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Effect of Metal Ions on the Reactions of the Cumyloxyl Radical with Hydrogen Atom Donors. Fine Control on Hydrogen Abstraction Reactivity Determined by Lewis Acid−Base Interactions

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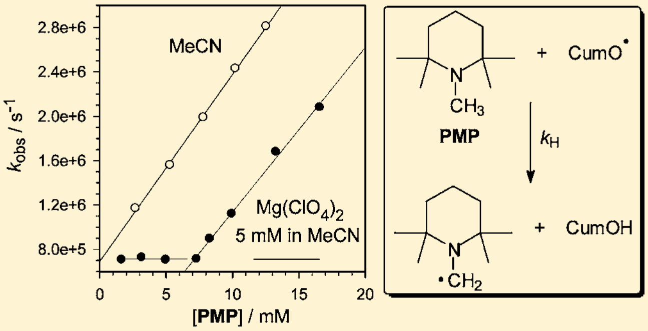
Supporting Information

ABSTRACT: A time-resolved kinetic study on the effect of metal ions (M^{n+}) on hydrogen abstraction reactions from C−H donor substrates by the cumyloxyl radical (CumO$^•$) was carried out in acetonitrile. Metal salt addition was observed to increase the CumO$^•$ β-scission rate constant in the order Li^+ > Mg^{2+} > Na^+. These effects were explained in terms of the stabilization of the β-scission transition state determined by Lewis acid−base interactions between M^{n+} and the radical. When hydrogen abstraction from 1,4-cyclohexadiene was studied in the presence of $LiClO_4$ and $Mg(ClO_4)_2$, a slight increase in rate constant (k_H) was observed indicating that interaction between M^{n+} and CumO$^•$ can also influence, although to a limited extent, the hydrogen abstraction reactivity of alkoxyl radicals. With Lewis basic C−H donors such as THF and tertiary amines, a decrease in k_H with increasing Lewis acidity of M^{n+} was observed (k_H(MeCN) > k_H(Li^+) > k_H(Mg^{2+})). This behavior was explained in terms of the stronger Lewis acid−base interaction of M^{n+} with the substrate as compared to the radical. This interaction reduces the degree of overlap between the α-C−H σ* orbital and a heteroatom lone-pair, increasing the C−H BDE and destabilizing the carbon centered radical formed after abstraction. With tertiary amines, a >2-order of magnitude decrease in k_H was measured after $Mg(ClO_4)_2$ addition up to a 1.5:1 amine/$Mg(ClO_4)_2$ ratio. At higher amine concentrations, very similar k_H values were measured with and without $Mg(ClO_4)_2$. These results clearly show that with strong Lewis basic substrates variations in the nature and concentration of M^{n+} can dramatically influence k_H, allowing for a fine control of the substrate hydrogen atom donor ability, thus providing a convenient method for C−H deactivation. The implications and generality of these findings are discussed.



■ INTRODUCTION

The role of medium effects on hydrogen atom abstraction reactions by free radicals is attracting increasing interest as these reactions play a key role in a variety of chemical and biological processes of great importance.[1−13] Solvent effects on these reactions have been studied in detail, in particular for the reactions of oxygen centered radicals, alkyl radicals, and the 2,2-diphenyl-1-picrylhydrazyl (dpph$^•$) radical, providing a fairly good mechanistic description of the role of the solvent on hydrogen abstraction reactions from O−H and C−H bonds.[14−27] More recently, useful mechanistic information has also been obtained on the role of Brønsted acids and bases in these processes.[28−31]

Ingold and co-workers have studied kinetic solvent effects (KSEs) on hydrogen abstraction reactions from the O−H group of phenols by tertiary alkoxyl radicals (RO$^•$: R = $(CH_3)_3C$ (tBuO$^•$), R = $PhC(CH_3)_2$ (CumO$^•$)).[16,17] In these studies, a significant decrease in the hydrogen abstraction rate constant (k_H) was observed on increasing the solvent hydrogen-bond acceptor (HBA) ability, and this behavior was explained on the basis of hydrogen bonding between the phenolic O−H group and the solvent hydrogen-bond-accepting moiety. These studies provided the first clear quantitative evidence of the role that hydrogen bonding plays in the hydrogen atom donor activity of phenols, the most extensive class of radical scavenging antioxidants.[1,14]

The KSEs observed for hydrogen abstraction reactions from phenols by dpph$^•$ and by peroxyl and alkyl radicals have been explained accordingly, on the basis of hydrogen-bond interactions between the phenolic O−H group and the solvent.[16,18,21,22]

For what concerns the role of solvent effects on hydrogen abstraction reactions from C−H bonds by alkoxyl radicals, our

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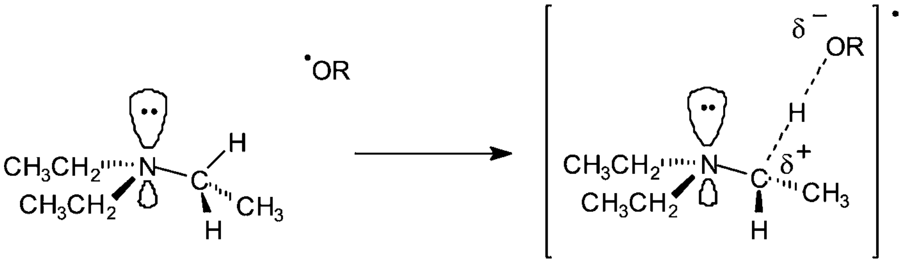
Scheme 1



group has recently carried out detailed time-resolved kinetic studies in different solvents on the reactions of CumO$^•$ with a variety of C−H hydrogen atom donors.[23−25] These studies have provided a general mechanistic description of the KSEs observed in hydrogen abstraction reactions from carbon by alkoxyl radicals, highlighting in particular the important role of solvent/substrate and solvent/radical hydrogen-bond interactions. Quite importantly, significantly smaller KSEs have been measured in the reactions of CumO$^•$ with C−H hydrogen atom donors as compared to the KSEs observed in the corresponding reactions of tertiary alkoxyl radicals with phenols.

