PERKIN 2

Proton chemical shifts in NMR. Part 8.[1] Electric field effects and fluorine substituent chemical shifts (SCS)

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A calculation of the effect of a linear electric field of a polar substituent on proton chemical shifts based on partial atomic charges is shown to give a complete account of fluorine SCS in rigid molecules for all long range protons (> three bonds). A value of the linear electric field coefficient A_Z of 3.67×10^{-12} esu (63 ppm au) is obtained. For vicinal protons (H·C·C·F) the electric field calculation is accurate for monofluorine substitution but considerably overestimates the effects for difluoro (CF_2) and trifluoro (CF_3) substituents. A model based on fluorine polarisability and correcting for di- and tri-fluoro substituents gives good agreement with the observed SCS.

The combined scheme predicts the proton chemical shifts of a variety of fluoroalkanes over 60 data points spanning *ca.* 6 ppm with an rms error of 0.11 ppm. The compounds include fluoroalkanes, cyclohexanes, bornanes, norboranes and steroids. Thus fluorine SCS can be quantitatively explained on the basis of a linear electric field model without recourse to either C−F bond anisotropy or van der Waals (*i.e.* steric) effects.

Introduction

The influence of a uniform external electric field (E) on proton shielding was first calculated by Marshall and Pople[2a] for the hydrogen atom in which by symmetry only an E^2 term is present. Buckingham[2b] extended their method to derive the shielding for a C−H proton. Their equation on the δ scale is given by eqn. (1), where A_Z is the linear electric field coefficient or

$$\delta_{\mathrm{electric}} = A_Z E_Z + BE^2 \qquad (1)$$

shielding polarisability and B the quadratic electric field coefficient or shielding hyperpolarisability. For a dipolar (*e.g.* C−X) substituent the linear electric field is proportional to r^{-3} and the quadratic term proportional to r^{-6} where r is the distance from the substituent or centre of the point charge to the proton considered. The quadratic electric field is different in origin from the steric or van der Waals term but has a similar geometric dependence and therefore it is not practical experimentally to distinguish between these effects.[3,4]

Buckingham also noted that the value of the linear coefficient is dependent upon the nature of the atom attached to the proton, thus C−H, N−H and O−H protons will have different values of A_Z. For the C_{sp^3}–H bond he suggested a value of 34 ppm au. Subsequent semi-empirical calculations gave values of A_Z from 44 to 83 ppm au[5–7] for the C_{sp^3}–H bond and the very recent SCF calculations of Grayson and Raynes[8] gave values between 62.0 and 80.2 ppm au, with an average of 70 ppm au for methane, ethane, acetonitrile, chloromethane and fluoromethane.

Although the basic theory of the electric field effect is thus well established, the experimental determination of the effect of the electric field on proton shielding and in particular the relative proportions of the linear and quadratic terms is still a matter of speculation and controversy. Early investigations on the density dependence of the proton shielding in gaseous trifluoromethane[4] and on the effect of solvent on the proton shifts of acetonitrile[9] gave values of A_Z of *ca.* 50–60 ppm au. Zürcher[3] analysed the proton SCS in steroids and bicycloheptenes using the methyl groups of the steroids with Cl, OH, CN and C=O substituents in terms of the bond anisotropy and both the linear and quadratic electric fields of the substituents. He obtained a value of A_Z of 72 ppm au and also found that the effects of bond anisotropy on SCS were important for the CN and C=O groups but not for Cl and OH. He included the quadratic term in evaluating Cl SCS but concluded that this term was not significant and ignored it subsequently.

More recent investigations have only partially clarified the situation. The proton SCS of ketones, thioketones[10–12] and ethers[13] were interpreted as arising from anisotropy and electric field effects but for alcohols electric field effects were regarded as the dominant term.[3,12,14–16]

For chloro and bromo substituents Davis *et al.*[14] suggested that apart from 1,3-*syn* diaxial protons the SCS could be explained by electric field effects alone and similar conclusions were obtained for the proton SCS in halosteroids[12,15] and for bromo-, chloro- and iodo-*trans*-decalins.[16] Recent studies on halobicycloheptanes[17] and halocamphors[18] suggested that linear electric field effects plus steric contributions could explain the SCS on the remote protons with a short range mechanism (anisotropy, van der Waals or inductive) needed for the vicinal protons.

