

On the Mechanisms of Oxidation of Organic Sulfides by H₂O₂ in Aqueous Solutions

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Abstract: The mechanism of oxidation of organic sulfides in aqueous solutions by hydrogen peroxide was investigated via ab initio calculations. Specifically, two reactions, hydrogen transfer of hydrogen peroxide to form water oxide and the oxidation of dimethyl sulfide (DMS) by hydrogen peroxide to form dimethyl sulfoxide, were studied as models of these processes in general. Solvent effects are included both via including explicitly water molecules and via the polarizable continuum model. The former was found to have a much more significant effect than the latter. When explicit water molecules are included, a mechanism different from those proposed in the literature was found. Specific interactions including hydrogen bonding with 2–3 water molecules can provide enough stabilization for the charge separation of the activation complex. The energy barrier of the oxidation of DMS by hydrogen peroxide was estimated to be 12.7 kcal/mol, within the experimental range of the oxidation of analogous compounds (10–20 kcal/mol). The major reaction coordinates of the reaction are the breaking of the O–O bond of H₂O₂ and the formation of the S–O bond, the transfer of hydrogen to the distal oxygen of hydrogen peroxide occurring after the system has passed the transition state. Reaction barriers of the hydrogen transfer of H₂O₂ are an average of 10 kcal/mol or higher than the reaction barriers of the oxidation of DMS. Therefore, a two-step oxidation mechanism in which, first, the transfer of a hydrogen atom occurs to form water oxide and, second, the transfer of oxygen to the substrate occurs is unlikely to be correct. Our proposed oxidation mechanism does not suggest a pH dependence of oxidation rate within a moderate range around neutral pH (i.e., under conditions in which hydronium and hydroxide ions do not participate directly in the reaction), and it agrees with experimental observations over moderate pH values. Also, without including a protonated solvent molecule, it has activation energies that correspond to measured activation energies.

Introduction

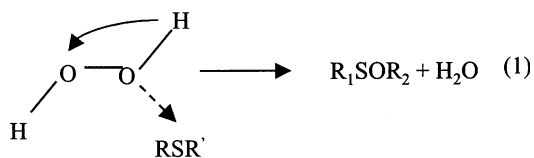
Oxidation is an important chemical process, prevalent throughout chemistry. It leads to significant changes in the properties of organic and biological compounds.^{1,2} Peroxides, including hydrogen peroxide, hydroperoxides, and peroxy acids, are efficient oxidants of organic sulfides in aqueous solutions.³ For instance, the oxidation of methionine groups by hydroperoxides is a major way by which therapeutic proteins are degraded.^{4–8} Designing a storage formulation that hinders oxidation of these sites and thus provides an acceptable shelf life is one of the most challenging tasks in the process of drug development. To move beyond trial and error, empirical approaches to design a storage formulation, an accurate quantitative, molecular-level understanding of the process would be helpful. Another example

is the oxidation of dimethyl sulfide (DMS) in the atmosphere. DMS is emitted steadily by ocean phytoplankton and is the major source of sulfur in the troposphere.⁹ Dimethyl sulfoxide (DMSO) is the first product of the aqueous phase oxidation of DMS by hydroperoxides and occurs in both rain^{10–12} and snow.¹³ Knowledge of the kinetics and mechanism of DMS oxidation should be helpful in understanding the contribution of DMS to acid rain formation and its effects on the climate.¹⁴ In summary, a correct understanding of the oxidation mechanism of organic sulfides by peroxides would be of use in organic chemistry, biochemistry, and atmospheric chemistry.

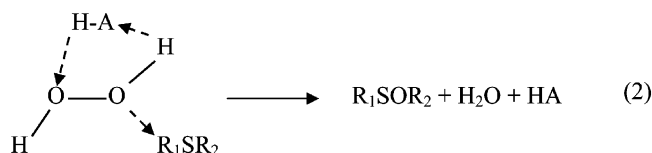
Before 1968, the oxygen transfer from hydroperoxides to nucleophilic substrates in solution was generally accepted to be an S_N2 type displacement (eq 1) reaction:^{3,15,16}

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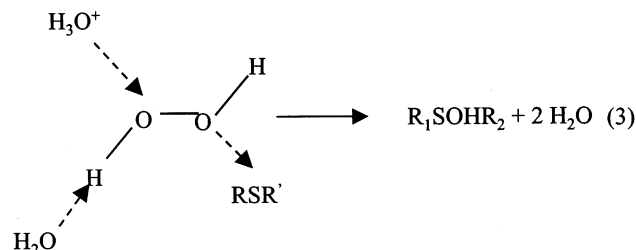


In this mechanism, the transfer of oxygen is associated with a hydrogen shift to the distal oxygen. In 1968, Dankeff et al.¹⁶ proposed the mechanism in eq 2, based on their data of solvent effects on the oxidation of thioxane by hydrogen peroxide. HA is a general acid, for example, a solvent molecule, and was thought to serve as an intermediate agent which reduced the charge separation of the activation complex via proton transfer.¹⁶ Specifically, they found that the rates of oxidation in different solvents correlate better to solvent acidity (pK_a) than to solvent polarity (dielectric constant). Moreover, transferring the reaction to an aprotic solvent led to an increase in the reaction order of hydrogen from 1 to 2, strong evidence that the second hydrogen peroxide played the role of the generalized acid. The schematic picture of eq 2 has been generally accepted to be the mechanism of oxidation of organic sulfides via peroxides.^{3,6,7,15–19}



Starting in 1991, to evaluate the plausibility of eq 2 and other hypothesized reaction mechanisms, ab initio studies on peroxide oxidation have been performed both for the hydrogen transfer reaction of hydrogen peroxide^{20,21} and for the oxidation of amines and sulfides with hydrogen peroxide.^{18,20,22} The attempt of those studies was to develop a more detailed understanding of the oxidation mechanism. Important questions that were discussed include the following: what are the roles of the general acid? What are the essential reaction coordinates? What is the order by which the transfer of oxygen and hydrogen proceeds? What are the predicted activation energies, and how do they compare with experimental values? The last question was the most important in that proposed reaction mechanisms were accepted or eliminated depending on how their energy barrier compared to experimental values. For example, the direct 1,2 hydrogen transfer of H₂O₂ in a vacuum was found via ab initio computations to have a very high energy barrier (56 kcal/mol),^{20,23} but typical observed activation barriers for peroxide oxidation of amines and organic sulfides in aqueous solutions are in the range of 10–20 kcal/mol.^{3,16,24,25} On this basis, the direct 1,2 hydrogen transfer of H₂O₂ was assumed not to be the correct mechanism. In general, however, ab initio calculations of the mechanism eq 2 yielded activation barriers in the

range of 28–50 kcal/mol,^{18,20–22} all much higher than the range of experimental data (10–20 kcal/mol).^{3,16,24,25} Therefore, Bach et al.¹⁸ concluded that general acid alone cannot catalyze the oxidation reaction. On the other hand, when both a protonated solvent and a general acid are present (eq 3), the calculated energy barriers lie between 5 and 15 kcal/mol, within the experiment range.¹⁸



