1.3855, was used as solvent. Sodium iodide, reagent grade, was dried overnight at 105° before use. The nitrate esters, prepared by nitration of the bromohydrins, were kindly furnished by Dr. Boris Franzus.

Reaction Rate Studies.—The reactions were run and the rates calculated substantially as described by Young.[2c] No salt corrections[2c] were made, nor did any appear necessary. In runs below 90°, the solutions were prepared at the reaction temperature in volumetric flasks and run in ground-glass stoppered volumetric flasks. At higher temperatures sealed tubes were used; as well as in some runs at 88°. The principal advantage of the use of *n*-propyl alcohol over methyl alcohol resides in its lower volatility.

The order of the reactions may be noted from the constancy of the rate constants with variation of reagent concentration (Table I).

Reaction of Iodine with Solvents.—An acetone solution, 0.005 *M* in iodine and 0.21 *M* in sodium iodide, lost about 50% of its iodine in 70 hours at 62.4°. A solution (in 99% aq. methanol), 0.025 *M* in iodine and 0.265 *M* in sodium iodide lost less than 2% of its iodine in 200 hours at 62.4°. A solution (in *n*-propyl alcohol), 0.065 *M* in iodine and 0.26 *M* in sodium iodide, lost less than 1% of its iodine in 200 hours at 62.4°.

BOULDER, COLORADO

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY (NO. 2028) AND THE DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Mechanism of Aminations of Halobenzenes[1]

BY JOHN D. ROBERTS,[2a] DOROTHY A. SEMENOW,[2b] HOWARD E. SIMMONS, JR., AND L. A. CARLSMITH

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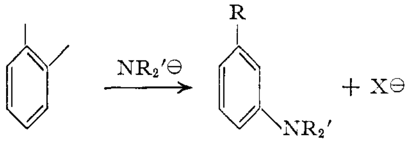
An elimination–addition mechanism, probably involving a "benzyne" intermediate, has been established for the rearrangements which often occur in the conversion of non-activated aryl halides to arylamines with metallic amides. The evidence for the "benzyne" intermediate was obtained through ^{14}C-tracer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

Introduction

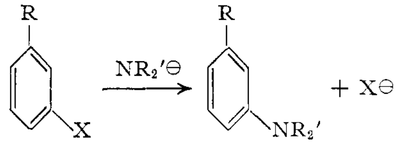
While a large number of the reported rearrangements in reactions of organic halides are initiated by electrophilic reagents, only a small number are initiated by strong nucleophilic reagents. Probably the most important examples of the latter are provided by aminations of non-activated aromatic halides with metallic amides. The first reports of such rearrangements were for aminations which proceed in low yields at high temperatures.[3] These rearrangements were not extensively investigated until it was found[4] that aryl halides could be aminated in fair to good yields 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 = $-OCH_3$,[5] $-OC_6H_5$,[5] $-OH$,[6] $-N(CH_3)_2$,[7] $-CF_3$,[8] $-SCH_3$[9] or $-SO_2CH_3$[9] and with X = I, Br or Cl give *m*-substituted anilines II free of the corresponding *o*- and *p*-isomers.[10]



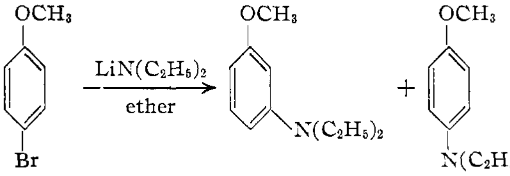
I II

Similarly, 2-bromo-5-trifluoromethylanisole and 2-bromo-6-methylanisole give the corresponding 3-aminoanisoles.[11] The aminations of *m*-substituted halobenzenes (III, R = $-OCH_3$,[7] $-CF_3$[8]) produce the corresponding *m*-anilines II with no detectable amounts of rearrangement products.



III II

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.[6]



The pattern of the rearrangements shows a considerable disregard for the influences governing the usual aromatic substitutions, as illustrated by the fact that halobenzenes with *o*-substituent groups, which are *either* strongly *o,p*-directing ($-OCH_3$ and –N-

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[2] (a) Gates and Crellin Laboratories of Chemistry, California Institute of Technology. (b) Skinner Fellow of Mt. Holyoke College, 1953–1954; National Science Foundation Predoctoral Fellow, 1954–1955.

[3] O. Kym, *J. prakt. Chem.*, **51**, 325 (1895); C. Haeussermann, *Ber.*, **32**, 1912 (1899); **33**, 939 (1900); **34**, 38 (1901).

[4] F. W. Bergstrom, R. E. Wright, C. Chandler and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

[5] H. Gilman and S. Avakian, THIS JOURNAL, **67**, 349 (1945).

[6] H. Gilman and R. H. Kyle, *ibid.*, **70**, 3945 (1948).

[7] H. Gilman, R. H. Kyle and R. A. Benkeser, *ibid.*, **68**, 143 (1946).

[8] R. A. Benkeser and R. G. Severson, *ibid.*, **71**, 3838 (1949).

[9] G. A. Martin, *Iowa State Coll. J. Sci.*, **21**, 38 (1946).

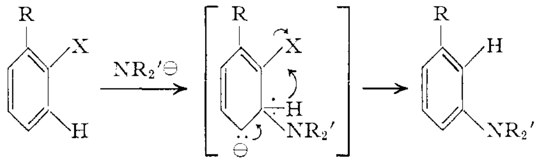
[10] Rearrangements similar to those observed with substituted halobenzenes have been reported in aminations of dibenzofuran[1] and dibenzothiophene derivatives; H. Gilman and J. F. Nobis, THIS JOURNAL, **67**, 1479 (1945).

[11] R. A. Benkeser and W. E. Buting, *ibid.*, **74**, 3011 (1952).

$(CH_3)_2$) or *m*-directing ($-CF_3$ and $-SO_2CH_3$) in aromatic nitration, aminate to yield *m*-substituted anilines.

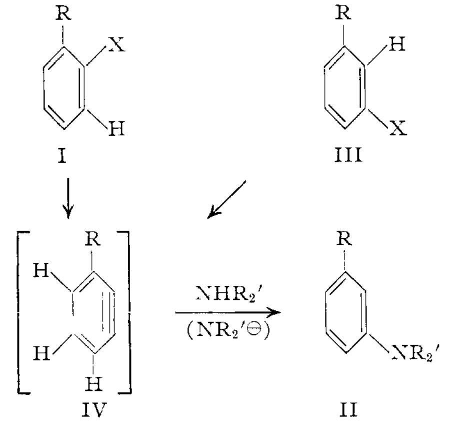
A number of other observations which are pertinent to formulations of the amination reaction mechanisms follow. (1) The entering amino group has never been found farther than one carbon away from the leaving halogen[5–11]; (2) the halides (*e.g.*, *o*-trifluoromethylchlorobenzene) and anilines (*e.g.*, *p*-trifluoromethyl- and *o*-methoxyanilines) are not isomerized under the reaction conditions; (3) the relative reactivities of unsubstituted halobenzenes with potassium amide in liquid ammonia are Br > I > Cl >> F.[4] Fluorobenzene is not aminated at an appreciable rate at $-33°$.[4]

Several mechanisms have been proposed for the halobenzene aminations.[12,13] 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.



