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Diffusion Controlled Hydrogen Atom Abstraction from Tertiary Amines by the Benzyloxyl Radical. The Importance of C−H/N Hydrogen Bonding

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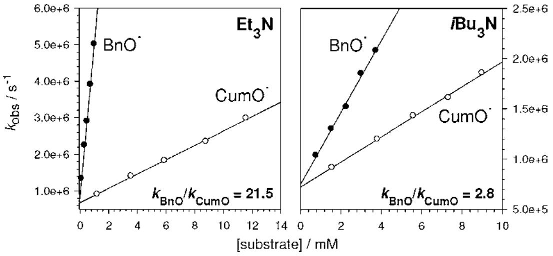
ABSTRACT



The rate constants for H-atom abstraction (k_H) from 1,4-cyclohexadiene (CHD), triethylamine (TEA), triisobutylamine (TIBA), and DABCO by the cumyloxyl (CumO$^\bullet$) and benzyloxyl (BnO$^\bullet$) radicals were measured. Comparable k_H values for the two radicals were obtained in their reactions with CHD and TIBA whereas large increases in k_H for TEA and DABCO were found on going from CumO$^\bullet$ to BnO$^\bullet$. These differences are attributed to the rate-determining formation of BnO$^\bullet$ C−H/amine N lone-pair H-bonded complexes.

Hydrogen atom abstraction reactions by alkoxyl radicals have attracted considerable interest because of the key role they play in a variety of important chemical and biological processes.[1−9] Several aspects of these processes have been studied in detail including the nature of the substrate and of the abstractable hydrogen atom (C−H[10−12] or X−H, where X = O,[6,13−15] N,[14b,16] S,[17] Si,[18] Ge,[19] Sn[19,20]) and the role of the solvent.[6,14,15,17,20−24] Most recently, a combined model based on the Marcus cross relation and on the analysis of kinetic solvent effects[6] has been developed and successfully applied to H-atom abstraction reactions from carbon by the *tert*-butoxyl radical ($(CH_3)_3CO^\bullet$, *t*BuO$^\bullet$).[25]

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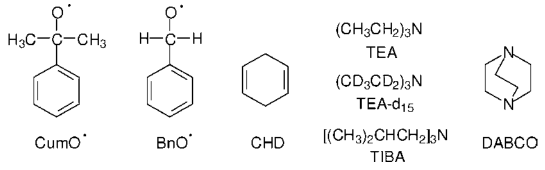
In connection with the foregoing, many studies of H-atom abstraction make use of *t*BuO$^\bullet$, or the structurally related cumyloxyl radical ($C_6H_5C(CH_3)_2O^\bullet$, CumO$^\bullet$), as a general model for alkoxyl and other oxygen centered radicals.[11] However, the structure of the alkoxyl radical itself is also of critical importance to the kinetics of H abstraction reactions. For example, recent studies of Tanko and coworkers on H-atom abstraction from the α-C−H groups of tertiary amines by *t*BuO$^\bullet$ indicate that, in solution, most of these processes are entropy controlled.[11a] In other words, the alkoxyl radical is so reactive toward these substrates that the rates are largely governed by the orientation of the reactants and accessibility to the H-atom, rather than by the strength of the C−H bond. It can be concluded from this work that alkoxyl radical structure, viz., steric bulk, will have a significant effect on the rate constants for these reactions. We are therefore surprised by the scarcity of kinetic data associated with H-abstraction reactions of unhindered alkoxyl radicals, especially in light of their relevance in biological and chemical processes.

The purpose of the present study is to develop an understanding of the reactivity of an unhindered alkoxyl, the benzyloxyl radical ($C_6H_5CH_2O^\bullet$, BnO$^\bullet$). To this end, we have carried out a time-resolved kinetic study on the H-abstraction reactions from carbon by BnO$^\bullet$, with comparisons to the more hindered CumO$^\bullet$ using laser flash photolysis (LFP). A variety of H-atom donors, viz., 1,4-cyclohexadiene (CHD), triethylamine (TEA), triethylamine-d_{15} (TEA-d_{15}), triisobutylamine (TIBA), and 1,4-diazabicyclo[2,2,2]octane (DABCO), were used in this work, the structures for which are displayed below. Computational modeling provides additional insights into some details of the BnO$^\bullet$ reaction kinetics.



