THE ELIMINATION-ADDITION MECHANISM
OF NUCLEOPHILIC
AROMATIC SUBSTITUTION

Thesis by

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ABSTRACT

Part I

The elimination-addition (benzyne) mechanism postulated for nucleophilic substitutions of non-activated halobenzenes provided the first coherent explanation of the rearrangements which frequently accompany these reactions. However, several less likely alternative mechanisms were able to explain the available data. These alternatives have been disproven by the finding that the amination of iodobenzene-1-^{14}C-2,4,6-$^{2}H_{3}$ gives the same extent of ^{14}C rearrangement in the resulting aniline as does iodobenzene-1-^{14}C.

Part II

Substituent effects in aminations of halobenzenes have been explained by inductive control of both the direction of formation of benzyne and the manner of addition of the nucleophile to the reactive benzyne bond. Although the intermediacy of benzyne in non-rearranging aminations of halobenzenes having electron-withdrawing substituents in the 3-position has been rationalized, the possibility of direct displacement remained. The intermediacy of benzyne has been confirmed by a determination of the isotope effect in reactions of 3-bromoanisole-2,4,6-$^{2}H_{3}$.

Part III

While leaving groups such as non-activated halogens react with amide ion in liquid ammonia via a benzyne intermediate, others react entirely or primarily via direct substitution. In order to obtain needed data on the leaving group characteristics which lead to benzyne formation, attempts have been made to find further non-activated substituted benzenes which react with amide ion.

Part IV

While all alternatives to the elimination-addition mechanism for amination of non-activated halobenzenes have been disproven one cannot rule out the possibility that benzyne exists as a C_6H_4-complex with halide ion or metal ion. In order to demonstrate the ability of benzyne to exist as a stable C_6H_4 hydrocarbon it would be desirable to pass benzyne through the vapor-phase. Several experiments of this nature have been attempted.

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PART I

FURTHER EVIDENCE FOR BENZYNE AS AN INTERMEDIATE IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

Introduction

The subject of nucleophilic aromatic substitution has received relatively little attention until recent years.* A large number of these substitutions involve rearrangements in which the entering nucleophile becomes attached one carbon away from the leaving halogen (2). This type of rearrangement was first coherently explained by the postulation of an elimination-addition mechanism involving a benzyne** (I) intermediate (3) (eq. 1). As required by the benzyne mechanism of substitution both chloro- and bromobenzene-1-C^{14} yield, on amination with potassium amide in liquid ammonia, a 1:1 mixture of aniline-1-C^{14} and aniline-2-C^{14} (eq. 2).

The scope of reactions which may take place via a benzyne-type intermediate has been reviewed (4) several times and will not be dealt with in detail here.

The mechanism by which the benzyne intermediate is formed has been partly elucidated by evidence obtained from deuterium isotope studies (1). The elimination of hydrogen halide has been formulated as

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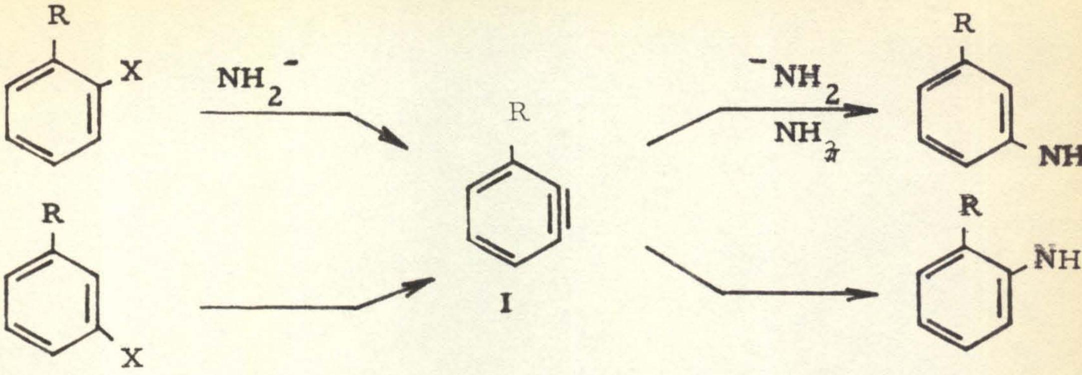
*A review of the field up to 1951 is found in ref. 1. Ref. 2 contains a summary of rearrangement reactions reported prior to its publication.

**Objections have been raised to the symbol used originally for benzyne by Roberts (5). The formula Ia has been proposed to "stress the undisturbed aromatic character" of the intermediate. If one wishes to stress this point, which has, in fact, been pointed out by Roberts (1), one may do so in terms of normal chemical nomenclature by drawing the reactive bond outside of the aromatic ring. The distinction is trivial.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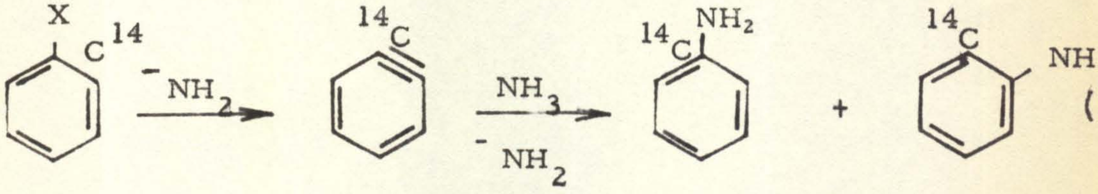
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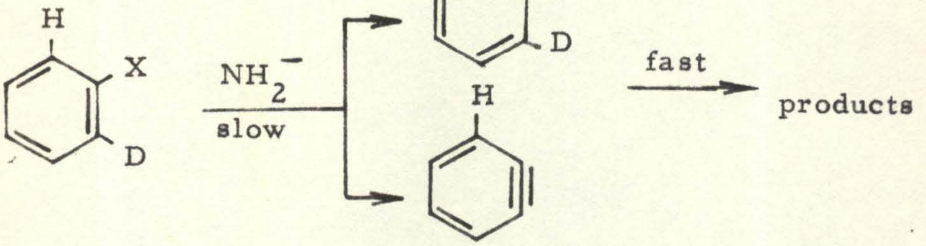
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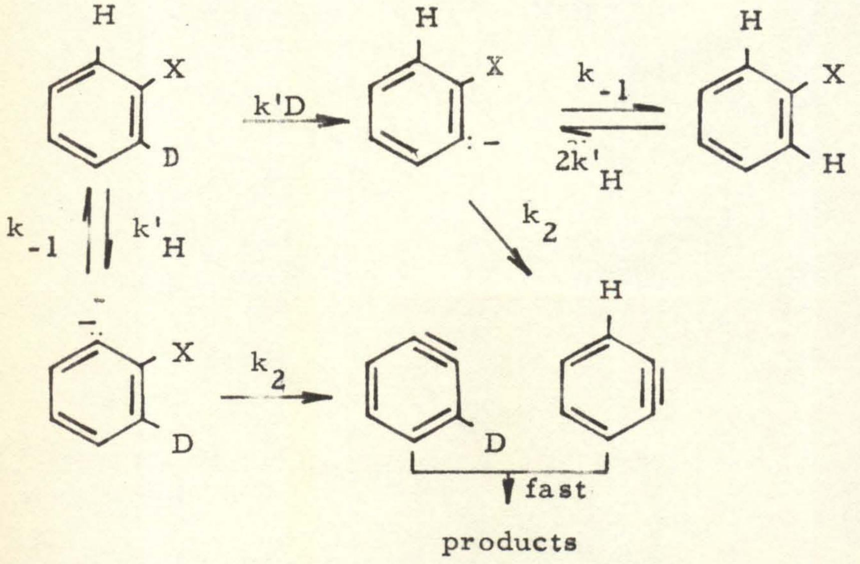
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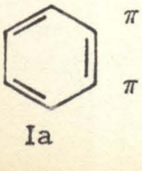

π
π

Ia

either a concerted (eq. 3) or as a stepwise (eq. 4) process. If the concerted mechanism is correct, the relative rates of reaction of *ortho*-deuterated and *ortho*-protonated halobenzenes should correspond to an isotope effect of 6-7. If, on the other hand, elimination proceeds via the stepwise mechanism the *ortho* deuterium would be partially exchanged with the solvent prior to the separation of the halide ion, and, as a result, the apparent isotope effect would be decreased. The data obtained (Table 1) from a study of deuterated halobenzenes is in agreement with the above explanation. Thus, chlorobenzene reacts with amide ion in liquid ammonia by the stepwise mechanism, while it reacts with lithium diethylamide by a concerted mechanism. In accord with the lower electronegativity of bromine, bromobenzene-2-^{2}H does not exchange with the solvent and appears to react by a concerted elimination in the presence of either reagent. However, an alternative mechanism has been proposed based on the rates of formation of benzyne from halobenzenes with lithium piperidide in the presence of added piperidine (5) (fig. 1). The influence of amine, which is to decrease the rate of reaction of fluorobenzene, is explained by the assumption of a two-step mechanism, the first step being a reversible metalation (eq. 5); excess amine suppresses the concentration of the *o*-lithiofluorobenzene, II, and thus reduces the rate of benzyne formation. The metalation step in reactions of the remaining halobenzenes is practically irreversible.

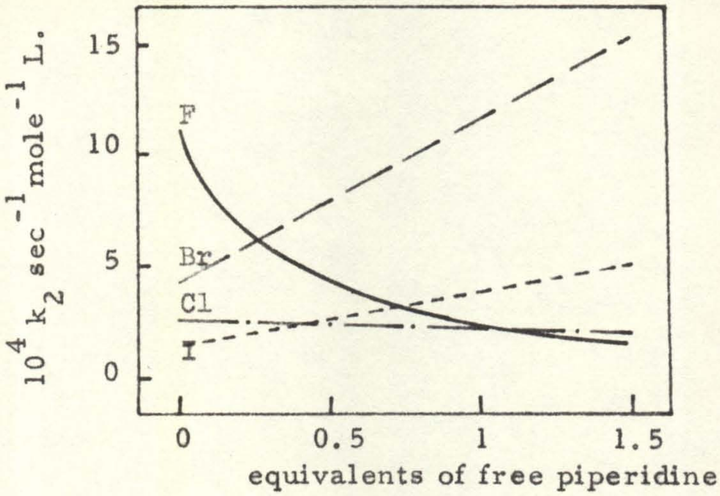
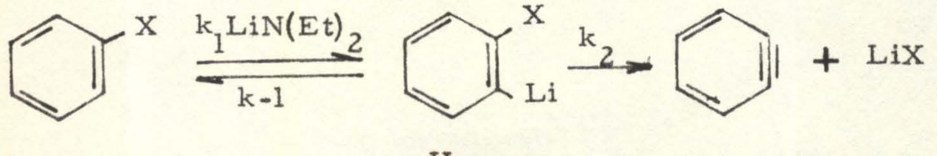


Fig. 1. Rate constants of benzyne formation from halogenobenzenes with lithium piperidide in ether at 20°: influence of piperidine.



(5)

II

X = Cl, Br, F, I .

Table I[a]

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

Halide	Reagent	Solvent	Mole % o-deuterated aryl halide		% Formation of halide ion at finish	k_H/k_D
			At start	At finish		
Fluorobenzene-2-^{2}H	KNH_2	NH_3	100.0	0	0	....
Chlorobenzene-2-^{2}H	KNH_2	NH_3	26.4	32.2	55.98	(2.60)
Bromobenzene-2-^{2}H	KNH_2	NH_3	25.7	37.7	69.55	5.54
Chlorobenzene-2-^{2}H	$LiN(C_2H_5)_2$	Ether	47.1	54.8	44.75	5.71
Chlorobenzene-2-^{2}H	$LiN(C_2H_5)_2$	$HN(C_2H_5)_2$, ether	35.0	45.1	53.78	5.79
Bromobenzene-2-^{2}H	$LiN(C_2H_5)_2$	Ether	24.6	30.6	47.48	5.81

[a] Data from ref. 1.

