

THE ISOTOPE EFFECT OF CARBON-14 IN THE DECOMPOSITION REACTION
OF p-NITROPHENETHYL-1-¹⁴C-TRIMETHYLAMMONIUM IODIDE

By

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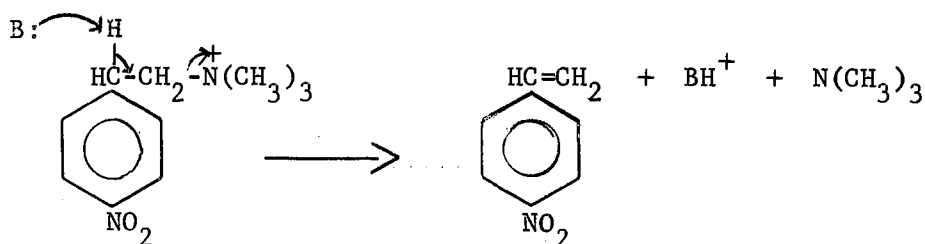
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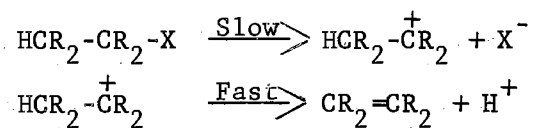
INTRODUCTION

The formation of olefins by the decomposition of tetraalkylammonium ions often proceeds by way of a concerted mechanism in which a proton beta to the ammonium group is abstracted by a base with the simultaneous elimination of a tertiary amine. In the case of the *p*-nitrophenethyltrimethylammonium ion this can be presented as shown (12).



This mechanism is bimolecular in nature.

Olefins are also known to be formed according to a unimolecular mechanism involving initial formation of a carbonium ion.

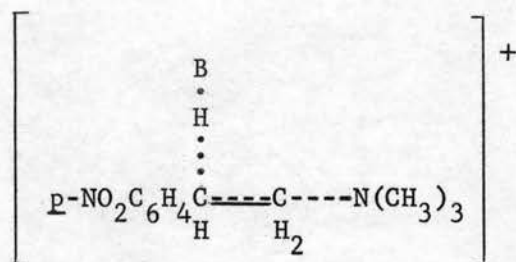


For example, X could be $\overset{+}{\text{N}}\text{R}_3$ (11). In 1933 Hughes and Ingold (9) studied the kinetics of the olefin-forming elimination of trimethylamine from *p*-nitrophenethyltrimethylammonium iodide and proposed the bimolecular mechanism.

To validate this mechanism, Hodnett and Flynn (7) in 1957 decomposed a sample of the iodide containing tracer amounts of tritium in the position beta to the ammonium group in aqueous solution at 100°. The observation

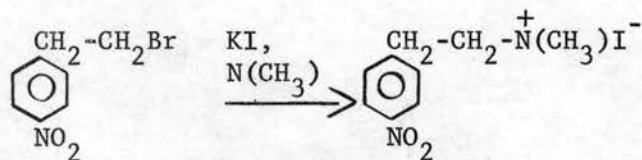
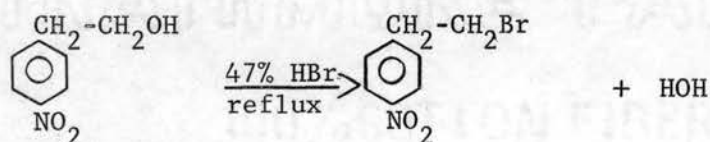
of a tritium isotope effect under these conditions established the mechanism of the decomposition as being that of an attack on the hydrogen atom in the position beta to the ammonium group.

In a further study of the elimination process, Hodnett and Sparapany (8) in 1964 observed a nitrogen-15 isotope effect. This suggests that the carbon-hydrogen and carbon-nitrogen bonds are broken simultaneously in the rate-determining step. They were able to propose the transition state as outlined.



The main purpose of this research was to determine whether a carbon-14 isotope effect was observable in the decomposition of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide. In addition it was anticipated that further evidence could be obtained concerning the transition state in the olefin-forming decomposition of tetraalkylammonium ions.

In the synthesis of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide it was necessary to prepare *p*-nitrophenethyl bromide and *p*-nitrophenethyl-trimethylammonium iodide.



Carbon-14 was placed in the position beta to the ring in both cases and the position of this isotopic carbon in the products was determined in order to gain information about the mechanisms of these reactions.

HISTORICAL

Isotope Effects

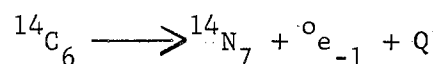
In the course of studying reaction mechanisms by the use of labeling techniques, it was found that isotopic substitution caused appreciable variation in the rates of certain reactions. This difference in reaction rates of isotopically substituted compounds is the isotope effect. It arises from the difference in masses of the nuclei of the isotopes.

Two atoms bound to each other are vibrating at a certain frequency, even in their lowest energy state. Associated with this vibration is a particular energy, the zero-point energy, which persists to absolute zero. The vibrational frequency of bonding is greater for a light isotope than for a heavy one, therefore, the zero-point energy will be greater for the light isotope. Since the C-H bond has a greater zero-point energy associated with it, than the C-D bond, for example, the C-H bond is less stable and will react faster than the C-D bond.

If the bond to a labeled atom is broken or stretched in the rate-determining step of a complex reaction, the isotope effect that results can be used to study the mechanism of the reaction. Wiberg and Stewart (14) found that in the oxidation of benzaldehyde by neutral permanganate, the C-H bond in the aldehyde group is broken in the rate-determining step. This was concluded from the fact that ordinary benzaldehyde at pH 7 is oxidized by permanganate at a rate 7.5 times as fast as C_6H_5CDO .

