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Unprecedented *N*(*H*)-bridged tetraaza[1.1.1.1]*m*,*p*,*m*,*p*-cyclophanes

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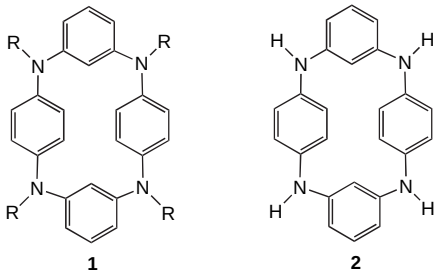
ABSTRACT

The first uncatalyzed preparation of tetraaza[1.1.1.1]*m*,*p*,*m*,*p*-cyclophanes (symmetrical and unsymmetrical) gave access to previously unknown *N*(*H*)-bridged derivatives that could be further substituted. NMR studies and theoretical calculations show that these macrocycles adopt an 1,3-alternated conformation.

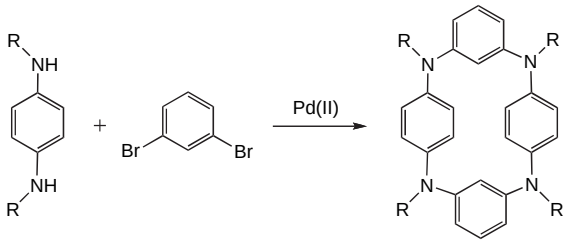
1. Introduction

Cyclophanes have attracted much attention owing to their remarkable electronic and spectroscopic properties but also as effective host molecules in molecular recognition chemistry.[1,2] Although carbon is the most common bridging element in useful macrocyclic compounds, such as calixarenes[3–5] and cyclophanes,[1,2] considerable efforts are now devoted to the synthesis of various heteroatom-bridged [1_4]-cyclophanes in order to obtain additional chemical and physical properties.[6–16] Among them, tetraazacyclophanes that contain two *p*-phenylenediamine units connected by a *m*-phenylene unit (i.e., *N*(*R*)-bridged [1_4]*m*,*p*,*m*,*p*-cyclophanes of type **1**) appeared very attractive for the preparation of stable radicals (R=aryl or CH_3),[17–20] hole transport materials[21] and/or organic light emitting diodes (OLEDs).[22–24]



1 **2**

The reported syntheses of *N*(*R*)-bridged [1_4]*m*,*p*,*m*,*p*-cyclophanes **1** (R=alkyl or aryl) are based on palladium-catalyzed aryl amination reactions (Scheme 1).[18–21] To the best of our knowledge, the access to the sole alkylated derivative of type **1** (R=CH_3) was described with an abysmal yield of 0.28% preventing its use in spintronic application despite a rare stability in the triplet state.[19]



1a R = aryl > 30 %
1b R = CH_3 0.28 %

Scheme 1. Synthesis of aza[1_4]*m*,*p*,*m*,*p*-cyclophanes by Pd catalyzed amination.[18,20,21]

N(*H*)-bridged [1_4]-*m*,*p*,*m*,*p*-cyclophanes of type **2** are hitherto unknown although they are much more attractive owing to possible direct substitutions of the NH sites, which open unprecedented perspectives in *m*,*p*,*m*,*p*-azacyclophane chemistry. The palladium-catalyzed synthesis of molecules **2** could not be performed probably due to the unstability of the *p*-diaminobenzene precursors (i.e., primary *p*-diamines) under these conditions so that their access is still a challenge of major interest.

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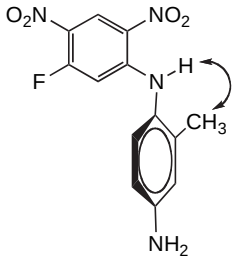
An alternative route that would: (1) not require the use of a catalyst, (2) give access to *N*(*H*)-bridged aza[1$_4$]*m*,*p*,*m*,*p*-cyclophanes of type **2**, and (3) allow further functionalization of the macrocycle, would be obviously of great interest to enlarge the scope of this family of compounds. Herein, we report a synthetic strategy, that is, based on stepwise nucleophilic aromatic substitutions (S_NAr), assisted by hydrogen bonding interactions for controlling the conformation of the key intermediates. The new *N*(*H*)-bridged aza[1$_4$]*m*,*p*,*m*,*p*-cyclophanes of type **2** could then be further directly *N*-substituted.

