π-Facial Diastereoselection in Reductions of Sterically Unbiased Ketones Containing the Norbornyl Framework: Further Tests for Theoretical Models

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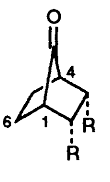
Ketones **3a–c** exhibit *syn*-face selectivity in borohydride reduction; MNDO and *ab initio* calculations on model and realistic transition states, respectively, reproduce the preference, but differ on the role of electrostatic and orbital effects.

We have recently demonstrated the profound influence of remote substituents in face selectivities of nucleophilic additions to 2,3-*endo*,*endo*-disubstituted norbornan-7-ones **1**[1a] as well as *endo*-mono and *endo*,*endo*-disubstituted bicyclo[2.2.2]octanones **2**.[1b] The observed trends in these and numerous other sterically unbiased substrates could be reproduced using a remarkably simple computational procedure based on the MNDO method and model transition states.[1d] While the dominant role in determining face selectivity was assigned to electrostatic effects, orbital interactions[2] were also suggested to be manifest in some cases.[1] On the other hand, *ab initio* calculations on realistic transition states on some norbornyl derivatives have been interpreted exclusively on the basis of electrostatic effects.[3] Further, the validity of the MNDO model was questioned on account of its failure to reproduce the face-selectivity in norbornenone.[3b] We now report an experimental study of face selectivity in the reductions of another set of sterically unbiased ketones, **3a–c**, with mild electronic perturbation and assess the theoretical models.



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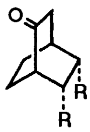
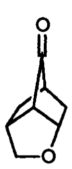


2

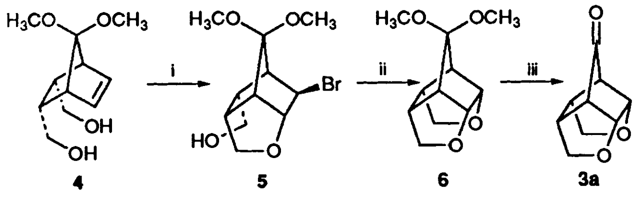
3a



3b

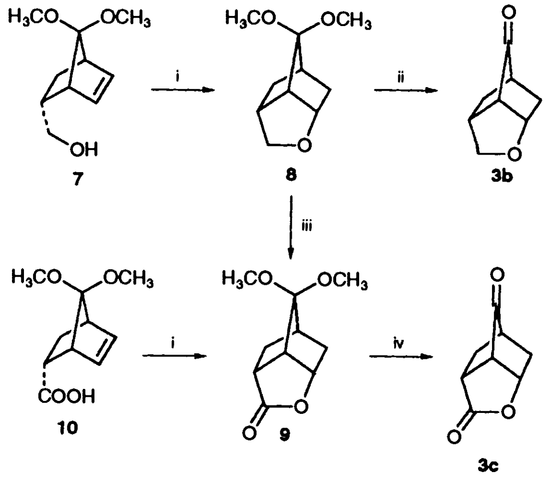
3c

The polycyclic ketones **3a–c** were synthesized as shown in Schemes 1 and 2.[4–7] Reduction of ketones **3a–c** with $NaBH_4$ furnished a mixture of diastereoisomeric *syn*-**11a–c** and *anti*-**12a–c** alcohols† in high yield, Scheme 3.



Scheme 1 *Reagents:* i, NBS–aq. acetone, RT, 12 h; ii, NaH–THF, reflux, 2 h; iii, Amberlyst-15–aq. acetone, reflux, 30 min

The ratios of the products were determined from the ^1H NMR integration of the crude reaction mixture. The diastereoisomeric pair of alcohols in each case was separated by column chromatography and fully characterized. The stereochemistry of the products in all the cases was determined unambiguously from the ^1H NMR spectra on the basis of greater deshielding of *exo*-methine protons attached to the oxygen atom in *syn*-**11a–c** alcohols compared with the corresponding *anti*-**12a–c** alcohols for which there is ample precedence.[1,8] The chemical shift values of these protons are indicated on the structures in Scheme 3.



Scheme 2 *Reagents:* i, $Hg(OAc)_2$–NaOH–$NaBH_4$, RT, 40 min; ii, Amberlyst-15–aq. acetone, RT, 6 h; iii, $RuCl_3$–$NaIO_4$–CCl_4–MeCN, H_2O; iv, H_2SO_4–DCM, RT, 4 h

These results can be readily reconciled in terms of the qualitative Cieplak hyperconjugative model.[2a] The inductive effect of the *endo* oxygen atoms in **3a** makes the C1–C6 and C4–C5 σ bonds more electron rich compared with the C1–C2 and C3–C4 bonds.‡ Therefore, nucleophile approach from the *syn*-face would be preferred in order to have a greater stabilizing interaction between the newly formed σ* orbital and the antiperiplanar electron rich σ bonds (see **13**). The corresponding product is the *anti*-alcohol **12a** formed predominantly (> 85%). The ketone **3b** with only one ether linkage at C2 also showed *syn*-preference with a reduced selectivity compared with **3a**. The lactone carbonyl in **3c** may be expected to compete with the electron-withdrawing effect of the oxygen atom, but may also enhance the inductive effect of the latter due to the contributing resonance structure shown in **14**. The two effects oppose each other and the net selectivity in **3c** is similar to that of the ether **3b**, Scheme 3.

