



## Orbital theory for diastereoselectivity in electrophilic addition



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### ABSTRACT

Electrophilic attack to a double bond is often observed anti to the most electron-donating  $\sigma$ -bond at the  $\alpha$ -position (hereafter, we refer to this as the extended anomeric effect). This preference is believed to result from the antiperiplanar effect between the bond that is formed between the double bond and the electrophilic reagent, and the donating vicinal  $\sigma$ -bond which is located on the substituent at the  $\alpha$ -position. From an orbital viewpoint, however, it is still unclear why the approach of the electrophile anti to the substituent results in stabilization or why the frontier molecular orbital (FMO) deforms, expanding toward the reagent with this antiperiplanar interaction. We demonstrate here that cyclic orbital interaction including geminal bond participation plays an important role in the diastereoselectivity in electrophilic addition. We examined our idea using the electrophilic addition of chlorine to 3-substituted propenes as a model reaction. Our bond model approach should contribute to a better understanding of orbital mixing in FMO.

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The stereoelectronic effect, which affects the selectivity and reactivity of organic reactions, has been investigated for a long time.<sup>1–3</sup> With regard to diastereoselectivity in electrophilic addition,<sup>4,5</sup> the extended anomeric effect, which here refers to a preference for the electron-donating vicinal  $\sigma$ -bond  $\sigma_{C-D}$  anti to the electrophile approach (Fig. 1a), is often considered.<sup>1–3</sup> The anomeric effect was originally recognized as a preference for a C–O bond at the axial position in the anomeric position, i.e., a C–O bond located vicinal to the oxygen in saccharides (Fig. 1b).<sup>6</sup> This preference is based on the antiperiplanar interaction between the lone pair on the oxygen and the  $\sigma^*$  orbital of the C–O bond. A similar electron flow is expected in the extended anomeric effect. Electron delocalization to the electrophile is supported by the donating  $\sigma_{C-D}$  bond at the vicinal position, which is anti to the electrophile approach. This mechanism depends on vicinal interaction, which originates from the antiperiplanar effect from the  $\sigma$  bond of the substituent *D* at the  $\alpha$ -position.

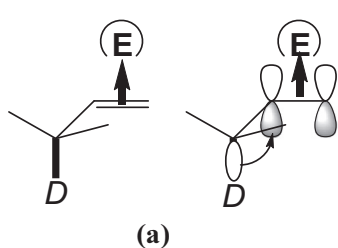
To explain this diastereoselectivity, the electrophile- $\pi$ -complex has previously been proposed to be stabilized with the vicinal donating  $\sigma$ -bond at the anti position (Fig. 2).<sup>3,4</sup> In this proposal, stabilization between  $\sigma_{C-D}$  and LUMO, which consists of  $\pi_{C=C}$  and the vacant orbital on the electrophile, should be essential for the diastereoselectivity. No destabilization should be expected from the interaction between LUMO and  $\sigma^*_{C-A}$  orbitals, since they are vacant orbitals. However, LUMO should mainly be a combination of  $\pi^*_{C=C}$  and the vacant orbital on the electrophile. Moreover, the electrophile should make a bond with the carbon at the terminal

$\text{CH}_2$  due to the Markovnikov rule, so that interaction between  $\pi_{C=C}$  and the vacant orbital on the electrophile should be considered at the terminal carbon. For the FMO theory, the electrophile, an acceptor, attacks in a direction so as to maintain the largest overlap with the HOMO as a result of the interaction between  $\pi_{C=C}$  and  $\sigma_{C-D}$  (Fig. 3). There are no explanations for why the HOMO shows larger expansion anti to the  $\sigma$  electron-donating substituent *D* with interaction between  $\pi_{C=C}$  and  $\sigma_{C-D}$ , or why the chlorine- $\pi$ -complex is stabilized with the vicinal donating  $\sigma$ -bond at the anti position. Thus, the theory still requires some empirical rule based on experimental results. If this rule could be consistent with theoretical chemistry, especially from the perspective of bond interaction, it would be a powerful tool for both experimenters and theoreticians for the rational design of new functional molecules and reactions with high efficiency and selectivity. Here we show that cyclic orbital interaction including geminal bond participation<sup>7</sup> is important for determining the  $\pi$ -facial selectivity of the double bond in the extended anomeric effect.

