Nature of the Electronic Factor Governing Diastereofacial Selectivity in Some Reactions of Rigid Saturated Model Substrates

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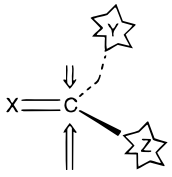
I. Introduction

π-Facial stereoselectivity is a phenomenon associated particularly with additions to trigonal carbon centers. It arises when the structural environment of the center renders the π-faces inequivalent. Consequently, preferential attack by various reagents in nucleophilic, electrophilic, radical, and pericyclic reactions occur on one face versus the other as shown below in a generalized system. An understanding of



the origins of this phenomenon is of vital importance in the quest to perform stereochemical syntheses with routine predictability.[1,2] Several control elements have been identified (steric, conformational, chelation, and electronic effects),[1,3,4] and some of them are now reasonably well understood. However, although several rigid model system studies (Figure 1 summarizes several of these systems)[5−10] have clearly demonstrated that remote substituents can influence the facial selectivity of addition reactions (particularly nucleophilic and electrophilic processes) to

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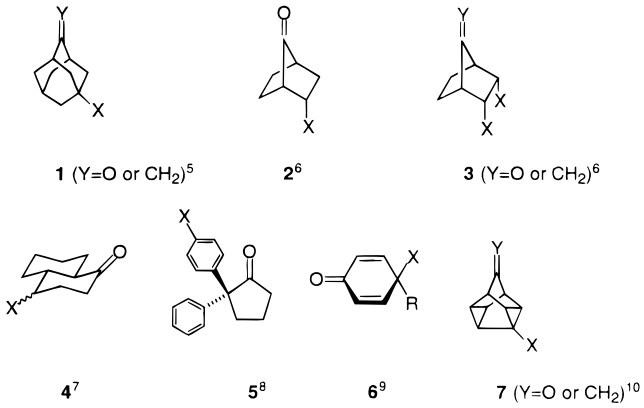


Figure 1. Some representative examples of rigid model substrates for segregating the electronic factor governing face selectivity in some addition reactions.

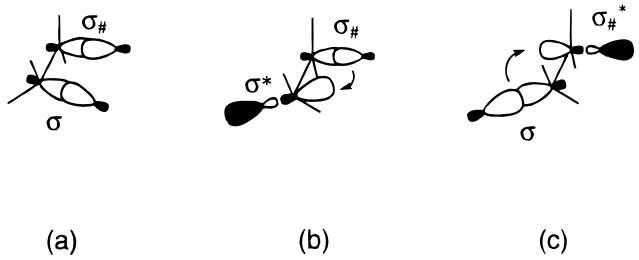
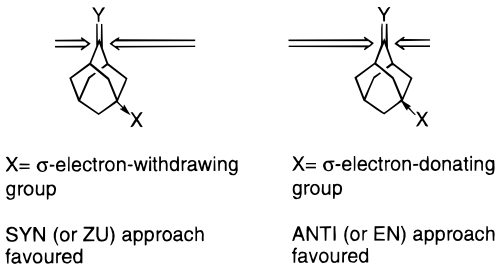


Figure 2. Orbital interactions in the transition state for a generalized addition process. (a) The Felkin model, a four-electron destabilizing interaction involving occupied σ- and $\sigma_{\ddagger}$-orbitals. (b) The Anh−Eisenstein model, a two-electron hyperconjugative stabilizing interaction involving occupied and unoccupied $\sigma_{\ddagger}$- and σ^*-orbitals, respectively. (c) The Cieplak model, a two-electron hyperconjugative stabilizing interaction involving occupied and unoccupied σ- and $\sigma_{\ddagger}^*$-orbitals, respectively.

Chart 1



trigonal carbon centers through their electronic effects, the nature and role of the electronic interaction remains a subject of continuing debate. Central to these deliberations is the relative importance of electrostatic and orbital effects determining the difference in energy between the respective diastereomeric transition states of the kinetically controlled addition processes.[11] Electrostatic interactions clearly need to be considered when polar substituents are present. Here the focus is on stabilizing and destabilizing Coulombic interactions between charges developed in the transition state and the substituent dipole or pole. Although some success in quantitatively calculating this influence in relatively small systems have been claimed,[7,12,13] it must be said that such computational approaches still cannot be applied with confidence to the more realistically sized systems usually encountered in organic chemistry.

Several models embracing orbital effects in both the initial state and transition state have been invoked over the years to explain π-facial stereoselection by, in particular, nucleophilic reagents in their additions to ketones. Since these have all been recently reviewed,[4,11] suffice to summarize in this paper those that have withstood scrutiny and are still under contention. All of these particular models concern the transition state rather than the reactants in their isolated states. Models featuring the latter have just not gained universal acceptance. The various important orbital interactions in the transition state advanced by Felkin,[14] Anh−Eisenstein,[15] and Cieplak[16] are shown pictorially in Figure 2 for a generalized addition process. The Felkin model concerns repulsive interactions (torsional effects) which are maximized when the incipient bond ($\sigma_{\ddagger}$) in the transition state eclipses a vicinal σ-bond (synperiplanar relationship). The other models (Anh−Eisenstein and Cieplak) focus on attractive hyperconjugative interactions between an electron-donor incipient bond ($\sigma_{\ddagger}$) or σ-bond antiperiplanar to an electron-acceptor antibonding orbital (σ^*) or incipient antibonding orbital ($\sigma_{\ddagger}^*$), respectively. The successful application of the Cieplak model[16] to cyclohexane based systems hinges on the controversial assumption[7] that a C−H bond is a better electron-donor than a C−C bond. Thus, contrasteric axial nucleophilic addition to cyclohexanone can then be rationalized. According to the Felkin model,[14] π-facial diastereoselection for axial attack on cyclohexanones is attributed to torsional interactions being minimized in the transition state for axial versus equatorial attack. These various orbital models have their adherents and critics.

Perhaps the most important model system studies underpinning the validity of the Cieplak model[16] are those in which 5-substituted (X) adamant-2-yl derivatives (**1** ; Figure 1) have been extensively deployed as the substrate. This model substrate has the advantageous feature of sterically equivalent π-faces in a rigid molecular framework which can be electronically perturbed through distal modifications. Hence, the electronic factor governing π-facial diastereoselection is effectively segregated and, therefore, ambiguities associated with conformational mobility and steric bias are precluded. A wide variety of addition reactions to trigonal carbon centers have been investigated by means of **1**. These are as follows: nucleophilic additions to ketones,[5a,17] electrophilic additions to alkenes,[5b] cycloaddition,[18] sigmatropic shifts,[19] and metal complexation of alkenes[20] as well as capture of carbocations,[5,17d,21] carbanions,[22] and radicals.[23] It was found that the stereochemical outcome of all of these reactions can be embraced by a general rule, namely, the preferred direction of attack is anti to the best electron-donor bonds. The experimental situation is summarized by the structures shown in Chart 1. le Noble et al.[5,17−23] have chosen to reconcile these results exclusively in terms of Cieplak's transition-state hyperconjugative model as illustrated in Chart 2. Central to this interpretation is the observation of a good linear Hammett type

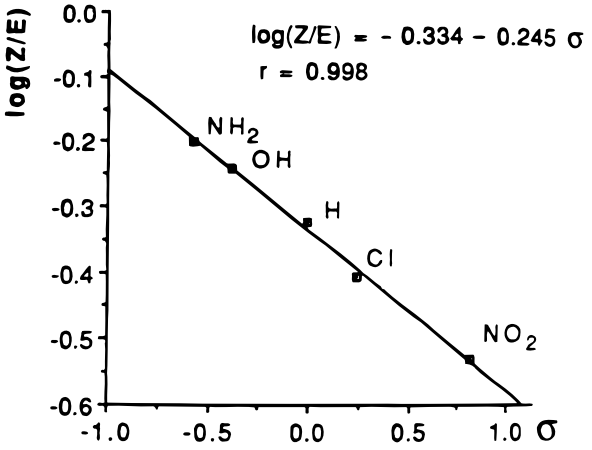
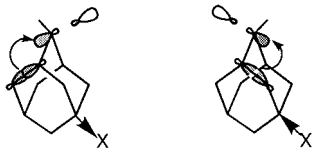


Figure 3. The 5-*p*-phenyl substituent effect (σ_p) in the reduction of adamantanones. The data are based on proton integration (C_2H) (Reprinted with permission from ref 17c, copyright 1990, Elsevier Science).

Chart 2



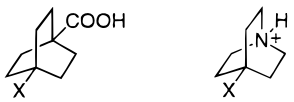
plot (log *Z*/*E* vs σ_p) for the $NaBH_4$ reductions of some para-substituted (*S*)-5-phenyl-2-adamantanones **1** (Y = O; X = *p*-SC_6H_4)[5a,17c] (see Figure 3).

The fact that the Cieplak model is able to accommodate the stereochemical outcome of such a wide variety of reactions with quite different mechanisms is an impressive result and superficially seems to leave little room to maneuver for debate. However, we must not lose sight of the fact that the function of the 5-substituent in system **1** is to differentiate electronically the π-faces of the reaction site located at carbon-2. Consequently, the interpretation of diastereoselectivity data from this important model substrate necessitates an appreciation of the means by which electronic information is transmitted in saturated systems. Over the years the origin of polar substituent effects has been a controversial issue and the focus of much attention. In the first section of this paper we will briefly summarize the picture that has emerged as defined by the use of reactivity probes (energy monitors). This material, which has been regularly and thoroughly reviewed over the years,[24−31] will serve as background information for a more extensive description of the situation which follows as probed by NMR chemical shifts (charge density monitors). The latter coverage will not be exhaustive but restricted largely to those studies which bear on the analysis and definition of the transmission of electronic information between the 2 and 5 positions of the adamantane ring system. In the latter part of the paper, the ramifications of these findings on the currently debated models (electrostatic versus hyperconjugative effects) of diastereoselectivity in the 5-substituted (X) 2-adamantyl system (**1**) will be examined.

II. Transmission Modes of Substituent Effects in Saturated Systems

A. Background Information

The commonly held view is that there are two basic electronic mechanisms by which a polar substituent conveys its influence to a remote probe (energy or charge density monitor) in saturated organic systems, viz. the field and σ-inductive mechanisms.[24−31] The field effect involves the direct through-space transmission to the probe of the electrostatic dipole (or pole) at the substituent. The σ-inductive effect, which pertains to the polarity of the substituent−substrate bond and, hence, is a manifestation of electronegativity (χ), involves propagation by successive but diminishing polarization of the intervening σ-bonds. These effects were first recognized in the very early days of electronic theory of organic chemistry.[32] However, at the time there was no available experimental evidence or underlying theory by which these mechanisms could be distinguished from one another. For no reason other than the fact that it would be confusing to adopt both, the σ-inductive effect became the preferred mechanism for discussing polar substituent effects. Later on, the classical work of Kirkwood and Westheimer[33] highlighted the importance of the electrostatic field model. Since then there have been numerous model systems and theoretical studies carried out to establish unambiguously the relative importance of the two mechanisms.[24−31] In many cases it has been difficult to describe polar substituent effects accurately by either mechanism.[30] There are major difficulties in the quantitative application of the Kirkwood−Westheimer equations[33] for the estimation of the free energy required for the removal of an acid proton in the presence of monopolar or dipolar substituents. This is largely associated with the effective dielectric constant term which is a complex mathematical function of the geometry and dielectric properties of the model substrate and the cavity it occupies in the solvent continuum.[33,34] Even the distance dependency term remains to be precisely defined.[35] Nevertheless, a general consensus seems to have been reached[31,36] that for remote probe groups (beyond two bonds) the direct field effect is clearly the dominant "inductive" mechanism and that the classical σ-inductive effect is insignificant beyond the first atom of attachment. An important distinction between the two mechanisms for correlative purposes[27] is that the former depends on the substituent group moment and is characterized by an empirical parameter scale ($\sigma_F \equiv \sigma_I$) underpinned by the acidities of 4-substituted (X) bicyclo[2.2.2]octane-1-carboxylic acids (**8**)[37,38] and -quinuclidinium ions (**9**).[37,39] By contrast, the latter being a bond polariza-



8 **9**

tion phenomena is characterized by electronegativity parameters (σ_χ).[40] The relationship between σ_F and

a group electronegativity scale (f)[41] has been recently evaluated.[42] However, there are difficulties choosing from the myriad of available group electronegativity scales.[41,43]

A noteworthy recent development is the demonstration that through-space electrostatic interactions can be useful and predictable design elements for construction of bioactive molecules.[44] Further consolidation of the field model has emerged from recent acidity studies of hexafluorobicyclo[1.1.1]pentane-1,3-dicarboxylic acid[45] and 3-halo (X) bicyclo[1.1.1]pentane-1-carboxylic acids.[46]

Proton-transfer equilibria, especially the ionization of carboxylic acids, have been the most frequently employed reactions for probing polar substituent effects in various rigid model substrates. However, the phenomenon has also been extensively investigated in polycyclic alkane systems (bicyclo[2.2.1]-heptane,[47] bicyclo[2.2.2]octane,[48] adamantane,[39,49] bicyclo[1.1.1]pentane,[50] and bicyclo[2.1.1]hexane[51]) by means of carbocation-mediated reactions. Although in some dispositions of these systems the analysis is complicated by exalted rate constants which can lead to fragmentation for some substituents,[39a,b,47a,b,51] in the main, the solvolytic rate constants correlate well against polar field parameters (σ_F). However, the patterns of polar susceptibility parameters (ρ_F)[52] are not simply a function of the spatial relationships between the polar substituent and reaction site. The extent of charge development and its distribution in the transition state as determined by through-bond and through-space orbital interactions is also an important factor. Unfortunately, a clear disentanglement of the direct electrostatic interaction between the substituent and probe site from delocalization phenomena for electronegative substituents cannot be achieved from these reactivity studies. This important point will arise further below.

