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# A Kinetic Study of the Reaction of *N*,*N*-Dimethylanilines with 2,2-Diphenyl-1-picrylhydrazyl Radical: A Concerted Proton−Electron Transfer?

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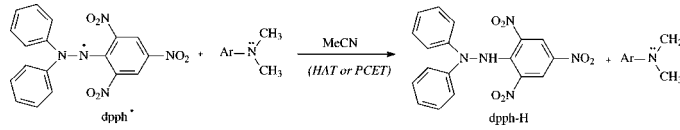


The reactivity of the 2,2-diphenyl-1-picrylhydrazyl radical (dpph•) toward the *N*-methyl C−H bond of a number of 4-X-substituted-*N*,*N*-dimethylanilines (X = OMe, OPh, $CH_3$, H) has been investigated in MeCN, in the absence and in the presence of $Mg(ClO_4)_2$, by product, and kinetic analysis. The reaction was found to lead to the *N*-demethylation of the *N*,*N*-dimethylaniline with a rate quite sensitive to the electron donating power of the substituent ($\rho^+ = -2.03$). With appropriately deuterated *N*,*N*-dimethylanilines, the intermolecular and intramolecular deuterium kinetic isotope effects (DKIEs) were measured with the following results. Intramolecular DKIE [$(k_H/k_D)_{intra}$] was found to always be similar to intermolecular DKIE [$(k_H/k_D)_{inter}$]. These results suggest a single-step hydrogen transfer mechanism from the *N*−C−H bond to dpph• which might take the form of a concerted proton−electron transfer (CPET). An electron transfer (ET) step from the aniline to dpph• leading to an anilinium radical cation, followed by a proton transfer step that produces an α-amino carbon radical, appears very unlikely. Accordingly, a rate-determining ET step would require no DKIE or at least different inter and intramolecular isotope effects. On the other hand, an equilibrium-controlled ET is not compatible with the small slope value ($-0.22$ kcal$^{-1}$ K$^{-1}$) of the log $k_H/\Delta G°$ plot. Furthermore, the reactivity increases by changing the solvent to the less polar toluene whereas the reverse would be expected for an ET mechanism. In the presence of $Mg^{2+}$, a strong rate acceleration was observed, but the pattern of the results remained substantially unchanged: inter and intramolecular DKIEs were again very similar as well as the substituent effects. This suggests that the same mechanism (CPET) is operating in the presence and in the absence of $Mg^{2+}$. The significant rate accelerating effect by $Mg^{2+}$ is likely due to a favorable interaction of the $Mg^{2+}$ ion with the partial negatively charged α-methyl carbon in the polar transition state for the hydrogen transfer process.

## Introduction

Since the pioneering work by Blois,[1] the 2,2-diphenyl-1-picrylhydrazyl radical (dpph•), a stable nitrogen centered radical, has found widespread application in studies concerning the quantitative assessement of the relative reactivity of antioxidants, particularly the phenolic ones.[2] In this respect, it is important to note that Mulder et al.[3] have recently shown that the relative reactivity of phenolic antioxidants measured against dpph• parallels that measured against peroxyl radicals, which is the very process where the antioxidant activity of phenols is actually displayed.

From the mechanistic point of view, dpph• is generally thought to react with phenols by a single-step hydrogen transfer mechanism (HAT or CPET).[4] However, there is evidence that in ionizing solvents, particularly alcohols, the so-called SPLET mechanism (sequential proton loss electron transfer mechanism)[10–13] involving the ionization of phenol followed by the ET reaction of dpph• with

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**SCHEME 1**

$$\text{dpph}^{\bullet} + \textit{N}\text{-Me-AcrH}_2 \rightarrow \textit{N}\text{-Me-AcrH}_2^{+\bullet} + \text{dpph}^{-} \quad (1)$$

$$\textit{N}\text{-Me-AcrH}_2^{+\bullet} + \text{dpph}^{-} \rightarrow \textit{N}\text{-Me-AcrH}^{\bullet} + \text{dpph-H} \quad (2)$$

$$\textit{N}\text{-Me-AcrH}^{\bullet} + \text{dpph}^{\bullet} \rightarrow \textit{N}\text{-Me-AcrH}^{+} + \text{dpph}^{-} \quad (3)$$

the formed phenolate anion, can operate. With phenolic antioxidant of low ionization potential, an ET step followed by proton transfer (ET−PT)[14] may also be envisaged, and accordingly, this possibility has been recently suggested for the reaction of dpph• with a vitamin E model in MeOH.[15] This proposal, however, has been strongly challenged.[13] Clearly, under the conditions where SPLET or ET mechanism work, dpph• may no longer be a good model of peroxyl radicals reactivity.[10]

Much less information is available for the reactivity of dpph• toward C−H bonds, probably because the N−H bond dissociation energy (BDE) in dpph-H is 79.6 kcal mol$^{-1}$,[16] and one can predict a significant reactivity of dpph• only toward substrates with relatively weak C−H bonds. Recently, it has been shown that dpph• reacts efficiently with *N*-methyl-9,10-dihydroacridine (*N*-Me-AcrH$_2$) to form the *N*-methylacridinium cation (*N*-Me-AcrH$^+$) in a process involving the 9-C−H bond.[17] This process might well involve a HAT mechanism as the 9-C−H BDE is as low as 80 kcal mol$^{-1}$.[18] However, it was found that the reaction rate is increased by addition of $Mg^{2+}$, and on this basis, it was suggested that the reaction of dpph• with *N*-Me-AcrH$_2$ most likely takes place by an ET mechanism where a radical cation is first formed that is then deprotonated (Scheme 1).

