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Understanding Kinetic Solvent Effects on Hydrogen Abstraction Reactions from Carbon by the Cumyloxyl Radical

Massimo Bietti,* Roberto Martella, and Michela Salamone

Dipartimento di Scienze e Tecnologie Chimiche, Università "Tor Vergata", Via della Ricerca Scientifica, 1 I-00133 Rome, Italy

bietti@uniroma2.it

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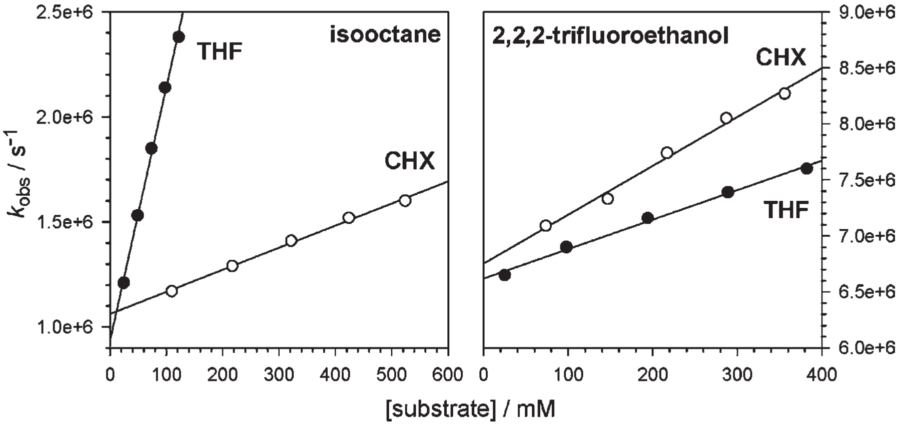
ABSTRACT



A kinetic study of the hydrogen abstraction reactions from tetrahydrofuran (THF) and cyclohexane (CHX) by the cumyloxyl radical was carried out in different solvents. With THF, a 4.5-fold decrease in rate constant (k_H) was observed on going from isooctane to 2,2,2-trifluoroethanol. An opposite behavior was observed with CHX, where k_H increased by a factor 4 on going from isooctane to 2,2,2-trifluoroethanol. The important role of substrate structure and of the solvent hydrogen bond donor ability is discussed.

The study of solvent effects on hydrogen atom abstraction continues to attract considerable interest as these reactions play a fundamental role in a variety of important chemical and biological processes such as the oxidative damage to biomolecules and polymers,[1,2] the radical scavenging activity of natural and synthetic antioxidants,[3−8] enzymatic reactions,[9,10] C−H functionalization,[11,12] and the degradation of volatile organic compounds in the atmosphere.[13]

In this context, we have recently shown the existence of sizable kinetic solvent effects (KSEs) on hydrogen abstraction reactions from carbon by the cumyloxyl radical ($PhC(CH_3)_2O^\bullet$, CumO$^\bullet$), by carrying out time-resolved kinetic studies in different solvents on the reactions of this radical with a number of hydrogen atom donors, namely, triethylamine (TEA),[14] propanal (PA), 2,2-dimethylpropanal (DMPA),[15] and 1,4-cyclohexadiene (CHD).[14,15] With TEA, PA, and DMPA, a 5- to 7-fold decrease in

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the hydrogen abstraction rate constant (k_H) was observed going from benzene to MeOH and/or 2,2,2-trifluoroethanol (TFE). This behavior was explained on the basis of the hydrogen bond donor (HBD) ability of the solvent that can engage in hydrogen bonding with the substrate heteroatom. This interaction decreases the electron density in proximity of the incipient carbon-centered radical leading to a destabilization of the transition state as compared to non-HBD solvents.[14,15] For the reactions with TEA, it was proposed that also the decrease in the degree of overlap between the α-C–H bond and the nitrogen lone pair determined by this interaction is responsible for the observed KSEs.[14]

An opposite behavior was observed for the reactions of CumO$^\bullet$ with CHD, where k_H increased by a factor 3 going from benzene to TFE.[15] With this substrate, no significant solvent HBD interaction can be expected, and accordingly, the increase in reactivity observed in strong HBD solvents was explained on the basis of a HBD interaction between the solvent and the CumO$^\bullet$ oxygen. This interaction determines a stabilization of the transition state as compared to the reactants and results in a corresponding increase in hydrogen abstraction reactivity as compared to weaker or non-HBD solvents.

