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Synthesis and characterization of a paramagnetic receptor based on cyclobis(paraquat-*p*-phenylene) tetracation

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ABSTRACT

Synthesis of a new class of π-electron-deficient tetracationic cyclophane ring, cyclobis(paraquat-*p*-phenylene), carrying one or two paramagnetic side-arms based on 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) moiety has been achieved in five steps starting from 2,5-dimethyl benzoic acid. The possibility of exploiting the proposed cyclophanes as hosts in rotaxane-like structures was tested preparing the monoradical receptor by the clipping procedure in the presence of 1,5-dimethoxynaphthalene (DMN). The addition of template allows the isolation of the monoradical complex with DMN.

Many areas of chemistry take advantage of the information obtained by the combination of molecules of open-shell configuration and chemical stability, owing to the properties displayed by long lifetime radicals to be isolated as pure compounds and observed by conventional spectroscopic methods. Stable radicals[1] have been used to obtain structural, dynamic and reactivity information using electron paramagnetic resonance (EPR) spectroscopy, and for this reason have been introduced in techniques such as spin labelling,[2] spin trapping[3] and EPR imaging,[4] as well as in the development of new materials displaying magnetic and conductivity properties,[5] or in metal-radical hybrid solid investigation towards molecule-based magnets.[6]

Amongst the open-shell species, nitroxides $R_2NO^{\cdot}$ represent the most well-known class of stable radicals.[7] The versatility of these radicals is further due to the opportunity of behaving like a 'normal' diamagnetic compound, with the possibility of performing diverse organic reactions on molecules carrying a nitroxide group without affecting the radical site itself.

Supramolecular chemistry[8] and host–guest chemistry[9] may benefit by this possibility, since introduction of a paramagnetic centre into a molecule acting as a component of the 'supermolecule' is potentially attractive to modulate the behaviour of molecular devices. Recent literature examples of macrocycles carrying paramagnetic centres are represented by paramagnetic calix[4]arenes[10] or cyclodextrin-labelled nitroxides.[11]

Here, we report the synthetic procedure for the preparation of a new class of π-electron-deficient tetracationic cyclophane ring, cyclobis(paraquat-*p*-phenylene) $(CBPQT)^{4+}$, carrying one or two paramagnetic side-arms (**1a**$^{\cdot}$ and **1b**$^{\cdot\cdot}$, respectively) based on 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) moiety as depicted in Figure 1.[12] The electron-deficient macrocycle was chosen because of its use as 'molecular shuttle' in most of the molecular devices proposed by Stoddart and co-workers.[13] The reported radical-armed $(CBPQT)^{4+}$ macrocycle represents a promising host for the preparation of paramagnetic supramolecular architectures, in which spin-spin interactions can be reversibly switched on–off by the movement of the paramagnetic shuttle.

In order to obtain the new macrocycles the bis-pyridinium precursors salts, either in the unsubstituted (**6a**) or in the one-armed (**6b**) form, were linked with a benzylic dibromide **5** containing the nitroxide functionality.

Scheme 1 outlines the synthesis of **5**. Ester **2**, obtained by the acid-catalyzed treatment of 2,5-dimethylbenzoic acid with ethanol,[14] was subjected to an NBS radical bromination with AIBN as the initiator to afford the benzylic dibromide **3**. Reduction of **3** using diisobutylaluminium hydride (DIBAL-H) as the reducing agent, gave the corresponding alcohol **4** in good yields. Subsequent esterification of **4** with 4-carboxy-TEMPO (4-COOH-TEMPO) afforded the dibromide radical **5**.

The modified dipyridinium salt **6b** was prepared by stirring **5** with 2 equiv of 4,4′-bipyridine in DMF at room temperature according to the reaction conditions reported in the Scheme 1. Chromatography by silica gel column ($MeOH/NH_4Cl/MeNO_2$) afforded **6b** as a reddish solid in good yield.

Formation of the cyclophanes shown in Figure 1 was achieved using the clipping methodology consisting in mixing **5** and salt **6a** or **6b** in refluxing acetonitrile for 24–48 h (Scheme 2).

