Oxidation of Amines and Sulfides with Hydrogen Peroxide and Alkyl Hydrogen Peroxide. The Nature of the Oxygen-Transfer Step

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Abstract: Ab initio molecular orbital methods have been used to study the oxidation of ammonia, dihydrogen sulfide, and dimethyl sulfide by hydrogen peroxide and methyl hydroperoxide. Geometries of reactants, complexes, transition states, and products were fully optimized at the MP2/6-31G* level, and relative energies were computed at the MP4/6-31G*//MP2/6-31G* level. Without protic solvent catalysis, a 1,2-hydrogen shift is needed before oxygen transfer from H_2O_2 takes place and the barriers are much too high (ca. 50 kcal/mol). One or two molecules of protic solvent reduce these barriers by ca. 10 kcal/mol. In the absence of protic solvents, the hydroperoxide itself can act as a general acid catalyst, leading to second-order kinetics in H_2O_2 (in agreement with experiment). An increase in pK_a of the general acid catalyst results in a decrease in activation energy for oxygen atom transfer from hydrogen peroxide. The mechanism for oxidation of sulfur is similar to that of oxidation of NH_3, and methyl substitution at sulfur results in a modest stabilization of the transition state. For methyl hydroperoxide oxidation of ammonia, an ionic pathway is slightly lower in energy and involves a proton shift occurring after transfer of HO^+. In agreement with experiment, protonation by strong acids has a much larger effect on the barrier than catalysis by weak acids such as H_2O, H_2O_2, and NH_3. However, the calculations show that under acidic conditions protonation occurs at the nucleophile rather than the peroxide, thereby greatly diminishing the catalytic effect. Nevertheless, all of these oxidation reactions have calculated barriers that are unreasonably high, in the range 35–50 kcal/mol. However, if proton transfer from solvent is combined with protic solvent stabilization of an ionic transition state, the calculated barriers are reduced to 5–15 kcal/mol, in good agreement with experiment. Thus the mechanism for amine or sulfide oxidation involves a protonated solvent molecule transferring a proton to the distal oxygen of the hydroperoxide in concert with a second molecule of solvent stabilizing the transfer of HO^+ from the hydroperoxide to the nucleophile.

Introduction

A detailed mechanistic picture of oxygen atom transfer from hydroperoxides to nucleophilic substrates remains a goal of both experimental and theoretical chemists.[1] Earlier mechanistic studies were aimed at the elucidation of the mechanism of the oxidation of amines, sulfides, and sulfoxides.[1] More recent efforts have concentrated on the design of model systems to examine the mechanism of oxygen donation from 4α-flavin hydroperoxide[2a] and iron-mediated catalase oxidations.[2b,c] Despite the importance of such reactions, until recently, very few high-level ab initio calculations involving oxygen–oxygen bond cleavage have appeared in the literature.[3]

The generally accepted mechanism for oxygen transfer from an alkyl hydroperoxide involves attack by the nucleophilic substrate (:NUC) on the distal oxygen with a direct S_N2 type displacement of the β-peroxy oxygen. Hydrogen migration to the departing alkoxide group is typically assumed to occur simultaneously (eq 1). However, a 1,2-hydrogen shift to a hetero

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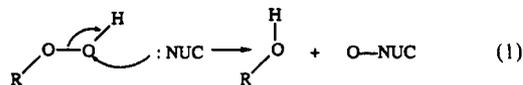
atom with a lone pair of electrons in molecules like H_2O_2, HO–NH_2, and HO–F is typically associated with activation energies of ca. 50 kcal/mol.[4] The barrier height for the 1,2-hydrogen shift in hydrogen peroxide to form the dipolar molecule water oxide (HO–HO → H_2O^+–O^-)[3b] is predicted to be 56.0 kcal/mol (MP4//MP2/6-31G*).[5a] The reverse reaction, affording the normal covalent hydrogen peroxide structure, has a very low activation barrier. We reported a barrier of 3.7 kcal/mol (with ZPE) for reversion of water oxide to hydrogen peroxide.[5a] Water oxide is a genuine minimum on the H_2O_2 potential energy hypersurface, and a recently reported[6] activation barrier of 3.2 kcal/mol for H_2OO → H_2O_2 using couple cluster methods with single and double excitations (CCSD) with a triple-ζ plus double polarization (TZ2p+f) basis set is in excellent accord with the MP4//MP2/6-31G* barrier.[5a] Since comparable barriers exist for 1,2-hydrogen shifts in alkyl hydrogen peroxides, we have suggested that a general mechanism for oxygen transfer from a hydroperoxide must accommodate the energetic requirements for the 1,2-hydrogen shift.[5]

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In the present study we address questions concerning the position of the hydrogen in the transition state and the solvation and catalysis requirements for facile O–O bond cleavage in oxygen atom transfer from a hydroperoxide. It is a well-established fact that hydroxide or alkoxide ion is a particularly poor leaving group in an S_N2 nucleophilic displacement reaction. We initiated this theoretical study with a probe of both dynamic and static correlation effects on the transition state for oxygen atom transfer from water oxide to ammonia. We then examined the relative activation barriers for the oxidation of ammonia by HOOH and CH_3OOH with particular emphasis upon whether the proton of the hydroperoxy group (–OOH) is transferred prior to or after the oxygen-transfer step. We have also examined the effect of the pK_a of the protic solvent upon the activation barrier for oxidation. Finally we examined the catalytic effect of transferring a proton to the departing hydroxide group of HO–OH in concert with O–O bond rupture.

Method of Calculation

Molecular orbital calculations were carried out using the Gaussian 92 program system[7a] utilizing gradient geometry optimization.[7b] The structures for the minima, reactant clusters, and the transition states for oxygen transfer have been optimized at the MP2 level with the 3-21G and 6-31G* basis sets. A full set of vibrational frequencies was calculated for all minima and transition structures using analytical second derivatives at the MP2/6-31G* level. Self-consistent reaction field (SCRF) calculations of solvation effects were carried out at the MP2/6-31G* level without further geometry optimization. Each TS is a first-order saddle point with only one imaginary frequency. All the post-SCF optimizations were carried out by including all the MOs, and the energies were computed with the frozen-core approximation. To answer some of the questions about the significance of electron transfer and biradical character in the transition states, a series of complete active-space multiconfigurational SCF (CASSCF) calculations were carried out for oxygen transfer from water oxide using geometries optimized by the QCISD(T) method with the 6-31G* basis set. The geometry of TS-1 was fully optimized at CASSCF. Unless noted otherwise, all relative energies and activation energies given below were computed at the MP4SDTQ/6-31G*//MP2/6-31G* level of theory and all ΔE^* were computed relative to a reactant cluster.

Results and Discussion

Oxygen Transfer from Water Oxide to Ammonia. The amount of enthalpy (ΔH^*) required to cleave homolytically a generic peroxide ZOOY (eq 2) varies from 47 kcal/mol for HOOH to

$$ZO\overset{\frown}{\underset{\smile}{-}}OY \rightarrow ZO\cdot + YO\cdot \qquad (2)$$

23 kcal/mol for phenylacetyl peroxide $[PhCH_2COO]_2$.[1b] Because of the historical difficulty attending the theoretical description of the dissociation of the O–O bond, we examined the potential energy curve for O–O bond rupture in hydrogen peroxide in both covalent (HO–OH) and dipolar (H_2O–O) forms.[5b] For calculations involving the O–O bond, dynamic correlation is essential in order to accurately estimate bond dissociation energies (D_e). For example, at the HF/6-31G* level, the O–O bond in H_2O_2 has a calculated D_e of only 0.14 kcal/mol. At the MP4SDTQ/6-31G*//MP2/6-31G* level, the O–O bond energy in H_2O_2, relative to two hydroxyl radicals, is 49.2 kcal/mol and D_0 (corrected for zero point energy) is 43.2 kcal/mol.[8d] The predicted D_e and D_0 values for H_2O_2 at the MP4//MP2/6-31+G* level are 48.0 and 42.3 kcal/mol, respectively.[8e] A scan of the total energies as a function of increased O–O bond length for both H_2O_2 and
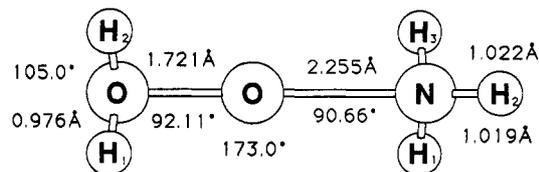
Figure 1. Transition structure (TS-1) for oxygen transfer from water oxide to ammonia. Geometry fully optimized at the QCISD(T)/6-31G* level.

H_2OO showed that energies calculated with the 6-31G* basis set at spin-restricted MP4SDTQ, QCISD(T), and conventional CI including the Davidson correction (CISD+DAV) give consistent results at O–O bond distances up to 2.5 Å. Only as the O–O bond stretches beyond 2.5 Å toward dissociation does the convergence of the Møller-Plesset series become sufficiently poor that the MP2, MP3, and MP4 surfaces are highly distorted and the corresponding calculated energies fall below that of the dissociation limit for the two oxygen-containing fragments. Since the transition structures that we have reported typically have O–O bond lengths less than 2.5 Å, we feel that the MP4//MP2/6-31G* level adequately reflects the energetic requirements for O–O bond stretching.[5] Theoretically predicted activation barriers for the epoxidation of alkenes with peroxyformic acid are also in excellent agreement with experiment.[9a,b]

The reliability of the HF single-reference wave function as an adequate reference for oxygen-transfer reactions must also be tested. Consequently, we studied the effects of static correlation corrections with complete active space SCF (CASSCF) calculations on a relatively small oxygen-transfer system. Fundamental questions that we wish to address are the extent of the electron population in the σ^* O–O orbital and its contribution to the reactivity of water oxide as an oxygen donor. Hydrogen peroxide is a powerful oxidant, but in the absence of a catalyst, it reacts slowly with some substrates such as alkenes. The reactive form of hydrogen peroxide in the gas phase is predicted to be water oxide.[5a] Both dynamic and static electron correlation effects have been examined for the transfer of an oxygen atom from H_2OO to ammonia (TS-1, Figure 1). The ratio of O–O to N–O bonds in TS-1 has been examined at MP2, QCISD, QCISD(T), and CASSCF with the 6-31G* basis set (Table 1). The MP2 level slightly underestimates these bond distances, while CASSCF affords longer bond distances relative to geometry optimization at the QCISD level. A relatively small active space with only one virtual orbital (12 electrons, 7 orbitals) showed a surprisingly small occupancy (0.05 electrons) for the LUMO.[5a] In this study the size of the active space was increased to 12 electrons and 9 orbitals (2 250 configurations) which should be capable of accounting for the structure-dependent internal correlation. The natural orbital occupations of the three lowest virtual orbitals of TS-1 were 0.025, 0.032, and 0.02 electrons, indicating that the σ^* orbital is relatively unaffected at this point along the reaction path. The value for the coefficient of the reference configuration was 0.976, suggesting that in a basis of CASSCF orbitals oxygen transfer from water oxide to ammonia can be adequately described as an essentially closed shell transformation. Geometry optimization at the CASSCF level resulted in an O–O bond elongation

