(CDCl$_3$) δ 0.79 (6 H, d, $J_{\text{H-H}}$ = 5.5 Hz, CH$_3$), 1.15–1.73 (13 H, m, CH$_2$CH$_2$, CH). Anal. (C$_{11}$H$_{19}$F) C, H.

1-*tert*-Butyl-4-fluorobicyclo[2.2.2]octane (1, X = C(CH$_3$)$_3$). 4-Methoxybicyclo[2.2.2]octane-1-carboxylic acid (6) was converted to 1-(α-chloroisopropyl)-4-methoxybicyclo[2.2.2]octane by following the procedures indicated above for the preparation of 1 (X = C(CH$_3$)$_2$Cl). Treatment of the chloride (1.3 g, 0.006 mol) with trimethylaluminum as previously described for the synthesis of 1-*tert*-butyl-4-(*p*-fluorophenyl)bicyclo[2.2.2]octane[22] afforded 1-*tert*-butyl-4-methoxybicyclo[2.2.21octane as a colorless oil (0.90 g, 77%) after Kugelrohr distillation. The latter compound (0.40 g, 0.002 mol) and acetyl fluoride (0.5 g, 0.008 mol) were treated at −10 °C with BF$_3$–H$_3$PO$_4$[15] (10 drops) and then stirred at 0 °C while being carefully monitored by GLC analyses. As soon as the reaction was complete, the mixture was quenched with ice/water. A workup in the standard manner followed by Kugelrohr distillation afforded 1 (X = C(CH$_3$)$_3$) as a colorless oil: 0.25 g (68%); bp 55–60 °C (2.0 mm); ^{1}H NMR (CDCl$_3$) δ 0.79 (9 H, s, CH$_3$), 1.45–2.18 (12 H, m, CH$_2$CH$_2$). The sample was found to be contaminated with 1-acetoxy-4-*tert*-butylbicyclo[2.2.2]octane (ca. 5%). No attempt was made to purify the compound.

1-Fluoro-4-phenylbicyclo[2.2.2]octane (1, X = C$_6$H$_5$). This compound was prepared from 1-hydroxy-4-phenylbicyclo[2.2.2]octane[4] as previously described.[14] Sublimation afforded a white solid, mp 131–132.5 °C (lit.[34] mp 132–133 °C).

1-Fluorobicyclo[2.2.2]octane (1, X = H). 1-Methoxybicyclo[2.2.2]oct-5-en-2-one was prepared as described by Evans et al.[41] The ketone was reduced by the modified Wolff–Kishner procedure[7] to give 1-methoxybicyclo[2.2.2]oct-2-ene: bp 84–86 °C (25 mm); 70%. Catalytic hydrogenation (5% Pd/C, 45 psi of H$_2$) of an ethanolic solution of the olefin afforded 1-methoxybicyclo[2.2.2]octane as an oil: 95% yield; bp 65–66 °C (10 mm) [lit.[16] bp 185–190 °C (760 mm)]. This latter compound was converted to 1 (X = H) by following a procedure described by Suzuki and Morita.[15] Sublimation afforded a white solid: 62% yield; mp 148–150 °C (lit.[15] mp 152 °C).

Registry No. 1 (X = COOCH$_3$), 78385-85-0; 1 (X = COOH), 78385-84-9; 1 (X = CONH$_2$), 81687-77-6; 1 (X = COCl), 81687-78-7; 1 (X = CN), 78385-80-5; 1 (X = NH$_2$), 78385-91-8; 1 (X = NCO), 81687-79-8; 1 (X = NHCOCH$_3$), 78385-93-0; 1 (X = N(CH$_3$)$_2$), 78385-92-9; 1 (X = N(CH$_3$)$_3^+$I$^-$), 81687-80-1; 1 (X = N(CH$_3$)$_3^+$Cl$^-$), 81687-81-2; 1 (X = NO$_2$), 32038-89-4; 1 (X = CHO), 78385-82-7; 1 (X = COCH$_3$), 78385-83-8; 1 (X = OCOCH$_3$), 22947-60-0; 1 (X = OH), 22947-61-1; 1 (X = OCH$_3$), 78385-90-7; 1 (X = F), 20277-40-1; 1 (X = Cl), 78385-86-1; 1 (X = Br), 78385-87-2; 1 (X = I), 78385-89-4; 1 (X = Sn(CH$_3$)$_3$), 78385-88-3; 1 (X = CH$_3$), 20417-60-1; 1 (X = CH$_2$CH$_3$), 81687-82-3; 1 (X = CH(CH$_3$)$_2$), 81687-83-4; 1 (X = C(CH$_3$)$_2$OH), 81687-84-5; 1 (X = C(CH$_3$)$_2$Cl), 81687-85-6; 1 (X = C(CH$_3$)$_3$), 81687-86-7; 1 (X = Ph), 22947-58-6; 1 (X = H), 20277-22-9; 2, 72653-14-6; 3, 72653-21-5; 4 (R = Me), 81687-87-8; 4 (R = Et), 81687-88-9; 5, 81687-89-0; 6, 773-34-2; 7, 81687-90-3; 8, 81687-91-4; 9, 23062-53-5; 10, 81687-92-5; 1-(α-chloroisopropyl)-4-methoxybicyclo[2.2.2]octane, 81687-93-6; 1-*tert*-butyl-4-methoxybicyclo[2.2.2]octane, 81687-94-7; 1-acetoxy-4-*tert*-butylbicyclo[2.2.2]octane, 81687-95-8; 1-methoxybicyclo[2.2.2]oct-5-en-2-one, 38213-08-0; 1-methoxybicyclo[2.2.2]oct-2-ene, 25489-02-5; 1-methoxybicyclo[2.2.2]octane, 7697-14-5.

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Substituent Effects in the Bicyclo[2.2.2]octane Ring System. A Carbon-13 and Fluorine-19 Nuclear Magnetic Resonance Study of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides[1]

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^{19}F and ^{13}C NMR spectra have been recorded for a large number of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (1) in which the substituents cover a wide range of electronic effects. Correlations of the ^{19}F substituent chemical shifts (SCS) for several solvents with substituent constants (σ_{I}, ι, and $\sigma_{\text{R}}{}^0$) indicate that these NMR substituent-probe parameters are predominantly manifestations of electric field and electronegativity effects. Moreover, it is also revealed that whereas the former effects are solvent dependent, the latter are essentially independent of the nature of the medium. In addition, the statistical analysis indicates that resonance effects involving orbitals of π symmetry appear not to be transmitted through the bicyclo[2.2.2]octyl skeletal framework. Compelling support for the validity of the overall statistical dissection is provided by an independent measure of the polar susceptibility parameters (ρ_{I} values) for each solvent. The coefficient (A) of the Buckingham equation for linear electric field effects on C$_{sp^3}$–F bonds is calculated for c-C$_6$H$_{12}$ as the solvent. A good correlation of solvent-induced changes (CDCl$_3$ to CF$_3$CO$_2$H) in the ^{19}F SCS vs. similar differential changes in the corresponding ^{13}C SCS for C1–F confirms the solvent independence of the electronegativity effect. The origin of this latter effect is considered, and some of the possibilities are probed by correlative analysis of the substituent-induced changes in the one-bond carbon–fluorine spin–spin coupling constants (Δ^1J_{CF}). The polar effects of alkyl groups are alluded to in the light of the new results for system 1.

During the course of an attempt to delineate dipolar electrostatic field contributions to the ^{19}F substituent chemical shifts (SCS) of para-substituted fluorobenzenes, Anderson and Stock[2] reported ^{19}F SCS for a limited number of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (1, X = F and COOEt). Although subsequent studies[3-6] have shown that the investigation was inappropriate for the objective in question, the results obtained for system 1 are of intrinsic interest since the ^{19}F SCS for *fluorine* and *ethoxycarbonyl* were found to be in the *opposite* direction

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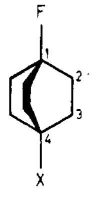

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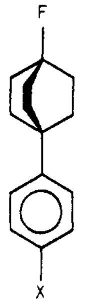

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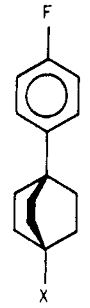

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(reverse substituent dependence) to expectations based on the electron density parameter dominating the decisive paramagnetic contribution to ^{19}F chemical shifts.[7] A consideration of several factors led Anderson and Stock[2] to suggest that the "anomalous" ^{19}F SCS are probably a consequence of substituent-induced structural deformation of the somewhat flexible bicyclo[2.2.2]octane skeletal framework.

Subsequently, we presented a limited study[8] of 1-fluoro-4-(para-substituted phenyl)bicyclo[2.2.2]octanes (**2**) which demonstrated unambiguously that the bona fide response of ^{19}F chemical shifts of system **1** to intramolecular electrostatic field effects is clearly in the *reverse* direction to current preconceptions. However, crude estimates of the likely electric field contributions to the ^{19}F SCS of system **1** for X = F and COOEt suggested that other factors must also contribute importantly to the overall screening term.[8] Two possibilities were tentatively mentioned: (i) substituent-induced structural effects; (ii) substituent-induced perturbation of hyperconjugative transfer of charge involving the bridging bonds of the bicyclo[2.2.2]octane ring system.

