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Conjugation of Spirocyclopropane with the Carbonyl Group. Conformational Analysis of Spiro[cyclopropane-1,2′-steroids]

Umesh R. Desai and Girish K. Trivedi*
Department of Chemistry, Indian Institute of Technology, Bombay—400 076, India

The conjugative ability of a spirocyclopropane on 4-en-3-one steroids was studied with the help of ^{13}C NMR and two-dimensional experiments such as COSY and NOESY. The conformational analysis of the A ring of these compounds indicates a 'normal' (1α,2β)- half-chair conformation rather than the expected 'inverted' (1β,2α)- half-chair conformation. Application of the modified McConnell equation for the shielding influence of the cyclopropane aids the analyses.

KEY WORDS Spirocyclopropanes Spiro[cyclopropane-1,2′-steroids] 2D NMR Conformational analysis

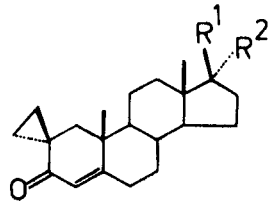
INTRODUCTION

With the advent of 2D NMR techniques, the field of conformational analysis of steroids has attracted renewed interest. The peculiar skeletal framework involving complicated spin systems, coupled with the variation in biological activity with structural variation, has made steroids an attractive target for the analysis of conformation. Although several papers have discussed the conformational analysis of 4-en-3-one steroids,[1–4] none has reported analyses of spiro[cyclopropane-1,2′-steroids]. These possess various biological activities including diuretic,[5] antiandrogenic,[6] contraceptive[7] and tranquilizing[8] properties. In a project designed to synthesize new steroid haptens for radioimmunoassay, we had occasion[9] to prepare these spirocyclopropane steroids. However, nucleophilic opening of the spirocyclopropyl ring failed completely; following this result, doubts were raised regarding the conjugative ability of the spirocyclopropyl group with the carbonyl group in these compounds. This paper discusses aspects of the conjugative ability of spirocyclopropane and the conformational analysis of the A ring of spiro[cyclopropane-1, 2′-steroids).

EXPERIMENTAL

Spiro[cyclopropane-1,2′-steroids] **1a–d** were synthesized according to a procedure developed in our laboratory[10] using Simmons–Smith cyclopropanation.

^1H and ^{13}C NMR spectra were recorded on Varian VXR 300S or Bruker AM500 spectrometers as solutions in $CDCl_3$ with TMS as internal standard at ambient temperature. DEPT experiments were performed using the conventional pulse sequence with polarization transfer optimized for $^1J(CH) = 125$ Hz. The ^{13}C resonances were assigned using DEPT, coupled spectral multiplicities, comparisons and known substituent effects. The 2D NMR experiments were performed on a solution of 100 mg of **1a** in 0.5 ml of $CDCl_3$ (Fig. 1) using an ASPECT 3000 computer. The homonuclear COSY experiment was performed using a standard pulse sequence with t_1 being incremented 256 times. The FIDs were processed on a 1K × 1K data matrix using shifted sine-squared bell window functions. The heteronuclear correlation experiment was performed with polarization transfer optimized for $^1J(CH) = 130$ Hz. The t_1 data points were 256 W and a delay of 1.5 s was used. The FIDs were Fourier transformed on a 4K × 0.5K data matrix with shifted sine-squared bell window functions. The NOESY experiment was performed using a mixing time of 1 s. The steady-state NOE difference experiment was performed by presaturation of the required signal and subtraction of the FID of the control spectrum from the FID on irradiation.



	R^1	R^2
a	$-C_8H_{17}$	H
b	-OH	H
c	$-OCOCF_3$	H
d	——O——	

Figure 1. Structures of the spiro[cyclopropane-1,2′-steroids] **1a–d**.

* Author to whom correspondence should be addressed.