CumO$^\bullet$ and BnO$^\bullet$ were generated by 266 nm LFP of N_2-saturated MeCN solutions ($T = 25$ °C) containing dicumyl and dibenzyl peroxide, respectively (eq 1). In MeCN solution, CumO$^\bullet$ and BnO$^\bullet$ are characterized by a broad absorption band in the visible region centered at 485 and 460 nm, respectively.[26,27] Under these conditions, CumO$^\bullet$ decays mainly by $C-CH_3$ β-scission,[24,27] while BnO$^\bullet$ decay can be mainly attributed to H-atom abstraction from the solvent.[28,29]

$$R = \begin{matrix} PhC(CH_3)_2 \\ PhCH_2 \end{matrix} \quad RO-OR \xrightarrow[266\text{nm}]{hv} 2\ RO^\bullet \qquad (1)$$

A number of rate constants (k_H) for H-atom abstraction from a CH_2 group of CHD,[20,23,30,31] TEA,[10b,11b,32,33] and DABCO[10b,11a,32,33] (eq 2), by *t*BuO$^\bullet$ and/or CumO$^\bullet$, are available in the literature (see Table 1).

$$RO^\bullet + H_2CR'R'' \xrightarrow{k_H} ROH + H\dot{C}R'R'' \qquad (2)$$

Our kinetic studies were carried out by following the decay of the CumO$^\bullet$ and BnO$^\bullet$ visible absorption bands at 490 and 460 nm, respectively, as a function of the H-atom donor concentration. The observed rate constants (k_{obs}) gave excellent linear relationships when plotted against substrate concentration and provided the second-order rate constants for H-atom abstraction from the substrates by CumO$^\bullet$ and BnO$^\bullet$ (k_H). Plots for H-atom abstraction reactions by CumO$^\bullet$ and BnO$^\bullet$ from the H-atom donors are displayed in the Supporting Information (SI, Figures S2−S7). All kinetic data are collected in Table 1 and are in reasonable agreement (where comparison is possible) with available literature values for analogous reactions with *t*BuO$^\bullet$ and/or CumO$^\bullet$.

The k_H values for reactions involving *t*BuO$^\bullet$ and CumO$^\bullet$ are rather similar, viz., $k_H(t\text{BuO}^\bullet)/k_H(\text{CumO}^\bullet) = 0.7$ to 1.7. This reflects the well-established similar reactivity displayed by these two radicals in H-atom abstraction reactions,[14c,34,35]

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Table 1. Second-Order Rate Constants (k_H) for the Reactions of the *tert*-Butoxyl (tBuO$^{\bullet}$), Cumyloxyl (CumO$^{\bullet}$), and Benzyloxyl (BnO$^{\bullet}$) Radicals with H-Atom Donor Substrates

	k_H/M^{-1} s^{-1}			
Substrate	tBuO$^{\bullet}$	CumO$^{\bullet}$	BnO$^{\bullet}$	k_H(BnO$^{\bullet}$)/ k_H(CumO$^{\bullet}$)
CHD	3.0×10^{7b} 5.3×10^{7c} 5.4×10^{7d}	$6.65 \times 10^{7\,e}$ $5.9 \times 10^{7\,f}$	$1.29 \times 10^{8\,a}$	1.9
TIBA	–	$1.27 \times 10^{8\,a}$	$3.51 \times 10^{8\,a}$	2.8
TEA	$1.1 \times 10^{8\,g}$ $1.6 \times 10^{8\,h}$ $1.8 \times 10^{8\,i}$	$2.0 \times 10^{8\,e}$ $1.47 \times 10^{8\,e,j}$ $1.6 \times 10^{8\,k}$	$4.3 \times 10^{9\,a}$ $3.0 \times 10^{9\,a,j}$	21.5
TEA-d_{15}	–	$1.16 \times 10^{8\,a}$ $1.2 \times 10^{8\,k}$	$4.28 \times 10^{9\,a}$	37
DABCO	$8 \times 10^{6\,g}$ $2.8 \times 10^{7\,i}$ $1.2 \times 10^{7\,l}$	*m* $9.6 \times 10^{6\,k}$	$1.05 \times 10^{10\,a}$	1094