More recently, we reported ^{19}F SCS for a new model system (benzobicyclo[2.2.2]octen-1-yl fluoride)[9] which, together with a further study of system **2**,[10] revealed that *reverse* substituent behavior of ^{19}F chemical shifts in aliphatic fluorides is a manifestation of dominant electron-density changes in the CF σ bond. Hence, in this light we have thought it desirable and timely to examine a series of system **1** which covers a wide range of substituent electronic effects. Besides providing insight into the factors underlying the effects of substituents on the ^{19}F chemical shifts of system **1**, we were hopeful that such a study should be further revealing concerning conjugative electronic transmission mechanisms in 1,4-disubstituted bicyclo[2.2.2]octane derivatives[11–14] as well as polar substituent phenomena in general.[15] Herein we report the results of our study.

Results and Discussion

The ^{19}F SCS of system **1** measured in a number of solvents are listed in Table I. A cursory examination of these data reveals that all the SCS are *negative* (*upfield* shifts) except for $SnMe_3$, which is *positive* (*downfield* shift). Furthermore, except for the nonpolar alkyl substituents, the ^{19}F SCS are markedly enhanced in trifluoroacetic acid as the solvent. We have explored the relationship between these ^{19}F SCS and various substituent parameters utilizing a standard statistical package similar to that recently employed in correlative analyses by Reynolds et al.[15–17] The substituent parameters chosen for investigation are those which characterize electric field (σ_I values)[15,16], electronegativity ($\Delta\iota = \iota_X - \iota_H$),[15,16,18] and π-resonance effects ($\sigma_R{}^0$ values).[19,20] Significant polar field contributions to the ^{19}F SCS of system **1** have been clearly implicated from our studies of system **2**.[8,10] In order to avoid likely solvent discrepancies in the known σ_I values of substituents[19–23] and, in addition, to avoid using statistically refined values which may not be strictly applicable to model systems where the substituent is directly attached to an sp^3-hybridized carbon atom, we have employed new σ_I scales for each solvent. These were derived from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (**3**)[5] which have all been remeasured under conditions of high dilution in the appropriate solvent. Since solvent-effect studies[24] have shown that Br is a "chemically inert" substituent, scaling was achieved by setting σ_I for this substituent equal to 0.44[20] for each solvent. The new σ_I scales are listed in Table II. Although we have not examined the ^{19}F chemical shifts of system **1** in CCl_4, CH_2Cl_2, and CH_3OH, we also list the appropriate σ_I values determined from system **3** in these solvents for the sake of completeness. Polar inductive parameters for the nonpolar substituents (alkyl groups and $Sn(CH_3)_3$), which are all zero,[25,26] are not listed in Table II.

The likelihood of an electronegativity contribution to the ^{19}F SCS of **1** is revealed by the observation that $Cr(CO)_3$ π complexation of system **2** (X = H) effects a significantly larger perturbation of the ^{19}F chemical shift (−1.44 ppm (CCl_4))[27] than the introduction of a *p*-NO_2 group (**2**, X = NO_2; −0.75 ppm (c-C_6H_{12})).[10] Purely on the basis of the σ_I values of $C_6H_5{\cdot}Cr(CO)_3$ and *p*-$NO_2C_6H_4$ derived from the ^{19}F SCS of system **3** (0.35[27] and 0.39 (see Table II), respectively), similar perturbations of the ^{19}F chemical shift of system **2** was expected. It is noteworthy, however, that $Cr(CO)_3$ complexation is known to enhance the effective electronegativity of arene ring carbon atoms.[28] Following the recent work of Reynolds,[15,16] we have employed $\Delta\iota$ ($\iota_X - \iota_H$)[18] to characterize substituent electro-

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Table I. ^{19}F Substituent Chemical Shifts (SCS)[a-c] of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides (1)

	SCS			
X	c-C_6H_{12}	$CDCl_3$	DMF	CF_3CO_2H
NO_2	-8.39	-9.89	-9.53	-17.45
CN	-4.15	-5.40	-4.79	-12.55
CF_3	-5.08	-6.05	-5.98	-10.12
COOH	-4.75	-5.68	-4.93	-10.57
$CONH_2$		-6.09	-4.87	-13.80
$COOCH_3$	-4.38 (-4.47)[d]	-5.29	-5.05	-10.19
$COCH_3$	-4.15	-5.11	-4.52	-10.56
CHO	-3.09	-4.10	-3.50	-9.92
OH[e,f]	-8.06	-9.24	-7.47	-14.96
OCH_3[g]	-6.40	-7.62	-7.15	-14.28
$OCOCH_3$	-6.08	-7.30	-7.11	-13.15
F[h]	-8.90 (-9.23)[d]	-10.32	-10.19	-16.13
Cl	-6.97	-8.14	-8.07	-12.66
Br[i]	-5.94	-7.07	-6.98	-11.50
I	-3.35	-4.29	-4.12	-8.22
NH_2	-6.60	-7.51	-6.28	
$N(CH_3)_2$	-4.66	-5.84	-5.31	
$NHCOCH_3$	-4.66	-5.82	-4.78	-14.86
$^+NH_3$				-17.97
$^+NH(CH_3)_2$				-19.09
$^+N(CH_3)_3$		-11.14[j]	-9.34[j]	-20.14[k]
CH_3	-3.81	-3.92	-3.90	-4.08
C_2H_5	-2.79	-2.91	-2.93	-2.97
i-C_3H_7	-2.68	-2.79	-2.82	-2.72
t-C_4H_9	-3.11	-3.20	-3.23	-3.04
C_6H_5	-3.37	-3.94	-3.68	-5.29
p-$NO_2C_6H_4$	-4.12	-4.78	-4.15	-8.10
$Sn(CH_3)_3$[l]	3.67	3.83	3.94	

[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 implies shielding. [b] Accurate to ±0.01 ppm. [c] X = H (relative to internal $FCCl_3$): -150.12 (c-C_6H_{12}), -148.38 ($CDCl_3$), -146.59 ppm (DMF). [d] Solvent CCl_4. Taken from ref 2. [e] SCS (ppm): -7.36 (THF), -6.61 (HMPA). [f] O^-K^+, SCS (ppm): -4.33 (THF), -2.73 (HMPA). [g] SCS (ppm): -6.77 (THF), -6.87 (HMPA). [h] J_{FF} = 19.0 Hz, J_{CF} = 189.2 Hz. Obtained from ^{13}C satellites in the $^{19}F\{^1H\}$ spectrum ($CDCl_3$). [i] SCS (ppm): -6.66 (C_2H_5OH), -6.93 (CH_3CO_2H), -8.53 (CF_3CH_2OH), -9.71 ($(CF_3)_2CHOH$), -6.46 (THF), -6.63 (HMPA). [j] Counterion I^-. [k] Counterion Cl^-. [l] Average $J_{^{117,119}Sn-^{19}F}$ values (Hz): 67.9 (c-C_6H_{12}), 72.6 ($CDCl_3$), 71.3 (DMF).

Table II. Polar Substituent Parameters (σ_I Values) Derived from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (3)[a]

	σ_I						
X	c-C_6H_{12}[b]	CCl_4[b]	$CDCl_3$[c]	CH_2Cl_2[d]	DMF[e]	CH_3OH[f]	CF_3CO_2H[g]
NO_2	0.66	0.66	0.65	0.64	0.60	0.62	0.74
CN	0.59	0.58	0.56	0.53	0.48	0.54	0.71
CF_3	0.44	0.44	0.40	0.40	0.42	0.42	0.37
COOH	0.23	0.29	0.32	0.30	0.21	0.25	0.44
$CONH_2$		0.29	0.33	0.30	0.19	0.29	0.69
$CON(CH_3)_2$	0.19		0.25	0.23	0.19	0.28	
$COOC_2H_5$	0.22	0.23	0.26	0.25	0.26	0.29	0.40
$COCH_3$	0.28	0.29	0.31	0.28	0.25	0.30	0.48
CHO	0.36	0.36	0.37	0.35	0.31	0.35	0.52
OH[h-j]	0.23	0.23	0.29	0.26	0.14	0.25	0.48
OCH_3[h,i,k]	0.19	0.21	0.26	0.24	0.22	0.30	0.50
$OCOCH_3$	0.29	0.29	0.33	0.33	0.34	0.37	0.45
F	0.39	0.39	0.42	0.41	0.40	0.41	0.52
Cl	0.43	0.43	0.43	0.43	0.43	0.43	0.44
Br	0.44	0.44	0.44	0.44	0.44	0.44	0.44
I	0.42	0.43	0.42	0.42	0.40	0.41	0.40
NH_2	0.12	0.13	0.19	0.18	0.08	0.26	
$N(CH_3)_2$	0.10	0.12	0.18	0.16	0.12	0.28	
$NHCOCH_3$	0.21	0.22	0.28	0.26	0.18	0.26	0.72
$^+NH_3$							0.87
$^+NH(CH_3)_2$							1.03
$^+N(CH_3)_3$			0.88[l]	0.92[l]	0.64[l]	0.78[l]	1.11[m]
C_6H_5[n-p]	0.15	0.16	0.17	0.17	0.16	0.17	0.18
p-$NO_2C_6H_4$[n,o,q]	0.39	0.39	0.33	0.31	0.26	0.28	0.34

