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# On the Influence of Water on the Oxidation of Dimethyl Sulfide by the $\bullet$ OH Radical

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## ABSTRACT.

Oxidative stress of sulfur-containing biological molecules in aqueous environments may lead to the formation of adduct intermediates that are too short lived to be experimentally detectable. In this study we have modeled the simplest of such oxidative reactions: the attack of dimethyl sulfide (DMS) by a hydroxyl radical ( $\bullet$ OH) to form radical adduct, whose subsequent heterolytic dissociation leads to a radical cation ( $\text{DMS}^+$ ) that is important for further reactions. We have modeled the aqueous environment with a limited number of discrete water molecules, selected after an original multistep procedure, and further embedded in a polarizable continuum model, to observe the impact of the water configuration on the heterolytic dissociation of the radical adduct. Molecular dynamics and quantum chemical methods (DFT, MP2 and CCSD) were used to elucidate the lowest energy structures resulting from the  $\bullet$ OH attack on DMS. Subsequent high level *ab initio* Valence Bond (BOVB) calculations revealed the possibility for the occurrence of subsequent heterolytic dissociation.

## Introduction.

Oxidation of peptides and proteins by  $\bullet\text{OH}$  radicals is a key event in the development of numerous pathologies and in all events related to radiation biology (radiotherapy, accidental irradiations, etc.).<sup>1</sup> The consequences of such oxidations are numerous. Among the main targets of these free radicals are Methionine (Met) residues<sup>2-9</sup> which can be implicated in neurodegenerative diseases as well as in the ageing processes. Their oxidation by  $\bullet\text{OH}$  has been the focus of numerous experimental and theoretical studies these last thirty years. In particular, the nature of the transient species has been investigated but controversies still exist about their structure. The adduct formation (addition of  $\bullet\text{OH}$  on the S atom) appears to be the most favorable, but the corresponding adduct is very short-lived (less than a few microseconds).<sup>7</sup> The formation of 2-center-3-electron (2c-3e) bonded radicals<sup>10</sup> in their cationic forms from Met residues have been observed by several experimental means, and proved stable by theoretical calculations in the gas phase or including the implicit solvent.<sup>11-13</sup>

The stability of the adducts and their dissociation process is of critical importance for the understanding of the oxidation mechanisms of sulfur containing molecules. Recently, several new theoretical studies that used various DFT and *ab-initio* methods along with the IEFPCM solvation model were applied to study the first steps of the dissociation mechanisms for Sulfur-amino residues, methionine (Met), cysteine (Cys) and dimethylsulfide (DMS).<sup>14-20</sup> The authors considered that one of the major mechanisms is the electron transfer between Met and  $\bullet\text{OH}$  in the adduct, followed by heterolytic dissociation leading to the formation of the radical cation  $\text{Met}\bullet+$ .

The ionic 2c-3e bond in general has been the subject of many fundamental theoretical studies.<sup>21-33</sup> However, these studies mainly focused on ionic 2c-3e bonded systems, with fewer studies on the neutral SO bonds formed in the adducts.<sup>34-35</sup> In particular, in reference 34 the (2c-3e) SO bonds of different radicals was carried out using various computational methods (BH&HLYP, MP2 and CCSD(T)) the possibility of the direct attachment of  $\bullet\text{OH}$  to S atom in

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3 neutral radicals was analyzed with the ELF method<sup>36-39</sup> and the 2c-3e character of the SO bond in  
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5 DMS- $\bullet$ OH was established.  
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9 The aim of the present work is to use appropriate theoretical tools to shed light on the  $\bullet$ OH  
10 radical addition and its dissociation in an advanced solvation model involving explicit water  
11 molecules. For this purpose dimethyl sulfide (DMS) has been selected, because it is the simplest  
12 organic sulfide to model the oxidation of sulfur in Met.<sup>40-50</sup> The presence or absence of stabilizing  
13 hydrogen bonds has to be carefully checked, since such bonds may modulate the  $\bullet$ OH-adduct  
14 stability. Many previous *ab initio* calculations were performed on systems of water-assisted  
15 mechanisms in order to study the influence water molecules on relatively simple reactions. One  
16 of the earlier of these studies concerned the amide hydrolysis.<sup>51</sup> In that study a water-formamide  
17 cluster was embedded in an implicit continuum solvent model and the thermodynamics of the  
18 reaction pathway were calculated. Other previous studies of solvation effects used various  
19 strategies to sequential add water molecules to small water clusters that microsolvate the  
20 solute.<sup>52-56</sup> The results of these calculations compared favorably to gas phase experimental data  
21 when available. Other groups have successfully used QM/MM embedding methods to model  
22 solvation in the liquid phase (for example the QMCF method used by Rhodes and coworkers<sup>57-</sup>  
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35 The oxidation of DMS and Met by H<sub>2</sub>O<sub>2</sub> resulting in the formation of MetSO and H<sub>2</sub>O has been  
36 studied previously<sup>41-42</sup>, using respectively an implicit solvation (PCM) model, and a QM/MM  
37 approach to describe the solvent classically. However, because the two dissociation channels of  
38 MetSOH, i.e. the “homolytic” (dissociation to DMS +  $\bullet$ OH) and the “heterolytic” (dissociation to  
39 DMS $\bullet^+$  +  $\bar{\text{O}}\text{H}$ ) channels generate neutral and ionic species, respectively, a more realistic  
40 solvation model involving in particular a quantum mechanical treatment of the first solvation  
41 shell may be of great importance for this reaction. We have thus used a multi-step methodology  
42 in order to carefully design a solvation model that describes the most important solvent water  
43 molecules quantum mechanically, while remaining tractable with current computer programs and  
44 resources. Similar mixed explicit-implicit solvation models have been successfully used in the  
45 past by other researchers to describe the influence on of solvation on chemical reactivity and  
46 spectroscopy.<sup>60-64</sup> It must be noted that in this study we focused on the non-entropic energies of  
47 the solutes. *Ab initio* Valence Bond BOVB calculations were performed since the theory that

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3 combines high accuracy with wide interpretative capabilities. This high level method is  
4 particularly suited to study resonant situations, like in the present case, the DMS- $\bullet$ OH system  
5 which from equilibrium to the dissociation limit could be described by either two neutral (DMS  
6 +  $\bullet$ OH) or two ionic (DMS $\bullet^+$  + OH $^-$ ) interacting fragments.  
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### 11 12 **Computational details.** 13

