

Roles of Lewis Acid Catalysts in Diels-Alder Reactions between Cyclopentadiene and Methyl Acrylate

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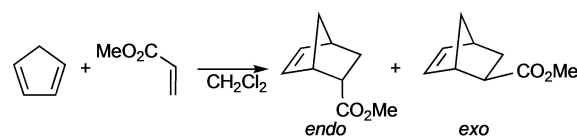
The Diels-Alder reaction of cyclopentadiene with methyl acrylate catalyzed by AlCl₃ has been theoretically investigated. M06-2X level DFT calculations have shown that the formation of two C–C bonds is asynchronous in the cycloaddition both in the *endo* path and in the *exo* path, thus making a good contrast to the well-known concept of [4+2] reactions based on the orbital symmetry arguments. It was found that the catalyst facilitates the cycloaddition and brings a higher *endo* selectivity in the highly asynchronous process, as compared with the reaction of the diene and the dienophile without the catalyst.

The Lewis acid catalyzed Diels-Alder reaction is a powerful tool for synthetic organic chemistry.^[1] In the catalytic cycloaddition between dienes and dienophiles, Lewis acid catalysts have been shown to accelerate the reactions and make the reaction highly stereo- and/or regio-selective.^[1,2] Houk and co-worker ascribed the reason why the Lewis acid facilitates the reaction with normal electron demand to the energy lowering of the LUMO in the dienophile part in the presence of Lewis acids.^[3] Electron delocalization from the diene part to the dienophile part is thus strengthened by the attachment of a Lewis acid to the dienophile. This idea has widely been accepted until now.^[4,5]

Our previous study of the Diels-Alder reaction catalyzed by the Lewis acid activated oxazaborolidine, showed, however, that the weakening of the overlap repulsion between the occupied orbitals of diene and those of dienophile is another important outcome of attaching the catalyst.^[6] Here, we examine in detail the mechanism of activation of the *endo*-cycloaddition by a Lewis acid catalyst, AlCl₃, in the reaction between cyclopentadiene and methyl

acrylate (Scheme 1), in which the *endo/exo* selectivity has been shown experimentally to be improved by adding the catalyst.^[7]

We investigated first the cycloaddition in the absence of Lewis acid by using M06-2X level DFT calculations.^[8,9] Six transition state structures were obtained at the M06-2X/6-311(*d,p*) level of theory as shown in Figure 1.^[10,11] Among the three transition states leading to the *endo* addition, called here TS_{endo-1}, TS_{endo-2} and TS_{endo-3}, TS_{endo-1} was calculated to be the lowest in energy. Calculations at the other levels of theory also show the same trend, though the barrier height obtained changes to some extent depending on the level of calculations as seen in Table 1. The most preferred transition state giving the *exo* addition, TS_{exo-1}, is located only 0.4 kcal/mol above TS_{endo-1}. The energy difference is very small and, therefore, it is suggested that the stereoselectivity would not be high (cal. *endo:exo* = 0.69:0.31 at 273 K),^[12] fairly in agreement with the experimental results.^[7]



	<i>endo</i> (%)	<i>exo</i> (%)	conv.(%)
without AlCl ₃ at 0 °C	82	18	22 - 51
with AlCl ₃ (10 mol%) at 0 °C	96	4	79 - 91
with AlCl ₃ (10 mol%) at -70 °C	99	1	67 - 72

Scheme 1. The Diels-Alder reaction between cyclopentadiene and methyl acrylate catalyzed by AlCl₃.^[7]

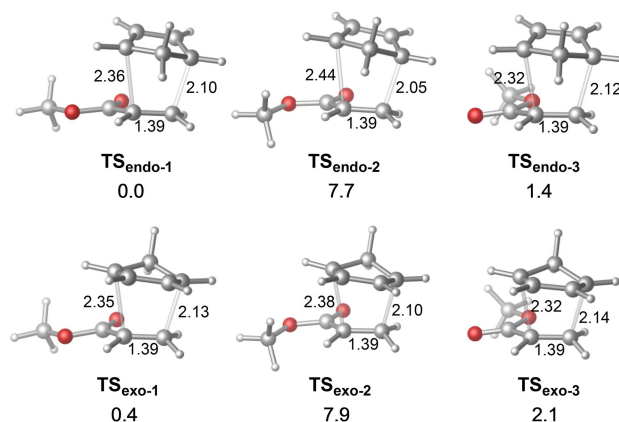


Figure 1. Transition state structures for the reaction without AlCl₃ at the M06-2X/6-311G(*d,p*) level of theory. Bond distances are in Å. Gibbs free energies at 273 K relative to TS_{endo-1} are in kcal/mol.

