I. THE MECHANISM OF AMINATIONS OF HALOBENZENES

II. QUANTUM MECHANICAL CALCULATIONS OF ELECTRICAL EFFECTS OF SUBSTITUENTS IN *PARA*-SUBSTITUTED ANILINES

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ABSTRACT

PART I. THE MECHANISM OF AMINATIONS OF HALOBENZENES.

An elimination-addition mechanism, probably involving a "benzyne" intermediate, was established for the rearrangements which often occur in the conversion of non-activated aryl halides to arylamines with metallic amides. The evidence for the "benzyne" intermediate was obtained through ^{14}C-tracer studies of rearrangements with iodobenzene, experiments designed to determine the role of the hydrogen atom located *ortho* to the displaced halogen atom and studies of orientations in the reactions of substituted halobenzenes.

PART II. QUANTUM MECHANICAL CALCULATIONS OF ELECTRICAL EFFECTS OF SUBSTITUENTS IN *PARA*-SUBSTITUTED ANILINES.

Calculations made by the simple molecular orbital method indicated that the relative basicities of aromatic amino groups *para* to electron-attracting substituents provide a reasonable measure of the charge on C_4.

PART I. THE MECHANISM OF AMINATIONS OF HALOBENZENES.

CHAPTER I

INTRODUCTION.

While a large number of the reported rearrangements in reactions of organic halides are initiated by electrophilic reagents, only a small number are initiated by strong nucleophilic reagents. Probably the most important examples of the latter are provided by aminations of non-activated aromatic halides with metallic amides.* The first reports of such rearrangements were for aminations which proceed in low yields at high temperatures.[2] These rearrangements were not extensively investigated until it was found[3] that aryl halides could be aminated in fair to good yield with excess sodium or potassium amide in liquid ammonia or with lithium diethylamide in diethyl ether.

The reported rearrangements in aminations of aryl halides show a remarkable independence of the nature of the substituent groups, the halogens, the solvents and the metallic amides. Upon treatment with sodium or potassium amide in liquid ammonia or with lithium diethylamide in ether, o-substituted halobenzenes (I) with the substituent $R = -OCH_3$,[4] $-OC_6H_5$,[4] $-OH$,[5] $-N(CH_3)_2$,[6] $-CF_3$,[7] $-SCH_3$[8] or $-SO_2CH_3$[8] and with X = I, Br or Cl give m-substituted anilines (II) free of the corresponding o- and p-isomers.

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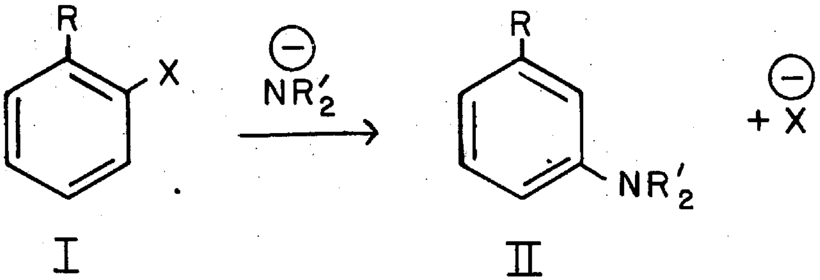
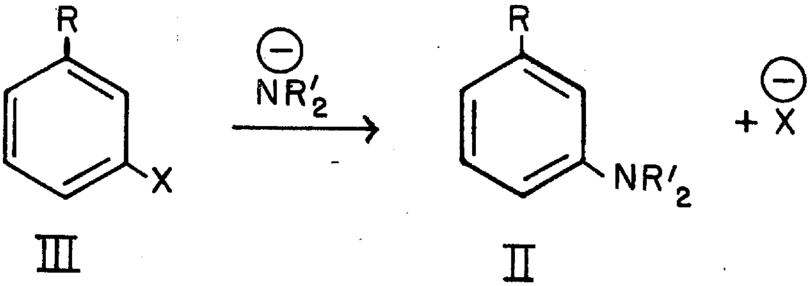
* For a complete literature survey of these aminations up to 1954 see Ref. 1.



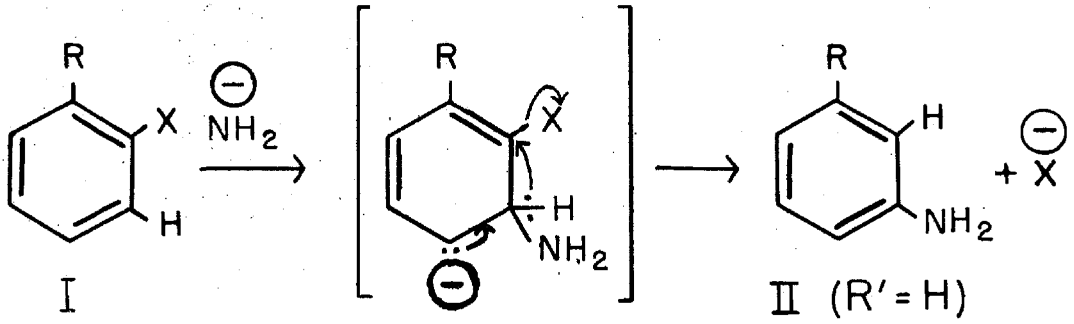
Similarly, 2-bromo-5-trifluoromethylanisole and 2-bromo-6-methylanisole give the corresponding 3-aminoanisoles.[9] The aminations of m-substituted halobenzenes (III, R = $-OCH_3$,[6] $-CF_3$[7]) produce the corresponding m-anilines (II) with no detectable amounts of rearrangement products.



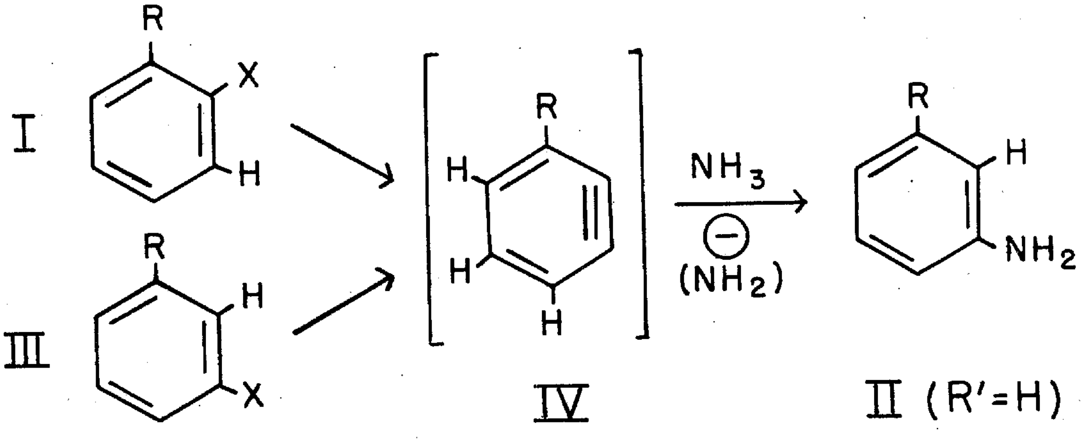
In the only published account of an amination of a p-substituted phenyl halide, it was reported that p-bromoanisole gives a 1:1 mixture of the m- and p - N, N-diethylaminoanisoles containing no o - N, N-diethylaminoanisole.[5] Thus, the pattern of rearrangements shows a considerable disregard for the influences governing the usual aromatic substitutions, and is well illustrated by the fact that halobenzenes with o-substituent groups which are either strongly o-, p ($-OCH_3$ and $-N(CH_3)_2$) or m- ($-CF_3$ and $-SO_2CH_3$) directing in aromatic nitration aminate to yield m-substituted anilines.

A number of other observations which are pertinent to formulations of reaction mechanisms for the aminations follow. (1) The entering amino group has never been found farther than one carbon away from the leaving halogen;[4-9] (2) the halides (e.g. o-trifluoromethylchlorobenzene) and anilines (e.g. p-trifluoromethyl- and o-methoxyanilines) are not isomerized under the reaction conditions;[10,11] (3) the relative reactivities of unsubstituted halobenzenes with potassium amide in liquid ammonia are Br > I > Cl >> F.[3] Fluorobenzene is not aminated at an appreciable rate at -33°.[3]

Several mechanisms have been proposed for the halobenzene aminations.[11,12] It has been suggested[12] that m-substituted halobenzenes react "normally" by a direct displacement mechanism to give the corresponding m-substituted anilines while the o-isomers react "abnormally" to give rearrangement products. The "abnormal" reactions are considered to take place by an initial addition of amide ion at the position ortho to the halogen, followed by a 1,2-hydride shift with concomitant loss of halide ion as shown in the following equation.



An elimination-addition mechanism has been suggested[11] which provides a common basis for both rearranging and non-rearranging aminations. This mechanism is featured by the formation of an electrically neutral "benzyne" intermediate, C_6H_3R(IV), through the removal of the elements of hydrogen halide from the aromatic halogen compound by metallic amide; ammonia (or amine) then adds to IV so as to give the observed product.



This latter mechanism is similar to the elimination-addition process considered in accounting for rearrangements in the coupling of aryl fluorides with phenyllithium.[13,14,15]

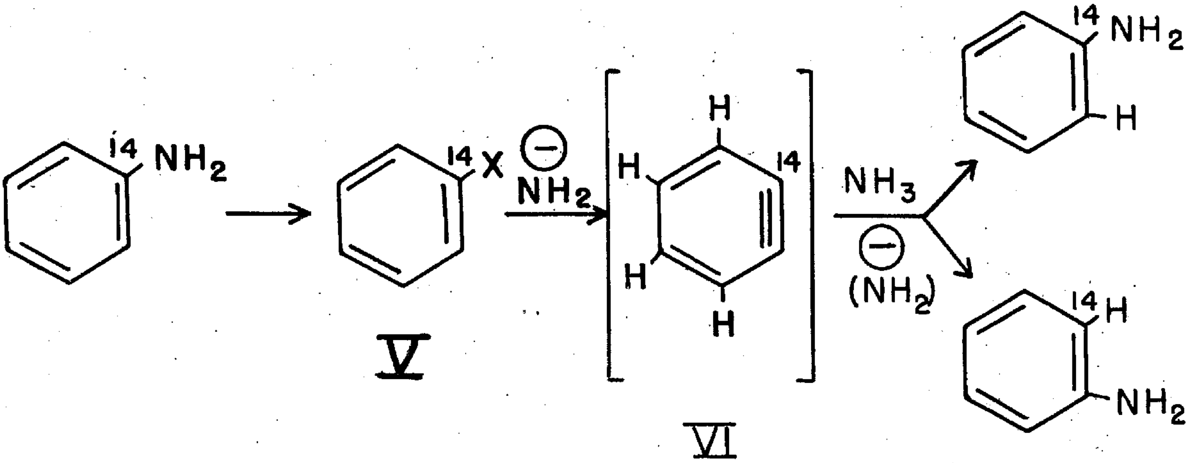
In the present research, evidence supporting the benzyne mechanism for amination reactions of halobenzenes was obtained through

(1) a study of the rearrangement with iodobenzene-1-^{14}C, (2) experiments designed to determine the role of the hydrogen atom located *ortho* to the displaced halogen atom and (3) studies of orientation in the reactions of substituted halobenzenes.

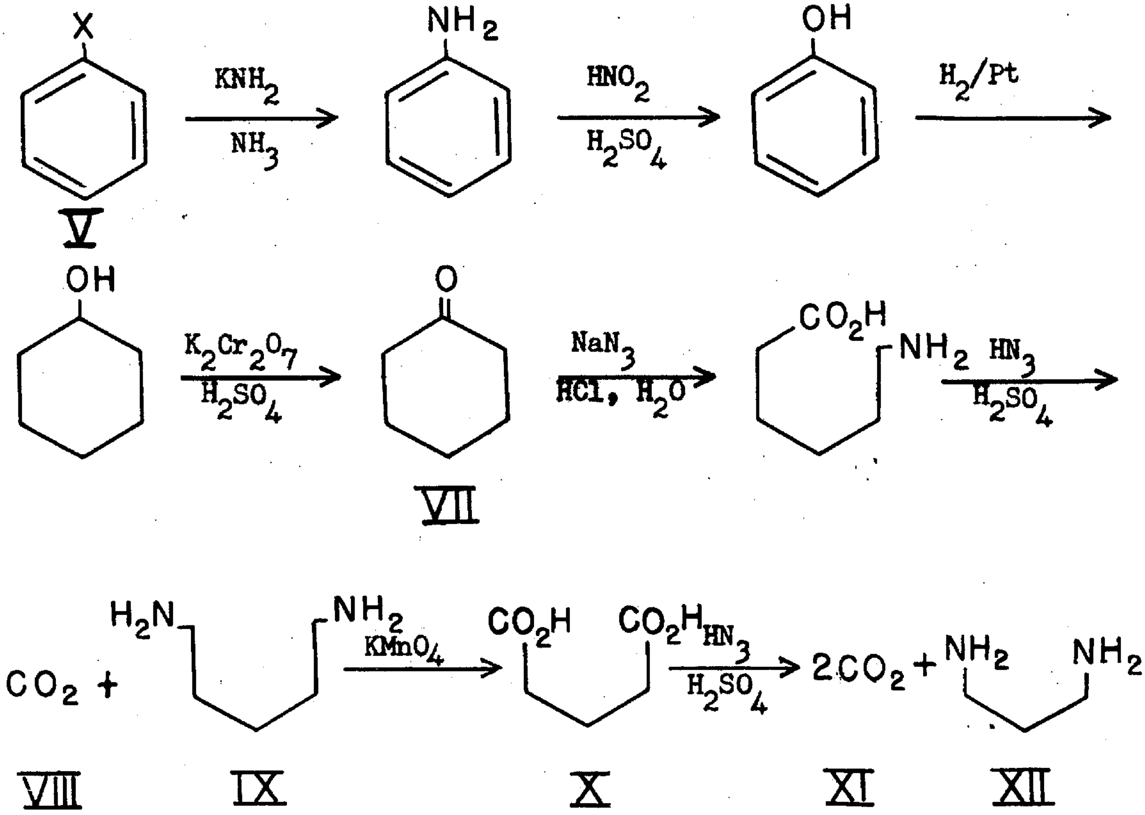
CHAPTER II

REARRANGEMENTS IN THE AMINATIONS OF CHLOROBENZENE-1-^{14}C AND IODOBENZENE-1-^{14}C

Operation of the benzyne mechanism[11] for aminations of aryl halides requires that rearrangements be observed with isotopically labeled phenyl halides. This possibility was investigated with chlorobenzene-1-^{14}C[1] and iodobenzene-1-^{14}C using potassium amide in liquid ammonia as the aminating agent. The required halides were prepared from aniline-1-^{14}C by Sandmeyer reactions of phenyl-1-^{14}C-diazonium ion.[16] The halides prepared in this manner are certainly labeled in the 1-position since rearrangements have never been observed in Sandmeyer reactions.



