DOI: 10.1002/ejoc.201001432

Synthesis and Properties of the Emerging Azacalix[1$_4$]arenes

Mounia Touil,[a,b] Mourad Elhabiri,[c] Mohammed Lachkar,[b] and Olivier Siri*[a]

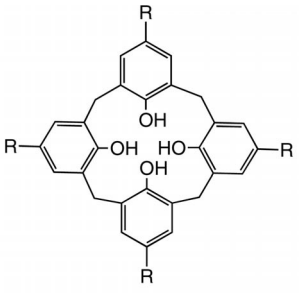
Keywords: Calixarenes / Hydrogen bonds / N ligands / Macrocycles / Aromatic substitution / Spectrophotometry

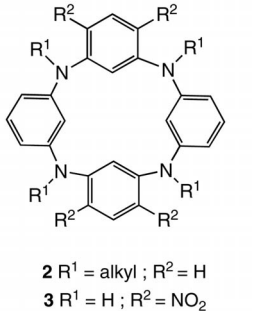
We describe the synthesis and spectrophotometric studies of novel N(H)-azacalix[4]arenes. The unprecedented direct functionalization of the N(H) bridges furnished N(*R*)-bridged aza[1$_4$]calixarene **11** that could complex a neutral guest (CH_2Cl_2) or could be further reduced into corresponding tetraamino derivative **12**.

Introduction

Calix[*n*]arenes **1** have received much attention over the last three decades in supramolecular chemistry due to their specific molecular structure, which allows the formation of numerous host–guest complexes.[1–3] Many structural modifications[4,5] of the upper and lower rims (i.e., functionalization of the phenyl rings) in **1** have been performed and studied in terms of conformational flexibility and inclusion behavior.[6–10] In contrast, functionalization of the bridges cannot be achieved easily,[11] whereas new and specific properties can be envisaged. Thus, considerable synthetic efforts are now devoted to the derivatization of basic calixarene skeletons, and more recent developments include the preparation of analogues by replacing the methylenic bridges by heteroatoms to tune the size of the cavity and to improve their binding properties.[12–20] Among the heteracalixarenes, N(*R*)-bridged azacalix[4]arenes of type **2**, also called aza[1$_4$]metacyclophanes, are an emerging class of macrocycles owing to the presence of the nitrogen bridges, which open new perspectives in molecular magnetism and in supramolecular chemistry as hosts.[15,21]

Curiously, inclusion properties of macrocycles of type **2** remain poorly explored, as only one example was described in the literature (R^1 = Me for K^+ complexation).[22] N(H)-bridged aza[1$_4$]metacyclophanes have been strikingly less investigated[19,21,23] but are much more attractive owing to the presence of additional hydrogen-bonding sites, and possible direct functionalization of the NH sites has curiously never been reported. The synthesis of symmetrical azacalix[4]arenes through Pd-catalyzed aminations[17,19,20,21,24] or efficient metal-free S_NAr[25,26] reactions has been much investigated since 2008, and in 2010, Katz et al. reported the first preparation of unsymmetrical analogues and inherently chiral *anti*-azacalix[4]arene regioisomers.[26] Thus, these tetraazamacrocycles are now considered as a new topical area in calixarene chemistry although only few of their properties have been reported. In N(H)-bridged azacalix[4]arenes of type **3**, all the amino bridges are in conjugation with the dinitrobenzene rings rather than with the two other phenyl rings because of the electron-withdrawing nature of the NO_2 groups.[25] Thus, unusual spectrophotometric and electronic properties can be envisaged for macrocycles of type **3** and physicochemical investigations appeared essential for a better understanding of their reactivity.





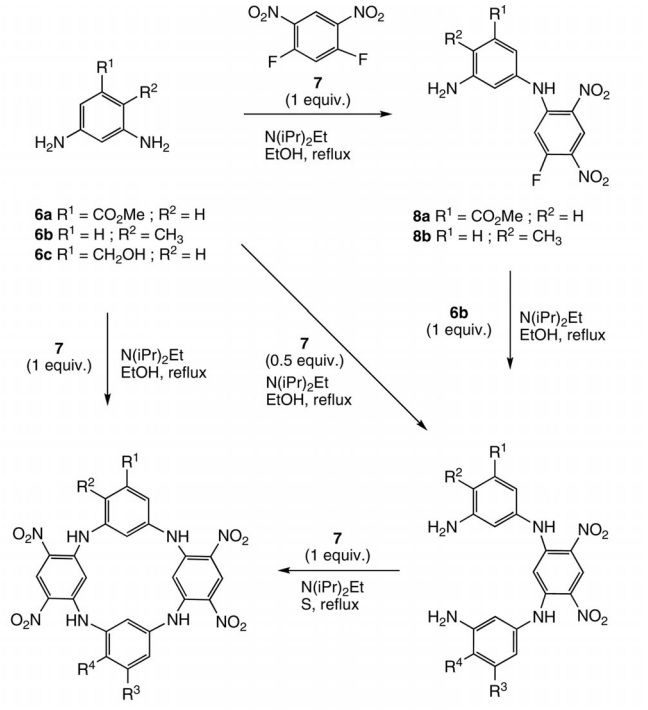
Herein, we wish to report the synthesis and unprecedented spectrophotometric properties of new symmetrical and unsymmetrical azacalix[4]arenes **10**. Our stepwise synthetic approach allows access to *syn*-azacalix[4]arene regioisomer **10b**, previously unknown. The first direct functionalization of the NH bridges furnished N(*R*)-bridged aza[1$_4$]calixarene **11** that could complex a neutral guest (CH_2Cl_2) or could be further reduced into corresponding tetraamino derivative **12**.

[a] Centre Interdisciplinaire de Nanoscience de Marseille (CINaM), UPR 3118 CNRS, Aix-Marseille Université, Campus de Luminy, case 913, 13288 Marseille cedex 09, France
Fax: +33-4-91829580
E-mail: siri@univmed.fr
[b] Université Sidi Mohamed Ben Abdellah, Faculté des Sciences Dhar El Mahraz, "L.I.M.O.M.", Unité Associée au CNRST (URAC 19), B. P. 1796 (Atlas), 30000 Fès, Morroco
[c] Laboratoire de Physico-Chimie Bioinorganique, Université de Strasbourg, Institut de Chimie de Strasbourg, UMR 7177 CNRS-UdS, ECPM, 25 rue Becquerel, 67200 Strasbourg, France

Results and Discussion

Synthesis

Similarly to the preparation of **9a** from **6a**,[25a] molecules **6b** were first treated with **7** (0.5 equiv.) in refluxing MeCN in the presence of base to afford [2+1] adduct **9b**, which precipitated in 84% yield (Scheme 1). Its ^{1}H NMR spectrum displays a downfield NH signal at δ = 9.60 ppm, which is in agreement with NH···O$_2$N hydrogen-bonding interactions that restrict the rotation of the uncyclized precursors.[25a] Further macrocyclization of **9b** by reaction with **7** in refluxing EtOH ($c \approx 10^{-2}$ M) afforded target molecule **10b** in 76% yield as an orange solid (Scheme 1). Similarly, cyclization reaction of **9c** – obtained by condensation of **6c** and **7** – led to **10c**, which precipitated as an orange solid in 35% yield.



