Additivity Relationships in Carbon-13 Nuclear Magnetic Resonance Spectra of Dihydroxy Steroids

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Received August 6, 1976

The ^{13}C NMR spectra of 26 dihydroxy steroids and 10 acetylated derivatives have been obtained and assigned. It was found that only for compounds with 1,2- or 1,3-dihydroxy groups are there significant differences between the observed chemical shifts and those calculated assuming additivity of the substituent effects found for the monosubstituted compounds. When there is steric interaction between the functionalities the deviation from additivity can be rationalized by considering the nature of the steric interactions which are introduced. It is demonstrated that in many cases the effect of OH–OH interactions can be approximated by the magnitude and direction of analogous OH–C or C–C interactions. Significant deviations from additivity were also found for a few compounds with no steric interaction between the substituents (1,3-trans and 1,2-diaxial diols). An upfield 1,3-syn-diaxial δ substituent effect is reported.

In connection with our artificial intelligence project directed toward the computerized identification of unknown steroids from their ^{13}C NMR spectra, we have undertaken a systematic study of the effects of various substituents on such spectra. In particular, we have studied the influence of those substituents most commonly found in steroids of biological interest, and in previous papers we reported on the spectra of monoketo[2] and monohydroxy[3,4] steroids. In these papers, the effects of the functional groups were quantified by empirical rules which are of value for both interpretative and predictive applications. However, since most steroids of biological interest are polyfunctional, it is necessary to understand the effect which the interaction of substituents has on the ^{13}C NMR spectra of polyfunctional molecules. We now present the ^{13}C NMR spectra of 26 dihydroxy steroids and examine them in light of the previously determined[3] empirical rules. Furthermore, the chemical shifts predicted assuming additivity of the substituent effects observed for monohydroxy steroids are compared to experimental values in order to determine the extent to which this assumption is valid for polysubstituted steroids. The observed deviations from additivity are discussed.

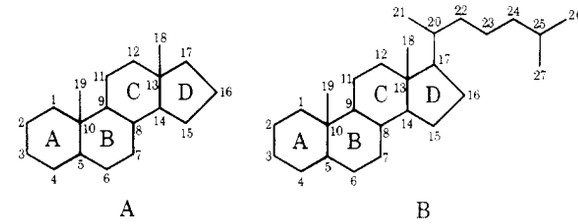
Experimental Section

A number of the dihydroxy steroids used in this investigation are from the authors' collections and have been described previously. Those remaining are all known compounds and were prepared by the following methods: **4** by treatment with lithium in ammonia[5] of 5α-cholestan-3β-ol-11-one; **5** by Jones oxidation of **4** followed by lithium aluminum hydride reduction; **8** and **9** by epoxidation[6] of 5α-cholest-1-en-3-one[7] with hydrogen peroxide followed by lithium aluminum hydride reduction;[6] **16** by hydroboration–oxidation[8,9] of cholest-4-en-3-one;[10] **18** by epimerization[11] of cholesterol followed by epoxidation with hydrogen peroxide and reduction with lithium aluminum hydride;[6] and **20** by treatment of cholest-4-ene with osmium tetroxide.[12] The acetoxy steroids were prepared by reaction of the alcohols with acetic anhydride in pyridine. The spectra were recorded as $CDCl_3$ solutions under the same conditions and with the same instruments as described previously.[3]

