

TRITIUM AND NITROGEN-15 ISOTOPE EFFECTS IN THE DECOMPOSITION OF *p*-NITRO- PHENETHYLTRIMETHYLAMMONIUM IODIDE

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THEORETICAL TREATMENT

Hughes and Ingold¹ reported that the decomposition of phenethyltrimethylammonium hydroxide in water at 100° is first order in hydroxide ion and first order in the cation. *p*-Nitrophenethyltrimethylammonium iodide and the corresponding bromide each decompose in water at 100° with unimolecular kinetics. These latter decompositions are retarded by acids, unaffected by neutral salts and accelerated by bases although the rate constants were not reported.

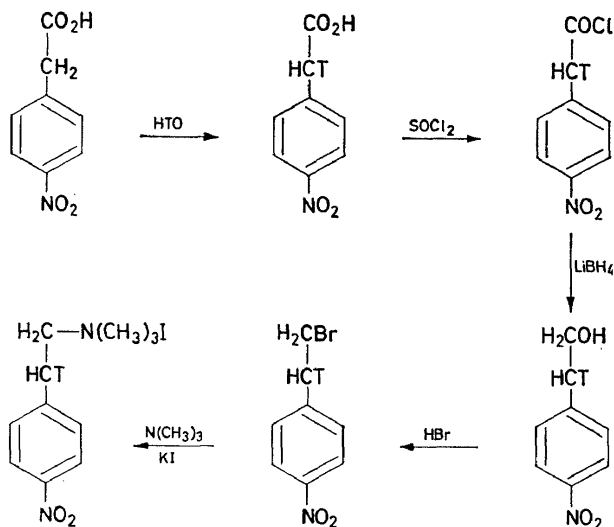
Hodnett and Flynn² investigated the decomposition of *p*-nitrophenethyltrimethylammonium iodide by measurement of the tritium isotope effect. The occurrence of an isotope effect in the decomposition of *p*-nitrophenethyl-2-*t*-trimethylammonium iodide indicates that the rate-determining step of the reaction involves the breaking of a carbon-hydrogen bond. However, the nature of the attacking reagent was not determined and a complete picture of the activated complex was not established. The decomposition could proceed by (i) a carbanion mechanism in which a β -hydrogen ion is extracted in the rate-determining step of the reaction with subsequent ejection of the trimethylamine group, or (ii) a concerted mechanism in which the carbon-nitrogen and carbon-hydrogen bonds are broken simultaneously.

In the present investigation *p*-nitrophenethyl-2-*t*-trimethylammonium iodide was prepared by the reactions indicated by the following equations (on page 386).

The kinetics of the decomposition of the salt were studied in both aqueous and non-aqueous media and the reaction rate constants for the decomposition were determined. Solutions of *p*-nitrophenethyl-trimethylammonium iodide were sealed in tubes and maintained at 98° for various times. The unreacted salt was precipitated as the picrate which was washed, dried and weighed to determine the extent of reaction. The labelled salt was treated in the same manner, and the picrates were assayed for tritium. For low extents of reaction the *p*-nitrostyrene formed by the decomposition was isolated, and the dibromo derivative of this compound was prepared. The *p*-nitrostyrene dibromide was purified and assayed for tritium. From these data it was possible to calculate the various tritium isotope effects in the reaction.

The nitrogen isotope effect was determined with the salt containing only

the natural abundance of nitrogen-15. Solutions of the salt were sealed in tubes and held at 98° for various times. When the solution was cooled, the unreacted salt precipitated from solution, and was filtered, washed and dried. The nitrogen in the unreacted salt was collected by the Dumas³ method,



dried by passage over barium oxide and sealed in tubes for mass spectrographic analysis.

EXPERIMENTAL STUDY

Preparation of *p*-nitrophenethyltrimethylammonium iodide

p-Nitrophenethyltrimethylammonium iodide was prepared by the method of Hodnett and Flynn², m.p. 203–204°.