B. NMR Shift Studies

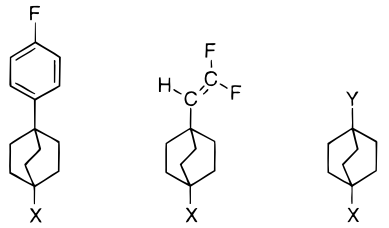
1. Introduction

The ability to be able to probe substituent electronic effects via changes in NMR chemical shifts (charge density monitors) has provided a different perspective to the problem of delineating electronic transmission modes in various model substrates.[53] Unlike rate or equilibria data, NMR chemical shifts are single-state property parameters (generally the neutral ground state) which respond sensitively to substituent-induced bond polarization phenomena. An important operational constraint in the utilization of chemical shifts as charge density monitors is that the probe site be properly chosen so that comparisons of chemical shifts are confined to a closely related series of stereochemically well-defined compounds and, at the same time, to those sites reasonably remote from the point of substitution such that steric, magnetic anisotropy, bond order, and neighboring group effects are unimportant. The pertinent experimental parameter is the substituent chemical shift (SCS) which is defined as the difference (in parts per million) between the chemical shift of the probe nucleus in the substituted compound and that of the parent compound (X = H). The accepted sign convention is that a positive value denotes deshielding (downfield shift).

The fluorine-19 and carbon-13 nuclei have provided the most useful information relating to the transmission of substituent effects. Because the chemical shifts of both nuclei are dominated by the paramagnetic term of the Ramsey equation,[54] certain approximations are usually unavoidable if they are to be discussed in the terms that have proved useful in the case of chemical reactivity.[53,55,56] Nevertheless, aryl ^{19}F and ^{13}C SCSs have been successfully correlated with various Hammett type substituent constants.[53] The large number of these constants calculated by use of ^{19}F SCS of meta- and para-substituted fluorobenzenes and the appropriate correlative equations is testament to the general value of these relationships.[37]

2. Field Effects

In connection with delineating the origin of polar effects determining aryl ^{19}F chemical shifts,[27b] it has been shown by correlative analysis that the ^{19}F SCS of 1-substituted (X) 4-(*p*-fluorophenyl)bicyclo[2.2.2]-octanes (**10**)[57] and 1,1-difluoro-2-(4-substituted-bicyclo-[2.2.2]oct-1-yl) ethenes (**11**)[58] are determined only by the electrostatic field effect of the substituent. Hence,



10 **11** **12**

the saturated linkage is acting effectively as a spacer group precluding resonance interactions between the substituent and the π-electron systems. This has also been similarly revealed by ^{13}C SCS for atoms contained in unsaturated probe linkages (**12**, Y = C_6H_5, C≡CH, CH=CH_2, CN, CHO, CO_2R, CH=CCl_2, and CH=CF_2).[57,59] The ^{19}F and ^{13}C SCS of **10** and the para carbon (C4) in **12** (Y = C_6H_5), respectively, provide excellent measures of σ_F values. The advantages of these systems over **8** and **9** for determining these empirical parameters are essentially 3-fold: (i) Reliable values can be obtained for solvents other than alcoholic or aqueous media. This is important since electrostatic field effects can vary markedly depending on the nature of the substituent-solvent interaction.[60−62] (ii) Values can be obtained for kinetically labile groups. (iii) Discrepancies in some values from **9** due to possible through-bond interactions (see later) are precluded in **10** and **12** (Y = C_6H_5). We have taken the opportunity in this article to bring together from different studies all the σ_F values determined from **10**[63] and **12** (Y = C_6H_5).[57,63a,b,64] These values, which complement a recent compilation of polar field parameters,[37] are listed in Tables 1 and 2. For the correlative analysis of refined data the use of these

Table 1. Polar Substituent Parameters (σ_F Values) Derived from the ^{19}F SCS of 1-X-4-(*p*-Fluorophenyl)bicyclo[2.2.2]octanes (10)[a]

X	c-C_6H_{12}[b]	CCl_4[b]	$CDCl_3$[c]	CH_2Cl_2[d]	DMF[e]	MeOH[f]	HFIP[g]	CF_3CO_2H[h]
NO_2	0.66	0.66	0.65	0.64	0.60	0.62	0.69	0.74
CN	0.59	0.58	0.56	0.53	0.48	0.54	0.56	0.71
CF_3	0.44	0.44	0.40	0.40	0.42	0.42	0.32	0.37
COOH	0.23	0.29	0.32	0.30	0.21	0.25	0.34	0.44
COCl	0.51		0.49		0.40			
COF	0.50		0.48					
$CONH_2$		0.29	0.33	0.30	0.19	0.29	0.44	0.69
$CON(CH_3)_2$	0.19		0.25	0.23	0.19	0.28		
$COOC_2H_5$	0.22	0.23	0.26	0.25	0.26	0.29	0.30	0.40
$COCH_3$	0.28	0.29	0.31	0.28	0.25	0.30	0.37	0.48
CHO	0.36	0.36	0.37	0.35	0.31	0.35	0.41	0.52
OH	0.23	0.23	0.29	0.26	0.14	0.25	0.37	0.48
OCH_3	0.19	0.21	0.26	0.24	0.22	0.30	0.38	0.50
$OCOCH_3$	0.29	0.29	0.33	0.33	0.34	0.37	0.35	0.45
F	0.39	0.39	0.42	0.41	0.40	0.41	0.45	0.52
Cl	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.44
Br	0.44	0.44	0.44	0.44	0.44	0.44	0.44	0.44
I	0.42	0.43	0.42	0.42	0.40	0.41	0.40	0.40
NH_2	0.12	0.13	0.19	0.18	0.08	0.26	0.79	0.87
$N(CH_3)_2$	0.10	0.12	0.18	0.16	0.12	0.28	1.05	1.03
$NHCOCH_3$	0.21	0.22	0.28	0.26	0.18	0.26	0.33	0.72
$^+N(CH_3)_3$			0.88	0.92	0.64	0.78		1.11
C_6H_5	0.15	0.16	0.17	0.17	0.16	0.17		0.18
p-$NO_2C_6H_4$	0.39	0.39	0.33	0.31	0.26	0.28		0.34
p-$NH_2C_6H_4$	0.08		0.14		0.10	0.14	0.18	
CH_2OH	0.10		0.14		0.04		0.21	0.32
CH_3	0.03		0.03		0.04			
C_2H_5	0.03		0.03		0.04			
i-C_3H_7	0.02		0.02		0.03			
t-C_4H_9	0.01		0.02		0.01			
$Si(CH_3)_3$	0.00		0.01	0.00				
$Ge(CH_3)_3$	0.01		0.02	0.01				
$Sn(CH_3)_3$	0.01		0.02	0.00				
$Pb(CH_3)_3$	0.05		0.05	0.04				
SiH_3	0.15			0.13				
$Si(OC_2H_5)_3$	−0.08			0.02				
$SiCl_3$	0.43			0.39				

[a] ^{19}F SCS = $\rho_F\sigma_F$. Polar susceptibility parameters (ρ_F values) were determined by setting σ_F for bromine equal to 0.44 for each solvent. [b] $\rho_F = 2.70$. [c] $\rho_F = 2.57$. [d] $\rho_F = 2.25$. [e] $\rho_F = 1.61$. [f] $\rho_F = 1.91$. [g] $\rho_F = 1.85$. [h] $\rho_F = 2.57$. [i] Counterion, I^-.

parameters, particularly those from **10** which were measured under conditions of high dilution, are highly recommended in order to avoid solvent discrepancies.

The ^{13}C SCS ($CDCl_3$ as solvent) for the carbonyl carbon (C2) of **1** (Y= O) as well as those for C_α (or C2) and C_β (or C11) for **1** (Y = CH_2) correlate well (eqs 1−3)[65] against the appropriate σ_F values (Table 1; $CDCl_3$). The less than perfect fit of the correlations

$$^{13}\text{C SCS (C2 of } \mathbf{1}\text{, Y = O)} = -9.27\sigma_F + 0.49$$
$$(r = 0.968,\ F\text{-test} = 210.88,\ \text{CL} = 99.99\%,\ n = 16) \quad (1)$$

$$^{13}\text{C SCS} = (\text{C}_\alpha \text{ of } \mathbf{1}\text{, Y = CH}_2) = -10.29\sigma_F + 0.13$$
$$(r = 0.977,\ F\text{-test} = 253.82,\ \text{CL} = 99.99\%,\ n = 14) \quad (2)$$

$$^{13}\text{C SCS} = (\text{C}_\beta \text{ of } \mathbf{1}\text{, Y = CH}_2) = 7.01\sigma_F - 0.30$$
$$(r = 0.975,\ F\text{-test} = 231.77,\ \text{CL} = 99.99\%,\ n = 14) \quad (3)$$

is probably not structural in origin since there is some evidence from X-ray diffraction analyses[18c,19b] to suggest that 5-substituents should not induce significant skeletal distortions at C2. However, the fact that significant $^4\Delta$ deuterium isotope effects are observed in **1** (Y = O and CH_2; X = D)[66] suggests through-bond effects (see later) as a likely source. 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. This phenomenon in saturated systems had previously been revealed unambiguously by ^{13}C SCS in **12**[59] for atoms contained in unsaturated probe linkages (see above). A noteworthy imprimatur of this transmission mechanism is 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 ($CDCl_3$ as solvent) of *p*-SC_6H_4 groups in **1** (Y = O)[65] correlate very well with substituent parameters (σ_F and σ_R).[67] The data set fulfills Taft's recommended minimal substituent set for such multiple correlations.[67] The correlative equa-

Table 2. Polar Substituent Parameters (σ_F Values) Derived from the ^{13}C Substituent Chemical Shifts (SCS, C4′) of 1-X-4-Phenyl-bicyclo[2.2.2]octanes (12, Y = C_6H_5)

X	c-C_6H_{12}[a]	$CDCl_3$[b]
$C(CN)_3$	0.88	0.89
$CH(CN)_2$		0.59
CH_2CN		0.32
CH_2OH		0.15
CH_2Cl		0.19
CH_2COOH		0.08
CH_2COOCH_3		0.10
$CH{=}CH_2$		0.14
$C{\equiv}CH$		0.28
$CH{=}CCl_2$		0.25
$CH{=}CF_2$		0.23
SiH_3	0.14	0.15
GeH_3	0.14	0.13
SnH_2CH_3	0.09	
$Si(CH_3)_3$	−0.01	0.03
$Ge(CH_3)_3$	−0.01	0.03
$Sn(CH_3)_3$	0.00	0.03
$Pb(CH_3)_3$	0.06	0.08
$Si(OC_2H_5)_3$		0.00
$Ge(OC_2H_5)_3$	0.18	0.24
$SiCl_3$		0.45
$GeCl_3$	0.60	0.63
$SnCl_2CH_3$		0.47
CH_3	0.03	0.04
C_2H_5		0.02
i-C_3H_7		0.02
t-C_4H_9	−0.01	0.01

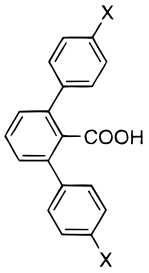
[a] $\rho_F = 1.37$. Value in CCl_4 (ref 59). [b] $\rho_F = 1.33$ (ref 59).

tion (eq 4) shows that both polar and resonance effects contribute to the ^{13}C SCS. Thus, the net

$$^{13}\text{C SCS (C2 of } \mathbf{1}\text{, Y = O; X = } p\text{-}SC_6H_4) = -1.44\sigma_F - 1.52\sigma_R - 0.22$$
$$(r = 0.991,\ F\text{-test} = 112.64,\ \text{CL} = 99.97\%,\ n = 7) \quad (4)$$

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. A recent study of the pK_a values of para-substituted 2,6-diphenylbenzoic acids (**13**) has clearly shown that *p*-XC_6H_4 groups act to significantly influence the acidity and hydrogen-bonding characteristics of the carboxylic acid by a similar composite through-space electrostatic interaction.[68]

Because the carbonyl ^{13}C SCS of the para-substituted (S) 5-phenyl-2-adamantanones **1** (Y = O; X = *p*-SC_6H_4)[65] 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[65] and

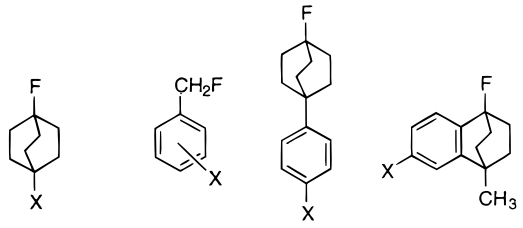


13

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*-$COOCH_3C_6H_4$, 0.073; *p*-FC_6H_4, 0.038; *p*-BrC_6H_4, 0.067; *p*-$CH_3OC_6H_4$, −0.009; *p*-$(CH_3)_2NC_6H_4$, −0.048. Note that the σ_F value of C_6H_5 determined from **10** is 0.17 (Table 1; $CDCl_3$).

