isocyanoacetate (174 mg, 1.75 mmol) at +10 °C. The mixture was stirred for 10 min at the same temperature and cooled at -70 °C before dropwise addition of aldehyde **9** (239 mg, 0.85 mmol) in THF. After warming to 0 °C over 150 min, the mixture was treated with water and extracted with Et_2O. After the usual treatment enamide **11** was isolated (251 mg, 0.72 mmol., 85%): IR 3380, 1690, 1640, 1600; ^1H NMR δ 8.5 (d, J = 7, 1 H, C_{12}-H); 8.38 (s, 1 H, C*H*O); 8.25 (bs, 1 H, N*H*CHO); 7.65 (s, 1 H, C_{17}-H); 7.39 (d, J = 7, 1 H, C_9-H), 7.32 (dd, J = 7, 1 H) and 7.27 (dd, J = 7, 1 H) (C_{10}-H and C_{11}-H); 4.27 (s, 1 H, C_{21}-H), 1.05 (t, J = 7, 3 H, C_{18}-H_3), MS, m/e 350, 349 $M^{\bullet+}$ (100%), 348, 334, 320; M_r 349.1734, calcd 349.1790 for $C_{21}H_{23}N_3O_2$; UV 203 (24 100), 259 (13 000), 317 (3680), MeOH + HCl 204, 254, 317.

Preparation of Vincamine (1). (±)-Vincamine (1). A solution of enamide **11** (79 mg, 0.225 mmol) in dry methanol-hydrochloric acid (prepared by addition of acetyl chloride (0.048 mL, 0.67 mmol) in anhydrous methanol (3.5 mL)) was refluxed for 4 h. After cooling to 15 °C, excess anhydrous sodium carbonate (143 mg, 1.35 mmol) was added, and the heterogeneous mixture was stirred for 30 min. After hydrolysis, the reaction medium was extracted with dichloromethane. The crude material obtained after the usual treatment was purified by chromatography (SiO_2, hexane-ethyl acetate 50:50) and afforded (±)-vincamine (**1**) (59 mg, 0.163 mmol, 73%): mp 230-231 °C (CH_2Cl_2-Et_2O) IR 3500, 2935, 2850, 1730; ^1H NMR δ 7.47 (m, 1 H) and 7.06 (m, 3 H) (aromatics), 3.93 (bs, 1 H, C_{21}-H), 3.82 (s, 3 H, CO_2CH_3), 0.74 (t, J = 7.5, 3 H, C_{18}-H_3), MS, m/e 355, 354 $M^{\bullet+}$, 353, 339, 325, 307, 295, 284, 267, 252.

Transmission of Polar Substituent Effects in Saturated Systems: Synthesis and ^{19}F NMR Study of 3-Substituted Adamant-1-yl Fluorides

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An extensive series of 3-substituted adamant-1-yl fluorides (**3**) covering a diverse range of substituents has been synthesized and characterized and the ^{19}F chemical shifts measured. By use of multiple linear regression analysis, it is revealed that there is no discernible relationship between the ^{19}F substituent chemical shifts (SCS; electron density monitors) of **3** and polar substituent constants (electric field (σ_F) and electronegativity ($\Delta\iota$) parameters). Most importantly, this result stands in stark contrast to the situation previously defined for the ^{19}F SCS of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (**1**) and the corresponding bicyclo[2.2.1]hept-1-yl fluorides (**2**). For these systems, the ^{19}F SCS are satisfactorily modelled by a linear two-parameter equation (SCS = $\rho_F\sigma_F + \rho_\iota\Delta\iota + c$). Factorization of the ^{19}F SCS of **3** into polar field ($\rho_F\sigma_F$) and residual contributions (^{19}F SCS - $\rho_F\sigma_F$) reveals the importance of the former solvent-dependent component. With respect to the origin of the solvent-independent residual contributions, several possible electronic transmission modes in the adamantane ring have been canvassed and discussed. It is concluded that the residuals are probably composite quantities which, in the main, are dominated by hyperconjugative and/or homohyperconjugative effects. For those substituents (D, CH_3, and $Sn(CH_3)_3$) with negligible polar field influences ($\sigma_F \approx 0$), an interesting parallel is noted between the pattern of σ-inductive or electronegativity effects as reflected by their ^{19}F SCS in **3**, on the one hand, and, on the other, the corresponding relative rates of solvolysis of 3-substituted adamant-1-yl bromides (or tosylates). A common electronic origin (inductive perturbation of C-C hyperconjugation and/or homohyperconjugation) is implicated.

Introduction

Suitable model compounds to study the transmission modes of polar substituent effects in saturated systems should be structurally rigid in order to avoid problems of uncertain conformation. In this respect, bridgehead-bridgehead disubstituted polycyclic alkanes are excellent model substrates and, over the years, several systematic substituent effect studies in these systems have been reported. For those investigations in which chemical reactivity probes (energy monitors) have been employed to monitor the polar substituent perturbation,[1-8] the appropriate experimental parameters ($\log_{10} K/K_0$ or $\log_{10} k/k_0$) have been found to correlate well against the polar field constant (σ_F),[9] i.e., a satisfactory description of the energy changes for equilibria or rate processes in these systems is achieved in terms of the electrostatic field model.

The ability to be able to probe substituent electronic effects via changes in NMR chemical shifts (charge density monitors) has provided a different perspective to the problem of the nature of electronic transmission modes in saturated systems. Unlike rate or equilibria data, NMR chemical shifts are single-state property parameters (generally the neutral ground state) which respond sen-

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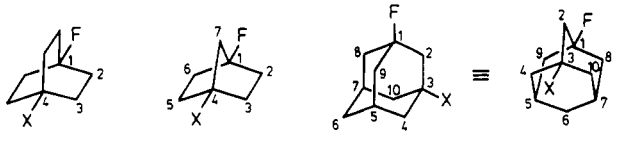
sitively to substituent-induced bond polarization phenomena. The picture that has emerged to date from the application of this methodology to polar substituent effects in saturated systems is not as clear cut as that mentioned above for reactivity probes. On the one hand, substituent chemical shifts (SCS) for nuclei contained in (carbon-13)[10-12] or attached (fluorine-19)[10,13] to unsaturated functional probe groups in the bicyclo[2.2.2]octane (BCO) ring system are predominantly proportional (fair to excellent correlations) to polar field effects (σ_F). On the other hand, SCS for several nuclei (carbon-13,[14,17] fluorine-19,[15,16] silicon-29,[17] tin-119,[17] and lead-207[17]) directly attached to the bridgehead carbon of the BCO or bicyclo[2.2.1]heptane (BCH) ring systems correlate poorly against σ_F. This appears to be due to the fact that the shifts are strongly regulated by σ-electron delocalization mechanisms as well as electrostatic field effects.

The ^{19}F SCS for 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (**1**)[15] and the corresponding bicyclo[2.2.1]hept-1-yl fluorides (**2**)[16] are of particular interest since the apparent



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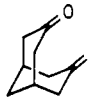
"through-bond" and "through-space" σ-electron delocalization contributions to these shift parameters seem proportional to substituent electronegativity effects. Because this result contrasts with recent analyses[18,19] of much chemical and physical data that failed to delineate any definitive evidence for the transmission of substituent electronegativity effects (beyond the first atom of attachment), we decided to extend our investigations to the much studied adamantane ring system (tricyclo[3.3.1.1^{3,7}]decane). A consideration of possible regulating hyperconjugative and homohyperconjugative interactions (see discussion) on the ^{19}F SCS of 3-substituted adamant-1-yl fluorides (**3**) suggests the possibility of an electronegativity-dependent polar transmission in this rigid aliphatic system as well. Thus, we have synthesized and measured the ^{19}F SCS (in several solvents) of an extensive series of **3** which cover a wide range of electronic substituent effects. It should be noted that the existing data base for system **3** (X = F,[20-22] Cl,[21] Br,[21] $COOC_2H_5$,[20] CH_3,[20] C_2H_5,[20] $(CH_3)_2CH$,[20] $(CH_3)_3C$[20]) is inadequate for a statistical evaluation of polar substituent effects in this system. We were hopeful that a substantial body of ^{19}F SCS data for **3** from a single source and subsequent empirical correlations might contribute to an improved appreciation of polar phenonema in saturated systems in general.

