Elucidation of Transition Structures and Solvent Effects for Epoxidation by Dimethyldioxirane

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Dioxiranes are versatile oxidizing reagents with particular utility in the epoxidation of olefins.[1] Synthetic and mechanistic investigations have revealed notable sensitivity of reaction rates and diastereoselectivity to solvent selection.[1−6] Baumstark and co-workers documented the greater reactivity of cis alkenes than trans isomers and that addition of H_2O to dimethyldioxirane (DMD) reactions in acetone also provides increased reactivity.[2] They invoked a polarized, spiro transition structure that would benefit from H-bond donation from solvent molecules. Recently, further quantification of diastereoselectivity and solvent effects has occurred;[3,4] substrates that can provide an internal H-bond in the transition structures were found to exhibit enhanced reaction rates,[4−6] and enantioselective epoxidations with chiral dioxiranes have been reported.[7] In the present computational study, the detailed origins of the selectivity and solvent effects are elucidated.

Ab initio density functional calculations at the B3LYP/6-31G* level were used to fully optimize geometries for reactants and transition structures for the reactions of DMD with *cis*- and *trans*-2-butene.[8−11] The resultant transition structures are illustrated in Figure 1 along with the computed electronic activation energies. The anti transition structure (TS) for *cis*-2-butene is an earlier TS than the more sterically crowded syn alternative, which is 3.4 kcal/mol higher in energy. The activation energy for addition to *trans*-2-butene is 1.7 kcal/mol higher in energy than that for the cis isomer, which is fully consistent with the observed 8−10-fold greater reactivity of cis alkenes.[2] Computation of the vibrational frequencies for the anti TS confirmed the nature of the stationary point and provided an enthalpy and entropy of activation at 298 K of 11.8 kcal/mol and −36.1 cal/(mol K). This is in reasonable accord with the limited, related experimental data, e.g., an enthalpy and entropy of activation of 7.4 kcal/mol and −35.5 cal/(mol K) for the epoxidation of cyclohexene by DMD in acetone[3] and an E_a of 14.1 ± 0.4 kcal/mol for the reaction with ethyl cinnamate.[1a] Key structural points for the anti TS are that the lengths of the forming bonds are 2.03 Å, the CO and OO bonds are lengthened from 1.40 and 1.51 Å in DMD to 1.49 and 1.89 Å in the TS, and the C═C bond length increases from 1.34 Å in *cis*-2-butene to 1.38 Å in the TS. All transition structures have a spiro geometry for the forming and breaking rings, as proposed on the basis of the cis/trans selectivity[2a] and found previously in ab initio studies of the epoxidation of ethene.[10,12] The transition structures reflect concerted O-atom transfer; diradical character has been deemed insignificant in the prior computational studies including CASSCF calculations.[10,12] Though oxygen insertion into C−H bonds by DMD likely involves free radicals,[13] the observed selectivity data and computational results support the concerted mechanism for epoxidation. The computed transition structures also indicate that enantioselection with chiral dioxiranes is more promising for trans rather than cis alkenes; there is close contact between a substituent of the double bond and a dioxirane substituent only in the TS for the trans isomer.[7]

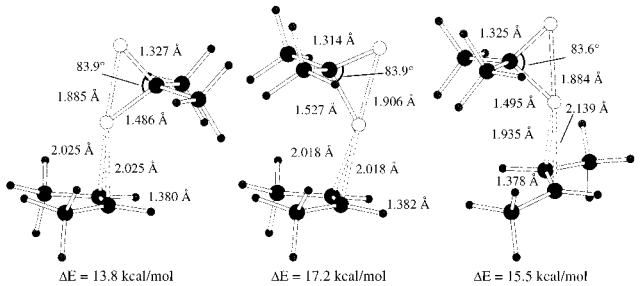

Figure 1. B3LYP/6-31G*-optimized transition structures and electronic activation energies for epoxidations of *cis*- and *trans*-2-butene by dimethyldioxirane.