The observed rate increase was attributed to the stabilization by $Mg^{2+}$ of dpph$^-$ formed in the electron transfer step (eq 1 of Scheme 1). It was also suggested that the kinetic effect of $Mg^{2+}$ might represent a reliable criterion to distinguish ET from HAT mechanisms, no rate accelerating effect by the metal cation being expected in the latter case.[19]

Clearly, the occurrence of an ET mechanism in the reaction of *N*-Me-AcrH$_2$ with dpph• is somewhat surprising because this mechanism is thermodynamically unfavored with respect to the HAT mechanism. Accordingly, the ET step is endergonic by almost 13 kcal mol$^{-1}$,[21] whereas the BDEs reported above indicate that the HAT mechanism is practically thermoneutral. Thus, it would appear that either dpph• has an intrinsic reactivity much higher in ET than in HAT processes or the HAT mechanism is strongly retarded by steric effects so that the ET mechanism can take over.[22]

We have found that dpph• can promote the *N*-demethylation of *N*,*N*-dimethylanilines (DMAs), a process that certainly involves the cleavage of a methyl C−H bond (vide infra). The BDE of this bond is around 90−92 kcal mol$^{-1}$,[23] (much higher than that of the 9-C−H bond in *N*-Me-AcrH$_2$), and at the same time, the reduction potentials of DMAs radical cations[24] are of the same order of magnitude or lower than that of *N*-Me-AcrH$_2^{+\bullet}$. Thus, if dpph• reacts with *N*-Me-AcrH$_2$ by an ET mechanism, it would seem very reasonably to anticipate that the same mechanism should also hold in the corresponding reaction with the DMAs.

We felt that a study aimed at testing this prediction would be certainly warranted because the use of dpph• in the assessement of the relative reactivity of antioxidants requires reliable information about the respective scopes of HAT (CPET), SPLET, or ET−PT mechanisms for this radical as well as the possible differences between processes involving cleavage of C−H bonds and processes involving cleavage of O−H bonds. It should be also considered that there is a continuous interest for the mechanistic aspects of the oxidative *N*-demethylation of tertiary methylamines induced by free radical species, a process of high biological interest.[25]

In this paper we report on a kinetic study of the *N*-demethylation reaction of a number of 4-X-substituted-*N*,*N*-dimethylanilines (**1**, X = H; **2**, X = $CH_3$; **3**, X = $OC_6H_5$; **4**, X = $OCH_3$) promoted by dpph• in MeCN. Substituent and solvent effects have been determined together with the intra- and intermolecular deuterium kinetic isotope effects (DKIEs). The kinetic effect of $Mg^{2+}$ ($Mg(ClO_4)_2$) has also been investigated.

## Results

For product studies, a solution of *N*,*N*-dimethyl-*p*-toluidine and dpph• (4:1 molar ratio) in $CH_3CN$ was stirred for 3 h at 25 °C under argon. After workup, GC-MS and $^1$H NMR analysis

(4) The transfer of a hydrogen atom formally involves the transfer of an electron and a proton. When electron and proton are transferred to the *same* center in the *same* step, we generally speak of HAT mechanism. Very recently, however, DFT theoretical calculations[5−7] have shown that quite energetically different situations can arise depending on whether the same or different sets of orbitals are involved in the transfer of the proton and the electron. In the former case, the mechanism continues to be designated as HAT; in the latter case, the process is described as a proton coupled electron transfer (PCET) or a concerted proton electron transfer (CPET). Theoretical calculations[8] have also shown that both HAT and CPET pathways are possible for the reaction of dpph• with phenols. It should, however, be noted that Huynh and Meyer[9] have expressed some reservation on the distinction discussed above. According to these authors, the CPET terminology should be strictly reserved to when proton and electron are transferred to orbitals located in well separated sites.