This was, thus, concluded by Bach et al. to be the reaction mechanism.^{18,26} Note that, by this mechanism (eq 3), the oxidation rate should decrease with increasing pH. However, after the proposal of this mechanism, it was found that the dependence on pH of the rate of oxidation of DMS ($\text{pH} = 2–10$)¹⁴ and of methionine residues in human parathyroid hormone ($\text{pH} = 2–8$)²⁷ was negligible in aqueous solution. In general, experimental observations do not indicate a pH dependence of peroxide oxidation between $\text{pH} = 2$ and $\text{pH} = 10$. However, an increase in oxidation rate is observed when the pH is low (<2), indicating that the mechanism proposed by Bach et al. (eq 3) could be valid at low pH values but is unlikely to occur at moderate pH values. Thus, the question remains: what is the mechanism of oxidation of sulfur sites in organics?

In this study, we address this question by analyzing proposed oxidation mechanisms using high level ab initio simulations with the objective of finding a mechanism that is consistent with all experimental observations in moderate pH ranges. We carefully include both the specific effects of solvent molecules and the effects of the solvent as a polarizable dielectric continuum. It turns out that including water molecules explicitly leads to a new reaction mechanism, which is consistent with all experimental data.

Methods of Calculations

Ab initio calculations were performed using the Gaussian 98 package.²⁸ B3LYP (Becke's three-parameter functional²⁹) with the 6-31++G(d,p) basis set was employed for geometry optimizations, transition-state searches, and frequency calculations throughout this study; a scaling factor of 0.9806³⁰ was used for zero-point-energies (ZPEs) corrections. All transition states reported have only one

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imaginary vibrational mode, found without imposing constraints during the process of geometry optimization. We have tested the accuracy of the B3LYP functional and the 6-31++G(d,p) basis set against higher levels of theories (MP2, MP4^{31,32} and CCSD, CCSD(T)^{33,34}) and larger basis sets (6-31++G(3df,3dp), cc-pVDZ, and aug-cc-pVDZ) for the 1,2 hydrogen transfer reaction of hydrogen peroxide.²⁰ The results indicate that the B3LYP/6-31++G(d,p) theory is sufficient to predict accurate geometries; details of our validation procedures can be found in the Supporting Information. To treat electron correlation in a reliable manner, the MP4 method is used for single energy corrections. The SAC (scaling-all-correlation)^{35,36} factor for the MP2//B3LYP6-31++G(d,p) calculations is found to be 1.1052 to scale to the MP4 calculations. Unless specifically mentioned, the energetics reported in this study are based on MP4//B3LYP/6-31++G(d,p) theory.

The polarized continuum model,^{37,38} PCM, was used to describe the long-range electrostatic polarization of the surrounding environment. Water is the only solvent considered ($\epsilon_r = 80$), and the united atom topological model³⁹ was used to build up the solute cavity. The effects of solvent polarization were examined at the B3LYP/6-31G++(d,p) level.

Results and Discussions

In this study, two reactions, the hydrogen transfer of H₂O₂ to form water oxide and the oxidation dimethyl sulfide (DMS) by H₂O₂, are studied using ab initio calculations to identify the mechanism by which organic sulfides are oxidized by H₂O₂ in solution. The hydrogen transfer of H₂O₂ corresponds to the rate-limiting step of a two-step mechanism,^{18,20} the first step being the formation of water oxide and the second step being the transfer of oxygen from H₂OO to the nucleophile. The activation barrier of the second step was estimated to be less than 5 kcal/mol for the oxidation of DMS.¹⁸ A correct mechanism must satisfy all experimental observations described earlier; that is, the activation energies estimated by the mechanism should be between 10 and 20 kcal/mol,^{3,16,24,25} and the mechanism should not suggest a pH dependence of oxidation rates between pH = 2 and 10.²⁷

Hydrogen Transfer of Hydrogen Peroxide To Form Water Oxide. Water oxide, H₂OO, is a local energy minimum in the potential energy surface of hydrogen peroxide and is 46–50 kcal/mol higher in energy than H₂O₂. The reported activation energies of the hydrogen transfer reaction of H₂O₂ in earlier ab initio studies were in the range of 29–50 kcal/mol,^{20,21} depending on the number of water molecules involved. The lower end of reported energy barriers is still much higher than the measured activation barriers (10–20 kcal/mol) for the oxidation of organic sulfides.

In this section, the potential role of the general acid in stabilizing the transition complex of the hydrogen transfer reaction of H₂O₂ is analyzed in detail. We would like to find out whether the rate-limiting step in the oxidation of organic sulfides is the formation of water oxide. Various reaction configurations as well as the effects of electrostatic polarization on activation barriers of the hydrogen transfer reaction of H₂O₂ are examined.