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RESULTS AND DISCUSSION

The A ring of 4-en-3-one steroids can exist as a 'normal' (1α,2β)- half-chair, an 'inverted' (1β,2α)- half-chair or a sofa conformation (Fig. 2). The sofa conformation requires the coplanarity of C-2, C-3, C-4, C-5 and C-10, and for spiro[cyclopropane-1,2'-steroids] to exhibit conjugative ability the A ring should possess the sofa conformation. This is a necessary condition since conjugation of the strongly distorted σ-bonds of cyclopropane with the carbonyl group requires a bisected conformation between the σ- and a π-system.[11,12]

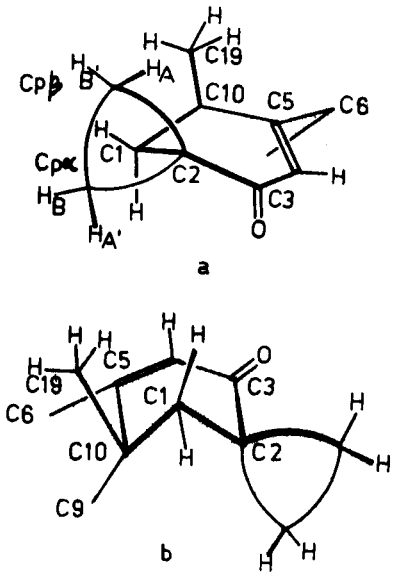

Figure 2. (a) 'Normal' (1α,2β)- half-chair and (b) inverted (1β, 2α)-half-chair conformations of spiro[cyclopropane-1,2'-steroids].

Examination of the ^{1}H NMR spectra of cyclopropyl derivatives **1a–d** (Fig. 3) reveals that, at best, two multiplet structures centred at δ 0.45 and 0.75 are observable, indicating strong deshielding for the other two protons. A homonuclear COSY experiment although largely uninformative, shows three cross-peaks for the multiplet at δ 0.45, indicating that all four protons are mutually coupled and resonate at δ 0.45, 0.75, 1.0 and 1.45. On the basis of a bisected conformation, the resonances would be expected to lie as pairs in shielded and deshielded regions, and hence the sofa conformation and thereby the conjugative ability are qualitatively negated.

Since the ^{13}C resonances are known to provide both electronic and structural information, the ^{13}C NMR spectra of **1a–d** were studied, and showed that the cyclopropyl carbons resonate at 12.0 and 21.5 ppm (Table 1). Helferty and Yates[13] reported that a lower threshold limit of 24 ppm for the cyclopropyl carbons appears to be necessary for 'spiroactivation', and hence the values of 21.5 and 12.0 ppm not only indicate the unsymmetrical nature of the two carbons but also a reduced conjugation with the carbonyl group. The C-2 signals for **1a** and **1b** were not observable, perhaps owing to coincidental equivalence. The DEPT experiments indicated a lowered intensity of the signals arising from the cyclopropyl carbons due to a larger ^1J(CH) value of about 163 Hz. Although the extent of sp hybridization of carbon atoms has been deduced from ^1J(CH) values,[14,15] and the extent of the π-character of cyclopropane estimated, the ^1J(CH) values

