water were added, and stirring was continued for 15 min. One gm of potassium sodium tartrate was then added, and the reaction mixture was filtered. The solid residue was washed several times with ether. The ether was removed, and the product was adsorbed on a 7 × 0.5 cm column of activity II alumina. Elution with hexane (20 ml) gave 28 mg (75%) of **4b** whose spectral properties were identical with those of the derivative obtained from the abietic acid rearrangement.

***cis*-1,10a-Dimethyl-7-isopropyl-1,2,3,9,10,10a-hexahydrophenanthrene (4a) from Reduction of 5a.** Following a procedure which was identical with that described for **4b**, 40 mg of **5a** gave 26 mg (69%) of **4a** whose spectral properties were identical with those for the derivative obtained from the abietic acid rearrangement.

Acknowledgment. We thank the Hercules Powder Co. for a generous sample of N-grade Rosin.

Registry No.—**2a**, 60606-84-0; **2b**, 60606-85-1; **3**, 514-10-3; **4a**, 49815-77-2; **4b**, 60606-86-2; **5a**, 60606-87-3; **5a** 2,4-DNP, 60606-88-4; **5b**, 60606-89-5; **6a**, 60606-90-8; **6b**, 60606-91-9; **9**, 60606-92-0; **10**, 51238-73-4; **11**, 60606-93-1; **11** 2,4-DNP, 60619-77-4; **12**, 60606-94-2; *trans*-3-penten-2-one, 3102-33-8; 3-methyl-3-buten-2-one, 814-78-8.

References and Notes

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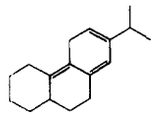
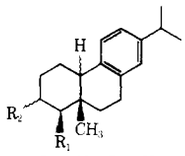


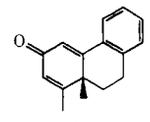
i

Kapoor[2] for trienes **1a** and **1b** is also compatible with all the data available to us.
(4) Like Mehta and Kapoor,[2] we observed decomposition of the trienes on attempted chromatography on $AgNO_3$–SiO_2.
(5) We also obtained the aromatic hydrocarbons ii and iii obtained by Mehta



ii, $R_1 = CH_3$; $R_2 = H$
iii, $R_1 = H$; $R_2 = CH_3$

and Kapoor, also isolated by catalytic hydrogenation of styrenes **4a** and **4b**.
(6) The ^1H NMR of **6a** is very similar to that of the model compound iv.[7]



iv

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Fluorine-19 Nuclear Magnetic Resonance. Electric Field Shifts of Bicyclic Fluorides

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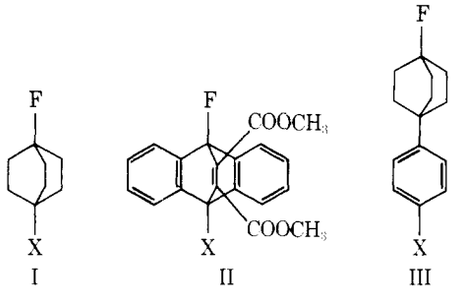
A number of 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octanes have been synthesized and their ^{19}F NMR spectra recorded. Significant *upfield* substituent chemical shifts (SCS) are observed for strong electron-withdrawing dipolar and charged substituents in a situation where substituent-induced structural effects cannot be invoked. The results strongly suggest that the previous interpretation of "anomalous" ^{19}F SCS for 4-substituted bicyclo-[2.2.2]octyl-1-fluorides in terms of structural effects alone requires reappraisal. Further, the results impinge importantly on the factors determining ^{19}F chemical shifts in general.

Substituent-induced *upfield* shifts have been detected by Anderson and Stock[1] for a limited number of 1-fluoro-4-substituted bicyclo[2.2.2]octanes (I, X = F and $COOC_2H_5$).



