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A Simple Computational Model for Predicting π-Facial Selectivity in Reductions of Sterically Unbiased Ketones. On the Relative Importance of Electrostatic and Orbital Interactions

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Various factors controlling the preferred facial selectivity in the reductions of a number of sterically unbiased ketones have been evaluated using a semiempirical MO procedure. MNDO optimized geometries do not reveal any significant ground-state distortions which can be correlated with the observed face selectivities. Electrostatic effects due to an approaching reagent were modeled by placing a test negative charge at a fixed distance from the carbonyl carbon on each of the two faces. A second series of calculations was carried out using the hydride ion as a test nucleophile. The latter calculations effectively include orbital interactions involving the σ and σ^* orbitals of the newly formed bond in the reaction. The computed energy differences with the charge model are generally much larger compared to those with the hydride ion. However, both models lead to predictions which are qualitatively consistent with the experimentally determined facial preferences for most of the systems. Thus, electrostatic interactions between the nucleophile and the substrate seem to effectively determine the face selectivities in these molecules. However, there are a few exceptions in which orbital interactions are found to contribute significantly and occasionally reverse the preference dictated by electrostatic effects. The remarkable success of the hydride model calculations, in spite of retaining the unperturbed geometries of the substrates, points to the unimportance of torsional effects and orbital distortions associated with the pyramidalized carbonyl unit in the transition state in most of the substrates considered. Additional experimental results are reported which provide useful calibration for the present computational approach.

Introduction

The possibility of inducing face selectivity in additions to trigonal carbon through remote electronic perturbation is currently being actively explored.[1,2] Subtle, but consistent, preferences have been determined in a number of carefully designed substrates in which the role of steric effects has been effectively eliminated. For example, face selectivities in nucleophilic additions have been obtained for remotely substituted adamantanones,[3,4] 7-norbornanones,[5] norbornenones,[6] benzonorbornenones,[7] cyclopentanones,[8] *trans*-decalones,[9] etc. The impressive volume of experimental data obtained in recent years provides a valuable testing ground for the numerous qualitative models[10,15] and quanitative studies[16–20] which have been employed for rationalizing and predicting face selectivity.

Two extreme theoretical approaches are now widely employed. In quantitative studies, the two possible transition state structures are precisely determined and the face selectivity is predicted from the corresponding energy difference.[21] Since the energy separation is usually very small, high-level ab initio calculations are needed for a reliable prediction. Many such successful studies have indeed been reported.[16–19] These studies have also led to

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(1) Review: Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199.

(2) For some leading references, see: (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (b) Fraser, R. R.; Stanciulescu, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 1580. (c) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (d) Macauly, T. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074. (e) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(3) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (b) Lin, M.-h.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155.

(4) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229.

(5) (a) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.*, **1990**, *112*, 6140. (b) Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006. (c) Mehta, G.; Khan, F. A. *J. Chem. Soc., Chem. Commun.* **1991**, 18. (d) Chasman, J. Ph.D. Thesis, University of Minnesota, 1978, private communication from Prof. Paul G. Gassman, (e) Present study, see footnote 38.

(6) Mehta, G.; Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065.

(7) (a) Okada, K.; Tomita, S.; Oda, M. *Tetrahedron Lett.* **1986**, *27*, 2645. (b) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459.

(8) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.

(9) Di Maio, G.; Migneco, L. M.; Vecchi, E. *Tetrahedron* **1990**, *46*, 6053.

(10) (a) Cram, D. J.; Abd Elfahez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. (c) Richer, J. C. *J. Org. Chem.* **1965**, *30*, 324.

(11) (a) Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86.

(12) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. (c) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656.

(13) (a) Klein, J. *Tetrahedron Lett.* **1973**, 4307. (b) Klein, J. *Tetrahedron* **1974**, 3349. (c) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. (d) Paquette, L. A.; Hsu, L.-Y.; Galluci, J. C.; Korp, J. D.; Bernal, I.; Kravetz, T. M.; Hatheway, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 5743.

(14) (a) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(15) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(16) (a) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (b) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (c) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (d) Wong, S. S.; Paddon-Row, M. N. *Aust. J. Chem.* **1991**, *44*, 765.

(17) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

(18) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. Preprint, kindly provided by Prof. Paddon-Row, and we thank him for the same.

(19) Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew, Chem., Int. Ed. Engl.* **1991**, *30*. 1146.

(20) Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353.

(21) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, J. *Science* **1986**, *231*, 1108.

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valuable insights concerning the contribution of different factors to the computed energy differences. While this rigorous approach would be the preferred alternative, especially in controversial systems, it cannot be used routinely. Precise determination of transition state structures is a nontrivial task. With certain models of nucleophiles, the potential energy surface may be flat or even lack a transition state.[16d,22]

Alternatively, numerous qualitative models have been advanced for interpreting the observed face selectivities. These include steric and torsional models emphasizing geometric features in the ground state as well as in the transition states,[10-12] orbital distortion effects,[13] electrostatic effects,[16] and different types of specific orbital interactions in the idealized transition states.[14,15] In a conformationally unconstrained substrate, the above factors may all be operative.[1] It has therefore been difficult to use the proposals unambiguously and to segregate the relative contributions of the various effects.

