

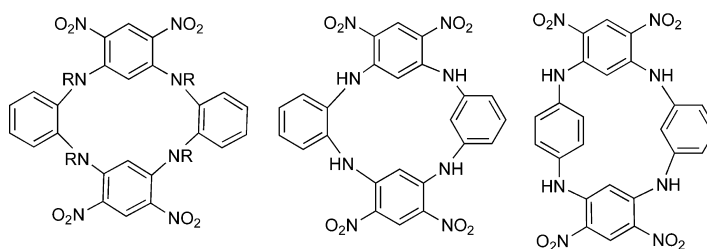
Unprecedented Tunable  
Tetraazamacrocycles

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## ABSTRACT



Novel nitrogen-bridged aza[14]cyclophanes with fine-tuned cavities have been synthesized by nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene with diaminobenzene derivatives.

Cyclophanes generate continuous interest because of their electronic properties and their importance in coordination chemistry but also as effective host molecules in supramolecular recognition chemistry.<sup>1</sup> Furthermore, extensive biological applications inspired by naturally occurring host–guest interactions have stimulated considerable development in the chemistry of macrocyclic complexes.<sup>2</sup> The recognition of a guest by a supramolecular host and of a metal ion by a ligand have in common that properties of the complexation products depend largely on whether, and in which way the two partners fit together. The size and rigidity of the host are important factors for molecular recognition.<sup>3</sup> In this respect, fine-tuning the cavity may have a crucial impact on the recognition properties of host molecules.

Besides the well-studied calix[*n*]arenes, in which four aromatic rings are linked together by methylene bridges, N(R)-bridged [14]*m*- and *m,p,m,p*-cyclophanes of types **1** and

**2** are of growing interest because the nitrogen bridges are likely to bring additional molecular properties to these macrocyclic entities.<sup>4</sup> For instance, the presence of nitrogen atoms increases the electron density of the  $\pi$ -cloud by conjugation with the aromatic rings and may also participate in the interactions with guest species.<sup>5</sup> In addition, they are the key sites for robust high spin stable polyradicals due to the presence of the nitrogen bridges as spin bearing sites, and the 1,3-phenylene subunits which act as ferromagnetic couplers.<sup>6</sup> Reported syntheses of N(R)-bridged [14]*m*- and *m,p,m,p*-cyclophanes **1** and **2** (R = H, alkyl, aryl) are based on palladium-catalyzed aryl amination reactions.<sup>7,5a,6d</sup> A straightforward, catalyst-free approach, based on a stepwise

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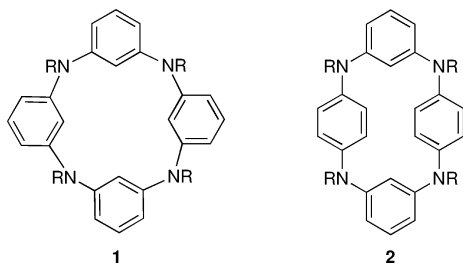
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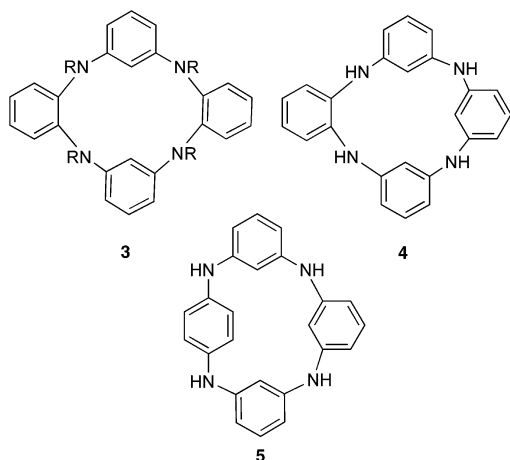
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nucleophilic aromatic substitution ( $S_NAr$ ), has been recently introduced, and proved valuable in the synthesis of compounds **1** and **2**.<sup>8</sup> However, because of synthetic challenges, only very few examples of aza[ $1_n$ ]cyclophanes having different geometries have been described to date.



Rajca et al. varied the size of the inner cavity by increasing the number of benzene rings and were able to generate aza[ $1_n$ ]metacyclophanes having up to 10 units.<sup>7b</sup> Another approach toward modulating the cavity of these macrocycles would be to alternate ortho-, meta-, and para-substituted phenylene rings while keeping a constant number of benzene moieties. To gain further insight into the structure–activity relationships of these macrocyclic systems, the efficient and convenient synthesis of unprecedented aza[ $1_4$ ]cyclophanes of types **3**, **4**, and **5** with a varied stereochemistry is therefore reported herein.

