THE SODIUM BOROHYDRIDE REDUCTION OF ORGANIC HALIDES AND RELATED DERIVATIVES IN APROTIC SOLVENTS

by

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To my parents, without whose constant sacrifice this work would never have been possible.

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I. INTRODUCTION

Since their initial synthesis in the mid to late 1940s by H. C. Brown, H. I. Schlesinger, and co-workers[1], two of the complex metal hydrides, lithium aluminum hydride and sodium borohydride, have been widely investigated as to their reduction products with most of the functional groups known to date in the field of organic chemistry. Due to the fact that lithium aluminum hydride is a much stronger reducing agent and shows, therefore, less "reductive selectivity" than does sodium borohydride, it will readily reduce most functional groups. However, the case is not as well defined for sodium borohydride, for much controversy has arisen in the literature particularly concerning the reduction of organic halides and aromatic nitro compounds with this material. The primary goal of this research project was to aid in the elucidation of the reduction product(s) of sodium borohydride with alkyl and aryl halides and to note carefully the effect of:

1) the type of leaving group
2) the type of alkyl group (primary, secondary, and tertiary)
3) the *para* substituent on the rate of reduction of *para*-substituted benzyl halides
4) substitution on the rate of reduction and the relative order of dehalogenation of selected, substituted aryl halides
5) the solvent

It is believed that the results of this research effort will be of important use in the field of organic reductions, especially as applied to synthetic work, because one has a wider range of both protic and aprotic solvents from which to choose for use with sodium borohydride as compared to only aprotic solvents for lithium aluminum hydride. Finally and most important of all, are the synthetic advantages to be derived from the greater reductive selectivity of sodium borohydride as a reducing agent.

II. HISTORICAL

There now exist five major ways of chemically converting an organic halogen compound to the corresponding hydrocarbon, and of the following five only the last two will be cited as they are relatively new methods of reduction, whereas the remaining three are well documented in the literature[2,3]:

1) $RX \xrightarrow{Mg} RMgX \xrightarrow{H_2O} RH$

2) $RX \xrightarrow{H^+,\ M} RH$

3) $RX + H_2 \xrightarrow{\text{catalyst}} RH$

4) $RX + (R')_3SnH \longrightarrow RH$

5) $RX + LiAlH_4 \longrightarrow RH$

The first method simply involves the hydrolysis of the Grignard reagent of the corresponding alkyl or aryl halide of the desired hydrocarbon. The yields of hydrocarbon are dependent solely upon the yield of the Grignard formed as hydrolysis is quantitative. The second method can be used only when R is an alkyl group, and M designates some metal, commonly zinc. The third method utilizes a reaction vessel containing a catalyst such as Raney nickel or palladium-calcium carbonate and may employ temperatures ranging from 20 to 400° C. and pressures from one to several thousand atmospheres. Even though these conditions may appear to be extreme, nevertheless, the reduction can be very selective and the yields extremely good depending on the type of catalyst and conditions chosen and the specific halide involved.

The fourth method concerns itself with the use of a relatively new reducing agent, an organotin hydride, where R may be alkyl, aryl, or acyl and R' either a phenyl or <u>n</u>-butyl group. The yields range from 70 to 90%, and the reduction is believed to proceed by a free-radical mechanism as opposed to an S_N1- or S_N2-type mechanism.

The final method illustrates the use of, perhaps, the most widely employed complex metal hydride, lithium aluminum hydride (hereafter abbreviated LAH). The products and mechanism of reduction of organic halides, in general, with LAH were extensively examined by many investigators between the late 1940s and mid 1950s, and from this work, the following general conclusions were drawn[3,4,5]:

1) the reduction of alkyl halides occurs by an S_N2 mechanism.

2) the order of reactivity of alkyl halides is primary > secondary > tertiary, the latter producing mostly olefins.

3) the order of reactivity of the halogen is iodide > bromide > chloride. Fluorides were not reduced.

4) aryl halides proved to be very much less reactive than alkyl halides.

5) the use of higher-boiling solvents (relative to ethyl ether) such as tetrahydrofuran for the more unreactive halides improved the yields obtained in some cases.

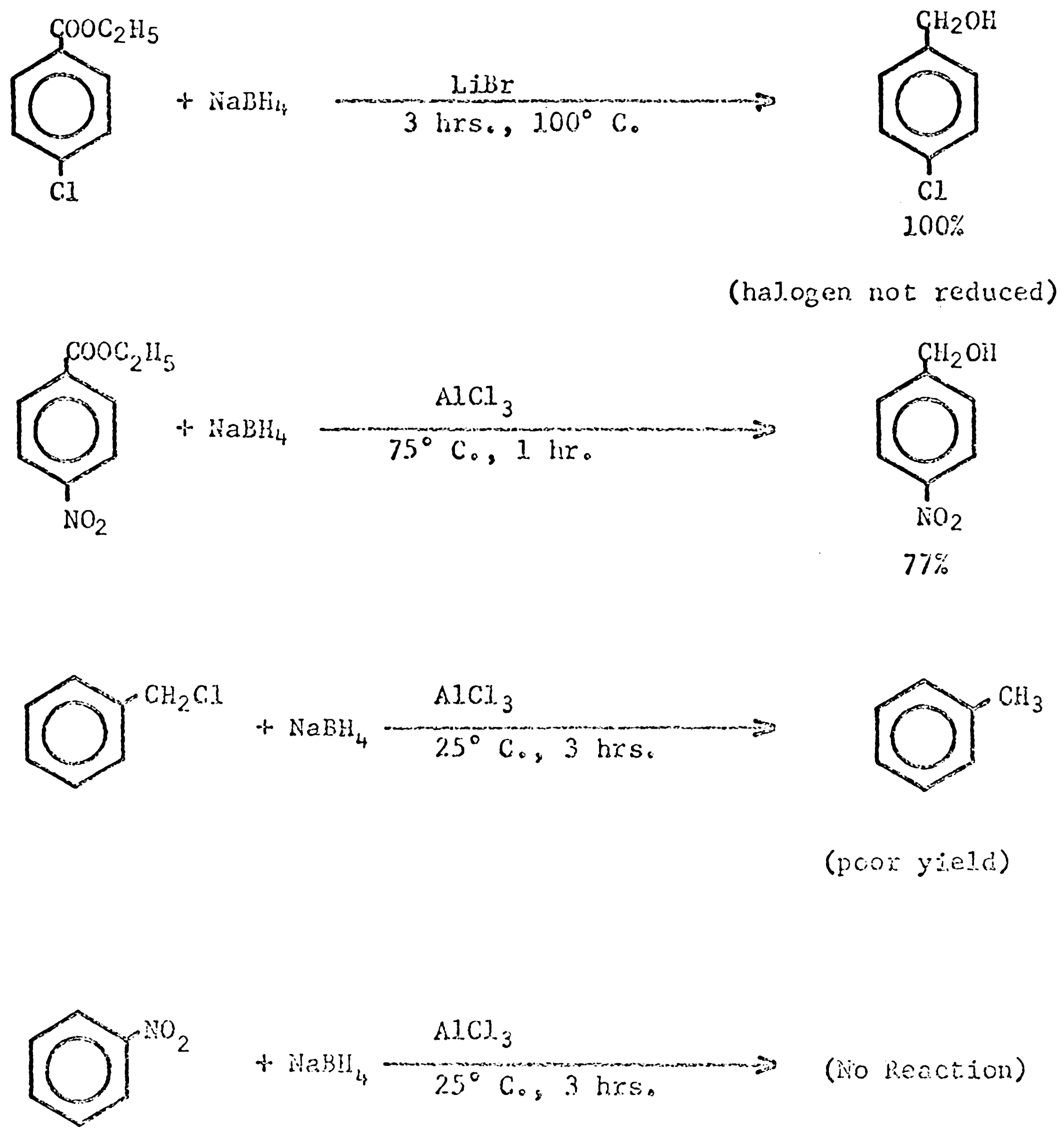
6) the use of a "hydrogen carrier" such as LiH accelerated the reductions and increased the hydrocarbon yields as well as decreasing the amounts of LAH required.

In 1955 Pearson and Adams[6] published their results of sodium borohydride (hereafter abbreviated SBH) reductions done in polyethylene glycol dialkyl ethers and stated that SBH solutions in these solvents had enhanced reducing reactivity toward alkyl halides, nitro groups, acetates, sulfides, esters, and silicates. Bromides were more reactive than chlorides, and gem-dihalides were less reactive to SBH than monohalides or gem-tri- and tetrahalides. Branching or lengthening the carbon chain decreased reactivity, and aromatic, alicyclic, and heterocyclic halides had reduced reactivity. In a typical experiment, methyl chloride in tetraglyme (tetraethylene glycol dimethyl ether) was reduced in a 1:1 molar ratio with SBH at liquid nitrogen temperatures to methane, diborane, and hydrogen, the diborane being a co-product. Similarly, carbon tetrachloride and nitrobenzene were reduced to methylene chloride and azobenzene, respectively. This, then, represented the first attempt at the SBH reduction of alkyl and aryl halides and nitro compounds. The fact that aprotic, dipolar solvents were employed was of only slightly lesser importance than the yields achieved, as this same type of solvent was also selected for use by our laboratory for reasons to be mentioned later (see page 15).

Other workers began contributing to the field of alkyl halide reductions with SBH. In 1957 Nad and Kocheshkov[7] reported that carbon tetrabromide was reduced in aqueous methanol by SBH to 74% bromoform, while iodoform had been reduced in 85% yield to methylene iodide. Some two years prior to this, H. C. Brown and his co-workers began investigating suitable solvents for SBH reductions and similarly found as had Pearson and Adams that diglyme (diethylene glycol dimethyl ether) was an excellent choice. These early reductions also involved a study of the effect of metal cations as well as solvent on SBH reductions, particularly in regard to reduction of an ester or carboxylate group in the presence of other reducible groups on the aromatic ring such as halogen or nitro. Figure 1 on page 7 shows several selective and non-selective reductions that Brown[8,9] performed. As Figure 1 shows, Brown reported no reaction between nitrobenzene and SBH, but during this same time period the report of a 58% reduction was published by Weill and Panson[10], who noted that higher temperatures and a longer reduction time were required. In a later experiment during the reduction of methyl chloride with SBH in diglyme, Brown noted the diborane formed as a co-product apparently was producing a 1:1 adduct with unreacted SBH to form NaB_2H_7 or "sodium diborohydride" because, "Rough kinetic experiments indicated that the rate [of reduction] showed a marked decrease following the conversion of the sodium borohydride to sodium diborohydride."[11] No further work was done until 1962 when a study of the reduction of secondary and tertiary halides and tosylates under solvolytic (S_N1) conditions was begun, primarily as a means of "trapping" the carbonium ions that formed upon ionization of the halide with hydride ion from SBH[12]. It was found that, "In nonionizing solvents [diglyme], secondary and tertiary alkyl halides react with sodium borohydride only slowly, in many cases yielding the olefin, rather than the desired saturated hydrocarbon. However, the addition of water to produce solvolyzing conditions brings about a rapid reaction, providing the corresponding hydrocarbon in good yield, along with the concomitant formation of the alcohol and the olefin as the usual solvolytic products."[13] As typical examples, benzhydryl chloride and triphenylmethyl chloride in 65% (vol.%) aqueous diglyme were reduced by SBH to give yields of 75% diphenylmethane and 96% triphenylmethane, respectively. It seemed that the greater the stability of the carbonium ion formed, the higher was

FIGURE 1

Selective and Non-Selective Reductions with Sodium Borohydride in Diglyme



the yield of hydrocarbon and the lower the yield of alcohol formed due to attack by water, since the hydride ion is a much stronger nucleophile than water. The effect of various para substituents in the ring on the stability of the carbonium ion (hence, hydrocarbon yield) was shown by the reduction of para-chloro- and para-methoxybenzhydryl chloride under identical conditions to give yields of 62% para-chlorodiphenylmethane and 97% para-methoxydiphenylmethane, respectively. Decreasing the volume percentage of water from 35% to 12% had no effect on the yield of hydrocarbon, but changing the halogen from chlorine to bromine had a very noticeable effect, as exemplified by an 87% yield of diphenylmethane from the solvolytic reduction of benzhydryl bromide. Both these observations are not in full agreement with a completely dissociated carbonium ion (S_N1) mechanism. Thus it was proposed that SBH was, perhaps, reacting with ion pairs. "In this event, the reaction course would not be independent of the leaving group. Moreover, the carbonium ion could then react preferentially with water clustered about the anion, rather than with water in the bulk."[14] The above work resulted primarily from their earlier studies of "classical and non-classical" bicyclic and tricyclic carbonium ions, produced by similar solvolytic reductions with SBH of their analogous bicyclic halides and tosylates[15,16]. Table I on page 9 summarizes their results.

