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Fused Azacalix[4]arenes

Rose Haddoub,[a] Mounia Touil,[a] Zhongrui Chen,[a] Jean-Manuel Raimundo,[a] Philippe Marsal,[a] Mourad Elhabiri,[b] and Olivier Siri*[a]

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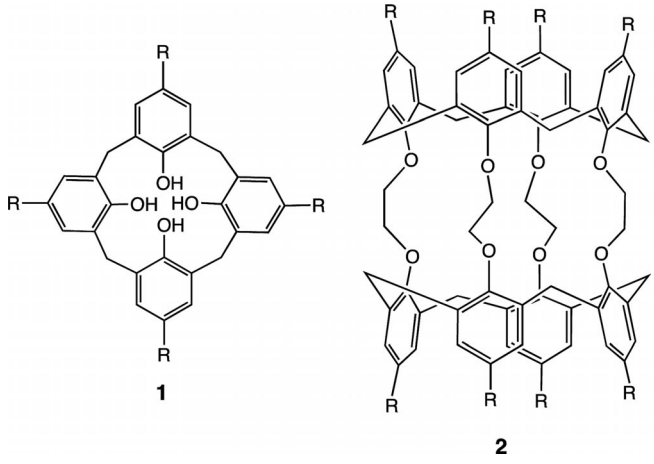
The synthesis of unprecedented fused azacalixarenes (dimers and trimer) through successive nucleophilic aromatic substitutions is described. Absorption spectrophotometric and theoretical studies demonstrated that these oligomers share common phenyl moieties that enable conjugation of the whole π-system and a multiconcave geometry with aligned cavities because of the high flexibility of these macrocycles.

Introduction

The design of host molecules for guest binding has generated continuous interest in areas such as highly selective and/or multimodal detection.[1] Among them, calix[4]arenes **1** have been widely studied for decades as hosts due to their unique three-dimensional structures and versatile complexation properties.[2] As such, they have found widespread application in sensing, selective metal extraction, recognition, catalysis, and host–guest interactions.[3] These complexation abilities are closely related to the conformational properties of calix[4]arene, which depend on the substituents at the intra-annular positions.[3] Thus, they can adopt four distinct conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate. The latter is of peculiar interest, because it furnishes a distinctive concave molecular architecture that is favorable for selective complexation according to the concept of concave reagents.[4]

The design and preparation of multicalixarene compounds with precise length and constitution is now attracting major interest in light of their potential applications in the field of material sciences.[5] For example, bis(calixarenes) have been extensively studied, because they have the potential to complex two different guests using two cavities independently or a single guest using two cavities cooperatively. In most cases, multiple calixarene molecules of type **2** were obtained by assembling calixarene subunits either in a covalent or noncovalent manner.[6] For instance, many research groups have reported on the synthesis of multicalixarene molecules covalently C_{sp^3}-bridged by a variety of linkers.[7] It was shown that the length and nature of the bridges between the calixarene units played an important role in the conformation of the binding sites and thus directly affect the binding properties.[8]



However, to take full advantage of these multicalixarene arrays, it appears important that individual components in such an array can interact with each other through suitable linkers. Such internal cooperation, for instance through electronic conjugation throughout the whole array and/or additive geometry, is expected to bring novel properties that go beyond the sum of each component's property.[9] In recent years it was found that substitution of the methylene bridges by nitrogen afforded azacalix[4]arenes[10–12] and the related azacalix[4]pyridines[13] or azacalix[2]arene[2]triazines.[14] As a new member in the calixarene family, azacalix[4]arenes attracted much attention by providing sites for functionalization not only on the phenyl units[10] but also on the bridging nitrogen atoms.[11] We recently reported on the synthesis of azacalix[4]arenes of type **3** and related macrocycles with 1,3-alternate conformations.[12] The synthetic strategy, based on catalyst-free, stepwise nucleophilic aromatic substitutions (S_NAr), allowed easy access to new macrocycles that could be subjected to further

[a] CINaM, UMR 7325 CNRS, Aix-Marseille Université
Campus de Luminy, case 913, 13288 Marseille Cedex 09, France
E-mail: olivier.siri@univ-amu.fr
http://www.cinam.univ-mrs.fr
[b] Laboratoire de Chimie Moléculaire, UMR 7509 CNRS – UdS, Equipe de Chimie Bioorganique et Médicinale, ECPM, Université de Strasbourg
25, rue Becquerel, 67200 Strasbourg, France
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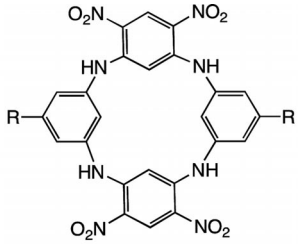
modifications.[11] The versatility of this method prompted us to explore the possible preparation of new extended architectures (i.e., multicalix[4]arenes scaffold) sharing a common subunit.



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Herein, we report the synthesis and absorption spectrophotometric studies of fused azacalixarene oligomers **8**, **13** and **16** in which two or three macrocyclic units are fused together. Unlike the previously described multicalixarenes,[6] our approach allows full electronic conjugation because of the fused assembly. Theoretical studies revealed geometries with aligned cavities based on one or two common phenyl subunits in **8** (and **16**) and **13**.

