

ISOTOPE EFFECT OF TRITIUM IN THE DECOMPOSITION OF  
2-(p-NITROPHENYL)ETHYL-2-t-(TRIMETHYL)AMMONIUM IODIDE

By

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## PREFACE

Hughes and Ingold (7) in 1933 studied the kinetics of the elimination of trimethylamine from 2-(p-nitrophenyl)ethyl(trimethyl)-ammonium iodide and 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 ion 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 agent in basic solution and that the water molecule was the reagent in neutral solution.

However the first-order kinetics of the reaction in neutral solution may also be explained by use of the general unimolecular mechanism (5). By this mechanism the trimethylamine breaks off in a slow ionizing step followed by a loss of a proton in a fast step to form the olefin.

Since the bimolecular mechanism involves the breaking of a hydrogen bond in the rate-determining step, and the unimolecular mechanism does not, use of 2-(p-nitrophenyl)ethyl(trimethyl)-ammonium iodide labeled with tritium on the carbon atom adjacent to the ring should distinguish between the two mechanisms. Occurrence of an isotope effect in the reaction would show the bimolecular mechanism to be correct. The absence of an isotope effect would show that some mechanism other than the bimolecular was responsible for the first-order rate in neutral solution.

The purpose of the research presented in this paper was to show whether or not this isotope effect exists and if it exists to measure it.

## HISTORICAL

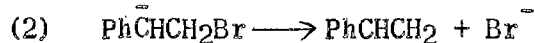
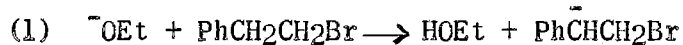
### Olefin-Forming Eliminations

Olefin-forming eliminations may proceed either by a bimolecular or by a unimolecular mechanism. The bimolecular mechanism has been demonstrated in the case of the formation of olefins from tetraalkylammonium salts, dialkyl sulfones, alkyl halides, tetraalkylphosphonium salts, and trialkylsulfonium salts (9). The mechanism has been shown to be probable also in the case of alkyl sulfonates, and certain carboxylates (9). The attacking nucleophilic reagents range in basicity from water to the amide ion. Second-order kinetics, an indication of bimolecular mechanism, have been formally established in the first three cases with hydroxide and ethoxide ions as the nucleophilic reagents. However, second-order kinetics are not proof of bimolecular mechanism. In some cases of unimolecular substitution, the strong nucleophile is necessary to produce the conjugate base of the substrate. This mechanism might be expected to have a certain range of application to olefin-forming eliminations.

A better method of distinguishing between the bimolecular and unimolecular eliminations has been shown by Skell and Hauser (12), who used an isotopic test. They found that the production of styrene from 2-phenylethyl bromide and ethoxide ion, which has been shown to have second-order kinetics, proceeds by the bimolecular mechanism:



The alternative possibility is



However, the first step of the alternate path must be reversible; and if the reaction was performed in a deuterioalcoholic solvent, the recovered reactant should contain deuterium. Skell and Hauser (16) found the recovered 2-phenylethyl bromide to be free of deuterium, showing the bimolecular mechanism to be correct.

The unimolecular mechanism has been established in certain olefin-forming eliminations of sulfonium salts, halides, and sulfonic esters (9). The unimolecular mechanism reactions generally have first-order reaction kinetics that are insensitive to added base. However deviations do occur which are due to salt effects that are characteristic of unimolecular processes.

In 1933 Hughes and Ingold (7) studied the olefin-forming elimination reaction of 2-(p-nitrophenyl)ethyl(trimethyl)ammonium iodide (the elimination reaction studied in the experimental part of this paper) in a neutral aqueous solution at 100°. They found the reaction to be first-order, but explained it as a pseudo first-order reaction in which the difference in the concentration of the water does not enter into the rate equation.

They prepared the iodide salt by methylation of 2-(p-nitrophenyl)-ethylamine with methyl iodide. Weighed portions of the iodide were separately enclosed in sealed tubes each with 5 ml. of water. The tubes were heated to 100° for known periods, cooled, opened, and the iodides extracted with water. The residual quaternary ammonium salt was then precipitated and weighed as the sparingly soluble



picrate. The value found for the first-order rate constant was  $0.146 \pm 0.010$ .

