



Pergamon

Tetrahedron Letters 40 (1999) 5817–5821

TETRAHEDRON
LETTERS

Isotope effects for Lewis acid catalyzed Diels–Alder reactions. The experimental transition state

Daniel A. Singleton,^{a,*} Steven R. Merrigan,^a Brett R. Beno^b and K. N. Houk^{b,*}

^a*Department of Chemistry, Texas A & M University, College Station, Texas 77843-3255, USA*

^b*Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, USA*

Received 21 April 1999; accepted 27 May 1999

Abstract

²H and ¹³C kinetic isotope effects were determined for all positions on isoprene in its reactions with methyl vinyl ketone, ethyl acrylate, and acrolein catalyzed by Et₂AlCl. The results are taken as supporting a highly asynchronous concerted [4+2] cycloaddition. Comparison of the experimental isotope effects with calculated values supports this conclusion and the accuracy of the calculated transition structure. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Diels–Alder reactions; isotope effects; transition states; catalysis.

Lewis acid catalysis considerably extends the useful scope of Diels–Alder reactions, increases their regioselectivity and *endo*-stereoselectivity, and allows enantioselective catalysis using chiral Lewis acids. Although it is generally accepted that most Diels–Alder cycloadditions proceed by a concerted mechanism, Lewis acid catalyzed reactions have been less thoroughly studied and the evidence in general is less clear-cut. Indeed, some Lewis acid catalyzed reactions clearly involve a two-step process.¹ However, the bulk of the properties of these reactions have fit well with the idea of their being pericyclic [4+2] cycloadditions with their reactivity and selectivity trends explainable by FMO considerations.²

This picture was recently called into question by calculations which suggested that the overall [4+2] cycloaddition of butadiene with acrolein·BF₃ can occur via an initial inverse electron demand [2+4] cycloaddition involving the C=O of acrolein followed by a Claisen rearrangement.³ Systematic high-level calculations by García and Mayoral have demonstrated that this result is an artifact of low-level calculations.⁴ Nonetheless, the theoretical controversy and the continuing effort of synthetic chemists to develop new enantioselective reactions underscore the importance of developing experimentally-based evidence on the transition state geometry for these reactions.

We have recently demonstrated that the comparison of a large set 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.⁵ Here we

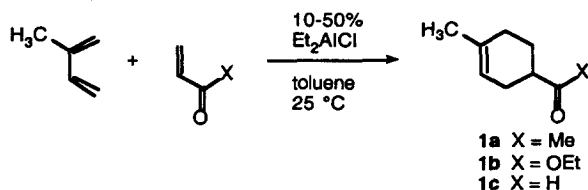
* Corresponding authors.

Table 1
Experimental and calculated KIEs (k_H/k_D or k_{12C}/k_{13C}) for the Lewis acid catalyzed Diels–Alder reactions of isoprene with acrolein, methyl vinyl ketone, and ethyl acrylate

	acrolein		methyl vinyl ketone		ethyl acrylate		calculated KIE
	exp. 1	exp. 2	exp. 1	exp. 2	exp. 1	exp. 2	
C1	1.030(3)	1.026(10)	1.028(3)	1.030(6)	1.026(4)	1.029(4)	1.031
C2	1.004(3)	1.006(9)	1.007(4)	1.002(6)	0.999(3)	1.002(4)	1.004
C3	1.001(2)	1.001(10)	1.003(4)	1.003(5)	1.002(4)	1.001(5)	1.000
C4	1.000(3)	1.001(10)	1.006(4)	1.005(5)	1.003(3)	1.005(4)	1.002
H1 _{in} +H1 _{out}	0.915(6)	0.916(7)	0.919(4)	0.919(3)	0.916(3)	0.915(3)	0.910
H3	0.965(5)	0.967(13)	0.970(7)	0.964(3)	0.970(6)	0.973(3)	0.934
H4 _{out}	0.978(6)	0.979(18)	0.979(9)	0.983(4)	0.978(9)	0.993(4)	0.986
H4 _{in}	0.951(4)	0.947(8)	0.972(5)	0.963(6)	0.950(6)	0.958(3)	0.968

apply this methodology to Lewis acid catalyzed Diels–Alder reactions. The results delimit the physical transition state for these reactions and provide direct experimental support for a highly asynchronous but concerted mechanism for the prototypical reactions studied. In addition, we show how comparisons of calculated and experimental KIEs can be used to suggest specific inaccuracies in calculated structures.

