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PAPER

Nitroxide biradicals as thread units in paramagnetic cucurbituril-based rotaxanes†

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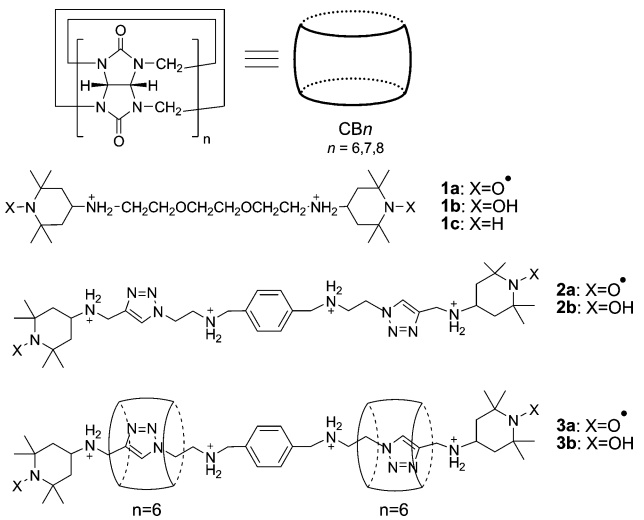
The first example of paramagnetic rotaxane containing cucurbit[6]urils has been reported and characterized both by ESR and NMR spectroscopy.

Introduction

The cucurbit[*n*]uril (CB*n*, where *n* = 5–8 and 10) family of macrocyclic host molecules, comprised of *n* glycoluril units bridged by 2*n* methylene groups, has been demonstrated to form particularly stable host–guest complexes with cationic organic and organometallic guests in aqueous solution, as a result of a hydrophobic cavity accessed through two restrictive polar carbonyl fringed portals.[1–4] CB*n* has also been employed in the preparation of a significant number of mechanically-interlocked supramolecular complexes, including rotaxanes, pseudorotaxanes, and catenanes, where CB*n* is the cyclic component.[5] With the polar carbonyl groups lining the rims of the cucurbiturils, the end groups on the threads can prevent dissociation of the rotaxanes into their cyclic bead and linear thread components through steric and/or electrostatic means. In principle, as already reported with α-cyclodextrin,[6] complexation of a nitroxide biradical can be exploited for the preparation of mechanically-interlocked paramagnetic aggregates, in which the properties of such assemblies can be merged with the use of nitroxides in materials science and their applications in the study of biological processes.[7] While the inclusion of mononitroxide radicals by CB*n* has been already reported,[8–12] preparation of nitroxide biradical-based rotaxane with CB*n* has never been reported. In the present study, we report the behaviour of CB6, CB7 and CB8 in the presence of nitroxide biradicals containing tetramethylpiperidine-*N*-oxyl (TEMPO) units to form host–guest complexes in the forms of paramagnetic pseudorotaxanes and rotaxane.

Results and discussion

We initially investigated the ESR behaviour of biradical **1a** (Scheme 1) in the presence of CB*n* having different sizes (*n* = 6, 7, 8) to verify if the TEMPO unit stopper is bulky enough to act as an end-cap group of a rotaxane consisting of CB*n*. The ESR spectrum of **1a** recorded in water (a_N = 16.90 G, g = 2.0056) is



Scheme 1

reported in Fig. 1 and is characterized by five lines, due to the exchange interaction between the paramagnetic fragments linked by the polyether chain, as the exchange coupling constant between unpaired electrons, J, is greater than the hyperfine splitting, a_N.[13] This exchange interaction, which leads to the appearance of extra lines in the ESR spectra, is operating through space and depends on the frequency of collisions between the paramagnetic moieties.

The complexation of the biradicals with the CB is expected to significantly reduce the probability of collisions of the nitroxide termini giving rise to the disappearance of the exchange peaks in the ESR spectra.[14] Thus, besides following a_N changes as usually done with mononitroxide, with biradicals monitoring of the variation in the intensity of exchange peaks as a function of host concentration could provide extra information on complexation behaviour. In Fig. 1 ESR spectral variations of **1a** observed by adding increasing amount of CB*n* are reported. The exchange lines in the spectra of **1a** decrease continuously with increased CB*n* concentration until complete disappearance at around 2 mM with CB7 and CB8 and *ca.* 20 mM with CB6. This is consistent with the complexation with the CB*n* units which reduces the exchange interaction. The disappearance of the exchange peaks

