Aromatic Denitration with Borohydride. Nucleophilic Displacement of Nitrite by Hydride

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Treatment of certain polysubstituted aromatic nitro compounds with sodium borohydride in dimethyl sulfoxide or alcohol solvent results in nucleophilic substitution of the nitro group by hydride. The reaction requires the presence of bulky substituents adjacent to the nitro group to prevent conjugation with the ring and electron-withdrawing groups to activate the ring toward attack.

The reaction of nitroaromatic compounds with sodium borohydride has been observed to proceed along a variety of paths depending upon the reaction conditions and the type of ring substitution. For instance, in polar aprotic solvents[2a] or ethanol,[2b] most unencumbered nitroaromatics are reduced to azoxybenzenes, azobenzenes, or anilines, depending on the nature of the other groups present on the ring. On the other hand, Bell and coworkers have observed dehalogenation of *o*- or *p*- iodo- or *o*-bromonitrobenzenes in aqueous dimethyl sulfoxide (DMSO) under mild conditions.[2c] With highly electron-deficient nitro compounds, ring attack occurs, resulting in eventual reduction of the nucleus to cyclohexene derivatives by borohydride[3] or the formation of stable hydride–Meisenheimer type adducts when more complex borohydrides are employed.[4]

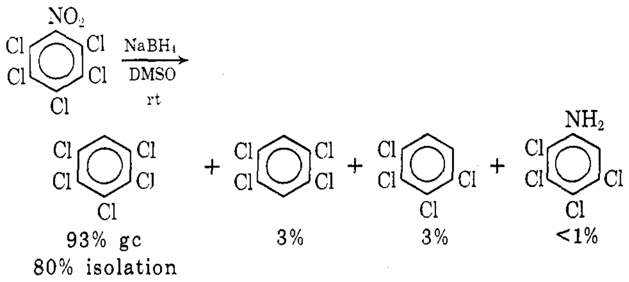
This article describes a further, apparently general, possibility for the reaction of nitroaromatics with borohydride in which the nitro group is displaced by hydride when certain steric and electronic requirements are met.

Results and Discussion

The scope of the denitration reaction is illustrated by the behavior of the substrates contained in Table I. When treated with sodium borohydride in DMSO, pentachloronitrobenzene (Scheme I) and 2,3,5,6-tetrachloronitrobenzene were rapidly denitrated in high yield to pentachlorobenzene and 1,2,4,5-tetrachlorobenzene, respectively (entries 1a and 2a). Chemical tests indicated that nitrite was formed in the reaction.[5]

In the presence of protic solvents, the reaction was somewhat slower than in DMSO alone (entries 1a *vs.* 1e and 1f). Other polychloronitrobenzenes reacted more slowly to give lower yields of denitration products and considerable amounts of side products resulting from reduction of the nitro group and/or removal of chlorines ortho or para to the nitro group. Ortho and meta chlorine substituents appeared to facilitate the reaction (entries 1a *vs.* 6a and 1a *vs.* 3) with para chlorine having less effect (entries 1a *vs.* 2 and 4b *vs.* 5). Thus, the denitration reaction has both steric and electronic requirements. First, the aromatic nucleus evidently must be activated by a suitable amount of electron deficiency induced by withdrawing substituents. Furthermore, substantial steric hindrance apparently must be provided by flanking bulky groups (entries 2a *vs.* 6b). Substrates in which the steric interference was present, but in which the aromatic ring was not sufficiently electron deficient, showed greatly reduced reactivity (entries 11 and 12). Without a significant degree of blockage, reduction of the nitro group competed favorably[2] (entries 8a and 8b).