The location of the ^{14}C in the starting material (V) and the aniline-x-^{14}C from the amination reactions was achieved by ^{14}C-analyses of the products of the following degradative scheme.



Complete degradation to XI and XII was carried through only for the product of the iodobenzene-1-^{14}C reaction. The results of the ^{14}C-analyses are given in Table I.

It is evident that the starting aniline-1-^{14}C was labeled as represented and that extensive rearrangement occurred in the amination reaction to give aniline-2-^{14}C. The very low activity of the diamine (XII) resulting from the complete degradation of the aniline

TABLE I*

Radioactivity Analyses of Degradation Products of Aniline-x-^{14}C.

Aniline-x-^{14}C		Cyclo-hexanone VII	CO_2 VIII	1,5-Diamino-pentane IX	Glutaric acid X	CO_2 XI	1,3-Diamino-propane XII
Aniline-1-$^{14}C^{a,b}$	Meas. act.^{c}	0.2502^{d}	0.2420^{f}	0.0004^{i}	-	-	-
	°/o Total act.	(100)	$(96.7 \pm 1)^{f,g}$	0.2 ± 1	-	-	-
From Chloro-benzene-1-$^{14}C^{a}$	Meas. act.^{c}	$0.4247^{d,e}$	0.1831^{f}	$0.2201^{i,j}$	-	-	-
	°/o Total act.	(100)	$(43.1 \pm 1)^{f,g}$	51.8 ± 1	-	-	-
From Iodo-benzene-1-^{14}C	Meas. act.^{c}	0.3804^{e}	0.1764^{h}	0.2015^{j}	0.0357^{k}	0.0353^{h}	0.00004^{l}
	°/o Total act.	(100)	46.4 ± 0.1	53.0 ± 0.2	(53.0)	52.4 ± 0.3	0.05 ± 0.3

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* Footnotes on following page.

TABLE I (cont.)

[a] Degradation by H.E. Simmons, Jr.; see Ref. 1.

[b] Obtained from Tracerlab, Inc. on allocation from the U.S. Atomic Energy Commission.

[c] Activities in microcuries per millimole (μc/mmole); determined using the vibrating reed electrometer method as described by O.K. Neville, J. Am. Chem. Soc. *70*, 3499 (1948).

[d] Cyclohexanone as 2,4-dinitrophenylhydrazone.

[e] Cyclohexanone as semicarbazone.

[f] Probably slightly low because of contamination with atmospheric CO_2.

[g] Since the barium carbonate activity was almost certainly low, the most accurate estimation for the per cent of aniline-2-^{14}C is obtained from the activity of IX.

[h] CO_2 from an improved isolation procedure with minimal atmospheric CO_2 contamination.

[i] 1,5-Diaminopentane as dibenzenesulfonamide.

[j] 1,5-Diaminopentane as dibenzamide.

[k] Glutaric acid as di-*p*-bromophenacyl ester.

[l] 1,3-Diaminopropane as dibenzamide.

from the amination of iodobenzene-1-^{14}C establishes conclusively that no aniline-3-^{14}C was formed in the reaction sequence. The absence of aniline-3-^{14}C is proof that iodobenzene-1-^{14}C did not rearrange in the presence of potassium amide in liquid ammonia prior to its amination. The argument is as follows: if iodobenzene-1-^{14}C were to rearrange to iodobenzene-2-^{14}C, then the latter compound would in turn be converted to iodobenzene-3-^{14}C which should yield at least some aniline-3-^{14}C. A similar argument can be used to prove that aniline-1-^{14}C did not rearrange to aniline-2-^{14}C in the amination reaction mixture.

The predicted extent of rearrangment (i.e. formation of aniline-2-^{14}C) based on the operation of the elimination-addition mechanism is 50 per cent <u>if</u> ^{12}C and ^{14}C react at <u>identical</u> rates in the addition of ammonia to the benzyne intermediate (VI). Reaction rates at ^{14}C-labeled positions have been noted to be as much as 10 per cent less than those at ^{12}C-positions.[17] A 10 per cent "isotope effect" in the addition of ammonia to VI would result in an observed value of 55 per cent for the extent of rearrangement. The measured degree of rearrangement (52-53 per cent) is consistent with exclusive formation of VI as the reaction intermediate and a 4-6 per cent greater reaction rate of ^{12}C compared to ^{14}C in the addition step.

Any possibility that the nearly 1:1 ratios of aniline-1-^{14}C to aniline-2-^{14}C result from a fortuitous combination of "normal" and "abnormal" displacements[12] is rendered highly unlikely by finding that chlorobenzene-1-^{14}C and iodobenzene-1-^{14}C give essentially the same product mixtures. It would be a remarkable coincidence if the two very different halogens had the same ratios of "normal" to "abnormal" reactions. By way of a crude comparison, it may be noted that the ratio of elimination (E2) to substitution (S_N2) for the reaction of _i_-propyl _iodide_ with sodium hydroxide in 60 per cent aqueous ethanol is 2.83 whereas the corresponding ratio for _i_-propyl _bromide_ is 1.41.[18]

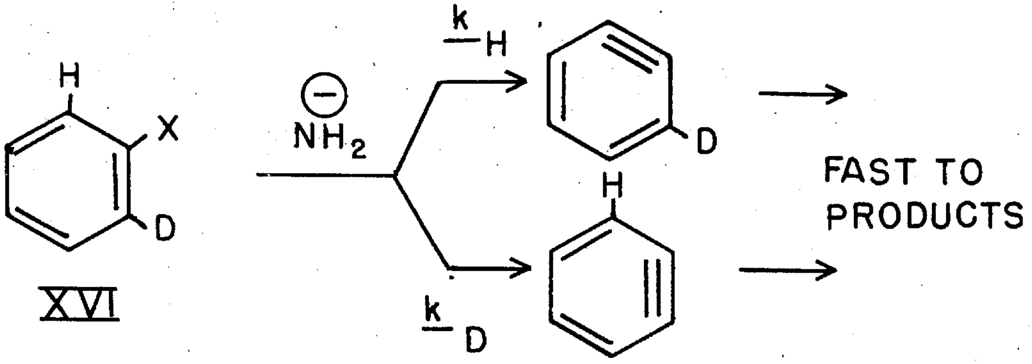
CHAPTER III

MECHANISMS OF BENZYNE FORMATION FROM HALOBENZENES; THE ROLE OF THE ORTHO HYDROGEN.

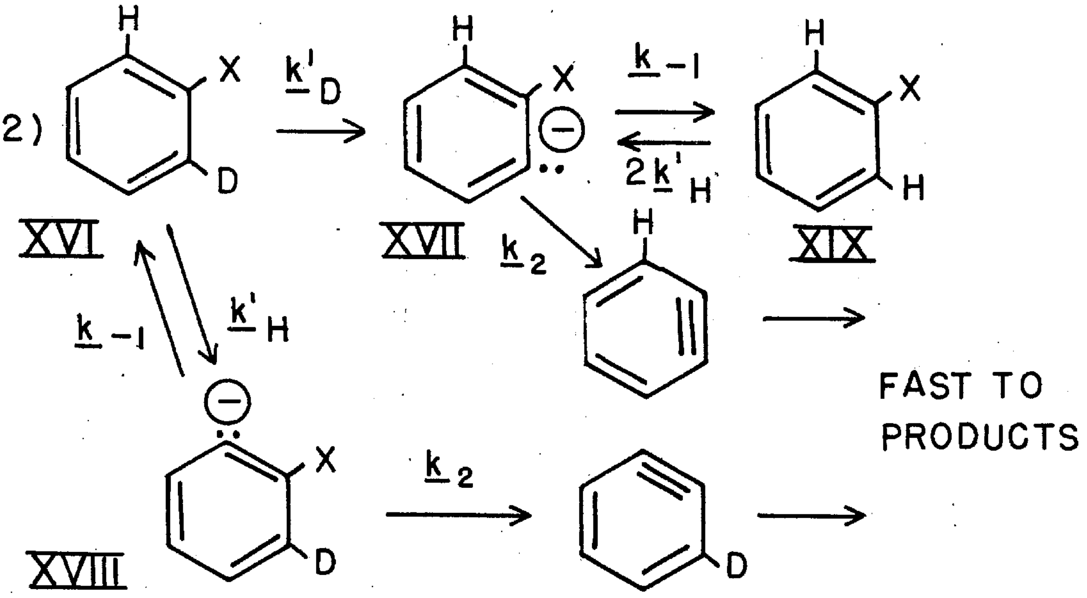
The benzyne mechanism for the aminations is characterized by removal of a hydrogen *ortho* to the halogen by the strong base, amide ion. Preliminary evidence for an important role of the *ortho* hydrogens in the amination reactions was adduced from unsuccessful attempts to aminate aryl halides with no hydrogens *ortho* to the halogen. No reaction occurred when bromomesitylene (XIII) or bromodurene (XIV) was treated with sodium amide in liquid ammonia, even on long standing.[19] 2-Bromo-3-methylanisole (XV) has been reported to be similarly unreactive toward sodium amide in liquid ammonia.[9] These results indicate that a hydrogen *ortho* to the halogen is necessary for facile amination, although it could be suggested that steric hindrance by the *ortho* groups in XIII, XIV and XV might prevent a direct displacement reaction.

The 1,2-elimination of hydrogen halide from a phenyl halide may be formulated as a concerted (Equation (1)) or stepwise (Equation (2)) process. In more conventional eliminations, these mechanisms have been distinguished fairly conclusively by using deuterium as a tracer for the hydrogen adjacent to the leaving halogen.[20-22]

(1)



(2)



If the hydrogen is removed in the rate-determining step as for the concerted process (1), the relative reaction rates of the *o*-deuterated and *o*-protated halobenzenes should correspond to an isotope effect k_H/k_D of approximately 6-7.* If the stepwise mechanism (2) operates,

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* An isotope effect of 6.7 was observed for the dehydrobromination of *i*-propyl bromide.[22] It might be expected that the isotope effect for any given dehydrochlorination would be somewhat greater than that for the corresponding dehydrobromination since the carbon-hydrogen bond is probably more nearly broken in the transition state for the former than for the latter elimination reaction.

the carbanions XVII and XVIII may either form benzyne by loss of halide ion or revert to aryl halide by abstraction of a <u>proton</u> from the solvent ammonia. In considering mechanism (2) it will be assumed that k_{-1} is detectably large, because if it is not, mechanisms (1) and (2) are indistinguishable by the experimental methods employed.[≠] The magnitude of the apparent isotope effect for an elimination proceeding by mechanism (2) will be less than for the same elimination proceeding by mechanism (1) (i.e. less than 6-7) and will depend on the ratio $\underline{k}_2/\underline{k}_{-1}$. The smaller this ratio, the smaller will be the apparent isotope effect. Indeed, if this ratio were very small, there would be no detectable isotope effect on the amination rate because the deuterated halobenzene would be completely converted to protated halobenzene before significant halide ion formation could occur.

The evidence bearing on the mechanisms of the reactions of fluoro-, chloro- and bromobenzenes-2-$\underline{d}$ with potassium amide in liquid ammonia will now be considered. Which mechanism ((1) or (2)) operates as well as the relative values for the specific rate constants when mechanism (2) operates depend on the nature of the halogen. Fluorobenzene-2-$\underline{d}$,[23] fluorobenzene-2,4,6-$\underline{d}_3$[1] and 4-fluorotoluene-3,5-$\underline{d}_2$[1] were found to exchange deuterium <u>ortho</u> to the fluorine extremely rapidly, even though these halides did not yield amination products at a significant rate. Here, $\underline{k}'_D$ is very large (exchange is complete in less than 10 sec.[23]), but $\underline{k}_2$ is negligible. Chlorobenzene-2-$\underline{d}$ is aminated by

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[≠] Several other reasonable assumptions were made in formulating mechanism (2). First, the same $\underline{k}'_H$ values for loss of a proton were assigned to XVI and XIX. Second, the $\underline{k}_2$ values for loss of halide ion from the anions XVII and XVIII were assumed to be equal. Finally, reversion of the anion XVII to the deuterated halide XVI was taken to be negligibly important in the presence of a large excess of ordinary ammonia.

mechanism (2); exchange of hydrogen for deuterium was demonstrated and a ratio for k_{-1}/k_2 of roughly 1.5 was computed from the experimental value of 2.7 obtained for the apparent isotope effect (see Chapter VII, p. 54 for details of the calculation). For bromobenzene-2-*d* the k_H/k_D value was 5.5 which is close to the 6-7 range expected for a concerted E2 dehydrobromination.[22]

Both chloro- and bromobenzenes-2-*d* appear to react with lithium diethylamide in ether by the concerted mechanism (1). The k_H/k_D value for chlorobenzene was 5.7. No exchange was observed when chlorobenzene-2-*d* was treated with lithium diethylamide in an ether solution which was made up to approximately 0.3 *M* in diethylamine, a potential proton donor. For bromobenzene k_H/k_D was 5.6. The closeness of this value and that obtained for bromobenzene in liquid ammonia strongly indicates that the aminations of bromobenzene in both diethyl ether and liquid ammonia proceed by the concerted mechanism (1).

The data referred to above is summarized in Table II. The observed isotope effects clearly indicate that the *ortho* hydrogen is involved in, or before, the rate-determining step of the amination reaction. The strongly basic character of amide ions warrants the conclusion that the hydrogen is removed as a proton rather than as a hydrogen atom or hydride ion.

The changeover in elimination mechanism in liquid ammonia from a stepwise process with chlorobenzene to a concerted process with bromobenzene provides the basis for an explanation of the reactivity order of phenyl halides,[3] Br > I > Cl >> F, in the amination reaction. Two influences are clearly important. First, the hydrogen is removed

TABLE II*

o-Deuterium Effects in Reactions of Aryl Halides with Metallic Amides.