It is highly desirable to have an intermediate semiquantitative model for predicting face selectivity. The approach should lead to unambiguous and reliable results, be applicable to relatively large substrates, and also provide insights into the origin of observed preferences. With the above goals in mind, we propose a simple computational model, evaluate its validity on the basis of comparisons with experimental and ab initio results, and derive some general conclusions on the factors contributing to facial selectivity in the reductions of a number of sterically unbiased ketones.

Computational Procedure

To enable the study of a large number of experimentally studied substrates, the MNDO method was chosen for the computational model.[23] The structures of all the ketones were optimized without any symmetry constraints in order to identify potential ground-state geometric effects.

Next, the effect of electrostatic interactions involving the nucleophilic reagent was modeled by placing a test negative charge on either face of the carbonyl π unit at a distance of 1.4 Å from the corresponding carbon.[24] The angle of approach of the charge with respect to the carbonyl group was kept at 90°. Importantly, the geometry of the substrate was left unchanged. The preferred direction of reagent approach is predicted on the basis of the computed SCF energies in the presence of the charge.

It is important to emphasize that the charge model is not identical to the use of molecular electrostatic potential maps (MEPS). The latter is the most direct approach for modeling electrostatic effects and has indeed been successfully applied for a number of studies of regiochemical and facial selectivities in conjunction with both ab initio[25,26] and semiempirical methods.[27] However, the present procedure incorporates an additional effect. Since the wave functions are recomputed in the presence of the test charge, electronic reorganization within the substrate due to the approaching reagent is taken into account. Thus, the model includes polarization effects.

In another series of calculations, the nucleophile was represented by a hydride ion. The distance, orientation, and angle of approach were identical to those used in the previous charge model. Again, the substrate geometry was unaltered, and the computed relative energies were used to account for the observed face selectivity.

The hydride model should include the consequences of partial bond formation, besides electrostatic interactions. The presence of the hydrogen s orbital at a strongly interacting distance from the carbonyl carbon should lead to a high-energy C–H σ bond and a low-energy C–H σ* orbital. The model should incorporate the interactions of these orbitals with adjacent fragment orbitals. In particular, the two-electron stabilizing interactions critical to the Cieplak model (C–H σ* orbital with the vicinal antiperiplanar σ bond)[15] and the Anh–Eisenstein model (C–H σ orbital with the vicinal antiperiplanar σ* orbital)[14] are both effectively included in the present calculations. Even the four-electron destabilizing interaction should contribute to the SCF energy. Therefore, the hydride model should, in principle, lead to more reliable predictions than either of the two idealized hyperconjugative theories of face selectivity. The procedure also includes the preference dictated by electrostatic effects. Therefore, the predictions of the charge and the hydride models can be used to gauge the relative importance of orbital effects.

There are a number of apparently arbitrary assumptions in the above models. Of these, the chosen orientation for the approach of the nucleophile is relatively easy to justify. The reagent interacts predominantly with the carbonyl carbon. However, retaining the structural parameters of the ketone unchanged in the model transition state is indeed a gross approximation. The assumption was made to keep the computational model as simple as possible. The problem of determining the transition-state structures is avoided. In principle, the rehybridization of the carbonyl carbon could have been idealized on the basis of some ab initio structures. However, the substrates considered are complex polycyclic systems in which structural parameters are strongly coupled. Since we were keen to ensure that no facial bias of any kind was introduced by the assumptions in the model, a simplified procedure was preferred. The geometric assumption also has an interpretative value. Torsional interactions involving the sp^3 rehybridized carbon with adjacent groups are not taken into account in the present procedures. Further, orbital distortions associated with s,p mixing which have been proposed[13,19] to contribute to face selectivity are also not described. The role of these factors can be inferred from the present results.

The choice of the distance and angle of approach of the hydride ion was on the basis of preliminary optimizations on a few test systems. With the substrate geometry kept fixed, the structural parameters of the hydride ion were optimized. The optimized C–H distances were found to vary between 1.35 and 1.45 Å, while the H—C═O angle was around 91–94°. To keep the model simple, an idealized distance and angle were chosen. The same choice was made for the charge calculations to enable a direct comparison of the two sets of predictions.

The use of a full negative charge may lead to an overestimation of electrostatic interactions. Calculations using the present hydride model as well as previous

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[22] At PM3 and AM1 levels, transition states cannot often be determined for hydride addition to ketones. In ref 20, a methanol molecule had to be used as a model nucleophile to obtain transition-state structures.

[23] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

[24] The "sparkle" option of the MOPAC program was used.

[25] (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7382. (b) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399.

[26] Sjoberg, P.; Politzer, P. *J. Phys. Chem.* **1990**, *94*, 3959.

[27] Broughton, H. B.; Green, S. M.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 998.

results[18] on realistic transition structures yield a Mulliken charge of around −1/2 on the nucleophile. However, the present study is aimed at only a qualitative prediction resulting from charge effects. The trends are expected to be similar with a different value of charge.

