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Electron-Transfer Mechanism in the *N*-Demethylation of *N,N*-Dimethylanilines by the Phthalimide-*N*-oxyl Radical

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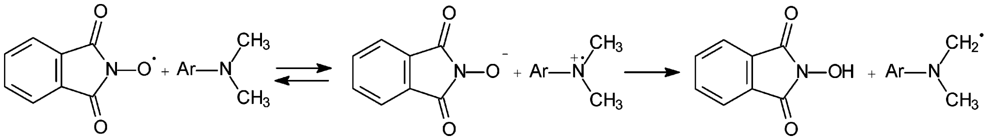

The reactivity of the phthalimide *N*-oxyl radical (PINO) toward the *N*-methyl C−H bond of a number of 4-X-substituted *N,N*-dimethylanilines (X = OMe, OPh, CF_3, CO_2Et, CN) has been investigated by product and kinetic analysis. PINO was generated in CH_3CN by reaction of *N*-hydroxyphthalimide (NHPI) with $Pb(OAc)_4$ or, for the kinetic study of the most reactive substrates (X = OMe, OPh), with *tert*-butoxyl radical produced by 266 nm laser flash photolysis of di-*tert*-butyl peroxide. The reaction was found to lead to the *N*-demethylation of the *N,N*-dimethylaniline with a rate very sensitive to the electron donating power of the substituent ($\rho^+ = -2.5$) as well as to the oxidation potential of the substrates. With appropriately deuterated *N,N*-dimethylanilines the intermolecular and intramolecular deuterium kinetic isotope effects (DKIEs) were measured for some substrates (X = OMe, CO_2Et, CN) with the following results. First, intramolecular DKIE $[(k_H/k_D)_{intra}]$ was found to be always different and higher than intermolecular DKIE $[(k_H/k_D)_{inter}]$; second, no intermolecular DKIE $[(k_H/k_D)_{inter} = 1]$ was observed for X = OMe, whereas substantial values of $(k_H/k_D)_{inter}$ were exhibited by X = CO_2Et (4.8) and X = CN (5.8). These results, while are incompatible with a single step hydrogen atom transfer from the *N*-C−H bond to the *N*-oxyl radical, as proposed for the reaction of PINO with benzylic C−H bonds, can be nicely interpreted on the basis of a two-step mechanism involving a reversible electron transfer from the aniline to PINO leading to an anilinium radical cation, followed by a proton-transfer step that produces an α-amino carbon radical. In line with this conclusion the reactivity data exhibited a good fit with the Marcus equation and a λ value of 37.6 kcal mol^{-1} was calculated for the reorganization energy required in this electron-transfer process. From this value, a quite high reorganization energy (>60 kcal mol^{-1}) is estimated for the PINO/NHPI(-H)$^-$ self-exchange reaction. It is suggested that the *N*-demethylated product derives from the reaction of the α-amino carbon radical with PINO to form either a cross-coupling product or an α-amino carbocation. Both species may react with the small amounts of H_2O present in the medium to form a carbinolamine that, again by hydrolysis, can be eventually converted into the *N*-demethylated product.

Introduction

N-Hydroxyphthalimide (NHPI) in combination with metal and nonmetal cocatalysts is a very efficient catalyst for the mild oxidative functionalization of alkanes and alkylaromatics.[1−11] There is general consensus that in these systems the active oxidant is the phthalimide *N*-oxyl radical (PINO),[5,6,12] which has stimulated research aimed at obtaining quantitative information on the reactivity of this radical toward a variety of C−H bonds. The studies carried out so far have concerned the C−H bonds of alkylaromatics, benzylic alcohols and benzaldehydes.[5,6,12−19] In addition, more recently also the reactivity of PINO toward the phenolic O−H bond has

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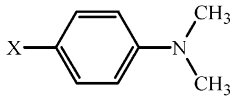
been investigated by our group.[20] A classical hydrogen atom transfer (HAT) mechanism has been suggested for the reaction of PINO with benzylic C−H bonds, whereas for the reaction with phenols, a proton coupled electron transfer (PCET) process seemed more in line with the experimental results.

We have now found that PINO is also very reactive toward the methyl C−H bond of *N,N*-dimethylanilines (DMAs) promoting the oxidative *N*-demethylation of the substrate, a reaction of great chemical and biological importance which has attracted particular attention in recent years.[21−34] Herein, we wish to report a detailed kinetic investigation of this process, where, for the first time, PINO generation has also been accomplished by the laser flash photolysis technique that has made possible the study of very reactive substrates.

