Nature of transmission of polar substituent effects in γ-disposed bicyclo[2.2.1]heptane (norbornane) and adamantane ring systems as monitored by ^{19}F NMR: A DFT- GIAO and – NBO Analysis

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Dedicated to Ted Sorensen on the occasion of his 75th birthday

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Abstract

An extensive series of mixtures of *exo*- and *endo*-6-substituted(X)-*exo*-2-fluorobicyclo[2.2.1] -heptanes (**4** and **5**, respectively) were synthesized and characterized by ^{13}C NMR and their ^{19}F chemical shifts measured. Additionally, the latter parameters for a more limited series of 4^{eq}- and 4^{ax}-substituted (X) 2^{eq}-fluoroadamantanes (**9** and **10**, respectively) were also obtained. The corollary from correlations of the ^{19}F substituent chemical shifts(SCS) of **4** and **5** *versus* the corresponding results for the known 4-substituted(X)bicyclo[2.2.1]hept-1-yl fluorides(**3**) is that electronegativity effects (σ_χ effect) underly the SCS of **4** and **5**. Differences between the SCS of **4** and **5** as well as **9** and **10** indicate that there is a stereoelectronic component to the polar effect significantly determining the ^{19}F SCS of **4** and **9**. ^{19}F NMR shieldings of **3**, **4**, **5**, 3-substituted(X) adamant-1-yl fluorides (**8**), **9** and **10** for a common set of substituents (X = H**,** NO_2, CN, NC, CF_3, COOH, F, Cl, HO, NH_2, CH_3, $Si(CH_3)_3$ and Li) were calculated using the DFT-GIAO theoretical model. The level of theory, B3LYP/6-31+G*, was chosen based on trial calculations which gave good agreement with experimental values where known. By means of NBO analysis various molecular parameters were obtained from the optimized geometries. Linear regression analysis was employed to explore the relationship between the calculated ^{19}F SCS and polar field and group electronegativity substituent constants(σ_F and σ_χ, respectively) and also the NBO derived molecular parameters(fluorine natural charges(Q_n), electron occupancies on fluorine of lone pairs(n_F), and occupation number of the C-F antibonding orbital(σ_{CF}*)). The key determining parameters appear to be n_F and σ_{CF}*(occup).

Keywords: Norbornane, adamantane, polar substituent effects, ^{19}F chemical shifts, electronegativity effects, σ-electron delocalization, DFT-GIAO, DFT-NBO

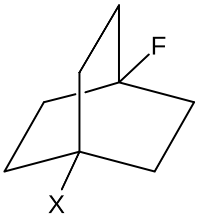
Introduction

Over the years we have reported systematic studies of polar substituent effects in several remotely substituted polycyclic alkanes utilizing ^{19}F chemical shifts as sensitive electronic probes.[1] The perturbation of these shifts resides in the dominant paramagnetic term(σ_p) to the shielding constant[2] and is generally expressed in a simplified form as shown in the equation for an atom A [where r = mean orbital radius term(related to effective nuclear charge), ΔE = mean excitation energy and Q_{AB} = bond-order electron density term].

$$\sigma_A{}^p \ \alpha \ <r^{-3}>_{np} \Delta E^{-1} \Sigma \ Q_{AB} \tag{1}$$

For a series of structurally similar compounds, it is generally assumed that ΔE remains constant and, therefore the charge dependence of the ^{19}F chemical shifts resides either in the $<r^{-3}>_{np}$ or $\Sigma \ Q_{AB}$ terms, or both. Consequently, approximations are unavoidable in order to analyse ^{19}F SCS in terms that have proved useful in the case of chemical reactivity. Nevertheless, for remotely substituted aryl and vinyl fluorides, ^{19}F SCS have been successfully correlated against field-inductive (σ_F) and resonance parameters (σ_R).[3] Moreover, *ab initio* calculations of charge distributions in *meta*- and *para*- substituted fluorobenzenes suggest that the shifts reflect primarily changes in π-electron density.[4] Thus, the latter parameter apparently dominates the decisive paramagnetic contribution to the shifts.

The relationship between the ^{19}F SCS of stereochemically well-defined polycyclic alkyl fluorides[1] and polar substituent parameters have been explored and, in stark contrast to the results from chemical reactivity probes ($\log_{10}K_X/K_0$ or $\log_{10}k_X/k_0$; energy monitors), which generally can be satisfactorily described in terms of an electrostatic field model (σ_F effect),[5] the SCS parameters (charge density monitors) appear to respond sensitively to electronegativity influences (σ_χ effect). Consequently, these studies provide a different perspective to reactivity investigations on the nature of transmission of polar substituent effects in saturated systems. Recently,[6] we presented computational studies (DFT-GIAO calculations) coupled with natural bond orbital (NBO) analyses of 4-substituted (X)bicyclo[2.2.2]oct-1-yl fluorides(**1**) and 3-substituted(X)bicyclo[1.1.1]pent-1-yl fluorides(**2**) which confirmed deductions drawn from model system studies,[1k] namely, that the ^{19}F chemical shifts of alkyl fluorides respond sensitively to the extent of electron delocalization into the antibonding MO of the C-F bond (σ_{CF}*).



