

Kinetic Isotope Effects as a Guide to Transition State Geometries for the Intramolecular Cope and Ylide Elimination Reactions. An *ab Initio* MO Study

Robert D. Bach,* Carlos Gonzalez, Jose L. Andres, and H. Bernard Schlegel

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received February 6, 1995

The quality of geometries given by electronic structure calculations may be readily verified by direct comparison with experimental data. Excellent agreement between theory and experiment is commonplace even at the Hartree-Fock level of theory provided that an adequate basis set is employed. When post-Hartree-Fock methods are included, the energetics of a great many reactions may be accurately determined, as confirmed by matching with experimentally derived thermochemistry. In the gas phase, calculated activation barriers are also found to be quite reliable. However, an assessment of the accuracy of transition state geometries remains a primary goal of the applied quantum chemist. An experimentally determined kinetic isotope effect (KIE) is one of the few available tools that can probe the geometry of a transition state.¹ A number of studies have been reported in which theoretically calculated KIE have been used in an effort to predict transition state structures.² In this paper we describe a direct comparison of calculated KIE to experimental values for several intramolecular elimination reactions to evaluate the accuracy of transition state geometries determined by *ab initio* methods.

The intramolecular Cope elimination (TS-2), involving the thermal decomposition of an amine oxide, provides an ideal test case for theoretical study of both primary and secondary isotope effects. Stereochemical³ and isotopic labeling studies⁴ have established this reaction to be an intramolecular *syn*-elimination. Deuterium labeling studies⁵ have also established a *syn*-periplanar transition state for the related Wittig modification⁶ of the Cope elimination. Comparison with the corresponding ylide pathway (TS-4) provides a probe of the effect of base

strength on the position of the transition structure along the reaction pathway for this five-membered E_i mechanism. Both reactants, although dipolar in nature, afford neutral elimination products, which simplifies the overall theoretical treatment.

Prior experience⁷ with zwitterionic structures such as water oxide (H₂O⁺-O⁻) suggested that the MP2/6-31G* level of theory would provide adequate geometries for dipolar reactants **1**, **3**, and **5** (Figures 1 and 2).⁸ Classical barrier heights for TS-2 and TS-4 are predicted to be 28.2 and 10.8 kcal/mol, respectively, at the MP2/6-31G* level of theory. Activation barriers of 29.1 and 11.4 kcal/mol were found for these two elimination reactions, respectively, using full fourth-order Møller-Plesset perturbation theory (MP4SDTQ/6-31G*/MP2/6-31G*). The barrier for the Cope elimination is consistent with experiment ($\Delta H^\ddagger = 24.3-29.4$ kcal/mol for 2-phenylethyldimethylamine oxide).^{11a} The lower barrier ($\Delta \Delta E^\ddagger = 17.7$ kcal/mol) for the ylide mechanism is a consequence of the more highly basic carbon atom that is reflected in a much earlier transition state. Accordingly, the Cope elimination is endothermic by 4.9 kcal/mol, while the overall ylide reaction affording isolated products is exothermic by 45.1 kcal/mol. The C_β-H₁ bond elongation is only 6% in TS-4 compared to 27% in the Cope elimination. In both transition structures the internal bond angles involving hydrogen abstraction are noticeably smaller than the anticipated ~108° H-O-N and H-C-N bond angles (Figure 1).^{1b} The percent C-N bond stretch in TS-2 (34%) and TS-4 (18%) also gives an indication of the position of the TS along the reaction coordinate, as does the extent of double-bond formation indicated by the change in C-C bond distances. Another indication in the amount of double-bond character in the TS is the approach toward planarity at C_α and C_β as measured by the sum of the three valence angles ($\Sigma\theta_i$) of the incipient alkene (Figure 1). The 20° change experienced by C_α in the cope elimination indicates a change in rehybridization nearly twice as large as that in the ylide reaction.

The secondary KIE, attending the change in hybridization from sp³ to sp², is still thought to be primarily a consequence of the change in out-of-plane bending fre-

(1) (a) Shiner, V. J., Jr. In *Isotope Effects in Chemical Reactions*; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand Reinhold: New York, 1970; Chapter 2. (b) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. (c) Gajewski, J. J. *Isotopes in Organic Chemistry, Vol. 7 Secondary and Solvent Isotope Effects*; Buncl, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987.