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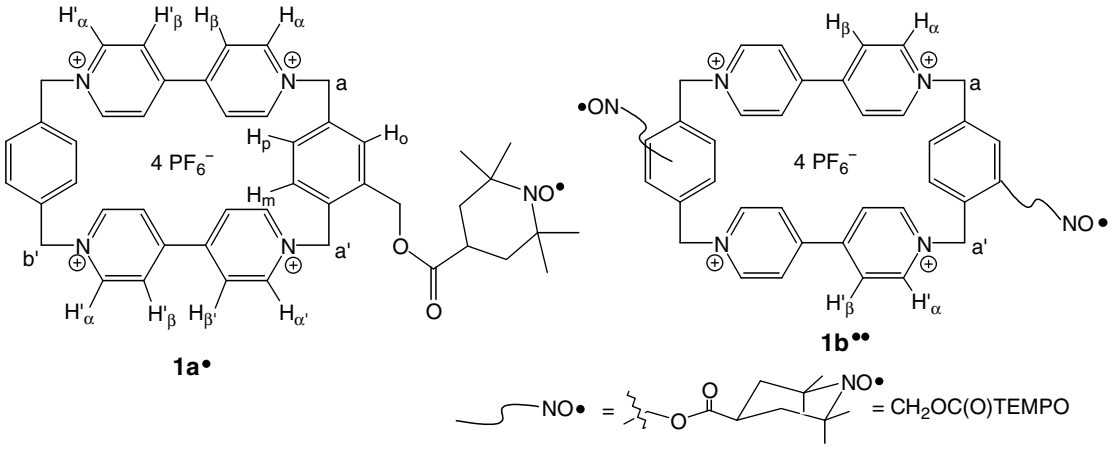
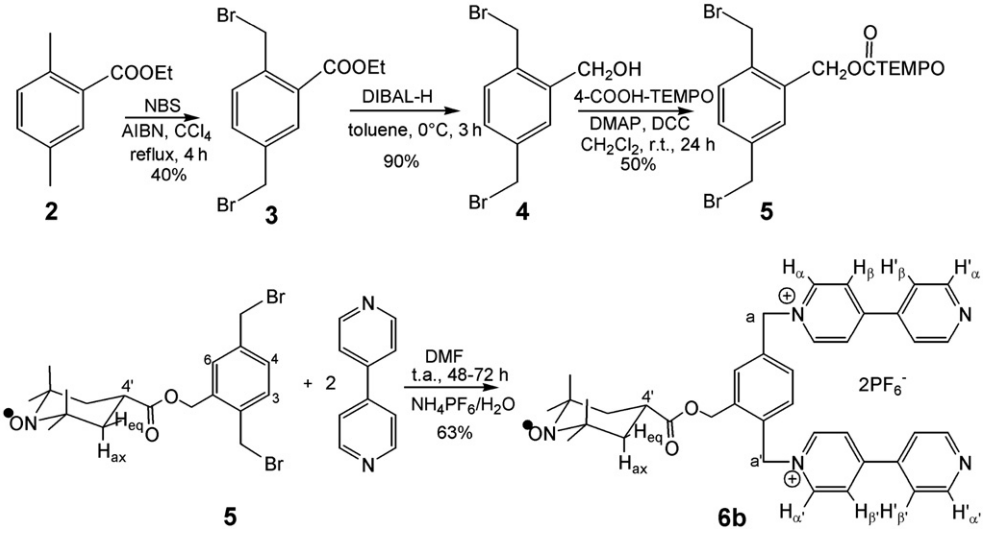
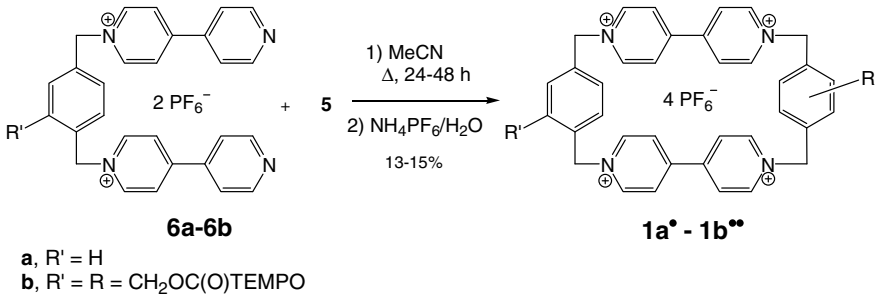


Figure 1. Structures of the paramagnetic macrocycles **1a**· and **1b**··.



