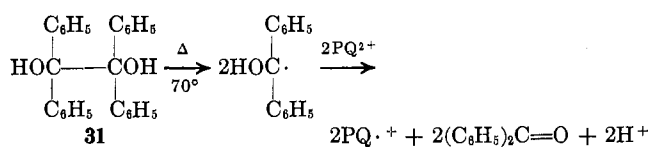


of  $\text{Ph}_2\dot{\text{C}}\text{OH}$  over its parent alcohol  $\text{Ph}_2\text{CHOH}$ . Interconversion of alkoxy radicals ( $\text{RCH}_2\text{O}\cdot$ ) and corresponding hydroxyalkyl radicals ( $\text{R}\dot{\text{C}}\text{HOH}$ ) is known to be extremely rapid,<sup>50</sup> and generation of the former, in basic media, would rapidly yield  $(\text{RCH}=\text{O})\cdot^-$ , as indicated in Scheme IV.

A similarly rapid interconversion of  $\text{RCH}_2\text{O}\cdot$  and  $\text{R}\dot{\text{C}}\text{HOH}$  will be likely in the photochemical oxidation of alcohols by  $\text{PQ}^{2+}$ . In this case,  $\text{R}\dot{\text{C}}\text{HOH}$  radicals must then be further oxidized by ground-state paraquat. Independent evidence for the latter process was obtained by studying thermal decomposition of benzpinacol (**31**) in methanol containing paraquat dichloride.<sup>51</sup>



Paraquat oxidation of semipinacol radicals ( $\text{Ph}_2\dot{\text{C}}\text{OH}$ )

(50) F. S. Dainton, I. V. Janovsky, and G. A. Salmon, *Chem. Commun.*, 335 (1969).

(51) K. Brown, A. S. Hopkins, and A. Ledwith, manuscript in preparation.

formed by unimolecular thermolysis of **31** was apparently very efficient. Reaction rates, monitored by observing the appearance of  $\text{PQ}\cdot^+$ , indicated an apparent activation energy of 28 kcal mole<sup>-1</sup> for decomposition of benzpinacol ( $k = 2.5 \times 10^{-6}$  sec<sup>-1</sup> at 64°); these figures are in good agreement with data extrapolated from those of Neckers and Colenbrander<sup>52</sup> for thermal decomposition of benzpinacol in the presence of oxygen.

It seems reasonable to conclude, therefore, that these preliminary experiments with paraquat cation radical and paraquat establish a potentially useful, and extremely convenient, new technique for quantitative scavenging of organic radicals by clearly defined electron transfer reactions. Cation radicals are likely to be increasingly recognized as intermediates in many well-known organic processes. Moreover, highly colored, stable cation radicals offer convenient tools for quantitative studies in suitable systems.

*It is a pleasure to acknowledge the stimulus provided by Professor C. E. H. Bawn, F.R.S., and the invaluable help of the collaborators listed in the references, in the development of this work.*

(52) D. C. Neckers and D. P. Colenbrander, *Tetrahedron Lett.*, 5045 (1968).

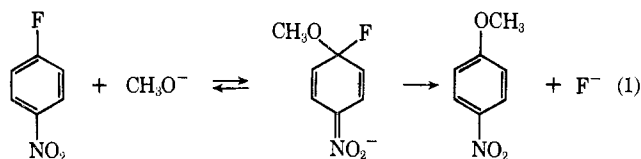
## The Base-Catalyzed Halogen Dance, and Other Reactions of Aryl Halides

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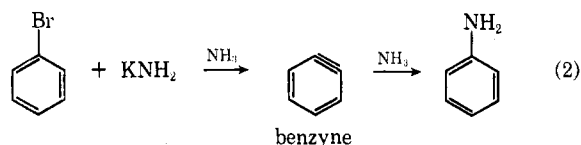
Received February 4, 1971

From textbooks one might conclude that reactions of aryl halides with basic or nucleophilic reagents are relatively few and relatively straightforward. They say that unsubstituted aryl halides are unreactive with nucleophiles under ordinary conditions, which is true. They point out that certain electron-attracting substituents, especially when ortho or para to halogen, greatly facilitate displacement of halogens by the  $\text{S}_{\text{N}}\text{Ar}$  mechanism<sup>1</sup> (cf. eq 1). They also teach that with very



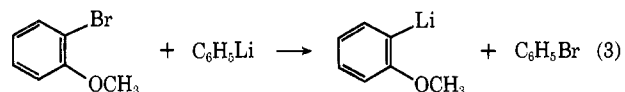
Joseph F. Bunnett is a native of Oregon, educated at Reed College (B.A.) and the University of Rochester (Ph.D.). He has taught at Reed College (1946-1952), the University of North Carolina (1952-1958), Brown University (1958-1966), and since 1966 at the University of California, Santa Cruz. His research has largely concerned mechanisms of reactions of aromatic compounds, especially aromatic nucleophilic substitution reactions. He is editor of *Accounts of Chemical Research*.

strong bases aryl halides may react by the aryne mechanism,<sup>2</sup> as exemplified in eq 2. But that is about all



most have to say.

Presentations which are more advanced and more current also describe the halogen-metal interconversion reaction<sup>3</sup> (cf. eq 3), the remarkably facile  $\text{S}_{\text{N}}\text{Ar}$  reactions



of hexafluorobenzene and related compounds,<sup>4</sup> the anal-

(1) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(2) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Amer. Chem. Soc.*, **78**, 601 (1956).

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

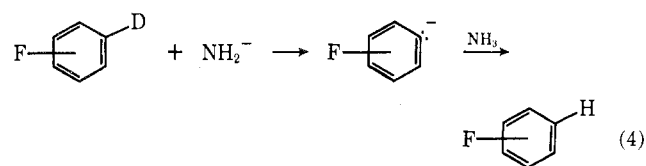
(4) J. Burdon, *Tetrahedron*, **21**, 3373 (1965).

ogous but less facile reactions of hexachlorobenzene,<sup>5</sup> and the rich chemistry of tetrafluorobenzene,<sup>6</sup> tetrachlorobenzene,<sup>7</sup> and their near relatives.

My coworkers and I are not unappreciative of the aforementioned chemistry, but we know that aryl halides will do a lot of other things in basic systems. In this Account some of their other adventures are related; saved for last is the frenzied base-catalyzed halogen dance.

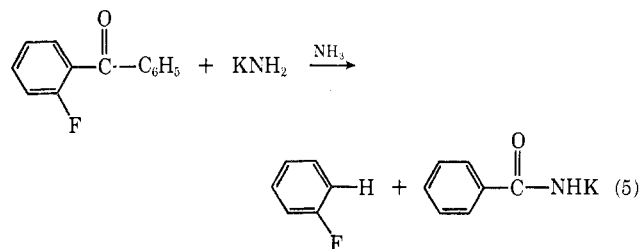
### *o*-Halophenyl Anions

Hydrogen atoms ortho to halogens are remarkably acidic. For example, fluorobenzene-2-*d* undergoes hydrogen isotope exchange with KNH<sub>2</sub> in liquid ammonia a million times faster than does deuteriobenzene.<sup>8</sup> Exchange occurs *via* an aryl anion intermediate (eq 4).