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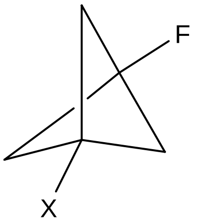

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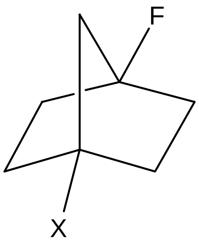

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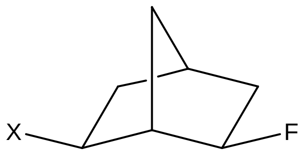
Consequently, shift trends are largely controlled by hyperconjugative (σ_{CF}*-$\sigma_{C\text{-}C(X)}$) or extended hyperconjugative (σ_{CF}*- $\sigma_{C\text{-}C}$ - $\sigma_{C\text{-}X}$(or $\sigma_{C\text{-}X}$ *)) orbital interactions which, in turn, are governed by the σ-inductive effect of the substituent (σ_χ effect). Furthermore, a decrease in the electron population of σ_{CF}* by σ-electron-withdrawing substituents lead to *negative* ^{19}F SCS (*upfield* shifts). The converse holds for σ-electron-donor groups. Most importantly, the aforementioned computational study also suggested that the occupation number of the p-type fluorine lone pair (n_F) may also be pertinent. This is significant since in remotely substituted aryl fluorides where the ^{19}F SCS are known to be governed by the perturbation of the π -electrons on fluorine,[4] the shift trends are diametrically *opposite* to those encountered for the influence of substituents on the occupation number of σ_{CF}*, namely, net electron-withdrawal leads to *positive* SCS and *vice-versa* for net electron-donation. Thus, the conundrum of the ^{19}F SCS trends previously noted for 4-substituted(X)-bicyclo[2.2.1]hept-1-yl fluorides (**3**),[1d] namely, *opposite* signs to those for the corresponding derivatives of **1**, may be a special case where perturbation of the π–electrons of fluorine of an alkyl fluoride is the dominant influence.

The major impetus of this study was to attempt to shed further light on the origin and nature of the 1,3 or γ-interactions in the norbornyl system underlying the ^{19}F SCS of **3**. Consequently, we extended our studies in this system to two other γ-disposed orientations, namely, *exo*- and *endo*-6-substituted(X)-*exo*-2-fluorobicyclo[2.2.1]heptanes (**4** and **5**, respectively) covering an extensive range of substituent electronic effects.



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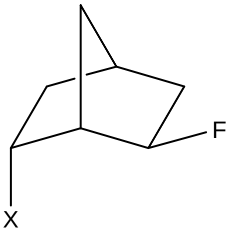

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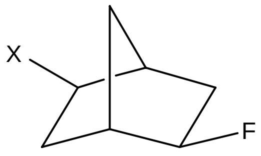

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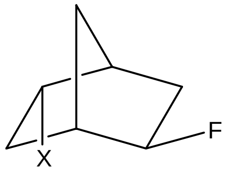

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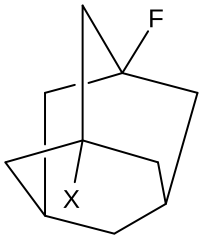
These two systems are of particular interest since although the number of intervening bonds between F and X are the same, their arrangements are quite different; W(**4**)- *versus* a sickle(**5**)-arrangement. Hence, any stereoelectronic component to the polar effect underlying the ^{19}F SCS in γ-dispositions should be exposed. As we shall see later, incidental to the synthesis and measurements of the ^{19}F SCS of **4** and **5** we also obtained the corresponding shift data for *exo*- and *endo*-5-substituted(X)-*exo*-2-fluorobicyclo[2.2.1]heptanes (**6** and **7**, respectively). We were hopeful that application of DFT-GIAO calculations coupled with NBO analyses to the γ-disposed BCH systems (**3**, **4**, and **5**) as well as 3-substituted(X)adamant-1-yl fluorides(**8**)[1e] and two other similarly disposed adamantane ring systems, 4^{eq}- and 4^{ax}-substituted (X) 2^{eq}-fluoroadamantanes (**9** and **10**, respectively), might provide some insight into the aforementioned problem.



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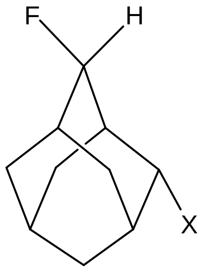

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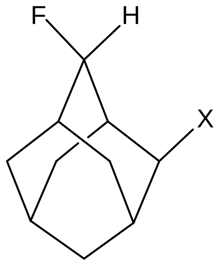

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As stated previously[6], the basic philosophy behind this approach is that if there is good agreement between the theoretical and experimental relative shielding effects, then confidence might be placed in an NBO analysis to provide molecular parameters which reveal the electronic interactions perturbing the local environment of the fluorine nucleus. With this in mind, in order to validate the calculated ^{19}F SCS of **9** and **10** we also report the ^{19}F SCS of a limited number of these larger systems (X=F, Cl, Br, I, OH, CH_3, and $Sn(CH_3)_3$). All these compounds were available from previous studies[7] except for the methyl derivatives. A mixture of these (**9**/**10**, X=CH_3) was obtained specifically for this investigation.