Herein we report the results of our study.

Results and Discussion

Synthesis of Compounds. Our synthetic strategy was similar to that previously employed for the preparation of most of the compounds of systems **1**[15,23] and **2**.[16] Thus, 3-fluoroadamantane-1-carboxylic acid (**3**, X = COOH) provides a convenient starting point for the synthesis of many of the required compounds of system **3** (except X = H, F, Cl, I, CH_3, $C(CH_3)_3$, C_6H_5, and p-$NO_2C_6H_4$). In general, most of the syntheses proved uneventful; however, for several reactions it was found that fluorine can be a surprisingly good nucleofuge at the adamantane bridgehead under conditions that provide electrophilic assistance (relatively strong hydrogen-bond donor (HBD) solvents, Lewis and strong protic acids). The latter conversions encountered in this work, which required modifications of the conditions successfully applied to **1**[23] and **2**,[16] are as follows. (i) An attempt to hydrolyze the acetate (**3**, X = $OCOCH_3$) to the corresponding alcohol (**3**, X = OH) under protic conditions ($NaOCH_3/CH_3OH$) led to considerable fragmentation[7] of the adamantane ring (formation of 7-methylidenebicyclo[3.3.1]nonan-3-one or "open-ketone" (**4**)). This problem was circumvented by effecting the



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hydrolysis under dipolar aprotic conditions (KOH/Me_2SO). It is of interest to note also that significant fragmentation was not encountered in converting the alcohol (**3**, X = OH) to the ether (**3**, X = OCH_3) in an aprotic medium (KH/CH_3I/THF). (ii) An attempt to convert the precursor acid (**3**, X = COOH) to the corresponding amine (**3**, X = NH_2) by the Curtius rearrangement led to the complete loss of fluorine; a mixture of 3-chloroadamantane-1-amine and 3-chloroadamantane-1-carboxylic acid was obtained. Trial experiments on 1-fluoroadamantane (**3**, X = H) demonstrated that fluorine is readily replaced with chlorine in this substrate on treatment with $SOCl_2$ (2 molar equiv/2 h/80 °C) or concentrated HCl (two-phase system with benzene under reflux). We found that the acid chloride (**3**, X = COCl), which was required as a precursor for the amide (**3**, X = $CONH_2$) and nitrile (**3**, X = CN) derivatives, could be obtained in good yield by treating the acid (**3**, X = COOH) with less $SOCl_2$ (1.2 molar equiv) at a lower temperature (50 °C) and shorter reaction time (45 min). The desired amine (**3**, X = NH_2) was eventually obtained from the amide (**3**, X = $CONH_2$) by a relatively new procedure (see Experimental Section) which precludes a strong electrophilic environment. (iii) A first attempt to obtain the bromo derivative (**3**, X = Br) from the acid (**3**, X = COOH) by the Hunsdiecker reaction utilizing 1,2-dibromoethane as solvent[24] led to a quantitative yield of 1,3-dibromoadamantane. However, the reaction was successfully performed in dichloromethane as solvent (Cristol–Firth modification).[25]

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The formation of polybrominated products[26] in this reaction can be minimized by ensuring that light is excluded from the reaction vessel and by avoiding the use of excess bromine. (iv) An attempt to prepare the iodo derivative (**3**, X = I) by treatment of the alcohol (**3**, X = OH) with a mixture[27] of aqueous HI/benzene/hexane at room temperature provided a mixture of 3-iodoadamantan-1-ol (~90%) and the "open-ketone" (**4**; ~10%). The desired iodide (**3**, X = I) was successfully obtained by treating the iodo alcohol (prepared conveniently by treating the "open-ketone" (**4**) with HI; see Experimental Section) with diethylaminosulfur trifluoride (DAST reagent; see Experimental Section).

In connection with the unexpected nucleofugality of the fluorine group noted in this study, it is significant to note that, recently, Bentley and Roberts[28] proposed the following nucleofugal order (F > OTs > Cl > Br > I) for 1-adamantyl substrates under conditions involving electrophilic assistance. However, in this latter study of electrophilic effects on the rates of substitution in adamantyl systems, fluorine was not specifically investigated. Finally, three other transformations encountered in this synthetic program are worthy of note. Firstly, despite successes reported by other workers,[29] the literature procedure for preparing the "open ketone" (**4**) (treatment of 1,3-dibromoadamantane with 3 molar equiv of NaOH in aqueous dioxane at 180 °C for 18 h) proved to be extremely capricious in our hands. Several attempts by us using this procedure led to varying yields of **4** (0 → 30%) with 1,3-dihydroxyadamantane always being the dominant product. However, we eventually found that **4** could be obtained in reproducible yields (>80%) from 1-acetoxy-3-bromoadamantane (see Experimental Section) by effecting hydrolysis under aprotic conditions (3 molar equiv of KOH/Me_2SO). Although this new synthetic procedure for **4** involves more steps than the literature method, it has the advantage of avoiding autoclave equipment and is most reliable. Secondly, it has been reported[30] that the introduction of the *tert*-butyl group at the bridgehead of adamantane is extremely difficult by conventional procedures. We have found that provided the temperature is strictly controlled (between −70 and −80 °C) the α-chloroisopropyl group can be converted to the *tert*-butyl substituent in good yield by treatment with trimethylaluminium in dichloromethane. However, if the reaction is performed at higher temperatures (~−20 °C), then a rearrangement occurs to provide the unwanted homoadamantane derivative. Thirdly, an attempt to prepare 1-bromo-3-fluoroadamantane (**3**, X = Br) by irradiating a solution of 1-fluoroadamantane in bromotrichloromethane, as described by Pincock and Perkins,[21] was unsuccessful and led to a mixture of products which proved difficult to separate. Combined gas chromatography–mass spectrometry (GC–MS) revealed the mixture contained mono-, di-, tri-, and possibly tetrabrominated products. It should be noted that the indiscriminate attack of free radical species on the adamantane ring has been reported.[26]

Correlative Analyses. The ^{19}F SCS for system **3** in c-C_6H_{12}, $CDCl_3$, DMF, and hexafluoro-2-propanol (HFIP) are assembled in Table I. It should be noted that, unlike systems **1** and **2**, ^{19}F SCS for **3** in CF_3CO_2H could not be determined due to the rapid solvolysis of the parent system (**3**, X = H) at ambient temperature in this very strong hydrogen-bond donor (HBD) solvent.[31] This result exemplifies dramatically the pronounced nucleofugal behavior of fluorine at the bridgehead of this model substrate (see above) under conditions of powerful electrophilic assistance. Solvolysis of the parent system (**3**, X = H) also occurs fairly rapidly in HFIP as evidence by our failure to obtain its ^{13}C NMR spectrum in this solvent. Fortunately, the rapidity of ^{19}F NMR measurements permitted ^{19}F SCS to be determined in this good HBD solvent.

Table I. ^{19}F Substituent Chemical Shifts (SCS)[a-c] of 3-Substituted Adamant-1-yl Fluorides (3)

X	SCS			
	c-C_6H_{12}	$CDCl_3$	DMF	$(CF_3)_2CHOH$
NO_2	−5.32	−6.60	−6.06	−10.43
CN	−4.06	−5.28	−4.65	−8.82
CF_3[d]	−4.44	−5.20	−5.01	−7.13
COOH	−3.49	−4.24	−3.29	−6.61
$CONH_2$	−2.84	−3.85	−2.73	−6.97
$COOCH_3$	−3.21	−3.94	−3.62	−6.36
$COCH_3$	−2.85	−3.68	−3.15	−6.36
OH	−4.04	−4.82	−3.49	−7.78
OCH_3	−3.03	−3.72	−3.43	−6.98
$OCOCH_3$	−3.23	−4.13	−3.76	−6.75
F[e]	−4.49	−5.46	−5..16	−8.60
Cl	−2.79	−3.72	−3.35	−6.52
Br	−1.11	−2.05	−1.62	−5.01
I	1.21	0.23	0.72	−2.73
NH_2	−3.71	−4.28	−3.37	−9.80
$N(CH_3)_2$	−1.79	−2.76	−2.05	−10.57
$NHCOCH_3$	−3.20	−4.17	−3.13	−6.62
$N{=}NCF_3$	−5.06	−5.87	−5.57	−8.23
CH_3	−2.77	−2.69	−2.69	−2.57
$C(CH_3)_3$	−0.46	−0.15	−0.35	0.12
CH_2OH	−2.90	−3.24	−2.53	−4.96
C_6H_5	−1.87	−2.19	−2.03	−3.39
p-$NO_2C_6H_4$	−2.52	−3.04	−2.55	−4.49
$Sn(CH_3)_3$[f]	2.36	2.51	2.51	
D[g,h]	−0.048	−0.046	−0.046	−0.042