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Table 1. Transition Structure (TS-**1**) for Oxygen Transfer from Water Oxide to Ammonia.[a]

	MP2	QCISD	QCISD(T)	CASSCF (12e,7orb)	CASSCF (12e,9orb)
$R(O_1O_2)$[b]	1.679	1.729	1.721	1.836	1.829
$R(O_1H_1)$	0.974	0.974	0.976	0.948	0.974
$R(O_2N)$	2.161	2.250	2.255	2.302	2.157
$R(NH_1)$	1.014	1.017	1.019	1.001	1.001
$R(NH_2)$	1.017	1.020	1.022	1.002	1.002
$\angle O_1O_2N$[c]	175.2	173.3	173.0	176.8	179.8
$\angle H_1O_1O_2$	94.73	93.07	92.11	96.84	91.42
$\angle H_1O_1H_2$	105.3	105.1	105.0	106.4	105.1
$\angle H_1NO_2$	96.33	91.48	90366	99.47	105.5
$\angle H_3NH_1$	108.5	107.9	107.8	108.3	108.0
E[d]	−207.439 34[e]	−207.432 95	−207.443 40		
$\Delta E^{\ddagger}$ (from HOOH)[f]	51.9	50.4	50.3		
$\Delta E^{\ddagger}$ (from H_2OO)	2.2	2.1	1.6		

[a] Geometry fully optimized with a 6-31G* basis set at the levels indicated. [b] Bond lengths in Å. [c] Angles in deg. [d] Total energies in hartrees. [e] MP4/6-31G*//MP2/6-31G*. [f] Barriers in kcal/mol.

of 0.15 Å relative to the MP2 geometry. The barrier heights for the formation of ammonia oxide vary from 2.9 (MP4//MP2) to 1.64 kcal/mol (QCISD(T)) when measured from water oxide (Table 1). The contribution of the triples at the QCISD level has virtually no effect upon either the geometry or the activation energy. The QCISD(T) barrier based upon the MP2 geometry (1.55 kcal/mol)[5a] suggests that the triple excitations do not appear to be essential for an accurate description of this relatively simple oxygen atom transfer process. These trends are quite consistent with previous calculations of the oxidation of ethane with water oxide where we also concluded that the O–O bond length was too long (0.3 Å) with CASSCF geometry optimization.[9c] Thus, dynamic correlation effects are much more important than static correlation effects for treating the O–O bond for oxygen transfer at least in this model system. Dynamic correlation also plays a significant role in oxygen donation from peroxy acids.[9a,b] The shortening of the O–O bond in TS-**1** at QCISD could be a function of much greater correlation effects in the QCISD wave function. The theoretical gas-phase barrier heights for oxygen transfer to ammonia are approximately 50 kcal/mol when measured from hydrogen peroxide. Since these energies approach the magnitude of homolytic bond dissociation for the O–O bond, solvent effects must obviously play a major role in oxidation reactions in the condensed phase where H_2O_2 is an effective oxygen donor.

General Acid Catalysis in Oxidations with Hydrogen Peroxide. Much of what is understood today about the influence of solvent on rates of oxidation reactions with hydrogen peroxide, alkyl hydroperoxides, and peroxyacids can be attributed to the seminal studies by Edwards and his collaborators.[10] They provided convincing experimental data that show that a hydroxylic solvent (e.g. ROH) can participate in a cyclic transition state where a proton relay can in principle afford a neutral leaving group (eq 3). On the basis of their kinetic data, they suggested that appreciable charge separation in the activated complex (eq 3) could be avoided by means of such proton transfers, where HA is a general acid (H_2O, ROH, ROOH). Upon change from a polar protic solvent to the nonpolar solvent dioxane, the reaction was found to be second order in hydrogen peroxide and the second molecule of H_2O_2 obviously played the role of HA in the 1,4-proton shift. The rate of oxidation was shown to increase linearly

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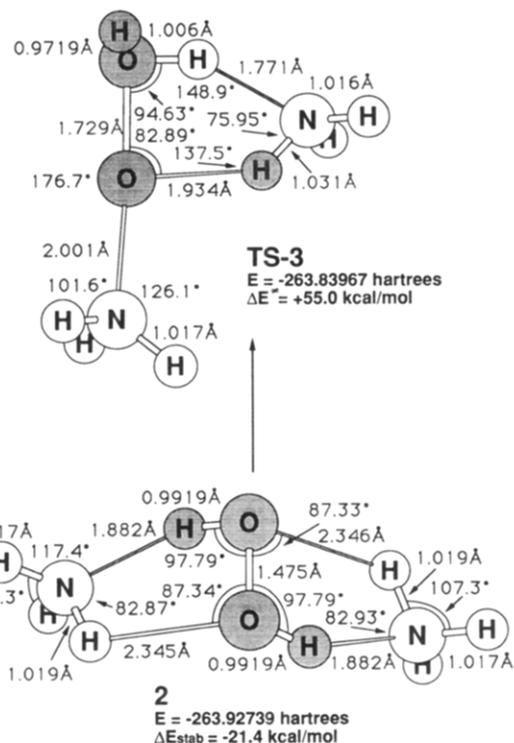
Figure 2. Oxygen atom transfer from hydrogen peroxide to ammonia catalyzed by one molecule of ammonia. Geometries are at MP2/6-31G*, and energies are at MP4/6-31G*//MP2/6-31G*.

(3)
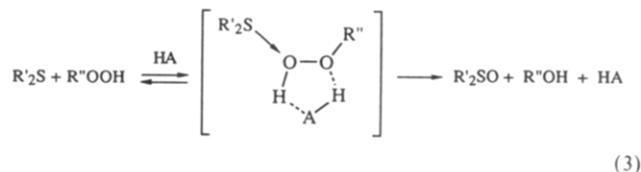
with the pK_a of solvent HA. In this part of the study we assess the effect of an increase of the pK_a of the general acid catalyst HA on the barriers for oxidation of ammonia by hydrogen peroxide.

(a) Ammonia Catalysis in Oxygen Atom Transfer from Hydrogen Peroxide. Although ammonia is a much weaker acid than water, it is also a stronger base and the possibility exists for ammonium ion catalysis resulting from partial proton transfer from H_2O_2 to NH_3. The enthalpy of complex formation between pyridine and *tert*-butyl hydroperoxide is about $\Delta H = -8$ kcal/mol.[8b] The equilibrium constant for complex formation between triethylamine and cumyl hydroperoxide in aqueous solution is $K = 0.18$ M^{-1}. The reactant cluster of $H_2O_2\cdot2NH_3$ (**2**) is stabilized (−21.4 kcal/mol) due to relatively strong hydrogen bonds (Figure 3) to about the same extent as two water molecules hydrogen bonding to H_2O_2 (**4** and **7**). The barrier height for the oxidation of ammonia (55.0 kcal/mol) is slightly higher than that calculated for oxidation with H_2O_2 without ammonia catalysis (51.9 kcal/mol, Figure 1), reflecting the stabilization of reactant cluster **2**. Although proton transfer from H_2O_2 to NH_3 was not in evidence in the ground state (**2**), the hydrogen was completely transferred from the proximal oxygen to catalyst ammonia in the transition state for the oxidation of ammonia (TS-**3**). The relatively high barrier (55.0 kcal/mol) is consistent with the water oxide nature of the transition structure resulting from a 1,4-hydrogen shift to form neutral water as a leaving group. *A molecule of ammonia hydrogen bonded to oxygen donor H_2O_2 does not exert a meaningful catalytic effect upon the rate of oxygen atom transfer.*

(b) Water Catalysis in Oxygen Atom Transfer from Hydrogen Peroxide. The potentially exorbitant barrier for oxygen transfer from H_2O_2 discussed above can be partially abated by the
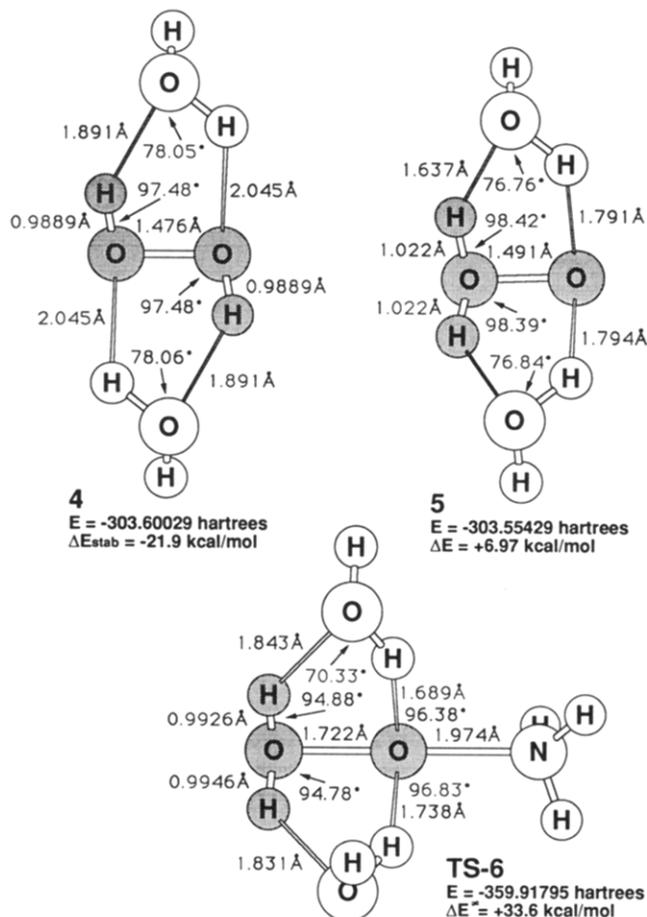
Figure 3. Hydrogen peroxide (**4**) and water oxide (**5**) hydrogen bonded to two water molecules and the transition state for oxygen atom transfer from water oxide complex **5** to ammonia (**TS-6**). Geometries were fully optimized at the MP2/6-31G* level, relative energies (MP4//MP2/6-31G*) for **4** and **5** are measured from isolated H_2O_2 and two water molecules, and the barrier for **TS-6** is computed relative to the reactant cluster with hydrogen peroxide **4**. The total energies for NH_3, H_2O, H_2O_2, and H_2OO are $-56.371\ 26$, $-76.207\ 33$, $-151.150\ 74$, and $-151.071\ 56$ au, respectively.

intervention of protic solvent molecules. The primary objective of this part of the study is to determine whether the proton shift in H_2O_2 occurs prior to or after the oxygen atom is transferred. Germane to this question is the relative energy of H_2O_2 and its dioxygen ylide form water oxide ($H_2O^+-O^-$) in solution. In a prior study[5a] we compared the oxygen donor potential of hydrogen peroxide hydrogen bonded to two molecules of H_2O (**4**) to the

comparable water oxide complex **5** (Figure 3). While $H_2O_2\cdot2H_2O$ (**4**) is stabilized by 21.9 kcal/mol, $H_2OO\cdot2H_2O$ is stabilized by 42.7 kcal/mol and is only 7.0 kcal/mol higher in energy than isolated H_2O_2 and $2H_2O$. Significantly, the energy difference between H_2O_2 and H_2OO is reduced from 49.7 to 28.9 kcal/mol when each is stabilized by two water molecules. Although water oxide is 49.7 kcal/mol higher in energy than its normal covalent form H_2O_2, it also is considerably more basic and forms much stronger hydrogen bonds to water.