Halide	Reagent	Solvent	Mole °/o o-deuterated aryl halide at start	Mole °/o o-deuterated aryl halide at finish	°/o Formation of halide ion at finish	k_H/k_D [a]
Fluorobenzene-2,4,6-d_3 [b]	KNH_2	NH_3	40.1	0[c]	~ 0	-
4-Fluorotoluene-3,5-d_2 [b]	KNH_2	NH_3	37.2	0[c] (120 min.)	~ 0	-
Fluorobenzene-2-d[d]	KNH_2	NH_3	100.0	0[c] (10 sec.)	~ 0	-
Chlorobenzene-2-d (1)[n]	KNH_2	NH_3	26.4	32.2[f,g]	55.98[h]	(2.60)[i]
(2)[n]	KNH_2	NH_3	26.1	31.3[f,g]	51.00[h]	(2.88)[i]
(3)[n]	KNH_2	NH_3	100.0	87.0[f,g]	28.42[h]	(-0.77)[i]
Bromobenzene-2-d (1)[n]	KNH_2	NH_3	25.7	37.7[f,j]	69.55	5.54[k]
(2)[n]	KNH_2	NH_3	22.4	34.2[f,j]	72.10	5.42[k]

* Table continued on next page.

TABLE II (cont.)

Halide	Reagent	Solvent	Mole °/o *o*-deuterated aryl halide at start	Mole °/o *o*-deuterated aryl halide at finish	°/o Formation of halide ion at finish	k_H/k_D[a]
Chlorobenzene-2-*d*(1)[n]	$LiN(C_2H_5)_2$	Ether[l]	47.1	54.8[f,g]	44.75	5.71
(2)[n]	$LiN(C_2H_5)_2$	$HN(C_2H_5)_2$, Ether[m]	35.0	44.1[f,g]	53.78	5.79
Bromobenzene-2-*d*(1)[n]	$LiN(C_2H_5)_2$	Ether	24.6	33.2[f,j]	59.77	5.46
(2)[n]	$LiN(C_2H_5)_2$	Ether	24.6	30.6[f,j]	47.48	5.81

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[a] Calculated as described in Chapter VII.

[b] Ref. 1.

[c] Estimated from curves recorded automatically with a Baird Infrared Spectrophotometer.

[d] Ref. 23.

[e] Estimated from curves recorded automatically with a Perkin-Elmer (Model 21) Infrared Spectrophotometer.

[f] Analysis by manual operation of a Perkin-Elmer (Model 21) Infrared Spectrophotometer.

[g] Analyses at 10.090 and 10.520 μ.

[h] Determined by Volhard titration of chloride ion.

[i] Apparent isotope effect calculated as if the reaction proceeded by mechanism (1). Analyses at 8.866 and 10.109 μ.

[k] Determined by Volhard titration of bromide ion.

[l] Essentially no diethylamine present.

[m] Approximately 0.3 *M* in diethylamine.

[n] Number in parentheses is number of run.

as a positive ion and the rate of this process is expected to follow the order F > Cl > Br > I, parallel with the electronegativities of the halogens. Second, halide ion must depart and the expected rate sequence for this process is I > Br > Cl > F.[24] The change in mechanism from (2) to (1) occurs where loss of halide ion becomes easier than removal of the hydrogen ion so that the two steps become synchronized. Bromobenzene appears to possess the optimum balance of *ortho*-hydrogen and halogen reactivities for the greatest reaction rate with potassium amide in liquid ammonia.

CHAPTER IV

ORIENTATIONS FOR AMINATIONS OF SUBSTITUTED HALOBENZENES IN LIQUID AMMONIA.

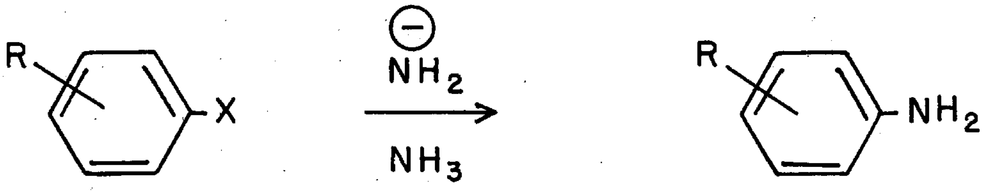
The degree of rearrangement in the reported aminations of substituted halobenzenes with metallic amides is profoundly influenced by the position of the substituent relative to the halogen atom. In the aminations mentioned in Chapter I, o- and m-substituted halides gave exclusively the m-substituted anilines while the p-substituted halide gave an equimolar mixture of the m- and p-substituted anilines.

In the present work, the isomeric product distributions for aminations of a number of substituted halobenzenes were determined in order to ascertain whether the orientations could be correlated and predicted on the basis of the benzyne mechanism. The experimental results are summarized in Table III. Explanation of the orientation results in terms of the benzyne mechanism may be conveniently divided into two parts -- the factors governing formation of particular benzyne isomers and the effects of the substituent groups on directing the addition of the elements of ammonia to the "triple" bond.

Clearly, o- (I) and p-substituted (XX) aryl halides can eliminate hydrogen halide to form only 3- (IV) and 4-substituted (XXI) benzynes respectively. A m-substituted halide (III) might yield either or both isomers.

TABLE III

Orientations in Aminations of Substituted Halobenzenes.

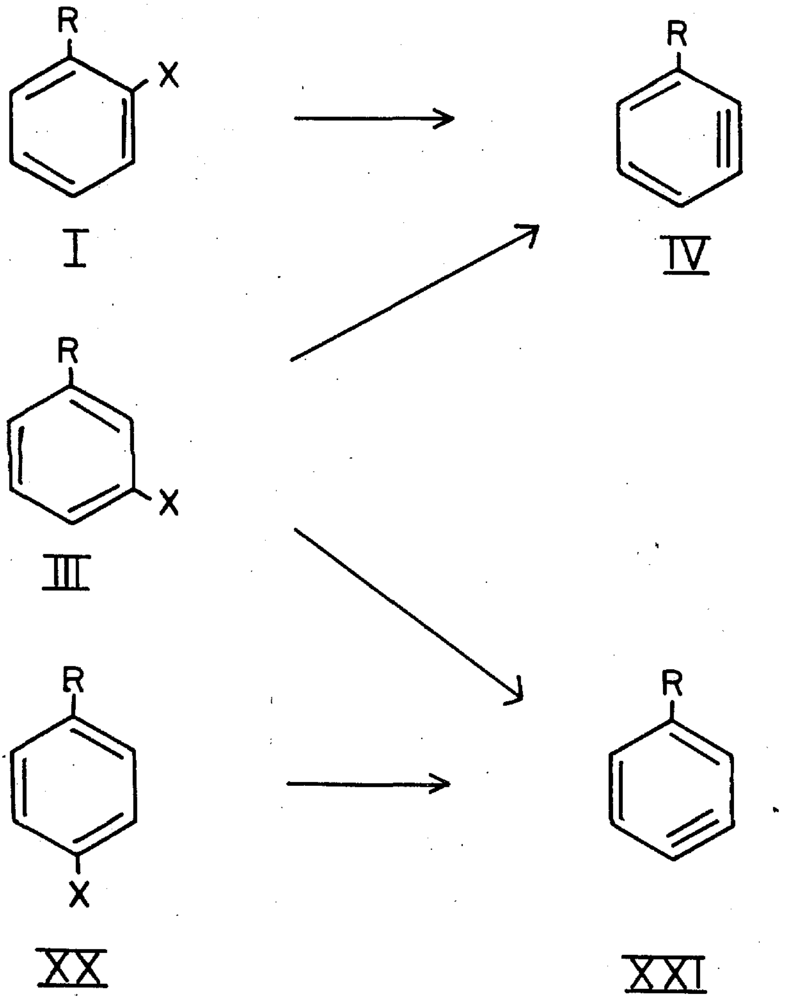


R	X	ORTHO	META	PARA
o-OCH_3	Br[a]	—	100	—
m-OCH_3	Br[b]	—	100	—
p-OCH_3	Br	—	49 ± 1	51 ± 1
o-CF_3	Cl[c]	—	100	—
m-CF_3	Cl[c]	—	100	—
p-CF_3	Cl[c]	—	50 ± 5	50 ± 5
p-F	Br	—	20 ± 1	80 ± 1
o-CH_3	Cl	45 ± 4	55 ± 4	—
m-CH_3	Br	22 ± 4	56 ± 4	22 ± 4
m-CH_3	Cl	40 ± 4	52 ± 4	8 ± 4
p-CH_3	Cl	—	62 ± 4	38 ± 4

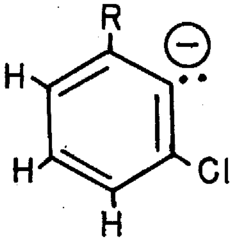
[a] Ref. 4.

[b] Ref. 46.

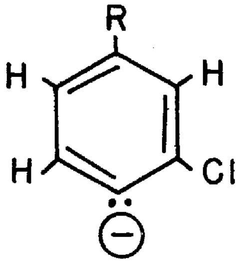
[c] Ref. 10.



The amination experiments with bromobenzene-2-d (Chapter III) indicate that the rate of the elimination step for this halide is equal to the rate of removal of the hydrogen ortho to the halide as a proton. Consequently, the direction of elimination for a m-substituted bromide should be predictable on the basis of which of the hydrogens adjacent to the halogen is more acidic. The experiments with chlorobenzene-2-d (Chapter III) show that it forms benzyne in liquid ammonia by a stepwise mechanism. Hence, the direction of elimination for a m-substituted chloride may depend not only on the relative acidities of the hydrogens adjacent to the chlorine but also on the relative abilities of the isomeric anions, XXII and XXIII, to lose chloride ions.



XXII



XXIII

As will be seen later, this latter factor may be expected to be important only when the acidities of the hydrogens adjacent to the chlorine are not very different.

It seems generally agreed[23] that the acidities of benzenoid hydrogens are largely determined by the *inductive* effects of the substituents; thus, the acidity order for electron-attracting groups is *o* > *m* > *p* and for electron-donating groups is *p* > *m* > *o*. The order for electron-attracting groups has been supported by the results of metalation studies[25] and further verified by direct measurements of the rates of deuterium-hydrogen exchange for substituted deuterobenzenes with potassium amide in liquid ammonia; the deuterium exchange data are summarized in Table IV.[23]

On the basis of the hydrogen acidities, the following predictions can be made. An aryl bromide with a substituent in the *m*-position which is electron-attracting by the inductive effect should eliminate hydrogen bromide to yield preferentially the 3-substituted benzyne, since the most acidic benzenoid hydrogen is the one

TABLE IV[a]

Pseudo First-Order Rate Constants for Deuterium-Protium Exchange of Substituted Deuterobenzenes (C_6H_4DR) with 0.6M Potassium Amide in Liquid Ammonia (at boiling point).

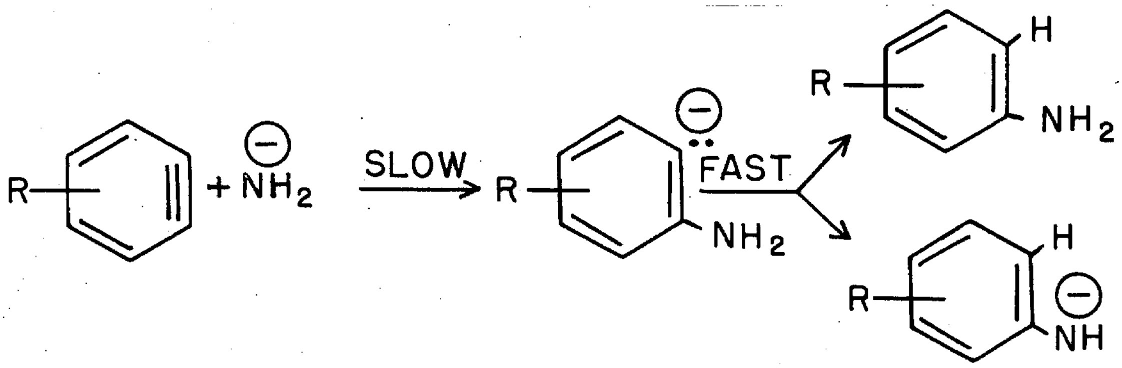
R	k sec.$^{-1}$
2-F	$> 4 \times 10^{-1}$
3-F	4×10^{-4}
4-F	2×10^{-5}
2-CF_3	6×10^{-2}
3-CF_3	1×10^{-3}
4-CF_3	1×10^{-3}
2-OCH_3	1×10^{-3}
3-OCH_3	$\sim 10^{-7}$
4-OCH_3	$\sim 10^{-8}$
H	$\sim 10^{-7}$

[a] Ref. 23.

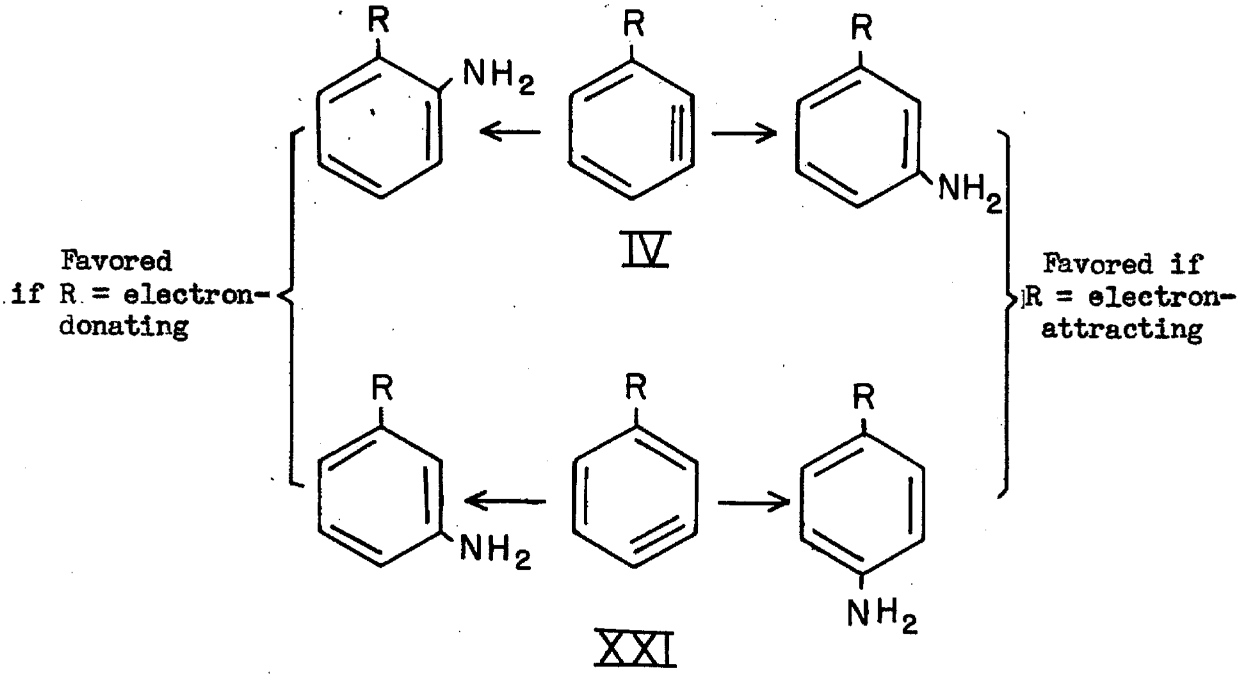
in the 2-position. This may be true also for m-substituted chlorides when R ($-OCH_3$, $-CF_3$) has a strong electron-attracting inductive effect, because the 2-hydrogen is then so much more acidic than the 4-hydrogen that the 4-anion (XXIII) may not be formed at all. The corresponding o-substituted halides can yield only the 3-substituted benzynes so that the same final amination products should be obtained from these isomeric o- and m-substituted halides.