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(21) The reduction potential of dpph• is 0.24 V vs SCE and that of *N*-Me-AcrH$_2^{+\bullet}$ is 0.8 V vs SCE, both values taken in MeCN.[17]

(22) In a more recent study, however, the reaction of *N*-Me-AcrH$_2$ with dpph• has been assumed to take place by a HAT mechanism.[3]

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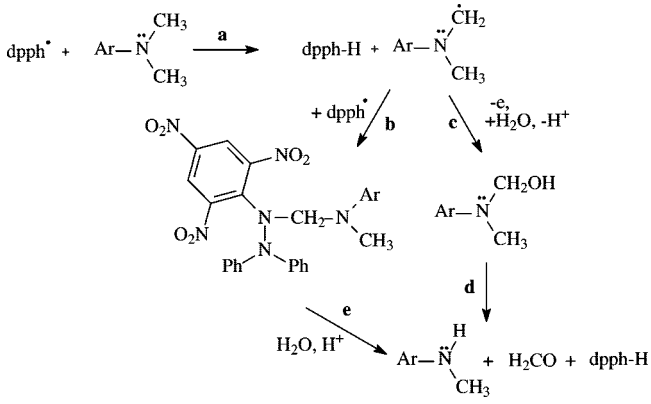
**TABLE 1. Substrate Oxidation Potentials, Kinetic Data, and Isotope Effects for the Reaction of dpph• with 4-X-Substituted *N*,*N*-Dimethylanilines in $CH_3CN$ at 25 °C**

| Substrate | $E^{\circ a}$ | $k_H$ ($M^{-1}$ $s^{-1}$)$^b$ | $k_D$ ($M^{-1}$ $s^{-1}$)$^{b,c}$ | $(k_H/k_D)_{inter}$$^b$ | $(k_H/k_D)_{intra}$$^{b,d}$ |
|---|---|---|---|---|---|
| **1** (X = H) | 0.76$^e$ | 1.6(2) × $10^{-3}$ | n.d. | 6.8(6)$^f$ | 5.5(4) |
| **2** (X = $CH_3$) | 0.61$^e$ | 8.0(2) × $10^{-3g}$ | 1.6(2) × $10^{-3}$ | 5.0(1)$^f$ 5.0(4)$^h$ | 5.2(2) |
| **3** (X = $OC_6H_5$) | 0.55$^i$ | 1.5(1) × $10^{-2}$ | 3.8(4) × $10^{-3}$ | 4.1(2)$^f$ 3.9(5)$^h$ | 3.6(1) |
| **4** (X = $OCH_3$) | 0.45$^e$ | 6.5(6) × $10^{-2j}$ | 1.7(1) × $10^{-2}$ | 3.6(3)$^f$ 3.8(3)$^h$ | 3.5(7) |

$^a$ V vs SCE in $CH_3CN$. $^b$ The number in bracket represents the error in the last digit. $^c$ Determined using 4-X-$C_6H_4N(CD_3)_2$ as substrates. $^d$ Determined by product analysis of the reaction of dpph• with 4-X-$C_6H_4N(CH_3)(CD_3)$. $^e$ Reference 24. $^f$ Determined by competitive experiments in the reaction of dpph• with equimolar mixture of 4-X-$C_6H_4N(CH_3)_2$ and 4-X-$C_6H_4N(CD_3)_2$. $^g$ $k_H$ = 7.5(5) × $10^{-2}$ $M^{-1}$ $s^{-1}$ in toluene. $^h$ Determined kinetically by the ratio $k_H/k_D$. $^i$ Reference 29. $^j$ $k_H$ = 1.0(1) $M^{-1}$ $s^{-1}$ in toluene.

**SCHEME 2**




indicated that two products were formed, namely *N*-methyl-*p*-toluidine and 1,1-diphenyl-2-picrylhydrazine (dpph-H). The formation of $CH_2O$ was also detected by its conversion into the dimedone adduct. $^1H$ NMR analysis of the reaction mixture performed before workup, however, indicated the presence of two additional singlets at 4.82 and 2.94 ppm (relative intensity = 2:3). These singlets were reasonably assigned (see Experimental Section) to a cross-coupling product of dpph• and an α-aminomethyl radical which, evidently, is converted into *N*-methyl-*p*-toluidine during workup. We made some attempts to isolate this intermediate, but it always decomposed during the chromatographic isolation procedure. The same products situation was observed when the reaction was run in the presence of $Mg(ClO_4)_2$ (1 mM), with the only difference that the reaction resulted much faster.

The most probable reaction sequence leading to the observed products is reported in Scheme 2. First, there is a hydrogen transfer step (Scheme 2, path **a**), whose mechanistic details will be discussed later, forming an α-amino carbon radical. This species can be easily oxidized (e.g., $E_{ox}$ = −0.85 V vs SCE for $C_6H_5N(CH_3)CH_2$•[26]) by dpph• ($E_{red}$ = 0.24 V vs SCE[21]) to the corresponding carbocation that, by reaction with adventitious water, undergoes *N*-demethylation with formation of formaldehyde and the secondary amine (eq 3, Scheme 2, paths **c**−**d**).

The other possibility is that the carbon radical couples with dpph• to form the adduct (Scheme 2, path **b**), from which the same *N*-demethylated product can be formed (path **e**). As steps **b** and **c** are expected to be very fast, there is no doubt that step **a** is the one controlling the reaction rate of the process, i.e., the disappearance rate of dpph•.

