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POLAR AND SOLVENT EFFECTS IN THE REDUCTION OF SUBSTITUTED CYCLOHEXANONES*

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THE direction of attack of the electrophilic reagent, perlauric acid, on olefinic bonds in cyclic compounds can be influenced by polar substituents, even when these are located across two or three saturated rings.[1] In order to determine the effect of a simple, linear dipolar substituent upon the direction of addition of a nucleophilic reagent to carbonyl bonds, we chose to study the reduction of chloro-cyclohexanones by borohydrides, the ketone-borohydride reaction usually being visualised as proceeding by intermolecular transference of hydride anions. Comparative experiments with the related reducing agents, diborane and lithium aluminium hydride, were also carried out.

Unhindered, alkyl substituted cyclohexanones react with complex hydrides to give equatorial alcohols as main products, for example, trans-4-methylcyclohexanol being formed in 80-84% yield on reduction of 4-methyl-

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[*] Some of the results reported in this paper were presented at the Conference on Stereochemistry held at the University of Alberta, Edmonton, September 1960.

[1] N.S. Crossley, A.C. Darby, H.B. Henbest, J.J. McCullough, B. Nicholls and M.F. Stewart, preceding paper.

cyclohexanone with lithium aluminium hydride.[2,3,4] The trans-4-methyl-alcohol is also the main product when the ketone is reduced with sodium borohydride (Table), but the proportion of trans:cis-methyl-alcohols depends upon the solvent. The solvent effects are not large, but it is noteworthy that the same order (yield of equatorial alcohol increasing in the sequence; methanol, tetrahydrofuran, isopropanol, acetonitrile) is observed in the reduction of 3-methylcyclohexanone, where cis-3-methylcyclohexanol is the major product. This dependence of product ratio upon solvent may be a steric effect, a reflection of the relative sizes of the solvation shells around each transition state. Further study is being made of this problem.

Results from the reduction of 4-chlorocyclohexanone show that the chlorine substituent has a considerable directing effect for, in contrast to the 4-methyl series, more cis- than trans- product was formed in each of four solvents; however, the relation between product ratio and solvent was different from that observed with the methyl-ketones. Preliminary experiments on the borohydride reduction of 12-oxospirostans show that a chlorine substituent at C_3 can exert a directing effect across the three saturated rings, the proportion of 12α-alcohol formed on reduction of the unsubstituted ketone being increased by 10-15% when a 3α- or 3β-chloro-group is present. These results, in conjunction with those of the mono-cyclic series, show that a chlorine substituent has the general effect of increasing the proportion of axial alcohol formed in reactions of cyclohexanones with borohydrides.

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[2] D.S. Noyce and D.B. Denney, J.Amer.Chem.Soc. **72**, 5743 (1950).

[3] E.L. Eliel and R.S. Ro, J.Amer.Chem.Soc. **79**, 5992 (1957).

[4] W.G. Dauben and R.E. Bozak, J.Org.Chem. **24**, 1956 (1959).

Ratios of trans:cis-Substituted Alcohols formed in the Reduction of Substituted Cyclohexanones

	4-Methyl cyclohexanone	4-Chloro cyclohexanone	3-Methyl cyclohexanone
Sodium borohydride in			
methanol	82:18	41:59	17:83
tetrahydrofuran[*]	83:17	47:53	14:86
propan-2-ol	85:15	37:63	13:87
acetonitrile[*]	89:11	48:52	8:92
Equilibration in			
propan-2-ol	73:27[**]	55:45	77-79% *cis* (refs.3,4)
Diborane in			
tetrahydrofuran	89:11	31:69	8:92
Lithium aluminium hydride in			
tetrahydrofuran	84:16	33:67	85-92% *cis* (refs.2,3)

A similar, less pronounced, effect of the chlorine substituent was observed when the *cis* and *trans*-isomers of the 4-methyl- and 4-chloro-cyclohexanols were each brought to equilibrium in the presence of aluminium 2-propoxide. The same ratio of chloro-alcohols was obtained using either tetrahydrofuran[5] or the usual solvent, propan-2-ol. In the former solvent,

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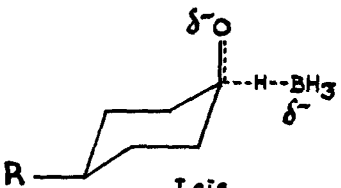
[*] Suspension of sodium borohydride in these solvents.

