Theoretical Analysis of Peroxynitrous Acid: Characterization of Its Elusive Biradicaloid (HO···ONO) Singlet States

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More than a decade has passed since the physiological significance of peroxynitrous acid (HO−ONO), a fleeting intermediate with a half-life of less than a second, was disclosed by Beckman et al.[1] The peroxynitrite anion (NO−OO⁻), formed by the direct combination of nitric oxide (NO) and superoxide anion (O_2^-), is stable in alkaline solution. At physiological pH the anion is partially protonated, and its fate in aqueous media is the primary point of contention. It was suggested that this strong oxidant might be a source of very potent biologically relevant hydroxyl radicals.[2] One of the more intriguing aspects of HO−ONO chemistry is the earlier suggestion that O−O bond homolysis was slow, and the reactive species is a vibrationally excited form of HOONO.[2d] However, its lifetime of ∼10^{-11} s would preclude its involvement in bimolecular reactions, and Pryor et al.[3] advocated the existence of a high-energy metastable form of peroxynitrous acid (HO−ONO*) that is in steady state with ground-state HO−ONO. Conventional wisdom has proposed homolysis to produce either •OH and •NO_2 or a caged radical (•OH···•NO_2). Careful experimentation has suggested that the yield of hydroxyl radicals at room temperature in deoxygenated and bicarbonate free water at pH 6.8 is about 10%.[4] However, reports of the yields of hydroxyl radicals from the decomposition of HO−ONO have ranged from 0 to 40%.[4a] To date no evidence, experimental or theoretical, has been presented for the presence of such a metastable species.

There have been several theoretical studies that have described the geometry,[5a] decomposition pathways,[5b] and reactivity[5c,d,6a] of peroxynitrous acid. A thermally excited form (HO−ONO*) of peroxynitrous acid has until now eluded description. We now report cis and trans higher-lying singlet minima of peroxynitrous acid (HO···ONO) at several levels of theory, including CASSCF. The ground state (GS) structures of HO−ONO have been well-studied by a number of theoretical groups.[5,6] While the GS cis is the ground state at BLYP, the perpendicular conformer is slightly more stable at the QCISD and CASSCF levels (Figure 1). We initiated our study with a search for the so-called "excited state" that would presumably have a highly elongated O−O bond. A potential problem associated with the location of such a biradicaloid species on the unrestricted potential energy surface (PES) is that despite attempting to optimize with an unrestricted (UB3LYP) description, the wave function can converge to the restricted PES ($\langle S^2 \rangle = 0$). However, you can be assured of at least starting the geometry search with an unrestricted initial guess by mixing HOMO and LUMO (guess = mix).[7a] Following this protocol, using a fairly flexible basis set [6-311+G(d,p) or larger] with a relatively small step size, we were able to readily locate a singlet species (A′ symmetry) having an elongated O−O distance of 2.17 Å that was only 14.4 kcal/mol [UB3LYP/6-311+G(3df,2p)] higher in energy than its cis-peroxynitrous acid precursor (Figure 1, cis-2). We were also able to locate a second higher-lying minimum (trans-2) derived from the trans conformer of HO−ONO that was 12.8 kcal/mol higher in energy than ground-state HO−ONO. At the UQCISD(T) level, trans-2 was
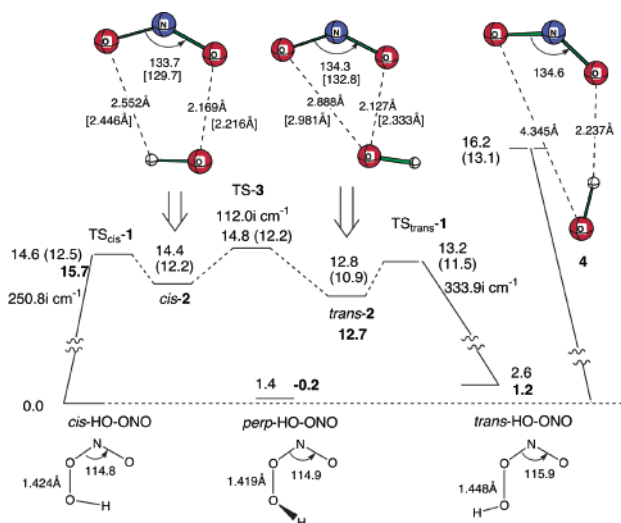

Figure 1. Energy diagram for the O−O bond elongation of cis- and trans-HO−ONO to form their respective higher-lying singlet biradicaloid minima. Plain numbers are at the UB3LYP/6-311+G(3df,2p) level. Bold numbers correspond to UQCISD(T)/6-311+G(d,p)//UQCISD/6-311+G(d,p). Geometrical data in brackets are at the CAS(12,10)/6-311+G(d,p) level.