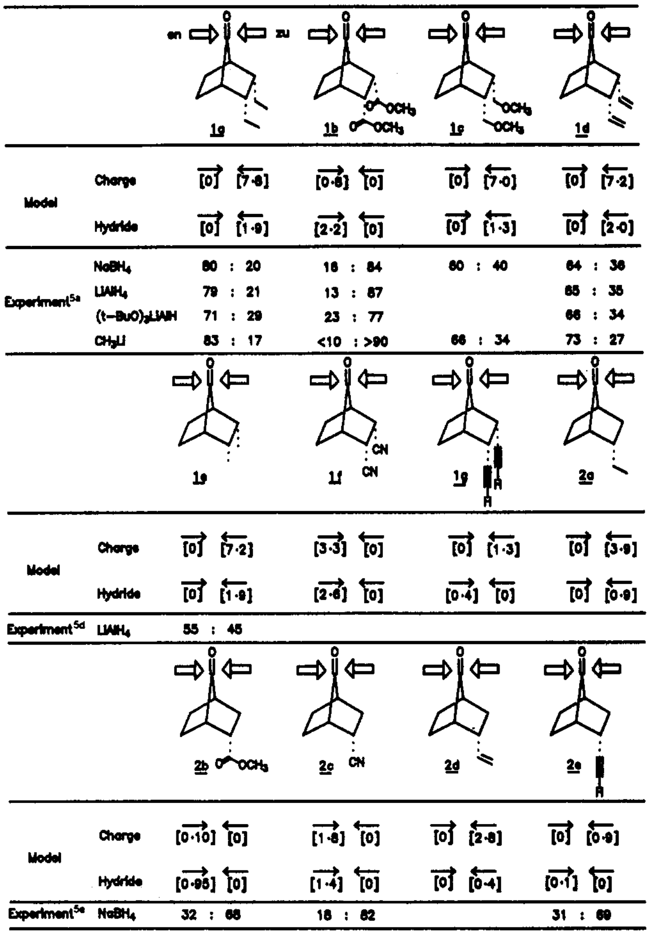
The hydride ion was chosen as a test nucleophile in order to remove potential steric contributions to the predicted face selectivity. The latter effects may be important in some experimentally studied systems. The calculations also do not include counterion interactions[28] as well as solvation or related medium effects.

The use of the MNDO methodology may appear to many as the most serious approximation requiring justification. Therefore, ab initio calculations with the hydride model were carried out for two representative 2,3-endo,endo-disubstituted 7-norbornanones (**1e** and **1f**). The split-valence 3-21G basis set was employed.[29] The hydride ion was augmented by a diffuse *s* function with an exponent of 0.036.[30] For the dimethyl derivative, the *en* face approach was predicted to be favored by 2.4 kcal/mol. In the case of the corresponding dicyano compound, the *zu* face attack is preferred by 4.8 kcal/mol. These values are consistent with the preferences obtained at the MNDO level, 1.9 and 2.6 kcal/mol, respectively. We therefore proceeded to use the MNDO procedure for a large number of 2,3-endo,endo-disubstituted 7-norbornanones (**1a–g**), the corresponding mono-substituted derivatives (**2a–e**), related compounds in which the substituents are annulated (**3a–i**), 5,6-endo,endo-disubstituted bicyclo[2.2.2]octan-2-ones (**4a–f**), the corresponding mono-substituted derivatives (**5a,b**), 5,6-endo,endo-disubstituted 7-norbornenones (**6a–f**), benzonorbornenones (**7a–c**), and remotely substituted adamantanone and azaadamantanone derivatives (**8a–c**).

Results and Discussion

The optimized geometries of the ketones **1–8** do not reveal any constitent feature which can be correlated with the observed face selectivity in the corresponding nucleophilic additions. In particular, the carbonyl unit is essentially planar. The sum of the angles around the corresponding carbon atom does not deviate by more than 2° from 360°. The presence of endo substituents in **1** and **2** does not lead to significant tilt of the carbonyl bridge toward either of the ethano bridges. The angles $C_7–M_{1,4}–M_{2,3}$ and $C_7–M_{1,4}–M_{5,6}$, where $M_{a,b}$ represents the midpoint of C_a and C_b, are nearly identical in these systems. The carbonyl unit in these compounds are also nearly eclipsed with the bridgehead hydrogen atoms. Hence, ground-state distortions and torsional interactions during the formation of the transition structures cannot be implicated for the face selectivity in these substrates. The conclusion is further confirmed by the direction of tilt noted for the diester derivative of norbornenone, **6d**. As pointed out recently,[31] the computed geometry as well as the X-ray structure reveal a tilt which is inconsistent with the preferred direction of nucleophilic approach. While the carbonyl tilt is away from the C=C unit, nucleophilic attack from the more hindered *zu* face is favored.[6]

Scheme I. Calculated Relative Energies (kcal/mol) between *en* and *zu* Approach to 1a–g, 2a–e, and Experimentally Observed Selectivities



		1a	1b	1c	1d
Model	Charge	$\overrightarrow{[0]}$ $\overleftarrow{[7{\cdot}6]}$	$\overrightarrow{[0{\cdot}6]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[7{\cdot}0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[7{\cdot}2]}$
	Hydride	$\overrightarrow{[0]}$ $\overleftarrow{[1{\cdot}9]}$	$\overrightarrow{[2{\cdot}2]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[1{\cdot}3]}$	$\overrightarrow{[0]}$ $\overleftarrow{[2{\cdot}0]}$
Experiment[5a]	$NaBH_4$	80 : 20	16 : 84	60 : 40	64 : 36
	$LiAlH_4$	79 : 21	13 : 87		65 : 35
	$(t–BuO)_3LiAlH$	71 : 29	23 : 77		66 : 34
	CH_3Li	83 : 17	<10 : >90	66 : 34	73 : 27

