PERKIN 1 COMMUNICATION

Nucleophilic additions to 4-substituted snoutanones: getting a measure of long range electrostatic and orbital control of π-face selectivity

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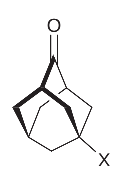
Pentacyclic ketones 10a–e (snoutan-9-ones) undergo nucleophilic additions with the same facial preference as the corresponding norsnoutanones 9a–e, but with markedly reduced selectivity, revealing the involvement of electrostatic effects in the former and implying the importance of hyperconjugative orbital interactions in determining π-face selectivity in the latter systems.

Control of π-face selectivity during nucleophilic additions to the carbonyl group is a core issue in stereogenesis. Recent studies with model systems, in which the carbonyl group is virtually in an isosteric environment, have demonstrated the importance of long range electronic effects in determining diastereofacial selectivity.[1] While the induction of facial selectivity through electronic perturbation by remote substituents has been unequivocally established, the precise nature of the electronic effects has remained contentious.[1–5] Hyperconjugative interactions at the transition state (Cieplak effect)[5] and electrostatic field effects[4,6,7] are the most commonly proffered explanations to account for the observed face-selectivities. In order to unravel the relative contributions of these factors, we[3] as well as others[2,4] have systematically examined, using experiment and theory, stereoinduction in several remotely functionalized and sterically unbiased ketones *e.g.* **1**–**8** in the past few years. Thus,



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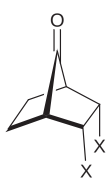

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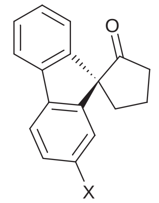

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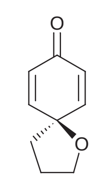

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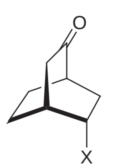

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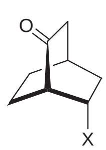

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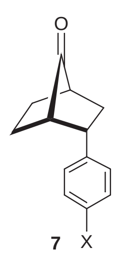

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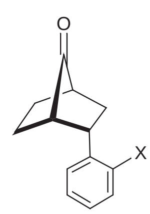

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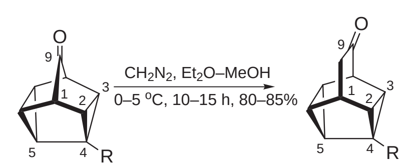
the Cieplak effect has been invoked to account for the observed selectivities in systems like 5-substituted adamantanones **1**[1,2] and *endo*-substituted norbornanones **2**,[3a,b] while electrostatic effects have also been implicated to explain the same results.[6,7] Additional studies by us on nucleophilic additions to monosubstituted bicyclo[2.2.2]octanones **5** and **6**,[3c] wherein the facial preferences were found to be similar, whether or not the substituent was ideally placed to transmit hyperconjugative interactions, have confirmed the role of electrostatic interactions in modulating face-selectivity.

While the Cieplak effect is manifested through orbital involvement, our recent work[3c,d] has shown that the electrostatic effects can operate in two ways: the approaching nucleophile can have a through-space interaction directly with the substituent and/or interact with the *exo*-face polarized by the substituent. Proof for the direct substituent–nucleophile field effect was obtained[3d] through face selectivity observed in *endo*-arylnorbornanones **7** and **8** in which the selectivity was found to be sensitive to the *ortho*- or *para*-location of polar substituents. We have further examined[3e] face-selectivities in 4-substituted norsnoutanones **9** in which substituent–nucleophile field effects are ruled out due to distal disposition (four-bond separation) of the substituent and the stereoinduction centre. The derivatives of **9** yielded facial preferences consistent with the Cieplak hyperconjugative model, although attractive interactions between the nucleophile and the polarized *exo*-face also seemed to contribute. In order to segregate these two effects, we have employed the corresponding snoutanone derivatives **10** as incisive diagnostic probes and investigated face selectivities during nucleophilic additions. The results are interpreted with the aid of *ab initio* level transition-state calculations.

