Polar and Steric Long-Range Transmission Effects in Cholestanes, Cholestenes, and 9-Substituted Decalins. Carbon-13 Nuclear Magnetic Resonance Shifts and Force Field and Linear Electric Field Calculations[1]

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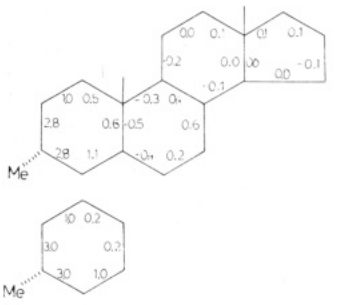
Shielding differences in cholestanes bearing halogen, oxygen, or methyl substituents in the 3α,β- (compounds I) and 5α,β- (V) positions are reported and compared to corresponding cyclohexanes (II) and decalins (VI). Geometry distortions by substituents are evaluated by force field (MM1/2) calculations and polar effects by electric field effect (LEF) calculations. Steric effects even of larger axial groups such as methyl are transmitted over not more than two bonds, as shown by force field calculations and by ^{13}C shifts. Through-space field effects of electronegative substituents extend over up to six bond distances. ^{13}C NMR shielding constants and LEF-induced charge variations can be correlated for Cδ with saturated systems such as I, with 470 ppm/eu; for 3-substituted cholest-5-enes (III), where the polarized double bond is asymmetric to the inducing dipole, only 90 ppm/eu (with 3β-X) or 210 ppm/eu (with 3α-X) is obtained.

The systematic investigation of steroid NMR spectra can provide insight into NMR shielding mechanisms as well as into chemically and pharmacologically important conformation and charge-density variations.[2] ^{13}C NMR shifts in substituted steroids[3] represent a wealth of numerical data, which so far have served mostly analytical purposes, although some studies have been adressed to conformational distortions by substituents[4] or other structural changes.[5]

The theoretical understanding of NMR shielding variations by substituents is still in a state of infancy. Steroids offer an almost unsurpassed possibility to investigate the effect of a substituent in a variable molecular environment on many observable carbon shifts. Although saturated androstanes, in view of their conformational rigidity, lend themselves particularly to the evaluation of polar effects, transmission of steric effects due to the strong conformational coupling in these skeletons must be taken into account also. We have made an effort to separate polar from steric effects (i) experimentally by introducing mainly electron-withdrawing substituents such as halogen and oxygen or, as a sterically demanding and unpolar substituent, the methyl group and (ii) theoretically by calculation of linear electric field (LEF) effects and of steric effects by the molecular mechanics (MM) method. A similar approach has been useful in the evaluation of some long-range ^{1}H and ^{13}C NMR shielding effects in selected steroids.[4a,c,6,7]

The principles and procedures of the force field method have been described elsewhere;[8] the calculation of electrostatic effects by a point pole appoximation and its limitations are also contained in earlier papers[7,9] and will not be repeated here.

Chart I. Torsional Angle Changes (deg) upon Introduction of an Axial Methyl Group in the 3α-Position of 5α*H*-Androstane and in Cyclohexane (MM2 Calculations)



While through-space electric field effects of electronegative substituents can lead to both charge density accumulation or attenuation at remote carbon atoms, which is in fact recognizable in some steroid reactions,[10] any through-bond inductive effects will generate diminished electron densities in the framework. Since the long-range effects found in the steroids are, with one exception, always shielding (see below), through-bond inductive mechanisms can already be eliminated as a major source for these ^{13}C shift alterations.

3-Substituted Cholestanes. NMR Shielding effects in topologically related skeletons are similar as long as the geometry of the systems either is not altered by substituents or is changed by them to the same degree. Force field calculations with Allinger's[8a] MM1 or MM2 program indicate no significant geometry change upon equatorial substitution with X = Hal, OR, or CH_3 in both the 3-position of cholestane and in cyclohexanes;[11] the introduction of an axial methyl group leads to the almost identical variations of "soft" torsional angles only (Chart I).

(1) Stereochemical and ^{13}C NMR investigations. 31. For part 30 see H.-J. Schneider, Nge Nguyen-Ba, and F. Thomas, *Tetrahedron*, in press.

(2) (a) P. A. Kollman, D. D. Giannini, W. L. Duax, S. Rothenberg, and M. E. Wolff, *J. Am. Chem. Soc.*, **95**, 2869 (1973); (b) W. L. Duax, C. M. Weeks, and D. C. Rohrer, *Top. Stereochem.*, **9**, 271 (1976); (c) H.-J. Schneider, U. Buchheit, W. Gschwendtner, and M. Lonsdorfer in "Molecular Structure and Biological Activity", J. F. Griffin and W. L. Duax, Eds., Elsevier, New York, 1982, p 165.

(3) (a) J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, **9**, 439 (1977); (b) W. B. Smith, *Annu. Rep. NMR Spectrosc.*, **8**, 199 (1978); (c) F. W. Wehrli and T. Nishida, *Fortschr. Chem. Org. Naturst.*, **36**, 104 (1979).

(4) (a) G. M. Schwenzer, *J. Org. Chem.*, **43**, 1079, (1978); (b) H. Eggert, C. L. Van Antwerp, N. S. Bhacca, and C. Djerassi, *ibid.*, **41**, 71 (1976); (c) H.-J. Schneider, W. Gschwendtner, and E. F. Weigand, *J. Am. Chem. Soc.*, **101**, 7195 (1979).

(5) (a) S. Q. A. Rizvi and J. R. Williams, *J. Org. Chem.*, **46**, 1127 (1981); (b) D. Marcano, A. Rojas, B. Méndez, and J. de Méndez, *Org. Magn. Reson.*, **16**, 205 (1981).