[a] Defined as the difference (in parts per million) 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] Accurate to ±0.01 ppm. [c] X = H (relative to internal $FCCl_3$): −130.76 (c-C_6H_{12}), −128.96 ($CDCl_3$), −126.49 ppm (DMF). [d] J_{FF} = 1.95 Hz. Obtained from ^{13}C satellites in the $^{19}F\{^1H\}$ spectrum ($(CF_3)_2CHOH$). [e] J_{FF} = 10.38 Hz, J_{CF} = 187.87 Hz. Obtained from ^{13}C satellites in the $^{19}F\{^1H\}$ spectrum ($CDCl_3$). [f] Average $J_{117,119Sn-19F}$ values (Hz): 28.07 (c-C_6H_{12}), 29.29 ($CDCl_3$), 29.30 (DMF). [g] Accurate to ±0.002 ppm. [h] J_{DF} = 0.59 Hz. Obtained from ^2H spectrum (46.06 MHz). Based on $\gamma_{^1H/^2H}$ = 6.5145, J_{HF} = 3.84 Hz.

A cursory examination of the data in Table I reveals that, except for the iodo group in c-C_6H_{12}, $CDCl_3$, and DMF, the SCS for all the *electronegative* substituents (including D, CH_3, and $C(CH_3)_3$) are *negative* (upfield shifts). In contrast, the SCS for the only *electropositive* group ($Sn(CH_3)_3$) is *positive* (downfield shift). Thus, in the main, the direction of the substituent-induced shifts in this model system are similar to that observed for **1**[15,32,33] but essentially diametrically opposed to the situation encountered for **2**.[16,32] However, the SCS of **3** cover a significantly smaller range than those of **1** (e.g., in c-C_6H_{12}, 7.68 ppm for **3** (Table I) vs. 12.06 ppm for **1**[15]). It is important to note that, except for groups with very weak polar field influences ($\sigma_F \approx 0$; D, CH_3, and $C(CH_3)_3$), the

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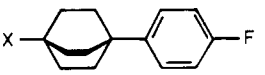
Table II. Polar Substituent Parameters (σ_F Values)[a] Derived from the ^{19}F SCS (ppm)[b] of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (5) in $(CF_3)_2CHOH$ (HFIP)

X	SCS	σ_F	X	SCS	σ_F
NO_2	1.27	0.69	$OCOCH_3$	0.65	0.35
CN	1.04	0.56	F	0.84	0.45
CF_3	0.60	0.32	Cl	0.80	0.43
COOH	0.63	0.34	Br	0.81	0.44
$CONH_2$	0.82	0.44	I	0.74	0.40
$COOC_2H_5$	0.56	0.30	NH_2	1.46	0.79
$COCH_3$	0.68	0.37	$N(CH_3)_2$	1.95	1.05
CHO	0.76	0.41	$NHCOCH_3$	0.62	0.33
CH_2OH	0.39	0.21	$N{=}NCF_3$[c]	0.84	0.45
OH	0.68	0.37	C_6H_5	0.36	0.19
OCH_3	0.70	0.38	p-$NO_2C_6H_4$	0.51	0.28

[a] ^{19}F SCS = $\rho_F\sigma_F$. Polar susceptibility parameter (ρ_F = 1.85 ($(CF_3)_2CHOH$)) was determined by setting σ_F for *bromine* equal to 0.44. [b] Accurate to ±0.01 ppm. [c] See Experimental Section for synthesis of **5**, X = $N{=}NCF_3$. ^{19}F SCS (ppm): 1.37 (c-C_6H_{12}), 1.18 ($CDCl_3$), 0.76 (DMF). See footnote *b* to Table II of ref 15 for appropriate ρ_F values for determining the σ_F constants in these solvents for the $N{=}NCF_3$ group (σ_F = 0.51 (c-C_6H_{12}), 0.46 ($CDCl_3$), 0.47 (DMF)).

^{19}F SCS in HFIP (Table I) are all significantly shifted *upfield* relative to the SCS in other solvents. This solvent phenomenon (see later) is also observed for **1**[15] and **2**[16] in CF_3CO_2H but is distinctly more pronounced due to the greater HBD characteristics of the latter solvent.[31] It is noteworthy that there is a major discrepancy between the ^{19}F SCS for Cl and Br (Table I) in this study and the literature[21] values for these groups.

In an attempt to relate the ^{19}F SCS of **3** (Table I) to polar substituent constants (electric field and electronegativity parameters), correlation analyses were performed by using multilinear regression techniques as previously employed for the data of **1**[15] and **2**.[16] The σ_F values used were those for the appropriate solvents derived from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (**5**).



5

The values for c-C_6H_{12}, $CDCl_3$, and DMF were available from previous work,[15,16,34] while those for HFIP were determined specifically for this study from the available compounds of model system **5** (see Table II). In addition, σ_F values in all four solvents were also determined for the $N{=}NCF_3$ group (Table II; see footnote *c*) since ^{19}F SCS for this substituent were available for **3** (Table I). Inamoto and Masuda's iota (ι) scale of electronegativities,[35] although not without some obvious uncertainties,[15] was again employed. The regression parameters for the statistical analysis are set out in Table III. It can be seen that the statistical fits (SE, *r*, and *F*)[36] indicate that the correlations are of very poor precision. These were not significantly improved by employing an electronegativity scale derived from the ^{19}F SCS of **1**.[16] In addition, it was found that inclusion of a third parameter (σ_R^0, the π-resonance constant)[19,37] did not effect any statistically significant improvement in the fit of the various correlations. Thus, in striking contrast to the situation for **1**[15] and **2**[16] where the ^{19}F SCS can be described to a fair degree of accuracy by a linear two-parameter equation (SCS = $\rho_F\sigma_F + \rho_\iota\Delta\iota + c$), the ^{19}F SCS for **3** cannot be fitted to a similar or expanded (including σ_R^0) linear model. The basis for this difference is not clear to us at this stage. We can only conclude that the results of the correlative analysis suggest that a factor or combination of factors, not characterized by available empirical electronic parameters, underlie the ^{19}F SCS of **3** which are either unimportant or not operative in **1** and **2**.

Polar Field Contribution. The electrostatic field contribution ($\rho_F\sigma_F$) to the ^{19}F SCS of alkyl fluorides has been shown to have its origin in the polarization of the CF σ bond;[38] its magnitude depends not only on the component of the electric field along the CF bond (E_z) but also on the longitudinal polarizability of the CF bond. Polar susceptibility parameters (ρ_F = −2.71 (c-C_6H_{12}), −5.31 ($CDCl_3$), −5.20 (DMF), −12.22 (HFIP)) for the fluorine probe of **3** may be determined independently by dividing the chemical shift difference between **3** (X = p-$NO_2C_6H_4$) and **3** (X = C_6H_5) [see Table I; ΔSCS (ppm) = −0.65 (c-C_6H_{12}), −0.85 ($CDCl_3$), −0.52 (DMF), and −1.10 (HFIP)] by $\Delta\sigma_F$ for p-$NO_2C_6H_4$ and C_6H_5 (0.24 (c-C_6H_{12})[15] 0.16 ($CDCl_3$),[15] 0.10 (DMF),[15] and 0.09 (HFIP; Table II))], as previously described for the ^{19}F SCS of **1**.[15,38] It is of interest to note that the ρ_F values (c-C_6H_{12}, $CDCl_3$, and DMF) for the latter system (−3.13, −5.25, and −4.70, respectively)[15,38] are very similar to the aforementioned corresponding values of **3**. This is not surprising since a consideration of angle and distance factors ($E_z = 2\mu\cos\theta/r^3$)[10] as well as the similar electronic character of the C–F bond in both systems (reflected by their respective $^1J_{CF}$ values, see later) suggests that this should be the case. The large difference between the enhanced ρ_F values for **3** and **1** in HFIP (−12.22) and CF_3CO_2H (−17.56), respectively, is undoubtedly a manifestation of the markedly different HBD characteristics of the two solvents.[31] We have previously ascribed the exalted ^{19}F SCS of alkyl fluorides in HBD solvents to strong hydrogen-bonding interactions between the fluorine probe and the solvent.[38] Such interactions have the tendency to increase the effective electronegativity of fluorine with a consequential increase in the p character of the exocyclic orbital of C1. This apparently leads to a marked increase in the longitudinal polarizability of the C(sp^3)–F σ bond and, hence, a concomitant increase in the polar susceptibility parameter (ρ_F).

