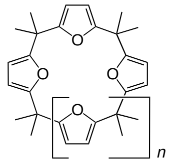
From Large Furan-Based Calixarenes to Calixpyrroles and Calix[*n*]furan[*m*]pyrroles: Syntheses and Structures**

Grazia Cafeo, Franz H. Kohnke,*
Giovanna L. La Torre, Andrew J. P. White, and
David J. Williams

Calixarenes have for many decades been the subject of intense research. These cyclophanes can be considered as "benzene based" since they are made up of a number of phenolic residues that are linked by a one-carbon-atom bridge to form a macrocyclic system.[1] Their heterocyclic analogues, on the other hand, especially those containing more than four aromatic units, have received considerably less attention.[2]

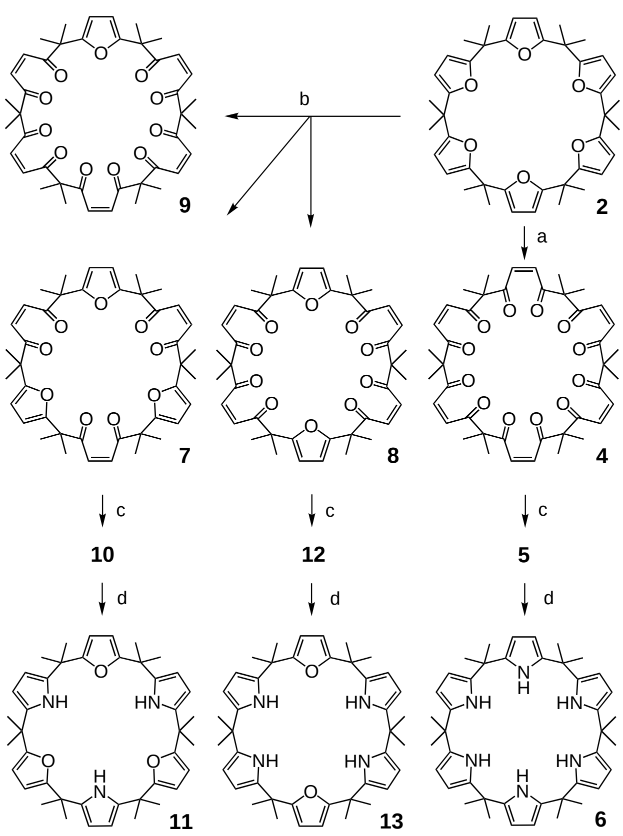
As part of our continuing research[3] on the functionalization of the furan-based analogues of the calixarenes **1** and **2**, obtained by the acid-promoted condensation of furan and acetone,[4] we have substantially improved both the yield and synthesis of the cyclic hexamer **2**, and also developed the first synthesis of the nonamer **3**.[5]



1 $n = 1$
2 $n = 3$
3 $n = 6$

Thus, with large quantities of **2** and **3** at our disposal, we were able to explore their potential as precursors for other heterocalixarenes through the conversion of all (or just some) of the furan rings into pyrrole, thiophene, or other heterocyclic units.[6] The homologation of the furan units of **2** and **3** into pyrroles[6a] appeared a particularly attractive target since calix[4]pyrroles[7] have recently been shown to bind both anions and neutral molecules,[8] and also to form a number of transition metal complexes that exhibit interesting redox properties.[9] Moreover, calix[*n*]pyrroles with $n > 4$ are far less accessible than calix[4]pyrroles because the direct condensation of ketones with pyrrole yields complex mixtures with the tetramer being by far the major component.[8b] A recent synthesis of a calix[6]pyrrole system[10] relies on the use of intermediate 1:2 condensation products of aryl ketones and pyrrole. The synthesis of a calix[5]pyrrole (as part of a larger molecule and which uses a calix[5]arene as template) has also been reported.[11]

Herein we describe a) the conversion of the calix[6]furan **2** into the corresponding calix[6]pyrrole **6**, b) its use as a precursor for the mixed heterocyclic systems calix[3]furan[3]pyrrole **11** and calix[2]furan[4]pyrrole **13** (Scheme 1), and c) the X-ray crystal structures of **6** and **11**.



Scheme 1. The conversion of calix[6]furan **2** into calix[6]pyrrole **6**, calix[3]furan[3]pyrrole **11** and calix[2]furan[4]pyrrole **13**. a) MCPBA (6.2 mol), $CHCl_3$; b) MCPBA (4 mol), $CHCl_3$; c) Zn/CH_3COOH (reduction of the olefinc double bonds to $-CH_2-CH_2-$ units); d) CH_3COONH_4/EtOH.

