Suppression of spin-spin coupling in nitroxyl biradicals by supramolecular host-guest interactions[†]

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The use of supramolecular architectures to control the spatially dependent spin exchange (spin communication) between two covalently linked radical centers (biradical) has been explored. Cucurbit[8]uril, through supramolecular steric effect, completely suppresses spin exchange between two adjacent radical centers in a biradical.

Recently there has been a renaissance in the application of dynamic nuclear polarization (DNP) as a general method of enhancement of NMR signal intensities with potential applications for magnetic resonance imaging (MRI).¹ The 'tuning' of the electron- and nuclear-spin systems can be achieved by rendering their spin transition frequencies degenerate. One such method is the use of biradicals as the coupling source.² In this case, the system corresponds to a three-spin pool of two coupled electrons and a coupled nuclear spin. The efficiency of DNP in the three-spin system can be controlled by optimizing the interaction between the coupled electrons in biradicals. A significant amount of work has been reported on nitroxyl biradicals.³ Mainly these studies show how spin-spin coupling can be controlled by the distance between the nitroxyl moieties. In this report, we demonstrate that control of spin-spin coupling in biradicals can also be achieved through supramolecular effects.

To unravel the value of supramolecular architectures in controlling spin communication between two nearby radical centers, we have examined the EPR spectra of three binitroxyls^{3a} namely (Scheme 1), di-4-(2,2,6,6-tetramethylpiperidine-1-oxyl)-terephthalate (1), di-4-(2,2,6,6-tetramethylpiperidine-1-oxyl)-isophthalate (2) and di-4-(2,2,6,6-tetramethyl-piperidine-1-oxyl)-phthalate (3) in water in the presence of hosts such as cucurbit[8]uril (CB8), cucurbit[7]uril (CB7), β -cyclodextrin (β -CD), γ -cyclodextrin (γ -CD), calixarene[8]octa sulfonic acid (CA8) and sodium dodecyl sulfate (SDS) micelle (see ESI†, Fig. S1). We find that the host CB8 is most effective

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Scheme 1 Binitroxyls (1-3), mononitroxyl (4) and corresponding diamagnetic derivative (5) examined in this study.

and completely suppresses spin exchange between the two radical centers in 3.

To compare guests (1–3) in the absence/presence of the various hosts, their reference EPR spectra were recorded in DMSO–water (1 : 1) in the case of the first two (due to low solubility in water) and in pure water in the case of 3. Experimental and simulated spectra are displayed in Fig. 1. The spectra were computed using the well-established procedure of Freed and co-workers.⁴ The most informative input parameters were the coupling constant between electron and nuclear spins $\langle A_N \rangle = (A_{xx} + A_{yy} + A_{zz})/3$ which is a measure of the environmental polarity of the nitroxides and the correlation time (τ) for the rotational diffusion motion of the spin probe which provides information about the guest mobility.

Binitroxyls 1 and 2 exhibit three-line spectra typical of mononitroxyls, indicative of their radical centers being too far apart for spin-spin exchange interactions. The EPR spectrum of compound 3 is distinctly different from that of 1 and 2. It showed a five-line spectrum, which means that each



Fig. 1 EPR spectra (black lines) and their simulations (red lines) for (a) **1** in 50% DMSO and 50% water (0.5 mM), $A_N = 16.5$ G, $\tau = 0.14$ ns, (b) **2** in 50% DMSO and 50% water (0.5 mM), $A_N = 16.4$ G, $\tau \approx 0.19$ ns; (c) **3** in water (1 mM) three-line component: $A_N =$ 16.9 G, $\tau = 0.06$ ns, five-line component: 88% and (d) **3**@CB8 (1 : 1), $A_N = 16.7$ G, $\tau = 0.21$ ns. Concentrations of host and guest: 1 mM.

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[†] Electronic supplementary information (ESI) available: Structures of hosts employed, ¹H NMR and EPR spectra of **4**, EPR spectra of **1**, **2** and **3** under various conditions, experimental procedure including synthesis and characterization of compounds **1–4**.

electron is coupled to both nitrogens of the binitroxyl. The EPR spectrum of **3** is attributable to fast inter-conversion between conformers exhibiting weak $(J \approx 0)$ and strong $(J \gg A_N)$ exchange interaction.

For computational convenience, we view this five-line spectrum as the sum of a three-line signal and a two-line signal. Both a three-line signal and a two-line signal (in between the three lines) were computed, and the experimental line shape was fitted by adding the two components at the proper relative percentages. The variation of the exchange interaction between two radical centers in various systems was estimated by calculating the intensity (in percentage) of a five-line signal expected for very strong exchange with respect to the overall spectral intensity obtained by double integration of the experimental spectra.