3. Through-Bond Effects

As exemplified above, the archetypal model saturated substrates for examining polar substituent effects are 1,4-disubstituted bicyclo[2.2.2]octanes. They offer the advantage of precluding π-resonance interactions as well as conformational and geometrical uncertainties. An early attempt to monitor the transmission of polar substituent effects through the bicyclo[2.2.2]octane ring system with fluorine directly attached to a bridgehead carbon appeared distinctly unpromising. On the basis of the idea that the substituents act by direct electrostatic polarization of the C−F σ-bond, the ^{19}F SCS of 4-substituted (X) bicyclo[2.2.2]oct-1-yl fluorides (**14**) for *fluorine* and *ethoxycarbonyl* (X = F and $COOC_2H_5$, respectively) were found[69] to be in the *opposite* direction (upfield shifts; reverse substituent dependence) to expectations from shift theory.[54,55] Hence, the SCS were



14 **15** **16** **17**

considered anomalous and probably a consequence of substituent-induced structural deformation of the bicyclooctyl framework rather than a manifestation of dipolar electrostatic-field effects. However, this gloomy outcome changed dramatically when it was discovered that the ^{19}F SCS of a series of meta- and para-substituted benzyl fluorides (**15**)[70] and 1-fluoro-4-(para-substituted phenyl)bicyclo[2.2.2]octanes (**16**)[71] also display a reverse substituent dependence which cannot be argued away by substituent-induced structural distortions. Furthermore, the shift response to electronic effects for both systems was systematic as evident by good dual substituent parameter (DSP) correlations (eqs 5 and 6 for **15** (para)[70] and **16**,[71b] respectively).

$$^{19}\text{F SCS} = -10.2\sigma_F - 17.2\sigma_R^{BA} \quad (f = 0.09; \text{CDCl}_3 \text{ as solvent}) \quad (5)$$

$$^{19}\text{F SCS} = -1.06\sigma_F - 0.62\sigma_R \quad (f = 0.11; \text{CDCl}_3 \text{ as solvent}) \quad (6)$$

Good DSP correlations of the ^{19}F SCS of **16** in other solvents (c-C_6H_{12}, C_6H_6, and DMF) are also observed.[71b] The *negative* susceptibility terms (ρ_F and ρ_R) are indicative of reverse substituent dependence. Thus, the intrinsic response of fluorine attached to an sp^3-hybridized carbon to electronic effects is not obviously in accord with simplified shift theory. A detailed empirical analysis[71b] revealed that the ^{19}F SCSs of **16** are due exclusively to CF σ-bond polarization as a result of the electrostatic field of the para-substituted phenyl groups (see above). Further studies of conformationally rigid model systems (**17**) in which the C−F bond is held in the nodal plane of the benzene ring implicated C−F hyperconjugation as another important factor underlying reverse ^{19}F SCS.[72] Substituent effects on the ^{19}F chemical shifts of **17** are extremely small yet being formally an analogue of **15** (para) it would have been expected to have quite similar ^{19}F shifts in the absence of conformational effects. Appreciable contributions to the ^{19}F chemical shifts of **15** (para) from conformational changes have been confirmed by variable temperature studies together with electronic structure calculations.[73]

The important points to emerge from the study of **15**, **16**, and **17** were 2-fold. (i) Despite the "anomalous" direction of the ^{19}F chemical shifts of alkyl fluorides to substituent electronic effects, their response is systematic. (ii) The shifts are governed not only by the degree of direct electrostatic polarization of the C−F σ-bond but also by the extent of electron delocalization into the antibonding MO of the C−F bond (σ_{CF}*). These revelations prompted a detailed systematic investigation of the ^{19}F SCS of **14**. The latter parameters are gathered together here from several sources[63c,e,f,71b,74] and set out in Table 3. Except for three substituents (C_6H_5, *p*-$NO_2C_6H_4$, and *p*-$NH_2C_6H_4$) the data for **16**[71] are not included. By means of multiple regression analysis the ^{19}F SCS of **14** were shown to be described to a fair degree of accuracy by a linear two-parameter equation (eq 7), i.e., a dependency on both electrostatic field (σ_F effect) and electronegativity (σ_χ effect) effects was revealed.[63c]

$$^{19}\text{F SCS} = \rho_F\sigma_F + \rho_\chi\sigma_\chi + c \quad (7)$$

The result was unprecedented at the time since all other known polar substituent perturbations in the bicyclo[2.2.2]octane ring system could be described satisfactorily in terms of an electrostatic field model (see above). Factorization of the SCS by a noncorrelative technique confirmed the picture. This was achieved by calculating the respective polar-field susceptibility parameters (ρ_F values) by dividing the chemical shift differences between X = *p*-$NO_2C_6H_4$ and X = C_6H_5 by $\Delta\sigma_F$ for these substituents (Table 1). Although the polar-field term ($\rho_F\sigma_F$) is significant, the solvent-independent residual contribution (^{19}F SCS − $\rho_F\sigma_F$) is clearly the dominant factor in most instances. The latter for c-C_6H_{12}, $CDCl_3$ and DMF are listed in Table 4. Given that a detailed study of **16** revealed that electric-field-induced ^{19}F chemical shifts are characterized by a concomitant proportional change in the ^{13}C chemical shifts of the carbon to which the fluorine nucleus is attached, the precise linear relationships displayed in Figure 4 dramatically confirms the invariance to solvent changes of the residual contributions (^{19}F SCS − $\rho_F\sigma_F$). After canvassing several possible factors with respect to the origin of the apparent electronegativity contribution to the ^{19}F SCS of **14** and bearing in mind the demonstrated sensitivity of ^{19}F chemical shifts of alkyl fluorides to the extent of electron delocalization into the σ*-orbital of the C−F bond, we ascribed the phenomenon to a through-three-bond electron delocalization mechanism which couples the C−X and C−F bond molecular orbitals through the intervening ethano σ-bonds (a σ-resonance effect or double hyperconjugation). Following the detailed molecular orbital description of similar through-bond effects by Hoffmann et al.,[75] the prevailing orbital interactions governing this resonance effect may be attributed essentially to σ_{CF}*−σ_{CC}−σ_{CX} and σ_{CF}*−σ_{CC}−σ_{CX}* for σ-electron-donating and -withdrawing groups, respectively. In valence bond terminology the σ-resonance effect in **14** may be denoted simplistically by

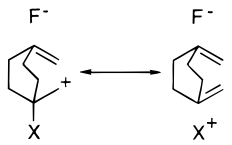
Table 3. ^{19}F Substituent Chemical Shifts (SCS, ppm) of 4-Substituted (X) Bicyclo[2.2.2]oct-1-yl Fluorides (14)

X	c-C_6H_{12}	$CDCl_3$	DMF	CF_3CO_2H
NO_2	−8.39	−9.89	−9.53	−17.45
CN	−4.15	−5.40	−4.79	−12.55
CF_3	−5.08	−6.05	−5.98	−10.12
COOH	−4.75	−5.68	−4.93	−10.57
COCl	−5.01	−6.14	−5.01	
$CONH_2$		−6.09	−4.87	−13.80
$COOCH_3$	−4.38	−5.29	−5.05	−10.19
$COCH_3$	−4.15	−5.11	−4.52	−10.56
CHO	−3.09	−4.10	−3.50	−9.92
OH	−8.06	−9.24	−7.47	−14.96
OCH_3	−6.40	−7.62	−7.15	−14.28
$OCOCH_3$	−6.08	−7.30	−7.11	−13.15
F	−8.90	−10.32	−10.19	−16.13
Cl	−6.97	−8.14	−8.07	−12.66
Br	−5.94	−7.07	−6.98	−11.50
I	−3.35	−4.29	−4.12	−8.22
NH_2	−6.60	−7.51	−6.28	−17.97
$N(CH_3)_2$	−4.66	−5.84	−5.31	−19.09
$NHCOCH_3$	−4.66	−5.82	−4.78	−14.86
$^+N(CH_3)_3$		−11.14	−9.34	−20.14
C_6H_5	−3.37	−3.94	−3.68	−5.29
p-$NO_2C_6H_4$	−4.12	−4.78	−4.15	−8.10
p-$NH_2C_6H_4$	−3.16	−3.77	−3.37	−7.68
CH=CH_2	−2.90	−3.32	−3.24	
C≡CH	−3.42	−4.27	−4.07	
CH=CCl_2	−3.02	−3.63	−3.40	
CH=CF_2	−3.71	−4.17		
CH_2OH	−2.61	−3.27	−2.47	−6.59
CH_3	−3.81	−3.92	−3.90	−4.08
C_2H_5	−2.79	−2.91	−2.93	−2.97
i-C_3H_7	−2.68	−2.79	−2.82	−2.72
t-C_4H_9	−3.11	−3.20	−3.23	−3.04
$Si(CH_3)_3$	1.54	1.61		
$Ge(CH_3)_3$	1.63	1.69		
$Sn(CH_3)_3$	3.67	3.83	3.94	
$Pb(CH_3)_3$	2.87	3.00		
D	−0.059	−0.060	−0.058	

Table 4. Calculated Residual Contributions (^{19}F SCS $- \rho_F\sigma_F$) to ^{19}F SCS (ppm) of 4-Substituted (X) Bicyclo[2.2.2]oct-1-yl Fluorides (14)

X	c-C_6H_{12}	$CDCl_3$	DMF
NO_2	−6.32	−6.48	−6.71
CN	−2.30	−2.46	−2.53
CF_3	−3.70	−3.95	−4.01
COOH	−4.03	−4.00	−3.94
COCl	−3.41	−3.57	−3.13
$CONH_2$		−4.36	−3.98
$COOCH_3$	−3.69	−3.92	−3.83
$COCH_3$	−3.27	−3.48	−3.34
CHO	−1.96	−2.16	−2.04
OH	−7.34	−7.72	−6.81
OCH_3	−5.80	−6.25	−6.12
$OCOCH_3$	−5.17	−5.57	−5.51
F	−7.68	−8.11	−8.31
Cl	−5.62	−5.88	−6.05
Br	−4.56	−4.76	−4.91
I	−2.03	−2.08	−2.24
NH_2	−6.22	−6.51	−5.90
$N(CH_3)_2$	−4.35	−4.89	−4.75
$NHCOCH_3$	−4.00	−4.35	−3.93
$^+N(CH_3)_3$		−6.52	−6.33
C_6H_5	−2.90	−3.05	−2.93
p-$NO_2C_6H_4$	−2.90	−3.05	−2.93
p-$NH_2C_6H_4$	−2.91	−3.03	−2.90
$CH{=}CH_2$		−2.58	
$C{\equiv}CH$		−2.80	
$CH{=}CCl_2$		−2.32	
$CH{=}CF_2$		−2.96	
CH_2OH	−2.31	−2.53	−2.28
CH_3	−3.72	−3.76	−3.71
C_2H_5	−2.70	−2.75	−2.74
i-C_3H_7	−2.62	−2.68	−2.68
t-C_4H_9	−3.08	−3.09	−3.18
$Si(CH_3)_3$	1.54	1.56	
$Ge(CH_3)_3$	1.60	1.58	
$Sn(CH_3)_3$	3.64	3.72	
$Pb(CH_3)_3$	2.71	2.74	

canonical structures **18** and **19** (depicted for only one of the three ethano bonds). Subsequent model system



18 **19**

studies (4-substituted (X) bicyclo[2.2.1]hept-1-yl fluorides (**20**),[63d] 10-substituted (X) 9-fluorotriptycenes (**21**),[63g] 4-substituted (X) 4′-fluorobibicyclo[2.2.2]-octanes (**22**)[63g] as well as (*E*)- and (*Z*)-5-substituted (X) adamant-2-yl fluorides (**23** and **24**, respectively)[63i,65] confirmed the proposal. Most importantly, the ^{19}F SCS of the latter two systems (listed in Table 5) highlight dramatically the stereoelectronic requirements for optimization of the through-three-bond interaction model put forward by Hoffmann et al.,[75] namely, an antiperiplanar relationship of the participant orbitals. This is met in the *E*-isomer (**23**) but not the *Z*-isomer (**24**). Note that whereas the substituent effects for the *E* series (**23**) are in the main quite pronounced those for the corresponding *Z* series (**24**) are extremely feeble (Table 5). A similar factorization of the ^{19}F SCS of **23** as described above for **14** give residual contributions (^{19}F SCS $- \rho_F\sigma_F$) (listed