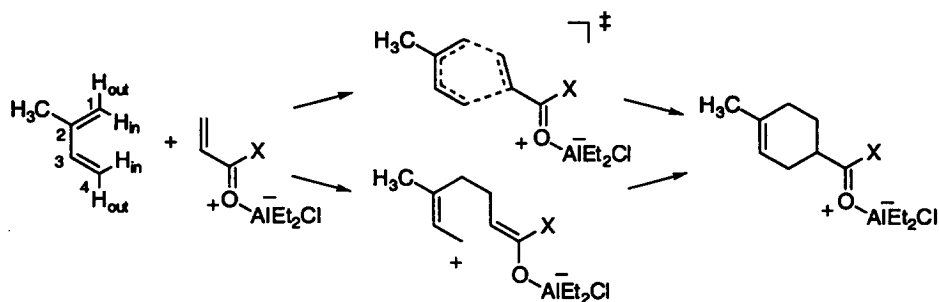
Complete sets of isotope effects for the Diels–Alder reactions of isoprene with purified methyl vinyl ketone, ethyl acrylate, and acrolein were determined combinatorially at natural abundance by recently reported methodology.⁶ The reactions were carried to 65–95% conversion under typical synthetic conditions on 1- and 5-mole scales at a 2–3 M concentration in toluene at 25°C using 10–50% diethylaluminum chloride as catalyst.⁷ At this temperature the non-catalyzed reactions were very slow and should contribute negligibly to the final isotope effects. These reactions were clean and produced in each case a >90% yield of the cycloadducts **1** (by GC versus an internal standard, based on reacted isoprene), with 94–>97% regioselectivity for formation of the ‘para’ product. After quenching of the reactions by the addition of ethylene diamine, the unreacted isoprene was recovered by an initial vacuum-transfer of ~50 mL of volatiles followed by a fractional distillation of the volatiles at atmospheric pressure. The recovered isoprene was analyzed by ¹³C and ²H NMR compared to a standard sample from the same commercial lot, and the changes in isotopic composition were calculated using the methyl group as an ‘internal standard’ with the assumption that its isotopic composition does not change in the reaction.⁸ From the changes in isotopic composition, the KIEs and errors were calculated as previously described.⁶ The results are summarized in Table 1.



On a qualitative basis, the ¹³C KIEs in Table 1 do not differentiate between stepwise and concerted mechanisms. The observation of large C1 KIEs and small KIEs at the other isoprene carbons is consistent with a stepwise mechanism (Scheme 1) with the first step being rate limiting. However, a highly asynchronous concerted mechanism would also be expected to exhibit large ¹³C KIEs at C1 and ¹³C KIEs near unity at C4.

However, the deuterium KIEs are clearly characteristic of a concerted mechanism. The key observation is the substantially inverse KIEs in the H4_{out} and H4_{in} positions, indicative of bond formation to C4 at the transition state. Inverse KIEs for H4_{out} and H4_{in} would not be expected for the stepwise mechanism.

Comparison of the experimental isotope effects with theoretically predicted values backs up the



Scheme 1.

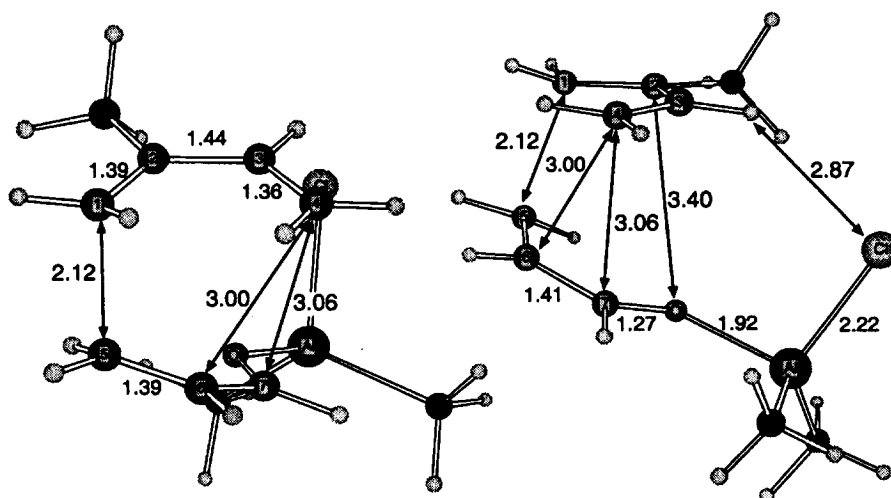


Figure 1. *endo s-cis* Transition structure for the reaction of isoprene with acrolein·AlMe₂Cl found in Becke3LYP/6-31G* calculations

