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Supporting Information

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

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General information

EPR spectra has been recorded on Bruker-ELEXYS spectrometer by using the following instrument settings: microwave power 0.79 mW, modulation amplitude 0.04 mT, modulation frequency 100 kHz, scan time 180 s, 2K data points. The hyperfine splittings were determined by computer simulation using a Monte Carlo minimisation procedure.[S1]

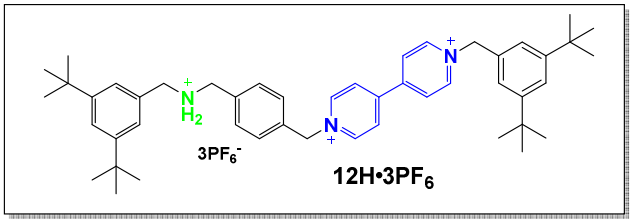
^{1}H NMR spectra of the rotaxanes **11H•3PF$_6$**, the dumbbell **12H•3PF$_6$** and macrocycle **8** together with its precursors were recorded at 298 K on a Varian Mercury spectrometer operating at 400 MHz in CD_3CN, CD_3COCD_3 and CD_3SOCD_3 solutions using the solvent peak as internal standard (1.94, 2.05, and 2.50 ppm). Chemical shifts are reported in parts per million (δ scale).

ESI-MS spectra were recorded on Waters Micromass ZQ 4000 spectrometer by using the following instrumental settings: positive ions; desolvation temp. 200° C; capillary voltage: 3.54 kV; cone voltage: 113 V;.

Stochastic Dynamic (SD) simulations were carried out with the Macro-Model 7.0 program. The N-O bond was modelled by the C=O bond owing to their similar geometries. Extended non-bonded cutoff distances were set to 7 and 12 Å for the van der Waals and electrostatic interactions, respectively. Calculations were performed in *vacuo*. All C-H lengths were held fixed by means of the SHAKE algorithm. The simulations were run at 298 K with time steps of 1.5 fs and an equilibrium time of 2000 ps before each dynamic run. The total simulation time was set to 20000 ps.

Elemental analysis of the rotaxane **11H•3PF$_6$** was performed on a Thermo Flash 2000 CHNS/O analyzer.

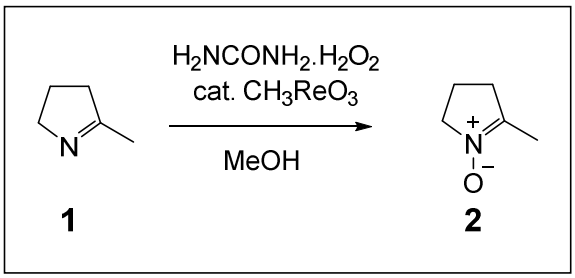
Compound **12H•3PF$_6$** was prepared following a procedure reported in the literature.[S2]



12H•3PF$_6$

All reagents were used without further purification and were commercially available. Dry solvents were bought dry and used directly.

Synthesis of ***5-methyl-3, 4-dihydro-2H-pyrrole-1-oxide*** *(**2**)*

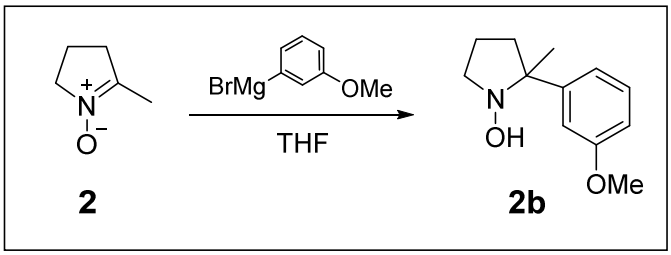


Compound **2** was prepared following the synthetic procedure reported in literature.[S3] To a stirred solution of the imine **1** (1.5 g, 18 mmol) in MeOH (36 mL), urea hydrogen peroxide (5.09 g, 54.13 mmol) and methyltrioxorhenium (0.089 g, 0.36 mmol) were added sequentially. The resulting yellow solution was stirred at room temperature until disappearance of the starting material (2 h). After removal of the solvent under reduced pressure the reaction mixture was added with CH_2Cl_2 and the undissolved urea filtered off. Removal of the solvent afforded the crude product which was purified by flash column chromatography on silica gel (SiO_2, h 20 cm, i.d. 40 mm, CH_2Cl_2/MeOH 9:1, Rf=0.4). Fractions containing the product were concentrated in *vacuo* to give a light yellow oil in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.04-2.12 (m, 2H), 2.69-2.75 (m, 2H), 3.95-4.02 (m, 2H).

GC-MS: *m/z* 99 (100, M), 83 (13), 55 (27), 41 (67).