First, we considered the orbital phase among the bonds.<sup>8</sup> Both the  $\pi$  and  $\sigma$  orbitals in the C=C double bond are orthogonal and cannot interact with each other. However, they should be combined in-phase toward the electrophile as a result of the extended anomeric effect, since the  $\pi$  and  $\sigma$  orbitals of the C=C double bond are donors and the vacant orbital of the electrophile  $\phi^*_E$ —such as the  $\sigma^*$  orbital in halogen molecule  $X_2$ —is an acceptor.

For cyclic orbital interaction to provide stabilization, the orbital phase requirements must be satisfied: (i) donating orbitals are out-of-phase; (ii) the donating and accepting orbitals are in-phase; and (iii) accepting orbitals are in-phase.<sup>8</sup>

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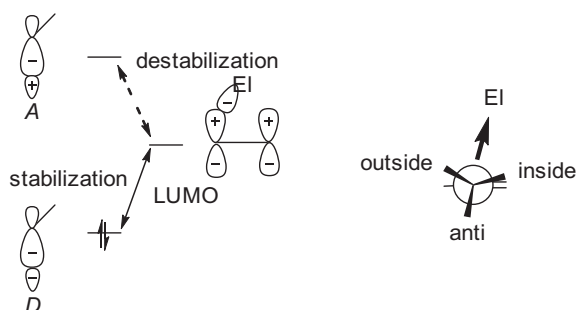


**Figure 1.** Vicinal bond interactions: the extended anomeric effect (a) and the (original) anomeric effect (b).

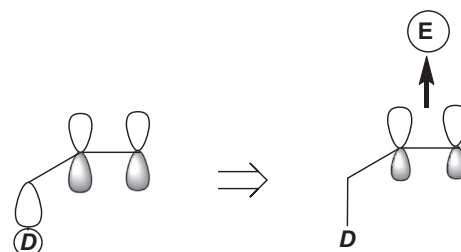
Cyclic orbital interactions are initially considered for interactions among three bodies. For interactions among more than three bodies, they are still applicable if (i) the cyclic orbital interaction is monocyclic, i.e., the bonds interact with adjacent bonds but not with those in a remote position; and (ii) the cyclic orbital interaction must be divided into only two parts, the donor and acceptor parts, and not into four, six, or so on.<sup>9</sup> The donor part consists of the donating orbitals only, such as lone pair(s)  $n$ ,  $\pi$  and  $\sigma$  orbitals. The acceptor part is solely a combination of vacant orbitals, such as  $\pi^*$  and  $\sigma^*$  orbitals. With these additional requirements, the cyclic orbital interaction satisfies the requirements for producing stabilization.

Now let us suppose cyclic orbital interaction including geminal bond participation. The vicinal  $\sigma_{C-D/vic}$  and geminal  $\sigma_{C-C/gem}$  orbitals should be out-of-phase, since they are donors.<sup>10,11</sup> The geminal  $\sigma_{C-C/gem}$  and  $\sigma_{C=C}$  orbitals should also be out-of-phase, since they are also donors. The energy gap between  $\sigma$  and  $\sigma^*$  orbitals is rather large, so that we can consider there to be little interaction between them. In addition, little interaction is expected between the  $\sigma_{C-C/gem}$  and  $\pi_{C=C}$  orbitals, since the  $\sigma_{C-C/gem}$  bond is initially on the nodal plane of the  $C=C$  bond, and interaction between the vicinal  $\sigma_{C-D/vic}$  and  $\sigma_{C=C}$  orbitals located in a rather remote position should be considerably small. Furthermore, the  $\sigma_{C-C/gem}$  and  $\sigma_{C-D/vic}$  orbitals, which overlap at the back lobe, are combined out-of-phase with the vacant orbital on the electrophile  $\phi^*_E$ . Although they are donor-acceptor interactions, delocalization from these orbitals to the electrophile  $\phi^*_E$  is suppressed since they cannot interact without destabilization. The phase of geminal bond interaction has been studied previously (Fig. 4).<sup>11</sup> Based on these considerations, the phase condition between  $\phi^*_E-\pi_{C=C}-\sigma_{C-D/vic}-\sigma_{C-C/gem}-\sigma_{C=C}$  is phase-continuous, as shown in Figure 5. The phase-continuous cyclic orbital interaction should stabilize the TS, which should accelerate the reaction.