The independently defined ρ_F values (see above), together with the appropriate polar substituent parameters (σ_F), may be employed to calculate polar field contributions ($\rho_F\sigma_F$) to the ^{19}F SCS of **3** for each substituent in the various solvents. A comparison of these contributions listed in Table IV with the observed ^{19}F SCS (Table I) reveals that the electrostatic field effect is a powerful regulator of the shifts in this model system and, in particular, is clearly the dominant factor for polar substituents (excluding CH_3, $C(CH_3)_3$, $Sn(CH_3)_3$, and D) in strong HBD solvents such as HFIP. This is identical with the situation similarly defined for the ^{19}F SCS of **1**.[15]

Polar field effects also contribute significantly to other NMR parameters which are highly dependent on the po-

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(36) (a) Three statistical tests of the precision of fit of the correlations are given in Table III (SE, *r*, and *F*). The most significant is the *F* test since it involves division by the number of parameters in the correlation equation.[36b] A larger value of *F* implies a better overall correlation or a greater significance of an individual regression coefficient. The limitations of *r* as an indicator of the precision of fit of linear correlations has been discussed.[36c] (b) Reynolds, W. F.; Dais, P.; MacIntyre, D. W.; Hamer, G. K.; Peat, I. R. *J. Magn. Reson.* **1981**, *43*, 81. (c) Davis, W. H.; Pyror, W. A. *J. Chem. Educ.* **1976**, *53*, 285.

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Table III. Results of Correlation Analysis[a] of ^{19}F SCS of 3-Substituted Adamant-1-yl Fluorides (3) vs. Polar Substituent Constants (σ_F and $\Delta\iota$)

solvent	independent variables	ρ_F[b]	ρ_ι[b]	c[c]	r[d]	S.E.[e]	F[f]	$F(\rho_F)$[f]	$F(\rho_\iota)$[f]	n[g]
c-C_6H_{12}	σ_F, $\Delta\iota$	−1.23 (±1.61)	−3.77 (±0.88)	−0.49	0.76	1.24	13.05[h]	0.58[i]	18.13[j]	21[s]
$CDCl_3$	σ_F, $\Delta\iota$	−2.87 (±1.74)	−2.59 (±0.91)	−1.41	0.73	1.16	10.08[k]	2.73[l]	8.19[m]	21[s]
DMF	σ_F, $\Delta\iota$	−3.23 (±1.59)	−4.15 (±0.83)	0.08	0.84	1.13	21.30[n]	4.14[o]	24.96[n]	21[s]
$(CF_3)_2CHOH$	σ_F, $\Delta\iota$	−8.56 (±2.74)	−3.89 (±2.27)	−0.44	0.75	2.57	10.73[p]	9.78[q]	2.93[r]	20[t]

[a] General form of correlation equation: SCS = $\rho_F\sigma_F + \rho_\iota\Delta\iota + c$. [b] Regression coefficient for individual terms plus or minus standard error of regression coefficient. [c] Intercept. [d] Multiple correlation coefficient. [e] Standard error of estimate. [f] F test of variance for overall correlation and individual coefficients. Superscripts indicate confidence level (CL) of test. [g] Number of data points in correlation. [h] 99.96% CL. [i] 54.40% CL. [j] 99.96% CL. [k] 99.88% CL. [l] 84.83% CL. [m] 98.96% CL. [n] 99.99% CL. [o] 94.31% CL. [p] 99.90% CL. [q] 99.39% CL. [r] 89.48% CL. [s] SCS of $CONH_2$, CH_2OH, and N=NCF$_3$ omitted from data set due to lack of $\Delta\iota$ parameters. D also excluded. [t] Same as s; SCS of $Sn(CH_3)_3$ was not measured in this solvent.

Table IV. Calculated Polar Field Contributions ($\rho_F\sigma_F$) to ^{19}F SCS (ppm) of System 3

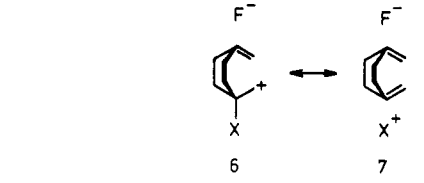
X	$\rho_F\rho_F$ c-C_6H_{12}[a]	$CDCl_3$[b]	DMF[c]	$(CF_3)_2CHOH$[d]
NO_2	−1.79	−3.45	−3.12	−8.43
CN	−1.60	−2.97	−2.50	−6.84
CF_3	−1.19	−2.12	−2.18	−3.91
COOH	−0.62	−1.70	−1.09	−4.15
$CONH_2$		−1.75	−0.99	−5.38
$COOCH_3$	−0.60	−1.38	−1.35	−3.67
$COCH_3$	−0.76	−1.65	−1.30	−4.52
OH	−0.62	−1.54	−0.73	−4.52
OCH_3	−0.51	−1.38	−1.14	−4.64
$OCOCH_3$	−0.79	−1.75	−1.77	−4.28
F	−1.06	−2.23	−2.08	−5.50
Cl	−1.17	−2.28	−2.24	−5.25
Br	−1.19	−2.34	−2.29	−5.38
I	−1.14	−2.23	−2.08	−4.89
NH_2	−0.33	−1.01	−0.42	−9.65
$N(CH_3)_2$	−0.27	−0.96	−0.62	−12.83
$NHCOCH_3$	−0.57	−1.49	−0.94	−4.03
N=NCF$_3$	−1.38	−2.44	−2.44	−5.50
CH_3	0.00	0.00	0.00	0.00
$C(CH_3)_3$	0.00	0.00	0.00	0.00
CH_2OH	−0.27	−0.74	−0.21	−2.57
C_6H_5	−0.41	−0.90	−0.83	−2.32
p-$NO_2C_6H_4$	−1.06	−1.75	−1.35	−3.42
$Sn(CH_3)_3$	0.00	0.00	0.00	0.00
D	0.00	0.00	0.00	0.00

[a] ρ_F = −2.71. [b] ρ_F = −5.31. [c] ρ_F = −5.20. [d] ρ_F = −12.22.

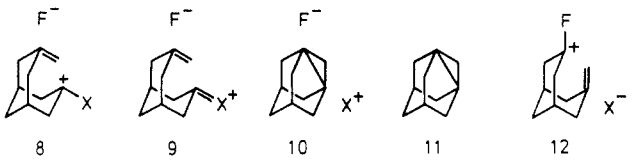
larization of the C–F bond (Δ^1J_{CF} and C1 SCS[38] values; listed in Table V for **3**). By use of the appropriate data for the p-$NO_2C_6H_4$ and C_6H_5 groups, ρ_F values (4.56 and −3.75) can be determined for the Δ^1J_{CF} and C1 SCS values of **3**, respectively, in a manner similar to that described above for the ^{19}F SCS. However, other factors must also contribute strongly to these parameters as evidenced by their very poor correlations against σ_F. It is noteworthy that these observations for Δ^1J_{CF} in **3** are similar to those for **2**[16] but in stark contrast to the good correlation (r = 0.977) previously noted for the Δ^1J_{CF} values of **1** vs. σ_F.[15]

Residual Contributions. Compared to the considerable fluctuations of the polar field contributions in the various solvents for system **3** (Table IV), the residuals (^{19}F SCS − $\rho_F\sigma_F$) listed in Table VI for this substrate are relatively solvent-independent. Although this observation is reminiscent of the results of similar factorization for **1**[15] and **2**,[16] the fact is that whereas the residuals for the latter systems are related to electronegativity there is no such parallel relationship for those of **3** (see correlative analyses above). In an attempt to shed some light on the origins of the residual contributions of **3** (Table VI), it is instructive to briefly review the factors identified by model system studies that appear to govern the magnitude and sign of ^{19}F SCS of alkyl fluorides.

