Tetrahedron Vol. 37, pp. 777 to 780
Pergamon Press Ltd., 1981. Printed in Great Britain

0040-4020/81/0215 0777/$02.00/0

THE CALCULATION OF HYDROXYL GROUP C-13 SUBSTITUENT CHEMICAL SHIFTS IN STEROIDS AND OTHER RIGID SYSTEMS

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(*Received in Germany* 2 *May* 1980)

Abstract—A four parameter equation, for the calculation of one-bond secondary OH group C-13 substituent chemical shifts in steroids and other rigid systems, is deduced from literature data by the use of a multiple regression analysis. The magnitude of the coefficients are shown to be consistent with deviations from simple additivity of C-13 shifts in various systems. Conformational information in non-rigid systems is evident from differences between the calculated and observed SCS values.

The interest in the ^{13}C NMR spectra of steroids continues unabated. Recently data from many sources have been collated and reviewed.[1,2] Within these collections the hydroxylated steroids are the most numerous, a consequence of their ready synthesis and biosynthesis. An inspection of the data for these immediately shows that the substituent chemical shifts (SCS) are not constant but vary according to the position at which substitution occurs within the steroid nucleus. Thus for the secondary alcohols the directly bonded SCS value varies from 32.7 to 48.3 ppm for 1α and 11α-substitution respectively.[1] Similar variations can be noted for the introduction of acetate and CO functions. The recognition of the factors causing these variations and hence the ability to predict the SCS values would be particularly helpful in the interpretation of the C-13 spectra of polyfunctional steroids, many of which are of considerable biological interest. Longer range SCS values also show substantial variations but in the present paper only directly bonded SCS values will be considered.

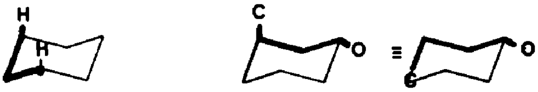
Several quantitative approaches have been presented relating the variation to specific interactions of the OH group. Thus Eggert *et al.*[3] analysed their data for the monohydroxylated androstanes and cholestanes using eqn (1), where a is the number of skew pentane interactions and b is the number of γ-gauche C atoms possessing H atoms that are able to interact with the OH group (Fig. 1, A and B). The standard error for the difference

$$\text{SCS.} = 45.0 + 3.5a - 3.5b \qquad (1)$$

between the experimental and calculated SCS values for the secondary alcohols of the androstane system (α- and β-epimers at the 1, 2, 3, 4, 6, 7, 11 and 12 positions) was 2.4 ppm. Large errors were noted for the 1β- and 7β-positions (−5.0 and −5.5 ppm, respectively). Similarly other systems could be predicted to within 2 ppm and it was implied that solvent and concentration effects were such that a better agreement between experimental and calculated values should not be expected. That this is not the case will be shown below.

A
Skew pentane interaction

B
Interaction of Y-gauche carbon atom possessing an hydrogen atom able to interact with the hydroxyl group



C
Hydrogen-carbon interaction

E
Four-bond interaction

Fig. 1. Types of interaction.

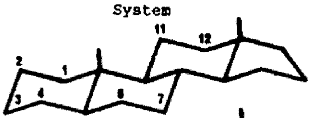
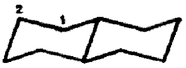
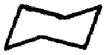
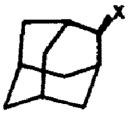
In this connection the SCS values for the same series of alcohols can be calculated by the method of Beierbeck *et al.*[4] reduced to the form shown in eqn (2), where Δ_{HC} is the difference in the number of H–C interactions in the substituted compound and the parent hydrocarbon (Fig. 1C) and a has the same significance as in eqn (1). The standard error in this case is

$$\text{SCS} = 43.37 + 4.55\,\Delta_{HC} + 1.97a \qquad (2)$$

2.8 ppm with the error being more randomly distributed than with the above method. The object of the present approach was to assess the applicability of the use of further parameters for the estimation of OH substituent chemical shifts in this and other systems of defined geometry.