An aryl bromide with a m-substitutent which is weakly electron-donating by the inductive effect should give both the 3- and 4-substituted benzynes with the 4-isomer predominating. The corresponding chloride should also give a mixture of the 3- and 4-substituted benzynes, but less of the latter may be formed than from the bromide because the anion XXII from the chloride, due to its more localized negative charge, may lose chloride ion (to form the 3-substituted benzyne) more readily than the isomeric anion XXIII (to form the 4-substituted benzyne).

The amination of a benzyne intermediate seems most likely to occur in two steps, the first being a rate-determining addition of amide ion and the second being a fast abstraction of a proton from solvent or an intramolecular proton shift.



The direction of addition might be predicted by considering the amide ion to add so as to produce the most favorable location of the negative charge with respect to the inductive effect of R.* On this basis, the benzenoid hydrogen acidity data may be employed to predict the following pattern of addition. Where R is electron-attracting by its inductive effect, the 3-substituted benzyne should give predominantly the *m*-substituted aniline and the 4-substituted benzyne may show some preference for forming the *p*-substituted aniline. Where R is weakly electron-donating by its inductive effect, the 3- and 4-substituted benzynes may give preferentially the *o*- and *m*-substituted anilines respectively; however, the preference in the case of the 3-substituted benzyne may be weakened somewhat due to steric hindrance in forming *o*-substituted anilines.



IV

XXI

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* An additional but probably secondary influence would be the gain in resonance energy in the transition state due to conjugation between the orienting substituent and the entering amino group.

In general, the orientations observed with the various substituents (Table III) are in accord with the above predictions based on the benzyne mechanism. Thus, all of the halides with electron-attracting o- and m-substituents give exclusively m-substituted anilines.

The results obtained from aminations of the halotoluenes are consistent with the formation of 60 per cent of 4- and 40 per cent of 3-methylbenzyne from m-bromotoluene and 21 per cent of the 4- and 79 per cent of the 3-isomer from m-chlorotoluene; 4-methylbenzyne gives the m- and p-toluidines in the ratio of approximately 2:1 whereas 3-methylbenzyne yields the o- and m-toluidines in the ratio of about 1:1.

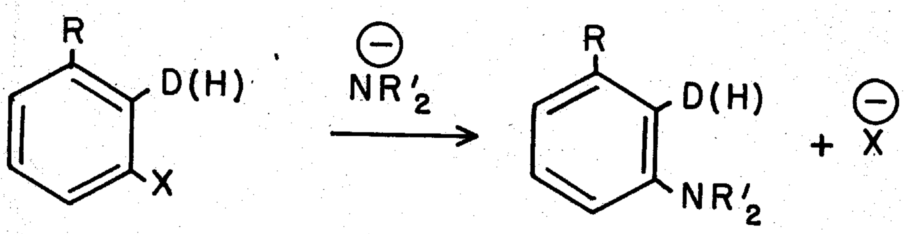
Ratios of m- to p-substituted anilines obtained from p-substituted phenyl halides can be correlated with k_m/k_p for exchange (see Table IV). When k_m/k_p is nearly unity as for $-CF_3$, the m- and p-substituted anilines are formed in substantially equal amounts. With fluorine k_m/k_p is about 20, and this correlates well with the substantially greater amount of p- over m-fluoroaniline obtained from p-bromofluorobenzene. The behavior of p-bromoanisole is exceptional in that roughly equal amounts of m- and p-anisidines are formed despite the fact that k_m/k_p for exchange seems to be substantially greater than unity.

CHAPTER V

A. OTHER POSSIBLE FORMULATIONS OF THE AMINATION REACTION MECHANISM.

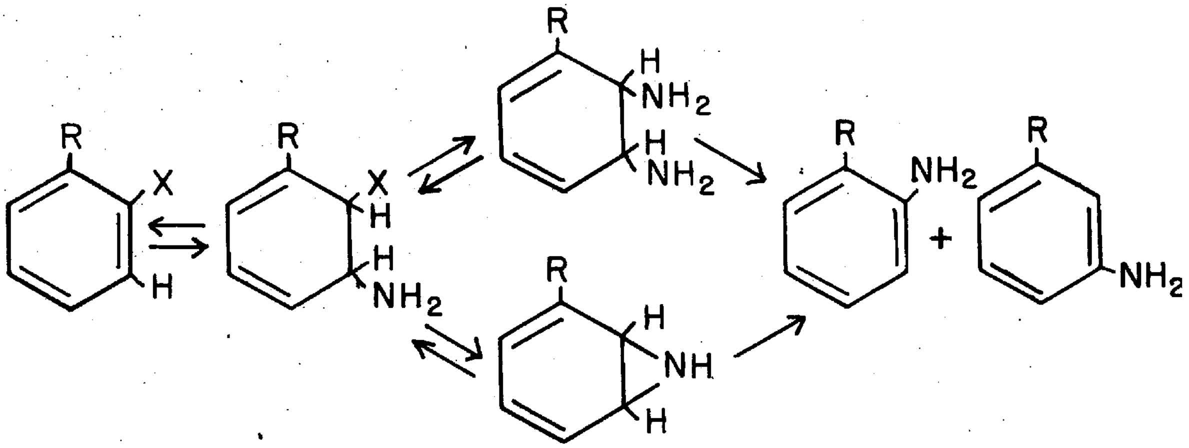
Although the facts discussed in earlier chapters strongly indicate that benzyne is the intermediate in the amide ion-induced amination of phenyl halides, they do not "prove" that it is. Therefore, other reaction mechanisms will be considered in order to determine whether a more satisfactory formulation can be found.

The evidence against a combination of "normal" and "abnormal" displacements[12] has already been discussed (p.10). This possibility could be more conclusively eliminated by demonstrating a deuterium isotope effect for a non-rearranging reaction as shown below.

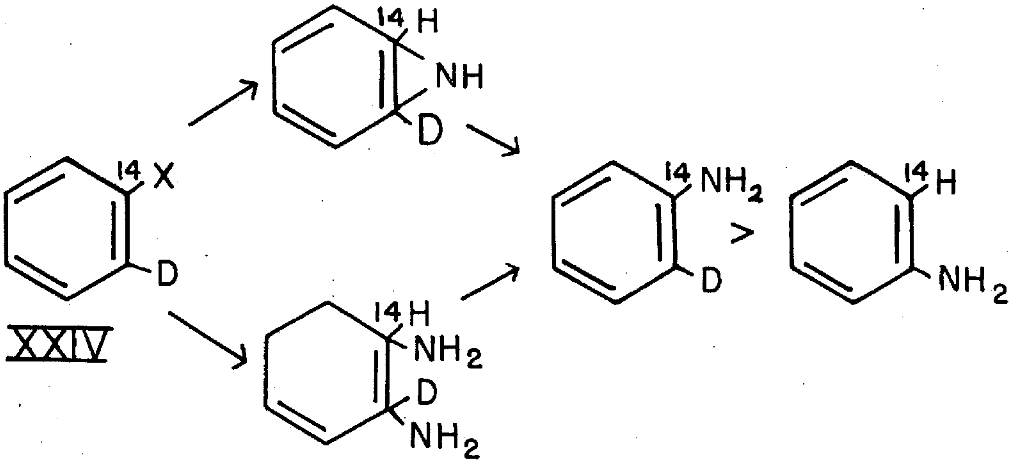


Such an isotope effect would be incompatible with the "normal" displacement mechanism.

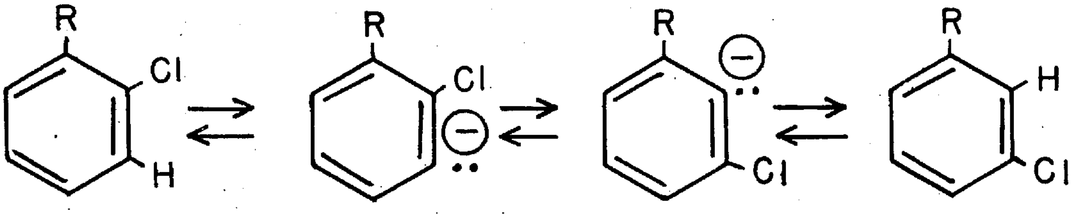
Formulation of the amination reaction as an addition-substitution-elimination process is unreasonable by virtue of the energetically unfavorable addition of ammonia in the first step (endothermic by about 24 kcal./mole) and the requirements, because of the deuterium isotope effect, that the final, probably highly-exothermic, loss of ammonia be rate-determining and that all prior steps be fast equilibria.



If deemed necessary, an unequivocal decision between the above addition-substitution-elimination mechanism and the elimination-addition (benzyne) mechanism could be achieved by a study of the ^{14}C-rearrangement in the amination of chlorobenzene-1-^{14}C-2-<u>d</u> (XXIV). The degree of ^{14}C rearrangement would not be affected appreciably by deuterium substitution for the benzyne mechanism (<u>i.e.</u>, 50 per cent ^{14}C rearrangement would be observed), but the ratio of aniline-1-^{14}C to aniline-2-^{14}C would be much greater than 1:1 if an addition-substitution-elimination mechanism like that shown above were to operate.

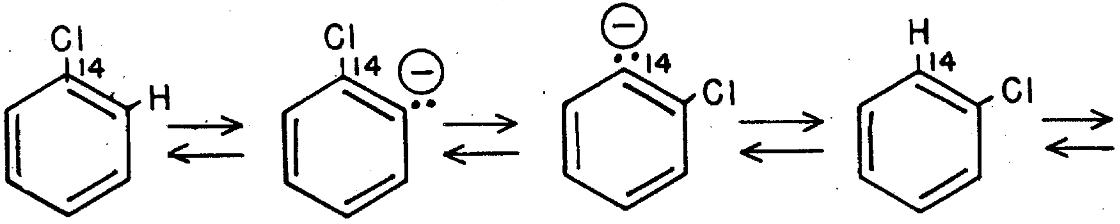


Rearrangement by equilibration of the isomeric anions XXVI and XXIII would necessitate the formation of some rearranged chloride (XXVII) since the chlorocarbanions are known to form aryl chlorides by abstraction of a proton from solvent (p. 15)

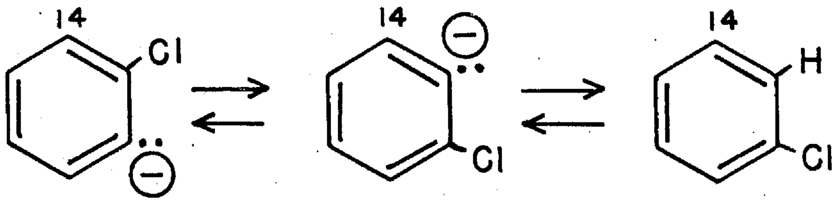


XXV XXVI XXIII XXVII

The failure of XXVII to form from XXV (when R = $-CF_3$[10]) under amination conditions rules out this mechanism for the aminations. Furthermore, the results obtained from aminations of halobenzenes-1-^{14}C are not in accord with the anion equilibration mechanism. Equilibration of the anion (XXVIII), formed from chlorobenzene-1-^{14}C, whith its 2-isomer (XXIX) would lead to chlorobenzene-2-^{14}C which would in turn give some chlorobenzene-3-^{14}C (via XXX and XXXI).



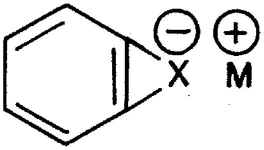
XXVIII XXIX



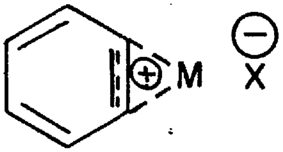
XXX XXXI

The halide labeled in the 3-position would yield some aniline-3-^{14}C. No aniline-3-^{14}C was formed from iodobenzene-1-^{14}C, and the similarity of the degree of rearrangement observed with iodo- and chlorobenzenes-1-^{14}C (Table I) would seem to indicate that no aniline-3-^{14}C was obtained from the chloro-compound.

Other possible symmetrical intermediates are XXXII and XXXIII.



XXXII

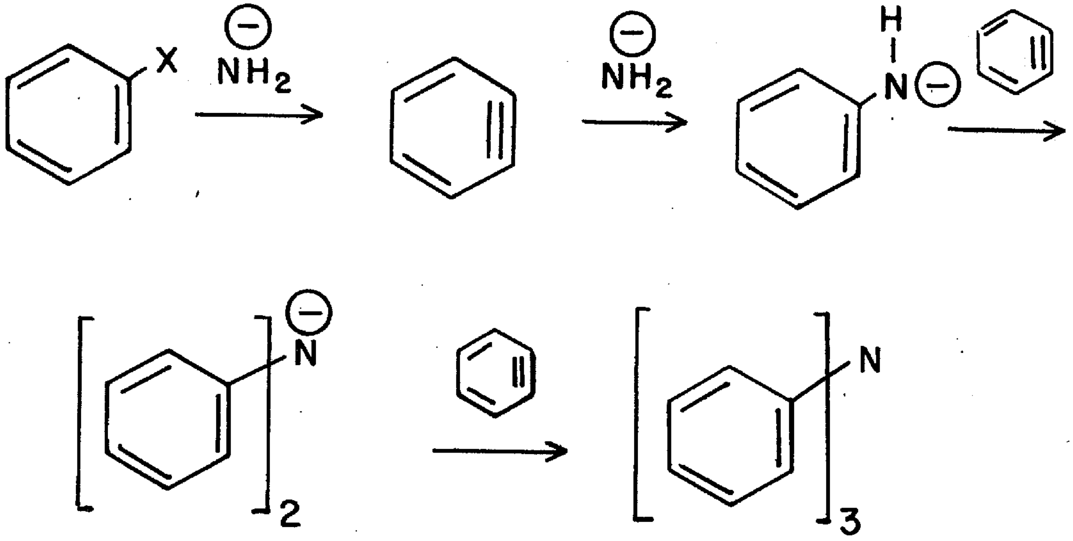


XXXII

XXXII is rendered unlikely as an intermediate by virtue of the fact that aryl fluorides appear to react smoothly with lithium diethylamide in ether to give the customary patternsof rearrangements.[26] It does not seem likely that fluorine as a first-row element could expand its valence shell to accommodate the ten electrons required for the halogen atom in XXXII. The cation complex XXXIII has analogies in substances like the silver ion-alkene complexes, but it is unreasonable that an alkali-metal cation would prefer to complex with an unsaturated compound in the presence of a large excess of liquid ammonia.