I II

An elimination–addition mechanism has been suggested[13] 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 products.[14]

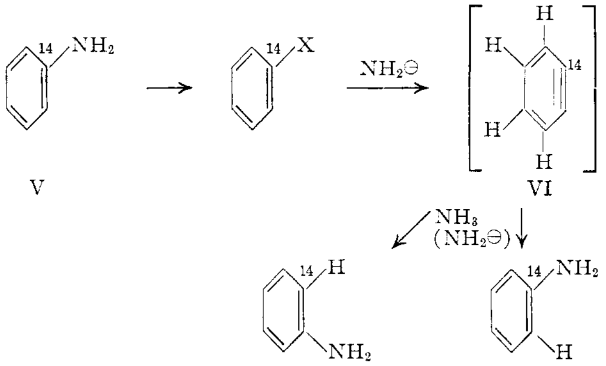


I III IV II

In the present research, evidence for the benzyne mechanism was obtained through a study of rearrangements in aminations of iodobenzene-1-^{14}C and chlorobenzene-1-^{14}C and experiments designed to determine the role of the hydrogen atom located *ortho* to the displaced halogen atom.

Results and Discussion

The benzyne mechanism[13] for aminations of aryl halides requires that rearrangements be observed with isotopically labeled phenyl halides.



V VI

This possibility was investigated with chlorobenzene-1-^{14}C[13] 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 (V) by Sandmeyer reactions of phenyl-1-^{14}C-diazonium ion.[15a] The halides so prepared are certainly labeled in the 1-position since rearrangements have not been observed in Sandmeyer reactions.[15b] 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 formation of aniline-2-^{14}C occurred in the amination of chloro- and iodobenzenes. The very low activity of the diamine XII resulting from the complete degradation of the aniline from the amination of iodobenzene-1-^{14}C establishes conclusively that no aniline-3-^{14}C was present. 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 follows. If iodobenzene-1-^{14}C were to rearrange to iodobenzene-2-^{14}C, then the latter would in turn be converted to iodobenzene-3-^{14}C which should yield at

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[12] R. A. Benkeser and G. S. Schroll, THIS JOURNAL, **75**, 3196 (1953).

[13] J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith and C. W. Vaughan, *ibid.*, **75**, 3290 (1953).

[14] This mechanism is analogous to the formation of vinyl ethyl ether from vinyl chloride and sodium ethoxide presumably by way of acetylene as an intermediate; *cf.* W. Reppe, German Patents 550,403 and 584,840; *C. A.*, **26**, P. 4825 (1932); **28**, P. 1058 (1934). It is also similar to the elimination–addition process considered by G. Wittig and co-workers (G. Wittig, G. Pieper and G. Fuhrmann, *Ber.*, **73**, 1193 (1940); G. Wittig, *Naturwiss.*, **30**, 696 (1942)) as one possibility for the coupling of fluorobenzene with phenyllithium except that Wittig formulated an unsymmetrical dipolar intermediate. R. Huisgen and H. Rist, *Naturwiss.*, **41**, 358 (1954); *Ann.*, **594**, 137 (1955), have recently considered the symmetrical benzyne-type structure in accounting for rearrangements in the coupling of aryl fluorides with phenyllithium.

[15] (a) M. Fields, M. A. Leaffer and J. Rohan, *Science*, **109**, 35 (1949); M. Fields, J. Gibbs and D. E. Walz, *ibid.*, **112**, 591 (1950). (b) In unpublished research, Mr. A. T. Bottini has found that no more than 7% of chlorobenzene-2-^{14}C could be present in the sample of ^{14}C-labeled chlorobenzenes used in the amination studies.

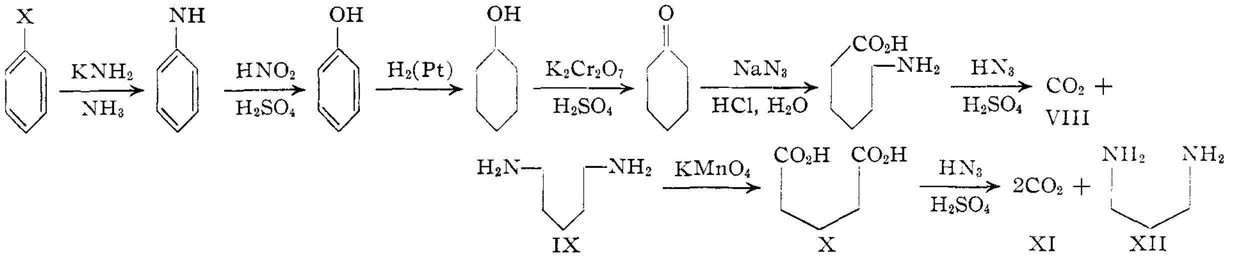

TABLE I

RADIOACTIVITY ANALYSES OF DEGRADATION PRODUCTS OF ANILINE-X-^{14}C

Aniline-x-^{14}C		Cyclohexanone (VII)	CO_2 (VIII)	1,5-Diaminopentane (IX)	Glutaric acid (X)	$2CO_2$ (XI)	1,3-Diaminopropane (XII)
Aniline-1-^{14}C[a]	Meas. act.[b]	0.2502[c]	0.2420[e]	0.0004[h]	......	....	....
	% Total act.	(100)	(96.7 ± 1)[e,f]	0.2 ± 1	......	....	....
From chlorobenzene-1-^{14}C	Meas. act.[b]	0.4247[c,d]	0.1831[e]	0.2201[h,i]	......	....	....
	% Total act.	(100)	(43.1 ± 1)[e,f]	51.8 ± 1	......	....	....
From iodobenzene-1-^{14}C	Meas. act.[b]	0.3804[d]	0.1764[g]	0.2015[i]	0.0357[j]	0.0353[g]	0.00004[k]
	% Total act.	(100)	46.4 ± 0.1	53.0 ± 0.2	(53.0)	52.4 ± 0.3	0.05 ± 0.3
From phenyl-1-^{14}C-trimethylammonium bromide	Meas. act.[b]	0.1451[d]	0.1390[g]	0.00617[i]	......	....	....
	% Total act.	(100)	95.8 ± 0.1	4.3 ± 0.4	......	....	....

[a] Obtained from Tracerlab, Inc., on allocation from the U. S. Atomic Energy Commission. [b] Activities in microcuries per millimole (μc./mmole); determined using the vibrating-reed electrometer method as described by O. K. Neville, THIS JOURNAL, **70**, 3499 (1948). [c] Cyclohexanone as the 2,4-dinitrophenylhydrazone. [d] Cyclohexanone as the semicarbazone. [e] Probably slightly low because of contamination with atmospheric CO_2. [f] Since the barium carbonate activity was almost certainly low, the most accurate estimation for the % aniline-2-^{14}C is obtained from the activity of IX. [g] CO_2 from an improved isolation procedure with minimal atmospheric CO_2 contamination. [h] 1,5-Diaminopentane as the dibenzenesulfonamide. [i] 1,5-Diaminopentane as the dibenzamide. [j] Glutaric acid as the di-*p*-bromophenacyl ester. [k] 1,3-Diaminopropane as the dibenzamide.

least some aniline-3-^{14}C. A similar argument proves that aniline-1-^{14}C did not rearrange to aniline-2-^{14}C in the amination reaction mixture.

