Radical and Concerted Mechanisms in Oxidations of Amines, Sulfides, and Alkenes by Peroxynitrite, Peroxynitrous Acid, and the Peroxynitrite−CO_2 Adduct: Density Functional Theory Transition Structures and Energetics

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Received June 10, 1996. Revised Manuscript Received October 18, 1996[⊗]

Abstract: The mechanisms of oxidations of amines, sulfides, and alkenes by peroxynitrous acid, as well as the mechanism for the conversion of peroxynitrous acid to nitric acid, have been investigated with density functional theory methods using the Becke3LYP functional and the 6-31G* basis set. Theoretical evidence is obtained for the mechanisms and transition states of oxidations by peroxynitrous acid both by one- and two-electron processes. Transition structures for two-electron oxidations of amines, sulfides, and alkenes are reported. An activated form of peroxynitrous acid, HOONO*, is often invoked to account for the potent oxidative chemistry of peroxynitrous acid and derivatives; a structure with the appropriate characteristics has been located. The structure of the CO_2 adduct of peroxynitrite is also explored, and a mechanistic scheme is proposed for the acceleration of peroxynitrite oxidations in the presence of CO_2. Energetics are described in detail for each of these species and oxidation transition structures.

Introduction

Peroxynitrite is formed in biological systems by the diffusion-controlled reaction ($k_2 = 6.7 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$)[1] of nitric oxide and superoxide:[2]

$$^{\bullet}NO + O_2^{\bullet -} \rightarrow ONOO^-$$

Although peroxynitrite is stable in solution, protonation ($pK_a = 6.8$) produces potent oxidants and nitrating agents which have cytotoxic potential.[3] Coordination of peroxynitrite with a variety of Lewis acids (CO_2,[4] metal porphyrins,[5] and perhaps SOD[6]) may have a similar effect. The role of the SOD−peroxynitrite reaction in disease states has been postulated.[6]

The mechanisms of oxidations by peroxynitrite and derivatives such as CO_2 adducts have been controversial. In particular, the relative importance of hydroxyl radicals formed by homolysis, versus activated intermediates formed by intramolecular rearrangements, has been debated.[2,7] Here, we provide theoretical evidence for the mechanisms of one- and two-electron oxidations by peroxynitrite and derived species such as CO_2 adducts. We report both reaction energetics and transition states for reactions of interest and establish which mechanisms are feasible.

Theoretical Methods

The geometries and energies were calculated with density functional theory (DFT) using the Becke3LYP functional[8] and the 6-31G* basis set using the Gaussian 94 program.[9] Minima and transition structures were fully optimized and characterized by harmonic vibrational frequency analysis. These calculations give accurate energetics of reactions such as homolytic processes.[10−12] Examples include recent ab initio studies on novel N_2O_4 isomers,[10] which showed that the Becke3LYP functional gave more accurate geometries than any other commonly used DFT functionals. The accuracy is exemplified by the dissociation of hydrogen peroxide (Becke3LYP/6-31G* bond dissociation energy (BDE) = 54.2 kcal/mol; experimental BDE = 50.9 kcal/mol[13]).

Results and Discussion

Peroxynitrite and Peroxynitrous Acid. Structures of peroxynitrite and peroxynitrous acid have been explored previously using ab initio calculations.[14,15] The Becke3LYP calculations

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[⊗] Abstract published in *Advance ACS Abstracts*, December 1, 1996.

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S0002-7863(96)01952-X CCC: $12.00

agree with G2 theory calculations[15] that the lowest energy conformation of peroxynitrous acid is a cis form with an intramolecular hydrogen bond (**1**, Figure 1). The trans form (**2**, Figure 1) is 4.7 kcal/mol higher in energy and has the oxygen−hydrogen bond nearly perpendicular to the plane defined by the nitrogen and oxygen atoms.

