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Electrophilic Additions to a 2-Methylenebicyclo[2.1.1]hexane System: Probing π-Face Selectivity for Electrostatic and Orbital Effects

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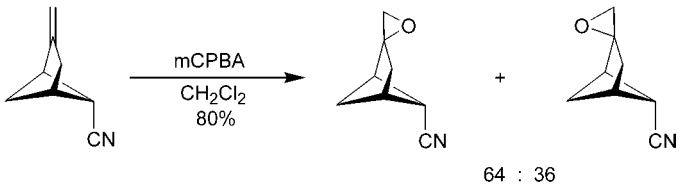
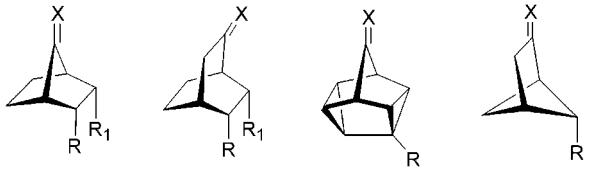
ABSTRACT



5-*exo*-Bicyclo[2.1.1]hexane derivatives with remote electron-withdrawing substituents exhibit very modest face selectivity during electrophilic additions due to interplay of several electronic factors. These experimental results have been probed through ab initio MESP maps, bond density calculations, and energetics involved in pre-reaction complexation.

The role of steric effects in controlling face selection during addition to π-systems is well recognized and often predictable. However, when a π-system is placed in an isosteric environment, the long-range electronic effects are the main determinants of the face selectivity as has been convincingly shown in the case of adamantanyl, norbornyl, and several related systems.[1] Whether such electronic control manifests through electrostatic or orbital contributions or through a subtle combination of both is a matter of continuing scrutiny and debate. Newer skeletal probes, with finer distal and directional variation in the location of the stereoinduction center and the remote substituent, as well as a variety of computational methods at different levels of theory, have been employed to address the issue.[1] We have reported that in endo-substituted bicyclo[2.2.1]heptanes **1**[2a−d] and in bicyclo[2.2.2]octane **2**,[2e−f] 4-substituted 9-norsnoutane **3**,[2g−h] and related systems, where the π-system is in a sterically neutral disposition,



1a. X=O **b.** X=CH_2 **2a.** X=O **b.** X=CH_2 **3a.** X=O **b.** X=CH_2 **4a.** X=O **b.** X=CH_2

distal substituents can influence the stereochemical outcome (syn vs anti addition) during nucleophilic and electrophilic additions in a profound way. Continuing our investigations in the area,[1b,2] we recently introduced 5-exo-substituted bicyclo[2.1.1]hexan-2-ones **4a** as a new probe system to explore the role of distal electronic modifications on π-face selectivity during hydride reduction.[3] We have now carried out complementary studies and investigated electrophilic

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(1) For recent reviews on diastereoselection, see a thematic issue: (a) le Noble, W. J.; Gung, B. W. *Chem. Rev.* **1999**, *99*, 1069−1480. (b) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437. (c) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199.

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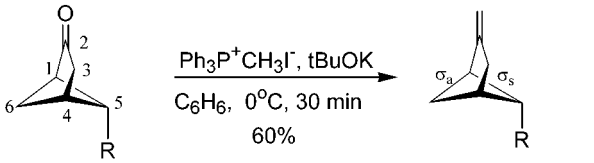
additions to 5-exo-substituted 2-methylene-bicyclo[2.1.1]-hexanes **4b** and provide interpretation of results on the basis of computation of molecular electrostatic potentials (MESP), electron densities, and energetics of pre-reaction complexes.

The skeleton of **4b** has some distinctive features, besides the broad structural resemblance to **1b** and **2b** and the isosteric environment around the exocyclic double bond. The exo substituent at C_5 in **4b** is farther removed from the stereoinduction center compared to that in **1b**, and the electronic effects are relayed through the intervening cyclobutane bonds. Further, the olefin bond in **4b** is in the "off" position from the vertical plane in which the C_5-substituent resides. Considering the difficulty of synthetic access to the bicyclo[2.1.1]system with the requisite functionality and stereochemistry,[3,4] only two derivatives of **4b** bearing a cyano-**6a** and an ester substituent **6b** were chosen for the present study and were prepared through Wittig olefination of the corresponding ketones **5a**,**b**, respectively, Scheme 1.[5]