Experimental Section

Synthesis of Compounds. Our synthetic strategy was similar to that previously employed for the preparation of most of the compounds of systems **1-3, 8**[1d,e,f,8] as well (E)/(Z)-5-substituted(X)adamant-2-yl fluorides[1g,h] and (E)/(Z)-4-substituted(X) adamant-1-yl fluorides.[1h] Consequently, we set out to prepare the fluoro-carboxylic acids of **4** and **5**(X=COOH) for appropriate functionalisation. However, after considerable initial exploratory work it quickly became apparent that the preparation of sufficient amounts of the isomeric acids in a pure form would be a protracted and difficult exercise. Hence, we decided to solve the problem using various mixtures of the isomeric fluoro – acids which, by established methodology, provided most of the desired compounds as isomeric mixtures covering a wide range of substituent effects(X = H, NO_2, CN, COOH, $COOCH_3$, $CONH_2$, Cl, Br, I, NH_2, OH, OCH_3, $OCOCH_3$, CH_3, CH_2OH, and $Sn(CH_3)_3$). The remaining mixtures(X = F, OH, OCH_3, and $OCOCH_3$) were obtained as indicated in the supporting information.

All the fluoride mixtures were unambiguously characterized by ^{13}C and ^{19}F NMR in conjunction with GC-MS and VPC analyses. The ^{13}C NMR spectral assignments followed unequivocally from the characteristic ^{13}C - ^{19}F coupling constants in the norbornane skeletal framework[9] as well as chemical shift additivity and APT technology. Relevant details of the syntheses together with the ^{13}C NMR data are available in the supporting information.

Most of the limited number of derivatives of **9** and **10** were available from other studies (X = F, Cl, Br, I, OH and $Sn(CH_3)_3$)[7]. The methyl derivatives of these adamantane systems(X =

CH_3)were obtained as a mixture(ca. **9**:**10** = 58:42) by catalytic hydrogenation of 4^{eq}- fluoro-2-methyleneadamantane[7b](30mg, 0.2mmol and 10% Pd/C(200mg) in absolute ethanol(10ml) was agitated with hydrogen(30 psi) for 8 hrs)which was characterized readily by ^{13}C NMR as described previously for the other aforementioned derivatives of **9** and **10**[7]: ^{13}C NMR($CDCl_3$, relative to Me_4Si, $J^{13}{}_{C}{-}^{19}{}_{F}$(Hz) in parenthesis), **9**(X=CH_3), 96.38(178.84), 37.99(16.79), 36.46(8.24), 36.23(9.46), 32.12(17.70), 31.92, 31.77, 30.66, 26.97, 24.99, 17.21(2.44); **10**(X=CH3), 92.59(175.48), 40.19(9.46), 38.48, 37.99(16.79), 32.89(18.00), 31.92, 31.77, 30.12(8.54), 26.59, 18.16. **9**(X=CH_3, calcd.): 97.22, 38.05, 37.36, 36.96, 32.45, 32.19, 32.10, 30.65, 27.14, 24.89; **10**(X=CH_3, calcd.): 89.02, 38.85, 38.05, 36.96, 33.09, 32.75, 32.19, 32.10, 29.16, 26.84.

Computational Methods. Full geometry optimizations of **3-10** were carried out at the B3LYP/6-31+G* level of theory utilizing the GAUSSIAN 98 program package. [10] The nuclear magnetic shielding constant calculations using GIAO and the NBO analyses were performed at the same level of theory. Initially, because of our previous success with calculations at a higher level (B3LYP/6-311+G (2d,p), we anticipated utilizing this level of theory in this investigation. However, trial calculations on **3, 4,** and **5** (X=H, NO_2, and CN) at this level as well as at the lower level of theory(B3LYP/6-31+G*) revealed that the latter provided calculated ^{19}F SCS(see Table 1) which are in as good as, or better, accord with the observed values(cyclohexane as solvent: **3**[1d], 8.63(NO_2) and 3.10(CN); **4**, -8.27(NO_2) and -2.95(CN); **5**, -11.28(NO_2) and -8.68(CN) than the latter.

Table 1. Trial GIAO calculations of ^{19}F substituent chemical shifts (SCS, ppm)[a] of some norbornyl fluorides(**3** - **5**)

	B3LYP/6-31+G*			B3LYP/6-311+G(2d, p)		
X	**3**	**4**	**5**	**3**	**4**	**5**
H	0.00[b]	0.00[c,d]	0.00[c,d]	0.00[e]	0.00[f,g]	0.00[f,g]
NO_2	8.46	-8.36	-12.64	8.91	-9.18	-12.70
CN	3.66	-2.13	-8.54	4.45	-1.37	-8.74

[a]Defined as the difference (in ppm) between the ^{19}F chemical shift of the substituted compound and that of the parent compound(X=H). A negative sign denotes shielding (upfield shift). [b]Theoretical chemical shift: -201.58 ppm relative to $CFCl_3$. [c]Theoretical chemical shift : -177.54 ppm relative to $CFCl_3$. [d]Isotropic shielding constant of $CFCl_3$: 173.46 ppm at the GIAO-B3LYP/6-31+G* level. [e]Theoretical chemical shift: -211.38 ppm relative to $CFCl_3$. [f]Theoretical chemical shift : -189.08ppm relative to $CFCl_3$.[g]Isotropic shielding constant of $CFCl_3$: 156.69 ppm at the GIAO-B3LYP/6-311+G (2d,p) level.

Consequently, we adopted the more economical level (B3LYP/6-31+G*) for all calculations reported in this study. The NBO approach is described in detail by Weinhold and co-workers[11] and no detailed account is necessary here. A brief account was given in our earlier studies. [6]

Results and Discussion

Empirical Analysis. The ^{19}F SCS (ppm) of the norbornyl fluorides 4 and 5 are listed in Table 2 together with the corresponding data for the previously published bridgehead fluorides (**3**)[1d]. The latter are listed in order to facilitate comparisons between these γ - disposed systems.

