AN ISOTOPIC STUDY OF CINE-SUBSTITUTION IN LIQUID AMMONIA

by

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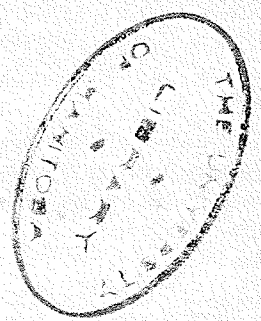

'As we conquer peak after peak we see in front of us regions full of interest and beauty, but we do not see our goal, we do not see the horizon; in the distance tower still higher peaks, which will yield to those who ascend them still wider prospects, and deepen the feeling, the truth of which is emphasized by every advance in science, that: "Great are the Works of the Lord".'

- Sir J. J. Thomson (61)

PREFACE

The author gratefully acknowledges all assistance received during his first venture into chemical research. Special thanks are due to Dr. G.E. Dunn, who formulated the basis of this investigation, and then keenly followed its progress with invaluable advice and criticisms; and to Mr. C. Brynko, who contributed largely to many stimulating discussions during the earlier stages of the work.

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ABSTRACT OF M.Sc. THESIS

submitted by Peter J. Krueger

Part I : An Isotopic Study of Cine-substitution in Liquid Ammonia

The reaction of o-deuterochlorobenzene with sodamide in liquid ammonia at -33° C. has been found to give aniline with 51 ± 6% loss of deuterium from the labelled position of the reactant. The deuterium in the product has been found to be about 55% in the meta position. These results are incompatible with the rearrangement mechanism of Bunnett and Zahler, and Levine and Fernelius, but are both predicted by the elimination-addition mechanism proposed by Roberts and co-workers, provided that negligible loss of deuterium by exchange with the solvent occurs from the reactant and the product before and after the reaction respectively. The exchange loss from o-deuteroaniline under these conditions has been found to be small, but some doubt remains as to the rate of exchange from o-deuterochlorobenzene in comparison with the amination rate.

The detailed mechanism for the above amination recently published by Roberts and co-workers, which includes both the amination and the deuterium exchange from o-deuterochlorobenzene, does not predict the product ratios observed in this investigation.

Part II : The Deuterium Isotope Effect in the Thermal Decarboxylation of o-Aminobenzoic Acids

Thermal decarboxylations of deuterated anthranilic and deuterated N-methylanthranilic acids have been carried out, and unexpectedly high deuterium concentrations found in the ortho position of the products. If the decarboxylation proceeds from the zwitterion as proposed by Stevens, Pepper, and Lounsbury, than apparent deuterium

isotope effects (k_D/k_H) of 1.70 $\pm$ 0.10 and 1.59 $\pm$ 0.04 respectively are involved.

These isotope effects are discussed in relation to a variety of possible reaction mechanisms.

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PART I

AN ISOTOPIC STUDY OF

CINE-SUBSTITUTION IN LIQUID AMMONIA

HISTORICAL REVIEW

On investigating the properties of the newly discovered elements sodium and potassium (Davy, 1807), Gay-Lussac and Thenard (13) independently prepared the corresponding amides by reacting the molten alkali metals with gaseous ammonia. A group of investigators subsequently studied this method of preparing the alkali metal amides, while another later used the action of liquid ammonia on the alkali metals in the presence of catalysts.

Although these reagents were discovered in the early part of the nineteenth century, they remained relatively obscure for a long time. Only the first decade of the twentieth century saw the application of the alkali metal amides to the field of organic syntheses. Among numerous other reactions they catalyze various condensations and cyclizations, introduce the amino group into molecules, and remove water or hydrohalic acid from molecules. For a detailed account of the chemistry of the alkali metal amides the reader is referred to the extensive reviews by Fernelius et al (5,6,50).

The use of liquid ammonia solutions of alkali metal amides to introduce the amino group into the aromatic nucleus is due to Bergstrom and co-workers (8,80). They found that chloro-, iodo-, and bromobenzene reacted extremely rapidly with a liquid ammonia solution of potassium amide at -33°C. to give aniline and diphenylamine, with smaller quantities of triphenylamine, p-aminobiphenyl, and other tarry products, depending on the experimental conditions. Fluorobenzene was found to be inert under the same conditions.

None of the reactions occurred with potassium amide in boiling ether or benzene. Since the formation of potassium anilide was shown to be fast, they formulated the reaction as follows:

(1) $C_6H_5X + KNH_2 \longrightarrow C_6H_5NH_2 + KX$

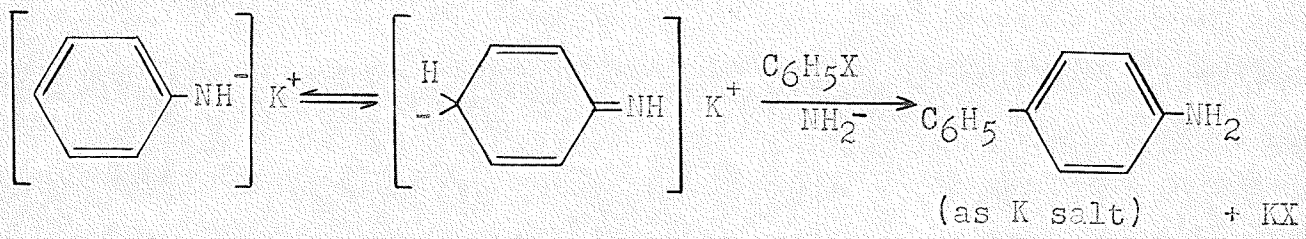
(2) $C_6H_5NH_2 + KNH_2 \longrightarrow C_6H_5NHK + NH_3$

(3) $C_6H_5NHK + C_6H_5X \xrightarrow{NH_3} (C_6H_5)_2NH + KX$

(4) $(C_6H_5)_2NH + KNH_2 \longrightarrow (C_6H_5)_2NK + NH_3$

(5) $(C_6H_5)_2NK + C_6H_5X \xrightarrow{NH_3} (C_6H_5)_3N + KX$

(6)



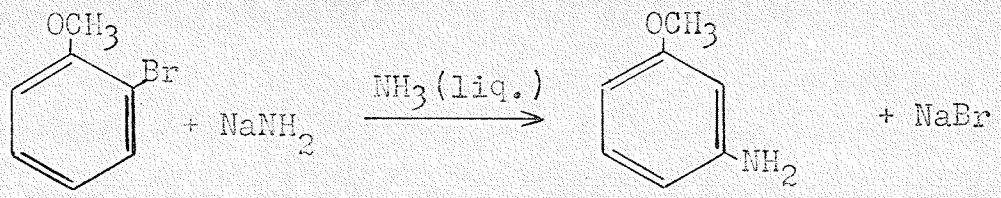
(as K salt) + KX

Acidification of the reaction mixture yielded aniline in 42-52% yield, as determined by bromine titration. The exact yield depended on the particular halide used, and the mole ratio of amide to aryl halide (the optimum yield being obtained when this ratio was slightly larger than 2). Quantitative dehalogenation of the aryl halide was observed when a liquid ammonia solution of excess potassium amide was employed. Competitive experiments gave the following order with regard to the halogen reactivity:

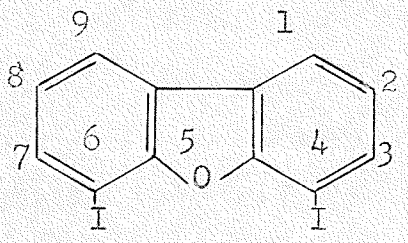
Br>I>Cl(>>>F)

The same order was observed for the replacement of halogen from phenyl dihalides of the type p-C_6H_4XY.

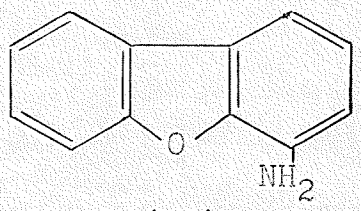
In 1945 Gilman and Avakian (23) reported that a number of o-halogenated ethers, among them o-chloro-, o-bromo-, and o-iodoanisole, on treatment with sodamide in liquid ammonia gave predominantly m-aminoethers, as illustrated by the equation:



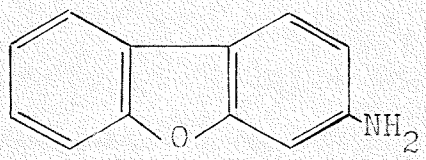
This rearrangement was first called to their attention when, in connection with the preparation of 4,6-diaminodibenzofuran for antimalarial studies, the amination of 4,6-diiododibenzofuran (I) with sodamide in liquid ammonia failed to give the desired product, but yielded instead 4-amino-, (II), 3-amino-, (III), 3,6-diamino-, (IV), and 3-amino-6-iododibenzofuran (V).



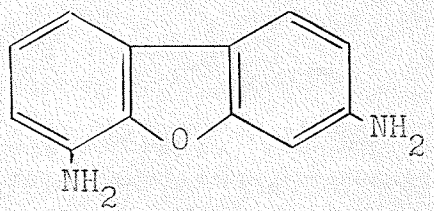
(I)



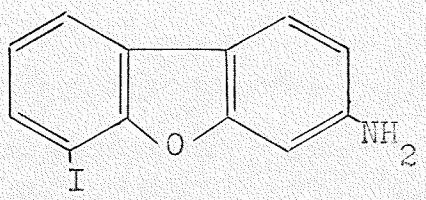
(II)



(III)



(IV)



(V)

This rearrangement was further substantiated when 4-iodo- and 4-bromodibenzofuran gave 3-aminodibenzofuran (III). 2-Bromo-and 2-iododibenzofuran gave direct amination products. From these observations they concluded that rearrangement in the amination reaction under these conditions was general when the halogen atom was situated ortho to an ether linkage in the molecule.

Bergstrom and Horning (7) found that the o-,m- and p-tolyl halides, except the fluoride, reacted readily with liquid ammonia solutions of potassium amide to give amine mixtures containing some of the amine corresponding in orientation to the halide used. Potassium amide rapidly converted 2-chloroquinoline to tar, but the ammonia insoluble calcium amide did not affect it appreciably. 2-Bromopyridine, 3-bromopyridine, 6-chloroquinoline, 4-bromoisoquinoline, p-chloronitrobenzene and sodium p-bromobenzenesulfonate were also not affected by alkali metal amides in liquid ammonia at room temperature. Secondary amine mixtures which were undoubtedly isomeric mixtures were obtained from the reactions of potassium amide with each of o- and m-chlorotoluene, o-iodotoluene, p-bromotoluene, and p-chlorophenetole. An attempt to prepare pure di- or tri-p-tolylamine by adding potassium amide to solutions of potassium p-toluide and p-bromotoluene in liquid ammonia gave an isomeric mixture of tritolylamines. More potassium halide was found to be liberated in all these reactions than was obtained from calculations based on an equation of the type

$$RX + 2KNH_2 \longrightarrow RNHK + KX + NH_3 ,$$

indicating that further reactions of the type

$$RNHK + RX \xrightarrow{KNH_2} (R)_2NK + KX + NH_3$$

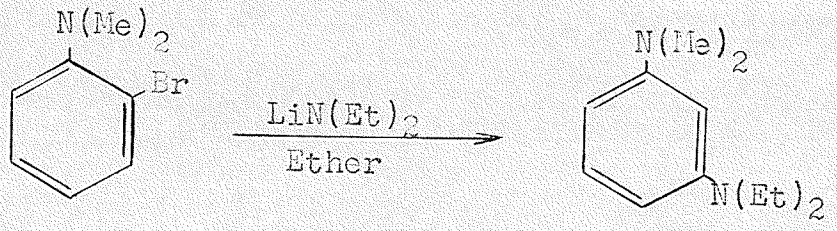
forming di- and triarylamines were involved. A tolylquinaldine (11% yield) of unknown orientation was obtained from potassium amide, quinaldyl potassium, and p-chlorotoluene in liquid ammonia.

Reactions of this nature were shown to be best carried out by adding the phenyl halide (alone or in ether or ligroin solution) to a well-stirred amide solution in liquid ammonia. Reversing the addition decreased the tar formation, but often increased the amount of secondary amine formation, complicating the separation of products. By working at -78°C. the yield of tolylamine from p-chlorotoluene was increased, but the rate of the reaction was decreased. Reactions of a given halide were found to be slower with sodamide than with potassium amide, in keeping with the lower conductance of liquid ammonia solutions of the former amide.

Rearrangement reactions that resembled these but were carried out under different conditions had been reported as early as 1894 by Kym (47), who found that 1-chloronaphthalene gave 2-p-toluidinonaphthalene when it was fused with p-toluidine and soda lime, and that 1-bromonaphthalene gave 2-anilinonaphthalene when it was fused with aniline and soda lime. p-Dibromobenzene, when heated to 350°C. with p-toluidine and soda-lime, gave NN'-di-p-tolyl-m-phenylenediamine. In 1901 Hauessermann (33,34) reported that o-chlorotoluene, when treated with potassium diphenylamine and aniline, gave N,N-diphenyl-m-toluidine. Further Hauessermann found that o-, m-, and p-dichlorobenzene, on reaction with po-

tassium diphenylamide, all gave NNN'N'-tetraphenyl-m-phenylenediamine, although the p-dihalide also gave some p-diamine.

Since 1945 the amination of substituted halobenzenes by metal amides in liquid ammonia has been found to give m-amino products when the halogen is ortho to ether (2,3,23,25,26), sulfide (29,31), sulfone (29), and trifluoromethyl (4) groups. Numerous cases have also been reported where the amination is normal under the same conditions, i.e. where the entering amino group replaces the halogen directly (23,72). The rearrangement reaction was also found to extend to condensations of substituted alkali metal amides with substituted halobenzenes in ether solution (24,25,27) as is illustrated by the equation:



p-Haloethers were also found to exhibit the tendency to undergo rearrangement to m-amino products when treated with lithium diethylamide in ether, but to a lesser extent, and the rearrangement was accompanied by the formation of some normal substitution product. (23)

Bunnett and Zahler (18) extensively reviewed these rearrangement reactions in 1951. They have proposed the name "cine-substitution" [a] for an aromatic nucleophilic substitution reaction in which the ring position taken by the entering group is not the same as that vacated by the leaving group. They exclude from this

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[a] From the Greek cine, to move.

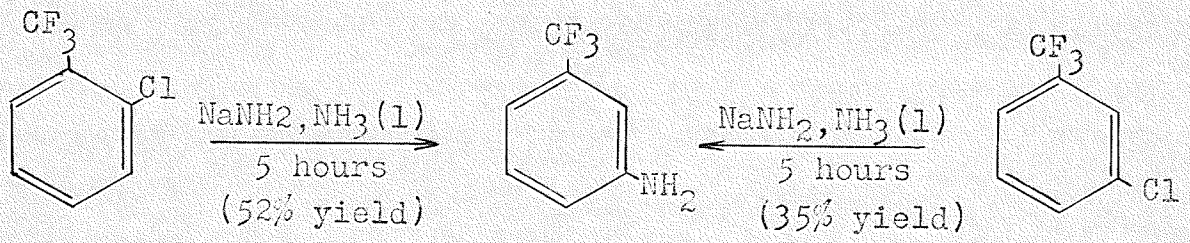
general class reactions of desubstitution-resubstitution type, where the two steps can be performed independently, as well as "normal" substitution followed by true rearrangement. According to them, the amination reactions under discussion fulfil these conditions, since (a) in cases where unreacted starting material has been recovered it has shown retention of the original orientation (26) (b) the various naphthyl halides under the same conditions have produced either α- or β - naphthylamines in clear-cut cases, showing that the product does not rearrange under these conditions, and (c) despite the fact that in many cases plain dehalogenated material accompanies the amination (some anisole being recovered in reactions with haloanisoles) it is impossible to introduce the amino group into the halogen-free compounds under these conditions. Thus the expulsion of the halogen and the introduction of the amino group are taken to be part of a single process (the existence of a metastable intermediate being, however, not excluded).

Table I lists cases of cine-substitution with alkali metal amides in liquid ammonia as reported in the literature. Table II summarizes the analogous reactions with substituted alkali metal amides in ether solution, and Table III gives some "normal" substitution reactions occurring under both the above sets of conditions. Due credit must be given to Bunnet and Zahler who compiled these reactions exhaustively up to 1951. The author has extended these tables to cover cases reported up to February, 1956.

Since the present investigation deals only with cine-substitution in liquid ammonia, little will be said about the material in

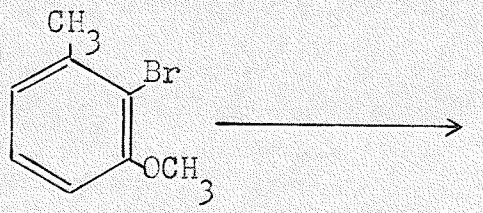
Table II, and the reader is referred directly to the literature for references given. The material in Tables I and III(a) will be discussed with special emphasis on the evidence available for the formulation of a mechanism for this type of cine-substitution.

Benkeser and Severson (4) have reported that this rearrangement occurs not only when the halogen atom is ortho to an electron-releasing group (such as methoxyl) but also when it is ortho to a strongly electron-withdrawing group (such as trifluoromethyl). The following reactions were carried out:



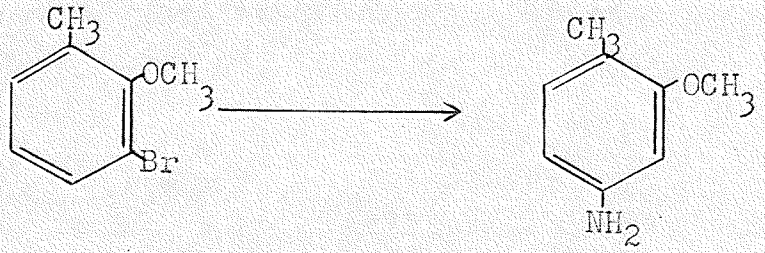
Benkeser and Buting (2) were first to study a series of compounds so substituted as to provide information about the possible mode of m-amine formation in the amination. The following reactions were carried out with sodamide in liquid ammonia:

(1)



no amine

(2)



(30% yield)

CINE-SUBSTITUTIONS IN LIQUID AMMONIA

Aryl Halide	Metal Amide	Product and Yield	Reference
1. o-iodoanisole	$NaNH_2$	m-anisidine (33%)	(23)
2. o-bromoanisole	$NaNH_2$	m-anisidine (33%)	(23)
3. o-chloroanisole	$NaNH_2$	m-anisidine (57.5%)	(25)
4. 2-iododiphenylether	$NaNH_2$	3-aminodiphenylether (22%)	(25)
5. 4-iododibenzofuran	$NaNH_2$	3-aminodibenzofuran (48%)	(24)
6. 4-bromodibenzofuran	$NaNH_2$	3-aminodibenzofuran (31%)	(24)
7. 4,6-diiododibenzofuran	$NaNH_2$	3-amino-6-iododibenzofuran (61%) and 3,6-diaminodibenzofuran (5%)	(24)
8. 4,6-diiododibenzofuran[a]	$NaNH_2$	3-aminodibenzofuran (42%)	(24)
9. 4-iododibenzothiophene	$NaNH_2$	3-aminodibenzothiophene (50%)	(31)
10. o-bromothioanisole	$NaNH_2$	m-thioanisidine (45%)	(54)
11. o-chlorothioanisole	KNH_2	m-thioanisidine (35%)	(54)
12. o-bromophenylmethylsulfone	$NaNH_2$	m-aminophenylmethylsulfone (15%)	(54)
13. o-chlorobenzotrifluoride	$NaNH_2$	m-aminobenzotrifluoride (52%)	(4)
14. 1-chloronaphthalene	KNH_2	2-naphthylamine (45%) and 1-naphthylamine (2%)[b]	(72)
15. 1-bromonaphthalene	KNH_2	2-naphthylamine (45%) and 1-naphthylamine (2%)[b]	(72)

a Using mixed solvents ether and liquid ammonia.
b Unrearranged amination product.

CINE-SUBSTITUTIONS IN LIQUID AMMONIA

	Aryl Halide	Metal Amide	Product and Yield	Reference
16.	1-iodonaphthalene	KNH_2	2-naphthylamine (45%) and 1-naphthylamine (2%)[b]	(72)
17.	2,6-dibromoanisole	$NaNH_2$	2-bromo-5-aminoanisole (92%)	(3)
18.	2,5-dichloroanisole	$NaNH_2$	2-chloro-5-aminoanisole (92%)	(3)
19.	2,4-dichloroanisole	$NaNH_2$	2-amino-4-chloroanisole,[b] 3-amino-4-chloroanisole and 2-chloro-5-aminoanisole	(3)
20.	2-bromo-6-methylanisole	$NaNH_2$	3-amino-6-methylanisole (30%)	(2)
21.	2-bromo-4-methylanisole	$NaNH_2$	3-amino-4-methylanisole (50%)	(2)
22.	2-bromo-5-trifluoromethylanisole	$NaNH_2$	3-amino-5-trifluoromethylanisole (71%)	(2)
23.	o-chloroanisole	$LiNH_2$	no appreciable reaction	(26)
24.	o-bromoanisole	$LiNH_2$	m-anisidine	(26)
25.	o-chlorophenylmethylsulfide	KNH_2	m-aminophenylmethylsulfide (53%)	(28)
26.	o-bromophenylmethylsulfide	$NaNH_2$	m-aminophenylmethylsulfide (57.5%)	(28)
27.	o-bromophenylmethylsulfone	$NaNH_2$	m-aminophenylmethylsulfone (15%)	(28)
28.	3-bromopyridine	$NaNH_2$	4-aminopyridine (10%)	(51)

b Unrearranged amination product.

CINE SUBSTITUTIONS IN ETHER

Aryl Halide	Metal Amide	Product and Yield	Reference
1. p-bromoanisole	$LiN(Et)_2$	N,N-diethyl-m-anisidine (mainly and N,N-diethyl-p-anisidine[c] (total 34%)	(25)
2. o-iodoanisole	$LiN(Et)_2$	N,N-diethyl-m-anisidine and anisole[d] (22%)	(24)
3. o-bromodimethylaniline	$LiN(Et)_2$	N,N-dimethyl-N',N'-diethyl-m-phenylene-diamine (29%)	(27)
4. p-bromotetraphenylsilane	$LiN(Et)_2$	m-dimethylaminotetraphenylsilane (15%)	(29)
5. 1-bromonaphthalene	$LiN(Et)_2$	2-diethylaminophthalene (27%)	(24)
6. 1-chloronaphthalene	$LiN(Et)_2$	2-diethylaminonaphthalene (27%)	(24)
7. 1-fluoronaphthalene	$LiN(Et)_2$	2-diethylaminonaphthalene (40%)	(24)
8. o-bromoanisole	$LiN(Et)_2$	3-diethylaminoanisole	(25)
9. o-chloroanisole	$LiN(Et)_2$	3-diethylaminoanisole	(25)
10. o-fluoroanisole	$LiN(Et)_2$	3-diethylaminoanisole	(25)
11. o-chloroanisole	$LiN(n\text{-butyl})_2$	3-di-n-butylanisole (higher yield than in No. 9)	(25)
12. o-bromophenol	$LiN(Et)_2$	m-diethylaminophenol	
13. 1-bromonaphthalene	Li didodecylamide	2-didodecylaminonaphthalene (42%)	(55)

c Rearranged amination product in lesser yield.
d Dehalogenated material accompanying amination products.

SOME NORMAL AMINATIONS BY ALKALI METAL AMIDES

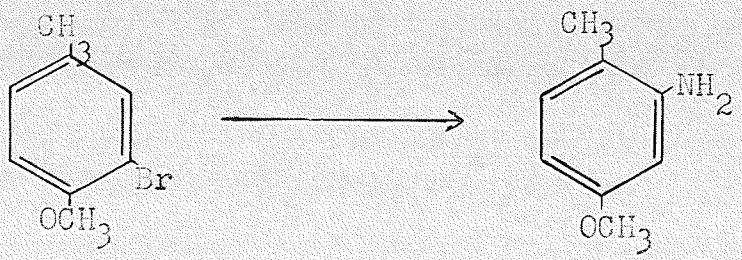
Aryl Halide	Metal Amide	Product and Yield	Reference
(A) IN LIQUID AMMONIA -			
1. 2-bromo-4-trifluoromethylanisole	$NaNH_2$	2-amino-4-trifluoromethylanisole (15-20%)	(2)
2. p-chlorophenetole	KNH_2	p-phenetidine[e] (31%)	(39)
3. 2-iododibenzofuran	$NaNH_2$	2-aminodibenzofuran (30%)	(23)
4. 2,8-diiododibenzofuran	$NaNH_2$	2,8-diamiondibenzofuran (6%)	(23)
5. 1-fluoronaphthalene	KNH_2	1-naphthylamine (64%)	(72)
6. 2-fluoronaphthalene	KNH_2	2-naphthylamine (11%)	(72)
7. 2-chloronaphthalene	KNH_2	2-naphthylamine (49%) and 1-naphthylamine[c] (3%)	(72)
8. 2-bromonaphthalene	KNH_2	2-naphthylamine (53%) and 1-naphthylamine[c] (3%)	(72)
9. 2-iodonaphthalene	KNH_2	2-naphthylamine (48%) and 1-naphthylamine[c] (3%)	(72)
10. m-chlorobenzotrifluoride	$NaNH_2$	m-aminobenzotrifluoride (35%)	(4)
11. 9-bromophenanthrene	KNH_2	9-aminophenanthrene	(7)
12. o-, m-, and p-tolyl halides (except fluoride)	KNH_2	p-tolylamine, di-p-tolylamine, tri-p-tolylamine and other secondary amines	(7)
13. 2-bromodibenzofuran	$NaNH_2$	2-aminodibenzofuran	(23)

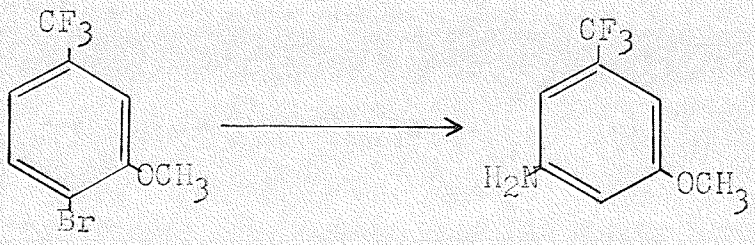
c Rearranged amination product in lesser yield.
e Accompanied by some other isomer which was not identified, and some secondary amines.

