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Chemical and Electrochemical Study on the Interactions of Aminoxyls with Superoxide Anion

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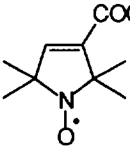
Abstract: The electrochemical behaviour of tetramethyl-pyrrolinic, -piperidinic, indolinonic and quinolinic aminoxyls and of oxygen was studied in DMF/H_2O in order to evaluate the feasibility of an electron transfer process between aminoxyls and superoxide anion. The rate constants of these reactions were calculated by applying the Marcus theory. A new mechanism for the reaction, which operates in competition with those already reported in the literature involving an electron transfer process, is proposed. Copyright © 1996 Elsevier Science Ltd

Aminoxyls can be divided into two main classes: those whose N-O$^•$ function is in-between two sp^3 carbons such as tetramethyl-pyrrolidine,[1] -piperidine,[1] imidazoline[2] and dialkyl[3] derivatives (aliphatic aminoxyls), and those whose N-O$^•$ function is conjugated with a benzene ring such as aryl,[3] indolinonic[4] and quinolinic[5] derivatives (aromatic aminoxyls). Both classes behave in a similar way with regard to the coupling reaction at the N-O$^•$ group with C-centered radicals;[6,7] however the reactivity of aromatic aminoxyls may also involve the conjugated benzene ring.[8] The compounds here described have been widely used as spin probes,[9] contrast agents,[10] antioxidants[11] and superoxide dismutase (SOD) mimics.[14] Furthermore they do not have very high redox potentials[12,13] and thus they can behave as electron donors or electron acceptors. It was in order to gain a deeper insight into the mechanism by which these aminoxyls mimic SOD that this study on the electrochemical behaviour of compounds **1-10** was carried out. Since the disproportionation of superoxide anion ($O_2^{-•}$) involves an electron transfer process, the voltammetric behaviour of dioxygen[15] was studied in the same experimental conditions in which the redox potentials of aminoxyls were measured in order to obtain comparable data.

Up to now, two mechanisms have been proposed for the aminoxyl-catalyzed dismutation of $O_2^{-•}$:[14] the first one, described in eqn.s 1 and 2, shows that at first the aminoxyl undergoes reduction to form the corresponding hydroxylamine which is oxidized in the second step to regenerate the starting aminoxyl; the second mechanism, described in eqn.s 3 and 4, shows that the aminoxyl is oxidized to an oxoammonium ion and subsequently reduced to the starting aminoxyl. However a careful determination of the redox potentials is necessary in order to evaluate the feasibility of the electron transfers shown in eqn.s 1-4 and the kind of mechanism which could be involved. The redox potentials measured in DMF/H_2O 6:4 (v/v) has allowed us to calculate the rate constants of eqn.s 1 and 3 by the application of the Marcus theory.[16]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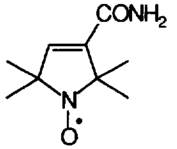
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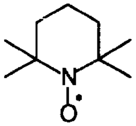
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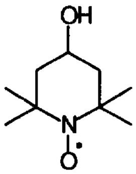
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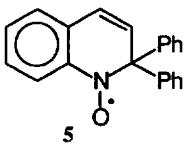
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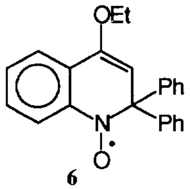
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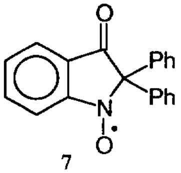
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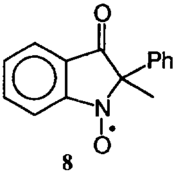
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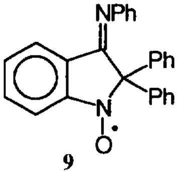
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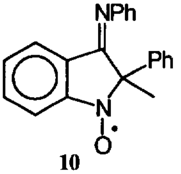
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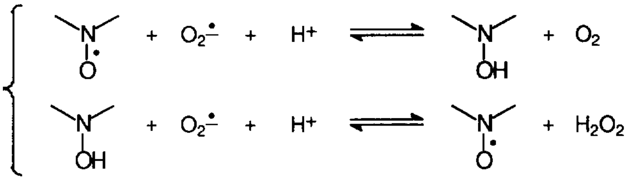
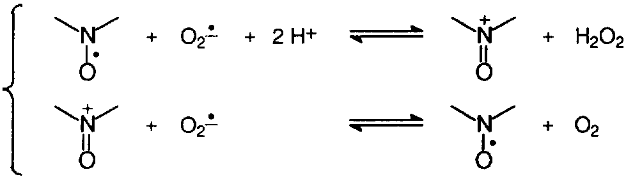
Mechanism 1


