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Absolute Rate Constants for Hydrogen Atom Transfer from Tertiary Amides to the Cumyloxyl Radical: Evaluating the Role of Stereoelectronic Effects

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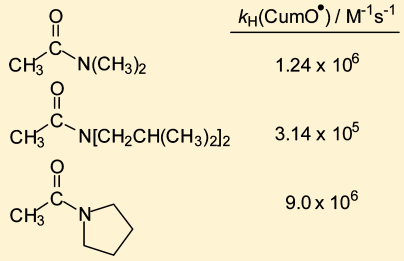
Supporting Information

ABSTRACT: A time-resolved kinetic study of the hydrogen atom transfer (HAT) reactions from a series of alkanamides to the cumyloxyl radical (CumO•) was carried out. With *N,N*-dialkylformamides HAT preferentially occurs from the formyl C−H bond, while in *N*-formylpyrrolidine HAT mostly occurs from the ring α-C−H bonds. With the acetamides and the alkanamides almost exclusive HAT from the C−H bonds that are α to nitrogen was observed. The results obtained show that alignment between the C−H bond being broken and the amide π-system can lead to significant increases in the HAT rate constant (k_H). This finding points toward the important role of stereoelectronic effects on the HAT reactivity and selectivity. The highest k_H values were measured for the reactions of CumO• with *N*-acylpyrrolidines. These substrates have ring α-C−H bonds that are held in a conformation that is optimally aligned with the amide π-system, thus allowing for the relatively facile HAT reaction. The lowest k_H value was measured for the reaction of *N,N*-diisobutylacetamide, wherein the steric bulk associated with the *N*-isobutyl groups increases the energy barrier required to reach the most suitable conformation for HAT. The experimental results are well supported by the computed BDEs for the C−H bonds of the most representative substrates.

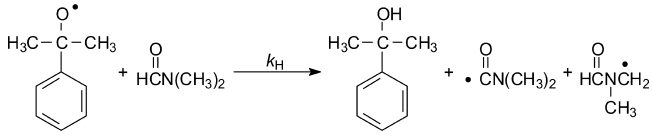


INTRODUCTION

Hydrogen atom transfer (HAT) reactions to reactive oxygen-centered radicals such as alkoxyls have attracted considerable interest, and several aspects of these reactions have been studied in detail.[1−8] Among these studies, the role of structural and medium effects on the HAT reactivity of alkoxyl radicals toward amines,[9−14] phenols,[15−19] and ethers and hydrocarbons[20−27] has been examined. However, limited information is presently available on the reactivity of alkoxyl radicals toward amides,[28] despite the great importance of this class of compounds. Amides are widely used as solvents for a variety of purposes and are often taken as simple models for peptide bonds in proteins and polypeptides. Moreover, HAT reactions from amides to alkoxyl radicals are currently being employed in an increasing number of synthetically useful C−H functionalization procedures.[29−40]

In order to obtain information on the role of structural effects on these reactions, we recently carried out a detailed time-resolved kinetic study in acetonitrile solution on the reactions of alkoxyl radicals with *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA).[41] This work led to a description of the reactions of the cumyloxyl radical ($PhC(CH_3)_2O^•$, CumO•) with DMF and DMA in terms of the direct HAT mechanism shown in Scheme 1 for DMF.

Scheme 1



In this study, information on the HAT selectivity was also provided, showing in particular that HAT to CumO• occurs from both the formyl and *N*-methyl C−H bonds of DMF (Scheme 1), with the formyl being the preferred abstraction site. The reaction of CumO• with DMA results in preferential HAT from the *N*-methyl groups, with HAT from the acetyl group occurring as a minor pathway.