The origin of the observed rate accelerations in polar, especially protic, solvents was investigated through Monte Carlo (MC) simulations with free-energy perturbation (FEP) theory.[14] The same methodology has been applied recently to studies of several pericyclic reactions.[15] The reactants at 8 Å separation for the forming bonds were perturbed to the anti and syn TS in periodic boxes containing 395 molecules of methyl acetate (CH_3OAc), methylene chloride (CH_2Cl_2), or methanol (CH_3OH), which had dimensions of approximately 33 × 33 × 50 Å, 30 × 30 × 46 Å, and 27 × 27 × 40 Å, respectively. The intermolecular interaction energies, ΔE_{ab}, are represented classically by Coulombic and Lennard−Jones terms between the atoms i in molecule a and the atoms j in molecule b:

$$\Delta E_{ab} = \sum_i \sum_j \{q_i q_j e^2/r_{ij} + 4\epsilon_{ij}[(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6]\}$$

The OPLS united-atom models for the solvents were adopted.[16] The charges for the solute atoms came from CHELPG calcula-

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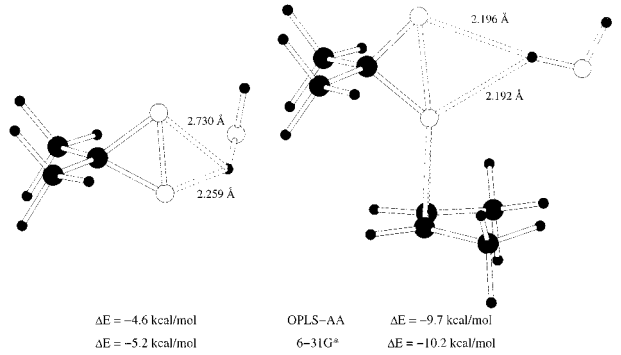

Figure 2. Complexes of DMD and the anti transition structure with a H_2O molecule. The structures are from optimizations of the 6 intermolecular degrees of freedom with RHF/6-31G* calculations using the B3LYP/6-31G*-optimized geometries for the separated species. The interaction energies are ΔE for the process DMD or TS + H_2O → complex.

tions with the B3LYP/6-31G* wave functions and standard OPLS all-atom (AA) Lennard−Jones parameters (σ, ϵ) were adopted for the solutes;[16] the parameters were scaled linearly along the reaction path. The intermolecular interactions were truncated at ca. 12 Å separations between molecular centers. The FEP calculations featured 4×10^6 configurations of equilibration and ca. 10^7 configurations of averaging for each of 47 windows at 25 °C and 1 atm.[14b] No internal degrees of freedom were varied; translations and rigid-body rotations were sampled.

The computed changes in free energies of solvation for the reactions are shown in Figure 2 of the Supporting Information. The net results are that the anti TS is better solvated than the reactants by 2.0 ± 0.1, 3.1 ± 0.1, and 4.6 ± 0.1 kcal/mol in CH_3OAc, CH_2Cl_2, and CH_3OH, and the corresponding numbers for the syn TS are 1.9 ± 0.1, 3.6 ± 0.1, and 5.6 ± 0.1 kcal/mol. Though the syn TS is somewhat better solvated, the difference is not enough to overcome the intrinsic favoring of the anti TS by 3.4 kcal/mol (Figure 1). Experimentally, rate data are available for epoxidation of cyclohexene by DMD in 1:1 volume ratios for a series of solvents with acetone at 25 °C.[3] The reactivity order, CH_3OH > CH_2Cl_2 > CH_3OH, is also observed with relative rates of 6:3:1.[3] The larger computed rate ratios (81:6:1) can be attributed, in part, to the use of the pure solvents in the calculations. It may also be noted that Baumstark and Vasquez reported a 13-fold rate enhancement for the epoxidation of *p*-methoxystyrene in going from pure acetone to aqueous acetone with a 0.64 mol fraction of water.[2]