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15 The multistep methodology is briefly outlined in the following, and described fully (including  
16 details concerning the MD simulation) in the Supplementary Information (SI). All of the purely  
17 QM (DFT) calculations were carried out with the Gaussian 09 suite of programs.<sup>65</sup>  
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21 Step one: DFT geometry optimizations of adducts of sulfur containing molecules were carried  
22 out using the BH&HLYP and PBE0 functionals, together with 631g(d) and 6-311+g(d,p) basis  
23 sets, and they used the CPCM implicit solvent model.<sup>66</sup> The use of two functionals and two basis  
24 functions provides some information about how the choice of basis sets and functionals may  
25 impact the optimized geometrical parameters. In particular, the BH&HLYP functional has been  
26 shown to well reproduce the bond distances in two-center three-electron bonds,<sup>67</sup> a type of  
27 bonding that most likely occurs in SO adducts, as we will see later. The CPCM model was used  
28 to enable comparisons with previous calculations that have been carried out using the same  
29 solvent model.  
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38 Step two: MD simulations, with geometries of the solute molecules taken from the previous  
39 step and kept fixed, were performed with an environment of a very large number of explicit  
40 water molecules, i.e. more than 2000 water molecules in each periodic boundary condition unit  
41 cell. The CHARMM CGenFF 3.0.1 force field was used for these solute molecules and the rigid  
42 CHARMM modified TIP3P water model (see SI for details). The molecules were solvated with  
43 20Å of TIP3P water in each direction. For the charged species, the force field parameters were  
44 obtained for the analogous neutral species and the net formal charge was placed on the sulfur  
45 atom. In a second stage of this “step 2”, from these MD simulations a nanodroplet of ~70 solvent  
46 water molecules is selected and further BH&HLYP partial geometry re-optimizations were  
47 carried out using the smaller 6-31+G\*\* basis set and a PCM explicit solvation model to account  
48 for the bulk water. From the latter, only the very few water molecules directly in interaction with  
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3 the active site of the solute, i.e. the sulfur atom of DMS and oxygen atom of the  $\bullet$ OH moieties,  
4 supposedly the most chemically important water molecules of the first solvation shell, will be  
5 retained and used in subsequent highest level quantum chemistry calculations.  
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10 Step three: further geometry optimizations using Gaussian09 has been carried out with the  
11 super system made of the solutes surrounded by a few (4-5) explicit water molecules as selected  
12 in the previous step and further embedded into an implicit solvent (CPCM). Both the BH&HLYP  
13 functional and the MP2 method were used in conjunction with the larger 6-311+g(d,p) basis set.  
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18 Step four: Starting from both the BH&HLYP and MP2 optimized geometries of the super  
19 systems (DMS,  $\bullet$ OH, DMS- $\bullet$ OH and explicit water molecules), the S...O distance was re-  
20 optimized at the CCSD level. In this step, the 6-311G(2d,2p) basis set was used on the two atoms  
21 that make the 2c-3e bond, i.e. the sulfur atom of DMS and oxygen atom of  $\bullet$ OH, and the 6-  
22 31G(d) basis was used for the other atoms. This SO bond distance re-optimization consisted of  
23 rigid scans where the SO bond is changed by increments of 0.02Å while keeping all other  
24 geometrical parameters fixed, and a following parabolic fit on the five lowest CCSD energy  
25 values to determine the CCSD re-optimized SO bond distances. These calculations were  
26 performed in presence of the CPCM continuum solvent. These geometries will be referred to as  
27 BH&HLYP/CCSD and MP2/CCSD geometries in the following.  
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37 Step 5: In order to grasp more insight into the nature of the bonding between DMS and  $\bullet$ OH,  
38 high level *ab initio* Valence Bond calculations were performed with the BOVB method,<sup>68-69</sup> that  
39 includes both static and differential dynamical correlation, using the XMVB 2.1 program.<sup>70-73</sup> The  
40 BOVB approach is presented in more detail in the SI. Single point BOVB calculations on both  
41 BH&HLYP/CCSD and MP2/CCSD optimized geometries for the super system made of the  
42 substrate and four explicit water molecules have been carried out using the same combination of  
43 basis sets as in step four. The PCM solvation model was used during the BOVB calculations to  
44 implicitly describe the outer solvation shells.  
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## 52 **Results.**

### 53 **1. Benchmarking of substituent effects by DFT methods**

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3 The influence of substituents X on the SO bond characteristics (SO distances, spin densities) in  
4 the  $X_2S-\bullet OH$  adducts ( $X=CH_3$ ,  $CO_2CH_3$ ,  $CO_2HNH$ ,  $CONH$ ) are tested with the PBE0 and  
5 BH&HLYP DFT functionals, that what were previously used for studying radicals. The results  
6 of spin densities and S-O distances are summarized in Table 1.  
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14 Several conclusions can be drawn from Table 1. First, the attack of the  $\bullet OH$  radical on the S  
15 atom produces (within a given methodology) the same optimized S-O distance and the same spin  
16 density sharing regardless of the substituent. Second, the S-O distance of 2.31-2.36 Å, as well as  
17 the spin density distribution that is largely shared between sulfur and oxygen, are both typical of  
18 a neutral 2-center-3 electron (2c-3e) bond, in agreement with a previous topological study of the  
19 neutral (2c-2e) S-O bond by one of us.<sup>34</sup> This point will be further developed in the following.  
20 Furthermore, it has been shown that for 2c-3e bonds the DFT functional that best reproduces the  
21 geometries and bond energies is the BH&HLYP “half and half” hybrid functional.<sup>67</sup> With this  
22 functional, the SO bond distances decreases by as much as 0.13-0.14Å when moving from the 6-  
23 31G(d) basis set to the larger 6-311+G(d,p) basis. As a consequence, we have used geometries  
24 from the BH&HLYP/6-311+g(d,p) level of theory for subsequent MD calculations.  
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## 35 **2. Analysis of the water solvation from MD simulations.**