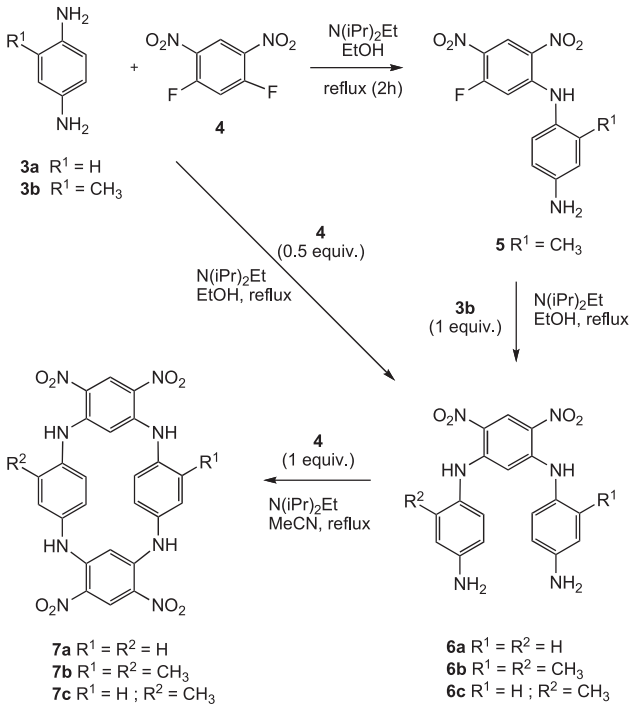
2. Results and discussion

The commercially available *p*-diaminobenzene derivatives were used as nucleophilic components for which introduction of substituents could be achieved and because of the possibility to prepare *N*(*H*)-bridged aza[1$_4$]cyclophanes of type **2**. 1,5-Difluoro-2,4-dinitrobenzene was identified as their coupling partner of choice owing to the presence of structural elements for S_NAr (the C–F carbon atoms are strongly electrophile due to the two electronwithdrawing NO_2 groups on the phenyl ring).

The condensation of the substituted diamine **3b** with **4** was first envisaged in order to discuss the regioselectivity of the reaction (i.e., the position of the methyl group in the formed product). Thus, 2,5-diaminotoluene **3b** was reacted with **4** (1 equiv) in EtOH in the presence of N(^{i}Pr)$_2$(Et) to give the [1+1] adduct **5**, which precipitated in 84% yield (Scheme 2). Its ^{1}H NMR spectrum shows the NH resonance at 10.07 ppm consistent with the presence of a NH···O$_2$N intramolecular hydrogen bond. The two doublets at 6.60 and 8.90 ppm correspond to the coupling of the aromatic protons with the fluoride atom ($^3J_{(HF)}$=14.5 Hz and $^4J_{(HF)}$=8.0 Hz, respectively). We anticipated that the presence of Me in **3b** should 'activate' the NH_2 function in *ortho* position by inductive donor effect (+I). As expected, the NMR data are in agreement with the formation of a single regioisomer **5** for which the location of the CH_3 group on the phenyl ring with respect to the NH bridge is in *ortho* position (only one isomer could be observed in solution). The assignment of the peaks was determined by HMQC, HMBC, NOESY and COSY 2D NMR experiments. More specifically, the NOESY NMR spectrum clearly indicates that the NH proton is coupled through space with the methyl group.



Similarly to the synthesis of **5**, molecules **3a**–**b** were reacted with **4** (0.5 equiv instead of 1) at C≈10^{-1} to 10^{-2} M in EtOH to afford the [2+1] adducts **6a**,**b**, which precipitated in good yields (Scheme 2). Their ^{1}H NMR spectra show two down-field NH protons at δ=9.51 and 9.52 ppm for **6a** and **6b**, respectively, in agreement with NH···O$_2$N hydrogen bonding interactions that restrict the rotation of the uncyclized precursors.[25] By analogy with **5**, the formation of only one regioisomer of type **6** is controlled by electronic effect (+I). Molecules **6a** and **6b** appeared then preorganized for an efficient cyclization. The macrocyclization from reactions between **6a** or **6b** and **4** in refluxing MeCN (C≈10^{-2} M) afforded the target molecules **7a** and **7b** in 84 and 50% yield, respectively (Scheme 2). These compounds are easily obtained in pure form as yellow (**7a**) or orange (**7b**) solids by precipitation (no need of purification by chromatography).



