The Stereochemistry of Hydride Reductions

BY WILLIAM G. DAUBEN, GERHARD J. FONKEN AND DONALD S. NOYCE

It has been shown that reductions of alkylcyclohexanones with lithium aluminum hydride, sodium borohydride and aluminum isopropoxide lead to increasing proportions of the axial (unstable) isomer. The mechanism of the reduction step is discussed with reference to the ease of formation of the initial metallo-organic complex (steric approach control) and to the relative energetics of the formation of the products once the complex is formed (product development control).

The reduction by metal hydrides of ketones which can yield diastereomeric alcohols has been the subject of numerous investigations and such studies have been carried out with a wide variety of ketones, including acyclic, alicyclic and polycyclic compounds.[1] Correlations of the stereochemical results have been proposed by numerous investigators[1-6] and for the most part the results of these summaries have been expressed in terms of conformational concepts, considering the most likely conformation of the initial ketone and the changes which must result during the reduction proper. One of the most descriptive postulates is that of Cram and Greene[7] in which it was considered that the reduction by lithium aluminum hydride of acyclic ketones proceeded by the formation of an initial complex between the hydride and the carbonyl oxygen atom and in this complex, the oxygen "becomes effectively the bulkiest group in the molecule and tends to orient itself between the two least bulky groups attached to the adjacent asymmetric carbon atom." The predominant isomer "would be formed by approach of the entering group from the least hindered side of the carbonyl complex."

Barton,[1c] on the other hand, has merely summarized the results and has pointed out that with an unhindered ketone, the predominant product in the alicyclic series is the equatorial isomer. Other previous workers, however, have paid little attention to the striking fact that the predominant product in any series *usually* is the more stable isomer. An excellent example of this generality is to be found in the study of the reduction of a series of 2-(α-piperazinyl)-benzylcyclohexanones[8] in which many structural changes were made and in all cases the stable equatorial isomer was formed in higher yield.

In view of the foregoing considerations, two interpretations of the stereochemical results of the hydride reduction appear worthy of evaluation, one, a steric postulate involving competitive attacks from a favored (unhindered) or an unfavored (hindered) side which for simplicity can be termed "steric approach control" and the other, an energy consideration involving the relative stability of the possible products and which can be termed "product development control." In the present investigation, additional results with cyclic ketones have been obtained, using a variety of reduction methods, which yield further information of value in attempting to assess the various influences at work in the control of the distribution of the isomers produced. These results are summarized in Table I.

TABLE I

DISTRIBUTION OF ISOMERS FORMED BY REDUCTION OF KETONES

Reagent	—Menthone— Menthol, %	Neo- men- thol, %	4-Methyl- cyclo- hexanone % trans	% cis	2-Methyl- cyclo- hexanone % trans	% cis
LiAlH₄	71	29[1a]	81	19[1a]	82	18
NaBH₄ in methanol	49	51	75	25	69	31
NaBH₄ in pyridine	..	..	60	40	56	44
Al(O-Pr^i)₃	30	70[9]	67	33[10]	42	58[1a]
NaBH(OCH₃)₃	..	..	..	..	70	30
Equilibrium	Mostly[11]		88	12	99	1

It is seen from the results in Table I that the reduction of alkylcyclohexanones with lithium aluminum hydride leads to the predominant formation of the stable isomer, while a change to sodium borohydride in either methanol or pyridine decreases the percentage of this isomer. It should be particularly noted, however, that whereas the 2- and 4-methylcyclohexanones appear to yield the same proportion of isomers, the important feature to consider in evaluating the *product development control* is the difference of these ratios from the equilibrium mixture of isomers. An accurate determination of the position of the equilibrium for the two methylcyclohexanols was performed and the results also are listed in Table I. The position of equilibrium at 99% *trans* for the 2-methylcyclohexanols as compared to 88% *trans* for the 4-methyl isomer is in line with conformational concepts.[12]

On the basis of results obtained in this present study, a more nearly complete picture of the reduction of the alkylcyclohexanones is at hand and allows one, for the first time, to examine critically the

(1) For summaries, see (a) D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950); (b) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **74**, 5828 (1952); (c) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

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(6) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(7) D. J. Cram and F. D. Greene, THIS JOURNAL, **75**, 6005 (1953).

(8) P. B. Russell and R. Baltzly, *ibid.*, **77**, 629 (1955).

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(10) L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 2641 (1949).