Scheme 1. Synthesis of azacalix[4]arenes **10**: S = EtOH except for **10a**[25a] and **10d** (where S = MeCN).

Our stepwise strategy also allowed the synthesis of unsymmetrical derivatives. Compound **8a**[25a] could be condensed with **6b** at $c \approx 10^{-2}$ M in EtOH to furnish unsymmetrical intermediate **9d** as an orange solid (73% yield). As expected, its ^{1}H NMR spectrum shows the presence of two NH signals at δ = 9.67 and 9.70 ppm, which is in agreement with two intramolecular H-bonds. The macrocyclization reaction of **9d** and **7** in refluxing MeCN afforded **10d** in 33% yield (Scheme 1). As already reported,[25a,26] these observations are consistent with S$_N$Ar reactions, which are more favored at higher concentrations and which prevent the formation of polymeric materials even under low dilution conditions.

The ^{1}H NMR spectra of azacalix[4]arenes **10** display unusual highfield chemical shifts of the intra-annular aromatic protons H$_a$ in the range $4.85 < \delta < 5.53$ ppm, which is in agreement with the 1,3-alternate conformation in which the H$_a$ protons are located inside the anisotropic shielding cone of the adjacent aromatic rings (Figure 1).[12,21,25] In addition, the X-ray data available for related macrocycles indicate that this conformation is preserved in the solid state with subtle variations induced by the substituents.[25b]

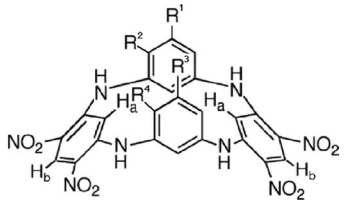
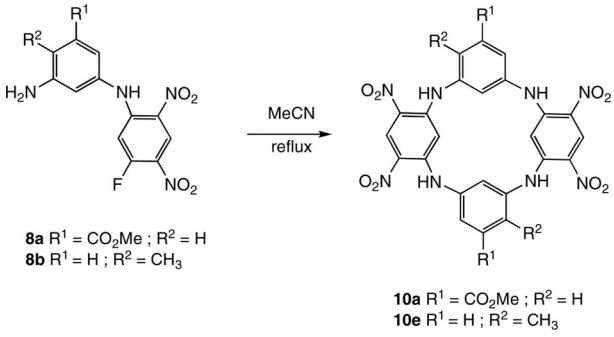


Figure 1. View of the 1,3-alternate conformation of molecules **10**.

When molecule **6c** was similarly treated with **7** (1 equiv.), macrocycle **10c** was directly obtained pure due to the solubility of the [1+1] reactive intermediate that can react with itself in EtOH (Scheme 1). The macrocyclization could also be achieved by dimerization (i.e., autocondensation) when the [1+1] adduct could be isolated, as already observed for the preparation of **10a** from **8a** in refluxing MeCN (Scheme 2).[25a]



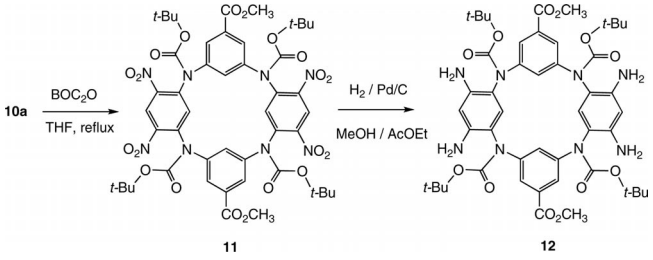
Scheme 2. Synthesis of **10** by dimerization reaction.

Similarly, reaction of **8b** – obtained by condensation of **6b** and **7** in refluxing EtOH in 87% yield – furnishes macrocycle **10e**, which has been recently obtained by Katz et al. directly from **6b** and **7** (**8b** was postulated as the single regioisomer intermediate).[26] Molecules **10b** and **10e** are therefore regioisomers (i.e., *syn* and *anti*, respectively), the former being only accessible by our stepwise synthesis (Scheme 1).

As expected, the ^{1}H NMR spectrum of **8b** shows the presence of NH resonance at δ = 9.84 ppm, which is consistent with the presence of a NH···O$_2$N intramolecular hydrogen bond. The two doublets at δ = 6.84 and 9.15 ppm correspond to the coupling of the aromatic protons with the fluoride atom ($^4J_{H,F}$ = 13.5 Hz and $^3J_{H,F}$ = 7.9 Hz, respectively). Importantly, the formation of single regioisomer **8b** for which the CH$_3$ group on the phenyl ring is located in

the *para* position with respect to the NH bridge could be established by X-ray analysis of the hydroxylated product of **8b**.[27]

Curiously, direct substitution of N(H)-bridged azacalix[4]arenes has never been reported, whereas this approach is very attractive for the introduction of coordinating units. For instance, molecule **10a** could be functionalized by reaction with BOC_2O (8 equiv.) in refluxing THF in the presence of DMAP, affording *N*-substituted azacalix[4]arene **11** as a yellow powder in 68% yield (Scheme 3). Its hydrogenation furnishes tetraamino derivative **12** (19% yield) that constitutes a candidate of choice for further substitution reactions and complexation owing the presence of four external NH_2 functions. It is noteworthy that the presence of the BOC protecting groups in **12** prevents the oxidation of the two electron-rich tetraaminobenzene subunits.



Scheme 3. Synthesis of functionalized azacalix[4]arenes **11** and **12**.

Interestingly, crystals suitable for X-ray diffraction measurements could be obtained by slow evaporation of **11** in CH_2Cl_2 in air.[28] Structure determination clearly established the unexpected formation of inclusion complex [**11**·CH_2Cl_2] in which the four BOC groups are positioned in the upper cap for interacting with the neutral guest (Figure 2). Although CH_2Cl_2 encaged in the host cavity is found to be disordered, the distances between the chloride atoms and the nearest C–H hydrogen atoms are in the range 2.577–3.546 Å, as expected for C–H···Cl hydrogen-bonding interactions.[29]

In the N(H)-bridged azacalix[4]arenes of type **3**, all the bridging nitrogen atoms are in conjugation with the dinitrobenzene rings rather than with the two other phenyl rings because of the electron-withdrawing nature of the NO_2 groups.[25] As a result, the two C–N bond lengths in the C–N(H)–C moieties are not equivalent (1.44 vs. 1.35 Å).[25b] For **11**, the two C–N bond lengths in the C–N(BOC)–C moieties are similar due to the conjugation of the nitrogen atoms, with the carbonyl groups rather than with the dinitrobenzene rings [for instance, N(1)–C(23) 1.426(3) and N(1)–C(1) 1.436(4) Å]. Although the conformation of **11** in [**11**·CH_2Cl_2] can be viewed as 1,3-alternate, the two nitrobenzene subunits are almost coplanar, whereas the two other C_6 rings appear almost parallel to each other and quasiorthogonal to the former (Figure 2). To the best of our knowledge, this "table-like" geometry has been previously observed only for methylene-bridged calixarenes and resorcinarenes.[30] In fluid solution, the factor of crystallinity is lost and the complex could not be characterized owing to its low stability (the weak C–H···Cl interactions cannot compete with the dynamic of rotation of the methyl groups).