[a] ^{19}F SCS (ppm) = $\rho_I\sigma_I$ (see ref 5). Polar susceptibility parameters (ρ_I values) were determined by setting σ_I for *bromine* equal to 0.44 for each solvent. [b] $\rho_I = 2.70$. [c] $\rho_I = 2.57$. [d] $\rho_I = 2.25$. [e] $\rho_I = 1.61$. [f] $\rho_I = 1.91$. [g] $\rho_I = 2.57$. [h] $\rho_I = 1.84$ (THF). [i] $\rho_I = 1.18$ (HMPA). [j] $\sigma_I(OH)$ = 0.13 (THF), 0.07 (HMPA); $\sigma_I(O^-K^+)$ = -0.33 (THF), -0.73 (HMPA). [k] $\sigma_I(OCH_3)$ = 0.21 (THF), 0.23 (HMPA). [l] Counterion, I^-. [m] Counterion Cl^-. [n] $\rho_I = 1.96$ (C_6H_6). [o] $\rho_I = 2.02$ (CH_3CO_2H). [p] $\sigma_I(C_6H_5)$ = 0.17 (C_6H_6), 0.16 (HMPA), 0.17 (CH_3CO_2H). [q] σ_I(*p*-$NO_2C_6H_4$) = 0.45 (C_6H_6), 0.26 (HMPA), 0.34 (CH_3CO_2H).

negativity (χ) in the correlative analyses.

Although no substituent parameter scale is available which specifically characterizes possible resonance effects in aliphatic substrates, we have employed σ_R^0 values[19,20,29,30] which are empirical measures of the resonance effects of substituents directly attached to a benzene ring system. Since the conjugative effect of a substituent is a function of the reference substrate, the use of σ_R^0 for aliphatic systems can only be justified if the *relative* magnitude of substituent resonance effects is independent of the nature of the substrate. This is probably the case for a basis set of substituents which are either strongly donor or acceptor dominant. It should be noted that since the nature of the CF bond of alkyl fluorides is similar to that of aryl fluorides[31] and since the ^{19}F chemical shifts of the latter systems are well-known to be very sensitive to substituent-induced π-electron perturbations,[32] the fluorine nucleus seems a most appropriate probe to test for possible resonance effects of π symmetry in 1,4-disubstituted bicyclo-[2.2.2]octanes.[14,33]

The results of the linear multiparameter regression analysis utilizing eq 1 are set in Table III. Since the

$$^{19}\text{F SCS} = \rho_I\sigma_I + \rho_\iota\Delta\iota + \rho_R\sigma_R^0 + C \qquad (1)$$

available σ_R^0 values are not applicable to "chemically active" solvents such as CF_3CO_2H, correlations utilizing all three substituent parameters were restricted to the data for c-C_6H_{12}, $CDCl_3$, and DMF. It can be seen that all the correlations listed (Table III) are significant at the 99.99% confidence level (CL). However, correlation of the data for *all* substituents ($n = 23$) against the three substituent parameters (σ_I, $\Delta\iota$, and σ_R^0) reveals only an approximate linear trend ($r = 0.89$–0.93) in each of the three solvents, indicating that approximately 78–86% of the variations are accounted for. Examination of the calculated SCS showed that a number of groups (CN, CF_3, Cl, and alkyl substituents) deviate considerably from the experimental values. It is possible that the group electronegativities of these substituents may be inadequately defined by their respective ι values and, hence, responsible for the deviations. Interestingly, it has been suggested that the group electronegativity of CF_3 appears to be overestimated by its ι value.[34] Furthermore, a more recent empirical group electronegativity scale[35] based on olefinic geminal ^{1}H NMR coupling constants ($^2J_{HH}$) indicates that ι values for CN and Cl relative to F may be incorrect; i.e., $\Delta\iota$ values for CN and Cl over- and underestimate, respectively, their electronegativities. Whatever the reason, the omission of the aforementioned seven substituents from the data set leads to an improvement of the precision of fit of the correlations ($n = 16$).[36] Note, however, that the CL associated with the $\rho_R\sigma_R^0$ term remains low, suggesting that the depen-

Table III. Results of Correlative Analysis[a] of ^{19}F SCS of System 1 with Substituent Parameters

solvent	independent variables	ρ_I[b]	ρ_ι[b]	ρ_R[b]	c[c]	SE[d]	r[e]	r^2	F[f,h]	F_I[f]	F_ι[f]	F_R[f]	n[g]
c-C_6H_{12}	σ_I, $\Delta\iota$, σ_R^0	−3.84 (±2.00)	−5.35 (±1.25)	1.76 (±1.85)	−1.05	1.29	0.885	0.784	22.95	3.70[k]	18.49[i]	0.91[m]	23[n]
$DCCl_3$	σ_I, $\Delta\iota$, σ_R^0	−6.83 (±1.70)	−5.66 (±1.06)	1.50 (±1.59)	−1.01	1.19	0.927	0.860	38.86	16.21[i]	28.66[h]	0.89[m]	23[n]
DMF	σ_I, $\Delta\iota$, σ_R^0	−7.28 (±1.81)	−5.23 (±1.07)	1.63 (±1.70)	−0.93	1.24	0.913	0.834	31.74	16.23[i]	23.85[h]	0.92[m]	23[n]
c-C_6H_{12}	σ_I, $\Delta\iota$, σ_R^0	−7.39 (±2.01)	−6.09 (±0.98)	1.48 (±1.52)	0.41	0.94	0.958	0.918	44.86	13.46[j]	38.65[h]	0.94[m]	16[n,o]
$DCCl_3$	σ_I, $\Delta\iota$, σ_R^0	−10.52 (±2.13)	−6.11 (±0.98)	1.71 (±1.40)	0.69	0.89	0.970	0.941	63.52	24.46[i]	38.97[h]	1.49[l]	16[n,o]
DMF	σ_I, $\Delta\iota$, σ_R^0	−10.45 (±1.95)	−6.04 (±0.92)	1.70 (±1.42)	0.65	0.90	0.967	0.935	57.31	28.70[h]	43.57[h]	1.43[l]	16[n,o]
c-C_6H_{12}	σ_I, $\Delta\iota$	−6.15 (±1.56)	−6.75 (±0.70)		0.18	0.93	0.955	0.912	67.12	15.59[j]	92.43[h]		16[n,o]
$DCCl_3$	σ_I, $\Delta\iota$	−8.97 (±1.74)	−6.95 (±0.71)		0.37	0.91	0.966	0.933	91.09	26.69[i]	95.87[h]		16[n,o]
DMF	σ_I, $\Delta\iota$	−9.05 (±1.58)	−6.79 (±0.68)		0.40	0.91	0.963	0.927	82.51	32.65[h]	98.42[h]		16[n,o]
CF_3CO_2H	σ_I, $\Delta\iota$	−15.76 (±1.83)	−6.11 (±1.01)		−1.04	0.99	0.970	0.941	80.07	74.29[h]	36.51[h]		13[n-p]
CF_3CO_2H	σ_I, $\Delta\iota$	−16.49 (±1.53)	−6.28 (±0.97)		0.55	0.97	0.983	0.966	157.4	116.7[h]	41.93[h]		14[n,o,q]

[a] General form of correlation equation: $\text{SCS} = \rho_I\sigma_I + \rho_\iota\Delta\iota + \rho_R\sigma_R^0 + c$. [b] Regression coefficients for individual terms ± standard error of regression coefficient. [c] Intercept. [d] Standard error of estimate. [e] Multiple correlation coefficient. [f] F test of variance for overall correlation and individual regression coefficients. Superscripts indicate confidence level (CL) of test. [g] Number of data points in correlation. [h] 99.99% CL. [i] 99.9% CL. [j] 99.5% CL. [k] 90.0% CL. [l] 75.0% CL. [m] 60.0% CL. [n] SCS of $CONH_2$ omitted from data set due to lack of substituent parameters. [o] SCS of CN, CF_3, Cl, and alkyl substituents omitted from data set. [p] SCS of ammonium substituents omitted from data set due to lack of $\Delta\iota$ parameters. [q] Hydrogen included as a substituent.