### Isotope Effect

The isotope effect is an important tool in the determination of organic reaction mechanisms. It arises from the difference in the masses of the isotopes and is apparent in changes in the equilibrium constants, rates of reaction, and bond strengths. Such effects are sufficiently great to enable separation of isotopes on a large scale. Beeck *et al* (1) found in the pyrolysis of propane that the  $C^{12}-C^{13}$  bond ruptured 8% more frequently than the  $C^{12}-C^{12}$  bond and obtained a higher isotope ratio in the first fraction of ethylene produced than was present in the original propane. Yankwich and Calvin (19) have observed that when malonic acid labeled with carbon-14 in one carboxyl group is partially decarboxylated the carbon dioxide evolved is depleted of carbon-14 while the remaining acetic acid is enriched.

### Isotope Effect of Tritium

Tritium has a half life of 12.5 years and disintegrates into helium-3 with the release of a beta particle. It is produced in the atomic pile by bombarding lithium with neutrons.

The masses of tritium and protium have a ratio of 3:1, the largest ratio shown by any pair of isotopes. Tritium shows the largest known isotope effect and should be very useful in the study of organic reactions. Because of the low energy of its radiation, 0.0189 Mev., and the possibility of exchange with hydrogen atoms during a reaction, not much work has been done using tritium.

With improved methods of analysis now available, work in

the field is beginning to increase. Wilzbach, Van Dyken, and Kaplan (18) have developed a method for the determination of tritium by ion-current measurement with the vibrating reed electrometer. The tritium is introduced into the ionization chamber as a gas and the disintegration rate measured by the radiation-induced ionization of the gas. Tritium in the combined state is converted into tritium gas and tritiated methane by reduction at 600° with zinc (17).

Samples of methanol and ethanol carrying tracer amounts of tritium were prepared and used for the reduction of the diazonium salts obtained from o- and m-nitroaniline. It was shown that the protium reacts seven times as fast as the tritium (12).

Sulfonation of bromobenzene (13) containing tracer amounts of bromobenzene-4-t carried out in nitrobenzene solution gave the reaction rate constants of tritium and hydrogen atoms in the ratio of 0.55.

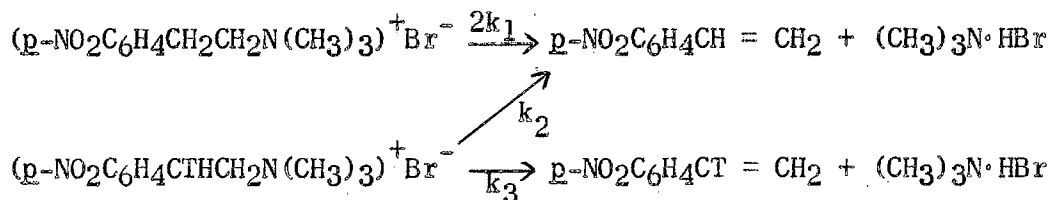
No isotope effect was noted in the nitration of benzene-t or bromobenzene-t (11).

INTRODUCTION TO EXPERIMENTAL WORK

The intramolecular isotope effect is the ratio of reactivities of a normal atom and an isotopic atom in the same molecule for a particular reaction.

The intermolecular isotope effect is the ratio of reactivities of a normal molecule and an isotopically labeled molecule for a particular reaction.

The object of this investigation was to measure the intramolecular ( $k_3/k_2$ ) and intermolecular ( $k_1/k_2$ ) isotope effects in the following reactions:



The equations which relate the rate constants to the radio-activity are:

$$(1) \quad \frac{k_2 + k_3}{2k_1} = 1 + \frac{\log \frac{N_1}{N_2}}{\log (1 - f)} \quad \begin{array}{l} f = \text{fraction reacted.} \\ N_1 = \text{molar activity of reactant} \\ \qquad \qquad \qquad \text{at time corresponding to } f. \\ N_2 = \text{molar activity of initial reactant.} \end{array}$$

$$(2) \quad \frac{k_3}{2k_1} = \frac{N_3}{N_2} \quad (\text{as } f \rightarrow 0) \quad N_3 = \text{molar activity of product}$$

It is seen from the equations that it is necessary to measure the extent of reaction and to isolate, purify, and measure the activity of the product at one or more low extents of reaction and that of the remaining reactant at several higher extents of reactions.

