

Reactions of the Cumyloxyl and Benzyloxyl Radicals with Strong Hydrogen Bond Acceptors. Large Enhancements in Hydrogen Abstraction Reactivity Determined by Substrate/Radical Hydrogen Bonding

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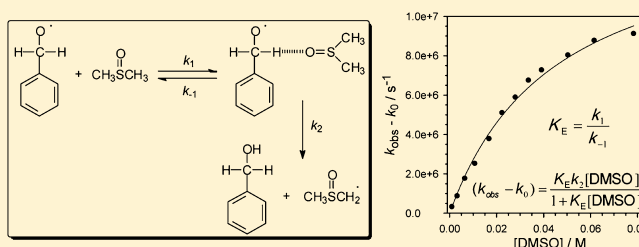
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S Supporting Information

ABSTRACT: A kinetic study on hydrogen abstraction from strong hydrogen bond acceptors such as DMSO, HMPA, and tributylphosphine oxide (TBPO) by the cumyloxyl (CumO[•]) and benzyloxyl (BnO[•]) radicals was carried out in acetonitrile. The reactions with CumO[•] were described in terms of a direct hydrogen abstraction mechanism, in line with the kinetic deuterium isotope effects, $k_{\text{H}}/k_{\text{D}}$, of 2.0 and 3.1 measured for reaction of this radical with DMSO/DMSO-*d*₆ and HMPA/HMPA-*d*₁₈. Very large increases in reactivity were observed on going from CumO[•] to BnO[•], as evidenced by $k_{\text{H}}(\text{BnO}^{\bullet})/k_{\text{H}}(\text{CumO}^{\bullet})$ ratios of 86, 4.8×10^3 , and 1.6×10^4 for the reactions with HMPA, TBPO, and DMSO, respectively. The $k_{\text{H}}/k_{\text{D}}$ of 0.91 and 1.0 measured for the reactions of BnO[•] with DMSO/DMSO-*d*₆ and HMPA/HMPA-*d*₁₈, together with the $k_{\text{H}}(\text{BnO}^{\bullet})/k_{\text{H}}(\text{CumO}^{\bullet})$ ratios, were explained on the basis of the formation of a hydrogen-bonded prereaction complex between the benzyloxyl α -C–H and the oxygen atom of the substrates followed by hydrogen abstraction. This is supported by theoretical calculations that show the formation of relatively strong prereaction complexes. These observations confirm that in alkoxy radical reactions specific hydrogen bond interactions can dramatically influence the hydrogen abstraction reactivity, pointing toward the important role played by structural and electronic effects.



INTRODUCTION

Hydrogen atom abstraction is one of the most fundamental chemical reactions and plays a major role in a variety of important chemical and biological processes. These reactions are involved in processes such as lipid peroxidation,^{1,2} the antioxidant activity of vitamin E,³ and other natural^{1,4} and synthetic⁵ phenolic and nonphenolic antioxidants, the reactions of various substrates with cytochrome P450^{6–9} and other metalloenzymes,^{10,11} the degradation of volatile organic compounds in the atmosphere,¹² as well as in a large number of synthetically useful procedures.^{13–17}

The abstracting species can be a radical or a different species such as a transition metal complex and an increasing number of studies have been devoted to the mechanistic understanding of the hydrogen abstraction reactions by these species.^{18–27} Among the abstracting radicals, highly reactive oxygen centered radicals such as hydroxyl (HO[•]) and alkoxy (RO[•]) have received most attention, as these radicals are able to abstract an hydrogen atom from a large variety of substrates, and accordingly their hydrogen abstraction reactivity has been studied in detail.^{28–42}

One aspect of these processes that is attracting considerable interest is the possible role of specific substrate–radical interactions. A number of recent computational studies on the hydrogen abstraction reactions from amino acids and model peptides by HO[•] have indicated that in these processes the formation of substrate–radical prereaction complexes can play an important role;^{43–46} this may account for the regioselectivity observed in these reactions, where abstraction occurs preferentially from the stronger side-chain C–H bonds as compared to the weaker backbone C–H bonds.^{47–49} Experimental evidence for the formation of hydrogen bonded prereaction complexes has been also provided in three recent studies on the hydrogen abstraction reactions from C–H and O–H bonds by transition metal complexes.^{50–52}

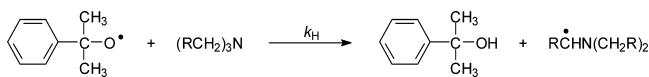
In this context, we recently carried out a time-resolved kinetic study on the hydrogen abstraction reactions from alkylamines by the cumyloxyl (PhC(CH₃)₂O[•], CumO[•]) and benzyloxyl (PhCH₂O[•], BnO[•]) radicals.^{53–55} These studies revealed large differences in reactivity between the two radicals.

Received: September 12, 2012

Published: November 15, 2012

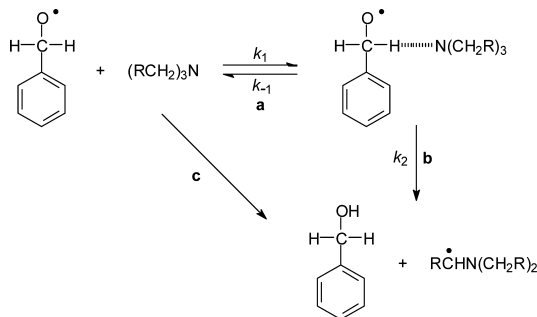
With all substrates, an increase in reactivity was observed on going from CumO^\bullet to BnO^\bullet , as shown by the hydrogen abstraction rate constant ratios, $k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet)$, that varied between 2.8 for the reactions with the relatively hindered triisobutylamine to >1000 for the reactions with amines such as 1,4-diazabicyclo[2,2,2]octane (DABCO), 1-azabicyclo[2,2,2]octane (ABCO), and *tert*-octylamine. Opposite reactivity trends were observed for the two radicals along different alkylamine series: k_{H} values were found to decrease on going from the tertiary to the primary amine for the reactions with CumO^\bullet , whereas an increase in reactivity was observed in the corresponding reactions with BnO^\bullet . These results were explained on the basis of different reactive pathways for the two radicals. The reactions of CumO^\bullet were described in all cases in terms of a *direct* hydrogen abstraction mechanism, i.e., a reaction that proceeds through the interaction of the radical center with the amine $\alpha\text{-C-H}$ and/or N-H bond, in line with previous studies,^{35,39,40,56} as described in Scheme 1 for a representative tertiary amine.