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37 The MD simulations corresponds to the “step 2” of the multi-step procedure presented in the  
38 “Computational Details” section in the route of creating an accurate and realistic solvation model  
39 of the species being study, however, as we will see below, the MD simulations also provide  
40 insightful information on the structure of the water solvation shells around the different solutes  
41 up to the bulk water, and determination of the most important water molecules hydrogen bonded  
42 to the solutes.  
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49 The MD simulations were performed using the previously optimized BH&HLYP/6-  
50 311+g(d,p)/CPCM geometries of the solutes (DMS, DMS adduct, DMS radical cation, hydroxyl  
51 radical and hydroxide anion), and more than 2000 explicit (rigid TIP3P) water molecules, see  
52 “Computational Details” of the SI for the complete methodology used. To analyze the water  
53 arrangements that were sampled in the 1ns NPT simulations, we have plotted water radial  
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3 distribution functions,  $g(r)$ , from: i) the oxygen atoms of both DMS- $\bullet$ OH and  $\bullet$ OH, and ii) the  
4 sulfur atoms of both DMS and DMS- $\bullet$ OH  
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8 The water radial distribution functions, around oxygen atom of DMS- $\bullet$ OH and that of the  
9 hydroxyl radical and around sulfur atom of DMS- $\bullet$ OH and that of DMS, are calculated from 1ns  
10 trajectories of our NPT simulations and presented in Fig. 1. So that radial distribution functions  
11 were reasonably smooth, snapshots were extracted every 1ps and the radial distribution functions  
12 were calculated on grids with a spacing of 0.1Å.  
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21 Unsurprisingly, we can see in Fig. 1a) that both the DMS- $\bullet$ OH adduct and the hydroxyl radical  
22 show peaks in the water radial distribution function at similar radial distances from the solute  
23 oxygen atom. The first small peak occurs for both at roughly 2.15Å, is slightly less high for the  
24 DMS- $\bullet$ OH adduct compared to the hydroxyl radical. The next peaks in the water radial  
25 distribution functions occur at 3.35Å for the DMS- $\bullet$ OH adduct and 3.25Å for the hydroxyl  
26 radical, with the latter peak being noticeably larger. These peaks correspond to an average of  
27 about 3 water molecules for the DMS- $\bullet$ OH adduct and 4 waters for the hydroxyl radical.  
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35 In Fig. 1b), we can see that, for both DMS and DMS- $\bullet$ OH alike, the first water molecules start  
36 appearing 2.5Å away from the sulfur atom. The solvation description around the sulfur atom of  
37 the DMS- $\bullet$ OH adduct is very similar to that around neutral DMS. Around 3.65Å there is a hint of  
38 another peak corresponding to an average of 2-3 water molecules.  
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44 While the larger water clusters may be more realistic for describing the solvation about the  
45 solute, it is likely that only water molecules that are close enough to the solute to form strong to  
46 moderate hydrogen bonds with the solute will have a noticeable effect on the electronic structure  
47 of the solute. Besides, given the small solute sizes in this study, very weak C-H hydrogen  
48 bonds<sup>74</sup> will be inconsequential compared to the strong hydrogen bonds that water makes with  
49 the sulfur and oxygen atoms of DMS and the DMS- $\bullet$ OH adduct. Therefore, it is only critical to  
50 have correct number of water molecules with about 4Å of the sulfur and oxygen atoms, and  
51 much less important to have the correct number of water molecules around the methyl groups.  
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It must be noted that other groups have developed techniques for finding the most chemically relevant water molecules near a solute rather than brute force including all the water molecules in the first two solvation shells (as was done by Rhode and coworkers for atomic ions).<sup>57-58</sup> Sequential adding water molecules to various sites and optimizing the geometry followed by high-level quantification of the thermodynamic stability of the various configurations was an approach pioneered by Perpète and Jacquemin.<sup>52-56</sup> While this method is elegant for gas phase microsolvation, it is conceivable that it may converge on water arrangements nearest to the solvent that are far less stable in the condensed liquid phase than in the gas phase. Hence our approach of going from a large number of water molecules down to a few water molecules is arguably a little more conceptually satisfying and requires far less computational effort.

### 3. High level optimization of solutes with explicit quantum water molecules

As a result of the previous steps, we have come to the conclusion to restrict the number of water molecules that should be treated quantum mechanically to those that are in direct interaction with the active site (sulfur and oxygen atoms) substrate, thus forming the first hydration shell. As an initial guess for those water molecules, several snapshots were extracted from the MD simulations considering only the water molecules included in spheres of 2.60 Å radius from the sulfur and oxygen of the solutes considered (DMS, DMS-•OH, •OH). The optimization of these two individual reactants, independently embedded in the implicit CPCM solvent model, were carried using the BH&HLYP/6-311+G(d,p) level of theory. The s representing the final optimized geometries of these super-systems are displayed in Table 2.

Mixed implicit-explicit solvent models have been shown by Antonczak and others to be problematic for estimating the entropic contributions to thermodynamic properties, indeed for each water molecule treated explicitly it was estimated that the entropic would increase by 10-12kcal/mol regardless of its interaction or lack of interaction with the solute.<sup>51, 75</sup> Since we do not use the mixed model for evaluating free energies, thermodynamic properties or quantifying solvent-solute interaction energies and only focus on the molecular properties of the solute this is not likely to be a serious issue.

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What came out from the geometry optimizations is that, when six (respectively four) water molecules are used to solvate the DMS (respectively the HO•), all the water molecules are linked together by H-bonds, but some of them are only linked with other water molecules and do not appear to interact with the solutes. As a consequence, we have further reduced the focus by considering only three, and then two water molecules surrounding the DMS, selecting water molecules at a distance less than 4 Å from the sulfur atom of the DMS; and two water molecules surrounding the HO• radical, selecting water molecules located at a distance less than 2 Å from it. As a result, only the clusters DMS+2H<sub>2</sub>O and HO•+2H<sub>2</sub>O displays, after geometry optimization, solvent molecules directly interacting with the substrate.

As the adduct DMS-•OH is concerned, table 3 displays the optimized geometries obtained at the BH&HLYP/6-311+G(d,p)/CPCM and MP2/6-311+G(d,p)/CPCM, when five (top) and four (middle and bottom) water molecules are embedded in the implicit solvent. Basically, both MP2 and BH&HLYP levels of theory conclude that the fifth water molecule has no direct connection with DMS or •OH, as it can be seen in the middle column of table 3. In particular, both the geometry and spin densities on the bonded sulfur and oxygen come out to be almost identical at the BH&HLYP level whether four or five solvent molecules are used. The major differences between the two methods are the SO bond lengths that differ significantly, and come out to be much shorter with the MP2 method than when using the BH&HLYP functional (2.16-2.21 Å instead of 2.31 Å). It is however well known that approximate density functionals tend to overestimate the bond length in 2c-3e bonds,<sup>67</sup> while the MP2 method tends to underestimate the 2c-3e bond distance in some cases.<sup>76-77</sup> The BH&HLYP also provides a more even sharing of the radical between the bonded sulfur and oxygen atom than the MP2 method, as illustrated by the spin density values on these atoms displayed in Table 3.