Thus, the kinetics of the reactions of *N*,*N*-dimethylanilines (DMAs) **1**−**4** with dpph• (30 μM) were studied in $CH_3CN$ at 25 °C by following the disappearance of dpph• spectrophotometrically at 517 nm. Using a strong excess of the substrate (at least 100 times), a first-order decay of dpph• was observed. From the first-order rate constants ($k_{obs}$) plotted against the substrate concentration, the second-order rate constants ($k_H$) for the hydrogen abstraction reaction of dpph• were calculated.[27] With substrate **2**, it was checked that there is no significant variation in the rate constant $k_H$ by changing the dpph• concentration in the range 15−90 μM or by addition of $dpph^-$ (15 μM). The values of $k_H$ for compound **1**−**4** are listed in the third column of Table 1. When the kinetic experiments were carried out in the presence of $Mg(ClO_4)_2$ (1 mM) a much faster decay of the dpph• absorption was observed for all the substrates investigated. Using a 10−100 molar excess of the substrate again a first-order decay of dpph• was observed. The second-order rate constants $k_H$ (obtained as before) for the reactions in the presence of $Mg^{2+}$ are reported in Table 2.

**TABLE 2. Kinetic Data and Isotope Effects for the Reaction of dpph• with 4-X-Substituted *N*,*N*-Dimethylanilines in $CH_3CN$ in the Presence of $Mg(ClO_4)_2$ (1 mM) at 25 °C**

| substrate | $k_H$ ($M^{-1}$ $s^{-1}$)$^a$ | $k_D$ ($M^{-1}$ $s^{-1}$)$^{a,b}$ | $(k_H/k_D)_{inter}$$^a$ | $(k_H/k_D)_{intra}$$^{a,c}$ |
|---|---|---|---|---|
| **1** (X = H) | 0.40(5) | 0.13(1) | 3.6(2)$^d$ 3.1(3)$^e$ | 4.0(2) |
| **2** (X = $CH_3$) | 2.6(2) | 0.9(1) | 3.2(1)$^d$ 2.9(4)$^e$ | 3.5(1) |
| **3** (X = $OC_6H_5$) | 0.71(8) | 0.24(2) | 3.6(3)$^d$ 3.0(5)$^e$ | 3.3(1) |
| **4** (X = $OCH_3$) | 4.6(3) | 1.5(1) | 3.1(1)$^d$ 3.1(3)$^e$ | 2.8(1) |

$^a$ The number in bracket represents the error in the last digit. $^b$ Determined using 4-X-$C_6H_4N(CD_3)_2$ as substrates. $^c$ Determined byproduct analysis of the reaction of dpph• with 4-X-$C_6H_4N(CH_3)(CD_3)$. $^d$ Determined by competitive experiments in the reaction of dpph• with equimolar mixture of 4-X-$C_6H_4N(CH_3)_2$ and 4-X-$C_6H_4N(CD_3)_2$. $^e$ Determined kinetically by the ratio $k_H/k_D$.

The intramolecular and the intermolecular DKIEs were also determined in the absence and in the presence of $Mg^{2+}$. The values of $(k_H/k_D)_{intra}$ were obtained by measuring (GC-MS and NMR analysis) the molar ratio between the dimedone adducts of $CH_2O$ and $CD_2O$ formed from the appropriate *N*-methyl-*N*-trideuteriomethylaniline. The values of $(k_H/k_D)_{inter}$ were obtained in two ways. First, by competitive experiments reacting equimolar mixtures of *N*,*N*-dimethylanilines and *N*,*N*-di(trideuteriomethyl)anilines with a much smaller amount of dpph• and measuring the molar ratio of the dimedone adducts of $CH_2O$ and $CD_2O$ produced in the reaction. Second, kinetically, by measuring the rate constants $k_D$ for the deuterium abstraction reaction from *N*,*N*-di(trideuteriomethyl)anilines (this, however, was not possible for **1** in the absence of $Mg^{2+}$, due to the too low reactivity) and comparing this value with the $k_H$ value for the hydrogenated counterpart. Generally, a good agreement was found between the $(k_H/k_D)_{inter}$ values determined by the two

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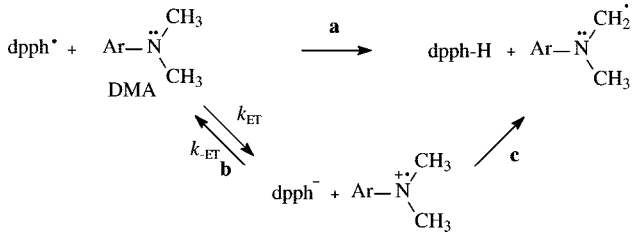
(27) Actually, the slope of plot was divided by two to obtain $k_H$ to account for the fact that two moles of dpph• are needed to form one mol of *N*-methylaniline.[28]

**SCHEME 3**




methods. All values of $(k_H/k_D)_{intra}$ and $(k_H/k_D)_{inter}$, in the presence and in the absence of $Mg^{2+}$, are collected in Tables 1 and 2, respectively.

