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The Effect of Solvent on a Lewis Acid Catalyzed Diels–Alder Reaction, Using Computed and Experimental Kinetic Isotope Effects

Orlando Acevedo and Jeffrey D. Evanseck*

Center for Computational Chemistry and the Department of Chemistry
and Biochemistry, Duquesne University, 600 Forbes Avenue,
Pittsburgh, Pennsylvania 15282-1530

evanseck@duq.edu

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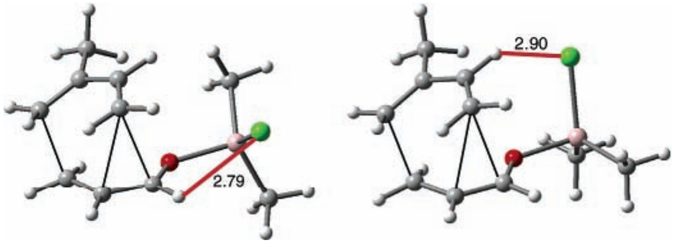
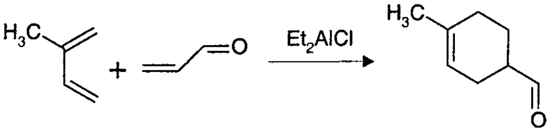
ABSTRACT



A new transition structure for the Diels–Alder reaction between isoprene and acrolein catalyzed by Et_2AlCl is found to reconcile reported discrepancies between computed and observed secondary kinetic isotope effects (KIEs). Including the effect of solvent realigns the computed results with experiment demonstrating the importance of nonbond interactions at transition structures. Comparison of experimental and newly predicted KIE data reaffirms the ability of theory and experiment to probe the mechanism and transition structure geometry of organic reactions.

Comparison of high-precision experimental kinetic isotope effects (KIEs) with high-level transition structure/KIE calculations is an extremely powerful tool for defining the mechanism and transition state geometry of organic reactions.[1−3] When predicted and observed KIEs match, then the computed transition structure can be used to support a specific reaction mechanism. A number of research groups have produced reasonable agreement between predicted and observed KIEs for pericyclic reactions that have controversial mechanisms ranging from concerted to stepwise processes.[1,4] Even though it is now well-established that Diels−Alder cycloadditions proceed through a concerted reaction mechanism,[5] how Lewis acid activation impacts the mechanism continues to be an active area of ongoing research.

Scheme 1. Diels-Alder Reaction between Isoprene and Acrolein in the Presence of a Lewis Acid, Et_2AlCl



Singleton and Houk have recently provided direct experimental support for a highly asynchronous but concerted mechanism for the reaction of isoprene and acrolein with an $AlMe_2Cl$ Lewis acid catalyst. The *endo-cis* transition

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[1] Singleton, D. A.; Merrigan, S. R.; Beno, B. R.; Houk, K. N. *Tetrahedron Lett.* **1999**, *40*, 5817.

[2] (a) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9675. (b) Wiest, O.; Houk, K. N.; Black, K. A.; Thomas, B., IV *J. Am. Chem. Soc.* **1995**, *117*, 8594.

[3] Saettel, N. J.; Wiest, O.; Singleton, D. A.; Meyer, M. P. *J. Am. Chem. Soc.* **2002**, *124*, 11552.

[4] Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984 and references within.

10.1021/ol027408g CCC: $25.00

structure was located in the presence of $AlMe_2Cl$, using the Becke three-parameter exchange functional[6] and the nonlocal correlation functional of Lee, Yang, and Parr[7] (B3LYP) with the 6-31G(d) basis set.[8] The computed transition structure (Figure 1) shows that the chlorine atom is only 2.87 Å from the nearest butadiene proton, suggesting a nontrivial energy of interaction. The calculations predict a large inverse KIE at H3 (Table 1). However, the specific experimental H3 kinetic isotope effect is not as strong as predicted by theory. It was reasoned from the gas-phase computations that substantial partial negative charge on the Cl atom (−0.44 e^- from a Mulliken analysis) is drawn toward the partial positive charge in isoprene (+0.29 e^-), which leads to a crowding effect increasing the out-of-plane bending force constant giving the large inverse KIE.[9] Consequently, the results were discounted as an artifact of gas-phase computations.

