Tris(3-methyl-2-thienyl)carbinol (1i). To a solution of (3-methyl-2-thienyl)lithium (37.6 mmol) in dry ether was added an ethereal solution of ethyl chloroformate (12.5 mmol) dropwise with stirring at −70 °C under an argon atmosphere. The stirring was continued for 2 h at the same temperature, and then the solution was allowed to warm up to room temperature and the stirring continued for 24 h. After hydrolysis with a saturated solution of ammonium chloride, the reaction mixture was extracted with ether and the organic layer was dried (Na_2SO_4) and evaporated under vacuum at room temperature. Compound **1i** was recrystallized from hexane (31% yield); mp 92 °C. Anal. Calcd for $C_{16}H_{16}OS_3$: C, 60.00; H, 5.00; S, 30.00. Found: C, 59.99; H, 5.23; S, 30.29.

(5-Methyl-2-thienyl)bis(2-thienyl)carbinol (1j) was prepared by the general procedure described for the preparation of 2-thienylcarbinols. The co-reagent was 2-carbethoxy-5-methylthiophene.[12] The reaction time was 24 h. The carbinol **1j** was obtained as an oil (75% yield) and was characterized by spectroscopical methods.

Tris(5-methyl-2-thienyl)carbinol (1k). To a solution of (5-methyl-2-thienyl)lithium (32 mmol) in dry ether was added an ethereal solution of ethyl chloroformate (10.5 mmol) dropwise with stirring at −5 °C. The stirring was continued for 16 h at room temperature. After hydrolysis with a saturated solution of ammonium chloride, the reaction mixture was extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated under vacuum at room temperature. Alcohol **1k** was recrystallized from hexane (45% yield). Anal. Calcd for $C_{16}H_{16}OS_3$: C, 60.00; H, 5.00; S, 30.00. Found: C, 60.02; H, 5.13; S, 30.08.

2-Furylbis(2-thienyl)carbinol (1l) was prepared by the general procedure described for the preparation of 2-thienylcarbinols. The co-reagent in this case was ethyl 2-furoate. The reaction time was 24 h. The residue obtained showed a great tendency toward polymerization and could not be purified. The yield (95%) is based on integration of the NMR spectra.

Preparation of Carbocations. Carbinols 1 (200 mg) were added to sulfuric acid (96%, 1 mL) with vigorous stirring at room temperature except where otherwise specified, and the NMR spectra of the resulting solutions were recorded. Carbinols **1h**, **1j**, and **1k** were previously dissolved in chloroform (1 mL), and the protonation was performed at 4 °C. Trifluoroacetic acid was used for the protonation of **1i** due to the instability of ion **2i** in sulfuric acid solution. Alcohol **1l** was protonated at −10 °C with trifluoromethanesulfonic acid in a chloroform (1 mL) solution.

Acknowledgment. This research was supported by the Comisión Interministerial de Ciencia y Tecnología (CICYT Projects 904/84 and PB87-0989). We acknowledge Mr. Santiago Centelles and Mr. Santiago Puchol for carrying out some of the experiments and Dr. Concepción Soriano for recording the carbon spectra.

(12) 2-Carbethoxy-5-methylthiophene was prepared in ethanol and sulfuric acid from 5-methylthiophene-2-carboxylic acid. This compound was obtained by reaction of (5-methyl-2-thienyl)lithium with CO_2 (see ref 13).

(13) Gilman, H.; St. John, N. B.; Schulze, F. *Organic Syntheses*; John Wiley & Sons: New York, 1943; Collect. Vol. II, p 425.

Transmission of Polar Substituent Effects in the Adamantane Ring System As Monitored by ^{19}F NMR: Hyperconjugation as a Stereoinductive Factor[1]

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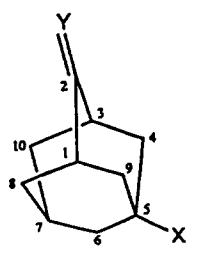
Received April 17, 1990

A limited series of (*E*)- and (*Z*)-5-substituted adamant-2-yl fluorides **8** and **9**, respectively, has been synthesized and characterized, and the ^{19}F chemical shifts have been measured in several solvents. A wide range of ^{19}F substituent chemical shifts (SCS, ppm) are obtained for the former system (ca. 9.1 (c-C_6H_{12}), 9.6 ($CDCl_3$), and 11.8 (HFIP)) compared to the latter (ca. 0.6 (c-C_6H_{12}), 0.7 ($CDCl_3$), and 2.3 (HFIP)). Factorization of the ^{19}F SCS into polar field ($\rho_F\sigma_F$) and residual contributions (^{19}F SCS − $\rho_F\sigma_F$) reveals the predominance of the latter solvent-independent component for the *E* fluorides (**8**). Comparison of **8** with a similar dissection of the ^{19}F SCS of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides **2** strongly suggests that the origin of the large residual contributions for **8** is "through-three-bond" electron delocalization or double hyperconjugation. The importance of this long-range electronic mechanism as a factor governing π-facial diastereoselection in 2,5-disubstituted adamantanes (**1**) is discussed. In particular, the assertion that the *p*-anilino substituent is an electron donor group at remote probe or reaction sites in saturated systems is addressed.

Introduction

Several recent papers by le Noble and co-workers[2] have reported on the effectiveness of 2,5-disubstituted adamantanes (**1**) as model systems for investigating the electronic effects of substituents on the stereoselectivity of addition reactions to trigonal carbon. These studies have disclosed several instances where a 5-substituent (X), depending on its electronic character, induces predominantly either anti or syn approach of the attacking species at the 2-position (see Chart I). This stereoselectivity has been rationalized in terms of a model proposed by Cieplak[3] that emphasizes the importance of transition-state sta-



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(1) Reported in part at the 1989 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December 17–22, 1989.

(2) (a) Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598; **1987**, *109*, 7239. (b) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (c) Lin, M. H.; Cheung, C. K.; le Noble, W. *J. Am. Chem. Soc.* **1988**, *110*, 6562. (d) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882. (e) Lin, M. H.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 998. (f) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836. (g) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3839.

(3) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

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Chart I

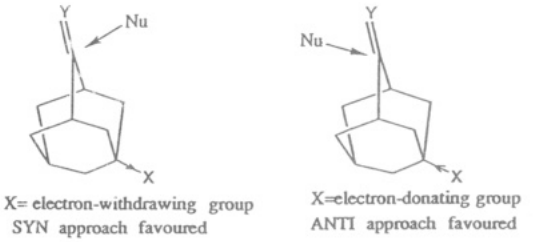
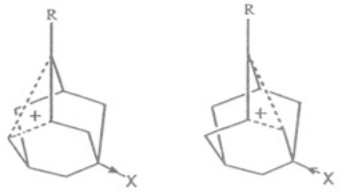


Chart II

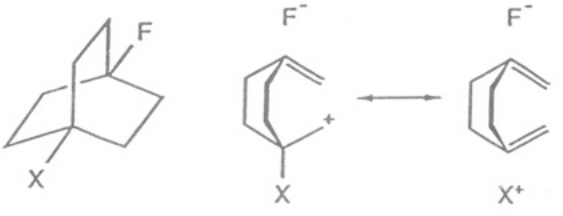
Chart III



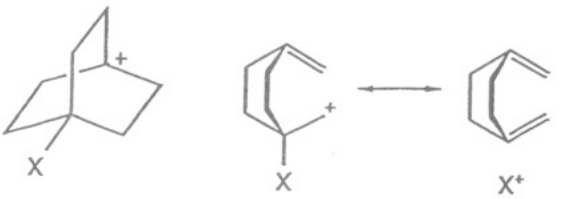
bilization by hyperconjugation involving electron-donor bonds and the adjacent incipient antibonding orbital (σ^*). According to this model,[4] the preferred direction of attack should place the developing bonding orbital(s) anti to the best electron-donor bonds (see Chart II).

le Noble et al.[2a,b,g] also found that stereoselectivity was most pronounced for those reactions mediated by intermediate 2-adamantyl cations. Here, the 5-substituent (X) induces predominantly either *retention* or *inversion*. The origin of this stereoselectivity has also been explained in terms of hyperconjugation with the proviso that stabilization for carbocations is greater before the nucleophile begins to bind. The cation intermediates have been depicted as bridged structures as shown in Chart III.

It has been pointed out by le Noble et al.[2] that the function of the 5-substituent (X) in **1** is to differentiate the hyperconjugative electron-donating abilities of the proximate (C_{1-9} and C_{3-4}) and distal (C_{1-8} and C_{3-10}) carbon–carbon bonds. However, the inductive electronic mechanism(s) by which this is accomplished was not specifically disclosed. For several years now we have been carrying out systematic model system studies with polycyclic alkane systems in an attempt to delineate the various transmission modes of polar substituents in saturated systems.[5] Pertinent to shedding further light on the origin of the substituent electronic effect responsible for system **1** being an effective stereochemical probe is the disclosure that ^{19}F substituent chemical shifts (SCS; charge density monitors) of 4-substituted (X) bicyclo[2.2.2]oct-1-yl fluorides **2** are strongly regulated by a "through-three-



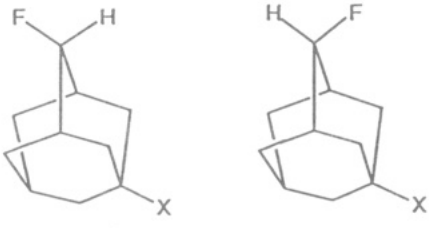
2 3 4



5 6 7

bond" electron delocalization interaction (electronegativity or σ_χ effect) that couples the C–X and C–F bonds through the intervening C–C single bonds (denoted by canonical structures **3** and **4**; depicted for only one of the three ethano bonds).[5a,c] Subsequently, we have shown that this through-bond coupling (or double hyperconjugation) is a significant mode of stabilization in the 4-substituted (X) bicyclooct-1-yl cation system **5** (denoted by canonical structures **6** and **7**).[6] The fact that the stereoelectronic requirement for optimization of double hyperconjugation (antiperiplanar relationship of the participant orbitals)[7] is met in the *E* isomer but not the *Z* isomer of 2,5-disubstituted adamantanes prompted us to intimate recently[5c] that this effect may be an important factor governing π-facial diastereoselection in the reactions of system **1**. If this proves to be the case then le Noble et al.'s[2] analysis of 5-substituent effects on the reactivity of 2-adamantyl compounds in terms of hyperconjugation will need to be modified.

