Electrostatic *vs* Hyperconjugative Effects as Stereoinductive Factors in the Adamantane Ring System[1]

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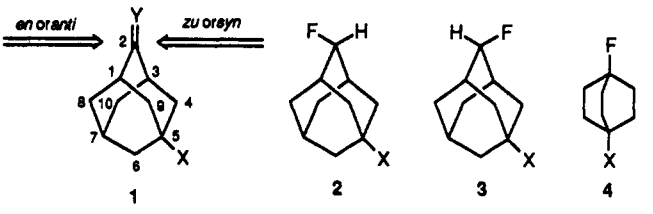
Received August 10, 1993 (Revised Manuscript Received December 13, 1993•)

A series of 5-substituted (X) adamant-2-yl derivatives 1 (Y = O and CH_2) have been synthesized and their ^{13}C NMR spectra measured. The carbonyl and ethylenic ^{13}C substituent chemical shifts (SCS) are shown to be proportional to substituent field effects (σ_F). By use of the polar field susceptibility parameter (ρ_F) for the former shifts, polar field parameters ($\Delta\sigma_F$ values) have been calculated for a series of *p*-SC_6H_4 substituents. Π-Facial diastereoselectivities for the reduction ($NaBH_4$) and methylation (MeLi) of *para*-substituted (S) phenyl derivatives of 1 (Y = O; X = *p*-SC_6H_4) and, as well, for the hydrochlorination of similarly substituted alkenes 1 (Y = CH_2; X = *p*-SC_6H_4) have been determined and correlated successfully against polar field parameters ($\Delta\sigma_F$ values). The slopes of these plots ($\log_{10}[Z]/[E]$ vs $\Delta\sigma_F$) provide polar-field susceptibility parameters (ρ_{FS}) which have been deployed to calculate appropriate diastereoselectivities of the aforementioned reactions for 5-substituted (X) derivatives of 1 (Y = O and CH_2) in general. A comparison of these calculated values with observed diastereoselectivities for a wide range of substituents reveals that direct electrostatic field interactions play a dominant role in governing the phenomena for nucleophilic additions of the ketones 1 (Y = O) and that it is unnecessary to invoke Cieplak's transition-state hyperconjugative model. This appears to be also the case for electrophilic additions to 1 (Y = CH_2) not involving final nucleophilic capture of an intermediate cation. However, hyperconjugation clearly impinges significantly on Π-facial diastereoselectivity for those reactions mediated by 2-adamantyl cations. New results for *methyl*-substituted derivatives of 1 (Y = O and CH_2, X = CH_3) reinforces the σ-electron-withdrawing character of this substituent with respect to γ- and δ-interactions in the neutral ground-state and cationic species.

Introduction

Π-Facial stereoselectivity by various reagents in nucleophilic, electrophilic, radical, and cycloaddition reactions to trigonal carbon centers continues to attract considerable theoretical and experimental attention.[2-7] Although model system studies have clearly demonstrated the importance of long-range electronic effects as a factor which impacts significantly on the diastereoselectivity of nucleophilic addition reactions,[3-6] the nature of the electronic interaction remains controversial. On the one hand, there are advocates of a hyperconjugative model[4,5a-e,6] and, in particular, the Cieplak orbital version,[2,8,9] which emphasizes the importance of the interaction between the best electron-donor bonds *antiperiplanar* to the σ* orbital of the incipient bond in the transition state. On the other hand, there are adherents[3] and recent converts[5f] of an electrostatic field model which simply focuses on stabilizing and destabilizing coulombic interactions. Current literature trends tend to favor the former model.

Prominent amongst the model system studies is the seminal work of le Noble et al.[4] in which 5-substituted (X) adamant-2-yl derivatives 1 have been deployed as stereochemical probe substrates. These stereochemically well-defined model systems seem ideal for assessing electronically-induced Π-facial selectivities since conformational uncertainties are avoided and, moreover, there is no steric bias. Thus, electronic effects can be delineated unambiguously. Several studies by le Noble et al.[4] of a variety of reactions indicate that the reagent prefers to attack the face which is *antiperiplanar* to the more electron-rich vicinal bonds (*zu* and *en* face preference in 1 when X equals an electron-withdrawing and -donating group, respectively). This generalization has been reconciled exclusively within Cieplak's transition-state hyperconjugation model.[8] Central to this interpretation is the observation of a good linear Hammett type plot ($\log[Z]/[E]$ vs σ_p) for the $NaBH_4$



• Abstract published in *Advance ACS Abstracts,* March 1, 1994.

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0022-3263/94/1959-1867$04.50/0

reductions of *para*-substituted (S) 5-phenyl-2-adamantanones 1 (Y =); X = *p*-SC_6H_4).[4a,10]

Recently, in an attempt to provide insight into the nature of polar substituent effects and their modes of transmission between the 2 and 5 (or 1 and 4) positions of the adamantane ring system, we presented ^{19}F substituent chemical shift (SCS) data for a limited series of (*E*)- and (*Z*)-5-substituted (X) adamant-2-yl fluorides (**2** and **3**, respectively).[11] ^{19}F chemical shifts are appropriate electronic probes for this purpose since for 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.[12] *Inter alia* two revelations from this study[11] are noteworthy. Firstly, the *p*-anilino substituent was shown to be a σ-electron-withdrawing group which induces preferential *zu* or *syn* attack by nucleophiles in 1 (Y = O, X = *p*-$NH_2C_6H_4$). This result was diametrically opposed to a previous report by le Noble et al.[4a] However, a subsequent revisit of the $NaBH_4$ reduction of 1 (Y = O; X = *p*-$NH_2C_6H_4$) by the latter workers confirmed our findings.[10] Secondly, the substituent (X) at C_5 in the adamantane ring system is shown unambiguously to induce a substantial differential in the electron-donating ability of the vicinal bonds ($C_{1,9}$ and $C_{3,4}$ *vs* $C_{1,8}$ and $C_{3,10}$) flanking the probe or reaction site (C_2). Moreover, the polar substituent effect is clearly hyperconjugative in origin (an electronegativity effect (σ_χ)). This disclosure coupled with the knowledge gained from a previous study of the electronic behavior of *p*-SC_6H_4 groups by means of the 4-fluorobicyclo[2.2.2]octyl tag as a sensitive monitor (4, X = *p*-SC_6H_4)[13] led us to raise doubts regarding le Noble et al.'s[4a,10] interpretation of the aforementioned Hammett plot. We speculated that it may be a manifestation of an electrostatic field influence (σ_F effect) rather than hyperconjugation (σ_χ effect).[11]

More recently,[14] an expanded study of an extensive series of **2** and **3** covering a wide range of electronic substituent effects has strongly reinforced our doubts concerning the origin of the successful Hammett-type plot (log [*Z*]/[*E*] vs σ_p) proposed by le Noble et al.[4a,10] The question that needs to be answered then is whether or not the differential induced by the C5-substituent in the hyperconjugative electron-donating ability of the vicinal bonds flanking C2, which is clearly revealed by the ^{19}F SCS of **2** and **3**,[11,14] effects a difference in the relative stabilities of the diastereomeric transition states for nucleophilic additions (hydride reduction and methylation) of 1 (Y = O).

The purpose of the work reported in this paper was several fold. Firstly, we wished to deploy ^{13}C NMR chemical shifts as sensitive charge density monitors to evaluate the transmission of polar substituent effects between the 2 and 5 (or 1 and 4) positions of the adamantane ring system. Since a previous study[15] in the bicyclo[2.2.2]octane ring system suggested that the ethylenic and carbonyl groups are appropriate probes, their ^{13}C SCS follow the field effect of substituents (σ_F) closely with no evidence for any significant electronegativity effect (σ_χ), we have synthesized and measured the ^{13}C NMR spectra of an extensive series of 1 (Y = O and CH_2). We were hopeful that carbon-13 and fluorine-19 nuclei as electronic probes would complement one another in the adamantane ring system since the former monitor exclusively through-space electrostatic field effects[15] and the latter predominantly through-bond effects.[11,12,14] Secondly, we were anxious to verify our earlier speculation (see above)[11] regarding the origin of the diastereoselectivity correlation (log [*Z*]/[*E*] vs σ_p) for 1 (Y = O; X = *p*-SC_6H_4).[4a,10] If correct, then linear plots of log [*Z*]/[*E*] vs $\Delta\sigma_F$ for 1 (Y = O and CH_2; X = *p*-SC_6H_4) should provide polar-field selectivity–susceptibility parameters (ρ_{FS}) for the reduction and methylation of 1 (Y = O) as well as for the hydrochlorination of 1 (Y = CH_2). Accordingly, we have synthesized an appropriate series of 1 (Y = O and CH_2; X = *p*-SC_6H_4) and measured their diastereoselectivities (*Z*/*E*) with respect to reduction ($NaBH_4$), methylation (MeLi), and hydrochlorination in order to effect the appropriate correlations. Finally, we wanted to utilize the aforementioned ρ_{FS} values to calculate polar-field induced diastereoselectivities ($\log_{10}$ [*Z*]/[*E*] = $\rho_{FS}\sigma_F$) of 1 (Y = O and CH_2) for a diverse range of groups. We were hopeful that a comparison of these calculated values with the experimentally observed product distributions would allow a quantitative evaluation of electrostatic *vs* hyperconjugative effects as stereoinductive factors in the adamantane ring system. This assessment is important since the validity of transition-state hyperconjugation in terms of Cieplak's model[8] is strongly underpinned by the diastereoselectivity data from this excellent model substrate. Given the sheer size of the adamantane ring system, model system studies of the kind described herein seem most appropriate as the application of computational methods are severely tested.