I II III

A consideration of several factors by these workers led to the conclusion that these substituent chemical shifts (SCS)[2] are anomalous and probably a consequence of substituent-induced structural deformation of the flexible bicyclooctyl skeletal framework rather than a manifestation of dipolar electrostatic-field effects: (1) upfield SCS are not in accord with preconceptions regarding the electron-withdrawing influence of dipolar substituents on chemical shifts; (2) ^{19}F chemical shifts of various unsubstituted bicyclic fluorides are structurally dependent; (3) the fact that substituents do measurably alter the structure of the more rigid bicyclo[2.2.1]-heptyl system; and (4) the observation that ^{19}F substituent chemical shifts (SCS) for the more rigid dibenzobicyclo[2.2.2]-octyl derivatives, in particular, adducts of 10-substituted 9-

fluoroanthracenes with dimethyl acetylenedicarboxylate (II), are in the anticipated *low-field* direction as well as corresponding reasonably well to the σ_I scale.

However, because inverse-substituent behavior by ^{19}F chemical shifts is known for some aliphatic fluorides[3] where structural effects cannot be invoked, we decided to examine a new model system (III, 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octanes) in order to determine unambiguously the "normal" response of ^{19}F chemical shifts for bicyclooctyl[2.2.2]fluorides to the electrostatic-field effect of remote polar groups. In this regard, the new system is superior to I since substitution is not being effected on a carbon atom which is incorporated directly in the bicyclooctyl skeletal framework, thus, substituent-induced structural effects are entirely eliminated. Further, unlike system II, the electronic structure of the chemical bonds in the immediate vicinity of the fluorine atom are similar to I, i.e., F–C (sp^3) *not* F–C (sp^2). Here we report our findings for system I.

A scrutiny of the data listed in Table I leads to a number of important conclusions. Firstly, it is clear that ^{19}F chemical shifts for system III, and thus system I, respond to an applied electric field in the *opposite* sense to expectations based on traditional ideas regarding the direction of chemical shifts induced by electron withdrawal or donation. This is dramatically exemplified by the relatively large positive SCS (*upfield* shift) listed for the powerful inductive monopole, NH_3^+.

Secondly, it can be seen that the SCS for Br ($\sigma_I = 0.44$; $\sigma_R^0 = -0.19$; $\sigma_{R(BA)} = -0.19$)[4] is significantly more positive than that for F ($\sigma_I = 0.50$; $\sigma_R^0 = -0.34$; $\sigma_{R(BA)} = -0.45$)[4] in both benzene and DMF, while the SCS for NH_2 ($\sigma_I = 0.12$; $\sigma_R^0 = -0.48$; $\sigma_{R(BA)} = -0.82$),[4] a weak dipolar substituent, is *negative*. The origin of these trends clearly lies in a significant contribution to the applied electric field at the CF bond by the charges set up in the phenyl π system through mesomeric interaction with the substituent (mesomeric-field effect[5] or secondary resonance effect[6]). Thus, while the electron-withdrawing primary field effect emanating from the polar substituent–substrate bond and the mesomeric-field effect are opposed for +F−M substituents (NH_2, Br, and F), they must reinforce one another for +F+M substituents (NO_2 and CN). This point is formalized by the fact that a dual substituent parameter (DSP) analysis[4,6,7] (eq 1–4) indicates a significant dependence on both substituent polarity (σ_I effect) and the mesomeric parameter (σ_R^0 or $\sigma_{R(BA)}$ effect). It can be seen that a slightly better fit was achieved with the $\sigma_{R(BA)}$ scale.[8]

$$SCS = 0.92\sigma_I + 0.37\sigma_{R(BA)} \quad \text{(benzene; } n = 5\text{; SD/RMS = 3\%)} \quad (1)$$

$$SCS = 0.91\sigma_I + 0.54\sigma_R^0 \quad \text{(benzene; } n = 5\text{; SD/RMS = 6\%)} \quad (2)$$

$$SCS = 0.67\sigma_I + 0.29\sigma_{R(BA)} \quad \text{(DMF; } n = 5\text{; SD/RMS = 7\%)} \quad (3)$$

$$SCS = 0.66\sigma_I + 0.42\sigma_R^0 \quad \text{(DMF; } n = 5\text{; SD/RMS = 14\%)} \quad (4)$$

