Tetrahedron Letters No. 18, pp. 1547-1550, 1970. Pergamon Press. Printed in Great Britain.

INTERACTIONS BETWEEN POLAR SUBSTITUENTS: CONFORMATIONAL PREFERENCES IN CYCLOHEXANE DERIVATIVES

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(Received in UK 23 February 1970; accepted for publication 19 March 1970)

Electrostatic interactions between polar substituents within the same molecule may make significant contributions to deciding conformational equilibria. Differences between observed and predicted equilibria have been used to estimate the magnitudes of such polar interactions.[1] Some effects are quite dramatic, including marked preferences for axial conformations of -OH and -Cl in 4-hydroxy-[2] and 4-chlorocyclohexanones;[3] an aspect of the $5\alpha \rightleftharpoons 5\beta$-equilibrium in 6-oxo-steroids has been attributed to the electrostatic effects of 3α-chloro-[4a] and other 3α-substituents.[4b]

Attempts to calculate the magnitude of these polar effects by classical methods have generally used Jeans' equation for the interaction between two dipoles:-[1]

$$E_\mu = \frac{\mu_1\mu_2}{r^3D} (\mathrm{Cos}\,\chi - 3\cos\alpha_1\cos\alpha_2) \text{ - - - - - - - - - - - - - - - - (i)}$$

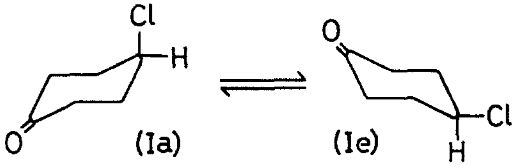
The derivation of equation (i) assumes the two interacting dipoles to be far apart compared with their effective lengths. The approximation could lead to significant errors in calculated interactions if the separation and lengths of dipoles are comparable, as in substituted cyclohexanes.

We attempted to calculate the equilibrium ratio of conformers in 4-chlorocyclohexanone (I) by use of equation (i). (Measurements throughout this work were taken from Dreiding models.) The calculated dipole/dipole interactions favour the axial conformer (Ia) by ca. 0.05 kcal/mole. Inclusion of the normal equatorial preference of -Cl (ca. 0.4 kcal/mole[5]) gives a net preference for the equatorial -Cl conformer (Ie) amounting to some 0.35 kcal/mole. The equatorial: axial ratio would be near 65:35. However, the band-width of the methine proton signal in the NMR spectrum of 4-chlorocyclohexanone indicated a ratio (31:69)[3] almost the reverse of that now calculated, the axial-Cl conformer actually being favoured by ca. 0.47 kcal/mole.[3]

We therefore examined an alternative method for calculating the electrostatic interaction energy, treating each dipole as two point charges. The Coulombic interactions between pairs of point charges were calculated, and summed according to the equation:-

$$E_q = \frac{1}{D}\sum \frac{\delta q_i \cdot \delta q_j}{r_{ij}} \qquad \text{- (ii)}$$

where D is the dielectric constant (we use the value D=2 throughout, as this is preferred by most authors[2,4]); δq_i and δq_j are the interacting point charges (see below); r_{ij} is the distance between charges.



(Ia) (Ie)

Calculations for 4-chlorocyclohexanone, using eqn. (ii), correctly indicate the axial-Cl conformer as the more stable. The exact magnitude of the calculated Coulombic interactions depends upon assumptions concerning the point charges and their locations. Most simply, we assume the charges to be located at the atomic centres, and their magnitudes given by: $\delta q = \frac{\text{bond dipole}}{\text{bond length}}$. It may be more appropriate to consider the point charges as acting within the bond; alternatively, the "negative end" of a dipole may lie <u>beyond</u> the atomic centre, e.g. for chlorine, where lone-pair electrons probably occupy orbitals extending well beyond the C-Cl bond. Similar considerations could apply to the carbonyl group.