Synthesis of ***2-(3-methoxyphenyl)-2-methylpyrrolidin-1-ol*** *(**2b**)*



Nitrone **2** (1 g, 10 mmol) dissolved in anhydrous THF (20 mL) was added dropwise at 0 °C over a period of 30 min to a solution of 3-Methoxyphenylmagnesium bromide 1 M in THF (12 mL). The reaction mixture was stirred for 2 h and after this period was quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and then the combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under

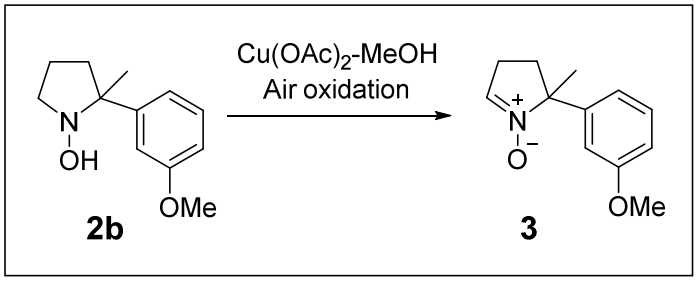
vacuum. The remaining oil was purified by column chromatography eluting with cyclohexane/ethyl acetate 6:4 (Rf=0.46) to give compound **2b** as a colorless oil in 48% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 3H), 1.92-2.10 (m, 3H), 2.29-2.38 (m, 1H), 3.25-3.33 (m, 2H), 3.82 (s, 3H), 6.80 (ddd, *J* = 8.0, 2.4 and 0.8 Hz, 1H), 7.09 (ddd, *J* = 8.0, 1.6 and 0.8 Hz, 1H), 7.13 (dd, *J* = 2.4 and 1.6 Hz, 1H), 7.26 (t, J = 8 Hz, 1H).

GC-MS: *m/z* 207 (1, M), 189 (14, M-OH), 176 (100, M-OCH_3), 162, 84.

ESI-MS: *m/z* 208.27 $(M+H)^+$.

Synthesis of ***2-(3-methoxyphenyl)-2-methyl-3,4-dihydro-2H-pyrrole-1-oxide*** (**3**)

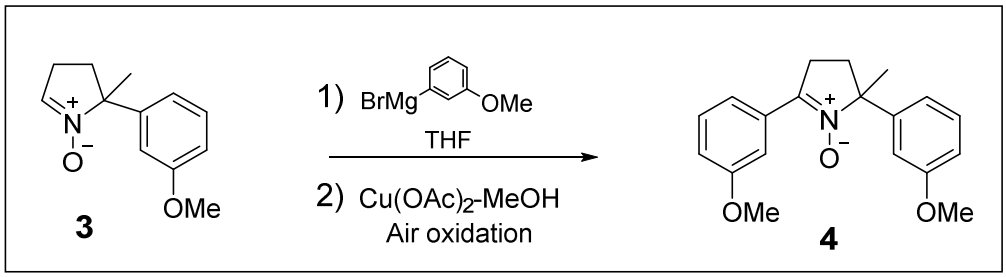


Compound **2b** (0.855 g, 4.12 mmol) was dissolved in MeOH (20 mL) containing concentrated NH_4OH (1.6 mL) and $Cu(OAc)_2$ (0.029 g, 0.144 mmol) and stirred under atmospheric oxygen until the pale yellow solution became dark forest green (2 h). The solution was concentrated and the residue was treated with $CHCl_3$, the combined organic extracts were washed with satured $NaHCO_3$ solution, brine, dried ($MgSO_4$) and the solvent evaporated. The crude product was chromatographed over silica gel column eluting with ethyl acetate and then CH_2Cl_2/MeOH 9:1 to obtain compound **3** as a brown oil in 71 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.32-2.42 (m, 1H), 2.50-2.74 (m, 3H), 3.81 (s, 3H), 6.83 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.91-7.10 (m, 3H), 7.28 (t, *J* = 8.0 Hz, 1H).

ESI-MS: *m/z* 206.25 $(M+H)^+$.

Synthesis of ***2,5-bis(3-methoxyphenyl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide*** *(****4****).*



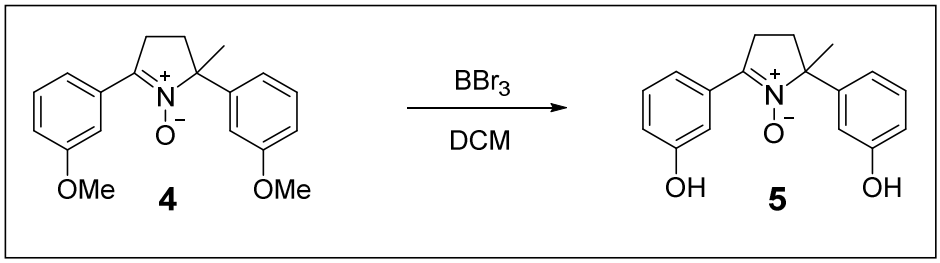
A solution 3-methoxyphenylmagnesium bromide 1 M in THF (0.64 mL) was treated as above with a solution of nitrone **3** (0.110, 0.54 mmol) in THF (1 mL). The reaction mixture was stirred for 5 h. The usual workup and purification using silica gel column (cyclohexane/ethyl acetate 6:4, Rf=0.38) followed by oxidation (see synthesis of compound **3**) gave **4** as a turbid oil in 72% overall yield from **3**.

^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.84 (s, 3H), 2.27-2.37 (m, 1H), 2.46-2.55 (m, 1H), 2.97 (m, 1H), 3.08 (m, 1H), 3.76 (s, 3H), 3.85 (s, 3H), 6.78-6.84 (m, 1H), 6.86-6.92 (m, 2H), 6.98-7.02 (m, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.37 (t, *J* = 2.0 Hz, 1H).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.37-2.46 (m, 1H), 2.55-2.62 (m, 1H), 2.91-3.02 (m, 1H), 3.09-3.27 (m, 2H), 3.79 (s, 3H), 3.90 (s, 3H), 6.84 (dd, *J* = 8.0 and 2.4 Hz, 1H), 6.88-6.92 (m, 2H), 7.10 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz,1H), 8.42 (*br* s, 1H).

ESI-MS: *m/z* 312.438 $(M+H)^+$.