We observed a profound catalytic effect of water solvent upon oxygen donation from H_2O_2 (Figure 3).[5a] On the basis of intrinsic reaction coordinate (IRC)[7c] following, the 1,2-hydrogen shift occurred prior to oxygen donation and the actual oxygen donor was solvated water oxide complex **5**. Reactant cluster **5** is 28.9 kcal/mol higher in energy than **4**, reflecting the higher energy of water oxide. The mechanism is consistent with an S_N2 attack on solvated water oxide **5** forming H_3N-O and 3 mol of water (**TS-6**). The barrier for the oxidation of ammonia by water oxide complexed to two molecules of water (**TS-6**) dropped to 11.2 kcal/mol when the barrier height was measured from isolated H_2O_2 and two H_2O molecules. However, the overall activation energy when computed from reactant cluster **4**, comprising solvated hydrogen peroxide, is predicted to be 33.6 kcal/mol.[5a]

An alternative mechanism involves proton transfer after O–O cleavage, as shown in Figure 4. In this ionic mechanism, solvated hydrogen peroxide (**7**) reacts with NH_3 to form NH_3OH^+ and the leaving group is solvated hydroxide ion ($HO\cdot2H_2O^-$). Hydrogen transfer from NH_3OH^+ to solvated hydroxide ion occurs after rate-limiting oxygen atom transfer. At this level of theory (MP4/MP2/6-31G*), hydroxide ion complexed to two water molecules (**9**) is stabilized by 73.8 kcal/mol and reactant complex **7** is stabilized by 23.7 kcal/mol. Although cyclic hydrogen peroxide cluster ($H_2O_2\cdot2H_2O$) **7** is 1.8 kcal/mol lower in energy than more symmetrical dihydrate **4**, we found that **TS-8** was 6.1 kcal/mol higher in energy than **TS-6**. The wave function for **TS-6** is RHF → UHF stable. Although **TS-8** has a small RHF → UHF instability with a negative eigenvalue (-0.036), the energy changes by less than 1 kcal/mol when recalculated at the PMP4 level (unrestricted MP4 with spin projection). Additional interactions with bulk solvent may further stabilize the ionic transition state (**TS-8**). Self-consistent reaction field (SCRF) calculations at the MP2/6-31G* level using a dielectric constant of 2.2 (dioxane solvent) predict that **TS-8** (dipole moment $\mu = 8.48$ D) is stabilized by 3.0 kcal/mol, and in a more polar solvent like acetonitrile ($\epsilon = 37.5$), **TS-8** is lowered by 7.6 kcal/mol. These data suggest that proton transfer might occur after oxygen donation if the TS is adequately solvated. Irrespective of the position of the hydrogen in the transition state, the barrier heights for hydrogen peroxide solvated by zero, one,
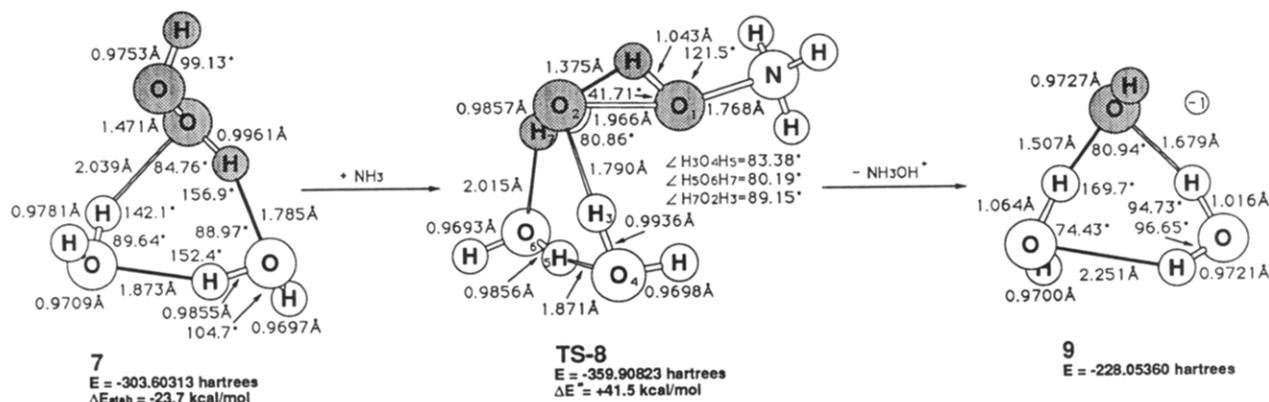
Figure 4. Ionic pathway for oxygen atom transfer from hydrogen peroxide catalyzed by two water molecules. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The activation energy ($\Delta E^\ddagger$) is computed relative to isolated NH_3 and hydrogen bonded complex **7**. The MP4//MP2/6-31G* energy of NH_3 is $-56.37\ 26$ au.

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10
E = -227.37359 hartrees
ΔE$_{stab}$ = -9.74 kcal/mol

11
E = -302.31745 hartrees
ΔE$_{stab}$ = -10.0 kcal/mol

12
E = -302.31987 hartrees
ΔE$_{stab}$ = -11.54 kcal/mol
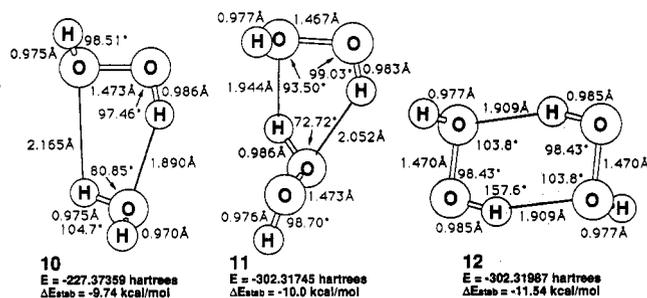
Figure 5. Hydrogen bonded complexes of hydrogen peroxide. Geometries are at MP2/6-31G*, and energies are at MP4/6-31G*//MP2/6-31G*.

or two molecules of water (40–55 kcal/mol) are still too high to be commensurate with the known oxygen donor potential of H_2O_2 in solution. Consequently, in order to get agreement with experiment, we must examine other ways of stabilizing the transition state for oxygen atom transfer from H_2O_2.

(c) Hydrogen Peroxide as the General Acid Catalyst. Spectral evidence[8b] suggests that hydroperoxide molecules may exist as cyclic hydrogen bonded dimers. Our calculations predict that the cyclic dimer of hydrogen peroxide with a water molecule (**10**) has a stabilization energy of 9.7 kcal/mol (Figure 5). The corresponding cyclic dimer of H_2O_2 (**11**) lies in a potential energy well that is 10.0 kcal/mol below two isolated H_2O_2 molecules. The more symmetrical chairlike H_2O_2 dimer **12** has a predicted $\Delta E_{stab} = -11.5$ kcal/mol. It was anticipated that H_2O_2 would hydrogen bond more strongly than H_2O because it is more acidic and the gas-phase proton affinity of its conjugate base calculated at the same level of theory (MP4//MP2/6-31G*) is 27.2 kcal/mol higher in energy (Table 2).

The stabilization energy for the complexation of $H_2O_2 \cdot H_2O$ (**10**) with NH_3 is 9.7 kcal/mol, and the barrier height for oxygen atom transfer from this reactant complex to ammonia is 39.1 kcal/mol.[5a] Reactant cluster **13** (Figure 6) derived from the lower energy chairlike H_2O_2 dimer **12** and ammonia has $\Delta E_{stab} = -24.6$ kcal/mol. Despite the potential for a proton relay involving H_2O_2 in the transition state, the barrier height for the oxidation of ammonia is still predicted to be 50.7 kcal/mol, (TS-14, Figure 6). When H_2O_2 was used as acid catalyst HA (eq 3), the activation barrier for TS-14 actually increased by 11.6 kcal/mol relative to the comparable water-catalyzed oxidative process.[5a] Although we anticipated an increased catalytic activity of H_2O_2 due to its lower pK_a of 11.75,[10b] much of this energy requirement is due to the fact that reactant cluster **13** lies 24.6 kcal/mol below isolated reactants H_2O_2 and NH_3. When the barrier height is computed relative to isolated reactants (i.e. **16** and NH_3), it is reduced to 37.6 kcal/mol (Table 2). The magnitude of this barrier is still too high to commensurate with typically observed experimental activation energies of 15–20 kcal/mol.[10]

Comparable results were obtained when five-membered ring H_2O_2 dimer **11** was attacked in an S_N2 manner by ammonia. The barrier height predicted for oxygen atom transfer (TS-**16**) was 48.1 kcal/mol when calculated from reactant cluster **15** (Figure 6). An SCRF calculation (MP2/6-31G*) using dioxane solvent ($\epsilon = 2.2$) lowered the energy of reactant cluster **15** by only 2.5 kcal/mol while TS-**16** was stabilized by 3.4 kcal/mol. Thus, the oxygen-transfer barrier in this nonpolar condensed phase is estimated to be only ~1 kcal/mol lower than the gas-phase barrier. In a manner analogous to that for oxidation with hydrogen peroxide catalyzed by two water molecules (TS-8, Figure 4), both TS-**14** and TS-**16** also involve hydroxyl transfer (HO$^+$) and the proton is transferred from the distal hydroxyl moiety on the product side of the reaction coordinate. It is particularly relevant that TS-**17**, which resembles water oxide solvated with a hydrogen peroxide molecule, is 4.0 kcal/mol higher in energy than TS-**16**. These data suggest that those oxidation reactions that were found to be second order in H_2O_2 in anhydrous nonpolar dioxane solvent[10] involved a transition state where proton transfer from the proximal oxygen (–OH) occurred *after* the oxygen-transfer step. The ionic pathway in TS-**16** also contrasts the preferred mode of water-catalyzed ammonia oxidation by CH_3OOH (TS-33) where proton transfer occurred *prior* to oxygen transfer (see below). Despite the apparent conformity of these transition structures to experimental kinetic data, *the magnitudes of predicted activation barriers are still at least a factor of 2 higher than experimental barriers.*

