Substituent Chemical Shifts (SCS) in NMR. Part 5.[1] Mono- and Di-fluoro SCS in Rigid Molecules

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The complete assignment of the proton, carbon and fluorine NMR spectra of fluorocyclohexane (axial and equatorial conformers), 4-methyl-1,1-difluorocyclohexane, 4-tert-butyl-1,1-difluorocyclohexane, 3-methyl-1,1-difluorocyclohexane and 2,2-difluoronorbornane is reported and the proton substituent chemical shifts obtained. The fluorocyclohexane substituent chemical shifts (SCSs) are in close agreement with monofluoro SCS data obtained from steroids, the SCS of the 2_{ax}- and 2_{eq}-H being independent of the orientation of the fluorine. The SCS obtained from fluorocyclohexane are not applicable to the difluorocyclohexane systems and this non-additivity is shown to be general for CF_2 and CF_3 groups. The proton chemical shift calculation scheme previously given for hydrocarbons can now be extended to include fluoroalkanes using the data presented here. It is shown that the proton chemical shifts of a variety of fluoroalkanes can be well predicted on this scheme.

The proton chemical shift is still the most important quantity in NMR spectroscopy, yet predictions of proton chemical shifts in organic molecules sufficiently accurate to be of use to the preparative chemist are still lacking. The reasons for this are well known. There has been until comparatively recently a lack of good data on molecules of rigid well defined geometry and this has prevented the multi-component analysis which is generally believed to be necessary to understand proton chemical shifts.[2,3] Recent investigations on alkyl substituted cyclohexanes,[4,5] substituted steroids and decalins[6] and other rigid molecules[7] have illustrated the wealth of data now available with present NMR instrumentation.

In previous parts of this series[1,8,9] the proton chemical shifts of some rigid molecules of well defined geometries (cyclohexanes, norbornanes and adamantanes) were presented together with data for substituted derivatives. These, together with the other recent investigations above have allowed the determination of the substituent chemical shifts (SCS) of a variety of functional groups in rigid molecules, the SCS being defined in the normal manner as $\delta(R-X) - \delta(R-H)$. Data for fluorine SCS are lacking, apart from the results of Schneider on steroids.[6] There is to our knowledge no other data on fluorine SCS on appropriate molecules of well defined geometry. It is important to stress the necessity for molecules of well defined geometry as we[10] and others[11] have shown that proton chemical shifts are very sensitive to the steric interactions between the protons in molecules and these in turn are critically dependent upon the precise geometry.

In a recent investigation on the conformations of simple fluoro alcohols in solution[12] it was noted that the $-CH_2F$ group behaves very differently from the $-CHF_2$ group, in that in the former the gauche effect occurs, i.e., the two CH_2F groups in 1,2-difluoroethane strongly favour the gauche conformer, whereas in the CHF_2 group no such effect is present and 1,1,2-trifluoroethane and 1,1,2,2-tetrafluoroethane favour the trans-conformers. It was therefore of some interest to determine the SCS of both the mono and difluoro groups in molecules of well defined geometry and we present the complete analysis and assignments of the ^1H, ^{19}F and ^{13}C NMR spectra of fluorocyclohexane [axial (1_{ax}) and equatorial (1_{eq}) conformers], 4-methyl-1,1-difluorocyclohexane (2), 4-tert-butyl-1,1-difluoro-

cyclohexane (3), 3-methyl-1,1-difluorocyclohexane (4) and 2,2-difluoronorbornane (5). Also we give data for fluoroethane and 1,1,1-trifluoroethane in dilute solution, which was not given previously.

The low temperature proton and fluorine NMR spectra of fluorocyclohexane at $-90\,^\circ C$ have been reported[13] but only the 1_{ax}- and 1_{eq}-H in each conformer were assigned. The integral of 1_{ax}-H vs. 1_{eq}-H and 1_{ax}-F vs. 1_{eq}-F gave a free energy difference of 0.15 kcal mol^{-1} in favour of the equatorial conformer.† The remaining hydrogen signals were not assigned due to severe overlapping. trans- and cis-4-tert-butylfluorocyclohexane have been prepared and their individual proton and fluorine NMR spectra recorded,[14] however the high field region of the proton spectrum proved too complex to assign.

Fluorine and carbon chemical shifts and C–F couplings in fluorinated norbornanes have been given,[15,16] but the complex and severely overlapping signals in the proton spectrum prevented assignment.

In this study SF_4 has been used to fluorinate a series of commercially available ketones: 4-methyl-, 4-tert-butyl- and 3-methyl-cyclohexanone, and norbornan-2-one.‡ The preparation of the difluoro compounds follows the reaction scheme given by Roberts,[15,16] Fawcett[17] and Hasek.[18] The carbonyl group is attacked by SF_4 and the difluoro product is formed via a proposed alkoxysul;ur trifluoride intermediate (Scheme 1).

Assignment.—The assignment of the fluoroethane and trifluoroethane spectra was obvious. This gave fluoroethane chemical shifts of δ 1.35 and 4.55 (H), 16.2 and 80.7 (C) and 211.3 (F), and couplings of 47.1 and 26.4 Hz (H–F) and 160.6 and 20.7 Hz (C–F). For trifluoroethane the corresponding data were, δ 1.87 (H), 20.6 and 126.2 (C) and 60.3 (F) and couplings 12.9 (H–F), 273.0 and 31.5 Hz (C–F). Proton, fluorine and carbon NMR spectra have been obtained for the individual conformers of fluorocyclohexane at $-80\,^\circ C$ and assigned as follows.