(6) H.-J. Schneider and W. Gschwendtner, *J. Org. Chem.*, **45**, 3507 (1980).

(7) (a) H.-J. Schneider, W. Gschwendtner, and U. Buchheit, *J. Magn. Reson.*, **26**, 175 (1977); (b) H.-J. Schneider, W. Freitag, W. Gschwendtner, and G. Maldener, *ibid*, **36**, 273 (1979).

(8) (a) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); (b) R. Bucourt, N. C. Cohen, and G. Lemoine, *Bull. Soc. Chim. Fr.*, 903 (1975); (c) J. P. Schmit and G. G. Rousseau, *J. Steroid Biochem.*, **9**, 921 (1978); (d) W. Gschwendtner, V. Hoppen, and H.-J. Schneider, *J. Chem. Res. Synop.*, 96 (1981); *J. Chem. Res., Miniprint*, 1201 (1981).

(9) H.-J. Schneider und W. Freitag, *J. Am. Chem. Soc.*, **99**, 8363 (1977).

(10) (a) P. E. Peterson and D. M. Chevli, *J. Org. Chem.*, **39**, 3684 (1974); (b) For long-range effects in steroids see, e.g., R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, **28**, 1945 (1972).

(11) H.-J. Schneider and E. F. Weigand, *J. Am. Chem. Soc.*, **99**, 8362 (1977).

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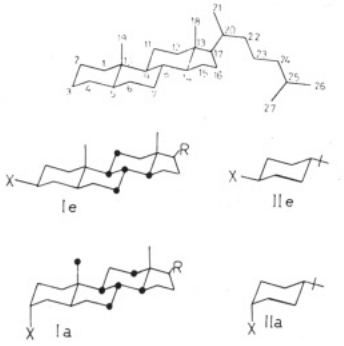


Figure 1. Cholestanes and cyclohexanes (filled circles indicate long-range effects).

Consequently, the substituent-induced ^{13}C NMR shifts SIS (Table I) deviate little between I and II[12] for the α–δ-carbon atoms, leading to linear shift correlations with coefficients $r \geq 0.998$ and $\psi \leq 7\%$[13] and slope $m = 1.00 \pm 0.02$ for Cα (C3), with $r \geq 0.95$, $\psi \leq 37\%$, and $m = 1.00 \pm 0.13$ for Cβ (C2, C4), and with $r \geq 0.93$, $\psi \leq 50\%$, and $m = 1.00 \pm 0.2$ for Cγ (C1, C5). Substituent effect differences between C2 and C4 or C1 and C5 can be related to deviations of the A ring geometry from the C_s symmetry which is indeed observed in the force field minimized structures.

Substituent effects on more remote carbon atoms such as Cγ are particularly amenable to the calculation of charge polarization by polar substituents since they are more free from high-order effects such as, e.g., from distortions by fluctuating Cα–X dipoles.[9] Thus, the SIS values observed for C10 in I (Table I) are well reproduced by a point pole approximation of the linear electric field with a sensitivity of 470 ± 50 ppm/electron charge (eu).[7b] This, and the agreement with the calculation for monosubstituted cyclohexanes (400 ppm/eu)[9] is at variance with Batchelor's[14] assumption of negligible linear field effects on quaternary carbon atoms. As has been pointed out earlier,[7b] the C6 shifts deviate substantially from the LEF calculated values, which can be due to their asymmetric situation with respect to the Cα–X dipole (see discussion of cholestenes below).

Figure 1 illustrates the presence of shielding effects by polar groups far beyond Cδ (filled circles). The possible steric origin of such long-range distortions was investigated by force field calculations, which showed the absence of changes in bond length l, bond angle θ, and torsional angle φ beyond Cγ ($\Delta l < 0.007$ Å, $\Delta\theta < 0.2°$, $\Delta\varphi < 0.9°$; see the supplementary material), even for the 3α-methyl steroid. Similar observations were made by Schwenzer[4] with steroids bearing hydroxy groups, which, however, can be expected to generate only very small geometry distortions as compared to bulkier methyl groups. The 3α-methylcholestane was prepared and measured in the present study as a suitable probe for long-range steric effects and indeed showed much *smaller* long-range shielding variations than I (αX = Hal, OR; Table I).

The electronegative substituents in I induce shielding at all remote positions, except at C11, and therefore cannot originate in through-bond but only in through-space effects. Calculation of charge polarizations on the basis of our earlier model and parametrization[7,9] does predict charge variations *within* the range as deduced from the observed shift changes (~0.001 eu for $\Delta \approx 0.5$ ppm), but the sign and magnitude are correctly obtained only for approximately 50% of the effects. Preliminary investigations[15] show that the small effects on remote atoms need further refinement of the calculational model, mainly by variation of the point of action of the electric field vector on the polarized bond.

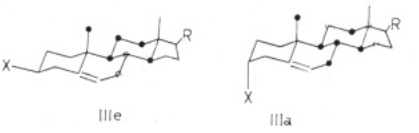


Figure 2. Cholestenes.