[a] This work. Average of at least two determinations. Error ≤5% (see SI). [b] Reference 23. [c] Reference 30. [d] Reference 31. [e] Reference 21. [f] Reference 20. [g] Reference 32. [h] Reference 11b. [i] Reference 33. [j] In the presence of 1 M H_2O. [k] Reference 10b. [l] Reference 11a. [m] The relatively high concentrations of DABCO required in this experiment prevented the determination of k_H for its reaction with CumO$^{\bullet}$ under the experimental conditions employed.

as expected on the basis of their similar steric features. Similarly, we found k_H(BnO$^{\bullet}$)/k_H(CumO$^{\bullet}$) = 1.9 in the reactions of CumO$^{\bullet}$ and BnO$^{\bullet}$ with CHD. This indicates that with a relatively unhindered substrate such as CHD the sterics of the alkoxyl radical play a minor role.

For the reactions of CumO$^{\bullet}$ and BnO$^{\bullet}$ with TEA and DABCO, very different rate constants were measured. With TEA, k_H(BnO$^{\bullet}$)/k_H(CumO$^{\bullet}$) = 21.5 was observed, while a dramatic 3 orders of magnitude increase in k_H (k_H(BnO$^{\bullet}$)/k_H(CumO$^{\bullet}$) = 1094) was found for DABCO. The k_H values measured for the reactions of BnO$^{\bullet}$ with TEA and DABCO (4.3×10^9 and 1.05×10^{10} M^{-1} s^{-1}, respectively) represent by far the highest measured rate constants for H-atom abstraction reactions from carbon by alkoxyl radicals, approaching the diffusion limit in the reaction with DABCO. Our k_H values clearly demonstrate that structural properties of the abstracting radical play a dramatic role in H-atom abstraction reactions from tertiary amines. Contrasting these findings with the small kinetic effects observed in the reactions involving CHD indicates that the nitrogen atom in the amines must play a fundamental role in these processes.

Although the k_H(DABCO)/k_H(TEA) ratio is close to 2 for BnO$^{\bullet}$, which is expected on the basis of the number of abstractable α-C−H atoms in the two substrates, a *decrease* in reactivity of DABCO relative to TEA (factor of 6−17) is observed in their reactions with CumO$^{\bullet}$ (and tBuO$^{\bullet}$).[10b,32,33] This has previously been explained in terms of a stereoelectronic effect: H-atom abstraction is more rapid from TEA than from DABCO because optimal overlap between the α-C−H bond being broken and the nitrogen lone pair can only be achieved in the transition state of the former reaction.[10b,33] However, our observations indicate that in the reaction between BnO$^{\bullet}$ and DABCO overlap between the α-C−H bond being broken and the lone pair no longer plays an important role. This suggests that the rate-determining step does not involve the cleavage of this bond. A similar conclusion can be drawn from the comparison of the k_H values obtained for the reactions of CumO$^{\bullet}$ and BnO$^{\bullet}$ with TEA and TEA-d_{15}. With the former radical $k_H/k_D = 1.7$ was measured, a value that is similar to the one measured previously for the same reaction ($k_H/k_D = 1.3$)[10b] and to that obtained for the reaction of tBuO$^{\bullet}$ with trimethylamine ($k_H/k_D = 1.4$).[33] In contrast, no kinetic deuterium isotope effect (KDIE) was observed in reactions involving BnO$^{\bullet}$.

Comparable reactivities have been observed for CumO$^{\bullet}$ and BnO$^{\bullet}$ in their reactions with TIBA (k_H(BnO$^{\bullet}$)/k_H(CumO$^{\bullet}$) = 2.8). We propose that both of these reactions proceed through the *direct* interaction of the alkoxyl O-atom with the abstractable H-atom (see below). The observation of similar reactivity ratios for TIBA and CHD indicates that in *direct* H-atom abstraction reactions steric effects in both the substrate and abstracting alkoxyl radical play a minor role.