Firstly, based on the demonstration that hyperconjugation (σ_{CF}*−π) is an important interaction controlling the shifts of benzyl fluorides,[39,40] we believe that the extent of delocalization of electrons from neighboring antiperiplanar C–C bonds into the σ* orbital of the C–F bond (hyperconjugation) is a significant factor governing the ^{19}F chemical shifts of polycyclic fluorides.[15,16,32,33] Further, utilizing the information that a *decrease* in σ_{CF}*−π (benzene) (e.g., electron-withdrawing *para* substituents in benzyl fluoride) results in *upfield* ^{19}F chemical shifts, it may be inferred that substituent-induced *upfield* shifts (*negative* ^{19}F SCS) in alkyl fluorides are likely manifestations of a *decrease* in σ_{CF}*−σ_{CC}. The converse situation applies for electron-donation. The favored geometry for hyperconjugation is optimized in **1** and **3** but not in **2**. For the latter system, structural distortions preclude the favored antiperiplanar alignment. We[15,16,32,33] have ascribed the electronegativity dependence of the ^{19}F SCS of **1** to the variation of the σ_{CF}*−σ_{CC} interaction due to hyperconjugation involving the C–X bond (σ_{CC}−σ_{CX} or σ_{CC}−σ_{CX}*; denoted by canonical structures **6** and **7**). In valence bond



6 7



8 9 10 11 12

terminology, hyperconjugation involving the C–F bond in **3** may be denoted by canonical structure **8**. Thus, a dependence of the ^{19}F SCS of **3** on substituent electronegativity can be envisaged on the basis of importance of this contributing resonance structure. It is expected that the structure would be promoted by electropositive substituents and decreased by electronegative groups. In other words, the same pattern of electronegativity effects observed for **1**[15,16,32,33] is expected for **3**. An alternative description in qualitative MO terms of substituent-induced hyperconjugative charge-transfer effects in **3** is that the

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Table V. ^{13}C NMR[a] Parameters for the Bridgehead Carbon (C1) of System 3

X	C1 SCS, ppm[b]	Δ^1J_{CF}, Hz[c,d]	X	C1 SCS, ppm[b]	Δ^1J_{CF}, Hz[c,d]
NO_2	−0.38	4.27	I	−1.17	6.23
CN	−2.44	2.81	NH_2	0.62	1.22
CF_3	−0.96	1.58	$N(CH_3)_2$	1.66	0.36
COOH	−0.48	0.86	$NHCOCH_3$	−0.18	1.22
$CONH_2$	−0.25	0.98	CH_3	0.75	−0.49
$COOCH_3$	−0.34	0.61	$C(CH_3)_3$	1.64	−1.22
$COCH_3$	−0.12	1.10	C_6H_5	0.71	−0.12
OH	0.88	2.20	p-$NO_2C_6H_4$	0.11	0.61
OCH_3	1.06	1.95	CH_2OH	0.60	0.98
$OCOCH_3$	0.37	2.44	$Sn(CH_3)_3$	−0.08	3.17
F	0.77	4.40			
Cl	−0.01	4.40			
Br	−0.31	5.45			

[a] Solvent, $CDCl_3$. [b] Defined as the difference between the ^{13}C chemical shift of the substituted compound and that of the appropriate carbon in the parent hydrocarbon (X = H. C1, 92.45 ppm ($CDCl_3$) relative to Me_4Si). Negative sign denotes shielding. Accurate to ±0.1 ppm. [c] $\Delta^1J_{CF} = {}^1J_{CF}$(substituted compound) − ${}^1J_{CF}$(parent, X = H). ${}^1J_{CF}$(X = H) = 183.47 Hz ($CDCl_3$). [d] Accurate to ±0.6 Hz.

Table VI. Calculated Residual Contributions[a,b] to ^{19}F SCS (ppm) of System 3

X	residual contributions			
	c-C_6H_{12}	$CDCl_3$	DMF	$(CF_3)_2CHOH$
NO_2	−3.53	−3.15	−2.94	−2.00
CN	−2.46	−2.31	−2.15	−1.98
CF_3	−3.25	−3.08	−2.83	−3.22
COOH	−2.87	−2.54	−2.20	−2.46
$CONH_2$		−2.10	−1.74	−1.59
$COOCH_3$	−2.61	−2.56	−2.27	−2.69
$COCH_3$	−2.09	−2.03	−1.85	−1.84
OH	−3.42	−3.28	−2.76	−3.26
OCH_3	−2.52	−2.34	−2.29	−2.34
$OCOCH_3$	−2.44	−2.38	−1.99	−2.47
F	−3.43	−3.23	−3.08	−3.10
Cl	−1.62	−1.44	−1.11	−1.27
Br	0.08	0.29	0.67	0.37
I	2.35	2.46	2.80	2.16
NH_2	−3.38	−3.27	−2.95	−0.15
$N(CH_3)_2$	−1.52	−1.80	−1.43	2.26
$NHCOCH_3$	−2.63	−2.68	−2.19	−2.59
$N{=}NCF_3$	−3.68	−3.43	−3.13	−2.73
CH_3	−2.77	−2.69	−2.69	−2.57
$C(CH_3)_3$	−0.46	−0.15	−0.35	0.12
CH_2OH	−2.63	−2.50	−2.32	−2.39
C_6H_5	−1.46	−1.29	−1.20	−1.07
p-$NO_2C_6H_4$	−1.46	−1.29	−1.20	−1.07
$Sn(CH_3)_3$	2.36	2.51	2.51	
D	−0.048	−0.046	−0.046	−0.042

[a] ^{19}F SCS (observed) − polar field contribution ($\rho_F\sigma_F$). [b] See Table III for polar field contributions.

pertinent orbital energy gap (ΔE) between σ_{CC} and σ_{CF}*, which largely governs the magnitude of hyperconjugation, is a sensitive function of substituent electronegativity (i.e., an inductive perturbation of E_{CC}[41]). Strong support for the likely importance of this hyperconjugative effect on the ^{19}F SCS of **3** emerges from recent suggestions that C–C hyperconjugation is the dominant factor stabilizing (delocalizing charge) the bridgehead parent 1-adamantyl cation.[42-44] However, it should be pointed out that a contrary viewpoint has been expressed, namely, that C–C hyperconjugation is only a significant stablizing factor of 1-adamantyl cations when p- or π-electron substituents are attached to C3.[7] This latter view suggests that canonical structure **9** is a possible contribution to the resonance hybrid of **3** (in MO terms, a π-resonance perturbation of E_{CC}[41]). This latter interaction should be manifested by a dependence of the ^{19}F SCS of **3** on σ_R^0.