MNDO calculations[9] on model transition states following the protocol proposed earlier[1c] are consistent with these interpretations. A point charge placed on either π face at a distance of 1.4 Å from the carbonyl carbon in the optimized structures of **3a–c** leads to energies with negligible facial preference (Table 1). However, when a hydride ion is used as the model nucleophile, a small but consistent *syn*-facial preference

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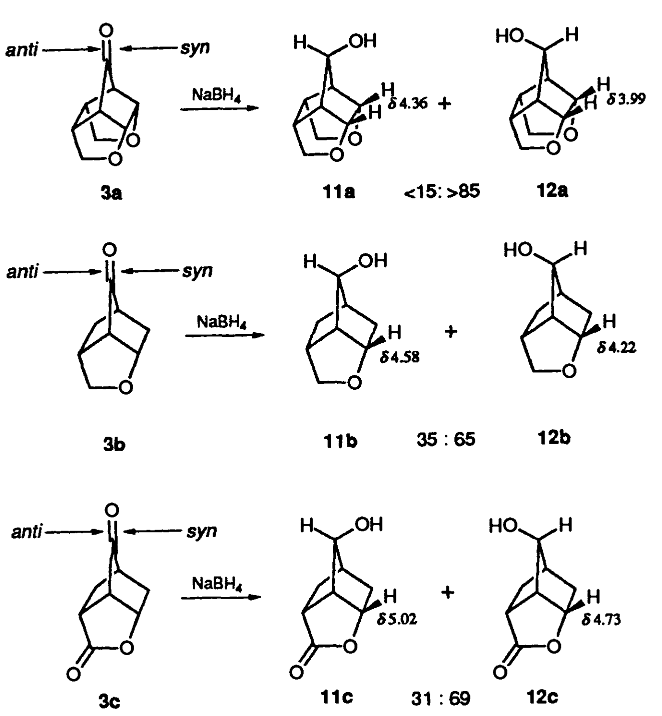
† For the sake of convenience, *syn* and *anti* terminology is used with reference to the C–O bond as indicated in Scheme 3.

‡ Carbon atom numbering corresponds to the norbornyl system.



Scheme 3

is obtained for all three substrates, in agreement with the experimental trends (Table 1). The results suggest that there is little facial bias in these substrates due to electrostatic interactions and the observed selectivity requires the consideration of orbital effects involving the newly formed bond.

Ab initio calculations on realistic transition structures were also examined.[10] The structures with vanishing gradients and Hessian of 1 for LiH addition to each of the two carbonyl π faces of **3a–c** were optimized with the 3–21G basis set.[11] The geometries were used in additional HF and MP2 calculations with the 6–31G* basis set. The energy differences are by and large consistent with the observed face selectivities (Table 1). Interestingly, almost the same energy differences are obtained in additional sets of calculations in which the LiH unit was replaced by a point charge (magnitude corresponding to the Mulliken values from HF/6-31G* wavefunctions). Precisely the same behaviour was noted in previous *ab initio* studies on norbornyl systems,[3] implying that electostatic effects are primarily responsible for the observed face selectivities.

Thus, the simple MNDO and more rigorous *ab initio* calculations predict the correct preference in selectivity but differ in interpretation. Therefore, further studies on additional sterically unbiased systems to isolate the contributions of orbital and electrostatic effects and critically to validate the computational models are indicated and efforts in that direction are underway.