Comparison of the rate constants for the reaction of BnO$^{\bullet}$ with TIBA, TEA, and DABCO reveals that steric hindrance around the nitrogen center results in a significant decrease in reactivity. Accessibility to the amine lone pair by the radical is required to achieve very high reaction rates. This observation, together with the lack of a KDIE in the BnO$^{\bullet}$ + TEA reaction and lack of stereoelectronic effects in the BnO$^{\bullet}$ + DABCO reaction (vide supra), provides support for the hypothesis that the latter two reactions proceed through a rate-determining formation of a prereaction complex.[36]

Additional qualitative insights into the mechanistic details of the reactions of BnO$^{\bullet}$ and CumO$^{\bullet}$ with DABCO were obtained by DFT modeling. The systems studied presented considerable technical difficulties,[40] which may be partially

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(36) One mechanism for complex formation could in principle involve an interaction between the amine lone pair and the BnO$^{\bullet}$ aromatic ring, wherein an n → π electron transfer (ET) mediated by the aromatic ring can follow. This is similar to the process described recently for the reactions of BnO$^{\bullet}$ and CumO$^{\bullet}$ with alkyl ferrocenes.[37] However, ET can be ruled out on the basis of the following: (a) the large difference in redox potential between BnO$^{\bullet}$ ($E°_{\mathrm{BnO^{\bullet}/BnO^{-}}} = -0.10$ V/SCE)[37] and both DABCO and TEA ($E° = 0.80$[38] and 0.88 V/SCE,[39] respectively); (b) the large difference in reactivity between BnO$^{\bullet}$ and CumO$^{\bullet}$ toward TEA and DABCO (k_H(BnO$^{\bullet}$)/k_H(CumO$^{\bullet}$) ≥ 21.5) despite the small difference in reduction potential between these two radicals ($\Delta E = 0.09$ V),[37] whereas comparable values of k_{ET} have been measured previously (k_{ET}(BnO$^{\bullet}$)/k_{ET}(CumO$^{\bullet}$) ≤ 5);[37] (c) the comparable reactivities observed for tBuO$^{\bullet}$ and CumO$^{\bullet}$ with the tertiary amines.

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(40) In the course of this work, we learned of a remarkable dependence of the binding strength in the BnO$^{\bullet}$−DABCO prereaction complex upon the amount of Hartree−Fock exchange (HFX) in the DFT. Binding energies from BHandHLYP (50% HFX) and BLYP (0% HFX) with 6-31+G(d,p) basis sets were 3.6 and 8.4 kcal/mol, respectively. This unusual finding is under investigation.

Table 2. Calculated Enthalpies[a] (kcal/mol) for Some Stationary Points along the Reaction Path of $BnO^{\bullet}$ and $CumO^{\bullet}$ + DABCO

Stationary point	$BnO^{\bullet}$ + DABCO	$CumO^{\bullet}$ + DABCO
Prereaction complex	−4.0	−0.1
Transition state complex	0.1	0.9
Postreaction complex	−5.1	−6.1
Separated products	−2.7	−4.1

[a] Relative to separated reactants.

related to the treatment of highly delocalized electrons.[41] Despite this, we tentatively settled upon the use of the B3LYP[42]/6-31+G(d,p) method,[43] the results from which are presented in Table 2.

The calculations reveal that the reaction of $BnO^{\bullet}$ with DABCO does indeed proceed through the formation of a strongly bound prereaction complex, having a binding enthalpy of 4.0 kcal/mol. An examination of the structure (Figure 1A) suggests that the reactants are interacting via a C−H/N hydrogen bond between an α-C−H donor on $BnO^{\bullet}$ and the DABCO lone-pair acceptor,[45] a hypothesis further supported by the significant charge transfer between the two moieties of ca. 0.1 e^-.

The C−H···N distance is only 1.91 Å, which is slightly shorter than those typical in uncharged H-bonded complexes.[46] Some secondary long-range interactions also exist between the $BnO^{\bullet}$ O and a DABCO C−H (R = 2.61 Å), and these may be responsible for the less than ideal H-bond angle (C_1-H_1-N) of 161.9°. The high acidity ($pK_a = -3$)[28] of the $BnO^{\bullet}$ α-C−H atoms accounts for the H-bond donor strength of this radical.[47]