## Discussion

As discussed in the introduction the main aim of our work was that of establishing whether the mechanism of the hydrogen transfer reaction of dpph• with DMAs (the initial step of the *N*-demethylation reaction) involves a two-step ET-PT mechanism (Scheme 3, paths **b** and **c**) as suggested for the reaction of dpph• with *N*-methylacridine[17] or a HAT(CPET) mechanism (Scheme 3, path **a**) as proposed for phenolic substrates.[2,8]

**Reaction in the Absence of $Mg^{2+}$.** Looking first to the reactivity data shown in Table 1, it can be clearly seen that the hydrogen transfer rate is increased by electron releasing substituents as expected for a reaction promoted by an electrophilic radical as dpph•. Using the substituents $\sigma^+$ values, a $\rho$ value of $-2.03$ is obtained by the very good Hammett plot ($r^2 = 0.994$) shown in Figure 1.[29]

This value may be compatible with an ET−PT mechanism, particularly when it is considered that a not much different $\rho$ value, $-2.5$, was obtained in the reaction of dimethylanilines with PINO, a reaction suggested to occur by an electron transfer process.[30] On the other hand, a $\rho$ value of around $-2$ may be also due to a hydrogen atom transfer mechanism involving a transitition state with significant polar character, a not rare situation in hydrogen transfer reactions induced by electrophilic radicals.[31,32]

A strong and decisive support to a single step hydrogen transfer mechanism comes, however, from the values of intermolecular and intramolecular deuterium kinetic isotope effect (DKIE) displayed in Table 1, which allow us to make a number of significant observations. First, for all substrates substantial values of DKIE are observed. Whereas this result confirms the key role of the C−H bond cleavage in the *N*-demethylation of *N*,*N*-dimethylanilines promoted by dpph• it also clearly excludes an ET-PT mechanism where the ET step is rate determining, since in this case DKIE values close to one would have been observed. Second, in all cases intermolecular and intramolecular DKIE values are very similar (practically within the experimental error) to one another. This result is that expected for a single step reaction and therefore perfectly fits in with a reaction where the hydrogen is transferred in a single step (path **a** in Scheme 2). The decrease of DKIE values by increasing the electron donating effect of the substituent can be reasonably accounted for by suggesting an earlier transition state (with a less extent of C−H bond cleavage) for substituents which make the reaction easier.[33,34]

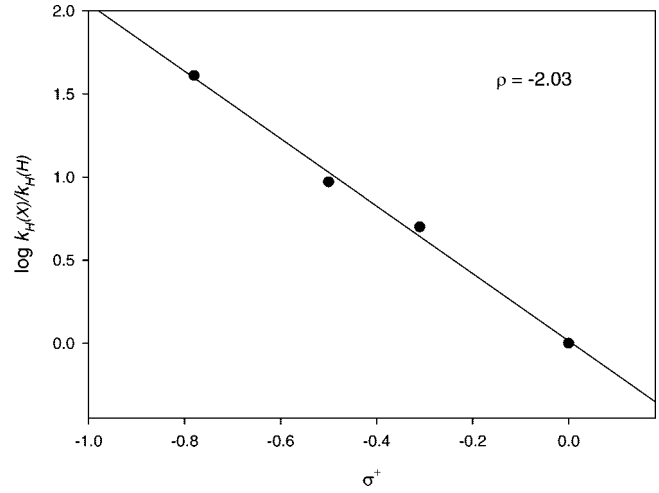



**FIGURE 1.** Dependence of the log $k_H(X)/k_H(H)$ for the reactions of *N*,*N*-dimethylanilines **1**−**4** with dpph• in $CH_3CN$ at 25 °C upon the Brown-Okamoto $\sigma^+$ constants.

For the two-step ET-PT mechanism, the observation of similar values of inter and intramolecular DKIE would require that the deprotonation of the radical cation (path **c** in Scheme 2) is rate determining and that the ET step is a preequilibrium. This possibility is made unlikely by the lack of a rate retarding effect by dpph⁻ shown by the excellent first order plots as well as by experiments in the presence of added dpph⁻.[36] Still more significantly, the slope value ($-0.22$ kcal$^{-1}$ K$^{-1}$) of the log $k_H/\triangle G°$ (kcal) plot (Figure 2) is very far from that predicted ($-0.73$ kcal$^{-1}$ K$^{-1}$) for an equilibrium-controlled electron transfer reaction.[37]

Further indication against the operation of an ET-PT mechanism can be found in the two following observations. First, the 4-methoxy derivative **4** reacts with dpph• at a slower rate than *N*-MeAcrH$_2$ whereas, in case of an ET-PT mechanism, the reverse should be expected as the oxidation potential of the former substrate (0.45 V vs SCE)[24] is much lower than that of the second (0.8 V vs SCE).[38] Second, the rate constants for the reactions of **2** and **4** were also measured in toluene and it was found that in this solvent the reactivity is higher than in MeCN (see footnotes g and j in Table 1). This result is in line with a

(28) Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 7947–7950.