Scheme 1.



Scheme 2.

Compounds **1a**· and **1b**·· were recovered by precipitation from the reaction mixture, and isolated without chromatography after exchanging the Cl^- counterions of the cyclophane with saturated aqueous NH_4PF_6, as an orange-brown solid.[15]

Structural assignment of the new CBPQT-based macrocycles **1a**· and **1b**·· was justified on the basis of ESI-MS and 1D, 2D NMR analyses. In Figure 2, the ^1H NMR spectrum (600 MHz, CD_3CN) of **1a**· (trace a) is reported. Because of the paramagnetic units the NMR spectrum shows a very low spectral resolution. In particular, the spectrum is characterized by the lack of the radical heterocyclic signals, and by very broad signals due to the CBPQT protons. In order to render the paramagnetic host suitable for a complete characterization by NMR, it was necessary to quantitatively convert it to the analogous *N*-hydroxy amine derivatives (**1a-OH**)

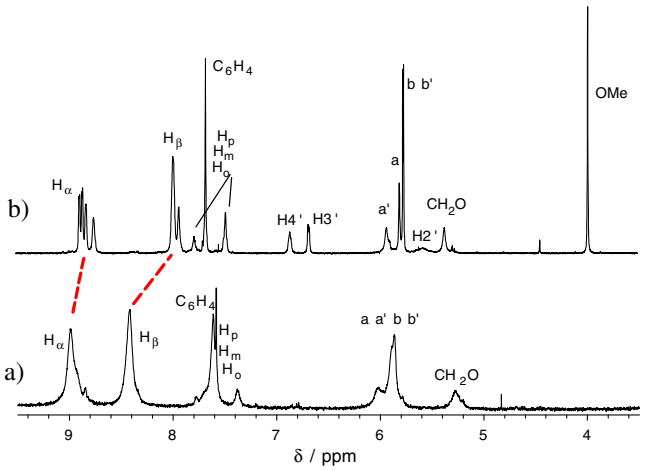


Figure 2. ^{1}H NMR spectra (600 MHz, CD_3CN, 298 K) of the monoradical host **1a**$^{\cdot}$ (a) and its complex with 1,5-dimethoxynaphthalene **7**$^{\cdot}$ (b). The signals were assigned on the basis of 2D ROESY experiments using the labels reported in Figure 1. The dashed lines indicate the most pronounced signal shifts of the complex relatively to the free host.

by adding directly inside the NMR sample stoichiometric amounts of phenylhydrazine.[16]

The spectrum of **1a-OH** (see Supplementary data) shows well-resolved signals for the viologen protons (H_α and H_β); the presence of the radical arm in the structure is evident by the peak shift of H'_α close to the substituent (assigned by 2D ROESY experiments), and by the splittings of the methylene signals (a and a′) of the 1,4-*para*-phenylene unit, as a consequence of the arm-modified symmetry of $CBPQT^{4+}$. Detection of new sharp signals relative to the piperidine moiety emerging after radical reduction allows the complete ^{1}H picture of the macrocycle.

