A New Form of Kinetic Isotope Effect. Dynamic Effects on Isotopic Selectivity and Regioselectivity

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Kinetic selectivity in chemistry is generally viewed as resulting from differing barriers for alternative reaction pathways. This is true even when a reaction has no enthalpic barrier, as most such cases involve an exothermic association process with an entropic barrier. It is thus normal to use transition state theory or its extensions to interpret product ratios or kinetic isotope effects (KIEs). However, dynamic effects can impact reaction selectivity outside of the realm of transition state theory.[1–4] We report here evidence that the topography of a reaction surface can allow a new type of kinetic isotope effect, dynamical in origin, in the absence of an enthalpic or entropic barrier. The potential for dynamics-derived selectivity on such a surface impacts the prediction of product ratios and the mechanistic interpretation of experimental observations.

Ene reactions of singlet ($^1\Delta_g$) oxygen ($^1O_2$) with simple alkenes exhibit *intramolecular* KIEs affecting product ratios (e.g., the formation of **2** and **3** from **1**) without corresponding *intermolecular* KIEs on the reaction rate.[5] This venerable mechanistic observation has been archetypal as proof of an intermediate. However, experimentally supported calculations predict no intermediate in the reaction of $^1O_2$ with *cis*-2-butene or tetramethylethylene.[6] Rather, the energy surface is predicted to involve two adjacent saddle points. The first is a C_s-symmetric rate-limiting transition state (**TS1**) for attack of the singlet oxygen on the alkene. The second (**TS2**), also C_s-symmetric, is perepoxide in character and is at the dividing point between two valleys for the unsymmetrical products. The minimum-energy path (MEP) connects the two saddle points but becomes unstable at the valley-ridge inflection (**VRI**), where trajectories will tend to diverge toward the alternative product valleys.[7–9]
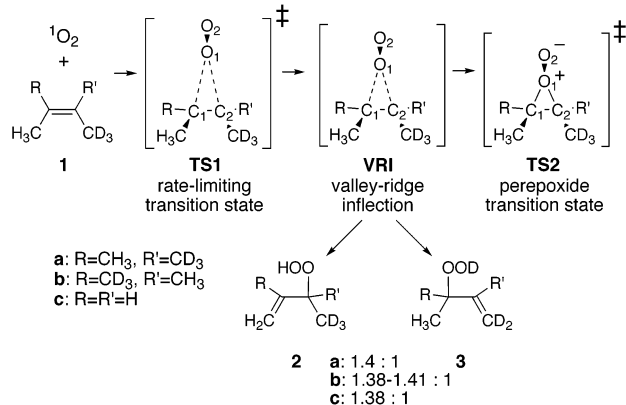
There is neither an enthalpic nor an entropic barrier to formation of the products;[6] yet, remarkably, the intramolecular KIEs exhibit selectivity. The reaction surface is desymmetrized on inclusion of zero-point energy (ZPE), but this effect is very slight.[10] In a dynamic reaction path analysis of a similar bifurcating surface, it was concluded that the isotope effect should be very small.[11]
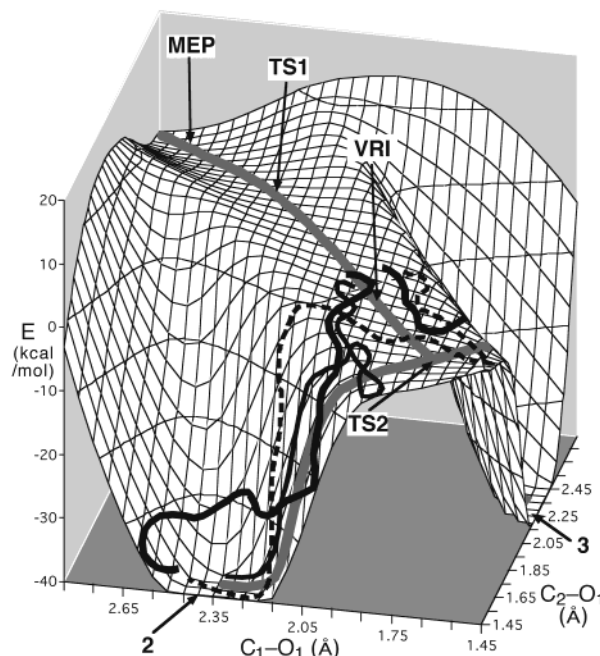

Figure 1. Qualitative potential energy surface for the reaction of $^1O_2$ with **1**, obtained by fitting an analytical function to CCSD(t)/6-31G*//B3LYP/6-31G* grid energies. The minimum-energy path (MEP) is shown in gray, and the patterned lines depict typical dynamics paths.