The predicted extent of rearrangement (*i.e.*, formation of aniline-2-^{14}C) based on the operation of the elimination–addition mechanism is 50% *if* ^{12}C and ^{14}C react at *identical* 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 16% less than those at ^{12}C-positions.[16] A 10% "isotope effect" in the addition of ammonia to VI would result in an observed value of 52.4% for the extent of rearrangement. The measured degree of rearrangement (52–53%) is consistent with exclusive formation of VI as the reaction intermediate and a $\leqq$13% greater reaction rate of ^{12}C compared to ^{14}C in the addition step and/or intramolecular ^{14}C isotope effects in the degradative reactions.

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, the ratio of elimination (E2) to substitution (SN2) for the reaction of *iso*-propyl *iodide* with sodium hydroxide in 60% aqueous ethanol is 2.83 whereas the corresponding ratio for *iso*-propyl *bromide* is 1.41.[17]

The benzyne mechanism 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. Bromomesitylene (XIII) or bromodurene (XIV) do not react with sodium amide in liquid ammonia, even on long standing.[18] 2-Bromo-3-methylanisole (XV) has been reported to be similarly unreactive toward sodium amide in liquid ammonia.[11] 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 (eq. 1) or a stepwise (eq. 2) process. In more conventional eliminations, these mechanisms have been distinguished conclusively by using deuterium as a tracer for the hydrogen adjacent to the leaving halogen.[19–21] 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*-protonated halobenzenes should correspond to an isotope effect k_H/k_D of approximately 6–7.[22] If the stepwise mechanism (2) operates, the carbanions XVII and XVIII may either

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(16) For references, see G. A. Ropp, *Nucleonics*, **10** [10], 22 (1952).

(17) E. D. Hughes and U. G. Shapiro, *J. Chem. Soc.*, 1177 (1937).

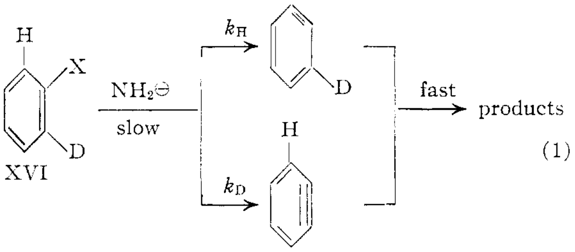
(18) Unpublished experiments by Mr. R. E. Harris and Dr. C. W. Vaughan.

(19) D. G. Hill, B. Stewart, S. W. Kantor, W. A. Judge and C. R. Hauser, THIS JOURNAL, **76**, 5129 (1954).

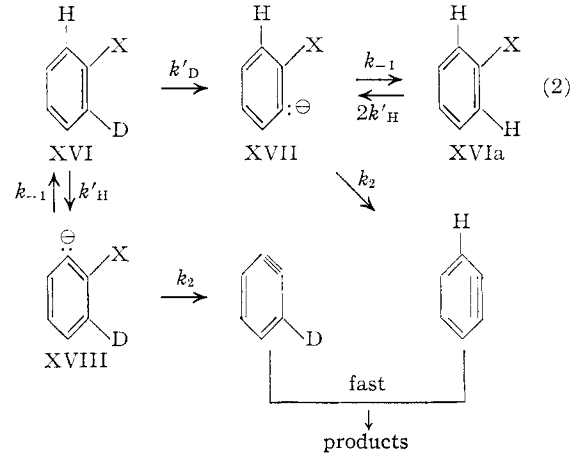
(20) S. J. Cristol and D. D. Fix, *ibid.*, **75**, 2647 (1953).

(21) V. J. Shiner, Jr., *ibid.*, **74**, 5285 (1952).

(22) An isotope effect of 6.7 was observed for the dehydrobromination of isopropyl bromide.[21]



(1)



(2)

form benzyne by loss of halide ion or revert to aryl halide at a specific rate k_{-1} by abstraction of a *proton* from the solvent. For mechanism (2) k_{-1} will be assumed to be detectably large, because if it is not, mechanism (1) and (2) are indistinguishable by the experimental methods employed.[22] 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 k_2/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 protonated halobenzene before significant halide ion elimination could occur.

The evidence bearing on the mechanisms of the reactions of fluoro-, chloro- and bromobenzenes-2-^{2}H (^{2}H = deuterium) with potassium amide in liquid ammonia will now be considered. Whether mechanism (1) or (2) operates, as well as the relative values for the specific rate constants, has been found to depend on the nature of the halogen. Fluorobenzene-2-^{2}H,[23] fluorobenzene-2,4,6-$^2H_3$ and 4-fluorotoluene-3,5-$^2H_2$ were found to exchange deuterium *ortho* to the fluorine extremely rapidly, even though amination products were not formed at a significant rate. Here, k'_D is very large (exchange is complete in less than 10 sec.[23]), but k_2 is negligible. Chlorobenzene-2-^{2}H is aminated by 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 Experimental Part for details of the calculation). For bromobenzene-2-^{2}H the k_H/k_D value was 5.5 which is close to the 6–7 range expected for a concerted E2 dehydrobromination.

Both chloro- and bromobenzenes-2-^{2}H 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-^{2}H 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 indicates that the aminations of bromobenzene in both diethyl ether and liquid ammonia proceed by the concerted mechanism (1).

The data referred to above are 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,[4] Br > I > Cl >> F, in the amination reaction. Two influences are clearly important. First, the *ortho*-hydrogen is removed as a positive ion and the rate of this process is expected to follow the order F > Cl > Br > I, in 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 maximum reaction rate with potassium amide in liquid ammonia.

The above facts strongly indicate but do not "prove" that benzyne is the intermediate in the amide ion-induced amination of phenyl halides. 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] already has been discussed. Formulation of the amination reaction as an addition–substitution–elimination process as shown in eq. 3 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 all prior steps fast equilibria.

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[22] Several other reasonable assumptions were made in formulating kinetic expressions for the operation of mechanism (2). First, the same k'_H values for loss of a proton were assigned to XVI and XVIa. Second, the 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.

[23] G. E. Hall, R. Piccolini and J. D. Roberts, This Journal, **77**, 4540 (1955).

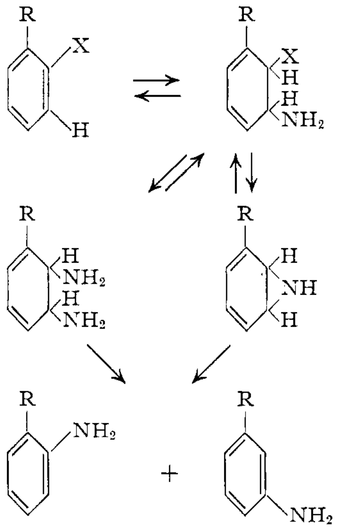
[24] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 339.