It appears that four water molecules are enough to describe the first solvation shells around the active sites of the solute from equilibrium (DMS-•OH adduct) to dissociation limit. Besides, it can be noted that the geometries obtained with the BH&HLYP method are similar to either the solute DMS-•OH+4H<sub>2</sub>O embedded in a CPCM, or surrounded by the explicit solvent as it was done in QM/MM calculations (see Table 4 in SI). This validates our choice to use the DMS-

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3  $\bullet$ OH+4H<sub>2</sub>O super system with more sophisticated *ab-initio* methods such as CCSD or BOVB  
4 with the water bulk represented by the implicit solvent (see also the SI).  
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11 To settle the issue of the contrasted SO bond distances and spin densities found with the  
12 BH&HLYP and MP2 methods, we have performed further CCSD geometry re-optimization of  
13 the SO bond distance only, starting from the full geometry optimized structures obtained at both  
14 the BH&HLYP and MP2 levels. The exact procedure used for the S-O bond distance  
15 optimization is described in the computational details section, and results displayed in table 3  
16 (bottom). At the CCSD level, the SO bond distances is largely reduced from the original  
17 BH&HLYP values, and slightly increased as compared with the original MP2 value, to values of  
18 2.19 and 2.22 for the MP2/CCSD and BH&HLYP/CCSD geometries respectively. The sharing  
19 of the spin densities between the bonded sulfur and oxygen, on its side, seems to depend not only  
20 on the SO bond distance but also on the overall geometry of the DMS- $\bullet$ OH+4H<sub>2</sub>O super-system,  
21 as well as on the location of the solvating water molecules also. However, in both final  
22 geometries the radical appears to be largely shared between the sulfur and oxygen centers,  
23 potentially indicative of a resonant 2c-3e bond, a point that will be tackled in the following  
24 section.  
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37 ----- insert table 4 near here -----  
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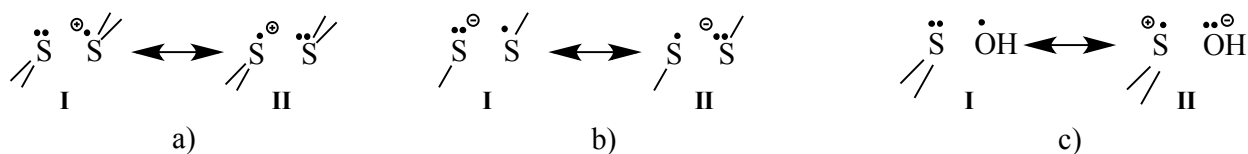
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40 The table 4 displays from bond dissociation energies of DMS-OH into the respective  
41 neutral DMS and  $\bullet$ OH fragments, for different solvation models and levels of theory. The  
42 explicit solvation model provides at the BH&HLYP level a zero Kelvin BDE some ~2 kcal/mol  
43 larger than the implicit model, which is consistent with a shorter bond length obtained with the  
44 former model. In addition, the BDE at the MP2 level (using the MP2 optimized geometry  
45 appears to be quite significantly larger than at the BH&LYP level. Last, it should also be noted  
46 that the “homolytic” dissociation (to DMS +  $\bullet$ OH) is energetically more favorable than the  
47 “heterolytic” dissociation (to DMS<sup>•+</sup> + <sup>-</sup>OH), by some 26 kcal/mol at the BH&HLYP/6-  
48 311+G(d,p)/CPCM level of theory, with both DMS and  $\bullet$ OH fragments (neutral or ionic alike)  
49 solvated by two explicit water molecules. Looking at this value alone one might be tempted to  
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rule out the heterolytic mechanism, however it will be insightful to inspect more closely the electronic structure in the solvated DMS- $\cdot\text{OH}$  adduct, as we will see in the following section.

#### 4. Valence Bond analysis.

When an  $\text{HO}\cdot$  radical attaches to the lone pair of a less electronegative atom like sulfur, two types of interactions may arise: either a weak electrostatic interaction, or a stronger resonating three electron bond. The conditions for a stable sulfur-oxygen three electron bond have been already studied in the past.<sup>35</sup> Because, as will be explained below, it can be postulated that only when a 2c-3e bond occurs that a heterolytic dissociation may take place, the main characteristics of this interaction is recalled here.

Two-centers three-electron (2c-3e) bonds have originally been described within Valence Bond (VB) theory by Pauling,<sup>78</sup> as arising from the resonance interaction between two VB structures that are connected by the shift of one electron. This type of interaction may arise when one fragment having a radical electron binds a second fragment having a lone pair. Prototype examples of cationic, anionic and neutral three-electron bonds involving a sulfur atom, as depicted in Scheme 1, are: a) the  $[\text{R}_2\text{S}]_2^+$  cation dimer (where R could be an alkyl group or any other substituents), b) the disulfide  $[\text{RS}]_2^-$  anion, that appears as long-living intermediates in bio(in)organic reactions involving reduction of a disulfide bridge, and: c) the adduct coming from the interaction of the  $\text{HO}\cdot$  free radical with a lone pair of a sulfur atom in a neutral fragment. The two-structures resonating VB description for these three prototype cases is displayed in scheme 1.



**Scheme 1.** Two-structures Valence Bond resonating descriptions of 2c-3e bonding for: a) the  $[\text{R}_2\text{S}\cdot\cdot\text{SR}_2]^+$  cation dimer, b) the  $[\text{RS}\cdot\cdot\text{SR}]^-$  anion dimer, c) the neutral  $[\text{R}_2\text{S}\cdot\cdot\text{OH}]$  adduct.

In the case of anionic and cationic three-electron bonded systems, each VB structure taken separately is generally only marginally stabilizing through pure electrostatic interactions with

