Theoretical Studies on the Diastereoselectivity in the *Lewis* Acid Catalyzed Carbonyl–Ene Reaction: A Fundamental Role of Electrostatic Interaction

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Lewis acids affect reactivity, selectivity, and mechanism in the carbonyl-ene reaction. The diastereoselectivity in the glyoxylate-ene reaction depends on *Lewis* acids. While the $SnCl_4$-promoted reaction can be achieved with a high level of *anti*-selectivity, the use of Al reagents leads to a high *syn*-selectivity. The origin of the *Lewis* acid dependency of the diastereoselectivity in the carbonyl–ene reaction of (*E*)-but-2-ene with glyoxylate was theoretically studied (HF/6-31G*) from the point of view of differences and similarities between the ene and the *Diels–Alder* reactions. Though it has been widely accepted that the *endo*-preference would be less obvious in the ene reaction than in the *Diels–Alder* reaction, our *ab initio* molecular studies showed that the electrostatic interaction between carbonyl O-atom lone pair and cationic allylic central C-atom of ene component exists in the *Lewis* acid-promoted carbonyl–ene reaction to affect the transition-state conformation. It is illustrated that such an electrostatic interaction is essential to control the *exo*/*endo*-selectivity, which provides the diastereoselectivity of the product in the transition state of the *Lewis* acid promoted carbonyl–ene reaction.

1. Introduction. – The ene reaction converts readily available alkenes with activation of an allylic C–H bond and allylic transposition of the C=C bond into more-functionalized products (for comprehensive reviews on ene reactions, see [1]). An ene reaction is defined as a six-electron pericyclic process between an alkene bearing an allylic H-atom (an 'ene') and an electron-deficient multiple bond (an 'enophile') to form two σ-bonds with migration of the π-bond. The ene reaction is indeed mechanistically related to the *Diels–Alder* (*DA*) reaction (*Fig. 1*) (for reviews, see [2]). The *exo*/*endo* selectivity is important in the *DA* reaction, where the *endo* transition state can be stabilized by the secondary orbital interaction to preferentially afford the *endo* product (for a review on diastereoselectivity in *DA* reactions, see [3])[4]. Since the ene reaction does not afford cyclic adducts, it has been widely

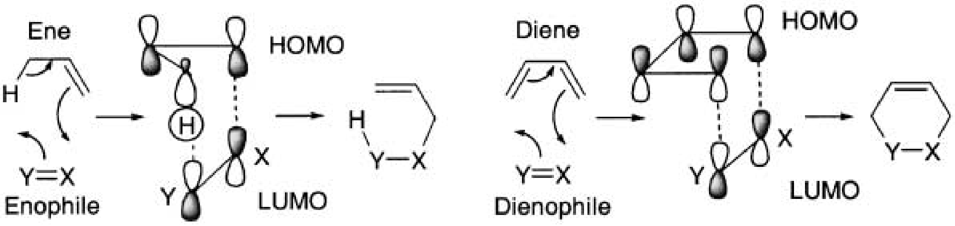
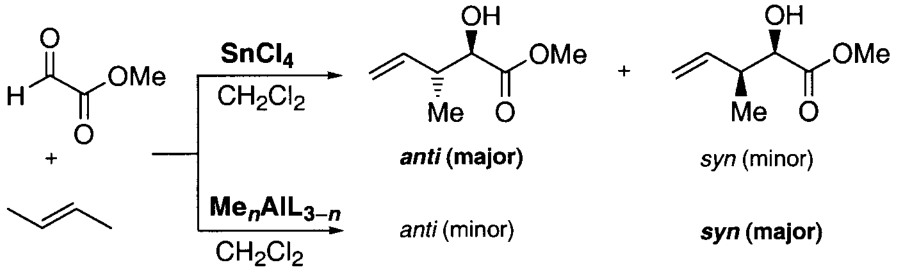


Fig. 1. *Schematic molecular-orbital interaction in ene and* Diels–Alder *reactions*

accepted that a distinction of *endo*/*exo* selectivity is less obvious in the ene reaction than in the *DA* reaction.