TABLE II

o-DEUTERIUM KINETIC ISOTOPE EFFECTS IN REACTIONS OF ARYL HALIDES WITH METALLIC AMIDES

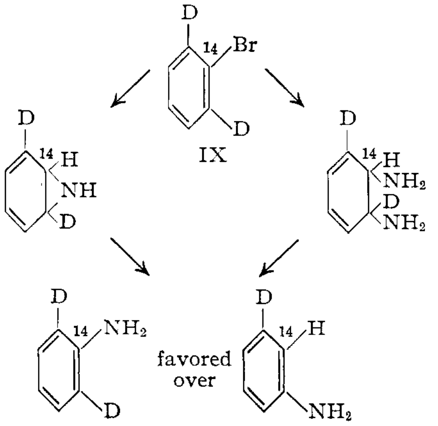
Halide	Reagent	Solvent	Mole % *o*-deuterated aryl halide at start	Mole % *o*-deuterated aryl halide at finish	% Formation of halide ion at finish	k_H/k_D[a]
Fluorobenzene-2,4,6-$^2H_3$	KNH_2	NH_3	40.1	0[b]	0	....
4-Fluorotoluene-3,5-$^2H_2$	KNH_2	NH_3	37.2	0[b] (120 min.)	0	....
Fluorobenzene-2-^2H[c]	KNH_2	NH_3	100.0	0[d] (10 sec.)	0	....
Chlorobenzene-2-^2H (1)[e]	KNH_2	NH_3	26.4	32.2[f,g]	55.98[h]	(2.60)[i]
(2)[e]	KNH_2	NH_3	26.1	31.3[f,g]	51.00[h]	(2.88)[i]
(3)[e]	KNH_2	NH_3	100.0	87.0[f,g]	28.42[h]	(−0.77)[i]
Bromobenzene-2-^2H (1)[e]	KNH_2	NH_3	25.7	37.7[f,j]	69.55[k]	5.54[i]
(2)[e]	KNH_2	NH_3	22.4	34.2[f,j]	72.10[k]	5.42[i]
Chlorobenzene-2-^2H (1)[e]	$LiN(C_2H_5)_2$	Ether[l]	47.1	54.8[f,g]	44.75	5.71
(2)[e]	$LiN(C_2H_5)_2$	$HN(C_2H_5)_2$, ether[m]	35.0	44.1[f,g]	53.78	5.79
Bromobenzene-2-^2H (1)[e]	$LiN(C_2H_5)_2$	Ether	24.6	33.2[f,j]	59.77	5.46
(2)[e]	$LiN(C_2H_5)_2$	Ether	24.6	30.6[f,j]	47.48	5.81

[a] Calculated as described in Experimental Part. [b] Estimated from curves recorded automatically with a Baird Infrared Spectrophotometer. [c] Ref. 23. [d] Estimated from curves recorded automatically with a Perkin-Elmer (Model 21) Infrared Spectrophotometer. [e] Numbers in parentheses are run numbers referred to in Tables IV, VII and VIII. [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). [j] 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.

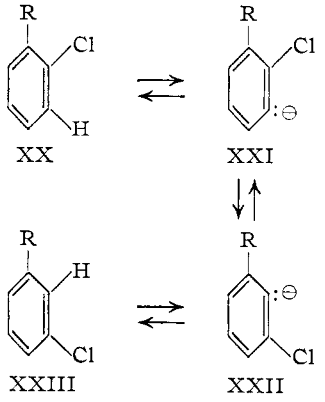


(3)

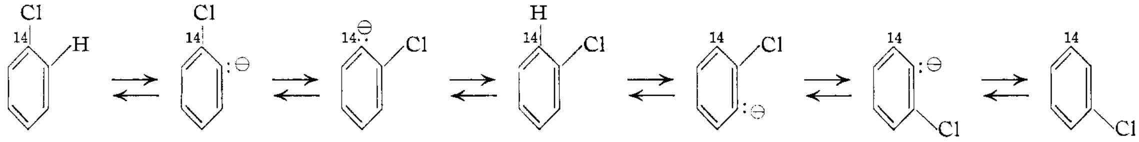
If deemed necessary, an unequivocal decision between the above addition-substitution-elimination mechanism and the elimination-addition (benzyne) mechanism could be achieved by a study of the ^{14}C-rearrangement in the amination of bromobenzene-1-^{14}C-2,6-$^2H_2$ (XIX). The degree of ^{14}C rearrangement would not be affected appreciably by deuterium substitution for the benzyne mechanism (*i.e.*, 53% ^{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 were to operate as shown below.



Rearrangement by equilibration of the isomeric anions XXI and XXII would necessitate the formation of some rearranged chloride XXIII since the chlorocarbanions are known to revert to aryl chlorides by abstraction of a proton from solvent (eq. 2, k_{-1}).



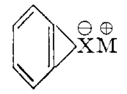
The failure of XXIII to form from XX (when R = $-CF_3$) under amination conditions rules out this mechanism for the aminations. Furthermore, the results obtained from aminations of halobenzenes-1-^{14}C are not in accord with the anion equilibration mechanism. Equilibration of the anion XXIV, formed,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



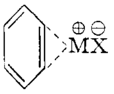
XXIV XXV XXVI XXVII

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) indicates that no aniline-3-^{14}C was obtained from the chloro compound.

Other possible symmetrical intermediates are XXVIII and XXIX.



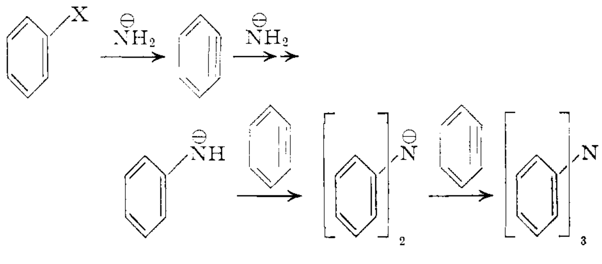
XXVIII



XXIX

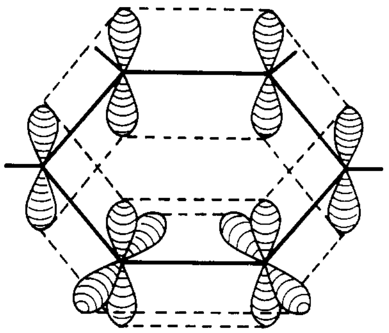
XXVIII is rendered unlikely as an intermediate by virtue of the fact that aryl fluorides appear to react smoothly with lithium diethylamide in ether to give the customary patterns of rearrangements.[25] It does not seem likely that fluorine as a first-row element could expand its valence shell to accommodate the ten electrons required for the halogen atom in XXVIII. The cation complex XXIX has analogies in the silver ion–alkene complexes, but an alkali–metal cation should hardly prefer to complex with an unsaturated compound even as highly reactive as benzyne in the presence of a large excess of liquid ammonia.

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, if there is a real intramolecular ^{12}C–^{14}C isotope effect in the reaction of benzyne with amide ion in ammonia, this would indicate 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



Furthermore, it has been found[26] that potassium amide greatly 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 (XXX) that the molecule might have essentially the same resonance energy as benzene provided the ring is taken to be a regular hexagon. 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.[27]



Applications to Other Reactions

Both 1- and 2-bromonaphthalenes appear to react by the elimination–addition mechanism with sodium amide in refluxing piperidine to form similar but not identical mixtures of 1- and 2-naphthylpiperidines.[28]

It has been reported[29] that 1- and 2-fluoronaphthalenes yield the corresponding 1- and 2-aminonaphthalenes with potassium amide in liquid ammonia, although only 2-diethylaminonaphthalene has been obtained[30] from 1- and 2-fluoronaphthalenes with lithium diethylamide in ether. No convincing explanation of the difference between the results with the different amides and solvents is presently available.

