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Metal-free synthesis of azacalix[4]arenes

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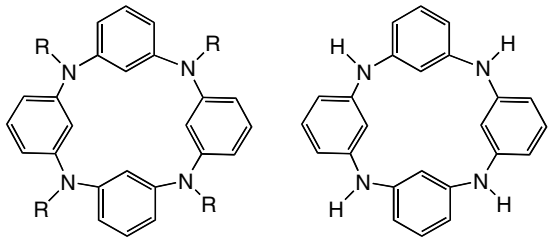
ABSTRACT

The facile preparation of N(H)-bridged azacalix[4]arenes has been achieved by stepwise nucleophilic aromatic substitutions assisted by hydrogen bonding interactions. The synthesis is uncatalyzed and affords previously unknown tetranitroazacalix[4]arenes.

Calix[*n*]arenes received much attention for decades in supramolecular chemistry due to their specific molecular structure, which allowed the formation of host-guest complexes.[1–3] Considerable efforts are now devoted in derivatizing the basic calixarene skeletons, and the more recent developments are the preparation of analogs by replacing the methylenic bridges by heteroatoms in order to tune and improve their properties.[4–12] Among the hetero-bridged calixarenes, N(R)-bridged azacalix[4]arenes of type **1**, also called [1_4]metacyclophanes, are of growing interest owing to the presence of the nitrogen bridges which: (i) conjugate with the aromatic rings to increase the electron density of the pi-cloud,[12] (ii) may participate to the complexation of species,[13] and (iii) are the key sites for robust high spin polyradicals.[7,14]

N(H)-bridged aza[1_4]metacyclophanes such as **2** have been less investigated,[11,14,15] but are much more attractive owing to the presence of additional hydrogen bonding and a possible tunable functionalization of the NH sites which open new perspectives in azacalixarene chemistry. Although the parent compound **2** (i.e., unsubstituted) was first reported by Smith in 1963,[15] only two recent articles—to the best of our knowledge—described the preparation of **2** or similar macrocyles.[11,14] Both are based on palladium-catalyzed aryl amination reactions, which were applied for the synthesis of all azacalix[4]arenes of types **1** and **2** reported in the literature.[9,10,12]



An alternative route that would not require the use of a catalyst and which would give access to new functionalized N(H)-bridged aza[1_4]metacyclophanes of type **2** could be useful 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 commercially available 1,3-diaminobenzene derivatives were used as nucleophilic components, for which introduction of functionality could be achieved. 1,5-Fluoro-2,4-dinitrobenzene was identified as their coupling partner of choice owing to the presence of structural elements for S_NAr and the possibility to prepare N(H)-bridged aza[1_4]metacyclophanes of type **2** functionalized by nitro groups.

Molecule **3b** was first reacted with **4** (1 equiv) in refluxing EtOH in the presence of base to afford the [1+1] adduct **5**,[16] which precipitated preventing the formation of polymeric materials (Scheme 1).

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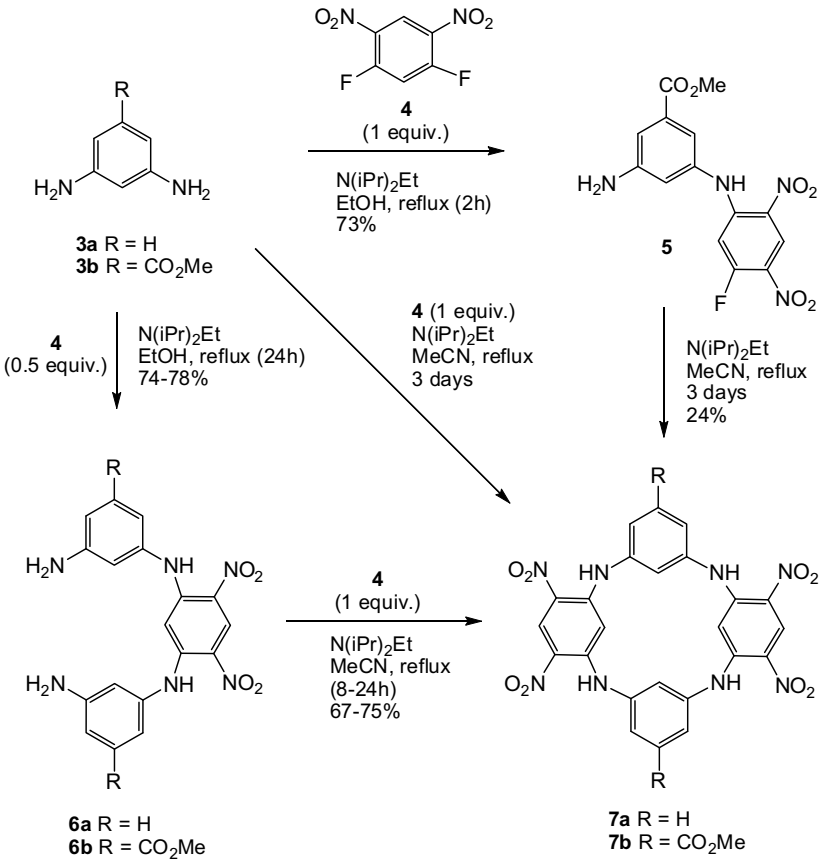