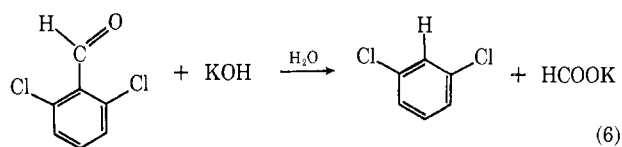


Meta fluorine also accelerates aryl anion formation, but a thousandfold less powerfully, and the accelerating effect of para fluorine is weaker yet. Similar trends obtain in analogous reactions with lithium cyclohexylamide in cyclohexylamine.<sup>9</sup> Rates of aryne formation from substituted bromobenzenes show that other halogens have similar effects.<sup>10</sup> As might be expected, hydrogens which are flanked by two ortho halogens are especially reactive with bases.<sup>11,12</sup>

The special accessibility of *o*-halophenyl anions is responsible for the facile cleavage of *o*-halobenzophenones by potassium amide in ammonia<sup>13</sup> (eq 5), for the



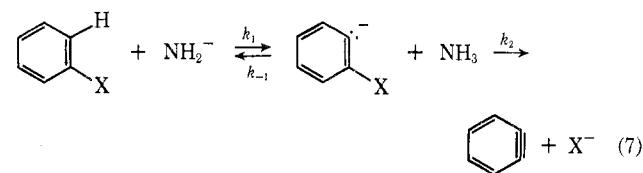
fact that 2,6-dichlorobenzaldehyde is cleaved by aqueous alkali to *m*-dichlorobenzene and formate ion<sup>14</sup> (eq 6), rather than undergoing Cannizzaro reaction, for the exceptional reactivity of *o*-dibromobenzene in halo-



gen-metal interconversion,<sup>15</sup> and probably for the formation of *o*-deuteriochlorobenzene from reaction of *o*-chlorobenzenediazonium ion with NaOCH<sub>3</sub> in CH<sub>3</sub>OD.<sup>16</sup>

### Halogen Release from *o*-Halophenyl Anions

The order of reactivity of the monohalobenzenes with KNH<sub>2</sub> in ammonia to form benzyne is a mixed one: Br > I > Cl ≫ F.<sup>17</sup> This is attributed to a change of rate-limiting step<sup>18</sup> (*cf.* eq 7). It is known, especially



from the relative yields of the two halide ions released from *m*-dihalobenzenes (with unlike halogens)<sup>19</sup> by the action of KNH<sub>2</sub> in ammonia, that the ease of halide ion expulsion from *o*-halophenyl anions is in the order I > Br > Cl > F. The rates of proton removal from positions ortho to halogen are in the opposite order.<sup>2,11</sup> In eq 7, the rate of the second step determines the overall reactivity order except for the relationship of iodo- and bromobenzene, for both of which the first step is rate limiting.

The effects of substituents on the relative rates of proton capture and of halide ion release by *o*-halophenyl anions (*e.g.*, the ratio  $k_{-1}/k_2$  in eq 7) have been determined for *o*-chlorophenyl anions in liquid ammonia<sup>20</sup> and for *o*-bromophenyl anions in methanol.<sup>21</sup> Surprisingly, the proton capture/halide release rate ratio is increased in both systems by electron-releasing (CH<sub>3</sub>, OCH<sub>3</sub>) as well as by electron-attracting substituents (Cl, CF<sub>3</sub>). The effect of a halogen substituent (other than the halogen which may be expelled) is especially strong. Thus, as an *o*-halophenyl anion accumulates further halogen substituents, it appears not only to be stabilized in a thermodynamic sense but also to become increasingly disposed, when it does react, to react with a proton donor or other electrophile rather than to expel halide ion.

### Nucleophilic Attack on Halogen

In the course of a search for further base-solvent

(5) D. J. Berry, I. Collins, S. M. Roberts, H. Suschitzky, and B. J. Wakefield, *J. Chem. Soc. C*, 1285 (1969).

(6) J. P. N. Brewer, I. F. Eckhard, H. Heaney, and B. A. Marples, *ibid.*, C, 664 (1968); D. E. Fenton and A. G. Massey, *Tetrahedron*, **21**, 3009 (1965).

(7) H. Heaney and J. M. Jablonski, *J. Chem. Soc. C*, 1895 (1968).

(8) G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Amer. Chem. Soc.*, **77**, 4540 (1955).

(9) A. Streitwieser, Jr., and F. Mares, *ibid.*, **90**, 644 (1968).

(10) R. Huisgen, W. Mack, K. Herbig, N. Ott, and E. Anneser, *Chem. Ber.*, **93**, 412 (1960).

(11) J. Hine and P. B. Langford, *J. Org. Chem.*, **27**, 4149 (1962).

(12) A. Streitwieser, Jr., J. A. Hudson, and F. Mares, *J. Amer. Chem. Soc.*, **90**, 648 (1968).

(13) J. F. Bunnett and B. F. Hrutford, *J. Org. Chem.*, **27**, 4152 (1962).

(14) J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *J. Amer. Chem. Soc.*, **83**, 2512 (1961).

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

(16) J. F. Bunnett, D. A. R. Happer, and H. Takayama, *Chem. Commun.*, 367 (1966); J. F. Bunnett and H. Takayama, *J. Amer. Chem. Soc.*, **90**, 5173 (1968).

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

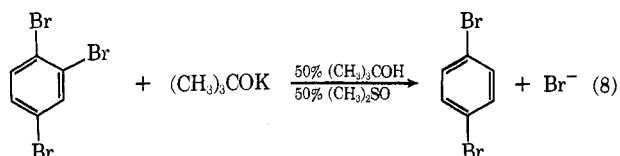
(18) For an early discussion in somewhat similar terms, see ref 2.

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

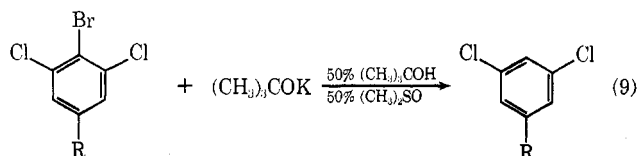
(20) J. A. Zoltewicz and J. F. Bunnett, *J. Amer. Chem. Soc.*, **87**, 2640 (1965).

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

systems in which the base-catalyzed halogen dance (*vide infra*) might be caused to occur, 1,2,4-tribromobenzene (**1**) was exposed to potassium *tert*-butoxide ((CH<sub>3</sub>)<sub>3</sub>COK) in 50% *tert*-butyl alcohol–50% dimethyl sulfoxide. The unexpected product was *p*-dibromobenzene, in 70% yield (eq 8).<sup>22</sup>



Further investigation<sup>23</sup> showed that the same reagent also effects deiodination, more readily than debromination. Dechlorination was not observed, though sought. Halogens located ortho to another halogen were preferentially removed, and halogens flanked by other halogens in both ortho positions were especially reactive. In a competition experiment, the 2-bromine of 1,2,3-tribromobenzene was totally removed before any reaction of its 1,2,4 isomer (**1**) was detectable. 4-Substituted 2,6-dichloro-1-bromobenzenes (eq 9) were more



reactive when the R group in the 4 position was chlorine or bromine rather than hydrogen.<sup>23</sup>

This pattern of halogen mobility suggested that the rate-limiting transition states had partial carbanion character and that aryl anions were intermediates. This interpretation was reinforced by the negative outcome of tests for aryl radical intermediates.

