

## Chemically modified tetranitro-oxacalix[4]arenes: synthesis and conformational preferences of tetra-*N*-(1-octyl)ureido-oxacalix[4]arenes

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In honor of Professor Nicolò Vivona on the occasion of his 70<sup>th</sup> birthday

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### Abstract

Tetranitro-oxacalix[4]arenes **1–5**, prepared by direct S<sub>N</sub>Ar reaction of 1,5-difluoro-2,4-dinitrobenzene with the appropriate aromatic diol (pyrocatechol, resorcinol, hydroquinone, 2,7-dihydroxynaphthalene, and 4,4'-dihydroxybiphenyl), were subjected to Raney-nickel reduction to provide the corresponding tetraamino-oxacalix[4]arenes **6–10**, which upon treatment with an excess of 1-octyl isocyanate were converted into the title compounds **11–15**, featuring a pair of 1,3-bis-[*N*-(1-octyl)ureido]phenylene moieties doubly connected at their 4,6-positions by rigid spacers of varied geometry. All new oxacalix[4]arenes were characterized by MALDI-TOF spectrometry and NMR spectroscopy. <sup>1</sup>H NMR data and *ab initio* calculations support saddle-shaped conformations for oxacalix[4]arenes incorporating pyrocatechol, resorcinol and 2,7-dihydroxynaphthalene nucleophilic components, and boat-shaped conformations for derivatives possessing hydroquinone and 4,4'-dihydroxybiphenyl spacers.

**Keywords:** *Ab initio* calculations, anion receptors, calixarenes, heterocalixarenes, macrocycles, nitro group reduction, ureido ligands

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### Introduction

The three-dimensional architecture of calixarenes, their easy preparation and functionalization, tunable size, unique conformational properties and versatile molecular recognition abilities, have established this class of compounds as one of the prime building blocks in host-guest and supramolecular chemistry.<sup>1</sup> Furthermore, the incorporation of bridging atoms other than carbon

within their framework provides a means to expand calixarene structural diversity, producing new-generation macrocyclic host molecules with unexplored chemical and physical properties. As a matter of fact, in the past few years heteroatom-bridged calix(hetero)arenes have received special attention as new potential scaffolds for the design of supramolecular structures.<sup>2</sup>

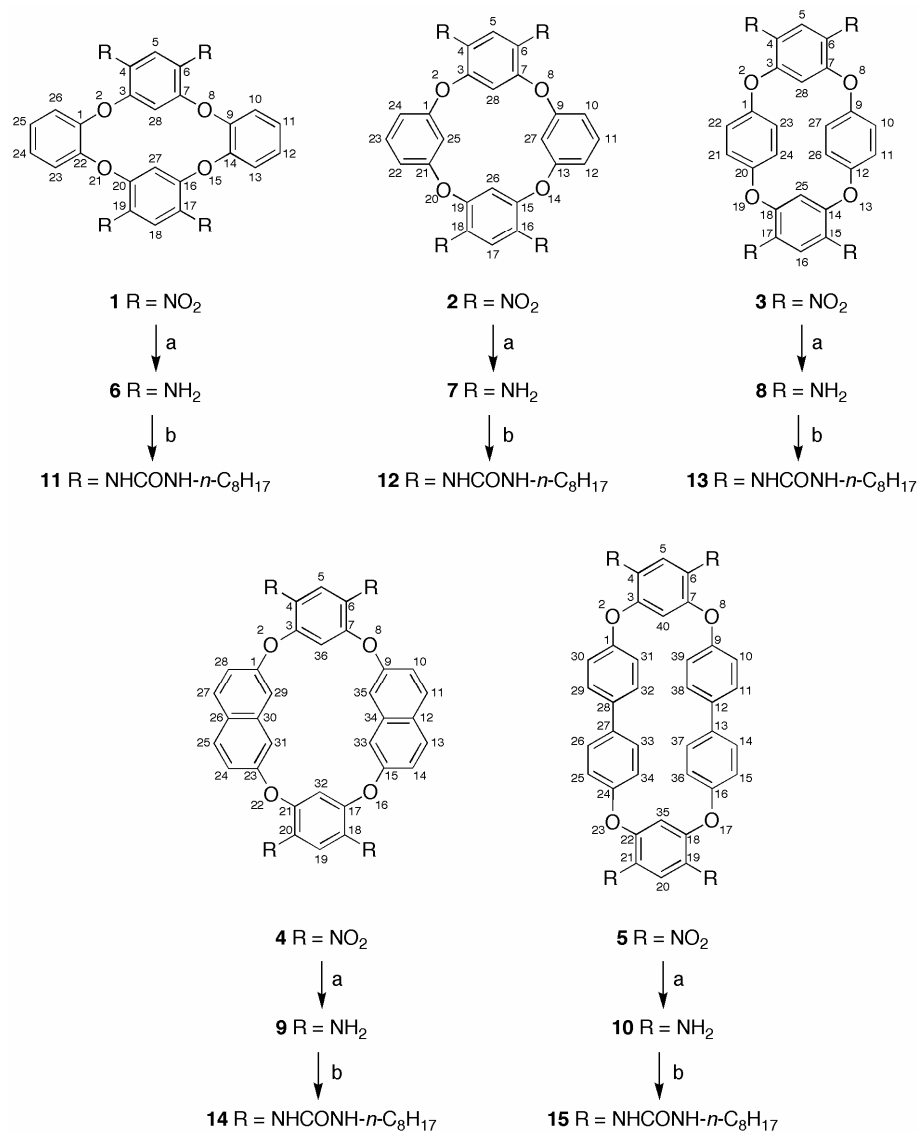
Oxygen-bridged calixarenes, henceforth referred to as oxacalixarenes, can be viewed as rigid crown ethers built up with fully aromatic rings only.<sup>3</sup> The *meta*-bridged (*m,m,m,m*-) 16-membered tetranitro-oxacalix[4]arene **2** was first synthesized in modest yield in 1966 by direct nucleophilic aromatic substitution (S<sub>N</sub>Ar) of resorcinol with 1,5-dichloro-2,4-dinitrobenzene.<sup>4</sup> Subsequently, papers in the mid-seventies extended this procedure to the preparation of isomeric 14- and 18-membered macrocycles with an alternating (*m,o,m,o*-) and (*m,p,m,p*-) bridging sequence, best exemplified by the parent compounds **1** and **3**, by using pyrocatechol and hydroquinones as the nucleophilic components, respectively.<sup>5,6</sup> Then, for almost three decades, only sporadic studies were conducted on related compounds,<sup>7,8</sup> probably due to the limited solubility of earlier materials, which hampered their purification and characterization.<sup>9</sup>