(2) (a) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 8343. (b) Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989. (c) Chantranupong, L.; Wildman, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 4151. (d) Wolfe, S.; Hoz, S.; Kim, C.-K.; Yang, K. *J. Am. Chem. Soc.* **1990**, *112*, 4186. (e) Axelsson, B. S.; Matsson, O.; Langstrom, B. *J. Am. Chem. Soc.* **1989**, *112*, 6661. (f) Jensen, F.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3139.

(3) (a) Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740. (b) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656. (c) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; Wiley-Interscience: New York, 1973.

(4) (a) Bach, R. D.; Andrzejewski, D.; Dusold, L. R. *J. Org. Chem.* **1973**, *38*, 1742. (b) Bach, R. D.; Braden, M. L. *J. Org. Chem.* **1991**, *56*, 7194.

(5) (a) Bach, R. D.; Knight, J. W.; Braden, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 4712. (b) Bach, R. D.; Bair, K. W.; Andrzejewski, D. *J. Am. Chem. Soc.* **1972**, *94*, 8608. (c) Bach, R. D.; Andrzejewski, D. *J. Am. Chem. Soc.* **1971**, *93*, 7118.

(6) Witting, G.; Polster, R. *Justus Liebigs Ann. Chem.* **1957**, *612*, 102.

(7) (a) Bach, R. D.; Owensby, A. L.; Gonzalez, C.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1991**, *113*, 6001. (b) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (c) Bach, R. D.; Su, M.-D.; Schlegel, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 5379.

(8) All geometries^{9a} given in the figures utilized gradient geometry optimization^{9b} at both HF and MP2 levels of theory. Analytical second derivatives and vibrational frequencies at the HF/6-31G* and MP2/6-31G* levels were computed using Gaussian^{9a} and CADPAC,^{9c} respectively. The rate constants were calculated without scaling by using nonvariational transition state theory^{10a} including Wigner's tunneling correction.^{10b}

(9) (a) Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90*; Gaussian: Pittsburgh, PA 1990. (b) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214. (c) Amos, R. D.; Rice, J. E. CADPAC: Cambridge Analytic Derivatives Package, Issue 4, Cambridge, 1988.

(10) (a) Steinfeld, J. I.; Francisco, J. S.; Hase, W. L. *Chemical Kinetics and Dynamics*; Prentice Hall: Englewood Cliffs, NJ, 1989. (b) Wigner, E. P. *Z. Phys. Chem.* **1932**, *B19*, 203. (c) Bell, R. P. *Trans. Faraday Soc.* **1959**, *55*, 1. (d) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973; Chapter 12.

(11) (a) Chiao, W.-B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2802. (b) Wright, D. R.; Sims, L. B.; Fry, A. *J. Am. Chem. Soc.* **1983**, *105*, 3714. (c) Lewis, D. E.; Sims, L. B.; Yamataka, H.; McKenna, J. *J. Am. Chem. Soc.* **1980**, *102*, 7411. (d) Miller, D. J.; Subramanian, Rm.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 3519.