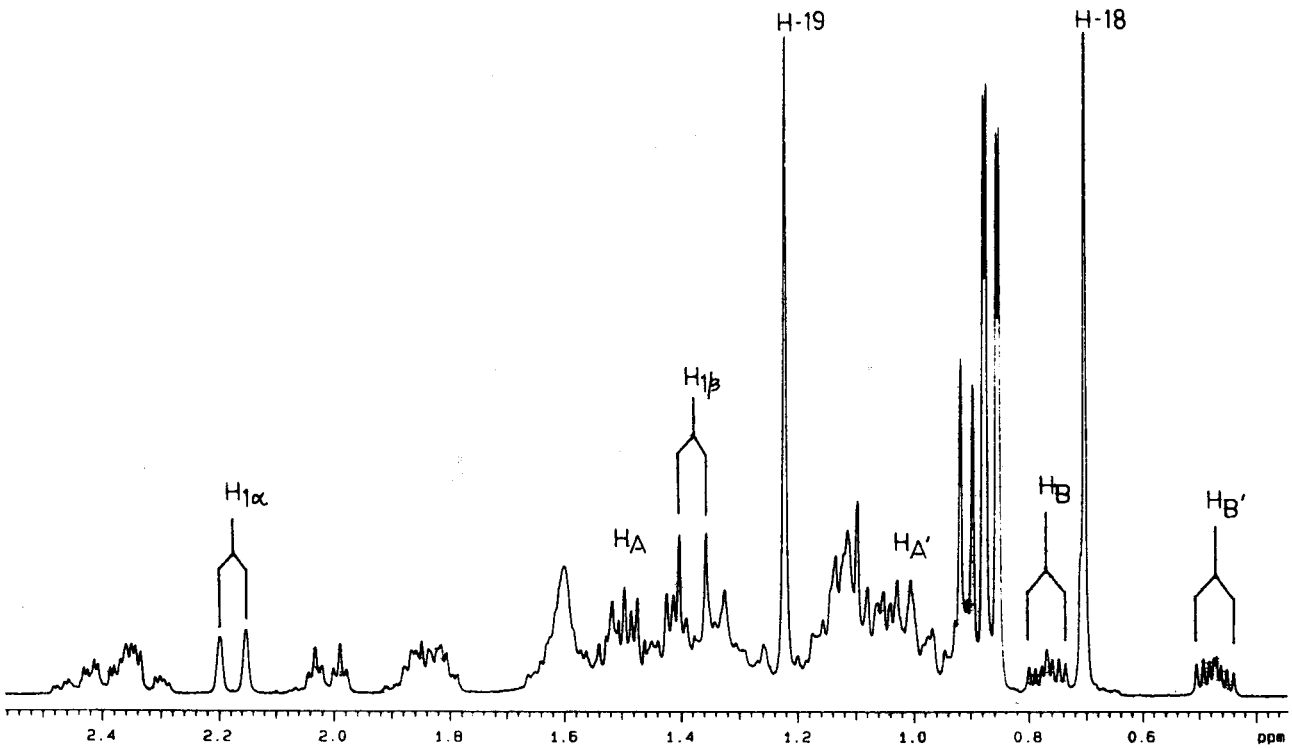

Figure 3. ^{1}H NMR spectrum of **1a** (300 MHz) in $CDCl_3$.

Table 1. ^{13}C NMR chemical shifts (ppm) of the A ring carbons

Carbon[a]	1a	1b	1c	1d
1	44.73	44.79	44.68	44.66
2	n.o.[b]	n.o.	23.67	23.63
3	199.72	199.68	199.40	199.21
4	124.33	124.47	124.60	124.62
5	171.01	170.59	169.70	169.48
19	18.92	18.95	18.87	18.83
cp β	12.03	12.08	12.06	12.02
	(164)[c]	(163.5)	(n.m.)[d]	(161.4)
cp α	21.46	21.55	21.55	21.50
	(n.m.)	(163.5)	(n.m.)	(167.4)

[a] cp = Cyclopropyl
[b] n.o. = Not observed.
[c] Values in parentheses are $^1J(CH)$ in Hz.
[d] n.m. = Not measured owing to severe overlapping.

Table 3. ^1H NMR chemical shifts (ppm) of the A ring protons

Proton	1a	1b	1c	1d
H_A	1.46	1.46	n.m.[a]	n.m.
$H_{A'}$	0.98	1.00	n.m.	n.m.
H_B	0.71	0.73	0.79	0.78
$H_{B'}$	0.41	0.46	0.49	0.49
19-H_3	1.22	1.24	1.24	1.13
H-4	5.79	5.79	5.81	5.82
H-1β	1.39	1.40	1.39	1.41
	(13.73)[b]	(13.36)	(13.55)	(13.73)
H-1α	2.18	2.19	2.20	2.21
	(13.73, 0.37)	(13.36)	(13.55, 0.37)	(13.73)

[a] n.m. = Not measured.
[b] Values in parentheses are $^1J(CH)$ in Hz.

do not perhaps indicate the true conjugative ability in our case. The 19-CH_3 resonance was observed at 18.92 ppm, indicating *syn* diaxial interactions of C-19 with a cyclopropane carbon.