Equatorial fluorocyclohexane 1_{eq}. This is the major component of the mixture which makes the assignment of the proton

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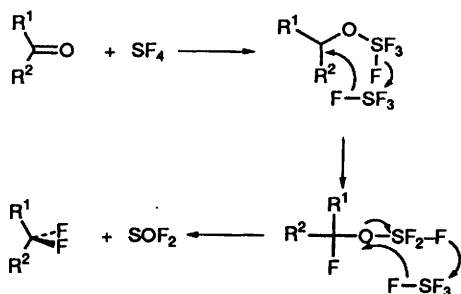
Scheme 1 Proposed mechanism of the fluorination process

chemical shifts very simple. The 1_{ax}-H resonance is at δ 4.49 and has a well resolved splitting pattern, $^2J_{H-F} \gg {}^3J_{H_{ax}-H_{ax}} > {}^3J_{H_{ax}-H_{eq}}$ (doublet of triplets of triplets). The DQF-COSY spectrum clearly identifies the $2,6_{ax}$-H and $2,6_{eq}$-H signals from the off-diagonal correlations, $2,6_{eq}$-H is the lowfield signal. The best resolved multiplet in the spectrum is a quartet of triplets at high field; this is the 4_{ax}-H signal, the 4_{eq}-H signal is assigned from the off-diagonal correlation. The remaining two protons are $3,5_{ax}$-H and $3,5_{eq}$-H; these are easily identified as a quartet at high field and a broad doublet at low field, respectively.

Axial fluorocyclohexane 1_{ax}. The 1_{eq}-H resonance is to low field at δ 4.94, and is a broad signal due to many small $^3J_{HF}$ and $^3J_{HH}$ couplings. DQF-COSY clearly shows the correlation between the 1_{eq}-H and $2,6_{ax}$-H, $2,6_{eq}$-H signals, however the $2,6_{ax}$-H resonance was not at all clear in the 1-D spectrum as it is swamped by other signals. A well separated signal at δ 1.75, with an integral corresponding to two protons in the axial conformer, can be identified as being due to two equatorial protons, this can only be $3,5_{eq}$-H as it correlates strongly to a geminal resonance at δ 1.63 assigning this resonance to $3,5_{ax}$-H. The $3,5_{ax}$-H atoms experience a through space interaction with the fluorine, which results in the unusually low field shift of δ 1.63. The direct correlations between protons in the axial form are complicated by overlapping correlations belonging to the equatorial form. For example, the $3,5_{eq}$-H signal has a weak off-diagonal correlation with a signal to high field, this is a $^3J_{eq-ax}$ coupling to 4_{ax}-H, however the correlation between 4_{ax}-H and 4_{eq}-H cannot be unambiguously identified due to overlapping correlations belonging to the equatorial form.

The problems caused by the overlapping signals were very much simplified by 1-D projections of the two individual forms extracted from the TOCSY$^{19-21}$ experiment.

4-Methyl-1,1-difluorocyclohexane **2**. The intense methyl signal is easily assigned and the DQF-COSY plot shows a strong correlation from the methyl to 4_{ax}-H. The 4_{ax}-H resonance correlates strongly to $3,5_{ax}$-H which in turn strongly correlates to $3,5_{eq}$-H. The remaining signals, $2,6_{ax}$-H and $2,6_{eq}$-H correlate to each other, with the axial hydrogens to high field. The axial fluorine resonance is very distinctive with large $^3J_{HF}$ couplings and is to high field of the broad equatorial multiplet.

4-tert-Butyl-1,1-difluorocyclohexane **(3)**. The methyl signals of the *tert*-butyl group, though readily assigned, do not provide a correlation to any other signal in the DQF-COSY plot due to intense T_1 noise and the weak $^4J_{HH}$ correlation. However, the remaining five signals are well separated from each other and the axial protons were readily distinguished from the broad equatorial multiplets. The $2,6_{ax}$-H signal is assigned simply due to its distinctive $^3J_{HF}$(*trans*) coupling with the axial fluorine, the remaining assignments follow very easily from the DQF-COSY plot. A strong correlation from $2,6_{ax}$-H to the low field broad multiplet identifies $2,6_{eq}$-H, the remaining strong correlation is between $3,5_{ax}$-H and $3,5_{eq}$-H with the axial signal to high field. The final signal is 4_{ax}-H and this correlates to $3,5_{ax}$-H as expected.

The fluorine chemical shifts are very simply assigned, the axial is to high field and is a distinctive pattern with well resolved $^3J_{HF}$(*trans*) couplings, the equatorial, however, is poorly resolved due to the small $^3J_{HF}$(*gauche*) couplings.

3-Methyl-1,1-difluorocyclohexane **(4)**.—The proton NMR spectrum is condensed into a region between δ 1 and 2, with ten individual resonances due to the asymmetry of the molecule. Large H–F couplings and a second order spin system result in multiplets that are up to 80 Hz wide. The result is a very congested and overlapping NMR spectrum that required DQF-COSY, HET-CORR and J-RES analysis to unravel.