Scheme 2. Synthesis of aza[1$_4$]*m*,*p*,*m*,*p*-cyclophanes **7a**–**c**.

The reported stepwise strategy also allowed the synthesis of the unsymmetrical mixed macrocycle **7c** from **5**. Indeed, compound **5** could be condensed with 1,4-diaminobenzene at C≈10^{-2} M in EtOH to furnish the unsymmetrical intermediate **6c** as a brown solid (70% yield). As expected, its ^{1}H NMR spectrum shows two NH signals at δ=9.50 and 9.52 ppm in agreement with two H-bonds that favour the cyclization step. The macrocyclization from reactions between **6c** and **4** in refluxing MeCN gave **7c** in 66% yield. These observations are consistent with S_NAr reactions assisted by H-bonding interactions, which prevent the formation of polymeric materials or linear oligomers even under low dilution conditions (C≈10^{-1} to 10^{-2} M).

The ^{1}H NMR spectra of **7b** and **7c** show unusual high-field chemical shifts. For instance, **7c** exhibits two resonances of the intraannular aromatic protons Ha at δ=5.43 and 5.64 ppm (Fig. 1).

These ^{1}H NMR data suggest that molecules of type **7** adopt a conformation in which the Ha protons (internal protons) are located inside the anisotropic shielding cone of the adjacent aromatic rings (Fig. 2). This conformation can be described as an 1,3-alternated saddle-shape geometry in which the two *p*-substituted phenyl units are tilted to the plane identified by the four bridging nitrogen atoms. The resonance of the corresponding

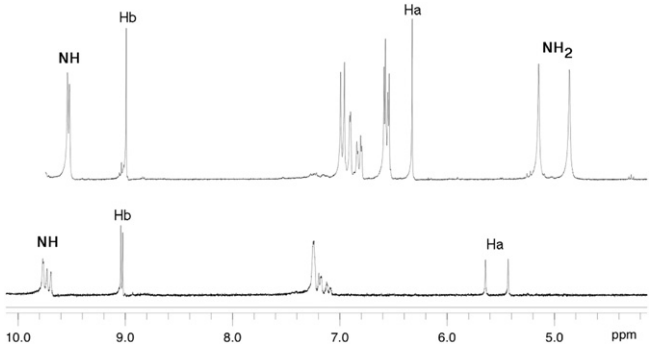


Figure 1. ^{1}H NMR spectra of **6c** (top) and **7c** (bottom) in DMSO-d_6. The range 0–4 ppm are omitted for clarity.

Ha proton in **6c** at δ=6.37 ppm further supports the geometry of **7c** (Ha in **6c** is poorly influenced by the adjacent aromatic rings due to a higher degree of freedom).

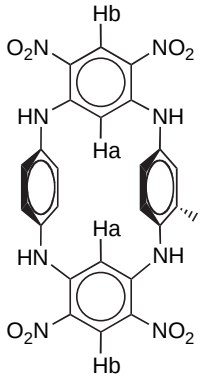


Figure 2. View of the 1,3-alternated conformation of molecule **7c**.

This geometry, suggested in solution, was also confirmed by theoretical studies. We performed a simulated annealing calculation to explore the potential energy surface at SAM1/d[27,28] level with AMPAC package,[29] defaults have been used. In a second step, we characterised the obtained global energy minima by B3LYP/6-31G(d),[30] geometry optimisation, and by frequency calculation (Gaussian03 package).[31] As expected, the obtained geometrical parameters show that macrocycle **7c** has an 1,3-alternated conformation in which the two *p*-substituted phenyl units are tilted to the plane identified by the four bridging nitrogen atoms by around 62° (for instance, the dihedral angle between atoms C(7)–N(1)–C(1)–C(2) is of 62.55°, see Fig. 3).