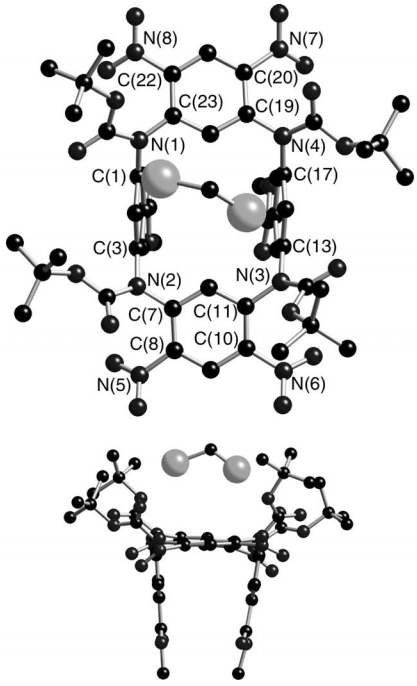


Figure 2. Top and side views of the structure of [**11**·CH_2Cl_2] in the crystal. The disorder of CH_2Cl_2 is omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)–C(23) 1.426(3), N(1)–C(1) 1.436(4), N(4)–C(19) 1.404(4), N(4)–C(17) 1.434(4), N(3)–C(11) 1.414(4), N(3)–C(13) 1.435(4), N(2)–C(3) 1.436(4), N(2)–C(7) 1.412(4), N(5)–C(8) 1.464(4), N(6)–C(10) 1.467(5), N(7)–C(20) 1.470(4), N(8)–C(22) 1.458(4); N(4)–C(19)–C(24) 118.8(2), N(2)–C(7)–C(12) 118.9(3), C(19)–N(4)–C(17) 117.5(2), C(3)–N(2)–C(7) 117.1(2).

Absorption and Acid-Base Properties

It is noteworthy that azacalix[4]arenes **10a**–**e** are slightly soluble in dichloromethane, dimethylformamide, and acetonitrile and sparingly soluble in water. The spectrophotometric and acid–base properties of azacalix[4]arenes **10a** and **10c** (the most soluble) were examined in a mixed solvent made of 90% acetonitrile and 10% water (by volume), which facilitates the dissolution of these compounds at ca. 10^{-4} M in aqueous solution. Calibration of the combined pHmetric glass electrode was accomplished by using commercial aqueous standard reference buffer solutions, thus leading to the reading of $^{s}_{w}$pH values (pH measured in acetonitrile/water with electrodes calibrated in water). Subsequent corrections[31] were applied to obtain the corresponding $^{s}_{s}$pH (acidity measured in acetonitrile/water, 90:10, with electrodes calibrated in the same mixed solvent). Azacalix[4]arenes **10a** and **10c** are characterized by intense absorption bands in the UV region centered at about 340 nm (**10a**, λ_{max} = 340 nm, $\varepsilon^{340} = 4.72 \times 10^4$ M^{-1} cm^{-1}; **10c**, λ_{max} = 343 nm, $\varepsilon^{343} = 3.77 \times 10^4$ M^{-1} cm^{-1}), together with a shoulder positioned at lower energies (λ_{max} ca. 400 nm, ε^{400} ca. $1–2.5 \times 10^4$ M^{-1} cm^{-1}). These spectroscopic data are in agreement with those measured for 1,5-diamino-2,4-dinitroben-

zene (λ_{max} = 321 nm, $\varepsilon^{321} = 2.9 \times 10^4$ M^{-1} cm^{-1}, λ_{max} = 397 nm, $\varepsilon^{397} = 10^4$ M^{-1} cm^{-1}) and therefore substantiate that, because of the electron-withdrawing effects of the nitro substituents and the strong intramolecular NH···O_2N hydrogen bonds, the four NH bridging atoms are primarily conjugated to the dinitrobenzene moieties. The observed absorptions therefore mainly originate from π–π* transitions of these two electronic independent diaminodinitrobenzene components;[32] those of the two other benzene rings are most likely centered at higher energies. Interestingly, the four bridging ionizable secondary amines can be either protonated or deprotonated, leading to potential positively and negatively charged hosts, respectively. For that reason, knowledge of their acid–base properties is of great importance regarding their high potential in ionic or molecular recognition processes. Preliminary spectral studies were thus performed by adding an excess amount of either base (NEt_4OH) or acid ($HClO_4$) on solutions of **10a** or **10c** (Figure 3). These spectrophotometric data show that, even with a large excess of acid with respect to the ligands (ca. 3000 equiv.), no significant variation could be observed. This observation suggests that the secondary amines cannot be protonated under our experimental conditions. The very low protonation constants of *p*-nitroaniline ($\log K^H$ = –0.3 in CH_3CN/H_2O, 75:25 w/w[33] and $\log K^H$ = 1.003 in H_2O[34]) and that of *o*-nitroaniline ($\log K^H$ = –0.282 in H_2O) further support this observation,[33] which may be due to important electronic effects (electron-withdrawing effect) of the dinitrobenzene rings (e.g., *o*-nitroaniline and *p*-nitroaniline) but also to the participation of the secondary amines in strong intramolecular NH···O_2N hydrogen-bonding interactions (e.g., *o*-nitroaniline).

In contrast, addition of base leads to drastic spectral changes with bathochromic shifts of the main absorption bands and simultaneous formation of new and less-intense absorptions in the visible region ($\lambda_{max} \approx 500$ nm, $\varepsilon^{500} \approx 1–1.5 \times 10^4$ M^{-1} cm^{-1}), thus conferring a red color to the basified solutions (Figures 3 and 4).

This spectral feature is most likely related to the deprotonation of the monobasic amine functions, leading to amide anions. In addition, the $\Delta\lambda_{max}$ values measured for **10a** (52 nm) and **10c** (54 nm) upon addition of base are significantly larger than those observed for related compounds,[35] which is an apparent signature for the presence of extended conjugated systems (quinoidal-type structure) with adjoining dinitrobenzene partners (Scheme 4).

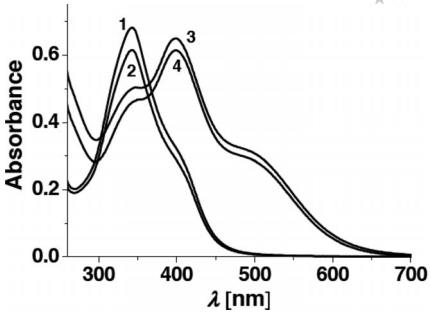


Figure 3. Absorption spectra of azacalix[4]arene **10c** measured under different experimental conditions. Solvent: CH_3CN/H_2O (9:1, v:v); T = 25.0(2) °C; I = 0.1 M (NEt_4ClO_4). (1) [**10c**] = 1.80×10^{-5} M; (2) [$HClO_4$]/[**10c**] ≈ 3000; (3) [NEt_4OH]/[**10c**] ≈ 2550; (4) [NEt_4OH]/[**10c**] ≈ 3800.