SCHEME I



93% gc
80% isolation
3%
3%
<1%

To account for the above observations, three types of mechanisms were envisioned as potentially responsible for the occurrence of denitration. The reaction could conceivably involve the formation of a substituted nitrobenzene radical anion followed by fragmentation to afford nitrite anion and a substituted phenyl radical. However, the available evidence concerning radical anions of halonitrobenzenes suggests alternate behavior; for example, 2,3,5,6-tetrachloronitrobenzene radical anion fragments with loss of a chlorine from an ortho position as chloride anion.[6] While this type of mechanism provides one account for the small per cent of dechlorination product obtained from the denitration of pentachloronitrobenzene, it appears not to be involved in the major path of the reaction. A second mechanistic possibility might involve a nucleophilic attack of borohydride on an oxygen atom of the nitro group with concomitant displacement of a substituted phenyl carbanion. Such a unique explanation seemed attractive since the denitration reaction with borohydride anion proceeded more readily and under milder conditions than reactions of other nucleophiles with these same polychloronitrobenzenes (*vide infra*). However, this possibility was ruled out by conducting the reduction in

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(1) National Science Foundation Undergraduate Research Participant 1971.

(2) (a) R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *J. Org. Chem.*, **36**, 803 (1971); G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1840 (1968). (b) H. J. Shine and E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962). In addition, sodium borohydride in combination with palladium on carbon gives only the corresponding aniline from aromatic nitro compounds; see T. Neilson, H. Wood, and A. Wylie, *J. Chem. Soc.*, 371 (1962). (c) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969), and private communication with H. M. Bell.

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TABLE I

DENITRATION OF AROMATIC NITRO COMPOUNDS WITH SODIUM BOROHYDRIDE

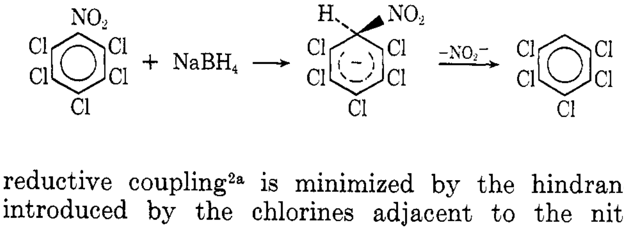
Registry no.	Entry	Substrate: Ar-1-NO_2–	Solvent	$ArNO_2$ concn, *M*	$NaBH_4$ concn, *M*	Temp, °C	Time, hr	% Yields[a] de-NO_2 product	Starting material	Other
82-68-8	1a	2,3,4,5,6-Cl_5	DMSO	0.10	0.20	Amb[e]	0.5	93	0	3,[b] 3,[c] 1[d]
	1b	2,3,4,5,6-Cl_5	DMSO	0.10	0.15	Amb[e]	0.5	93	0	
	1c	2,3,4,5,6-Cl_5	DMSO	0.10	0.10	Amb[e]	0.5	71	14	
	1d	2,3,4,5,6-Cl_5	DMSO	0.30	0.45	Amb[e]	0.5	80[f]		
	1e	2,3,4,5,6-Cl_5	DMSO–H_2O[h]	0.10	0.20	Amb[e]	20	56[f]		
	1f	2,3,4,5,6-Cl_5	2-Propanol	0.067	0.133	75	1.0	40[g]	23[g]	
117-18-0	2a	2,3,5,6-Cl_4	DMSO	0.10	0.20	Amb[e]	2.0	95	0	
	2b	2,3,5,6-Cl_4	DMSO	0.30	0.45	Amb[e]	2.0	89[f]		
3714-62-3	3	2,3,4,6-Cl_4	DMSO	0.12	0.25	Amb	18	60	0	8,[i] 3[j]
18708-70-8	4a	2,4,6-Cl_3	DMSO	0.07	0.13	Amb	20	2	65	
	4b	2,4,6-Cl_3	DMSO	0.10	0.20	65	44	20	0	8[k]
	4c	2,4,6-Cl_3	DMSO	0.5	1.0	[l]	1.0	27[g]	0	13[g,k]
601-88-7	5	2,6-Cl_2	DMSO	0.08	0.16	60	92	28	13	
879-39-0	6a	2,3,4,5-Cl_4	DMSO	0.05	0.10	19[m]	4.0	33	0	23[d]
	6b	2,3,4,5-Cl_4	DMSO	0.05	0.10	Amb[e]	4.0	56	0	8[d]
	6c	2,3,4,5-Cl_4	DMSO	0.15	0.30	Amb[e]	0.5	45	0	8[d]
89-69-0	7	2,4,5-Cl_3	DMSO	0.125	0.25	Amb[e]	3.0	14	0	19[j]
618-62-2	8a	3,5-Cl_2	DMSO	0.10	0.20	Amb[e]	1.75	0	0	[o]
	8b	3,5-Cl_2	95% ethanol	0.167	0.33	Amb[e]	0.25	0		72[f,p]
40587-63-1	9	2,6-Cl_2-4-CO_2Et	DMSO	0.10	0.20	Amb	1.0	49	0	
40587-64-2	10	2,6-Br_2-4-CO_2Et	DMSO	0.10	0.20	Amb	1.0	23	1	
108-67-8	11	2,4,6-$(CH_3)_3$	DMSO	0.24	0.9[q]	85	190	0	~80	~15
3463-36-3	12	2,3,5,6-$(CH_3)_4$-4-NO_2	DMSO	0.10	0.2	75	92	2[n]	98	