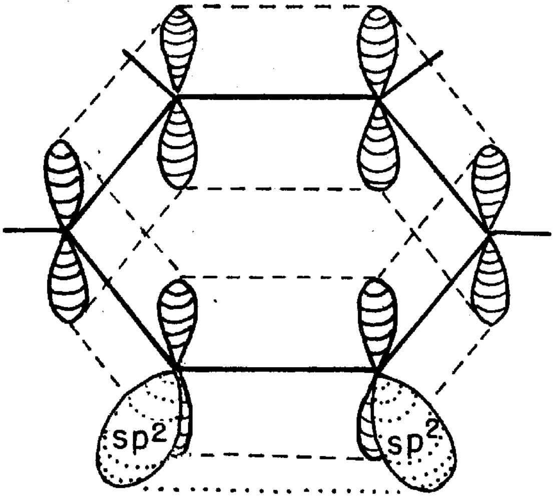
B. THE STABILITY OF THE BENZYNE INTERMEDIATE.

If one allows that the crucial reaction intermediate is actually benzyne, the question of its stability is of substantial interest. The following evidence may be cited in favor of the idea that the intermediate has an appreciable half-life. First, there is a definite ^{12}C-^{14}C isotope effect in the reaction of benzyne with amide ion in ammonia (see Table I and discussion in Chapter II), which indicates that the conversion of the intermediate to aniline is at least not a diffusion-controlled process. Second, there are indications of competition for the intermediate by nucleophilic agents other than amide ion or ammonia. Thus, when amide ion is not used in large excess, substantial quantities of diphenyl- and triphenylamines are formed by secondary reactions as follows.



Furthermore, it has been found[27] that potassium amide grealy enhances the rate of production of tetraphenylmethane through the reaction of chlorobenzene with potassium triphenylmethide in liquid ammonia. The simplest explanation of this phenomenon is that potassium amide acts to dehydrohalogenate the aryl halide, and the resulting benzyne intermediate is converted by potassium triphenylmethide to tetraphenylmethane.

It can be inferred from simple atomic orbital diagrams for benzyne (XXXIV) that the molecule might have essentially the same resonance energy as benzene provided that the ring is taken to be a regular hexagon.



XXXIV

Such a system, containing a "triple bond" in a six-membered ring, may be estimated to have an amount of angle strain (i.e. 120° of distortion from the normal angles) comparable in magnitude to that of cyclopropene, a known substance. It is interesting in this regard that a bent excited state of acetylene has been established conclusively by spectral studies.[28]

CHAPTER VI

APPLICATIONS OF THE BENZYNE MECHANISM TO OTHER REACTIONS.

The reaction of fluorobenzene-1-^{14}C with phenyllithium in ether has been found to proceed with a degree of rearrangement consistent with a symmetrical benzyne intermediate.[15] It is possible that similar mechanisms may operate in the Fittig-type coupling reactions of aryl halides.

Hydrolyses of aryl halides with base at high temperatures often yield rearrangement products similar to those observed in aminations with metallic amides; the mechanisms of reactions of this type are being investigated currently.[29]

It should not be inferred that all nucleophilic displacements in aromatic derivatives without activation of the type provided by nitro, cyano and similar electron-accepting groups proceed exclusively by the benzyne mechanism. Thus, phenyl-1-^{14}C-trimethylammonium bromide is attacked by potassium amide in liquid ammonia to give about 20 per cent of ^{14}C-labeled aniline which was shown by degradation to consist of 96 per cent of aniline-1-^{14}C and 4 per cent of aniline-2-^{14}C (see Table V for data). The small degree of rearrangement in this reaction may be associated with facilitation of amide-ion attack at the 1-carbon by the positive nitrogen of the ammonium group. Similar lack of rearrangement has been reported for displacement reactions of substituted diphenyliodonium salts.[30]

TABLE V

Radioactivity Analyses of Degradation Products of Aniline-x-^{14}C from Amination of Phenyl-1-^{14}C-trimethylammonium Bromide.

	Cyclo hexanone VII[b]	CO_2 VIII[c]	1,5-Diamino pentane IX[d]
Meas. act.[a]	0.1451	0.1390	0.00617
°/o Total act.	(100)	95.8±0.1	4.3±0.4

[a] Activities in microcuries per millimole (µc/mmole); determined using the vibrating reed electrometer method as described by O.K. Neville, J. Am. Chem. Soc., <u>70</u>, 3499 (1948).

[b] Cyclohexanone as semicarbazone.

[c] CO_2 from an isolation procedure with minimal atmospheric CO_2 contamination.

[d] 1,5-Diaminopentane as dibenzamide.

CHAPTER VII

EXPERIMENTAL PART.

^{14}C Studies.

Starting Materials. A. Iodobenzene-1-^{14}C.- This halide was prepared from aniline-1-^{14}C* essentially as described previously.[31] The reaction was carried out using 12.3 g. (0.098 mole) of aniline-1-^{14}C hydrochloride containing 183 μc. of radioactive carbon, 7.10 g. (0.10 mole) of sodium nitrite, 35.5 ml. (0.43 mole) of concentrated hydrochloric acid and 16.3 g. (0.43 mole) of potassium iodide. Unlabeled iodobenzene (8.3 g., 0.041 mole) was added to the reaction mixture as a carrier prior to the steam distillation step. The steam distillate was extracted with ether, the ethereal extract dried over calcium sulfate and the ether removed through Vigreux column No. 2.≠ Distillation of the residue afforded 23 g. (78 per cent) of iodobenzene-1-^{14}C, b.p. 83.0-83.5° (25.3-25.6mm.), n_D^{25} 1.6160.

B. Phenyl-1-^{14}C-trimethylammonium Bromide.- Aniline-1-^{14}C* was converted to a mixture of N-methylaniline-1-^{14}C and N,N-dimethylaniline-1-^{14}C by a modification of the procedure of Knoevenagel.[32] Aniline-1-^{14}C (15.3 g., 0.168 mole, 260 μc. of ^{14}C) was heated with 15.3 g. (0.48 mole) of methanol and 0.35 g. of iodine in a sealed tube at 220-230° for 9 hours. The reaction did not seem to be complete so 0.5 ml. of water and 0.2 g. of iodine were added and the mixture heated

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* This material was obtained from Tracerlab, Inc. on allocation from the U.S. Atomic Energy Commission.

≠ See Appendix I for descriptions of fractionating columns.

at 220-230° for 24 hours. The methanol and water were removed by distillation through a column packed with glass helices and the residual material dried over barium oxide. The barium oxide was removed by filtration and thoroughly washed with ether. Fractionation of the ethereal solution gave 13.7 g. of a mixture of N-methylaniline-1-^{14}C and N,N-dimethylaniline-1-^{14}C, b.p. 95.0-96.0° (34.5 mm.), n_D^{25} 1.5630. The infrared spectrum of the product indicated that it did not contain aniline and was approximately an equimolar mixture of mono- and dimethylanilines.

The product was converted to N,N-dimethylaniline-1-^{14}C by reductive methylation.[33] The aniline mixture (13.7 g.) was dissolved in 90 ml. of 2.5 M hydrochloric acid. The solution was stirred and cooled in an ice-salt bath to 12° at which point 12 ml. of 37 per cent aqueous formaldehyde was added in one portion. After 3 minutes, 25 g. of zinc dust was added portionwise at such a rate so that the temperature remained below 25°. Concentrated hydrochloric acid (80 ml.) was added to the mixture over a period of 10 minutes, the temperature being kept below 25° by the addition of ice. The reaction mixture was stirred for 45 minutes and then allowed to stand overnight. The mixture was filtered and basified to approximately pH 10 with concentrated ammonia solution. Solid sodium hydroxide was then added until the pH was greater than 13 and the aqueous solution was extracted with ether. The ethereal extract was dried over barium oxide, the ether removed and the residue distilled. The yield of N,N-dimethylaniline-1-^{14}C was 11.0 g., b.p. 86.0-87.0° (19.6 mm.), n_D^{25} 1.5552. The infrared spectrum of this material indicated that it was pure N,N-dimethylaniline.

Phenyl-1-^{14}C-trimethylammonium bromide was prepared by methylation of N,N-dimethylaniline-1-^{14}C with methyl bromide. A mixture of 11.0 g. (0.090 mole) of N,N-dimethylaniline-1-^{14}C and 17.0 g. of methyl bromide (0.18 mole) in 25 ml. of methanol was heated in a sealed tube at 78° for 14 hours. The tube was cooled to -80°, opened, and the excess methyl bromide removed first at room temperature and finally at 50°. Anhydrous ether was added to the residue until crystallization began and then 50 ml. of ether was added. The mixture was kept in a refrigerator for 3 hours and the quaternary salt filtered and dried. The crude product was recrystallized from absolute ethanol and yielded 17.0 g. (88 per cent) of phenyl-1-^{14}C-trimethylammonium bromide as white needles, m.p. 215.0-216.0° (lit., m.p. 215° [34]).

Aminations. A. Aniline-x-^{14}C from Iodobenzene-1-^{14}C. - Potassium amide was prepared in the usual manner[3] from 24 g. (0.60 g.-atom) of potassium metal and 350 ml. of anhydrous liquid ammonia in a 1-l. three-necked flask equipped with a Dry Ice reflux condenser, an efficient mechanical stirrer and a dropping funnel. Iodobenzene-1-^{14}C (22.5 g., 0.11 mole) was added rapidly and, after 8 minutes, the reaction was quenched by addition of 35 g. of ammonium chloride. Ether (100 ml.) was added and the Dry Ice condenser removed. After the mixture had warmed to room temperature, water and ether were added, the phases separated and the aqueous portion continuously extracted with ether overnight. The ethereal portions were extracted with hydrochloric acid, the acid extract basified with solid sodium hydroxide to a pH above 13 and the alkaline portion continuously extracted with ether overnight.

The ethereal solution was dried over barium oxide and distilled. The yield of aniline-x-^{14}C was 4.26 g. (42 per cent); b.p. 83.9-84.4° (23.7 mm.), $\underline{\underline{n}}_{D}^{25}$ 1.5826.

B. Aniline-x-^{14}C from Phenyl-1-^{14}C-trimethylammonium Bromide.- The procedure was essentially as described in the preceding experiments; from 24 g. (0.60 g.-atom) of potassium, 325 ml. of liquid ammonia, and 22.5 g. (0.105 mole) of phenyl-1-^{14}C-trimethylammonium bromide, after a reaction period of 9 minutes, was obtained 8.3 g. of a mixture of aniline and N,N-dimethylaniline; b.p. 82.0-84.5° (30.6-32.0 mm.), $\underline{\underline{n}}_{D}^{25}$ 1.5615. The infrared spectrum of the mixture indicated it to be comprised of aniline (25 per cent) and N,N-dimethylaniline (75 per cent). The yield of aniline was approximately 2.1 g. (22 per cent). The aniline mixture was used directly in the succeeding degradation steps without any attempts at separation.

Sample Degradative Procedures. A. Phenol-x-^{14}C.-Aniline-x-^{14}C was converted to phenol-x-^{14}C by diazotization and addition of the cold diazonium salt solution to boiling 10 per cent surlfuric acid.[35] In a typical experiment, 4.2 g.(0.045 mole) of aniline-x-^{14}C, 0.38 moles of sulfuric acid and 3.1 g. (0.045 mole) of sodium nitrite yielded 3.4 g. (80 per cent) of yellowish phenol-x-^{14}C, b.p. 87.0-88.0° (22.0 mm.).

B. Cyclohexanol-x-^{14}C.- Phenol-x-^{14}C (3.4 g., 0.036 mole) in 30 ml. of 95 per cent ethanol was shaken with 0.7 g. of platinic oxide under an initial pressure of hydrogen of about 3 atm. at room temperature (28°). After 18 hours the theoretical amount of hydrogen had been consumed. Unlabeled cyclohexanol (2.00 g.) was added as a carrier, the catalyst removed by filtration and the ethanol distilled through Vigreux column No. 2 at 60 mm. The crude residual cyclohexanol amounted to 5.3 g. (92 per cent) and was used directly in the succeeding experiments.

__C__. __Cyclohexanone-x-^{14}C__. - A cold solution of potassium dichromate (10.7 g., 0.036 mole) and concentrated sulfuric acid (9.4 g.) in 53 ml. of water was added to 5.29 g. (0.053 mole) of cyclohexanone-x-^{14}C. The mixture was swirled vigorously and occasionally immersed in an ice bath to keep the temperature below 50°. When the exothermic reaction appeared to be complete, the mixture was allowed to stand at room temperature for an hour and then steam distilled until 250 ml. of distillate was collected. The distillate was saturated with sodium chloride and continuously extracted with ether overnight. The ethereal solution was dried over magnesium sulfate; the ether was removed through packed column No. 1. The residual crude cyclohexanone-x-^{14}C weighed 3.5 g. (68 per cent) and was not further purified. For isotopic assay some of the material was converted to the semicarbazone. The semicarbazone had m.p. 166.5-167.2° (lit.,[36] 166-167°) after two recrystallizations from 75 per cent ether - 25 per cent methanol.

__D__. __6-Aminohexanoic-x-^{14}C Acid__.- Cyclohexanone-x-^{14}C was converted to 6-aminohexanoic acid hydrochloride by the procedure of Loftfield.[37] From 2.25 g. (0.023 mole) of cyclohexanone-x-^{14}C and 7.4 g. (0.113 mole) of sodium azide was obtained, after recrystallization from absolute ethanol, 3.05 g. of 6-aminohexanoic-x-^{14}C acid hydrochloride (82 per cent).