We hypothesized that the intramolecular KIEs could result dynamically from the intrinsic asymmetry of the vibrational modes on isotopic substitution. To test this, quasiclassical direct dynamics calculations were carried out for ene reactions of **1a** with singlet oxygen on a B3LYP/6-31G* potential energy surface. This surface overestimates the energy of $^1O_2$ but closely models the CCSD(T) surface as the $^1O_2$ draws close to the alkene (Figure 1).[6] The trajectories were started in an area between **TS1** and **VRI**, centered on the MEP with O–C_1 and O–C_2 distances of 1.95 Å. The starting atomic positions were randomized using a linear sampling of possible displacements for each normal mode. The trajectories were initialized in two ways: at "0 K", giving each mode in total only its zero-point energy with a random sign for its initial velocity, or at "263 K", using a Boltzmann sampling of vibrational levels along with a Boltzmann sampling of translational energy for the C_s-symmetric approach of the O_2 toward the olefinic carbons. Employing a Verlet algorithm, 0.5 or 1 fs steps were taken until either **2a** or **3a** was formed.[12]

It should be clearly noted that the trajectories were followed on a symmetrical potential energy surface that is unbiased toward reaction of H versus D. Even so, reaction of H predominates!

Out of 183 runs at 0 K, 122 afforded **2a**, while only 61 afforded **3a**. With 95% confidence, the simulation's nominal k_H/k_D of 2.1 is between 1.3 and 3.4. The selectivity was lower for the higher-

temperature 263 K simulation − out of 257 runs, 149 gave **2a**, and 108 gave **3a** for a nominal k_H/k_D of 1.38. With this necessarily limited number of runs, the standard deviation on k_H/k_D is 0.17.

The agreement of the 263 K results with experiment is quite striking, but quantitatively accurate KIE predictions probably should not be expected. These simulations are subject to all of the usual problems with classical dynamics calculations, including intramolecular vibrational energy redistribution,[13] and they do not allow for the effect of solvent collisions. Nevertheless, the results demonstrate that substantial dynamically based selectivity is possible on a symmetrical barrierless energy surface. This selectivity is a new form of isotope effect, unrelated to the usual effect of zero-point energies on barriers. The experimental intramolecular isotope effects are consistent with this selectivity.

Why should this happen? Although the potential energy surface is symmetrical in Cartesian coordinates, it is not so in mass-weighted coordinates. The vibrational modes in the isotopically labeled compound are inherently asymmetric. For example, the C−H bond stretching modes are extended more often and due to a greater zero-point energy, with a greater amplitude than the C−D stretches. Because these modes are anharmonic, the average C−H bond length is also longer than that for C−D (see the Supporting Information). It takes only a small asymmetric perturbation to influence trajectories around the VRI toward preferential formation of one product. Unlike previously proposed dynamic effects on selectivity, the effect here does not require a nonstatistical distribution of atomic kinetic energies.

Dynamics effects can account for not only the surprising isotopic selectivity but also a surprising lack of selectivity in another form. Singlet oxygen ene reactions exhibit relatively low regioselectivity among simple cis alkyl groups (eq 1), except for notable steric effects.[14] As seen with *cis*-2-butene, the reaction of *cis*-2-pentene with $^1O_2$ has a single rate-limiting transition state on the CCSD-(t)/6-31G*//B3LYP/6-31G* surface. Unlike *cis*-2-butene, the energy surface with **4** lacks symmetry, and the MEP does not bifurcate. Following the MEP downhill on the B3LYP surface leads only to **6**, so one might predict high selectivity.[15] Of course, this is anti-intuitive for a "nearly symmetrical" system, but the conventional analysis has no methodology for predicting a mixture of products in this reaction.
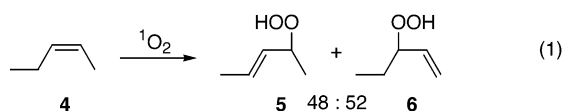
Dynamics calculations on the reaction of $^1O_2$ with **4** were started from a point on the MEP with O−C_1 and O−C_2 distances of 2.04 and 2.06 Å, respectively. The atomic positions and velocities were randomized as before, using a 298 K Boltzmann sampling of vibrational levels. A total of 20 dynamics runs on the B3LYP/6-31G* surface afforded **5** 13 times and **6** 7 times. Dynamics correctly predicts that a mixture of products will be formed. Recent papers by Doubleday[4c] and Shaik and Schlegel[16] have discussed examples of the control of product selectivity by dynamics effects in the absence of a barrier. The current result supports the relevance of dynamic effects to synthetically useful organic reactions in solution.