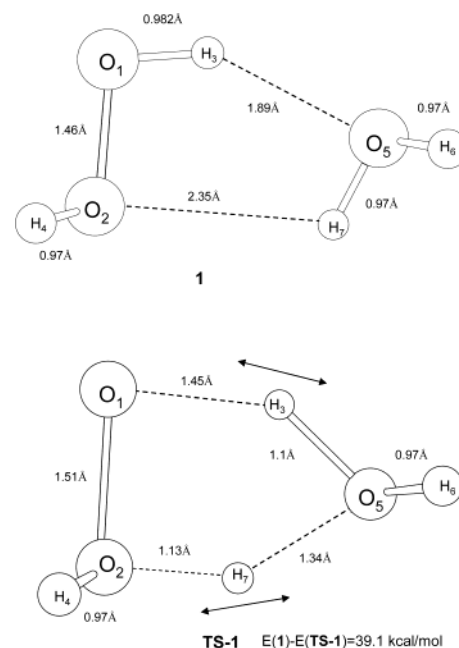


Figure 1. The hydrogen transfer reaction of hydrogen peroxide with a single water molecule. Reactant cluster **1** and transition state **TS-1** cluster were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

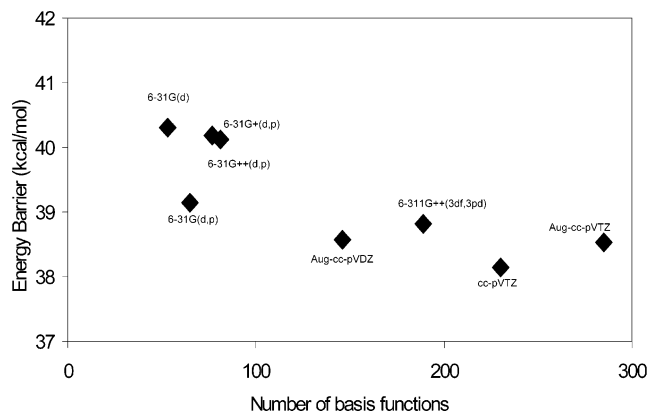


Figure 2. Sensitivity of the energy barrier between **1** and **TS-1** to the number of basis functions. Post-SCF calculations were performed at the MP2 level.

Figure 1 shows optimized geometries of the reactant cluster **1** and the transition state **TS-1** of the hydrogen transfer reaction with a single water molecule. The MP4/6-31++G(d,p)//B3LYP6-31++G(d,p) energy difference is 39.1 kcal/mol. This value is similar to the result in a previous study with an MP2/6-31G* calculation (42.7 kcal/mol).²⁰ For the transition state **TS-1**, the imaginary vibrational mode corresponds to the 1,4 hydrogen transfer, and the water molecule serves as a catalyst by accepting the H₃ atom from O₁ and donating the H₇ atom to O₂. To test the sensitivity of the calculated energy barrier with respect to the number of basis sets, post-SCF calculations on the B3LYP/6-31++G(d,p) geometries were performed with a number of basis sets at the MP2 level; results are shown in Figure 2. The energy barriers are not very sensitive to the number of basis functions, although a slight decrease in ΔE with an increase in the number of basis functions was observed between basis sets with < 100 basis functions and those with > 100 basis functions. Differences are within 2.5 kcal/mol in all cases.

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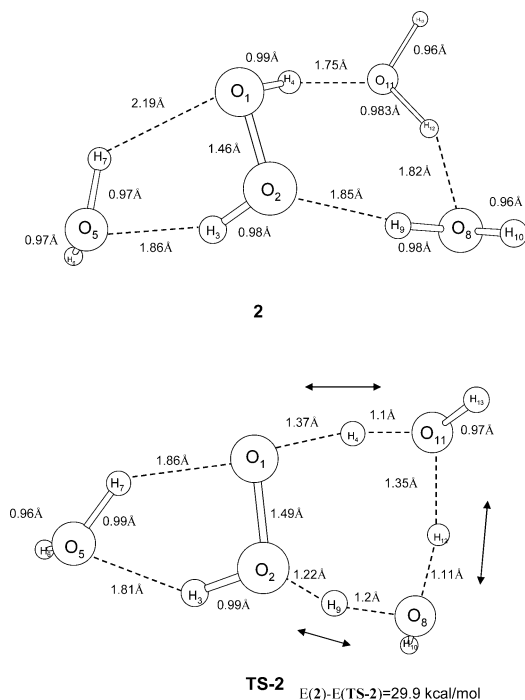


Figure 3. The hydrogen transfer reaction of hydrogen peroxide with three water molecules, two at one side and the third one at the other side of H₂O₂. Two water molecules are involved in the concerted proton transfer at the transition state. Reactant cluster **2** and transition state **TS-2** were fully optimized at the B3LYP/6-31++G(d,p) level; energetics were calculated at the MP4//B3LYP/6-31++G(d,p) level.

As compared to the direct 1,2 hydrogen transfer of H₂O₂ ($\Delta E = 54.6$ kcal/mol), the 1,4 hydrogen transfer pathway in the presence of a single water molecule has an activation energy that is lower by ~ 15 kcal/mol, indicating that solvent molecules can efficiently reduce the activation barrier of this reaction. We have also explored various reaction configurations involving 2 and 3 water molecules, and our results show that the second and the third water molecules do have significant effects on reducing the activation barrier. For example, the configurations with 2 water molecules have activation barriers that are 7.5–8.0 kcal/mol lower than the one-water model, and the configurations with 3 water molecules have activation barriers that are 3–6 kcal/mol lower than the two-water configurations. However, the fourth water molecule does not result in a significant difference of activation barrier as compared to the three-water cases (difference < 1 kcal/mol).

As compared to the results of earlier theoretical studies of the hydrogen transfer reaction of H₂O₂ (the lowest value reported: 29.5 kcal/mol^{20,21}), the activation energy (with ZPE) of reactant cluster **2** and **TS-2** shown in Figure 3 is lower (26.2 kcal/mol). The major cause of this reduction is the specific inclusion of water molecules with the reactant (Figure 3). Two water molecules are involved in the hydrogen transfer process in **TS-2**, and this type of 1,6 of hydrogen transfer has been reported.^{20,21} The third water molecule in **TS-2** is not involved in the hydrogen transfer process, but it is hydrogen bonded to H₂O₂, and the presence of the third water molecule has reduced the barrier by ~ 5 kcal/mol. This type of configuration has not been explored in earlier studies. This result indicates that specific interactions with solvent molecules can have significant stabilization effects on the reaction.