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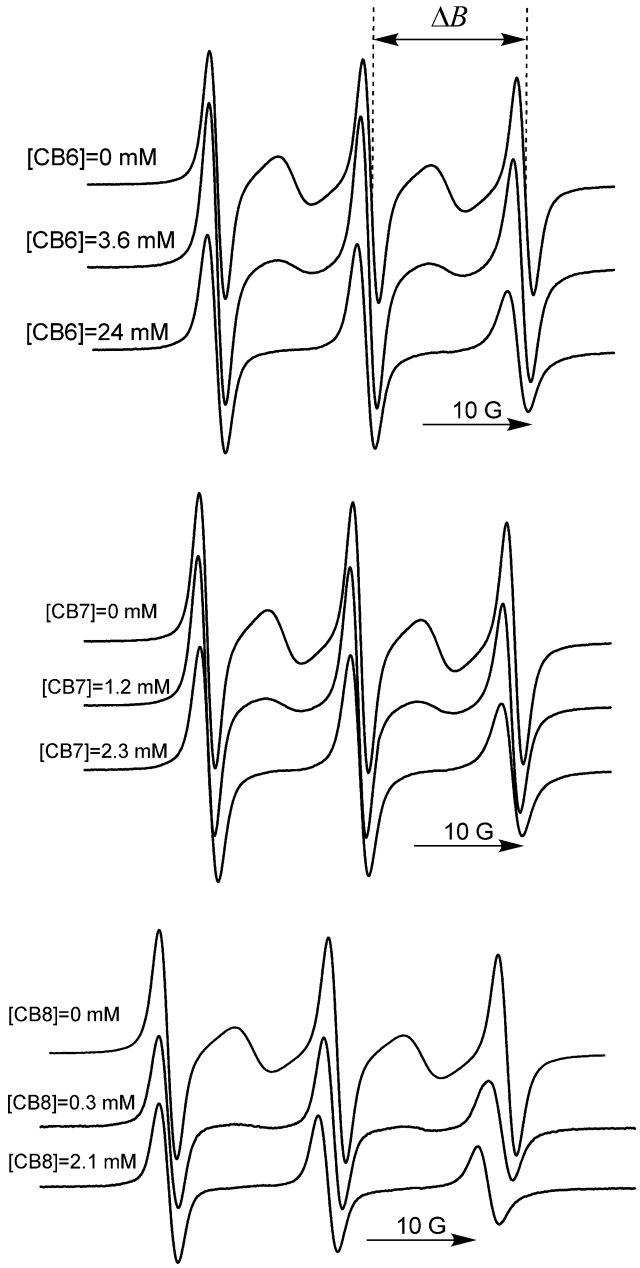
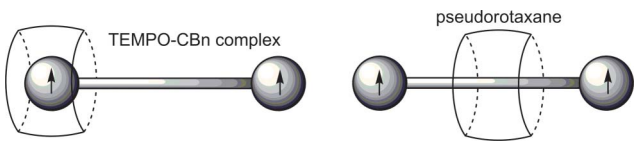


Fig. 1 ESR spectra of **1a** (0.26 mM) in the presence of different amount of CB*n* in water at 298 K.

is compatible both with the formation of a pseudorotaxane *i.e.* with a symmetric complex in which the ethylene glycol units are surrounded by the macrocycle and also with the inclusion of one or two nitroxide units (Scheme 2).



Scheme 2

In order to check if the observed changes in the ESR spectra are caused by formation of a pseudorotaxane or are simply due to a TEMPO–CBn interaction, we followed the variation of field separation between the ESR central and high field lines (ΔB, see Fig. 1) as a function of macrocyclic concentration in water at 298 K (Fig. 2).[15]

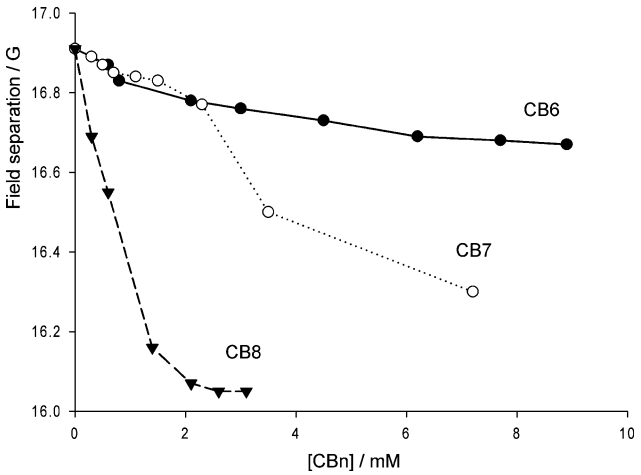


Fig. 2 Field separation between the ESR central and high field lines (ΔB) for biradical **1a** in the presence of different amount of CB6 (●), CB7 (○) and CB8 (▼) in water at 298 K. With CB6 NaCl 0.1 M was added to the solution.