The first step was to prepare the normal compound 2-(p-nitrophenyl)ethyl(trimethyl)ammonium iodide, for use in studying the reaction and for dilution of the tritiated compound. The inactive compound was prepared by nitration of phenylethylamine (5) and then methylation with methyl iodide (7). Oxidation of the product to p-nitrobenzoic acid showed the absence of 2-(o-nitrophenyl)-ethylamine.

From the 2-(p-nitrophenyl)ethyl(trimethyl)ammonium iodide, a 0.3M aqueous solution was prepared. One-milliliter portions of this solution were heated to 70° and to 90°, but no reaction occurred until the solution was heated to 100°. The salt used in the 100°-reaction was that prepared by the Mannich reaction (10), m.p. 199°. It was found later that the reason the salt prepared by the method of Hughes and Ingold (7), m.p. 206°, did not react was the acidity of the solution and not the temperature. The first-order rate constant for the reaction was found by following the extent of reaction by precipitation of the remaining reactant as the picrate and weighing.

If exchange should occur between tritium atoms in the compound and hydrogen atoms of water, the measurement of the isotope effect would be seriously affected. Therefore, tritiated water was prepared in which to carry out the reaction in order to determine if such exchange of hydrogen atoms between the compound and water occurred. Assay of the unreacted compound showed the exchange to be negligible.

The tritiated compound was prepared by introduction of tritium into the 2-position of p-nitrophenylacetic acid by exchange with

tritiated water. This was then converted into 2-(p-nitrophenyl)-3-dimethylaminopropionic acid by a Mannich reaction (10). The amino acid was then decarboxylated to 2-(p-nitrophenyl)ethyl(dimethyl)amine and the latter converted to the quaternary ammonium salt with methyl iodide.

It was found necessary to perform the reaction in a buffered solution of pH 7 because of the failure of the dead salt (m.p. 206°; lit. (7) 199°) to react in regular distilled water. The reason for the reaction in the case of the quaternary ammonium iodide prepared by the Mannich reaction (10) (melting at 199°) and that prepared by Ingold (5) (melting at 199°) reacting in unbuffered solution must have been caused by basic impurities.

The decomposition of 2-(p-nitrophenyl)ethyl-2-t-(trimethyl)-ammonium iodide was effected in water at 100° to 8% and to 17.3% of completion. In each case 100 mg. of product, p-nitrostyrene, was isolated, converted into the dibromide and assayed for activity. One hundred milligrams of the remaining reactant was isolated at 50, 65, and 80% reaction as the picrate and the activity of the latter measured in each case. These data were then used to calculate the isotope effect in the reaction.

### EXPERIMENTAL WORK

#### Preparation of 2-(p-Nitrophenyl)ethyl(trimethyl)ammonium Iodide

Ten grams of phenylethylamine were added in the course of 1.5 hours to fuming nitric acid at  $-10^{\circ}$ . Nitration appeared to follow almost instantaneously, but the mixture was warmed to  $0^{\circ}$  before being mixed with ice and basified with sodium hydroxide. The products were then extracted with ether and isolated as their hydrochlorides by re-extracting the ethereal solution with sufficient dilute hydrochloric acid and evaporating this solution to dryness.

A single crystallization from the minimal quantity of boiling 95% alcohol gave 6 g. of almost colorless plates of 2-(p-nitrophenyl)ethylamine hydrochloride, m.p.  $209^{\circ} - 210^{\circ}$ ; lit. (4)  $210^{\circ}$ .

Potassium permanganate solution was added dropwise to a boiling solution of 2-(p-nitrophenyl)ethylamine hydrochloride in water with just enough sodium hydroxide to make the solution basic. When enough potassium permanganate had been added to make the solution pink, the solution was cooled and made acidic with sulfuric acid. Sodium sulfite was added to remove the manganese dioxide. The solution was then filtered and the residue, p-nitrobenzoic acid, recrystallized from methyl alcohol and dried. The crystals melted at  $240^{\circ}$ ; lit. (15)  $242^{\circ}$ .