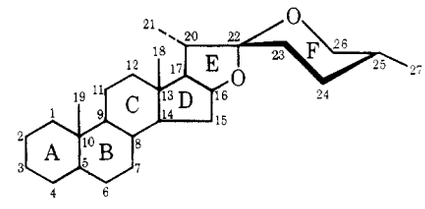
Results

Based on the previously published data for monohydroxy steroids,[3,4] the substituent-induced shifts caused by the presence of one hydroxyl group were obtained for each hydroxyl position by subtracting the chemical shift of each carbon atom in the parent hydrocarbon[2,3,13] from the chemical shift of the corresponding carbon atom in the appropriate hydroxy steroid. For each of the dihydroxy steroids studied in the present investigation, the chemical shift of each carbon atom was then calculated by adding the substituent-induced shifts obtained above for each of the two hydroxyl positions to the chemical shift of the parent hydrocarbon. It is necessary to use a complete table of substituent effects instead of only the effects at α, β, and γ carbon atoms summarized previously.[3] Substituent effects at δ carbons and at carbon atoms farther removed become nonnegligible when adding the effects of two hydroxyl groups. The calculated chemical shifts agree with those observed within 0.4 ppm at every carbon atom (0.8 ppm for carbinol carbon atoms, owing to their greater dependence on sample concentration) for the following compounds of the present study: (1) 5α-androstane-3β,6β-diol, (2) 5α-androstane-3β,7α-diol, (3) 5α-androstane-3β,7β-diol, (4) 5α-androstane-3β,11α-diol, (5) 5α-androstane-3β,11β-diol, (6) 5α-androstane-11α,17β-diol.

This is also the case for 5α-cholestane-3β,6α-diol, 5α-cholestane-3β,6β-diol, 5α-androstane-3β,17β-diol, and 5α-androstane-3α,17β-diol previously reported.[14,15] For those compounds where the difference at one or more carbon atoms is outside this limit, the chemical shifts are given in Table I together with the deviation from the calculated values. Table I also includes for comparison the previously assigned[2,13] chemical shifts for the parent hydrocarbons, 5α-androstane (A), 5α-cholestane (B), and (25*R*)-5α-spirostane (C).



A B



C

The ^{13}C NMR spectra of the 26 dihydroxy steroids studied were assigned by a combination of techniques as described previously.[3] In this study, however, the shift reagent Eu(fod)$_3$ was used only to differentiate the signals of carbon atoms close to a hydroxyl group from those of carbons further removed. Table II lists the assigned chemical shifts of the acetylated dihydroxy steroids which were studied for assignment purposes.

The ^{13}C NMR data for certain polyhydroxy steroids have

Table I. ^{13}C Chemical Shifts in Dihydroxy Steroids[a]