E. 1,5-Diaminopentane-x-^{14}C. - 6-Aminohexanoic-x-^{14}C acid hydrochloride was converted to 1,5-diaminopentane-x-^{14}C and carbon dioxide-^{14}C (isolated as barium carbonate) by a Schmidt reaction essentially as described previously.[37] A description of a typical moderate-scale experiment follows. 6-Aminohexanoic-x-^{14}C acid hydrochloride (3.75 g., 0.0223 mole) was mixed with 7.5 ml. of concentrated sulfuric acid and the resulting hydrogen chloride removed by heating to 70° under reduced pressure. The system was filled with carbon dioxide-free nitrogen and 55 ml. of a 1.69 M (0.093 mole) solution of hydrazoic acid in sulfuric acid-washed chloroform was added over 40 minutes. The reaction was allowed to proceed at 45° for 15 hours; the evolved carbon dioxide was bubbled through a 5 per cent solution of potassium permanganate in 1 N sulfuric acid and precipitated in a 0.5 N barium hydroxide solution. After the reaction was complete, the system was swept with carbon dioxide-free nitrogen for 45 minutes. The bubblers containing the barium carbonate precipitate were transferred to a dry box containing carbon dioxide-free nitrogen and the barium carbonate collected by filtration. The precipitate was washed with 900 ml. of boiled distilled water and 300 ml. of acetone. After drying for 15 hours at 110° under reduced pressure, the sample weighed 3.7 g. (84 per cent). The carbon dioxide isolated by this procedure was uncontaminated by atmospheric carbon dioxide (see Table I, p. 8).

A small proportion of the residual sulfuric acid solution from the Schmidt reaction was basified and shaken with excess benzoyl chloride. The resulting 1,5-diaminopentane-x-^{14}C dibenzamide was recrystallized three times from benzene-ethyl acetate and dried at 78° under reduced pressure for 10 hours. The m.p. of the sample used for ^{14}C-analysis was 133.4-133.8° (lit.,[37] 135°). The same m.p. was obtained after an additional recrystallization.

<u>F.</u> <u>Glutaric-x-^{14}C Acid</u>.-The balance of the sulfuric acid solution from the Schmidt reaction described above was brought to pH 8 with 1 <u>N</u> sodium hydroxide solution and then mixed with a solution of 16 g. (0.10 mole) of potassium permanganate in 320 ml. of water. The mixture was refluxed for 30 minutes, at the end of which time a faint permanganate color remained but the odor of 1,5-diaminopentane was absent. Unlabeled glutaric acid (0.80 g.) was added to the reaction mixture as a carrier; the manganese dioxide was removed by filtration and washed with 250 ml. of hot distilled water. The filtrate was acidified with concentrated hydrochloric acid and continuously extracted with ether overnight. The ethereal extract was concentrated and extracted with five 10-ml. portions of 20 per cent sodium hydroxide solution. The alkaline extracts were combined and an additional 0.4 g. of unlabeled glutaric acid was added to the solution which was then acidified with concentrated hydrochloric acid and continuously extracted with ether overnight. The ether was removed and the residue recrystallized from benzene and dried in a vacuum desiccator. The yield of glutaric acid was 0.530 g., m.p. 90.1-92.0°. Part of the final product (0.13 g.) was converted to the di-<u>p</u>-bromophenacyl ester for ^{14}C-analysis. The yield of twice-recrystallized (95 per cent ethanol) di-<u>p</u>-bromophenacyl glutarate-x-^{14}C was 0.074 g., m.p. 136.2-136.7° (lit.,[36(b)] 136.8°).

The ^{14}C-analysis of the diester indicated that the yield in the permanganate oxidation of 1,5-diaminopentane was about 10 per cent.

G. 1,3-Diaminopropane-x-^{14}C. - Glutaric-x-^{14}C acid (0.40 g., 0.003 mole) was mixed with 2.4 g. of sulfuric acid and treated with 0.011 mole of hydrazoic acid in chloroform, essentially as described above for the preparation of 1,5-diaminopentane. The reaction was allowed to proceed for 12 hours at room temperature and then for 1 hour at 45°. The resulting radioactive barium carbonate was slightly tan and was regenerated in two portions with 3 M perchloric acid in a carbon dioxide-free system and isolated as before. The yield of barium carbonate (white) was 85 per cent. The 1,3-diaminopropane in the residual sulfuric acid solution was isolated as the dibenzamide derivative. The yield of dibenzamide was 0.687 g. (80 per cent); the m.p. was 146.5-147.0° after crystallization from benzene. The ^{14}C-sample was recrystallized twice from cyclohexane-ethyl acetate and had m.p. 150.0-150.5° (lit.,[39] m.p. 147°).

Deuterium Studies.

Starting Materials. A. Chlorobenzene-2-d. The Grignard reagent from 138 g. (0.58 mole) of o-chloroiodobenzene and 14.0g.(0.58 g.-atom) of magnesium turnings in 500 ml. of anhydrous diethyl ether was decomposed with 60 g. (1 mole) of deuteroacetic acid obtained by hydrolysis of redistilled acetic anhydride with the calculated amount of deuterium oxide. Water was added to dissolve the magnesium salts and the ethereal layer separated. The ethereal solution was washed with sodium hydroxide to remove the excess acetic acid, dried over magnesium sulfate and distilled. Together with some impure material there was obtained, after two distillations, 31.6 g. (50 per cent) of chlorobenzene-2-d, b.p. 129.7-130.4° (742 mm.), $\underline{n}_{\underline{D}}^{25}$ 1.5210.

B. Bromobenzene-2-d. - Toluene-2-d was prepared by decomposition of the Grignard reagent from 2-bromotoluene with deuteroacetic acid as described for the preceding preparation. In an 0.8 mole run, the yield of toluene-2-d was 58.0 g. (79 per cent), b.p. 108.5-109.5° (745 mm.).

A mixture of 65 g. (0.70 mole) of toluene-2-d, 255 g. (1.61 mole) of potassium permanganate, 15 ml. of 10 per cent aqueous sodium hydroxide and 3060 ml. of water was stirred vigorously and gradually heated to the reflux temperature. After 11 hours, all of the permanganate and toluene appeared to be completely reacted. The mixture was filtered hot and the manganese dioxide washed with several portions of hot water. The filtrate was concentrated to 1500 ml. and decolorized with charcoal. The solution was slowly acidified with concentrated hydrochloric acid and the resulting precipitate of benzoic acid filtered with suction and dried. The crude acid was converted to silver benzoate-2-d as described previously.[40] The silver benzoate-2-d was dried at 100° under reduced pressure for several hours. The yield of dried salt was 135.9 g. (85.5 per cent based on toluene-2-d).

Bromobenzene-2-d (78 g., b.p. 152.5-154.0°, 50 per cent) was obtained from the reaction of 233 g. of silver benzoate-2-d and 162 g.

of bromine in dried carbon tetrachloride essentially as described previously.[40b] The crude bromobenzene-2-d was washed with saturated sodium bisulfite solution in order to remove the contaminant, bromine. The product was dried over calcium chloride and distilled through packed column No. 1 to yield 71 g. of bromobenzene-2-d, b.p. 154.0°, n_D^{25} 1.5567.

Halobenzenes-2-d with Potassium Amide in Liquid Ammonia.

A. Amination of Chlorobenzene-2-d.- The apparatus used for these experiments was similar to that employed by Schlatter.[41] for the sodium amide-induced cyclization of γ-chlorobutyronitrile. The general procedure will be illustrated by a typical experiment using chlorobenzene-2-d. A mixture (0.149 moles, 16.81 g.) containing 26.5 mole per cent of chlorobenzene-2-d and 73.6 mole per cent of chlorobenzene-2-h was stirred with approximately 150 ml. of anhydrous liquid ammonia in a 500-ml. flask (A) until solution was complete (about 10 minutes). A mixture of potassium amide (0.21 mole, from 8.4 g. of potassium metal) and 200 ml. of anhydrous ammonia in a 500-ml. flask (B) was cooled to about -50° and was then forced into flask A under dry air pressure as rapidly as was permitted by the boiling of the ammoniacal chlorobenzene solution. The addition time was about 1.5 minutes; 3.5 minutes after the addition was complete flask A was cooled in a Dry Ice bath, and 30 seconds later 50 g. (0.5 mole) of powdered ammonium nitrate was added as rapidly as possible. Anhydrous ether (150 ml.) was added to the reaction mixture and the ammonia allowed to evaporate. The residue was treated with 150 ml. of water, the contents of the flask transferred quantitatively to a separatory funnel and the aqueous layer removed.

The ethereal layer was washed several times with water and the washings were added to the original aqueous layer. The aqueous solution was boiled to remove ether and excess ammonia, then quantitatively diluted to 500 ml. and triplicate analyses made for chloride ion by the Volhard method.[42] In all cases the values obtained in the determinations of halide ions were precise to better than 2 parts/1000.

The ethereal extract containing the organic reaction products was shaken with a total of 500 ml. of 3 M hydrochloric acid to remove amines and then washed with water. The ether solution was dried over magnesium sulfate, the ether removed and the residue fractionated through Vigreux column No. 2. The recovered chlorobenzene amounted to 5.3 g., b.p. 129.5-130.1°, n_D^{25} 1.5208-1.5210. The chlorobenzene was analyzed for chlorobenzene-2-d using a Perkin-Elmer (Model 21) Infrared Spectrophotometer at 10.090 μ and 10.520 μ. The analyses were made by the "base-line" procedure[43] using 0.025 mm. cells. Calibration graphs were constructed from the absorptions of five known mixtures at each wavelength; these plots were linear. The analyses at the two wavelengths agreed to 0.3 per cent or better. The experimental data are summarized in Tables VI and VII.

B. Bromobenzene-2-d.-The procedure was as described above for chlorobenzene-2-d. Triplicate analyses were made for bromide ion by the Volhard method.[42] The infrared analyses were done at 8.865 μ and 10.110 μ. The experimental data are summarized in Tables VIII and IX.

TABLE VI

Infrared Analyses of Standard Mixtures of Chlorobenzene-2-d and Chlorobenzene-2-h.

Mole per cent chlorobenzene-2-d[a]	Wavelength, μ[b]	I_B[c]	I[d]	$\log_{10} I_B/I$
100.00	10.090	77.0	31.0	0.3952
	10.520	82.0	52.0	0.1979
66.02	10.090	76.0	42.0	0.2577
	10.520	80.5	60.0	0.1277
48.67	10.090	76.0	49.0	0.1906
	10.520	81.0	65.5	0.0923
47.08	10.090	76.5	50.25	0.1824
	10.520	81.5	66.0	0.0916
25.57	10.090	76.0	60.5	0.0990
	10.520	80.5	73.0	0.0425

[a] Mixtures made up by weight.

[b] Wavelength at which absorption maximum occurs.

[c] Intensity of base-line absorption measured as per cent transmission; see Ref. 43.

[d] Intensity of sample absorption measured as per cent transmission; see Ref. 43.

TABLE VII

Infrared Analyses of Mixtures of Chlorobenzene-2-d and Chlorobenzene-2-h Recovered from Aminations in Liquid Ammonia.

Run	Wavelength, μ [b]	I_B [c]	I [d]	$\mathrm{Log}_{10}\ I_B/I$	Mole per cent chlorobenzene-2-d [a]
1	10.090	76.0	57.0	0.1249	32.34
	10.520	80.5	70.5	0.0577	32.03
2	10.092	76.0	57.5	0.1212	31.41
	10.528	80.5	70.75	0.0561	31.26
3	10.090	76.0	34.5	0.3430	87.11
	10.520	80.5	54.25	0.1715	86.97

[a] Calculated from the $\log_{10} I_B/I$ values in the preceding column and the data in Table VI.

[b,c,d] See corresponding footnotes for Table VI.

TABLE VIII

Infrared Analyses of Standard Mixtures of Bromobenzene-2-d and Bromobenzene-2-h.

Mole per cent bromobenzene-2-d[a]	Wavelength, μ[b]	I_B[c]	I[d]	$\text{Log}_{10}\ I_B/I$
100.00	8.863	81.5	41.5	0.2932
	10.111	73.5	15.5	0.6760
49.88	8.866	84.0	50.5	0.1498
	10.113	69.0	27.5	0.3994
33.46	8.865	85.0	67.0	0.1035
	10.110	67.0	32.5	0.3143
27.26	8.865	85.0	69.75	0.0859
	10.109	67.0	35.0	0.2819
24.85	8.866	85.0	71.0	0.0781
	10.110	66.5	36.0	0.2664

[a,b,c,d] See corresponding footnotes for Table VI.

TABLE IX

Infrared Analyses of Mixtures of Bromobenzene-2-d and Bromobenzene-2-h Recovered from Aminations in Liquid Ammonia.

Run	Wavelength, μ [b]	I_B [c]	I [d]	$\log_{10} I_B/I$	Mole per cent bromobenzene-2-d [a]
1	8.866	81.5	62.5	0.1152	37.7
	10.110	67.0	31.0	0.3347	37.7
2	8.865	85.0	66.75	0.1048	34.2
	10.110	67.5	32.75	0.3145	34.2

[a] Calculated from the $\log_{10} I_B/I$ values in the preceding column and the data in Table VIII.

[b,c,d] See corresponding footnotes for Table VI.

Halobenzenes-2-d with Lithium Diethylamide in Ether. -

A. Chlorobenzene-2-d. - A solution of phenyllithium was prepared from 18 g. (0.115 mole) of bromobenzene, 1.81 g. (0.26 g.-atom) of lithium metal and 150 ml. of ether. After the reaction was complete, the small excess of lithium metal was removed with a spatula, and a solution of 10.7 g. (0.146 mole) of purified diethylamine in 50 ml. of anhydrous ether was added dropwise over a period of an hour. The mixture was allowed to stir for an additional hour at room temperature. A mixture (10.04 g., 0.0889 mole) containing 47.1 mole per cent of chlorobenzene-2-d and 52.9 mole per cent of purified chlorobenzene-2-h was added in one portion. The reaction mixture was stirred for 14.3 hours at room temperature. Water (100 ml.) was added, the mixture stirred for 15 minutes and the aqueous and ethereal layers separated. The ethereal layer was extracted with sodium carbonate solution since lithium chloride is somewhat soluble in ether whereas lithium carbonate is completely insoluble in ether. The sodium carbonate extract and the original aqueous layer were combined, boiled to remove diethylamine, taken to pH 7 with sulfuric acid and then diluted to 250 ml. in a volumetric flask. The bromide ion (from the bromobenzene used in the preparation of phenyllithium) was quantitatively removed as described by Swift[44] and triplicate analyses were made for chloride ion by the Volhard method.[42] The ethereal extract of the reaction mixture, upon treatment as described in the previous experiment, yielded 2.1 g. of unreacted chlorobenzene, b.p. 129.0-130.0°, n_D^{25} 1.5208. The chlorobenzene was analyzed for chlorobenzene-2-d by the infrared method. The data for this and similar experiments are given in Tables VI and X.