In order to consolidate these ideas further, we decided to extend our model system studies utilizing ^{19}F NMR chemical shifts as an electronic probe to the 2,5-disposition of the adamantane ring system. ^{19}F chemical shifts are most appropriate for this purpose since in alkyl fluorides they respond sensitively to the extent of delocalization of electrons from neighboring antiperiplanar carbon–carbon bonds into the σ^* orbital of the C–F bond (negative hyperconjugation).[5] Accordingly, we have synthesized a limited series of (*E*)- and (*Z*)-5-substituted (X) adamant-2-yl fluorides (**8** and **9**, respectively) and measured their ^{19}F SCS in a range of solvents.



8 9

(4) (a) It should be noted that the Cieplak model is not without its critics. An alternative model (Anh–Eisenstein)[4b] of transition-state stabilization by hyperconjugation proposes that the interaction between the incipient bonding orbital (σ) and the adjacent electron-acceptor bonds is dominant. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) For leading references to the different viewpoints of this controversy, see refs 3, 4d–g. (d) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (e) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (f) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (g) Lin, M.-h.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1990**, *55*, 3597.

(5) (a) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2957 and references cited therein. (b) Adcock, W.; Kok, G. B. *J. Org. Chem.* **1987**, *52*, 356 and references cited therein. (c) Adcock, W.; Iyer, V. S. *J. Org. Chem.* **1988**, *53*, 5259 and references cited therein.

(6) Adcock, W.; Krstic, A. R.; Duggan, P. J.; Shiner, V. J., Jr.; Coope, J.; Ensinger, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 3140.

(7) (a) Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. (b) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1. (c) Gleiter, R.; Stohrer, W.-D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893. (d) Krijner, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. *J. Am. Chem. Soc.* **1989**, *111*, 4433 and references cited therein.

Table I. ^{19}F Substituent Chemical Shifts (SCS)[a-c] of (*E*)- and (*Z*)-5-Substituted (X) Adamant-2-yl Fluorides 8 and 9, Respectively

	E isomer			*Z* isomer		
X	c-C_6H_{12}	$CDCl_3$	HFIP[d]	c-C_6H_{12}	$CDCl_3$	HFIP[d]
F	−7.54[e]	−8.01[e]	−10.03[e]	0.24[f]	−0.17[f]	−1.88[f]
Cl	−6.66	−7.07	−8.78	−0.15	−0.56	−2.15
Br	−5.99	−6.42	−8.13	−0.21	−0.63	−2.25
I	−4.63	−5.01	−6.56	−0.32	−0.72	−2.24
C_6H_5	−4.18	−4.34	−5.11	0.12	−0.01	−0.69
p-$NO_2C_6H_4$	−4.41	−4.65	−5.61	0.00	−0.23	−1.09
p-$NH_2C_6H_4$	−4.18	−4.33	−5.09	0.20	0.05	−0.61
$Si(CH_3)_3$	0.12	0.23[g]	0.39	−0.20	−0.21[h]	−0.19
$Sn(CH_3)_3$	1.55	1.64[i]	1.79	−0.23	−0.25[j]	−0.31

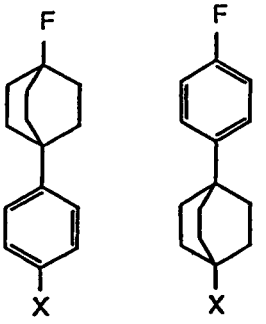
[a] Defined as the difference (in parts per million) between the ^{19}F chemical shift of the substituted compound and that of the parent compound (X = H). A negative sign denotes shielding (upfield shift). [b] Accurate to ±0.01 ppm. [c] X = H (relative to internal $FCCl_3$): δ −174.53 (c-C_6H_{12}) and −174.41 ($CDCl_3$). [d] HFIP ≡ Hexafluoroisopropyl alcohol. [e] J_{FF} (Hz) = 4.64 (c-C_6H_{12}), 5.86 ($CDCl_3$), 7.32 (HFIP). [f] J_{FF} not observed. [g] $J_{^{29}Si-^{19}F}$ = 3.90 Hz. Obtained from ^{29}Si NMR spectrum ($CDCl_3$, δ 4.73 relative to $SiMe_4$). [h] $J_{^{29}Si-^{19}F}$ not observed in ^{29}Si NMR spectrum ($CDCl_3$, δ 4.49 relative to $SiMe_4$). [i] Average $J_{^{117,119}Sn-^{19}F}$ = 43.45 Hz. Obtained from $^{19}F\{^1H\}$ spectrum ($CDCl_3$, $J_{^{119}Sn-^{19}F}$ = 43.95 Hz; obtained from ^{119}Sn NMR spectrum ($CDCl_3$, δ 1.53 relative to $SnMe_4$). [j] $J_{^{119}Sn-^{19}F}$ not observed in ^{119}Sn NMR spectrum ($CDCl_3$, δ −2.27 relative to $SnMe_4$).

Herein we report the results of our studies.

Results and Discussion

Synthesis of Compounds. Most of the fluorine compounds (8 and 9) were obtained as mixtures by treatment of the corresponding *E*/*Z* alcohol mixtures (see later text) with diethylaminosulfur trifluoride (DAST).[8] The two exceptions, X = $Sn(CH_3)_3$ and *p*-$NH_2C_6H_4$, were also obtained as mixtures but by stannylation and reduction, respectively, of the corresponding bromo fluoride (8 and 9, X = Br) and *p*-nitrophenyl fluoride (8 and 9, X = *p*-$NO_2C_6H_4$) mixtures. All the mixtures were unambiguously characterized by ^{13}C NMR (Tables IX and X; available as supplementary material). Spectral assignments for the compounds followed unequivocally from the characteristic $^{13}C-^{19}F$ coupling constants in the adamantane skeletal framework[5b,9a] as well as additivity of substituent effects on chemical shifts of the adamantane ring.[9b] (Tables XI and XII; calculated chemical shifts available as supplementary material.) Standard assignment procedures such as intensity considerations and general chemical shift considerations played only a minor role. Isomer identification in the ^{19}F NMR spectra of the fluoride mixtures (8 and 9) was based on relative intensities (see later text). This was unambiguously confirmed for several of the mixtures by obtaining pure samples of 8 (X = F, Cl, Br, I, and $Sn(CH_3)_3$) and 9 (X = F, Cl, Br, I, $Si(CH_3)_3$, and $Sn(CH_3)_3$).

^{19}F SCS for Systems 8 and 9. Several significant points need to be made before examining the results set out in Tables I–V. First, the ^{19}F chemical shifts of alkyl fluorides respond to the electronic influences of substituents in the opposite direction to expectations based on either intuition or current chemical shift theory.[10] Notwithstanding this apparent anomaly, model system studies have shown that the shift response to remote substituents appears to be systematic.[5,10,11] Second, the number and range of substituents for 8 and 9 are inadequate to provide significant correlations of the ^{19}F SCS versus polar substituent parameters by multiple regression analysis. However, we have shown previously[5,10,11] that polar-field susceptibility parameters (ρ_F values)[12] for the fluorine probe may be determined independently by dividing the chemical shift difference (ΔSCS) between the *p*-$NO_2C_6H_4$ and C_6H_5 substituents by $\Delta\sigma_F$[12] for these groups ($\Delta\sigma_F$ = 0.24 (c-C_6H_{12}),[5a] 0.16 ($CDCl_3$),[5a] and 0.09 (HFIP)[5b]). Finally, the assertion by le Noble et al.[2] that the *p*-anilino group functions as an electron-donor group at remote probe or reaction sites in a saturated system is not supported by the ^{19}F SCS of 1-fluoro-4-(*p*-substituted phenyl)bicyclo[2.2.2]octanes **10**.[10] Estimates of σ_F values[12]



10 **11**

from this system for the *p*-$NH_2C_6H_4$ group (0.08 (c-C_6H_{12}), 0.14 ($CDCl_3$), 0.09 (DMF)) suggests that it is an electron-withdrawing group (relative to hydrogen). This is corroborated by the σ_F values (0.08 (c-C_6H_{12}), 0.14 ($CDCl_3$), 0.10 (DMF), 0.14 (CH_3OH), 0.18 (HFIP)) derived from the ^{19}F SCS of 1-X-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes (11, X = *p*-$NH_2C_6H_4$)[14] and the appropriate ρ_F values.[5a,b] The corresponding values for the C_6H_5 substituent derived from 11 are as follows:[5a,b] 0.15 (c-C_6H_{12}), 0.17 ($CDCl_3$), 0.16 (DMF), 0.17 (CH_3OH), and 0.19 (HFIP). It is important to note that system 11 is an established model for determining such parameters.[13]

The ^{19}F SCS of 8 and 9 in c-C_6H_{12}, $CDCl_3$, and hexafluoroisopropyl alcohol (HFIP) are assembled in Table I.

Table II. ^{13}C NMR Parameters ($CDCl_3$) for C2 of Systems 8 and 9

	system 8 (*E* isomer)		system 9 (*Z* isomer)	
X	$^1J_{CF}$[a]	δ_{CF}[a,b,c]	$^1J_{CF}$[a]	δ_{CF}[a,b,c]
H	178.46	95.53 (0.00)	178.46	95.53 (0.00)
F	179.69	93.35 (−2.18)	180.78	92.60 (−2.93)
Cl	180.30	93.09 (−2.44)	180.79	92.38 (−3.15)
Br	180.42	92.91 (−2.62)	180.78	92.31 (−3.22)
I	180.66	92.78 (−2.75)	181.15	92.30 (−3.23)
C_6H_5	179.08	94.96 (−0.57)	178.96	94.23 (−1.31)
p-$NO_2C_6H_4$	179.44	94.28 (−1.25)	179.20	93.65 (−1.88)
$Si(CH_3)_3$	178.22	95.82 (0.29)	178.22	95.58 (0.05)
$Sn(CH_3)_3$	178.71	95.34 (−0.19)	178.46	95.53 (0.00)

[a] Digital resolution of 0.12 Hz (spectral width 1000 Hz, 16K/8K data points). [b] Relative to central peak of $CDCl_3$ triplet set at 77.0 ppm. [c] SCS (ppm) in parenthesis. ρ_F ($CDCl_3$, *E* isomer) = −4.25. ρ_F ($CDCl_3$, *Z* isomer) = −3.56.