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	TS _{endo-1}	TS _{endo-2}	TS _{endo-3}	TS _{exo-1}	TS _{exo-2}	TS _{exo-3}	endo:exo
M06-2X/6-311G(d,p)	22.9	30.6	24.3	23.3	30.8	25.0	0.69:0.31
M06-2X/6-311 + + G(3df,3pd)//M06-2X/6-311G(d,p)	24.4	31.3	25.8	24.9	31.7	26.7	0.75:0.25
M06-2X(IEF-PCM)/6-311 + + G(3df,3pd) //M06-2X/6-311G(d,p) ^[a]	24.6	29.3	25.7	25.8	30.2	27.1	0.90:0.10
SCS-MP2/6-311G(d,p)//MP2/6-311G(d,p)	23.8	32.0	25.2	24.5	32.8	26.0	0.79:0.21
CCSD(T)/6-311G(d,p)//MP2/6-311G(d,p)	24.7	32.6	26.1	25.3	33.4	26.9	0.77:0.23
SCS-MP2/6-311 + + G(3df,3pd)//MP2/6-311G(d,p)	21.8	28.9	23.2	22.7	29.8	24.3	0.83:0.17
RHF/6-311G(d,p)	51.7	61.0	53.2	52.1	61.4	54.0	0.71:0.29

[a] Dichloromethane is chosen as a solvent.

The AlCl₃-catalyzed reaction system gives also the six transition-state structures shown in Figure 2.^[13] Among the three transition-state structures giving the *endo* product, TS'_{endo-1r}, TS'_{endo-2r}, and TS'_{endo-3r}, the first has the lowest energy. In contrast to the non-catalyzed case, TS'_{exo-1} and TS'_{exo-3} are shown to be very similar in energy among the three *exo* transition-state structures with an attached AlCl₃. The difference in energy between TS'_{endo-1} and TS'_{exo-3} is 2.8 kcal/mol, which is considerably larger than that between TS_{endo-1} and TS_{exo-1}. The attachment of AlCl₃ is shown to lead to a larger energy difference between the *endo* and *exo* transition states and, therefore, to a higher stereoselectivity (calc. *endo:exo* = 0.99:0.01 at 273 K) also in good agreement with the experimental observations.^[12] Calculations at the other levels of theory show the same trend except for the

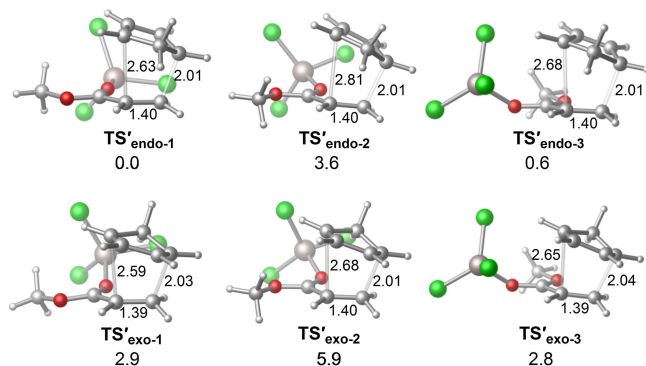


Figure 2. Transition state structures for the reaction with AlCl₃ at the M06-2X/6-311G(d,p) level of theory. Bond distances are in Å. Gibbs free energies at 273 K relative to TS'_{endo-1} are in kcal/mol.

PCM calculations (Table 2). The three *endo* transition-state structures are shown to be located more closely in energy and the three *exo* transition-state structures are so in dichloromethane, as compared with the results *in vacuo*. The energy difference between the *endo* and *exo* transition states remains similar to those obtained without the effect of solvent.