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4 respect to the separate fragments at infinite distance, and thus the large overall stabilization  
5 energy (up to ~60 kcal/mol in some cases) mainly comes from the *large resonance energy*  
6 arising from the mixing of *the two VB structures together*. This resonance energy stabilization  
7 could be interpreted as coming from the dynamical shift of charge between the two fragments,  
8 thus classifying this type of bond as a complete « charge shift bond ». <sup>79-81</sup>  
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13 One important condition for having a stable 2c-3e bond is that the two VB structures should be  
14 close in energy, because simple perturbation theory shows that the resonance energy between the  
15 two structures is inversely proportional to their energy difference. The ideal case occurs when  
16 the two structure are degenerated, as in the prototype cases of  $[\text{H}_2\text{S}]_2^+$  or  $[\text{RS}]_2^-$  already  
17 mentioned, a situation that can strictly happen only in case of anionic or cationic dimers  
18 composed of identical fragments.  
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25 Three-electron bonds are much less common in neutral systems, because in this case one VB  
26 structure is a neutral one and the second is necessarily a di-ionic structure, as displayed in  
27 scheme 1c) in the case of  $\text{S}:\cdot\text{O}$  bonding, so the two VB structures are usually largely separated  
28 in energy (note that in the following we will use the symbol “ $\cdot\cdot$ ” originally proposed by Asmus<sup>2</sup>  
29 to identify a resonating 2c-3e type of bonding). The two VB structures may reasonably be close  
30 in energy when the Ionization Potential (IP) of the fragment initially containing the lone pair is  
31 close to the Electron Affinity (EA) of the second (initially radical) fragment. In the case of a  $\text{S}:\cdot$   
32 O adduct, it is when sufficiently donating substituents are bonded to the sulfur atom that this  
33 condition can be fulfilled. Otherwise, when the two VB structures are much different in energy,  
34 the system in its ground electronic state is basically described by the neutral VB structure only,  
35 i.e. it is an adduct stabilized by weak non-covalent interactions.  
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46 At the *ab initio* BOVB level of theory, a two-structure wave function corresponding to the  
47 resonance mixing  $\mathbf{I} \leftrightarrow \mathbf{II}$  is variationally optimized, where  $\mathbf{I}$  is the neutral VB structure and  $\mathbf{II}$  the  
48 di-ionic one, as depicted in scheme 1c). Details about the BOVB method and the definition of the  
49 structure weights are provided in the SI. Assessing whether a true  $\text{S}:\cdot\text{O}$  2c-3e bonding or a weak  
50 adduct occurs in the case of  $\text{DMS}^+$  could simply be done by inspecting the structure weights  
51 coming out of the BOVB wave function optimization. A true 2c-3e bonding will indeed be  
52 characterized by similar weights for the two structures, in the range of ~50-70% (resp. ~30-  
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3 50%) for the major neutral VB structure (resp. minor di-ionic VB structure), whereas in the case  
4 of a weak non-covalent adduct the neutral structure will have a very largely dominant weight of  
5 ~90% or more.  
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10 It is particularly important here to identify the nature of the interaction between DMS and  $\bullet\text{OH}$ ,  
11 because it is only in cases where a 2c-3e is found, i.e. with similar weights on structures **I** and **II**,  
12 that the mechanism of heterolytic dissociation may takes places. Structure **I** corresponds to the  
13 electronic structure of the reactants indeed, DMS and  $\bullet\text{OH}$ , while structure **II** corresponds to the  
14 electronic structure of the products of the heterolytic dissociation, namely  $\text{DMS}^{\bullet+}$  and  $\text{OH}^-$ .  
15 When  $\bullet\text{OH}$  attaches to the sulfur atom of DMS, if it is a weak non-covalent adduct that is  
16 formed, the super system ground state VB wave function will mainly be composed of structure **I**,  
17 which means that structure **II** only mixes marginally into the ground state wave function. Thus  
18 an excitation to an electronic state mainly composed of structure **II**, a prerequisite for the  
19 heterolytic dissociation pathway, would represent a too high of an energy barrier to overcome.  
20 On the other hand, if the interaction that takes place is a true 2c-3e one, that means structure **II**  
21 will mix strongly into the ground state VB wave function when the DMS and  $\bullet\text{OH}$  approach  
22 together, and thus that the adduct can more easily dissociate into a state corresponding to  
23 structure **II** only, i.e. take the pathway of heterolytic dissociation to  $\text{DMS}^{\bullet+}$  and  $\text{OH}^-$  fragments.  
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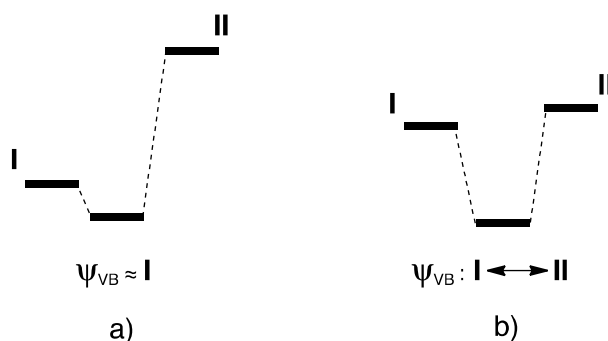
36 From the above analysis, we can infer that the larger the weight of structure **II** in the ground  
37 state VB wave function, the more likely the heterolytic dissociation mechanism becomes.  
38 Alternatively, a second more quantitative indicator is the energy difference  $\Delta E_{I/II}$  of the two VB  
39 structures that compose the multi-structures VB wave function  $\psi_{\text{VB}}$ , as defined by equation 2:  
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$$44 \quad \Delta E_{I/II} = E_{\text{VB}}(\text{II}) - E_{\text{VB}}(\text{I}) \quad (2)$$

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48 Note that  $E_{\text{VB}}(\text{I})$  and  $E_{\text{VB}}(\text{II})$  correspond to the energy of the structures **I** and **II**, respectively,  
49 each with their own set of orbitals optimized in two separate calculations, and distinct to the total  
50 multi-structure  $\psi_{\text{VB}}$  where the two structures are mixed and are optimized (as well as their  
51 relative weights) in the presence of each other (see the SI for more details). As illustrated in  
52 scheme 2a), a large  $\Delta E_{I/II}$  correspond to the case where the ionic structure **II** is much higher in  
53 energy than the neutral structure **I** and thus does not mix much into the ground state wave  
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function, so in such a case the ground state is essentially a neutral adduct and the heterolytic mechanism would be quite unlikely. On the other hand, in case where  $\Delta E_{I/II}$  is small, as illustrated in scheme 2b)), structure **II** will substantially mix into the ground state wave function, and thus the heterolytic mechanism could be reasonably envisaged.



**Scheme 2.** The two cases of adducts: a) large  $\Delta E_{I/II}$  energy difference between separate structures **I** and **II** leading to a weak mixing of **II** into  $\psi_{VB}$ ; b) small  $\Delta E_{I/II}$  leading to a large mixing of **II** into  $\psi_{VB}$ .