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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.[17] 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 recently been discussed.[36b] (b) Davis, W. H.; Pyror, W. A. *J. Chem. Educ.* **1976**, *53*, 285.

dence of the ^{19}F SCS on resonance is statistically insignificant. This point is confirmed by the fact that the exclusion of $\sigma_R{}^0$ leads to a statistically significant improvement in the fit of the correlations (note that the *F* test of the variance actually increases).[36] Hence, the ^{19}F SCS correlate best against a combination of σ_I and $\Delta\iota$ in all solvents. The correlation coefficients ($r = 0.96$–0.98), which may be considered reasonable rather than excellent ($r > 0.99$),[16] indicate that about 91–97% of the observed variations are now accounted for at a confidence level of 99.99%. Moreover, the intercepts are small for most of these correlations (c-C_6H_{12}, $CDCl_3$, and DMF); hence, the SCS of the parent compound (**1**, X = H; SCS = 0.00) is satisfactorily predicted. It should be noted, however, that a small intercept for the CF_3CO_2H correlation could only be achieved by including hydrogen as a substituent in the data set. The less than perfect fits for the correlations can probably be attributed mainly to uncertainties in the electronegativity parameters and, moreover, to the fact that disproportionality between σ_I and $\Delta\iota$ cannot be complete.[17] However, it should be borne in mind that perturbations due to other factors [second-order field effects ($E_z{}^2$)[37], van der Waals interactions,[38] and magnetic anisotropic influences[39]] may also be operating but in a very minor way.

Several significant conclusions may be drawn from the statistical analysis. First, the ^{19}F SCS of system **1** are determined predominantly by a blend of electric field (σ_I effect) and electronegativity ($\Delta\iota$ effect) effects. Furthermore, the former contribution is solvent dependent whereas the latter is essentially independent of the solvent. Second, the *negative* susceptibility terms (ρ_I and ρ_ι) are indicative of reverse substituent dependence. Thus, polar field and electronegativity effects act in concert to perturb the electron-density in the CF σ bond[9,10] of system **1**. Third, although theoretically possible,[11,14,33] resonance effects involving orbitals of π symmetry appear not to be transmitted through the bicyclo[2.2.2]octyl skeletal framework. A corollary of this conclusion is that the ^{19}F SCS of system **1** are *not* a manifestation of the π electrons in the $2p_x$ and $2p_z$ orbitals but of the σ electrons in the $2p_y$ orbital. In this connection it is noteworthy that CNDO/2 calculations of some derivatives of system **1**[40] indicate that although substituents perturb the charge density of the $2p_y(\sigma)$ orbital, the charge density for both the $2p_x$ and $2p_z$ orbitals remains unchanged.

Compelling support for the overall validity of the statistical dissection and, therefore, the aforementioned qualitative conclusions which follow is provided by an independent determination of polar susceptibility parameters (ρ_I values) for system **1**. We have already shown[10] that this may be achieved by dividing the appropriate ^{19}F SCS for NO_2 in system **2**[41] by the *differential* between the appropriate σ_I values for C_6H_5 and p-$NO_2C_6H_4$ (Table II). The polar susceptibility parameters determined in this way[41b] are as follows: ρ_I(c-C_6H_{12}) = −3.13, ρ_I($CDCl_3$) = −5.25, ρ_I(DMF) = −4.70, ρ_I(CF_3CO_2H) = −17.56. Note that these well-defined values agree within a factor of 2 (or better) with those listed in Table III for the best correlations against σ_I and $\Delta\iota$ [−6.15 (c-C_6H_{12}), −8.97 ($CDCl_3$), −9.05 (DMF), −16.49 (CF_3CO_2H)]. Given that the efficacy of statistical methodology for disentangling electronic influences hinges critically on a strong nonlinear relationship between the appropriate substituent parameters[19,20] and given that the disproportionality between σ_I and $\Delta\iota$ cannot be complete,[16] this level of correspondence between the ρ_I values must be considered reasonable. It is noticeable, however, that the agreement between the respective ρ_I values is particularly good for CF_3CO_2H in which polar field effects are dominant.

Table IV. Calculated Polar Field Contributions ($\rho_I\sigma_I$) to ^{19}F SCS (ppm) of System 1

	$\rho_I\sigma_I$			
X	c-C_6H_{12}[a]	$CDCl_3$[b]	DMF[c]	CF_3CO_2H[d,e]
NO_2	−2.07	−3.41	−2.82	−12.99 (−11.34)
CN	−1.85	−2.94	−2.26	−12.47 (−10.88)
CF_3	−1.38	−2.10	−1.97	−6.50 (−5.67)
CO_2H	−0.72	−1.68	−0.99	−7.73 (−6.74)
$CONH_2$		−1.73	−0.89	−12.12 (−10.57)
$COOCH_3$	−0.69	−1.37	−1.22	−7.02 (−6.13)
$COCH_3$	−0.88	−1.63	−1.18	−8.43 (−7.35)
CHO	−1.13	−1.94	−1.46	−9.13 (−7.97)
OH	−0.72	−1.52	−0.66	−8.43 (−7.35)
OCH_3	−0.60	−1.37	−1.03	−8.78 (−7.66)
$OCOCH_3$	−0.91	−1.73	−1.60	−7.90 (−6.89)
F	−1.22	−2.21	−1.88	−9.13 (−7.97)
Cl	−1.35	−2.26	−2.02	−7.73 (−6.74)
Br	−1.38	−2.31	−2.07	−7.73 (−6.74)
I	−1.32	−2.21	−1.88	−7.02 (−6.13)
NH_2	−0.38	−1.00	−0.38	
$N(CH_3)_3$	−0.31	−0.95	−0.56	
$NHCOCH_3$	−0.66	−1.47	−0.85	−12.64 (−11.03)
$^+NH_3$				−15.28 (−13.33)
$^+NH(CH_3)_2$				−18.09 (−15.78)
$^+N(CH_3)_2$		−4.62	−3.01	−19.49 (−17.00)
CH_3	0.00	0.00	0.00	00.00 (0.00)
C_2H_5	0.00	0.00	0.00	0.00 (0.00)
i-C_3H_7	0.00	0.00	0.00	0.00 (0.00)
t-C_4H_9	0.00	0.00	0.00	0.00 (0.00)
C_6H_5	−0.47	−0.89	−0.75	−3.15 (−2.76)
$Sn(CH_3)_3$	0.00	0.00	0.00	

[a] $\rho_I = -3.13$. [b] $\rho_I = -5.25$. [c] $\rho_I = -4.70$. [d] $\rho_I = -17.56$. [e] $\rho_I = -15.32$. Calculations pertaining to this value are listed in parentheses.

The independently defined ρ_I values (vide supra), together with the appropriate polar substituent parameters (Table II), may be employed to calculate polar field contributions ($\rho_I\sigma_I$) to the ^{19}F SCS of system **1** for each substituent in the various solvents and, hence, also the residual contributions to the shift parameter. The latter quantities are identifiable with the electronegativity term of the statistical dissection. An inspection of these results (Tables IV and V) reveals that in most instances the electronegativity contribution to the ^{19}F SCS of system **1** is greater than the corresponding polar field perturbation in c-C_6H_{12}, $CDCl_3$, and DMF as solvents. In striking contrast, the converse situation clearly holds in CF_3COOH. Most importantly, however, it can be seen that the solvent dependencies of the two effects are clearly in accord with the results of the statistical analysis, namely, that whereas the polar field contributions are quite sensitive to the nature of the solvent, the so-called electronegativity terms remain

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(41) (a) A shift parameter which reflects solely polar field effects.[10] (b) For the solvent systems under study (c-C_6H_{12}, $CDCl_3$, DMF, and CF_3CO_2H), the ^{19}F SCS of system **2** may be derived from the appropriate data listed in Table I [^{19}F SCS (**1**, X = p-$NO_2C_6H_4$) − ^{19}F SCS (**1**, X = C_6H_5)]. ^{19}F SCS for NO_2 in system **2** for some other solvents are as follows: −0.65 (C_6H_6), −0.66 (CH_3CO_2H), −0.57 (CH_3OH), −0.25 (HMPA). These values divided by the appropriate σ_I differentials (see footnote *p* and *q* of Table II) lead to the following polar susceptibility parameters for system 1: −2.32 (C_6H_6), −3.88 (CH_3CO_2H), −4.75 (CH_3OH), −2.50 (HMPA).