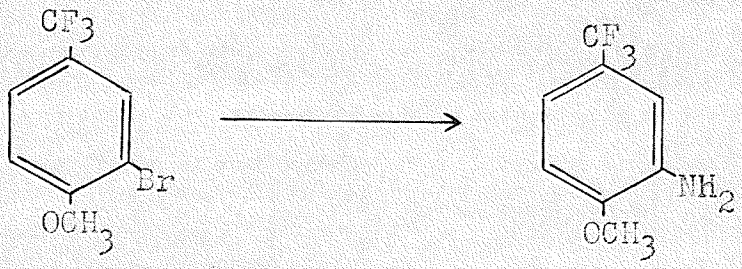
TABLE III (Continued)

SOME NORMAL AMINATIONS BY ALKALI METAL AMIDES

Aryl Halide	Metal Amide	Product and Yield	Reference
(B) IN ETHER -			
1. m-chloroanisole	$LiN(Et)_2$	3-diethylaminoanisole	(26)
2. 2-chloroquinoline	$LiN(Et)_2$	2-diethylaminoquinoline (58%)	(24)

(3)  (>50% yield)

(4)  (71% yield)

(5)  (15-20% yield)

These reactions yield the following information:

(a) Reaction 1. indicates that the position ortho to the halogen is involved, and that it is not the 5-position that is attacked to give m-amine. This is confirmed by the absence of any 2-methyl -m-anisidine in reaction 2. Thus the position adjacent to the halogen atom must contain a hydrogen atom for the reaction to go.

(b) Absence of direct substitution product in reaction 1. indicates that it does not occur to any significant extent, and that where the m-substitution cannot take place, no reaction of any kind occurs.

(c) In reaction 5. direct substitution occurs, and although the halogen is ortho to the methoxyl group, it is meta to the trifluoromethyl group. In the light of Benkeser and Severson's results

(see page 9) this indicates that the effect of the trifluoromethyl group on this reaction is greater than that of the methoxyl group (d) In reaction 3. yields of above 50% were obtained, indicating that a group adjacent to the meta position does not affect the ease of entry into that position, at least not if the group is methyl.

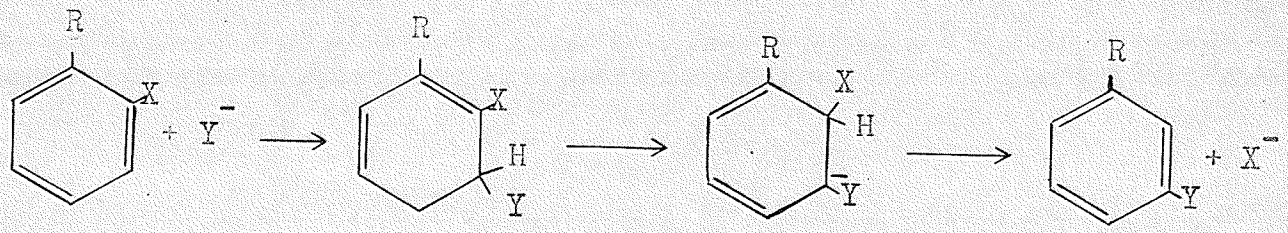
(e) The excellent yield (71%) in reaction 4. is not unexpected since the bromine atom is ortho to the methoxyl group and para to the trifluoromethyl group, both of which seem to favour meta rearrangement from previous work.

Urner and Bergstrom (72) have shown that this rearrangement reaction also proceeds with the naphthyl halides and sodamide in liquid ammonia. There, too, the halogen is quantitatively removed, and 1-chloro-, 2-bromo-, and 1-iodonaphthalene give 2-naphthylamine in 40-55% yield along with 2-3% of 1-naphthylamine. Although fluorobenzene was shown to be inert by Bergstrom (8), 1-fluoronaphthalene reacts slowly with sodamide in liquid ammonia at -33°C. to give only 1-naphthylamine (the yield being increased somewhat by carrying out the reaction at room temperature in a bomb). All the 2-naphthyl halides give 2-aminonaphthalene under these conditions.

Gilman and Kyle (26) found that potassium amide and sodamide in liquid ammonia gave comparable yields in these amination reactions, but that lithium amide did not react appreciably with o-chloroanisole under the same conditions, although it showed rearrangement with o-bromoanisole. Lithium diethylamide in ether showed rearrangement with o-fluoroanisole as well as with o-

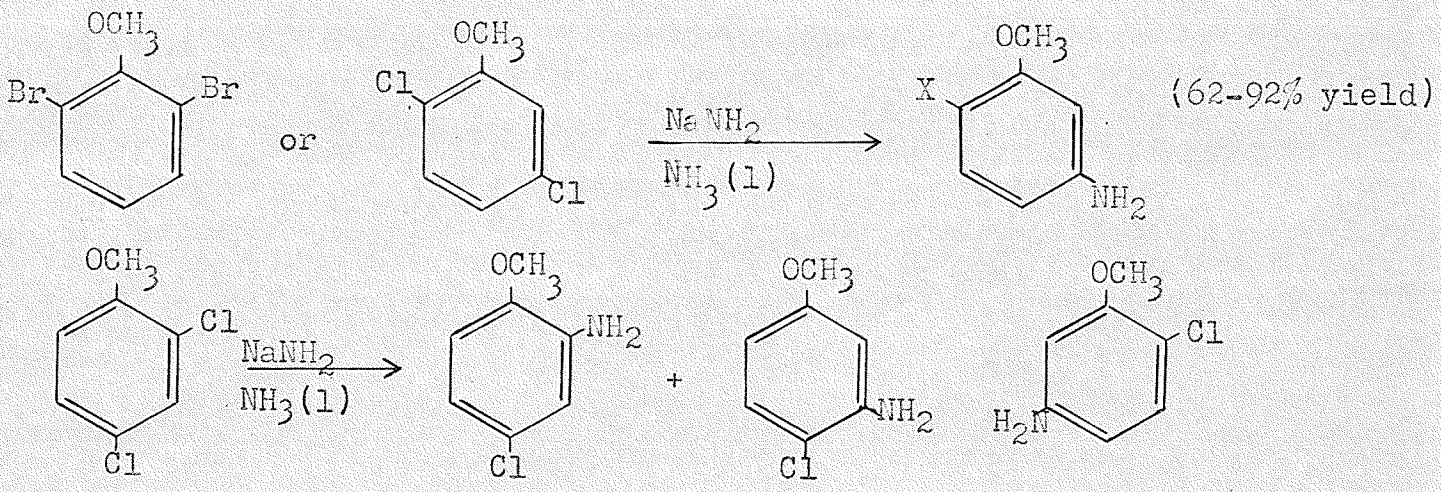
chloro-, o-bromo-, and o-iodoanisole. This may be of interest since fluorobenzene does not react at all with sodamide in liquid ammonia, and 1-fluoronaphthalene reacts slowly but does not rearrange. m-Chloroanisole gave the expected m-amine. It was also found that o-chloroanisole in ether gave a higher yield with lithium di-n-butylamide than it did with lithium diethylamide. o-Halophenols were found to behave like o-haloethers with lithium diethylamide in ether. Cyclic amides like lithium piperidide and lithium morpholide showed the same rearrangement observed with lithium diethylamide in ether solution. It is also shown by Gilman and Kyle that the anisole obtained in almost all the reactions with o-haloanisoles apparently does not owe its formation to a halogen-metal interconversion reaction which would give an anisyllithium compound that would hydrolyze to give anisole.

It was early recognized that it would be difficult to reconcile these findings into a single all-inclusive mechanism consistent with modern concepts of structure. Bunnet and Zahler (18) were first to suggest a mechanism for cine-substitution reactions in general on 2-substituted halobenzenes. Their proposal, to which the author shall henceforth simply refer as the "rearrangement mechanism", can be represented by the following scheme:

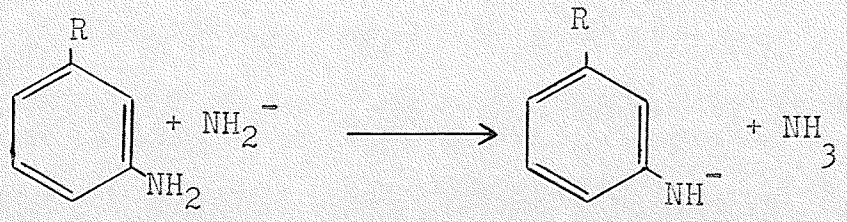


In the amination reactions under discussion Y^- would be the amide ion and X^- the halide ion. This is a nucleophilic amide ion attack accompanied by a synchronous hydrogen shift from the 6- to the 1-position of the halobenzene resulting in loss of the halide ion.

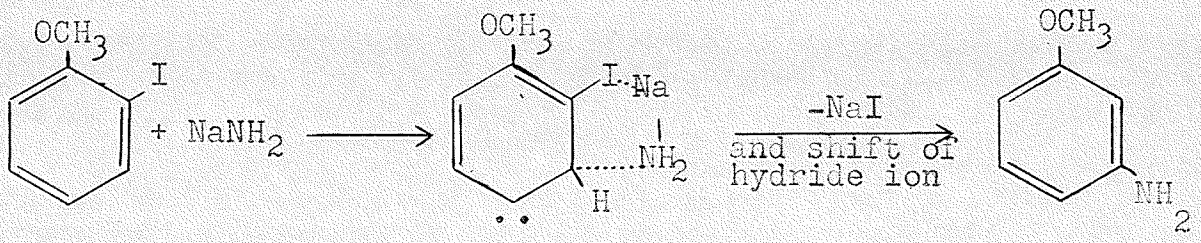
This mechanism received support from Benkeser and Schroll (3) who, operating with dihaloanisoles and sodamide in liquid ammonia, observed the following reactions:



In the above results they saw a partial positive test of the rearrangement mechanism. They argued that on the basis of that mechanism only monoamines would be predicted since (a) simultaneous attack by two amide ions would be unlikely since it involves a termolecular collision (b) attack by a second negative NH_2^-, in a stepwise sequence, should be greatly inhibited by the two strongly electron releasing groups $-OCH_3$ and $-NH^-$ on the benzenoid nucleus. They proposed that, since NH_2^- ions are more basic than anilide ions, the amine formed by the rearrangement mechanism would undergo the reaction:

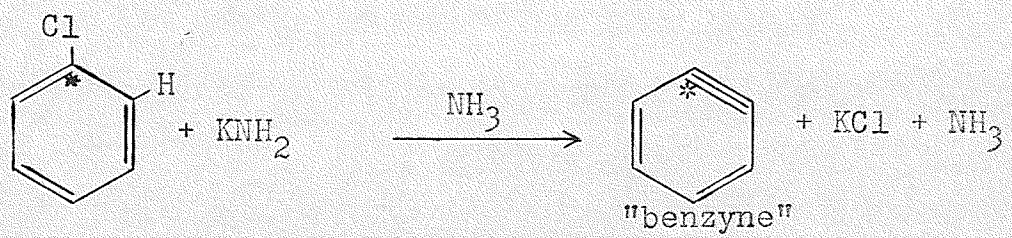


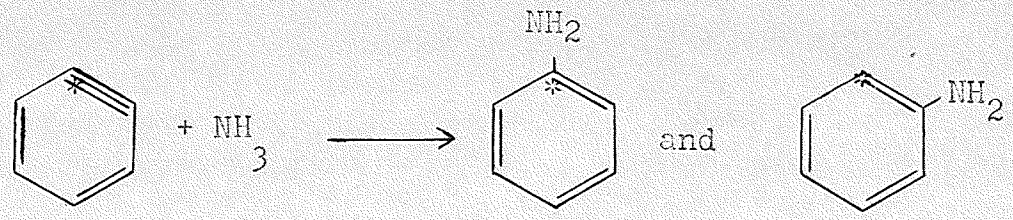
Levine and Fernelius (50) have also supported a variation of this mechanism, which can be formulated as follows for the case of o-iodoanisole:



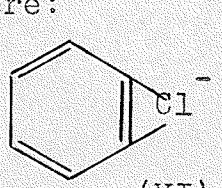
Here a quasi five-membered ring is involved. An electron-releasing group o- or p- to the carbon atom bearing the halogen atom increases the electron density at that carbon and facilitates the removal of the halide ion. This would not explain the rearrangement observed with o-chlorotrifluoromethylbenzene (page 9).

Roberts, Simmons, Carlsmith, and Vaughan (64) in 1953 introduced a unique elimination-addition concept to explain cine-substitutions of the type under discussion, which shall later be referred to simply as the "elimination" mechanism. They found that the amination of chlorobenzene-1-C^{14} with potassium amide in liquid ammonia produced aniline-1-C^{14} and aniline-2-C^{14} in almost equal amounts. An explanation of this phenomenon required that the rates of direct halogen displacement and cine-substitution be equal, or that the reaction involve the same symmetrical intermediate. This, as well as the orientation data obtained for the amination of substituted benzenes, may be accomodated by the following mechanism which involves a transitory electrically neutral "benzyne" intermediate.

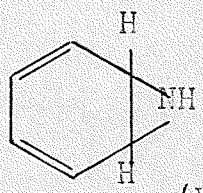




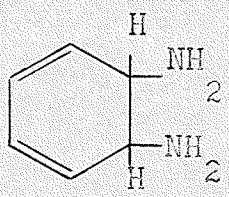
Aniline-1-C^{14} and aniline-2-C^{14} contributed 43.1±1% and 51.8±1% respectively to the total aniline activity. A blank degradation of aniline-1-C^{14} had shown that the method gave slightly low results. Other possible symmetrical intermediates they suggested as being consistent with the tracer results and fitting the whole character of the reaction to a more or less satisfactory degree were:



(VI)

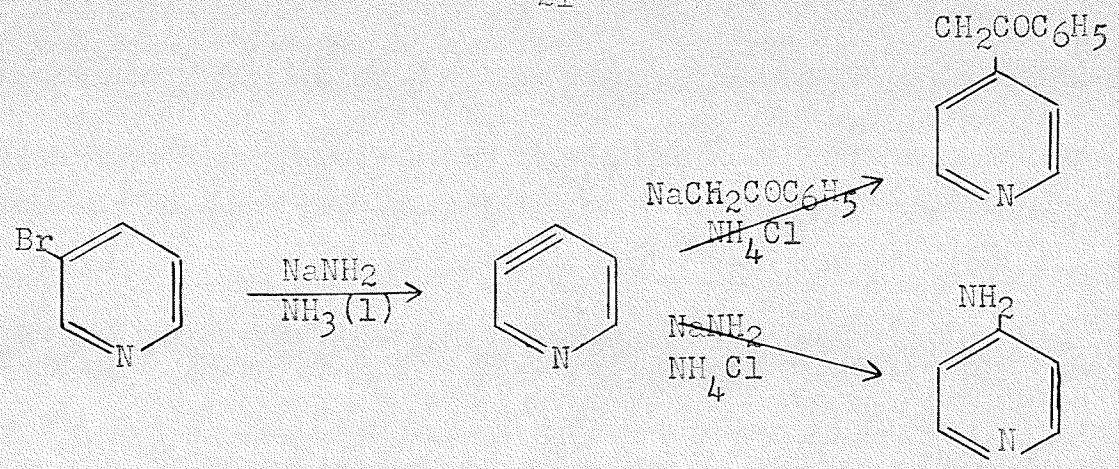


(VII)



(VIII)

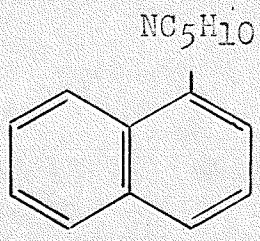
An investigation by Levine and Leake (51) as to the possibility of forming the unknown 3-phenacylpyridine from the reaction of sodioacetophenone with 3-bromopyridine led to a suggested extension of the elimination-addition mechanism to the heterocyclic field. The reaction failed in refluxing toluene, but in the presence of an excess of sodamide in liquid ammonia a large amount of nitrogenous material was isolated, from which were obtained 13.5% 4-phenacylpyridine and 10% 4-aminopyridine. The formation of these compounds was rationalized by means of the following mechanism:



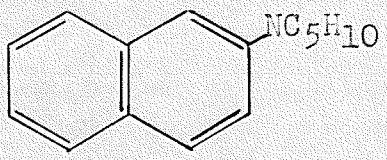
Bunnett and Brotherton (17) point out that unactivated aryl halides differ from activated aryl halides (having o- and p- electron withdrawing groups) in the reactions with strong nucleophiles, not only in the more dependence of reaction rate on the presence or absence of the activating groups, but also in the order of replaceability of the four halogens. In activated aryl halides it is F>>Cl~Br~I, while in the unactivated phenyl halides it is I>Br>Cl>F, just as in the alkyl halides. Hammond and Parks (36) suggest that if the latter order exists, the elimination-addition mechanism is involved, and that the former order applies in direct displacements. This attractive hypothesis was dispelled by Bunnett and Brotherton who showed that it is not universally applicable.

In the reaction of piperidine with the halonaphthalenes alone or in the presence of potassium amide the order of halogen replaceability would indicate that the elimination-addition mechanism were operating. The reaction of α-bromonaphthalene with sodamide and piperidine produced 32% α-naphthylpiperidine (IX) and 68% β - naphthylpiperidine (X). Under the same conditions the product

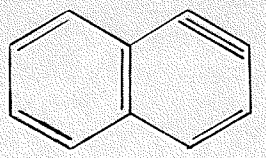
from β - bromonaphthalene consisted of 26% (IX) and 74% (X). This was interpreted on the basis of the formation of "α-naphthalyne" (XI) the proportions of (IX) and (X) reflecting the ease of addition of piperidine to the "triple bond" of (XI).



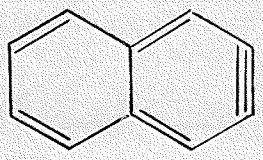
(IX)



(X)



(XI)



(XII)

In the reaction of β -bromonaphthalene, formation of a substantial amount of (IX) indicates that (XI) is also a dominant intermediate in the process, but the fact that from the β -bromo isomer significantly more of (X) is produced than from the α-isomer suggests that "β -naphthalyne" (XII) is also generated. One should note that the addition of piperidine to (XII) forms only (X) and no (IX). Their data allowed them to estimate the ratio of (XI) to (XII) from β-bromonaphthalene to be about 4, assuming no direct displacement of halogen.

With piperidine alone reacting with α- and β - bromonaphthalene, Bunnet and Brotherton found that the corresponding unrearranged napthylamines were formed. Cine-substitution is thus excluded from this reaction, although the halide replaceability order is still the same as in the previous case. This negation of the Hammond and Parks postulate did not suggest anything new as far as the mechanism of the unactivated substitutions are con-

cerned. A belief held by Bunnet and Brotherton is that in the reaction of the activated aryl halides with strong nucleophilic reagents the rate-determining step is the formation of a metastable adduct intermediate, and the various halides affect the rate by influencing the rate of attachment of the reagent to the substrate. In the reactions of unactivated aryl halides with these reagents, it is suggested that these metastable adducts play little or no part. Partial breaking of the C-X bond is postulated for these cases, and the rates reflect the ease of expulsion of the halogen atoms. In conclusion they suggest that for the present it appears that each case of unactivated nucleophilic substitution will have to be considered individually to determine whether the elimination-addition mechanism or the direct displacement mechanism is operating.

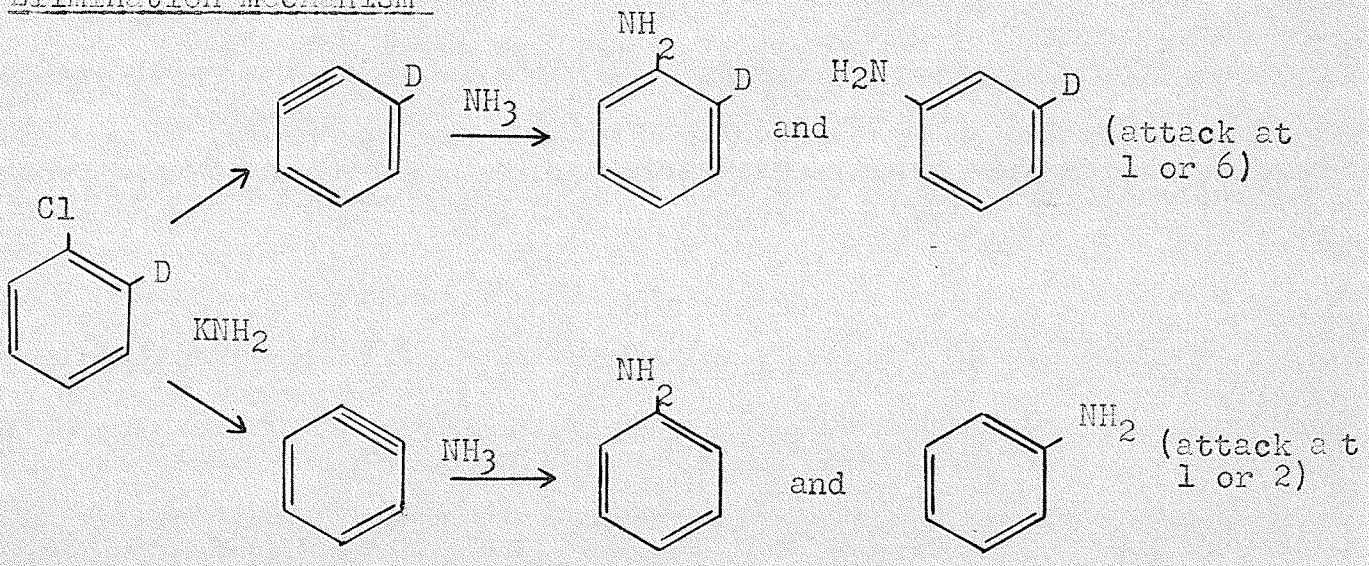
Huisgen and Rist (40) obtained a mixture of 1-phenyl-2-naphthoic acid and 2-phenyl-1-naphthoic acid on carbonation of the product of the reaction between α-fluoronaphthalene and phenyllithium. From β-fluoronaphthalene they obtained the above two acids plus 2-phenyl-3-naphthoic acid. They also postulated "naphthalyne" intermediates to explain these results. The ratios of the products they obtained indicated that the phenyl group of phenyllithium attacked preferentially, but not exclusively, the 2-position of (XI), and that (XI) is formed in greater proportion than (XII) from β-fluoronaphthalene. These results are in good qualitative agreement with those of Bunnett and Zahler.

OBJECT AND METHODS OF THE PRESENT INVESTIGATION

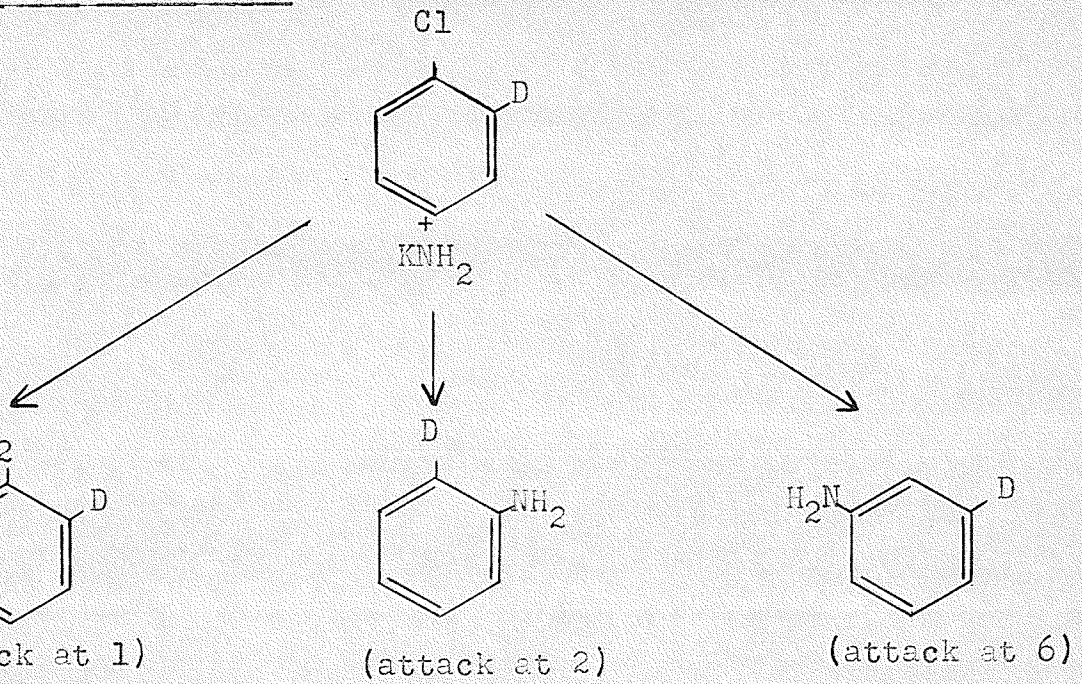
An outstanding point of difference between the rearrangement mechanism of Bunnett and Zahler (page 17) and the elimination mechanism of Roberts (page 19) is the fate of the hydrogen atom ortho to the halogen atom. In the former mechanism the halogen atom is replaced by the hydrogen atom from the o-position of the halobenzene, whereas in the latter mechanism the o-hydrogen is lost to the solvent and a new hydrogen atom from the solvent replaces the halogen. This investigation was planned to test this point by subjecting o-deuterochlorobenzene to amination by sodamide in liquid ammonia at -33° C. and comparing the deuterium content of the product aniline with that of the starting chlorobenzene. According to the rearrangement mechanism there should be no loss of deuterium; according to the elimination mechanism there should be a loss of deuterium, the magnitude of which would depend upon the deuterium isotope effect (77) in the elimination step.

