

Synchronous or Asynchronous? An “Experimental” Transition State from a Direct Comparison of Experimental and Theoretical Kinetic Isotope Effects for a Diels–Alder Reaction

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Theory and experiment agree that the concerted mechanism for the parent Diels–Alder (DA) reaction is favored by 2–7 kcal/mol over an alternative stepwise diradical pathway.¹ However, the question of the synchronous or asynchronous character of concerted transition states has not been definitively settled.² Synchronous transition structures are predicted for symmetrically substituted addends,^{1–3} but there are also exceptions.⁴ Experimentally, kinetic isotope effects (KIEs) provide the strongest evidence for synchronicity in symmetrical DA reactions.⁵ KIEs calculated for DA reactions^{6,7a} and other pericyclic processes⁷ agree reasonably with those obtained by experiment.⁵ However, experimental KIEs have not been precise enough to distinguish between a synchronous transition state and the combination of two regioisomeric asynchronous transition states. Furthermore, theoretically predicted KIEs have

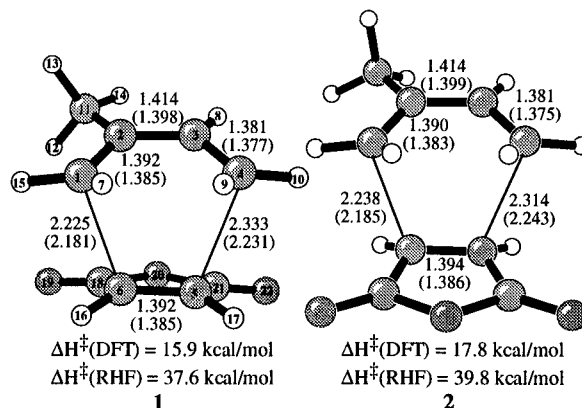


Figure 1. Becke3LYP/6-31G* endo (1) and exo (2) transition structures for the Diels–Alder reaction of isoprene and maleic anhydride. Becke3LYP and RHF/6-31G* bond lengths are in plain text and parentheses, respectively. All bond lengths are in angstroms (Å).

been limited to the parent system or lightly substituted derivatives, while more highly substituted cases have been studied experimentally.

We report here RHF and DFT transition structures and KIEs for the DA reaction of isoprene with maleic anhydride. This is the first direct comparison of high-level transition structure/KIE calculations with high-precision experimental KIEs in a DA reaction. The results have implications toward the synchronicity of symmetrical DA reactions in general and the accuracy of conventional KIE predictions using the harmonic approximation on a highly flexible transition state.

The structures reported here were obtained with Gaussian 94,⁸ using the Becke3LYP⁹ hybrid HF–DFT method with the 6-31G* basis set.¹⁰ This combination has been used with excellent results for the study of several pericyclic reactions^{7a} including the parent DA reaction.^{1e,h,j} Transition structures and KIEs were also calculated at the RHF/6-31G* level. Vibrational frequency analyses were carried out on all stationary points. The predicted KIEs were calculated using the method of Bigeleisen and Mayer¹¹ as implemented in the program QUIVER,¹² with Becke3LYP and RHF vibrational frequencies scaled by 0.963 and 0.8929, respectively.¹³ Tunneling corrections were applied using the one-dimensional infinite parabolic barrier model.¹⁴

Transition structures and activation enthalpies for the endo (1) and exo (2) pathways are shown in Figure 1. The DFT gas

(8) Gaussian 94 (Revision C.2); Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Latham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.: Pittsburgh, PA, 1995.

(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. For reviews of density-functional methods, see: (c) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651. (d) *Density Functional Methods in Chemistry*; Labanowski, J., Andzelm, J., Eds.; Springer: Berlin, 1991. (e) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(10) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(11) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225.

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

(13) (a) Rauhut, G.; Pulay, P. *J. Phys. Chem.* **1995**, *99*, 3093. (b) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345.

(14) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: London, 1980; pp 60–63. Identical Becke3LYP results (to ± 0.001) were obtained using a Wigner tunneling correction, although the RHF results differed by as much as ± 0.005 (Wigner, E. P. *Z. Phys. Chem.* **1932**, *B19*, 203). See also: ref 21.

[†] University of California, Los Angeles.

[‡] Texas A&M University.