(1)

(2)

Mechanism 2


(3)

(4)

RESULTS

Electrochemical Measurements

The electrochemical study of compounds **1-10** in DMF/H_2O 6:4 (v/v) with tetramethylammonium perchlorate (TEAP), as supporting electrolyte, was carried out at a pulsed (polarographic experiments) or static (voltammetric experiments) glassy-carbon (GC) electrode, using a $SCE_{(DMF)}$[13a] as reference electrode.

Cathodic reduction of compounds **1-10.** While compounds **5-10** exhibit a well-defined polarographic wave, compounds **2-4** give a rather sloping wave, typical of irreversible systems, whereas compound **1** gives an undefined wave not measurable at GC. The half-wave potentials ($E_{1/2\ red}$) are reported in Table 1. Cyclic voltammograms show a *quasi*-reversible system for aminoxyls **5-10** and an irreversible broadened cathodic peak for aminoxyls **1-4**: the reduction occurs by one electron transfer leading to the formation of the corresponding hydroxylamino anion which probably undergoes fast protonation in the case of aminoxyls **1-4.** The E_{pc} values are reported in Table 1. Typical voltammograms of an aliphatic and an aromatic aminoxyl are reported in Figure 1.

Anodic oxidation of compounds **1-10.** All compounds **1-10** show a well-defined polarographic wave and their half-wave potentials ($E_{1/2\ ox}$) are reported in Table 1. Oxidation starts with the loss of one electron leading to the corresponding oxoammonium ion. Cyclic voltammograms show a reversible system for aminoxyls **1-4**, where only one electron is involved, whereas for compounds **5-10** the system is irreversible and involves more than one electron, as previously described.[13c,d] The E_{pa} values are reported in Table 1. Typical voltammograms of an aliphatic and an aromatic aminoxyl are reported in Figure 1.

Cyclic voltammetry of dioxygen. Dioxygen was studied in DMF/TEAP and in DMF/H_2O/TEAP, with an increasing ratio of water, at a static glassy carbon electrode *vs.* $SCE_{(DMF)}$,[13a] in the range of potentials +1.3 V ÷ -2.5 V.

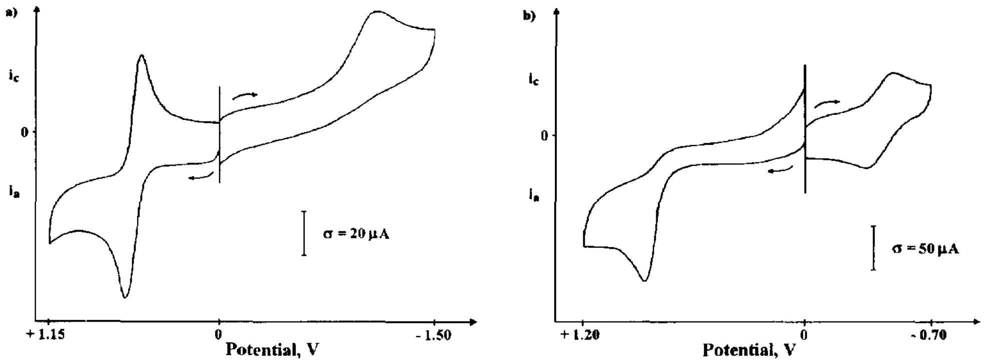


Figure 1. Cyclic voltammograms of (a) **3** and (b) **5** (1 × 10^{-3} M) in DMF/H_2O 6:4 (v/v) with TEAP 0.1 M, at GC electrode *vs.* $SCE_{(DMF)}$; scan rate 0.200 V s^{-1}.

According to the literature, cyclic voltammogram of dioxygen in aprotic medium exhibit two monoelectronic cathodic peaks: the first shows the corresponding anodic one (reversible process) while the irreversibility of the second peak may be due to the fast protonation of dianion O_2^{2-} to give HO_2^-, even in dry DMF (traces of water or the solvent itself). For increasing amounts of water, both peaks shift toward more positive potentials and when the ratio rises to 80% and beyond, the second wave merges with the first one and the cyclic voltammetry exhibits only one irreversible cathodic peak. Three significative voltammograms recorded in a) DMF, b) DMF/H_2O 6:4 (v/v), c) H_2O are shown in Figure 2. All the voltammograms exhibit an anodic peak at very positive potentials (+0.8 ÷ +1.0 V) rising from the protonation of the second reduction product of dioxygen that could be assigned to the system $HO_2^-/HO_2^\bullet$.