Since the actual experimental rate data[10] pertain to the oxidation of sulfur, we have also examined the preferred pathway for oxygen atom transfer to H_2S and $(CH_3)_2S$. We chose the higher energy H_2O_2 dimer **11** as the oxygen donor since it exhibited the lower barrier for oxidation of ammonia. We located a reactant cluster for H_2O_2 dimer complexed to H_2S (**18a**) and water oxide complexed to H_2O_2 and H_2S (**18b**). The barrier heights for H_2S oxidation relative to **18a** and **18b** are predicted to be 45.7 and 12.8 kcal/mol, respectively (Figure 7). This significant difference in barrier heights is a reflection of the higher ground state energy difference of water oxide (H$_2$OO) and the fact that **18b** is 32.9 kcal/mol higher in energy than **18a**. The barrier computed from isolated H_2S and dimer **11** is predicted to be 41.6 kcal/mol (TS-**19**). The comparable barrier for oxidation of ammonia calculated from dimer **11** and NH_3 is 35.7 kcal/mol. This relative order of reactivity for H_2S versus NH_3 is consistent with predicted gas-phase oxidation barriers with peroxyformic acid.[11]

We have also examined the effect on the activation barrier when the sulfur nucleophile is substituted with methyl groups (Figure 8). The barrier for the oxidation of dimethyl sulfide is 40.8 kcal/mol (TS-**21**) when the barrier is measured relative to reactant cluster **20a**. This is a reduction in activation energy of 4.9 kcal/mol when compared to the oxidation of H_2S at the same

Table 2. Effect of the pK_a of the General Acid (HA) on the Activation Energy (kcal/mol) for the Oxidation of Nucleophiles (:NUC = NH_3, H_2S, $(CH_3)_2S$) by Hydrogen Peroxide Complexed to HA ($H_2O_2 \cdot HA$, as in eq 3).

reactant complex	:NUC	pK_a of HA (rel to H_2O)	gas-phase proton affinity, A	gas-phase proton affinity, :NUC	transition state	ΔE^*
$H_2O_2 \cdot NH_3$ (**48**)[b]	NH_3	38	-443.0[c]	-218.5[d]	TS-3	44.5 (55.0)
$H_2O_2 \cdot H_2O$ (**49**)[b]	NH_3	15.7	-430.4	-218.5	TS-50[b]	39.6
$H_2O_2 \cdot H_2O_2$ (**12**)	NH_3	11.6	-403.2	-218.5	TS-14	37.6 (50.7)
$H_2O_2 \cdot NH_4^+$ (**22**)	NH_3	9.2	-218.5	-218.5	TS-35	6.7 (30.1)
$H_2O_2 \cdot (CH_3)_2OH^+$ (**39**)	NH_3	-3.5	-196.7	-218.5	TS-41	-3.9 (33.6)
$H_2O_2 \cdot H_3O^+$ (**36**)	NH_3	-1.7	-175.4	-218.5	TS-38	-13.8 (36.9)
$H_2O_2 \cdot H_2O_2$ (**11**)	H_2S	11.6	-403.2	-174.0	TS-23	41.6 (45.7)
$H_2O_2 \cdot H_2O_2$ (**12**)	$(CH_3)_2S$	11.6	-403.2	-203.8	TS-21	37.3 (40.8)
$H_2O_2 \cdot (CH_3)_2OH^+$ (**39**)	H_2S	-3.5	-196.7	-174.0	TS-44	6.3 (15.1)
$H_2O_2 \cdot H^+$ [e]	NH_3			-218.5	TS-24	-25.0 (47.8)
$H_2O_2 \cdot H^+$ [e]	$(CH_3)_2S$			-203.8	TS-29	-21.1 (33.2)

[a] The activation energies are computed relative to isolated reactants (i.e. $H_2O_2 \cdot HA$ and :NUC). The barriers in parentheses are computed relative to the reactant cluster ($H_2O_2 \cdot HA \cdot NUC$). All energies are at the MP4//MP2/6-31G* level. *[b]* See ref 5a for the structure and energies. *[c]* $NH_2^- + H^+ \rightarrow NH_3 + 443.0$ kcal/mol at the MP4//MP2/6-31G* level. *[d]* $NH_3 + H^+ \rightarrow NH_4^+ + 218.5$ kcal/mol. *[e]* Protonated hydrogen peroxide ($H_3O_2^+$) in the absence of A$^-$. The gas-phase proton affinities of H_2O_2 and H_2OO are -167.5 and -217.1 kcal/mol, respectively.

Figure 6. Optimized geometries for reactant clusters **13** and **15** and the transition structures for oxygen atom transfer from hydrogen peroxide dimer (TS-**14**, TS-**16**) and water oxide (TS-**17**) complexed to a molecule of hydrogen peroxide ammonia.

level of theory (Figure 7). The predicted barrier height from H_2OO cluster **20b** is predicted to be 4.7 kcal/mol. The enthalpy of activation for the oxidation of thioxane in anhydrous dioxane solvent is reported to be 15.7 kcal/mol.[10a] While the peroxide fragment in TS-**19** (Figure 7) resembles water oxide, it appears that the 1,4-proton transfer to the leaving group is actually part of the reaction vector. In TS-**21**, as evidenced by the normal mode of the imaginary frequency in the TS and by the O–H bond distances for the transferring hydrogen of 1.576 and 1.032 Å, proton transfer also occurs in concert with O–O bond cleavage. The methyl groups do exert a modest stabilizing influence on the TS for dimethyl sulfoxide formation. However, the activation barrier for TS-**21** is not yet consistent with experiment, suggesting that *general acid catalysis by such weak acids as ROH and H_2O_2 cannot provide a sufficient reduction in activation energy to render alkyl hydroperoxides useful as oxidants* in solution. Although these calculations do provide excellent support for the observed

kinetic behavior and for the involvement of a proton shift (eq 3),[10] our theoretical data suggest that additional catalytic forces must be brought into play. It should be emphasized at this juncture that activation barriers for peroxy acid epoxidation of alkenes computed at this level of theory are in excellent agreement with experiment.[5d]

Specific Acid Catalysis in Oxidations with Hydrogen Peroxide. The above calculations suggest that the activation barriers for oxygen atom transfer from H_2O_2 are only modestly decreased by general acid catalysis of HA (eq 3) when the acids (NH_3, H_2O, H_2O_2) are relatively weak. Fully protonated hydrogen peroxide ($HO–OH_2^+$) is at the other end of this reactivity spectrum. Addition of a strong acid to H_2O_2 to the level of 1 M in H^+ can raise the rate of oxidation by 2 powers of 10. In the presence of strong acids, the concentration of hydroperoxonium ion should be significant and hydroxylation by this powerful oxygen donor

Oxidation of Amines and Sulfides with Peroxides

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18b
E = -701.083601 hartrees
ΔE = +18.8 kcal/mol

ΔE‡ = 12.8 kcal/mol

TS-19
E = -701.06320 hartrees

18a
E = -701.136089 hartrees
ΔEstab = -14.2 kcal/mol

ΔE‡ = 45.7 kcal/mol
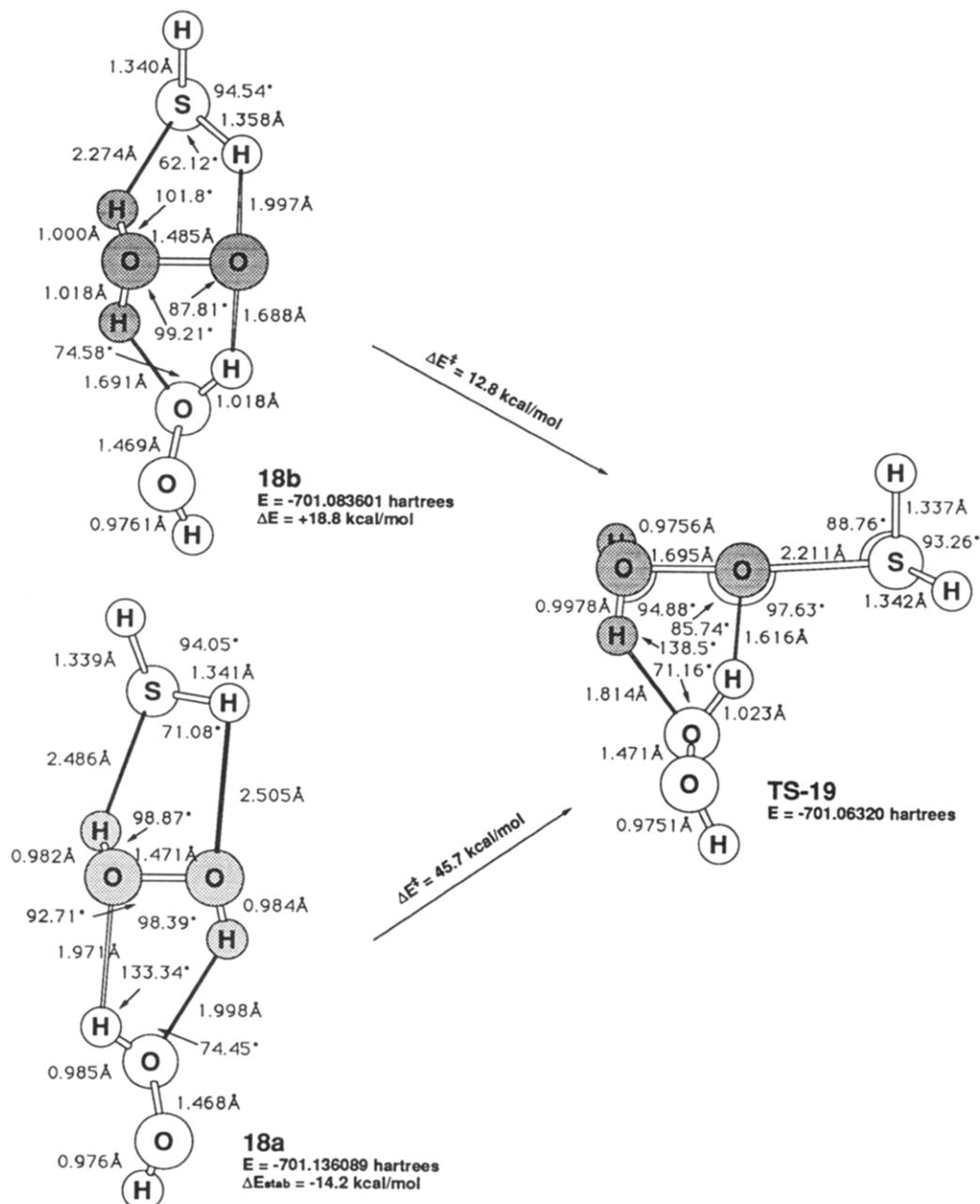
Figure 7. Oxygen atom transfer from hydrogen peroxide dimer to H_2S. Geometries are at MP2/6-31G*, and energies are at MP4/6-31G*//MP2/6-31G*. The total energy of H_2S is -398.812 00 au.

occurs by specific acid catalysis involving a two-step process (eq 4).[12] Hydroperoxonium ion is also a strong acid, and in solution,

$$\text{HOOH} + \text{H}^+ \rightleftharpoons \text{HO}-{}^+\text{OH}_2 \xrightarrow{:\text{NUC}} \text{NUC}-\overset{\oplus}{\text{OH}} + \text{H}_2\text{O} \qquad (4)$$

$$\text{NH}_3 + \text{HOO}^+\text{H}_2 \rightleftharpoons [\text{H}_3\text{N}\text{---}\text{HO}-\text{OH}_2]^+ \qquad \mathbf{23}$$

