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The Energetic Advantage of 5-Exo Versus 6-Endo Epoxide Openings: A Preference Overwhelmed by Antibody Catalysis

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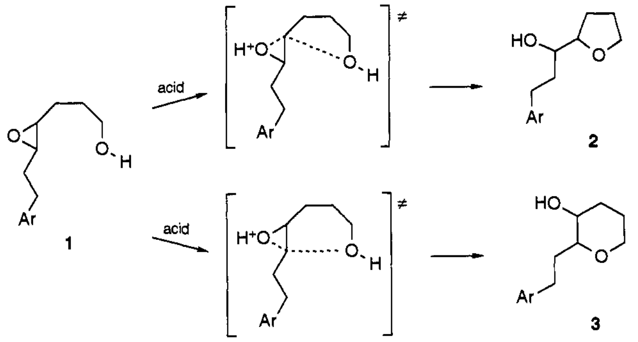
Janda, Shevlin, and Lerner recently reported the generation of an antibody which catalyzes the Baldwin's Rules-disfavored cyclization[1] of oxirane **1** to form product **3**[2] (Scheme I). This antibody catalyst overwhelms the normal preference for five-membered ring formation (**2**) observed in the acid-catalyzed cyclization of the hydroxy epoxide. In the acid-catalyzed reaction, formation of **2** is observed, while antibody catalysis causes the six-membered **3** to become the major product. How much of a free energy barrier is overcome by the catalytic antibody? What are the precise geometrical or electronic differences in the transition states which favor five-membered ring formation but are selectively stabilized in the six-membered case by the antibody? Answers to these questions given by the theoretical study reported here reveal new insights into the relationship between haptens and antibodies.

In order to calculate the energy difference between 5-exo and 6-endo epoxide openings, we have carried out ab initio calculations to locate the transition structures for both processes. Our model calculations were carried out with hydrogen in place of the benzyl group present in **1**. Geometries were completely optimized, and transition states were characterized by harmonic frequency analysis.[3]

Scheme I



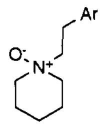


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Table I. Summary of Activation Energies and Reaction Energies (kcal/mol)

	theory level basis set				
	HF/ AM1	HF/ STO-3G	HF/ 6-31G*	HF/6-31G*/ (SCRF)	MP2/ 6-31G*[a]
			5-Exo		
E_a	7.7	43.7	10.4	–1.3	16.4
ΔE_{rxn}[b]	–24.8	–22.4	–12.2		–8.7
			6-Endo		
E_a	6.1	45.8	11.3	–0.5	18.3
ΔE_{rxn}	–21.0	–4.7	–10.7		–5.6
$E_a(6)$-$E_a(5)$	–1.6	2.1	0.9	0.8	1.9
			H_2O + Oxirane-H^+		
E_a			–10.5[c]		
ΔE_{rxn}			–25.1[c]		

[a] Single-point calculations on 6-31G* optimized geometries. [b] $\Delta E_{rxn} = E_{product} - E_{reactant}$. [c] Reference 6.

Table I summarizes the activation energies, reaction energies, and calculated energy difference between the two ring-opening processes. Activation energies are calculated from the energy difference between the optimized ground state of the reactant **1**, which has a "coiled" conformation with a stabilizing interaction between the protonated oxirane and the hydroxyl group, and the optimized transition state. Initial calculations with AM1[4] incorrectly predict that the six-membered process is favored by 1.6 kcal/mol, but all ab initio levels predict a preference for the five-membered cyclization. With the inclusion of correlation energy at the MP2 level,[5] the 5-exo process is favored by 1.9 kcal/mol, which translates to a 96:4 product ratio at 25 °C, assuming a negligible entropic difference in the two transition states.[6] To simulate roughly the energetics of the reaction in solution, calculations at the RHF/6-31G* level were repeated in the presence of a solvent using the self-consistent reaction field (SCRF) method.[7] The solute radius for both reactions was set at 4.17 Å, and the dielectric constant for water was chosen to mimic aqueous conditions. Although activation energies for both processes were lowered by several kcal/mol in the solvent cavity, the ΔE_a of 0.8 kcal/mol in water is essentially the same as the RHF/6-31G* value of 0.9 kcal/mol in the gas phase. This result shows that the amount of charge transfer and its stabilization through solvation are similar in both reactions. Hence, the MP2-calculated difference of 1.9 kcal/mol will be only slightly altered to about 1.8 kcal/mol in aqueous solution.