Another aspect of interest is the possible role of stereoelectronic effects in HAT reactions from amides. Stereoelectronic effects have been studied in detail for HAT from the α-C−H bonds of amines and ethers to alkoxyl radicals.[12−14,25−27,42] These studies reveal that the reaction is most rapid when the α-C−H bond being broken is eclipsed with the heteroatom lone pair. This eclipsing allows for the

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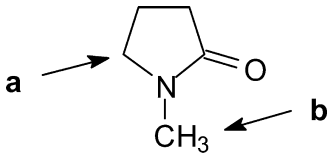
optimal orbital overlap required to impart the greatest amount of stabilization through the delocalization of the developing excess spin on the carbon center from which the hydrogen atom is transferred. The time-resolved kinetic studies therefore provide quantitative information on the role played by stereoelectronic effects in these reactions. Despite this fact, limited information is available on the role of stereoelectronic effects on HAT from amides to alkoxyl radicals; to the best of our knowledge, there is only one kinetic study that deals with such effects, and it involves an aminoxyl radical (see below).[43] The operation of stereoelectronic effects has been proposed in order to account for the peculiar inter- and intramolecular selectivities observed in HAT reactions from amides and lactams to a variety of hydrogen-abstracting species. For example, in product studies of the reactions of 1-methyl-2-pyrrolidone and other lactams with the *tert*-butoxyl radical,[44] the ethyl radical,[45] and photoexcited tetrabutylammonium decatungstate,[46] preferential formation of products derived from HAT from the ring C−H bonds adjacent to nitrogen (Scheme 2, **a**) as compared to the exocyclic methyl C−H

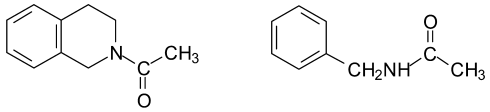
Scheme 2



bonds (Scheme 2, **b**) was observed, as quantified by the product ratios derived from the two competitive pathways that are between 6 and 13.

In a kinetic study of the reactions of the benzotriazole-*N*-oxyl radical (BTNO) with acetamides,[43] significantly higher rate constants for HAT (k_H) from the benzylic C−H bonds α to nitrogen were measured for *N*-acetyltetrahydroisoquinoline in comparison to *N*-benzylacetamide (Scheme 3).

Scheme 3



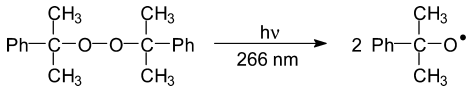
k_H = 26 M^{-1} s^{-1} k_H = 0.49 M^{-1} s^{-1}

The results of these studies were rationalized on the basis of the favorable alignment between the ring C−H bonds and the nitrogen lone pair orbital[47] and clearly show that in the reactions of amides stereoelectronic effects can strongly influence both the HAT reactivity and selectivity.

Within this framework, we have extended our recent time-resolved kinetic study in acetonitrile solution on the reactions of CumO• with DMF and DMA to the reactions of this radical with a wide variety of tertiary amides, namely *N*,*N*-diethylformamide (DEF), *N*,*N*-diethylacetamide (DEA), *N*,*N*-diisobutylacetamide (DIA), *N*-formylpyrrolidine (FPRD), *N*-acetylpyrrolidine (APRD), *N*-acetylpiperidine (APPD), *N*-(2,2-dimethylpropanoyl)pyrrolidine (PvPRD), *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, with the goal of uncovering the role of substrate structure and of stereoelectronic effects on these reactions.

RESULTS

CumO• was generated by 266 nm laser flash photolysis (LFP) of nitrogen-saturated acetonitrile solutions (T = 25 °C) containing dicumyl peroxide, as described in eq 1.