The influence of the quadratic electric field or steric effect has been examined in the proton chemical shifts of hydrocarbons where the linear electric field term will be comparatively small. Boaz[19] suggested that the observed chemical shifts of the axial protons in cyclic alkanes were dependent upon the number of 1,3-*syn*-axial protons, and interpreted this as arising from the C−H dipoles. Later workers[20,21] considered the C−H linear electric field term, steric and anisotropy effects in hydrocarbons but found that inclusion of the C−H linear electric field term did not improve the fit of a scheme which already included magnetic anisotropy and steric interactions (see below).

As fluorine is a small, highly polar and almost non-polarisable atom fluorine SCS could be regarded as the ideal data to examine electric field effects, but until recently there was little systematic data on fluorine SCS in rigid molecules. The only complete SCS data were for 3α- and 3β-

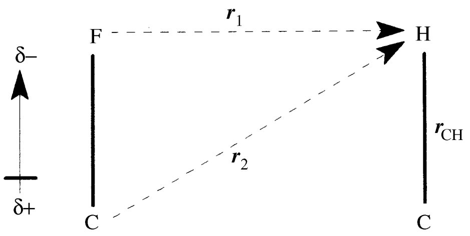

Fig. 1 Model used to calculate C−F electric field effects

fluoroandrostan-17-one[12] and 3-*endo* and 3-*exo* fluorocamphor[18] and in neither case were the calculated SCS given. In previous parts of this series[22,23] the proton spectra of a number of fluorocyclohexanes and norbornanes were analysed and the fluorine SCS obtained and reasonable agreement was obtained between the observed shifts and those calculated from the CHARGE scheme. The longer range H···F SCS were well represented by an r^{-3} term, in direct contrast to the SCS for H···C and H···Cl which were better reproduced by an r^{-6} term. Furthermore, there was no 'push–pull' effect in the fluorine SCS data again contrasting with the methyl and chlorine SCS. These results imply that the major mechanism operating for distant protons in fluoroalkanes may be a linear C−F electric field (r^{-3} function) while in the chloroalkanes the steric term also plays an important role. Here, we provide a quantitative examination of this hypothesis and show that the linear electric field calculation does reproduce the fluorine SCS.

Theory

In the CHARGE scheme[23] the effect of the fluorine substituent on atoms up to three bonds away is due to through bond contributions which are α (one bond), β (two bond) and γ (three bond) effects. The α effect is dependent on the relative electronegativities of fluorine and carbon and was derived from experimental dipole moments;[24] the β effect is a function of the electronegativity of fluorine and the polarisability of the proton and the γ effect is a function of both the fluorine and proton polarisability. The β proton SCS in CH_3F, CH_2F_2 and CHF_3 were non-additive and correction factors were included for CF_2 and CF_3 groups. The γ effect of fluoro substituents was observed to be non-orientational and also non-additive and similar correction factors for CF_2 and CF_3 groups were included. The long range SCS of fluorine (*i.e.* > three bonds) was given simply as an r^{-3} term.

To calculate the electric field of a substituent in a scheme based on partial atomic charges it is computationally simpler and more accurate to directly calculate the electric field at the protons due to the partial atomic charges on the substituents rather than the field due to a C−F dipole. Thus for the C−F bond the charge on the carbon atom ($\delta+$) was taken as the same magnitude as the charge on the fluorine ($\delta-$) but of opposite sign (Fig. 1). The vector components of the electric field were calculated from the fluorine and from the carbon to the proton and summed to give the component of the total field along the C−H bond [eqns. (2) and (3)].

$$\delta_{\text{electric}} = A_Z|E|i_E i_{CH} \qquad (2)$$

$$E = -e\left\{\frac{\mathbf{r}_1}{|r_1|^3} - \frac{r_2}{|r_2|^3}\right\} \qquad (3)$$

E is the field vector and $|E|$ the magnitude of the field vector; i_E is the unit vector of E, along E; i_{CH} is the unit vector along the C−H bond; e is the charge on the substituent atom; $|r_1|$ is the magnitude of vector r_1; and $|r_2|$ is the magnitude of vector r_2.

Hence, the effect of a C−F bond on a parallel C−H proton is deshielding. Alternatively the effect of a C($\delta-$)–H($\delta+$) bond on a parallel C−H proton is shielding. This approach differs from the point dipole approximation[3] in several ways. It is more accurate at close interatomic distances r_i and also the charge on the substituent atom (*e.g.* F) will vary depending on the chemical environment of the substituent as opposed to a fixed C−F dipole. In particular the charge on a fluorine atom decreases in the order $CH_2F > CHF_2 > CF_3$; thus the electric field contribution will decrease in this order also.