The 2_{ax}-H resonance can be readily assigned, due to its distinctive well resolved splitting pattern and also from the DQF-COSY correlation to only two other resonances 2_{eq}-H and 3_{ax}-H. For 2_{ax}- and 6_{ax}-Hs, 2_{ax}-H lacks the correlation to 3_{eq}-H (the methyl group) whereas 6_{ax}-H has a weak correlation to 5_{eq}-H. The HET-CORR confirmed the assignments of 2_{ax}-, 2_{eq}- and 3_{ax}-H. The C-6 signal is a distinctive triplet from which 6_{ax}- and 6_{eq}-H are assigned, the axial to high field. The remaining signals 4_{ax}-, 4_{eq}-, 5_{ax}- and 5_{eq}-H are assigned from the HET-CORR, as C-4 has a larger coupling to the fluorines than C-5.

2,2-Difluoronorbornane **(5)**. The proton NMR spectrum is very congested due to overlapping signals and complicated by large long range H–F couplings and the second order nature of the spectrum. The bridgehead protons are well separated and are easily identified, 1-H couples to the fluorine nuclei and is to low field of 4-H which does not couple. Both 1- and 4-H have weak correlations to 7_a- and 7_s-H, with the *syn*-hydrogen to low field. 1- and 4-H strongly correlate to the *exo* protons only and this assigns 3_{exo}-, 5_{exo}- and 6_{exo}-H. The 3_{endo}-, 5_{endo}- and 6_{endo}-H were subsequently assigned using the HET-CORR correlations.

The complete assignments of the ^{1}H, ^{13}C and ^{19}F chemical shifts of axial (1_{ax}) and equatorial (1_{eq}) fluorocyclohexane, 4-methyl-1,1-difluorocyclohexane (2), 4-*tert*-butyl-1,1-difluorocyclohexane (3), 3-methyl-1,1-difluorocyclohexane (4), and 2,2-difluoronorbornane (5) are presented in Table 1 and the fluorine SCS in Table 2 from the proton chemical shifts in Table 1 using the known proton chemical shifts of the parent compounds.[4,8,9]

Results and Discussion

Inspection of Table 2 shows excellent agreement between the experimental proton SCS data of axial and equatorial fluorocyclohexane and the data from conformationally rigid steroid systems,[6] the only significant difference being for the $3,5_{ax}$-H in the axial form, $+0.15$ *vs.* -0.14 ppm. There is therefore no significant intrinsic temperature effect on the chemical shifts of fluorocyclohexane in the non-polar solvent used, a 50:50 (w/v) mixture of $CFCl_3$ and $CDCl_3$. This also shows that steroids are valid model compounds for deducing SCSs in cyclohexanes.

Proton Chemical Shifts in Fluoroethanes.—The results obtained here of the fluorine SCSs in the conformationally locked cyclohexanes (we assumed that **2** is as conformationally biased as is methylcyclohexane) and norbornane are conveniently discussed in the framework of the well documented CHARGE calculation of partial atomic charges, in which the charge on the proton is made up of one-, two- and three-bond additive contributions. It was shown that there is an excellent correlation between the calculated charge on the proton and the proton chemical shift for a wide variety of substituted methanes and ethanes.[23] More recently the proton chemical shifts of a variety of alkanes have been successfully predicted by the

Table 1 Proton, carbon and fluorine NMR chemical shifts (ppm) and H–F and C–F coupling constants (Hz) of mono (1_{ax}, 1_{eq}) and difluoro (2, 3, 4) cyclohexanes and 2,2-difluoronorbornane (5)

	1_{ax}^b	1_{eq}^b	2	3	4		5^e
Hydrogen chemical shift^a							
$1_{ax,eq}$-H	4.94	4.49	—	—	—		—
2_{ax}-H	1.43	1.42	1.67	1.68	1.29	1-H	2.43
2_{eq}-H	2.03	2.15	2.02	2.09	2.02	3_x-H	1.94
3_{ax}-H	1.63	1.28	1.27	1.31	1.72	3_n-H	1.59
3_{eq}-H	1.75	1.86	1.70	1.80	0.96	4-H	2.36
4_{ax}-H	1.28	1.12	1.47	1.07	0.91	5_x-H	1.62
4_{eq}-H	1.58	1.65	0.95	0.89	1.69	5_n-H	1.34
5_{ax}-H	1.63	1.28	1.27	1.31	1.54	6_x-H	1.51
5_{eq}-H	1.75	1.86	1.70	1.80	1.76	6_n-H	1.72
6_{ax}-H	1.43	1.12	1.67	1.68	1.54	7_a-H	1.34
6_{eq}-H	2.03	1.65	2.02	2.09	2.05	7_s-H	1.69
Fluorine chemical shifts^a							
F_{ax}	165.5	—	102.5	103.7	101.1	F_n	87.25
F_{eq}	—	185.9	92.6	92.1	89.0	F_x	110.52

Carbon chemical shifts^a

	1^d	1_{ax}^b	1_{eq}^b	2	3	4		5
C-1	92.1	91.2	93.6	123.8	123.9	124.4	C-1	45.7
C-2	32.9	31.1	33.4	34.4	34.8	43.0	C-2	132.0
C-3	23.5	20.7	24.4	31.9	24.4	30.6	C-3	43.9
C-4	25.9	25.8	25.3	31.7	47.4	34.0	C-4	36.8
C-5	23.5	20.7	24.5	31.9	24.4	23.0	C-5	28.4
C-6	32.9	31.1	33.4	34.4	34.8	34.5	C-6	21.8
CH_3	—	—	—	21.6	28.1	22.4	C-7	37.7
C	—	—	—	—	32.8	—	—	—