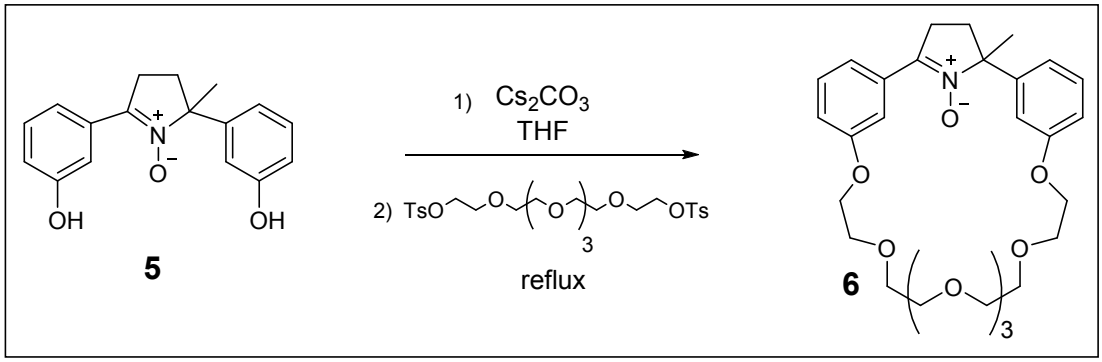
Synthesis of ***2,5-bis(3-hydroxyphenyl)-2-methyl-3,4-dihydro-2H-pyrrole 1-oxide*** *(****5****).*



To a stirred solution of **4** (0.178 g, 0.571 mmol) in CH_2Cl_2 (6 mL) was added a solution of BBr_3 in CH_2Cl_2 (1.7 mL). After 5 h at 0 °C a mixture of ice and water was added and the resulting mixture was stirred for 30 minutes and then extracted using $CHCl_3$/isopropanol (3:1), dried ($MgSO_4$) and the solvent evaporated. The crude product was purified by using silica gel column (CH_2Cl_2/MeOH, 95:5, Rf=0.26) followed by crystallization from $CHCl_3$-cyclohexane to give **5** as a white powder in 31% yield.

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.73 (s, 3H), 2.23-2.33 (m, 1H), 2.33-2.41 (m, 1H), 2.85 (quint., *J* = 8.4 Hz, 1H), 3.05 (ddd, *J* = 17.0, 8.4 and 2.8 Hz, 1H), 6.63-6.67 (m, 1H), 6.69 (t, *J* = 2 Hz, 1H), 6.73-6.77 (m, 1H), 6.86 (dd, *J* = 8.4 and 2.8 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 8.11 (t, *J* = 1.8 Hz, 1H), 9.37 (s, 1H), 9.55 (s, 1H).
ESI-MS: *m/z* 282.3 $(M-H)^-$.

Synthesis of macrocycle ***6***



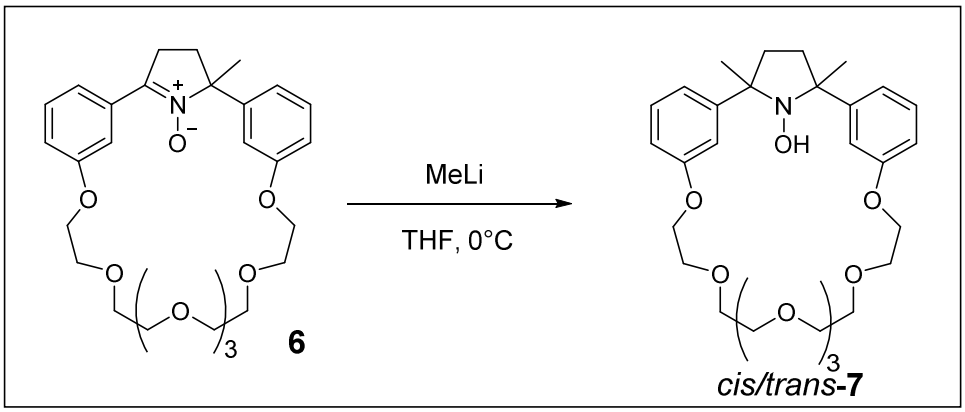
A solution of nitrone **5** (0.071g, 0.25 mmol) in THF (5 mL) was added to a suspension of Cs_2CO_3 (0.414 g, 1.27 mmol) in THF (13 mL). After 15 minutes the reaction mixture was diluted with THF (50 mL), and ditosylate **II** (0.155 g, 0.375 mmol) in THF (50 ml) was added dropwise over 1h while the mixture was refluxed. The resulting mixture was heated at 90°C for 3h and then 70°C for 12h. The solvent was evaporated in vacuo, water added and the aqueous layer was extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), concentrated and purified by column chromatography eluting with EtOAc to obtain the unreacted products and then with CH_2Cl_2/MeOH 95:5 (Rf=0.27) to give compound **6** (0.040 g) as colorness oil in 30% yield.