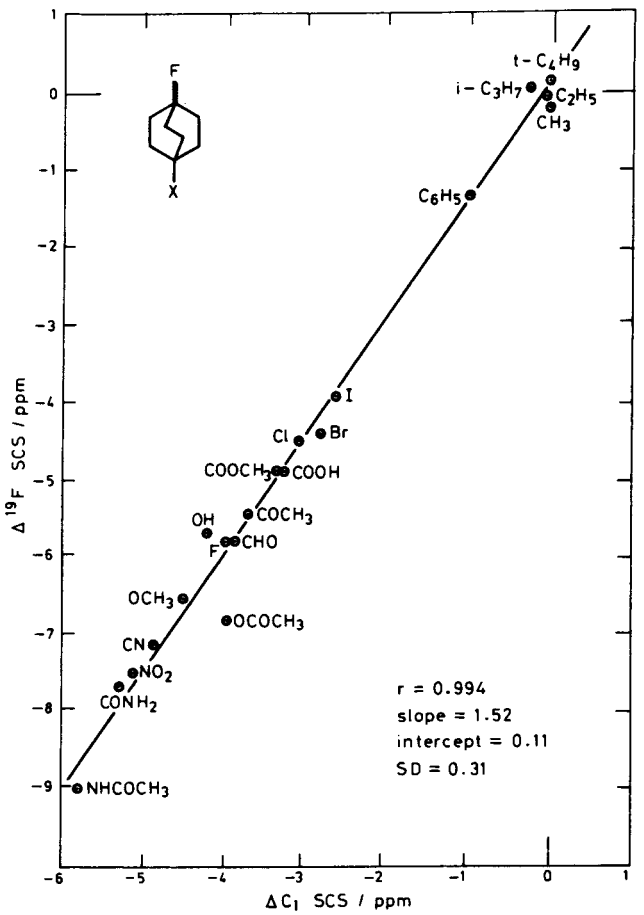
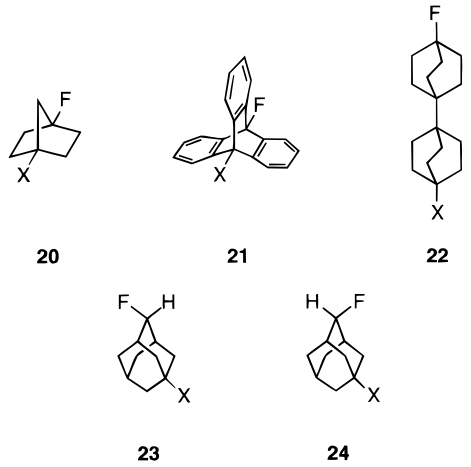


Figure 4. Plot of ^{19}F SCS (CF_3CO_2H) − ^{19}F SCS ($CDCl_3$) versus ^{13}C1 SCS (CF_3CO_2H) − ^{13}C1 SCS ($CDCl_3$) for system **14** (ref 63c).



20 **21** **22**

23 **24**

in Table 6) which parallel to a large degree the corresponding values for the latter (Table 4). This was to be expected since in both systems (**14** and **23**) the substituent and fluorine probe are disposed similarly to each other (1,4-disposition) and, moreover, their bonds are orientated trans-coplanar with respect to the bridging ethano bonds such as to maximize double hyperconjugation. However, the precise relative magnitude of through-three-bond effects in the bicyclooctane and adamantane ring systems is difficult to assess quantitatively since it depends not only on the number of pathways but also on various parameters governing the orbital interac-

Table 5. ^{19}F Substituent Chemical Shifts (SCS, ppm) of (*E*)- and (*Z*)-5-Substituted (X) Adamant-2-yl Fluorides (23 and 24, respectively)

	E isomer (**23**)			*Z* isomer (**24**)		
X	c-C_6H_{12}	$CDCl_3$	HFIP[a]	c-C_6H_{12}	$CDCl_3$	HFIP[a]
NO_2	−6.51	−7.05	−9.26	−0.17	−0.66	−2.73
CN	−3.46	−3.90	−5.97	−0.53	−0.99	−2.95
CF_3	−4.31	−4.34	*b*	−0.53	−0.57	*b*
CO_2H	−3.63	−3.94	−5.41	−0.22	−0.50	−1.80
$CONH_2$	−3.53	−3.99	−5.95	−0.05	−0.38	−2.02
$COOCH_3$	−3.48	−3.82	−5.23	−0.09	−0.40	−1.61
OH	−7.27	−7.62	−9.34	0.00	−0.09	−1.55
OCH_3	−6.37	−6.77	−8.74	0.25	−0.04	−1.59
$OCOCH_3$	−6.38	−6.72	−8.25	0.36	0.03	−1.34
F	−7.54	−8.01	−10.03	0.24	−0.17	−1.88
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
NH_2	−6.69	−6.92	−9.71	−0.15	−0.18	−3.03
$N(CH_3)_2$	−5.46	−5.77	−10.39	0.26	0.00	−3.53
$^+N(CH_3)_3$	*b*	−8.38	*b*	*b*	−0.49	*b*
N═NCF_3	−5.54	−5.94	*b*	−0.10	−0.47	*b*
CH_3	−4.43	−4.35	−4.33	0.00	0.00	0.00
$C(CH_3)_3$	−4.00	−4.10	*b*	0.15	0.02	*b*
CH_2OH	−3.38	−3.55	−4.66	0.03	−0.13	−0.95
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-CNC_6H_4	−4.37	−4.59	−5.43	0.00	−0.19	−1.00
p-$COOCH_3C_6H_4$	−4.26	−4.43	−5.22	0.11	−0.12	−0.80
p-FC_6H_4	−4.37	−4.45	−5.14	0.07	0.00	−0.63
p-BrC_6H_4	−4.41	−4.53	−5.23	−0.07	−0.11	−0.71
p-$CH_3OC_6H_4$	−4.24	−4.41	−5.04	0.16	0.00	−0.63
p-$NH_2C_6H_4$	−4.18	−4.33	−5.09	0.20	0.05	−0.61
p-$(CH_3)_2NC_6H_4$	*b*	−4.39	*b*	*b*	−0.09	*b*
$Si(CH_3)_3$	0.12	0.23	0.39	−0.20	−0.21	−0.19
$Sn(CH_3)_3$	1.55	1.64	1.79	−0.23	−0.25	−0.31
D	0.00	0.00	0.00	0.00	0.00	0.00

[a] HFIP = hexafluoroisopropyl alcohol. [b] Not measured.

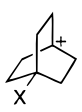
Table 6. Calculated Residual Contributions (^{19}F SCS − $\rho_F\sigma_F$) to ^{19}F SCS (ppm) of (*E*)-5-Substituted (X) Adamant-2-yl Fluorides (23)

X	c-C_6H_{12}	$CDCl_3$	HFIP
NO_2	−5.88	−5.79	−5.42
CN	−2.89	−2.81	−2.86
CF_3	−3.89	−3.56	
CO_2H	−3.41	−3.32	−3.52
$CONH_2$	−3.25	−3.35	−3.50
$COOCH_3$	−3.27	−3.32	−3.56
OH	−7.05	−7.06	−7.28
OCH_3	−6.19	−6.27	−6.63
$OCOCH_3$	−6.10	−6.08	−6.30
F	−7.17	−7.20	−7.53
Cl	−6.25	−6.24	−6.39
Br	−5.57	−5.57	−5.68
I	−4.23	−4.20	−4.34
NH_2	−6.57	−6.55	−5.32
$N(CH_3)_2$	−5.36	−5.42	−4.55
$^+N(CH_3)_3$		−6.67	
N═NCF_3	−5.05	−5.05	
CH_3	−4.38	−4.29	
$C(CH_3)_3$	−3.99	−4.06	
CH_2OH	−3.28	−3.28	−3.49
C_6H_5	−4.04	−4.01	−4.06
p-$NO_2C_6H_4$	−4.04	−4.01	−4.05
p-CNC_6H_4	−4.09	−3.99	*a*
p-$COOCH_3C_6H_4$	−4.04	−3.94	*a*
p-FC_6H_4	−4.19	−4.04	*a*
p-BrC_6H_4	−4.20	−4.06	*a*
p-$CH_3OC_6H_4$	−4.11	−4.10	*a*
p-$NH_2C_6H_4$	−4.10	−4.10	−4.09
p-$(CH_3)_2NC_6H_4$		−4.16	
$Si(CH_3)_3$	0.12	0.23	0.39
$Sn(CH_3)_3$	1.55	1.64	1.79
D	0.00	0.00	0.00

[a] Appropriate σ_F values not available.

tions (orbital coefficients, resonance integrals, and energy differentials).

The well-defined through-bond contributions to the ^{19}F SCS of **14** and **23** (see Tables 4 and 6, respectively) is a significant result since it demonstrates unambiguously that besides electrostatic field effects long-range polar σ-inductive effects can be transmitted efficiently by a conjugative effect in saturated systems. These effects have been difficult to define unambiguously with reactivity probes, particularly with the usual basis set of σ-electron-withdrawing groups, because of the camouflaging envelope of the dominant field mechanism.[48a−c,49b,76] However, because it is generally accepted that hyperconjugative interactions are more pronounced in excited or electron-deficient species such as carbocations than in the neutral ground state, the aforementioned ^{19}F chemical shift studies of **14** and **23** strongly suggested that double hyperconjugation should be an important mode of cation stabilization in the bicyclo[2.2.2]octyl and adamantyl systems (**25** and **26** (*E*-cation), respectively) as illustrated by canonical structures **27** and **28** for the former and **29** and **30** for the latter.



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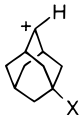

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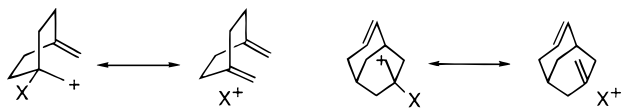
The metalloidal substituents (MMe_3; M = Si, Ge, and Sn) seemed ideal for this purpose since they are good σ-electron donors but exert negligible field influences ($\sigma_F \approx 0$; see Tables 1 and 2). This was confirmed by appropriate kinetic studies which revealed large accelerative effects for the metalloidal substituents in both systems.[77,78] In line with stereoelectronic



27 **28** **29** **30**

requirements the stabilizing double hyperconjugative effect is very prominent in the *E*-cation (**26**) but virtually precluded in the corresponding *Z* species.[78] High-level ab initio molecular orbital calculations provide strong corroboration for the stabilizing effect in **25**.[79]

For full details of the analysis of the ^{19}F SCS of **14**, **23**, and **24**, the reader is referred to the original papers.[63c,i,65,71] However, several points concerning the residual contributions (^{19}F SCS − $\rho_F\sigma_F$) of **14** (Table 4) and **23** (Table 6) are noteworthy in connection with delineating the origin of the electronic factor governing the stereoselectivity of the reactions of **1**. First, the relative values provide an empirical scale of ground-state induction conveyed by a conjugative mechanism which is essentially governed by hyperconjugation between $\sigma_{CC}-\sigma_{CX}^*$ and $\sigma_{CC}-\sigma_{CX}$ for σ-electron-acceptor and -donor substituents, respectively.

According to simple PMO theory,[80] such conjugative interactions are proportional to $c^2\beta^2/\Delta E$, where c is the coefficient of the carbon atom of attachment (overlap factor), β is the resonance integral associated with the appropriate orbitals, and ΔE is the energy gap between the orbitals. The relationship between these molecular orbital parameters and electronegativity has been discussed.[81] An approximate parallel between the polar residual contributions and group electronegativity parameters (σ_χ effect) is understandable in terms of c dominating the numerator of the aforementioned expression. The fact that the effects in **14** do not precisely parallel those in **23** ($r = 0.96$)[65] emphasizes that conjugative effects of a substituent are also a function of the reference substrate, i.e., dependent on ΔE. Because resonance is a dynamic property it is important to bear in mind the limitations of the aforementioned empirical scale of inductive power based on the neutral ground state when applied to chemical reactivities. Depending on the extent of electron demand in the latter situations, the reactivities of the σ-electron-acceptor and -donor effects may be seriously perturbed. For example, whereas positive charge development in the substrate may magnify and distort the latter effects, the former should remain essentially unchanged. The converse would hold for negative charge development.

Second, it can be seen that the alkyl groups have significant *negative* residual contributions in both systems (as large as or larger than the other carbon-based electronegative substituents such as CN, CF_3, COOH, $CONH_2$, $COOCH_3$, and C_6H_5 in **23**) and are, therefore, very much σ-electron-withdrawing relative to hydrogen. This result is significant in view of the continuing debate concerning the relative electron-donating ability of C−C and C−H bonds in saturated systems.[7,16,82] However, it is in line with other observations (NMR and reactivity parameters) from various model polycycloalkane systems (1,4-disubstituted bicyclo[2.2.2]octanes,[48,83] 1,4-disubstituted bicyclo-[2.2.1]heptanes,[63d] 1,4-disubstituted cubanes,[84] 2,6-disubstituted bicyclo[2.2.1]heptanes,[85] 1,3-disubstituted adamantanes,[39b,63f,86] 1,3-disubstituted bicyclo-[1.1.1]pentanes,[50a] 1,5-disubstituted bicyclo[3.1.1]-heptanes,[51] 1,5-disubstituted trishomobarrelenes,[87] and 5-substituted 2-adamantyl derivatives[5a,49b,63i,65,88,89]). Thus, the experimental evidence from rigid polycycloalkanes, the archetypal model substrates for delineating electronic substituent effects, is overwhelmingly in favor of the C−H bond being a better donor than C−C for long-range interactions (γ- and δ-effects) in the neutral ground-state and electron-deficient species. It is pertinent to note that most of the various group electronegativity scales[41,43] rank CH_3 as being more electronegative than H, which is in line with the above conclusion.

Finally, it can be seen that the hyperconjugative influence of the p-SC_6H_4 groups, as measured by the residuals of **14** and **23** (Tables 4 and 6, respectively), is independent of the nature of the para-substituent (S) i.e., the σ electron-withdrawing effect of p-SC_6H_4 groups remains constant irrespective of the electronic character of S.