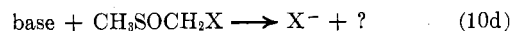
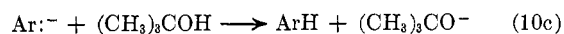
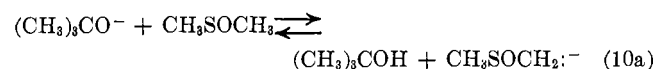
At the outset, the role of dimethyl sulfoxide was not clear. Was its effectiveness due merely to its "physical" properties, as a dipolar, aprotic solvent constituent,<sup>24</sup> or was it participating in a more "chemical" way?

To answer this question, we investigated other dipolar, aprotic solvents as "cosolvents," by measuring the extent of debromination of 1-bromo-2,6-dichlorobenzene effected by (CH<sub>3</sub>)<sub>3</sub>COK in various 50% (CH<sub>3</sub>)<sub>3</sub>COH–50% cosolvent media. Cosolvents found to be effective (though less effective than (CH<sub>3</sub>)<sub>2</sub>SO) were *N,N*-dimethylacetamide, *N*-methylpyrrolidone, and tetramethylene sulfone. Ineffective as cosolvents were diphenyl sulfoxide, dimethylformamide, and hexamethylphosphorotriamide.<sup>23</sup>

What is the unifying characteristic of the effective cosolvents which sets them apart from the ineffective ones? Clearly it is not a physical property such as dielectric constant or effect on the activity coefficient of a representative low-polarizability anion.<sup>24</sup> However, there is a unifying structural characteristic: all

the effective cosolvents have a methylene group  $\alpha$  to a carbonyl, sulfonyl, or sulfinyl group, and all the ineffective ones lack this feature. We therefore postulate that the capacity to form a carbanion in strongly basic medium is the unifying feature.

Putting these components together, we suggest the mechanism of eq 10 (for the reaction in (CH<sub>3</sub>)<sub>3</sub>COH–(CH<sub>3</sub>)<sub>2</sub>SO).<sup>23</sup> Of the four steps, (10a) and (10c) are



amply precedented,<sup>25</sup> (10b) is a nucleophilic displacement by a carbanion *on* halogen which results in positive halogen transfer, and (10d) is unclear but feasible. Possibilities for the last step are S<sub>N</sub>2 displacement of halogen by either (CH<sub>3</sub>)<sub>3</sub>CO<sup>-</sup> or CH<sub>3</sub>SOCH<sub>2</sub><sup>-</sup>,  $\alpha$  elimination of HX, or  $\gamma$  elimination to form a thirane oxide<sup>26</sup> (as in the Favorskii or Ramberg–Bäcklund reaction<sup>27</sup>).

In step 10b, the carbanion nucleophile attacks the halogen itself, rather than the carbon to which it is attached, and displaces an aryl anion. The net result is transfer of a positive halogen moiety (X<sup>+</sup>) from one carbon to another, much as in a Brønsted acid–base reaction a proton is transferred. In neither case is it implied that the positive moiety being transferred (H<sup>+</sup> or X<sup>+</sup>) has free existence as such.

Positive halogen transfer resulting from nucleophilic attack on halogen is also known in aliphatic systems.<sup>28</sup>

### Radical-Induced Deiodination in Alkaline Methanol

The unexpected result is sometimes the seed of discovery. However, rarely does one experiment bear two seeds which lead to discoveries of dissimilar character. Such was an experiment performed by Alan Happer at Brown University in 1964. The action of methanolic NaOCH<sub>3</sub> on 1-(2-iodo-4-chlorophenyl)-2-benzenesulfonylhydrazide (**3**) was studied, for the purpose of ascertaining the relative rates of proton capture (to form *m*-chloriodobenzene, **6**) and iodide ion loss (to form aryne **5** and ultimately chloroanisoles **7** and **8**) from anion **4**. Because of a quantitative discrepancy between two nearly identical runs, Happer studied the effect of NaOCH<sub>3</sub> concentration on product proportions and discovered (a) that the chloroanisole para/meta ratio depends on [NaOCH<sub>3</sub>] and (b) that in 2 M NaOCH<sub>3</sub> 31% chlorobenzene was formed. Observation (a) later blossomed into a method for determining the relative nucleophilicities of methoxide ion and methanol *vs.* 4-chlorobenzene, and (b) was the seed of the deiodination reaction now to be described.

(25) E. Bunce, E. A. Symons, and A. W. Zabel, *Chem. Commun.*, 173 (1965); J. J. Brauman, J. A. Bryson, D. C. Kahl, and N. J. Nelson, *J. Amer. Chem. Soc.*, **92**, 6679 (1970).

(26) I am grateful to Professor F. G. Bordwell for pointing out the  $\gamma$ -elimination possibility.

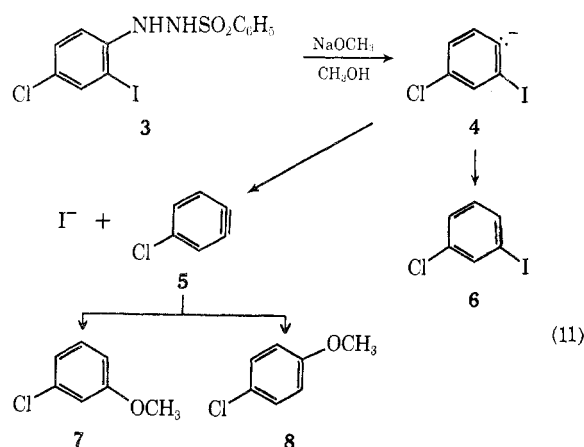
(27) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(28) W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968); C. Y. Meyers, A. M. Malte, and W. S. Matthews, *ibid.*, **91**, 7510 (1969).

(22) C. E. Moyer, Jr., Dissertation, Brown University, 1964.

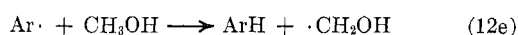
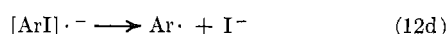
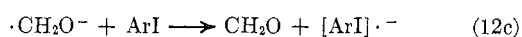
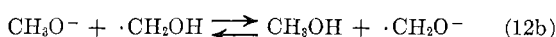
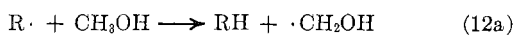
(23) J. F. Bunnett and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968); R. R. Victor, Ph.D. Dissertation, Brown University, 1968.

(24) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).



It was soon shown that chlorobenzene was formed in the system of eq 11 by deiodination of *m*-chloriodobenzene (**6**). A thoroughgoing study of the deiodination<sup>30</sup> revealed that **6** did not deiodinate unless *both* NaOCH<sub>3</sub> and a radical source (*e.g.*, peroxydisulfate ion or phenylazotriphenylmethane) were present. The facts that deiodination of **6** in CH<sub>3</sub>OD solution afforded chlorobenzene virtually free of deuterium and that reaction in the presence of benzene produced *m*-chlorobiphenyl indicated the intermediacy of *m*-chlorophenyl radicals. Even when both NaOCH<sub>3</sub> and a radical source were present, deiodination was blocked by the presence of nitrobenzene; this suggested electron transfer to be involved.<sup>30</sup>

A mechanism compatible with these observations is set forth in eq 12, in which "ArI" stands for **6** or other aryl iodide. Initiation and termination steps are not



shown. Of the several steps, (12a) and (12e) are familiar, and (12b) is an acid-base reaction. (12c) is an electron-transfer process, in which  $\cdot\text{CH}_2\text{O}^-$ <sup>31</sup> donates an electron to the aryl iodide, forming formaldehyde and an aryl iodide radical anion. The latter rapidly expels iodide ion, in step 12d, generating an aryl radical; it is possible that steps 12c and 12d are not discrete, but concerted. Nitrobenzene, a better electron-acceptor than **6**, blocks deiodination by stealing an electron from  $\cdot\text{CH}_2\text{O}^-$  and thereby is reduced to the nitrobenzene radical anion which then acts as a radical chain terminator.<sup>30</sup>

### A Radical Mechanism of Aromatic Nucleophilic Substitution

According to the aryne mechanism hypothesis, 5- and 6-iodopseudocumene (**9** and **10**, respectively) should

(29) J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Amer. Chem. Soc.*, **88**, 5250 (1966); J. F. Bunnett and C. Pyun, *J. Org. Chem.*, **34**, 2035 (1969).