The relative Gibbs free energy diagram is shown in Figure 3. The energy of TS_{endo-1} relative to the two reactant molecules in an isolated state which corresponds to the activation energy is calculated here to be 22.9 kcal/mol. On the other hand, the energy difference between the reactant molecules (cyclopentadiene + AlCl₃-attached methyl acrylate) and the transition state TS'_{endo-1} is 13.1 kcal/mol. The activation energy for AlCl₃-catalyzed reaction is much lower than that for the non-catalyzed reaction. The calculations demonstrate not only that the *endo* selectivity is enhanced but also that the reaction is accelerated by an attachment of AlCl₃.

For the transition state TS'_{endo-1r}, IRC calculations were performed.^[14] The calculations show clearly that the formation of the two C–C bonds is highly asynchronous in the presence of AlCl₃, as illustrated in Figure 4(a). The C²–C⁶ bond, which is located farther from the methoxycarbonyl group, is formed much faster than the other bond, C³–C⁷. The C²–C⁶ bond is 2.01 angstrom at the transition state, but the C³–C⁷ bond reaches the same bond length at a much later stage of the reaction, *s* ~ 4.0 amu^{1/2} bohr. The fragment charge profile based on NPA charges, presented in Figure 4(b), demonstrates that electronic charge is shifted from the diene fragment to the dienophile fragment at an early

Table 2. Gibbs free energy (273 K) of the transition states for the reaction in the presence of AlCl₃ relative to cyclopentadiene and AlCl₃-attached methyl acrylate (kcal/mol).

	TS' _{endo-1}	TS' _{endo-2}	TS' _{endo-3}	TS' _{exo-1}	TS' _{exo-2}	TS' _{exo-3}	endo:exo
M06-2X/6-311G(d,p)	13.1	16.7	13.7	16.0	19.0	15.9	0.99:0.01
M06-2X/6-311 + + G(3df,3pd)//M06-2X/6-311G(d,p)	14.8	18.6	15.5	17.2	20.7	17.8	0.99:0.01
M06-2X(IEF-PCM)/6-311 + + G(3df,3pd) //M06-2X/6-311G(d,p) ^[a]	16.1	15.8	15.9	19.1	18.0	18.5	0.99:0.01
SCS-MP2/6-311G(d,p)//MP2/6-311G(d,p)	15.8	19.6	16.2	18.8	22.0	17.5	0.97:0.03
CCSD(T)/6-311G(d,p)//MP2/6-311G(d,p)	16.4	20.1	16.7	19.3	22.6	18.5	0.98:0.02
SCS-MP2/6-311 + + G(3df,3pd)//MP2/6-311G(d,p)	12.5	16.8	13.3	16.0	19.4	15.3	0.99:0.01
RHF/6-311G(d,p)	41.0	43.1	41.4	43.2	46.1	42.6	0.94:0.06

[a] Dichloromethane is chosen as a solvent.

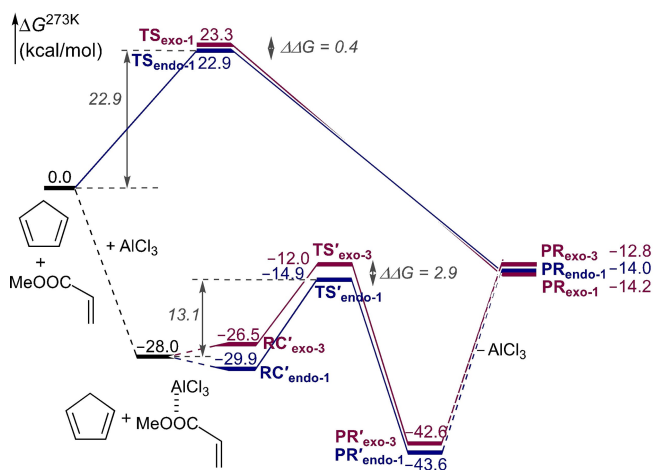


Figure 3. Relative Gibbs free energy diagram (273 K) at the M06-2X/6-311G(*d,p*) level of theory (kcal/mol).

