and σ effects.[2] For the substituents Ph, NH_2, BH_2, NO_2, and CO_2Me, MNDO calculations on the perpendicular form indicate little change in acidity, due to small and parallel effects on the heats of formation of the acid and anion forms, as shown in Table I. The small effect on the anion's enthalpy for the good π-acceptor groups BH_2 and CO_2H and good π-donor group NH_2, agrees with the conclusion above, that there is little π interaction between the allyl anion's π system and the substituent. The energy of the anion's HOMO (vertical electron affinity) is virtually unaffected by rotation of the substituent. For the netural propenes, rotation of the substituent does not appreciably affect the heat of formation but does destabilize the HOMO and LUMO (vertical electron affinity) for the good π-acceptor groups.

Gas-phase acidities may be expressed as a function of the homolytic bond strength of the acidic hydrogen and the electron affinity of the radical thereby produced, as in eq 4.[32] For the aliphatic alcohols, the RO–H bond

$$\Delta H^\circ_{acid}(AH) = DH(AH) + IP(H\cdot) - EA(A\cdot) \qquad (4)$$

strength is nearly constant and the variation in the alcohols' acidity is attributable to the difference in electron affinity of the alkoxy radicals.[33] If the binding energy of the HOMO of the allyl anions here is taken as the vertical electron affinity, by Koopman's theorem, then we can derive the C–H bond strength of the propenes by an inversion of eq 4. This data is presented in Table I. A nearly constant bond strength of 91 ± 2 kcal/mol is found for most propenes, even though the electron affinities range from 14 (Z = H) to 44 ($Z = NO_2$) kcal/mol. The experimental value for the parent propene bond strength is 86.3 ± 1.5 kcal/mol.[34] This small effect of the substituents on the allyl radical stability is consistent with the relatively small π interactions occuring in the allyl form and the lack of polar effects on radical stabilities.

Acknowledgment. We thank the National Science Foundation, Grant CHE 79-19528, for support of the work, and the Dow Chemical Company for a Summer Scholarship for R.D.B.

---

[32] Baughn, E. C.; Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1941**, *37*, 377.

[33] Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986.

[34] McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493.

Transmission of Polar Substituent Effects in Bicycloalkane Systems. Synthesis and Nuclear Magnetic Resonance Study (Carbon-13 and Fluorine-19) of 4-Substituted Bicyclo[2.2.1]hept-1-yl Fluorides[1]

William Adcock,* Anil N. Abeywickrema, and Gaik B. Kok

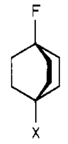
School of Physical Sciences, The Flinders University of South Australia, Bedford Park, S.A., 5042 Australia

Received October 17, 1983

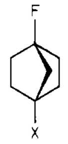
A number of 4-substituted (X) bicyclo[2.2.1]hept-1-yl fluorides (2) have been synthesized, and their ^{13}C and ^{19}F NMR spectra have been recorded. The synthesis of all these compounds, except for the parent (**2**, X = H) of the series, has been accomplished from 4-fluorobicyclo[2.2.1]heptane-1-carboxylic acid (**2**, X = COOH) by, in the main, functionalization procedures previously employed for the synthesis of 4-substituted (X) bicyclo[2.2.2]oct-1-yl fluorides (1) from the corresponding acid (**1**, X = COOH). The key new precursor compound (**2**, X = COOH) was prepared by a new route to 1,4-disubstituted bicyclo[2.2.1]heptane derivatives. A standard multiple linear least-squares regression analysis of the ^{19}F substituent chemical shifts (SCS) against polar substituent parameters reveals that these NMR substituent-probe parameters of system **2** are predominantly manifestations of electric field and electronegativity effects. Most importantly, the long-range electronegativity effects are found to be of *opposite* sign to those observed in system **1**. A qualitative explanation for this striking phenomenon is advanced in terms of σ-electron delocalization mechanisms ("through-bond" and "through-space" effects). The implication of these results with respect to the transmission of polar substituent effects in saturated systems as monitored by chemical reactivity probes is noted.

Introduction

1,4-Disubstituted bicycloalkanes, being geometrically rigid aliphatic substrates in which the substiuent and side-chain probe are located at sterically remote sites, are attractive model systems for investigating the nature of polar substituent effects without the concomitant encumbrances of stereochemical phenomena and π-resonance effects.[2-4] In this connection, we recently presented a systematic ^{13}C and ^{19}F NMR study of an extensive series of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (1).[5,6]



1



2

Based on the results of a standard multiple linear least-squares regression analysis of the ^{19}F substituent chemical shifts (SCS) of system 1 vs. polar substituent parameters[7,8]

---

[1] A preliminary communication of this work has appeared: Adcock, W.; Abeywickrema, A. N.; Kok, G. B. *Tetrahedron Lett.* **1982**, *23*, 3615.

[2] Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400, and references cited therein.

[3] Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119, and references cited therein.

[4] Applequist, D. E.; Renken, T. L.; Wheeler, J. W. *J. Org. Chem.* **1982**, *47*, 4985, and references cited therein.

[5] Adcock, W.; Abeywickrema, A. N. *Tetrahedron Lett.* **1981**, *22*, 1135.

[6] Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2957.

0022-3263/84/1949-1387$01.50/0

(σ_F[9] and $\Delta\iota$[10]) and, in addition, independent measures of polar field susceptibility parameters (ρ_F values), we concluded that both electrostatic field (σ_F effect)[9] and electronegativity ($\Delta\iota$ effect)[10] effects contribute significantly to the *reverse* ^{19}F SCS[11] of system **1**.[5,6]

The importance of the latter substituent factor as a *long-range* electronic influence is of considerable interest, since other evidence[7,8,12] suggests that its effect, traditionally viewed as being transmitted to the probe site by successive polarization of the intervening σ bonds (σ-inductive effect), should be unimportant at probe sites more than two bonds removed from the substituent. However, based on a correlative analysis of the substituent-induced changes in the one-bond carbon–fluorine spin–spin coupling constants (Δ^1J_{CF} values) of system **1**[6] against polar substituent parameters (σ_F and $\Delta\iota$),[9,10] we concluded that the σ-inductive effect, as well as structural effects, cannot be invoked as explanations for the substantial electronegativity contributions to the ^{19}F SCS of system **1**.[6] Thus virtually by default we[6] ascribed the phenomenon to "through-bond" (or "indirect") and "through-space" (or "direct") σ-electron delocalization mechanisms.[13-16] Because the internuclear distance between the bridgehead carbon atoms (C1–C4) in bicyclo[2.2.2]octane (BCO) is considerable (2.59 Å),[17] the former was favored as the dominant transmission mechanism of the electronegativity effect.[6]

In order to shed further light on the aforementioned speculative proposal, we have synthesized and measured the ^{19}F SCS of a series of 4-substituted bicyclo[2.2.1]hept-1-yl fluorides (**2**) possessing a reasonably diverse substituent set. We reasoned that since such a structural change (**1** → **2**) of the intervening connective bonds between the substituents and probe center leads to a significant change in the blend of possible "through-bond" and "through-space" effects underlying appropriate quantum mechanical[13a] and physicochemical[18,19] parameters, then experimental support for our proposal may be forthcoming from the ^{19}F SCS of this new model system (**2**).

Herein we report the results of our study.

Results and Discussion

Synthesis of Compounds. In view of our recent successful syntheses of a large number of derivatives of system **1** from 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid (**1**, X = COOH),[20] 4-fluorobicyclo[2.2.1]heptane-1-carboxylic acid (**2**, X = COOH) was chosen as the target bicyclic structure from which a series of system **2** was to be prepared by similar standard functional group manipulations. We explored two possible approaches (Schemes I and II) to the precursor acid (**2**, X = COOH) based on starting materials [**3** (R = CH_3 and C_2H_5) and **9**] which are now accessible in large quantities from recently published procedures.[20] During initial trial experimentation, the methods outlined in Scheme I led to the successful synthesis of small amounts of the desired acid (**2**, X = COOH). However, we eventually abandoned this approach in favor of the alternative pathway (Scheme II) for two main reasons. Firstly, the initial conversion of Scheme I (**3** → **4**), which is effected by the use of acetic anhydride and tin tetrachloride as reagents,[21] is exceedingly slow. GLC analyses, in conjunction with ^{13}C and ^{1}H NMR, indicated that ca. 85% of **3** (R = CH_3 and C_2H_5) is consumed after 10 days at room temperature. Although increasing the temperature to 45 °C leads to a slight increase in the rate of the reaction (ca. 97% of **3** is consumed in 10 days), it also leads to more by products (OCH_3 replaced by Cl). Secondly, considerable difficulties were encountered in selectively replacing the hydroxyl group at the bridgehead position with fluorine (sulfur tetrafluoride as reagent) in the presence of the carbonyl moiety (**5** → **6**). We found by ^{13}C NMR analysis that **6** was always heavily contaminated with methyl and ethyl 2,2,4-trifluorobicyclo[2.2.2]octane-1-carboxylate.

It is worth noting that to date, *unsymmetrical* derivatization of the bridehead positions of bicyclo[2.2.1]heptane has been achieved with considerable difficulty via a symmetrical precursor,[22,23] namely, 1,4-dichlorobicyclo[2.2.1]heptane.[24] Clearly, since both the methoxyl and carboxyl groups are versatile manipulable functions, the ready accessiblity of 4-methoxybicyclo[2.2.1]heptane-1-carboxylic acid in quantity by the methods (Scheme II) described below now opens up an additional attractive pathway for the synthesis of *unsymmetrical* 1,4-disubstituted bicyclo[2.2.1]heptanes.

The new derivatives of system **2** were unambiguously characterized by ^{13}C NMR (Table VII; see experimental section). An interesting spectral feature of one of the

---

(7) Reynolds, W. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 985, and references cited therein.

(8) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1982**, *14*, 165.

(9) (a) In this and future publications we shall adhere to the nomenclature recently suggested by Reynolds[8] to represent various electronic substituent effects. Thus, the symbol σ_F is employed in place of σ_I in view of the overwhelming evidence that σ_I is a manifestation of polar field effects.[7,8,9b] For our correlative analyses we use σ_F values derived from the ^{19}F SCS of 1-substituted 4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes.[5,6] (b) Adcock, W.; Aldous, G. L.; Kitching, W. *J. Organometal. Chem.* **1980**, *202*, 385.

(10) (a) $\Delta\iota$ ($\iota_X - \iota_H$)[10b] is a parameter employed to characterize substituent electronegativity (χ).[7,8] (b) Inamoto, N.; Masuda, S. *Tetrahedron Lett.* **1977**, 3287.