Compd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
A 5α-Androstane	38.8	22.3	26.9	29.2	47.1	29.2	32.6	36.0	55.1	36.4	20.9	39.0	40.8	54.7	25.5	20.5	40.5	17.6	12.3
B 5α-Cholestane	38.8	22.3	26.9	29.2	47.1	29.2	32.2	35.6	54.9	36.3	20.9	40.2	42.6	56.7	24.2	28.3	56.4	12.2	12.2
C (25*R*)-5α-Spirostane	38.7	22.2	26.8	29.0	47.1	29.0	32.4	35.2	54.8	36.3	20.7	40.2	40.6	56.5	31.8	80.8	62.3	16.5	12.3
7 5α-Cholestane-1α,2β-diol	74.3 (−3.5)	72.3 (−2.2)	29.0 (+1.8)	23.7 (+0.5)	39.6	28.5	31.7	34.7	48.1	39.6	20.5	39.9	42.6	56.4	24.2	28.2	56.4	12.1	12.4 (−3.0)
8 5α-Cholestane-1α,3α-diol	72.7 (+7.8)	36.2 (+0.5)	67.8 (+8.0)	33.6* (−1.6)	32.2* (+1.2)	28.4	31.7	35.4	46.8	40.3	20.2	39.7	42.6	56.3	24.2	28.2	56.3	12.1	12.3
9 5α-Cholestane-1α,3β-diol	73.2 (+3.5)	38.3* (+1.2)	66.7 (+2.0)	38.1* (+0.6)	37.4 (+0.6)	28.6	31.7	35.5	46.9	39.8 (+0.5)	20.7	39.8	42.6	56.4	24.3	28.2	56.2	12.1	13.0
10 (25*R*)-5α-Spirostane-2α,3α-diol	40.9 (−0.8)	69.0* (−5.7)	69.1* (−6.8)	34.3	38.1	27.6	32.0	34.4	54.2	37.0	20.7	40.0	40.6	56.2	31.7	80.7	62.2	16.5	12.4
11 (25*R*)-5α-Spirostane-2α,3β-diol	45.1* (−1.3)	73.0 (−4.2)	76.4 (−4.1)	35.6 (−1.0)	44.9* (+0.7)	27.9	32.1	34.5	54.3	37.6 (+0.9)	21.2	40.0	40.6	56.1	31.8	80.7	62.2	16.5	13.5
12 (25*R*)-5α-Spirostane-2β,3α-diol	40.1 (+1.6)	71.7 (−3.1)	70.6 (−2.9)	31.8 (+1.3)	39.0	28.2	32.1	34.6	55.2	35.9	20.8	40.1	40.6	56.3	31.8	80.7	62.2	16.5	14.4 (+0.7)
13 5α-Cholestane-3α,4α-diol	31.5*	27.1	69.5 (−6.3)	72.0 (−5.0)	45.8	22.8 (+0.7)	31.7*	35.3	54.4	37.1	21.0	40.1	42.6	56.6	24.2	28.3	56.4	12.2	12.7
14 5α-Cholestane-3α,4β-diol	31.7	24.6 (+0.8)	70.3 (−3.1)	76.1 (−3.0)	44.0 (+2.0)	25.2	32.4	35.6	55.2	35.9	20.3	40.0	42.6	56.6	24.3	28.3	56.3	12.2	14.3 (+0.6)
15 (25*R*)-5α-Spirostane-3α,4β-diol	31.7	24.6 (+0.7)	70.2 (−3.3)	76.0 (−2.9)	43.8 (+1.8)	25.0	32.5	35.1	55.1	35.9	20.0	39.9	40.5	56.3	31.6	80.7	62.1	16.5	14.4 (+0.5)
16 5α-Cholestane-3β,4α-diol	36.2	28.3 (−1.3)	76.4 (−4.3)	75.6 (−3.7)	50.8 (−1.0)	22.7	31.5	35.0	54.4	37.3 (+0.6)	21.0	40.0	42.5	56.3	24.2	28.3	56.3	12.1	13.6
17 5α-Cholestane-3β,4β-diol	37.0	26.0	72.2 (−6.1)	74.8 (−6.6)	48.9 (+1.1)	26.0	32.4	35.6*	55.3	35.4*	20.6	40.0	42.6	56.6	24.2	28.2	56.3	12.1	14.7
18 5α-Cholestane-3α,5α-diol	25.5* (+0.5)	29.0 (+1.3)	67.5 (+7.2)	39.4 (−1.7)	75.0 (+9.9)	34.0	26.5*	34.8	45.7	—	21.0	40.0	42.7	56.2	24.1	28.2	56.2	12.2	15.8 (+0.7)
19 5α-Androstane-3β,5α-diol	31.0 (+1.2)	31.0 (+0.9)	67.2 (+2.0)	44.0 (+0.6)	75.2 (+4.3)	34.5	26.3	35.1	46.2	38.9	21.4	38.9	40.9	54.3	25.4	20.5	40.4	17.6	16.3
20 5α-Cholestane-4α,5α-diol	30.5	19.5 (+0.5)	30.0	71.3 (−4.2)	75.1 (−4.9)	28.4	26.0	34.5	45.9	40.2	20.9	40.0	42.5	56.2	24.1	28.3	56.2	12.1	15.5 (−1.9)
21 5α-Cholestane-5α,6α-diol	31.8	20.7*	20.4*	28.5 (+0.5)	75.0 (−4.8)	70.9 (−4.5)	35.8	33.6	45.0 (−0.5)	39.6	20.7	39.9	42.6	56.0	24.1	28.2	56.2	12.1	15.3 (−1.9)
22 5α-Cholestane-6α,7α-diol	38.6	21.8	26.2	22.8 (+0.5)	45.3* (−0.6)	72.2 (−5.4)	71.3 (−6.4)	38.4	45.4*	36.7	20.6	39.5	42.5	50.2	23.6	28.2	56.0	11.8	12.3
23 5α-Cholestane-6β,7α-diol	40.3	22.0	27.0	25.5	43.3 (+1.4)	76.5 (−3.6)	71.9 (−3.7)	34.6	45.7 (−0.6)	36.2	20.4	39.6	42.7	50.1	23.6	28.1	56.2	11.8	15.3 (+0.6)
24 5α-Cholestane-12β,15α-diol	38.8	22.1	26.7	28.9	46.8	28.9	32.0	34.5	53.5	36.4	29.8	79.1 (−1.0)	46.6 (−0.6)	60.3	75.3	33.0	36.0	13.0	12.2
25 5α-Androstane-15β,17β-diol	38.8	22.2	26.9	29.1	47.4	28.9	31.5	31.5	55.5	36.6	20.4	38.5	42.4 (−0.5)	56.1	69.4 (−1.0)	43.1 (−1.0)	81.4 (−0.6)	13.9	12.3
26 5α-Androstane-16β,17β-diol	38.7	22.2	26.8	29.0*	47.1	28.9*	31.9	35.0	55.1	36.4	20.2	37.5	42.5	47.6 (−0.5)	35.0	70.1 (−11.9)	80.9 (−15.0)	12.0 (−0.7)	12.3