Furthermore, the distribution of deuterium among the positions on the aniline ring should be different in the two mechanisms. This can be seen from the following equations for the amination of o-deuterochlorobenzene.

Elimination mechanism



Rearrangement mechanism

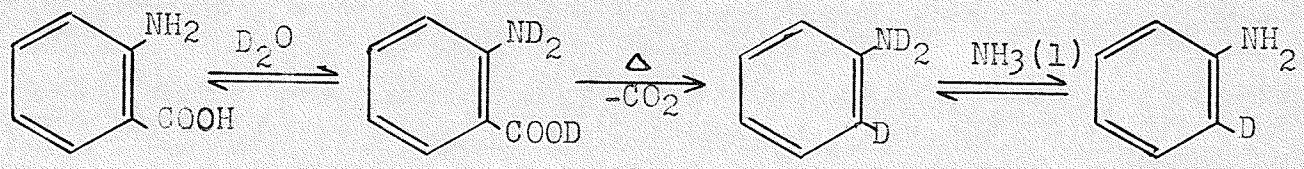


According to the elimination mechanism the amount of o- and m-deuteroaniline in the product should be exactly equal; according to the rearrangement mechanism they could only be equal if the rate of substitution at the 6-position should fortuitously equal the sum of the rates of substitution at the 1- and 2-positions. Since Roberts and co-workers have shown (64) that in chlorobenzene-1 - C^{14} the rates of displacement of halogen and protium are equal, the fortuity would require that the rate of substitution at the 2-position be negligible. Since this is unlikely, it can be expected that the rearrangement mechanism would not give equal amounts of o- and m-deuteroaniline. The ratio of o- and m-deuteroaniline obtained in this investigation was determined by the method of Lauer and Errede (48), which involved the conversion of the aniline to 2,4,6-tribromoaniline, whereby the deuterium in the m-position remains while that in the o-position is lost.

To place this deuterium tracer work on a firmer basis it was also required that blank runs be carried out with the starting material, o-deuterochlorobenzene, and with the product, deuteroaniline, to determine whether these amination conditions resulted in deuterium exchange before and after the cine-substitution.

Since the rate of cine-substitution is only described in the literature as being "extremely rapid" (8), it was found necessary to determine an approximate upper limit of the time required for it to go to completion.

Opportunity for an interesting side-investigation arose out of the method used to prepare o-deuteroaniline (XV) for the blank run already mentioned. The exchange reactions employed are schematically illustrated below:



(XIII) (XIV) (XV)

The analysis of the total deuterium content of (XIII), (XIV), and (XV) could be used, in principle, to calculate the deuterium isotope effect in the decarboxylation of anthranilic acid, and hence shed some more light on the mechanism of that reaction. The interpretation of the results would require a knowledge of the distribution of deuterium between the amino group and the carboxyl group in (XIII), and between the amino group and the ortho position

in (XIV). Due to difficulties encountered in an attempt to obtain this information by infrared spectroscopy, the isotopic studies of this type of decarboxylation mechanism were extended to what appeared to be a simpler case; namely, the decarboxylation of deuterated N-methyl anthranilic acid.

Due to the close connection of most of this secondary investigation with the major problem of this thesis, all the experimental work is discussed in the next section, but for obvious reasons the interpretation of the decarboxylation work is reserved for a separate section (Part II, page 82).

EXPERIMENTAL WORK

The experimental work is discussed under the following headings:

1) Starting Materials.
2) Preparation of Deuterated Compounds.
3) Reactions in Liquid Ammonia.
4) Combustions and Water Purifications.
5) Deuterium Analyses:
    a) The Spectrophotometric Method.
    b) The Gradient Density Method.

STARTING MATERIALS

Anhydrous ether. Commercial diethyl ether was dried with sodium wire and fractionated through a 15-plate column.

p-Dioxane. To remove aldehydic decomposition products p-dioxane (Eastman) was purified by the method of Fieser (22). A litre of p-dioxane was refluxed with 10 ml. concentrated hydrochloric acid and 200 ml. water for about 12 hours, bubbling nitrogen

through the solution to entrain the aldehyde. The water and acid were then removed by adding solid potassium hydroxide pellets until no aqueous layer formed on standing. The product was refluxed with sodium metal for several hours, and then fractionated through a 15-plate column, collecting the fraction which boiled at 99-100.5° C./741 mm.

Carbon tetrachloride. Eastman spectrophotometric grade was used without purification.

Anthranilic acid. Eastman (recrystallized) product was employed.

Deuterium oxide. This was obtained from the Commercial Products Division of the Atomic Energy Commission, and was reported by the supplier to have a mass spectrometric analysis of 99.83 atom % deuterium.

o-Iodochlorobenzene. Eastman product was used directly.

Chlorobenzene. Eastman product was used directly.

Aniline. Eastman spectro grade was used, carefully fractionating it through a 10 cm. Vigreux column just before use. The product was colorless, and had a boiling point of 183°C./745 mm., n_D^{20} = 1.5776.

Liquid ammonia. Supplied by Canadian Industries Limited. The anhydrous solvent was forced directly from the cylinder (placed in the recommended position) through a hard rubber tube into the reaction flask.

N-Methylaniline. Eastman c.p. grade was used, purifying it further according to Vogel (74). The N-nitroso derivative was prepared, distilled under reduced pressure, and then reduced back to N-methylaniline with tin and hydrochloric acid. Follwing steam

distillation, a colorless liquid with b.p. 193-194°C./750 mm. was obtained.

N-Methylanthranilic acid. Eastman product was used without further purification.

N,N-Dimethylaniline. Eastman product was fractionated twice through a 10 cm. Vigreux column, collecting over the range 188-189°C./749.5 mm.

Magnesium turnings. Supplied by Matheson, Coleman and Bell.

Bromobenzene. Eastman c.p. grade was fractionated through a 15-plate column, collecting material boiling at 154-155°C./745 mm.

n-Heptane. Matheson, Coleman and Bell c.p. grade was fractionated through a 15-plate column, collecting at 98-98.1°C./745 mm.

PREPARATION OF DEUTERATED COMPOUNDS

o-Deuterochlorobenzene. (typical preparation)

A 1-litre three-necked flask with ground glass joints was fitted with a reflux condenser, a dropping funnel, and a glass-seal mechanical stirrer. After adding 4.169 g. (0.171 mole) of magnesium turnings the system was thoroughly flamed with a stream of dry nitrogen passing through it. When cool the stopcock of the funnel was closed, and a slight positive pressure of nitrogen was maintained during the rest of the preparation, as indicated by an open manometer which also acted as a safety valve to relieve sudden pressure increases.

75 ml. of anhydrous ether and a tiny crystal of iodine were added to the magnesium turnings. The o-iodochlorobenzene (40.0 g., 0.168 mole) was dissolved in another 75 ml. of anhydrous ether and placed in the dropping funnel. A little of the dihalide solu-

tion was added and the flask was warmed gently to initiate the reaction. The rest of the dihalide solution was added over the period of an hour, maintaining gentle refluxing of the ether. The funnel was rinsed with another 10 ml. anhydrous ether, and the Grignard reaction was carried to completion by refluxing the dark brown solution for another hour.

To check for completeness of conversion an aliquot portion of the ethereal solution was withdrawn with a pipette, added to 25 ml. N/10 sulfuric acid, and a back-titration was carried out with N/10 sodium hydroxide solution. The total volume of the Grignard solution was rapidly measured with a dry graduated cylinder. Titration showed the presence of 90-97% of Grignard reagent.

The flask, to which the Grignard solution had been returned, was immersed in an ice bath and 4 grams (0.200 mole) deuterium oxide were added very slowly, accompanied by rapid stirring. Gilman's Colour Test I (44) was negative. Some water was then added; the ether layer was removed and dried with anhydrous potassium carbonate. The o-deuterochlorobenzene was recovered from the ether layer, washed with a sodium thiosulphate solution if it showed traces of iodine, and carefully fractionated through a 10 cm. Vigreux column, collecting from 128-132° C./742 mm. Yields ranged from 45-65%. ($n_D^{21.8}$ = 1.5261) The infrared spectrum of material prepared by this method is given in Fig. 6, page 101.

The material obtained from runs carried out on this scale was combined and diluted with ordinary chlorobenzene as required.

Deuterated Anthranilic Acid.

30 g.(0.219 mole) of anthranilic acid were dissolved in 70 ml. of dioxane in a 125 ml. distilling flask. To this solution were added 6.6 g.(0.330 mole) of deuterium oxide, and the solution was allowed to equilibrate for 160 hours at room temperature. To remove the water and dioxane the system was fitted with a condenser and receiver and kept under partial vacuum for 24 hours. Last traces of solvent were removed by warming the flask (pressure reduced to 20 mm.) to 85°C. by means of a water bath. A 1.92 gram sample of exchanged acid (D) was removed for analysis in connection with the isotope effect in the decarboxylation. Before storing it in a tightly closed weighing bottle it was kept at 2 mm. and 100°C. in a drying pistol for an hour.

In a second exchange (E) 30 g.(0.219 mole) of anthranilic acid were equilibrated with 2.2 grams (0.110 mole) of deuterium oxide in 45 ml. of dioxane for 160 hours. 6.14 grams were removed for analysis. The infrared spectrum of this material is given in Fig. 7, page 102.

Decarboxylation of Deuterated Anthranilic Acid.

Immediately after removal of the solvent from the exchanged acid, a condenser with a removable jacket was thoroughly cleaned, flamed, re-assembled and fitted to the distilling flask containing the acid. The flask was immersed in an oil bath and the temperature raised rapidly to 200-210°C, when decarboxylation occurred. The crude aniline (16.2g.) obtained from decarboxylation (D), which appeared to be complete after one hour, was placed in a 25 ml. flask and distilled with a 4 cm. plug of glass wool in its neck.

The yield was 16.2 g.(0.205 mole), b.p. 179-183°C. (uncorr.)/742.0 mm., $n_D^{21.7}$ = 1.5826. This represents a yield of 85% for the exchange and decarboxylation. The infrared spectrum of this material is given in Fig. 8, page 103. A portion (3.1 g.) of this material was saved in a self-sealing serum vial for analysis in connection with the decarboxylation isotope effect.

Decarboxylation of the acid from the second exchange (E) yielded 12.8 grams of deuterated aniline (76% yield). 5.0 grams of this were retained for analysis.

Re-exchange of Deuterated Aniline.

Since the aniline obtained from the decarboxylation of deuterated anthranilic acid would have N-D bonds in it as well as ortho C-D bonds, it was necessary to remove the former by a re-exchange process.

13.1 g.(p.140 mole) of deuterated aniline prepared as described above were placed in a 60 ml. separatory funnel and 40 ml. (2.22 mole) of distilled water were added. The funnel was closed and shaken well at intervals of 10 minutes. After an hour the aniline layer was removed, and the process repeated with three more successive portions of water. To recover the aniline dissolved in the water the aqueous portions were combined and extracted with ether. The total amount of o-deuteroaniline recovered was 10.4 g., b.p. 179-183°C./739.5 mm. This would represent a 79% recovery from the re-exchange process. Since spectrophotometric analysis (discussed on page 46) showed some deuterium still bonded to the nitrogen atom, the product was further treated with liquid ammonia.

8.7 g. of the o-deuteroaniline (D) were dissolved in ca. 500 ml. of liquid ammonia and the solvent allowed to evaporate away overnight. Ether was then added to the flask, and it was warmed under reflux to drive off any residual ammonia still present. The dried ether yielded, after two successive distillations at reduced pressure, 7.14 g. aniline, b.p. 60-65°C./2.5 mm., $n_D^{21.8}$ = 1.5834. Spectrophotometric analysis of the 1498 mμ peak showed that all N-D bonds had been converted to N-H bonds. The infrared spectrum of this material is given in Fig. 8, page 103.

7.8 grams of deuterated aniline from the second decarboxylation (E) were treated with liquid ammonia only, and 4.3 grams were recovered. Here too all the deuterium had been removed from the nitrogen atom.

Deuterated N-Methylanthranilic Acid.

30 grams (0.198 mole) of N-methylanthranilic acid were dissolved in 60 ml. of dioxane by gentle warming. Deuterium oxide (2.0 g., 0.100 mole) was added and 48 hours allowed for the equilibrium to be established. Due to the limited solubility of the acid in dioxane, the solution was kept warm during this period. The solvent was then removed as already described (page 31). 4.6 grams of exchanged acid were removed, kept at 1 mm. and 100°C. in a drying pistol for one-half hour, and saved for analysis. The infrared spectrum of this material is given in Fig. 9, page 104

Decarboxylation of Deuterated N-Methylanthranilic Acid.

This was carried out as already described (page 31), except that the oil bath was kept at 240-250°C. for an hour to effect

complete decarboxylation. The crude product (16.9 g.) was fractionated in a Vigreux column to give 15.1 g. of colorless deuterated N-methylaniline, b.p. 192-194°C.(uncorr.)/745 mm., n_D^{21} = 1.5700. This represents a yield of 94% for the exchange and decarboxylation. The infrared spectrum of the deuterated material is given in Figure 10, Page 105. 5.1 grams of this material were retained for analysis.

Re-exchange of Deuterated N-Methylaniline.

The liquid ammonia procedure has already been described (page 33). Starting with 10 grams of N-methylaniline having both N-D and ortho C-D bonds, 8.0 grams of the deuterated material were obtained which had no deuterium attached to the nitrogen atom (spectrophotometric analysis described on page 46). This product had a b.p. of 192-193°C./745 mm., n_D^{21} = 1.5698. The infrared spectrum is given in Fig. 11, page 106.

Bromination of Deuteroaniline.

To determine the amount of deuterium in the meta position of the aniline obtained from the cine-substitution the 2,4,6-tribromo derivative of the product was prepared. This would remove the deuterium from the ortho position.

About 1.0 - 1.5 g. of deuterated aniline were placed in a small conical flask and 20 ml. water added. The flask was cooled in ice water, and bromine in 95% ethyl alcohol (0.28 g./ml.) was added from a buret until the first appearance of a yellow tinge in the pasty mass. The precipitate was filtered with suction through a small Buchner funnel, and washed with water to remove traces of bromine and hydrobromic acid. The product was dissolved in warm absolute alcohol, and re-precipitated by adding water. The

recrystallized material was colorless, and melted sharply at 118°C. (uncorr.).

The sym-tribromo derivative of o-deuteroaniline (E) was also prepared and analyzed to demonstrate the feasibility of this method of removing ortho deuterium from the nucleus.

REACTIONS IN LIQUID AMMONIA

Except where otherwise stated, all reactions in liquid ammonia were carried out without cooling the reaction flask, or the use of a Dry Ice condenser. The anhydrous solvent was forced into the vessel from the commercial cylinder placed on an incline with the valve at the lower end. Frost on the outside of the flask acted as a convenient insulation, and the solvent remained at its boiling point, -33°C.

Conversion of o-Deuterochlorobenzene to Aniline with Sodamide.

600 ml. of liquid ammonia were forced into a 1-litre three-necked flask fitted with a glass mechanical stirrer and an ammonia vent leading into a well ventilated fume hood. Sodamide was prepared by the method of Vaughan, Vogt and Nieuwland (73). A tiny crystal (ca. 0.4 g.) of ferric nitrate nonahydrate was added to the rapidly stirred ammonia, followed by about 1 gram of sodium metal. After about 5 minutes the remaining 4.2 grams of sodium metal were added (total of 0.226 gm. atom), and 25 minutes allowed for the conversion to go to completion. By this time the characteristic blue alkali metal solution had turned deep grey in color.

The ammonia delivery tube was then replaced by a 60 ml. dropping funnel, and 15 g. (0.133 mole) of o-deuterochlorobenzene

(stock sample A) were added dropwise over a period of 20 minutes. The halide had been pre-cooled to -20°C. to prevent excessive evaporation of the solvent. Following the addition the stirring was continued uninterrupted for another 40 minutes, when 11 g. (0.202 mole) of ammonium chloride were added and stirred into the solution to destroy any excess sodamide, and to hydrolyze the aniline salt produced. The solvent was allowed to evaporate overnight in the fume hood.

Ether was added to the residue and the flask was warmed under reflux to drive off any residual ammonia still remaining. The ether-insoluble salt was dissolved in water, and the aniline was extracted from the solution with ether. After being dried with anhydrous potassium carbonate, the solvent was removed, and the aniline was carefully distilled off at reduced pressure to separate it from the other amines formed in the reaction.

The product was fractionated twice through a 10 cm. Vigreux column, in an effort to achieve quality at the expense of quantity. Material collected at 60-65°C./2 mm. in the second distillations was as follows:

	Amount	% of Theoretical
Run I	2.22 g.	18
Run II	2.31	27
Run III	2.69	22

These samples were checked for purity spectroscopically, and the 1498 mμ peak was found to be quantitatively reproduced (within the limits of experimental error) when checked against a calibration curve for ordinary aniline at that wavelength (Fig. 2, line 2, page 49).

In analogous runs carried out with ordinary chlorobenzene, but using the acid extraction method of Bergstrom (8), yields of 35-40% were realized. However, this method could not be used in deuterated runs due to the acid-catalyzed deuterium exchange from the ring in aniline (9). To determine the extent of the deuterium loss that might be involved if this method were used, 1.6 grams of o-deuteroaniline (D) were dissolved in 20 ml. 3 N hydrochloric acid, and the solution immediately made basic with 6 N sodium hydroxide. The aniline (1.0 g.) was recovered by ether extraction, and analyzed for deuterium (No. 17, TABLE VI).

Blank Run No. 1 - o-Deuteroaniline with Sodamide.

To a stirred solution of sodamide from 5.2 g. (0.226 gm. atom) of sodium metal in ca. 600 ml. of liquid ammonia prepared in a 1 litre three-necked flask by the procedure already described, were added slowly 3.0 g. (0.032 mole) of o-deuteroaniline (D) over a period of 20 minutes. After another 40 minutes of stirring, 12 g. (0.222 mole) of ammonium chloride were added and the solvent was allowed to evaporate. The aniline was recovered by ether extraction, 1.81 g. (0.020 mole), b.p. 60-65°C./2 mm. being obtained.

Determination of the Approximate Rate of the Cine-Substitution.

5.2 g. (0.226 gm. atom) of sodium metal were converted to sodamide in ca. 400 ml. liquid ammonia. In a separate 1 litre three-necked flask 15 g. (0.133 mole) of ordinary chlorobenzene were dissolved in 200 ml. liquid ammonia. In a third flask a solution of 11 g. (0.202 mole) of ammonium chloride in 150 ml. liquid

ammonia was prepared. The chlorobenzene solution was stirred rapidly, and the sodamide was added by means of air pressure over a period of 20 seconds. This was immediately followed by the addition of the ammonium chloride solution, about half of it having been added 30 seconds after the reaction was started. Addition was completed 45 seconds after the reaction started. The aniline was recovered from this run by the acid extraction method, a 35% yield being obtained, quite comparable with the yields (35-40%) obtained by a similar process where the reaction was allowed about an hour to go to completion.

Blank Runs with o-Deuterochlorobenzene and Sodamide.

To determine the extent of any deuterium exchange on the reactant due to the influence of a liquid ammonia solution of sodamide, blank runs with excess o-deuterochlorobenzene were carried out under two sets of conditions:

(Blank No. 2) 15 g. (0.133 mole) of o-deuterochlorobenzene (stock sample B) were added over a period of 20 minutes to a solution of sodamide from 1.52 g. (0.066 gm. atom) of sodium metal. After another 40 minutes of stirring 4 g. (0.075 mole) of ammonium chloride were added, the solvent was allowed to evaporate, and the unreacted chlorobenzene was recovered by ether extraction and distillation.

Two fractionations through a 10 cm. Vigreux column were insufficient to remove traces of aniline from the product, as revealed by infra-red spectra. After two more successive fractionations the aniline content was down to less than 0.5 mole %. 3.2 grams were recovered, b.p. 129-131°C./740 mm. This sample was analyzed for the deuterium content (No. 4, TABLE VI).

(Blank No. 3) This blank run was carried out exactly like the run used to place a rough time limit on the rate of the reaction (page 37). 15 grams (0.133 mole) of o-deuterochlorobenzene (stock sample C) and sodamide from 1.52 g.)0.066 gm. atom) of sodium metal were employed, and the unreacted material was recovered by ether extraction and distillation. The recovered o-deuterochlorobenzene was carefully fractionated two times through a 10 cm. Vigreux column, and was shown to be free of aniline by the spectrophotometric method. 3.5 grams were recovered and analyzed for deuterium (No. 5, TABLE VI).

Run to test for Gas Evolution.

A solution of 0.5 g. (0.022 gm. atom) sodium metal in 100 ml. liquid ammonia was prepared in a 300 ml. three-necked flask and converted to sodamide in the usual way. The flask was cooled to -34°C. with a Dry Ice-acetone mixture and the system was closed by inserting a 60 ml. dropping funnel in one neck and attaching the other to an azotometer tube filled with dilute hydrochloric acid. A solution of 1.0 g. (0.009 mole) of undeuterated chlorobenzene in 30 ml. liquid ammonia was placed in the funnel and added rapidly to the cold stirred sodamide solution. With this crude arrangement 12 ml. of gas (25°C., 742 mm.) were collected over a period of half an hour, which may be assumed to be air displaced from the system since about 220 ml. of gas could be expected if the ortho hydrogen atom from chlorobenzene was lost as a hydride ion and converted to hydrogen gas during the reaction. Bergstrom and Horning (7) also report no evolution of hydrogen or nitrogen gas.

Reaction of a Grignard reagent with Liquid Ammonia.

In connection with a metalation mechanism discussed later (page 67), the reaction of o-ClC_6H_4MgI with liquid ammonia was investigated.

30 ml. of ethereal Grignard solution containing ca. 0.029 moles of Grignard reagent were withdrawn from one preparation of o-deuterochlorobenzene (page 29) and added to 200 ml. liquid ammonia. A white amorphous precipitate formed immediately, which was shown to be ether insoluble as well. Dilute hydrochloric acid decomposed the precipitate to give chlorobenzene. Since no aniline or other amines were obtained, no more attention was given to this reaction. It may be noted in passing that Hennion and Wolf (38) have ascribed the complex formula $RMgNH_2 . (MgX_2)_2 . Mg(NH_2)_2 . (NH_3)_6$ to precipitates they obtained under similar conditions.

COMBUSTIONS AND WATER PURIFICATIONS

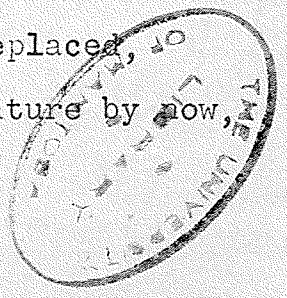
To analyze a compound for deuterium a sample large enough to yield from 0.2 to 0.4 grams of water of combustion was burned in a combustion apparatus, and the water collected. From the density of the purified water the weight percent deuterium oxide in it could be obtained, and this was used to calculate the deuterium content of the original compound.

The Combustion Train.

A three unit macro combustion furnace with a Vycor tube having a standard 12/20 taper joint as an outlet was used. Near the outlet was placed a plug of silver wool, or a roll of clean copper gauze was inserted into the joint itself, to trap halogens.

In the combustions of the tribromoaniline samples this was found insufficient, and the water in the trap was allowed to stand with a few clean pieces of copper wire for several hours before starting the purification. The rest of the tube up to the middle of the central heating unit was filled with copper oxide, a roll of copper gauze about two inches long being used to retain the oxide in that section of the tube. With this arrangement the sample to be combusted could be placed against the copper gauze and still rest in the central section of the furnace. Oxygen from a cylinder was passed through a calcium chloride drying tower, two Greiner-Friedrichs gas washing bottles filled with concentrated sulfuric acid, and another u-tube filled with calcium chloride before it entered the side-arm of the combustion tube. The receiver for the water consisted of a Pyrex glass u-tube with a 12/20 standard taper joint at right angles to one end, and a capillary opening at the other end.