(8) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574 and references cited therein.

(9) (a) Olah, G. A.; Shih, J. G.; Krishnamurthy, V. V.; Singh, B. P. *J. Am. Chem. Soc.* **1984**, *106*, 4492. (b) Srivastava, S.; Cheung, C. K.; le Noble, W. J. *Magn. Reson. Chem.* **1985**, *23*, 232.

(10) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2945.

(11) Adcock, W.; Abeywickrema, A. N.; Kok, G. B. *J. Org. Chem.* **1984**, *49*, 1387.

(12) The symbol σ_F is probably best employed in place of σ_I in view of the overwhelming evidence that σ_I is a manifestation of polar field effects.[13]

(13) Reynolds, W. F.; Gomes, A.; Moron, A.; MacIntyre, D. W.; Tanin, A.; Hamer, G. K.; Peat, I. R. *Can. J. Chem.* **1983**, *61*, 2376.

(14) The ^{19}F SCS (ppm) of 11 (X = *p*-$NH_2C_6H_4$) are as follows: 0.21 (c-C_6H_{12}); 0.37 ($CDCl_3$); 0.17 (DMF); 0.27 (CH_3OH); 0.34 (HFIP).

Table III. Calculated Polar Field ($\rho_F\sigma_F$) and Residual ($\rho_X\sigma_X$) Contributions (ppm) to ^{19}F SCS (ppm) of (*E*)-5-Substituted (X) Adamant-2-yl Fluorides 8

X	$\rho_F\sigma_F$			$\rho_X\sigma_X$[d]		
	c-C_6H_{12}[a]	$CDCl_3$[b]	HFIP[c]	c-C_6H_{12}	$CDCl_3$	HFIP
F	−0.37	−0.81	−2.50	−7.17	−7.20	−7.53
Cl	−0.41	−0.83	−2.39	−6.25	−6.24	−6.39
Br	−0.42	−0.85	−2.45	−5.57	−5.57	−5.68
I	−0.40	−0.81	−2.22	−4.23	−4.20	−4.34
C_6H_5	−0.14	−0.33	−1.05	−4.04	−4.01	−4.06
p-$NO_2C_6H_4$	−0.39	−0.64	−1.56	−4.04	−4.01	−4.05
p-$NH_2C_6H_4$	−0.08	−0.27	−1.00	−4.10	−4.06	−4.09
$Si(CH_3)_3$	0.00	0.00	0.00	0.12	0.23	0.39
$Sn(CH_3)_3$	0.00	0.00	0.00	1.55	1.64	1.79

[a] $\rho_F = -0.96$. [b] $\rho_F = -1.94$. [c] $\rho_F = -5.56$. [d] ^{19}F SCS (observed) − $\rho_F\sigma_F$.

Table IV. Calculated Polar Field ($\rho_F\sigma_F$) and Residual ($\rho_X\sigma_X$) Contributions (ppm) to ^{19}F SCS (ppm) of (*Z*)-5-Substituted Adamant-2-yl Fluorides 9

X	$\rho_F\sigma_F$			$\rho_X\sigma_X$[d]		
	c-C_6H_{12}[a]	$CDCl_3$[b]	HFIP[c]	c-C_6H_{12}	$CDCl_3$	HFIP
F	−0.20	−0.58	−2.00	0.44	0.41	0.12
Cl	−0.22	−0.59	−1.91	0.07	0.03	−0.24
Br	−0.22	−0.61	−1.95	0.01	−0.02	−0.30
I	−0.21	−0.58	−1.78	−0.11	−0.14	−0.46
C_6H_5	−0.08	−0.24	−0.84	0.20	0.23	0.15
p-$NO_2C_6H_4$	−0.20	−0.46	−1.24	0.20	0.23	0.15
p-$NH_2C_6H_4$	−0.04	−0.19	−0.80	0.24	0.24	0.19
$Si(CH_3)_3$	0.00	0.00	0.00	−0.20	−0.21	−0.19
$Sn(CH_3)_3$	0.00	0.00	0.00	−0.23	−0.25	−0.31

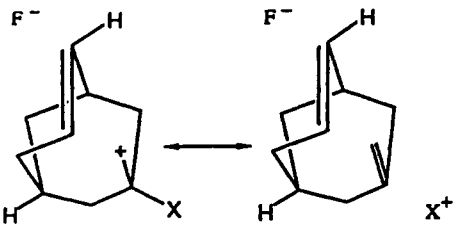
[a] $\rho_F = -0.50$. [b] $\rho_F = -1.38$. [c] $\rho_F = -4.44$. [d] ^{19}F SCS (observed) − $\rho_F\sigma_F$.

Table V. ^{19}F Substituent Chemical Shifts (SCS, ppm)[a] of 4-Substituted Bicyclo[2.2.2]oct-1-yl Fluorides 2 in c-C_6H_{12}: Polar Field ($\rho_F\sigma_F$)[b] and Residual ($\rho_X\sigma_X$) Contributions

X	SCS	$\rho_F\sigma_F$	$\rho_X\sigma_X$
F	−8.90	−1.22	−7.68
Cl	−6.97	−1.35	−5.62
Br	−5.94	−1.38	−4.56
I	−3.35	−1.32	−2.03
C_6H_5	−3.37	−0.47	−2.90
p-$NO_2C_6H_4$	−4.12	−1.22	−2.90
p-$NH_2C_6H_4$	−3.16	−0.25	−2.91
$Si(CH_3)_3$	1.54	0.00	1.54
$Sn(CH_3)_3$	3.67	0.00	3.67

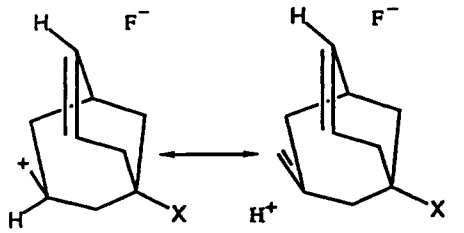
[a] Taken from refs 5a, 10, and 15. $\rho_F = -3.13$.

A cursory examination of the data reveals that there is a significant and striking difference between the two sets of SCS. Note that whereas the substituent effects for the *E* series 8 are in the main quite pronounced those for the corresponding *Z* series 9 are extremely feeble. It is significant to note that this situation is not just simply a question of the fluorine probe monitoring the electron density fluctuations of the adjacent carbon. This is evidenced by the fact that the relative magnitude of the ^{13}C SCS for carbon-2 (C2) of 8 and 9 (Table II) is diametrically opposite to that observed for the fluorine probe. Factorization of the ^{19}F SCS of 8 and 9 (Tables III and IV, respectively) is most revealing with respect to the origin of their differences. It can be seen that, although the polar-field term ($\rho_F\sigma_F$) for 8 is significant, the solvent-independent residual contribution ($\rho_X\sigma_X$) is clearly the dominant factor. By contrast, the latter contribution for 9 is virtually nonexistent. Most significantly, the overall trend and pattern of the residual contributions to the shifts for the former system parallel to a considerable degree those observed for the corresponding derivatives of 2[5a,15] (listed in Table V for c-C_6H_{12} in order to facilitate comparisons). This similarity between 2 and 8 but not 2 and 9 fulfills expectations referred to in the introduction and, hence, confirms the importance of double hyperconjugation as a mechanism for transmitting the σ-inductive influence (σ_X effect) of substituents between the 2- and 5-positions of the adamantane ring. The prevailing orbital interactions (σ_{CF}*−σ_{CC}−σ_{CX}) governing this resonance effect are optimally aligned in systems 2 and 8 but not in 9 (illustrated by canonical structures 12 and 13 for 8). The canonical



12 13

structures 14 and 15 denoting double hyperconjugation in the latter system highlights why the substituent has such a small influence on the ^{19}F chemical shifts in this particular orientation (*Z* isomers).



14 15

Thus, the ^{19}F SCS of 8 and 9 clearly demonstrate that 5-substitution in the adamantane ring system markedly affects the ability of the proximate carbon–carbon bonds to participate in hyperconjugation in comparison to the otherwise equivalent distal bonds as envisaged by le Noble et al.[2] However, it is also clear that the hyperconjugative model proposed by these workers needs to be modified to embrace both single and double hyperconjugation. Because these interactions are more pronounced in excited or electron deficient species such as carbocations than in the neutral ground state, double hyperconjugation is a particularly important mode of stabilization in the 4-substituted (X) bicyclo[2.2.2]oct-1-yl[6] (see previous text) and (*E*)-5-substituted (X) adamant-2-yl (see later in discussion) cation systems when X is a relatively good σ-electron-donor group (H, $(CH_3)_3Si$, $(CH_3)_3Ge$, and $(CH_3)_3Sn$).

There are several other points worthy of comment before closing the discussion on the ^{19}F chemical shift study of 8 and 9:

1. We have already indicated that both systems 2 and 8 have the substituent and fluorine probe disposed similarly to each other (1,4-disposition) and, moreover, that their bonds are oriented trans-coplanar with respect to the bridging ethano bonds such as to maximize double hyperconjugation. However, in the bicyclooctyl case there are three hyperconjugating CC bonds while in the adamantyl case there are only two. Thus, on the basis of the number of pathways the through-three-bond interaction is expected to be smaller in 8 compared to 2. Assuming that the shift/charge density response for the fluorine probe in 2 and 8 is fairly similar,[16] then the relative

(15) Adcock, W.; Iyer, V. S. *J. Org. Chem.* **1985**, *50*, 1538.

magnitude of the $\rho_\chi\sigma_\chi$ contributions for $(CH_3)_3Si$ and $(CH_3)_3Sn$ in these systems (Tables III and V) support this prediction although the values for 8, particularly those for $(CH_3)_3Si$, are very much smaller than expected. By contrast, it is noteworthy that the accelerative effects of (*E*)-5-$(CH_3)_3Si$ and (*E*)-5-$(CH_3)_3Sn$ on the rates of solvolysis of 2-adamantyl brosylate are similar to the corresponding substituent effects in the bicyclooctyl system.[17] This may be related to the fact that the former is a secondary cation and the latter is tertiary. Consequently, different demands are placed on the conjugative abilities of the C–M bonds in both systems.