Herein we report the results of our study.

Results and Discussion

^{13}C NMR Study. In Table 1 we list the ^{13}C SCS for the carbonyl carbon (C2) of 1 (Y = O), together with the same parameters for C_α (or C2) and C_β (or C11) for 1 (Y = CH_2). A linear least-squares regression analysis of these shifts (carbonyl SCS for *p*-SC_6H_4 groups where S = CN, $COOCH_3$, F, Br, OCH_3, and NMe_2 were omitted from the data set) give correlations with $\sigma_F(\equiv\sigma_I)$[12] of reasonable precision (eqs 1–3). It is possible that the precision of fit is compromised slightly by the influence of a very weak electronegativity effect (σ_χ; double hyperconjugation). In

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Table 1. ^{13}C Substituent Chemical Shifts (SCS)[a,b] for Some 5-Substituted (X) Adamant-2-yl Derivatives 1 (Y = O and CH_2)

X	Y = O	Y = CH_2	
	CO[c]	C_α[d]	C_β[e]
NO_2	-5.11		
CN	-4.81	-5.08	3.08
$COOCH_3$	-2.13	-2.56	1.45
$CONH_2$	-1.89		
OCH_3	-1.86	-2.74	1.82
$OCOCH_3$	-3.00		
F	-3.67	-4.32	2.89
Cl	-3.66	-4.62	2.83
Br	-3.97	-4.83	3.01
I	-4.18	-4.74	3.04
$N(CH_3)_2$	-0.72		
CH_3	0.24	-0.76	0.22
C_6H_5	-0.52 (0.00)[f]	-1.46	0.90
p-$NO_2C_6H_4$	-1.90 (-1.38)[f]		
p-CNC_6H_4	-1.79 (-1.27)[f]	-2.46	1.54
p-$COOCH_3C_6H_4$	-1.19 (-0.67)[f]		
p-FC_6H_4	-0.87 (-0.35)[f]	-1.77	1.06
p-BrC_6H_4	-1.14 (-0.62)[f]	-1.94	1.18
p-$CH_3OC_6H_4$	-0.44 (0.08)[f]		
p-$(CH_3)_2NC_6H_4$	-0.08 (0.44)[f]		
$Si(CH_3)_3$	0.29	0.22	-0.41
$Sn(CH_3)_3$	-0.23	-0.05	-0.30

[a] Solvent, $CDCl_3$. [b] Accurate to ±0.05 ppm. [c] X = H, 218.43 ppm relative to Me_4Si. [d] X = H, 158.48 ppm relative to Me_4Si. [e] X = H, 100.57 ppm relative Me_4Si. [f] SCS of p-SC_6H_4 groups based on the phenyl derivative as parent (1, X = C_6H_5).

$$^{13}C\ SCS\ (C2\ of\ 1,\ Y = O) = -9.27\sigma_F + 0.49$$

($CDCl_3$; r = 0.968, F-test = 210.88, CL = 99.99%, n = 16) (1)

$$^{13}C\ SCS\ (C_\alpha\ of\ 1,\ Y = CH_2) = -10.29\sigma_F + 0.13$$

($CDCl_3$; r = 0.977, F-test = 253.82, CL = 99.99%, n = 14) (2)

$$^{13}C\ SCS\ (C_\beta\ of\ 1,\ Y = CH_2) = 7.01\sigma_F - 0.30$$

($CDCl_3$; r = 0.975, F-test = 231.77, CL = 99.99%, n = 14) (3)

this regard, the recent report of significant $^4\Delta$ deuterium isotope effects in 1 (Y = O and CH_2; X = D) is pertinent.[16] Although the problem of disordered crystals has precluded crystal structure analysis of simple substituted adamantanes,[17,18] other X-ray diffraction analyses[18] suggest that 5-substituents should not induce significant skeletal distortions at C2.

It can be seen from the regression equations that the polar susceptibility parameters (ρ_F values) are quite large (-9.27, -10.29, and 7.01; eqs 1, 2, and 3, respectively) and highlight the importance of Π polarization of these groups as a result of polarization of the Π electrons of the C=O and C=CH_2 linkages ($C^{\delta-}$ = $O^{\delta+}$ and $C^{\delta-}$ = $CH_2^{\delta+}$, respectively) by an electrostatic-field effect transmitted through space.[15] Noteworthy in this regard are the *opposing* signs of the ρ_F values of C_α and C_β of 1 (Y = CH_2). The ^{13}C SCS for these two carbons correlate against one another with a very high precision of fit (r = 0.996, F-test = 1513.19, CL = 99.99%, n = 14).

By use of multiple linear least-squares analysis, the carbonyl ^{13}C SCS of p-SC_6H_4 groups in 1 (Y = O; listed in parentheses in Table 1) correlate very well with substituent parameters (σ_F and σ_R).[19] The data set fulfills Taft's recommended minimal substituent set for such multiple correlations.[19] The correlative equation (eq 4)

$$^{13}C\ SCS\ (C2\ of\ 1,\ Y = O;\ X = p\text{-}SC_6H_4) = -1.44\sigma_F - 1.52\sigma_R - 0.22$$

($CDCl_3$; r = 0.991, F-test = 112.64, CL = 99.97%, n = 7) (4)

shows that both polar and resonance effects contribute to the ^{13}C SCS. Thus, the net electric field acting to polarize the C=O linkage is the result of fields associated with the substituent dipole (primary field) and the charges induced in the benzene ring by the substituent (secondary field). It is important to note that since the latter charges are due to both polar and resonance effects, the statistical factorization does not provide a distinct separation of the two contributing electric fields. Hence, the $\rho_F\sigma_F$ term embodies the effects of the primary field as well as a contribution from the effects of field-induced Π polarization of the aromatic ring. Interestingly, the blend of the susceptibility parameters for the correlation (eq 4; ρ_R/ρ_F = 1.06) is significantly different from that observed for the corresponding correlation of the ^{19}F SCS of 4 (X = p-SC_6H_4; ρ_R/ρ_F = 0.58).[13] This result highlights a major difference between the two model systems. Thus, whereas in 4 the substituent and the CF bond are both aligned along the major axis of the ring system, no such alignment occurs in 1 (Y = O). Consequently, orientational factors for the various charges and dipoles are quite different for both systems and, in particular, difficult to specify for 1. Moreover, solvent intrusion into the space between the substituent and probe is probably also different for both systems. This could impact significantly on the respective effective dielectric constants.[20] An important ramification of this insight is that substituent constants for pendant groups (p-SC_6H_4, Me_3Sn, etc.), defined from model systems with strict linear geometry (e.g., 4) may not be appropriate for systems where the alignment is drastically different (e.g., 1).

Because the carbonyl ^{13}C SCS of the *para*-substituted (S) 5-phenyl-2-adamantanones 1 (Y = O; X = p-SC_6H_4) respond sensitively and systematically to the electronic effect of the *para*-substituent (S), these are excellent data for setting up an empirical scale of $\Delta\sigma_F$ values for p-SC_6H_4 substituents applicable to the 2,5-disposition of the adamantane ring system in general. By use of the appropriate ^{13}C SCS (Table 1) and ρ_F value (-9.27; eq 1) the following constants ($\Delta\sigma_F$) may be calculated: p-$NO_2C_6H_4$, 0.150; p-CNC_6H_4, 0.138; p-$COOH_3C_6H_4$, 0.073; p-FC_6H_4, 0.038; p-BrC_6H_4, 0.067; p-$CH_3OC_6H_4$, -0.009, p-$Me_2NC_6H_4$, -0.048.