The DSP analysis also indicates that the less positive SCS values in DMF compared to those in benzene for NO_2, CN, F, and Br (Table I) have their origin in both terms; however, the effect is more pronounced for the substituent polarity function ($\rho_I\sigma_I$). We believe that the attenuation of the primary field effect as a result of a greater effective dielectric constant in the polar solvent (DMF) is primarily responsible for the solvent effects observed for NO_2, CN, F, and Br.[9,10] However, the more negative SCS for NH_2 in DMF compared to that in benzene is probably the consequence of an enhanced σ_R value for this substituent due to specific substituent–solvent interactions in the former solvent.

Table I. ^{19}F SCS for Some 1-Fluoro-4-Para-Substituted Phenylbicyclo[2.2.2]octanes (III)

Substituent	SCS,[a,b] ppm Benzene	DMF
NO_2	+0.65	+0.47
CN	+0.58	+0.39
F	+0.28	+0.21
Br	+0.34	+0.28
NH_2	−0.18	−0.31
NH_3^+	+1.93[c]	

[a] Relative to 1-fluoro-4-phenylbicyclo[2.2.2]octane: δ (internal $FCCl_3$) +152.77 ppm (CCl_4); δ (external $FCCl_3$) +150.35 ppm (CCl_4). [b] A positive sign denotes shielding. [c] Solvent CF_3CO_2H.

It is of interest to note that on the basis that the substituent parameters for NH_3^+ in CF_3CO_2H are $\sigma_I = 1.08$ and $\sigma_R^0 = -0.26$,[11] and by utilizing the DSP correlative equation for system III in DMF (eq 4), the calculated SCS for this monopole in system III is approximately +0.6 ppm. In this light, the relatively large upfield SCS (+1.93 ppm) observed for $NH_3^+(CF_3CO_2H)$ in III (Table I) is somewhat perplexing. We believe that part of the problem associated with this charged +F−M substituent is that unlike the groups employed in the correlative analysis (NO_2, CN, F, Br, and NH_2), the induced charges in the phenyl π system due to this group are determined mainly by substituent polarity (σ_I), not mesomerism (σ_R).[12] Thus, contrary to expectations derived from the DSP equations, the secondary field effect emanating from the charges in the π system for NH_3^+ actually reinforces the primary field.

Thirdly, the results for system III (Table I), together with the previously reported *negative* ^{19}F SCS for system II, strongly suggest that two opposing factors (deshielding and shielding contributions) control the response of ^{19}F chemical shifts to an applied electric field and that, moreover, their relative importance is markedly determined by the electronic structure of the chemical bonds in the immediate vicinity of the fluorine atom. Various formulations of ^{19}F NMR shifts in terms of localized bond parameters[1,13] suggest that these two factors can probably be identified with charge density and bond order terms associated with the CF bond. Both terms are important but strongly opposed in these formulations. It should be noted that Stock and Anderson[1] have already proposed the idea that changes in bond order resulting from the interaction between the nonbonding orbitals of the fluorine atom and the endocyclic carbon–carbon bond orbitals may be responsible for some unusual ^{19}F chemical shift trends for unsubstituted bicyclic tertiary fluorides.[14] Interestingly, application of Pople's CNDO/2 method to some 4-substituted bicyclo[2.2.2]octyl-1-fluorides (system I) indicates that although substituents perturb the charge density of the $2p_y$ (σ) orbital, and this appears to correspond well to the σ_I scale, the charge density for both the $2p_z$ and $2p_x$ orbitals remains unchanged, i.e., no π-electronic effects on the fluorine are indicated.[15]

Finally, although the limits of expectation for estimating electric-field contributions are not good owing to uncertainties associated with the distance and effective dielectric constant terms, it is of value to note the crude estimates for COOEt ($\sigma_I = 0.30$)[4] and F ($\sigma_I = 0.50$)[4] in system I based on the polar effect contribution ($\rho_I\sigma_I$) for system III (eq 1) and some simple distance dependency laws (r^{-2} and r^{-3})[5b,16] that have been indicated for electric-field induced chemical shifts. The calculated values are as follows:[17] COOEt = +1.10 ppm (r^{-2}) and +2.21 ppm (r^{-3}); F = +1.84 ppm (r^{-2}) and +3.68 ppm (r^{-3}). However, the observed ^{19}F SCS for COOEt and F are +4.47