ΔE‡ = 13.7 kcal/mol

$$\underset{\oplus \quad \mathbf{25}}{\text{H}_3\text{NOH} + \text{H}_2\text{O}} \qquad (5)$$
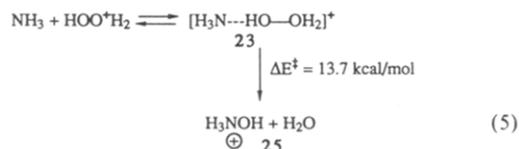
it could rapidly transfer a proton to the attacking nucleophile. Upon the basis of proton affinities (Table 2), $\text{HO}-{}^+\text{OH}_2$ is a stronger acid than H_3O^+ (7.9 kcal/mol) and much stronger than NH_4^+ (51.0 kcal/mol). In this section we examine the activation barrier for the hydroxylation of ammonia by the highly activated

hydroperoxonium ion (eq 5). In order to examine its oxygen donor potential and even attempt to relate these gas-phase data to solution chemistry, the relative energies of the protonated species and gas-phase reactant clusters must be examined. We first considered the isolated reactants H^+, NH_3, and H_2O_2 and their energies of complexation (Figure 9). Ammonia forms a hydrogen bonded complex with hydrogen peroxide with the liberation of 11.4 kcal/mol, while the complexation of ammonium ion with hydrogen peroxide has a stabilization energy of 22.3 kcal/mol (**22**, Figure 9). In order to generate reactant cluster **23**, which has an effective nucleophile with a lone pair of electrons on nitrogen, a proton shift within global minimum **22** is required. Intramolecular proton transfer from the ammonium ion of complex **22** to the hydrogen peroxide moiety affording reactant cluster **23** as a local minimum (Figure 9) is endothermic by 34.1 kcal/mol as a consequence of the differences in proton affinity between NH_3 and HOOH (Table 2). As anticipated, the barrier

(11) Predicted activation barriers (MP2/6-31G*) for the oxidation of ammonia and dihydrogen sulfide with peroxyformic acid are 21.5 and 24.9 kcal/mol, respectively (unpublished results).

(12) Edwards, J. O. In *Peroxide Reaction Mechanisms*; Edwards, J. O., Ed.; Interscience: New York, 1962; pp 67–106. See data and references cited in this review.
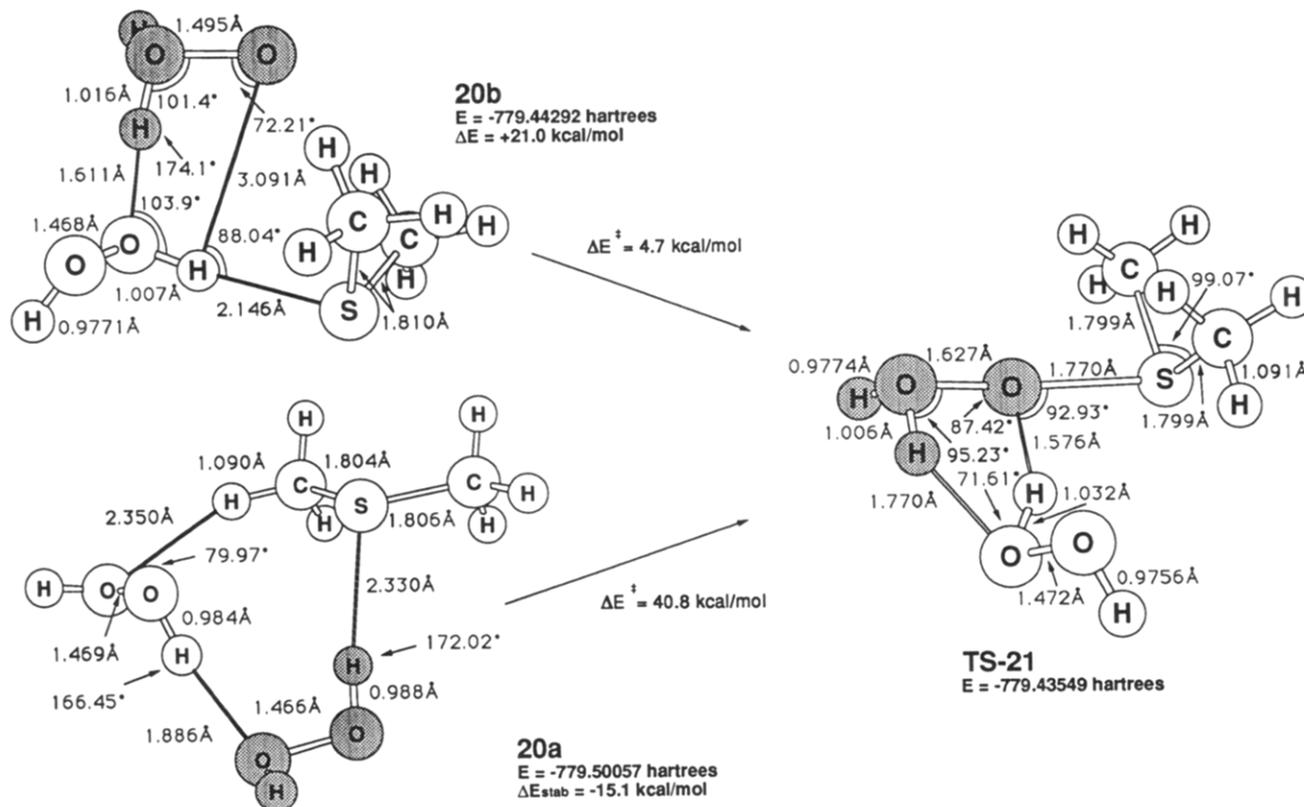
Figure 8. Oxygen atom transfer from hydrogen peroxide dimer to $(CH_3)_2S$. Geometries are at MP2/6-31G*, and energies are at MP4/6-31G*//MP2/6-31G*. The total energy of $(CH_3)_2S$ is 477.174 987 au.
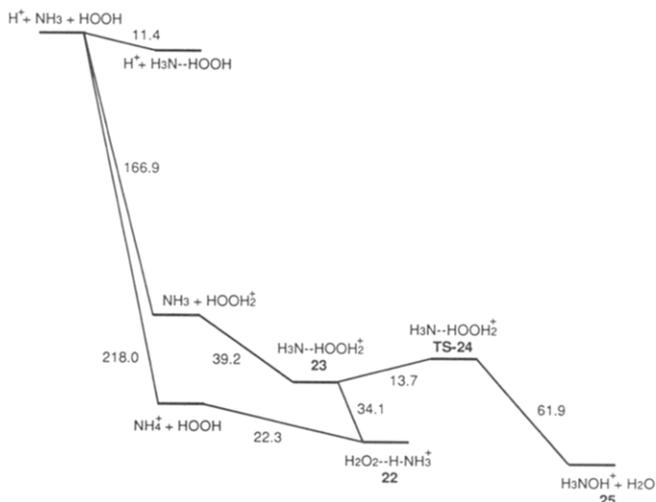
Figure 9. Relative energies (MP4//MP2/6-31G*) for the complexation of ammonium ion with hydrogen peroxide and the hydroxylation of ammonia by hydroperoxonium ion.

Figure 10. Optimized geometries of the complex of H_2O_2 with NH_4^+ (**22**), NH_3 with HO^+–OH_2 (**23**), the transition state for oxygen atom transfer from the hydroperoxonium ion to ammonia (**TS-24**), and the reaction product (**25**). Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The total energies of NH_3, NH_4^+, and HO–OH_2 are $-56.371\,26$, $-56.718\,61$, and $-151.417\,60$ au, respectively.

height for hydroxylation of ammonia (**23** → **TS-24**) affording product cluster ($H_3NOH^+ + H_2O$) **25** is only 13.7 kcal/mol, reflecting the greatly enhanced reactivity of the hydroperoxonium ion as an oxidizing agent (Figure 10). This is a relatively early TS since the developing N–O bond is quite long (2.25 Å) while the O–O bond is shorter (1.556 Å) than that typically observed (Figure 10).[5a] However, it should be recognized that at equilibrium an effective concentration of complex **23** would be insignificant and the overall gas-phase barrier from H_4N^+---HOOH complex **22** to **TS-24** is 47.8 kcal/mol. Barriers of this magnitude can be partially abated by solvation phenomena in the condensed phase.

We have also examined the barrier height for the oxidation of the more experimentally relevant substrate dimethyl sulfide by the highly reactive hydroperoxonium ion. A reactant complex

between dimethyl sulfide and neutral H_2O_2 (**26**) is stabilized by 8.9 kcal/mol (Figure 11). Due to the differences in proton affinity of $(CH_3)_2S$ and H_2O_2 (36.3 kcal/mol), the initial complex (**27**) formed between dimethyl sulfide and protonated hydrogen peroxide should resemble hydrogen peroxide hydrogen bonded to protonated dimethyl sulfide, $\Delta E_{stab} = -17.9$ kcal/mol (Figure 11). Intramolecular proton transfer in **27** to afford reactant cluster **28** is endothermic by 28.0 kcal/mol. The barrier height for hydroxylation of dimethyl sulfide (**28** → **29**) in this gas-phase reaction is markedly reduced relative to the uncatalyzed oxygen-transfer reactions described above. The $\Delta E^\ddagger = 5.1$ kcal/mol for **TS-29** is consistent with the established reactivity of hydrogen peroxide in the presence of strong acids. For example, the predicted barrier height for the hydroxylation of isobutane at this level of theory is 2.16 kcal/mol when computed relative to
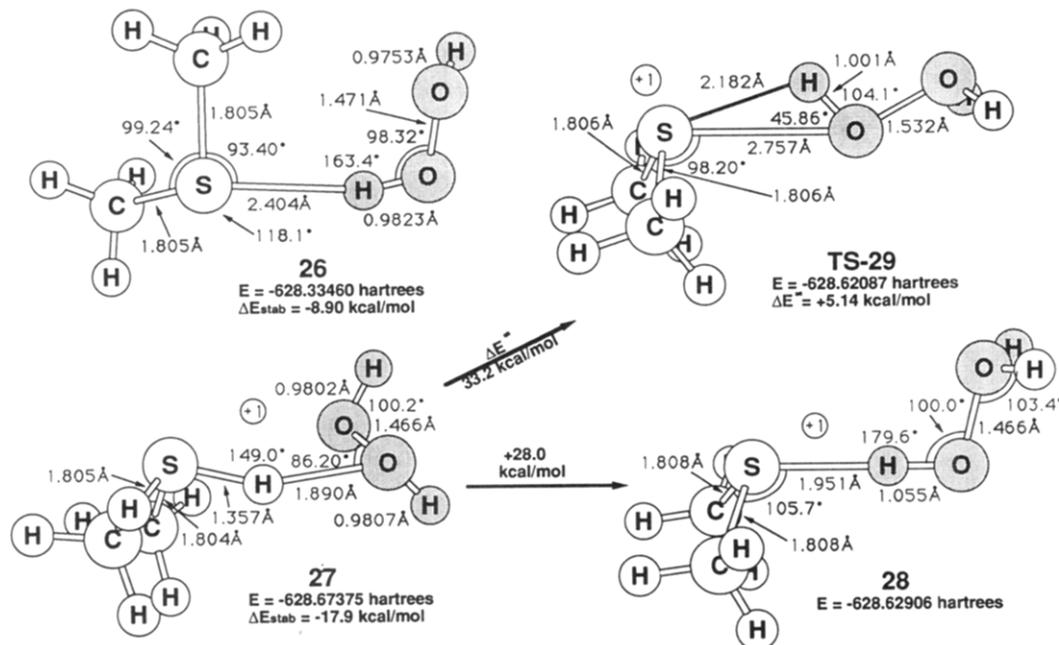
Figure 11. Oxygen atom transfer from protonated hydrogen peroxide to dimethyl sulfide. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The total energies of $(CH_3)_2S$, $(CH_3)_2SH^+$, and H_2O_2 are $-477.169\,68$, $-477.494\,51$, and $-151.150\,74$ au, respectively.

a gas-phase reactant cluster.[5e] The overall gas-phase barrier (**27** → **29**) of 33.2 kcal/mol represents a significant reduction in activation energy for this type of oxidation reaction. These data also point out a serious dilemma for the experimentalist. Although a protonated hydroperoxide is a powerful oxidant, in the presence of strong acid, the nucleophile is typically a stronger base and it is also protonated, incapacitating its nucleophilicity. However, a comparison of the barrier heights for TS-**29** when measured from **27** versus **28** strongly implicates a mechanism in the condensed phase where **28** can be derived from a proton relay involving bulk solvent.

