Substituent Chemical Shifts in NMR.
Part 5*: Mono and Difluoro S.C.S. in rigid molecules.

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ABSTRACT.
The complete assignment of the proton, carbon and fluorine NMR spectra of fluorocyclohexane (axial and equatorial conformers), 4-Methyl-1,1-difluorocyclohexane, 4-t-butyl 1,1-difluorocyclohexane, 3-methyl-1,1-difluorocyclohexane and 2,2-difluoronorbornane is reported and the proton substituent chemical shifts obtained. The fluorocyclohexane S.C.S. are in close agreement with monofluoro S.C.S. data obtained from steroids, the S.C.S. of the 2a and 2e hydrogens being independent of the orientation of the fluorine. The S.C.S. obtained from fluorocyclohexane are not applicable to the difluorocyclohexane systems and this non-additivity is shown to be general for CF2 and CF3 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.

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INTRODUCTION.

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 of proton chemical shifts 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 d (R-X) - d (R-H). Data for fluorine SCS is 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 fluoroalcohols in solution(12) it was noted that the -CH2F group behaves very differently from the -CHF2 group, in that in the former the gauche effect occurs, ie, the two CH2F groups in 1,2-difluoroethane strongly favour the gauche conformer, whereas in the CHF2 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, 19F and 13C NMR spectra of fluorocyclohexane (axial(1a) and equatorial(1e) conformers), 4-methyl-1,1-difluorocyclohexane(2), 4-tbutyl-1,1-difluorocyclohexane(3), 3-methyl-1,1-difluorocyclohexane(4) and 2,2-difluoro norbornane(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°C have been reported(13) but only the 1ax and 1eq hydrogens in each conformer were assigned. The integral of H1a vs H1e, and F1a vs F1e gave a free energy difference of 0.15kcal/mol in favour of the equatorial conformer. The remaining hydrogen signals were not assigned due to severe overlapping. Trans and cis 4-tbutylcyclohexane 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 over-lapping signals in the proton spectrum prevented assignment.
In this study SF4 has been used to fluorinate a series of commercially available ketones: 4-methylcyclohexanone, 4-tbutylcyclohexanone, 3-methylcyclohexanone 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 SF4 and the difluoro product is formed via a proposed alkoxysulphurtrifluoride intermediate (figure 1).

Figure 1. The proposed reaction mechanism of the fluorination process.

ASSIGNMENT.
The assignment of the fluoroethane and trifluoroethane spectra was obvious. This gave for fluoroethane chemical shifts of 1.35 and 4.55 d (protons), 16.2 and 80.7 ppm.(carbon) and 211.3 ppm.(fluorine) 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 was, shifts 1.87 d (proton), 20.6 and 126.2 ppm (carbon) and 60.3 ppm (fluorine) and couplings 12.9 Hz. (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°C and assigned as follows.
Equatorial fluorocyclohexane (1e).
This is the major component of the mixture which makes the assignment of the proton chemical shifts very simple. The 1a proton is at 4.49d and has a well resolved splitting pattern, 2JH-F >> 3JHax-Hax > 3JHax-Heq (doublet of triplets of triplets). The DQF-COSY spectrum clearly identifies the 2,6a and 2,6e signals from the off diagonal correlations, 2,6e is the lowfield signal. The best resolved multiplet in the spectrum is a quartet of triplets at high field, this is the 4a signal, the 4e signal is assigned from the off diagonal correlation. The remaining two protons are 3,5a and 3,5e, these are easily identified as a quartet at high field and a broad doublet a low field, respectively.
Axial fluorocyclohexane (1a).
The 1e proton is to low field at 4.94d , it is a broad signal due to many small 3JHF and 3JHH couplings. DQF-COSY clearly shows the correlation between the 1e and 2,6a 2,6e protons, however the 2,6a resonance was not at all clear in the 1-

