Isomerization and Disproportionation of Trihalobenzenes Catalyzed by Potassium Anilide in Liquid Ammonia[1,2]

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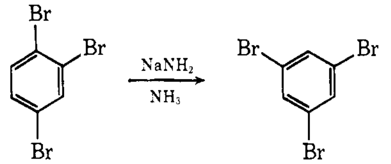
Abstract: On treatment with potassium anilide in liquid ammonia, 1,2,4-tribromobenzene (**1**) rearranges to 1,3,5-tribromobenzene (**2**), and there is a small amount of disproportionation to di- and tetrabromobenzenes. Similarly, 1-iodo-2,4-dibromobenzene (**3**) rearranges to its 1,3,5 isomer and also disproportionates to **1**, a little **2**, and some 1-bromo-3,5-diiodobenzene (**5**). Potassium anilide in ammonia also causes isomerization and/or disproportionation of 1-bromo-2,4-dichlorobenzene, 1-iodo-2-bromo-4-chlorobenzene (**6**), and 1-iodo-2,4,6-tribromobenzene (**16**). A conceivable mechanism involving aryne intermediates is ruled out by several items of evidence. However, a mechanism involving a series of nucleophilic displacements by aryl anions on the halogen of an aryl halide, effecting the transfer of a positive halogen moiety so as to form a new aryl halide and a new aryl anion, accounts for most of the evidence. In reactions with **3**, **5**, and **16**, which contain both iodine and bromine, KNH_2 liberates mainly bromide ion and potassium anilide releases mainly iodide ion; two conceivable explanations are discussed.

In the course of a study of the action of sodium amide in liquid ammonia on several di- and trihalogenated benzenes, Wotiz and Huba[5] observed that the recovered neutral material from 1,2,4-tribromobenzene (**1**) was, to their surprise, 1,3,5-tribromobenzene (**2**). There was no precedent for the isomerization of a trihalobenzene under basic conditions. We therefore undertook an investigation of this unusual reaction.



1 2

This investigation revealed that the isomerization of **1** to **2** is but one example of a class of surprisingly facile reactions. The present paper is the first of a set concerning these reactions, and describes a pioneering, exploratory study. Accompanying papers[6-8] present further studies which probe more deeply into specific features.

Reactions of 1,2,4-Tribromobenzene (1). In early experiments, conditions were sought under which this isomerization could be achieved in good yield. Whereas Wotiz and Huba had reported a 33% yield of **2** (besides 3,4-dibromoaniline), we obtained **2** in yields of only 7–13% using either $NaNH_2$ or KNH_2 (Table I, runs 1–3). However, potassium anilide in liquid ammonia gave much better yields of **2**, up to about 60% (Table I, runs 4–11). Representative runs are summarized in Table I.[9]

Other base–solvent systems were also investigated. Potassium *N*-methylanilide was an effective catalyst (run 17), about as good as potassium anilide. Sodium amide in piperidine at reflux[10] gave 2% **2** in one run (run 18), but no detectable amount of **2** in two other runs (not tabulated). Potassium *tert*-butoxide in *tert*-butyl alcohol at reflux for 5 hr had little effect on **1**; 91% of it was recovered, and no **2** was detectable (run 19). Potassium *tert*-butoxide in 50% *tert*-butyl alcohol–50% dimethyl sulfoxide at 53° reacted with **1**, but the product, unexpectedly, was *p*-dibromobenzene in 70% yield (run 20); this dehalogenation reaction has since been extensively investigated.[11]

Potassium anilide catalyzed isomerization is quite rapid. As demonstrated by runs 9–11, Table I, and in comparison with runs 4–8, virtually the same extent of isomerization was obtainable in 15–30 min as when the reaction time was 120 or 480 min. In no case, however, was isomerization complete; a substantial but variable amount of **1** was always recovered.

Careful glpc analysis of one product mixture indicated that small amounts (1–2%) of *p*-dibromobenzene and also of a mixture of tetrabromobenzenes were formed. The infrared spectrum of the tetrabromobenzene fraction closely matched that of a mixture of 60% authentic 1,2,3,5-tetrabromobenzene and 40% authentic 1,2,4,5-tetrabromobenzene. The **1** employed as starting material was free of di- and tetrabromobenzenes, as judged by glpc analysis. The di- and tetrabromobenzenes represent disproportionation of **1**.

When isomerization of **1** was effected in the presence of a large amount of added KI[12] (run 15) or KCl (run 16), the results were similar to those obtained in the absence of these salts; there was no evidence of incorporation of iodine or chlorine into the reaction products.

A sample of **1** fully deuterated at all hydrogen positions (0.001 mol) was exposed to potassium anilide (from 0.005 mol of KNH_2 and 0.01 mol of aniline

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[1] (a) Based on the dissertation of C. E. Moyer, Jr., Brown University, June 1964; *Diss. Abstr.*, **25**, 4412 (1965); (b) preliminary communication: C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963).

[2] Supported in part by the National Science Foundation and the Army Research Office (Durham).

[3] University of California, Santa Cruz, California 95060.

[4] Union Carbide Fellow, Summer 1962.

[5] J. H. Wotiz and F. Huba, *J. Org. Chem.*, **24**, 595 (1959).

[6] J. F. Bunnett and G. Scorrano, *J. Amer. Chem. Soc.*, **93**, 1190 (1971).

[7] D. J. McLennan, and J. F. Bunnett *ibid.*, **93**, 1198 (1971).

[8] J. F. Bunnett and I. Feit, *ibid.*, **93**, 1201 (1971).

[9] Complete data on all reactions of trihalobenzenes with bases, on the synthesis of compounds, and on identification of products are given in the dissertation of C. E. M.[1a]

[10] *Cf.* J. F. Bunnett and T. K. Brotherton, *J. Amer. Chem. Soc.*, **78**, 6265 (1956).

[11] J. F. Bunnett and R. R. Victor, *ibid.*, **90**, 810 (1968); R. R. Victor, Dissertation, Brown University, 1968.

[12] KI is quite soluble in liquid ammonia: J. J. Lagowski, "The Chemistry of Non-Aqueous Solvents," Vol. II, Academic Press, New York, N. Y., 1967, p 329.