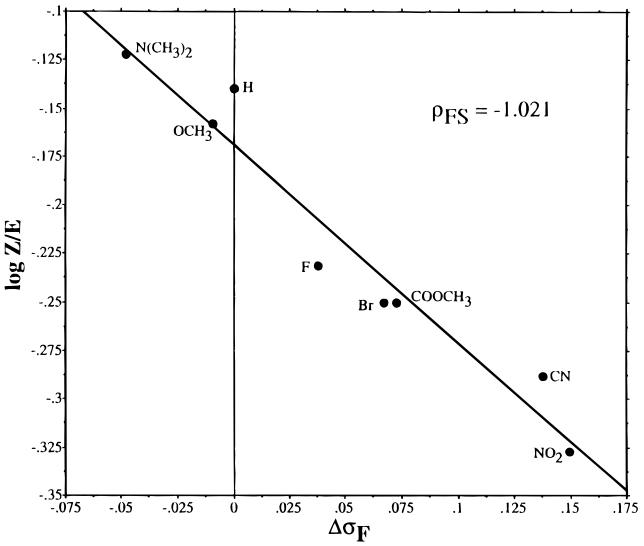


Figure 5. Plot of log Z/E for the $NaBH_4$ reduction of para-substituted (S) 5-phenyl-2-adamantanones **1** (Y = O; X = p-SC_6H_4) versus $\Delta\sigma_F$ ($y = -1.021x - 0.169$, $r^2 = 0.945$) (ref 65).

III. Diastereofacial Selectivity

A. Nucleophilic Addition Reactions of 5-Substituted (X) 2-Adamantanones (1, Y = O)

The linear plot shown in Figure 3 has been interpreted by le Noble et al.[5a,17c] as evidence for the conclusion that face selection for nucleophilic additions to **1** (Y = O) (see Chart 1) can be explained exclusively within the framework of Cieplak's transition-state hyperconjugation model. Originally,[5a] the plot included the p-anilino substituent (p-$NH_2C_6H_4$) with the assertion that this group acts as an electron donor at remote probe or reaction sites in saturated systems. Subsequently, we showed[63i,90] by means of model systems **10**, **14** (or **16**), and **23** that this substituent is an electron-withdrawing group by both polar field and σ-inductive effects (see Tables 1, 4, and 6 for appropriate parameters) and, moreover, that it induces preferential zu or syn attack by nucleophiles in **1** (Y = O, X = p-$NH_2C_6H_4$). The latter result was diametrically opposite to the earlier report.[52] These findings were later confirmed by le Noble et al.[17c] which led to the revised plot (Figure 3). As noted above, p-SC_6H_4 substituents in saturated systems act to influence remote probe sites by a direct composite through-space electrostatic interaction as well as by perturbing the hyperconjugative donor ability of appropriately aligned proximate σ_{CC}-bonds. However, the latter contribution is invariant to the nature of the para-substituent (S). Consequently, taken at face value the linear plot (Figure 3) clearly suggests that diastereofacial selectivities (Z/E) for $NaBH_4$ reduction are dependent on the $\Delta\sigma_F$ effect of the substituent (p-SC_6H_4). The plots displayed in Figures 5 and 6 for $NaBH_4$ reduction and methylation of a series of para-substituted (S) 5-phenyl-2-adamantanones **1** (Y = O; X = p-SC_6H_4) show that the logarithms of Z/E do indeed correlate well linearly with the respective $\Delta\sigma_F$ values (see above).[65] This result nicely confirms that the stereochemical outcome of these nucleophilic addition reactions is

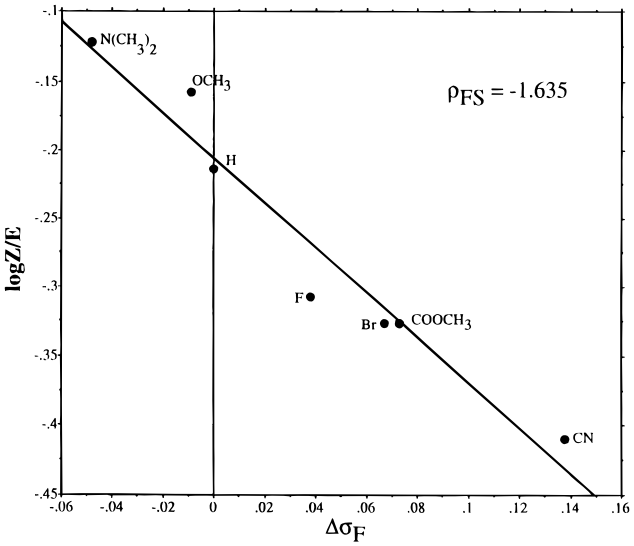


Figure 6. Plot of log Z/E for the methylation (CH_3Li) of para-substituted (S) 5-phenyl-2-adamantanones **1** (Y = O; X = *p*-SC_6H_4) versus $\Delta\sigma_F$ ($y = -1.635x - 0.206$, $r^2 = 0.949$) (ref 65).

Table 7. Calculated Polar Field Induced π-Facial Selectivities[a] versus Observed Product Distributions for the Reduction ($NaBH_4$) of 5-Substituted (X) Adamantan-2-ones (1, Y = O)[b]

	obsd		calcd	
X	%*E*	%*Z*	%*E*	%*Z*
NO_2	75	25	81	19
CN	69	31	78	22
CF_3	59	41	73	27
CO_2CH_3	57	43	66	34
F	59	41	72	28
Cl	63	37	73	27
Br	60	40	74	26
I	64	36	72	28
OCH_3	64	36	67	33
$OCOCH_3$	62	38	70	30
$N(CH_3)_2$	65	35	66	34
C_6H_5	58	42	60	40
CH_3	51	49	52	48
$C(CH_3)_3$	50	50	51	49
$Si(CH_3)_3$	50	50	50	50
$Sn(CH_3)_3$	48	52	51	49
$Sn(CH_3)_3$	48	52	48[c]	52[c]

[a] log $Z/E = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.01$. σ_F values for CH_3OH or $CDCl_3$ (Table 1). [b] Taken from ref 65. [c] $\sigma_F = -0.04$ (see ref 65).

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.

By use of the polar susceptibility parameters (ρ_{FS}) obtained from the linear plots (Figures 5 and 6) together with the appropriate σ_F values listed in Table 1 (CH_3OH or c-C_6H_{12}) and the Hammett-type equation (log $Z/E = \rho_{FS}\sigma_F$), polar field induced π-facial selectivities can be calculated for nucleophilic addition reactions (reduction and methylation) of **1** (Y = O).[65] These are listed in Tables 7 and 8 with the experimentally observed product distributions. It can be seen that in several instances, mainly for weak to moderately polar groups ($\sigma_F < 0.30$), there is good agreement between the calculated and observed

Table 8. Calculated Polar Field Induced π-Facial Selectivities[a] versus Observed Product Distributions for the Methylation (MeLi) of 5-Substituted (X) Adamantan-2-ones (1, Y = O)[b]

	obsd		calcd	
X	%*E*	%*Z*	%*E*	%*Z*
CN	68	32	90	10
CF_3	72	28	84	16
CO_2CH_3	55	45	69	31
F	66	34	81	19
Cl	62	38	83	17
Br	60	40	84	16
I	57	43	83	17
OCH_3	63	37	67	33
$N(CH_3)_2$	63	37	61	39
C_6H_5	62	38	64	36
CH_3	54	46	55	45
$Si(CH_3)_3$	49	51	50	50
$Sn(CH_3)_3$	48	52	51	49
$Sn(CH_3)_3$	48	52	46[c]	54[c]

[a] log $Z/E = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.61$. σ_F values for c-C_6H_{12} (Table 1). [b] Taken from ref 65. [c] $\sigma_F = -0.04$ (see ref 65).

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 a not a singular comparison where the latter situation is reversed. This is important because the Cieplak effect[16] operates to reinforce the diastereoselectivity induced by electrostatic interactions. A particular noteworthy feature is that the facial selectivity order induced by the substituents does not parallel the relative residual contributions to the ^{19}F SCS of **23** (see Table 6). Given that the orbital interactions governing the relative through-bond contributions to the ^{19}F SCS of **23** and **24** are analogous to the corresponding interactions determining the energy difference between the Cieplak diastereomeric transition states (see Chart 2), a correspondence was expected if transition-state hyperconjugation prevailed in determining facial selectivity.

Perhaps the most pertinent substituents with respect to revealing the importance of transition-state hyperconjugation, or otherwise, are the congeneric Group 14 substituents, namely, $(CH_3)_3C$, $(CH_3)_3Si$, and $(CH_3)_3Sn$. Although these groups are similar in that they exert virtually no electrostatic field influence ($\sigma_F \approx 0$; Table 1) they differ markedly with respect to their double hyperconjugative interaction mode as revealed by the ^{19}F SCS of **14** and **23** (Tables 4 and 6, respectively). Model system reactivity studies (see later) under conditions of high electron demand have confirmed and heightened this distinction.[63i,77,78,91] Note, however, that the selectivities exerted by these groups (Tables 7 and 8) are feeble and, moreover, the observed selectivities are in accord with expectations based purely on electrostatic grounds. Thus, the overall picture portrayed by the results (Tables 7 and 8), namely, the unimportance of transition-state hyperconjugation governing diastereofacial selectivity in the nucleophilic additions of **1** (Y = O), is strongly reinforced. However, it should be noted that some evidence for a hyperconjugative model in the case of σ-electron donor groups has emerged from $LiAlH_4$ (in ether) and DIBAL-H

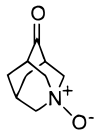
Table 9. Product Distributions for Hydride Reductions of Some 5-Substituted (X) Adamantan-2-ones (1, Y = O)[a]

	$NaBH_4$		$LiAlH_4$		DIBAL-H[b]	
X	%*E*	%*Z*	%*E*	%*Z*	%*E*	%*Z*
F	59	41	60	40	61	39
Br	60	40	60	40	60	40
$C(CH_3)_3$			50[c]	50[c]		
$Si(CH_3)_3$	50	50	44	56	48	52
$Sn(CH_3)_3$	48	52	38	62	42	58

[a] Taken from ref 91. [b] Diisobutylaluminium hydride ($(((CH_3)_2CHCH_2)_2AlH$). [c] Taken from ref 5a.

(in toluene) reductions of some derivatives of **1** (Y= O); Table 9). This work was prompted by the discovery that binding a methyl cation to the carbonyl oxygen atom of **1** (Y = O) appears to increase the selectivity of hydride reduction[91] as a result of enhanced electron demand promoting double hyperconjugation (see later in section B). Additional impetus derived from the fact that the crystal structure of the antimony pentachloride complex of **1** (Y = O, $X = C_6H_5$)[92] and the ab initio calculated (RHF/3-21G* level) transition-state geometry for reduction of adamantanone (**1**, Y = O; X = H) with AlH_3[93] exhibit structural manifestations of hyperconjugation. Both $LiAlH_4$ and DIBAL-H are believed to ligate to oxygen to varying degrees prior to hydride transfer. It can be seen that while the stereoselectivities for the strong σ-electron-withdrawing groups (F and Br) remain largely unaffected there does appear to be a significant general enhancement of selectivities for the σ-electron donors ($Si(CH_3)_3$ and $Sn(CH_3)_3$), particularly for $LiAlH_4$. The latter selectivities contrast markedly with the complete lack of influence exerted by the σ-electron-withdrawing $(CH_3)_3C$ group. The overall results highlight the different nature of the electronic effects associated with these disparate substituent types. Apparently in the case of $Si(CH_3)_3$ and $Sn(CH_3)_3$, the donor double hyperconjugative interaction mode is particularly sensitive to electron demand as well as to the ease of pyramidal distortion of the reaction center. Thus, provided the intrinsic donor and acceptor abilities of the substituent and reaction site, respectively, are appropriately matched hyperconjugation can be an important factor governing facial preferences in nucleophilic additions.