Before using the freshly filled combustion tube it was burned out for several hours with a slow stream of oxygen passing through it. To prepare for a combustion itself the copper oxide in the long section of the furnace was heated to dull redness while oxygen was passed through it. The other two sections were allowed to remain cold. A cleaned receiver was then attached and flamed in the stream of oxygen. The stopper at the other end of the Vycor tube was removed, and the sample rapidly introduced, making sure that the container rested right up against the copper gauze in the centre furnace section. The stopper was tightly replaced, and the receiver, which had cooled down to room temperature by now,



was immersed in a Dry Ice-acetone mixture (-80°C.) in a Dewar flask. The oxygen flow was then adjusted to about 2 bubbles per second.

After a combustion, when all the furnace sections had been heated to dull redness and the receiver had been removed, the Vycor tube was allowed to cool with a slow stream of dry air or nitrogen passing through it. When cool the tube was tightly closed, and the entire procedure was repeated for another combustion.

Combustion of Liquid Samples.

Liquid samples burned consisted of chlorobenzene, aniline, and N-methylaniline. These were introduced into the tube in Pyrex glass ampules of about 1½ ml. capacity. To fill the ampules, the tip was placed below the liquid level of the sample, and the air partly removed from the ampule in a vacuum desiccator. When dry air was returned to the desiccator the required amount of material was forced into the ampule. The ampule was then placed in a special wire cradle on a porcelain boat and pushed into the combustion tube until the ampule tip touched the copper gauze.

The centre section of the furnace was closed and the element turned on at a very low setting of the rheostat control to assist in distilling out the sample. It was found that this part of the procedure required very careful attention to prevent flashbacks in the tube, and varied with the boiling points of the liquids employed. When the ampule was almost empty the temperature of the centre section was increased to a dull red heat along with the short heating unit, which pre-heated the entering oxygen and had been hitherto shut off completely. The flow of oxygen was continued

for about 20 minutes to sweep last traces of water into the receiver. The total average time for the liquids used was about 1½-2 hours. After this period the capillary tip of the receiver was sealed by melting the glass, the u-tube was separated from the furnace and rapidly closed with a standard taper stopper to prevent possible deuterium losses by exchanging with atmospheric moisture.

In the combustions of chlorobenzene the yields of water were 97-98% of the theoretical amount, in agreement with the almost quantitative recovery obtained by Warkentin (75) using the same method. In the combustion of nitrogenous materials, oxides of nitrogen are produced in the process which dissolve in the water, making it distinctly acidic, and also leading to apparent water recoveries slightly in excess of the theoretical amounts.

Combustion of Solid Samples.

Solid materials combusted were anthranilic acid and N-methyl anthranilic acid. With the combustion tube ready to start a combustion, solid exchanged acid samples of the appropriate size were weighed out rapidly directly in a porcelain boat and introduced as described above. The central section of the furnace was adjusted to melt the sample fairly rapidly. When the boat was practically dry, the temperature of all the furance sections was increased and the combustion completed as already described. Average time for these combustions was 1½ hours.

Purification of Water Samples.

Water samples obtained in the combustion process were purified according to the method of Keston, Rittenberg and Schoenheimer (43)

with slight modifications. The purification apparatus consisted of five Pyrex glass u-tubes and a Pyrex receiver having standard 12/20 taper joints. All parts were thoroughly cleaned with chromic acid, washed with dilute ammonium hydroxide, rinsed well with water and dried in an oven before every run.

To start a purification the u-tubes were arranged as shown in Fig. 1, minus tube 1., which was the receiver in the combustion and now contained the water sample to be purified. The rest of the train was evacuated to 5 mm. with a vacuum pump and thoroughly flamed. After it had cooled to near room temperature, air was admitted through stopcock A (Fig. 1) through three u-tubes filled with anhydrous magnesium perchlorate. Cotton batting had been firmly packed above the drying agent in these tubes to prevent fine particles of drying agent from being swept into receiver 6. Milligram amounts of potassium permanganate and calcium oxide were now introduced into tube 2., an excess of barium carbonate was added to the water in receiver 1. (to tie up the oxides of nitrogen produced in the combustion), and the latter was attached to the rest of the system. Tube 2. was then immersed in a Dry Ice-acetone mixture, and the system evacuated to 5 mm. By warming tube 1. with a micro-burner the water was carefully distilled into tube 2. On completion of this transfer the system was restored to atmospheric pressure, tube 1 removed, tube 2 closed with a standard taper stopper, and the freezing mixture moved to tube 3. The water in tube 2 was then refluxed over the alkaline permanganate at atmospheric pressure for a few minutes. This should

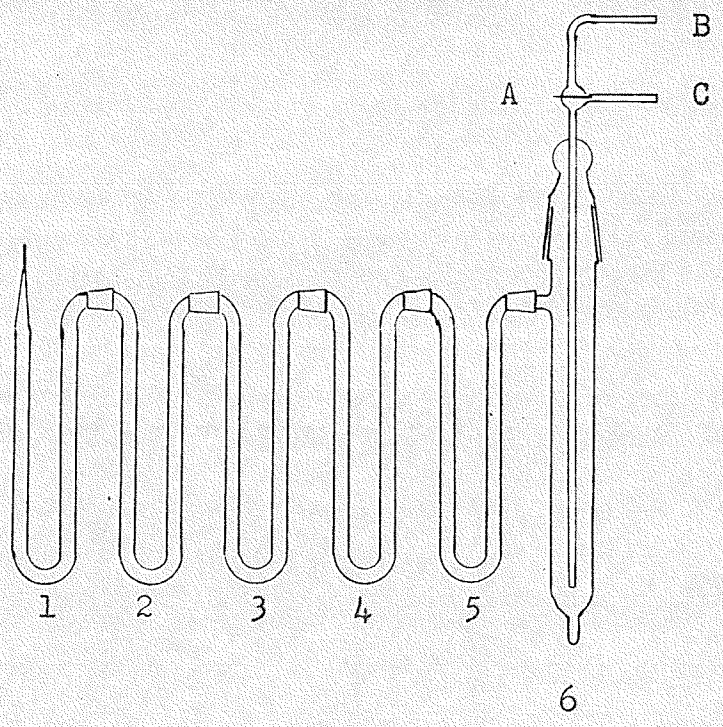


Fig. 1. Water Purification Train

A, two-way stopcock; B, through anhydrous magnesium perchlorate drying tubes and Dry Ice trap to manometer and vacuum pump; C, to atmosphere through three u-tubes filled with anhydrous magnesium perchlorate.

remove carbon dioxide and oxidize any traces of organic material present. When the water had cooled to room temperature the system was again evacuated to 5 mm. and distillation carried out into tube 3. This process was repeated until the water sample had been distilled four times after the initial distillation unto the purifying agents. By means of a dry Pyrex glass tube with a freshly drawn out capillary tip and a rubber suction bulb the purified water sample was rapidly transferred from receiver 6 to a cleaned and flamed serum vial with a self-sealing rubber stopper.

DEUTERIUM ANALYSES

The Spectrophotometric Method.

All spectrophotometric work was done with a Beckmann Model DK-1 instrument having quartz optics. Matched 1 cm. x 1 cm. x 4.5 cm. Corex cells (with loose lids), a tungsten light source, and a lead sulfide detector were used in the infra-red region. Carbon tetrachloride was used as solvent over the range 2850-1000 mμ wherever solubility permitted its use. p-Dioxane was substituted for more polar solutes, shortening the spectral range to 2350-1200 mμ.

Before use the instrument was adjusted for 0% and 100% transmittance, with pure solvent in both cells, at the wavelength where transmittance measurements were to be made. Where spectra were to be recorded over a range, 0% and 100% lines were recorded first by the same procedure. The sensitivity control of the instrument was set at 10, giving a maximum peak-to-peak noise level of about 0.5%. Scanning was carried out at decreasing wavelength, scanning

speed = 10, time constant = 0.1, and chart drive of 2 inches/minute. Transmittance measurements at any single well-resolved peak were obtained by scanning (at wavelength drive = 30) across the desired peak with the wavelength increasing and decreasing alternately to obtain the average of five peak heights.

The solutions themselves were made up by weight, and the concentration in moles/litre of solution computed by using the following densities[f] at 25°C., and assuming no volume change on mixing:

p-dioxane = 1.0353 grams/cc.
carbon tetrachloride = 1.5843
aniline = 1.0173
N-methylaniline = 0.9824

In the case of solid solutes the volume occupied by the solid was assumed to be negligible since the solutions were very dilute.

Attempted Analysis of Benzenoid Deuterium.

Since the spectra of o-deuterochlorobenzene (Fig. 6) and o-deuteroaniline (Fig. 8) showed no well-resolved peaks characteristically different from those in the spectra of the respective undeuterated analogues in the wavelength range accessible to the DK-1 instrument, this method of benzenoid deuterium analysis was abandoned. Since no pure deuterium isomers of any compound were prepared, this method would have required standardization against some other method if it had been found suitable.

Analysis of Deuterium on the Amino Group.

Wulf and Liddel (81) have attributed the absorption of primary and secondary amines in the 1500 mμ region to the first overtone

f From the International Critical Tables, published for the National Research Council of the U.S.A. by McGraw-Hill Book Co., Inc., N.Y. 1933.

of the N-H stretching frequency.

In aniline this characteristic peak which was found to occur at 1498 mμ, deviated slightly from Beer's Law (Fig. 2 - line 2). In N-methylaniline this peak (1493 mμ) was decreased in intensity (Fig. 10), and obeyed Beer's Law in the dilute region (Fig. 2- line 3). In N,N-dimethylaniline no absorption occurred in this region (Fig. 11).

Substitution of deuterium or some other heavy group for an amino proton should result in a new absorption band (N-D) appearing at a longer wavelength, beyond the range of the quartz infrared spectrophotometer. Nevertheless, the intensity of the peak in the 1500 mμ region should be a measure of the amount of unsubstituted material present in the sample, and hence the amount of deuterium attached to the nitrogen should be obtainable by difference.

To test this method of analysis a sample of aniline was exchanged with deuterium oxide in dioxane, and presumably should have all the deuterium present bonded to the nitrogen atom (see infrared spectrum in Fig. 10). Spectrophotometric analysis yielded 49.7 ± 1.6 atom % deuterium bonded to the nitrogen, whereas the combustion method gave 59.64 ± 1.66 atom % deuterium (No. 18, TABLE VI). The method was further subjected to a critical test by a determination of the "atom % methyl" attached to the nitrogen atom in N-methylaniline. A value of 24.5% was obtained as compared with the theoretical value of 50%. This suggested that the introduction of one heavy group for a proton attached to the nitrogen atom may affect the intensity of the remaining N-H

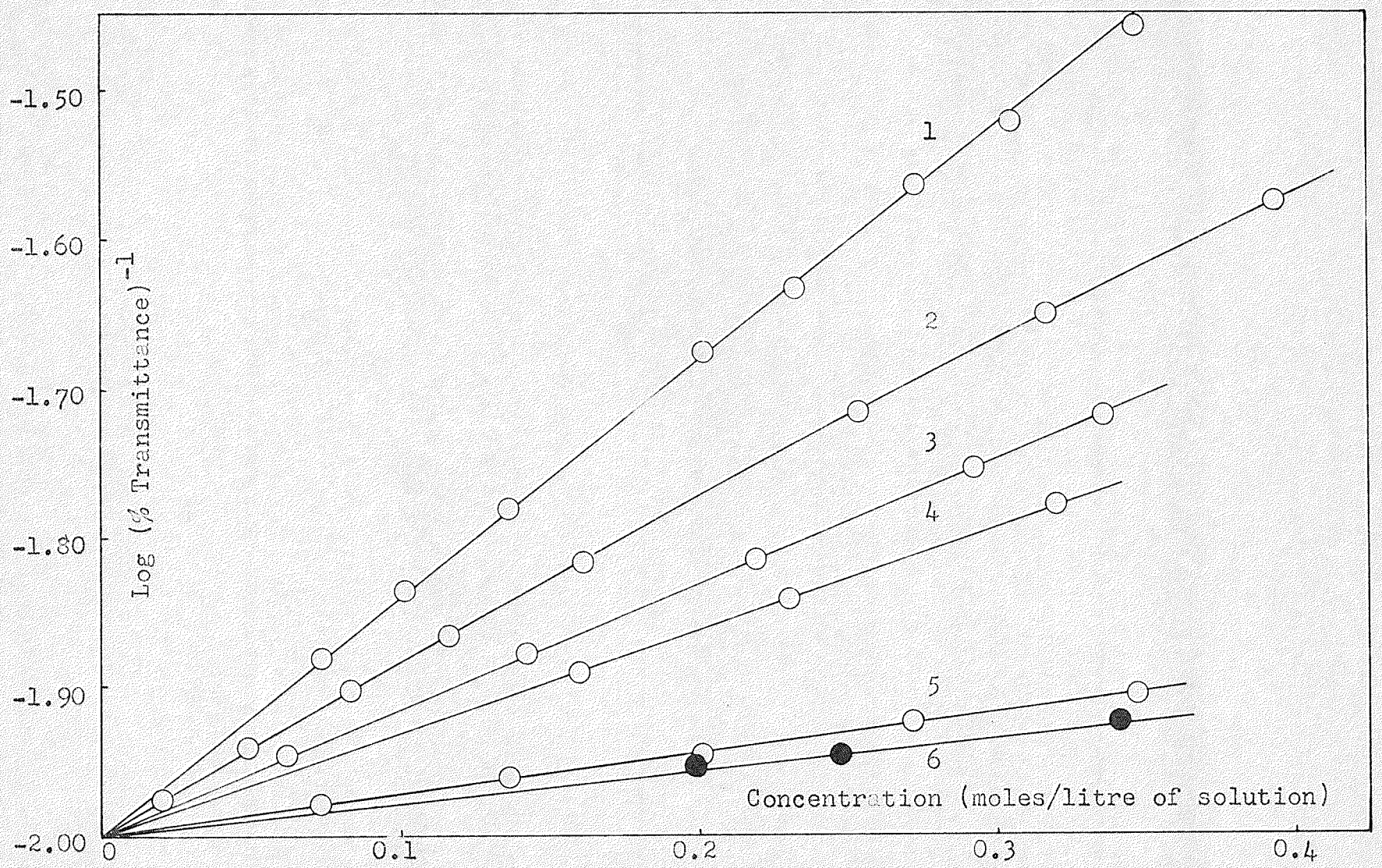
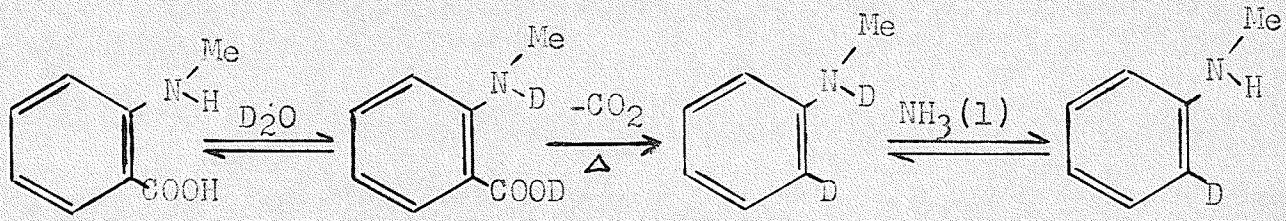


Fig. 2. Beer's Law Plots. 1, o-NHMeØCOOH in dioxane (2020 mμ); 2, $ØNH_2$ in CCl_4 (1498 mμ); 3, ØNHMe in CCl_4 (1493 mμ); 4, o-DØNDMe in CCl_4 (1493 mμ); 5, o-NHMeØCOOH in dioxane (1535 mμ); 6, o-NDMeØCOOD in dioxane (1535 mμ).

vibration without changing the frequency appreciably. Difficulties in spectroscopic work due to the fact that there are two hydrogen atoms attached to the nitrogen atom in the amino group are also noted by Nakamoto, Margoshes, and Rundle (58). This method of analysis was therefore abandoned without applying it to the deuterated anthranilic acid used in the decarboxylation (page 31), where it was originally thought that this method of attack would discriminate between the two deuterated functional groups in the molecule.

The method described above was, however, extended to the analysis of deuterium attached to the nitrogen atom in deuterated N-methylanthranilic acid (XVII) and the deuterated N-methylaniline (XVIII) obtained from it on decarboxylation (page 33), since both these compounds have only one hydrogen bonded to the nitrogen atom. The following scheme illustrates the series carried out as described elsewhere:



(XVI) (XVII) (XVIII) (XIX)

The intensity of absorption at the 1493 mμ peak was determined for three concentrations of (XVIII) in carbon tetrachloride (Fig. 2 - line 4), and the amount of deuterium bonded to the nitrogen calculated to be 18.0 atom % from the slopes of lines 3 and 4. The combustion analysis of (XVIII) gave the total deuterium content of the material, equal to 35.67 ± 1.58 atom % deuterium in the two labelled positions (No. 22, TABLE VI). By difference the

amount of deuterium in the ortho position of (XVIII) should be obtained as follows:

(2 x 35.67 ± 1.58) - (18.0) = 53.3 ± 3.2 atom %

Combustion analysis of (XIX), which had no deuterium bonded to the nitrogen, gave 56.77 ± 0.82 atom % deuterium (No. 23, TABLE VI), in agreement with the above value.

A similar treatment of the 1535 mμ peak of (XVII) in p-dioxane was not satisfactory since the absorption is very weak in that solvent, and is also not well resolved (Fig. 9). Figure 2 - line 1 is a Beer's Law plot of the 2020 mμ peak in (XVI), which was used to show (in a blank run) that the dioxane used as a solvent in the preparation of (XVII) could be removed by the method used. Line 5 in the same figure shows the Beer's Law plot for th 1535 mμ peak in (XVI), and line 6 shows the same relationship for (XVII). No precise significance can be placed on the deuterium analysis obtained from the slopes of lines 5 and 6, which indicated that about 17 atom % of deuterium were attached to the nitrogen atom in (XVII). No other solvent could be obtained that was transparent at this wavelength, and would dissolve the polar solute without interacting with it to such an extent that accurate transmittance measurements were impossible. It has been shown (20) that the oxygen atoms of dioxane enter into a high degree of hydrogen bonding with suitable solutes, e.g. those containing amino groups.

The Gradient Density Method

The gradient density tube method described by Anfinsen (1) was used to determine the weight percent deuterium oxide in the

purified water of combustion. This method is based on Fick's principle, which states that a linear gradient of densities is produced at the juncture of two miscible liquids of unequal specific gravities. The details of this method have been given by Brynko (16) and by Warkentin (75) and only a brief description will be given here.

The gradient tube itself consisted of a 35 cm. Pyrex glass tube having a diameter of 5 cm., the ends of which were sealed to the neck of a 1 litre round-bottomed flask and to the bottom of a 500 ml. round-bottomed flask respectively. The assembly was mounted vertically in a glass-fronted thermostat controlled to 25.00 ± 0.01°C., with the neck of the tube protruding above the level of the water in the tank. The tube was fitted with a ground glass cap to keep dust out of the system and to prevent evaporation of the gradient components.

Some anhydrous magnesium perchlorate was placed in the bottom flask and the tube filled to the mid-point with a n-heptane-bromobenzene solution having a specific gravity of about 1.019. A similar solution of specific gravity 0.998 was carefully layered over the heavier solution by means of a separatory funnel with a long stem, the tip of which was kept just below the surface of the liquid in the tube. The tube was filled to within the neck of the 500 ml. flask.

A stirrer, made of clean copper wire, and having a spiral in the plane perpendicular to the stem, was gently lowered to the interface at the center of the tube, and the solution stirred

with strokes of increasing length until at the tenth stroke upward the entire length of the tube between the two flasks had been traversed. The system was allowed at least 24 hours to attain equilibrium. Gradients prepared in this manner covered the range 0-10 weight % deuterium oxide, and standard water-deuterium oxide samples to bracket unknown samples (Table IV) were prepared from purified glass-distilled water and 99.83% deuterium oxide. It may be noted that the enrichment of O^{18} which occurs in the preparation of heavy water would have a negligible effect on the densities of these solutions as far as this investigation is concerned (46).

TABLE IV

Water - Deuterium Oxide Standards

Standard No.	Weight Percent D_2O
1	0.000
2	2.019
3	3.982
4	5.949
5	8.028
6	9.817

A hypodermic needle, attached by means of a Luer joint to a 10 cm. length of Pyrex glass tubing having a 1/4 mm. bore was used to withdraw the water samples through the stoppers of the serum vials. In this way contact of the sample with the atmosphere was largely avoided. A rubber policeman was slipped over the other

end of the capillary tube to act as a suction bulb. The needle and capillary tube were rinsed with a few drops of the sample, then re-inserted and refilled. The tip of the needle was lowered below the level of the gradieht solution, gentle pressure applied to the policeman, and the drop released by raising the needle out of the solution. Before introducing another sample the needle and capillary tube were washed with distilled water under pressure. They were dried by blowing dry nitrogen gas through them, and were then stored in a desiccator until further use.

Standards were always introduced with each series of unknowns, placing the drops carefully by looking at the horizontal cross-section of the tube in the well-illuminated bath. Heavier drops were introduced first to prevent collisions. After three hours the drops had attained equilibrium, and the height at the top and bottom of each drop was read by means of a vertical cathetometer accurate to 0.1 mm. The drops produced by this method were fairly consistent in size, having a diameter of about 3 mm. The centre of each drop was recorded as its height, and it was shown that dmall variations in the drop size had no effect on the height of the centre. For the low deuterium oxide concentrations involved it may be shown that a plot of weight percent deuterium oxide versus height is as nearly linear as a plot of density versus height. Thus the gradients used were calibrated directly in weight percent deuterium oxide. The analysis of an unknown drop was obtained by interpolation between the two standards that bracketed it.

After the equilibrium heights of a series of drops had been recorded, the drops were withdrawn from the gradient solution by means of a piece of moistened filter paper wrapped around one end of a thin glass rod. A second method used was to sprinkle pulverized anhydrous magnesium perchlorate into the tube, thus carrying the water drops down into the layer of drying agent at the bottom. If the density gradient had been preserved, it could be used again after 24 hours. Gradients 2 and 3 (Fig. 3) resulted from gradient I in this manner.

The water samples in this investigation were analyzed on 6 different gradients. Plots of cathetometer readings versus weight percent deuterium oxide are given in Fig. 3. Gradients that exhibited curvature at the ends of the range were not used in those regions, but were still found to be quite satisfactory in the centre section. Gradient 4 was checked with auxiliary standards prepared at 1% D_2O intervals to check this. To check the consistency of results obtained from this method of analysis several samples were analyzed using different gradients. All analytical results are listed in TABLE VI.

To determine the magnitude of the deuterium loss due to proton exchange during the combustion and purification processes standard water-deuterium oxide samples covering the range 0-20 weight percent oxide were put through both processes. They were then analyzed in the gradient and the deuterium loss determined. Since the loss was found to be quite substantial at higher deuterium oxide concentrations (see TABLE V), all analyses reported were corrected from the curve shown in Fig. 4.

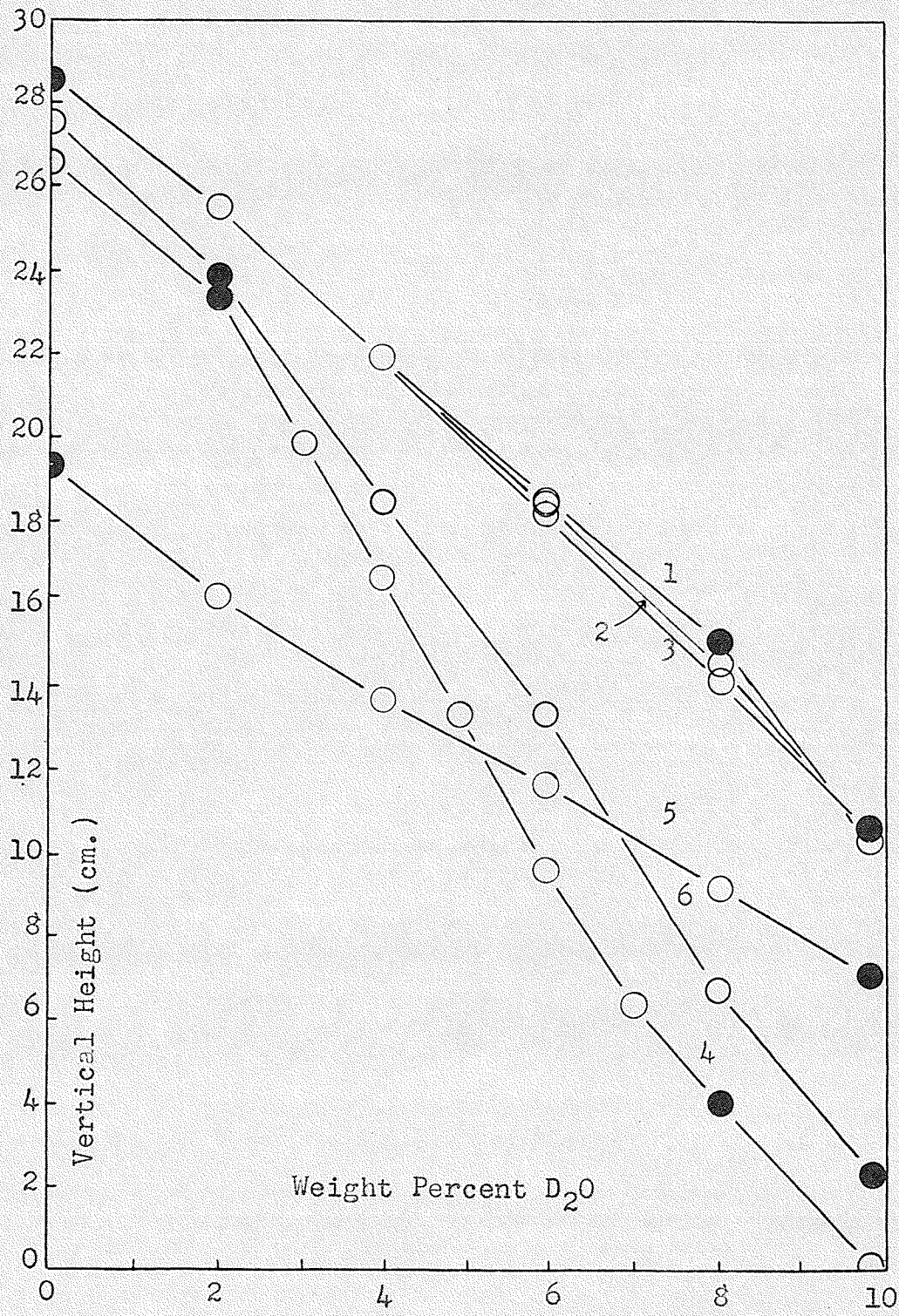


Fig. 3. Plot of Cathetometer Readings versus Weight Percent D_2O for the Density Gradients used. Density determinations were made in the ranges between the dark circles.