Table I. Reactions of 1,2,4-Tribromobenzene (**1**) with Diverse Bases

Run no.	Amount of **1**, mol	Base[a]	Amount of base, mol	Amount of free $C_6H_5NH_2$, mol[b]	Solvent	Amount of solvent, ml	Time, min[c]	Yield of **2**, %	Recovered **1**, %	Anal. method[d]
1	0.02	$NaNH_2$	0.10		NH_3	800	1080	7	40	cc, mp, ir
2	0.01	KNH_2	0.005		NH_3	250	240	7	57	cc, mp, ir
3	0.01	KNH_2	0.01		NH_3	500	480	13	44	cc, mp
4	0.01	PhNHK[a]	0.005		NH_3	500	480	37	35	cc, mp, ir
5	0.01	PhNHK	0.005	0.005	NH_3	500	480	42	35	gc, w
6	0.01	PhNHK	0.01		NH_3	500	480	43	6	cc, mp
7	0.01	PhNHK	0.02	0.02	NH_3	500	480	40	8	cc, mp
8	0.01	PhNHK	0.005	0.005	NH_3	500	30	34	49	gc, is
9	0.001	PhNHK	0.001		NH_3	50	15	41	35	gc, is
10	0.001	PhNHK	0.001		NH_3	50	30	60	23	gc, is
11	0.001	PhNHK	0.001		NH_3	50	120	61	8	gc, is
12	0.01	None			NH_3	500	480	Nil	88	cc, mp
13	0.01	None		0.01	NH_3	500	480	Nil	90	cc, mp
14	0.01	None	*e*	0.01	NH_3	500	480	Nil	86	cc, mp
15	0.01	PhNHK	0.01	*f*	NH_3	500	480	47	12	cc, mp
16	0.01	PhNHK	0.01	*g*	NH_3	500	480	58	6	cc, mp
17	0.001	$KN(CH_3)Ph$[h]	0.001		NH_3	50	480	55	34	gc, w
18	0.02	$NaNH_2$	0.06		$C_5H_{10}NH$[i]	20	10	2	25	cc, ir
19	0.01	*tert*-BuOK[j]	0.05		*tert*-BuOH[k]	90	300	Nil	91	cc, mp
20	0.01	*tert*-BuOK[j]	0.05		*tert*-BuOH–DMSO[l]	100	540[m]	*n*	Trace	rx, mp, ir

[a] PhNHK signifies potassium anilide. [b] Moles of aniline added in excess of moles of KNH_2 originally present. [c] Reaction at reflux, unless otherwise noted. [d] Analytical methods are symbolized: cc, column chromatography on alumina; gc, gas–liquid partition chromatography, with retention time analysis; ir, identity of infrared spectrum with that of authentic sample; mp, melting point; w, yields by weight of neutral fraction and relative yield by gc; is, yields by gc, with reference to diphenyl ether as internal standard; rx, recrystallization from ethanol. [e] $Fe(NO_3)_3$ was present. [f] KI (0.10 mol) was present. [g] KCl (0.10 mol) was present. [h] Potassium *N*-methylanilide. [i] Piperidine. [j] Potassium *tert*-butoxide. [k] *tert*-Butyl alcohol. [l] 50% *tert*-butyl alcohol–50% dimethyl sulfoxide (v/v). [m] Reaction at 53°. [n] The product was *p*-dibromobenzene, in 70% yield.

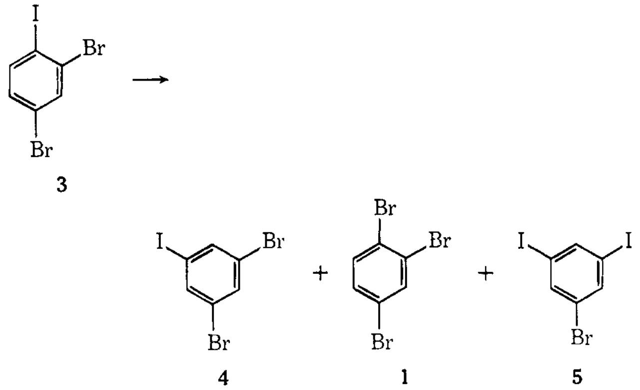
in 250 ml of ammonia) for 15 min. By chromatography on alumina, 12% isomerization product **2** was isolated and 48% **1** was recovered. The infrared spectra of both the **2** that was formed and the **1** that was recovered in this experiment were identical with those of ordinary samples of these compounds. Thus, complete loss of deuterium had occurred both in the formation of **2** and in the "unreacted" **1**.

Experiments with 1,3,5-Tribromobenzene (2). When **2** (0.01 mol) in 500 ml of ammonia was exposed either to 0.005 mol of potassium anilide plus 0.005 mol of excess aniline for 8 hr, or to 0.01 mol of potassium anilide without excess aniline for 0.5 hr, no detectable amount of reverse isomerization to **1** occurred. In both experiments, 86% **2** was recovered. Analysis in the former was by chromatography on alumina with infrared and melting point identification of the **2**, and in the latter by glpc with retention time analysis.

Reactions of 1-Bromo-2,4-dichlorobenzene. The behavior of this substance on treatment with potassium anilide in ammonia was analogous to that of **1**. Isomerization to 1-bromo-3,5-dichlorobenzene (33% in one run, 46% in another) occurred, and some unreacted starting material was recovered.

Reactions of 1-Iodo-2,4-dibromobenzene (3). The principal products from reaction with potassium anilide in ammonia were those shown in Scheme I, namely, 1-iodo-3,5-dibromobenzene (**4**) (*ca.* 28%), 1,2,4-tribromobenzene (**1**) (*ca.* 12%), and 1-bromo-3,5-diiodobenzene (**5**) (*ca.* 4%). The former is an isomer of the starting material and the latter two are disproportionation products. Trace amounts of 1,3,5-tribromobenzene (**2**), *p*-bromoiodobenzene, and *m*- and *p*-dibromobenzenes were also formed.

Scheme I



The aqueous washings from a typical run were titrated potentiometrically for halide ion; 9.9% bromide ion and 14.5% iodide ion were formed.[13] The $Br^-:I^-$ ratio is 0.68.

One reaction of **3** with potassium anilide was carried out in the presence of a tenfold excess of KBr; formation of tribromobenzenes was no greater than when there was no external KBr.

A reaction of **3** (0.01 mol) with KNH_2 (0.02 mol) for 60 min afforded 97% bromide ion, 21% iodide ion,[13] 3% **4**, and 18% unreacted **3**. The $Br^-:I^-$ ratio is 4.6. It is noteworthy that with KNH_2 more bromide than iodide ion is released, whereas with potassium anilide iodide ion was formed in greater amount.