Thus, the question of the relative magnitude of through-three-bond effects in the bicyclooctane and adamantane ring systems clearly involves other considerations besides the number of pathways. This is not surprising given the various parameters governing the orbital interactions (orbital coefficients, resonance integrals, and energy differentials) of single and double hyperconjugation.

A final point to note is that whereas the $\rho_\chi\sigma_\chi$ contributions for the σ-electron donor groups appear to be manifestations of only double hyperconjugation (σ_{CF}*-σ_{CC}-σ_{CX}); illustrated by canonical structures 4 and 13 for systems 2 and 8, respectively), the corresponding values for the σ-electron acceptors (Tables III and IV) embody single hyperconjugation effects as well. In terms of bond MO interactions, the latter influence is the *decrease* of the σ_{CF}*–σ_{CC} interaction (illustrated by canonical structures 3 and 12 for systems 2 and 8, respectively) as a consequence of significant σ_{CC}–σ_{CX}* interactions for σ-electron acceptor groups.

2. It is of interest to note that the observation of five-bond long-range coupling constants ($^5J_{X\text{-}Y}$) for 8 (see footnotes *e*, *g*, and *i* of Table I) but not for 9 (see footnote of *f*, *h*, and *j* of Table I) further highlights that the participating bond molecular orbitals are optimally aligned for through-bond transmission in the former but not the latter system. Note also that in line with the reduced number of coupling pathways the $^5J_{X\text{-}Y}$ values for 8 are significantly less than the corresponding parameters for 2.[5,15,18]

3. On the basis of the fact that the $\rho_F\sigma_F$ term has its origin in the direct polarization of the C–F σ bond,[5,10,11] the relative magnitude of this contribution to the ^{19}F SCS of 8 and 2 (Tables III and V, respectively) is in accord with spatial considerations (angles and distances). However, the somewhat similar $\rho_F\sigma_F$ contributions for 8 and 9 (Tables III and IV, respectively) was unexpected on the same grounds. The latter result highlights the importance of indirect polarization of the C–F σ bond by field-induced polarization of bonds (e.g., C–H) attached to the same carbon nucleus as the fluorine probe. The marked enhancement of $\rho_F\sigma_F$ contributions to the ^{19}F SCS of alkyl fluorides in hydrogen-bond donor (HBD) solvents has been previously observed and its origin defined.[5,10,11]

Stereochemical Course of Reduction of 5-Substituted (X) Adamantan-2-ones 1 (*Y* = 0). The ^{19}F SCS of 8 and 9 (Table I) and their dissections (Tables III and IV) clearly demonstrate inter alia that the *p*-$NH_2C_6H_4$ group is a σ-electron acceptor in the same vein as the C_6H_5 substituent and, in addition, that the $(CH_3)_3Sn$ group is a significantly better σ-electron donor than $(CH_3)_3Si$. The effect of the latter substituent in 8 is surprisingly small in light of the results for 2 (Table V). This may result from the energies of the participating bond MO's being unfavorably disposed for interaction in 8 compared to 2. Within the framework of Cieplak's model,[3] these results lead to the following predictions concerning the stereoselectivity of reduction of the appropriately substituted derivatives of 1 (*Y* = 0; X = *p*-$NH_2C_6H_4$, $(CH_3)_3Si$, and $(CH_3)_3Sn$): (i) the *p*-$NH_2C_6H_4$ group should lead to predominantly syn approach of the borohydride anion toward the carbonyl group (see Chart II) to give a mixture of alcohols in which *E* > *Z*; (ii) the degree of anti-face selectivity induced by the $(CH_3)_3Sn$ group should be significantly greater than that for $(CH_3)_3Si$ (see Chart II). In fact, if the stabilizing hyperconjugative interactions in the transition state are not considerably pronounced compared to the neutral ground state, then $(CH_3)_3Si$ may be an ineffectual bystander as far as directive influences are concerned. Because these predictions are not in accord with the observations reported by le Noble et al.,[2a,f] we decided to reexamine the reduction of the appropriate ketones 1 (*Y* = 0; X = *p*-$NH_2C_6H_4$, $(CH_3)_3Si$, and $(CH_3)_3Sn$). These results are set out in Table VI together with the product distribution for the other ketones that were reduced in connection with synthesizing the fluorines 8 and 9. The previously reported data of le Noble et al.[2a,f] are given in parentheses. It can be seen that the new data for *p*-$NH_2C_6H_4$, $(CH_3)_3Si$, and $(CH_3)_3Sn$ are in line with the aforementioned predictions. Note in particular the major discrepancy between the *E*/*Z* ratio from this study and the literature result[2a] for *p*-$NH_2C_6H_4$. It is important to note that our preliminary report[1] of this result has prompted le Noble et al. to reinvestigate the reduction of 5-*p*-anilinoadamantan-2-one.[19] Their revised result is clearly in line with that reported here. Although not as marked, there is also a significant discrepancy between the two sets of results for $(CH_3)_3Si$ and $(CH_3)_3Sn$.[2f] The very weak directing influence of the latter substituent highlights that double hyperconjugation appears not to be a very significant interaction in the transition state for the re-

Table VI. Product Distribution in the Reduction of 5-Substituted (X) Adamantan-2-ones 1 (*Y* = 0)

X	alcohol % *E*	alcohol % *Z*	analytical method
F	59 (62)[a]	41 (38)[a]	^{13}C NMR[b]
F	59	41	VPC
Cl	62 (60)[a]	38 (40)[a]	^{13}C NMR[b]
Cl	63	37	VPC
Br	59 (59)[a]	41 (41)[a]	^{13}C NMR[b]
Br	60	40	VPC
I	60	40	^{13}C NMR[b]
I	64	36	VPC
C_6H_5	55 (57)[a]	45 (43)[a]	^{13}C NMR[b]
C_6H_5	57	43	^1H NMR[c]
p-$NO_2C_6H_4$	70 (64)[a]	30 (36)[a]	^{13}C NMR
p-$NO_2C_6H_4$	66	34	^1H NMR[c]
p-$NH_2C_6H_4$	60 (34)[a]	40 (66)[a]	^{13}C NMR[b]
p-$NH_2C_6H_4$	54	46	^1H NMR[c]
$Si(CH_3)_3$	49 (45)[d]	51 (55)[d]	^{13}C NMR[b]
$Si(CH_3)_3$	50	50	VPC
$Sn(CH_3)_3$	45	55	^{13}C NMR[b]
$Sn(CH_3)_3$	48	52	VPC
$Sn(CH_3)_3$	47 (43.5)[d]	53 (56.5)[d]	^1H NMR[c]

[a] Taken from ref 2a. [b] Based on average of peak intensities. [c] Based on proton integration (C_2H; δ ($CDCl_3$) 3.96 and 3.87 ppm). [d] Taken from ref 2f.

(16) The similarity of some ^{19}F SCS for (*E*)-4-substituted adamant-1-yl fluorides (to be published) vs the corresponding parameters for 8 suggests that the shift/charge density ratio for secondary and tertiary alkyl fluorides is not significantly different.

(17) Adcock, W.; Coope, J.; Shiner, V. J., Jr.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.

(18) Adcock, W.; Gangodawila, H.; Kok, G. B.; Iyer, V. S.; Kitching, W.; Drew, G. M.; Young, D. *Organometallics* **1987**, *6*, 156.

(19) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, *31*, 4391.

Table VII. Product Distribution in the Fluorination of Some Pure Epimers (*E* or *Z*) of 5-Substituted (X) Adamantan-2-ols

X	epimer	fluorides % *E* (8)	fluorides % *Z* (9)	analytical methods
Br	*E*	27	73	VPC
Br	*E*	27	73	^{19}F NMR
Br	*Z*	10	90	VPC
Br	*Z*	9	91	^{19}F NMR
$Si(CH_3)_3$	*E*	86	14	^{19}F NMR
$Si(CH_3)_3$	*Z*	86	14	^{19}F NMR
$Sn(CH_3)_3$[a]	*E*	100	0	^{19}F NMR
$Sn(CH_3)_3$[b]	*Z*	0	0	^{19}F NMR

[a] Fragmentation predominant. Fluoride minor product. [b] Exclusively fragmentation.

duction of the ketones **1** ($Y = 0$).

Interestingly, central to le Noble et al.'s[2a] conclusion that stereoselectivity of nucleophile capture by a carbonyl group in **1** ($Y = 0$) is electronic in origin was the observation of a reasonable linear Hammett plot ($\log_{10}[Z]/[E]$ vs σ_p) for the $NaBH_4$ reductions of para-substituted 5-phenyl-2-adamantanones **1** ($Y = 0$; X = p-SC_6H_4). The new result for p-$NH_2C_6H_4$ has led to a revision of this plot.[19] It has been interpreted as evidence for the conclusion that face selection can be explained by transition-state hyperconjugation.[2a,19] However, taken at face value the plot clearly suggests a dependence on the $\Delta\sigma_F$ (or $\Delta\sigma_I$) effect[12] of the substituent (p-SC_6H_4).[10,20] Hence, because our analysis of the ^{19}F SCS of **8** (Table III) suggests that the differential in hyperconjugation between the proximate and distal bonds in **1** is not a function of σ_F but the σ_X effect of the substituent, a σ_F dependency implies that an additional electronic factor may influence face selectivity, i.e., direct electrostatic field effects.[21]

A consideration of both σ_F[5a,12] and σ_X (as indicated by the ^{19}F SCS of **8** and **9**, Tables I, III, and IV) effects suggest that the degree of stereoselectivity for reduction of the ketones should be in the order F > Cl > Br > I > p-$NO_2C_6H_4$ > C_6H_5 > p-$NH_2C_6H_4$. Note that this prediction is clearly not in accord with the results listed in Table VI. Thus, the overall picture of stereoselectivity portrayed is not completely consistent with the predictions of Cieplak's model[3] as proposed by le Noble et al.[2a,f] We are unable to offer any satisfactory explanation for this rather puzzling situation.