Fluorobenzene-1-^{14}C with phenyllithium in ether has been found to give biphenyl with a degree of rearrangement consistent with a symmetrical benzyne intermediate.[31] As mentioned earlier, Huisgen[14] has demonstrated that rearrangement oc-

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[25] H. Gilman and R. H. Kyle, This Journal, **74**, 3027 (1952).

[26] (a) R. E. Wright and F. W. Bergstrom, *J. Org. Chem.*, **1**, 179 (1936); R. A. Seibert and F. W. Bergstrom, *ibid.*, **10**, 544 (1945); unpublished research by Mr. F. Scardiglia.

[27] (a) C. K. Ingold and G. W. King, *J. Chem. Soc.*, 2702 (1953); (b) C. K. Ingold, *ibid.*, 2991 (1954).

[28] J. F. Bunnett and T. K. Brotherton, This Journal, **78**, 155 (1956).

[29] R. S. Urner and F. W. Bergstrom, *ibid.*, **67**, 2108 (1945).

[30] H. Gilman, N. N. Crounse, S. P. Massie, Jr., R. A. Benkeser and S. H. Spatz, *ibid.*, **67**, 2106 (1945).

[31] E. Jenny and J. D. Roberts, *Helv. Chim. Acta*, **38**, 1248 (1955)

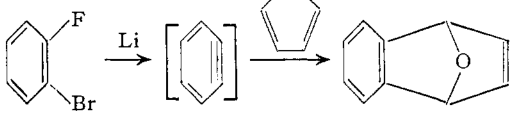
curs in the coupling of aryl fluorides with phenyllithium. It is possible that other Fittig-type coupling reactions proceed in a similar manner.

Hydrolyses of aryl halides with base at high temperatures often yield rearrangement products similar to those observed in aminations with metallic amides; some success in the correlation of degree of rearrangement with mechanism for reactions of this type has been achieved.[32]

It should not be inferred that all aromatic nucleophilic displacements without activation of the type provided by nitro, cyano and similar electron-accepting groups proceed exclusively by the benzyne mechanism. Thus, both 1- and 2-bromonaphthalene react with piperidine at 230° to form the respective N-naphthylpiperidines.[28] Phenyl-1-^{14}C-trimethylammonium bromide is attacked by potassium amide in liquid ammonia to give about 20% of ^{14}C-labeled aniline which consists of 96% of aniline-1-^{14}C and 4% of aniline-2-^{14}C (see Table I). The small degree of rearrangement in this reaction may be associated with facilitation of attack of amide ion at the 1-carbon by the electron-attracting nitrogen of the ammonium group. Similar lack of rearrangement has been reported for displacement reactions of substituted diphenyliodonium salts.[33]

ADDED IN PROOF.—It has been shown recently, W. W. Leake and R. Levine, *Chem. and Ind.*, **37**, 1160 (1955), and C. Osuch, A. D. Miller, W. W. Leake and R. Levine, Absts. of 128th Meeting of the Am. Chem. Soc., p. 8-O (1955), that the amide catalysis of reactions between relatively weak nucleophiles and aryl halides discovered by Bergstrom[4,26] can be extended to the phenylation and pyridylation of ketones. In this Laboratory, Mr. F. Scardiglia has found that the similar reaction between *p*-bromotoluene and sodium phenylacetylide induced by sodium amide gives a mixture of *m*- and *p*-tolylphenylacetylenes having about the same composition of isomers as obtained in the sodium amide amination of *p*-bromotoluene, J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, THIS JOURNAL, **78**, 611 (1956).

Benzyne has been postulated as a dienophile in the elegant condensation between furan and *o*-bromofluorobenzene in the presence of lithium amalgam worked out by G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).



Experimental

^{14}C Studies. Starting Materials.—Chlorobenzene-1-^{14}C of high specific activity[15a,34] was diluted with redistilled nonradioactive chlorobenzene to an activity of 0.90 μc./mmole.

Iodobenzene-1-^{14}C was prepared from aniline-1-^{14}C[34] essentially as described previously,[35] 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. Redistilled 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 solution fractionated through a 23-cm. Vigreux column to give 23 g. (78%) of iodobenzene-1-^{14}C, b.p. 83.0–83.5° (25.3–25.6 mm.), n^{25}D 1.6160.

Phenyl-1-^{14}C-trimethylammonium Bromide.—Aniline-1-^{14}C[34] 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.[36] 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 at 220–230° for 24 hours. The methanol and water were removed by distillation through a 30-cm. 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. Distillation 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^{25}D 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.[37] 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% 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 *p*H 10 with concentrated ammonia solution. Solid sodium hydroxide was then added until the *p*H 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^{25}D 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%) of phenyl-1-^{14}C-trimethylammonium bromide as white needles, m.p. 215.0–216.0° (lit. m.p. 215°[38]).

Aminations. Aniline-x-^{14}C from Iodobenzene-1-^{14}C.—Potassium amide was prepared in the usual manner[4] 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 *p*H 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%); b.p. 83.9–84.4° (23.7 mm.), n^{25}D 1.5826.

Aniline-x-^{14}C from Phenyl-1-^{14}C-trimethylammonium Bromide.—The procedure was essentially as described in

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[32] J. D. Roberts, A. T. Bottini and D. A. Semenow, *Science*, **122**, 881 (1955).

[33] F. M. Beringer, A. Brierly, M. Drexler, E. M. Gindler and C. C. Lumpkin, THIS JOURNAL, **75**, 2708 (1953).

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

[35] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 351.

[36] E. Knoevenagel, *J. prakt. Chem.*, **89**, 30 (1913).

[37] E. C. Wagner, THIS JOURNAL, **55**, 724 (1933).

[38] M. J. McDowell and C. A. Kraus, *ibid.*, **73**, 2170 (1951).

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.), n^{25}D 1.5615. The infrared spectrum of the mixture indicated a composition of aniline (25%) and N,N-dimethylaniline (75%). The yield of aniline was approximately 2.1 g. (22%). The aniline mixture was used in the succeeding degradation steps without further separation.

Degradative Procedures. 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% sulfuric acid.[39] In a typical experiment, 4.2 g. (0.0045 mole) of aniline-x-^{14}C, 0.38 mole of sulfuric acid and 3.1 g. (0.045 mole) of sodium nitrite yielded 3.4 g. (80%) of yellowish phenol-x-^{14}C, b.p. 87.0–88.0° (22.0 mm.).

Cyclohexanol-x-^{14}C.—Phenol-x-^{14}C (3.4 g., 0.036 mole) in 30 ml. of 95% ethanol was shaken with 0.7 g. of platinic oxide under an initial hydrogen pressure of about 3 atm. at room temperature. 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 a 23-cm. Vigreux column at 60 mm. The crude residual cyclohexanol amounted to 5.3 g. (92%) and was used directly in the succeeding step.

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 a 30-cm. column packed with glass helices. The residual crude cyclohexanone-x-^{14}C weighed 3.5 g. (68%) 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.[40a] 166–167°) after two recrystallizations from 75% ether–25% methanol.

6-Aminohexanoic-x-^{14}C Acid.—Cyclohexanone-x-^{14}C was converted to 6-aminohexanoic acid hydrochloride by the procedure described previously.[41] 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%).