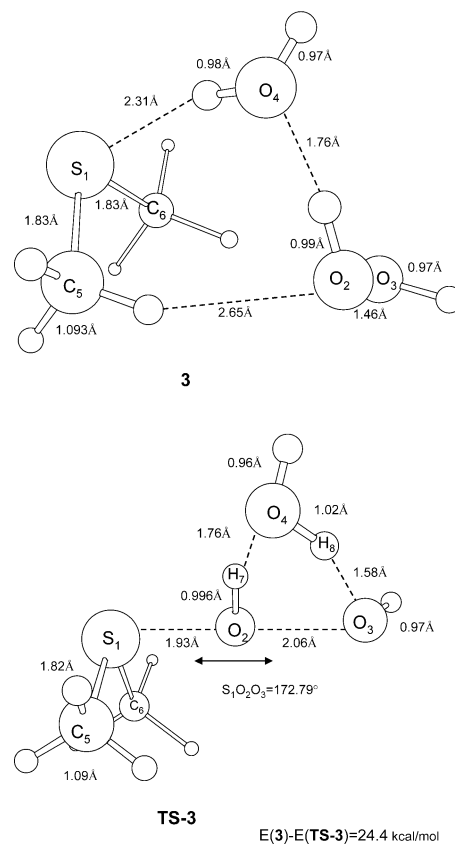


Figure 4. Oxidation of dimethyl sulfide with a single water molecule. Reactant cluster **3** and transition state **TS-3** cluster were fully optimized at the B3LYP/6-31++G(d,p) level; energetics were calculated at the MP4//B3LYP/6-31++G(d,p) level.

In addition, the effects of the long-range electrostatic polarization of the solvent ($\epsilon_r = 0$ in the gas phase and $\epsilon_r = 80$ in aqueous solution) have been analyzed by incorporating Tomasi's polarizable continuum model (PCM)^{37,38} in locating the geometries of the reactant clusters and transition states and in total energy calculations. Including polarization in this way does not lead to a significant difference (< 1.5 kcal/mol) in reaction activation energies as compared to those in a vacuum. This result indicates that solvent molecules stabilize the hydrogen transfer reaction of H₂O₂ via specific interactions rather than dielectric polarization; it is also consistent with the experimental observation that the reaction rate of peroxide oxidation is insensitive to solvent dielectric constants.¹⁴ Although the minimum activation energy obtained (26.2 kcal/mol) is lower than that obtained in previous studies,^{18,20,21} it is still too high as compared to experimentally determined activation energies of the oxidation of organic sulfides by hydrogen peroxide (10–20 kcal/mol).

Oxidation of Dimethyl Sulfide (DMS). Dimethyl sulfide (CH₃–S–CH₃) is an organic sulfide and can be oxidized with H₂O₂ to dimethyl sulfoxide (DMSO) in aqueous solution.¹⁵ As mentioned previously, DMS is the major source of sulfur in the troposphere,⁹ and the fact that DMSO is present in rain^{10–12} and snow¹³ makes it important to understand the oxidation mechanism of DMS.³ DMS oxidation in aqueous solution is also of biological interest, because it represents part of the methionine side chain, and oxidation of the sulfur atom in methionine residues by peroxides is one of the major degradation pathways of therapeutic proteins.^{4,6,8,40} Our starting point is the

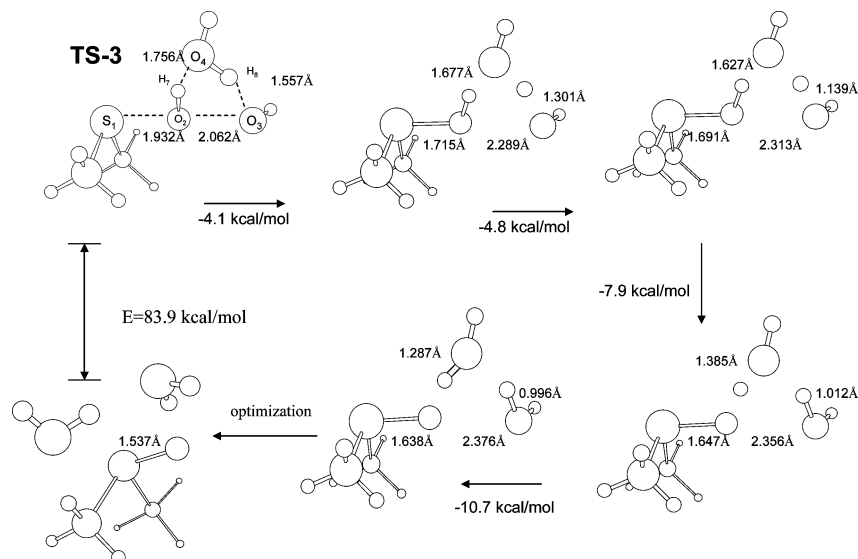


Figure 5. Reaction path analysis of DMS oxidation with a single water molecule; snapshots are from IRC calculations (reference to Figure 4).

fact that of the mechanisms previously proposed in the literature, as presented in the Introduction and as studied in the previous section, none of them is consistent with experimental data, including both the pH dependence of the rates of oxidation and the estimated activation energies. Aside from the mechanism proposed by Bach et al.¹⁸ (eq 3), the activation energies estimated in previous theoretical studies are too high as compared to experimental estimations.^{3,16,24,25} The problem with the mechanism of Bach et al. (eq 3) is that it implies a marked pH dependence of rates of oxidation of organic sulfides via H₂O₂, but a subsequent experimental study reported that the rates of oxidation of DMS are independent of pH over the range of pH = 2–10 in aqueous solutions.¹⁴ Note that eq 3 may still be the route at low pH values, because an increase in the rates of oxidation of DMS was observed for pH < 2.¹⁴ We wish to determine the mechanism of the oxidation process in a moderate pH range (2–10), including understanding the governing factors that bring about this reaction. Not only will this add to our understanding of a class of important chemical reactions, but also it will enhance our ability to develop ideas to hinder this process, when desired.

Figure 4 shows geometries optimized at the B3LYP/6-31++G(d,p) level for the reactant cluster **3** and the transition state **TS-3** for DMS oxidation by H₂O₂ in the presence of a single water molecule. At **TS-3**, the reaction mode is mainly the transfer of O₂ to S₁ and does not exhibit significant hydrogen transfer character. This indicates that the proper reaction coordinate involves the S₁–O₂ distance and the O₂–O₃ distance and that our picture is different from the mechanism found earlier for DMS oxidation where the transfer of hydrogen to form water oxide occurs before the transfer of oxygen.¹⁸ A reaction-path-following analysis^{41,42} shows that the transfer of hydrogen indeed occurs after the transfer of oxygen. Selected reaction frames and corresponding energies are shown in Figure 5.