A comparison of the two transition structures (Figure 1) and that reported earlier for the intermolecular reaction between water and protonated oxirane[8] shows why the five-membered process is favored, in accordance with Baldwin's Rules.[1] In the reaction of water with protonated oxirane, the OCO angle is 155°, quite far from linearity. This occurs because the angle of attack of water with respect to the CC bond is 105°, while the OCC angle in the opening oxirane is only 50°. The attack angle in the transition state for five-membered ring formation is only slightly distorted (100°), while in the six-membered transition state this angle has been badly distorted to 88°. The C–OC angles of 100°

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(2) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490. See also: Danishefsky, S. *Science* **1993**, *259*, 469.

(3) All ab initio calculations were performed using GAUSSIAN 92: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *GAUSSIAN 92*: *Revision A*; Gaussian, Inc.: Pittsburgh PA, 1992.

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(5) Calculations at this level provide reasonable relative energies for cations and for conformations of oxygen-containing molecules. (a) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1985. (b) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.

(6) From 6-31G* frequency calculations, the entropy difference between the two transition states is 0.3 eu.

(7) (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Chem. Phys.* **1991**, *95*(12), 8991.

(8) Ford, G. P.; Smith, C. T. *J. Am. Chem. Soc.* **1987**, *109*, 1325.

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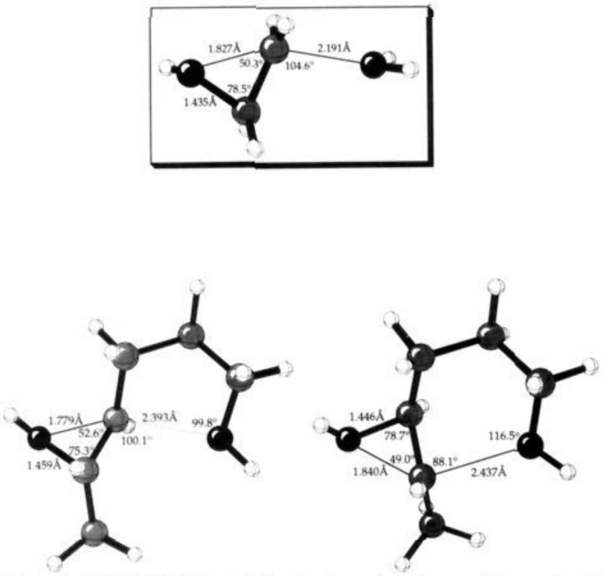


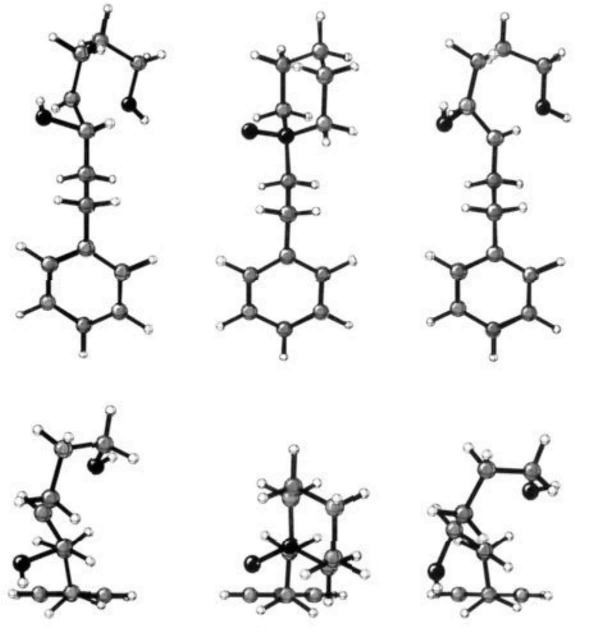
Figure 1. RHF/6-31G* transition structures for inter- and intramolecular acid-catalyzed ring openings.

in five-membered ring formation and 117° in the six-membered transition state are distorted to a similar extent from tetrahedral. The five-membered transition state is very similar to the intermolecular reaction transition state; it is less strained, primarily due to the nearly ideal attack angle, and consequently has a lower energy than the six-membered transition state.

