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# A COMMENT ON THE MECHANISM OF REDUCTION OF CYCLOHEXANONES BY COMPLEX HYDRIDES

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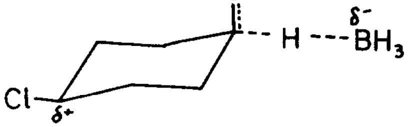
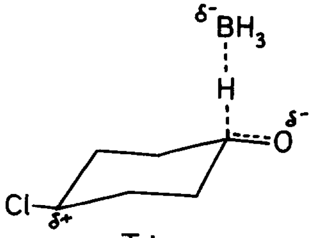
The classification of cyclohexanone reductions by complex hydrides as either "product-development controlled" (transition state resembling products) or "steric approach controlled" (reactant-like transition state) (1) is no longer accepted (2). "Product development" now seems to be an unnecessary concept (3). The preferential formation of equatorial alcohols from sterically "unhindered" cyclohexanones has instead been attributed to a previously neglected aspect of "approach control", namely the avoidance of "1,2-eclipsing" (torsional strain) in a reactant-like transition state (3).

One experimental result cited in support of a product-like transition state has, however, been only partially explained (4) in terms of approach control. 4-Chlorocyclohexanone, and cyclohexanones with other electronegative substituents at $C_{(4)}$, give unusually high proportions of axial (cis) alcohols (5,6), although 4-alkyl-cyclohexanones afford quite normally high proportions of the equatorial (trans) alcohols. The influence of a 4-chloro-substituent was interpreted (5) in terms of an intramolecular electrostatic interaction between the $Cl-C_{(4)}$ and $C_{(1)}-O$ groups, considered to stabilize a product-like transition state of the type (Ia), with oxygen carrying most of the negative charge. The alternative



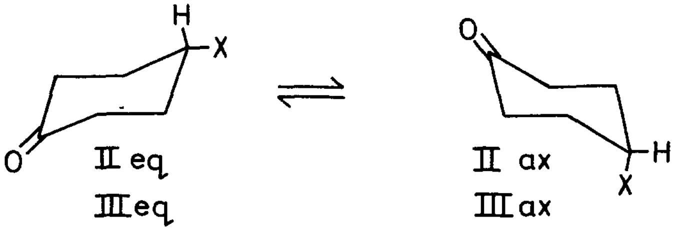
Ia



Ib

transition state (Ib) was considered to be relatively less stable, because the $-O^{\delta-}$ is further from $C_{(4)}$.