		1e	1f	1g	2a
Model	Charge	$\overrightarrow{[0]}$ $\overleftarrow{[7{\cdot}2]}$	$\overrightarrow{[3{\cdot}3]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[1{\cdot}3]}$	$\overrightarrow{[0]}$ $\overleftarrow{[3{\cdot}9]}$
	Hydride	$\overrightarrow{[0]}$ $\overleftarrow{[1{\cdot}9]}$	$\overrightarrow{[2{\cdot}6]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0{\cdot}4]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[0{\cdot}9]}$
Experiment[5d]	$LiAlH_4$	55 : 45			

		2b	2c	2d	2e
Model	Charge	$\overrightarrow{[0{\cdot}10]}$ $\overleftarrow{[0]}$	$\overrightarrow{[1{\cdot}6]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[2{\cdot}6]}$	$\overrightarrow{[0]}$ $\overleftarrow{[0{\cdot}9]}$
	Hydride	$\overrightarrow{[0{\cdot}95]}$ $\overleftarrow{[0]}$	$\overrightarrow{[1{\cdot}4]}$ $\overleftarrow{[0]}$	$\overrightarrow{[0]}$ $\overleftarrow{[0{\cdot}4]}$	$\overrightarrow{[0{\cdot}1]}$ $\overleftarrow{[0]}$
Experiment[5e]	$NaBH_4$	32 : 68	18 : 82		31 : 69

The computed energy differences for the *en* and *zu* face nucleophilic approach in the substituted norbornanones, **1** and **2**, are quite large with the charge model (Scheme I). The exaggerated preferences are a direct consequence of the use of a full negative charge at a relatively short interaction distance. While the relative energies should not be taken as a quantitative indicator of facial selectivity, the large values lead to unambiguous conclusions. The hydride model generally yields smaller and more realistic energy differences. However, these values should also not be considered to be of quantitative accuracy in view of the neglect of details of the transition-state structures.

Qualitatively, the observed face selectivities in the reductions of **1a–e** are correctly reproduced by both the charge and the hydride models (Scheme I). For example, donor substituents like ethyl and methyl groups have a greater preference for the *en* face attack.[5a] In contrast, electron-withdrawing groups, as in the diester **1b**, induce a *zu* face selectivity. It is tempting to interpret these results in terms of Cieplak theory,[15] since the nucleophile seems to be directed antiperiplanar to the relatively electron rich C–C bond. However, the charge model which does not include the corresponding orbital interactions also yields the correct qualitative predictions. Donor groups in **1a**, **1c**, and **1e** are calculated to have a large repulsive interaction with the test charge. In the diester, **1b**, Coulombic attraction of the charge with the exo-face hydrogen atoms is compensated by long-range repulsive interaction with the oxygen atoms on the endo substituents. The net interaction would be sensitive to the

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(28) For a discussion of the chelate effect involving the counterion and the substrate, see ref 16c.

(29) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Theory*; Wiley: New York, 1986.

(30) Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5609.

(31) Amarendra Kumar, V.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *Tetrahedron Lett.* **1992**, *33*, 3069.

orientations of the ester groups. The relative energetics of the charge and hydride models suggest the possible presence of orbital effects, but which merely reinforce the preference dictated by electrostatic interactions.

The apparently anti-Cieplak behavior of the divinyl derivative **1d**[5a] provides an excellent test for the computational model. Inductive effect of the vinyl groups should reduce the hyperconjugative stabilization due to the C_1–C_2 and C_3–C_4 σ bonds with the newly formed σ^* orbital. Hence a *zu* face preference is predicted on qualitative grounds, in disagreement with the observed selectivity. Both the charge and the hydride models correctly reproduce the *en* face preference. Significant electrostatic repulsion between the test charge and the substituents is indicated to be responsible for the reversal of the favored direction of attack expected on the basis of orbital effects alone. Thus, the observed face selectivities in substituted norbornanones are indicated to be predominantly determined by electrostatic factors.

The present results generally parallel those obtained using ab initio calculations at the MP2/6-31G* level using transition structures for LiH additions optimized with the 6-31G* basis set.[18] The high-level theory successfully reproduced the experimental preferences for nucleophilic additions to substituted norbornanones. Further, model calculations with a test charge of −0.5 yielded the same preferences for a selected set of derivatives, pointing to the dominant role of electrostatic effects in determining the facial selectivities. These results provide a useful calibration for the reliability of the present simple computational models. Use of an approximate MO method as well as the neglect of transition-state structural details in the present study have not altered the basic qualitative conclusions.

In the disubstituted norbornanones, intersubstituent interactions lead to conformational uncertainities. While the hyperconjugative effects should be relatively insensitive to the orientation of the endo units, electrostatic effects with the approaching nucleophile may vary, as also noted in previous calculations.[18] Therefore, we examined the behavior of dicyano- and diethynylnorbornanones, **1f** and **1g**, and also that of a set of monosubstituted derivatives, **2a–e**. To provide a critical test, experimental face selectivities for hydride reduction with $NaBH_4$ were also determined for some of the mono-endo-substituted norbornanones. These results are included in Scheme I.