Results

The electric field calculation was included in the CHARGE4 program[23] in place of the previous r^{-3} term for fluorine SCS with the remainder of the program unchanged. Thus the partial atomic charges on the atoms are obtained directly from the CHARGE4 routine. The observed and calculated fluorine SCS were then compared. The geometries used were obtained as previously[1] from *ab initio* calculations at the RHF/6-31G* level.[25] The calculated C−F bond lengths for this basis set were slightly less than the experimental values (*cf.* fluoroethane 1.372 *vs.* 1.397 Å[26]) and to compensate for this the value of A(C,F), the carbon to fluorine integral, was changed from 40.0 to 39.0. Better bond lengths may be obtained using higher basis sets or second-order theory (MP2) but the calculations are impractical on molecules as large as steroids. The effect of solvent on the molecular geometries may be safely neglected as all the experimental data were obtained in low concentrations in non-polar solvents (*i.e.* CCl_4 or $CDCl_3$).

For the monofluoro-substituted compounds, for which there were 40 data points including ethanes, cyclohexanes, bornanes and steroids, it was found that for long range fluorine SCS (*i.e.* > three bonds) good agreement was obtained for a value of A_Z of 3.67×10^{-12} esu, *i.e.* 63 ppm au. This calculation gave SCS effects for the CF_2 groups which were slightly too large and the calculated SCS for this group was reduced by moving the position of the atomic charge from the fluorine atom towards the bond centre and similarly for the attached carbon atom. This is equivalent to assuming the electron density is more towards the bond centre in CF_2 groups (see later). A displacement of the CF_2 centres by 10% of the bond length gave good results. Unfortunately, there were no data available to us to determine the long range effects of CF_3 groups in rigid molecules.

When the above electric field calculation was applied to the γ (H·C·C·F) protons for the monofluoro-substituted compounds good agreement with the observed SCS was obtained. However, for CF_2 and CF_3 groups the calculated shifts were much too large. Reducing the value of A_Z is not an option as this would destroy the above agreement for the long range SCS data. It has been noted previously[22] that the effect of the two fluorines in a CF_2 group on the SCS of the vicinal protons is non-additive. In 1,1-difluorocyclohexane the SCS of H2ax is additive (*i.e.* is the sum of the monofluoro SCS) but that of H2eq is *less* than the individual SCS for the monofluoro compounds. Similarly the SCS for the 1-CH proton in 2,2-difluoronorbornane is +0.24 ppm in contrast to +0.30 and +0.16 ppm for the corresponding proton in the 3-*endo* and 3-*exo* fluorocamphor (see Table 4). Furthermore, the γ SCS varies for CH_3, CH_2 and CH protons whereas the long range effects on CH and CH_2 protons are the same. For example, 3-methyl-1,1-difluorocyclohexane the SCS for H3ax and H5ax are +0.40 and +0.34 ppm, respectively (see Table 3). The γ SCS are clearly electronic effects and an electric field term would not be expected to reproduce them. Thus the electric field term was only applied to the long range protons. The γ proton SCS were calculated as given previously,[22] the only amendment being a 17% increase of the SCS for monofluoro-substitution as the previous calculations overall underestimated the SCS.

The excellent agreement between the observed and calculated SCS for the long range protons demonstrates unequivocally the presence of a linear electric field effect on the proton chemical shifts of these protons. It follows that this effect will be present for all polar groups including the C–H bond. It was therefore felt necessary to include the electric field of the C–H bonds in the calculations for all but the γ protons. This was performed with the additional constraint for these much smaller effects of a cut-off to avoid the calculation of a large number of essentially negligible contributions. The cut-off was taken as the same value as that used previously for the H–H steric contributions (3.19 A).[23] As this amendment affects the calculated shifts of all the alkanes studied previously the CHARGE4 parametrisation was repeated with the CH electric field included. This has been given for the hydrocarbons elsewhere.[1] The major effect of this change is in decreasing the values of the H–H steric parameters to compensate for the CH electric field, the calculated shifts for the hydrocarbons are virtually unchanged.

The calculated values of the proton chemical shifts and fluorine SCS on the above model for all the protons in the compounds considered are given in Tables 1–5 together with the observed data.