12.7 kcal/mol higher in energy than GS cis-HO−ONO, in excellent agreement with the DFT calculations. The ONO fragment of the metastable states appeared to correlate with the ²A₁ state of the NO_2 radical with an ONO bond angle of 134°.

The transition state for O−O bond stretching (TS$_{cis}$-**1**, R_{O-O} = 1.947 Å, ν = 314.5i cm⁻¹) was found to be only 0.2 kcal/mol higher in energy than cis-**2**. The TS associated with formation of a slightly more stable singlet, trans-**2**, was 13.2 kcal/mol above the GS cis minimum for HO−ONO (TS$_{trans}$-**1**, R_{O-O} = 1.889 Å, ν = 333.9i cm⁻¹). We were also able to locate the TS for interchanging cis-**2** and trans-**2** (TS-**3**) by a simple in-plane migration of the OH group between the two terminal oxygens of the ONO radical fragment (ν = 112.0i cm⁻¹). The expectation values of the S^2 operator ($\langle S^2 \rangle$ = 0.76 and 0.73) for cis-**2** and trans-**2** suggested a significant contamination of the singlet wave function with triplet character. In such cases, a complete active space (CASSCF) calculation[7b] is advisable to assess the multireference character of the wave function. We used an active space comprising 12 electrons and 10 active orbitals [CAS(12,10)] that included the three σ bonds of the O−O, O−N, and N−O framework, an in-plane lone pair on oxygen, and the two highest π-orbitals in the occupied space. The virtual orbitals included the three antibonding σ-orbitals and one π-orbital (see Supporting Information). With a 6-311+G(d,p) basis set, the optimized geometries of cis-**2** and trans-**2** were quite close to those obtained with the DFT method (Figure 1). Another indication of the closeness of the DFT and CASSCF geometries was gleaned from single-point Brueckner Doubles calculations[7a] on the energy differences between the GSs and cis-**2** and trans-**2**. At the

BD(TQ)/6-311+G(d,p) level, the energy difference between GS *cis*-HO−ONO and *cis*-**2** was 15.5 kcal/mol with the DFT geometry and 15.2 kcal/mol with the CASSCF geometries. These energy differences were also in good accord with the DFT energies provided in Figure 1. Similarly, the energy differences between minimum, GS *perp*-HO−ONO, and *trans*-**2** were 14.0 and 13.0 kcal/mol at the DFT and CASSCF geometries, respectively. A CIPT2[7c] correlation correction to the CASSCF wave function suggested an energy difference between the GS *perp*- and *trans*-**2** of 4.9 kcal/mol. A multireference configuration interaction (MRCI)[7c] calculation with the above active space (6.8 million contracted configurations) gave energy differences between GS and metastable conformers of 11.7 and 9.0 kcal/mol for *cis*-**2** and *trans*-**2**, respectively.

The O−O bond dissociation enthalpy for GS *cis*-HO−ONO was calculated to be 22.0 kcal/mol at the G2 level of theory.[6b] The calculated dissociation limits for the GS *cis*-, GS *perp*-, and GS *trans*-HO−ONO were 17.3, 15.9, and 14.6 kcal/mol. With zero-point energy corrections (ZPE at B3LYP/6-311+G(3df,2p)) these dissociation limits were 15.3, 14.3, and 13.4 kcal/mol, values well above the energies of the higher-lying minima located. The O−O dissociation energy of 15.3 kcal/mol for GS *cis*-HO−ONO was in good accord with the Gibbs experimental enthalpy and free energy of activation (18 ± 1 kcal/mol, $\Delta S^{\ddagger} = 3$ e.u. and 17 ± 1 kcal/mol, $\Delta S^{\ddagger} = 12$ e.u.) for the isomerization of peroxynitrite to its nitrate form (presumably by a dissociative mechanism). However, the calculated Gibbs free energy for dissociation of *cis*-HO−ONO (5.9 kcal/mol, $\Delta S = 36$ e.u.) was significantly less than the experimental value for O−O dissociation in solution. While gas phase and solution entropies are not directly comparable, the existence of *cis*-**2** and *trans*-**2** in the gas phase remains an open question. Similar questions concerning the weakly bound HO• and NO₂• radicals reported by Houk[5e] (**4**, Figure 1) were also raised by Musaev.[8]