[a] In parts per million relative to Me_4Si. Values in parentheses give the deviation from additivity ($\delta^{obsd} - \delta^{calcd}$). Assignments of close-lying peaks marked with an asterisk may be interchanged. Chemical shifts for the side chain carbon atoms are all unchanged relative to the parent compounds and are not included. Dash (—) indicates peak not observed.

Table II. ^{13}C Chemical Shifts in Acetylated Diols[a]

Compd[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	CH_3[b]	C=O	CH_3[b]	C=O
5α-Cholestane-2β,3α-diol 3α-acetate	40.0	68.5	73.0	28.7	40.5	28.2	31.9	34.9	55.1	35.4	20.9	40.0	42.6	56.5	24.1	28.2	56.3	12.1	14.2	21.4	170.3		
5α-Cholestane-3α,4β-diol 4β-acetate	31.5	24.8	67.0	77.0	42.7	25.0	32.2	35.5	55.1	35.9	20.5	40.0	42.6	56.6	24.2	28.3	56.3	12.1	13.7	21.1	170.3		
5α-Cholestane 3α,4β-diacetate	32.0	22.3	69.6	73.3	44.1	24.7	32.0	35.4	55.0	35.6	20.4	40.0	42.5	56.5	24.2	28.2	56.3	12.1	13.6	21.2	169.3	21.2	169.4
(25R)-5α-Spirostane 3α,4β-diacetate	32.0	22.2	69.4	73.2	44.0	24.6	32.0	34.9	54.9	35.6	20.2	39.8	40.4	56.2	31.7	80.6	62.2	16.4	13.7	21.1	169.3	20.9	169.2
5α-Cholestane 3β,4α-diacetate	35.8	26.0	75.4*	74.0*	49.3	22.9	31.3	35.0	54.2	37.3	21.0	40.0	42.5	56.2	24.1	28.2	56.2	12.1	13.4	21.0	170.5	21.0	170.3
5α-Cholestane-3α,5α-diol 3α-acetate	25.6*	25.6*	70.8	37.5	73.0	33.6	26.8*	34.9	45.2	—	20.9	40.1	42.7	56.2	24.0	28.3	56.2	12.1	15.9	21.4	168.8		
5α-Cholestane-3β,6β-diol 6β-acetate	38.3	31.3	71.3	35.0	46.4	73.6	36.5	31.1	54.0	35.5	21.1	39.9	42.7	56.1*	24.2	28.2	56.3*	12.2	15.3	21.4	170.5		
5α-Cholestane 3β,6β-diacetate	38.0	27.3	73.3	31.0	46.2	73.3	36.4	31.0	53.8	35.5	21.0	39.8	42.6	56.0	24.2	28.0	56.2	12.1	15.1	21.3	170.1	21.3	170.1
5α-Cholestane-3β,7α-diol 3β-acetate	36.9	27.4	73.5	33.6	36.1	36.5	67.7	39.5	45.7	35.5	21.0	39.5	42.6	50.5	23.6	28.2	56.1	11.8	11.1	21.3	170.2		
5α-Cholestane-4α,5α-diol 4α-acetate	30.4	19.4	26.3	75.2	74.2	29.2	25.9	34.5	45.4	40.7	20.9	40.0	42.5	56.2	24.1	28.3	56.2	12.1	15.4	20.9	169.9		