Because of the greater strain necessary to bring the side chain into the geometry necessary to form the six-membered ring, the transition state has shifted to a looser, S_N1-like geometry. The partial C···O bonds are 0.05–0.06 Å longer than those in the five-membered transition state. This is reflected in the charges at the carbon undergoing substitution; the CHELPG[9] charges, which are appropriate for the estimation of interactions with external charged groups, are 0.16 in the five-membered and 0.35 in the six-membered transition state.

In the RHF/6-31G* transition state for the S_N2 reaction of methanol at C_2 of protonated methyloxirane, the O–CC attack angle decreases from 105° to 92°. The sensitivity of this attack angle to steric effects is further illustrated in the reaction between methanol and protonated *trans*-dimethyloxirane, where the extra methyl group widens the O–CC angle to 98°, a value almost identical to that for the five-membered transition state (100°). RHF/6-31G* or MP2/6-31G* calculations for intermolecular reactions show that a deviation from the optimum angle by 10° raises the energy by 0.8–1.5 kcal/mol.

We have also carried out calculations on the ring openings involving alkoxide attack on the unprotonated epoxide. The transition states located at the RHF/6-31+G* level have geometries tighter than but similar to those from the protonated reactions. As before, the attacking O–CC angle in the five-membered process (108° versus 101° in the six-membered reaction) has a value close to that in the intermolecular reaction between methoxide and methyloxirane (109°). The MP2/6-31+G*-calculated energy difference between the two transition states is 1.9 kcal/mol in favor of the five-membered transition state.



5-membered TS hapten 6-membered TS

Figure 2. Comparison of the transition-state structures and the RHF/6-31G* optimized hapten.

Hapten **4** was designed by Janda *et al.* to elicit functionality in the antibody to selectively stabilize the six-membered transition state. The HF/6-31G* optimized structure of the simple *N*-methyl analog is shown next to the five- and six-membered transition states in Figure 2.[10] In both views, they are arranged so that the substituted side chains in **4** and in the transition states are aligned. In the top view, the overall shapes of the two transition states are seen to be very similar to each other and to **4**. In the bottom views, the trimethylene chains are seen to be displaced rather differently in the transition states as compared to **4**. The greater charge at carbon in the six-membered transition state and its location in approximately the location of the nitrogen in the *N*-oxide hapten appear to be the important factors which differentiate the six- from the five-membered transition states. The six-membered transition state is most likely better stabilized by cation stabilizing groups elicited by **4** in the antibody binding site.[11] The scaffolding of a strategically located charge distribution, rather than incorporation of a six-membered ring, appears to be the design feature important in the hapten.[12]

The energetic advantage achieved by the catalytic antibody can be estimated from our results. Formation of the 5-exo product is predicted to be favored by about 1.8 kcal/mol in aqueous solution. This should produce a 96:4 5-exo:6-endo ratio.[13] To favor the 6-endo product by a similar amount, the catalytic antibody must lower the 6-endo activation energy 3.6 kcal/mol more than it lowers the 5-exo activation energy.

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[9] Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

[10] The MP2/6-31+G**//6-31G* energy difference between the two chair conformers is 2.5 kcal/mol, with a preference for oxygen in the axial position. Experimentally, *N*-oxides have axial oxygens: Cook, M. J.; Katritzky, A. R.; Mañas, M. M. *J. Chem. Soc. B* **1971**, 1330.

[11] (a) Activation of 6-endo over the 5-exo hydroxy epoxide opening has been achieved by allylic substitution of the 6-endo carbon, which, like the antibody, stabilizes charge in the transition state for 6-endo cyclization. See: Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) See also: Jung, M. E.; Clevenger, G. L. *Tetrahedron Lett.* **1991**, *43*, 6089.

[12] A recent report of epoxide hydrolysis involves a hapten and various transition states with different ring sizes: Sinha, S. C.; Keinan, E.; Reymond, J.-L. *J. Am. Chem. Soc.* **1993**, *115*, 4893.

[13] In the acid-catalyzed reaction, only a few percent of a minor product, presumably from the 6-endo reaction, was detected by HPLC.