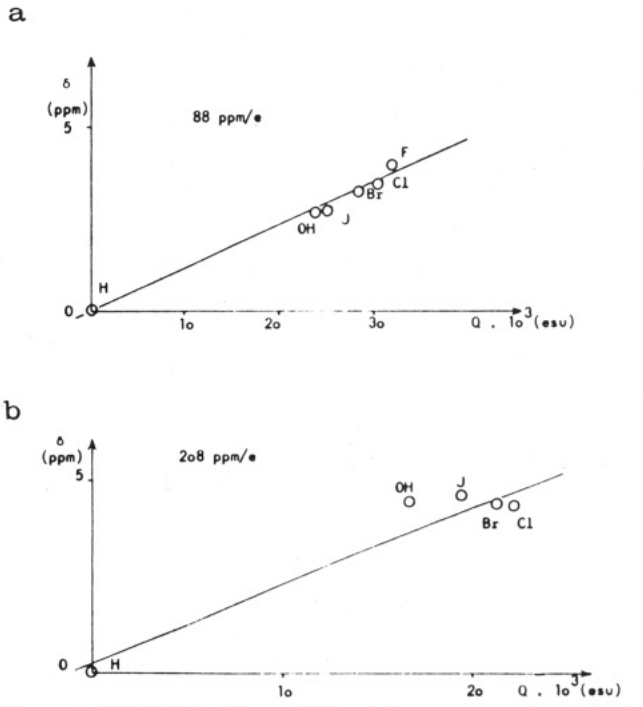


Figure 3. ^{13}C NMR shifts at C6 in cholestenes as a function of electron density changes, ΔQ, by the linear electric field effect of substituent X: a, β-X series; b, α-X series.

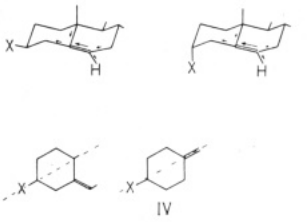


Figure 4.

3-Substituted Cholest-5-enes. The presence of double bonds in unsaturated steroids as III (Figure 2) is expected to lead to larger electric field effects in view of the increased polarizability as compared to saturated systems.[16] Relatively large shielding effects even on remote double bonds have been found and analyzed on the basis of point pole approximations.[7a,14,17] The observed shielding variations at C6 in the cholestene series (Figure 3) do show correlations with LEF-calculated charge densities such as 90 ± 10 ppm/eu for β-substituted and 210 ± 20 ppm/eu for α-substituted compounds. Clearly, the sensitivity is

(12) H.-J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978).
(13) r and $\psi = [n(1 - r^2)/(n - 2)]$, where n is the number of data, are used to qualify the correlations: J. Shorter, "Correlation Analysis in Organic Chemistry", Clarendon Press, Oxford, England, 1973.
(14) J. G. Batchelor, *J. Am. Chem. Soc.*, **97**, 3410 (1975).
(15) G. Schmidt and H.-J. Schneider, unpublished results.
(16) K. Seidman and G. E. Maciel, *J. Am. Chem. Soc.*, **99**, 3254 (1977).
(17) (a) Cf.: E. A. Hill and H. E. Guenther, *Org. Magn. Reson.*, **16**, 177 (1981); (b) M. E. Van Dommelen, J. W. de Haan, and H. M. Buck, *Org. Magn. Reson.*, **13**, 447 (1980); **148** 497 (1980). For data on cholestenes cf. K. N. Scott and T. H. Mareci, *Can. J. Chem.*, **57**, 27 (1979).

Table I. Substituent Effects on ^{13}C NMR Shifts in 3-Substituted Cholestanes[a,b]

	compound					
C no.	2, X = β-F (h)	3, X = α-F	4, X = β-Cl	5, X = α-Cl	6, X = β-Br	7, X = α-Br
γ-1	(−2.37) ^{22}ac	−6.84 ac^{V7}	−0.07 a^{V4}	−6.94 a^{V7}	0.61 a^{V4,12}	−5.87 a^{V2,6,7}
β-2	(6.28) ^{25}ac	4.90 ac	10.99 a	7.97 a^{V6}	11.97 a	8.78 a^{V1,6,7}
α-3	65.85 ac	62.39 ac	33.01 a	33.42 a	24.45 a	28.47 a^{V9}
β-4	(6.17) ^{20}ac	4.81 ac	10.38 a^{V1}	7.48 a^{V8}	(10.70) ^{12}a^{V1,12}	8.17 a
γ-5	−2.82 ac	−7.75 ac^{V12}	−0.25 ad	−7.91 ad^{V12}	0.97 ad	−7.13 ad
δ-6	(−0.49) ^{2}ad^{V16}	−0.75 ad^{V16}	−0.65 d	(−1.17) ^{25}ad^{V16,2}	−0.65 ad^{V16}	(−1.20) ^{25}ad^{V1,2,7}
7	−0.16 d	0.24 d^{V1}	−0.43 d	−0.03 d^{V1}	−0.25 d	−0.48 d^{V1,2,6}
8	(−0.10)^{10}d	−0.09 d	−0.20 d	−0.12 d^{V4}	(−0.25) ^{10}d	−0.18 d
9	−0.55 d	−0.71 d	−0.63 d	−0.87 d	−0.55 d	−1.00 d^{V3}
δ-10	(−0.78) ^{8}ab	−0.60 ab	−0.99 ab	−0.21 ab	(−0.93) ^{8}ab	(−0.08) ^{22}bd
11	0.42 d	−0.10 d	0.23 d	−0.10 d	−0.07 d	−0.10 d
12	−0.20 d	−0.18 d^{V5}	−0.25 d	−0.21 d^{V5}	(−0.38 ^{4}d^{V1,4})	−0.28 d
13	−0.03 bd	−0.01 bd	−0.03 bd	−0.01 bd	0.02 bd	−0.05 bd
14	−0.22 d	−0.15 d	−0.32 d^{V17}	−0.19 d^{V17}	(−0.32) ^{17}d	−0.20 d
19	0.00 d	−1.15 d	0.01 d	−0.44 d	−0.10 d	−0.47 d