With substrates characterized by the presence of an HBA site in proximity to the abstractable C−H (such as aliphatic aldehydes, triethylamine (TEA), and tetrahydrofuran (THF)), a decrease in k_H by increasing solvent HBD ability has been observed. It is generally accepted that the transition state for hydrogen abstraction from carbon by oxygen centered radicals is characterized by a certain extent of charge separation, with the development of a partial negative charge on the radical oxygen and a partial positive charge on the incipient carbon centered radical (Scheme 1, showing the reaction between a generic alkoxyl radical RO$^•$ and TEA).[26,32] On the basis of this picture, the KSEs observed in these reactions have been explained in terms of polar contributions to the transition state for hydrogen abstraction. HBD solvents can engage in hydrogen bonding with the heteroatom of these substrates leading to a decrease in electron density at the incipient radical center and to a destabilization of the transition state as compared to non-HBD solvents.[23−25]

For substrates in which an heteroatom is directly bound to the C−H carbon, such as TEA and THF, the hyperconjugative overlap between the C−H σ^* orbital and a heteroatom lone-pair orbital slightly reduces the C−H bond order, thereby decreasing the strength of this bond. When an HBD solvent interacts with the heteroatom lone-pair, there is reduced electron transfer to the C−H σ^* orbital via hyperconjugation, resulting in an increased C−H BDE and a consequent decrease in the hydrogen abstraction rate constant.[23−25] Following hydrogen abstraction, delocalization of the heteroatom lone-pair into the p-type orbital of the carbon-centered radical increases the stability of the system. Interactions between such radicals and HBD solvents reduce the degree of delocalization and thus radical stabilization. Taken together, these factors will contribute to the destabilization of the transition state for hydrogen abstraction, accounting for the observed KSEs.

On the other hand, an increase in k_H by increasing solvent HBD ability has been observed in the reactions of CumO$^•$ with cyclohexane (CHX) and 1,4-cyclohexadiene (CHD).[23−25] Hydrocarbon substrates lack HBA sites; therefore, solvent hydrogen bonding to the radical oxygen atom dominates kinetic solvent effects. On the basis of the partial charge separation in the transition state for hydrogen abstraction discussed above, solvent-radical hydrogen bonding will increase in strength along the reaction coordinate.[33] This will lead to a greater stabilization of the transition state as compared to the reactants and will result in a corresponding increase in hydrogen abstraction reactivity as compared to weaker or non-HBD solvents. Accordingly, with CHX and CHD the highest k_H values have been measured in the very strong HBD solvent 2,2,2-trifluoroethanol (TFE).[23,24]

On the basis of this mechanistic description, it is reasonable to expect that similar kinetic effects will be observed in the presence of metal ion salts, which display Lewis acid character and act as lone pair acceptors. By interacting with the radical oxygen or with substrates that bear a Lewis basic site in proximity of an abstractable hydrogen atom, metal ions are expected to influence the hydrogen abstraction reactivity of alkoxyl radicals (and of other oxygen centered radicals) as well as the substrate hydrogen atom donor ability.

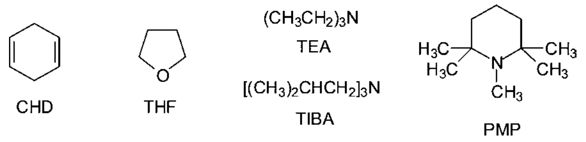
Lewis acids (LAs) are routinely employed as catalysts in a variety of organic reactions, where the catalytic activity can be explained on the basis of the increased reactivity of a reactant determined by the interaction of a donor site with the LA, through the formation of a Lewis acid−base complex.[34−36]

In recent years, LAs have been widely employed in synthetic procedures based on free radical reactions, where particular attention has been devoted to the role of the LA on the reaction stereoselectivity.[37,38] The effect of LAs on hydrogen abstraction reactions has been also investigated; however, these studies have been limited to the reactions of carbon centered radicals with tin and germanium hydrides.[37] The stereoselectivity observed in these reactions has been generally explained in terms of the complexation of a radical donor site with a chiral LA, followed by selective hydrogen atom transfer from the hydride to the complex.

No quantitative information is presently available on the effect of LAs on hydrogen abstraction reactions from C−H bonds. Synthetic procedures based on hydrogen abstraction by free radicals have attracted considerable interest as these reactions provide convenient methods for C−H bond functionalization, a research area in rapid expansion.[10−12,39] The use of LAs may represent an extremely useful tool in this respect, enabling the modulation of the substrate hydrogen atom donor ability and of the radical hydrogen abstraction reactivity while influencing the reaction regioselectivity in substrates characterized by the presence of different hydrogen atom abstracting sites.

In view of the relevance of these reactions and to develop an understanding of the role of metal ions on hydrogen abstraction reactions by alkoxyl radicals, we have carried out a detailed time-resolved kinetic study in acetonitrile solution and in the presence of different metal ion salts on the hydrogen abstraction reactions by CumO$^\bullet$ from the following hydrogen atom donors, CHD, THF, TEA, triisobutylamine (TIBA), and 1,2,2,6,6-pentamethylpiperidine (PMP), whose structures are displayed in Chart 1.

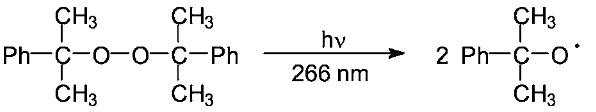
Chart 1



As mentioned above, KSEs on the reactions of CumO$^\bullet$ with CHD, THF, and TEA have been previously investigated,[23−25] while the kinetic study of the reactions of CumO$^\bullet$ with TIBA and PMP has been limited to acetonitrile.[40,41]

■ RESULTS AND DISCUSSION

The reactions of CumO$^\bullet$ with the substrates shown in Chart 1 were studied by laser flash photolysis (LFP). CumO$^\bullet$ was generated by 266 nm LFP of nitrogen-saturated acetonitrile solutions (T = 25 °C) containing dicumyl peroxide, as described in eq 1.



$$\mathrm{Ph{-}C(CH_3)_2{-}O{-}O{-}C(CH_3)_2{-}Ph} \xrightarrow[266\ \mathrm{nm}]{h\nu} 2\ \mathrm{Ph{-}C(CH_3)_2{-}O^\bullet} \quad (1)$$

In acetonitrile solution, CumO$^\bullet$ is characterized by an absorption band in the visible region of the spectrum centered at 485 nm.[42,43] Under these conditions, CumO$^\bullet$ decays mainly by C−CH$_3$ β-scission, while hydrogen abstraction from the solvent plays a negligible role.[43,44]

Prior to the kinetic studies, the stability of dicumyl peroxide to the metal ion salts was investigated. These studies were performed at room temperature in nitrogen saturated acetonitrile solution employing UV−vis spectroscopy. The absorption spectra of acetonitrile solutions containing dicumyl peroxide and the salt, respectively, were recorded (spectra A and B), and their sum spectrum (A + B) was compared to the absorption spectrum recorded from a solution of dicumyl peroxide and the salt at the same concentrations of the individual spectra (spectrum C). The time evolution of spectrum C was then monitored for 30 min. In the Supporting Information (Figure S1a), the sum spectrum A + B recorded from acetonitrile solutions containing dicumyl peroxide 4 mM (A) and LiClO$_4$ 1.0 M (B), respectively (solid line), and the spectrum recorded from an acetonitrile solution containing dicumyl peroxide 4 mM and LiClO$_4$ 1.0 M (C, circles) are compared showing excellent overlap. Figure S1b shows the time evolution of spectrum C in the time interval 0−30 min. No significant spectral change can be observed, showing the stability of dicumyl peroxide under these experimental conditions.