These results clearly indicate that in these hydrogen abstraction reactions from carbon by CumO$^\bullet$ the magnitude of the observed KSE is essentially governed by solvent–substrate and/or solvent–radical hydrogen bond interactions. The former interactions appear to play a major role when the substrate bears an heteroatom in proximity of the abstractable C–H, and the largest KSEs are observed in strong HBD solvents. The "direction" of the effect is instead related to the possibility for the substrate and/or the radical to act as a hydrogen bond acceptor (HBA).

Very recently, El-Sheshtawy et al. reported a time-resolved kinetic and computational study on hydrogen abstraction reactions from a series of C–H donors by the cumyloxyl radical and singlet-excited 2,3-diazabicyclo-[2.2.2]oct-2-ene (^{1}[DBO]*).[16] On the basis of previous results by the same group,[17] and the results of one of our above-mentioned studies,[14] the authors raised the issue of a controversial discussion on the solvent dependence of hydrogen abstraction reactivity from C–H donors. The existence of controversial results was also mentioned by another group in a more recent study.[18]

As pointed out in ref 16, the aim of the authors was not to exaggerate the solvent effects but to clearly pinpoint the effects, even if expectedly subtle, and to relate them directly to the solvent polarity. For this purpose, MeCN, ethyl acetate (EtOAc), and EtOAc/MeCN mixtures were selected as the solvents.

Very small to small KSEs were measured for the reactions of CumO$^\bullet$ with the hydrogen atom donors (CHD, 2,5-dihydrofuran (DHF), tetrahydrofuran (THF), hexamethylbenzene (HMB)), where a 5–40% increase in k_H was observed going from MeCN to EtOAc. On the basis of these observations and of the results of DFT calculations, the authors concluded that KSEs on hydrogen abstractions by alkoxyl radicals from C–H donors are small, but significant, and originate from the selective stabilization of the reactants. Whenever observed, these effects are inverted, indicative of a higher reactivity in nonpolar solvents.[16]

In ref 16, the authors quoted our recent kinetic study on the reaction between CumO$^\bullet$ and CHD,[14] stating that we found no KSE for this pair. Close inspection of our kinetic data provides, however, a different picture. An approximately 20% increase in k_H was observed on going from MeCN, benzene, and PhCl to MeOH and 2-methyl-2-propanol (*t*-BuOH), KSEs that are small but comparable in magnitude to those observed by El-Sheshtawy et al., and, most importantly, go in the *opposite direction*, indicative of a higher reactivity in protic solvents. As mentioned above, a significantly larger (3-fold) increase in k_H was then observed when the same reaction was carried out in the stronger HBD solvent TFE.[15]

Along this line, in order to provide a deeper and more general understanding of the role of solvent effects on hydrogen abstraction reactions from carbon by alkoxyl radicals, aimed in particular at the resolution of this apparent controversy, we have extended our study to two hydrogen atom donors: THF and cyclohexane (CHX), the former able to act as a HBA, whereas no hydrogen bond interaction with the solvent can be expected with the latter one. For this purpose, we have carried out a detailed time-resolved kinetic study in different solvents (2,2,4-trimethylpentane (isooctane), MeCN, *t*-BuOH, MeOH, and TFE) for the reactions of CumO$^\bullet$ with THF and CHX.

To gain information on the role of alkoxyl radical structure on these processes, the rate constants for hydrogen abstraction from THF and CHX by the benzyloxyl radical (PhCH$_2$O$^\bullet$, BnO$^\bullet$) have also been determined, limited however to MeCN solvent.

