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A computational approach towards predicting π-facial selectivity in sterically unbiased olefins: an evaluation of the relative importance of electrostatic and orbital effects

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ABSTRACT

Computational studies are presented to show that electrostatic interactions significantly impact the stereochemical outcome in electrophilic addition to a number of sterically unbiased alkenes. Transition states have been located for the reaction of different electrophiles with all the sterically unbiased alkenes studied here and the calculations effectively include interactions involving the σ and σ* orbitals of the newly formed bond. Electrostatic interaction between the substrates and electrophiles was modelled by removing the electrophiles from the transition state geometry and placing the calculated charge at a distance from a selected atom as observed in TS structures. Electrostatic interactions between the electrophiles and the substrate seem to effectively determine the face selectivities in the systems studied and our model calculations indicate that it may not be important to invoke Cieplak type orbital interactions to rationalize the observed face selectivities. The face selectivities predicted for these alkenes and electrophiles with DFT B3LYP/6-31G* and ab initio MP2/6-31G* levels are generally in good agreement.

1. Introduction

Induction of face selectivity in electrophilic addition to the olefinic group through remote electronic perturbation is an elegant approach towards stereoselective bond formation. Systems have been designed where the carbonyl group is positioned in an isosteric environment but remote electronic modification through distal substituents can be used to achieve significant diastereoselectivity during electrophilic additions through face-selection (Scheme 1).[1] It is now well recognized that long range electronic effects can play decisive roles in determining π-facial selectivity. However, precise nature of these effects and how exactly they engender stereo-differentiation during electrophilic addition is still a challenge, despite devising and investigating many experimental probes and invoking a variety of theoretical models.[2] Geometric and orbital distortions, electrostatic effects, different types of specific orbital interactions (Felkin–Anh and Cieplak type) have been employed to understand the observed results.[3] The Cieplak model highlights the importance of anti-periplanar C–C σ bond donations to the σ* of the incipient bond C–H at the transition state.[3e,f] The role of electrostatic interactions, Felkin–Anh model, transition state model, desymmetrization of the π-orbital, pre-complexation model, cation complexation model[4j,k,5j–l,n] etc. constitute some of the other attempts put forward to rationalize the face selectivities.[3a–d,3h,4]

Modelling face selectivity has been a challenging task for theoretical and computational methodologies.[5] The quest for devising chemically intuitive models to predict π-face selectivity and to discern the factors responsible for such selectivities continues to engage attention. The semi-empirical MNDO model and the transition state model to predict the π-face selectivity for the nucleophilic addition to sterically unbiased ketones helped to segregate the importance of orbital and electrostatic effects.[2d,5d,6] However, segregation of the various electronic factors responsible for the π-face selectivity in electrophilic additions to sterically unbiased alkenes has received only limited attention.[1e,f,n,o,2g,7] The assessment of electrostatic effects with electrophiles is not known to fully rationalize the face selectivity in addition to trigonal carbons; presumably placing the charge on a particular position of a multi-centre electrophile is a non-trivial exercise. Recently, we have evaluated the origin of reversal of facial selectivity in peracid and diazomethane addition to 5,6-*cis*,*exo*-disubstituted bicyclic[2.2.2]oct-2-enes employing a newly developed model for the approach of electrophiles to the olefinic systems that segregates electrostatic

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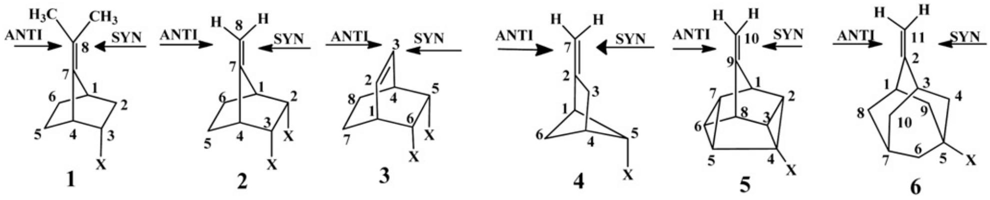


X = -CN, -COOMe, $-CH_2CH_3$, -F, $-CH_3$; X-X = -OCOO-

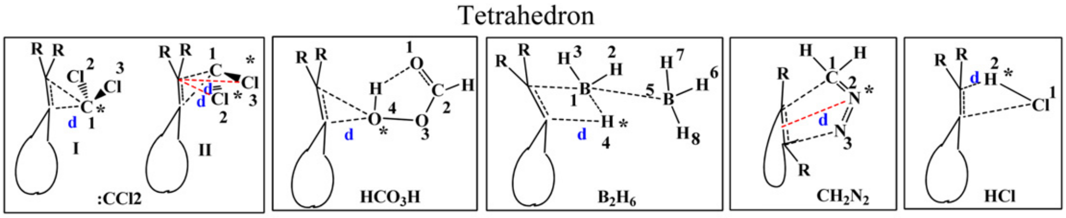
Scheme 1.