D spectrum as it is swamped by other signals. A well separated signal at 1.75d, 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 3,5e as it correlates strongly to a geminal resonance at 1.63d assigning this resonance to the 3,5a hydrogens. The 3,5a protons experience a through space interaction with the fluorine, which results in the unusually low field shift of 1.63d. The direct correlations between protons in the axial form are complicated by overlapping correlations belonging to the equatorial form. For example, the 3,5e signal has a weak off diagonal correlation with a signal to high field, this is a 3Jeq-ax coupling to 4a, however the correlation between 4a and 4e cannot be unambiguously identified due to over-lapping 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(19,20,21) 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 the 4a proton. The 4a proton correlates strongly to 3,5a which in turn strongly correlates to 3,5e. The remaining signals, 2,6a and 2,6,e correlate to each other, with the axial hydrogens to high field. The axial fluorine resonance is very distinctive with large 3JHF couplings and is to high field of the broad equatorial multiplet.

4-tbutyl 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 T1 noise and the weak 4JHH correlation. However, the remaining 5 signals are well separated from each other and the axial protons readily distinguished from the broad equatorial multiplets. The 2,6a signal is assigned simply due to its distinctive 3JHF(trans) coupling with the axial fluorine, the remaining assignments follow very easily from the DQF-COSY plot. A strong correlation from 2,6a to the low field broad multiplet identifies 2,6e; the remaining strong correlation is between 3,5a and 3,5e with the axial signal to high field. The final signal is 4a and this correlates to 3,5a as expected.

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

3-methyl 1,1-difluorocyclohexane (4).

The proton NMR spectrum is condensed into a region between 1 - 2d, 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 80Hz wide. The result is a very congested and overlapping NMR spectrum that required DQF-COSY, HET-CORR, and J-RES analysis to unravel.

The 2a hydrogen can be readily assigned, due to its distinctive well resolved splitting pattern and also from the DQF-COSY correlation to only two other resonances 2e and 3a. For the 2a and 6a hydrogens 2a lacks the correlation to 3e (the methyl group) whereas 6a has a weak correlation to 5e. The HET-CORR confirmed the assignments of 2a, 2e, and 3a. The C6 signal is a distinctive triplet from which 6a and 6e are assigned, the axial to high field. The remaining signals 4a, 4e, 5a, and 5e are assigned from the HET-CORR, as C4 has a larger coupling to the fluorines than C5.

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, H1 couples to the fluorine nuclei and is to low field of H4 which does not couple. Both H1 and H4 have weak correlations to H7a and H7s, with the syn hydrogen to low field. H1 and H4 strongly correlate to the exo protons only and this assigns 3exo, 5exo and 6exo. The 3endo, 5endo and 6endo protons were subsequently assigned using the HET-CORR correlations.

The complete assignments of the 1H, 13C, and 19F chemical shifts of axial(1a) and equatorial(1e) fluorocyclohexane, 4-methyl-1,1-difluorocyclohexane(2), 4-tbutyl-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).

Table 1. Proton, carbon and fluorine NMR chemical shifts (ppm) and HF and CF coupling constants (Hz) of mono (1a,1e) and difluoro (2,3,4) cyclohexanes and 2,2-difluoronorbornane (5).

Hydrogen chemical shifts.(a)

	1a(b)	1e(b)	2.	3.	4.		5.(e)
H1a/e	4.94	4.49	-	-	-		-
H2a	1.43	1.42	1.67	1.68	1.29	H1	2.43
H2e	2.03	2.15	2.02	2.09	2.02	H3x	1.94
H3a	1.63	1.28	1.27	1.31	1.72	H3n	1.59
H3e	1.75	1.86	1.70	1.80	0.96	H4	2.36
H4a	1.28	1.12	1.47	1.07	0.91	H5x	1.62
H4e	1.58	1.65	0.95	0.89	1.69	H5n	1.34
H5a	1.63	1.28	1.27	1.31	1.54	H6x	1.51
H5e	1.75	1.86	1.70	1.80	1.76	H6n	1.72
H6a	1.43	1.12	1.67	1.68	1.54	H7a	1.34
H6e	2.03	1.65	2.02	2.09	2.05	H7s	1.69

Fluorine chemical shifts.(a)

	1a(b)	1e(b)	2.	3.	4.	5.		
Fax	165.5	-	102.5	103.7	101.1	Fn	87.25	
Feq	-		185.9	92.6	92.1	89.0	Fx	110.52