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(12) For the case of the 2-methylcyclohexanols, previous workers [R. Cornubert, M. Lafont-Lemoine and N. Nadjme-Abadi, *Compt. rend.*, **237**, 469 (1953)], using the less precise phenylurethan method of analysis, have reported that the equilibrium mixture contains 95% *trans*.

effect of structure on isomer production. For the sake of simplicity, the case of menthone (I) will be considered first, for here the conformational arrangement of the original ketone is largely fixed with both alkyl groups in the equatorial arrangement. (To place both groups in an axial conforma-

I   II   III
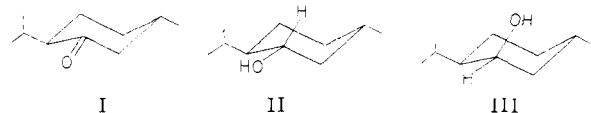
tion would require an undue expenditure of energy.) In this compound, the isopropyl group occupies a position which flanks the carbonyl carbon very nearly equally on each side of the molecule thus making attack by a small reagent from either side equally favored as far as this substituent is concerned. The results of the lithium aluminum hydride reduction show that an axial approach resulting in the introduction of a hydrogen atom in an axial position and the formation of an equatorial hydroxyl group (II) (*i.e.*, the formation of menthol) is the favored reaction. Thus, an example of mainly *product development control* is seen. When menthone is reduced with sodium borohydride in methanol, a reagent which appears to be stereochemically more selective,[7] the amount of neomenthol (III) (hydroxyl group axial) formed is larger, indicating that equatorial approach is becoming more important. This may be considered as indicating a greater effective size of the borohydride species and a case where *steric approach control* is beginning to exhibit competition with *product development control*.[13] The reduction of menthone with sodium borohydride in pyridine is complicated by the fact that concurrent with the reduction of the carbonyl group, inversion of the asymmetric center adjacent to the carbonyl group also occurs to some extent and hence no results of significance to this study are obtained.

In these reductions it is most probable that the reaction involves the preliminary formation of a metallo-organic complex between the carbonyl group and the hydride species. It is in this complex that hydride transfer occurs and as the transfer begins, the sp² bonding of the carbonyl group begins to change to the sp³ bonding of the product. In so doing, the intermediate stages of the reduction take on the steric requirements of the products and hence the relative stabilities of the products reflect themselves in this early stage of the reduction. Thus, one sees there are two features of the reduction which must be examined, first, the ease of formation of the initial complex or *steric approach control* and, second, the relative energetics of the formation of the products once the complex is formed or *product development control*. In the case of the reduction of menthone with lithium alu-

(13) Various other workers have reported results which also indicate a greater effective size of the borohydride species. For example, T. G. Halsall, R. Hodges and E. R. H. Jones [*J. Chem. Soc.*, 3019 (1953)] have reported that in methyl b-oxopolyporenate A a-acetate, lithium aluminum hydride reduces the carbonyl while sodium borohydride gives no reduction and H. B. Henbest, E. R. H. Jones, A. A. Wagland and T. I. Wrigley [*ibid.*, 2477 (1955)], have reported that in a 9-bromo-11-oxo-steroid, lithium aluminum hydride attacks the hindered 11 oxo group while sodium borohydride attacks only the 9-bromo atom leaving the 11-oxo group untouched.

minum hydride, since this reducing agent is a relatively small group and since, as discussed above, either side of the molecule (*i.e.*, an equatorial or axial attack) is equally favored sterically for attack of the hydride, the developing sp³ hybridization is essentially the controlling factor; the result is the formation of a greater predominance of the more stable isomer (equatorial hydroxyl). As the size of the reducing species is effectively increased, such as with sodium borohydride in methanol, consideration must be given to steric interactions between the β-axial hydrogen atoms on the ketone and the reducing moiety approaching in the axial position. This axial–axial type of interaction results in an increasing proportion of equatorial approach with the resultant formation of more of the less stable isomer with an axial hydroxyl group.[14]

Interpretation of the results obtained with the 2-methyl- and the 4-methylcyclohexanones requires consideration of the two possible conformations of the ketones. In the case of the 4-methyl isomer, due to the remote position of the alkyl substituent, the two conformations IV and V are identical as far as the substituents α and β to the carbonyl group are concerned.