TABLE V

Determination of Deuterium Exchange Losses

True Weight Percent D_2O	Gradient Used	Weight Percent by Analysis
(a) Combustions with sample in pyrex glass ampule:		
3.982	4	3.89
8.028	4	7.71
10.103	5	9.91
14.161	5	13.66
20.023	5	18.48
(b) Combustions with sample in a porcelain boat:		
3.982	5	3.88
9.817	5	9.52
14.161	5	13.70
20.023	5	19.30

The following expression, which is easily derived from fundamental principles, was used to convert the weight percent D_2O from an analysis to the amount of deuterium present in the corresponding organic compound:

$$\text{Atom \% D in n' positions} = \frac{100}{\frac{n'}{90n}(1000 - Q)}$$

where n' = the number of hydrogen positions in the molecule that consisted partly of deuterium atoms[g],

n = the total number of hydrogen atoms in a non-deuterated molecule of the compound,

and Q = the weight percent deuterium oxide in the water of combustion of the compound.

g For deuterated anthranilic acid and its decarboxylation product n' = 3; for deuterated N-methylanthranilic acid, its decarboxylation product, and for aniline exchanged with D_2O, n' = 2; and for o-deuteroaniline with no deuterium attached to the nitrogen atom n' = 1.

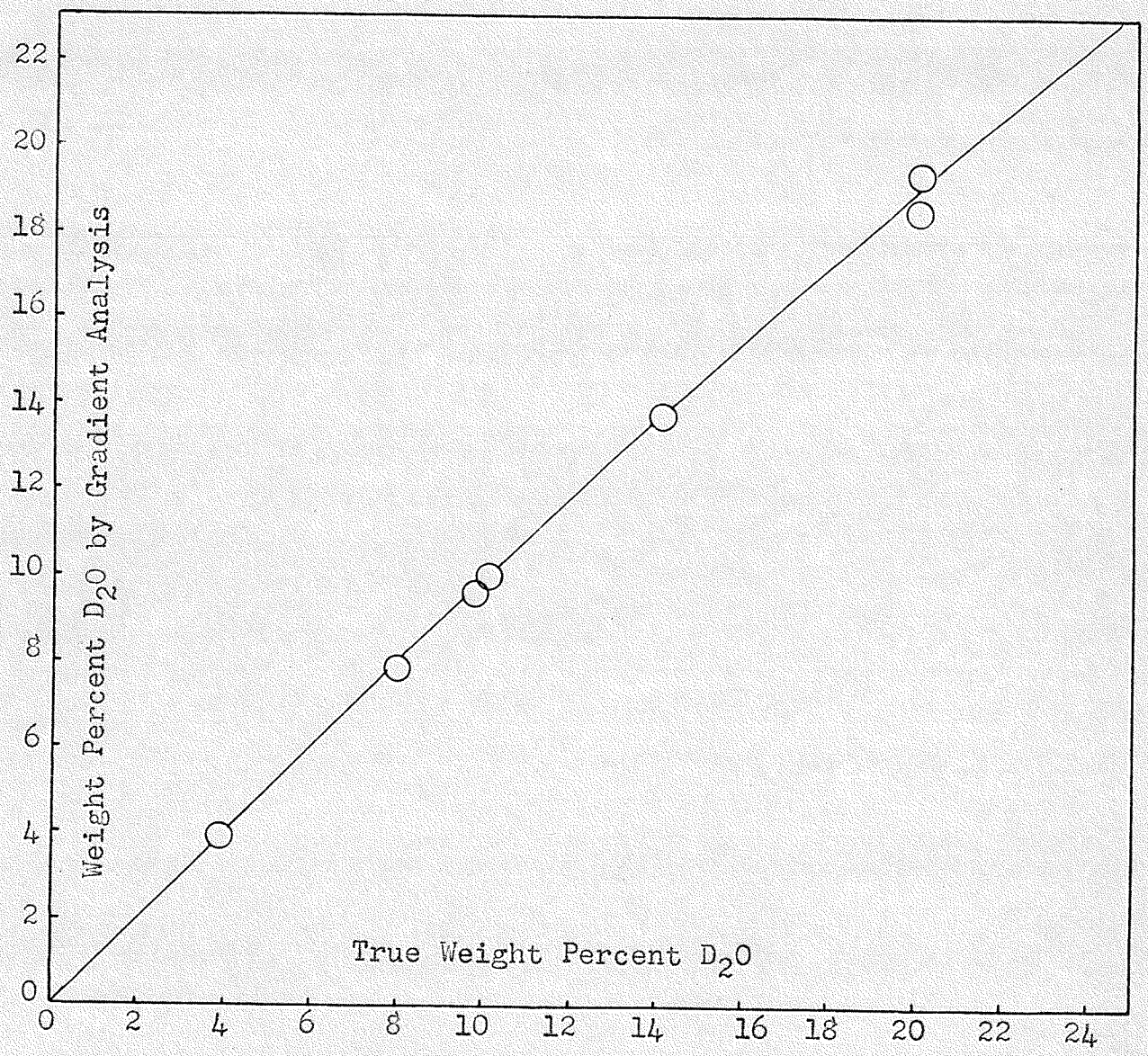


Fig. 4. Correction Curve to Account for Deuterium Exchange Losses in the Combustion and Water Purification Processes.

DEUTERIUM ANALYSES

No.	Sample Source	Combustion No.	Gradient Used	Wt. % D_2O in Combustion Water[h] Trials	Wt. % D_2O in Combustion Water[h] Mean[i]	Atom % D in Labelled Position[i]
1.	o-Deuterochlorobenzene (A)	1	4	14.36	14.09 ± 0.42	64.31 ± 1.89
		1	5	13.67		
		2	4	13.96		
		3	4	14.38		
2.	o-Deuterochlorobenzene (B)	1	5	7.65	7.55 ± 0.10	32.24 ± 0.45
		2	5	7.50		
		3	5	7.50		
3.	o-Deuterochlorobenzene (C)	1	6	9.81	9.71 ± 0.33	44.12 ± 1.49
		2	6	9.94		
		3	6	9.38		
4.	o-Deuterochlorobenzene (B) recovered from Blank No. 2	1	5	6.53	6.50 ± 0.03	29.44 ± 0.14
		2	5	6.47		
5.	o-Deuterochlorobenzene (C) recovered from Blank No. 3	1	6	10.10	9.70 ± 0.40	44.08 ± 1.80
		2	6	9.31		
		3	6	9.69		
6.	Aniline from o-deuterochlorobenzene (A) (Run 1)	1	4	5.59	5.59 ± 0.01	35.42 ± 0.06
		2	4	5.60		
		3	4	5.58		
7.	Aniline from o-deuterochlorobenzene (A) (Run 2)	1	4	4.87	4.86 ± 0.19	30.77 ± 1.20
		2	4	4.75		
		2	5	5.05		
		3	4	4.76		
8.	Aniline from o-deuterochlorobenzene (A) (Run 3)	1	4	4.79	4.80 ± 0.02	30.39 ± 0.13
		2	4	4.82		
		3	4	4.80		

TABLE VI (continued)

DEUTERIUM ANALYSES

No.	Sample Source	Combustion No.	Gradient Used	Wt. % D_2O in Combustion Water[h] Trials	Mean[i]	Atom % D in Labelled Position[i]
9.	Tribromo derivative of aniline from Run 2	1	5	4.78	4.78	17.29
10.	Tribromo derivative of aniline from Run 3	1	5	4.57	4.57	16.53
11.	o-ND_2ØCOOD (D)	1	1	19.27	18.86 ± 0.42	40.37 ± 0.90[j,k]
		2	1	18.44		
12.	o-ND_2ØCOOD (E)	1	5	12.71	12.57 ± 0.15	26.73 ± 0.32[j,k]
		2	5	12.57		
		3	5	12.42		
13.	o-DØND_2 (D)	1	3	22.42	22.96 ± 0.54	49.35 ± 1.19[j]
		2	3	23.09		
		3	3	22.88		
		3	5	22.54		
14.	o-DØND_2 (E)	1	5	13.04	13.11 ± 0.07	27.90 ± 0.15[j]
		2	5	13.18		
		3	5	13.12		
15.	o-DØNH_2 (D)	1	2	13.24	13.27 ± 0.32	84.73 ± 2.04
		2	2	13.59		
		3	2	13.32		
		3	5	13.04		
		4[l]	5	13.14		
16.	o-DØNH_2 (E)	1	5	7.36	7.34 ± 0.02	46.58 ± 0.13
		2	5	7.33		
		3	5	7.33		
17.	o-DØNH_2 (D) treated with dilute acid and recovered	1	1	12.78	12.83 ± 0.05	81.88 ± 0.32
		2	1	12.87		

DEUTERIUM ANALYSES

No.	Sample Source	Combustion No.	Gradient Used	Wt. % D_2O in Combustion Water[h] Trials	Mean[i]	Atom % D in Labelled Position[i]
18.	$\emptyset ND_2$ (from exchange of aniline with D_2O	1	4	18.70	18.58 ± 0.51	59.64 ± 1.66[m]
		2	4	18.97		
		3	4	18.07		
19.	o-Deuteroaniline (D) recovered from Blank No. 1	1	4	13.05	13.09 ± 0.19	83.56 ± 1.23
		2	4	12.95		
		3	4	13.28		
20.	Tribromo derivative of o-deuteroaniline (E)	1	5	nil		-
		2	5	nil		-
21.	o-$NDCH_3\emptyset COOD$	1	6	8.68	8.73 ± 0.08	35.67 ± 0.32[m]
		2	6	8.81		
		3	6	8.68		
22.	o-$D\emptyset NDCH_3$	1	6	9.06	8.73 ± 0.39	35.67 ± 1.58[m]
		2	6	8.79		
		3	6	8.34		
23.	o-$D\emptyset NHCH_3$	1	6	6.96	6.96 ± 0.01	56.77 ± 0.82
		2	6	6.97		
		3	6	6.96		
24.	Undeuterated aniline	1	2	nil		-

h Corrected for exchange losses in the combustion and purification processes
i Mean value of each set of individual analyses plus or minus the maximum deviation from the mean.
j Calculated with n' = 3. Except where otherwise noted all others are calculated with n' = 1.
k This value may be too low because of retention of traces of solvent (Dioxane) in the sample.
l This sample was diluted with ordinary aniline before the combustion.
m Calculated with n' = 2.

DISCUSSION OF RESULTS

A comparison of analyses 6., 7., and 8. with 1. shows that a large fraction of deuterium is lost from o-deuterochlorobenzene on amination with sodamide in liquid ammonia. To determine the numerical value of this loss it is necessary to know how much deuterium is lost by exchange with the solvent from the chlorobenzene before the reaction, and from the aniline after the reaction.

Comparison of analyses 19. with 15. shows that the loss of deuterium from o-deuteroaniline under the amination conditions (Blank No. 1) amounts to about 1.4% of that initially present.

Since the reaction was shown to be fast it seems reasonable to suppose that the deuterium loss from o-deuterochlorobenzene before the amination would be negligible, provided that the exchange here would be comparable in rate to that demonstrated for o-deuteroaniline. On this basis the amination reaction results in a decrease of deuterium content at the labelled position from 64.3 ± 1.9 atom % in o-deuterochlorobenzene to 32.7 ± 3.3 atom % in the aniline obtained from it. This corresponds to a loss of 51 ± 6% of the deuterium from o-deuterochlorobenzene, where the ± 6% is derived from the maximum deviation of a run from the mean.

Two attempts were made to determine the amount of deuterium exchange from o-deuterochlorobenzene. In Blank No. 2 (Page 38), o-deuterochlorobenzene (stock sample B) was treated with one-half equivalent of sodamide in liquid ammonia, and the excess chloro-

benzene was recovered. Comparison of analyses 2. and 4. shows that the excess chlorobenzene had lost about 14% of the deuterium initially present. No precise significance can be attached to this figure, however, since the recovered chlorobenzene was subjected to conditions considerably different from those encountered by the chlorobenzene that reacted. The excess chlorobenzene was exposed, not to sodamide, but to the weaker base sodium anilide. At the same time it was exposed to the basic ammonia solution for a much longer time than was the chlorobenzene that reacted.

Blank No. 3 (Page 39) was carried out in such a manner that the unreacted chlorobenzene would be in contact for a short time with half an equivalent of sodamide and with the sodium anilide as it formed, after which period ammonium chloride was added to leave the excess chlorobenzene in contact with the product, aniline, and liquid ammonia only. Comparison of analyses 3. and 5. shows that no appreciable deuterium was lost from the excess chlorobenzene. Since the deuterium exchange loss seems to arise after the amination reaction, the 14% deuterium loss as obtained from Blank No. 2 may be regarded as a very conservative upper limit.

Comparison of analyses 9. and 10. with 7. and 8. shows that approximately 55% of the deuterated aniline obtained by the amination of o-deuterochlorobenzene with sodamide in liquid ammonia had its deuterium in the m-position.

The approximately 50% deuterium decrease observed in the amination and the approximately equal distribution of o- and m-deuteroaniline in the product are both predicted by the elimination mechanism and not by the rearrangement mechanism. The rearrangement mechanism is thus refuted.

If the elimination mechanism is accepted the surprisingly large deuterium loss must be accounted for. A deuterium loss of 51 ± 6% in the amination means that the deuterium isotope effect involved is very close to unity. Since the deuterium content of the reactant does not change as the reaction progresses, the deuterium isotope effect (k_H/k_D) is equal to the mole ratio of deuterated aniline to normal aniline in the product for one mole of 100% o-deuterochlorobenzene. Using the upper and lower values of the deuterium loss observed experimentally, this leads to isotope effect values k_H/k_D equal to 0.8 and 1.3 respectively.

The introduction of a heavy isotope into a molecule should cause the reaction to proceed at a slower rate if the isotopically substituted bond is involved in the rate-determining step. If the substituted position is not involved in the rate-determining step of the reaction the rate should not be influenced. In passing to the transition state the bond that ultimately breaks has already begun to weaken. From theoretical principles the maximum predictable isotope effect can be calculated, corresponding to a tight binding of the isotope in the reactant, and a completely free isotope in the transition state. Following the Bigeleisen treatment based on the absolute reaction rate theory, Wiberg (77) gives the following simplified expression for this maximum deuterium isotope effect:

$$k_H/k_D = e^{(E_H - E_D)/2RT}$$

where E_H is the zero-point energy of the bond to protium, E_D is the zero-point energy of the corresponding bond to deuterium, R is the gas constant, and T the absolute temperature. According

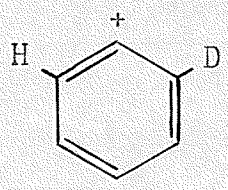
to this a theoretical maximum k_H/k_D value of 11.1 is predicted at -33°C., the temperature at which these amination reactions are carried out. An isotope effect is most pronounced with the isotopes of hydrogen because the relative changes in the isotopic masses are larger than for any other element. For a more detailed theoretical treatment of isotope effects the reader is referred to Bigeleisen (10, 11).

In the amination of o-deuterochlorobenzene it would be harder to break a C-D bond than it would be to break the corresponding C-H bond, and this should reveal itself as an isototpe effect if the scission of that bond is part of the step that decides the product ratio. Moreover, the low temperature of the reaction should make this rate difference even more noticeable. An isotope effect of close to unity may be interpreted to mean that the ortho C-H bond has not weakened appreciably in the transition state of that step. It is proposed that the ortho hydrogen atom is lost in a fast step that follows the product-determining step. Any intermediate that must be involved in this reaction must have lost the hydrogen atom in the ortho position in such a way that there would be a 50/50 chance of losing either deuterium or protium in that step, and it must be symmetrical with regard to the 1- and 2-positions.

There are three species present in this reaction that can conceivably attack the chlorobenzene molecule, the ammonia molecules which are present in large excess, the NH_2^- ions, and the Na^+ ions.

The attack by an amide ion on the ortho hydrogen atom would be expected to lead to an isotope effect, and is ruled out. Nucleophilic amide ion attack which would lead to the attachment of the amino group to the ring would bring an extra pair of electrons with it. When the hydrogen atom is expelled in a subsequent step it would leave as a hydride (H^-) ion. It is known from experimental work (5) that hydrides react with liquid ammonia, liberating hydrogen gas. Since no gas is evolved in this amination, the direct attachment of the NH_2^- ion seems highly unlikely.

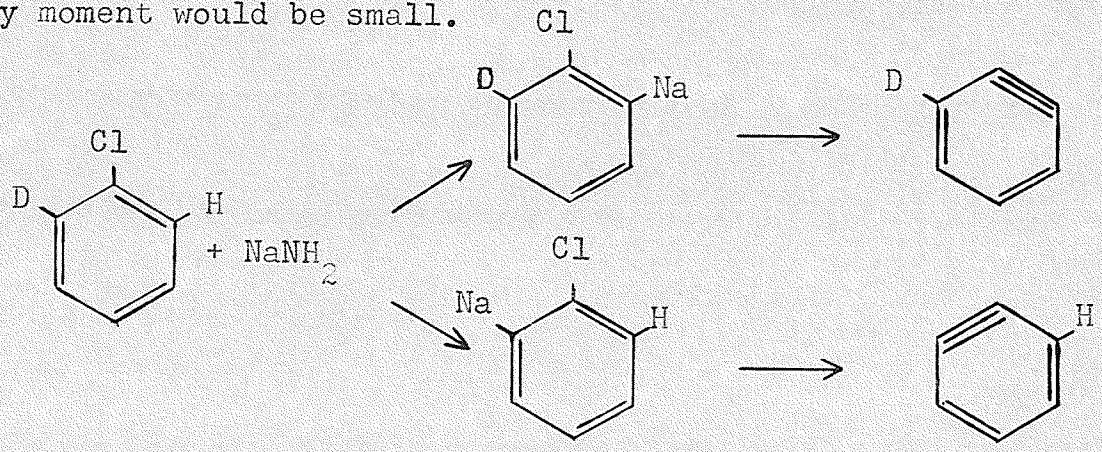
If the chlorine atom from the chlorobenzene molecule were lost as a chloride ion by some process, a structure of the type (XX) would result. This might be vulnerable to attack by nucleophilic reagents, and could lead to benzyne or one of the other intermediates suggested by Roberts (VII and VIII, Page 20 . Inter-



(XX)

mediate (XX), as well as (VII) and (VIII), still retains the hydrogen atoms that were ortho to the chlorine atom, and an isotope effect would be expected in the subsequent bond rupture. The only reasonable way to visualize the formation of Roberts' intermediate (VI) is to postulate the prior loss of an ortho hydrogen (involving an isotope effect on substitution of deuterium), followed by the intramolecular attack of the chlorine atom to give the desired intermediate.

The only attacking species yet to be considered is the sodium ion. Its attack on the ortho carbon atom would be analogous to a metalation reaction (30). Isotopic substitution on carbon atoms 2. and 6. probably would not influence the attack of the sodium ions on these carbon atoms if the loss of the ortho hydrogen (or deuterium) is postulated to be a fast step following the attachment of the sodium ion to that particular carbon atom. Since o-chlorophenylsodium would result, which would be very reactive, sodium chloride may split out intramolecularly to give the benzyne intermediate. This may be formulated as follows, where the steps shown could be equilibria, since the concentration of benzyne at any moment would be small.



In the nitration of benzene, which is known to be an electrophilic attack of the nitronium ion (NO_2^+), Melander (57) observed hydrogen isotope effects of unity. In metalation reactions themselves the hydrogen isotope effects involved have not as yet received much attention. Bryce-Smith, Gold and Satchell (15) reported that in the metalation of d-benzene at 75°C. with ethyl potassium, where the hydrogen is also lost from the ring, they obtained an isotope effect of $k_D/k_H = 0.50 \pm 0.10$. Here the rupture

of the C-H and C-D bonds is evidently part of the rate-controlling step. However, the isotope effect is small in comparison with other deuterium isotope effects. The same authors suggest that the influence of the metal may well be greater in certain reactions.

On the whole the evidence obtained in this investigation supports the elimination-addition mechanism of Roberts, but cannot be considered a conclusive proof of the same.

ADDENDUM

Recent Publications

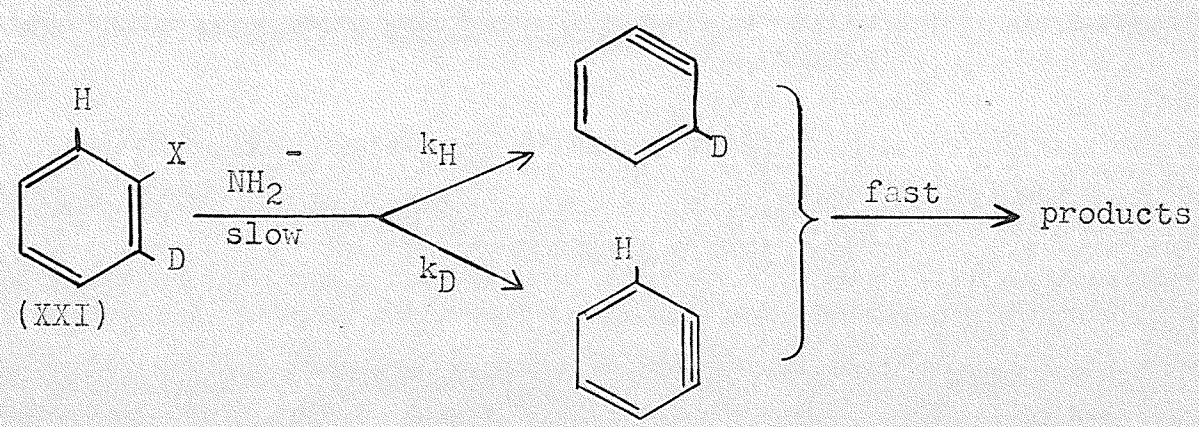
In a paper published after this investigation was completed and the thesis was written in part, Roberts and co-workers (63) reported the results of further experimental work designed to establish the elimination-addition mechanism. The amination of iodobenzene-1-C^{14} with potassium amide in liquid ammonia was found to yield aniline in which 53.0 ± 0.2% of the total activity of the product was due to aniline-2-C^{14} and 46.4 ± 0.1% of the activity was due to unrearranged aniline. They proved conclusively that iodobenzene and aniline do not rearrange under the reaction conditions. Since C-1 and C-2 become equivalent in the benzyne intermediate, equal amounts of aniline-1-C^{14} and aniline-2-C^{14} should form, except if a C^{12}-C^{14} isotope effect were involved in the addition of ammonia to the intermediate. The degree of rearrangement observed (52-53%) would require that the reaction rate at the C^{12} carbon atom be $< 13\%$ faster than the reaction at the C^{14} atom. Examples are known (66) in which the reaction at the C^{14} atom was shown to be as much as 16% slower than the reaction at the C^{12} atom. The concept that "normal" and "rearranging" sub-

stitution reactions might independently be involved and proceed fortuitously at the same rate is held to be very unlikely, since iodobenzene-1-C^{14} was found to give essentially the same product ratio as was obtained from the earlier work with chlorobenzene-1-C^{14} (64).