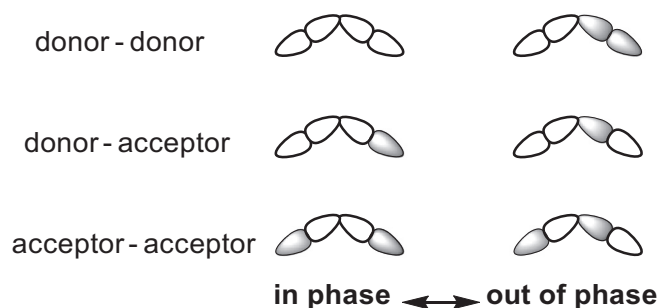
To examine our idea, we performed calculations for a model reaction, i.e., the electrophilic addition of chlorine to propene (substituent  $D=H$ ).<sup>12,13</sup> We located the  $\pi$ -complex ( $\Delta E = -1.9$  kcal/mol) and two TS's ( $\Delta H^\ddagger = 22.3$  kcal/mol and



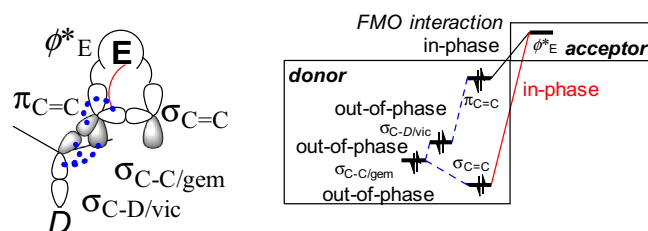
**Figure 2.** Proposed orbital interaction in diastereoselective electrophilic addition.<sup>3</sup> Note that the direction of the arrow is corrected to show the electron flow.



**Figure 3.**



**Figure 4.** Phase relationship in geminal delocalization.<sup>10,11</sup>



**Figure 5.** Cyclic orbital interaction  $\phi^*_E-\pi_{C=C}-\sigma_{C-D/vic}-\sigma_{C-C/gem}-\sigma_{C=C}$ .

26.2 kcal/mol, respectively; BMK/6-311+G(d)//B3LYP/6-31G(d),<sup>14,15</sup> Fig. 6). Interestingly, the syn-TS leads to the syn addition of chloride, while anti addition is more common in electrophilic addition. Based on careful inspection with IRC calculations, it seems to avoid the large charge separation in the chloride attack to the anti face of the three-membered ring that includes chlorine cation. A preference for anti addition in electrophilic addition seems to occur in polar solvents, where the solvent acts as a nucleophile, or with the participation of multiple molecules.

The electronic structure of the TS was subjected to the bond model analysis (BMA).<sup>16,17</sup> We used the bond model shown in Figure 7. The overlaps  $S_{ij}$  and the elements of the density matrix  $P_{ij}$  are shown in Table 1. The phase should be evaluated when  $S_{ij} > 0$ . For the bond interactions  $\sigma_{C-H/vic}-\sigma_{C-C/gem}$  and  $\sigma_{C-C/gem}-\sigma_{C=C}$ , the overlaps  $S_{ij}$  are negative. The sign of  $P_{ij}$  should be reversed with a change in the sign of one of the two orbitals. Finally, the combination of two orbitals is in-phase when  $P_{ij} > 0$ , and out-of-phase when  $P_{ij} < 0$ . Overall, the net phase condition is not in agreement with our prediction (Table 1). However, in TS, the  $\pi_{C=C}$  orbital strongly interacts with  $Cl^+$  ion, and chlorine is more electronegative than carbon. Thus, the occupied  $\pi_{C=C}$  orbital should be considerably electron-deficient. The interaction between the occupied orbitals of  $\pi_{C=C}$  and  $\sigma_{C-H/vic}$  should no longer be repulsive. This is confirmed by a low value (0.8086) of the orthogonal element of the density matrix  $P_{ii}$  of  $\pi_{C=C}$ , and the bonding nature of bond interaction between  $\pi_{C=C}$  and  $\sigma_{C-H/vic}$ , evaluated with the interbond energy IBE ( $IBE_{ij} = -0.0184$  a.u.).<sup>18</sup>

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