Quite recently, Katz *et al.* achieved an important breakthrough in oxacalix[4]arene chemistry when they found that various tetranitro-oxacalix[4]arenes can be generated in excellent yield by the room temperature S<sub>N</sub>Ar reaction of resorcinols (nucleophilic components) with 1,5-difluoro-2,4-dinitrobenzene (electrophilic component) in dimethylsulfoxide (DMSO) under basic conditions.<sup>10</sup> The excellent yields of the cyclic tetramer over potentially accessible larger structures can be attributed to thermodynamic product control under equilibrating conditions.<sup>11</sup> The reaction did not require high dilution conditions, and tolerated a wide range of substituents (alkyl, formyl, ester, hydroxyl, and even porphyrin<sup>12</sup>) on the nucleophilic component, chosen either to impart better solubility characteristics to the macrocycles, or to pursue specific structural modifications by further derivatization.<sup>13</sup> The use of dihalo-*N*-heterocycles as the electrophilic component in the S<sub>N</sub>Ar reactions with aromatic diols, has expanded calixarene structural diversity to include oxacalix[2]arene[2]pyridines,<sup>14</sup> -[2]pyrazines,<sup>14c</sup> -[2]pyrimidines,<sup>14c,15</sup> -[2]triazines,<sup>16</sup> and oxacalix[2]naphthalene[2]naphthyridines as well.<sup>17</sup>

Although tetranitro-oxacalix[4]arenes are ideal precursors of more sophisticated amino-containing molecular architectures, the chemical alteration of the nitro functions in such compounds has lagged behind, probably as a consequence of their scarce solubility.<sup>18</sup> In this paper we report the preparation of a series of tetranitro-oxacalix[4]arenes **1–5**, their successful reduction to the corresponding tetraamino derivatives **6–10**, and smooth conversion into tetra-*N*-(1-octyl)ureido-oxacalix[4]arenes **11–15**. The conformational preferences of all oxacalix[4]arenes synthesized have been deduced with the aid of <sup>1</sup>H NMR spectroscopy and calculations of equilibrium geometries. The title compounds show the potential to act as neutral hydrogen-bonding anion receptors in polar media.<sup>19</sup>

## Results and Discussion

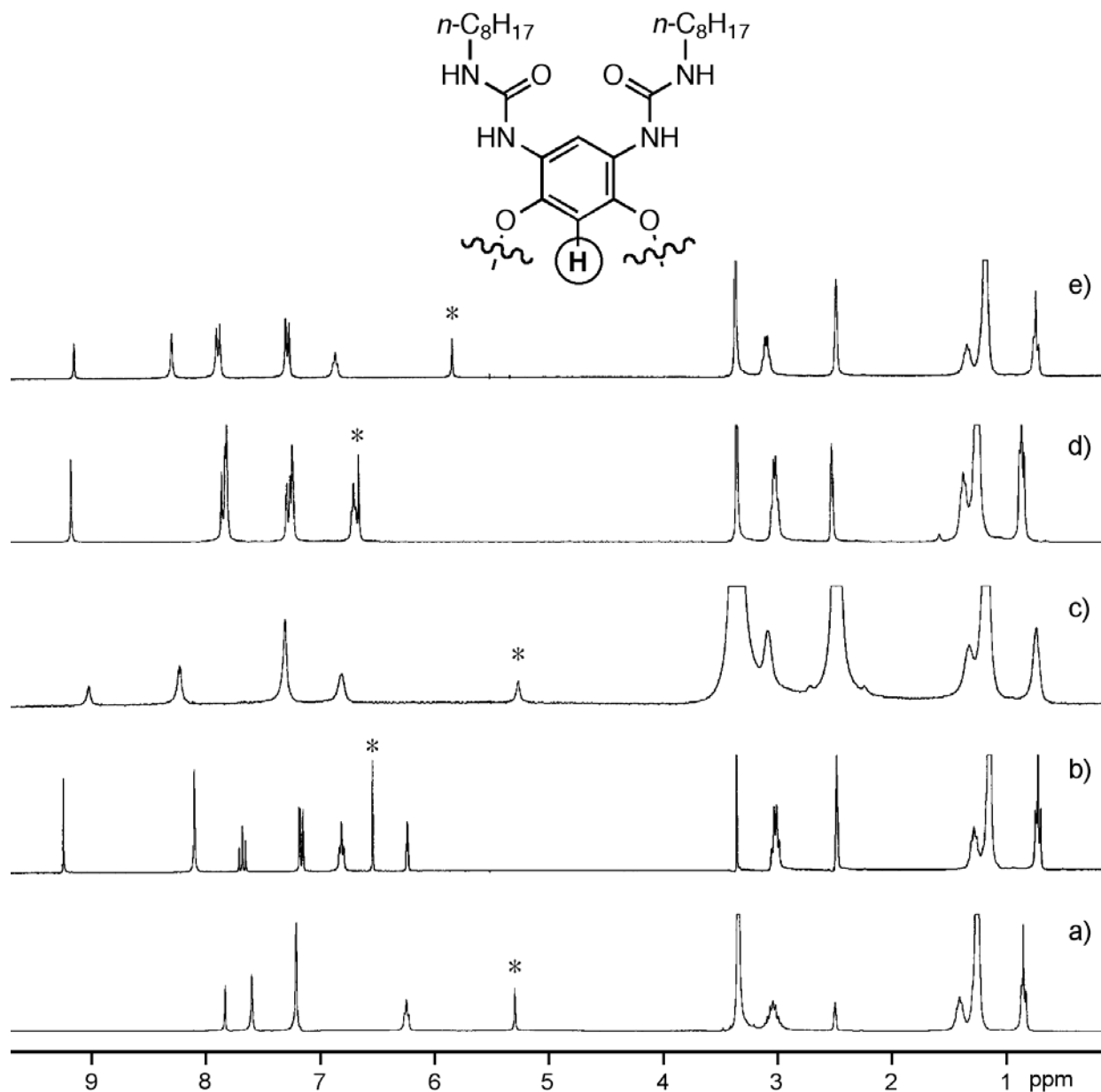
The synthetic sequence to oxacalix[4]arenes **1–15** described in this paper and relevant ring-system numbering schemes are shown in Scheme 1. The starting tetranitro-oxacalix[4]arenes **1–5** were obtained in 58–82% yield by direct nucleophilic aromatic substitution ( $S_NAr$ ) of 1,5-difluoro-2,4-dinitrobenzene with the appropriate aromatic diol (pyrocatechol, resorcinol, hydroquinone, 2,7-dihydroxynaphthalene, or 4,4'-dihydroxybiphenyl) in refluxing *N,N*-dimethylformamide (DMF) in the presence of triethylamine (TEA).



