(The reaction mixture is 0.375 *M* in lithium aluminum hydride and 0.25 *M* in compound.) After 24 hr, 5.0 mmol of ethylbenzene was added as internal standard. After the destruction of the residual hydride as usual and work-up, gas chromatographic examination of the ethereal layer indicated a 95% yield of chlorobenzene, traces of benzene, and 4% of unreacted *m*-chloroiodobenzene. No iodobenzene was detected.

Registry No.—Lithium aluminum hydride, 16853-85-3; tetrahydrofuran, 109-99-9.

The Reduction of Organic Halogen Compounds by Sodium Borohydride[1]

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Treatment of organic halogen compounds and related derivatives with sodium borohydride in dimethyl sulfoxide or diglyme results in reduction of the carbon–halogen bond; the reactivity in dimethyl sulfoxide is somewhat greater than that in diglyme. The order of reactivity of simple haloalkanes and related derivatives is consistent with a typical S_N2 displacement by borohydride on carbon, but some more complex derivatives exhibit unusual reactivity. Thus, carbon tetrachloride reacts very rapidly in aqueous diglyme or dimethyl sulfoxide to produce chloroform and dichloromethane, whereas chloroform is unreactive under the same conditions. The behavior of *o*-nitroiodobenzene is similar; reduction to nitrobenzene is rapid and quantitative in aqueous solvents. Substitution of deuterium oxide for the water results in almost quantitative incorporation of deuterium in the *ortho* position. In addition to the synthetic utility with respect to organic substrate, the reaction can be used as a convenient method for preparing solutions of diborane.

The reduction of organic halogen compounds and related derivatives with complex metal hydrides is a fairly well-established reaction.[3-8] The stoichiometry for the two most common cases is shown below.

$$\mathrm{RX} + \mathrm{BH_4^-}\ (\text{or } \mathrm{AlH_4^-}) \longrightarrow \mathrm{RH} + \mathrm{X^-} + \mathrm{BH_3}\ (\text{or } \mathrm{AlH_3})$$

Lithium aluminum hydride reductions are ordinarily performed in ether or tetrahydrofuran; evidence indicates that the mechanism involves a typical S_N2 displacement on carbon.[4-6] The stability of sodium borohydride in aqueous solvents permits a greater variety of reaction conditions than in the case of lithium aluminum hydride. Thus, it was observed that secondary and tertiary alkyl derivatives could be reduced by sodium borohydride in aqueous diglyme.[7] This reduction of secondary and tertiary derivatives under conditions leading to S_N1 behavior has been studied in some detail; however, the reduction of primary derivatives under the usual S_N2 conditions has received only limited attention.[9-11] We therefore undertook a study of this reaction; in addition to the more common primary and secondary alkyl derivatives, we have investigated in a preliminary manner the borohydride reduction of aromatic halides and polyhaloalkanes.

Results and Discussion

Because of the rate enhancements realized when performing nucleophilic substitution reactions in dimethyl sulfoxide (DMSO),[12] it was of considerable interest to study the behavior of sodium borohydride in this solvent. Sodium borohydride is quite soluble in DMSO, and at room temperature no noticeable reaction between the two is observed. It has been reported that sulfoxides undergo a slow reaction with solutions of diborane;[13] this presented no difficulty in the current investigation, since the fate of the diborane was of no particular interest. Several reductions were also performed in diglyme, and in aqueous solutions of diglyme and DMSO.

Reductions of Simple Monohaloalkanes in DMSO and Diglyme.—In Table I we have summarized the results of the reduction of a number of simple primary and secondary derivatives in DMSO. Excellent yields are realized for primary iodides, bromides, and tosylates, as well as for secondary iodides. Only the more reactive chlorides, such as the benzyl derivatives, can be reduced in good yield under such mild conditions. The relative reactivity, as evidenced by the rate of gas evolution and overall yield of product, is iodide > bromide > tosylate > chloride, and methyl > ethyl > propyl > isopropyl; this is consistent with an S_N2 mechanism. No alkene was found in the analysis of the above reactions. However, this does not rule out a small amount of elimination, followed by rapid hydroboration of the alkene produced.