Scheme 1



With BnO^\bullet , the kinetic data were explained on the basis of a mechanism that proceeds through the rate-determining formation of a hydrogen bonded complex between the relatively acidic $\alpha\text{-C-H}$ of BnO^\bullet and the amine lone pair,⁵⁷ wherein fast hydrogen abstraction occurs (Scheme 2, paths a and b).^{53–55} This mechanistic picture is well supported by the results of computational studies.^{53,55}

Scheme 2



With the relatively hindered triisobutylamine, steric effects prevent the formation of a sufficiently stable complex, and the reaction of this substrate with BnO^\bullet has been described as a *direct* hydrogen abstraction (Scheme 2, path c).⁵⁵

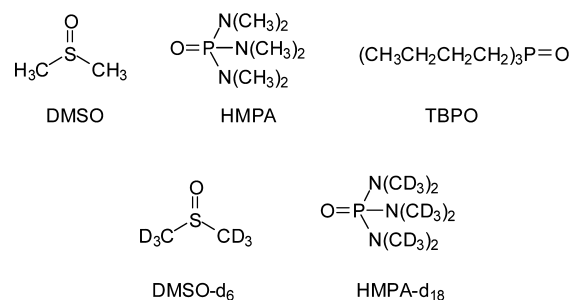
On the basis of this reaction scheme, it clearly appears that in the reactions of alkoxy radicals with alkylamines specific substrate–radical hydrogen-bond interactions can dramatically influence the hydrogen abstraction reactivity, where a major role is played by substrate sterics and hydrogen bond acceptor (HBA) ability, and by the possibility for the radical to act as a hydrogen-bond donor (HBD).

In view of the relevance of these reactions and to develop a clearer mechanistic understanding of the role of substrate–radical hydrogen-bond interactions on hydrogen abstraction reactions by alkoxy radicals, we thought it important to study the reactions of CumO^\bullet and BnO^\bullet with very strong HBA

substrates, specifically those commonly used as solvents. The substrate HBA ability can be quantitatively expressed in terms of Abraham's β_2^{H} parameter, which ranges in magnitude from 0.00 for a non-HBA substrate such as an alkane to 1.00 for hexamethylphosphoric acid triamide (HMPA).⁵⁹ Alkylamines are relatively good hydrogen bond acceptors, being characterized by β_2^{H} values between 0.58 and 0.73 ($\beta_2^{\text{H}} = 0.58\text{--}0.62$ for tertiary amines (0.67 for triethylamine) and 0.69–0.73 for primary and secondary amines).⁵⁹

Along this line, we have carried out a detailed time-resolved kinetic study in acetonitrile solution on the reactions of CumO^\bullet and BnO^\bullet , selecting as hydrogen atom donors dimethyl sulfoxide (DMSO), tributylphosphine oxide (TBPO), and HMPA, all characterized by very high HBA abilities ($\beta_2^{\text{H}} = 0.78, 0.98, \text{ and } 1.00$, respectively),⁵⁹ whose structures are displayed in Chart 1. For mechanistic purposes, the reactions of dimethyl sulfoxide-*d*₆ (DMSO-*d*₆) and hexamethylphosphoric acid triamide-*d*₁₈ (HMPA-*d*₁₈) have also been investigated.

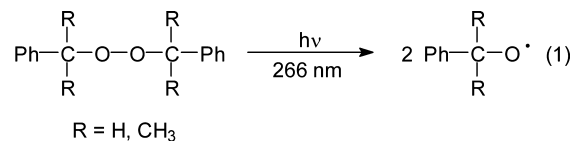
Chart 1



Limited information is available on the reactivity of these substrates in hydrogen abstraction reactions, and to the best of our knowledge, no information is presently available on their reactions with alkoxy radicals. DMSO and HMPA are very important compounds that are widely used as solvents for a variety of reactions. In addition, DMSO is a compound of atmospheric interest, that has been identified as an important intermediate in the atmospheric oxidation of dimethyl sulfide (DMS),⁶⁰ while HMPA, due to its toxicity, represents an environmental contaminant of potential concern.⁶¹ Moreover, HMPA is routinely employed as a cosolvent in reductive radical chemistry based on the use of samarium(II) reagents.⁶² Therefore, the assessment of the reactivity of these substrates in hydrogen abstraction reactions appears of great importance.

RESULTS

The reactions of CumO^\bullet and BnO^\bullet , with the substrates shown in Chart 1, were studied by laser flash photolysis (LFP). The alkoxy radicals were generated by 266 nm LFP of nitrogen-saturated acetonitrile solutions ($T = 25^\circ\text{C}$) containing dicumyl or dibenzyl peroxide, as described in eq 1.



In acetonitrile solution, CumO^\bullet and BnO^\bullet are characterized by an absorption band in the visible region of the spectrum centered at 485 and 460 nm, respectively.^{63,64} Under these

conditions, CumO[•] decays mainly by C–CH₃ β-scission,^{64,65} while the decay of BnO[•] can be mainly attributed to hydrogen abstraction from the solvent.⁵⁸

The kinetic studies were carried out by LFP following the decay of the CumO[•] and BnO[•] visible absorption bands at 490 and 460 nm, respectively, as a function of the substrate concentration. The observed rate constants (k_{obs}) gave excellent linear relationships when plotted against substrate concentration and the second-order rate constants for hydrogen abstraction from the substrates (k_{H}) by the alkoxy radicals were obtained from the slopes of these plots. Figure 1 shows