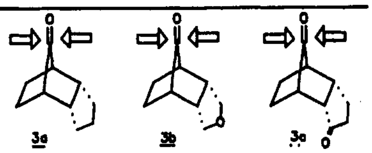
The monoester **2b** shows the same *zu* face preference for reduction as the diester, but by a smaller magnitude. The charge model yields a negligible energy difference for the two directions of approach in **2b**. The selectivity is correctly reproduced by the hydride model, indicating the role of hyperconjugation in this system. The cyano derivative **2c** exhibits a strong *zu* face selectivity. Both the charge and the hydride models yield the same preference. The larger substituent effect of a cyano group relative to an ester found experimentally is attributable to the relative magnitudes of electrostatic interactions in the idealized *zu* face transition states in the two systems. In **2c** the approaching nucleophile is stabilized by the net positive charge on the exo face. The effect is partly dampened by the ester oxygen atoms, reducing the overall preference for *zu* face attack in **2b**.

The observed facial selectivity for the ethynyl compound **2e** is also revealing. Unlike in the case of the divinyl derivative, the preferred face for reduction in **2e** is constitent with the Cieplak effect expected from an electron-withdrawing group. The charge model reveals a smaller magnitude of electrostatic repulsion due to the substituent in **2e** and **1g** for the *zu* face attack compared to that in the vinyl derivatives **2d** and **1d**. The computed *zu* face preference with the hydride model for **1g** is supportive of the presence of orbital interactions proposed by the Cieplak model.

An alternative approach to reduce intersubstituent interactions is to fuse the groups in cyclic structures. The face selectivities in the reductions of a number of such derivatives, **3a–e**, have been reported.[32] The present models yield results which are generally consistent with the observed selectivities (Scheme II). For example, the *endo*-cyclopentyl unit in **3a** is predicted to behave like the corresponding diethyl derivative, **1a**. The *en* face preference is reduced by the introduction of a carbonyl group in the substituent. A subtle comparison of the facial selectivities induced by an sp^2 and an sp^3 carbon atoms at the endo positions is made with the pentacyclic substrate,[5b] **3e**. The preferred approach of the nucleophile from the side of the double bonds is correctly reproduced by the calculations. In these systems, electrostatic effects seem to be generally responsible for the overall facial selectivity on the basis of the reliability of the charge model.

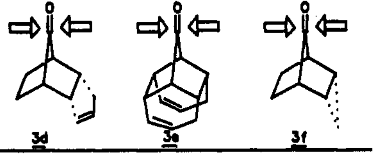
Experimental face selectivities for a couple of norbor-

Scheme II. Calculated Relative Energies (kcal/mol) between *en* and *zu* Approach to 3a–i and Experimentally Observed Selectivities



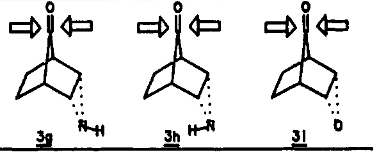
3a 3b 3c

		3a	3b	3c
Model	Charge	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}6]}$	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}1]}$	$\overrightarrow{[0]}\ \overleftarrow{[3{\cdot}1]}$
	Hydride	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}2]}$	$\overrightarrow{[0{\cdot}05]}\ \overleftarrow{[0]}$
Experiment[32]	$NaBH_4$	76 : 24	50 : 50	55 : 45
	$LiAlH_4$	75 : 25		
	CH_3Li	86 : 14		



3d 3e 3f

		3d	3e	3f
Model	Charge	$\overrightarrow{[0]}\ \overleftarrow{[7{\cdot}4]}$	$\overrightarrow{[0]}\ \overleftarrow{[1{\cdot}8]}$	$\overrightarrow{[0]}\ \overleftarrow{[6{\cdot}8]}$
	Hydride	$\overrightarrow{[0]}\ \overleftarrow{[1{\cdot}8]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[2{\cdot}4]}$
Experiment[5b,32,33]	$NaBH_4$	63 : 37		
	$LiAlH_4$	61 : 39	57 : 43	
	CH_3Li	78 : 22	61 : 39	95 : 5



3g 3h 3i

		3g	3h	3i
Model	Charge	$\overrightarrow{[1{\cdot}3]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[7{\cdot}3]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}9]}$
	Hydride	$\overrightarrow{[1{\cdot}3]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[2{\cdot}3]}$	$\overrightarrow{[0{\cdot}7]}\ \overleftarrow{[0]}$
Experiment[33]		00 : 100(for NPh)		

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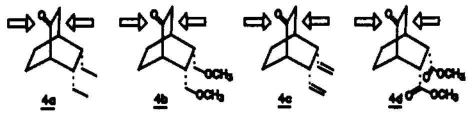
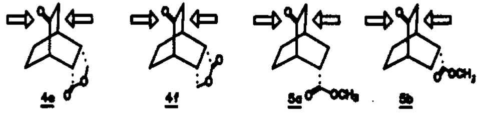
(32) Mehta, G.; Praveen, M. *Tetrahedron Lett.* **1992**, *33*, 1759.