The key compound in the synthesis of **6** is the dodecaketone **5** which was obtained by the method described by Williams and Le Goff.[12, 13] This compound was treated with ammonium acetate in ethanol to give **6** in 42% yield. Using our improved synthesis of **2**[5] the preparation of **6** involves five simple steps (from acetone and furan) and does not require the use of chromatography.

The X-ray crystal structure of **6**[14] (Figure 1) showed the crystals to be solvated with both water and ethanol. The macrocycle adopts a tennis-ball-seam conformation with three of the N−H bonds oriented outwards whilst the other three are directed towards the center of the cavity within which the water molecule is trapped (the ethanol molecule is positioned on the periphery of the macrocycle and is disordered). The binding of the water molecule is in accord with that predicted theoretically[15a] and demonstrated experimentally[15b] for the solvation of water by pyrrole. In the present structure the water molecule is involved in no fewer than six hydrogen-bonding interactions with the hexapyrrole: three $N-H\cdots O$ and three $O-H\cdots\pi$ interactions (Figure 1).

Encouraged by the successful synthesis of **6**, we turned our attention to the possibility of converting only some of the furan rings of **2** into pyrroles. The oxidative ring-opening of only three or four of the furan units in **2** can only produce, in each case, three regioisomers, which differ with respect to the regiochemistry of the newly formed 1,4-eneketone units.

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[*] Prof. F. H. Kohnke, Dr. G. Cafeo, Dr. G. L. La Torre
Dipartimento di Chimica Organica e Biologica
Università di Messina
Salita Sperone 31, 98166 Messina (Italy)
Fax: (+39) 090-393-895
E-mail: franz@scirocco.unime.it

Dr. A. J. P. White, Prof. D. J. Williams
Chemical Crystallography Laboratory
Department of Chemistry
Imperial College of Science Technology and Medicine
South Kensington, London SW7 2AY (UK)

[**] This work was sponsored by the MURST in Italy.

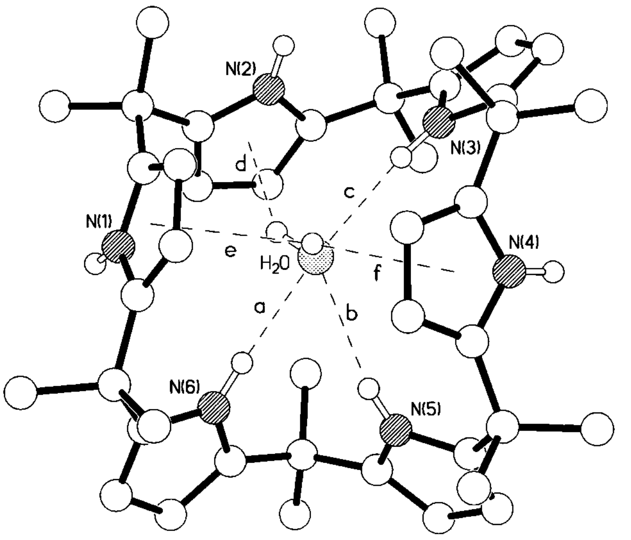

Figure 1. The X-ray crystal structure of **6**. The H-bonding geometries are: a) N$\cdots$O 3.07, H$\cdots$O 2.18 Å, N–H$\cdots$O 174°; b) N$\cdots$O 3.21, H$\cdots$O 2.38 Å, N–H$\cdots$O 152°; c) N$\cdots$O 3.15, H$\cdots$O 2.25 Å, N–H$\cdots$O 173°; d) H$\cdots\pi$ 2.36 Å, O–H$\cdots\pi$ 145°; e) H$\cdots\pi$ 2.75 Å, O–H$\cdots\pi$ 109°; f) H$\cdots\pi$ 2.70 Å, O–H$\cdots\pi$ 113°.

