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Hydrogen Atom Abstraction Selectivity in the Reactions of Alkylamines with the Benzyloxyl and Cumyloxyl Radicals. The Importance of Structure and of Substrate Radical Hydrogen Bonding

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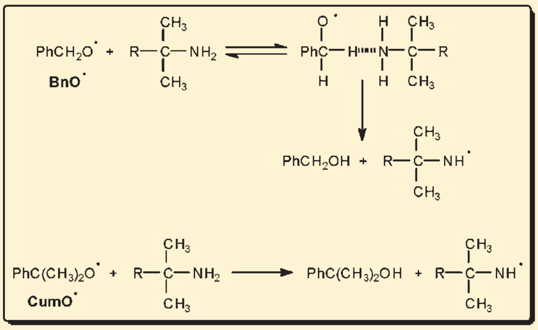
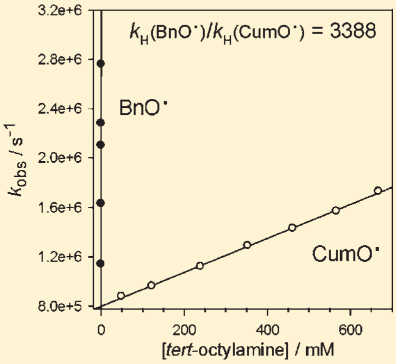
S *Supporting Information*

ABSTRACT:





A time-resolved kinetic study on the hydrogen abstraction reactions from a series of primary and secondary amines by the cumyloxyl ($CumO^•$) and benzyloxyl ($BnO^•$) radicals was carried out. The results were compared with those obtained previously for the corresponding reactions with tertiary amines. Very different hydrogen abstraction rate constants (k_H) and intermolecular selectivities were observed for the reactions of the two radicals. With $CumO^•$, k_H was observed to decrease on going from the tertiary to the secondary and primary amines. The lowest k_H values were measured for the reactions with 2,2,6,6-tetramethylpiperidine (TMP) and *tert*-octylamine (TOA), substrates that can only undergo N−H abstraction. The opposite behavior was observed for the reactions of $BnO^•$, where the k_H values increased in the order tertiary < secondary < primary. The k_H values for the reactions of $BnO^•$ were in all cases significantly higher than those measured for the corresponding reactions of $CumO^•$, and no significant difference in reactivity was observed between structurally related substrates that could undergo exclusive α-C−H and N−H abstraction. This different behavior is evidenced by the $k_H(BnO^•)/k_H(CumO^•)$ ratios that range from 55−85 and 267−673 for secondary and primary alkylamines up to 1182 and 3388 for TMP and TOA. The reactions of $CumO^•$ were described in all cases as *direct* hydrogen atom abstractions. With $BnO^•$ the results were interpreted in terms of the rate-determining formation of a hydrogen-bonded prereaction complex between the radical α-C−H and the amine lone pair wherein hydrogen abstraction occurs. Steric effects and amine HBA ability play a major role, whereas the strength of the substrate α-C−H and N−H bonds involved appears to be relatively unimportant. The implications of these different mechanistic pictures are discussed.

1. INTRODUCTION

Hydrogen atom abstraction represents one of the most fundamental reactions and plays a key role in a variety of important chemical and biological processes such as the oxidative damage to biomolecules and polymers,[1−3] the radical scavenging activity of natural and synthetic antioxidants,[2,4−7] enzymatic reactions,[8,9] C−H functionalization,[10−12] and the degradation of volatile organic compounds in the atmosphere.[13] Developing a detailed understanding of the factors that govern hydrogen atom abstraction reactivity has been a main research goal, and accordingly these reactions have been investigated from both the experimental and theoretical point of view.[14−20] One important aspect of these processes that attracts continuous interest is the reaction selectivity,[21] and accordingly various studies have dealt with the intra- and intermolecular selectivity in hydrogen atom abstraction reactions by radical and radical-like species.[14,15f,22−29]

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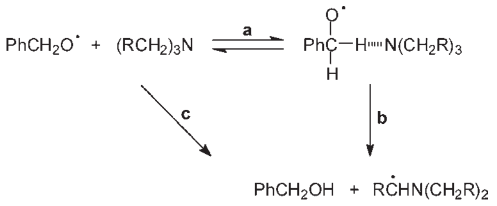
Scheme 1



Among the abstracting species, alkoxyl radicals have attracted considerable interest, and several aspects of their hydrogen atom abstraction reactivity have been studied in detail. These include the nature of the substrate and of the abstractable hydrogen atom (C−H[30−32] or X−H, where X = O,[33−35] N,[33c,36] S,[37] Si,[38] Ge,[39] or Sn[39]), the role of the solvent,[33,40−44] the reaction selectivity,[20a,45−48] and the possible competition with other reactive pathways.[44−46,49]

One aspect that has received very limited attention is the role of the alkoxyl radical structure on these processes.[40,50] In this context, we recently carried out a time-resolved kinetic and computational study on the hydrogen atom abstraction reactions from tertiary amines by the cumyloxyl ($PhC(CH_3)_2O^\bullet$, CumO$^\bullet$) and benzyloxyl ($PhCH_2O^\bullet$, BnO$^\bullet$) radicals, which showed the existence of very large differences in reactivity between the two radicals.[51,52] A large increase in the rate constant for hydrogen atom abstraction (k_H) from the amines was observed on going from CumO$^\bullet$ to BnO$^\bullet$, with the reactivity ratio (k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$)) that goes from 13 for the reactions with tripropylamine (TPA) up to 1094 and 2027 for those with the bicyclic diamine and amine 1,4-diazabicyclo[2,2,2]octane (DABCO) and 1-azabicyclo[2,2,2]octane (ABCO). On the other hand, comparable reactivities were found for the two radicals in their reactions with the relatively hindered triisobutylamine (TIBA), viz., k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) = 2.8.

These results were explained in terms of the rate-determining formation of a hydrogen-bonded prereaction complex between the relatively acidic BnO$^\bullet$ α-C−H and the amine lone pair, followed by intracomplex hydrogen atom abstraction.[51,52] Efficient complex formation is possible only for relatively unhindered amines (Scheme 1, paths *a*,*b*).