(11) (a) A study of a series of 1-fluoro-4-(para-substituted-phenyl)bicyclo[2.2.2]octanes[11b] has clearly demonstrated that ^{19}F SCS of aliphatic fluorides reflect primarily changes in fluorine σ-electron density. Moreover, it was shown that a *decrease* in σ-electron density leads to *negative* ^{19}F SCS (*upfield* shift). The converse situation holds for an *increase* in σ-electron density. Since this response to electron-density changes is in the *opposite* direction to conventional expectations,[11c] the shifts are often viewed as being *reverse* or "*abnormal*". However, it is important to note that despite their "abnormal" behavior, the ^{19}F chemical shifts of stereochemically well-defined model aliphatic fluorides appear to respond systematically to the electronic effects of remote substituents.[6,11b,d,e] (b) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2945. (c) It is of interest to note that theoretical studies have been presented which suggest that an *increase* in the total electronic population is accompanied by a *downfield* shift (sp^3 C, carbonyl C, and dialkyl ether O atoms) when the increase in charge is dictated by that of the σ population (Fliszár, S.; Cardinal, G.; Béraldin, M. T. *J. Am. Chem. Soc.* **1982**, *104*, 5287). (d) Béguin, C. *Bull. Soc. Chim. Fr.* **1967**, 4214. (e) Bromilow, J.; Brownlee, R. T. C.; Page, A. V. *Tetrahedron Lett.* **1976**, 3055. Brownlee, R. T. C.; Craik, D. J. *Ibid* **1980**, 1681.

(12) Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, *89*, 379, and references cited therein.

(13) (a) Hoffman, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. (b) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.

(14) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 696.

(15) Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.

(16) (a) Pasman, P.; Rob, F.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1982**, *104*, 5127. (b) Dewey, H. J.; Miller, R. D.; Michl, J. *Ibid.* **1982**, *104*, 5298. (c) Goldberg, A. H.; Dougherty, D. A. *Ibid.* **1983**, *105*, 284.

(17) Yokozeki, A.; Kuchitsu, K.; Morino, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2017.

(18) Kawamura, T.; Matsunaga, M.; Yonezawa, T. *J. Am. Chem. Soc.* **1978**, *100*, 92.

(19) (a) Barfield, M.; Brown, S. E.; Canada, E. D.; Ledford, N. D.; Marshall, J. L.; Walter, S. R.; Yakali, E. *J. Am. Chem. Soc.* **1980**, *102*, 3355. (b) Barfield, M.; Della, E. W.; Pigou, P. E.; Walter, S. R. *Ibid.* **1982**, *104*, 3549.

(20) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2951.

(21) Suzuki, Z.; Morita, K. *J. Org. Chem.* **1967**, *32*, 31.

(22) Wilcox, C. F.; Leung, C. *J. Org. Chem.* **1968**, *33*, 877.

(23) Wiberg, K. B.; Bailey, W. F.; Jason, M. E. *J. Org. Chem.* **1976**, *41*, 2711. Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Am. Chem. Soc.* **1977**, *99*, 2297.

(24) Marchand, A. P.; Weimar, W. R. *J. Org. Chem.* **1969**, *34*, 1109.

Table I. ^{19}F Substituent Chemical Shifts (SCS)[a-c] of 4-Substituted Bicyclo[2.2.1]hept-1-yl Fluorides (**2**)

X	SCS			
	c-C_6H_{12}	$CDCl_3$	DMF	CF_3CO_2H
NO_2	8.63	7.91	7.73	2.16
CN	3.10	2.41	2.29	−3.21
COOH	5.58	4.94	5.16	0.74
$CONH_2$		5.50	5.84	0.04
$COOCH_3$	5.43	4.88	4.82	0.74
$COCH_3$	6.11	5.56	5.66	1.20
OH	11.42	10.79	11.06	5.96
$OCOCH_3$	7.78	7.12	7.12	2.83
F[d]	10.59	10.08	10.11	6.15
Cl	7.48	6.84	6.74	3.15
Br	5.73	5.08	4.98	1.37
I	2.78	2.10	1.99	−1.32
NH_2	11.25	10.56	11.13	
NH_3^+				0.53
CH_3	6.86	6.55	6.66	6.80
CH_2OH	6.50	6.07	6.52	2.29
C_6H_5	6.61	6.21	6.34	5.16
p-$NO_2C_6H_4$	6.73	6.02	6.18	3.15
p-$NH_2C_6H_4$	6.74	6.38	6.63	
p-$NH_3^+C_6H_4$				3.42
$Sn(CH_3)_3$[e]	−2.65	−2.67	−2.54	

[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 positive sign implies deshielding (downfield shift). [b] Accurate to ±0.01 ppm. [c] X = H (relative to internal $FCCl_3$): −183.51 (c-C_6H_{12}), −182.73 ($CDCl_3$), −180.53 ppm (DMF). [d] J_{FF} = 4.4 Hz, $^1J_{CF}$ = 213.4 Hz. Obtained from ^{13}C satellites in the $^{19}F\{^1H\}$ spectrum ($CDCl_3$). [e] Average $J_{^{117,119}Sn-^{19}F}$ values (hertz): 6.84 (c-C_6H_{12}), 5.86 ($CDCl_3$), 6.84 (DMF).

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

X	SCS			
	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
COOH	−4.75	−5.68	−4.93	−10.57
$CONH_2$		−6.09	−4.87	−13.80
$COOCH_3$	−4.38	−5.29	−5.05	−10.19
$COCH_3$	−4.15	−5.11	−4.52	−10.56
OH	−8.06	−9.24	−7.47	−14.96
$OCOCH_3$	−6.08	−7.30	−7.11	−13.15
F	−8.90	−10.32	−10.19	−16.13
Cl	−6.97	−8.14	−8.07	−12.66
Br	−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	
NH_3^+				−17.97
CH_3	−3.81	−3.92	−3.90	−4.08
C_6H_5	−3.37	−3.94	−3.68	−5.29
p-$NO_2C_6H_4$	−4.12	−4.78	−4.15	−8.10
p-$NH_2C_6H_4$[b]	−3.16	−3.77	−3.37	
p-$NH_3^+C_6H_4$				−7.68
$Sn(CH_3)_3$	3.67	3.83	3.94	

[a] Taken from ref 6. [b] ^{19}F SCS (in parts per million) for some additional substituents in system **1** are as follows. $CH{=}CH_2$: −2.90 (c-C_6H_{12}), −3.32 ($CDCl_3$), −3.24 (DMF). $C{\equiv}CH$: −3.42 (c-C_6H_{12}), −4.27 ($CDCl_3$), −4.07 (DMF). $CH{=}CCl_2$: −3.02 (c-C_6H_{12}), −3.63 ($CDCl_3$), −3.40 (DMF). $CH{=}CF_2$: −3.71 (c-C_6H_{12}), −4.17 ($CDCl_3$). (Adcock, W.; Kok, G. B., unpublished work.) [c] Taken from ref 11b.

compounds (**2**, X = F) is that the resonance for C2, C6 (or C3, C5) exhibits six lines characteristic of the X part of an ABX system.[25] In contrast, the corresponding carbon center in system **1** (X = F) displays a deceptively simple triplet.[20]

Since this study focused primarily on the measurement of ^{19}F SCS of derivatives of system **2** and, moreover, since these NMR parameters can be obtained accurately and unambiguously on samples that are not necessarily analytically pure, elemental analyses were not sought for several of the new derivatives of system **2**, particularly when purification was likely to be a significant problem due to volatility, lability, or limited quantities of the sample.

Correlative Analyses. The ^{19}F SCS of system **2** for various solvents are listed in Table I. In order to facilitate comparisons, the previously reported[6] corresponding values of system **1** are listed in Table II. A cursory examination of the data (Tables I and II) reveals a striking contrast between the two systems. Note that for c-C_6H_{12}, $DCCl_3$, and DMF as solvents, the *signs* of the ^{19}F SCS of **2** (Table I) for every substituent are diametrically *opposed* to those observed for **1** (Table II). Thus, whereas polar electron-withdrawing groups (e.g., NO_2, CN, F, etc.) effect *upfield* shifts in **1**, *downfield* shifts are observed in **2** for the corresponding substituents. The converse situation holds for classical polar electron-donor substituents (e.g., $SnMe_3$). Based on the empirically established shift/charge density relationship for ^{19}F chemical shifts of alkylfluorides,[11a,b] these results imply that electron-withdrawing groups lead to a *decrease* and an *increase* in the σ-electron population in the local vicinity of the fluorine in **1** and **2**, respectively.

However, despite this apparent dichotomous situation, the fact that there is an approxmate linear relationship (r = 0.90) between the ^{19}F SCS of both systems in c-C_6H_{12} suggests that similar substituent factors may underlie these electronic probe parameters in both bicycloalkane systems. Significantly, the linear trend between the ^{19}F SCS deteriorates markedly in the other solvent systems [r = 0.85 ($DCCl_3$) and 0.79 (DMF)] and is completely destroyed in CF_3CO_2H (r = 0.15). The only really obvious common feature to both data sets in CF_3CO_2H (Tables I and II) is that the SCS for the fairly polar substituents are all significantly shifted *upfield* relative to the SCS in the other solvents.

In an attempt to establish whether or not the ^{19}F SCS of systems **1** and **2** have a common origin, we have explored the relationship between the shift parameters for **2** and polar substituent constants (σ_F and $\Delta\iota$)[9,10] in the manner previously outlined for the data of **1**.[6] The regression parameters for the standard mulitple linear least-squares regression analysis are set out in Table III. It can be seen that most of the correlations listed are significant at the 99.9% confidence level (CL). The exceptions are those for CF_3CO_2H (99.95 and 90%). A significant improvement of the precision of fit[26] of the correlations was found if CN and Cl are omitted from the data set. Interestingly, this was also found previously to be the case for the correlations of system **1**. Thus, the group electronegativities of these two substituents as defined by their respective ι values[10] must be viewed with suspicion. The *F* test of the variance

---

[25] (a) This phenomenon has been noted with appropriate carbon centers in the proton-decoupled ^{13}C NMR spectra of *o*-, *m*-, *p*-difluorobenzenes.[25b] (b) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 2361.

[26] (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.[26b] A larger value of *F* implies a better overall correlation or a greater significance of an individual regression coefficient.[7,8] The limitation of *r* as an indicator of the precision of fit of linear correlations has recently been discussed.[26c] (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.; Pryor, W. A. *J. Chem. Educ.* **1976**, *53*, 285.

