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# A computational and experimental re-examination of the reaction of the benzyloxyl radical with DMSO

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## ABSTRACT

A detailed density-functional theory study on the reaction of the benzyloxyl radical (BnO<sup>•</sup>) with dimethyl sulfoxide (DMSO) was performed. The calculations reveal that BnO<sup>•</sup> transfers a hydrogen atom to DMSO via a proton-coupled electron transfer reaction to form benzaldehyde, in agreement with the mechanism proposed in the literature for the reaction of ethoxyl radical with substituted pyridines. The radical formed from this reaction, DMSO-H, is predicted to be unstable owing to population of the S–O antibonding  $\pi$ -orbital and decompose without barrier to form dimethyl sulfide and hydroxyl radical. The calculated exergonicity of the reaction is 16.6 kcal/mol. Our previous laser-flash photolysis (LFP) studies reported a kinetic deuterium isotope effect (KDIE),  $k_H(\text{DMSO})/k_D(\text{DMSO-}d_6)$ , of 0.91 for this reaction, which is consistent with the foregoing mechanism, and with the value calculated in this work of 0.77. New LFP data reported herein for the reaction of BnO<sup>•</sup>-*d*2 with DMSO give an experimental KDIE of 3.06, compared with a calculated value of 2.8. Taken collectively, our computational and experimental re-examination of the reaction between BnO<sup>•</sup> and DMSO leads to the conclusion that BnO<sup>•</sup> transfers a hydrogen atom to, rather than abstracts a hydrogen atom from, DMSO.

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## 1. Introduction

Radical-induced damage to biomaterials such as proteins and lipids has been implicated in a variety of disease states [1–3]. This damage is often induced by reactive oxygen species (ROs), which abstract hydrogen atoms from substrate species and thereby induce structural damage to the biomaterials. Hydroxyl and alkoxy radicals are important examples of biologically relevant ROs [4,5]. Further investigation of these chemical species provides insight into the importance of physical interactions in radical-substrate complexes and their impact on the mechanism and kinetics of these reactions [6–9]. These insights are important for discerning the chemoprotective role played by antioxidants in biological systems.

Our recent work in this area has focused on the reactivity of the prototypical alkoxy radicals, cumyloxy (CumO<sup>•</sup>, C<sub>6</sub>H<sub>5</sub>C(CH<sub>3</sub>)<sub>2</sub>O<sup>•</sup>) and benzyloxy (BnO<sup>•</sup>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O<sup>•</sup>), with a view to shedding light on various aspects of their hydrogen atom abstraction reactions.

Using time-resolved laser flash photolysis experimental studies, combined with dispersion-corrected density-functional theory based gas-phase simulations, much of our effort has led to insights into the role of hydrogen-bonding interactions between the alkoxy radicals and the substrates with which they react [10–14]. For example, we showed that hydrogen atom abstraction reaction rates from amines by BnO<sup>•</sup> trended in opposite directions from those of CumO<sup>•</sup> with changes in the degree of alkyl substitution on amine substrates [12,14]. The differences in reactivity were attributed to the ability of BnO<sup>•</sup> to form a hydrogen bond between the radical  $\alpha$ -C–H moiety and the amine nitrogen atom. The benzylic hydrogen atoms of BnO<sup>•</sup> are acidic due to the strongly electron withdrawing oxygen-centered radical [15,16]. CumO<sup>•</sup> has methyl groups on the benzylic carbon atom and therefore cannot engage in strong hydrogen bonding.

Studies of CumO<sup>•</sup> and BnO<sup>•</sup> with the strong hydrogen bond acceptors dimethyl sulfoxide (DMSO, (CH<sub>3</sub>)<sub>2</sub>SO) and hexamethylphosphoramide (HMPA, ((CH<sub>3</sub>)<sub>2</sub>N)<sub>3</sub>PO) appeared to confirm the important role of hydrogen bonding in differentiating the reactivity of the two radicals [11]. Specifically, we showed that rate constants associated with the reaction of CumO<sup>•</sup> with DMSO and HMPA (in acetonitrile) are  $1.8 \times 10^4$  and  $1.9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ , respectively. Rate constants for the reaction of BnO<sup>•</sup> with the same

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substrates increase by factors of 1600 and 86, respectively. The enhancement in reactivity was explained by the ability of  $\text{BnO}^\bullet$ , and not  $\text{CumO}^\bullet$ , to form strong hydrogen bonded pre-reaction complexes that allow for more facile abstraction of a substrate methyl hydrogen atom.

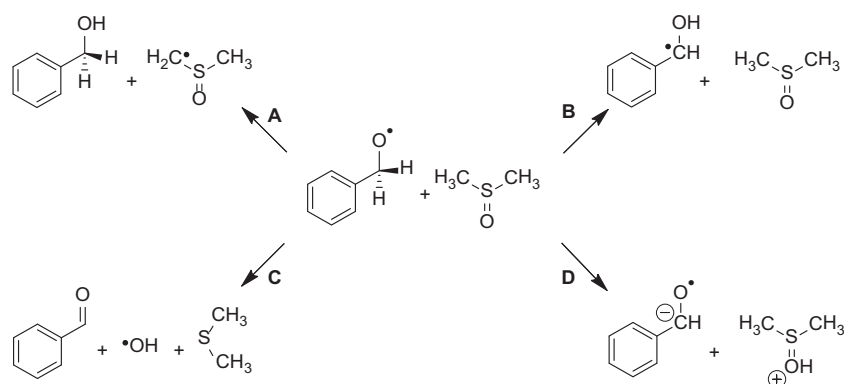
Another interesting aspect of the reactivity of the  $\text{CumO}^\bullet$  and  $\text{BnO}^\bullet$  radicals with DMSO, is the differences in their respective kinetic isotope effects (KIE) [11]. For  $\text{CumO}^\bullet$ , the KIEs for  $\text{DMSO}/\text{DMSO-d}_6$  was measured to be 2.0. This finding was rationalized on the basis that  $\text{CumO}^\bullet$  abstracts a methyl H or D via *direct* atom transfer rather than first forming a strongly bound pre-reaction complex. On the other hand, the KIE for  $\text{BnO}^\bullet$  was found to be 0.91 for  $\text{DMSO}/\text{DMSO-d}_6$ . This suggests that the rate-limiting step in the reaction is not associated with cleavage of a substrate C–H/C–D bond, but rather the formation of the pre-reaction, hydrogen bonded complex which is nearly diffusion-controlled [11].