The relationship of the above gas-phase calculations to HO−ONO under physiological conditions now becomes the more relevant question. While we cannot address this question directly, we have carried out full geometry optimizations of *cis*- and *trans*-**2** using the COSMO solvent model.[7a] In THF solvent the energy difference between GS *cis*-HO−ONO and *cis*-**2** and *trans*-**2** was 12.3 and 10.2 kcal/mol [B3LYP/6-311+G(d,p)]. The energy differences between the GSs and their metastable forms with this smaller basis set in the gas phase were 12.2 and 9.9 kcal/mol. In methanol solvent, these energy differences increased to 13.9 and 12.4 kcal/mol, and in water media, the energy increases were 14.3 and 12.7 kcal/mol (15.4 and 14.2 kcal/mol with the larger 6-311+G-(3df,2p) basis set). Significantly, *cis*-**2** and *trans*-**2** both existed as energy minima in polar media with elongated O−O distances (2.140 Å and 2.089 Å) for *cis*-**2** and *trans*-**2** in water. Since hydrogen bonding is not explicitly treated in the COSMO solvent model, we examined the stability of *trans*-**2** H-bonded to water molecules. We located minima for *trans*-**2** H-bonded to one, two, three, and four H₂O molecules (see Supporting Information) with O−O distances of 2.13, 2.12, 2.15, and 2.11 Å [BLYP/6-311+G(d,p)]. As anticipated, the overall complexation energy increased almost linearly with increasing numbers of H₂O molecules (−5.6, −15.9, −28.2, and −34.7 kcal/mol). The water molecules exhibited very little affinity for O−N−O with all of the H-bonding being to the hydroxyl fragment. A water molecule placed near the O−N−O fragment migrated to the vicinity of the nearest hydroxyl group. Attempts to optimize *cis*-**2** H-bonded to three waters resulted in a *perp*-**2**·3H₂O complex (<HOON = 68°). The energy difference between this complex (shown below) and *trans*-**2** H-bonded to 3H₂O was only 0.3 kcal/mol. By contrast, the weak interaction between the radical pairs in **4**[5e] (Chart 1) completely dissociated

Chart 1
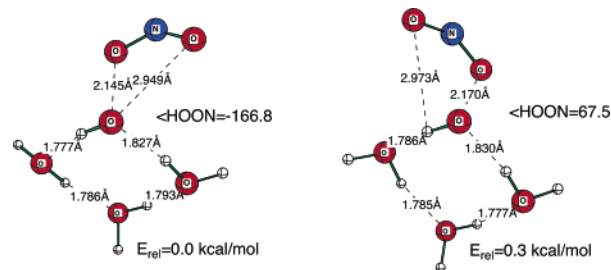
upon inclusion of just two H₂O molecules.[8] Both *cis*- and *trans*-**2** when H-bonded to 3H₂O resulted in perpendicular complexes (<HOON = 91.4° and 116.2°, $\Delta E = 0.3$ kcal/mol). The energy differences between *trans*-**2**·3H₂O and the corresponding GS *perp*-HO−ONO·3H₂O were 12.1 and 12.2 kcal/mol for the *perp*-**2**·3H₂O complex, thereby supporting the existence of these higher-lying singlets in aqueous media. We suggest that solvated forms of *cis*-**2**·3H₂O and *trans*-**2**·3H₂O represent the elusive higher-lying biradicaloid minima that have been advocated as the metastable forms of peroxynitrous acid (HOONO*)[3] largely responsible for the rich chemistry associated with this highly reactive oxidant.

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