Stereochemical Course of Fluorination of (*E*)- and (*Z*)-5-Substituted (X) Adamantan-2-ols. The conversion of alcohols to alkyl fluorides by treatment with DAST in dichloromethane proceeds either by an S_N1 or S_N2 mechanism.[8,22] Because the latter is precluded in 2-adamantyl substrates, the fluorinations described in this study occur by the former and, hence, are initiated by the formation of intermediate carbocations.

$$ROH + Et_2NSF_3 \longrightarrow ROSF_2NEt_2 + HF$$

$$\downarrow$$

$$RF + OSFNEt_2 \longleftarrow [R^+\ ^-OSF_2NEt_2]$$

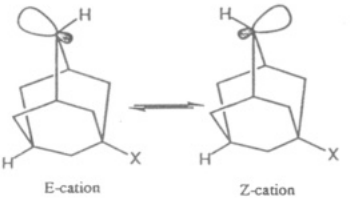
The fluorination results of the 5-substituted (X) adamantan-2-ols are listed in Tables VII and VIII. The former are for some pure epimers (*E* or *Z*) that were available from other studies.[17] These reactions were carried out on a small scale (ca. 20 mg). The latter were obtained from mixtures of alcohols (*E*/*Z*) that were fluorinated on a preparative scale (0.2–3.25 g; see Experimental Section). The composition of the precursor alcohol mixtures are those listed in Table VI except for $(CH_3)_3Si$ and $(CH_3)_3Sn$, which are given in the Experimental Section (ca. *E*:*Z* = 60:40). An examination of Tables VII and VIII reveals that for $(CH_3)_3Si$ the epimeric precursor alcohols (*E* or *Z*) and their mixture give the same product mixture. The dominant product is the *E* fluoride. Thus, the overall stereochemical result is predominantly *retention* and *inversion* for the *E* and *Z* epimeric alcohols, respectively. Following the proposals of le Noble[2a] and Sorensen,[23] this reaction outcome can be explained by invoking a rapidly equilibrating pair of nonplanar (partially pyramidalized) cations (Chart IV) prior to fluoride ion capture to form the products. When X is a σ-electron donor group ($(CH_3)_3Si$ or $(CH_3)_3Sn$), the *E* cation is more stable than the *Z* cation because double hyperconjugation involving the C–M (M = Si or Sn) bond is an important factor stabilizing the former species (illustrated by canonical structure **16**). It should be noted that recent calculations[23b] indicate that a nonplanar 2-adamantyl cation is energetically preferred to a bridged species (Chart III). Moreover, nonplanarity ensures that the stereoelectronic requirement for optimizing double hyperconjugation is met. It is therefore of interest to conjecture that pyramidalization may be more pronounced in the *E* cation than the *Z* cation (Chart IV)

Table VIII. Product Distribution in the Fluorination of Mixtures (*E* and *Z* Isomers) of 5-Substituted (Z) Adamantan-2-ols[a,b]

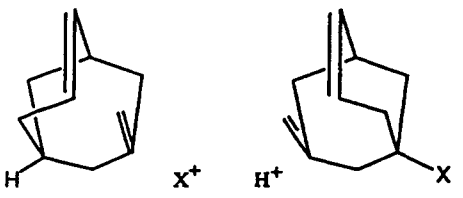
X	fluorides % *E* (8)	fluorides % *Z* (9)	analytical method
F	10	90	^{13}C NMR
F	6	94	VPC
F	4	96	^{19}F NMR
Cl	15	85	^{13}C NMR
Cl	15	85	VPC
Cl	16	84	^{19}F NMR
Br	18	82	^{13}C NMR
Br	19	81	VPC
Br	18	82	^{19}F NMR
I	32	68	^{13}C NMR
I	35	65	VPC
I	38	62	^{19}F NMR
C_6H_5	41	59	^{13}C NMR
C_6H_5	38	62	^{19}F NMR
p-$NO_2C_6H_4$	35	65	^{13}C NMR
p-$NO_2C_6H_4$	35	65	^{19}F NMR
$Si(CH_3)_3$	84	16	^{13}C NMR
$Si(CH_3)_3$	86	14	^{19}F NMR
$Sn(CH_3)_3$[c]	100	0	^{13}C NMR
$Sn(CH_3)_3$[c]	>98	trace	^{19}F NMR

[a] Except for $Si(CH_3)_3$ and $Sn(CH_3)_3$, see Table VI for composition of percursor alcohol mixtures. [b] See Experimental Section for composition of $Si(CH_3)_3$ and $Sn(CH_3)_3$ alcohol mixtures. [c] Fragmentation predominant. Fluorides are minor products.

Chart IV



(20) Adcock, W.; Khor, T. C. *J. Org. Chem.* **1977**, *42*, 218.
(21) For a summary of other models proposed for explaining stereoelectronic effects in π-facial diastereoselection, see refs 3b, 4d–g.
(22) (a) Rozen, S.; Faust, Y.; Ben-Yakov, H. *Tetrahedron Lett.* **1979**, 1823. (b) Leroy, J.; Hebert, E.; Wakselman, C. *J. Org. Chem.* **1979**, *44*, 3406.
(23) (a) Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7816. (b) Dutler, R.; Rauk, A.; Sorensen, T. S.; Whitworth, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 9024. (c) Buffam, D. J.; Sorensen, T. S.; Whitworth, S. M. *Can. J. Chem.* **1990**, *68*, 1889.



16 17

when X is a σ-electron-donor group.

The importance of double hyperconjugation is particularly highlighted by the results for the more powerful σ-electron donating $(CH_3)_3Sn$ substituent. Here, fragmentation is the dominant reaction pathway (>90%) and the fluorides are only minor products (Tables VII and VIII). Note the almost exclusive formation of the *E* fluoride from the *E* alcohol and the *E*/*Z* alcohol mixture. It appears that after the formation of the *Z* cation it rapidly isomerizes irreversibly by inversion to the more stable *E* cation, which fragments before being intercepted by the fluoride ion. The isomerization of the more stable *E* cation to the less stable *Z* cation seems not to occur presumably because the barrier to inversion[23b] is now too high. These striking results prompted a solvolysis study of (*E*)- and (*Z*)-5-[$(CH_3)_3$M]-2-adamantyl brosylate esters (M = Si and Sn) that have revealed large solvolytic rate enhancements as well as pronounced fragmentation for both the *E* and *Z* tin compounds.[17] It is of interest to note our qualitative observations that the rates of fluorination with DAST were obviously effected by the nature of the substituent. For example, whereas the reaction was complete at room temperature in less than an hour for $(CH_3)_3Si$, the reaction was still incomplete after 3 days at reflux for F (see Experimental Section).

The product mixtures obtained from the *E* and *Z* bromo alcohols (Table VII) are not the same and indicate that the isomerization of the cations does not reach equilibrium. This result is in direct contrast to the situation observed previously for the $(CH_3)_3Si$ group but is in line with le Noble et al.'s[2a] observations for some other reactions mediated by secondary 2-adamantyl cations when the 5-substituent is a σ-electron acceptor. For the epimeric bromo alcohols, the *Z* fluoride is clearly the dominant product in both mixtures, indicating *retention* and *inversion* for the *Z* and *E* epimeric alcohols, respectively. This stereochemistry is diametrically opposed to that observed for $(CH_3)_3Si$ because now the *Z* cation is more stable than the *E* cation when X is a σ-electron-acceptor group. Preferential stabilization of the former cation by double hyperconjugation is illustrated by canonical structure 17. It appears that the increased barrier to inversion[23b] ensures that for these cases (X = σ-electron acceptor) isomerization of the *Z* cation to the *E* cation is slow compared to fluoride ion capture.

Finally, it is of interest to note that the results listed in Table VIII clearly demonstrate that the degree of stereoselectivity for fluorination of 5-substituted (X) adamantan-2-ols is in the order F > Cl > Br > I > *p*-$NO_2C_6H_4$ ~ C_6H_5 for the σ-electron-acceptor groups. It is pertinent that this order parallels the differential in hyperconjugative abilities of the respective carbon–carbon bonds (C_{1-9} and C_{3-4} vs C_{1-8} and C_{3-10}) as monitored by the ^{19}F SCS (see Tables I, III, and IV).

Experimental Section

General Procedures. Melting and boiling points are uncorrected. Liquid samples were purified by distillation on a Kugelrohr apparatus (Büchi, GKR-50). Hence, boiling points quoted pertain to this equipment. Analytical vapor-phase chromatographic (VPC) analyses were performed on a Perkin-Elmer 8410 gas chromatograph with use of a 6-ft column of 10% silicone-OV17 on 100/120 Chromosorb WHP or a 30-m capillary column (RSL-300, 0.53-mm column). Mass spectra were recorded on a Kratos MS25RF spectrometer. NMR spectra were obtained as previously described.[5,10,11,18]

Compounds. Adamantan-2-one was purchased from the Aldrich Chemical Co., Inc. The syntheses of 5-hydroxy-,[24] 5-chloro-,[24,25] 5-bromo-,[25] and 5-phenyladamantan-2-ones[24] were performed following literature procedures. The 5-fluoro ketone[2a] was obtained from the corresponding bromo derivative following a procedure (AgF, cyclohexane) outlined by Pincock and Bhandari[26] for the synthesis of 1,3-difluoroadamantane. 5-Phenyladamantan-2-one was nitrated according to a method outlined by Tanida and Muneyuki[27] to afford the 5-(*p*-nitrophenyl) derivative (ca. 75%) as well as two other isomers (17 and 8%). It is of interest to note that this is contrary to the report of le Noble et al.[2a] that only the para isomer is formed. Recrystallization (2 × 1) of the crude product from hexane/ethyl acetate afforded the 5-(*p*-nitrophenyl) derivative in a pure state (70% yield), mp 125–128 °C (lit.[2a] mp 127–128 °C). An ethyl acetate solution of this compound was reduced to give 5-(*p*-aminophenyl)-adamantan-2-one by use of a standard catalytic procedure (10% Pd on C) similar to that described for the preparation of 1-fluoro-4-(*p*-aminophenyl)bicyclo[2.2.2]octane (**10**, X = *p*-$NH_2C_6H_4$).[20] The desired ketone 1 (X = *p*-$NH_2C_6H_4$, *Y* = 0) was obtained as a white solid: mp 141–143 °C (lit.[2a] mp 126–130 °C); *m*/*e* 241.1475, calcd for $C_{16}H_{19}NO$ 241.1466. 1-(*p*-Fluorophenyl)-4-phenylbicyclo[2.2.2]octane (11, X = C_6H_5) was prepared from fluorobenzene and 1-bromo-4-phenylbicyclo[2.2.2]octane[28] by modifying a method described by Chapman et al.[29] for the preparation of 1,4-diphenylbicyclo[2.2.2]octane. The reaction was carried out at −5 °C with freshly sublimed aluminum chloride (ca. 0.3 mol equiv) and was constantly monitored by VPC. The reaction mixture was quenched after 3 h and worked up in a standard manner. Recrystallization of the crude product from hexane followed by sublimation gave the desired phenyl compound 11 (56%, X = C_6H_5), mp 154–156 °C (lit.[30] mp 156–158 °C). This compound was nitrated by the method of Tanida and Muneyuki[27] to give 1-(*p*-fluorophenyl)-4-(*p*-nitrophenyl)bicyclo[2.2.2]octane (11, X = *p*-$NO_2C_6H_4$), mp 195–198 °C (lit.[30] mp 195–198 °C), which was reduced[20] to give the *p*-aminophenyl derivative 11 (X = *p*-$NH_2C_6H_4$): mp 164–166 °C; *m*/*e* 295/1735, calcd for $C_{20}H_{22}NF$ 295.1736. The ^{13}C NMR spectra of the compounds were in accord with the assigned structures.