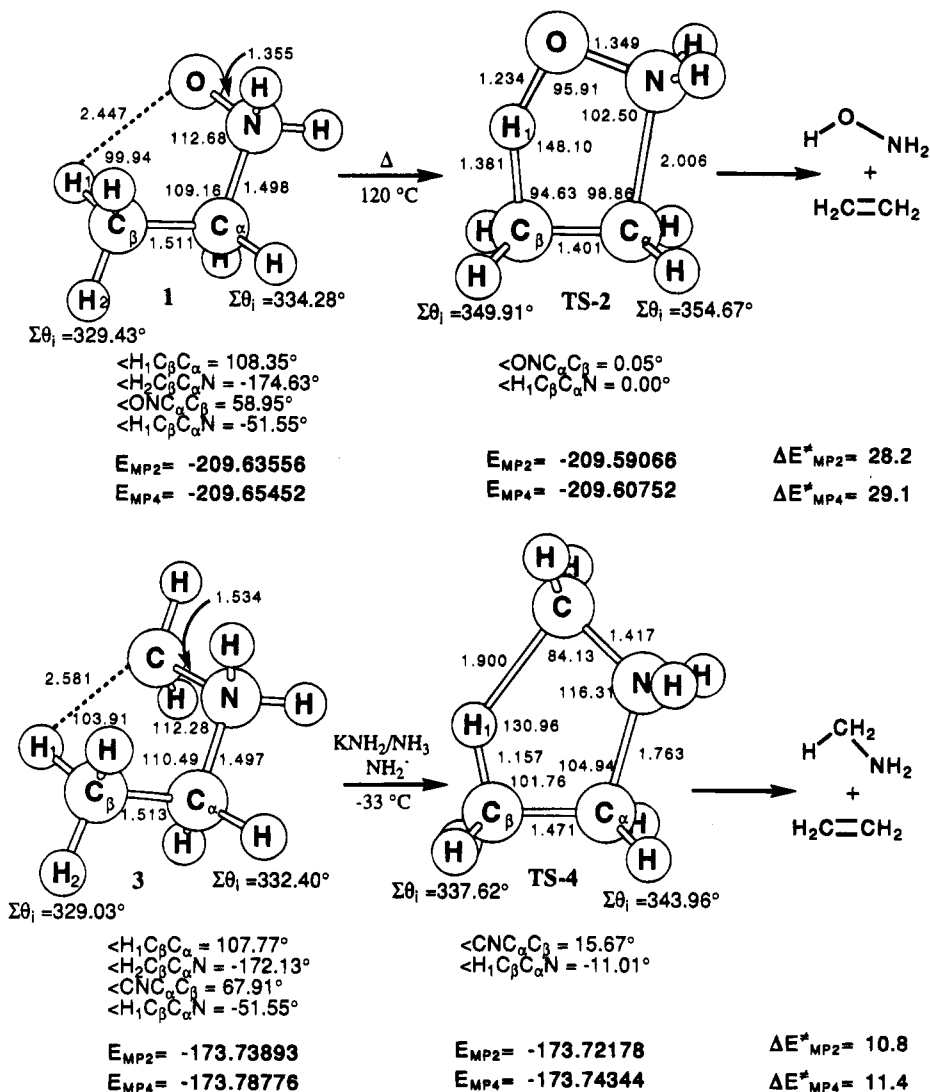


Figure 1. Geometries (MP2/6-31G*) for the starting materials and transition states of the Cope elimination reaction (TS-2) and its respective ylide elimination (TS-4) with experimental conditions shown over the arrow. Total energies are in au, and activation barriers at the level indicated given in kcal/mol.

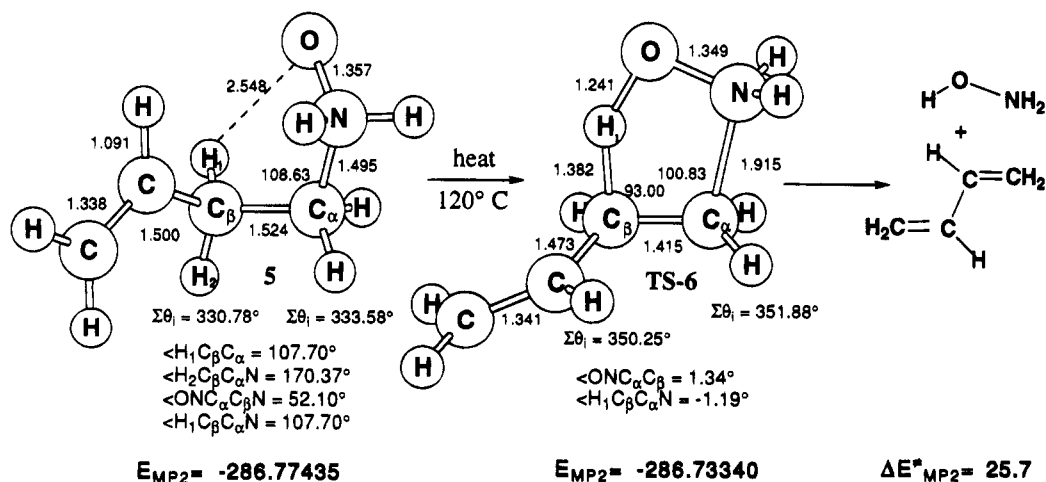


Figure 2. Geometry and transition state (MP2/6-31G*) for the Cope elimination reaction (TS-6) affording 1,3-butadiene and hydroxylamine. Energies are in au and relative energies in kcal/mol. Bond distances are in Å and angles in degrees.

quency.¹² The above analysis of the geometry of the two transition structures is quite consistent with the magnitude of the calculated KIE (Table 1). These data are in excellent accord with experimental values, and the

agreement with the secondary KIE is particularly gratifying. By comparison, the KIE calculated from Hartree-Fock structures are significantly poorer in agreement with experiment because of the lesser extent of rehybrid-