Stereoselectivity Studies. (a) Polar-Field Selectivity-Susceptibility Parameters (ρ_{FS}). The diaste-

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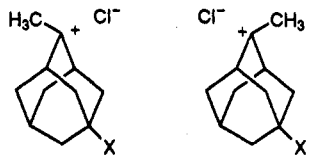
Table 2. Product Distribution in the Reduction ($NaBH_4$) and Methylation (MeLi) of *para*-Substituted (S) 5-Phenyl-2-adamantones 1 (Y = O; X = *p*-SC_6H_4)

	reduction[a]		methylation[b]	
S	% *E*	% *Z*	% *E*	% *Z*
H	58 (59)	42 (41)	62	38
NO_2	68 (66)	32 (34)		
CN	66 (65)	34 (35)	72	28
$COOCH_3$	*c* (64)	*c* (36)	68	32
F	63 (65)	37 (35)	67	33
Br	64 (65)	36 (35)	68	32
OCH_3	59 (60)	41 (40)	59	41
$N(CH_3)_2$	57 (57)	43 (43)	57	43

[a] Ratios determined by ^1H and ^{13}C NMR. The results of the latter are listed in parentheses. Values given for the former are the average of two determinations measured at 300 and 500 MHz. [b] Ratios determined by ^{13}C NMR. [c] Could not be determined because of the coincidence of C_2H and CH_3 peaks in the ^1H NMR spectrum.

reoselectivities (*Z*/*E*) for the $NaBH_4$ reduction and methylation of a series of *para*-substituted (S) 5-phenyl-2-adamantanones 1 (Y = O; X = *p*-SC_6H_4) are presented in Table 2. It should be noted that the new data (reduction) for the C_6H_5 and *p*-$NO_2C_6H_4$ substituents are in accord with those previously reported.[4a,11] The plots in Figures 1 and 2 show that the logarithms of [*Z*]/[*E*] correlate well linearly with the respective $\Delta\sigma_F$ values (see above), thereby confirming that the stereochemical outcome of these nucleophilic addition reactions is governed by the electrostatic field influence of the remote substituent; i.e., the relative stabilities of the two diastereomeric transition states for *syn* and *anti* additions is predominantly determined by electrostatic interactions. The relative magnitude of the ρ_{FS} values (−1.01 *vs* −1.61) highlights the ability of the methylation reaction to differentiate more than hydride reduction. This has been noted previously by le Noble et al.[21] and Mehta et al.[5a,c] but in a less formalized manner. We believe the phenomenon is probably a manifestation of greater charge development in the transition-state for methylation versus that for reduction (i.e., late *vs* early transition state, respectively). However, the possibility of electrostatic effects being transmitted more effectively in solvents of lower polarity[20] ($(C_2H_5)_2O$ *vs* CH_3OH) cannot be entirely ignored (see later).

The product distributions for the hydrochlorination of a limited series of 2-methylene-5-(*para*-substituted (S) phenyl)adamantanes 1 (Y = CH_2; X = *p*-SC_6H_4) in CH_2Cl_2 and NO_2CH_3 are set out in Table 3. An excellent correlation is observed (Figure 3) between the $\log_{10}$ [*Z*]/[*E*] values for CH_2Cl_2 as solvent and $\Delta\sigma_F$. Thus, diastereofacial selectivity for electrophilic addition in this weakly polar solvent (ϵ = 8.9) is strongly controlled by the electrostatic field resulting from the substituent (S)-induced charges and dipoles in the benzene ring. Given that HCl addition to alkenes in CH_2Cl_2 is mediated by the formation of intimate ion pairs[22,23] (5 and 6 from 1, Y = CH_2) whose relative stabilities are largely governed by hyperconjugation, the electric field dependency (Figure 3) can be explained in terms of preferential field-induced suppression or enhancement of stabilizing charge dispersal in the product-determining transition state proceeding from 6 (*E* species). This explanation seems to be supported by



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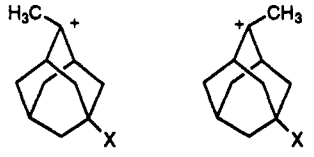
the fact that in NO_2CH_3, a highly polar solvent (ϵ = 37.5), the diastereoselectivity for HCl addition to 1 (Y = CH_2; X = *p*-SC_6H_4) is essentially indifferent to the electronic character of the substituent on the phenyl ring ($\rho_{FS} \approx 0$; Table 3). Apparently, the fields exerted by the charges and dipoles in the benzene ring, which are on the edge of the molecular cavity, now act through regions of much higher effective dielectric constant[20] and, therefore, are effectively dampened to zero. The effect of charges in the molecular cavity (e.g., at C5) remain unperturbed as evidenced by the similar diastereoselectivity in CH_2Cl_2 and NO_2CH_3 for addition to 1 (Y = CH_2) when X = C_6H_5 (Table 3). However, it is important to bear in mind that there is a mechanistic distinction for HCl addition in CH_2Cl_2 *vs* NO_2CH_3. Whereas for the former the reaction involves the formation of tight ion pairs, in the latter free ions are expected to mediate the reaction (7 and 8 from 1, Y = CH_2). NMR[24] and reactivity studies[4a] have shown that free tertiary 2-adamantyl cations rapidly equilibrate to a pair of epimeric ions (Z^+ and E^+; 7 and 8, respectively);[25]thus, a preequilibrium step occurs prior to



7 8

product formation in the addition of HCl to 1 (Y = CH_2) in NO_2CH_3. This transformation is shown in Scheme 1.

Scheme 1

$$(E)\text{-Cl} \xleftarrow{k_3} E^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Z^+ \xrightarrow{k_4} (Z)\text{-Cl}$$

A general equation has been derived for such a situation which relates the product ratio (P_∞ = [(*Z*)-Cl]/[(*E*)-Cl]) with the equilibrium constant ($K = k_1/k_2$) and the

(21) (a) Lin, M.-h.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155. (b) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836.

(22) Dewar, M. J. S.; Fahey, R. C. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 245.

(23) (a) Although the stereochemistry of the addition of hydrogen chloride to alkenes is usually discussed in terms of the formation of a cationic intermediate (Ad_E2 mechanism),[23b] limited studies have revealed higher order kinetics in aprotic solvents which suggest that a termolecular process (Ad_E3)[23b] may also be important. However, higher order kinetics is also consistent with addition through ion-pair or free-ion intermediates.[23c] (b) Fahey, R. C. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley & Sons, Inc.: New York, 1968. (c) Pocker, Y. *J. Chem. Soc.* **1960**, 1292.

(24) (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.

(25) (a) For expedience, structures 7 and 8 are drawn in an abbreviated form, but it is implicit that any full description of these ions must include the solvent and/or counterion as indicated by Sorensen et al.[24a] One reviewer remains unconvinced that the 2-methyl-2-adamantyl cation is a nonplanar species and suggests that ion-pair phenomena is probably responsible for its unusual behavior.[24a] However, it is important to note that the $^1J_{^{13}C_2-H}$ constant for this tertiary cation strongly implies that the C^+ center is significantly distorted from planarity[25b] (ca. 36°; we thank Dr. D. P. Kelly for kindly providing us with this information). (b) Kelly, D. P.; Aherne, K.; Delgado, F.; Giansiracusa, J. J.; Jensen, W. A.; Karavokiros, R. A.; Mantello, R. A.; Reum, M. E. *J. Am. Chem. Soc.* **1993**, *115*, 12010.

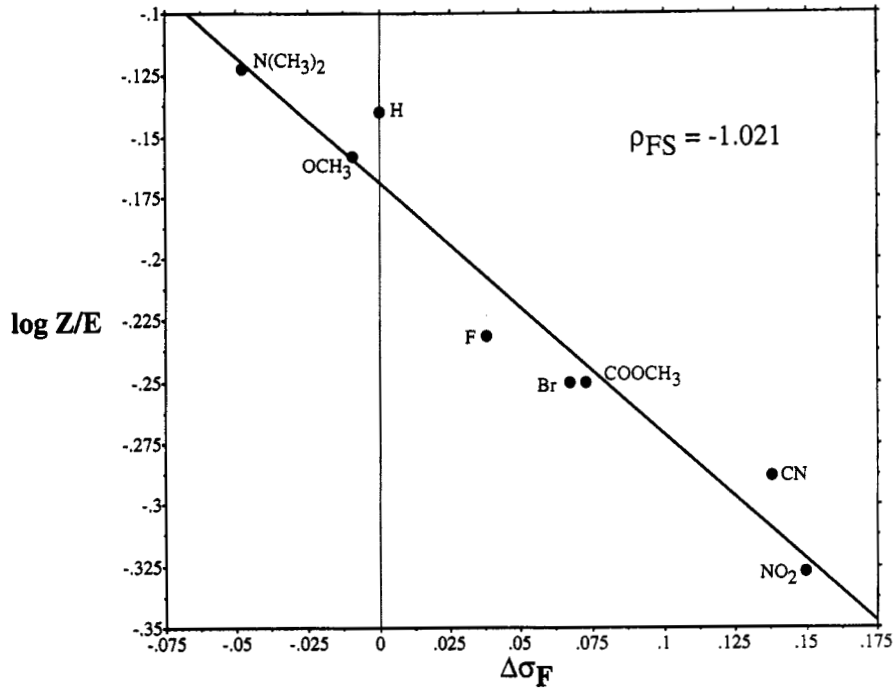


Figure 1. Plot of $\log_{10}[Z]/[E]$ for the $NaBH_4$ reduction of *para*-substituted (S) 5-phenyl-2-adamantanones 1 (Y = O; X = *p*-SC_6H_4) versus $\Delta\sigma_F$ ($y = -1.021x - 0.169$, $r^2 = 0.945$).