The reactivity of a number of 4-X-substituted *N,N*-dimethylanilines (**1**−**5**) was studied and the intermolecular and intramolecular deuterium kinetic isotope effects were also determined. The results led to the very interesting conclusion that the reaction of PINO with DMAs behaves differently from the previously investigated systems, involving an electron-transfer mechanism.



1 X = CN
2 X = CF_3
3 X = $CO_2C_2H_5$
4 X = OC_6H_5
5 X = OCH_3

Results

For product studies, the PINO radical was generated in CH_3CN by reaction of NHPI with $Pb(OAc)_4$ as previously described[15,20] and was allowed to react with DMAs **1**−**5** at 25 °C. At the end of the reaction, after workup, GC−MS and ^{1}H NMR analysis indicated that the corresponding *N*-methylanilines were formed as the major reaction products in relatively low yields (from 12% to 20% referred to the starting material) probably because part of PINO is used in the competitive dimerization reaction. Formation of CH_2O was also detected by its conversion into the dimedone adduct. When ^{1}H NMR analysis of the reaction mixture was performed before work-up, two additional singlets at 5.2−5.3 ppm and 3.1−3.2 ppm (relative intensity = 2:3) were observed. These singlets were reasonably assigned (see the Experimental Section) to a cross-coupling product of PINO and the α-aminomethyl radical formed by the PINO-induced hydrogen abstraction from the N-Me group of the substrate. Evidently, this adduct is converted during workup into the *N*-demethylated product (vide infra), as the above signals were absent in the final mixture. We made some attempts to isolate this intermediate, which, however, were unsuccessful because it was unstable during the chromatographic isolation procedure, always decomposing into the *N*-methylaniline and NHPI.

The same reactions were carried out with the anilines **1**, **3**, and **5** where a single *N*-methyl group was replaced by a *N*-trideuteriomethyl group, that allowed us to determine the product (intramolecular) deuterium isotope effects $(k_H/k_D)_{intra}$ by measuring, by GC−MS analysis, the molar ratio between *N*-trideuteriomethylaniline and *N*-methylaniline produced in the reaction. In line with the hydrogen abstraction process, in all cases we observed substantial values of $(k_H/k_D)_{intra}$, as listed in the last column of Table 1.

The kinetics of the reactions of DMAs **1**−**5** with PINO were studied in CH_3CN at 25 °C. With the less reactive substrates **1**−**3**, PINO was generated as in the products study, and its decay was followed spectrophotometrically at 380 nm (λ_{MAX}).[12] The spontaneous slow decay of PINO was strongly accelerated in the presence of DMAs **1**−**3**, following clean first-order kinetics in the presence of an

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TABLE 1. Substrate Oxidation Potentials and Kinetic Data for the Reaction of PINO with 4-X-Substituted *N,N*-Dimethylanilines in CH_3CN at 25 °C

substrate	E° ^{a}	$k_H{}^b$ ($M^{-1}s^{-1}$)	$k_D{}^{b,c}$ ($M^{-1}s^{-1}$)	$(k_H/k_D)_{inter}{}^b$	$(k_H/k_D)_{intra}{}^{b,d}$
1 (X = CN)	1.29^e	$4.5(4) \times 10^{2\,f}$	77(5)^f	5.8(5)	10.5(5)
2 (X = CF_3)	1.25^g	$1.4(1) \times 10^{3\,f}$	n.d.	n.d.	n.d.
3 (X = $CO_2C_2H_5$)	1.21^h	$3.5(4) \times 10^{3\,f}$	$7.3(8) \times 10^{2\,f}$	4.8(5)	9.6(5)
4 (X = OC_6H_5)	0.80^g	$3.0(3) \times 10^{5\,i}$	n.d.	n.d.	n.d.
5 (X = OCH_3)	0.69^e	$3.7(4) \times 10^{6\,i}$	$3.7(3) \times 10^{6\,i}$	1.0(2)	5.8(5)

[a] V vs NHE in CH_3CN. [b] The number in parentheses represents the error in the last digit. [c] Determined using 4-X-$C_6H_4N(CD_3)_2$ as substrate. [d] Determined by product analysis of the oxidation of 4-X-$C_6H_4N(CH_3)(CD_3)$. [e] Reference 37. [f] Determined spectrophotometrically. [g] Calculated by the correlation of the oxidation potential of 4-X-substituted *N,N*-dimethylanilines vs Hammett σ^+ values. Reference 37. [h] Reference 38. [i] Determined by laser flash photolysis.