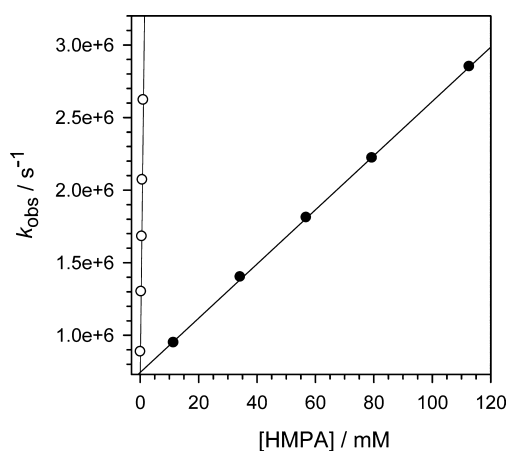


Figure 1. Plots of the observed rate constant (k_{obs}) against [HMPA] for the reactions of the cumyloxy radical (CumO[•], filled circles) and benzyloxy radical (BnO[•], empty circles), measured in nitrogen-saturated MeCN solution at $T = 25\text{ }^{\circ}\text{C}$ by following the decay of CumO[•] and BnO[•] at 490 and 460 nm, respectively. From the linear regression analysis: CumO[•] + HMPA: intercept = $7.44 \times 10^5\text{ s}^{-1}$, $k_{\text{H}} = 1.87 \times 10^7\text{ M}^{-1}\text{ s}^{-1}$, $r^2 = 0.9998$; BnO[•] + HMPA: intercept = $6.55 \times 10^5\text{ s}^{-1}$, $k_{\text{H}} = 1.73 \times 10^9\text{ M}^{-1}\text{ s}^{-1}$, $r^2 = 0.9999$.

the plots of k_{obs} vs [HMPA] for the reactions of this substrate with CumO[•] (filled circles) and BnO[•] (open circles) for measurements carried out in acetonitrile solution at $T = 25\text{ }^{\circ}\text{C}$.

Additional plots for the hydrogen abstraction reactions by CumO[•] and BnO[•] from the other substrates are displayed in the Supporting Information (Figures S1–S8). All of the kinetic data thus obtained are collected in Table 1 together with the pertinent $k_{\text{H}}(\text{BnO}^{\bullet})/k_{\text{H}}(\text{CumO}^{\bullet})$ and $k_{\text{H}}/k_{\text{D}}$ ratios.

DISCUSSION

Starting from the reactions of CumO[•], a striking observation derived from the analysis of the data displayed in Table 1 is the extremely low rate constant measured for the reaction of this radical with DMSO, $k_{\text{H}} = 1.8 \times 10^4\text{ M}^{-1}\text{ s}^{-1}$, a value that is among the lowest known rate constants for bimolecular reactions of CumO[•]. The observation of a sizable kinetic deuterium isotope effect ($k_{\text{H}}/k_{\text{D}} = 2.0$) in the reactions of CumO[•] with DMSO and DMSO-*d*₆ strongly supports the hypothesis that this reaction can be described as a *direct* hydrogen abstraction from the methyl group of DMSO (and DMSO-*d*₆) to give a methylsulfinyl methyl radical as described in Scheme 3.

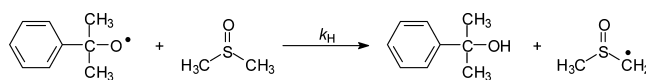
The value displayed in Table 1 represents the first absolute rate constant for hydrogen abstraction from DMSO by an alkoxy radical and provides a quantitative evaluation of the hydrogen atom donor ability of DMSO in these reactions.

Table 1. Second-Order Rate Constants (k_{H}) for the Reactions of the Cumyloxy (CumO[•]) and Benzyloxy (BnO[•]) Radicals with Different Substrates

substrate	$k_{\text{H}}^a\text{ (M}^{-1}\text{ s}^{-1}\text{)}$		$k_{\text{H}}(\text{BnO}^{\bullet})/k_{\text{H}}(\text{CumO}^{\bullet})$
	CumO [•]	BnO [•]	
DMSO	$1.8 \pm 0.1 \times 10^4$	$2.88 \pm 0.04 \times 10^8$	1.6×10^4
DMSO- <i>d</i> ₆	$9.0 \pm 0.2 \times 10^3$	$3.16 \pm 0.04 \times 10^8$	3.5×10^4
$k_{\text{H}}/k_{\text{D}}$	2.0	0.91	
HMPA	$1.87 \pm 0.02 \times 10^7$	$1.6 \pm 0.1 \times 10^9$	86
HMPA- <i>d</i> ₁₈	$6.03 \pm 0.03 \times 10^6$	$1.58 \pm 0.02 \times 10^9$	262
$k_{\text{H}}/k_{\text{D}}$	3.1	1.0	
TBPO	$5.6 \pm 0.4 \times 10^5$	$2.68 \pm 0.03 \times 10^9$	4.8×10^3

^aMeasured in N₂-saturated MeCN solution at $T = 25\text{ }^{\circ}\text{C}$ employing 266 nm LFP: [dicumyl peroxide] = 10 mM or [dibenzyl peroxide] = 8 mM. k_{H} values were determined from the slope of the k_{obs} vs [substrate] plots, where in turn k_{obs} values were measured following the decay of the CumO[•] or BnO[•] visible absorption bands at 490 and 460 nm, respectively. Average of at least two determinations.