Further data pertinent to the mechanism of benzyne formation is presented in Table II which shows that the rate of aryne formation from aryl halides increases in the series bromobenzene, bromonaphthalene, 9-bromophenanthrene (5). It may be argued that the data is evidence for a concerted mechanism in which the aryne contributes to the transition state, since the order of reactivity is the order of stability of the aryne bond. Huisgen states that this argument is invalidated by the high rate constant of 2-bromo-1-methylnaphthalene as compared to that of o-bromotoluene. However, this interpretation of the data may be incorrect as shown by the following argument. According to Huisgen's proposed mechanism, the ratio of the rate constants of 2-bromonaphthalene to 1-bromonaphthalene should be a measure of the relative acidities of the α to the β protons of naphthalene. Thus, again according to the Huisgen mechanism, the reaction rate of 2-bromo-1-methylnaphthalene should be compared to that of 1-bromonaphthalene since in both these cases a β-hydrogen is removed. The methyl compound reacts 0.19 times as fast as the unsubstituted bromonaphthalene. If, to a first approximation, it is assumed that the effect of an adjacent methyl group is the same in reactions of benzenes and naphthalenes, one may use the ratio of the rate of o-bromotoluene to that of bromobenzene, 0.25, as a measure of this effect, which should be predominantly inductive. Thus, rather that the rate constant of 2-bromo-1-methylnaphthalene being unusually high, as stated by Huisgen, it is, in fact, lower than may be expected on the basis of relative hydrogen

Table II[a]

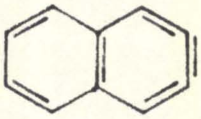
Rate Constants of Aryne Formation

(Reaction of aryl bromides with lithium piperidide + piperidine in ether at 20°)

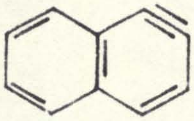
Aryl Halide	$10^4 k_2$ (sec.$^{-1}$mole^{-1})
Bromobenzene	11.7
o-Bromotoluene	2.9
1-Bromonaphthalene	39.5
2-Bromonaphthalene	67.2
2-Bromo-1-methylnaphthalene	7.7
9-Bromophenanthrene	228

[a] Data from ref. 5.

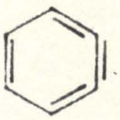
acidities alone. The data of Table II therefore supports the concerted mechanism of benzyne formation. The low rate of 2-bromo-1-methylnaphthalene relative to that of the other bromonaphthalenes is due to the relative instability of structures such as IV relative to IVa, as has been pointed out by Coulson (7) for analogous benzyne structures, V and Va .



IV



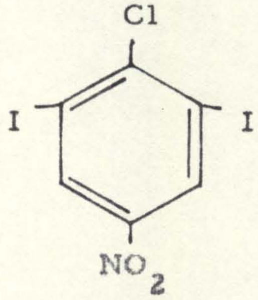
IVa



V

Va

Although there is a large body of evidence in support of the elimination-addition mechanism, alternative mechanisms can account for the rearrangements observed in these amination reactions. For example, the 1:1 ratio of aniline-1-^{14}C to aniline-2-^{14}C could conceivably result from a conbination of two reactions proceeding at nearly identical rates, one reaction being a direct displacement and the other leading to rearrangement. This possibility may be regarded as unlikely in view of the nearly identical product mixtures obtained from the amination of iodobenzene-1-^{14}C and chlorobenzene-1-^{14}C; these halides should hardly have the same ratio of "direct" to "abnormal" reactions. However, the argument involves a value judgment which, in some quarters, might be regarded as less reasonable than the postulation of benzyne as an intermediate. To be sure, the dual-path mechanism is inconsistent with the observation that hydrogens ortho to the leaving halide must be present for reaction to occur, as witnessed by the fact that bromodurene (VI) and bromomesitylene (VII) are not aminated by sodium amide in liquid ammonia. The lack of reactivity of VI and VII could be ascribed to steric hindrance provided by the ortho groups but this can, in turn, be countered by the finding that two ortho-iodines only slightly increase the reactivity of the activated chlorobenzene (VIII) towards substitution by piperidine (8). Furthermore,

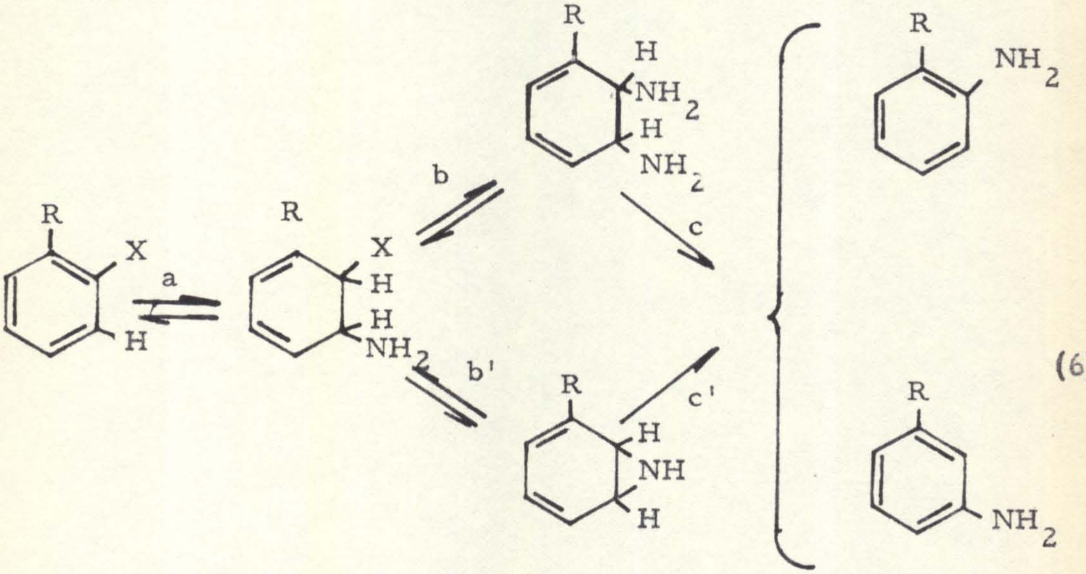


VIII

if the dual mechanism were correct, the overall hydrogen-deuterium kinetic isotope effect of nearly 6 found for amination of bromobenzene-

2-^{2}H (9) would infer an isotope effect of almost 12* for that part of the reaction which proceeds with rearrangement, because, by all rights, the direct mechanism would have at most a 10-20% secondary hydrogen kinetic isotope effect.

A further explanation for the 1:1 ratio of isomeric products resulting from these amination reactions involves addition-substitution-elimination (eq. 6). This formulation is rendered unlikely by virtue of



(6)

the large (5.5-5.8) kinetic isotope effect found in aminations of bromobenzene-2-^{2}H. The argument is as follows. The hydrogen kinetic isotope effect implies that the bond to the ortho hydrogen is broken in

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*The isotope effects in question are calculated from the percent reaction and the deuterium content of recovered halobenzene relative to that of the starting material. If a dual mechanism were correct, both parts of the mechanism would contribute equally to raising the percent reaction. However, only the rearranging mechanism would affect the isotopic ratio. Thus the calculated isotope effect would be lower than the true value. (For a given isotopic ratio a smaller percent reaction represents a larger isotope effect.)

the rate-determining step; therefore, the slow step in (6) would have to be the final, probably exothermic, step (c) involving loss of ammonia or rearrangement of a proton and re-establishment of the aromatic system. The highly endothermic addition of ammonia in step (a) and the loss of halogen (b or b') would thus both be required to be rapid equilibria.*

The present research is directed at determining whether or not any direct halogen displacement occurs, either by an S_N2-like reaction or through the path of equation 1, in amination reactions which have been postulated to involve benzyne intermediates.

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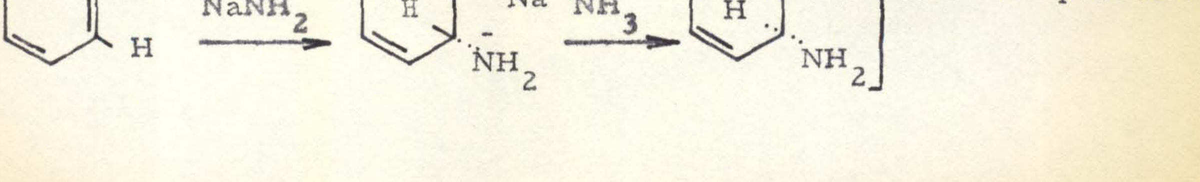
*A variant of the above mechanism involves (10), as has already been pointed out, a most unfavorable intermediate. Moreover, this mechanism appears to be inconsistent with the lack of rearrangement found in the amination of substances like m-bromoanisole.



Discussion of Results

Information as to direct halogen displacement was sought through an investigation of the extent of rearrangement in the amination of iodobenzene-1-^{14}C-2,4,6-^{2}H$_3$. The deuterium substituted iodobenzene, rather than the corresponding chloro- or bromo-compound, was chosen for study since, in the apparently analogous hydrolysis of halotoluenes (11), iodotoluene showed the greater tendency for direct substitution.

Iodobenzene-1-^{14}C-2,4,6-^{2}H was prepared from commercially available aniline-1-^{14}C which was deuterated by repeated equilibration with 99% deuterium oxide prior to diazotization. The calculated deuterium purity of the iodobenzene-1-^{14}C-2,4,6-^{2}H$_3$ used was 98.5%. Carbon-hydrogen absorption peaks at 10.03, 13.70 and 14.65µ in the infrared spectrum of normal iodobenzene were not present in the spectrum of the deuterated iodobenzene. The amination was carried out with potassium amide in anhydrous liquid ammonia and the aniline formed was degraded by methods described previously (1).

The observed extent of rearrangement (Table III) in the amination of iodobenzene-1-^{14}C-2,4,6-^{2}H$_3$ is nearly identical to that found in the amination of iodobenzene-1-^{14}C. If the amination had occurred by a combination of direct and rearranging substitutions, the presence of the ortho-deuterium atoms would act to slow down the rearranging

Table III

Radioactivity Analyses of Degradation Products

		Cyclohexanone	CO_2 (aniline-1-^{14}C)	1,5-Diaminopentane (aniline-2-^{14}C)
Iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$	Meas. act.[a]	0.1195$\pm$0.0020	0.0566$\pm$0.005	0.0632$\pm$0.0010
	% Total act.	(100)	47.4$\pm$0.9	52.8$\pm$1.2
Iodobenzene-1-^{14}C	% Total act.	(100)	46.4$\pm$0.1[b]	53.0$\pm$0.2[b]

[a] Activities in microcuries per millimole.

[b] Data from ref. 2.

reaction (as a result of the kinetic isotope effect) by a factor of 8-12 relative to the non-rearranging substitution. Similarly, if the formulation of equation 6 were correct, the final step (c) would proceed preferentially with the loss of hydrogen, rather than deuterium, thus increasing the proportion of unrearranged product. In either case, the product mixture resulting from the amination of iodobenzene-1-^{14}C-2,4,6-$^{2}H_{3}$ would have a higher ratio of aniline-1-^{14}C to aniline-2-^{14}C than is found for the amination of iodobenzene-1-^{14}C.

The 1:1 ratio of ^{14}C-labelled anilines obtained in the amination of iodobenzene-1-^{14}C-2,4,6-$^{2}H_{3}$ is consistent only with an elimination-addition mechanism: the ortho deuterium is removed during the formation of benzyne and has no influence on the manner of addition of ammonia to the reactive benzyne bond. If one considers the most adverse limits of error and accepts the value of 53.0±0.2% of activity in the 2-position (i.e., aniline-2-^{14}C formed) as a measure of the ^{12}C-^{14}C isotope effect, it is possible to calculate an upper limit for the extent of direct substitution accompanying the amination of iodobenzene-1-^{14}C of about 0.2%.

Experimental

Deuteration of Aniline. Trial I.- Aniline hydrochloride (2 g., 0.0155 mole), prepared from freshly distilled aniline and dry hydrogen chloride, was placed in a long neck 5 ml. flask. Deuterium oxide (95%, 1.86 ml., 0.093 mole) was added (12). The sealed flask was heated in boiling water for 24 hrs. The water in the mixture was removed under vacuum, recovered in a Dry Ice trap, and analyzed by a refractive index method. The deuterium content of the recovered water was 65±2% (theoretical 66.6%).