A study of this nature also presents a dilemma for the theoretician. Ideally gas-phase barriers should be reported relative to a gas-phase reactant cluster. However, the series of general acids (HA) included in this study covers a wide range of acidities that markedly influence the depth of the potential energy well for the reactant cluster. The nucleophiles employed also exhibit differences in basicity that influence the relative energy of the starting material (cluster) and the transition state. For example, reactant cluster **18a** derived from H_2O_2 dimer and the weakly basic nucleophile H_2S has a $\Delta E_{stab} = -14.2$ kcal/mol. By contrast, ΔE_{stab} for reactant cluster **40** comprising $(CH_3)_2OH^+$, H_2O_2, and NH_3 is 62.9 kcal/mol below the energy of its isolated components. If solvation effects in the condensed phase do not parallel the gas-phase stabilities then a comparison between relative activation barriers in the two phases may be in error. The effect of the pK_a on these activations barriers is dramatically demonstrated by a calculation of $\Delta E^{\ddagger}$ from isolated reactants (Table 2). When the pK_a is varied from 38 (NH_3) to -1.7 (H_3O^+), the activation barrier decreases from 44.5 to -13.8 kcal/mol.

Oxygen Atom Transfer from Methyl Hydroperoxide. Replacement of one of the hydrogens of H_2O_2 with an alkyl group has an effect upon the dissociation enthalpy ($\Delta H°$) of the O–O bond. For example, while HO–OH has a bond energy of 49.7 kcal/mol,[8e] the O–O bond energies of CH_3O–OH and CH_3O–OCH_3 are 45 and 38 kcal/mol, respectively.[8a] However, the activation energy for unimolecular heterolysis (eq 6) in the gas

$$ZO{-}OY \rightarrow YO^+ + YO^- \qquad (6)$$

phase is predicted to be 5–8 times larger than that for homolytic cleavage. The estimated energies required for heterolytic cleavage of HO–OH, CH_3O–OH, and CH_3O–OCH_3 are 313, 194, and

193 kcal/mol, respectively.[8a] Replacement of a hydrogen with a methyl group has a significant effect upon the stability of oxacation CH_3O^+. In the gas phase, a larger alkyl group such as *tert*-butyl would have an even greater effect upon heterolytic cleavage, while in solution in protic solvent, it may not be as well solvated as the smaller methyl group. Obviously solvent polarity and a reduction in charge separation in the transition state for oxygen atom transfer will play a major role in oxygen-transfer reactions involving the formation of ion pairs in solution. Coulombic effects that serve to stabilize the developing negative charge of an alkoxide leaving group can also dramatically lower the activation barrier for oxygen transfer.[5f]

We next examined the effect of replacing a hydrogen with an alkyl group on the position of the proton in the transition state for oxygen atom transfer. In heterolytic S_N2 displacement reactions of this type the net atomic event is the transfer of an electrophilic HO^+ to the nucleophilic substrate. A major question to be addressed in this part of the study is whether the stabilizing influence of a methyl substituent could alter the mechanism for oxygen atom transfer from a hydroperoxide. We first examined the pathway similar to that found for HOOH (TS-**1**) where the proton is transferred *prior* to oxygen transfer. The predicted barrier height for direct oxygen transfer from methanol oxide to ammonia (TS-**30**) is 53.0 kcal/mol when the barrier is measured from CH_3OOH (Figure 12). This barrier is actually 1.1 kcal/mol higher than that for TS-**1**. Although we were unable to locate a transition state for oxygen atom transfer from H_2O_2 to ammonia where OH^- is the leaving group in the absence of water catalysis,[5a] the stabilizing influence of the methyl group does provide a pathway where the proton shift occurs *after* the oxygen-transfer step (TS-**31**, Figure 12). In this reaction the nucleophile electron pair of NH_3 attacks the distal peroxide oxygen, with a transition state involving N–O bond formation in concert with O–O bond breaking. An IRC analysis[7c] has established the proton shift from H_3NOH^+ to CH_3O^- to occur *after the barrier is crossed* (Figure 13). However, the normal mode for the single imaginary frequency for TS-**31** still has a large component of hydrogen transfer. Significantly, TS-**31** is 6.5 kcal/mol lower in energy than oxygen atom transfer from methanol oxide (TS-**30**) where proton transfer has occurred prior to oxygen atom transfer. The reversal in the mechanism for CH_3OOH versus HOOH[5a] is a reflection of the stabilizing influence of a methyl group on a
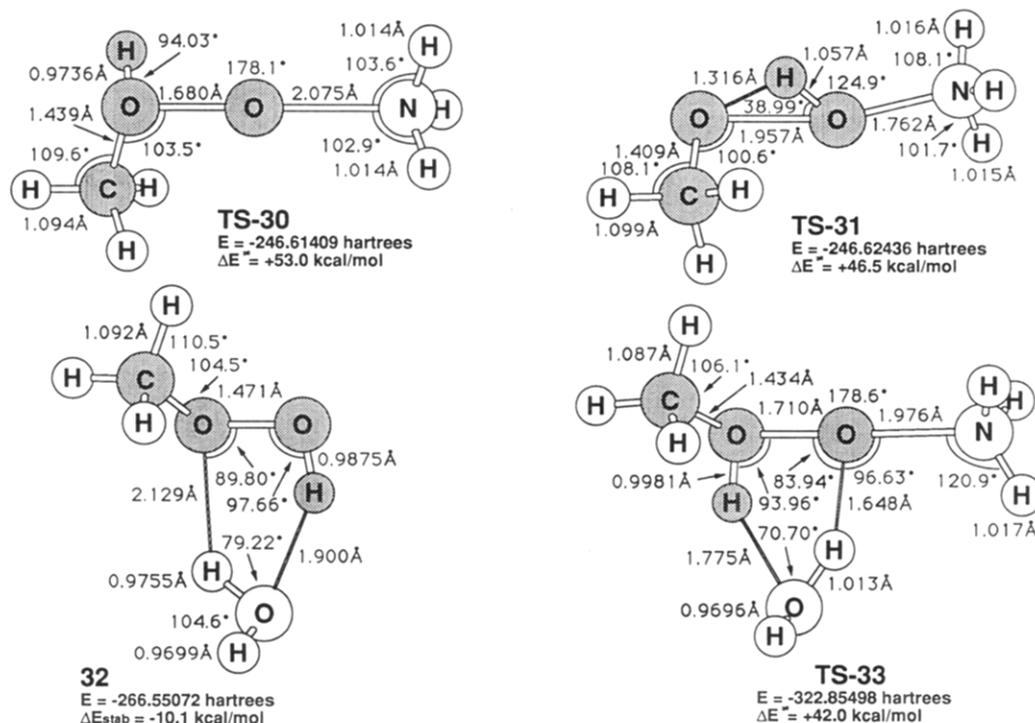
Figure 12. Transition structures for oxygen atom transfer from methyl hydroperoxide with proton transfer before (TS-**30**) and after (TS-**31**) oxygen atom transfer with (TS-**33**) and without (TS-**31**) water catalysis. Geometries were calculated at MP2/6-31G* and barriers at MP4/6-31G*//MP2/6-31G*. The total energy of CH_3OOH is −190.327 24 au.
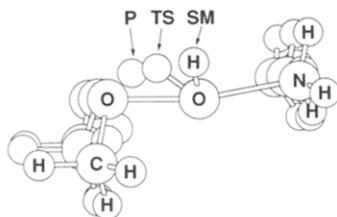
Figure 13. Three points along the reaction path for oxidation of ammonia by methyl hydroperoxide by the reaction path following the algorithm at the MP2/6-31G* level of theory: SM, a point along the reaction path from starting materials; TS, transition state (TS-**31**); P, a point on the reaction path toward the products.

gas-phase anion. A qualitative estimate of the greater stability of CH_3O^- as a leaving group can be obtained by calculating the difference in proton affinity of CH_3O^- and OH^- (22.3 kcal/mol). In the absence of water catalysis, these data are consistent with a reaction pathway for oxygen atom transfer from an alkyl hydroperoxide where *proton transfer to the departing alkoxide group occurs after the barrier is crossed*. A similar mechanism has been invoked for oxygen transfer from peroxy acids where an intramolecular 1,4-hydrogen transfer to the carbonyl oxygen is involved.[9a,b] However, at this level of theory, the barrier heights for oxidation of ammonia by HCO_3H and CH_3OOH are 21.5 and 46.5 kcal/mol in the absence of water catalysis.

