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Transition States of the Asymmetric Michael Reactions of Aldehydes Catalyzed by Trimethylsilyl-Protected Diphenylprolinol

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The asymmetric Michael reactions of aldehydes and nitroalkenes catalyzed by trimethylsilyl-protected diphenylprolinol were investigated by using density functional theory calculations. As a result of the stereospecific blockade of the bulky diphenylsiloxymethyl group on the pyrrolidine ring, the *Re* face of the enamine double bond is effectively shielded. For acetaldehyde, there are two different conformers of the enamine intermediate. On the basis of the two conformers of the enamine intermediate, four different reaction pathways were considered and four different transition states were searched for the enantioselective asymmetric Michael reaction of acetaldehyde and nitroalkene. The lowest- and second-lowest-energy transition states are both formed via the same intermediate IM2. The enantiomeric excess, calculated to be 96 % *ee*, is in good agreement with the experimental value. For propanal, on the basis of the four different conformers of the prolinol–enamine intermediate, eight different reaction pathways were considered and eight transition states were searched for the enantioselective asymmetric Michael reaction. The calculated *ee* value is 99.5 %, which is in good agreement with the experimental *ee* value of 99 %. The lowest- and second-lowest-energy transition states are formed via different enamine intermediates, which is different from the case of acetaldehyde. The calculations also reveal that the intermediates play an important role in the reactions.

Introduction

The research of organocatalysis has undergone a great development and has become a hot topic in the field of organic chemistry in the last few years.[1–5] In comparison with metal catalysts, organocatalysts are ease to manipulate, "green", and highly efficient. Asymmetric organocatalysis is catching up with transition-metal catalysis in terms of efficiency and selectivity.[6] The proline-catalyzed direct aldol reaction rediscovered by List et al.[7] was the starting point for the ground-breaking development of highly stereoselective organocatalyzed transformations. Subsequently, many other organocatalysts were developed, such as proline derivatives[8,9] and *N*-alkyl-2,2′-bipyrrolidine derivatives.[10] Many α-functionalization reactions of aldehydes and ketones have been catalyzed by organocatalysts, including the aldol reaction,[11] the Mannich reaction,[12] amination,[13] oxygenation,[14] fluorination,[15] chlorination,[16] bromination,[17] the Michael reaction,[18–20] and so on.

By using an enamine catalyst, Beeson et al.[9] and Marigo et al.[21] recently reported α-fluorination of aldehydes; the transition states of α-fluorination of aldehydes were located by Dinér et al.[22] Hayashi et al.[23] reported the α-amination of ketones and located the transition states. It is well known that the Michael reaction is a useful method for forming carbon–carbon bonds, and the products of Michael addition are important chiral intermediates that possess synthetically useful functional groups. The TMS-protected (TMS = trimethylsilyl) diphenylprolinol catalyst has been developed recently for Michael reactions of aldehydes and nitroalkenes.[24–28] By using TMS-protected diphenylprolinol as a catalyst, Hayashi et al. reported the asymmetric Michael reaction of aldehydes.[24,25] The Michael addition products of acetaldehyde are more useful, as they still contain an active hydrogen atom in comparison to other aldehydes. The catalysis reaction can form products in good yield and excellent enantioselectivity, but the catalysis mechanism has not been reported yet. The investigation of the reaction mechanism can give insight into the reaction and may broaden the applicability of this reaction. In this paper, we investigated the reaction mechanism for the Michael reaction of aldehydes and nitroalkenes in the presence of TMS-protected diphenyprolinol. The calculated results are in good agreement with the experimental observations.

Computational Details

In the Michael reaction (see Figure 1), aldehydes and TMS-protected diphenyprolinol form an enamine intermediate. The enamine intermediate and the nitroalkene then

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form an addition product. Lastly, the addition product is hydrolyzed, which leads to the formation of the product. As shown in Figure 1, the configuration of the product is determined by the second step, so we only searched the transition states of this step and did not consider the hydrolysis process. Solvent effects were computed by the CPCM model[29,30] by using the gas-phase optimized structures. Although the solvent used in the experiment was hexane, the electronic and physical properties of hexane are similar to those of heptane; we examined the solvent effects of heptane. Unless otherwise specified, all discussed relative energies refer to the gas-phase calculations. The Gaussian 03 program package[31] was employed in all calculations.