	compound							
C no.	8, X = β-I	9, X = α-I (h)	10, X = β-OH	11, X = α-OH (h)	12, X = β-OAc (i)	13, X = α-OAc (i)	14, X = β-Me (j)	15, X = α-Me (k)
γ-1	2.38 a^{V4}	−4.53 a^{V2,7}	−1.70	−6.53	−1.94	(−5.81) ^{4}a	(1.17) ^{5}a	(−9.68) ^{6}a
β-2	14.20 a	10.33 a^{V1,7}	9.17	6.83	5.29	3.90 a	7.41 ^{9}a	(5.71) ^{3}a
α-3	2.83 a	10.07 a^{V4}	44.29	39.57	46.80	43.25 a	6.08 ^{9}a^{+}	(0.52) ^{2}a
β-4	13.64 a^{V1}	9.34 a^{V3}	8.95	6.73	4.93	(3.80)	(6.49) ^{8}a^{+}	5.68 a^{+}
γ-5	2.41 ad	−5.27 ad	−2.18	−7.96	−2.40	(−7.02) ^{12}ad	0.24 a	−7.15 ^{1}a
δ-6	(−1.01) ^{16}ad^{V3}	−1.40 ad^{V16}	−0.39	−0.52	−0.50	−0.72 ad	−0.07 ad	(−0.07) ^{1}d
7	−0.42 d	−0.42 d^{V1,2}	−0.19	−0.16	−0.21	−0.32 d	0.03 d	0.03 d
8	(−0.29) ^{10}d	−0.29 d	(−0.15)^{10}	−0.03	−0.05	−0.07 d	(0.06) ^{4}d	0.06 d
9	−0.52 d	−1.25 d	−0.45	−0.52	−0.59	−0.59 d	−0.03 d	−0.03 d
10	(−0.97) ^{8}bd	0.20 bd	(−0.83)^{8}	−0.19	−0.81	−0.49 bd	0.29 ab	−0.62 ab
11	−0.03 d	−0.03 d	0.39	−0.10	0.42	−0.06 d	−0.03 d	−0.03 d
12	−0.36 d	−0.36 d	−0.15	−0.13	−0.18	(−0.17) ^{5}d	0.00 d	0.00 d
13	−0.13 bd	−0.13 bd	−0.01	0.00	−0.01	0.03 bd	0.06 d	0.06 d
14	−0.45 d	−0.45 d	−0.15	−0.13	−0.35	−0.09 d	0.04 d	0.04 d
19	0.04 d	1.14 d	−0.31	−1.04	−0.01	−0.87 d	−0.09 d	−0.09 d

[a] In parts per million relative to the parent hydrocarbon (X = H);[3] measured in 30% w/v $CDCl_3$ unless noted otherwise, with 5% internal Me_4Si as the reference. The shifts of all other carbon atoms differ by <0.05 ppm from those of the hydrocarbon (X = H). Explanations at the individual signals are as follows. Assignment criteria: (a) comparison to cyclohexanes; (b) low-power noise decoupling for quaternary carbon atoms; (c) ^{13}C-^{19}F coupling; (d) small deviations due to remote substitution center; (e) typical shift region;[3] (f) off-response decoupling experiments; (g) lanthanide-induced shifts. Assignments for X = OH and OAc agree with the literature.[3] (h) Measured in 10% $CDCl_3$ solution. (i) OAc: C=O, 170.35 ppm; CH_3, 21.38 ppm from Me_4Si. (j) Me, (22.85)[27] ppm from Me_4Si. (k) Me, (18.75)[21] ppm from Me_4Si (methyl isomers were measured as a mixture; therefore, C1 in 14 and C5 in 15 are overlapping). [b] A number n in parentheses indicates overlap with another signal m: $(n)^m$; a superscript Vm indicates that assignments for signal n and m are interchangeable.

below the usual values, which, however, are necessarily quite susceptible to the errors and parametrizations involved.[9] Nevertheless, it is interesting that a larger sensitivity is observed in olefinic systems, where the double bond is situated in the X–Cα–H plane, such as in IV.[17b,18] Only in such a symmetric arrangement will those field vector components cancel which are not longitudinal to the polarized bond (Figure 4). This is also the case in the saturated systems I or II, which do show the theoretically expected effects at C10, but obviously not in the cholestenes III, for which neglect of nonlongitudinal vectors will therefore lead to additional errors.

Although shielding at γ-carbon atoms such as C5 in III cannot be analyzed solely in terms of linear field effects,[9] it is worthwhile to subtract the usual γ effects[12] from the SIS values and to compare the remaining additional shielding with calculated charge polarizations. For α substituents (X = F, Cl, Br, I) only ~0.003 eu of charge at C5 is obtained, whereas for the β halides −0.035 ± 0.005 eu of charge accumulation is predicted. It is remarkable that the γ effect of the α halides is indeed not larger than in the saturated analogue, whereas the β halides do show

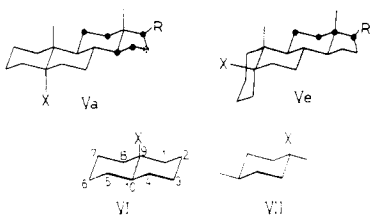


Figure 5. 5-Substituted cholestanes and model compounds.

approximately 2 ppm additional shielding. Thus, both the sign and magnitude of the shifts are understandable on the basis of the electron flow induced by the different substituents. The close similarity of "steric" shielding effects by axial groups on olefinic and saturated γ carbon atoms was noted earlier[19,20] and was associated with the presence of syn-axial p_z orbitals instead of C–H bonds[19] in such systems.

The shieldings at the sp^3 carbon atoms in III are, in view of the altered A-ring geometry, surprisingly similar to the shifts in I and II. The C3 SIS values correlate with $r \geq 0.9995$, $\psi \leq 3.6\%$, and $m = 1.00 \pm 0.08$; the β effects at C2

(18) P. Iratçabal, M. F. Grenier-Loustalot, A. Lichanot, and F. Métras, *Org. Magn. Reson.*, 11, 575 (1978).