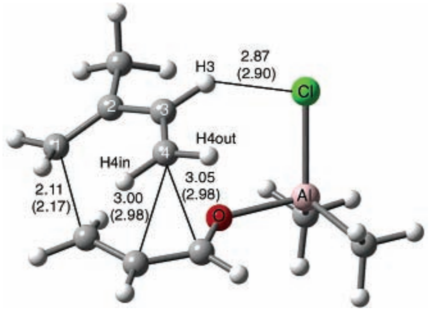

Figure 1. First *endo s-cis* transition structure[1] for the isoprene and acrolein reaction with $AlMe_2Cl$ at B3LYP/6-31G(d). Computed PCM values are given in parentheses. Distances are in Å.

Table 1. The Experimental and Calculated KIEs (k_H/k_D or $k_{^{12}C}/k_{^{13}C}$) for the Lewis Acid Catalyzed Diels−Alder Reaction of Isoprene and Acrolein[1]

	exp. 1[1]	exp. 2[1]	calcd
C1	1.030(3)	1.026(10)	1.031
C2	1.004(3)	1.006(9)	1.004
C3	1.001(2)	1.001(10)	1.000
C4	1.000(3)	1.001(10)	1.002
H1in + H1out	0.915(6)	0.916(7)	0.910
H3	0.965(5)	0.967(13)	0.934
H4out	0.978(6)	0.979(18)	0.986
H4in	0.951(4)	0.947(8)	0.968

Inspired by Corey's findings on unusually strong aldehyde proton interactions with Lewis acids, we investigated a second transition structure to exploit this possible interaction.[10,11] In X-ray crystallographic studies of α,β-unsaturated aldehyde complexes with fluorine and alkyl ether containing boron Lewis acids, Corey and co-workers found a ground state conformational preference in which the formyl group and the B−F or B−O bond are coplanar.[11−13] It has been proposed that this conformational preference is due to an electrostatic interaction, known as nontraditional (O═C−H···X) hydrogen bonding.[12,14] Previous theoretical investigations have considered the electronic reasons for such stabilization.[15]

Figure 2 shows the second transition structure calculated at the B3LYP/6-31G(d) level of theory, which takes advantage of nontraditional hydrogen bonding. Frequency analyses of both transition structures were computed to confirm that the stationary points are true transition structures, and are provided in the Supporting Information. Crowding of the H3 atom in the new transition structure is computed to be reduced, with the Cl atom at a distance of 3.63 Å away from the H3 hydrogen. In a vacuum, we do not find the perfectly eclipsed ground-state situation described by Corey, where the transition structure dihedral angle ∠OCHCl = 30.4°. The observed deviation from planarity is likely due to bad steric interactions that develop between the methyl substituent on aluminum and the diene moiety, where the closest hydrogen−hydrogen distance is 2.51 Å. Alternatively, different nontraditional hydrogen bonding behavior for transition structures as compared to the ground state, or discrepancy between

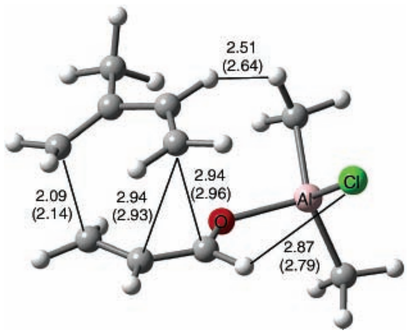

Figure 2. Second *endo s-cis* transition structure for the Diels−Alder reaction between isoprene and acrolein in the presence of $AlMe_2Cl$, using B3LYP/6-31G(d). Computed PCM values are given in parentheses. Distances are in Å.

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(5) (a) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (b) Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K. *J. Mol. Struct. (THEOCHEM)* **1997**, *398−399*, 169.

(6) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(7) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *37*, 785.

(8) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.

(9) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326.

(10) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (b) Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, *15*, 1321.

(11) (a) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351. (b) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 1699.

(12) Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38*, 33.

(13) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37.

(14) Alkorta, I.; Rozas, I.; Elguero, J. *Chem. Soc. Rev.* **1998**, *27*, 163.

(15) (a) Mackey, M. D.; Goodman, J. M. *Chem. Commun.* **1997**, *24*, 2388. (b) Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219. (c) Gung, B. W. *Tetrahedron Lett.* **1991**, *32*, 2867. (d) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370. (e) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692.

chloro and fluoro substituents, as originally defined by Corey are possible explanations to rationalize the nonplanarity. The new transition structure is different that that reported earlier and should result in modified kinetic isotope effects particularly at H3.