Reactions of 1-Iodo-2-bromo-4-chlorobenzene (6). Reaction of this substance with potassium anilide in ammonia afforded a complex set of products, as shown in Scheme II. The yield of 1-bromo-3-chloro-5-iodo-

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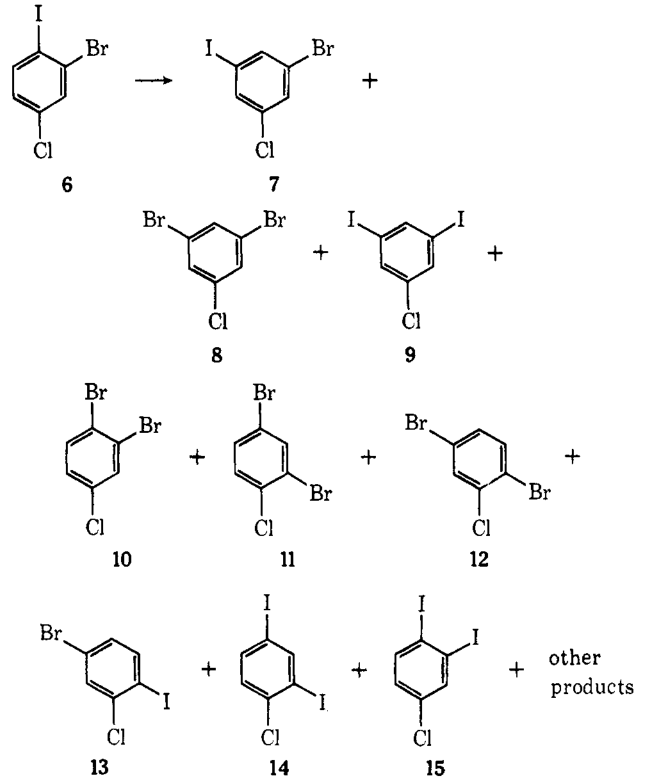
[13] Yields of halide ions are expressed on the basis of one halide ion per molecule of trihalobenzene.

Scheme II



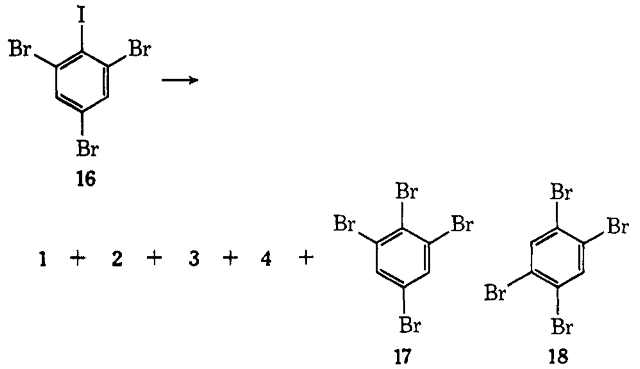
benzene (7), an isomer of the starting material, was 18%. There were also strong indications that another isomer, 4-bromo-2-chloro-1-iodobenzene (13), was a component of a product fraction inseparable by glpc. The yields of disproportionation products 8 and 9, both of 1,3,5 orientation, were very small. The three dibromochlorobenzenes of 1,2,4 orientation, 10, 11, and 12, were obtained in a total yield of 7% as a mixture, the components of which were recognized by the match of infrared and nmr spectra with those of an authentic mixture of these substances. Two diiodochlorobenzenes of 1,2,4 orientation were also obtained, in trace amounts, as a mixture the composition of which was ascertained in similar manner.

Reaction of 6 with a twofold excess of potassium anilide in ammonia afforded 24% iodide ion and 13% bromide ion,[13] but no chloride ion, for a $Br^-:I^-$ ratio of 0.53. However, reaction of 6 with an equimolar amount of KNH_2 gave 30% bromide ion, 16% iodide ion, and 10% chloride ion, for a $Br^-:I^-$ ratio of 1.9. Again this ratio inverts with change of base.

Reactions of 1-Iodo-2,4,6-tribromobenzene (16). The action of potassium anilide in ammonia on this substance also afforded several products, as shown in Scheme III. The major product was 1,3,5-tribromobenzene (2) (44%), representing deiodination of the starting material. Another dehalogenation product, 1-iodo-2,4-dibromobenzene (3), was obtained in 4% yield. Two further products, 1,2,4-tribromobenzene (1) (10%) and 1-iodo-3,5-dibromobenzene (4) (1.6%), represent at least in a formal sense rearrangement of the foregoing dehalogenation products. Also, small amounts of 1,2,3,5- and 1,2,4,5-tetrabromobenzene (17 and 18) were obtained.

Reaction of 16 with a twofold excess of potassium anilide released 74% iodide ion and 18% bromide ion,[13] for a $Br^-:I^-$ ratio of 0.24. It is evident that

Scheme III



the iodine removed in conversion of 16 to 1 or 2 appears largely as iodide ion. From reaction of 16 with a twofold excess of KNH_2 for 5 min, 44% bromide ion and 18% iodide ion were obtained, for a $Br^-:I^-$ ratio of 2.4; 47% 16 was recovered.

Instances of Little or No Isomerization. Several attempts to observe potassium anilide induced isomerization of 1,2,4-triiodobenzene were unsuccessful, and in the preliminary communication[1b] this isomerization was stated not to occur. However, a later run with 8-hr reaction time, analyzed by chromatography on alumina, gave a trace of product with infrared spectrum resembling that of 1,3,5-triiodobenzene. Subsequently, this isomerization has been observed to occur in yields as high as 5% during 8-hr exposure to potassium anilide in ammonia.[14] Reaction of 1,2,4-triiodobenzene (0.01 *M*) with KNH_2 (0.02 *M*) for 15 min released 1.10 mol of iodide ion/mol of $C_6H_3I_3$ introduced; 36% starting material was recovered, but no isomerization product could be found.

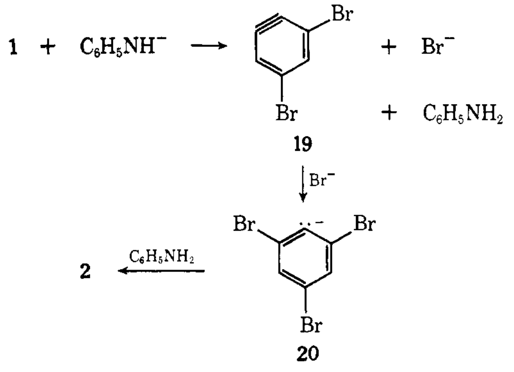
All efforts to effect isomerization of 1,2,4-trichlorobenzene through the action of potassium anilide in ammonia have been unsuccessful. It is remarkable that of the 1,2,4-trihalobenzenes, the tribromo compound is the only one which undergoes isomerization to its 1,3,5 isomer with ease, if at all.

Potassium anilide in ammonia was without effect on *o*-bromoanisole.

Discussion

The Possibility of an Aryne Mechanism. An early working hypothesis was that these reactions occur *via* aryne intermediates. For example, transformation of 1 to 2 was visualized as in Scheme IV. The action of

Scheme IV



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[14] J. F. Bunnett and D. J. McLennan, *J. Amer. Chem. Soc.*, 90, 2190 (1968).

potassium anilide on **1** was thought to form aryne **19** and bromide ion, and bromide ion was thought to re-add to form carbanion **20**, protonation of which formed **2**.