^{1}H NMR (400 MHz, (CD_3CN): δ 1.81 (s, 3H), 2.30-2.52 (m, 2H), 2.90-2.99 (m, 1H), 3.10 (m, 1H), 3.46-3.60 (m, 16), 3.62-3.44 (m, 2H), 3.78-3.83 (m, 2H), 3.98-4.02 (m, 2H), 4.15-4.20 (m, 2H), 6.75 (t, *J* = 2.4 Hz, 1H), 6.80-6.84 (m, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 8.47 (t, *J* = 1.6 Hz, 1H).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 1.82 (s, 3H), 2.33-2.47 (m, 1H), 2.58 (ddd, *J* = 12.4, 8.0, 2.0 Hz, 1H), 2.93 (quint., *J* = 8.0 Hz, 1H), 3.13 (ddd, *J* = 17.0, 8.0, 2.0 Hz, 1H), 3.49-3.73 (m, 18), 3.84-3.87 (m, 2H), 4.01-4.05 (m, 2H), 4.19-4.22 (m, 2H), 6.83 (ddd, *J* = 8.0, 2.4 and 0.8 Hz, 1H), 6.94 (t, *J* = 2.2 Hz, 1H), 7.02-7.07 (m, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.64-7.67 (m, 1H), 8.70 (dd, *J* = 2.8 and 1.6 Hz, 1H).

ESI-MS: *m/z* 530.44 $(M+H)^+$.

*Synthesis of macrocycle **7***



To a stirred solution of nitrone **6** (0.030 g, 0.056 mmol) in THF (3 mL) at 0 °C was added MeLi (0.5 mL, 1.5 in diethyl ether). After 30 minutes the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$, dried ($MgSO_4$), concentrated and purified by column chromatography using CH_2Cl_2/MeOH 95:5 to give compound **7** (in 6.5:3.5 cis/trans ratio) as light yellow oil in overall quantitative yield.

^{1}H NMR (400 MHz, (CD_3CN): δ 1.57, 1.59 (s, 3H, cis+trans), 1.79-1.85 (m, 2H), 2.00-2.15 (m, 2H), 3.50-3.65 (m, 16H), 3.72-3.85 (m, 4H), 4.07-4.17 (m, 4H), 6.72-6.78 (m, 2H, cis+trans), 6.97-6.99, 7.04-7.08 (m, 2H, cis+trans), 7.22, 7.23 (t, *J* = 8.0 Hz, 2H, cis+trans), 7.49 (dd, *J* = 2.8 and 2.0 Hz and Hz, trans), 7.59 (dd, *J* = 2.4 and 2.0 Hz, cis).

^{1}H NMR (400 MHz, ($CD_3)_2CO$): δ 1.63, 1.64 (s, 3H, cis+trans), 1.84-1.98 (m, 2H), 2.04-2.16 (m, 2H), 3.55-3.69 (m, 16H), 3.81-3.88 (m, 4H); 4.12-4.20 (m, 4H), 6.74, 6.79 (dd, *J* = 8.0 and 2.4 Hz 2H, cis+trans), 6.97, 7.04 (d, *J* = 8.0 Hz, 2H, cis+trans), 7.19, 7.21 (t, *J* = 8.0 Hz, 2H, cis+trans), 7.64, 7.70 (*br* s, 2H, cis+trans).

ESI-MS: *m/z* 546.67 $(M+H)^+$.

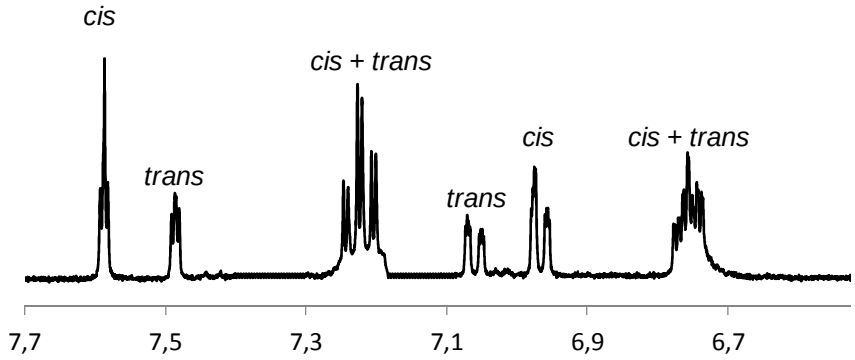
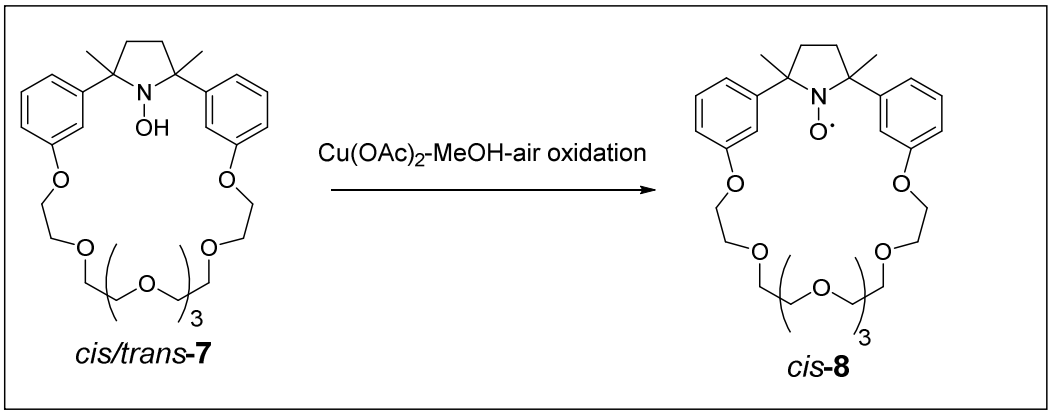


Figure S1. *Partial ^{1}H NMR spectrum (400 MHz, (CD_3CN, 298 K) of a mixture containing cis/trans-* **7**.