Analogous behavior was observed when 1.0 M concentrations of NaClO$_4$, Mg(ClO$_4$)$_2$, and LiOTf were employed. On the other hand, similar experiments carried out in the presence of trivalent triflates such as Y(OTf)$_3$ and Sc(OTf)$_3$ showed decomposition of dicumyl peroxide, in line with the significantly stronger Lewis acid character of these salts as compared to LiClO$_4$, LiOTf, NaClO$_4$, and Mg(ClO$_4$)$_2$.[45] The spectral analysis of the stability of dicumyl peroxide in the presence of Sc(OTf)$_3$ is shown in the Supporting Information as Figure S2. On the basis of these findings, LiClO$_4$, LiOTf, NaClO$_4$, and Mg(ClO$_4$)$_2$ were selected for the kinetic studies described below.

We first investigated the effect of LiClO$_4$, NaClO$_4$, and Mg(ClO$_4$)$_2$ on the decay kinetics of CumO$^\bullet$. The time-resolved kinetic studies were carried out by LFP in acetonitrile following the decay of the CumO$^\bullet$ visible absorption band at 490 nm, as a function of the metal salt concentration. With all three salts the decay rate constants (k_{decay}) were observed to increase linearly with increasing concentration, as shown in Figure 1 where the plots of k_{decay} versus [metal salt] for measurements carried out in acetonitrile solution at T = 25 °C are displayed. The slopes of these plots ($k_{\mathrm{M}n+}$) provide a quantitative evaluation of the effect of the metal ion on the decay of CumO$^\bullet$. The following values were obtained: $k_{\mathrm{M}n+} = 1.14 \times 10^6$, 8.82×10^5, and 4.10×10^5 M^{-1} s^{-1}, for LiClO$_4$, Mg(ClO$_4$)$_2$, and NaClO$_4$, respectively. Rather than a bimolecular reaction between CumO$^\bullet$ and the metal ion, these results reasonably reflect the effect of the metal ion on the unimolecular reactivity of the radical (see below). The hypothesis of a relevant role of salt effects on reactivity can be reasonably ruled out on the basis of the almost 3-fold decrease in reactivity observed on going from LiClO$_4$ to NaClO$_4$, as well as of the slight decrease observed on going from the monovalent metal salt LiClO$_4$ to the divalent metal salt Mg(ClO$_4$)$_2$.

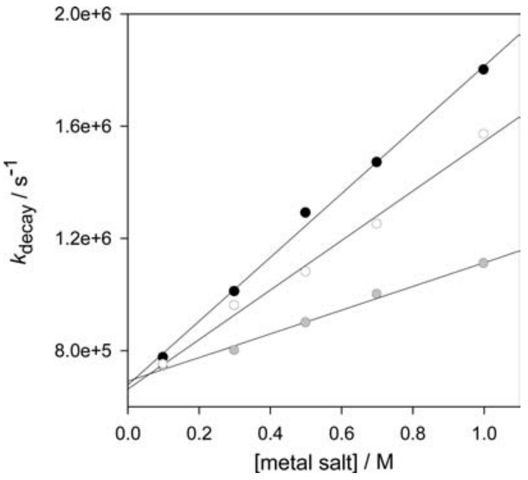
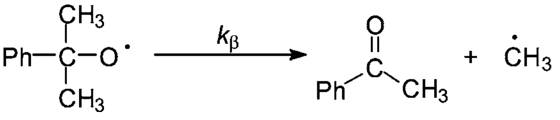


Figure 1. Plots of the decay rate constant (k_{decay}) for the cumyloxyl radical (CumO$^\bullet$) against metal ion salt concentration, measured in nitrogen-saturated MeCN solution at T = 25 °C, monitored at 490 nm. From the linear regression analysis: CumO$^\bullet$ + LiClO$_4$ (black circles), intercept = 6.78×10^5 s^{-1}, $k_{\mathrm{Li}+} = 1.14 \times 10^6$ M^{-1} s^{-1}, r^2 = 0.9961; CumO$^\bullet$ + Mg(ClO$_4$)$_2$ (white circles), intercept = 6.64×10^5 s^{-1}, $k_{\mathrm{Mg2}+} = 8.82 \times 10^5$ M^{-1} s^{-1}, r^2 = 0.9917; CumO$^\bullet$ + NaClO$_4$ (gray circles): intercept = 6.91×10^5 s^{-1}, $k_{\mathrm{Na}+} = 4.10 \times 10^5$ M^{-1} s^{-1}, r^2 = 0.9928.

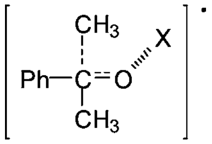
As mentioned previously, in acetonitrile the main reaction pathway of CumO$^\bullet$ is represented by C−CH$_3$ β-scission to give acetophenone and a methyl radical as described in eq 2.[43,44]



$$\mathrm{Ph{-}C(CH_3)_2{-}O^\bullet} \xrightarrow{k_\beta} \mathrm{Ph{-}C({=}O){-}CH_3} + {}^\bullet\mathrm{CH_3} \quad (2)$$

It is well-known that the rate constant for alkoxyl radical β-scission (k_β) is accelerated by polar solvents, with the maximum kinetic effect being observed in protic solvents such as TFE and H_2O.[46,47] This effect has been explained on the basis of the stabilization of the transition state for β-scission via solvent hydrogen bonding with the incipient carbonyl group as described in Scheme 2 (X = SOH).[43,44,46]

Scheme 2



Accordingly, the increase in the CumO$^\bullet$ decay rate constant observed with increasing metal salt concentration can be explained on the basis of the interaction of the metal ion (M^{n+}) with the radical oxygen atom. The strength of this interaction is expected to increase on going from the radical to the transition state for β-scission (Scheme 2, X = M^{n+}), leading to a corresponding increase in k_β.

