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A computational study on the possible role of oxygen in the oxidation of methionine and dimethylsulfide initiated by OH radicals

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ABSTRACT

The oxidation of methionine residues (Met) is related with the pathogenesis of diseases like Alzheimer's. Density functional theory (B3LYP) calculations are used to investigate the thermochemistry of several possible reactive intermediates that may be involved in the oxidation of Met and its radical cation. The computational results are calibrated using dimethyl sulfide (DMS) as a model system which has been studied at the DFT, CCSD(T) and G3(MP2)//B3LYP levels of theory. The results suggest that molecular oxygen may be an important participant in the OH-radical initiated oxidation of Met.

1. Introduction

Methionine is an essential amino acid and it plays an important role in many biochemical processes, mostly during the beginning of protein synthesis in ribosomes but it is also an important antioxidant agent of the organism [1,2]. Methionine is easily oxidized because of the presence of sulfur in its side chain and its redox chemistry has attracted a lot of interest because of its postulated link with the pathogenesis of diseases like Alzheimer's [3–14] and Parkinson's [15]. Alzheimer's disease (AD) is a neurodegenerative disorder and is related with extensive oxidative stress conditions in the brain, and pathologically is characterized with the formation of senile plaques which the major component is the β-amyloid peptide (βAP). Various studies have shown that βAP causes protein oxidation, lipid peroxidation and the formation of reactive species of oxygen to the neurons and the synaptosomes [16–20]. The role of methionine and its oxidation to the neurotoxicity of βAP [3–14] is considered to be very important, as studies present attenuation of the oxidative stress with the absence of methionine from the βAP.

The main oxidized form of methionine in proteins is methionine sulfoxide (MetSO) a compound directly related with AD and which formally is the result of a two-electron oxidation of sulfur [1,2,10,11,21–24]. The one-electron oxidation leading to the formation of sulfur radical cation of methionine ($MetS^{\cdot+}$) can be carried out radical species like peroxy ($ROO^{\cdot}$), sulfide ($RS^{\cdot}$) and hydroxyl radicals ($OH^{\cdot}$). In particular the $OH^{\cdot}$ oxidation continues to attract a lot of attention [25,26]. The radical cation can be stabilized by forming S—O and S—N two-center three-electron (2c–3e) bonded complexes something that is expected to increase its lifetime [13,27–33]. Studies on the formation of peroxy radicals from the radical cation have also been published [34,35].

The aim of this work is to study possible intermediates in the oxidation of methionine by OH radicals and in particular the reactions of molecular oxygen with these intermediates. In this effort dimethyl sulfide (DMS) has been used as the simplest organic sulfide to model the oxidation of sulfur in Met. DMS itself is a significant product of biomass decay in oceans, and its oxidation by OH radicals has been studied computationally and experimentally due to its importance in the atmosphere [36–43].

2. Computational methods

All structures were optimized on the basis of the hybrid density functional theory ((U)B3LYP) and the 6-31G(d) and 6-31+G(d) basis sets as implemented in Gaussian 03 [44] and Gaussian 09 [45] suite of programs. Minima and transition-state structures were confirmed by vibrational analysis. For the small molecules and the model compounds (dimethyl sulfide (DMS) and its derivatives, R=H in Fig. 1) single-point energy calculations were carried out at the CCSD(T) level with the 6-31G(d) and 6-31+G(d) basis sets (CCSD(T)/6-31G(d)//(U)B3LYP/6-31G(d) and CCSD(T)/6-31+G(d)//(U)B3LYP/6-31+G(d)) and with the G3(MP2)//B3LYP (G3MP2B3 for