5-Iodoadamantan-2-one. By use of the procedure of Molle and co-workers[31] for converting 1-adamantanol to 1-iodoadamantane, freshly distilled hydriodic acid (10.5 mL of 55% w/v solution) was added to a solution of 5-hydroxyadamantan-2-one[24] (2.5 g, 15 mmol) in hexane (3.85 mL) and benzene (15 mL), and the mixture was placed under reflux for 24 h. The mixture was then cooled before additional benzene (10 mL) was added and the aqueous layer removed. The benzene layer was then washed successively with water, aqueous sodium thiosulfate, and sodium bicarbonate solutions and then dried, and finally the solvent was removed. Sublimation of the product (2.80 g, 67%) gave the title compound as a very pale cream solid: mp 83–85 °C; ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 50.56 (C1, 3), 213.90 (C2), 49.94 (C4, 9), 52.35 (C5), 41.22 (C6), 31.52 (C7), 37.26 (C8, 10); exact mass spectrum calcd for $C_{10}H_{12}IO$ 276.00129, found 276.0005.

Sodium Borohydride Reduction. In a typical reaction, an aqueous solution of $NaBH_4$ (3 mol equiv) at 0 °C was added dropwise to a well-stirred methanol solution of 5-substituted (X) adamantan-2-one (1 mol equiv) maintained at 0 °C. After addition was complete, the mixture was placed under reflux for 10 min before allowing it to stir overnight at room temperature. The reaction was quenched with a saturated aqueous ammonium

(24) Geluk, H. W. *Synthesis* **1972**, 374.
(25) Geluk, H. W.; Schlatmann, M. A. *Tetrahedron* **1968**, *24*, 5369.
(26) Pincock, R. E.; Bhandari, K. S. *Synthesis* **1974**, 655.
(27) Tanida, H.; Muneyuki, R. *J. Am. Chem. Soc.* **1965**, *87*, 4794.
(28) Adcock, W.; Khor, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 7799.
(29) Chapman, N. B.; Sotheeswaran, S.; Toyne, K. J. *J. Org. Chem.* **1970**, *35*, 917.
(30) Khor, T. C. Ph.D. Dissertation, The Flinders University of South Australia, 1978.
(31) Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4120.

chloride solution and then extracted with dichloromethane. The extract was washed with a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered and the solvent evaporated to afford the reaction product mixture. This was then analyzed by VPC and NMR to determine the relative proportion of isomers (*E* and *Z*).

Except for the (*E*)- and (*Z*)-5-iodoadamantan-2-ols, which are new, the ^{13}C NMR data ($CDCl_3$, relative to Me_4Si) for all the *E* and *Z* alcohols were in accord with those reported in the literature.[2a,f] The results for the former compounds are as follows: (*E* isomer) δ 38.78 (C1, 3), 72.27 (C2), 50.82 (C4, 9), 48.46 (C5), 52.18 (C6), 32.19 (C7), 29.11 (C8, 10); (*Z* isomer) δ 39.04 (C1, 3), 71.84 (C2), 45.56 (C4, 9), 47.81 (C5), 52.18 (C6), 31.56 (C7), 34.33 (C8, 10). It should be noted that the reduction of 5-iodoadamantan-2-one by the aforementioned procedure led to a mixture of the iodo alcohols (*E*/*Z* = 68/32, determined by VPC) contaminated with (*Z*)-2,5-dihydroxyadamantane (ca. 5–10% by ^{13}C NMR). The latter compound is apparently formed as a result of preferential hydrolysis of (*Z*)-5-iodoadamantan-2-ol. This side reaction was circumvented by adding the $NaBH_4$ portionwise as a powder rather than as an aqueous solution to the methanol solution of the iodo ketone.

Synthesis of (*E*)- and (*Z*)-5-Substituted (X) Adamant-2-yl Fluorides 8 and 9, Respectively. The basic fluorination procedure employing DAST[6] as the reagent is described for the preparation of 2-fluoroadamantane (8 or 9, X = H). In the case of σ-electron donors (X = $(CH_3)_3Si$ and $(CH_3)_3Sn$), the reaction was rapid and complete in less than 1 h at room temperature. A satisfactory rate and level of conversion (>80%) for the alcohol mixtures with σ-electron acceptors was achieved by placing the reaction mixture under reflux for varying lengths of time depending on the substituent, e.g., X = C_6H_5 (ca. 1 day) and F (ca. 3 days). The progress of the reactions was monitored by VPC.

2-Fluoroadamantane (8 or 9, X = H). The DAST reagent[6] (0.05 g, 3.62 mmol) was added dropwise to a well-stirred solution of adamantan-2-ol (0.5 g, 3.29 mmol) in dry dichloromethane (20 mL) maintained at 0 °C. After addition was complete, the mixture was allowed to warm to room temperature and left to stir overnight before being quenched with a cold aqueous solution of sodium bicarbonate. Evaporation of the dried dichloromethane extracts followed by sublimation afforded 2-fluoroadamantane as a white solid (420 mg, 83%): mp 244–246 °C (lit.[9a] mp 254–255 °C); exact mass spectrum calcd for $C_{10}H_{15}F$ 154.11577, found 154.1159.

(*E*/*Z*)-2-Bromo-5-fluoroadamantane (8 and 9, X = Br). The crude product (2.7 g) obtained from fluorinating (reaction time 2 days) a mixture of (*E*/*Z*)-5-bromoadamantan-2-ol (3 g, 12.99 mmol) was purified by column chromatography (basic alumina with hexane as the eluent) and sublimation followed by HPLC (prepacked silica gel column) with hexane as the eluent. **(*E*)-2-Bromo-5-fluoroadamantane (8, X = Br)**: yield 150 mg; mp 125–128 °C; ^{13}C NMR (see Table IX, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FBr$ 232.02634/234.02437, found 153.1079 ($M^{\bullet+}$ – Br), calcd for ($M^{\bullet+}$ – Br) 153.10795. **(*Z*)-2-Bromo-5-fluoroadamantane (9, X = Br)**: yield 1.20 g; mp 130–132 °C; ^{13}C NMR (see Table X, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FBr$ 232.02634/234/02437, found 153.1079 ($M^{\bullet+}$ – Br), calcd for ($M^{\bullet+}$ – Br) 153.10795.

(*E*/*Z*)-2-Fluoro-5-iodoadamantane (8 and 9, X = I). The crude product obtained from fluorinating (reaction time, 10 h) a mixture of (*E*/*Z*)-5-iodoadamantan-2-ol (3.25 g, 11.69 mmol) was purified by column chromatography (basic alumina with hexane as the eluent) followed by Kugelrohr distillation to afford a colorless oil (1.84 g, 56%). Separation of the *E*/*Z* isomers (32:68 by VPC) was affected by HPLC (prepacked silica gel column) with hexane as the eluant. **(*E*)-2-Fluoro-5-iodoadamantane (8, X = I)**: yield 260 mg; mp 62–65 °C; ^{13}C NMR (see Table IX, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FI$ 280.01261, found 153.1087 ($M^{\bullet+}$ – I), calcd for ($M^{\bullet+}$ – I) 153.10795, found 281.0187 ($M^{\bullet+}$ + 1, NH_3, CI), calcd for ($M^{\bullet+}$ + 1) 281.01596. **(*Z*)-2-Fluoro-5-iodoadamantane (9, X = I)**: yield 1.0 g; $^{25}n_D$ 1.5690; ^{13}C NMR (see Table X, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FI$ 280.01261, found 153.1087 ($M^{\bullet+}$ – I), calcd for ($M^{\bullet+}$ – I) 153.10795, found 281.0187 ($M^{\bullet+}$ + 1, NH_3, CI), calcd for ($M^{\bullet+}$ + 1) 281.01596.

It should be noted that the first attempt to prepare the *E*/*Z* mixture of the fluoroiodides led to the formation of predominant amounts (ca. 60%) of the difluoro derivatives 8 and 9 (X = F; 5% and 95%, respectively) as a consequence of the bridgehead iodine being replaced by fluorine in the presence of hydrogen fluoride. This problem was circumvented by carrying out the fluorination in the presence of a suspension of finely powdered anhydrous potassium carbonate and sodium fluoride.

(*E*/*Z*)-2,5-Difluoroadamantane (8 and 9, X = F). The crude product obtained from fluorinating (reaction time 3 days) a mixture of (*E*/*Z*)-5-fluoroadamantan-2-ol (0.42 g, 2.4 mmol) was sublimed to afford a white solid (0.30 g, 70%): ^{13}C NMR (see Tables IX and X, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}F_2$ 172.10635, found 172.1066. See Table VIII for composition of mixture. An attempt at purification by HPLC (silica gel/hexane) was not successful.