In Table 1 for the fluoro-propanes and -butanes where more than one possible conformer exists, the data for both forms are given. The *gauche* and *trans* forms of the fluoroethanes have the same calculated shifts as the fluorine γ effect is non-orientational.

Table 1 Observed *vs.* calculated proton chemical shifts (δ) of acyclic fluoroalkanes

Molecule		Obs.[a]	Calc.
CH_3F	CH_3	4.27	4.26
CH_2F_2	CH_2	5.45	5.46
CHF_3	CH	6.41	6.41
CH_3CH_2F	CH_2	4.55	4.60
	CH_3	1.35	1.26
CH_3CHF_2	CH	5.94	5.76
	CH_3	1.56	1.42
CH_3CF_3	CH_3	1.87	1.76
CH_2FCH_2F	CH_2	4.59	4.80
CH_2FCHF_2	CH	5.93	5.85
	CH_2	4.45	4.87
CHF_2CHF_2	CH	5.64	5.88
CF_3CH_2F	CH_2	4.55	5.03
$CH_3CH_2CH_2F$[b]	CH_2F	4.30	4.65(*g*), 4.53(*t*)
	CH_2	1.68	1.59(*g*), 1.59(*t*)
	CH_3	0.97	0.98(*g*), 0.96(*t*)
$(CH_3)_2CHF$	CH	4.84	4.93
	CH_3	1.34	1.32
$(CF_3CH_2)_2$	CH_2	2.46	2.33(*g*), 2.31(*t*)

[a] Data from ref. 22. [b] (*g*) *gauche*, (*t*) *trans* conformer.

Discussion

From the comparison of the observed and predicted shifts in Tables 1–5 it can be seen that the model replicates the experimental data very well. Thus, the C–F linear electric field calculations give a quantitative interpretation of the long range fluorine SCS in these systems. The value obtained for A_Z of 63 ppm au is also in excellent agreement with both Zürcher's value and the recent calculations of Grayson and Raynes further supporting these results.

The 10% reduction in the field required for the difluoro (CF_2) group is also explained on this basis as this non-linear effect is well known in quantum mechanical calculations of fluoro compounds. The geminal fluorine atoms strongly interact with each other, the F·C·F angle is much less than tetrahedral and the CF bond dramatically shortened in the CF_2 and CF_3 groups[22] due to resonance forms such as $F^+{=}C{-}F^-$. On this basis the electron distribution in the CF bond would be greater between the atoms in the CF_2 and CF_3 groups than in the CF bond. A similar explanation has been proposed previously to explain the correction for the β and γ protons.[22] These corrections are *ca.* 68% for both the CF_2 and CF_3 groups, though here it is clear that although there will be electric field effects at these protons electronic effects are also present.

The alternative explanation that the partial atomic charge on the fluorine atom should be reduced by 10% from that calculated in the CHARGE scheme is not supported by the dipole moments calculated by CHARGE4 which are in excellent agreement with the observed values.[24]

Detailed inspection of the observed SCS data in the fluorocyclohexanes (Tables 2 and 3) shows good agreement with an intriguing inconsistency for the C-4 protons. For H4eq in axial fluorocyclohexane, and both H4ax and H4eq in the equatorial form the SCS is negative, *i.e.* shielding in contrast to the expected deshielding effect (as calculated). However, the H4eq SCS data in 3-methyl-1,1-difluorocyclohexane is +0.01 ppm, compared to the sum of the monofluoro SCS of −0.13 ppm and also the 4-methyl- and 4-*tert*-butyl-difluoro SCS data are deshielding on the 4 position protons again as expected. One possible explanation of this discrepancy is solvent and/or temperature effects, since the monofluoro data were obtained at low temperatures.

In the 2,2-difluoronorbornane (Table 4) the calculated SCS are also in excellent agreement with the observed data, particularly for the heavily deshielded 6-*endo* proton (SCS obs. +0.56 ppm *vs.* calculated +0.55 ppm).