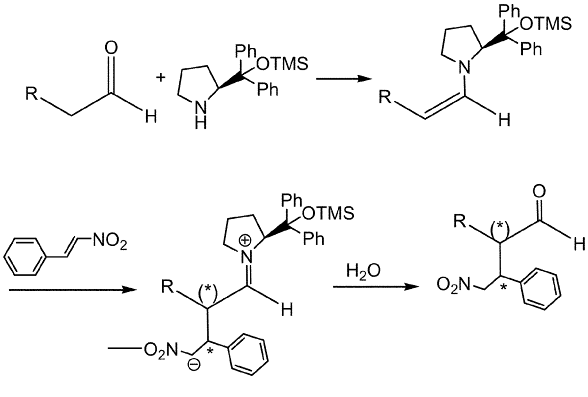


Figure 1. Mechanism for the asymmetric Michael reaction of aldehydes (R = H, Me) and nitroalkenes.

Results and Discussion

Michael Reaction of Acetaldehyde

Acetaldehyde and the TMS-protected diphenylprolinol catalyst can form two enamine intermediates IM1 and IM2. The *Re* face of the enamine is effectively shielded, so the enamine intermediates only approach the nitroalkene by the *Si* face (Figure 2). For example, if enamine IM1 approaches from the above face of the nitroalkene (Figure 2a), the reaction yields a product with *S* configuration. If enamine IM1 approaches from below the nitroalkene (Figure 2a), the reaction yields a product with *R* configuration. As shown in Figure 2b, the *S* product can be obtained by approach of the intermediate from above the nitroalkene and the *R* product can be obtained by approach of the intermediate from below the nitroalkene. There are four reaction pathways, and we have located the four different transition states (TS1–TS4) by using of density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory. Frequency calculations were performed on the transition states. There is only one negative vibrational frequency for each transition state, and the transition structures were confirmed by animation of their vibrational modes. The calculated relative energies of the transition states are given in Table 1. The negative vibrational frequencies for the transition states are given in the Supporting Information; the optimized structures and the C···C distances of the transition states are shown in Figure 3. Enamines IM1 and IM2 were also optimized at the B3LYP/6-31G(d) level of theory. The calculated relative energies are given in Table 2.

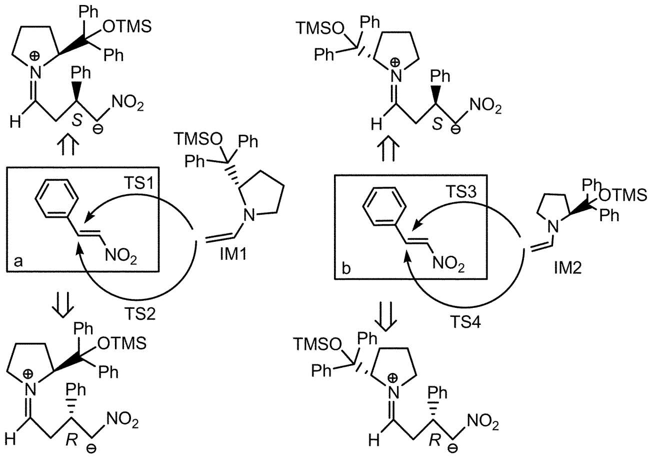


Figure 2. Reaction pathways of acetaldehyde and nitroalkene.

Table 1. Relative energies of the transition states for the Michael reaction at the B3LYP/6-31G(d) level of theory.

	ΔE [kcal mol^{-1}]		ΔE [kcal mol^{-1}]
TS1	5.04[a]	TS7	15.10[b]
TS2	4.13[a]	TS8	12.69[b]
TS3	0.00[a]	TS9	0.00[b]
TS4	2.40[a]	TS10	10.58[b]
TS5	9.92[b]	TS11	6.87[b]
TS6	4.71[b]	TS12	7.61[b]

[a] Energies are given relative to TS3. [b] Energies are given relative to TS9.

Calculations indicate that the lowest-energy transition state is TS3. The corresponding activation energy is 21.77 kcal mol^{-1} (see Supporting Information). It is formed when enamine IM2 approaches from the above face of the nitroalkene. This pathway can lead to the formation of the *S* product. The second-lowest-energy transition state is TS4 and it is 2.4 kcal mol^{-1} higher in energy than TS3. TS4 is formed when IM2 approaches from below the nitroalkene, and this pathway leads to the formation of the *R* product. The energy difference between TS3 and TS4 corresponds to an enantiomeric excess in favor of the *S* product of 96% *ee*, which is in good agreement with the experimental result.[25] TS1 and TS2 are 5.04 and 4.13 kcal mol^{-1} higher in energy than TS3, respectively. As a result of the higher energy of these two transition states, the corresponding pathways are disadvantageous.