[a] See footnote *a*, Table I. [b] Acetoxy methyl group. [c] Registry no. are, respectively, 61010-51-3, 61010-52-4, 20834-79-1, 61010-53-5, 21157-50-6, 17305-80-6, 26358-65-6, 3514-29-2, 40823-41-4, 5748-95-8.

been reported previously.[14-23] Of these, the data for cholestane-3β,5α-diol and cholestane-3β,5α,6α-triol 3β-acetates[18] and 5α-cholestane-3β,6β-diol[14,15] were used in the assignments for compounds **19, 21,** and **1**, respectively.

Discussion

In a previous paper[3] we suggested an empirical correlation relating the α and β substituent effects to the type and number of specific steric interactions of the hydroxyl group in monosubstituted cyclic compounds. Thus, when a hydroxyl group is situated γ-gauche to a carbon atom, not only the γ-gauche carbon experiences the well-known upfield shift, but the hydroxyl substituent parameters for α and β carbons in the path of the γ-gauche interaction are modified by −3.5 and −2.4 ppm, respectively, for each interaction of this kind. It is a consequence of these rules that whenever the substituents of polyhydroxy steroids give rise to steric interactions which are not present or are different from those in the monosubstituted derivatives, deviation from additivity of substituent effects is expected. Inspection of Table I reveals that with one exception (**24**), only compounds with 1,2- or 1,3-dihydroxy groups give rise to deviations of more than 0.4 ppm (0.8 ppm, respectively, see above) between the experimental chemical shifts and those calculated by assuming additivity of the substituent effects observed in the monosubstituted compounds.

The 1,2 (vicinal) diols can be separated into three categories according to the stereochemistry of the hydroxyl groups: diequatorial, equatorial–axial, and diaxial. In the diequatorial cases (compounds **11** and **16**) the chemical shifts of both carbinol (α) carbon atoms in each compound deviate from the calculated values by −4.0 ppm (±0.3 ppm). In this arrangement each hydroxyl group experiences an additional γ-gauche interaction (with the other OH group) which is not accounted for when adding the individual substituent effects. The difference, then, can be considered to be the result of the mutual interaction of the two hydroxyl groups, and it is close to the value of −3.5 ppm found for the analogous carbon atoms in systems with hydroxyl–carbon[3] and carbon–carbon[24,25] γ-gauche interactions. Hence, the equation which for cyclic monohydroxy compounds relates the substituent effects of a hydroxyl group to its steric interactions also predicts the correct value (within the limit given) for the carbinol carbons in the diequatorial diols.

The vicinal hydroxyl groups in the axial–equatorial cases (compounds **10, 13, 17, 20,** and **21**) also experience an additional γ-gauche interaction relative to the monosubstituted compounds. In this arrangement, however, the deviation from additivity at the α carbons is larger (see Table III). This increase probably reflects a greater steric interaction between an axial and an equatorial OH group, vis-à-vis two equatorial OH groups, caused by a smaller dihedral angle between the two HO–C bonds. It is known that the six-membered rings in the steroid skeleton are slightly flattened compared to a perfect chair form.[26] As a consequence of this, the dihedral angle φ between two vicinal bonds is decreased in the case of axial–equatorial bonds (ϕ_{ae}) but increased in the case of two equatorial vicinal bonds (ϕ_{ee}) relative to the ideal value of 60°. Furthermore, if the axial vicinal bond carries a substituent, ϕ_{ae} is expected to be further decreased by deformations introduced to relieve the steric interactions of the axial substituent. X-ray data for 3α- and 3β-hydroxyandrostan-17-one[27,28] illustrate this point. The above is consistent with the finding that the intramolecular hydrogen bonds are stronger for axial–equatorial than for equatorial–equatorial 1,2-diols.[29,30] The deviations from additivity for the carbinol carbon atoms in the 4α,5α- and 5α,6α-diols (**20** and **21**) are smaller (ca. −4.6 ppm) than in the other axial–equatorial 1,2-diols (ca. −6.0 ppm). In spite of the large number of 1,3-