The time-resolved absorption spectra observed after LFP of a nitrogen-saturated acetonitrile solution containing 5.0 mM dicumyl peroxide are displayed in the Supporting Information (Figure S3). The spectrum recorded 96 ns after the laser pulse shows the characteristic CumO$^\bullet$ visible absorption band centered at 485 nm.[42,43] The decay of this band is accompanied by a corresponding buildup of absorption at 240 and 280 nm assigned, in agreement with previous studies,[43,46,47] to acetophenone (an isosbestic point is visible at 300 nm). The observation of almost identical time-resolved absorption spectra after addition of 1.0 M $LiClO_4$ (compare Figures S3 and S4), and in particular of the acetophenone absorption bands, confirms that CumO$^\bullet$ undergoes β-scission as the main reaction pathway also in the presence of the metal salt.

Among the three salts employed, the largest kinetic effect was obtained with $LiClO_4$, where an approximately 3-fold increase in k_β was observed on going from acetonitrile ($k_\beta = 6.3 \times 10^5$ s^{-1})[44] to a 1.0 M solution of $LiClO_4$ in acetonitrile ($k_\beta = 1.8 \times 10^6$ s^{-1}). This value is significantly lower than the values measured for β-scission of CumO$^\bullet$ in TFE and H_2O ($k_\beta = 6.1 \times 10^6$ and 1.0×10^7 s^{-1}, respectively),[46,47] indicating, at least at this salt concentration and with these salts, that solvent hydrogen bonding results in a greater kinetic effect as compared to Lewis acid–base interactions.[48]

The same conclusion can be also derived from the analysis of medium effects on the position of the CumO$^\bullet$ visible absorption band maximum (λ_{max}). Previous studies have shown that, as compared to acetonitrile for which λ_{max} = 485 nm (Figure S3),[42,43] the CumO$^\bullet$ λ_{max} is significantly red-shifted by protic solvents (λ_{max} = 520–540 nm in TFE,[15,46] and 515 nm in MeCN/H_2O 1:1 (v/v)).[43] No change in λ_{max} was instead observed when the time-resolved absorption spectrum was recorded in an acetonitrile solution containing 1.0 M $LiClO_4$ (see Supporting Information, Figure S4). On the other hand, significant changes in the EPR and visible absorption spectra of both phenoxyl[49,50] and aminoxyl[51] radicals have been observed after addition of alkali and alkaline earth metal salts. This different behavior can be explained on the basis of a stronger interaction between the radical oxygen and the metal ion for the phenoxyl and aminoxyl radicals as compared to alkoxyl radicals, in line with the greater negative charge density on the oxygen atom of the former radicals as compared to alkoxyls.[21,42,52]

The effect of the metal ions on the hydrogen abstraction reactions from CHD, THF, TEA, PMP, and TIBA by CumO$^\bullet$ was then investigated. $LiClO_4$, LiOTf, and $Mg(ClO_4)_2$ were employed in these studies. The time-resolved kinetic studies were carried out by LFP in acetonitrile, at constant salt concentration (between 0.005 and 1.0 M), following the decay of the CumO$^\bullet$ visible absorption band at 490 nm, as a function of the hydrogen 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 hydrogen abstraction from the hydrogen atom donors by CumO$^\bullet$ (k_H) from the slopes of these plots. Figure 2 shows the plots of k_{obs} versus [THF] for the reactions of this substrate with CumO$^\bullet$ in acetonitrile solution (black circles), in the presence of 1.0 $LiClO_4$ (white circles), and of 1.0 M $Mg(ClO_4)_2$ (gray circles). The different intercepts of the three plots reflect the effect of the metal ion on the unimolecular reactivity of CumO$^\bullet$ discussed above. Additional plots for hydrogen abstraction from CHD, THF, TEA, PMP, and TIBA by CumO$^\bullet$ in the presence of the different salts are displayed in the Supporting Information (Figures S7–S13).

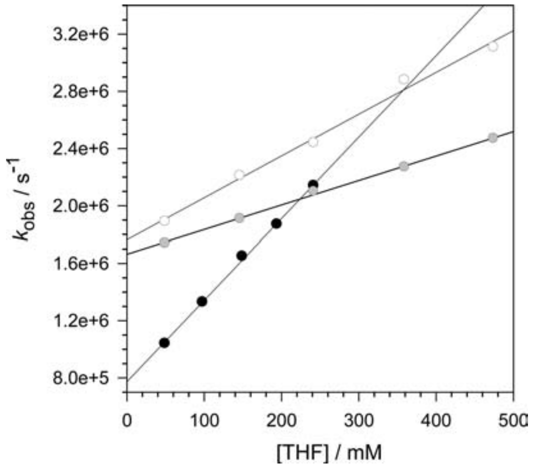


Figure 2. Plots of the observed rate constant (k_{obs}) against [THF] for the reactions of the cumyloxyl radical (CumO$^\bullet$) measured at T = 25 °C in nitrogen-saturated MeCN solution (black circles), in the presence of 1.0 M $LiClO_4$ (white circles), and in the presence of 1.0 M $Mg(ClO_4)_2$ (gray circles), by following the decay of CumO$^\bullet$ at 490 nm. From the linear regression analysis: acetonitrile, intercept = 7.72×10^5 s^{-1}, $k_H = 5.69 \times 10^6$ M^{-1} s^{-1}, $r^2 = 0.9986$; 1.0 M $LiClO_4$ in acetonitrile, intercept = 1.76×10^6 s^{-1}, $k_H = 2.90 \times 10^6$ M^{-1} s^{-1}, $r^2 = 0.9922$; 1.0 M $Mg(ClO_4)_2$ in acetonitrile, intercept = 1.66×10^6 s^{-1}, $k_H = 1.71 \times 10^6$ M^{-1} s^{-1}, $r^2 = 0.9979$.

All of the kinetic data thus obtained are collected in Table 1, together with the k_H values measured previously in the absence of salts, and the pertinent $k_H(MeCN)/k_H(M^{n+})$ ratios that quantify the kinetic effect of metal ion salt addition.