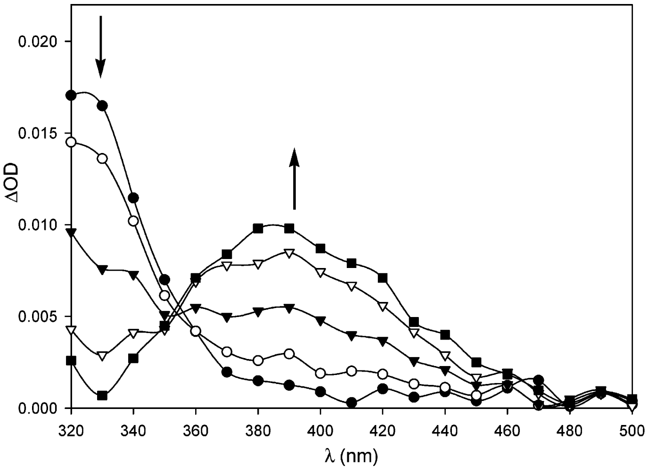

FIGURE 1. Transient absorption spectra measured 200 ns (filled circles), 640 ns (empty circles), 2 μs (filled triangles), 6.3 μs (empty triangles), and 20 μs (filled squares) after laser excitation of a solution of di-*tert*-butyl peroxide (0.5 M) and NHPI (0.6 mM) in CH_3CN.

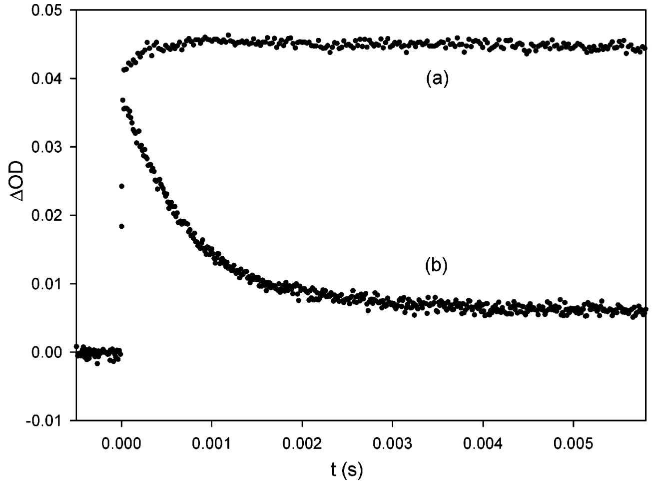

FIGURE 2. Time-resolved absorbance measured at 380 nm after laser excitation of a solution of di-*tert*-butyl peroxide (1.0 M) and NHPI (10 mM) in CH_3CN in the absence (a) or in the presence (b) of 4-CH_3O-$C_6H_4N(CH_3)_2$ (0.4 mM).

excess of substrate. With the more reactive DMAs **4** and **5**, the laser flash photolysis technique was used. PINO was produced by hydrogen atom abstraction from NHPI by the *tert*-butoxyl radical generated by 266 nm laser flash photolysis of di-*tert*-butyl peroxide in CH_3CN at 25 °C. The time-resolved spectrum obtained in a laser photolysis experiment carried out with a solution of di-*tert*-butyl peroxide (0.5 M) and NHPI (0.6 mM) is reported in Figure 1, where it can be observed that the absorption that appears 200 ns after the laser pulse (filled circles), due to the *tert*-butoxyl radical,[35] is replaced after 20 μs (filled squares) by the absorption due to PINO (λ_{MAX} =380 nm).[12] An isosbestic point can be identified at $\lambda = 355$ nm.

The PINO signal is stable on the millisecond time scale, but, in the presence of an excess of **4** or **5**,[36] a much faster decay of PINO is observed that follows first-order kinetics (Figure 2).