**Scheme 1.** Synthesis of tetraureido-oxacalix[4]arenes **11–15** starting from tetranitro-derivatives **1–5**. Reagents: (a) H<sub>2</sub>, Raney-nickel, THF or DMF; (b) CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>NCO, CHCl<sub>3</sub> or DMSO. See Experimental Section for details.

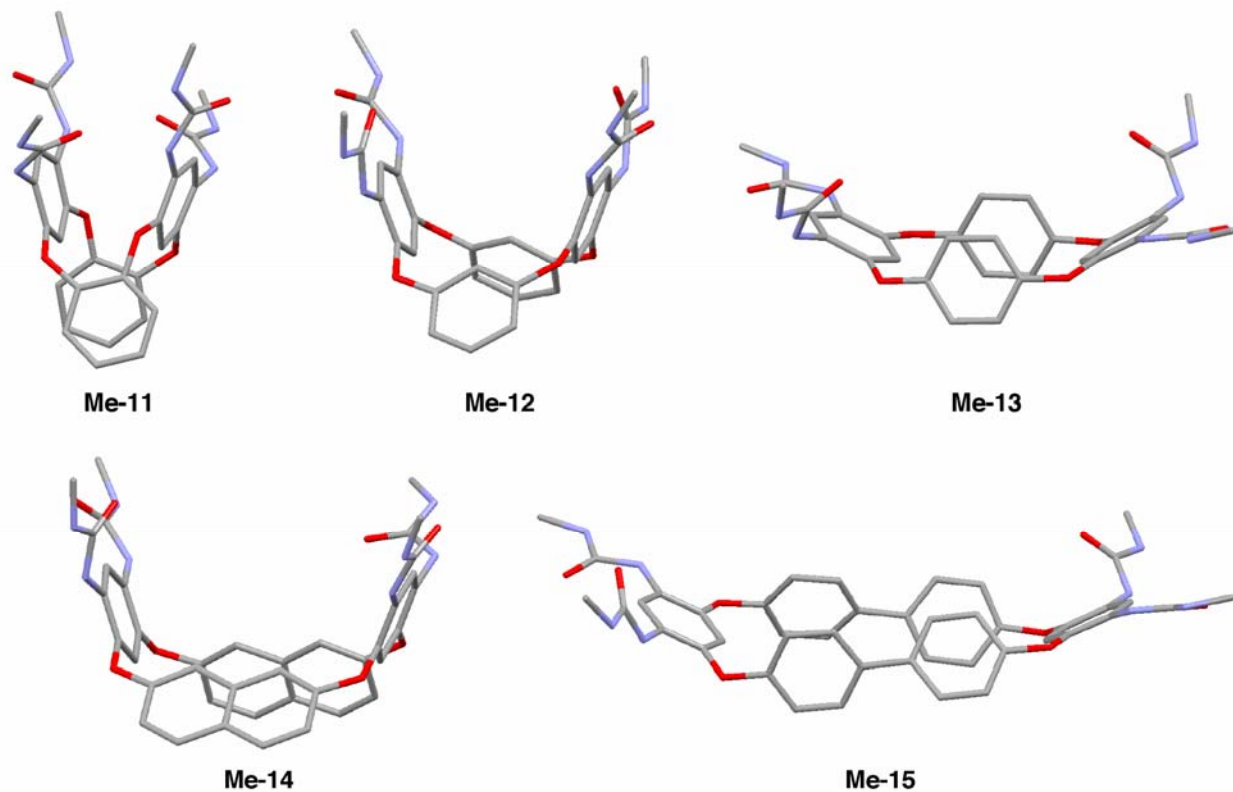
The cyclic tetramers, precipitating out from the cooled reaction mixtures, after thorough washing with methanol were pure enough for the subsequent step. By following a synthetic protocol previously used for the preparation of (bis)ureido-calix[5]arenes,<sup>20</sup> when a slurry of tetranitro-oxacalix[4]arene in freshly distilled tetrahydrofuran (THF, compds **1**, **2**, **4** and **5**) or *N,N*-dimethylformamide (DMF, compd **3**) was subjected to H<sub>2</sub> (1 atm) in the presence of Raney-nickel, the corresponding tetraamino-oxacalix[4]arenes were obtained (76–86% yield for **6**, **7** and **9**, respectively). Tetraamino derivatives **8** and **10**, derived from hydroquinone and 4,4'-dihydroxybiphenyl nucleophilic components, were not isolated. Their formation was demonstrated by <sup>1</sup>H NMR but, owing to their very low solubility in most common organic solvents (*vide infra*), they were used without further purification in the following step after removal of the nickel catalyst. Progress of the reaction was conveniently monitored by <sup>1</sup>H NMR spectroscopy in DMSO-*d*<sub>6</sub>, by following the disappearance of the low-field resonance of the aromatic proton between the two nitro groups of the electrophilic component moiety ( $\delta$  = 8.70–9.05 ppm), and the appearance of a high-field resonance for the newly formed amino groups ( $\delta$  = 4.05–4.63 ppm). Subsequent conversion of amino compounds **6–10** into tetra-*N*-(1-octyl)ureido-oxacalix[4]arenes **11–15** was achieved by treatment with an excess of 1-octyl isocyanate in dry DMSO (for **11** and **13–15**) or CHCl<sub>3</sub> (for **12**). Ureido-oxacalix[4]arenes **11**, **12**, and **14** were isolated in 22, 37 and 23% yield, respectively, whereas **13** and **15** were obtained in 26 and 36% yield (calculated over two steps from the corresponding tetranitro precursors **3** and **5**). Completion of the reaction is signaled by the total disappearance of the broad amino resonance, which is in turn replaced by a lower field (D<sub>2</sub>O exchangeable) singlet–triplet pattern for the newly formed NHC(O)NHC<sub>8</sub>H<sub>17</sub> groups. In general, oxacalix[4]arenes **1–15** show limited solubility in high-boiling polar solvents (DMF, DMSO, *ortho*-dichlorobenzene, nitrobenzene, hexamethyl phosphoramide, etc.) at room temperature.