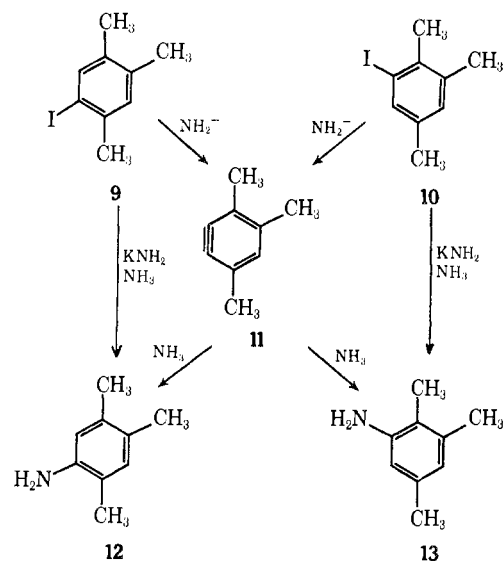
(30) J. F. Bunnett and C. C. Wamser, *J. Amer. Chem. Soc.*, **89**, 6712 (1967).

(31) K.-D. Asmus, A. Wigger, and A. Henglein, *Ber. Bunsenges. Phys. Chem.*, **70**, 862 (1966).

react with KNH<sub>2</sub> in ammonia to form the same aryne (**11**) and the same proportion of aminopseudocumenes **12** and **13**. This expectation is fulfilled by the chloro and bromo analogs of **9** and **10**, which afford these amino compounds in a 6-amino/5-amino (**13/12**) ratio of 1.5.<sup>32a</sup>

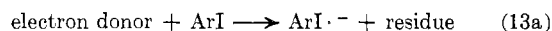
However, the 6-amino/5-amino ratios from reactions of **9** and **10** with excess (0.29 *M*) KNH<sub>2</sub> in NH<sub>3</sub> are not identical; the **13/12** ratio is 0.63 from **9** and 5.9 from **10**. Thus each iodo compound gives preferentially the amine of the same orientation. A mixture of aryne mechanism (to account for the considerable degree of cine substitution which does occur) and of a mechanism of substitution without rearrangement is indicated.<sup>32a</sup>

Nucleophilic aminodeiodination by the S<sub>N</sub>Ar mechanism is unlikely. I know of no authentic example of such displacement, with KNH<sub>2</sub> in NH<sub>3</sub> at -33°, in an unactivated halobenzene. Moreover, activated aryl iodides are generally less reactive than the corresponding bromides and chlorides in that type of reaction.

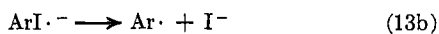


A clue to the mechanism of substitution without rearrangement is provided by the fact that reactions of **9** and **10** with KNH<sub>2</sub>-NH<sub>3</sub> in the presence of tetraphenylhydrazine afford **12** and **13** with 6-amino/5-amino ratios much closer to the "aryne ratio" of 1.5. With tetraphenylhydrazine, the ratios are 1.4 from **9** and 2.0 from **10**. Tetraphenylhydrazine is a scavenger for reactive radicals. The fact that it suppresses substitution without rearrangement is evidence for a radical mechanism.<sup>32a</sup>

This conclusion is substantiated by the fact that non-rearranging substitution is promoted by addition of potassium metal to the KNH<sub>2</sub>-NH<sub>3</sub> system.<sup>32b</sup> In reacting with KNH<sub>2</sub> and K metal, both in excess, **9** afforded **12** uncontaminated by isomers, and **10** formed **13** with only a trace of **12**; in both cases, there was also substantial (30-40%) formation of pseudocumene. The mechanism of eq 13a-e gives an account of these observations.



(32) (a) J. K. Kim and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 7463 (1970); (b) *ibid.*, **92**, 7464 (1970).



Potassium metal in ammonia solution exists as potassium ion and the solvated electron, a superb electron donor.<sup>33</sup> Steps analogous or identical to (13a), (13b), and (13d) are well known from prior work.<sup>30,34</sup> The combination of an aryl radical with a nucleophile as in step 13c has less precedent, but has been reported for reactions of *p*-nitrophenyl radical with cyanide ion and nitrite ion;<sup>35</sup> also, it should be noted that step 13c resembles the reverse of step 13b. Steps 13b, 13c and 13d constitute a propagation cycle; yields of aniline derivatives greater than 100% on the basis of K metal furnished have been observed. When K metal is not present in the medium, the identity of the electron donor in step 13a is less clear; perhaps it is a substituted anilide ion.

The mechanism of eq 13a-e closely resembles mechanisms which have been advanced on good evidence for substitutions at saturated carbon, some of which were earlier thought to be S<sub>N</sub>2 reactions.<sup>36</sup> We have suggested<sup>32a</sup> that such mechanisms be symbolized S<sub>RN</sub>1, which stands for *substitution, radical-nucleophilic, unimolecular*. The mechanism is unimolecular in the same sense as S<sub>N</sub>1, except that unimolecular bond fission occurs in a radical anion instead of in a neutral molecule. An associated problem in terminology, perhaps best discussed in a social context, is whether the fission is homolytic or heterolytic.

By promoting the S<sub>RN</sub>1 mechanism through addition of K metal, one can cause aryl halides to undergo aminodehalogenation without rearrangement on reacting with KNH<sub>2</sub>-NH<sub>3</sub>, in the teeth of the aryne mechanism with its proclivity to cine substitution.<sup>32b</sup> The reaction of *o*-bromoanisole with KNH<sub>2</sub> or NaNH<sub>2</sub> in ammonia to form *m*-anisidine<sup>37</sup> epitomizes cine substitution by the aryne mechanism.<sup>2</sup> Yet by conducting this reaction in the presence of excess K metal, one can entirely eclipse the aryne mechanism, obtaining *o*-anisidine free of its meta isomer.<sup>32b</sup>