Different behaviours were observed depending on the size of the macrocycle. The addition of CB6 to the biradical solution showed no significant changes in ΔB value even at high concentration (>20 mM). At these concentrations, however, the ESR spectra of the biradicals showed only three lines. This behaviour is consistent with a weak complexation of **1a** in which the nitroxide moiety is not included inside the hydrophobic cavity of CB6, but is instead dissolved in the bulk water with the nitroxide function located among the carbonyl groups of the macrocylcle.

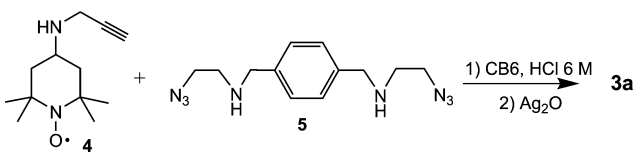
With CB7, the exchange coupling is completely suppressed at 2.0 mM of macrocycle. At this concentration however, the field separation is still very close to the value measured in water ($\Delta\Delta B$ = –0.15 G). Both observations strongly support the formation of a pseudorotaxane (see Scheme 2) in which the macrocycle is located on the center of the linear chain, thus forcing the biradical to adopt an elongated conformation having TEMPO units exposed to the bulk water and suppressed spin exchange (J = 0). The formation of a strong complex between nitroxide **1a** and CB7 is also expected on the basis of the strong interaction between the ammonium site and the carbonyl oxygens of CB7, as already found with protonated amines.[16] This was confirmed by following the ESR spectral variations observed by changing the pH from 7 to 13 (see Supporting information). Around pH 7 the ESR spectrum of a solution containing CB7 (5.5 mM) and biradical **1a** (0.4 mM) showed the three line spectrum due to the paramagnetic pseudorotaxane. The increase of solution basicity to pH ≈ 12 with NaOH reverted the ESR spectrum to the original five lines signals. This observation strongly suggests that the deprotonated biradical is released from the pseudorotaxane to the bulk water. The process is reversible: addition of HCl to give back pH 7 results in the formation of three lines spectrum and of the pseudorotaxane.

The thermodynamic stability of the pseudorotaxane was checked by measuring the equilibrium constant K for the association between the diamagnetic analogue (**1c**) of the biradical

and CB7 by ^{1}H NMR. The signals of the free and bound guests protons are simultaneously observed, revealing that the rate of exchange between these species is slow in the NMR time scale (see ESI†). Integration of the separate signals as a function of CB7 concentration provides the corresponding association equilibrium constant (K) as 1879 ± 256 M^{-1}. This value is one order of magnitude smaller than the K value measured for the inclusion of TEMPO monoradical by the same host,[8] indicating that the presence of substituents on the piperidine ring results in a significant decrease in the stability of the complex (*vide infra*). Only in the presence of a large excess of CB7 (>3 mM), complexes with higher CB7/**1a** stoichiometry, in which TEMPO units are included inside hydrophobic cavity of CB7, are formed, as indicated by the significant decrease of ΔB in the corresponding ESR spectra.

Finally, with CB8, a strong decrease of both field separation and intensity of exchange lines was observed when increasing macrocyle concentration in water solution. This behaviour indicated that complexation by CB8 occurs preferentially in the immediacy of TEMPO radical units rather than on the ethylene glycol units. We have previously shown[8–9] that with CB8 the larger size of the cavity and the presence of a strong interaction between the ammonium cation and the carbonyl groups should favour a geometry in which the longer axis of the nitroxide is parallel to the short principal axis of the macrocyle. This is not possible in the presence of the smaller macrocycle, CB7, where TEMPO radical is forced to be inserted with the NO group lying on the plane passing through the equatorial carbon–carbon bonds of the host and with the geminal methyl groups pointing toward the carbonyl portals.