C–F Couplings

	1^d	1_{ax}^b	1_{eq}^b	2	3	4		5
C-1	169.7	165.5	170.4	239.5	238.9	238.7	C-1	21.3
				241.9	241.9	242.2		23.6
C-2	19.0	21.3	17.2	22.4	21.2	20.4	C-2	251.7
				25.5	25.7	25.1		255.6
C-3	7.8	0.0	11.7	9.7	10.1	9.4	C-3	22.4
								24.9
C-4	1.6	0.0	2.2	0.0	0.0	2.0	C-4	2.2
								4.3
C-5	7.8	0.0	11.7	9.7	10.1	9.7	C-5	0.0
C-6	19.0	0.0	17.2	22.4	21.2	22.2	C-6	6.0
	—	—	—	25.5	25.7	25.5		6.0
CH_3	—	—	—	2.8	0.0	0.0	C-7	5.3
C	—	—	—	—	1.84	—	—	—

H–F couplings

	1_{ax}^b	1_{eq}^b	2	3	4		5
HF_{trans}	46.6	c	c	34.2	34.1	F_n	multiplet
HF_{gauche}	8.95	c	c	11.3	10.2	F_x	multiplet

^{a} ^{1}H referenced to Me$_4$Si. ^{13}C referenced to CDCl$_3$ at 77.7 ppm. ^{19}F referenced to CFCl$_3$ at 0.00 ppm, positive shifts are upfield. Shifts are in ppm, couplings are in Hz. ^{b} Axial (ax) and equatorial (eq) fluorocyclohexane (3%) obtained at $-80\ ^\circ$C. ^{c} Complex multiplet. ^{d} 298 K. ^{e} Abbreviations: a, anti; s, syn; x, exo; n, endo.

addition to this scheme of a longer range (>three bonds) 'steric' interaction between the protons and other near nuclei and also an orientation dependent γ effect of a carbon substituent (i.e. H–C–C–C).[10]

As all the protons considered here are attached to carbon the one-bond effect is constant, and remains unchanged from the hydrocarbon value. The next substituent effect is over two-bonds (i.e. H–C–F) and in order to evaluate this it is necessary to consider the proton chemical shifts in simple fluoroalkanes. A selection of these from the literature together with the results obtained here are given in Table 3. Inspection of this data shows immediately that the fluorine β effect is not additive for the fluoromethanes. The effect of the introduction of one fluorine atom on the chemical shift of the protons in methane is much greater than the effect of the second or third fluorine atom. This

non-additivity is well known both theoretically and experimentally and CF$_2$ and CF$_3$ groups are very different electronically from the CH$_2$F group. There is a dramatic shortening in the CF bond length, from 1.385 (CH$_3$F) to 1.357 (CH$_2$F$_2$) to 1.332 Å (CHF$_3$).[26] The CF bond in the CF$_3$ group is shorter (and therefore stronger?) than the CF bond in fluorobenzene (1.354 Å) or vinyl fluoride (1.347 Å). Indeed considerations of the much greater stability of the CF$_2$ group over the CH$_2$F group in cyclohexanes led us to pursue the successful preparative strategy of this work.

This non-additivity can be easily included in the CHARGE routine using the experimental proton shifts of the fluoromethanes as the basis for the parametrization. This amendment does not affect the good agreement between the observed and calculated dipole moments of these compounds.

**Table 2** SCS (ppm) for fluorocyclohexanes and norbornane

	$\mathbf{1}_{ax}$	ax[a]	$\mathbf{1}_{eq}$	eq[a]	**2**	**3**	**4**	**5**	
Hydrogen									
$1_{ax,eq}$-H	3.26	3.13	3.30	3.24	—	—	—		—
2_{ax}-H	0.24	0.11	0.23	0.16	0.47	0.51	0.41	1-H	0.24
2_{eq}-H	0.35	0.32	0.47	0.46	0.34	0.34	0.34	3_x-H	0.47
3_{ax}-H	0.44	0.46	0.09	0.10	0.39	0.37	0.40	3_n-H	0.43
3_{eq}-H	0.15	−0.14	0.18	0.10	0.02	0.05	0.10	4-H	0.17
4_{ax}-H	0.09	—	−0.07	—	0.15	0.13	0.03	5_x-H	0.15
4_{eq}-H	−0.10	—	−0.03	—	0.09	0.05	0.01	5_n-H	0.18
5_{ax}-H	0.44	0.46	0.09	0.10	0.39	0.37	0.34	6_x-H	0.04
5_{eq}-H	0.15	−0.14	0.18	0.10	0.02	0.05	0.08	6_n-H	0.56
6_{ax}-H	0.24	0.11	0.23	0.16	0.47	0.51	0.43	7_a-H	0.16
6_{eq}-H	0.35	0.32	0.47	0.46	0.34	0.34	0.37	7_s-H	0.51

Carbon SCS of equatorial and axial fluorocyclohexane[b]

	δ_{ax}	δ_{eq}	δ_{ax}[c]	δ_{eq}[c]
C-1	64.1	66.5	61.4	64.5
C-2	4.0	6.3	3.1	5.6
C-3	−6.4	−2.7	−7.2	−3.4
C-4	−1.3	−1.8	−2.0	−2.5

[a] SCS for steroids, ref. 6. [b] From cyclohexane $\delta_C = 27.1$. [c] Ref. 22.