[a] All products were identified by coinjection on gc and most by comparison of ir and mass spectra with those of authentic materials. The per cent yields of products were determined by glpc using internal standards and corrected for detector response. [b] 1,2,4,5-Tetrachlorobenzene. [c] 1,2,3,4-Tetrachlorobenzene. [d] 2,3,4,5-Tetrachloroaniline. [e] Reaction very exothermic; cooling was applied to prevent overflow due to rapid gas evolution. [f] Isolated yield. [g] Product mix isolated, weighed, and analyzed by gc methods. [h] 4:1 v/v DMSO–H_2O. [i] 1,2,4-Trichlorobenzene. [j] 2,4,5-Trichloroaniline. [k] 2,4-Dichloroaniline. [l] After 20-min induction period at 50–60° under application of heat, reaction became extremely exothermic, reaching 135° in 5 min. Water heated in same apparatus at same settings reached only 53° in 1 hr. [m] Temperature maintained by cooling. [n] Thought to be mononitro compound. [o] Only products observed were reductive coupling products. [p] 3,3′,5,5′-Tetrachloroazoxybenzene. [q] $^2/_3$ added initially, $^1/_3$ added after 95 hr.

D_2O–DMSO-d_6. The low degree of deuterium incorporation (*ca.* 15%) in the resulting pentachlorobenzene demonstrated that a significant amount of pentachlorophenyl carbanion was not produced. The small amount of incorporation observed most probably arose *via* base-catalyzed exchange between D_2O and pentachlorobenzene, which was found to occur in the presence of sodium borohydride or sodium deuteroxide in DMSO–D_2O. With sodium borohydride in DMSO-d_6 as solvent, little deuteration occurred during denitration.

The third, and most attractive, mechanistic possibility involves the addition–elimination pathway for aromatic nucleophilic substitution as illustrated for pentachloronitrobenzene in Scheme II. Ostensibly, reductive coupling[2a] is minimized by the hindrance introduced by the chlorines adjacent to the nitro group. Borohydride anion, acting as a source of nucleophilic hydride, attacks the most electropositive nitro-attached ring carbon; attacks of this type are not usually hindered by bulky ortho substituents.[7] The formation of the tetrahedral carbon should relieve steric crowding and inductive stabilization of the intermediate anion would be provided by the five chlorine atoms; subsequent loss of nitrite ion furnishes pentachlorobenzene. Furthermore, any addition of hydride to the positions ortho or para to the nitro substituent would not be highly favored, since this group is turned out of planarity with the ring and thus the developing anion is not stabilized by conjugation. The meager amounts of dechlorinated by-products produced could be explained by such attacks, but alternate explanations are equally plausible. As previously mentioned, loss of ortho chlorine may occur from the radical anion to furnish 2,3,4,5-tetrachloronitrobenzene,[6] which can undergo denitration or reduction to 2,3,4,5-tetrachloroaniline (Table I, entry 6). The small amount of 1,2,4,5-tetrachlorobenzene formed may occur from a dechlorination–denitration sequence or by reduction of pentachlorobenzene. This latter compound does slowly furnish 1,2,4,5-tetrachlorobenzene upon treatment with sodium borohydride.