The final and one of the most synthetically interesting applications of SBH to the reduction of alkyl halides and their related derivatives involves a type of reductive cyclization through "neighboring-group participation"[17] by the oxide ion of a β-haloketone or aldehyde to form

TABLE I

Reduction of Selected Organic Derivatives with 4.0 M Borohydride[a]

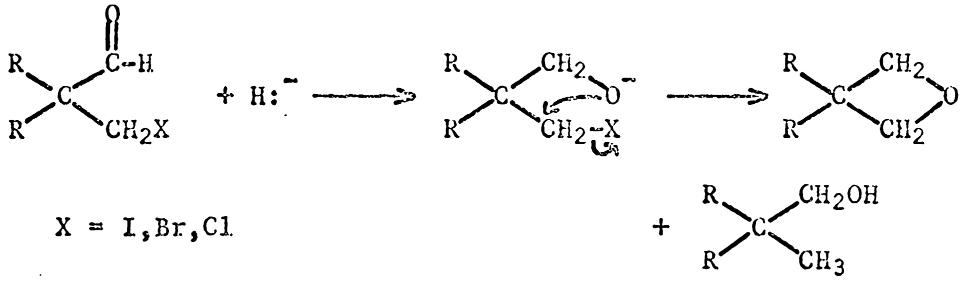
Derivative	Hydrocarbon	Olefin	Alcohol
t-Cumyl chloride	81%	8%	6%
α-Phenylethyl chloride	75%	2%	21%
Benzhydryl chloride	99%	--	b
1,1-Diphenylethyl chloride	66%	32%	b
Triphenylmethyl chloride	96%	--	b
t-Amyl chloride	40%	35%	25%
1-Methylcyclopentyl chloride	40%	46%	12%
cyclooctyl *p*-Toluenesulfonate	40%	49%	11%
7-chloronorbornadiene	95%[c]	--	b
2-Phenyl-*exo*-norbornyl chloride	81%[c]	12%	5%

[a] Solvent system was 65% diglyme-20% water by volume.

[b] Not analyzed.

[c] Sodium borohydride, 1.8 M.

primarily the correspondingly-substituted oxirane or oxetane I and the saturated alcohol II, as shown below[18]:



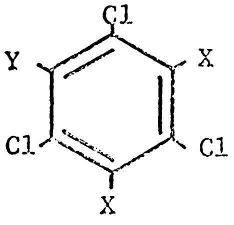
(I)

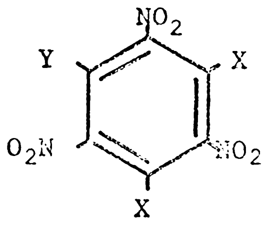
(II)

It was found that the product ratio was dependent on both the solvent and the structure of the starting compound.

Aryl halides are extremely resistant to attack by LAH, the degree of reduction of the halogen being dependent upon (1) the specific halogen involved, (2) the relative amounts of reducing agent and organic halide used, (3) the reduction time, (4) the reaction temperature, and perhaps most importantly of all, (5) the nature and relative positions on the ring of other competitive groups[19]. It was not until the recent work of Karabatsos and Shone[20] that good to quantitative yields of the corresponding aryl reduction products were achieved, as Gaylord[21] had earlier noted that all the yields of the reductions reported prior to this time were generally quite low. However, the above co-workers noted that the best results were achieved when a strong electron-withdrawing group was located _ortho_ to the leaving halogen and when diglyme at a reaction temperature of 100° C. was the solvent. These conditions are very drastic when compared to the room temperature conditions utilized in our laboratory with the much milder SBH. The same order of reactivity among the halogens was established as previously stated for the alkyl halides (see page 4).

At the time of publication of his book, Gaylord[22] reported that the only attempted reduction of an aryl halide with SBH had been unsuccessful. However, in 1963 Severin[23] and co-workers announced that they had achieved the SBH reduction of several substituted and unsubstituted polynitroaromatic compounds to the corresponding polynitrocyclohexanes and/or polynitrocyclohexenes in good yields in a methanol-tetrahydrofuran-formamide solvent system at room or ice-bath temperatures under alkaline conditions. Similarly, Kaplan[24] reported the following year that under Severin's conditions he obtained the usual cycloaliphatic products from the reduction of mono- and dichloro-substituted *sym*-trinitrobenzenes, but benzenoid products when *sym*-trichlorotrinitrobenzene was reduced. Thus, 2-chloro-1,3,5-trinitrobenzene (IV) and 2,4-dichloro-1,3,5-trinitrobenzene (V) both yielded *sym*-trinitrocyclohexane, but the reduction of *sym*-trichlorotrinitrobenzene (I) produced 2,4,6-trichloro-1,3-dinitrobenzene (II) which could further be reduced to 2,4,6-trichloronitrobenzene (III).





I, $X = Y = NO_2$

II, $X = NO_2$; $Y = H$

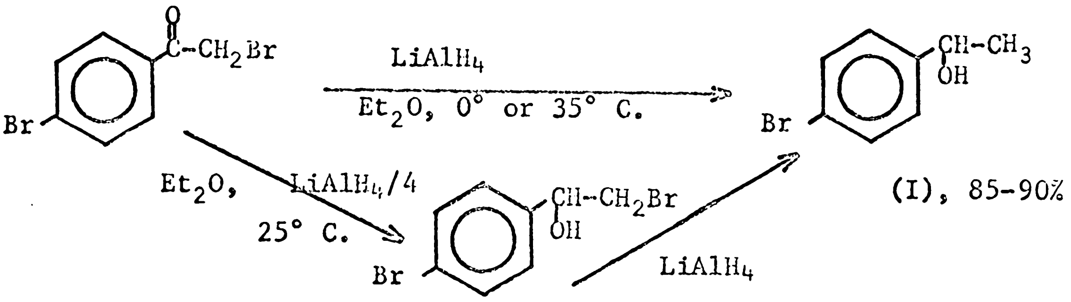
III, $X = H$; $Y = NO_2$

IV, $X = H$; $Y = Cl$

V, $X = Cl$; $Y = H$

Kaplan rationalized the formation of products II and III by suggesting that the relative "leaving ability" of the chloro and nitro groups was primarily determined by the degree of resonance interaction of the nitro groups with the π-electron system of the ring. That is, the further the plane of any given nitro group varied from being coplanar with the ring, the more susceptible the nitro group was to displacement by hydride ion. X-ray diffraction studies showed the C-2 nitro group of structurally similar compound V to be 76° out of the plane of the ring, thus supporting the idea of non-coplanarity of the three nitro groups in compounds I-III. Conversely, the finding that the C-4 and C-6 nitro groups of compound V were only 3.6° and 37°, respectively, out of the plane of the ring seemed to indicate that the increased resonance interaction of these two nitro groups could render positions C-1 and C-3 especially electron deficient, and therefore, very vulnerable to nucleophilic attack by hydride ion. This, then, could account for the loss of halogen substituents instead of nitro groups from compounds IV and V to give sym-trinitrobenzene which Severin[23] had showed previously could undergo further ring reduction to sym-trinitrocyclohexane.

The field of selective reductions (that is, where there are two or more groups in the molecule that could undergo reduction) with LAH and SBH was initiated using α-halo derivatives of ketones, acids, acid chlorides, esters, etc. Whether or not the halo group was reduced with LAH was dependent upon the first four factors listed for aryl halides (page 10) and upon the nature of the group(s) alpha to the halogen. For example, the points concerning the ratio of reducing agent to substrate and the nature of the *alpha* group(s) can be illustrated using the work of Lutz and co-workers as shown below[25]:



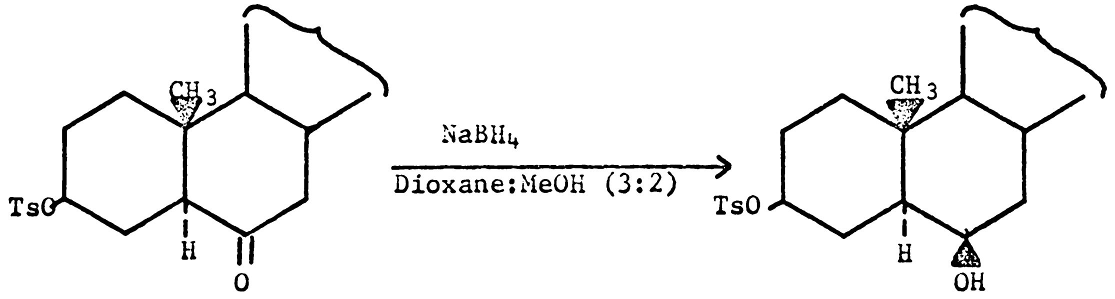
(I), 85-90%

(II), 69%

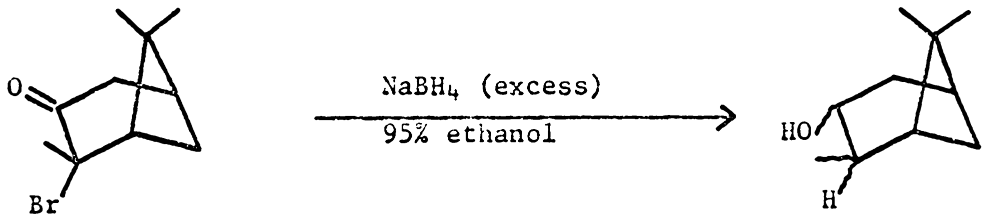
It was found that the bromohydrin II could be isolated only in very small yield when LAH was used in a slight equimolar excess over the starting ketone, but if only enough LAH was added to reduce the carbonyl group, a moderate yield of II was obtained. II could then be further reduced to I by an equimolar amount of LAH. Generally speaking, reduction of the more reactive group or groups *alpha* to the halogen will occur first. The reactivity of the halogen follows the same order as for the simple monohaloalkanes. Fluorides have not yet been reported as reduced under any conditions, chlorides are generally not reduced except under vigorous reaction conditions, and bromides are reduced in yields which depend upon the amount of LAH used, but generally the product from the reduction of the more reactive carbonyl group predominates[26]. Any attempted reductions of *α*-iodo derivatives with LAH have not yet been reported.

