



# Hydrogen atom transfer from tertiary alkanamides to the cumyloxy radical. The role of substrate structure on alkali and alkaline earth metal ion induced C–H bond deactivation



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## ABSTRACT

The effect of metal ions on the reactions of the cumyloxy radical with tertiary amides has been studied. With *N,N*-dialkylacetamides addition of  $\text{Li}^+$  and  $\text{Ca}^{2+}$  leads to strong C–H deactivation, whereas with *N,N*-dimethylalkanamides deactivation was observed to decrease with increasing the alkanoyl group sterics. C–H deactivation has been rationalized in terms of the increase in the extent of positive charge on the amide determined by metal ion binding. The implications of these findings are discussed in the framework of the development of selective C–H functionalization procedures.

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## 1. Introduction

Aliphatic C–H bond functionalization procedures based on hydrogen atom transfer (HAT) to radical or radical-like species are attracting continuous interest, as these processes fall within a mainstream topic of modern synthetic organic chemistry that currently represents one of the most investigated approaches to develop new synthetic methodology.<sup>1–10</sup> As a consequence of the electrophilic nature of the majority of the reagents employed in these HAT based procedures,<sup>11</sup> functionalization of a given substrate generally occurs at the more electron rich C–H bonds (i.e., the C–H bonds that are  $\alpha$  to a heteroatom in substrates such as amines, alcohols and ethers, or a tertiary site over secondary and primary sites in hydrocarbon substrates).

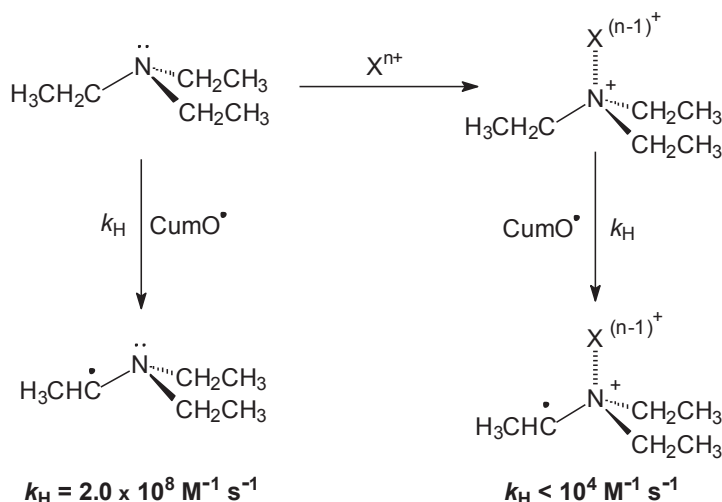
Functionalization of remote C–H bonds of substrates bearing electron rich oxygen and nitrogen functionalities represents, on the other hand, a major synthetic challenge. Accordingly, great efforts are currently devoted toward the development of functionalization procedures that occur selectively at unactivated aliphatic C–H bonds over C–H bonds that are adjacent to a functional group.<sup>12–14</sup> In this framework, remote, non-directed HAT based aliphatic C–H functionalization of amines has been successfully achieved following deactivation of the proximal C–H bonds via protonation or

Lewis acid complexation at the nitrogen center.<sup>15,16</sup> These interactions convert an electron donating group into a strong electron withdrawing group thus inverting the polarity of the adjacent C–H bonds and decreasing their reactivity toward electrophilic hydrogen atom abstracting species.<sup>17</sup>

Along these lines, recent time-resolved kinetic and computational studies have provided a quantitative evaluation of the effect of acid-base interactions on the deactivation of tertiary aliphatic amine  $\alpha$ -C–H bonds toward a genuine and electrophilic HAT reagent such as the cumyloxy radical ( $\text{PhC}(\text{CH}_3)_2\text{O}\cdot$ ,  $\text{CumO}\cdot$ ).<sup>18–21</sup> These studies have shown that by decreasing the electron density of the  $\alpha$ -C–H bonds, protonation or  $\text{Mg}^{2+}$  complexation can lead to a greater than 4-order of magnitude decrease in the rate constant for HAT ( $k_{\text{H}}$ ) from a variety of amine substrates to  $\text{CumO}\cdot$  (Scheme 1, showing the effect of  $\text{X}^{\text{n}+}$  ( $\text{X}^{\text{n}+}=\text{H}^+$ ,  $\text{Mg}^{2+}$ ) on the reaction of  $\text{CumO}\cdot$  with triethylamine).