Experimental

General Procedure for the $NaBH_4$ *Reduction of Ketones.*—A solution of the ketone (0.2 mmol) in dry MeOH (3 cm^3) was cooled (ice-bath) and sodium borohydride (0.2 mmol) was added. The reaction mixture was stirred for 15–30 min until the starting ketone was fully consumed (TLC). Methanol was removed at room temperature and the residue diluted with water (5 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). Removal of the solvent gave a mixture of *syn-* and *anti*-alcohols in quantitative yield which was separated by column chromatography. The product ratios were determined by ^1H NMR analyses of the crude reaction mixture. Selected spectral data: **11a**: δ_H(200 MHz; $CDCl_3$) 4.49 (1 H, s, >C*H*OH), 4.36 (2 H, br s, >C*H*–O–), 4.04 (2 H, $\frac{1}{2}$AB system, J = 9 Hz, –CH_2–O–), 3.70 (2 H, $\frac{1}{2}$AB system, J = 9 Hz, –CH_2O–) and 2.52 (4 H, br s); δ_C(50 MHz; $CDCl_3$) 78.12, 72.06, 69.00, 50.12 and 39.29; **12a**: δ_H(200 MHz; $CDCl_3$) 4.17 (1 H, s, >C*H*OH), 4.11 (2 H, $\frac{1}{2}$AB system, J = 9 Hz, –CH_2O–), 3.99 (2 H, dd, J_1 = J_2 = 2.2 Hz, >C*H*–O–), 3.78 (2 H, dd of $\frac{1}{2}$AB system, J_1 = 9 Hz, J_2 = J_3 = 1.8 Hz, –CH_2O–), 2.83 (2 H, br s) and 2.56 (2 H, m); δ_C(50 MHz; $CDCl_3$) 77.06, 69.24, 68.47, 51.23 and 39.53; **11b**: δ_H(100 MHz; $CDCl_3$) 4.58 (1 H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C*H*–O–), 4.26 (1 H, br s, >C*H*OH), 3.79 (1 H, d of $\frac{1}{2}$AB system, J_1 = 8 Hz, J_2 = 4 Hz, –CH_2O–), 3.61 (1 H, $\frac{1}{2}$AB system, J_1 = 8 Hz, –CH_2O–), 2.54–1.76 (5 H, series of m) and 1.34–1.00 (2 H, m); δ_C(25.0 MHz; $CDCl_3$) 80.53, 80.00, 75.00, 51.23, 38.70, 36.47, 36.17 and 35.59; **12b**: δ_H(100 MHz, $CDCl_3$) 4.22 (1 H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C*H*–O–), 4.01 (1 H, s, >C*H*OH), 3.76 (2 H, m, –CH_2O–), 2.76–2.04 (3 H, series of m), 1.92 (1 H, br s), 1.80–1.48 (1 H, m) and 1.32–1.06 (2 H, m); δ_C(25.0 MHz; $CDCl_3$) 79.18, 77.30, 74.18, 51.70, 38.94, 38.06, 37.41 and 34.47; **11c**: δ_H(200 MHz; $CDCl_3$) 5.02 (1 H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C*H*OCO–), 4.36 (1 H, br s, >C*H*OH), 3.11–3.02 (1 H, m), 2.63–2.28 (2 H, series of m), 2.13–1.97 (1 H, m) and 1.95–1.55 (3 H, series of m); δ_C(50.0 MHz; $CDCl_3$) 180.92, 81.48, 79.62, 50.51, 40.86, 37.32, 34.15 and 30.83; **12c**: δ_H(200 MHz; $CDCl_3$) 4.73 (1 H, dd, J_1 = 7 Hz, J_2 = 5 Hz, >C*H*OCO–), 4.26 (1 H, br s, >C*H*OH), 3.12 (1 H, m), 2.80 (1 H, dd, J_1 = 11 Hz, J_2 = 5 Hz), 2.59–2.43 (1 H, m), 2.31 (1 H, m) and 1.95–1.55 (3 H, series of m); δ_C(50.0 MHz; $CDCl_3$) 181.33, 78.44, 78.26, 51.27, 41.34, 38.40, 35.33 and 31.27.

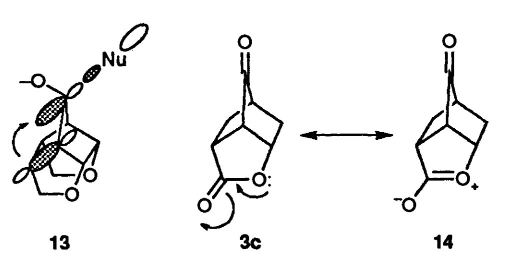


Table 1 Computed relative energies (kJ mol^{-1}) of model and realistic transition states (energies for the electrostatic model in parentheses)

	3a		3b		3c	
Method	*anti*	*syn*	*anti*	*syn*	*anti*	*syn*
Model TS						
MNDO	3.5 (0.0)	0.0 (0.8)	2.3 (0.8)	0.0 (0.0)	1.8 (0.0)	0.0 (0.4)
TS for LiH addition						
HF/3-21G	6.5	0.0	1.4	0.0	4.0	0.0
HF/6-31G*	5.7 (7.1)	0.0 (0.0)	1.1 (1.9)	0.0 (0.0)	4.1 (5.2)	0.0 (0.0)
MP2/6-31G*	2.9 (4.3)	0.0 (0.0)	0.0 (0.4)	0.7 (0.0)	3.9 (4.4)	0.0 (0.0)
Exptl. (at 25 °C)	4.3	0.0	1.5	0.0	2.0	0.0

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