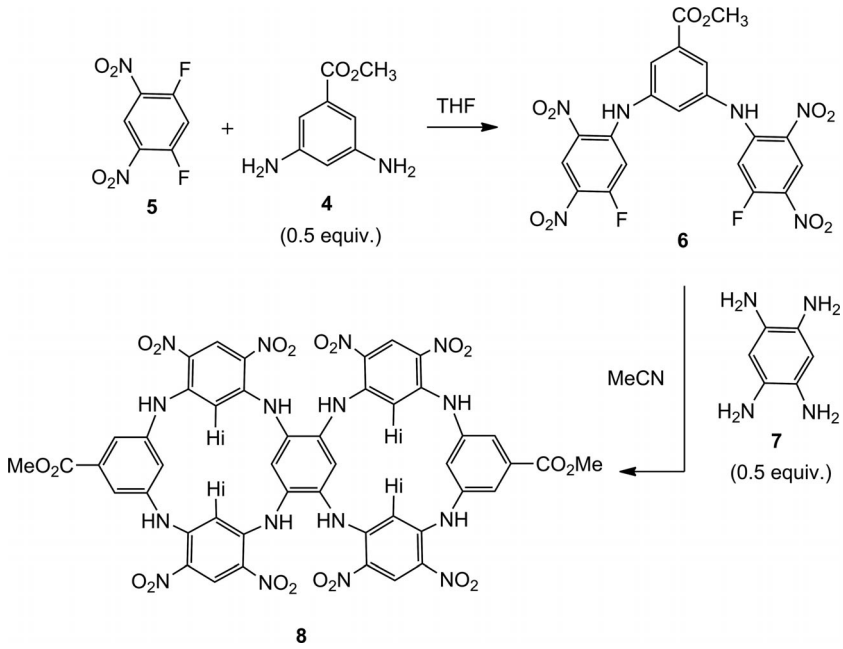
Results and Discussion

The synthesis of dimer **8** is summarized in Scheme 1. Commercially available *m*-diaminobenzene **4** (1 equiv.) was used as the nucleophilic component, and 1,5-difluoro-2,4-dinitrobenzene (**5**) was identified as the coupling partner of choice owing to the presence of structural elements that were suitable for S_NAr.[12]

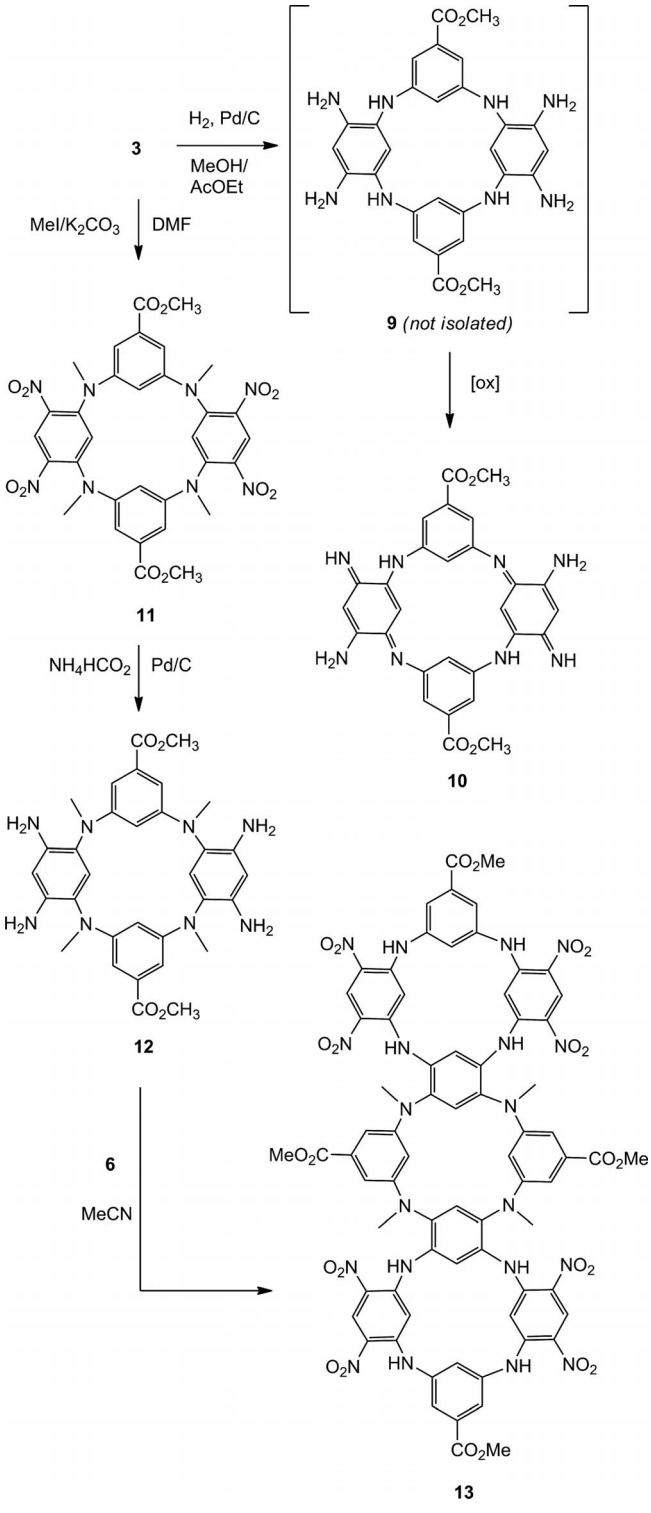
The reaction took place at low temperature, and led to the formation of the [1+2] product **6**, which precipitated in EtOH in 90% yield. Compound **6** was then subjected to an S_NAr reaction with tetraaminobenzene **7** and a large excess of Hünig's base at 80 °C. Dimer **8**, having two azacalixarenes cavities fused through a shared phenyl subunit, was then obtained by filtration with a relatively good yield (54%). Its ^1H NMR spectrum showed signals with unusual high-field chemical shifts of the intra-annular aromatic (H_i) protons at δ = 4.98 ppm. This observation suggests that the dimer adopts the 1,3-alternate conformation in which the H_i protons are located inside the anisotropic shielding cone of the adjacent aromatic rings, as already observed for monomer **3**.[10,12]