From the observed pseudo-first-order rate constants (k_{obs}) plotted against the substrate concentration (see Figures S1−S5 in the Supporting Information), the second-order rate constants (k_H) for the hydrogen abstraction reaction of compounds **1**−**5** with PINO were calculated. With the DMAs **1**, **3**, and **5**, the intermolecular deuterium kinetic isotope effect $(k_H/k_D)_{inter}$ was also determined by measuring the rate constants for the deuterium abstraction reaction (k_D) from 4-CN-$C_6H_4N(CD_3)_2$, 4-CO_2-Et-$C_6H_4N(CD_3)_2$, and 4-CH_3O-$C_6H_4N(CD_3)_2$, respectively (see Figures S1, S3, and S5 in the Supporting Information). All of the kinetic data are collected in Table 1.

Discussion

From the results presented above, it appears that PINO is able to promote the *N*-demethylation of DMAs by a process involving a hydrogen transfer from the N-CH_3 group to PINO. It can also be concluded that such a transfer does not occur by a classical free radical hydrogen abstraction mechanism (as suggested for the PINO reactions with benzylic C−H bonds)[5,6,12−20] as substantial differences are observed between inter- and intramolecular deuterium kinetic isotope effects (Table 1), a situation inconsistent with a single-step mechanism.[30,32]

A two-step mechanism (Scheme 1, paths a and b), involving a reversible electron transfer from the substrate to PINO in the first step, is a reasonable hypothesis that is supported by several lines of evidence.

First, the reactivity data reported in Table 1 show that the reaction rate is very sensitive to the electron donating power of the substituent as well as to the oxidation potential of the substrates, increasing as the former increases and the second becomes lower. Good linear correlations are obtained by plotting log k_H against the substituent σ^+ constants ($\rho^+ = -2.5$, $r^2 = 0.987$) and the

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(36) From the initial ΔOD we can estimate that the PINO concentration is about 0.03 mM.

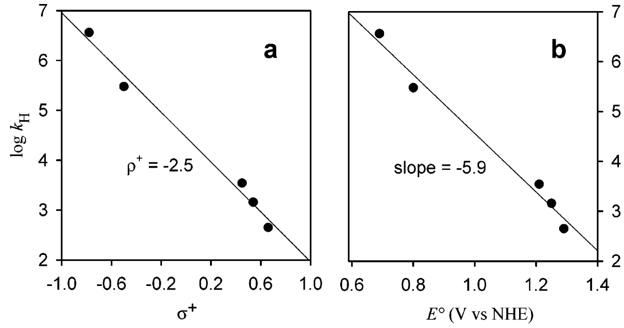
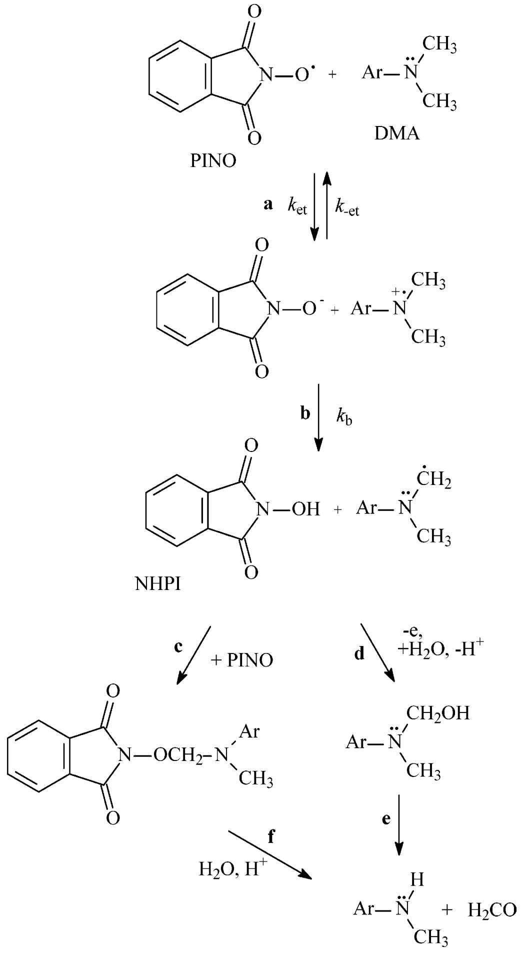


FIGURE 3. Dependence of the bimolecular rate constants of PINO with *N,N*-dimethylanilines **1**−**5** in CH_3CN at 25 °C upon the Hammett σ^+ constants (**a**) and on the oxidation potential (**b**).

