

# Reagent-Specific Electrostatic Effects on Electrophilic $\pi$ -Facial Stereoselectivity. Interpretation of the Stereochemical Variation of Electrophilic Additions to 7-Isopropylidenebenzonorbornenes

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Electrostatic interactions account for the stereochemical variations in electrophilic additions to 7-isopropylidenebenzonorbornenes. Different electrophilic reagents have very different electrostatic profiles. This conclusion is supported by electrostatic potential analyses of 7-methylenenorbornene and 7-methylenebenzonorbornene or by calculations on the interactions of point charges with the two faces of the  $\pi$  system.

## Introduction

Electrostatic interactions are becoming increasingly prominent as factors which influence reactivity and selectivity in organic reactions.<sup>1-3</sup> Electrostatic interactions join steric effects and orbital interactions as factors which merit consideration in understanding stereoselectivities of many processes. With the development of computational algorithms and visualization tools,<sup>4</sup> electrostatic forces have been invoked to explain  $\pi$ -facial stereoselectivities of Diels-Alder reactions,<sup>1a</sup> nucleophilic additions to carbonyls,<sup>2</sup> and electrophilic additions to double bonds.<sup>3</sup> We report here that electrostatic effects rationalize the stereoselectivities of electrophilic additions to rigid alkenes, a reaction subject to intensive and often contradictory discussions.<sup>5-8</sup> Most importantly, the electrostatic potentials of both electrophilic reagent and substrate must be considered to understand the role of these polar effects in stereochemistry.

## Background

In a systematic study of electrophilic additions to substituted 7-isopropylidenebenzonorbornenes, Paquette *et al.* demonstrated the electronic effects of both electrophile and alkene on stereoselectivity.<sup>9</sup> As shown in Figure 1 and Table I, the results can be summarized as follows: (1) epoxidation by *m*-chloroperbenzoic acid (*m*-CPBA) and ene reactions with *N*-methyltriazolinedione (NMTD), singlet oxygen (<sup>1</sup>O<sub>2</sub>), or *N*-bromosuccinimide (NBS) give predominant anti addition; the preference for anti addition decreases in the series 1 > 2 > 3; (2) dichlorocarbene prefers syn addition; (3) Friedel-Crafts acylation and hydroxymethylation (Prins reaction) occur with completely syn addition; (4) ene chlorination with *tert*-butyl hypochlorite changes from predominant anti addition in methyl formate solution to predominant syn addition in a 1:1 mixture of methyl formate and formic acid.

Paquette and Gleiter suggested that the syn addition is intrinsically favorable for steric reasons, but there is a fundamental difference in electronic interactions in transition structures between weak electrophiles and strong electrophiles.<sup>9a</sup> For the attack of weak electrophiles, such as *m*-CPBA, NMTD, <sup>1</sup>O<sub>2</sub>, and NBS, large polarization is required in the relatively late transition states, and anti attack is favored because of  $\pi$ -involvement as shown in 5. For the attack of strong (especially positively charged) electrophiles, the  $\pi$ -involvement becomes unimportant because polarization is unnecessary. The syn addition becomes favorable because of preassociation between the electrophile and the aromatic ring, as shown in structure 6.

In addition to  $\pi$ -orbital participation, an anti-periplanar  $\sigma$ -orbital effect may also influence the stereoselectivity. That is, an electron-donating C-C<sub>sp3</sub> bond placed anti-periplanar to the attacking electrophile can cause more electron donation to the electron-demanding reaction center than a C-C<sub>sp2</sub> bond; this will favor syn attack. This effect, as well as the  $\pi$ -orbital involvement, is important