Secondly, the relative ^{19}F chemical shifts of a series of polycyclic fluorides suggests that "back-lobe" orbital interactions between the bridgehead carbons attached to the substituent and the fluorine probe (homohyperconjugation or through-space effect) may be an important factor.[45] In valence bond terms, homohyperconjugation in **3** may be denoted by canonical structure **10**. An electronegativity dependence of the ^{19}F SCS of **3** due to this interaction can be envisaged which is identical with that forecast above for hyperconjugation. The possible importance of a homohyperconjugative contribution to the ^{19}F SCS of **3** is further suggested by the fact that 1,3-dehydroadamantane (**11**) is readily synthesized from 1,3-dihaloadamantanes.[46] In addition, there is evidence for 1,3-bridging interactions being significant in various cationic processes.[47,48] On the other hand, it should be mentioned that homohyperconjugation in adamantyl systems, once in favor as a mechanism for delocalizing charge in the bridgehead cation,[49] but no longer,[43] is suggested to be unlikely from the result of MO calculations.[42,50] It is noteworthy that a recent X-ray structure analysis of the 3,5,7-trimethyl-1-adamantyl cation appears to support the importance of C–C hyperconjugation but not homohyperconjugation.[51] Unfortunately, no totally unambiguous operational distinction can be drawn between the hyperconjugative and homohyperconjugative mechanisms for stabilizing 1-adamantyl cations. However, the substantial shift difference (~20 ppm) between the ^{19}F chemical shifts of 1-fluoroadamantane (**3**, X = H,; footnote *c* to Table I) and 1-fluorobicyclo[2.2.2]octane (**1**, X = H; see footnote *c* to Table I in ref 15) may well be a manifestation of a significant homohyperconjugative effect in the former (canonical structure **10**, X = H) but not the latter system. The considerable internuclear distance

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Table VII. Synthetic Methods, Yields, Physical Properties, and Elemental Analyses of 3-Substituted Adamant-1-yl Fluorides (3)[a]

3, X =	precursor[b]	method	yield (%)	mp or bp, °C
H	1-AdOH	$DAST/CH_2Cl_2$[70]	92	249–251.5 (lit.[22] 225)
CH_3	1,3-CH_3AdOH	SF_4[67,68]	50	105–106
$C(CH_3)_3$	1,3-$(CH_3)_3$CAdOH	SF_4[67,68]	88	105.5–107.5
C_6H_5	1,3-C_6H_5AdOH	$DAST/CH_2Cl_2$[70]	91	66–67.5
p-$NO_2C_6H_4$	3, X = X_6H_5	$(CH_3CO)_2O/HNO_3$	75	128–130
F	1,3-HOAdOH	SF_4[67,68]	40[c]	251.5–253.5 (lit.[22] 239)
Cl	1,3-ClAdOH	$DAST/CH_2Cl_2$[70]	54	175–177 (lit.[71] 177–178)
Br	3, X = COOH	$Br_2/HgO/CH_2Cl_2$[25]	81	135–136 (lit.[21] 136–137)
I	1,3-IAdOH	$DAST/CH_2Cl_2$[70]	54	49–50.5
CH_2OH	3, X = COOH	$H_3BS(CH_3)_2$	97	119–120
$COCH_3$	3, X = COOH	$CH_3Li/O(C_2H_5)_2/(CH_3)_3SiCl$[72]	73	60.5–61.5
$OCOCH_3$	3, X = $COCH_3$	m-$ClC_6H_4CO_3H/CH_2Cl_2$/4 days/25 °C	93	43.5–45
OH	3, X = $OCOCH_3$	Me_2SO/KOH/100 °C/30 min	94	244 (lit.[73] 182–185)
OCH_3	3, X = OH	$CH_3I/KH/THF$	92	80–85 (6.0 mmHg) n^{25}_D 1.6349
$CONH_2$	3, X = COOH	1. $SOCl_2$ (1.2 equiv)/50 °C/45 min; 2. NH_3	90	146.5–148
CN	3, X = $CONH_2$	$(CF_3CO)_2O$/pyridine/dioxane	86	195.5–196.5
NH_2	3, X = $CONH_2$	$OIC_6H_5/CH_3CN/HCOOH/H_2O$[74]	66	211–212.5
$NHCOCH_3$	3, X = NH_2	CH_3COCl/pyridine[75]	62	142–144
$N(CH_3)_2$	3, X = NH_2	$HCHO/H_2O/H_2/Pd$–C	70	70–75 (0.15 mmHg)
NO_2	3, X = NH_2	m-$ClC_6H_4CO_3H/CH_2Cl_2$[4]	74	187–192
D	3, X = Br	$(n$-$Bu)_3SnD$/AIBN	90	252–253
$Sn(CH_3)_3$	3, X = Br	$(CH_3)_3SnLi/THF$	50	65.5–68
$N{=}NCF_3$	3, X = NH_2	CF_3NO/CH_3OH[63]	80	23–27
CF_3	3, X = $N{=}NCF_3$	$h\nu/(CH_3)_3COH$/20 days[63]	35	*d*

[a] All new compounds in this table gave satisfactory C and H analyses. [b] Ad ≡ adamantane. [c] A mixture (1:1) of 3 (X = F) and 3 (X = Cl) was obtained. Separated by preparative VPC. [d] Distillation (90–100 °C/55 mmHg) afforded a pale-yellow liquid. VPC analysis indicated a mixture which was characterized by ^{13}C and ^{19}F NMR. Composition of mixture: 3 (X = CF_3) (~35%), 3 (X = $N{=}NCF_3$ (~50%), and 3 (X = OH) (~15%). A pure sample of 3 (X = CF_3) for ^{13}C and ^{19}F NMR measurements was obtained by preparative VPC. Elemental analyses not sought.

between the bridgehead carbon centers (2.5 Å) precludes this effect in system **1**. On the basis of hyperconjugation (σ_{CF}*–σ_{CC}; both systems have three antiperiplanar C–C bonds) and ionicity (see below), no major difference between the ^{19}F chemical shifts of these two parent systems is expected.

Thirdly, the ^{19}F SCS of **2**,[16] which display electronegativity contributions *opposite* in sign to those revealed for **1**, suggests the importance of either a through-space effect of a different nature (back-lobe interactions of σ* orbitals, i.e., no charge transfer)[16] or a through-two-bond effect which allows coupling of the C–F and C–X bonds. A possible mechanism for the latter is by σ-conjugative interactions.[52] However, it should be stressed that we do not understand the basis of the electronegativity phenomenon in **2**.

Fourthly, the ionicity of the C–F σ bond is an important factor governing the ^{19}F chemical shifts of alkyl fluorides.[38,45] On the basis of the Fermi contact term being the dominant determinant of changes in $^1J_{CF}$ values for a series of structually similar compounds,[53] the various $^1J_{CF}$ (Hz) values for the parent systems (X = H) of **1**, **2**, and **3** (**1**, $^1J_{CF}$ = 185.30 (CCl_4), 182.5 ($CDCl_3$), 176.3 (CF_3CO_2H); **2**, $^1J_{CF}$ = 210.32 (CCl_4), 207.6 ($CDCl_3$), 202.6 (CF_3CO_2H); **3** $^1J_{CF}$ = 186.22 (CCl_4), 183.47 ($CDCl_3$)) indicate that ionicity of the C–F σ bond is highly dependent on the HBD characteristics of the solvent (see above). Besides electrostatic field perturbations (see above) and possible structural deformations at the bridgehead carbon (C1), the ionicity contribution to the ^{19}F SCS of **3** may be influenced by hyperconjugative interactions involving the C–X bond (canonical structure **12**) where X is a very electronegative group (favorable σ_{CX}* energy level). This effect on the direction of the shift would be indistinguishable from the electronegativity-dependent hyperconjugative and homohyperconjugative interactions.

With these various factors in mind, it is clear that there is a distinct possibility that the residual contributions of **3** (Table VI) are composite quantites. Hence, a possible explanation for these parameters not paralleling substituent electronegativity may hinge on the fact that counteractive factors are important (hyperconjugation and/or homohyperconjugation effects vs. the opposing effect observed in **2**) and, moreover, their "mix" may vary with each substituent. Another possibility is that a systematic electronegativity trend is being obscured by substituent-induced structural factors. Whatever the reason, the signs of the various residual contributions to the ^{19}F SCS of **3** for most substituents (Table VI; except Br, I, and $C(CH_3)_3$) and, in particular, those for D which are *opposite* in sign to the $^2H/^1H$ isotopic shifts in **2**[32] but identical with **1**,[32] suggest the general dominance of the hyperconjugative and/or homohyperconjugative modes of transmission. The almost identical residual contributions observed for NO_2 and NH_2 in **3** for c-C_6H_{12}, $CDCl_3$, and DMF as solvents (Table VI; two groups with vastly different σ_F and σ_R values[37]), which is a result expected on the basis of their similar electronegativity[18,19] and which is observed for **1**,[15] strongly suggests that π-resonance effects in **3** (canonical structure **9**) are unimportant.