The sheer size of derivatives of **1** (Y = O) coupled with the obviously small energy differences between the diastereomeric transition states makes the application of computational methodology a daunting exercise. Nevertheless, computational procedures have been employed to evaluate the relative importance of electrostatic and orbital effects controlling the preferred facial selectivity in the reduction of **1** (Y = O). Chandrasekhar, Mehta, and co-workers[94] have proposed a semiquantitative computational model in which the effect of electrostatic and polarization interactions is exclusively modeled using a test charge, while the role of orbital interactions is assessed by use of the hydride ion. It was found that for **1** (Y = O, X = F) the calculations support the Cieplak model.[16] Coxon et al.[93] have carried out semiempirical calculations (AM1) of the transition-state energetics for AlH_3 addition to several derivatives of **1** (Y = O). The predictions appear to parallel experimental results for $NaBH_4$ reduction but with a notable exception (**1**, Y = O; X = $C(CH_3)$). The origin of the face selectivity was ascribed to orbital effects (hyperconjugation and torsional strain) based on ab initio structural studies of the four-center transition state for the reduction (AlH_3) of 2-adamantanone and 5-azaadamantanone *N*-oxide (**31**) which revealed changes in bond lengths consistent with differential hyperconjugative interactions. The reduction ($NaBH_4$) of **31**[95] is the most celebrated example of face selectivity (syn/anti = 96/4) for a nucleophilic addition involving a remotely substituted 2-adamantanone. It was chosen for investigation by



31

le Noble et al.[95] based on the belief that replacement of C_5-F in **1** (Y = O, X = F) by the isoelectronic N−O function should enhance the differential hyperconjugating abilities of the vicinal σ_{CC}-bonds flanking the reaction site at C2. The fact that preference for syn delivery of hydride does indeed become more pronounced and, as well, that changing the solvent from methanol to water or even saturated sodium chloride did not influence stereoselection as might have been expected for dominant Coulombic interactions, strongly suggested the operation of the Cieplak model.[95] An extension of this idea has confirmed an augmented syn approach by the reagent in electrophilic and sigmatropic reactions as well[96] for the same structural change of the substrate. However, high-level ab initio molecular orbital calculations indicate that incorporating nitrogen into the skeletal framework induces structural distortions which introduces steric bias into the model substrate.[97] Thus, the idea that electronic effects are exclusively responsible for face selectivity in **31** is compromised. Gung et al.[97] have proposed that the observed diastereofacial selectivity can be easily understood in terms of a steric effect related to the Bürgi−Dunitz trajectory. Recently, le Noble et al.[98] compared the reduction ($NaBH_4/D_2O$) ratio of **1** (Y = O, $X = N(CH_3)_2$) with that of its methyl iodide salt (*E*/*Z* = 65/35 and 86/14, respectively). The increase in diastereoselectivity for this structural modification appears to be a clear manifestation of an enhanced polar field effect (see σ_F values for $N(CH_3)_2$ and $^+N(CH_3)_3$ in Table 1).

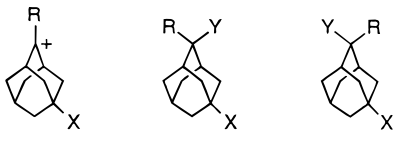
Studies of face preferences for nucleophilic addition in 2-endo-substituted norbornan-7-ones (**2**) and 2,3-endo,endo-disubstituted norbornan-7-ones (**3**, Y = O) by Mehta et al.[6a,94] have revealed that the electronic factor of remote substituents in these sterically unbiased substrates is more pronounced than that showed in **1** (Y = O) (e.g., X = CN, *E*/*Z* = 68/32 for **1** (Y = O)[65] and 88/12 for **2**). Originally, the results of **2** and **3** (Y = O) were reconciled in terms of Cieplak theory[16] since the nucleophile seems to be directed antiperiplanar to the relatively electron-rich C−C bonds. An advantageous feature that **2** and **3** (Y =

O) have over **1** (Y = O) is that they are significantly smaller and, hence, more amenable to MO calculations. Application of the latter methodologies at varying levels of sophistication point to the observed face selectivities in **2** and **3** (Y = O) being predominantly controlled by electrostatic effects.[13,94] This result has been confirmed by the determination of a polar field susceptibility parameter ($\rho_{FS} = -1.513$) for the reduction of **2** and **3** (Y = O) which permit polar field induced π-facial selectivities to be calculated. The predictions agree well with the experimental results.[6c] It is worth noting that the larger ρ_{FS} value for **2** and **3** (Y = O) compared to **1** ($Y = 0$) is in accord with expectations based on the fact that the substituent(s) in the former systems is closer to the stereoinductive center. The observed diastereoselectivities for reduction ($NaBH_4$) of 4-substituted norsnoutanones (**7**, Y = O)[10a] also show a marked increase in face selectivity as compared to **1** (Y = O) (e.g., X = CN, *E*/*Z* ratios = 68/32 for **1** (Y = O)[65] and 84/16 for **7** (Y = O)) despite the substituent in the former being fartherest removed from the reaction site. From calculations at varying levels of computational theory, the cyano group is predicted to induce greater syn-face selectivity in **7** (Y = O) than **1** (Y = O).[10a] This has been ascribed to a combination of electrostatic and Cieplak-type hyperconjugative effects but their relative importance was not quantitatively evaluated. However, available experimental evidence[99] together with orbital energy considerations suggest that in **7** (Y = O) the dominant orbital interaction in the transition state is more likely to be homoconjugative (1,3-σ,σ*) rather than hyperconjugative in nature. This factor would act to reinforce the polar field induced syn preference because Coulombic forces of repulsion would be minimized by polarizing the carbon atoms of the face remote from the σ-electron-withdrawing substituent.

The facial selectivity data for **4**,[7] **5**,[8] and **6**[9] also strongly underline the importance of electrostatic interactions. The original interpretation of the results for **5**[8] in terms of Cieplak's model is incompatible with the way *p*-XC_6H_4 groups act to perturb remote probe sites (see above).

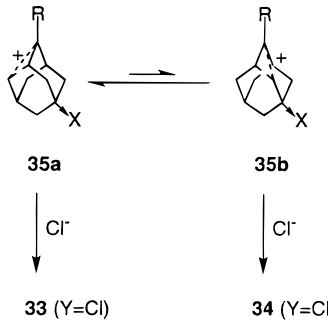
B. Nucleophilic Capture of 5-Substituted (X) 2-Adamantyl Cations (32)

The most conspicuous examples of diastereoselectivity among the various 5-substituted (X) 2-adamantyl substrates (**1**) are those involving reactions which are mediated by the formation of secondary (2°) and tertiary (3°) 5-substituted (X) adamant-2-yl cations (**32**).[5,17d,21,63i,65,78] For example, powerful σ-electron-



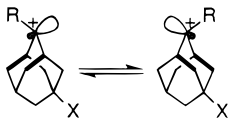
32 **33** **34**

withdrawing and -donor groups such as X = F and $Sn(CH_3)_3$, respectively, can lead to nucleophilic capture ratios in excess of 9:1 but with diametrically opposite stereochemistry. Syn (or zu) approach of the nucleophile is favored by the former and anti (or en) by the latter (see Chart 1). The stereoselectivity has been rationalized in terms of transition-state hyperconjugation as shown in Chart 2. Although this proposition has been a noncontroversial issue, the precise nature of the hyperconjugative mode responsible for differentiating the energies of the diastereomeric transition states has been modified and refined since the original proposal by le Noble et al.[5a] In their early seminal paper[5a] these workers described inter alia the results of reaction between several epimeric pairs of tertiary 5-substituted (X) 2-adamantanols (**33** and **34**; R = CH_3, Y = OH) and HCl gas in dichloromethane. The substituent in all cases was a σ-electron-withdrawing group (X = F and CF_3). The mixtures obtained from either alcohol in each case were found to be identical. The dominant product is the Z chloride (**33**, Y = Cl) by a factor of 3 to 1 or more. Thus, the overall stereochemical result is predominantly retention and inversion for the Z and E epimeric alcohols (**33** and **34**; R = CH_3, Y = OH, respectively), respectively. Most importantly, it was clearly established that the face selectivities are kinetically controlled and not a manifestation of the thermodynamic stability of the products. The obvious conclusion was that the product mixtures from each epimer is derived from a common carbocation intermediate which was depicted as a rapidly equilibrating pair of nondegenerate bridged or σ-delocalized ions (**35a**⇌**35b**). In their early paper[5a] and others,[5b,21b]



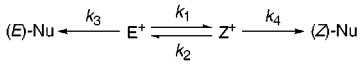
le Noble et al. explained the origin of stereoselectivity in terms of hyperconjugation with the proviso that stabilization for carbocations is greater before the nucleophile begins to bind.

Subsequently, Sorensen and co-workers concluded from variable temperature ^{13}C NMR chemical shift studies of **32** (R = CH_3, X = CH_3)[88a,c] and ab initio studies of **32** (R = H, X = H)[88b] that the cationic center (C2) is not planar but partially pyramidalized, being displaced from the symmetrical position moving back and forth in a double-minimum potential (rapid equilibrium between **36a** (*Z* cation) and **36b** (*E* cation)). The distortion of the C^+ center in each



36a **36b**

Scheme 1



invertomer facilitates C−C (shown in bold) hyperconjugative interactions with the vacant p-like orbital. The calculations[88b] clearly indicate that a nonplanar cation is energetically preferred to a bridged species. Other NMR studies[99] have revealed that the $^1J_{^{13}C^+-H}$ constant for **32** (R = CH_3, X = CH_3) also strongly implies that the C^+ center is significantly distorted from planarity (ca. 36°) in this 3° cation. An X-ray crystal structure of the 2-phenyladamant-2-yl cation (**32**, R = C_6H_5, X = H) has confirmed these structural manifestations of preferential C−C hyperconjugation on one face of C2.[101] Furthermore, recent theoretical studies provide additional corroborative evidence for the distortion of C^+ centers in order to facilitate hyperconjugative interactions.[102]

Preferred pathways for nucleophilic (Nu^-) capture of free 2° and 3° 5-substituted (X) 2-adamantyl cations (**32**) must be examined, therefore, in terms of a possible preequilibrium step of nonplanar cations prior to product formation. This transformation is shown in Scheme 1.

A general equation has been derived for such a situation which relates the product ratio (P_∞ = [(*Z*)-Nu]/[(*E*)-Nu]) with the equilibrium constant (K = k_1/k_2) and the individual rate constants (eq 8).[103] If the

$$P_\infty = K\frac{k_4(k_1 + k_2 + k_3)}{k_3(k_1 + k_2 + k_4)} \qquad (8)$$

equilibrium step is rapid, which appears to be the case generally for 3° ions (**32**, R = CH_3 or C_6H_5), a reasonable assumption is that $k_1,k_2 \gg k_3,k_4$ and therefore eq 8 reduces to eq 9. Thus, the relative

$$P_\infty = \mathrm{K}\frac{k_4}{k_3} \qquad (9)$$

stability of the epimeric cations, which is governed predominantly by hyperconjugation, also impinges significantly on facial selectivity in these circumstances. Further, under conditions where nucleophilic trapping of the epimeric cations is diffusion controlled then facial selectivity (P_∞) will be entirely controlled by *K*, i.e., the relative concentration of the ions rather than their reactivity will be the determining factor. Interestingly, the barrier to inversion of the C^+ center in the gas phase for the parent 2° ion (**32**; R = H, X = H) has been calculated at a high-level of theory (MP2 6-31G*+ZPVE 6-31G) to be 8.47 kJ/mol. However, because the phenomenon is a consequence of the relative degree of preferential C−C hyperconjugation on each face flanking C2, the barrier height is expected to depend markedly on electron demand at the reaction center as well as the electronic character of the 5-substituent (X). The former is clearly a function of R (see **32**) as well as the extent of solvation and ion-pairing effects. The available evidence suggests that 3° ions (**32** ; R = CH_3 or C_6H_5) in general have low barriers and, therefore, the initially formed ion irrespective of the precursor (*Z* or *E* diastereomer) fully equilibrates prior to interception by the nucleophile.[5a,b,65,104] A similar situation prevails for 2° ions (**32** ; R = H) substituted with σ-electron donors (e.g., X = $Si(CH_3)_3$, see below)[63i,78] but not for the parent (**32** ; R = H, X = H or D)[5a] or its derivatives bearing σ-electron withdrawing groups in the 5-position.[5a,21b,63i] For the latter the barrier is sufficiently high enough that the initially formed ion either does not equilibrate at all or only partially before nucleophilic capture.

Table 10. Products for the Solvolysis of 5-Metalloidal Substituted (X) 2-Adamantyl Brosylates at 25 °C[a]

			substitution	
X	solvent[b]	fragmentation[c]	%*E*-OR	%*Z*-OR
(*E*)-$Si(CH_3)_3$	97T	0	91	9
	70E	0	95	5
(*Z*)-$Si(CH_3)_3$	97T	0	88	12
	70E	0	88	12
(*E*)-$Sn(CH_3)_3$	97T	88	12[d]	
	70E	77	23	0
	90E	70	30	0
(*Z*)-$Sn(CH_3)_3$	97T	85	15[d]	
	90E	30	70	0

[a] Taken from ref 78. [b] 97T is 97 wt % trifluoroethanol − 3 wt % water. 70E and 90E are 70 and 90 vol % ethanol with 30 and 10 vol % water. [c] 7-Methylenebicyclo[3.3.1]non-2-ene. [d] *E*/*Z* ratio not determined.

Table 11. Product Distribution in the Fluorination (DAST) in Dichloromethane of 5-Metalloidal Substituted (X) 2-Adamantanols[a]

	fluorides	
X	%*E*-F	%*Z*-F
(*E*)-$Si(CH_3)_3$	86	14
(*Z*)-$Si(CH_3)_3$	86	14
(*E*)-$Sn(CH_3)_3$[b]	100	0
(*Z*)-$Sn(CH_3)_3$[c]	0	0

[a] Taken from ref 63i. [b] Fragmentation predominant but not quantitatively determined. [c] Exclusively fragmentation.