Starting the discussion from the reactions of CHD, the data displayed in Table 1 show a small and reproducible increase in the k_H value for reaction with CumO$^\bullet$ by addition of 1.0 M $LiClO_4$ or $Mg(ClO_4)_2$ ($k_H(MeCN)/k_H(M^{n+})$ = 0.89 and 0.95, respectively). These effects can be explained on the basis of the interaction of the metal ion with the radical oxygen atom, and indicate that, in addition to the unimolecular reactivity (see

Table 1. Second-Order Rate Constants (k_H) for Reaction of the Cumyloxyl Radical (CumO$^•$) with Different Substrates, Measured in MeCN at T = 25 °C, in the Presence of Metal Ion Salts^a

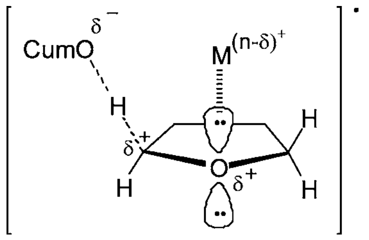
substrate	conditions	k_H/M^{-1} s^{-1}	$k_H(MeCN)/k_H(M^{n+})^b$
CHD		$(6.65 \pm 0.02) \times 10^{7c}$	
	$LiClO_4$ 1.0 M	$(7.49 \pm 0.04) \times 10^7$	0.89
	$Mg(ClO_4)_2$ 1.0 M	$(7.0 \pm 0.1) \times 10^7$	0.95
THF		$(5.8 \pm 0.1) \times 10^{6d}$	
	$LiClO_4$ 0.5 M	$(3.44 \pm 0.06) \times 10^6$	1.7
	$LiClO_4$ 1.0 M	$(2.87 \pm 0.04) \times 10^6$	2.0
	LiOTf 1.0 M	$(2.8 \pm 0.2) \times 10^6$	2.1
	$Mg(ClO_4)_2$ 1.0 M	$(1.8 \pm 0.1) \times 10^6$	3.2
TEA		$(2.0 \pm 0.1) \times 10^{8c}$	
	$LiClO_4$ 1.0 M	$(9.37 \pm 0.01) \times 10^7$	2.1
	$Mg(ClO_4)_2$ 0.005 M	$<1 \times 10^{6e}$	>200
PMP		$(1.70 \pm 0.02) \times 10^{8f}$	
	$LiClO_4$ 1.0 M	$(9.0 \pm 0.3) \times 10^7$	1.9
	$Mg(ClO_4)_2$ 0.005 M	$<1 \times 10^{6g}$	>170
		1.50×10^{8h}	1.14
TIBA		$(1.27 \pm 0.02) \times 10^{8i}$	
	$LiClO_4$ 1.0 M	$(1.2 \pm 0.1) \times 10^8$	1.06
	$Mg(ClO_4)_2$ 0.005 M	$<1 \times 10^{6j}$	>130
		1.1×10^{8k}	1.15
	$Mg(ClO_4)_2$ 0.01 M	$<1 \times 10^{6l}$	>130
		1.0×10^{8m}	1.27
	$Mg(ClO_4)_2$ 0.1 M	$<1 \times 10^{6n}$	>130
	$Mg(ClO_4)_2$ 0.5 M	$<1 \times 10^{6n}$	>130
	$Mg(ClO_4)_2$ 1.0 M	$<1 \times 10^{6n}$	>130

[a] Measured in N_2-saturated MeCN solution at T = 25 °C employing 266 nm LFP: [dicumyl peroxide] = 10 mM. k_H values were determined from the slope of the k_{obs} versus [substrate] plots, where in turn k_{obs} values were measured following the decay of the CumO$^•$ visible absorption bands at 490 nm. [b] Ratio of the hydrogen abstraction rate constants measured in acetonitrile in the absence (k_H(MeCN)) and in the presence of added metal salt ($k_H(M^{n+})$). [c] Reference 25. [d] Reference 23. [e] Estimated on the basis of the negligible effect on k_{obs} observed up to [TEA] = 7.1 mM. [f] Reference 41. [g] Estimated on the basis of the negligible effect on k_{obs} observed up to [PMP] = 7.3 mM. [h] Obtained from the slope of the k_{obs} versus [PMP] plot in the 7.3−16.6 mM range. [i] Reference 40. [j] Estimated on the basis of the negligible effect on k_{obs} observed up to [TIBA] = 7.0 mM. [k] Obtained from the slope of the k_{obs} versus [TIBA] plot in the 10−35 mM range. [l] Estimated on the basis of the negligible effect on k_{obs} observed up to [TIBA] = 11.6 mM. [m] Obtained from the slope of the k_{obs} versus [TIBA] plot in the 27−48 mM range. [n] Estimated on the basis of the negligible effect on k_{obs} observed up to [TIBA] = 25−33 mM.

above), metal ions can also influence, although to a very limited extent, the hydrogen abstraction reactivity of alkoxyl radicals. The slightly higher k_H value observed with $LiClO_4$ as compared to $Mg(ClO_4)_2$ is in agreement with the relatively stronger interaction of the former metal ion with CumO$^•$ discussed above. These effects are however significantly smaller than the KSEs observed in the reactions of CumO$^•$ with CHX and CHD, where a 3- and 4-fold increase in k_H, respectively, was observed on going from acetonitrile to TFE,[23,24] an observation that is again indicative of a greater kinetic effect for solvent hydrogen bonding to the radical as compared to Lewis acid−base interactions.

Moving to THF, a substrate that can act as a Lewis base, the data displayed in Table 1 show that salt addition leads to a decrease in the k_H values for hydrogen abstraction by CumO$^•$ (k_H(MeCN)/$k_H(M^{n+})$ between 1.7 and 3.2). This observation supports the idea that there is a stronger interaction of the metal ion with the substrate as compared to the radical. In keeping with the mechanistic rationale provided for the KSEs observed on these reactions, this behavior can be explained on the basis of the Lewis acid−base interaction of the metal ion (M^{n+}) with an oxygen lone pair of THF (Scheme 3). This interaction is expected to increase the α-C−H BDE by reducing the amount of electron density hyperconjugatively delocalized into the C−H σ^* through overlap with the oxygen lone-pair, as described above. The decrease in reactivity observed on going from $LiClO_4$ to $Mg(ClO_4)_2$ is in line with the stronger Lewis acidity measured for the latter salt as compared to the former one.[45]

Scheme 3



Quite importantly, the kinetic effects determined by salt addition are comparable in magnitude to the KSEs observed for this reaction, where a 4.5-fold decrease in k_H was measured on going from isooctane to TFE (~2-fold on going from acetonitrile to TFE).[23] The almost identical k_H values measured with $LiClO_4$ and LiOTf point toward a negligible role for the lithium counterion in these hydrogen abstraction reactions.