Table 3 Proton chemical shifts and SCSs (ppm) in simple fluoromethanes and ethanes

	δ	SCS
CH_4	0.27[a]	
CH_3F	4.27[b]	3.99
CH_2F_2	5.45[b]	1.19
CHF_3	6.41[b]	0.96
CH_3–CH_3	0.880[c]	
CH_3–CH_2F	1.368[c]	0.49
CH_3–CHF_2	1.555[c]	0.20
CH_3–CF_3	1.870[d]	0.32

[a] Ref. 10. [b] Ref. 24. [c] Ref. 25. [d] This work.
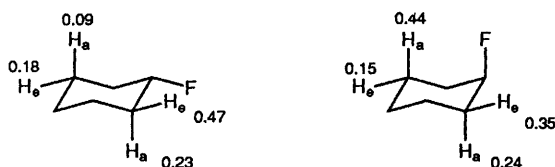
Fig. 1 Fluorine SCSs (ppm) for 2- and 3-H in axial and equatorial fluorocyclohexane

The γ fluorine effect (H–C–C–F) is also non-additive, as can be seen from the data for the fluoroethanes also given in Table 3, but much less so than the β effect. Again this can be easily included in the CHARGE scheme. Of considerable interest in this respect is the data on fluorocyclohexane. The effect of equatorial and axial fluorine on the $2,6_{ax}$-Hs is remarkably similar, with SCS values of 0.24 and 0.23 ppm respectively (Fig. 1). The SCS is independent of the orientation of the fluorine. The SCS of an equatorial and axial fluorine on the $2,6_{eq}$-H are also quite similar, 0.35 and 0.47 ppm, respectively. Again, there appears to be no orientation dependence of the fluorine SCS. This is very different to carbon SCS,[10] in which the SCS is very dependent on the dihedral angle to the γ carbon, with a *gauche* orientation giving a shielding effect and a *trans* orientation a deshielding one.

Both the conformations and the SCS of the difluorocyclo-hexanes **2–4** are very similar. The 2_{ax} SCS is 0.47, 0.51 and 0.41

ppm respectively and the 2_{eq} 0.34, 0.34 and 0.34 ppm, respectively. The SCS from fluorocyclohexane are 0.24 ppm for 2_{ax}-H and 0.40 ppm for 2_{eq}-H. If the monofluoro SCS are additive then the difluoro SCS would be 0.47 ppm for 2_{ax}-H and 0.82 ppm for 2_{eq}-H. The experimental data gives an average SCS of 0.46 ppm for 2_{ax}-H, in excellent agreement with an additive SCS, but the difluoro SCS for 2_{eq}-H is 0.34 ppm, less than the monofluorine SCS of 0.35–0.47 ppm observed in fluorocyclohexane. The γ fluorine SCS for the 3_{exo}- and 3_{endo}-H in difluoronorbornane are both 0.43 ppm, in good agreement with the SCS data from the difluorocyclohexanes. Thus, the γ fluorine SCS can be modelled very easily in the CHARGE routine by a dihedral independent term which is parametrized separately for CF_2 and CF_3 groups. The results of this parametrization are given in Table 4 and will be discussed later.

H–F Steric Interaction.—The results obtained here for the fluorocyclohexanes and norbornanes show clearly the existence of a non-bonded 'steric' effect of a fluorine atom on the chemical shift of a nearby proton. This is seen in the SCS of an axial fluorine on the 3_{ax}-H protons in cyclohexane, with no comparable effect of an equatorial fluorine substituent. Taking the average of the SCS for compounds 1_{ax}, **2**, **3** and **4** gives a deshielding, at 3_{ax}-H due to 1-F_{ax}, of 0.39 (+0.05) ppm. The separation of the fluorine and hydrogen atoms in these molecules is 2.67 (+0.01) Å from GAUSSIAN 92 calculations at the RHF/6-31G* level.[27] There are closer non-bonded distances in the difluoronorbornane and this results in a slightly larger deshielding of 7_s-H of 0.51 ppm (H–F distance 2.65 Å) and of 6_n-H of 0.56 ppm (H–F distance 2.46 Å). Similar through-space deshielding effects have been observed in 3-*endo*-fluorocamphor,[28] between the 3-*endo*-F and the 5-*endo*-H, where the downfield shift of 0.55 ppm is in close agreement with the difluoronorbornane SCS data.

In the calculation of hydrocarbon chemical shifts the non-bonded chemical shift effects were described by the same potential as is used to calculate non-bonded interactions in molecular mechanics (MM) calculations. In this case a Morse curve was used with parameter values (E_{min}, r_{min}) for H and C taken from the COSMIC force field.[29] This approach could not be applied to the fluorine steric effects obtained here, mainly due to the small size of the fluorine atom. (Note that in MM