SCHEME II



Support for the addition–elimination mechanism for denitration is amply demonstrated by the reactions of other nucleophiles with polychloronitrobenzenes. Nucleophiles which afford products by replacement of the nitro group include azide,[8] fluoride,[9a,b] chloride,[9c]

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hydroxide,[10] and methoxide[11] ions, ammonia,[12a,b] and amines.[12b] Indeed the displacement of nitro from even mildly deactivated rings occurs with surprising ease and is documented for a variety of nucleophiles,[12c,13-15] although nucleophilic replacement by hydrogen is relatively rare,[16] apparently because other reactions with hydride reagents, such as reduction, usually, compete effectively.

Experimental Section

Analyses.—Analyses by gas chromatography were performed on a Hewlett-Packard 5250B gas chromatograph (T.C. detector) employing a 6–10 ft × 0.125 in. column of 10% OV-1 on Chromosorb W. Yields were determined using internal standards (1,3,5-trichlorobenzene or *p*-dichlorobenzene) with predetermined detector response factors. The standards were inert to the conditions. All products were identified by glc coinjection techniques and most by comparison of ir and mass spectra with those of authentic samples. Mass spectra were obtained from a Hitachi Perkin-Elmer RMU-6 coupled to a gas chromatograph. Microanalyses were performed by A. Bernhardt, Microanalytical Laboratory, West Germany. Melting points are uncorrected.

Materials.—All organic materials were obtained commercially (except for entries 9 and 10 in Table I) and were used as obtained or recrystallized if not of satisfactory purity. Solvents were commercial reagent grade and used as received. In the deuteration experiments, DMSO-d_6 was 99.5% D grade and D_2O was 99.8% grade.

Ethyl 3,5-dibromo-4-nitrobenzoate was prepared by a method similar to that described for 3,5-dibromo-4-nitrobenzonitrile[17] except that ethyl *p*-aminobenzoate was substituted for *p*-aminobenzonitrile. The light green crystals obtained from ethanol had mp 76.5–77.5°.

Anal. Calcd for $C_9H_7Br_2NO_4$: C, 30.98; H, 2.02. Found: C, 31.23; H, 2.24.

Ethyl 3,5-dichloro-4-nitrobenzoate was prepared by a similar method to that preceding. The colorless crystals from 95% ethanol had mp 77.5–78.5°.

Anal. Calcd for $C_9H_7Cl_2NO_4$: C, 41.57; H, 2.71. Found: C, 41.64; H, 3.12.

General Denitration Procedure.—A solution of the nitroaromatic in the appropriate solvent was prepared in a three-neck flask maintained if necessary at the desired temperature (Table I) and equipped with a magnetic stirrer, condenser, and drying tube. The appropriate amount of sodium borohydride (Table I) was then added directly or as a slurry in the same solvent. Reaction mixtures were worked up by adding about five volumes of water and extracting with ether, chloroform, or carbon tetrachloride. Extracts were dried over anhydrous magnesium sulfate and used for glc analysis and/or concentrated for isolation of products. Progress of the reactions were followed in several cases by removing and working up small aliquots of the reaction mixture for glc analysis as described above. Specific denitration procedures are illustrated below.

Denitration of 2,3,5,6-Tetrachloronitrobenzene. Product Isolation.—To a stirred solution of 2,3,5,6-tetrachloronitrobenzene (7.83 g, 0.03 mol) in 90 ml of DMSO at room temperature was added a mixture of sodium borohydride (1.70 g, 0.045 mol) in 10 ml of DMSO. The reaction mixture was kept at 25–40° by occasional cooling with an ice bath. After 2.5 hr, the mixture was poured into 700 ml of water and extracted with two 50-ml portions of chloroform. The extract was washed with water, dried, and evaporated in a stream of air. The solid residue was recrystallized from 9:1 ethanol–dioxane, giving 5.79 g (89%) of off-white needles, mp 137–139°, mmp with 1,2,4,5-tetrachlorobenzene 137–139°. The ir and mass spectra of the two materials were superimposable.

Denitration of 2,3,5,6-Tetrachloronitrobenzene. Gc Analysis.—Sodium borohydride (0.38 g, 0.01 mol) was added to 2,3,5,6-tetrachloronitrobenzene (1.305 g, 0.005 mol) in 50 ml of a stirred DMSO solution containing 1,3,5-trichlorobenzene (0.907 g, 0.005 mol) as internal standard. At intervals a 1.5-ml aliquot was removed, diluted with 7.5 ml of water, and extracted with 0.5 ml of chloroform, and the extract dried and analyzed by gc. After 2 hr the reaction appeared complete (Table I, entry 2).