*Decomposition of $KO_2^\bullet$ in water in the presence of TEMPO (**3**) and/or dimethylamine*

On adding $KO_2^\bullet$ to a solution of dimethylamine in H_2O/OH^- it was possible to observe the signal of the dimethylaminoxyl formed by $^1O_2$ oxidation of dimethylamine.[17] The signal is stable for approximately 8 hours. The same experiment carried out adding TEMPO to the solution of dimethylamine in H_2O/OH^- gave similar results.

Table 1. Electrochemical data of compounds **1-10** (1 × 10^{-3} M) in DMF/H_2O 6:4 with TEAP 0.1 M at a GC electrode, *vs.* $SCE_{(DMF)}$ (NHE = $SCE_{(DMF)}$ + 0.253 V); scan rate 0.200 V·s^{-1}.

Aminoxyl	E_{pc}; (V)	$E_{1/2\,red}$;(V)	E_{pa}; (V)	$E_{1/2\,ox}$;(V)
1	- (*)	- (*)	+ 0.845	+ 0.785
2	- 1.190	- 0.950	+ 0.865	+ 0.820
3	- 1.100	- 0.835	+ 0.625	+ 0.580
4	- 1.155	- 0.825	+ 0.695	+ 0.645
5	- 0.460	- 0.400	+ 0.865	+ 0.760
6	- 0.440	- 0.380	+ 0.880	+ 0.785
7	- 0.310	- 0.260	+ 1.060	+ 0.970
8	- 0.325	- 0.280	+ 1.105	+ 1.010
9	- 0.415	- 0.345	+ 0.920	+ 0.855
10	- 0.430	- 0.350	+ 0.980	+ 0.905

(*) Voltammetric curves not well resolved because of the presence of the carboxylic function.

DISCUSSION

It is well known that in biological systems SOD[18] and catalase[19] are two enzymes which dismutate $O_2^{-\bullet}$ and decompose hydrogen peroxide, respectively, thus preventing the formation of radicals such as

$$O_2^{\bullet-} + H^+ \rightleftharpoons HOO^\bullet \tag{5}$$

$$HOO^\bullet + O_2^{\bullet-} + H^+ \xrightarrow{k = 10^8} O_2 + H_2O_2 \tag{6}$$

$$O_2^{\bullet-} + H_2O_2 \longrightarrow O_2 + HO^\bullet + HO^- \tag{7}$$

$$Fe(II)/Cu(I) + H_2O_2 \longrightarrow HO^\bullet + HO^- + Fe(III)/Cu(II) \tag{8}$$

hydroperoxyl and hydroxyl radicals. In fact, even though $O_2^{-\bullet}$ may be considered a weak base, it undergoes a very rapid protonation in water, being the protonation equilibrium (eqn. 5) shifted to the right because the formed hydroperoxyl is rapidly reduced to hydrogen peroxide (eqn. 6).[20,21] The high rate constant for eqn. 6 is justified by the high oxidant power of $HOO^\bullet$[22] and the low oxidation potential of $O_2^{-\bullet}$.[23] On the other hand if hydrogen peroxide is not decomposed to oxygen and water by catalase, it could lead to the formation of the dangerous hydroxyl radical (eqn.s 7 and 8).[24]