Table II shows the results of some reductions in anhydrous diglyme. Clearly, the reaction is slower than in DMSO; only the methyl derivatives and primary iodides can be reduced in good yield in a reasonable time at a temperature below 50°.

Reduction of Benzylic Derivatives.—In Table III we have summarized the results of an investigation of the reduction of benzylic halides. In each case, the product is the corresponding toluene derivative; borohydride did not react with any of the *para* substituents under the reaction conditions used. Because of the greater reactivity of the *p*-methoxy and *p*-nitro derivatives, it was felt that the data for 1-hr reaction

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[1] Based in part on the M.S. thesis submitted to Virginia Polytechnic Institute by C. W. V. (1968).

[2] National Science Foundation Undergraduate Research Participant, Summer 1968.

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TABLE I
REDUCTION OF SIMPLE MONOHALOALKANES AND RELATED DERIVATIVES IN DMSO[a]

Compd	Time, hr	Temp, °C	Alkane, %
Methyl iodide	0.2	25	96
Methyl tosylate	0.3	25	90
Dimethyl sulfate	0.2	25	97[b]
Ethyl iodide	1.5	25	96
Ethyl bromide	2.0	25	95
Ethyl tosylate	1.5	45	96
n-Propyl iodide	1.0	25	89
n-Propyl bromide	2.5	25	91
n-Propyl tosylate	1.0	45	90
n-Propyl chloride	8	35	16
n-Octyl chloride	4	45	42
β-Phenylethyl chloride	3	45	27
Isopropyl iodide	2.5	45	94
Isopropyl bromide	8	45	71
2-Iodooctane	2.0	45	85

[a] Sodium borohydride, 0.16 *M*; halide, 0.03 *M*. [b] Yield is based on removal of only one methyl group.

TABLE II
REDUCTION OF SIMPLE MONOHALOALKANES AND RELATED DERIVATIVES IN DIGLYME[a]

Compd	Time, hr	Temp, °C	Alkane, %
Methyl iodide	0.2	25	99
Dimethyl sulfate	0.2	25	99[b]
Methyl chloride	1.0	25	92[c]
Ethyl iodide	1.0	25	91
Ethyl bromide	2.0	25	65
Ethyl tosylate	1.0	45	35
1-Iodooctane	1.0	45	91
1-Bromooctane	2.0	45	77

[a] Sodium borohydride, 0.16 *M*; halide, 0.03 *M*. [b] Yield is based on removal of only one methyl group. [c] Sodium borohydride, 0.93 *M*; halide, 0.15 *M*, data of Brown.[10]

TABLE III
REDUCTION OF *para*-SUBSTITUTED BENZYL HALIDES IN DMSO[a]

Compd	% reduction 4 hr	1 hr	0.1 hr
Benzyl chloride	86	49	10
Benzyl bromide		99	
p-Methoxybenzyl chloride		87	24
p-Methylbenzyl chloride		56	
p-Chlorobenzyl chloride		68	
p-Fluorobenzyl chloride		58	
p-Nitrobenzyl chloride		94	20
t-Cumyl chloride		1	

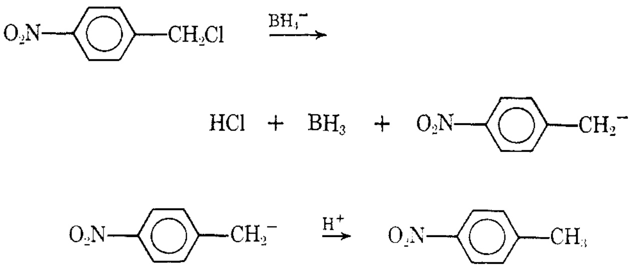
[a] Sodium borohydride, 0.2 *M*; halide, 0.1 *M*; room temperature.

