of the salt to proceed by a concerted mechanism in which the carbon-hydrogen bond on the carbon atom β to the ammonium group ruptured simultaneously with the carbon-nitrogen bond.

The kinetic isotope effects observed in the decomposition of the quarternary ammonium salt are as follows:

Reaction of Tritium Labeled Salt	Intermolecular Isotope Effect	Intramolecular Isotope Effect	Secondary Isotope Effect
Aqueous Solutions (pH = 6.0)	2.12	1.76	1.20
Aqueous Solution (pH = 6.6)	2.47	1.99	1.20
6.01% Formamide in Ethanol	2.28	2.35	0.97
5.97% N,N-Dimethylformamide in Ethanol	2.20	2.27	0.97

Nitrogen-15 isotope effect 1.024 ± 0.004

Isotope effects for these reactions were calculated from theoretical considerations and the results compared with experimental values of the isotope effect.

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VITA

John Joseph Sparapany

Candidate for the Degree of

Doctor of Philosophy

Thesis: TRITIUM AND NITROGEN-15 ISOTOPE EFFECTS IN THE DECOMPOSITION OF p-NITROPHENETHYLTRIMETHYLAMMONIUM IODIDE

Major Field: Organic Chemistry

Biographical:

Personal Data: Born November 11, 1928, Albany, New York.

Undergraduate Study: Bachelor of Science Degree, Buena Vista College, Storm Lake, Iowa, 1948-1951.

Graduate Study: Master of Science Degree, North Dakota State Agricultural College, Fargo, North Dakota, 1951-1953.

Professional Experience: Physical Sciences Assistant, Army Chemical Corps, Army Chemical Center, Maryland, 1953-1955. Technical Writer, Army Chemical Center, Maryland, 1955.