Table 4 Calculated proton chemical shifts (δ) of fluorohydrocarbon molecules

		Calc.	Expt.	Ref.
CH_3F		4.26	4.27	24
CH_2F_2		5.45	5.45	24
CHF_3		6.44	6.41	24
CH_3CH_2F		1.25	1.35	25
CH_3-CH_2F		4.60	4.55	25
CH_3-CHF_2		1.33	1.56	25
CH_3-CHF_2		5.76	5.94	25
CH_3-CF_3		1.89	1.87	This work
CH_3-CH_2-CH_2F		0.88	0.97	30
CH_3-CH_2-CH_2F		1.68	1.68	30
CH_3-CH_2-CH_2F		4.40	4.30	30
CH_3-CHF-CH_3		1.28	1.34	25
CH_3-CHF-CH_3		4.87	4.84	25
CH_2F-CH_2F		4.86	4.59	31
CF_3-CH_2F		5.28	4.55	31
CH_2F-CHF_2		4.91	4.45	31
CH_2F-CHF_2		5.99	5.93	31
CHF_2-CHF_2		6.03	5.64	32
CF_3-CH_2-CH_2-CF_3		2.65	2.46	33
Fluorocyclohexane (1_{ax})	1_{eq}-H	5.24	4.94	This work
	$2,6_{ax}$-H	1.58	1.43	
	$2,6_{eq}$-H	2.05	2.03	
	$3,5_{ax}$-H	1.58	1.63	
	$3,5_{eq}$-H	1.68	1.75	
	4_{ax}-H	1.20	1.28	
	4_{eq}-H	1.68	1.58	
Fluorocyclohexane (1_{eq})	1_{ax}-H	4.84	4.49	
	$2,6_{ax}$-H	1.58	1.42	
	$2,6_{eq}$-H	2.05	2.15	
	$3,5_{ax}$-H	1.20	1.28	
	$3,5_{eq}$-H	1.68	1.86	
	4_{ax}-H	1.20	1.12	
	4_{eq}-H	1.68	1.65	
4-Methyl-1,1-difluorocyclohexane (2)	$2,6_{ax}$-H	1.65	1.67	
	$2,6_{eq}$-H	2.12	2.02	
	$3,5_{ax}$-H	1.18	1.27	
	$3,5_{eq}$-H	1.57	1.70	
	4_{ax}-H	1.31	1.47	
	CH_3	0.90	0.95	
3-Methyl-1,1-difluorocyclohexane (4)	2_{ax}-H	1.26	1.29	
	2_{eq}-H	2.01	2.02	
	3_{ax}-H ·	1.71	1.72	
	CH_3	0.90	0.96	
	4_{ax}-H	0.80	0.91	
	4_{eq}-H	1.57	1.69	
	5_{ax}-H	1.58	1.54	
	5_{eq}-H	1.68	1.76	
	6_{ax}-H	1.65	1.54	
	6_{eq}-H	2.12	2.05	
2,2-Difluoronorbornane (5)	1-H	2.58	2.43	
	3_x-H	1.90	1.94	
	3_n-H	1.73	1.59	
	4-H	2.17	2.36	
	5_x-H	1.46	1.62	
	5_n-H	1.29	1.34	
	6_x-H	1.46	1.51	
	6_n-H	1.83	1.72	
	7_a-H	1.20	1.34	
	7_s-H	1.57	1.69	

calculations fluorine is much smaller than hydrogen.) The accepted literature value of r_{min} for fluorine of *ca.* 2.9 Å gave poor agreement with the observed shifts as the curve is too steep at the experimental distances to reproduce the above results. Other values were tried without any success. However it was found that a simple r^{-3} function with a cut-off at r_{min} gave good agreement with the observed data and in the absence of further data on molecules with well-defined H–F distances this simple procedure was adopted.

The calculated proton chemical shifts, based on the CHARGE routine with the above amendments incorporated, of a representative selection of the compounds studied here and

some fluoroalkanes from the literature are given in Table 4, together with the observed values. All geometries are from GAUSSIAN 92 using the RHF/6-31G* basis set.[29] It can be seen that there is generally very reasonable agreement which is encouraging. There are some significant discrepancies, for example the γ fluorine effect appears to vary with the number of fluorines on the protonated carbon, CH_3-CH_3 vs. CH_3-CH_2F, cf. CH_2F-CH_3 vs. CH_2F-CH_2F, etc. Clearly there are more complexities to fluorine SCS than the simple scheme outlined above would predict. Nevertheless the general agreement is such that the scheme could be used in a predictive capacity, which would be of considerable use.

^{13}C *NMR Chemical Shifts and C–F Coupling Constants.*— The carbon chemical shifts and SCS for fluorine in cyclohexane obtained here are essentially the same as those reported previously.[22] The C–F couplings are geometry dependent. $^1J_{CF_{eq}}$ (170.4 Hz) > $^1J_{CF_{ax}}$ (165.5 Hz), this is analogous to the Perlin effect[34,35] observed in many $^1J_{CH}$ systems. The equatorial CF bond is stronger and shorter than the axial CF bond, and since the Fermi-contact term makes the principal contribution to the coupling between directly bonded nuclei, it is not surprising that the magnitude should vary inversely with the CF bond length.[34] C-3, -5 and -4 in axial fluorocyclohexane do not couple to the fluorine, $^3J_{3,5-F}$ is a *gauche* coupling and therefore expected to be smaller than the *trans* coupling, however it is surprising that the coupling is less than the resolution (*ca.* 0.5 Hz). C-3, -5 and -4 in the equatorial conformer have significant couplings to the fluorine, 11.7 and 2.2 Hz, respectively, the large $^3J_{3,5-F}$ coupling is presumably due to the *trans*-C–C–C–F orientation.

Conclusions

The complete assignment of the proton, carbon and fluorine NMR spectra of compounds 1–5 provide data allowing the fluorine SCS to be obtained. The SCS data from axial and equatorial fluorocyclohexane agrees with the SCS of monofluorosteroids. γ Monofluoro SCS are independent of the orientation of fluorine and are not additive, the CF_2 and CF_3 groups have to be treated separately.

