Investigation of the Mechanism of Reductive Dehalogenation of Haloanisoles under Aryne-Forming Conditions[1a]

Edward R. Biehl,* Susan Lapis,[1b] and Perry C. Reeves

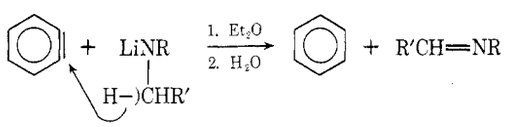
Department of Chemistry, Southern Methodist University, Dallas, Texas 75275

Received January 15, 1974

Separation of the reductive dehalogenation mechanism proceeding *via* aryne (mechanism A) from direct halogen displacement mechanisms (mechanisms B and C) has been achieved. In the presence of large excesses of di-*n*-propylamine as compared with lithium di-*n*-propylamide and haloanisole, aryne reduction is essentially eliminated. With the exception of *o*- and *p*-iodoanisole, haloanisole appears to undergo nonaryne reduction *via* mechanism B, hydride attack on ring halogen. Mechanism C, amide ion nucleophilic attack on ring halogen, most likely operates in the reduction of *o*- and *p*-iodoanisole. An explanation in terms of the influence of the methoxy group on (a) the relative benzenoid hydrogen atom acidities and (b) the relative stabilities of possible carbanion intermediates is presented.

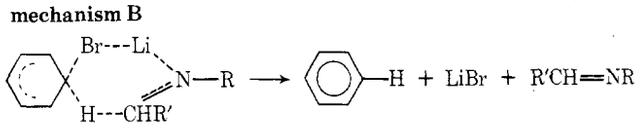
Three mechanisms have been proposed for the reduction of haloaromatic compounds under aryne-forming conditions. Mechanism A, introduced by Wittig,[2] postulates the reduction of aryne *via* a hydride transfer from the α-carbon atom of the appropriate lithium dialkylamide. In support of this mechanism, aryne intermediates have been trapped by furan,[3] and reduction does not occur in the presence of bases lacking α-hydrogen atoms, such as lithium diphenylamide.[4]

mechanism A



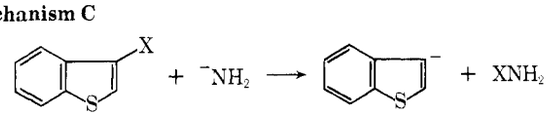
Benkeser and DeBoer[4] have proposed a direct displacement of aromatic halogen by a similar hydride transfer (mechanism B) on the basis that certain haloaromatic compounds containing no hydrogen atom ortho to halogen are reduced under aryne-forming conditions.[5]

mechanism B



Recently, Reinecke[6] and deBie[7] have suggested a third mechanism (mechanism C) to account for the reduction of

mechanism C



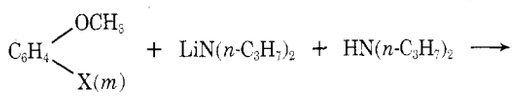
certain halothianaphthenes with metal amides. In this mechanism, halothianaphthenes are reduced by direct nucleophilic attack of amide onto ring halogen with subsequent formation of haloamine and thianaphthene anion. In support of this mechanism, 1,1′-bipiperidine—the expected product from the reaction of *N*-bromopiperidine and metal piperidide—can be isolated from the reaction of halothiaphenes with metal piperidide and piperidine.[6]

Wittig[3] has shown, by product analysis, that the mechanism of reduction of *p*-iodo- and *p*-fluorotoluene is dependent upon the halogen atom. On the basis of the relative polarizability and electronegativity of these two halogen atoms, *p*-fluorotoluene appears to be reduced *via* the corresponding 4-toluyne (mechanism A). However, the *p*-iodo isomer is reduced *via* direct displacement of iodine (mechanism B and/or C). We[8] have recently established a method for determining the extent of reduction occurring *via* the aryne and the direct displacement pathways by comparing the anisole–*m*-(*N*,*N*-di-*n*-propyl)anisidine product distribution from the reaction of *o*-haloanisole with lithium di-*n*-propylamide in varying amounts of di-*n*-propylamine. As the amount of amine was increased relative to haloanisole and dialkylamide, less of the 3-methoxybenzyne was converted to anisole since free amine does not reduce aryne.[9] At very large excess of amine, nearly all aryne formed dialkylanisidine instead of anisole. Consequently, at high amine/amide concentrations, reduction occurred chiefly by the direct displacement mechanism (B and/or C). The extent of reduction varied as the haloanisole was varied along the series I (76%) > F (9%) ~ Br (10%) > Cl (5%).