Table 2. ^{19}F substituent chemical shifts (SCS)[a-c] of norbornyl fluorides(3-7)

X	**3**[d]	**4**[e]	**5**[e]	**6**[e]	**7**[e]
NO_2	8.63(7.91)	-8.27(-9.36)	-11.28(-11.53)	-3.49(-4.02)	-0.32(-0.63)
CN	3.10(2.41)	-2.95(-3.42)	-8.68(-8.62)	-1.45(-1.83)	-0.25(-0.60)
COOH	5.58(4.94)	-2.57(-3.00)	-7.01(-6.91)	-1.82(-2.10)	0.15(0.16)
$COOCH_3$	5.43(4.88)	-2.62(-3.03)	-7.21(-6.94)	-1.74(-2.13)	0.11(0.05)
$CONH_2$	-[f] (5.50)	-2.58(-2.88)	-8.32(-7.63)	-1.84(-1.99)	-[f] (0.19)
F	10.59(10.08)	-14.54(-14.79)	-16.05(-15.92)	-4.25(-4.91)	1.46(1.20)
Cl	7.48(6.84)	-7.18(-7.69)	-13.44(-13.40)	-4.35(-4.37)	0.74(0.44)
Br	5.73(5.08)	-5.10(-5.59)	-11.70(-11.65)	-4.03(-4.83)	0.23(0.07)
I	2.78(2.10)	-1.60(-2.12)	-8.72(-8.58)	-3.73(-4.03)	-0.61(-0.82)
NH_2	11.25(10.56)	-7.54(-7.34)	-15.37(-14.14)	-3.25(-3.42)	1.81(2.09)
OH	11.42(10.79)	-11.40(-11.40)	-16.18(-15.45)	-3.72(-4.11)	1.69(1.80)
OCH_3	-[g]	-11.16(-11.07)	-15.17(-14.6 8)	-3.31(-3.56)	1.37(1.35)
$OCOCH_3$	7.78(7.12)	-11.31(-11.60)	-13.73(-13.61)	-3.59(-3.92)	1.19(0.97)
CH_3	6.86(6.55)	-1.82(-1.67)	-10.28(-9.76)	-2.53(-2.37)	2.02(2.11)
CH_2OH	6.50(6.07)	-1.58(-1.83)	-8.25(-8.18)	-1.88(-1.91)	1.75(1.61)
$Sn(CH_3)_3$	-2.65(-2.67)	6.45(6.72)	2.41(2.82)	-1.12(-0.90)	-0.21(-0.01)

[a]See footnote a to Table 1. [b]Cyclohexane as solvent. Results in parenthesis are forCDCl$_3$.[c]Accurate to ± 0.05 ppm. [d]Taken from Ref. 1d. [e]X=H [relative to internal 1,1,2,2-tetrachloro-3,3,4,4-tetrafluoro- cyclobutane(TCTFCB)]: -46.50ppm(cyclo-C_6H_{12}), -46.81ppm (CDCl3). TCTFCB relative to internal CFCl3: -114.25ppm(cyclo-C_6H_{12}), -113.78ppm(CDCl3). [f]Not measured. [g]Compound not available.

For the sake of completion the results for the δ-disposed systems (**6** and **7**) are also listed, however, we do not wish to focus much attention on the latter data except to point out that they span a very narrow range. This was to be expected given that the alignment of the intervening bonds are well removed from the preferred stereoelectronic requirement (antiperiplanarity of the participating orbitals)[12] for through-three-bond transmission of the polar effect (extended hyperconjugation; $\sigma_{C\text{-}X}$– $\sigma_{C\text{-}C}$ – σ_{CF}*)[1k]. Note that this is particularly the case for **7**.

Scrutiny of the data for the γ-disposed systems reveals that the SCS of systems **4** and **5** are diametrically *opposite* in sign to those of **3.** However, despite this contrast correlations of the SCS of **4** and **5** *versus* the corresponding results for **3** expose a rough linear trend (r = 0.87 and 0.92, respectively) between the data. Thus, based on the previous detailed regression analyses of the ^{19}F SCS of **3**[1d], an obvious corollary is that a σ_χ effect(s) is the dominant factor underlying the SCS of **4** and **5** as well. Most importantly, although the latter two systems have the same number of intervening bonds between the substituent and probe, there are significant differences in magnitude for most of the shifts. Note, that a similar pattern is revealed on comparison of the SCS for the similarly orientated adamantane systems (**9** and **10**; see Table 3).

Table 3. ^{19}F Substituent Chemical Shifts (SCS, ppm)[a,b] of 3-Substituted(X) Adamant-1-yl Fluorides(**8**)[c] and (*anti* and *syn*)-4-Substituted(X) Adamant-2-yl Fluorides(9 and 10 , respectively)

X	**8**[c]	**9**[d]	**10**[d]
F	-4.49(-5.46)	-8.00 (-8.25)	-11.82(-11.75)
Cl	-2.79(-3.72)	-2.25(-2.85)	-11.94(-12.11)
Br	-1.11(-2.05)	0.03(-0.56)	-10.94(-11.12
I	1.21(0.23)	3.86(3.20)	-8.74(-8.89)
OH	-4.04(-4.82)	-6.45(-6.56)	-12.13(-11.78)
CH_3	-2.77(-2.69)	-0.83(-0.80)	-7.99(-7.70)
$Sn(CH_3)_3$	2.36(2.51)	6.17(6.10)	1.48 (1.46)