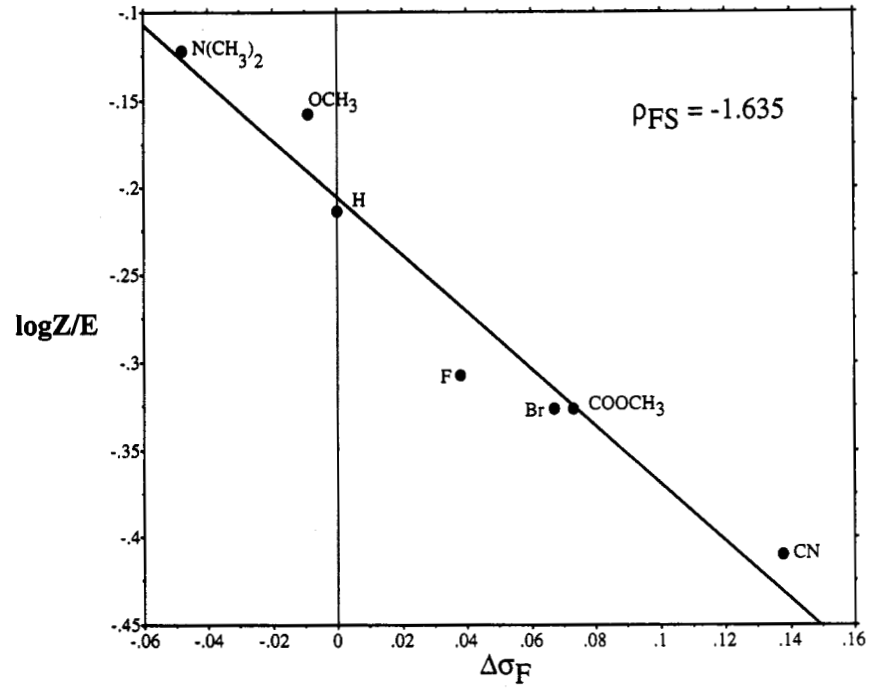


Figure 2. Plot of $\log_{10}[Z]/[E]$ for the methylation (CH_3Li) of *para*-substituted (S) 5-phenyl-2-adamantanones 1 (Y = O; X = *p*-SC_6H_4) versus $\Delta\sigma_F$ ($y = -1.635x - 0.206$, $r^2 = 0.949$).

individual rate constants (eq 5).[26]

$$P_\infty = K\frac{k_4(k_1 + k_2 + k_3)}{k_3(k_1 + k_2 + k_4)} \quad (5)$$

Because the available evidence suggests that the equilibration step is rapid, a reasonable assumption is that k_1, $k_2 \gg k_3$, k_4, and therefore, eq 5 reduces to eq 6. Thus, the relative stability of the epimeric cations 7 and 8, which is governed predominantly by hyperconjugation, impinges

$$P_\infty = K\frac{k_4}{k_3} \quad (6)$$

importantly on facial selectivity in NO_2CH_3. Therefore, the major factor governing the diastereoselectivity of electrophilic addition in the two solvents (CH_2Cl_2 and NO_2CH_3) is the same. An important difference, however, is that stabilization by hyperconjugation should be more pronounced for 7 and 8 than 5 and 6 because of the charge localizing influence of the anion in the latter species.

(b) Calculated Polar-Field Induced II-Facial Selectivities *vs* Experimentally Observed Product Dis-

(26) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

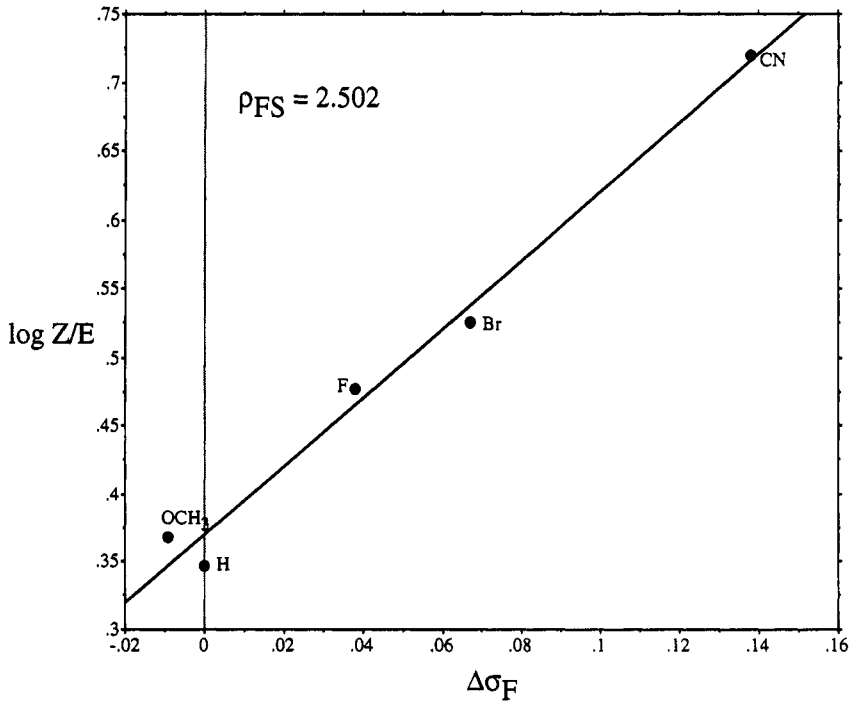


Figure 3. Plot of $\log_{10}[Z]/[E]$ for the hydrochlorination (CH_2Cl_2 as solvent) of 2-methylene-5-(*para*-substituted (S) phenyl)adamantanes 1 (Y = CH_2; X = *p*-SC_6H_4) versus $\Delta\sigma_F$ ($y = 2.502x + 0.37$, $r^2 = 0.986$).

Table 3. Product Distribution for the Hydrochlorination of 2-Methylene-5-(*para*-substituted (S) phenyl)adamantanes 1 (Y = CH_2; X = *p*-SC_6H_4)

	CH_2Cl_2[a]		NO_2CH_3[a]			CH_2Cl_2[a]		NO_2CH_3[a]	
S	% *E*	% *Z*	% *E*	% *Z*	S	% *E*	% *Z*	% *E*	% *Z*
H[b]	35	65	34	66	OCH_3	30	70	42	58
F	25	75	39	61	CN[b]	16	84	32	68
Br	23	77	32	68					

[a] Ratios determined by ^{13}C NMR. [b] Values given are the average of two determinations, which agreed within 1% in each case.

tributions. By use of the ρ_{FS} values derived above, the known appropriate σ_F values[11,12] and the Hammett-type equation ($\log[Z]/[E] = \rho_{FS}\sigma_F$), polar-field induced Π-facial selectivities have been determined for the aforementioned nucleophilic and electrophilic additions reactions of 1 (Y = O and CH_2, respectively). These are listed in Tables 4–6 together with the experimentally observed product distributions. A scrutiny of the data for nucleophilic addition (Tables 4 and 5) reveals that in several instances, mainly for weak to moderately polar groups ($\sigma_F < 0.30$), there is good agreement between the calculated and observed results. However, for strongly polar substituents ($\sigma_F > 0.30$), the predicted selectivity is in general significantly greater than the observed situation. Most significantly, there is not a singular comparison where the latter situation is reversed. This is important because the Cieplak effect[2,8] operates to reinforce the diastereoselectivity induced by electrostatic interactions. Perhaps the most pertinent substituent with respect to revealing the importance of transition-state hyperconjugation, or otherwise, is Me_3Sn. Previous reactivity studies have drawn attention to the importance of double hyperconjugation for this powerful σ-electron donor group.[11,27,28] Note, however, that the selectivity exerted by this group (Tables 4 and 5) is feeble (this study) and, moreover, the observed selectivity is in accord with expectations based purely on electrostatic grounds. Thus, the overall picture painted by all the results (Tables 4 and 5), namely, the unimportance of transition-state hyperconjugation, is strongly reinforced. It should be noted that the two σ_F values listed for Me_3Sn have been determined from the ^{19}F and ^{13}C SCS of 1-*X*-4-(*p*-fluorophenyl)bicyclo[2.2.2]octanes[12b] and 1 (Y = CH_2, Cβ), respectively. As mentioned above, σ_F values for pendant groups may differ for model systems with quite different orientational relationships between the substituent and probe groups.