In table 5 the BOVB total energy, structure weights and  $\Delta E_{I/II}$  are displayed, for both the BH&HLYP/CCSD and MP2/CCSD optimized geometries (see “Computational details”). For the calculation of  $\Delta E_{I/II}$ , the energies  $E_{VB}(\mathbf{I})$  and  $E_{VB}(\mathbf{II})$  correspond to the energies of each of the two VB structures *computed separately*, i.e. obtained from a separate wave function optimization calculation, thus providing for each one their own optimal set of orbitals. The BH&HLYP/CCSD geometry corresponds to both the lowest BOVB and CCSD total energy. However, the energy difference between the two geometries is not very large, so the two different arrangement of the water cluster obtained from the BH&HLYP and MP2 geometry optimizations could both be considered as representing two realistic arrangements. In both cases, the VB structures **I** and **II** comes out with similar weights from the BOVB calculations of the  $\mathbf{I} \leftrightarrow \mathbf{II}$  resonance mixing, **I** being the dominant structure in the BH&HLYP/CCSD geometry, while **II** is slightly more dominant in the MP2/CCSD geometry. The same trend is found when looking to the  $\Delta E_{I/II}$  energy difference. A value of only 16.8 kcal/mol is found for  $\Delta E_{I/II}$  when computed using the BH&HLYP/CCSD geometry, which indicates that the two individual VB structures are rather close in energy; and it is found to be even as small as 2.8 kcal/mol when the MP2/CCSD geometry is used, showing that the two structures are almost degenerate in that case



----- insert table 5 near here -----

The BOVB method not being a routine electronic structure method requires theoretical expertise in Valence Bond theory and specific technical know-how to be properly used. Furthermore, the method remains quite computationally demanding, and thus is limited to the model systems studied so far. Thus it would be highly desirable to be capable of obtaining the same type of analysis from a more routine *ab initio* wave function method. In the specific case of the 2c-3e bond, it is possible to retrieve an estimate of the weights of the two VB structures from the spin density analysis computed from any wave-function method. This is because, for a 2c-3e bond: i) each VB structure displays a different and distinct number of active electrons on the sulfur and oxygen centers and: ii) the spin density is essentially shared between the sulfur and oxygen atoms making the 2c-3e bond. Hence, the spin polarization is due to the three-electron bond and not from other electron pairs. The structure weights  $\omega(\mathbf{I})$  and  $\omega(\mathbf{II})$ , expressed in %, may indeed be estimated using the spin densities of equation 3. Specifically  $\rho(\text{O})$  and  $\rho(\text{S})$  are the spin densities on oxygen and sulfur atoms, respectively, computed at any given level of theory. These weights are simply the renormalized spin densities.

$$\omega_I = 100 \times \frac{\rho(\text{O})}{\rho(\text{S}) + \rho(\text{O})} \quad (3)$$

$$\omega_{II} = 100 \times \frac{\rho(\text{S})}{\rho(\text{S}) + \rho(\text{O})} \quad (4)$$

The spin densities computed at the CCSD and BOVB levels of theory, along with the inferred structure weights calculated using equations 3 and 4, are displayed in table 6. It can be noted that the BOVB weights estimated this way are remarkably close to the original Coulson-Chirgwin weights shown in table 5. This fully validates the approach of equation 3 and underlying approximation in the case of a 2c-3e bond. Let us remark that although CCSD and BOVB methods both include some electronic correlation, this is to a much larger extent for the CCSD method, so it is reasonable to consider that the latter method provides a more accurate description of the system. However, it is unfortunately impossible to estimate CCSD values for the  $\Delta E_{I/II}$  energy difference, as this quantity would require the computation of separate structure energies, which could only be provided by a method, like BOVB, capable of computing

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3 individual diabatic states. However, it is clear from the CCSD structure weights that, at this level  
4 of theory, the structure **II** comes out to be the major one, by a tiny amount when the  
5 BH&HLYP/CCSD geometry is considered but more significantly when the MP2/CCSD  
6 geometry is used. This result clearly supports the possibility of a heterolytic dissociation  
7 mechanism.  
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13 ----- insert table 6 near here -----  
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16 One can see from the previous data, that two different arrangements of the four water  
17 molecules surrounding the HO•DMS adduct while close in energy correspond to respective  
18 structures with weights differing by some ~10%. Such a sensitivity of the VB weights with  
19 respect to the first solvation shell vs. a much smaller sensitivity of the total energy was quite  
20 unexpected, and calls for further investigation.  
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26 In ambient temperature the water molecules dynamically move around the HO-DMS adduct,  
27 exploring configurations that are close in energy, so it is legitimate to try to answer the following  
28 questions: i) what is the overall range in variations of the structure **I** vs. **II** weights, ii) is there a  
29 situation with even more contrasted **I** vs. **II** weights, and: iii) what is the overall statistical  
30 significance of situations where the S•O bond is dominantly described by structure **II**, i.e. an  
31 electronic situation prone to heterolytic dissociation. To answer this question, the same structure  
32 weight estimation based on CCSD spin-density analysis were performed on a set of  
33 configurations with four water molecules extracted directly from the molecular dynamics, with a  
34 fixed SO bond length of 2.45Å. These configurations selected were each more than 200ps apart  
35 from each other in the molecular dynamics trajectory, which is sufficient to ensure that the  
36 snapshots are decorrelated. The results are displayed in table 7. Minimum potential energy  
37 snapshots tend to have two water molecules hydrogen bonded to the •OH moiety of the DMS  
38 adduct while the maximum potential energy snapshots tend to have none. The coordinates and  
39 figures of two snapshots, with either minimum or maximum potential energy, can be found in  
40 table S6 of the SI.  
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3 In these snapshots, the three lowest in potential energy give the two weights of structure **I** and  
4 **II** to be equal or slightly favor structure **II**. The other three snapshots, which are significantly  
5 higher in potential energy, the weight of structure **I** is found to be slightly more dominant with  
6 the most extreme case being a 56.2/43.8 ratio. All in all, it can be concluded that the SO bond in  
7 the HO $\cdot$ :DMS adduct incorporates a substantial amount of the diabatic electronic state  
8 corresponding to the products of an heterolytic dissociation (HO $^-$  and DMS $^{*+}$ ), with a **I/II** ratio  
9 that could vary roughly between  $\sim$ 60/40 and  $\sim$ 40/60 depending on the dynamic arrangement of  
10 the water molecules belonging to the first solvation shell; and, consequently, that an heterolytic  
11 dissociation mechanism is a hypothesis that is backed up by this analysis.  
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## 20 **Conclusion.**