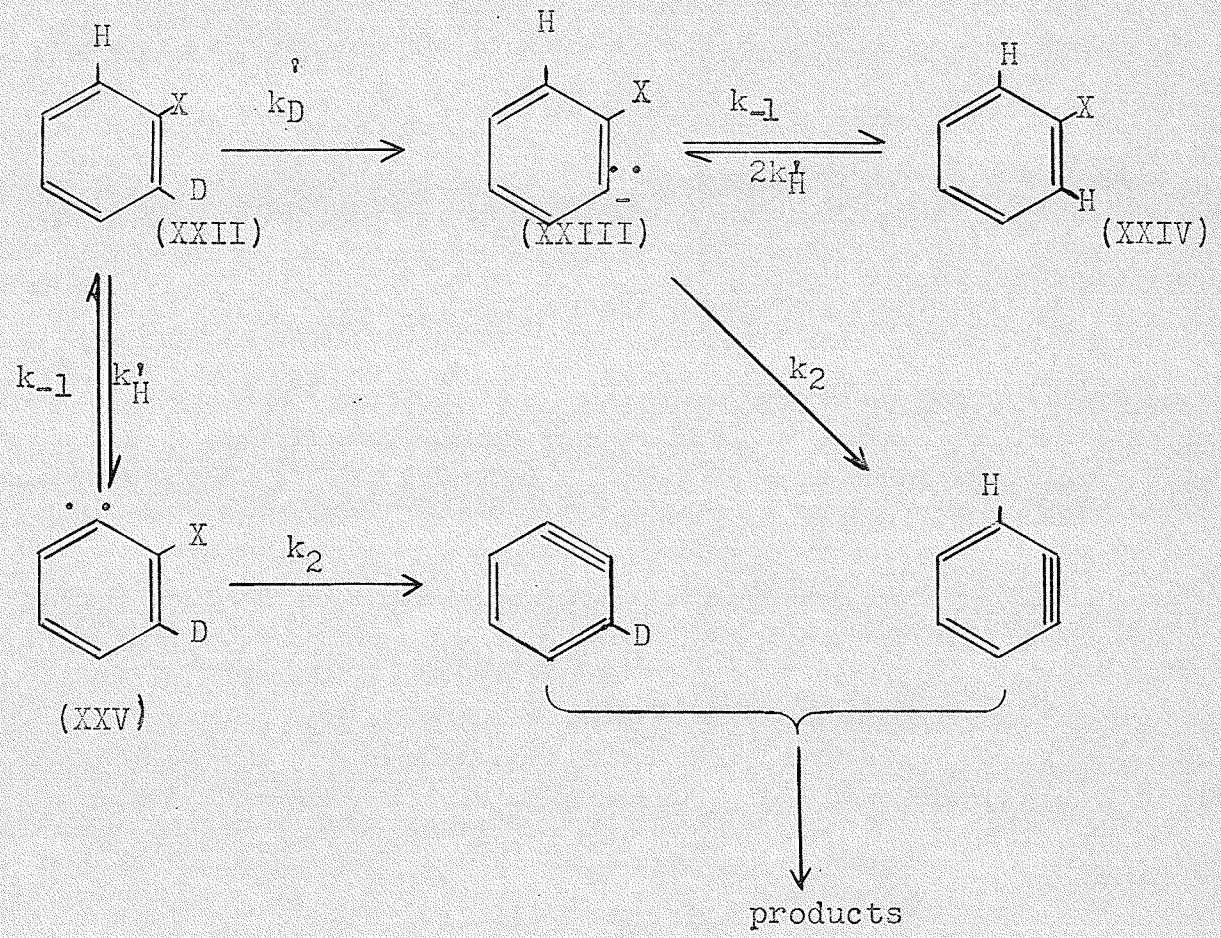
The obvious importance of the hydrogen atom ortho to the halogen atom was also not overlooked by these investigators. They quote some previously unpublished results indicating that bromomesitylene and bromodurene cannot be aminated under these conditions, which, barring steric hindrance, confirms the necessity of an ortho hydrogen atom for this reaction to proceed (see also the work of Benkeser and Buting, Page 9).

The 1,2-elimination of hydrogen halide in the formation of benzyne was formulated as one of two possible processes, a stepwise mechanism (1) or a concerted mechanism (2). Since many more conventional cases of the same nature have been settled by deuterium tracer work, Roberts and co-workers subjected o-deuterohalobenzenes to these amination conditions, both with lithium deithylamide in ether and potassium amide in liquid ammonia, and analyzed unreacted starting material by means of the intensity of fundamental C-D bands in the infrared spectral region. Reactions were carried out to different percentage completeness, which was established by Volhard titration of the halide ion liberated.

(1)



(2)



Supposing the removal of hydrogen to be the rate-determining step as in (1) the relative rates of o-deuterated and o-protonated halobenzenes were predicted to have an isotope effect k_H/k_D of approximately 6 or 7. Partial confirmation for an isotope effect of this order of magnitude was found in the dehydrobromination of isopropyl bromide, where Shiner (70) observed an isotope effect of 6.7.

For a consideration of mechanism (2) several reasonable assumptions were made. The same specific rate constants k_H' were assigned

to the loss of proton from (XXII) and (XXIV), the k_2 value for loss of halide ion from anions (XXIII) and (XXV) was assumed to be equal, and the reversion of (XXIII) to (XXII) was taken to be negligible due to the large excess of ordinary ammonia. The magnitude of the apparent isotope effect for an elimination by this mechanism was predicted to be less than for mechanism (1), and to be a function of k_2/k_{-1}. The smaller the ratio of the rate (k_2) of loss of halide ion from the anion to the rate (k_{-1}) of reversion to starting material by proton abstraction from the solvent, the smaller would be the apparent isotope effect. If the ratio were very small, it was argued that there would be no detectable isotope effect on the amination rate because the deuterated halobenzene would be completely converted to the protonated halobenzene before significant reaction occurred.

The mechanisms assigned to the aminations studied and the relative values of the specific rate constants were found to depend on the nature of the halogen. o-Deuterofluorobenzene, 2,4,6-trideuterofluorobenzene, and 4-methyl-2,6-dideuterofluorobenzene were found to exchange their ortho deuterium very rapidly with the solvent, whereas the amination products appeared at an insignificant rate. Here k_2 was taken to be negligible and k_D' was taken to be very large, since 100% o-deuterofluorobenzene lost all its deuterium in 10 seconds under the reaction conditions. It seems reasonable to assume that the magnitude of k_D' would depend on the acidity of the hydrogen involved. Previous work by Hall, Piccolini, and Roberts (35,69) had established the following relative acidity order for hydrogens in substituted benzenes:

o-F>>o-CF_3>m-CF_3~ o-OCH_3~ p-CF_3>m-F>p-F>m-OCH_3>p-OCH_3

>20,000 3000 70 60 50 25 (1.0) 0.01 0.001

From this it might be concluded that the relative acidity of the ortho hydrogen atoms in the monohalobenzenes would follow the sequence F>Cl>Br>I, and that exchange might predominate at the beginning of the series whereas amination would predominate at the end.

The amination of o-deuterochlorobenzene was interpreted on the basis of mechanism (2), having the ratio $k_{-1}/k_2 = 1.5$ as calculated from the experimental value of 2.7 obtained for the apparent isotope effect k_H/k_D. For o-deuterobromobenzene k_H/k_D was found to be 5.5. In ether with lithium diethylamide o-deuterobromo- and o-deuterochlorobenzene were found to have k_H/k_D equal to 5.6 and 5.7 respectively, the calculations being based on mechanism (1). Exchange of deuterium from o-deuterochlorobenzene in ether was shown to be of no importance. Since the reaction with o-deuterobromobenzene gave essentially the same isotope effect both in ether and in liquid ammonia, this was interpreted as proton removal being the rate-determining step in both solvents. The evaluation of these isotope effects from their experimental data is discussed in the next section.

The change in elimination mechanism from chlorobenzene to bromobenzene in liquid ammonia was shown to be the basis for the order of halogen reactivity Br>I>Cl>>F in the amination. The removal of a hydrogen atom as a positive ion would be an important factor in the rate, and was expected to follow the order F>Cl>Br>I

parallel with the electronegativities. Secondly, loss of halide ion would be expected to follow the rate sequence I>Br>Cl>F (see page 21). The change in mechanism (2) to (1) was taken to occur where halide ion loss became easier than proton removal, and the two steps became synchronized as a result. Bromobenzene seems to have the optimum o-hydrogen and halogen reactivities to give the maximum rate with potassium amide in liquid ammonia.

This experimental evidence certainly favors the benzyne intermediate, which is preferred by Roberts and co-workers over several other possible intermediates that could be postulated (see Page 20).

Of some interest is the discussion they give about the stability of an intermediate like benzyne, which, it is concluded, must have an appreciable half-life because : (i) if the intramolecular C^{12}-C^{14} isotope effect observed was real, this would indicate that the addition of ammonia to the intermediate was slow enough to discriminate between isotopes, (ii) evidence exists which indicates that there is competition for the intermediate by nucleophilic reagents other than ammonia, leading to the formation of diphenyl- and triphenylamines in secondary reactions, and (iii) it has been found (80) that potassium amide increases the yield of tetraphenylmethane from chlorobenzene and potassium triphenylmethide in liquid ammonia, which, it is suggested, may be due to the formation of benzyne.

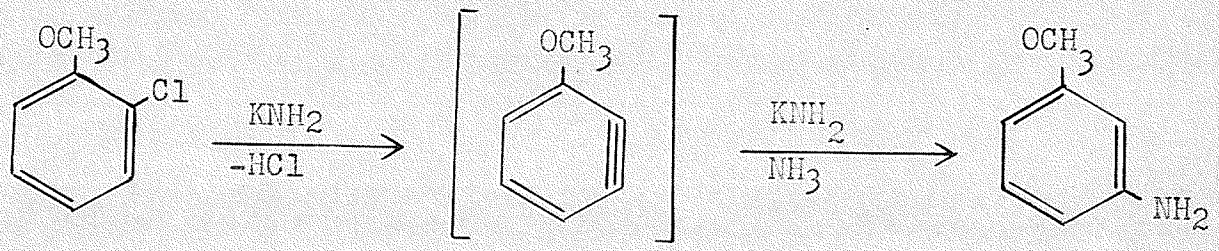
From the simple atomic orbital method it is inferred that the resonance energy of benzyne may be comparable to that of benzene, if the ring is taken to be an undistorted regular hexagon.

Although the "triple bond" in the ring would result in a large amount of distortion (120°) from the preferred angle, this would not result in a greater strain than is present in cyclopropene, a known substance. Furthermore, bent excited states of acetylene have been established from spectroscopic evidence (41).

More evidence is given which suggests the extension of the benzyne intermediate to other reactions. Fluorobenzene -1-C^{14} with phenyllithium in ether gave biphenyl with the orientation of the activity being consistent with a symmetrical benzyne intermediate (42). An extension to the Fittig-type coupling reactions is suggested. The mechanism has been correlated with the hydrolysis of aryl halides with base at high temperatures (62), and also with certain Diels-Alder reactions (79). It is also reported that the amide inn catalysis of the reaction between weak nucleophiles and aryl halides (80) can be extended to the phenylation and pyridylation of ketones (49), and that a similar reaction in Robert's laboratory has yielded from p-bromotoluene and sodium phenylacetylide, under the influence of sodamide, a mixture of m- and p-tolylphenylacetylenes having the same isomeric composition as that obtained in the amination of p-bromotoluene with sodamide (65). In conclusion the authors note that by no means should it be inferred that all nucleophilic reactions proceed exclusively by the benzyne mechanism.

Further, Roberts, Vaughan, Carlsmith, and Semenow (65) have recently reported on their qualitative studies of the isomeric amines produced in the amination of substituted halobenzenes under these conditions. Their aim was to rationalize these on the basis

of the benzyne mechanism, illustrated for a typical case below.



a substituted "benzyne"

The formation of a particular isomer was thought to be governed by the effect of the substitutent group on the direction of elimination (predicted on the basis of the relative acidity of the hydrogens as determined by the inductive effect of the group) and on the direction of addition of the elements of ammonia to the "triple bond" (predicted by considering the amide ion to add so as to place the negative charge on the ring in the most favorable position relative to the inductive effect of the substituent group). On this basis their predictions met with good success.

Kinetic Treatment

The derivation of an apparent isotope effect equation for mechanism (1) required several reasonable assumptions. The reaction was assumed to take place with constant volume, to be first order with regard to chlorobenzene, to involve only the ortho hydrogen atoms, and to form products from benzyne in a fast and irreversible step. With D = o-DØCl and H = ØCl, the following kinetic expressions were set up.

(1) $$-\frac{d[D]}{dt} = (k_D + k_H)[D][NH_2^-]^n$$

(2) $$-\frac{d[H]}{dt} = 2k_H[H][NH_2^-]^n$$

The value of n was not known, but was assumed to be unity. Division of equation (1) by (2) and integration yielded:

$$(3) \qquad k_H/k_D = \tfrac{1}{2}\left[\ln\left([D]_t/[D]_o\right)/\ \ln\left([H]_t/[H]_o\right)\right] - 1$$

On the basis of this equation isotope effects of 2.60, 2.88, and 0.77 were obtained for three runs carried out with o-DØCl having respectively 26.4, 26.1, and 100 atom % ortho deuterium.

For the step-wise mechanism (2) the following kinetic expression can be set up for the disappearance of o-DØCl:

$$(4) \qquad -\frac{d[D]}{dt} = (k'_H + k'_D)[D][NH_2^-] - k_{-1}[\text{anion (XXV)}]$$

The application of the steady-state approximation to anion (XXV) gave the following expression for its concentration:

$$(5) \qquad [\text{anion (XXV)}] = \frac{k'_H[D][NH_2^-]}{k_{-1} + k_2}$$

Substitution of (5) into (4) yielded:

$$(6) \qquad -\frac{d[D]}{dt} = (k'_H + k'_D)[D][NH_2^-] - \frac{k_{-1}k'_H}{k_{-1} + k_2}\left([D][NH_2^-]\right)$$

A similar expression can be obtained for the rate of disappearance of ØCl.

$$(7) \qquad -\frac{d[H]}{dt} = 2k'_H[H][NH_2^-] - \frac{k_{-1}}{k_{-1} + k_2}\left(2k'_H[H][NH_2^-] + k'_D[D][NH_2^-]\right)$$

For convenience the following ratios were re-defined,

$k_{-1}/(k_{-1} + k_2) = F$ = the fraction of intermediate anions returning to starting material, and

$k'_H/k'_D = i$.

Division of (6) by (7) then gave

(8) $$\frac{d[D]}{d[H]} = \frac{[i(1 - F) + 1][D]}{2i(1 - F)[H] - F[D]}$$

which on division by $[D]$, treatment of $[i(1 - F) + 1]$, $2i(1 - F)$, and $-F$ as constants, and integration yielded the equation:

(9) $$\ln \left[D \right]_{[D]_o}^{[D]_t} + \frac{1 + i - iF}{1 - i + iF} \ln \left[(-1 + i - iF) \frac{[H]}{[D]} - F \right]_{\frac{[H]_o}{[D]_o}}^{\frac{[H]_t}{[D]_t}} = 0$$

It was then assumed by Roberts et al that the k_H/k_D value of 5.7 obtained with o-deuterochlorobenzene in ether solution, where exchange had been shown to be unimportant, could be assigned to k'_H/k'_D. On this basis the values of F were calculated to be 0.48, 0.44, and 0.76 for the three independent runs mentioned earlier (average 0.56 ± 0.13), corresponding to a ratio k_{-1}/k_2 of an order of 1.5.

On the basis of these calculations mechanism (2) was favored for the amination of chlorobenzene with potassium amide in liquid ammonia, because deuterium exchange was demonstrated to be important in this case and the isotope effects as calculated for mechanism (1) are small and even negative.

Discussion

The method of Roberts et al depends on the analyses of the reactant (deuterated chlorobenzene) at zero time and at some known time = t. The present investigation relies on the analyses of the reactant (deuterated chlorobenzene) at zero time and the product (deuterated aniline) at time = t. In principle these two

methods of approach should be reconcilable on the basis of Roberts' proposed mechanism (2).

If equation (9) is modified by the following substitution in the first term,

(10) $$[D]_t = (\text{ØCl remaining}) \times (\text{fraction which is deuterated})$$
$$= ([D]_o + [H]_o)(1 - P)\frac{[D]_t}{[D]_t + [H]_t}$$

where P = the fraction of ØCl that has reacted at time t, than the following equation can be obtained:

(11)
$$\ln (1 - P) = -\frac{(1 + i - iF)}{(1 - i + iF)} \ln \left[\frac{(-1 + i - iF)\dfrac{[H]_t}{[D]_t} - F}{(-1 + i - iF)\dfrac{[H]_o}{[D]_o} - F} \right] + \ln \left[\frac{[H]_t}{[D]_t} + 1 \right]$$
$$- \ln ([D]_o + [H]_o)$$

Furthermore, from mechanism (2) the rates of formation of deuterated aniline (A_D) and protonated aniline (A_H) may be formulated as follows:

(12) $$\frac{d[A_D]}{dt} = k_2 [\text{anion (XXV)}][NH_3]$$

(13) $$\frac{d[A_H]}{dt} = k_2 [\text{anion (XXIII)}][NH_3]$$

Substitution of the anion concentrations as derived from steady-state treatment, division of (13) by (12), and simplifying gives:

(14) $$\frac{d[A_H]}{d[A_D]} = 2\frac{[H]_t}{[D]_t} + \frac{1}{i}$$

Using the mean value of F = 0.56 and i = 5.7 according to Roberts *et al*, and $[H]_o/[D]_o$ = 0.526 as in the *o*-deuterochlorobenzene (stock sample A) used in Runs I, II, and III in this investigation, equations (11) and (14) were solved for P and d $[A_H]$/d $[A_D]$ for a series of $[H]_t/[D]_t$ ratios. Values of P were then plotted against the corresponding d $[A_H]$/d $[A_D]$ values, and a graphical integration carried out to determine $[A_H]/[A_D]$ between the values of P = 0 and P = 0.71 (where this value is derived from a 71% recovery of chloride ion, as silver chloride, from a run with undeuterated chlorobenzene carried out as described on page 35). This integrated value should represent the overall ratio of protonated to deuterated aniline in the product formed up to 71% reaction.

Similar calculations were carried out for the minimum and maximum F values obtained by Roberts *et al*. The results of these calculations are listed below:

F	$[A_H]/[A_D]$	$100\,[A_D]/([A_D] + [A_H])$	Percent of Original D Retained in Labelled Position
0.44	0.810	55.3	86.0
0.56	0.864	53.6	83.5
0.76	1.090	47.9	74.5

It is seen that the loss of deuterium (*ca*. 50%) observed in this investigation in the amination of *o*-deuterochlorobenzene to give aniline is not predicted by the work of Roberts and coworkers. If i = 5.7 then a larger F value is required to lower the predicted deuterium content of the aniline to the observed value. At F= 0.44 a smaller i value would bring about the same result, while at F = 0.76 the situation is reversed.

A similar calculation with i = 5.7 and F = 0.56 for Blank No. 3 showed that the atom percent deuterium in the unreacted o-deuterochlorobenzene at P = 0.25 (assuming complete reaction of all the sodamide employed) should have risen from 44.1 to 45.8 atom % deuterium, which might not have been detected by the analytical method used. Thus the results obtained for Blank No. 3 are in apparent agreement with the work of Roberts and co-workers.

The loss of deuterium in Blank No. 2 remains unexplained at the present time, unless the deuterium exchange is due to prolonged contact of the o-deuterochlorobenzene with sodium anilide in liquid ammonia.

CONCLUSIONS

(1) The amination of o-deuterochlorobenzene with sodamide in liquid ammonia has been found to produce aniline in which 51 ± 6% of the deuterium is lost from the labelled position of the reactant. Furthermore, the deuterium in the aniline produced has been found to be about 55% in the meta position. Assuming negligible loss of deuterium from the product and the reactant themselves under the reaction conditions, these results support the elimination-addition mechanism of Roberts, and the benzyne intermediate. These results are not compatible with the re-arrangement mechanism.

(2) On the basis of the above interpretation an apparent deuterium isotope effect of close to unity is calculated, which is interpreted to mean that the ortho hydrogen atom is not lost in the product-determining step.

(3) A mechanism is suggested in which the rate-determining step is the attack of sodium ions on the carbon atom ortho to the halogen, after which sodium chloride is lost intramolecularly to give the benzyne intermediate.

(4) The detailed mechanism recently proposed by Roberts et al does not seem to predict the product ratios observed in this investigation.

RECOMMENDATIONS FOR FUTURE INVESTIGATIONS

The author proposes to extend these investigations during the summer of 1956, with the aim of testing Roberts' equation and the extension to it under strictly comparable conditions. It is proposed to carry out a reaction with 100% o-deuterochlorobenzene to partial completion, to determine the percent reaction, and to analyze both the unreacted chlorobenzene and the product aniline for deuterium.

PART II

THE DEUTERIUM ISOTOPE EFFECT IN

THE THERMAL DECARBOXYLATION OF o-AMINOBENZOIC ACIDS

PART II - THE THERMAL DECARBOXYLATION OF o-AMINOBENZOIC ACIDS

INTRODUCTION

It has been shown that the decarboxylations of carboxylic acids in general proceed by unimolecular or bimolecular mechanisms. The field of thermal decarboxylations has been reviewed extensively by Brown (14), and the reader is referred to his treatment for specific examples of the general types about to be listed.

Kinetic work first showed that many organic acids decarboxylate in the form of their anions, as illustrated by the general equation:

(S_E1 - No. 1) $RCO_2^- \longrightarrow R^- + CO_2$ Rate = $k_1 (RCO_2^-)$

The subsequent observation that certain acids capable of forming zwitterions decarboxylate more readily as free acids led to the concept of a unimolecular decomposition from the zwitterionic form.

(S_E1 - No. 2) $RCO_2H \rightleftharpoons H^+RCO_2^- \longrightarrow HR + CO_2$ Rate = $k_1'(H^+RCO_2^-)$

Measurements of rates show that some acids decarboxylate unimolecularly as anions only, others decarboxylate as zwitterions, and some show decarboxylation according to both mechanisms simultaneously, depending on the molecular structure.

In 1948 Schenkel and Schenkel-Rudin (68) suggested that anthracene-9-carboxylic acid decarboxylated in a bimolecular manner, illustrated in general terms by the equation:

(S_E2 - No. 1) $RCO_2H + H^+ \longrightarrow RH + CO_2 + H^+$ Rate = $k_2(H^+)(RCO_2H)$

A bimolecular reaction could also take place between a proton and an acid anion:

(S_E2 - No. 2) $H^+ + RCO_2^- \longrightarrow HR + CO_2$ Rate = $k_2'(H^+)(RCO_2^-)$

It should be pointed out that kinetically mechanism S_E1 - No. 2 is not distinguishable from mechanism S_E2 - No. 2.

LITERATURE REVIEW

Pawlewski (60) was first to report that anthranilic acid decarboxylated when heated above its melting point, and that it was a first order reaction. McMaster and Shriner (56) found that the decarboxylation from boiling water also exhibited first order kinetics.

Stevens, Pepper and Lounsbury (71), verified the supposition that the thermal decarboxylation of anthranilic acid does not occur below the melting point, and also found that it is first order from the melt. The aqueous decarboxylation from boiling water was found to be first order with regard to anthranilic acid initially (with a rate constant of about 0.025 $hr.^{-1}$, in good agreement with the value reported by McMaster and Shriner), but fell off as the reaction progressed because the procedure employed allowed the aniline concentration to build up in the vessel. The decarboxylation was found to be acid catalyzed up to a 1 N concentration of acid, but for more acidic solutions the rate decreased, the reaction being first order with regard to anthranilic acid. Sodium anthranilate could not be decarboxylated. Samples of carbon dioxide from the partial thermal, aqueous, and aqueous acid catalyzed decarboxylations of anthranilic acid having C^{13} in the carboxyl group were analyzed by mass spectrometer to determine the C^{13} isotope effects involved. It was found that under all conditions the isotope effect was very close to unity, an order of magnitude smaller than that reported for any previous decarboxylation. (It should be noted that at best carbon isotope effects are small due to the small relative mass changes involved, and

that the high temperature of this reaction would tend to make the rate differences still smaller.) This was accepted as evidence that the reaction is not a simple unimolecular one, since an isotope effect is to be expected if the rate-determining step would be the carbon-carbon bond cleavage.

The acid catalysis and base inhibition observed were taken to indicate a bimolecular electrophilic mechanism in solution (more precisely a "pseudo-bimolecular" mechanism since the attacking particle was part of the attacked molecule). Of the anthranilic acid species likely to be present, the neutral molecule and the zwitterion (which was shown by Bjerrum (12) to be present in appreciable amounts) were considered to be the most probable reactants, with the rate-determining step being the attack of a proton on the α-carbon atom, followed by a rapid carbon-carbon cleavage with a low activation energy. Of the two species, the zwitterion was favored because the proton attack on its α-carbon atom would require a higher activation energy than an analogous attack on the neutral molecule, since the mesomeric effect of the o-amino group would increase the electron density at that carbon in the neutral molecule and hence make it easier for the proton to attack. In the zwitterion the inductive effects of the NH_3^+ and CO_2^- groups would probably offset each other.