With TIBA, steric hindrance in proximity of the nitrogen lone pair prevents efficient complex formation; accordingly, its reactions with both radicals were described as *direct* hydrogen atom abstractions, with no significant prereaction complex formation, i.e. reactions that proceed through the direct interaction of the radical center with the abstractable hydrogen atom (Scheme 1, path **c**). With CumO$^\bullet$ the presence of α-methyl groups prevents hydrogen bond formation and its reactions with the amines were described in all cases as *direct* hydrogen atom abstractions. These results demonstrate that alkoxyl radical structure can play a dramatic role in these processes, and that control over the intermolecular hydrogen abstraction selectivity can be achieved through specific substrate radical hydrogen-bond interactions.

Solvent−substrate and/or solvent−radical hydrogen-bond interactions have often been invoked to account for the kinetic solvent effects observed on hydrogen atom abstraction reactions.[33,40,41,43,53] However, substrate radical hydrogen bonding has received limited attention. Nevertheless, these interactions appear to play an important role in these processes. For example, the peculiar selectivity observed in the hydrogen atom abstraction reactions from model peptides by the hydroxyl radical[54,55] where, as compared to the weaker backbone C−H bonds, abstraction was observed to occur preferentially from the stronger side-chain C−H bonds, was explained in terms of specific substrate radical hydrogen-bond interactions. A number of computational studies support this hypothesis and point toward the formation of hydrogen-bonded prereaction complexes between the substrate and the radical prior to hydrogen atom abstraction.[56−58] A similar selectivity pattern was also observed for the reactions of the chlorine atom with α-amino acids.[59] The formation of hydrogen-bonded prereaction complexes in hydrogen atom abstractions was also proposed in three very recent studies on the reactions of a manganese(IV) oxo complex with hydrocarbons,[60] a cobalt(III) tris(2,2-biimidazoline) complex with 1-hydroxyl-2,2,6,6-tetramethylpiperidine,[61] and a ruthenium(IV) oxo complex with 1-propanol.[62]

Chart 1

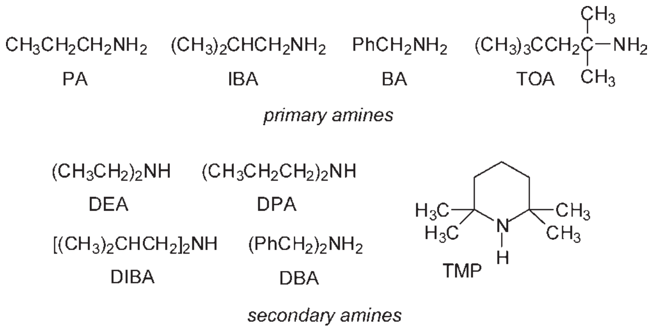
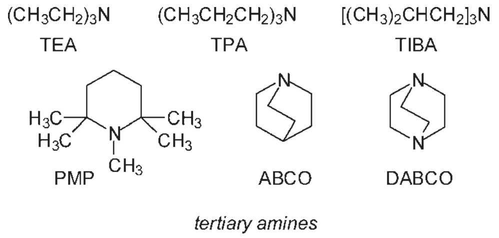


Chart 2



In view of the relevance of these processes, and in order to develop a deeper mechanistic understanding of hydrogen atom abstraction reactions from amines by alkoxyl radicals, we have carried out a detailed time-resolved kinetic study in acetonitrile solution on the reactions of BnO$^\bullet$ with a variety of primary and secondary alkylamines with comparisons to the more hindered CumO$^\bullet$. Particular attention has been devoted to the role of substrate radical hydrogen-bond interactions on the hydrogen abstraction selectivity. The following alkylamines have been selected for this purpose: diethylamine (DEA), propylamine (PA), dipropylamine (DPA), isobutylamine (IBA), diisobutylamine (DIBA), benzylamine (BA), dibenzylamine (DBA), 2,2,6,6-tetramethylpiperidine (TMP), and *tert*-octylamine (TOA), the structures for which are displayed in Chart 1.

For the sake of clarity, the structures of the previously studied tertiary amines triethylamine (TEA),tripropylamine (TPA), triisobutylamine (TIBA), 1,2,2,6,6-pentamethylpiperidine (PMP), 1-azabicyclo[2,2,2]octane (ABCO), and 1,4-diazabicyclo[2,2,2]-octane (DABCO) are displayed in Chart 2.

2. RESULTS

The reactions of CumO$^•$ and BnO$^•$ with the alkylamines were studied using the laser flash photolysis (LFP) technique. CumO$^•$ and BnO$^•$ were generated by 266 nm LFP of nitrogen-saturated MeCN solutions (T = 25 °C) containing dicumyl and dibenzyl peroxide, respectively (eq 1). In some experiments, CumO$^•$ was also generated by 355 nm LFP of nitrogen-saturated MeCN solutions (T = 25 °C) containing dicumyl peroxide.

$$\mathrm{RO-OR} \xrightarrow[266\ \mathrm{nm}]{h\nu} 2\mathrm{RO}^• \qquad (1)$$

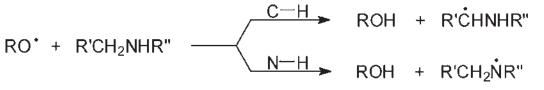
$$\mathrm{R} = \begin{matrix} \mathrm{PhC(CH_3)_2} \\ \\ \mathrm{PhCH_2} \end{matrix}$$

In acetonitrile solution, CumO$^•$ and BnO$^•$ are characterized by a broad 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−CH$_3$ β-scission.[44,64] The decay of BnO$^•$ can be mainly attributed to hydrogen atom abstraction from the solvent.[65,66]

It is well established that the reactions of the alkoxyl radicals with tertiary amines proceed by α-C−H abstraction from the substrates, as described in eq 2.[30b,31,41,51,52,67,68]

$$\mathrm{RO}^• + \mathrm{R'CH_2NR_2''} \rightarrow \mathrm{ROH} + \mathrm{R'\dot{C}HNR_2''} \qquad (2)$$