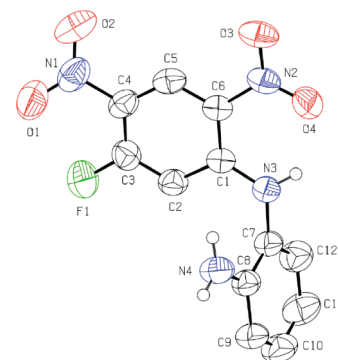


In planning our synthesis (Scheme 1), 1,2-diaminobenzene derivatives **6a** and **6b** were used as nucleophilic components to be functionalized by 1,5-fluoro-2,4-dinitrobenzene **7**. The reaction between **6a** or **6b** and **7** (0.5 equiv) led to the formation of the [2+1] products **9a** or **9b** which precipitated in EtOH with good yields. Their <sup>1</sup>H NMR spectra showed a downfield NH at  $\delta$  9.38 and 9.23 ppm for **9a** and **9b**, respectively, in agreement with a  $NH\cdots O_2N$  hydrogen bonding interaction that restricts the rotation of the uncyclized precursors.<sup>8a</sup>

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To access the azacyclophane **3c**, a stepwise synthesis was envisaged. Compound **6a** was first reacted with **7** (1 equiv) at 0 °C in EtOH in the presence of  $N(iPr)_2Et$  (*N,N*-diisopropylethylamine) to afford the [1+1] precursor **8** (65% yield). X-ray analysis of **8** shows that the N(3)–C(1) bond length is much shorter than the N(3)–C(7) distance due to the conjugation of the N(3) lone pair with the nitro group (1.346(3) vs 1.432(3) Å).<sup>9</sup> The hybridization of the bridging nitrogen can then be viewed as pseudo- $sp^2$ . Interestingly, the N(2)–C(6)–C(1) angle is smaller than that of N(1)–C(4)–C(3) (121.6(2) vs 122.7(3)°) due to a strong intramolecular hydrogen bonding interaction between N(3)–H and O(4) [ $d(NH\cdots O_2N)$  = 1.997 Å], which preorganizes the backbone of the uncyclic intermediate for the cyclization step (Figure 1).

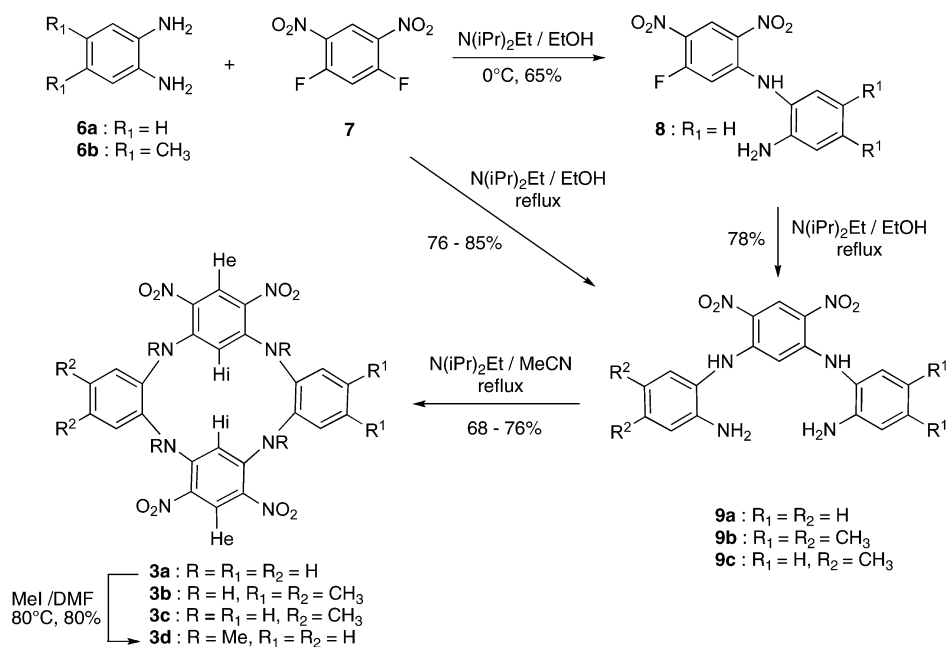


**Figure 1.** ORTEP view of the crystal structure of **8**. Displacement parameters include 50% of the electron density. Selected bond distances (Å) and angles (deg): C(1)–N(3) = 1.346(3), C(2)–C(1) = 1.402(4), C(2)–C(3) = 1.351(4), C(3)–C(4) = 1.398(4), C(4)–C(5) = 1.365(4), C(6)–C(5) = 1.379(4), C(1)–C(6) = 1.425(3), C(4)–N(1) = 1.454(4), C(6)–N(2) = 1.446(4); C(1)–C(2)–C(3) = 122.1(3), C(2)–C(1)–N(3) = 120.2(2), N(3)–C(1)–C(6) = 124.2(2), N(2)–C(6)–C(1) = 121.6(2), N(1)–C(4)–C(3) = 122.7(3).