The rate of decarboxylation of p-aminobenzoic acid has been found to be about half that for o-aminobenzoic acid by McMaster and Shriner (56). However, Bjerrum (12) has shown that the ratio of neutral molecules to zwitterions is greater for the p-acid than for the o-acid. From this it has been concluded by Stevens and co-

workers that the decarboxylation from the zwitterion would be the preferred mechanism.

Since many acids decarboxylate by a unimolecular mechanism from the zwitterion, they further conclude that the activation energy for carbon-carbon bond rupture in the zwitterion must be less than in the neutral molecule. On the whole the mechanism favored by the evidence available is more complex than the normal S_E2 reaction, but it best explains the lack of a C^{12}-C^{13} isotope effect. However, proton attack on the α-carbon of the neutral molecule, or even on the carbonyl oxygen of the neutral molecule, could not be excluded. The mechanism favored was held to be equally applicable to the acid catalyzed, aqueous uncatalyzed, and thermal decarboxylations, the ionization of the anthranilic acid itself supplying the protons under the last two conditions.

EXPERIMENTAL WORK

The experimental work related to Part II has been described in conjunction with that for Part I. Two thermal decarboxylations of deuterated anthranilic acid (at different concentrations of deuterium) were carried out, and one analogous decarboxylation with deuterated N-methylanthranilic acid.

DISCUSSION OF RESULTS

The method of calculating the deuterium isotope effect in the thermal decarboxylation of anthranilic and N-methylanthranilic acids depends <u>a priori</u> on the mechanism, and thus the isotope effect does not establish the mechanism conclusively without

additional experimental evidence. The two most probable mechanisms as proposed by Stevens will be discussed in the light of the deuterium isotope effect, and variations will be suggested.

The isotope effect calculations for each of these mechanisms rests on the following assumptions:

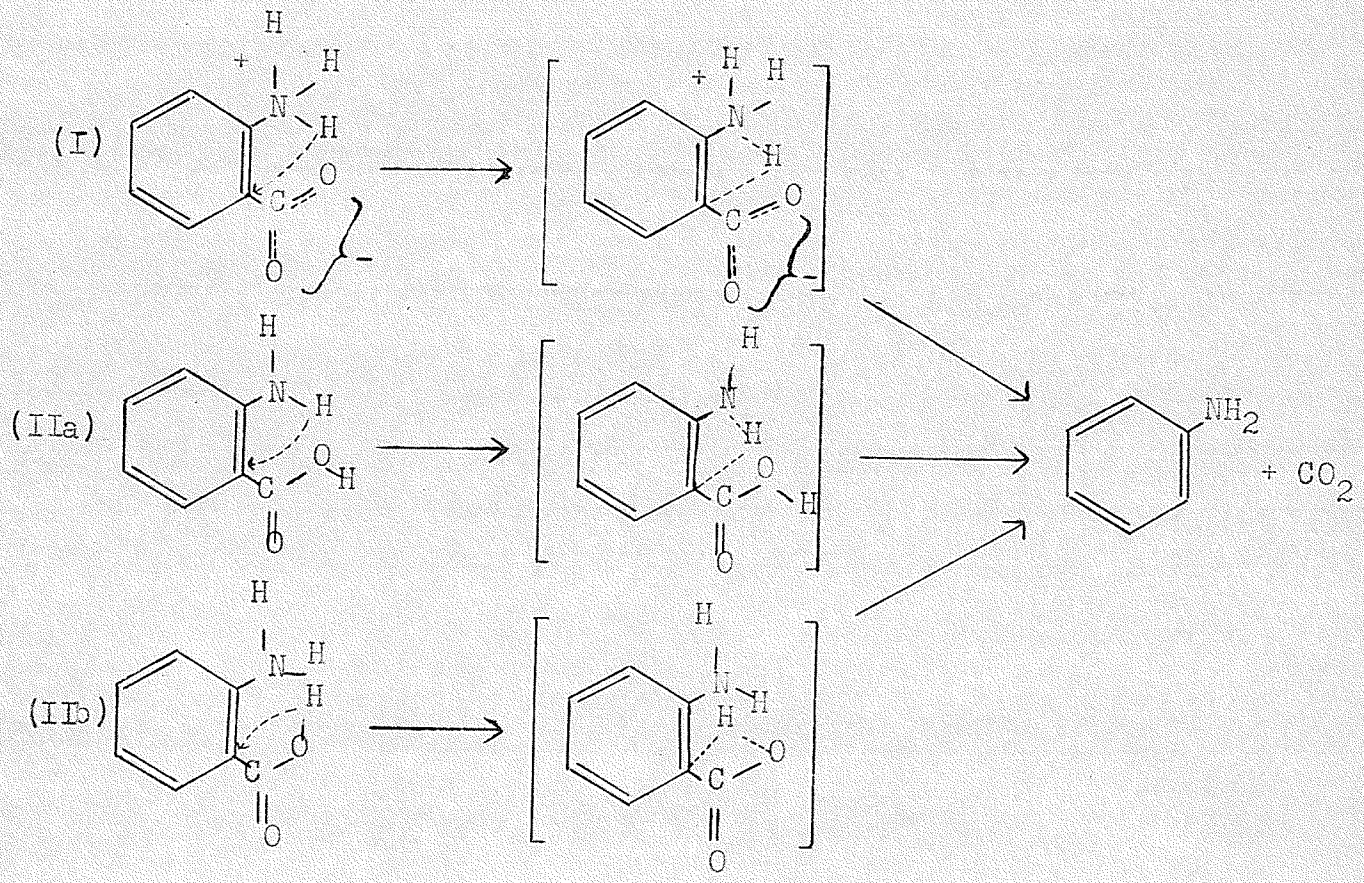
(1) In the molten state it is reasonable to suppose that the acid species (zwitterions, neutral molecules, etc.) will rapidly attain equilibrium as far as the deuterium at the various exchangeable hydrogen positions is concerned.

(2) There should be no overall deuterium loss in a decarboxylation reaction that is driven to completion, although the deuterium may re-distribute itself during the process. Therefore, for purposes of calculation, it is assumed that the overall composition of the anthranilic acid samples (D) and (E) will have been equal to the overall composition of the aniline (o-D$\emptyset$ND$_2$) samples (D) and (E) respectively, the latter being the decarboxylation products. Low deuterium analyses obtained for the anthranilic acid samples is ascribed to unremoved solvent (compare Nos. 9 and 11; 10 and 12; TABLE VI). This difficulty was not present in the run with deuterated N-methylanthranilic acid (compare Nos. 21 and 22, TABLE VI),

(3) The decarboxylation of anthranilic acid occurs at 200-210°C., and since the boiling point of aniline is 184°C., it seems reasonable to suppose that the aniline will leave the melt extremely rapidly in the vapor state, without giving its two exchangeable hydrogen atoms time to equilibrate with the three exchangeable hydrogen atoms in the residual melt. Similarly the decarboxylation temperature of N-methylanthranilic acid (240-250°C.) is much above the

normal boiling point of N-methylaniline (195.7°C.). Thus in both cases the residual acid will have a fixed equilibrium composition (re deuterium) equal to its original composition, if it is an intramolecular process, and the aniline and N-methylaniline will leave the melt with that same overall equilibrium composition.

On this basis the mechanisms of Stevens may be schematically illustrated as follows:



After removing the deuterium from the nitrogen atom of the decarboxylation products, it was found that the amount of deuterium in the ortho position was unexpectedly high for each of these three detailed mechanisms.

If the decarboxylation occurs from the zwitterion (Mechanism I), all the deuterium and protium atoms in the acid molecule will be attached to the nitrogen atom just before the decomposition. Then the relative rates of deuterium and protium transfer to the ortho position of the benzene ring can be expressed simply as the ratio of the atom % deuterium in the labelled positions of the product (the o-position in this case) to the atom % deuterium in the labelled positions of the reactant. Using the deuterium analyses from TABLE VI the following values were calculated:

(a) for anthranilic acid (D), k_D/k_H = (84.73 ± 2.04)/(49.35 ± 1.19) = 1.72 ± 0.08

(b) for anthranilic acid (E), k_D/k_H = (46.58 ± 0.13)/(27.90 ± 0.15) = 1.67 ± 0.02

(c) for N-methylanthranilic acid, k_D/k_H = (56.77 ± 0.82)/(35.67 ± 0.32) = 1.59 ± 0.04

Since the two runs with deuterated anthranilic acid at widely differing concentrations of deuterium agree within experimental error, this gives some justification of assumptions (1) to (3).

If Mechanism II is in operation, two factors of utmost importance are:

(1) The hydrogen atom that attaches itself to the α-carbon of the ring can come from either the amino group or the carboxyl group, giving rise to the subclassification indicated on the previous page.

(2) The distribution of deuterium between the amino group and the carboxyl group must be known. As has already been described (Page 48), this could not be obtained for deuterated anthranilic acid,

and only a very rough estimate could be made for deuterated N-methylanthranilic acid.

An approximation of the deuterium distribution in the neutral anthranilic acid molecule may be obtained from the following equilibria for benzoic acid and aniline with water, for which the values of the equilibrium constants at room temperature are known (32).

(1) $\phi COOH + HOD \underset{}{\overset{K_1}{\rightleftharpoons}} H_2O + \phi COOD$

$$K_1 = \frac{[H_2O][\phi COOD]}{[\phi COOH][HOD]} = 0.52$$

(2) $\phi NH_2 + HOD \overset{K_2}{\rightleftharpoons} \phi NHD + H_2O$

$$K_2 = \frac{[\phi NHD][H_2O]}{[\phi NH_2][HOD]} = 0.55$$

The deuterated aniline produced in (2) is involved in a further equilibrium (3), for which the statistical equilibrium constant may be used(32).

(3) $\phi NH_2 + \phi ND_2 \overset{K_3}{\rightleftharpoons} 2\phi NHD$

$$K_3 = \frac{[\phi NHD]^2}{[\phi NH_2][\phi ND_2]} = 4$$

Combination of equilibria (1) and (2) yields:

(4) $\phi COOD + \phi NH_2 \overset{K_4}{\rightleftharpoons} \phi COOH + \phi NHD$

$$K_4 = \frac{[\phi COOH][\phi NHD]}{[\phi COOD][\phi NH_2]} = 1.058$$

These equilibria are applied to anthranilic acid by considering it to be an equimolar mixture of aniline and benzoic acid. In one mole of deuterated anthranilic acid (D) there would be 0.494 x 3 = 1.482 gram-atom of deuterium present, i.e.

(5) $[\phi NHD] + 2[\phi ND_2] + [\phi COOD] = 1.482$

Relations (3), (4) and (5) may be incorporated into the cubic equation

(6) $[\phi COOD]^3 - 5.345[\phi COOD]^2 + 0.119[\phi COOD] + 1.626 = 0$

which has as a solution $[\phi COOD] = 0.60$, which in turn leads to the following concentrations: $[\phi ND_2] = 0.20$

$[\phi NHD] = 0.49$

$[\phi NH_2] = 0.31$

A similar consideration of deuterated anthranilic acid (E), where

(7) $[\phi NHD] + 2[\phi ND_2] + [\phi COOD] = 0.837$

yields the cubic equation

(8) $[\phi COOD]^3 - 4.055[\phi COOD]^2 - 4.285[\phi COOD] + 2.072 = 0$

which has the solution $[\phi COOD] = 0.37$, through which the following concentrations can be obtained: $[\phi ND_2] = 0.05$

$[\phi NHD] = 0.36$

$[\phi NH_2] = 0.59$

For both these sets of synthetic calculations we get the following constant ratio:

(9) $$\frac{(D/H)\text{amino group}}{(D/H)\text{carboxyl group}} = 0.50$$

If the fact that the two functional groups are <u>ortho</u> to each other does not upset this deuterium equilibrium, then isotope effects of the following order of magnitude are calculated. (As before, the isotope effect is equal to the ratio of the atom % deuterium in the labelled <u>ortho</u> position of the product to the atom % deuterium in the labelled position(s) of the reactant).

Mechanism	Acid Sample (D)	Acid Sample (E)
(IIa)	(84.73/44.5) = 1.91	(46.58/23.0) = 2.02
(IIb)	(84.73/60.0) = 1.41	(46.58/37.0) = 1.26

Since the isotope effect observed should be independent of the deuterium tracer concentration, mechanism (IIa) might be favored on the basis of the above results.

On the other hand some spectrophotometric evidence was obtained (see page 50) which supported mechanism (IIb). The distribution of deuterium in deuterated N-methylanthranilic acid was found to be such that the amount of deuterium attached to the carboxyl group is comparable to the amount of deuterium attached to the α-carbon atom after the decarboxylation. If verified conclusively this would discredit the deuterium distribution calculations carried out, and favor mechanism (IIb) with an isotope effect close to unity.

Whatever the mechanism of the thermal decarboxylation of o-aminobenzoic acids, the unusual isotope effect must fall into one of the following two categories:

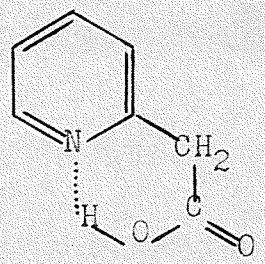
(i) It may be an apparent isotope effect arising out of the preferential orientation of deuterium in the deuterated molecule, the hydrogen from this position attacking the α-carbon atom in the decarboxylation. A normal isotope effect could still be involved in the actual hydrogen transfer.

(ii) It may be a real inverse isotope effect arising out of the energy changes involved in the reaction.

The possibility that deuterium atoms may be involved in reactions proceeding at a greater rate than protium atoms in the

corresponding positions is not excluded theoretically. Bigeleisen (11) has shown that k_D/k_H may exceed unity, but that for all other elements the heavier isotope is theoretically predicted to react slower. If deuterium reacted faster than protium, this would mean that the hydrogen isotopes are bonded more tightly in the transition state than in the ground state of the reaction.

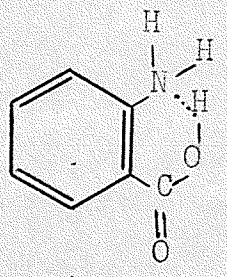
The explanation may, however, lie in the stereochemistry of the system. A pronounced factor which cannot be overlooked in o-aminobenzoic acids is intramolecular hydrogen bonding, or chelation. Hydrogen bonded forms have previously been suggested in the mechanisms of decarboxylation reactions. Westheimer and Jones (76) proposed a chelated intermediate in the decarboxylation of $\alpha\alpha$-dimethylacetoacetic acid. It has been argued that since nuclear configurations in it and in the corresponding zwitterion are almost identical, the latter may nevertheless be a likely contributor to the hydrogen bonded form. King (45) extended this to the mechanism for the decarboxylation of malonic acid. Brown (14) suggested that the thermal decarboxylation of 2-pyridylacetic acid may also occur through a hydrogen bonded form of the type illustrated in (XXVI).



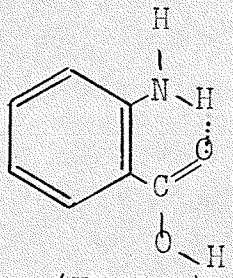
(XXVI)

In the neutral anthranilic acid molecule two types of hydrogen bonds could conceivably exist, OH...N bonds (as in XXVII)

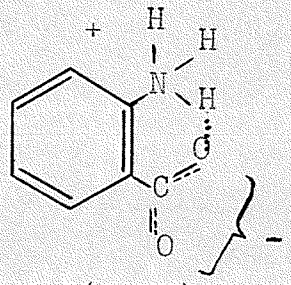
and NH...O bonds (as in XXVIII). Nakamoto, Margoshes, and Rundle (58) report that the spectral frequency shifts observed for bonds of the first type exceed those for the second, and that hence the first variety are probably stronger. Presumably hydrogen bonding could also exist in the zwitterion (as in XXIX).



(XXVII)



(XXVIII)



(XXIX)

In partly deuterated o-aminobenzoic acids, the hydrogen bonds would consist partly of protium bonds and partly of deuterium bonds. Concerning the relative strength of protium and deuterium bonds, Ferguson (21) claims the deuterium bond is slightly stronger than the protium bond, and gives the following bond energies from the literature:

Bond Type	Compound	Bond Energy (kcal./mole
O-H...O	$(CH_3COOH)_2$, vapor	7.65
O-D...O	$(CH_3COOD)_2$, vapor	7.95
F-H...F	$(HF)_6$, vapor	6.80
F-D...F	$(DF)_6$, vapor	6.85

Lewis and MacDonald (52) and Lewis and Schultze (53) ascribed a co-ordinate nature to hydrogen bonds, and from the lower volatility of deuterium modifications of compounds like H_2O and NH_3 (which yield associated liquids but unassociated vapors) they inferred that the deuterium bond must be stronger than the protium bond. Wilson (78) corroborated this conclusion from theoretical principles,

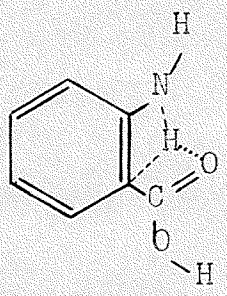
and stated that such a co-ordinate bond would give its own increment in the zero-point energy of the molecule, and since the restoring force on electrically identical isotopes must be the same, the zero-point energy increment for the bond would be smaller for the heavier isotope, the dissociation energy of that bond being correspondingly greater. Hawthorne (37) assumed that as far as hydrogen bonding in the transition state was concerned, the hydrogen isotope effect would be small, the deuterium bridge being the more stable. He also suggested that the higher melting point of deuterated piperidinium salts might be due to greater strength of deuterium bonds in the crystal lattice.

In contrast to the above, Rundle and Parasol (67) concluded that the oxygen-hydrogen interaction was decreased on substitution of deuterium for protium in the short and probably symmetrical hydrogen bonds in nickel dimethylglyoxime. In the Robertson-Ubbelohde effect, i.e. the "isotope effect" observed in crystals when deuterium is substituted for protium, it is typical to find the bond length of short hydrogen bonds to increase, and of long O-H bonds to contract under these conditions. Nordman and Lipscomb (59) state that an increase in bond length is normally associated with weaker binding, but admit that a variety of compensating effects may be operative.

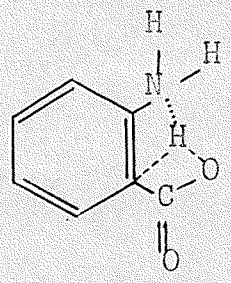
If deuterium bonds are stronger than protium bonds, this may favor the deuterium in the hydrogen bond between the nitrogen and the oxygen atoms. These "bridged" hydrogen atoms are nearest to the α-carbon atom, and if they attacked it a larger amount of

deuterium would become attached to it.

A novel suggestion can be made which combines the views discussed in a mechanism with a hybrid nature. The stereochemistry of the system is such that it is not unreasonable to speculate about a reaction in which the hydrogen atom that attacks the α-carbon atom remains hydrogen bonded throughout the process. Mechanism (IIs) would then lead to a transition state in which the attacking hydrogen is partly bonded to the α-carbon, partly bonded to the nitrogen, and hydrogen bonded to the carbonyl oxygen as in (XXX). Mechanism (IIb) would have an analogous transition state, with partial bonds to the hydrogen atom from the α-carbon and the oxygen, the hydrogen bond being toward the nitrogen in this case (XXXI). In mechanism (I) the situation could be complicated further by the existence of a bifurcated hydrogen bond (58) to both oxygens of the carboxylate ion.



(XXX)



(XXXI)

The transition state in these suggested mechanisms may aptly be termed a "non-classical zwitterion". The observation that the attacking hydrogen atom in these mechanisms is bonded to at least three other atoms in the transition state leads to the hypothesis that this may be a case where the hydrogen atoms are more tightly bonded in the transition state than in the ground state, and hence

the inverse isotope effect may arise as a perfectly natural consequence.

CONCLUSIONS

(1) The method of introducing deuterium into organic molecules by thermal decarboxylation of a suitable deuterated acid, which has previously been developed in this laboratory (19,75), has been extended to the synthesis of partly deuterated o-deuteroaniline and o-deutero-N-methylaniline. The method is simple and the products are obtained in good yields.

(2) If the thermal decarboxylation of anthranilic acid and N-methylanthranilic acid proceed through the zwitterionic form, then this investigation indicates that apparent hydrogen isotope effects (k_D/k_H) of 1.70 ± 0.10 and 1.59 ± 0.04 respectively are involved.

(3) If the decarboxylations proceed from the neutral acid molecules the isotope effects cannot be determined on the basis of this investigation because they depend on the distribution of deuterium between the amino group and the carboxyl group, and also on the origin of the hydrogen atom that displaces the carboxyl group.

(4) In the case of N-methylanthranilic acid some evidence is presented to suggest that the distribution of deuterium between the amino group and the carboxyl group favors the latter to a large extent, and that the amount of deuterium attached to the carboxyl group is comparable in magnitude to the amount of deuterium in the ortho position of the N-methylaniline obtained on decarboxylation. This may indicate that it is the carboxyl hydrogen that attacks the α-carbon atom in the decarboxylation, but at

the same time throws some doubt on the supposition that the hydrogen attack is the rate-controlling step.

(5) Intramolecular hydrogen bonding is suggested as a factor that might possibly account for the results obtained, and a hypothetical hydrogen-bonded transition state is envisaged for the reaction.

RECOMMENDATIONS FOR FUTURE INVESTIGATIONS

The distribution of deuterium in deuterated anthranilic acid and deuterated N-methylanthranilic acid should be established. The sign of Hammet's rho for the decarboxylation of o-aminobenzoic acids (indicating whether an increase in the electron density at the α-carbon atom will aid or hinder the reaction) should be determined by observing the decarboxylation rates of several properly substituted o-aminobenzoic acids. This should prove conclusively whether the attack of a proton is the rate controlling step. The deuterium isotope effect should be determined for the decarboxylation of p-aminobenzoic acid, since this would show whether intramolecular hydrogen bonding is involved. Investigations into the relative strengths of deuterium and protium bonds in chelated systems might also be helpful in the complete elucidation of this decarboxylation mechanism.