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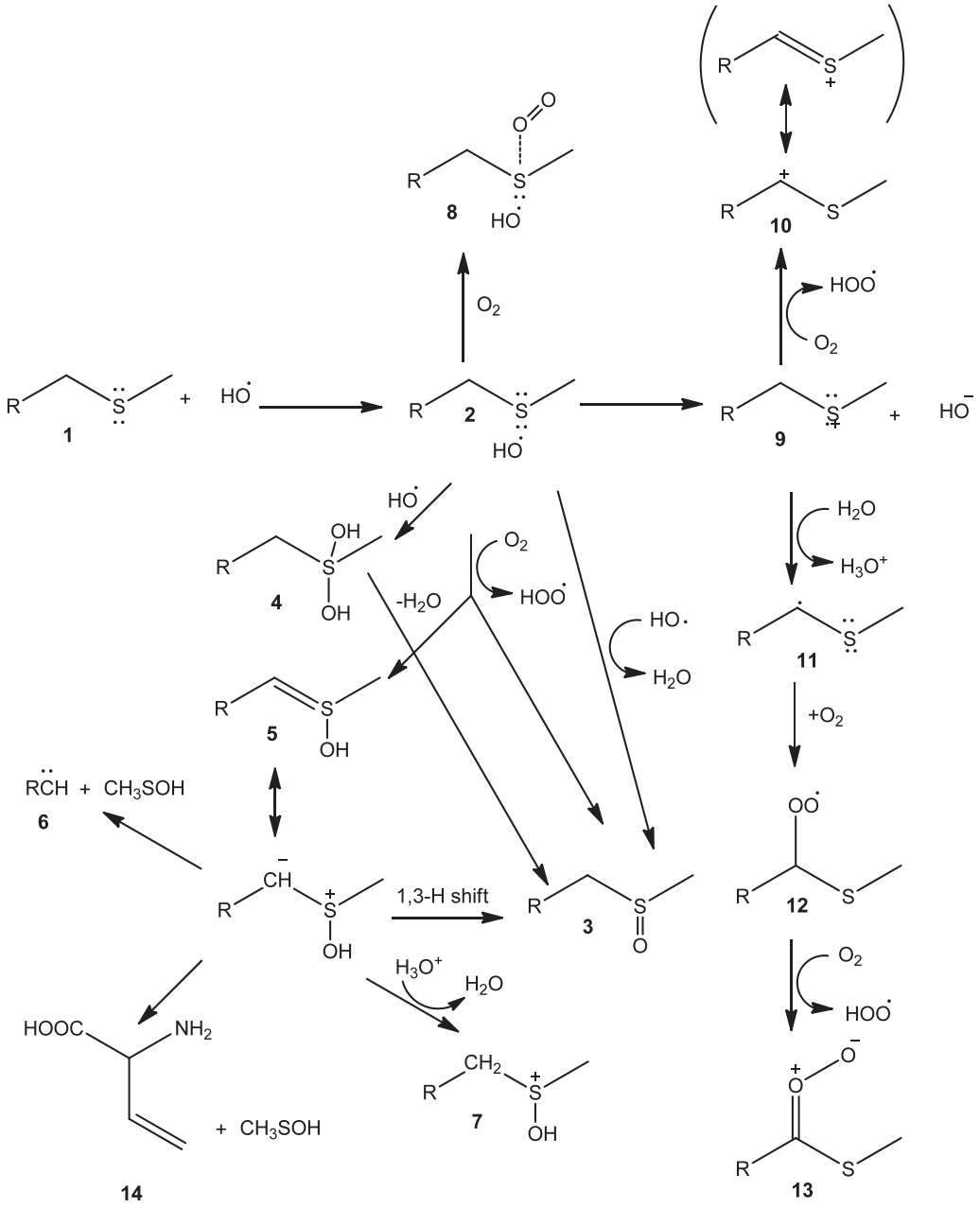

Fig. 1. Reaction pathways for oxidation of DMS (R═H, **1H**) and Met (R═(H_2N)(COOH)$CHCH_2$—, **1M**).

short) method [46]. G3MP2B3 energies were converted to heats of formation using published procedures [47]. Enthalpies and free energies at 298 K were obtained from the electronic energies using standard approaches for assessing thermal contributions as implemented in Gaussian 03 and Gaussian 09. Free energies for solvation were computed within the polarizable continuum model (PCM) [44,48]. It is assumed that the G3MP2B3 reaction energies are more reliable than the density functional theory (DFT) ones, and that their difference is approximately the same for the model compounds (R═H in Fig. 1) and methionine derivatives (R═(NH_2)(COOH)$CHCH_2$— in Fig. 1). Based on this assumption estimated G3MP2B3 values (Table 3) for the reactions of methionine have been obtained by "correcting" their B3LYP/6-31+G(d) energies with the difference between the G3MP2B3 and B3LYP/6-31+G(d) energies of the corresponding reaction with DMS. Unless otherwise noted, energy values in the text refer to the G3MP2B3 level of theory.

3. Results and discussion

The reactions which were studied are shown in Fig. 1 and the computed energies in Tables 1–3. DMS (**1H**) and its derivatives (Fig. 1, R═H) have been computed at the B3LYP, CCSD(T) and G3MP2B3 levels of theory. The G3MP2B3 model chemistry is expected to provide thermochemical data within chemical accuracy [46]. This is demonstrated for the compounds of this study in Table 1, where the computed heats of formation are in very good agreement with the experimental values. Thus, the G3MP2B3 reaction enthalpies of Table 2 can be used to evaluate the DFT and CCSD(T) results. At the DFT and CCSD(T) levels the inclusion of diffuse functions in the basis set is not that significant except where anions are involved. With few exceptions the DFT reactions energies are close to the CCSD(T) ones despite the big difference in computational cost (Table 3). With the 6-31+G(d) basis set the