However, treatment of **2** with four moles of *meta*-chloroperbenzoic acid gave (after chromatography on SiO_2, hexane:EtOAc 7:3) only the eneketones **7** (24%) and **8** (52%), which are derived from the opening of furan units at the 1,3,5 and 1,2,4,5 positions within the macrocyclic ring respectively. A small amount of the pentaoxidation product—the decaeneketone **9** (14%)—was also obtained. Thus this oxidation process appears to take place with considerable regioselectivity; the mechanism and/or the origin of this selectivity has not yet been investigated. The reduction of the olefinic bonds in **7** and **8** was best achieved with Zn/AcOH, catalytic hydrogenation with Pd/C in EtOAc at 1.5 atm did not proceed to completion. Treatment of the saturated ketones **10** and **12** with CH_3COONH_4 as described for **5** gave the calix[3]furan[3]pyrrole **11** and the calix[2]furan[4]pyrrole **13**, respectively. The ^1H and ^{13}C NMR spectra of **7**, **10**, **11** and **8**, **12**, **13** are consistent with the "averaged" D_{3h} and D_{2h} symmetries of the two sets of compounds respectively, thus indicating the regiochemistry of the chemical tranformation sequences.

Single crystals of **11**[16] were obtained from EtOH. The X-ray structure shows that the desired alternating pattern of furan and pyrrole rings has indeed been achieved (Figure 2) as expected on the basis of the NMR spectroscopic data. Here, unlike in **6**, the crystals are free from included solvent, though the conformation of the macrocycle is similar, again having a tennis-ball-seam geometry. This conformation is in part stabilized by an intramolecular N–H$\cdots$O hydrogen bond between the N(4) pyrrole and O(3) furan ring atoms. Surprisingly, there are no hydrogen-bonding interactions involving either the N(2) or N(6) pyrrole hydrogen atoms. In the absence of included water the conformation is virtually self-filling, though there is a small cleft between the O(1) and O(5) furan rings, which are separated by approximately 5.4 Å. This cleft is partially filled by the edge of the O(1) furan ring of a centrosymmetrically related molecule.

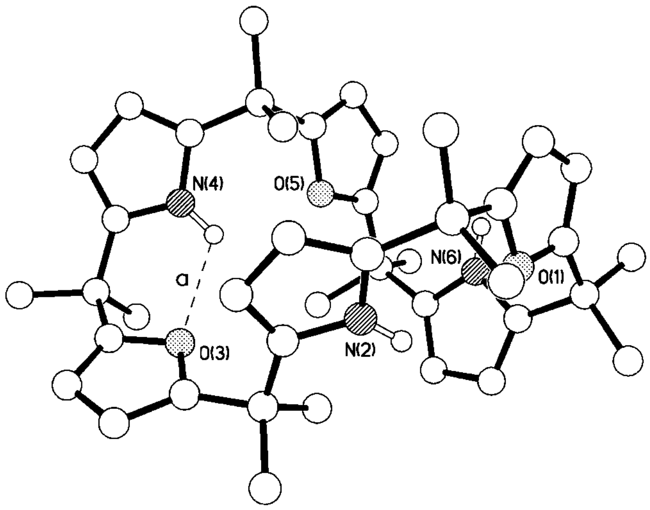

Figure 2. The X-ray crystal structure of **11**. The N–H$\cdots$O hydrogen bond (a) has N$\cdots$O 2.80, H$\cdots$O 2.25 Å, and N–H$\cdots$O 119°.

The anion binding by calix[4]pyrroles proceeds by a perching geometry that utilizes N–H$\cdots$anion hydrogen bonds[8a] rather than by encapsulation since the cavity of the macrocycle is in general too small. In contrast, the "hexameric" mixed furan/pyrrole ring systems **6**, **11**, and **13** have larger cavities and thus have the potential to bind anions though inclusion[17] and thus discriminate by size[18] more effectively than the calix[4]pyrroles. The mixed systems **11** and **13** also provide arrays of pyrrole units which should be especially suited for the recognition of nonspherical anions. Furthermore, the ready access to these mixed systems provided by the above synthetic protocols, conjures up the prospect of the formation of novel metal complexes of deprotonated **6**, **11**, and **13**, and the exploration of enticing new areas of chemistry. In addition, the availability[5] of calix[9]furan **3** provides the opportunity for an extension of this current research to this larger system.

Experimental Section

General: Column chromatography was conducted on silica gel (230–400 mesh, 60 Å, from Aldrich). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively. Mass spectra were measured by electron impact (EI) on a Finnigan Mat 90 spectrometer. Melting points were determined on a Kofler hot stage apparatus, and are not corrected. Abbreviations: py = pyrrole, fr = furan.