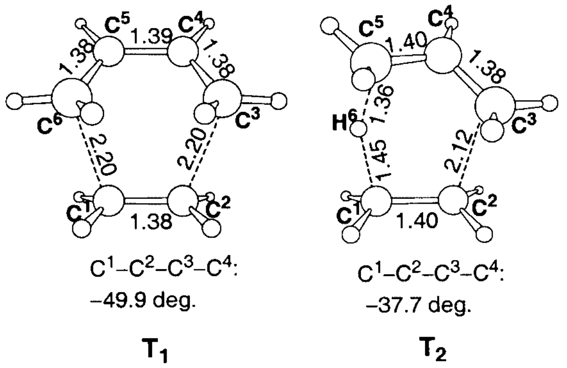
The ene reaction encompasses a number of variants in terms of the enophiles used. In particular, the class of ene reaction involving a carbonyl compound as the enophile, which we refer to as 'carbonyl–ene reaction', constitutes a more efficient alternative to the carbonyl-addition reaction of allylmetal species (for a review on carbonyl–ene reactions, see [5]). In the case where active carbonyl compounds such as glyoxylate are used as enophiles, alcohols are exclusively formed in a stereoselective manner. As shown in a pioneering work of *Snider*, coordination of *Lewis* acids to carbonyl compounds as enophiles accelerates the carbonyl–ene reaction (for a review on *Lewis* acid promoted ene reaction, see [6]). On the other hand, we have reported that the diastereoselectivity in the carbonyl–ene reaction of (*E*)-but-2-ene with glyoxylate much depends on *Lewis* acids [7]. While the $SnCl_4$-promoted reaction can be achieved with a high level of *anti*-selectivity, the use of Al reagents leads to high *syn*-selectivity (*Scheme 1*). To investigate the origin of the diastereoselectivity depending on *Lewis* acids, we carried out *ab initio* molecular-orbital calculations [8] and a natural-population analysis [9] of the *Lewis* acid promoted carbonyl–ene reaction at the HF/6-31G* level [10]. It is herein illustrated that the electrostatic interaction between carbonyl O-atom lone pair and cationic allylic central C-atom of the ene component is regarded as fundamental for controlling the diastereoselectivity in the *Lewis* acid catalyzed carbonyl–ene reaction.

Scheme 1. Lewis *Acid Catalyzed Glyoxylate–Ene Reaction*



2. Results and Discussion. – *Transition-State Conformations.* We first studied transition-state conformations of the carbonyl–ene and hetero-*Diels–Alder* (*HDA*) reactions with or without coordination of a *Lewis* acid (*e.g.*, $AlCl_3$) from the point of view of the differences and similarities between the ene and the *DA* reactions. The concerted ene reactions maximize allylic resonance by turning the axis of the breaking C–H single bond parallel to the p orbitals of the neighboring C=C bond. The 3-21G [11] and 6-31G* [12] transition structures for the thermal and concerted ene reaction of propene with ethylene have been reported by *Houk*.

Our calculations were perormed similar in fashion to *Houk*'s calculation. As shown in *Fig. 2*, the transition-state structure $\mathbf{T_1}$ is highly symmetric, and that of $\mathbf{T_2}$ is asymmetric due to the different types of bonds being formed, namely C–C and C–H bonds. In the transition state of the ene reaction, $\mathbf{T_2}$, the H-atom is somewhat halftransferred, and the forming C–C bond length is comparable to that in the *DA* transition state $\mathbf{T_1}$. The transition-state geometry was characterized as an envelope conformation (for the earliest review on ene reactions, see [13]), although the forming and breaking $C^1-H^6-C^5$ angle is not 180° but 156°. It is noted that C^4 was slightly distorted to maximize the overlap of p orbitals at C^3, C^4, and C^5. Thus, the π-bonding interaction between C^4 and C^5 was significantly developed, keeping the π-bonding interaction between C^3 and C^4 (The bond lengths of C^3-C^4: 1.38 Å, C^4-C^5: 1.40 Å).