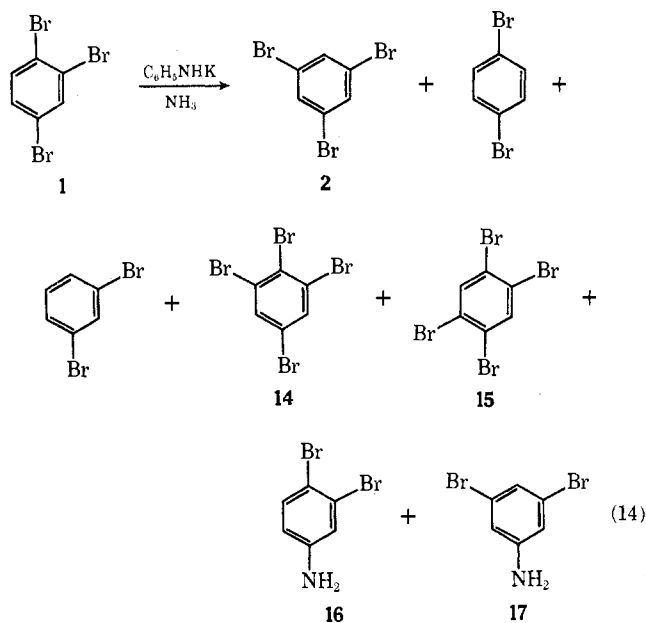
Moreover, S<sub>RN</sub>1 reactions promoted by K metal enable substitutions to occur in situations where the aryne mechanism is impossible. For example, a halogen flanked on both sides by ortho substituents can be caused to undergo aminodehalogenation with KNH<sub>2</sub>-NH<sub>3</sub>, and a phenoxy group of diphenyl ether can be replaced by an amino group.<sup>32b</sup> Other nitro anion

nucleophiles as well as carbanion nucleophiles also take part in aromatic S<sub>RN</sub>1 reactions, but the scope of such reactions is not well established.

### The Base-Catalyzed Halogen Dance

Twelve years ago, in the course of an exploration of reactions of NaNH<sub>2</sub> in liquid ammonia with several di- and trihalobenzenes, it was discovered that the tribromobenzene recovered from the reaction of 1,2,4-tribromobenzene (**1**) was its 1,3,5 isomer (**2**).<sup>38</sup> There was no precedent for base-catalyzed isomerization of a trihalobenzene. We therefore undertook to study this phenomenon.

An early finding was that potassium anilide in ammonia is much more satisfactory than NaNH<sub>2</sub> or KNH<sub>2</sub> as an isomerization catalyst.<sup>39</sup> With this reagent, isomerization of **1** is quite rapid; 30-min reaction time at *ca.* -33° is usually sufficient. Isomerization product **2** (often in 40-60% yield) is accompanied by small amounts (5% or less) of disproportionation products: *p*- and to a lesser extent *m*-dibromobenzene, and tetrabromobenzenes **14** and **15**. Some unisomerized **1** always remains.<sup>39</sup>



Also produced are significant amounts of dibromoanilines **16** and **17**, but little if any dibromodiphenylamine.<sup>40</sup> The dibromoanilines are doubtless formed *via* aryne intermediates.

A sample of **1** fully deuterated at all hydrogen positions was exposed to potassium anilide in ammonia. Both the **2** that was formed and the **1** that was recovered were free of deuterium.<sup>39</sup> Exchange undoubtedly occurred *via* aryl anion intermediates. This experiment demonstrates that *o*-bromoaryl anion intermediates are generated (and reprotonated) repeatedly in these systems. Their tendency to reprotonate rather than

(33) M. Szwarc, *Progr. Phys. Org. Chem.*, **6**, 379 (1968).

(34) M. Anbar, *Advan. Phys. Org. Chem.*, **7**, 115 (1969); J. G. Lawless and M. D. Hawley, *J. Electroanal. Chem.*, **21**, 365 (1969); L. M. Dorfman, *Accounts Chem. Res.*, **3**, 224 (1970).

(35) D. E. Bartak, W. C. Danen, and M. D. Hawley, *J. Org. Chem.*, **35**, 1206 (1970); A. L. J. Beckwith and R. O. C. Norman, *J. Chem. Soc. B*, 403 (1969).

(36) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Amer. Chem. Soc.*, **88**, 5661 (1966); G. A. Russell and W. C. Danen, *ibid.*, **90**, 347 (1968); N. Kornblum and F. W. Stuehal, *ibid.*, **92**, 1804 (1970).

(37) H. Gilman and S. Avakian, *ibid.*, **67**, 349 (1945); G. B. R. de Graaff, H. J. den Hertog, and W. C. Melger, *Tetrahedron Lett.*, 963 (1965).

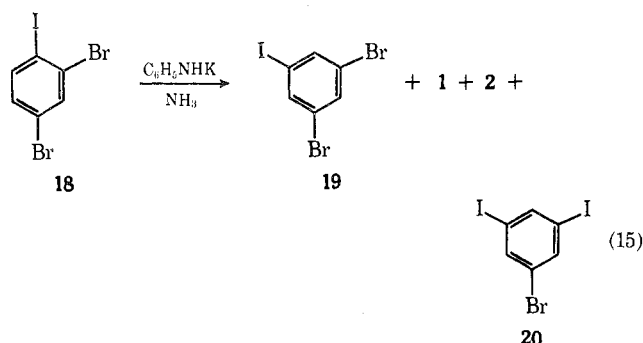
(38) J. H. Wotiz and F. Huba, *J. Org. Chem.*, **24**, 595 (1959).

(39) (a) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); (b) *ibid.*, **93**, 1183 (1971).

(40) J. F. Bunnett and I. N. Feit, unpublished observations.

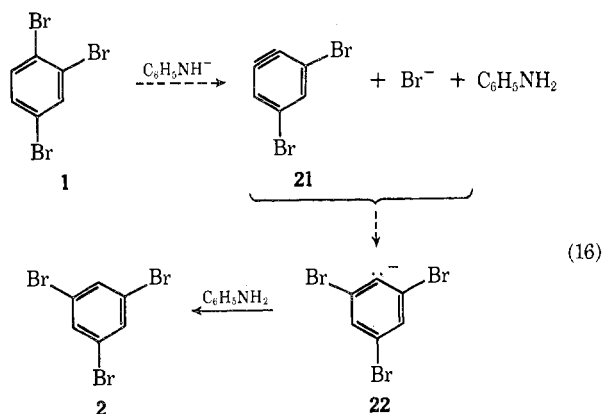
expel bromide ion is intelligible in terms of substituent effects discussed above.

**Halogen Transfer between Rings.** The products from the action of potassium anilide in ammonia on 1-iodo-2,4-dibromobenzene (**18**) were highly informative of mechanism. Besides a substantial amount (28%) of isomerization product **19**, there were formed tribromobenzenes **1** (12%) and **2** (trace amount), as



well as 1-bromo-3,5-diiodobenzene (**20**) (4%).<sup>39</sup> Obviously, halogen atoms were transferred between benzene rings; whatever the mechanism of disproportionation, it must be intermolecular in character.

**The Aryne Mechanism Possibility.** Our first working hypothesis was an aryne mechanism, as in eq 16. This was attractive for several reasons: halo-



benzenes were known to afford arynes on treatment with strong bases in liquid ammonia,<sup>2</sup> benzyne was known to be able to add halide ions,<sup>41</sup> and nucleophiles were known to attach to 3-halobenzenes preferentially at the position more remote from the 3-halogen.<sup>42</sup> Also, it could account for the interchange of halogens between rings. Thus, **18** might yield two or more arynes, liberating both bromide and iodide ions. One of these arynes (e.g., **21**) might then add the "wrong" halide ion, forming a disproportionation product.

