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CONFORMATIONAL STUDIES. XI. NMR STUDIES OF TRANSANNULAR SUBSTITUENT EFFECTS IN CYCLOHEXANOLS

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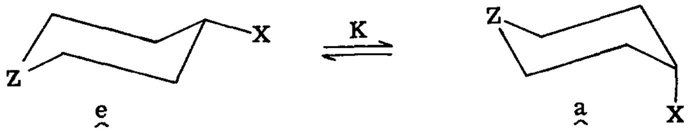
Among the many examples of monosubstituted cyclohexanes (1) which have been studied, not a single valid case has been reported in which the chair conformation with the substituent *axial* (a) predominates at equilibrium (1). However, when the structure of a monosubstituted cyclohexane is altered by introduction of a symmetrical transannular substituent, Z, to give 2, the conformational equilibrium constant, K, may then be quite different from what it was for 1.



1 $Z = H_2C$

2 $Z = Y_2C$, $Y{=}C$, Y_2N^+, O, S, O_2S, etc.

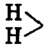
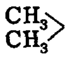
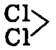
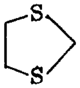
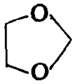
Indeed, for certain combinations of X and Z groups, conformation 2a predominates. We wish to report progress toward elucidation of the interactions between X and Z which may influence the relative free energies of 2a and 2e.

Compare cyclohexanol (3) with the other compounds (2, X = OH) listed in Table I. First, observe that introduction of a *nonpolar* transannular substituent into 3 to give 4, or 5, produces no significant change in the conformational equilibrium in benzene solution (2). However, introduction of a strongly *electron attracting* transannular substituent into 3 to give 6, or 7, actually reverses the direction of the conformational equilibrium in benzene solution; 6a and 7a predominate. Weaker electron attracting substituents in 8, 9, and 10 produce a smaller change than is found for 6 and 7.

Table I

X-Proton Band Width (W) vs. Symmetrical Transannular Substituent (Z) for Cyclohexanols in Benzene Solution at 33°

e a

Compound i	Z	W_i, Hz[a]	%a[b]	ΔG° kcal/mole[c]
3		25.3	24	+0.7
4		25.3	24	+0.7
5		25.4	24	+0.7
6		20.2	53	-0.1
7[d,f]	O=	19.7	56	-0.15
8	$H_2C=$	23.5	35	+0.4
9		23.3	36	+0.4
10[e,f]		23.9	32	+0.45

[a] ± 0.2 Hz, except compounds 3, 4, 5, and 9, ± 0.5 Hz. See ref. 6.

[b] ± 3%, assuming W_{ie}, 29.6 ± 0.1 Hz, and W_{ia}, 12.0 ± 0.1 Hz.

[c] ± 0.1 kcal/mole, with the above assumption.

[d] 4-Hydroxycyclohexanone-2,2,6,6-d_4 (7).

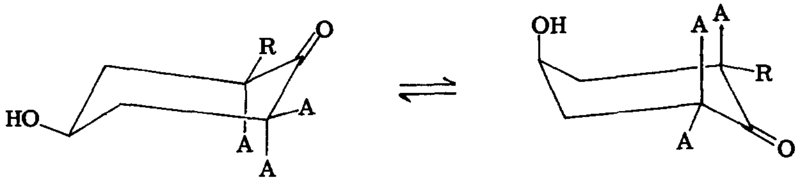
[e] 1,4-Dioxaspiro[4.5]decan-8-ol-2,2,3,3,6,6,10,10-d_8 (10).

[f] No absorption attributable to intramolecular hydrogen bonding was detected in the infrared spectrum, 0.004 M in CCl_4. Therefore nonchair populations are negligible for 7 and 10, and by analogy, it is reasonable to assume nonchair populations are also negligible for 3-6, 8, and 9.

Therefore, the relative population of the axial conformation (2a) appears to increase with the electron attracting ability of the Z group in 3-10.

Second, note that 4 and 6 with tetrahedral Z groups of similar steric size, give extremely different conformational equilibria. Furthermore, 7 and 8, each with a trigonal Z group, give quite different conformational equilibria. Compounds 6 and 7, with very different Z group geometry, give strikingly similar conformational equilibria. Therefore differences in geometry between 3 and 4-10 appear to play a minor role in altering relative conformational energies.

These results suggest that rather than an indirect steric effect, the major influence exerted by group Z upon conformational equilibria of 2 may be a polar effect. One type of polar effect, a transannular dipole-dipole interaction, has been considered in the case of chemical equilibration of the stereoisomeric *cis*- and *trans*-2-*t*-butyl-4-hydroxycyclohexanones (11 and 12), where 11 (or 13) may be taken as a model for 7e, and 12 (or 14), for 7a (3).



7e R = A = D 7a

11 R = $C(CH_3)_3$, A = H 12

13 R = $C(CH_3)_3$, A = D 14

Excellent agreement between the free energy differences is observed for $7e \rightleftharpoons 7a$ (Table I), ΔG°_7, - 0.15 ± 0.08 kcal/mole, and $11 \rightleftharpoons 12$ (3), ΔG°, - 0.09 ± 0.01 kcal/mole at 33° in benzene solution. The quantity, $(\Delta G^\circ_3 - \Delta G^\circ_7) = 0.85$ kcal/mole, gives an independent measure of the substantial influence a transannular carbonyl group exerts upon the conformational equilibrium of the hydroxyl group (3). Calculations of dipole-dipole interaction energies, analogous to that reported for $11 \rightleftharpoons 12$ (3), show that the quantities $(\Delta G^\circ_3 - \Delta G^\circ_i)$, derived from Table I, may be accounted for (to *ca.* ± 0.1 kcal/mole) for the compounds i = 6, 7, and 8. However, for 10, there is found a striking discrepancy which places in doubt any simple correlation between conformational energies and Z group-X group transannular dipole-dipole interactions evaluated in the manner reported previously (3). For 10, $\Delta G^\circ_{\text{found}}$ is + 0.45 kcal/mole, while

ΔG°_{calcd} is + 0.95 kcal/mole. Unlike the Z groups in 6-8, the ketal group dipole is directed *toward* the cyclohexane ring (4). The calculated stabilization of 10e relative to 10a is clearly *not* observed. Therefore, we conclude that the apparent correlation between transannular dipole-dipole interactions and conformational energies for 6-8, and for 11 $\rightleftharpoons$ 12 (3), may be fortuitous. There remains an observed correlation between the electron attracting ability of Z and conformational energies for 3-10, but the mechanism of electrostatic interaction between X and Z is still a subject for speculation, and further study (5).

In the present work, model compounds 13 and 14 were used in interpretation of the nmr X-proton band widths of 3-10 (6). The band width of the C-4 proton of 13, 29.6 ± 0.1 Hz in benzene solution at 33°, has been taken as W_{ie}; the band width of the C-4 proton of 14, 12.0 ± 0.1 Hz in benzene solution, has been taken as W_{ia}, where i = 3-10, $W_i = N_{ia}W_{ia} + N_{ie}W_{ie}$, and $N_{ia} + N_{ie} = 1$. Then, the relation, $N_{ia} = (29.6 - W_i)/17.6$, gives the mole fraction of the axial conformer (a) for each compound, reported as percent in Table I. The corresponding conformational free energies (ΔG°) are also given in Table I. Although 13 and 14 were designed as specific model compounds for 7e and 7a, they yield reasonable values of ΔG° for compounds 3 and 4 (1,2). The assumption that W_{ie} and W_{ia} are constants over the range of compounds 3-10 appears to be a reasonable and useful approximation.

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