Carbon chemical shifts.(a)

	1(d)	1a(b)	1e(b)	2.	3.	4.	5.	
C1	92.1	91.2	93.6	123.8	123.9	124.4	C1	45.7
C2	32.9	31.1	33.4	34.4	34.8	43.0	C2	132.0
C3	23.5	20.7	24.4	31.9	24.4	30.6	C3	43.9
C4	25.9	25.8	25.3	31.7	47.4	34.0	C4	36.8
C5	23.5	20.7	24.5	31.9	24.4	23.0	C5	28.4
C6	32.9	31.1	33.4	34.4	34.8	34.5	C6	21.8
CH3	-	-	-	21.6	28.1	22.4	C7	37.7
C	-	-	-	-	32.8	-	-	-

Table 1.(continued).

Carbon-Fluorine Couplings.

	1(d)	1ax.	1eq.	2.	3.	4.	5.	
C1	169.7	165.5	170.4	239.5	238.9	238.7	C1	21.3
				241.9	241.9	242.2		23.6
C2	19.0	21.3	17.2	22.4	21.2	20.4	C2	251.7
				25.5	25.7	25.1		255.6
C3	7.8	0.0	11.7	9.7	10.1	9.4	C3	22.4
								24.9
C4	1.6	0.0	2.2	0.0	0.0	2.0	C4	2.2
								4.3
C5	7.8	0.0	11.7	9.7	10.1	9.7	C5	0.0
C6	19.0	0.0	17.2	22.4	21.2	22.2	C6	6.0
	-	-	-	25.5	25.7	25.5		6.0
CH3	-	-	-	2.8	0.0	0.0	C7	5.3
C	-	-	-	-	1.84	-		-

H-F couplings.

	1a(b)	1e(b)	2.	3.	4.	5.		
HFtrans		46.6	(c)	(c)	34.2	34.1	Fn	multiplet
HFgauche		8.95	(c)	(c)	11.3	10.2	Fx	multiplet

(a) 1H referenced to TMS. 13C referenced to CDCl3 at 77.7ppm. 19F referenced to CFCl3 at 0.00ppm, positive shifts are upfield. Shifts are in ppm, couplings are in Hz.
(b) Axial(Ax) and equatorial(Eq) fluorocyclohexane(3%) obtained at -80°C
(c) Complex multiplet.
(d) Room temperature. (298K)
(e) Abbreviations a anti, s syn, x exo, n endo.

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

Hydrogen.

	1a	ax(a)	1e	eq(a)	2.	3.	4.	5.	
H1a/e	3.26	3.13	3.30	3.24	-	-	-		-
H2a	0.24	0.11	0.23	0.16	0.47	0.51	0.41	H1	0.24
H2e	0.35	0.32	0.47	0.46	0.34	0.34	0.34	H3x	0.47
H3a	0.44	0.46	0.09	0.10	0.39	0.37	0.40	H3n	0.43
H3e	0.15	-0.14	0.18	0.10	0.02	0.05	0.10	H4	0.17
H4a	0.09	n/a	-0.07	n/a	0.15	0.13	0.03	H5x	0.15
H4e	-0.10	n/a	-0.03	n/a	0.09	0.05	0.01	H5n	0.18
H5a	0.44	0.46	0.09	0.10	0.39	0.37	0.34	H6x	0.04
H5e	0.15	-0.14	0.18	0.10	0.02	0.05	0.08	H6n	0.56
H6a	0.24	0.11	0.23	0.16	0.47	0.51	0.43	H7a	0.16
H6e	0.35	0.32	0.47	0.46	0.34	0.34	0.37	H7s	0.51

Carbon SCS of Equatorial and Axial Fluorocyclohexane.(b)

	dAx	dEq	dAx(c)	dEq(c)
C1	64.1	66.5	61.4	64.5
C2	4.0		6.3	3.1 5.6
C3	-6.4	-2.7	-7.2	-3.4
C4	-1.3	-1.8	-2.0	-2.5

(a) SCS for steroids,ref. 6.
(b) from cyclohexane dC=27.1ppm.
(c) ref. 22 .