Natural Charge

$\mathbf{T_1}$	$\mathbf{T_2}$
C^1: –0.45	C^1: –0.62
C^2: –0.45	C^2: –0.39
C^3: –0.40	C^3: –0.46
C^4: –0.26	C^4: –0.19
C^5: –0.26	C^5: –0.60
C^6: –0.40	H^6: +0.24

Fig. 2. *Transition-state structures* $\mathbf{T_3}$ *and* $\mathbf{T_4}$ *of the* DA *and ene reactions (HF/6-31G*)*. Bond lengths are given in Å.

As shown in *Fig. 3*, the *HDA* reaction of butadiene with formaldehyde has a symmetric transition-state structure $\mathbf{T_3}$ similar to that of the normal *DA* reaction. The transition-state structure $\mathbf{T_4}$ for the carbonyl–ene reaction of propene with formaldehyde also resembles that for the normal ene reaction with ethylene. The geometries of the ene and diene moieties in the carbonyl–ene and *HDA* reactions are almost the same as those in the normal versions ($\mathbf{T_1}$ and $\mathbf{T_2}$ in *Fig. 2*). The forming C–C bond is shortened by *ca.* 0.2 Å in both cases because of the larger orbital coefficient on C^2 than in ethylene. In the transition-state structure $\mathbf{T_3}$, the electronic repulsion between the *endo* lone pair of the O-atom and π-orbital at C^4 and C^5 affords the small twisting around C^2-C^3 axis. The transition-state structure $\mathbf{T_4}$ shows a tendency similar to that of the *HDA* reaction (*Fig. 2*).

The extraordinary influence of *Lewis* acid catalysts on the rate and stereochemical selectivities of the carbonyl–ene reactions has been investigated as well as the *HDA* reactions. The $AlCl_3$-catalyzed *HDA* and carbonyl–ene reactions of formaldehyde showed very large asynchronicity in the transition-state structure (*cf.* $\mathbf{T_5}$ and $\mathbf{T_6}$ in *Fig. 3*). Since the *Lewis* acids lower the formaldehyde LUMO energy level, and the more-polarized LUMO increases the coefficient of carbonyl C-atom (C^2), the forming C–C bonds are shortened in both the carbonyl–ene and *HDA* reactions. The transition-state structures $\mathbf{T_5}$ and $\mathbf{T_6}$ have thus a significant amount of zwitterionic character with partial positive charge on the ene or diene, and partial negative charge on the formaldehyde O-atom. In particular, the $AlCl_3$-catalyzed carbonyl–ene transition state, $\mathbf{T_6}$, shows a forming C–C bond length that is by 0.35 Å shorter than that of the parent transition state $\mathbf{T_4}$. In the transition-state structure of $\mathbf{T_5}$, the