Preparation of *p*-nitrophenethyl-2-t-trimethylammonium iodide

p-Nitrophenylacetic acid (10 g) was dissolved in a solution of 1 ml of tritiated water⁴ (92 mc/g), 10 ml of dioxan and a trace of sodium hydroxide. The exchange was allowed to proceed for three days at 98°. The water-dioxan solution was distilled on a vacuum line and the organic acid was recrystallized from boiling water by the addition of hydrochloric acid. The tritiated acid was refluxed with thionyl chloride (10 ml) until fuming ceased and the excess thionyl chloride removed by vacuum distillation. The acid chloride was then reduced with lithium borohydride and the resulting alcohol was refluxed with 30 ml of 47 per cent hydrobromic acid. The *p*-nitrophenethyl-2-t bromide was recrystallized from petroleum ether (boiling range 61–75°), m.p. 66–68° (lit.⁵ 68°).

p-Nitrophenethyl-2-t bromide (6.5 g) was placed in an Erlenmeyer flask with 6 g of potassium iodide and 16 ml of a 25 per cent solution of trimethylamine in methanol. The mixture was allowed to react at 2° for 3 days. The solid which crystallized was separated and washed with cold

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water to remove the excess potassium iodide. The crude *p*-nitrophenethyl-2-t-trimethylammonium iodide was recrystallized twice from 95 per cent ethanol and dried *in vacuo*, m.p. 200–203° (lit.¹ 199°).

Kinetics in aqueous solution

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 Lubs⁶. Approximately 2.4 g of the iodide salt was dissolved in enough buffer solution to bring the total volume to 50 ml. Five-millilitre aliquots were pipetted into several vials and the vials were sealed and placed in a constant-temperature bath maintained at 98°. At various times the samples were removed from the bath and the unreacted salt precipitated as the picrate by the addition of 30 ml of saturated picric acid solution. The mixture was filtered and the dried picrate weighed to determine the extent of reaction.

Kinetics in non-aqueous solutions

The experimental procedure for studying the kinetics of the decomposition in non-aqueous solutions was the same as for the studies in aqueous solutions except that the iodide salt was weighed separately into each vial and the appropriate amount of solution pipetted into each vial. The solutions used for the non-aqueous studies were 6.01 per cent by weight of formamide in absolute ethanol, and 4.97 per cent by weight of *N,N*-dimethylformamide in absolute ethanol.

Kinetic isotope effect with tritium

Samples of the labelled salt were weighed into vials and the solvent to be used was added to each vial. The vials were sealed and placed in an oil bath at 98°. Samples were removed at various times corresponding to approximately 5, 40, 50, 60, and 80 per cent completion of the reaction and the unreacted iodide salt was precipitated as the picrate. The picrates were filtered, weighed and assayed according to the method of Wilzbach *et al.*^{7, 8}. Two samples were removed from the bath when the reaction was approximately 5 per cent complete; one was used to determine the extent of reaction, and the second one was extracted with carbon tetrachloride to remove the *p*-nitrostyrene formed by the decomposition. The dibromo derivative formed by the addition of bromine to the latter compound was recrystallized from water-methanol solution, dried and assayed for tritium. All assays were made using a vibrating reed electrometer.

Kinetic isotope effect with nitrogen-15

The nitrogen-15 isotope effect was studied in aqueous solutions buffered at a pH of 6.0. Approximately 0.5 g of the iodide salt were weighed into each of three reaction vials and 10 ml of buffer solution added. The vials were sealed and placed in an oil bath at 98° until 80 per cent of the starting material had reacted. The unreacted salt was precipitated by cooling the solution. All the nitrogen of the unreacted salt was converted to nitrogen

gas by a modified Dumas method and assayed for nitrogen-15 on a mass spectrograph.

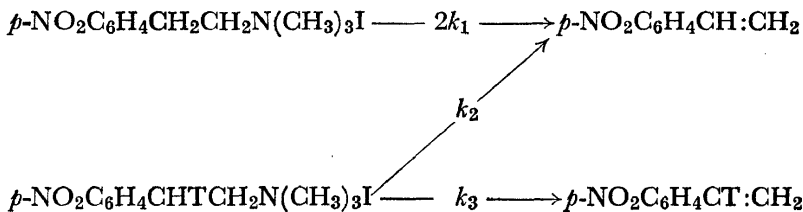
RESULTS

First-order kinetics were obtained for all reactions, and linear dependency on the hydroxide ion concentration was shown. When more than one experiment was carried out at the same pH, the values of the first-order reaction rate constants were averaged and the average value was divided by the hydroxide ion concentration to obtain the second-order rate constant. The second-order rate constants are listed in *Table 1*.