CumO$^\bullet$ and BnO$^\bullet$ were generated by 266 nm laser flash photolysis (LFP) of nitrogen-saturated solutions (T = 25 °C) containing dicumyl and dibenzyl peroxide, respectively (eq 1).

$$\begin{array}{l} \mathrm{RO{-}OR} \xrightarrow[266\ \mathrm{nm}]{h\nu} 2\mathrm{RO}^\bullet \\ \mathrm{R} = \begin{array}{l} \mathrm{PhC(CH_3)_2} \\ \mathrm{PhCH_2} \end{array} \end{array} \qquad (1)$$

In isooctane, MeCN, and *t*-BuOH solution, CumO$^\bullet$ is characterized by a broad absorption band in the visible region of the spectrum centered at 485 nm,[19,20] whose position is red-shifted in MeOH and TFE (λ_{max} = 500 and 520 nm, respectively).[21,22] For BnO$^\bullet$, λ_{max} = 460 nm in

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MeCN.[19] With the exception of the experiments carried out in MeOH solution, where hydrogen abstraction from the solvent is the predominant reaction of CumO$^{\bullet}$,[21] in all of the other solvents employed, the decay of CumO$^{\bullet}$ mostly reflects C−CH$_3$ β-scission.[20,23] The decay of BnO$^{\bullet}$ can be mainly attributed to hydrogen abstraction from the solvent.[24]

The reactions of CumO$^{\bullet}$ and BnO$^{\bullet}$ with THF and CHX were carried out by LFP. It is well-established that these reactions proceed by hydrogen abstraction from the THF α-CH$_2$ groups and the CHX CH$_2$ groups by the alkoxyl radical.[16,17,23,25] The kinetic studies were carried out following the decay of the CumO$^{\bullet}$ and BnO$^{\bullet}$ visible absorption bands at 490−520 and 460 nm, respectively, as a function of the substrate concentration. The observed rate constants (k_{obs}) gave excellent linear relationships when plotted against substrate concentration and provided the second-order rate constants for hydrogen abstraction from the substrates by CumO$^{\bullet}$ and BnO$^{\bullet}$ (k_{H}) from the slopes of these plots. The plots for hydrogen abstraction from THF and CHX by CumO$^{\bullet}$ in the different solvents and from THF and CHX by BnO$^{\bullet}$ in MeCN are displayed in the Supporting Information (Figures S1−S12). The kinetic data for the reactions of CumO$^{\bullet}$ with THF and CHX in the different solvents are collected in Table 1.

Table 1. Second-Order Rate Constants (k_{H}) for Reaction of the Cumyloxyl Radical (CumO$^{\bullet}$) with Tetrahydrofuran (THF) and Cyclohexane (CHX), Measured in Different Solvents at t = 25 °C[a]

	k_{H}/M^{-1} s^{-1}[b]	
solvent	THF	CHX
isooctane	$(1.21 \pm 0.02) \times 10^{7}$	$(1.08 \pm 0.03) \times 10^{6}$
MeCN	$(5.8 \pm 0.1) \times 10^{6}$	$(1.1 \pm 0.1) \times 10^{6}$ 1.2×10^{6}[c]
t-BuOH	$(5.8 \pm 0.2) \times 10^{6}$	$(1.63 \pm 0.04) \times 10^{6}$ 1.3×10^{6}[c]
MeOH	$(4.9 \pm 0.1) \times 10^{6}$	$(2.4 \pm 0.3) \times 10^{6}$
TFE	$(2.7 \pm 0.1) \times 10^{6}$	$(4.39 \pm 0.02) \times 10^{6}$

[a] 266 nm LFP, N$_2$-saturated, [dicumyl peroxide] = 10 mM. [b] Determined from the slope of the k_{obs} vs [substrate] plots, where in turn k_{obs} values have been measured following the decay of the CumO$^{\bullet}$ visible absorption band at 490 and 520 nm. Average of at least two determinations. [c] Ref 23.

The hydrogen abstraction reactivity of CumO$^{\bullet}$ and BnO$^{\bullet}$ in MeCN solution is compared in Table 2, where the k_{H}(BnO$^{\bullet}$)/k_{H}(CumO$^{\bullet}$) ratios are also displayed.