The γ fluorine SCS for mono and difluoro compounds are given a simple treatment in the proton chemical shift calculation routine, corresponding to deshielding contributions of *ca.* 0.32 and 0.40 ppm, respectively. Through-space H–F deshielding effects are treated with an r^{-3} function, if the interatomic distance is less than the sum of the van der Waals radii of hydrogen and fluorine.

Experimental

NMR Studies.—The fluorocyclohexanes were made up in an approximately 50:50 (v/v) mixture of $CDCl_3$ and $CFCl_3$ to no more than 3% (w/v). Proton, carbon and fluorine NMR spectra were obtained on a Bruker AMX-400 instrument operating at 400.135 MHz for proton, 100.634 MHz for carbon and 376.503 MHz for fluorine. Proton spectra were referenced to internal Me_4Si (TMS), ^{13}C spectra were referenced to $CDCl_3$ at (77.7 ppm) and ^{19}F spectra were referenced to $CFCl_3$ (with all fluorine signals to high field, *i.e.* negative Φ^*). Proton spectra were obtained over a spectral width of 3300 Hz with 32 K data points, giving an acquisition time of 5 s and FID-RES of 0.1 Hz, transformed with SI = 128 K. Proton decoupled carbon spectra were obtained over a spectral width of 16 000 Hz with 64 K data points giving an acquisition time of 2 s and FID-RES of 0.25 Hz, transformed with SI = 128 K. Gated decoupled carbon spectra were obtained over a spectral width of 20 000 Hz with 64 K data points giving an acquisition time of 2 s and FID-

RES of 0.25 Hz, transformed with SI = 128 K. Fluorine spectra were initially obtained over a spectral width of 100 000 Hz with 128 K data points giving an acquisition time of 0.66 s and a FID-RES of 0.8 Hz, transformed with SI = 128 K. Subsequently fluorine spectra were obtained with better digitization, these were run over a spectral width of 5600 Hz with 32 K data points giving an acquisition time of 3 s and a FID-RES of 0.17 Hz, transformed with SI = 128 K. Proton–proton DQF–COSY NMR spectra were obtained over *ca.* 750 Hz in both dimensions, 1 K data points (F2) and 256 experiments (F1), 16 scans per experiment, transformed to 1 K (F2) and 0.5 K (F1). Proton–proton total correlation 2-D NMR spectra (TOCSY)[19-21] were obtained on a Bruker AMX-400 instrument. The pulse program was MLEVTP,[36] a phase sensitive pulse sequence using the MLEV-17 pulse train to achieve isotropic mixing. A spectral width of 2000 Hz in both dimensions, with 4 K data points (F2) and 512 (F1) experiments, transformed to 4 K (F2) and 1 K (F1). The high power 90 pulse was a standard 1 dB 12.5 μs pulse, the low power mixing pulse was 3 dB 27 μs, the loop cycle (L1) was repeated 30 times to give an isotropic mixing time of 65 ms. The 1-D projections were extracted from the 2-D TOCSY, 2 K data points over 4.8 ppm. $^{13}C-^1H$ HETCORR[36,37] were typically recorded with a carbon spectral width of 40 ppm with 4 K data points, proton spectral width of 2 ppm with 128 experiments, transformed to 4 K and 256 in F2 and F1, respectively.

Synthetic Studies.—Samples of 4-methyl-, 4-*tert*-butyl-, 3-methyl-cyclohexanone, and norbornan-2-one (Aldrich) were used without further purification. Each reaction was performed in a 125 cm^3 Hastalloy 'C' autoclave, fitted with an electromagnetic operated flip-flop stirrer, pressure transducer and thermocouple thermometer which were connected to a programmable control panel. The autoclave was charged with the carbonyl compound and sealed, then pressure tested to 30 bar (1 bar = 10^5 Pa) to test for leaks. The vessel was purged with nitrogen, then cooled in liquid nitrogen to -80 °C, and a pre-weighed amount of SF_4 condensed in by vacuum distillation. The apparatus was allowed at warm to room temperature, an electric furnace warmed the sample to the desired temperature, and the magnetic stirrer was switched on for the duration of the experiment. When the reaction had finished the furnace was removed and the reaction vessel was allowed to cool to room temperature. The gases still inside the autoclave, SOF_2, SF_4 and HF, were slowly vented, firstly through a water scrubber and then a caustic scrubber (KOH solution). When the autoclave and scrubbers had been purged with nitrogen the autoclave was dismantled and the product, a liquid in each case, poured into an HF resistant plastic container. The crude product was neutralized by removing residual traces of HF with *ca.* 10 cm^3 saturated sodium carbonate solution.

4-*Methyl*-1,1-*difluorocyclohexane* (2). Fluorination of 4-methylcyclohexanone (5.6 g, 0.05 mol) was achieved using SF_4 (85.2 g, 0.8 mol), with stirring at 70 °C for 6 h at a constant pressure of 32.4 bar. The solution was neutralized with saturated sodium carbonate solution (10 cm^3), the crude product was then extracted with dichloromethane (10 cm^3). Analysis by GC–MS identified a molecular ion, m/z 134, which is consistent with that of the product. The pure product was obtained using a small scale distillation apparatus, 1 atm, *ca.* 80 °C; 21.2%, 1.44 g; purity = 99.7% by GC; m/z 134 (M^+, 2.7%), 119 (12.8, M – Me), 114 (52.6, M – HF), 99 (84.4, M – HF – Me), 94 (39.4, M – 2HF), 79 (33.9), 77 (43.3), 74 (40.3), 73 (23.0), 72 (33.7), 55 (100.0, C_4H_7), 41 (61.7, C_3H_5) and 39 (40.7, C_3H_3); v/cm^{-1} 2938.0, 2869.0, 1450.0, 1435.0, 1375.0, 1358.0, 1315.0, 1273.0, 1262.0, 1196.0, 1166.0, 1149.0, 1118.0, 1073.0, 1014.0, 992.0, 925.0, 793.0 and 741.0.