This paper reports the extension of this method to the reaction of *m*- and *p*-haloanisole in order to obtain more information on the role of the halogen atom. In addition, the influence of the position of the nonhalogen substituents on the mechanism of reduction under these reaction conditions will be studied.

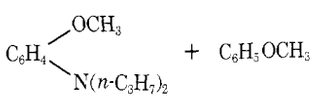
Results

Table I lists the product distribution as % anisole (**5**)/% *N*,*N*-di-*n*-propyl-*m*-anisidine (**4**) from the reaction of *m*-haloanisole and lithium di-*n*-propylamide (**2**) with varying molar excesses of di-*n*-propylamine (**3**). Similarly, Table II



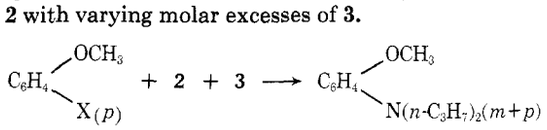
1 2 3

X = F, Cl, Br, I



4 5

lists the product distribution as % **5**/*N*,*N*-di-*n*-propyl-*m*- and -*p*-anisidines (**7**) from the reaction of *p*-haloanisole (**6**) and **2** with varying molar excesses of **3**.



6 7

X = F, Cl, Br, I

A high-boiling, acid-soluble residue was formed in those reactions conducted in the absence of amine **3**. This residue has not been fully identified but appears to be a mixture of higher phenylated aryne products as indicated by infrared, nmr, and mass spectra. The amount of residue, however, rapidly decreases with increasing amounts of **3**, no appre-

Table I
Product Distribution as % Anisole (5)/% *N,N*-Di-*n*-propyl-*m*-anisidine (4) from *m*-Haloanisoles

1:2:3 X =	Ratio % 5/% 4 F	Cl	Br	I
1:2:0	18/69	14/72	17/72	19/69
1:2:1	13/80	13/85	10/83	13/84
1:2:2	12/86	10/89	10/86	12/87
1:2:4	8/89	6/92	7/91	8.2/90
1:2:6	6/90	3.5/95	5.0/92	6.4/90
1:2:8	6/90	3.2/96	4.6/92	6.5/89

Table II
Product Distributions as % Anisole (5)/% Di-*n*-propylanisidine (7) from *p*-Haloanisoles

6:2:3 X =	Ratio % 5/% 7 F	Cl	Br	I
1:2:0	20/52	25/53	26/46	45/32
1:2:1	16/69	17/70	19/69	37/48
1:2:2	13/73	15/76	15/78	35/55
1:2:4	10/80	12/84	10/83	29/65
1:2:6	7.4/83	11/88	10/85	29/65
1:2:8	7.4/83	10/87		

Table III
Partitioning of Methoxyaryne[a]

1 or 6:2:3	*m*-F	*m*-Cl	*m*-Br	*m*-I	*p*-F	*p*-Cl	*p*-Br	*p*-I
1:2:2	0.07	0.08	0.06	0.06	0.08	0.07	0.06	0.11
1:2:4	0.02	0.03	0.03	0.02	0.03	0.02	0	0

[a] Results expressed as ratio per cent anisole *via* mechanism A *vs.* per cent **4** or **7**. Per cent anisole calculated by subtracting residual yield of amine from total yield of anisole for a particular reaction listed in Tables I and II.

ciable residue being observed for reactions employing 2 or more molar equiv of **3**.