Table 2. Second-Order Rate Constants (k_{H}) for Reaction of the Cumyloxyl (CumO$^{\bullet}$) and Benzyloxyl (BnO$^{\bullet}$) Radicals with Tetrahydrofuran (THF) and Cyclohexane (CHX), Measured in MeCN at t = 25 °C[a]

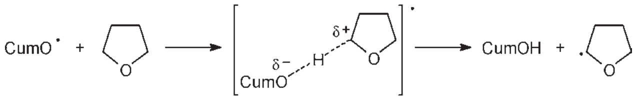
	k_{H}/M^{-1} s^{-1}[b]	
	THF	CHX
BnO$^{\bullet}$	$(7.64 \pm 0.09) \times 10^{6}$	$(1.30 \pm 0.03) \times 10^{6}$
CumO$^{\bullet}$	$(5.8 \pm 0.1) \times 10^{6}$	$(1.1 \pm 0.1) \times 10^{6}$
k_{H}(BnO$^{\bullet}$)/k_{H}(CumO$^{\bullet}$)	1.3	1.2

[a] 266 nm LFP, N$_2$-saturated, [dicumyl peroxide] = 10 mM, [dibenzyl peroxide] 8 mM. [b] Determined from the slope of the k_{obs} vs [substrate] plots, where in turn k_{obs} values have been measured following the decay of the CumO$^{\bullet}$ and BnO$^{\bullet}$ visible absorption bands at 490 and 460 nm, respectively. Average of at least two determinations.

The data displayed in Table 1 show that in C−H abstraction reactions from THF by CumO$^{\bullet}$ the rate constant decreases as the solvent HBD ability increases,[26−28] decreasing by a factor 4.5 going from isooctane to TFE.

This difference in reactivity is very similar to those observed previously for the reactions of CumO$^{\bullet}$ with PA and DMPA, where a ~5-fold decrease in reactivity was observed on going from benzene and PhCl to MeOH and TFE,[15] and for the reactions of CumO$^{\bullet}$ with TEA, where a ~7-fold decrease in reactivity was observed on going from benzene to MeOH.[14] The KSEs observed in the reactions of CumO$^{\bullet}$ with THF can be explained in terms of polar contributions to the transition state for hydrogen abstraction as well as the overlap between the α-C−H bond and the heteroatom lone pair, as described previously for the corresponding reactions of TEA.[14,15] In the transition state for hydrogen abstraction, electron density is moved toward the CumO$^{\bullet}$ oxygen, leading to the development of a partial negative charge on the oxygen atom and a partial positive charge on the incipient carbon-centered radical. HBD solvents can engage in hydrogen bonding with the heteroatom lone pairs of TEA and THF that are fairly strong hydrogen bond acceptors.[29,30] These interactions determine a decrease in electron density at the incipient radical center leading to a destabilization of the transition state as compared to non-HBD solvents.[14,15] The transition state for reaction of THF with CumO$^{\bullet}$ is displayed in Scheme 1.

Scheme 1



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The decrease in the degree of overlap between the α-C−H bond and the heteroatom lone pairs of THF and TEA determined by solvent hydrogen bonding is also responsible for the decrease in reactivity observed on increasing solvent HBD ability.[14] Very importantly, in the presence of a HBD solvent, the lone pairs will be less available for conjugative carbon delocalization to stabilize a radical center on the adjacent carbon atoms. Thus, the α-C−H BDE of TEA and THF is expected to increase as the solvent HBD ability is increased, and this effect will contribute significantly to the observed KSEs.[14,31−33]

With PA and DMPA, the polar contribution to the transition state described above is expected to play a major role[15] because the geometry of the C=O bond does not allow efficient overlap between the oxygen lone pair and the aldehydic C−H bond.