(19) J. B. Grutzner, M. Jautelat, J. B. Dence, P. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).

(20) Cf. J. B. Stothers and C. T. Tan, *Can. J. Chem.*, **54**, 917 (1976).

Table II. Substituent Effects on ^{13}C NMR Shifts in 3-Substituted Cholest-5-enes[a]

	compound						
C no.	25, X = β-F	26, X = β-Cl (j)	27, X = α-Cl (p)	28, X = 3β-Br	29, X = α-Br (p)	30, X = β-I	31, X = α-I
γ-1	−3.24 ac	−0.71 a	−7.11 a^{V2}	0.43 a	−6.20 a	1.99 a	(−4.11) ^{20}a
β-2	6.14 ac	10.87 a	7.03 a^{V1}	11.78 a	7.91 a	13.99 a	9.30 a
α-3	64.38 ac	31.89 a	32.26 a	23.76 a	26.98 a	1.66 a	9.81 a
β-4	6.45 ac	10.61 a	7.32 a	11.39 a	8.12 a	13.50 a	9.94 a
γ-5	−4.23 e	−2.47 be	−6.26 ef	−1.86 e	−6.19 e	−0.65 be	−5.51 ef
δ-6	3.73 e	3.35 e	4.30 e	3.13 be	4.41 e	2.51 e	4.63 e
7	(−0.11) ^{8}d	(−0.03) ^{8}d	(−0.26) ^{8}d	(−0.17) ^{8}d	(−0.26) ^{8}d	(−0.30) ^{8}d	(−0.20) ^{8}d
8	(−0.11) ^{7}d	(−0.03) ^{7}d	(−0.26) ^{7}d	(−0.17) ^{7}d	(−0.26) ^{7}d	(−0.30) ^{7}d	(−0.20) ^{7}d
9	−0.67 d	−0.45 d	−1.02 d	−0.45 d[o]	−0.98 d	−0.29 d	−0.81 d
δ-10	−1.07 a	−1.07 bd	−0.58 f	−1.14 bd	−0.58 d	−1.07 bd	−0.44 f
11	0.24 d	0.20 d	−0.22 d	0.10 d	0.01 d	−0.06 d	−0.09 d
12	−0.24 d	−0.09 d	−0.31 d	−0.22 d	(−0.50) ^{24}d	−0.26 d	−0.21 d
13	−0.07 d	0.06 bd	−0.11 df	−0.03 bd	0.04 df	−0.03 bd	−0.05 df
14	−0.31 d	−0.13 d	−0.35 d	−0.23 d	−0.26 d	−0.26 d	−0.33 d
19	−0.19 d	−0.16 d	−0.34 d	−0.23 d	0.04 d	−0.26 d	0.92 d

	compound					
C no.	32, X = β-OH (j)	33, X = α-OH	34, X = β-OAc (j)	35, X = α-OAc	36, X = β-OCH_3 (j)	37, X = β-Me
γ-1	−2.53 a	−6.81 a	−3.06 a^{u}	−6.55 a	−2.66 a	−0.25 a
β-2	9.05 a	6.25 a	5.07 a	3.40 a	(5.44) ^{25}a	8.63 a
α-3	43.64 e	38.80 a	45.53 a	42.23 a	52.49 a	7.22 a
β-4	(9.43) ^{13}a	(6.81) ^{12}a	5.03 a	3.13 a	5.78 a	8.73 a
γ-5	−2.47 be	−4.89 ef	−4.32 ef	−5.53 ef	−2.47 be	0.04 f
δ-6	2.54 e	4.37 e	3.05 e	2.56 e	2.54 e	−0.11 e
7	(0.06) ^{8}d	(−0.08) ^{8}d	(−0.19) ^{8}d	(−0.22) ^{8}d	(0.10) ^{8}d	(−0.03) ^{8}d
8	(0.06) ^{7}d	(−0.08) ^{7}d	(−0.19) ^{7}d	(−0.22) ^{7}d	(0.10) ^{7}d	(−0.03) ^{7}d
9	−0.39 d	−0.45 d	−0.83 d	−0.91 d	−0.35 d	−0.22 d
δ-10	−0.91 bd	−0.27 f	−1.08 f	−0.70 f	−0.55 bd	−0.65 df
11	0.33 d	−0.09 d	0.27 d^{VCH_3}	0.12 d	0.33 d	0.13 d
12	0.00 d	(−0.18) ^{4}d	−0.56 d	−0.29 d	−0.03 d	−0.05 d
13	(0.06) ^{4}bd	−0.09 d	−0.21 df	−0.21 df	0.06 bd	−0.03 df
14	−0.06 d	−0.23 d	−0.94 d	−0.37 d	−0.06 d	−0.08 d
19	0.00 d	(−0.77) ^{21}d	−0.24 d	(−0.71) ^{21}d	0.00 d	−0.08 d

[a] See corresponding footnotes in Table I (measured in 20% $CDCl_3$ solution). The following shifts deviate by >0.05 ppm from the parent hydrocarbon. X = α-Cl: C-17, −0.30; C-20, −0.19; C-22, −0.28; C-23, −0.17; C-24, −0.19. X = 5Br; C-17, −0.22. X = β-OAc: c-16, −0.44; C-17, 0.17; C-20, −0.20; C-22, −0.22; C-23, −0.19; C-26, −0.16. X = α-OAc: C-15, −0.22; C-16, −0.17; C-17, −0.28; C-20, −0.24; C-22, −0.22; C-23, −0.19; C-24, −0.25; C-25, −0.18; C-26, −0.20. Substituent shifts (in parts per million from Me_4Si): X = β-OAc, 21.03 ^{V11} (CH_3), 169.62, (C=O); X = α-OAc, 21.11 (CH_3), 170.00 (C=O); X = β-OCH_3 55.70 (CH_3); X = β-Me 22.60 ^{26} (CH_3).