TABLE X

Infrared Analyses of Mixtures of Chlorobenzene-2-d and Chlorobenzene-2-h Recovered from Aminations in Diethyl Ether.

Run	Wavelength, μ [b]	I_B [c]	I [d]	$\text{Log}_{10}\ I_B/I$	Mole per cent chlorobenzene-2-d [a]
1	10.090	76.5	46.75	0.2138	54.66
	10.520	81.0	63.6	0.1052	54.96
2	10.090	76.5	51.5	0.1718	44.12
	10.528	80.5	66.5	0.0828	44.15

[a,b,c,d] See corresponding footnotes for Table VII.

TABLE XI

Infrared Analyses of Mixtures of Bromobenzene-2-d and Bromobenzene-2-h Recovered from Aminations in Diethyl Ether.

Run	Wavelength, μ [b]	I_B [c]	I [d]	$\text{Log}_{10}\ I_B/I$	Mole per cent bromobenzene-2-d [a]
1	8.865	83.25	65.75	0.1025	33.10
	10.110	67.0	32.75	0.3109	33.30
2	8.866	85.0	68.2	0.0955	30.80
	10.110	68.0	34.5	0.2947	30.40

[a,b,c,d] See corresponding footnotes for Table VII.

B. Bromobenzene-2-d.- The reactions with bromobenzene-2-d were carried out similarly except that iodobenzene was used for the preparation of phenyllithium and, for determination of the per cent of reaction, the iodide in the aqueous extract was removed by oxidation with nitrous acid and extraction with carbon tetrachloride. Triplicate analyses were then made for bromide ion by the Volhard method.[42] The experimental results are summarized in Tables VII and XI.

Calculations of Deuterium Isotope Effects. - Kinetic hydrogen isotope effects (conveniently expressed as k_H/k_D) were computed from the relative reactivities of halobenzenes-2-d and the corresponding undeuterated halobenzenes toward amide ion in ammonia or ether on the basis of the concerted dehydrohalogenation mechanism (Equation 1, p.13). In the formulation of appropriate kinetic expressions the following assumptions were made: all of the reactions are constant volume processes; the reactions are first order with respect to halobenzene; only hydrogens or deuteriums *ortho* to the halogens are involved in the overall amination reactions; and the reaction of benzyne to give products is not rate-determining or reversible. The rates of disappearance of chlorobenzene-2-d (D) and chlorobenzene-2-h (H) are then

$$(3) \qquad \frac{-d[D]}{dt} = [k_D + k_H]\,[D]\,[NR_2'^{\ominus}]^n$$

and

$$(4) \qquad \frac{-d[H]}{dt} = 2k_H[H]\,[NR_2'^{\ominus}]^n$$

where n is unknown but likely to be unity.* Dividing the first of these

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* It is assumed that the anilide ions formed in the reaction are insufficiently reactive to compete effectively with amide ions in a rate-determining process, since potassium anilide does not react with chlorobenzene in liquid ammonia at -33°.[3]

expressions (3) by the second (4), rearranging and integrating leads to the following expression for k_H/k_D.

$$(5) \qquad \frac{k_H}{k_D} = \cfrac{1}{2\,\cfrac{\ln\frac{[D]_t}{[D]_o}}{\ln\frac{[H]_t}{[H]_o}}} .$$

Calculated values for k_H/k_D obtained through the use of Equation (5) are given in Table II, pp. 16-17.

When the elimination reaction is stepwise (Equation 2, p. 13) with k_{-1} comparable in magnitude of k_2 (as for chlorobenzene in liquid ammonia), the values of k_H/k_D are small or even negative (Table II) because the chlorobenzene-2-*d* is converted to ordinary chlorobenzene. If k'_H/k'_D is taken to have the value obtained for k_H/k_D (5.7) from experiments in ether, where exchange is not important, then k_{-1}/k_2 can be computed with the aid of the assumption (in addition to those listed above) that the steady state approximation may be applied to the concentration of the intermediate anion. The rate of disappearance of chlorobenzene-2-*d* is expressed by

$$(6) \qquad \frac{-d[D]}{dt} = (k'_H + k'_D)\ [D]\ [NH_2^{\ominus}] - k_{-1}\ [\text{Anion XVIII}].$$

Application of the steady state approximation gives for the concentration of anion XVIII

$$(7) \qquad [\text{Anion XVIII}] = \frac{k'_H[D]\ [NH_2^{\ominus}]}{k_{-1} + k_2} .$$

Substituting (7) into (6) gives

$$(8) \qquad \frac{-d[D]}{dt} = (k'_H + k'_D)\ [D]\ [NH_2^{\ominus}] - \frac{k_{-1}\,k'_H}{k_{-1} + k_2}\ [D]\ [NH_2^{\ominus}] .$$

Similarly, expression (9) is obtained for the rate of disappearance of chlorobenzene-2-*h*.

$$(9)\qquad \frac{-d[H]}{dt} = 2k'_H\,[H]\,[NH_2^{\ominus}] - \frac{k_{-1}}{k_{-1}+k_2}\left(2k'_H[H][NH_2^{\ominus}] + k'_D[D][NH_2^{\ominus}]\right).$$

Let $k_{-1}/(k_{-1}+k_2) = F$ (fraction of intermediate anion returning to starting material) and $k'_H/k'_D = i$, then

$$(10)\qquad \frac{d[D]}{d[H]} = \frac{(i(1-F)+1)[D]}{2i(1-F)[H] - F[D]}\quad .$$

Division of (10) by [D] and treatment of $i(1-F)+1$, $2i(1-F)$ and $-F$ as constants, gives on integration

$$(11)\qquad \ln|D|\,\Bigg]_{[D]_0}^{[D]_t} + \frac{1+i-iF}{1-i+iF}\,\ln\left[(-1+i-iF)\frac{[H]}{[D]} - F\right]\Bigg]_{\frac{[H]_0}{[D]_0}}^{\frac{[H]_t}{[D]_t}} = 0\ .$$

Values of F, and hence k_{-1}/k_2, were obtained from (11).

Orientations in Aminations of Substituted Halobenzenes.

A. Amination of *p*-Bromofluorobenzene. - The amination procedure was as previously described for iodobenzene-1-^{14}C (p.38). *p*-Bromofluorobenzene (32.0 g., 0.183 mole) and a solution of potassium amide prepared from 16.2 g. (0.36 g.-atom) of potassium and 250 ml. of liquid ammonia yielded, upon distillation through Holzman column No.3, 6.21 g. (30.5 per cent) of a mixture of *m*- and *p*-fluoroanilines (5 fractions), b.p. 77.0-87.5° (20.5 mm.), n_D^{25} 1.5378-1.5386. The experimental data are summarized in Tables XII and XIII.

TABLE XII

Infrared Analyses of Standard Mixtures of *m*-[e] and *p*-Fluoroanilines[f].

Mole per cent *m*-fluoroaniline[a]	Mole per cent *p*-fluoroaniline[a]	Wavelength, μ [b]	I_B [c]	I [d]	$\mathrm{Log}_{10}\ I_B/I$
100.0	0.0	9.987	57.0	8.5	0.8265
74.8	25.2	9.987 5.374	59.5 79.2	13.5 74.5	0.6442 0.0265
50.4	49.6	9.987 5.374	55.0 79.5	19.0 67.75	0.4617 0.0693
29.0	71.0	9.987 5.374	58.0 79.5	31.0 62.5	0.2720 0.1045
0.0	100.0	5.374	80.3	56.0	0.1565

[a,b,c,d] See corresponding footnotes for Table VI, p. 47.

[e] Analysis at 9.987 μ.

[f] Analysis at 5.374 μ.

TABLE XIII

Infrared Analyses of the Mixture of *m*- and *p*-Fluoroanilines Obtained from the Amination of *p*-Bromofluorobenzene[a].

Wavelength, μ [b]	I_B [c]	I [d]	$\text{Log}_{10}\ I_B/I$	Weight of fraction, g.	Mole per cent *m*-fluoroaniline	Mole per cent *p*-fluoroaniline
9.987	60.2	37.0	0.2113	0.360	19.3	
5.374	80.1	60.5	0.1219			80.5
9.987	59.4	36.5	0.2113	0.719	19.3	
5.374	79.9	60.0	0.1245			81.6
9.987	60.3	37.0	0.2122	1.785	19.3	
5.374	79.9	60.0	0.1245			81.6
9.987	58.5	36.0	0.2108	2.712	19.2	
5.374	80.3	60.5	0.1229			80.8
9.987	58.8	36.0	0.2130	0.633	19.4	
5.374	80.2	60.5	0.1225			80.8

[a] The infrared bands characteristic of *o*-fluoroaniline at 5.67μ and 9.75μ were not present in the infrared spectra of any fractions of the product mixture.

[b,c,d] See corresponding footnotes for Table VI, p. 47.

p-Fluoroaniline. - *p*-Nitroaniline (31.9 g., 0.231 mole) was converted to *p*-nitrobenzenediazonium fluoroborate (51.9 g., 0.224 mole) by the procedure previously described.[44a] The fluoborate was pyrolyzed (in 15 g. portions), diluted with about 2.5 times its volume of barium sulfate, by the procedure previously described for the *meta* isomer;[44b] 15 g. (47 per cent) of *p*-fluoronitrobenzene was obtained; b.p. 91.3-93.0° (18.5 mm.), n_D^{25} 1.5295. The Raney nickel-catalyzed reduction of *p*-fluoronitrobenzene (15.0 g., 0.106 mole) in 150 ml. of absolute ethanol at an initial hydrogen pressure of 2 atm. produced *p*-fluoroaniline in 92 per cent yield. The material used for the infrared analyses was distilled through Vigreux column No. 2, b.p. 85.5° (20.6 mm.), n_D^{25} 1.5376.

m-Fluoroaniline. - The procedure was as described for the *p*-isomer; *m*-fluoroaniline of b.p. 86.5° (21.0 mm.) and n_D^{25} 1.5421 was obtained.

o-Fluoroaniline. - The procedure was as described for the *p*-isomer. *o*-Fluoroaniline of b.p. 70.1° (22.0 mm.) and n_D^{25} 1.5400 was obtained.

B. Amination of p-Bromoanisole. - The amination procedure was as previously described (p.38). *p*-Bromoanisole (30.0 g., 0.16 mole), 25.0 g. (0.64 g.-atom) of potassium and 300 ml. of ammonia gave, after distillation through Holzman column No, 3, 6.12 g. (31 per cent) of a mixture of *m*- and *p*-anisidines, b.p. 125.0-127.5° (15.4 mm.). The infrared results are summarized in Tables XIV and XV.

TABLE XIV

Infrared Analyses of Standard Mixtures of m-[g] and p-[h]Anisidines in Benzene Solution.

Mole per cent m-anisidine[a,e]	Mole per cent p-anisidine[a,f]	Wavelength, μ [b]	I_B[c]	I[d]	$\log_{10} I_B/I$
0.9303	0.0000	8.255	85.8	44.0	0.2900
0.6103	0.2418	8.255	87.1	56.0	0.1917
		8.021	85.9	61.0	0.1485
0.4249	0.4263	8.255	87.1	64.75	0.1287
		8.021	85.9	46.0	0.2711
0.2917	0.5254	8.255	86.2	71.5	0.0813
		8.021	85.3	39.75	0.3316
0.0000	0.7405	8.021	85.6	29.25	0.4663

[a,b,c,d] See corresponding footnotes for Table VI, p. 47.

[e] m-Anisidine was prepared by the platinum-catalyzed hydrogenation of m-nitroanisole in 95 per cent ethanol. The m-anisidine was distilled through Holzman column No. 3, b.p. 129.0° (15.4 mm.), n_D^{25} 1.5784.

[f] p-Anisidine was distilled through Holzman column No. 3, b.p. 123.0-123.3° (59.5-60.0 mm.).

[g] Analysis at 8.255μ .

[h] Analysis at 8.021μ .

TABLE XV

Infrared Analyses (of Benzene Solutions) of the Mixture of m- and p-Anisidines Obtained from the Amination of p-Bromoanisole[a].

Wavelength, μ[b]	I_B[c]	I[d]	$\text{Log}_{10}\ I_B/I$	Mole per cent m-anisidine	Mole per cent p-anisidine
8.255	85.8	64.25	0.1254	0.416	
8.021	85.4	45.00	0.2784		0.436

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[a] The infrared bands characteristic of o-anisidine at 7.83, 8.16, 8.76 and 11.04 μ were absent from the spectrum of the product mixture.

[b,c,d] See corresponding footnotes for Table VI, p. 47.

C. Aminations of o-, m- and p-Chlorotoluenes and m-Bromotoluene.- The usual amination procedure was employed (p.38). A four-fold excess of potassium amide was used in each case. The products were distilled through Holzman column No. 3. o-Chlorotoluene gave a 66 per cent yield of a mixture of o- and m-toluidines, b.p. 96.0-100.0° (21.4 mm.). m-Chlorotoluene gave a 66 per cent yield of a mixture of o-, m- and p-toluidines, b.p. 95.0-99.2° (23.7 mm.). p-Chlorotoluene gave a 35 per cent yield of a mixture of m- and p-toluidines, b.p. 96.5-99.2° (21.4 mm.). m-Bromotoluene gave a 61 per cent yield of a mixture of o-, m- and p-toluidines, b.p. 90.0-93.1° (16.9 mm.). The experimental data are summarized in Tables XVI and XVII.

TABLE XVI

Infrared Analyses of Standard Mixtures of o-[g], m-[h] and p-Toluidines in Carbon Disulfide Solution.

Wt. per cent o-toluidine[a,e]	Wt. per cent m-toluidine[a,f]	Wt. per cent p-toluidine[a]	Wavelength, μ [b]	I_B [c]	I[d]	$\mathrm{Log}_{10}\ I_B/I$
15.671	0.000	0.000	14.05	35.0	13.5	0.4136
9.970	5.154	1.814	14.05 14.54	34.3 33.2	18.2 12.9	0.2747 0.4106
5.126	6.665	0.000	14.05 14.54	46.2 43.9	32.9 12.0	0.1473 0.5633
0.000	8.483	3.006	14.54	44.7	9.3	0.6818
0.000	9.326	0.000	14.54	53.5	9.5	0.7507

[a,b,c,d] See corresponding footnotes for Table VI, p. 47.

[e] The o-toluidine was distilled through Holzman column No. 3, b.p. 96.7-96.8°(23.5 mm.), n_D^{25} 1.5702.

[f] The m-toluidine was distilled through Holzman column No. 3, b.p. 100.6-100.7°(24.4 mm.), n_D^{25} 1.5661.