(*E*)-2,5-Difluoroadamantane (8, X = F). Xenon difluoride[32] (27 mg, 0.161 mmol) was added to a well-stirred solution of (*E*)-2-fluoro-5-iodoadamantane (41 mg, 0.146 mmol; see previous text) in dry dichloromethane (1.5 mL) under nitrogen at room temperature. After 45 min, the reaction mixture developed a deep blue color. The reaction was found to be complete after 2 h (monitored by VPC). The reaction mixture was then diluted with dichloromethane (10 mL) and left to stir overnight after the addition of an aqueous solution of sodium metabisulfite. Evaporation of the dried dichloromethane extract followed by sublimation afforded the title compound as a white solid (17 mg, 67%): mp 247–250 °C; ^{13}C NMR (see Table IX, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}F_2$ 172.10635, found 172.1066.

(*Z*)-2,5-Difluoroadamantane (9, X = F). A solution of (*Z*)-2-fluoro-5-iodoadamantane (160 mg, 0.56 mmol) in dry dichloromethane (5 mL) was treated with xenon difluoride[32] (105 mg, 0.628 mmol) in the manner described previously for the corresponding *E* isomer. The reaction mixture developed a deep purple color after 15 min, at which time a VPC analysis indicated that fluorodeiodination was complete. Workup as described previously followed by sublimation afforded a white solid (76 mg, 77%): mp 264–266 °C; ^{13}C NMR (see Table X); exact mass spectrum calcd for $C_{10}H_{14}F_2$ 172.10635, found 172.1066.

(*E*/*Z*)-2-Chloro-5-fluoroadamantane (8 and 9, X = Cl). The crude product obtained from fluorinating (reaction time 3 days) a mixture of (*E*/*Z*)-5-chloroadamantan-2-ol (1 g, 5.36 mmol) was chromatographed (basic alumina with hexane as the eluent) and sublimed to form a white solid (0.47 g, 60% based on converted alcohol). See Table VIII for composition of mixture. HPLC (silica gel/hexane as eluent) of a sample of the mixture (70 mg) afforded only the *Z* isomer in a pure state. **(*Z*)-2-Chloro-5-fluoroadamantane (9, X = Cl)**: mp 166–169 °C; ^{13}C NMR (see Table X, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FCl$ 188.0768, 190.07385, found 188.0763, 190.0735.

(*E*)-2-Chloro-5-fluoroadamantane (8, X = Cl). A solution of (*E*)-2-fluoro-5-iodoadamantane (70 mg, 0.25 mmol) and iodine monochloride (44.6 mg, 0.275 mmol) in tetrachloromethane (6 mL) was stirred in the dark at room temperature[11] until monitoring by VPC analyses indicated that all the iodide was consumed (48 h). Workup as previously described afforded a white solid (40 mg) that was purified by HPLC (silica gel/hexane as eluent) to give the title compound (20 mg, 42%): mp 145–148 °C; ^{13}C NMR (see Table IX, supplementary material); exact mass spectrum calcd for $C_{10}H_{14}FCl$ 188.0768, 190.07385, found 188.0763, 190.0735.

(*E*/*Z*)-2-Fluoro-5-phenyladamantane (8 and 9, X = C_6H_5). The crude product obtained from fluorinating (reaction time 1 day) a mixture of (*E*/*Z*)-5-phenyladamantan-2-ol (380 mg, 1.6 mmol) was sublimed to afford a white solid (250 mg, 65%); see Table VIII for composition of mixture: exact mass spectrum calcd for $C_{16}H_{19}F$ 230.14707, found 230.1466; ^{13}C NMR (Tables IX and X, supplementary material). An attempt at separating the isomers by HPLC (silica gel/hexane) was not successful.

(*E*/*Z*)-2-Fluoro-5-(*p*-nitrophenyl)adamantane (8 and 9, X = *p*-$NO_2C_6H_4$). The crude red oil obtained from fluorinating (reaction time, 36 h) a mixture of (*E*/*Z*)-5-(*p*-nitrophenyl)-

(32) (a) *New Fluorinating Agents in Organic Synthesis*; German, L., Zemskov, S., Eds.; Springer-Verlag: Berlin, New York, 1989; Chapter 1. Xenon difluoride by Bardin, V. V.; Yagupolskii, Yu. L. (b) Treatment of 1-iodoadamantane with elemental fluorine[32c] or xenon difluoride[32d] leads to replacement of iodine by fluorine. (c) Rozen, S.; Brand, M. *J. Org. Chem.* **1981**, *46*, 733. (d) Della, E. W.; Head, N. Unpublished work.

adamantan-2-ol (0.8 g, 2.93 mmol) was subjected to Kugelrohr distillation to afford a very pale yellow solid (0.53 g, 66%); see Table VIII for composition of mixture: exact mass spectrum calcd for $C_{16}H_{18}NO_2F$ 275.13215, found 275.1320; ^{13}C NMR (Tables IX and X, supplementary material).

(*E*/*Z*)-2-Fluoro-5-(*p*-aminophenyl)adamantane (8 and 9, X = *p*-$NH_2C_6H_4$). A solution of (*E*/*Z*)-2-fluoro-5-(*p*-nitrophenyl)adamantane (0.2 g, 0.727 mmol; 8 and 9, X = *p*-$NO_2C_6H_4$) in ethyl acetate with 10% Pd/C was hydrogenated (45 psi of H_2) for ca. 14 h. After a standard workup,[20] the title mixture of compounds was obtained as a very pale pink solid (135 mg, 76%). ^{13}C NMR (Tables IX and X, supplementary material) and ^{19}F NMR indicated that the isomeric ratio of the mixture was identical with its precursor (8 and 9, X = *p*-$NO_2C_6H_4$; see Table VIII). Exact mass spectrum calcd for $C_{16}H_{20}FN$ 245.15797, found 245.1583.

(*E*/*Z*)-2-Fluoro-5-(trimethylsilyl)adamantane (8 and 9, X = $(CH_3)_3Si$). The crude product (0.95 g, 94%) obtained from fluorinating (reaction time 1 hr) a mixture of (*E*/*Z*)-5-(trimethylsilyl)adamantan-2-ol (1 g, 4.4 mmol; *E*/*Z* = 60/40, see preparation in the following text) was subjected to Kugelrohr distillation to afford a colorless low-melting solid: exact mass spectrum calcd for $C_{13}H_{23}SiF$ 226.15530, found 226.1554; ^{13}C NMR (Tables IX and X, supplementary material). See Table VIII for composition of mixture. An attempt at separating the isomers was not successful.

(*Z*)-2-Fluoro-5-(trimethylsilyl)adamantane (9, X = $(CH_3)_3Si$). A solution of (*Z*)-2-bromo-5-fluoroadamantane (300 mg, 1.29 mmol) in HMPA (1 mL) was treated with Me_3SiNa[33] in the same manner as described for the preparation of 1-fluoro-4-(trimethylsilyl)bicyclo[2.2.2]octane (2, X = $(CH_3)_3Si$).[34] A standard workup afforded a pale yellow oil. VPC and ^{13}C NMR analysis indicated that the product was a mixture containing the title compound (ca. 48%) and 2-fluoroadamantane (ca. 52%). Kugelrohr distillation gave the desired *Z* isomer as a white solid (80 mg, 27%): mp 47–50 °C; ^{13}C NMR (see Table X, supplementary material); exact mass spectrum calcd for $C_{13}H_{23}SiF$ 226.1553, found 226.1554.

(*E*/*Z*)-2-Fluoro-5-(trimethylstannyl)adamantane (8 and 9, X = $(CH_3)_3Sn$). A solution of (*E*/*Z*)-2-bromo-5-fluoroadamantane (400 mg, 1.72 mmol; *E*/*Z* = 19/81) in dry tetrahydrofuran (10 mL) under N_2 was treated with Me_3SnLi[35] in the same manner as described for the preparation of 1-fluoro-4-(trimethylstannyl)bicyclo[2.2.2]octane (2, X = $(CH_3)_3Sn$).[36] A standard workup followed by Kugelrohr distillation afforded a colorless low-melting solid (300 mg, 55%): exact mass spectrum calcd for $C_{13}H_{23}SnF$ 318.08057, found 318.0811 (based on Sn^{120}); ^{13}C NMR (Tables IX and X, supplementary material) indicated that the composition of the mixture was ca. *E*/*Z* = 20/80.

An attempt to prepare the tin fluoride mixture was also made by fluorinating an *E*/*Z* mixture (60:40) of the tin alcohols (see preparation in the following text). Because of the sensitivity of carbon–tin bonds to undergo protiodestannylation, the reaction was carried out in the presence of anhydrous potassium carbonate and sodium fluoride. However, it should be noted that fragmentation (>90% by ^{13}C NMR) was the dominant pathway of the reaction. The minor fluorination pathway yielded almost exclusively the *E* fluoride with only a trace of the *Z* isomer (see Table VIII).

(*E*)-2-Fluoro-5-(trimethylstannyl)adamantane (8, X = $(CH_3)_3Sn$). A solution of (*E*)-2-fluoro-5-iodoadamantane (150 mg, 0.535 mmol) in dry tetrahydrofuran (3 mL) under N_2 was treated with Me_3SnLi[35] (365 mg, 2.14 mmol) as indicated previously. A standard workup followed by Kugelrohr distillation afforded the title compound as a colorless solid (110 mg, 65%), mp 69–71 °C; ^{13}C NMR (see Table IX, supplementary material); exact mass spectrum calcd for $C_{13}H_{23}SnF$ 318.08057, found 318.0811 (based on Sn^{120}).

(*Z*)-2-Fluoro-5-(trimethylstannyl)adamantane (9, X = $(CH_3)_3Sn$). A solution of (*Z*)-2-bromo-5-fluoroadamantane (200 mg, 0.858 mmol) in dry tetrahydrofuran (5 mL) under N_2 was treated with Me_3SnLi[35] (0.58 g, 3.43 mmol) as indicated previously. A standard workup followed by Kugelrohr distillation afforded the title compound as a colorless solid (120 mg, 44%): mp 54–57 °C; ^{13}C NMR (see Table X, supplementary material); exact mass spectrum calcd for $C_{13}H_{23}SnF$ 318.08057, found 318.0811 (based on Sn^{120}).