Table 1. Calculated Primary and Secondary KIE for the Cope Elimination (TS-2) and the Wittig Modification of the Hofmann Elimination (Ylide) of Ethylene (TS-4) Using MP2/6-31G* Analytical Frequencies (KIE in Parentheses are Computed from an Analytical Frequency at HF/6-31G*)

| | Cope elimination | | | | ylide elimination | | | |
|----------------------------|-------------------------------------|-------------------------------------|----------------------------|-----|----------------------|----------------|----------------------------|-----|
| | KIE _{calcd} | | KIE _{obsd} | ref | KIE _{calcd} | | KIE _{obsd} | ref |
| | 25 °C | 120 °C | | | 25 °C | -33 °C | | |
| | Primary KIE | | | | | | | |
| β -d ₁ | 4.83 3.92 ^a (5.48) | 3.37 2.90 ^a (3.80) | 3.5 (110°) ^b | 4a | 1.53 | 1.66 (8.96) | 1.69 (-33°) ^{b,h} | 5c |
| | | | 2.2 (120°) ^c | 4b | | | 1.23 (25°) ^{b,i} | 5b |
| | | | 2.9 (60°) ^{e,g} | 11a | | | 1.52 (25°) ^{b,j} | 5b |
| | Secondary KIE | | | | | | | |
| α -d ₁ | 1.16 (1.07) | 1.11 (1.05) | | | 1.16 | 1.20 (1.09) | | |
| β -d ₁ | 1.05 (1.09) | 1.04 (1.06) | 1.06 (120°) ^c | 4b | 1.03 | 1.03 (1.11) | | |
| α -d ₂ | 1.29 (1.11) | 1.19 (1.08) | | | 1.29 | 1.39 (1.15) | | |
| β -d ₂ | 1.11 (1.22) | 1.09 (1.16) | | | 1.07 | 1.09 (1.30) | | |
| | Heavy Atom KIE | | | | | | | |
| α - ¹⁴ C | 1.059 | 1.049 ^d | 1.061 (65°) ^e | 11b | 1.160 | 1.188 | | |
| β - ¹⁴ C | 1.017 | 1.015 ^d | 1.036 (65°) ^e | 11b | 1.023 | 1.025 | | |
| ¹⁵ N | 1.016 | 1.015 ^d | 1.013 (40°) ^{e,f} | 11c | 1.045 | 1.055 | | |

^a KIE without Wigner tunneling correction. ^b Formation of *cis*-cyclooctene in liquid ammonia. ^c Formation of apopinene. ^d Calculated at the experimental temperature. ^e Formation of styrene. ^f Hofman elimination. ^g In DMSO solvent. ^h Average for three different amine leaving groups for a *syn*-elimination. ⁱ *tert*-Butyl lithium in ether. ^j *n*-Butyl lithium in pentane.

ization at both carbon atoms. The discrepancy between the calculated β d₁ primary KIE for the ylide elimination (TS-4) at the HF and MP2 levels is a case in point. While the MP2 KIE ($k_H/k_D = 1.66$) is in excellent agreement with experiment, the primary β -deuterium isotope effect calculated at HF is much higher ($k_H/k_D = 8.96$). The transition state calculated at HF comes much later along the reaction coordinate with a C _{β} -H₁ bond distance of 1.379 Å and an H₁-CH₂ bond distance that has been reduced from 1.900 to 1.455 Å. Calculation of heavy isotope effects, especially ¹⁵N,^{11c} has presented difficulties when other theoretical methods have been used.¹¹ Appreciable k_H/k_D and heavy atom k_{12}/k_{13} β -carbon tunneling corrections (1.015–1.025) have been required to reach agreement between calculated and observed values.^{1b}

Since a great many of the substrates used in the experimental studies contained a phenyl substituent in conjugation with the developing carbon-carbon double bond, we elected to add a vinyl substituent to our model alkene precursors. The predicted classical activation barrier for elimination of butadiene from amine oxide **5** is 25.7 kcal/mol (MP2/6-31G*). Thus, we see only a 2.5 kcal/mol decrease in barrier height when a vinyl group is placed in conjugation with the developing double bond in TS-6 (Figure 2). The geometrical parameters in TS-6 are very similar to those for Cope elimination affording ethylene (TS-2). The primary KIE computed (Table 2) at 120 °C ($k_H/k_D = 3.40$) is very close to that found for a Cope elimination affording styrene ($k_H/k_D = 3.5$ at 110 °C).^{4a} This is about the magnitude anticipated for a nonlinear transition state where the C-H-O bond angle is 146.7°. We predict a KIE for β -deuterium substitution to be slightly higher (1.079 vs 1.06) than that observed.^{4b} We calculate a slightly smaller α -¹⁴C KIE than that observed, and we found virtually no effect for β -¹⁴C isotopic substitution (Table 2).