Various tautomers were explored in order to determine if they were involved in oxidations. However, structures **3** and **4** (Figure 1) are 23 and 43 kcal/mol, respectively, higher in energy than **1**, and these isomers undergo spontaneous proton transfer back to **1** and **2** without a barrier upon attempted optimization. Related isomers were at one time invoked for peroxyacid oxidations.[16]

Peroxynitrous Acid Oxidations. Peroxynitrous acid is both a one- and two-electron oxidant. For example, methionine undergoes a one-electron oxidation with formation of ethylene.[17] The reaction may occur by direct electron transfer to peroxynitrous acid, which is calculated to have an electron affinity (EA) of 0.42 eV. The calculated EA of HOONO is 0.6 eV larger than that calculated for H_2O_2 (−0.16 eV), leading to an estimated reduction potential of 2.4 V for HOONO (experimental reduction potential for H_2O_2 = 1.776 V).[18]

$$\mathrm{HOONO} + \mathrm{A} \rightarrow \mathrm{HOONO}^{\bullet-} + \mathrm{A}^{\bullet+}$$

Alternatively, one-electron oxidations may occur with the intermediacy of the hydroxyl radical. The peroxide bond in peroxynitrous acid is calculated to have a homolysis enthalpy of only 22.5 kcal/mol, while the free energy of this homolysis is predicted to be only 9.0 kcal/mol.

$$\mathrm{HOONO} \rightarrow \mathrm{HO}^{\bullet} + \mathrm{ONO}^{\bullet}$$

An experimental free energy barier of 17 kcal/mol has been measured for the isomerization of peroxynitrous acid to nitric acid.[2,7] Recent spin trap experiments suggest that homolysis does occur in this system, although the concentration of free hydroxyl radical produced is too low to account for the cytotoxicity exhibited by peroxynitrite,[19] and the utility of the spin trap method for proving radical formation in this system has been questioned.[20] The viscosity test has given evidence against the formation of free hydroxyl radicals.[21] Our results suggest an alternative which requires that the hydroxyl radical is formed in a tight cage in aqueous solution, still capable of performing one-electron oxidations. The experimental EA of $HO^{\bullet}$ is 1.83 eV.[11] Thus, dissociation of HOONO, followed or accompanied by electron transfer, is exothermic overall by 0.8 eV. This mechanism is discussed in detail later.

Two-electron oxidations (that is, oxygen transfers) of amines, sulfides,[17] and selenides[22] by HOONO have been observed experimentally.

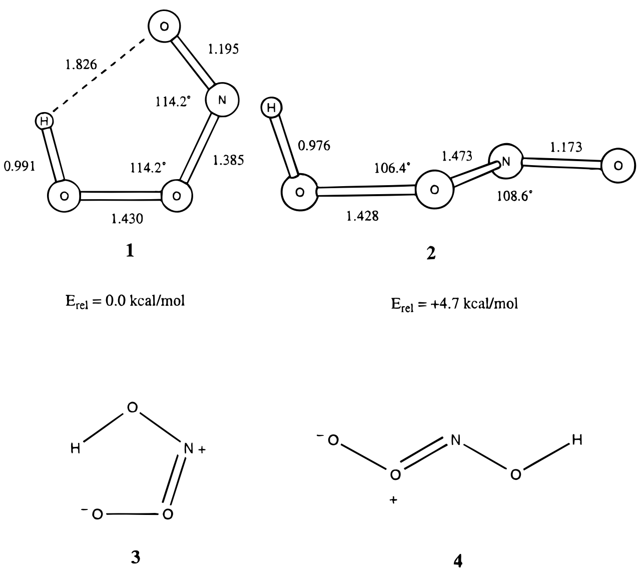

Figure 1. Becke3LYP/6-31G*-optimized structures of *cis*- and *trans*-peroxynitrous acid.