(CCl_4) and +9.23 ppm (CCl_4), respectively.[1] Thus, although electrostatic-field effects contribute significantly to the overall ^{19}F SCS for system I, other factors must also contribute importantly to the overall screening term. This conclusion is strongly supported by the fact that the *phenyl* substituent, a very weak polar substituent ($\sigma_I = 0.10$), induces a substantial upfield shift (2.35 ppm)[18] in system I. While a structural effect (electronic or steric in origin) of the kind proposed by Stock and Anderson[1] is a definite possibility, it should be noted that hyperconjugative transfer of charge involving the bridging bond in bicyclo[2.2.2]octyl systems could also be a possible mechanism for affecting ^{19}F SCS in these systems.[18b,19-21]

Experimental Section

Compounds. 1-Fluoro-4-phenylbicyclo[2.2.2]octane (I, X = Ph). Two methods (A and B) were employed. Method B proved to be superior.

A. 1-Methoxy-4-phenylbicyclo[2.2.2]octane[22] (1.5 g, 0.007 mol) was treated with acetyl fluoride (1.1 g, 0.018 mol) according to the procedure described by Suzuki and Morita.[23] The solid obtained on workup was sublimed to afford a white product (0.6 g, 46%): mp 131–132.5 °C (lit.[24] 132–133 °C); ^1H NMR ($CDCl_3$) δ 1.95 (12 H, m, aliphatic), 7.17 (5 H, broad singlet, aromatic).

B. A solution of 1-hydroxy-4-phenylbicyclo[2.2.2]octane[22] (8 g, 0.04 mol) in pyridine–hydrogen fluoride (60 ml)[25] was stirred overnight at room temperature. The white slurry was poured onto ice and the solid collected by filtration. Sublimation afforded 1-fluoro-4-phenylbicyclo[2.2.2]octane (6.8 g, 84%), mp 131–132.5 °C.

1-Fluoro-4-*p*-fluorophenylbicyclo[2.2.2]octane (III, X = F). 1-Hydroxy-4-*p*-fluorophenylbicyclo[2.2.2]octane[22] (0.49 g, 0.00158 mol) was treated with pyridine/HF as described above for the preparation of I. The solid obtained on workup was sublimed to afford a white product (0.2 g, 50%): mp 87.5–89.5 °C; ^1H NMR ($CDCl_3$) δ 1.88 (12 H, m, aliphatic), 7.1 (4 H, m, aromatic).

Anal. Calcd for $C_{14}H_{16}F_2$: C, 75.7; H, 7.3. Found: C, 75.4; H, 7.4.

1-Fluoro-4-*p*-bromophenylbicyclo[2.2.2]octane (III, X = Br). A solution of bromine in carbon tetrachloride (10 ml, 0.5 M solution) was added with stirring to a slurry of silver trifluoroacetate[26] (1.0 g, 0.054 mol) and I (1.0 g, 0.0049 mol) in CCl_4 (10 ml). The reddish brown color of bromine was discharged instantaneously and after addition was complete (30 min) the heavy precipitate of silver bromide was filtered off and washed with a small amount of ether. The solvent was removed under reduced pressure to yield a residue which was sublimed and recrystallized from methanol to afford a white, microcrystalline solid (1.1 g, 79%): mp 130.5–132 °C; ^1H NMR ($CDCl_3$) δ 1.97 (12 H, m, aliphatic), 7.28 (4 H, m, aromatic).

Anal. Calcd for $C_{14}H_{16}BrF$: C, 59.4; H, 5.7. Found: C, 59.3; H, 5.7.