Table III. Results of Correlative Analysis[a] of ^{19}F SCS of 4-Substituted Bicyclo[2.2.1]hept-1-yl Fluorides (2) with Substituent Parameters (σ_F and $\Delta\iota$)

solvent	independent variables	ρ_F[b]	ρ_ι[b]	c[c]	SE[d]	r[e]	r^2	F[f]	F_F[f]	F_ι[f]	n[g]
c-C_6H_{12}	σ_F, $\Delta\iota$	−3.95 (±2.63)	9.53 (±1.42)	3.11	1.78	0.89	0.79	22.95[i]	2.25[j]	44.90[i]	15
c-C_6H_{12}	σ_F, $\Delta\iota$	−2.59 (±2.51)	9.56 (±1.20)	2.78	1.47	0.93	0.87	34.56[i]	1.06[k]	63.54[i]	13[o]
c-C_6H_{12}	$\Delta\iota$		9.06 (±1.10)	2.33	1.47	0.93	0.87	67.67[i]		67.67[i]	13[o]
$DCCl_3$	σ_F, $\Delta\iota$	−3.36 (±2.59)	9.50 (±1.20)	2.56	1.40	0.94	0.88	35.50[i]	1.69[j]	62.81[i]	13[o]
$DCCl_3$	$\Delta\iota$		8.76 (±1.08)	1.94	1.45	0.93	0.87	65.24[i]		65.24[i]	13[o]
DMF	σ_F, $\Delta\iota$	−4.65 (±2.40)	9.61 (±1.12)	2.79	1.39	0.94	0.88	37.54[i]	3.75[l]	73.61[i]	13[o]
DMF	$\Delta\iota$		8.83 (±1.17)	1.99	1.56	0.92	0.84	57.06[i]		57.06[i]	13[o]
CF_3CO_2H	σ_F, $\Delta\iota$	−11.73 (±2.27)	7.91 (±1.33)	3.56	1.20	0.92	0.84	21.32[h]	26.65[m]	35.15[i]	11[o,p]
CF_3CO_2H	$\Delta\iota$		4.74 (±2.32)	0.40	2.36	0.56	0.32	4.15[n]		4.15[n]	11[o,p]

[a] General form of correlation equation: $SCS = \rho_F\sigma_F + \rho_\iota\Delta\iota + c$. [b] Regression coefficients for individual terms plus or minus 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. SCS of CH_2OH, $CONH_2$, p-$NO_2C_6H_4$, and p-$NH_2C_6H_4$ substituents omitted from all correlations. [h] 99.95% CL. [i] 99.99% CL. [j] 85% CL. [k] 60% CL. [l] 80% CL. [m] 99.9% CL. [n] 90% CL. [o] SCS of CN and Cl omitted from data set. [p] SCS of $Sn(CH_3)_3$ and NH_3^+ omitted from data set.

Table IV. Results of Correlative Analysis[a] of ^{19}F SCS of 4-Substituted Bicyclo[2.2.1]hept-1-yl Fluorides (2) with Substituent Parameters (σ_F and $\Delta\chi$[b])

solvent	independent variables	ρ_F	ρ_χ	c	SE	r	r^2	F	F_F	F_χ	n
c-C_6H_{12}	σ_F, $\Delta\chi$	−4.37 (±1.11)	9.96 (±0.57)	2.18	0.75	0.98	0.96	154.9[c]	15.43[d]	304.2[c]	15[f]
c-C_6H_{12}	$\Delta\chi$		9.17 (±0.78)	1.33	1.09	0.96	0.91	139.5[c]		139.5[c]	15[f]
$DCCl_3$	σ_F, $\Delta\chi$	−5.49 (±1.23)	10.00 (±0.57)	2.06	0.75	0.98	0.96	148.6[c]	20.06[d]	286.30[c]	15[f]
$DCCl_3$	$\Delta\chi$		8.83 (±0.83)	0.96	1.17	0.95	0.90	112.4[c]		112.4[c]	15[f]
DMF	σ_F, $\Delta\chi$	−4.95 (±1.56)	9.44 (±0.74)	2.28	1.01	0.97	0.93	81.98[c]	10.09[d]	163.7[c]	15[f]
DMF	$\Delta\chi$		8.77 (±0.92)	1.26	1.32	0.94	0.87	90.56[c]		90.56[c]	15[f]
DMF	σ_F, $\Delta\chi$	−8.09 (±1.30)	10.67 (±0.66)	2.53	0.81	0.98	0.95	132.1[c]	38.8[c]	263.8[c]	16[g]
DMF	$\Delta\chi$		8.95 (±1.15)	1.22	1.55	0.90	0.81	61.0[c]		61.0[c]	16[g]
CF_3CO_2H	σ_F, $\Delta\chi$	−11.74 (±1.59)	9.94 (±1.22)	1.44	1.01	0.95	0.91	47.91[c]	54.92[c]	66.30[c]	13[h]
CF_3CO_2H	$\Delta\chi$		7.53 (±2.86)	−2.20	2.45	0.62	0.39	6.93[e]		6.93[e]	13[h]

[a] See footnote to Table III for definition of terms. [b] See ref 28. [c] 99.99% CL. [d] 99.90% CL. [e] 98.0% CL. [f] SCS of CH_2OH, $CONH_2$, p-$NO_2C_6H_4$, and p-$NH_2C_6H_4$ substituents omitted from correlations. [g] SCS of CH_2OH, p-$NO_2C_6H_4$, and p-$NH_2C_6H_4$ substituents omitted in correlation. [h] SCS of NH_3^+ omitted from correlation.

Table V. Results of Correlative Analysis[a,b] of ^{19}F SCS of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides (1) with Substituent Parameters (σ_F and $\Delta\iota$)

solvent	independent variables	ρ_F	ρ_ι	c	SE	r	r^2	F	n
c-C_6H_{12}	σ_F, $\Delta\iota$	−6.15 (±1.56)	−6.75 (±0.70)	0.18	0.93	0.96	0.92	67.12	16
$DCCl_3$	σ_F, $\Delta\iota$	−8.97 (±1.74)	−6.95 (±0.71)	0.37	0.91	0.97	0.94	91.09	16
DMF	σ_F, $\Delta\iota$	−9.05 (±1.58)	−6.79 (±0.68)	0.40	0.91	0.96	0.92	82.51	16
CF_3CO_2H	σ_F, $\Delta\iota$	−15.76 (±1.83)	−6.11 (±1.01)	−1.04	0.99	0.97	0.94	80.07	13

[a] Taken from ref 6. [b] See footnotes to Table III for definition of terms.

of the correlations[26a] for c-C_6H_{12}, $DCCl_3$, and DMF indicate a clear trend between the ^{19}F SCS and $\Delta\iota$ values (electronegativity effects) but only a marginal statistical dependence on σ_F (polar field effect). In contrast, the ^{19}F SCS in CF_3CO_2H correlate best against a combination of σ_F and $\Delta\iota$.

However, because the statistical fits[26] indicate that the correlations (Table III) are of poor precision, they are, therefore, of dubious value with regards definitive conclusions on the relative importance of the main substituent factors underlying the ^{19}F SCS of 2. Thus, we sought to improve the situation by removing the uncertainties in the electronegativity parameters.[27] This was accomplished by employing the essentially solvent-independent electronegativity contributions to the ^{19}F SCS of system 1,[6] which were previously factored out quantitatively by a method independent of correlative analysis.[28] The values for c-C_6H_{12} as solvent were chosen and placed on the ι scale[10] by setting the contribution for *fluorine* as substituent equal to 1.05.[28] These new electronegativity parameters ($\Delta\chi$) are as follows: NO_2, 0.86; CN, 0.31; COOH, 0.55; $COOCH_3$, 0.50; $COCH_3$, 0.45; $OCOCH_3$, 0.71; OH, 1.00; NH_2, 0.85; F, 1.05; Cl, 0.77; Br, 0.62; I, 0.28; CH_3, 0.52; C_6H_5, 0.40; and $SnMe_3$, −0.50.

The regression parameters for the repeat correlations of the ^{19}F SCS of 2 utilizing the new $\Delta\chi$ values are listed in Table IV. It can be seen (Table IV) that unlike those in Table III, the precision of the statistical fits[26] for these correlations are clearly best against a combination of σ_F and $\Delta\chi$ substituent constants and, moreover, are now respectable for all solvents (r = 0.95–0.98), indicating that 91–96% of the variations are accounted for. It should be noted that the correlation against both constants for DMF was significantly improved by employing $\Delta\chi$ values determined from the residual contributions to the ^{19}F SCS of system 1[28] for this solvent rather than c-C_6H_{12}. We

---

(27) (a) Inamoto et al.[27b] have recently published new ι values, which were calculated by a revised method. We found that the correlations listed in Table III became significantly less precise on employing these new σ-inductive constants. (b) Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1007.

(28) ^{19}F SCS (system 1): polar field contributions ($\rho_F\sigma_F$) are listed in Table V of ref 6. These are equated to $\Delta\chi$ multiplied by a constant. The constant is determined by setting $\Delta\chi$ for *fluorine* equal to 1.05.

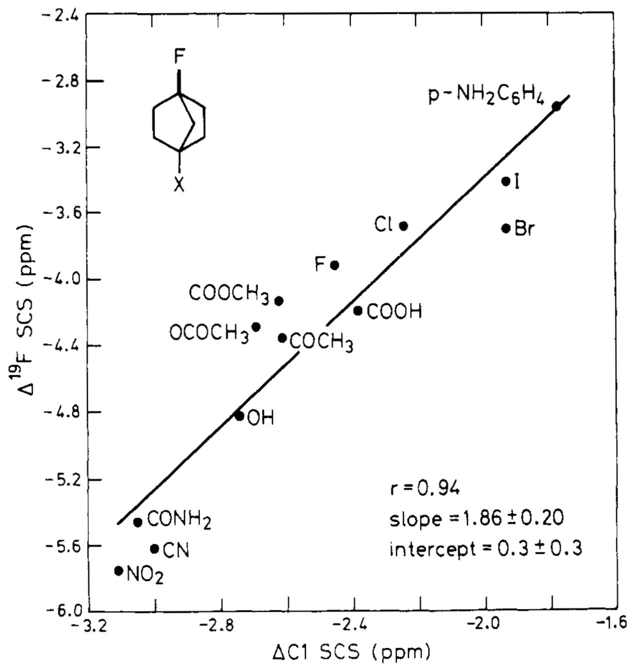


Figure 1. Plot ^{19}F SCS (CF_3CO_2H)–^{19}F SCS ($CDCl_3$) vs. ^{13}C1 SCS (CF_3CO_2H)–^{13}C1 SCS ($CDCl_3$) for system **2**.

ascribe this result chiefly to the significant solvent dependency of the $\Delta\chi$ values in DMF for the strong H-bond donor substituents ($CONH_2$, COOH, OH, and NH_2).

Several significant conclusions follow from a comparison of the results of the statistical analysis listed in Table IV for system **2** with those previously reported for system **1** (a summary of the latter correlations are assembled in Table V). First, similar to **1**, the ^{19}F SCS of **2** are determined predominantly by a blend of electric field (σ_F effect) and electronegativity ($\Delta\chi$ effect) effects. Second, the solvent dependencies of these two dominant substituent influences are essentially the same for both systems, viz., whereas the polar field contributions are quite sensitive to the nature of the solvent, the so-called electronegativity terms remain essentially invariant. The fair correlation (Figure 1) between the solvent-induced changes ($DCCl_3$ to CF_3CO_2H) in the ^{19}F and ^{13}C SCS for **2** (Tables I and VI, respectively) serves to reinforce this point. It should be noted that a similar but more precise linear relationship ($r = 0.99$) was previously presented for system **1**.[6] Third, although the ^{19}F SCS of **1** and **2** clearly have a common origin, the respective electronegativity susceptibility parameters (ρ_χ) have *opposite* signs. Thus, the substituent factor responsible for the remarkable difference between the ^{19}F SCS for **1** and **2** appears to have been unequivocally identified. Finally, the relatively large intercepts for the correlations of **2** (Table IV) compared to **1** (Table V) suggest that substituents in the former system can perturb the ^{19}F chemical shift merely by their presence irrespective of their polar electronic character. We believe that this could imply the importance of substituent-induced structural factors in **2**. In this connection two points are noteworthy. (1) The bridgehead positions in 1,4-dichlorobicyclo[2.2.1]heptane are both flattened relative to the parent unsubstituted bicyclo[2.2.1]heptane.[29] Thus, similar structural differences probably occur between substituted derivatives of **2** and the appropriate parent compound (**2**, X = H). This could lead to a fairly constant structural contribution to the ^{19}F SCS of **2**. (2) Δ^1J_{CF} values of **2** (Table VI), an NMR parameter that is known to reflect structural changes of the bridgehead carbon atom in bicycloalkane systems,[11b,30] are poorly correlated against σ_F [$r = 0.82$; $F = 25.33$; $n = 15$ ($CDCl_3$)], as well as a combination of σ_F and $\Delta\iota$ [$r = 0.86$; $F = 16.53$; $n = 15$ ($CDCl_3$)]. The correlation for CF_3CO_2H as solvent is even worse ($r = 0.66$; $n = 11$). It is significant that these results stand in stark contrast to the good correlation ($r = 0.977$) previously observed for the Δ^1J_{CF} values of **1** vs. σ_F.