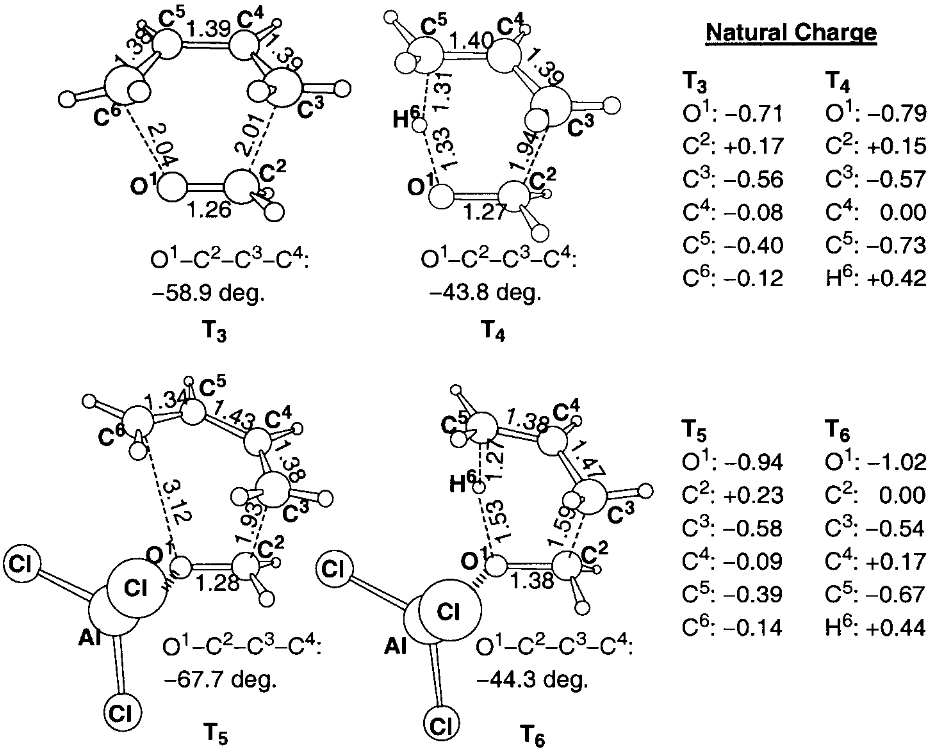


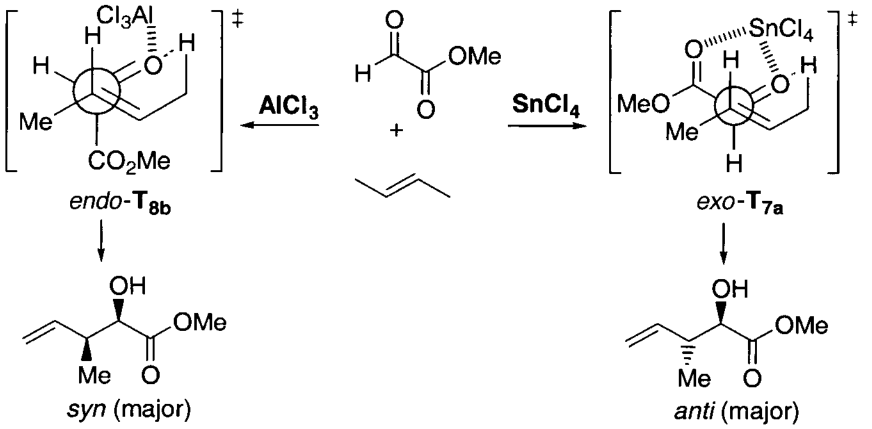
Fig. 3. *Transition-state structures* $\mathbf{T}_3$ *and* $\mathbf{T}_5$ *of the* HDA *and* $\mathbf{T}_4$ *and* $\mathbf{T}_6$ *of the carbonyl–ene reactions without or with coordination of* $AlCl_3$ *(HF/6-31G*)*. Bond lengths are given in Å.

developing negative charge on O^1 (-0.94) leads to a larger repulsion between the O^1 lone pair and the butadiene C^4-C^5 π-system to afford a larger twisting around the C^2-C^3 axis and a substantial increase of the O^1-C^6 length. The twisting around the C^2-C^3 axis in the carbonyl–ene reaction ($\mathbf{T}_6$) is comparable to that in the parent carbonyl–ene reaction ($\mathbf{T}_4$), although the negative charge on O^1 (-1.02) is significantly increased in $\mathbf{T}_6$. This is due to the electrostatic interaction between the O^1 lone pair and the cationic C^4 of the propene. Thus, the electrostatic interaction between carbonyl O-atom lone pair and cationic allylic central C-atom of the ene component considerably affect the transition-state conformations of *Lewis* acid catalyzed carbonyl–ene reaction.

Diastereoselectivity of Lewis *Acid Catalyzed Glyoxylate-Ene Reaction.* While the $SnCl_4$-promoted reaction can be achieved with a high level of *anti*-selectivity *via* the *exo* transition state $\mathbf{T}_{7a}$, the use of Al reagents leads to a high *syn*-selectivity *via endo* transition state $\mathbf{T}_{8b}$ (*Scheme 2*). The $SnCl_4$ complexed to the glyoxylate in a *syn*-fashion affords the *exo* and *endo*-transition states, $\mathbf{T}_{7a}$ and $\mathbf{T}_{7b}$, which provide the *anti* and *syn* products, respectively (*Fig. 4*). The *exo*-transition state $\mathbf{T}_{7a}$ is by 2.8 kcal/mol lower in energy than the *endo*-$\mathbf{T}_{7b}$. The 2.8-kcal/mol-energy difference leads to the high level of *anti*-selectivity in agreement with the experimental result. The steric repulsion between