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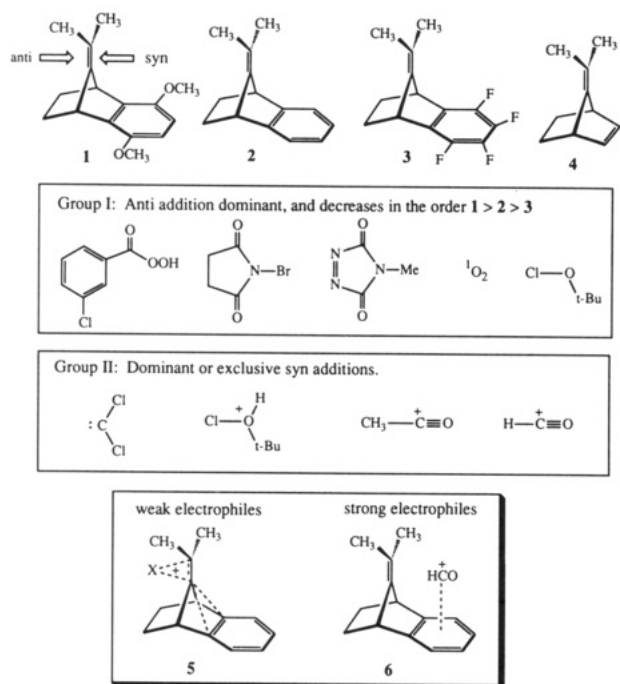
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**Figure 1.** Summary of experimental stereoselectivities of electrophilic additions to 1-4 and a schematic illustration of electronic interactions in transition structures of weak electrophilic attack and strong electrophilic attack proposed by Paquette and Gleiter.

**Table I. Experimental Stereoselectivities in Electrophilic Additions to 1-4<sup>a</sup>**

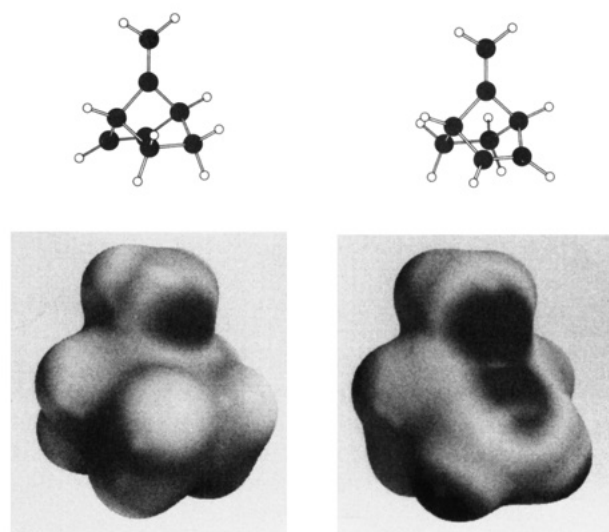
	1 syn:anti	2 syn:anti	3 syn:anti	4 syn:anti
<i>m</i> -CPBA (25 °C, CH <sub>2</sub> Cl <sub>2</sub> )	11:89	17:83	37:63	
MTAD (25 °C, CH <sub>2</sub> Cl <sub>2</sub> )	16:84	19:81	57:43	5:95
NBS (25 °C, aqueous glyme)	14:86	19:81	55:45	
<sup>1</sup> O <sub>2</sub> (CH <sub>2</sub> Cl <sub>2</sub> )	21:79	20:80	54:46	14:86
(methanol)	17:83	24:76	56:44	
:CCl <sub>2</sub>	80:20	65:35	87:13	88:12
<sup>t</sup> BuOCl (HCOOCH <sub>3</sub> )	24:76	15:85	47:53	
(formic acid, MF)	67:33	80:20	91:9	
AcCl-AlCl <sub>3</sub> (-10 °C, CH <sub>2</sub> Cl <sub>2</sub> )	100:0	100:0	100:0	100:0

<sup>a</sup> From ref 9c.

only for the reactions where large extent of carbonium character develops, as demonstrated for the solvolysis of a variety of norbornene derivatives.<sup>10</sup> However, for most electrophilic addition reactions, only a small portion of positive charge develops at the alkene moiety, and hyperconjugative stabilization by an anti-periplanar donor is not significant. The insignificance of anti-periplanar  $\sigma$ -orbital effects has been shown in nucleophilic additions to cyclohexanone and related compounds;<sup>11</sup> we concluded that the preference of axial attack by small nucleophiles

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**Figure 2.** Optimized geometry of 7-methylenenorbornene and electron density surfaces encoded by the electrostatic potentials calculated at the RHF/6-31G\* level.

is largely caused by torsional strain in the equatorial transition structure, as suggested by Felkin *et al.* in 1968.<sup>12</sup> Anti-periplanar electron donation (the Cieplak effect)<sup>13</sup> is of no importance.