Table III. Substituent Effects on ^{13}C NMR Shifts in 5α-Substituted Cholestanes[a]

	compound				
C no.	16, X = F (j)	17, X = Cl	18, X = Br	19, X = OH	20, X = OAc
syn-γ-1	−6.19 a	−6.75 a	−5.49 a	−7.18 ag	−7.18 a
δ-2	−1.64 a	−1.13 $a^{V3,11}$	−1.04 a^{V11}	(−1.30) ^{11}ai	(−1.24) ^{3,11}a
syn-γ-3	−3.84 a	−5.65 $a^{V2,11}$	−4.48 a	−6.21 ag	(−5.89) ^{2,11}a
β-4	3.71 ac	7.57 a^{V6}	8.84 a^{V6}	5.29 ag^{V6}	(1.18) $^{25}a^{V6}$
α-5	54.34 ac	38.97 af	45.18 af	25.94 af	40.57 af
β-6	3.51 ac	7.44 a^{V4}	8.61 a^{V4}	5.52 ag^{V4}	(−0.96) $^{16}a^{V4}$
syn-γ-7	−5.49 a^{V11}	−5.33 a	(−4.26) ^{25}a	−5.96 ag	−5.64 a
δ-8	−1.04 a	−0.85 a	−0.88 a	−0.75 ag	−0.81 a
syn-γ-9	−8.58 a	−8.15 a	−6.66 a	−8.80 ag	−8.72 a
β-10	3.18 ac	4.74 af	5.33 af	2.99 af	(3.26) ^{24}af
11	−0.31 d^{V7}	−0.29 $d^{V2,3}$	−0.39 d^{V2}	(0.03) ^{2}d	(0.09) ^{2,3}d
12	−0.25 d	−0.26 d	−0.39 d	−0.13 d	−0.14 d
13	−0.10 d	0.06 df	0.00 df	0.03 df	0.07 df
14	−0.63 d	−0.48 d^{V17}	−0.65 d	(−0.45) ^{17}d	−0.35 d^{V17}
15	−0.21 d	−0.20 d	−0.23 d	−0.17 d	−0.19 d
16	−0.33 d	−0.03 d	−0.06 d	−0.03 d	−0.11 d
17	−0.36 d	−0.29 d^{V14}	−0.32 d	(−0.19) ^{14}d	−0.29 d^{V14}
18	−0.07 d	0.07 d	0.07 d	0.00 d	0.08 d
anti-γ-19	3.95 ac	3.82 a	3.08 a	3.76 a	3.42 a

[a] See corresponding footnotes in Table I; measured in 20–30% $CDCl_3$ solutions. For j, 3β-acetoxy-5α-fluorocholestane relative to 3β-acetoxy cholestane.

and C4 as well as the Cγ shift at C1 show small differences between I and III; long-range effects are again noticeable at C19, C7, C8, C11, C12, and C14 (Table II).

5α-Substituted Cholestanes and 9-Substituted Decalins. Substituents at sterically crowded positions, such as at 5α in Va (Figure 5) could give rise to stronger distortions of geometry and electron density. The ^{13}C NMR shielding effects found for Va (Tables III and IV), indeed unusual, led us to investigate also structurally similar decalins VI (Table V), for which ^{13}C NMR data are

Table IV. Substituent Effects on ^{13}C NMR Shifts in 5β-Substituted Cholestanes[a]

C no.	compound 21, X = Cl	22, X = Br	23, X = OH
syn-γ-1	−6.03 a^{V7}	−4.99 a^{V7}	−6.30 ai^{V7}
δ-2	−1.25 $a^{V3,11}$	−1.28 $a^{V3,11,19}$	−0.95 ai^{V3}
syn-γ-3	−4.80 $a^{V2,11}$	−3.63 $a^{V2,11,19}$	−5.32 ai^{V2}
β-4	7.20 a^{V8}	8.46 a^{V8}	5.25 ai
α-5	39.05 af	43.54 af	29.67 if
β-6	11.67 a	13.36 a	8.81 ai
anti-γ-7	2.80 a^{V1}	3.64 a^{V1}	2.05 ai^{V1}
δ-8	−1.15 a^{V4}	−1.05 a^{V4}	−0.95 ai
anti-γ-9	2.95 a	2.56 a	2.58 ai
β-10	5.57 af	6.16 af	(3.93) ^{12}afi
11	0.97 $d^{V2,3}$	0.88 $d^{V2,3,19}$	0.27 d
12	−0.29 d	−0.23 d	(−0.31) ^{10}d
13	−0.33 df	−0.33 df	−0.22 df
17	−0.24 d	−0.31 d	−0.23 d
syn-γ-19	−4.82 a	−2.06 $a^{V2,3,11}$	−7.18 ai

[a] See corresponding footnotes in Table I.