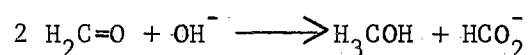
Isotope Effects of Carbon-14

Carbon-14 is a naturally occurring unstable isotope of carbon. It has a half-life of 5,570 years and decays by β -emission according to the following reaction (10).



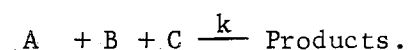
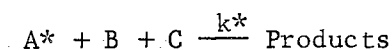
The emitted electron has an average energy of 0.049 Mev. Because the carbon-14 radiation is easily measured and because the isotope is easily placed in specific reaction centers, it is used widely in the study of mechanisms.

Downes and Harris (4) found in the Cannizzaro reaction that a



carbon-14 isotope effect of 0.9434 exists. In determining the isotope effect of this reaction, Downes and Harris used the following mathematical treatment.

Consider a reaction involving A^* and A , where A^* represents the labeled reactant compound and A the unlabeled one. Consider the reaction is of order n with respect to this compound and of orders p, q with respect to other reactants (unlabeled) B, C



If A^*_0 represents a trace concentration, the rate expressions for the reactions involving A^*_0 and A_0 , where A^*_0 and A_0 are initial concentrations, are:

$$- d(A)/dt = k (A)^n (B)^p (C)^q \quad \text{Eq. 1}$$

$$- d(A^*)/dt = k^* (A^*) (A)^{n-1} (B)^p (C)^q \quad \text{Eq. 2}$$

Division of Eq. 2 by Eq. 1 and integration from the initial concentrations A_0^* and A_0 to some extent of reaction where the concentrations of the isotopes are A^* and A respectively leads to a new equation

$$\log (A^*)/(A_0^*) = k^*/k \log (A)/(A_0) \quad \text{Eq. 3}$$

Assume that $(A^*)/(A_0^*)$ and $(A)/(A_0)$ are equal to the fractions of A^* and A unreacted, respectively. Then if we let x^* and x represent the fractions of A^* and A that have reacted, $(1-x^*) = (A^*)/(A_0^*)$ and $(1-x) = (A)/(A_0)$. Substituting these terms into Eq. 3 and taking antilogs give an expression for each.

$$(1-x^*) = (1-x)^{k^*/k} \quad \text{Eq. 4}$$

$$(1-x) = (1-x^*)^{k/k^*} \quad \text{Eq. 5}$$

Division of Eq. 4 by Eq. 5 gives Eq. 6.

$$(1-x^*)/(1-x) = (1-x)^{(k^*/k)-1} \quad \text{Eq. 6}$$

Since the labeled reactant, A^* , occurs in such a small amount of a macroscopic sample of A , the unlabeled reactant, the fraction of A reacted can be treated as the fraction of total reaction f , that is, $(1-f)$ is equal to $(1-x)$, the fraction of reactant unchanged. Substitution of this term into the right side of Eq. 6 and original values for $(1-x^*)$ and $(1-x)$ into the left side gives, after rearrangement Eq. 7.

$$\frac{(A^*)/(A)}{(A_0^*)/(A_0)} = (1-f)^{(k^*/k)-1} \quad \text{Eq. 7}$$

$r(A^*)/(A)$ and $r(A_0^*)/(A_0)$ are molar radioactivities, N^* and N , after the extent of reaction, f , and at initial value. In terms of molar

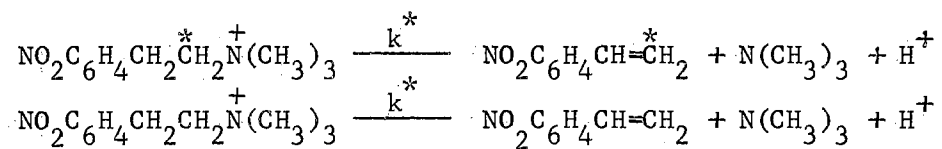
radioactivities, after converting to logarithms and rearranging we have:

$$k^*/k = 1 + \frac{\log N^*/N}{\log (1-f)} \quad \text{Eq. 9}$$

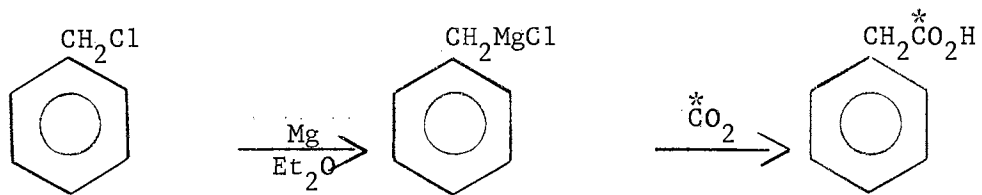
This expression was used to calculate the isotope effect in this work.

INTRODUCTION TO THE EXPERIMENTAL

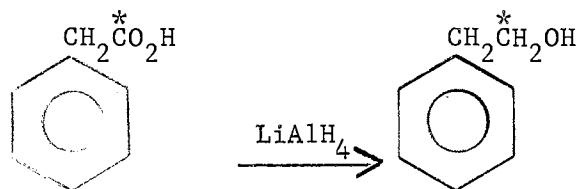
To determine isotope effect, a known isotopic mixture is subjected to an incomplete reaction, the unreacted starting material is isolated and examined for any change in the isotopic composition occurred during the reaction. The required labeled and unlabeled compounds were decomposed in the reactions shown.