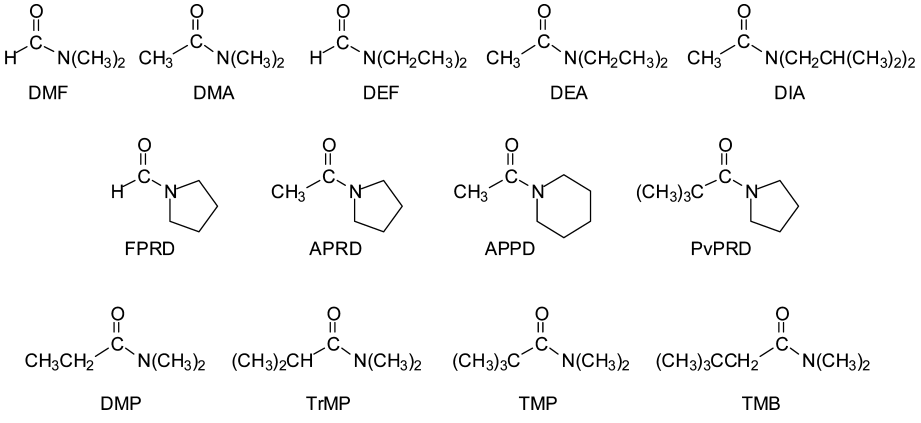
(1)

In acetonitrile solution, CumO• is characterized by an absorption band in the visible region of the spectrum centered at 485 nm,[48−50] and its main decay pathway is represented by C−CH_3 β scission.[24,49]

Time-resolved kinetic studies of the reactions of CumO• with the amides shown in Chart 1 were carried out by LFP following the decay of the CumO• visible absorption band as a function of the amide concentration. The observed rate constants (k_{obs}) gave excellent linear relationships when plotted against substrate concentration, and the second-order rate constants for HAT from the amides to CumO• (k_H) were obtained from the slope of these plots. As an example, Figure 1 shows the k_{obs} vs [substrate] plots for the reactions of CumO• with APRD (filled circles) and DIA (open circles) for measurements carried out in acetonitrile at T = 25 °C.

Additional plots for HAT from the other amides to CumO• are displayed in the Supporting Information (Figures S1−S9).

Chart 1



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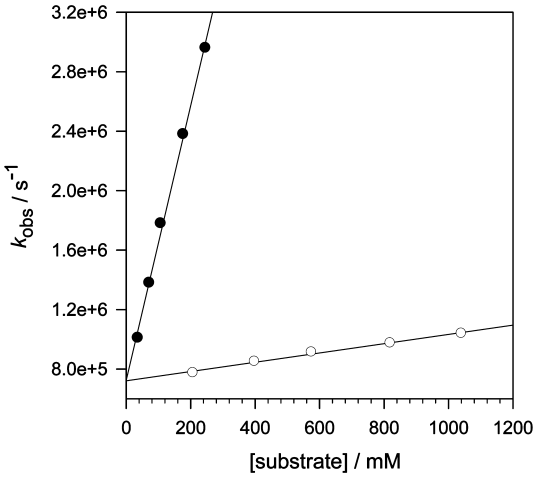

Figure 1. Plots of the observed rate constant (k_{obs}) against [substrate] for the reactions of the cumyloxyl radical (CumO•) with *N*-acetylpyrrolidine (APRD, filled circles) and *N*,*N*-diisobutylacetamide (DIA, open circles), measured in nitrogen-saturated MeCN solution at T = 25 °C by following the decay of CumO• at 490 nm. From the linear regression analysis the following values are obtained: CumO• + APRD, intercept 7.24×10^5 s^{-1}, $k_H = 9.24 \times 10^6$ M^{-1} s^{-1}, $r^2 = 0.9965$; CumO• + DIA, intercept 7.21×10^5 s^{-1}, $k_H = 3.12 \times 10^5$ M^{-1} s^{-1}, $r^2 = 0.9915$.