All these observation led to the conclusion that TEMPO unit cannot pass through the CB6 cavity, while with the larger member of the cucurbituril family the reversible formation of a pseudorotaxane or a complex between the tetramethylpiperidine ring and the cucurbituril is possible. Thus we decided to construct a CB6-based rotaxane having the 2,2,6,6-tetramethylpiperidine-*N*-oxyl ring as the end-cap group. The synthesis of the rotaxane was achieved using CB6 as catalyst in the 1,3-dipolar cycloaddition between suitably functionalized alkyne and azide groups to give 1,4-disubstituted triazole.[17] By this approach the *N*-propargyl derivative of 4-amino-TEMPO **4** (0.18 mmol) and diazide **5** (0.09 mmol) were added to CB6 (0.18 mmol) dissolved in aqueous HCl 6 M and the resulting solution was stirred at 60 °C for 24 h (Scheme 3). After reduced pressure solvent removal, the bis-*N*-hydroxy derivative of paramagnetic [3]rotaxane (**3b**) was obtained as a light yellow solid in 75% yield. The rotaxane diradical **3a** was recovered by treating **3b** in water solution with an excess of Ag_2O.[18]



Scheme 3 Structures of the alkyne **4** and of the azide **5** used in the synthesis of the [3]rotaxane **3a**.

The formation of the interlocked molecule is evidenced when comparing ^{1}H NMR spectral data of the thread recorded in D_2O, with those of rotaxane.[19]

In the proton spectrum of the [3]rotaxane **3b** (see Fig. 3, line b) the presence of the macrocycle wrapping the diradical thread is detected by significant complexation-induced chemical shifts (CIS) of the dumbbell with respect to the resonances of the free thread **2b** (Fig. 3, line a). The sign of CIS ($\Delta\delta = \delta_{bound} - \delta_{free}$) gives a rough indication of the position of the thread within CB, negative $\Delta\delta$ revealing the part of the thread located inside the macrocycle, and the contrary being for positive values of CISs.[5] According with these assumptions, analysis of the CIS values reported in Fig. 3 shows that the triazole moieties of the thread are positioned within the two CB6 macrocycles, as the consistent upfield shift (–1.64 ppm) displayed by the aromatic proton of the heterocycle is indicative of the strong involvement of the triazole proton in complexation.

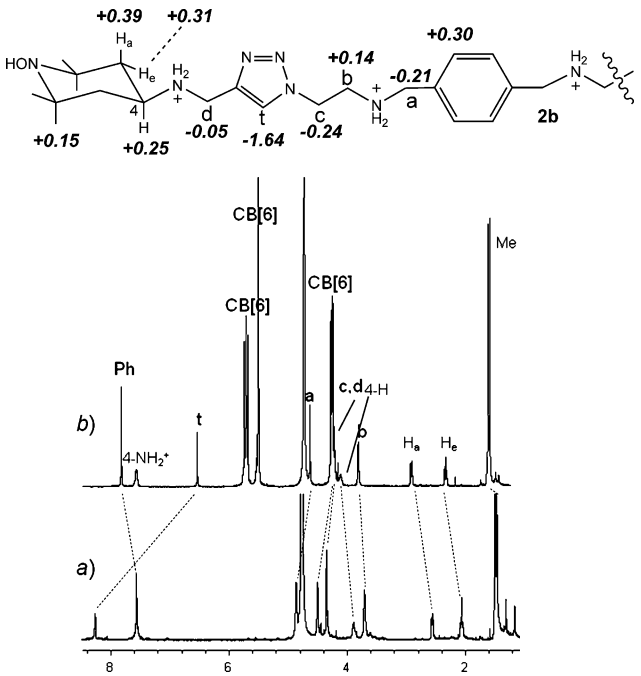


Fig. 3 ^{1}H NMR spectrum in D_2O of *a*) thread **2b** (1 mM); *b*) [3]rotaxane **3b** (1 mM) with complexation induced chemical shifts ($\Delta\delta$ in ppm).

