Supplementary Materials for

Transition states for cysteine redox processes modeled by DFT and solvent-assisted proton exchange

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Theoretical Methods

Reactions in scheme 1 were modeled based upon the solvent-assisted proton exchange (SAPE) pathways shown in scheme 2. SAPE models incorporate a network of protic solvent molecules to approximate the solution-phase acid/base chemistry that facilitates proton exchange. The solvent molecules connect the sites of protonation in the reactants and products such that a proton is shuttled through the hydrogen-bonding network concurrent with heavy atom bond breaking/forming. The SAPE network is intended to mimic (in a first approximation) the role of solvent in a process involving proton exchange rather than to reproduce solvation of the chemical system. The reactant complexes are lowest local minimum subject to the constraint that the hydrogen bonding networks in scheme 2 remain intact and are not necessarily the absolute global minimum for the reactant-water cluster. The number of solvent molecules has been limited (generally to 2-4 explicit waters) in order to reduce conformations available to the cluster. As a result of the small number of explicit water molecules, the reaction steps in scheme 2 are necessarily concerted processes. The dependence of the activation barrier on the number of water molecules in the SAPE network has been examined by several groups. For the reduction of PhSeOH by MeSH, our group[1a] showed that a four-water network allowed for an improved angle of approach for the nucleophilic attack than a smaller two-water network. As a result, the activation barrier for the four-water network (scheme 2c), used in this study for CysSOH + CysSH → CysSSCys +H_2O, was half that of the two-water system. For the oxidation of alkenes to epoxides, Lundin et al compared the activation barriers of systems with increasing numbers of water molecules in the SAPE networks.[2] The most substantial reduction versus the direct transfer was observed for the addition of one water molecule. Similar $\Delta G^{\ddagger}$ values (uncorrected for bulk solvation) were obtained by our group for the oxidation of ebselen and other small organoselenium compounds by MeOOH using two and three-water SAPE networks.[1b] The analogous two-water networks were used in this study for the oxidation of CysSOH and $CysSO_2H$ (Scheme 2b).

Geometries were optimized using the B3PW91[3] exchange-correlation functional as implemented in the PQS[4] software package. The Wadt-Hay basis set augmented with diffuse and polarization functions was used for sulphur ((4s4p1d)/[3s3p1d]).[5] Oxygen and nitrogen were represented by the Dunning triple-ζ basis set with diffuse and polarization functions.[6] Hydrocarbon fragments were double-ζ quality with polarization functions included on carbon.[7] All stationary points were characterized at either minima or transition states by vibrational analysis. The imaginary frequency for reported transition states is consistent with motion along the reaction coordinate. Reported energies include zero-point energy (ZPE), thermal and entropy corrections based upon the harmonic oscillator approximation. This method for calculating the entropy corrections may be unreliable due to the contribution of soft vibrational modes of the water clusters. Corrections for bulk solvation in water, chlorobenzene and cyclohexane (ε = 78.38, 5.62 and 2.02, respectively) were calculated using COSMO.[8] Full optimizations of the reactant, transition state and product clusters result in similar trends in the activation barriers found in Table 1.

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