Importance of Orbital and Electrostatic Interactions in Determining π-Facial Selectivities in Nucleophilic Additions to *endo*-Substituted Bicyclo[2.2.2]octan-2-ones

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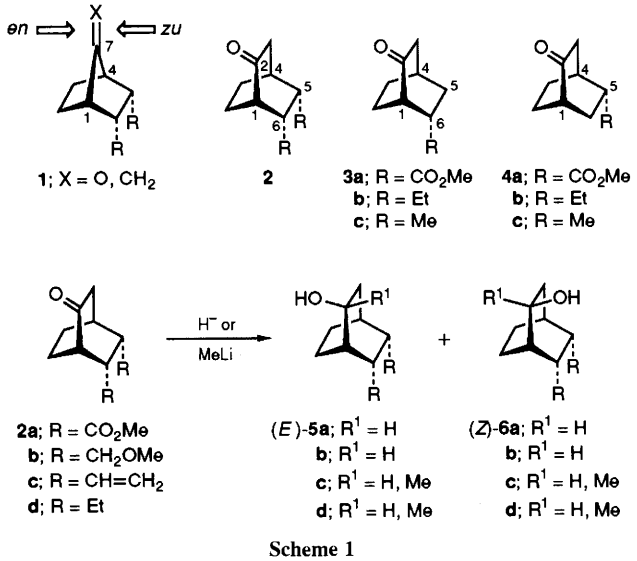
The diastereoselectivities in nucleophilic additions to bicyclo[2.2.2]octan-2-ones can be modulated by distal *endo*-substituents; both orbital and electrostatic interactions contribute to the observed stereoselectivity.

Evaluation of various factors that can control the π-face selectivities in additions to trigonal carbon atoms is currently a subject of animated discussion.[1] In order to segregate electronic and steric components and to remove conformational uncertainties, it is essential to study rigid sterically unbiased substrates which can be electronically perturbed through distal modifications.[2] Recently, we demonstrated that π-face selectivities in additions to norbornan-7-ones **1** can be controlled (*zu* face preference when R = CO_2Me and *en* face when R = Et) by the remote 2,3-*endo,endo*-substituents.[3–5] To gauge further the generality of these observations, we have investigated nucleophilic additions to the 5,6-*endo,endo*-bicyclo[2.2.2]octan-2-ones **2**. While retaining the desirable features of **1** for evaluating electronic factors in π-face selection, the bicyclo[2.2.2]octane system provides an additional handle to probe the role of orbital interactions. The mono-*endo*-substituted derivatives **3** and **4** enable a critical assessment to be made of the hyperconjugative model of π-facial selectivity.[1,6,7] Herein we report the results of nucleophilic additions to the series of bicyclic ketones **2–4**.

5,6-*endo,endo*-Disubstituted bicyclo[2.2.2]octan-2-ones **2a–d** were prepared from the corresponding norbornan-7-ones[3a] *via* diazomethane mediated (Et_2O–MeOH, 0–5 °C, 10–24 h, *ca.* 50%) ring expansion protocol.†‡ The ketones **2a–d** were subjected to hydride reduction with $NaBH_4$ and DIBAL-H (diisobutylaluminium hydride) and methylation with MeLi to furnish (*E*)-**5a–d** and (*Z*)-alcohols **6a–d** (Scheme 1) in near quantitative yield.‡ The diastereoselectivities (*E*:*Z*) are presented in Table 1. The stereostructures **5a–d**, **6a–d** have been unambiguously deduced on the basis of (*a*) the relative deshielding (0.3 ppm) of the *exo*-6-H proton in (*Z*)-alcohols **6a–d** compared to (*E*)-alcohols **5a–d** and (*b*) relative shielding (4–6 ppm) of the C-6 resonance in the (*Z*) series and of C-7 in the (*E*) series.



Scheme 1

The data in Table 1 clearly indicate that the remote *endo*-substituents have a profound bearing on the face-selectivity in nucleophilic additions to **2**. For example, the *zu* face preference in **2a** is completely reversed in favour of *en* face addition in **2d**. On the other hand, the *endo*-substituents like methoxymethyl (**2b**) and vinyl (**2c**), with relatively modest inductive contribution, exhibit no facial bias (*cf.* **1**).[3] These results are generally consistent with those obtained for the norbornyl derivatives **1**, and can be reconciled in terms of the Cieplak model.[6] Thus, for **2a** with electron-withdrawing substituents, hyperconjugation from the more electron rich C(1)–C(7) σ bond favours the *zu* approach of the nucleophile, as shown in **7**. On the same basis, the donor groups in **2d** lead to preferential addition to the *en* face.