An opposite kinetic behavior was observed in the reactions of CumO$^•$ with CHX. Almost identical k_H values were measured in isooctane and MeCN, while a slight increase in k_H was measured in *t*-BuOH. Larger KSEs were observed in MeOH and TFE, where a 4-fold increase in k_H was measured going from isooctane to the latter solvent. These effects are very similar to those observed previously for the reaction between CumO$^•$ and CHD[14,15] and can be explained accordingly. TFE can engage in hydrogen bonding with the CumO$^•$ oxygen, and, on approaching the transition state, as negative charge develops on the oxygen atom, the strength of the hydrogen bond interaction increases.[15] This interaction results in a greater extent of stabilization for the transition state as compared to the reactants and in a corresponding increase in hydrogen abstraction reactivity as compared to weaker or non-HBD solvents.

Taken together, the results on the reactions of CumO$^•$ with THF and CHX described herein and those obtained previously for the corresponding reactions with TEA, PA, DMPA, and CHD[14,15] provide a general description of the KSEs observed in hydrogen abstraction reactions from carbon by alkoxyl radicals. A decrease in k_H by increasing the solvent HBD ability appears to be a general feature of these processes when the substrate bears a HBA site in proximity of the abstractable C−H. Accordingly, this kinetic behavior is observed in hydrogen abstraction reactions from aldehydes, amines, and ethers, substrates where in all cases the C−H carbon is directly bound to an heteroatom. On the other hand, an increase in k_H by increasing solvent HBD ability can be expected with substrates that lack HBA sites such as hydrocarbons. Solvent hydrogen bonding now involves the radical oxygen atom, and the KSEs, although small, are maximized in very strong HBD solvents.

The analysis provided by El-Sheshtawy et al.,[16] aimed at the understanding of KSEs on hydrogen abstraction from carbon by alkoxyl radicals, was limited to MeCN and EtOAc, and relatively small KSEs were observed. Our results clearly show that significantly larger KSEs are observed when HBD solvents are employed, and most importantly, that substrate structure plays a key role in determining the direction of these effects.

The data displayed in Table 2 show that CumO$^•$ and BnO$^•$ react with THF and CHX with very similar rate constants (k_H(BnO$^•$)/k_H(CumO$^•$) = 1.3 and 1.2, respectively). These observations clearly indicate that, with these substrates, alkoxyl radical sterics play a negligible role. Comparable reactivity ratios (k_H(BnO$^•$)/k_H(CumO$^•$) between 1.2 and 1.9) were previously determined by us for the reactions of PA, DMPA, and CHD with the two radicals.[14,15] With TEA and other amines, a very large increase in k_H was observed going from CumO$^•$ to BnO$^•$ (k_H(BnO$^•$)/k_H(CumO$^•$) = 21.5 for the reactions with TEA).[34−36] These effects were explained on the basis of the formation of a hydrogen-bonded prereaction complex between the BnO$^•$ α-C−H and the amine lone pair. The large difference in k_H(BnO$^•$)/k_H(CumO$^•$) observed between THF and TEA suggests that, as discussed previously for PA and DMPA,[15] the lower HBA ability of THF as compared to TEA[29,30] does not allow the formation of a sufficently stable hydrogen bonded complex.

In conclusion, on the basis of new kinetic data and of the results of previous studies on hydrogen abstraction from C−H donors by CumO$^•$, we have provided a rationale for understanding the magnitude and direction of KSEs on these important processes. Our results clearly show that a key role in this respect is played by substrate structure and solvent HBD ability. Additional studies, underway in our laboratories, will probe the generality of these findings.

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Supporting Information Available. Experimental section. Plots of k_{obs} vs [substrate] for the reactions of CumO$^•$ and BnO$^•$ with THF and CHX. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) The solvent HBA ability can be expressed in terms of the β_2^H parameter, which represents a general, thermodynamically related scale of solute hydrogen bond basicities in CCl_4 and ranges in magnitude from 0.00 for a non-HBA solvent such as an alkane to 1.00 for HMPA: β_2^H = 0.51 and 0.67 for THF and TEA, respectively.[30]

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(33) The study of solvent effects on hydrogen abstraction from carbon by radicals where no significant development of negative charge is expected (for example alkyl radicals) may provide information on the relative contribution of this effect to the observed KSEs.

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