Finally, it is of interest to note that the pattern of σ-inductive or electronegativity effects for the weak polar field groups ($\sigma_F \approx 0$; D, CH_3, and $Sn(CH_3)_3$) on the ^{19}F SCS of **3** (Table VI) parallel the observed solvolytic rate decrease (D[42] and CH_3[7]) and increase ($Sn(CH_3)_3$[7]) induced by these substituents in 3-substituted 1-adamantyl bromides and 1-adamantyl toluenesulfonates. We believe a common electronic origin is implicated for both types of parameters, namely, inductive perturbation of C–C hyperconjugation and/or homohyperconjugation, i.e., for system **3**, a *decrease* and *increase* in the importance of canonical structure **8** (and/or **10**) for electronegative (CH_3 and D) and electropositive ($Sn(CH_3)_3$) substituents, respectively.

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Table VIII. ^{13}C NMR Chemical Shifts[a,b] of 3-Substituted (X) Adamant-1-yl Fluorides (3)

X	chemical shift, ppm							
	C1	C2	C3	C4,10	C5,7	C6	C8,9	others
H	92.44	42.81	31.53	35.93	31.53	35.93	42.81	
	(183.59)	(17.09)	(9.77)	(1.95)	(9.77)	(1.95)	(17.09)	
NO_2	92.10	45.47	86.06	39.60	31.04	33.98	41.06	
	(187.50)	(22.95)	(11.23)	(1.46)	(10.25)	(1.96)	(17.58)	
CN	90.02	44.47	33.57	38.66	30.28	34.11	41.26	123.17 (CN)
	(186.53)	(21.48)	(11.72)	(1.96)	(10.26)	(1.96)	(17.58)	(1.95)
CF_3	91.48	40.01	43.20	33.42	30.16	34.67	41.74	127.38 (CF_3)
	(185.05)	(21.00)	(10.75)	(1.95)	(9.77)	(1.95)	(17.57)	(2.44)
		(1.95)[c]	(25.88)[c]	(1.95)[c]				(280.27)[c]
COOH	91.96	43.39	44.73	37.34	30.80	34.74	41.78	182.46 (COOH)
	(184.32)	(20.75)	(10.38)	(1.83)	(9.77)	(1.83)	(17.70)	(2.44)
$CONH_2$	92.26	44.12	44.92	38.02	30.99	34.79	41.80	178.22 ($CONH_2$)
	(184.33)	(19.53)	(9.15)	(1.83)	(9.77)	(1.83)	(17.09)	(1.83)
$COOCH_3$	92.10	43.76	44.92	37.64	30.91	34.85	41.85	51.84 ($COOCH_3$)
								176.22 ($COOCH_3$)
	(184.32)	(20.14)	(10.37)	(1.83)	(9.77)	(1.83)	(17.70)	(1.83)
$COCH_3$	92.39	43.20	50.80	37.01	30.89	34.89	41.88	24.54 ($COCH_3$)
								211.28 ($COCH_3$)
	(184.33)	(19.53)	(9.16)	(1.84)	(10.38)	(2.44)	(17.09)	(1.83)
OH	93.32	50.44	71.01	43.78	31.41	34.43	41.39	
	(186.04)	(17.09)	(11.72)	(1.47)	(10.26)	(1.95)	(17.58)	
OCH_3	93.50	46.11	74.85	39.64	31.13	34.82	41.76	48.48 (OCH_3)
	(185.54)	(17.58)	(11.72)	(1.47)	(10.26)	(1.95)	(17.58)	
$OCOCH_3$	92.81	46.64	81.02	39.74	31.34	34.55	41.57	22.46 ($OCOCH_3$)
	(186.15)	(19.54)	(12.21)	(1.22)	(9.76)	(1.83)	(17.70)	170.05 ($OCOCH_3$)
F	93.21	48.09	93.21	41.24[d]	31.39	34.25	41.24[d]	
	(187.99)		(187.99)					
	(13.67)	(19.05)	(13.67)		(10.25)	(1.96)		
Cl	92.46	52.34	66.79	46.04	32.51	33.95	40.98	
	(187.98)	(19.53)	(11.72)	(1.45)	(9.76)	(2.44)	(18.09)	
Br	92.13	53.77	61.69	47.38	33.26	33.87	40.91	
	(188.97)	(20.01)	(11.72)	(1.46)	(9.77)	(1.96)	(17.58)	
I	93.31	56.71	42.66	50.32	34.01	33.94	41.00	
	(189.94)	(19.53)	(10.25)	(1.95)	(9.28)	(1.95)	(17.58)	
NH_2	93.06	51.21	51.34	44.65	31.34	34.60	41.52	
	(184.08)	(16.60)	(10.74)	(1.46)	(10.25)	(2.44)	(17.58)	
$N(CH_3)_2$	93.71	42.88	58.11	36.90	31.04	35.13	42.10	37.51 (CH_3)
	(184.08)	(17.58)	(10.26)	(1.95)	(10.25)	(1.96)	(17.57)	
$NHCOCH_3$	92.34	46.46	54.99	40.09	30.96	34.67	41.67	24.36 ($COCH_3$)
	(184.57)	(19.05)	(12.20)	(1.95)	(10.25)	(1.95)	(17.58)	169.63 ($COCH_3$)
CH_3	93.19	49.40	34.62	43.01	31.54	35.15	42.01	30.00 (CH_3)
	(183.10)	(16.11)	(9.27)	(1.95)	(10.26)	(1.95)	(17.09)	(1.46)
$C(CH_3)_3$	94.08	41.85	44.44	34.93	31.38	35.52	42.38	24.86 ($C(CH_3)_3$)
	(182.13)	(17.09)	(10.74)	(1.95)	(9.77)	(1.95)	(17.09)	34.72 ($C(CH_3)_3$)
CH_2OH	93.04	44.10	39.62	37.62	31.03	35.47	42.34	72.25 (CH_2OH)
	(183.10)	(17.58)	(9.28)	(1.96)	(9.77)	(1.96)	(17.58)	(0.97)
C_6H_5[e]	93.16	47.70	41.00	41.87	31.56	35.06	42.01	148.70 (i), 124.77 (o), 128.31 (m), 126.05 (p)
	(183.59)	(17.58)	(9.77)	(1.95)	(10.25)	(1.95)	(17.09)	
p-$NO_2C_6H_4$[e]	92.61	47.36	41.62	41.58	31.38	34.82	41.79	156.08(i), 125.96(o), 123.60(m), 146.29(p)
	(184.09)	(18.07)	(9.28)	(1.95)	(9.77)	(1.95)	(17.09)	(1.46)
$N{=}NCF_3$	92.56	52.39	89.17	38.40	31.42	34.13	41.20	120.44 (CF_3)
	(186.77)[c]	(19.53)[c]	(12.21)[c]	(1.47)[c]	(9.77)[c]	(2.44)[c]	(18.32)[c]	(273.44)[c]
$Sn(CH_3)_3$[f]	92.38	46.75	29.98	40.17	32.73	35.97	42.82	−12.89 ($Sn(CH_3)_3$)
	(186.52)	(16.11)	(5.37)	(1.96)	(8.30)	(1.95)	(17.58)	
	[n.o.]	[10.25]	[n.o.]	[10.75]	[55.17]	[3.42]	[6.35]	[303.71]
								[290.53]

[a] Chemical shifts for $CDCl_3$ solution relative to Me_4Si. Accurate to ±0.04 ppm. Positive shifts indicate decreased shielding. [b] ^{13}C–^{19}F coupling constants (in hertz) are given in parentheses. [c] ^{13}C–CF_3 coupling constants. [d] Six-line pattern characteristic of the X part of an ABX spin system (see ref 22). [e] The aromatic carbons are designated ipso (i), ortho (o), meta (m), and para (p) with respect to the adamantyl substituent. [f] ^{13}C–$^{117,119}Sn$ coupling constants (in hertz) are given in brackets.

Experimental Section

General. Melting and boiling points are uncorrected. Liquid samples were purified by distillation in a Kugelrohr apparatus (Bucki: GKR-50). Hence, the boiling points quoted pertain to the glass oven temperature of the latter equipment. Analytical vapor-phase chromatographic (VPC) analyses were performed on a Varian 1740 gas chromatograph using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W. Preparative VPC were carried out on a Varian 920 gas chromatograph.