Scheme 1. Synthesis of calix[4]arenes **7a**–**7b**.

The ^{1}H NMR spectrum of **5** shows the NH resonance at 10.07 ppm, which suggests the presence of an intramolecular hydrogen bond. X-ray analysis of **5** confirms the NH···O$_2$N interaction, which preorganizes the backbone of the uncyclic intermediate for the cylization step (Fig. 1).[17]

The cyclization reaction by dimerization of **5** in refluxing MeCN was unsuccessful at $C \approx 5 \cdot 10^{-4}$ M (starting material recovered), but succeeded at $C \approx 5 \cdot 10^{-2}$ M affording **7b** in 24% yield (Scheme 1). These observations suggest in one hand that high dilution conditions are not necessary to prevent the formation of polymers or linear oligomers, and in other hand that higher concentrations favor the formation of the target calix[4]arenes. We also envisaged the use of **6a** and **6b** for which a similar conformation controlled by two intramolecular H-bonds, instead of one in **5**, should favor the formation of the macrocycle.[11] The reaction between **3a** or **3b** and **4** (0.5 equiv) led to the formation of the [2+1] products **6a** or **6b**, which precipitated in EtOH in good yields (Scheme 1).[18] Their ^{1}H NMR spectra show two down-field NH at δ 9.57 and 9.63 ppm for **6a** and **6b**, respectively, in agreement with NH···O$_2$N hydrogen bonding interactions that restrict the rotation of the uncyclized precursors. The macrocyclization from reactions between **6a** or **6b** and **4** in refluxing MeCN ($C \approx 5 \cdot 10^{-4}$ M) afforded the target molecules **7a** and **7b** in 38% and 14% yield, respectively (Scheme 1). These compounds are easily obtained pure as yellow solids by precipitation (no need of purification by chromatography).[19] When the same reaction was carried out at $C \approx 5 \cdot 10^{-2}$ M, the yields increased up to 75% and 67% for **7a** and **7b**, respectively, which confirms the strong influence of the concentration on the formation of the macrocyles. It is noteworthy that **7a** could be directly obtained in 46% yield from **3a** and **4** in refluxing MeCN at $C \approx 5 \cdot 10^{-2}$ M (Scheme 1). The yield dropped to 15%,

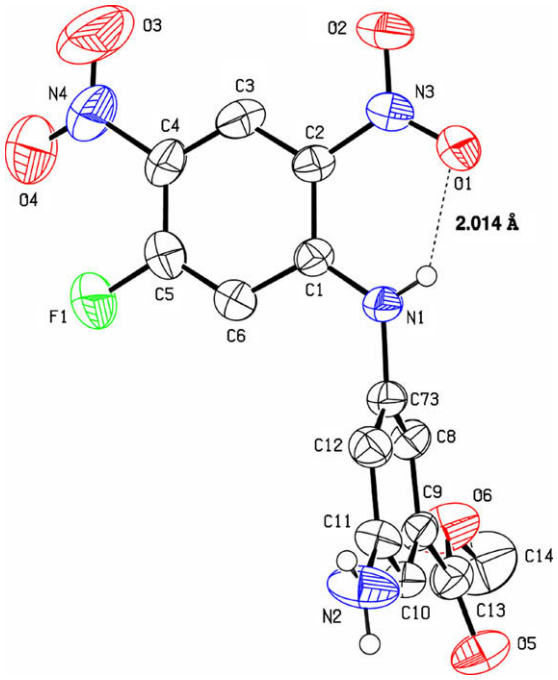

Figure 1. ORTEP view of the crystal structure of **5**. Displacement parameters include 50% of the electron density. Selected bond distances (Å) and angles (°): C(1)–N(1) = 1.345(4), C(2)–C(1) = 1.418(4), C(2)–C(3) = 1.380(5), C(3)–C(4) = 1.366(6), C(4)–C(5) = 1.397(6), C(6)–C(5) = 1.344(6), C(1)–C(6) = 1.413(5), C(2)–N(3) = 1.433(5), C(4)–N(4) = 1.444(5); C(1)–C(2)–N(3) = 122.1(3), C(2)–C(1)–N(1) = 123.8(3), N(4)–C(4)–C(3) = 119.2(4).