[a] See footnote a-c to Table 2. Solvent, cyclo-C_6H_{12}. Results in parenthesis are for $CDCl_3$. [b] X=H [relative to internal 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane(TCTFCB)]: -60.59ppm (cyclo-C_6H_{12}), -60.74ppm ($CDCl_3$). TCTFCB relative to internal $CFCl_3$: -114.25ppm(cyclo-C_6H_{12}), -113.78ppm($CDCl_3$). [c] Taken from ref. 1e. [d] ^{119}Sn NMR($CDCl_3$,relative to internal $SnMe_4$): δ -7.56ppm(**9**, $J_{Sn\text{-}F}$ = 51.17Hz) -8.52ppm(**10**, $J_{Sn\text{-}F}$ = 4.78Hz).

Given the W-*versus* sickle-arrangement of the bonds between F and X in **4/9** and **5/10**, respectively, the results suggests that there is a stereoelectronic component to the polar effect underlying the ^{19}F SCS of the former systems (orbital interactions optimally aligned) but not the latter. Because of the similar orientation between the fluorine probe and the substituent in **3** and **4,** the possible importance of extended hyperconjugation[13] (coupling of the n-orbital of F and X with the σ*-orbital of the C-X and C-F bond via the C_3-C_4 σ-bond; n_F - $\sigma_{C\text{-}C}$ - $\sigma_{C\text{-}X}$ * and n_X - $\sigma_{C\text{-}C}$ - $\sigma_{C\text{-}F}$*, respectively) is implicated in the former system as well.

A result strongly signifying the operation of extended hyperconjugation (n_F - $\sigma_{C\text{-}C}$ - $\sigma_{C\text{-}X}$ *) in **9** is the sign of the SCS for I. Note that it is *positive* (Table 3) implying that a typical electronegative substituent is a σ-electron-donor! This phenomenon was previously noted in another γ-disposed adamantane system (**8**; see Table 3) several years ago[1e]. Confirmation of the origin of this apparent "anomaly" emerges from the relative $\Delta^1J_{C\text{-}F}$ trends set out in Table 4 for the halogen series in **3**, **4**, **5**, **9** and **10.** Given that $^1J_{C\text{-}F}$ couplings are sensitive to changes in the π-bond order of the C-F bond[14], the considerably larger $\Delta^1J_{C\text{-}F}$ values for the halogens in **3**/**4**, **8** and **9** compared to those in **5** and **10,** respectively, strongly signifies the operation of extended hyperconjugation (n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}X}$ *) increasing the C-F π-bond order in the neutral ground state.

Table 4. $\Delta^1J_{C\text{-}F}$ (Hz)[a] Values of **3**, **4**, **5**, **8**, **9** and **10**

X	**3**[b]	**4**[c]	**5**[c]	**8**[d]	**9**[e]	**10**[e]
F	6.10	1.50	-3.50	4.40	3.20	-2.20
Cl	6.60	3.50	-2.40	4.40	5.30	-1.80
Br	7.00	4.90	-1.70	5.40	6.10	-1.50
I	7.40	5.50	2.20	6.35	7.30	-0.40

[a]Solvent, $CDCl_3$. [b]Ref. 1d. $^1J_{C\text{-}F}$ = 207.6Hz(**3**, X=H). [c]This study $^1J_{C\text{-}F}$ = 181.5Hz(**4**/**5**, X=H). [d]Ref. 1e. $^1J_{C\text{-}F}$ = 183.6Hz (**8,** X=H). [e]Ref.1h. $^1J_{C\text{-}F}$ = 178.2Hz (**9**/**10**, X=H).

Interestingly, Duddeck et al[15] has shown that the $\Delta^1J_{C\text{-}F}$ values of **9** (X=F, Cl, Br, OH and CH3) but not the corresponding derivatives of **10** reflect intramolecular interactions n,σ* of substituents in a W- arrangement. This effect on the ^{19}F chemical shifts will be in the *opposite* direction to that of hyperconjugation involving σ_{CF}* and the C3-C4(X) bonding orbital (σ_{CF}*-$\sigma_{C\text{-}C(X)}$). Hence, unlike the SCS for **5** and **10**, which are essentially controlled by the latter interaction, the SCS for **4, 8** and **9** are composite quantities determined by two different effects which are diametrically opposed; modulation of the donor ability of the C-C(X) bond by the σ-inductive influence(σ_χ effect) of X(F>Cl>Br>I) and perturbation of the F π-electron population by extended hyperconjugation governed by the energy levels of $\sigma_{C\text{-}X}$* (I>Br>Cl>F)[16]. A third factor to consider underlying the ^{19}F SCS of π-electron donor substituents in **4**, **8**, and **9** is a n_X-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}F}$* interaction which acts to promote *downfield* shifts (X=NH2>HO>F>Cl>Br>I).[17] The *positive* SCS for I in **8** and **9** is therefore a case where the n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}X}$ * interaction dominates. If this argument is extended to **3** then all the ^{19}F SCS of this system reflect the dominance of the n_F-$\sigma_{C\text{-}C}$ -$\sigma_{C\text{-}X}$ * and n_X-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}F}$* interactions over the competing hyperconjugation (σ_{CF}*-$\sigma_{C\text{-}C(X)}$) and extended hyperconjugation ($\sigma_{C\text{-}X}$-$\sigma_{C\text{-}C}$-σ_{CF}*). The latter being less than optimal as a result of the intervening bond alignments.