Table 2. Primary and Secondary KIE for the Cope Elimination Reaction (TS-6) Affording 1,3-Butadiene and Hydroxylamine Calculated with and without (Parentheses) Wigner Tunneling Corrections

| type | 25 °C | 65 °C | 120 °C |
|--|----------------------------|----------------------------|---------------|
| KIED ₁ | 4.930 (4.030) | 4.110 (3.445) | 3.399 (2.936) |
| KIED _{α} | 1.110 (1.110) | 1.098 (1.096) | 1.079 (1.079) |
| KIED _{β} | 1.099 (1.091) | 1.091 (1.083) | 1.079 (1.074) |
| KIED _{$\alpha\alpha$} | 1.280 (1.278) | 1.244 (1.240) | 1.200 (1.197) |
| KIE ¹⁵ N | 1.024 (1.021) ^a | 1.020 (1.017) | 1.015 (1.013) |
| KIE ¹⁴ C _{α} | 1.070 (1.064) | 1.059 (1.053) ^b | 1.046 (1.042) |
| KIE ¹⁴ C _{β} | 1.014 (1.007) | 1.012 (1.005) ^c | 1.009 (1.004) |

^a Calculated 1.0202 (1.020) at 40 °C; experimental: 1.013 at 40 °C for the formation of styrene; ref 11c. ^b Experimental: 1.061 for the formation of styrene, ref 11b. ^c Experimental: 1.036 for the formation of styrene, ref 11b.

Except for the primary KIE in the Cope reaction, tunneling correction by the Wigner formalism^{10b} changed the remaining KIE by less than 0.01. The KIE obtained using tunneling corrections calculated by the more accurate procedure developed by Bell^{10c} were approximately 1–3% higher than the values obtained with the Wigner tunneling corrections. In the case of primary KIE however, the use of Bell's tunneling corrections predicted larger values by a factor of 2. This significant difference can be attributed to the tendency of the Wigner correction to underestimate the tunneling effects whenever the magnitude of the imaginary frequency is smaller than 1000 cm⁻¹, as discussed in detail by Melanders and Saunders.^{1b} In all cases the trends are reproduced and agreement is quite good considering the fact that we are using a model system and substituents should exert an influence on the KIE. The transition vector for the Cope elimination has a much larger component of the primary hydrogen motion than the ylide TS and could potentially require a more sophisticated tunneling correction.¹³

(12) (a) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326. (b) Poirier, R. D.; Wang, Y.; Westaway, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 2526.

(13) (a) Skodje, R. T.; Truhlar, D. G.; Garret, B. C. *J. Chem. Phys.* **1982**, *77*, 5955. (b) Steckler, R.; Dykema, K. J.; Brown, F. B.; Hancock, G. C.; Truhlar, D. G.; Valenich, T. J. *J. Chem. Phys.* **1987**, *87*, 7024.

In conclusion, the excellent agreement between the calculated and experimental KIE allows a much greater confidence in the geometry of the transition structures calculated at the MP2/6-31G* level of theory. Transition states calculated at this *ab initio* level appear to provide reliable data for the calculation of secondary KIE in *syn*-elimination reactions. Since little double-bond character is present in TS-4, these data provide a rationale for how the ylide pathway with cyclooctylammonium salts can form the highly strained (9 kcal/mol) *trans*-cyclooctene as the major product.⁵

Acknowledgment. This work was supported in part by grants from the National Science Foundation (CHE-93-06341), the National Institutes of Health (CA 47348-02), and the Ford Motor Co. We are very thankful to the Pittsburgh Supercomputing Center and the Ford Motor Co. for generous amounts of computing time. J.L.A. gratefully acknowledges a fellowship from the CIRIT of the Generalitat de Catalunya (Catalonia, Spain), which has made his stay at Wayne State University possible.

JO950226Y