All of the kinetic data thus obtained are collected in Table 1. Also included in this table are the k_H values measured previously for the reactions of CumO• with DMF and DMA.[41]

In order to provide a better understanding of the HAT selectivity observed in the reactions of CumO• with the tertiary amides displayed in Chart 1 (see below), we calculated the bond dissociation enthalpies (BDEs) for the C−H bonds of DEF, FPRD, DEA, DIA, and APRD. The BDEs were computed using the B3P86[51,52]/6-311G(2d,2p) density functional theory approach, as described previously.[53] In some cases, the CBS-QB3 composite ab initio approach[54] was also used. Calculations were generally performed using the Gaussian-09 program package.[55] In some cases, the Gaussian-03 package was used. The calculated BDEs for the different C−H bonds of these substrates are displayed in Table 2, together with the previously calculated values for DMF and DMA.[41]

Table 1. Second-Order Rate Constants (k_H) for the Reactions of the Cumyloxyl Radical (CumO•) with Tertiary Amides

	k_H/M^{-1} s^{-1} [a]
Formamides	
DMF[b]	$(1.24 \pm 0.02) \times 10^6$
DEF	$(1.25 \pm 0.02) \times 10^6$
FPRD	$(4.93 \pm 0.02) \times 10^6$
Acetamides	
DMA[b]	$(1.24 \pm 0.03) \times 10^6$
DEA	$(6.64 \pm 0.07) \times 10^5$
DIA	$(3.14 \pm 0.02) \times 10^5$
APRD	$(9.0 \pm 0.2) \times 10^6$
APPD	$(3.17 \pm 0.02) \times 10^6$
Alkanamides	
DMP	$(1.55 \pm 0.05) \times 10^6$
TrMP	$(1.69 \pm 0.08) \times 10^6$
TMP	$(1.41 \pm 0.06) \times 10^6$
TMB	$(1.6 \pm 0.1) \times 10^6$
PvPRD	$(5.17 \pm 0.02) \times 10^6$

[a]Measured in N_2-saturated acetonitrile 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} vs [substrate] plots, where in turn k_{obs} values were measured following the decay of the CumO• visible absorption band at 490 nm. Average of at least two determinations. [b]Reference 41.

Table 2. Calculated Bond Dissociation Enthalpies (BDEs) for the C−H Bonds of Tertiary Amides (kcal mol^{-1})

molecule	bond[a]	B3P86	CBS-QB3
$HCON(CH_3)_2$[b] (DMF)	H−CO	94.7	95.0
	α-C−H (*trans*)	93.6	94.7
	α-C−H (*cis*)	93.8	94.8
$HCON(CH_2CH_3)_2$ (DEF)	H−CO	94.3	
	α-C−H (*trans*)	91.5	
	α-C−H (*cis*)	92.3	
$HCON(CH_2)_4$ (FPRD)	H−CO	93.9	
	α-C−H (*trans*)	90.1	
	α-C−H (*cis*)	90.5	
$CH_3CON(CH_3)_2$[b] (DMA)	H−CH_2CO	99.3	99.6
	α-C−H (*trans*)	91.8	92.5
	α-C−H (*cis*)	93.9	94.1
$CH_3CON(CH_2CH_3)_2$ (DEA)	H−CH_2CO	98.8	
	α-C−H (*trans*)	91.0	
	α-C−H (*cis*)	93.0	
$CH_3CON(CH_2)_4$ (APRD)	H−CH_2CO	98.8	
	α-C−H (*trans*)	89.6	
	α-C−H (*cis*)	91.0	
$CH_3CON[CH_2CH(CH_3)_2]$ (DIA)	H−CH_2CO	98.8	99.1
	α-C−H (*trans*)	91.5	93.0
	α-C−H (*cis*)	93.6	94.8

[a]*cis* and *trans* refer to the stereochemical relationship between the carbonyl group and an *N*-alkyl group (in DMF, DEF, DMA, DE,A and DIA) or an α-CH_2 moiety of the pyrrolidine ring (in FPRD and APRD). [b]Reference 41.