An analogous explanation can be put forward to account for the decrease in k_H observed in the reactions of TEA and PMP with CumO$^•$ after addition of 1.0 M $LiClO_4$ (k_H(MeCN)/$k_H(M^{n+})$ = 2.1 and 1.9, respectively). In these cases, the lithium ion interacts with the nitrogen lone pair of the amines.

It is well-known that the reactions of *t*BuO$^•$ and CumO$^•$ with tertiary alkylamines lead to the formation of α-aminoalkyl radicals,[25,53,54] characterized by relatively weak absorption bands in the 300−500 nm range. For TEA, the 1-diethylaminoethyl radical formed after α-C−H abstraction ($CH_3CH^•N(CH_2CH_3)_2$) is characterized by an absorption band centered at 330.[54,55] Figure 3 shows the kinetic traces observed after LFP of nitrogen-saturated acetonitrile solutions containing dicumyl peroxide and TEA (●) or dicumyl peroxide, TEA, and 1.0 M $LiClO_4$ (○), recorded at 330 and 490 nm.

The traces at 490 nm show the decay of CumO$^•$, while those at 330 nm a corresponding buildup of absorption followed by a decay assigned to the formation and subsequent decay of the 1-diethylaminoethyl radical. The very similar kinetic behavior observed with and without $LiClO_4$ and in particular the direct observation of the 1-dimethylaminoethyl radical confirms that in both cases CumO$^•$ undergoes α-C−H abstraction from TEA. The time-resolved absorption spectra observed after reaction of CumO$^•$ with TEA in acetonitrile solution and in acetonitrile

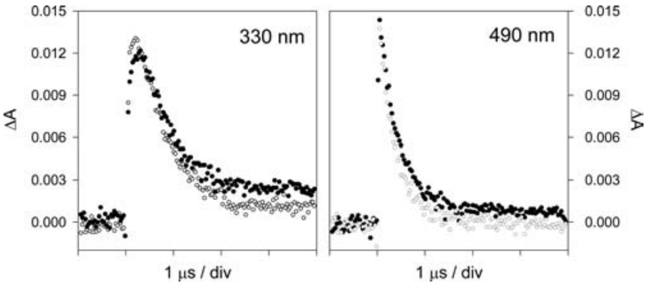


Figure 3. Kinetic traces observed after 266 nm laser flash photolysis of nitrogen-saturated acetonitrile solutions containing (a) dicumyl peroxide 10 mM and triethylamine (TEA) 10 mM (●), and (b) dicumyl peroxide 10 mM, TEA 17.8 mM, and $LiClO_4$ 1.0 M (○), recorded at 330 and 490 nm.

solution containing 1.0 M $LiClO_4$ are reported in the Supporting Information (Figures S5 and S6, respectively).

When TEA was added to an acetonitrile solution containing dicumyl peroxide and 1.0 M $Mg(ClO_4)_2$, a precipitate assigned to a strongly bound Mg^{2+}–TEA Lewis acid–base complex formed immediately. This observation is in full agreement with the stronger Lewis acidity of $Mg(ClO_4)_2$ as compared to $LiClO_4$,[45] and, most importantly, with the significantly stronger Lewis basicity of TEA as compared to THF.[56,59] Very interestingly, when hydrogen abstraction from TEA by $CumO^\bullet$ was studied in an acetonitrile solution containing 5 mM $Mg(ClO_4)_2$, no significant increase in k_{obs} was observed up to [TEA] = 7.1 mM, while a ~40% increase in k_{obs} was observed at [TEA] = 9.6 mM. At this higher concentration, however, the formation of a precipitate occurred shortly after TEA addition. This behavior appears to reflect the initial formation of a strongly bound Mg^{2+}–TEA complex in which the interaction between Mg^{2+} and the nitrogen atom reduces to a large extent the electron delocalization from the lone pair to the α-C–H σ^* orbitals, causing a dramatic decrease in the hydrogen atom donor ability of TEA. On the basis of the negligible effect on k_{obs} observed up to [TEA] = 7.1 mM, an upper limit to the hydrogen abstraction rate constant from TEA by $CumO^\bullet$ can be estimated in this concentration range as $k_H < 1 \times 10^6$ M^{-1} s^{-1}, indicating that addition of $Mg(ClO_4)_2$ determines a decrease in k_H of at least 200 times. By increasing TEA concentration, hydrogen abstraction appears to take over at [TEA] > 7.1 mM, clearly indicating that above this concentration binding of TEA to Mg^{2+} is significantly weaker and that a sizable concentration of free amine exists in solution. Unfortunately, the rapid formation of a precipitate limited the kinetic study to [TEA] ≤ 9.6 mM. Very importantly, the kinetic effect determined by $Mg(ClO_4)_2$ addition ($k_H(MeCN)/k_H(M^{n+}) > 200$) is significantly larger than the KSEs observed for this reaction, where a 7-fold decrease in k_H was measured on going from isooctane to MeOH (~5-fold on going from acetonitrile to MeOH).[25,41] This observation indicates that very strong Lewis acid–base interactions such as those occurring between Mg^{2+} and TEA can lead to significantly larger kinetic effects on hydrogen abstraction as compared to solvent–substrate hydrogen-bond interactions.

Additional support to this picture is provided by PMP, for which, in an acetonitrile solution containing 5 mM $Mg(ClO_4)_2$, hydrogen abstraction by $CumO^\bullet$ could be studied at relatively higher concentration as compared to the corresponding experiment carried out with TEA, as shown by the k_{obs} versus [PMP] plot displayed in Figure 4.