The calculated results demonstrate that IM1 is 3.04 kcal mol^{-1} higher in energy than IM2. It is thus probable that the higher energies of TS1 and TS2 partly originated from the higher energy of IM1.

Solvent effect calculations show the relative energy between TS3 and TS4 decreases from 2.40 to 1.82 kcal mol^{-1} in heptane (see Supporting Information for details), which indicates that the solvent employed can affect the reaction to some degree.

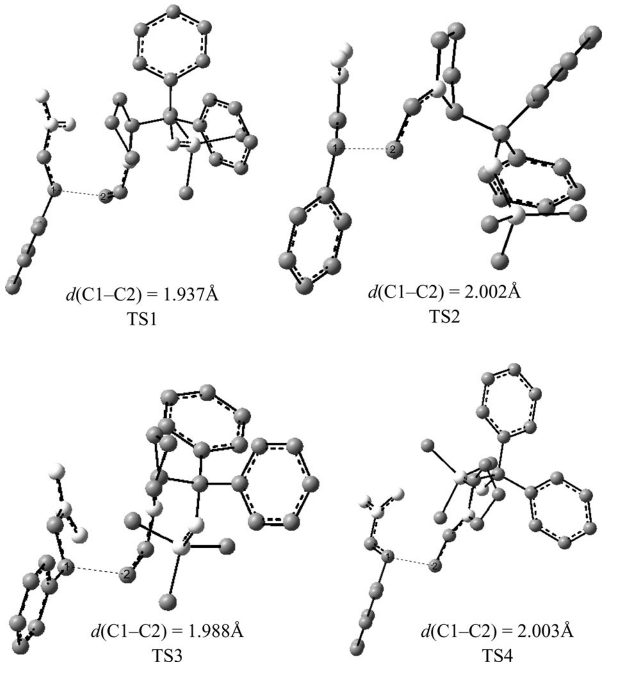


Figure 3. The optimized structures of the four different transition states for the Michael reaction of acetaldehyde and nitroalkene at the B3LYP/6-31G(d) level of theory.

Michael Reaction of Propanal

Propanal and the TMS-protected diphenylprolinol catalyst can form four enamine intermediates IM3, IM4, IM5, and IM6. The four intermediates were optimized at the B3LYP/6-31G(d) level of theory. The calculated relative energies are given in Table 2. Similar to IM1 and IM2, the *Re* faces of the four enamines are effectively shielded by the two phenyl and OTMS groups of the catalyst, so the possible reaction pathways reduce from 16 to 8. The four enamine intermediates (IM3, IM4, IM5, and IM6) may approach from the two faces of the nitroalkene, which corresponds to eight different reaction pathways. We investigated the eight different reaction pathways and located the eight transition states (TS5–TS12) by using the DFT method at the B3LYP/6-31G(d) level of theory. Frequency calculations were performed on the transition states. There is only one negative frequency for each transition state, and the transition structures were confirmed by animation of their vibrational modes. The calculated relative energies of the transition states are given in Table 1. The negative vibrational frequencies for the transition states are given in the Supporting Information. The reaction pathways and the optimized structures of the eight transition states are shown in Figures 4 and 5, respectively.

Table 2. Relative energies of the enamine conformers at the B3LYP/6-31G(d) level of theory.

	ΔE [kcal mol^{-1}]		ΔE [kcal mol^{-1}]
IM1	3.04[a]	IM4	8.59[b]
IM2	0.00[a]	IM5	0.00[b]
IM3	3.10[b]	IM6	3.40[b]

[a] Energies are given relative to IM2. [b] Energies are given relative to IM5.

The calculations show that lowest-energy transition state TS9 occurs when enamine intermediate IM5 approaches from the above face of the nitroalkene. The corresponding activation energy is 22.05 kcal mol^{-1} (see Supporting Information). The second-lowest-energy transition state is TS6. It is 4.7 kcal mol^{-1} higher in energy than TS9 and is obtained when IM3 approaches from below the nitroalkene. The hydrolysis of the products of reactions via TS6 and TS9 leads to the formation of a pair of enantiomers. The energy difference between the two transition states corresponds to an enantiomeric excess value of 99.5 %, which is in good agreement with the experimental value of 99 %.[24]