(29) The correlation was much worse using the Hammett $\sigma$ constants.

(30) Baciocchi, E.; Bietti, M.; Gerini, M. F.; Lanzalunga, O. *J. Org. Chem.* **2005**, *70*, 5144–5149.

(31) Russell, G. A. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vol. 1, Chapter 7.

(32) For example, a $\rho$ ($\sigma^+$) value of $-1.6$ was obtained for the reaction of *N*,*N*-dimethylanilines with peroxyl radicals, a reaction that should occur by a HAT mechanism.[20]

(33) The same trend has been observed in the reaction of *N*,*N*-dimethylanilines with the *tert*-butoxyl radical, a reaction thought to involve a single-step hydrogen transfer.[25]

(34) The value of DKIE for the unsubstituted aniline **1** (ca. 7) suggests an almost symmetrical transition state with this substrate in spite of the endothermic character of the reaction. Other cases where the maximum isotope effect is on the endothermic side are reported.[35]

(35) Pryor, W. A.; Kneipp, K. G. *J. Am. Chem. Soc.* **1971**, *93*, 5584.

(36) It should be noted, however, that if deprotonation of the radical cation, eq 2 in Scheme 1, is carried out exclusively by dpph⁻, no retarding effect by dpph⁻ is expected in a preequilibrium ET mechanism. However, it is probable that substantial deprotonation by the solvent is also occurring in view of the extremely small concentration of dpph⁻ at the equilibrium.

(37) Kitaguchi, H.; Ohkubo, K.; Ogo, S.; Fukuzumi, S. *J. Phys. Chem. A* **2006**, *110*, 1718–1725.

(38) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305.

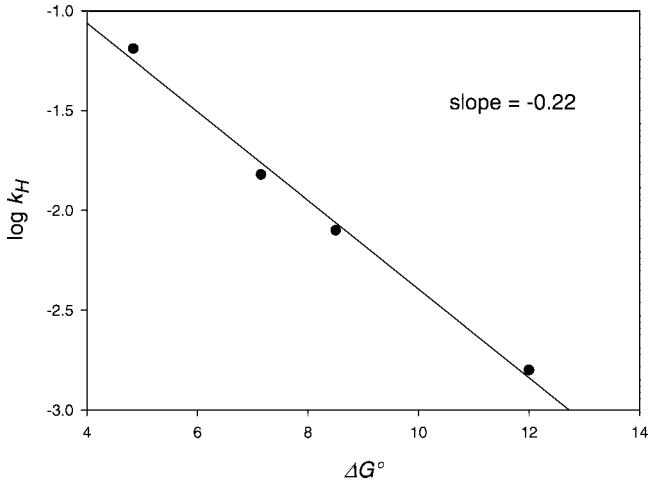
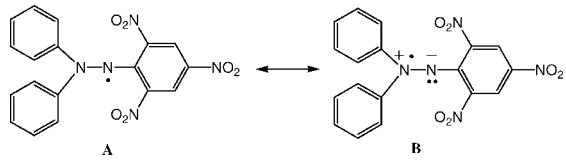


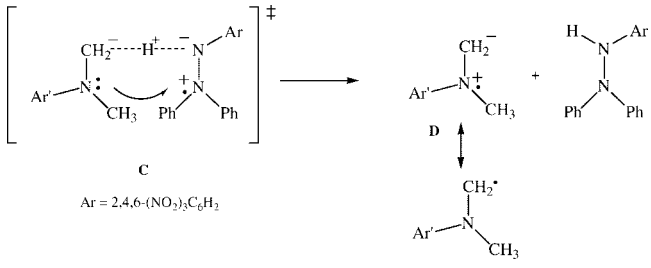

**FIGURE 2.** Dependence of the log $k_H$ for the reactions of *N*,*N*-dimethylanilines **1**−**4** with dpph• in $CH_3CN$ at 25 °C upon $\Delta G°$ values.

hydrogen transfer mechanism,[39,40] whereas the opposite solvent effect should be expected for an electron transfer mechanism.

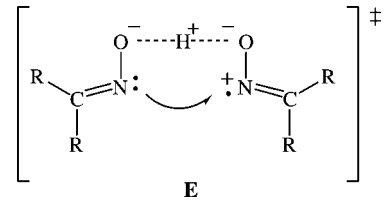


Summing up, it seems fairly safe to conclude that the reaction of dpph• with DMAs in MeCN, in the absence of $Mg^{2+}$, takes place by a HAT(CPET) mechanism characterized by a transition state with a substantial development of a positive charge at the amine nitrogen. The relatively large substituent effect appears more in line with a CPET rather than a HAT pathway (see ref 4). Accordingly, because dpph• is a resonance hybrid between structures **A** and **B**, it is possible to envisage a transition state structure (**C**) with the proton moving from the *N*-methyl group of the substrate to the partial negatively charged $N_1$ of dpph• whereas the electron moves from the amino group of the substrate to the partial positively charged $N_2$ of dpph• (Scheme 4).