METHOD AND RESULTS

In order to achieve our objective it was first necessary to have a sufficient number of varied data

Compound No.	System	Compounds	Ref.
1 to **16**		1α,β; 2α,β; 3α,β; 4α,β; 6α,β; 7α,β; 11α,β; 12α,β.	1
17 to **23**		3α,β; 6α; 7α; 11α,β; 12α.	1
24 to **27**		1α,β; 2α,β.	6
28 to **35**		1α,β; 2α,β; 3α,β; 4α,β.	6
36, **37**		equatorial, axial	7
38			8
39	$CH_3.CHX.CH_3$		9
40			10
41, **42**		equatorial, axial	11
43	$(CH_3)_3C.CHX.CH_3$		12

Scheme. Systems for which SCS data were used in the regression analyses.

sets on which to test the correlations and secondly to use multiple regression analysis to assess the usefulness of any particular parameter set. To satisfy the first of these criteria published data for secondary alcohol SCS values in different types of strain-free rigid systems of known geometry (Scheme) were abstracted to give 43 independent SCS values. Multiple linear regression analyses were performed on a PDP-10 computer using a standard statistical analysis package.[5]

From trial analyses with the steroid data **1**–**16** it was evident that using the approach of Eggert *et al.* better fits could be obtained if the axial and equatorial data were separated. This implies that their analysis could be improved if a further parameter relating equatorial and axial SCS values is defined. This can be incorporated into the analysis by introducing the number of trans hydrogen atoms to the OH group (d) as a parameter. Thus the two parameters used by Eggert *et al.* have been used in the linear form shown in eqn (3). Considerable improvement occurs upon

$$SCS = SCS_o. + Aa + Bb \qquad (3)$$

incorporating d to give eqn (4). The results of these analyses on

$$SCS = SCS_o. + Aa + Bb + Dd \qquad (4)$$

the entire data are given in the Table. Substantial improvement is indicated over eqn (3) with the R factor ratio, R, of 1.467 and a confidence level of better than 99.5%.[13,14]

Careful inspection of the equatorial OH SCS values of the steroids and the deviations from additivity in Me substituted norbornan-2-ols and bicyclooctan-2-ols[15,16] suggested that a further parameter is necessary to account for the four bond interaction of the form shown in Fig. 1E. For consistency this interaction is also counted once for the interaction of the equatorial OH group and C4 of the 6-membered ring. Alternative possible configurations of the OH group and interacting carbon were considered but no improvement in the final analysis was observed. Thus the final four parameter expression is given by eqn (5), where e is the number of four bond interactions. Regression analysis gives

$$SCS = SCS_o + Aa + Bb + Dd + Ee \qquad (5)$$

the coefficients in the Table† and indicates a significant improvement in the correlation over that for eqn (4) with R of 1.195 and an associated confidence level of better than 99.5%. Further refinement is excluded by

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† An example of the calculation using equation 5 is for 10-methyl-*trans*-decan-4-ol, where $a = 1$, $b = 2$, $d = 2$ and $e = 0$, to give a calculated SCS value of 41.9 ppm (observed 42.5 ppm).

Table. Coefficients and regression analysis parameters for eqns (3)–(5)

Equation	S.C.S$_0$.	Coefficients (Std. error of coef.) A	B	D	E	Mult. correl. coef.	Std. error	F value	R factor
3	44.31	3.294 (0.447)	-3.137 (0.238)			0.931	1.62	130.46	0.365
4	44.43	2.097 (0.356)	-4.112 (0.219)	1.728 (0.258)		0.969	1.12	197.44	0.249
5	42.18	2.044 (0.302)	-3.834 (0.198)	2.653 (0.317)	1.621 (0.401)	0.978	0.95	210.25	0.208

the number of available observations and by the accuracy and consistency of the literature data.

The SCS values in ring D of the steroids and in other 5-membered ring systems cannot be calculated as the same geometrical relationships no longer apply.

A preliminary analysis of the limited number of tertiary alcohol data (16 SCS values) indicates that the most meaningful equation involves only interaction B ($SCS_{tert} = 41.20 - 3.51b$, Std. error 1.34 ppm, correl. coef. 0.974, F value 260.4).