$$\mathrm{HOONO} + \mathrm{A} \rightarrow \mathrm{HONO} + \mathrm{A{=}O}$$

Our theoretical studies suggest that HOONO should provide oxidative reactivity comparable to that of organic peroxyacids. Transition structures have been located for the concerted peroxynitrous acid oxidations of H_2S, NH_3, and ethylene (Figure 2). The activation energies of these reactions are 13−18 kcal/mol, suggesting that these two-electron oxidations by HOONO are energetically feasible. For comparison, transition structures were also calculated for the peroxyformic acid oxidation of H_2S, NH_3, and ethylene at the Becke3LYP/6-31G* level; these are very similar in both energetics and geometries to those calculated earlier by Bach and co-workers at the MP2/6-31G* level.[16]

Each transition structure involves substantial stretching of the O−O bond and only slight hydrogen transfer. The oxidation of ethylene is noteworthy in that an asymmetric "spiro" transition state is calculated. When constrained to C_S symmetry with equal forming carbon−oxygen bond lengths, the energy increases by only 0.1 kcal/mol. The formation of sulfoxides from sulfides by peroxynitrous acid is well-established,[17] but the expectation that alkenes can be epoxidized is novel. Experimental studies of epoxidations by peroxynitrous acid are complicated by the short lifetime of this reagent; epoxidations have not yet been observed.

Peroxynitrite Anion Oxidations. Although the peroxynitrite anion is a poor one-electron oxidant, calculations indicate that it is capable of epoxidation. It has a substantially longer lifetime than peroxynitrous acid in solution, and recent work demonstrates the reactivity of this anion toward electrophilic centers.[22]

The transition structure for the oxidation of ethylene by peroxynitrite is shown in Figure 3. This reaction is exothermic ($\Delta E = -21.0$ kcal/mol) with an activation barrier of only 11.6 kcal/mol based on the energy of the separated reactants relative to the energy of the transition structure. As expected, for the gas phase, there is an ion−molecule complex which is 4.8 kcal/mol more stable than the reactants. This transition structure differs markedly from that found for the HOONO-mediated oxidation: the peroxide bond is still quite short (1.63 Å) and the transition structure is highly asymmetrical. This is a nucleophilic addition transition state, and the second phase of

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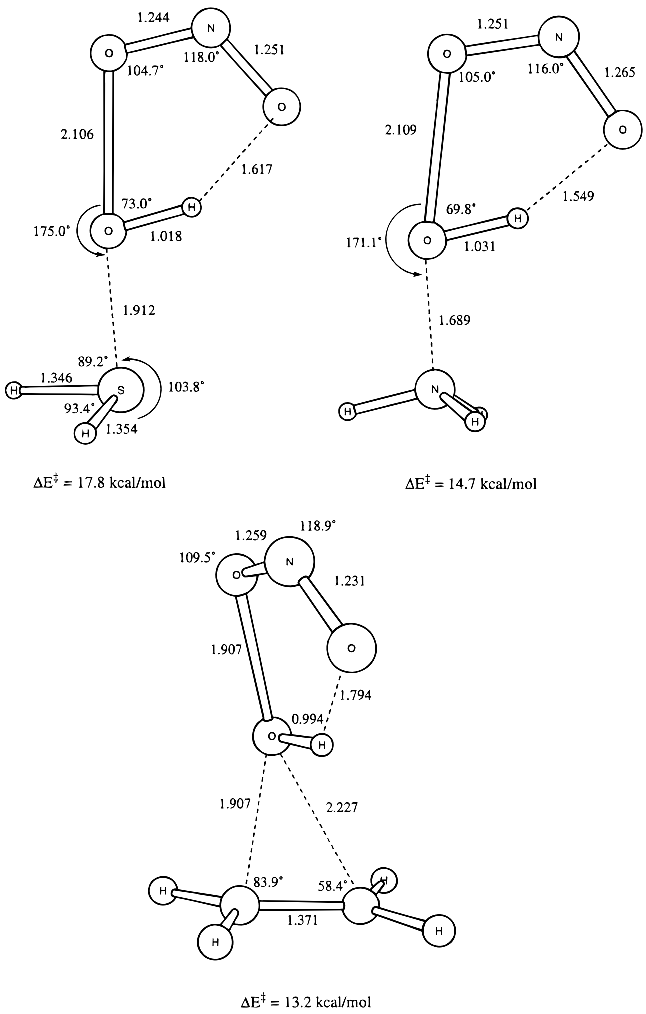

Figure 2. Becke3LYP/6-31G* transition structures for peroxynitrous acid oxidations of H_2S, NH_3, and ethylene.