*Synthesis of macrocycle **8***



Compound **7** (0.030 g, 0.055 mmol) was dissolved in MeOH (15 mL) containing $Cu(OAc)_2 \bullet H_2O$ and one drop of concentrated NH_4OH and stirred until the pale blue solution became light green (12h). The solution was concentrated and the residue was treated with $CHCl_3$, the combined organic extracts were washed with satured $NaHCO_3$ solution, brine, dried ($MgSO_4$) and the solvent evaporated. The crude product was chromatographed over silica gel column by using CH_2Cl_2/MeOH 95:5 to obtain compound **8** (0.029 g) as an orange oil in quantitative yield relative to the hydroxylamine isomer *cis*-**7**. From the column a fraction containing pure unreacted hydroxylamine *trans*-**7** was also recovered.

ESI-MS: *m/z* 567 $(M+Na)^+$, 545 $(M+H)^+$, 562 $(M+NH_4)^+$.

EPR (CH_2Cl_2): a_N=14.35 G, g = 2.0061.

UV-visible: λ=273 nm, ε=2625 M^{-1} s^{-1}; λ=423 nm, ε=78 M^{-1} s^{-1}, ACN, rt.

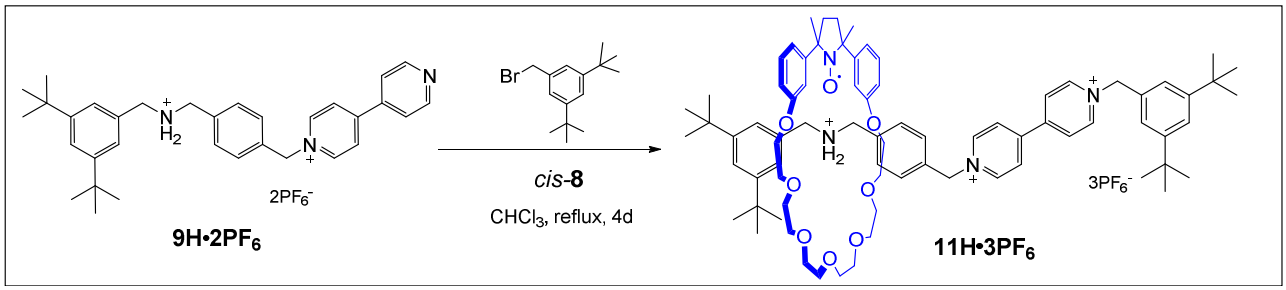
^{1}H NMR (400 MHz, (CD_3CN) of *cis*-**8**: δ 3.50-3.65 (m), 3.75-3.85 (m), 4.06-4.11 (m), 6.70-6.78 (m), 6.95-7.10 (m), 7.15-7.25 (m), 7.35-7.40 (m).

Reduction with phenylhydrazine of the NMR sample tube containing the nitroxide gave the corresponding *cis*-hydroxylamine after 10-15 minutes.

^{1}H NMR (400 MHz, (CD_3CN) of the reduction of *cis*-**8**: δ 1.57 (s, 3H), 1.79-1.85 (m, 2H), 2.04-2.15 (m, 2H), 3.50-3.65 (m, 16H), 3.72-3.85 (m, 4H), 4.13-4.17 (m, 4H), 6.75 (dd, J = 8.0 and 2.4 Hz, 2H), 6.98 (m, 2H), 7.23 (t, J = 8.0 Hz, 2H), 7.59 (dd, J = 2.4 and 2.0 Hz, 2H).

^{1}H NMR (400 MHz, (CD_3CN) of *trans*-**7**: δ 1.59 (s, 3H), 1.90-1.98 (m, overlap with the solvent peak), 2.02-2.10 (m, 2H), 3.56-3.63 (m, 16H), 3.76-3.79 (m, 4H), 4.08-4.12 (m, 4H), 6.76 (ddd, J = 8.0, 2.4, and 0.8 Hz, 2H), 7.06 (ddd, J = 8.0, 1.6, and 0.8 Hz 2H), 7.22 (t, J = 8.0 Hz, 2H), 7.49 (dd, J = 2.4 and 1.6 Hz, 2H).

Synthesis of rotaxane ***11H•3PF$_6$***



A solution of macrocycle *cis*-**8** (0.013 g, 0.024 mmol) in $CHCl_3$ (1 mL) was added to a stirred suspension of compound **9•2PF$_6$** (0.009 g, 0.0117 mmol) in $CHCl_3$ (1 mL) and the mixture was heated under reflux for 30 minutes under nitrogen atmosphere. After this period a solution of 1-(bromomethyl)-3,5-di-tert-butylcyclohexane (0.019 g, 0.066 mmol) was added and the reaction mixture was stirred under reflux for 4 days. After cooling the solution was concentrated *in vacuo* and the reaction mixture was purified by silica gel column (h 10 cm, i.d. 25 mm, CH_2Cl_2-CH_3OH 9:1, then CH_3OH/2M NH_4Cl/H_2O 7:0.5:2.5). The fractions containing the product were concentrated in vacuo, dissolved in a minimum volume of water, and treated with NH_4PF_6 aqueous solution. The resulting solid was collected by filtration, washed with water to remove the excess of NH_4PF_6, and dried to afford the rotaxane **11H•3PF$_6$** as a beige powder in 30% yield.

EPR (CH_2Cl_2): a_N=14.39 G, g = 2.0061.

ESI-MS: *m/z* 1371 (**11**•2PF_6 -PF_6^-)$^+$.

UV-visible: ε=18230 M^{-1} s^{-1}, λ=259 nm, ACN, rt.