The calculated SCS for 3-fluoro-5α-androstanes (Table 5) are encouraging, in that they reflect the observed trends in all but

Table 2 Observed[a] *vs.* calculated proton chemical shifts (δ) and SCS[b] (ppm) of 1-equatorial and 1-axial fluorocyclohexane

	Proton chemical shifts				SCS			
	Axial		Equatorial		Axial		Equatorial	
Proton	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
1ax (CH)	—	—	4.49	4.52	—	—	3.30	3.42
1eq (CH)	4.94	5.11	—	—	3.26	3.41	—	—
2,6ax	1.43	1.41	1.42	1.37	0.24	0.30	0.23	0.26
2,6eq	2.03	1.98	2.15	1.98	0.35	0.29	0.47	0.29
3,5ax	1.63	1.48	1.28	1.19	0.44	0.37	0.09	0.09
3,5eq	1.75	1.75	1.86	1.83	0.15	0.06	0.18	0.14
4ax	1.28	1.13	1.12	1.22	0.09	0.02	−0.07	0.11
4eq	1.58	1.76	1.65	1.78	−0.10	0.07	−0.03	0.09

[a] Data from ref. 22. [b] Calc. SCS *cf.* cyclohexane (ax = 1.11, eq = 1.69 ppm).

Table 3 Observed[a] *vs.* calculated proton chemical shifts (δ) and SCS[b] (ppm) of 1,1-difluorocyclohexanes

Proton chemical shifts

	3-Me			4-Me		4-Bu^t	
Proton	Obs.	Calc.	Proton	Obs.	Calc.	Obs.	Calc.
2ax	1.29	1.12	2,6ax	1.67	1.55	1.68	1.50
2eq	2.02	1.97	2,6eq	2.02	2.11	2.09	2.09
3ax (CH)	1.72	1.76	3,5ax	1.27	1.22	1.31	1.30
3eq CH_3	0.96	1.02	3,5eq	1.70	1.72	1.80	2.00
4ax	0.91	0.93	4ax (CH)	1.47	1.45	1.07	1.10
4eq	1.69	1.69	4eq (Me)	0.95	1.02	—	—
5ax	1.54	1.54	4eq (Bu^t)	—	—	0.89	0.95
5eq	1.76	1.86					
6ax	1.54	1.54					
6eq	2.05	2.11					

SCS

	3-Me			4-Me		4-Bu^t	
Proton	Obs.	Calc.	Proton	Obs.	Calc.	Obs.	Calc.
2ax	0.41	0.41	2,6ax	0.47	0.41	0.51	0.41
2eq	0.34	0.40	2,6eq	0.34	0.39	0.34	0.39
3ax (CH)	0.40	0.42	3,5ax	0.39	0.40	0.37	0.40
3eq CH_3	0.10	0.05	3,5eq	0.02	0.15	0.05	0.15
4ax	0.03	0.11	4ax (CH)	0.15	0.10	0.13	0.10
4eq	0.01	0.12	4eq (Me)	0.09	0.04	—	—
5ax	0.34	0.40	4eq (Bu^t)	—	—	0.05	0.02
5eq	0.08	0.15					
6ax	0.43	0.41					
6eq	0.37	0.40					

[a] Data from ref. 22. [b] Calc. SCS *cf.* cyclohexane (ax = 1.11, eq = 1.69 ppm).

Table 4 Observed[a] *vs.* calculated[b] SCS (ppm) in 3-*endo*- and 3-*exo*-fluorocamphor and 2,2-difluoronorbornane

	3-*endo*		3-*exo*		2,2-Difluoro	
Proton	Obs.	Calc.	Obs.	Calc.	Obs.[c]	Calc.[d]
1	—	—	—	—	0.24	0.19
2*n*	—	0.33	—	0.30	—	—
2*x*	—	0.25	—	0.29	—	—
3*n*	—	—	2.53	3.48	0.43	0.40
3*x*	2.50	3.26	—	—	0.47	0.38
4 (CH)	0.30	0.15	0.16	0.15	0.17	0.19
5*n*	0.55	0.65	−0.01	0.01	0.18	0.14
5*x*	−0.22	0.03	0.08	0.14	0.15	0.10
6*n*	0.09	0.10	0.00	0.09	0.56	0.55
6*x*	0.09	0.07	−0.03	0.12	0.04	0.14
7*a*	—	—	—	—	0.16	0.17
7*s*	—	—	—	—	0.51	0.43
8-Me	0.04	0.06	0.13	0.12	—	—
9-Me	0.07	0.05	0.01	0.03	—	—
10-Me	0.06	0.04	0.06	0.04		