Theoretical analysis. The DFT-GIAO calculated isotropic ^{19}F SCS for **3** - **10** are given in Table 5. A common basic set of twelve substituents, which were previously employed for the study of **1** and **2**, were adopted so as to cover a wide range of electronic effects. An examination of the calculated shifts (Table 5) for the norbornyl fluorides (**3** – **7**) reveals that there is good agreement between these and the available observed ^{19}F SCS (Table 2). This is exemplified by the very good to excellent linear correlations between them: r = 0.960, 0.994, 0.994, 0.998, and 0.947 for **3** – **7**, respectively. Although there are significantly greater deviations between the calculated and observed ^{19}F SCS for the larger adamantane systems (**8** – **10**, Table 3), the parallel trends are unmistakeable. For **8**, the only one of these larger systems for which there are a sufficient number of observed SCS available (n = 8) to effect a sensible regression, a strong linear trend is formally defined(r = 0.904). Thus, the level of theory employed in this study appears to define adequately the relative shielding trends (SCS). The calculated ^{19}F SCS of **3**, **4**, **5**, **8**, **9**, and **10** (Table 5) were correlated against polar substituent parameters (σ_F and σ_χ) by means of regression analysis. A summary of the statistical analysis is set out in Table 6. It can be seen that except for the adamantane system **8** the electronegativity constant (σ_χ) is adequate in describing the ^{19}F SCS of the norbornyl fluorides (**3** – **5**) as well as **9** and **10**. The dual dependency (σ_F and σ_χ) of the observed shifts for **8** was previously reported and independently verified by a non-correlative procedure[1e]. The significant polar field contribution ($\rho_F\sigma_F$) has been ascribed to the marked longitudinal polarizability of the C-F bond in adamant-1-yl fluorides[1e,h]. It should be emphasized that the incomplete disproportionality (r = 0.831) between (σ_F and σ_χ) for the substituent set may be responsible for the lack of statistical definition of σ_F in the other systems. Nevertheless, it is clear that the correlations for **3-5** and **9-10** indicate that electrostatic effects play only a minor role at best.

Table 5. Calculated (B3LYP/6-31+G*) ^{19}F substituent chemical shifts (SCS, ppm)[a] for systems **3**- **7**, **9** and **10**

X	**3**[b]	**4**[c]	**5**[c]	**6**[c]	**7**[c]	**8**[d]	**9**[e]	**10**[e]
H	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NO_2	8.46	-8.36	-12.64	-3.43	-0.85	-4.46	-4.11	-6.91
CN	3.66	-2.13	-8.54	-1.39	-0.15	-3.13	0.16	-4.89
NC	6.59	-7.40	-13.62	-2.90	-0.07	-4.42	-3.10	-10.25
CF_3	5.20	-2.25	-7.04	-2.46	0.22	-3.27	-0.89	-6.23
COOH	6.17	-3.00	-7.55	-1.95	-0.30	-2.81	-0.84	-6.12
F	11.00	-13.72	-16.06	-4.34	1.14	-3.48	-6.63	-11.13
Cl	7.52	-6.70	-12.91	-4.48	0.32	-0.89	-0.76	-11.01
HO	12.12	-10.89	-16.01	-3.95	1.36	-2.81	-4.00	-11.16
NH_2	8.66	-6.08	-15.04	-3.44	2.54	-3.78	-2.72	-9.66
CH_3	6.37	-1.55	-9.96	-2.70	2.05	-2.66	-0.48	-7.37
$Si(CH_3)_3$	-0.10	5.20	-0.82	-1.78	0.46	1.34	4.09	-0.15
Li	-11.21	18.34	15.11	0.98	-0.81	11.69	17.38	12.40

[a] See footnote a to Table 1. [b] Theoretical chemical shift: -201.58 ppm relative to $CFCl_3$. [c] Theoretical chemical shift: -177.54 ppm relative to $CFCl_3$. Isotropic shielding constant of $CFCl_3$: 173.46 ppm at the GIAO-B3LYP/6-31+G* level. [d] Theoretical chemical shift : -153.07 ppm relative to $CFCl_3$. [e] Theoretical chemical shift : -192.43 ppm relative to $CFCl_3$.

The relative magnitude of the electronegativity susceptibility parameters (ρ_χ) indicate that the σ_χ effect is clearly more pronounced in the norbornyl (**4** and **5**) than the corresponding adamantane systems (**9** and **10**).

Evidently, the greater electron donor capacity of the strained C_1-C_6 bond in norborn-2-yl fluoride is more responsive to σ-inductive effects than the unstrained C_3-C_4 bond in adamant-2-

yl fluoride. Significantly, the ρ_χ values for **4** and **9** are less than those for **5** and **10**, respectively. This quantitates our empirical deductions above that there appears to be an *opposing* influence (n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}X}$*) to hyperconjugation involving σ_{CF}*(σ_{CF}*-$\sigma_{C\text{-}C(X)}$) underlying the ^{19}F SCS of **4** and **9,** which is not operative in the respective γ-disposed systems (**5** and **10**). Most importantly, it can be seen (Table 6) that the ρ_χ value for **3** , as expected, has a sign *opposite* to the other γ-disposed systems which we have attributed (see above) to the possible dominance of the n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}X}$ * interaction.