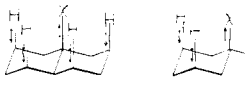
Table V. Substituent Effects on ^{13}C NMR Shifts in 9-Substituted *trans*-Decalins[a]

C no.	substituent H[b,c]	F[d]	Cl	Br	I	CH_3[c]	OH
β-1,8	34.45	3.25	7.8	8.85	11.31	7.70	5.39
γ-2,7	26.94	−4.84	−4.77	−3.86	−2.04	−4.93	−5.23
δ-3,6	26.94	−0.55	−0.54	−0.54	−0.42	0.25	−0.55
δ-4,5	34.45	−5.27	−5.20	−4.09	−1.82	−5.38	−5.79
α-9	43.77	49.49	33.60	36.78	31.82	−9.44	26.30
β-10	43.77	0.13	3.10	4.14	5.08	1.95	0.49

[a] In parts per million relative to the hydrocarbon (X = H); measured in 30% w/v $CFCl_3$, except for ROH (20% $CDCl_3$ solution) at ambient temperature with 5% Me_4Si as an internal reference. [b] Shifts relative to Me_4Si. [c] Cf. D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Am. Chem. Soc.*, 95, 3718 (1973). The *trans*-decalin shifts reported therein are larger than ours by 0.25–0.5 ppm but are used to calculate SIS values for X = CH_3. [d] ^{13}C–^{19}F coupling constants (in hertz): ^1J = 173.5, ^2J(C1,8) = 23.5, ^2J(C10) = 22.1. Other coupling constants are < 2 Hz.

available so far mostly for nonbridgehead-substituted derivatives containing oxygen or alkyl groups only.[21]

Compared to the cyclohexane analogues IIa and VII,[12] both Va and VI show large shielding deviations, which can amount to reversed signs of substituent effects, even of the methyl group. Thus, bromine or iodine leads to a deshielding at Cα, increasing by up to 200% in the order IIa, VII, VI, V, whereas the axial methyl group produces increased shielding from ~0 ppm in cyclohexane IIa to almost −10 ppm in decalin VI. Since the deshielding of the halides is enhanced along with an increase of the C–Hal bond polarizability, the origin of this particular effect can be sought for in the polarization of the C–X bond by four diaxial C–H bonds which are present in tertiary bridgehead compounds such as VI. In normal cyclohexanes only two diaxial C–H dipoles can induce an additional electron flow toward X.



The reversed shielding order for X = CH_3 could be ascribed to conformational changes by this relatively bulky and less polarizable group. Force field calculations for the different compounds not only indicate Cα–Cβ bond elongations upon introduction of an axial methyl, increasing from 0.0005 Å in II to up to 0.015 Å in V, but also show Cβ–Cα–Cβ bond angles, which are closer to 109.5° in the decalin type than to the angle in cyclohexanes.[22] The manifold conformational changes in methyl compounds such as I–VI (X = CH_3) and the subsequent variations of sterically induced NMR shifts need further investigations. It is clear, however, that axial methyl groups in sterically demanding positions lead to consistent bond length and particularly angle variations around Cα, which in view of the higher symmetry in compounds such as V and VI contribute to shielding relative to simple cyclohexanes, as the latter are more easily distorted by axial substituents. This reasoning is in accordance with earlier findings by other workers[4a,b] on the reduction of the hydroxyl effect on Cα shifts with an increasing number of axial hydrogens or gauche interactions. Although the interpretation of hydroxyl substituent effects is complicated by its intermediacy between steric and polar interactions as well by its additional torsional isomers around the Cα–O bond, preliminary calculations[22] suggest similar but attenuated conformational effects as found with the methyl substituent.

The substituent effects on the different β-carbon atoms usually deviate little with the noticeable exception of the fluoro compounds. Since the β-carbon deshielding results generally from square electric field effects which vary with r^{-6} from the Cβ···X distance r,[9,23] fluorides having short C–F bonds are expected to be particularly sensitive to geometry distortions. The attenuation of the β effect on tertiary or quaternary carbon atoms as compared to secondary atoms (compare C10 in Va and VI) was ascribed earlier to a change of linear electric field components, which can amount to 5–6 ppm.[24]

Spectacular variations of the syn-γ-carbon shielding by all substituents are observed by comparison of Va, V, and VII or II. Since, e.g., an increase from $\Delta\gamma \simeq 5$ ppm in VII[12] to almost 9 ppm in Va (C9) is detectable not only for larger substituents such as X = OH but also for X = F, these alterations must be associated with general geometry differences between cyclohexanes and steroids and subsequent field-effect variations and not primarily with substituent-induced geometry distortions. Force field calculations do indicate substituent-induced variations of torsional angles including Cγ atoms, but some of these seem to cancel each other; bond lengths and bond angles show no significant changes around Cγ even for X = CH_3.

The anti-γ effect of *all* electronegative substituents in Va on C19 is deshielding, in contrast to the shielding observed for the effects of the first-row elements in secondary cyclohexanes such as in IIe or Ie. The latter have been rationalized by a hyperconjugative charge-transfer model,[25] which is at variance with the present finding. That anti-γ effects of oxygen and fluorine substituents are not only deshielding for bridgehead compounds[25] but also normally deshielding for all derivatives lacking axial hydrogens at Cα and Cβ has been noted already[12,26] and observed for several hydroxy compounds.[21a]

The shifts at Cδ atoms are similar to those observed in

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VII or II. They can be rationalized by through-space field effects, as are those on more remote carbon atoms (see above) which are constantly shielded by the substituent. Even though substituents at the 5α-position are under more strain as compared, e.g., to the 3α compounds, force field calculations shown no significant alterations of bond length Δl, bond angles $\Delta\theta$, or torsional angles $\Delta\varphi$ beyond the A or B ring[2c,6] ($\Delta l < 0.001$ Å, $\Delta\theta < 0.5°$, $\Delta\varphi < 2°$; see supplementary material also). That the smallest but most electronegative substituent fluorine in Va exerts higher shielding effects on remote carbon atoms than other groups indicates the predominance of linear field effects over any conformational steric transmission.

5β-Substituted Cholestanes. Essentially all ^{13}C signals from ring A and B carbon atoms can be used to differentiate between the 5α/5β epimers. As observed in cyclohexanes and bicyclic compounds,[12] the functional Cα shifts often show less stereospecific substituent effects than Cβ or Cγ. In the 5β compounds, where X of course is axial as well as equatorial, the SIS values on Cα are the same within 0.2–3 ppm as in the 5α series (Tables III and IV). The shift differences at C5 for the basic hydrocarbons Va,b (X = H) are thus maintained in the substituted compounds and are sufficiently large for configurational assignments. The β effects show, as expected, at C4 a resemblance to axially substituted cyclohexanes, whereas C6 is even slightly more deshielded than in equatorially substituted analogues such as Ie or IIe.