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 3,5ax hydrogen in the axial form, +0.15ppm vs -0.14ppm. 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 CFCl3 and CDCl3. This also shows that steroids are valid model compounds for deducing SCS in cyclohexanes.

Proton Chemical Shifts in Fluoroethanes.

The results obtained here of the fluorine SCS in the conformationally locked cyclohexanes (we assume that 2 is as conformationally biased as is methyl cyclohexane) 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-bond, two-bond 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 addition to this scheme of a longer range (> three bonds) "steric" interaction between the protons and other near nuclei and also an orientation dependant g 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 beta 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 CF2 and CF3 groups are very different electronically from the CH2 F group. There is a dramatic shortening in the CF bond length, from 1.385 Å (CH3F) to 1.357 Å (CH2F2) to 1.332 Å (CHF3)(26). The CF bond in the CF3 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 CF2 group over the CH2 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 parameterisation. This amendment does not affect the good agreement between the observed and calculated dipole moments of these compounds.

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

	d	SCS		
CH4	0.27(a)			
CH3F		4.27(b)	4.00	
CH2F2	5.45(b)	1.18		
CHF3	6.41 (b)	0.96		
CH3-CH3	0.880(c)			
CH3-CH2F	1.368(c)	0.49		
CH3-CHF2	1.555(c)	0.19		
CH3-CF3	1.870(d)	0.32		

(a) ref 10, (b) ref 24, (c) ref 25, (d) this work.

The g 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 beta 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 2,6ax hydrogens is remarkably similar, with SCS of 0.24 and 0.23ppm respectively (Figure 2). The SCS is independent of the orientation of the fluorine. The SCS of an equatorial and axial fluorine on the 2,6eq hydrogens are also quite similar, 0.35ppm and 0.47ppm 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 g carbon, with a gauche orientation giving a shielding effect and a trans orientation a deshielding one.

Figure 2. Fluorine SCS(ppm) for C-2 and C-3 hydrogens in axial and equatorial fluorocyclohexane.

Both the conformations and the SCS of the difluorocyclohexanes 2ð4 are very similar. The 2ax SCS is 0.47, 0.51 and 0.41ppm respectively and the 2eq 0.34, 0.34 and 0.34ppm respectively. The SCS's from fluorocyclohexane are 0.24ppm for the 2-axial hydrogens and 0.40ppm for the 2-equatorial hydrogens. If the mono fluoro SCS's are additive then the difluoro SCS would be 0.47ppm for 2ax and 0.82ppm for the 2eq. The experimental data gives an average SCS of 0.46ppm for 2ax, in excellent agreement with an additive SCS, but the difluoro SCS for 2eq is 0.34ppm, less than the mono fluorine SCS of 0.35 to 0.47ppm observed in fluorocyclohexane. The g fluorine SCS's for the 3exo and 3endo hydrogens in difluoronorbornane are both 0.43ppm, in good agreement with the SCS data from the difluorocyclohexanes. Thus the g fluorine SCS can be modelled very easily in the CHARGE routine by a dihedral independent term which is parameterised separately for CF2 and CF3 groups. The results of this parameterisation are given in Table 4 and will be discussed later.

The 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 near-by proton. This is seen in the SCS of an axial fluorine on the H-3ax protons in cyclohexane, with no comparable effect of an equatorial fluorine substituent. Taking the average of the SCS for compounds 1a, 2, 3 and 4 gives a deshielding at H-3ax due to an axial fluorine at C-1 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 H-7s of 0.51 ppm (H-F distance 2.65 Å) and of H-6n of 0.56 ppm (H-F distance 2.46 Å). Similar through-space deshielding effects have been observed in 3endo fluoro camphor(28), between the 3endo fluorine and the 5endo hydrogen, where the downfield shift of 0.55ppm 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 (Emin, rmin) 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 calculations fluorine is much smaller than hydrogen). The accepted literature value of rmin 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 rmin 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 GAUSSIAN92 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 g fluorine effect appears to vary with the number of fluorines on the protonated carbon, CH3-CH3 vs CH3-CH2 F cf CH2F-CH3 vs CH2F-CH2F 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 capability which would be of considerable use.