With use of the QUIVER program,[16] the KIEs were calculated for the new transition structure and scaled to the B3LYP/6-31G(d) level of theory by using the same procedure described by Singleton and Houk.[1,2] The QUIVER program employs the Bigeleisen and Meyer formulation,[17] based on statistical mechanics and classical transition state theory.[18] The transition structures were calculated with the Gaussian 98 program.[19] The H3 discrepancy between the experimental and calculated KIE is now resolved from the newly computed transition structure. The computed KIE value of 0.964 for the H3 atom nearest the Cl atom is within the experimental accuracy of 0.965(5) and 0.967(13) (see Table 2). However, the vacuum electronic energy of the Singleton−Houk transition structure is favored by 0.33 kcal/mol ($\Delta\Delta H^{\ddagger} = 0.38$ kcal/mol). In essence, the new transition structure explains the experimental KIE data, but is slightly disfavored energetically as compared to the Houk and Singleton transition structure in the gas phase.

Table 2. Calculated KIEs (k_H/k_D or $k_{^{12}C}/k_{^{13}C}$) for the Two TSs of the Lewis Acid Catalyzed Diels−Alder Reaction of Isoprene and Acrolein at B3LYP/6-31G(d)[a]

	Singleton/Houk TS	our TS	exp. 1[1]	exp. 2[1]
C1	1.032 [1.033]	1.032 [1.033]	1.030(3)	1.026(10)
C2	1.003 [1.002]	1.003 [1.002]	1.004(3)	1.006(9)
C3	0.999 [0.999]	0.999 [0.999]	1.001(2)	1.001(10)
C4	1.003 [1.003]	1.004 [1.003]	1.000(3)	1.001(10)
H3	0.943 [0.946]	0.964 [0.962]	0.965(5)	0.967(13)
H4out	0.985 [0.987]	0.975 [0.980]	0.978(6)	0.979(18)
H4in	0.963 [0.961]	0.968 [0.957]	0.951(4)	0.947(8)

[a] KIEs from the B3LYP/6-311G(3df) computations are given in brackets.

Density functional theory (DFT) methods give comparable energetic and structural accuracy compared to more sophisticated and resource demanding computational methods. Specifically, the Becke three-parameter exchange functional and the nonlocal correlation functional of Lee, Yang, and Parr[7] with the 6-31G(d) basis set[8] have been shown to produce realistic structures and energies for pericyclic reactions.[20] To confirm that this level of theory is accurate for atoms used in the Lewis acid, such as Al and Cl, a larger basis set, 6-311G(3df), was used for comparison. When the Lewis acid-catalyzed reaction between isoprene and acrolein was carried out with B3LYP/6-311G(3df), the vacuum electronic energy was very similar to the results seen with the smaller basis set. The Singleton−Houk transition structure is favored by 0.37 kcal/mol ($\Delta\Delta H^{\ddagger} = 0.34$ kcal/mol), using the larger basis set. The KIEs were also computed by using the larger basis set (Table 2), and found to be similar to the smaller basis set and experiment. This gives confidence that the B3LYP/6-31G(d) level of theory accurately represents the transition structures for this particular pericyclic reaction.

Consequently, the effect of solvent upon both transition structures was approximated by using the polarizable continuum model (PCM)[21] with the B3LYP/6-31G(d) level of theory, as we have reported before for other Diels−Alder reactions.[22] The solvent and dielectric constant used was diethyl ether ($\epsilon = 4.335$). Full geometry optimizations were carried out for both transition structures as shown in Figures 1 and 2. In solution, the Singleton−Houk transition structure geometry was altered slightly, where the distance between the Cl and the H3 atoms increased from 2.87 to 2.90 Å. In the second transition structure, Corey's interaction strengthens by reducing the distance between the Cl atom and the formyl hydrogen from 2.87 Å (vacuum) to 2.79 Å (solution). In addition, when solvent is included the dihedral angle is reduced to $\angle$OCHCl = 9.2° at the transition structure, which is more in line with Corey's description. The strengthening of the unusual aldehyde nonbond interaction explains why the second transition structure becomes slightly favored, with a computed electronic energy difference of 0.18 kcal/mol ($\Delta\Delta H^{\ddagger} = 0.27$ kcal/mol). The computed energy differences are small and should not be over interpreted, yet the trend is to favor the transition structure that takes advantage of nontraditional hydrogen bonding as solvent is included in the model. If the energies are correct, then both transition structures would contribute to the observed KIEs. The influence of solvent suggests a switch in the preference to the newly computed transition structure, which is in agreement with experimental KIE values.