In general, reductive dehalogenation of haloanisoles (**1** or **6**) to anisole **5** decreased, and their conversion to anisidines (**4** or **7**), *via* the corresponding methoxybenzyne intermediates, increased as the quantity of amine was increased. The extent of reductive dehalogenation of *m*-haloanisoles appears to be independent of the halogen atom since the four meta isomers yielded similar **5/4** product distributions for a given quantity of **3**. For example, **5/4** ratios of 12/86 (F), 10/89 (Cl), 10/86 (Br), and 12/87 (I) were obtained using a 2 molar excess of **3**. A similar relationship appears to hold for the *p*-bromo, -chloro, and -fluoro isomers of **6**. However, the **5/4** product ratios listed in Table II indicate that *p*-iodoanisole was reduced to a larger extent than the other *p*-haloanisoles. In addition, comparison of **5/4** product ratios for a particular halogen atom and a given molar excess of **3** indicates that reduction occurred to a greater extent with *p*- than with *m*-haloanisoles. For example, *p*-iodoanisole was converted to anisole (**5**) in 35% yield whereas the corresponding meta isomer afforded **5** in 12% yield in the presence of a 2 *M* excess of **3**.

The anisole/anisidine yield ratio was observed to reach a limiting value in all systems, indicating that reduction *via* aryne (mechanism A) was essentially eliminated in the presence of large (>4) molar excesses of **3**. Further, the amount of reductive dehalogenation *via* aryne should be approximated by subtracting the limiting yield of anisole *via* mechanism B and/or C from the yield of anisole for a particular reaction. Accordingly, the ratio of yield of anisole *via* aryne to yield of dialkylanisidine for a given molar ratio of **2** and **3** should be an indication of the partitioning of methoxyaryne, and should be independent of the halogen atom in the starting material. As shown in Table III, this appears to be approximately the case in all reactions studied.

Discussion

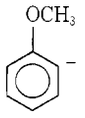
The relative reactivity of haloanisoles toward aryne formation and direct reduction of the carbon–halogen bond is influenced by the position of the methoxy group. Deuterium exchange experiments have shown that the 2-hydrogen atom in anisole is much more acidic than the 3- and 4-hydrogen atoms.[10] Consequently, the enhanced acidity of the 2-hydrogen atom in *m*-haloanisoles results in aryne formation with subsequent conversion to anisole or anisidines predominating over direct reduction of the carbon–halogen bond. The strong influence of the methoxy group is further demonstrated in the directing effect, since nucleophilic attack by **3** occurred solely at the meta position of 3-methoxybenzyne.

The hydrogen atom ortho to the halogen is farther from the electron-withdrawing methoxy group in *p*-haloanisoles than in the corresponding meta isomers, and is thus less acidic. Consequently, less aryne is formed and more nonaryne reduction occurs in the para system than in the meta system. The directing effect of the methoxy group is also weakened by distance in 4-methoxybenzyne as compared to 3-methoxybenzyne, and this results in the production of a mixture of meta and para anisidines.

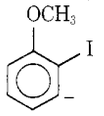
A partial assessment of the relative amounts of reduction *via* mechanisms B and C in the *o*-, *m*-, and *p*-haloanisole series can be made by considering the variation in the anisole yield as a function of the halogen atom at limiting conditions in which only nonaryne reduction occurs. Mechanism C, nucleophilic attack on halogen, suggests that anisole formation would be greatest for the iodo isomer. Also its rate of formation would decrease as the halogen is varied along the series I, Br, Cl, F, on the basis of the relative polarizabilities of the halogen atoms. Similar considerations are not possible for mechanism B since the relative extents of (a) carbon–halogen bond breaking, (b) carbon–hydrogen bond making, and (c) lithium–halogen bond making in the corresponding transition states are not known. Since (a) would be expected to operate in the opposite direction of (b) and (c), a small change in anisole yield as the halogen atom is varied along the series, F, Cl, Br and I would not be unreasonable. Accordingly, the small variation observed in this study for meta and para isomers of fluoro-, chloro-, and bromoanisoles and the corresponding ortho isomers in a previously reported investigation[8] are in accordance with mechanism B.