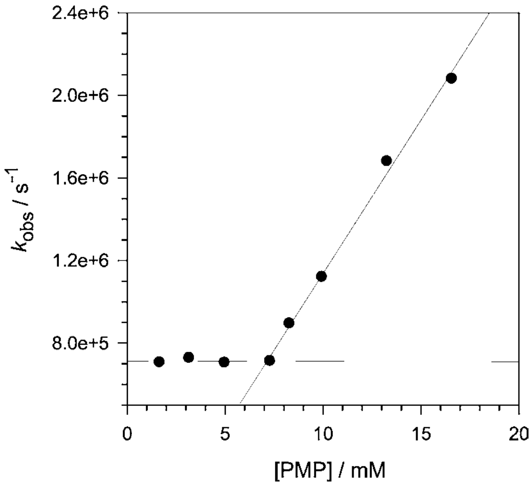


Figure 4. Plot of the observed rate constant (k_{obs}) against [PMP] for reaction of the cumyloxyl radical ($CumO^\bullet$) measured at T = 25 °C in a nitrogen-saturated MeCN solution containing 0.005 M $Mg(ClO_4)_2$, by following the decay of $CumO^\bullet$ at 490 nm. From the linear regression analysis in the 7.3–16.6 mM range: $k_H = 1.50 \times 10^8$ M^{-1} s^{-1}, r^2 = 0.9960.

Also with this substrate, no significant increase in k_{obs} was observed up to [PMP] = 7.3 mM, providing an upper limit to the hydrogen abstraction rate constant from PMP by $CumO^\bullet$ in this concentration range as $k_H < 1 \times 10^6$ M^{-1} s^{-1}. On the other hand, above this concentration k_{obs} was found to increase linearly with increasing [PMP]. The rate constant for hydrogen abstraction was obtained from the slope of this plot in the 7.3–16.6 mM range as $k_H = 1.50 \times 10^8$ M^{-1} s^{-1}, a value that is at least 150 times higher than the value estimated at [PMP] ≤ 7.3 mM. Most importantly, the k_H value measured in this experiment in the 7.3–16.6 mM PMP range is very similar to the value measured in the absence of $Mg(ClO_4)_2$ ($k_H = 1.70 \times 10^8$ M^{-1} s^{-1}).[41] These results clearly show that variations in metal ion concentration and in the strength of the Lewis acid–base interaction can dramatically influence the rate constants for hydrogen abstraction from substrates characterized by very strong Lewis basicities such as tertiary amines, thereby allowing for fine control of the substrate hydrogen atom donor ability. Quite importantly, the very similar k_H values measured in the absence of $Mg(ClO_4)_2$ and at $[Mg(ClO_4)_2]$ = 5 mM in the 7.3–16.6 mM PMP range provide an additional indication that under these conditions $CumO^\bullet$ undergoes α-C–H abstraction from PMP and more generally from alkylamines (see below).

The effect of $LiClO_4$ and $Mg(ClO_4)_2$ on the hydrogen abstraction reactions by $CumO^\bullet$ from TIBA, a tertiary acyclic amine characterized by larger alkyl groups as compared to TEA, was also investigated. The kinetic data displayed in Table 1 clearly show that no significant effect on k_H was observed by addition of 1.0 M $LiClO_4$ ($k_H(MeCN)/k_H(M^{n+})$ = 1.06), in contrast with the results obtained for the corresponding reactions with TEA and PMP where $k_H(MeCN)/k_H(M^{n+})$ ratios of ~2 were measured. On the other hand, $Mg(ClO_4)_2$ addition led to very large decreases in the rate constants for the reactions between $CumO^\bullet$ and TIBA, pointing toward similar effects of Mg^{2+} on the hydrogen atom donor ability of the three amines.

Previous studies have shown the existence of large differences in reactivity between $CumO^\bullet$ and the benzyloxyl radical ($PhCH_2O^\bullet$, $BnO^\bullet$) in their hydrogen abstraction reactions from TEA and PMP, as quantified by the (k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) ratios of 21.5 and 25, respectively.[40,41] This behavior was explained on the basis of two different mechanisms. With CumO$^\bullet$ the reactions were described in both cases as direct hydrogen abstractions. The higher k_H values measured for the corresponding reactions with BnO$^\bullet$ were explained in terms of the rate-determining formation of a prereaction complex where the radical α-C−H engages in hydrogen bonding with the amine nitrogen, followed by hydrogen abstraction within the complex.[40,41,60,61] A significantly smaller rate constant ratio was measured with the relatively hindered amine TIBA (k_H(BnO$^\bullet$)/k_H(CumO$^\bullet$) = 2.8). With this amine steric effects prevented the formation of a sufficiently stable hydrogen-bonded complex with BnO$^\bullet$, and a direct hydrogen abstraction mechanism was proposed for the reactions of this substrate with the two alkoxyl radicals.[40] Along this line, the negligible effect of $LiClO_4$ on the hydrogen abstraction reaction from TIBA by CumO$^\bullet$ can be explained accordingly on the basis of steric effects that prevent a sufficiently strong interaction between the lithium ion and the nitrogen atom. The different kinetic behavior observed after $Mg(ClO_4)_2$ addition indicates that the formation of a very strong complex can overcome steric hindrance, suggesting that the strength of this interaction can induce a conformational change in the substrate.

In the reactions of CumO$^\bullet$ with TIBA, $Mg(ClO_4)_2$ was employed in the following concentrations: 1.0, 0.5, 0.1, 0.01, and 0.005 M. At [$Mg(ClO_4)_2$] between 0.1 and 1.0 M, no significant increase in k_{obs} was observed up to [TIBA] between 25 and 33 mM, providing in all cases an upper limit to the hydrogen abstraction rate constant from TIBA by CumO$^\bullet$ as $k_H < 1 \times 10^6$ M^{-1} s^{-1}. When the reaction was studied in an acetonitrile solution containing 10 mM $Mg(ClO_4)_2$, no significant increase in k_{obs} was observed up to [TIBA] = 11.6 mM, a slight increase in k_{obs} was observed up to [TIBA] = 20.0 mM, while above this concentration k_{obs} was observed to increase linearly with increasing [TIBA], and a rate constant for hydrogen abstraction was obtained from the slope of this plot in the 27−48 mM range as $k_H = 1.0 \times 10^8$ M^{-1} s^{-1}. The k_{obs} versus [TIBA] plot for the reaction with CumO$^\bullet$ measured in acetonitrile containing 10 mM $Mg(ClO_4)_2$ is displayed in the Supporting Information as Figure S14. When the reaction was studied in an acetonitrile solution containing 5 mM $Mg(ClO_4)_2$, no significant increase in k_{obs} was observed up to [TIBA] = 7.0 mM, above this concentration k_{obs} was observed to increase linearly with increasing [TIBA], and a rate constant for hydrogen abstraction was obtained from the slope of this plot in the 10−35 mM range as $k_H = 1.1 \times 10^8$ M^{-1} s^{-1}. The k_{obs} versus [TIBA] plot for the reaction with CumO$^\bullet$ measured in acetonitrile containing 5 mM $Mg(ClO_4)_2$ is displayed in the Supporting Information as Figure S15.

