Triplet ground state ($S = 1$) pegylated bis(aminoxyl) diradical: synthesis and the effect of water on magnetic properties†

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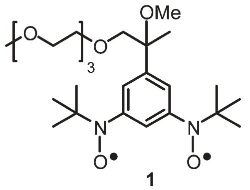
The synthesis and magnetic characterization of pegylated bis(aminoxyl) diradical with an $S = 1$ ground state are presented, revealing water-induced changes in the molecular conformation and magnetic properties.

Triplet ground state ($S = 1$) organic diradicals with strong ferromagnetic coupling are widely used as building blocks for organic and organometallic magnets.[1–3] Only a few diradicals are both stable at ambient conditions and possess ferromagnetic coupling of such strength that the singlet–triplet energy gap ($2J$) is far greater than the thermal energy at room temperature.[1,3] Nonadditive properties of such strongly-coupled $S = 1$ diradicals, which are enhanced compared to those of two independent (or weakly coupled) $S = ½$ radicals, have not been significantly explored beyond organic magnetism. In particular, understanding of the effect of water on structure and magnetic properties of $S = 1$ diradicals (and high-spin polyradicals) is important for their applications in biological media.[4]

In biological and polymer sciences, organic radicals, especially aminoxyls, are intensively studied as spin labels, contrast agents for magnetic resonance imaging (MRI), antioxidants, and mediators for controlled radical polymerization.[5–9] Numerous synthetic approaches to water soluble aminoxyls have been reported,[9] to facilitate biological applications and polymerization in water. Recently, water soluble bis(aminoxyl)s and oligo(aminoxyl)s were investigated in biological sensing and magnetic imaging;[6–8,10] however, only weakly-coupled bis(aminoxyl)s and oligo(aminoxyl)s, which may be viewed as ensembles of independent $S = ½$ radicals at room temperature (above ~1 K), were prepared and studied.

One of the specific areas, in which water-soluble and strongly-coupled $S = 1$ diradicals would be of great interest, includes contrast agents for MRI, currently dominated by the complexes of $S = 7/2$ $\mathrm{Gd^{III}}$ and other paramagnetic metal ions.[11] In conjunction with the favorable *in vivo* properties of aminoxyls and theoretically predicted proportionality of relaxivity to $S(S + 1)$,[12,13] bis(aminoxyl)s and oligo(aminoxyl)s with $S > ½$ at room temperature provide novel insight into the design and understanding of contrast agents for MRI.[6,7]

In this paper, we describe the synthesis of polyethylene glycol (PEG) functionalized (pegylated) $S = 1$ diradical **1** and $S = ½$ monoradical **2**, and their magnetic characterization in various media, including water.



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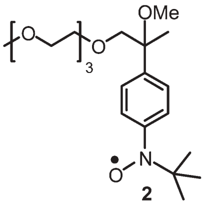

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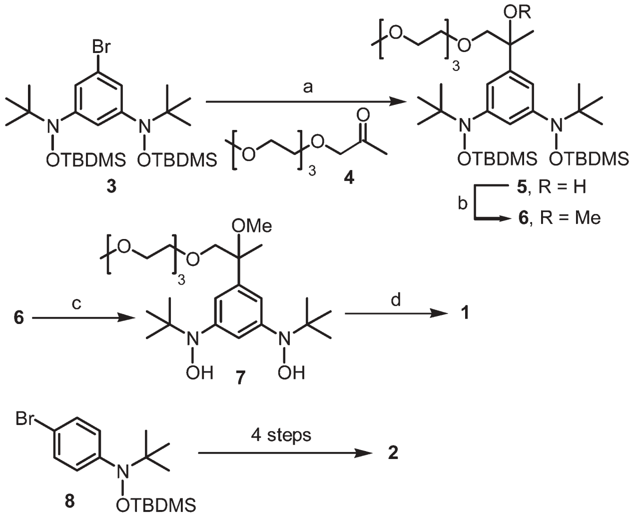
The synthesis of diradical **1** is outlined in Scheme 1.‡ The Li–Br exchange on bromobenzene **3**,[14] followed by the addition of pegylated ketone **4**, provides alcohol **5**. After etherification of **5**, the ether **6** is treated with TBAF, to give dihydroxylamine **7**. Oxidation of **7** with Ag_2O yields diradical **1**. An analogous synthetic route, starting from **8**[15] (Scheme 1), provides monoradical **2** in overall yield of 33% for four steps.‡ This synthetic approach should be readily applicable to the preparation of pegylated radicals.

The EPR spectra of 1 mM **1** in toluene, ethanol, water–ethanol (1 : 2), and water–glycerol (2 : 1) at 140 or 135 K show the expected dipolar patterns for $S = 1$ states, including a moderately intense half-field signal. The spectra in toluene, obtained after slow cooling from room temperature to 140 K, are assigned to a single $S = 1$ diradical, with zero-field splitting (zfs) parameters,



Scheme 1 *Reagents and conditions:* (a) *n*-BuLi (1.2 equiv.), THF, −78 °C to room temperature (65%); (b) NaH (5 equiv.), MeI (5 equiv.), THF, 0 °C to 45 °C (90%); (c) TBAF (4.6 equiv.), THF, room temperature (95%); (d) Ag_2O (10 equiv.), $CHCl_3$, room temperature (44%).