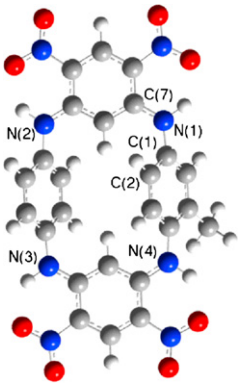


Figure 3. Geometry optimisation of **7c**.

Interestingly, the ^{1}H NMR spectrum of **7b** in DMSO-d_6 at room temperature shows four resonances at 5.08, 5.10, 5.562 and 5.564 ppm integrating for 0.5H, in agreement with the presence of two conformational isomers depending on the relative location of the two methyl groups pointing to the same (*syn*) or opposite direction (*anti*). This observation was supported by theoretical calculations, which showed that the two conformers can co-exist in solution because they are almost degenerated in energy (1.4 kJ/mol) (Fig. 4).

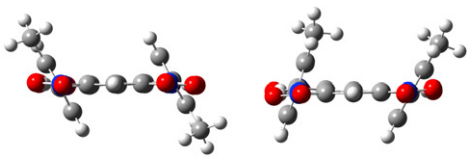


Figure 4. Geometry optimisation of the two conformers (*syn* and *anti*) of **7c**.

It is noteworthy that the parent *N*(*H*)-brided cyclophane **7a** could not be characterized in solution due its lack of solubility even in DMSO. This result would suggest the formation of a supramolecular polymer for which the *p*-substituted phenyl rings interact intermolecularly with: (i) the dinitro substituted rings via strong π–π interactions based on donor/acceptor principle, and/or (ii) the *p*-substituted phenyl bridges. This hypothesis was supported by X-ray powder diffraction studies of **7a**, which revealed the presence of several peaks consistent with an organized arrangement of the molecules in different directions (Fig. 5).

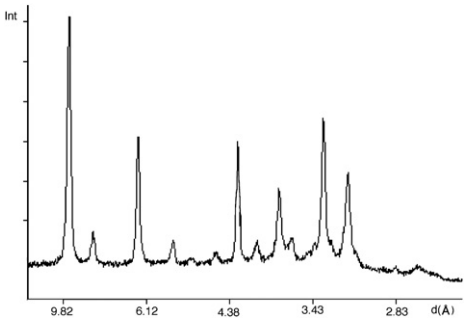
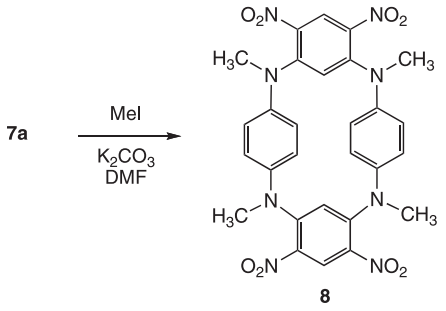


Figure 5. X-ray diffraction spectrum of **7a**.

Introduction of one (**7c**) or two (**7b**) substituents (Me) on such phenyl units leads to soluble molecules due to the breaking of the supramolecular network. The *N*-methyl analogue **8**—which could be prepared in 65% yield by alkylation of **7a** with MeI in refluxing DMF (Scheme 3)—is also insoluble. This observation supports that molecule **8** leads in the solid-state to the formation of a supramolecular polymer similar to that of **7a** (the presence of *N*-Me substituents do not disturb the π stacking).



Scheme 3. Synthesis of *N*-methylated aza[1$_4$]*m*,*p*,*m*,*p*-cyclophane **8**.

Interestingly, molecule **1** for which R=CH_3 is soluble in organic solvents ($CHCl_3$ and AcOEt).[19] This drastic difference of the solubility between **1** (R=CH_3) and **8** can be explained by a 'pseudo' change of the nitrogen hybridation. Indeed, the bridging nitrogen atoms are sp^3 for **1** (R=CH_3) preventing strong π–π interactions due to their flexibility. In contrast, they are strongly conjugated with the nitro groups in **8** and as such, can be viewed as 'pseudo' sp^2 nitrogen atoms by analogy with related tetranitro-tetraazacyclophanes.[26] As a result, compound **8** is a more rigid macrocycle, which favours the orientation of the phenyl rings for optimal π–π interactions. This experimental assumption has been supported by theoretical calculations performed on the analogous **7c**, which showed that nitrogen N(1) is 'pseudo' sp^2 hybridized, making a bond of 1.36 Å length with C(7), and of 1.42 Å with C(1). A similar behaviour has been observed for N(2), N(3) and N(4) (Fig. 3).