Compounds. Adamantane, 1-bromoadamantane (1-AdBr), and 1-adamantanecarboxylic acid (1-AdCOOH) were purchased from the Aldrich Chemical Company, Inc. 1-AdBr and 1-AdCOOH were also prepared from adamantane and 1-AdBr, respectively, following literature procedures.[54,55] An improved Koch–Haaf reaction as described by Chapman et al.[56] was employed for the preparation of AdCOOH. 1-Methyl-[57] and 1-*tert*-butyladamantane[30] (1-$AdCH_3$[57] and 1-$AdC(CH_3)_3$,[30] respectively) were synthesized from 1-AdBr and 1-AdCOOH following procedures employed for introducing CH_3 and $C(CH_3)_3$ groups at the

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bridgehead of the bicyclo[2.2.2]octane (BCO) ring system.[23,58] Literature procedures were followed in the preparation of 1-adamantanol (1-AdOH),[55] 1-phenyladamantane (1-AdC_6H_5),[55] and several 1,3-disubstituted adamantane derivatives (1,3-XAdY: X = Y = Br;[59] X = Y = OH;[60] X = Br, Y = COOH;[3a,54] X = OH, Y = COOH;[3a] X = Cl, Y = OH;[60] X = CH_3, Y = Br;[61,62] X = CH_3, Y = OH;[55,62] X = $C(CH_3)_3$, Y = Br;[29a,61] X = $C(CH_3)_3$, Y = OH[55] (mp 131–132 °C); X = C_6H_5, Y = OH.[29a] Treatment of **5** (X = NH_2)[10] with trifluoronitrosomethane as described in the literature[63] afforded **5** (X = N=NCF_3) almost quantitatively as a yellow solid after sublimation (mp 93.5–96.5 °C). Diethylaminosulfur trifluoride (DAST reagent) was prepared in the manner outlined by Kirsanov and co-workers.[64]

7-Methylidenebicyclo[3.3.1]nonan-3-one (4). 3-Bromoadamantane-1-carboxylic acid[3a,54] (3.0 g, 0.012 mol) was converted into 1-acetyl-3-bromoadamantane (mp 62–64 °C) and then 1-acetoxy-3-bromoadamantane (mp 45.5–46 °C; lit.[65] mp 45–46 °C) according to methods outlined by Adcock and Abeywickrema[23] for the preparation of **1** (X = $OCOCH_3$) from the corresponding carboxylic acid **1** (X = COOH).

A mixture of 1-acetoxy-3-bromoadamantane (4.6 g, 0.017 mol), Me_2SO (30 mL), and potassium hydroxide (2.8 g of 85% pellets; 0.05 mol) was heated under reflux for 16 h. A standard workup followed by sublimation afforded **4** as a colorless solid (2.1 g; 83%). Recrystallization from hexane gave colorless plates, mp 160–162.5 °C (lit.[29a] mp 163–166 °C). ^{13}C NMR ($CDCl_3$, relative Me_4Si): δ 30.82 (C1,5), 41.42 (C2,4), 210.83 (C3), 47.34 (C6,8), 141.70 (C7), 32.06 (C9), 114.58 (C10).

3-Iodoadamantan-1-ol (13). This compound was first obtained inadvertently from an attempt to prepare the iodo derivative of **3** (X = I) from the corresponding alcohol (**3**, X = OH; see Table VII). By use of the procedure of Molle and co-workers[27] for converting 1-adamantanol to 1-iodoadamantane, freshly distilled hydriodic acid (1.4 mL of 55% w/w solution) was added to a solution of 3-fluoroadamantan-1-ol (**3**, X = H; 0.5 g, 2.94 mmol) in hexane (0.5 mL) and benzene (2 mL), and the mixture was stirred under nitrogen for 36 h. The mixture was then shaken with additional benzene (5 mL) before removal of the aqueous phase. The benzene layer was then washed successively with water, aqueous sodium thiosulfate, and sodium bicarbonate solutions and then dried, and finally the solvent was removed. A VPC and ^{13}C NMR analysis of the crude product indicated a mixture of 3-iodoadamantan-1-ol (**13**; ~90%) and the open ketone (**4**; ~10%). Sublimation of the crude product followed by recrystallization (2 × 1) from hexane gave the iodo alcohol **13** as colorless prisms, mp 109–111 °C. ^{13}C NMR ($CDCl_3$, relative Me_4Si): δ 69.93 (C1), 59.66 (C2), 45.40 (C3), 50.58 (C4,10), 34.06 (C5,7), 33.63 (C6), 43.36 (C8,9).

The open ketone (**4**; 1.0 g, 6.7 mmol) was treated with hydriodic acid in the manner outlined above. After stirring for 1 day, a VPC analysis indicated a mixture of **13** and **4** (~7:3, respectively). After a further 2 days, the composition of the reaction mixture was ca. 1:1 of **13** and **4**. After a standard workup and sublimation, the mixture was obtained as a white solid (1.15 g). No attempt was made to separate the reaction mixture.

Preparation of 3-Substituted Adamant-1-yl Fluorides (3). By use of the esterification procedure of Clinton et al.,[66] a solution of 3-hydroxyadamantane-1-carboxylic acid[3a] (6.6 g; 0.034 mol) in absolute methanol (4.5 g) and 1,2-dichloroethane (20 mL) containing concentrated sulfuric acid (0.5 mL) was refluxed with stirring for 20 h. A standard workup followed by distillation afforded the methyl ester as a viscous colorless oil (6.8 g; 96%): bp 90–100 °C (0.4 mm).

The methyl ester (11.3 g; 0.054 mol) was treated with sulfur tetrafluoride[67] (15 g; 0.139 mol) in the manner previously outlined for the preparation of 1-fluoro-4-methyl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene.[68] A workup following the usual precautions, followed by distillation, afforded methyl 3-fluoroadamantane-1-carboxylate (**3**, X = $COOCH_3$) as a colorless viscous oil (10.8 g; 94%): bp 100–105 °C (1.8–2 mm). A sample was purified by preparative gas chromatography to give a colorless solid, mp 31–33 °C (lit.[3a] mp 32–34 °C).

The fluoro ester **3** (X = $COOCH_3$; 4.8 g, 0.023 mol) was treated with potassium hydroxide (1.6 g of 85% pellets; 0.024 mol) in 50% aqueous ethanol (17 mL) in the manner previously outlined for the corresponding BCO derivative (**1**, X = $COOCH_3$).[33] A standard workup afforded a white solid (3.9 g; 87%) which was recrystallized from ethanol, mp 152–154 °C (lit.[3a] mp 152 °C).

Summarized details of the synthetic methods, yields, physical properties, and elemental analyses of the other derivatives of **3** are listed in Table VII. Unless otherwise indicated, the references for the various functionalization methods may be found in previous papers describing the syntheses of **1**,[23] **2**,[16] and other BCO systems.[13,14,17] All the fluoro derivatives (**3**), including the main precursor ester (**3**, X = $COOCH_3$) and acid (**3**, X = COOH), were unambiguously characterized by ^{13}C NMR (Table VIII). Assignments for these compounds followed unequivocally from the characteristic ^{13}C–^{19}F coupling constants in the adamantane skeletal framework.[21,22,53] Standard assignment procedures such as chemical shift, intensity, and substituent-effect[69] considerations played a minor role.

NMR Spectra. The broad-band proton-decoupled ^{13}C NMR spectra were recorded in the pulse Fourier transform mode on a JEOL FX-90Q spectrometer operating at 22.53 MHz. The probe temperature was 295 ± 2 K. The spectra were obtained on $CDCl_3$ solutions (ca. 0.5 M) in 5-mm tubes with Me_4Si as an internal reference (spectral widths 2000/4000/5000 Hz, 16K/8K data points, minimum digital resolution of 0.25/0.5/0.6 Hz).

The ^{19}F NMR spectra were obtained under proton-decoupled conditions in the pulse Fourier transform mode with a JEOL FX-90Q spectrometer operating at 84.26 MHz. Spectral widths of 2000 and 1000 Hz, respectively, were used, and the data were collected into 16K/8K data points giving a digital resolution of 0.24 and 0.12 Hz, respectively. Each sample consisted of the substituted compound (**3**; <1 mg) and the parent system (**3**, X = H; <1 mg) in 0.5 mL of the appropriate solvent.

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