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Paramagnetic Rotaxanes

Synthesis and Characterisation of a Paramagnetic [2]Rotaxane Based on a Crown Ether-Like Wheel Incorporating a Nitroxide Motif

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Abstract: The synthesis of the new nitroxide crown ether **8** and its use as the wheel in a bistable [2]rotaxane, containing dialkylammonium and 4,4′-bipyridinium recognition sites, is reported. The synthesis of **8** was achieved by the sequential addition of substituted phenyl groups to a nitrone derivatives leading to the preferential formation of the *cis* stereoisomer. Due to charge–dipole interactions between the nitroxide unit and the bipyridinium moiety, it was possible to probe the movement of the macrocycle between the two molecular stations of the [2]rotaxane after addition of a base by measuring the nitrogen hyperfine splitting in the corresponding EPR spectra. The equilibrium constant for the complexation of dibenzyl viologen by the macrocycle **8** was also determined by EPR titration.

Introduction

Nitroxide radicals are an important group of open-shell molecules with intriguing catalytic and magnetic properties, giving rise to diverse and important applications in many fields of chemistry and related sciences. These applications include the biomedical field (diagnostic spin probes,[1] spin traps[2] and potential antioxidant therapeutics),[3] the development of sustainable chemical processes (catalysts in aerobic oxidation)[4] and material chemistry (radical initiators for living and other controlled polymerisations).[5]

However, with the notable exception of the alkyl nitronyl nitroxide organic magnet systems,[6] the use of nitroxides in molecular-level assembly processes remains largely unexplored, certainly in comparison with the use of ethers, amides, imines, ureas and guanidinium units.[7] This is somewhat surprising given their desirable intrinsic properties: nitroxides possess one of the largest dipole moments known for any functional group (close to 3 D),[8] making them potentially useful for the control of the molecular orientation. The N–O• motif is a good hydrogen-[9] and halogen-bond[10] acceptor and it offers a simple reversible route to diamagnetic species through a one-electron electrochemical oxidation.[11] Rotaxanes and catenanes containing nitroxide units have been described in the literature,[12] but in all cases the paramagnetic unit was used as a spin probe and linked to the macrocycle or to the thread without participating in the recognition process. In most of these examples, spin exchange interactions between two radical units were used to probe the shuttling process of the macrocycle between two different recognition sites triggered by protonation or electron transfer.[12] Although the dimerisation of radical ions has been proposed to move a macrocyclic ring between different molecular recognition sites in a [2]rotaxane,[13] to the best of our knowledge no examples of mechanical interlocked molecules like rotaxanes or catenanes in which a nitroxide functionality could be used as recognition unit has been reported so far.

Based on this, we decided to prepare and characterise the first example of a nitroxide-containing rotaxane in which the N–O• motif acts not only as an EPR probe for the shuttling process, but could also be directly involved in the recognition process of a molecular site. This was achieved by inserting a dialkyl nitroxide functionality in a crown ether-like frame containing seven ethereal oxygen atoms (**8**, Scheme 1) and by using this macrocycle for complexation of cationic guests. We will show that the EPR read-out discriminates between dialkylammonium (NH_2^+) and 4,4′-bipyridinium (BPY^{2+}) recognition sites and this favourable feature can be used to probe the shuttling process of the paramagnetic wheel in a bistable [2]rotaxane.