With a view to gaining further insight into the conformational preference of these steroids, it was decided to examine the H-1α and H-1β signals in order to detect any long-range shielding influence of the cyclopropyl group on these protons. It is well known that the cyclopropyl group exerts a shielding influence on suitably located protons,[16,17] and this effect has been shown to vary predictably with the location of a given proton on the face of the cyclopropane ring.[17] Shieldings due to the cyclopropane group can be calculated on the basis of a modified McConnell equation, developed by Tori and Kitahonoki:[17]

$$\Delta\delta = \frac{\Delta\chi}{3}\sum_{i=1}^{3}\frac{3\cos^2\theta_i - 1}{R_i^3} \qquad (1)$$

where $\Delta\delta$ is the additional shift in ppm, due to cyclopropane, on the proton under consideration in a particular conformation, R_i is the distance (Å) between the mid-point of a C—C bond of the cyclopropane ring and the affected proton, θ_i is the acute angle of the line R_i with the C—C bond and $\Delta\chi$ is an empirically deduced constant equal to -20×10^{-30} cm^3 per molecule.[17]

The expected shieldings for H-1α in the (1β,2α)-conformation was found to be 0.48 ppm (Table 2) and that for H-1β in the (1α,2β)-conformation was 0.269 ppm. The COSY experiment indicates a ^4J coupling for the proton resonating at δ 2.2 (Table 3) with the 19-CH_3 protons, while the NOESY experiment indicates a dipolar coupling of the 19-CH_3 protons with the proton resonating at δ 1.4 (see Fig. 4 for the NOESY connectivities). This assigns the β-proton to the signal at δ 1.4 and the α-proton to that at δ 2.2. Hence H-1β, although equatorial, is shielded. Although studies have not been performed on related *gem*-dimethyl compounds, the majority of 4-en-3-one steroids possessing the (1α,2β)- half-chair conformation exhibit H-1β resonance between δ 2.0 and 2.2[2] and that of H-1α between δ 1.7 and 1.8. Thus a shielding of 0.7 ppm is found for H-1β whereas deshielding is observed for H-1α. Although the quantitative values of the shielding and deshielding do not compare favourably with those derived from the McConnell equation, the relative signs are in order. In addition, the application of the modified McConnell equation [Eqn (1)] is limited owing to the unanalysed proportionality constant $\Delta\chi$.

Table 2. Additional shift due to the cyclopropyl group (in ppm)[a]

1β,2α-Conformation		1α,2β-Conformation	
H-1β	H-1α	H-1β	H-1α
−0.57	+0.48	+0.269	−0.269

[a] Negative values indicate deshielding and positive values shielding.

The results derived from the above calculations are supported by the observation of the dipolar coupling between the 19-CH_3 protons and the cyclopropyl proton absorbing at δ 1.45. Similarly, H-1β exhibits a dipolar coupling with the cyclopropyl proton absorbing at δ 0.7. The heteronuclear correlation experiment shows that the protons absorbing at δ 0.4 and 1.45 are attached to the carbon absorbing at 12.03 ppm and those absorbing at δ 0.7 and 1.0 to the carbon absorbing at 21.46 ppm. Thus the cyclopropyl β-carbon is assigned to the 12.03 ppm absorption and the α-carbon absorbs at 21.46 ppm. This demonstrates a (1α,2β)-half-chair conformation for spiro[cyclopropane-1,2'-steroids]. However, in such a conformation a dipolar coupling between 19-CH_3 and the cyclopropyl proton