4-tert-*Butyl*-1,1-*difluorocyclohexane* (3). Fluorination of 4-*tert*-butylcyclohexanone (7.71 g, 0.05 mol) was achieved using

SF_4 (54.0 g, 0.5 mol), with mixing at 25 °C for 20 h at a constant pressure of 7.9 bar. The solution was neutralized with a saturated solution of sodium carbonate (10 cm³) and extracted into Et_2O (7 cm³). Vacuum distillation yielded the pure product; 30.8%, 2.74 g; purity = 99.8% by GC; m/z [M^+, 176 (parent ion not observed)], 161 (8.1%, M − Me), 141 (21.5, M − HF − Me), 121 (11.7, M − 2HF − Me), 119 (7.9, M − Bu^t), 99 (38.2, M − HF − Bu^t), 77 (13.5), 57 (100.0, Bu^t), 56 (80.0, C_4H_8), 43 (53, C_3H_7), 41 (77.0, C_3H_5), 39 (27.4, C_3H_3) and 29 (27.0, C_2H_5); v/cm^{-1} 2962.0, 2873.0, 1481.0, 1471.0, 1450.0, 1380.0, 1369.0, 1359.0, 1318.0, 1274.0, 1259.0, 1196.0, 1181.0, 1128.0, 1107.0, 985.0, 961.0, 930.0, 915.0, 827.0, 766.0 and 745.0.

3-*Methyl*-1,1-*difluorocyclohexane* (**4**). Fluorination of 3-methylcyclohexanone (7.8 g, 0.07 mol) was achieved using SF_4 (86.4 g, 0.8 mol) with stirring at 60 °C for 10 h at a constant pressure of 20.9 bar. The crude produce was extracted with dichloromethane (10 cm³), the pure product, bp 112 °C (*cf.* 169 °C of the starting material), was obtained by vacuum distillation; 13.9%, 1.3 g; purity = 99.8% by GC; m/z 134 (M^+, 8.0%), 119 (19.0, M − Me), 114 (53.8, M − HF), 94 (7.2), 99 (100.0, M − HF − Me), 91 (43.6), 79 (19.4, M − 2HF − Me), 77 (47.9), 55 (85.5, C_4H_7), 42 (39.8, C_3H_6), 41 (49.5, C_3H_5), 39 (38.7, C_3H_3); v/cm^{-1} 2957.0, 1459.0, 1451.0, 1433.0, 1371.0, 1351.0, 1328.0, 1281.0, 1271.0, 1246.0, 1217.0, 1169.0, 1128.0, 1061.0, 1038.0, 996.0, 951.0, 894.0, 855.0 and 810.0.

2,2-*Difluoronorbornane* (**5**). Fluorination of norcamphor (5.0 g, 0.045 mol) was achieved using SF_4 (33.4 g, 0.31 mol) with stirring at 25 °C for 16 h at a constant pressure of 4.4 bar. The crude produce was extracted with dichloromethane (10 cm³), partial vacuum distillation at 700 mbar slowly removed the solvent, to give a clear colourless crystalline product. The liquor was decanted off the crystals and the crystals vacuum dried; 11.3%, 0.67 g; purity = 100.0% by GC; m/z 132 (M^+, 11.1%), 117 (28.6, M − Me), 112 (34.2, M − HF), 104 (23.9, M − C_2H_4), 97 (37.1, M − HF − Me), 92 (2.7), 90–91 [33.2, 31.7, M − 2HF) − (H or 2H) alternatively M − (C_3H_5 or C_3H_6)], 77 (27.6), 67–68 (100.0, 86.6, M − $C_2H_2F_2$ − (H or 2H) and 39 (41.1, C_3H_3); v/cm^{-1} 2924.0, 2857.0, 1460.0, 1377.0, 1346.0, 1311.0, 1264.0, 1245.0, 1225.0, 1212.0, 1185.0, 1138.0, 1104.0, 1062.0, 980.0, 897.0, 848.0, 817.0 and 723.0.

GC-MS.—GC-MS results were obtained using a Fisons GC 8000 instrument with a SE-30 (30 m × 0.32 mm i.d.) stationary phase column operating at 60 °C for 2 min ramping at 10 °C min⁻¹ to 300 °C, the GC was connected to a Trio 1000 MS instrument.

IR Spectroscopy.—IR spectra were recorded using a Perkin-Elmer 883 instrument, as KBr disks, neat sample for the liquid products, Nujol mull for solid products; 4000–200 cm⁻¹, sweep time = 3 min, slit prog. = 2, smooth = 1, filter = 1.

GC.—Gas chromatography was performed using a Varian 3400 instrument, fitted with a 25 mOV1 non-polar boiling point column, operating at: 180 °C column, 200 °C injector port, 250 °C detector, ramping 20 °C min⁻¹. Samples were observed using a flame ionization detector (FID), burning H_2, helium was the carrier gas. The purity of samples was measured using the uncalibrated GC peak area.

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