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EFFECT OF SYMMETRY ON C^{19} N.M.R. SHIFTS IN STEROIDS (1)

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Several investigators (2,3) have observed additivity relations for chemical shifts of angular methyl protons of steroids. In these studies "replacement constants"(3) are assigned to various substituent groups of the molecule. When added together these replacement constants accurately predict the variation in chemical shift of angular methyl protons upon the introduction of substituent groups into the parent molecule. The replacement constant for a given substituent group varies according to its position in the molecule. In this communication we wish to point out the significance of structural symmetry on such additivity relations.

We have investigated the C_{19} methyl proton shifts of a large number of steroid derivatives (see Table I). Measurements were made with a Varian DP-60 High Resolution N. M. R. Spectrometer on compounds dissolved in deuterated chloroform. Values for the replacement constants of various groups in different positions of the steroid nucleus were determined by a method of least squares and are listed in Table II. As shown in Table I, in almost all cases the predicted chemical shifts using values in Table II are in excellent agreement with the experimental result, the experimental error being $\pm$ 0.01 to 0.02 p.p.m.

Upon studying the variations in the values for cholestane (trans A/B) derivatives we find that the replacement constants for bromine in the 2α, 4α and 6α positions are identical. Again, the replacement

TABLE I

Chemical Shifts of C_{19} Methyl Protons

Compound	τ(ppm) obs.	τ(ppm) calc.
A/B-trans		
Cholestane	9.23	---
3α-OH-	9.23	9.20
3β-OH-	9.19	9.18
3β-OAc-	9.17	9.18
3-keto-	9.01	9.00
2α-Br,3α-OH-	9.13	9.10
2β-Br,3α-OH-	8.92	8.93
2α-Cl,3-keto-	8.91	8.91
2β-Cl,3-keto-	8.83	8.80
2α-Br,3-keto-	8.91	8.92
2β-Br,3-keto-	8.79	8.75
3β-OH,7-keto-	8.94	8.95
3β-OAc,7-keto-	8.93	8.95
3-keto,5α-Cl-	8.77[3]	8.76
3-keto,6β-Br-	8.73[3]	8.75
3-keto,7-keto-	8.75	8.77
2α-Cl,2β-Cl,3-keto-	8.73	8.71
2α-Br,3-keto,4α-Br-	8.82	8.84
2α-Br,3-keto,5α-Cl-	8.69[3]	8.68
2α-Br,3-keto,6β-Br-	8.67[3]	8.67
2β-Br,3-keto,5α-Cl-	8.53[3]	8.51
3β-OAc,6α-Br,7-keto-	8.85	8.87
3β-OAc,6β-Br,7-keto-	8.70	8.70
3-keto,5α-Br,6β-Br-	8.42	8.43
2α-Cl,3-keto,5α-Br,6β-Br-	8.32[3]	8.34
2α-Br,3-keto,5α-Br,6β-Br-	8.39	8.35
A/B-trans (cont.)		
Cholestane (cont.)		
2β-Br,3-keto,5α-Cl,6β-Cl-	8.27[3]	8.26
2β-Br,3-keto,5α-Br,6β-Br-	8.18[3]	8.18
3β-OAc,6α-Br,6β-Br,7-keto-	8.68	8.62
5α-Androstane		
3-keto,17β-OAc-	8.99	9.01[a]
2α-Br,3-keto,17β-OAc-	8.90	8.93[a]
A/B-cis		
Coprostane	9.08	---
3-keto-	8.97	8.97
3-keto,4β-Br-	8.92	8.92
2β-Br,3-keto,4β-Br-	8.88	8.87
Methyl cholanate	9.09	9.08[b]
3-keto-	8.98	8.97[b]
3-keto,7-keto-	8.70	8.74[c]
3-keto,12-keto-	8.90	8.91
3-keto,7-keto,12-keto-	8.63	8.64

[a] Value for corresponding cholestane derivative.

[b] Value for corresponding coprostane derivative.