The <sup>1</sup>H NMR spectra of the oxacalix[4]arenes **1–15** are characterized by high field resonances for the intra-annular aromatic protons of the electrophilic component ( $\delta$  = 5.12–6.72 ppm, see Figure 1 for **11–15**), owing to the diamagnetic shielding arising from the flanking aromatic rings, which is a function of the molecular conformation.<sup>5,9,21</sup> This suggests that tetranitro-oxacalix[4]arene precursors **1**, **2** and **4** and their amino (**6**, **7**, **9**) and ureido (**11**, **12**, **14**) derivatives (see Scheme 1) preferentially adopt a saddle-shaped (1,3-alternate) conformation in solution. This particular conformation is presumably enforced by the tendency to maintain conjugation between the bridging oxygen atoms and the originally electron-poor (nitro-bearing) aromatic rings. This conclusion, based on <sup>1</sup>H NMR data, is in good agreement with the results of a series of X-ray diffraction studies on related oxacalix[4](hetero)arenes. The structural data have shown that the aromatic rings of the electrophilic component approach coplanarity; while the rings of the nucleophilic component are eclipsing and nearly parallel.<sup>10,16,17</sup> On the other hand, although the intra-annular protons of the electrophilic component in tetranitro-oxacalix[4]arenes **3** and **5** and their amino (**8**, **10**) and ureido (**13**, **15**) derivatives resonate at the usual high field strengths ( $\delta$  = 5.12–6.23 ppm),<sup>22</sup> the geometric features of their nucleophilic components impart to these molecules equally plausible boat or chair conformations.



**Figure 1.**  $^1\text{H}$  NMR spectra (300 MHz,  $\text{DMSO-}d_6$ , 22  $^\circ\text{C}$ ) of tetra-*N*-(1-octyl)ureido-oxacalix[4]arenes **11–15** (traces *a* to *e*, respectively). The asterisks indicate the peaks for the intra-annular hydrogen atoms.

In order to gain an insight into the overall geometry of ureido-oxacalix[4]arenes **11–15**, so as to evaluate optimal geometrical fitting of putative (poly)anion guests for cooperative binding to the facing ureido functions, in the absence of single crystals suitable for an X-ray analysis, *ab initio* calculations were performed by using the Hartree-Fock method with the 6-31G\* basis set.<sup>23</sup> To decrease the degrees of freedom, and simplify the calculations, the *n*-octyl moieties were replaced by methyl groups (compds **Me-11–Me-15**, Figure 2).



**Figure 2.** Optimized ground-state geometries for model compounds **Me-11–Me-15** (derived from ureido-oxacalix[4]arenes **11–15** by replacement of the *n*-octyl moieties with methyl groups), obtained by HF/6-31G\* *ab initio* calculations. Hydrogen atoms omitted for clarity.

The first interesting observation was that all the structures calculated adopt a boat-like conformation, featuring the ureido-bearing aryl groups in a *syn* relationship with respect to the mean plane generated by the four bridging oxygen atoms. Ureido-oxacalix[4]arenes **Me-13** and **Me-15** share great similarities. The ureido-bearing aryl groups lie in a wide-open and slightly twisted arrangement, the angles between the rings mean planes being 124.9° and 124.2°, respectively. The distances between the centroids of these rings vary considerably (7.87 and 12.12 Å, respectively) according to the length of the spacer. Compounds **Me-11**, **Me-12** and **Me-14** on the other hand, present with the ureido-aryl rings facing each other in a slightly divergent arrangement. The angles formed by the mean planes of these aryl rings are in the 30–40° range (Table 1), while the distances between their centroids are 3.78, 5.60 and 8.12 Å, respectively. The structural features of the latter model compounds indicate that tetraureido-oxacalix[4]arenes **11**, **12**, and **14** are the best candidates for an initial screening of the anion-complexation abilities. Indeed, it is likely that as a result of the relatively small angle formed by the aryl groups, the ureido moieties may have the correct geometry to act cooperatively for a tweezers-type complexation of suitably-sized anions.

The calculated geometries of the ureido-oxacalix[4]arenes **Me-11–Me-15** are additionally substantiated by careful analysis of the  $^1\text{H}$  NMR spectra of their parent compounds (Figure 1). The chemical shift observed for the intra-annular hydrogen atoms of compounds **12** and **14** (H-26/28 and H-32/36, respectively) are in good agreement with their calculated spatial arrangement (Figure 1, traces *b* and *d*, respectively). Inspection of the molecular models **Me-12** and **Me-14** suggests that, because of the angle imposed by the resorcinol and 2,7-dihydroxynaphthalene spacers, the pertinent intra-annular hydrogen atoms can not enjoy the shielding of the nearby aromatic spacers and as a result resonate at modestly high fields ( $\delta = 6.32\text{--}6.62$  ppm). Conversely, the analogous intra-annular hydrogen atoms for **11**, **13** and **15** reside closer to the shielding cones of their spacers, and therefore resonate at much higher fields ( $\delta = 5.12\text{--}5.66$  ppm) with respect to **12** and **14** (Figure 1, traces *a*, *c*, and *e*, respectively).