There are several precedents for this mechanism. The action of strong bases in liquid ammonia on halobenzenes is known to form arynes,[15] the addition of halide ions to arynes has been observed,[16] and addition of nucleophiles to 3-halobenzynes is known to be directed preferentially to the aryne carbon more remote from the halogen.[17]

The aryne mechanism could also give an account of, for example, the disproportionation of **3** to tribromobenzenes and a diiodobromobenzene. If aryne formation occurred both by loss of bromine and of iodine, thus producing various arynes, the "wrong" halide ion might participate in the readdition step, forming ultimately a disproportionation product.

However, there is compelling evidence against the aryne mechanism. First, it predicts that reactions performed in the presence of a foreign halide ion, *e.g.*, reaction of **1** in the presence of added KI, should form products representing incorporation of the foreign halogen. However, no such products were obtained from reaction of **1** in the presence of either KI or KCl. Also, the products and product ratios from reaction of **3** in the presence of added KBr are the same as in its absence. A supporter of the aryne mechanism might argue that perhaps the ejected halide ion does not become quite free of the aryne during the reaction, and thus is favored for readdition over halide ions in the general solution; however, in that case the aryne mechanism would not be able to account for halogen transfer between rings.

A second objection is that the aryne mechanism leads to an incorrect prediction as to which tribromobenzene should be formed preferentially from **3**. Addition of bromide ion to aryne **19**, a postulated intermediate from the action of potassium anilide on **3**, would according to well-recognized orientation patterns in the addition of nucleophiles to 3-haloarynes[17,18] form mainly carbanion **20** and therefore mainly 1,3,5-tribromobenzene (**2**). However, 1,2,4-tribromobenzene (**1**) is formed to a much greater extent than **2**.

A third difficulty is that the aryne mechanism cannot, unless elaborated in an unprecedented fashion, account for the formation of di- and tetrabromobenzenes from **1**. Admittedly, such disproportionation might be attributed to an independent side reaction. Nevertheless, a mechanism which accounted for the formation of di- and tetrabromobenzenes as well as rearranged tribromobenzene would be preferred.

A Mechanism of Positive Halogen Transfer. A much better account of our observations is given by a mechanism in which the essential feature is transfer of positive halogen from a halobenzene to an aryl anion. Insofar as isomerization and disproportionation of trihalobenzenes is concerned, this mechanism may be formulated in what are conveniently designated as six-halogen and seven-halogen versions. The former was presented in our preliminary communication[1b] and in a published lecture.[19] The seven-halogen version was first formulated in response to more recent experimental evidence.[6]

The essential feature of this mechanism is nucleophilic displacement by an aryl anion *on halogen* of an aryl halide, with displacement of an aryl anion

$$\text{Ar:}^- + \text{X–Ar}' \longrightarrow \text{Ar–X} + {}^-\text{:Ar}'$$

This effects transfer of a positive halogen moiety from an aryl halide (Ar′–X) to an aryl anion (Ar:$^-$), forming a new aryl halide (Ar–X) and a new aryl anion (Ar′:$^-$). The process may be likened to proton transfer, in which a base reacts with a Brønsted acid to form a new base and a new acid. In neither case is it implied that the positive hydrogen or halogen has free existence during the transfer process. Nucleophilic displacements by carbanions on halogens are known in other connections.[20]

Unsubstituted phenyl anions are species of very high energy, unlikely to be formed in appreciable amount in liquid ammonia solution.[21] However, halogen-substituted phenyl anions are energetically much more accessible, particularly *o*-halophenyl anions, which are formed several orders of magnitude more rapidly than *m*- or *p*-halophenyl anions.[22,23] It is therefore expected that aryl anions are formed far more readily in the potassium anilide–ammonia system when the anionic center is ortho to halogen, both when the carbanion is formed by proton abstraction and when it is formed by positive halogen abstraction. In other words, the initial formation of aryl anions occurs most readily by abstraction of a proton ortho to halogen, and the ensuing positive halogen transfers, insofar as they occur, are most apt to occur by attack on a halogen which is ortho to another halogen. "Most" in the preceding sentence implies a difference of reaction rate or equilibrium concentration of several orders of magnitude, a difference so great that *proton or positive halogen abstraction except* ortho *to halogen is of negligible significance.*

Evidence that aryl anion intermediates are formed in the type of system under consideration is the fact that perdeuterated **1** underwent complete exchange of deuterium for hydrogen on reaction with potassium anilide in ammonia.

Bearing in mind that *o*-bromophenyl anions are intermediates in the formation of benzyne from the action of KNH_2 on bromobenzene, and that the *o*-bromophenyl anion in ammonia expels bromide ion much more frequently than it recaptures a proton from the solvent,[15] one might question the feasibility of any mechanism which involved a series of *o*-bromo- and/or *o*-iodophenyl anion intermediates. Such misgivings are assuaged by the aforementioned deuterium exchange experiment. Moreover, they are answered at a more fundamental level by demonstration, both

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[15] J. D. Roberts, D. A. Semenov, H. E. Simmons, and L. A. Carlsmith, *J. Amer. Chem. Soc.*, **78**, 601 (1956).

[16] G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2729 (1962).

[17] G. B. R. de Graaff, H. J. den Hertog, and W. C. Melger, *Tetrahedron Lett.*, 963 (1965).

[18] J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenov, *J. Amer. Chem. Soc.*, **78**, 611 (1956).

[19] J. F. Bunnett, *Intra-Sci. Chem. Rep.* **3**, 235 (1969).

[20] *Cf.* W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).

[21] A. Streitwieser, Jr., and R. A. Caldwell *ibid.*, **87**, 5394 (1965).

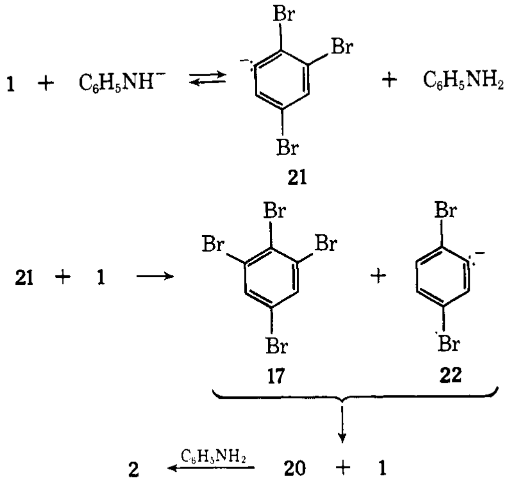
[22] G. E. Hall, R. Piccolini, and J. D. Roberts, *ibid.*, **77**, 4540 (1955); A. Streitwieser, Jr., and F. Mares, *ibid.*, **90**, 644 (1968); J. Hine and P. B. Langford, *J. Org. Chem.*, **27**, 4129 (1962).