The energy difference between the reactant cluster and the transition state in this model is 24.4 kcal/mol at the MP4//B3LYP/6-31++G(d,p) level. Although this value is still too

high as compared to experimental observations, it is lower than the activation energy of a similar reaction: oxidation of DMS with two H₂O₂ molecules calculated at the MP4//MP2/6-31G(d) level, in which the transfer of hydrogen occurs first to form water oxide. The reported energy barrier of this process was 40.8 kcal/mol.¹⁸ A sensitivity analysis of the reaction energy barriers with respect to the number basis functions was performed and is shown in Figure 6; all data points were calculated at the MP2 level of theory. By including diffuse functions^{43,44} with 6-31(d) and 6-31(d,p) basis functions, the calculated energy difference is decreased by ~10 kcal/mol. Among the cases investigated, only the 6-311G(3df,3dp) basis set can predict a reasonable energy barrier without diffuse functions. In conclusion, including diffuse functions can greatly enhance the performance of the 6-31G(d) and 6-31G(d,p) basis sets and is necessary to predict correct energy barriers of DMS oxidation by H₂O₂ with a water molecule, and the 6-31++G(d,p) basis set is sufficiently accurate as compared to larger basis sets.

The effects of the electrostatic polarization of the surrounding solvent were also analyzed with the PCM model for DMS oxidation with a single water molecule. The difference in activation energy between the unsolvated phase and the solvated phase is insignificant (0.2 kcal/mol). The insensitivity of activation energy to dielectric polarization of solvent for this reaction is similar to the hydrogen transfer reaction of H₂O₂ as described earlier and, again, is also consistent with the experimental observation that the reaction rate of peroxide oxidation is insensitive to solvent dielectric constants.¹⁴

We analyzed the charge distribution along the reaction path of **TS-3** using the Merz–Singh–Kollman (MSK) scheme^{45,46} to understand the charge separation in the S_N2 oxidation of DMS by H₂O₂. The sulfur atom of DMS, S₁, has an atomic charge of –0.22 in the reactant cluster **3**, Figure 4. Both of the two oxygen atoms of H₂O₂ have similar atomic charges, –0.43 for O₂ and –0.48 for O₃, indicating the symmetric nature of hydrogen

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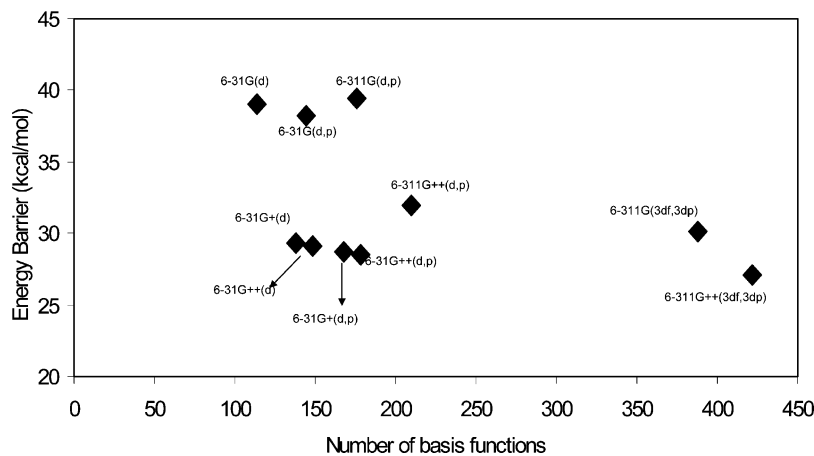


Figure 6. Sensitivity of the energy barrier between **3** and **TS-3**. Post-SCF calculations were performed at the MP2 level of theory for all data points.

peroxide. As the hydrogen peroxide molecule approaches DMS ($S_1-O_2 = 2.8 \text{ \AA}$, $S_1-O_3 = 4.2 \text{ \AA}$ in reactant cluster **3**), the atomic charges of O_2 and O_3 became different ($O_2 = -0.24$, $O_3 = -0.45$). During this part of the reaction, the energy is increased by 9 kcal/mol. Note that the O_2-O_3 bond length remains near the equilibrium value of 1.46 \AA at this point. In this part of the reaction, the hydrogen peroxide and the water molecule rearrange such that the S_1 , O_2 , and O_3 atoms lie on a line, and the O_3-H_8 and O_4-H_7 hydrogen bonds are formed (reference to Figure 4). This arrangement results in a more significant change of the atomic charge on the transferring oxygen (-0.41 to -0.24) than on other atoms. The O_2-O_3 bond then starts to break. The negative charge on the distal oxygen, O_3 , begins to increase, and the sulfur atom, S_1 , begins to lose its negative charge. For the transferring oxygen, O_2 , however, the MSK charge remains around the value of -0.24 . At the transition state, **TS-3**, the charges are: S_1 (0.15), O_2 (-0.24), and O_3 (-0.83) (reactant, S_1 (-0.22), O_2 (-0.43), and O_3 (-0.48)). The atomic charge on the sulfur atom goes from negative in the reactant to positive in the transition state. This trend continues after passing the transition state. Although the values of the point charges depend on the method used for population analysis, the nature of charge separation and transfer is qualitatively the same if other population analysis methods were used, such as the Mulliken population analysis and the natural orbital analysis. The analysis of charge separation during the oxidation process also provides insight into how solvent molecules may stabilize the reaction. For example, hydrogen bonding to the more negative distal oxygen may stabilize the transition state structure more than the reactant cluster so that the activation energy can be decreased.

On the basis of the experience of the H₂O₂ hydrogen transfer reaction, we anticipate that the number of water molecules in the theoretical model can dramatically change the reaction energy barrier. Three configurations were studied for the model containing two water molecules. For configurations 1 (**4** and **TS-4**) and 2 (**5** and **TS-5**), two water molecules are at the same side of H₂O₂, as shown in Figures 7 and 8, respectively. The difference is that the two water molecules are at the trans side with respect to the methyl groups of DMS in the first configuration (**TS-4**, Figure 7), and at the cis side in the second (**TS-5**, Figure 8). For the third configuration, each water molecule is at one side of the hydrogen peroxide (**TS-6**, Figure 9). Geometries were optimized in the unsolvated systems only.