Table 1. Conformational free energies and equilibria for 4-chlorocyclohexanone (see text for methods of calculation)

Method	Assumed charge separation or dipole location		$-\Delta G^o_{Cl}$ (kcal/mole)[a]	*ax*:*eq*.ratio
	C=O(Å)	C-Cl(Å)		
Dipole/dipole	1.06[b]	1.56[b]	+0.35	36:64
Charge/charge	1.22[c]	1.2	-0.55	71:29
" "	1.22[c]	1.5	-0.37	65:35
" "	1.22[c]	1.77[c]	-0.20	58:42
" "	1.22[c]	2.0	-0.15	56:44
" "	1.06[b]	1.5	-0.42	67:33
Experimental value	-	-	-0.37	65:35

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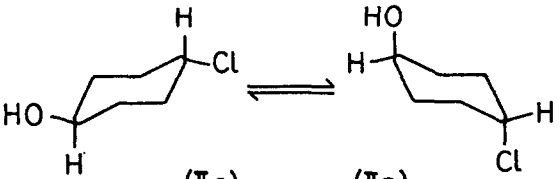
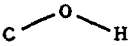
[a] see ref. 1, p.433; [b] Distance from C (7/8 of bond length); [c] Bond length.

Trial calculations, using different $C^{\delta+}$-$Cl^{\delta-}$ distances (and different δq values, since these are inversely proportional to the effective dipole length), gave a range of Coulombic energies. Table 1 lists the calculated total energy differences, after allowing for the normal $-\Delta G^{o}_{Cl} = 0.4$ kcal/mole.[5] The axial-Cl conformer is always preferred, although these figures cannot be considered quantitatively accurate because conformational distortions, entropy terms, and Coulombic interactions involving hydrogen atoms[6] are neglected (separate calculations suggest that inclusion of the latter may modify the total energy differences only by *ca*. 0.1-0.2 kcal/mole). Similar calculations for some other systems suggest that eqn. (ii) may be more generally reliable than eqn. (i), although the latter gives equally good agreement with experimental data in some instances. The preference for axial-OH in 4-hydroxycyclohexanone[2b] and its 2-t-butyl derivative[2a] emerged from use of eqn. (i); eqn. (ii) produces a similar conclusion. Both equations show axial-Br to be favoured in 2-bromo-cyclohexanone.

We have commented previously[3] upon the conformational and configurational equilibria in 4-chlorocyclohexanol, showing why the *cis*-isomer is the major product from reduction of 4-chlorocyclohexanone with borohydride. Our calculated percentage composition of the equilibrated 4-chlorocyclohexanols, however, ignored polar interactions, and we now see the agreement with the experimentally-determined *cis*:*trans* equilibrium ratio as fortuitous. This system provided a practical test of eqns. (i) and (ii). Calculations of polar interactions between the substituents in *trans*-4-chlorocyclohexanol (II), with allowance for the conformational free energies of Cl and OH separately, indicated a net preference of 1.08 kcal/mole for the diequatorial conformer (IIe) (eqn.(i)) or 0.76 kcal/mole (eqn.(ii)). (OH conformations were taken as the weighted average of *gauche* and *anti* conformations, using data kindly provided by Professor R.D. Stolow.



(IIe) (IIa)

The resultant dipole of the  system was used in eqn. (i), and appropriate fractional charges on each of the three atoms for eqn.(ii).)

The actual conformational equilibrium was determined for trans-4-chlorocyclohexanol by examination of its NMR spectra (in C_6D_6 at room temperature). The C-1 and C-4 proton multiplets overlapped at 60 MHz, but a spectrum at 220 MHz, kindly determined by Dr. J.C. Jankowski, NMR Applications Laboratories, Varian, California, separated the two signals ($C\underline{H}Cl$ at $\delta = 3.591$ ppm; $C\underline{H}OH$ at $\delta = 3.264$ ppm, relative to Me_4Si). The mean bandwidth (24.5 Hz) implies that the diequatorial conformation is favoured by 0.54 kcal/mole (see refs. 2 and 3 for method of calculation). This figure is comparable with the separate $-\Delta G^o$ values for either Cl or OH,[5] implying an electrostatic contribution towards stabilising the diaxial conformation (IIa) when both groups are present. The experimental value is in reasonable agreement with that calculated (above) from eqn. (ii), but disagrees with the result from eqn. (i). The diequatorial:diaxial ratio is now estimated as 73:27, and not 86:14, as implied in the earlier paper.[3]

Refinements and further applications of eqn. (ii) are being explored, and will be reported later, with details of the present work.

We are grateful to Professor Dr. E. Havinga for valuable discussions.

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