IV   V
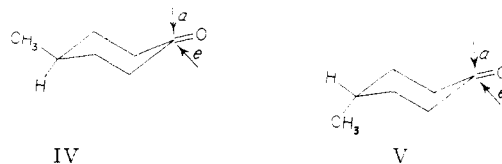
In either conformation, approach of the reducing species from either side of the carbonyl group is equally favored and the reduction with lithium aluminum hydride should be *product development controlled* and yield mainly an equatorial school. From conformation IV, this would result in the formation of mostly the *trans* isomer while from conformation V, a *cis* isomer would be formed. The relative contribution of each pathway will depend on the difference in the energies of the various transition states. Since conformation V has an axial methyl group, it would be expected to lead to transition states of higher energies than those from conformation IV. Consequently the former should be of lesser importance but still allow for the formation of more *cis* isomer than from a compound with a frozen conformation. It is seen in Table I that whereas the equilibrium mixture has only 12% of the *cis*, the lithium aluminum hydride reduction mixture contains 19% of the *cis*, a result in line with the prediction.

With the 2-methyl isomer, the presence of the methyl group on the carbon atom adjacent to the carbonyl group introduces further complexities. With regard to the approach of the reagent to the carbonyl group, in conformation VI both equatorial and axial approach is equally favored and reaction should be *product development controlled*. In conformation VII, the equatorial approach is subject to some interference by the axial methyl

(14) It should be emphasized that the difference in free energy between any two isomers in such a series is small (∼1–3 kcal.) and, in addition, the isomer ratio obtained is the result of an even smaller difference in free energy of activation (∼0–1 kcal.) between the two attacks leading to the two isomers.

VI   VII
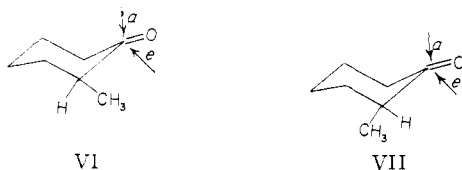
group and reactions will be *steric approach controlled*. The former will yield a mixture of isomers similar to that found in the equilibrium mixture but the latter will yield a mixture more rich in the *cis*. Again, transition states arising from conformation VI should be more favored, but the amount of *cis* isomer produced from the transition states from conformation VII should be more than in the 4-methyl case. Consequently, the total amount of *cis* isomer, as compared to the equilibrium concentration, should be larger for the 2-methyl isomer when it is reduced with lithium aluminum hydride and it is seen from Table I that the equilibrium concentration of *cis* is 1% while 18% *cis* is formed in the reduction. Thus, the stable *trans* isomer predominates but the values differ from the equilibrium concentration in the proper direction.

Reduction of these methylcyclohexanones with more bulky hydrides, such as sodium borohydride, is similar to that discussed with menthone. The result should be an increasing amount of the unstable *cis* isomer and in the case of the 2-methyl compound this effect should be even more predominant. These postulated results are borne out well in the results shown in Table I.

Many results obtained with different alicyclic compounds also are adequately explained by utilization of these same concepts. For example, in the reduction of cholestanone where the carbonyl group is unhindered by α- or β-axial groups, the reaction should be *product development controlled* and it is found that the more stable equatorial isomer is formed in 90% yield by the use of lithium aluminum hydride.[15] When the more spacially demanding sodium borohydride is used, some *steric approach control* should be exerted and it is found that the amount of the equatorial isomer is less.[15c] Reduction of an 11-ketosteroid illustrates the role of axial groups so placed that they may even block the axial approach of lithium aluminum hydride and allow the reaction to be completely *steric approach controlled*. In such a case, the product is the 11β-axial hydroxyl compound.[5,13]

Experimental

Reduction of Methylcyclohexanones.—The product compositions were determined by density measurements. The reference densities used for these analyses were those reported by Jackman, Macbeth and Mills.[10] The d^{30}_4 for the 4-methylcyclohexanols were: *trans*, 0.9040; *cis*, 0.9173. For the 2-methylcyclohexanols the values were: *trans*, 0.9174; *cis*, 0.9274. The values for the *trans* isomers were in agreement with those obtained in this Laboratory for materials generated from the pure 3,5-dinitrobenzoate esters. All densities were taken with a calibrated 10-ml. pycnometer in a constant temperature bath calibrated against a National Bureau of Standards thermometer.

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a. Lithium Aluminum Hydride.—The reaction was conducted as described by Noyce and Denney[1a] and the product from 2-methylcyclohexanone had a d^{30}_4 0.9191 (18% *cis*) and a n^{20}D 1.4625.

b. Sodium Borohydride in Methanol.—In a three-necked flask fitted with a sealed stirrer and a reflux condenser was placed 6.6 g. (0.178 mole) of sodium borohydride dissolved in 20 ml. of water which, in turn, had been diluted with 100 ml. of methanol. Over a period of 30 minutes, a solution of 20 g. (0.178 mole) of 4-methylcyclohexanone in 50 ml. of methanol was added at such a rate to the stirred solution that a moderate reflux was obtained. After completion of the addition, the mixture was refluxed for 4 hours, 150 ml. of 2 N sodium hydroxide added and the heating continued for an additional 2 hours.[16] The hydrolyzed solution was extracted continuously with ether for 24 hours and the product distilled through an 18" column, b.p. 90–91° (50 mm.),[17] d^{30}_4 0.9073 (25% *cis*), n^{25}D 1.4543, yield 18.3 g. (91%).