Also with this amine, the k_H values measured in the latter two experiments ($k_H = 1.0 \times 10^8$ and 1.1×10^8 M^{-1} s^{-1}) are very similar to the value measured in acetonitrile solution in the absence of $Mg(ClO_4)_2$ ($k_H = 1.27 \times 10^8$ M^{-1} s^{-1}).[40]

CONCLUSIONS

Taken together, the results discussed above clearly show that by interacting with the radical oxygen atom as well as with substrates bearing a Lewis basic site in proximity of the abstractable hydrogen atoms such as THF and tertiary amines, metal ions can influence hydrogen abstraction reactions from carbon by alkoxyl radicals, in keeping with the mechanistic picture provided for the KSEs observed for these reactions. With hydrocarbon substrates metal ion salt addition can increase, although to a limited extent, the hydrogen abstraction reactivity of the cumyloxyl radical. With THF and tertiary amines, a decrease in k_H by metal ion salt addition was observed, indicating that Lewis acidity of the metal ion and substrate Lewis basicity play a key role and pointing toward the significantly stronger interaction of the metal ions with these substrates as compared to the cumyloxyl radical. Dramatic decreases in reactivity were observed when the reactions of CumO$^\bullet$ with strong Lewis bases such as tertiary amines were studied in the presence of the relatively strong Lewis acid $Mg(ClO_4)_2$. Most importantly, in these reactions, variations of the substrate/metal salt ratio allowed a careful modulation of the substrate hydrogen atom donor ability. Mg^{2+} can strongly bind up to 1.5 equivalents of amine leading to a greater than 2 order of magnitude decrease in the rate constant for α-C−H hydrogen abstraction. By increasing amine concentration, an increase in reactivity was observed, pointing toward a significantly weaker binding of the amine. The metal ion now appears to play a negligible role, and the k_H values measured under these conditions were very similar to those measured in the absence of $Mg(ClO_4)_2$. These results show that strong Lewis acid−base interactions can depress to a very large extent the hydrogen abstraction reactivity of the α-C−H bonds of aliphatic amines, indicating that metal ion addition can provide a convenient method for C−H deactivation. This observation suggests that with suitable substrates characterized by the presence of different abstractable hydrogen atoms, metal ion addition can allow a fine control of the hydrogen abstraction regioselectivity. Very importantly, the results obtained in this study suggest that these metal ion effects are not limited to hydrogen abstraction reactions by alkoxyl radicals, and that a similar behavior should be observed in the reactions of other radicals and hydrogen abstracting species with hydrogen atom donor substrates characterized by the presence of Lewis basic sites in proximity of the abstractable hydrogen atoms. The generality and scope of these findings is currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Materials. Spectroscopic grade acetonitrile was used in the kinetic experiments. 1,4-Cyclohexadiene (CHD) and tetrahydrofuran (THF) were of the highest commercial quality available and were used as received. Triethylamine (TEA), 1,2,2,6,6-pentamethylpiperidine (PMP), and triisobutylamine (TIBA) were of the highest commercial quality available (≥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%.

Lithium perchlorate ($LiClO_4$), lithium triflate (LiOTf), sodium perchlorate ($NaClO_4$), magnesium perchlorate ($Mg(ClO_4)_2$), scandium triflate ($Sc(OTf)_3$), and yttrium triflate ($Y(OTf)_3$) were of the highest commercial quality available and were used as received.

Dicumyl peroxide was of the highest commercial quality available and was used as received.

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 × 10 mm) was used in all experiments. Nitrogen saturated acetonitrile solutions containing dicumyl peroxide (10 mM) were employed. 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 2−5 individual values and were reproducible to within 5%.

The rate constants for decay of the cumyloxyl radical in the presence of the metal ion salts were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxyl radical visible absorption band at 490 nm) versus [metal ion] plots. In these experiments, the metal ion salt concentration was varied between 0.1 and 1.0 M.

Second-order rate constants for the reactions of the cumyloxyl radical with the hydrogen atom donor substrates in the presence of M^{n+} were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxyl radical visible absorption band at 490 nm) versus [substrate] plots at constant metal ion salt concentration (between 0.005 and 1.0 M). Fresh solutions were used for every substrate concentration. In the reactions of $CumO^•$ with CHD and THF, the concentration variation was performed through direct addition of the substrate to acetonitrile solutions containing dicumylperoxide and the metal ion salt. The same procedure was employed in the reactions of $CumO^•$ with TEA, PMP, and TIBA in the presence of $LiClO_4$. The reactions of $CumO^•$ with TEA, PMP, and TIBA in the presence of $Mg(ClO_4)_2$ were carried out by addition of an acetonitrile solution of the amine to acetonitrile solutions containing dicumylperoxide and $Mg(ClO_4)_2$. This procedure was preferred to the previous one as the formation of a precipitate was generally observed at significantly higher substrate concentration. In these experiments, particular care was taken to mantain the metal ion salt concentration constant throughout the experiment.

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 ≤5%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Time-resolved absorption spectra and plots of k_{obs} versus substrate concentration for the reactions of $CumO^•$. 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.

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(56) Lewis basicity can be conveniently expressed on the basis of Gutmann's donor number (*DN*), defined as the negative ΔH values for 1:1 adduct formation between $SbCl_5$ and electron-pair donor solvents in the noncoordinating solvent 1,2-dichloroethane, as well as in terms of the scale established by Gal and Maria based on the molar enthalpies of complex formation ($-\Delta H^\circ_{D-BF3}$) between BF_3 and electron-pair donor solvents (D).[57,58] *DN* = 20.0 and 61.0 kcal mol^{-1}, and $-\Delta H^\circ_{D-BF3}$ = 90.40 and 135.87 kJ mol^{-1}, for THF and TEA, respectively.

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(59) As correctly pointed out by a reviewer, acetonitrile is also expected to interact with the metal ions thus behaving as a competitive solvent. However, the significantly stronger Lewis basicity of tertiary amines and THF as compared to acetonitrile (for which *DN* = 14.1 kcal mol^{-1}, and $-\Delta H^\circ_{D-BF3}$ = 60.39 kJ mol^{-1})[56−58] reasonably accounts for the kinetic effects observed after addition of metal ion salts on the hydrogen abstraction reactions from these Lewis basic substrates.

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