**Table 1.** Centroid-centroid distances and interplanar angles formed by the aryl moieties bearing the ureido groups for model compounds **Me-11–Me-15**.

	<b>Me-11</b>	<b>Me-12</b>	<b>Me-13</b>	<b>Me-14</b>	<b>Me-15</b>
centroid distance (Å)	3.78	5.60	7.87	8.12	12.12
mean planes angle (°)	29.6	37.3	124.9	40.2	124.2

## Conclusions

A new family of oxacalix[4]arenes endowed with *extra*-annular ureido functionalities was synthesized, by applying methodologies which had previously proved successful for classical calix[*n*]arenes. Their structures and conformations were established by a combination of MALDI-TOF spectrometry, NMR investigations and computational methods. The results obtained from the *ab initio* calculations were found to be in excellent agreement with the spectroscopic data presented. Future studies will be directed to the evaluation of the anion binding abilities of the tetra-*N*-(1-octyl)ureido-oxacalix[4]arenes towards mono- and polyanions, and to the design and synthesis of new tetraureido-oxacalix[4]arene derivatives with improved solubility in organic solvents and water.

## Experimental Section

**General Procedures.** Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Unless otherwise stated,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at room temperature in DMSO-*d*<sub>6</sub> at 300 and 75 MHz, respectively.  $^{13}\text{C}$ NMR spectra of compds **3**, **5** and **8** could not be recorded because of very poor solubility of the samples. THF and  $\text{CHCl}_3$  were dried by standard methods<sup>24</sup> prior to use; other chemicals were reagent grade and were used without further purification. MALDI-TOF mass spectra were performed using a Voyager STR

instrument (Applied Biosystems, Framingham, MA) equipped with a nitrogen laser ( $\lambda = 337$  nm) and delayed extraction technology. Ions generated by the pulsed laser beam were accelerated through a 24 kV electric field. Mass spectra are the result of 256 laser shots. High resolution positive-ion mass spectra were acquired in reflector mode. External mass calibration was performed, and mass accuracy was better than 20 ppm. Briefly, 0.5  $\mu$ L of each sample, dissolved in DMSO, was deposited onto a stainless-steel MALDI sample plate, with the same volume of matrix solution and left to dry at room temperature for two days. Among the three different matrix solutions tested ( $\alpha$ -cyano-4-hydroxycinnamic acid, 2-(4-hydroxyphenylazo)-benzoic acid, and 5-chloro-2-mercaptobenzothiazol), the best results were obtained with  $\alpha$ -cyano-4-hydroxycinnamic acid (10 mg/mL in CH<sub>3</sub>OH). All attempts to get MALDI-TOF mass spectra of compds **4**, **5**, **8** and **10** under the experimental conditions used were unsuccessful. Elemental analyses were carried out by Redox s.n.c. (Monza, Italy).

**General procedure for the synthesis of tetranitro-oxacalix[4]arenes 1–5.** A slight modification of Lehmann's procedure<sup>5</sup> was used. A stirred solution of 1,5-difluoro-2,4-dinitrobenzene (204 mg, 1 mmol), the appropriate diol (1 equiv.), and TEA (0.3 mL, 2.2 equiv.) in dry DMF (10 mL) was refluxed for 0.5–2 h. After cooling, the precipitate was collected by filtration, and thoroughly washed with methanol to leave a pale yellow powder, which analyzed correctly for the desired macrocycle.

**4,6,17,19-Tetranitro-2,8,15,21-tetraoxacalix[4]arene (1).** 156 mg, 57% yield; Mp > 350 °C (lit.<sup>5</sup>, M.p. > 350 °C); <sup>1</sup>H NMR  $\delta$  5.68 (s, 2 H, 27,28-ArH), 7.44–7.60 (AA'BB', 8 H, 10,11,12,13,23,24,25,26-ArH), 8.70 (s, 2 H, 5,18-ArH) ppm; <sup>13</sup>C NMR  $\delta$  106.2, 125.4, 125.7, 129.2, 131.9, 143.2, 153.2 ppm.

**4,6,16,18-Tetranitro-2,8,14,20-tetraoxacalix[4]arene (2).** 200 mg, 73% yield; M.p. > 350 °C (lit.<sup>4,5,9</sup>, Mp > 350 °C); <sup>1</sup>H NMR  $\delta$  6.72 (s, 2 H, 26,28-ArH), 7.19 (dd,  $J = 2.0, 8.2$  Hz, 4 H, 10,12,22,24-ArH), 7.21 (t,  $J = 2.0$  Hz, 2 H, 25,27-ArH), 7.57 (td,  $J = 1.5, 8.2$  Hz, 2 H, 11,23-ArH), 8.93 (s, 2 H, 5,17-ArH) ppm; <sup>13</sup>C NMR  $\delta$  108.9, 110.5, 117.9, 124.8, 132.6, 134.2, 154.5, 155.1 ppm.

**4,6,15,17-Tetranitro-2,8,13,19-tetraoxacalix[4]arene (3).** 165 mg, 60% yield; Mp > 350 °C (lit.<sup>5,6</sup>, Mp > 350 °C); <sup>1</sup>H NMR  $\delta$  7.44, 7.56, 8.94 (s, 4:1:1, 12 H, 10,11,21,22,23,24,26,27-ArH, 25,28-ArH, and 5,16-ArH, respectively) ppm.