(1) (a) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (b) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478. (c) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B.; Wolber, G. J. *J. Org. Chem.* **1989**, *54*, 2931. (d) Bernardi, F.; Bottoni, A.; Field, M. J.; Guest, M. F.; Hillier, I. H.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1988**, *110*, 3050. (e) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036. (f) Stanton, R. V.; Merz, K. M., Jr. *J. Chem. Phys.* **1993**, *100*, 434. (g) Carpenter, J. E.; Sosa, C. P. *J. Mol. Struct. (THEOCHEM)* **1994**, *311*, 325. (h) Jursic, B.; Zdravkovski, Z. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1223. (i) Baker, J.; Muir, M.; Andzelm, J. *J. Chem. Phys.* **1995**, *102*, 2063. (j) Barone, V.; Arnaud, R. *Chem. Phys. Lett.* **1996**, *251*, 393. Doering, W. v. E.; Roth, W. R.; Breuckmann, R.; Figge, L.; Lennartz, H.-W.; Fessner, W. D.; Prinzbach, H. *Chem. Ber.* **1988**, *121*, 1. (k) Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190. (l) Bernardi, F.; Bottini, A.; Robb, M. A.; Field, M. J.; Hillier, I. H.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1081.

(2) (a) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213. (b) Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203.

(3) (a) Houk, K. N.; Li, Y.; Evansek, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682 and references therein. (b) Coxon, J. M.; Grice, S. T.; MacLagan, R. G. A. R.; McDonald, D. Q. *J. Org. Chem.* **1990**, *55*, 3804. (c) Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172. (d) Karcher, T.; Sicking, W.; Sauer, J.; Sustmann, R. *Tetrahedron Lett.* **1992**, *33*, 8027. (e) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936. (f) Jursic, B.; Zdravkovski, Z. *J. Mol. Struct. (THEOCHEM)* **1994**, *309*, 249. (g) Jursic, B. S. *J. Mol. Struct. (THEOCHEM)* **1995**, *358*, 139. (h) Jursic, B. S. *J. Org. Chem.* **1995**, *60*, 4721.

(4) (a) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499. (b) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330. (c) RHF calculations predict asynchronous transition structures for the DA reactions of butadiene with acetylene dicarboxaldehyde, malealdehyde, and maleic acid (Singleton, D. A.; Leung, S.-W. Unpublished results).

(5) (a) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R.; Huang, Y. C. *J. Am. Chem. Soc.* **1989**, *111*, 9078. (b) Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5545. (c) Seltzer, S. *J. Am. Chem. Soc.* **1963**, *85*, 1360. (d) Van Sickle, D. E.; Rodin, J. O. *J. Am. Chem. Soc.* **1964**, *86*, 3091. (e) Taagepera, M.; Thornton, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 1168.

(6) (a) Storer, J. W.; Raimondi, L.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9675. (b) Houk, K. N.; Li, Y.; Storer, J.; Raimondi, L.; Beno, B. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1599.

(7) (a) Wiest, O.; Houk, K. N.; Black, K. A.; Thomas, B., IV. *J. Am. Chem. Soc.* **1995**, *117*, 8594. (b) Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565. (c) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336.

phase ΔH^\ddagger overestimates the experimental result of 11.8 kcal/mol (benzene solvent, 298 K)¹⁵ by 4.1 kcal/mol. However, the inclusion of solvation via the SCIPCM model using a dielectric constant of 2.274 D (benzene, 298 K)¹⁶ brings the Becke3LYP ΔH^\ddagger to within 2.0 kcal/mol of the experimental value. The gas-phase ΔS^\ddagger values for the endo and exo pathways are -43.6 and -40.9 eu, respectively, in reasonable agreement with the experimental ΔS^\ddagger of -37.1 eu.¹⁵ The calculated $\Delta\Delta G^\ddagger$ (298 K) of 1.1 kcal/mol favors the endo pathway. At 353 K, the $\Delta\Delta G^\ddagger$ is predicted to be 0.9 kcal/mol, in excellent agreement with the 1.2 kcal/mol value measured for the DA reaction of 1,4-D₂-butadiene and maleic anhydride.¹⁷ Although the RHF method overestimates the activation barrier (37.6 kcal/mol), the calculated $\Delta\Delta G^\ddagger$ (353 K) of 1.6 kcal/mol favoring the endo pathway is in good agreement with the butadiene/maleic anhydride experiment.

Both levels of theory predict that the methyl substituent induces a small amount of asynchronicity in the two transition structures, although the Becke3LYP structures are slightly more asynchronous. The differences in forming C-C bond lengths are 0.11 and 0.08 Å for the DFT endo (**1**) and exo (**2**) structures, respectively, and bond formation is more advanced at the C1 position of isoprene, as expected.¹⁸ The lengths of both forming C-C bonds are within ± 0.06 Å of those in the Becke3LYP/6-31G* transition structure of the parent DA reaction.^{1e} The Becke3LYP bond order¹⁹ for the isoprene-C1 forming bonds is 0.32 in **1** and **2**, while the bond orders for the isoprene-C4 forming bonds in **1** and **2** are 0.27 and 0.28, respectively. Structure **1** is very flexible, with vibrational frequencies associated with asynchronicity and diene/dienophile twisting of 127 and 54 cm⁻¹, respectively.

