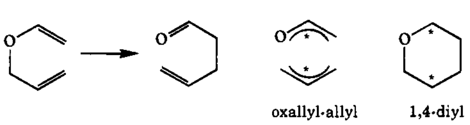
Transition Structures and Kinetic Isotope Effects for the Claisen Rearrangement

Hi Young Yoo and K. N. Houk*

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024-1569

Received April 20, 1993
Revised Manuscript Received August 31, 1994

Claisen rearrangements are important [3,3] sigmatropic shifts used widely in synthesis.[1] Substitutent effects on rates and mechanisms of these processes have been investigated extensively.[2−5] The rate-determining transition state is generally thought to be closer to the oxallyl−allyl end of the spectrum than to the 1,4-diyl; there is still discussion about the degree of zwitterionic character in the transition state.[3,5]



The nature of the transition state is very important in understanding a number of phenomenon, such as the origin of solvent effects on the rates of Claisen rearrangements,[6,7] the mechanism of catalysis of a Claisen rearrangement by the enzyme chorismate mutase,[5,8−12] and the nature of two catalytic antibodies, which differ widely in the mechanism by which they catalyze the chorismate−prephenate rearrangement.[13−15]

We previously reported an ab initio RHF/6-31G* transition structure for the Claisen rearrangement.[2] We have now calculated isotope effects to compare with experiment and have located the transition structure with more complete theoretical models as well. The geometry and polarity of the transition state can be defined more exactly in this way.

In order to probe bond-breaking and bond-making in the transition state, secondary kinetic isotope effects for hydrogen, carbon, and oxygen have been investigated experimentally.[16−18] The RHF/6-31G* force constants for allyl vinyl ether and the chair transition structure at the RHF level[2] were first used to calculate the theoretical isotope effects using the program QUIVER.[19] Figure 1 compares the theoretical and experimental[16−18] kinetic isotope effects. The normal secondary deuterium kinetic isotope effect at the C(4) position and the inverse isotope effect at the C(6) position are expected (Figure 1). However, there are significant discrepancies in the magnitudes of the RHF/6-31G* and experimental isotope effects; this shows that the calculated geometries and force constants must differ from the experimental values. We have shown that excellent predictions of isotope effects are possible if the transition state geometry is correct.[20] The larger experimental isotope effects[16−18] at O and C(4) imply more CO bond-breaking than in the RHF/6-31G* ab initio transition structure. The smaller isotope effects at C(6) measured experimentally imply that less bond-making occurs here than is predicted by the RHF/6-31G* structures. Consequently, the real transition state should resemble an oxally−allyl radical pair more than predicted by RHF/6-31G* calculations. Consequently, higher level calculations were carried out with several methods. First, an MP2/6-31G* transition structure was located. It has even more 1,4-diyl character than that optimized at the RHF/6-31G* level. The bond-breaking and bond-making distances at the MP2/6-31G* level are 1.797 and 2.199 Å, respectively. This shift toward the 1,4-diyl structure is the same trend found for the Cope rearrangement.[20]

Because MP2 takes the transition structure in the wrong direction, the reaction has also been studied by using a six electron/six orbital complete active space CASSCF calculation with the 6-31G* basis set. The transition structure is compared to the RHF/6-31G* level in Figure 2. The calculated activation energy is 42.5 kcal/mol, whereas the experimental and RHF/6-31G* values are 30.6 and 48.8 kcal/mol, respectively. The optimized CASSCF/6-31G* transition structure indicates much more bond-breaking and much less bond-making, as shown by the O(3)−C(4) and C(1)−C(6) distances of 2.100 and 2.564 Å, respectively (Figure 2). These are 0.2 and 0.3 Å, respectively, longer than the distance by RHF/6-31G* calculations. The calculated secondary kinetic isotope effects summarized in Figure 1 also indicate more bond-breaking than bond-making. The heavy atom isotope effects are now in better agreement with experiment. The deuterium isotope effects err in the opposite direction, indicating that the MCSCF/6-31G* calculations overestimate the extent of bond-breaking character compared to the experimental results. We have searched for a second transition state or intermediate, as found in the similar calculations on the Cope rearrangement,[21] but we have not found

---

(1) (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. (b) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*. 1. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (e) Bennett, G. B. *Synthesis* **1977**, 589. (f) Barlett, P. A. *Tetrahedron* **1980**, *36*, 1.

(2) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

(3) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.

(4) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.

(5) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

(6) (a) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794. (b) Storer, J. W.; Giesen, D. G.; Hawkins, G. D.; Lynch, G. C.; Cramer, C. J.; Truhlar, D. G.; Liotard, D. A. In *Structure and Reactivity in Aqueous Solution*; ACS Symposium Series 568; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994; p 24. (c) Davidson, M. M.; Hillier, I. H.; Hall, R. J.; Burton, N. A. *J. Am. Chem. Soc.* **1994**, *116*, 9294.

(7) (a) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966. (b) Severance, D. L.; Jorgensen, W. L. In *Claisen Rearrangement of Allyl Vinyl Ether. Computer Simulations of Effects of Hydration and Multiple-Reactant Conformers*; ACS Symposium Series 568; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994; Chapter 17. (c) Gao, J. *J. Am. Chem. Soc.* **1994**, *116*, 1563.

(8) Berchtold, G. A.; Pawlak, J. L.; Padykula, R. E.; Kronis, J. D.; Aleksejczyk, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 3374.

(9) Guilford, W. J.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5013.

(10) Stewart, J.; Wilson, D. B.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 4582.

(11) Bartlett, P. A.; Johnson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 7792 and references therein.

(12) (a) Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974. (b) Ganem, B. *Tetrahedron* **1978**, *34*, 3353.