Table 4. Calculated proton chemical shifts (d) of fluorohydrocarbon molecules.

		Calc.	Expt.	Ref.
CH3F		4.26	4.27	24
CH2F2		5.45	5.45	"
CHF3		6.44	6.41	"
CH3-CH2F	CH3	1.25	1.35	25
	CH2	4.60	4.55	"
CH3-CHF2	CH3	1.33	1.56	"
	CH	5.76	5.94	"
CH3-CF3		1.89	1.87	this work
CH3-CH2-CH2 F				CH3 0.88 0.97 30
				CH2 1.68
1.68	"			
				CH2 F 4.40 4.30
"				
CH3-CHF-CH3	CH3	1.28	1.34	25
	CH	4.87	4.84	"
CH2F-CH2 F				4.86 4.59
31				
CF3-CH2 F				5.28 4.55
"				
CH2F-CHF2				CH2 4.91 4.45
"				
				CH 5.99
5.93	"			
CHF2-CHF2				6.03 5.64 32
CF3-CH2-CH2 -CF3				2.65 2.46 33
ax-Fluorocyclohexane		1e	5.24	4.94 this work
(1a)		2,6a	1.58	1.43
	2,6e	2.05	2.03	
	3,5a	1.58	1.63	
	3,5e	1.68	1.75	
	4a	1.20	1.28	
	4e	1.68	1.58	
eq-Fluorocyclohexane		1a	4.84	4.49
(1e)		2,6a	1.58	1.42
	2,6e	2.05	2.15	
	3,5a	1.20	1.28	
	3,5e	1.68	1.86	
	4a	1.20	1.12	
	4e	1.68	1.65	

4-Methyl-1,1-difluoro cyclohexane (2)	2,6a	1.65	1.67
	2,6e	2.12	2.02
	3,5a	1.18	1.27
	3,5e	1.57	1.70
	4a	1.31	1.47
	CH3	0.90	0.95
3-Methyl-1,1-difluoro cyclohexane (4)	2a	1.26	1.29
	2e	2.01	2.02
	3a	1.71	1.72
	CH3	0.90	0.96
	4a	0.80	0.91
	4e	1.57	1.69
	5a	1.58	1.54
	5e	1.68	1.76
	6a	1.65	1.54
	6e	2.12	2.05
2,2-Difluoronorbornane (5)	1	2.58	2.43
	3x	1.90	1.94
	3n	1.73	1.59
	4	2.17	2.36
	5x	1.46	1.62
	5n	1.29	1.34
	6x	1.46	1.51
	6n	1.83	1.72
	7a	1.20	1.34
	7s	1.57	1.69

13C 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 carbon-fluorine couplings are geometry dependent. 1JCFeq (170.4Hz) > 1JCFax (165.5Hz), this is analogous to the Perlin effect(34,35) observed in many 1JCH 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). The 3,5 and 4 carbons in axial fluorocyclohexane do not couple to the fluorine, 3J3,5C-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.). The 3,5 and 4 carbons in the equatorial conformer have significant couplings to the fluorine, 11.7 and 2.2Hz respectively, the large 3J3,5C-F coupling is presumably due to the trans C-C-C-F orientation.

CONCLUSION.

The complete assignment of the proton, carbon and fluorine NMR spectra of compounds 1ð5 provide data allowing the fluorine SCS to be obtained. The SCS data from axial and equatorial fluorocyclohexane agrees with the SCS of monofluoro-steroids. g monofluoro SCS are independent of the orientation of fluorine and are not additive, the CF2 and CF3 groups have to be treated separately.

The g 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. 0.32ppm and 0.40ppm respectively. Through space hydrogen-fluorine 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.

a) N.M.R. Studies.