With respect to the reduction of *α*-halo compounds with SBH, Gaylord states, "In no case has reduction of the halogen atom been reported."[27]

Working with a related derivative, Shoppee and Stephenson[28] reported that the toluene-p-sulfonate (tosyl) group was also not reduced in the presence of the more reactive keto group, as shown below:



This is most selective because the tosyl group is reported to be at least as good or an even better leaving group than iodo in S_N2 reactions[29]. However, more recently Goldsmith and Joines[30] have shown that reduction of the α-bromo group of bicyclic ketone I does, indeed, occur to give the corresponding saturated alcohol II in good yield:



(I) (II), 90%

It was decided that a more thorough investigation into the reducing ability of SBH toward organic halides as a whole be undertaken for several important reasons. Primarily, although Brown and Bell[13] had reported that secondary and tertiary alkyl halides were reduced only very slowly and in poor yield in aprotic solvents, nevertheless, earlier reports of Brown[11] and others[6,7] of a quantitative yield of methane from the reduction of methyl chloride by SBH seemed to indicate that other primary alkyl halides might at least be reduced to some degree, or in perhaps, moderate to excellent yield. Secondly, except for the work of Severin[23] and Kaplan[24], no work had been done using specifically SBH to study the necessary requirements for the reduction of aryl halides, as Karabatsos and Shone[20] had done with LAH. Thirdly and finally, Brown's[8] success with dipolar, aprotic solvents such as diglyme prompted our own use of similar solvents for the following reasons:

1) most of the limited work with SBH in halide reductions had been performed using either water and/or low molecular weight alcohols as solvents, and

2) recent advances[31] in the studies of solvent effects on S_N2 reaction rates indicated that newly developed dipolar, aprotic solvents like dimethyl sulfoxide (DMSO) and hexamethylphosphoramide were known to produce rate increases of several thousand fold over alcoholic media.

III. DATA AND RESULTS

The Use of DMSO and Diglyme in the Reduction of

A. Simple Primary Monohaloalkanes and Related Derivatives

The reduction of an organic halide or a related derivative may be represented by reaction 1 where R may be alkyl or aryl and X denotes the leaving group:

$$RX + NaBH_4 \xrightarrow[25^\circ\ C.]{DMSO} RH + BH_3 + NaX \qquad (1)$$

During either the usual water work-up or a reaction employing an aqueous solvent, reaction 2 would occur:

$$BH_3 + 3H_2O \longrightarrow B(OH)_3 + 3H_2\uparrow \qquad (2)$$

Product identification and determination of yields throughout the entire project were performed using the external and internal standard methods of gas-liquid chromatography (glc).

For the analysis of methane produced by the reduction of methyl iodide, standards of methane in nitrogen were used. Positive identification of methane was made by comparison of its retention time to that of the standard. The resulting value of the single trial performed is shown in Table II on page 17. The reduction products of methyl tosylate were analyzed analogously. The verification of a 1:3 ratio of hydrocarbon to hydrogen was not quantitatively accessible due to the erratic response of hydrogen to the thermal conductivity detectors, but since

TABLE II

Reduction of Simple Monohaloalkanes and Related Derivatives in Anhydrous DMSO[a,b]

RX	% Reduction[c]
Methyl iodide	96
Methyl tosylate	90
Ethyl bromide	95
Ethyl iodide	96
Ethyl tosylate	96
n-Propyl chloride	16
n-Propyl bromide	91
n-Propyl iodide	89
n-Propyl tosylate	90
Isopropyl bromide	71
Isopropyl iodide	94

---

[a] Sodium borohydride, 0.16 M; halide, 0.03 M.

[b] Most reactions were run at room temperature for periods ranging from 1-3 hours. See "Experimental" for details (pp. 38-42).

[c] Percentage reduction was calculated as described on page 29.

the yields of methane were almost quantitative and the volumes of gas evolved were close to the calculated theoretical volumes based on this ratio, the ratio of products was believed to be correct.

Ethane, from the reduction of the compounds listed in Table II, was also analyzed by an external standard method. The retention time of this product was checked against a pure sample obtained by an alternate method and was shown to be identical to it. However, since the small amount of ethane prepared by the alternate route could not be pumped and mixed with air for use as a standard, the problem was resolved by determining the area under the chromatographic curve for propane in a known mixture of propane and air. By applying the "Relative Molar Thermal Response Values" of propane and ethane (1.27 and 1.0, respectively) as obtained from the literature[32], the area that an identical molar concentration of ethane *would* yield was computed.

The analysis of the several *n*- and isopropyl compounds reduced were also treated by the external standard method using standards of propane in air. Since elimination might become an important competing side reaction with secondary halides, propene was synthesized by an alternate route and used to check for the possible presence of this product in the analysis of the reduction products. No propene was detected in any case. Table II gives the results of these reductions.

To examine any solvent effects, the following selected halides were chosen to be reduced in *diglyme* using a 1:1 ratio of borohydride to halide and were analyzed by the same procedure as above.

TABLE III

Reduction of Selected Simple Monohaloalkanes in Diglyme[a]

RX	% Reduction
Methyl iodide	92
Ethyl iodide	88
Ethyl bromide	68

[a] Most trials were run at room temperature for 1-5 hours using a borohydride to halide ratio ranging from 1:1 to 5:1. See "Experimental" for details (pp. 42-43).

B. Para-Substituted Benzyl Halides

All of the following compounds composing the benzylic halide series were reduced to the corresponding toluene in the yields reported in Table IV on page 21. In the case of the para-chloro and para-fluoro compounds, no check was made to determine if the aryl halogen had been reduced. However, as will be explained in the section on "Discussion of Results and Conclusions", this was believed to be highly improbable. Product verifications were made by comparing the retention times of the reduction products and known standards of the compounds. Quantitative analyses were performed using both internal and external standard methods. These methods gave results which generally agreed within 7% or less, the external method usually being the lower of the two. The yields in Table IV are all internal standard values. The internal standards used in analyses were chosen on the basis of their close structural proximity to the reduction products formed, as this would hopefully aid not only in affecting an approximately equal extraction of each, but would also give similar behavior on the chromatographic column used.

Benzyl bromide and benzyl chloride were both reduced using benzene as the internal standard. Once it was established that a quantitative yield of toluene could be obtained from the bromide in one hour or less at room temperature, benzyl chloride and its para-substituted derivatives were also run for a one hour time period to compare the "substituent effect" on a relative basis. However, a 4.5 hour trial was run for the unsubstituted chloride to determine the time necessary (still

TABLE IV

Reduction of Para-Substituted Benzyl Halides in Anhydrous DMSO[a]

	% Reduction		
RX	4.5 hrs.	1 hr.	6 min.
Benzyl chloride	86	49	10[b,c]
Benzyl bromide		100	
p-Methoxybenzyl chloride		87	24[b]
p-Methylbenzyl chloride		56	
p-Chlorobenzyl chloride		68	
p-Fluorobenzyl chloride		58	
p-Nitrobenzyl chloride		94	20[b]

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

[b] Yields with hydrolysis after 6 minutes.

[c] Yields with 16% water-84% DMSO (vol.%) as the solvent.

at room temperature) to affect almost complete reduction. Several six-minute trials were also performed for reasons to be explained shortly.

The reduction of _para_-methoxybenzyl chloride at room temperature was performed with anisole as the internal standard and gave an unexpected yield of 87% _p_-methylanisole after one hour (Table IV, p. 21). A six-minute trial was performed to examine more carefully the effect of the methoxy group on the rate of reduction relative to benzyl chloride and _p_-nitrobenzyl chloride.

The following compounds were employed as internal standards in the reduction of _p_-methyl-, _p_-chloro-, and _p_-fluorobenzyl chloride, respectively: toluene for the former and _p_-xylene for the latter two. See Table IV for the results of these reductions.

It was at first believed that the reduction of _p_-nitrobenzyl chloride was proceeding by some mechanism other than S_N2 because of the formation of brilliantly-colored solutions which lasted approximately ten to twelve minutes after addition of the substrate. However, no coloration occurred after further purification of the chloride by recrystallization from ethyl ether. It also appeared in the beginning that water was, perhaps, catalyzing the reduction of this _p_-nitro derivative, as relatively large rate increases were observed in a solvent system of 84% DMSO-16% water (vol.%). Subsequent experimentation showed that the most likely cause was a slightly higher reaction temperature rather than some interaction between water and the transition state of the reaction as first proposed.

Benzyl chloride and _p_-nitrobenzyl chloride were the only halides studied in diglyme. Table V on page 23 shows the results observed under identical conditions as those described above for DMSO. Note the

TABLE V

Reduction of Selected Benzylic Halides in Anhydrous Diglyme[a]

RX	% Reduction	
	1 hr.	6 min.
Benzyl chloride	6[b] (8[c])	1
p-Nitrobenzyl chloride	48	---

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

[b] 89% recovery of unreacted benzyl chloride.

[c] Solvent system was 80% diglyme-20% water by volume.

apparently large solvent effect operating for both and the excellent mass balance obtained in the case of benzyl chloride.

3. Secondary and Tertiary Alkyl Halides

The three compounds listed in Table VI (p. 25) were analyzed using the external standard method. The conditions and concentrations of SBH and halide utilized were the same as those shown in Table V (p. 23). No checks for unreacted starting material were made because of their high boiling points and poor behavior on the glc columns tried.

4. Aryl Halides

Only two aryl halides were reduced in this series, *o*-fluoro- and *o*-nitroiodobenzene (see Table VII, p. 26). Products were analyzed by the internal standard method using as standards toluene and *p*-nitrotoluene, respectively. Qualitative analyses were done as usual by a comparison of retention times of the products formed with pure samples of each. The reduction time and other conditions were the same as those previously used for the benzyl series. The reader's attention is called to the excellent mass balance achieved for the *o*-fluoro compound and the high yield obtained from the *o*-nitro derivative.

5. Polyhalomethanes

Carbon tetrachloride was chosen as an exemplary polyhalomethane for study because of its ready availability, and the need to establish the number of possible reduction products and their relative ratios.

Two sets of one-hour trials were performed in dry DMSO. One set employed the usual water work-up followed by extraction with ethyl ether, while the second set employed a methyl iodide quench to destroy unreacted

TABLE VI

Reduction of Selected Secondary and Tertiary Alkyl Halides in DMSO[a]

RX	RH	% Reduction 1 hr.
Benzhydryl chloride	Diphenylmethane	2
p-Nitrobenzhydryl chloride	*p*-Nitrodiphenylmethane	7
t-Cumyl chloride	Cumene	1

[a] Same conditions as in Table V.

TABLE VII

Reduction of Aryl Halides in DMSO[a]

RX	RH	% Reduction (1 hr.)
o-Fluoroiodobenzene	Fluorobenzene	14[b]
o-Nitroiodobenzene	Nitrobenzene	90

[a] Same conditions as in Table V.

[b] 87% recovery of unreacted o-FC_6H_4I.

SBH prior to the addition of water. The results are shown in Table VIII on page 28. The difference in behavior of the two cases will be discussed briefly in the section on "Discussion of Results and Conclusions".

TABLE VIII

Reduction of Carbon Tetrachloride in DMSO[a]

RX	% Reduction (1 hr.)		
	$CHCl_3$	CH_2Cl_2	unreacted CCl_4
CCl_4	56 (28[b])	30 (1 - 2[b])	none (70[b])

[a] Same conditions as in Table V.