component from the orbital effects.[1o] Our intent was to invoke this electrostatic model to evaluate π-face selectivity in sterically unbiased olefins like *endo*-substituted 7-isopropylidenenorbornanes (**1**); 2,3-*endo*,*endo*-7-methylenenorbornanes (**2**); 5,6-*cis*,*exo*-disubstituted bicyclic[2.2.2]oct-2-enes (**3**); 5-*exo*-bicyclo[2.1.1]hexane (**4**); 4-substituted 9-methylenenorsnoutanes (**5**) and 2,5-disubstituted adamantanes (**6**) during addition of different electrophiles like *m*-chloroperbenzoic acid (*m*-CPBA), diazomethane (CH_2N_2), chlorocarbene ($:CCl_2$), diborane (B_2H_6) and Hydrochloric acid (HCl). The origin of face selectivities observed in polycyclic systems **1**–**6** with different electrophiles were earlier considered[1c,e–h,n] in terms of the dominant role played by the Cieplak type hyperconjugative interactions. Generally, electrostatic effect were suggested to be less important to control the face selectivities in such systems, except in the case of **4**, where the diastereofacial selection was reported through the interplay of electrostatic and Cieplak type orbital effects.[1n] MESP analysis was performed in selected cases to examine the efficacy of electrostatic effects in explaining the observed diastereoselectivites in sterically unbiased olefins. However, a direct comparison of the electrostatic and orbital models was not available in these cases as was reported for the nucleophilic addition to the carbonyl groups.[5a,d] Herein, we disclose the results of a computational study to gauge the role of electrostatic and orbital interactions directly, employing the response of substrates **1**–**6** (Scheme 1) towards different electrophiles and discern their relative importance to explain the experimentally observed face selectivities. The structural diversity of substrates **1**–**6**, harbouring both *endo*- and *exo*cyclic double bonds and substitution patterns was expected to provide an intriguing testing bed for our model and the approach of the electrophiles.

2. Computational details

All the substrates and electrophiles and the transition state geometries for the *syn*- and *anti*-addition of these systems were fully optimized with B3LYP/6-31G* level of theory.[8] B3LYP/6-31G* level has been used in other π-facial studies.[4j,k,5o,t,9c] The importance of computational methods and models to qualitatively predict the π-facial selectivity of nucleophilic addition to sterically unbiased ketones has been reported.[5p] The relative energies calculated with B3LYP/6-31G* level were also corrected with zero point vibrational energies (ZPVE). Enthalpy corrected relative energies are given in the Supplementary data (Table S7). Scheme 2 shows the model transition state geometries for the addition of various electrophiles to the substrates **1**–**6**. The harmonic vibrational frequencies were computed to determine the minima and the first order saddle points in each case. Further, MP2/6-31G* calculations[10] were performed using B3LYP/6-31G* optimized geometries to calculate the energy differences for *syn*- and *anti*-addition of electrophiles to the above mentioned substrates.

To segregate the electrostatic effects from orbital effects, the charge model derived to explain the face selectivity of 5,6-*cis*,*exo*-disubstituted bicyclic[2.2.2]oct-2-enes was employed in all cases.[1o] The electrophile modelled with point charge (PC) to examine the reactivity of the acetaldehyde enolate has been reported.[11] It is important to emphasize that the charge model is not identical to the use of molecular electrostatic potential maps (MESP). The latter method is a more direct approach to examine the electrostatic effects and has indeed been successfully applied for a number of studies of regiochemical and facial selectivities in conjunction with both ab initio and semi-empirical methods.[12] 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. The electrostatic interactions were modelled with the CHelpG charges[10,13] of the specific atom of the electrophiles obtained in the transition state calculations and placing them at the calculated distance (d) as shown in Scheme 2. The atoms modelled for the charge calculations in different electrophiles are those, which remain in the final products. In the case of dichlorocarbene ($:CCl_2$) addition to these substrates, there is a possibility of attack from both ends of the double bond, as shown in **I** and **II** (Scheme 2). In **I**, the charge on the carbon atom of $:CCl_2$ and in **II** the charge of chlorine atoms are used to perform the charge model calculations. For convenience, performic acid was considered as a model for *m*-CPBA.[14] In case of performic acid, the charge calculations are performed by removing the electrophile and adding the charge in place of the $\mathbf{O_4}$ oxygen atom. For diborane (B_2H_6) addition, the charge of the hydrogen ($\mathbf{H_4}$) is taken in each case. In the case of diazomethane (CH_2N_2), the CHelpG charge of the nitrogen atom ($\mathbf{N_2}$), which is not involved in the bond formation with the substrate is taken for the



R = H or CH_3

Scheme 2. '*' denotes the atom on which the CHelpG charge is placed in the charge model calculation using the transition state geometries.