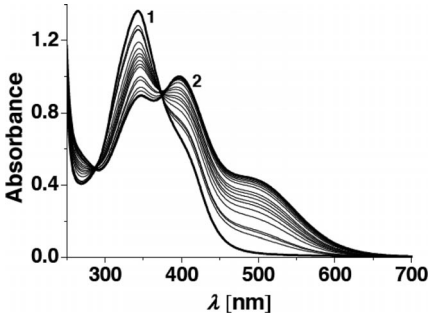


Figure 4. Spectral variations of **10c** recorded upon the addition of an excess amount of base (NEt_4OH). Solvent: CH_3CN/H_2O (9:1, v:v); T = 25.0(2) °C; I = 0.1 M (NEt_4ClO_4). [**10c**] = 3.27×10^{-5} M; (1) [NEt_4OH]/[**10c**] = 0; (2) [NEt_4OH]/[**10c**] = 595.

To determine the acid–base properties of the chromophoric azacalix[4]arene, absorption spectrophotometric titrations versus pH were carried out in CH_3CN/H_2O (9:1, v:v). The spectrophotometric and potentiometric data of **10a** between pH 9.79 and 16.47 and that of **10c** between pH 10.93 and 16.48 are given in Figure 5.

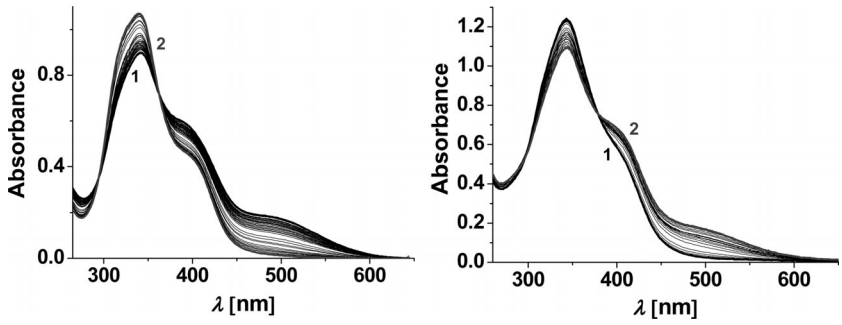
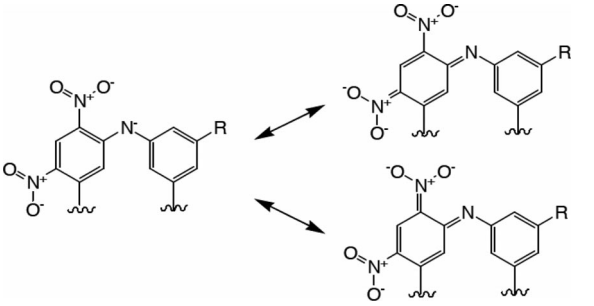


Figure 5. Spectrophotometric vs. pH titrations of **10a** (left) and **10c** (right). Solvent: CH_3CN/H_2O (9:1, v:v); T = 25.0(2) °C; I = 0.1 M (NEt_4ClO_4). (Left) [**10a**] = 2.27×10^{-5} M; (1) ^s_spH = 9.79; (2) ^s_spH = 16.47. (Right) [**10c**] = 3.28×10^{-5} M; (1) ^s_spH = 10.93; (2) ^s_spH = 16.48.



Scheme 4. Schematic mesomeric forms within the deprotonated azacalix[4]arene derivatives.

As previously observed, an increase in pH induces significant spectrophotometric changes such as a bathochromic shift of the main absorption band as well as the appearance of broad absorption in the visible region at ca. 500 nm. No spectral variation was observed below pH 9–10 for both compounds. It is noteworthy that compounds **10a** and **10c** possess four amino sites that can be deprotonated. Statistical treatment[36–39] of the spectrophotometric versus pH data led to the determination of two protonation constants [Equations (1) and (2)]. The reported errors on the protonation constants are given as 3σ (σ = standard deviation).

$$\mathbf{L}H_n^{n-4} + H^+ \underset{}{\overset{K_n^H}{\rightleftharpoons}} \mathbf{L}H_{n+1}^{n-3} \text{ with } 1 \le n \le 4 \text{ ; } \mathbf{L} = \mathbf{10a} \text{ or } \mathbf{10c} \quad (1)$$

$$K_n^H = \frac{[\mathbf{L}H_{n+1}^{n-3}]}{[\mathbf{L}H_n^{n-4}][H^+]} \quad (2)$$

For **10a**, the logarithmic values of the protonation constants are $\log K_3^H$ = 17.0(8) and $\log K_4^H$ = 15.0(1). For **10c**, comparable values were determined [$\log K_3^H$ = 17.2(8) and $\log K_4^H$ = 14.7(2)], thus signifying that the substitution of the two face-to-face phenyl rings has little influence on the acid–base properties of the bridging secondary amines. These data are in agreement with the absence of electronic communication (i.e., conjugation) between the two types of aromatic units. In addition, these pK_a values are, regardless of the experimental conditions, significantly lower that those determined for some reference compounds (for *p*-nitroaniline: $\log K^H$ = 20.9 in DMSO and ca. 19 in DMSO/water, 8:2, v:v).[40] Large Δlog K = $\log K_3^H$ – $\log K_4^H$ values[41] of about 2.0(8) and 2.5(9) with respect to pure statistical effects ($\log K_3^H$ – $\log K_4^H$ is expected to be 0.37 for four identical and independent sites) were calculated for compounds **10a** and **10c**, respectively. These data reflect strong electrostatic repulsions and geometrical effects between the molecular subunits within the constrained azacalix[4]arene edifice. The two higher protonation constants could not be determined under our experimental conditions. The electronic spectra of the protonated species of **10a** and **10c** are given in Figure 6.

Deprotonation of neutral azacalix[4]arenes **10a** and **10c** affording the amide monoanion led to moderate spectral variation by comparison with those experienced during the formation of the amide dianion. As suggested above, the spectral changes triggered by deprotonation of the bridging amine functions are likely associated to the formation of extended conjugated quinoidal systems (Scheme 4). Interestingly, the mesomeric forms of the mono- and bis-deprotonated species allowed the attribution of the deprotonation sites. Deprotonation of both bridging secondary amines borne by the same 5-substituted-1,3-diaminobenzene unit is not favored due to geometrical constrains (it forces the system to become coplanar by formation of a more extended conjugated system involving three adjacent aromatic units).

Conclusions

We described the stepwise synthesis of novel azacalix[4]arenes and an unprecedented *syn*-regioisomer analogue (i.e., **10b**). The first absorption spectrophotometric and potentiometric studies of the two representative amphoteric azacalix[4]arenes (i.e., **10a** and **10c**) allowed determination of their acid–base properties. Under our experimental conditions, the protonation constants related to the formation of ammonium cations could not be determined due to electronic (electron-withdrawing effects) and structural (strong intramolecular NH···O_2N hydrogen bonds) constraints. In contrast, deprotonation of these bridging secondary amines, which affords the corresponding amide anions,