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) essentially as described previously.[41] 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% 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 an air-tight 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. The sample was dried for 15 hours at 110° under reduced pressure and, at the end of this time, amounted to 3.7 g. (84%). The carbon dioxide isolated by this procedure was apparently uncontaminated by atmospheric carbon dioxide (see Table I).

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.[41] 135°). The m.p. was not changed after an additional recrystallization.

Glutaric-x-^{14}C Acid.—The balance of the sulfuric acid solution from the Schmidt reaction described above was brought to *p*H 8 with 1 *N* 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 heated under reflux 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% 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-*p*-bromophenacyl ester for ^{14}C-analysis. The yield of twice-recrystallized (95% ethanol) di-*p*-bromophenacyl glutarate-x-^{14}C was 0.074 g., m.p. 136.2–136.7° (lit.[40b] m.p. 136.8°). The ^{14}C-analysis of the diester indicated that the yield in the permanganate oxidation of 1,5-diaminopentane was about 8%.

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 by treatment with 3 *M* perchloric acid in a carbon dioxide-free system and isolated as before. The yield of barium carbonate (white) was 85%. 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%); 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.[42] m.p. 147°).

Deuterium Studies. Starting Materials. Fluorobenzene-2,4,6-$^2H_3$.—Aniline-2,4,6-$^2H_3$ was prepared as described previously.[43] The product was calculated to contain 85% of the theoretical amount of deuterium on the basis of the known partition coefficients.

Aniline-2,4,6-$^2H_3$ was converted in 49% yield to fluorobenzene-2,4,6-$^2H_3$, b.p. 84.5° (760 mm.), n^{30}D 1.4608, by the procedure described previously.[44] The infrared spectrum of the deuterated fluorobenzene showed bands characteristic of *o*-deuterium atoms at 7.85, 8.97, 9.62, 10.57 and 13.50 μ.

4-Fluorotoluene-3,5-$^2H_2$ was prepared in 38% over-all yield from 4-aminotoluene by a procedure analogous to that described above for fluorobenzene-2,4,6-$^2H_3$.[43,44] The infrared spectrum of 4-fluorotoluene-3,5-$^2H_2$, b.p. 115.5° (760 mm.), n^{20}D 1.4700, showed bands characteristic of deuterium *ortho* to the fluorine at 8.88, 11.10, 11.30, 11.57, 13.00, 14.05 and 14.40 μ.

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(39) H. J. Lucas and D. Pressman, "Principles and Practice in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 396.

(40) (a) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 383; (b) p. 98.

(41) R. B. Loftfield, This Journal, **73**, 4707 (1951).

(42) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd Ed., 1948, p. 234.

(43) A. P. Best and C. L. Wilson, *J. Chem. Soc.*, 239 (1946).

(44) "Organic Reactions," **5**, 217 (1949); "Organic Syntheses," Coll. Vol. II, 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 295.

Chlorobenzene-2-^{2}H.—The Grignard reagent from 138 g. (0.58 mole) of *o*-chloroiodobenzene and 14.0 g. (0.58 mole) 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%) of chlorobenzene-2-^{2}H, b.p. 129.7–130.4° (742 mm.), n^{25}D 1.5210.

Bromobenzene-2-^{2}H.—Toluene-2-^{2}H 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-^{2}H was 58.0 g. (79%), b.p. 108.5–109.5° (745 mm.).

A mixture of 65 g. (0.70 mole) of toluene-2-^{2}H, 255 g. (1.61 mole) of potassium permanganate, 15 ml. of 10% 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-^{2}H as described previously.[45] The silver benzoate-2-^{2}H was dried at 100° under reduced pressure for several hours. The yield of dried salt was 135.9 g. (85.5% based on toluene-2-^{2}H).

Bromobenzene-2-^{2}H (78 g., b.p. 152.5–154.0°, 50%) was obtained from the reaction of 233 g. of silver benzoate-2-^{2}H and 162 g. of bromine in dried carbon tetrachloride essentially as described previously.[45b] The crude product was washed with saturated sodium bisulfite solution in order to remove some contaminating bromine, dried over calcium chloride and distilled through a 30-cm. column packed with glass helices to yield 71 g. of bromobenzene-2-^{2}H, b.p. 154.0°, n^{25}D 1.5567.

Halobenzenes-2-^{2}H with Potassium Amide in Liquid Ammonia.—Fluorobenzene-2,4,6-^{2}H$_3$ (2.78 g.) was diluted with unlabeled fluorobenzene (3.00 g.) and 4.00 g. (0.042 mole) of the mixture was stirred for 2 hours with an equivalent amount of potassium amide in 200 ml. of liquid ammonia. Ammonium chloride (5 g.) and ether (100 ml.) were added. The ammonia was allowed to evaporate and the ethereal solution dried over magnesium sulfate. After fractionation through a 30-cm. column packed with a coil of platinum wire, 1.91 g. (48%) of pure fluorobenzene, b.p. 84.5° (760 mm.), n^{25}D 1.4636, was obtained. The infrared spectrum of this material showed none of the characteristic bands of the deuterium atoms at the 2,6-positions of fluorobenzene-2,4,6-^{2}H$_3$.

4-Fluorotoluene-3,5-^{2}H$_2$ (2.39 g.) was diluted with unlabeled fluorotoluene (3.00 g.) and 4.00 g. (0.0364 mole) of the mixture was stirred for 10 seconds with an equivalent amount of potassium amide in 200 ml. of liquid ammonia. The products were isolated as described above. The infrared spectrum of the recovered 4-fluorotoluene (2.63 g., 66%), b.p. 115° (760 mm.), n^{20}D 1.4699, showed none of the deuterium absorption bands of the starting material.

Amination of Chlorobenzene-2-^{2}H.—The apparatus used for these experiments was similar to that employed for the sodium amide-induced cyclization of γ-chlorobutyronitrile.[46] The general procedure will be illustrated by a typical experiment using chlorobenzene-2-^{2}H. A mixture (0.149 mole, 16.81 g.) containing 26.5 mole % of chlorobenzene-2-^{2}H and 73.6 mole % of ordinary chlorobenzene was stirred with approximately 150 ml. of anhydrous liquid ammonia in a 500-ml. flask (A)[46] until solution was complete (about 10 minutes). A mixture of potassium amide (0.21 g.-atom) from 8.4 g. of potassium metal and 200 ml. of anhydrous ammonia in a 500-ml. flask (B)[46] 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 were transferred quantitatively to a separatory funnel and the aqueous layer was 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. In all cases, the halide ions determinations were precise to 0.2%.

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 a 23-cm. Vigreux column. The recovered chlorobenzene amounted to 5.3 g., b.p. 129.5–130.1°, n^{25}D 1.5208–1.5210. The chlorobenzene was analyzed for chlorobenzene-2-^{2}H using a Perkin–Elmer (Model 21) Infrared Spectrophotometer at 10.090 and 10.520 μ. The analyses were made by the "baseline" procedure[47] using 0.025-mm. cells. Calibration graphs were constructed from the absorptions of five known mixtures at each wave length; these plots were linear. The analyses at the two wave lengths agreed to 0.3% or better. The experimental data are summarized in Tables III and IV.