In addition, whereas *m*-iodoanisole is reduced to approximately the same extent as the other *m*-haloanisoles, *o*-iodo- and, to a lesser extent, *p*-iodo- are considerably more reduced than the other *o*- and *p*-haloanisoles. This indicates that *m*-iodoanisole is probably undergoing reduction *via* mechanism B; however, the ortho and possibly para iodo isomers are being reduced in part by mechanism C.

The much larger yield of anisole (76%) as compared to aryne product **4** (14%), observed previously for *o*-iodoanisole,[8] probably reflects the greater tendency by the dialkylamide ion (**2**) to attack the iodine atom (mechanism C) rather than the ortho hydrogen atom of *o*-iodoanisole. Methoxyphenyl carbanion (**8**), produced in the former case, would be stabilized by the methoxy group to a larger extent than iodoanisole anion (**9**) formed in the latter case. In con-

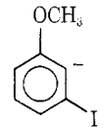


8

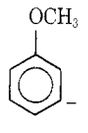


9

trast, amide ion **3** would be expected to attack the ortho hydrogen atom to a greater extent than the iodine atom in *m*-anisole since the former yields a more stable iodoanisole anion, **10**, than the carbanion, **11**, produced by the latter.

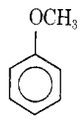


10



11

The decreased acidity of the hydrogen atom in *p*-iodoanisole as compared to that of *m*-iodoanisole apparently allows amide ion attack on iodine to compete with aryne formation. However, that the yield of anisole is less for *p*-iodoanisole (28%) than for *o*-iodoanisole (76%) is a result of the lower stability of carbanion **12** as compared to carbanion **8**.



12

Experimental Section

Glpc analyses were performed on a Beckman GC-5 chromatograph using nitrogen as carrier gas at a flow rate of 60 ml/min, inlet temperature of 150°, detection temperature of 200°, and column temperature of 100°. A 10 ft × 0.125 in. i.d. column packed with 10% SE-30 (silicone rubber) on Chromosorb W, acid-washed, 80–100 mesh, was used to analyze anisole. Nmr spectra were obtained using a Perkin-Elmer R-12B nmr spectrophotometer.

Materials. Di-*n*-propylamine was obtained from Eastman Kodak Co. and was dried, distilled, and then stored over anhydrous potassium carbonate. *n*-Butyllithium, 1.9–2.2 *M* in hexane, was obtained from Alfa Inorganics Inc., and was manipulated in a nitrogen-atmosphere glove bag. *m*- and *p*-fluoroanisoles were procured from Pierce Chemical Co.

m- and *p*-iodoanisoles,[11] *m*-bromoanisole,[12] and *m*- and *p*-chloroanisoles[13] were synthesized according to literature procedures.

General Procedure. The reactions were carried out using oven-dried glassware and under a nitrogen atmosphere. In a typical reaction, 0.05 mol of *n*-butyllithium was added dropwise to a stirred solution containing 25 ml of anhydrous ether and the appropriate amount of di-*n*-propylamine, and the solution was refluxed for 10 min to ensure complete amide formation. After 0.025 mol of haloanisole followed by 25 ml of anhydrous ether was added, the solution was refluxed (overnight) for at least 18 hr. The reaction was then quenched by the dropwise addition of water until the brightly colored solution changed to cloudy white. The ether solution was washed with water, extracted three times with 10% hydrochloric acid (25 ml each) to remove the basic aryne products, dried ($CaCl_2$), and concentrated by careful evaporation of ether to yield anisole. Anisole was quantitatively analyzed by vpc using phenetole as internal standard. The acidic aqueous extracts were combined, made basic with 10% sodium hydroxide, and extracted with three 25-ml portions of ether. After the basic ether extracts were combined, dried ($MgSO_4$), and concentrated, an oily residue was obtained which yielded the appropriate aryne amine product(s) upon vacuum distillation. *m*-haloanisoles yielded *N,N*-di-*n*-propyl-*m*-anisidine in these reactions, whereas the para isomeric anisoles gave a mixture of the corresponding meta and para isomeric anisidines. Infrared and nmr spectra were consistent with proposed structures. Nmr spectrum of the meta anisidine showed a singlet at τ 6.35 corresponding to the methoxy hydrogen atoms, whereas in the spectrum of the meta–para mixture two singlet peaks were observed in this region.