The synthesis of azacalixarene-based trimer was then envisaged (Scheme 2). To this end, compounds **3** (R = CO_2Me)[12] and **6** were chosen as starting materials. Indeed, macrocycle **3** appeared to be a precursor of choice owing to the presence of four NO_2 groups that could be reduced into four nucleophilic amino functions. However, the direct reduction of **3** (catalytic hydrogenation) led to the formation of the corresponding electron-rich tetraamino derivative **9** (not isolated), which, under air, is converted into a very poorly soluble quinoid-type structure **10**. This latter could be isolated after precipitation from CH_3CN as a green solid in 25% yield.

The ^1H NMR spectrum of **10** revealed the presence of two resonances at δ = 5.67 and 5.74 ppm that are consistent with nonaromatic protons. Noteworthy, no NMR spectral changes could be observed in the range 300–380 K as expected for **10**, which is more rigid than azacalix[4]arenes of type **3**[11,12] due to the presence of bridging double bonds. Formation of **10** was further supported by electrospray HRMS mass spectrometry, which showed a peak at *m*/*z* = 537.1999 amu in the positive mode corresponding to [**10** + H]$^+$. Introduction of *N*-CH_3 substituents was then envisaged to prevent the oxidation of the octaamino macrocycle.



Scheme 1. Synthesis of dimer **8**.



Scheme 2. Synthesis of trimer **13**.

Thus, *N*-alkylation of **3** using methyl iodide in *N*,*N*-dimethylformamide (DMF) at 70 °C furnished tetramethylazacalixarene **11** as a yellow solid in 87% yield (Scheme 2). Its reduction in the presence of Pd/C and ammonium formate (NH_4HCO_2) afforded **12** as a black solid in 77% yield. The ^{1}H NMR spectrum of **11** shows a singlet at δ = 8.77 ppm, in agreement with the resonance of the aromatic protons located in *ortho* positions with respect to the nitro groups. In **12**, the signal of such protons appears at δ = 6.19 ppm due to the replacement of the electron-withdrawing NO_2 groups by the electron-donating NH_2 functions, which exhibit a broad singlet at δ = 4.48 ppm. Finally, **12** was used as the nucleophilic compound, undertaking an S_NAr reaction with the [2+1] difluorotriaryl product **6** to give **13** after precipitation in 30% yield. Unfortunately, trimer **13** could not be characterized in solution due to its low solubility. In contrast, its formation was clearly supported by solid-state NMR spectroscopy, elemental analysis and mass spectrometry, which showed one peak at *m*/*z* = 1607.4 amu in the positive mode corresponding to [**13** + Na]$^+$.

We carried out a conformational analysis for **3**, **8**, and **13** to explore the potential energy surface at the PM6[15] level. In a second step, we performed geometry optimization and frequency calculations on their obtained global energy minima. To this end, we used the Density Functional Theory (DFT) level, with a 6-31G** split-valence basis set (Gaussian 03 package),[16] combined to a hybrid potential including both Becke and Hartree–Fock exchange and Lee, Yang and Parr correlation (B3LYP) in the gas phase.[17] As expected, the obtained geometrical parameters show an 1,3-alternate conformation for each oligomer in

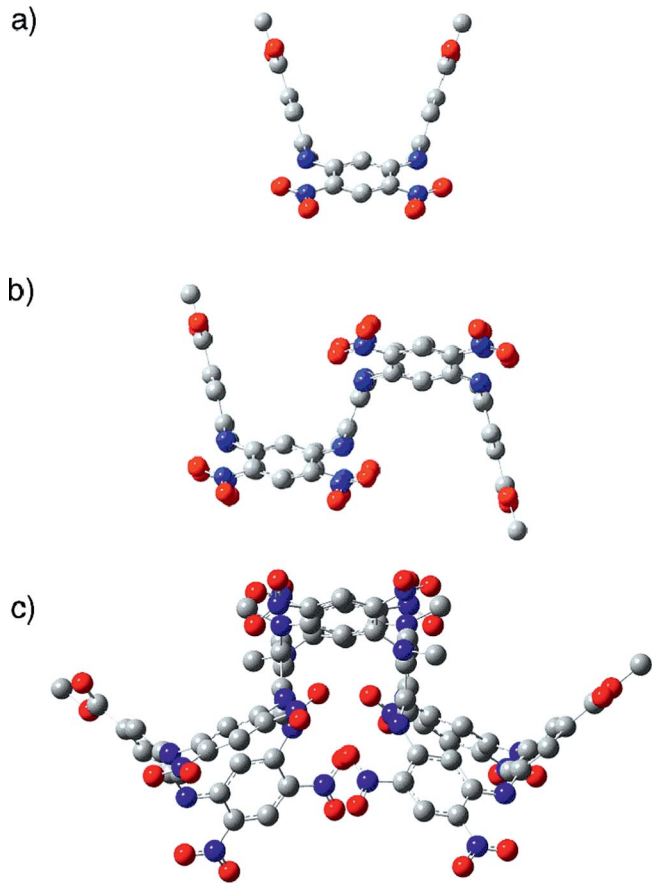


Figure 1. Geometry optimization of oligomers **3**, **8** and **13** (hydrogen atoms have been omitted for clarity).

global minima leading to multiconcave molecules with one, two or three aligned cavities for **3**, **8** and **13**, respectively (Figure 1).