times might not accurately reflect their rate of reaction relative to benzyl chloride. Consequently, these reactions were also performed for 0.1 hr.[14] However, the data show no significant reactivity difference as a function of *para* substituent; the yields are consistent with a simple SN2 attack by borohydride on the benzylic carbon. Also consistent with this mechanism is the slow rate of reaction of the α,α-dimethyl derivative, *t*-cumyl chloride. This slow reaction is in contrast to the rapid reduction to cumene when the reaction is performed under conditions suitable for the solvolytic generation of carbonium ions.[7] The difference in DMSO and diglyme as solvent is clearly shown in the case of benzyl chloride. Using the same conditions as in Table III but substituting diglyme for DMSO reduced the yield of toluene from 49 to 7%.

Two considerations made the reduction of *p*-nitrobenzyl chloride especially interesting. First, the reduction to *p*-nitrotoluene clearly demonstrates the selectivity of the borohydride; the analogous lithium aluminum hydride reduction would fail because of the simultaneous reduction of the nitro group. Second, although the rate of reduction of this material was not unusually high, the possibility that *p*-nitrotoluene was being produced by some mechanism other than the usual SN2 displacement by borohydride on carbon seemed worth investigating. Two alternate mechanisms were considered, a radical–anion process and nucleophilic displacement on halogen.

Kornblum has shown that *p*-nitrobenzyl derivatives can undergo substitution *via* radical–anion intermediates;[15] therefore, the question of a mechanism involving radical anions for the borohydride reduction of *p*-nitrobenzyl chloride seemed not unreasonable. However, little or no evidence was found which required their existence. Thus, the rate of reaction with borohydride was somewhat higher than anticipated, but not large enough to be alarming. No esr signal could be observed while the reaction was in progress, and oxygen did not substantially inhibit the reaction.

The other possibility which was considered for the reduction of *p*-nitrobenzyl chloride involves borohydride attack on halogen as shown below, but again,



evidence indicated that this process does not play a significant role in *p*-nitrotoluene production. Thus, the reaction of *p*-nitrobenzyl chloride in 80% aqueous DMSO and diglyme was found to proceed at about the same rate as in the anhydrous solvents, and performing the reaction in 80% DMSO–20% deuterium oxide resulted in less than 5% deuterium incorporation in the *p*-nitrotoluene.

Reduction of Carbon Tetrachloride.—In the series methyl chloride, dichloromethane, chloroform, and carbon tetrachloride, there can be little doubt that a decrease in SN2 (on carbon) reactivity should parallel an increase in the number of halogen atoms. Data for the borohydride reduction of methyl chloride, dichloromethane, and chloroform are consistent with this interpretation. Methyl chloride can be converted to methane in good yield,[10] but dichloromethane and chloroform (0.1 *M*) were very slow in reacting with 0.2 *M* borohydride, both in diglyme and in DMSO. In each case, approximately 90–95% of starting material was detected after 30 min at 30°. On the other hand, carbon tetrachloride gave indications of greater re-

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[14] The rapid reaction of methyl iodide with borohydride makes it well suited to serve as a quenching agent for such reactions.

[15] R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, **87**, 4520 (1965).

activity. In a typycal experiment, 0.1 *M* carbon tetrachloride was allowed to react with 0.2 *M* sodium borohydride in DMSO for 1 hr at 30°. After excess borohydride was decomposed with methyl iodide,[14] analysis indicated 65–70% unreacted carbon tetrachloride, 29–30% chloroform, and 0–2% dichloromethane. This product distribution was somewhat difficult to reproduce, for traces of water appeared to cause greater reactivity. Indeed, performing the above reaction in 80% aqueous DMSO resulted in a very rapid reaction, as evidenced by hydrogen evolution. After 5 min, analysis indicated 65–70% chloroform, 25–30% dichloromethane, and a trace amount of methane. Results in diglyme were similar. Our interest in this reaction was heightened by the observation that no dichloromethane was produced when 0.1 *M* chloroform was treated with borohydride in aqueous DMSO or diglyme. Thus, it would appear that the dichloromethane cannot be produced by the subsequent reduction of chloroform.