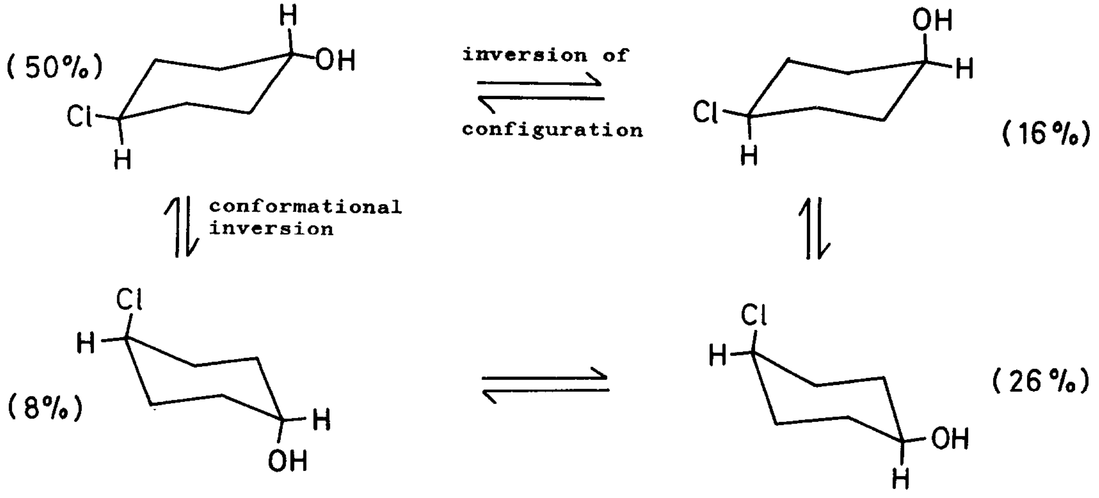
This argument rests upon the premise, now found to be mistaken, that 4-chlorocyclohexanone exists mainly in the equatorial-Cl conformation (II eq.). Stolow and Groom (7), however, have recently shown from NMR measurements that 4-hydroxycyclohexanone exists mainly in the form (III ax.), with axial-OH; a transannular polar interaction appears to be responsible. The NMR spectrum of 4-chlorocyclohexanone (in $CCl_4$ at 60 MHz), examined in this Department, indicates that this too exists mainly in the axial conformation (II ax.). The narrower $C_{(4)}$-H signal (width 17.5 Hz), compared with 24 Hz determined for >C<u>H</u>Cl in chlorocyclohexane, represents in increased population of axial-Cl conformer. If the couplings with vicinal protons are assumed to have the same values as those used for cyclohexanol and 4-hydroxycyclohexanone (7), the ratio II ax.:II eq. is calculated to be 69:31 at 27°C, corresponding to a free-energy difference favouring II ax. by 0.47 $kcal.mole^{-1}$. A similar calculation for chlorocyclohexane shows the equatorial conformer to be favoured by 0.45 $kcal.mole^{-1}$ (literature value (8) _ca._ 0.4).



II: X = Cl ; III: X = OH

Since the reduction of a sterically unhindered ketone with complex hydrides affords the equatorial-OH as the major product, the _cis_-alcohol (V) _must_ arise in greater proportion than usual, much of it from normal attack upon the conformer (II ax.) with axial-Cl. Electrostatic repulsion of the $BH_4^-$ ion by the negative end of the C-Cl dipole may further accentuate the preponderance of _cis_-alcohol, as proposed by Wheeler and Wheeler (4).

The non-relevance of the charge-dipole interaction implied by (I) is suggested also by a consideration of the <u>equilibria</u>:-



IV (<u>trans</u> isomer)
Total 58%

V (<u>cis</u> isomer)
Total 42%

Using the accepted $\Delta G^{o}_{X}$ values (8): 0.4 kcal/mole for Cl; 0.7 kcal/mole for OH, a Boltzmann distribution between the four forms (neglecting higher-energy boat conformations) gives the percentages indicated. The calculated <u>trans</u>:<u>cis</u> ratio (58:42) agrees well with the equilibrium ratio (55:45) (5). (A similar calculation for the 4-methylcyclohexanols, using $\Delta G^{o}_{Me}$ = 1.7 kcal/mole (8), gave the <u>trans</u>:<u>cis</u> ratio 73:27, exactly as found.) The equilibrium distribution is therefore virtually independent of dipole-dipole interactions, implying either that these are essentially equal for all conformers, or that they are of negligible magnitude. Either way, this finding suggests that polar effects of the type illustrated by diagrams (Ia) and (Ib) are unlikely to have more than a marginal influence on the stereochemistry of the reduction process.*

The foregoing conclusions should apply, in a qualitative sense, to all cyclohexanone derivatives with electronegative substituents at $C_{(4)}$. "Approach control" is adequate to explain the stereochemistry of reduction of these compounds.

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* It is interesting to note that a naïve assumption that the conformers of 4-chlorocyclohexanone are reduced in their equilibrium proportion, each to give the "normal" ratio of *ca*. 85% equatorial alcohol:15% axial alcohol, leads to a "calculated" product ratio of 64% *cis*:36% *trans* 4-chlorocyclohexanols, not greatly different from some of the ratios observed (5,6). These ratios vary according to the solvent employed, so that a close numerical correspondence with an estimate based upon NMR data in $CCl_4$ solution is probably fortuitous.