As a compliment to our earlier work on the role of water catalysis with hydrogen peroxide,[5a] we have also the examined the stabilizing influence of a water molecule upon the heterolytic cleavage of the O–O bond in CH_3OOH. Nucleophilic attack by ammonia on the reactant cluster of CH_3OOH and H_2O (**32**, Figure 12) resulted in oxygen atom transfer (TS-**33**) with an activation barrier (42.0 kcal/mol) that is 4.5 kcal/mol lower than oxidation in the absence of water catalysis (TS-**31**). When a water molecule is present, the reaction pathways involves a *1,4-hydrogen shift from the water catalyst to the departing methoxide anion prior to the oxygen-transfer step (TS-**33**) in excellent agreement with the mechanism suggested by eq 3.*

Proton Transfer to Hydrogen Peroxide in the Oxygen-Transfer Step. Both H_2O_2 and ROOH are viable oxidizing agents of

moderate reactivity at room temperature. Some form of activation of the O–O bond such as an α-carbonyl group in a peroxy acid or metal catalysis is often employed in order to increase the efficacy of the −OOH moiety as an oxidizing agent. Indeed, the magnitudes of the predicted barrier heights (48–52 kcal/mol) for general acid catalyzed oxidation with hydrogen peroxide dimers **11** and **12** strongly suggest that some additional type of catalysis is essential in order to get agreement with experiment. We therefore devised a model system that examined the possibility that a concerted proton transfer from bulk solvent to the leaving group was actually responsible for the discrepancies between the computed and experimentally observed activation barriers. To test this hypothesis we utilized initially the ammonion ion as a weak acid catalyst. In principle, as noted above, this acid catalyst can be derived in solution by a proton transfer from H_2O_2 to an amine. The binding energy of the initial complex between NH_4^+ and H_2O_2 affording **26** (Figure 10) is 22.3 kcal/mol. The reactant cluster (**34**) derived from **26** and the nucleophile ammonia is further stabilized by 23.4 kcal/mol (Figure 14). The ammonium ion exerts a strong catalytic influence upon the activation energy for oxygen atom transfer from H_2O_2. In the absence of NH_4^+ catalysis, the barrier height for the oxidation of NH_3 is 62.8 kcal/mol when calculated relative to the $H_3N \cdot H_2O_2$ cluster.[5a] Oxygen atom transfer for reactant cluster **2** ($H_2O_2 \cdot 2NH_3$) has a barrier of 55.0 kcal/mol (TS-**3**). However, with NH_4^+ catalysis, TS-**35** is only 30.1 kcal/mol above reactant cluster **34** and 6.7 kcal/mol above the energies of isolated reactants **22** and NH_3. We attribute the 24.9 kcal/mol reduction in the activation energy to the acidity of NH_4^+ but, more specifically, to the concerted proton transfer in the TS that affords water as a neutral leaving group. Significantly, the proton transfer from NH_4^+ to the departing hydroxide ion leaving group is part of the reaction vector. In TS-**35** the N–H bond that is breaking and the developing H–O bond have bond distances of 1.398 and 1.141 Å, respectively.

If the above contention concerning the concerted nature of the intermolecular proton transfer in the transition state has merit, then the hydronium ion, a much stronger acid than NH_4^+ ($\Delta\Delta E$ = 43.1 kcal/mol), should prove to be an even more effective
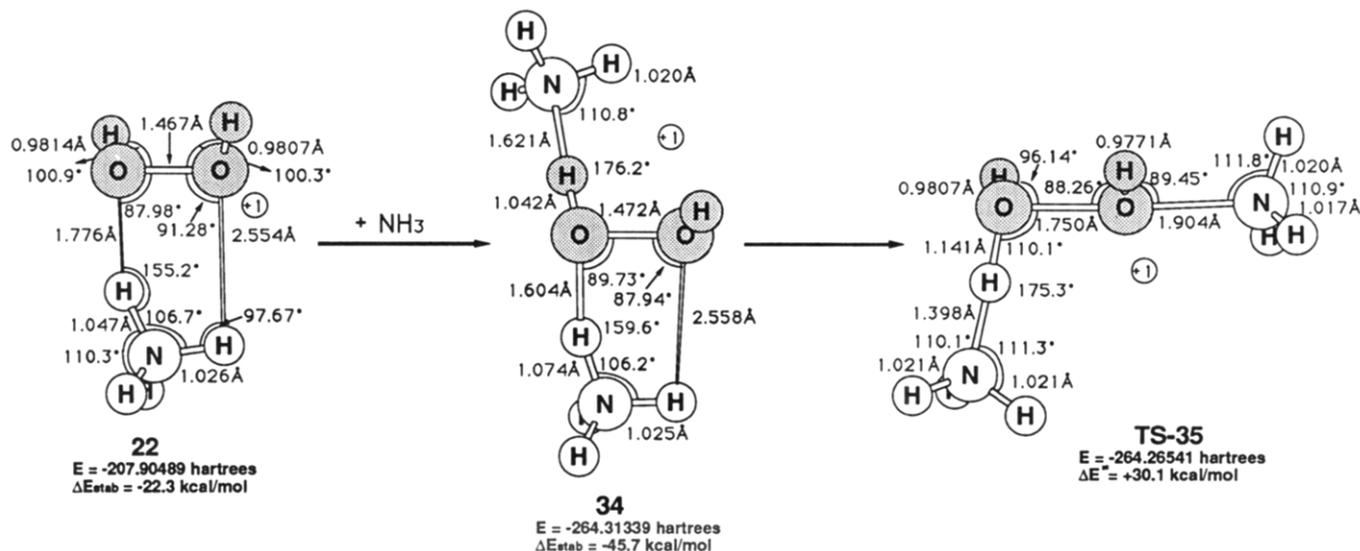
Figure 14. Concerted oxygen atom transfer from hydrogen peroxide to ammonia catalyzed by the ammonium ion. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The total energy is NH_3 is −56.371 26 au.
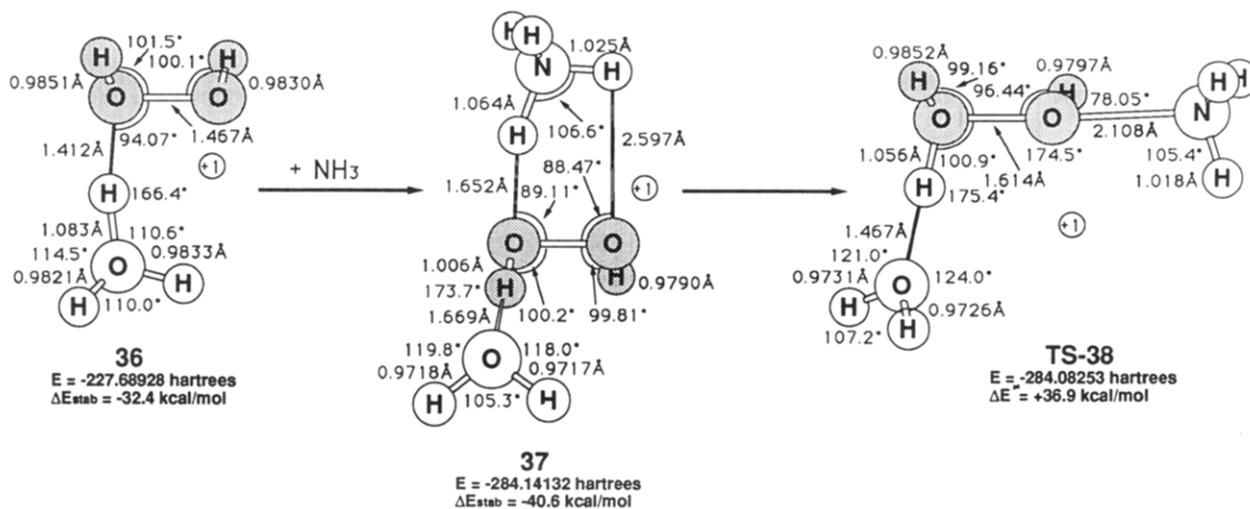
Figure 15. Hydronium ion catalyzed oxygen atom transfer from hydrogen peroxide to ammonia. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The total energies of H_3O^+, NH_3, and H_2O_2 are −76.486 87, −56.371 26, and −151.150 74 au, respectively.

catalyst. The binding energy of H_3O^+ and H_2O_2 (**36**) is −32.4 kcal/mol (Figure 15). However, formation of the reactant cluster **37** between **36** and NH_3 is attended by a proton transfer to NH_3 and **37** is 40.6 kcal/mol below its isolated reactants. Although the transition state (TS-**38**) for the oxidation of ammonia is 13.8 kcal/mol *below* isolated reactants **36** and NH_3, its barrier height relative to reactant cluster **37** is 36.9 kcal/mol as a consequence of the depth of the potential well for the reactant cluster. As anticipated on the basis of the increased acidity of catalyst H_3O^+ relative to NH_4^+, TS-**38** comes earlier along the reaction coordinate than TS-**35** and the proton transfer is more complete.

The fundamental reaction studied by Edwards and his collaborators[10] in their definitive kinetic experiments on the oxidation of disulfides employed H_2O_2 in anhydrous dioxane solvent (ϵ = 2.2). In an effort to mimic this experiment, we utilized initially NH_3 as the substrate and dimethyl ether oxonium ion as the putative acid catalyst produced in bulk solvent from proton transfer from hydrogen peroxide to dioxane (Figure 16). Although these oxidation reactions were second order in hydrogen peroxide, computational limitations preclude our using the dimer of hydrogen peroxide for the oxidation of NH_3. Using H_2O_2 monomer as the oxygen donor, our calculations predict that reactant cluster **40** is 37.5 kcal/mol below NH_3 and hydrogen bonded complex **39** (Figure 16). The barrier height for the oxidation of NH_3 (TS-**41**) is predicted to be 33.6 kcal/mol above

reactant cluster **40** as a consequence of the depth of the potential energy well for **40** relative to its isolated components (−62.9 kcal/mol). In TS-**41** proton transfer from protonated dimethyl ether to the departing hydroxide ion leaving group takes place in concert with the transfer of HO^+ to the nucleophile ammonia.