^{1}H NMR (400 MHz, (CD_3CN): δ 1.27-1.32 (m, 36H), 3.11-4.10 (m), 4.25 (*br* s, 2H), 4.20 (br s, 2H), 5.77 (*br* s, 4H), 7.29-7.60 (m, 10H), 7.77-7.81 (m, 1H), 8.31-8.41 (m, 3H), 8.80-9.02 (m, 4H).

^{1}H NMR (400 MHz, ($CD_3)_2CO$): δ 1.29-1.32 (m, 36H), 3.38-378 (m), 4.59-4.64 (m, 2H), 4.67-4.72 (m, 2H), 6.15 (s, 2H), 6.18 (s, 2H), 7.34-7.84 (m, 10H), 7.94-8.00 (m, 1H), 8.68-8.90 (m, 3H), 9.35-9.60 (m, 2H).

Anal. Calcd for $C_{78}H_{106}F_{18}N_4O_8P_3$: C, 56.35; H, 6.43; N, 3.37. Found: C, 56.05; H, 6.47; N, 3.28.

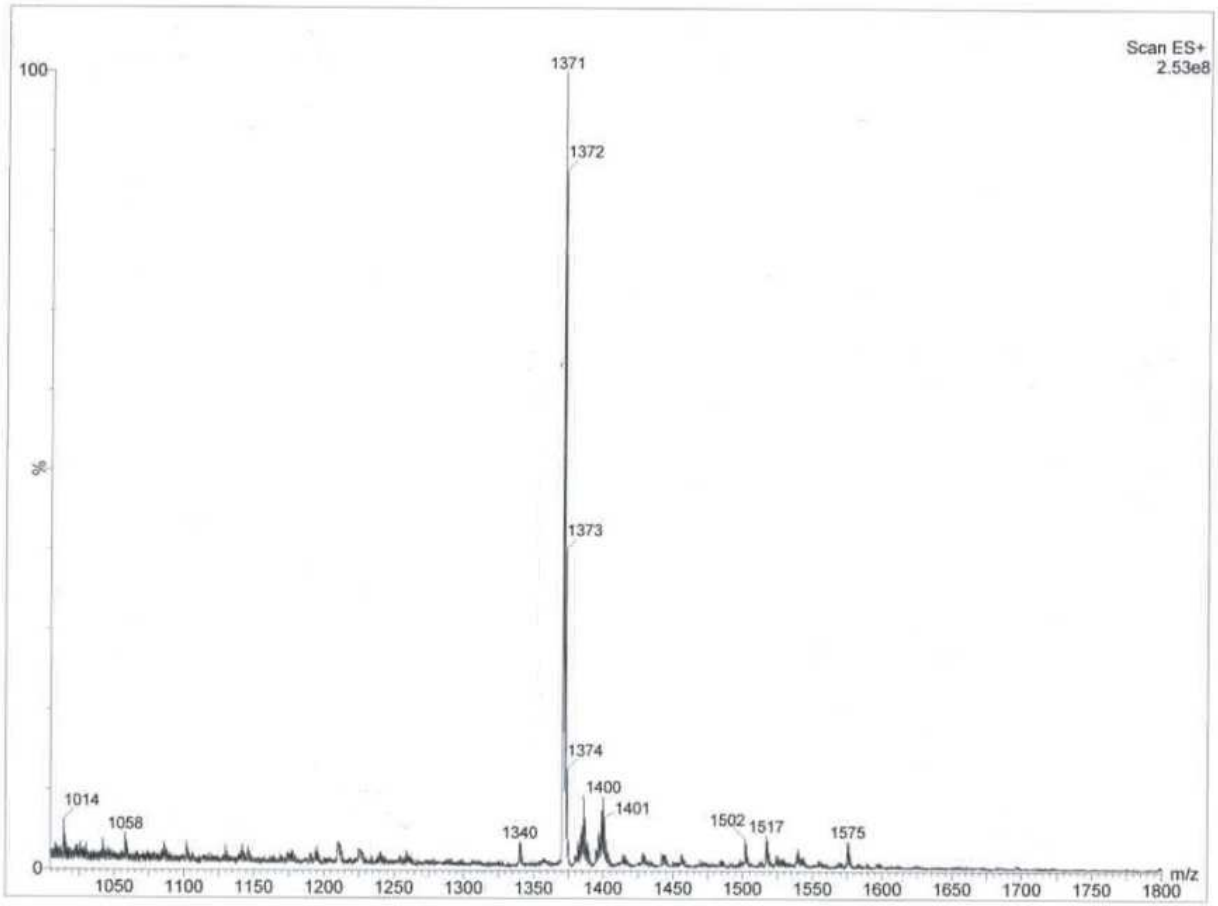


Figure S2. *ESI-MS spectrum of rotaxane* ***11H•3PF$_6$.*** *The spectrum was recorded with Waters Micromass ZQ4000 spectrometer by using the following instrumental settings: positive ions; desolvation temp. 200° C; capillary voltage: 3.54 kV; cone voltage: 113 V; hexapole extractor: 3 V.*