We also demonstrated that electrostatic effects of remote substituents can significantly influence the stereoselectivity of nucleophilic additions.<sup>2a,f,14</sup> Paquette, Gleiter, *et al.* cited such electrostatic effects to rationalize the stereoselectivities of electrophilic attack on benzobicyclo[2.2.2]octadienes.<sup>9e</sup> In their original publications, Paquette and Gleiter calculated the electrostatic potentials of 1-3, but they suggested that the electrostatic potential had a minor influence on stereoselectivity relative to the effects described above.<sup>9c</sup>

## Results and Discussion

In this paper, we investigated the structures and electrostatic potentials of 7-methylenenorbornene and 7-methylenebenzonorbornene. The geometries were optimized with the 6-31G\* basis set<sup>15</sup> using the GAUSSIAN 90 program,<sup>16</sup> and electrostatic potentials were calculated and the graphics were prepared with the SPARTAN programs.<sup>4</sup>

In Figure 2, the geometry of 7-methylenenorbornene optimized at the HF/6-31G\* level is shown. The cyclopentene ring is flatter than the cyclopentane ring by 6° due to the shorter length of a C=C double bond. This is

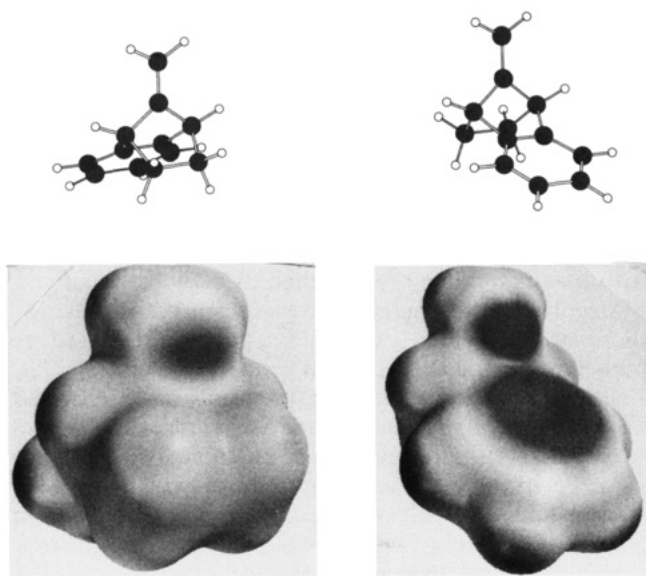
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**Figure 3.** Optimized geometry of 7-methylenenorbornene and electron density surfaces encoded by the electrostatic potentials calculated at the RHF/6-31G\* level.

indicated by the  $C=C-C-C_{sp^2}$  torsional angle of  $133^\circ$  compared to the  $C=C-C-C_{sp^3}$  of  $120^\circ$ . As a result, the syn addition by an electrophile is slightly favored by torsional effects. The approach from the syn face occurs with slightly less eclipsing than attack from the anti face. Similar distortion is found in the HF/6-31G\* geometry of 7-methylenenorbornene as shown in Figure 3.