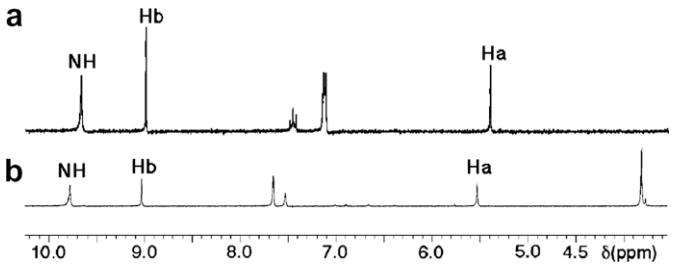

Figure 2. ^{1}H NMR spectra in DMSO-d_6 of **7a** (a) and **7b** (b). The range 0–3.5 ppm is omitted for clarity.

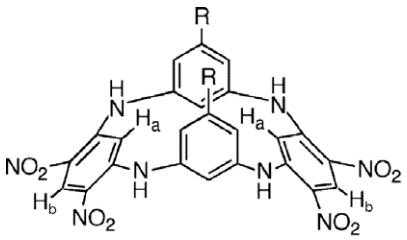

Figure 3. View of the 1,3-alternate conformation of **7a** and **7b**.

when the same reaction occurs in a protic solvent such as EtOH. Similarly, the macrocyclization from reactions between **6a** and **4** ($C \approx 5 \cdot 10^{-2}$ M) gave **7a** in lower yield (17%) in EtOH than in MeCN (75% yield). These observations are consistent with S_NAr reactions assisted by H-bonding interactions, which are more favored at higher concentrations and which prevent the formation of polymeric materials in spite of low dilution conditions.

The ^{1}H NMR spectra of **7a** and **7b** show unusual high-field chemical shifts of the intraannular aromatic protons Ha at δ 5.38 and 5.53 ppm for **7a** and **7b**, respectively (Fig. 2). These ^{1}H NMR data suggest that **7a** and **7b** adopt the 1,3-alternate conformation, in which Ha protons are located inside the anisotropic shielding cone of the adjacent aromatic rings (Fig. 3).[4,14] This conformation is supported by the resonance of the corresponding Ha proton in **6a** and **6b** (δ 6.63 and 6.40 ppm, respectively), which are poorly influenced by the adjacent aromatic rings due to a higher degree of freedom.

Interestingly, the comparison between the resonances of the intra- and extraannular aromatic protons (Ha and Hb) for **7a** and **7b** shows rare chemical shift differences between two aromatic protons linked to the same benzene ring ($\Delta\delta$ = 3.66 and 3.50 ppm, respectively).

In summary, we described the first metal-free synthesis of azacalix[4]arenes, which allowed the access to new N(H)-bridged aza[1$_4$]metacyclophanes **7a** and **7b**. ^{1}H NMR analysis clearly demonstrated that these macrocycles adopt an 1,3-alternate conformation in solution. In addition to the NH-bridging sites, the potential presence of four NH_2 functions (reduction of the NO_2 groups) open unprecedented pespectives in azacalixarene chemistry, currently under investigations.