[c] Value obtained by adding shift for 7- or 3-keto group in the cholestane series to the τ value of the C_{19} - methyl signal in coprostan-3-one.

constants for bromine in the 2β and 4β positions are equal to each other. Furthermore, the replacement constant for a ketone in position 3 is identical to that for a ketone in position 7. Such equivalence in the trans A/B series provides us with information concerning the conformations of rings A and B (see Fig. 1). Theories of diamagnetic bond anisotropy predict that chemical shift is, among other things, a function of bond angles and interatomic distances. The effect of a substituent group on chemical shift will be dependent upon the exact location and structural orientation of the substituent group relative to the proton in question. From symmetry considerations relative to the freely rotating protons of the C_{19} methyl group we have come to the conclusion that there is in operation here a rule reminiscent of Freudenberg's (4) "Rule of Shift" for optical rotation: the same change in substituents at analogous positions (vis-a-vis the methyl group under study) will produce the same replacement constant. Therefore, for the trans A/B compounds listed in Table I, ring A must be symmetrical with respect to a plane passing through C_3 and C_{10}; furthermore, rings A and B must be symmetrical relative to a plane passing through C_5 and C_{10}. Such symmetry is, of course, predicted on the basis of conformational analysis.

If the A/B ring junction is cis, then the symmetry between rings A and B relative to C_{19} is destroyed (see Fig. 2) and equivalence between groups in the two rings is not to be expected. There will, however, be equivalence between the 2- and 4- positions with respect to C_{19}. The values in Table II are in full accord with these symmetry considerations.

We can use some of the data in Table I for testing the rule of shift. Thus, the introduction of a bromine in the 2α-position produces

TABLE II

Replacement Constants for C_{19} Methyl Protons

Substituent	R_{19} (ppm)
trans A/B-Steroids	
2α-Cl	.09
2β- or 6β-Cl	.20
5α-Cl	.24
2α-, 4α- or 6α-Br	.08
2β- or 6β-Br	.25
5α-Br	.32
3α-OH	.03
3β-OH	.05
3β-Ac	.05
3- or 7-keto	.23
cis A/B-Steroids	
2β- or 4β-Br	.05
3-keto	.11
7-keto	.27
12-keto	.07

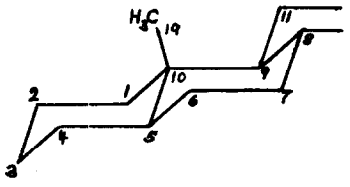

Figure 1

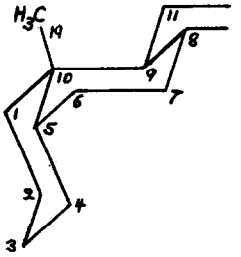

Figure 2

the same shift in 17β-acetoxyandrostan-3-one as in cholestan-3-one. In cholanic acid derivatives the A ring disposition is the same as in coprostane whereas the disposition of the B ring vis-a-vis the C_{19}-methyl is the same as in cholestane. It will be noticed that the introduction of a 3-keto group causes the same shift in the C_{19}-methyl signal in coprostane

and methyl cholanate. Again, the shift for introducing the 7-keto group in methyl 3-ketocholanate or methyl 3,12-diketocholanate is 0.27 p.p.m., which is very close to the shift of 0.23 p.p.m. observed on introducing a 7-keto group in a cholestane derivative. The small variation in these two values may indicate slightly varying amounts of distortion in the ring systems under comparison.

The position of the proton signal of the C_{19} methyl groups depends largely on substituents in the A, B and C rings, and very little on the substituents in the D ring. Therefore, for a cis A/B or trans A/B steroid substituted in the A ring, the chemical shift of the C_{19} methyl group can be directly obtained from the corresponding coprostane or cholestane derivative which differs only in the D ring substitution. Replacement constants for substituents in ring B of either cis or trans A/B steroids can be obtained from the more available cholestane derivatives. The data in Table I indeed show that this is true.

Furthermore, by taking note of the equivalence of positions 2, 4, 6 and of 3 and 7 in a trans A/B steroid, it is possible to predict the chemical shift of C_{19} methyl protons in a wide variety of steroids using the values in Table II. Deviations from additivity would indicate deviation from the normal conformation of the ring systems. The quantitative Correlations discussed here should also be useful for examining ring systems other than steroids.

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