SCHEME 1



oxidation potentials of the DMAs (slope = −5.9, r^2 = 0.983), as shown in Figure 3. Clearly, these observations indicate a transition state characterized by a substantial development of positive charge.[39]

Whereas the substituent effects on the rate as well as the strong rate dependence on the $E°$ values are certainly consistent with the occurrence of an electron-transfer step, a decisive support in this respect comes from the observation that the intermolecular DKIE decreases on going from electron-withdrawing to electron-donating substituents.[27] Accordingly, $(k_H/k_D)_{inter}$ is 5.8 with **1** (CN), 4.8 with **3** (CO_2Et), and 1.0 (no DKIE!) with **5** (OMe).[40] This trend, when coupled with the observation that intramolecular DKIEs $[(k_H/k_D)_{intra}]$ are always different and higher than $(k_H/k_D)_{inter}$, is a strong evidence in favor of a mechanism where the electron transfer from DMA to PINO is reversible and is followed by a proton-transfer step (Scheme 1, paths a and b).[27,30,31]

According to this mechanism, any NHPI(-H)$^-$/DMA$^{+\bullet}$ pair formed in the first step can partition either toward the product by proton transfer (k_b) or the initial reactants (k_{-et}). The value of $(k_H/k_D)_{inter}$ will therefore depend on the ratio of the rate constants of the back electron transfer (k_{-et}) to that of the proton transfer (k_b).[31] With **5**, the electron transfer is exergonic (the reduction potential of PINO is 0.92 V vs NHE[41]). It is therefore reasonable to suggest that since the back electron transfer will be rather slow, k_{-et} may be much smaller than k_b. It follows that the electron-transfer step is rate determining and no intermolecular DKIE is observed. On the other hand, as expected, the product intramolecular DKIE is substantial as it originates from the deprotonation step. Conversely, the radical cations formed from **3** and **1** will be much less stable (their formation is endergonic), hence larger values of k_{-et} are expected. Thus, it is plausible that the deprotonation step too may contribute to determine the reaction rate leading to substantial values of $(k_H/k_D)_{inter}$.[42] Nevertheless, it has to be noted that not even with **1** and **3** does the deprotonation step become completely rate determining since a large difference between $(k_H/k_D)_{inter}$ and $(k_H/k_D)_{intra}$ is still present in both cases.

Very interestingly, a pattern of results very close to ours [decrease of $(k_H/k_D)_{inter}$ by increasing the electron donating power of the substituent and different values of $(k_H/k_D)_{inter}$ and $(k_H/k_D)_{intra}$] were obtained by Watanabe et al. in the *N*-demethylation of DMAs catalyzed by high valent metal−oxo species O=Fe^{IV}TMP$^{\bullet+}$ (TMP = 5,10,-15,20-tetramesitylporphyrin dianion).[31] In this case too, the results were interpreted with a mechanism involving a reversible electron transfer from the aniline to O=Fe^{IV}-TMP$^{\bullet+}$.[43] The similar mechanism of the reaction of DMAs with PINO and O=Fe^{IV}TMP$^{\bullet+}$ is further supported by the observation that both reactions exhibit a linear dependence of the rate constants k_H upon the substrate oxidation potential with similar slopes, −5.9 for PINO and −7.76 for O=Fe^{IV}TMP$^{\bullet+}$.

In line with an electron-transfer mechanism is also the quite satisfactory fit (Figure 4) obtained when the PINO

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[39] Actually, the kinetic data correlate better with the σ rather than with the σ^+ constants ($\rho = -4.2$, $r^2 = 0.997$), that probably indicates that the partial positive charge in the transition state should be mainly localized on the nitrogen atom and not on the aromatic ring.

[40] Secondary isotope effects are likely obscured by the error limit.

[41] Gorgy, K.; Lepretre, J.-C.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal C.; Pierre, J.-L. *Electrochim. Acta* **1998**, *44*, 385.

[42] Of course, substituents also influence the rate of the second step. However, the effect on the electron-transfer step should be much more important, as also shown by the observed electronic effects of the substituents.