Determination of Deuterium Oxide in Deuterium Oxide-Water Mixtures. Refractive indices of mixtures were measured with a Zeiss immersion refractometer used with an auxiliary prism. Percent deuterium oxide was plotted against refractometer readings for several standard mixtures made up from 99.5% deuterium oxide and ordinary distilled water. The calibration curve was linear to within ± 2% (Table IV).

Deuteration of Aniline- Trial II. -Aniline hydrochloride (10 g., 0.0775 mole), prepared from freshly distilled aniline and dry hydrogen chloride, was equilibrated with a three-mole excess of deuterium oxide (12.55 ml., 0.675 mole) for 24 hrs. in a 100° furnace. The equilibration was repeated three times, one third of the material being removed

Table IV

Refractive Index Analyses of D_2O-H_2O Mixtures

Sample	Refractometer Reading	Wt. % D_2O
D_2O	1.60	100
Standard 1	3.30	87±2
2	5.02	73.6
3	7.00	59.4
4	8.28	45
5	9.95	31
6	11.45	16
H_2O	13.20	0
Recovered	6.0	65

each time and the aniline recovered. Infrared spectra of all three samples were nearly identical with each other but differed from that of normal aniline. Although several aniline absorption peaks in the 8-13 micron region were absent from the spectra of deuterated samples, no spectral variations of analytical value were found. The n.m.r. spectra were more useful in this respect. The ratios of phenyl proton peak areas of deuterated to normal aniline of 0.65 and 0.42 for the first and third equilibrations agree well with the calculated values of 0.55 and 0.42. Thus, equilibration is complete under the conditions used.

The spectra of normal aniline exhibits three phenyl proton peaks which have been assigned to the ortho-, meta- and para-hydrogens, respectively (13). The deuterated samples have one major peak at the position of the meta-hydrogen absorption. If the assignment of peaks is correct, the deuterated aniline is deuterated as expected solely and fairly completely in the ortho and para positions.

Iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$.- Aniline-1-^{14}C hydrochloride* (68.0 mg., 0.168 mc.) was diluted with 18.15 g. of aniline hydrochloride (0.14 mole) prepared from freshly distilled aniline and dry hydrogen chloride and purified by recrystallization until a sample remained nearly colorless on heating in water to 100° for 24 hrs. The mixture

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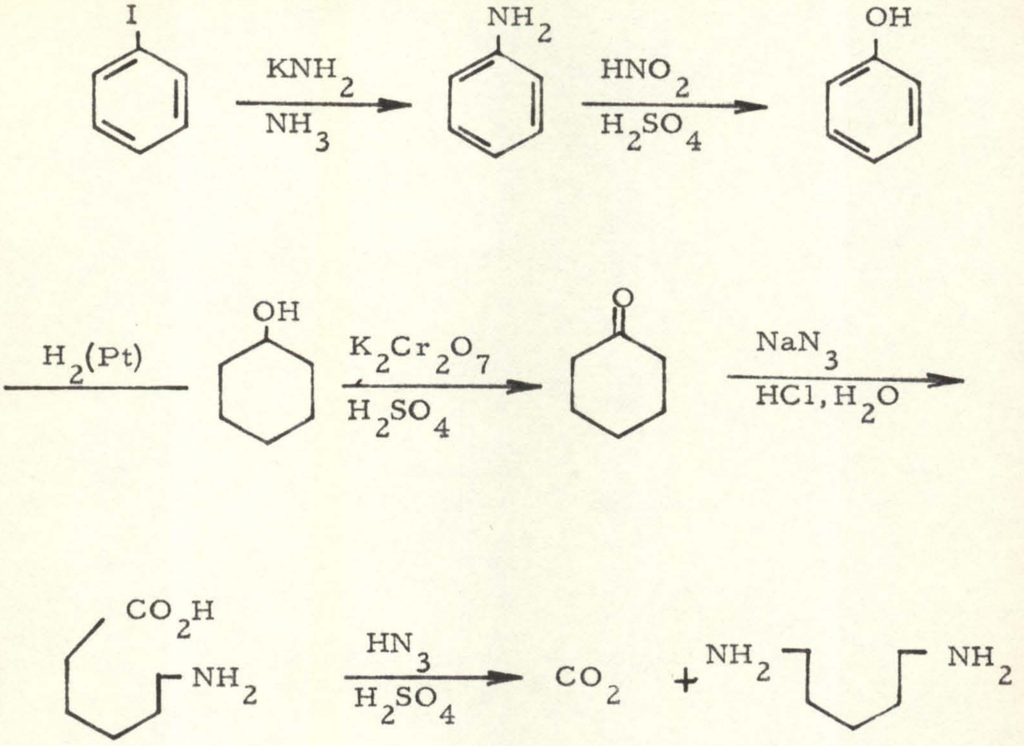
*Obtained from Tracerlab, Inc.

was equilibrated five times with 15 ml. (0.64 mole) of 99.5% deuterium oxide (12). The calculated isotope purity of the deuterated material was 98.5%. Aniline-1-^{14}C-2,4,6-$^{2}H_3$ was converted to iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$ by diazotization and addition of potassium iodide.

Amination and Degradation of the labeled iodobenzene and the aniline formed therefrom were carried out as described (1) previously for iodobenzene-1-^{14}C (eq. 7). The ^{14}C activities of the derivatives were determined by the vibrating-reed electrometer method.(14).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HNO2
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OH
H2(Pt)
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K2Cr2O7
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CO2H
NH2
HN3
H2SO4
CO2
+
NH2
NH2

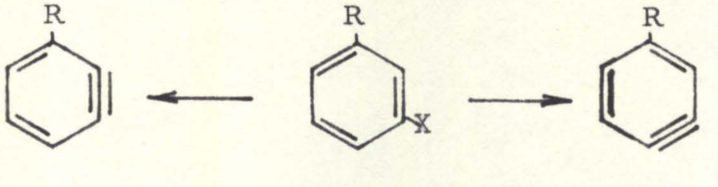
(7)

PART II

ORIENTATION IN AMINATIONS OF SUBSTITUTED HALOBENZENES

Introduction

Substituent effects in amination reactions proceeding via an elimination-addition mechanism have been coherently explained on the basis of the inductive effects of the substituents (9). Thus, a *m*-substituted halobenzene, which can form either a 3-substituted benzyne (IX) or a 4-substituted benzyne (X), preferentially will lose the most acidic proton* in benzyne formation (eq. 8). In agreement



(8)

IX X

with the above explanation is the formation of only 3-substituted benzynes from *m*-bromoanisole and m-chlorobenzotrifluoride. The acidities of the *ortho* and *para* hydrogens of these compounds differ greatly as can be seen from the reported rates of hydrogen-deuterium exchange for substituted deuterobenzenes (Table V).

Similarly, product formation may be explained by postulating the addition of amide ion to the benzyne so as to place the resulting

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*As has been pointed out previously (1), the strongly basic nature of the reagents involved warrants the conclusion that the hydrogen is lost as a proton rather than as a hydrogen atom or hydride ion.

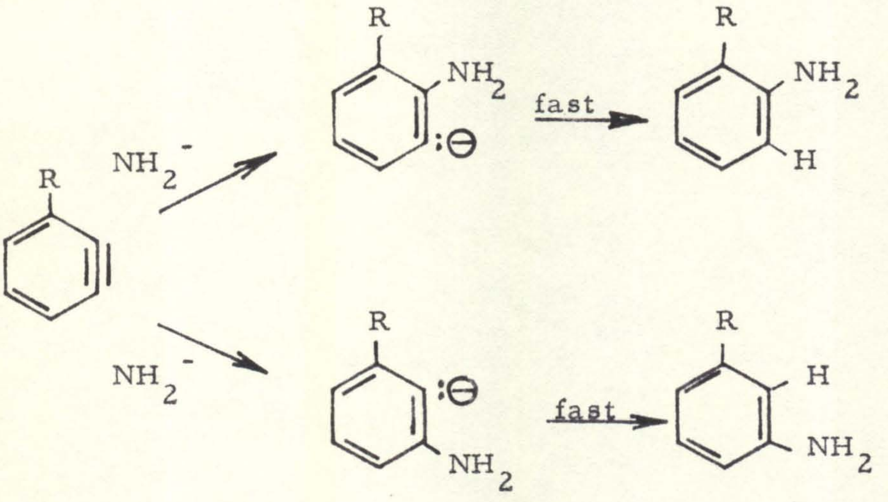
Table V

Pseudo First-Order Rate Constants for Deuterium-Protium Exchange of Substituted Deuterobenzenes (C_6H_5DR) with 0.6 $\underline{M}$ Potassium Amide in Liquid Ammonia.[a]

R	k, $sec.^{-1}$	R	k, $sec.^{-1}$
$2\text{-}CF_3$	$6x10^{-2}$	2-F	$>4x10^{-1}$
3-CF	$1x10^{-3}$	3-F	$4x10^{-4}$
$4\text{-}CF_3$	$1x10^{-3}$	4-F	$2x10^{-5}$
$2\text{-}OCH_3$	$1x10^{-3}$		
$3\text{-}OCH_3$	10^{-8}		
$4\text{-}OCH_3$	10^{-7}		
H	10^{-7}		

[a] Data from ref. 15.

negative charge in a position which is most favorable with respect to the inductive effect of the substituent (eq. 9). The stability of XI in



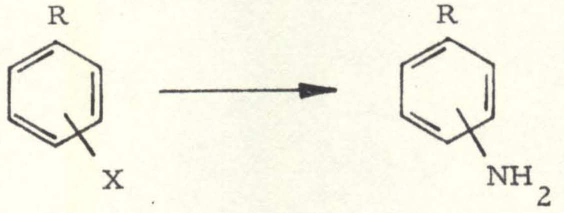
XI XII

cases where R is electron attracting insures the formation of XII as the sole product.

The correlation between these directive effects and the data of Table V is evident from the observed ratios of <u>meta</u> and <u>para</u>-products obtained from 4-substituted benzynes (Table VI), which are the only intermediates formed from <u>p</u>-substituted halobenzenes. Thus the $k_{\underline{m}}/k_{\underline{p}}$ of about 20 for the fluorine compound correlates with the greater proportion of <u>para</u>- with respect to <u>meta</u>-substituted product obtained from p-bromofluorobenzene. If such a correlation exists throughout all the observed reactions, it is evident that, since $k_{\underline{o}}/k_{\underline{p}}$ for anisole is approximately 10^{-5}, only a negligible amount of 4-substituted benzyne would be formed. Similarly, since k_o/k_m is about 10^{-4}, addition

Table VI

Orientations in Amination of Substituted Halobenzenes[a]



R	X	Ortho %	Meta %	Para %
o-OCH_3	Br	---	100	---
m-OCH_3	Br	---	100	---
p-OCH_3	Br	---	49±1	51±1
o-CF_3	Cl	---	100	---
m-CF_3	Cl	---	100	---
p-CF_3	Cl	---	50±5	50±5
o-CH_3	Cl	45±4	55±4	---
m-CH_3	Cl	40±4	52±4	8±4
p-CH_3	Cl	---	62±4	38±4
p-CH_3	Br	---	61±4	39±4
p-F	Br	---	20±1	80±1

[a] Data from ref. 9.

to the 3-substituted benzyne would be essentially completely directed to the meta-position. In the analogous case of the trifluoromethyl group, for which $k_{\underline{o}}/k_{\underline{m}}$ is about 60, it is reasonable that the expected trace (< 1) of o-aminobenzotrifluoride formed in the amination of m-chlorobenzotrifluoride would not have been detected by the infrared method of analysis used.