Table VI. ^{13}C NMR Parameters for the Bridgehead Carbon (C1) of System **2**

	$CDCl_3$		CF_3CO_2H	
X	C1 SCS, ppm[a,b]	$\Delta\,^1J_{CF}$, Hz[c,e]	C1 SCS, ppm[a,b]	$\Delta\,^1J_{CF}$, Hz[d,e]
NO_2	−6.46	8.1	−9.57	11.8
CN	−3.30	4.4	−6.28	8.8
COOH	−2.33	3.0	−4.71	6.4
$CONH_2$	−2.54	3.3	−5.59	7.9
$COOCH_3$	−2.28	3.0	−4.90	5.9
$COCH_3$	−2.30	3.3	−4.90	6.4
OH	−5.59	3.0	−8.31	7.4
$OCOCH_3$	−6.33	3.7	−9.02	7.4
F	−7.40	6.1	−9.85	9.3
Cl	−5.69	6.6	−7.93	8.8
Br	−5.50	7.0	−7.41	8.8
I	−5.61	7.4	−7.54	8.8
NH_2	−3.97	2.2		
NH_3^+			−8.68	11.3
CH_3	−1.45	0.8		
C_6H_5	−1.67	0.9		
p-$NO_2C_6H_4$	−2.05	2.0		
p-$NH_2C_6H_4$	−1.54	0.9		
p-$NH_3^+C_6H_4$			−3.31	3.0
$Sn(CH_3)_3$	0.78	2.9		

[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). Negative values indicate shielding. Accurate to ±0.04 ppm. [b] C1, 103.90 and 108.64 ppm ($DCCl_3$ and CF_3CO_2H, respectively) relative to Me_4Si. [c] Accurate to ±0.6 Hz. [d] Accurate to ±1.0 Hz. [e] $^1J_{CF}$ = 207.6 and 202.6 Hz ($CDCl_3$ and CF_3CO_2H, respectively).

Polar Field Contribution. Our previous study[11a,b] of a series of 1-fluoro-4-(para-substituted-phenyl)bicyclo[2.2.2]octanes (**1**, X = p-YC_6H_4) has clearly shown that the electric field contribution ($\rho_F\sigma_F$) to the ^{19}F SCS of alkyl fluorides has its origin in the polarization of the CF σ bond. Thus, the magnitude of the polar field term 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.[31] By utilizing the known structural parameters for the carbon skeleton of 1,4-dichlorobicyclo[2.2.1]heptane[29] and other relevant information,[32] a classical electric field calculation[32] for **2** (X = Cl) affords an E_z value (75×10^3 esu) that is significantly larger than the value (56.42×10^3 esu)[6] for the corresponding derivative of **1** (X = Cl). However, because the polarizability of the CF bond of **2** is undoubtedly *less* than that of **1**[31] and, in addition, because an examination of molecular models suggests that the solvent is more likely to impinge significantly on the lines of force in **2** than in **1**, it seems not unreasonable to expect that field contributions ($\rho_F\sigma_F$) for both systems should not be dramatically different. A comparison of the appropriate susceptibility parameters (ρ_F values) listed in

---

(29) Chiang, J. F.; Wilcox, C. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1968**, *90*, 3149.

(30) Della, E. W.; Cotsaris, E.; Hine, P. T. *J. Am. Chem. Soc.* **1981**, *103*, 4131.

(31) The longitudinal polarizability of the C (sp^3)–F σ bond *increases* significantly with a *decrease* in the s character of the exocyclic orbital of the bridgehead carbon (C1).[11b]

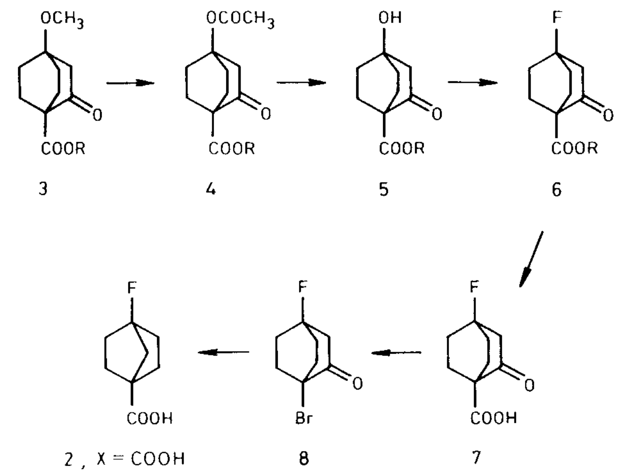
(32) Adcock, W.; Khor, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 7799.

Table VII. ^{13}C NMR Chemical Shifts[a,b] of 4-Substituted Bicyclo[2.2.1]hept-1-yl Fluorides (2)

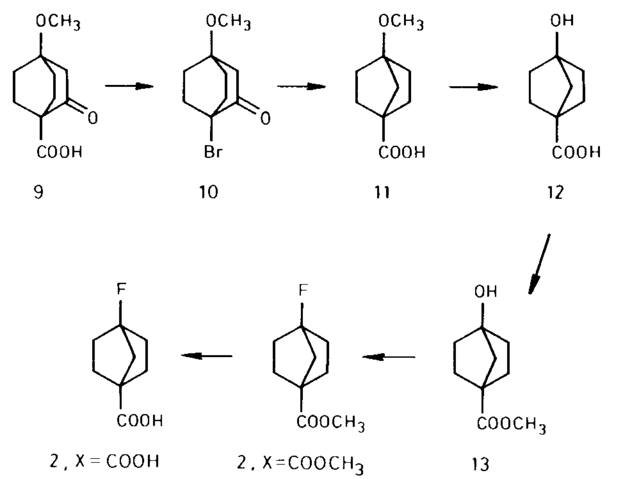
X	C1	C2,C6	C3,C5	C4	C7	others
	chemical shift, ppm					
H	103.90 (207.6)	32.03 (19.8)	29.62 (8.4)	33.00 (8.4)	40.99 (17.6)	
NO_2	97.44 (215.7)	32.52 (21.2)	33.46 (7.3)	85.34 (8.4)	44.76 (20.5)	
CN	100.60 (212.0)	31.42 (20.5)	33.70 (7.7)	33.07 (9.9)	45.06 (20.2)	121.72 (CN)
COOH	101.57 (210.6)	32.12 (20.5)	32.10 (8.1)	47.21 (8.1)	43.99 (19.4)	181.45 (CO)
$CONH_2$	101.36 (210.9)	32.34 (20.5)	32.77 (8.1)	no[c]	43.55 (18.7)	no[c] (CO)
$COOCH_3$	101.62 (210.6)	32.20 (20.5)	32.29 (8.1)	47.35 (7.7)	43.99 (19.4)	51.78 (CH_3), 175.06 (CO)
$COCH_3$	101.60 (210.9)	32.33 (20.5)	31.84 (8.1)	54.56 (8.1)	43.39 (18.7)	25.91 (0.7) (CH_3), 210.25 (CO)
OH	98.31 (210.6)	33.35 (20.5)	35.91 (7.0)	76.63 (9.5)	46.79 (16.1)	
$OCOCH_3$	97.57 (211.3)	32.86 (20.5)	32.77 (7.3)	81.78 (9.9)	44.45 (18.3)	21.58 (CH_3), no[c] (CO)
NH_2	99.93 (209.8)	33.41 (20.1)	36.96 (6.6)	57.30 (8.4)	48.73 (15.4)	
F[d,e]	96.50 (213.7, 10.1)	33.12	33.12	96.50 (213.7, 10.1)	44.44 (17.2)	
Cl	98.21 (214.2)	34.14 (20.9)	38.99 (7.3)	64.46 (9.5)	49.14 (17.9)	
Br	98.40 (214.6)	34.59 (20.9)	40.35 (7.7)	55.64 (9.2)	49.98 (17.6)	
I	98.29 (215.0)	35.15 (20.9)	43.57 (8.1)	30.05 (8.8)	52.22 (17.6)	
CH_3	102.45 (208.4)	33.76 (19.8)	36.46 (8.1)	39.94 (7.3)	47.35 (16.5)	22.06 (CH_3)
C_6H_5[f]	102.23 (208.5)[g]	33.34 (20.0)	36.61 (8.3)	46.67 (7.3)	45.01 (17.6)	145.38 (i), 125.55 (o) 128.29 (m), 126.16 (p)
p-$NO_2C_6H_4$[f]	101.85 (209.6)[g]	33.14 (20.0)	36.52 (8.3)	46.98 (7.8)	44.90 (18.6)	153.10 (i), 126.55 (o) 123.63 (m), 146.44 (p)
p-$NH_2C_6H_4$[f]	102.36 (208.5)	33.40 (20.0)	36.71 (7.8)	45.98 (6.8)	45.32 (17.1)	135.54 (i), 126.42 (o) 115.04 (m), 144.54 (p)
$Sn(CH_3)_3$[h]	104.68 (210.5) [75.2, 78.1]	33.24 (20.5) [39.1]	34.32 (9.3) [10.3]	31.30 (4.4) [no][c]	44.51 (16.6) [6.4]	−11.44 (CH_3) [307.6, 321.3]

[a] Chemical shifts for $CDCl_3$ solution relative to Me_4Si. Accurate to ±0.02 ppm. Positive shifts indicate decreased shielding. [b] $^{13}C-^{19}F$ coupling constants (in hertz) are given in parentheses. [c] no = not observed. [d] C1 (or C4) appears as a doublet of doublets. [e] C2, C6 (or C3, C5) gives six lines characteristic of the X part of an ABX spin system. $^2J_{CF} + {}^3J_{CF} = 28.2$ Hz. [f] The aromatic carbons are designated ipso (i), ortho (o), meta (m), and para (p) with respect to the bicycloheptyl substituent. [g] Accurate to ±0.2 Hz (spectral width of 1000 Hz, 16K/8K data points). [h] $^{13}C-^{117,119}Sn$ coupling constants (in hertz) are given in brackets.