TABLE III

INFRARED ANALYSES OF STANDARD MIXTURES OF CHLOROBENZENE-2-^{2}H AND ORDINARY CHLOROBENZENE

Mole % chlorobenzene-2-^{2}H[a]	Wave length, 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	.1979
66.02	10.090	76.0	42.0	.2577
	10.520	80.5	60.0	.1277
48.67	10.090	76.0	49.0	.1906
	10.520	81.0	65.5	.0923
47.08	10.090	76.5	50.25	.1824
	10.520	81.5	66.0	.0916
25.57	10.090	76.0	60.5	.0990
	10.520	80.5	73.0	.0425

[a] Mixtures made up by weight. [b] Wave length at which absorption maximum occurs. [c] Intensity of base-line absorption measured as % transmission; see ref. 47. [d] Intensity of sample absorption measured as % transmission; see ref. 47.

TABLE IV

INFRARED ANALYSES OF MIXTURES OF CHLOROBENZENE-2-^{2}H AND ORDINARY CHLOROBENZENE RECOVERED FROM AMINATIONS IN LIQUID AMMONIA

Run	Wave length, μ[b]	I_B[c]	I[d]	Log$_{10}$ I_B/I	Mole % chlorobenzene-2-^{2}H[a]
1	10.090	76.0	57.0	0.1249	32.34
	10.520	80.5	70.5	.0577	32.03
2	10.092	76.0	57.5	.1212	31.41
	10.528	80.5	70.75	.0561	31.26
	10.090	76.0	34.5	.3430	87.11
	10.520	80.5	54.25	.1715	86.97

[a] Calculated from the log$_{10}$ I_B/I values in the preceding column and the data in Table III. [b,c,d] See corresponding footnotes for Table III.

Bromobenzene-2-^{2}H.—The procedure was as described above for chlorobenzene-2-^{2}H. Triplicate analyses were

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(45) (a) J. W. H. Oldham and A. R. Ubbelohde, *J. Chem. Soc.*, 368 (1941); W. G. Dauben and H. Tilles, THIS JOURNAL, **72**, 3185 (1950).

(46) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 223.

(47) J. J. Heigl, M. F. Bell and J. U. White, *Anal. Chem.*, **19**, 293 (1947).

made for bromide ion by the Volhard method. The infrared analyses were done at 8.865 and 10.110 μ. The experimental data are summarized in Tables V and VI.

TABLE V

INFRARED ANALYSES OF STANDARD MIXTURES OF BROMOBENZENE-2-^{2}H AND ORDINARY BROMOBENZENE

Mole % bromobenzene-2-^{2}H^a	Wave length, μ^b	$I_B{}^c$	I^d	Log$_{10}$ I_B/I
100.00	8.863	81.5	41.5	0.2932
	10.111	73.5	15.5	.6760
49.88	8.866	84.0	50.5	.1498
	10.113	69.0	27.5	.3994
33.46	8.865	85.0	67.0	.1035
	10.110	67.0	32.5	.3143
27.26	8.865	85.0	69.75	.0859
	10.109	67.0	35.0	.2819
24.85	8.866	85.0	71.0	.0781
	10.110	66.5	36.0	.2664

^{a,b,c,d} See corresponding footnotes for Table III.

TABLE VI

INFRARED ANALYSES OF MIXTURES OF BROMOBENZENE-2-^{2}H AND ORDINARY BROMOBENZENE RECOVERED FROM AMINATIONS IN LIQUID AMMONIA

Run	Wave length, μ^b	$I_B{}^c$	I^d	Log$_{10}$ I_B/I	Mole % bromobenzene-2-^{2}H^a
1	8.866	81.5	62.5	0.1152	37.7
	10.110	67.0	31.0	.3347	37.7
2	8.865	85.0	66.75	.1048	34.2
	10.110	67.5	32.75	.3145	34.2

^{a} Calculated from the log$_{10}$ I_B/I values in the preceding column and the data in Table V. ^{b,c,d} See corresponding footnotes for Table III.

Halobenzenes-2-^{2}H with Lithium Diethylamide in Ether. A. Chlorobenzene-2-^{2}H.—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 % of chlorobenzene-2-^{2}H and 52.9 mole % of purified ordinary chlorobenzene 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 *p*H 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[48] and triplicate analyses were made for chloride ion by the Volhard method. 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^{25}D 1.5208. The chlorobenzene was analyzed for chlorobenzene-2-^{2}H by the infrared method. The data for this and similar experiments are given in Tables III and VII.

B. Bromobenzene-2-^{2}H.—The reactions with bromobenzene-2-^{2}H were carried out similarly except that iodobenzene was used for the preparation of phenyllithium and, for determination of the % 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. The experimental results are summarized in Tables V and VIII.

TABLE VII

INFRARED ANALYSES OF MIXTURES OF CHLOROBENZENE-2-^{2}H AND ORDINARY CHLOROBENZENE RECOVERED FROM AMINATIONS IN DIETHYL ETHER

Run	Wave length, μ^b	$I_B{}^c$	I^d	Log$_{10}$ I_B/I	Mole % chlorobenzene-2-^{2}H^a
1	10.090	76.5	46.75	0.2138	54.66
	10.520	81.0	63.6	.1052	54.96
2	10.090	76.5	51.5	.1718	44.12
	10.528	80.5	66.5	.0828	44.15

^{a,b,c,d} See corresponding footnotes for Table IV.

TABLE VIII

INFRARED ANALYSES OF MIXTURES OF BROMOBENZENE-2-^{2}H AND ORDINARY BROMOBENZENE RECOVERED FROM AMINATIONS IN DIETHYL ETHER

Run	Wave length, μ^b	$I_B{}^c$	I^d	Log$_{10}$ I_B/I	Mole % bromobenzene-2-^{2}H^a
1	8.865	83.25	65.75	0.1025	33.10
	10.110	67.0	32.75	.3109	33.30
2	8.866	85.0	68.2	.0955	30.80
	10.110	68.0	34.5	.2947	30.40

^{a,b,c,d} See corresponding footnotes for Table VI.

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-^{2}H and the corresponding undeuterated halobenzenes toward amide ion in ammonia or ether on the basis of the concerted dehydrohalogenation mechanism (eq. 1). 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 over-all amination reactions; and the reaction of benzyne to give products is not rate determining or reversible. The rates of disappearance of chlorobenzene-2-^{2}H (D) and ordinary chlorobenzene (H) are then

$$\frac{-\mathrm{d}[\mathrm{D}]}{\mathrm{d}t} = [k_\mathrm{D} + k_\mathrm{H}][\mathrm{D}][\mathrm{NR_2}'^{\ominus}]^n \qquad (4)$$

and

$$\frac{-\mathrm{d}[\mathrm{H}]}{\mathrm{d}t} = 2k_\mathrm{H}[\mathrm{H}][\mathrm{NR_2}'^{\ominus}]^n \qquad (5)$$

where n is unknown but likely to be unity.[49] Division of the first of these expressions (4) by the second (5), rearrangement and integration leads to the following expression for k_H/k_D.

$$\frac{k_\mathrm{H}}{k_\mathrm{D}} = 1/2[\ln([\mathrm{D}]_t/[\mathrm{D}]_0)/\ln([\mathrm{H}]_t/[\mathrm{H}]_0)] - 1 \qquad (6)$$

Calculated values for k_H/k_D obtained through the use of eq. 6 are given in Table II.