Discussion of Results

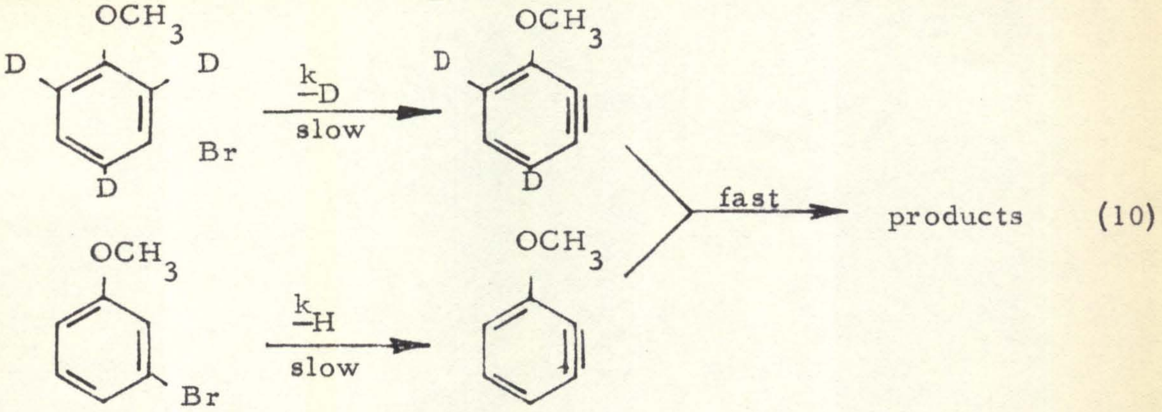
Despite the coherency of the explanation offered for the lack of rearrangement in aminations of m-haloanisoles, there is no evidence which rules out the possibility that m-haloanisoles react with amide ion in liquid ammonia by a direct substitution mechanism, rather than by an elimination-addition mechanism. Substituents which do not lead to rearrangement when in the meta position (eq. $-OCH_3$, $-CF_3$) are inductively electron-attracting and might activate a meta-halogen towards direct nucleophilic substitution. It is conceivable that such activation could alter the course of the amination reaction.

In order to determine the mechanisms by which 3-bromoanisole reacts with potassium amide in liquid ammonia and with lithium diethylamide in ether, aminations were carried out with mixtures of 3-bromoanisole and 3-bromoanisole-2,4,6-$^2H_3$. If 3-bromoanisole is aminated by an elimination-addition mechanism, the presence of the ortho-deuterium atom should result in a kinetic isotope effect, and the undeuterated compound should react faster than the deuterated. The experimental isotope effects, k_H/k_D, summarized in Table VII, are calculated on the assumption that the ortho hydrogen is removed in the rate determining step (eq. 10). That k_H/k_D is much larger than unity confirms participation of the ortho hydrogen and, hence, offers strong evidence for the intermediacy of 3-methoxybenzyne.

Table VII

Deuterium Kinetic Isotope Effects

Reagent	Solvent	Mole % deuterated haloanisole: At start	At finish	% Formation of halide ion at finish	$\underline{k}_H/\underline{k}_D$ (apparent)
KNH_2	NH_3	28.5 ± 2	38.5 ± 2	54.3 ± 0.3	1.9 ± 0.1
$LiN(Et)_2$	Ether	27.0 ± 2	71.0 ± 2	84.1 ± 0.4	3.1 ± 0.1



(10)

The "apparent" isotope effects are considerably lower than those expected (- 5.7)* if the ortho hydrogen were removed in a concerted elimination (eq. 10) as is assumed in the calculations. The low isotope effect may imply that considerable exchange of hydrogen for deuterium is taking place prior to the loss of the bromine to form 3-methoxybenzyne. This conclusion is suggested by the relatively high rate constant for the exchange of deuterium ortho to a methoxy group (15) (Table V).

The isotope effect of 3.1 found for the reaction of 3-bromoanisole-2,4,6-$^2H_3$ with lithium diethylamide in ether probably represents the actual isotope effect for the reaction.** This low value

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*The isotope effect resulting from the reactions of halobenzenes with lithium diethylamide in ether is 5.5-5.8. In these reactions, exchange is not important (1). The value of 5.7 may, therefore, be considered the actual value of k_H/k_D, as distinct from the "apparent" value which is lowered by exchange. The k_H/k_D ratio of 5.7 is close to the 6-7 range reported for concerted E2 dehydrobrominations (16).

compared to those found for chloro- and bromobenzene-2-$^2H_2$ could conceivably result from competing elimination-addition and direct-substitution reactions. However, it seems more reasonable that the isotope effect is smaller because of a decrease in the zero-point energy change of the _ortho_ hydrogen between ground and transition states resulting from the strong inductive effect of the methoxy group. This explanation is consistent with evidence from similar reactions, _e.g._, the known dependence of the magnitude of the isotope effect on electron density at the reactive center (17).

**As no 100% deuterated 3-bromoanisole was available, the possibility of exchange with the approximately 0.25 mole excess of diethylamine which was present in these reactions cannot be ruled out. The 90% deuterated 3-bromoanisole used in these experiments yielded, upon treatment with lithium diethylamide in ether with three moles excess diethylamine, recovered 3-bromoanisole which was 100% deuterated. As the expected isotope effect would cause an increase in deuterium content of well over 10%, there is no way to evaluate the extent of the exchange. The results at least rule out the unlikely possibility of equilibration of starting material with the small amount of excess amine present in the reaction mixture.

Experimental

3-Bromoanisole-2,4,6-$^2H_3$. - m-Anisidine-2,4,6-$^2H_3$ was prepared by repeated equilibrations of m-anisidine hydrochloride with deuterium oxide (12). The isotopic purity, calculated on the basis of complete equilibration, was 95% and was confirmed by the infrared spectrum.

The deuterated m-anisidine was converted to 3-bromoanisole-2,4,6-$^2H_3$ by the Sandmeyer reaction (18). The material used in the aminations gave only one peak on analysis by vapor-phase chromatography.

3-Bromoanisole-2,4,6-$^2H_3$ with Potassium Amide in Liquid Ammonia. - The method used was similar to that described previously (1). 3-Bromoanisole-2,4,6-$^2H_3$ (3.1616 g.) was diluted with normal 3-bromoanisole (8.3288 g.), and 9.9388 g. (0.0528 mole) of the mixture was dissolved in 300 ml. of anhydrous liquid ammonia. A mixture of potassium amide (0.0883 mole) prepared from 3.4 g. of potassium metal and 80 ml. of anhydrous liquid ammonia was added to the 3-bromoanisole over a period of 30 sec. The reaction was allowed to run for 5 min. and was then quenched by the addition of 22 g. of ammonium nitrate. Anhydrous ether (100 ml.) was added and the ammonia allowed to evaporate. The residue was extracted several times with water. The water washings (400 ml. total) were combined, boiled to remove excess ether and ammonia quantitatively to 500 ml. Bromide ion was determined by the Volhard method with a precision of 0.3%.

The ethereal solution, containing the unreacted 3-bromoanisole, was washed with 250 ml. of 3 M hydrochloric acid to remove anisidine and the 3-bromoanisole distilled through a 20-cm. semimicro column (20). The recovered bromoanisole (b.p. 89°, 8 mm.) showed only one peak on analysis by vapor-phase chromatography.

3-Bromoanisole-2,4,6-$^2H_3$ with Lithium Diethylamide in Ether. - Lithium diethylamide was prepared from diethylamine (4.52 g., 0.062 mole) and freshly prepared methyllithium in ether (70 ml., 0.90 N., 0.055 mole). A mixture of 3-bromoanisole-2,4,6-$^2H_3$ and 3-bromoanisole (10.7039 g., 0.0554 mole) was added over a period of 2 min. The initially strongly exothermic reaction subsided within 5 min. The reaction mixture was stirred for 3 hr. and the quenched by the addition of 20 ml. of water. The ether layer was extracted with 400 ml. of water; the water extract was boiled to remove excess ether and diluted to 500 ml. The Volhard method was used for the analysis for bromide ion. Iodide (from the methyl iodide used in the preparation of methyllithium) was removed by oxidation with 0.05 N nitrous acid (21). Analyses were precise to 0.4%. The ether layer, which contained the unreacted bromoanisole, was washed with 400 ml. of 3 *N* hydrochloric acid to remove amines. The bromoanisole was distilled and then purified for analysis by vapor-phase chromatography.

Analysis of Mixtures of 3-Bromoanisole-2,4,6-$^{2}H_{3}$ and 3-Bromoanisole. - Mixtures were analyzed for deuterium by the "base-line" method at 11.061μ (19) with a Perkin-Elmer (Model 21) Infrared Spectrophotometer.

Transmittances of undiluted mixtures were measured in a 0.05-mm. cell. The 0.05-mm. cell in the reference beam was filled with pure protonated 3-bromoanisole. In this manner, the deuterium absorption peak was made sufficiently large for the desired accuracy without interference from adjacent hydrogen absorption. A calibration graph was prepared from several standard mixtures. The plots were linear to within 1% over the concentrations calibrated. Duplicate analyses agreed to within 1%.

Calculation of Kinetic Isotope Effects. - "Apparent" kinetic deuterium isotope effects were calculated on the basis of a concerted dehydrohalogenation mechanism (eq. 3). The following assumptions were made in formulating the kinetic expression below: only the 2-hydrogen of 3-bromoanisole is involved in the amination*, the reactions

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*One may assume that no 4-substituted benzyne is formed because, if it were, *p*-substituted product would result; *p*-bromoanisole, which can form only a 4-substituted benzyne, yields an almost 1:1 mixture of *m*- and *p*-anisidine. (The manner of addition to a benzyne bond is independent of the manner in which the benzyne was formed; *p*-chloro- and *p*-bromotoluene yield identical ratios of *m*- and *p*-anisidine.

of benzyne are not rate-determining nor reversible, and the initial elimination reaction is first order with respect to 3-bromoanisole. The rate of disappearance of 3-bromoanisole-2,4,6-$^2H_3$(D) and 3-bromoanisole (H), respectively, are:

$$\frac{-d[D]}{dt} = \underline{k}_D[D][NR'_2{}^-]^n \qquad (11)$$

and

$$\frac{-d[H]}{dt} = \underline{k}_H[H][NR'_2{}^-]^n \qquad (12)$$

Division of (12) by (11) integration yields

$$\frac{\underline{k}_H}{\underline{k}_D} = \frac{\ln\frac{[H_t]}{[H_o]}}{\ln\frac{[D_t]}{[D_o]}} \qquad (13)$$

<u>3-Bromoanisole-2,4,6-$^2H_3$ with Lithium Diethylamide.</u> - 3-Bromoanisole-2,4,6-$^2H_3$ (2.0 g., 0.01 mole, approximately 90% deuterated) was treated with methyllithium (0.01 mole) and diethylamine

(2.92 g., 0.04 mole) as described above for 3-bromoanisole-2,4,6-$^2H_3$. The volume of ether used (70 ml.) resulted in a 0.4-0.5 N solution of diethylamine. After a 75 min. reaction, unreacted 3-bromoanisole-2,4,6-$^2H_3$ was recovered. The infrared spectrum of this material showed no evidence of protonated 3-bromoanisole.

Amination of p-Bromotoluene. - Sodium amide was prepared from sodium (10 g., 0.43 g.-atom) and 300 ml. of distilled liquid ammonia. p-Bromotoluene (18.8 g., 0.11 mole) was added over a period of 10 min., and the reaction quenched after a further 10 min. with ammonium chloride. The residue remaining after evaporation of the ammonia was dissolved in water and extracted with ether overnight. The extract was dried over barium oxide and the ether removed through a 90-cm. Helipak column. Distillation of the product through a 30-cm. semimicro column yielded 3.4 g. (0.034 mole) of mixed toluidines. The composition of the mixture as determined by the "base line" method of infrared analysis was 61±4% m-toluidine and 39±4% p-toluidine.

Table VIII

Infrared Analyses of Mixtures of 3-Bromoanisole and 3-Bromoanisole-2,4,6-$^{2}H_3$ from Amination Reactions

Reagent	Solvent	Mixture	$\underline{I}_B$	$\underline{I}$	Log$_{10}$ $\underline{I}_B/\underline{I}$	% 3-Bromoanisole-2,4,6-$^{2}H_3$[a]
KNH_2	NH_3	Starting	91.9	66.0	0.1443	28.5
KNH_2	NH_3	Recovered	90.3	57.1	0.2004	38.5
$LiN(C_2H_5)_2$	Ether	Starting	91.7	69.3	0.1402	27.7
$LiN(C_2H_5)_2$	Ether	Recovered	77.6	31.2	0.4150	74.7

[a] Calculated from log$_{10}$ $\underline{I}_B/\underline{I}$ values in preceding column and data in Table VII.