Scheme I



Scheme II



Tables IV and V generally supports this crude expectation.

However, it is important to bear in mind that although the correlative analyses provide unequivocal evidence for a statistically significant electric field contribution to the ^{19}F SCS of both systems (1 and 2), the σ_F and $\Delta\chi$ polar constants are not sufficiently nonparallel to accept that the regression treatment leads to a precise separation of this effect ($\rho_F\sigma_F$) from the dominant concomitant electronegativity influence ($\rho_\chi\Delta\chi$). Previously, because we had unambiguously shown that the ^{19}F SCS of 1 (X = p-YC_6H_4) reflect solely polar field effects,[11b] we were able to determine reasonably accurate polar field susceptibility parameters (ρ_F) for system 1 by dividing the chemical-shift difference between 1 (X = p-$NO_2C_6H_4$) and 1 (X = C_6H_5) by $\Delta\sigma_F$ for p-$NO_2C_6H_4$ and C_6H_5.[5,11b] The susceptibility parameters for 1 determined in this way are as follows: ρ_F (c-C_6H_{12}) = −3.13, ρ_F ($DCCl_3$) = −5.25, ρ_F (DMF) = −4.70, ρ_F (CF_3CO_2H) = −17.56. It was noted that these values agree within a factor of 2 (or better) with those derived from the correlative analysis (Table V). If we are prepared to assume that the ^{19}F SCS of 1-fluoro-4-(para-substituted-phenyl)bicyclo[2.2.1]heptanes (2, X = p-YC_6H_4) are also manifestations of only electric field influences, then a similar factorization of the ^{19}F SCS of system 2 can be achieved by dividing the SCS differentials between 2 (X = p-$NO_2C_6H_4$) and 2 (X = C_6H_5) (Table I) by the appropriate $\Delta\sigma_F$ values [0.24 (c-C_6H_{12}), 0.16 ($DCCl_3$), 0.10 (DMF), and 0.16 (CF_3CO_2H)].[6] In general, the ρ_F values for 2 [0.50 (c-C_6H_{12}), −1.19 ($DCCl_3$), −1.60 (DMF), and −12.56 (CF_3CO_2H)] determined by this method are in relatively poor agreement with those derived by correlative analysis (Table IV). The one exception, namely, the ρ_F value for CF_3CO_2H, is probably fortuitous, given that the correlation for this solvent is the least precise (smallest r and F values.[26a] Since the small *positive* ρ_F value determined for 2 in c-C_6H_{12} is clearly anomalous and, moreover, since the ρ_F values for both systems in $DCCl_3$ are quite disparate [−5.25 (system 1) vs. −1.19 (system 2)],[33] it seems appropriate to conclude that the ^{19}F SCS of 2 (X = p-YC_6H_4), unlike those of 1 (X = p-YC_6H_4), are not manifestations of pure polar field perturbations. The possibility of resonance interactions via the methylene bridge may be the cause. With this in mind we chose another substituent pair (CH_3 and CH_2OH) that would clearly minimize this problem and, at the same time, provide ^{19}F SCS differences (Table I) that reflect only the appropriate $\Delta\sigma_F$ values.[34] The latter requirement is expected to be fulfilled by CH_3 and CH_2OH, since recent theoretical calculations indicate that these two substituents have very similar electronegativity constants.[35] Thus, dividing the ^{19}F SCS differentials (Table I) for this substituent pair by the appropriate $\Delta\sigma_F$ values[34] leads to the following ρ_F values for system 2: −3.60 (c-C_6H_{12}), −3.43 ($DCCl_3$), −3.50 (DMF), and −14.09 (CF_3CO_2H).

Clearly, these new independently defined ρ_F values for 2 agree reasonably well with those indicated by correlative analysis (Table IV) and, hence, provide compelling support for the overall validity of the statistical dissection. The origin of the striking solvent effect for CF_3CO_2H (exalted ρ_F value) has been previously discussed in connection with our studies of 1[6,11b] and will not be reiterated here.

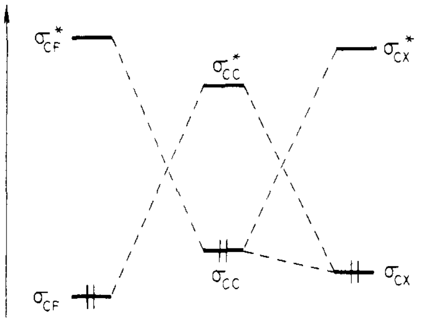


Figure 2. A partial energy diagram showing the interaction of the ethano-bond orbitals (σ_{CC} and σ_{CC}*) of system 1 with adjacent C–F and C–X bond orbitals (σ_{CF}, σ_{CF}*, σ_{CX}, and σ_{CX}*).

Electronegativity Contribution. By definition, the concept of electronegativity pertains to the polarity of the substituent–substrate bond.[7,8] Thus, there are only a limited number of substituent factors that can be invoked to account for the solvent-independent electronegativity contributions (vide supra) to the ^{19}F SCS of systems 1 and 2. These were canvassed in detail in our previous paper[6] and, therefore, will not be reiterated here. Suffice it to state that we believe a plausible explanation for the *opposing* electronegativity contributions in 1 and 2 can only be achieved in terms of the σ-electron delocalization mechanisms.[13-16] The available evidence[13,18,19] is that "through-three-bond" delocalization (TB-3) is antagonistic to both "through-two-bond" (TB-2) and "through-space" or nonbonded interactions (NBI). Thus, accepting our previous conclusion that the TB-3 mechanism is dominant in 1,[6] then the ^{19}F SCS trends of 2 relative to 1 are sensible only if the TB-2 and NBI interactions now control the long-range electronegativity influence in this particular bicycloalkane system; i.e., whereas the TB-3 effect for *electronegative* substituents is *shielding* (upfield shifts) and dominant in 1, the TB-2 and NBI effects are *deshielding* (downfield shifts) and dominant in 2. The converse situation prevails for *electropositive* groups. A change in the blend and nature of the TB and NBI effects in proceeding from 1 to 2 was anticipated on simple structural grounds (see introduction).

Although current ^{19}F chemical-shift theory[36] is unable to provide an obvious framework within which these effects can be confidently discussed, it is instructive to qualitatively examine these puzzling shift variations in terms of the dominant orbital interactions governing the electron delocalization mechanisms. Previously,[6] after scrutiny of pertinent bond molecular orbital parameters (orbital coefficients, resonance integrals, and energy differentials) related to electronegativity[37] and, moreover, in the light that a *decrease* in hyperconjugation (π–σ_{CF}*) in benzyl fluorides leads to signficant *negative* ^{19}F SCS[38] (*upfield* shifts, e.g., electron-withdrawing para substituents), we proposed that the dominant TB-3 interaction in 1 for *electronegative* substituents is largely governed by the extent of the interaction between σ_{CC} (ethano-bond molecular orbital) and σ_{CF}* (i.e., the best intrinsic donor–acceptor interaction).[37] Although we did not explicitly mention it in our previous paper[6], it follows that perturbation of the other significant donor–acceptor interaction

---

[33] The similar values for the Δ^1J_{CF} differentials ($DCCl_3$) of 1 and 2 (X = p-$NO_2C_6H_4$ and C_6H_5; 1.0[11b] and 1.1 Hz (Table VII), respectively), additional monitors of polar field influences,[11b] strongly suggest that ρ_F values for 1 and 2 should be almost the same.

[34] The ^{19}F SCS (in parts per million) of 1-(hydroxymethyl)-4-(p-fluorophenyl)bicyclo[2.2.2]octane[9a] in the various solvents are as follows: 0.26 (c-C_6H_{12}), 0.37 ($DCCl_3$), 0.07 (DMF), and 0.83 (CF_3CO_2H). These values divided by the appropriate ρ_F values[6] lead to the following σ_F constants for CH_2OH: 0.10 (c-C_6H_{12}), 0.14 ($DCCl_3$), 0.04 (DMF), 0.32 (CF_3CO_2H). The σ_F value for CH_3 is zero.[6]

[35] Marriott, S.; Topsom, R. D. *Tetrahedron Lett.* **1982**, 1485.

[36] Ebraheem, K. A. K.; Webb, G. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1977**, *11*, 149, and references cited therein.

[37] Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. *Top. Curr. Chem.* **1977**, *70*, 1, and references cited therein.

[38] Adcock, W.; Abeywickrema, A. N. *Tetrahedron Lett.* **1979**, 1809.

(σ_{CF}–σ_{CC}*) also contributes, particularly for *electropositive* substituents. A simplified perturbation diagram showing these orbital interactions is displayed in Figure 2. It should be noted that although the energy levels for σ_{CX} and σ_{CX}* in this diagram are arbitrarily assigned for generalization purposes, the relative ordering levels for σ_{CF} and σ_{CC} are based on known bond ionization potentials.[37] If we accept that donor–acceptor orbital interactions in the neutral ground state are matrix element controlled,[37,39,40] than 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 and, thus, results in an *upfield* shift,[38] as observed.

For the replacement of hydrogen at the bridgehead by an *electropositive* substituent, it is reasonable to expect in terms of this simple PMO model[37,41] an *increase* in the σ_{CX}–σ_{CC}* interaction with a consequential *decrease* in σ_{CF}–σ_{CC}*. This would lead to an *increase* in the electron density in the vicinity of the fluorine nucleus and, hence, *downfield shifts*,[11a,b] as observed. An alternative explanation for these substituents can be advanced based on an *increase* in the σ_{CC}–σ_{CX} interaction, which would ensure that conjugative transfer of charge from σ_{CC} to σ_{CF}* is *increased*. This would be possible if the energy ordering levels (see Figure 2) are such that σ_{CX} (X = SnMe$_3$) is lower than σ_{CC}. In this connection it is interesting to note that if the energy of σ_{CC} can be equated to the first ionization potential of bicyclo[2.2.2]octane (9.53 eV),[42] then this may well be the case.[43]

It is important to note that the notion expressed above that conjugative charge transfer involving the σ_{CF} and σ_{CF}* bond MO orbitals is an important contributing determinant of the polar ^{19}F SCS of system 1 provides a qualitative explanation for the magnitude and sign of inductively induced *vicinal* ^{19}F SCS of saturated fluorides.[44] In these systems, replacing a substituent that is vicinal to fluorine by a more electronegative group causes pronouned *upfield* shifts (*reverse* ^{19}F SCS).[11a] The effect is maximal in the antiperiplanar arrangement. Most significantly, the geometric requirement for the dominant σ_{CX}–σ_{CF}* and σ_{CF}–σ_{CX}* interactions are optimally met in this conformation.[37] Now since *increasing* the electronegativity of X *decreases* and *increases* the former and latter orbital interactions (i.e., charge transfer into and out of σ_{CF}* and σ_{CF} is *decreased* and *increased*, respectively), large *upfield* shifts are to be expected (vide supra).