A mechanism consistent with these observations is given below. The first step involves an on-halogen displacement by borohydride, producing the trichloromethyl anion and the elements of borane and hydrogen chloride. The trichloromethyl anion either abstracts a proton to produce chloroform or is converted to dichloromethane *via* dichlorocarbene.[16]

$$CCl_4 + BH_4^- \longrightarrow CCl_3^- + HCl + BH_3$$

$$CCl_3^- \xrightarrow{H^+} CHCl_3$$

$$CHCl_3 \xrightarrow{-Cl^-} CCl_2$$

$$CCl_2 + BH_4^- \longrightarrow CHCl_2^- + BH_3$$

$$CHCl_2^- \xrightarrow{H^+} CH_2Cl_2$$

Reduction of Aryl Halides.—Two compounds were investigated, *o*-fluoroiodobenzene and *o*-nitroiodobenzene. Reduction of 0.1 *M* *o*-fluoroiodobenzene with 0.2 *M* sodium borohydride in anhydrous DMSO at 50–55° produced 34% fluorobenzene and 58% unreacted *o*-fluoroiodobenzene after 75 min. Benzene and iodobenzene were not present. In 80% aqueous DMSO, the same conditions produced 80% fluorobenzene and 9% *o*-fluoroiodobenzene. Again, benzene and iodobenzene were not present.

The reactivity of *o*-nitroiodobenzene was more pronounced; after only 15 min at room temperature, 0.1 *M* halide reacted with 0.2 *M* borohydride in 80% aqueous DMSO to produce a 95% yield of nitrobenzene. Substituting deuterium oxide for water resulted in *o*-deuterionitrobenzene of 88% purity; the analogous reduction in 80% diglyme–20% deuterium oxide produced *o*-deuterionitrobenzene of 98% purity. Nitrobenzene did not incorporate deuterium under the reaction conditions.

The above observations point to a mechanism analogous to that proposed for the formation of chloroform from carbon tetrachloride. The greater reactivity of iodine compared to fluorine and the deuterium incorporation in the case of *o*-nitroiodobenzene are clearly more consistent with nucleophilic attack on halogen than with direct substitution on carbon. A similar mechanism was recently proposed by Bunnett for aryl halide reductions by potassium *t*-butoxide in *t*-butyl alcohol–DMSO mixtures.[17] We intend to explore the generality of this reaction in some detail.

$$BH_4^- + ArX \longrightarrow BH_3 + HX + Ar{:}^-$$

$$Ar{:}^- \xrightarrow{H^+(\text{or } D^+)} ArH \text{ (or D)}$$

Diborane Generation.—In addition to its application to the synthesis of organic materials, it is clear from the stoichiometry that the borohydride reduction of halogen compounds should be useful for the generation of solutions of diborane (or borane etherate).[11] For the production of organic derivatives, the excess borohydride as used in the above reactions is not undesirable. However, for the purpose of generating diborane, an equimolar amount of borohydride and halide would be the ideal reaction mixture, and for successful results, the reaction should be rapid, even with low concentrations of both reactants. Owing to their high reactivity toward nucleophilic displacement, we felt that methyl derivatives would be best suited for this application. In addition to their reactivity, the fact that the reduction product is gaseous was considered advantageous. The two derivatives investigated, methyl iodide and dimethyl sulfate, both reacted quantitatively with an equimolar amount of sodium borohydride in dry diglyme at room temperature. Furthermore, addition of water to the reaction mixture produced additional gas evolution, consistent with the decomposition of 3 mol of "hydride" per mol of methane.