Table IX

Infrared Analyses of Standard Mixtures
of 3-Bromoanisole and 3-Bromoanisole-
-2,4,6-$^2H_3$

% 3-Bromo-anisole-2,4,6-$^2H_3$ [a]	$\underline{I}_{\underline{B}}$ [b]	$\underline{I}$ [c]	$\text{Log}_{10}\underline{I}_{\underline{B}}/\underline{I}$
20.55	93.3	74.5	0.0972
26.15	91.4	67.2	0.1332
30.77	90.5	62.8	0.1584
32.34	90.6	62.6	0.1632
40.78	88.2	53.8	0.2143
70.4 [d]	79.5	30.8	0.3971
72.8 [d]	80.4	32.2	0.4081
86.8 [d]	77.1	26.5	0.4639

[a] Mixtures made up by weight. [b] Intensity of base line absorption at 11.061 microns measured as % transmission; see ref. 19.
[c] Intensity of sample absorption at 11.061 microns measured as % transmission; see ref. 19. [d] High concentration values plotted separately.

After the preparation of this thesis, it was discovered that a lower-boiling distillation fraction derived from the purification of 3-bromoanisole-2,4,6-$^{2}H_{3}$, which was recovered from the reaction with lithium diethylamide (page 32), had not been discarded. Accordingly, in the light of the observed reduction of iodobenzene (page 65), it was analysed for anisole. Anisole was present in an amount sufficient to account for at least the greater part of the decrease in isotope effect discussed above (page 30).

PART III

LEAVING GROUPS IN BENZYNE FORMATION

Discussion

While halobenzenes have been shown to react with strong nucleophiles via an elimination-addition mechanism, substituted benzenes having other leaving groups react to give direct substitution. For example, phenyl-1-^{14}C-trimethylammonium bromide is attacked by potassium amide in liquid ammonia to yield ^{14}C-labeled aniline consisting of 96% aniline-1-^{14}C and only 4% aniline-2-^{14}C. The lack of rearrangement in this case has been explained by facilitation of attack of nucleophile at the 1-carbon by the electron attracting onium group (1). In order to obtain a clearer picture of the factors governing the enzyme mechanism it would be desirable to investigate leaving groups of various other types.

It has been suggested that arylsulfonic acids react with molten alkali and alkali amide by a benzyne-type mechanism (5). While the rearrangements (22, 23) observed in these reactions are consistent with an elimination-addition mechanism, they are also consistent with a desulfonation process. In fact, there is evidence to suggest that the desulfonation mechanism is correct; alkali fusion of p-hydroxybenzenesulfonic acid yields phenol as well as smaller quantities of resorcinol (24). Significantly, under the same conditions phenol is converted to resorcinol. Furthermore, p-toluenesulfonic acid yields only p-cresol and no rearranged products when fused with potassium hydroxide (25). Unidentified traces of isomeric products reported probably result from impurities in the p-toluenesulfonic acid used.

It is possible, however, that these fusion reactions are temperature sensitive in the same manner as the hydrolyses of halobenzenes, and that at higher temperatures rearrangement may become more prominent. It was therefore of interest to determine the reactivity of p-toluenesulfonic acid with sodium amide in liquid ammonia. The acid proved to be unreactive towards this reagent at -33° and at room temperature.

A further possible reactant was a sulfonate ester; nitrophenyl benzene sulfonates are cleaved by aromatic amines to yield diarylamines (26). However, treatment of p-cresyl-p-toluenesulfonate with liquid ammonia at -33° resulted in ammonolysis of the ester. This result is consistent with the predominant transesterification observed in reactions of similar esters with phenoxide ion (27).

Experimental

Attempted Amination of p-Toluenesulfonic Acid. - Sodium amide was prepared from sodium (15 g., 0.65 g.-atom) and liquid ammonia (300 ml.) using ferric chloride as a catalyst. p-Toluenesulfonic acid (20 g., 0.12 mole) was added to the well-stirred amide mixture over a period of 15 min., and the mixture was stirred for an additional 20 min. before being quenched with excess ammonium chloride. The gray dry powder remaining after evaporation of the ammonia was dissolved in water and extracted overnight with ether. The ethereal solution was extracted with 6 N hydrochloric acid and the aqueous extract was neutralized and extracted overnight with ether in order to isolate basic material. The ether extract, after the solvent was removed, yielded about 5 mg. of yellow oil, the infrared spectra of which showed no peaks characteristic of toluidine. The oil probably arose from impurities in the reagents.

Attempted Amination of p-Toluenesulfonic Acid at Room Temperature. - Sodium amide in liquid ammonia, prepared from 15 g. (0.65 g.-atom) of sodium and 30 ml. of anhydrous liquid ammonia, was poured into a precooled 500-ml. stainless steel Parr bomb. p-Toluenesulfonic acid (20 g., 0.12 mole) was placed in a small beaker suspended above the surface of the amide solution in the bomb. After the sealed bomb had warmed to room temperature it was inverted to mix the reactants and placed on a Parr shaker for 3 hr. At the end of this time it was cooled in Dry Ice and the reaction quenched with excess ammonium chloride. The gray solid remaining after evaporation of the ammonia was extracted overnight with ether. Concentration of this extract yielded a few mg. of the same yellow oil found in the attempted amination at -33° reported above.

Attempted Amination of *p*-Cresyl-*p*-toluenesulfonate. - Sodium amide was prepared from 19 g. (0.82 g.-atom) of sodium and 300 ml. anhydrous liquid ammonia. *p*-Cresyl *p*-toluenesulfonate (39.3 g., 0.15 mole) was added over a period of 20 min. and the reaction was allowed to proceed for a further 10 min. before it was quenched by the addition of excess ammonium chloride. The gray solid remaining after evaporation of the ammonia was worked up as described for the attempted amination of p-toluenesulfonic acid. No basic product was obtained. *p*-Cresol was recovered from the acidified aqueous extract.

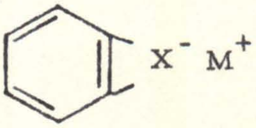
IV. ATTEMPTED PASSAGE OF BENZYNE THROUGH THE VAPOR-PHASE

Introduction

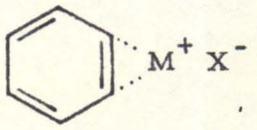
While the elimination-addition mechanism has been confirmed for the amination of the non-activated halobenzenes, and postulated for several other reactions, the nature of the benzyne intermediate has not been conclusively demonstrated. That benzyne is an intermediate, rather than a transition state, appears almost certain. In support of this postulate are the many reactions in which benzyne is trapped by a reactant other than the one which caused the elimination. For example, benzyne formed from the decomposition of o-fluorophenyllithium or o-fluorophenylmagnesium bromide reacts as a dienophile with furan (28). Furthermore, this condensation appears to be general for this type of diene (29), and for anthracene (30). Similarly, halobenzenes react with alkali amide to yield benzyne which may be trapped by a second nucleophile. Thus, benzyne formed from p-bromotoluene and sodium amide in liquid ammonia in the presence of sodium phenylacetylide gives the expected mixture of m- and p-tolylphenylacetylenes, and naphthalyne formed from bromonaphthalenes with sodium amide in refluxing piperidine reacts with piperidine rather than with amide ion (31). That benzyne formation is not initiated by piperidine is evident from the observation that both 1- and 2-bromonaphthalene react with piperidine by a direct substitution mechanism.

Of particular pertinence to the question of the stability of benzyne are the phenyllithium-lithium piperidide competition studies carried out by Huisgen (32). Fluorobenzene, 1-fluoronaphthalene and 9-chlorophenanthrene were allowed to react with mixtures of various proportions of phenyllithium and lithium piperidide. Although the latter reacts with fluorobenzene to form benzyne seventy times faster than does phenyllithium, phenyllithium adds preferentially to the reactive benzyne bond. The ratio of phenyl- to piperidyl-substituted product formed for a given ratio of reagents (Fig. 2) is thus a measure of the stability of the aryne; the more reactive aryne will show the least selectivity. The increasing selectivity demonstrated by the arynes which one would expect to be the most stable helps confirm the suggestion that benzyne and arynes in general are intermediates of moderately long half life.

Although the benzyne intermediate probably exists as a C_6H_4 hydrocarbon, the symmetry requirements and kinetic data which have been reported (Part II) are consistent with C_6H_4-complexes with halide ion (XIII) or with metal ion (XIV). An intermediate such as XIII is rendered unlikely by virtue of the fact that aryl fluorides enter into



XIII



XIV

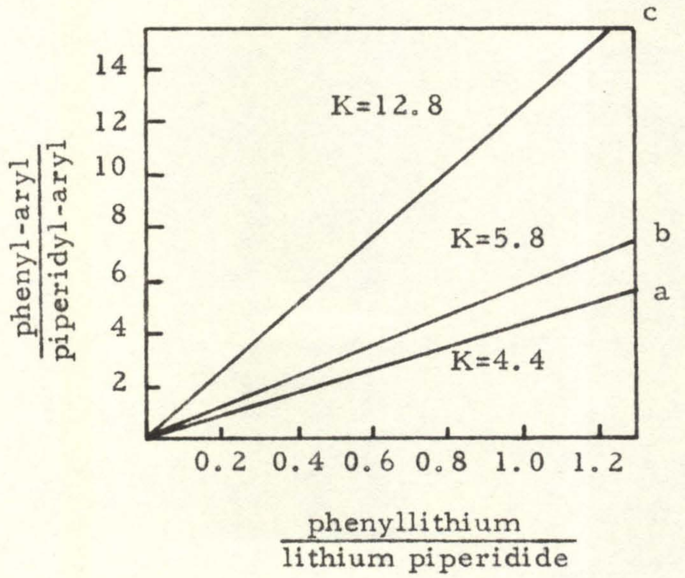


Fig. 2. Competition of phenyllithium and lithium piperidide with benzyne (a), 1,2-naphthyne (b), and 9,10-phenanthryne (c). (K, the selectivity constant, is the ratio of phenyl to piperidyl substitution for an equimolar mixture of reagents.)

benzyne formation with lithium dithylamide and phenyllithium, and that o-fluorophenyllithium decomposes directly to benzyne. It is unlikely that fluorine could expand its valence shell to accommodate the ten electrons required for the halogen in XIII; no compounds are known in which fluorine holds more than eight valence electrons (33). The cation complex, XIV, is improbable since a metal ion would not be expected to complex with an unsaturated compound in the presence of a large excess of liquid ammonia. In any case, such a structure, which is analogous to the silver ion-olefin complex, is unknown for alkali metals.

It is therefore reasonable to expect that benzyne exists as a C_6H_4 hydrocarbon. This possibility would best be demonstrated if the hydrocarbon could be passed through the gas phase unaccompanied by halide or metal ion, and shown to react, in a trap or in the gas phase, as expected for the benzyne intermediate. However, it should be noted that passage of benzyne through the gas phase would not yield direct information as to the nature of the intermediate in solution, but might be used as an argument against XIII or XLV. It is of course possible that the intermediate is stabilized by solvation and can exist only in solution, or else that it is so reactive that it disappears before it can be volatilized.

Discussion of Results

The pyrolysis and photolysis of o-diiodobenzene were the first of several possible reactions investigated to produce benzyne in the gas phase. o-Diiodobenzene was chosen because one may expect, if there is any extra C-C bonding between the "triple-bonded" atoms of benzyne, that the rate of decomposition of o-iodophenyl radicals to benzyne and iodine atoms might well be greater than the rate of loss of the first iodine to form o-iodophenyl radicals. This suggestion is consistent with the fact that the C-I dissociation energy of β-iodoethyl radicals to form ethylene (8-11 kcal./mole) is lower than that of ethyl iodide to form ethyl radicals (51.5 kcal./mole). Furthermore, the possibility of repulsive interactions between the o-iodines might act to lower the decomposition temperature relative to that of iodobenzene, which decomposes to phenyl radicals at 600°(34, 35).

