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136. Flexional Effects in Bridged Bicyclic Molecules Progressive Flattening of Chair Cyclohexane

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(15 V 70)

Summary. Measures of the progressive flattening of the chair conformation in a series of constrained cyclohexanols are obtained and compared by proton NMR. coupling constants and by molecular mechanics.

The shapes of six membered rings have continued to receive attention both from theoretical [1] and practical [2] viewpoints. It is now recognized that the perfect chair conformation represents an ideal state of affairs since electron diffraction reveals that even cyclohexane itself is flatter than supposed [3], the internal C–C–C angle being 111.55° not 109.4°. Furthermore, substitution on the ring causes additional deviations from the chair conformation. When two methyl groups are substituted in a *syn*-axial disposition, the operation of the Reflex effect brings the ***trans*** anti-parallel pair of *syn*-axial substituents closer together (fig. 1a) [4]. Contrariwise, *syn*-axial placement of an ethane bridge, as exemplified by bicyclo[3.2.1] octane,

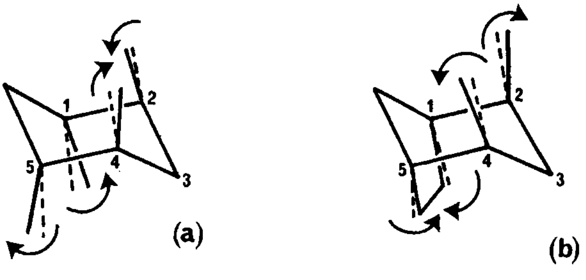


Fig. 1. *Operation of the Reflex Effect (a) and its inverse (b)*

leads to the inverse Reflex effect in that "pinching" on one side of the chair results in the prising apart of the appropriate pair of axial bonds on the other side (fig. 1 b) [5].

Apart from these two cases, which may be considered as representing two discrete flexomers of cyclohexane, no study has been undertaken of the progressive application of flexional constraint to the chair conformation. In the "pinching" process depicted above (cf. (a) and (b), fig. 1) C-3 moves towards the plane described by carbons 1, 2, 4, and 5. Consequently, the vicinal coupling constants of the methine proton of the derived equatorial C-3 alcohols should constitute a sensitive index of conformational changes around the C2-C3-C4 fragment (Fig. 2a). In the table are listed data of a series of such equatorial cyclohexanols (I–V) in which increasing constraint is applied across the *syn*-axial positions on C-1 and C-5.

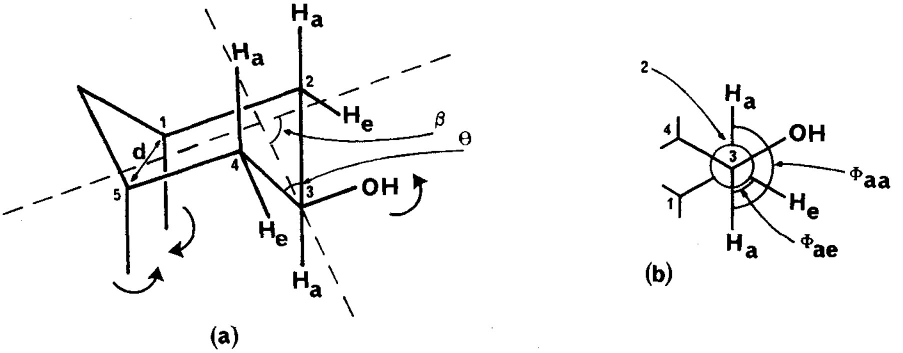


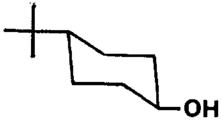
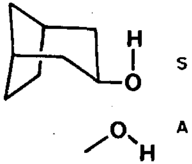
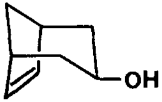
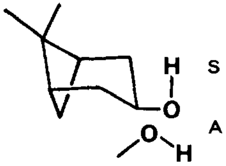
Fig. 2. *Flattening of the chair and its measurement in terms of (a) the flattening angle (β), the valence angle (θ), the internuclear C1-C5 distance* (d), *and (b) the* gauche *and* trans *dihedral angles* (Φ_{ae}, Φ_{aa}) *as calculated from the* Karplus *equation* (ref. [6])

$^3J = A\cos^2\Phi + \cos\Phi$ when $\Phi_{ae} = \Phi = 0$–$90°$, A = 9.3; when $\Phi_{ac} = \Phi = 90$–$180°$, A = 12.7

The signals of the C-3 methine proton by first order analysis and on the basis of the presumed C_S symmetry of the compounds afforded just two constants ^3Jaa and ^3Jae. It is clearly seen that both constants vary uniformly with the severity of "pinching" of the cyclohexane chair. Indeed ^3Jaa decreases to about the same extent as ^3Jae increases. By using a modified *Karplus* equation, dihedral angles corresponding to these coupling constants were obtained (Fig. 2b). It was assumed that atoms C-2, C-3, and C-4 were pure [sp^3] hybrids and that they possessed the usual tetrahedral geometry. Although this is probably not true, it does not affect the correctness of the angles so obtained as the *Karplus* equation has quite a margin of error. The variations in the *gauche* (ϕ_{ae}) and the *trans* (ϕ_{aa}) dihedral angles give a quantitative measure of the progressive flattening of the chair [6].