Scheme 3



The very low k_{H} value measured for this reaction can be explained on the basis of polar effects, as hydrogen abstraction reactions from electron-deficient C–H bonds by *electrophilic* alkoxy radicals are known to be relatively slow processes.^{24,66,67} The indication of DMSO as a very poor hydrogen atom donor has been also obtained from a study of the benzophenone-photosensitized alkylation of arylalkenes.⁶⁸

Lissi and co-workers performed a product study of the reaction of dimethyl sulfide (DMS) with the *tert*-butoxy radical (*t*-BuO[•]) in benzene solution, and showed that the reaction proceeds through hydrogen abstraction with $k_{\text{H}} = 3.5 \times 10^6\text{ M}^{-1}\text{ s}^{-1}$ at $T = 37\text{ }^{\circ}\text{C}$.⁶⁹ *t*-BuO[•] and CumO[•] are known to display very similar hydrogen abstraction reactivities,^{40,70} and accordingly, the k_{H} value measured for the reaction of the former radical with DMS can be conveniently compared with the value measured for the reaction of CumO[•] with DMSO ($k_{\text{H}} = 1.8 \times 10^4\text{ M}^{-1}\text{ s}^{-1}$, at $T = 25\text{ }^{\circ}\text{C}$). The comparison shows that a greater than 2 order of magnitude increase in k_{H} is observed on going from DMSO to DMS, despite the very similar recommended bond dissociation energies (BDEs) available for the C–H bonds of these substrates (BDE = 94, and 93.7 kcal mol⁻¹ for DMSO and DMS, respectively),^{71,72} where, however, the available BDE value for DMSO has been estimated on the basis of a thermochemical cycle.⁷² In an effort to explore this apparent discrepancy, we calculated the BDEs for the C–H bonds of DMSO and DMS, as well as of HMPA, using a previously outlined procedure based on the density-functional theory (DFT) B3P86/6-311G(2d,2p) method.⁷³ The calculated C–H BDEs for these substrates are displayed in Table 2, along with the available experimental values.^{71,72} To the best of our knowledge, no BDE value is presently available for the C–H bonds of HMPA.

The data displayed in Table 2 show very similar calculated and experimental BDE values for DMS. However, calculations predict the C–H BDE for DMSO to be 8.1 kcal/mol higher than the recommended literature value. Following computation validation studies (see the Supporting Information), we

Table 2. Calculated and Experimental C–H Bond Dissociation Energies (BDEs) for DMSO, DMS, and HMPA (kcal mol⁻¹)

molecule	BDE	
	calcd ^a	exptl
DMSO	102.1	94 ^b
DMS	95.2	93.7 ^c
HMPA	94.4	

^aB3P86/6-311G(2d,2p) as described in ref 73. ^bExperimental data taken from ref 72. ^cExperimental data taken from ref 71.

conclude that our computational BDE value for the C–H bonds of DMSO is likely to be closer to the true value than the presently available literature value. On the basis of these findings, it appears that the large decrease in k_H observed for the reactions of CumO• on going from DMS to DMSO can be mostly associated to the BDE differences in the C–H bonds of these substrates.

Table 1 shows that a rate constant $k_H = 1.87 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ has been measured for the reaction of CumO• with HMPA. Also in this case, the observation of a kinetic deuterium isotope effect, $k_H/k_D = 3.1$, in the reactions of CumO• with HMPA and HMPA-*d*₁₈, indicates that the reaction proceeds through hydrogen abstraction from the methyl groups. To the best of our knowledge, this represents the first absolute rate constant for hydrogen abstraction from HMPA. The measured value is in line with the computed C–H BDE given in Table 2, viz., 94.4 kcal mol⁻¹. The results indicate that HMPA is a fairly good hydrogen atom donor, displaying, in acetonitrile solution and on a per hydrogen basis, a reactivity toward CumO• comparable to that observed for hydrogen abstraction from the α -C–H bonds of THF ($k_H = 5.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$)⁷⁴ and significantly higher than that observed for hydrogen abstraction from alkanes ($k_H = 1.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for cyclohexane).⁷⁴

HMPA is generally assumed to be an inert solvent in free-radical reactions as evidenced by its wide use as a cosolvent in a variety of reactions involving samarium(II) compounds.⁶² The present finding of a relatively high rate constant for hydrogen abstraction from HMPA by CumO• indicates that care should be taken when this compound is employed in processes that may produce reactive hydrogen-abstrating species.

It is interesting to note that evidence for hydrogen abstraction from HMPA has been also provided in a study on the photoreduction of aromatic ketones in HMPA solution, where the formation of a cross-coupling product between the ketyl radical of the ketone and the HMPA carbon-centered radical formed following hydrogen abstraction from HMPA was observed.⁷⁵ This observation is in agreement with the comparable hydrogen abstraction reactivity displayed by alkoxy radicals and n,π^* excited carbonyl compounds in their reactions with a variety of substrates.⁷⁶ Very recently, the formation of the HMPA radical following hydrogen abstraction from HMPA by the hydrogen atom (H•) was proposed to occur in the reduction of *p*-nitrophenol in HMPA solution by alkali metal.⁷⁷

The data displayed in Table 1 show that CumO• reacts with TBPO with a rate constant $k_H = 5.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. This value is at least 2 orders of magnitude lower than the values measured for the reactions of CumO• with trialkyl and triarylphosphites ((RO)₃P: $k = 6.2 \times 10^8$ and $5.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, for R = Me and *t*-Bu, respectively. (PhO)₃P: $k = 2.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$),⁷⁸ and with triphenylphosphine (Ph₃P: $k = 1.04 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$),⁷⁹ in acetonitrile solution. It is well-known that the reactions of

alkoxy radicals with trivalent organophosphorus compounds (L₃P) proceed by addition of the radical to the phosphorus center to give intermediate phosphoranyl radicals L₃P•OR.^{78,80} On the other hand, the addition of free radicals to pentavalent organophosphorus compounds of the type L₃P=O has been discarded on thermochemical grounds, on the basis of the great strength of the P=O bond.⁸⁰ Along this line, the k_H value measured for the reaction of CumO• with TBPO can be reasonably assigned to an hydrogen abstraction from the α -CH₂ groups.