Table III. Deviations from Additivity (ppm) for Proximate Diols[a]

			α carbons[b]		β carbons[b]		
1,2 Diequatorial	11	2α, 3β	−4.2 (2)	−4.1 (3)	−1.3 (1)		−1.0 (4)
	16	3β, 4α	−4.3 (3)	−3.7 (4)	−1.3 (2)		−1.0 (5)
1,2 Axial–equatorial	10	2α, 3α	−6.8 (3)	−5.7 (2)	— (4)		−0.8 (1)
	13	3α, 4α	−6.3 (3)	−5.0 (4)	— (2)		— (5)
	17	3β, 4β	−6.6 (4)	−6.1 (3)	+1.1 (5)		— (2)
	20	4α, 5α	−4.9 (5)	−4.2 (4)	— (6)		— (3)
					— (10)		
	21	5α, 6α	−4.8 (5)	−4.5 (6)	+0.5 (4)		
					— (10)		— (7)
	22	6α, 7α	−6.4 (7)	−5.4 (6)	— (8)		−0.6 (5)
1,2 Trans-diaxial	7	1α, 2β	−3.5 (1)	−2.2 (2)	+1.8 (3)		— (10)
	12	2β, 3α	−3.1 (2)	−2.9 (3)	+1.6 (1)		+1.3 (4)
	14, 15	3α, 4β	−3.2 (3)	−3.0 (4)	+0.8 (2)		+1.9 (5)
	23	6β, 7α	−3.6 (6)	−3.7 (7)	+1.4 (5)		— (8)
1,2-Cis, ring D	26	16β, 17β	−11.9 (16)	−15.0 (17)	— (15)		— (13)
1,3-Syn-diaxial	8	1α, 3α	+7.8 (1)	+8.0 (3)	— (10)	+0.5 (2)	−1.6 (4)
	18	3α, 5α	+7.2 (3)	+9.9 (5)	+1.3 (2)	−1.7 (4)	— (6)
	25	15β, 17β	−1.0 (15)	−0.6 (17)	−0.5 (13)	— (14)	−1.0 (16)
1,3-Trans	9	1α, 3β	+3.5 (1)	+2.0 (3)	— (10)	+1.2 (2)	+0.6 (4)
	19	3β, 5α	+2.0 (3)	+4.3 (5)	+0.9 (2)	+0.6 (4)	— (10)

[a] Values given are the difference between observed and predicted shieldings assuming additivity of substituent effects. A dash indicates negligible deviation from additivity (≤0.4 ppm). [b] Carbon atom number given in parentheses.

diaxial interactions, the decrease in the dihedral angle ϕ_{ae} is much less pronounced in **20** and **21** owing to the rigid trans fusion at the site of substitution, resulting in a smaller steric interaction between the hydroxyl groups than in the other cases. In each of these compounds, the deviation from additivity is greater for the axially substituted carbon than for the equatorially substituted one (Table III).

The hydroxyl groups are trans diaxial in compounds **7, 12, 14,** and **23.** In this arrangement the substituents are spatially remote from one another to the extent that no additional steric interactions are expected to be introduced beyond those already encountered in the two corresponding monohydroxy compounds. The chemical shifts of the hydroxyl-bearing carbons, however, are all 3.0 ppm (±0.8 ppm) upfield from the values calculated assuming additivity of substituent effects. The chemical shifts of the remaining carbon atoms do not provide any evidence to suggest that the vicinal diaxial substitution causes appreciable distortions of the molecule relative to the corresponding monosubstituted compounds. Such distortions should affect the chemical shifts of all (or most) carbon atoms whose environment is sterically perturbed by the hydroxyl groups. However, deviations from additivity in this class of compounds are in most cases restricted to the hydroxylated (α) carbon atoms and the adjacent (β) carbon atoms. Stothers et al.[31-33] have recently studied the interactions of hydroxyl and methyl groups in a series of methylnorbornanols and bicyclo[2.2.2]octane derivatives. They concluded that when vicinal methyl and hydroxyl groups are well separated, the observed shieldings agree well with values predicted assuming additivity of the substituent effects. However, the dihedral angles relating the methyl and hydroxyl groups were all in the 0–120° range, with no examples of vicinal diaxial groups. If the ^{13}C NMR data[15] for 10-methyl-*trans*-1α-decalol are analyzed in light of the data for the mono- and unsubstituted decalins, it becomes apparent that also in this case the CH_3–OH vicinal diaxial arrangement gives rise to shifts upfield from those calculated for the carbons bearing the substituents.