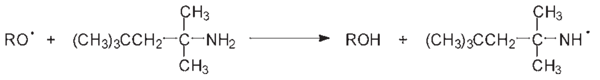
With primary and secondary amines competition between α-C−H and N−H abstraction is observed, leading to α-aminoalkyl and aminyl radicals, respectively (eqs 3a and 3b, R″ = H, alkyl).[30b,68−72] A number of studies have indicated that in the reaction of these substrates with the *tert*-butoxyl radical ((CH$_3$)$_3$CO$^•$, tBuO$^•$) α-C−H abstraction (eq 3a) is generally favored over N−H abstraction (eq 3b).[68,70,71] However, it has been shown that temperature and amine concentration can influence the competition between these reactive pathways.[69]



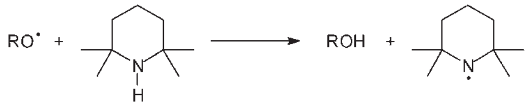
(3a)

(3b)

With TOA and TMP, which lack the presence of α-C−H atoms, only N−H abstraction can occur (eqs 4 and 5).[30b,68,71]



$$\mathrm{RO}^• + \mathrm{(CH_3)_3CCH_2{-}}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{{-}NH_2} \longrightarrow \mathrm{ROH} + \mathrm{(CH_3)_3CCH_2{-}}\underset{\mathrm{CH_3}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{{-}NH}^• \qquad (4)$$



(5)

A number of rate constants for the reactions of primary, secondary, and tertiary alkylamines with tBuO$^•$ and CumO$^•$, measured under different experimental conditions, are available in the literature.[30b,31,41,67,68,71]

Our 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 alkylamine concentration. The observed rate constants (k_{obs}) gave excellent linear relationships when plotted against substrate concentration and provided the second-order rate constants for hydrogen atom abstraction from the substrates by CumO$^•$ and BnO$^•$ (k_{H}). As an example, Figure 1 shows the plots of k_{obs} vs [substrate] for the reactions of TIBA (black circles), DIBA (white circles) and IBA (gray circles) with CumO$^•$ (**a**) and BnO$^•$ (**b**) for measurements carried out in MeCN solution at T = 25 °C.

Additional plots for hydrogen atom abstraction reactions by CumO$^•$ and BnO$^•$ from the other alkylamines are displayed in the Supporting Information (SI, Figures S1−S14). All the kinetic data thus obtained are collected in Table 1 together with the pertinent k_{H}(BnO$^•$) / k_{H}(CumO$^•$) ratios. Also included in Table 1 are the rate constants obtained previously under analogous experimental conditions for the reactions of CumO$^•$ and BnO$^•$ with the tertiary amines TEA, TPA, TIBA, PMP, ABCO, and DABCO.[51,52]

3. DISCUSSION

We begin our discussion with the reactions involving CumO$^•$. The kinetic data displayed in Table 1 show that the k_{H} values decrease on going from the tertiary to the secondary and, where available, primary amines. In the ethylamine and propylamine series, the k_{H} values decrease by a factor of 2 on going from the tertiary to the secondary amine. The smaller differences observed in the k_{H} values for the isobutylamine series, as compared to those of the ethylamine and propylamine series is a consequence of the lower k_{H} value measured for the reaction with TIBA as compared to TEA and TPA. This behavior can be attributed to the sterics associated with the isobutyl group. An additional one order of magnitude decrease in reactivity is observed in the propylamine and isobutylamine series on going from the secondary to the primary amine. Similar results were obtained previously for the reactions of tBuO$^•$ and CumO$^•$ with alkylamines,[30b,68,71] and were explained in terms of the bond dissociation enthalpy (BDE) differences of the α-C−H and N−H bonds involved.[71] This explanation was based on the available α-C−H and N−H BDEs for trimethylamine (TMA), dimethylamine (DMA), methylamine (MA), and ammonia (α-C−H BDE = 84, 87, and 94 kcal mol^{-1}, for TMA, DMA, and MA, respectively. N−H BDE = 92, 100, and 107 kcal mol^{-1}, for DMA, MA, and NH$_3$, respectively).[71] More recent recommended N−H BDEs for DMA, MA, and NH$_3$ (N−H BDE = 94.6, 101.6, and 108 kcal mol^{-1}, respectively)[73] are in agreement with this explanation. On the other hand, the observation that the recommended BDEs available for the α-C−H bonds of tertiary, secondary, and primary alkylamines are very similar to each other (between 88.6 and 91 kcal mol^{-1} for the ethylamine and propylamine series)[73] appears to be in contrast with this hypothesis. Along this line, in order to obtain additional information in this respect, we calculated the BDEs of the α-C−H and N−H bonds of triethylamine (TEA), diethylamine (DEA), and ethylamine (EA) using the B3[74]P86[75]/6-311G(2d,2p)//B3P86/6-31G(d) density functional theory (DFT) approach, according to a previously outlined procedure.[76] The calculated α-C−H and N−H BDEs for the ethylamine series are displayed in Table 2. Also included are the experimental α-C−H BDEs for the three amines.