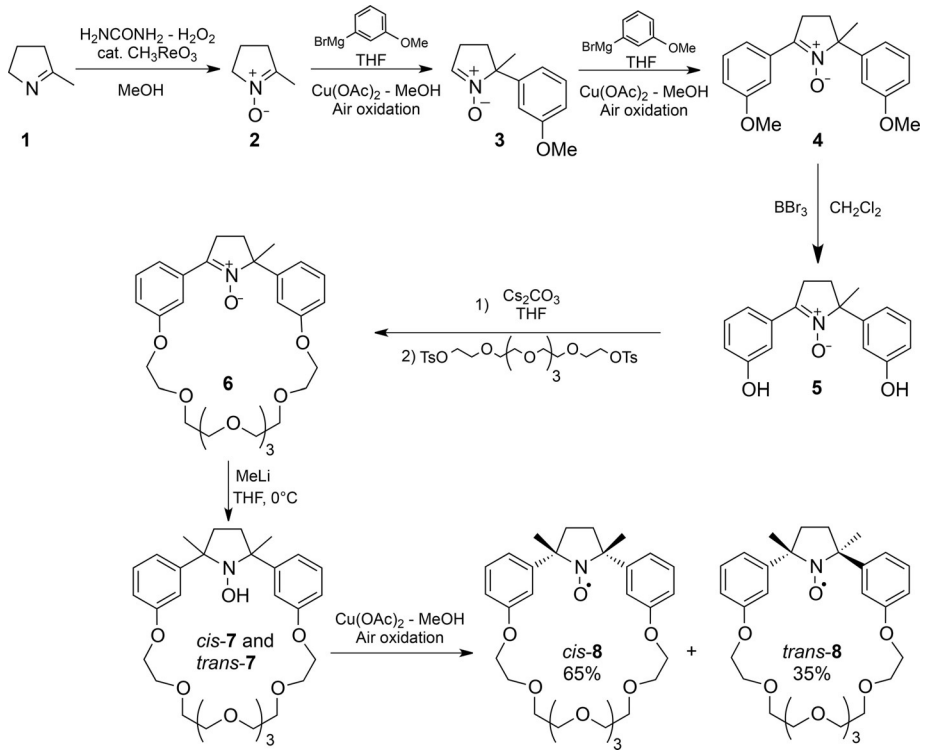
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Scheme 1. Reaction scheme for the preparation of the paramagnetic macrocycle **8**.

Results and Discussion

Nitroxide-based crown ether-like macrocycles are not new and were reported as far back as 1983 by Keana and co-workers.[14] In such examples, the crown ether is inserted in both the aromatic rings at the *ortho* position in a 2,5-dimethyl-2,5-diphenylpyrrolidine-*N*-oxyl radical. In order to reduce the steric hindrance around the nitroxidic functionality, we decided to prepare the new derivative **8** where the two aromatic rings are linked through a *meta* substitution to the nitroxide and to the polyether moieties. By adapting the original procedure proposed by Keana et al.[14] for the preparation of the *ortho* derivative, we prepared the new *meta*-substituted macrocycle **8** as described in Scheme 1. An important point, which deserves a comment, concerns the reaction of nitrone **6** with MeLi that provided the hydroxylamine derivative **7** in quantitative yield as a mixture of *cis* and *trans* isomers in a molar ratio of 6.5:3.5, as assessed by ^{1}H NMR spectroscopy (see the Supporting Information). Although we were not able to obtain a single crystal of **7** for X-ray structure determination, we attributed the stereochemistry of the main isomer to the *cis* form by following the model presented by Shibata et al., who reported that an organometallic reagent attacks the pyrrolidine nitrone from the less hindered side.[15] In our case, MeLi is expected to add to nitrone **6** from the side opposite to the bulky phenyl group to give the *cis*-hydroxylamine **7**.

The mixture of the two isomers (*cis*-**7** and *trans*-**7**) was oxidised with air in the presence of Cu^{2+} ions. After purification of the crude mixture by column chromatography, a main fraction containing the nitroxide isomer *cis*-**8** was recovered together with less abundant fractions corresponding to the other isomer of the nitroxide (i.e., *trans*-**8**) and unreacted *trans*-**7**. Assignment of the *cis* stereochemistry to the main fraction was obtained by NMR analysis after reduction of the compound with phenylhydrazine.[16] Interestingly, the two nitroxide isomers show different relative rates of reduction. Whereas the *cis*-**8** isomer can be reduced to the corresponding hydroxylamine in 10–15 minutes, the *trans* isomer is much more resistant toward reduction, requiring several days. This observation is in agreement with a previous report on *trans*-azethoxyl acid, which was found to be the most resistant toward reduction if compared to its analogous *cis* derivative.[17] These findings corroborate the hypothesis previously exposed on the attribution of the stereoisomers. On this basis, the presence of unreacted *trans*-**7** after oxidation of the mixture of the hydroxylamines **7** suggests that also this step occurs more efficiently for the *cis* than the *trans* isomer because of the lower steric hindrance around the N–OH functionality in the former one.

The CH_2Cl_2 solution of the macrocycle *cis*-**8** shows a typical nitroxide three-line EPR spectrum, which is characterised by $a_N = 14.35$ G and $g = 2.0061$. The EPR analysis of the CH_2Cl_2 solution containing *trans*-**8** was virtually identical, apart from a very small difference in the nitrogen coupling ($a_N = 14.39$ G, see the Supporting Information).