DISCUSSION

With the formamide series as a starting point, identical rate constants were measured for DMF and DEF, and a 4-fold increase in k_H was observed on going from these two amides to *N*-formylpyrrolidine (FPRD). In the acetamide and alkanamide series, ~2- and 4-fold decreases in k_H were observed on going from DMA to DEA and DIA, respectively, whereas very small increases in k_H were observed on going from DMA to DMP, TrMP, TMP, and TMB (i.e., by replacing the acetyl methyl group of DMA with ethyl, isopropyl, *tert*-butyl, and neopentyl groups, respectively). Within the last two series, significant increases in k_H were observed on going from the acyclic amides to the *N*-acylpyrrolidines and piperidines (APRD, PvPRD, and APPD), with an increase in k_H that approaches a factor of 30 when the least reactive amide (DIA, $k_H = 3.14 \times 10^5$ M^{-1} s^{-1}) is compared with the most reactive one (APRD, $k_H = 9.0 \times 10^6$ M^{-1} s^{-1}).

Our previous findings on the selectivity of the reaction between CumO• and DMA,[41] combined with the observation that the C−H bonds of *tert*-butyl groups display an extremely low reactivity toward alkoxyl radicals,[56] indicate that HAT from TMP to CumO• occurs almost exclusively from the *N*-methyl groups. Accordingly, the very similar k_H values measured for

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DMA, DMP, TrMP, TMP, and TMB point toward the *N*-methyl groups of these substrates as the preferred sites for HAT.

On the basis of these observations, and of the calculated BDEs for DMA, DEA, and DIA which indicate that the C−H bonds adjacent to the carbonyl group are at least 5 kcal mol^{-1} stronger than the α-C−H bonds of the *N*-alkyl groups, it can be concluded that also the k_H values measured for the reactions of CumO$^\bullet$ with DEA and DIA mostly reflect HAT from the latter bonds. On the basis of this observation, the decrease in k_H measured on going from DMA to DEA and DIA, despite the corresponding decrease in the *N*-alkyl α-C−H BDE and the different numbers of abstractable hydrogen atoms (6 for DMA and 4 for DEA and DIA, respectively), points toward the operation of stereoelectronic effects. The observed decrease in k_H can be accounted for by the increase in steric bulk associated with the replacement of the *N*-methyl groups in DMA with ethyl and isobutyl groups that reduces the accessibility of the abstractable hydrogen atoms to CumO$^\bullet$. The bulkier groups will also have associated with them larger rotational barriers separating the molecules from the most suitable conformation for HAT, where optimal overlap between the α-C−H bond and the amide π-system can be achieved.

The up to 30-fold increase in k_H observed on going from DMA, DEA, and DIA to APRD and from TMP to PvPRD can be explained using similar arguments on the basis of orbital overlap. In APRD and PvPRD, the four pyrrolidine α-C−H bonds are held in a conformation that allows for weakening of these bonds through the overlap of the C−H antibonding orbital with the delocalized amide π-system. This conformation similarly allows for favorable overlap between the developing p orbital nominally containing the unpaired electron and the amide π-system. These orbital interactions, which are illustrated in Figure 2, provide a significant kinetic advantage for HAT in comparison to the corresponding acyclic *N*,*N*-dialkylamides, where similar orbital overlaps are not maintained by a rigid molecular structure. The calculated α-C−H BDEs (Table 2) support the role of orbital overlap in these systems, where