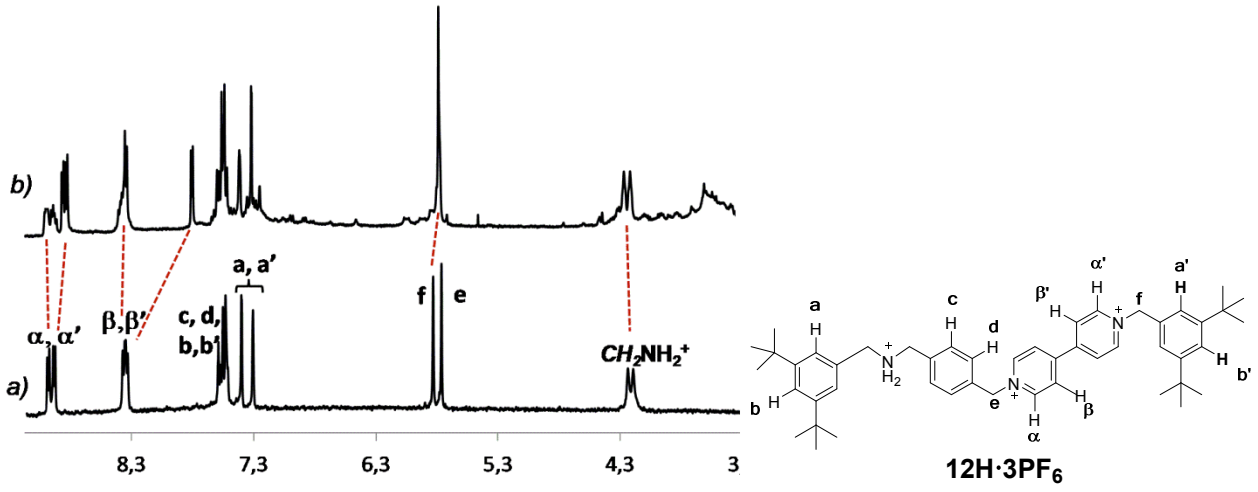


Figure S3. *Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) dumbbell* ***12H•3PF$_6$****; b) rotaxane* ***11H•3PF$_6$.*** *Red dashed lines evidence the shift of some guest protons. Signals were labelled according the structure of the dumbbell reported.*

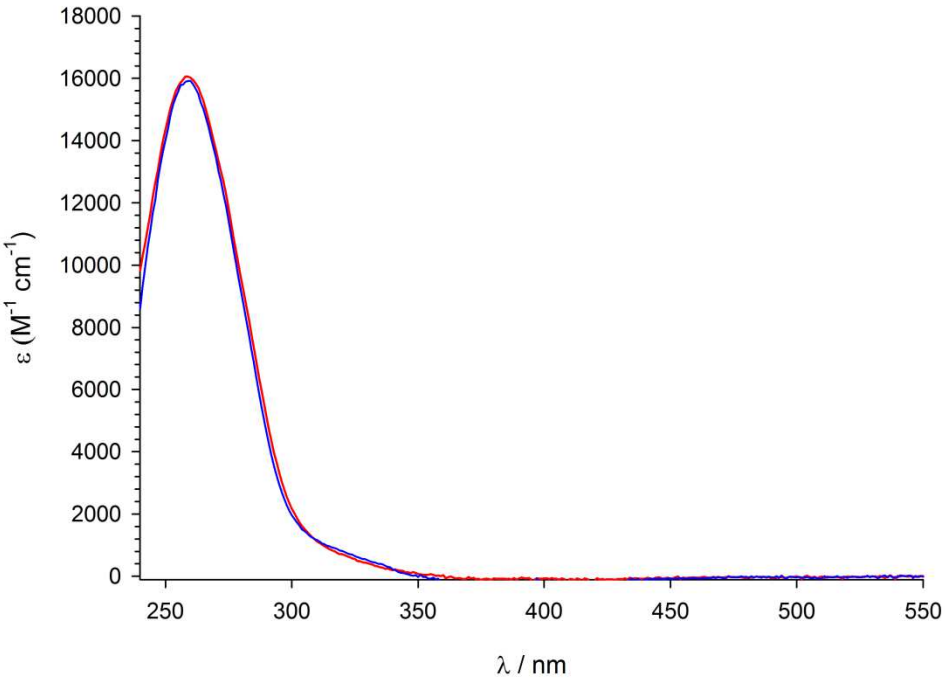


Figure S4. *Absorption spectra of free dumbbell* ***12•2PF$_6$*** *before (red line) and after addition of 1.5 eq of base (blue line) in ACN at 298 K.*