[43] Actually, for this reaction Watanabe et al. assumed that the radical cation undergoes a hydrogen atom transfer and not a proton-transfer reaction. At present, we cannot exclude that such a possibility occurs also in our case, the radical cation reacting with PINO to form an α-amino carbocation that can either be converted into the carbinolamine or react with the *N*-hydroxyphthalimide anion, produced in step a, to give the adduct (Scheme 1).

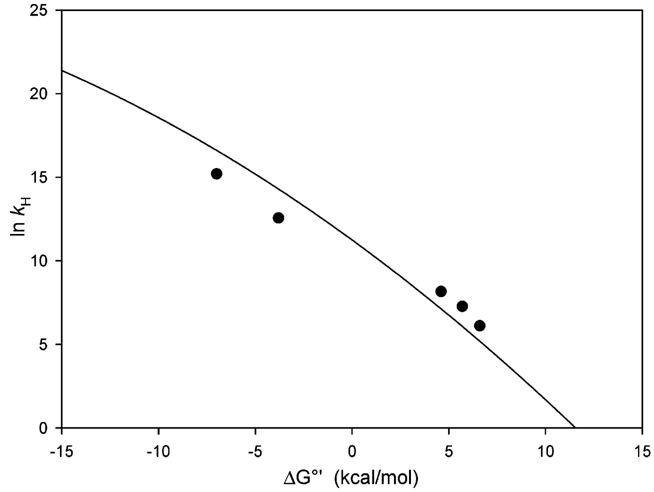

FIGURE 4. Diagram of ln k_H vs $\Delta G^{\circ\prime}$ for the reactions of 4-substituted *N,N*-dimethylanilines with PINO. The solid circles correspond to the experimental values; the curve is calculated by nonlinear least-squares fit to the Marcus equation with $Z = 6 \times 10^{11}$.

reactivity data were treated according to the Marcus equation[44] (eq 1, where $\Delta G^{\ddagger}$ is the activation free energy for the electron-transfer step (path a), $\Delta G^{\circ\prime}$ is the standard free energy for the same step corrected for the electrostatic interaction arising from the charge variation in the reactants upon electron transfer,[45] and λ is the reorganization energy).

$$\Delta G^{\ddagger} = \frac{\lambda}{4}\left(1 + \frac{\Delta G^{\circ\prime}}{\lambda}\right)^2 \tag{1}$$

From the nonlinear least-squares fitting, a λ value of 37.6 kcal mol^{-1} was calculated for the reorganization energy required in the transfer of one electron from DMA to PINO. Since the reorganization energy for the DMA$^{+\bullet}$/DMA self-exchange reaction is rather low (<15 kcal mol^{-1}),[24] a substantial reorganization energy (>60 kcal mol^{-1}) can be calculated for the PINO/NHPI(-H)$^-$ self-exchange reaction. Such a high value is not surprising since significant reorganization energies are generally observed for the electron-transfer reactions of oxygen centered radicals.[33] In this respect, it is interesting to note that Fukuzumi et al. have recently reported a λ value as high as 160 kcal mol^{-1} for the $C_6H_5C(CH_3)_2OO^{\bullet}$/$C_6H_5C(CH_3)_2OO^-$ self-exchange reaction.[33] Such a high value might explain why peroxyl radicals react with *N,N*-dimethylanilines by a hydrogen atom transfer mechanism and not by an electron-transfer mechanism, although their reduction potential (0.89 V vs NHE)[33] is not much different than that of PINO.[41]

To better understand the origin of the reorganization energy for the PINO/NHPI(-H)$^-$ self-exchange reaction, DFT calculations at the B3LYP/6-311G** level of theory were performed to estimate the energy required for the adjustment in nuclear geometry needed to convert PINO into its anion (Supplementary Information). The intramolecular reorganization energy (λ_i) was calculated by the method proposed by Nelsen[46] and Larsson.[47] The energy of the optimized radical was calculated (E_1). By adding an electron to the radical freezing its geometry the energy E_2 was calculated. Then the energy of the optimized anion was calculated (E_3) and by removing an electron to the anion freezing its geometry the energy was calculated (E_4). The difference $E_2 - E_3$ is the λ_i for the anion and the difference $E_1 - E_4$ is the λ_i for the radical. The sum of these two reorganization energies is the total λ_i. A rather low value was found (8.2 kcal mol^{-1}) as expected, indicating that most of the reorganization energy must involve the reorganization of the solvent.