**8** was then reacted with **6b** in refluxing EtOH to give **9c** (78% yield). Finally, the macrocyclization reactions between **9a–c** and **7** in refluxing MeCN ( $C = 10^{-2}$  M) furnished the target molecules **3a–c** in 75%, 76%, and 68% yield, respectively. When the same reaction was carried out at lower concentration ( $C = 5 \times 10^{-4}$  M), lower yields were obtained, confirming the strong influence of the concentration on the formation of the macrocycles by  $S_NAr$  assisted by H-bonding interactions.<sup>8a</sup> Noteworthy, all compounds were isolated as pure yellow solids by a simple filtration step without the need for further purification by column chromatography. The presence of NH bridges in **3a–c** is very attractive because of their possible substitutions. For instance, compound **3d** was obtained from **3a** by N-alkylation by using methyl iodide in DMF at 80 °C (80% yield). The <sup>1</sup>H NMR spectrum of **3a**, **3b**, and **3c**

(9) Selected data for **8**: monoclinic space group  $P121/n1$  with  $a = 15.1272(5)$  Å,  $b = 5.4965(2)$  Å,  $c = 16.8300(8)$  Å,  $\beta = 114.777(2)^\circ$  at 293(2) K with  $Z = 4$ . Refinement of 3015 reflections, and 190 parameters, yielded  $R2 = 0.1268$  for all data (1767 reflections with  $I > 2\sigma(I)$ ).

### Scheme 1. Synthesis of Tetraaza[14]orthocyclophanes **3a–d**



revealed that these macrocycles adopt a 1,3-alternated conformation in solution, in which the intraannular aromatic protons  $H_i$  are located inside the anisotropic shielding cone of the adjacent aromatic rings. This assumption was supported by the observed high-field chemical shifts at  $\delta$  4.98, 4.90, and 4.91 ppm for  $H_i$  protons of **3a**, **3b**, and **3c**, respectively. In addition, the NH resonance at around 9 ppm is consistent with the presence of a  $NH \cdots O_2N$  intramolecular hydrogen bond. In contrast, the corresponding  $H_i$  protons in **9a**, **9b**, and **9c** appeared at 5.99, 5.90, and 5.91 ppm, respectively, thereby indicating that the [2+1] products have a higher degree of freedom (see for instance the chemical shift of  $H_i$  in **9b** and **3b**, Figure 2).

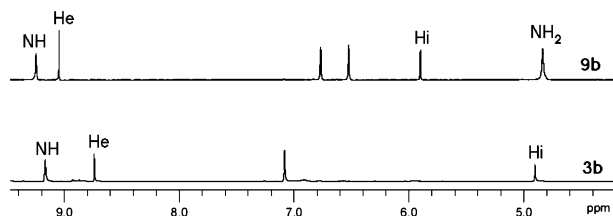


Figure 2.  $^1H$  NMR spectra of **9b** and **3b** in  $DMSO-d_6$ .

Conversly, the  $^1H$  NMR of **3d** at room temperature showed two resonances at 6.33 and 5.31 ppm for the  $H_i$  protons in agreement with the presence of an equilibrium between the cone-shape and 1,3-alternated conformations, respectively. This observation was further proved by  $^{13}C$  solid NMR (which confirmed the purity of **3d**) and temperature-dependent  $^1H$  NMR experiments (for more details see the

Supporting Information). The existence of two different conformers in solution for **3d** might be explained by a gain in flexibility by comparison with **3a–c** due to the presence of *N*-methyl substituents, which prevents H-bonding interaction with the  $NO_2$  groups. This hypothesis is supported by the X-ray structure of **8**, which reveals that the  $N(2)O_2$  group is coplanar with respect to the molecular plane formed by the  $C_1-C_6$  ring and the  $N(3)-H$  bridge. In contrast, the  $N(1)O_2$  function in **8** is tilted about  $17^\circ$  with respect to this molecular plane owing to a lack of intramolecular interaction (i.e., higher degree of freedom). The UV–vis spectrum of **3a–d** in MeCN showed a broad electron-absorption band (with a shoulder) at  $\lambda_{max}$  330, 335, 325 nm for **3a–c**, respectively, which is shifted to 260 nm for compound **3d** (Figure 3).