Denitration of Pentachloronitrobenzene in Deuterium-Labeled Solvent Mixture.—Sodium borohydride (0.019 g, 0.5 mmol, Ventron Analytical Grade) was added to a stirred solution of pentachloronitrobenzene (0.074 g, 0.25 mmol) in 2 ml of DMSO-d_6 and 0.5 ml of D_2O contained in the usual apparatus and isolated from the atmosphere by a bubble trap. After 1 hr at room temperature, 7.5 ml of D_2O was added and the mixture was extracted with 0.5 ml of carbon tetrachloride. The mass spectrum of the pentachlorobenzene in the extract indicated 15% deuterium incorporation by comparison of the relative peak heights in the parent peak group (248–258) with those of authentic pentachlorobenzene. When the denitration reaction was conducted only in DMSO-d_6 with sodium borohydride, there was little indication of deuterium incorporation.

Dechlorination of Pentachlorobenzene.—A solution of pentachlorobenzene (0.752 g, 3.0 mmol) and sodium borohydride (0.215 g, 5.7 mmol) in 45 ml of DMSO with 1,3,5-trichlorobenzene (0.544 g, 3.0 mmol) as internal standard was stirred at room temperature for 6 days. Glpc analysis showed a 2.5% yield of 1,2,4,5-tetrachlorobenzene (coinjection) with 97% pentachlorobenzene remaining and no observable 1,2,3,4-tetrachlorobenzene or 1,2,3,5-tetrachlorobenzene (coinjection).

Hydrogen–Deuterium Exchange between Pentachlorobenzene and Deuterium Oxide. A. In the Presence of Sodium Deuteroxide.—Sodium (*ca.* 0.05 g, 2–3 mmol) was dissolved in D_2O (2 ml, 110 mmol), and a solution of pentachlorobenzene (0.250 g, 1.0 mmol) in DMSO (13 ml) was added. The stirred solution was protected from atmospheric H_2O by a mineral oil bubble trap. After 20 hr at room temperature, the mixture was worked up with 12 ml of D_2O and extracted with two 10-ml portions of CCl_4. The extracts were dried ($MgSO_4$) and the CCl_4 was evaporated, giving a white crystalline residue which by mass spectral analysis was pentachlorobenzene with 29% D incorporation.

B. In the Presence of Sodium Borohydride.—Sodium borohydride (0.080 g, 2.1 mmol) dissolved in DMSO (5 ml) was added to a solution of pentachlorobenzene (0.250 g, 1 mmol) in DMSO (8 ml), and D_2O (2 ml) was added. After stirring for 20 hr at room temperature in isolation from the atmosphere, the solution was worked up and analyzed as in A, and showed 52% D incorporation in the pentachlorobenzene.

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Registry No.—Ethyl *p*-aminobenzoate, 94-09-7; sodium borohydride, 16940-66-2; pentachlorobenzene, 608-93-5.

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[15] (a) Nitro is actually often replaced more readily than most other groups, including fluoro (ref 15b) and chloro (ref 9c). (b) J. F. Bunnett, E. W. Garbish, Jr., and K. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957).

[16] (a) Replacement of one or two nitro groups by hydrogen from 1,3,5-trinitro-2,4,6-trichlorobenzene by borohydride has been observed [*cf.* L. A. Kaplan, *J. Amer. Chem. Soc.*, **86**, 740 (1964)] and the absence of chloro displacement was attributed to lack of planarity between the nitro groups and the aromatic ring. (b) A small yield of naphthalene resulted from the reaction of 1-nitronaphthalene with borohydride anion [H. J. Shine and M. Tsai, *J. Org. Chem.*, **23**, 1592 (1958)]. (c) A photoinduced denitration of certain nitro aromatics by borohydride has been observed [W. C. Petersen and R. L. Letsinger, *Tetrahedron Lett.*, 2197 (1971)].

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