In Figure 3 is instead reported the spectrum of the diradical CBPQT **1b**$^{\cdot\cdot}$. It should be noted that it exhibits separate signals of H_α and H'_α per viologen unit, and a couple of methylene proton resonances (a and a′), due to the presence of a radical substituent in each phenyl ring of the tetracationic cyclophane. In the spectrum of the paramagnetic host appears also one set of peaks belonging to the nitroxyl heterocyclic ring, despite the existence of a paramagnetic centre.[17]

The possibility of using the proposed receptors as a component in rotaxane-like structure was verified by repeating the clipping procedure for preparation of the macrocycles in the presence of 1,5-dimethoxynaphthalene (DMN), as it is well established that the latter is an effective guest for electron-deficient $CBPQT^{4+}$-based cyclophanes.[18] Actually, addition of the template favours the clippage at room temperature between the bis-pyridinium salt **6a** and the radical dibromide **5** in DMF, and affords a powder after 5 days.[13] Separation of the TLC purple spots of the crude on a silica gel column (MeOH/NH_4Cl (2M)/CH_3NO_2 4:4:2) and product isolation after treatment with saturated aqueous NH_4PF_6 give [**1a**$^{\cdot}\subset$**DMN**] (**7**$^{\cdot}$) complex as a purple solid in 33% yield.[19] The schematic representation[18] of **7**$^{\cdot}$ is reported in Figure 4.

Proof of the formation of the host-guest complexation has been attained by UV–vis and NMR measurements. The absorption spectrum of **7**$^{\cdot}$ (Fig. 5) recorded in water at 298 K shows a broad band in the visible region (λ_{max} = 530 nm, ε = 275 M^{-1} cm^{-1}) resulting from charge transfer interaction between DMN and the π-electron-deficient bipyridinium units of the cyclophane **1a**$^{\cdot}$ and DMN.

Two main features may be outlined looking at the ^{1}H NMR spectrum of the radical complex (Fig. 2, trace b). (i) The viologen host signals (H_α and H_β) are significantly shifted towards lower frequencies ($\Delta\delta$ = 0.2, 0.45 ppm). The most pronounced shifts are recorded for H_β, which owing to their central location in the macrocycle are most affected from the inclusion of the guest. Also the guest undergoes proton displacements after involvement in the complex, substantial upfield shifts being measured for all the aromatic protons. (ii) All the radical host signals in the complexed form (trace b) show much better resolution than those of the free macrocycle (trace a), the signals of H_α and H_β being splitted in four and two sets of resonances, respectively. Because line broadening of nuclear magnetic resonances in spin-labelled molecules is distance dependent,[20] the last observation must be related to the position assumed by the radical arm in the free macrocycle and

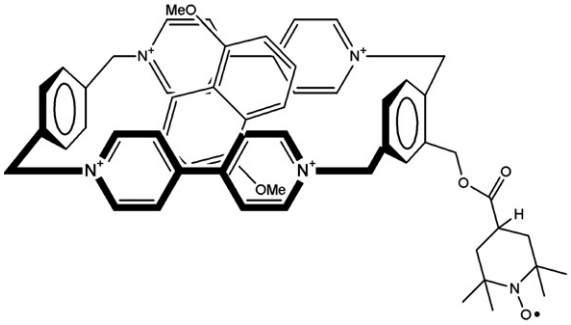


Figure 4. Schematic complex structure.

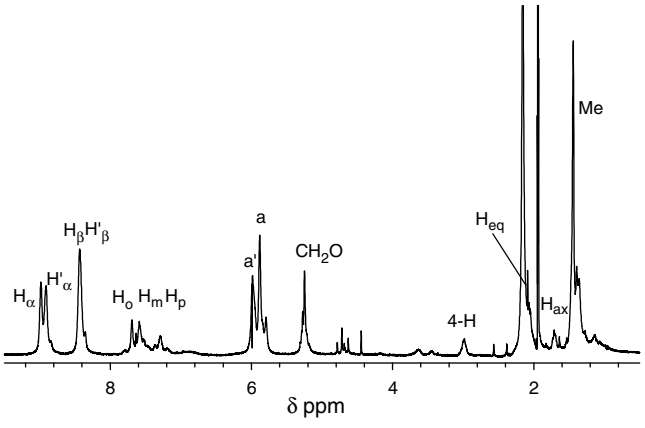


Figure 3. ^{1}H NMR spectra (600 MHz, CD_3CN, 298 K) of **1b**$^{\cdot\cdot}$. The signals were assigned on the basis of 2D ROESY experiments by using the labels reported in the molecular structure of Scheme 1.