From the aforementioned simple orbital interaction model proposed for the TB-3 effect on ^{19}F SCS, we would predict that benzo annelation of 1 should markedly reduce the influence of this polar transmission mechanism owing to an increase in the s character of the two hybrid orbitals forming the pertinent bridging σ bond (σ_{CC}).[45] The lowering and raising in energy of σ_{CC} and σ_{CC}* (Figure 2) weakens the dominant orbital interactions (σ_{CF}*–σ_{CC}–σ_{CX}* and σ_{CF} –σ_{CC}*–σ_{CX}) governing the TB-3 effect. In line with this prediction, Stock et al.[46] observed a dramatic perturbation (electron-withdrawing substituents) of the ^{19}F SCS of 1 on dibenzo annelation (*negative* to *positive* signs), which they erroneously attributed to substituent-induced structural phenomena.[6] The puzzling apparent dichotomous ^{19}F SCS results of the dibenzo derivatives of 1[46] are now understandable in terms of a much reduced TB-3 effect (shielding contribution), which allows the NBI interaction (deshielding contribution) to prevail over polar field effects (shielding contribution). The NBI effect increases and prevails in 2 because the bridgehead carbons are now closer together,[17,29,47] and the TB-3 effect is inefficient due to an unfavorable geometry.[13]

Based on overlap and differential energy considerations,[37] the dominant orbital interaction governing the NBI effect on the ^{19}F SCS is probably σ_{CF}*–σ_{CX}* (see Figure 2). The extent of this interaction probably determines the magnitude of the average excitation energy term (ΔE) in the expression for the dominant paramagnetic contribution to ^{19}F chemical shifts.[36] As the substituent becomes more electronegative, the σ_{CF}*–σ_{CX}* orbital interactions will *increase* and, hence, further lower the energy of the appropriate delocalized LUMO to which excitation occurs. This would lead to a decrease in ΔE and, therefore, *downfield* shifts for the NBI effect of electronegative substituents, as observed.

Finally, it should be pointed out that we do not have a simple interpretation of the mode of action of the TB-2 effect on the ^{19}F SCS of system **2**. Furthermore, we are unable to comment on its importance relative to the concomitant NBI interaction. However, it is pertinent to note that whereas the σ_{CC} and σ_{CC}* bond molecular orbitals in 1 couple the symmetric (S) and antisymmetric (A) combinations of σ_{CF}*–σ_{CX}* and σ_{CF}–σ_{CX} (TB-3 effect),[48] respectively, the HOMO of σ_{CH_2} (A) and LUMO of σ_{CH_2}* (S) couple the A and S combinations of σ_{CF}*–σ_{CX}* and σ_{CF}–σ_{CX} (TB-2 effect), respectively; i.e., the effects on these grounds are diametrically opposed.[49]

Conclusions

This study, together with our previous work,[6] provides compelling experimental evidence that, besides polar field effects, long-range electronegativity influences contribute significantly to the ^{19}F SCS of system 1 and 2. Most importantly, these latter influences are diametrically *opposed* in these two bicycloalkane systems. We have proposed that σ-electron delocalization mechanisms provide a plausible explanation for this remarkable phenomenon.

Further, it is significant to note that these results stand in stark contrast to previous studies of polar substituent effects in these bicycloalkane model systems[2,3,50] and others,[3,4] as monitored by chemical reactivity probes. Here the overwhelmingly dominant influence is the polar field effect.[7,8] This point highlights an important distinction between the nature and transmission of polar effects as monitored by neutral NMR probes, on the one hand, and

---

(39) Bernardi, F.; Mangine, A.; Epiotis, N. D.; Larson, J. R.; Shaik, S. *J. Am. Chem. Soc.* **1977**, *99*, 7465.

(40) Adcock, W.; Cox, D. P.; Kitching, W. *J. Organometal. Chem.* **1977**, *133*, 393.

(41) Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Press: New York, 1975.

(42) (a) Bodor, N.; Dewar, M. J. S.; Worley, S. D. *J. Am. Chem. Soc.* **1970**, *92*, 19. (b) It should be noted that bridgehead substituents appear to have little effect on the first ionization potential.[42a]

(43) See Pitt, C. G. *J. Organometal. Chem.* **1973**, *61*, 49, for vertical ionization potentials of σ orbitals for the group IVB series [M(CH$_3$)$_3$].

(44) Phillips, L.; Wray, V. *J. Chem. Soc. Perkin Trans. 2* 1972, 223, and references cited therein.

(45) An enhancement of the TB-3 effect has recently been ascribed to an increase in the p character of the σ bond orbital through which coupling occurs.[16b]

(46) Anderson, G. L.; Stock, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 6804.

(47) (a) Dalhinga, G.; Toneman, L. H. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 795. (b) Doms, L.; Van den Enden, L.; Geise, H. J.; Van Alsenoy, C. *J. Am. Chem. Soc.* **1983**, *105*, 158.

(48) The mirror plane is perpendicular to the threefold axis in system 1.

(49) (a) Theoretical calculations (ab initio STO-3G) for 1 indicate *virtual orbitals* of relatively low energy which would provide a "through-bond" path for electron delocalization in this system but not for 2.[48b] (b) Topsom, R. D.; Adcock, W., unpublished results.

(50) Grob, C. A.; Rich, R. *Tetrahedron Lett.* **1978**, 663. Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2793.

charged probes, on the other.[8,51] Although, in general, "through-bond" effects cannot compete with direct polar field interactions in the case of chemical reactivity, we believe the apparent electron-withdrawing influence of alkyl groups (polar field effects are *zero*; $\sigma_F = 0$)[6] on the solvolysis of 4-substituted bicyclo[2.2.2]octyl *p*-nitrobenzenesulfonates[50] is a possible manifestation of the "through-three-bond" interaction (TB-3 effect) that is encountered in system **1**. In addition, it is worth noting that this polar conjugative mechanism may also be responsible for the fact that the half-wave reduction potentials for a limited series of 4-substituted bicyclo[2.2.2]oct-1-yl iodides[52] are poorly correlated against polar field parameters (σ_F values).

Finally, it should be mentioned that from this work and our other studies[6,11b,38] three important factors have been identified that control the magnitude and direction of ^{19}F chemical shifts of bicyclic fluorides. It is of interest that the interplay of these factors clearly provides a qualitative understanding of the unusual ^{19}F chemical shift trend recently reported for a series of these derivatives.[53] Thus, an initial high field trend followed by a *reversal* to lower field may be understood in terms of a *decrease* in σ_{CC} (and σ_{CH})–σ_{CF}* interactions (shielding influence) with a concomitant *decrease* in the ionicity of the CF σ bond (shielding influence)[53c] as one proceeds to the more highly strained systems and, then, suddenly these considerable effects becoming masked by the large *deshielding* "through-space" effect.[53b,d]

Experimental Section

General Information. Mass spectra were obtained on an AEI MS30 spectrometer using an ionizing energy of 70 eV. Vapor-phase chromatographic analyses were performed on a Varian 1740 gas chromatograph with 10-ft column of 5% SE-30 on 100/120 chromosorb W. Melting and boiling points are uncorrected. The former were all determined by using sealed capillary tubes. Small liquid samples (up to 5 mL) were usually purified by distillation in a Kugelrohr apparatus (Büchi GKR-50). Hence, the boiling points quoted for these cases pertain to the glass-oven temperatures of the latter equipment.

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. In general, routine spectra were obtained on $DCCl_3$ solutions (ca. 2 M) in 5-mm tubes with Me_4Si as an internal reference (spectral width of 4000 or 6002 Hz, 16K/8K data points). However, for the alicyclic ring carbons of system **2**, the data (Table VII) were taken from spectra obtained on fairly dilute $DCCl_3$ solutions (ca. 0.2 M) with a spectral width of 3000 Hz and 16K/8K data points (digital resolution of 0.37 Hz). Some of these compounds were remeasured with a spectral width of 4000 (**2**, X = CN, C_6H_5, *p*-$NO_2C_6H_4$, and *p*-$NH_2C_6H_4$) and 5000 Hz (**2** X = $COOCH_3$ and $COCH_3$) to obtain the chemical shifts of other carbon centers. The ^{13}C NMR data for system **2** in CF_3CO_2H as solvent (Table VI) were obtained from spectra recorded on solutions (ca. 0.2 M) in 5-mm tubes containing Me_4Si and C_6D_6 (10%, v/v) as an internal reference and lock, respectively. A spectral width of 4000 Hz with 16K/8K data points was employed (digital resolution of 0.49 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. A spectral width of 2000 Hz was used, and the data were collected into 8K/4K data points, giving a resolution of better than 0.01 ppm. Each sample consisted of a mixture of the unsubstituted (X = H, <1 mg) and substituted (<1 mg) compounds dissolved in 0.5 mL of the appropriate solvent.

^{1}H NMR specta were measured with a Varian A60 spectrometer.

1-Bromo-4-methoxybicyclo[2.2.2]octan-2-one (10). 4-Methoxy-2-oxobicyclo[2.2.2]octane-1-carboxylic acid[20] (**9**; 21.5 g, 0.11 mol) in 1,2-dibromoethane as solvent[54] was treated with mercuric oxide following the procedure of Cristol and Firth.[55] A workup in the usual fashion afforded crude 1-bromo-4-methoxybicyclo[2.2.2]octan-2-one (**10**) as a brown viscous oil (16 g, 70%). A sample was chromatographed on alumina and then sublimed to afford a white solid: mp 68–70 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 66.20 (C1), 202.51 (C2), 47.84 (C3), 72.51 (C4), 31.10 (C5), 33.91 (C6), 49.89 (OCH_3). Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.25; H, 5.60.

4-Methoxybicyclo[2.2.1]heptane-1-carboxylic Acid (11). A mixture of crude **10** (19.3 g, 0.08 mol) and a 12% aqueous solution of potassium hydroxide was heated under reflux for 48 h.[56] The solution was cooled and then extracted with ether before being carefully acidified with concentrated hydrochloric acid. The acidified solution was saturated with sodium chloride and then subjected to continuous extraction with dichloromethane. A workup in the usual manner, followed by sublimation (8.5 g, 60%) and recrystallization from hexane, afforded colorless prisms of the acid (**11**): mp 67–68.5 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 48.25 (C1), 35.52 (C2), 31.21 (C3), 87.01 (C4), 43.05 (C7), 52.81 (OCH_3), 181.18 (COOH). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.85; H, 8.18.

4-Hydroxybicyclo[2.2.1]heptane-1-carboxylic Acid (12). A mixture of **11** (22.6 g, 0.13 mol), 48% aqueous hydrobromic acid (134 g), and acetic anhydride (134 g) was refluxed under a nitrogen atmosphere for 24 h.[57] The solution was cooled, poured into water (150 mL), and left to stand for 2 h. The solution was then saturated with sodium chloride and subjected to continuous extraction with dichloromethane. A workup in the usual manner, followed by sublimation (16.4 g, 81%) and recrystallization from a hexane–ethanol mixture, afforded 4-hydroxybicyclo[2.2.1]heptane-1-carboxylic acid (**12**) as colorless plates: mp 136–137 °C; ^{13}C NMR (D_2O, relative to external Me_4Si) δ 50.07 (C1), 33.69 (C2), 35.25 (C3), 82.20 (C4), 46.43 (C7), 181.57 (COOH). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.41; H, 7.64.