Table 4. Calculated Polar-Field Induced Π-Facial Selectivities[a] *vs* Observed Product Distributions for the Reduction of 5-Substituted (X) Adamantan-2-ones 1 (Y = O)

		obsd		calcd[a]	
X	σ_F[b]	% *E*	% *Z*	% *E*	% *Z*
NO_2	0.62	75 (75)[c,d]	25 (25)[c,d]	81	19
CN	0.54	69 (68)[c,d]	31 (32)[c,d]	78	22
CF_3	0.42	59[e]	41[e]	73	27
$COOCH_3$	0.29	57 (55)[c]	43 (45)[c]	66	34
F	0.41	59[f]	41[f]	72	28
Cl	0.43	63[f]	37[f]	73	27
Br	0.44	60[f]	40[f]	74	26
I	0.41	64[f]	36[f]	72	38
OCH_3	0.30	64 (64)[c]	36 (36)[c]	67	33
$OCOCH_3$	0.37	62 (63)[c]	38 (37)[c]	70	30
$N(CH_3)_2$	0.28	65 (66)[c]	35 (34)[c]	66	34
C_6H_5	0.17	58 (59)[c]	42 (41)[c]	60	40
CH_3	0.03[g]	(51)[c]	(49)[c]	52	48
$C(CH_3)_3$	0.02[h]	50[e]	50[e]	51	49
$Si(CH_3)_3$	0.01[h]	50[f]	50[f]	50	50
$Sn(CH_3)_3$	0.02[h]	48[f]	52[f]	51	49
$Sn(CH_3)_3$	−0.04[i]	48[f]	52[f]	48	52

[a] $\log[Z]/[E] = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.01$. [b] $\sigma_F(\equiv \sigma_I)$ values for CH_3OH taken from ref 12a. [c] This study. Ratios determined by ^1H and ^{13}C NMR. The latter are listed in parentheses. [d] Capillary VPC analysis, 75/25 (X = NO_2) and 68/32 (X = CN). [e] Taken from ref 4a. [f] Taken from ref 11. [g] Taken from ref 12d. [h] Taken from ref 12b. [i] This study (see text).

(27) Adcock, W.; Krstic, A. R.; Duggan, P. J.; Shiner, V. J., Jr.; Coope, J.; Ensinger, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 3140.
(28) Adcock, W.; Coope, J.; Shiner, V. J., Jr.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.

Table 5. Calculated Polar-Field Induced II-Facial Selectivities[a] *vs* Observed Product Distributions for the Methylation of 5-Substituted (X) Adamantan-2-ones 1 (Y = O)

		obsd[b]		calcd[a]	
X	σ_F[c]	% *E*	% *Z*	% *E*	% *Z*
CN	0.59	68[d]	32[d]	90	10
CF_3	0.44	72[e]	28[e]	84	16
$COOCH_3$	0.22	55[d]	45[d]	69	31
F	0.39	66 (67)[d,f]	34 (33)[d,f]	81	19
Cl	0.43	62 (63)[d]	38 (37)[d]	83	17
Br	0.44	60 (61)[d]	40 (39)[d]	84	16
I	0.42	57 (57)[d]	43 (43)[d]	83	17
OCH_3	0.19	63 (65)[d]	37 (35)[d]	67	33
$N(CH_3)_2$	0.12	63 (63)	37 (37)	61	39
C_6H_5	0.15	62	38	64	36
CH_3	0.05[h]	54 (53)	46 (47)	55	45
$Si(CH_3)_3$	0.00[h]	49	51	50	50
$Sn(CH_3)_3$	0.01[h]	48 (36.5)[g]	52 (63.5)[g]	51	49
$Sn(CH_3)_3$	−0.04[h]	48 (36.5)[g]	52 (63.5)[g]	46	54

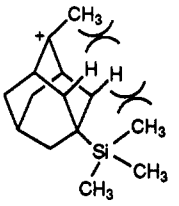
[a] $\log [Z]/[E] = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.61$. [b] This study. Determined by ^{13}C NMR. Values in parentheses determined by ^1H NMR. [c] σ_F (≡ σ_I) values for c-C_6H_{12} taken from ref 12a. [d] This study. Results by VPC are as follows: CN (67/33), $COOCH_3$ (53/47), F (67/33), Cl (62/38), Br (57/43), I (55/45), and OCH_3 (63/37). [e] Taken from ref 4a. [f] 70/30 by VPC. See ref 4a. [g] Taken from ref 21b. [h] See footnotes *h* and *i* in Table 4.

Table 6. Calculated Polar-Field Induced II-Facial Selectivities[a] *vs* Observed Product Distributions for the Hydrochlorination of 5-Substituted (X) 2-Methyleneadamantanes 1 (Y = CH_2)

		obsd (CH_2Cl_2)[b]		obsd (NO_2CH_3)[b]		calcd[a]	
X	σ_F[c]	% *E*	% *Z*	% *E*	% *Z*	% *E*	% *Z*
CN	0.53	13	87			5	95
$COOCH_3$	0.25	28 (29)	72 (71)	26	74	20	80
F	0.41	10 (5)[d]	90 (95)[d]	0 (0)[d]	100 (100)[d]	9	91
Cl	0.43	17	83	3	97	8	92
Br	0.44	22	78	17	83	8	92
I	0.42	34	66	26	74	9	91
OCH_3	0.24	14 (14)[e]	86 (86)[e]	15	85	21	79
C_6H_5	0.17	35 (35)[e]	65 (65)[e]	34	66	28	72
CH_3	0.03[f]	39 (44)[e]	61 (56)[e]	44	56	46	54
$Si(CH_3)_3$	0.01[g]	65 (69)[e]	35 (31)[e]	50	50	49	51

[a] $\log [Z]/[E] = \rho_{FS}\sigma_F$; $\rho_{FS} = 2.451$. [b] This study. Ratios determined by ^{13}C NMR. [c] σ_F (≡ σ_I) values for CH_2Cl_2 taken from ref 12a. [d] Ratios determined by ^{19}F NMR. [e] Ratios determined by ^1H NMR. [f] Taken from ref 12d. [g] Taken from ref 12b.

An examination of the data in Table 6 for electrophilic addition brings to light several noteworthy features. Firstly, it can be seen that the Me_3Si and Me groups (Group 14 substituents), two substituents with virtually no electrostatic field influence ($\sigma_F \approx 0$),[12b,d] exert significant effects on diastereoselectivity but clearly in opposite directions. The result strikingly highlights the differential charge demands of the C–Si and C–C bonds versus the C–H bond in double hyperconjugation,[27,28] i.e., it is consistent with the hyperconjugative σ-electron-donor and -withdrawing character of these two groups, respectively, regulating the relative energies of the diastereomeric transition states proceeding from **5** and **6**. Under free-ion conditions (NO_2CH_3 as solvent), where hyperconjugation as a stereoinductive factor is expected to be even more paramount (see above), the result for CH_3 is in line with that observed in CH_2Cl_2 and was expected. By contrast, the failure of Me_3Si to exert any influence on facial selectivity whatsoever by double hyperconjugation in NO_2CH_3 is surprising. This is more so in the light of the stereochemical result (*E*/*Z* = 86/14) previously observed for the fluorination (DAST/CH_2Cl_2) of (*E*)- and (*Z*)-5-(trimethylsilyl)-2-adamantanols.[11] The latter reaction is similarly mediated by the formation of rapidly equilibrating free secondary ions. We believe the apparently dichotomous result for Me_3Si in NO_2CH_3 (Table 6) can be explained by invoking a long-range steric interaction by the relatively bulky substituent[29] in the free *E*-cation (**8**, X = Me_3Si) which is transmitted via the axial 4,9-hydrogen atoms (see **9**). The consequential destabilizing interaction



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would offset the energy gain as a result of double hyperconjugation. Optimization of the latter electronic mechanism (antiperiplanar relationship of participant orbitals) is also seriously compromised structurally by such a steric effect.[30] This steric phenomenon is apparently concealed by the results for HCl addition in CH_2Cl_2 to 1 (Y = CH_2; X = $SiMe_3$) because the fairly similar effective steric size for Cl and CH_3[31] ensures that its contribution to the relative energies of the product-determining transition states (ion-pair-like; **5** and **6**) essentially cancels out.