The stereochemical outcome of the solvolysis of (*Z*)- and (*E*)-5-(trimethylsilyl)- and 5-(trimethylstannyl)-2-adamantyl sulfonates (**33** and **34**; R = H, Y = *p*-$BrC_6H_4SO_3$; X = $Si(CH_3)_3$ and $Sn(CH_3)_3$, respectively)[78] as well as the fluorination of the corresponding alcohols with DAST in dichloromethane[63i] highlight the importance of double hyperconjugation for σ-electron-donating groups (see Tables 10 and 11). This interaction ensures that the *E* cation (**36b**) is more stable than the *Z* cation (**36a**) because the stereoelectronic requirement of this transmission mode is fulfilled in the former but not in the latter species (see above). Of course this situation also applies to the transition state leading to the *E* but not the *Z* product. Thus, preferential anti-face selectivity is clearly observed (Tables 10 and 11) in accord with expectations from a hyperconjugative model (see Chart 2). The importance of the stabilizing through-bond interaction (see canonical structures **29** and **30**) is graphically illustrated by the extent of fragmentation for the powerful σ-electron-donating $Sn(CH_3)_3$ substituent in both reactions. Double hyperconjugation clearly results in charge transfer from the C−X bond to the "vacant" orbital at C2 in the *E* cation

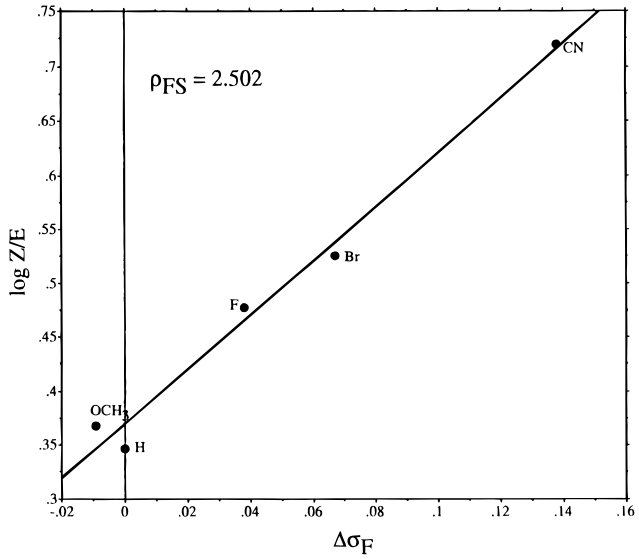


Figure 7. Plot of log *Z*/*E* for the hydrochlorination (CH_2Cl_2 as solvent) of 2-methylene-5-(para-substituted (S) phenyl)adamantanes **1** (Y = CH_2; X = *p*-SC_6H_4) versus $\Delta\sigma_F$ ($y = 2.502x + 0.37$, $r^2 = 0.986$) (ref 65).

(**36b**) and, in the extreme, can merge into fragmentation.

The different nature of the hyperconjugative mode governing facial selectivity in the nucleophilic capture of 2-adamantyl cations (**32**) bearing σ-electron-withdrawing (or acceptor) substituents is emphasized by the linear plot shown in Figure 7. It can be seen that there is an excellent correlation between log *Z*/*E* values for hydrochlorination in CH_2Cl_2 of a series of 2-methylene-5-(para-substituted (S) phenyl)adamantanes (**1**, Y = CH_2, X = *p*-SC_6H_4) and $\Delta\sigma_F$.[65] 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 (see above). Given that the primary interaction in the cation of the transition states leading to the respective products (**33** and **34**; R = CH_3, Y = Cl, X = *p*-SC_6H_4) is hyperconjugation between the electron-deficient center (C2) and the flanking C−C bonds and, moreover, given that the intrinsic electron donor capacity of the proximate C−C bonds remains invariant to the electronic character of S, the electric field dependency can be explained in terms of preferential hyperconjugative charge dispersal such that Coulombic forces of repulsion are minimized. This is achieved by delocalizing the positive charge away from the electrostatic field of the σ-electron-withdrawing substituent. Thus, preferential syn-face selectivity is induced. The explanation seems to be supported by 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 ($\rho_{FS} \approx 0$).[65] 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,[33,34] 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 diastereoselectivities in CH_2Cl_2 and NO_2CH_3 for addition to **1** (Y = CH_2) when X = C_6H_5 (see Table 12).

Table 12. Calculated Polar Field Induced π-Facial Selectivities[a] versus Observed Product Distributions for the Hydrochlorination of 5-Substituted (X) 2-Methyleneadamantanes (1, Y = CH_2)[b]

	obsd (CH_2Cl_2)		obsd (NO_2CH_3)		calcd (CH_2Cl_2)	
X	%*E*	%*Z*	%*E*	%*Z*	%*E*	%*Z*
CN	13	87			5	95
$COOCH_3$	28	72	26	74	20	80
F	10	90	0	100	9	91
Cl	17	83	3	97	8	92
Br	22	78	17	83	8	92
I	34	66	26	74	9	91
OCH_3	14	86	15	85	21	79
C_6H_5	31	69	34	66	28	72
CH_3	44	56	44	56	46	54
$C(CH_3)_3$	45	55	47	53	49	51
$Si(CH_3)_3$	65	35	50	50	49	51

[a] log $Z/E = \rho_{FS}\sigma_F$; ρ_{FS} =2.502. σ_F values for CH_2Cl_2 or $CDCl_3$ (Table 1). [b] Taken from refs 65 and 91.

The calculated diastereoselectivities for electrophilic addition (HCl in CH_2Cl_2) to **1** (Y = CH_2) based on the ρ_{FS} value from Figure 7 are listed in Table 12 together with the experimentally observed product distributions.[65,91] It can be seen that there is a quite good agreement between the observed and calculated polar-field-induced selectivities in CH_2Cl_2 for most of the σ-electron-withdrawing substituents. Thus, the main conclusion to be drawn from these results is that the electrostatic field effect (σ_F effect) of these groups plays an important role governing diastereoselectivity in the capture of **32** (R = CH_3, X = σ-electron-withdrawing group). This is corroborated by the unexpectedly large response of the solvolytic rate constants of (*E*)-5-substituted (X) 2-adamantyl nisylates (**34**; R = H, Y = *p*-$NO_2C_6H_4SO_3$) to the σ_F effects of σ-electron-withdrawing substituents.[49b,52] The pronounced sensitivity is due to the fact that hyperconjugative charge dispersal in the *E* cation of the transition state is directed toward the substituent. It is important to realize that the dominant perturbation between the C^+ center and the antivicinal C−C bond in the cation of en- or anticonfigurated transition states ensures that the hyperconjugating influence of the substituent (σ_{CC}−σ_{CX}*) has only a minor effect on the intrinsic donor capacity of the proximate C−C bonds. This conclusion follows readily from orbital energy gap considerations.

There are two significant discrepancies in Table 12 worth noting, namely, the selectivity order for the halogens (F > Cl > Br > I (observed) vs F ≈ Cl ≈ Br ≈ I (calculated)) and the unexpected lack of stereoselectivity observed for the $Si(CH_3)_3$ group in NO_2CH_3 compared to in CH_2Cl_2. Particular attention has been drawn to these matters in the original reports.[65,91] One point that was emphasized in connection with the latter discrepancy is that there is a mechanistic distinction for HCl addition in CH_2Cl_2 versus 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.[105] On this basis long-range steric phenomena[65] as well as the demanding stereoelectronic requirement of the double hyperconjugative interaction mode[91] have been raised as possible origins of the anomaly. However, because the discussions are somewhat speculative, these will not be reiterated here and interested readers are referred to the original papers.[65,91] What can be said, however, is that more experiments are needed to resolve these and other matters.

A preference for syn face electrophilic addition is also shown by **1** (Y = CH_2, X = F) for neutral electrophiles (RCO_3H, :CCl_2, and B_2H_6) which proceed mechanistically in a single step.[5b] Compared to stepwise processes involving the intermediate formation of carbocations (addition of HCl (see Table 12), CF_3CO_2H, and $Hg(OCOCH_3)_2$) the selectivity is modest (*E*/*Z* = 66/34 for epoxidation of **1** (Y = CH_2, X = F)).[5b] The results have been interpreted in terms of Cieplak's hyperconjugative model. A similar picture has emerged from studies of face preferences for corresponding electrophilic additions (except HCl and CF_3CO_2H) to **3** (Y = CH_2),[6b] endo-substituted 7-isopropylidenenorbornanes,[106] and **7** (Y = CH_2).[10b] The observed selectivities have also been ascribed primarily to Cieplak-type hyperconjugative interactions. Unfortunately, these studies did not include a strong σ-electron donor ($Si(CH_3)_3$ or $Sn(CH_3)_3$) in the substituent data set which may have provided results to consolidate the conclusion. However, the facial selectivity of the epoxidation of **1** (Y = CH_2, X = $Sn(CH_3)_3$), which yields a 50:50 mixture of the stereoisomeric epoxides, raises serious doubts about the proposed hyperconjugative origin of stereoselectivity for concerted electrophilic addition reactions. Given the dramatic effect of the (*E*)-5-$Sn(CH_3)_3$ group on the stability and stereoselectivity of the 2-adamantyl carbocation (see above), the ineffectual influence of this group on facial selectivity of epoxidation is more in accord with a situation under electrostatic control given its weak polar field effect ($\sigma_F \approx 0$; see Table 1). Houk et al.[107] have invoked electrostatic control to explain the facial selectivity of single step additions of neutral electrophiles to 7-isopropylidenebenzonorbornane. Their electrostatic potential field calculations suggest preferential attack on the less electron-rich face of the alkene because neutral electrophiles bearing lone pair of electrons are effectively "negative" in their ground states, i.e., they possess nucleophilic character. Following this proposal it is of interest to note that the PM3 calculated electrostatic potential of **1** (Y = CH_2, X = F)[108] indicates that the electrostatic potential field between the two faces is small but correctly predicts preferential syn attack. An interesting question concerning the nucleophilic capture of **32** is the extent to which stereoselectivity is a function of electron demand. This matter was first investigated by le Noble et al.[21a] who reported on the borohydride and chloride ion capture of 2-para-substituted phenyl derivatives of **32** (R = *p*-SC_6H_4 (S = H, OCH_3, CH_3), X = F and R = *p*-SC_6H_4 (S = H, Br, CF_3), X = F, respectively, as well as the borohydride trapping of the oxonium ion (**32**, R = OCH_3 and X = F). These experiments showed that the *Z*/*E* ratio for the former (*Z*/*E* ≈ 3−4) was virtually independent of the para substituent and that the latter exhibited an unexpectedly large preference (*Z*/*E* ≈ 5) given that the methoxy group is a known powerful π-electron donor. On the basis of the assumption that selectivity is exclusively controlled by hyperconjugation (Cieplak model), these workers concluded "that σ delocalization cannot be swamped by means of donating substituents at the electron deficient center". Thus, a distinction was drawn between π-participation on one hand and σ-participation on the other. The former can be completely suppressed by α-substituents such as the *p*-anisyl group as revealed by the classical studies of Gassman and Fentiman.[109] Contrary to the observations of le Noble et al.,[21a] Liu et al.[110] have reported kinetic and facial selectivity data for 3° 5-fluoro-2-adamantyl cations (**32**, R = *p*-SC_6H_4 where S = H, CF_3, and CH_3, X = F) which suggest that the tool of increasing electron demand is applicable.[109] Further information has been provided from hydride trapping (Et_3SiH/CH_2Cl_2 and $C_6H_5SiH_3/CH_2Cl_2$) of **32** (R = OCH_3) for a series of substituents (X) covering a wide range of electronic effects.[91] These are listed in Table 13. It can be seen that the selectivity data for both hydride sources is fairly similar except for the phenyl substituents. The latter *Z*/*E* ratios for $C_6H_5SiH_3$ are in accord with expectations (*E* > *Z*) from electronic considerations but those for Et_3SiH (*Z* > *E*) are not. Hence, a steric factor was invoked to explain the apparent anomalous latter diastereoselectivities for the phenyl groups (*Z* > *E*).[91] When the results in Table 13 are appropriately compared with the facial selectivity data shown in Tables 11 and 12 for the trapping of 2° (**32**, R = H) and 3° (**32**, R = CH_3) 2-adamantyl cations with fluoride and chloride ions in CH_2Cl_2, respectively, it is clear that, in the main, facial selectivity in **32** (R = OCH_3) is significantly suppressed as a result of reduced electron demand effected by the powerful π-electron-donating methoxyl groups. Furthermore, the marked propensity of the tin species (**32**, R = H and X = $Sn(CH_3)_3$) to undergo fragmentation (see above) is effectively "tamed". It is also clear that except for the σ-electron-withdrawing methyl group, which is weakly polar, the stereoselectivity induced by both types of substituents is not completely swamped. We ascribe this to the residual electrostatic field influence of the polar σ-electron-withdrawing substituents on one hand and to the double hyperconjugative influence of the σ-electron donor groups on the other. Thus, the distinction drawn between

Table 13. Product Distribution for the Hydride Trapping (Et_3SiH/CH_2Cl_2) of 32 (R = OCH_3)[a,b]

	ethers			ethers	
X	%*E*	%*Z*	X	%*E*	%*Z*
F	77 (76)	23 (24)	*p*-$NO_2C_6H_4$	45 (60)	55 (40)
Cl	69 (62)	31 (38)	*p*-BrC_6H_4	47 (59)	53 (41)
Br	66 (58)	34 (42)	CH_3	51	49
OCH_3	74 (71)	26 (29)	$Si(CH_3)_3$	35 (41)	65 (59)
$COOCH_3$	64 (65)	36 (35)	$Sn(CH_3)_3$	28 (24)	72 (76)
C_6H_5	47 (58)	53 (42)			

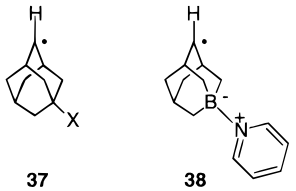
[a] Taken from ref 91. [b] Data in parentheses is for $C_6H_5SiH_3$ as the reducing agent.