This calculated high flexibility – typical in the calixarene family – is consistent with experimental data obtained with **8** and **13**, and the X-ray analysis of a closely related analogue of **3** for which R = H.[10d]

Although molecules **3**, **8** and **13** are not planar because of the 1,3-alternate conformation, we undertook an absorption spectrophotometric study of **8** and **13** (that of **3** being already reported by our group)[11] to highlight a possible conjugation of the π-system between the macrocyclic subunits.[12] For solubility reasons, their absorption spectroscopic properties were examined in DMF and compared to those of model **3** under the same experimental conditions. Neutral azacalix[4]arenes **3**, **8** and **13** are both characterized by an intense absorption ($\varepsilon \approx 5–8 \times 10^4$ M^{-1} cm^{-1}) in the UV region (ca. 340–350 nm; Figure 2), together with a shoulder lying at lower energies ($\lambda_{max} \approx 400–420$ nm). Simulated spectra based on TD-DFT calculations[17] confirmed absorption bands in the UV region as expected for a flexible geometry (1,3-alternate conformation).

These absorption bands originate from π–π* transitions of the electronically independent 1,5-diamino-2,4-dinitrobenzene units,[18] those of the *para*-substituted benzene rings being centered at much higher energies. The bridging secondary amines of **3**, **8** or **13** can be – in principle – either protonated or deprotonated, leading to potential positively and negatively multicharged hosts, respectively. However, the electron-withdrawing effect of the NO_2 groups and the presence of strong intramolecular NH···O_2N hydrogen bonds[11] prevent easy protonation of the bridging amines. In contrast, addition of base (NaOH) leads to significant spectral changes with bathochromic shifts of the main absorption bands ($\Delta\lambda_{max}$ = 57, 64 and 66 nm for **3**, **8** and **13**, respectively), and simultaneous formation of new and less intense absorption bands in the visible region ($\lambda_{max} \approx$ 500 nm, $\varepsilon^{500} \approx 2–6 \times 10^4$ M^{-1} cm^{-1}; Figure 2). These spectral features for **8** and **13** suggest that each macrocycle subunit does not behave independently but accounts for an unprecedented internal cooperation through electronic conjugation compared with **3**. However, it is noteworthy that the degree of conjugation between each macrocycle subunit in **8** and **13** is clearly limited by the high flexibility of the oligomers, which prevents a full overlap of the p-orbitals (a more planar geometry would have led to a more significant bathochromic shift as observed in the more rigid fused oligoporphyrins).[9]

To gain further insight into the structure–activity relationships of these oligomeric systems, modulation of the cavity of the dimer could be also envisaged by alternating the position of the two NH_2 groups in the substituted phenylene precursor while keeping a constant number of benzene moieties.

By analogy with the synthesis of **8**, compound **5** was subjected to a step of aromatic substitution with *o*-diaminobenzene (**14**) (0.5 equiv.), affording the [2+1] products **15** (91% yield; see Scheme 3). Macrocyclization with tetra-

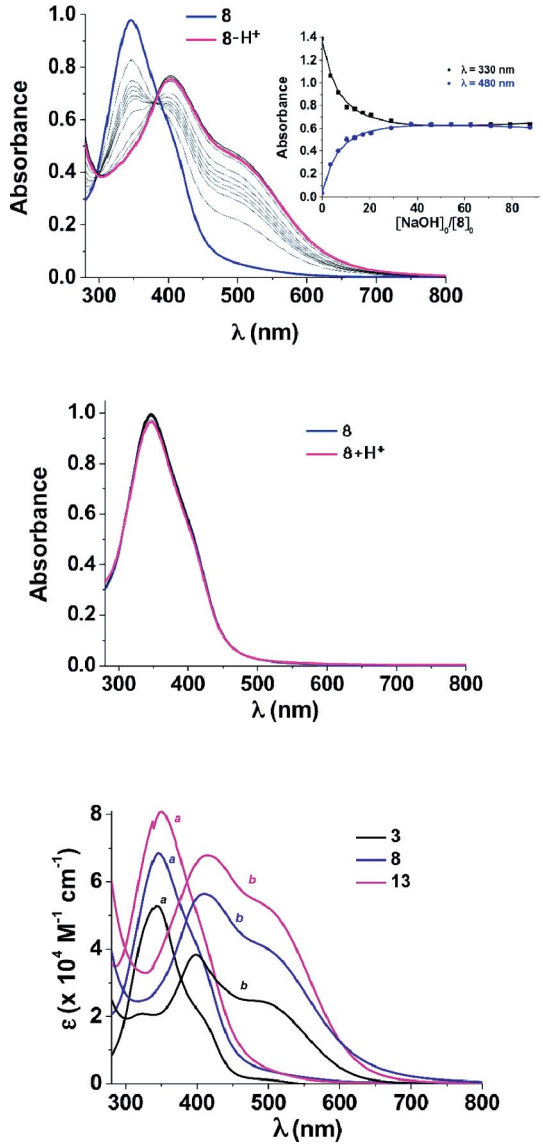
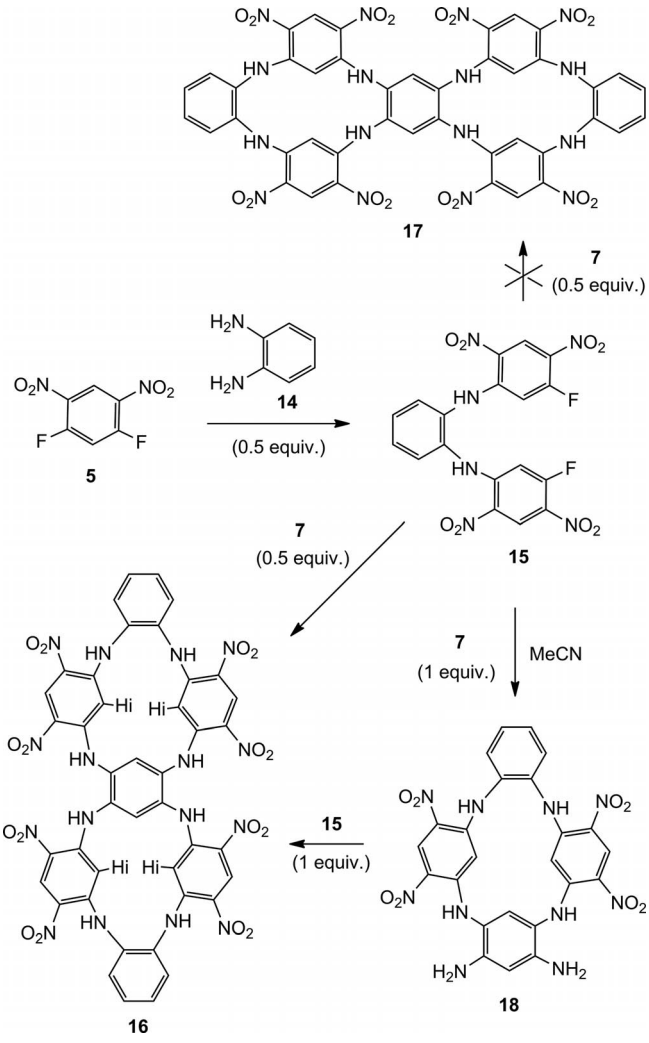