Secondly, a notable Group 14 substituent missing from the data in Table 6, as a result of its protolytic instability, is the Me_3Sn group. However, it is significant that direct epoxidation of 1 (Y = CH_2; X = $SnMe_3$) with *m*-chloroperbenzoic acid in CH_2Cl_2 provides a 50:50 mixture of the stereoisomeric epoxides (see Experimental Section). Thus, in this concerted electrophilic addition reaction, which is not mediated by carbocation formation, the powerful σ-electron-donor Me_3Sn group is merely an ineffectual bystander with respect to facial selectivity, as a consequence of its weak field effect ($\sigma_F \approx 0$).[12b]

Thirdly, it can be seen (Table 6) that although there is quite good agreement between the observed and calculated polar-field-induced selectivities in CH_2Cl_2 for some of the σ-electron-withdrawing substituents, there are several significant discrepancies, in particular, the selectivity order for the halogens (F > Cl > Br > I (observed) *vs* F ~ Cl ~ Br ~ I (calculated)). Given that the diastereoselectivity of this reaction is mainly governed by the differential hyperconjugative stabilization between the appropriate cationic species which, in turn, is more a function of the σ-inductive perturbation of C_5, the pattern of results is not particularly surprising. However, it highlights that data for the halogen subset (F, Cl, Br, and I) are imperative for reactivity studies in order to unambiguously reveal electronegativity effects (σ_χ) for σ-electron-withdrawing groups. These particular substituents have similar σ_F values but vastly different σ_χ parameters.[32] It is of interest to note that the effect of hyperconjugation of σ-electron-withdrawing groups on the stability of 4-substituted (X)

(29) Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153.
(30) Krijiner, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdeurijk, D. *J. Am. Chem. Soc.* **1989**, *111*, 4433 and references cited therein.
(31) Hounshell, W. D.; Iroff, L. D.; Iverson, D. J.; Wroczynski, R. J.; Mislow, K. *Isr. J. Chem.* **1980**, *20*, 65 and references cited therein.
(32) See ref 12 of ref 27.

Table 7. Product Distribution for the Hydrochlorination[a] of Mixtures (*E* and *Z* Isomers) of 5-Substituted (X) 2-Methyladamantan-2-ols[b]

X	chlorides % *E*	chlorides % *Z*	analytical methods
F	27	73	^{13}C NMR
F	25	75	^{19}F NMR
Cl	30	70	^{13}C NMR
Cl	29	71	^{1}H NMR
Br	39	61	^{13}C NMR
CH_3	41	59	^{13}C NMR
CH_3	41	59	^{1}H NMR
$Si(CH_3)_3$	61	39	^{13}C NMR
$Si(CH_3)_3$	60	40	^{1}H NMR
C_6H_5	42	58	^{13}C NMR
p-FC_6H_4	39	61	^{13}C NMR
p-FC_6H_4	39	61	^{19}F NMR
p-BrC_6H_4	38	62	^{13}C NMR
p-$CH_3OC_6H_4$	43	57	^{13}C NMR

[a] $HCl/CaCl_2/CH_2Cl_2$. [b] See Tables 2 and 5 for composition of alcohol mixtures.

bicyclo[2.2.2]oct-1-yl[33] and (*E*)-5-substituted (X) adamant-2-yl cation systems[34] (10 and 11, respectively) is blurred as the appropriate solvolysis rates correlate very well against an alternative electrostatic field parameter (σ_I^q).[35] However, the fact that the δ interaction is stronger than the γ interaction in the 2-adamantyl ion[34] (substituent at C5 and C4, respectively) exposes the hyperconjugative mode of transmission of polar effects for electronegative substituents.[36] The importance of double hyperconjugation as a mode of stabilization of 10 and 11 is unequivocal[11,27,28] for good σ-electron-donor groups (Me_3Si and Me_3Sn) as their σ_F values are effectively *zero*.

It is noteworthy that the electronegativity order of selectivity of HCl addition for the halogen substituents (F > Cl > Br > I) is also observed in NO_2CH_3 (Table 6). The enhanced facial selectivity for these groups in the latter solvent can be ascribed to stabilization by hyperconjugation being more pronounced for the free ions (7 and 8) then the ion-pair-like transition states (5 and 6). On this point it is important to note that there is no evidence in the literature to suggest that the σ-electron-withdrawing power of halogen substituents ($C^{\delta+}$–$X^{\delta-}$) is increased by greater separation of charge in the σ bonds and dispersion of charge at the *negative* end of the dipole, which protrudes into the media, as a result of solvation by highly polar aprotic solvents.

It is of interest to note that the selectivity of these tertiary 2-adamantyl cation-mediated reactions is significantly suppressed (Table 7) when the tertiary methyl alcohols 1 (Y = Me, OH) are used to generate the free cation with HCl in CH_2Cl_2[4a] containing anhydrous $CaCl_2$. This phenomenon has been previously noted by le Noble et al.[37] for the situation where X = F. These workers have suggested that it may have something to do with the presence of a water molecule in the activated complex. Unfortunately, even with a much larger data base we are unable to add constructively to this suggestion. However, a noteworthy result is the significant selectivity observed for the Me_3Si group (Table 7) which is similar to that observed for HCl addition to 1 (Y = CH_2; X = $SiMe_3$) in CH_2Cl_2 but not NO_2CH_3 (Table 6). In accord with the aforementioned rationalization of the selectivity difference of the Me_3Si group for HCl addition to 1 (Y = CH_2) in CH_2Cl_2 and NO_2CH_3, the selectivity result from the alcohols for this substituent (Table 7) suggests that the initially formed free cations may first lose a proton to yield the alkene which then leads to the product distribution being mediated by the formation of ion-pair-like (5 and 6) diastereomeric transition states.

Table 8. Product Distribution in the Fluorination[a] of Mixtures (*E* and *Z* Isomers) of 5-Substituted (X) Adamantan-2-ols[b]

X	fluorides % *E*	fluorides % *Z*	analytical method	X	fluorides % *E*	fluorides % *Z*	analytical method
NO_2[c]	5	95	^{13}C NMR	$OCOCH_3$[c]	20	80	VPC
NO_2[c]	9	91	VPC	$OCOCH_3$[c]	22	78	^{19}F NMR
NO_2[c]	7	93	^{19}F NMR	$N(CH_3)_2$[c]	28	72	^{19}F NMR
CN[c]	11	89	^{13}C NMR	CH_3[c]	41	59	^{13}C NMR
CN[c]	11	89	VPC	CH_3[c]	38	62	^{1}H NMR
CN[c]	14	86	^{19}F NMR	CH_3[c]	36	64	^{19}F NMR
CO_2CH_3[c]	30	70	^{13}C NMR	$Si(CH_3)_3$[d]	84	16	^{13}C NMR
CO_2CH_3[c]	28	72	VPC	$Si(CH_3)_3$[d]	86	14	^{19}F NMR
CO_2CH_3[c]	30	70	^{19}F NMR	$Sn(CH_3)_3$[d]	100	0	^{13}C NMR
F[d]	10	90	^{13}C NMR	$Sn(CH_3)_3$[d]	>98	trace	^{19}F NMR
F[d]	6	94	VPC	C_6H_5[d]	41	59	^{13}C NMR
F[d]	4	96	^{19}F NMR	C_6H_5[d]	38	62	^{19}F NMR
Cl[d]	15	85	^{13}C NMR	*p*-$NO_2C_6H_4$[d]	35	65	^{13}C NMR
Cl[d]	15	85	VPC	*p*-$NO_2C_6H_4$[d]	35	65	^{19}F NMR
Cl[d]	16	84	^{19}F NMR	*p*-CNC_6H_4[c]	35	65	^{13}C NMR
Br[d]	18	82	^{13}C NMR	*p*-CNC_6H_4[c]	35	65	^{19}F NMR
Br[d]	19	81	VPC	*p*-$CO_2CH_3C_6H_4$[c]	39	61	^{13}C NMR
Br[d]	18	82	^{19}F NMR	*p*-$CO_2CH_3C_6H_4$[c]	41	59	^{19}F NMR
I[d]	32	68	^{13}C NMR	*p*-FC_6H_4[c]	41	59	^{13}C NMR
I[d]	35	65	VPC	*p*-FC_6H_4[c]	43	57	^{19}F NMR
I[d]	38	62	^{19}F NMR	*p*-BrC_6H_4[c]	36	64	^{13}C NMR
OCH_3[c]	34	66	^{13}C NMR	*p*-BrC_6H_4[c]	38	62	^{19}F NMR
OCH_3[c]	33	67	VPC	*p*-$CH_3OC_6H_4$[c]	45	55	^{13}C NMR
OCH_3[c]	35	65	^{19}F NMR	*p*-$CH_3OC_6H_4$[c]	46	54	^{19}F NMR
$OCOCH_3$[c]	20	80	^{13}C NMR	*p*-$(CH_3)_2NC_6H_4$[c]	39	61	^{19}F NMR

[a] $DAST/CH_2Cl_2$. [b] See Tables 2 and 4 for composition of alcohol mixtures. [c] See ref 14. [d] Taken from ref 11.