**4,6,18,20-Tetranitro-2,8,16,22-tetraoxacalix[2]arene[2]naphthalene (4).** 267 mg, 82% yield; M.p. 347–350 °C (dec); <sup>1</sup>H NMR  $\delta$  6.59 (s, 2 H, 32,36-ArH), 7.35 (dd,  $J = 2.4, 8.9$  Hz, 4 H, 10,14,24,28-naphth), 7.60 (d,  $J = 2.4$  Hz, 4 H, 29,31,33,35-naphth), 7.98 (d,  $J = 8.9$  Hz, 4 H, 11,13,25,27-naphth), 9.05 (s, 2 H, 5,19-ArH) ppm; <sup>13</sup>C NMR (125 MHz)  $\delta$  110.3, 114.4, 119.6, 125.2, 128.2, 130.9, 134.2, 134.5, 152.9, 154.5 ppm. *Anal.* Calcd. for C<sub>32</sub>H<sub>16</sub>N<sub>4</sub>O<sub>12</sub>: C 59.27; H 2.49; N 8.64. Found: C 58.98; H 2.60; N 8.69.

**4,6,19,21-Tetranitro-2,8,17,23-tetraoxacalix[2]arene[2]biphenyl (5).** 280 mg, 80% yield; M.p. > 350 °C; <sup>1</sup>H NMR  $\delta$  5.87 (s, 2 H, 35,40-ArH), 7.24 and 7.70 (ABq,  $J = 8.6$  Hz, 16 H,



10,11,14,15,25,26,29,30,31,32,33,34,36,37,38,39-*biph*), 8.97 (s, 2 H, 5,20-*ArH*) ppm. *Anal.* Calcd. for C<sub>36</sub>H<sub>20</sub>N<sub>4</sub>O<sub>12</sub>: C 61.72; H 2.88; N 8.00. Found: C 61.43; H 2.97; N 8.07.

**4,6,17,19-Tetraamino-2,8,15,21-tetraoxacalix[4]arene (6).** A suspension of **1** (388 mg, 0.708 mmol) and Raney-nickel in THF (40 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 18 h, then filtered on celite and washed with DMF. The filtrate was evaporated under reduced pressure, and the resulting solid was precipitated from DMF/THF and collected by suction filtration to afford **6** (234 mg, 77% yield). M.p. 187–190 °C (dec); <sup>1</sup>H NMR δ 4.05 (br s, 8 H, NH<sub>2</sub>), 5.02, 5.85, 7.09 (s, 1:1:4, 12 H, 5,18-*ArH*, 27,28-*ArH*, and 10,11,12,13,23,24,25,26-*ArH*, respectively) ppm; <sup>13</sup>C NMR (125 MHz) δ 103.4, 103.9, 125.3, 125.5, 131.9, 136.2, 147.2 ppm. MALDI-TOF, *m/z* 428.1 [M]<sup>+</sup>. *Anal.* Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>: C 67.28; H 4.71; N 13.08. Found: C 66.95; H 4.81; N 12.94.

**4,6,16,18-Tetraamino-2,8,14,20-tetraoxacalix[4]arene (7).** A suspension of **2** (1.89 g, 3.45 mmol) and Raney-nickel in THF (150 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 18 h, and then filtered on celite. The solvent was evaporated under reduced pressure, and the residual solid was triturated with acetone and collected by suction filtration to afford **7** (1.13 g, 76% yield); M.p. 287–290 °C (dec); <sup>1</sup>H NMR δ 4.51 (br s, 8 H, NH<sub>2</sub>), 5.95 (t, *J* = 2.3 Hz, 2 H, 25,27-*ArH*), 6.14, 6.28 (s, 1:1, 4 H, 5,17-*ArH*, 26,28-*ArH*), 6.71 (dd, *J* = 2.3, 8.2 Hz, 4 H, 10,12,22,24-*ArH*), 7.24 (t, *J* = 8.2 Hz, 2 H, 11,23-*ArH*) ppm; <sup>13</sup>C NMR δ 98.8, 102.3, 110.2, 114.8, 130.1, 130.3, 138.2, 160.3 ppm. MALDI-TOF, *m/z* 428.6 [M]<sup>+</sup>. *Anal.* Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>·<sup>1</sup>/<sub>2</sub>H<sub>2</sub>O: C 65.90; H 4.84; N 12.81. Found: C 65.72; H 4.98; N 12.68.

**4,6,15,17-Tetraamino-2,8,13,19-tetraoxacalix[4]arene (8).** A suspension of **3** (140 mg, 0.255 mmol) and Raney-nickel in DMF (14 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 18 h. The residual Raney-nickel catalyst was mechanically removed from the reaction mixture with a magnetic bar and the resulting suspension was evaporated. The crude solid (90 mg, 82% yield) was used without further purification in the subsequent step. <sup>1</sup>H NMR δ 4.46 (br s, 8 H, NH<sub>2</sub>), 5.05, 6.17, 6.86 (s, 1:1:4, 12 H, 5,16-*ArH*, 25,28-*ArH*, and 10,11,21,22,23,24,26,27-*ArH*, respectively) ppm.

**4,6,18,20-Tetraamino-2,8,16,22-tetraoxacalix[2]arene[2]naphthalene (9).** A suspension of **4** (200 mg, 0.309 mmol) and Raney-nickel in THF (15 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 18 h, then filtered on celite and washed with DMF. The filtrate was evaporated under reduced pressure, and the resulting solid was precipitated from DMF/THF and collected by suction filtration to afford **9** (140 mg, 86% yield); M.p. 298–301 °C (dec); <sup>1</sup>H NMR δ 4.59 (br s, 8 H, NH<sub>2</sub>), 6.33, 6.51 (s, 1:1, 4 H, 5,19-*ArH*, 32,36-*ArH*), 6.80 (d, *J* = 2.4 Hz, 4 H, 29,31,33,35-*naphth*), 7.18 (dd, *J* = 2.4, 8.9 Hz, 4 H, 10,14,24,28-*naphth*), 7.78 (d, *J* = 8.9 Hz, 4 H, 11,13,25,27-*naphth*) ppm; <sup>13</sup>C NMR δ 102.7, 106.6, 116.4, 116.6, 124.6, 129.1, 130.3, 135.1, 138.9, 158.2 ppm. MALDI-TOF, *m/z* 528.9 [M]<sup>+</sup>. *Anal.* Calcd. for C<sub>32</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>·<sup>1</sup>/<sub>2</sub>H<sub>2</sub>O: C 71.50; H 4.69; N 10.42. Found: C 71.27; H 4.76; N 10.38.