The 4-substituted pentacyclo[$4.4.0.0^{2,4}.0^{3,8}.0^{5,7}$] decan-9-ones (snoutanones) **10a**–**e** are not known in the literature and were synthesized from the corresponding norsnoutanones **9a**–**e**[3e] *via* a diazomethane mediated ring expansion protocol, Scheme 1.



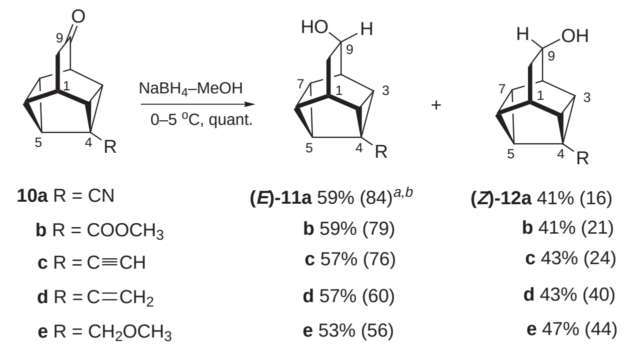
9a–e **10a–e**

Scheme 1

The ketones **10a**–**e** were subjected to reduction with sodium borohydride in order to directly compare the results obtained earlier[3e] with **9a**–**e**. In each case, (*E*)- and (*Z*)-alcohols **11a**–**e** and **12a**–**e**, respectively, were obtained in near quantitative yield. The observed diastereoselectivities were estimated from ^{1}H NMR integrations and are presented in Scheme 2. The stereostructures **11a**–**e** and **12a**–**e** have been unambiguously deduced on the basis of relative shielding (*ca.* 4–5 ppm) of the carbon resonances of C-7 in the (*E*)-series and C-3 in the (*Z*)-series due to the *syn*-transannular γ-shielding effect induced by

Table 1 Calculated total energies and relative energies (data using the charge model in parentheses) for the *syn* and *anti* LiH addition transition states for **9a** and **10a**

	10a		**9a**	
	anti	*syn*	*anti*	*syn*
HF/6-31G(d)//HF/3-21G				
Total energy (Hartree)	−559.048 62	−559.049 31	−519.988 02	−519.989 47
Relative energy (kJ mol^{-1})	1.8 (2.2)	0.0 (0.0)	3.8 (1.7)	0.0 (0.0)
MP2/6-31G(d)//HF/3-21G				
Total energy (Hartree)	−560.810 01	−560.810 56	−521.617 34	−521.618 99
Relative energy (kJ mol^{-1})	1.5 (1.9)	0.0 (0.0)	4.2 (2.1)	0.0 (0.0)



Scheme 2 [a] Values in parentheses indicate E:Z ratios for hydride additions to norsnoutanones **9a**–**e**. [b] Ratios based on ^{1}H NMR integrals of crude mixture (±5%).

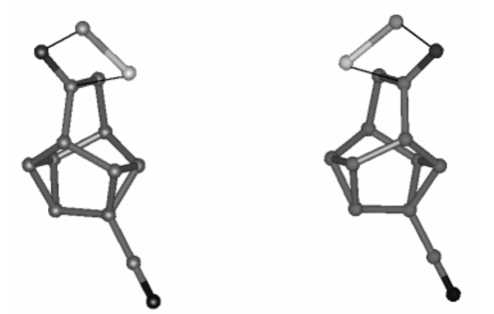
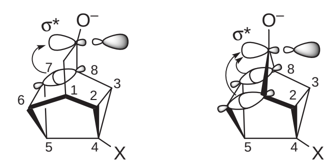


Fig. 1 HF/3-21G optimised transition state geometries for *syn* (left) and *anti* (right) face addition of LiH to **10a**



13 **14**

the C-9 hydroxy groups. Other spectral parameters (^{1}H and ^{13}C NMR) for (E)-**11a**–**e** and (Z)-**12a**–**e** are in full agreement with these assignments.