However, several observations were incompatible with the aryne mechanism, and forced its dismissal. No iododibromobenzenes were formed when **1** was isomerized in ammonia loaded with KI.<sup>39</sup> The predominant tribromobenzene obtained from **18** was **1**, whereas **2** would have been predicted. Also, as dis-

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

(42) K. Herbig, Dissertation, University of Munich, 1960; R. Huisgen in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, p 36.

cussed below, the failure of **2** to revert to **1** on treatment with potassium anilide in ammonia unless a "cocatalyst" is supplied is inconsistent with the aryne mechanism.

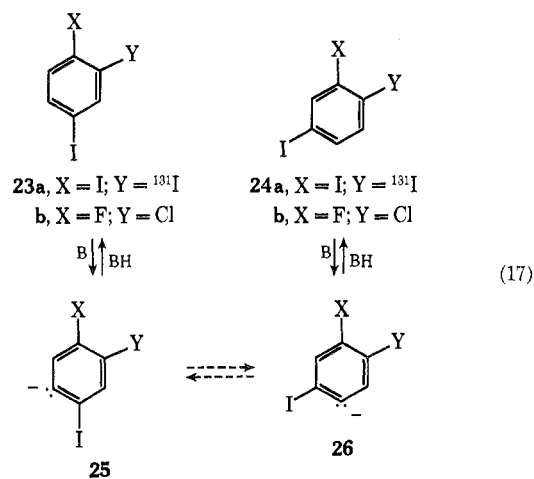
#### Scrambling of Halogens in 1,2,4-Trihalobenzenes.

A sample of 1,2,4-tribromobenzene with radiobromine in the 1 position was exposed to potassium anilide in ammonia for 15 min. Both **1** and **2** were isolated from the product mixture, and both had radioactivity equal to the original. In the recovered 1,2,4 isomer, the radiolabel was found to be equally distributed among the 1, 2, and 4 positions.<sup>43</sup>

Statistical redistribution of radiolabel also occurred when a sample of 1,2,4-triiodobenzene with iodine-131 in the 2 position was treated with potassium anilide in ammonia for 8 hr.<sup>44</sup> Rearrangement of this triiodo compound to its 1,3,5 isomer is quite slow; only 5% of the latter was obtained.

Incidentally, these experiments involved a practical problem: how does one determine the distribution of radiolabel in a 1,2,4-trihalobenzene? The answer appears in a footnote.<sup>46</sup>

**The 1,2-Shift Possibility.** Although disproportionation of halogens between rings is clearly intermolecular, isomerization and isotope-scrambling reactions might nevertheless be intramolecular in character. Conceivably, *o*-halophenyl anions might undergo 1,2 shift of halogen. Thus, the scrambling of 1,2,4-triiodobenzene-2-<sup>131</sup>I (**23a**) might occur in part as in eq 17, wherein **25** and **26** would be interconvertible by 1,2 shift of iodine.<sup>44</sup> A similar 1,2 shift might be invoked to explain the transformation of **1** to **2**. 1,2 shifts of



(43) D. J. McLennan and J. F. Bunnett, *J. Amer. Chem. Soc.*, **93**, 1198 (1971).

(44) J. F. Bunnett and D. J. McLennan, *ibid.*, **90**, 2190 (1968).

(45) Answer: To determine the radioactivity in the 2 position of radiolabeled **1** or 1,2,4-triiodobenzene, treat with (CH<sub>3</sub>)<sub>3</sub>COK in 50% (CH<sub>3</sub>)<sub>2</sub>COH-50% (CH<sub>3</sub>)<sub>2</sub>SO (cf. eq 8). Subtraction of the molar activity of the resulting *p*-dihalobenzene from that of the original trihalobenzene gives the activity in the 2 position. **1** reacts with magnesium to give a Grignard reagent, and carbonation affords 3,4-dibromobenzoic acid; subtraction of its molar activity from that of the original **1** gives the activity in the 4 position. The activity in the 1 position is reckoned by simple arithmetic. 1,2,4-Triiodobenzene does not form a Grignard reagent satisfactorily, but treatment of it with a radical source and NaOCH<sub>3</sub> in CH<sub>3</sub>OH (cf. eq 12) affords a mixture of *m*- and *p*-diiodobenzene; the molar activity of the former is that of the triiodo compound less that in the 1 position, and the activity in the 4 position follows directly.<sup>43,44</sup>

halogen occur in connection with certain sigmatropic rearrangements.<sup>46</sup>

The 1,2-shift possibility was tested by exposing the isomeric chlorofluoriodobenzenes **23b** and **24b**, separately, to potassium anilide in ammonia. These isomers differ characteristically in their infrared and nmr spectra. However each, after an 8-hr exposure, was recovered with pristine spectra showing it to be uncontaminated by the other isomer.<sup>47</sup> The failure of isomerization to occur vitiates the 1,2-shift mechanism. The cocatalysis phenomenon, discussed below, is of similar import.

#### The Efficacy of Potassium *tert*-Butoxide as a Catalyst.

Potassium *tert*-butoxide in dimethylformamide or hexamethylphosphorotriamide solution is an excellent isomerization catalyst.<sup>47</sup> Typically, reactions are over within 1 min at room temperature. One must, however, take precautions to exclude water and *tert*-butyl alcohol, both of which retard isomerization. Exclusion of water is easily accomplished by the septum-and-syringe technique. Reactions catalyzed by *tert*-BuOK in dimethylformamide or hexamethylphosphorotriamide are much more convenient to conduct than those in liquid ammonia.

**The Cocatalysis Phenomenon.** It was curious and bothersome that **2** would not revert to **1**, even to the least extent, on treatment with  $(\text{CH}_3)_3\text{COK}$  in dimethylformamide or potassium anilide in ammonia, and yet that **1** hardly ever isomerized completely to **2**. Incompleteness of isomerization might, *a priori*, be ascribed either to kinetic or to thermodynamic limitations. The fact that isomerization of **1** to **2** was virtually always incomplete, despite wide variation in conditions, made it unlikely that exhaustion of the catalyzing base was the limiting factor. On the other hand, the possibility that a state of equilibrium was attained seemed to be contradicted by the fact that **2** did not revert to **1**.

An escape from this quandary was provided by discovery that **2** would revert to **1** if a small amount of a tetrabromobenzene (**14** or **15**) were added as a cocatalyst.<sup>40,47</sup> This was observed both with  $(\text{CH}_3)_3\text{COK}$  in dimethylformamide and with potassium anilide in 50% ammonia-50% diethyl ether solution. In either system, the ultimate ratio of **1**:**2** was essentially the same, whether the initial reactant was **1** or **2**. Thus a state of equilibrium was attained, in which **1** and **2** were present in roughly equal amounts, depending somewhat on the solvent.<sup>47</sup>