**4,6,19,21-Tetraamino-2,8,17,23-tetraoxacalix[2]arene[2]biphenyl (10).** A suspension of **5** (200 mg, 0.285 mmol) and Raney-nickel in THF (15 mL) was stirred under H<sub>2</sub> (1 atm) at room temperature for 18 h. The excess of Raney-nickel was mechanically removed from the reaction

mixture with a magnetic bar and the resulting suspension was evaporated. The crude solid (115 mg) was used without further purification in the subsequent step.  $^1\text{H}$  NMR  $\delta$  4.63 (br s, 8 H,  $\text{NH}_2$ ), 5.64, 6.23 (s, 1:1, 4 H, 5,20-ArH, and 35,40-ArH, respectively), 6.90 and 7.54 (ABq,  $J = 8.5$  Hz, 16 H, 10,11,14,15,25,26,29,30,31,32,33,34,36,37,38,39-biph) ppm;  $^{13}\text{C}$  NMR  $\delta$  102.3, 109.6, 119.5, 126.8, 133.0, 135.2, 135.4, 157.6 ppm.

**4,6,17,19-Tetra-*N*-(1-octyl)ureido-2,8,15,21-tetraoxacalix[4]arene (11).** A solution of **6** (110 mg, 0.257 mmol) and *n*-octyl isocyanate (351 mg, 2.26 mmol) in dry DMSO (14 mL) was stirred at room temperature under nitrogen for 18 h. Solvent removal under reduced pressure gave a crude product which was filtered through a short-path layer of silica gel ( $\text{SiO}_2$ , toluene/ $\text{CH}_3\text{CN}$  8:3 v/v). Precipitation of the residue from  $\text{CHCl}_3/\text{CH}_3\text{CN}$  gave a solid which was collected by suction filtration to afford **11** (60 mg, 22% yield); M.p. 234–236 °C (dec);  $^1\text{H}$  NMR  $\delta$  0.84 (t,  $J = 6.7$  Hz, 12 H,  $\text{CONHC}_7\text{H}_{14}\text{CH}_3$ ), 1.16–1.48 (m, 48 H,  $\text{CH}_2$ ), 2.93–3.13 (m, 8 H,  $\text{CONHCH}_2\text{C}_7\text{H}_{15}$ ), 5.30 (s, 2 H, 27,28-ArH), 6.24 (t,  $J = 5.3$  Hz, 4 H,  $\text{CONHC}_8\text{H}_{17}$ ), 7.17–7.24 (m, 8 H, 10,11,12,13,23,24,25,26-ArH), 7.59 (s, 4 H, CONH), 7.83 (s, 2 H, 5,18-ArH) ppm;  $^{13}\text{C}$  NMR  $\delta$  13.9, 22.1, 26.6, 28.8, 28.9, 29.8, 31.3, 102.7, 117.1, 122.7, 125.1, 126.5, 142.5, 145.9, 155.4 ppm. MALDI-TOF,  $m/z$  1071.7  $[\text{M}\cdot\text{Na}]^+$ , 1087.7  $[\text{M}\cdot\text{K}]^+$ . *Anal.* Calcd. for  $\text{C}_{60}\text{H}_{88}\text{N}_8\text{O}_8\cdot\text{H}_2\text{O}$ : C 67.51; H 8.50; N 10.50. Found: C 67.32; H 8.39; N 10.44.

**4,6,16,18-Tetra-*N*-(1-octyl)ureido-2,8,14,20-tetraoxacalix[4]arene (12).** A solution of **7** (200 mg, 0.467 mmol) and *n*-octyl isocyanate (957 mg, 6.16 mmol) in dry  $\text{CHCl}_3$  (110 mL) was stirred at room temperature under nitrogen for 4 days. Solvent removal under reduced pressure gave a residue, which was triturated with acetone and filtered to afford **12** (179 mg, 37% yield); M.p. 247–250 °C (dec);  $^1\text{H}$  NMR  $\delta$  0.83 (t,  $J = 6.7$  Hz, 12 H,  $\text{CONHC}_7\text{H}_{14}\text{CH}_3$ ), 1.17–1.41 (m, 48 H,  $\text{CH}_2$ ), 2.96–3.04 (m, 8 H,  $\text{CONHCH}_2\text{C}_7\text{H}_{15}$ ), 6.03 (t,  $J = 2.3$  Hz, 2 H, 25,27-ArH), 6.32 (s, 2 H, 26,28-ArH), 6.57 (t,  $J = 5.5$  Hz, 4 H,  $\text{CONHC}_8\text{H}_{17}$ ), 6.91 (dd,  $J = 2.3, 8.3$  Hz, 4 H, 10,12,22,24-ArH), 7.39 (t,  $J = 8.3$  Hz, 2 H, 11,23-ArH), 7.79 (s, 4 H, CONH), 8.87 (s, 2 H, 5,17-ArH) ppm;  $^{13}\text{C}$  NMR  $\delta$  13.9, 22.1, 26.5, 28.7, 28.8, 29.7, 31.3, 103.3, 109.9, 112.0, 113.3, 128.4, 131.0, 137.6, 154.7, 158.7 ppm. MALDI-TOF,  $m/z$  1072.9  $[\text{M}\cdot\text{Na}]^+$ , 1088.9  $[\text{M}\cdot\text{K}]^+$ . *Anal.* Calcd. for  $\text{C}_{60}\text{H}_{88}\text{N}_8\text{O}_8\cdot\frac{1}{2}\text{H}_2\text{O}$ : C 68.09; H 8.48; N 10.59. Found: C 67.94; H 8.34; N 10.56.