Two grams of the 2-(p-nitrophenyl)ethylamine hydrochloride was then neutralized with 6 N sodium hydroxide and the amine extracted with ether and the ether evaporated. To the freed amine

was added 5 g. of sodium carbonate, 5 ml. of absolute ethyl alcohol, and with care 7 ml. of methyl iodide. The reaction which took place with the evolution of heat was completed by refluxing over a water bath. The carbonates were then removed by filtration, washed with ether, and neutralized with 47% hydriodic acid. The quaternary ammonium iodide was then collected by filtration, washed with acetone and ethyl ether, and crystallized from 95% ethyl alcohol. It formed 2 g. of feathery lemon-yellow leaflets melting at 206°. The melting point of this compound reported by Hughes and Ingold (7) is 199°.

#### Reaction Kinetics

A weighted portion of 2-(p-nitrophenyl)ethyl(trimethyl)ammonium iodide (0.5802 g.) was dissolved in 10 ml. of water. Upon heating of the solution all of the salt dissolved and nine one-milliliter portions were taken from the flask. Three of the one-milliliter portions were each treated with 6 ml. of saturated picric acid solution and the solid picrate was filtered off, washed with water, dried, and weighed.

The solubility of the picrate was found to be 0.8 mg./ml. so that it was necessary to measure the volume of wash water and apply a correction for the picrate dissolved.

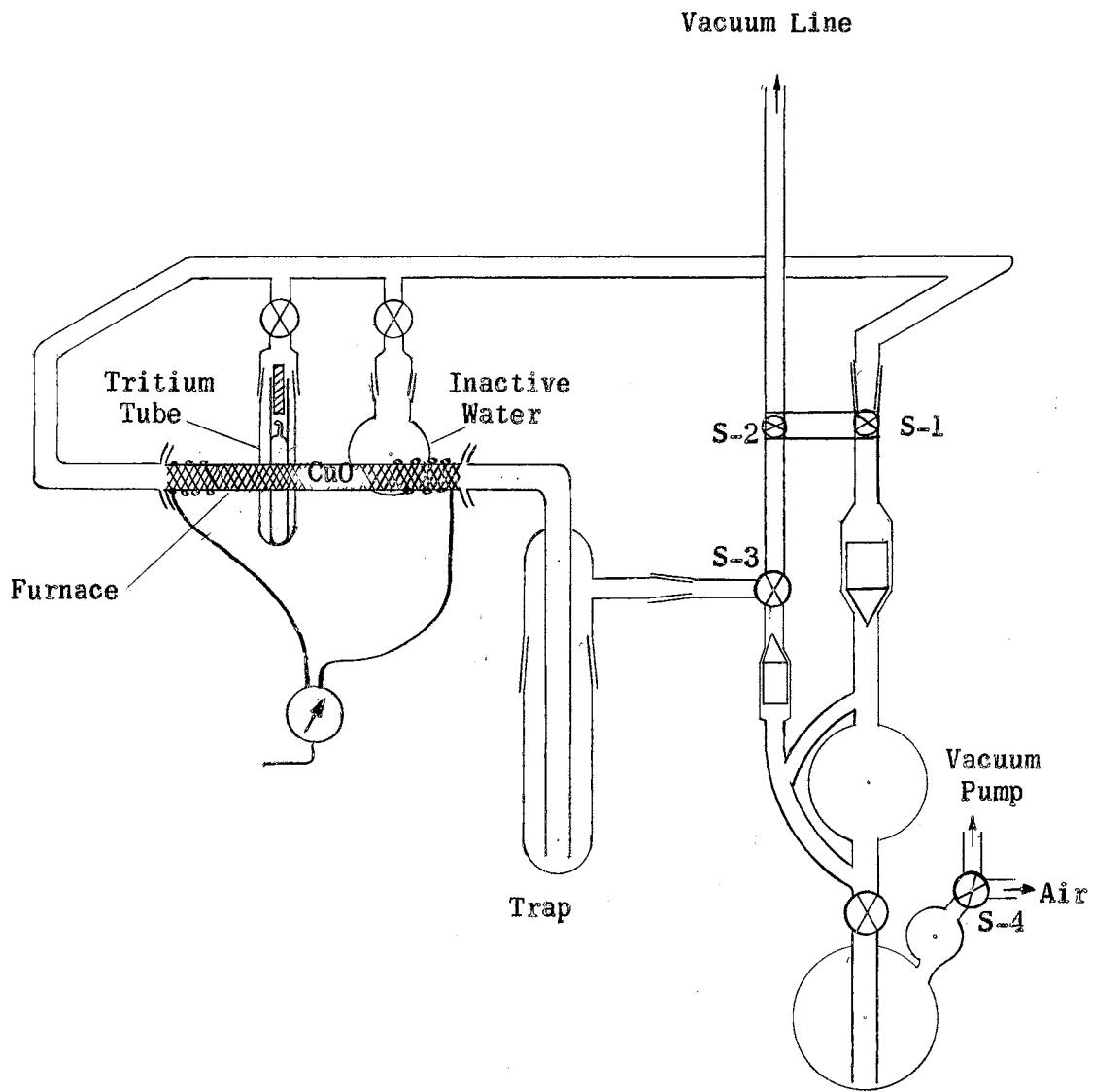
The remaining portions were sealed in tubes and heated to 100° in a mineral oil bath for the desired time. The tubes were then broken and the solution filtered. The tubes were washed with 2 ml. of water. Six milliliters of saturated picric acid was added to the filtrate. The precipitate formed was then washed with water, dried and weighed. The reaction constant was found to be 0.140 ± 0.007.