The electronic properties of these new macrocycles were examined on **7c** (the most soluble) by cyclic voltammetry as well as UV–vis spectroscopy. The redox potentials were measured in

a 0.1 M solution of tetrabutylammonium hexafluorophosphate ($TBAPF_6$) in DMF using a Ag/AgCl reference electrode and a platinum working electrode (1.6 mm^2).

The voltammogram of **7c** exhibited an irreversible oxidation wave at 1.270 V consistent with an EC mechanism due to a chemical evolution after formation of the cation radical $[\mathbf{7c}]^{+\bullet}$ (Fig. 6). As expected, molecule **7c** appeared much more difficult to oxidize than the *N*(*R*)-bridged azacyclophanes **1** described in the lit.[18,19] due to the presence of the four nitro groups. In contrast, as electron-poor macrocycle, **7c** is—to the best of our knowledge—the first example of tetraaza[1.1.1.1]*m*,*p*,*m*,*p*-cyclophanes that could be reversibly reduced (at −0.978 V). By analogy with related azacyclophanes,[11,19] the access to useful anion radicals might be now envisaged owing to the stabilization of the charge by delocalization over the macrocycle.

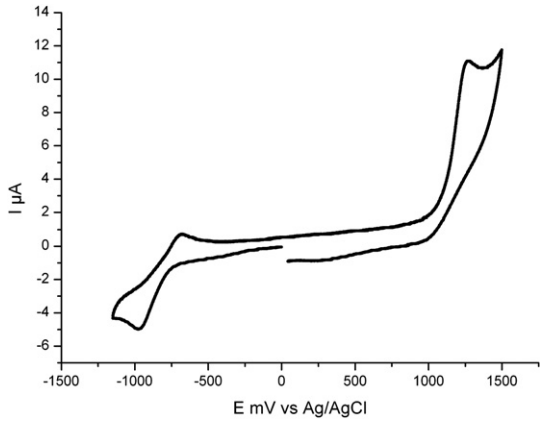


Figure 6. Cyclic voltammogram of **7c** in DMF at 25 °C.

The UV–vis spectrum of **7c** showed two major absorption peaks at 226 (log ε=3.28) and 343 nm (log ε=3.54) in MeCN at room temperature (Fig. 7). The small shoulder lying at the longer wavelength (near 400 nm) can be assigned to the $n \rightarrow \pi$ transition while the peaks at the shorter λ should be caused by the $\pi \rightarrow \pi^*$ transitions.

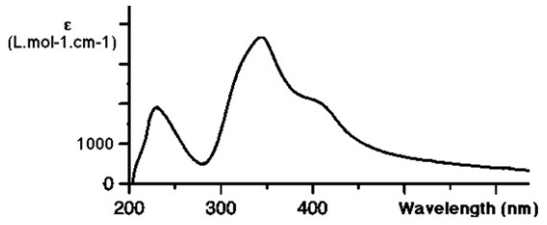


Figure 7. UV–vis spectrum of **7c** in MeCN at room temperature.

3. Conclusion

In summary, we described the first metal-free synthesis of tetraaza[1.1.1.1]*m*,*p*,*m*,*p*-cyclophanes, which allowed the access to unprecedented *N*(*H*)-bridged derivatives **7a–c** (symmetrical and unsymmetrical). This preparation has been achieved by S_NAr assisted by hydrogen bonding interactions, which preorganize the intermediates for an efficient cyclization (no polymerization observed even under low dilution conditions). In addition to the NH bridging sites that can be further directly substituted (**8**), the potential presence of four NH_2 functions (by reduction of the NO_2 groups) open new pespectives as electron-rich molecules for the preparation of high-spin organic materials,[19] as new hosts in supramolecular chemistry[2,5,32,33] and/or as new *N*-donor ligands in coordination chemistry[34–39] (possible further substitutions). The new macrocycles **7** adopt in solution an 1,3-alternated conformation (^{1}H NMR analysis), which was further supported by theoretical calculations. Such compounds could be also easily and reversibly reduced (electrochemical studies). This observation opens new perspectives for this class of macrocycles (**1**, **2** and **7**) because it should now be possible to use them as *n*-dopable materials for the generation of radicals anions as conductive species,[40] or for the formation of ionometallic phases.[41]