All the substituents examined prefer *syn*-face attack by the nucleophile, Scheme 2. However, the selectivities are uniformly low (*cf.* **9**),[3e] with little variation over the range of substituents examined. The results suggest very small differences in activation barriers for the *syn* and *anti* approaches and are in marked contrast to those obtained for the corresponding norsnoutanones.[3e] For example, the product ratio was 84:16 in favour of the (E)-alcohol (*syn*-approach) for the reduction of the cyano substituted **9a**, while it is 59:41 for **10a**. Electrostatic interactions between the approaching nucleophile and the *exo*-face hydrogen atoms should favour *syn* attack in both snoutanones **10** and norsnoutanones **9**. In the latter, the nucleophile interacts with two hydrogen atoms (C-2H and C-3H), but the line of approach to C-9 is midway between the C2–C3 bond. In snoutanones **10**, only one hydrogen (C-3H) can interact effectively, but it is closer to the approaching nucleophile. Therefore, the overall magnitude of the electrostatic attraction on the *syn*-face may be expected to be comparable in the two sets of substrates derived from **9** and **10**. On the other hand, a difference in selectivity is predicted within the Cieplak orbital model.[5] The C-4 substituents examined are inductively electron withdrawing, to varying extents. Since the σ* orbital of the newly formed bond would gain greater stabilization if it is antiperiplanar to the relatively electron rich C–C bond, *syn*-approach is predicted for the substrates **9a**–**e** and **10a**–**e**. In **10a**–**e**, the hyperconjugative facial discrimination is achieved with the Cieplak effect operating only through the C7–C8 bond (see **13**). In the norsnoutanone derivatives **9a**–**e**, the substituent weakens the donor ability of two (C1–C2 and C3–C8) bonds, and thus greater stabilization occurs for *syn*-face addition due to the interaction between the σ* orbital of the newly formed bond and the antiperiplanar C1–C6 and C7–C8 bonds (see **14**). The lower selectivity observed in snoutanones **10** can therefore be attributed to reduced orbital control compared to that in norsnoutanones **9**.

The foregoing interpretations have been quantitatively assessed using *ab initio* calculations.[8] The transition states for *syn* and *anti* addition of LiH to **10a** were optimized at the HF/3-21G level (Fig. 1). The structures have vanishing energy gradients and have one imaginary vibrational frequency corresponding to the addition reaction coordinate. These geometries which resemble LiH addition transition states computed earlier [3e,7] were employed in higher level calculations using HF and MP2 methods with the larger 6-31G(d) basis set. At all levels, addition from the *syn*-face is correctly predicted to be preferred (Table 1). The computed relative energies are lower than those obtained for 4-cyanonorsnoutanone, **9a**, consistent with the experimental trend. The selectivity resulting from electrostatic effects was estimated using a procedure employed earlier.[3e,7] The energies of the transition state structures were computed by replacing the LiH unit by a partial negative charge at the hydrogen site (corresponding to the Mulliken charge of the atom at the transition state). These data suggest that electrostatic interactions are nearly of the same magnitude in both **9a** and **10a** for addition transition states. Thus, calculations fully complement the qualitative reasoning proposed above.

In summary, our results indicate that face selectivities observed in snoutanones **10a**–**e** are primarily due to electrostatic factors and additionally reaffirm our earlier surmise that orbital interactions contribute significantly in determining *syn*-face selectivity in norsnoutanones **9a**–**e**.