Scheme III. Calculated Relative Energies (kcal/mol) between *en* and *zu* Approach to 4a–f, 5a,b, and Experimentally Observed Selectivities

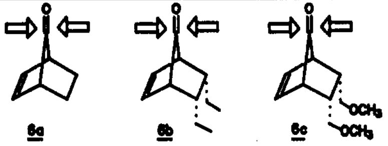


		4a	4b	4c	4d
Model Geometry 1	Charge	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}3]}$	$\overrightarrow{[0]}\ \overleftarrow{[7{\cdot}9]}$	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}1]}$	$\overrightarrow{[0{\cdot}25]}\ \overleftarrow{[0]}$
	Hydride	$\overrightarrow{[0{\cdot}5]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[1{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}06]}$	$\overrightarrow{[2{\cdot}5]}\ \overleftarrow{[0]}$
Model Geometry 2	Charge	$\overrightarrow{[0]}\ \overleftarrow{[8{\cdot}4]}$	$\overrightarrow{[0]}\ \overleftarrow{[7{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}6]}$	$\overrightarrow{[0{\cdot}64]}\ \overleftarrow{[0]}$
	Hydride	$\overrightarrow{[0]}\ \overleftarrow{[2{\cdot}0]}$	$\overrightarrow{[0]}\ \overleftarrow{[1{\cdot}4]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}4]}$	$\overrightarrow{[2{\cdot}7]}\ \overleftarrow{[0]}$
Model Geometry 3	Charge	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}0]}$	$\overrightarrow{[0]}\ \overleftarrow{[4{\cdot}2]}$	$\overrightarrow{[0]}\ \overleftarrow{[5{\cdot}0]}$	$\overrightarrow{[0]}\ \overleftarrow{[3{\cdot}6]}$
	Hydride	$\overrightarrow{[0{\cdot}3]}\ \overleftarrow{[0]}$	$\overrightarrow{[0{\cdot}1]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}6]}$	$\overrightarrow{[0{\cdot}1]}\ \overleftarrow{[0]}$
Experiment[34]	$NaBH_4$	61 : 39	50 : 50	50 : 50	30 : 70
	DIBAL–H	66 : 34		50 : 50	33 : 67
	CH_3Li	66 : 34		46 : 54	

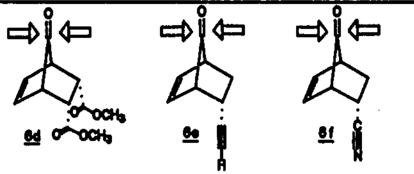


		4e	4f	5a	5b
Model	Charge	$\overrightarrow{[0{\cdot}6]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[1{\cdot}0]}$	$\overrightarrow{[0]}\ \overleftarrow{[3{\cdot}3]}$	$\overrightarrow{[1{\cdot}4]}\ \overleftarrow{[0]}$
	Hydride	$\overrightarrow{[1{\cdot}4]}\ \overleftarrow{[0]}$	$\overrightarrow{[0{\cdot}6]}\ \overleftarrow{[0]}$	$\overrightarrow{[0{\cdot}6]}\ \overleftarrow{[0]}$	$\overrightarrow{[1{\cdot}6]}\ \overleftarrow{[0]}$
Experiment[34]	$NaBH_4$	34 : 66	39 : 61	35 : 65	38 : 62

Scheme IV. Calculated Relative Energies (kcal/mol) between *en* and *zu* Approach to 6a–f and Experimentally Observed Selectivities



		6a	6b	6c
Model	Charge	$\overrightarrow{[0]}\ \overleftarrow{[6{\cdot}0]}$	$\overrightarrow{[0]}\ \overleftarrow{[12{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[8{\cdot}5]}$
	Hydride	$\overrightarrow{[1{\cdot}3]}\ \overleftarrow{[0]}$	$\overrightarrow{[0]}\ \overleftarrow{[0{\cdot}2]}$	$\overrightarrow{[0{\cdot}5]}\ \overleftarrow{[0]}$
Experiment[6,35]	$NaBH_4$	85 : 15		88 : 12
	CH_3Li	77 : 23		75 : 25
	CH_3MgI	96 : 4		94 : 6



		6d	6e	6f
Model	Charge	$\overrightarrow{[0]}\ \overleftarrow{[5{\cdot}2]}$	$\overrightarrow{[0]}\ \overleftarrow{[6{\cdot}7]}$	$\overrightarrow{[0]}\ \overleftarrow{[3{\cdot}5]}$
	Hydride	$\overrightarrow{[4{\cdot}1]}\ \overleftarrow{[0]}$	$\overrightarrow{[1{\cdot}5]}\ \overleftarrow{[0]}$	$\overrightarrow{[2{\cdot}6]}\ \overleftarrow{[0]}$
Experiment[6,35]	$NaBH_4$	45 : 55	72 : 28	44 : 56
	CH_3Li	10 : 90		
	CH_3MgI	80 : 20		

nanones with an endo three-membered ring are known.[33] The two π faces of the carbonyl groups are not sterically quite equivalent in view of the distortions introduced by the small ring.[18] However, the present models with a test charge and a nucleophile yield relative energies which parallel the observed face selectivities (Scheme II). In qualitative terms, the preference for the cyclopropyl derivativ **3f** is consistent with the Cieplak model. The reversed face selectivity observed for the aziridine with an *N*-phenyl substituent evoked considerable surprise.[33b] The present models suggest that the observed preferences result primarily from electrostatic terms. The sensitivity of the predicted face selectivity on the orientation of the nitrogen lone pair (also noted in previous ab initio calculations)[18] provides additional support to this interpretation. In the experimetnally examined *N*-phenyl derivative, the preferred conformation is likely to be that of **3g** rather than **3h**. The corresponding predictions are consistent with the observed preference for exclusive *zu* face attack.