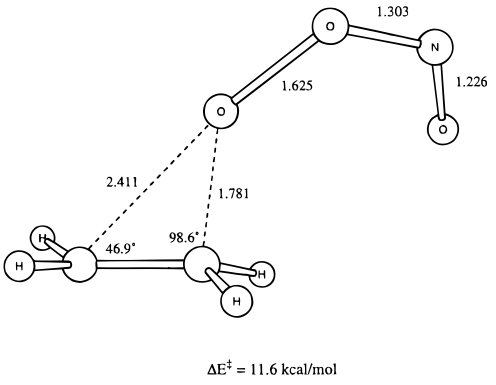

Figure 3. Becke3LYP/6-31G* transition structure for oxidation of ethylene with $ONOO^-$.

the reaction would involve cyclization and NO_2^- ejection. This reaction would be especially facile for electron-deficient alkenes, analogous to the facile epoxidation of enones by basic hydrogen peroxide.[23] The oxidation of amines and sulfides, on the other hand, will be highly disfavored.

Conversion of Peroxynitrous Acid to Nitric Acid and the Nature of HOONO*. In the absence of oxidizable substrates, peroxynitrous acid is rapidly converted to nitric ($k_{obs} = 1.3$ s^{-1} at 25 °C).[2,7] The mechanism for this transformation is problematic. It has been proposed that this is a concerted rearrangement, and the activated complex can also serve as a potent oxidant.[7] Our extensive searches have led to no viable concerted mechanism for this reaction. Recently, the transition state for the rearrangement of HOONO to HNO_3 was found to lie 60 kcal/mol higher in energy than HOONO (MP4SDQ/6-31G*//HF/6-31G* with SCRF solvation).[24,25] This is far too high to have any relevance to solution chemistry.

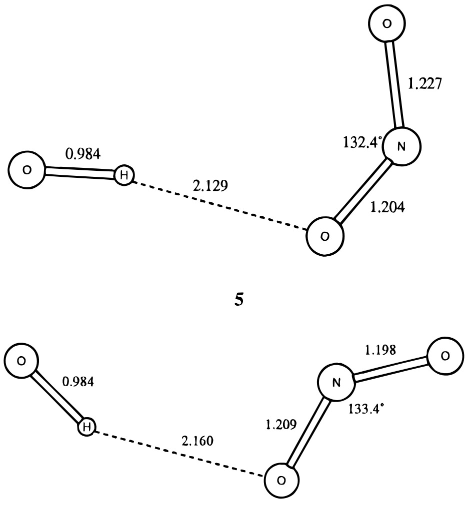

Figure 4. Becke3LYP/6-31G*-optimized complexes of NO_2 and hydroxyl radical. A hydrogen-bonded radical pair is proposed as the structure of HOONO*.

On the basis of semiempirical calculations, it was previously proposed that an activated species, HOONO*, is both a transition state for the rearrangement and a powerful one-electron oxidant form of peroxynitrous acid.[7] Later, it was recognized that HOONO* must be a trappable intermediate in the rearrangement.[2] This species has been invoked frequently in the literature.[7,17,21,22,26] The energy of HOONO* has been estimated at 17 kcal/mol above peroxynitrous acid.[2,7] The concerted pathway for rearrangement is very high in energy, but we have located a stepwise process involving hydrogen-bonded radical pairs. The homolysis of **1** occurs to produce the hydrogen-bonded species **5**, shown in Figure 4. There is a second hydrogen-bonded species, **6**, which involves hydrogen bonding to an exo lone pair of NO_2. Both of these species are diradicals, with degenerate singlet and triplet states. The hydrogen bonds are weak, and **5** and **6** are only 1.9 and 2.5 kcal/mol, respectively, more stable than $^\bullet NO_2$ plus $HO^\bullet$. Nitrogen dioxide is a σ radical, with the odd electron occupying an in-plane orbital. Complexes **5** and **6** can recombine to peroxynitrous acid or nitric acid readily, merely by reorientations which break the hydrogen bonds. Calculations we have performed and those in the literature[27] show there is no barrier to the recombination of $HO^\bullet$ and $^\bullet NO_2$ to peroxynitrous acid or nitric acid, except for the energy required to disrupt the hydrogen bonds.