[b] Denotes methyl iodide quench prior to hydrolysis.

IV. EXPERIMENTAL

A. General

As mentioned earlier all quantitative analyses were determined by the internal and/or external standard method using glc. The former method involves the preparation of a standard solution containing a known amount of the expected reduction product from an alternate source and a known amount of the "internal" standard. From this solution the areas of each component can be determined and a ratio of their "relative molar thermal responses" termed the "Thermal Conductivity Correction Ratio" (T.C.C.R.) can be calculated using the following equation:

$$\text{T.C.C.R. (product)} = \frac{\text{area of product} \times \text{mmoles of std.}}{\text{area of std.} \times \text{mmoles of product}} \qquad (1)$$

The number of millimoles of the reduction product formed can then be calculated by adding a known amount of the "internal" standard to the reaction solution and determining the area produced by each, followed by substitution of the areas and mmoles of each into equation 2 below:

$$\text{mmoles product} = \frac{\text{area of product} \times \text{mmoles of std.}}{\text{area of std.} \times \text{T.C.C.R.}} \qquad (2)$$

This method has the advantage over the external method of being independent of the sample size and the volume of solvent containing the sample. Finally, the percentage yield of reduction product is determined by dividing the number of mmoles of product by the mmoles of starting material, adjusting for the purity of the starting material (if less than 100%), and then multiplying by 100%.

The external standard method simply requires that a standard solution of known volume containing only the reduction product be made up and the resulting peak area be measured. By then measuring the peak area of the reduction product in a known volume of reaction solution and applying equation 3 below, the number of mmoles of reduction product can be obtained:

$$\text{mmoles product} = \frac{\text{area of product} \times \text{vol. reaction soln.} \times \text{molarity std.}}{\text{area of std.}} \qquad (3)$$

The percentage yield is then calculated in exactly the same manner as described above for the internal standard method. Equation 3 was also used for the analyses of methane, ethane, and propane except that solutions of a gas in a gas were prepared instead of a liquid in a liquid. Table IX on page 31 gives a summary of the types of glc columns and packings used in all the analyses performed.

All melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Refractive indices were taken using a Bausch & Lomb Abbé refractometer.

B. Chemicals

Sodium borohydride (Metal Hydrides, Inc.) was of 98% or higher purity and was used without further purification.

DMSO (Fisher Scientific Company) was vacuum distilled from calcium hydride and stored over molecular sieve under dry nitrogen.

Diglyme (The Ansul Company) was vacuum distilled from lithium aluminum hydride and stored under dry nitrogen.

TABLE IX

Columns for Gas-Liquid Chromatographic Analyses[a]

Column	Description
M.S.	6 ft. x $\frac{1}{4}$ in. copper, Activated "Linde"-type 5A Molecular Sieve
B	6 ft. x $\frac{1}{4}$ in. copper, 20% Squalane on 60/80 mesh Gas Chrom R
C	3 ft. x $\frac{1}{4}$ in. copper, 18% Carbowax 20M on 60/80 mesh Gas Chrom R
D	3 ft. x $\frac{1}{4}$ in. copper, 20% Apeizon L on 60/80 mesh Gas Chrom R
E	3 ft. x $\frac{1}{4}$ in. copper, 17% Didecyl phthalate on 60/80 mesh Gas Chrom R
F	3 ft. x $\frac{1}{4}$ in. copper, 18% Tricresyl phosphate on 60/80 mesh Gas Chrom R
H	3 ft. x $\frac{1}{8}$ in. aluminum, 2-2.5% SE-52 on 80/100 mesh DMCS-treated, acid-washed Chromosorb G

[a] Carrier gas was helium.

Nitrogen (Air Reduction Company) was further dried by passage through a column of sodium hydroxide pellets.

Methane (The Matheson Company) was of 99.99% purity and was used as received from the manufacturer.

Ethane was prepared[33] via hydrolysis of the Grignard of ethyl bromide and was used to determine its retention time only.

Propane, taken from the gas line in the laboratory, was estimated to be 96% pure by glc analysis and was used without further purification.

Methyl iodide (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.5298; lit.[34] n_D^{20}, 1.5297).

Methyl tosylate, prepared by the method of Roos[35], was available in the laboratory (n_D^{20}, 1.5189; lit.[36] n_D^{24}, 1.5170).

Ethyl iodide (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.511; lit.[34] n_D^{20}, 1.512).

Ethyl bromide (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.4238; lit.[37] n_D^{20}, 1.4239).

Ethyl tosylate (Eastman Kodak) was used without further purification (m.p., 32-34° C.; lit.[38] m.p., 33° C.)

n-Propyl iodide (Eastman Kodak) was used without further purification (n_D^{20}, 1.5054; lit.[34] n_D^{20}, 1.5051).

n-Propyl tosylate, prepared by the method of Roos[35], was available in the laboratory (n_D^{20}, 1.5070; lit.[39] n_D^{20}, 1.5077).

n-Propyl bromide (Eastman Kodak) was used without further purification (n_D^{20}, 1.4338; lit.[34] n_D^{20}, 1.4341).

Propene was prepared by the method of Waldmann[40] and was used to determine its retention time only.

n-Propyl chloride (Eastman Kodak) was distilled at 710 mm. and the fraction collected boiling from 44.5-45.0° C. (lit.[41] b.p., 46.6° C.)

Isopropyl iodide (Eastman Kodak) was used without further purification (n_D^{20}, 1.4995; lit.[34] n_D^{20}, 1.4997).

Isopropyl bromide (Eastman Kodak) was used without further purification (n_D^{20}, 1.4255; lit.[37] n_D^{20}, 1.4251).

n-Pentane was technical grade but was not distilled as the impurities present did not interfere with any product peaks in any of the chromatographic analyses performed.

Benzene was used without further purification (n_D^{20}, 1.5010; lit.[34] n_D^{20}, 1.5014).

Toluene was used without further purification (n_D^{20}, 1.4962; lit.[34] n_D^{20}, 1.4962).

p-Xylene was used without further purification (n_D^{20}, 1.4959; lit.[34] n_D^{20}, 1.4956).

Benzyl bromide (Eastman Kodak) was vacuum distilled, and the fraction boiling from 28-30° C. at 2 mm. (lit.[42] b.p., 199° C. at 760 mm.) was collected.

Benzyl chloride was vacuum distilled, and the fraction boiling from 60-61° C. at 10 mm. (lit.[42] b.p., 179° C. at 760 mm.) was collected.

p-Methylbenzyl chloride (K & K Laboratories) was vacuum distilled at 0.1 mm., and the fraction collected boiling from 40.3-42.0° C. (lit.[43] b.p., 202° C. at 760 mm.).

p-Chlorobenzyl chloride (Eastman Kodak) was used without further purification (m.p., 25° C.; lit.[44] m.p., 29° C.).

p-Chlorotoluene (Eastman Kodak) was used without further purification (n_D^{20}, 1.5208; lit.[34] n_D^{20}, 1.521).

p-Fluorobenzyl chloride (Pierce Chemical Company) was used without further purification (n_D^{20}, 1.5136; lit.[45] n_D^{20}, 1.5130).

p-Fluorotoluene (Eastman Kodak) was used without further purification (n_D^{20}, 1.4684; lit.[34] n_D^{20}, 1.470).

p-Nitrobenzyl chloride (Eastman Kodak) contained a small amount of an unidentified impurity which was removed by recrystallization from ethyl ether to give a white solid which melted between 72.5 and 73.0° C. (lit.[42] m.p., 71° C.).

p-Nitrotoluene (Eastman Kodak) was used without further purification (m.p., 52.9-54.0° C.; lit.[46] m.p., 51.3° C.).

o-Nitrotoluene (Eastman Kodak) was used without further purification (n_D^{20}, 1.5463; lit.[47] n_D^{20}, 1.5462).

p-Methoxybenzyl chloride was prepared by the method of Dankova[48] (n_D^{19}, 1.5490; lit.[49] n_D^{19}, 1.5492).

p-Methyl anisole (Eastman Kodak) was used without further purification (n_D^{20}, 1.5121; lit.[34] n_D^{20}, 1.512).

Anisole (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.5167; lit.[34] n_D^{20}, 1.517).

o-Fluoroiodobenzene (Columbia Organic Chemicals) was used without further purification (n_D^{25}, 1.5877; lit.[50] n_D^{25}, 1.580).

Fluorobenzene (Eastman Kodak) was used without further purification (n_D^{20}, 1.4650; lit.[34] n_D^{20}, 1.4646).

o-Nitroiodobenzene (Eastman Kodak) was used without further purification (m.p., 49.5-50.9° C.; lit.[51] m.p., 50-51° C.).

Nitrobenzene (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.5521; lit.[47] n_D^{20}, 1.5529).

Benzhydryl chloride (Eastman Kodak) was used without further purification (n_D^{20}, 1.5962; lit.[52] n_D^{20}, 1.5959).

Diphenylmethane (Fisher Scientific Company) was used without further purification (n_D^{26}, 1.5773; lit.[53] n_D^{26}, 1.575).

p-Nitrobenzhydryl chloride was prepared by first converting p-nitrodiphenylmethane into p-nitrodiphenylcarbinol by the method of Brittain[54]. The alcohol was then converted into the corresponding carbinyl chloride by the method of Altscher[55]. Although no physical measurements were made to determine the purity of the final product, an n.m.r. spectrum showed no unreacted alcohol present.

t-Cumyl chloride (common name to be used for 2-chloro-2-phenylpropane) was prepared by the method of Brown and Okamoto[56] and vacuum distilled at 0.1 mm. pressure. The fraction boiling at 29.3° C. was collected and gave a refractive index of 1.5233 at 20° C. (lit.[56] n_D^{20}, 1.5210).

Cumene was vacuum distilled at approximately 15 mm. pressure and the fraction boiling between 43.4° and 46.0° C. collected (n_D^{20}, 1.4922; lit.[34] n_D^{20}, 1.4930).

p-Nitrodiphenylmethane, prepared by the method of Baeyer and Villiger[57], was available in the laboratory (m.p., 29.3-30.8° C.; lit.[58] m.p., 31° C.).

Carbon tetrachloride (Fisher Scientific Company) was used without further purification (n_D^{20}, 1.4607; lit.[34] n_D^{20}, 1.4607).

Chloroform was used without further purification (n_D^{20}, 1.4451; lit.[34] n_D^{20}, 1.4467).

Ethylene chloride was used without further purification (n_D^{20}, 1.4445; lit.[34] n_D^{20}, 1.4443).

Methylene chloride was used without further purification (n_D^{20}, 1.4247; lit.[37] n_D^{20}, 1.4237).

C. Apparatus

The chromatograph primarily used in all the analyses was a Micro Tek DSS Series dual column, dual thermal conductivity detector model equipped with a manual (trajectory) programmer. The recorder employed with this instrument was a Honeywell Model 143X58 Electronik having a one second full-scale deflection time and equipped with a Disk Chart Integrator. A Perkin-Elmer Model 900 dual column gas chromatograph equipped with a 150 ft. capillary column and flame ionization detector was used in one analysis. Connected to this instrument was a Leeds & Northrup Speedomax G Model S 60000 Series recorder also having a one second full-scale deflection time and Disk Chart Integrator.