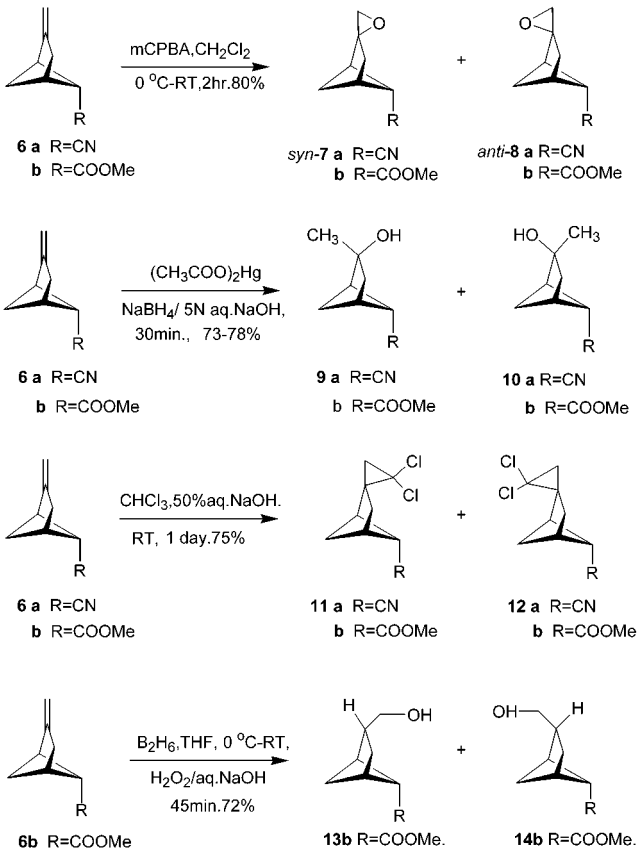
Scheme 1



5a R=CN, **b** R=COOCH$_3$ **6a** R=CN, **b** R=COOCH$_3$

Bicyclic olefins **6a**,**b** were subjected to epoxidation, oxymercuration, hydroboration, and dichlorocarbene addition. The reaction conditions, yields, and products obtained are depicted in Scheme 2. The observed π-face selectivities (syn/anti addition ratio) during the electrophilic additions are summarized in Table 1 and were obtained through GLC and ^{1}H NMR analyses. The stereostructures of all fourteen diastereomers, the syn products **7ab**, **9ab**, **11ab**, and **13b**, and the anti products **8ab**, **10ab**, **12ab**, and **14b** were unambiguously determined[5] on the basis of the relative deshielding of the H(6) endo protons in the anti series compared to that in the syn series. The H(6) endo proton in all the diastereomers appeared as a diagnostic triplet ($J \approx 7$ Hz) due to long-range (four-bond) coupling with the H(5) endo proton and could be readily recognized.

Scheme 2



The notable feature of the stereoselectivities observed during electrophilic additions to **6a**,**b** was that the syn face preference of the remote electron-withdrawing substituents such as a cyano and an ester is not only diminished but even marginally reversed in the bicyclo[2.1.1]hexane system **6a**,**b** compared to that in the norbornyl system **1**.[2b−d] While epoxidation and hydroboration of **6a**,**b** proceeds preferentially from the syn face, dichlorocarbene addition occurs from the anti face. In the case of oxymercuration, dominance of syn alcohols **9a**,**b** could mean that they originate through the collapse of a charged C2 intermediate with water. The marked diminution in the face selectivity in the bicyclo[2.1.1]-hexane-based probe system **6a**,**b** compared to the norbornyl system, wherein we had explained the results in terms of the Cieplak effect,[2b−d,6] was suggestive of the intervention of additional electronic effects.