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23 In this work we have revisited the oxidation of dimethyl sulfide by  $\cdot$ OH radical, by carefully  
24 taking into account explicit water molecules surrounding dimethyl sulfide (DMS), the hydroxyl  
25 radical and their adduct in the quantum calculations. The role of explicit water molecules were  
26 previously found to be important in another oxidation mechanism, namely the oxidation of DMS  
27 by hydrogen peroxide, however the previous study only considered the neutral reactants and  
28 products<sup>42</sup>.  
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35 First, we have pointed out that in the formation of the  $>$ S $\cdot$ OH the influence of the substituents  
36 of the sulfur atom is negligible, thus the choice of DMS to model larger molecules such as Met  
37 (notably in its extended conformation).  
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42 Second, for the three systems in our study, namely DMS,  $\cdot$ OH and their adduct [DMS-OH] $\cdot$ ,  
43 we performed MD simulations with thousands of water molecules surrounding them, which  
44 allowed us to analyze the changes concerning mainly the first solvation shell. From these MD  
45 simulations, we extracted small clusters of water molecules most likely forming the first  
46 solvation shells, and used two different methodologies: i) QM/MM calculations, and ii) full  
47 quantum DFT calculations (BH&HLYP) with an implicit solvent, to determine accurately what  
48 are the water molecules in direct interaction with the solvated molecule. Both methodologies  
49 agreed. The resulting minimal clusters were subsequently used in high level CCSD and BOVB  
50 calculations.  
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3 Finally, BOVB a high level Valence Bond method was used to compute the weights of the two  
4 possible diabatic states that mix in the ground state wave function of DMS- $\bullet$ OH, i.e. the ratio of  
5 the charged (ionic) diabatic structure [DMS $\bullet^{++}$ -OH] to the neutral diabatic structure [DMS-OH $\bullet$ ].  
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7 When the weights of the two diabatic structures are similar it corresponds to the existence of a  
8 resonant 2c-3e (two-center three-electron) bond between the sulfur atom of DMS and the oxygen  
9 atom of  $\bullet$ OH. Meanwhile a substantially larger weight for the neutral diabatic state corresponds  
10 to a weakly bonded adduct. Our calculations revealed that the readily accessible configurations  
11 of water molecules in the first solvation shell modulate the covalent/ionic character of the adduct  
12 S-O bond noticeably. BOVB calculations on snapshots obtained directly from MD simulations  
13 suggest that the neutral/ionic character of the bond varies from approximately 40/60% to  
14 60/40%, depending on the instantaneous water configuration. We have shown that in the case of  
15 3e-2c bonds, the structure weights can be estimated from the spin density on the atoms involved  
16 in the 3e-2c bond (i.e. the sulfur of DMS and oxygen of  $\bullet$ OH) computed at the MP2, BH&HLYP  
17 or CCSD level, and that these estimates correlate well with the weights obtained from BOVB  
18 calculations. The results from these model calculations provide guidance for future investigations  
19 of oxidation reactions involving larger sulfur-containing biological molecules.  
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38 **Supporting Information.** Detailed description of the methodology for the molecular dynamics  
39 simulations (including solute geometries and force field parameters) and additional background  
40 information for the Valence Bond methods is included in the SI.  
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#### 43 **ACKNOWLEDGMENT**

44 Pr. Wei Wu is gratefully thanked for making his XMVB program available to us.  
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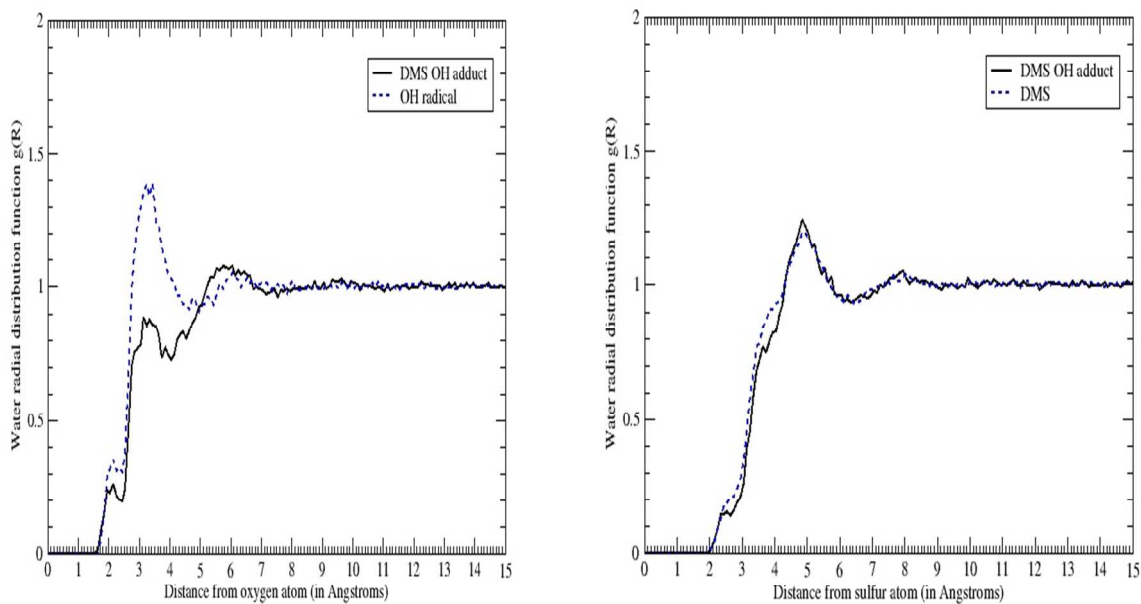
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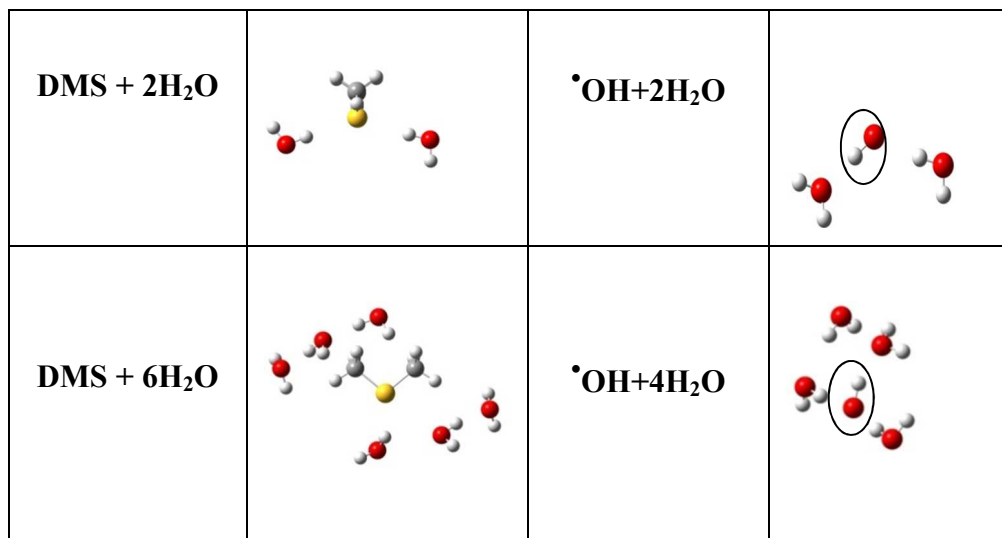
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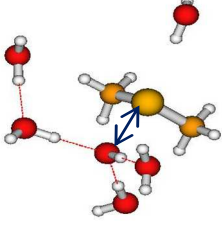
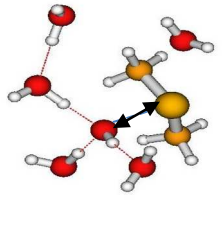
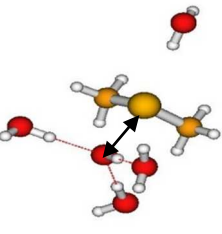
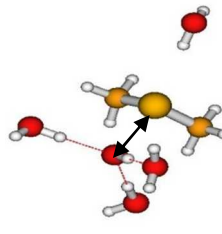
**Figure 1:** Radial distribution of water around: a) the oxygen atom of  $\bullet\text{OH}$  in the  $\text{DMS}\text{-}\bullet\text{OH}$  (solid line) and in the hydroxyl radical alone (dotted line) ; b) the sulfur atom of DMS in  $\text{DMS}\text{-}\bullet\text{OH}$  (solid line) and in the DMS fragment alone (dotted line).