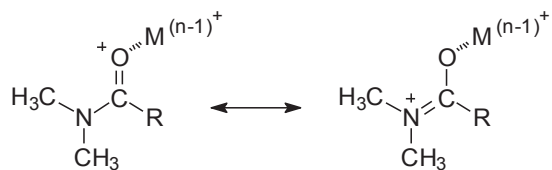
C–H bond deactivation has been also observed in the reactions of  $\text{CumO}\cdot$  with tertiary amide substrates such as *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) following addition of alkali and alkaline earth metal ions.<sup>22</sup> Strong C–H deactivation has been observed in acetonitrile solution after addition of  $\text{Li}^+$  and  $\text{Ca}^{2+}$ , whereas addition of  $\text{Mg}^{2+}$  resulted in a weaker C–H bond deactivation for the first two substrate equivalents followed by a relatively stronger deactivation for two additional equivalents. This behavior has been explained in terms of metal ion ( $\text{M}^{\text{n}+}$ ) binding to the oxygen atom that increases the extent of positive charge on the amide (Scheme 2,  $\text{R}=\text{H}$ ,  $\text{CH}_3$ ), leading for

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Scheme 1.

both substrates to C–H bond deactivation toward HAT to CumO•, where the different reactivity patterns observed with Li<sup>+</sup>, Ca<sup>2+</sup> and Mg<sup>2+</sup> have been rationalized in terms of the interplay between Lewis acidity, charge and size of the metal ion.



Scheme 2.

picture on the effect of alkali and alkaline earth metal ions on the HAT reactivity and selectivity of aliphatic amides could be obtained by extending our investigation to a broader range of substrates. For this purpose, and in order to obtain information on the role of substrate structure, we have carried out a detailed time-resolved kinetic study in acetonitrile solution on the effect of Li<sup>+</sup>, Ca<sup>2+</sup> and Mg<sup>2+</sup> on the reactions of CumO• with a series of *N,N*-dialkylacetamides and *N,N*-dimethylalkanamides, namely *N,N*-diethylacetamide (DEA), *N,N*-diisobutylacetamide (DIA), *N,N*-dimethylpropanamide (DMP), *N,N*,2-trimethylpropanamide (TrMP), *N,N*,2,2-tetramethylpropanamide (TMP), and *N,N*,3,3-tetramethylbutanamide (TMB), whose structures are displayed in Chart 1.

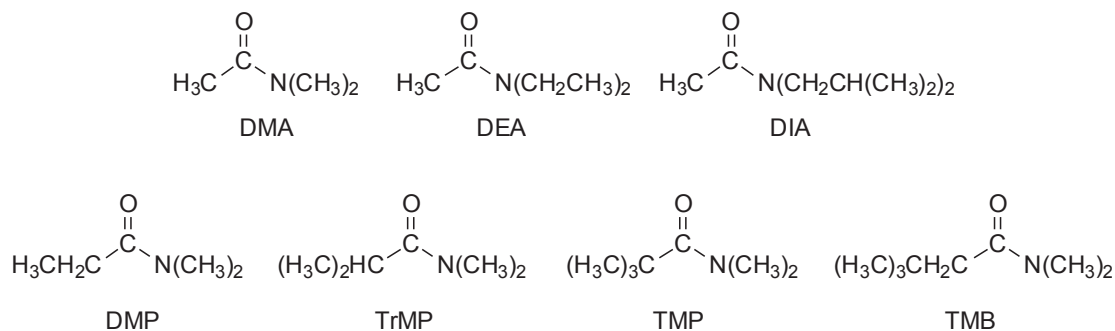


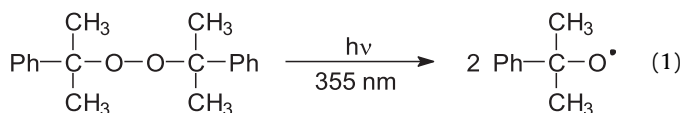
Chart 1. Structure of the tertiary amides employed in the kinetic studies.

Additional support to this mechanistic picture has been derived from the observation that in DMSO no C–H deactivation occurs after metal ion addition, a behavior that reflects the significantly stronger Lewis basicity of DMSO as compared to acetonitrile and to the amide substrates and thus favorable competition of this solvent for Lewis acid–base interaction with the metal ions.<sup>22</sup> Taken together, these results clearly show that C–H deactivation can be modulated varying Lewis acidity of the metal ion and solvent Lewis basicity allowing for careful control over the HAT reactivity of amide substrates towards alkoxy (and, more generally, electrophilic) radicals.

On the basis of this picture and in view of the importance of developing efficient procedures for selective functionalization of unactivated aliphatic C–H bonds, we felt that a more complete

## 2. Results and discussion

CumO• was generated at  $T=25^\circ\text{C}$  following 355 nm laser flash photolysis (LFP) of argon-saturated acetonitrile solutions containing 1.0 M dicumyl peroxide as described in Eq. 1.



Under these conditions, CumO• is characterized by an absorption band centered at 485 nm and a lifetime in the  $\mu\text{s}$  time

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