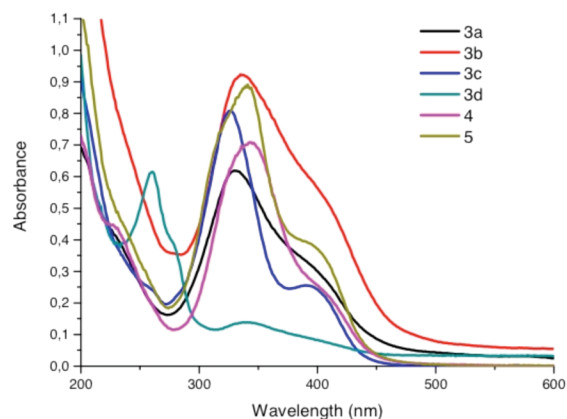
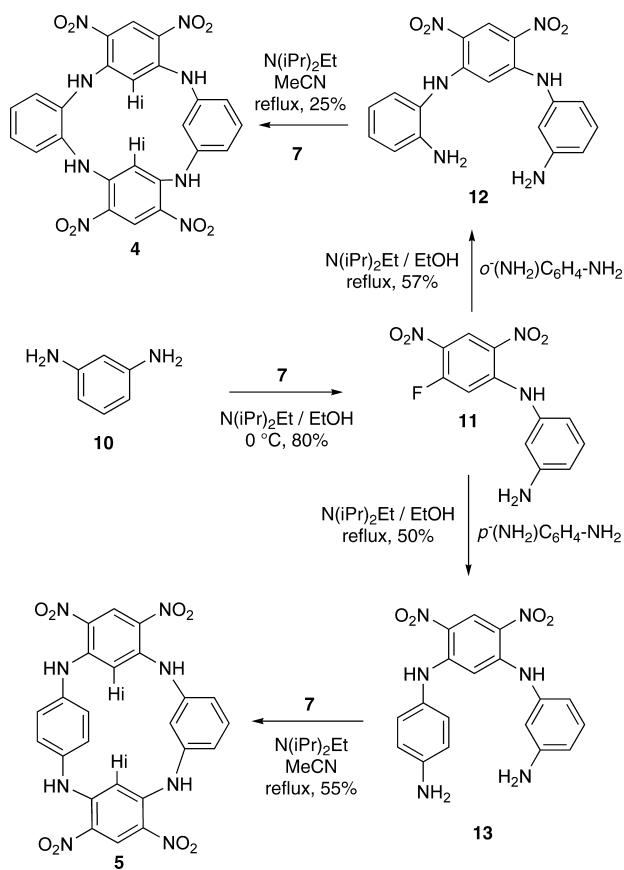


Figure 3. UV–vis spectra of **3–5** in MeCN.

**Scheme 2. Synthesis of the Tetraazacyclophanes **4** and **5****



This hypsochromic effect is probably due to the methyl substitution that modifies the electronic properties by changing the geometry of the macrocycles. To extend this class of tetraazamacrocycles, the synthesis of mixed tetraaza[1<sub>4</sub>]-*m,m,m,o*- and tetraaza[1<sub>4</sub>]-*m,m,m,p*-cyclophanes **4** and **5** was then undertaken. **7** and the *m*-diaminobenzene **10** were chosen as coupling partners to yield the [1+1] adduct **11** in EtOH at 0 °C with 80% yield (Scheme 2).

**11** was then subjected to another step of aromatic substitution with either *o*- or *p*-diaminobenzene (1 equiv), affording the [2+1] products **12** (57% yield) and **13** (50% yield), respectively. Finally, macrocyclization with **7** in

refluxing MeCN ( $C = 10^{-2}$  M) led to the desired products **4** and **5** with acceptable yields. Unfortunately, attempts to synthesize the tetraaza[1<sub>4</sub>]-*m,o,m,p*-cyclophane using the same strategy failed, probably due to unfavorable steric constraints. As with **3a–c**, the <sup>1</sup>H NMR spectra of **4** and **5** showed high field chemical shifts of the H<sub>i</sub> protons at δ 5.78 and 5.17 ppm, respectively. On the contrary, the H<sub>i</sub> protons in **12** and **13** appeared at 6.16, and 6.46 ppm, respectively, which suggest that **4** and **5** adopted also a 1,3-alternated conformation. The UV–vis spectra of the mixed tetraazacyclophanes **4** and **5** in MeCN have essentially the same features, showing one band at 341 nm with a shoulder (Figure 3).

In summary, while retaining several features of the typical N(R)-bridged [1<sub>4</sub>] cyclophanes, the new tetraazamacrocycles **3a–d**, **4**, and **5** synthesized herein have modified cavities in terms of shape and size. These novel entities open up new perspectives in supramolecular chemistry owing to the substitution pattern of the bridging nitrogen atoms, which is likely to lead to specific electronic and spectroscopic properties.

The N-methylated aza[1<sub>4</sub>]cyclophanes **3d** will be of great interest to generate stable radical for spintronic application. Interestingly, further fine-tuning of the cavities can be readily performed through suitable functionalization of the NH bridges or by reduction of the nitro groups and subsequent derivatization of the corresponding amines. These two approaches are currently under investigation.

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**Supporting Information Available:** Detailed experimental procedures, characterization of all new compounds, spectroscopic data, and the X-ray crystallographic file for **8** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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