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$|D/hc| = 1.24 \times 10^{-2}$ cm^{-1} and $|E/hc| = 1.13 \times 10^{-3}$ cm^{-1} (Fig. 1). For rapidly cooled water-containing solutions of **1** (water–ethanol and water–glycerol), the EPR spectra may be assigned to two $S = 1$ diradicals, presumably conformers. The spectral simulations of the $\Delta m_s = 1$ regions show that the major and the minor $S = 1$ diradicals have relatively smaller ($\sim 1.2 \times 10^{-2}$ cm^{-1}) and larger ($\sim 1.7 \times 10^{-2}$ cm^{-1}) values of $|D/hc|$, respectively. For **1** in water–ethanol (1 : 2), the relative content of the $|D/hc| \approx 1.7 \times 10^{-2}$ cm^{-1} diradical is about 10% *vs.* 30% in water–glycerol (2 : 1). These results suggest that **1** in water at room temperature may exist as two conformers (diastereomers) with different dihedral angles between the nitroxide moieties and 1,3-phenylene.[16] Such conformers would possess, in principle, different singlet–triplet energy gaps ($2J$).

The $S = 1$ ground state and the value of $2J$ were determined by SQUID magnetometry. Plots of χT *vs.* T (χ, molar magnetic susceptibility) for neat diradical **1** show a maximum of $\chi T_{\max} = 0.91$ emu K mol^{-1} near 100 K, with significant drop-offs at both higher and lower temperatures (Fig. 2). An excellent numerical fit to these data is obtained with three variable parameters (eqn (1S), ESI†): singlet–triplet energy gap ($2J/k = 650$ K or $2J = 1.3$ kcal mol^{-1}), mean-field parameter for intermolecular interactions ($\theta = -2.2$ K), and mass factor ($w = 0.93$).[17] These results indicate that diradical **1** possesses the $S = 1$ ground state. However, the singlet–triplet energy gap of **1** exceeds RT at room temperature by a factor of 2–3 only, leading to significant population of the singlet excited state at room temperature. The value of $2J/k$ may be affected by out-of-plane twisting of the aminoxyl moeties, caused by the sterically large PEG-based substituent.[16]

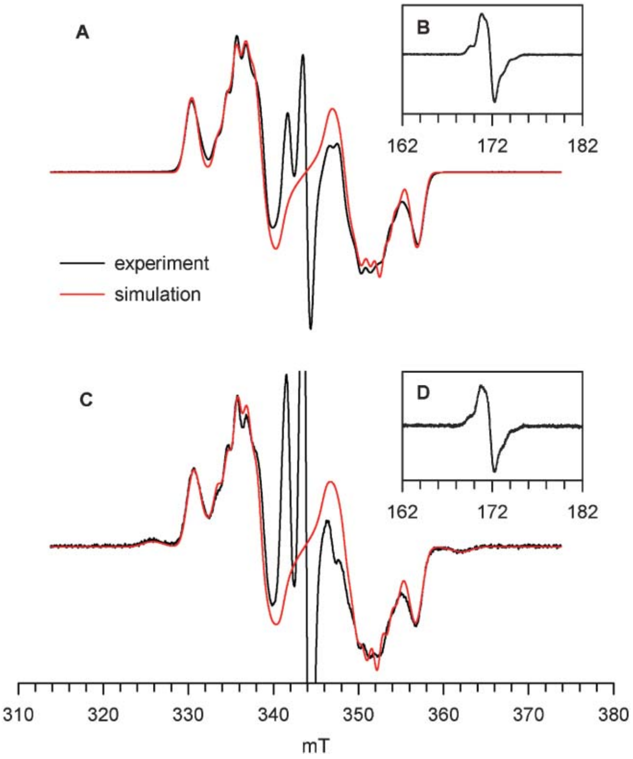

Fig. 1 X-Band EPR spectra for diradical **1** in toluene (plots A for $\Delta m_S = 1$ and B for $\Delta m_S = 2$) and EtOH–water (2 : 1, plots C for $\Delta m_S = 1$ and D for $\Delta m_S = 2$) at 135–140 K. In plots A and C, the simulations correspond to one $S = 1$ diradical and a mixture of two $S = 1$ diradicals, respectively. The center lines, most likely corresponding to $S = ½$ monoradical impurities, are not simulated. Parameters for the simulations are shown in Fig. 11S–13S (ESI).†