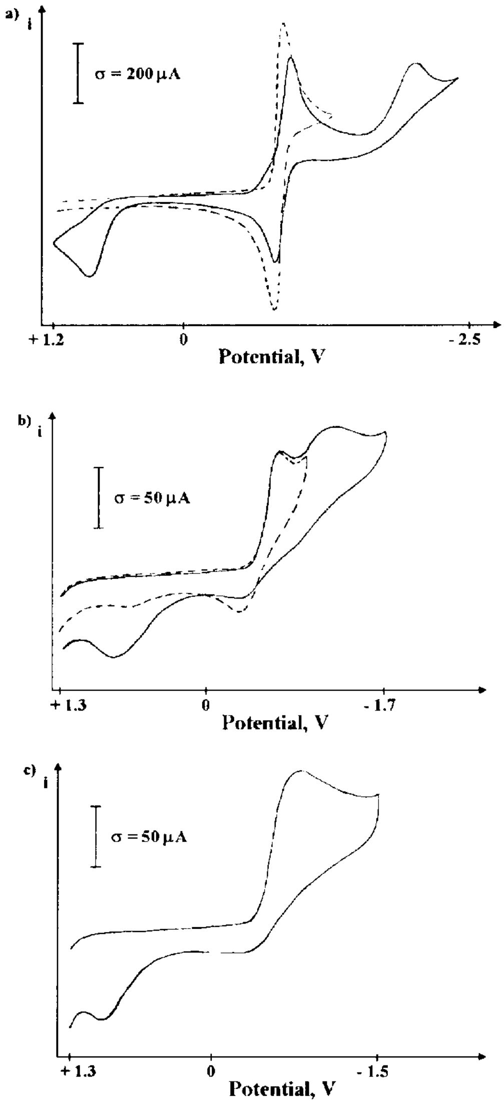


Figure 2. Cyclic voltammogram of O_2 in: a) DMF; b) DMF/H_2O 6:4 (v/v); c) H_2O.

To find other compounds able to mimic SOD is of extreme importance, as an alternative for detoxifying superoxide anion.[25] As stated in the introduction, two series of aminoxyls belonging to piperidine derivatives (six-membered ring), and oxazolidine and pyrrolidine derivatives (five-membered ring) have already been studied as SOD mimics.[14] On the basis of the obtained experimental data for piperidinyl and pyrrolidinyl derivatives, an aminoxyl-catalyzed dismutation mechanism, in agreement with that described in eqn.s 3 and 4 has been proposed; however such interpretation deserves more careful evaluation. In fact, one must bear in mind that the species responsible for oxidation of the aminoxyl to oxoammonium cation in eqn. 3, is the protonated form of $O_2^{-\bullet}$ and not superoxide itself as reported by Krishna et al.[14b] since the reduction potential of the latter is too negative to justify the oxidation of the aminoxyl.

The homogeneous electrochemical data for aminoxyls **1**-**10** and dioxygen in DMF/H_2O 6:4 reported in this paper can now be applied to discuss mechanisms 1 and 2.

Mechanism 1

For this mechanism the following two requisites are necessary:

i) the redox potential of the couple $N\text{-}O^\bullet/N\text{-}O^-$ must be less negative than the redox potential of the couple $O_2/O_2^{-\bullet}$ ($E_{1/2}$ = -0.575 V *vs.* $SCE_{(DMF)}$) (eqn. 1);

ii) the redox potential of the couple $N\text{-}O^\bullet/N\text{-}O^-$ must be more negative than the potential of the couple $O_2^{-\bullet}$, H^+/H_2O_2 (eqn. 2), or rather $HO_2^\bullet/HO_2^-$ (E_{pa} = +0.89 V *vs.* $SCE_{(DMF)}$).

From the data reported in Table 1 only aminoxyls **5-10** satisfy both conditions.

Mechanism 2

For this mechanism the following two requisites are necessary:

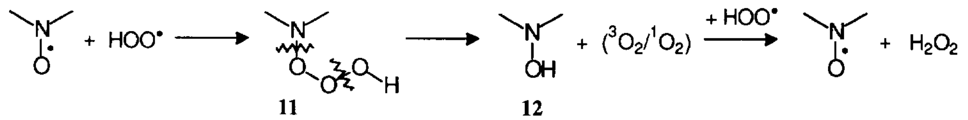
i) the redox potential of the couple $N{=}O^+/N\text{-}O^\bullet$ must be more negative than the redox potential of the couple $O_2^{-\bullet}$, H^+/H_2O_2 (eqn. 3);

ii) the redox potential of the couple $N{=}O^+/N\text{-}O^\bullet$ must be less negative than the redox potential of the couple $O_2/O_2^{-\bullet}$ (eqn. 4).