Preparation and Assay of Tritiated Water

The system shown in the diagram was connected to the vacuum line and evacuated. Stopcocks 1 and 3 were adjusted so the Toepler pump could be filled with hydrogen without filling the system. Hydrogen at atmospheric pressure was let into the bulb of the Toepler pump. Stopcock 2 was then closed to the line, and the furnace containing copper oxide wire was heated to 300°, and liquid nitrogen bath was then placed about the trap, and the break-off tip of the tube containing 100 mc. of tritium was broken with a magnet. After several minutes, stopcock 1 was opened, allowing hydrogen to enter the system. Stopcock 4 was opened to the air and the mercury in the Toepler pump rose until the pressure of the hydrogen in the system was atmospheric. Stopcock 3 was then opened to the Toepler pump and stopcock 4 opened to the vacuum, causing the mercury in the pump to fall. By alternately opening stopcock 4 to air and to vacuum the hydrogen was forced through the copper oxide furnace, forming water which froze in the trap. Water was first seen on the exit side of the furnace but with continued circulation the pressure was lowered, and the water moved to the trap. When most of the hydrogen in the system was used up, the Toepler pump was again filled with hydrogen and this was introduced into the system as before. When this hydrogen had reacted, the furnace was allowed to cool, and the stopcock on the container of water was opened. When the system had been flushed with 2-3 ml. of water the trap was removed, and inactive water added to the prepared water to dilute it. The final weight of water was 14.44 g.

A 5-mg. sample of the tritiated water was weighed into an





Apparatus for the Synthesis of Tritiated Water

ampoule, sealed, and enclosed in an evacuated reaction tube containing 1 g. of zinc and 100 mg. of nickelic oxide. The ampoule of water was then broken inside the reaction tube, and the tube heated to 625° for three hours. After the tube had cooled, the gas in the tube was transferred to an ionization chamber by means of the vacuum line. The chamber was then filled to atmospheric pressure with methane and attached to the vibrating reed electrometer for measurement of the activity. The chamber was evacuated and filled with methane to obtain a background reading.

For calculation of the activity, certain volumes were needed. These were obtained by using a bulb of known volume and applying Boyle's law. Correction was made for the varying volume of the manometer by calculating its volume per unit length.

#### Summary of Volume Determinations

Standard Bulb 210 ml.

Line Volume 60.3 ml.

Bulb Stem 6.7 ml.

Break-off Tube 104.5 ml.

No. 1 Chamber 256.7 ml.

No. 2 Chamber 256 ml.

Manometer Correction 0.28 ml./cm.