4. Experimental

4.1. General remarks

Commercial analytical-grade reagents were obtained from commercial suppliers and were used directly without further purification. Solvents were distilled under argon prior to use and dried by standard methods. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with a AC250 Bruker spectrometer, operating at 250 and 62 MHz, respectively. HMBC, HMQC NOESY and COSY 2D NMR spectra were recorded in DMSO-d_6 with AC400 or AC500 Bruker spectrometers. Chemical shifts are reported in δ units, in parts per million (ppm). Splitting patterns are designed as s, singlet; d, doublet; m, multiplet; br, broad. Elemental and MS analyses were performed by the Spectropole of Marseille. ESI mass spectral analyses were recorded on a 3200 QTRAP (Applied Biosystems SCIEX) mass spectrometer. Cyclic voltammetric (CV) data were acquired using a BAS100 Potentiostat (Bioanalytical Systems) and a PC computer containing BAS100 W software (v2.3). A three-electrode system with a Pt working electrode (diameter 1.6 mm), a platinum counter electrode and an Ag/AgCl (with 3 M NaCl filling solution) reference electrode was used. Tetrabutylammonium hexafluorophosphate, was used as received. The compound was studied at 1.10^{-3} M in DMF/TBAH 0.1 M. and cyclic voltammogram recorded at a scan rate of 100 mV s^{-1}. Ferrocene was used as internal standard. The diffraction powder measurements were realized in transmission mode by using an INEL diffractometer equipped with a linear detector INEL CPS 120. The powder was disposed into a glass capillary of 1 mm in diameter. The radiation length was 1.5418 Å corresponding to Cu K_α.

4.2. Synthesis and characterization of the intermediates

*4.2.1. N^1-(5-Fluoro-2,4-dinitrophenyl)2-methylbenzene-1,4-diamine (**5**).* To a solution of 1,5-difluoro-2,4-dinitrobenzene **4** (*m*=200 mg, 0.98 mmol, 1 equiv) and diisopropylethylamine (*v*=0.83 mL, 4.9 mmol, 5 equiv) in 10 mL of EtOH, was added 2,5-diaminotoluene **3b** (*m*=116 mg, 0.98 mmol, 1 equiv) at room temperature. The mixture was then stirred at under reflux for 6 h and the reaction was monitored by TLC. The obtained precipitate was isolated by filtration and washed with hot water and cold ethanol affording **5** as a brown solid in 84% yield (*m*=205 mg).

^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 2.07 (s, 3H, CH_3), 5.16 (br s, 2H, NH_2), 6.60 (d, 1H, $^3J_{HF}$=14.5 Hz, aromatic H), 6.66 (d, 1H, $^3J_{HH}$=8.3 Hz, aromatic H), 6.90 (m, 2H, aromatic H), 8.90 (d, 1H, $^4J_{HF}$=8.0 Hz, aromatic H), 10.07 (br s, 1H, NH); $^{13}C\{^1H\}$ NMR (62 MHz, DMSO-d_6): δ ppm 17.34 (s, CH_3), 102.70 (d, $^2J_{CF}$=26 Hz, HC–CF), 114.24, 122.08, 124.41, 124.88, 127.10, 127.44, 127.67, 146.36, 148.90, 149.11 (s, aromatic C), 158.79 (d, $^1J_{CF}$=302 Hz, C–F); MS (ESI): 307 $[M+H]^+$; calculated for $C_{13}H_{11}N_4O_4F$: C 50.98, H 3.62, N 18.29; found: C 51.27, H 3.74, N 18.27.

*4.2.2. N,N′-(4,6-Dinitro-1,3-phenylene)dibenzene-1,4-diamine (**6a**).* To a solution of *p*-phenylenediamine **3a** (*m*=353 mg,

1.96 mmol, 2 equiv) and diisopropylethylamine (v=0.85 mL, 4.9 mmol, 5 equiv) in EtOH was added 1,5-difluoro-2,4-dinitrobenzene **4** (m=200 mg, 0.98 mmol, 1 equiv). The mixture was then stirred for 24 h under reflux affording **6a** (precipitate), which was isolated by filtration as a brown solid (m=320 mg, 86% yield).