[23] W. J. Trepka and R. J. Sonnenfeld, *J. Organometal. Chem.*, **16**, 317 (1969).

for *o*-chlorophenyl anions in ammonia[24] and for *o*-bromophenyl anions in methanol,[25] that additional halogen substituents increase the tendency for *o*-halophenyl anions to capture a proton from the solvent rather than expel halide ion. *o*-Halophenyl anions derived from trihalobenzenes have two halogen substituents in addition to the one which might be expelled to form an aryne, and thus it is to be expected that their relative tendency to capture a positive hydrogen from ammonia or aniline, or a positive halogen from a suitable aryl halide, would be greatly enhanced.

Scheme V shows how isomerization of **1** to **2** is rationalized according to the six-halogen version of the positive halogen transfer mechanism. Aryl anion **21**, one of three aryl anions in equilibrium with **1**, attacks and captures the 2-bromine of **1**, forming 1,2,3,5-tetrabromobenzene (**17**) and carbanion **22**. The latter then attacks and captures the 2-bromine of **17**, regenerating **1** and forming aryl anion **20** which, on protonation, becomes 1,3,5-tribromobenzene (**2**). Both transition states for halogen transfer carry a total of *six* halogen atoms.

Scheme V

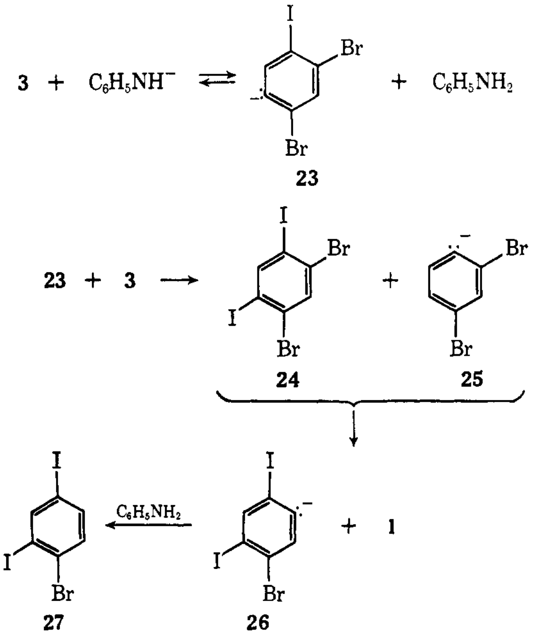


It might be expected that some of the dibromophenyl anions (**22**) would, instead of reacting with **17**, capture protons from aniline or ammonia. In that case, a di- and a tetrabromobenzene would be formed, and indeed small amounts of such products are formed.

However, the very likelihood that **22** would escape frequently from **17** is a disquieting feature of Scheme V as a mechanism for isomerization. One might doubt whether *p*-dibromobenzene would be acidic enough to be reconverted to **22** in amounts sufficient to carry on the mechanism to the ultimate formation of **2**. These doubts were intensified by our inability to obtain any 1-bromo-2,5-dichlorobenzene from the action of potassium anilide in ammonia on a mixture of **17** and *p*-dichlorobenzene. We have suggested[1b] that **17** and **22** may remain associated with each other in a charge-transfer complex before their further reaction to form **20** and **1**, but we have no direct evidence of such complexing.

As to the reactions of 1-iodo-2,4-dibromobenzene (**3**), the formation of isomer **4** may be interpreted by a mechanism analogous to that of Scheme V. However, 5-anion **23** must be invoked as an intermediate in order to rationalize the conversion of **3** to **1**, as shown in Scheme VI.

Scheme VI



In Scheme VI, a sequence of two positive halogen transfer steps is again postulated, the first an iodine transfer through attack of **23** on the iodine of **3**, the second a bromine transfer through attack of anion **25** on one of the (equivalent) bromines of **24**. Scheme VI predicts the formation of **27** as well as **1**; **27** was not identified as a product, but its isomer **5** was, and **5** may be a product of isomerization of **27**. It is possible to write another scheme, much like Scheme VI, which also rationalizes the formation of **1** from **3**; it differs from Scheme VI in that bromine transfer to **23** occurs first, and an iodine transfer second.

Inasmuch as the 3-hydrogen of **1** or **3** is undoubtedly the most acidic, one might ask why the corresponding anions are not invoked as intermediates. There are two reasons. One is that the greater stability of the 3-anion may be largely offset by lower inherent nucleophilicity related to its lower p*K*. The other is that halogen capture by such an anion would lead to a 1,2,3,4-tetrahalobenzene, a species energetically unfavorable because of multiple crowding between halogen atoms.

For isomerization of **1** to **2** according to the seven-halogen version of the positive halogen transfer mechanism, the key step involves interaction of a trihalophenyl anion with a tetrahalobenzene. The transformation is sketched in Scheme VII. In Scheme VII, the first and third steps are proton transfers and the second step is a positive halogen transfer. The mechanism requires 1,2,3,5-tetrabromobenzene to be present, but it is to be noted that this substance is produced by the action of potassium anilide on **1**, probably according to the first two steps of Scheme V.

Other isomerization and disproportionation reactions which we have described can be rationalized, with one or two exceptions noted below, either *via* six-halogen schemes similar to Schemes V and VI, or

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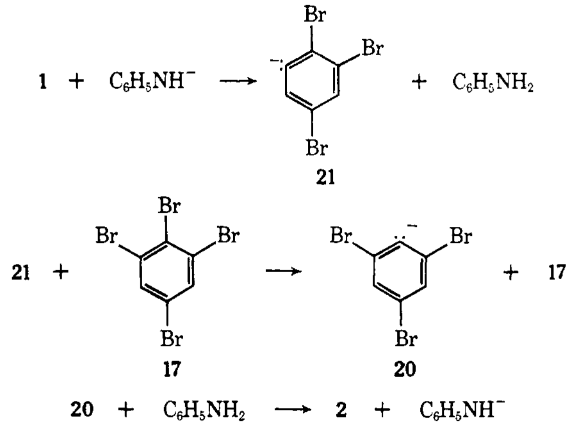
[24] J. A. Zoltewicz and J. F. Bunnett, *J. Amer. Chem. Soc.*, **87**, 2640 (1965).

[25] J. F. Bunnett and D. A. R. Happer, *J. Org. Chem.*, **31**, 2369 (1966).