[g] Analysis at 14.05 μ.

[h] Analysis at 14.54 μ.

TABLE XVII

Infrared Analyses of Mixtures of *o*-, *m*- and *p*-Toluidines Obtained from the Aminations of Halotoluenes[h].

Starting halotoluene[a]	Wavelength, μ[b]	I_B[c]	I[d]	$\log_{10} I_B/I$	Wt. % toluidines ortho	Wt. % toluidines meta	Wt. % toluidines para
o-Chloro-	14.05	44.9	31.3	0.1565	5.75		
toluene	14.54	43.3	12.0	0.5573		6.96	
							0.00[e]
m-Chloro-	14.05	36.5	24.7	0.1697	6.26		
toluene	14.54	34.0	7.3	0.6682		8.27	
							1.210[f]
p-Chloro-	14.53	47.2	13.7	0.5372		6.73	
toluene							4.10[f]
					0.00[g]		
m-Bromo-	14.05	37.3	30.3	0.0902	3.40		
toluene	14.54	34.4	6.5	0.7237		8.78	
							3.55[f]

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[a] The infrared spectrum of each halotoluene indicated that it was free from contamination by its isomers.

[b,c,d] See corresponding footnotes for Table VI, p. 47.

[e] The infrared bands characteristic of *p*-toluidine at 8.89μ and 12.34μ were absent from the spectrum of the product mixture.

[f] Calculated from the total weight of toluidines in the solutions and the weight per cent results obtained by the infrared method for the *o*- and *m*-toluidines.

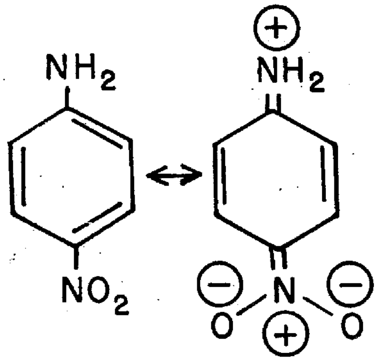
[g] The infrared bands characteristic of *o*-toluidine at 13.35μ and 14.05μ were absent from the spectrum of the product mixture.

[h] The infrared analyses were done on carbon disulfide solutions of the toluidines.

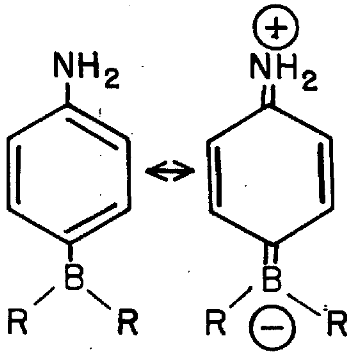
PART II. QUANTUM MECHANICAL CALCULATIONS OF ELECTRICAL EFFECTS OF SUBSTITUENTS IN *PARA*-SUBSTITUTED ANILINES.

QUANTUM MECHANICAL CALCULATIONS OF ELECTRICAL EFFECTS OF SUBSTITUENTS IN PARA-SUBSTITUTED ANILINES

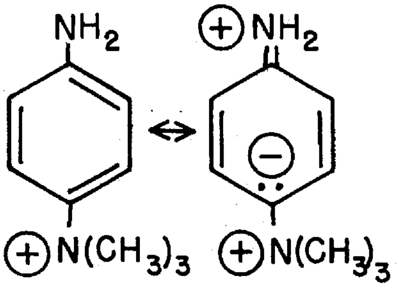
Base strength measurements with substituted anilines indicate direct conjugation between the amino groups and electron-attracting unsaturated substituent groups such as $-NO_2$, $-C\equiv N$, etc. (I). Such conjugation delocalizes the unshared electron-pair of nitrogen and confers a formal (+) charge on the amino group. Somewhat analogous behavior might be anticipated for substituents which do not carry multiple bonds but which, like tercovalent boron, could accept an electron-pair or, like a positively charged trimethylammonium group, could stabilize an adjacent negatively charged center as in the "ylides". Resonance forms may be written which symbolize each of these situations (I-III).



I



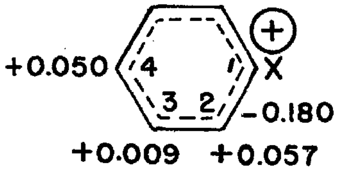
II



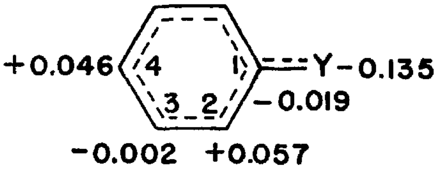
III

In order to determine whether the extent of delocalization of the unshared pair of electrons on nitrogen in para-substituted anilines is, at least theoretically, dependent on the character of the substituent, calculations were made by the simple molecular orbital method[1] of the charges on the amino nitrogen in such compounds where the para-substituent is: (1) $X^{\oplus}$ bearing a unit positive charge (analogous to $-N(CH_3)_3^{\oplus}$); (2) $-Y$ carrying an empty p-orbital (analogous to $-BR_2$); and (3) $-\overset{|}{C}=Z$ where Z (analogous to oxygen) is more electronegative than carbon and the polarization of the $-\overset{|}{C}=Z$ p-π-bond results in an incompletely filled p-orbital on carbon. The substituent $-X^{\oplus}$ is regarded as being formally unable to "conjugate" with a para-amino group, whereas $-Y$ and $-\overset{|}{C}=Z$ are both able to take part in such conjugation. $-Y$ and $-\overset{|}{C}=Z$ differ from each other only in the degree of unsaturation of the p-orbitals (on Y and C respectively) and in the electron affinities of Y and Z.

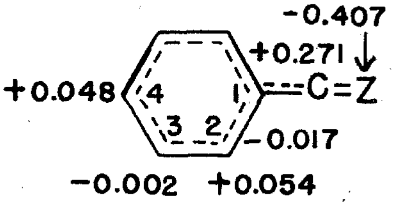
The condition was imposed that systems IV, V and VI have the same charges (e.g., +0.05 e.) at C_2, C_4 and C_6 before introduction of a para-amino group, so that the only important variable in the para-substituted anilines is the electron-accepting power of the substituent.



IV



V



VII

This was achieved by assigning appropriate coulomb integrals, $\alpha + \delta\beta$, to atoms having electron affinities different from a "normal" carbon atom with coulomb integral α --- $\delta > 0$ for larger and $\delta < 0$ for smaller electron affinities than a "normal" carbon atom. The δ values used for atoms adjacent to the source of polarization[2] (i.e., C_2 and C_6 in IV, C_1 in V and C_7 in VI) were one-tenth the δ values for the atom at the source (*i.e.*, C_1 in IV, Y in V and Z in VI); coulomb integrals for which δ was less than 0.05 were set equal to α. Resonance integrals between non-adjacent atoms were neglected and, in general, those between adjacent atoms were assigned a value of β. Coulson[3] has stated that the deviation from β of resonance integrals involving hetero-atoms is small and can be shown[3,4] to exert only a second-order effect on charge distribution. Since the orbitals of the central atom of the $-X^{\oplus}$ group in IV (like N in $-N(CH_3)_3^{\oplus}$) are used in four *sp*^{3} bonds, the π-electron resonance integral for the $C_1-X^{\oplus}$ bond was assumed to be zero. Thus, the only electrical effect considered for $-X^{\oplus}$ was inductive generation of a positive charge on C_1, increasing the electron affinity of that atom and to lesser extent the electron affinities of C_2 and C_6. The values of the parameters used are summarized in Table I. The resulting charge distributions in the *para*-amino derivatives are shown in VII, VIII and IX.

TABLE I

Coulomb Integrals Used in Calculations

System	Coulomb Integral
IV and VII	$C_1 = \alpha + 0.50\beta$ $C_2 = C_6 = \alpha + 0.05\beta$
V and VIII	$Y = \alpha - 1.40\beta$ $C_1 = \alpha - 0.14\beta$
VI and IX	$Z = \alpha + 0.80\beta$ $C_7 = \alpha + 0.08\beta$
VII, VIII and IX	$N = \alpha + 2.00\beta$ [a] $C_4 = \alpha + 0.20\beta$
IV - IX	Carbon atoms not otherwise designated = α

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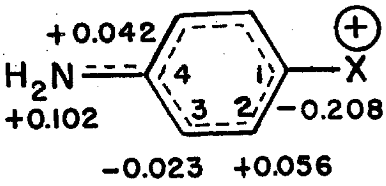
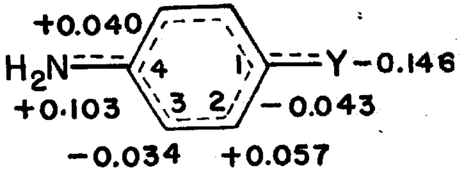
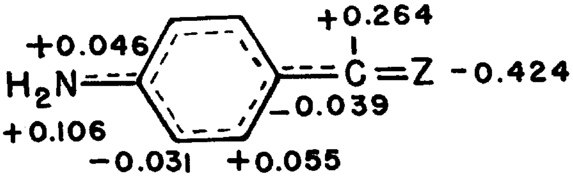
[a] The value chosen for the coulomb integral of nitrogen is not critical; the value of $\alpha + 2\beta$ is commonly used, although it is probably not the best value for nitrogen.[3]



VII



VIII



IX

The calculated charges on the amino nitrogens for VII-IX are essentially the same.* Thus, $-X^{\oplus}$, $-Y$ or $-\overset{|}{C}=Z$ are calculated to be equally effective in causing delocalization of para-amino electrons provided that C_4 initially has the same charge in each case. It is concluded, therefore, that so far as the LCAO method is concerned, the relative basicities of amino groups para to electron-attracting substituents provide a reasonable measure of the charge on C_4 as

---

* If the charges on C_2, C_4 and C_6 in the $-X^{\oplus}$ and $-\overset{|}{C}=Z$ systems are initially +0.15 e.. instead of 0.05 e., the calculated charges on a para-amino group are again practially equal (approximately +0.14 e.). A comparable calculation has not been made for the $-Y$ system, but there is no reason to expect that the result would be different.

postulated previously.[5] The failure of p-amino- and p-dimethylaminophenyltrimethylammonium salts to be weak bases relative to the corresponding m-isomers is thus regarded as strong experimental evidence against important preferential induction by the trimethylammonium group of charged centers in the 2- and 4-positions.[5b,≠]

[≠] A somewhat different interpretation has recently been expressed by C.K. Ingold; see Ref. 6.

APPENDIX I

DESCRIPTION OF FRACTIONATING COLUMNS

Column No. 1. - A 1.2 x 30 cm. glass helice (3.1 mm.) packed column with an electrically heated jacket and a total condensation, partial takeoff head.

Column No. 2. - A 1.0 x 23 cm. Vigreux column with an evacuated jacket and a total condensation, partial takeoff head.

Column No. 3. - A 0.8 x 26 cm. column[1] packed with a tantalum wire coil and carrying an evacuated jacket and a partial reflux head.

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APPENDIX I

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PROPOSITIONS

1. The cis-dinitrito-bis-(ethylenediamine)-cobalt (III) ion (red) has been reported to isomerize to the corresponding dinitro-ion (yellow).[1] It is proposed that: (1) x-ray studies should be performed to establish definitely this type of isomerism; (2) the reaction in the presence of isotopically labeled nitrite ion should be studied in order to elucidate the mechanism of the isomerization.

2. Coordination complexes of the type $[M\ N\text{-}(CH_2\ CH_2\ NH_2)_3]X_2$ where $M^{++} = Pt^{++}$, Pd^{++} or Ni^{++} and $X^- = SCN^-$ or I^- have been prepared.[2] The geometry of the "tetradendate" coordinating amine does not permit the usual square planar configurations (associated with dsp^2 orbital hybridization and a zero magnetic moment) for these complex cations. It is proposed that the magnetic moments, the fine structures of the K x-ray absorption edges and the structures (by x-ray examinations of the single crystals) be determined for these complexes. The corresponding complex for Cu^{++} should be prepared and its properties determined.

3. A dimeric structure, bis-(o-phenylene)-dimercury, has been suggested[3] for a compound with the empirical formula C_6H_4Hg. The monomeric structure, o-phenylenemercury, was eliminated by chemical studies. It is proposed that the trimeric structure, tris-(o-phenylene)-trimercury, is most favorable on the basis of the

C-Hg-C angle (180° for the trimer) and the Hg-Hg distance (3.8A for the trimer). A molecular weight determination is not feasible; however, an x-ray study on a single crystal should distinguish between the possibilities.

4. Lysergic acid and the hydrazide of *iso*-lysergic acid have been synthesized recently.[4] The acids differ by the configuration of the carboxyl group, but the specific configurations have not been established conclusively.[5,6] A means of accomplishing this by using stereospecific reactions is proposed.

5. It has been reported that when lysergic acid or *iso*-lysergic acid was heated in acetic anhydride the same -lactam was obtained.[7] A non-cyclic α, -unsaturated acid was suggested as the common intermediate for these reactions.[7] It is proposed that the kinetics of these reactions of the 8-protated and 8-deuterated acids be studied using a spectroscopic method; it should be possible to detect the intermediate and perhaps to trap it. Similar mechanisms may operate in the high-temperature decarboxylations of lysergic and *iso*-lysergic acids, the isomerization of lysergic to *iso*-lysergic acid in boiling water and the formation of some 3-methyl-2-piperidone from the Raney nickel catalyzed hydrogenation of ethyl nicotinate.[8] These possibilities should be investigated.

6. A synthesis of a 6,7-epoxytropanone is proposed. Synthesis of the physiologically active material scopolamine by a similar route may be possible.

7. It is proposed that a study of the Wolff-Kishner reduction of triphenylacetaldehyde should provide a means of distinguishing between the free radical and carbanion mechanisms suggested for the second step of the reductions.[9]

8. α-Lactones have been suggested as intermediates in certain reactions.[10] It is proposed to synthesize such a compound and to study its physical and chemical properties.

9. The unusual reactivity of aryl fluorides with lithium dialkyamides and phenyllithium in ether solution (this thesis, pp. 30, 34) suggests that the lithium ion may aid the departure of the fluoride ion. Such an effect would be of synthetic value. It is proposed that the relative rates of the reactions of aryl halides (*i.e.*, X = I, Br, Cl and F) with lithium diethylamide in ether be determined in an effort to elucidate the details of the mechanisms of the halide ion departures.

10. It is proposed that the auxin activity of α-deutero-2,4-dichlorophenoxyacetic acid should give information concerning the mechanism of the action of auxins. A synthesis of this compound is proposed.

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