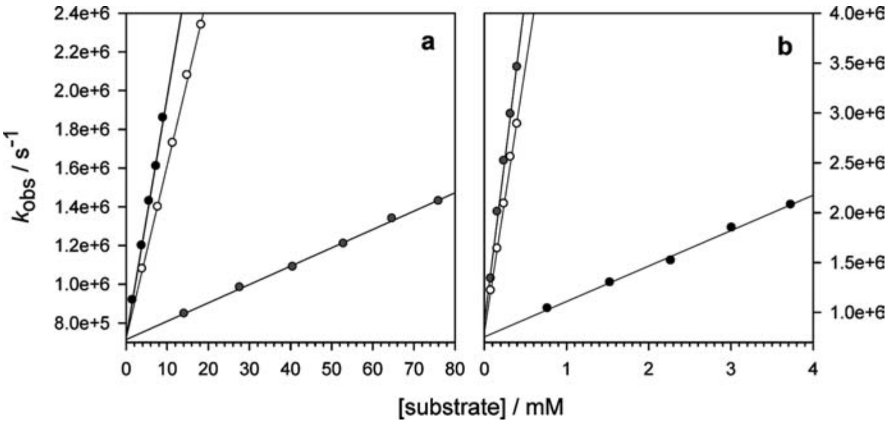


Figure 1. Plots of the observed rate constant (k_{obs}) against [substrate] for the reactions of the cumyloxyl radical (CumO$^\bullet$, a) and benzyloxyl radical (BnO$^\bullet$, b) with triisobutylamine (TIBA, black circles), diisobutylamine (DIBA, white circles) and isobutylamine (IBA, gray circles), measured in nitrogen-saturated MeCN solutions at $T = 25$ °C, following the decay of CumO$^\bullet$ and BnO$^\bullet$ at 490 and 460 nm, respectively. From the linear regression analysis: (a) CumO$^\bullet$ + TIBA: intercept = 7.24×10^5 s^{-1}, $k_H = 1.25 \times 10^8$ M^{-1} s^{-1}, $r^2 = 0.9981$; CumO$^\bullet$ + DIBA: intercept = 7.21×10^5 s^{-1}, $k_H = 8.93 \times 10^7$ M^{-1} s^{-1}, $r^2 = 0.9988$; CumO$^\bullet$ + IBA: intercept = 7.15×10^5 s^{-1}, $k_H = 9.47 \times 10^6$ M^{-1} s^{-1}, $r^2 = 0.9986$. (b) BnO$^\bullet$ + TIBA: intercept = 7.54×10^5 s^{-1}, $k_H = 3.55 \times 10^8$ M^{-1} s^{-1}, $r^2 = 0.9964$; BnO$^\bullet$ + DIBA: intercept = 8.00×10^5 s^{-1}, $k_H = 5.32 \times 10^9$ M^{-1} s^{-1}, $r^2 = 0.9973$; BnO$^\bullet$ + IBA: intercept = 8.95×10^5 s^{-1}, $k_H = 6.51 \times 10^9$ M^{-1} s^{-1}, $r^2 = 0.9943$.

Table 1. Second-Order Rate Constants (k_H) for the Reactions of the Cumyloxyl (CumO$^\bullet$) and Benzyloxyl (BnO$^\bullet$) Radicals with Alkylamines

	k_H / M^{-1} s^{-1} [a]		
substrate	CumO$^\bullet$	BnO$^\bullet$	k_H(BnO$^\bullet$)/ k_H(CumO$^\bullet$)
TEA	$2.0 \pm 0.1 \times 10^8$ [b]	$4.3 \pm 0.1 \times 10^9$ [c]	21.5
DEA	$1.1 \pm 0.1 \times 10^8$	$6.5 \pm 0.2 \times 10^9$	59
TPA	$2.3 \pm 0.1 \times 10^8$ [d]	$3.0 \pm 0.1 \times 10^9$ [d]	13.0
DPA	$1.01 \pm 0.03 \times 10^8$	$5.5 \pm 0.1 \times 10^9$	55
PA	$1.04 \pm 0.06 \times 10^7$	$6.51 \pm 0.03 \times 10^9$	626
TIBA	$1.27 \pm 0.02 \times 10^8$ [c]	$3.51 \pm 0.05 \times 10^8$ [c]	2.8
DIBA	$9.1 \pm 0.2 \times 10^7$	$5.1 \pm 0.2 \times 10^9$	56
IBA	$9.6 \pm 0.1 \times 10^6$	$6.46 \pm 0.05 \times 10^9$	673
DBA	$3.75 \pm 0.05 \times 10^7$ [e,f]	$3.17 \pm 0.02 \times 10^9$	85
BA	$1.8 \pm 0.1 \times 10^7$ [e,g]	$4.8 \pm 0.1 \times 10^9$	267
ABCO	3.7×10^6 [h]	$7.5 \pm 0.4 \times 10^9$ [d]	2027
DABCO	9.6×10^6 [h]	$1.05 \pm 0.05 \times 10^{10}$ [c]	1094
PMP	$1.70 \pm 0.02 \times 10^8$ [d]	$4.26 \pm 0.07 \times 10^9$ [d]	25
TMP	$3.13 \pm 0.02 \times 10^6$ [e]	$3.7 \pm 0.1 \times 10^9$	1182
TOA	$1.34 \pm 0.04 \times 10^6$ [e]	$4.54 \pm 0.06 \times 10^9$	3388

[a] Measured in N_2-saturated MeCN solution at $T = 25$ °C by 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$^\bullet$ or BnO$^\bullet$ visible absorption bands at 490 and 460 nm, respectively. Average of at least two determinations. [b] Reference 41. [c] Reference 51. [d] Reference 52. [e] 355 nm LFP, [dicumyl peroxide] = 1.0 M. [f] In O_2-saturated MeCN solution. [g] An identical k_H value was obtained in O_2-saturated MeCN solution. [h] Reference 30b.

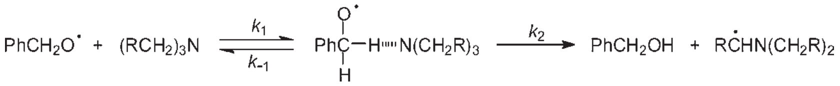
Table 2. Calculated α-C−H and N−H Bond Dissociation Enthalpies (BDEs) for the Ethylamine Series (kcal mol^{-1})

	α-C−H		N−H
molecule	expt [a]	B3P86 [b]	B3P86 [b]
Et_3N (TEA)	90.7	90.3	−
Et_2NH (DEA)	88.6	90.8	92.9
$EtNH_2$ (EA)	90.1	90.9	99.0

[a] Recommended experimental data taken from reference 73. [b] B3P86/6-311G(2d,2p)//B3P86/6-31G(d) as described in reference 76.

The data collected in Table 2 show very similar trends for the B3P86 and experimental α-C−H BDE values. The calculated N−H BDEs are also in reasonably good agreement with the experimental ones measured for DMA and MA (N−H BDE = 94.6 and 101.6 kcal mol^{-1}, respectively).[73] With DEA and EA, the N−H BDEs are higher than the α-C−H BDEs, in line with expectations and with the available experimental data for the methylamine series.[73] These calculated data clearly indicate that the decrease in k_H measured for the reactions of CumO$^\bullet$ on going from tertiary to secondary and primary alkylamines cannot be simply explained in terms of the BDE differences of the α-C−H and N−H bonds involved. In this context, Tanko and co-workers have recently pointed out that, in hydrogen atom abstraction reactions from tertiary amines by *t*BuO$^\bullet$, the activation energies are independent of BDE for substrates characterized by α-C−H BDEs < 92 kcal mol^{-1}.[31a] At room temperature, these processes are entropy controlled and appear to be governed by issues of orientation, trajectory, accessibility, rather than by the strength of the α-C−H bonds involved, suggesting in particular that an important role is played by the alkoxyl radical sterics. A number of studies have clearly shown that *t*BuO$^\bullet$ and CumO$^\bullet$ display very similar hydrogen atom abstraction reactivities,[51,77−79] and accordingly, the concepts outlined above for *t*BuO$^\bullet$ can be reasonably extended to the reactions of CumO$^\bullet$. On the basis of the available α-C−H BDEs for alkylamines (which are, in all cases, < 92 kcal mol^{-1}) a possible explanation for the observed reactivity trends can be put forward in terms of the degree of order in the transition state of the hydrogen abstraction reaction that is expected to increase by decreasing the number of alkyl groups bound to nitrogen. In other words, the entropy requirements in the transition states of these reactions may become increasingly stringent on going from tertiary to secondary and primary amines.