The host properties of the most abundant isomer *cis*-**8** towards cations, which are known to be selectively complexed by crown ether derivatives, were then investigated by EPR spectroscopy. Na^+ and K^+ picrate salts are insoluble in CH_2Cl_2. However, when a solution containing an excess of *cis*-**8** was added to the suspension, complete solubilisation of the metal salts was observed. This clearly suggests that the paramagnetic

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macrocycle *cis*-**8** maintains the complexation ability of crown ethers towards alkaline cations. Unexpectedly, the EPR spectra of the nitroxide *cis*-**8** recorded in the presence of alkaline metal cations did not show any significant variation in the spectroscopic parameters compared to those measured in the absence of charged guests. The striking conclusion is that, despite the position of the nitroxide group with respect to the ion binding cavity, the radical unit is not participating in the complexation process of the metal cation (which thus is expected to interact only with the crown ether moiety, maintaining the cation far from the nitroxide). A similar result was obtained in the presence of dibenzylammonium hexafluorophosphate, which did not produce a significant change in the EPR spectrum of *cis*-**8**. Stochastic dynamic (SD) simulations performed in vacuo at 298 K on the dibenzylammonium@*cis*-**8** complex by using the AMBER* force field (see the Supporting Information), suggested that the radical unit is indeed not participating to the complexation process of the ammonium group (see Figure 1 a).

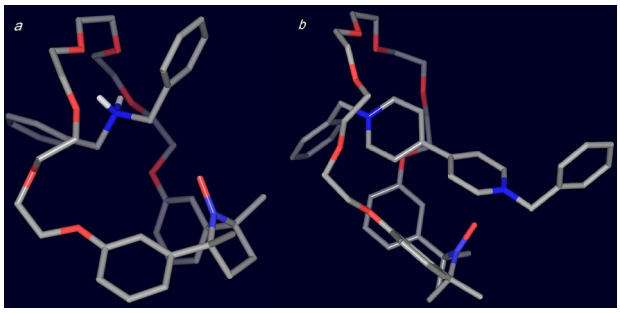
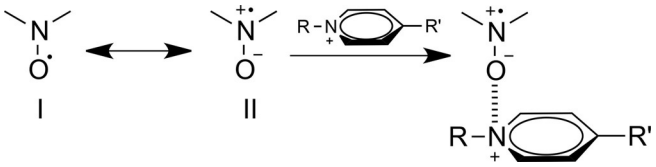


Figure 1. Stochastic dynamic simulations snapshots providing possible structures of the a) dibenzylammonium@*cis*-**8** and b) DBV@*cis*-**8** (DBV = dibenzyl viologen) complexes.

A different spectroscopic behaviour was instead observed when the EPR spectrum of *cis*-**8** was recorded in the presence of bis-cation dibenzyl viologen (DBV) as the hexafluorophosphate salt. In this case the complete solubilisation of the bis-pyridinium salt was accompanied by an increase of the nitrogen coupling (a_N) value in the EPR spectrum of *cis*-**8**. For example, in acetone at room temperature a_N increases from 14.17 to 14.32 G in the presence of 0.042 M DBV.

Although the nature of the interaction is not fully defined, SD calculations (Figure 1 b) suggest that binding of the bis-pyridinium salt occurs in such way that, in the complex, one of the two cationic portions is interacting with the nitroxide unit by a charge–dipole interaction. In this model, the increase of a_N can be explained on the basis of the two canonical forms I and II of the nitroxide function (Scheme 2). The greater the interaction with the positive charge of the pyridinium unit, the more favoured will be structure II, bearing a larger electron density on the oxygen atom and spin density on the nitrogen atom.

As shown in Figure 2, the changes in the value of a_N as a function of the DBV concentration were well-modelled in acetone at 298 K by a 1:1 binding model by using standard curve fitting methods and K_{eq} was found to be $(69 \pm 19)\ M^{-1}$.[18] This



Scheme 2. Charge–dipole interaction between a dialkyl nitroxide and a pyridinium unit.