In order to determine the effectiveness of this procedure, the diborane thus prepared was used for the hydroboration of some representative alkenes. Because hydroboration–oxidation is known to produce alcohols in high yield, we felt that the yield of alcohols in this case could be used as a measure of the effectiveness of the diborane synthesis. We have summarized in Table IV our findings for the hydroboration of some alkenes in diglyme and tetrahydrofuran.

TABLE IV

HYDROBORATION–OXIDATION OF REPRESENTATIVE ALKENES

		Alcohol, %[a]	
Alkene	"Halide"	Diglyme	Tetrahydrofuran
1-Hexene	Dimethyl sulfate	78[b]	88 (74)[c]
	Methyl iodide	80[b] (72)	
Styrene	Dimethyl sulfate	93	95
	Methyl iodide	91	
Cyclopentene	Dimethyl sulfate		92 (80)
	Methyl iodide	91	
Cyclohexene	Dimethyl sulfate		93 (78)

[a] Total alcohol by glpc; the expected isomer distributions were observed. [b] Some product was lost during diglyme removal prior to analysis. [c] Values in parentheses are isolated yields.

To obtain the diglyme data, the halide was added to a stirred solution of alkene and sodium borohydride over a 30-min period at room temperature, and after 1 additional hour, the organoborane was oxidized in the usual manner. The tetrahydrofuran data were obtained by allowing a well-stirred suspension of sodium borohydride to react with dimethyl sulfate for 2 hr at 40–45° in the presence of the alkene prior to oxidation.

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(16) Efforts to trap the trichloromethyl anion by performing the reduction in deuterium oxide were inconclusive because of the rather facile exchange of the hydrogen of chloroform with deuterium oxide in DMSO under the reaction conditions.

(17) J. F. Bunnett and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968).

Both methyl iodide and dimethyl sulfate appear to give very satisfactory results; however, only dimethyl sulfate is recommended for general use. The high volatility of methyl iodide is undesirable, and the iodide ion produced in the initial reaction interferes with the subsequent oxidation of organoborane, owing to its tendency to catalyze the decomposition of hydrogen peroxide.[18–20]

The excellent yield of alcohols, both in diglyme and in tetrahydrofuran, indicates that this procedure for generating diborane is indeed satisfactory. The internal generation as reported here is suitable for most hydroborations, but the procedure clearly could be applied to external generation for any application.[21] The convenience and ease of handling of dimethyl sulfate makes this method compare very favorably with the most widely used procedure for diborane generation, *i.e.*, treatment of sodium borohydride with boron trifluoride etherate.

Experimental Section

Materials.—All of the materials were either commercial products or were synthesized by standard procedures. In most cases, the commercial materials were redistilled or recrystallized prior to use. Dimethyl sulfoxide was vacuum distilled from calcium hydride; diglyme was vacuum distilled from lithium aluminum hydride.

Analytical Procedure.—Reaction product mixtures were analyzed for reduction product and, in some cases, unreacted starting material by gas chromatography. A molecular sieve column was used for the analysis of methane; the usual glpc support-coated columns were used for all other analyses. Methane, ethane, and propane were analyzed as gaseous solutions.

Reaction Procedures.—The following reactions are representative.

A. Reduction of Methyl Iodide in Diglyme.—In a stirred, 50-ml flask attached to a gas buret was placed 16 ml of dry diglyme and 0.12 g (3.2 mmol) of sodium borohydride. After the sodium borohydride had dissolved, 0.083 g (0.58 mmol) of methyl iodide dissolved in 4 ml of diglyme was added. Rapid gas evolution, amounting to 27 ml in less than 1 min (27°, 709 mm), was observed; no additional gas evolution was seen during the next 15 min. At this time, 0.5 ml of water containing a little sodium hydroxide was added, and an additional 69 ml of gas was produced. After the gas was thoroughly mixed, analysis indicated 0.57 mmol (99%) of methane.