Table 6. Regression statistics[a] for calculated ^{19}F SCS versus polar substituent parameters for **3 - 5**, **8 – 10**

System	Dependent Variable	Independent Variable	ρ_F[b]	ρ_χ[b]	c[c]	r^2[d]
3	^{19}F SCS	σ_F	11.563		2.538	0.621
		σ_χ		16.808	2.28	0.927
		σ_F, σ_χ	-1.176	17.987	2.34	0.929
4	^{19}F SCS	σ_F	-16.233		0.432	0.687
		σ_χ		-22.914	0.684	0.967
		σ_F, σ_χ	-0.018	-22.896	0.685	0.967
5	^{19}F SCS	σ_F	-17.334		4.456	0.674
		σ_χ		-24.602	-4.166	0.959
		σ_F, σ_χ	0.307	-24.910	-4.181	0.951
8	^{19}F SCS	σ_F	-9.435		0.537	0.820
		σ_χ		-11.464	0.389	0.856
		σ_F, σ_χ	-4.534	-6.921	0.614	0.911
9	^{19}F SCS	σ_F	-12.241		2.415	0.738
		σ_χ		-16.425	2.469	0.938
		σ_F, σ_χ	-2.097	-14.324	2.573	0.945
10	^{19}F SCS	σ_F	-13.051		-2.845	0.669
		σ_χ		-18.310	-2.659	0.931
		σ_F, σ_χ	-0.277	-18.037	-2.646	0.931

[a] Number of data points in all correlations, n = 13. [b] Regression coefficients for individual terms. [c] Intercept. [d] Multiple correlation coefficient squared.

By means of regression analysis we explored the relationship between the calculated ^{19}F SCS of the γ-disposed systems (**3-5** and **8-10**) and the most pertinent NBO-derived molecular parameters (fluorine natural charge (Q_n), occupation numbers of the fluorine lone pairs (n_F), and occupancy of the C-F antibonding orbital ($\sigma_{C\text{-}F}$*(occup)) (see Table 12 in the Supporting Information). The occupancy of the C-F bonding orbital ($\sigma_{C\text{-}F}$ (occup)) is essentially invariant to changes of the substituent, hence, it was not included in the analysis. A summary of the regression parameters are presented in Table 7. Before interpreting these results it should be borne in mind that there is a degree of interdependence of the molecular parameters that makes outcomes somewhat inconclusive. Nevertheless, it can be seen that most of the fits are extremely poor. This should not be too surprising since none of these parameters corresponds exclusively to a particular transmission mechanism. Exceptions are the fits for the ^{19}F SCS of **4**, **5**, **8**, **9** and **10** *versus* σ_{CF}*(occup) which clearly indicate linear trends. Multiple regression analysis of these shifts against σ_{CF}*(occup) and n_F(or Q_n) did not improve the precision of fits(smaller F values). Most noticeably, the corresponding correlation for **3**(SCS *versus* σ_{CF}*(occup)) indicates no sensible relationship at all. This was somewhat anticipated from the discussion above. The best of these very poor correlations is the regression of the ^{19}F SCS *versus* n_F. However, if the strongest π-electron donors (F, HO, NH_2 and CH_3) are excluded from the data set for the correlation between the ^{19}F SCS of **3** and n_F, the precision of fit dramatically improves($r^2 = 0.925$ and F = 85.986). Clearly, this good linear relationship offers strong support for the idea expressed above that the ^{19}F SCS for most of the substituents in **3** are largely manifestations of the coupling of n_F and $\sigma_{C\text{-}X}$ * via the intervening $\sigma_{C\text{-}C}$ (n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}X}$ *), perturbation of n_F being dominant rather than the occupancy of σ_{CF}*. The latter parameter is clearly important for π-electron donors (F, HO, NH_2 and CH_3) in **3** which can engage in a dominant n_X-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}F}$* interaction. Strong support for this latter interaction in the γ-disposed systems with a W arrangement of the intervening bonds between F and X, comes from the calculated`^{19}F SCS of O^- and NH^- in **3**, **4**, **8** and **9** compared to those of the appropriate neutral congeners, OH or NH_2 .These calculations are listed in Table 8 together with the values for the latter substituents (see Table 5) in order to facilitate comparison. Note the pronounced downfield shifts induced by these powerful π-electron donors compared to the neutral congeners. This signifies the expected response to enhanced electron delocalization into the antibonding MO of the C-F bond (σ_{CF}*) due to the increased n_X-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}F}$* interaction (see σ_{CF}*(occup) values in Table 12 in the Supporting information).

Finally, it is of interest to note that the electronic effect of the carbonyl group as monitored by the fluorine probe indicates that this group is more electron-withdrawing in the 2,6-disposition(**11,** ^{19}F SCS(ppm)= -14.45(cyclo-C_6H_{12}), -15.12($CDCl_3$); calculated ^{19}F SCS (ppm)= -12.34) compared to the 2,5-disposition(**12,** ^{19}F SCS(ppm)= -2.29(cyclo-C_6H_{12}), -3.14($CDCl_3$);

Table 7. Regression statistics[a] for calculated ^{19}F SCS *versus* calculated molecular parameters[a-c] for **3**, **4**, **5**, **8** – **10**