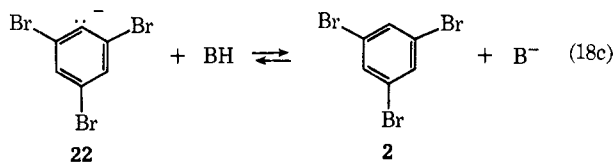
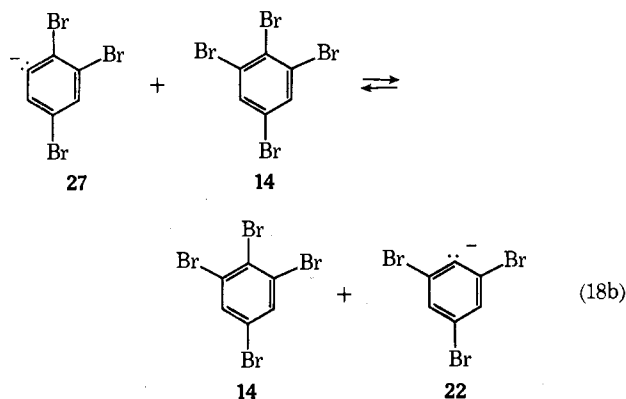
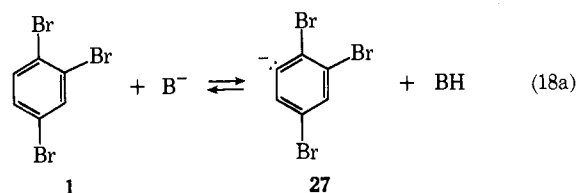
The principle of microscopic reversibility dictates that reactions which require cocatalysis in the reverse direction must also require it in the forward direction. Was it possible that all our samples of **1** had, despite our care to use pure materials, been contaminated with tetrabromobenzenes? To test this possibility, we ultrapurified a sample of **1**, by glpc and zone melting, but found that it isomerized just as readily as ordinary good samples.<sup>47</sup> We conclude that a tetrabromoben-

zene does not need to be introduced in order to facilitate the isomerization of **1**. Another dilemma!

In this case, the resolution of the paradox is already before our eyes, in eq 14. Tetrabromobenzenes are generated internally from **1**. There is no need to add cocatalyst from external sources. Incidentally, the fact that **14** and **15** are readily interconverted by the basic catalysts employed<sup>22,40</sup> helps us to understand why either is effective as cocatalyst.

The need for a cocatalyst in order to achieve reversion of **2** to **1**, and therefore progression of **1** to **2**, requires that any acceptable mechanism for isomerization assign a central role to the cocatalyst. Since neither the aryne mechanism nor the 1,2-shift mechanism provides any function for a tetrabromobenzene cocatalyst, both are disqualified.

**A Mechanism of Positive Halogen Transfer.** We know that, to interconvert **2** and **1**, we need a basic catalyst, a tetrabromobenzene cocatalyst, and that rearrangement is retarded by adding the conjugate acid of the base. The mechanism of eq 18<sup>47</sup> is compatible with these facts and with others mentioned. The key step in this mechanism is (18b), in which an aryl anion effects nucleophilic attack on bromine, displacing another aryl anion. The consequence is transfer of a positive bromine fragment from one carbon to another.<sup>39</sup> It should be noted that **14** is both consumed and generated in step 18b. Steps 18a and 18c are straightforward acid-base reactions.



The key step (eq 18b) finds analogy in the halogen-metal interconversion reaction (*cf.* eq 3). Somewhat

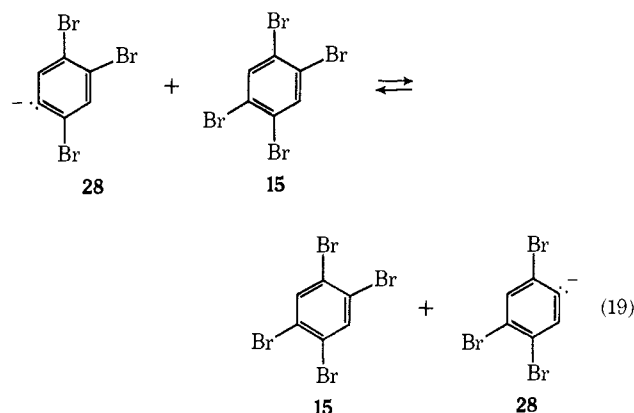
(46) C. W. Bird, *Chem. Commun.*, 1486 (1969).

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

similar schemes have been advanced to account for base-induced isomerization and disproportionation reactions among bromine derivatives of thiophene<sup>48,49</sup> and other heterocycles.<sup>50</sup>

When catalysis is provided by  $(\text{CH}_3)_3\text{COK}$  in dimethylformamide or by potassium anilide in ammonia, mechanisms such as that of eq 18 are apparently feasible only if the various intermediate phenyl anions are made energetically accessible by the presence of halogens ortho to the anionic sites and if the halogen to be transferred is bromine or iodine. (Chlorine and fluorine are known to be rather unreactive in halogen-metal interconversion<sup>3</sup> and related reactions.<sup>51</sup>) In these terms the failure of **23b** and **24b** to interconvert is intelligible: the only transferable halogen is iodine, and it is not ortho to another halogen. Isomerization of **23b** to **24b** (or *vice versa*) would be expected to occur if a good iodine-donor cocatalyst were supplied, and indeed it does occur on exposure of **23b** to potassium anilide and 1-iodo-2,4,6-trichlorobenzene in 91% ammonia-9% ether; 1,3,5-trichlorobenzene and several fluorochlorodiodobenzenes are also formed.<sup>47</sup>

There has been no experimental demonstration of need for cocatalysis in order to effect scrambling of halogens in radiolabeled **1** or 1,2,4-triiodobenzene. Nevertheless a mechanism involving cocatalysis by internally generated 1,2,4,5-tetrahalobenzene, analogous to that of eq 18, is attractive.<sup>43</sup> The key step would be as represented in eq 19. In the absence of



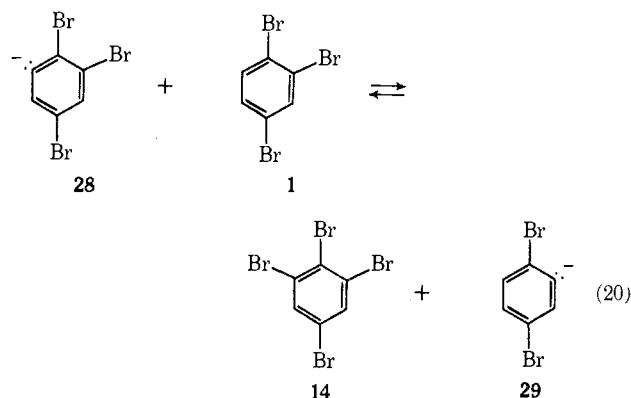
radiolabels, this step is degenerate; it causes no chemical change. However, it is superb as a mechanism for scrambling because of the equivalence, except for radiolabels, of the four halogens of a 1,2,4,5-tetrahalobenzene.

The type of mechanism represented in eq 18 and 19 may be characterized as a  $(2n + 1)$ -halogen version of the positive halogen transfer mechanism. The transition state for the key halogen transfer step involves attack

of an  $n$ -halophenyl anion on halogen of an  $(n + 1)$ -halobenzene; altogether, it contains  $2n + 1$  halogen atoms. When isomerization, disproportionation, or scrambling of a trihalobenzene is at issue, the mechanism as represented in eq 18 and 19 may be designated a seven-halogen version.<sup>39b,47</sup>

The analogous mechanism for the isomerization of 1,2,3,5- to 1,2,4,5-tetrabromobenzene, or *vice versa*,<sup>40</sup> involves attack of a tetrabromophenyl anion on a pentabromobenzene; in this case,  $2n + 1$  is nine.

