Electrostatic origin towards the reversal of π-facial selectivity of 5,6-cis,exo-disubstituted bicyclic[2.2.2]oct-2-enes with *m*-chloroperbenzoic acid and diazomethane: a computational study

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ABSTRACT

A computational (B3LYP/6-31G* and MP2/6-31G*) study shows that electrostatic interaction is controlling the π-facial selectivity for the addition of peracid and diazomethane to 5,6-cis,exo-disubstituted bicyclic[2.2.2]oct-2-enes (**1**). The nitrogen centre of diazomethane which does not participate in bond formation governs the π-face selectivity in 1,3-dipolar cycloaddition reactions with **1**. The calculated results show that Cieplak model is less important in controlling the face selectivity in these cases.

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The origin of π-facial diastereoselection has been the subject of intense debate for half a century and being an active area of research.[1–8] The possibility of inducing π-facial selectivity in addition to trigonal carbon through remote electronic perturbation has been of considerable interest.[2–8] A number of carefully designed substrates in which the role of steric effects has been avoided were used to examine the relative preferences with remote substituents.[5] The impressive volume of experimental data obtained in recent years provides a testing ground for the numerous qualitative models,[6] semi-quantitative models[7] and quantitative studies[8] which have been employed for rationalizing and predicting π-face selectivity. Qualitative models employed for interpreting the observed face selectivities include steric and torsional models emphasizing geometrical features in the ground state as well as in the transition states,[6,10] orbital distortion effects,[11] electrostatic effects[8,9] and different types of specific orbital interactions (Cieplak and Felkin-Anh type) in the idealized transition states.[7,11a,b] In a conformationally unconstrained substrate, the above factors may all be operative. However, in a sterically unbiased substrate, the geometrical features may not be very important. The debated Cieplak model (σ–σ* hyperconjugative hypothesis) rationalized a large body of experimental data,[4,7] however, soon turned controversial as it was considered to weaken the forming bond.[12] The Cieplak model highlights the importance of anti-periplanar σ bond

donations to the σ* of the incipient bond at the idealized transition state.[7] Newer skeletal probes with remote substituents have been employed to examine the role of hyperconjugative interactions towards the face selectivity.[4] Gandolfi et al. have employed torsionally and sterically unbiased 5,6-cis,exo-disubstituted bicyclic[2.2.2]oct-2-enes (**1**) (bearing electron-withdrawing groups) with electrophiles to probe the diastereoselectivity through remote substituents and to conform the prediction based on Cieplak model.[13] The high *syn* selectivity observed in epoxidation of **1** is in favour of the Cieplak model. However, dominance of an *anti* attack in the reactions of diazomethane is in contrast with the predictions based on the Cieplak theory.[13] The dramatic reversal of π-facial selectivity of **1** with diazomethane questioned the σ–σ* type hyperconjugative interaction in the transition state and remained a puzzle (Scheme 1, Table 1).[13] In this Letter, we have demonstrated the origin of reversal of facial selectivity of peracid and diazomethane with **1**. The density functional and ab initio calculations revealed that π-facial selectivity can be controlled by the atom centres of an electrophile, which is not directly involved in the bond formation while interacting with substrates.

The skeleton of 5,6-cis,exo-disubstituted bicyclic[2.2.2]oct-2-enes (**1**) is sterically and torsionally unbiased. Both centres of the π bond are equivalently controlled, and the presence of strong electron-attracting groups at positions C(5) and C(6) significantly decreases (through inductive effects) the electron-donating power of C(1)–C(6)/C(4)–C(5) bonds thus imbalancing the electron-donating power with respect to that of C(1)–C(7)/C(4)–C(8) bonds

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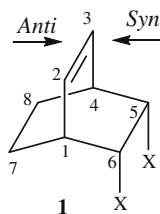
a: X=CN; b: X=OH; c: X=OAc; d: X=OSO$_2$Me;
e: X–X=OCMe$_2$O; f: X–X=OCOO

Scheme 1.

Table 1
Syn/anti ratios of *m*-chloroperbenzoic acid (*m*-cpba) and diazomethane (CH$_2$N$_2$) reactions with bicyclooctenes **1**[13]

Reagent	CN syn:anti	OH syn:anti	OAc syn:anti	OSO$_2$Me syn:anti	OCMe$_2$O syn:anti	OCOO syn:anti
m-cpba	95:5	83:17	82:18	96:4	90:10	96:4
CH$_2$N$_2$	31:69	–	–	30:70	–	38:62

(–) experimental ratios are not available.