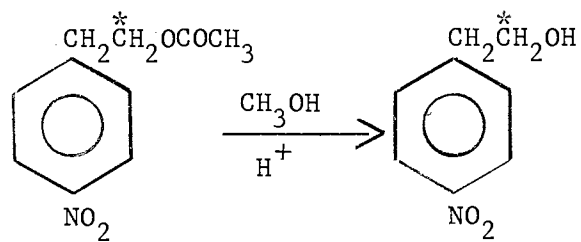
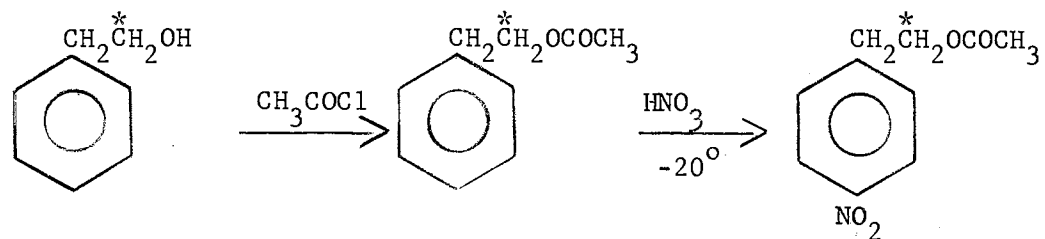
The labeled salt was prepared according to the procedure on the following page.



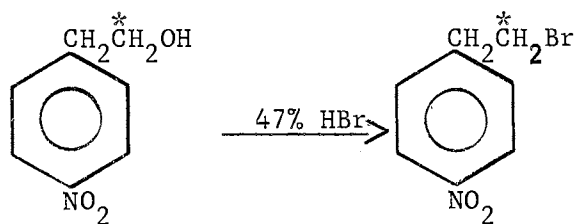
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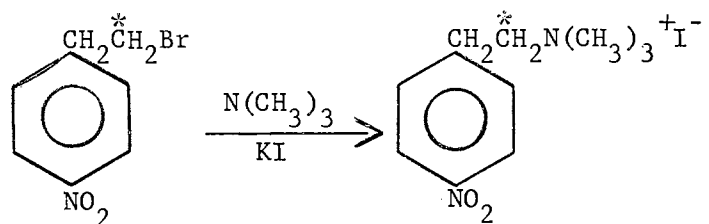
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3



4



5

After each reaction (1-5) a portion of the product was oxidized to the corresponding benzoic acid derivative by basic permanganate, and the acid was purified and assayed for carbon-14 to show whether any rearrangement of the side chain had occurred in each reaction. In the *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide used in this investigation, 99.46% of the carbon-14 was found to be in the position beta to the ring.

The isotope effect measured in this work was an inter-molecular effect or a measure of the reactivity of a normal molecule relative to that of an isotopically labeled molecule for a particular reaction. The mathematical equation used to determine this ratio is Eq. 9:

$$k^*/k = 1 + \frac{\log N^*/N}{\log(1-f)} \quad \text{Eq. 9}$$

f = fraction reacted

k* = rate of reaction of the labeled compound

k = rate of reaction of the normal compound

N* = molar activity of the isotopic mixture of reactant
after fraction of reaction f.

N = molar activity of initial reactant.

In order to use this expression it was necessary to:

1. Know the activity of the starting material, N
2. Allow the reaction to proceed to a degree of completion, f
3. Isolate, purify and determine the activity, N*, of the unreacted starting material at extent of reaction, f.

To determine these values about one gram of the isotopic mixture of the iodide salt was dissolved in 25 ml. of a solution buffered to pH 7. Two 5-ml. portions were removed and the iodide was precipitated as the picrate with a saturated solution of sodium picrate. The picrate was

dried, recrystallized from hot water and assayed for carbon-14. From this value the molar activity of the starting material, or N , was determined. The remaining three 5-ml. portions were sealed in separate reaction tubes and allowed to react at 100° for about 5 hr.

The reacted portions were precipitated with the saturated sodium picrate solution; the picrate precipitate was dried and weighed. This amount of picrate divided by the amount of picrate at initial reaction time gave the fraction of unreacted starting material or the value of $(1-f)$. This picrate precipitate was recrystallized and assayed, which gave N^* , the molar activity of the unreacted starting material at the extent of reaction f .

The wet oxidation method of assay was used to determine the carbon-14 activities of the samples. Samples were oxidized by Van Slyke-Folch solution, prepared by the method given by Calvin *et al.* (1). The apparatus in Figure 1 was used. The sample was placed in tube C; the oxidizing solution was added by using stopcock I and the sample heated to effect complete oxidation. The carbon dioxide produced passed through the U-tube E, which contained stannous chloride to remove halogens. From there it passed through tube E', which contained lead peroxide to remove nitrogen oxides, and from there into the ionization chamber.

The instrument used to measure the ion current was an Applied Physics Corporation Model 30 vibrating reed electrometer. The activity of the carbon dioxide was recorded in millivolts by this instrument and was converted to molar activity by the factor developed below:

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

$$1 \text{ disintegration of carbon-14 in } \text{CO}_2 = 1.39 \times 10^{-16} \text{ coulombs (14)}$$