#### Calculation of Activity

$$1 \text{ curie} = 3.7 \times 10^{10} \text{ disintegrations/sec.}$$

$$1 \text{ disintegration of tritium in methane} = 3.09 \times 10^{-17} \text{ coulombs (14)}$$

$$1 \text{ c.} = 3.7 \times 10^{10} \times 3.09 \times 10^{-17} \text{ coulombs/sec.}$$

$$= 11.37 \times 10^{-7} \text{ amperes}$$

Resistor No. 2 =  $0.96 \times 10^{10}$  ohms

1 c. =  $11.37 \times 10^{-7} \times 0.96 \times 10^{10}$  ampere ohms

=  $10.98 \times 10^3$  volts

1  $\mu$ c. = 10.98 mv.

1 mv. = 0.0912  $\mu$ c.

The portion of the total activity of the sample which is transferred to the ionization chamber is

$$\frac{\text{Volume of chamber}}{\text{Volume of chamber} + \text{break-off tube} - \text{reaction tube}} = F$$

Therefore to find the specific activity of a sample the following expression is used:

$$\text{mv.} \times 0.0912 \times \frac{1}{F} \times \frac{1}{\text{weight (in mg.)}} = \mu\text{c./mg.}$$

Three determinations of the activity of the water gave values of 7.11, 7.10, and 7.18 mc./g. Since 14.44 g. of water was produced, the activity yield was 103 mc.

#### Exchange Reaction

Ninety-five milligrams of 2-(p-nitrophenyl)ethyl(trimethyl)-ammonium iodide was weighed into a reaction tube and 1 ml. of tritiated water (7.13 mc.) added. The tube was then sealed and placed in a mineral oil bath at 100° for five and one-half hours (corresponding to about 50% reaction). The tube was opened and the contents were filtered. Picric acid was added to the filtrate to precipitate the remaining reactant. The precipitate was then filtered off, washed with water, recrystallized once from 95% ethyl alcohol, and then dried and analyzed for tritium activity. The increase in activity was found to be .12  $\mu$ c/m mole indicating an exchange of less than 0.1%.

### Preparation of p-Nitrophenylacetic-2-t Acid

Phenylacetic acid (1.8 g.) was sealed in a tube with 1 ml. of tritiated water (7.13 mc./g.). The tube was sealed and heated to 100° for four days, cooled, broken, and the tritiated water recovered by distillation on the vacuum line. The acid was then recrystallized once from water and dried, m.p. 151-2°; lit. (11) 1.4 g. 78% yield. The activity of the acid was 77.7  $\mu\text{c.}/\text{m mole}$ .

Heating of p-nitrophenylacetic acid in basic tritiated water resulted in what was believed to be polymerization.

### Preparation of 2-(p-Nitrophenyl)-3-dimethylaminopropionic-2-t Acid

The tritiated p-nitrophenylacetic acid was shaken with 2 ml. of water and neutralized with a concentrated water solution of dimethylamine. Formaldehyde (1 ml. of formalin) was added and the solution allowed to stand for four days at room temperature. The solid which crystallized out on standing was filtered off. More compound crystallized out on further standing. Unreacted p-nitrophenylacetic acid could be recovered by acidifying the mixture with hydrochloric acid. The desired product was recrystallized from hot water, m.p. 164°; lit. (10) 167°, 1.0 g. 54% yield.

Analysis of the product for tritium showed an activity of 54  $\mu\text{c.}/\text{m mole}$ .

### Isotope Effect in the Mannich Reaction

The molar activity of the 2-(p-nitrophenyl)-3-dimethylaminopropionic-2-t acid should be one-half (38.8  $\mu\text{c.}/\text{m mole}$ ) that of the p-nitrophenyl acetic acid (77.7  $\mu\text{c.}/\text{m mole}$ ) if no intermolecular isotope effect were shown. The activity found for the amino acid was 53.7  $\mu\text{c.}/\text{m mole}$ , which showed the presence of an isotope effect.

Preparation of 2-(p-Nitrophenyl)ethyl-2-t-(trimethyl)ammonium Iodide

The labeled amino acid (1 g.) was mixed with 50 mg. of copper carbonate and 1 ml. of pyridine. The mixture was refluxed until the bubbler attached to the refluxing apparatus showed the evolution of gas had stopped. The pyridine was removed by adding water until a reddish-brown oil separated. The water-pyridine layer was discarded and the oil layer again washed with water.