The fluorocyclohexanes were made up in an approximately 50:50(v/v) mixture of CDCl3 and CFCl3 to no more than 3%(w/v). Proton, carbon, and fluorine nmr spectra were obtained on a Bruker AMX-400 instrument operating at 400.135MHz for proton, 100.634MHz for carbon and 376.503MHz for fluorine. Proton spectra were referenced to internal TMS, 13C spectra were referenced to CDCl3 at (77.7ppm) and 19F spectra were referenced to CFCl3 (with all fluorine signals to high field, ie. negative F*). Proton spectra were obtained over a spectral width of 3,300Hz with 32K data points, giving an acquisition time of 5 seconds and FID-RES of 0.1Hz, transformed with SI=128K. Proton decoupled carbon spectra were obtained over a spectral width of 16,000Hz with 64K data points giving an acquisition time of 2 seconds and FID-RES of 0.25Hz, transformed with SI=128K. Gated decoupled carbon spectra were obtained over a spectral width of 20,000Hz with 64K data points giving an acquisition time of 2 seconds and FID-RES of 0.25Hz, transformed with SI=128K. Fluorine spectra were initially obtained over a spectral width of 100,000Hz with 128K data points giving an acquisition time of 0.66 seconds and a FID-RES of 0.8Hz, transformed with SI=128K. Subsequently fluorine spectra were obtained with better digitisation, these were run over a spectral width of 5,600Hz with 32 K data points giving an acquisition time of 3 seconds and a FID-RES of 0.17Hz, transformed with SI=128K. Proton-proton DQF-COSY nmr spectra were obtained over c.a. 750Hz in both dimensions, 1K data points(F2) and 256 experiments(F1), 16 scans per experiment, transformed to 1K(F2) and 0.5K(F1). Proton-proton total correlation 2-D nmr spectra(TOCSY(19, 20, 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 2,000Hz in both dimensions, with 4K data points(F2) and 512(F1) experiments, transformed to 4K(F2) and 1K(F1). The high power 90 pulse was a standard 1dB 12.5us pulse, the low power mixing pulse was 3dB 27us, the loop cycle(L1) was repeated 30 times to give an isotropic mixing time of 65ms. The 1-D projections were extracted from the 2-D TOCSY, 2K data points over 4.8ppm. 13C-1H HETCORR(36, 37) were typically recorded with a carbon spectral width of 40ppm with 4K data points, proton spectral width of 2ppm with 128 experiments, transformed to 4K and 256 in F2 and F1 respectively.

b) Synthetic studies.

The samples of 4-methylcyclohexanone, 4-tbutyl-cyclohexanone, 3-methylcyclohexanone, and norbornan-2-one were obtained from Aldrich and used without further purification. Each reaction was performed in a 125ml 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 to test for leaks. The vessel was purged with nitrogen, then cooled in liquid nitrogen to -80C, and a pre-weighed amount of SF4 condensed in by vacuum distillation. The apparatus was allowed at warm to room temperature, an electric furnace raised to warm the sample to the desired temperature, and the magnetic stirrer switched on for the duration of the experiment. When the reaction had finished the furnace was switched off and lowered, the reaction vessel was allowed to cool to room temperature. The gases still inside the autoclave, SOF2, SF4 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 a HF resistant plastic container. The crude product was neutralised by removing residual traces of HF with c.a. 10ml saturated sodium carbonate solution.

4-methyl-1,1-difluorocyclohexane (2).

Fluorination of 4-methylcyclohexanone (5.6g, 0.05 mol) was achieved using SF4 (85.2g, 0.8 mol), with stirring at 70°C for 6 hours at a constant pressure of 32.4 bar. The solution was neutralised with saturated sodium carbonate solution