Experimental

General procedure for diazomethane ring expansion of pentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonan-9-one (norsnoutan-9-one) derivatives 9a–e to pentacyclo[4.4.0.0^{2,4}.0^{3,8}.0^{5,7}]decan-9-one (snoutan-9-one) 10a–e

To a solution of norsnoutanone derivatives **9a**–**e** (0.5 mmol) in dry diethyl ether (6 cm^3) containing methanol (0.6 cm^3) was added an excess of an ethereal solution of diazomethane at 0 °C. The reaction mixture was allowed to stand in the dark at 0–5 °C for 10–15 h and monitored by TLC. Excess of diazomethane was destroyed (acetic acid) and the residue obtained on evaporation of the solvent was filtered through neutral alumina to afford pure ketones **10a**–**e** in 80–85% yield. The ketones were fully characterized. Selected spectral data: δ_C(50 MHz, $CDCl_3$); **10a**: 210.3, 119.0, 47.6, 40.7, 40.4, 36.6, 34.9, 32.0, 31.6, 31.4, 27.3. **10b**: 212.1, 171.5, 51.8, 47.6, 45.8, 42.3, 41.9, 37.3, 34.5, 31.0, 30.9, 28.8. **10c**: 212.6, 83.0, 68.3, 48.0, 40.8, 40.7, 37.3, 35.0, 33.8, 32.0, 31.2, 31.1. **10d**: 213.7, 136.6, 112.0, 48.1, 47.0, 39.7, 39.2, 37.9, 35.0, 31.0, 30.8, 30.7. **10e**: 214.1, 72.4, 58.5, 47.9, 44.2, 37.9, 35.5, 35.4, 34.9, 31.5, 31.2, 31.1.

General procedure for sodium borohydride reduction of 10a–e

A solution of the ketones **10a**–**e** (0.5 mmol) in dry methanol (3 cm^3) was cooled in an ice-bath and sodium borohydride (0.5 mmol) was added. The reaction mixture was stirred for 15–30 minutes, until the starting ketone was fully consumed (TLC). Methanol was removed at rt and the residue was diluted with water (4 cm^3). The aqueous layer was extracted with ethyl acetate (3 × 5 cm^3) and the combined organic layer was washed and dried. Removal of solvent furnished the mixture of *syn*-**12a**–**e** and *anti*-**11a**–**e** alcohols in quantitative yield. The product ratios were determined by ^{1}H NMR analysis (±5%) of the crude reaction mixture by comparing the integrations of appropriate protons. The diastereomeric alcohols were separated in each case by chromatography on alumina and duly characterized (IR, ^{1}H and ^{13}C NMR, analysis or MS). Selected spectral data: δ_C(50 MHz, $CDCl_3$); **11a**: 120.4, 65.8, 40.5, 39.8, 38.6, 31.8, 31.2, 29.9, 27.3, 25.1, 23.9. **12a**: 120.8, 66.1, 40.2, 38.7, 36.4, 32.0, 31.3, 30.4, 29.5, 28.7, 22.7. **11b**: 172.8, 66.5, 51.6, 42.6, 42.4, 41.7, 38.5, 32.5, 31.0, 29.4, 24.3, 23.9. **12b**: 173.4, 66.8, 51.6, 42.2, 41.5, 38.7, 37.8, 32.8, 31.1, 29.8, 29.0, 25.4. **11c**: 84.8, 66.9, 66.4, 40.5, 39.8, 38.8, 32.5, 31.3, 29.6, 29.2, 28.4, 24.5. **12c**: 85.1, 67.2, 66.7, 40.2, 38.9, 35.6, 32.6, 31.4, 30.6, 30.1, 29.3, 27.2. **11d**: 138.3, 110.6, 67.0, 43.6, 39.1, 38.9, 38.5, 33.0, 31.4, 29.4, 25.7, 24.1. **12d**: 138.6, 110.5, 67.1, 42.3, 38.9 (2C), 33.9, 33.1, 31.3, 29.9, 29.1, 26.9. **11e**: 73.3, 67.0, 58.5, 40.6, 38.7, 34.8, 34.2, 33.1, 31.2, 29.8, 26.8, 24.4. **12e**: 73.6, 67.0, 58.5, 39.3, 38.7, 34.3, 33.0, 31.2, 30.2, 29.5, 29.2, 28.1.

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