Electrostatic *vs.* orbital effects as stereoinductive factors in nucleophilic additions to the *endo*-substituted norbornan-7-one ring system

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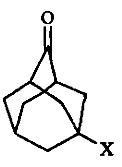
Polar-field susceptibility parameters as well as a ^{13}C NMR probe based on the transmission of polar substituent effects in *endo*-norbornan-7-ones points to the involvement of electrostatic effects in determining π-face selectivities during nucleophilic additions to this ring system.

The vexatious issue of the precise nature of the stereoelectronic factors that control π-face selectivities in nucleophilic additions to the carbonyl group has garnered much attention in recent years. Newer probe systems, particularly substrates with the carbonyl group in an isosteric environment, have been explored both experimentally and theoretically to assess the relative importance of orbital (hyperconjugative) *vs.* electrostatic effects in determining diastereoselectivity.[1] However, a definitive, consistent interpretation that accounts for all the observations is yet to emerge and this only underscores the need to address this issue further. Recently, one of us reported good linear correlations of the logarithm of the facial selectivities $\{\log_{10} [Z]/[E]\}$ *vs.* electrostatic field parameters ($\Delta\sigma_F$) for nucleophilic carbonyl additions (hydride reduction and methylation) of a diverse series of *para*-substituted 5-phenyladamantan-2-ones **1** ($X = p\text{-}YC_6H_4$).[1] The successful plots emphasize that facial selectivity induced at a remote reaction site by *para*-substitution in a phenyl ring is controlled by an electrostatic field effect and not by orbital interactions. Polar-field selectivity–susceptibility parameters (ρ_{FS}) were obtained from the Hammett-like plots which, when coupled with well-known polar field substituent constants (σ_F),[2] allowed the calculation of polar-field induced diastereoselectivities ($\log_{10} [Z]/[E] = \rho_{FS}\sigma_F$) of system **1** for a diverse range of groups.[1] A comparison of the calculated and observed facial selectivities led to the conclusion that it is unnecessary to invoke transition-state hyperconjugation in terms of Cieplak's model[3] to explain π-facial selectivity for the nucleophilic additions reactions of **1**. For the most part, the results appear to be predominantly accommodated by an electrostatic field model.[1]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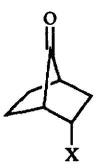
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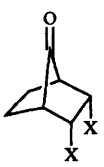
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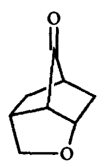
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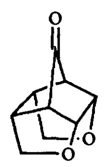
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Studies of face preferences for nucleophilic addition in 2-*endo*-substituted and 2,3-*endo*,*endo*-disubstituted norbornan-7-ones (**2** and **3**, respectively) by Mehta *et al.*[4] have revealed that the electronic factor of remote substituents in these sterically unbiased substrates is more pronounced than that showed in **1**. Consequently, because these systems (**2** and **3**) are significantly smaller than **1** and, therefore, more amenable to high-level MO calculations, the experimental data from these has become crucial for evaluating the various models employed for rationalizing and predicting face selectivity. Originally,[4a] the results of **2** and **3** were reconciled in terms of Cieplak theory[3] since the nucleophile seems to be directed antiperiplanar to the relatively electron rich C–C bonds. Subsequently, MO calculations of varying levels of sophistication point to the observed face selectivities in **2** and **3** being predominantly controlled by electrostatic effects.[4b,5] In an attempt to throw further light on the origin of the electronic factor determining the facial selectivities of **2** and **3**, we report herein the application of the aforementioned methodology of Adcock *et al.*[1] to these systems.

Table 1 Calculated polar-field induced π-facial selectivities[a] *vs.* observed product distributions for the reduction of some derivatives of **2** and **3**

			Observed[4,6]		Calculated	
System	X	σ_F[b]	%*E*	%*Z*	%*E*	%*Z*
2	CO_2CH_3	0.29	68	32	73	27
2	CN	0.54	88	12	87	13
2	C≡CH	0.28[c]	69	31	73	27
2	C_6H_5	0.17	45	55	64	36
3	$CH{=}CH_2$	0.14[c]	36	64	73[d]	27[d]
3	CO_2CH_3	0.29	84	16	88[d]	12[d]

[a] $\log [Z]/[E] = \rho_{FS}\sigma_F$; $\rho_{FS} = -1.513$. [b] σ_F ($\equiv\sigma_I$) values for CH_3OH taken from ref. 2(*a*). [c] $CDCl_3$ taken from ref. 9. [d] Calculations based on additivity of substituent effects.

Face preference data for the reduction ($NaBH_4$) of the 2-*endo*-phenyl and 2-*endo*-*p*-nitrophenyl derivatives of **2** have been determined [*Z*(alcohol)/*E*(alcohol) = 55/45 (**2**, $X = C_6H_5$) and 42/58 (**2**, $X = p\text{-}NO_2C_6H_4$)],[6] thus, by means of eqn. (1), defined by the successful selectivity correlations for p-YC_6H_4 groups in system **1**,[1] the ρ_{FS} value for the reduction of substituted norbornan-7-ones (**2** and **3**) can be calculated ($\rho_{FS} = -1.513$). Although ideally the determination of a ρ_{FS} value in the manner previously employed for system **1** requires facial selectivity data for several *para*-substituted phenyl derivatives **2** ($X = p\text{-}YC_6H_4$), it is doubtful whether this time-consuming correlation refinement would significantly improve the precision of ρ_{FS} for **2** given that the $p\text{-}NO_2C_6H_4$ group has the largest known $\Delta\sigma_F$ value (0.15).[1] The calculated polar-field induced π-facial selectivities together with the experimentally observed product distributions are listed in Table 1. It can be seen that there is good agreement between the calculated and

$$\log_{10}([Z]/[E])p\text{-}YC_6H_4 - \log_{10}([Z]/[E])C_6H_5 = \rho_{FS} \times \Delta\sigma_F \quad (1)$$