An alternative explanation for the interesting findings associated with the reaction of  $\text{BnO}^\bullet$  with DMSO and HMPA can be derived from a recent study involving the reactivity of primary alkoxy radicals with pyridine derivatives [17]. In that work, the authors propose that  $\text{CH}_3\text{O}^\bullet$  and  $\text{CH}_3\text{CH}_2\text{O}^\bullet$  radicals react as hydrogen atom donors with substituted pyridines to produce formaldehyde or acetaldehyde and *N*-hydropyridinyl radicals. This proposal is supported by measured KIEs ( $k_{\text{CH}_3\text{O}^\bullet}/k_{\text{CD}_3\text{O}^\bullet}$ ) of 6.5. Density-functional theory (DFT) based calculations also supported the mechanism associated with hydrogen atom donation from the alkoxy radicals.

In light of the findings reported in Ref. [17], and the weakness of the benzylic C–H bond in  $\text{BnO}^\bullet$  relative to that in  $\text{CH}_3\text{CH}_2\text{O}^\bullet$  (viz., 12.5 kcal/mol versus 15.4 kcal/mol, respectively [18,19]), we decided to re-examine the reaction between  $\text{BnO}^\bullet$  and DMSO using DFT modeling with corrections for solvent and laser-flash photolysis experiments, with particular focus on  $\text{BnO}^\bullet$  as a *hydrogen atom donor*. Our study reveals that the most likely mechanism for the reaction of  $\text{BnO}^\bullet$  with DMSO is through a hydrogen atom transfer from the radical to DMSO via proton-coupled electron transfer.

## 2. Computational methods and details

We carried out density-functional theory (DFT) calculations for the present study using the Gaussian-09 program package [20]. Several functionals were utilized for calculations including B3LYP [21,22] M05-2X [23], and M06-2X [24]. We also used the B3LYP approach in conjunction with dispersion-correcting potentials (DCP) [25,26] in order to correct for some of the deficiencies that the DFT method has when it comes to modeling noncovalent interactions (this approach is referred to as B3LYP-DCP). For preliminary calculations, we used 6-31+G(d,p) basis sets and larger, 6-31+G(2d,2p) basis sets were used for the reported results.



**Scheme 1.** Reactions of  $\text{BnO}^\bullet$  with dimethyl sulfoxide (DMSO) studied in this work.

The  $\text{BnO}^\bullet$  radical may react with DMSO according to the reactions presented in **Scheme 1**. Reaction 1A represents the hydrogen atom transfer reaction in which the radical abstracts a hydrogen atom from the substrate. This reaction was studied previously using gas-phase calculations [11]; 1B shows the 1,2-hydrogen atom shift that occurs in  $\text{BnO}^\bullet$  that may be assisted by interactions with DMSO. In acetonitrile solvent with water as an additive, this rearrangement has a measured rate constant of  $3.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$  [27,28]; 1C shows a proposed mechanism for the transfer of a hydrogen atom from  $\text{BnO}^\bullet$  to DMSO. As far as we know, this mechanism has not been proposed in the literature prior to the present work, although it is analogous to a mechanism proposed in Ref. [17]; reaction 1D represents a proton transfer between the radical and DMSO.

In general, multiple relative orientations of reactants were explored in an effort to determine the appropriate transition state (TS) structures for reactions 1A–1C. The TS structure for the proton transfer reaction in 1D is likely equivalent to that for the hydrogen atom transfer reactions represented in 1C. Initial guesses for the TS structures were made by fixing the X–H–Y distances (where X and Y represent the atoms on the substrate and radical between which the hydrogen is transferred) at *ca.* 1.25 Å, and performing constrained geometry optimizations followed by frequency calculations. The force constants from the frequency calculation were then used to perform optimizations to the TS structures with all geometry constraints removed. In this way, TS structures were obtained for most of the reactions using the B3LYP/6-31+G(d,p) approach, and these structures and their associated force constants were then used as initial guesses to obtain optimized TS structures using other DFT methods and basis sets. All optimized TS structures (except that for 1B, *vide infra*) possessed a single imaginary vibration mode that connect reactants to products. The visualization of vibration frequencies was performed with the Chemcraft program [29].

For the 1,2-hydrogen atom shift (1B), we were unable to locate a genuine TS structure. In an effort to develop some insight into the effect of DMSO on this reaction, we placed a DMSO molecule near the shifting hydrogen atom in the gas-phase TS structure associated with 1B. The C···H···O atoms in the TS structure were constrained to maintain their positions in space while the remainder of the benzoyloxyl and the adjacent DMSO molecule were subjected to geometry optimizations. The resulting structures were then subjected to the usual (*vide supra*) TS structure optimizations. In all of our attempts, a small additional imaginary frequency persisted. However, we feel that our approach does provide us with an approximation to the DMSO assisted 1,2-hydrogen atom shift.

In most cases, the pre-reaction and post-reaction complexes were determined by performing geometry optimization calculations starting from a number of different relative orientations of

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