The most striking result is a triple-digit agreement between most of the Becke3LYP and experimental KIEs (Figure 2). The experimental KIEs originally reported were *relative* values, based on assumed methyl group H/D and ¹²C/¹³C KIEs of 1.000.²⁰ Although this assumption is predicted to be very close to correct, the experimental results were recalculated assuming methyl group H/D and ¹²C/¹³C KIEs of 0.996 and 1.001 to match the predicted values. With this assumption, seven out of the nine independent sets of KIEs agree within experimental error, five within 0.001! The RHF KIEs show much larger deviations from the appropriately scaled experimental values.

Larger errors in predicted primary KIEs are found for H-transfer reactions due to variational transition state and multidimensional tunneling effects.²¹ Such effects are minimal here. Errors in the frequencies and the anharmonicity of the vibrational modes, particularly the low-frequency modes associated with the floppy transition state, also appear to cause little error in the KIE predictions.²²

(15) Dewar, M. J. S.; Pyron, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 3098. Activation parameters were derived from this paper's experimental raw data in a standard fashion.

(16) *Handbook of Chemistry and Physics*, 68th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1987; p E49.

(17) Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 417.

(18) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(19) See ref 7 and references therein.

(20) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

(21) Lu, D.-h.; Maurice, D.; Truhlar, D. G. *J. Am. Chem. Soc.* **1990**, *112*, 6206.

(22) An error analysis indicates that moderate errors in the low frequencies should not significantly affect the predicted KIEs.

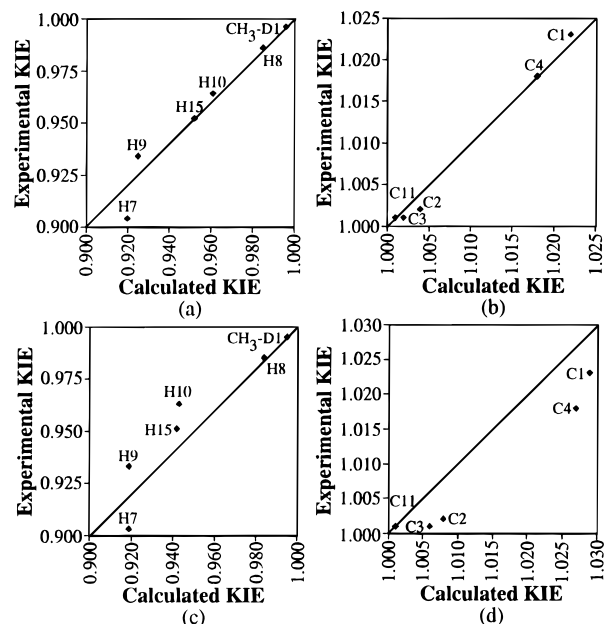


Figure 2. Comparison of experimental and calculated kinetic isotope effects: (a) Becke3LYP ²H secondary KIEs; (b) Becke3LYP ¹³C KIEs; (c) RHF ²H secondary KIEs; (d) RHF ¹³C KIEs. The numbering system is shown in Figure 1.

The only errors in the calculated Becke3LYP KIEs outside of experimental error are observed with the large KIEs of the "in" hydrogens H7 (underestimated by $\approx 1.6\%$) and H9 (overestimated by $\approx 0.9\%$). Since the KIEs for the "out" hydrogens (H10 and H15) are within the error ranges of the experimental results, the errors in the calculated "in" hydrogen KIEs do not necessarily imply that the actual transition state structure is more asynchronous than predicted. A significant population of the isoprene skew conformation at the experimental temperature could account for the errors, or these small discrepancies might even result from specific solvent interactions with the "in" hydrogens.

Altogether, the experimental KIEs are consistent with a moderately asynchronous transition state closely resembling transition structure **1**. The comparison of a large set of high-level calculated and high-precision experimental KIEs essentially provides an *experimental* picture of the transition state. In the current example, the most direct knowledge so far available has been obtained for the synchronicity of a complex Diels-Alder reaction.

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Supporting Information Available: Coordinates and energies of all structures reported and tables of KIEs (5 pages). See any current masthead page for ordering and Internet access instructions.

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