The gaseous products and co-products of all the analyses were measured using either a 100 or 500 cc., water-filled gas buret and reservoir which was attached to a "cold-finger" condenser *via* rubber tubing. These condensers, in turn, were attached to either 50 or 100 ml. stirred flasks, respectively, equipped with a single injection port. The combined volume of the flask, condenser, tubing, and buret empty, down to the zero mark of the buret, was known in all cases.

D. Procedures Used in Borohydride Reductions

1. General

Using the apparatus described on page 36, a solution of the halide in several milliliters of solvent was injected via syringe into a stirred flask under a dry-nitrogen atmosphere containing a solution of SBH in the same solvent. The cold-finger condenser was cooled only when either the starting material or the resulting product was volatile, and therefore, might be blown out of solution by hydrogen evolution caused by diborane hydrolysis. The reduction was terminated at the end of the allotted reduction period by adding usually a concentrated aqueous sodium hydroxide solution, or in certain cases when the substrate was base sensitive, a sodium chloride solution. The purpose of the base was to both stabilize the unreacted SBH and help "salt out" the solvent layer from the pentane layer used in extraction of the liquid reduction product. For several halides it was necessary to remove all unreacted SBH just prior to hydrolysis in order to quench the reduction immediately after a given amount of time had elapsed. This was done by adding excess methyl iodide in a small amount of solvent to the reaction flask followed by hydrolysis as usual. The pentane layer containing the reduction product (and internal standard where applicable) was separated from the solvent layer and then analyzed by glc on one of the columns shown on page 31.

Gaseous reduction products were analyzed exclusively by the external standard method using a standard solution of the gaseous hydrocarbon in either nitrogen or air.

2. Monohaloalkanes

Reduction of Methyl Iodide in Anhydrous DMSO

To a 50 ml. stirred flask maintained at room temperature and fitted with a cold-finger condenser at -78° C., was added a solution of 15 ml. of DMSO and 0.12 g. (3.0 mmole) of SBH. In approximately 2 ml. of DMSO was injected 0.1240 g. (0.88 mmole) of methyl iodide. After 15 minutes 45 ml. of gas had evolved, and 1 ml. of aqueous NaOH was added to hydrolyze any diborane formed, as it was apparent that the reduction had ceased (evidenced by no further gas evolution from the reaction solution). This resulted in a final, net gas volume of 100 ml. (calculated, 80 ml.) upon warming the condenser to room temperature and washing with several ml. of DMSO. After mixing the collected gases with a syringe, several 2 ml. aliquots were analyzed on column M.S. at a flow rate of 45 ml. per minute and column temperature of 80° C. Analysis showed a methane yield of 96%.

Reduction of Methyl Tosylate in Anhydrous DMSO

In three separate trials methyl tosylate was reduced to methane using a constant SBH to tosylate ratio of 4.5:1. All reaction and chromatographic conditions and method of work-up were the same as those used in the reduction of methyl iodide except that the condenser was not cooled because of the high boiling point of the tosylate. After noting an apparent cessation in the reduction after the first 20 minutes, final, net gas volumes of 116, 103, and 112 ml. (calculated, 80 ml.), respectively, were recorded following hydrolysis, as were methane yields of 70, 92, and 89%. The average of the last two trials is shown in Table II on page 17.

Reduction of Ethyl Iodide in Anhydrous DMSO

Duplicate trials were performed using a 5:1 ratio of SBH to halide under identical conditions as those described for methyl iodide, but with a reduction time of 1.5 hours instead of 15 minutes. The observed net gas volumes were 101 and 103 ml. (calculated, 80 ml.). The reduction product ethane was analyzed on column P at 0° C. with a flow rate of 29 ml. per minute. Both trials gave ethane yields of 96% using propane standards accordingly adjusted as previously described (see p. 18).

Reduction of Ethyl Bromide in Anhydrous DMSO

Ethyl bromide was similarly reduced to ethane in 2 hours under identical conditions as those described for ethyl iodide. The observed, net gas volumes were 96, 100, and 105 ml. (calculated, 80 ml.) for the three trials, and the ethane yields were 90, 100, and 100%, respectively.

Reduction of Ethyl Tosylate in Anhydrous DMSO

In the first of two trials performed using the same 5:1 SBH to halide ratio, ethyl tosylate in a solution of DMSO and SBH was heated to 41° C. for 45 minutes and to 53° C. for an additional 1.5 hours to give a net gas volume of 97 ml. (calculated, 84 ml.) and an ethane yield of 98%. The flask was heated for only 65 minutes at 53° C. in the second trial to give a volume of 100 ml. and a yield of 93% ethane. The average of these trials is given in Table II.

Reduction of n-Propyl Iodide in Anhydrous DMSO

The reduction of *n*-propyl iodide to propane was performed using the same apparatus and SBH to halide ratio as described for the C_1 and

C_2 derivatives, but with the flask and condenser maintained at room temperature. After approximately 50 minutes, the reduction was stopped and analyzed on column P at 25° C. with a flow of 29 ml. per minute. Net gas volumes of 105, 123 ml. (calculated, 106 ml. for 1 mmole of halide), 114, and 103 ml. (calculated, 80 ml. for 0.75 mmole of halide) and yields of 83, 87, 89, and 89% were observed, respectively, for the four trials performed. In no case was propene observed, as established by the absence of a peak in the chromatogram corresponding to the retention time of pure propene prepared by an independent method[41].

Reduction of n-Propyl Bromide in Anhydrous DMSO

The reduction of *n*-propyl bromide to propane was affected in 2.5 hours under the same conditions as described for methyl iodide. Net gas volumes of 95 and 92 ml. (calculated, 79 ml.) and yields of 93 and 89%, respectively, were observed for the two trials performed. Propene again was not detected.

Reduction of n-Propyl Tosylate in Anhydrous DMSO

In three separate trials using the same ratio of reducing agent to organic substrate, *n*-propyl tosylate was reduced to propane in reduction times varying from 1 to 1.5 hours, depending on the temperature of the reaction flask. In the first trial the flask was not heated for the first 20 minutes but was heated to 53° C. for another hour to give a resulting net gas volume of 88 ml. (calculated, 79 ml.) and a propane yield of 78%. The second trial was performed exactly as the first trial for a total of 1.5 hours to give a gas volume of 78 ml. (calculated, 82 ml.) and a propane yield of 90%. In a third and final trial, after continuously heating the flask at 43° C. for 1 hour, the gas volume was 81 ml. and the propane yield was again 90%. The average of only the last two trials is shown in Table II on page 17.

Reduction of n-Propyl Chloride in Anhydrous DMSO

The flask was continuously heated in the two trials performed at 35-40° C. for 8 and 22 hours, respectively, to give net gas volumes of 20 ml. (calculated, 80 ml.) in each case and propane yields of 18 and 13%. No propene was observed in either trial.

Reduction of Isopropyl Iodide in Anhydrous DMSO

The reduction of isopropyl iodide to propane in 93% yield was affected in 2.5 hours with the entire system (flask and condenser) at room temperature. The rate of gas evolution was approximately 1 ml. per minute, and the net gas volume at the end of the reduction period was 87 ml. (calculated, 78 ml.). Again, the presence of propene could not be detected. A second trial with the flask at 41° C. for 75 minutes gave a net gas volume of 94 ml. and a propane yield of 96%.

Reduction of Isopropyl Bromide in Anhydrous DMSO

In the first of three trials performed, the flask was not heated for the first 20 minutes of the reduction, but due to no appreciable gas volume change, the reaction temperature was raised to 41° C. and the condenser packed for the next 8 hours. At the conclusion of this period, the net gas volume was 77 ml. (calculated, 90 ml.), and the propane yield was 65%. With the condenser now at room temperature and the flask again at 41° C., no further appreciable reduction occurred after an additional 14 hours. The final corrected gas volume and propane yield were 101 ml. and 69%, respectively. After heating the flask for 20 hours at 41° C., a net corrected gas volume of 107 ml. (calculated, 77 ml.) and a propane yield of 79% were obtained for the second trial. A third reaction yielded a gas volume of 95 ml. and a propane yield of 73%. The average of the first and third trials is shown in Table II.

Reduction of Methyl Iodide in Anhydrous Diglyme

Using a 1:1 SBH to halide ratio under identical conditions as described for the same reduction in DMSO, methyl iodide was reduced in 20 minutes to give a 96% yield of methane and a net gas volume of 266 ml. (calculated, 266 ml. for 4 mmole of halide). A duplicate trial yielded a gas volume of 275 ml. and a methane yield of 89%. The average is given in Table III.

Reduction of Ethyl Bromide in Anhydrous Diglyme

In the first of four trials performed, ethyl bromide was reduced in 5 hours to give a 70% yield of ethane and a net gas volume of 60 ml. (calculated, 80 ml. for 0.8 mmoles of halide). A second trial under the same conditions gave a gas volume of 235 ml. (calculated, 270 ml. for 4 mmole of halide) and an ethane yield of 61%. The third trial used a 2:1 SBH to halide ratio instead of the 1:1 ratio used in the first trial, and the flask was heated at 30° C. for 5.5 hours of the 7 hour reduction period. A final net gas volume of 80 ml. (calculated, 84 ml.) and an ethane yield of 70% were realized. The fourth trial utilized a 5:1 SBH to halide ratio with the flask at room temperature to give after three hours a gas volume of 58 ml. (calculated, 80 ml.) and an ethane yield of 65%. The average of the first, third, and fourth trials, is given in Table III on page 19.

Reduction of Ethyl Iodide in Anhydrous Diglyme

Using a 1:1 ratio of SBH to halide, ethyl iodide was reduced in 2 hours to ethane in 56% yield accompanied by a net gas volume of 101 ml. (calculated, 88 ml.). A second trial using a 2:1 ratio in approximately the same time period yielded 89% ethane and a gas volume of 164 ml. (calculated, 88 ml.). A third trial identical to the second one gave an observed gas volume of 134 ml. and a ethane yield of 88%. The average of the second and third trials is shown in Table III.

3. Benzylic Halides

Reduction of Benzyl Bromide in Anhydrous DMSO

To a 100 ml. stirred flask maintained at room temperature and fitted with a cold-finger condenser at -78° C., was added 30 ml. of a solution of 0.32 g. (8.0 mmole) of SBH in dry DMSO. A solution of 0.6927 g. (4.04 mmole) benzyl bromide and 0.3098 g. (3.98 mmole) benzene (internal standard) in 12 ml. DMSO was then added. The initial rate of gas evolution was 13 ml. per minute, and after 12 minutes a net gas volume of 95 ml.* had been collected. In 50 minutes the volume was 108 ml. prior to hydrolysis by the addition of 20 ml. of aqueous NaOH solution (pH > 11.5), after which the resulting net gas volume was 256 ml. (calculated, 330 ml.). After warming and washing the condenser with 15 ml. of pentane, the reaction mixture was transferred to a separatory funnel and extracted twice more with 10 ml. portions of pentane. The upper pentane layer when separated from the lower DMSO-water layer measured 27 ml. and

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*The volume of gas produced may vary slightly due to the gradual hydrolysis of diborane caused by the extremely hydroscopic nature of DMSO and diglyme.

was analyzed by the internal standard method on column D at 65° C. using a flow rate of 95 ml. per minute. Comparison of the peak areas of the product and internal standard with a standard solution of toluene and benzene in ethyl ether showed 100% reduction of the bromide to toluene. A duplicate trial also indicated complete reduction.