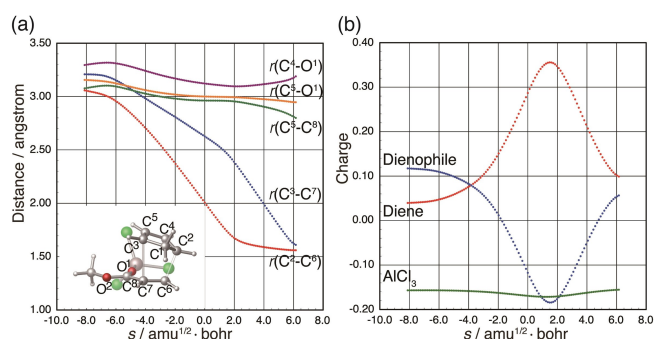


Figure 4. (a) Change in bond lengths along IRC of TS'_{endo-1} . (b) Change in fragment charges at along IRC of TS'_{endo-1} .

stage of the reaction involving the transition state, and the net electronic charges on the fragments begin to be reduced at the later stage, after passing the point, $s \sim 1.8 \text{ amu}^{1/2} \text{ bohr}$. This signifies that the C^2-C^6 bond formation is brought about primarily by electron delocalization from the diene part to the dienophile part, while the C^3-C^7 bond formation is associated mainly with electron delocalization in an opposite direction. In this point, the Lewis-acid catalyzed Diels-Alder cycloaddition studied here makes a clear contrast to the well-established concept of symmetry-allowed [4+2] cycloadditions.^[15] The attached $AlCl_3$ part is seen to retain almost the same amount of negative charge throughout the reaction coordinate in this case.

Houk and co-worker proposed that the attached Lewis acid lowers the energy of LUMO of dienophile and, hence, accelerates the Diels-Alder reaction of normal electron demand.^[3] One should note now that the dienophile molecule is polarized by the attachment of the Lewis acid molecule, as to reduce the π -type electron population on the terminal carbon, C^6 , and increase the π -type electron population on the other carbon, C^7 , of the $C=C$ bond. This change in electron population is reflected in the electron-

accepting orbital of the dienophile that shows a considerably larger amplitude on C^6 and in the electron-donating orbital that shows a larger amplitude on C^7 , in comparison with the dienophile without the catalyst (see, Figures S2 and S3 in Supporting Information).^[16] The unoccupied and occupied interaction orbitals are lowered in energy by 2.05 eV and 1.79 eV, respectively, by attaching $AlCl_3$. Electron delocalization from the diene to the dienophile, dominantly onto C^6 , is thus strengthened, whereas that from the dienophile part to the diene part, dominantly from C^7 , is not enhanced. In addition, the increase in electron population on C^7 leads to the strengthening of repulsion with C^3 of the diene that arises from the overlap between the occupied orbitals of the diene and those of the dienophile. On the other hand, the overlap repulsion between C^6 and C^2 is lightened. As a result, asynchronous formation of new C–C bonds should become marked in the catalyzed case. This view of bond formation is fully supported by a partitioning of overlap population of the C^2-C^6 and C^3-C^7 bonds into the repulsive and attractive orbital interactions (see, Tables S2 and S3 in Supporting Information).

In the Diels-Alder reactions, the *endo* transition state is placed generally under a stronger overlap repulsion between the occupied orbitals of the diene part and those of the dienophile part, but the repulsion is reduced by introducing electron-withdrawing groups into the dienophile part, as we have already seen in the cycloaddition between cyclopentadiene and maleic anhydride.^[17] There the electrostatic attraction and delocalization-polarization are shown to be strong enough to cover the overlap repulsion that have been suppressed considerably by the electron deficiency in the dienophile ring. The “normal electron demand” in the reaction and the high *endo* selectivity are connected to each other at this point.^[17,18] Introduction of electron-releasing groups into the diene part in place of introducing electron-withdrawing groups into the dienophile part is not a way to achieve high *endo* selectivity, as the path will suffer from an intense overlap repulsion. Though the barrier height obtained in this study depends slightly on the level of DFT calculations, the difference in the activation Gibbs free energy between TS_{endo-1} and TS_{exo-1} remains in a narrow range, 0.4–1.2 kcal/mol (see Table 1), and that between TS'_{endo-1} and TS'_{exo-1} does so in the range of 2.2–3.5 kcal/mol (see Table 2), indicating that the *endo* transition state is preferred at all the levels of calculation. The RHF/6-311G(*d,p*) level calculation also gives similar results, as it did in the calculations on the cycloaddition between cyclopentadiene and maleic anhydride previously studied.^[17]