π- and σ-participation by le Noble at al[21a,111] is basically upheld despite the erroneous premise on which it was originally based, namely, that the selectivity of capture of **32** (R = *p*-SC_6H_4, X = F) is controlled exclusively by single hyperconjugation.

Finally, it is worth noting that in contrast to the trends noted above the stereoselectivities for the hydride reduction of the oxonium ions (**32**, R = OCH_3) are, in the main, *enhanced* compared to the corresponding data for the $NaBH_4$ reduction of the corresponding ketones (**1**, Y = O; see Table 7). This is particularly the case for the σ-electron donor groups and, hence, suggests that facial selectivities for hydride reduction of ketones can be enhanced by increasing electron demand. This has been confirmed (see above; Table 9).

C. Atom Abstraction Reactions of 5-Substituted (X) 2-Adamantyl Radicals (37)

Over the last 10−15 years free radical mediated reactions have become an important part of the organic chemists' arsenal for the synthesis of a diverse array of organic compounds.[112] A large part of this development can be attributed to the progress that has been made in the understanding of the elements controlling the various forms of selectivity of these reactions.[113,114] However, an important aspect still in a rudimentary stage of understanding is the nature of the electronic factor governing π-facial diastereoselectivity of capture of carbon centered radicals. It is only just recently that this phenomenon for remote substituent groups was investigated utilizing 5-substituted (X) 2-adamantyl radicals (**37**) as model substrates.



37 **38**

The first experiments by le Noble et al.[23a] found that the 5-phenyl-2-adamantyl radical (**37**, X = C_6H_5) is captured by molecular bromine to give an *E*/*Z* mixture of bromides in a ratio of 38:62, respectively, i.e., a dominant face preference is induced which is *antiperiplanar* to the more electron-rich vicinal C−C bonds flanking C2. Cieplak's hyperconjugative model was invoked to explain the result. Subsequently, le Noble et al.[23b] reported that the 5-boraadamant-2-yl radical (**38**) exhibits en- or anti-face selectivity (65:35) in its deuterium atom abstraction reaction with *n*-Bu_3SnD. This directive effect by an apparent σ-electron donor substituent is diametrically opposite to that noted above for a modest σ-electron withdrawer (X = C_6H_5). Hence, it was concluded that Cieplak's transition-state hyperconjugation model is corroborated. However, it is significant that **38** was chosen for study for much the same reasons enunciated above in connection with the use of **31** as a probe substrate, i.e., incoporating the electropositive boron atom into the skeletal framework should allow its "inductive effect" to magnify the preferred direction of attack governed by hyperconjugation. Unfortunately, it is possible it may not be free of steric bias because of structural distortions of the skeletal framework but in the opposite sense to that of **31**.

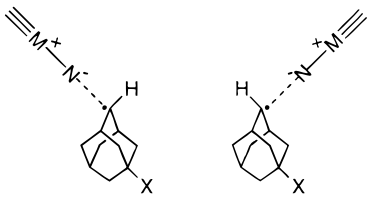
Table 14. Product Distribution in the Atom Capture of 5-Substituted (X) Adamant-2-yl Radicals (37)[a]

X	atom source	%*E*	%*Z*
F	*n*-Bu_3SnD	36	64
F	CCl_4	30	70
F	$CF_3CHClBr$	25	75
F	CF_3CH_2I	29	71
$Sn(CH_3)_3$	*n*-Bu_3SnD	59	41
$Sn(CH_3)_3$	CCl_4	66	34

[a] Taken from ref 115.

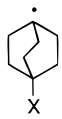
More recently, facial selectivity data for the 5-F- and 5-$Sn(CH_3)_3$-substituted 2-adamantyl radicals (**37**, X = F and $Sn(CH_3)_3$, respectively) in their deuterium and halogen abstraction reactions with *n*-Bu_3SnD and various haloalkanes, respectively, have been reported (listed in Table 14).[115] These two strong σ-electron-withdrawing and -donating groups (F and $Sn(CH_3)_3$, respectively) are of particular interest since they provide the most conspicuous examples of diastereoselectivity in the nucleophilic capture of 5-substituted (X) 2-adamantyl cations (**32**; see above), the archetypal electron-deficient species of the probe substrate (**1**). It is important to note that the distinct unambiguous facial preferences for **37** (X = $Sn(CH_3)_3$; see Table 14) confirm that an earlier result of iodine atom abstraction for this radical, which suggested capture with essentially random stereochemistry, is clearly spurious.[115] Doubts had initially been expressed regarding the latter result on the grounds that the radical was generated in a complex free radical chain reaction and that the iodo-tin compounds were minor components (14−26%) of the product mixtures.[96]

Although the preferential syn- (or zu) and anti- (or en) face selectivity induced by 5-fluoro- and 5-trimethylstannyl-substitution in the 2-adamantyl radical (**37**, X = H), respectively (see Table 14), is clearly in accord with expectations from the Cieplak model, we[115] have recently pointed out that there is an alternative equally plausible explanation based on an early reactant-like transition-state (TS) model. A considerable body of stereoselectivity data of atom transfer reactions involving acyclic radicals is available which is consistent with the supposition.[114] Moreover, strong corroboration is provided by recent high-level ab initio calculated transition states for hydrogen abstraction by alkyl radicals (1°, 2°, and 3°) from stannane and trimethylstanne.[117] Within this framework the diastereomeric transition states for the capture of **37** are depicted by structures **39** and **40** where ≡M−N represents the deuterium or halogen atom source (M = C or Sn; N = D, Cl, Br, or I). The 2-adamantyl radical (**37**, X = H) has been shown to be planar[118] and ab initio high-level calculations (UHF/6-31G*) suggests that this is also the case for the 5-F- and 5-$Sn(CH_3)_3$-substituted derivatives as well. However, some degree of pyramidalization of the radical center is to be expected in the TS structures (**39** and **40**). There are two possible factors



39 40

which may be envisaged to operate to differentiate the energies of **39** and **40**: (i) Radical stabilization due to spin delocalization of the unpaired electron by double hyperconjugation. The possible importance of this mechanism has recently been revealed by the discovery that 4-fluoro- and 4-trimethylstannyl-substitution stabilizes (0.81−1.15 kcal/mol[119] and 2.58−3.04 kcal/mol,[120] respectively) the bicyclo[2.2.2]-oct-1-yl radical (**41**, X = H) by enhanced delocalization of the unpaired electron.[121] Given that on ste-



41

reoelectronic grounds (antiperiplanarity of participating orbitals) similar effects should be at play in the *E* but not the *Z* species of **37** (X = H), both F and $Sn(CH_3)_3$ would be expected to stabilize **39** relative to **40** and, therefore, induce preferential anti- (or en) face selectivity in atom transfer reactions. The selectivity is expected to be more pronounced for the latter substituent. (ii) The electrostatic field of the remote substituent interacts with the polar bonds of the atom transfer agent ($\equiv M^{\delta+}-N^{\delta-}$). Unfortunately, existing theory is not good enough to be able to confidently predict the relative stability of **39** and **40** as a consequence of this Coulombic interaction. However, because of the polarity of the $M^{\delta+}-N^{\delta-}$ bond it seems not unreasonable to view the atom transfer agents as nucleophilic-like species and, therefore, preferential syn- (or zu) face selectivity is to be expected in line with electrostatically controlled nucleophilic additions to para-substituted 5-phenyl-2-adamantanones (see above, Figures 4 and 5). This Coulombic factor will be important for strongly polar substituents (e.g., F, $\sigma_F = 0.40$, see Table 1) but not for the $Sn(CH_3)_3$ group ($\sigma_F \approx 0$, Table 1). Thus, the preferential syn- (or zu) and anti- (or en) face selectivity observed for **37** (X = F and $Sn(CH_3)_3$, respectively) is comprehensible in terms of a predominant electrostatic field and double hyperconjugative influence for F and $Sn(CH_3)_3$, respectively.

It is noteworthy that the selectivity induced by 5-bromo (*Z*/*E* = 65/35) substitution in **37** (X = Br) for bromine atom transfer from $CF_3CHClBr$ is significantly lower than that for 5-fluoro (*Z*/*E* = 75/25; Table 14) even though its syn- (or zu) directing polar field effect is slightly larger ($\sigma_F = 0.40$ (F) versus 0.44 (Br), Table 1). However, bromo is more effective than fluoro at radical stabilization by double hyperconjugative electron delocalization. This is evident from through-three-bond stabilization of **41** by 4-Br (1.61−2.21 kcal/mol)[112] versus 4-F (0.81−1.15 kcal/ mol)[119] substitution. Consequently, the net result of Coulombic (favors **40**) and delocalization (favors **39**) influences on facial selectivity for Br will be less than that for F. The selectivity result is also explicable in terms of the Cieplak model since there is evidence in the neutral ground state from ^{19}F NMR chemical shifts (Tables 4 and 6) that F is more effective than Br at reducing the electron donor capabilities of the proximate vicinal C−C bonds.

A particularly pertinent result is the strikingly different facial selectivity data for the nucleophilic capture of **37** (X = $Sn(CH_3)_3$, *Z*/*E* = 1/1)[115,116] and **37** (X = F, *Z*/*E* = 56/44)[116] by $(CH_3)_3Sn^-$ (a super nucleophile)[122] *versus* the corresponding data for capture by atom transfer reactions (Table 14). It can be seen that the face preferences for the former are markedly reduced compared to the latter. In fact **37** (X = $Sn(CH_3)_3$) is captured by $(CH_3)_3Sn^-$ with random stereochemistry while that for **37** (X = F) is modest to say the least. Possible reasons for these unexpected results are as follows: (i) The TS for nucleophilic capture of **37** is electron rich, thus, the stabilizing double hyperconjugative interaction for F and $Sn(CH_3)_3$ in the *E*-configurated TS of the atom transfer processes is now enhanced and turned "off", respectively. In relation to the former possibility it is noteworthy that 4-fluorobicyclo[2.2.2]oct-1-yllithium readily fragments as a result of a powerful double hyperconjugative interaction between the C−F and C−Li bonds.[63e] The small but distinct syn- (or zu) facial preference for F (56/44) suggests that the competing electrostatic field influence is just managing to win out. (ii) The rate of capture of **37** (X = $Sn(CH_3)_3$ and F) maybe at, or close to, the diffusion limit.[123] Under these circumstances stereochemistry will be lost irrespective of the electronic character of the substituent.

IV. Conclusions

The overall picture painted in this brief review is that an appreciation of the nature of the electronic factor governing facial selectivity in reactions of 5-substituted (X) 2-adamantyl derivatives (**1**) requires consideration of both electrostatic and hyperconjugative effects. Either effect or both may be important depending on electron demand at the reaction center as well as the electronic character of the substituent. For example, diastereoselectivity data from reactions with electron deficient transition states of low electron demand appear to be reasonably well accommodated by an electrostatic field model. On the other hand, for reactions with transition states of increasing electron demand the appropriate model for describing π-facial selectivity depends importantly on the substituent type. Thus, hyperconjugation is clearly the dominant factor for σ-electron donor groups which usually have negligible polar field influences. However, the rationalization of selectivity results for σ-electron-withdrawing groups, the substituents which usually make up the basis set in most model system studies, necessitates consideration of both polar field and hyperconjugative effects. What is abundantly clear is that the idea that

transition-state hyperconjugation is the only component of the electronic factor controlling face selection of addition reactions in **1** is overly simplistic. There is much evidence to suggest that this is indeed the case for other conformationally constrained systems as well.

Central to reaching the aforementioned conclusions has been information gleaned from model system studies in which magnetically active nuclei (carbon-13 and fluorine-19) have been deployed as sensitive electronic probes. The most crucial aspects of substituent effects given definition by these studies are as follows: (i) The polar field effects of alkyl, metalloidal, and para-substituted phenyl groups (p-SC_6H_4) have been unambiguously characterized by the accurate determination of σ_F values. (ii) The long-range electronic influence of p-SC_6H_4 groups relative to phenyl (S = H) has been demonstrated to be due to a composite electrostatic field interaction. This result has important ramifications concerning the origin of diastereoselectivity data obtained from model system studies based on the electronic influence of p-SC_6H_4 groups. The obvious corollary is that Cieplak's model is not applicable to such situations. We have drawn attention to this point in the text in connection with nucleophilic additions to **5**.[8] However, this also holds for similar studies of other reaction types (*cis*-dihydroxylation[124] and epoxidation[125] of alkenes as well as Diels−Alder cycloaddition[126]). (iii) The recognition that ^{19}F chemical shifts of alkyl fluorides respond sensitively to the extent of delocalization of electrons into the σ^*-orbital of the C−F bond has allowed these parameters to provide useful information on through-bond effects in saturated systems. In this regard, their use has shown that long-range polar σ-inductive effects can be transmitted efficiently by a conjugative mechanism provided the intervening bonds are rigidly aligned in an antiperiplanar array. This has led to a revival of the concept of double hyperconjugation which is particularly important for σ-electron donor substituents in reactions proceeding via electron-deficient transition states of high electron demand. (iv) Alkyl groups have been shown to be σ-electron-withdrawing relative to hydrogen, i.e., a C−H bond is a better donor than a C−C bond.

V. References

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