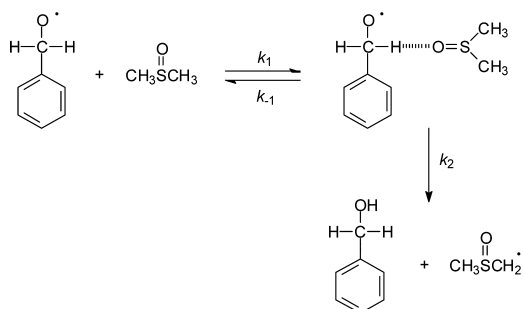
The data displayed in Table 1 show that with all three substrates very large increases in k_H have been observed on going from CumO• to BnO•: $k_H = 1.8 \times 10^4$, 1.87×10^7 , and $5.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, for the reactions of CumO• with DMSO, HMPA, and TBPO, respectively, as compared to 2.88×10^8 , 1.6×10^9 , and $2.68 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the corresponding reactions with BnO•. The increase in reactivity can be quantitatively expressed by the rate constant ratios $k_H(\text{BnO}^\bullet)/k_H(\text{CumO}^\bullet) = 86$ and 4.8×10^3 for HMPA and TBPO, respectively, and as high as 1.6×10^4 for DMSO (3.5×10^4 for DMSO-*d*₆), where the magnitude of the ratio is strongly influenced by the k_H values measured for the reactions with CumO•, i.e., by the reactivity displayed by these substrates in a *direct* hydrogen abstraction reaction.

As mentioned above, large increases in reactivity were previously observed for the hydrogen abstraction reactions from alkylamines on going from CumO• to BnO•, where with the exclusion of the relatively hindered triisobutylamine, the k_H values for reaction with BnO• were at least 1 order of magnitude higher than those measured for the corresponding reactions of CumO•, approaching the diffusion limit with the substrates characterized by the most unhindered nitrogen atoms such as ABCO and DABCO ($k_H = 7.5 \times 10^9$, and $1.05 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, respectively).^{53–55} The very high rate constants measured for the reactions of BnO• with the amines ($k_H \geq 3.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), as well as the large $k_H(\text{BnO}^\bullet)/k_H(\text{CumO}^\bullet)$ ratios (between 13 and 3380, for tripropylamine and *tert*-octylamine, respectively), were rationalized in terms of the rate-determining formation of a hydrogen bonded preassociation complex between BnO• and the amine, wherein hydrogen abstraction occurs, as described in Scheme 2, paths a and b. This behavior reflects the strong HBD ability of BnO•,⁵⁸ as well as the relatively high HBA ability of the alkylamines.⁵⁹

DMSO, TBPO, and HMPA are all characterized by significantly higher HBA abilities than alkylamines, as measured by the values of Abraham's β_2^H parameter of 0.78, 0.98, and 1.00, respectively, as compared to $\beta_2^H = 0.58$ – 0.62 for tertiary amines (0.67 for triethylamine) and 0.69–0.73 for primary and secondary amines.⁵⁹ We therefore expect that, in analogy to the reaction of BnO• with the amines, the reactions of DMSO, TBPO, and HMPA with BnO• occur by the rate-determining formation of a hydrogen bonded complex between BnO• and the substrate,⁵⁷ followed by a fast intramolecular hydrogen abstraction step, as shown in Scheme 4 for DMSO.⁸¹

Strong support for this mechanistic picture is provided by the study of the kinetic deuterium isotope effects for the reactions of BnO• with DMSO/DMSO-*d*₆ and HMPA/HMPA-*d*₁₈. The observation of k_H/k_D ratios of 0.91 and 1.0 clearly indicates that in these substrate/radical couples C–H bond cleavage does not occur in the rate-determining step of the reaction. The observation of an inverse kinetic deuterium isotope effect in the reaction of BnO• with DMSO/DMSO-*d*₆ may be a consequence of the slightly larger electron releasing effect

Scheme 4



displayed by CD_3 groups as compared to CH_3 in some processes,⁸³ an effect that would result in the formation of a more stable prereaction complex and in a corresponding increase in the rate of complex formation. However, this is at most a working hypothesis that would require support from additional studies.

Further support for this mechanistic picture comes from the modeling of the prereaction complex and transition-state (TS) structures associated to the reactions of BnO^\bullet with DMSO and HMPA. The calculations utilized newly developed dispersion correcting potentials (DCPs) along with the B3LYP/6-31+G(2d,2p). The new DCPs correct the erroneous long-range behavior of the B3LYP functional and enable the method to very accurately simulate organic systems in which non-covalent interactions are important.⁸⁴ The most stable structure for the prereaction complex between BnO^\bullet and DMSO is shown in Figure 2a, and involves a strong hydrogen bond interaction (binding enthalpy of $7.4 \text{ kcal mol}^{-1}$) between the acidic BnO^\bullet $\alpha\text{-C-H}$ and the oxygen lone pair of DMSO, along with secondary interactions between the DMSO C-H groups and the oxygen atom of BnO^\bullet . General dispersion interactions also contribute to the strong binding of the BnO^\bullet -DMSO complex. Most importantly, the calculated binding enthalpy of the BnO^\bullet -DMSO complex exceeds that of the BnO^\bullet -acetonitrile and the acetonitrile-DMSO complexes by 4.0 and 1.3 kcal/mol, respectively, suggesting that formation of the prereaction complex is an exothermic process. Interestingly, despite the fact that CumO^\bullet is unable to engage in strong hydrogen bonding with the DMSO oxygen, it nevertheless forms a strongly bound dipole-dipole complex having a

binding enthalpy of $6.4 \text{ kcal mol}^{-1}$. However, this complex does not orient the reactants in a manner that is favorable for subsequent hydrogen abstraction along the lowest energy pathway. This suggests that the complex may act as a kinetic trap for the reactants, thus contributing to a lower rate constant for the hydrogen abstraction reaction (see the Supporting Information, Figure S10).

The prereaction BnO^\bullet -DMSO complex can get to the TS structure for C-H abstraction by a ca. 1.8 \AA relative lateral displacement of the DMSO and a rotation of ca. 45° of the H_2CO group relative to the plane of the BnO^\bullet ring (see Figure 2b). The transition structure is about 10° off linearity with an enthalpy barrier of $3.7 \text{ kcal mol}^{-1}$ relative to the separated reactants. Secondary interactions between the BnO^\bullet aromatic ring and DMSO are also present.