It has been suggested[34] that anti-periplanar arrangements involving O, N, or F atoms give rise to a hyperconjugative interaction of free electron pairs of the heteroatom with the C–C bond. This transmission of electronic effects has been invoked to explain the upfield shift observed in the resonance signal of a carbon atom situated γ-trans to the heteroatom (O, N, F). It is possible that a similar electronic effect causes the upfield shifts observed in the anti-periplanar arrangement of two hydroxyl groups by interaction of free electron pairs on both oxygen atoms with the intervening C–C bond, increasing the electron density on those carbon atoms. It is worth noting that for compounds **7, 12, 14,** and **23** the carbon atoms adjacent to the sites of substitution (β carbons, see Table III) appear to be deshielded compared to the predicted chemical shifts, thus suggesting an alternating (electronic) effect.

In compound **25** the hydroxyl groups are cis on a five-membered ring and probably more closely eclipsed than gauche. (The corresponding dihedral angle in 16β,17β-dibromo-5α-androstane is 30°).[35] The steric interactions between the vicinal hydroxyl groups are therefore expected to be very strong and the deviations from additivity for C-16 and C-17 in **25** are the largest (−12 and −15 ppm) among the compounds studied, although the chemical shifts of all the remaining carbons in this compound may be predicted within 0.7 ppm employing additivity parameters.

From the above it is clear that the mutual interaction of vicinally situated hydroxyl groups, as reflected in the deviation between observed and predicted carbon chemical shifts, varies as a function of the dihedral angle between the two C–OH bonds. When the dihedral angle is small the signals of the carbon atoms bearing the substituents are shifted considerably upfield from the predicted positions, while increasing the dihedral angle results in progressively smaller deviations. The smallest deviation measured (~−3 ppm) occurs in the trans-diaxial cases; however, our set of compounds does not include samples with a dihedral angle around 120°, for which almost complete substituent effect additivity has been found[31-33] for vicinal hydroxyl–methyl substituents.

The hydroxyl groups are 1,3 syn-diaxial in compounds **8** and **18** and the deviations from additivity at the hydroxyl-bearing carbons are large (7–10 ppm downfield, Table III). This is not surprising as 1,3 syn-diaxial substituted compounds possess steric interactions which are not present in the monosubstituted analogues, namely the OH–OH skew pentane interaction. Furthermore, where these interactions appear, they replace a hydroxyl γ-gauche interaction present in the corresponding monosubstituted compounds. On the basis of our study of monohydroxy steroids[3] both these changes are (for methyl or hydroxyl substitution) expected to result in downfield carbinol carbon shifts, totaling approximately 7

ppm. This value is very close to that actually observed (Table III), showing again that the OH–OH interactions can be approximated by the OH–CH_3 interactions observed previously, although the present data indicate a somewhat larger parameter value (~+4.5 ppm instead of +3.5 ppm, cf. ref 3) associated with the OH–OH skew pentane interaction. The chemical shifts of carbons 15 and 17 of compound **25** agree well with the predicted values (Table III). Although this is a 1,3 syn arrangement of the hydroxyl groups, both are on the five-membered ring D and hence oriented away from one another, making the total change in steric interactions for the diol compared to the two corresponding monohydroxy compounds small.