$$\text{reistor} = 1 \times 10^{10} \text{ ohms}$$

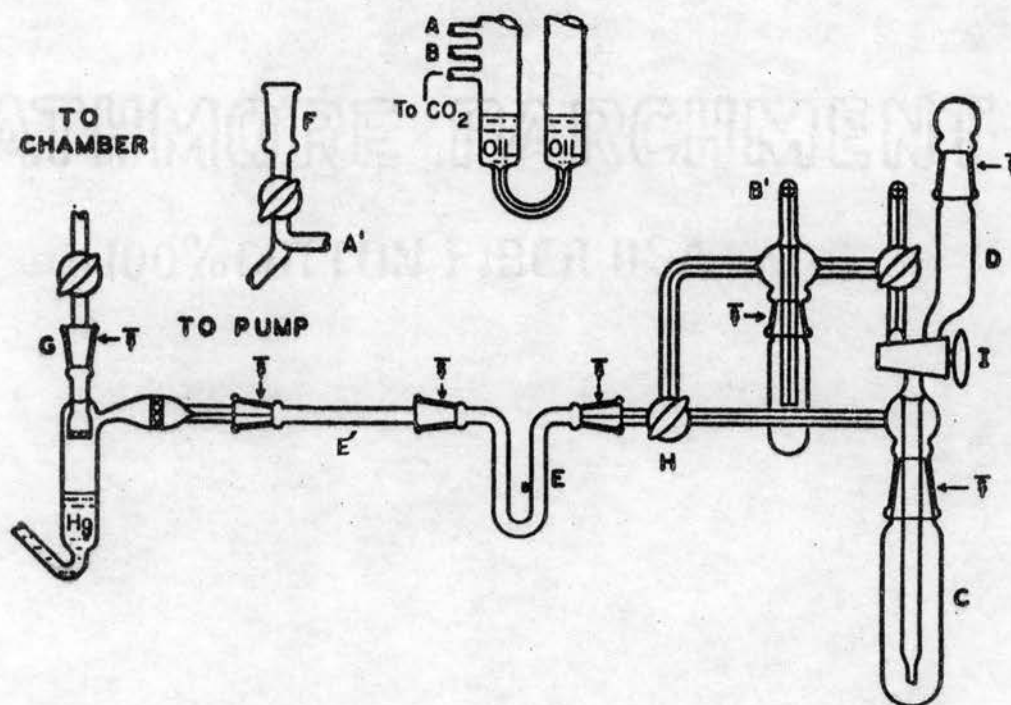


Fig. I Carbon-14 Assay Apparatus

$$1 \text{ curie} = 3.7 \times 10^{10} \times 1.39 \times 10^{-16} \text{ coulombs/sec.}$$

$$= 5.143 \times 10^{-6} \text{ amperes}$$

$$= 5.143 \times 10^{-6} \times 10^{12} \text{ ampere ohms}$$

$$= 5.143 \times 10^{-6} \text{ volts}$$

$$1. \text{ microcurie} - 5.143 \times 10^3 \text{ millivolts}$$

$$1 \text{ millivolt} = 1.944 \times 10^{-4} \text{ microcuries}$$

Converting the millivoltage recorded by the vibrating reed electrometer to molar activity was done by means of the following equation.

$$\frac{\text{millivolts} \times 1.944 \times 10^{-4} \mu\text{c/mv}}{\text{sample weight in mg.}} = \frac{\mu\text{c./mmole}}{\text{mg./mmole}}$$

EXPERIMENTAL

Preparation of Phenylacetic Acid-carboxyl-¹⁴C

The compound was synthesized, with modifications, according to the method of Calvin et al. (1). The Grignard reagent was prepared under nitrogen atmosphere using 0.55 g.(23 mmoles) of magnesium turnings and 2.55 g.(21 mmoles) of α -chlorotoluene in 20 ml. of anhydrous ether. The Grignard reagent was analyzed by decomposing a known volume of the reagent with an excess of standard hydrochloric acid. The excess hydrochloric acid was titrated with standard sodium hydroxide, giving the volume of acid equivalent to the volume of Grignard reagent. From this the concentration of the Grignard reagent was found to be 0.82 M.

The carbonation of the Grignard was effected on the vacuum line using the apparatus in Figure 2. Liquid nitrogen was used to freeze the Grignard solution; the apparatus was evacuated and the carbon dioxide-¹⁴C generated by concentrated sulfuric acid from 1.62 g.(8.2 mmoles, containing 1.2 mc. of carbon-14) of barium carbonate was trapped and sealed in the reaction tube with the Grignard solution. The mixture was placed in an ice-salt slush(-20°) and allowed to react at this temperature. The Grignard complex was worked up according to the diagram on the following page.