Scheme VII



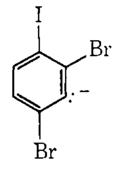
via seven-halogen schemes resembling Scheme VII. Evidence presented in an accompanying paper[6] calls for the seven-halogen (Scheme VII) rather than the six-halogen version (Scheme V) for the isomerization of **1** to **2** under certain conditions, but the six-halogen version of the mechanism remains a distinct possibility for other conditions and/or other substrates.

The Possibility that Anilide Ion Acts as a Positive Halogen Carrier. One could conceive that, instead of positive halogen being transferred directly from aryl halide to aryl anion, it were transferred first to anilide ion, forming an *N*-haloaniline which then handed the halogen on to an aryl anion. Arguments against such a mechanism are: (a) that a chain-carrying step would require encounter between two reactive intermediates (*N*-haloaniline and aryl anion), (b) that isomerization–disproportionation is also catalyzed by oxygen bases,[6] and (c) that an *N*-haloaniline in the presence of anilide ion would be likely to form hydrazobenzene and halide ion rather than wait for an aryl anion to come along. This possibility is therefore dismissed.

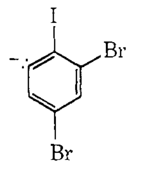
Related Work of Other Investigators. The positive halogen transfers invoked in Schemes V–VII bear a close resemblance to the well-known halogen–metal interchange reaction.[23,26,27] Rearrangements have been observed to occur during reactions of brominated thiophenes with organolithium reagents; they have been interpreted in terms of a succession of halogen–metal interchanges.[28] Isomerization and disproportionation occur in the course of reactions of certain halothiophenes,[29] haloisothiazoles,[30a] and haloimidazoles[30b] with $NaNH_2$ or KNH_2 in ammonia; interpretation in terms of positive halogen transfer much as we suggest has been offered.[29,30]

Halide Ion Products. In many cases, as related above, the yields of halide ions produced in reactions of trihalobenzenes with potassium anilide and with KNH_2 in ammonia were determined. When both iodine and bromine were present, potassium anilide in all cases liberated more iodide than bromide ion, whereas KNH_2 liberated more bromide ion.

Two explanations come to mind. One assumes that halide ions are liberated chiefly as by-products in the formation of arynes. It acknowledges that both the original oligohalobenzene (*e.g.*, **3**) and its isomerization or disproportionation products may undergo elimination of HX to form arynes. With respect to the original oligohalobenzene, it considers the various possible *o*-haloaryl anion intermediates in aryne formation. From 1-iodo-2,4-dibromobenzene (**3**), for example, these are 3-anion **28**, 5-anion **23**, and 6-anion **29**. When potassium anilide is the base, all three



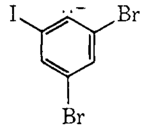
28



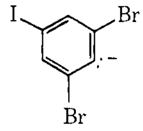
29

anions are in acid–base equilibrium with **3**, and halide ion expulsion from the anion is the rate-limiting step in aryne generation. Inasmuch as iodine is expelled more readily than bromine, other things being equal,[31] aryne formation may occur predominantly from 6-anion **29**, providing that the kinetic factor favoring iodide ion release from **29** is sufficiently great to overcome the thermodynamic factor which favors **28** in the equilibrium between **23**, **28**, and **29**.

From isomerization product **4** (from **3**), two aryl anions, **30** and **31**, may be formed. Formation of **31**



30



31

is probably favored to some extent both kinetically and thermodynamically,[31] and **30** is favored statistically. When **30** and **31** are in acid–base equilibrium with **4**, as with potassium anilide in ammonia, the kinetic factor favoring release of iodide ion from **30** probably more than offsets any thermodynamic preference for **31** (which must necessarily release bromide ion), so that iodide ion is released preferentially. Similar considerations would apply to disproportionation products, such as **1** and **5** (from **3**). Even when the base is KNH_2, it is very probable that iodide ion release is relatively more favored from disproportionation–isomerization products **1**, **4**, and **5** than from **3**. However, if with KNH_2 isomerization and disproportionation are relatively slow compared to aryne formation, as seems to be the case, a lesser proportion of iodide ions should be released than in reactions with potassium anilide.

Another explanation is demanded by the fact that 1-iodo-2,4,6-tribromobenzene (**16**), on treatment with potassium anilide, affords preponderantly tribromobenzenes **2** (44%) and **1** (10%), without concomitant accumulation of iodine atoms in pentahalobenzenes, but with abundant release of iodide ion (72 or 77%). This shows that there is some mechanism for removal of iodine, ultimately to appear as iodide ion, other than aryne formation. Indeed, the structure of **16**

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(26) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).

(27) D. E. Fenton and A. G. Massey, *Tetrahedron*, **21**, 3009 (1965).

(28) S. Gronowitz, *Advan. Heterocycl. Chem.*, **1**, 75 (1963); P. Moses and S. Gronowitz, *Ark. Kemi*, **18**, 119 (1961).

(29) M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, **90**, 511 (1968); M. G. Reinecke, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969; *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, C68 (1969).

(30) (a) D. A. deBie and H. C. van der Plas, *Tetrahedron Lett.*, 3905 (1968); (b) *Recl. Trav. Chim. Pays-Bas*, **88**, 1246 (1969).

(31) J. F. Bunnett and F. J. Kearley, Jr., *J. Org. Chem.*, **36**, 184 (1971).

precludes its direct conversion to an aryne by elimination of the elements of HI, and many of the conceivable disproportionation products from **16** would be subject to the same restriction.

A possibility is that anilide ion attacks the iodine atom of **16**, so as to capture a positive iodine moiety, forming aryl anion **29** and *N*-iodoaniline. Proton capture by **20** would form **2**, a major product. The *N*-iodoaniline might react with more anilide ion, by nucleophilic displacement on nitrogen, to release iodide ion and form hydrazobenzene. Amide ion is presumed to have lesser nucleophilicity toward iodine, owing to its lower polarizability.[32] This mechanism, which bears a close resemblance to that proposed for dehalogenations effected by the potassium *tert*-butoxide–dimethyl sulfoxide–*tert*-butyl alcohol system,[8] gives a good account of the abundant formation of iodide ion and of tribromobenzenes **1** and **2**, and for the low Br^-/I^- ratio.

There is less support for this mechanism insofar as reactions of **3** and **6** are concerned. Neither gave more than a few per cent of dihalobenzenes. Nucleophilic displacement on iodine should be especially favored when it is flanked by two ortho halogens, as it is in **16**.