There are no apparent steric interactions between the hydroxyl groups in the 1,3-trans diols **9** and **19**, but there are nonetheless significant deviations from additivity at the α carbon atoms. The resonances of the equatorially and the axially substituted carbons are respectively 2 and 4 ppm downfield from the predicted values. The same pattern in deviations from additivity of substituent effects is observed for 1,3-trans methyl–hydroxyl substituents (equatorial hydroxyl, axial methyl) in monohydroxy steroids,[3] *trans-anti-trans*-perhydrophenanthrene,[25] and various trans decalins.[15] Upfield hydroxyl-induced γ-trans shifts have been reported to be general,[34] but in all the above mentioned 1,3-trans-substituted compounds, downfield rather than upfield γ-trans shifts are encountered at the axially substituted carbons, all of which are γ-trans to the equatorial hydroxyl group. These observations show that the γ-trans shifts caused by second row heteroatoms[34] in anti-periplanar geometries are also dependent on the presence and steric environment of atoms removed from the γ-trans fragment. This is emphasized by considering that γ-trans shifts on methyl groups are downfield for a hydroxyl substituent[3,4] but become large upfield shifts (~−6 ppm) when the oxygen atom is part of a cyclic ether.[13,34]

The deviations from additivity for β carbons (one bond removed from the nearest hydroxylated site) in the vicinal diols are all less than 2 ppm. In general the deviation for a β carbon next to an equatorial hydroxyl group is negligibly small or negative, whereas for a β carbon next to an axial hydroxyl group it is negligible or positive (see Table III). Interestingly, these effects are largest for the diequatorial diols (**11** and **16**) and the trans-diaxial cases (**7**, **12**, **14**, and **22**). In the 1,3 diols, the deviations from additivity for all β carbons are also in the range of ±2 ppm, although most are negligible. No patterns or trends could be discerned.

The chemical shifts for γ carbon atoms are with few exceptions predicted well (to within 1 ppm) employing additivity parameters. However the C-19 methyl resonance is off by −1.9 ppm in compounds **20** and **21** and by −3.0 ppm in **7**. In all of these compounds, one of the hydroxyl groups of a vicinal pair is γ-trans to C-19. In compound **7** the two hydroxyl groups and the C-19 methyl group form an extended anti-periplanar arrangement, as there are three consecutive carbon atoms axially substituted. An upfield shift of 3 ppm relative to the predicted value is also found at C-19 in 5α,6β-diols (using ^{13}C NMR data from ref 17 and 18) where the same extended anti-periplanar geometry occurs. Clearly, the γ-trans hydroxyl substituent effect (see above) is varied by introduction of a vicinal hydroxyl group when this hydroxyl group and the C-19 methyl group are syn-diaxial (as in **7**). This may cause the hydroxyl syn-diaxial δ substituent effect to become upfield,[18] in direct contrast to what has previously been found.[3,15,31-33]

For the other vicinal diaxial cases (**12**, **14**, **15**, and **23**) the hydroxyl 1,3-syn-diaxial δ substituent effects become slightly larger (0.6–0.7 ppm) than in the monosubstituted compound.

To summarize, additivity of substituent effects adequately approximates the chemical shifts of most carbon atoms in dihydroxy steroids, except for positions at which the interaction of the substituents perturbs the steric or electronic environment. Since the effects of these interactions on the chemical shifts are regular, knowledge of them will be quite useful for both the interpretation and prediction of ^{13}C NMR spectra of polyfunctional molecules.

Acknowledgments. The Varian XL-100-15 NMR spectrometer at Stanford University was purchased under Grant GP-28142 from the National Science Foundation and the Brucker WH-90 NMR spectrometer at Copenhagen was purchased by Statens Naturvidenskabelige Forskningsraad. Partial financial support by NATO (Grant RG 939) and the National Institutes of Health (Grants AM-17896 and GM-06840) is gratefully acknowledged.

Registry No.—A, 438-22-2; B, 481-21-0; C, 5012-14-6; **7**, 20834-84-8; **8**, 571-01-7; **9**, 571-00-6; **10**, 61046-17-1; **11**, 511-96-6; **12**, 61046-18-2; **13**, 20834-98-4; **14**, 20834-88-2; **15**, 61010-49-9; **16**, 20835-09-0; **17**, 20834-99-5; **18**, 570-96-7; **19**, 5223-92-7; **20**, 19536-21-1; **21**, 566-30-3; **22**, 20835-05-6; **23**, 20834-91-7; **24**, 61010-50-2; **25**, 13864-58-9; **26**, 32810-91-6.

References and Notes

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