When a weaker base such as H_2S is used as the nucleophile, reactant complex **43** (Figure 17) is predicted to be stabilized by only 8.75 kcal/mol relative to its isolated components (H_2S + **42**). However, **43** is 34.1 kcal/mol lower in energy than its isolated components. Significantly, the barrier height for the oxidation of H_2S (TS-**44**) is only 15.1 kcal/mol. This barrier is now in good accord with experiment where the E_a for the oxidation of thioxane in dioxane is reported to be 16.3 kcal/mol. If we were to use dimethyl sulfide as the substrate and the dimer of hydrogen peroxide as the oxidant then this barrier would obviously be lowered. A word of caution is in order when discussing the magnitude of these barrier heights because as noted above the basicity of the nucleophile determines the depth of the potential energy well for these gas-phase clusters. Consequently, the activation barriers will also parallel to some extent the relative stability of these reactant clusters. Therefore in the absence of solvation, we place much more emphasis upon the reduction in activation barriers within a given series that has a common nucleophile (Table 2).
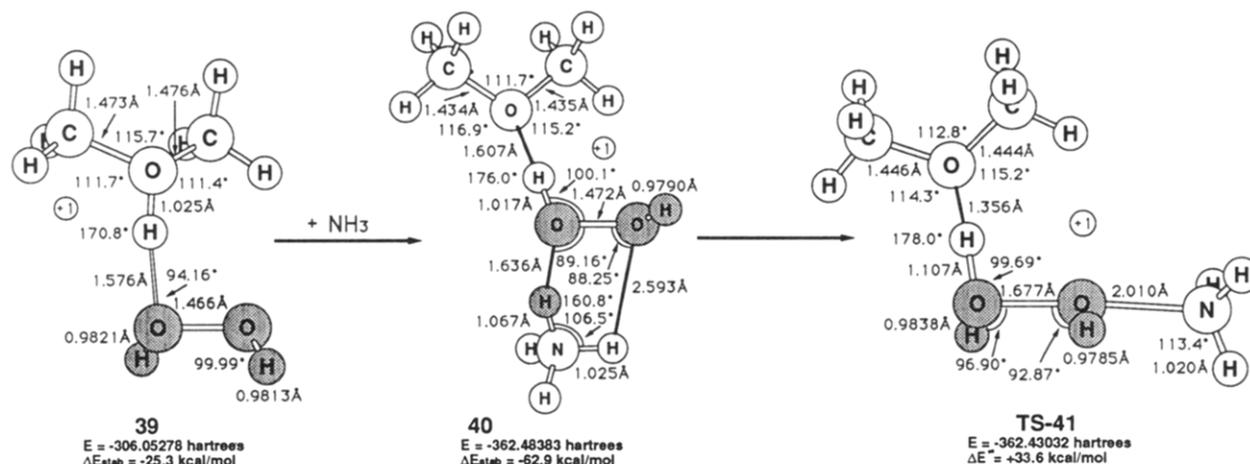
Figure 16. Concerted oxygen atom transfer from hydrogen peroxide to ammonia catalyzed by ammonium and dimethyl ether oxonium ions. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*.
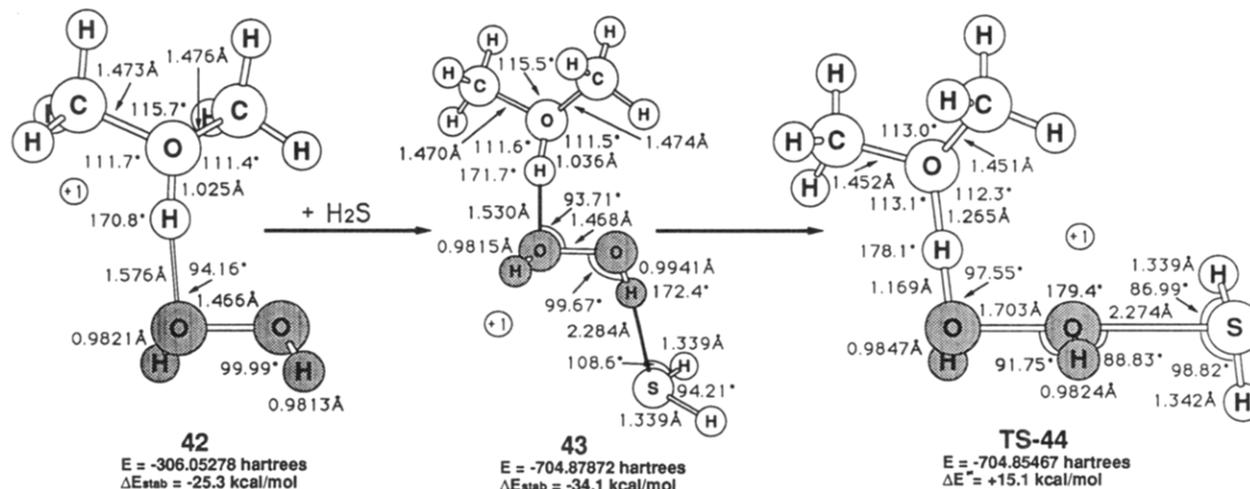
Figure 17. Oxygen atom transfer to dihydrogen sulfide catalyzed by dimethyl ether oxonium ion. Geometries are at MP2//MP2/6-31G*, and energies are at MP4//MP2/6-31G*. The total energies for $(CH_3)_2OH^+$, H_2O_2, and H_2S are -154.861 65, -151.150 74, and -398.812 00 au, respectively.

Summary

Two of the most fundamental questions concerning the mechanism of oxygen atom transfer from the hydroperoxy functional group (–OOH) have been examined: firstly, the position of the hydrogen in the transition state, and secondly, the effect of acid catalysis on the activation barrier for the oxygen-transfer step. In the absence of general acid catalysis by water, oxidation reactions involving an alkyl hydrogen peroxide (CH_3-OOH) proceed by an ionic pathway where proton transfer takes place after rate-limiting oxygen transfer (TS-**31**). With water catalysis, a 1,4-hydrogen shift precedes the oxygen-transfer step and methanol is formed as a neutral leaving group (TS-**33**).

With general acid catalysis by weak acids (H_2O, H_2O_2), oxidation by hydrogen peroxide involves proton transfer after O–O bond cleavage (TS-**8**, TS-**16**) and the net atomic motion involves transfer of a "hydroxyl cation" to the nucleophile. A 1,4-hydrogen shift mechanism is favored for oxidation of H_2S and $(CH_3)_2S$ by hydrogen peroxide dimer **11** (TS-**19**, TS-**21**) in excellent accord with experiment. Thus, a delicate balance exists between an ionic mechanism and a concerted 1,4-hydrogen shift that is a function of both the alkyl group on the ROOH and the nature of the nucleophile. However, *all of the above oxidation reactions have activation barriers ranging from 36 to 48 kcal/ mol. Barrier heights of this magnitude tend to exclude general acid catalysis by weak acids as the primary source of activation of O–O bond rupture in hydroperoxides.*

Hydroperoxonium ion is a highly reactive hydroxylation reagent, and the hydrogen remains firmly bonded to the "electrophilic" oxygen atom until after the oxygen-transfer step (TS-**24**, TS-**29**). The low barrier heights and transition structures support the two-step specific acid-catalyzed pathway suggestion by eqs 4 and 5.

Ab initio calculations provide strong support for the kinetic data,[10] implicating general acid catalysis with weak acids HA for hydroperoxides in both nonpolar and protic solvents (eq 3). Additionally, a concerted proton transfer from bulk solvent to the departing hydroxide (alkoxide) ion has been invoked in order to reduce the overall activation energy to a point where it is consistent with experiment (TS-**44**).

As a result of the above theoretical study on the nature of the transition state for oxygen transfer from a hydroperoxide, we now suggest a unifying mechanism that is consistent with both experiment and theory. We propose a reaction pathway where HA (e.g. H_2O) serves to stabilize the OH group of –OOH by hydrogen bonding (**45**) and a proton transfer from bulk solvent that provides a neutral leaving group (**46**, Figure 18). Although inclusions of protonated bulk solvent in the TS for H_2S oxidation reduced the barrier for TS-**44** to 15.1 kcal/mol, when both protonated solvent (H_3O^+) and a general acid catalyst $HA(H_2O)$ are employed, the barrier height for the transfer of HO^+ is reduced to 5.96 kcal/mol (TS-**47**) when computed relative to reactant cluster **46**. It is significant that the barrier height for H_2S oxidation is less than 6 kcal/mol despite the fact that the reactant cluster is 60.6 kcal/mol below its isolated components. The stabilization energy of **46** relative to **45** and H_2S is only 7.5 kcal/
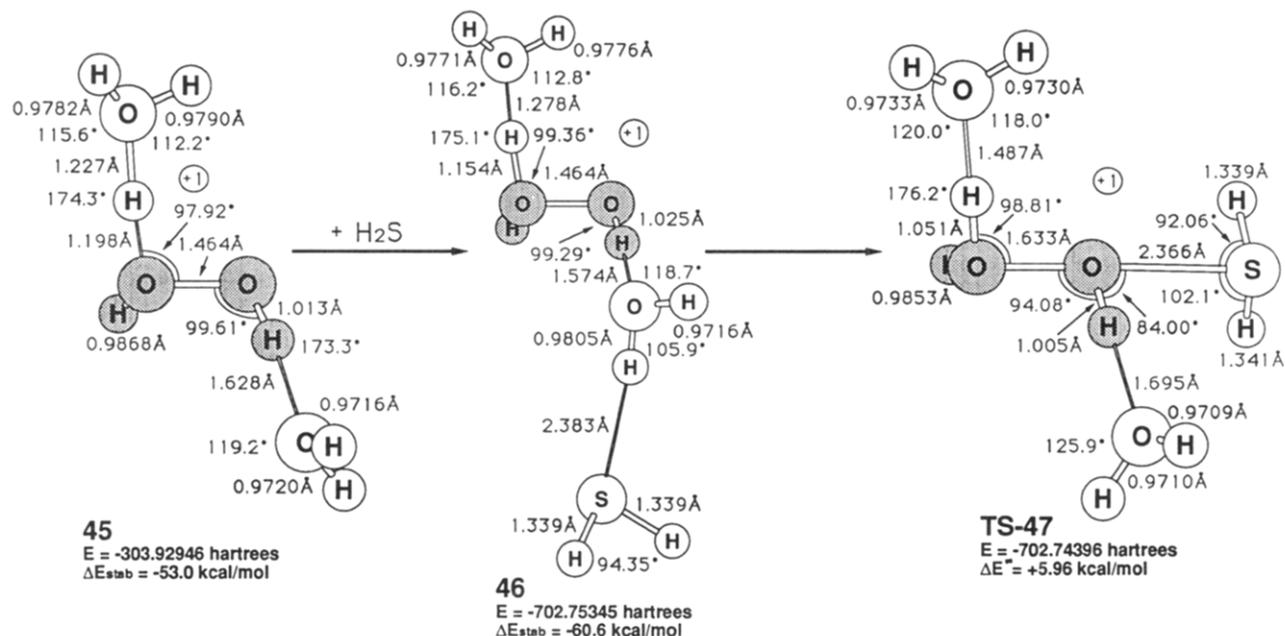
Figure 18. Oxidation of H_2S by H_2O_2 with H_3O^+ catalysis and H_2O stabilization of H_2SOH^+. Geometries are at MP2/6-31G*, and energies are at MP4//MP2/6-31G*.

mol, reflecting the weakly basic nucleophile H_2S. These data suggest that the primary role of HA in eq 7 is to stabilize the

$$R'_2S + HOOR'' \xrightarrow{R_2OH^+} \left[\begin{array}{c} R'_2S \\ \vert \\ O-O\cdots H-O^+ \overset{R}{\underset{R}{\diagdown}} \\ \vert \\ H \\ \vdots \\ HA \end{array} \right] \longrightarrow R'_2S\text{-}OH\cdots AH + R''OH + R_2O$$
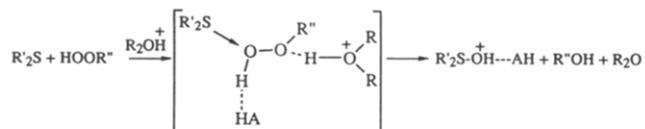
(7)

developing positive charge on the kinetic product of oxygen transfer, the R'_2SOH group, while a concerted proton transfer from bulk solvent (R_2O-H^+) to the distal oxygen provides a neutral leaving group (eq 7). When both HA and protonated solvent act in unison to stabilize the transition state, the activation barrier

for oxygen atom transfer is now reduced to a point consistent with the observed reactivity of hydroperoxides. Consistent with this suggestion, the rate of sulfide oxidation does exhibit a linear relationship with the pK_a of the protic solvent.[10] The overall mechanism involves proton transfer from the solvent to the peroxide, transfer of OH^+ to the nucleophile stabilized by HA, and deprotonation of the product.