^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 5.15 (br s, 4H, NH_2), 6.24 (s, 1H, NH–C=C*H*–C–NH), 6.51 (d, 4H, J_{ortho}=8.65, aromatic H), 6.90 (d, 1H, J_{ortho}=8.65, aromatic H), 9.01 (s, 1H, O_2N–C=CH–C–NO_2), 9.51 (br s, 2H, NH); ^{13}C{^{1}H} NMR (62 MHz, DMSO-d_6): δ ppm 93.44, 113.45, 123.46, 124.70, 125.20, 127.90, 146.18, 146.48 (aromatic C); MS (ESI): 381 $[M+H]^+$; calculated for $C_{18}H_{16}N_6O_4$: C 56.84, H 4.24, N 22.10; found: C 56.51, H 4.25, N, 21.60.

*4.2.3. N,N′-(4,6-Dinitro-1,3-phenylene)bis(2-methylbenzene-1,4-diamine) (**6b**).* To a solution of *p*-phenylenediamine **3b** (m=431 mg, 1.96 mmol, 2 equiv) and diisopropylethylamine (v=0.85 mL, 4.9 mmol, 5 equiv) in EtOH was added 1,5-difluoro-2,4-dinitrobenzene **4** (m=200 mg, 0.98 mmol, 1 equiv). The mixture was then stirred for 24 h under reflux affording **6b** (precipitate), which was isolated by filtration as an orange solid (m=310 mg, 77% yield).

^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 2.01 (s, 6H, CH_3), 4.94 (br s, 4H, NH_2), 6.33 (s, 1H, NH–C=C*H*–C–NH), 6.56 (d, 4H, J_{ortho}= 8.09 Hz, aromatic H), 6.80 (m, 4H, aromatic H), 9.02 (s, 1H, O_2N–C=CH–C–NO_2), 9.52 (br s, 2H, NH); ^{13}C{^{1}H} NMR (62 MHz, DMSO-d_6): δ ppm 17.36 (CH_3), 93.97, 114.00, 121.76, 123.18, 124.08, 125.47, 126.40, 128.54, 145.09, 146.70; MS (ESI): 409 $[M+H]^+$; calculated for $C_{20}H_{20}N_6O_4$: C 58.82, H 4.94, N 20.58; found: C 58.77, H 4.97, N 20.21.

*4.2.4. N^1-(4-Amino-2-methylphenyl)-N^3-(4-aminophenyl)-4,6-dinitrobenzene-1,3-diamine (**6c**).* To a solution of *p*-phenylenediamine **3a** (m=117.6 mg, 0.65 mmol, 1 equiv) and diisopropylethylamine (v=0.65 mL, 3.26 mmol, 5 equiv) in MeCN was added **5** (m=306 mg, 0.65 mmol, 1 equiv). The mixture was then stirred for 8 h under reflux to afford **6c** (precipitate), which were isolated by filtration as an orange solid (m=180 mg, 70% yield).

^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 2.03 (s, 3H, CH_3), 4.94 (br s, 2H, NH_2), 5.19 (br s, 2H, NH_2), 6.37 (s, 1H, NH–C=C*H*–C–NH), 6.53 (dd, 4H, J_{ortho}=8.6 Hz, J_{meta}=3.3 Hz, aromatic H), 6.77 (dd, 1H, J_{ortho}= 8.36 Hz, J_{meta}=2.36 Hz, aromatic H), 6.85 (d, 1H, J_{meta}=2.36 Hz, aromatic H), 6.92 (d, 1H, J_{ortho}=8.36 Hz, aromatic H), 9.00 (s, 1H, O_2N–C=CH–C–NO_2), 9.50 (br s, 1H, NH), 9.52 (br s, 1H, NH); ^{13}C{^{1}H} NMR (62 MHz, DMSO-d_6): δ ppm 17.36 (CH_3), 94.08, 114.04, 114.09, 121.72, 122.95, 124.11, 124.14, 125.34, 125.50, 126.04, 128.55, 144.98, 146.42, 147.01, 147.24 (aromatic C), only 16 peaks instead of 19 could be observed due to signal overlap; MS (ESI): 395 $[M+H]^+$; calculated for $C_{19}H_{18}N_6O_4\cdot 1/3H_2O$: C 57.00, H 4.70, N 20.99; found: C 57.08, H 4.57, N 20.72.