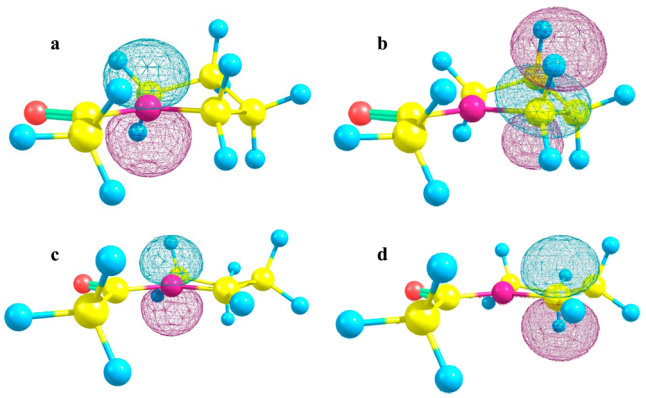

Figure 2. Selected natural orbitals[59] for *N*-acetylpyrrolidine (APRD) (a, b) and the associated carbon centered radical (c, d). For the sake of clarity, the orbitals shown in a and c represent the nitrogen p-type orbital that is part of the delocalized amide bond. The obital shown in b represents an APRD C−H antibonding orbital, and the orbital in d represents the carbon p-type orbital of the radical. The relative phases of the orbitals are shown with different colors. The interactions between the N and C centers within the molecular and radical species can be understood by envisioning the overlap of the orbitals in a and b and the orbitals in c and d.

increased BDEs are found on going from APRD to DEA and DMA. A similar explanation can be put forward to explain the increase in k_H observed on going from DMA, DEA, and DIA to APPD, where, however, the ∼3-fold decrease in k_H observed on going from APRD to APPD reasonably reflects the role of the chairlike conformation of the piperidine ring in APPD where, in comparison to APRD, optimal overlap with the amide π-system can be achieved only for the two axial α-C−H bonds.

As pointed out in our previous study on the reaction of CumO$^\bullet$ with DMA in acetonitrile solution,[41] HAT preferentially occurs from the *N*-methyl group that is in a *trans* relationship to the carbonyl group. This result is in line with the 2.1 kcal mol^{-1} lower BDE value calculated for the α-C−H bonds of the *trans* *N*-methyl group in comparison to those of the group in the *cis* arrangement. The similar differences in the BDEs for the *trans* and *cis* α-C−H bonds of DEA, DIA, and the *N*-methylene groups of APRD (between 1.4 and 2.1 kcal mol^{-1}; see Table 2) suggest that also HAT involving these substrates preferentially occurs from the C−H bonds of the methylene group that is in a *trans* relationship to the carbonyl group. Along this line, the ca. 2-fold decrease in k_H measured on going from APRD to PvPRD can be explained on the basis of steric effects, where the presence of the bulky *tert*-butyl group limits the accessibility to CumO$^\bullet$ of the α-C−H bonds of the *trans* *N*-methylene group.

As mentioned previously, HAT from DMF to CumO$^\bullet$ occurs from both the formyl and *N*-methyl C−H bonds (see Scheme 1), with the formyl being the preferred abstraction site.[41] When the decrease in k_H observed on going from DMA to DEA, which largely reflects HAT from the α-C−H bonds of the *N*-alkyl groups, is taken into account, a similar decrease in reactivity should also be observed for HAT from the α-C−H bonds of the *N*-alkyl groups on going from DMF to DEF. The almost identical k_H values measured for the reactions of CumO$^\bullet$ with DMF and DEF (k_H = 1.24 × 10^6 and 1.25 × 10^6 M^{-1} s^{-1}, respectively) are indicative of an increase in the rate constant for HAT from the formyl C−H bond on going from DMF to DEF. This behavior is consistent with the electrophilic character of alkoxyl radicals[7] and with the electron-releasing character of the dialkylamino group that increases on going from DMF to DEF[57,58] and points toward the role of polar effects in these reactions.

The increase in k_H observed on going from DMF and DEF to FPRD can be explained by the operation of stereoelectronic effects, where orbital overlaps between the four pyrrolidine α-C−H bonds and the amide π-system analogous to those illustrated in Figure 2 make HAT from these bonds the preferred reaction pathway. This is again consistent with the calculated α-C−H BDEs (Table 2) that are between 1 and 3 kcal mol^{-1} lower than those measured for the α-C−H bonds of the *N*-alkyl groups of DMF and DEF.

