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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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A B S T R A C T

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.

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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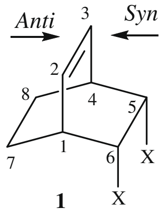


a: X=CN; b: X=OH; c: X=OAc; d; X=OSO_2Me;
e: X-X=$OCMe_2O$; f: X-X=OCOO

Scheme 1.

Table 1
Syn/anti ratios of *m*-chloroperbenzoic acid (*m*-cpba) and diazomethane (CH_2N_2) reactions with bicyclooctenes **1**[13]

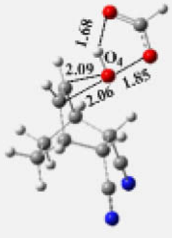
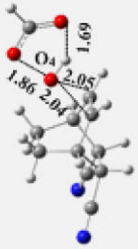
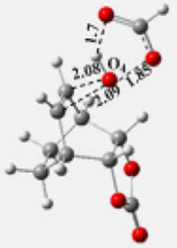
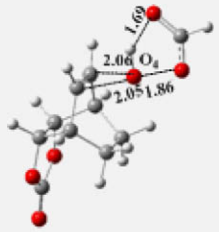
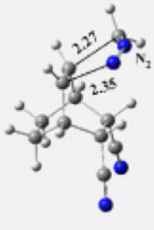
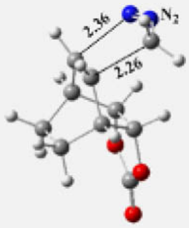
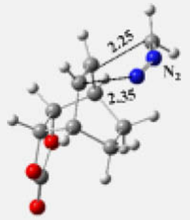
Reagent	CN *syn:anti*	OH *syn:anti*	OAc *syn:anti*	OSO_2Me *syn:anti*	$OCMe_2O$ *syn:anti*	OCOO *syn:anti*
m-cpba	95:5	83:17	82:18	96:4	90:10	96:4
CH_2N_2	31:69	—	—	30:70	—	38:62

(—) 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/	TS	0.0(0.0)	11.7(5.4)	0.0(0.0)	11.8 (8.4)
6-31G*	Charge on O_4	0.0	10.0	0.0	12.0
MP2/	TS	0.0(0.0)	13.1(6.7)	0.0(0.0)	14.8(10.9)
6-31G*	Charge on O_4	0.0	9.5	0.0	11.9
		 **1a**(*syn*)	 **1a**(*anti*)	 **1f**(*syn*)	 **1f**(*anti*)
B3LYP/	TS	3.0(4.8)	0.0	0.5(1.3)	0.0
6-31G*	Charge on N_2	3.9	0.0	0.8	0.0
MP2/	TS	3.1(4.6)	0.0	0.7(0.6)	0.0
6-31G*	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].