1-Fluoro-4-*p*-cyanophenylbicyclo[2.2.2]octane (III, X = CN) was prepared from the above bromo compound (III) in the general manner outlined by Friedman and Shechter[27] for a number of aromatic nitriles. Sublimation of the crude product followed by chromatography on a silica gel column using hexane as the eluent afforded a white solid (0.44 g, 54%): mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 2.0 (12 H, m, aliphatic), 7.5 (4 H, m, aromatic).

Anal. Calcd for $C_{15}H_{16}NF$: C, 78.6; H, 7.0. Found: C, 78.6; H, 7.2.

1-Fluoro-4-*p*-nitrophenylbicyclo[2.2.2]octane (III, X = NO_2). Concentrated nitric acid (1 ml, sp gr 1.42) was added dropwise to a vigorously stirred suspension of I (1.0 g, 0.0049 mol) and acetic anhydride (10 ml) at 0 °C. After addition was complete, the mixture was stirred for 1 h and then water was added. The ight yellow precipitate was collected and recrystallized from methanol to afford white needles (0.8 g, 65%): mp 121.5–123 °C; ^1H NMR ($CDCl_3$) δ 2.03 (12 H, m, aliphatic), 7.47 (2 H, d, aromatic), 8.13 (2 H, d, aromatic).

Anal. Calcd for $C_{14}H_{16}FNO_2$: C, 67.5; H, 6.5. Found: C, 67.4; H, 6.5.

1-Fluoro-4-*p*-aminophenylbicyclo[2.2.2]octane (III, X = NH_2). A suspension of V (0.9 g, 0.0036 mol) in ethanol (50 ml) was reduced with hydrogen (60 psi) over Adams' catalyst (0.05 g). After 1 h the solution was filtered and the solvent evaporated in vacuo. The residue was dissolved in warm methylene chloride and then diluted with warm hexane until precipitation occurred. The white, needle-shaped crystals were collected (0.6 g, 68%) and dried over P_2O_5 in a nitrogen atmosphere as the amine proved to be unstable to air (mp 190 °C dec). An attempt to purify the amine by recrystallization from aqueous methanol afforded an unknown impurity (10% by GLC): ^1H NMR ($CDCl_3$) δ 1.94 (12 H, m, aliphatic), 3.48 (2 H, broad, NH_2), 6.58 (2 H, d, aromatic) 7.07 (2 H, d, aromatic).

Anal. Calcd for $C_{14}H_{18}FN$: C, 76.7; H, 8.3. Found: C, 76.1; H, 8.4.

Spectra. The ^{19}F NMR spectra were obtained at 84.66 MHz on a Bruker WH-90 Fourier transform NMR spectrometer. The proton broad-band decoupled spectra were recorded at 6000 and 600 Hz spectral widths with 16K/8K data points. Probe temperature was 310 K. The spectra were obtained for benzene and DMF solutions containing 5% w/w of the 1-fluoro-4-para-substituted phenylbicyclo[2.2.2]octane and 10% w/w of 1-fluoro-4-phenylbicyclo[2.2.2]octane. The relative chemical shifts are accurate to at least ±1 Hz.

^1H NMR spectra were measured with a Varian A-60 spectrometer. Gas chromatographic analysis was performed on a Varian 1740 gas chromatograph using a 10-ft column of 5% SE-30 on 100/120 Chromosorb W.

Acknowledgments. We wish to thank Monash University (Dr. I. D. Rae) for the use of their NMR facilities.

Registry No.—I (X = Ph), 22947-58-6; III (X = F), 60526-63-8; III (X = Br), 60526-64-9; III (X = CN), 60526-65-0; III (X = NO_2), 60526-66-1; III (X = NH_2), 60526-67-2; 1-hydroxy-4-phenylbicyclo[2.2.2]octane, 2001-62-9; pyridine HF, 32001-55-1; 1-hydroxy-4-*p*-fluorophenylbicyclo[2.2.2]octane, 60526-68-3.