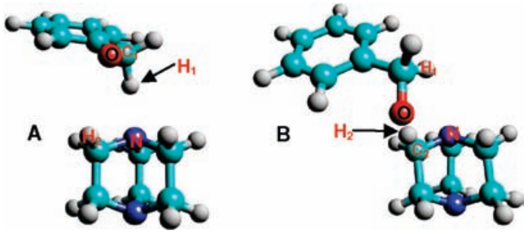

Figure 1. Calculated structure of the prereaction (**A**) and transition state (**B**) complexes in the $BnO^{\bullet}$ + DABCO reaction. Structural parameters (distances in Å, angles in deg): (**A**) $R(C_1-H_1) = 1.16$, $R(O-C_1) = 1.34$, $R(H_1-N) = 1.91$, $R(H_2-O) = 2.61$, $\theta(C_1-H_1-N) = 161.9$. (**B**) $R(C_2-H_2) = 1.26$, $R(O-H_2) = 1.28$, $R(H_1-N) = 2.93$, $\theta(C_2-H_2-O) = 172.6$.

To reach the transition state (TS) (Figure 1B), the H-bond involving the $BnO^{\bullet}$ C−H and the DABCO N-atom must be partially broken (increased by more than 1 Å). The H-bond stretching is concurrent with a decrease (by ca. 1.3 Å) in the distance between the O-atom and the abstracted H. The TS structure lies 4.1 kcal/mol above the H-bonded complex and 0.1 kcal/mol above the separated reactants.

Given the foregoing, the large differences in reactivity between $BnO^{\bullet}$ and $CumO^{\bullet}$ (and $tBuO^{\bullet}$) toward DABCO (and other tertiary amines) become clear: α-methyl groups in $CumO^{\bullet}$ eliminate the possibility of H-bond formation. This substitution prevents $CumO^{\bullet}$ from forming a prereaction complex with DABCO of significant stability and results in a slightly higher barrier for *direct* H-abstraction.

In conclusion we have shown that structural effects in both the abstracting radical and the substrate can play a dramatic role in H-abstraction reactions from carbon by alkoxyl radicals. Computational studies support the experimental data indicating that the reaction of $BnO^{\bullet}$ with relatively unhindered tertiary amines proceeds through the rate-determining formation of a complex where C−H/N hydrogen bonding between the $BnO^{\bullet}$ α-C−H and the amine lone pair assists in the H-abstraction process. It appears that the presence of an unhindered basic N-atom in the substrate is critical. The generality of this mechanistic picture is currently under investigation. These findings confirm that caution should be used when taking $tBuO^{\bullet}$ and $CumO^{\bullet}$ as chemical models for (structurally different) reactive oxygen centered radicals.

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Supporting Information Available: Time-resolved spectra observed after reaction of $BnO^{\bullet}$ with DABCO. Plots of k_{obs} vs [substrate]. Computational details of the $BnO^{\bullet}$/$CumO^{\bullet}$ + DABCO reaction paths. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) The $(CH_3)_2CHO^{\bullet}-N(CH_3)_3$ complex displays similar HFX dependencies as the $BnO^{\bullet}$−DABCO complex. Using the smaller system for benchmarking purposes, we computed a binding energy of 3.7 using CCSD(T)/611+G(2d,2p)//B3LYP/6-311+G(2d,2p) with counterpoise corrections,[44] which compares to 3.4 kcal/mol obtained by B3LYP/6-31+G(d,p).

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(47) In agreement with this picture is the observation of a decrease in k_H for the reaction between $BnO^{\bullet}$ and TEA upon addition of 1 M H_2O (see Table 1). A similar kinetic solvent effect was previously observed for the reaction between $CumO^{\bullet}$ and TEA[21] and has been ascribed to H-bonding interactions between water and the amine lone pair. In the present case, strong H-bonding with water decreases the extent of complex formation and reduces the overall reactivity.

(48) As pointed out by a reviewer, the high acidity of the $BnO^{\bullet}$ α-C−H may promote a proton transfer reaction from the radical to the amine to give a ketyl radical anion/ammonim ion couple that, following proton exchange, would give the ketyl radical and the amine. In other words, the amine acting as a base would promote a 1,2-H shift in $BnO^{\bullet}$. No computational support to this hypothesis has been obtained, and moreover, this mechanism can be ruled out on the basis of the following: (a) the previous observation that tertiary amines *do not* promote a 1,2-H shift in $BnO^{\bullet}$ (see ref. 28); (b) the lack of spectroscopic evidence for the formation of an intermediate ketyl radical or radical anion in the reaction between $BnO^{\bullet}$ and DABCO (see Supporting Information, Figure S8).