Considerable negative CISs are detected also for the adjacent protons labeled with **c** and **d** letters, while phenyl and piperidine ring protons exhibit positive shift, confirming their position outside the cavity near the carbonyl portals of the macrocycle. Unexpectedly, spectrum of **3b** shows an additional peak at 7.6 ppm, which, on the basis of ROESY experiments, was assigned to the ammonium protons linked to the 4-position of *N*-hydroxy TEMPO (see ESI†). The presence of such slow-exchangeable protons in deuterated water strongly supports that the ammonium protons linked to the 4-position of *N*-hydroxy TEMPO are hydrogen-bonded to the CB carbonyl-lined portal in the [3]rotaxane.[20]

The room-temperature ESR spectrum of rotaxane **3a** in water (a_N = 16.75 G, g = 2.0057, see Fig. 4b) consists of three lines as expected for a nitroxide biradical in the extended conformation in which the TEMPO fragments behave as two single nitroxide radicals. This spectrum is clearly different form that obtained under the same experimental condition with the free thread **2a** (a_N = 16.80 G, g = 2.0057), which is characterized by broaden exchange peaks, due to the exchange interaction between the

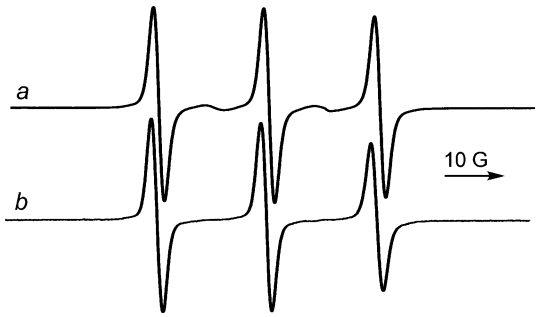


Fig. 4 ESR spectra of free thread **2a** (a) and rotaxane **3a** (b) in water at 340 K.

paramagnetic fragments (see Fig. 4a). The high field ESR line of **3a** is characterized by a lower height respect to that obtained with **2a**, this being due to the slower motion in solution of the rotaxane biradical, resulting in incomplete averaging of the anisotropic components of the hyperfine and *g*-tensors.

Conclusions

In conclusion, we reported the first example of a paramagnetic rotaxane containing CB6 as wheel. We also showed that it is possible to reversibly trigger spin exchange by simply changing the pH of the solution in the presence of nitroxide biradical **1a** and the larger CB7 derivative. In our view, the presence of persistent radical centers in pseudorotaxanes and rotaxanes is potentially an attractive functionality that can be exploited to modulate the behavior of molecular devices.

Experimentals

General

ESR spectra has been recorded by using the following instrument settings: microwave power 0.79 mW, modulation amplitude 0.04 mT, modulation frequency 100 kHz, scan time 180 s, 2 K data points.

^{1}H and 2D NMR spectra were recorded at 298 K on a Varian Inova spectrometer operating at 600 MHz in D_2O solutions using the solvent peak as an internal standard (4.76 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury operating at 100 MHz in D_2O solutions using DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt) as an external standard. Chemical shifts are reported in parts per million (δ scale). ROESY data were collected using a 90° pulse width of 6.7 μs and a spectral width of 6000 Hz in each dimension, respectively. The data were recorded in the phase sensitive mode using a CW spin-lock field of 2 KHz, without spinning the sample. Acquisitions were recorded at mixing times 300 ms. Other instrumental settings were: 64 increments of 2 K data points, 8 scans per *t*, 1, 1.5 s delay time for each scan.

ESI-MS spectra were recorded with Micromass ZMD spectrometer by using the following instrumental settings: positive ions; desolvation gas (N_2) 230 L h^{-1}; cone gas (skimmer): 50 L h^{-1}; desolvation temp. 120° C; capillary voltage: 3.2 kV; cone voltage: 40 and 100 V; hexapole extractor: 3 V.

UV-Vis spectra were taken on a Jasco V-550 spectrometer.

All reagents were commercially available and were used without further purification. Compound **4** was synthesized according to literature procedure.[21]

Synthesis of *N*,*N*′-(1,4-phenylenebis(methylene))bis(2-azidoethanamine) 5

A solution of 1,4-bis(bromomethyl)benzene (0.38 g, 1.45 mmol) in CH_2Cl_2 (10 ml) was added dropwise to freshly prepared azidoethylamine[22] (1.25 g, 14.5 mmol) at room temperature. The resulting solution was stirred at room temperature for 24 h. A white precipitate was obtained which was filtered and dissolved in HCl 2N. The solvent was removed under reduced pressure and the solid residue was recrystallised from ethanol/diethyl ether 2 : 1, obtaining the product (0.238 g, 60%) as white crystals.