The three lines (1, 3 and 5) or the two lines (2 and 4) in the five-line EPR spectra of **3** in water are separated by 16.9 G, slightly lower than the hyperfine splitting of a 2,2,6,6-tetramethyl-piperidine-1-oxyl radical (monoradical) in water (17.1 G). The correlation time (τ) of 0.06 ns is characteristic of fast rotating nitroxyl radicals.⁵ The estimated relative percentage of the exchange coupling (1 : 2 : 3 : 2 : 1) is 88%, which indicates that the two nitroxyl groups in the biradical dynamically approach each other in water resulting in strong spin–spin exchange.

Of the three compounds, 3 is clearly the best candidate to test the influence of supramolecular hosts on spin-spin exchange between two radical centers. It is well known that mononitroxyls such as 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and 4-(N,N,N-trimethylammonium)-2,2,6,6-tetramethylpiperidine-N-oxyl bromide (a positively charged TEMPO derivative) can be included within the cavities of CD, CB and CA and micelles. The question is whether such an inclusion would affect the exchange interaction between two nearby nitroxyl centers in molecules such as 3. In Fig. 1(d), the EPR spectra (experimental and simulated) of 3 in the presence of one equivalent of CB8 are displayed. Interestingly, the change of the five-line spectrum to a three-line spectrum in the presence of CB8 is suggestive that one equivalent of this host is sufficient to eliminate the spin-spin exchange interaction. The absence of any effect on the spectrum on addition of more than one equivalent of CB8 suggests that only one of the two nitroxyls is included within CB8. From simulation of the EPR spectrum, it is observed that τ increases from 0.06 ns in pure water to 0.21 ns in the presence of one equivalent of CB8. The conclusion that only one nitroxyl group of 3 is complexed to CB8 is supported by two observations: (a) almost no change was observed for τ between one and two equivalents of CB8 (0.21 ns vs. 0.24 ns); (b) estimated polarities of the nitroxyl environment based on the hyperfine splitting constant (A_N) decreases slightly in the presence of CB8 from that in pure water (16.9 G for 3 in water and 16.7 G for 3@CB8 in water).⁶ Further addition of CB8 did not change $A_{\rm N}$. Similarities in polarity experienced by the nitroxyl radical in 3 and 3@CB8 in water suggest that one of the two nitroxyl groups in 3@CB8 remains uncomplexed and is exposed to water. It was confirmed by double integration of the EPR signal of 3 free in solution and 3@CB8 that both nitroxyl radicals in 3 in the presence of CB8 are contributing to the 3-line signal intensity



Scheme 2 Schematic representation of the possible conformers of 3 and 3@CB8.

(for details see Fig. S6 in ESI[†]). No nitroxyl radicals were lost due to chemical reactions. Based on these results we conclude that the supramolecular steric effect provided by encapsulation of one paramagnetic moiety of **3** with CB8 is sufficient to eliminate the spin communication between the two nitroxyl radicals, one complexed to CB8 and one free (Scheme 2). In Scheme 2 we have shown three of the many possible conformations of **3**. Because of the broad NMR signals ¹H NMR NOESY spectra were not useful in identifying the preferred conformation for this molecule. We conclude that spin communication is suppressed by adoption of a conformation where the two nitroxyl groups in **3**@CB8 are separated far enough not to exchange each other's spin or the CB8 cage wall is a barrier for spin–spin coupling.

¹H NMR and EPR experiments with monoradical 4, a molecule analogue to 3 (Scheme 1) but with one diamagnetic N-CH₃ group and one paramagnetic NO group supported our conclusion about the formation of a 1:1 (guest to host) complex with CB8. NMR spectra of 4 in CDCl₃, D₂O and in the presence of one equivalent of CB8 are shown in Fig. S2 (ESI[†]). In water, the paramagnetic nitroxyl probably broadens the ¹H NMR signals of the tetramethyl groups of the adjacent *N*-methylpiperidinyl suggesting the existence of $electron^{-1}H$ spin communication between the two groups. Addition of one equivalent of CB8 to 4 in water resulted in sharper ¹H NMR signals as well as an upfield shift of the signals of N-methylpiperidinyl group. Addition of more than one equivalent of CB8 resulted in a turbid solution that prevented recording of the NMR spectrum. Thus, inclusion of one of the two groups within CB8 was sufficient to arrest the influence of paramagnetic nitroxyl on the diamagnetic N-methylpiperidine group. To probe which of the two groups is included within CB8 we recorded the EPR spectrum (experimental and simulated spectra are provided in ESI[†]; Fig. S3). Computation of the EPR spectra of 4 in the absence/presence of CB8 showed that the hyperfine splitting is almost the same (free: $A_{\rm N} = 16.9$ G; and complexed to CB8: $A_{\rm N} = 17$ G) suggesting that the paramagnetic nitroxyl moiety is located in water outside the CB8 cage. However, the rotational correlation time of 4 in the presence of CB8 was slightly larger compared to 4 free in solution (complexed: 0.14 ns; free: 0.04 ns) which is probably caused by steric hindrance of the rotational