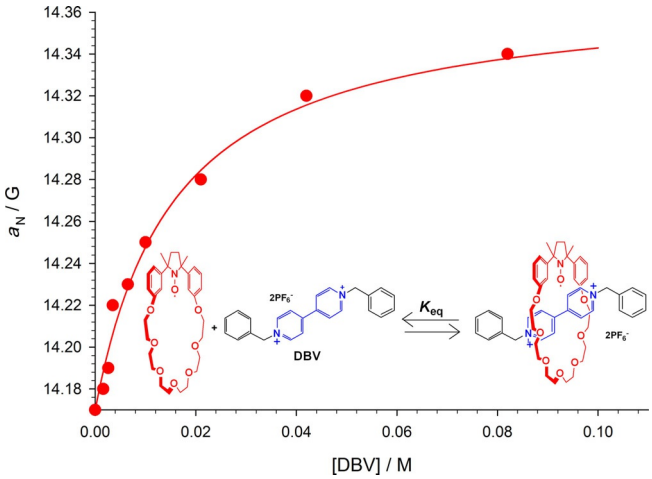


Figure 2. Plot of the EPR nitrogen coupling, a_N, in *cis*-**8** (0.05 mM) versus the concentration of DBV at 298 K in acetone. The line represents the theoretical dependence of a_N on the DBV concentration calculated by taking into account the formation of a 1:1 complex and $K_{eq} = 69\ M^{-1}$.

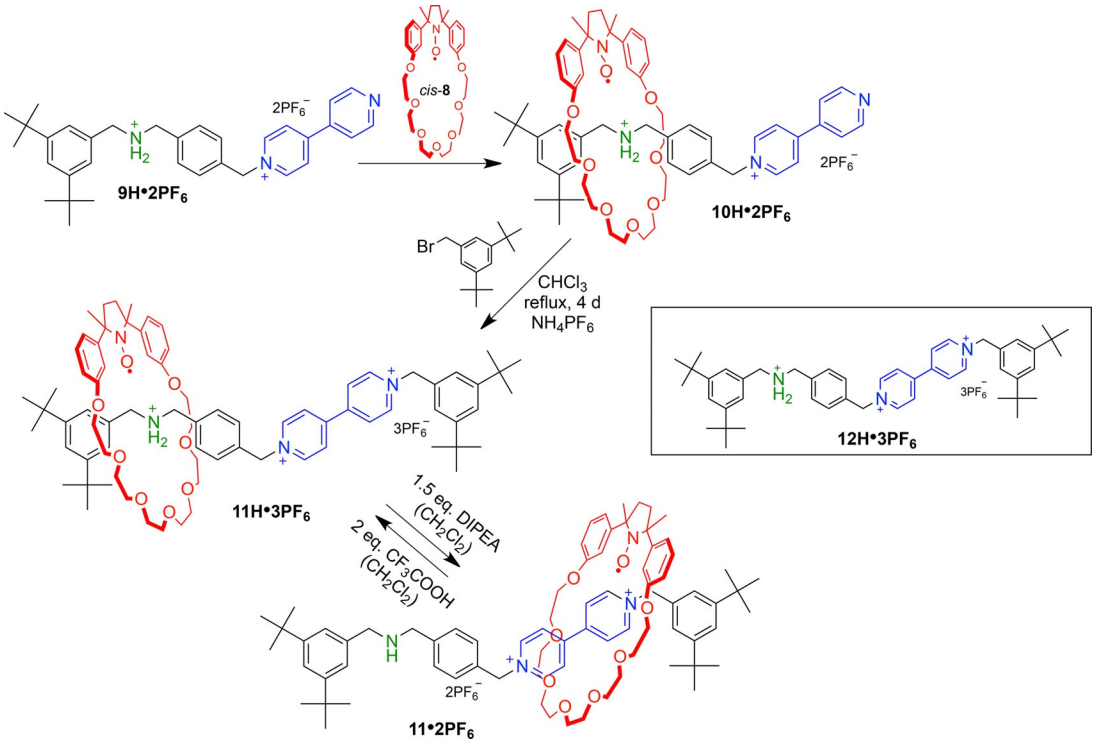
value is very close to the one measured in acetonitrile at 298 K ($K_{eq} = 82\ M^{-1}$) for the complexation of DBV by the closely related diamagnetic macrocycle dibenzo[24]crown-8.[19]

Because the EPR read-out discriminates between different cationic guests, we evaluated the possibility of using the radical macrocycle *cis*-**8** in a bistable [2]rotaxane containing dialkylammonium and 4,4′-bipyridinium recognition sites in the thread. The rotaxane **11H·3PF$_6$** (see Scheme 3) was prepared by following the classical threading–stoppering approach, which involves the in situ self-assembly of the pseudorotaxane **10H·2PF$_6$** between the ring *cis*-**8** and the half-dumbbell intermediate **9H·2PF$_6$**.