Figure 2. UV/Vis absorption titration of dimer **8** by (top) NaOH or (middle) $HClO_4$, and (bottom) electronic absorption spectra of the neutral (*a*) and deprotonated (*b*) forms of oligomers **3**, **8** and **13**. The inset in the top shows the variation of the absorbance at 330 and 480 nm of dimer **8** upon addition of the base. Solvent: DMF; T = 25.0(2) °C. NaOH titration: $[\mathbf{8}]_0 = 1.43 \times 10^{-5}$ M; (1) $[NaOH]_0/[\mathbf{8}]_0 = 0$; (2) $[NaOH]_0/[\mathbf{8}]_0 = 88$. $HClO_4$ titration: $[\mathbf{8}]_0 = 1.43 \times 10^{-5}$ M; (1) $[HClO_4]_0/[\mathbf{8}]_0 = 0$; (2) $[HClO_4]_0/[\mathbf{8}]_0 = 4055$. In the presence of base, the absorption spectrophotometric data have been processed and allowed an apparent deprotonation constant to be measured according to the equilibrium: $LH_n^{n-4} + OH^- \overset{K_{app}}{\rightleftarrows} LH_{n-1}^{n-5} + H_2O$. For **3**, $\log K_{app}$ = 4.2(1); for **8**, $\log K_{app}$ = 3.8(2); for **3**, $\log K_{app}$ = 3.5(2).

aminobenzene **7** in CH_3CN (10^{-2} M) heated to reflux led to the formation of dimer **16** in 25% yield (Scheme 3). The formation of **16** instead of **17** could be fully demonstrated by condensation between **15** and **18** (1 equiv.) in dimethyl sulfoxide (DMSO), which gave **16** as a yellow solid in 63% yield. Compound **18** could be obtained in one step by S_NAr reaction between **15** and tetraaminobenzene **7** (1 equiv.) in

79% yield without protection of the amino groups. This high selectivity can be explained by the higher nucleophilic character of the NH_2 group in *meta* position with respect to the first amino group that reacted [the two other NH_2 groups in the *ortho* and *para* position are "deactivated" by the mesomeric effect (+M)]. Similar to **8**, the ^1H NMR spectrum of **16** showed high-field signals of the intra-annular aromatic protons (H_i) at δ = 5.88 ppm, suggesting that **16** adopted an 1,3-alternate conformation in solution in which the H_i protons are located inside the anisotropic shielding cone of the adjacent aromatic rings.



Scheme 3. Synthesis of dimer **16**.

Similar to **8**, TD-DFT geometry optimization and frequency calculations on **16** also show an 1,3-alternate conformation but revealed smaller aligned cavities (Figure 3). This observation can be explained by the *ortho* substitution of two phenyl rings in **16**, which increases the strength of the macrocyclic cavities (the angle between the *o*-diaminobenzene subunit and the molecular plane is smaller than in **8**).