Despite a fuller understanding of transition structure nonbond interactions for α,β-unsaturated aldehyde Diels−Alder reactions, Singleton and Houk have experimentally observed the same inverse KIE at the H3 position for similar Diels−Alder reactions, which do not have the ability to exploit nontraditional hydrogen bonding. To investigate the origin of the inverse KIEs for these closely related systems, the reaction between isoprene and methyl vinyl ketone has been computed at the B3LYP/6-31G(d) level of theory and compared to experiment.

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(16) Saunders, W.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989.

(17) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M.; Hout, R. F.; Hehre, W. *J. Am. Chem. Soc.* **1980**, *102*, 3296.

(18) Glassstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941.

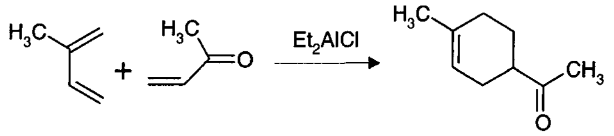
(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.9; Gaussian, Inc., Pittsburgh, PA, 1998.

(20) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378.

(21) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(22) Kong, S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418.

Scheme 2. Diels-Alder Reaction between Isoprene and Methyl Vinyl Ketone in the Presence of Et_2AlCl



Even though the nontraditional hydrogen bond is not possible for the isoprene and methyl vinyl ketone reaction, the transition structure is determined by other forces. Steric repulsions produce a staggering between the methyl group of the dieneophile and other subtituents on the catalyst, as shown by the inset in Figure 3 (dihedrals = 50.6° and 62.3°). The result eases the crowding effect seen in Singleton and Houk's acrolein system, not allowing the Cl group to crowd fully the H3 atom. Three transition structures were found with the Cl rotated about the aluminum approximately 60° each time. Figure 3 shows the lowest energy structure. The other two transition structures have less than a 2 kcal/mol relative deviation ($\Delta\Delta H^{\ddagger} = 0.58$ and 1.64 kcal/mol). Kinetic isotope effects calculated for all three transition structures give an average KIE value of 0.967 for the H3 atom. This is in very good agreement with experimental values, as shown in Table 3. A competition between transition structures may explain the experimentally observed values.

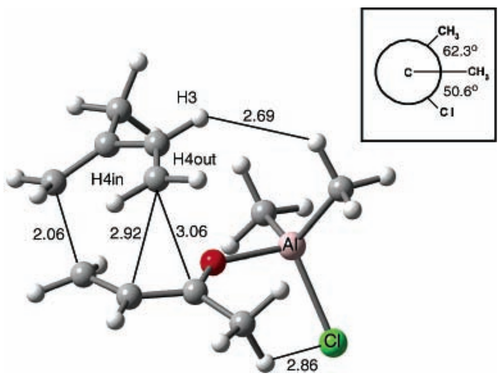


Figure 3. Lowest energy calculated *endo s-cis* transition structure for the isoprene and methyl vinyl ketone reaction with $AlMe_2Cl$ at B3LYP/6-31G(d). The inset shows a Newman projection along the carbonyl carbon and aluminum atom axis. Rotation about the Al−O bond gives two other possible transition structures.

Table 3. Calculated KIEs (k_H/k_D or $k^{12}{}_{C}/k^{13}$) for the TS Shown in Figure 3 and an Average of All Three Possible TSs of the Lewis Acid Catalyzed Diels−Alder Reaction of Isoprene and Methyl Vinyl Ketone at B3LYP/6-31G(d)

	Figure 3 calcd	av calcd	exp. 1[1]	exp. 2[1]
C1	1.033	1.033	1.028(3)	1.030(6)
C2	1.002	1.002	1.007(4)	1.002(6)
C3	1.000	1.000	1.003(4)	1.003(5)
C4	1.004	1.004	1.006(4)	1.005(5)
H3	0.973	0.967	0.970(7)	0.964(3)
H4out	0.986	0.984	0.979(9)	0.983(4)
H4in	0.954	0.955	0.972(5)	0.963(6)

In conclusion, comparison of the earlier KIE data with our new transition structure data reaffirms the ability of theory and experiment to probe the mechanism and transition structure geometry of organic reactions. Specifically, a new transition structure for the Diels−Alder reaction between isoprene and acrolein catalyzed by Me_2AlCl is found to reconcile the original discrepancies between computed and observed KIEs. Two transition structures are possible, and are close in energy. Including the effect of solvent realigns the computational results with experiment, switching the preferred reaction path from that computed in a vacuum. The refined picture from the newly computed transition structures and KIE data presented here supports an asynchronous concerted mechanism of Lewis acid-catalyzed Diels−Alder reactions.

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Supporting Information Available: Energies, frequencies, coordinates and QUIVER outputs of all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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