**SCHEME 4**



This should lead to **D** that is an important resonance structure of the α-amino carbon radical. Of course, **C** is a limit structure and the electron might be transferred as well to the SOMO orbital delocalized on the two nitrogen atoms of the radical. Clearly, the transition state of this reaction path should be characterized by the presence of a significant extent of positive charge on the amine nitrogen, which might justify the relatively large and negative $\rho$ value,[42] as well as of negative charge on the amine carbon. It is very interesting to note that the five-center cyclic transition state **C** has a close resemblance with that (**E**) proposed by DiLabio and Ingold[6] on the basis of theoretical calculations, for the iminoxyl/oxime self-exchange reaction. In the transition state **E** preliminary formation of a H-bond was considered, however recently Di Labio et al. have suggested that this requirement may not be necessary.[7]



**E**

**Reactions in the Presence of $Mg^{2+}$.** Given the previous conclusion of a HAT (or CPET) mechanism, no kinetic effect by $Mg^{2+}$ was expected on the basis of the mechanistic criterion devised by Fukuzumi et al.[19] However, the outcome was completely different from expectations as shown by the results displayed in Table 2. Clearly, the presence of $Mg^{2+}$ ($1 \times 10^{-3}$ M) exerts a significant rate accelerating effect, still larger than that found with *N*-MeAcr$H_2$. A rate increase of about 300 times is observed for *N*,*N*-dimethylaniline and its 4-methyl derivative, for a 1 mM concentration of $Mg(ClO_4)_2$.[43] The rate acceleration is somewhat less with 4-methoxy and 4-phenoxy substituted anilines and this may be attributed to some coordination of $Mg^{2+}$ with the substituent oxygen, which somewhat reduces the substituent electron donating effect. Substantial values of DKIE were also measured in the presence of $Mg^{2+}$, but smaller than in the absence of this cation. However, inter and intramolecular DKIEs were again very similar, as observed in the absence of $Mg^{2+}$. Thus, there is no significant difference in the pattern of results (substituents and DKIEs) between the reaction in the presence and in the absence of $Mg^{2+}$.

This makes difficult to attribute the observed effect of $Mg^{2+}$ to a $Mg^{2+}$-induced mechanistic changeover for the reaction of DMAs: HAT(CPET) mechanism in the absence of $Mg^{2+}$ and ET mechanism in its presence. Accordingly, for the reactions in the presence of $Mg^{2+}$ too the similarity of inter and intramolecular DKIEs would require an equilibrium controlled ET, which is made unlikely by the relatively small substituent effects, as previously discussed. As a matter of fact, the *p*Me/H reactivity ratio is the same in the absence and in the presence of $Mg^{2+}$. Thus, it seems more reasonably to suggest that in the presence of $Mg^{2+}$ the mechanism remains unchanged (CPET pathway) and that the kinetic effect of this cation is probably due to a favorable interaction with the partial negative charge which, as already seen (structure **C**), should develop on the methyl carbon in the transition state. The observation of smaller DKIEs for the faster reaction in the presence of $Mg^{2+}$ may be

(39) Koner, A. L.; Pischel, U.; Nau, W. M. *Org. Lett.* **2007**, *9*, 2899–2902.
(40) This appears to be a general outcome for reactions involving hydrogen transfer from a C−H bond. These processes are generally slightly faster in solvents of lower polarity even when the transition state has a polar character. Entropy compensation effects are probably at play.[41]
(41) DeZutter, C. B.; Horner, J. H.; Newcomb, M. *J. Phys. Chem. A* **2008**, *112*, 1891–1896.
(42) In the HAT transition state, a partial positive charge should develop on the methyl carbon, which should make it more difficult to rationalize the $\rho$ value observed.
(43) Interestingly, in the reaction of dpph• with **2**, it was observed that the rate increases linearly with the $Mg^{2+}$ concentration and a reaction order of ca 0.3 was calculated (see Figure S6 in the Supporting Information).

again reasonably ascribed to an earlier position of the transition state along the reaction coordinate.

Finally, it seems important to point out that if our interpretation is correct, the present results cast some doubt on the generality of the hypothesis that the metal cation kinetic effect can represent per se a reliable criterion to distinguish HAT(C-PET) mechanisms from a full fledged ET mechanism.[17,19] There is little doubt that other proofs appear necessary before an ET mechanism can be firmly established.