The observed face selectivity in the reductions of 5,6-endo,endo-disubstituted bicyclo[2.2.2]octan-2-ones parallel the pattern found for the corresponding 2,3-endo,-endo-disubstituted norbornanones.[34] To confirm whether the origin of the face selectivities in the two series of compounds is similar, calculations were carried out on a number of derivatives, **4a–d**, Scheme III. Unfortunately, for each system a number of conformers with similar stabilities (within 1 kcal/mol) were obtained which were computed to have significantly varying face selectivities (Scheme III). These results are clearly indicative of electrostatic interactions between the test charge and the endo substituents. The problem is aggravated by the unsymmetrical disposition of the reaction center with respect to the substituents. It is therefore not possible to obtain reliable predictions of facial selectivity using the present models for these systems.

As we have pointed out recently,[34] the unsymmetrical location of the carbonyl unit in the bicyclo[2.2.2]octan-2-one system can be used advantageously to unravel the relative magnitudes of electrostatic and orbital effects. With the appropriate choice of monosubstituted derivatives, hyperconjugative interactions can be turned on, e.g. **5a**, or off, e.g. **5b**. We have shown that the face selectivity induced by a single ester substituent is as effective at the on position as in the alternative isomer. The present computational model was employed to point out the importance of electrostatic interactions in these systems which contribute to the observed face selectivities (Scheme III).

The origin of face selectivity found in 7-norbornenone has long been a contentious problem.[35] The charge model is consistent with the major products obtained with nucleophiles such as BH_4^- and CH_3Li (Scheme IV). The hydride model which is supposed to include additional interactions leads to an incorrect prediction for these systems. This result represents the first serious failure of the hydride model. However, carbonyl reduction in the norbornenone system is known to be rather complex.[6,35] The preferred direction of reagent approach is sensitive to the medium and the choice of the nucleophile. Potential interactions between the counterion and the C=C unit can also be a complicating factor. We have therefore

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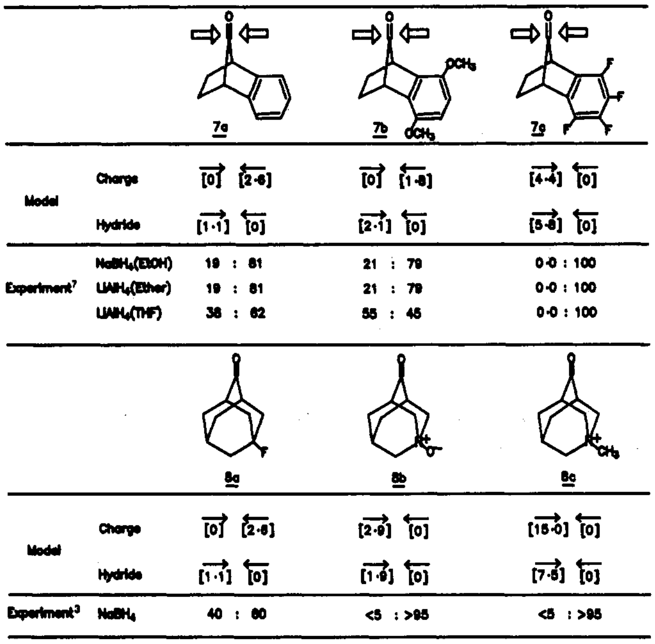
(33) (a) Gassman, P. G.; Shaffhausen, J. H.; Raynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6408. (b) Gassman, P. G.; Schaffhausen, J. H.; Starkey, F. D.; Raynolds, P. W. *Ibid.* **1982**, *104*, 6411.

(34) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1711.

(35) (a) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811. (b) Erman, W. F. *J. Org. Chem.* **1967**, *32*, 765. (c) Warkentin, J. *Can. J. Chem.* **1970**, *48*, 1391. (d) Clark, F. R. S.; Warkentin, J. *Can. J. Chem.* **1971**, *49*, 2223. (e) Gassman, P. G.; O'Reilly, N. *J. Org. Chem.* **1987**, *52*, 2481.

Scheme V. Calculated Relative Energies (kcal/mol) between *en* and *zu* Approach to 7a–c, 8a–c, and Experimentally Observed Selectivities



		7a	7b	7c
Model	Charge	$\overrightarrow{[0]}$ $\overleftarrow{[2{\cdot}6]}$	$\overrightarrow{[0]}$ $\overleftarrow{[1{\cdot}8]}$	$\overrightarrow{[4{\cdot}4]}$ $\overleftarrow{[0]}$
	Hydride	$\overrightarrow{[1{\cdot}1]}$ $\overleftarrow{[0]}$	$\overrightarrow{[2{\cdot}1]}$ $\overleftarrow{[0]}$	$\overrightarrow{[5{\cdot}8]}$ $\overleftarrow{[0]}$
Experiment[7]	$NaBH_4$(EtOH)	19 : 81	21 : 79	0·0 : 100
	$LiAlH_4$(Ether)	19 : 81	21 : 79	0·0 : 100
	$LiAlH_4$(THF)	38 : 62	55 : 45	0·0 : 100