Reduction of Benzyl Chloride in Anhydrous DMSO

Utilizing the same procedure and conditions as described for the bromide, benzyl chloride was reduced in 4.5 hours to give an 86% yield of toluene and a net gas volume of 181 ml. (calculated, 323 ml.). Two additional, identical trials gave gas volumes of 198 and 178 ml., respectively, and toluene yields of 95 and 86%. The average of the first and third trials is shown in Table IV.

Three one-hour trials were run under the same conditions using the same procedure to give net gas volumes of 118, 127, and 89 ml. (calculated, 327 ml.), respectively, and toluene yields of 50, 59, and 48%. The first and third values were averaged to give the value shown in Table IV. Finally, in two more identical trials, benzyl chloride was shown to be reduced to only a 10% extent in 6 minutes.

Reduction of Benzyl Chloride in Anhydrous Diglyme

Under the same conditions and work-up used in DMSO, two separate reductions lasting 6 minutes and 1 hour gave respective yields of 1 and 6% as calculated by the internal standard method.

Reduction of Benzyl Chloride in Aqueous Diglyme

In one hour under the usual conditions using a solvent system of 80% diglyme-20% water (vol.%), benzyl chloride was reduced in 8% yield to toluene with an 88% recovery of unreacted chloride as determined by the internal and external standard methods, respectively.

Reduction of p-Methylbenzyl Chloride in Anhydrous DMSO

p-Methylbenzyl chloride was reduced in 1 hour under the same conditions using the same work-up procedure as for the unsubstituted bromide and chloride to give a 56% yield of *p*-xylene and a net gas volume of 169 ml. (calculated, 325 ml.). The internal standard was toluene, and the analysis was performed using column D at a temperature of 90° C. and flow rate of 57 ml. per minute. Another duplicate trial gave a gas volume of 171 ml. and *p*-xylene yield of 55%.

Reduction of p-Chlorobenzyl Chloride in Anhydrous DMSO

In the same manner as the *p*-methyl derivative, *p*-chlorobenzyl chloride was reduced in 1 hour at room temperature to give a 67% yield of *p*-chlorotoluene and a net gas volume of 104 ml. (calculated, 354 ml.). A duplicate trial showed a gas volume of 112 ml. (calculated, 324 ml.) and a product yield of 69%. *p*-Xylene was the internal standard used in both trials, and the analyses were performed using column D at a temperature of 125° C. and flow rate of 55 ml. per minute.

Reduction of p-Fluorobenzyl Chloride in Anhydrous DMSO

As with the other *para*-substituted compounds, *p*-fluorobenzyl chloride was reduced in 60% yield to *p*-fluorotoluene in 1 hour at room temperature. The accompanying net gas volume was 172 ml. (calculated, 333 ml.). In a duplicate trial, a 58% yield and 151 ml. gas volume (calculated, 324 ml.) were realized by analysis with column D at a temperature of 103° C. and flow rate of 55 ml. per minute. The internal standard employed in both instances was *p*-xylene.

Reduction of p-Nitrobenzyl Chloride in Anhydrous DMSO

p-Nitrobenzyl chloride was reduced, using the same previously described procedure, to p-nitrotoluene in 94% yield in 1 hour at room temperature. The net gas volume was 338 ml. (calculated, 330 ml.), and the analysis was performed using column D at 155° C. and a flow rate of 55 ml. per minute. A duplicate trial gave a 93% yield of product and a gas volume of 312 ml. The internal standard was o-nitrotoluene.

Although the p-nitrobenzyl chloride appeared pure (m.p., 72.0-72.7° C.; lit.[42] m.p., 71° C.) as it came from the manufacturer, an unidentified impurity was present as the clear solutions of SBH in DMSO turned a vivid violet-blue color upon addition of this particular halide and remained colored for 10-12 minutes. It was at first believed that the coloration was due to an intermediate (perhaps a carbanion or radical anion), but all attempts to "trap" the proposed intermediate isotopically or to view it spectroscopically (e.s.r.) failed. Furthermore, four recrystallizations of the halide from ethyl ether produced a white solid (previously pale yellow) which failed to produce any colored solutions and which gave product yields that were in excellent agreement with those reported above. Because this impurity had apparently not interfered with the reduction, no further attempts to isolate and identify it were made.

Due to the much higher yield of the correspondingly-substituted toluene obtained from this halide after 1 hour as compared to those obtained from the other para derivatives, the reduction time was accordingly reduced to 6 minutes in order better to estimate its relative reactivity. A methyl iodide quench followed by the usual work-up produced a yield of 19% p-nitrotoluene.

Reduction of p-Nitrobenzyl Chloride in Anhydrous Diglyme

Only one trial was performed in diglyme, and after 1 hour under the same previously described conditions used for DMSO, a 48% yield of the substituted toluene was realized.

Reduction of p-Methoxybenzyl Chloride in Anhydrous DMSO

Utilizing the same conditions and work-up as described for the other benzyl halides, p-methoxybenzyl chloride was reduced in 1 hour at room temperature to p-methoxyanisole in 88% yield with a net gas volume of 172 ml. (calculated, 330 ml.). A duplicate trial afforded an 86% yield and a gas volume of 164 ml. The average yield is given in Table IV on page 21.

Two subsequent six-minute trials employing a methyl iodide quench in both anhydrous DMSO and 80% DMSO-20% water (vol.%) followed by the usual work-up gave respective yields of 24 and 47%. All analyses were determined using column D at 140° C. and a flow rate of 55 ml. per minute with anisole as the internal standard.

4. Secondary and Tertiary Halides

Reduction of Benzhydryl Chloride in Anhydrous DMSO

Using previously described conditions and work-up, benzhydryl chloride was reduced to diphenylmethane in 2% yield after 1 hour with the system at room temperature. The net gas volume was 9 ml. (calculated, 322 ml.). The analysis was performed using the external standard method on column D at a temperature of 200° C. and flow rate of 55 ml. per minute.

Reduction of p-Nitrobenzhydryl Chloride in Anhydrous DMSO

Under the usual conditions and method of work-up, *p*-nitrobenzhydryl chloride was reduced in 1 hour at room temperature to *p*-nitrodiphenylmethane in 7% yield with a net gas volume of 33 ml. (calculated, 160 ml.). As in the case of the impure *p*-nitrobenzyl chloride, this halide also produced a highly colored solution (deep red). No attempt was made to determine the origin of the color. The single analysis was performed using column H at a temperature of 180-205° C. (manual program) and a flow rate of 25 ml. per minute in conjunction with an external standard.

Reduction of t-Cumyl Chloride in Anhydrous DMSO

t-Cumyl chloride was reduced under the usual conditions and method of work-up to cumene in 1% yield in 1 hour at room temperature. Methyl iodide was employed to destroy any unreacted SBH just prior to the work-up. Analysis was by the external standard method on a 150 foot fluorosilicone-coated (QF-1) capillary column at a temperature of approximately 80° C.

Reduction of o-Fluoroiodobenzene in Anhydrous DMSO

o-Fluoroiodobenzene was reduced to fluorobenzene in 14% yield in 1 hour at room temperature using the same 2:1 SBH to halide ratio and work-up employed for the benzyl systems. Product analysis was on column D using a programmed temperature range of 65-100° C. and flow rate of 55 ml. per minute with toluene as the internal standard. Analysis on the same column using the same flow rate but employing a column temperature of 175° C. showed an 87% yield of unreacted starting material.

Reduction of o-Nitroiodobenzene in Anhydrous DMSO

From the reduction of o-nitroiodobenzene in 1 hour at room temperature under the same reaction conditions and method of work-up employed for the o-fluoroiodo compound, an 80% yield of nitrobenzene was realized. However, the bright yellow color of the DMSO-water layer after having extracted as usual with pentane indicated that the extraction was apparently incomplete. Therefore, the residual nitrobenzene was extracted with seven 30 ml. portions of ethyl ether in which it was more soluble. The final product yield was 90%. Analysis was on column D at a temperature of 180° C. and flow rate of 33 ml. per minute with p-nitrotoluene as the internal standard.

5. Polyhalomethanes

Reduction of Carbon Tetrachloride in Anhydrous DMSO

In the first of two identical trials, carbon tetrachloride was reduced in 1 hour at room temperature to 35% methylene chloride and 52% chloroform, no unreacted tetrachloride having been detected. Water was used as usual to hydrolyze the diborane formed, but the extracting solvent was ethyl ether instead of pentane. The accompanying net gas volume was 173 ml. (calculated, 167 ml.). A second trial afforded 24 and 61% yields of methylene chloride and chloroform, respectively, and the same gas volume as in the first trial.

A third trial was performed under the same conditions as the first two, except that a methyl iodide quench was used prior to hydrolysis to remove any unreacted SBH. The following yields were realized: 2-4% methylene chloride, 26% chloroform, and 67% unreacted carbon tetrachloride. A fourth and final trial identical to the third was performed and gave the following results: no detectable methylene chloride, 29% chloroform, and 73% unreacted carbon tetrachloride. All four trials employed ethylene chloride as the internal standard with analyses having been done on column F at a temperature of 73° C. and flow rate of 50 ml. per minute. The averages of the two sets of trials are shown in Table VIII on page 28.

V. DISCUSSION OF RESULTS AND CONCLUSIONS

Mechanism

With the exception of carbon tetrachloride and, perhaps, aryl halides, all the compounds studied are presumed to undergo reduction with SBH by an S_N2 displacement on carbon. It was mentioned earlier that the mechanism of halide reductions with LAH had been widely investigated and was definitely known to be S_N2 in nature[3,4,5]. As can be seen in the generalized equation below for the stoichiometry of a hydride reduction, the species involved are analogous[3]:

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

Therefore, although no work has been done on the reduction of optically active compounds with SBH, it is still felt that the mechanisms are identical. Further proof of this will be discussed later in context with the benzyl system.

Monohaloalkanes

The reduction of the simple monohaloalkanes with SBH as reported in this thesis is in full agreement with the work of Pearson and Adams[6] and Brown[11], both of whom studied the SBH reduction of methyl chloride as a typical monohaloalkane[*]. Pearson and Adams further stated that bromides were more reactive than chlorides, and lengthening the carbon

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[*] Only methyl iodide and methyl tosylate were examined in our series as the other methyl halides were gases and would have posed more experimental problems.

chain decreased the reactivity of the halide. These two points are, perhaps, not quite as well exemplified as had been hoped for the C_1-C_3 *primary* halides shown in Table II (page 17). The methyl, ethyl, and *n*-propyl iodides, tosylates, and bromides are all within 6-7% of one another, and since the percentages given throughout the thesis are estimated to have an accuracy of ±3%, some overlap is possible. These observed differences should have been much larger, had a constant reduction time based on the reactivity of the most reactive halide, methyl iodide, been established. However, ignoring overlap for the moment, the decreases in yield between the C_2 and C_3 primary iodides, tosylates, and bromides could be attributed to increasing steric hinderance about the central carbon atom. For it is well known that in direct displacement reactions, an increase in the degree of alkyl substitution about the central carbon "...results in a substantial decrease in displacement rate"[59]; e.g., relative rates for direct displacement for the series methyl, ethyl, *n*-propyl may vary in the ratio 4-150:1-1.5:1[60]. Streitwieser states that the best explanation for this phenomenon thus far in the case of simply alkyl halides "...must be due to an overriding [relative to electronic effects] steric hindrance"[61]. However, Hammett[62] and co-workers point out that the usual decrease in reactivity shown by *n-propyl* halides is primarily due to a decrease in the entropy of activation.