Acknowledgments

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16. *Synthesis of* **5**: A mixture of **4** (100 mg, 0.49 mmol, 1 equiv), methyl 3,5-diaminobenzoate (114.8 mg, 0.69 mmol, 1 equiv) and N(iPr)$_2$Et (0.21 ml, 1.2 mmol, 2.5 equiv) in refluxing EtOH was stirred for 2 h. The obtained precipitate was isolated by filtration and washed with water affording **5** as an orange solid (m = 250 mg, 73% yield). ^{1}H RMN (250 MHz, acetone-d_6) δ 3.85 (s, 3H, CH_3), 5.30 (br s, 2H, NH_2), 6.95 (m, 1H, aromatic H), 7.01 (d, 1H, $^3J_{HF}$ = 12.6 Hz, aromatic H), 7.22 (m, 1H, aromatic H), 7.33 (m, 1H, aromatic H), 9.07 (d, $^4J_{HF}$ = 8.0 Hz, 1H, aromatic H), 10.07 (br s, 1H, NH). MS (ESI)$^+$: m/z = 351 [M+H]$^+$. Calcd for $C_{14}H_{11}FN_4O_6 \cdot 1/6EtOH$: C, 48.10; H, 3.38; N, 15.65. Found: C, 48.46; H, 3.32; N, 15.91.
17. *Crystal data for* **5**: monoclinic, space group $P21/c$ with a = 11.4771(4), b = 9.6376(4), c = 14.1523(5), α = 90, β = 95.901, γ = 90 at 293(2) K with Z = 4, $R1$ = 0.0977, $R2$ = 0.1472, GOF = 1.127. Crystallographic data for the structures **5** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 693854). Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +40(0)-1223-336033 or e-mail: http://www.wdeposit@ccdc.cam.ac.uk].
18. *General procedure for the synthesis of* **6a** *and* **6b**: To a solution of **3** (1.96 mmol, 2 equiv) in ethanol containing N(iPr)$_2$Et (2.45 mmol, 2.5 equiv), was added 1,5-difuoro-2,4-dinitrobenzene **4** (0.98 mmol, 1 equiv). The mixture was then stirred for 24 h under reflux affording **6a** and **6b**, which were isolated as orange precipitates by filtration.
Compound **6a**: m = 378 mg, 78% yield. ^{1}H NMR (250 MHz, DMSO-d_6) δ 5.28 (br s, 4H, NH_2), 6.40 (m, 3H, aromatic H), 6.63 (s, 1H, HN–C=*CH*–C–NH), 7.02 (m, 2H, aromatic CH), 9.01 (s, 1H, O_2N–C=CH–C–NO_2), 9.57 (br s, 2H, NH). MS (MALDI-TOF)$^+$: m/z = 381 [M+H]$^+$. Calcd for $C_{18}H_{16}N_6O_4 \cdot 1/4EtOH$: C, 56.70; H, 4.50; N, 21.45. Found: C, 56.53; H, 4.35; N, 21.67.
Compound **6b**: m = 360 mg, 74% yield. ^{1}H NMR (250 MHz, acetone-d_6) δ 3.78 (s, 6H, CH_3), 5.53 (br s, 4H, NH_2), 6.40 (s, 1H, HN–C=*CH*–C–NH), 6.68 (m, 2H, aromatic H), 6.90 (m, 2H, aromatic H), 7.01 (m, 2H, aromatic H), 9.01 (s, 1H, O_2N–C=CH–C–NO_2), 9.63 (br s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ 51.9 (OCH_3), 96.3, 112.1, 112.5, 113.5, 125.0, 128.2, 131.2, 138.6, 146.0, 149.9 (aromatic C), 165.9 (C=O). MS (ESI)$^+$: m/z = 497 [M+H]$^+$. Calcd for $C_{22}H_{20}N_6O_8 \cdot 1/2H_2O$: C, 52.28; H, 4.19; N, 16.63. Found: C, 52.02; H, 4.01; N, 16.33.
19. *General procedure for the synthesis of* **7a** *and* **7b**: To a solution of **6a** or **6b** in CH_3CN in the presence of N(iPr)$_2$Et (5 equiv), was added dropwise 1,5-difuoro-2,4-dinitrobenzene **4** (1 equiv) at room temperature. After stirring under reflux, the solution was concentrated under vacuum to afford a yellow precipitate of **7a** or **7b**, which was isolated by filtration.
Compound **7a**: m = 38 mg, 75% yield. ^{1}H RMN (250 MHz, DMSO-d_6) δ 5.38 (s, 2H, HN–C=*CH*–C–NH, called Ha), 7.14 (m, 6H, aromatic H), 7.47 (m, 2H, aromatic H), 9.04 (m, 2H, O_2N–C=CH–C–NO_2, called Hb), 9.72 (br s, 4H, NH). MS (MALDI-TOF)$^+$: m/z = 545 [M+H]$^+$. Calcd for $C_{24}H_{16}N_8O_8$: C, 52.95; H, 2.96; N, 20.58. Found: C, 53.09; H, 3.12; N, 20.31.
Compound **7b**: m = 180 mg, 67% yield. ^{1}H RMN (250 MHz, DMSO-d_6) δ 3.81 (s, 6H, CH_3), 5.53 (s, 2H, HN–C=*CH*–C–NH, called Ha), 7.52 (m, 2H, aromatic H), 7.65 (m, 4H, aromatic H), 9.03 (s, 2H, O_2N–C=CH–C–NO_2, called Hb), 9.78 (br s, 4H, NH); MS (ESI)$^+$: m/z = 661 [M+H]$^+$. Calcd for $C_{28}H_{20}N_8O_{12}$: C, 50.92; H, 3.05; N, 16.96. Found: C, 50.60; H, 3.33; N, 16.56.