Table 1. Decomposition of *p*-nitrophenethyltrimethylammonium iodide in aqueous solution at 98°

pH of solution	First-order rate (h^{-1})	Concentration of hydroxide ion (mole/l. $\times 10^{10}$)	Second-order rate constant (l./mole-sec)
4.60	0.000857	3.98	597 \pm 21
5.30	0.00421	20.0	586 \pm 61
6.00	0.0218	100	606 \pm 51
6.20	0.0316	159	553 \pm 63
6.60	0.0774	398	542 \pm 39
7.00	0.151	1000	447 \pm 28

Three reactions are involved in the decomposition of *p*-nitrophenethyl-2-t-trimethylammonium iodide:



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 , can be calculated from the following equations⁹:

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

and

$$k_3/2k_1 = N_3/N_1 \text{ (as } f \rightarrow 0\text{)}$$

where f is the fraction reacted, N_2 is the molar activity of the reactant at that time, N_1 is the initial molar activity of the reactant and N_3 is the molar activity of the reaction product.

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 Table 2. Decomposition of *p*-nitrophenethyl-2-t-trimethylammonium iodide

<i>Solution</i>	<i>Extent of reaction (%)</i>	<i>Activity of picrate ($\mu\text{C}/\text{mmole}$)</i>	<i>Activity of p-nitrostyrene dibromide ($\mu\text{C}/\text{mmole}$)</i>	$\frac{k_3}{2k_1}$	$\frac{k_2 + k_3}{2k_1}$
Water, pH = 6.0	0	5.94	2.58	0.424	0.662
	4.4	6.22			
	48.7	7.45			
	53.6	7.75			
	75.9	9.19			
Water, pH = 6.0	0	4.06	1.71	0.408	0.623
	7.7	4.32			
	48.7	5.22			
	55.7	5.53			
	72.7	6.00			
Water, pH = 6.0	0	4.05	1.71	0.416	
Water, pH = 6.6	0	3.96	1.71	0.417	0.642
	9.3	4.28			
	44.2	4.86			
	54.5	5.36			
	74.2	6.16			
Ethanol, 6.01% formamide	0	4.13	2.17	0.517	0.731
	7.7				
	39.4	4.79			
	44.6	4.95			
	52.0	5.00			
80.2	6.40				
Ethanol, 6.01% formamide	0	4.26	2.19	0.515	
	7.5				
Ethanol, 4.97% <i>N,N</i> -dimethyl- formamide	0	4.01	2.07	0.517	0.693
	10.0				
	21.1	4.31			
	34.1	4.36			
	57.4	4.95			
80.5	6.04				

The data obtained in the investigation of the tritium isotope effect are summarized in Table 2; each radioactivity value represents 2 to 6 assays for which the average deviation is not greater than ± 0.5 per cent. The magnitudes of the various isotope effects have been calculated and are listed together with their average deviations in Table 3.

Table 3. Tritium isotope effects

<i>Solvent</i>	<i>Intermolecular</i> k_1/k_2	<i>Intramolecular</i> k_3/k_2	<i>Secondary</i> k_1/k_3
Water, pH 6.0	2.12 ± 0.31	1.76 ± 0.28	$1.20_5 \pm 0.01_5$
Water, pH 6.6	2.47 ± 0.12	1.99 ± 0.31	$1.20_0 \pm 0.01_5$
Ethanol, 6.01% formamide	2.28 ± 0.22	2.35 ± 0.25	0.97 ± 0.02
Ethanol, 4.97% <i>N,N</i> -dimethylformamide	2.20 ± 0.30	2.27 ± 0.31	0.97 ± 0.01

These values do not differ widely from those obtained by Hodnett and Flynn² except for the value of k_3/k_2 . Since the values of $(k_3 + k_2)/2k_1$ and $k_3/2k_1$ differ by a small amount there is considerable uncertainty in the value of k_3/k_2 . However the magnitude of the ratio $k_3/2k_1$ has little uncertainty. The values given in *Table 3* for the various isotope effects are considered to be more nearly correct than previous values reported².

Table 4. Assay of the iodide salt for nitrogen-15

<i>Extent of reaction (%)</i>	<i>Nitrogen-15, (atom-%)</i>			<i>Average</i>
0	0.358	0.357	0.357	0.357 ± 0.001
	0.358	0.356	0.359	
	0.359	0.355	0.358	
80	0.362	0.363	0.363	0.364 ± 0.001
	0.365	0.362	0.362	
	0.363	0.368	0.365	
	0.365	0.364	0.365	

Data obtained in the nitrogen-15 isotope effect study are summarized in *Table 4*. Since the iodide salt contains two nitrogen atoms per molecule and since only one of these is directly involved in the decomposition, the difference in the observed values for nitrogen-15 is one-half of the actual difference due to the isotope effect. The value of the nitrogen isotope effect may then be calculated from the following equation¹⁰,

$$\frac{k^*}{\bar{k}} = 1 + \frac{\log(^{15}\text{N}/^{14}\text{N}) / (^{15}\text{N}_0 / ^{14}\text{N}_0)}{\log(1 - f)}$$

where f is the fraction reacted, $(^{15}\text{N}/^{14}\text{N})$ is the ratio determined at f , and $(^{15}\text{N}_0 / ^{14}\text{N}_0)$ is the initial ratio of nitrogen-15 to nitrogen-14. The magnitude of the nitrogen isotope effect is 1.024 ± 0.004 .