Table 1. Experimental Ratios of Syn and Anti Products from **6a**,**b** with *m*-Cpba, $(CH_3COO)_2Hg$, $:CCl_2$, and B_2H_6

	m-Cpba		$(CH_3CO_2)_2Hg$		$:CCl_2$		B_2H_6	
compd	syn	anti	syn	anti	syn	anti	syn	anti
6a	64	36	85	15	45	55		
	7a	**8a**	**9a**	**10a**	**11a**	**12a**		
6b	56	44	75	25	47	53	45	55
	7b	**8b**	**9b**	**10b**	**11b**	**12b**	**13b**	**14b**

(2) (a) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140. (b) Mehta, G.; Khan, F. A. *J. Chem. Soc., Chem. Commun.* **1991**, 18. (c) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734. (d) Mehta, G.; Khan, F. A.; Gadre, S. R.; Shirsat, R. N.; Ganguly, B.; Chandrasekhar, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1390. (e) Mehta, G.; Khan, F. A.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1711. (f) Tsuji, M.; Ohwada, T.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 6693. (g) Mehta, G.; Ravikrishna, C.; Ganguly, B.; Chandrasekhar, J. *J. Chem. Soc., Chem. Commun.* **1997**, 75. (h) Mehta, G.; Ravikrishna, C.; Gadre, S. R.; Suresh, C. H.; Kalyanraman, P.; Chandrasekhar, J. *Chem. Commun.* **1998**, 975.

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(5) All new compounds reported here were fully characterized on the basis of complementary spectroscopic (IR, ^{1}H and ^{13}C NMR, and MS) data. Experimental details and characterization data are provided in Supporting Information.

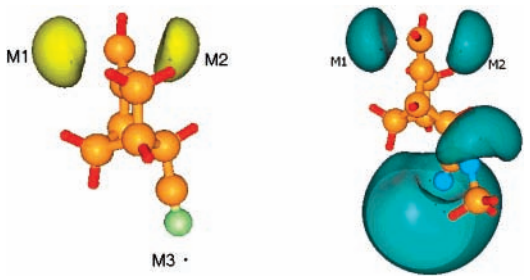

Figure 1. MESP isosurfaces with values of −6.27 and −11.29 kcal/mol, respectively.

To probe the relative importance of the electrostatic[7] and orbital effects in the present system, a topographical investigation of molecular electrostatic potential (MESP)[8] and electron density was carried out by locating the corresponding critical points (CPs).[8,9] The geometry optimization of the systems was done at HF/6-31G(d,p) using the GAUSSIAN 94 suite of programs.[10] Single-point calculations were carried out at HF/6-31++G(2d,2p). The scalar fields and their topographies were evaluated using the package INDPROP[9b,11] and visualized with UNIVIS-2000 (displayed in Figures 1 and 2).[12] For both **6a** and **6b**, the MESPs about the two π-faces are somewhat unsymmetrical for the (3, +3) CPs, indicating a marginal difference in the localization of the electron cloud. The minimum value is found to be more negative on the anti face (cf. Table 2). Though the difference in MESPs on the two faces is small, a slight preference for the electrophiles approaching from the anti face is indicated. Contribution of orbital interactions to face selectivity was evaluated through electron density CPs. The unsymmetrical donor abilities of the σ_a (C4−C6) and σ_s (C4−C5) bonds (see structures **6a**,**b**) were characterized in terms of the electron densities at the bond critical points (Table 2). In both **6a** and **6b**, the σ_a (C4−C6) bond has a greater density and Cieplak-type[6] orbital interaction would favor syn selectivity with the approach of the electrophile from the face opposite to the electron-rich periplanar bond.

Table 2. MESP Values (in kcal/mol) at the (3, +3) Minimum and Electron Density Values (in Atomic Units) at the (3, −1) Critical Points

	MESP at critical point		density at bond critical point	
compd	anti	syn	anti (C_1−C_6)	syn (C_1−C_5)
6a	−12.36	−11.42	0.2515	0.2450
6b	−20.58	−20.02	0.2506	0.2435

Thus, electrostatic[7] and Cieplak-type[6] orbital effects seem to act in opposing directions. However, these interpretations are derived without taking into account the nature of the electrophile. To gain insights into this aspect, the structure and energetics of the pre-reaction complexes involving the substrates **6a** and **6b** and model electrophiles were examined. The pre-reaction complexes were optimized using density functional methods involving B3PW91 functionals at the LANL2DZ effective core potential basis with the GAUSSIAN 94 suite of programs.[9] All the opimized structures were subjected to frequency calculations and confirmed to be minima. The detailed geometries are given in Supporting Information. The model electrophiles used were peracetic acid for epoxidation, $(HCOO)_2Hg$ for oxymercuration, and BH_3 for hydroboration. The interaction energies of the pre-reaction complexes defined as $\Delta E_{AB} = E_{AB} - (E_A + E_B)$ are presented in Table 3. The interaction energies indicate a small but clearly discernible syn preference for all the electrophiles studied, in agreement with the experimental trends. This is attributable to an *electrostatic stabilization* between the C_5 acidic hydrogen bearing the cyano or ester substituent and a complementary site of the electrophile and is in consonance with the accepted EPIC model.[13a,b] The acidity of the involved hydrogen is brought out through MESP-derived charges calculated by the CHELPG[14] scheme in the G94 suite of programs.[10] The C5-endo-hydrogens in **6a** and **6b** have charges of 0.108 and 0.120 au, respectively, compared to the charge of 0.082 au for the hydrogen in the parent system without a substituent.