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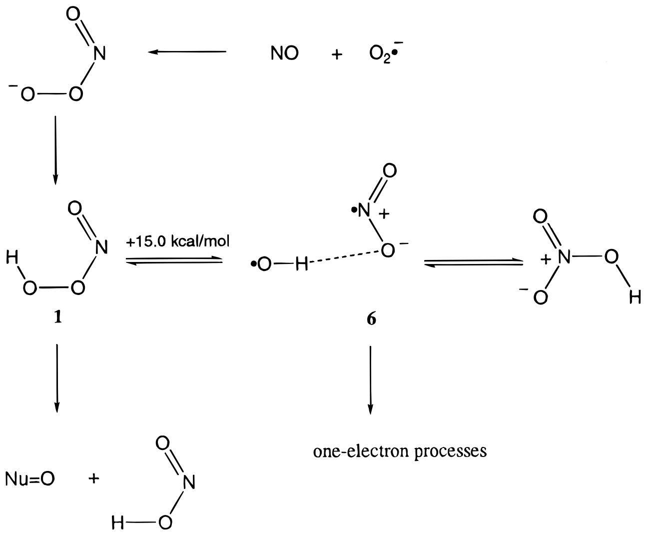

Figure 5. Becke3LYP/6-31G* energetics of peroxynitrous acid reactions.

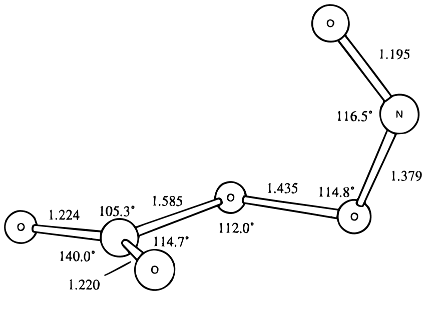

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Figure 6. Becke3LYP/6-31G*-optimized structure for $ONOOCO_2^-$ (**7**).

The hydrogen-bonded complexes **5** and **6** have free energies of 15.6 and 15.0 kcal/mol, respectively, relative to *cis*-peroxynitrous acid (**1**). This is comparable to the experimental free energy of 17 kcal/mol for the conversion of **1** to nitric acid and for the first-order oxidations by peroxynitrous acid.[7]

Thus, we have found species which are stabilized by hydrogen bonding and should have the high oxidation ability known for $HO^\bullet$ in solution. Complexes **5** and **6** are proposed as a structures for the activated form of peroxynitrous acid, HOONO*. The various reactions of peroxynitrous acid are summarized in Figure 5.

Reaction of Peroxynitrite with Carbon Dioxide. Peroxynitrite reacts rapidly with CO_2.[4,28] Calculations indicate that the process is not only exothermic ($\Delta E = -25.7$ kcal/mol) but also that there is no barrier to the formation of $ONO_2CO_2^-$ (**7**). The optimized geometry of **7** is shown in Figure 6. As is typical for peroxides, these molecules exhibit a near 90° dihedral angle (78.9°) about the OO bond.