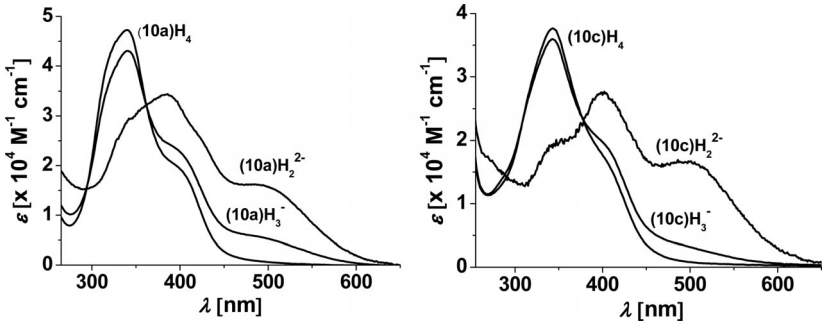
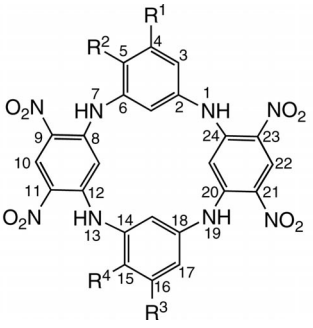


Figure 6. Electronic spectra of the protonated species of **10a** (left) and **10c** (right). Solvent: CH_3CN/H_2O (9:1); T = 25.0(2) °C; I = 0.1 M (NEt_4ClO_4).

could be studied and was easily monitored by absorption spectrophotometric means. The spectral variations were rationalized in terms of the formation of stable quinoidal-type structures in solution favored by the adjoining nitro groups. The first direct functionalization of N(H)-bridged aza[1$_4$]metacyclophanes **11** allowed the preparation of inclusion complex [**11**·CH_2Cl_2], which was fully characterized in the solid state. The *N*-substituent of the four bridges interacts with CH_2Cl_2 through C–H···Cl hydrogen bonds, and the complex adopts a table-like geometry that should favor its anchoring on substrates. In addition, reduction of **11** led to **12**, which are rare examples of azacalixarenes that can be functionalized at the bridges through NH substitutions, but also at the rim by substitution of the four NH_2 functions. These approaches are currently under investigation.

Experimental Section

General Methods: Commercial- analytical-grade reagents were obtained from commercial suppliers and were used directly without further purification. Solvents were distilled under an atmosphere of argon prior to use and dried by standard methods. ^{1}H NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO with AC250 spectrometers, operating at 250 MHz. Chemical shifts are reported in δ units relative to the singlet at δ = 7.26 for $CDCl_3$. Elemental and MS analyses were performed by Marseille Spectropole. ESI mass spectral analyses were recorded with a 3200 QTRAP (Applied Biosystems SCIEX) mass spectrometer. HRMS mass spectral analysis was performed with a QStar Elite (Applied Biosystems SCIEX) mass spectrometer. Molecules **8a**, **9a**, and **10a** were prepared as described in the literature.[25] For the nomenclature quote of the macrocycles, the following numbering of the atoms has been used:



***N*^{1}-(5-Fluoro-2,4-dinitrophenyl)-4-methylbenzene-1,3-diamine (8b):** A mixture of 1,5-difluoro-2,4-dinitrobenzene (200 mg, 0.98 mmol, 1 equiv), 2,3-diaminotoluene (120.5 mg, 0.98 mmol, 1 equiv.), and diisopropylethylamine (0.85 mL, 4.9 mmol, 2.5 equiv.) in refluxing EtOH was stirred for 24 h. The obtained precipitate was isolated by filtration and washed with water to afford **8b** as an orange solid (260 mg, 87% yield). M.p. 202 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 3.80 (br. s, 2 H, NH_2), 6.55 (m, 1 H, aromatic H), 6.60 (d, J = 2.0 Hz, 1 H aromatic H), 6.84 (d, $^3J_{HF}$ = 13.5 Hz, 1 H, aromatic H), 7.15 (d, J = 7.8 Hz, 1 H, aromatic H), 9.15 (d, $^4J_{HF}$ = 7.9 Hz, 1 H, aromatic H), 9.84 (br. s, 1 H, NH) ppm. MS (MALDI-TOF+): m/z = 307 [M + H]$^+$. $C_{13}H_{11}FN_4O_4$·1/3H_2O (312.26): calcd. C 50.00, H 3.77, N 17.94; found C 50.27, H 3.74, N 17.00.

***N*^{1}-[5-(3-Amino-4-methylphenylamino)-2,4-dinitrophenyl]-4-methylbenzene-1,3-diamine (9b):** A mixture of 1,5-difluoro-2,4-dinitrobenzene (200 mg, 0.98 mmol, 1 equiv.), 2,3-diaminotoluene (141 mg, 1.96 mmol, 2 equiv.), and *N*-diisopropylethylamine (0.85 mL, 4.90 mmol, 2.5 equiv.) in refluxing EtOH was stirred for 24 h. The obtained precipitate was isolated by filtration and washed with water to afford **9b** as an orange solid (335 mg, 84% yield). M.p. 209 °C. ^{1}H NMR (250 MHz, [D_6]acetone): δ = 2.78 (s, 6 H), 6.44 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 2.2 Hz, 2 H, aromatic H), 6.61 (d, J_{meta} = 2.2 Hz, 2 H, aromatic H), 6.71 (s, 1 H, aromatic H), 6.95 (d, J_{ortho} = 7.8 Hz, 2 H, aromatic H), 9.10 (s, 1 H, aromatic H), 9.56 (br. s, 2 H, NH) ppm. MS (MALDI-TOF+): m/z = 408.16 [M]$^+$. $C_{20}H_{20}N_6O_4$ (408.42): calcd. C 58.82, H 4.94, N 20.58; found C 58.61, H 4.94, N 20.56.

***N*^{1}-{5-[3-Amino-5-methyl(hydroxy)phenylamino]-2,4-dinitrophenyl}-5-methyl(hydroxy)benzene-1,3-diamine (9c):** To a solution of 3,5-diaminobenzylalcool (414 mg, 1.96 mmol, 2 equiv.) and *N*-diisopropylethylamine (0.67 mL, 4.9 mmol, 5 equiv.) in EtOH was added of 1,5-difluoro-2,4-dinitrobenzene (200 mg, 0.98 mmol, 1 equiv.). The mixture was stirred at reflux for 24 h. The obtained precipitate was isolated by filtration and washed with water to afford **9c** as an orange solid (354 mg, 82% yield). M.p. 218 °C. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 4.34 (d, J = 5.6 Hz, 4 H), 5.16 (t, J = 5.7 Hz, 2 H, OH), 5.31 (s, 4 H, NH_2), 6.35 (s, 4 H, aromatic H), 6.40 (s, 2 H, aromatic H), 6.61 (s, 1 H, aromatic H), 9.02 (s, 1 H, aromatic H), 9.58 (br. s, 2 H, NH) ppm. MS (ESI+): m/z = 441.1 [M + H]$^+$, 463.1 [M + Na]$^+$. $C_{20}H_{20}N_6O_6$·1/2H_2O (449.42): calcd. C 53.45, H 4.71, N 18.70; found C 53.79, H 4.60, N 18.65.