Scheme 2



Among the acyclic secondary amines, up to 3-fold increases in reactivity were measured on going from DBA to DEA, DPA, and DIBA. Very similar behavior was observed previously for the reactions of *t*BuO$^\bullet$, where a 2−3-fold increase in reactivity was measured on going from tribenzylamine (TBA) to TEA,[31,67] despite the slight increase in the α-C−H BDE value (BDE = 89.1 and 90.7 kcal mol^{-1}, for TBA and TEA, respectively).[73,80] Again, this behavior may be indicative of the above-mentioned entropic control over the hydrogen abstraction reaction, where the sterics associated with the alkoxyl radical play an important role.[31] A similar explanation can be reasonably put forward also for the reactions of the secondary amines with CumO$^\bullet$.

The reactions of CumO$^\bullet$ with tertiary amines can only result in α-C−H abstraction, whereas competition between α-C−H and N−H abstraction can occur with primary and secondary amines. In TMP and TOA, which lack the presence of hydrogen atoms bound to the α-carbons, only N−H abstraction can occur. Accordingly, the low k_H values measured for the reactions of CumO$^\bullet$ with TMP and TOA ($k_H = 3.13 \times 10^6$ and 1.34×10^6 M^{-1} s^{-1}, respectively) are indicative of N−H abstraction. These values are in very good agreement with those measured previously for the reactions of CumO$^\bullet$ with TMP ($k_H = 2.8 \times 10^6$ M^{-1} s^{-1}),[30b] and of *t*BuO$^\bullet$ with *tert*-butylamine ($k_H = 3.3 \times 10^6$ M^{-1} s^{-1}).[68] These are, by far, the lowest k_H values among those displayed in Table 1, in line with the significantly higher BDEs of N−H bonds as compared to α-C−H BDEs.[73] Along this line, the (statistically corrected) 4.7-fold decrease in reactivity observed on going from TMP to TOA reflects the corresponding increase in N−H BDE for the two amines.

The k_H values measured for the reactions of TMP and TOA can be taken as representative for N−H abstraction by CumO$^\bullet$ from secondary and primary alkylamines, respectively, and can be used to evaluate the relative importance of α-C−H and N−H abstraction pathways in the reactions of the other primary and secondary amines displayed in Table 1. Based on the analysis of the kinetic data for the ethylamine, propylamine and isobutylamine series, the statistically corrected rate constants for abstraction from the α-CH_2 group of the secondary amines ($k_{C-H} = 2.2{-}2.7 \times 10^7$ M^{-1} s^{-1}) are almost one order of magnitude higher than that for N−H abstraction ($k_{N-H} = 3.1 \times 10^6$ M^{-1} s^{-1}), and similar differences in reactivity apply for the primary amines for which $k_{C-H} = 4.5{-}4.9 \times 10^6$ and $k_{N-H} = 6.7 \times 10^5$ M^{-1} s^{-1}.

For the reactions of BnO$^\bullet$ with the alkylamines, the k_H values are in all cases higher than those measured for the corresponding reactions of CumO$^\bullet$. The large differences in reactivity observed for the reactions of these two radicals with tertiary amines were discussed by us in two recent papers.[51,52] The increases in rate constant observed on going from CumO$^\bullet$ to BnO$^\bullet$ (with k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) ratios that range from 2.8 for TIBA to 2027 for ABCO) were explained in terms of the mechanism shown in Scheme 1, paths *a*,*b*. The results of computational modeling pointed toward the formation of a relatively stable complex where the acidic α-C−H of BnO$^\bullet$ engages in hydrogen bonding with the amine lone pair.[51] The kinetic data were thus explained in terms of the rate-determining formation of a hydrogen-bonded prereaction complex wherein fast hydrogen atom abstraction occurs, as described in Scheme 2. In this scheme, k_1 and k_{-1} are the rate constants for the formation and dissociation of the hydrogen-bonded prereaction complex and k_2 is the rate constant for hydrogen atom abstraction within the complex. Under these conditions, $k_2 \gg k_{-1}$ applies, and k_1 corresponds to the measured k_H values displayed in Table 1.[52]

Support for this mechanistic picture was derived from the following experimental observations:

(I) The Role of Amine Structure

The rate constants for hydrogen abstraction by BnO$^\bullet$ were observed to increase by decreasing steric hindrance in the proximity of the nitrogen lone pair, supporting the hypothesis that bulky alkyl groups prevent efficient prereaction complex formation. Accordingly, the lowest k_H value was measured for the reaction of BnO$^\bullet$ with the relatively hindered amine TIBA ($k_H = 3.51 \times 10^8$ M^{-1} s^{-1}), and the largest k_H values were measured with the cyclic and bicyclic amines and diamines 1,4-dimethylpiperazine, ABCO and DABCO ($k_H = 8.0 \times 10^9$, 7.5×10^9 and 1.05×10^{10}, respectively),[51,52] substrates characterized by the presence of unhindered nitrogen atoms. Similar rate constants were measured for the reactions of CumO$^\bullet$ and BnO$^\bullet$ with TIBA (k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) = 2.8) and this behavior was explained in both cases in terms of a *direct* hydrogen atom abstraction reaction, as described in Scheme 1, path *c*.