B. Reduction of *n*-Octyl Chloride in DMSO.—In a stirred, 50-ml flask attached to a small vapor trap maintained at −80° was placed 17 ml of DMSO and 0.12 g (3.2 mmol) of sodium borohydride, followed by 0.080 g (0.53 mmol) of *n*-octyl chloride dissolved in 2 ml of DMSO. After 4 hr at 45–50°, 0.050 g (0.35 mmol) of decane internal standard dissolved in 10 ml of pentane was added, the trap was flushed with 5 ml of pentane, and the layers were separated. The DMSO layer was extracted with 15 ml of ether, and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. Analysis indicated 0.22 mmol (42%) of octane and 0.31 mmol (58%) of *n*-octyl chloride.[22]

C. Reduction of *o*-Nitroiodobenzene in DMSO–Deuterium Oxide.—A mixture of 14 ml of DMSO, 4 ml of deuterium oxide, and 0.15 g (3.9 mmol) of sodium borohydride contained in a stirred 50-ml flask equipped with a gas buret was cooled to approximately 18°, and 0.50 g (2.0 mmol) of *o*-nitroiodobenzene dissolved in 2 ml of DMSO was added. In 3 min, the mixture had warmed to 27°, and 150 ml of gas had evolved; during the next 12 min, further gas evolution amounted to only 10 ml. Decomposition of excess borohydride with 0.29 g (2 mmol) of methyl iodide produced an additional 190 ml of gas.[23] After a 4-hr liquid–liquid extraction with pentane, analysis indicated 1.9 mmol (95%) of nitrobenzene. The pentane was removed, and the product was isolated by vacuum distillation. Analysis by mass spectrometry indicated that 88% of the nitrobenzene was monodeuterated; analysis by nmr indicated that the deuterium was *ortho*.

D. Hydroboration of Cyclopentene in Tetrahydrofuran.—In a dry, 250-ml round-bottomed flask equipped with magnetic stirrer, thermometer, dropping funnel, reflux condenser, and drying tube was placed 60 ml of tetrahydrofuran and 10.2 g (0.15 mol) of cyclopentene. Stirring was commenced, and 2.08 g (0.055 mol) of pulverized sodium borohydride was added, followed by 6.9 g (0.055 mol) of dimethyl sulfate dissolved in 10 ml of tetrahydrofuran, added over a period of 5 min. Stirring was continued for 2 hr, with the temperature maintained at 35–45°. The mixture was cooled in an ice bath, and the excess hydride was decomposed by the careful addition of 10 ml of water. The organoborane was oxidized at 20–30° by adding 16 ml of 3 *N* sodium hydroxide, followed by the dropwise addition of 16 ml of 30% hydrogen peroxide. The reaction mixture was stirred for an additional 20 min and saturated with sodium chloride. The layers were separated, and the tetrahydrofuran layer was washed once with brine and dried over anhydrous magnesium sulfate. After removal of the tetrahydrofuran by rotary evaporation, the product was distilled, giving 10.3 g (80%) of cyclopentanol: bp 62° (28 mm); n^{20}_{D} 1.4530.

Registry No.—Sodium borohydride, 1303-74-8.

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[18] H. A. Liebhafsky and A. Mohammad, *J. Amer. Chem. Soc.*, **55**, 3977 (1933).

[19] Some years ago, Brown more or less discarded methyl iodide for much the same reasons.[11]

[20] With the excess peroxide normally employed in organoborane oxidations, the action of iodide is perhaps more of a nuisance than a detriment, for the yields are not noticeably lower than with dimethyl sulfate.

[21] G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 32 (1963).

[22] The thermal conductivity molar response factors for octane and *n*-octyl chloride, relative to 100 for decane, are 80 and 97, respectively.

[23] Total gas evolution amounted to 12.7 mmol; this is in good agreement with the 13.6 mmol of excess hydride predicted for complete reduction of the *o*-nitroiodobenzene.