PART III

APPENDIX OF INFRARED ABSORPTION SPECTRA

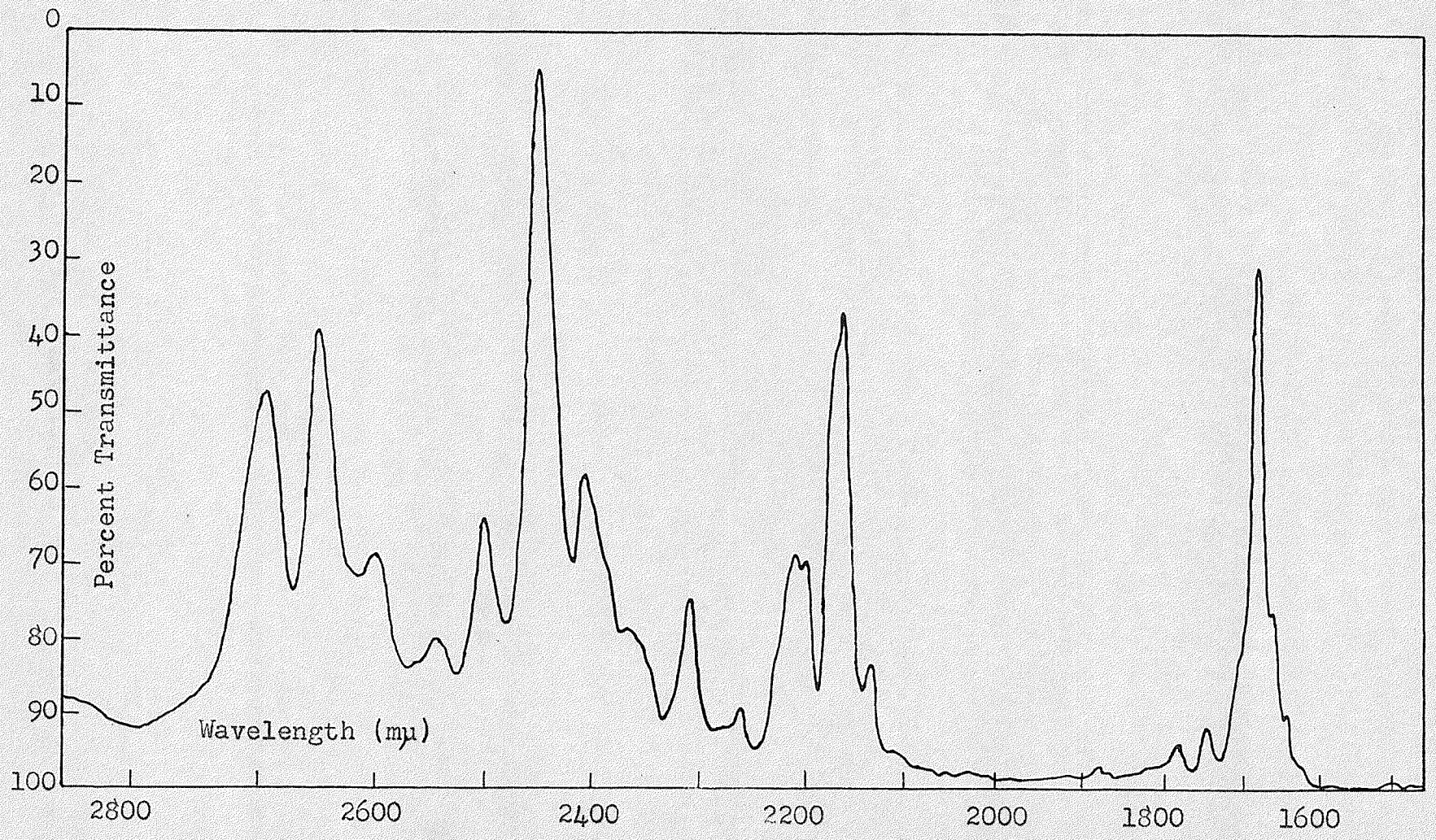


Fig. 5. Infrared Absorption Spectrum of o-Iodochlorobenzene in Carbon Tetrachloride (0.596 molar solution)

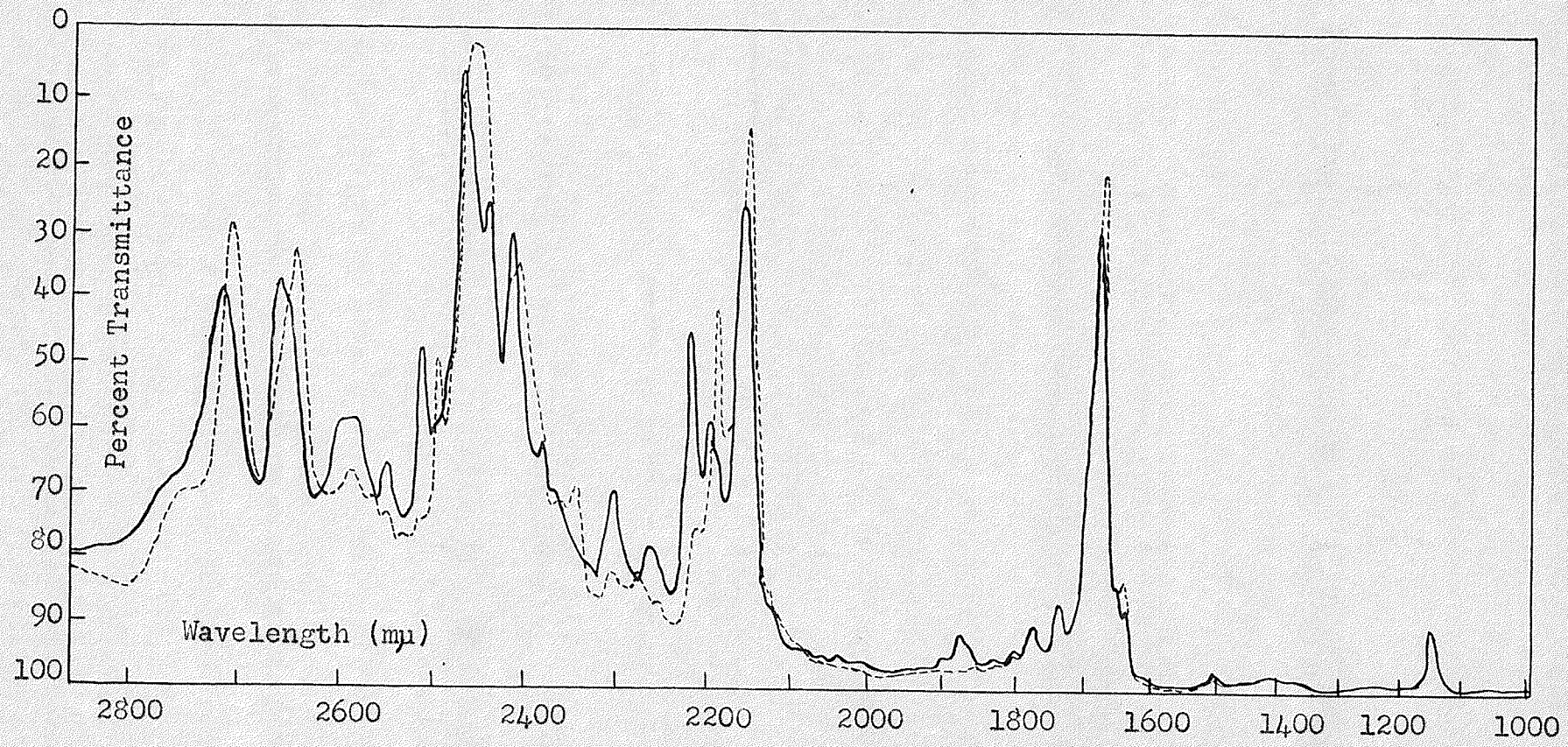


Fig. 6. Infrared Absorption Spectra of Chlorobenzene (---; 0.829 molar solution) and o-Deuterochlorobenzene (——; 86.7 ± 1.9 atom % D; 0.829 molar solution) in Carbon Tetrachloride. The broken line follows the solid line where not indicated otherwise.

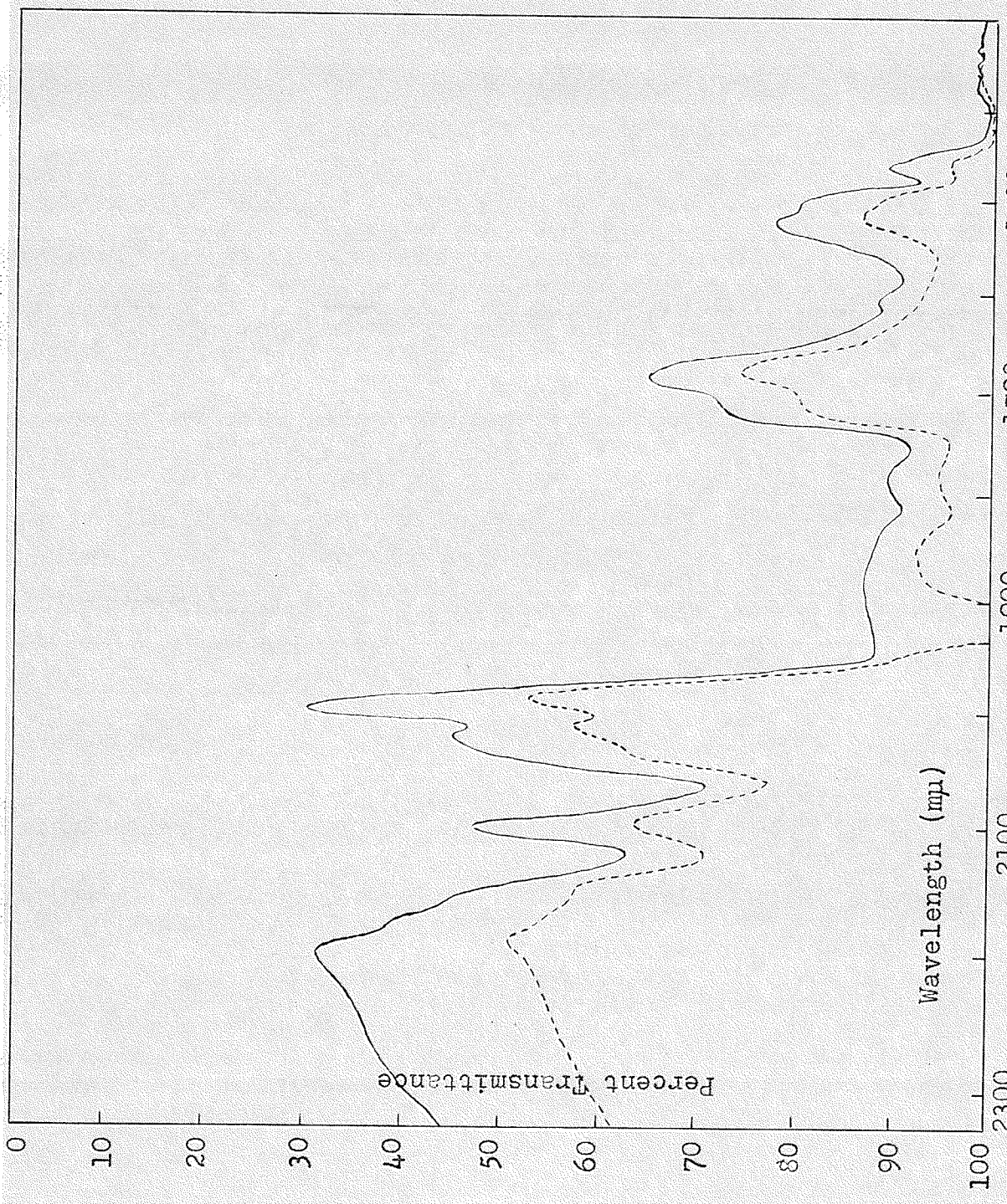


Fig. 7. Infrared Absorption Spectra of Anthranilic Acid (——; 0.254 molar solution) and Deuterated Anthranilic Acid (E) (- - -; 26.73 ± 0.32 atom % D; 0.195 molar solution) in p-Dioxane.

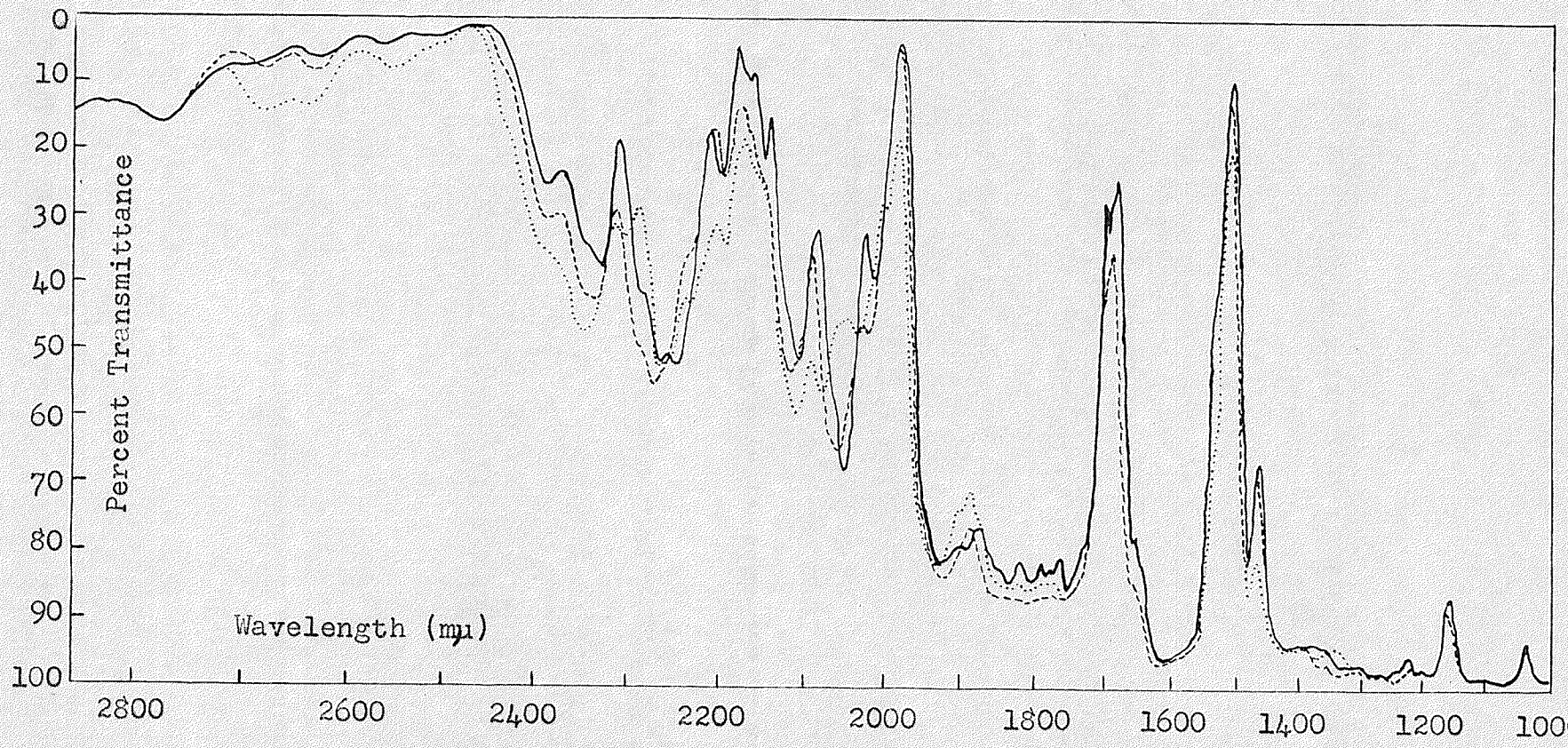


Fig. 8. Infrared Absorption Spectra of Aniline (——; 1.049 molar solution) and the Deuterated Analogues o-DØND$_2$ (D) (····; 84.73 ± 2.04 atom % o-D and 31.66 ± 2.81 atom % D on the nitrogen atom; 1.046 molar solution) and o-DØNH$_2$ (D) (----; 84.73 ± 2.04 atom % D; 1.020 molar solution) in Carbon Tetrachloride. The broken line follows the solid line except where indicated otherwise. Similarly the dotted line follows the broken line.

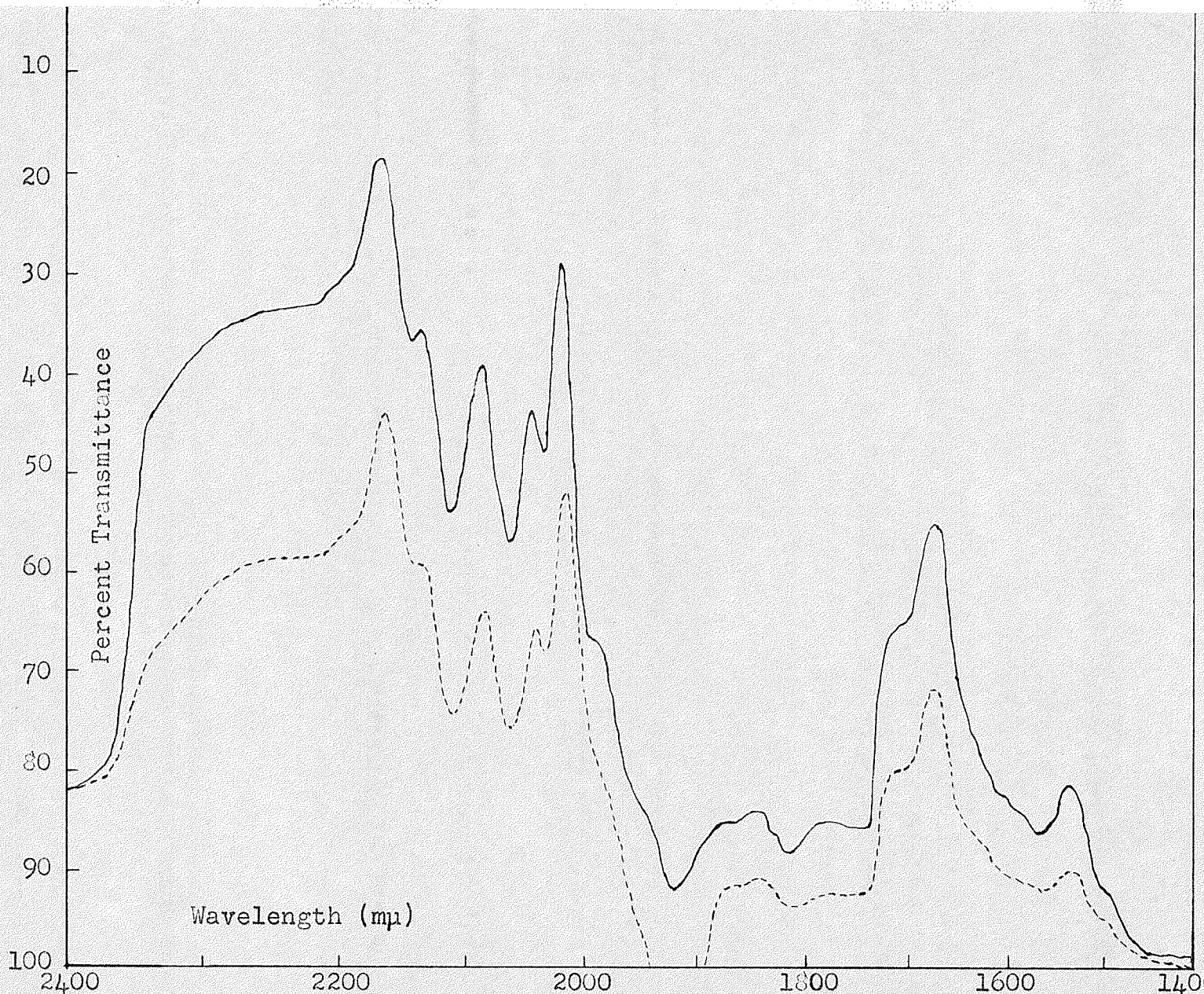


Fig. 9. Infrared Absorption Spectra of N-Methylanthranilic Acid (——; 0.345 molar solution) and deuterated N-Methylanthranilic Acid (----; 35.67 ± 0.32 atom % D; 0.255 molar solution) in p-Dioxane.

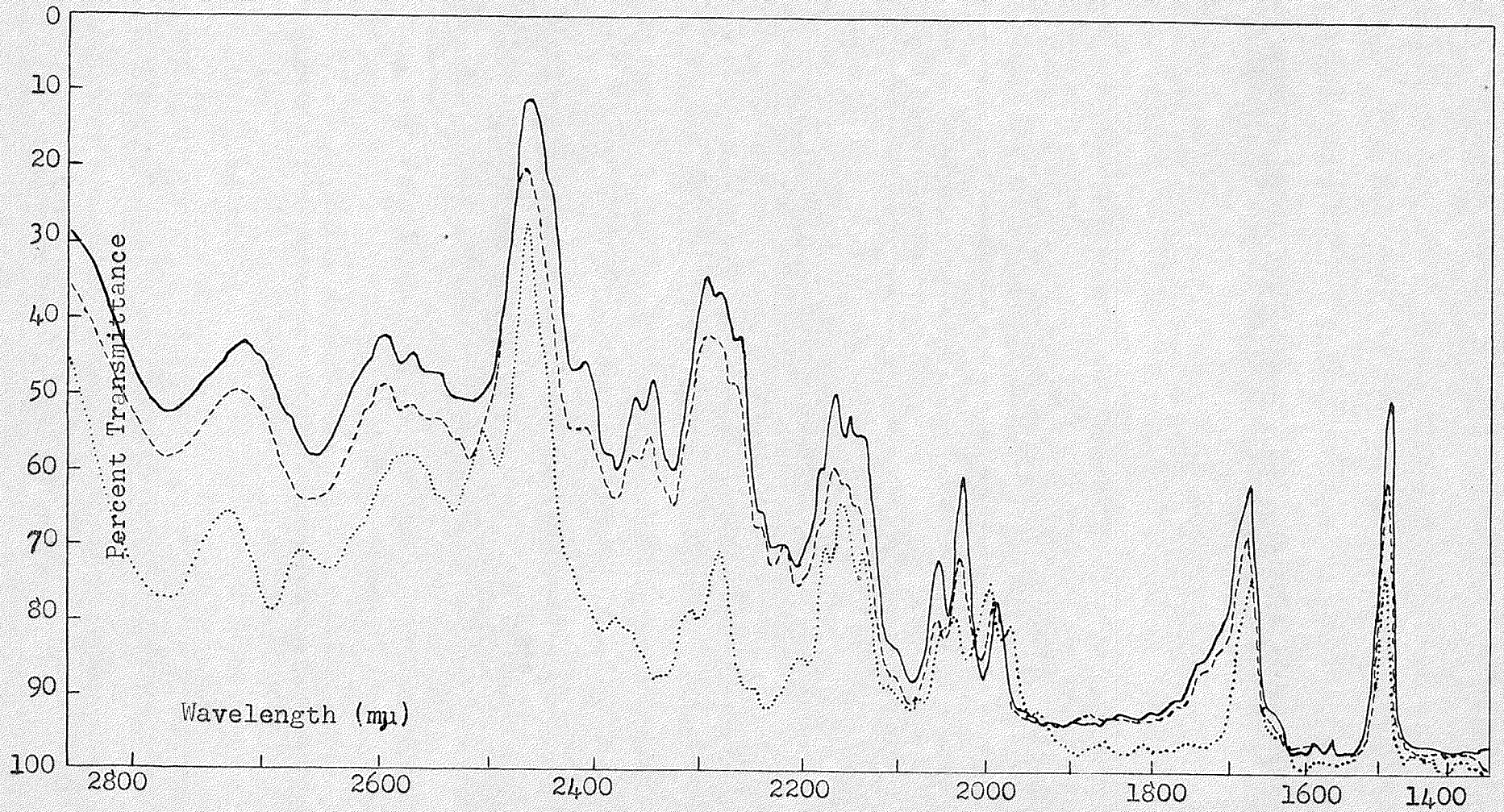


Fig. 10. Infrared Absorption Spectra of N-Methylaniline (——; 0.375 molar solution), o-DØNDMe (----; 56.77 ± 0.82 atom % o-D; 14.57 ± 2.34 atom % D on the nitrogen atom; 0.319 molar solution) and $ØND_2$ (····; 59.64 ± 1.66 atom % D; 0.239 molar solution) in Carbon Tetrachloride. The broken line follows the solid line except where indicated otherwise. Similarly the dotted line follows the broken line.

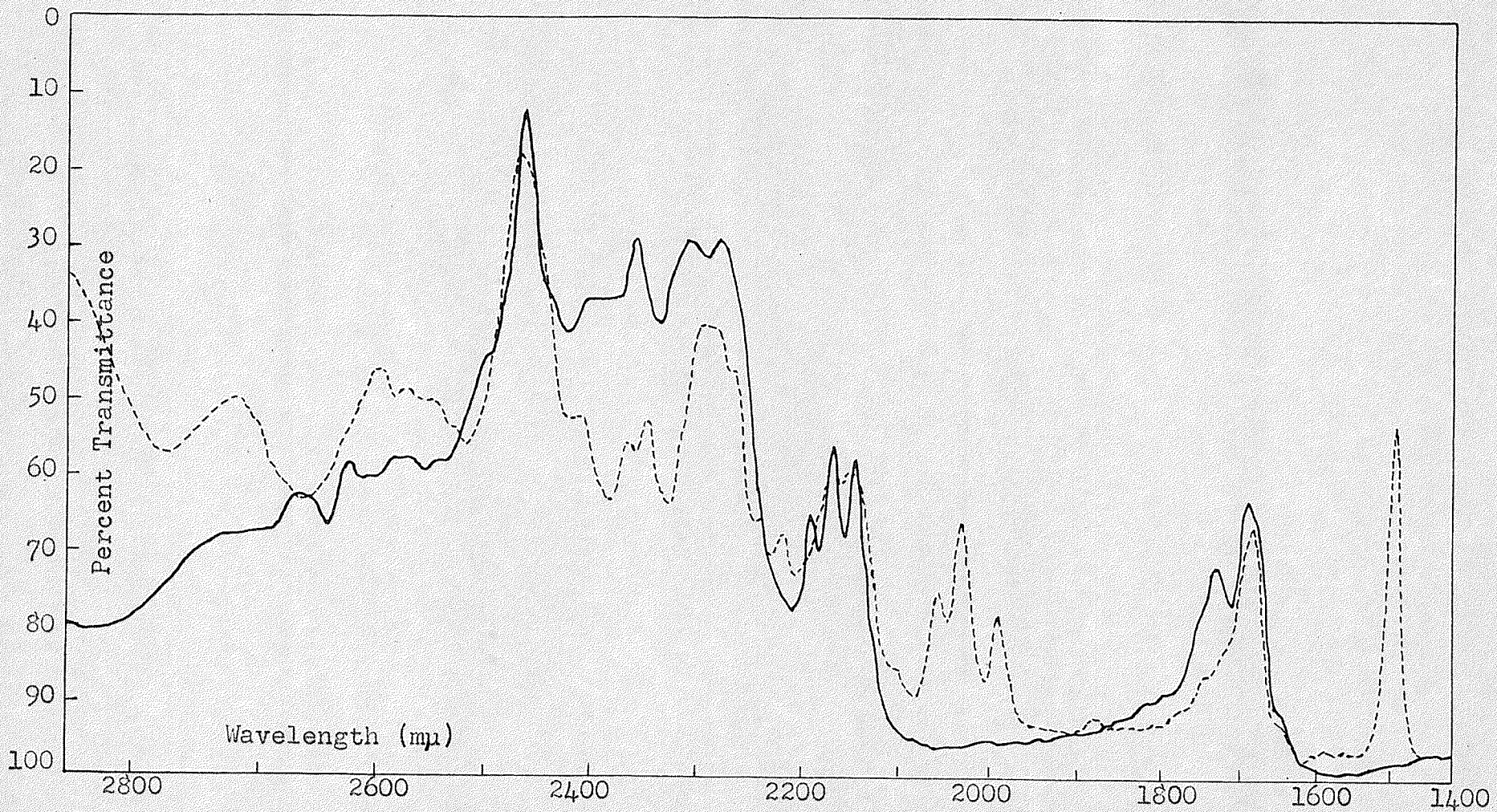


Fig. 11. Infrared Absorption Spectra of N,N-Dimethylaniline (——; 0.351 molar solution) and o-DØNHMe (----; 56.77 ± 0.82 atom % D; 0.335 molar solution) in Carbon Tetrachloride. The broken line follows the solid line where not indicated otherwise.

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