Finally, for the sake of completeness, it should be noted that the results for fluorination ($DAST/CH_2Cl_2$) of 5-substituted (X) adamantan-2-ols (Table 8) also exhibit product ratios largely governed by hyperconjugation. The electronegativity order of facial selectivity for the halogen substituents is particularly pertinent with respect to the comments above concerning σ-electron-acceptor groups. However, in examining these results it is important to bear in mind two points. Firstly, the fluoride mixtures were obtained from mixtures of alcohols (*E*/*Z*) whose compositions are shown in Tables 2 and 4. Secondly, the fluorination of pure epimers (*E* or *Z*) for X = Br and $SiMe_3$ reveal that the isomerization of free secondary 2-adamantyl cations in CH_2Cl_2 may not be complete when the 5-substituent is a strong σ-electron acceptor.[11] In the light of the sensitivity of facial selectivity of HCl addition to 1 (Y = CH_2; X = *p*-SC_6H_4) in CH_2Cl_2 (Table 6) to the electronic character of the substituent (S) on the phenyl ring (see Figure 3), the apparent invariance to S of the product ratios obtained from the fluorination ($DAST/CH_2Cl_2$) of a series of *para*-substituted (S) 5-phenyladamantan-2-ols (Table 8) is puzzling. The latter situation was encountered for HCl addition to 1 (Y = CH_2; X = *p*-SC_6H_4) in NO_2CH_3 (Table 6) and was rationalized in terms of a drastic attenuation of the field effect by the much higher effective dielectric constant in this highly polar solvent. However, the fluorination results of the 5-*p*-SC_6H_4-2-adamantanols

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(Table 8) in CH_2Cl_2 cannot be similarly explained away and, therefore, must remain a conundrum.

Conclusions

The results disclosed above strongly suggest that it is unnecessary to invoke transition-state hyperconjugation in terms of Cieplak's model[2,8,9] to explain π-facial selectivity for the reduction and methylation of 5-substituted (X) 2-adamantanones 1 (Y = O). For the most part, the results appear to be accommodated by an electrostatic field model.[3] However, the significant discrepancies between the calculated polar-field induced diastereoselectivities and the observed results for strongly polar substituents raise the possibility of transition-state hyperconjugation (Felkin–Anh model)[9] as a significant factor in some cases. The results of this study also suggest that the qualitative success of Dannenberg et al.'s[38] polarized π-frontier molecular orbital (PPFMO) method in predicting diastereofacial selectivities for the reduction of norbornanones and adamantanones is probably due to the dominant perturbation of the frontier orbitals by electrostatic field effects. By contrast, hyperconjugation is clearly the dominant factor governing the diastereoselectivity of the hydrochlorination of 5-substituted (X) 2-methyleneadamantanes 1 (Y = CH_2). This highlights the known enhancement of hyperconjugative interactions in electron-deficient species such as carbocations. However, the product distribution results for the epoxidation of 1 (Y = CH_2; X = $SnMe_3$) suggest that the stereochemical course of electrophilic addition reactions not mediated by carbocations[2,5b,6b,37,39] is most likely regulated by direct field effects.[7g]

Finally, in view of the continuing debate concerning the relative electron-donating ability of C–C and C–H bonds in saturated systems,[2,3,40] it is important to emphasize that the results of this study clearly indicate that CH_3 is a σ-electron withdrawing group. This is in accord with other studies of 5-methyl-substituted 2-adamantyl derivatives.[4a,11,14,24,34,41] Thus, coupled with NMR and reactivity data from other polycycloalkane derivatives (1,4-disubstituted bicyclo[2.2.2]octanes,[12a,b,27,33] 1,4-disubstituted bicyclo[2.2.1]heptanes,[42] and 1,4-disubstituted cubanes;[43] 2,6-disubstituted bicyclo[2.2.1]heptanes;[44] 1,3-disubstituted adamantanes[12c,45] and 1,3-disbustituted bicyclo[1.1.1]pentanes;[44] and 1,5-disubstituted bicyclo[3.1.1]heptanes[47] and 1,5-disubstituted trishomobarrelenes[48]), the experimental evidence is overwhelmingly in favor of C–H being a better donor than C–C for γ- and δ-interactions in the neutral ground-state and electron-deficient species. Most importantly, it should be borne in mind that rigid polycycloalkanes are the archetypal model substrates for delineating electronic influences unequivocally in the absence of complicating steric and conformational phenomena. Although there is still no general consensus concerning a group electronegativity scale, it is pertinent to note that most of the various scales rank CH_3 as being more electronegative than H,[49] which is in line with the above conclusion.

Experimental Section

General. 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 using a 15-m capillary column (RSL-300, 0.53-mm column). Mass spectra were recorded on a Kratos MS25RF spectrometer. NMR spectra were recorded on JEOL FX-90Q and Varian Gemini-300 spectrometers operating at 22.53 MHz (^{13}C), 84.26 MHz (^{19}F), and 300.75 MHz (^1H), 75.46 MHz (^{13}C), 282.328 MHz, (^{19}F), and 111.9 MHz (^{119}Sn), respectively. The $CDCl_3$ solutions for recording the ^{13}C NMR spectra for SCS determinations were all ca. 0.1 M or less. Routine ^1H NMR spectra were measured with a Hitachi RR-1200 (60 MHz).

All the anhydrous solvents used in this study were dried by standard procedures.

Compounds. Adamantan-2-one was purchased from the Aldrich Chemical Co., Inc.

Synthesis of 5-Substituted (X) Adamantan-2-ones 1 (Y = O). Several of the ketones (X = OH,[50] F,[11] Cl,[50,51] Br,[51] I,[11] COOH,[52] $COOCH_3$,[52] C_6H_5,[50] p-$NO_2C_6H_4$,[11] p-$NH_2C_6H_4$,[11] p-$CH_3OC_6H_4$,[4a] $SiMe_3$,[11] and $SnMe_3$[11]) were prepared by literature procedures. Details of the standard functionalizing procedures employed for preparing the new substituted derivatives of 1 (Y = O; X = $CONH_2$, CN, NH_2, NO_2, NMe_2, OCH_3, $OCOCH_3$, p-CNC_6H_4, p-$COOCH_3C_6H_4$, p-FC_6H_4, p-BrC_6H_4, and p-$Me_2NC_6H_4$) together with yields, physical properties, and mass and ^{13}C NMR spectral data are contained in the supplementary material. A new synthesis of 5-methyladamantan-2-one (1; Y = O, X = CH_3) is described below.

Synthesis of 5-Substituted (X) 2-Methyleneadamantanes 1 (Y = CH_2). Except for the methyl and trimethylstannyl derivatives (X = CH_3 and $SnMe_3$, respectively; see below), all the alkenes (X = H, CN, $COOCH_3$, F, Cl, Br, I, CH_3O, $SiMe_3$, C_6H_5, p-CNC_6H_4, p-FC_6H_4, p-BrC_6H_4, and p-$CH_3OC_6H_4$) were prepared from the corresponding ketones by a standard procedure described below for the bromo derivative (X = Br). Details of the physical properties, NMR, and mass spectral data are contained in the supplementary material.

1-Bromo-4-methyleneadamantane (1, Y = CH_2; X = Br). By use of a procedure similar to that of Olah et al.,[53] a solution of n-butyllithium (21 mL of 1.6 M hexane solution; 33.63 mmol) was added over a 5-min period to a stirred slurry of methyltriphenylphosphonium iodide (13.59 g, 33.63 mmol) in dry ether (80 mL) under N_2. The reaction mixture was allowed to stir for 4 h at room temperature before adding dropwise a solution of 5-bromoadamantan-2-one (7 g, 30.58 mmol) in dry ether (80 mL). The mixture was stirred overnight, the precipitate was removed by filtration, and the filter cake was washed with a little ether.

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The combined extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to afford a yellow oil. Chromatography (silica gel/hexane as eluent) gave the title compound as a colorless oil (4.79 g, 72%): n_D^{25} = 1.5500; ^{1}H NMR ($CDCl_3$ δ 1.81–1.86 (m, 4H), 2.43–2.63 (m, 9H), 4.57 (s, 2H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 64.75 (Cl), 50.44 (C2,9), 42.21 (C3,5), 153.65 (C4), 37.54 (C6,10), 32.37 (C7), 48.93 (C8), 103.58 (C11); MS *m/z* (M^+) calcd for $C_{11}H_{15}Br$ 226.0357, 228.0337, found 226.0370, 228.0337.

