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FLUORINE AND PROTON NMR STUDIES OF THE CONFORMATIONS OF 4,4-DIFLUOROCYCLOHEXANOL AND ITS BENZOATE (1)

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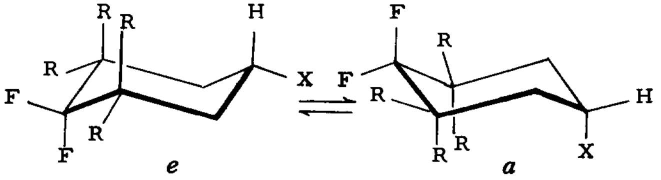
Fluorine substitution into a polar flexible molecule may be expected to significantly alter the conformational equilibria for that molecule because of electrostatic (or other) interactions between polar substituents and the fluorine atoms. Therefore, the "fluorine-labeling technique" which has been used successfully in conformational studies of hydrocarbons (4,5), should not be extended to polar flexible molecules without taking account of the interactions introduced by the fluorine atoms and their effect on the conformational energies. We report here studies of conformational equilibria by fluorine and proton nmr directed toward evaluation of the transannular interactions introduced when a 4,4-difluoro group is substituted into cyclohexanol (and other related polar flexible molecules).

Conformational populations have been determined from fluorine nmr peak area ratios obtained by integration of spectra recorded at 56.4 MHz and -83° to -104° for 4,4-difluorocyclohexyl benzoate (I), 4,4-difluorocyclohexyl-3,3,5,5-d_4 benzoate (II), 4,4-difluorocyclohexanol (III) and 4,4-difluorocyclohexanol-3,3,5,5,-d_4 (IV).



I R = H, X = OBz
II R = D, X = OBz
III R = H, X = OH
IV R = D, X = OH
V R = H, X = Cl

At these low temperatures, conformational interconversion is slow on the nmr time scale for I-V, and the observed spectrum is the superposition of the spectra of the individual conformers, *a* and *e*. Each conformer gives an AB quartet. For I*a*, I*e*, III*a* and III*e*, each quartet consists of a relatively narrow downfield pair of peaks and a relatively broad upfield pair of peaks. For II*a*, II*e*, IV*a*, and IV*e*, with vicinal deuterium-fluorine couplings in place of the proton-fluorine couplings of I and III, all peaks are relatively narrow. In each quartet, the upfield pair of peaks is attributable to an axial fluorine atom(5).

The downfield equatorial fluorine peak area ratio for II*a* and II*e* in acetone-fluorotrichloromethane solution at -104° corresponds to 74 ± 2% of the major conformer, and 26 ± 2% of the minor conformer. That II*a* with the benzoate group axial is the major conformer follows from the relative areas of the C-1 proton nmr peaks of II*a* and II*e* under the same conditions(6). However, at 60 MHz, the downfield narrower peak of larger area attributable to II*a* overlapped the upfield broader peak of smaller area attributable to II*e*. Consequently, the proton nmr spectrum of II only gives a qualitative area ratio, but it does allow unequivocal assignment of structure to the major conformer by comparison with model compounds (7). Taken together, the fluorine and proton nmr spectra at -104° are consistent with a free-energy difference for II*e* $\rightleftarrows$ II*a* of $\Delta G^\circ_{-104^\circ}$, -0.35 ± 0.04 kcal/mole (see Table I). If $\Delta G^\circ_{-104^\circ}$ for cyclohexyl benzoate is taken to be equal to $\Delta G^\circ_{-83^\circ}$ for cyclohexyl acetate (+0.72 kcal/mole (8)) then the change of ΔG° resulting from introduction of the 4,4-gem-fluoro group is about 1.1 kcal/mole.

The 60-MHz proton nmr spectrum at -93° of 4,4-difluorocyclohexanol-3,3,5,5-d_4 (IV), 100 mg in 0.15 ml of methanol-d_4 plus 0.15 ml of fluorotrichloromethane, shows a broad peak for the C-1 proton of IV*e* overlapped on its downfield side by a narrower peak of comparable area for the C-1 proton of IV*a*. Under the same conditions, the downfield equatorial fluorine peak areas corresponded to a nearly equal mixture of IV*a* and IV*e*, with 51 ± 2% of one, and 49 ± 2% of the other. Assignment of conformation to each pair of peaks (Table I) is based upon analogy with II. The spectra of II and IV are so similar (Table I) that there is a very high probability that the assignment is correct. The assignment, of course, is not crucial in evaluating the negligible free-energy difference for IV*e* $\rightleftarrows$ IV*a*, $\Delta G^\circ_{-93^\circ}$ = -0.01 ± 0.03 kcal/mole.