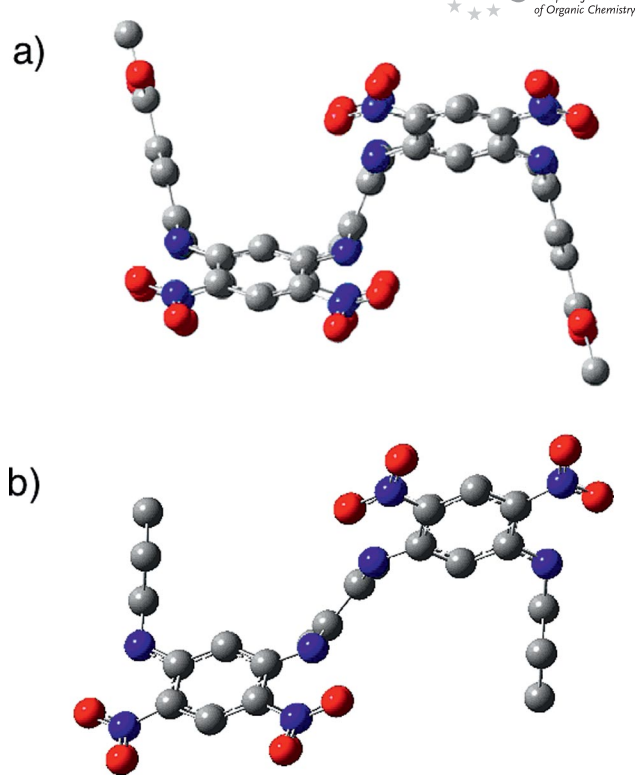


Figure 3. Geometry optimization of dimers **8** and **16** (hydrogen atoms have been omitted for clarity).

Conclusions

The synthesis of fused azacalixarenes (dimers **8**, **16** and trimer **13**) has been achieved through successive S_NAr reactions. These macrocycles share common structural properties with an 1,3-alternate conformation, which allows alignment of two or three concave cavities for the dimers and the trimer, respectively. These novel receptors with multipoint recognition sites are thus expected to exhibit new physicochemical properties that are distinct from simple azacalix[4]arenes (for instance **3**) owing to their larger dimension and higher degree of flexibility. In addition, **8**, **16** and **13**, possess cavities that can be easily and highly functionalized and will thus constitute useful and valuable building blocks for the construction of higher orders of multicavity macrocycles. We also described a new class of conjugated macrocycles (**10**) in which the presence of quinoid subunits opens new perspectives in color chemistry (as new acidichromes) or coordination chemistry (as new ligands) by analogy with related 12π-electron quinones[19] and a new class of macrocycles named azacalixphyrins.[20]

Experimental Section

General Remarks: All solvents for the syntheses were of analytic grade; spectroscopic measurements were carried out with spectroscopic-grade solvents. NMR spectra were recorded at room temp.

with a Bruker AC250 spectrometer operated at 250, 62.5, and 235 MHz for ^{1}H, ^{13}C, and ^{19}F nuclei, respectively. Data are listed in parts per million (ppm) and are reported relative to tetramethylsilane (^{1}H and ^{13}C); residual solvent peaks of the deuterated solvents were used as an internal standard. NMR spectra were recorded in $CDCl_3$, [D$_6$]acetone or [D$_6$]DMSO. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm) using the residual protonated solvent as an internal standard [$CDCl_3$: δ = 7.26 ppm; [D$_6$]DMSO: δ = 2.50 ppm; [D$_6$]acetone: δ = 2.05 ppm]. Splitting patterns are described as s (singlet), br. (broad), d (doublet), m (multiplet). Elemental and MS analyses were performed by Marseille Spectropole. ESI MS analyses were recorded with a 3200 QTRAP (Applied Biosystems SCIEX) mass spectrometer. HRMS MS analysis was performed with a QStar Elite (Applied Biosystems SCIEX) mass spectrometer.

Absorption Spectrophotometric Studies: For solubility reasons, the acido-basic properties of systems **3**, **8** and **13** were examined in DMF (Prolabo, AnalaR Normapur), which was further deoxygenated by using CO_2- and O_2-free argon prior to use (Sigma Oxiclear cartridge). All the stock solutions were prepared by weighing solid products with an AG 245 Mettler Toledo analytical balance (precision 0.01 mg). The complete dissolution of the ligands was achieved by using an ultrasonic bath (Bandelin Sonorex RK102). The effects of acid ($HClO_4$, 10^{-1} M from Sigma–Aldrich, ca. 70%, 99.999% trace metals basis) and base (NaOH, 10^{-1} M from NaOH, BdH, AnalaR) on compounds **3**, **8** and **13** was probed by absorption spectrophotometry (250–800 nm) with a Varian Cary 50 spectrophotometer.

Synthesis of 6: To a stirred solution of 1,5-difluoro-2,4-dinitrobenzene (**5**) (100 mg, 0.49 mmol, 2 equiv.) in THF (10 mL) placed at 0 °C under nitrogen, was added dropwise a mixture of N*i*Pr$_2$Et (DIPEA; 0.73 mmol, 3 equiv.) and **4** (40 mg, 1 equiv.) in THF (5 mL). The mixture was allowed to warm to room temp. for 12 h, then the crude mixture was concentrated and taken up in EtOH. The obtained precipitate was isolated by filtration, washed with hot water and Et$_2$O, and dried to afford **6** (118 mg, 90%). ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 10.27 (s, 2 H, 2 NH), 9.08–9.05 (d, *J* = 7.5 Hz, 2 H), 8.07 (dd, *J* = 0.5, 1.75 Hz, 2 H), 7.98 (dt, *J* = 0.25, 2.0 Hz, 1 H), 7.26–7.20 (d, *J* = 14.0 Hz, 2 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (62 MHz, [D$_6$]acetone): δ = 166.8 (*C*=O), 163.4 (*J* = 267 Hz, *C*-F), 149.9 (*J* = 13 Hz), 141.5, 135.6, 130.9, 129.3, 129.0, 127.1 (Ar*C*H), 106.1 (*J* = 25 Hz, *C*H-CF), 54.0 (*C*H$_3$-O) ppm. HRMS: calcd. for [M + NH$_4$]$^+$ 552.0921; found 552.0926.