Evidence for the formation of the pseudorotaxane in $CHCl_3$ was obtained by observing complete solubilisation of the half-dumbbell **9H·2PF$_6$**, which is almost completely insoluble in chlorinated hydrocarbons. The pseudorotaxane was then reacted with (3,5-di-*tert*-butyl)-benzyl bromide by a S_N2-mediated stoppering reaction to afford the rotaxane **11H·3PF$_6$** in 30% yield. The rotaxane formation was detected by ESI-MS (see the Supporting Information), UV/Vis and EPR spectroscopy.

Figure 3 compares the absorption spectra of **11H·3PF$_6$** and its constituents, that is, the free dumbbell **12H·3PF$_6$** and the macrocycle *cis*-**8**. The most intense absorption feature in the rotaxane arises from the viologen unit ($\varepsilon = 18230\ M^{-1}\,s^{-1}$, $\lambda =$ 259 nm). This band overlaps with a weaker band due to the aromatic rings of the macrocycle unit and it is essentially unperturbed on going from **12H·3PF$_6$** to **11H·3PF$_6$**. This spectral fea-

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Scheme 3. Reaction scheme for the preparation of the rotaxane **11H·3PF$_6$** and the switching process between **11H·3PF$_6$** and **11·2PF$_6$**.

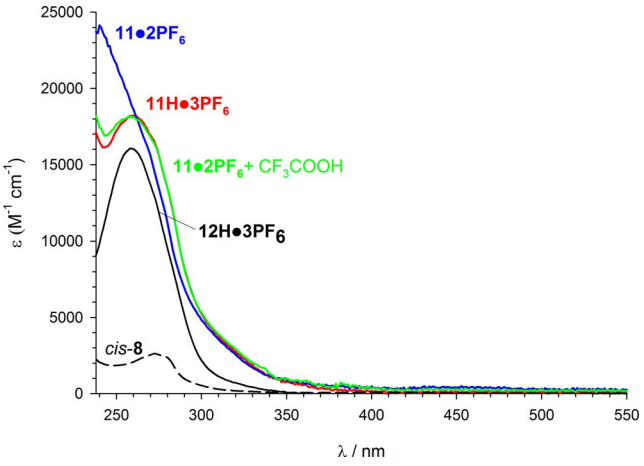


Figure 3. Absorption spectra of the macrocycle *cis*-**8** (dashed black line), the free dumbbell **12·2PF$_6$** (black line) and the rotaxane **11H·3PF$_6$** before (red line) and after subsequent addition of 1.5 equivalents of base (blue line) and CF_3COOH (green line) in acetonitrile at room temperature.

ture suggests that the macrocycle is not significantly interacting with the BPY^{2+} unit, which is consistent with it being localised predominantly over the ammonium site of the thread as expected.

Figure 4 (green line) shows the EPR spectrum of the rotaxane **11H·3PF$_6$** recorded in CH_2Cl_2 at 298 K, exhibiting typical nitroxide EPR signals with the high-field line broadened due to restricted tumbling and, thus, incomplete averaging of the anisotropic components of the hyperfine and *g* tensor. The a_N hyperfine splitting and the rotational correlation time τ, are reported in Table 1.[20] The value of $a_N = 14.39$ G is very close to that observed both for the free macrocycle and the dibenzylammonium@*cis*-**8** complex. According to the UV analysis, the EPR data strengthens the conclusion that the macrocycle predominantly encircles the ammonium station. The higher affinity shown by *cis*-**8** for the complexation of the dibenzylammo-

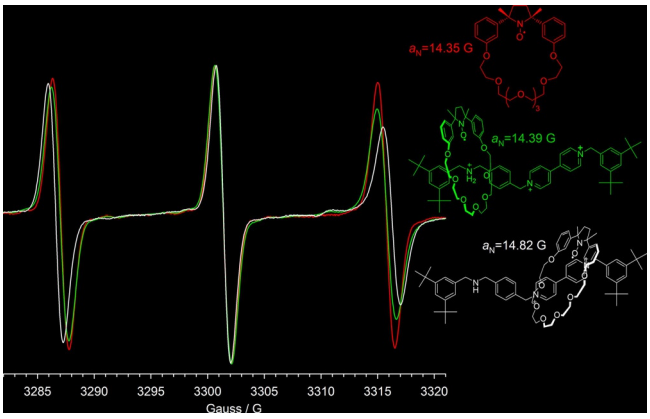


Figure 4. EPR spectra of the macrocycle *cis*-**8** (red line) and the rotaxanes **11H·3PF$_6$** (green line) and **11·2PF$_6$** (white line) in CH_2Cl_2 at 298 K.