$SnCl_4$ and allylic moiety of but-2-ene is not important for the energy difference between transition states $\mathbf{T}_{7a}$ and $\mathbf{T}_{7b}$ (*e.g.*, the nearest Sn–H lengths are 2.75 and 3.02 Å in $\mathbf{T}_{7a}$, and 2.99 and 3.38 Å in $\mathbf{T}_{7b}$). The energy difference can be rationalized from the point of view of stereoelectronic effect. The lone pair on the carbonyl O-atom O^1 is located in *endo* orientation with respect to the central C-atom C^4 of but-2-ene in the *exo*-$\mathbf{T}_{7a}$ to cause the electrostatic interaction between the O^1 lone pair and the cationic C^4 of but-2-ene (the natural charges: O^1, −1.01; C^4, +0.06)[1]). In contrast, the O^1 lone pair is located in *exo* orientation with respect to C^4 of but-2-ene in the *endo*-$\mathbf{T}_{7b}$, and, hence, such an electrostatic interaction is not present.

Scheme 2. *Diastereoselectivity Depending on* Lewis *Acids*



The $AlCl_3$ complexed to the glyoxylate in an *anti*-fashion affords the *exo*- and *endo*-transition states, $\mathbf{T}_{8a}$ and $\mathbf{T}_{8b}$, which afford the *anti* and *syn* products, respectively (*Fig. 5*). In contrast to the $SnCl_4$-promoted reaction, the *exo*-transition state $\mathbf{T}_{8a}$ is by 1.0 kcal/mol less stable than the *endo*-$\mathbf{T}_{8b}$. The energy difference between *exo*-$\mathbf{T}_{8a}$ and *endo*-$\mathbf{T}_{8b}$ is in accordance with the experimental results, *i.e.*, the *syn* product is preferentially obtained. Since the coordinated $AlCl_3$ is located somewhat far from the allylic moiety of but-2-ene, the steric effect is relatively less important for controlling the diastereoselectivity. In the *endo*-$\mathbf{T}_{8b}$, the lone pair on the carbonyl O-atom O^1 is located in *endo* orientation with respect to the central C-atom C^4 of but-2-ene, leading to the electrostatic interaction between the O^1 lone pair and the cationic C^4 of the but-2-ene (the natural charges: O^1, −1.01; C^4, +0.15). However, the *exo*-$\mathbf{T}_{8a}$ has no electrostatic interaction between the O^1 lone pair and cationic C^4 of but-2-ene due to *exo*-location of the O^1 lone pair with respect to C^4. Thus, the diastereoselectivity in the *Lewis* acid promoted carbonyl–ene reaction is originated in the *exo*/*endo* selectivity that can be controlled by the electrostatic interaction rather than secondary orbital interaction.

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[1]) A similar electrostatic interaction has been reported in the thermal imine–ene reaction [14].