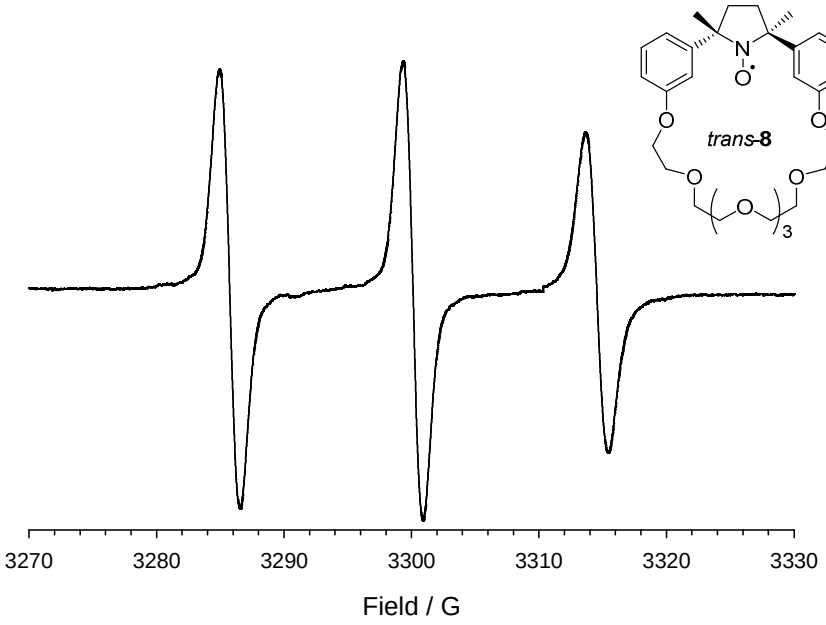


Figure S5. *EPR spectrum of macrocycle trans-**8** in CH_2Cl_2 at 298 K.*

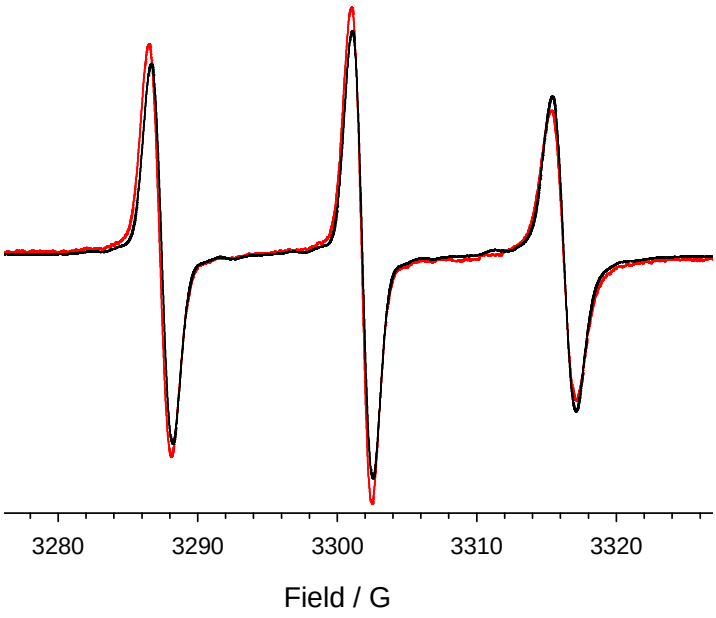


Figure S6. *EPR spectra of rotaxane **11H•3PF$_6$** before (black) and after (red) a complete base- and acid-induced switching cycle in CH_2Cl_2 at 298 K.*

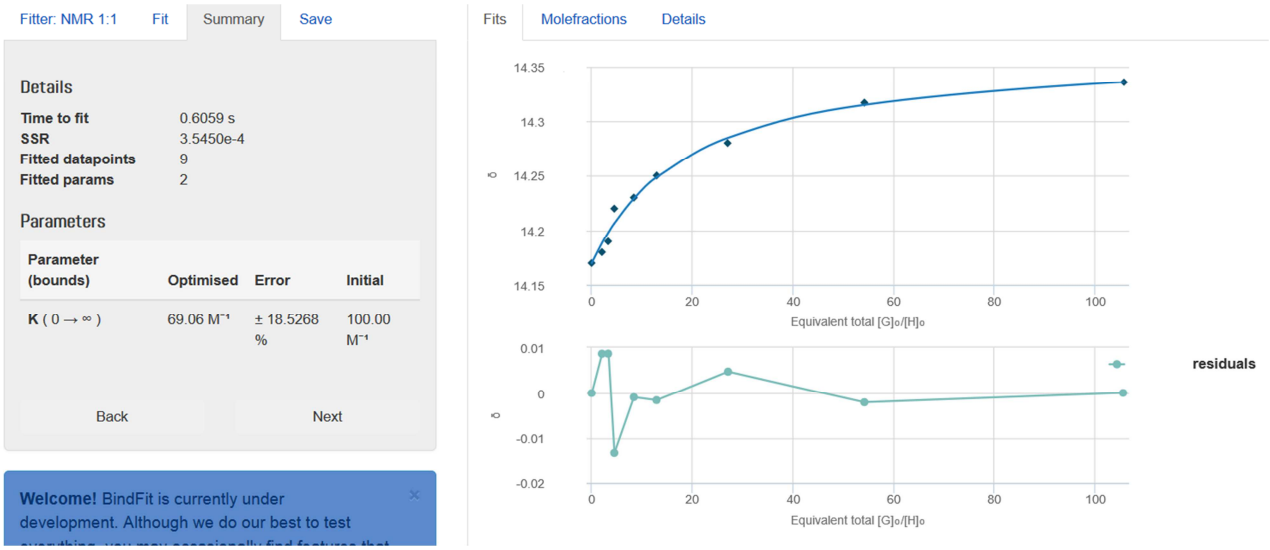


Figure S7. Plot of the EPR nitrogen coupling, a_N, in *cis*-**8** (0.05 mM) versus the concentration of DBV at 298 K in acetone. The line represents the theoretical dependence of a_N on DBV concentration calculated by taking into account the formation of 1:1 complex and K_{eq}=69 M^{-1} . The data treatment was performed by Open Access data analysis resource at website http://supramolecular.org.

References

[S1] M. Lucarini, B. Luppi, G. F. Pedulli, B. P. Roberts, *Chem. Eur. J*. **1999**, *5*, 2048–2054.

[S2] P. R. Ashton, R. Ballardini, V. Balzani, I. Baxter, A. Credi, M. C. T. Fyfe, M. T. Gandolfi, M. Gómez-López, M.-V. Martínez-Díaz, A. Piersanti, N. Spencer, J. F. Stoddart, M. Venturi, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942.

[S3] G. Soldaini, F. Cardona, A. Goti, *Org. Lett*. **2007**, *9*, 473-476.