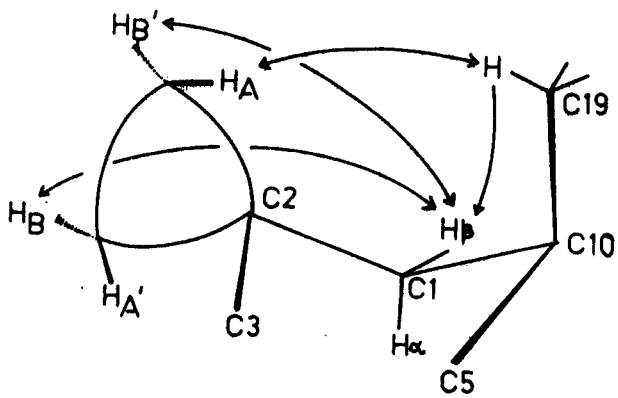

Figure 4. Observed NOESY connectivities.

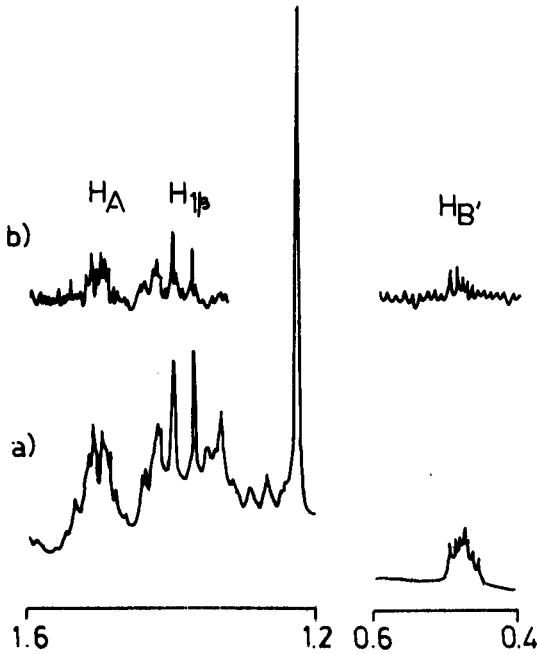

Figure 5. NOEs observed on irradiation of 19-CH_3 at δ 1.22. (a) Control spectrum; (b) difference spectrum.

absorbing at δ 0.4 ($H_{B'}$) should also have been observed in the NOESY spectrum. The non-observance of this cross-peak was intriguing. On performing a steady-state NOE difference experiment with irradiation of the 19-CH_3 signal, major enhancements were observed in the signals of H-1β and H_A (Fig. 5), together with a weak enhancement of the signal at δ 0.4 assigned to H_B. This weak NOE could be the reason for the non-occurrence of the NOESY cross-peak between 19-CH_3 and $H_{B'}$.

Conformational analysis indicates that all 2β-substituted steroids have the 'inverted' (1β,2α)- half-chair conformation owing to increased 1,3-diaxial interactions. This also demonstrates the subtle difference between *gem*-dimethyl substitution and spirocyclopropyl substitution. The spirocyclopropyl group makes the ring more 'open' and exhibits reduced 1,3-diaxial interactions, which confirms the enormous bioactivity observed for these molecules. The spirocyclopropanation increases the energy barrier between the (1α, 2β)- and (1β,2α)- half-chair conformations, thereby increasing the bioactivity associated with the (1α,2β)-half-chair conformation.

CONCLUSION

The spiro[cyclopropane-1,2'-steroids] **1a–d** exist in a 'normal' (1α,2β)- half-chair conformation, which is contrary to the expected 'inverted' conformation. 'Spiroactivation' is not observed and the conjugative ability of the cyclopropane with the carbonyl group is destroyed. The increased energy barrier as a result of spirocyclopropanation could be the force behind the enhanced bioactivities of these compounds.

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