The oil layer, after extraction with ether and evaporation of the ether, was heated with 3 ml. of methyl iodide in a water bath for one hour, and the iodide which crystallized out on cooling filtered off, recrystallized from 95% ethyl alcohol, and dried, m.p. 197°; Lit. (7) 199°, 0.3 g. yield 21%. Overall yield 9%.

The entire synthesis was repeated until the total amount of salt was 1.23 g. having an activity of approximately 50  $\mu\text{c.}/\text{m mole}$ .

Decomposition of 2-(p-Nitrophenyl)ethyl-2-t-(trimethyl)ammonium Iodide in Water at 100°

Because the iodide salt prepared by methylation of 2-(p-nitrophenyl)ethylamine (7) did not decompose in distilled water at 100°, a buffer solution of pH 7 was prepared from potassium dihydrogen phosphate and sodium hydroxide as given by Clark and Lub (3a).

The first-order reaction constant was found to be 0.202  $\pm$  0.090 in the buffered solution.

The 1.23 g. of labeled salt was diluted with inactive salt to 3 g. This was dissolved in 30 ml. of buffered solution and the mixture heated to dissolve the iodide. The 1-ml. portions were removed for determination of the initial concentration. Two 1-ml. portions and one 2-ml. portion were removed and sealed

in small tubes for the 50%, 65%, 80% reactions. The remaining solution (24 ml.) and the latter three portions were placed in an oil bath at 100°. After 45 minutes the 24-ml. portion was removed from the bath and two 1-ml. portions were removed from it for determination of the extent of reaction by precipitation and weighing of the picrate of the remaining reactant. Because the reaction proceeded faster than calculated, the extent of the reaction was 17%.

The remainder of the 24-ml. portion of the reaction solution was shaken with petroleum ether to extract the p-nitrostyrene. The petroleum ether was then evaporated off and the residue dissolved in 1 ml. of carbon tetrachloride and treated with 5 drops of bromine. The mixture was heated in a water bath for five minutes and the liquid evaporated off with the help of nitrogen gas. The residue was recrystallized from methyl alcohol and water, m.p. 71°; lit. (3) p-nitrostyrene dibromide 72-73°.

The other reaction solutions were removed from the bath at the proper times and the extents of reaction determined by precipitation of the remaining reactant as the picrate which was dried and weighed.

The solution remaining from the reaction mixture stopped at 17% was used for a second run which was stopped at 8%. The solution remaining from this run was used for more trials of the 50%, 60%, and 80% reactions, the picrates of the original and the remaining reactants were assayed for radioactivity.

One hundred milligrams of the 2-(p-nitrophenyl)ethyl-2-t- (trimethyl)ammonium iodide was oxidized with acid dichromate solution

to *p*-nitrobenzoic acid, m.p. 232; lit. 242 (15). The *p*-nitrobenzoic acid showed no detectable radioactivity.

RESULTS

Table I

Decomposition of 2-(p-Nitrophenyl)ethyl-2-t-(trimethyl)ammonium Iodide in Water at 100°

Run	Extent of Reaction (%)	Activity of Picrate ( $\mu\text{c}/\text{mmole}$ )	Activity of p-Nitrostryene Dibromide ( $\mu\text{c}/\text{mmole}$ )
I	0	11.25	
		11.57	
		11.83	
		11.58	
		11.45	
	17.3		5.41 5.45
	43.7	15.10	
		14.80	
	61.8	19.50	
		19.35	
II	0	12.42	
		12.25	
		12.20	
		12.45	
	8.6		5.27 5.05 5.12 5.28
		12.75	
		12.65	
	82.6	29.30	
		29.85	
	III	0	12.75
12.42			
12.75			
50		18.20	
		17.94	
65.4		22.4	
		22.6	
		22.3	
71.1		22.8	



Table II

## Summary of Results

Decomposition of 2-(p-Nitrophenyl)ethyl-2-t-(trimethyl)ammonium Iodide in Water at 100°