The calculated results demonstrate that other transition states are much higher in energy than TS9, indicating that the corresponding pathways are disadvantageous. The two lowest-energy transition states TS6 and TS9 are formed via the two lowest-energy enamine intermediates IM3 and IM5,

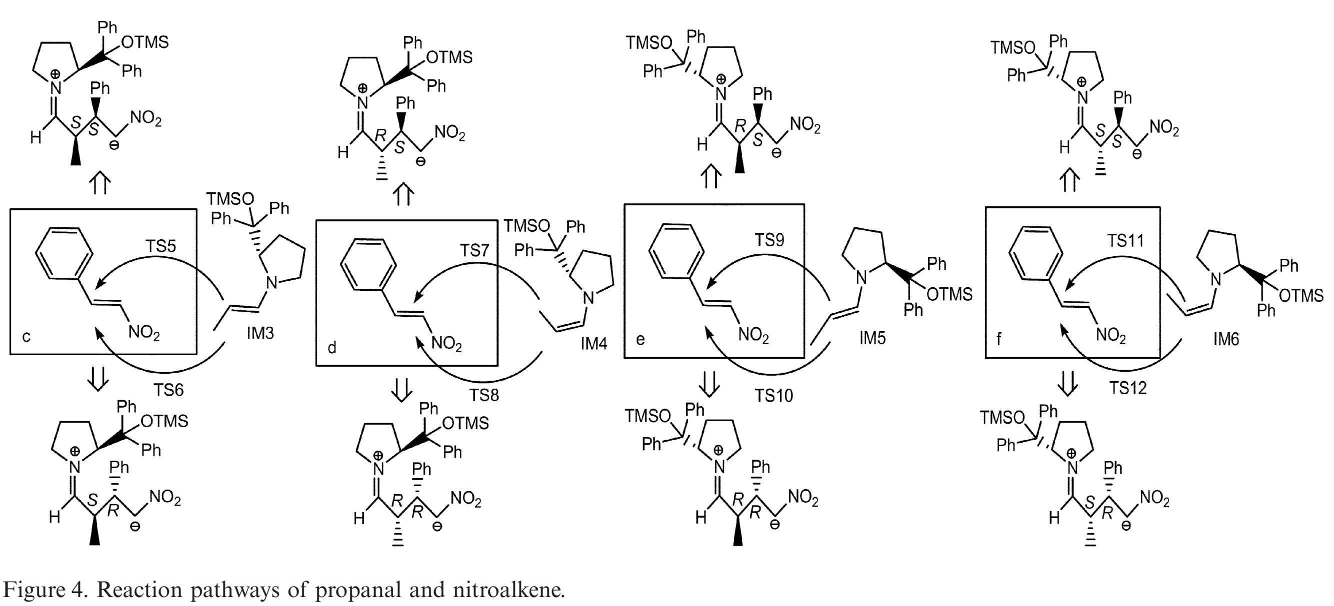
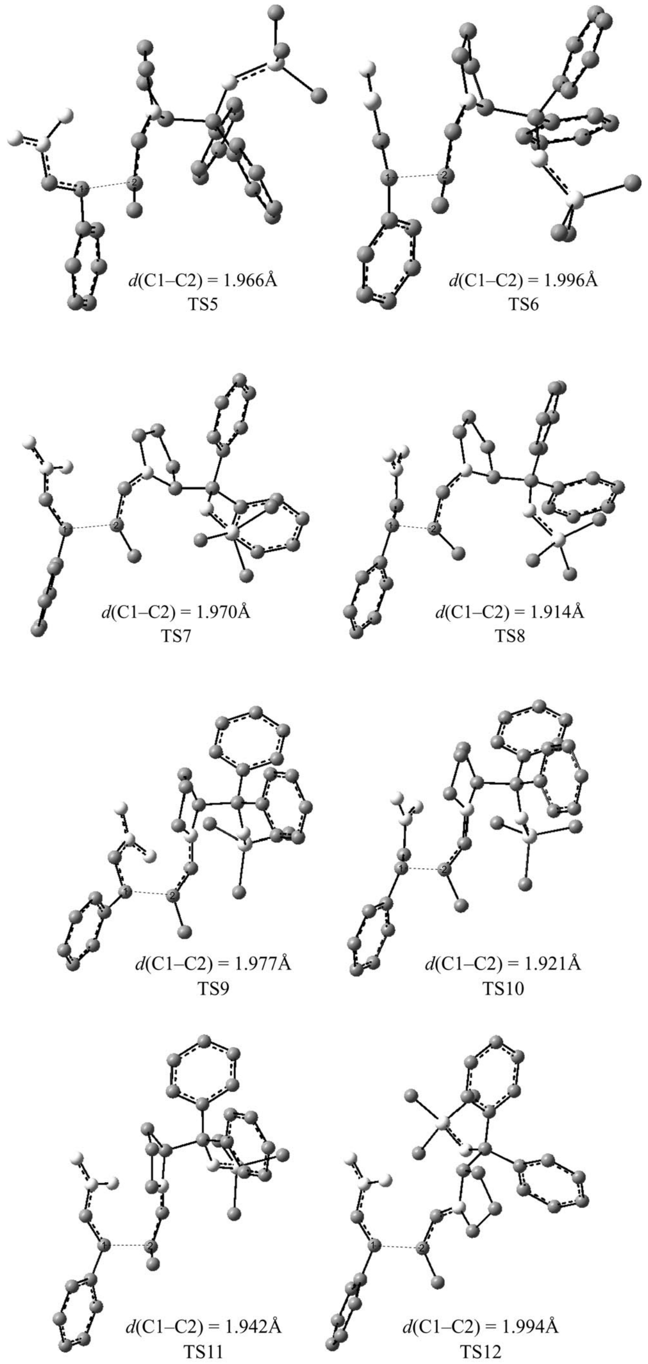