Experimental Section

Reactants and Authentic Samples of Products. The greatest part of the labor of this investigation was in synthesis of starting materials and of authentic samples of products or suspected products for comparison purposes. Some 57 oligohalobenzenes or intermediates in the preparation thereof were synthesized in the course of this work. Also, several substances were purchased from commercial sources. Most of the syntheses involved conventional methods, and most of the intermediates or products were known compounds with physical properties in agreement with those recorded in the literature. Details on the methods used and the substances obtained are given in the dissertation of C. E. M.[1a] The substances listed in Table II are new compounds or have physical properties quite different from those previously recorded in the literature; all the structures assigned are supported by elemental analyses, a rational method of synthesis, and often other evidence.

Table II. New Compounds

	Mp, °C	Bp, °C (*P*, torr)
3-Bromo-5-iodoaniline	75–76	
3-Bromo-4,5-diiodoaniline	143–144	
4-Bromo-4,5-diiodobenzene	50.5–52	
4-Chloro-1,2-diiodobenzene	39–40.5	
2-Bromo-4-chloro-1-iodobenzene (**6**)	33	111 (2.5)[a]
3-Bromo-4-chloro-1-iodobenzene	39.5–40.5	
4-Bromo-2-chloro-1-iodobenzene (**13**)	32–33	103–104 (1.5)[b]
2-Chloro-5-iodoaniline	61–61.5[c]	
4-Chloro-1,3-diiodobenzene[d]		129 (2)

[a] $n^{25.5}\text{D}$ 1.6700. [b] $n^{25.5}\text{D}$ 1.6722. [c] B. B. Dey, R. K. Maller, and B. R. Pai (*J. Sci. Ind. Res., Sect. B*, **10,** 134 (1951)) reported mp 159°. [d] Preparation of 4-chloro-1,3-diiodobenzene was claimed by C. Istrati, *Bul. Soc. Sciinte*, **6,** 47 (1897); *Chem. Zentralbl.*, **1,** 1167 (1897).

1,2,4-Tribromobenzene-*3,5,6-d*$_3$. This preparation is described here because it is of special interest. A mixture of **1** (3.0 g) and 12 ml of 1.39 *M* $NaOCH_3$ in CH_3OD[33] was sealed in glass and heated 6 days at 102°. The cooled reaction mixture was diluted with water and extracted with ether. Titration of the water layer with $AgNO_3$ showed that 0.43 mol of bromide ion had been formed per mole of **1** introduced. From the ether layer deuterated **1**, mp 43–44°, was isolated in 49% yield. Its infrared spectrum was significantly different from that of ordinary **1**, and its nmr spectrum was virtually blank, showing only a suggestion of proton resonance at the highest sensitivity of the Varian A-60 spectrometer.

General Reaction Procedure. For a typical reaction, a 1-l. round-bottomed, three-necked flask was equipped with a nitrogen inlet, a sealed mechanical stirrer, and a Y tube, one branch of which was fitted as an inlet for ammonia gas and the other connected to a condenser cooled by solid CO_2. With nitrogen flowing, the apparatus was flamed, and then 500 ml of liquid ammonia was condensed in the flask by distillation from a commercial cylinder. Small pieces of potassium metal were added until the dark color persisted for several minutes. A little crushed ferric nitrate was added followed by potassium metal (0.005–0.02 g-atom). Disappearance of the dark blue color indicated complete conversion to KNH_2. If potassium anilide was to be the base, aniline was added in amount equal to or greater than the amount of potassium metal used. The oligohalobenzene (0.005–0.02 mol) was then added, frequently with a small amount of anhydrous ethyl ether to facilitate transfer. In general, when KNH_2 was the base, the solution darkened and all the material appeared to dissolve after a few minutes, but when potassium anilide was the base, the reaction mixture appeared to be a slurry and complete solution did not occur.

After the desired reaction time, ammonium nitrate was added to neutralize the base, and the ammonia was allowed to evaporate. The residue was taken up in water and ether and the layers were separated. Halide ion in the water layer was often determined, by potentiometric titration with silver nitrate. The ether layer was extracted with dilute hydrochloric acid (except in the experiments with deuterated **1** and **2**), dried, and evaporated. The neutral fraction thus obtained was analyzed by chromatography on alumina, with elution by petroleum ether (bp 30–60°), or it was analyzed by glpc. The acid-soluble fraction was discarded.

Reactions of 1,2,4-Tribromobenzene. Blank Experiments. It was shown that isomerization did not occur during work-up, either on extraction with dilute HCl or on chromatography on alumina, and that it did not occur in liquid ammonia alone, in liquid ammonia with aniline, or in liquid ammonia with aniline and added ferric nitrate (which was always present in trace amounts since it was used to catalyze the formation of KNH_2).

Reactions of 1-Bromo-2,4-dichlorobenzene. Two experiments were performed. In one, 0.01 mol of the 1,2,4 isomer was exposed to 0.005 mol of potassium anilide with 0.005 mol of excess aniline in 500 ml of ammonia for 8 hr; 33% of the 1,3,5 isomer was produced, and 24% of the 1,2,4 isomer recovered; products were chromatographed on alumina and identified by melting point and infrared spectra. In the other, 0.01 mol of the 1,2,4 isomer in 500 ml of ammonia was exposed to 0.02 mol of potassium anilide without excess aniline for 30 min; 46% of the 1,3,5 isomer was formed, and 8% of the 1,2,4 isomer recovered; products were identified by glpc retention time analysis with reference to diphenyl ether as internal standard.

Reactions of 1-Iodo-2,4-dibromobenzene (3). Reaction of **3** (0.01 mol) with potassium anilide (0.005 mol) in 500 ml of ammonia was allowed to occur for 30 min. Products **4** (28%), **1** (12%), and **5** (4%) and recovered **3** (30%) were all identified by the match of their infrared spectra with those of authentic samples, and in most cases as well by melting point and mixture melting point. In other experiments of similar character, trace amounts of **2**, identified by its infrared spectrum, and of *p*-bromoiodobenzene and *m*- and *p*-dibromobenzenes were detected. Our only evidence for the structures of these three dihalobenzenes is from glpc retention time analysis, but in view of the system under study, we believe them to be correctly identified. The glpc analysis also showed trace amounts of further products, some of which are perhaps tetrahalobenzenes.

Reactions of 1-Iodo-2-bromo-4-chlorobenzene (6), From 30-min exposure of **6** (0.01 mol) to potassium anilide (0.01 mol) in 500 ml of liquid ammonia, a grand mixture of products was obtained. By glpc analysis on an SE-30 column, fractions were eluted in the order in which they are now discussed. First were three unidentified fractions, possibly dihalobenzenes, each in perhaps 1% yield. (All yields are against an internal standard of diphenyl ether.) 1-Chloro-3,5-dibromobenzene (**8**), identified by its retention time, infrared spectrum, melting and mixture melting point with an authentic sample, appeared in 1.5% yield. A mixture of chlorodibromoben-

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(32) R. G. Pearson, *Surv. Progr. Chem.*, **5**, 1 (1969).