Finally, concerning the pathway by which the α-amino carbon radical, formed in path b of Scheme 1, is converted into the *N*-demethylated aniline, a possibility is the reaction with PINO to form the cross-coupling product (Scheme 1, path c). This adduct can react with the small amounts of H_2O present in the solvent and form a carbinolamine that is then converted into the *N*-methylaniline (path f) and CH_2O, detected as its dimedone adduct. However, it is also possible that in part the α-amino carbon radical is oxidized to a carbocation by PINO. The reaction of the carbocation with H_2O may lead to the carbinolamine (paths d and e) and then to the final product.

Conclusions

PINO reacts with the *N*-Me C−H bonds of *N,N*-dimethylanilines in CH_3CN, leading ultimately to the formation of the *N*-demethylated product. The rates of this process resulted very sensitive to the electronic effects of substituents ($\rho^+ = -2.5$) as well as the E° values of the substrates. The intermolecular and intramolecular deuterium kinetic isotope effects (DKIEs) were measured for some substrates (X = OMe, CO_2Et, CN) and two important results were obtained. First, intramolecular DKIE [$(k_H/k_D)_{intra}$] was always different and higher than intermolecular DKIE [$(k_H/k_D)_{inter}$]; second, no intermolecular DKIE [$(k_H/k_D)_{inter} = 1$] was observed for X = OMe, whereas substantial values of $(k_H/k_D)_{inter}$ were exhibited by X = CO_2Et (4.8) and X = CN (5.8). These results, while are incompatible with a single step hydrogen atom transfer from the *N*-C−H bond to the *N*-oxyl radical, can be nicely interpreted on the basis of a two-step mechanism involving a reversible electron transfer from the aniline to PINO leading to an anilinium radical cation, followed by a proton-transfer step, that produces an α-amino carbon radical (Scheme 1, paths a and b). Moreover, a good fit was obtained by applying the Marcus equation to the reactivity data with a λ value of 37.6 kcal/mol for the reorganization energy required in the electron-transfer process. From this value, a quite high reorganization energy (>60 kcal mol^{-1}) is estimated for the PINO/PINO(-H)$^-$ self-exchange reaction.

Summing up, the mechanism of the reaction of PINO with DMAs appears to be different from the one (hydro-

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gen atom transfer) found to be operating in the reactions of this radical with a variety of benzylic C−H bonds. However, it should be noted that, with respect to the benzylic systems, *N*,*N*-dimethylanilines are characterized by generally lower oxidation potentials (that makes electron transfer more favorable) and higher BDEs of the scissile C−H bond (that makes the hydrogen atom transfer less favorable).[48] Both factors may be at play in causing the mechanistic changeover on passing from benzylic systems to *N*,*N*-dimethylanilines.

Experimental Section

Product Analysis. The substrate (0.080 mmol) in 10 mL of CH_3CN, $Pb(OAc)_4$ (0.022 mmol) in 3 mL of 1% CH_3COOH in CH_3CN, and NHPI (0.052 mmol) in 3 mL of CH_3CN were separately degassed with argon for 20 min. By mixing the solutions of NHPI and $Pb(OAc)_4$, the PINO was generated and added to the solution of the substrate under argon. The reaction mixture was stirred at 25 °C for 10 min. The solvent was then removed under reduced pressure and the residue was treated with dilute HCl, then neutralized with NaOH 2 N. The mixture was then extracted with CH_2Cl_2 and the collected organic extracts were dried over anhydrous Na_2SO_4 and analyzed by GC−MS and ^1H NMR. With all the substrates the major product was the corresponding *N*-methylaniline (comparison with authentic specimens). The yields, however, were rather small (from 12% to 20% referred to the starting material) probably because part of PINO is used in the competitive dimerization reaction.[12,19] ^1H NMR analysis of the reaction mixture carried out before the workup showed two additional singlets at 5.2−5.3 ppm and 3.1−3.2 ppm (the position depends on the substituent in the aniline), with relative intensity = 2:3. These singlets can be reasonably assigned to the cross-coupling product of PINO and the α-aminomethyl radical (shown in Scheme 1); in particular, a singlet at 5.2−5.3 ppm can be predicted for the methylene group of this adduct on the basis of the additive effect of the $C_6H_4(CO)_2NO$ and $C_6H_5N(CH_3)$ substituents on the shielding constant. Moreover, the singlet at 3.1−3.2 ppm can be attributed to the *N*-methyl group of the adduct being slightly shielded with respect to the substrate *N*-methyl groups by the effect of the $CH_2ON(CO)_2C_6H_4$ substituent. Attempts to isolate this adduct were unsuccessful because it was unstable during the chromatographic isolation procedure, always decomposing into the *N*-methylaniline and NHPI. Formation of CH_2O was detected by its dimedone adduct. In this case 10 mL of water and 10 mL of CH_2Cl_2 were added to the reaction mixture at the end of the reaction. Then the aqueous layer was incubated with 3 mL of a 0.2 M dimedone solution in 0.2 M NaOH at room temperature. Then dilute HCl was added dropwise until the mixture became acidic. The dimedone adduct was extracted with CH_2Cl_2 and analyzed by GC−MS (m/z = 292). Product (intramolecular) deuterium isotope effects $(k_H/k_D)_{intra}$ were determined, by GC−MS analysis, as the ratio of the corrected signal intensities of the *N*-trideuteriomethylanilines and *N*-methylanilines (m/z 135 and 132 in the oxidation of 4-cyano-*N*-methyl-*N*-trideuteriomethylaniline; m/z 182 and 179 in the oxidation of 4-ethoxycarbonyl-*N*-methyl-*N*-trideuteriomethylaniline; m/z 140 and 137 in the oxidation of 4-methoxy-*N*-methyl-*N*-trideuteriomethylaniline).