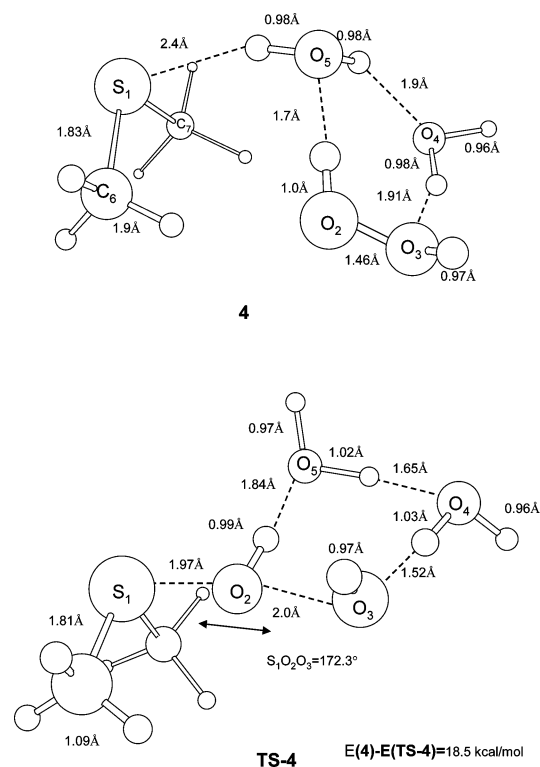


Figure 7. Oxidation of dimethyl sulfide with two water molecules, configuration 1. The two water molecules are at the same side of H₂O₂ and at the trans side of the methyl groups of the DMS molecule at the transition state. Reactant cluster **4** and transition state **TS-4** were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

Recall that both theoretical calculations (DMS oxidation with one water molecule) and experimental observations suggest that the oxidation rates of organic sulfides are not strong functions of the dielectric constant of the media.¹⁶ We conclude that calculations performed in the unsolvated systems can provide adequate information for the reaction kinetics if enough water molecules are included explicitly.

Reactant cluster **4** (Figure 7) has the lowest energy among the three reactant clusters. It is 0.1 kcal/mol lower than that in **5** (Figure 8), and 1.7 kcal/mol lower than that in **6** (Figure 9). The predicted energy barriers for the three configurations with two water molecules are 18.5 kcal/mol (**4** and **TS-4**), 18.9 kcal/mol (**5** and **TS-5**), and 14.0 kcal/mol (**6** and **TS-6**), respectively. At **TS-4** and **TS-5**, the oxygen atom of the second water

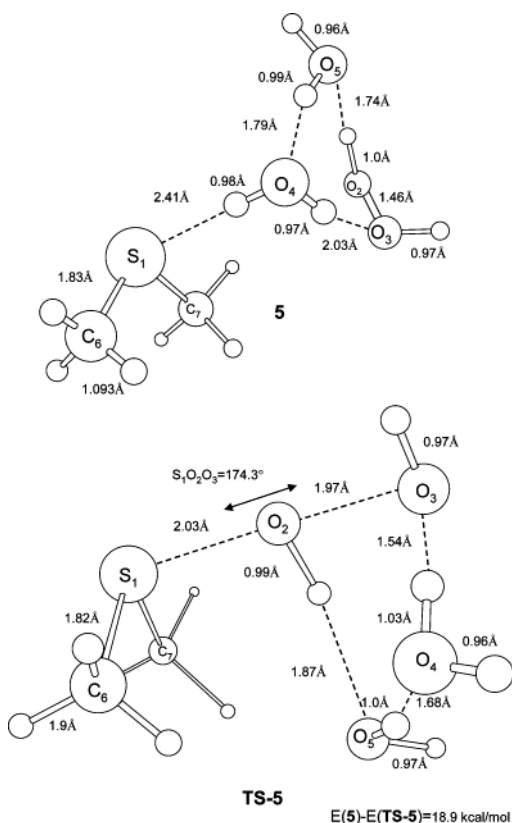


Figure 8. Oxidation of dimethyl sulfide with two water molecules, configuration 2. The two water molecules are at the same side of H_2O_2 and at the cis side of the methyl groups of the DMS molecule at the transition state. Reactant cluster **5** and transition state **TS-5** were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

molecule, O_5 , forms a hydrogen bond with the hydrogen atom bonded to O_2 , and the hydrogen atom of the other water is hydrogen bonded to the distal oxygen, O_3 . In the one-water case (**TS-4**, Figure 4), the two hydrogen bonds are formed by the single water molecule. The arrangement of the second water molecule results in a decrease of 5–7 kcal/mol in the energy barrier. For **TS-6**, the hydrogen atom of the second water molecule forms a hydrogen bond to O_3 , and the other water retains a configuration similar to that in **TS-4**. Therefore, the additional hydrogen bond to the more negative distal oxygen in **TS-6** versus **TS-4** and **TS-5** is responsible for the lower activation energy of configuration 3, again, as a result of the stabilization of the charge separation in the transition state.

The imaginary vibrational modes for all transition states demonstrate that the characteristic mode at the transition state is oxygen transfer to the sulfur atom, but not the transfer of hydrogen. A reaction-path-following analysis for transition state **TS-4** is shown in Figure 10. First, the $\text{O}_2\text{--O}_3$ bond breaks, and the H_8 transfers from O_5 to O_3 . Second, H_7 transfers to O_5 from O_4 . Finally, H_6 transfers to O_4 from O_2 , forming the leaving water molecules. In this reaction, both water molecules are involved in the hydrogen transfer process after passing the transition state. For **TS-5**, a reaction-path-following analysis is shown in Figure 11. In this case, the transfer of O_2 to S_1 also occurs before the transfer of hydrogen. The hydrogen atom H_4 goes directly to the distal oxygen, O_3 from O_2 . Water molecules only stabilize the system via hydrogen bonding. For **TS-6**, the hydrogen transfer process is similar to that in the one-water

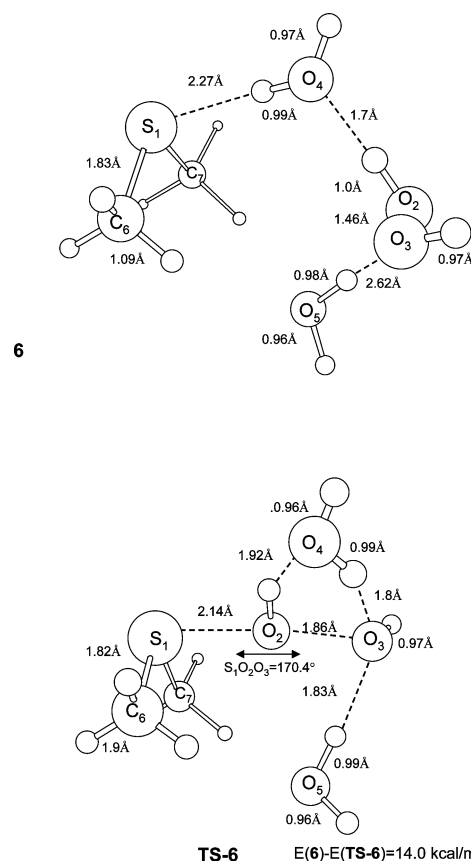


Figure 9. Oxidation of dimethyl sulfide with two water molecules, configuration 3. Each water molecule is on one side of H_2O_2 . Reactant cluster **6** and transition state **TS-6** were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

model, Figure 5. The hydrogen atom of the second water molecule forms a hydrogen bond with O_3 , but is not involved in the transfer of hydrogen. As compared to the one-water case, this arrangement has lowered the activation energy by ~ 10 kcal/mol.