(Scheme 1). Such a difference in the donating power of C–C bonds can influence the approach of an electrophile to the dissymmetric π-faces of olefinic bond of **1**.[7] Preliminary semi-empirical calculations performed by Gandolfi et al. suggested that the allylic *anti* σ bonds bear an almost exact anti-periplanar relationship to the 1,3-dipolar diazomethane addition to **1**.[13]

To investigate the observed difference in the selectivities of **1** with *m*-cpba and diazomethane, we have performed density

functional and ab initio calculations with B3LYP/6-31G* and MP2/6-31G* levels of theory using the GAUSSIAN 03 suite of programs.[14] Detailed computational study has been discussed in the Supplementary data. Performic acid was considered as a model for *m*-cpba.[15] The respective transition states for *syn*- and *anti*-additions of performic acid and diazomethane to **1a** and **1f** were located at B3LYP/6-31G* level (Table 2). The substrates **1a** and **1f** were selected to avoid conformational flexibility in calculations.[8a] MP2/6-31G* single point calculations were also performed to compare the relative energies with B3LYP/6-31G* optimized transition state geometries of *syn*- and *anti*-addition of electrophiles to **1a** and **1f**. Additionally, solvent effect was considered on the transition states by performing PCM continuum model calculations.[16] Dichloromethane was used as a solvent for performic acid addition to **1a** and **1f**, whereas, diethyl ether was employed for diazomethane addition as performed experimentally. The butterfly transition states have been located for the addition of performic acid to the olefinic double bonds of **1a** and **1f**.[17] The transition states calculated for the 1,3-dipolar cycloaddition of diazomethane to **1a** and **1f** are concerted in nature similar to earlier reports.[18] The formation of incipient bonds is unsymmetrical in nature. The B3LYP- and MP2-calculated results suggest that the approach of performic acid to **1a** and **1f** is energetically preferred from the *syn*-face compared to the corresponding *anti*-face in excellent agreement to the observed results (Table 2).[13] Solvent phase calculations also reproduced the *syn* selectivity though the energetic preferences were reduced compared to the gas phase results. The *anti* selectivity with diazomethane for **1a** and **1f** was also borne out in the transition state energy differences at B3LYP and MP2 levels of theory (Table 2). Solvent calculations were also in agreement with the gas phase results. Based on Cieplak model, the electron-withdrawing groups (X=CN **1a** and X–X = OCOO **1f**) substituted to **1** should dictate the

Table 2
The B3LYP/6-31G* relative energies calculated for *syn*- and *anti*- transition states (TS) of **1a** and **1f** with performic acid and diazomethane in gas and solvent phase [in parentheses] with ZPVE corrections (kJ/mol)

		1a(*syn*)	**1a**(*anti*)	**1f**(*syn*)	**1f**(*anti*)
B3LYP/6-31G*	TS	0.0(0.0)	11.7(5.4)	0.0(0.0)	11.8 (8.4)
	Charge on O$_4$	0.0	10.0	0.0	12.0
MP2/6-31G*	TS	0.0(0.0)	13.1(6.7)	0.0(0.0)	14.8(10.9)
	Charge on O$_4$	0.0	9.5	0.0	11.9

		1a(*syn*)	**1a**(*anti*)	**1f**(*syn*)	**1f**(*anti*)
B3LYP/6-31G*	TS	3.0(4.8)	0.0	0.5(1.3)	0.0
	Charge on N$_2$	3.9	0.0	0.8	0.0
MP2/6-31G*	TS	3.1(4.6)	0.0	0.7(0.6)	0.0
	Charge on N$_2$	4.8	0.0	0.7	0.0

Single point MP2/6-31G* relative energies (kJ/mol) are shown here. Bond lengths are in (Å). The relative energies (in kJ/mol) derived with charge model is also shown here. [Nitrogen: blue; carbon: grey; oxygen: red; hydrogen: white].

syn approach of electrophiles. The *syn* selectivity predicted with performic acid in the transition state calculations is in the line of agreement with Cieplak model, however, the *anti* selectivity predicted for the approach of diazomethane towards **1a** and **1f** is in contrary to this model. The apparent failure of hyperconjugative effects in sterically unbiased **1a** and **1f** to explain the stereoselectivity with diazomethane suggests that other factors are important to dictate the selectivity in this case. The electrostatic effects of remote substituents suggested to be important on the stereoselectivities of nucleophilic additions on bicyclic systems.[8,9e] In the semi-quantitative model, electrostatic effect was modelled with a charge placed at 1.4 Å away from the reactive carbon centre,[8a] and in another model study, the electrostatic interactions between substituents and nucleophile, the negative charge was placed at the location of the hydride in the LiH transition structures.[9e] Similar evaluation of electrostatic effects with electrophiles is not known to rationalize the face selectivity for trigonal carbons, presumably placing the charge on a particular position of a multi-centre electrophile is non-trivial and hence a unique model cannot be made. Combination of ab initio MESP maps and pre-reaction complexation was formulated to explain the stereoselectivity for electrophilic additions to sterically unbiased systems.[4b] However, the formation of such pre-reaction complexations may be unlikely with electrophiles like diazomethane or other linear 1,3-dipolar systems.