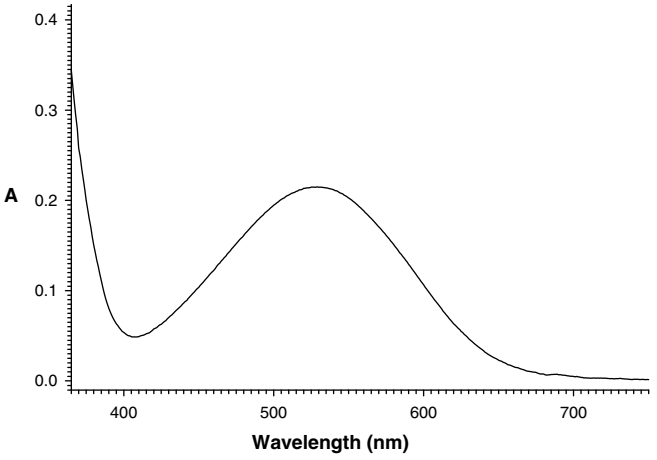


Figure 5. Spectrum UV–vis of the complex [**7a**$^{\cdot}$]·**4Br** in H_2O (0.8 mM). In the same spectral region **1a**$^{\cdot}$ does not show any significant absorption.

in the complex. In the former case, the broadening of the lines indicates that the nitroxide could be located in a position close to the macrocyclic receptor[21] similar to that found by Cooke et al. in their armed $CBPQT^{4+}$ derivative containing a pyrrole moiety.[22] Reasonably, complexation displaces the radical substituent from its original position to a new position in which the free radical part is farther from the macrocycle, thus resulting in an improvement of spectral resolution.

Further support for the hypothesis that the heterocycle position changes upon complexation comes from the observation of downfield shifts for the piperidine protons when passing from the reduced free macrocycle **1a**-**OH** to the corresponding diamagnetic complex **7**-**OH** (the NMR signals due to the heterocylic protons are too broad to be detected in the spectrum of **1**· and **7**·).

EPR spectra of CH_3CN solutions containing **1**· or **7**· were also recorded. The spectra show typical nitroxide EPR signals with the high field line slightly broadened due to restricted tumbling. Quite unexpected, the two radicals show very similar ^{14}N hyperfine splittings, a_N (15.82 G for **1**· and 15.75 G for **7**·), indicating that the complexation does not significantly affect the spin distribution on the nitroxide moiety.

Attempts to isolate the complex between the diradical $CBPQT^{4+}$ (**1b**··) with DMN were unsuccessful, thus indicating that formation of host–guest complex with DMN is considerably less favourable in this case, presumably owing to the steric hindrance of the two arms opposing to the insertion of the guest.

In conclusion, we have described the preparation of two new receptors based on CBPQT tetracation bringing one or two substituents on the paraphenylene units, whereby the arms contain persistent paramagnetic centres. In particular, the monoradical receptor **1a**· is able to complex eletron-rich molecules. The complex with DMN, isolated by flash chromatography, provides evidence that replacement of the radical arm with DMN in the complex imparts a drastic change upon the spectral proton signals of the cavity, that appear well resolved and separated, contrary to what happens in the free receptor which displays broad signals. Therefore, the radical arm becomes a probe to detect inclusion complex formation. We believe that the reported radical-armed macrocycles may represent promising hosts for the preparation of more complexed paramagnetic supramolecular architectures, that is, rotaxanes or catenanes, which can be employed as molecular magnetic devices.

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Supplementary data

Supplementary data (spectroscopic characterization of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.088.