The corresponding prereaction complex and TS structures for the reactions of HMPA with BnO^\bullet and CumO^\bullet are shown in the Supporting Information as Figures S11 and S12. As compared to DMSO, the most stable prereaction complex structure between HMPA and BnO^\bullet involves a stronger hydrogen-bond interaction (binding enthalpy of $8.4 \text{ kcal mol}^{-1}$) between the BnO^\bullet $\alpha\text{-C-H}$ and the oxygen lone pair of HMPA, in line with the greater HBA ability of HMPA as compared to DMSO.⁵⁹ The associated TS structure is about 5 degrees off linearity, with an enthalpy barrier of $-4.2 \text{ kcal mol}^{-1}$ relative to (i.e., below) the separated reactants. There are also a number of secondary interactions between the BnO^\bullet aromatic ring and HMPA C-H bonds present in these structures. The relatively lower calculated barrier associated with the BnO^\bullet -HMPA reaction compared to BnO^\bullet -DMSO is consistent with the measured rate constants presented in Table 1 that show a significant increase in rate constant for the reactions of BnO^\bullet on going from DMSO to HMPA. The calculated enthalpy vs reaction coordinate diagrams for the reactions of BnO^\bullet and CumO^\bullet with DMSO and HMPA are displayed in the Supporting Information as Figure S13.

Taken together, the results of the computational and time-resolved kinetic studies point toward the great importance of specific hydrogen-bond interactions in hydrogen abstraction reactions by primary alkoxy radicals, where substrate HBA ability plays a major role.

Large $k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet)$ ratios have been observed only for hydrogen atom donor substrates characterized by high

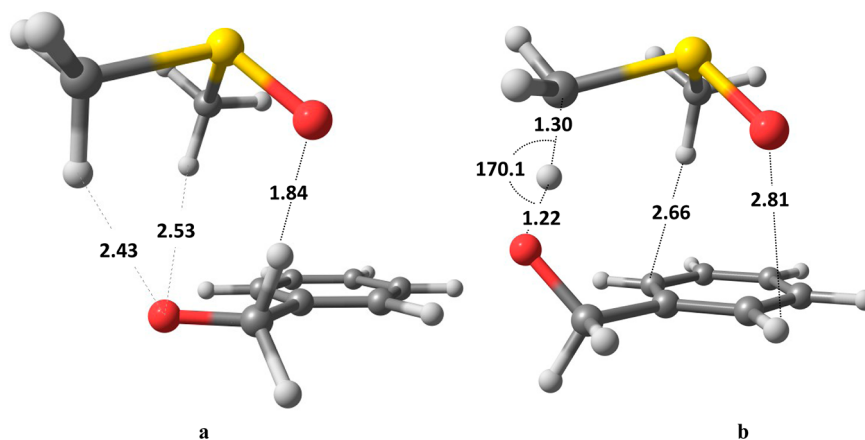


Figure 2. Predicted hydrogen bonded prereaction complex between BnO^\bullet and dimethyl sulfoxide (DMSO) (a) and associated transition-state structure (b) obtained using B3LYP/6-31+G(2d,2p) with dispersion-correcting potentials. Indicated distances and angles are given in angstroms and degrees. Key: H = white, C = gray, S = yellow, O = red.

HBA abilities such as alkylamines, DMSO, TBPO, and HMPA. On the other hand, $k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet)$ ratios < 2 have been observed in the reactions of the two radicals with substrates characterized by lower HBA abilities such as THF ($\beta_2^{\text{H}} = 0.51$),⁷⁴ aliphatic aldehydes ($\beta_2^{\text{H}} = 0.39$),³⁴ and hydrocarbons ($\beta_2^{\text{H}} = 0.00$),^{34,74} results that are indicative of a *direct* hydrogen abstraction mechanism for the reactions of both radicals with these substrates.

In Schemes 2 and 4, k_1 and k_{-1} represent the rate constants for the formation and dissociation of the hydrogen-bonded prereaction complex and k_2 is the rate constant for intramolecular hydrogen abstraction within the complex. Based on the discussion outlined above, on the very strong HBA abilities of DMSO, TBPO, and HMPA, and on the observation of $k_{\text{H}}/k_{\text{D}}$ ratios very close to unity for the reactions of BnO^\bullet with DMSO/DMSO- d_6 and HMPA/HMPA- d_{18} , for these substrates $k_2 \gg k_{-1}$ reasonably applies. Thus, the reaction rate can be expressed in terms of the rate constant for complex formation k_1 as $v = k_1 [\text{substrate}][\text{BnO}^\bullet]$, where k_1 corresponds to the k_{H} values displayed in Table 1 for the reactions of BnO^\bullet with the three substrates.

On the basis of these results, the differences in k_{H} observed for the reactions of BnO^\bullet with the different substrates reflect the role of structural and electronic effects on the formation of the hydrogen-bonded complex. With the amines, the increase in k_{H} observed on going from acyclic tertiary amines to cyclic and bicyclic amines and diamines, and within an alkylamine series, on going from the tertiary to the secondary and primary amine, have been explained on the basis of the accessibility of the nitrogen lone pair and of the slightly higher HBA ability of primary and secondary amines as compared to tertiary amines.⁵³ The rate constants measured for the reactions of the amines with BnO^\bullet (k_{H} between 3.0×10^9 and $1.05 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$)^{53–55} are in all cases higher than those measured with DMSO, HMPA, and TBPA, despite the lower HBA abilities displayed by the amines as compared to the latter substrates. This behavior may be indicative of steric effects reflecting, at least in part, the sp^2 nature of the oxygen atom of DMSO, HMPA, and TBPA, where substrate–radical hydrogen bonding is expected to bring the two species in closer proximity as compared to the amines, which are characterized by the presence of an sp^3 HBA nitrogen center.