Although heterolysis of **7** to NO_2^+ and CO_3^{2-} is highly endothermic (+360 kcal/mol) in the gas phase, the formation of NO_2^+ or transfer of NO_2^+ from **7** to a nucleophilic species should be a favorable process in aqueous solution (see Figure 7). This conclusion follows from experimental or estimated enthalpies of hydration (ΔH_{hydr}) for the ionic species involved in the reaction.[29] The ΔH_{hydr} for CO_3^{2-} is -334 kcal/mol. The ΔH_{hydr} for NO_2^+ can be approximated from typical values for larger cations ($\Delta H_{hydr}[Cs^+] = -68$ kcal/mol; $\Delta H_{hydr}[NH_4^+] = -76$ kcal/mol). A comparable dioxygenated cation has a more exothermic hydration enthalpy ($\Delta H_{hydr}[UO_2^+] = -174$ kcal/mol). From these values, we estimate $\Delta H_{hydr}[NO_2^+] = -125$ kcal/mol. Similarly, consideration of ΔH_{hydr} of ionic species similar in electronic structure to **7** ($\Delta H_{hydr}[HCO_3^-] = -92$ kcal/mol; $\Delta H_{hydr}[CH_3CO_2^-] = -102$ kcal/mol) provides an estimated $\Delta H_{hydr}[\mathbf{7}] = -100$ kcal/mol. The net change in hydration enthalpy ($\Delta\Delta H_{hydr}$) for the heterolysis of **7** to give NO_2^+ and CO_3^{2-} is thus estimated to be about -359 kcal/mol. This analysis suggests that the heterolytic cleavage of **7** should be approximately thermoneutral in aqueous solution. This process provides a potential source of the potent nitrating agent NO_2^+, most likely by direct transfer to nucleophilic species. Nitration of tyrosine is invoked as an origin of disease states influenced by peroxynitrite.[6]

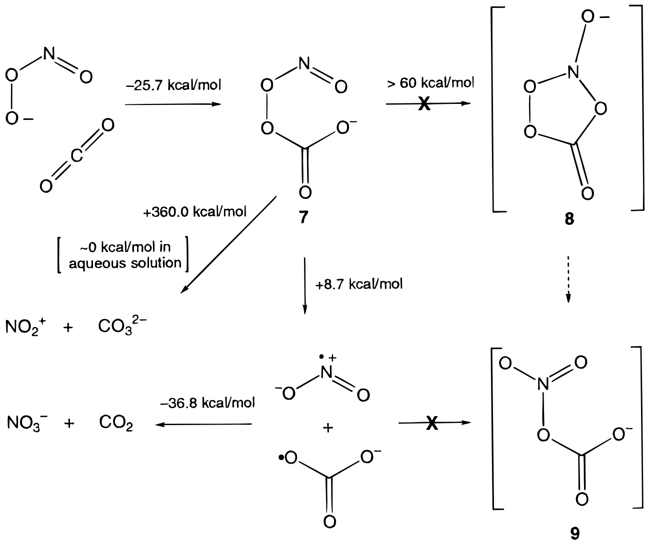

Figure 7. Becke3LYP/6-31G* energetics of pathways for conversion of peroxynitrite to nitrate.

The energetics of other reactions of the peroxynitrite adduct with CO_2 are also shown in Figure 7. Homolysis to form $^\bullet NO_2$ and the carbonate radical ($^\bullet CO_3^-$) requires only 8.7 kcal/mol. Protonation of $^\bullet CO_3^-$ gives the bicarbonate radical ($pK_a = 7.0-8.2$),[30] a reactive oxidant and cytotoxic agent.[31] It is known that $^\bullet NO_2$ reacts at near diffusion-controlled rates (1×10^9 M^{-1} s^{-1}) with $^\bullet CO_3^-$ in an oxygen transfer reaction to give CO_2 and nitrate.[32] Our calculations show that $^\bullet CO_3^-$ reacts with $^\bullet NO_2$ to transfer an oxygen without a barrier; this reaction generates CO_2 and nitrate ion and is exothermic by 37 kcal/mol. Thus, CO_2 is even more efficient than H^+ in catalyzing the homolysis of HOONO and subsequent nitrate formation.

We also investigated possible intramolecular nucleophilic addition of the carbonate oxygen in **7** at the nitrogen center, thus yielding the hypothetical intermediate **8**. Attempts to cyclize **7** in this way led to spontaneous fragmentation of the O−O bond in the molecule. Although it was possible to constrain the O−O bond and the newly formed N−O bond in **8** to prevent such fragmentation, attempted optimization of **8** in this manner gave energies in excess of 60 kcal/mol higher than the reactant.