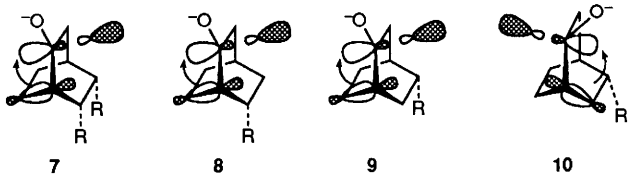
The hyperconjugative model leads to the prediction of preferential *zu* face addition for the mono-substituted ketone **3a**, as shown in **8**, and no facial preference in the regioisomeric ketone **4a**, as neither of the two vicinal [C(1)–C(6) and C(1)–C(7)] σ bonds is perturbed by the C-5 substituent (see **9** and **10**). However, both **3a** and **4a** exhibit a moderate *zu* selectivity when subjected to $NaBH_4$ (*E*:Z ratio of 65:35 in **3** and 62:38 in **4**) and DIBAL-H (*E*:*Z* ratio of 66:34 in **3** and 61:39 in **4**) reduction. Thus, there is little difference in the face selectivity whether the *endo*-substituent is at the 'on' or the 'off' position for orbital interactions.

To unravel the origin of the observed face selectivites, we employed a simple computational model.[5,8] First, the geometries of the substrates were optimized at the MNDO level.[9] To probe the role of electrostatic effects, a test negative charge was placed above the carbonyl carbon atom orthogonal

Table 1 Product ratios in nucleophilic additions to **2a–d**

	E:*Z* ratio[a]		
Substrate	$NaBH_4$[b]	Bu^i_2AlH[c]	MeLi[d]
2a	70:30	67:33	—
	5a 6a	**5a 6a**	
2b	52:48	—	—
	5b 6b		
2c	50:50	50:50	54:46
	5c 6c	**5c 5c**	**5c**, R^1 = Me **6c**, R^1 = Me
2d	39:61	35:65	34:66
	5d 6d	**5d 6d**	**5d**, R^1 = Me **6d**, R^1 = Me

[a] Ratios based on ^1H NMR integration of the total mixture (±5%). [b] Reduction in methanol at 0–5 °C, until the starting ketone was consumed (TLC). [c] In toluene–CH_2Cl_2 at −78 °C. [d] In diethyl ether at −15 °C.



† *endo*-Substituted bicyclo[2.2.2]octan-2-ones are difficult to obtain by direct synthesis and are conveniently accessed *via* ring expansion of norbornan-7-ones.

‡ All new compounds were fully characterised on the basis of spectral/analytical data.

to the π plane, at a typical interaction distance of 1.4 Å. The computed energy difference with the charge on either face of the carbonyl group is indicative of the preference induced by electrostatic effects. A similar calculation with a test nucleophile, H^-, leads to a prediction which effectively incorporates orbital interactions also.

A point negative charge placed at the *zu* face of the carbonyl unit in **3a** is computed to be less favourable than the alternative *en* face approach by 3.3 kcal mol^{-1} (1 cal = 4.184 J). However, in the hydride model, the preference is reversed, making the *zu* face interaction more attractive by 0.6 kcal mol^{-1}, in agreement with the experimental product ratio. Thus, hyperconjugative interactions involving the electron rich C–C σ bond have to overcome unfavourable electrostatic interactions to effect the observed face selectivity.

In **4a**, the electrostatic contribution favours the *zu* face attack (1.4 kcal mol^{-1}). Use of the hydride ion as a probe yields essentially the same energy preference, confirming the absence of face-selective hyperconjugative interactions in this system. Overall, the selectivity remains similar to that observed for **3a**.

The computed charge distributions provide a clue to the reversal of the electrostatic preference for **3a** and **4a**. The ester group produces significant positive charges at C-5, C-6 and the *exo* hydrogen atoms in both **3a** and **4a**, leading to favourable interaction with a negative charge near the *zu* face. However, a large build-up of negative charge on the ester oxygen atoms leads to considerable repulsion in **3a** relative to **4a**. Calculations on **3b** and **3c** show that charge interactions with the alkyl groups are repulsive. The resulting *en* face preference is further reinforced by orbital interactions. In contrast, no facial preference is computed with the charge and the hydride models for **4b**,**c**, confirming that both electrostatic and orbital interactions are unimportant in these substrates.

In summary, *endo* substituents do modulate π-facial selectivity in the nucleophilic addition to the bicyclo[2.2.2]octan-2-one derivatives. While the majority of results can be reconciled exclusively within the Cieplak model, the facial preferences observed in mono-substituted ketones point to the presence of additional factors. Model calculations reveal the presence of significant electrostatic contributions from electron withdrawing groups to face selectivity.[1c,10] Competing electrostatic and orbital effects as suggested for **3a** may be responsible for many apparent failures of Cieplak stereoelectronic theory.[11]

Received, 25th June 1992; Com. 2/03357G

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