Table V. Calculated Residual Contributions[a,b] to ^{19}F SCS (ppm) of System 1

	residual contribution			
X	c-C_6H_{12}	$CDCl_3$	DMF	CF_3CO_2H[c]
NO_2	−6.32	−6.48	−6.71	−4.46 (−6.11)
CN	−2.30	−2.46	−2.53	−0.08 (−1.67)
CF_3	−3.70	−3.95	−4.01	−3.62 (−4.45)
CO_2H	−4.03	−4.00	−3.94	−2.84 (−3.83)
$CONH_2$		−4.36	−3.98	−1.68 (−3.23)
$COOCH_3$	−3.69	−3.92	−3.83	−3.17 (−4.06)
$COCH_3$	−3.27	−3.48	−3.34	−2.13 (−3.21)
CHO	−1.96	−2.16	−2.04	−0.79 (−1.95)
OH	−7.34	−7.72	−6.81	−6.53 (−7.61)
OCH_3	−5.80	−6.25	−6.12	−5.50 (−6.62)
$OCOCH_3$	−5.17	−5.57	−5.51	−5.25 (−6.26)
F	−7.68	−8.11	−8.31	−7.00 (−8.16)
Cl	−5.62	−5.88	−6.05	−4.93 (−5.92)
Br	−4.56	−4.76	−4.91	−3.77 (−4.76)
I	−2.03	−2.08	−2.24	−1.20 (−2.09)
NH_2	−6.22	−6.51	−5.90	
$N(CH_3)_2$	−4.35	−4.89	−4.75	
$NHCOCH_3$	−4.00	−4.35	−3.93	−2.22 (−3.83)
$^+NH_3$				−2.69 (−4.64)
$^+NH(CH_3)_2$				−1.00 (−3.31)
$^+N(CH_3)_3$		−6.52	−6.33	−0.65 (−3.14)
CH_3	−3.81	−3.92	−3.90	−4.08 (−4.08)
C_2H_5	−2.79	−2.91	−2.93	−2.97 (−2.97)
i-C_3H_7	−2.68	−2.79	−2.82	−2.72 (−2.72)
t-C_4H_9	−3.11	−3.20	−3.23	−3.04 (−3.04)
C_6H_5	−2.90	−3.05	−2.93	−2.13 (−2.53)
$Sn(CH_3)_3$	3.67	3.83	3.94	

[a] ^{19}F SCS (observed) − polar field contributions ($\rho_I\sigma_I$). [b] See Table IV for polar field contributions. [c] Results in parentheses were determined from the correspondingly listed $\rho_I\sigma_I$ values in Table IV.

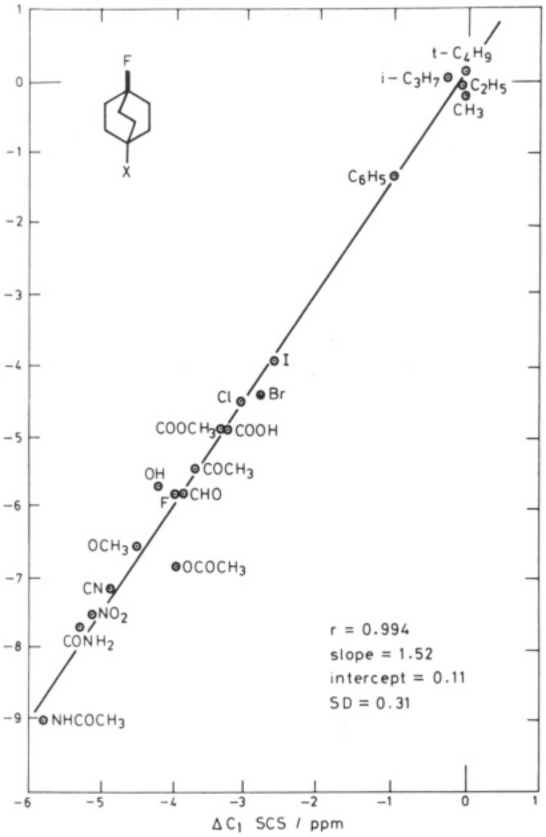

Figure 1. Plot of ^{19}F SCS (CF_3CO_2H) − ^{19}F SCS($CDCl_3$) vs. ^{13}Cl SCS(CF_3CO_2H) − ^{13}Cl SCS($CDCl_3$) for system **1**.

Table VI. ^{13}C NMR Parameters for the Bridgehead Carbon (C1) of System 1

	$CDCl_3$		CF_3CO_2H	
X	C1 SCS, ppm[a,b]	Δ^1J_{CF}, Hz[c,d]	C1 SCS, ppm[a,b]	Δ^1J_{CF}, Hz[c,d]
NO_2	−2.64	5.2	−7.76	9.3
CN	−2.71	4.0	−7.57	7.8
COOH	−0.72	2.1	−4.02	4.4
$CONH_2$	−0.71	1.8	−6.00	6.8
$COOCH_3$	−0.62	1.5	−3.96	3.9
$COCH_3$	−0.54	1.5	−4.25	4.9
CHO	−0.67	1.8	−4.65	4.9
OH	−1.98	3.0	−6.19	6.3
OCH_3	−2.21	3.4	−6.71	6.3
$OCOCH_3$	−2.65	3.3	−6.62	7.3
F	−3.00	6.4	−6.88	8.3
Cl	−3.10	3.7	−6.18	5.3
Br	−3.84	4.0	−6.64	5.3
I	−5.00	3.4	−7.62	4.9
NH_2	−1.10	1.5		
$N(CH_3)_2$	−1.57	2.1		
$NHCOCH_3$	−1.84	2.7	−7.63	7.8
$^+NH_3$			−9.10	9.7
$^+NH(CH_3)_2$			−10.13	11.2
$^+N(CH_3)_3$			−10.54	11.7
CH_3	0.28	−0.1	0.27	−0.5
C_2H_5	0.27	0.0	0.22	0.0
i-C_3H_7	0.20	0.0	−0.07	0.5
t-C_4H_9	0.12	0.6	0.11	1.0
C_6H_5	0.17	0.6	−1.23	1.4
$Sn(CH_3)_3$	−0.24	−1.2		

[a] 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). Positive values indicate deshielding. Accurate to ±0.04 ppm. [b] Cl, 94.60 and 102.75 ppm ($DCCl_3$ and CF_3CO_2H, respectively) relative to Me_4Si. [c] Accurate to ±0.6 Hz. [d] $^1J_{CF}$ = 182.5 and 176.3 Hz ($DCCl_3$ and CF_3CO_2H, respectively).

essentially invariant. Although the latter perturbations (Table V) appear to display some significant changes in CF_3CO_2H compared to the other solvent systems, the excellent correlation (Figure 1) between the solvent-induced changes ($CDCl_3$ to CF_3CO_2H) in the ^{19}F and ^{13}Cl SCS (Tables I and VI, respectively) strongly suggests otherwise. Given that we have already shown from our detailed study of system **2**[10] that, in the absence of other complicating factors, electric-field-induced ^{19}F chemical shifts in alkyl fluorides are characterized by a concomitant proportional change in the ^{13}C chemical shifts of the carbon to which the fluorine nucleus is attached, the precise linear relationship displayed in Figure 1 clearly implies that other contributions to the chemical shifts of both nuclei,[42] other than polar field phenomena, remain invariant to solvent changes. Interestingly, the proportionality constant (1.52) of the correlation shown in Figure 1 is similar to that (1.35)[10] obtained from the excellent linear relationship between the polar field–induced ^{19}F and ^{13}Cl SCS in system **2** ($DCCl_3$ as solvent). Thus, the apparent solvent-induced variations in the electronegativity term indicated by the results in CF_3CO_2H as solvent (Table V) must be ascribed to uncertainties associated with defining the large ρ_I value for this solvent (−17.56). Note that the results listed in

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(42) (a) It should be noted that the ^{19}F SCS ($DCCl_3$) of system **1** correlate poorly (r = 0.54) against the corresponding ^{13}Cl SCS ($DCCl_3$). Thus, apart from polar field effects, the additional factors underlying the effects of substituents on the chemical shifts of both nuclei are probably dissimilar or, alternatively, are similar but blend quite differently with the polar field influence. Wiberg et al.[42b] have recently drawn attention to the intricacies of substituent effects on ^{13}C chemical shifts in aliphatic systems in general and, in particular, to ^{13}C chemical shifts in bridgehead-substituted bicyclo[2.2.2]octanes. (b) Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Org. Chem.* **1980**, *45*, 4936; *Tetrahedron Lett.* **1978**, 4861, 4865.

Table VII. Electric Field Calculations for System 1

X	μ, D[a]	C-X, Å[b]	r, Å[c]	$10^{-3}E_{CF}$, esu[d]	$\rho_I\sigma_I$[e]	$10^{12}A$, esu
NO_2	3.63	2.10	4.33	89.43	−2.07	−23.15
CN	4.04	2.62	4.88	69.53	−1.85	−26.61
F	1.96	1.38	3.97	62.65	−1.22	−19.47
Cl	2.06	1.79	4.18	56.42	−1.35	−23.93
Br	2.18	1.94	4.25	56.79	−1.38	−24.30
I	2.04	2.13	4.35	49.57	−1.32	−26.63

[a] Dipole moment. [b] Dipole length. [c] Distance between origin of dipole and midpoint of C–F bond. [d] $E_{CF} = 2\mu/r^3$. [e] Taken from Table IV (c-C_6H_{12}).

parentheses for CF_3CO_2H (Tables IV and V) are based on a ρ_I value of −15.32. This latter polar susceptibility parameter, which was determined by setting the electronegativity contribution for Br in CF_3CO_2H equal to the value observed for this substituent in $CDCl_3$ (−4.76), clearly leads to calculated electronegativity contributions for the dipolar substituents in CF_3CO_2H which are very similar to those for the other solvents.