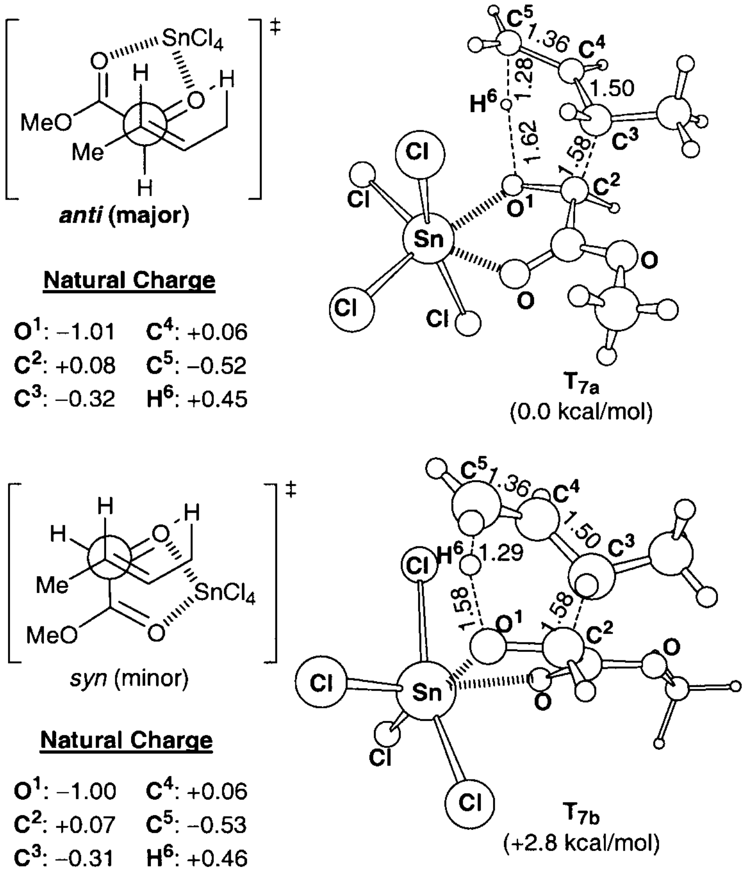

Fig. 4. *The transition-state structures of $SnCl_4$-catalyzed carbonyl–ene reaction* (HF/6-31G*). Bond lengths are given in Å.

3. Conclusions. – Our theoretical studies (HF/6-31G*) showed that the normal *DA* and ene reactions, as well as the *HDA* and carbonyl–ene reactions, afford similar concerted transition-state conformations. In contrast, coordination of *Lewis* acids significantly affects transition-state conformations in the *HDA* and carbonyl–ene reactions, resulting in their zwitterionic character. In the *HDA* reaction, coordination of *Lewis* acids develops the negative charge on the carbonyl O-atom to provide a larger repulsion between the carbonyl O-atom lone pair and central π-system of butadiene leading to a very distorted transition-state structure. On the other hand, in the carbonyl–ene reaction, coordination of *Lewis* acids also develops the negative charge on the carbonyl O-atom, but the carbonyl O-atom lone pair electrostatically interacts with the cationic central C-atom of the ene component to make the transition-state structure less deformed. The present studies also illustrated that such an electrostatic interaction can control the diastereoselectivity caused by the *exo*/*endo* selectivity in the *Lewis* acid-catalyzed carbonyl–ene reaction. The electrostatic interaction is, thus,

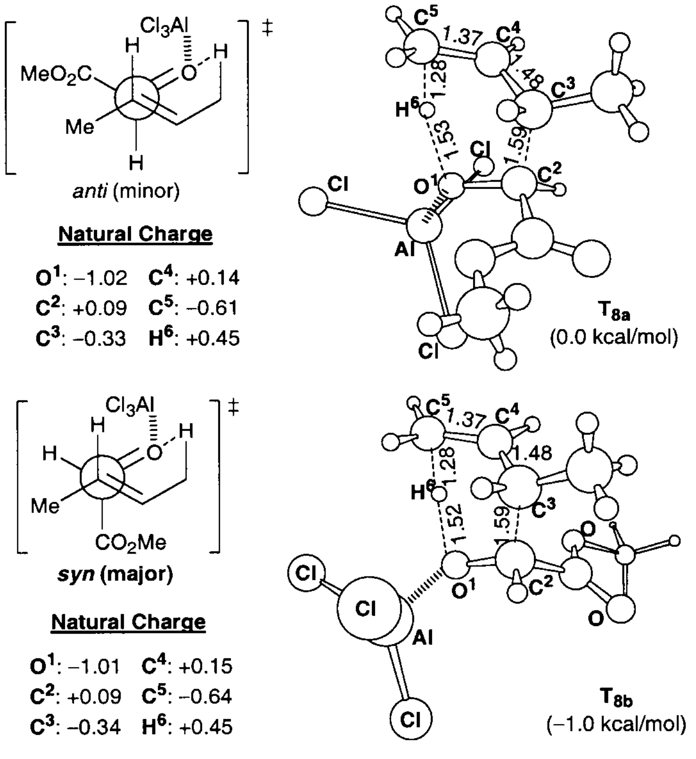

Fig. 5. *The transition-state structures of AlCl$_3$-catalyzed carbonyl–ene reaction* (HF/6-31G*). Bond lengths are given in Å.

regarded as fundamental for the diastereoselectivity in the *Lewis* acid catalyzed carbonyl–ene reaction.

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