1-Methyl-4-methyleneadamantane (1, Y = CH_2; X = CH_3). Trimethylaluminum (2.06 mL, 21.60 mmol) was added dropwise over a 1-min period to a well-stirred solution of 1-bromo-4-methyleneadamantane (4.90 g, 21.60 mmol) in dry dichloromethane (130 mL) maintained at −80 °C under N_2. The reaction mixture was allowed to warm to room temperature and then stirred for 1 h before cooling back to −80 °C. The mixture was then carefully quenched with a solution of pyridine (50 mL) and methanol (25 mL) in dichloromethane (25 mL). After 1.5 h at room temperature, the solvent was evaporated in vacuo and the residue distilled (Kugelrohr, 40 °C/0.5 mm) to afford a colorless oil (2.20 g, 62%): ^{1}H NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.50–1.77 (m, 11H), 2.52 (bs, 2H), 4.50 (s, 2H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 30.09 (C1), 46.24 (C2,9), 39.29 (C3,5), 157.67 (C4), 38.87 (C6,10), 28.80 (C7), 44.24 (C8), 100.86 (C11), 30.50 (CH_3); MS *m/z* (M^+) calcd for $C_{12}H_{18}$ 162.1408, found 162.1389.

5-Methyladamantan-2-one (1, Y = O; X = CH_3). Ozone (ca. 5% in O_2) was bubbled into a well-stirred solution of 1-methyl-4-methyleneadamantane (1 g, 6.09 mmol) in dry dichloromethane (100 mL) maintained at −78 °C. After a pale blue coloration developed (ca. 60 min), the gas flow was stopped, and dimethyl sulfide (0.46 mL, 6.84 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated in vacuo, and the residual orange oil was chromatographed (alumina/pentane as eluent) to afford a colorless oil which solidified on standing. Careful sublimation (30 °C/0.5 mm) gave the title compound as a white solid (0.5 g, 50%), mp 104–106 °C. Recrystallization (2 × 1) from petroleum ether (−78 °C) followed by further chromatography (alumina/pentane as eluent) and sublimation (40 °C/0.1 mm) gave a white crystalline solid: mp 112–113 °C (lit.[54] 125–126 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 1.69–1.80 (m, 6H), 1.92–1.94 (m, 4H), 2.08 (bs, 1H), 2.48 (bs, 2H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) 46.63 (C1,3), 218.72 (C2), 45.57 (C4,9), 30.02 (C5), 43.35 (C6), 28.04 (C7), 38.62 (C8,10), 29.25 (CH_3); MS *m/z* (M^+) calcd for $C_{11}H_{16}O$ 164.1201, found 164.1185. Anal. Calcd for $C_{11}H_{16}O$: C, 80.50; H, 9.75; O, 9.75. Found: C, 80.15; H, 9.91; O, 9.49.

2-Methylene-5-(trimethylstannyl)adamantane (1, Y = CH_2; X = $SnMe_3$). A solution of (trimethylstannyl)lithium (ca. 5.0 mmol) in anhydrous THF prepared in the standard way[55] was added dropwise to a solution of 1-bromo-4-methyleneadamantane (0.46 g, 2.02 mmol) in anhydrous THF (7 mL) at 0 °C under a nitrogen atmosphere. A standard workup followed by Kugelrohr distillation (50 °C/0.04 mm) afforded the title compound as a white solid (310 mg, 49%): mp 39–40 °C; ^{1}H NMR ($CDCl_3$) δ −0.04 (s, 9H; J_{Sn-H} = 47.94, 50.16 Hz), 1.90–2.01 (m, 11H), 2.48 (bs, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$, relative Me_4Si) δ 40.20 (C1,3), 158.43 (C2), 44.32 (C4,9), 28.00 (C5), 41.71 (C6), 29.05 (C7), 39.65 (C8,10), 100.22 (C11), −12.93 ($SnMe_3$; $^1J_{C-Sn}$ = 282.40, 295.10 Hz); MS *m/z* (M^+) calcd for $C_{14}H_{24}Sn$ 312.0945 (based on ^{120}Sn), found 312.0934.

Epoxidation of 2-Methylene-5-(trimethylstannyl)adamantane (1, Y = CH_2; X = $SnMe_3$). Following a procedure outlined by Cieplak et al.,[56] a solution of *m*-chloroperbenzoic acid (83 mg, 0.48 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of the tin–alkene (100 mg, 0.032 mmol) in dry dichloromethane (1.5 mL) at 0 °C before an aqueous solution of Na_2SO_3 was added. The mixture was extracted with dichloromethane which was then washed with a saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to afford a white solid (100 mg, 95%). An analysis by ^{13}C NMR indicated a 50:50 mixture of (*E*)- and (*Z*)-5-(trimethylstannyl)-2-adamantanespirooxiranes. This was confirmed by VPC and ^{119}Sn NMR. **(*E*)-5-(Trimethylstannyl)-2-adamantanespirooxirane:** ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 36.77 (C1,3), 64.67 (C2), 41.31 (C4,9), 26.14 (C5), 41.44 (C6), 27.80 (C7), 35.15 (C8,10), 54.77 (C11), −12.88 ($SnMe_3$); ^{119}Sn NMR ($CDCl_3$, relative to Me_4Sn) δ 1.18. **(*Z*)-(Trimethylstannyl)-2-adamantanespirooxirane:** ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 36.73 (C1,3), 64.76 (C2), 39.42 (C4,9), 26.11 (C5), 41.44 (C6), 27.87 (C7), 36.94 (C8,10), 54.70 (C11), −12.81 ($SnMe_3$); ^{119}Sn NMR ($CDCl_3$, relative to Me_4Sn) δ −0.80. The spectra were assigned by the additivity of substituent effects on chemical shifts of the adamantane ring.[57] *E*-Isomer (calcd): 36.44 (C1,3), 64.46 (C2), 41.04 (C4,9), 26.71 (C5), 41.26 (C6), 27.55 (C7), 34.96 (C8,10), 54.65 (C11). *Z*-Isomer (calcd): 36.44 (C1,3), 64.46 (C2), 39.25 (C4,9), 26.58 (C5), 41.26 (C6), 27.68 (C7), 36.75 (C8,10), 54.65 (C11).

A duplicate experiment confirmed the above results.

General Procedure for Sodium Borohydride Reduction of Ketones 1 (Y = O). The procedure was identical with that previously described.[11] ^{13}C NMR chemical shift data for the (*E*)- and (*Z*)-5-substituted (X) 2-adamantanols 1 (Y = H, OH), which were assigned by additivity methodology,[57] are contained in the supplementary material.

General Procedure for Methylation of Ketones 1 (Y = O). To a well-stirred solution of the ketone (100 mg) in anhydrous ether (3–5 mL) maintained at 0 °C was added an excess of methyllithium (1.5–2.0 mol equiv). The mixture was stirred at room temperature overnight, diluted with ether, washed with saturated aqueous NH_4Cl, and then dried (Na_2SO_4). After filtration and solvent evaporation, the methyl alcohol products (80–90%) were analyzed.

Ketones possessing sensitive functionality (X = Br, I, CN, *p*-BrC_6H_4, *p*-CNC_6H_4, *p*-$CO_2CH_3C_6H_4$, and CO_2CH_3) were treated with 1 mol equiv of methyllithium. ^{13}C NMR chemical shift data for the 5-substituted (X) (*E*)- and (*Z*)-2-methyl 2-adamantanols 1 (Y = CH_3, OH), which were assigned by additivity methodology,[57] are contained in the supplementary material.

General Procedure for Hydrochlorination of Alkenes 1 (Y = CH_2). To a well-stirred solution of the alkene (30 mg) in dry dichloromethane or nitromethane (3 mL) maintained at 0 °C under nitrogen was added a saturated solution of HCl gas in CH_2Cl_2 or NO_2CH_3 (4 mL). The mixture was stirred at room temperature overnight (except for the iodoalkene, X = I, which was allowed to stir for only 1 h), followed by solvent evaporation to yield the methyl chloride products quantitatively. These were analyzed by NMR. ^{13}C NMR chemical shift data for the 5-substituted (X) (*E*)- and (*Z*)-2-chloro-2-methyladamantanes 1 (Y = Cl, CH_3), which were assigned by additivity methodology,[57] are contained in the supplementary material.

Acknowledgment. We are grateful to the Australian 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 (500 MHz).

Supplementary Material Available: Experimental procedures and data of ketone derivatives 1 (Y = O), melting points, refractive indices, and exact mass data of the alkene derivatives of 1 (Y = CH_2), and ^{13}C NMR data for the ketones and alkenes 1 (Y = O and CH_2) as well as the (*E*)- and (*Z*)-isomers of the secondary and tertiary alcohols 1 (Y = H, OH and CH_3, OH, respectively) and the methyl chlorides 1 (Y = CH_3, Cl) (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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