The polar field contributions to the ^{19}F SCS of system 1 (Table IV) for several substituents (NO_2, CN, F, Cl, Br, and I) may be employed to determine the coefficient (A) for the Buckingham equation (SCS = AE_z; E_z is the electric field component acting along the CF bond).[37] In order to minimize reaction field effects and bulk dielectric influences, the calculations are restricted to the data for cyclohexane as solvent.[43] Structural and molecular parameters were employed as previously indicated.[5] Results are summarized in Table VII. The average A value (-24.02×10^{-12} esu) obtained from those listed in Table VII is considerably less than the value (-59.0×10^{-12} esu) estimated from the $\rho_I\sigma_I$ term for the DSP correlation of the ^{19}F SCS (c-C_6H_{12}) of system 2.[10] The discrepancy is clearly in line with our belief[10] that the $\rho_I\sigma_I$ term for system 2 embodies, apart from the electric field emanating from the substituent dipole, a significant contribution from a secondary field as a result of field-induced π polarization of the benzene ring.

Next let us consider the origins of the two major contributions (polar field and electronegativity effects) to the ^{19}F SCS of system 1. Our study of system 2[10] has clearly shown that the solvent-dependent electric field term ($\rho_I\sigma_I$) arises from CF σ bond polarization and, moreover, that a *decrease* in σ-electron density leads to *negative* ^{19}F SCS (*upfield* shift). The magnitude of the polarization due to the field effect of the substituent depends on the component of the electric field along the CF bond as well as on the polarizability of the CF σ bond. A consequence of the latter dependency is the pronounced increase in the polar susceptibility parameter [ρ_I = −15.32 (Table IV)] for system 1 in CF_3CO_2H as the solvent due to strong hydrogen bonding interactions between the fluorine probe and the solvent.[10] This striking solvent effect is also manifest in the exalted ^{19}F SCS observed for the "chemically inert" *bromo* substituent[24] in CF_3CH_2OH and $(CF_3)_2CHOH$ (Table I, footnote *i*). Like CF_3CO_2H, these fluorinated alcohols are weakly self-associated and strong hydrogen bond donor (HBD) solvents.[44] It is noteworthy that none of the weaker strongly self-associated HBD solvents (CH_3CO_2H, CH_3OH, and C_2H_5OH)[44] lead to significantly enhanced ρ_I values[41b] or ^{19}F SCS (Table I, footnote *i*). However, the larger value of ρ_I for $CDCl_3$ (−5.25) than for c-C_6H_{12} (−3.13) is indicative of the phenomenon. This is not surprising since Taft et al.[24,44] have drawn attention to the potential strong HBD capability of this weakly self-associated solvent. The polarizability of the CF σ bond and, hence, the magnitude of ρ_I for system 1 should also be a function of the dielectric constant of the solvent since greater charge separation in the CF σ bond is to be expected in more polar solvents.[45] However, this effect will tend to be obscured by the concomitant attenuation of the electric field due to the solvent impinging on the effective dielectric constant.[5,45] In this connection, it is pertinent to note that whereas ρ_I for DMF (−4.70) is greater than that for c-C_6H_{12} (−3.13) the value for HMPA (−2.50)[41b] is smaller.

Several factors may be invoked to account for the solvent-independent electronegativity contributions to the ^{19}F SCS of system 1.

(i) Through-Bond Effects. Two modes of transmission fit into this category. First, the polarity of the substituent–substrate bond (C_{sp^3}–X) can be propagated to the probe site by successive polarization of the intervening σ bonds (σ-inductive effect).[15,16,33] Although most researchers now view this mechanism as a short-range effect,[15,16] being unimportant beyond two bond lengths, two noted authorities[46,47] have recently challenged this viewpoint. It is noteworthy, however, that calculations[14,48] at varying levels of sophistication offer no support for this mechanism as a long-range effect (beyond two bond lengths). Second, the CX and CF σ bonds may be coupled via the bridging ethano bonds.[11-13] This interaction may be viewed as a resonance effect involving orbitals of σ symmetry. The parameters governing the appropriate orbital interactions (orbital coefficients, resonance integrals, and energy differentials) are clearly related to electronegativity.[49]

(ii) Structural Effects. Unfortunately there is a dearth of experimental information concerning substituent-induced structural distortions of the bicyclo[2.2.2]octane skeletal framework. Anderson and Stock[2] have proposed that the presence of a polar electron-withdrawing substituent and the highly electronegative fluorine at opposite bridgehead positions of bicyclo[2.2.2]octane may effect an elongation of the C1–C4 nonbonded distance, presumably by mutual electrostatic repulsion. However, substituent-induced structural effects based on electronegativity considerations may be envisaged in another way. Replacement of hydrogen at a bridgehead position of bicyclo[2.2.2]octane with fluorine will lead to an increase in the p character of the exocyclic orbital[50] with an attendant flattening of the bridgehead position.[51] Since it is rea-

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Table VIII. Results of Correlative Analysis[a] of Δ^1J_{CF} Values of System 1 with Substituent Parameters

solvent	independent variables	ρ_I[b]	ρ_ι[b]	c[c]	SE[d]	r[e]	r^2	F[f,h]	F_I[f,h]	F_ι[f]	n[g]
$DCCl_3$	σ_I, $\Delta\iota$	7.08 (±0.94)	2.12 (±0.53)	−0.61	0.70	0.936	0.877	67.54	56.84	15.94[i]	22[k]
$DCCl_3$	σ_I	8.29 (±0.80)		−0.13	0.67	0.922	0.850	108.00	108.00		21[k,l]
CF_3CO_2H	σ_I, $\Delta\iota$	9.83 (±0.92)	2.48 (±0.76)	−0.31	0.77	0.969	0.940	126.6	113.9	10.68[j]	19[k]
CF_3CO_2H	σ_I	11.32 (±0.81)		0.15	0.83	0.962	0.924	196.1	196.1		18[k,l]
CF_3CO_2H	σ_I	10.78 (±0.54)		0.31	0.78	0.977	0.954	391.9	391.9		21[k-m]

[a] General form of correlation equation: $\Delta^1J_{CF} = \rho_I\sigma_I + \rho_\iota\Delta\iota + c$. [b] Regression coefficients for individual terms ± standard error of regression coefficient. [c] Intercept. [d] Standard error of estimate. [e] Multiple correlation coefficient. [f] F test of variance for overall correlation and individual regression coefficients. Superscripts indicate confidence level (CL) of test. [g] Number of data points in correlation. [h] 99.99% CL. [i] 99.9% CL. [j] 99.5% CL. [k] Δ^1J_{CF} of $CONH_2$ omitted from data set due to lack of substituent parameters. [l] Δ^1J_{CF} of F omitted from data set. [m] Δ^1J_{CF} of $^+NH_3$, $^+NH(CH_3)_2$, and $^+N(CH_3)_3$ included in data set.

sonable to expect that the degree of flattening accompanying fluorine substitution would depend significantly on the flexibility of the bicyclo[2.2.2]octane ring system as well as on coulombic interaction forces, the presence of a substituent at the other bridgehead position may lead to different bridgehead (C1–F) angles for system 1, depending on the size and electronegativity of X.

(iii) Through-Space Effect. The CX and CF σ bonds may interact directly via "back or rear lobe" orbital overlap.[12,52-54] This effect would depend on the electronegativity of X for the same basic reasons indicated above for the other electron-delocalization mechanism (σ-resonance effect).

(iv) π-Electron Effect. The change in the effective electronegativity of the carbon atom attached to X could lead to a perturbation of the possible π interaction[11] between the fluorine lone pairs and the bicyclo[2.2.2]octane moiety due to a preferential change in the energy of the appropriate orbitals associated with the latter structure (a so-called shielding–deshielding mechanism).[55] However, since orbital energies are usually dominated by resonance rather than inductive effects[49] and since the statistical analysis (Table III) indicated that the ^{19}F SCS of system 1 are not significantly dependent on resonance, this π-electron effect must be viewed as being a very unlikely possibility (vide supra).