(10cm3), the crude product was then extracted with dichloromethane (10ml3). Analysis by g.c./m.s. identified a molecular ion with a mass of 134 a.m.u. which is consistent with that of the product. Pure product was obtained using a small scale distillation apparatus, 1 atmosphere. c.a. 80°C.
Compound 2. (21.2%, 1.44g (Lit.=25%)); Purity=99.7% by g.c.
m/z. 134(M+, 2.7%), 119(12.8, M - Me), 114(52.6, M - HF), 99(84.4, M - HF and Me), 94(39.4, M - HF and HF), 79(33.9), 77(43.3), 74(40.3), 73(23.0), 72(33.7), 55(100.0, C4H7), 41(61.7, C3H5), 39(40.7, C3H3).
i.r. ; 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, 741.0.
4-tbutyl-1,1-difluorocyclohexane (3).
Fluorination of 4-tbutylcyclohexanone (7.71g, 0.05 mol) was achieved using SF4 (54.0g, 0.5 mole), with mixing at 25°C for 20 hours at a constant pressure of 7.9 bar. The solution was neutralised with a saturated solution of sodium carbonate (10cm3), and extracted in Et2O (7cm3). Vacuum distillation yielded pure product.
Compound 3 (30.8%, 2.74g (Lit.(ref)=19%)); Purity=99.8% by g.c.
m/z. (M+, 176 parent ion not observed), 161(8.1%, M- Me), 141(21.5, M- HF and Me), 121(11.7, M- HF and HF and Me), 119(7.9, M- tButyl), 99(38.2, M- HF and tBu), 77(13.5), 57(100.0, tert-Butyl), 56(80.0, C4H8), 43(53, C3H7), 41(77.0, C3H5), 39(27.4, C3H3), 29(27.0, C2H5).
i.r. 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, 745.0.

3-methyl-1,1-difluorocyclohexane (4).
Fluorination of 3-methylcyclohexanone (7.8g, 0.07 mol) was achieved using SF4 (86.4g, 0.8 mole) with stirring at 60°C for 10 hours at a constant pressure of 20.9 bar. The crude produce was extracted with dichloromethane (10cm3), pure product 3-methyl 1,1 difluorocyclohexane, which has a b.p. of 112°C compared to 169°C of the starting material, was obtained by vacuum distillation.
Compound 4. (13.9%, 1.3g (Lit.(ref)=35%); Purity=99.8% by g.c.
m/z. 134(M+, 8.0%), 119(19.0, M- Me), 114(53.8, M- HF), 94(7.2), 99(100.0, M- HF and Me), 91(43.6), 79(19.4, M- HF and HF and Me), 77(47.9), 55(85.5, C4H7), 42(39.8, C3H6), 41(49.5, C3H5), 39(38.7, C3H3).
i.r. 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, 810.0.
2,2-difluoronorbornane (5).
Fluorination of norcamphor (5.0g, 0.045 mol) was achieved using SF4 (33.4g, 0.31 mole) with stirring at 25°C for 16 hours at a constant pressure of 4.4 bar. The crude produce was extracted with dichloromethane (10cm3), partial vacuum distillation at 700 mbar slowly removed the solvent, a clear colourless crystalline product came out of solution. The liquor was decanted off the crystals, and the crystal vacuum dried.
Compound 5. (11.3%, 0.67g (Lit.(ref)=55%). Purity=100.0% by g.c.
m/z. 132(M+, 11.1%), 117(28.6, M- Me), 112(34.2, M- HF), 104(23.9, M- C2H4), 97(37.1, M- HF and Me), 92(2.7), 90-91(33.2, 31.7, M- HF and HF and one or two hydrogens alternatively M- C3H5, C3H6), 77(27.6), 67-68(100.0, 86.6, M- C2H2F2 and one or two hydrogens), 39(41.1, C3H3).
i.r. 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, 98.0, 897.0, 848.0, 817.0, 723.0.

Gas chromatography/mass spectrometry were recorded using a Fisons g.c. 8000 instrument using a SE-30 (30m x 0.32mm i.d.) stationary phase column operating at 60°C for 2 minutes ramping at 10°C per minute to 300°C, the g.c. was connected to a Trio 1000 mass spectrometer.
Infra red spectra were recorded using a Perlin Elmer 883 instrument, using KBr disks, neat sample for the liquid products, nujol mull for solid products. 4000ð200cm-1, sweep time= 3min, slit prog.=2, smooth=1, filter=1.

Gas chromatography was performed using a Varian 3400 instrument, fitted with a 25m OV1 non-polar boiling point column, operating at; 180°C column, 200°C injector port, 250°C detector, ramping 20°C per minute. Samples were observed using a flame ionisation detector (F.I.D.), burning H2, Helium was the carrier gas. Purity of samples has been measured using the uncalibrated g.c. peak area.

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