(II) The Role of Alkoxyl Radical Structure

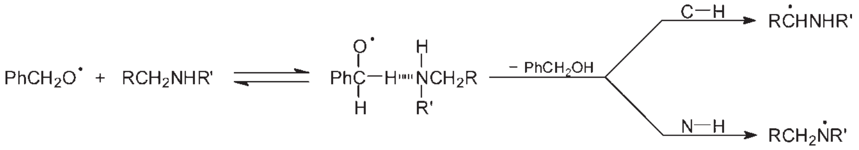
As compared to the reactions of CumO$^\bullet$ and BnO$^\bullet$ with cyclic and bicyclic amines and diamines, and with tertiary alkylamines, where k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) ratios up to 2027 were observed,[51,52] very small rate constant ratios were measured for the corresponding reactions of the two radicals with hydrogen atom donors such as propanal, 2,2-dimethylpropanal, and 1,4-cyclohexadiene ((k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) = 1.2, 1.6 and 1.9, respectively).[40,51] Quite importantly, similar rate constant ratios (between 1.8 and 2.1) were also observed for the addition reactions of CumO$^\bullet$ and BnO$^\bullet$ to trialkyl phosphites $(RO)_3P$ (*R* = Me, Et, *i*Pr).[81] These observations clearly indicate that alkoxyl radical sterics play a minor role in both the hydrogen abstraction and addition processes.

The decrease in the k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) ratio observed on going from the amines to the other substrates is in agreement with the mechanistic picture presented above (Schemes 1 and 2) as tertiary alkylamines are characterized by significantly greater HBA abilities (expressed in terms of Abraham's β_2^H parameter:[82] β_2^H = 0.58−0.67)[83] as compared to aliphatic aldehydes (β_2^H = 0.39) and 1,4-cyclohexadiene (β_2^H = 0.00).[83]

(III) Kinetic Deuterium Isotope Effects (KDIEs)

No KDIE was observed in the reactions of BnO$^\bullet$ with TEA and TEA-d_{15} ($k_H/k_D = 1.0$), whereas $k_H/k_D = 1.7$ was measured for the corresponding reactions of CumO$^\bullet$.[51,84]

Scheme 3



(IV) Stereoelectronic Effects
Previous studies on hydrogen atom abstraction from tertiary amines by *t*BuO• and CumO• have clearly shown that the reaction is most rapid when the α-C−H bond being broken can be eclipsed with the nitrogen lone pair. In DABCO and ABCO these bonds are locked in a conformation that reduces overlap, resulting in α-C−H abstractions that occur with rate constants that are significantly lower than those measured for the corresponding reactions of conformationally free amines.[30b,31a,68] Close to diffusion control k_H values were measured for the reactions of BnO• with the bicyclic amines ABCO and DABCO ($k_H = 7.5 \times 10^9$ and 1.05×10^{10} M^{-1} s^{-1}, respectively),[51,52] compared to significantly lower rate constants obtained for the corresponding reactions of CumO• ($k_H = 3.7 \times 10^6$ and 9.7×10^6 M^{-1} s^{-1}, respectively).[30b] The very high k_H(BnO•)/k_H(CumO•) ratios observed for these reactions (2027 and 1094, for ABCO and DABCO, respectively), clearly indicate that the stereoelectronic effects responsible for the low rate constants measured for the reactions of ABCO and DABCO with CumO• and *t*BuO•, do not play a role in the reactions with BnO•.

3.1. Kinetic Solvent Effects. An increase in reactivity was observed for the reactions of BnO• with TEA on going from MeCN to isooctane ($k_H = 4.3 \times 10^9$ and 9.6×10^9 M^{-1} s^{-1}, respectively),[52] in line with the higher hydrogen bond donor (HBD) ability of MeCN as compared to isooctane ($\alpha_2^H = 0.09$ and 0.00, respectively).[85,86] MeCN can compete with BnO• as a hydrogen bond donor for the amine lone pair. This interaction results in a decrease in the efficiency of complex formation and a corresponding decrease in reactivity as compared to isooctane where no such interaction can occur.[87] As pointed out previously,[52] the observation of an increase in k_H for the reaction between BnO• and TEA on going from MeCN to isooctane, despite an increase in viscosity,[88a,89] and a corresponding decrease in the diffusion-control limit ($k_d = 2.0 \times 10^{10}$ and 1.4×10^{10} M^{-1} s^{-1}, respectively),[88,90] provides support to the hypothesis that the observed differences in k_H reflect the role of structural and electronic effects in the amines on the formation of the prereaction complex.

Taken together, these findings strongly support the mechanistic picture outlined in Scheme 2, where points III and, most importantly, IV indicate in particular that in the reactions of relatively unhindered tertiary amines with BnO• the cleavage of the α-C−H bond does not contribute to the rate determining step.[52]

Interestingly, when comparing the reactions of CumO• and BnO• with tertiary, secondary and primary amines, the analysis of Figure 1 and of the data displayed in Table 1 clearly show the existence of opposite reactivity trends. The kinetic plots for the reactions of the two radicals with TIBA, DIBA and IBA displayed in Figure 1 show that, as mentioned above, with CumO• the k_H values decrease on going from the tertiary to the secondary and primary amine. The opposite behavior was observed in the corresponding reactions of BnO•, where the highest k_H value was measured for the primary amine IBA. This behavior is reflected in the k_H(BnO•)/k_H(CumO•) ratios that increase from 2.8 to 56 up to 673 for the reactions with TIBA, DIBA and IBA, respectively. A very similar trend was also observed in the ethylamine, propylamine and benzylamine series, where the higher k_H(BnO•)/k_H(CumO•) ratios observed for the reactions of TEA and TPA as compared to TIBA were explained in terms of steric effects in the latter amine that prevented efficient complex formation.[51,52] Along this line, the significantly larger increase in reactivity observed for the reactions of BnO• on going from TIBA to DIBA ($k_H = 3.51 \times 10^8$ and 5.1×10^9 M^{-1} s^{-1}, respectively) as compared to those observed for the other amine couples ($k_H = 4.3 \times 10^9$ and 6.5×10^9 M^{-1} s^{-1}, for TEA and DEA, and $k_H = 3.0 \times 10^9$ and 5.5×10^9 M^{-1} s^{-1}, for TPA and DPA), again points to the very important role of substrate sterics in these reactions.