Since at least two of these factors (σ-inductive effect and structural effects), if important, would lead to a change in the hybridization state of the bridgehead carbon attached to fluorine, it seemed to us that the most appropriate NMR parameter for probing the situation further is the change in the one-bond carbon–fluorine spin–spin coupling constant (Δ^1J_{CF}), which is known to reflect changes in the s character of the exocyclic orbital of the bridgehead carbon atom.[10,56] The relationship between the appropriate Δ^1J_{CF} values (Table VI) and substituent parameters (σ_I and $\Delta\iota$; vide supra) was explored by linear multiparameter regression analysis. Results are summarized in Table VIII. It can be seen from the first correlation ($DCCl_3$ as solvent) that Δ^1J_{CF} is strongly dependent on σ_I but only weakly, at best, on $\Delta\iota$. In fact, provided the fluorine substituent is omitted from the data set ($DCCl_3$), the exclusion of $\Delta\iota$ leads to a slight improvement in the precision of fit (F test)[36] of the correlation. However, these correlations ($DCCl_3$) are of relatively low precision; thus, the situation is best exposed by the data in CF_3CO_2H as the solvent (Table VI) since here the greater range of Δ^1J_{CF} values leads to quite good correlations ($r > 0.96$; Table VIII). Note that the best correlation ($r = 0.977$), achieved by including the ammonium substituents but omitting fluorine from the data set, indicates that at least 95% of the variations of Δ^1J_{CF} can be accounted for in terms of σ_I alone. Hence, it may be safely concluded that Δ^1J_{CF} is largely a consequence of electric field-induced polarization of the CF σ bond.[10] The important corollary is that the σ-inductive effect as well as structural effects are not significantly responsible for the electronegativity contribution to the ^{19}F SCS of system 1. However, it should be noted that the abnormally large Δ^1J_{CF} value for fluorine may be indicative of a significant elongation of the bridgehead (C1–F) angles of system 1 (X = F). In this connection, it is of interest to also note that the Δ^1J_{CF} value for $Sn(CH_3)_3$ (Table VI) may indicate some flattening of these angles for an electropositive substituent.

Thus, by default we are left to ascribe the so-called electronegativity contribution to the ^{19}F SCS of system 1 to the remaining factors ("through-bond" and "through-space" electron-delocalization mechanisms).[12,13] Unfortunately, it is not possible to make a priori predictions from theoretical considerations as to the relative magnitude of these two effects. However, because the internuclear distance between the bridgehead carbon atoms (C1···C4) in bicyclo[2.2.2]octane is considerable (2.59 Å),[57] it is doubtful whether the "through-space" effect is the dominant contributing factor in this bicyclic system. This supposition is supported by evaluations of "through-space" contributions by INDO-type calculations to the long-range hyperfine coupling constant (δ proton) for the bicyclo[2.2.2]octyl free radical[53] as well as to the appropriate

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(51) (a) A recent X-ray crystallographic study[51b] of some 1-X-4-phenylbicyclo[2.2.2]octanes offers strong support for this deduction. The sums of the three internal skeletal angles around the bridgehead atom (C–X) are 324.8° and 330.3° for X = H and F, respectively. It is also pertinent to note that the bridgehead positions in 1,4-dichlorobicyclo[2.2.1]heptane are both flattened relative to the parent unsubstituted bicyclo[2.2.1]heptane.[51c] (b) Bourne, P. E. Ph.D. Dissertation, The Flinders University of South Australia, 1980. (c) Chiang, J. F.; Wilcox, C. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1968**, *90*, 3149.

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nuclear spin–spin coupling constants ($J_{^{13}C-^{1}H}$ and $J_{^{13}C-^{13}C}$)[54] for some bridgehead-substituted bicyclo[2.2.2]octanes. It appears, therefore, that the "through-bond" effect affords the most plausible explanation for the electronegativity-induced perturbation of the ^{19}F chemical shifts of system **1**. Within the framework of perturbational molecular orbital (PMO) theory,[49] a consideration of the factors controlling orbital interactions suggests that this effect will be largely governed by the interaction of σ_{CC} with σ_{CF}* and σ_{CX}*. Furthermore, essentially on the basis of matrix element control of these orbital interactions,[49] an *increase* in the electronegativity of the bridgehead substituent will enhance the σ_{CC}–σ_{CX}* interaction at the expense of the σ_{CC}–σ_{CF}* interaction; i.e., conjugative transfer of charge from σ_{CC} to σ_{CF}* is *decreased* on increasing the electronegativity of the bridgehead substituent. The results disclosed herein suggest that this phenomenon is manifested by solvent-independent *upfield* shifts. In this connection it is pertinent to note that a recent model system study[9] has clearly shown that a *decrease* in charge transfer to σ_{CF}* in benzylic fluorides also leads to *reverse* ^{19}F SCS.

Other possible manifestations of the "through-bond" effect among the data reported in this and the accompanying paper[10] is the extraordinarily large F–Sn coupling constant in system **1** [X = $Sn(CH_3)_3$; see footnote *l* to Table I][58] as well as the fact that $^5J_{CF}$ is greater than $^4J_{CF}$ for the alkyl-substituted compounds (**1**; X = CH_3, C_2H_5, *i*-C_3H_7, and *t*-C_4H_9).[59]

Finally, in view of the continuing discussion concerning the polar effects of alkyl substituents,[60-63] we would like to draw specific attention to several aspects of their ^{19}F SCS in system **1** (Table I). First, it can be seen that there is no significant difference between the ^{19}F SCS of the alkyl groups in c-C_6H_{12} and CF_3CO_2H, yet, as we have seen above, such a solvent change leads to a fivefold increase in the polar susceptibility parameter (ρ_I) for system **1**. We believe this result is further irrefutable experimental evidence in support of the notion that polar inductive parameters (σ_I values) for all alkyl groups must be *zero*.[25] Second, the insensitivity of the ^{19}F SCS for the alkyl groups (Table I) to solvent effects strongly suggests that these parameters have their origin in the so-called electronegativity contribution (Table V) to the ^{19}F chemical shifts of system **1**. Thus, if we take the results at their face value, the *negative* ^{19}F SCS of the alkyl substituents imply that these groups have a σ-inductive effect which is electron withdrawing (or attracting) relative to hydrogen when attached to an sp^3-hybridized carbon atom. Although this conclusion is not in accord with current preconceptions,[60] it concurs with the results of recent theoretical work[64] as well as with a more recent empirical group electronegativity scale[35] and other experimental evidence.[65] The relative magnitude of the ^{19}F SCS (Table I) indicates that successive replacement of the hydrogen atoms of a methyl group by two methyl substituents leads to a progressive *decrease* in the electron-withdrawing power of the alkyl group. However, it can be seen that with the third replacement the trend is dislocated. An examination of the Δ^1J_{CF} values of the alkyl groups (Table VI), which are all *zero* (within experimental error) except for that of the *tert*-butyl group, suggests that the anomalous inductive trend (CH_3 > *t*-C_4H_9 > C_2H_5 > *i*-C_3H_7) is probably a manifestation of a small sterically induced structural effect by the large *tert*-butyl group. Third, it is significant to note that our conclusion from this study concerning the transmission of π resonance effects in the bicyclo[2.2.2]octane ring system (vide supra) conflicts with our recent explanation[26] of small changes in the $\sigma_R{}^0$ value of the bicyclo[2.2.2]octyl group[25] on bridgehead substitution with alkyl groups. Unfortunately, we are unable to offer an explanation which reconciliates these discordant observations. Hence, the interpretation above of the ^{19}F SCS of the alkyl groups for system **1** as manifestations of pure electronegativity effects must be viewed with caution. Interestingly, these substituents were found to be the most deviant in our attempts to relate the ^{19}F SCS of system **1** to substituent parameters (vide supra).

Experimental Section

Synthesis of Compounds. Except for one compound (**1**, X = CF_3), the syntheses of the 4-substituted bicyclo[2.2.2]oct-1-yl fluorides are described in the accompanying paper.[66] An attempt was made to prepare the trifluoromethyl derivative (**1**, X = CF_3) by treating the corresponding carboxylic acid (**1**, X = COOH; 0.6 g, 0.0035 mol) with sulfur tetrafluoride in the manner described below for the preparation of the same derivative of system **3** (X = CF_3). After a standard workup, a crude product was obtained which was found (GLC and mass spectral analysis) to be a mixture containing a small amount of the desired compound plus a predominant quantity of the acyl fluoride (**1**, X = COF) and an unknown compound. Treatment of the crude product with a 10% aqueous solution of sodium hydroxide under reflux for 2 h led to the isolation, in the usual manner, of the trifluoromethyl compound (**1**, X = CF_3; 0.02 g) which was still heavily contaminated with the acyl fluoride. This was confirmed by ^{13}C NMR. Although not all the carbon resonances were observed, a characteristic doublet (29.91 ppm, J_{CF} = 20.02 Hz) and a doublet of quartets (25.92 ppm, J_{CF} = 10.74 and 1.95 Hz) was clearly observed for the C2 and C3 carbons, respectively, of **1** (X = CF_3).

Most of the 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (**3**) required for defining the polar inductive scales were available from a previous study.[5,67] Only two (**3**, X = $N(CH_3)_2$ and CF_3) were specifically synthesized in connection with this investigation. The former compound (mp 60–62 °C) was readily prepared in good yield from the amine precursor (**3**, X = NH_2)[5] in the same manner as described for a similar derivative of **1** (X = $N(CH_3)_2$).[66] The latter compound (mp 82–84 °C) was obtained by heating (150 °C) the corresponding carboxylic acid (**3**, X = COOH; 1.5 g, 0.006 mol) with excess sufur tetrafluoride (15 g, 0.14 mol) in a sealed stainless-steel autoclave for 24 h. After a standard workup, the desired compound (**3**, X = CF_3) was obtained in reasonable yield (0.7 g). No attempt was made to remove a minor contaminant (**3**, X = COF).