4.3. Synthesis and characterization of the *N*(*H*)-bridged macrocycles 7a–c

*4.3.1. General procedure for the synthesis of **7a**–**c**.* To a solution of **6a**–**c** in MeCN in the presence of diisopropylethylamine (5 equiv) was added 1,5-difluoro-2,4-dinitrobenzene **4** (1 equiv). The mixture was then stirred for 24 h under reflux to afford a precipitate of **7a**–**c**, which was isolated by filtration.

*4.3.2. Characterization of **7a**–**c**.*

*4.3.2.1. 8,10,19,20-Tetranitro-1,6,12,17-tetraaza[1$_4$]cyclophane (**7a**).* Yellow solid (m=105 mg, 84% yield): MS (ESI): 543 $[M-H]^+$; calculated for $C_{24}H_{16}N_8O_8$: C 52.95, H 2.96, N 20.58; found: C 52.44, H 3.07, N 20.22.

*4.3.2.2. 3,15-Dimethyl-8,10,19,20-tetranitro-1,6,12,17-tetraaza[1$_4$]-cyclophane (**7b**).* Orange solid (m=140 mg, 50% yield): ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 2.38 (s, 6H, CH_3), 5.08 (s, 0.5H, Ha), 5.10 (s, 0.5H, Ha), 5.562 (s, 0.5H, Ha), 5.564 (s, 0.5H, Ha), 7.20 (m, 6H) aromatic H, 9.08 (m, 2H, Hb), 9.78 (m, 4H, NH); MS (ESI): 573 $[M+H]^+$; calculated for $C_{26}H_{20}N_8O_8\cdot 1/3H_2O$: C 53.98, H 3.60, N 19.37; found: C 53.61, H 3.63, N 18.97.

*4.3.2.3. 3-Methyl-8,10,19,20-tetranitro-1,6,12,17-tetraaza[1$_4$]cyclophane (**7c**).* Orange solid (m=112 mg, 66% yield); ^{1}H NMR (250 MHz, DMSO-d_6): δ ppm 2.09 (s, 3H, CH_3), 5.43 (s, 1H, Ha), 5.64 (s, 1H, Ha), 7.12 (m, 7H, aromatic H), 9.02 (s, 1H, Hb), 9.04 (s, 1H, Hb), 9.68 (br s, 1H, NH), 9.70 (br s, 1H, NH), 9.72 (br s, 1H, NH), 9.96 (br s, 1H, NH); MS (ESI): 557 $[M-H]^+$; calculated for $C_{25}H_{18}N_8O_8\cdot 1/3H_2O$: C 53.20, H 3.33, N 19.85; found: C 53.09, H 3.33, N 19.44.

4.4. Synthesis and characterization of the *N*(*R*)-bridged macrocycle

*4.4.1. N,N′,N″,N‴-Tetramethyl-8,10,19,20-tetranitro-1,6,12,17-tetraaza[1$_4$]cyclophane (**8**).* To a stirred solution of **7a** (m=250 mg, 0,46 mmol, 1 equiv) in 10 mL of anhydrous DMF was added potassium carbonate (m=634 mg, 4,60 mmol, 10 equiv) under an Ar atmosphere. The solution turns immediately into a dark red colour and is left at room temperature for 20 min. To this red solution was added methyl iodide (v=242 μl, 3,68 mmol, 8 equiv) and the obtained solution was then stirred overnight at 80 °C affording **8**, which was isolated by filtration as an orange solid and washed with MeCN (m=208 mg, 65% yield).

MS (ESI): 601 $[M+H]^+$; calculated for $C_{28}H_{24}N_8O_8\cdot CH_3CN\cdot 1/2\,K_2CO_3$: C 51.54, H 3.83, N 17.74; found: C 51.69, H 3.39, N 18.25.

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