Figure 4. Reaction pathways of propanal and nitroalkene.



d(C1–C2) = 1.966Å
TS5

d(C1–C2) = 1.996Å
TS6

d(C1–C2) = 1.970Å
TS7

d(C1–C2) = 1.914Å
TS8

d(C1–C2) = 1.977Å
TS9

d(C1–C2) = 1.921Å
TS10

d(C1–C2) = 1.942Å
TS11

d(C1–C2) = 1.994Å
TS12

Figure 5. The optimized structures of eight different transition states for the Michael reaction of propanal at the B3LYP/6-31G(d) level of theory.

respectively. TS7 and TS8, formed via the highest-energy IM4, are as much as 15.10 and 12.69 kcal mol^{-1} higher in energy than TS9, respectively. Thus, it can be concluded that the intermediates play an important role in the Michael reaction of propanal catalyzed by TMS-protected diphenylprolinol. Meanwhile, TS6 formed via IM3 is the second-lowest energy transition state and is even lower in energy than TS10 formed via IM5, although IM5 is lower in energy than IM3, demonstrating that the direction of approach is also crucial in the reactions.

IM3 is 3.10 kcal mol^{-1} higher in energy than IM5. The two competing pathways are the addition of nitroalkene to the less-shielded face of the two different intermediates IM3 and IM5 (TS6 and TS9); however, the two lowest-energy transition states in the reaction of acetaldehyde are formed via the same intermediate IM2.

Solvent effect calculations show the relative energy between TS6 and TS9 decreases from 4.71 to 3.74 kcal mol^{-1} in heptanes (see Supporting Information for details).

Although the calculated *ee* values are in agreement with the experimental values, it is not certain that the employed method is accurate enough. It must be noted that the calculated relative energies of the transition states should be a little different when a method with a more balanced treatment of long-range correlations is employed. We also located TS3, TS4, TS6, and TS9 at the BHandHLYP/6-31G(d) level of theory. The calculations demonstrate that TS4 is 3.26 kcal mol^{-1} higher in energy than TS3, whereas TS6 is 4.83 kcal mol^{-1} higher in energy than TS9, which is a little different from the values calculated at the B3LYP/6-31G(d) level of theory.

Conclusions

A DFT study was performed on the Michael reactions of nitroalkenes with acetaldehyde and propanal catalyzed by TMS-protected diphenylprolinol. For acetaldehyde, there are four different transition states; the energy difference between the two lowest-energy transition states is 2.4 kcal mol^{-1}, and the calculated enantiomeric excess value of 96% is in good agreement with the experimental result. For propanal, there are eight possible reaction pathways and eight transition states involved. The energy difference between the two lowest-energy ones is 4.7 kcal mol^{-1}, and the calculated enantiomeric excess value of 99.5% is also in good agreement with the experimental result. The calculations also reveal that the intermediates play an important role in the reactions.

Supporting Information (see footnote on the first page of this article): Mechanism of the Michael reaction; pathways of the Michael reaction; energies and negative vibrational frequencies; salvation energies and activation energies; computed geometries of intermediates and transition states in the Michael reaction; Cartesian coordinates of all computed intermediates and transition states.

Acknowledgments

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