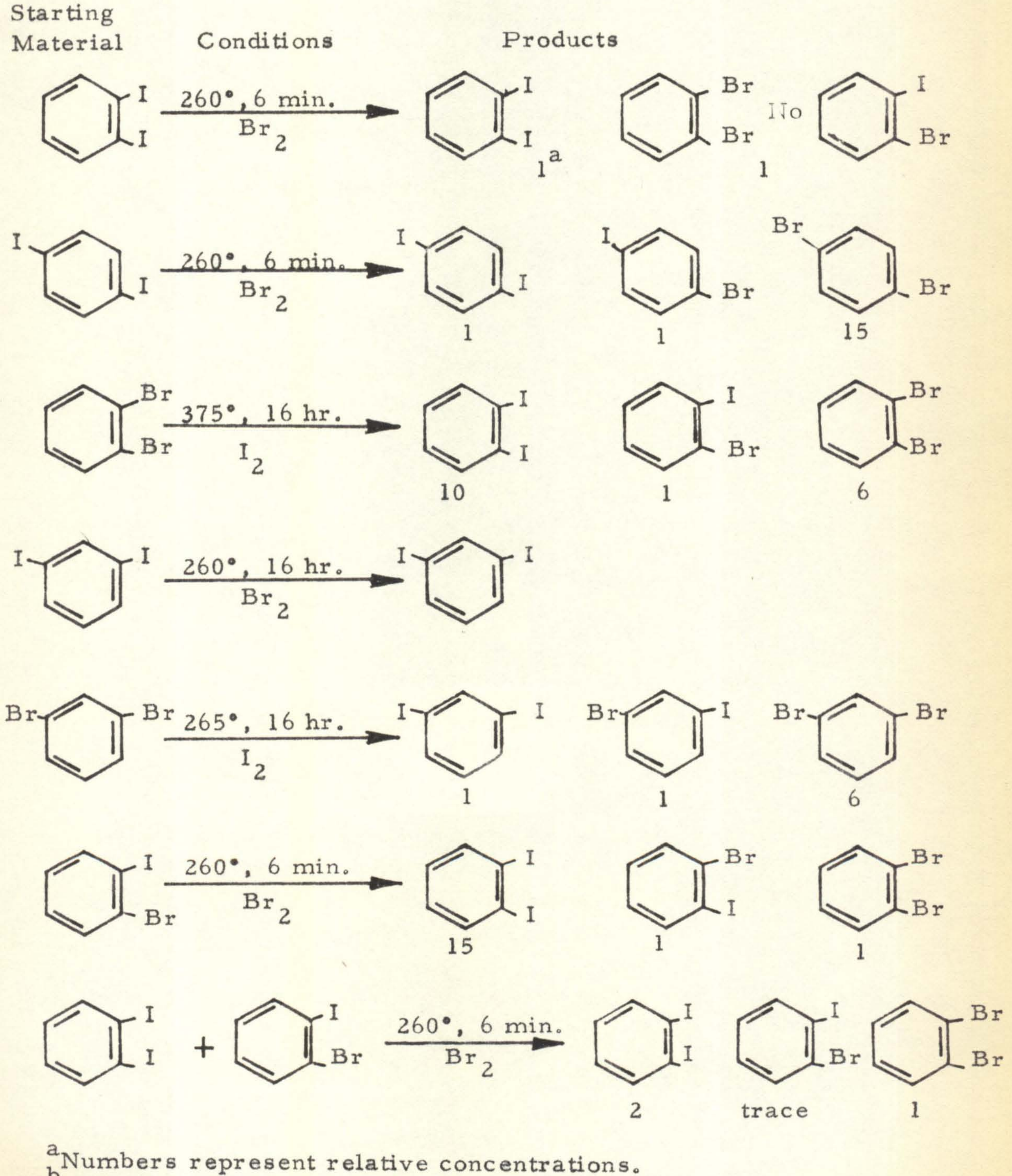
o-Diiodobenzene was found to liberate iodine on heating to 260°. Furthermore, pyrolysis of o-diiodobenzene at 260° in the presence of bromine resulted in a mixture of o-diiodobenzene and o-dibromobenzene, but no o-bromoiodobenzene, thus suggesting the intermediacy of benzyne. Alternatively, this reaction may have involved successive substitution of individual halogen atoms, in which case the absence of o-bromoiodobenzene in the products would have resulted from activation of the second iodine by the adjacent bromine. Such a reaction would be similar to the light catalysed exchange of bromobenzene with chlorine (36) and with radioactive bromine (37) at room temperature. To aid in clarifying this point, several other dihalobenzenes were prepared and pyrolyzed under similar conditions. The results of these experiments are summarized in Table X. All pyrolyses in the presence of bromine were accompanied by extensive bromination and the formation of hydrogen bromide. As the bromination reactions were only slightly slower than the substitutions, the experiments were limited to rather short reaction times so that the yields were low and not reproducible.

The formation of approximately 6% of *p*-bromoiodobenzene from p-diiodobenzene and bromine suggests that the exchange reactions involve substitution of individual halogen atoms rather than benzyne formation. However, the predominance of disubstituted product leaves open the possibility that part of the reaction proceeds through an elimination-addition mechanism involving *p*-phenylene, although the fact that the stabilized *p*-aryne, 9,10-anthracyne, is not formed from the decomposition of 9-chloro-10-dithioanthracene, and that the phenylation of 9-bromoanthracene does not exhibit piperidine catalysis (40) makes the importance of *p*-phenylene unlikely. *m*-Diiodobenzene could not be studied because the substitution, if it occurred at all, was far slower than the bromination.

Since the iodination of benzene with molecular iodine in the absence of oxidizing reagents does not occur, the corresponding dibromobenzenes were pyrolysed in the presence of iodine. The decomposition

Table X

Results of Pyrolyses of Dihalobenzenes in the Presence of Halogen.



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[a] Numbers represent relative concentrations.

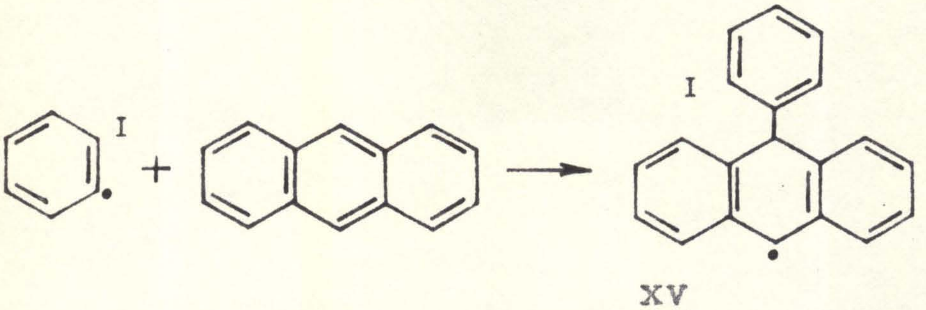
[b] Present in large excess.

of the bromine compounds was very slow even at 375°, and no solid products were formed. Although pyrolysis of *o*-dibromobenzene in the presence of iodine yielded all three possible dihalobenzenes, the predominance of *o*-diiodobenzene was again suggestive of benzyne formation. Furthermore, if the reaction had occurred by successive substitutions of halogen atoms, the low yield of *o*-bromoiodobenzene would mean that the substitution of the second bromine is enhanced by the adjacent iodine. This conclusion is inconsistent with that drawn from the pyrolysis of diiodobenzenes in the presence of bromine, in which case an *ortho* bromine appears to activate iodine towards substitution.

o-Bromoiodobenzene in the presence of bromine forms both *o*-diiodobenzene and *o*-dibromobenzene. This behavior is consistent with the other available data. However, benzyne formation is precluded in this case by the fact that *o*-bromoiodobenzene alone is stable under identical conditions. While the possibility remains that benzyne is formed in certain of these reactions, a determination of the course of the two or more reactions taking place in these experiments would require a comprehensive kinetic study.

The photolysis of *o*-diiodobenzene in refluxing hexane with an ultraviolet light source yielded a complex mixture of products including iodobenzene, but no diphenylene or triphenylene, the products which would be expected if benzyne were formed. The presence of iodobenzene means that at least part of the reaction proceeded via the formation of o-iodophenyl radicals. As in the pyrolyses, the intermediacy of benzyne, while unlikely, was not ruled out. In any case, the complexity of the reaction appeared to make it useless as a source of benzyne in the gas phase.

An attempt to trap any benzyne formed in the pyrolysis of o-diiodobenzene with anthracene resulted in the formation of a black, insoluble solid which accounted for almost all of the starting materials. No triptycene or unreacted anthracene could be detected in the products of the reaction. Since anthracene itself was stable under the conditions of the pyrolysis, the black solid probably resulted from the reaction of anthracene with the initially formed o-iodophenyl radicals. These radicals might initiated polymerization of the anthracene by addition to the 9-position (eq. 8), to yield the intermediate XV, which could then react with further anthracene molecules to form the observed polymer.



(8)

XV

This mechanism is similar to the use of anthracene to trap free radicals. For example, anthracene reacts with benzyl radicals in solution to form 9,10-dibenzylanthracene (38). The formation of polymer rather than 9,10-(o-iodophenyl)-anthracene was probably due to the great difference in concentration; the pyrolysis was run in molten anthracene.

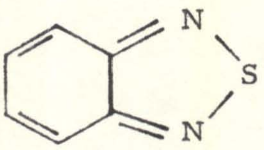
Several vapor-phase decompositions of *o*-diiodobenzene were also carried out. *o*-Diiodobenzene was passed through an evacuated quartz combustion tube heated to 500°. Bromine was bled into the exit gases from the furnace and the reaction products were collected in a cold trap. Besides starting material only *o*-iodobromobenzene and *o*-dibromobenzene were detected. The result implies that the initial product of decomposition of *o*-diiodobenzene is the *o*-iodophenyl-radical.

An attempt was made to trap any benzyne formed in vapor-phase pyrolyses with furan. *o*-Diiodobenzene was passed through the combustion tube at 600°, and furan was bled into the exit gases from the furnace. Although considerable decomposition of the *o*-diiodobenzene occurred, as witnessed by the formation of carbonaceous material in the tube, none of the benzyne-furan adduct could be detected in the trap or on the walls of the vacuum line, although a solid was deposited beyond the furan inlet. Significantly, no free iodine was detected. The extensive formation of polymeric material implies that any benzyne formed reacted immediately with *o*-iodophenyl radicals and iodine atoms.

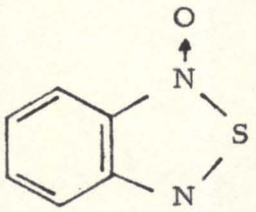
A further series of experiments was carried out with *o*-fluorophenyllithium which is known to decompose in solution to give benzyne which can be trapped through formation of a Diels-Alder adduct with furan. *o*-Fluorophenyllithium was prepared from n-butyllithium and *o*-bromofluorobenzene at -80° and allowed to warm up to its decomposition temperature, about -45° (39), under vacuum. No benzyne was trapped with furan, either in a cold trap or in the vapor phase. The solvent, ether, could not be completely removed from the *o*-fluorophenyllithium below 0° and no decomposition products distilled below about 10°. At these temperatures the *o*-fluorophenyllithium had decomposed.

Some *o*-substituted nitrogen-containing compounds were investigated in the hope that they would decompose to give benzyne. 2,1,3-Benzothiadiazole (XVI) (40) was found to be stable at temperatures as high as 400°. 2,1,3-Benzodiazole-N-oxide (XVII) (41) detonated on heating.

The thermal decomposition of *o*-diazonium benzoate to benzyne has been recently reported (42). In refluxing furan, *o*-diazonium benzoate forms the adduct of benzyne and furan, and when it is heated in benzene in the presence of anthracene the expected adduct, triptycene, results. It is not known whether *o*-diazonium benzoate would decompose in a similar manner, *i.e.*, to benzyne, in the solid or gaseous states; the solid has been reported to detonate on heating. In order to investigate the possibility of decomposing the solid under vacuum and trapping



XVI



XVII

the benzyne, if formed, o-diazonium benzoate was prepared from diazotized anthranilic acid. The benzoate was heated to 68° under vacuum. Nitrogen was used as a carrier gas to sweep any benzyne evolved into a Dry-Ice cooled trap which contained furan. The benzoate appeared merely to sublime; no furan adduct was isolated from the trap.