Spectrophotometric Kinetic Studies. PINO was generated by the oxidation of NHPI (0.30 mM) with $Pb(OAc)_4$ (0.03 mM) in CH_3CN at 25 °C and under an argon atmosphere. A solution of the substrate (**1**-**3**) was added into the PINO solution in the cuvette (substrate concentration in the range 0.2−2 mM) and the absorbance change was monitored at 380 nm. For all the substrates investigated each kinetic trace obeyed a first-order kinetic. Second-order rate constants were obtained by the plot of the observed rate constant k_{obs} vs the substrate concentration. It was verified that the self-decomposition of PINO, generated by the oxidation of NHPI (0.30 mM) with $Pb(OAc)_4$ (0.03 mM) in CH_3CN (at 25 °C under argon) was slow enough to allow the study of the reaction of PINO with the *N*,*N*-dimethylanilines.

Laser Flash Photolysis Experiments. Laser flash photolysis experiments were carried out with a laser kinetic spectrometer using the fourth harmonic (266 nm) of a Q-switched Nd:YAG laser. A 3 mL Suprasil quartz cell (10 mm × 10 mm) was used for all the experiments. Argon-saturated CH_3CN solutions containing di-*tert*-butyl peroxide (1.0 M), *N*-hydroxyphthalimide (10 mM), and dimethylanilines **4**−**5** (0.1−1.0 mM) were used. All the experiments were carried out at $T = 25 \pm 0.5$ °C under magnetic stirring. Rate constants were obtained by monitoring the change of absorbance at 380 nm and by averaging three to five values. Each kinetic trace obeyed a first-order kinetic and second-order rate constants were obtained by the plot of the observed rate constant k_{obs} vs the substrate concentration.

DFT Calculations. All computations were performed with the Gaussian 98 program[49] using the three-parameter hybrid functional B3LYP[50] with the 6-311G** basis set.[51] Such functional was chosen because it is reported to yield accurate geometries and reasonable energies.[52] Harmonic vibrational frequencies were calculated at B3LYP/6-311G** level to confirm that optimized structures correspond to local minima. Spin contamination due to states of multiplicity higher than the doublet state was negligible, the value of the $\langle S^2 \rangle$ operator was, in all cases, well within 5% of the expectation value for a doublet (0.75). The atomic charges and unpaired electron spin densities were calculated using the Mulliken population analysis.

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Supporting Information Available: Instrumentation, materials, synthesis of *N*,*N*-dimethylanilines, *N*,*N*-bis(trideuteriomethyl)anilines, and *N*-methyl-*N*-trideuteriomethylanilines, dependence of k_{obs} on the concentration of *N*,*N*-dimethylanilines **1**−**5**, calculation of $\Delta G^{\circ\prime}$ values, and computational data of PINO and NHPI(-H)$^-$. This material is available free of charge via the Internet at http://pubs.acs.org.

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