Methyl-3-[5-(3-amino-4-methylphenylamino)-2,4-dinitrophenylamino]-5-aminobenzoate (9d): To a solution of **8a** (500 mg, 1.43 mmol, 1 equiv.) in EtOH was added 2,4-diaminotoluene (**6b**; 174.28 mg, 1.43 mmol, 1 equiv.) and diisopropylethylamine (0.62 mL, 3.57 mmol, 2.5 equiv.). The mixture was heated at reflux for 24 h. The obtained precipitate was isolated by filtration and washed with water to afford **9d** as an orange solid (480 mg, 73% yield). M.p. 214 °C. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 1.97 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 4.99 (s, 2 H, NH_2), 5.61 (s, 2 H, NH_2), 6.52 (dd, J_{ortho} = 8.0 Hz, J_{meta} = 2.2 Hz, 1 H, aromatic H), 6.65 (m, 1 H, aromatic H), 6.74 (s, 1 H, aromatic H), 6.87 (m, 1 H, aromatic H), 6.96 (d, J_{ortho} = 8.0 Hz, 1 H, aromatic H), 7.11 (m, 1 H, aromatic H), 7.15 (m, 1 H, aromatic H), 9.17 (s, 1 H, aromatic H), 9.67 (br. s, 1 H, NH), 9.70 (br. s, 1 H, NH) ppm. MS (ESI+): m/z = 453.1 [M + H]$^+$. $C_{21}H_{20}N_6O_6$·1/2H_2O (461.43): calcd. C 54.66, H 4.59, N 18.21; found C 54.98, H 4.38, N 18.11.

5,15-Dimethyl-9,11,21,23-tetranitro-1,7,13,19-tetraaza[1$_4$]cyclophane (10b): To a solution of **9b** (700 mg, 1.71 mmol, 1 equiv.) in EtOH was added *N*-diisopropylethylamine (1.5 mL, 4.29 mmol, 2.5 equiv.) and 1,5-difuoro-2,4-dinitrobenzene (345 mg, 1.69 mmol, 1 equiv.). The mixture was heated at reflux for 20 h. The obtained precipitate was isolated by filtration and washed with water to afford **10b** as a yellow solid (750 mg, 76% yield). M.p. >300 °C (decomp.). ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 2.20 (s, 6 H, CH_3), 4.85 (s, 1 H, aromatic H), 4.97 (s, 1 H, aromatic H), 6.91 (d, J_{meta} = 1.9 Hz, 2 H, aromatic H), 7.04 (dd, J_{ortho} = 7.9 Hz, J_{meta} = 2.2 Hz, 2 H, aromatic H), 7.32 (d, J_{ortho} = 8.1 Hz, 2 H, aromatic H), 9.00 (s, 1 H, aromatic H), 9.04 (s, 1 H, aromatic H), 9.66 (br. s, 2 H, NH), 9.67 (br. s, 2 H, NH) ppm. MS (ESI+): m/z = 573.1 [M + H]$^+$. $C_{26}H_{20}N_8O_8$ (572.49): calcd. C 54.55, H 3.52, N 19.57; found C 55.57, H 3.63, N 19.10.

4,16-Bis[methyl(hydroxy)]-9,11,21,23-tetranitro-1,7,13,19-tetraaza-[1$_4$]cyclophane (10c): A mixture of 3,5-diaminobenzyl alcohol (**6c**; 258 mg, 1.22 mmol, 1 equiv.), *N*-diisopropylethylamine (1.06 mL, 6.11 mmol, 5 equiv.), and 1,5-difluoro-2,4-dinitrobenzene (**7**; 250 mg, 1.22 mmol, 1 equiv.) was heated at reflux in EtOH for 5 h.

The obtained precipitate was isolated by filtration and washed with water to afford **10c** as an orange solid (275 mg, 35% yield). M.p. 290 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 4.46 (d, J = 5.6 Hz, 4 H), 5.37 (t, J = 5.7 Hz, 2 H, OH), 5.64 (s, 2 H, aromatic H), 7.07 (s, 6 H, aromatic H), 9.04 (s, 2 H, aromatic H), 9.69 (br. s, 4 H, NH) ppm. MS (ESI+): m/z = 605.1 [M + H]$^+$. $C_{26}H_{20}N_8O_{10}$·2/3EtOH·1/3H_2O (641.21): calcd. C 51.20, H 3.88, N 17.48; found C 51.10, H 3.84, N 17.62.

4-Methyl(ester)-15-methyl-9,11,21,23-tetranitro-1,7,13,19-tetraaza-[1$_4$]cyclophane (10d): A mixture of **9d** (300 mg, 0.66 mmol, 1 equiv.), diisopropylethylamine (0.58 mL, 3.31 mmol, 5 equiv.), and 1,5-difuoro-2,4-dinitrobenzene (135.4 mg, 0.66 mmol, 1 equiv.) was heated at reflux in acetonitrile for 20 h. The obtained precipitate was isolated by filtration and washed with water to afford **10d** as an orange-brown solid (136 mg, 33% yield). M.p. 253 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.07 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 5.21 (s, 1 H, aromatic H), 5.25 (s, 1 H, aromatic H), 7.03 (m, 1 H, aromatic H), 7.29 (d, J_{ortho} = 8.0 Hz, 1 H, aromatic H), 7.41 (m, 1 H, aromatic H), 7.62 (m, 1 H, aromatic H), 7.66 (m, 2 H, aromatic H), 9.00 (s, 1 H, aromatic H), 9.03 (s, 1 H, aromatic H), 9.72 (br. s, 4 H, NH) ppm. MS (ESI+): m/z = 617 [M + H]$^+$. $C_{27}H_{20}N_8O_{10}$·H_2O (634.52): calcd. C 51.11, H 3.49, N 17.66; found C 51.55, H 3.58, N 17.25.

***N*,*N*′,*N*″,*N*‴-Tetraboc-4,16-bis[methyl(ester)]-9,11,21,23-tetranitro-1,7,13,19-tetraaza[1$_4$]cyclophane (11):** To a solution of **10a** (200 mg, 0.3 mmol, 1 equiv.) in dry THF (20 mL) was added BOC_2O (529, 2.42 mmol, 8 equiv.) under an atmosphere of nitrogen and 4-DMAP (42 mg, 0.34 mmol, 1.14 equiv.). The mixture was heated at reflux for 4 h, the solvent was removed under vacuum, and the residue was purified by column chromatography (silica gel; cyclohexane/ethyl acetate, 7/3) to give **11** (220 mg, 68% yield) as a yellow solid. M.p. 257 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO at 60 °C): δ = 1.38 (s, 36 H, *t*Bu), 3.82 (s, 6 H, OCH_3), 6.85 (s, 2 H, aromatic H), 7.45 (s, 2 H, aromatic H), 7.74 (s, 4 H, aromatic H), 8.93 (s, 2 H, aromatic H) ppm. MS (ESI+): m/z = 1061.3 [M + H]$^+$, 1078.5 [M + NH_4]$^+$. $C_{48}H_{52}N_8O_{20}$·1/2AcOEt (1105.04): calcd. C 54.35, H 5.11, N 10.14; found C 54.55, H 5.21, N 9.92.