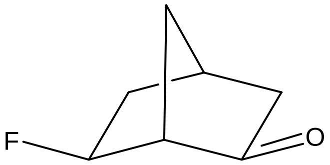
System	Dependent variable	Independent variable	r^{2d}	F^e
3	^{19}F SCS	n_F	0.589	15.796
		Q_n	0.519	11.883
		σ_{CF}*(occup)	0.282	4.324
4	^{19}F SCS	n_F	0.386	6.924
		Q_n	0.726	29.093
		σ_{CF}*(occup)	0.834	55.085
5	^{19}F SCS	n_F	0.119	1.481
		Q_n	0.516	11.734
		σ_{CF}*(occup)	0.795	42.781
8	^{19}F SCS	n_F	0.050	0.522
		Q_n	0.792	38.039
		σ_{CF}*(occup)	0.906	43.572
9	^{19}F SCS	n_F	0.485	10.371
		Q_n	0.724	28.925
		σ_{CF}*(occup)	0.842	58.574
10	^{19}F SCS	n_F	0.011	0.121
		Q_n	0.476	10.006
		σ_{CF}*(occup)	0.754	33.694

[a] n_F = average occupation numbers of the fluorine lone pairs. [b] Q_n = fluorine natural charge. [c] σ_{CF}* = occupancy of the C-F antibonding orbital. [d] Multiplecorrelation coefficient squared. [e] F-test of variance for overall correlation.

Table 8. Calculated ^{19}F SCS of O$^-$ and NH$^-$ for systems **3-4** and **8-9**

X	3	4	8	9
H	0.00	0.00	0.00	0.00
HO^a	12.12	-10.89	-2.81	-4.00
O$^-$	26.10	-4.51	13.58	3.64
NH$_2$^{a}	8.66	-6.08	-3.78	-2.72
NH$^-$	14.35	4.59	12.47	1.38

^{a} Calculated SCS values taken from Table 5.
calculated ^{19}F SCS(ppm)= -2.28).[18]



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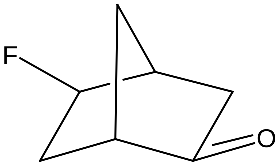

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This result reflects the dominant influence of hyperconjugation involving σ_{CF}* and the C1-C2(C=O) bonding orbital (σ_{CF}*-$\sigma_{C-C(C=O)}$) over the possible n_O-σ_{C-C}-σ_{C-F}* resonance interaction. By contrast, in substituted 2-norbornyl cations the carbonyl group appears to have an electron donor influence from the 6- position compared to the 5-position[13]. The result highlights that electron-donating resonance interactions are more pronounced in electron deficient species such as carbocations than in the neutral ground state as a result of high electron demand.

Conclusions

The results of this model system study coupled with a DFT-GIAO and DFT-NBO analysis reinforce the view that the dominant factor governing the electronic perturbation of the ^{19}F chemical shifts of alkyl fluorides is the electron population of the C-F antibonding orbital [σ_{CF}*(occup)]. However, in an exceptional case, namely, 4-substituted(X)bicyclo[2.2.1]hept-1-yl fluorides(**3**), the electronically induced shift perturbations appear to reflect primarily changes in π-electron density(n_F). This insight provides an explanation for the diametrically *opposite* signs of the ^{19}F SCS for the latter system compared to those for all other model alkyl fluorides.

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Supporting Information Available

General methods, instrumentation, and parameters for spectral measurements; details of the synthesis of mixtures of substituted norbornyl fluorides (**4**, **5**, **6**, and **7**); ^{13}C NMR chemical shifts(observed and calculated) for **3**, **4**, **5**, **6**, and **7** as well as the observed SCS of *exo*- and *endo*-2-substituted (X) norbornanes; NBO molecular parameters (fluorine natural charges(Q_n), electron occupancies on fluorine of lone pairs(n_F), and occupation number of the C-F antibonding orbital(σ_{CF}*)) for **3**, **4**, **8**, **9**, and **10**.

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17. (a) Such interactions are akin to the through-bond effects considered responsible for facile fragmentation in the solvolysis reactions of $2^{eq},4^{eq}$-disubstituted adamantanes[b] and exo-, exo-2,6- disubstituted norbornanes[c] bearing strong π-electron donors. Furthermore, the latter systems react 1261 to 40 times faster than calculated on the basis of their σ_i^q values as a result of resonance effects, n_X- $\sigma_{C1\text{-}C6} - p_{C(2)}$, stabilizing the transition state. (b) Sasaki, T.; Eguchi, S.; Toru, T. *J. Org. Chem.* **1971**, *36*, 3460. (c) Fischer, W.; Grob, C.A.; Hanreich, R.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta.* **1981**, *64*, 2298.
18. It is noteworthy that there is good agreement between the observed in cyclo-C_6H_{12} and the calculated values. Thus, confidence can be placed in the optimized geometries of both **11** and **12** at the B3LYP/6-31+G* level of theory. Consequently, it is pertinent to note that the geometry at the carbon center bearing the fluorine probe is identical for both systems except for the C_1-C_6(1.545Å, **10**) and C_4-C_5(1.536Å, **11**) bonds. Further, the C_1- C_2O bond in **11**(1.530Å) is also significantly longer than the corresponding bond in **12**(1.520Å). These relative bond lengths suggest extended hyperconjugative interactions, n_O-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}F}$*and n_F-$\sigma_{C\text{-}C}$-$\sigma_{C\text{-}O}$ *, in the former but not the latter system. However, the relative ^{19}F SCS clearly indicate that these influences are swamped by hyperconjugation involving σ_{CF}* and the C1-C2(C=O) bonding orbital, σ_{CF}*-$\sigma_{C\text{-}C(C=O)}$.