For the three-water model, two water configurations were considered. In the first configuration, two water molecules are at one side of H_2O_2 , but at the trans side of the methyl groups (**7** and **TS-7**, Figure 12). This configuration corresponds to configuration 1 in the two-water model, and the third water molecule forms a hydrogen bond with the distal oxygen, O_3 , at the transition state. In configuration 2, two water molecules are at the cis side of the methyl groups, and the other one is at the trans side (**8** and **TS-8** in Figure 13). This configuration corresponds to configuration 3 in the two-water model, and, in this case, the third water molecule forms a hydrogen bond with the transferring oxygen, O_2 , at the transition state. Because the distal oxygen is more negative than the transferring oxygen at the transition state, it is expected that the third water molecule in configuration 1 will have more stabilization effect. This is indeed the case. The energy barriers are 12.6 kcal/mol between **7** and **TS-7** and 13.7 kcal/mol between **8** and **TS-8**. As compared to configuration 3 in the two-water model, the third water molecule in configuration 2 yields only 0.3 kcal/mol in stabilization energy. However, as compared to configuration 1 in the two-water model, the third water molecule of configuration 1 has a significant stabilization effect, reducing the activation energy by 5.9 kcal/mol. These results indicate that

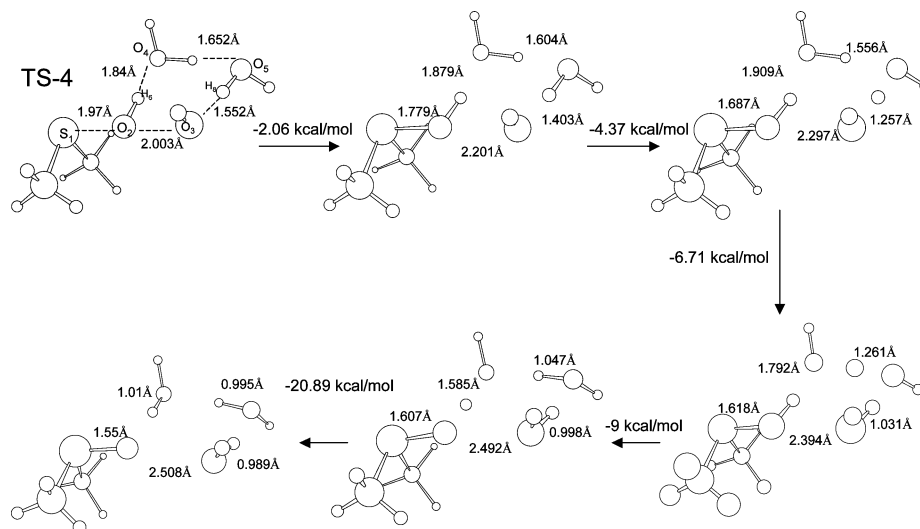


Figure 10. Reaction-path-following analysis of DMS oxidation with two water molecules for TS-4. Bond lengths in each snapshot correspond to the dotted lines connecting the indicated atoms of the upper-left frame.

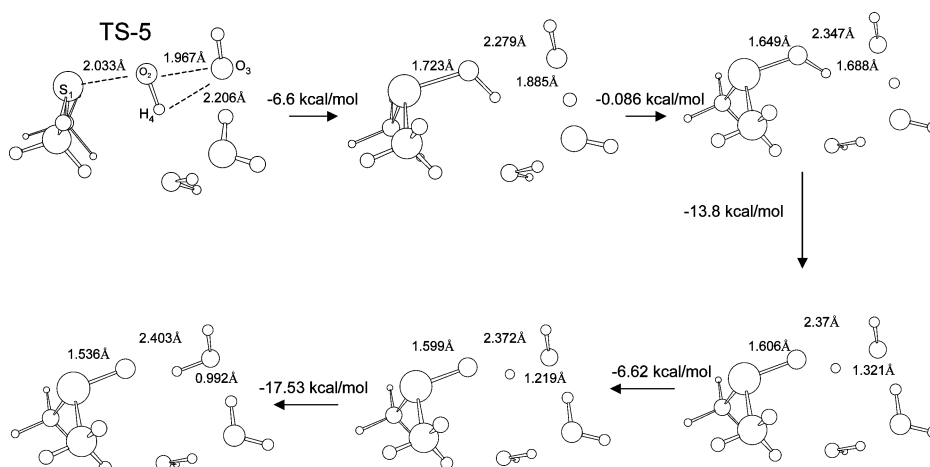


Figure 11. Reaction-path-following analysis of DMS oxidation with two water molecules for TS-5. Bond lengths in each snapshot correspond to the dotted lines connecting the indicated atoms of the upper-left frame.

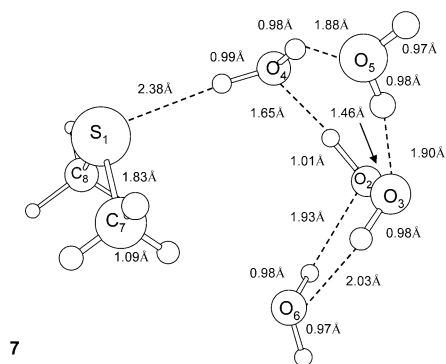
forming a hydrogen bond with the more negative distal oxygen at the transition state has more stabilization effect than doing this with the less negative O₂ atom. For both configurations, the calculated activation energies are within the experimentally observed range of organic sulfides (10–20 kcal/mol).^{3,16,24,25} When compared to the activation energy (13.5 kcal/mol) for thioxane oxidation by hydrogen peroxide in aqueous solution, the above result is also quite close.