By way of comparison, we have also listed in the table, the dihedral angles and the valence angle at C-3 (θ) calculated by the *Wiberg-Hendrickson-Allinger* method [7]. From the same calculations we have obtained the angle of flattening (β) and the internuclear distance *d* between C-1 and C-5 (Fig. 2a). It is seen that the valence angles θ remain fairly constant at about 112–113°, whereas the value of β is a good guide to flattening. Both sets of dihedral angles calculated by the two methods agree well. Calculation further shows that flattening goes hand-in-hand with a narrowing

Coupling constants and calculated geometric parameters for some constrained cyclohexanols

		J_{aa} Hz	J_{ae} Hz	Dihedral Angles Φ_{aa} from J		Φ_{ae} from J		β	Valence angle θ at C-3	d (Å) calc.	*Dreiding* models	Ref.
					calc.		calc.					
I		11.2	4.0	170°	164°	52°	55°	47°	112°	2.58	2.64	[9]
II		11.1	4.3	167°	163°	49°	53°	46°	112°	2.52	2.52	[10]
III		10.0	5.5	158°	148°	44°	40°	40° 41°	114° 113°	2.37	2.40	[5] [9] [11]
IV		9.5	6.5	155°	146°	39°	33°	28°	114°	2.36	2.32	[12]
V		9.2	7.6	153°	144° 119°	32°	30° 9°	32° 15°	111° 113°	2.03	2.08	This work

Note: All measurements were made in CCl_4 except IV which was taken in $CDCl_3$. For I and II the calculated values were obtained from the corresponding hydrocarbons. *Dreiding* models were constructed as follows:

I Using six cyclohexane [*sp*^{3}] carbons and putting the *syn*-axial methyl-methyl distance at 8.5 cm (≡ 3.4 Å).
II Regular chair.
III Model composed of five cyclopentane and three cyclohexane [*sp*^{3}] carbons.
IV Three cyclopentane and three cyclohexane [*sp*^{3}] carbons and two cyclopentene [*sp*^{2}] carbons.
V Four cyclobutane and three cyclopentane [*sp*^{3}] carbons.

of the C1-C5 internuclear distance (*d*). In fact the values for *d* compare favourably with those measured directly on appropriately constructed *Dreiding* models.

A consequence of the energy minimization process [7] is that two rotamers are possible for compounds III and V. For III, the syn- and apotropic (*S* and *A*) rotamers

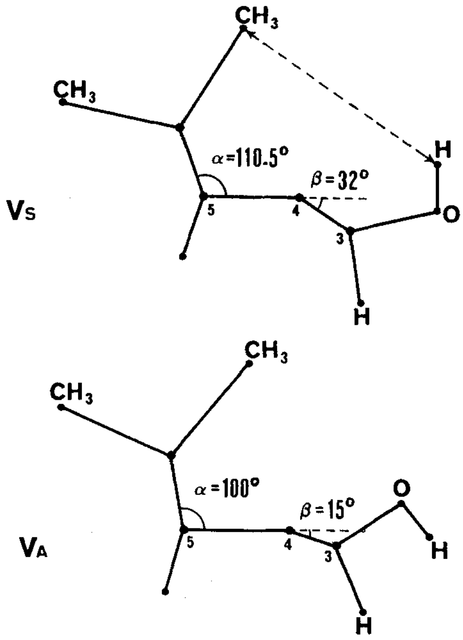


Fig. 3. *Projection of conformations of* α*-isonopinol* (*V*) *showing the difference in flattening in the syntropic* (V_S) *and apotropic* (V_A) *rotamers*

have the same energy. However, for α-isonopinol (V) they have different energies. Moreover, the more stable rotamer is predicted to be the syntropic one in which the hydroxyl group is directed towards the *gem*-dimethyl grouping. This paradoxical conclusion is substantiated by the NMR. spectrum. In rotamer V_S, the hydroxyl-methyl non-bonded interaction produces appreciably larger angles of flattening (β and α) than those found in V_A, the unstable rotamer, where the interaction is absent (Fig. 3). These differences are reflected in the dihedral angles ϕ and it is significant that the values obtained from the *Karplus* equation accord best with those calculated for V_S.

These findings indicate that the origin of the inverse Reflex effect is not simply due to disrotation about the C4-C5 and C2-C1 bonds, but that the shortening of the internuclear distance *d* plays a dominant rôle. In addition it has to be anticipated that substituents can provoke ring distortion in an unforeseen manner.

It can also be noted that, despite previously cited shortcomings [8], the *Karplus* equation can be a good measure of conformation, especially in a homogenous series. *X*-ray structure analysis of these cyclohexanols will provide a complementary frame of reference; such studies are in progress and will be reported elsewhere.

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137. Fluorine NMR. Spectra of Conformationally Constrained *Gem*-Difluorocyclohexanes

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(15. V. 70)

Summary. The ^{19}F chemical shifts and geminal coupling constants have been measured for 3,3-dimethyl- (I), 3,3,5-trimethyl- (II) and 3,3,5,5-tetramethyl-1,1-difluorocyclohexane (III) and 3,3-difluorobicyclo[3.2.1]octane (IV). The *Eyring* parameters for the ring inversion were obtained for I and III. Representative values for the *Arrhenius* activation energy (*Ea*), $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ are: 11.0, 9.4, 10.4 kcal/mole and 4.5 e.u. for I, and 10.0, 8.3, 9.7 kcal/mole and 8.3 e.u. for III. It appears that the *syn*-axial methyl-fluorine interaction has a negligible effect on the inversion process. However, the *syn*-axial methyl-methyl interaction, as found in III, significantly increases the rate of inversion. Substituent effects on the ^{19}F shifts are marked. Introduction of methyl at C-3 in an equatorial position leads to shielding of the equatorial and axial fluorines (+1.8 and +1.3 ppm). Substitution in the axial C-3 position causes deshielding of the equatorial and axial fluorines (– 5.9 and – 4.9 ppm).

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