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15. Compound **1a**·: A solution of **6a** (0.240 g, 0.34 mmol) and **5** (0.164 g, 0.34 mmol) in dry acetonitrile (50 ml) was heated under reflux for 24 h. More dibromide **5** (0.071 g, 0.14 mmol) was added and the reaction mixture was refluxed for an additional 24 h. After the solution was cooled down to room temperature, the precipitate was filtered off and washed with acetonitrile (10 ml) and Et_2O (10 ml). The solid was dissolved in water and treated with a saturated aqueous solution of NH_4PF_6 until no further precipitation was observed. The precipitate was filtered off and washed with water, MeOH, Et_2O and dried, affording a reddish powder (0.058 g, 0.044 mmol) in 13% yield. ^1H NMR (600 MHz, CD_3CN, 298 K): δ = 8.80–9.20 (m, 8H, H_α, H'_α, $H_{\alpha'}$), 8.30–8.50 (m, 8H, H_β, H'_β, $H_{\beta'}$), 7.40–7.80 (m, 7H, H_{Ar}, C_6H_4), 5.75–6.10 (m, 8H, a, a′, b, b′), 5.20–5.35 (br s, 2H, CH_2O); positive ESI-MS: *m/z* 1167.7 $[M-PF_6]^+$, 511.2 $[M-2PF_6]^{2+}$. Compound **1b**··: A solution of **6b** (0.140 g, 0.15 mmol) and **5** (0.071 g, 0.15 mmol) in dry acetonitrile (23 ml) was heated under reflux for 24 h. After the solution was cooled down to room temperature, the precipitate was filtered off and washed with acetonitrile (10 ml) and Et_2O (10 ml). The solid was dissolved in water and treated with a saturated aqueous solution of NH_4PF_6 until no further precipitation was observed. The precipitate was filtered off and washed with water, MeOH, Et_2O and dried, affording a brown powder (0.036 g, 0.023 mmol) in 15% yield. ^1H NMR (600 MHz, CD_3CN, 298 K): δ = 8.98 (br s, 4H, H_α), 8.90 (br s, 4H, H'_α), 8.43 (br s, 8H, H_β, H'_β), 7.20–7.80 (m, 6H, H_{Ar}), 5.75–6.10 (m, 8H, a, a′), 5.10–5.40 (br s, 4H, CH_2O), 2.92–3.20 (m, 1H, 4-H), 2.02–2.12 (m, 2H, H_{eq}), 1.64–1.76 (m, 2H, H_{ax}), 1.44 (s, 12H, Me).
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19. Compound **7a**·: A solution containing **2a** (0.1 g, 0.14 mmol), **5** (0.066 g, 0.14 mmol), DMN (0.079 g, 0.42 mmol) and NaI (0.007 g) in dry DMF (10 ml) was stirred at room temperature for 5 days under nitrogen. The solvent was removed under vacuum and the residue was chromatographed over a silica gel column (length 6 cm, i.d. 1.5 cm) using a mixture of MeOH/NH_4Cl (2 M)/CH_3NO_2 (4:4:2) as eluent. The fractions containing the complex, indicated by purple spots of TLC analysis (R_f 0.40), were combined together and concentrated in vacuo. The residue was dissolved in water and a saturated aqueous solution of NH_4PF_6 was added to afford **7a**·. The precipitate was washed with water and dried, furnishing the complex as a purple solid in 33% yield. ^1H NMR (600 MHz, CD_3CN, 298 K): δ = 8.88 (d, *J* = 4.8 Hz, 2H, H'_α), 8.86 (d, *J* = 4.8 Hz, 2H, H'_α), 8.83 (s, 2H, H_α), 8.75 (s, 2H, $H_{\alpha'}$), 7.99 (s, 6H, H_β, H'_β), 7.93 (s, 2H, $H_{\beta'}$), 7.78 (br s, 1H, H_o) 7.67 (s, 4H, C_6H_4), 7.48 (br s, 2H, H_m, H_p), 6.86 (m, 2H, H-3′), 6.67 (d, *J* = 7.2 Hz, 2H, H-2′), 5.88–5.98 (m, 2H, a′), 5.80 (s, 2H, a), 5.77 (s, 2H, b) 5.76 (s, 2H, b), 5.50–5.65 (m, 2H, H-4′), 5.37 (br s, 2H, CH_2O), 3.98 (s, 6H, OMe).
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