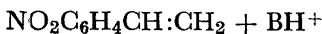
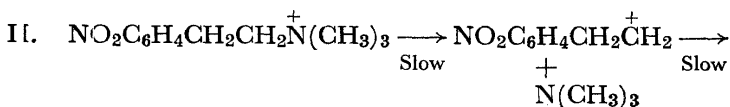
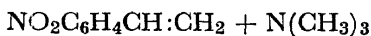
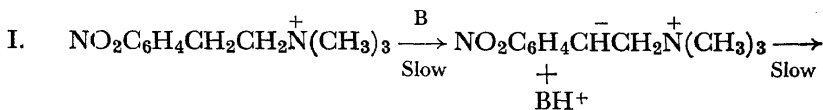
DISCUSSION

The kinetic studies show that the active reagent in aqueous solution is the hydroxide ion, while in the alcohol solutions the basic molecule is formamide or *N,N*-dimethylformamide. No decomposition was observed in alcohol solutions in the absence of formamide and *N,N*-dimethylformamide.

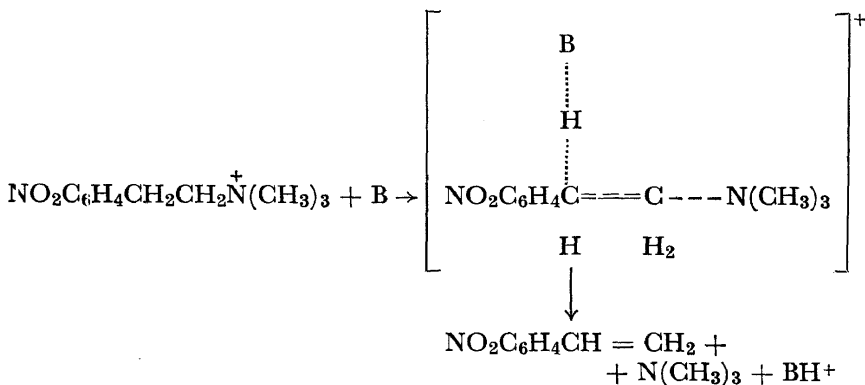
The difference in the reaction rates for the compounds containing tritium and nitrogen-15 indicates that the bond between a hydrogen atom and the carbon atom adjacent to the ring and the bond between a carbon atom and the ammonium nitrogen atom are both broken in the rate-determining step of the reaction. If the mechanism involved removal of only the hydrogen atom or the trimethylamine group in the rate-determining step of the reaction, with subsequent removal of the second group in a fast step, both isotope effects would not have been exhibited. On the other hand, if the

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removal of the second group were also a slow step the decomposition could proceed by either of the following mechanisms.



If mechanism I is correct, the first step of the reaction should be reversible. However, Hodnett and Flynn² studied the decomposition of the iodide salt in tritiated water and found no tritium in the remaining reactant. If mechanism II is correct, the first step should again be reversible. However, Hughes and Ingold¹ have studied the rates of decomposition in solutions with and without excess trimethylamine and found no difference in reaction rates. The reaction therefore appears to have a concerted mechanism which is presented by the following equations:



Maximum values for kinetic isotope effects in three-centre reactions are found when bond formation and bond breaking occur at the same rate. If reasonable assumptions are made, the magnitude of the maximum tritium isotope effect in this reaction can be calculated by the Wiberg equation¹¹ to be 8.58. Since the tritium isotope effects found for this reaction are far less than the maximum, it is evident that in the transition state the C-H bond is still quite strong or that the B-H bond is already strong. In this case the transition state is assumed to be more like the product than like the reactant; that is, the proton is considerably detached from the carbon atom. This judgement is based on the well-known electron-attracting ability of the nitro group which should activate the hydrogen atom on the carbon next to the ring.

When the maximum nitrogen-15 isotope effect is calculated by either the Bigeleisen equation¹² or the Eyring-Cagle equation¹³, the value of 1.041 is obtained. This value is much higher than the observed value of 1.024. Again the transition state may be more like the product than like the reactant. The carbon-nitrogen bond may be quite weak and the carbon-carbon bond almost double.

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