Table 3. Interaction Energies of Pre-reaction Complexes in kcal/mol

	per acid		$(HCOO)_2Hg$		BH_3	
compd	syn	anti	syn	anti	syn	anti
6a	−3.41	−2.96	−10.43	−10.20	−11.57	−10.89
6b	−3.01	−2.96			−12.27	−11.65

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

(7) (a) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (b) Broughton, H. B.; Green, S. M.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 998.

(8) MESP is defined as

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(r')}{|r - r'|} d^3r'$$

Here $\{Z_A\}$ values are the nuclear charges located at $\{R_A\}$, and $\rho(\mathbf{r})$ denotes the molecular electron density. The critical points (CP) of the function are defined as the points at which $\nabla V(\mathbf{r}) = 0$ and the minima are characterized as (3, +3). Lone pairs, π-bonds, etc. appear as negative-valued minima in MESP.

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(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision E.2; Gaussian, Inc.: Pittsburgh, PA, 1995.

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(12) UNIVIS-2000: An Indigenously Developed Visualization Package Limaye, A. C.; Gadre, S. R. *Curr. Sci. (India)* **2001**, *80*, 1296.

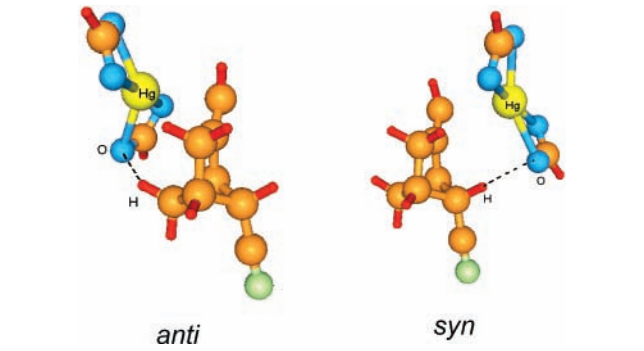

Figure 2. $(HCOO)_2Hg$ forming a pre-reaction complex with **6a** on the anti and syn side. O···H weak bonding distance is 2.9 and 2.4 Å for the anti and syn structures, respectively.

The pre-reaction complexes bring out the stabilization effects that would be present even in the transition state. Thus, the difference in the activation energies for the syn and anti selectivities would be mainly due to this electrostatic stabilization. A representative calculation (available in Supporting Information) of structures and energetics of pre-reaction complexes and transition states at the HF/6-31G** level supports this surmise. For example, the difference in complexation energies of **6a** with BH_3 on the syn and anti faces is −0.1 kcal/mol. The corresponding values of activation barriers calculated at the same level are 14.42 and 14.50 kcal/mol, and the energy difference of −0.08 kcal/mol is quite comparable to that obtained from pre-reaction complexation energetics. Considering the computational complexity involved in the calculation of transition structures of larger substrates, one may employ precomplexation energetics as indicators of facial selectivity.

The structures of the pre-reaction complexes for syn- and anti-face addition for oxymercuration are presented in Figure 2. The distances between the acidic hydrogen of the substrate and a negative site on the electrophile are also indicative of the electrostatic stabilization that induces a syn preference (see Figure 2). Similar trends are observed for the pre-reaction complexes with other electrophiles.

In summary, we have studied electrophilic additions to the novel 2-methylene-bicyclo[2.1.1]hexane system and find that the face selectivity in this system is modulated through the interplay of electrostatic and Cieplak-type orbital effects whose involvement have been gleaned through MESP topographical analysis and bond density calculations. A study of energetics of pre-reaction complexes provides evidence of dependence of the facial selectivity on the electrostatic stabilization through interaction between the substrate and the electrophile.

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Supporting Information Available: Description of experimental procedures and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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