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APPLICATION OF 220 MHZ NMR TO THE STUDY OF STEREOCHEMICAL AND ANISOTROPIC EFFECTS OF THE CYCLOPROPANE RING IN STEROIDS

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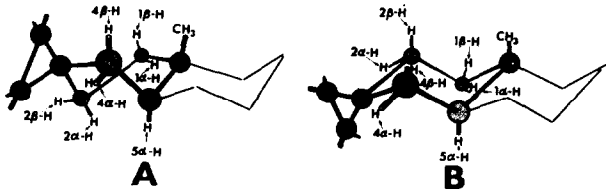
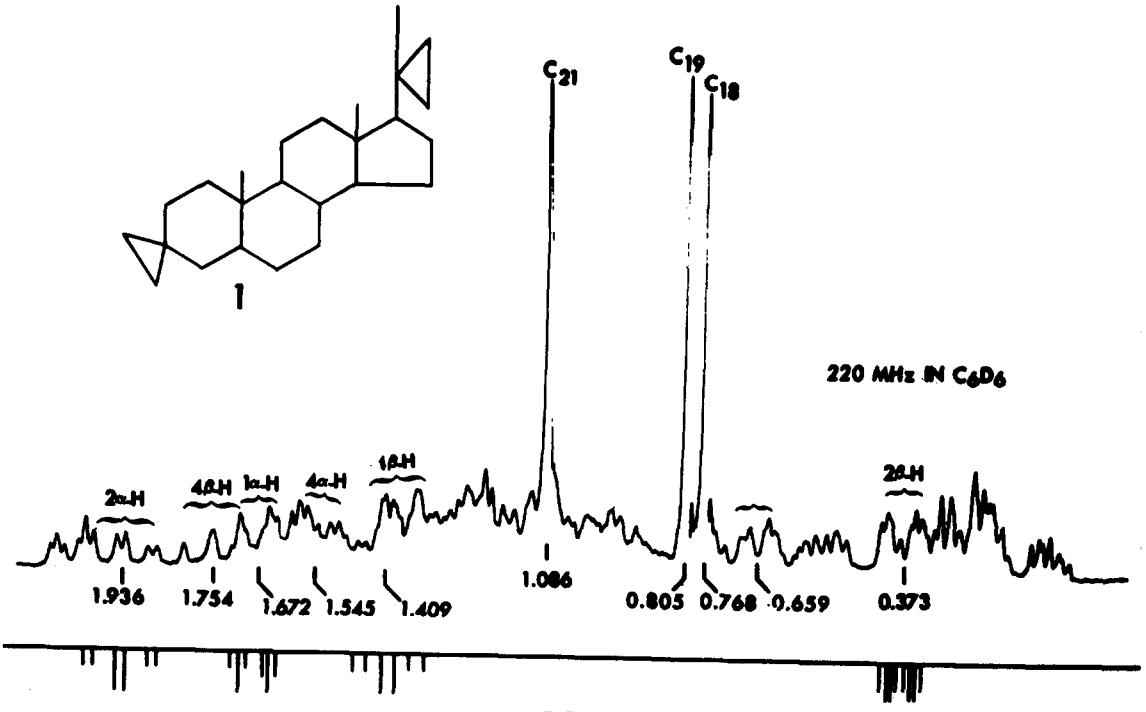
We describe the investigation of long range anisotropic effects (1) of the three-membered ring in 3-spirocyclopropyl steroids (2) using a 220 MHz spectrometer (Varian HR-220) and iteratively computed (3) line fitting. To facilitate discussion of the spectral analysis, we first consider the most likely conformations of ring A. These are the conventional chair (B) in which the equatorial 2α-H and 4α-H are deported over the face



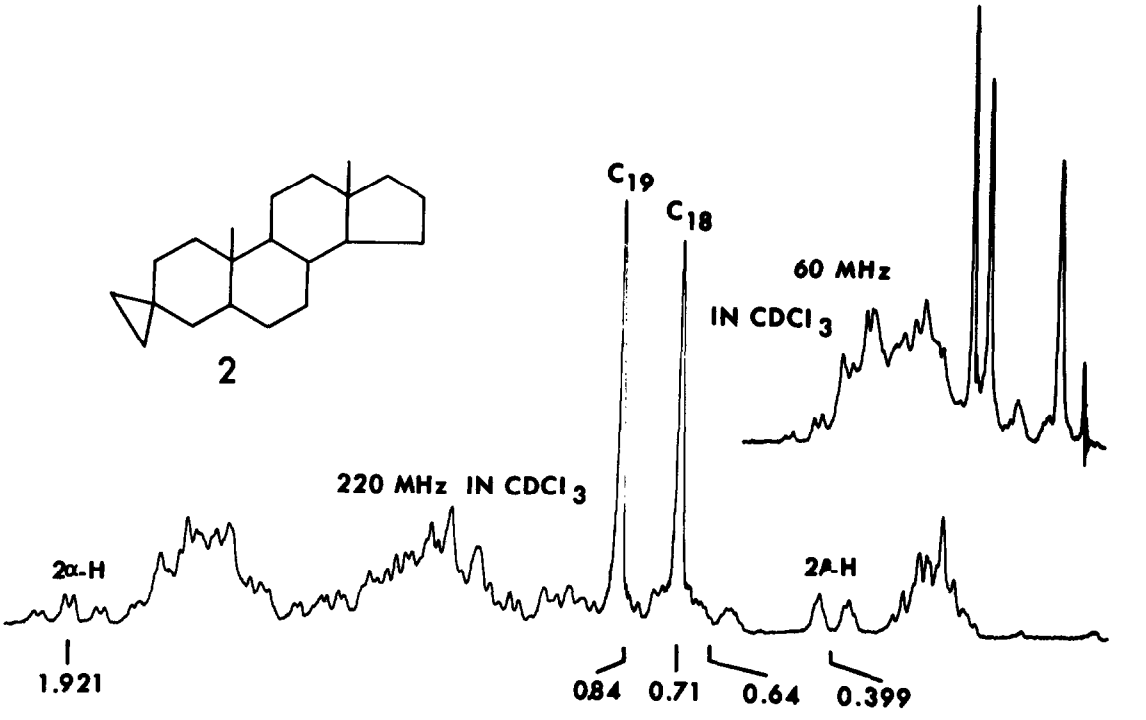
of the cyclopropane ring and the respective α- and β- protons at C-2 and C-4 are symmetrical with reference to cyclopropane. By contrast, in the 2, 5-bow:stern twist-boat form (A) (θ=60°) the spatial relationships of the respective α- and β-protons at C-2 and C-4 are not symmetrical relative to the cyclopropane ring (4). Here the 2β-H and 1α-H become boat-equatorial (5) whereas the 2α-H and 1 β-H become boat-axial, but the usual dihedral angle relationships between axial and equatorial apply. The boat-equatorial 2β-H is located in the region of maximum shielding of the cyclopropane ring, whereas the boat-axial 2α-H is deshielded. By contrast, both protons at C-4 are in a shielding environment. The 3,10-bow:stern form (θ=0°) is not considered because of the inherent instability of these forms as well as the special hindrance of the cyclopropane ring by the C-19 group in this case.