Methods	Models	$\rho_S$	$\rho_O$	ds-o
Pbe0/6-31g(d)	“CH <sub>3</sub> ”	0.38	0.64	2.315
	“CO <sub>2</sub> CH <sub>3</sub> ”	0.37	0.65	2.315
	‘CO <sub>2</sub> HNH <sub>2</sub> ’	0.37	0.65	2.315
	“CONH”	0.37	0.65	2.315
BH&HLYP/6-31g(d)	“CH <sub>3</sub> ”	0.21	0.83	2.491
	“CO <sub>2</sub> CH <sub>3</sub> ”	0.20	0.84	2.504
	‘CO <sub>2</sub> HNH <sub>2</sub> ’	0.20	0.84	2.504
	“CONH”	0.20	0.84	2.504
BH&HLYP/6-311+g(d,p)	“CH <sub>3</sub> ”	0.38	0.64	2.363
	“CO <sub>2</sub> CH <sub>3</sub> ”	0.38	0.65	2.363
	‘CO <sub>2</sub> HNH <sub>2</sub> ’	0.38	0.65	2.364
	“CONH”	0.38	0.65	2.362

**Table 1.** The distances of the SO bond and the spin densities of S and O for various substituents of S, using different DFT functionals and basis sets, and embedded in the implicit solvent CPCM.



**Table 2.** Optimized geometries of the water molecules around solutes (DMS and •OH) at the BH&HLYP/6-311+G(d,p)/CPCM level of theory.

	BH&HLYP	MP2
	<b>DMS-<sup>•</sup>OH+5H<sub>2</sub>O</b>	
		
dSO (Å)	2.31	2.21
ρS ρO	0.54 0.50	0.78 0.35
	<b>DMS-<sup>•</sup>OH+4H<sub>2</sub>O</b>	
		
dSO (Å)	2.31	2.16
ρS ρO	0.54 0.50	0.70 0.40
	<b>BHandHLYP/CCSD<sup>(*)</sup></b>	<b>MP2/CCSD<sup>(*)</sup></b>
	<b>DMS-<sup>•</sup>OH+4H<sub>2</sub>O</b>	
dSO (Å)	2.22	2.19
ρS ρO	0.52 0.52	0.63 0.41

**Table 3.** Bond Dissociation Energies in kcal/mol of the DMS-<sup>•</sup>OH adduct with implicit CPCM solvation only (left), and of the DMS-<sup>•</sup>OH+4H<sub>2</sub>O super system (center and right) further embedded into CPCM. The 6-311+G(d,p) basis set has been used, and the geometries are those optimized at each given level of theory. Arrows represent the S-O bond and dotted lines represent hydrogen bonds present in the super system.

	DMS- $\dot{\text{O}}\text{H}$	DMS- $\dot{\text{O}}\text{H}+4\text{H}_2\text{O}$	
	BH&HLYP	BH&HLYP	MP2
BDE kcal/mol	5.51	7.42	13.11

**Table 4.** Bond Dissociation Energies of the SO bond in the adduct DMS- $\dot{\text{O}}\text{H}$  are calculated with two models of solvent: implicit one (CPCM) alone and with 4 water molecules for BH&HLYP and MP2

Optimized geometry	$\Delta E_{\text{BOVB}}$ (kcal/mol)	Weights I/II (%)	$\Delta E_{\text{I/II}}$ (kcal/mol)
MP2/CCSD	6.3	49.5 / 50.5	2.8
BH&HLYP/CCSD	0.0	57.3 / 42.7	16.8

**Table 5.** Relative BOVB total energy ( $\Delta E_{\text{BOVB}}$ ) using the most stable geometry as the energy zero, Chirgwin Coulson structure weights (see SI), and the energy difference of the individual structures  $\Delta E_{\text{I/II}}$  (see text), computed on the MP2/CCSD and BH&HLYP/CCSD optimized geometries respectively.

Geometry	CCSD		BOVB	
	$\rho(\text{S}) / \rho(\text{O})$	$\omega(\text{I}) / \omega(\text{II})$	$\rho(\text{S}) / \rho(\text{O})$	$\omega(\text{I}) / \omega(\text{II})$
MP2/CCSD	0.627 / 0.407	39.4 / 60.6	0.492 / 0.481	49.4 / 50.6
BH&HLYP/CCSD	0.522 / 0.518	49.8 / 50.2	0.411 / 0.563	57.8 / 43.2

**Table 6.** Spin densities on sulfur and oxygen, and corresponding structure weights defined as renormalized spin densities from equations (3), at both the CCSD and BOVB levels, computed using the MP2/CCSD and BH&HLYP/CCSD optimized geometries respectively.



Snapshots	$\Delta E_{\text{BOVB}}$ (kcal/mol)	Spin density (S/O)	Weights I/II(%) via equation (1)
min E npt snapshot	0.0	0.533 / 0.510	48.9 / 51.1
min E nvt snapshot 1	0.0	0.533 / 0.517	49.2 / 50.8
min E npt snapshot	0.8	0.515 / 0.535	50.9 / 49.1
max E npt snapshot	9.7	0.440 / 0.552	55.6 / 44.4
max E nvt snapshot 2	13.0	0.476 / 0.574	54.7 / 45.3
max E nvt snapshot	9.3	0.458 / 0.587	56.2 / 43.8

**Table 7.** Relative BOVB total energies ( $E_{\text{BOVB}}$ ) using the most stable geometry as the energy zero, computed from snapshots selected from the Molecular Dynamics (see text). Spin densities on sulfur and oxygen, and structure weights defined as renormalized spin densities from equations (3), at both the CCSD and BOVB levels. Coordinates and figures of snapshots 1 and 2 are summarized in tableS6.

## TOC GRAPHICS :