(13) Hilvert, D.; Nared, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 5593.

(14) Hilvert, D.; Carpenter, S. H.; Nared, K. D.; Auditor, M.-T. M. *Proc. Natl. Acad. Sci U.S.A.* **1988**, *85*, 4953.

(15) Jackson, D. Y.; Jacobs, J. W.; Sugasawara, R.; Reich, S. H.; Barlett, P. A.; Schultz, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 4841.

(16) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.

(17) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.

(18) Kupczyk-Subotkowska, L.; Saunders, W. H.; Shine, H. J.; Subotkowski, W. *J. Am. Chem. Soc.* **1993**, *115*, 5957.

(19) Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989. All the calculated frequencies are reduced by 10% to correct for anharmonicity and basis set effects.

(20) Gustafson, S. M.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 8565.

(21) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 9756.

0002-7863/94/1516-12047$04.50/0

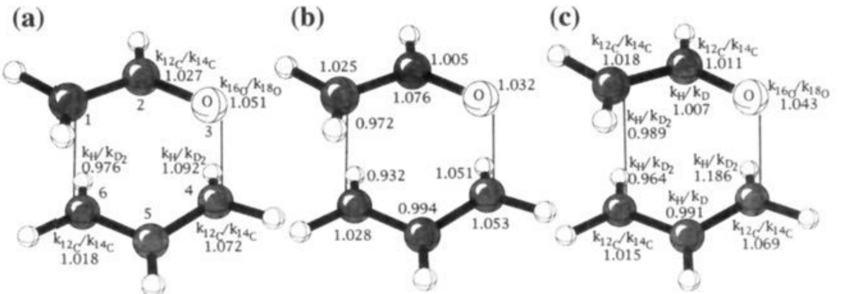


Figure 1. Secondary deuterium kinetic isotope effects at the C(4) and C(6) positions and heavy-atom primary kinetic isotope effects at the C(2), O(3), C(4), and C(6) positions. (a) Experimental data,[16-18] (b) RHF/6-31G* predicted values, and (c) CASSCF/6-31G* values for 160 °C. Deuterium isotope effects are shown inside the structures, and heavy-atom isotope effects are shown outside the structures. The uncertainties in the experimental results for the deuterium and the heavy-atom isotope effects are ±0.005[16,17] and ±0.0005–0.0008,[18] respectively.

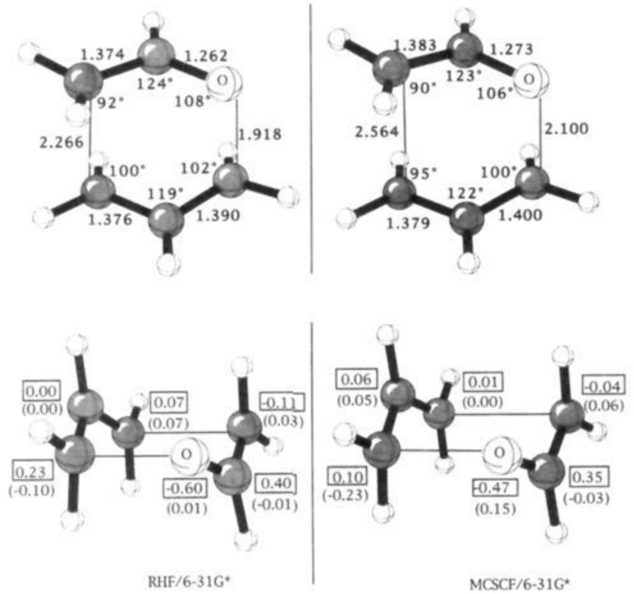


Figure 2. Two views of the optimized transition structures for the Claisen rearrangement of allyl vinyl ether at RHF/6-31G* and MCSCF/6-31G* levels. Bond lengths are given outside the structure and angles inside the structures. Mulliken charges with hydrogen charges summed into heavy atoms are shown in boxes, and changes in charges between ground and transition state are shown in parentheses.

any other stationary points.[22] Linear extrapolation between the RHF and MCSCF results to fit experimental deuterium isotope effects leads to predicted transition state values of 1.97 and 2.68 Å for CO and CC bond lengths, respectively.

The changes in charges upon going from ground to transition state, calculated by RHF and MCSCF techniques, are shown in Figure 2. There is less than half as much ionic character in the oxally–allyl radical pair in the MCSCF/6-31G* level as compared to the RHF/6-31G* level, but the changes in charges are larger, since a polar species is partially converted into a diradical pair, not an ion pair, in the transition state.

Empirical Bebovib calculations of isotope effects predict C–O and C–C bond orders of 0.3–0.5, and 0.1–0.3, respectively.[18] Gajewski and Conrad deduced 0.33 and 0.17, based upon deuterium isotope effects.[16] Our MCSCF results give bond orders of 0.31 for the C–O bond and 0.18 for the C–C bond, using the calculated bond lengths and the modified Pauling bond order equation.[23]

This significant refinement of transition state structure[24] and charge distribution should facilitate mechanistic discussion and catalyst design. Studies of this type will be reported shortly.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to Dr. Yi Li and Susan M. Gustafson for assistance and preliminary calculations.

Supplementary Material Available: Graph of the calculated and experimental isotope effects (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

[22] CASSCF-MP2 calculations using various large basis sets predict only a single "aromatic" transition state for the Cope rearrangement: Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072, 4529.

[23] Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542. The constant 0.6, rather than 0.3, is used: $n_p = n_o \exp[(R_0 - R)/0.6]$; personal communication with J. J. Gajewski, based upon work with E. R. Davidson and V. J. Shiner.[20]

[24] For related DFT results, see: Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.*, in press.