Synthesis of 8: To a solution of **6** (150 mg, 0.28 mmol, 2 equiv.) in CH_3CN (5×10^{-2} M) in the presence of DIPEA (0.39 mL), was added tetraaminobenzene tetrahydrochloride **7**·4HCl (0.14 mmol, 1 equiv.) at room temp. under nitrogen. After stirring and heating to reflux for 48 h, the obtained precipitate was isolated by filtration and washed with water, methanol, ethanol, and CH_3CN to afford the desired product (85 mg, 54%) as a brown solid. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.94 (s, 2 H), 9.33 (s, 2 H), 9.02 (s, 2 H), 7.66 (br. s, 4 H), 7.38 (s, 1 H), 5.70 (s, 1 H), 3.72 (s, 3 H) ppm. Solid-state ^{13}C NMR: δ = 164.7, 147.2, 140.6, 133.9, 126.1, 98.7, 52.5 ppm. $C_{46}H_{30}N_{16}O_{20}\cdot{}^3/_2CH_3OH\cdot{}^1/_2C_2H_5OH$ (1197.48): calcd. C 48.63, H 3.28, N 18.71; found C 48.69, H 2.99, N 18.27. MALDI-TOF: calcd. for [M]$^{+\cdot}$ 1126.2; found 1126.2.

Synthesis of 10: A solution of **3** (200 mg, 0.30 mmol) in CH_3OH/EtOAc (2:1, v/v) was hydrogenated (60 bars) in the presence of Pd/C (5%) for 24 h. After filtration of the reaction mixture through Celite, which was washed with methanol, the filtrate was concentrated under reduced pressure, and the solid in suspension was isolated by filtration. This solid was then taken up in CH_3CN and stirred at room temperature under air for 24 h. After slow evaporation of the solvent, macrocycle **10** was isolated as a green solid (40 mg, 25%). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 3.77 (br. s, 6 H, OCH_3), 5.67 (s, 2 H, olefinic H), 5.74 (s, 2 H, olefinic H), 6.90 (br. s, 2 H, ArH), 7.13 (m, 4 H, ArH), 7.80 (br. s, 8 H, NH and NH_2) ppm. HRMS: calcd. for [M + H]$^+$ 537.1993; found 537.1999.

Synthesis of 11: To a solution of **3** (1 g, 1.51 mmol) and dried K_2CO_3 (2.5 g, 18 equiv.) in DMF (20 mL) was added MeI (1 mL, 12 equiv.) under argon. After stirring at 70 °C for 12 h, the crude reaction mixture was filtered, DMF was then evaporated under reduced pressure, and the residue was taken up in water. Successive extractions with EtOAc and washing with brine afforded **11** (87%) as an orange solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.16 (s, 12 H, NCH_3), 3.94 (s, 6 H, OCH_3), 6.39 (t, *J* = 2.2 Hz, 2 H, ArH), 6.52 (s, 2 H, MeN-C-C*H*=C-NMe), 7.44 (d, *J* = 2.2 Hz, 4 H, ArH), 8.77 (s, 2 H, O_2N-C-C*H*=C-NO_2) ppm. ^{13}C NMR (62 MHz, $CDCl_3$): δ = 40.6 (N-CH_3), 52.1 (OCH_3), 114.3, 117.7, 121.9, 128.1, 133.2, 134.66, 146.6, 146.7 (ArC), 165.5 (C=O) ppm. $C_{32}H_{28}N_8O_{12}\cdot{}^5/_4$EtOAc (826.25): calcd. C 54.48, H 4.76, N 13.92; found C 54.66, H 4.73, N 13.91. MS (ESI): calcd. for [M + H]$^+$ 717.1; found 717.1.

Synthesis of 12: A solution of **11** (300 mg, 0.42 mmol) in CH_3OH/THF (1:1, 300 mL) was reduced in the presence of catalytic Pd/C (10%) and azeotropically (toluene) dried ammonium formate (530 mg, 20 equiv.) for 12 h. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc, and washed with water. The organic phase was then concentrated in vacuo to give **12** (192 mg, 77%) as a black-green solid. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.95 (br. s, 12 H, NCH_3), 3.82 (s, 6 H, OCH_3), 4.48 (s, 8 H, NH_2), 5.61 (t, *J* = 2.2 Hz, 2 H, ArH), 6.04 (s, 2 H, MeN-C-CH=C-NMe), 6.19 (s, 2 H, H_2N-C-CH=C-NH_2), 6.72 (d, *J* = 2.2 Hz, 4 H, ArH) ppm. ^{13}C APT NMR (62 MHz, [D$_6$]DMSO): δ = 167.9, 150.9, 144.5, 131.0, 127.1, 123.4, 104.2, 101.9, 101.3, 52.3, 40.7 ppm. HRMS: calcd. for [M + Ag]$^+$ 703.1905; found 703.1910.