Among the rate constants measured for reaction of BnO^\bullet with substrates characterized by high HBA abilities, the lowest value was measured with DMSO, $k_{\text{H}} = 2.88 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, which is more than 5 times lower than the value measured for the corresponding reaction with HMPA and at least 1 order of magnitude lower than the values measured for TBPO and for the alkylamines. The observation of a relatively low value suggests that, on the basis of the kinetic scheme displayed in Scheme 4, by increasing DMSO concentration (i.e., by shifting the position of the pre-equilibrium), kinetic evidence for the formation of a BnO^\bullet –DMSO prereaction complex may be obtained. For this purpose, the kinetic study of the reaction between DMSO (and DMSO- d_6) and BnO^\bullet has been extended to significantly higher substrate concentrations as compared to the experiments shown in the Supporting Information (Figures S5 and S6) whose results are displayed in Table 1. The corresponding plot of k_{obs} versus $[\text{DMSO}]$ displayed in Figure 2 shows a significant curvature at substrate concentrations $\geq 0.01 \text{ M}$, where k_{obs} appears to approach a limiting (plateau) value. The saturation behavior of k_{obs} is diagnostic for the formation of a prereaction complex between DMSO and BnO^\bullet ,

where the limiting value of k_{obs} corresponds to the *intrinsic* rate constant (k_{H}') for hydrogen atom transfer within the complex, indicated as k_2 in Scheme 4.^{50,85} Accordingly, the curved kinetic plot can be evaluated on the basis of eq 2, from which k_{H}' and the preequilibrium constant $K_{\text{E}} = k_1/k_{-1}$ can be obtained.⁸⁶

$$(k_{\text{obs}} - k_0) = K_{\text{E}}k_{\text{H}}'[\text{substrate}]/(1 + K_{\text{E}}[\text{substrate}]) \quad (2)$$

In this equation, k_0 represents the rate constant for decay of BnO^\bullet in the absence of the hydrogen atom donor (DMSO) that, as mentioned above, is mostly due to hydrogen abstraction from the solvent.⁵⁸

A very good fit of the experimental data to eq 2 has been obtained (Figure 3), leading to the following values of the

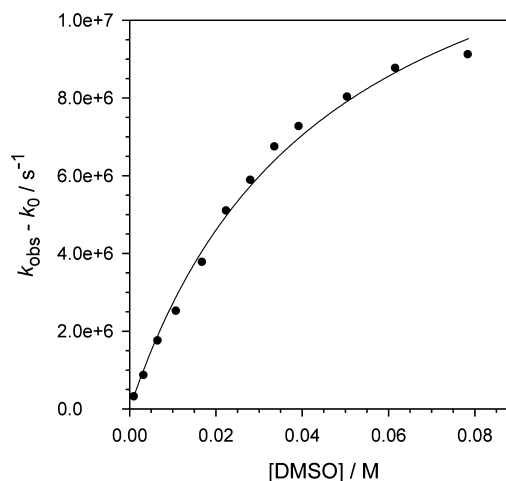


Figure 3. Plot of the observed rate constant (k_{obs}) against $[\text{DMSO}]$ for reaction with the benzoyloxy radical (BnO^\bullet), measured in nitrogen-saturated acetonitrile solution at $T = 25^\circ \text{C}$, following the decay of BnO^\bullet at 460 nm. The solid line represents the fit of the experimental data to eq 2. From the regression analysis: $K_{\text{E}}k_{\text{H}}' = 3.3 \pm 0.2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $K_{\text{E}} = 22.1 \pm 2.4 \text{ M}^{-1}$, $r^2 = 0.9932$.

intrinsic hydrogen abstraction rate constant and preequilibrium constant for the reaction between BnO^\bullet and DMSO: $k_{\text{H}}' = 1.5 \times 10^7 \text{ s}^{-1}$ and $K_{\text{E}} = 22.1 \text{ M}^{-1}$. A saturation behavior has been also observed for the reaction of BnO^\bullet with DMSO- d_6 , as shown in the Supporting Information, Figure S9, from which the following values have been obtained: $k_{\text{D}}' = 1.3 \times 10^7 \text{ s}^{-1}$ and $K_{\text{E}} = 29.0 \text{ M}^{-1}$. These findings indicate that, at least with DMSO, the overall second order rate constant is a composite of the preequilibrium constant K_{E} and of the *intrinsic* rate constant for hydrogen atom transfer k_{H}' .

This kinetic behavior is in full agreement with the mechanism displayed in Scheme 4, indicating in particular that the formation of a hydrogen-bonded prereaction complex between BnO^\bullet and the HBA substrates provides a significant kinetic advantage for the subsequent *intracomplex* hydrogen abstraction step. This is clearly revealed through the comparison of the k_{H} and k_{H}' values measured for the reactions of CumO^\bullet and BnO^\bullet with DMSO: $k_{\text{H}} = 1.8 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{H}}' = 1.5 \times 10^7 \text{ s}^{-1}$, respectively. At this stage, we do not have any clear explanation for the very small intramolecular kinetic deuterium isotope effect observed in these reactions, $k_{\text{H}}'/k_{\text{D}}' = 1.15$, as compared to the value observed for hydrogen abstraction from DMSO and DMSO- d_6 by CumO^\bullet ($k_{\text{H}}/k_{\text{D}} = 2.0$). This behavior may be a consequence of the preorganization of the radical-substrate couple in the prereaction complex,

as well as the result of the deviation from linearity of the transition state for the intramolecular reaction (Figure 2b) as compared to the linear transition state expected for an intermolecular reaction.⁸⁷ Future experiments are certainly needed in order to obtain additional information in this respect.

The rate constants for hydrogen abstraction derived from the kinetic analysis of the reactions of BnO^\bullet with DMSO and $\text{DMSO-}d_6$ are very similar to the intramolecular rate constant measured previously for the 1,5-hydrogen abstraction reaction of an alkoxy radical ($k = 2.7 \times 10^7 \text{ s}^{-1}$),⁸⁸ indicating that when possible, intramolecular hydrogen abstractions by alkoxy radicals are very fast processes.

The observation of a larger preequilibrium constant in the reaction of $\text{DMSO-}d_6$ with BnO^\bullet , as compared to the corresponding reaction with DMSO, is in line with the slightly larger electron releasing effect of the CD_3 groups as compared to CH_3 mentioned above.