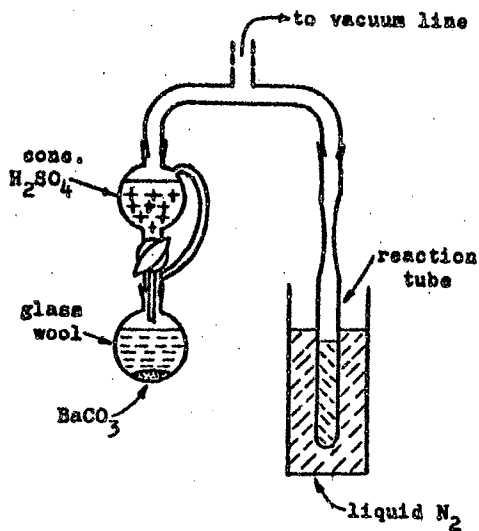
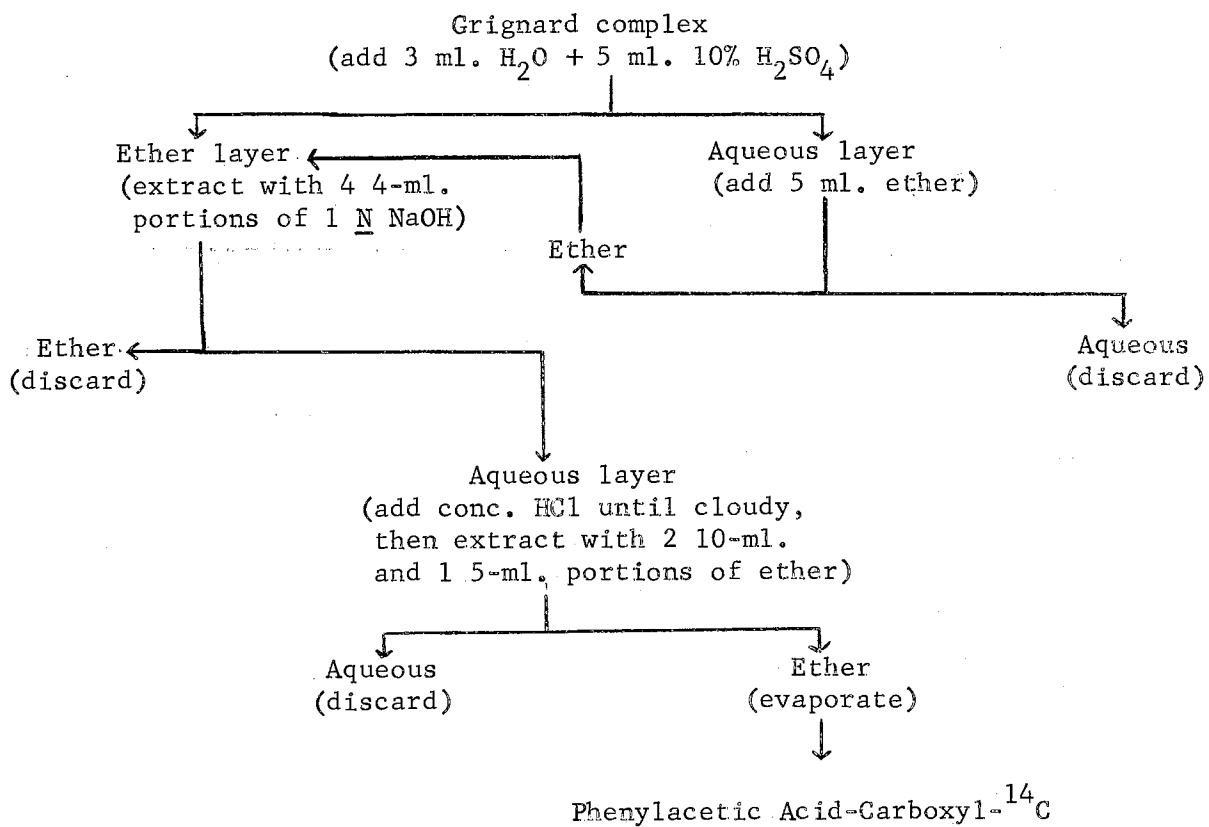


Fig. II. Carbonation Apparatus



The yield of phenylacetic acid-carboxyl- ^{14}C was 0.85 g. (6.2 mmoles) (76%), melting point 74.5° ; lit., 76.5° (1). The activity of the acid was $125 \mu\text{c}/\text{mmole}$. The radioactivity yield was 65%. Oxidation to benzoic acid and assay thereof showed 99.95% of the carbon-14 in the position beta to the ring.

Preparation of 2-Phenylethanol-1- ^{14}C

The 0.85 g. (6.2 mmoles) of phenylacetic acid-carboxyl- ^{14}C was diluted to 13.6 g. (100 mmoles) with normal phenylacetic acid and reduced with 4.35 g. (115 mmoles) of lithium aluminum hydride according to the directions of Nystrom and Brown (3). The product was purified by vacuum distillation. The yield was 11.5 g. (94 mmoles, 94% of theory) of 2-phenylethanol-1- ^{14}C which gave on assay an activity of $8.23 \mu\text{c}/\text{mmole}$. The radioactivity yield based on phenylacetic acid was 96%. Oxidation to benzoic acid and assay thereof showed 99.81% of the carbon-14 in the position beta to the ring.

Preparation of 2-(p-Nitrophenyl)ethanol-1- ^{14}C

The nitration of 2-phenylethanol-1- ^{14}C was essentially the procedure of Woodburn and Stuntz (16), with modifications. After the 2-phenylethanol-1- ^{14}C (11.5 g.) was diluted to 30 g. (406 mmoles) with normal 2-phenylethanol, the resulting mixture was esterified with 20 g. of acetyl chloride. The ester was added dropwise to 150 ml. of fuming nitric acid (sp. gr. 1.5) which was cooled to -20° by a dry ice-acetone-chloroform mixture. After complete addition of the ester, the mixture was poured over crushed ice and the product extracted with several portions of ether. The ethereal solution was dried overnight with anhydrous magnesium sulfate and the ether was evaporated. The oil that remained was refluxed one hour

with 80 ml. of a solution containing 2% of hydrogen chloride in methanol. The methyl acetate from the transesterification and the excess methanol were distilled leaving a dark red oil. The oil was a mixture of the ortho and para nitro isomers of the product. Separation was effected by cooling the oil to -10° and filtering the slush while it was cold. A yellowish mass of crystals remained that was recrystallized from carbon tetrachloride. Ten and two-tenths grams (45 mmoles, 25% of the theoretical yield) of 2-(p-nitrophenyl)ethanol-1- ^{14}C was isolated. It melted at 60° ; lit., 62° (16). The radioactivity was 3.15 $\mu\text{c.}/\text{mmole}$, and the radioactivity yield from 2-phenylethanol was 18.4%. Oxidation to p-nitrobenzoic acid and assay thereof showed that 99.69% of the carbon-14 was in the position, beta to the ring.