Table 2 Calculated[a] *vs.* observed ^{13}C SCS ($CDCl_3$)[b] for some derivatives of **2** and **3**

System	X	σ_F	Observed[c]	Calculated
2	CO_2CH_3	0.26	−2.84	−2.63
2	CN	0.56	−5.31	−5.67
2	C≡CH	0.28[d]	−1.67	−2.84
2	C_6H_5	0.17	−0.47	−1.72
2	*p*-$NO_2C_6H_4$	0.32	−1.99	−3.24
3	CH=CH_2	0.14	−1.13	−2.84[e]
3	CO_2CH_3	0.26	−5.72	−5.27[e]

[a] ^{13}C SCS = $\rho_F\sigma_F$; $\rho_F = -10.13$. [b] Negative sign implies shielding. X = H δ 216.20 relative Me_4Si ($CDCl_3$). [c] $CDCl_3$ taken from refs. 4(*a*) and 6. [d] Taken from ref. 9. [e] Calculation based on additivity of substituent effects.

observed results for the three most polar substituents (CN, CO_2CH_3 and C≡CH). This result points strongly to electrostatic effects as the controlling element of the stereoselectivity induced by these groups in this system and that a minor orbital contribution, if any, is only further reinforced. Hence the predictions of MO calculations,[4b,5] particularly those at the higher level,[5] are corroborated. However, it can also be seen (Table 1) that the calculated polar field-induced facial selectivities for the vinyl and phenyl groups are not in agreement with the experimental trends.[4a,6] This suggests that an additional factor is operating for these fairly weak polar groups which induces facial selectivities opposite to the electrostatic steering effect. Either torsional strain phenomena[7] or orbital effects[4a] (or both) are distinct possibilities.

An extension of the aforementioned methodology to facial selectivity data recently reported for two cyclic derivatives of norbornan-7-one (**4** and **5**)[4c] is possible by, first of all, determining σ_F values for the heterocyclic rings from appropriate ^{13}C substituent chemical shift (SCS) data. A polar field susceptibility parameter (ρ_F) for the carbonyl ^{13}C SCS of norbornan-7-ones may be determined by dividing the chemical shift difference between *p*-$NO_2C_6H_4$ and C_6H_5 for system **2** (X = *p*-$NO_2C_6H_4$ and C_6H_5, see Table 2) by $\Delta\sigma_F$ (0.15)[1] for these substituents. The validity of this technique for SCS of carbon centres has been previously substantiated.[8] The large ρ_F value (−10.13) indicates that polarization of the π electrons of the CO linkage ($C^{\delta-}$=$O^{\delta+}$) by a direct field effect[8] is significant for substituted norbornan-7-ones and, in particular, more pronounced than that observed for **1** ($\rho_F = -9.27$).[1] The latter observation was expected based on angle and distance considerations of **2** *vs.* **1**. By use of ρ_F (−10.13) and the appropriate ^{13}C SCS data of **4** and **5** (−3.10 and −8.82 ppm, respectively), which are based on the chemical shift differences between the carbonyl carbons of **4** and **5** (δ 213.07 and 208.42, respectively) and **2** and **3** (X = C_2H_5; δ 216.17 and 217.24, respectively). σ_F Values for the heterocyclic ring in **4** and **5** can be calculated (0.31 and 0.87, respectively). These values should be valid measures of the electrostatic field influence of the C–O bonds given that magnetic contributions to the ^{13}C SCS by the oxygen centres are expected to be small. In this connection it is worth noting that there is reasonably good agreement between the calculated and observed ^{13}C SCS for the CO_2CH_3 and CN substituents in **2** and **3** (Table 2). Note, however, that this situation does not hold for the other groups (C≡CH, CH=CH_2, C_6H_5 and *p*-$NO_2C_6H_4$) which are probably associated with magnetic perturbations of the chemical shift. This is not surprising given that it is known that the C≡CH group can contribute significant magnetic contributions to SCS of proximate NMR probe centres.[10] For example, Taft's fluorophenyl tag provides a much smaller σ_F value (0.15)[10] than that (0.28) determined from the ^{13}C SCS of remote probe centres (*para*-carbon in 1-substituted 4-phenylbicyclo[2.2.2]-octane)[9] or by chemical reactivity methods.[10] Interestingly, the anomalous σ_F value of 0.15 for C≡CH gives a calculated SCS (−1.52 ppm) for **2** which is in good agreement with the observed result (−1.67 ppm; see Table 2). This appears to confirm a magnetic contribution to the shift in **2** for C≡CH.

A comparison of the calculated polar-field induced π-facial selectivities [*Z*(alcohol)/*E*(alcohol)] of **4** and **5** (25/75 and 5/95, respectively) and the observed values [35/65 and <15/>85, respectively][4c] again highlights the role of electrostatic effects in determining facial selectivity in these systems. Most importantly, it corroborates the recent results of *ab initio* calculations on realistic transition structures for these systems but not MNDO calculations on model transition states.[4c] Both sets of calculations predict the correct preference in selectivity for the $NaBH_4$ reduction of **4** and **5**. However, whereas the rigorous *ab initio* calculations suggest electrostatic effects are primarily responsible, the MNDO results point to the consideration of orbital effects.[4c]

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