The effect of the leaving group for primary halides as shown in the same table seems to follow the order in DMSO, $Ts^- \gtrsim I^- > Br^- >> Cl^-$. The low yield (16%) of propane obtained from the reduction of *n*-propyl chloride can be due solely to neither the steric hinderance of the alkyl group nor to entropy effects, as n-propyl iodide and bromide both gave very high yields, but must rather be due to a powerful leaving-group effect. Similarly the large difference in the degree of reduction of isopropyl iodide (94%) and isopropyl bromide (71%) in DMSO cannot be due solely to steric hinderance and electronic effects because of the identical alkyl group involved. This, then, also indicates another leaving group effect of considerable magnitude, both of which could be explained, perhaps, as occurring by a combination of effects, such as an increased carbon-halogen bond strength, decreased halogen polarizability, and increased steric hinderance.

Finally, no elimination product was observed from the reduction of either of the above simple, secondary alkyl halides even as the leaving group was made successively poorer and the corresponding yield of the saturated product was seen to decrease. This further supports the proposed mechanism for these reductions as being S_N2 and not S_N1. The other more complex secondary halides prepared will be discussed later as being α-substituted benzyl halides.

Table III (page 19) shows the results of three selected, simple monohaloalkanes reduced in anhydrous diglyme to study the effect of solvent. Methyl and ethyl iodide were reduced 4 and 8% less, respectively, in diglyme under the same conditions in the same amount of time as they were in DMSO. These differences are, again, within experimental error. Ethyl bromide was reduced 27% less in diglyme in twice the time at a temperature (30° C.) slightly above the room temperature (25° C.) conditions employed for DMSO. Because both ethyl iodide and ethyl bromide were reduced to exactly the same extent (96%) in DMSO, and ethyl iodide was reduced 20% more than the bromide in half the time in diglyme, it appears that the solvent is slightly enhancing the difference in "leaving-group ability" between these two groups as the alkyl group is successively substituted by β-methyl groups. However, as will be mentioned later in more detail under a discussion of "Solvent Effects", S_N2 reactions in dipolar, aprotic solvents are subject to variable rates depending on the dipole moment and dielectric constant of the solvent chosen, among other factors. Hence, it is felt that the difference in yield of 27% in the two solvents is not unexpected and represents no major difference.

para-Substituted Benzyl Halides

Generally speaking, "When the carbon atom attached directly to the reaction center is unsaturated, a marked increase in reactivity is observed,"[63] as exemplified by the fact that benzylic halides are at least equal to if not more reactive than their corresponding methyl halides toward nucleophilic bimolecular substitution[64]. This increased reactivity has been visualized as being due to the sp^2 instead of sp^3 character of the carbon attached to the reactive center (α-carbon). Sterically the sp^2 orbital would offer less hinderance toward the attacking and leaving nucleophiles in the transition state than would the sp^3 orbital. Stabilization by overlap of the orbital by which the two nucleophiles are transiently bound with the "p" orbital on the adjacent carbon atom may also be important[63].

The results of the reduction of a series of p-substituted benzyl halides is shown in Table IV (p. 21). This series was chosen to examine the effect of the systematic variation of the following four parameters on the rate of halide reduction (actually observed as a product yield within a fixed time interval):

1) leaving group
2) para substituent
3) reductive selectivity of SBH
4) solvent

The order of "leaving group ability" was clearly $Br^- > Cl^-$ for the two unsubstituted halides reduced, and it was felt that the extended order listed for the simple monohaloalkanes was applicable to the benzyl series.

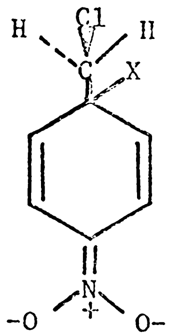
Of more importance was the effect of the para substituent on the rate of reduction of a series of para-substituted benzyl chlorides. However, as Hine notes,

> "Because of the complications produced by the possibility of steric interference with the attack of the nucleophilic reagent, of steric acceleration of the departure of the group displaced, and of entropy effects due to interference with rotation around single bonds and changes in the extent of solvation, it is very difficult to learn what influences electronic effects have on the S_N2 reactivity of alkyl halides and even more difficult to predict the reactivity that will result from the addition of an electronic effect to the other effects described."[65]

Nevertheless, a considerable effort in this area has been made by many investigators with regard to the benzyl system[64,66], and the results generally tend to indicate that electron-withdrawing substituents are rate enhancing whereas electron-donating group are rate retarding under S_N2 conditions. Hine, using the explanation of Swain and Langsdorf[67], rationalizes this finding by stating that, if in the transition state the new bond has been formed to the attacking nucleophile to a greater extent than the old one to the departing group has been broken,

> "...the alkyl group will be more negative than it was in the reacting molecule, and the reactivity will be increased by electron-withdrawing substituents, since substituents of this type are stabilized by being made negative. On the other hand, if the old bond has been broken to a greater extent than the new one has been formed, the alkyl group will be more positive in the transition state, and the reactivity will be increased by electron-donating groups, since these groups tend to be positive."[68]

Therefore, it should be clear that "...the reactivity of a compound for which bond making and bond breaking have proceeded to an approximately equal extent in the transition state may be increased by either type of group..."[68] The fact that most activating-group effects are small is in good agreement with the results shown in Table IV (p. 21) as the yields obtained for benzyl, *p*-fluorobenzyl, and *p*-methylbenzyl chloride utilizing the same reduction time and conditions were all within experimental error. The same cannot be said for the *p*-chloro, *p*-nitro, and *p*-methoxy compounds, as they showed increases in reduction of 20, 38, and 42%, respectively, over the unsubstituted chloride. The first two of these three compounds seem to be following the previously mentioned observation that the greater the electron-withdrawing effect of the group, the greater the rate of displacement of the leaving group (actually manifested as an increase in product yield). At the same time, the activating effect of the *p*-chloro and *p*-nitro groups further support an S_N2-type mechanism, as Brown[69,70] and co-workers earlier found that these two substituents were correspondingly deactivating under S_N1 conditions. Similarly, they found that *p*-methyl[71] and *p*-methoxy substituents caused respective rate increases relative to hydrogen of 26 and 3360 fold. Therefore, the only substituent which appears to be behaving anomalously in our series is the *p*-methoxy group, as it should have produced a considerably lower yield compared to the unsubstituted chloride, which it did not. The paradox, then, that seemingly exists between the fact that equally high yields of product were obtained from both the *para*-substituted methoxy compound and the nitro compound, even though the substituents, themselves, exactly oppose one another with respect to their electronic effect can, perhaps, only be explained by invoking the assumption that bond rupture and bond formation in the transition state must proceed to an approximately equal extent for both these substituted halides during reduction. The same reasoning should also hold true for the benzyl, *p*-methylbenzyl, and *p*-fluorobenzyl chlorides as these were very close to one another regarding percentage yield. Streitwieser[72] has suggested that structures such as the one shown below where "neighboring orbital overlap" might play an important role could account for the unusually large activating effect of the nitro substituent in benzyl systems:



X = entering nucleophile

Also shown in Table IV are the results of several six-minute trials run in anhydrous DMSO, and which agree reasonably well with the one-hour trials performed, in that both sets of trials indicate that the *p*-nitro and *p*-methoxy derivatives are reduced to almost twice the extent of benzyl chloride in identical time periods. The 42% decrease in yield when diglyme was employed for the reduction of the p-nitro compound is not thought to be extreme due to the differences in DMSO and diglyme regarding their "solvating power" as measured by the different dielectric constants and dipole moments of each. This matter will be discussed later under "Solvent Effects".

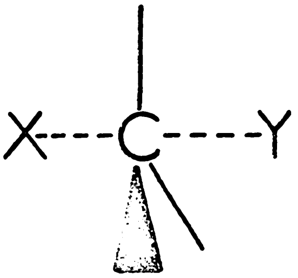
Secondary and Tertiary Alkyl Halides

The reduction of the two secondary and one tertiary halide shown in Table VI (page 25) illustrates the drastic decrease in yield, and therefore reaction rate, obtained when successive substitutions are made for the two alpha hydrogens of benzyl chloride. For as Hine[68] states, "...since the α-carbon atom is bound [to both the entering and leaving group] by relatively short, partial covalent bonds in the S_N2 transition state, the reaction rate is quite sensitive to steric hindrance." The established order of reactivity, namely, 1° > 2° > 3°, seen in comparing the benzylic halides to the secondary and tertiary halides mentioned above, is in direct agreement with the already well-known results for S_N2 displacements on carbon. Disregarding any possible overlap of the percentage yields listed due to experimental error, the slight increase found in the reduction of p-nitrobenzhydryl chloride relative to benzhydryl chloride is attributed to the electron-withdrawing effect of the nitro group, which would influence the charge distribution in the transition state in the same manner as previously discussed for p-nitrobenzyl chloride (55-56). As mentioned in the experimental section of the thesis (p. 48), the red-colored solution that appeared during the reduction of the p-nitrobenzhydryl compound was most likely due to an impurity in the starting material.

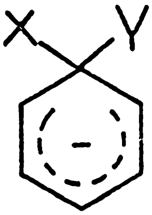
Aryl Halides

In a review on nucleophilic aromatic substitution reactions, Bunnett[73] states that, "The vast majority of aromatic nucleophilic substitution reactions display kinetics and response to structural and environmental factors which indicate a bimolecular mechanism [as opposed to a unimolecular mechanism which is known in a few selected cases] according to criteria stated by Hughes."[74]

Unlike the usual model of an S_N2 transition state proposed for displacement at a saturated carbon atom (case I), in which the central carbon atom possesses bipyramidal geometry, the transition state for bimolecular nucleophilic aromatic substitutions is thought to involve a tetrahedral central carbon atom and a loss of resonance due to charge dispersal over the ring as shown (case II)[75]:



Case I



Case II

X = attacking nucleophile

Y = leaving group

Therefore, as case II clearly illustrates, electron-withdrawing substituents should aid in the negative charge delocalization and increase the rate of displacement of Y^-. This is, indeed, so, "...provided these [activating groups] are located in either the ortho or para positions, or both."[76] Bunnett also notes that, "The many studies of the comparative displaceability of the halogen in various aromatic nucleophilic substitution reactions make it abundantly clear that the four halogens do not stand in any constant order of replaceability."[77] In fact, the invariable order of $I^- > Br^- > Cl^- >> F^-$ of alkyl halides is frequently reversed for aryl halides indicating that the electronegativity of the halogen, not the carbon-halogen bond strength, is more important in determining the order of dehalogenation.

Bunnett[78] has recently proposed another S_N2-type mechanism for aryl halide substitutions which involves a postulated "on halogen" displacement instead of the usual "on carbon" mode of attack, as given below:

1) $t\text{-BuO}^- + CH_3S(O)CH_3 \rightleftarrows t\text{-BuOH} + CH_3S(O)CH_2{:}^-$

2) $CH_3S(O)CH_2{:}^- + ArX \rightarrow Ar{:}^- + CH_3S(O)CH_2X$

3) $Ar{:}^- + t\text{-BuOH} \rightarrow ArH + t\text{-BuO}^-$

4) $\text{base} + CH_3S(O)CH_2X \rightarrow X^- + ?$ (no detectable organic products)

The order of decreasing ease of dehalogenation was $I^- > Br^- > Cl^-$ and it was found that less easily displaced halogens and other electron-withdrawing groups in the positions ortho and para to the most reactive halogen (based on the above order) greatly facilitated the dehalogenation[79], in agreement with Roberts. As mentioned earlier, the work of Karabatsos and Shone[20] also supported both this same order of halogen reactivity and the effect of other ring substituents on dehalogenation. They specifically noted that except for unsubstituted iodides, the bromides and chlorides required ortho- and para-activating, electron-withdrawing groups to achieve good yields, and that even in the presence of such groups, chlorides gave low yields.