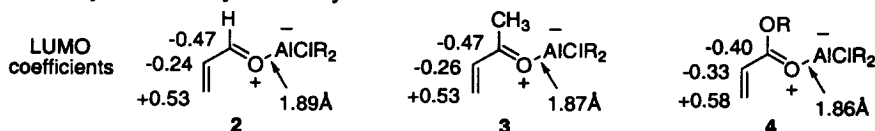
conclusion of a highly asynchronous but concerted mechanism and provides a more quantitative view of the transition state. The *endo s-cis* transition structure for the reaction of isoprene with acrolein·AlMe₂Cl was found in Becke3LYP calculations using a 6-31G* basis set, and is shown in Fig. 1.^{4,9} The *endo s-cis* structure has been strongly favored over *exo* and *s-trans* structures in previous calculations, and neither *exo* nor *s-trans* structures were explored here. No other transition structures were located in a search of other rotamers around the O–Al bond. The asynchronicity of this structure is in approximate accord with other calculations on Lewis acid catalyzed Diels–Alder reactions.^{3,4,9} However, with a C2–O distance of 3.40 Å, there is no hint whatsoever in this structure of bonding between the carbonyl oxygen and C2 of isoprene or [2+4] character. A notable feature of this structure is [4+3] character¹⁰ — C4 of isoprene is nearly as close to the carbonyl carbon (C7) as it is to the C6 (to which it will ultimately be bound). The FMO origin of this interaction has been previously discussed¹⁰ and recent calculations have supported its importance.⁴

Theoretical KIEs for this transition structure were calculated by the method of Bigeleisen and Mayer¹¹ from the scaled theoretical vibrational frequencies,¹² and tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.¹³ The results are summarized in Table 1.⁸ With a single exception, there is outstanding agreement between the calculated and experimental KIEs. The H1_{in}/H1_{out} KIE and all of the ¹³C KIEs are predicted within experimental error, and the relative values of the H4_{in} and

H₄_{out} are predicted well. Our conclusion is that the calculated transition structure is a good representation of the physical transition state, but with one difference.

The anomaly in the comparison of calculated and experimental KIEs comes at H3. The calculations predict a large inverse KIE at H3, while a much smaller effect is observed experimentally. The explanation for this difference is that in the calculated structure the chlorine atom is only 2.87 Å from H3. This crowding of H3 adds substantially to the scaled predicted C–H stretching frequency (3072 cm⁻¹, compared to 3014 in the starting isoprene), which accounts for the prediction of a large inverse KIE. The experimental H3 KIE is in fact more inverse than observed in the reaction of isoprene with maleic anhydride, suggestive of some degree of crowding, but apparently not as great as predicted. A consistent explanation for the discrepancy between the experimental and theoretical results is that the substantial partial negative charge on the Cl atom (-0.44 e⁻ in a Mulliken analysis) is drawn toward the partial positive charge in the isoprene (+0.29 e⁻) in these gas phase calculations. In solution this electrostatic attraction would be decreased.

A notable and perhaps surprising observation in the experimental isotope effects is their similarity through the acrolein, methyl vinyl ketone and ethyl acrylate series. In this regard the ¹³C KIEs are not precise enough to show whether there is any trend across the series or not, but the ²H KIEs are distinctly nearly constant. The suggestion in this observation is that the transition states for the three reactions are similarly asynchronous. It might have been expected that donation by the methyl and ethoxy groups in **3** and **4** (R=Et) compared to **2** would lead to more synchronous transition states. However, this expectation is mitigated by a tighter binding of the Lewis acid, as can be seen in decreasing predicted O–Al bond lengths across the series **2–4** (R=H) in RHF/3-21G calculations. As a result, the differences in the LUMO ('outer') coefficients on the α and β carbons in **2**, **3**, and **4** are all very similar. This would be expected to engender similar asynchronicity in the cycloadditions.



Acknowledgements

We thank the National Science Foundation, NIH grant # GM-45617, and The Robert A. Welch Foundation for support of this research.

References

1. Thompson, H. W.; Melillo, D. G. *J. Am. Chem. Soc.* **1970**, *92*, 3218.
2. Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
3. Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1995**, *117*, 10994.
4. García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415.
5. (a) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984. (b) Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385. (c) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383. (d) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Straßner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.
6. Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.
7. This reaction is highly exothermic. It was necessary to add the catalyst last in small portions over several hours.

8. The assumption of a negligible KIE in the standard peak is dubious for the deuterium isotope effect in the methyl group. To allow for this in comparing experimental and theoretical values, the theoretical 2H KIEs are calculated relative to the methyl ²H KIE.
9. Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.
10. Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563.
11. (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225.
12. The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614. (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502).
13. Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: London, 1980; pp. 60–63.