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Epoxidations by Peracid Anions in Water: Ambiphilic Oxenoid Reactivity and Stereoselectivity

Ilyas Washington and K. N. Houk*

Department of Chemistry and Biochemistry, University of California,
Los Angeles, California 90095-1569

houk@chem.ucla.edu

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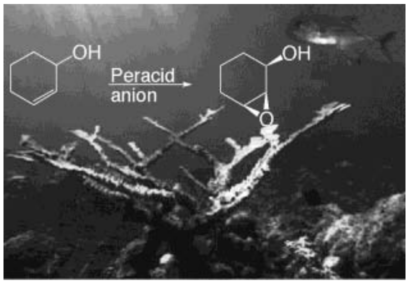
ABSTRACT

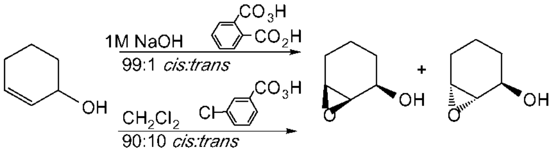


Transition structures have been located for oxygen transfer from performate anion to ethylene, propene, vinylamine, vinyl chloride, vinyl cyanide, and 2-propen-1-ol at the B3LYP/6-31+G(d,p) level in a CPCM continuum model for water. Oxygen transfer is concerted, except for acrylonitrile, which is stepwise. Peracid anions react as ambiphilic oxygen donors. Predictions are made about the diastereoselectivity of epoxidations of acylic, chiral, and allylic alcohols in an alkaline solution, and one is verified experimentally.

Peracids are electrophilic oxidants that transfer oxygen preferentially to electron-rich alkenes. However, base catalysis can increase the stereoselectivity of peracid epoxidations.[1] To understand the nature of epoxidations by peracid in the presence of aqueous base, we have located transition structures for oxygen transfer from peracid anions to various alkenes with quantum mechanical methods. We report on the reactivities of peracid anions and the origins of their highly selective epoxidations of cycloalkenols. We also make predictions about the stereoselectivities of epoxidations of acyclic allylic alcohols and report on the highly diastereoselective epoxidation of a chiral *Z*-allylic alcohol.

The highly selective *syn*-epoxidation of a series of cycloalkenols by monoperoxyphthalic acid in an aqueous solution of 1 M NaOH has been reported (Scheme 1).[2] Epoxidations in aqueous base are far more selective, leading to *cis*-hydroxyepoxides, than epoxidations in nonpolar solvents. The regioselective 2,3-epoxidation of *trans*-3,7-dimethyl-2,6-octadien-1-ol (geraniol) by *m*-chloroperoxybenzoic acid in the presence of aqueous NaOH has also been observed.[3]

Scheme 1



It is believed that directed epoxidations by peracids in nonpolar solvents are a result of hydrogen bonding between

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(1) For a general discussion see: Sawaki, Y. Epoxidation and Hydroxylation. In *The Chemistry Hydroxyl, Ether and Peroxide Groups*; Patai, S., Ed.; John Wiley and Sons; Sussex, UK, 1993; pp 598−600.

(2) Ye, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1997**, *62*, 3748.

(3) (a) Nakamura, M.; Tsutsui, N.; Takeda, T. *Tetrahedron Lett.* **1984**, *25*, 3231. (b) Fringuelli, F.; Pizzo, F.; Germani, R. *Synlett* **1991**, 475. (c) Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F. *J. Org. Chem.* **1992**, *57*, 1198

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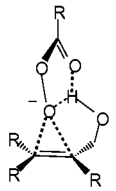
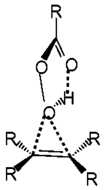
the hydroxyl group and the peracid oxygens. Hydrogen bonding delivers the peracid to one face of the alkene.[4] This effect is diminished in polar solvents.[4] However, reactions are even more selective in aqueous base, as described above. In general, alkaline media have been used for the preparation of epoxides that are acid labile[5] or epoxides of electron-deficient alkenes.[6] In addition to epoxidations, base-promoted oxidations by peroxy acids have found utility in the oxidation of sulfoxides to sulfones[7] and the preparation of nitroxyl radicals from amines.[8]

The pK_a values of peracids are around 8.2,[9] and the pK_a values of monoperoxyphthalic acid in water are 3.0 and 8.2.[10] Thus, in a 1 M solution of NaOH, pH 12, peracids exist as anions, and monoperoxyphthalic acid as a dianion. The selectivities of the base-promoted directed epoxidations have been rationalized by the transition state shown in **1**.[2,3c] In **1** the peracid anion attacks the alkene and the hydroxyl hydrogen serves as a surrogate for the peracid hydrogen in the butterfly transition state. This transition state is analogous to that for neutral epoxidations of **2**. In the regioselective epoxidation of geraniol, the allylic double bond is argued to be more accessible to the peracid in the aqueous phase.[3a] On the basis of the observation that certain electron-deficient *Z*- and *E*-alkenes give the same epoxide product (Scheme 2), a two-step mechanism has been proposed involving nucleophilic attack at the β-C, to form an α-C anion, followed by ring closure.[11] Recently, it has been suggested that in basic media a peracid may be in equilibrium with the oxydioxirane, **3**, and the latter may be responsible for oxygen transfer.[12] We have explored all of these eventualities with computational methods.