When the elimination reaction is stepwise (eq. 2) 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-^{2}H 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[22]) that the steady-state approximation may be applied to the concentration of the intermediate anion. The rate of disappearance of chlorobenzene-2-^{2}H is expressed by

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[48] E. H. Swift, "A System of Chemical Analysis," Prentice-Hall, Inc., New York, N. Y., 1939, p. 455.

[49] 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°.[4]

$$\frac{-\mathrm{d}[\mathrm{D}]}{\mathrm{d}t} = (k_{\mathrm{H}}' + k_{\mathrm{D}}')[\mathrm{D}][\mathrm{NH_2}\ominus] - k_{-1}\,[\text{Anion XVIII}] \tag{7}$$

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

$$[\text{Anion XVIII}] = \frac{k_{\mathrm{H}}'[\mathrm{D}][\mathrm{NH_2}\ominus]}{k_{-1} + k_2} \tag{8}$$

Substitution of (8) into (7) gives

$$\frac{-\mathrm{d}[\mathrm{D}]}{\mathrm{d}t} = (k_{\mathrm{H}}' + k_{\mathrm{D}}')[\mathrm{D}][\mathrm{NH_2}\ominus] - \frac{k_{-1}k_{\mathrm{H}}'}{k_{-1} + k_2}[\mathrm{D}][\mathrm{NH_2}\ominus] \tag{9}$$

Similarly, expression (10) is obtained for the rate of disappearance of chlorobenzene-2-^{2}H.

$$\frac{-\mathrm{d}[\mathrm{H}]}{\mathrm{d}t} = 2k_{\mathrm{H}}'[\mathrm{H}][\mathrm{NH_2}\ominus] - \frac{k_{-1}}{k_{-1} + k_2}(2k_{\mathrm{H}}'[\mathrm{H}][\mathrm{NH_2}\ominus] + k_{\mathrm{D}}'[\mathrm{D}][\mathrm{NH_2}\ominus]) \tag{10}$$

Let $k_{-1}/(k_{-1} + k_2) = F$ (fraction of intermediate anion returning to starting material) and $k_{\mathrm{H}}'/k_{\mathrm{D}}' = i$, then

$$\frac{\mathrm{d}[\mathrm{D}]}{\mathrm{d}[\mathrm{H}]} = \frac{[i(1 - F) + 1][\mathrm{D}]}{2i(1 - F)[\mathrm{H}] - F[\mathrm{D}]} \tag{11}$$

Division of (11) by [D] and treatment of $[i(1 - F) + 1]$, $2i(1 - F)$ and $-F$ as constants, gives on integration

$$\ln[\mathrm{D}]\Big]_{\mathrm{D}_0}^{\mathrm{D}_t} + \frac{1 + i - iF}{1 - i + iF}\ln\left[(-1 + i - iF)\frac{[\mathrm{H}]}{[\mathrm{D}]} - F\right]_{\frac{[\mathrm{H}]_0}{[\mathrm{D}]_0}}^{\frac{[\mathrm{H}]_t}{[\mathrm{D}]_t}} = 0 \tag{12}$$

Values of F, and hence k_{-1}/k_2, were obtained from (12). Chlorobenzene-^{2}H gave F as 0.48, 0.44 and 0.76 in runs 1, 2 and 3, respectively (Table II). The average value 0.56 ± 0.13 corresponds to a k_{-1}/k_2 on the order of 1.5.

PASADENA 4, CALIF.

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Orientation in Aminations of Substituted Halobenzenes[1]

BY JOHN D. ROBERTS, C. WHEATON VAUGHAN, L. A. CARLSMITH AND DOROTHY A. SEMENOW[2]

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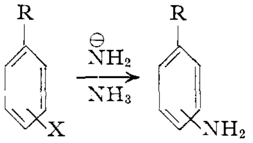
The respective orientations of amine and substituent groups resulting from aminations of a number of substituted halobenzenes have been determined qualitatively and correlated with the aid of a previously postulated elimination–addition ("benzyne") mechanism.

The degree of rearrangement in 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 the accompanying paper,[3] a number of *o*- and *m*-substituted halides gave exclusively *m*-substituted anilines while a *p*-substituted halide gave an equimolar mixture of the corresponding *m*- and *p*-substituted anilines.

In the present work, amination product distributions for several substituted halobenzenes were determined qualitatively in order to ascertain whether the orientations could be rationalized on the basis of the benzyne mechanism.[3] The experimental results are summarized in Table I. It is to be emphasized that the isomer distributions in Table I may not represent more than qualitatively the actual percentages of isomers formed in the amination reactions. The yields were usually low because of partial conversion of the first-formed products to diphenyl- and triphenylamines.[4] Some preferential isomer destruction is to be expected in such secondary reactions. Indeed, in some preliminary experiments with chlorotoluenes (see Table I) using long reaction times and relatively low amide concentrations (such as would favor secondary reactions) somewhat different proportions of isomeric products were apparently obtained. In addition some of the anilines may react directly with amide ions (see later).

TABLE I

ORIENTATIONS IN AMINATIONS OF SUBSTITUTED HALOBENZENES



R	X	Yield, %	*Ortho*, %	*Meta*, %	*Para*, %
o-$\mathrm{OCH_3}$	Br[a]	33	.....	100	.....
m-$\mathrm{OCH_3}$	Br	59	.....	100	.....
p-$\mathrm{OCH_3}$	Br	31	.....	49 ± 1	51 ± 1
o-$\mathrm{CF_3}$	Cl	28	.....	100	.....
m-$\mathrm{CF_3}$	Cl	16	.....	100	.....
p-$\mathrm{CF_3}$	Cl	25	.....	50 ± 5	50 ± 5
p-F	Br	30	.....	20 ± 1	80 ± 1
o-$\mathrm{CH_3}$	Cl	66[b]	45 ± 4[b]	55 ± 4[b]	.....
o-$\mathrm{CH_3}$	Br	64	48.5 ± 2	51.5 ± 2	.....
m-$\mathrm{CH_3}$	Br	61	22 ± 4	56 ± 4	22 ± 4
m-$\mathrm{CH_3}$	Cl	66[c]	40 ± 4[c]	52 ± 4[c]	8 ± 4[c]
p-$\mathrm{CH_3}$	Cl	35[d]	.....	62 ± 4[d]	38 ± 4[d]

[a] H. Gilman and S. Avakian, THIS JOURNAL, **67**, 349 (1945). [b] One equivalent of sodium amide and a reaction time of 5 hr. gave *o*- and *m*-toluidines in the ratio of about 2:1 (19% yield). [c] One equivalent of sodium amide and a reaction time of 5 hr. gave *o*-, *m*- and *p*-toluidines in the proportions of roughly 6:3:1 (15% yield). [d] One equivalent of sodium amide and a reaction time of 5 hr. gave *m*- and *p*-toluidines in the ratio of about 1:1 (7% yield).

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[2] National Science Foundation Fellow, 1954–1955.

[3] J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., L. A. Carlsmith, THIS JOURNAL, **78**, 601 (1956).

[4] F. W. Bergstrom, R. E. Wright, C. Chandler and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).