The results here have general implications. The observation of any form of selectivity in product formation that is not manifested in the rate-limiting step has in broad ways been taken as proof of an intermediate. This argument is compromised. Several reactions surfaces involving VRIs have been previously noted despite their symmetry requirements,[7−9,17] and the more general phenomenon of adjacent saddle points on a potential energy surface should occur often. Whenever a reaction surface involves adjacent saddle points, the usual theoretical characterization in terms of transition structures and reaction paths may not be adequate. The effects of temperature, reaction conditions, structure, and isotopic mass on product selectivity under these circumstances are neither known nor are they qualitatively predictable. We are currently investigating these issues.

Supporting Information Available: Calculational programs and discussion of applicability of quasiclassical dynamics (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Carpenter, B. K. *Angew. Chem., Int. Ed.* **1998**, *37*, 3340.
(2) Carpenter, B. K. *J. Am. Chem. Soc.* **1995**, *117*, 6336. Reyes, M. B.; Carpenter, B. K. *J. Am. Chem. Soc.* **2000**, *122*, 10163. Reyes, M. B.; Lobkovsky, E. B.; Carpenter, B. K. *J. Am. Chem. Soc.* **2002**, *124*, 641. Carpenter, B. K. *J. Am. Chem. Soc.* **1996**, *118*, 10329.
(3) (a) Yamataka, H.; Aida, M.; Dupuis, M. *Chem. Phys. Lett.* **1999**, *300*, 583. (b) Bakken, V.; Danovich, D.; Shaik, S.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 130.
(4) (a) Doubleday, C., Jr.; Bolton, K.; Hase, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 5251. (b) Doubleday, C.; Nendel, M.; Houk, K. N.; Thweatt, D.; Page, M. *J. Am. Chem. Soc.* **1999**, *121*, 4720. (c) Doubleday, C. *J. Phys. Chem.* **2001**, *105*, 6333. (d) Doubleday, C., Jr.; Bolton, K.; Hase, W. L. *J. Phys. Chem. A* **1998**, *102*, 3648.
(5) (a) Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 3111. (b) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607. (c) Kopecky, K. R.; van de Sande, J. H. *Can. J. Chem.* **1972**, *50*, 4034.
(6) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319.
(7) Valtazanos, P.; Ruedenberg, K. *Theor. Chim. Acta* **1986**, *69*, 281.
(8) (a) Metiu, H.; Ross, J.; Silbey, R.; George, T. F. *J. Chem. Phys.* **1974**, *61*, 3200. (b) Tachibana, A.; Okazaki, I.; Koizumi, M.; Hori, K.; Yamabe, T. *J. Am. Chem. Soc.* **1985**, *107*, 1190. (c) Valtazanos, P.; Elbert, S. T.; Ruedenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3147. (d) Windus, T. L.; Gordon, M. S.; Burggraf, L. W.; Davis, L. P. *J. Am. Chem. Soc.* **1991**, *113*, 4356. (e) Kraus, W. A.; DePristo, A. E. *Theor. Chim. Acta* **1986**, *69*, 309.
(9) Ramquet, M.-N.; Dive, G.; Dehareng, D. *J. Chem. Phys.* **2000**, *112*, 4923.
(10) Starting from the C_s-symmetric **VRIc**, the ZPE difference (B3LYP) between shortening C_1−O_1 versus C_2−O_1 by 0.1 Å was 0.019 kcal/mol.
(11) Taketsugu, T.; Kumeda, Y. *J. Chem. Phys.* **2001**, *114*, 6973.
(12) In about 10% of the runs, the O_2 bounced away from the alkene. When the O−C_1 and O−C_2 distances exceeded 2.2 Å, the runs were discarded.
(13) (a) Ben-Nun, M.; Levine, R. D. *J. Chem. Phys.* **1994**, *101*, 8768. (b) Based on average C−H stretching amplitudes, the high-energy C−H stretching modes lose 20−30% of their energy to other modes slowly over the course of 700 fs. Most of the dynamics runs "commit" to formation of a particular product within the first 100 fs, suggesting that the impact of vibrational energy redistribution is minimal.
(14) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595.
(15) We note that one would also have expected significant selectivity from a surface involving a perepoxide *intermediate*. Starting from the perepoxide minimum on the RHF/6-31G* surface, the transition state leading to **6** is favored by 0.7 kcal/mol over the transition state leading to **5** at the CCSD-(t)/6-31G*//RHF/6-31G* level.
(16) (a) Bakken, V.; Danovich, D.; Shaik, S.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 130. (b) Yamataka, H.; Aida, M.; Dupuis, M. *Chem. Phys. Lett.* **1999**, *300*, 583.
(17) Caramella, P.; Quadrelli, P.; Toma, L. *J. Am. Chem. Soc.* **2002**, *124*, 1130.

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