[a] Expt. SCS *cf.* 3-*exo*- and 3-*endo*-fluorocamphor, ref. 18 (*n* = *endo*, *x* = *exo*). [b] Calc. SCS *cf.* bornane (2/6*n* = 0.97, 2/6*x* = 1.53, 3/5*n* = 1.09, 3/5*x* = 1.80, 4 = 1.75, 8/9-Me = 0.82, 10-Me = 0.99 ppm). [c] Ref. 22. [d] Calc. SCS *cf.* norbornane (1/4 = 1.92, 7*a*/*s* = 1.30, *endo* = 1.30, *exo* = 1.50 ppm; *a* = *anti*, *s* = *syn*).

one case. The observed effect of the 3α-fluoro-substituent on the 1β proton of −0.14 ppm is contrary to the same effect in cyclohexanes, *i.e.* the SCS of the 3-equatorial proton of axial fluorocyclohexane is +0.15 ppm, suggesting that the reported steroid value may be anomalous. The long range effects on protons in the *C* and *D* rings are small as predicted. These SCS are for a single substituent in a bifunctional compound and this assumes no interaction between the functional groups. This would appear reasonable for the 3-haloandrostan-17-ones[12] in which the substituent groups are far apart. However for the 3-*endo* and 3-*exo*-fluorocamphors[18] where the halogen and ketone groups are close the substituent groups may interact and additional solvent effects may occur. Thus, the observed SCS should be considered less definitive.

An exception to the generally good agreement occurs with fluoro-substituted adamantanes. However, adamantane proton chemical shifts are not well calculated with the CHARGE4 routine and clearly there are additional mechanisms[27] influencing the proton chemical shifts in this system. The adamantane system is considered in detail elsewhere.[28]

Conclusions

The proton chemical shifts of these fluoro ethanes, cyclohexanes, bicycloheptanes and steroids comprising over 60 data points spanning a range of *ca.* 0.9 to 6.4 ppm are predicted with an rms error of 0.11 ppm, which is not much larger than the experimental error in many cases. We may conclude that fluorine SCS over more than three bonds are determined solely by linear electric field effects without the need to invoke the steric and/or quadratic electric field terms.

The determination of the value of A_Z for the linear electric field calculation in the CHARGE4 scheme in such good agreement with the theoretical value lends considerable support to the extension of this calculation to other polar groups, such as chloroalkanes, ethers, alcohols and ketones *etc.* In these cases other effects (*e.g.* steric, anisotropic) may also play a role and these substituents are being investigated in our laboratories at present.

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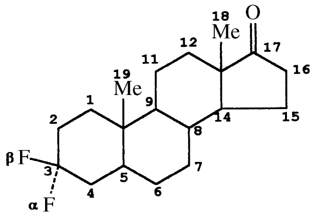
Table 5 Observed[a] *vs.* calculated.[b] SCS (ppm) for fluoroandrostanes



Proton	3α-Fluoro Obs.	3α-Fluoro Calc.	3β-Fluoro Obs.	3β-Fluoro Calc.
1α	0.43	0.37	0.09	0.09
1β	−0.14	0.06	0.10	0.14
2α	0.31	0.29	0.47	0.29
2β	0.10	0.29	0.11	0.25
3α	—	—	3.24	3.41
3β	3.13	3.41	—	—
4α	0.34	0.33	0.45	0.31
4β	0.12	0.27	0.22	0.25
5 (CH)	0.50	0.47	0.04	0.05
6α	−0.01[c]	0.05	0.10[c]	0.06
6β	−0.09[c]	−0.01	0.10[c]	0.06
7α	0.05	0.04	0.01	0.01
7β	0.03	0.00	0.03	0.03
8 (CH)	0.01	−0.01	−0.02	0.02
9 (CH)	0.10	0.07	−0.04	0.00
11α	0.01	0.01	−0.02	0.01
11β	0.02	−0.01	0.05	0.02
12α	0.01	0.02	0.00	0.00
12β	0.01	0.00	−0.01	0.02
14 (CH)	0.03	0.02	0.00	0.00
15α	0.02	0.01	0.00	0.00
15β	0.01	−0.01	−0.02	0.01
16α	0.02	0.01	0.01	0.01
16β	−0.03	0.00	−0.03	0.01
17α	—	0.01	—	0.00
17β	—	0.00	—	0.01
18-Me	0.00	0.00	0.00	0.00
19-Me	0.01	0.01	0.05	0.05

[a] Expt. SCS *cf.* 3α- and 3β-fluoroandrostan-17-one, ref. 12. [b] Calc. SCS *cf.* 3α- and 3β-fluoroandrostane *vs.* 5α-androstane (Ref. 1). [c] Unresolved.

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