## Experimental Section

**Product Analysis.** In a Schlenk tube, *N*,*N*-dimethyl-*p*-toluidine (0.057 mmol) was added to a solution of dpph• (0.015 mmol) in 4 mL of $CH_3CN$ degassed with argon for 20 min. The reaction mixture was stirred at 25 °C for 3 h. The solvent was then removed under reduced pressure, and the residue was treated with dilute HCl, then neutralized with NaOH 2N. 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 $^1$H NMR. Two products were observed: *N*-methyl-*p*-toluidine and 1,1-diphenyl-2-picrylhydrazine (dpph-H) (comparison with authentic specimens).

$^1$H NMR analysis of the reaction mixture carried out before the workup showed two additional singlets at 4.82 and 2.94 ppm, with relative intensity = 2:3. These singlets can be reasonably assigned to the to the cross-coupling product of dpph• and the α-aminomethyl radical (shown in Scheme 2); in particular, a singlet at 4.82 ppm can be predicted for the methylene group of this adduct on the basis of the additive effect of the diphenylpycrylhydrazyl and $C_6H_5N(CH_3)$ substituents on the shielding constant. Moreover, the singlet at 2.94 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 diphenylpycrylhydrazyl substituent. Clearly, the adduct is converted into the *N*-methyl-*p*-toluidine during the reaction workup. Attempts to isolate this adduct were unsuccessful because it was unstable during the chromatographic isolation procedure. 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). For the reaction in the presence of $Mg(ClO_4)_2$, *N*,*N*-dimethyl-*p*-toluidine (0.023 mmol) was added to a solution of dpph• (0.007 mmol) and $Mg(ClO_4)_2$ (0.002 mmol) in 2 mL of $CH_3CN$ degassed with argon for 20 min. The reaction mixture was stirred at 25 °C for 5 min. The solvent was then removed under reduced pressure and the residue was analyzed by $^1$H NMR. The major products were again *N*-methyl-*p*-toluidine, the adduct, and 1,1-diphenyl-2-picrylhydrazine (dpph-H).

The intramolecular $(k_H/k_D)_{intra}$ deuterium isotope effects were determined using the reaction procedure described above with *N*-methyl-*N*-trideuteriomethylanilines as substrates and measuring the ratio of the corrected signal intensities at $m/z$ = 292 and $m/z$ = 294 (corresponding to the dimedone adducts of $CH_2O$ and $CD_2O$ respectively). The results were confirmed in some cases by measuring the *N*-trideuteriomethylaniline/*N*-methylaniline ratio in the reaction mixtures. In the same way, intermolecular deuterium isotope effects $(k_H/k_D)_{inter}$ were determined by treating an equimolar mixture of *N*,*N*-dimethylanilines and *N*,*N*-di(trideuteriomethyl)anilines with dpph• and measuring the ratio of the corrected signal intensities at $m/z$ = 292 and 294.

**Spectrophotometric Kinetic Studies.** A solution of the substrate (**1**−**4**) was added into the solution of dpph• (30 μM) in $CH_3CN$ or toluene in the spectrophotometric cuvette (final substrate concentration in the range 20−80 mM for **1**, 5−60 mM for **2**, 4−30 mM for **3**, 3−60 mM for **4**) thermostatted at 25 °C. The absorbance changes at a single wavelength (517 nm) were recorded over total times ranging from 5 to 200 min. 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, at least 4 kinetic traces were averaged. It was verified that the decay of the absorbance in the absence of the substrate was negligible in the time span of the kinetics. Using the substrate **2**, it was checked that no significant variation of the rate constant $k_H$ was observed by changing the dpph• concentration in the range 15−90 μM or by the addition of dpph$^-$ (15 μM). For the experiments in the presence of $Mg(ClO_4)_2$, a solution of the substrate (**1**−**4**) (final concentration in the range 0.3−0.7 mM for **1**, 0.2−0.9 mM for **2**, 0.3−0.6 mM for **3**, 0.2−0.5 mM for **4**) was added into an MeCN solution of $Mg(ClO_4)_2$ (1 mM) and dpph• (30 μM) in the cuvette, and the absorbance change was monitored at 517 nm over total times ranging from 5 to 100 min. The effect of the $Mg^{2+}$ concentration (in the range 0.5−5.5 mM) on the reaction rate was analyzed in the reaction of dpph• (30 μM) with **2** (0.6 mM). Intermolecular DKIEs were determined kinetically, by the ratio of the $k_H$ values and the rate constants $k_D$ determined in the reaction with *N*,*N*-di(trideuteriomethyl)anilines.

**Acknowledgment.** Financial support from the Ministero dell'Università e della Ricerca (MUR) is gratefully acknowledged.

**Supporting Information Available:** Instrumentation, materials, dependence of $k_{obs}$ on substrate concentration for the reaction of *N*,*N*-dimethylanilines [**1**−**4**] with dpph• in $CH_3CN$ and toluene, and dependence of $k_{obs}$/[4-Me-DMA] on $Mg^{2+}$ concentration for the reaction of 4-methyl-*N*,*N*-dimethylaniline with dpph• in $CH_3CN$. This material is available free of charge via the Internet at http://pubs.acs.org.

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