The anti-γ effects on C7 and C9 again are deshielding as observed with other tertiary functionalities (see above). Syn-γ effects can be measured as usual not only on ring methylene carbon atoms but also on methyl atoms; they agree well with the usual range and particularly with those found in comparable 2,2-dimethylcyclohexanes.[24] The different number of gauche interactions in the 5α and 5β hydrocarbon epimers leads to large shielding differences at C7, C9, and C19;[3] in the 5-X-substituted epimers these differences necessarily are smaller since there are now additional gauche interactions with the X group. Consequently, we observe only 1–6-ppm differences instead of 5–14 ppm as in the hydrocarbons V (X = H).

Beyond the A and B ring the ^{13}C shifts in the 5α/β epimers differ by less than 0.3 ppm (~1 ppm at C9), which indicates the absence of a long-range transmission of the A–B cis/trans interconversion into the C and D ring. This is in accord with the absence of significant geometry differences in the force field calculated structures.

Conclusions

Geometrically well-defined steroids bearing a sufficiently large range of substituents at one particular site are suitable models for the analysis of both NMR shielding and conformational transmission mechanisms of substituent effects. The ^{13}C shifts at least for the 3α,β-substituted compounds correlate well with those of comparable cyclohexanes, which is in full accord with force field calculated geometries. Several deviations, mostly with the tertiary 5α,β-substituted systems and noted too in the decalins, are also of practical importance for the application of substituent-induced shifts. In view of the calculated geometries, the shielding effect of an axial CH_3 group on Cα seems to be unusual more in secondary cyclohexane systems, which are more susceptible to distortions by axial groups, than in the corresponding tertiary decalins or steroids. The Cα SIS attenuation, known so far for X = OH[4a,b] but more noticeable, e.g., with X = I, is also indicative of a secondary C–X polarization by axial C–H bonds. The larger differences of β and particularly γ effects between cyclohexanes and steroids are reflected in force field calculated geometry differences. A more quantitative correlation to the associated changes of linear and high-order field as well as anisotropy effects and sterically induced charge polarizations by improved calculational models should ultimately contribute to the deduction of both density and geometry variations from chemical shifts.

Quantitative correlations at the present time are limited to cases where high-order shielding effects are negligible and where single interactions are still large enough, e.g., to Cγ for sterically induced or to Cδ for linear electric field contributions. It is, however, already possible to specify from the ^{13}C shifts the limit of substituent-induced charge variations at remote carbon atoms, particularly on the basis of the strong sensitivity of ~300 ppm/eu observed in the LEF studies.

Conformational transmission effects of sterically demanding but unpolar substituents die away very quickly, as is particularly obvious from both ^{13}C shifts and force field (FF) calculations for 3α-methylcholestane, and therefore should play only a minor role also in structure–activity,[2c,27] interpretations. Small but polar substituents such as fluorine, which is used in many pharmacologically active steroids, generate no recognizable conformational distortions but do generate theoretically predictable and experimentally observable electron density variations over large distances, which are the product of through-space and not of through-bond effects.

Experimental Section

The preparation of the compounds has been described elsewhere: I and V, ref 6 and 8d; III, ref 8d; VI, ref 28 (X = Hal), ref 29 (X = OH); or in the reference cited therein.

^{13}C measurements were carried out as usual[4c] under the conditions given in the tables. In the force field (FF) calculations 17β-isopropylandrostane was used as a model for cholestane; the computational details for the FF and the linear electric field (LEF) calculations are outlined in earlier publications[4c,6,7] (see also the supplementary material). The LEF calculations for III were based on an X-ray-derived crystal structure determination of 3β-chloroandrost-5-en-17β-ol[30] by using standard bond lengths for C–X bonds.

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Registry No. 2, 3824-61-1; **3**, 3856-83-5; **4**, 1474-58-4; **5**, 5847-30-3; **6**, 51154-61-1; **7**, 2309-03-7; **8**, 82863-87-4; **9**, 29108-97-2; **10**, 80-97-7; **11**, 516-95-0; **12**, 1255-88-5; **13**, 1107-59-1; **14**, 38544-61-5; **15**, 74164-13-9; **16**, 3800-94-0; **17**, 56114-17-1; **18**, 74098-17-2; **19**, 910-19-0; **20**, 41721-99-7; **21**, 74098-16-1; **22**, 74098-15-0; **23**, 20220-17-1; **25**, 474-75-9; **26**, 910-31-6; **27**, 2863-79-8; **28**, 516-91-6; **29**, 2871-53-6; **30**, 2930-80-5; **31**, 36049-79-3; **32**, 57-88-5; **33**, 474-77-1; **34**, 604-35-3; **35**, 1059-85-4; **36**, 1174-92-1; **37**, 52753-84-1; *trans*-decalin, 493-02-7; *trans*-9-fluorodecalin, 82823-26-5; *trans*-9-chlorodecalin, 5597-82-0; *trans*-9-bromodecalin, 7731-69-3; *trans*-9-iododecalin, 82823-27-6; *trans*-9-methyldecalin, 2547-27-5; *trans*-9-hydroxydecalin, 1654-87-1.

Supplementary Material Available: ^{13}C NMR shifts of reference compounds (steroids and decalins), parametrizations and charge changes (LEF calculations), and internal coordinates for representative steroids (MM1 or MM2 calculations) (9 pages). Ordering information is given on any current masthead page.

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