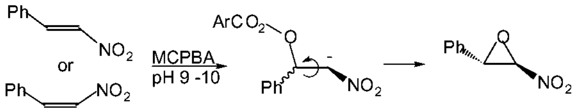


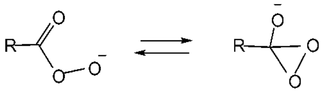
1



2

Scheme 2





3

All calculations[13] were performed at the B3LYP/6-31+G(d,p)[14] level with a water solvent continuum model (CPCM,[15] $\epsilon = 78.4$). Performate, peracetate, and perbenzoate were found to have two energy minima; these are summarized in Figure 1. Performate has a small, 0.4 kcal/mol, preference for *syn* conformation **A**, while larger *syn* preferences were found for peracetate and perbenzoate anions. Electrostatic potential derived charges for all three peracids show that the charge is shared about equally between the

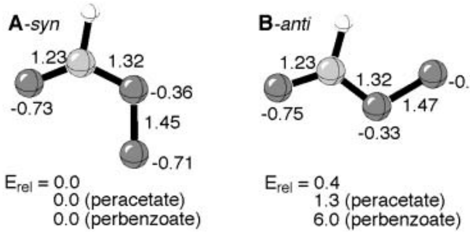


Figure 1. B3LYP/6-31+G(d,p) CPCM ($\epsilon = 78.4$) optimized structures for performate anion: **A**, syn conformation, and **B**, anti conformation. Relative energies for the corresponding peracetate and perbenzoate are also shown. Energies are in kcal/mol. Distances are in angstroms.

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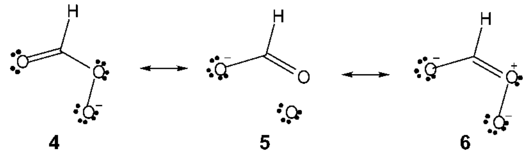
[13] All calculations were performed with Gaussian 98, Revision A.7: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998. Calculations used Maximum and RMS displacement thresholds of 0.002 and 0.002, respectively (defaults are maximum 0.0018 and RMS 0.0012). All energies are converged to 10^{-4} hartrees.

[14] Studies of performic acid, dioxirane, peroxynitrous acid, and oxaziridine epoxidations have shown that B3LYP/6-31G* calculations provide transition structure and energies in accord with available experimental data and QCI calculations. See: (a) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (b) Bach, D. R.; Glukhovtsev, N. M.; Gonzalez, C. *J. Am. Chem. Soc.* **1998**, *120*, 9902.

[15] Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.

carbonyl and terminal peroxy oxygens. Three resonance structures for performate are drawn in **4**−**6**. Computed charges suggest that the peracid anion may be represented mainly as **4** and **5**, the latter structure representing a performate anion coordinated to a singlet oxygen atom, a so-called oxene. The charge-separated structure, **6**, does not contribute substantially.



4 **5** **6**

Figure 2 shows transition structures for epoxidation of ethylene by the *syn* and *anti* conformers of performate and by the oxydioxirane. The activation energies for epoxidation by peracetate and perbenzoate anions are also shown. The transition state involving the *syn* conformation of the peracid anion is disfavored for performate but favored for peracetate and perbenzoate. Apparently, the inherent electronic preference for attack in conformation **B** is overcome by steric hindrance. Attack in conformation **A** is a better model for substituted peracids. All transition states are spiro and show concerted oxygen transfer. This arrangement allows maximum overlap between the π-HOMO of the peracid and the LUMO of the alkene, with simultaneous overlap between the alkene HOMO and the σ* orbital of the oxidant. Gas-phase transition states for **C** and **D** were more asynchronous and nucleophilic in nature with performate anion; forming bond lengths of 2.16 and 1.84 Å for **C** and 2.37 and 1.87 Å for **D** were calculated. The high dielectric constant stabilizes charge-separated structures, and thus results in concerted oxygen transfer. A concerted mechanism is consistent with the observation of 95% stereospecific epoxidation of styrylsulfones.[11]