mobility of the paramagnetic moiety by the complexation of the diamagnetic moiety with CB8. The above results thus suggest that the less hydrophobic piperidine moiety is included within CB8.

To further confirm that only one of the two groups in **3** was included within CB8 we synthesized diamagnetic equivalent compound **5** and recorded its ¹H NMR spectra in water in the presence and absence of CB8 (Fig. S4 and S5 in ESI†). Upon addition of one equivalent of CB8 only the N–CH₃ signal was upfield shifted indicating that only this group is included within CB8. Consistent with this, signals due to the four methyl groups of the *N*-methylpiperidyl ring alone were upfield shifted. Addition of more than one equivalent of CB8 resulted in no change in the spectra suggesting that **5** similar to **3** and **4** forms 1 : 1, not 1 : 2 (guest : host), complex with CB8. Since **5** and **5**@CB8 complex had a very limited solubility in water we could not carry out NOESY studies to ascertain the conformation of complexed and uncomplexed **5**.

Having established CB8's ability to fully suppress the spin-spin exchange between adjacent nitroxyl groups in 3 we were interested in comparing this feature with hosts such as CB7, β -CD, γ -CD, CA8 and SDS micelles.⁷ The EPR (experimental and simulated) spectra obtained upon addition of two equivalents (guest to host: 1:2) of the first four hosts and in the presence of excess of SDS surfactant are provided in Fig. S8 (ESI⁺). A large excess of SDS (1 : 1200) was necessary to avoid the presence of two or more molecules of 3 in one SDS micelle, which causes intermolecular spin-spin interaction due to Heisenberg exchange. Even in the presence of a large excess of SDS a 'broad' single line EPR Heisenberg component (Fig. S8g, inset, ESI⁺) contributes to the overall EPR signal for about 45%. This component was present even in the case of γ -CD complex to the extent of 10%, which is probably caused by the poor solubility of γ -CD complex. The % of five-line spectrum (strong spin-spin exchange component) thus obtained for various hosts are displayed in the form of histograms in Fig. 2. The exchange interaction that totally disappeared in the presence of CB8 persisted to various degrees (28–79%) in other hosts. While the most exciting result was obtained with CB8, the most surprising result was



Fig. 2 Comparison of percentage of spin–spin exchange interaction in **3**; note the exchange interaction in CB8 was 0%. For γ -CD and SDS micelles the broad Heisenberg component was subtracted before calculation of % exchange interaction. **3** : host = 1 : 2 and in SDS (1 : 1200).

reserved for SDS micelle. In spite of **3** being solubilized within the micelle as indicated by the decrease of the hyperfine splitting, A_N (see Fig. S9a in ESI†), and by the increase of the rotational correlation time (Fig. S9b, ESI†), the percentage of exchange interaction is close to that in water. This is most likely due to the soft flexible nature of the micellar interior that allows the molecule to rotate freely within its core.⁸

The quenching of spin communication due to internalization of one nitroxyl radical into a cage may arise from two effects: (a) the cage wall creates a barrier to spin exchange; (b) conformational modifications due to complexation that keeps the two nitroxyls apart. Due to the paramagnetic nature of 3we could not perform NOESY experiments to gain an insight into the conformational change that might have occurred upon complexation. We are currently pursuing our belief that the 'supramolecular steric effect' that has been exploited in this study to control the spin-spin exchange in biradicals can be extended to other polyradicals. Given the role of nitroxyl polyradicals for use in dynamic nuclear polarization (DNP) a method to enhance NMR signal intensities by two to three orders of magnitude by controlling their spin-spin interaction is likely to gain momentum in the near future. In this context supramolecular assemblies such as the ones described here could play a significant role.

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