(33) J. F. Bunnett and J. D. Reinheimer, *J. Amer. Chem. Soc.*, **84**, 3284 (1962).

zenes of 1,2,4 orientation appeared as an unresolved peak; the retention time was identical with that of **10**, **11**, or **12**, the infrared spectrum of eluted material was very complex, and the nmr spectrum closely resembled that of an authentic mixture of **10**, **11**, and **12**; on the basis of the nmr spectrum, this is taken to be a mixture of these three isomers. The combined yield of **10**, **11**, and **12** was 7%. 1-Bromo-3-chloro-5-iodobenzene (**7**) appeared in 18% yield; identification was by the match of infrared and nmr spectra with those of an authentic sample, by melting point and mixture melting point with authentic **7**, and by retention time analysis. A mixture of substances diagnosed as bromochloroiodobenzenes of 1,2,4 orientation appeared in 23% yield; the retention time was that of **6**, **13**, or 1-iodo-3-bromo-4-chlorobenzene, a mixture of which was inseparable on the column employed; the infrared and nmr spectra of an eluted sample were complex, and the nmr spectrum showed absorptions characteristic of **6** and **13** as well as further absorptions which, however, could not be attributed to 1-iodo-3-bromo-4-chlorobenzene; this mixture is believed to comprise unreacted **6**, product **13**, and at least one further bromochloroiodobenzene of 1,2,4 orientation. Following a trace of an unidentified product, a trace of 1-chloro-3,5-diiodobenzene (**9**) appeared; identification was by retention time and the near-match of the infrared spectrum of an eluted sample with that of authentic **9**. The last clearly defined fraction, which appeared in trace amounts, was a mixture of 1-chloro-2,4-diiodobenzene (**14**) and 1-chloro-3,4-diiodobenzene (**15**); identification was by retention time and by the fact that infrared and nmr spectra matched almost perfectly those of an authentic mixture of **14** and **15**.

Reactions of 1-Iodo-2,4,6-tribromobenzene (16). From 10-min exposure of **16** (0.005 mol) to potassium anilide (0.01 mol) in 500 ml of ammonia, a mixture of products was obtained. By glpc analysis on an SE-30 column, product fractions were eluted in the order in which they are now discussed. The first four products were 1,3,5-tribromobenzene (**2**), in 44% yield, 1,2,4-tribromobenzene (**1**) (10%), 1-iodo-3,5-dibromobenzene (**4**) (1.6%), and 1-iodo-2,4-dibromobenzene (**3**) (4%), all identified by retention time and by the match of infrared spectra of eluted samples with those of the authentic compounds. The next fraction (7% yield) was subjected to further glpc on an SE-30/Bentone 34 column which effected partial resolution into two subfractions; the infrared spectra of the eluted subfractions indicated them to be composed, respectively, of 1,2,3,5-tetrabromobenzene (**17**) contaminated with 1,2,4,5-tetrabromobenzene (**18**), and of **18** contaminated with **17**. After an unidentified fraction in trace amount, unreacted **16** (12%) appeared; identification was by its infrared spectrum.

Further details concerning glpc materials and procedures, the analysis of various reaction mixtures, and the identification of specific products are given in the Dissertation of C. E. M.[1a]

Experiments Which Illuminate the Mechanism of Base-Catalyzed Isomerization and Disproportionation of Trihalobenzenes[1]

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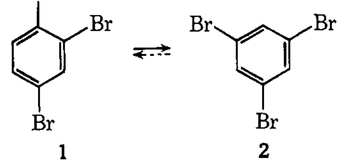
Contribution from the University of California,
Santa Cruz, California 95060. *Received February 12, 1970*

Abstract: On treatment with potassium anilide in 50% ammonia–50% diethyl ether at reflux (−29°), 1,2,4-tribromobenzene (**1**) isomerizes to its 1,3,5 isomer (**2**) and disproportionates to di- and tetrabromobenzenes. Potassium *tert*-butoxide (*tert*-BuOK) in DMF or HMPA at room temperature is also an effective catalyst. The fact that 1-chloro-2-fluoro-4-iodobenzene (**7**) and 1-chloro-2-fluoro-5-iodobenzene (**8**) do not interconvert on treatment with potassium anilide is evidence against a conceivable mechanism of 1,2 shift of iodine in an *o*-iodoaryl anion. Although isomerization of **1** is incomplete because **1** and **2** are nearly equal in free energy, **2** does not isomerize on treatment with potassium anilide in ammonia or with *tert*-BuOK in DMF. However, **2** does isomerize with cocatalysis by 1,2,3,5-tetrabromobenzene (**12**); this clarifies the reaction mechanism, which is now indicated to be the "seven-halogen" positive halogen transfer mechanism of Scheme II. In accord with the clarified mechanism, **7** and **8** do interconvert when 1-iodo-2,4,6-trichlorobenzene is supplied as cocatalyst. In HMPA, *tert*-BuOK brings about isomerization of **2** without requirement for cocatalysis, and equilibration between 1,2,4- and 1,3,5-triiodobenzene is easily effected, starting from either isomer; this exceptional reactivity is attributed to the high free energy of *tert*-BuO$^-$ in HMPA.

The isomerization of 1,2,4-tribromobenzene (**1**) to its 1,3,5 isomer (**2**) is catalyzed by NaNH$_2$[3] or KNH$_2$ in ammonia, but much more effectively by potassium anilide.[4,5] Some disproportionation to di- and tetrabromobenzenes also occurs. The action of potassium anilide in ammonia on 1-iodo-2,4-dibromobenzene or 1-iodo-2-bromo-4-chlorobenzene brings about redistribution of halogens between rings as well as isomerization.[4,5] On the basis of these and other observations, a mechanism involving series of positive halogen transfers from aryl halides to aryl anions has been proposed.[4,5]



1 2

Closely related is the scrambling of the iodine atoms of 1,2,4-triiodobenzene which occurs on treatment with potassium anilide in ammonia, more rapidly than isomerization to 1,3,5-triiodobenzene.[6] This also has been interpreted in terms of the positive halogen transfer mechanism.[6]

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(2) Grateful recipient of a NATO Fellowship awarded by the Consiglio Nazionale delle Ricerche d'Italia, 1967–1968.

(3) J. H. Wotiz and F. Huba, *J. Org. Chem.*, **24**, 595 (1959).

(4) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963).

(5) (a) J. F. Bunnett and C. E. Moyer, Jr., *ibid.*, **93**, 1183 (1971); (b) C. E. Moyer, Jr., Dissertation, Brown University, Providence, R. I., 1964.

(6) J. F. Bunnett and D. J. McLennan, *J. Amer. Chem. Soc.*, **90**, 2190 (1968).