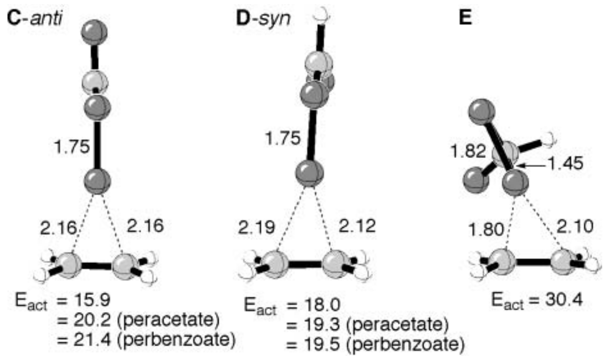
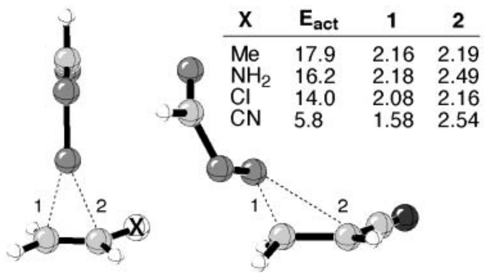


Figure 2. B3LYP/6-31+G(d,p) CPCM (ϵ = 78.4) transition states: **C** and **D** for epoxidation of ethylene by anti and syn performate, respectively, and second-order saddle point, **E**, for epoxidation of ethylene by the oxydioxirane isomer of performate.

A transition structure could not be located for epoxidation by the oxydioxirane isomer of performate. However, constrained gas-phase optimization gave structure **E**, which has two imaginary frequencies and a single point energy of 30.4 kcal/mol relative to separated reactants in a dielectric of ϵ = 78.4.

Activation energies and transition state bond lengths for epoxidations of propene, vinylamine, vinyl chloride, and acrylonitrile by performate, in conformation **A**, are shown in Figure 3. The activation energy remains the same for ethylene and for the more electron-rich propene. For vinylamine, an electron-rich alkene, the activation energy decreases by 2 kcal/mol. For chloro and cyano substituents, electron acceptors, the activation energy decreases by 4 and 13 kcal/mol, respectively, compared to ethylene. In contrast, for neutral performic acid, the activation energy for epoxidation of propene and vinylamine decreases by 2 and 8 and kcal/mol, respectively, and increases for acrylonitrile by 4 kcal/mol, at the B3LYP/6-31G* level.[16]



X	E_{act}	1	2
Me	17.9	2.16	2.19
NH_2	16.2	2.18	2.49
Cl	14.0	2.08	2.16
CN	5.8	1.58	2.54

Figure 3. B3LYP/6-31+G(d,p) CPCM (ϵ = 78.4) transition states for epoxidation of substituted ethylenes by performate. The geometry shown on the left is for X = Cl and that shown on the right is for X = CN.

The TS for epoxidation of vinylamine by performic acid is highly asynchronous. Bond formation to the more electron-rich carbon (the unsubstituted terminus) is 0.43 Å more advanced than bond formation to the carbon bearing the amino group. A similar (0.31 Å) difference in bond lengths was calculated for epoxidation of vinylamine by performate. Here, the performate anion appears to be acting as an electrophile. The TS for epoxidation of vinyl chloride has the longer forming bond to the carbon attached to chlorine. The chlorine atom stabilizes the transition state by stabilizing the negative charge that is formed.[17] This is opposite to what is observed for epoxidation of electron-poor alkenes by performic acid. Here, performate appears to be acting as a nucleophile. For the epoxidation of acrylonitrile the mechanism becomes two-step, and the activation energy for nucleophilic attack is lower by 12 kcal/mol. A two-step mechanism is consistent with the observation that strongly electron-poor alkenes give nonstereospecific epoxides.[11]

Transition states for the epoxidation of allyl alcohol by performate are shown in Figure 4. Structure **F** has the lowest

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[16] Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 3790.

[17] Schleyer, P. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

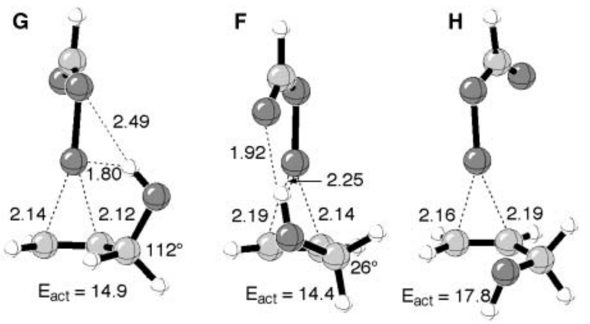
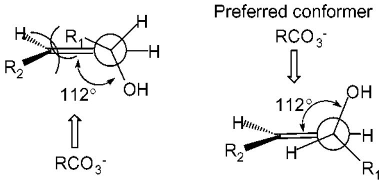


Figure 4. B3LYP/6-31+G(d,p) CPCM ($\epsilon = 78.4$) transition states for epoxidation of 2-propen-1-ol by performate. Angles are C=C−C−O dihedrals.