To evaluate the electrostatic effects with charge model in the transitions states, it is therefore important to locate the position of an electrophile to place the charge that can have a significant influence on the stereoselectivity. Analyzing the CHelpG charges,[19] it has been found that the performic acid oxygen (O_4) participates in the bond formation bears a considerable negative charge on it, whereas, the nitrogen atom (N_2) not involved in the bond formation with **1a** and **1f** of diazomethane bears a large positive charge (Fig. 1). The *m*-cpba showed similar charge distribution as observed for modelled performic acid on respective atoms (see Supplementary data). The B3LYP/6-31G(d)-computed electrostatic potentials $V_s(r)$ on the surface of performic acid and diazomethane show that the negative potential $V_{s,min}$ on O_4 is −100.46 kJ/mol, whereas, positive potential $V_{s,max}$ on N_2 is 76.18 kJ/mol (Fig. 1).[20] Examining the transition state geometries of **1a** and **1f** with performic acid and diazomethane it appears that these atom centres of electrophiles are appropriately placed for the interaction of positive charges on C(5) and C(6) carbon atoms compared to C(7) and C(8) atoms in Scheme 1. Hence the attractive interaction with the performic acid oxygen atom (O_4) would be larger with *syn*-face, whereas, the deleterious repulsive interaction should occur more on *syn*-face with the nitrogen atom (N_2) of diazomethane. The calculations performed with the relative CHelpG charges taken from the respective transition states for oxygen atoms (O_4) and placing them at their positions in transition state geometries suggest that the *syn*-face is preferred over *anti*-face.[21] The relative energies cal-

culated with the charge model are similar to the transition state energies computed at the same levels of theory (Table 2). Similar analysis with CHelpG charges on (O_3) oxygen atoms also predicted the observed trend of selectivity, however, the energy differences are much smaller compared to (O_4) oxygen atoms (see Supplementary data). Performing similar analysis, *anti* selectivity was predicted while placing the relative CHelpG charges on the nitrogen atom (N_2) positions in diazomethane TSs in agreement with the observed results.[13] The relative CHelpG charges on the interacting carbons and hydrogens in the transition states of **1a** and **1f** with performic acid and diazomethane also corroborates the above analysis (see Supplementary data). These results clearly indicate that the face selectivity observed for **1** with peracid and diazomethane is primarily governed by electrostatic effects. The Cieplak-type orbital interactions are less important in these cases (see Supplementary data). The relative energy difference predicted with transition states and charge model for the addition of diazomethane to **1f** is smaller than that of **1a**. Comparing the selectivities observed for the addition of diazomethane with **1f** is also lower compared to those with **1a**.[13] The difference in the selectivities for **1a** and **1f** presumably arises due to the transition state distortions with diazomethane. The single-point calculations performed without diazomethane for *syn*- and *anti*-transition states geometry suggest that there is no preference in energy for **1a**, whereas, the geometry obtained from *syn*-addition of diazomethane to **1f** is 1.3 kJ/mol stable compared to *anti* addition, which contributes to dampen the *anti* preference for the latter case (see Supplementary data).

We report the origin of π-facial selectivity of **1** with performic acid and diazomethane computationally. The reversal of selectivity observed with electrophiles performic acid and diazomethane arises due to the electrostatic effect. Cieplak-type hyperconjugative interaction is less important to control the face selectivity for **1**. The combined transition state and charge model calculations showed that the atom centre of an electrophile which is not directly involved in the bond formation can contribute to govern the face selectivity, besides other factors known in the literature.[6–11] The application of such charge models will be useful to rationalize or to predict the face selectivity with electrophiles in other cases as well.

Acknowledgements

Supplementary data

Absolute energies and Cartesian coordinates and frequencies of transition states **1a** and **1f** with performic acid and diazomethane are given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.100.

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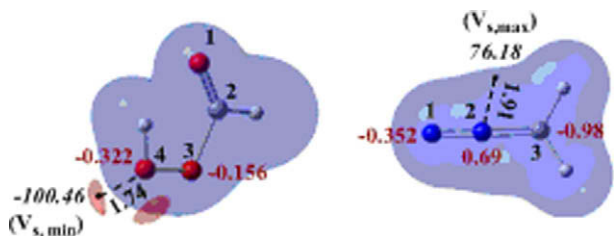
Figure 1. The CHelpG charges (in brown) at B3LYP/6-31G(d) of performic acid and diazomethane are given here. The computed B3LYP/6-31G(d) $V_{s,min}$ and $V_{s,max}$ on the electrostatic isopotential surface[20] in kJ/mol for performic acid and diazomethane are shown in italics. The locations of $V_{s,min}$ and $V_{s,max}$ are given in Å.

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