In a similar manner, 20 g. of 2-methylcyclohexanone was reduced to yield 18.2 g. (90%) of product, b.p. 90–92° (50 mm.), d^{30}_4 0.9205 (30% *cis*), n^{25}D 1.4625.

c. Sodium Borohydride in Pyridine.—The reduction was conducted as described in methanol except 6.16 g. of sodium borohydride was dissolved in 150 ml. of dry pyridine and the 20 g. of 4-methylcyclohexanone was dissolved in 50 ml. of dry pyridine. After heating the reaction mixture at 70° for 6 hours, 100 ml. of 2 N sodium hydroxide was added and the heating continued for an additional 2 hours. Extraction of the reaction mixture with ether using a continuous extractor for 24 hours, followed by distillation yielded 14.3 g. (71%) of 4-methylcyclohexanol, b.p. 90–91° (50 mm.), d^{30}_4 0.9092 (40% *cis*), n^{25}D 1.4566.

In a similar manner, 20 g. of 2-methylcyclohexanone was reduced to yield 19.8 g. (97%) of product, b.p. 90–92° (50 mm.), d^{30}_4 0.9218 (44% *cis*).

d. Sodium Trimethoxyborohydride in Pyridine.—In a 1-l. three-necked flask equipped with a sealed stirrer, a thermometer and a dropping funnel, was placed 107 g. (0.6 mole) of sodium trimethoxyborohydride in 600 ml. of dry pyridine and then 60 g. (0.54 mole) of 2-methylcyclohexanone was added, dropwise. The temperature rose to 47° upon the beginning of the addition and the rate of addition was adjusted to keep the temperature between 45–50°. The addition required 45 minutes and then the reaction was stirred for an additional 3 hours at this same temperature. Upon cooling, the mixture was poured into 2-l. of water containing 200 ml. of concentrated hydrochloric acid and 500 g. of ice. After extraction with ether the product was distilled, b.p. 165–166°, yield 36.8 g. (60%), d^{30}_4 0.9204 (30% *cis*), n^{20}D 1.4627.

Equilibration of Methylcyclohexanols.—The corresponding alcohol (30 g.) was heated under reflux with 18.6 g. of aluminum isopropoxide and 1 ml. of acetone in 300 ml. of isopropyl alcohol for 72 hours. Time studies with each isomer showed that no change in isomer composition occurred after this reaction time. The reaction solution then was poured into 1500 ml. of water containing 100 ml. of concentrated hydrochloric acid and the product extracted with ether.

For the 2-methyl isomer, the starting alcohol had a d^{30}_4 of 0.9218 (44% *cis*) and the final product a d^{30}_4 of 0.9175 (1% *cis*). For the 4-methyl isomer the equilibrium was approached from each side. In one case, the starting alcohol had a d^{30}_4 of 0.9094 (40% *cis*) and the final material a d^{30}_4 of 0.9056 (12% *cis*) and in the second case, the starting alcohol had a d^{30}_4 of 0.9040 (0% *cis*) and the final product a d^{30}_4 of 0.9057 (12% *cis*).

Reduction of 1-Menthone with Sodium Borohydride in Methanol.—The reduction was conducted as described above using 4.8 g. of sodium borohydride in 50 ml. of water and 150 ml. of methanol and 20 g. of 1-menthone ([α]^{25}D −23.3, homog.) in 50 ml. of methanol. The product was distilled, b.p. 120–135° (55 mm.), yield 18.2 g., [α]^{25}D −15.9, homog.

(16) Low recovery of product was obtained with acid hydrolysis. It was ascertained that the alkali treatment had no effect on the density of the product. In a trial experiment the starting alcohol has a d^{30}_4 of 0.9218 and the final product after alkali treatment had a value of 0.9217.

(17) The absence of ketone in this and all subsequent products was shown by the absence of the carbonyl band in the infrared spectrum under such conditions where 2% would be detected.