The 6-31G\* electrostatic potentials are encoded onto the electron density surfaces of 7-methylenenorbornene and 7-methylenenorbornene in Figures 2 and 3, respectively.<sup>4</sup> The surfaces represent values of the electron density equal to  $0.002 e/\text{\AA}^3$ . The most negative electrostatic potentials above the  $\pi$  systems are represented by dark areas, while the most positive electrostatic potentials on the hydrogens are also darkened. For 7-methylenenorbornene, the electrostatic potentials range from  $-27$  kcal/mol over the  $\pi$  system to  $+23$  kcal/mol near the hydrogens. The negative potential corresponds to a region of high electron density and attraction for a plus charge or repulsion of a negative charge. Similarly, the electrostatic potentials range from  $-29$  kcal/mol to  $+22$  kcal/mol on the electron density surfaces of 7-methylenenorbornene (Figure 3). These surfaces clearly demonstrate that positively-charged electrophiles will preferentially attack the bridged double bond from darker regions to give syn attack, as a result of electrostatic effects. "Negative" electrophiles will avoid more negative syn  $\pi$ -face and undergo anti attack. Note that the electrostatic potential directly at the  $\pi$  bond being attacked, as well as in the neighborhood produced by the proximity of the alkene or aromatic ring, has become decidedly more negative.

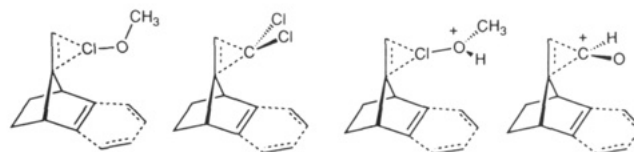
A simple calculation can provide similar information of a quantitative nature. Table II gives a 6-31G\* energies of 7-methylenenorbornene with or without an added partial charge placed 2.0 Å away from C7, either above (syn) or below (anti) the alkene plane. A 0.2 unit of positive charge at Q(syn) results in 5.9 kcal/mol stabilization, or 2.7 kcal/mol stabilization when it is at Q(anti). A 0.2 unit of negative charge at syn position results in 3.3 kcal/mol destabilization and has almost no effect when the charge is placed at the anti position. This clearly indicates that

**Table II.** 6-31G\* Energies of 7-Methylenenorbornene with an Additional Charge of 0.2e Placed 2.0 Å Above or Below the C7 Atom

	charges	$E_{rel}$ (kcal/mol)
	Q(syn) = +0.2	-5.9
	Q(anti) = +0.2	-2.7
	Q(syn) = -0.2	3.3
	Q(anti) = -0.2	-0.3

the cyclopentene  $C=C$  double bond stabilizes a positively charged electrophile and destabilizes a negatively charged electrophile. Calculations show that the electrostatic potentials are  $-34.0$  and  $-28.4$  kcal/mol at Q(syn) and Q(anti) positions, respectively.

The nature of the electrophiles was also explored with electrostatic potentials. Considering the expected trajectories shown below for four electrophiles, the interactions with the  $\pi$ -systems of norbornene and benzenorbornene will be repulsive with  $t\text{BuOCl}$  ( $\text{CH}_3\text{OCl}$  calculated as the model), attractive with  $\text{CCl}_2$ , and very attractive with the positively charged electrophiles.



The results lead to the following explanations of the experimental data. In the concerted transition structure of ene reaction of  $^1\text{O}_2$  with propene,<sup>17</sup> *ab initio* calculations suggest that there is no significant polarization of the O-O bond and no significant charge transfer from the alkene to  $\text{O}_2$ . The same phenomenon has been found for epoxidation of ethylene by performic acid.<sup>18</sup> On the other hand, reactions of strong electrophiles ( $\text{CH}_3\text{CO}^+$  and  $\text{HCO}^+$ ) involve bridged complexes, and there is a larger charge transfer in transition structures.<sup>19</sup> Therefore, the alkene moiety in the transition structures involving strong electrophiles has more positive charge development than those involving weak electrophiles. This would imply that  $\pi$ -involvement should be stronger for the reactions of strong electrophiles, which is opposite to Paquette's reasoning (5 and 6).