DISCUSSION

From the analysis of the C-13 spectra of the conformationally homogeneous dimethyl cyclohexanols and cyclohexanes[7] it was found necessary to introduce a parameter to account for the presence of a β-Me group. On average this interaction modified the OH SCS value by -3.8 ppm (1 eqOH–2eqCH$_3$ $-$ 3.1, 1eqOH $-$ 2axCH$_3$ $-$ 3.3, 1axOH $-$ 2eqCH$_3$ $-$ 4.9 ppm) which corresponds closely with the B value evaluated here and expected in such a system for introduction of a β Me group.

Deviations from simple additivity are expected in systems in which Me and OH groups are substituted in a fashion such that one or more of the interactions evaluated above are produced. For the methyl bicyclooctan-2-ol system,[15] Fig. 2 (n = 2), significant deviations from simple additivity are found when a four bond interaction is present (Fig. 2 I, predict + 1.6 ppm) and when interactions of type A and B have been changed (Fig. 2 II, predict + 5.9 ppm). A similar situation is found for the methyl norbornan-2-ols,[15,16] Fig. 2 (n = 1); here the interactions are larger than predicted, although of the correct sign, because of the increased strain in the system.

Significant deviations of the calculated and experimental SCS values can give conformational information in non-rigid systems. Thus the axial and equatorial SCS values for C1 of 2,2-dimethylcyclohexanol are predicted correctly (axial 33.3, observed 34.2 ppm; equatorial 36.1, observed 37.4 ppm), while those for 2,2,6,6-tetramethyl cyclohexanol are too small (axial 26.8 and equatorial 28.5, observed 30.7 ppm). A reduction in the number of interactions of type B, with a consequent increase in the SCS value, would be caused by a twist of the structure from the chair conformation, a conclusion in agreement with that reached previously.[17]

For 3-hydroxymenthane the SCS value for C3 of 41.2 ppm is nearer to that calculated for rotational isomer III, Fig. 3, than for rotamers I and II. A predominance of this isomer in the equilibrium mixture is indicated, in keeping with conclusions reached from considerations of the chemical shifts of the isopropyl fragment.[11]

For the steroids the linear correlations of the OH group SCS values with those of the acetoxyl group (slope 0.872, intercept 8.023, correl. coef. 0.987) and of the mean value of the axial and equatorial OH group SCS values with those of the CO carbon (slope 1.398,

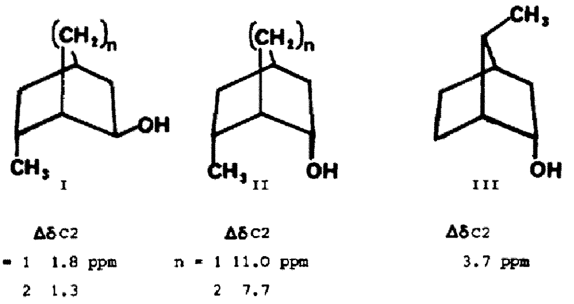
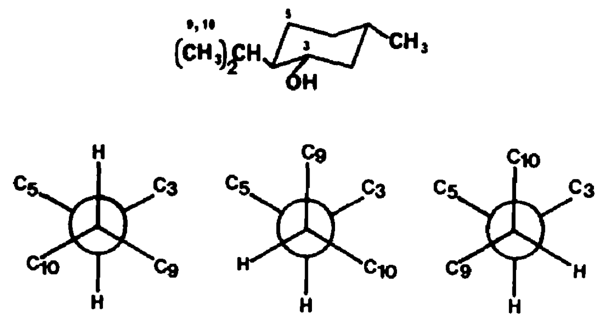


Fig. 2. Deviations, $\Delta\delta$, from simple additivity in the methyl norbornan-2-ol (n = 1) and bicyclooctan-2-ol (n = 2) systems, with a positive value indicating a lower shielding than predicted by simple additivity.



	I	II	III
Calculated S.C.S. (ppm)	45.9	45.9	40.0

Fig. 3. Rotamers about the C4-C8 bond in 3-hydroxymenthane.

intercept 124.47, correl. coef. 0.985) indicates that these SCS values are influenced in a like manner by the same interactions.[18] Hence this approach can be applied for other substituents when more data are available.

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[5] The program uses subroutines CORRE, ORDER, MINV and MULTR from the Scientific Subroutine Package available from the Digital Equipment Corporation User's Society. The statistical terms used in the package are defined in B. Ostle, *Statistics in Research* Chap. 8. The Iowa State College Press (1954).

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