activation energy of 14.4 kcal/mol. In **F**, the alkene has a C=C−C−O dihedral angle of 26°, and the hydroxyl group forms two hydrogen bonds with distances of 1.92 and 2.25 Å to O1 and O2, respectively. Structure **G** is similar in energy, only 0.5 kcal/mol higher, and has a C=C−C−O dihedral angle of 112°. In this structure the hydroxyl group forms two hydrogen bonds with distances of 1.80 and 2.49 Å to O1 and O2, respectively. Structure **H**, where hydrogen bonding is absent, is 3.4 kcal/mol higher in energy. The calculated activation energies for epoxidation of allyl alcohol by performate are in accord with the experimentally observed *cis*:*trans* epoxide ratio found in epoxidation of cyclohexenol and other cyclic, allylic alcohols by monoperoxyphthalic acid in aqueous NaOH. On average, these reactions give a 99:1 ratio of *cis:trans* products. The 0.5 kcal/mol preference for **F** over **G** is due to the preference for 2-propen-1-ol to exist in the conformation shown in **F**. For epoxidation of cyclic allylic alcohols the alkene conformation shown in **F** is not easily achieved, and a transition structure analogous to **G** is more likely.

In our transition state model, performate shows a preference for hydrogen bonding to the hydroxyl rather than water (modeled by a continuum dielectric). Intramolecular hydrogen bonding plus hydrogen bonding by water better solvates performate than water alone. Directed epoxidations in aqueous base bear resemblance to dichlorocarbene cyclopropanation of allylic alcohols in the presence of aqueous NaOH. For example, cyclohex-2-en-1-ol gives the *cis* and *trans* cyclopropanes in a 10:1 ratio.[18]

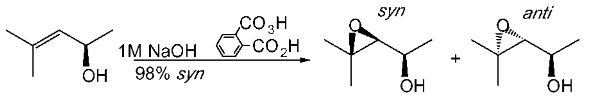
For directed epoxidations of acyclic, chiral allylic alcohols under neutral conditions, the diastereoselectivity is determined by the preferred C=C−C−O dihedral angles in various transition states.[19] Transition structure **G** has a dihedral angle of 112°, which is favored for **7**, but not for **6**, due to $A^{1,3}$ strain. The epoxidation of a chiral *Z*-allylic alcohol occurs via **7** for peracids.



6 **7**

To test whether **7** is also preferred for peracid anions as is predicted theoretically from the results in Figure 4, alkene **8**[19] was synthesized and treated with monoperoxyphthalic acid in 1 M NaOH (Scheme 3).[2] Alkene **8** yielded the *syn* epoxide, **9**, in 98% selectivity by ^{1}H NMR analysis[20] and in nearly quantitative yield.[21] Compared to other oxidants, including metal-catalyzed systems, the diastereoselectivity observed here for the epoxidation of **8**[22] is comparable. Other systems are reported to give a 95:5 ratio of *syn*:*anti* products.[22] Peracid anions behave as ambiphilic oxygen donors. Electron donating and withdrawing groups on an alkene both lower the activation energy for epoxidation. For unactivated, electron-rich and moderately electron-poor alkenes, oxygen transfer occurs in a spiro, concerted process. For highly electron-poor alkenes the mechanism becomes stepwise. For the epoxidation of allylic alcohols, optimal directivity should occur when the allylic hydroxyl group is able to hydrogen bond to the peracid. Epoxidations of chiral *Z*-allylic alcohols in alkaline solution yield the *syn* epoxide.

Scheme 3



8 **9** **10**

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(19) Adam, W.; Peters, K.; Peters, E. M.; Stegmann, V. R. *J Am. Chem. Soc.* **2000**, *122*, 2958. **4-Methylpent-3-en-2-ol (8)**. Prepared from $LiAlH_4$ reduction of 4-methyl-pent-3-en-2-one according to the literature procedure. ^{1}H and ^{13}C NMR specta were identical with those reported in the literature.[19]

(20) Palombi, L.; Bonadies, F.; Scettri, A. *Tetrahedron*, **1997**, *53*, 11369.

(21) **Epoxidation of 8**. Epoxidation of **8** (0.5 g) was performed according to the literature procedure.[19] The reaction mixture was worked up to give 0.58 g of a clear oil, the ^{1}H and ^{13}C NMR spectra of which were identical with those reported in the literature for *syn*-**9**.[20] The diastereomer ratio was determined by integration of peaks at 2.6 and 2.7 ppm, corresponding to the epoxide proton of the anti and syn isomer, respectively,[20] in the 500 MHz, ^{1}H NMR spectrum of the crude reaction mixture. Upon close inspection of the ^{1}H NMR spectrum a small doublet peak could be found at 2.6 ppm that had an area of around 2% of the peak found at 2.7 ppm.

(22) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.