Experimental

o-Diiodobenzene. - Nitrosylsulfuric acid was prepared by dissolving sodium nitrite (7.3 g., 0.055 mole) in 53 ml. of concentrated sulfuric acid at 70°. o-Phenylenediamine (5.4 g., 0.05 mole) was added slowly to the nitrosylsulfuric acid so as to maintain the ice-cooled reaction flask below 30°. The resulting solution was diluted with 50 ml. of glacial acetic acid and added in a steady stream to a well-stirred solution of sodium iodide (42 g., 0.28 mole) in 200 ml. of water. The iodide solution was maintained below 30°; it formed a thick paste when cooled to about 10°. Considerable oxidation of iodide occurred during the addition. After 2 hr. iodine was destroyed with solid sodium bisulfite. The solution was diluted with an equal volume of water and an organic phase separated. The mixture was extracted with ether and the ethereal solution washed with 5% aqueous sodium hydroxide. The ether was removed through a 30-cm. Helipak column and the product separated from a small amount of lower-boiling impurity by fractionation through a 30-cm. semimicro column at 130° (7 mm.) to yield 6.14 g. (40%) of product. Considerable difficulty was experienced in this and subsequent preparations from a red impurity, formed presumably by air oxidation. The impurity was not detectable in a vapor-phase chromatogram nor in the infrared spectrum, which was identical to that of an authentic sample of o-diiodobenzene. This oxidation product was not formed when o-diiodobenzene was refluxed in the absence of air. The color could be removed by washing with aqueous bisulfite. On careful distillation, the impurity distilled with the first fractions of o-diiodobenzene. The yield in several preparations varied from 40% to 45%.

m-Diiodobenzene. - m-Phenylenediamine (5.44 g., 0.050 mole) was tetrazotized (43) at -5° in 1 hr. with 5.76 g. sodium nitrite and 34 ml. of concentrated sulfuric acid in 145 ml. of water, and the solution was poured into aqueous potassium iodide (46 g., 0.3 mole). Extraction with ether and distillation yielded 2 g. (20%) of pale yellow m-diiodobenzene which was pure according to vapor-phase chromatography (v.p.c.).

p-Diiodobenzene was prepared as described previously from p-phenylenediamine (2.18 g., 0.02 mole), phosphoric acid (70 ml.), sodium nitrite (3 g. in 30 ml. water), and excess potassium iodide. The crude product (6 g.) was sublimed (60°, 7 mm.) to yield 5 g. (75%) of light yellow p-diiodobenzene which was pure according to v.p.c.

m-Dibromobenzene. - m-Phenyldiamine (5.44 g., 0.0504 mole) was tetrazotized (43) at -5° with hydrobromic acid (180 ml. 48%) and sodium nitrite (5.6 g., 0.05 mole). The solution was added to excess freshly prepared cuprous bromide, and then allowed to stand overnight. Steam distillation gave a yellow oil which was distilled through a micro column to yield 3.5 g. (30%) of m-dibromobenzene which was pure according to v.p.c.

Pyrolysis of o-Diiodobenzene in the Presence of Bromine. I. - o-Diiodobenzene (3 g., 0.0092 mole) and bromine (6.92 g., 0.043 mole, 4.73 mole excess) were heated in a sealed, thick-walled Pyrex tube at 300° for 24 hr. At the end of this period the tube contained a brown liquid which solidified on cooling, as well as a gas which was shown in a later experiment to be hydrogen bromide by its reaction with sodium hydroxide and silver nitrate. Treatment of the contents of the tube with aqueous sodium bisulfite left a nearly white solid. An attempted fractional sublimation of the solid yielded nine fractions, each of which melted over a 20° to 30° range varying from 90° to 300°. The melting points and infrared spectra were consistent with a mixture of brominated benzenes, although halogenated biphenyl is not excluded. Similar results were obtained from experiments involving reaction times and temperatures as low as 15 min. and 260°, respectively.

Pyrolysis of o-Diiodobenzene in the Presence of Bromine. II. - o-Diiodobenzene (2.78 g., 0.0086 mole) and bromine (2.58 g., 0.0172 mole, 2 mole excess) were heated in a sealed, thick-walled Pyrex tube to 260° for 6 min. The furnace was controlled by a Leeds and Northrup thermoregulator to ± 3°. The reaction time was taken as the time from which the cold tube was placed in the furnace until it was removed and allowed to cool. Because the reaction times were short, the conditions relatively drastic, and extensive bromination occurred (cf. previous experiment), the yields of dihalobenzenes were variable (10-50%) and are not reported.

The contents of the tube after pyrolysis were washed with aqueous sodium bisulfite and the organic phase was shown by v.p.c. to contain almost equal quantities of starting material and o-dibromobenzene. The presence of the bromo compound was confirmed by its infrared spectrum. The experiment was repeated, but in neither case was any o-bromoiodobenzene detected.

Pyrolysis of Dihalobenzenes. - All pyrolyses were carried out as described for the pyrolysis of o-iodobenzene under the conditions shown in Table X. A nearly two-mole excess of halide over dihalobenzene was used in each case. Analyses were performed on Perkin-Elmer (Column C) and F and M (silicone rubber) chromatographic columns. The approximate product ratios reported correspond to the ratios of chromatographic peak areas. Lower boiling fractions of brominated material which appeared on the chromatogram were not considered in determining ratios.

Pyrolysis of o-Diiodobenzene in the Presence of Anthracene. - Anthracene (10 g., 0.042 mole) and o-diiodobenzene (2 g., 0.006 mole) were heated in a sealed thick-walled Pyrex tube to 300° for 48 hr. The black solid which resulted was extracted with ether; very little material dissolved. This extract contained no o-diiodobenzene and no triptycene. The black solid remaining (11.2 g.) could not be dissolved in organic solvents. It burned in a flame leaving considerable ash. The solid was suspended in 300 ml.of benzene and refluxed with a five-mole excess of maleic anhydride (21 g., 0.21 mole) for 5 hr. The solid was recovered (11.1 g.) and the benzene solution stirred with 200 ml. of 10% sodium hydroxide solution overnight, washed with a further 50 ml. of sodium hydroxide, and washed with 50 ml. of water. The infrared spectrum of the trace of residue from the benzene solution showed no evidence of triptycene. The sodium hydroxide solution yielded no maleic anhydride-anthracene adduct.

Anthracene was recovered unchanged from an attempted pyrolysis of the pure material at 300°.

Photolysis of *o*-Diiodobenzene. - A solution of *o*-diiodobenzene (5.71 g., 0.0175 mole) in 750 ml. of n-heptane in a Pyrex vessel was irradiated at 98° with a water-cooled General Electric A-H6 mercury arc lamp (Pyrex jacket). After 2.8 hr., v.p.c. analysis showed that approximately 90% of the *o*-diiodobenzene was consumed. The solvent was removed through a 30-cm. Helipak column, and the residue fractionated through a micro distillation apparatus. The infrared spectra and vapor-phase chromatograms of the various fractions (bath temp. 80°, 8 cm.; 100°, 6 mm.; 140°, 0 mm.) and the residue showed no evidence of biphenylene or triphenylene, but did show the presence of iodobenzene in the lowest boiling fraction (180°, 760 mm.).

Vapor-Phase Pyrolysis of *o*-Diiodobenzene. I. - *o*-Diiodobenzene was distilled from a flask at room temperature through an evacuated quartz combustion tube heated to 500° by a 16- cm. electric furnace. Bromine was bled into the exit gases from the furnace, and the products of the reaction were trapped in a Dry-Ice cooled U-tube. The temperature of the tube at the bromine inlet was not over 80°. After 8 hr. the trap became clogged with solid, and the experiment was halted. The contents of the trap were analysed by v.p.c. o-Diiodobenzene, o-dibromobenzene and o-bromoiodobenzene were present in a 8:3:3 ratio. Although the bromine vapors backed up when the trap clogged, undistilled o-diiodobenzene recovered from the flask was pure according to v.p.c.

Vapor-Phase Pyrolysis of o-Diiodobenzene. II. - A train was constructed consisting successively of a flask equipped with a capillary inlet to admit nitrogen as a carrier gas, a quartz combustion tube heated by a 15-cm. furnace, a capillary inlet through which furan was admitted, and a Dry-Ice cooled trap of 250-ml. capacity. The flask was charged with 3 g. of o-diiodobenzene and the train evacuated with the aid of a mercury diffusion pump. Nitrogen passed through a Dry-Ice trap was then admitted to the flask at a rate which maintained the pressure of the line within the operating range of the mercury diffusion pump ($<$ 10 mm.). A heat lamp was directed at the flask so as to heat the incoming nitrogen as well as the o-diiodobenzene. The combustion tube was maintained at 600° for 12 hr. during which time 200 ml. of furan were bled into the tube. The entire system was then allowed to come to room temperature under nitrogen. The combustion tube was found to be lined with carbonaceous material. Small deposits of a yellow solid were found on the wall of the tube as it left the furnace, and again, immediately beyond the furan inlet. A small amount of solid was also found in the inner tube of the Dry-Ice trap. The solid material in the tube was insoluble in ether, benzene, and ligroin, and was very slightly soluble in acetone. The amount of this polymeric material which could be scraped from the tube was insufficient for further study. The contents of the trap were concentrated to 0.5 ml. with a 30-cm. Helipak column and analysed by v.p.c. (Perkin-Elmer Column K). Recovered o-diiodobenzene was the sole component other than residual furan. No material with a retention time close to that of the benzyne-furan adduct was found. Undistilled o-diiodobenzene (1.8 g.) was recovered from the flask.

Decomposition of o-Fluorophenyllithium. - n-Butyllithium (45) (1.3 N in ether, 20 ml.) was placed in a nitrogen-flushed 50-ml. flask and cooled to -70° under a nitrogen atmosphere. o-Fluorobromobenzene (3.5 g., 0.02 mole), prepared by the Schiemann reaction from o-bromoaniline (46), in 5 ml. of ether was run slowly into the flask from a Dry-Ice cooled separatory funnel and reacted smoothly to form a clear solution. The flask was maintained at Dry-Ice temperatures and placed on a vacuum line equipped with a capillary bleed for carrier gas and two liquid nitrogen-cooled traps. The line was evacuated by a mercury diffusion pump for 12 hr. with the o-fluorophenyllithium maintained at -70° and for 20 hr. at -60° to -70° at which time the rate of distillation of ether had become negligible, although a clear solution remained. The flask was allowed to warm up to 0° over a period of 10 hr. during which time the remaining ether evaporated to leave a white solid which turned yellow-red as the flask warmed to 25° over a two hr. period. With the flask at room temperature, furan (5 ml.) was added through the carrier gas so as to condense in the liquid nitrogen-cooled trap. The vacuum was broken and a further 10 ml. of furan was added to the trap, which was then allowed to come to room temperature. Furan (20 ml.) was added to the flask, the contents of which were then extracted with ether and the ethereal solution concentrated to 1 ml. with a 30-cm. Helipak column. The residue was shown by vapor-phase chromatography to contain no benzyne-furan adduct. The contents of the trap were concentrated to a few drops of yellow oil, the vapor-phase chromatogram of which was essentially identical with that of the residue from the flask and also showed no peak corresponding to that of benzyne-furan adduct.

In a similar experiment (1.5 g. of o-fluorobromobenzene; 15 ml. of 1.0 N n-butyllithium) furan (200 ml.) was admitted at a point 4 cm. from the surface of the o-fluorophenyllithium solution while the flask was allowed to warm up under vacuum. No furan-benzyne adduct was detected in the trap.

Benzo-2,1,3-thiadiazole was prepared essentially as described previously (40) from o-phenylenediamine (21.6 g., 0.2 mole) in 300 ml. of benzene, and thionyl chloride (47.6 g., 0.4 mole). After the mixture was refluxed for 8 hr. the solvent and excess thionyl chloride were removed at aspirator pressure, and the residue steam distilled to yield two fractions of product, the first pure white (2.73 g.), the second yellow (3.55 g.). Total yield was 50%. The first fraction was recrystallized from 5 ml. of 95% ethanol, and sublimed at 50° and atmospheric pressure to give material of m.p. 45-45.5° (lit. 44°).

Pyrolysis of 2,1,3-Benzothiadiazole. - 2,1,3-Benzothiadiazole (1.0 g., 0.0072 mole) was heated in a sealed Pyrex tube to 400° for 2 weeks. The melting point of the recovered material was unchanged from that of the starting material. Unchanged starting material was also recovered from a similar attempted pyrolysis in the presence of copper powder.