Run	Extent of Reaction (%)	Activity of Picrate ( $\mu\text{c}/\text{mmole}$ )	Activity of p-Nitrostyrene Dibromide ( $\mu\text{c}/\text{mmole}$ )	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
I	0	11.53			
	17.3	12.33	5.43	0.455	
	43.7	14.95			0.550
	61.8	19.42			0.458
II	0	12.33			
	8.6	12.70	5.18	0.414	
	82.6	29.58			0.500
III	0	12.64			
	50.0	18.07			0.484
	65.4	22.43			0.459
	71.1	22.80			0.510

## DISCUSSION OF THE RESULTS

The gradual increase in the tritium activity of the remaining reactant as the reaction proceeds shows the presence of an isotope effect in the reaction. The magnitude of the isotope effect is not known as precisely as desired, because of experimental difficulties, but there is no question of its existence. Experimental data are given in Table I, and are summarized in Table II together with calculated values of  $k_3/2k_1$  and  $(k_2 + k_3)/2k_1$ .

The value of  $k_3/2k_1$  for zero extent of reaction can be calculated by extrapolation from the 8.6% and 17.3% reactions; the value obtained in this way is 0.369. The value of  $k_3/2k_1$  can also be calculated by dividing the activity of the product by the average of the activities of the reactant before and after reaction; the values obtained in this way are 0.414 for the 8.6% reaction and 0.455 for the 17.3% reaction. The low value of  $k_3/2k_1$  on extrapolation to zero may be due to the non-linearity of the activity of the reactant to the extent of reaction at high extents of reaction. The value of 0.455 for this ratio may also be due to failure of the method at high extents of reactions. The average value of  $k_3/2k_1$  without the extrapolated value is  $0.434 \pm 0.020$ . If this value is used,  $k_1/k_3$  becomes 1.15, which indicates a 15 percent secondary isotope effect which is in agreement with other known values of the secondary isotope effect of tritium.

The average value of  $(k_2 + k_3)/2k_1$  is found to be 0.493 with an average deviation of 0.027. Using this average value, the intermolecular isotope effect,  $k_1/k_2$ , is found to be 8.5 and the intramolecular isotope effect,  $k_3/k_2$ , is 7.4.

The average deviation in the determination of the extent of reaction in experiments with the inactive 2-(*p*-nitrophenyl)-ethyl(trimethyl)ammonium iodide was found to be not greater than  $\pm 1\%$ . Measurement of the activities gave average deviations no greater than  $\pm 1\%$ .

Using these uncertainties, the value of  $k_3/2k_1$  is known to be 0.434 with a probable error of  $\pm 0.020$ . The value of  $(k_2 + k_3)/2k_1$  is 0.493 with a probable error of  $\pm 0.010$ . The ratio  $k_1/k_2$  is 8.5 with a probable error of  $\pm 3.2$ . The value of  $k_3/k_2$  is then 7.4 with a probable error of  $\pm 2.8$ . The average value of  $k_1/k_3$  is 1.15 with a probable error of  $\pm 0.05$ .

These ratios indicate beyond doubt that the decomposition of 2-(*p*-nitrophenyl)ethyl-2-*t*-(trimethyl)ammonium iodide in water at 100° has a different rate from that of the normal compound. According to the presently accepted theory of the isotope effect this difference in rates is a clear indication that the bond between the hydrogen atom and carbon atom adjacent to the ring is broken in the rate-determining step of the reaction. The point of attack on the molecule is therefore a hydrogen atom on the carbon atom beta to the ammonium group. This mode of attack is general for bimolecular eliminations. Although Hughes and Ingold (7) found unimolecular kinetics for this reaction it must be only pseudo-unimolecular.

### SUMMARY

The tritium isotope effect in the decomposition of 2-(p-nitro-phenyl)ethyl-2-t-(trimethyl)ammonium iodide in water at 100° has been measured. The normal molecule reacts at a rate 8.5 times as fast as the labeled molecule. A hydrogen atom, on the carbon atom adjacent to the ring is removed from a labeled molecule 7.4 as rapidly as a tritium atom in the same position. A hydrogen atom in this same position in an inactive molecule is removed 1.15 as fast as a hydrogen atom in the corresponding position of the labeled molecule.

The existence of these differences in rate of reaction establish the mechanism of the decomposition as being that of an attack on the hydrogen atom in the beta position to the ammonium group.

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