The increased reactivity in polar solvents can be readily assigned to enhanced polarization of the TS relative to the reactants. The B3LYP/6-31G* dipole moments are 2.9 D for DMD, 4.9 D for the anti TS, 5.3 D for the syn TS, and 4.9 D for the TS with *trans*-2-butene. Consistently, the CHELPG charges on the oxygens of DMD, −0.26 e, increase in magnitude to −0.33 e for the epoxidizing oxygen and −0.52 e for the incipient acetone oxygen in the anti TS. Even more striking are the results of optimizations for complexes of a single H_2O molecule with DMD and the anti TS in Figure 2. Both the force field calculations (present model for DMD and the TS with a TIP4P H_2O molecule) and RHF/6-31G* results find a 5 kcal/mol enhancement of the optimal H-bond in going from reactants to TS. Consistently, the distributions of individual solute−solvent interaction energies from the MC simulations in Figure 3 clearly reflect the enhanced solvation of the TS. In CH_3OH, a strong H-bonding band appears for the anti TS

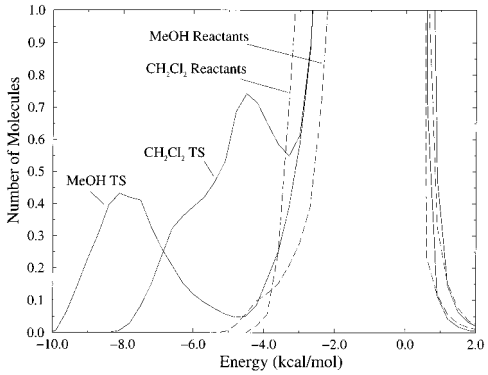

Figure 3. Distributions of individual solute−solvent interaction energies from MC simulations for the reactants and anti TS. Units for the ordinate are number of solvent molecules per kcal/mol.

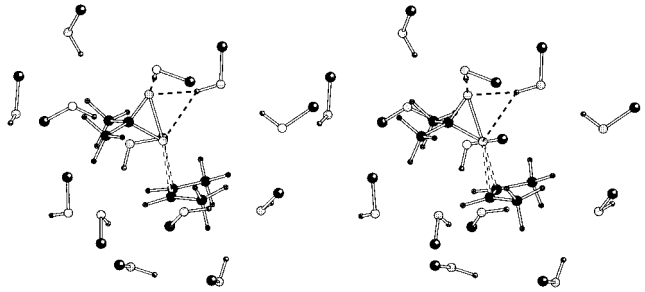

Figure 4. Stereoplot of a typical configuration form the Monte Carlo simulation of the anti transition structure in CH_3OH. Only CH_3OH molecules in the first solvent shell are shown for clarity.

between −10 and −5 kcal/mol and contains one CH_3OH molecule with a second CH_3OH being included upon integration to −2.5 kcal/mol. However, for the reactants, little H-bonding is apparent and integration to −2.5 kcal/mol only yields 0.5 CH_3OH molecule. Even in CH_2Cl_2, the polarization of the TS leads to the development of two strong interactions with solvent molecules with interaction energies in the −8.0 to −3.2 kcal/mol range. Finally, the stereoplot in Figure 4 illustrates the typical arrangement for the TS with the strong H-bond for the CH_3OH bridging the two DMD oxygens and the second H-bond between a CH_3OH molecule and the distal DMD oxygen. In CH_2Cl_2, the structure for the most attractive interaction also has the solvent molecule placed between the two oxygens of the TS with its $-CH_2-$ group nearest the oxygens at C−O distances of ca. 3.25 Å.

In summary, the present calculations have clarified the transition structures for epoxidations by DMD, the cis/trans selectivity, the basis for potential enantioselectivity, and the origin of the increased reactivity in polar solvents. The polarization of the transition structures leads to a remarkable enhancement of H-bonding. The results indicate that placement of a H-bond-donating group in the substrate to interact with both dioxirane oxygens in the TS, as in Figure 4, would yield high reactivity and a basis for pronounced facial selectivity.

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Supporting Information Available: B3LYP/6-31G*-optimized structures in PDB format and electronic energies for all reactants and transition structures, and CHELPG charges and Lennard-Jones parameters for the reactants and syn and anti TS (7 pages). See any current masthead page for ordering and Internet access instructions.

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