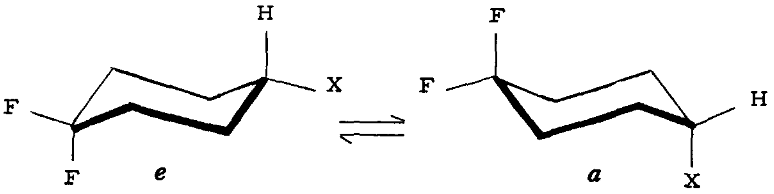
The upfield axial fluorine peak areas give an independent measure of the same quantity under the same conditions. The result, 46.5 ± 3% of IV*a*, gives for IV*e* $\rightleftarrows$ IV*a*, $\Delta G^\circ_{-93^\circ}$, + 0.05 ± 0.05 kcal/mole. An average of the two independent values gives $\Delta G^\circ_{-93^\circ}$, + 0.02 ± 0.08 kcal/mole. We conclude that the conformational free energies of IV*a* and IV*e*, under these conditions, are essentially equal.

In protic solvents, the conformational free-energy difference for cyclohexanol is + 0.87 kcal/mole in favor of the equatorial conformation (9). Therefore, introduction of a gem-fluoro group into cyclohexanol at C-4 to give IV reduces this free-energy difference to about + 0.02, a change of about 0.85 kcal/mole, a significant destabilization of the equatorial conformer relative to the axial conformer.

The fluorine nmr parameters were reported previously for 1-chloro-4,4-difluorocyclohexane (V), along with the magnitude (but not the sign) of the free-energy difference for V*e* $\rightleftarrows$ V*a* (5). The observed pattern of fluorine chemical shifts (absolute values, δ, and differences, $\nu_0\delta$), show a striking similarity (Table I) between II and V only if V*a* is more stable than V*e*. That conformer V*a* with chlorine axial is more stable than V*e* has been demonstrated unequivocally for V in propene solution at -93°; the relative C-1 proton nmr peak areas of V*a* and V*e* require > 60% of V*a* to be present. Therefore, for V*e* $\rightleftarrows$ V*a* in propene solution, $\Delta G^\circ_{25^\circ}$, -0.32 kcal/mole (3), may be contrasted with the reported value of the free-energy difference between the corresponding conformations of chlorocyclohexane,

TABLE I

Fluorine Magnetic Resonance Parameters and Conformational Free Energy Differences for Cyclohexane Derivatives II, IV, and V



		Conformation *e*				Conformation *a*				*e* ⇌ *a*
X	T, °C	Chemical shift, Hz upfield from $FCCl_3$ Eq	Ax	$\nu_0\delta$ Hz	J_{FCF} Hz	Chemical shift, Hz upfield from $FCCl_3$ Eq	Ax	$\nu_0\delta$ Hz	J_{FCF} Hz	$\Delta G°$,[d] kcal/mole at T°
OBz[a]	-104	5295	5782	487	237	5003	5890	888	236	-0.35
OH[b]	- 93	5305	5781	477	237	4958	5888	930	236	-0.01
Cl[c]	- 75	5342	5836	494	236	5084	5880	796	236	-0.16

[a] 4,4-Difluorocyclohexyl-3,3,5,5-d_4 benzoate (II) in acetone-Cl_3CF

[b] 4,4-Difluorocyclohexanol-3,3,5,5-d_4 (IV) in D_3COD-Cl_3CF

[c] 4,4-Difluorocyclohexyl chloride (V) in acetone, recorded by S. L. Spassov, and reported in Ref. 5 without assigning the sign of $\Delta G°$.

[d] Based upon the equatorial fluorine peak areas.

ΔG° = + 0.43 kcal/mole (9) (+0.53 kcal/mole at −83° (8)) favoring the equatorial conformation. The difference, about 0.8 kcal/mole, is again a substantial stabilization of the axial conformer relative to the equatorial conformer upon introduction of a *gem*-fluoro group at C-4. It should be noted that this difference in stabilization is too large to be chalked up to simple dipole-dipole repulsions calculated as though acting through a medium of dielectric constant equal to 2.0. The nature of the electrical effects operating in these systems will be the subject of later papers.

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(6) The Varian A-56/60A Spectrometer used in this work can be switched easily from ^{19}F to ^{1}H resonance without disturbing the sample.

(7) In general, axial C-1 proton band widths are about 2.5 times the equatorial C-1 proton band widths for related compounds. See N. C. Franklin and H. Feltkamp, *Angew. Chem. Internat. Ed.* **4**, 774 (1965).

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