From the data reported in Table 1 none of the studied aminoxyls can be oxidized to the corresponding oxoammonium ion by the couple $O_2^{-\bullet}/O_2^{2-}$ whose value is even more negative than that of the couple $O_2/O_2^{-\bullet}$ (-0.575V *vs.* $SCE_{(DMF)}$). Instead, when comparing the redox couple $HO_2^\bullet/HO_2^-$ with aminoxyls, whose E_{pa} varies from +0.625 V to +1.105 V, we can conclude that aminoxyls having a $E_{1/2\ ox}$ less positive than that of $HO_2^\bullet/HO_2^-$ can be oxidized by $HOO^\bullet$ radical. Thus, from Table 1 it may be deduced that only aminoxyls **3-6** can be oxidized to the corresponding oxoammonium ion.

Other Mechanism

In addition to the mechanisms already proposed for the SOD mimic activity of aminoxyls, we have hypothesized that another type of mechanism could occur and therefore compete with the two mentioned above. This mechanism foresees a coupling between the $HOO^\bullet$ radical and aminoxyl forming adduct **11** as shown in Scheme 1. This intermediate could then cleave in the solvent cage giving off oxygen and hydroxylamine **12**. The aminoxyl is then regenerated by hydrogen abstraction on the hydroxylamine by $HOO^\bullet$ which forms hydrogen peroxide thus completing the catalytic cycle (Scheme 1).



Scheme 1

In order to obtain some evidence for this new mechanism, the decomposition of $O_2^{-\bullet}$, generated by $KO_2^\bullet$ in water, in the presence and in the absence of aminoxyl **3** was tested by EPR, using dimethylamine as spin trap for singlet oxygen,[17] whose formation has been excluded or admitted in very low yield[21] during the evolution of $HO_2^\bullet$. In the presence of aminoxyl **3** the decomposition of the intermediate **11** should increase the production of singlet oxygen. The experiments carried out in the EPR cavity showed that the intensity of the dimethylaminoxyl signal in the presence and in the absence of aminoxyl **3** was the same. Although the experiment did not support the formation of singlet oxygen from the decomposition of **11**, it, however, confirmed that singlet oxygen is produced in the termination reaction of $HO_2^\bullet$.

The mechanism proposed in Scheme 1 is in agreement with the results obtained by others using tertiary peroxy radicals[26] where alkylated hydroxylamines were formed from the decomposition of adducts similar to **11**. Also the self-reaction of tertiary peroxy radicals where intermediate tetroxides and trioxides are formed, is in accord with the proposed mechanism.[27]

Marcus' treatment

To know the order of magnitude of the rate constants of the first steps of mechanisms 1 and 2, the Marcus theory[16b] was applied to the electron transfer processes reported in eqn.s 1 and 3. For the Marcus treatment, the redox potentials measured in DMF/H_2O 6:4 were used and the reorganization energies (λ) were taken from the literature.[16b,28] Figure 3 shows the linear behaviour of the log *k* against the redox potentials and the aminoxyls that could be involved in both mechanisms.

Table 2. Free energy of activation and rate constants for eqn.s 1 and 3.

Aminoxyl	Eqn. 1		Eqn. 3	
	$\Delta G^{\#}$ (Kcal mol^{-1})	k_1 (M^{-1} s^{-1})	$\Delta G^{\#}$ (Kcal mol^{-1})	k_3 (M^{-1} s^{-1})
1	-	-	6.66	1.26E6
2	14.18	3.66	7.08	6.14E5
3	12.60	5.31E1	4.45	5.3E7
4	12.47	6.65E1	5.10	1.76E7
5	7.47	4.45E5	6.37	2.06E6
6	7.27	4.46E5	7.45	3.28E5
7	6.10	3.21E6	9.03	2.24E4
8	6.29	2.34E6	9.59	8.66E3
9	6.92	8.06E5	7.51	2.94E5
10	6.97	7.4E5	8.16	9.89E4

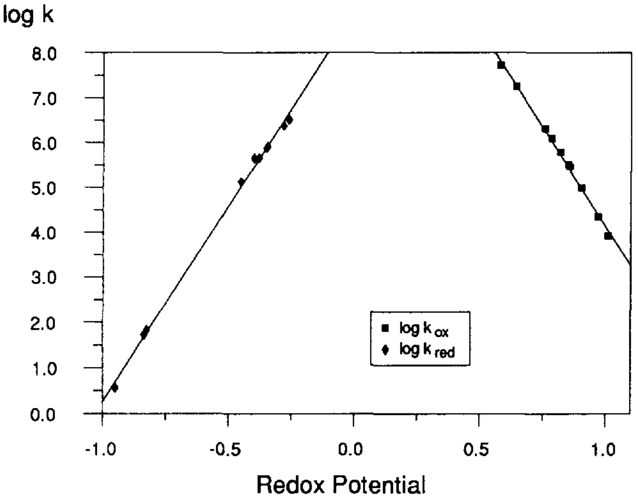


Figure 3. Linear behaviour of log k against E_{ox} (■) and E_{red} (♦) of aminoxyls **1-10**.