All the weak electrophiles which prefer anti addition bear lone-pair electrons and have high electron densities on their surfaces. They are effectively "negative" or "nucleophilic" in their ground states: Hehre, Chamberlin, and Kahn aptly and amusingly described such reagents as "transvestial"!<sup>3d</sup> Other electrophiles of this type are osmium tetroxide and permanganates.<sup>3</sup> Additions of these electrophiles to alkenes occur preferentially from the less electron-rich  $\pi$ -face of the alkenes. Dichlorocarbene, which gives moderate syn preference, has an electrophilic carbon which is slightly positively charged.  $\text{CH}_3\text{CO}^+$  and  $\text{HCO}^+$ , which lead to complete syn additions, have large positive charges at the attacking carbon. We suggest that electrostatic effects play an important role in

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determining the direction of addition of both weak and strong electrophiles. A "negative" electrophile gives anti addition because the electrostatic repulsion between the electrophile and the electron-rich aromatic ring in the syn transition structure steers attack to the anti face. This differs from earlier explanations because it emphasizes that syn addition is disfavored, not that anti addition has special stabilization. A positive electrophile favors syn addition because both torsional effects and electrostatic attractions are favorable in the syn transition structure.

The effects of substituents on the aromatic ring are consistent with this explanation. The syn addition by "negative" electrophiles is reduced by electron-donating substituents on the aromatic ring and enhanced by electron-acceptor substituents. That is, when the aromatic ring becomes more electron-rich, the "negative" electrophiles are repelled more and more anti addition is observed. The same pattern would be observed as a result of the neighboring-group participation proposed by Paquette and Gleiter, and both effects may operate to some extent.

*tert*-Butyl hypochlorite gives mainly anti addition, but protonated *tert*-butyl hypochlorite gives mainly syn addition. This can also be rationalized in terms of electrostatic interactions between electrophiles and substrates.

Electrostatic effects are traditionally thought to be important in reactions of ionic species, or "hard" electrophiles, where the reaction is said to be under charge control. Orbital overlap interactions are generally invoked for the reactions of neutral or "soft" species.<sup>20</sup> Electrostatic interactions involving a positively charged electrophile are significant in the early stage of the reaction and become smaller as charge transfer occurs. On the other hand, electrostatic repulsive interactions involving a neutral electrophile should increase along the reaction path as more electron density is transferred to the electrophile. Electrostatic effects on the stereoselectivities of electrophilic additions have been proposed previously in several different ways. The complex formation for strong electrophiles proposed by Paquette and Gleiter involves electrostatic and charge-transfer stabilization.<sup>9</sup> The frontier molecular orbital interactions in carbene addition by

Okada *et al.* are related, although they emphasize orbital, not electron density repulsions.<sup>21</sup> The electron-density surface analysis applied by Hehre *et al.*<sup>1-3</sup> to electrophilic additions to acyclic alkenes has been applied here. It is useful when the ground state is approximately the same geometry as the transition state.

How does this electrostatic potential explanation compare with frontier orbital descriptions of reactivity and  $\pi$ -facial selectivity? When electron-donating and electron-withdrawing groups are attached directly to an alkene, the frontier orbital energies and coefficients are influenced to a large extent.<sup>20</sup> These changes can be used to understand changes in reactivity and regioselectivity. The same effects alter electrostatic potentials, and Hehre and Kahn have shown that some regioselectivities and stereoselectivities can alternatively be explained with electrostatic potentials. In such cases, the two explanations are related and probably nonseparable, since changes in orbitals ultimately lead to changes in total electron densities and electrostatic potentials.

However, for the cases studied here, the substituents have no significant effect on the  $\pi$  orbitals. There are no significant alterations of either the  $\pi$  orbital energies or coefficients. In such cases, it is the long-range electrostatic interactions of reagents with the electrostatic field of the substrate which control stereoselectivities.

### Conclusion

The  $\pi$ -facial stereochemical variation of electrophilic additions to methylenenorbornenes can be attributed to simple electrostatic effects. For positively charged or partially charged electrophiles, electrostatic attractions between the electrophile and electron-rich  $\pi$ -face of the double bond favor the syn attack. On the other hand, electrostatic repulsion between the electron-rich  $\pi$ -face of the double bond and the "negative" electrophiles results in the preferred anti attack.

**Acknowledgment.** We are grateful to the National Institutes of Health for financial support of this research.

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