2,1,3-Benzodiazole-N-oxide was prepared as described previously (41) from o-nitroaniline and sodium hypochlorite. Sublimation (100°, 1 mm.) yielded pale yellow crystals (m.p. 70°).

Pyrolysis of 2,1,3-Benzodiazole-N-oxide. - 2,1,3-Benzodiazole-N-oxide (1 g., 0.007 mole) was sealed in a thick-walled Pyrex tube and placed in a furnace (350°). Within several minutes (the temperature of the contents of the tube was not known) the compound detonated, shattering the lining of the furnace. At a lower temperature (150°) the compound was found to merely sublime. No attempt was made to determine the decomposition temperature.

Anthranilic Acid Diazonium Chloride was prepared as described previously (47) from anthranilic acid (5.5 g., 0.004 mole) and 8 g. of isoamylnitrite to yield 2.5 g. (35%) of product.

Decomposition of o-Diazonium Benzoate. - o-Diazonium benzoate was prepared as described previously from 0.5 g. of anthranilic acid diazonium chloride and excess silver oxide. The solution was filtered into a 50 ml. flask and the solvent, methanol, removed under aspirator pressure. The flask was placed on a vacuum line similar to that used for the decomposition of o-fluorophenyllithium, and the line was evacuated by a mechanical pump. The flask was heated to 68°, and furan (250 ml.) was bled at intervals into the line at a point 5 cm. from the surface of the solid material. The o-diazonium benzoate appeared to sublime into a cool part of the line. After 2 days of pumping the Dry-Ice cooled trap was opened and the contents concentrated to 0.5 ml. with a 30-cm. Helipak column. No benzyne-furan adduct was found on vapor-phase chromatographic analysis. Evaporation of the solution to dryness left a few mg. of an ether-insoluble yellow tar.

Appendix I

The hydrogen-deuterium kinetic isotope effects in amination reactions of o-deuterohalobenzenes have been reported (Table I) for the bromo and chloro compounds. The postulated mechanism requires that o-deuteroiodobenzene should have an isotope effect similar to that of o-deuterobromobenzene, *i.e.*, a k_H/k_D or about 6 (1). An attempt was made to confirm this isotope effect by the amination of iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$. The reaction was carried out with lithium diethylamide in ether, and deuterium concentrations were calculated from the relative ^{14}C-activities of benzoic acid-1-^{14}C samples prepared from starting and recovered iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$. The apparent isotope effect as calculated by the formula given above (Experimental, Part II) is 1.3 ± 0.1. As this result is in such contrast to that expected, the possibility of reduction of the type reported for slightly activated halobenzenes, such as o-bromoanisole, was investigated (48). It was shown that lithium diethylamide does, in fact, reduce iodobenzene to benzene. Since the percent reaction in the isotope experiment was determined by a titration of iodide liberated, the value found is much higher than the percent of amination reaction. As discussed above (page 11), this high percent reaction results in a low calculated isotope effect.

Experimental

Iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$ with Lithium Diethylamide in Ether. - Iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$ (0.6505 g., 98.5% deuterated, *cf.* page 19) was diluted with 1.6517 g. normal iodobenzene. Benzoic acid-1-^{14}C was prepared from 0.6816 g. of the mixture by treatment with ethyllithium and carbonation. The remainder of the iodobenzene (1.6206 g., 0.00795 mole) was treated with lithium diethylamide prepared from diethylamine (0.58 g., 0.0078 mole) and ethyllithium (0.8 N, 8 ml.) as described above for aminations of 3-bromoanisole-2,4,6-$^{2}H_3$ (page 32). After a reaction time of 10.5 hr., the reaction was quenched and 1.3 g. of crude iodobenzene-1-^{14}C was recovered. The recovered material was used without purification for preparation of benzoic acid-1-^{14}C. As the actual amount of iodobenzene was not known, an excess of ethyllithium was used. Ethyllithium was chosen because difficulty was found in separating the aliphatic acids produced from an excess of higher alkyllithiums from small amounts of benzoic acid. Benzoic acid derivatives were purified by recrystallization from water and sublimation, and melted over 0.5 to 0.6° ranges. The extent of reaction, as determined by titration of the aqueous extract with 0.1000 N potassium iodate, was 32.5 ± 0.3%. Deuterium content of the starting material was 30.9%; that of recovered material was 33.1% as calculated from the ratio of ^{14}C-activities.

A second experiment, similar to the first except that 8 g. (0.039 mole) of iodobenzene was used and the reaction allowed to proceed for 18 hr., gave a 45% yield of benzene as calculated from ratios of vapor-phase chromatogram peaks of a concentrated ethereal solution to those of a standard mixture. Carbonation of the reaction mixture before work-up yielded no benzoic acid and only a few mg. of unidentified acidic material.

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PROPOSITIONS

1. The reduction of the slightly activated aromatic halides, 1-chloro- and 1-bromonaphthalene and o-bromoanisole, by lithium dialkylamides including lithium piperidide has been reported (1). The reduction takes place concurrently and to nearly the same extent as benzyne formation, and is indistinguishable from the substitution kinetically when rates are followed by titration of halide ion liberated. Recent work has shown that the occurrence of this reduction is more general than previously suspected (2). It is necessary to investigate a series of aromatic halides to determine the extent of the reduction reaction.

The kinetics of benzyne formation determined by Huisgen (3) must be re-investigated to determine the partial rate constant of benzyne formation before the data can be properly interpreted.

2. The reduction of aromatic halides by lithium dialkylamides has been explained by a mechanism which involves transfer of an α-hydrogen of the amide to the aromatic ring (4). However, the evidence in support of this mechanism is not conclusive. The fact that diphenylamide does not cause reduction is rendered meaningless by the observation that dimethylamide, which is of similar low basicity, does not cause reduction although it has α-hydrogens. Furthermore, a lithium-

halogen interconversion is not precluded by the lack of carboxylic acid formation on carbonation of reaction mixtures.

It is proposed to study the Benkeser mechanism by the reaction of o-bromoanisole with lithium α,α-deuterobenzylphenylamide in a solution containing excess dimethylamine. If the Benkeser mechanism is correct, the anisole formed will be totally deuterated in the o-position. If lithium-halogen interconversion occurs, the excess amine will reduce the o-methoxyphenyllithium with normal hydrogen.

3. Westheimer has studied the lanthanum hydroxide gel catalysed hydrolysis of phosphate esters (5). This hydrolysis had been shown to exhibit an optimum rate at the same pH as does alkaline phosphatase, a Mg^{++}-requiring enzyme (6). The mechanism proposed for the non-enzymatic catalysis is not conclusive because the steric requirements of the solid hydroxide cannot be evaluated. The same esters should be investigated over a broad pH range with Mg^{++} and Zn^{++}, which ions will be soluble at the desired pH, to determine if the same catalysis and pH optimum is involved.

An attempt should be made to find parallel behavior of metal ions in enzymatic and non-enzymatic hydrolysis. Although this type of behavior is usually not found, the present case may be an exception because of the similarity in pH optima discussed above.

4. The rate of solvolysis of monoesters of phosphoric acid exhibits a maximum at pH 3-6, the region in which the predominant species is the monoanion (7). The nature of this greatly enhanced reactivity of the monoanion is of great interest because the pH optimum of acid phosphomonoesterase is in the same region (8) and, hence, appears to be due at least partially to the reactivity of the monoanion. It has been suggested that the reaction intermediate is a hydrogen bonded water ester complex. The possibility of a heterolysis not involving a water molecule has also been advanced. While it is not possible to determine the molecularity of the reaction directly, the use of methanol as a "water analogue" (9) should be able to determine the molecularity for the enzymatic hydrolysis. If water is bound to the enzyme, methanol will act as a non-competitive inhibitor. Other possibilities can also be distinguished kinetically.

In the non-enzymatic case, if methanolysis does not exhibit the pH sensitivity that hydrolysis does, a heterolysis not involving water is indicated since the steric effect of the methyl group should not be sufficient to completely prevent the hydrogen bonding postulated.

5. A wide variety of substituted benzoic acids are able to function as plant growth substances (auxins). Considerable work has been carried out to rationalize the substituent requirements of active benzoic acids. The most reasonable of several interpretations which have been

presented is that the benzoic acids react by a two-point attachment mechanism involving the carboxyl group and a nucleophilic attack on a ring position (10). Molecular orbital calculations of Fukui *et al.* (11) have been presented as evidence for nucleophilic attack at the *ortho* position.

It is proposed to investigate the action of benzoic acids by a study of the substituent distribution in 2,3,5-triiodobenzoic acid-4,6-$^{2}H_{2}$ recovered from nutrient media in which avena coleoptile have been grown. Since there is evidence that auxin binding is reversible (12), if binding occurs at a specific ring location the corresponding substituent should be absent in recovered material. The synthesis of the relatively complicated benzoic acid is warranted because of its very high activity, 50% of that of natural auxin, indoleacetic acid.

On the basis of the many exceptions in the correlations between Fukui's data and auxin activity, it is suggested that the *para*-deuterium will be lost.

6. The reaction of pyridine with amide ion is a very convenient method for obtaining α-aminopyridines. Unfortunately, the reaction has yielded poor results when applied to substituted amides. A modification of the reaction has been reported (13) in which yields of 10-40% are obtained. However, the authors claim that the reaction does not go via a

substituted amide ion because when sodium and amine are refluxed in toluene in the absence of pyridine no reaction takes place.

It is proposed that pyridine is able to promote the formation of amide ion by an equilibrium between sodium piperidine and amine. The promotion may be investigated by a study of strong base catalysis of the reaction.

7. An investigation of the role of metal salts in the reaction of pyridine with substituted amide ions is suggested. Since the Chichibabin reaction (14) takes place very slowly with very pure sodamide, it appears to be catalysed by metal, probably the iron salts which are used in the preparation of sodium amide. The addition of transition metal salts to reactions of substituted amide ions with pyridine may result in a synthetic procedure equally valuable to the Chichibabin reaction.

8. The deuterium-hydrogen kinetic isotope effect observed in the photo-chlorination of chloroform and deuterochloroform varies with temperature (15). Similar results have been obtained in inorganic reactions such as that of chlorine with tritium hydride (16). In neither case were the results in agreement with theory. The possibility of variation of isotope effects in organic reactions has tended to be ignored in the interpretation of data obtained at different temperatures. An investigation should be made of the isotope effect-temperature relationship in

an elimination such as the reaction of isopropylbromide with ethoxide ion. Since theory, at present, is unable to predict isotope effects, this investigation would form a basis of comparison for isotope effects in similar reactions.

9. It has been shown that n-butyllithium in n-heptane reacts rapidly with iodobenzene to form phenyllithium (17). However, bromobenzene does not react detectably in one hour. This very specific reactivity would be of synthetic value if the system were investigated in a semiquantitative fashion (after the manner of Gilman) with a series of aromatic halides and alkyllithiums.

This system may prove of value in gaining an insight into the role of ether in alkyllithium reactivity. Kinetics of the iodobenzene-n-butyllithium interchange should be run in dilute heptane solution (about 0.1 N) with similar low quantities of added ether. At these low concentrations of ether, solvent effects should be small. If the reaction involves a specific ether complex, information as to its composition may be obtained from the molecularity of the reaction.

10. Within the last 15 years considerable work has been done on the mechanism of phosphate ester hydrolysis (18). However, the corresponding amides have received little attention although they are also of biological interest. An investigation of a series of amides would

yield information as to the effect of substituents on rate which could be applied to the study of phosphoamidase.

11. Both anilines and aminopyridines form nitramines which may then rearrange to the corresponding ring nitro-substituted compounds. Hughes has shown that the rearrangement of a phenylnitramine is totally intra-molecular, and has proposed a mechanism for the reaction (19). While at first glance the pyridylnitramine rearrangement is analogous to the phenylnitramine case, certain critical differences exist. Whereas a phenylnitramine rearranges to form 93% ortho and only 7% para nitroaniline, 2-pyridylnitramine yields a predominance of 5-nitro over 3-nitro product(20).The Hughes mechanism for the rearrangement does not account for this ratio which, however, would be the expected result of an inter-molecular reaction. It is therefore desirable to determine whether the rearrangement of a pyridylamine involves an inter- or intra-molecular reaction by running the rearrangement in the presence of ^{15}N-labeled nitric acid.

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