Very importantly, the observation of opposite reactivity trends in the reactions of CumO• and BnO• with the alkylamine series, together with the above-mentioned dramatic decrease in the k_H(BnO•)/k_H(CumO•) ratios observed on going from the amines to aliphatic aldehydes and 1,4-cyclohexadiene, rules out the hypothesis that the large increase in hydrogen abstraction reactivity observed on going from CumO• to BnO• is the result of the reduced steric hindrance in proximity of the oxygen center for the latter radical as compared to the former one.

These very large kinetic effects clearly indicate that the factors responsible for the decrease in reactivity observed for the reactions of CumO• on going from the tertiary to the primary amines no longer operate in the corresponding reactions of BnO•. Thus, in the latter reactions, the strength of the α-C−H and N−H bonds involved does not appear to play any significant role, an observation that is again in line with the mechanistic hypothesis outlined in Schemes 1 and 2, viz., of the rate-determining formation of a hydrogen-bonded prereaction complex.

Even more striking are the differences in reactivity observed for the reactions of the two radicals with TMP and TOA where only N−H abstraction can occur. With both substrates, dramatic increases in reactivity were observed on going from CumO• to BnO• (k_H(BnO•)/k_H(CumO•) = 1182 and 3388, for TMP and TOA, respectively). Relatively low k_H values were measured in the reactions of TMP and TOA with CumO• ($k_H = 3.13 \times 10^6$ and 1.34×10^6 M^{-1} s^{-1}, respectively), and this behavior is explained in terms of the higher BDEs of N−H bonds as compared to α-C−H BDEs. Along this line, the >3-orders of magnitude increase in k_H observed for the two amines on going from CumO• to BnO• again indicates that N−H bond strengths play a negligible role in the reactions of the latter radical. Comparison of the k_H values displayed in Table 1 for the reactions of CumO• and BnO• with PMP and TMP, substrates

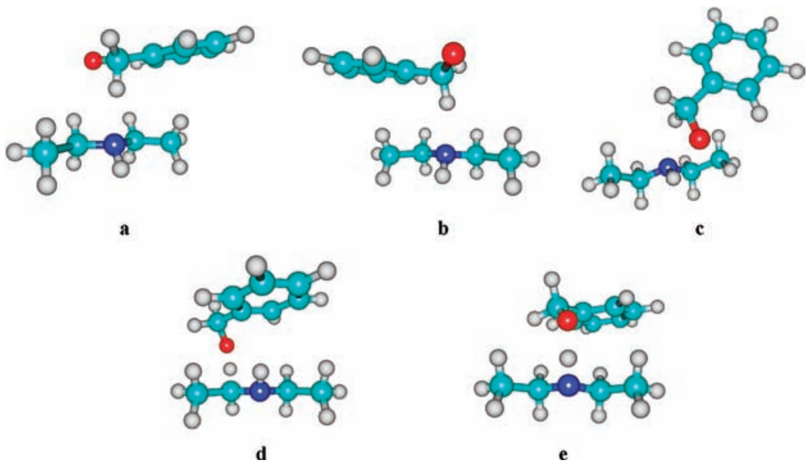


Figure 2. Density functional theory predictions of hydrogen-bonded complexes of BnO$^{\bullet}$ with diethylamine (DEA) (a−c) and associated transition state structures (d,e). The computed binding energies/enthalpies, in kcal mol^{-1} are: (a) 4.5/3.0, (b) 3.7/2.2, and (c) 3.3/1.9. On the basis of the calculated enthalpies, the Boltzmann populations of the complexes are 70.3, 18.5, and 11.1% for a, b, and c, respectively. The free energies associated with formation of the transition state structures are: (d) 3.9 kcal·mol^{-1} (relative to a) and (e) 4.4 kcal·mol^{-1} (relative to c). Key internuclear distances and angles, are as follows: (a) α-C−H···N = 2.13 Å, C−H−N = 153.3°, O···α-C−H = 2.56 Å, O−H−C = 132.8°, (b) α-C−H···N = 2.18 Å, C−H−N = 161.2°, (c) α-C−H···N = 2.36 Å, C−H−N = 140.4°, NH···**O** = 2.60 Å, O−H−N = 121.4°, (d) α-C−H···O = 1.40 Å, C−H−O = 172.9°, OH···**C** = 1.20 Å, (e) O−H···N = 1.11 Å, O−H−N = 156.3°, NH···O = 1.34 Å. Color key: C = light blue, N = dark blue, O = red, H = white.

that can undergo exclusive hydrogen atom abstraction from the N−CH_3 and N−H groups, respectively, is informative in this respect. A 54-fold decrease in reactivity was observed for CumO$^{\bullet}$ on going from the tertiary to the secondary amine, whereas no relevant kinetic effect was measured for the corresponding reactions of BnO$^{\bullet}$.

On the basis of these observations and on the data displayed in Table 1, the mechanism proposed for the reactions of the tertiary amines with BnO$^{\bullet}$ (Scheme 1) can be conveniently extended to the reactions of the secondary and primary amines as described in Scheme 3 (R′ = H, CH_2R), in which hydrogen atom abstraction can now occur from the α-C−H and/or N−H bonds, depending on substrate structure and following the rate-determining formation of the hydrogen-bonded prereaction complex.

On the basis of this mechanistic picture, no direct information on the competition between α-C−H and N−H abstraction can be obtained. In order to probe this issue and to provide support to the proposed mechanism, we modeled the prereaction complex and transition state structures associated with the reaction between BnO$^{\bullet}$ and DEA (Scheme 3, R = CH_3, R′ = CH_2CH_3) with density-functional theory (DFT) augmented with dispersion-correcting potentials to more accurately capture noncovalent interactions.[91] The calculations predict that three hydrogen-bonded complexes can form, as described in Figure 2. The most stable structure is shown in Figure 2a, and involves a relatively strong hydrogen-bond interaction between the α-C−H group of BnO$^{\bullet}$ and the DEA nitrogen lone pair, and a secondary interaction between the BnO$^{\bullet}$ oxygen atom and the amine α-C−H. Complex **2a** is predicted to have a binding energy (enthalpy) of 4.5 (3.0) kcal mol^{-1}, with a Boltzmann population among the three noncovalently bound complexes of ∼70%. This structure can lead to a transition state (TS) structure for α-C−H abstraction with minimal rearrangement of the two components (Figure 2d). The calculated free energy barrier ($\Delta G^{\ddagger}$) associated with the hydrogen abstraction, relative to complex **2a** (separated reactants), is 3.9 (11.8) kcal mol^{-1}.