[**] W.G. Dauben and R.E. Bozak, preceding reference, give a ratio of 71:29.

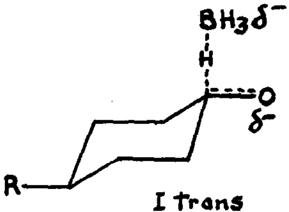
[5] Equilibration of the chloro-alcohols occurred more quickly in tetrahydrofuran (than in propan-2-ol), and this solvent may therefore offer advantages for alkoxide-ketone interconversions in general.

the dominant species at equilibrium should be aluminium complexes of the chloro-alcohols. There would be a greater tendency for the free chloro-alcohols to be present in propan-2-ol, but since the chloro-alcohols can be expected to be more acidic than propan-2-ol, they may also be present as complexes to a large extent.

The effect of the chlorine substituent in changing the ratio of _trans_ : _cis_-products in the reduction and equilibration experiments can be explained by intramolecular electrostatic interactions between the $Cl-C_4$ and C_1-O groups, such interactions being more favourable in structures related to the _cis_-chloro-alcohol than in those related to the _trans_-chloro-alcohol. Calculations, to be reported later, support this viewpoint of the results, one of the factors contributing to the increased stability of a _cis_-structure being the attractive force between its oxygen atom (in an axial position) and the electron deficient carbon at the 4-position; this attraction is greater with axial than with equatorial oxygen (in _trans_-structures) because of its smaller distance from C_4 (3.40 and 4.12 A respectively).

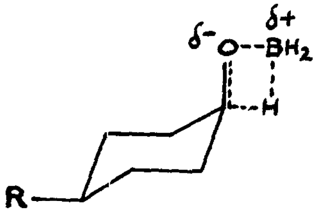


I _cis_

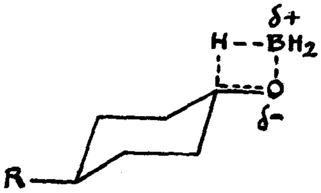


I _trans_

According to this interpretation of the results, the oxygen carries the greatest negative charge in the transition states of ketone-borohydride reactions; there is therefore an increased preference for the development of transition state (I _cis_) when R equals chlorine. The fact that a smaller proportion of _cis_-chloro-alcohol is obtained on equilibration of the alcohols than on reduction of the chloro-ketone suggests that the species present, e.g., $ClC_6H_{10}OAl(OCHMe_2)_2$, at equilibrium are less polar (smaller δ- charge on oxygen) than are the transition states for ketone reduction, and this is in accord with their essentially covalent structures.



II *cis*



II *trans*

Ketones are reduced by diborane,[6] and this reagent gave even larger differences in isomer ratio when the reductions of 4-methyl- and 4-chloro-cyclohexanones were compared, the yields of *cis*-chloro-alcohol being 69 and 75% in tetrahydrofuran and dichloromethane respectively. Therefore these reactions also have polar transition states, the bulk of the δ- and δ+ charges probably being in the vicinity of the oxygen and the BH_2 groups (*cf.* II *cis* and *trans*).

Reduction of 4-chlorocyclohexanone with lithium aluminium hydride also gave a larger proportion of *cis*-product than from 4-methylcyclohexane, the *trans* : *cis* ratio being closer to that for diborane than that for borohydride reduction. This may be indicative of reduction proceeding by attack of aluminium hydride[7] rather than aluminohydride anions, but further experiments are required to decide this question. The reaction between 4-methoxy-

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[6] H.C. Brown, H.I. Schlesinger and A.B. Burg, *J.Amer.Chem.Soc.* *61*, 673 (1939).

[7] D.M.S. Wheeler and J.W. Huffman, *Experientia* *16*, 516 (1960), have suggested that aluminium hydride may be the active species in reductions of alkyl-ketones.

cyclohexanone and lithium aluminium hydride has been reported[8] to give a 70% yield of cis-4-methoxycyclohexanol. Although the methoxyl group is a bent dipole it exhibits therefore the same directing effect as chlorine in this reaction.

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[8] D.S. Noyce, G.L. Woo and B.R. Thomas, J.Org.Chem. **25**, 260 (1960).