To see next the reason why the *endo*-path is preferred in this highly asynchronous process, let us compare the reacting system with $AlCl_3$ and the system without $AlCl_3$ that are produced by removing the $AlCl_3$ part from TS'_{endo-1} and TS'_{exo-1} , respectively, freezing the geometry of other atoms as they were in those structures. A simple partitioning analysis of the interaction energy at the RHF/6-311G(*d,p*) level^[19] and an analysis of the M06-2X/6-311G(*d,p*) level DFT

interaction energy by a scheme proposed by Su and Li^[20] indicate that the difference in energy between TS'_{endo-1} and TS'_{exo-1} , comes not from the orbital interaction terms but mainly from the electrostatic attraction.^[21] The sum of the repulsive and attractive orbital interaction terms, i.e., exchange and overlap repulsive interactions and electron delocalization between the diene and the dienophile with the associated polarization within the two parts, is very similar in magnitude in the *endo*- and *exo*-paths (see, Tables S4 and S5, and Figure S4 in Supporting Information). The electrostatic attraction between the diene part and the dienophile part is stronger in the *endo* structure than in the *exo* structure, the attraction between the positive charge on C⁸ in the dienophile and the negative charges on C⁴ and C⁵ atoms in the diene part being added in the *endo* structure. Thus, the *endo*-addition is preferred even in the absence of AlCl₃. The difference in electrostatic attraction between the two transition states becomes more significant, because the positive charges on C⁸ gets larger in the dienophile polarized by attached AlCl₃ (the electrostatic potential maps and atomic charges of the reactants are shown in Figures S8 and S9, respectively, in Supporting Information). The energy difference between TS'_{endo-3} and TS'_{exo-3} can also be interpreted in this manner (Tables S6 and S7, and Figure S5 in Supporting Information).^[22] In conclusion, electron delocalization strengthened in the presence of the Lewis acid lowers the barrier height of the cycloaddition to accelerate the reaction both in the *endo*- and *exo*-paths, while the electrostatic attraction favors the *endo*-path.

In summary, the reactivity and stereoselectivity in the Diels-Alder reaction between cyclopentadiene and methyl acrylate catalyzed by a Lewis acid are controlled by a combination of several interaction terms. An AlCl₃ molecule attached to the carbonyl oxygen atom of methyl acrylate lowers the energy of orbitals in acrylate and also polarizes the molecule.^[23] The unoccupied interaction orbital of the dienophile that plays the dominant role in electron delocalization from the diene is lowered in energy and shows a larger amplitude on of the two reaction sites, C⁶, which is placed farther from the carbonyl group. Thus, the electron-accepting ability of the terminal carbon is enhanced. In contrast, the occupied interaction orbital tends to show a larger amplitude on the other reaction site, C⁷, but the orbital is also lowered considerably in energy by the presence of AlCl₃. The electron-donating ability of that carbon is weakened. The electron redistribution caused by the attached Lewis acid reduces overlap repulsion in the C²–C⁶ bond region and strengthens the repulsion in the C³–C⁷ bond region. As a consequence, the formation of new C–C bonds is highly asynchronous in the Lewis-acid catalyzed Diels-Alder reaction between cyclopentadiene and methyl acrylate, the formation of the C²–C⁶ bond preceding the formation of the C³–C⁷ bond. Lower barrier heights are provided both for the *endo*-path and for the *exo*-path than those in the reaction without AlCl₃. Here again the electrostatic interaction is shown to play an important role in bringing the high *endo* selectivity to this

cycloaddition, as we have seen previously in the Diels-Alder reactions in which the formation of two C–C bonds take place in a synchronous manner.^[17,24]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cycloaddition reactions · Lewis acids · density functional calculations · orbital interactions

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- [12] Six transition states were taken into account for the calculation of the ratio.
- [13] The other transition state structures (TS'_{endo-4} , TS'_{endo-5} and TS'_{exo-4}) were also found. However, these free energies are much higher than that of TS_{endo-1} by 14.5, 12.8 and 16.0 kcal/mol, respectively. See, Figure S1 in Supporting Information.
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- [22] Much the same results were obtained also for the AlCl₃-catalyzed reaction between 1,3-butadiene and methyl acrylate, indicating that the methylene moiety of the C1 atom in cyclopentadiene has little influence on the stereoselectivity. See, Figure S10 in Supporting Information.
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