In conclusion, the results discussed above on the reactions of CumO^\bullet and BnO^\bullet with substrates characterized by very high HBA abilities confirm that substrate–radical hydrogen bonding can play a very important role in hydrogen abstraction reactions by alkoxy radicals. With all substrates, very large increases in reactivity were observed on going from CumO^\bullet to BnO^\bullet , as quantified by the $k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet)$ ratios that vary from 86 for the reactions with HMPA to 1.6×10^4 for those with DMSO. The reactions with BnO^\bullet proceed through the formation of hydrogen bonded substrate–radical pre-reaction complexes, followed by hydrogen abstraction within the complex. With CumO^\bullet , which cannot act as a HBD, the reactions have been described in all cases in terms of a *direct* hydrogen abstraction mechanism, that is, without the formation of a strongly bound pre-reaction complex. Strong support for this mechanistic picture is provided by the results of computational studies and by the observation of sizable kinetic deuterium isotope effects in the reactions of DMSO and HMPA with CumO^\bullet and of kinetic deuterium isotope effects close to unity for the corresponding reactions with BnO^\bullet . Kinetic evidence for the formation of a pre-reaction complex has also been obtained for the reactions of BnO^\bullet with DMSO and $\text{DMSO-}d_6$. These results provide quantitative information on the very important role played by specific substrate–radical interactions in these processes, showing in particular that with BnO^\bullet (and with other primary and secondary alkoxy radicals) the presence of a strong HBA site in the hydrogen atom donor promotes complex formation and preorganizes the reactants for hydrogen abstraction leading to dramatic rate enhancements as compared to the corresponding reactions of radicals that cannot act as HBDs. The implications of these findings are currently under investigation in our laboratory.

A very important aspect of this study is that the rate constants measured for the reactions of CumO^\bullet with DMSO and HMPA provide, for the first time, a quantitative evaluation of the hydrogen abstraction reactivity of these widely employed compounds.

EXPERIMENTAL SECTION

Materials. Spectroscopic grade acetonitrile was used in the kinetic experiments. Dimethyl sulfoxide (DMSO), dimethyl sulfoxide- d_6 ($\text{DMSO-}d_6$), tributylphosphine oxide (TBPO), hexamethylphosphoric acid triamide (HMPA), and hexamethylphosphoric acid triamide- d_{18} ($\text{HMPA-}d_{18}$), were of the highest commercial quality available. The purity of the substrates was checked by GC prior to the kinetic experiments and was in all cases >99%.

Dicumyl peroxide was of the highest commercial quality available and was used as received. Dibenzyl peroxide was prepared according to a previously described procedure by reaction of KO_2 with benzyl bromide in dry benzene, in the presence of 18-crown-6 ether.^{58,89}

Laser Flash Photolysis Studies. LFP experiments were carried out with a laser kinetic spectrometer using the fourth harmonic (266 nm) of a Q-switched Nd:YAG laser, delivering 8 ns pulses. The laser energy was adjusted to ≤ 10 mJ/pulse by the use of the appropriate filter. A 3.5 mL Suprasil quartz cell (10 mm \times 10 mm) was used in all experiments. Nitrogen-saturated acetonitrile solutions of dicumyl peroxide and dibenzyl peroxide (10 and 8 mM, respectively) were employed. These concentrations were chosen in order to ensure prevalent absorption of the 266 nm laser light by the precursor peroxides. The photochemical stability of the substrates at the laser excitation wavelength (266 nm) was checked by LFP of acetonitrile solutions containing substrate concentrations comparable to the highest concentrations employed in the kinetic experiments. All of the experiments were carried out at $T = 25 \pm 0.5$ °C under magnetic stirring. The observed rate constants (k_{obs}) were obtained by averaging at least three individual values and were reproducible to within 5%.

Second-order rate constants for the reactions of the cumyloxy and benzyloxy radicals with the substrates were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxy and benzyloxy radicals visible absorption bands at 490 and 460 nm, respectively) vs [substrate] plots. Fresh solutions were used for every substrate concentration. Correlation coefficients were in all cases >0.992. The given rate constants are the average of at least two independent experiments, typical errors being $\leq 10\%$.

Calculations. All calculations were performed using the Gaussian-09 package of programs⁹⁰ utilizing the B3LYP⁹² and B3P86⁹³ approaches implemented therein. The B3LYP calculations utilized a new family of dispersion-correcting potentials that allow that functional to accurately predict noncovalent interactions. Additional information on the B3LYP dispersion-correcting potentials is available at www.ualberta.ca/~gdilabio.

ASSOCIATED CONTENT

Supporting Information

Plots of k_{obs} vs substrate concentration for the reactions of CumO^\bullet and BnO^\bullet and details of the calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) is gratefully acknowledged. We thank Prof. Lorenzo Stella for the use of a LFP equipment.

DEDICATION

This paper is dedicated to Prof. Steen Steenken on the occasion of his 75th birthday.

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- (81) Previous studies have shown that the hydroxyl radical reacts with DMSO both in the gas phase and in aqueous solution by addition at sulfur.⁸² Along this line, a reviewer has pointed out that the difference in reactivity observed between CumO^\bullet and BnO^\bullet in their reactions with DMSO ($k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet) = 1.6 \times 10^4$) may reflect the diminished steric bulk of the latter radical as compared to the former one, which results in a shift from hydrogen abstraction to addition on going from CumO^\bullet to BnO^\bullet . However, previous kinetic studies on the addition of CumO^\bullet and BnO^\bullet to trialkyl phosphites ($(\text{RO})_3\text{P}$, R = Me, Et, iPr) have clearly shown that in these reactions steric effects in the attacking radical play a minor role, as evidenced by the very small rate constant ratios ($k_{\text{H}}(\text{BnO}^\bullet)/k_{\text{H}}(\text{CumO}^\bullet) \sim 2$) measured for the reactions of the two radicals with the three phosphites.⁷⁸ On the basis of the very different behavior displayed by CumO^\bullet and BnO^\bullet in their reactions with DMSO and $(\text{RO})_3\text{P}$, addition of BnO^\bullet to DMSO can be reasonably ruled out, and the very large increase in rate constant observed on going from CumO^\bullet to BnO^\bullet in their reactions with DMSO (and with TBPO and HMPA) appears to be in line with the mechanism shown in Scheme 4.
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