**4,6,15,17-Tetra-*N*-(1-octyl)ureido-2,8,13,19-tetraoxacalix[4]arene (13).** A suspension of **8** (80 mg of crude product from the previous step) and *n*-octyl isocyanate (287 mg, 1.85 mmol) in dry DMSO (15 mL) was heated to 50 °C under nitrogen for 3 days. The solvent was then removed under reduced pressure and the resulting residue was triturated with  $\text{CHCl}_3$  and collected by filtration (62 mg, 26% yield from **3**); M.p. 292–295 °C (dec);  $^1\text{H}$  NMR  $\delta$  0.85 (t,  $J = 6.7$  Hz, 12 H,  $\text{CONHC}_7\text{H}_{14}\text{CH}_3$ ), 1.16–1.47 (m, 48 H,  $\text{CH}_2$ ), 3.02–3.10 (m, 8 H,  $\text{CONHCH}_2\text{C}_7\text{H}_{15}$ ), 5.12 (s, 2 H, 25,28-ArH), 6.58 (t,  $J = 4.9$  Hz, 4 H,  $\text{CONHC}_8\text{H}_{17}$ ), 7.04 (s, 8 H, 10,11,21,22,23,24,26,27-ArH), 7.91 (s, 4 H, CONH), 8.67 (s, 2 H, 5,16-ArH) ppm;  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  13.9, 22.1, 26.4, 26.7, 28.68, 28.74, 29.7, 31.2, 122.9, 123.9 $\times$ 2, 143.7, 151.7, 155.1 ppm. MALDI-TOF,  $m/z$  1050.9  $[\text{M}\cdot\text{H}]^+$ , 1072.9  $[\text{M}\cdot\text{Na}]^+$ , 1088.9  $[\text{M}\cdot\text{K}]^+$ . *Anal.* Calcd. for  $\text{C}_{60}\text{H}_{88}\text{N}_8\text{O}_8\cdot\text{H}_2\text{O}$ : C 67.51; H 8.50; N 10.50. Found: C 67.76; H 8.58; N 10.39.

**4,6,18,20-Tetra-*N*-(1-octyl)ureido-2,8,16,22-tetraoxacalix[2]arene[2]naphthalene (14).** A solution of **9** (130 mg, 0.246 mmol) and *n*-octyl isocyanate (504 mg, 3.25 mmol) in dry DMSO (15 mL) was heated to 50 °C under nitrogen for 4 days. After being cooled to room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in CHCl<sub>3</sub> and precipitated twice from CH<sub>3</sub>CN to afford a pale gray powder (65 mg, 23% yield); M.p. 237–240 °C (dec); <sup>1</sup>H NMR δ 0.83 (t, *J* = 6.6 Hz, 12 H, CONHC<sub>7</sub>H<sub>14</sub>CH<sub>3</sub>), 1.13–1.40 (m, 48 H, CH<sub>2</sub>), 2.94–3.05 (m, 8 H, CONHCH<sub>2</sub>C<sub>7</sub>H<sub>15</sub>), 6.62 (s, 2 H, 32,36-ArH), 6.66 (t, *J* = 5.4 Hz, 4 H, CONHC<sub>8</sub>H<sub>17</sub>), 7.20 (d, *J* = 2.4 Hz, 4 H, 29,31,33,35-naph), 7.24 (dd, *J* = 2.4, 8.9 Hz, 4 H, 10,14,24,28-naph), 7.78 (s, 4 H, CONH), 9.14 (s, 2 H, 5,19-ArH) ppm; <sup>13</sup>C NMR (125 MHz) δ 13.9, 22.0, 26.4, 28.6, 28.7, 29.6, 31.2, 104.5, 108.4, 111.9, 114.5, 117.1, 125.1, 129.0, 130.3, 136.5, 154.7, 157.6 ppm. MALDI-TOF, *m/z* 1171.4 [M·Na]<sup>+</sup>, 1187.5 [M·K]<sup>+</sup>. *Anal.* Calcd. for C<sub>68</sub>H<sub>92</sub>N<sub>8</sub>O<sub>8</sub>·<sup>1</sup>/<sub>2</sub>H<sub>2</sub>O: C 70.50; H 8.09; N 9.67. Found: C 70.22; H 8.07; N 9.65.

**4,6,19,21-Tetra-*N*-(1-octyl)ureido-2,8,17,23-tetraoxacalix[2]arene[2]biphenyl (15).** A suspension of **10** (103 mg of crude product from the previous step) and *n*-octyl isocyanate (242 mg, 1.56 mmol) in dry DMSO (15 mL) was heated to 50 °C under nitrogen for 18 h. After being cooled to room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was triturated with CHCl<sub>3</sub> and collected by filtration (110 mg, 36% yield from **5**); M.p. 292–295 °C (dec); <sup>1</sup>H NMR δ 0.84 (t, *J* = 6.8 Hz, 12 H, CONHC<sub>7</sub>H<sub>14</sub>CH<sub>3</sub>), 1.20–1.48 (m, 48 H, CH<sub>2</sub>), 3.02–3.11 (m, 8 H, CONHCH<sub>2</sub>C<sub>7</sub>H<sub>15</sub>), 5.66 (s, 2 H, 35,40-ArH), 6.62 (t, *J* = 4.8 Hz, 4 H, CONHC<sub>8</sub>H<sub>17</sub>), 7.01 and 7.58 (ABq, *J* = 8.6 Hz, 16 H, 10,11,14,15,25,26,29,30,31,32,33,34,36,37,38,39-biph), 7.97 (s, 4 H, CONH), 8.77 (s, 2 H, 5,20-ArH) ppm; <sup>13</sup>C NMR δ 14.0, 22.1, 26.4, 28.7, 28.8, 29.8, 31.3, 104.9, 112.8, 120.9, 124.7, 127.3, 134.4, 141.8, 155.1, 155.4 ppm. MALDI-TOF, *m/z* 1201.7 [M·H]<sup>+</sup>, 1223.7 [M·Na]<sup>+</sup>, 1239.7 [M·K]<sup>+</sup>. *Anal.* Calcd. for C<sub>72</sub>H<sub>96</sub>N<sub>8</sub>O<sub>8</sub>·H<sub>2</sub>O: C 70.91; H 8.10; N 9.19. Found: C 70.54; H 7.79; N 9.23.

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