Methyl 4-Hydroxybicyclo[2.2.1]heptane-1-carboxylate (13). By use of the esterification procedure of Clinton et al.,[58] a solution of the carboxylic acid (**12**; 5.9 g, 0.038 mol) in absolute methanol (4.5 g) and 1,2-dichloroethane (17 mL) containing concentrated sulfuric acid (0.5 mL) was refluxed with stirring for 18–20 h. A standard workup afforded a crude product contaminated with an unknown impurity (ca. 5%). Distillation afforded the ester (6.0 g, 92%) as a colorless oil: bp 100–105 °C (4.5 mm); n^{25}_D 1.4797; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 49.03 (C1), 33.04 (C2), 35.25 (C3), 81.68 (C4), 46.68 (C7), 51.76 ($COOCH_3$), 176.23 ($COOCH_3$). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.15; H, 8.21.

The ester was also obtained in high yields (virtually quantitative) by treating the acid (**12**) with an ether solution of diazomethane.[59]

---

(51) Adcock, W.; Cox, D. P. *J. Org. Chem.* **1979**, *44*, 3004.

(52) Abeywickrema, R. S.; Della, E. W. *Aust. J. Chem.* **1981**, *34*, 2331.

(53) (a) Bradshaw, T. K.; Hine, R. P.; Della, E. W. *Org. Magn. Reson.* **1981**, *16*, 26. (b) Chemical shifts (in parts per million) relative to $FCCl_3$:[53a] 1-fluoroadamantane, −127.78; 1-fluorobicyclo[2.2.2]octane, −147.60; 1-fluorobicyclo[2.2.1]heptane, −182.04; 1-fluorobicyclo[2.1.1]hexane, −157.37; 1-fluorobicyclo[1.1.1]pentane, −132.46. (c) The change in the ionicity of the CF σ bond is manifested by changes in $^1J_{CF}$. Thus, based on a proportionality constant (Δ^{19}F SCS = −0.84 Δ^1J_{CF}) previously determined[11b] and the differential in $^1J_{CF}$ values[30] for 1-fluoroadamantane and 1-fluorobicyclo[1.1.1]pentane, the latter is predicted to be 123.14 ppm *upfield* of the former based on the change in the ionicity of the CF σ bond alone. Note that, owing to the counteractive "through-space" effect, the *upfield* differential is only 4.68 ppm. (d) It is of interest to note that since similar factors (hyperconjugation, hybridization, and "through-space" effects) probably govern the intrinsic relative stability of the bridgehead carbonium ions of the corresponding bicycloalkanes, it is not surprising to find that the relative stabilities of these electron-deficient species (Dr. E. W. Della, unpublished work) parallel the trend of the ^{19}F shifts of the bicyclic fluorides.

(54) Baker, F. W.; Holtz, H. D.; Stock, L. M. *J. Org. Chem.* **1963**, *28*, 514.

(55) Cristol, S. J.; Firth, W. C. *J. Org. Chem.* **1961**, *26*, 280.

(56) Abeywickrema, R. S.; Della, E. W. *Org. Prep. Proced. Int.* **1980**, *12*(6), 357.

(57) Adcock, W.; Abeywickrema, A. N. *Aust. J. Chem.* **1981**, *34*, 1253.

(58) Clinton, R. O.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *70*, 3135.

Methyl 4-Fluorobicyclo[2.2.1]heptane-1-carboxylate (2, X = $COOCH_3$). The alcohol **13** (5.5 g, 0.032 mol) was treated with sulfur tetrafluoride[60] (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.[57] A workup following the usual precautions, followed by distillation, afforded compound **2** (X = $COOCH_3$) as a colorless oil (4.8 g, 85%): bp 70–75 °C (1 mm); $n^{16}{}_D$ 1.4526. Anal. Calcd. for $C_9H_{13}FO_2$: C, 62.78; H, 7.61. Found: C, 62.94; H, 7.52.

Several preparations of the fluoro compound (2, X = $COOCH_3$) revealed that the yield, which varied between 50 and 85%, was markedly dependent on the quality of the commercial grade sulfur tetrafluoride.

4-Fluorobicyclo[2.2.1]heptane-1-carboxylic Acid (2, X = COOH). The ester (2, X = $COOCH_3$; 3.4 g, 0.02 mol) was treated with aqueous ethanolic potassium hydroxide in the manner previously outlined for the corresponding BCO derivattive (1, X = $COOCH_3$).[20] Sublimation of the crude acid, followed by recrystallization from hexane, afforded colourless plates (2.8 g, 90%): mp 121–123 °C. Anal. Calcd for $C_8H_{11}O_2F$: C, 60.75; H, 7.01. Found: C, 60.96; H, 7.15.

4-Fluorobicyclo[2.2.1]heptan-1-amine (2, X = NH_2). The carboxylic acid (2, X = COOH; 0.47 g, 0.003 mol) was converted into the amine (2, X = NH_2) according to a method outlined by Wiberg and Lowry.[61] Sublimation afforded a colorless solid (0.26 g, 68%). The amine was stored and handled under an atmosphere of nitrogen. Elemental analyses were not sought.

1-Fluoro-4-nitrobicyclo[2.2.1]heptane (2, X = NO_2). By use of the procedure of Kornblum and Jones,[62] a stirred slurry of the amine (2, X = NH_2; 0.17 g, 0.0013 mol), magnesium sulfate (0.20 g), acetone (4 mL) and water (1 mL) was treated portionwise with potassium permanganate (1.31 g, 0.0083 mol) over a period of 30 min, while the temperature was maintained at 25–30 °C. After the mixture was stirred for a further 48 h at room temperature, the reaction mixture was worked up in a standard manner. Sublimation of the crude residue afforded **2** (X = NO_2) as a colorless solid, (0.12 g, 57%). Recrystallization from hexane gave colorless microcrystals, mp 118–120 °C. Anal. Calcd for $C_7H_{10}O_2FN$: C, 52.83; H, 6.33; F, 11.94. Found: C, 52.72; H, 6.25; F, 12.30.

4-Fluorobicyclo[2.2.1]heptane-1-carbonitrile (2, X = CN). The carboxylic acid (2, X = COOH; 0.47 g, 0.003 mol) was treated with thionyl chloride in a standard manner to give the acid chloride (2, X = COCl). A solution of the crude acid chloride in ether (15 mL) was cooled to 0 °C, and dry ammonia gas was bubbled in for 20–30 min. A standard workup, followed by sublimation, afforded **2** (X = $CONH_2$) as a white solid (0.43 g, 82%): mp 220 °C; mass spectrum, *m/e* 157 (M^+).

A suspension of the amide (2, X = $CONH_2$; 0.43 g, 0.0024 mol) in dry pyridine (0.47 g, 0.006 mol) and dry dioxane (30 mL) was treated with trifluoroacetic anhydride (0.45 mL, 0.003 mol) at 10 °C according to a procedure outlined by Campagna et al.[63] A standard workup, followed by sublimation (0.26 g, 68%) and recrystallization from hexane, gave a colorless microcrystalline solid, mp 95–96.5 °C. Anal. Calcd for $C_8H_{10}FN$: C, 69.04; H, 7.24. Found: C, 69.20; H, 7.12.

1-Acetyl-4-fluorobicyclo[2.2.1]heptane (2, X = $COCH_3$). An ethereal solution of methyllithium (13 mL of 1 M solution, 0.0013 mol) was slowly added to a well-stirred solution of the carboxylic acid (2, X = COOH; 1.0 g, 0.0063 mol) in dry ether (7 mL).[64] The resulting slurry was then refluxed under a nitrogen atmosphere for 2 h. A standard workup, followed by distillation in a Kugelrohr apparatus, afforded the ketone (2, X = $COCH_3$) as a colorless oil: 0.6 g (52%); bp 75–80 °C (4.5 mm); ^1H NMR (CCl_4) δ 1.53–2.18 (10 H, m, CH_2CH_2 and CH_2), 2.08 (3 H, s, $COCH_3$). GLC analysis and ^1H NMR indicated that the ketone was contaminated with a small amount of the tertiary alcohol [2, X = $C(CH_3)_2OH$]. A sample of the ketone was not purified for elemental analysis.

1-Acetoxy-4-fluorobicyclo[2.2.1]heptane (2, X = $OCOCH_3$). A solution of the acetyl compound (2, X = $COCH_3$; 1.32 g, 0.0085 mol) in dichloromethane (50 mL) was stirred with *m*-chloroperbenzoic acid (3.74 g of ca. 85% purity, ca. 0.018 mol) in the dark at 45 °C for 2 weeks.[65] During this time the reaction was monitored by GLC analyses. Additional amounts of *m*-chloroperbenzoic acid were added at frequent intervals in order to maintain a reasonable reaction rate. The reaction was 90% complete after 2 weeks. A standard workup, followed by distillation, afforded the acetate (2, X = $OCOCH_3$) as a colorless oil: 1.06 g (69%); bp 110–115 °C (33 mm); ^1H NMR (CCl_4) δ 1.58–2.28 (10 H, m, CH_2CH_2 and CH_2), 1.95 (3 H, s, $OCOCH_3$).

4-Fluorobicyclo[2.2.1]heptan-1-ol (2, X = OH). The acetate (2, X = $OCOCH_3$; 0.86 g, 0.005 mol) was treated with sodium methoxide (0.63 g, 0.011 mol) in refluxing methanol (8 mL) as previously described for the corresponding BCO derivative.[20] A standard workup, followed by sublimation, afforded the alcohol as a white waxy solid (0.57 g, 74%) with an indefinite mp: mass spectrum, *m/e* 130 (M^+).

1,4-Difluorobicyclo[2.2.1]heptane (2, X = F). The alcohol (2, X = OH; 0.52 g, 0.004 mol) was treated with sulfur tetrafluoride[60] in the manner indicated above for the preparation of **2** (X = $COOCH_3$). A careful workup led to the volatile fluoride (2, X = F) being obtained as a solution in fluorotrichloromethane. The solvent was removed carefully by distillation through a 15-cm column packed with glass helices. GLC analysis of the pale yellow liquid residue indicated that the fluoride (2, X = F) was >95% pure. No attempt was made to purify the compound because of its high volatility.

1-Bromo-4-fluorobicyclo[2.2.1]heptane (2, X = Br). The carboxylic acid (2, X = COOH; 0.47 g, 0.003 mol) was treated with red mercuric oxide and bromine in dichloromethane as previously described for the preparation of the corresponding BCO derivative.[20] A standard workup, followed by distillation, afforded the bromo compound (2, X = Br) as a colorless oil: 0.20 g (35%); bp 90 °C (40mm); mass spectrum, *m/e* 192, 194 (M^+).