Table 1. EPR parameters of the nitroxides in CH_2Cl_2 at 298 K.[20]

Nitroxide	a_N [G]	Line width of the central line [G]	Signal ratio h_0/h_{-1}	Correlation time τ [s]
cis-**8**	14.35	1.38	1.10	4.6×10^{-11}
11H·3PF$_6$	14.39	1.42	1.47	2.0×10^{-10}
11·2PF$_6$	14.82	1.41	1.65	2.6×10^{-10}

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nium site compared to the BPY^{2+} one, is in line with the complexation behaviour shown by the related macrocycle dibenzo[24]crown-8 dibenzyl for which the association constant with the dibenzylammonium cation is about five times higher (K_{eq} = 420 M^{-1})[21] than that measured with dibenzyl viologen (K_{eq} = 82 M^{-1})[19] in acetonitrile at 298 K.

The rotational correlation time measured in the EPR spectrum of **11H·3PF$_6$** is 4.3 times higher than that measured in the spectrum of *cis*-**8** (Table 1). This substantial reduction of the tumbling rate is typical for spin labels attached to larger molecules and can be considered as a further indication for the formation of the rotaxane structure.

Although we found some differences comparing the ^{1}H NMR data of the dumbbell and the rotaxane,[22] NMR studies are not particularly useful for the characterisation of **11H·3PF$_6$** because most of the signals were broadened by the presence of the paramagnetic centre. It is worth noting that attempts to reduce the rotaxane with phenylhydrazine to the diamagnetic hydroxylamine derivative were unsuccessful, denoting a considerable inertness of the nitroxidic interlocked assembly to this reaction condition.

Thus, the shuttling of the macrocycle towards the secondary BPY^{2+} station (Scheme 3) was followed by UV/Vis and EPR spectroscopy. Treatment of the rotaxane **11H·3PF$_6$** in CH_2Cl_2 with the non-nucleophilic diisopropylethylamine (*i*Pr$_2$EtN, DIPEA), which is strong enough to deprotonate the NH_2^+ centre,[23] led to perturbation of the dominant viologen UV-absorption features around λ = 259 nm. As shown in Figure 3 (blue line), deprotonation is accompanied by a small blueshift and an increase in the absorbance of the viologen band. This behaviour is consistent with the displacement of *cis*-**8** to predominantly encircle the bipyridinium station, leading to a stabilisation of the ground state of BPY^{2+} due to charge–dipole interactions between this unit and the nitroxidic moiety. In contrast, deprotonation of the free dumbbell **12H·3PF$_6$** did not cause an appreciable variation in the corresponding absorption band (see the Supporting Information).[24]

Finally, the addition of a stoichiometric amount of trifluoroacetic acid (TFA) to the rotaxane after addition of the base caused the quantitative recovery of the initial absorption spectrum (see Figure 3, green line), which is consistent with the system returning to its state in which the macrocycle predominantly encircles the ammonium station.

Addition of increasing amounts of *i*Pr$_2$EtN to the rotaxane also produces a noticeable increase in the EPR nitrogen coupling, which reaches a plateau after addition of one equivalent of base (a_N = 14.82, Δa_N = +0.43 G, see Figure 4, white line). The increase in the value of a_N is similar to that observed when free DBV is complexed by the macrocycle *cis*-**8** (see Figure 2).

During the titration with *i*Pr$_2$EtN, the protonated (**11H·3PF$_6$**) and the deprotonated (**11·2PF$_6$**) forms of the rotaxane are present in solution simultaneously and in equilibrium with one another. It has been reported that, in a related diamagnetic rotaxane, base-induced shuttling of a dibenzo[24]crown ether macrocycle to the BPY^{2+} station is complete in seconds and an acid-induced reverse of this process occurs on a timescale of tens of milliseconds.[25] If we assume that the proton transfer between **11H·3PF$_6$** and **11·2PF$_6$** takes place on similar timescales the exchange between the protonated and deprotonated states will be significantly slower than the EPR timescale. Thus, during the titration the EPR spectrum is expected to be the superposition of the two signals for **11H·3PF$_6$** and **11·2PF$_6$**. However, due to the large spectral line width, the detection of separate EPR signals is prevented and the variation in the relative amount of the radical co-conformations is expected to only give rise to a variation in the corresponding apparent field separation of the spectral lines.