M. p.: > 300° C (decomp).

Elemental analysis for $C_{12}H_{20}N_8$ Calc.: C, 52.16; H, 7.29; N, 40.55; Found: C, 52.21; H, 7.39; N, 40.40. ^{1}H NMR (600 MHz, D_2O): δ 3.26 (t, 4H, J = 6.0 Hz, CH_2), 3.75 (t, 4H, J = 6.0 Hz, CH_2), 4.30 (s, 4H, CH_2), 7.55 (s, 4H, Ph). ^{13}C NMR (100 MHz, D_2O, DSS): δ 48.48, 49.43, 53.15, 133.32, 134.58. Positive ESI-MS: m/z 274.9 (M - H)$^+$.

Synthesis of diradical 2a

$CuSO_4$ (0.01 g, 0.04 mmol) and ascorbic acid (0.014 g, 0.08 mmol) were added to a solution of azide **5** (0.027 g, 0.1 mmol) and alkyne **4** (0.045 g, 0.21 mmol) in water (4 ml). The resulting suspension was stirred at room temperature overnight. The product was purified by gel filtration over a Sephadex G-15 column to yield a light orange solid (0.075 g, 50%). Positive ESI-MS: m/z 715.3 (M + Na)$^+$.

Elemental analysis for $C_{36}H_{60}N_{12}O_2$ Calc.: C, 62.31; H, 8.86; N, 24.22; Found: C, 62.50; H, 8.65; N, 23.94. UV-Vis (H_2O): λ 376 nm. EPR: (a_N = 16.85 G, g = 2.0057). ^{1}H NMR (600 MHz, D_2O): δ 3.30–3.80 (m, 4H, **b**), 3.80–4.50 (m, 4-H, **c**, **d**), 7.44 (bs, 4H, Ph), 8.00–8.60 (m, 2H, **t**).

The proton spectrum of **2b** was obtained by $Na_2S_2O_4$ reduction of the NMR sample containing **2a** to afford the corresponding bis-*N*-hydroxy amine.

^{1}H NMR (600 MHz, D_2O): δ 1.47 (s, 12H, CH_3), 1.50 (s, 12H, CH_3), 2.07 (t, 4H, J = 13.2 Hz, H_a), 2.56 (d, 4H, J = 13.2 Hz, H_e), 3.71 (bs, 4H, **b**), 3.89 (m, 2H, 4-H), 4.35 (s, 4H, **d**), 4.50 (bs, 4H, **c**), 4.87 (s, 4H, **a**), 7.57 (s, 4H, Ph), 8.27 (s, 2H, **t**).

Synthesis of [3]Rotaxane 3b

CB6 (0.183 g, 0.18 mmol) was dissolved in HCl 6 M (3 ml) and the resulting solution was stirred for 30 min. Alkyne **4** (0.038 g, 0.18 mmol) and subsequently azide **5** (0.025 g, 0.09 mmol) were added under vigorous stirring at room temperature. The resulting solution was stirred at 60 °C for 24 h. The solvent was removed under reduced pressure to obtain a light yellow solid (0.181 g, 75%). M. p.: > 300° C (decomp). Uv-Vis (H_2O): λ 312 nm.

^{1}H NMR (600 MHz, D_2O): δ 1.62 (s, 12H, CH_3), 1.65 (s, 12H, CH_3), 2.37 (t, 4H, J = 13.2 Hz, H_a), 2.95 (d, 4H, J = 13.2 Hz, H_e), 3.85 (t, 4H, J = 6.7 Hz, **b**), 4.15 (m, 2H, 4-H), 4.26 (t, 4H, J = 6.7 Hz, **c**), 4.30 (s, 4H, **d** overlapped with CB6), 4.29 (d, 12H, J = 15.6 Hz, CB6), 4.30 (d, 12H, J = 15.6 Hz, CB6), 4.66 (s, 4H, **a**), 5.54 (s, 24H, CB6), 5.73 (d, 12H, J = 15.6 Hz, CB6), 5.76

(d, 12H, J = 15.6 Hz, CB6), 6.57 (s, 1H, t), 7.61 (bs, 4H, NH_2^+), 7.85 (s, 4H, Ph). ^{13}C NMR (100 MHz, D_2O, DSS): δ 21.94, 29.94, 41.50, 42.96, 48.12, 48.45, 52.16, 53.67, 53.96, 54.17, 70.62, 72.97, 122.88, 133.06, 135.62, 141.21, 158.97, 159.43. Positive ESI-MS: m/z 672.6 $(M)^{4+}$, 897.2 $(M)^{3+}$.

The rotaxane diradical **3a** was recovered by treating **3b** in water solution with an excess of Ag_2O.

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