Preparation of p-Nitrophenethyl-1- ^{14}C Bromide

Ten and two-tenths grams (45 mmoles) of 2-(p-nitrophenyl)ethanol-1- ^{14}C was boiled for 24 hr. with 7.5 ml. of 48% hydrobromic acid and 0.5 ml. of concentrated sulfuric acid. The product was extracted with benzene and recrystallized from ethanol. The melting point of the p-nitrophenethyl-1- ^{14}C bromide was 64° ; lit., 68° (6). The yield was 12.6 g. (55 mmoles, 83% of theory). The radio activity was 3.12 $\mu\text{c.}/\text{mmole}$. and the radioactivity yield from 2-(p-nitrophenyl)ethanol was 89%. The assay of the oxidized product, p-nitrobenzoic acid showed that 99.49% of the carbon-14 was in the position beta to the ring.

Preparation of p-Nitrophenethyl-1- ^{14}C -trimethylammonium Iodide

Two 5-g. (22 mmoles) portions of p-nitrophenethyl-1- ^{14}C bromide were placed in Erlenmeyer flasks with 3 g. (18 mmole) of potassium iodide

and 22.5 ml. of a 25% trimethylamine in methanol solution. The mixture was allowed to react at room temperature for two weeks. Yellow crystals formed on the bottom and sides of the flask and were filtered and re-crystallized from ethanol. The yield was 7 g. (21 mmoles, 51% of theory) of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide which melted at 207°; lit., 199° (9). The radioactivity was 3.10 μc./mmole. The radioactivity yield was 45%. When the oxidation product, *p*-nitrobenzoic acid, was assayed it showed that 99.46% of the carbon-14 was in the carbon atom beta to the ring.

Decomposition of *p*-Nitrophenethyl-1-¹⁴C-trimethylammonium Iodide

The decomposition was done by dissolving approximately 1.2 g. (3.6 mmole) of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide in 25 ml. of a buffer solution of pH 7 made according to the procedure of Clark and Lubs (3). Two 5-ml. samples were precipitated at zero reaction time to determine the activity of the starting material. The remaining 5-ml. portions were sealed in reaction tubes and allowed to react at 100° for approximately 5 hr. This gave a conversion of approximately 70%. The reaction was stopped, the unreacted starting material was precipitated as the picrate, recrystallized from hot water and assayed. This gave the molar activity of the unreacted starting material.

Three decompositions were run according to this procedure. Each sample was assayed four times and the average activities of the four taken. Results are given in Table I, II, and III. From these data the isotope effect for the decomposition was calculated using Equation 9.

Rearrangement in the Reaction of 2-(p-Nitrophenyl)ethanol-1-¹⁴C with Hydrogen Bromide

Five hundred mg. (2.2 mmole) of p-nitrophenethyl-1-¹⁴C bromide (3.15 μ c./mmole) prepared as previously described was boiled for 3 hr. with 1.6 g. of potassium permanganate, 0.4 g. of sodium hydroxide and 15 ml. of water. The solution was filtered while hot to remove manganese dioxide, made acidic with concentrated hydrochloric acid, and extracted with ether. Evaporation of the ether left a yellowish mass which after recrystallization from ethanol, gave p-nitrobenzoic acid m.p. 242^o; lit., 241^o (2).

Three samples of the p-nitrobenzoic acid were assayed. The results given in Table IV, showed that the acid had a radioactivity of 0.0164 μ c./mmole or 0.52% of the carbon-14 was in the position alpha to the ring. However, previous reactions leading to the preparation of 2-(p-nitrophenyl)ethanol-1-¹⁴C had caused rearrangement to the extent of 0.31%. These results indicate that the reaction with hydrogen bromide had caused rearrangement of the side chain to the extent of 0.21%.

Rearrangement in the Reaction p-Nitrophenethyl-1-¹⁴C Bromide with Potassium Iodide and Trimethylamine

A solution of 400 mg. (1.2 mmole) of p-nitrophenethyl-1-¹⁴C-trimethylammonium iodide (3.10 μ c./mmole) prepared as described previously, 1.6 g. (10 mmole) of potassium permanganate, 0.4 g. (10 mmole) of sodium hydroxide and 15 ml. of water was boiled for 20 min. Filtration of the hot solution removed manganese dioxide. The filtrate was made acidic with concentrated hydrochloric acid and extracted with ether. Evaporation of

the ether left a yellowish mass, which after recrystallization from ethanol, gave *p*-nitrobenzoic acid, m. p. 241°; lit. 241° (2).

Assay of three samples of this *p*-nitrobenzoic acid, on which data are given in Table V, showed that the acid had a radioactivity of 0.0168 μ c./mmole or 0.54% of the carbon-14 was in the position alpha to the ring. Previous reactions leading to the preparation of *p*-nitrophenethyl-1-¹⁴C bromide had caused rearrangement to the extent of 0.52%. The reaction of *p*-nitrophenethyl-1-¹⁴C bromide with potassium iodide and trimethylamine caused rearrangement to the extent of 0.02%.

RESULTS

TABLE I

DECOMPOSITION OF p-NITROPHENETHYL-1-¹⁴C-TRIMETHYLAMMONIUM

IODIDE, RUN 1

Sample Number	Radioactivity of picrate, $\mu\text{c./mmole}$	Standard deviation	Fraction unreacted (1-f)
1	2.86		
	2.89		
	2.87		
	2.67*		
	Ave. 2.87	0.02	1.00
2	2.84		
	2.81		
	2.80		
	2.83		
	Ave. 2.82	0.02	1.00
3	3.10		
	3.43*		
	3.00		
	3.03		
	Ave. 3.04	0.05	0.371
4	3.02		
	2.93		
	3.07		
	3.20		
	Ave. 3.05	0.11	0.396
5	2.97		
	3.03		
	3.11		
	3.05		
	Ave. 3.04	0.06	0.395

* Discarded Value

TABLE I (Continued)

Isotope effect	
$(1-f)_{\text{ave.}}$	= 0.387
$N^*_{\text{ave.}}$	= 3.04
$N_{\text{ave.}}$	= 2.84
k^*/k	= 0.929