NMR Spectra. The ^{13}C NMR data of system **1** with $CDCl_3$ as the solvent were taken from the accompanying paper.[66] The corresponding ^{13}C NMR spectra with CF_3CO_2H as the solvent were recorded for solutions (ca. 0.2 M) on the same instrument in 5-mm tubes containing $Si(CH_3)_4$ and C_6D_6 (10% by volume) as an internal reference and lock, respectively. A spectral width of 4000 Hz with 16K/8K data points was employed to give a minimum digital resolution of 0.02 ppm.

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The ^{19}F NMR spectra were obtained as described in the accompanying paper[10] for solutions (0.5 mL) containing the unsubstituted (X = H, 1 mg) and substituted (1 mg) compounds in the appropriate solvent.

Registry No. 1 (X = COF), 81725-03-3; 1 (X = NO_2), 32038-89-4; 1 (X = CN), 78385-80-5; 1 (X = CF_3), 78385-81-6; 1 (X = COOH), 78385-84-9; 1 (X = $CONH_2$), 81687-77-6; 1 (X = $COOCH_3$), 78385-85-0; 1 (X = $COCH_3$), 78385-83-8; 1 (X = CHO), 78385-82-7; 1 (X = OH), 22947-61-1; 1 (X = OCH_3), 78385-90-7; 1 (X = $OCOCH_3$), 22947-60-0; 1 (X = F), 20277-40-1; 1 (X = Cl), 78385-86-1; 1 (X = Br), 78385-87-2; 1 (X = I), 78385-89-4; 1 (X = NH_2), 78385-91-8; 1 (X = $N(CH_3)_2$), 78385-92-9; 1 (X = $NHCOCH_3$), 78385-93-0; 1 (X = $^+NH_3$), 81725-04-4; 1 (X = $^+NH(CH_3)_2$), 81725-05-5; 1 (X = $^+N(CH_3)_3$ I^-, 81687-80-1; 1 (X = $^+N(CH_3)_3$) Cl^-, 81687-81-2; 1 (X = CH_3), 20417-60-1; 1 (X = C_2H_5), 81687-82-3; 1 (X = *i*-C_3H_7), 81687-83-4; 1 (X = *t*-C_4H_9), 81687-86-7; 1 (X = C_6H_5), 22947-58-6; 1 (X = *p*-$NO_2C_6H_4$), 60526-66-1; 1 (X = $Sn(CH_3)_3$), 78385-88-3; 1 (X = H), 20277-22-9; 1 (X = OH) K, 81725-06-6; **3** (X = NO_2), 63385-88-6; **3** (X = CN), 61541-38-6; **3** (X = CF_3), 81725-07-7; **3** (X = COOH), 68756-19-4; **3** (X = $CONH_2$), 81725-08-8; **3** (X = $CON(CH_3)_2$), 68756-35-4; **3** (X = $COOC_2H_5$), 68756-20-7; **3** (X = $COCH_3$), 64872-40-8; **3** (X = CHO), 68756-33-2; **3** (X = OH), 60526-68-3; **3** (X = OCH_3), 61541-36-4; **3** (X = $OCOCH_3$), 61565-42-2; **3** (X = F), 60526-63-8; **3** (X = Cl), 61541-33-1; **3** (X = Br), 61541-34-2; **3** (X = I), 61541-35-3; **3** (X = NH_2), 10207-00-8; **3** (X = $N(CH_3)_2$), 81725-09-9; **3** (X = $NHCOCH_3$), 10207-01-9; **3** (X = $^+NH_3$), 63385-89-7; **3** (X = $^+NH(CH_3)_2$), 81725-10-2; **3** (X = $^+N(CH_3)_3$) I^-, 81725-11-3; **3** (X = $^+N(CH_3)_3$) Cl^-, 81725-12-4; **3** (X = C_6H_5), 68756-32-1; **3** (X = *p*-$NO_2C_6H_4$), 68756-36-5; **3** (X = OH) K, 81725-13-5.

Potential Bile Acid Metabolites. 6.[1] Stereoisomeric 3,7-Dihydroxy-5β-cholanic Acids

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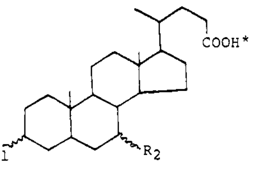
New synthetic routes to the four possible 3,7-dihydroxy acids are described. The principal reactions involved were inversions with DMF and Me_2SO–crown ether and reduction of 12-oxo tosylhydrazones. Inversion of 3α-tosylates by the Me_2SO–crown ether method succeeded but that of the corresponding mesylates did not. A table of ^1H NMR chemical shift reference data of monosubstituted methyl cholanates pertinent to bile acid characterization has been expanded.

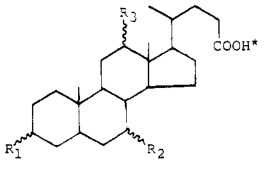
Of the four possible 3,7-dihydroxycholanic[3] acids, the 3α,7α [chenodeoxycholic (**1**)] and 3α,7β [ursodeoxycholic (**2**)] stereoisomers are commercial products, the 3β,7α isomer (**4**) is known but not generally available, and the 3β,7β isomer (**3**) has not been described[4] (see Chart I). As part of a program in our laboratory to make available potential bile acid metabolites for use as reference standards, and incidentally to reexamine existing methodology in bile acid synthesis, we have briefly reported new methods for preparing acids **1**[5] and **2**.[6] This paper covers synthesis of the two remaining stereoisomers of the 3,7-dihydroxy group, acids **3** and **4**, and presents additional details and observations encountered in the synthesis of acid **1** and alternative routes to acid **2**.

Conventional syntheses of the known 3,7 isomers involve reduction of the appropriate ketones, produced by selective oxidation, to the corresponding epimeric alcohols which are usually separated by chromatography. The syntheses herein reported do not proceed through intermediary ketones. The reactions used in the several syntheses are either direct inversions of an α-hydroxy derivative or conversion of a 12-oxo compound to its methylene analogue. Inversion of C-3 tosylates can be effected either by a previously described DMF reaction or a newly applied KO_2–crown ether reaction, while the C-7 hydroxy inversion

Chart I



	R_1	R_2
1	α-OH	α-OH
2	α-OH	β-OH
3	β-OH	α-OH
4	β-OH	β-OH
5	β-OAc	α-OH
6	β-OAc	α-OMs
7	α-OMs	α-OMs
8	α-OMs	β-OH
9	α-OMs	H,H
10	α-OTs	α-OMs
11	α-OTs	α-OH
16	α-OAc	α-OAc
22	α-OCO_2Et	α-OH
23	α-OCO_2Et	α-OMs
24	α-OAc	α-OMs
27	α-OTs	β-OH
28	α-OAc	α-OH
29	α-OH	α-OAc
30	α-OCO_2Et	H,H



	R_1	R_2	R_3
12	α-OH	α-OH	=0
13	α-OAc	α-OAc	=NNHTs
14	α-OH	α-OH	=NNHTs
15	α-OH	α-OAc	=NNHTs
17	α-OH	α-OAc	=0
18	α-OAc	α-OAc	=0
19	α-OH	α-OH	α-OH
25	α-OH	β-OH	=0
26	α-OH	β-OH	=NNHTs

*The corresponding C-24 methyl esters are designated "a".

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[1] Paper 5 of the series: F. C. Chang, *Synth. Commun.* 11, 875 (1981).

[2] On leave, Nihon University, Japan.

[3] All cholanic acid derivatives in this work are of the 5β series; the 5β designations are omitted in their names. The older name cholanic acid is used throughout in place of the newer IUPAC-suggested "cholanoic acid".

[4] The 3β,7β-acid 4 was mentioned in the patent literature [Japanese Kokai 77 78963; *Chem. Abstr.*, 87, 201898 (1977)] as an undescribed minor product and was evidently prepared by reduction of methyl 7β-hydroxy-3-oxocholanate [B. Dayal, E. Bagan, C. S. Tint, S. Schefer and G. Salen, *Steroids*, 259 (1979)], but the product was characterized only by R_f (TLC) and t_R (GC) values.

[5] T. Iida and F. C. Chang, *J. Org. Chem.*, 46, 2786 (1981). Both acids 1 and 2 are currently being used as gallstone-dissolving drugs. A. Steihl, P. Zygan, B. Komerell, H. J. Weis, and K. H. Holtermuller, *Gastroenterology*, 75, 1016 (1978).

[6] T. Iida, H. R. Taneja, and F. C. Chang, *Lipids*, 16, 863.

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