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Reversals in Regiospecificity. The Reactivity of Vinylogous Amides toward Bis Electrophiles

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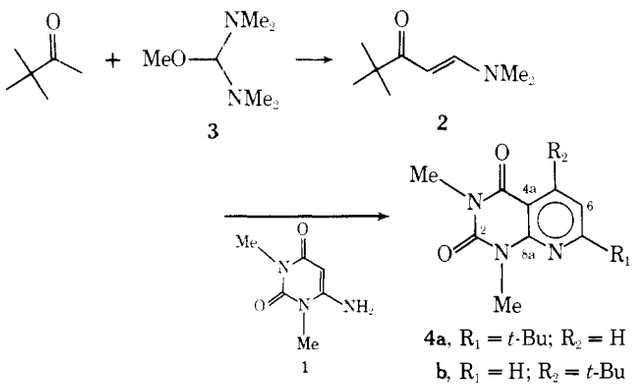
Several examples demonstrating the regiospecific reactivity of vinylogous amides toward bis electrophiles are presented. A reversal in this regiospecificity was accomplished by transformation of the vinylogous amide into the corresponding lithium imide prior to reaction with a bis electrophile.

The regioselective reactivity of primary enamino ketones such as 1,3-dimethyl-6-aminouracil (**1**) toward both mono and bis electrophiles has been established.[1-11] Furthermore, reversals of this regioselectivity have been accomplished by manipulation of catalyst and solvent.[2,4,10] Accompanying several of these examples were mechanistic proposals based on the difference in reactivity between the primary, exocyclic amino moiety and C-5 toward electrophiles.[1,2,10] The question of reactivity was reduced to one of C- vs. N-alkylation of the vinylogous amide bidentate system.[12]

No cases involving alkylation have been reported in which changes in nucleophilicity of the enamino ketone have resulted in reversal of regiospecificity. We wish to report an example of such a reversal and several others confirming the normal regioselective reactivity of enamino ketones.

Reaction of enamino ketone **1** with the tertiary enamino ketone **2**, prepared by the aminoformylation of pinacolone with Bredereck reagent **3**,[14] regiospecifically afforded only one of the two possible pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **4a** and **4b**.

Scheme I



Compound **4a** would result from an orientation of reactants as depicted in Chart I, whereas **4b** would result from the orientation of Chart II.

The product obtained was assigned structure **4a** based upon a comparison of the product's ^{13}C NMR spectrum with the calculated resonances[15] for structures **4a** and **4b** (Table I), as well as the ^{13}C NMR off-resonance (sfor) carbon–hydrogen spin–spin splitting patterns for C-5 (d) and C-7 (s).

Chart I

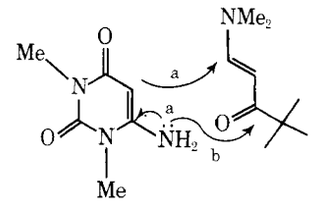
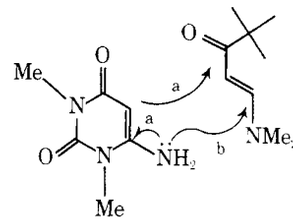


Chart II



Two reaction mechanisms, one involving initial C–C bond formation (pathway a) or one involving as its first step C–N bond formation (pathway b), can be postulated for the formation of **4a**.

There is adequate literature precedent[1,6] for postulating pathway a based on the reactivity of compound **1** toward mono electrophiles. It is to be expected that reaction at nitrogen would be less favorable for vinylogous amides than for enamines owing to the direct electron withdrawal by the carbonyl in the former. Nevertheless, N-acylation of various vinylogous amide systems has been observed.[16a]

It was anticipated that a reagent possessing a more significant difference in reactivity between its two electrophilic centers would be useful in providing further proof concerning the reaction mechanism. The reaction of such an electrophile, chlorosulfonyl isocyanate, with compound **1** also afforded a single product.

Scheme II depicts the various products that could arise from $ClSO_2NCO$ and **1** via reaction pathways a and b. From these products, **6c** and **6d** could be eliminated on the basis of an elemental analysis. The mass spectrum with a M^+ at *m/e* 198 helped eliminate structures **6a** and **6b** from consideration, but