CONCLUSIONS

The data here described demonstrate that the species showing the most important role during the dismutation of $O_2^{-\bullet}$ in water is the hydroperoxyl radical and that both the mechanisms based on electron transfer can take place. This depends on the redox potential of the aminoxyl used. Moreover, an alternative mechanism could be operating in competition with those involving the electron transfer processes.

EXPERIMENTAL

Compounds **1**,[29] **2**,[29] **5**,[5] **6**,[5] and **7-10**,[4] were prepared according to the literature. Compounds **3** (TEMPO), **4** and dimethylamine hydrochloride were purchased from Aldrich and used without further purification. EPR spectra were recorded on a Varian E4 spectrometer interfaced with a PC and containing a ruby in the cavity as reference.

Electrochemical measurements

A three-electrode multipolarograph (AMEL 472) coupled with a digital x/y recorder (AMEL 863) was employed for the voltammetric measurements, carried out at a pulsed (polarographic measurements) or static (cyclic voltammetries) glassy-carbon electrode on nitrogen purged solutions of compounds **1-10**. Substrate concentration was about 1×10^{-3} M in DMF/H_2O 6:4 (v/v) containing TEAP 0.1 M to assure a good solubility for all of them in a partially aqueous medium. Hg-Hg_2Cl_2-NaCl (sat.aq.)-DMF-Et_4NClO_4/sintered glass disk[13a] was used as reference electrode, while a platinum wire was used as counter electrode. Cyclic voltammetric experiments were performed at the sweep rate of 0.200 V s^{-1} and polarographic ones at 0.005 V s^{-1}, both in reduction and oxidation scan. The same apparatus was used to study the electrochemical behaviour of dioxygen in: a) DMF/TEAP 0.1 M (saturated solution concentration of about 4.8×10^{-3} M); b) DMF/TEAP 0.1 M with increasing ratio of water (20%, 40%, 60%, 80%); c) H_2O/TEAP 0.1 M (saturated solution concentration of 1.3×10^{-3} M). Deionized water by Millipore Milli-Q Purification System was used. Throughout all the measurements the temperature was kept constant within 0.1°C. The accuracy of potentials reported in Table 1 is ±5 mV.

Decomposition of $KO_2^{\bullet}$ in water in the presence of TEMPO and/or dimethylamine

0.02 g of $KO_2^{\bullet}$ was added to solutions of dimethylamine (0.5 M, 5 ml) in H_2O/NaOH in the absence or presence of TEMPO (12.5×10^{-5} M). The resulting solutions were degassed with argon and tested after half an hour using 100 μl capillary tubes. The signal of dimethylaminoxyl was recorded and measured and compared with the signal of a ruby present in the cavity.

Marcus theory treatment

The results of the Marcus-type calculations are reported in Table 2. The standard free energy change of the putative ET step was not corrected by an electrostatic term. To compute the $\Delta G^{\#}$ by the Marcus expression [$\Delta G^{\#} = \lambda/4\ (1 + \Delta G^{\circ\prime}/\lambda)^2$ where $\Delta G^{\circ\prime} = (E^{\circ}_{ox} - E^{\circ}_{red}) \times 23.06$ Kcal mol^{-1} V^{-1}] the following data were used. Reorganization energy: $\lambda(NO^{\bullet}/NO^{-}) = 25$; $\lambda(O_2/O_2^{-\bullet}) = 50$; $\lambda(NO^{+}/NO^{\bullet}) = 20$; $\lambda(HO_2^{\bullet}/HO_2^{-}) = 30$. Redox potential: for aminoxyls see $E_{1/2}$ in Table 1; for dioxygen: $E^{\circ}(O_2/O_2^{-\bullet}) = -0.575$ V *vs.* $SCE_{(DMF)}$ and $E^{\circ}(HO_2^{\bullet}/HO_2^{-}) = +0.75$ V *vs.* $SCE_{(DMF)}$ (estimated from the cyclic voltammogram). For the calculation of the rate constant, the Arrhénius equation was used.

ACKNOWLEDGEMENTS

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