For each model of DMS oxidation, the activation barrier is about 10 kcal/mol or more lower than that of the corresponding hydrogen transfer reaction of hydrogen peroxide to water oxide. Therefore, it is unlikely that oxidation occurs in two steps in which the hydrogen transfers first to form water oxide. Instead, oxidation occurs via stretching of the O–O bond of H₂O₂ and reduction in the S–O distance. Solvent molecules stabilize the charge separation at the transition state via specific interactions, including hydrogen bonding, and may also be involved in the transfer of hydrogen after the system has passed the transition state. Hydrogen bonding to the more negative distal oxygen at the transition state has a significant stabilization effect as shown in the two-water and three-water models. Reaction-path-following analyses of transition states indicate that one or two water molecules can be involved in the hydrogen transfer

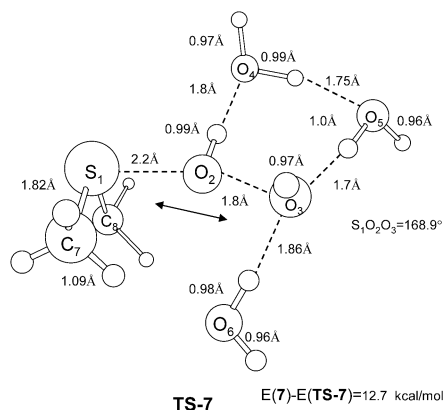
process, similar to the hydrogen transfer reaction of hydrogen peroxide in which both 1,4 and 1,6 concerted proton transfers have been observed. In addition, a direct 1,2 hydrogen transfer to the distal oxygen occurring after the system has passed the transition state was also observed (Figure 8). Because the transfer of hydrogen occurs after the transition state is passed, it is not the determining factor of the activation barriers. Instead, 2–3 explicit water molecules can provide enough stabilization energy for the oxidation of organic sulfides by peroxides. Water molecules stabilize the charge separation at the activation complex via specific interactions including hydrogen bonding. This mechanism is also in agreement with the experimentally observed pH-independent rates over moderate pH ranges, because an additional proton is not involved in this model. Our results imply that unprotonated water molecules can provide enough stabilization for the oxidation of organic sulfides by hydrogen peroxide. At extremely low pH conditions, of course, high concentrations of protonated solvent molecules may result in different oxidation pathways.^{14,18}

Conclusions

The following conclusions can be drawn from the above theoretical analysis:



7



TS-7

E(7)-E(TS-7)=12.7 kcal/mol

Figure 12. Oxidation of dimethyl sulfide with three water molecules, configuration 1. Reactant cluster **7** and transition state **TS-7** were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

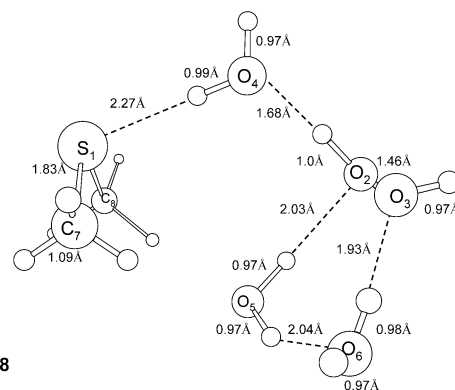
(1) For moderate pH values, perhaps between 2 and 12, the reaction coordinate leading to oxidation of dimethyl sulfide by H_2O_2 is the separation (breaking) of the O–O bond together with the formation of the S–O bond. Thus, under these conditions, water molecules stabilize the transition complex via specific interactions including formation of hydrogen bonds with H_2O_2 but not proton transfer as was previously assumed in the literature.^{3,6,7,15–19}

(2) Hydrogen transfer does occur during oxidation of DMS, but it is not the determining factor of the activation barrier. Hydrogen transfer can occur via multiple different pathways depending on the local solvent configuration (Figures 5, 10, and 11).

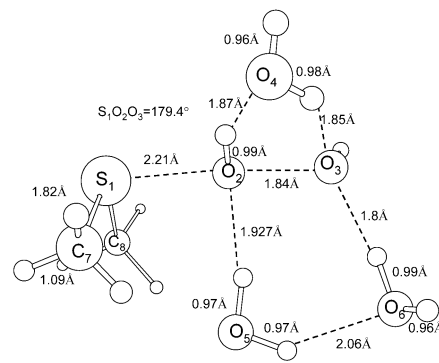
(3) During DMS oxidation, an uneven charge distribution between the oxygen atoms of H_2O_2 is developed. The distal oxygen is more negative than the transferring oxygen. Water molecules stabilize the charge separation by local polarization and via formation of hydrogen bonds with H_2O_2 .

(4) For hydrogen transfer reactions involving H_2O_2 and DMS oxidation with a single water molecule, including solvent via a polarizable continuum model, results in small effects on activation energies (<1 kcal/mol in most cases). This is also consistent with the experimental observation that the rates of oxidation of organic sulfides are not a strong function of the solvent dielectric constant.^{3,15,16}

(5) The energy barrier of DMS oxidation with 3 water molecules is estimated to be 12.7 kcal/mol at the MP4//B3LYP/6-31++G(d,p) level, within the experimental range of barriers of oxidation of organic sulfides.^{3,16,24,25}



8



TS-8

E(8)-E(TS-8)=13.7 kcal/mol

Figure 13. Oxidation of dimethyl sulfide with three water molecules, configuration 2. Reactant cluster **8** and transition state **TS-8** were fully optimized at the B3LYP/6-31++G(d,p) level; energies were calculated at the MP4//B3LYP/6-31++G(d,p) level.

(6) The activation energies of the hydrogen transfer reaction of hydrogen peroxide are an average of 10 kcal/mol or more higher than those for the oxidation of DMS by H_2O_2 . This, combined with conclusions 1–5, indicates that a two-step mechanism in which the hydrogen transfer of H_2O_2 occurs, first, to form water oxide followed by, second, the transfer of oxygen to the nucleophile from water oxide is not the mechanism by which organic sulfides are oxidized by hydrogen peroxide.

(7) Our proposed oxidation mechanism does not suggest a pH dependence of oxidation rates within a moderate range around neutral pH (i.e., under conditions in which hydronium and hydroxide ions do not participate directly in the reaction). In this respect, it agrees with experimental observations over moderate pH values.^{14,27} It also predicts activation energies corresponding to measured activation energies without including a protonated solvent molecule.

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Supporting Information Available: Tables of Cartesian coordinates (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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