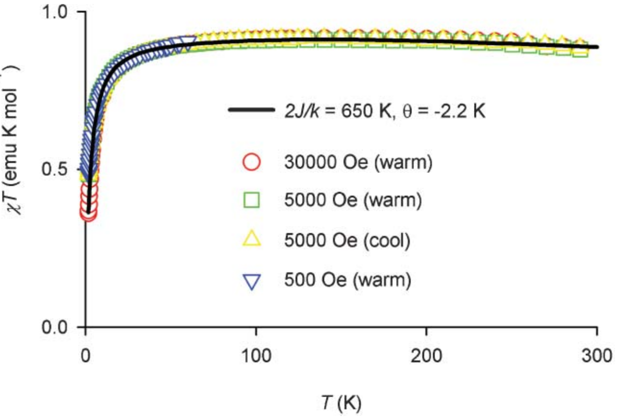

Fig. 2 Plots of χT *vs.* T for diradical **1**. For the plot at magnetic field $H = 500$ Oe, the temperature range is $T = 1.8$–60 K; for all other plots, $T = 1.8$–290 K. The solid line shows an example of numerical fit to the experimental data at $H = 30000$ Oe, using eqn (1S) (ESI).†

For 17–25 mM **1** in D_2O, qualitatively similar χT *vs.* T plots are obtained. Notably, intermolecular antiferromagnetic interactions remain significant ($\theta \approx -2$ K), suggesting aggregation of **1** in water. Partial population of the singlet excited state at room temperature is also consistent with the values of magnetic susceptibility obtained from ^1H NMR using the Evans method: $\chi T = 0.81 \pm 0.03$ emu K mol^{-1} for 15–21 mM **1** in H_2O–D_2O ($\sim$1 : 1) at 295–298 K is obtained.[18] Notably, a ^1H NMR resonance for the *tert*-butyl groups of the aminoxyl moieties appears at −6.9 ppm in D_2O *vs.* at −2.3 ppm in $CDCl_3$. The upfield ^1H chemical shift in D_2O suggests increased localization of spin density at the aminoxyl moieties, as observed in sterically hindered bis(aminoxyls), in which aminoxyl moieties are twisted out of the plane of the 1,3-phenylene.[19] This out-of-plane twisting is also consistent with the EPR spectra of **1** in water-containing matrices showing the presence of a conformer with relatively large value of $|D/hc| \approx 1.7 \times 10^{-2}$ cm^{-1}.[20]

We postulate that strong solvation of the PEG moiety of **1** in the presence of water increases its effective volume, to increase the twisting of the aminoxyls out of the plane of the 1,3-phenylene. This in turn, weakens the exchange coupling between the aminoxyls, thus decreasing the singlet–triplet energy gap for **1** in water.

Longitudinal relaxation times (T_1) of protons in water were measured at 200 MHz, as a function of the concentration of **1** and **2** at 298 K. Relaxivities are obtained from the slopes of $1/T_1$ *vs.* concentration plots (Fig. 3). Relaxivities of 0.20 and 0.14 s^{-1} mM^{-1} are obtained for **1** and **2**, respectively.[21] Therefore, the experimental relaxivity per aminoxyl moiety is significantly lower in diradical **1** *vs.* monoradical **2**. This is in contrast to the higher relaxivity per aminoxyl in an $S = 1$ diradical predicted from the relative values of $S(S + 1) = 0.75$, 1.5, and 2.0 for an $S = ½$ monoradical, a weakly coupled diradical, and an $S = 1$ diradical, respectively. This is consistent with the weakened exchange coupling for **1** in water but it implies that other factors decrease

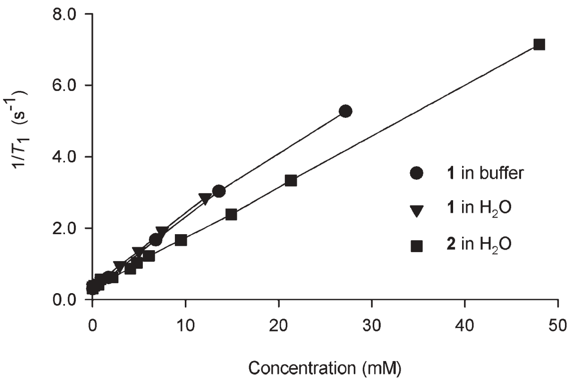

Fig. 3 Plots of $1/T_1$ (for protons of water) *vs.* mM concentration of diradical **1** and monoradical **2** in H_2O or phosphate buffer (50 mM, pH 7.2).

the relaxivity in **1** as well. Aggregation of **1** would affect both rotational correlation time and access of water (the exchange rate of water). Furthermore, the electronic T_1 of **1** may be lowered, due to modulation of zfs and/or $2J$.[13]

In summary, a versatile synthetic route to pegylated aminoxyls is developed, making available water-soluble high-spin diradicals for biologically related studies. Furthermore, discovery of the water-induced changes in molecular conformation and magnetic properties in the present work suggests that structures with constrained, planarized conformations may be required to obtain high-spin diradicals with $2J >> RT$ in water at room temperature. The synthesis of such diradicals and their assembly into well-defined, water accessible, high-symmetry structures with negligible zfs is in progress in this laboratory.

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Notes and references

‡ For details of synthesis and characterization of compounds **1**, **2** and their synthetic intermediates (*e.g.*, **4–6** for **1**), see ESI.

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