Indeed, Figure 5 shows the changes in the field separation ΔG between the central line and the high-field line, observed experimentally by EPR spectroscopy upon addition of increasing amounts of *i*Pr$_2$EtN to **11H·3PF$_6$**. When the amount of *i*Pr$_2$EtN is less than one equivalent (referred to the rotaxane) both nitroxides **11H·3PF$_6$** and **11·2PF$_6$** are present and ΔG reflects the relative amount of protonated and deprotonated species.

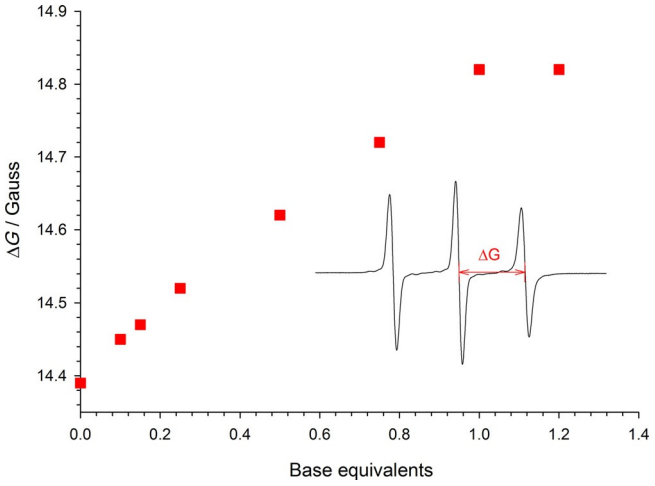


Figure 5. Field separation, ΔG, between the central line and the high field line, monitored by EPR spectroscopy upon addition of *i*Pr$_2$EtN to **11H·3PF$_6$**.

The switching of the rotaxane also leads to a slight increase of the rotational correlation time τ from 2.0×10^{-10} to 2.6×10^{-10} s (see Figure 4 and Table 1). The change in the rotational correlation time when passing from one co-conformation to the other can be associated to the reduced ability of the "wheel" to rotate relative to the thread when it is located at the BPY^{2+} station.

Conversely, base addition performed on a 1:1 mixture of the non-interlocked rotaxane components (*cis*-**8** and the free dumbbell **12H·3PF$_6$**) caused neither variations in the nitrogen splitting nor in the correlation time. Such a control experiment confirms that the observed EPR spectral parameter changes arise from the interaction between the radical unit and the bipyridinium unit, which becomes possible as a result of ring shuttling in the deprotonated rotaxane.

The addition of a stoichiometric amount of TFA to **11·2PF$_6$** caused the quantitative recovery of the initial EPR spectrum

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($a_N = 14.39$ G, see the Supporting Information) as a consequence of the macrocycle returning to predominantly encircle the ammonium station. The complete base- and acid-induced switching cycle of the EPR pattern was repeated several times without an appreciable signal loss, highlighting the reversibility of the process.

Conclusion

In conclusion, we have reported the synthesis of the first nitroxide rotaxane in which the nitroxide unit not only acts as EPR probe for the switching, but also interacts with a recognition site (bipyridinium) in the thread. Whereas in previous work the shuttling process was detected by EPR spectroscopy due to switching between the non-coupled (three-line EPR spectrum) and coupled (five-line EPR spectrum) states of nitroxide radicals connected to the ring and dumbbell, in this work we have shown that a simple change in the nitrogen coupling reports on the switching process between dialkylammonium and 4,4′-bipyridinium recognition sites. The nitroxide behaves as a spin probe of the shuttling process because it is able to interact with the bipyridinium unit by charge–dipole interactions. Finally, the presence of nitroxide units provides an unusual functional addition to the diversity of templates available for assembling rotaxanes and could potentially lead to new generations of radical molecular machines and superstable radicals.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: EPR spectroscopy · nitroxides · rotaxanes · spin probes · supramolecular chemistry

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