The product was reoxidized with sodium dichromate[18] to

(18) *Organic Syntheses*, Coll. Vol. I, John Wiley and Sons, Inc., New York 16, N. Y., 1944, p. 340.

menthone ($[\alpha]^{25}$D $-23.7°$) showing no change in the configuration of the starting material had occurred.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

A New Powerful Reducing Agent—Sodium Borohydride in the Presence of Aluminum Chloride and Other Polyvalent Metal Halides[1,2]

BY HERBERT C. BROWN AND B. C. SUBBA RAO[3]

The addition of aluminum chloride to sodium borohydride in the dimethyl ether of diethylene glycol (diglyme) gives a clear solution with enormously more powerful reducing properties than those of sodium borohydride itself. Esters, lactones and carboxylic acids are readily reduced to the corresponding alcohols. Sodium salts of the carboxylic acids are not reduced, so that the reagent permits the selective reduction of an ester group in the presence of the carboxylate group. Nitro groups are not attacked by the reagent, permitting the ready reduction of nitro esters to the corresponding nitro alcohols. Nitriles are reduced to primary amines in good yield. A survey was made of the reactivity of various functional groups toward the reagent by examining the hydrogen utilization by various representative compounds under standard reaction conditions. The results lead to the following conclusions. Simple acid amides form only salts (by reaction with one of the active hydrogen atoms of the amide group) which do not undergo reduction, whereas reduction does occur with the disubstituted amides. Aldehydes, ketones, epoxides and anhydrides utilize hydride corresponding to reduction to the alcohol. Disulfides and sulfonyl chlorides are reduced, whereas a simple sulfone was not. Pyridine-N-oxide is reduced at 25°, whereas pyridine itself does not react at this temperature. Benzyl chloride was not affected at 25°, but appeared to undergo reaction at 75°. Other polyvalent metal halides, such as gallium trichloride and titanium tetrachloride, also appear capable of greatly increasing the reducing potentialities of sodium borohydride.

In the past decade sodium borohydride[4,5] and lithium aluminum hydride[6,7] have revolutionized the reduction of functional groups in organic chemistry. Of these two reagents, sodium borohydride is a relatively mild reducing agent which is practically specific for the carbonyl group in aldehydes and ketones. On the other hand, lithium aluminum hydride is an exceedingly powerful reagent which attacks almost all reducible groups.

There would be advantages in possessing reagents with reducing capacities somewhere between these two extremes. One possible means of achieving this end would be to increase the reducing properties of the borohydride; another, to diminish the reducing properties of the aluminohydride. Both procedures are under active investigation in our laboratories.

It is quite clear that the reducing capacity of the borohydride is markedly affected by the metal ion present in the salt. Thus sodium borohydride reduces typical esters, such as ethyl acetate and ethyl benzoate, only very slowly, whereas lithium borohydride[8,9] reduces such esters quite easily.[10]

Kollonitsch, Fuchs and Gabor achieved the successful reduction of simple esters by sodium borohydride in tetrahydrofuran in the presence of lith-

ium and magnesium iodides,[11] as well as by the application of calcium, strontium and barium borohydrides.[12]

The dimethyl ether of diethylene glycol (diglyme) is an excellent solvent for sodium borohydride. The addition of lithium bromide or magnesium chloride to such solutions provides a reagent which permits the ready reduction of esters.[13] In continuing this line of investigation, we have discovered that the addition of anhydrous aluminum chloride or other polyvalent metal halides, such as gallium chloride or titanium tetrachloride, provides solutions of tremendously enhanced reducing capacities.[14] We, therefore, turned our attention to a detailed examination of the potentialities of these new reducing systems.

Results

Mixture of freshly prepared solutions of aluminum chloride (2 M) and sodium borohydride (1.0 M), in diglyme in a molar ratio $AlCl_3 : 3NaBH_4$ gives a clear solution which exhibits very powerful reducing properties. Preliminary experiments revealed that esters, such as ethyl benzoate, ethyl stearate and ethyl p-nitrobenzoate, were essentially completely reduced by the reagent in one hour at room temperature.

The precise order of mixing the reagents does not appear to be important. At least no significant difference in results was observed in (1) adding the aluminum chloride solution to a mixture of sodium borohydride and ester in the solvent, (2) adding the sodium borohydride solution to a mixture of the ester and aluminum chloride in the solvent or (3) adding the ester to a mixture of aluminum chloride and sodium borohydride in diglyme. We fi-

(1) Addition Compounds of the Alkali Metal Halides. IV.

(2) Based upon a thesis submitted by B. C. Subba Rao in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Parke, Davis and Co. Fellow at Purdue University, 1952–1955.

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