Calculations were also performed to assess the magnitude of the barrier heights associated with HAT from the α-C−H bonds of DEA, DIA, and APRD to CumO$^\bullet$. Transition states were verified through the vibration frequency analysis, which showed in all cases a single imaginary mode that connects reactants to products. Gas-phase free-energy barriers with respect to infinitely separated reactants were computed to be 12.6 and 15.0 kcal mol^{-1} for DEA and DIA, respectively. Despite being too high in consideration of the measured rate constants, these results support the notion that steric repulsion plays a relatively larger role in the reaction involving DIA. The gas-phase free energy barrier for the reaction involving APRD is

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instead 7.6 kcal mol^{-1}, which is consistent with the favorable alignment of the α-C−H from which the hydrogen atom is being transferred with the amide bond π-orbital, thus supporting the important role played by stereoelectronic effects in these reactions.

In conclusion, detailed information on the role of structural effects on HAT reactions from tertiary amides to CumO$^{\bullet}$ has been provided by means of time-resolved kinetic and computational studies. The results show that optimal orbital overlap between the C−H antibonds in the molecule and p-type orbitals in the corresponding carbon-centered radicals that are α to nitrogen and the amide π-system determines a significant kinetic advantage for HAT. Accordingly, the highest k_H values have been measured for HAT from *N*-acylpyrrolidines, substrates for which the pyrrolidine α-C−H bonds are held in a conformation that allows optimal overlap between these bonds and the delocalized amide π-system, whereas, in the acetamide series, a decrease in k_H with increasing substitution at the α-carbon has been observed. These results provide a quantitative evaluation of the role played by stereoelectronic effects in these reactions, showing moreover that these effects can influence both the HAT reactivity and selectivity. The implications of these findings and the possible exploitation of the observed effects in synthetically useful procedures are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Materials. Spectroscopic grade acetonitrile was used in the kinetic experiments. Dicumyl peroxide was of the highest commercial quality available and was used as received. *N*,*N*-Diethylformamide (DEF), *N*-formylpyrrolidine (FPRD), *N*,*N*-diethylacetamide (DEA), *N*,*N*-dimethylpropanamide (DMP), and *N*,*N*,2-trimethylpropanamide (TrMP) were of the highest commercial quality available and were used as received. *N*,*N*-Diisobutylacetamide (DIA),[60] *N*-acetylpyrrolidine (APRD),[61] *N*-acetylpiperidine (APPD),[61] *N*,*N*,2,2-tetramethylpropanamide (TMP),[62] *N*,*N*,3,3-tetramethylbutanamide (TMB),[63] and *N*-(2,2-dimethylpropanoyl)pyrrolidine (PvPRD)[64] were synthesized by reaction of the pertinent acyl chloride (acetyl chloride, 2,2-dimethylpropanoyl chloride, or 3,3-dimethylbutanoyl chloride) with a 2-fold excess of the secondary amine (pyrrolidine, piperidine, diisobutylamide, and dimethylamine). In all cases the product was purified by flash chromatography (silica gel, eluent dichloromethane or dichloromethane/methanol 50/1) and identified by ^{1}H NMR (Supporting Information, Figures S10−S15).

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 of dicumyl peroxide (10 mM) were employed. All of the experiments were carried out at T = 25 ± 0.5 °C with magnetic stirring. The observed rate constants (k_{obs}) were obtained by averaging three to five individual values and were reproducible to within 5%.

Second-order rate constants for the reactions of the cumyloxyl radical with the amides were obtained from the slopes of the k_{obs} (measured following the decay of the cumyloxyl radical visible absorption band at 490 nm) vs [amide] plots. Fresh solutions were used for every amide concentration. Correlation coefficients were in all cases >0.99. The rate constants displayed in Table 1 are the average of at least two independent experiments, typical errors being ≤10%.

ASSOCIATED CONTENT

Supporting Information

Figures and tables giving plots of k_{obs} vs substrate concentration for the reactions of CumO$^{\bullet}$, ^{1}H NMR spectra, and details of the calculations. 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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