Based on the above information, two selected *ortho*-substituted aryl iodides, *o*-fluoroiodo- and *o*-nitroiodobenzene, were chosen for study by this laboratory. It was hoped that the products from the reduction of the former compound would help establish an order of dehalogenation, while the latter one should serve to examine the influence of a change in the electron-withdrawing ability of another substituent on the ring. *Ortho* substitution was chosen primarily because of the success Karabatsos had had using LAH, as mentioned above. Table VII (p. 26) shows the results, namely, that iodide is a better leaving group than fluoride, and that the more electron-withdrawing the *ortho* substituent, the faster the reduction.

These results tend to support the "on halogen" mechanism of Bunnett rather than the usual "on carbon" displacement, as not only was the order of dehalogenation the same, but also no iodobenzene was detected as would have been expected from a normal S_N2 attack on carbon.

Polyhalomethanes

The mechanism of the reduction of carbon tetrachloride by SBH is unclear at the moment, for water apparently catalyzes the reduction in some as yet unknown manner. Table VIII on page 28 shows the differences in yields obtained for the resulting two* major reduction products with and without a methyl iodide quench prior to hydrolysis. When the excess SBH was destroyed with methyl iodide and the diborane hydrolyzed, a 28%

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*Methyl chloride and methane were detected in trace amounts.

yield of chloroform, 1-2% yield of methylene chloride, and 70% yield of unreacted starting material were realized. The direct hydrolysis without using methyl iodide gave yields of 56 and 30%, respectively, of chloroform and methylene chloride, but no unreacted carbon tetrachloride. Furthermore, it has been demonstrated in both aqueous and anhydrous DMSO that chloroform alone will not undergo further reduction to methylene chloride or any of its subsequent reduction products[80]. Therefore, the question is one of how does water increase the yield of both chloroform and methylene chloride, especially since the latter compound is not produced using chloroform as the starting material?

Although the exact mechanism remains as yet unsolved, the absence of larger amounts of methyl chloride and methane tend not to support an S_N2 displacement on carbon, since the large amount of chloroform produced should have undergone further reduction to the tri- and tetrahydro products as the steric hinderance about the carbon atom became progressively less. This question and others will require further investigation.

Solvent Effects

One reason that DMSO and diglyme were chosen as solvents was because both are aprotic, a necessary criterion for the stability of SBH in them. In addition, SBH is soluble in both at room temperature in concentrations up to approximately 1.6 M. Furthermore, several workers[31,81] have recently reported that S_N2 reactions run in dipolar, aprotic solvents exhibited rate increases of 10^3-10^{10} fold over the usual protic solvents such as water and the lower molecular weight alcohols. Delpuech and Pascal[82] further substantiated this finding by their observation that the activation energies required in S_N2 reactions decreased from 20-21 Kcal/mole to 16-17 Kcal/mole (occasionally as low as 13 Kcal/mole) in changing from protic to aprotic solvents. Based on this information, it was felt that solvents such as these would aid in enhancing the yields of reduction products obtained from the halides to be studied in our investigation.

Because DMSO and diglyme are sometimes referred to as "electron-donating" solvents, one might expect that anions would be poorly solvated in such solvents, whereas cations should be solvated extremely well. This, indeed, is the case. Thus, the reactivity of the BH_4^- anion should be at a maximum due to the preferred solvation of its sodium cation, leaving the anion relatively "bare" and in a very reactive state[83]. Chan and Smid[84,85] have recently found supporting evidence for this idea in both DMSO and diglyme using the 9-fluorenyl salts of sodium and lithium, which were shown to exist as "solvent-separated" ion pairs in these two solvents. Only one solvent molecule of either DMSO or diglyme was demonstrated as actually separating the ion pair, and in the case of diglyme, the coordinating ability of oxygen toward lithium was considerably greater than toward sodium[86].

The large rate increases in changing from protic solvents to DMSO, for example, could possibly be attributed to the above selective solvation effect and to the fact that DMSO can "...solvate extended charged structures such as transition states"[87], or to a combination of these effects. The same combination of effects should hold true between DMSO and diglyme as it is known that a solvent's "ion solvating power" is a function of several factors, two of which are its dielectric constant and dipole moment, as mentioned earlier. Furthermore, solvation increases with <u>increasing</u> dipole moment[88]. The dielectric constants of DMSO and diglyme at 25° C. are approximately 48[89] and 7[90], respectively, while their dipole moments also differ widely, being 4.3 D[89] and 1-2 D*, in like order.

Conclusions

As mentioned in the "Introduction," the goal in preparing this manuscript was to supply a definite answer to the question of whether or not SBH would reduce organic halides and their related derivatives, especially primary alkyl and aryl halides, and to extend this to a consideration of the necessary structural criteria, if any, for reduction to occur. The results of this investigation (Tables I-VIII) have shown that SBH is an excellent reducing agent for most simple, primary iodides, tosylates, and bromides, usually providing yields of 70-100% at room temperature in reaction times varying from 0.5-7 hours. The use of higher reaction temperatures would, of course, shorten the reduction period considerably. Primary chlorides are generally reduced with difficulty and in poor yield unless an unsaturated substituent such as a phenyl or, perhaps, allyl[63] group is attached to the reactive carbon. The reduction of simple, secondary bromides and iodides also produces high yields of the corresponding hydrocarbons. However, it is expected that even simple secondary chlorides such as isopropyl chloride would give low yields as evidenced by the poor results obtained with _n_-propyl chloride (Table II, p. 17). More complex secondary halides,

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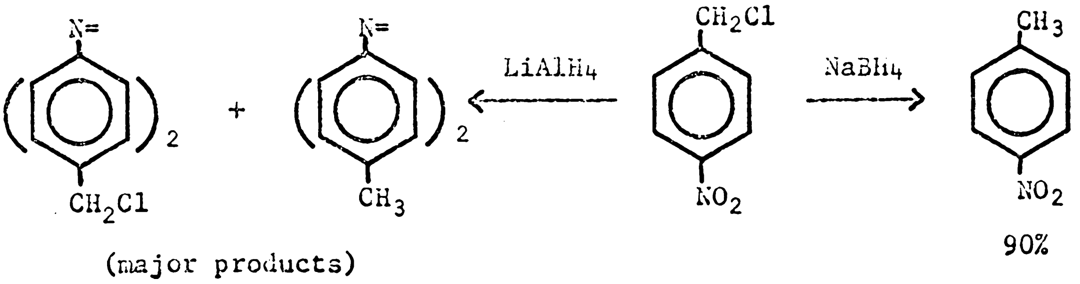
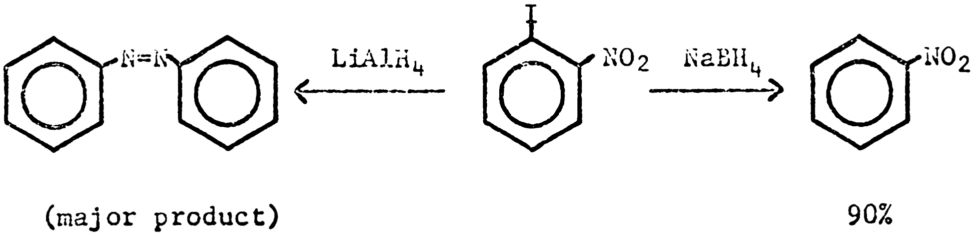
*Estimated from the dipole moment (1.4 D)[91] of a structurally similar ether, dioxymethylene dimethyl ether ($CH_3OCH_2OCH_2OCH_3$).

such as the benzhydryl compounds where two bulky phenyl substituents are attached to the reactive center and tertiary halides where the steric hinderance is still more severe, give very poor (1-8%) yields for this reason. Finally, aryl halides generally follow the same order of ease of dehalogenation, namely, $I^- > Br^- > Cl^- >> F^-$, as do the alkyl halides, and the yields may be considerably enhanced by substituting a strong electron-withdrawing group(s) such as nitro or, perhaps, trifluoromethyl[20] in the positions *ortho* and *para* to the halogen. However, as seen from the fact that a 90% yield of nitrobenzene was realized from the reduction of *o*-nitroiodobenzene, one nitro group *ortho* to the halogen is apparently sufficiently activating to give good results with the *iodo* group. The work of Ramachandran[92] on the quantitative determination of the 2,4-dinitrophenyl moiety in proteins with SBH by the postulated reduction of one or both nitro groups to form a highly-colored azo dye tends to discourage the further activation of aryl halides by more than one nitro group. Carbon tetrachloride was reduced primarily to chloroform in the absence of water, but the yield of methylene chloride was substantially increased by the addition of water in the presence of unreacted SBH.

This leads to the "reductive selectivity" of SBH, which can frequently be taken advantage of, as illustrated by the reduction of *p*-nitrobenzyl chloride in 90% yield to *p*-nitrotoluene, or conversely, the reduction of a more reactive group than halogen in a halogen-containing compound, as exemplified by the reduction of 3-bromo-1,1,1-trifluoropropanone to 3-bromo-1,1,1-trifluoro-2-propanol[27].

Finally, as mentioned previously, the advantages of SBH over LAH are twofold as follows: 1) greater selectivity and 2) a wider choice of solvents. The first point can be illustrated by the following two examples:





The second point stems from the fact that aqueous solvent systems can never be employed with LAH but are frequently used with SBH. Solvents containing linkages which are reduced readily by LAH, such as the sulfuryl (=S=O) group in DMSO, are also unacceptable. However, as indicated by our results, both DMSO and diglyme have proved to be excellent solvents for borohydride reductions because of the reasonably short reduction times and high yields obtained.

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THE SODIUM BOROHYDRIDE REDUCTION OF ORGANIC HALIDES AND RELATED DERIVATIVES IN APROTIC SOLVENTS

by

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Abstract

Sodium borohydride reduces alkyl halides and their related tosylate derivatives in the order primary > secondary > tertiary, while the relative order of leaving-group ability is $Ts^- \geq I^- > Br^- >> Cl^-$. The yields obtained ranged from 90-100% for most simple, primary and secondary iodides, bromides, and tosylates, to 1-2% for the tertiary compounds. As in the case of the more reactive lithium aluminum hydride, the reduction is believed to occur by an S_N2 displacement on carbon.

The reduction of a series of *para*-substituted benzyl chlorides revealed that the electronic effects of groups ranging from *p*-methoxy to *p*-nitro had a rather small effect on the rate of reduction.

Aryl halides are reduced by sodium borohydride in yields dependent upon the particular halogen involved, the presence of other *ortho* and *para* electron-withdrawing substituents, and the reaction temperature, among other factors. The same relative order of dehalogenation displayed by the alkyl halides was found.

Polyhalomethanes such as carbon tetrachloride react with sodium borohydride to give the monohydro and dihydro compounds as the major

products, the former predominating. The exact mechanism of the reduction is as yet undetermined, as water apparently catalyzes the reaction in some unknown manner.