		8a	8b	8c
Model	Charge	$\overrightarrow{[0]}$ $\overleftarrow{[2{\cdot}6]}$	$\overrightarrow{[2{\cdot}9]}$ $\overleftarrow{[0]}$	$\overrightarrow{[15{\cdot}0]}$ $\overleftarrow{[0]}$
	Hydride	$\overrightarrow{[1{\cdot}1]}$ $\overleftarrow{[0]}$	$\overrightarrow{[1{\cdot}9]}$ $\overleftarrow{[0]}$	$\overrightarrow{[7{\cdot}5]}$ $\overleftarrow{[0]}$
Experiment[3]	$NaBH_4$	40 : 60	<5 : >95	<5 : >95

focused attention on the effect of endo substituents on the face selectivity in 7-norbornenones.

The effect of acceptor type groups is particularly unambiguous. The predicted face selectivity is unaltered on going from **6a** to the diester **6d** within the charge model (Scheme IV). However, use of the hydride ion probe clearly yields a greater preference for attack from the substituent side in **6d**. Only the latter result is consistent with the experimentally observed face selectivities. The data for the cyano derivative, **6f**, also support the importance of hyperconjugative interactions in these systems. The acceptors weaken the ability of the C_1–C_6 and C_4–C_5 σ bonds to stabilize the newly formed antiperiplanar σ^* orbital. The trends are in accord with the Cieplak model for these systems.

Comparison of the calculated data with the experimental face selectivities[7] for the benzonorbornenones **7a** and **7b** also reveals the importance of orbital effects (Scheme V). For both these systems, the charge model makes an incorrect prediction of face selectivity.[36] On the other hand, the hydride model is consistent with the observed results. The nucleophile is predicted to prefer the approach over the aromatic ring in these systems. In the tetrafluoro derivative, **7c**, the selectivity is reinforced by strong electrostatic interactions.

The remarkable face selectivity found for 5-fluoroadamantanone,[3] **8a**, was one of the key observations that generated excitement in the possible role of relative hyperconjugative interactions in the transition states. Our present calculations support the original interpretation. Use of a test charge leads to the incorrect anti preference (Scheme V). The hydride model restores the energy difference in favor of the observed syn face attack. More recent data[37] obtained for the azaadamantanone derivatives, **8b** and **8c**, are also reproduced by the present calculations. However, in these systems, the highly polar nature of the substituents leads to strong electrostatic interactions. The final preference is essentially determined by these terms.

Conclusions

A simple semiquantitative computational model is proposed for rationalizing and predicting π-face selectivities in nucleophilic additions to sterically unbiased carbonyl compounds. The effect of electrostatic and polarization interactions is exclusively modeled using a test charge, while the role of orbital interactions are included in a series of calculations with a hydride ion. Use of two sets of calculations keeping a variety of factors constant leads to valuable insights into the origin of π-face selectivity. In most cases, especially endo-substituted norbornanones and bicyclo[2.2.2]octan-2-ones, the observed face selectivities are reproduced within the charge model. Orbital effects are either small or reinforce electrostatic effects in these systems. However, orbital interactions are found to be essential even to make correct qualitative predictions in a few cases.

The hydride model leads to correct face selectivities in virtually all cases. The failures are surprisingly few and correspond to contentious systems. At least in the set of sterically unbiased series of ketones considered in this study, details of the transition-state structures and associated torsional effects are indicated to be unimportant.

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[36] The previous qualitative analysis of electrostatic effects in benzonorbornanones **7a** and **7b** given in ref 17 is not supported by the present calculations. However, the suggestion of large electrostatic interactions in the fluoro derivative, **7c**, is consistent with our results.

[37] Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.

[38] Monosubstituted 7-norbornanones **2b–d** were synthesized from the 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene–acrylic acid Diels–Alder adduct,[39] closely following the steps outlined earlier for the disubstituted 7-norbornanones.[5a,6] The acetylenic compound **2e** was prepared from the corresponding formyl precursor in two steps:

$$-\text{CHO} \xrightarrow[\text{THF}]{\text{Ph}_3\text{P}{=}\text{CHCl}} -\text{C}{=}\text{CHCl} \xrightarrow[\text{THF}]{\text{K}^+\text{tBuO}^-} -\text{C}{\equiv}\text{CH}$$

All new compounds referred to here were adequately characterized on the basis of spectral (^{1}H and ^{13}C NMR) and analytical data. Additions with hydride reducing agents ($NaBH_4$, LAH, etc.) were carried out as described earlier,[5a,6] and the composition of diastereomers was estimated (±5%) from the ^{1}H NMR integration of the crude reaction mixtures. Stereochemistry of the individual diastereomers was secured on the basis of incisive analyses of ^{1}H and ^{13}C NMR data, as was done previously.[5a,6]

[39] Gossinger, E.; Muller, R. *Tetrahedron* **1989**, *45*, 1377. McBee, E. T.; Birch, J. E.; Diveley, W. R. *J. Am. Chem. Soc.* **1955**, *77*, 385.