1-Fluoro-4-iodobicyclo[2.2.1]heptane (2, X = I). The carboxylic acid (2, X = COOH; 2.25 g, 0.014 mol) was treated with *tert*-butyl hypoiodite and then irradiated in the same manner as previously described for the preparation of the corresponding BCO derivative.[20] A standard workup, followed by chromatography on alumina, afforded the iodide as a colorless liquid (2.57 g, 72%): mass spectrum, *m/e* 240 (M^+). An attempt to distill the compound [pot temperature: 60 °C (3.5 mm)] led to substantial decomposition. Thus, the compound was used in subsequent syntheses (see below) without further purification.

1-Chloro-4-fluorobicyclo[2.2.1]heptane (2, X = Cl). A solution of the iodide (2, X = I; 0.35 g, 0.0015 mol) and iodine monochloride (0.33 g, 0.002 mol; prepared by passing a known volume of dry chlorine gas into iodine)[66] in fluorotrichloromethane (2 mL) was stirred in the dark at room temperature[67] until monitoring by GLC analyses indicated that all the iodide was consumed. The solution was diluted with fluorotrichloromethane and then washed with a sodium thiosulfate solution. The organic layer was dried before the solvent was removed through a short column packed with glass helices. The chloride (0.20 g) was obtained almost quantitatively as a very pale yellow liquid: mass spectrum, *m/e* 150 (M^+).

1-Fluoro-4-(*p*-nitrophenyl)bicyclo[2.2.1]heptane (2, X = *p*-$NO_2C_6H_4$). A solution of the iodide (2, X = I; 0.53 g, 0.0022 mol) in dry spectral grade benzene (25 mL) was irradiated for 96 h following the general photochemical procedure of Kropp et al.[68] After this time, GLC analyses indicated the reaction was only 50% complete. A standard workup, followed by column chromatography (alkaline alumina; pentane as eluant) of the crude

---

(59) Vogel, A. I. "Practical Organic Chemistry"; Longmans: London, 1970; pp 971–973.

(60) Boswell, G. A.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1.

(61) Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188.

(62) Kornblum, N.; Jones, W. J. *Org. Synth.* **1963**, *43*, 87.

(63) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

(64) (a) Tegner, C. *Acta. Chim. Scand.* **1952**, *6*, 782. (b) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.

(65) (a) Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2802. (b) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914.

(66) Woollett, G. H. Johnson, W. W. In "Organic Syntheses"; Wiley: New York, 1943; Coll. Vol. II, p 343.

(67) Kauer, J. C. *Prepr., Div. Pet. Chem., Am. Chem. Soc.* **1970**, *15*, B14–B18.

(68) Kropp, P. J.; Poindexter, G. S.; Pienta, N. J.; Hamilton, D. C. *J. Am. Chem. Soc.* **1976**, *98*, 8135.

J. Org. Chem. **1984**, *49*, 1397–1402 **1397**

reaction mixture, afforded 1-fluoro-4-phenylbicyclo[2.2.1]heptane (**2**, X = C_6H_5) as a white solid (0.08 g, 38% based on unreacted iodide). Recrystallization from hexane gave colorless prisms: mp 42–44 °C; mass spectrum, *m/e* 190 (M^+).

A vigorously stirred suspension of the phenyl derivative (**2**, X = C_6H_5; 0.107 g, 0.00056 mol) in acetic anhydride (1.5 mL) was treated with concentrated nitric acid (0.11 mL, sp gr 1.42) in the same manner as previously described for the corresponding BCO derivative.[69] A workup in the usual fashion afforded the nitro derivative (**2**, X = *p*-$NO_2C_6H_4$) as a cream solid (0.084 g, 64%) after sublimation. Recrystallization from methanol afforded colorless needles, mp 97–98 °C. Anal. Calcd for $C_{13}H_{14}FNO_2$: C, 66.37; H, 6.00. Found: C, 66.16; H, 5.84.

The amine (**2**, X = *p*-$NH_2C_6H_4$) was prepared by catalytic hydrogenation (H_2, 50 psi; 5% Pd/C) of the nitro compound (**2**, X = *p*-$NO_2C_6H_4$; 0.07 g, 0.0003 mol) in absolute ethaol (20 mL). A standard workup, followed by sublimation, afforded the amine (**2**, X = *p*-$NH_2C_6H_4$) as an off-white solid (0.035 g, 57%), mp 100–111 °C.

1-Fluoro-4-(trimethylstannyl)bicyclo[2.2.1]heptane [2, X = $Sn(CH_3)_3$]. A solution of the iodide (**2**, X = I; 0.51 g, 0.002 mol) in tetrahydrofuran (6 mL) was treated with trimethyltin lithium in tetrahydrofuran in a standard manner.[70] A workup in the usual fashion, followed by Kugelrohr distillation (2 times) of the crude product, afforded the tin compound [**2**, X = $Sn(CH_3)_3$] as a colorless liquid (0.22 g, 40%): bp 67–70 °C (2 mm); mass sectrum, *m/e* 274, 276, 278 (M^+).

1-Fluoro-4-methylbicyclo[2.2.1]heptane (2, X = CH_3). The carboxylic acid (2, X = COOH; 1.0 g, 0.0063 mol) was reduced with borane–methyl sulfide by following the procedure of Lane and co-workers.[71] A conventional workup, followed by distillation, afforded the hydroxymethyl derivative (**2**, X = CH_2OH) as a colorless oil (0.68 g, 75%), which solidified on standing: bp 105–110 °C (13 mm); mass spectrum, *m/e* 144 (M^+).

Treatment of the alcohol (**2**, X = CH_2OH; 0.65 g, 0.006 mol) in dry pyridine (1.5 mL) with *p*-toluenesulfonyl chloride (0.45 g)[72] afforded the tosylate (**2**, X = CH_2OTs; 1.20 g, 90%) as a white solid after a standard workup.

A solution of the tosylate (2, X = CH_2OTs; 1.20 g, 0.004 mol) in dry tetrahydrofuran (3.0 mL) was treated with lithium triethylborohydride in tetrahydrofuran (0.008 mol; 8.0 mL of 1 M solution) at 0 °C.[73] The resulting mixture was heated at 65 °C for 3 h and left to stir overnight at room temperature. After cooling, the reaction mixture was quenched with water, followed by 3 M NaOH (4 mL) and 30%, w/w, H_2O_2 (4 mL). The two phases were separated, and the aqueous layer was extracted several times with fluorotrichloromethane. The combined organic phase was then washed thoroughly with water to remove tetrahydrofuran. The organic layer was dried before distillation and afforded the volatile methyl derivative (**2**, X = CH_3) as a concentrate in fluorotrichloromethane. The solvent was finally removed by careful distillation through a short column packed with glass helices. A GLC analysis of the pale yellow residue revealed that the methyl compound was >95% pure: mass spectrum, *m/e* 128 (M^+).

1-Fluorobicyclo[2.2.1]heptane (2, X = H). 1-Norbornanol or bicyclo[2.2.1]heptan-1-ol (0.8 g, 0.007 mol)[74] was treated with a 3- to 4-fold excess of sulfur tetrafluoride as described above for the conversion of **13** to **2** (X = $COOCH_3$). After standing for 48 h, the excess sulfur tetrafluoride was carefully vented from the bomb, and the residue was extracted with fluorotrichloromethane. The extract was washed with aqueous sodium bicarbonate and dried, and the solvent was carefully removed through a short column packed with glass helices. Sublimation of the residue into a liquid-nitrogen cooled receive afforded **2** (X = H) as a colorless solid (0.6 g, 76%): mp 95–98 °C; mass spectrum, *m/e* 114 (M^+); ^1H NMR ($CDCl_3$) δ 1.26–1.93 (11 H, m). Anal. Calcd for $C_7H_{11}F$: C, 73.65; H, 9.71. Found: C, 73.61; H, 9.88.

Registry No. **2** (X = H), 78142-52-6; **2** (X = NO_2), 84553-37-7; **2** (X = CN), 84553-38-8; **2** (X = COOH), 84553-40-2; **2** (X = $CONH_2$), 88888-22-6; **2** (X = $COOCH_3$), 84553-41-3; **2** (X = $COCH_3$), 84553-39-9; **2** (X = OH), 84553-46-8; **2** (X = $OCOCH_3$), 84553-47-9; **2** (X = F), 84553-42-4; **2** (X = Cl), 84553-43-5; **2** (X = Br), 84553-44-6; **2** (X = I), 84553-45-7; **2** (X = NH_2), 84553-48-0; **2** (X = $NH_2{\cdot}CF_3CO_2H$), 88888-23-7; **2** (X = CH_3), 84553-50-4; **2** (X = CH_2OH), 88888-24-8; **2** (X = C_6H_5), 84553-49-1; **2** (X = *p*-$NO_2C_6H_4$), 88888-25-9; **2** (X = *p*-$NH_2C_6H_4$), 88888-26-0; **2** (X = *p*-$NH_2C_6H_4{\cdot}CF_3CO_2H$), 88888-27-1; **2** (X = $Sn(CH_3)_3$), 84010-89-9; **2** (X = CH_2OTs), 88888-32-8; **9**, 81687-89-0; **10**, 88888-28-2; **11**, 88888-29-3; **12**, 88888-30-6; **13**, 88888-31-7; 1-norbornanol, 51566-98-4.

---

[69] Adcock, W.; Khor, T. C. *J. Org. Chem.* **1977**, *42*, 218.

[70] Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237.

[71] Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052.

[72] Vogel, A. I. "Practical Organic Chemistry"; Longmans: London, 1978; p 1103.

[73] Brown, H. C.; Krishnamurthy, S. *J. Org. Chem.* **1976**, *41*, 3064. *Ibid.* **1979**, *45*, 849.

[74] We thank Dr. E. W. Della for providing a sample of 1-norbornanol.

Diastereoface-Differentiating Synthesis of Substituted β-Lactams from Chiral Imines and/or Chiral α-Chloro Iminium Chlorides

Ewa Rogalska and Czeslaw Belzecki*

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Kasprzaka 44, Poland

Received July 11, 1983

Reaction of imines carrying a chiral substituent at a nitrogen atom with symmetric or prochiral α-chloro iminium chlorides leads in a diastereoface-differentiating reaction to a mixture of diastereoisomeric or epimeric β-lactams. Attempts were made to determine the absolute configuration of obtained chiral β-lactams. Reaction of prochiral imines with chiral α-chloro iminium chlorides also provides mixtures of diastereoisomeric β-lactams or their enantiomers with a clear selectivity.

Chiral Imines

Reaction of α-chloro iminium chlorides with imines, as reported by Ghosez,[1] can be applied to asymmetric syntheses by the use of chiral imines, as was confirmed in our first communication.[2] In the present study, we extend this synthesis to new examples and determine the absolute configuration of the obtained substituted β-lactams.

The substrates used are listed in Table I and Table II.

The reaction leads to β-lactams having two (type A) or one (type B) newly created chiral center, depending on

---

[1] Ghosez, L.; Haveaux, B.; Viehe, H. C. *Angew. Chem., Int. Ed. Engl.* **1969**, *6*, 454.

[2] Belzecki, C.; Rogalska, E. *J. Chem. Soc., Chem. Commun.* **1981**, 57.

0022-3263/84/1949-1397$01.50/0