Synthesis of 13: To a solution of **6** (71 mg, 0.13 mmol, 2 equiv.) in CH_3CN (5×10^{-2} M) in the presence of DIPEA (2.6 mmol, 20 equiv.), was added **12** (40 mg, 0.067 mmol, 1 equiv.) at room temp. under nitrogen. After stirring and heating to reflux for 72 h, the obtained precipitate was isolated by filtration and washed with water, MeOH, EtOH, and MeCN to afford the desired product (32 mg, 30%) as a red solid. Solid-state ^{13}C NMR: δ = 165.4, 148.9, 144.3, 140.2, 132.4, 127.3, 103.9, 52.2, 38.8, 30.2, 18.1 ppm. $C_{72}H_{56}N_{20}O_{24}\cdot 2C_2H_5OH\cdot CH_3OH$ (1078.49): calcd. C 54.10, H 4.25, N, 16.39; found C 54.30, 4.22, 16.35. MALDI-TOF: calcd. for [M + Na]$^+$ 1607.4; found 1607.4.

Synthesis of 15: Compound **5** (2.52 g, 12.35 mmol) was dissolved in THF, and the solution was cooled with an ice/water bath. A solution of **14** (0.66 g, 6.16 mmol) in THF (50 mL) was added dropwise, and the mixture was stirred at 0 °C for 3 h and at room temperature for 48 h. The progress of the reaction was monitored by TLC (silica; EtOAc/cyclohexane, 50:50). After evaporation of the solvent under reduced pressure, acetone was added, leading to a suspension that was isolated by filtration, washed with EtOH, and dried under vacuum to give **15** (2.66 g, 5.58 mmol, 91%). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 6.98 (d, *J* = 14.0 Hz, 2 H, C=CH-CF), 77.58 (m, 4 H, ArH), 8.82 (d, *J* = 8.0 Hz, 2 H, O_2NC=CH-CNO_2), 10.15 (br. s, 2 H, NH) ppm. ^{13}C APT NMR (62 MHz, [D$_6$]DMSO): δ = 160.6 (d, *J* = 263 Hz, *C*-F), 147.7 (d, *J* = 13 Hz, FC-*C*-NO_2), 134.0 (NHC-*C*-NO_2), 129.0 (Ar*C*H), 128.5 (Ar*C*H), 128.1 (*C*-NH), 126.8 (NO_2C-*C*H), 126.3 (d, *J* = 10 Hz, FC-*C*-NH), 104.4 (d, *J* = 27 Hz, NHC-*C*H-CF) ppm.

$C_{18}H_{10}F_2N_6O_8$ (476.05): calcd. C 45.39, H 2.12, N 17.64; found C 45.92, H 2.21, N 17.13. ESI-MS (positive mode): *m*/*z* = 494.0 [M + NH_4]$^+$.

Synthesis of 16. Method 1: Compound **15** (168 mg, 0.353 mmol) was dissolved in DMSO (5 mL), and the solution was degassed with argon in an ultrasonic bath for 20 min. DIPEA (0.49 mL) and tetraaminobenzene **7**·4HCl (50 mg, 0.176 mmol) were added under argon, and the mixture was heated at 80 °C for 24 h. The progress of the reaction was monitored by TLC. The obtained suspension was cooled to room temperature, and EtOH was added. The resulting solid was collected by filtration and washed with EtOH and acetonitrile. Product **16** (43.8 mg, 0.043 mmol, 25%) was obtained after washing with hot acetone. **Method 2:** Compounds **18** (52 mg, 0.091 mmol) and **15** (43 mg, 0.090 mmol) were dissolved in DMSO (5 mL), and DIPEA (40 μL) was added. The solution was then heated at 75 °C for 24 h, then anhydrous EtOH was added to this hot suspension. The resulting suspension was filtered, the residue washed with EtOH, and then dried under vacuum to give **16** (57 mg, 0.056 mmol, 63%). ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 5.88 (s, 4 H, CH-C=CNO_2), 7.19 (s, 2 H, NHC=CH-CNH), 7.33 (m, 8 H, ArH), 8.96 (s, 4 H, NO_2C=CH-CNO_2), 9.11 (br. s, 4 H, NH), 9.81 (br. s, 4 H, NH) ppm. $C_{42}H_{26}N_{16}O_{16}$·$^4/_5$DMSO (1072.58): calcd. C 48.79, H 2.89, N 20.88, S 2.39; found C 48.79, H 3.03, N 20.50; S 1.95. ESI-MS (positive mode): *m*/*z* = 1011.2 [M + H]$^+$.

Synthesis of 18: In a 100 mL flask, **15** (417 mg, 0.875 mmol) was dissolved in MeCN (25 mL), and tetraaminobenzene **7**·4HCl (251 mg, 0.884 mmol) was then added under argon. The mixture was heated at 50 °C and DIPEA (1.25 mL) was added dropwise. The obtained red solution was heated to reflux for 22 h, then EtOH was added to the hot suspension, and the solution was cooled to room temperature. The orange solid was collected by filtration, washed with EtOH and Et_2O, and finally dried under vacuum to give the desired product **18** (393 mg, 0.684 mmol, 79%). ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 4.99 (br. s, 4 H, NH_2), 5.62 (s, 2 H, CH-C=CNO_2), 6.03 (s, 1 H, NH_2C=CH-CNH_2), 6.46 (s, 1 H NHC=CH-CNH), 7.35–7.26 (m, 4 H, ArH), 8.82 (br. s, 2 H, NH), 8.94 (s, 2 H, NO_2C=CH-CNO_2), 9.53 (br. s, 2 H, NH) ppm. $C_{24}H_{18}N_{10}O_8$·$^1/_3$EtOH·$^2/_3H_2O$ (601.49): calcd. C 49.23, H 3.57, N 23.17; found C 49.39, H 3.27, N 23.19. ESI-MS (positive mode): *m*/*z* = 575.0 [M + H]$^+$.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all key intermediates and final products, theoretical data of the calculated geometries.

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