It is conceivable that migration of halogen may occur in some cases by a  $2n$ -halogen version of the positive halogen transfer mechanism. We initially suggested a six-halogen version for isomerization, disproportionation, and scrambling of trihalobenzenes,<sup>39a,44,52</sup> and  $2n$ -halogen versions have been advocated by other authors for such reactions in halogenated heterocyclic systems.<sup>49,50</sup> Although the six-halogen version is now excluded for isomerization of **1** to **2** in ammonia or dimethylformamide by the cocatalysis observations described above, one of its key steps<sup>39</sup> is presented as eq 20 because it is nevertheless relevant.



Equation 20 depicts a positive halogen transfer, forming a tetrabromobenzene (**14**) and a dibromophenyl anion (**29**). If **29** were then to attack and capture the 2-bromine of **14**, the consequence would be regeneration of **1** and formation of an aryl anion (**22**) which would be protonated to **2**. However, in the potassium anilide-ammonia and  $(\text{CH}_3)_3\text{COK}$ -dimethylformamide systems this follow-up halogen transfer is apparently eclipsed by a more rapid protonation of anion **29**, forming *p*-dibromobenzene. Thus reaction 20 appears to serve as a step in disproportionation to di- and tetrabromobenzenes,<sup>39,47</sup> but not as a step in isomerization, except as it forms a tetrabromobenzene cocatalyst. However, circumstances in other systems may allow or even favor isomerization, etc., by  $2n$ -halogen versions of the mechanism.

**Reactions with  $(\text{CH}_3)_3\text{COK}$  in Hexamethylphosphorotriamide.** We have seen that with base catalysis oligohalobenzenes may undergo isomerization, disproportionation, and scrambling of halogens in a set of transformations conveniently described as the base-catalyzed halogen dance. The dance becomes frenzied

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

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

(50) D. A. de Bie and H. C. van der Plas, *Tetrahedron Lett.*, 3905 (1968); *Recl. Trav. Chim. Pays-Bas*, **88**, 1246 (1969).

(51) F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

(52) J. F. Bunnett, *Intra-Sci. Chem. Reports*, **3**, 235 (1969).



in the  $(\text{CH}_3)_3\text{COK}$ -hexamethylphosphorotriamide system. Things happen which do not happen in other systems. For example, **2** isomerizes to **1** without need for cocatalysis by a tetrabromobenzene.<sup>47</sup>

In the reaction of **2** with  $(\text{CH}_3)_3\text{COK}$  in hexamethylphosphorotriamide,<sup>47,53</sup> a substantial amount of reaction occurs within the first half minute (at room temperature), and the equilibrium ratio of **1** to **2** is attained within 1 min. Also, there is appreciable formation of tetrabromobenzenes. Apparently the basicity of the *tert*-butoxide ion in hexamethylphosphorotriamide is sufficiently high to generate remarkably higher concentrations of aryl anions and thereby to enable capture of halogens which are not ortho to other halogens, thus forming tetrabromobenzenes and enabling the halogen dance to occur according to the usual seven-halogen choreography.

1,2,4-Trichlorobenzene resists isomerization in all base-solvent systems investigated, even in  $(\text{CH}_3)_3\text{COK}$ -hexamethylphosphorotriamide containing a little tetrachlorobenzene as a possible cocatalyst. However, 1,2,3,5-tetrachlorobenzene does isomerize with  $(\text{CH}_3)_3\text{COK}$ -hexamethylphosphorotriamide, as well as disproportionate to tri- and pentachlorobenzenes.<sup>53</sup>

**Isomer Proportions at Equilibrium.** Inasmuch as the equilibrium proportions among dibromobenzenes are about 5% ortho, 61% meta, and 34% para,<sup>54</sup> it may seem odd that **1** (with ortho, meta, and para relationships between pairs of halogens) is present at equilibrium to approximately the same extent as **2** (in which there are only meta relationships). The explanation lies in a symmetry contribution to the entropy of **2**.<sup>47</sup> For every substance such a contribution is negative, of magnitude  $R \ln \sigma$ , where  $\sigma$  is the symmetry number.<sup>55</sup> Inasmuch as  $\sigma$  is 6 for **2** but 1 for **1**, the former suffers an entropic penalty from which the latter is exempt, and this serves approximately to offset enthalpic factors which favor **2**.

The equilibrium ratio of **2/1** is somewhat dependent on solvent, being 1.6 in 50% ammonia-50% diethyl ether ( $\mu$  1.5 and 1.2 D, respectively), 1.0 in dimethylformamide ( $\mu$  3.8 D), and 0.5 in hexamethylphosphorotriamide ( $\mu$  5.4 D). Inasmuch as **1** has a dipole moment whereas **2** does not, owing to its symmetry, the trend toward a greater proportion of **1** in solvents of higher dipole moment is plausibly attributed to dipole-dipole attractions between **1** and solvent molecules.

In liquid ammonia solvent, isomer proportions at

equilibrium may also depend on solubilities.<sup>56</sup> **2** is much less soluble than **1** in ammonia, and one can take advantage of this to effect nearly quantitative isomerization of **1** to **2** (by running the reaction at high reactant concentration). Such conditions probably prevailed in the initial instance of this isomerization, in which the **2** obtained was reported to be free of **1**.<sup>38</sup> However, under other conditions isomerizations with potassium anilide in ammonia "shut themselves off" before equilibrium is attained, owing to a special kinetic factor.<sup>56</sup>

### Concluding Remarks

The unusual reactions I have described may be regarded as an expression of certain fundamental characteristics of aryl halides or of reactive intermediates derived therefrom. The special accessibility of aryl anions when there is an ortho halogen substituent and the proclivity of certain oligohalobenzenes to yield a positive halogen moiety to an attacking carbanion underlie both the base-catalyzed halogen dance and dehalogenation by the action of  $(\text{CH}_3)_3\text{COK}$  in  $(\text{CH}_3)_2\text{COH}-(\text{CH}_3)_2\text{SO}$ . The capability of aryl halides to accept electrons from suitable donors and the tendency of the resulting radical anions to eject halide ions forming aryl radicals are prominent features both of radical-induced deiodination in alkaline methanol and of "nucleophilic" substitution by the  $\text{SRN1}$  mechanism.

These unusual reactions have pragmatic significance. All of them occur under conditions similar to those commonly used to effect nucleophilic substitution by the  $\text{SNAr}$  and/or the aryne mechanism. Clearly, side reactions of one or more of these unusual types may attend or even eclipse the intended substitution. Thus an understanding of these less common reactions will enable the synthetic chemist to comprehend or to avoid complications to the reactions he employs. Moreover,  $\text{SRN1}$  reactions have great potentialities in synthesis.<sup>57</sup>

*In writing this Account, I have with one exception omitted names of the scientists responsible for discoveries, in order to allow undiverted attention to the chemistry described. The footnotes, however, reveal the names of my coworkers who really did the work. I am deeply grateful to them, not only for collaboration in the experiments but also for critical discussions and many fruitful ideas. I am also grateful to the National Science Foundation for major support of research in this area, and to the Army Research Office (Durham) and the American Chemical Society Petroleum Research Fund for support of certain aspects.*

(53) J. F. Bunnett and M. Mach, unpublished observations.

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(55) G. N. Lewis, M. Randall, K. S. Pitzer, and L. Brewer, "Thermodynamics," 2nd ed, McGraw-Hill, New York, N. Y., 1961, p 428.

(56) J. F. Bunnett and I. N. Feit, *J. Amer. Chem. Soc.*, **93**, 1201 (1971).

(57) R. A. Rossi and J. F. Bunnett, *ibid.*, **94**, 683 (1972).