***N*,*N*′,*N*″,*N*‴-Tetraboc-4,16-bis[methyl(ester)]-9,11,21,23-tetraamino-1,7,13,19-tetraaza[1$_4$]cyclophane (12):** A mixture of **11** (200 mg) in methanol/ethyl acetate (3:2, 25 mL) and palladium on carbon (5%) was stirred under an atmosphere of hydrogen overnight at room temperature. The catalyst was filtered off over Celite, and the filtrate was concentrated under vacuum. Quenching with ethyl acetate and removing the solvent gave a beige solid (33 mg, 19% yield). M.p. 232 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO, 90 °C): δ = 1.42 (s, 36 H, *t*Bu), 3.88 (s, 6 H, OCH_3), 4.16 (s, 8 H, NH_2), 6.11 (s, 2 H, aromatic H), 6.34 (s, 2 H, aromatic H), 6.47 (s, 2 H, aromatic H), 8.06 (s, 4 H, aromatic H) ppm. HRMS (ESI+): calcd. for $C_{48}H_{60}N_8O_{12}$ [M + NH_4]$^+$ 958.4669; found 958.4663.

Physicochemistry

Starting Materials and Solvents: The acid–base properties of ligands **10a** and **10c** were examined in acetonitrile/water (9:1, v:v). Distilled water was further purified by passing through a mixed bed of ion-exchanger (Bioblock Scientific R3–83002, M3–83006) and activated carbon (Bioblock Scientific ORC-83005). The distilled water, spectroscopic grade acetonitrile, and CH_2Cl_2 (Merck, Uvasol, p.a.) were de-oxygenated using CO_2- and O_2-free argon prior to use (Sigma Oxiclear cartridge). All the stock solutions were prepared by weighing solid products using an AG 245 Mettler Toledo analytical balance (precision 0.01 mg). Complete dissolution of the ligands was achieved with the help of an ultrasonic bath. The ionic strength was adjusted to 0.1 M with tetraethylammonium perchlorate (NEt_4ClO_4, Fluka, puriss). *CAUTION: Perchlorate salts combined with organic ligands are potentially explosive and should be handled in small quantities and with the necessary precautions.*[42]

Potentiometry: Ag/AgCl combined glass electrode (Metrohm 6.0234.500, Long Life) filled with 0.1 M NaCl (Fluka, p.a.) in water was calibrated (^s_wpH: pH measured in acetonitrile/water with electrodes calibrated in water) with commercial aqueous standard reference buffer solutions (Merck CertiPUR, pH = 1.68, 4.00, 6.86, 7.41, and 9.18). Potential differences were given by a Materlab PHM240 (Radiometer Analytical) millivoltmeter and the experiments were carried out at 25.0(2) °C maintained with the help of a Haake FJ thermostat. The use of δ values reported in the literature allowed the ^s_wpH values to be converted into the corresponding ^s_spH values (^s_spH: pH measured in acetonitrile/water with electrodes calibrated in the same acetonitrile/water mixture).

Protonated Species of 10a and 10c: Solutions of **10a** (2.27×10^{-5} M) and **10c** (3.28×10^{-5} M) were prepared by quantitative dissolution of a solid sample in acetonitrile/water (9:1). An aliquot of 40 mL was introduced into a jacketed cell (Metrohm 6.1414.150) maintained at 25.0(2) °C by the flow of a Haake FJ thermostat. The solution was continuously de-oxygenated by bubbling with oxygen free argon. The titration of **10a** ($9.79 < {}^s_s\text{pH} < 16.47$) or **10c** ($10.93 < {}^s_s\text{pH} < 16.48$) was carried out by addition of known volumes of a 0.1 M standardized tetraethylammonium hydroxide solution. Special care was taken to ensure that complete equilibration was attained. Absorption spectra vs. ^s_spH were recorded using a Varian CARY 50 spectrophotometer fitted with Hellma optical fibers (Hellma, 041.002-UV) and an immersion probe made of quartz suprazil (Hellma, 661.500-QX).

Refinement of the Data: The spectrophotometric and potentiometric data were processed with the Specfit program, which adjusts the stability constants and the corresponding molar extinction coefficients ($M^{-1}\,cm^{-1}$) of the species at equilibrium. Specfit[36–39] uses factor analysis to reduce the absorbance matrix and to extract the eigenvalues prior to the multiwavelength fit of the reduced data set according to the Marquardt algorithm.[43,44] Distribution curves of the various species were calculated using the Haltafall program.[45] Origin 5.0 was used to process the analytical results.[46] For the sake of simplicity, charges are omitted in all the chemical equilibria. The errors are given as 3σ with σ = standard deviation.

X-ray Crystal Data: Selected single crystals were mounted on a Nonius Kappa-CCD area detector diffractometer. The structures were solved by direct methods (SIR97) and refined against F^2 using the SHELXL97 software. The data were not corrected for absorption. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated according to stereochemistry and refined using a riding model in SHELXL97. CCDC-730533 (for **11**·CH_2Cl_2) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

This work was supported by the Centre National de la Recherche Scientifique, the Ministère de la Recherche et des Nouvelles Technologies, and the Agence Universitaire de la Francophonie (PhD grant of M.T.). We also thank Michel Giorgi for the determination of the crystal structure (Spectropole, Marseille).

[1] a) O. V Surov, M. I. Voronova, A. G. Zakharov in *Macrocyclic Chemistry* (Eds.: D. W. Fitzpatrick, J. H. Ulrich), Nova Science Publishers, Inc., Hauppage, NY, **2010**, p. 51; b) F. Vögtle, W. M. Müller, *J. Inclusion Phenom.* **1984**, *1*, 369.

[2] a) F. Sansone, L. Baldini, A. Casnati, R. Ungaro, *New J. Chem.* **2010**, *34*, 2715; b) H. Takemura, *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *42*, 169.

[3] a) R. Lalor, A. P. Gunning, V. J. Morris, S. E. Matthews, *Chem. Commun.* **2010**, *46*, 8665; b) C. Bavoux, R. Baudry, I. Dumazet-Bonnamour, R. Lamartine, M. Perrin, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *40*, 221.

[4] a) G. G. Talanova, V. S. Talanov, *Supramol. Chem.* **2010**, *22*, 838; b) I. Ling, Y. Alias, C. L. Raston, *New J. Chem.* **2010**, *34*, 1802; c) D.-S. Guo, K. Wang, Y. Liu, *J. Inclusion Phenom. Macrocyclic Chem.* **2008**, *62*, 1.

[5] a) A. Dondoni, A. Marra, *Chem. Rev.* **2010**, *110*, 4949; b) P. Jose, S. Menon, *Bioinorg. Chem. Appl.* **2007**, 1; c) A. Sirit, M. Yilmaz, R. A. Bartsch in *Macrocyclic Chemistry* (Eds.: D. W. Fitzpatrick, J. H. Ulrich), Nova Science Publishers, Inc., Hauppage, NY, **2010**, p. 325.

[6] a) M. J. McIldowie, M. Mocerino, M. I. Ogden, *Supramol. Chem.* **2010**, *22*, 13; b) J. J. González, R. Ferdani, E. Albertini, J. M. Blasco, A. Arduini, A. Pochini, P. Prados, J. D. Mendoza, *Chem. Eur. J.* **2000**, *6*, 73.

[7] a) W. Sliwa, T. Girek, *J. Inclusion Phenom. Macrocyclic Chem.* **2010**, *66*, 15; b) T. Tuntulani, G. Tumcharern, V. Ruangpornvisuti, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *39*, 47.