The complex shown in Figure 2b is the next most strongly bound (binding energy (enthalpy) = 3.7 (2.2) kcal mol^{-1}), and does not lead directly to a TS structure. As such, the formation of this type of complex can reduce the rate of hydrogen abstraction by trapping reactants in a potential energy well.

The least strongly bound prereaction structure is shown in Figure 2c (binding energy (enthalpy) = 3.3 (1.9) kcal mol^{-1}) and represents ∼11% of the Boltzmann population of complexes. This structure can lead to the TS associated with hydrogen abstraction from the N−H group with a small rearrangement of the two reactants (Figure 2e), and the computed $\Delta G^{\ddagger}$ relative to this complex (separated reactants) is 4.4 (11.0) kcal mol^{-1}.

On the basis of these computational results, α-C−H abstraction appears to be favored over N−H abstraction. Product studies on intramolecular hydrogen abstraction selectivity will however be needed in order to obtain conclusive information in this respect.

The increase in rate constant observed along the different series on going from the tertiary to the primary amine likely reflects the decrease in steric hindrance around the nitrogen lone pair as a result of the sequential replacement of alkyl groups by hydrogen. It is, however, important to point out that the strength of the hydrogen bond between BnO$^{\bullet}$ and the amine is expected to play a role in this respect as a relatively large increase in the amine hydrogen bond acceptor (HBA) ability is observed on going from tertiary to secondary and primary amines (β_2^{H} = 0.58−0.62 for tertiary amines (0.67 for TEA) and 0.69−0.73 for primary and secondary amines).[83]

In summary, the data displayed in Table 1 show that very different intermolecular selectivities are observed for the hydrogen atom abstraction reactions from the alkylamines by CumO$^{\bullet}$ and BnO$^{\bullet}$, where the possibility of forming a sufficiently stable hydrogen-bonded prereaction complex plays a very important role in this respect. Along this line, CumO$^{\bullet}$, with which no such complex can be formed,[51] reacts preferentially with tertiary amines as compared to secondary and primary amines. This observed selectivity appears to be the result of the above-mentioned entropy control over the hydrogen abstraction reaction and of the differences in α-C−H and N−H bond strengths. In some cases, the selectivity reflects the important role of stereoelectronic effects. The reactions involving CumO$^\bullet$ can be described in all cases as *direct* hydrogen atom abstractions.

Distinctly different behavior is observed for BnO$^\bullet$. This radical reacts preferentially with unhindered cyclic and bicyclic tertiary amines and diamines and, within the acyclic alkylamine series, with primary and secondary amines. This selectivity is governed by the formation of a hydrogen-bonded prereaction complex between the BnO$^\bullet$ α-C−H and the amine lone pair. Within the complex rapid hydrogen atom abstraction occurs. Accordingly, steric effects and amine HBA ability play a major role, whereas α-C−H and N−H bond strengths as well as stereoelectronic effects appear to be relatively unimportant.

These observations clearly indicate that the hydrogen abstraction selectivity can be strongly influenced by the structures of both the amine substrate and the alkoxyl radical. Noncovalent interactions, viz., the formation of a hydrogen-bonded complex (possible only for primary and secondary alkoxyl radicals) and steric effects play important roles in the hydrogen abstraction reaction. Along this line, the observed reactivity and selectivity trends may find useful application in important processes such as the selective *N*-dealkylation[98] and α-C−H functionalization[99] of tertiary amines. The generality and scope of these findings is currently under investigation in our laboratories.

4. EXPERIMENTAL SECTION

4.1. Materials. Spectroscopic grade acetonitrile was used in the kinetic experiments. Diethylamine (DEA), propylamine (PA), dipropylamine (DPA), isobutylamine (IBA), diisobutylamine (DIBA), benzylamine (BA), dibenzylamine (DBA), 2,2,6,6-tetramethylpiperidine (TMP), and *tert*-octylamine (TOA) were of the highest commercial quality available ($\geq$99%) and were further purified prior to use by filtration over neutral alumina. The purity of the substrates was checked by GC prior to the kinetic experiments and was in all cases >99.5%.

Dicumyl peroxide was of the highest commercial quality available and was used as received. Dibenzyl peroxide was prepared in small portions by reaction of KO_2 with benzyl bromide in dry benzene, in the presence of 18-crown-6 ether, according to a previously described procedure.[66,100]

4.2. 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 $\leq$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 solutions of dicumyl and dibenzyl peroxide (10 and 8 mM, respectively) were employed. These concentrations were chosen in order to ensure that, in the presence of the amines, prevalent absorption of the 266 nm laser light by the precursor peroxides. The photochemical stability of the amines 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. The kinetic study of the reactions of the cumyloxyl radical with BA, DBA, TMP, and TOA was carried out using 355 nm LFP, due to the absorption of the former two amines at 266 nm and to the very high substrate concentrations employed in the experiments with the latter two amines. For this purpose, the experiments were carried out using the third harmonic (355 nm) of a Q-switched Nd:YAG laser, delivering 8 ns pulses, and 1.0 M nitrogen-saturated solutions of dicumyl peroxide were used.

All 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 4−8 individual values and were reproducible to within 5%.

Second-order rate constants for the reactions of the cumyloxyl and benzyloxyl radical with the amines were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxyl and benzyloxyl radical visible absorption bands at 490 and 460 nm, respectively) vs [amine] plots. Fresh solutions were used for every amine concentration. In the reaction of CumO$^\bullet$ with DBA, overlap between the absorption bands of CumO$^\bullet$ and of the α-amino benzyl radical formed after hydrogen atom abstraction did not allow a reliable determination of the k_{obs} values at relatively high substrate concentration. Accordingly, the k_H value for this reaction was measured in oxygen-saturated solution. As a matter of comparison, no difference in k_H value was observed when the reaction between CumO$^\bullet$ and BA was carried out in nitrogen- and oxygen-saturated solution (see Table 1).

Correlation coefficients were in all cases >0.992. The given rate constants are the average of at least two independent experiments, with typical errors being $\leq$5%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Plots of k_{obs} vs amine concentration for the reactions of CumO$^\bullet$ and BnO$^\bullet$, details of the calculations, and the full citations for references 92 and 97. This material is available free of charge via the Internet at http://pubs.acs.org.

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