The hypothetical intermediate **9** was found to be unstable, since it undergoes spontaneous homolysis to give $^\bullet NO_2$ and

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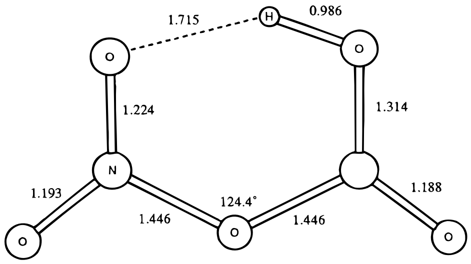

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Figure 8. Becke3LYP/6-31G*-optimized structure for **9′**.

$^{\bullet}CO_3^-$. Protonation of **9** gives the stable intermediate **9′** (Figure 8); this species lies 15.2 kcal/mol higher in energy than HNO_3 and CO_2. The additional hydrogen bond stabilizes this species toward homolysis. Such an intermediate would likely be short-lived, given that spontaneous homolysis takes place upon deprotonation of **9′**, which is estimated to have a pK_a somewhat less than 6.4−8.2. This value is estimated from the pK_a of H_2CO_3 = 6.4[33] and the pK_a of the radical $HCO_3^{\bullet}$ = 7.0−8.2,[30] along with the expectation that NO_2 is anion stabilizing and will reduce the pK_a. Figure 9 illustrates the pK_a values for the protonated forms of peroxynitrite and derived intermediates in the conversion to nitric acid. The conjugate acid **7′** of the CO_2 adduct **7**, is also predicted to be a potent oxidation and nitration intermediate. Homolysis and heterolysis of **7′** are slightly endothermic and very exothermic in aqueous solution, respectively.[34]

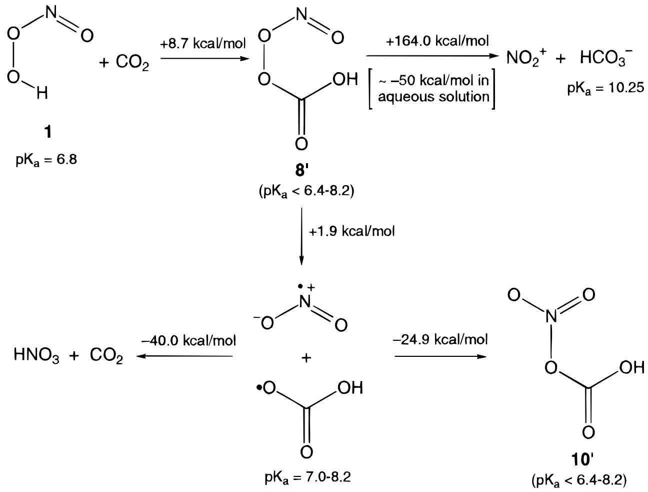

Figure 9. Energetics and pK_a values for peroxynitrous acid and derived intermediates (values in parentheses are estimated).

Conclusion

Theory has shown how peroxynitrous acid can effect both one- and two-electron oxidations, both in energetically feasible fashions. The peroxynitrite−CO_2 adduct offers additional pathways by which potent oxidants can be formed. Hydrogen-bonded **5** and **6** are novel complexes suggested as attractive structures for the potent oxidizing intermediate HOONO*.

Acknowledgment. We are grateful to the National Science Foundation for support through grant CHE9120588 (K.N.H.) and to the National Institutes of Health for a postdoctoral fellowship (K.R.C.). W.A.P. thanks the National Institute of Environmental Health Sciences of NIH for support through grant ES-06754.

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(34) The hydration energy of **7′** is estimated at −3 kcal/mol on the basis of the hydration enthalpy of acetic acid,[33] while the hydration energies of NO_2^+ and HCO_3^- are −125 and −92 kcal/mol, respectively.[29]