A higher boiling by-product, which was present in reactions with no excess amine solvent as a residue after vacuum distillation of the normal anisidine product, was pooled from a number of reactions and vacuum distilled, bp 153–154 (0.3 mm). The nmr spectrum was not clearly resolved, indicating a mixture, but showed aromatic hydrogens (τ 2.5–3.7), methoxy group (τ 6.3–6.4), and aliphatic hydrogens (τ 6.6–9.3). Mass spectrographic analysis was difficult to interpret due to polymerization. Infrared spectrum contained no N–H bands.

References and Notes

(1) (a) Sponsored in part by Grant N-118 of the Robert A. Welch Foundation, Houston, Texas; (b) Robert A. Welch Predoctoral Fellow.
(2) G. Wittig, H. J. Schmidt, and R. Renner, *Chem. Ber.*, **95**, 2377 (1962).
(3) G. Wittig, C. N. Rentzea, and M. Rentzea, *Justus Liebigs Ann. Chem.*, **744**, 8 (1971).
(4) R. A. Benkeser and C. E. DeBoer, *J. Org. Chem.*, **21**, 281 (1956).
(5) R. A. Benkeser and C. E. DeBoer, *J. Org. Chem.*, **21**, 365 (1956); J. F. Bunnett and T. K. Brotherton, *ibid.*, **22**, 832 (1957); J. F. Bunnett and T. K. Brotherton, *J. Amer. Chem. Soc.*, **78**, 6265 (1956).
(6) M. G. Reinecke and T. A. Hollingworth, *J. Org. Chem.*, **37**, 4257 (1972).
(7) D. A. deBie, H. C. van der Plas, G. Geurtsen and K. Nijdam, *Recl. Trav. Chim. Pays-Bas*, **92**, 245 (1973).
(8) E. R. Biehl, S. M. Smith, S. Lapis, and P. C. Reeves, *J. Org. Chem.*, **37**, 3529 (1972).
(9) E. R. Biehl, S. M. Sith, R. Patrizi, and P. C. Reeves, *J. Org. Chem.*, **37**, 137 (1972).
(10) G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Amer. Chem. Soc.*, **77**, 4540 (1955).
(11) F. B. Dains and F. Eberly, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 355.
(12) L. A. Bigelow, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 135.
(13) C. S. Marcel and S. M. McElvain, ref 12, p 170.

Solvolysis of Arylvinyl Bromides and Tosylates

Keith Yates* and Jean-Jacques Périé

Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Received January 11, 1974

The bromides and tosylates of the 1-(4-methylphenyl)vinyl, 1-(2,4-dimethylphenyl)vinyl, and 1-(2,4,6-trimethylphenyl)vinyl systems have been prepared and their rates of solvolysis measured in alcohol–water mixtures and in acetic acid in the temperature range 35–88°. Rate enhancements of up to 4×10^5 over the parent 1-phenylvinyl systems have been obtained, with ortho-methyl substitution leading to significant steric acceleration of these normally slow solvolytic reactions. The kinetics, medium effects, and leaving-group effects are all in accord with a simple S$_N$1 type solvolysis mechanism leading to vinyl cation intermediates. However, the Winstein–Grunwald *m* values, Schleyer *Q* values, and insensitivity to solvent nucleophilicity all point to a weak nucleophilic assistance component in these vinyl solvolyses. Solvent effects in these solvolytic reactions are compared with those in electrophilic additions leading to analogous cationic intermediates.

In connection with some previous work of one of us,[1] concerning the relative ease of formation of carbonium ions and vinyl cations, as well as solvation effects on these species in electrophilic additions, we have been interested in investigating the rates and solvent effects of related solvolytic reactions leading to similar vinyl cationic intermediates. A second objective was to obtain more quantitative information about the reactivity of vinylic substrates,