5-(Trimethylsilyl)adamantan-2-one. An *E*/*Z* mixture (60:40) of 5-bromoadamantan-2-ol (6 g, 26.32 mmol), prepared by $NaBH_4$ reduction (see the previous text) of 5-bromoadamantan-2-one, was converted to a mixture of silyl ethers (5 g, 63%; 100 °C (0.5 mm)) and then treated with $(CH_3)_3SiNa$[33] and desilylated in the same manner as recently described for the conversion of 4-bromobicyclo[2.2.2]octan-1-ol to 4-(trimethylsilyl)bicyclo-[2.2.2]octan-1-ol.[6] VPC and ^{13}C NMR analysis indicated that the product mixture (2.5 g) contained adamantan-2-ol (ca. 48%) and an *E*/*Z* mixture of 5-(trimethylsilyl)adamantan-2-ol (ca. 52%). The epimers were shown by ^{13}C NMR to be in the ratio of 69:31 (*E*/*Z*). In connection with another study,[17] the mixture was separated by HPLC (silica gel column) with 30% ethyl acetate-/hexane as the eluent. The physical properties and NMR spectra of the *E* and *Z* silyl alcohols have been presented in the report of that work.[17]

Finely powdered pyridinium chlorochromate[37] (3.27 g, 15.18 mmol) was gradually added to a well-stirred solution of the aforementioned mixture of *E*/*Z* silyl alcohols and adamantan-2-ol (1.7 g, 7.58 mmol) in dry dichloromethane at room temperature. The dark brown reaction mixture was left to stir overnight before being diluted with CH_2Cl_2 and then filtered through a column of Florisil. Evaporation of the solvent afforded an orange colored oil that partially solidified on standing. Sublimation afforded a white solid (0.9 g, 53%) shown by ^{13}C NMR to be a mixture of the title compound and adamantan-2-one. A sample of pure 5-(trimethylsilyl)adamantan-2-one was obtained by differential sublimation: mp 74–76 °C (lit.[2f] 68–71 °C); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 46.66 (C1, 3), 218.47 (C2), 38.89 (C4, 9), 21.40 (C5), 35.96 (C6), 26.83 (C7), 39.96 (C8, 10), −5.39 ($Si(CH_3)_3$); exact mass spectrum calcd for $C_{13}H_{22}SiO$ 222.14398, found 222.1433.

5-(Trimethylstannyl)adamantan-2-one. An *E*/*Z* mixture (60:40) of 5-bromo-2-(trimethylsiloxy)adamantane (3.3 g, 10.98 mmol) was stannylated and desilylated in the same manner as recently described for the conversion of 1-bromo-4-(trimethylsiloxy)bicyclo[2.2.2]octane to 4-(trimethylstannyl)bicyclo-[2.2.2]octan-1-ol.[6] VPC and ^{13}C NMR analysis of the product (1.9 g) indicated a mixture of adamantan-2-ol (ca. 10%) and an *E*/*Z* mixture of 5-(trimethylstannyl)adamantan-2-ol (ca. 90%). The epimers were in the ratio of 60:40. In connection with another study,[17] the mixture was separated by HPLC (silica gel column) with 30% ethyl acetate/hexane as the eluent. The physical properties and NMR spectra of the *E* and *Z* tin alcohols have been presented in the report of that work.[17]

By use of the procedure of Lou,[38] a solution of chromium trioxide (226 mg, 2.27 mmol) in water (9 mL) was added over 15 min to a two-phase diethyl ether/water (4:1) mixture (25 mL) containing the aforementioned mixture of *E*/*Z* tin alcohols and adamantan-2-ol (600 mg). The reaction mixture was allowed to stir with the temperature carefully maintained at 25–30 °C. After 15 min, oxidation was complete (monitored by VPC) and the reaction mixture was then poured into a cold aqueous solution of sodium bicarbonate before being extracted with diethyl ether (3×). Evaporation of the dried ether extracts followed by sublimation afforded 5-(trimethylstannyl)adamantan-2-one as a white solid (400 mg, 80%): mp 79–82 °C (lit.[2f] 81–82 °C); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 48.32 (C1, 3), 217.92 (C2), 44.36 (C4, 9), 26.79 (C5), 40.65 (C6), 28.10 (C7), 39.02 (C8, 10), −12.67 ($Sn(CH_3)_3$).

Attempts to prepare the title compound by oxidation of the tin alcohol mixture with pyridinium chlorochromate met with only limited success. Even under buffered conditions, cleavage of carbon–tin bonds seemed to be a problem.

Acknowledgment. We are grateful to the Australian

(33) Shippey, M. A.; Dervan, P. B. *J. Org. Chem.* **1977**, *42*, 2654.
(34) Adcock, W.; Iyer, V. S. *J. Org. Chem.* **1985**, *50*, 1538.
(35) Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237.
(36) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2951.
(37) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(38) Lou, J.-D. *Chem. Ind.* **1989**, 32.

Research Council for partial financial support of this work. We thank Dr. W. Kitching (University of Queensland) for providing access to their high-field NMR facility (JEOL-GX-400 spectrometer).

Supplementary Material Available: ^{13}C NMR parameters (observed shifts (Tables IX and X) and calculated shifts (Tables XI and XII)) of (*E*)- and (*Z*)-5-substituted (X) adamant-2-yl fluorides 8 and 9 (respectively), photocopies of the ^{13}C NMR spectra of 8 (X = F, Cl, Br, I, and $Sn(CH_3)_3$) and 9 (X = F, Cl, Br, I, $Si(CH_3)_3$, and $Sn(CH_3)_3$) as well as the mixtures 8 and 9 (X = F, Cl, Br, I, C_6H_5, *p*-$NO_2C_6H_4$, *p*-$NH_2C_6H_4$, $Si(CH_3)_3$, and $Sn(CH_3)_3$) (24 pages). Ordering information is given on any current masthead page.

Aromatic Iodination: Evidence of Reaction Intermediate and of the σ-Complex Character of the Transition State

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Received June 5, 1990

The reactivity of four different procedures of aromatic iodination is compared under the same experimental conditions, and their selectivity toward two substrates in competition, i.e., mesitylene (1,3,5-trimethylbenzene, MES) and durene (1,2,4,5-tetramethylbenzene, DUR), is evaluated. Two of these procedures, namely, $S_2O_8^{2-}/I_2$ and Ce^{IV}/I_2, present strong oxidizing capacity. Since the same MES/DUR relative reactivity is obtained from the four procedures, it becomes possible to state that a common reactive intermediate, most likely the I^+ ion, is generated. The use of the MES/DUR mechanistic probe allows one to describe the reactivity picture of the iodination reaction as one of electrophilic substitution at the aromatic nucleous, with a transition state properly represented in terms of a σ-complex. The radical cation of durene also forms when the iodination is carried out by means of oxidizing agents, but it is solely responsible for the formation of side-chain substitution products and is not involved in the nuclear substitution process.

Due to the importance that the iodo derivatives, and in particular the aryl iodides, have under the form of valuable synthetic intermediates[1] and also in view of their wide medical or biochemical applications,[2] a host of experimental procedures have been developed to obtain them.[3]

$$ArH + I_2 \rightarrow ArI + HI \quad (1)$$

Since the iodine molecule is the least reactive among the halogens toward an electrophilic substitution process,[4] most of the synthetic effort has been placed in converting molecular iodine into a more active species. One way of achieving this employs a strong Lewis acid such as Ag^+, which polarizes the iodine molecule, making it more electrophilic and more reactive toward ArH.[3,5] Another way exploits mixed anhydrides such as acetyl (or trifluoroacetyl) hypoiodite, CH_3CO_2I, where a rather mobile electrophilic iodine atom is embedded.[6] An alternative approach requires oxidizing agents. These are suggested to transform I_2 (or even I^-) into a robust electrophilic species, possibly I^+. Several of these oxidants have been described, and their capabilities to drive the iodination to valuable conversion vary considerably.[3] Interestingly, some of these oxidants are strong enough that the oxidation of electron-rich aromatic substrates into a radical cation ($ArH^{\bullet+}$) becomes feasible as well.

Such a variety of experimental procedures could well conceal nonhomogeneous mechanistic pathways, such as electrophilic, atom-transfer or electron-transfer mechanisms, featuring different reactive intermediates. In addition, it is not clear from the literature how much the different efficiency of the various iodination procedures depends on the relative merits of the promoting agents, with the experimental conditions being so different from case to case. It seemed of interest to deepen the knowledge of these points.

A classical mechanistic test to ascertain whether different experimental procedures give rise to the same reactive intermediate is a competitive experiment toward two substrates. Whenever different procedures afford the same reaction products and the same relative reactivity of substrate, there is good reason to conclude that the same reactive intermediate was involved in all cases. In this paper the above mechanistic criterion has been applied to the iodination reaction, to verify if the same reactive intermediate was originated from a number of widely different iodinating agents. These were (a) I_2 with an Ag^+ salt,[3] (b) I_2 and $(NH_4)_2S_2O_8$,[7] (c) catalytic amounts of $NO^+BF_4^-$ (or $NaNO_3$) in combination with O_2 and I_2 (Radner method),[8] (d) I_2 with a Ce(IV) salt (Sugiyama method).[9] Mesitylene and durene were the two aromatic substrates competing for the iodinating species. The choice of these two substrates was not trivial, as it will appear later on. The experimental results of this study are reported herein.

Methods and Results

For a meaningful comparison of the reactivity among the above iodination methods, the same reaction medium had to be employed. This was a mixture 60:8:8:24 v/v of CH_3CO_2H/CF_3CO_2H (TFA)/$(CF_3CO)_2O$ (TFAA)/CH_3CN. The composition of this mixed solvent resulted from "averaging" those employed in the original a–d methods. The iodination reactions were run at room temperature. Typical concentrations were on the order of [DUR] 0.3,

(1) (a) Fanta, P. E. *Synthesis* **1974**, 9. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345.
(2) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575.
(3) (a) Merkushev, E. B. *Russ. Chem. Rev. (Engl. Transl.)* **1984**, *53*, 343. (b) *Synthesis* **1988**, 923.
(4) De La Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976; p 159.
(5) Derbyshire, D. H.; Waters, W. A. *J. Chem. Soc.* **1950**, 3694.
(6) Barnett, J. R.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 6129.
(7) Wirth, H. O.; Königstein, O.; Kern, W. *Liebigs Ann. Chem.* **1960**, *634*, 84.
(8) Radner, F. *J. Org. Chem.* **1988**, *53*, 3548.
(9) Sugiyama, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2847.

0022-3263/91/1956-3238$02.50/0 © 1991 American Chemical Society