[8] a) E. A. Shokova, V. V. Kovalev, *Russ. J. Org. Chem.* **2009**, *45*, 1275; b) A. Arduini, M. Cantoni, E. Graviani, A. Pochini, A. Secchi, A. R. Sicuri, R. Ungaro, M. Vincenti, *Tetrahedron* **1995**, *51*, 599.

[9] a) K. Ohto, *Solvent Extr. Res. Dev., Jpn.* **2010**, *17*, 1; b) A. Arduini, W. M. McGregor, A. Pochini, A. Secchi, F. Ugozzoli, R. Ungaro, *J. Org. Chem.* **1996**, *61*, 6881.

[10] a) T. Amaya, J. Rebek Jr., *Chem. Commun.* **2004**, 1802; b) C. Dielemann, D. Matt, P. G. Jones, H. Thönnessen, *Acta Crystallogr., Sect. C* **2003**, *59*, o247.

[11] a) K. Kogan, N. Itzhak, S. E. Biali, *Supramol. Chem.* **2010**, *22*, 704; b) N. Itzhak, S. E. Biali, *J. Org. Chem.* **2010**, *75*, 3437; c) I. Columbus, S. E. Biali, *Org. Lett.* **2007**, *9*, 2927; d) S. Simaan, S. E. Biali, *J. Phys. Org. Chem.* **2004**, *17*, 752.

[12] J. L. Katz, M. B. Feldman, R. R. Conry, *Org. Lett.* **2005**, *7*, 91.

[13] W. Maes, W. Dehaen, *Chem. Soc. Rev.* **2008**, *37*, 2393.

[14] B. König, M. Hechavarria Fonseca, *Eur. J. Inorg. Chem.* **2000**, 2303.

[15] K. Ishibashi, H. Tsue, N. Sakai, S. Tokita, K. Matsui, J. Yamauchi, R. Tamura, *Chem. Commun.* **2008**, 2812.

[16] N. Morohashi, F. Narumi, N. Iki, T. Hattori, S. Miyano, *Chem. Rev.* **2006**, *106*, 5291.

[17] a) A. Ito, Y. Ono, K. Tanaka, *New J. Chem.* **1998**, *22*, 779; b) A. Ito, Y. Ono, K. Tanaka, *J. Org. Chem.* **1999**, *64*, 8236.

[18] P. Lhoták, *Eur. J. Org. Chem.* **2004**, 1675.

[19] W. Fukushima, T. Kanbara, T. Yamamoto, *Synlett* **2005**, *19*, 2931.

[20] H. Tsue, K. Ishibashi, H. Takahashi, R. Tamura, *Org. Lett.* **2005**, *7*, 2165.

[21] M. Vale, M. Pink, S. Rajca, A. Rajca, *J. Org. Chem.* **2008**, *73*, 27.

[22] H. Tsue, K. Ishibashi, S. Tokita, K. Matsui, H. Takahashi, R. Tamura, *Chem. Lett.* **2007**, *36*, 1374.

[23] G. W. Smith, *Nature (London U. K.)* **1963**, *198*, 879.

[24] a) H. Tsue, K. Ishibashi, R. Tamura, *Top. Heterocycl. Chem.* **2008**, *17*, 73; b) K. Ishibashi, H. Tsue, S. Tokita, H. Takahashi, R. Tamura, *Org. Lett.* **2006**, *8*, 5991.

[25] a) M. Touil, M. Lachkar, O. Siri, *Tetrahedron Lett.* **2008**, *49*, 7250; b) H. Konishi, S. Hashimoto, T. Sakakibara, S. Matsubara, Y. Yasukawa, O. Morikawa, K. Kobayashi, *Tetrahedron Lett.* **2009**, *50*, 620.

[26] J. L. Katz, B. A. Tschaen, *Org. Lett.* **2010**, *12*, 4300.

[27] M. Touil, M. Lachkar, O. Siri, *Tetrahedron Lett.* **2011**, submitted.

[28] Crystal data for [**11**·CH_2Cl_2]: monoclinic, space group $P2_1/c$ with a = 16.4792(2) Å, b = 15.9940(2) Å, c = 21.9291(3) Å, α = 90°, β = 95.26°, γ = 90° at 293(2) K with Z = 4, R_1 = 0.0848, GOF = 1.068. CCDC-730533.

[29] C. B. Aakeröy, T. A. Evans, K. R. Seddon, I. Pálinkó, *New J. Chem.* **1999**, *23*, 145.

[30] a) E. Dahan, S. E. Biali, *J. Org. Chem.* **1989**, *54*, 6003; b) J. Lipkowski, O. I. Kalchenko, J. Slowikowska, V. I. Kalchenko, O. V. Lukin, L. N. Markovsky, R. Nowakowski, *J. Phys. Org. Chem.* **1998**, *11*, 426.

[31] a) L. G. Gagliardi, C. B. Castells, C. Rafols, M. Roses, E. Bosch, *Anal. Chem.* **2007**, *79*, 3180; b) S. Rondinini, P. R. Mussini, T. Mussini, *Pure Appl. Chem.* **1987**, *59*, 1549; c) J. Barbosa, V. Sanz-Nebot, *Anal. Chim. Acta* **1991**, *244*, 183; d) J. Barbosa, V. Sanz-Nebot, *Fresenius J. Anal. Chem.* **1995**, *353*, 148.

[32] a) J. P. Idoux, K. Hancock, *J. Org. Chem.* **1968**, *33*, 3498; b) R. R. Minesinger, M. J. Kamlet, *J. Am. Chem. Soc.* **1969**, *91*, 4155.

[33] S. Subramanian, V. V. Giridhar, C. Kalidas, *J. Chem. Eng. Data* **1987**, *32*, 154.

[34] B. Garcia, J. M. Leal, L. A. Herrero, J. C. Palacios, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1759.

[35] B. P. Bubnis, G. E. Pacey, *Talanta* **1984**, *31*, 1149.

[36] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 95.

[37] F. J. C. Rossoti, H. S. Rossoti, R. J. Whewell, *J. Inorg. Nucl. Chem.* **1971**, *33*, 2051.

[38] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1986**, *33*, 943.

[39] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 257.

[40] a) F. G. Bordwell, D. Algrim, N. R. Vanier, *J. Org. Chem.* **1977**, *42*, 1817; b) J. C. Hallé, F. Terrie, R. Schaal, *Bull. Soc. Chim. Fr.* **1973**, 1225; c) R. A. Bartsch, D. K. Roberts, B. R. Cho, *J. Org. Chem.* **1979**, *44*, 4105.

[41] B. Perlemutter-Hayman, *Acc. Chem. Res.* **1986**, *19*, 90.

[42] a) W. C. Wolsey, *J. Chem. Educ.* **1978**, *55*, A355; b) K. N. Raymond, *Chem. Eng. News* **1983**, *61*, 4.

[43] D. W. Marquardt, *J. Soc. Indust. Appl. Math.* **1963**, *11*, 431.

[44] M. Maeder, A. D. Zuberbühler, *Anal. Chem.* **1990**, *62*, 2220.

[45] N. Ingri, W. Kakolowicz, L. G. Sillen, B. Warnqvist, *Talanta* **1967**, *14*, 1261.

[46] *MicrocalTM OriginTM*, Microcal Software, Inc., Northampton, USA.

Received: October 20, 2010
Published Online: February 15, 2011