Using the equation[1d] $\Delta\delta(\text{ppm}) = -\sum_{i=1}^{3} \frac{3\cos\theta\, i - 1}{R_i^3}$ calculations were made to establish the magnitude of anisotropic effects of the C-3 cyclopropane on ring A protons. The results for the twist-boat indicate that a shielding effect of 0.82 ppm is exerted on the 2β-H by the cyclopropane ring whereas the 2α-H is deshielded by 0.29 ppm. Thus, for protons at C-2, a large difference (1.11 ppm) is due solely to the influence of cyclopropane. This is not the case at C-4, where a small difference (0.30 ppm) is predicted for the 4α-H and 4β-H. By contrast, in the chair conformation, a large shielding (>0.8 ppm) is calculated for the 2α-H and the 4α-H, and a large difference in position (>1.0 ppm) is estimated between the two protons attached to C-2 as well as those at C-4.

The observed spectra are in harmony only with the twist-boat conformation (A). In the example shown, the most readily decipherable multiplets are the signals at 0.373δ and 1.936δ, each representing one hydrogen. The resonance at 0.373δ, being a doublet of triplets, indicates that the responsible proton is spin-coupled to a geminal proton with a coupling of -13.5 Hz and also to two vicinal protons with very nearly equal couplings of about 3 Hz. The presence of the large geminal coupling of -13.5 Hz was verified by double resonance experiments at 100 MHz. The 0.373δ signal fits the case of the 2 β-H where the boat-equatorially oriented proton bisects the angle between the C-1 methylene hydrogens and the boat-equatorial:boat-axial splitting is very nearly equal to the boat-diequatorial splitting (∿3 Hz). The six line pattern at 1.936δ is due to the 2α-H where the two large couplings of about 13.5 Hz arise from interactions of the 2α-H with its neighbor as well as with the boat-axial 1β-H, and the smaller splitting of 3.3 Hz is caused by coupling of the 2α-H with the boat-equatorial 1α-H. Only a tentative assignment can be made for C-1 and C-4 protons, and the magnitude of other factors affecting the respective peak positions (e.g. axial-equatorial differences) cannot readily be estimated, especially for the twist-boat form. Nevertheless, there is no high field peak corresponding to the 4α-H in any of the spectra examined in either $CDCl_3$ or C_6D_6, as required by the chair conformation. Consequently, the only possible explanation for these spectral features is that ring A is in the twist-boat conformation. Coupling constants are in excellent agreement with this conformation:


1
C21
C19
C18
220 MHz IN C6D6
2α-H
4β-H
1α-H
4α-H
1β-H
2β-H
1.936
1.754
1.672
1.545
1.409
1.086
0.805
0.768
0.659
0.373

LAOCN 3


2
C19
C18
60 MHz
IN CDCl3
220 MHz IN CDCl3
2α-H
2A-H
1.921
084
0.71
0.64
0.399

Expected and Observed Coupling Constants

	$J_{1\alpha1\beta}$	$J_{1\alpha2\alpha}$	$J_{1\alpha2\beta}$	$J_{2\alpha2\beta}$	$J_{1\beta2\beta}$	$J_{1\beta2\alpha}$	$J_{4\alpha4\beta}$
Twist-boat	-13.0	1.8[a]	3.5[a]	-13.0	1.8[a]	16.o[a]	-13.0
Observed[b]	-13.0	3.3	3.5	-13.5[c]	2.8	13.4	-13.5

a Calculated from substitution of dihedral angles taken from Dreiding models in the Karplus equation. b Values obtained from LAOCN3 computation best values. From decoupling experiment.

A striking feature of the 220 MHz spectrum of 3-spirocyclopropyl-5α-androstane was the nmr pattern caused by a proton occurring at unusually high field, (δ = 0.64). This pattern can arise from the 6α-H, 7β-H or 11α-H. Each of these protons is spin-coupled to four other hydrogens, with one large coupling to the geminal neighbor and three smaller couplings to vicinal neighbors. Since this nmr pattern is not observed in the 220 MHz spectrum of 5α-androstane, the high field position of these signals is clearly due to the cyclopropane ring. The nature of the responsible effect is unknown, since the McConnell calculation[1d] indicates a negligible anisotrophy due to cyclopropane at this distance.

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