TABLE II
 DECOMPOSITION OF p-NITROPHENETHYL-1-¹⁴C-TRIMETHYLAMMONIUM
 IODIDE, RUN 2

Sample Number	Radioactivity of picrate, $\mu\text{c./mmole}$	Standard deviation	Fraction unreacted, (1-f)
1	3.01		
	3.00		
	3.02		
	3.01		
	Ave. 3.01	0.01	1.00
2	3.04		
	3.00		
	3.10		
	2.97		
	Ave. 3.02	0.06	1.00
3	3.31		
	3.10*		
	3.30		
	3.27		
	Ave. 3.30	0.02	0.315
4	3.27		
	3.29		
	3.34		
	3.43		
	Ave. 3.33	0.07	0.305
5	3.23		
	3.17		
	3.07		
	3.27		
	Ave. 3.18	0.09	0.310

* Discarded Value

TABLE II (Continued)

Isotope effect

$$(1-f)_{\text{ave.}} = 0.310$$

$$N_{\text{ave.}}^* = 3.27$$

$$N_{\text{ave.}} = 3.01$$

$$k^*/k = 0.930$$

TABLE III
 DECOMPOSITION OF p-NITROPHENETHYL-1-¹⁴C-TRIMETHYLAMMONIUM
 IODIDE, RUN 3

Sample Number	Radioactivity of picrate, $\mu\text{c.}/\text{mmole}$	Standard deviation	Fraction unreacted, (1-f)
1	3.09		
	3.05		
	3.27*		
	3.00		
	Ave. 3.05	0.04	1.00
2	2.92		
	2.74*		
	2.96		
	2.96		
	Ave. 2.95	0.02	1.00
3	3.26		
	3.30		
	3.30		
	3.62*		
	Ave. 3.29	0.02	0.306
4	3.55		
	3.19		
	3.35		
	3.29		
	Ave. 3.29	0.16	0.300
5	3.29		
	3.19		
	3.27		
	3.04		
	Ave. 3.25	0.13	0.302

* Discarded Value

TABLE III (Continued)

Isotope effect

$$(1-f)_{\text{ave.}} = .303$$

$$N_{\text{ave.}}^* = 3.28$$

$$N_{\text{ave.}} = 3.00$$

$$k^*/k = 0.926$$

TABLE IV

REARRANGEMENT IN THE REACTION OF 2-(p-NITROPHENYL)ETHANOL-1-¹⁴C
AND HYDROGEN BROMIDE

Sample Number	Weight, mg.	Mv.	Radioactivity, $\mu\text{c./mmole}$
1	4.795	1.80	0.0167
2	4.315	1.55	0.0165
3	7.490	2.70	0.0161
			Ave. 0.0164

$\frac{0.0164 \mu\text{c./mmole}}{3.15 \mu\text{c./mmole}} = 0.52\%$ of carbon-14 in the position alpha to the ring
 0.52% (total rearrangement) - 0.31% (rearrangement due to previous reactions) = 0.21%

TABLE V

REARRANGEMENT IN THE REACTION OF p-NITROPHENETHYL-1-¹⁴C
BROMIDE WITH POTASSIUM IODIDE AND TRIMETHYLAMINE

Sample Number	Weight, mg.	Mv.	Radioactivity, $\mu\text{c./mmole}$
1	2.745	1.40	0.0170
2	4.110	2.00	0.0158
3	4.945	2.70	0.0177
			Ave. 0.0168

$\frac{0.0168 \mu\text{c./mmole}}{3.10 \mu\text{c./mmole}} = 0.54\%$ of carbon-14 in the position alpha to the ring
 0.54% (total rearrangement) - 0.52% (rearrangement due to previous reactions) = 0.02%

THEORETICAL EVALUATION OF THE ISOTOPE EFFECT

Eyring and Cagle (5) have developed an equation for calculation of theoretical isotope effects.

$$k^*/k = \frac{\sinh(h\nu^*/2kT)}{\sinh(h\nu/2kT)} \quad \text{Eq. 10}$$

k^*/k = isotope effect

h = Planck constant

ν = vibrational frequency of the $^{12}\text{C}-^{14}\text{N}$ bond

ν^* = vibrational frequency of the $^{14}\text{C}-^{14}\text{N}$ bond

k = Boltzman constant

T = absolute temperature

The bonds ruptured in the reaction are the $^{12}\text{C}-^{14}\text{N}$ bond and the $^{14}\text{C}-^{14}\text{N}$ bond. (Other isotopes of carbon and nitrogen are present in such small concentrations that the effects of their bonding can be neglected.) The vibrational frequencies of carbon-14 bonds have not been determined but they can be calculated approximately from the carbon-12 vibrational frequencies using the relationship:

$$\frac{\omega^*}{\omega} = \sqrt{\frac{\mu}{\mu^*}} \quad \text{Eq. 11}$$

ω^* = vibrational frequency of the $^{14}\text{C}-^{14}\text{N}$ bond

ω = vibrational frequency of the $^{12}\text{C}-^{14}\text{N}$ bond

μ = reduced mass of the nuclei involved in the $^{12}\text{C}-^{14}\text{N}$ bond

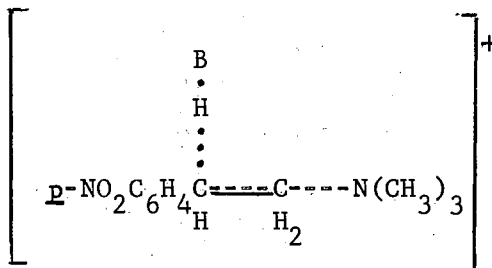
μ^* = reduced mass of the nuclei involved in the $^{14}\text{C}-^{14}\text{N}$ bond

The infrared spectrum of p-nitrophenethyltrimethylammonium iodide in a potassium bromide pellet was determined on a Beckman IR-5A spectrometer. The stretching frequency for the bond between the ammonium nitrogen atom and the phenethyl carbon could not be definitely assigned. However, Lorenzelli and Möller (11) have assigned, from the Raman spectrum of tetramethylammonium chloride, a fundamental vibrational frequency of 955 cm^{-1} for the carbon-nitrogen bond for this particular compound. If this value is used to calculate by Eq. 10 the theoretical carbon-14 isotope effect in the decomposition of p-nitrophenethyl-1- ^{14}C -trimethylammonium iodide, a value of 0.929 is obtained. The experimentally determined value agrees well with this value.

DISCUSSION OF RESULTS

In the decomposition of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide, the presence of an isotope effect could be detected if there were an increase in molar activity of the unreacted starting material after some extent of reaction. This would indicate that the labeled compound reacted at a lower rate than the unlabeled compound.

The main objective of this research was to investigate this decomposition to determine if a carbon-14 isotope effect existed and the value of such an effect. Hodnett and Sparapany (8) found that a nitrogen-15 isotope effect exists in the reaction and proposed the transition state below.



The carbon-14 isotope effect of 0.928 ± 0.002 shows that the carbon-nitrogen bond is broken in the rate determining step of the elimination. This fact, with the tritium isotope effect determined by Hodnett and Flynn (7), supports the transition state as proposed.

The results of three runs gave isotope effects in the decomposition of *p*-nitrophenethyl-1-¹⁴C-trimethylammonium iodide at 100° in solution buffered to pH 7 of:

Run 1 = 0.929

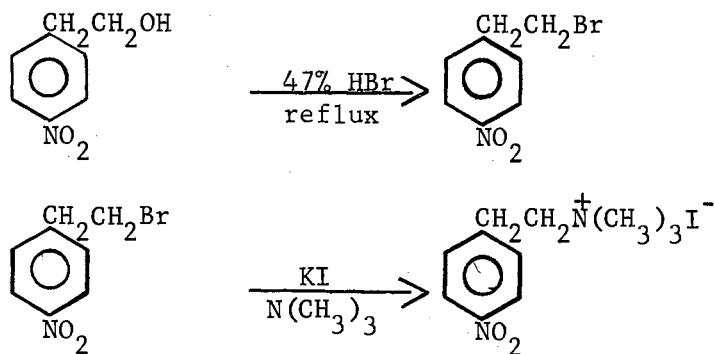
Run 2 = 0.930

Run 3 = 0.926

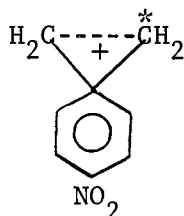
Ave. = 0.928 ± 0.002

This value agrees well with the theoretically calculated value of 0.929.

Another objective of this research was to investigate the possibility of side-chain rearrangement in the synthesis of *p*-nitrophenethyltrimethylammonium iodide. The substitution reaction of 2-(*p*-nitrophenyl)ethanol with hydrogen bromide and the substitution reaction of *p*-nitrophenethyl bromide with potassium iodide and trimethylamine are nucleophilic and are subject to rearrangement.



There has been some question about the mechanisms of these reactions, that is, whether an S_N1 or S_N2 mechanism is operative. If the S_N1 mechanism is assumed, a stable carbonium ion of the phenonium type shown below could be expected. This could lead to a possible rearrangement of the side chain with the carbon-14 atom changing from the position beta to the



ring to the position alpha to the ring depending on the site of the attack of the entering group. If the reactions proceed through an S_N2 mechanism, the nucleophilic bromide ion or trimethylamine molecule would attack the site of substitution in the slow step of the reaction. The attacking species would enter and the leaving group would leave simultaneously; there would be inversion of configuration about the reaction center and no rearrangement of carbon-14 would result. Inversion has no meaning since the reaction center is not optically active. However, absence of rearrangement of the side chain would indicate the bimolecular mechanism.

Rearrangement to the extent of 0.21% was found in the reaction of 2-(p-nitrophenyl)ethanol-1- ^{14}C with hydrogen bromide. The reaction of p-nitrophenethyl-1- ^{14}C bromide with potassium iodide and trimethylamine led to 0.02% rearrangement.

These facts can be explained if the inductive effect of the p-nitro group as operative in the transition state is considered. For phenyl migration to occur, the phenyl group would have to be a competing nucleophile, attacking the carbon-14 labeled center as the hydroxyl group was leaving. The p-nitro group on the phenyl ring would retard stabilization of the incipient ion and prevent side-chain rearrangement.

SUMMARY

The isotope effect in the decomposition of p-nitrophenethyl-1-¹⁴C-trimethylammonium iodide has been determined at 100° in aqueous solution buffered to pH 7. The isotope effect for this decomposition was found to be 0.928 ± 0.002 . This shows that the carbon-nitrogen bond is ruptured in the rate-determining step of the reaction, verifying the transition state for this reaction as proposed by Hodnett and Sparapany (8).

Side-chain rearrangement in the reaction of 2-(p-nitrophenyl)ethanol with hydrogen bromide and the reaction of p-nitrophenethyl bromide with potassium iodide and trimethylamine has been determined. These reactions proceed with side-chain rearrangement to the extents of 0.21% and 0.02% respectively. These facts indicate that a S_N2 mechanism is operative in these reactions.

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VITA

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Thesis: THE ISOTOPE EFFECT OF CARBON-14 IN THE DECOMPOSITION REACTION OF
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