Preparation of **6**, **11**, and **13** from **5**, **10**, and **12** respectively: CH_3COONH_4 (1.5 mol per mol of 1,4-diketone units in the macrocycles) was added to the polyketones in absolute EtOH (50 $mg\,mL^{-1}$). The mixture was heated at reflux for 30 h under N_2, concentrated in vacuo, and dissolved in a mixture of $CHCl_3$ and H_2O. The organic phase was dried ($MgSO_4$), concentrated, then treated as indicated below for each compound.

6: The crude product was dissolved in a mixture of hexane and EtOAc and quickly filtered through SiO_2. The filtrate was concentrated and crystallized from EtOH: 41%, m.p. 232–234 °C. ^1H NMR: $\delta = 1.53$ (s, 36H, CH_3), 5.85 (d, 12H, py-H_β), 7.95 (brs, 6H, NH); ^{13}C NMR: $\delta = 29.4$ (CH_3), 35.5 ($C(CH_3)_2$), 103.3 (CH), 138.5 (*Cq*); EI-MS: *m/z*: 642 [M^+].

11: The crude product was crystallized from EtOH (86 mg). An additional amount (50 mg) was obtained from the mother liquor by column chromatography (hexane:EtOAc 9:1). Total yield 39%, m.p. 162–164 °C from EtOH. ^1H NMR: $\delta = 1.50$ (s, 36H, CH_3), 5.71 (d, 6H, py-H_β), 5.85 (s, 6H, fr), 7.95 (brs, 3H, NH); ^{13}C NMR: $\delta = 27.6$ (CH_3), 36.0 ($C(CH_3)_2$), 102.5 and 103.7 (fr-CH and py-CH), 136.8 (py-C*q*), 159.8 (fr-C*q*); EI-MS: *m*/*z*: 646 $[(M{+}\mathrm{H})^{+\bullet}]$.

13: The residue was subjected to column chromatography (hexane:EtOAc 9:1) to give **13** as the first eluted fraction: 17 %, m.p. 170–171 °C from EtOH. ^{1}H NMR: $\delta = 1.48$ (s, 24 H, CH_3 next to frs), 1.55 (s, 12 H, CH_3 between pys), 5.72 (d, 4 H, fr), 5.76–5.78 and 5.84–5.86 (2 × m, 2 × 4 H, py-H_β), 7.78 (br s, 4 H, NH); ^{13}C NMR: $\delta = 27.7$ (fr-C(CH_3)$_2$-py), 29.5 (py-C(CH_3)$_2$-py), 35.5 (py-*C*(CH_3)$_2$-py), 36.1 (fr-*C*(CH_3)$_2$-py), 103.0, 103.1 and 103.7 (fr and py-CH), 136.9 and 138.2 (py-C*q*), 159.7 (fr-C*q*); EI-MS: *m*/*z*: 644 $[M^{+\bullet}]$.

Partial oxidation of calix[6]furan: A solution of *meta*-chloroperbenzoic acid (1.168 g, 6.8 mmol) in $CHCl_3$ (10 mL) was added over a few minutes to a solution of **2** (1.0 g, 1.5 mmol) in $CHCl_3$ (50 mL) at 0 °C. The mixture was stirred for 18 h while allowing it to reach room temperature, washed ($NaHCO_3$ aq), dried ($MgSO_4$), and concentrated. Column chromatography (hexane:EtOAc 7:3) of the residue afforded, in order of elution: **7**: 250 mg, 24 %, m.p. 148–149 °C from EtOH. ^{1}H NMR: $\delta = 1.48$ (s, 36 H, CH_3), 6.12 and 6.23 (2 × s, 2 × 6 H, olefin and fr); ^{13}C NMR: $\delta = 22.8$ (CH_3), 48.2 (*C*(CH_3)$_2$), 107.0 (fr-CH), 134.8 (olefin), 156.6 (fr-Cq), 202.7 (CO); EI-MS: *m*/*z*: 697 $[M^{+\bullet}]$. **8**: 554 mg, 52 %, m.p. 154–156 °C from EtOH. ^{1}H NMR: $\delta = 1.42$ (s, 12 H, COC(CH_3)$_2$CO), 1.46 (s, 24 H, COC(CH_3)$_2$-fr), 6.16 (s, 4 H, fr), 6.39 and 6.44 (AB system, $J_{AB} = 12$ Hz, 8 H, olefin); ^{13}C NMR: $\delta = 20.8$ (COC(CH_3)$_2$CO), 22.6 (COC(CH_3)$_2$-fr), 48.1 (CO*C*(CH_3)$_2$-fr), 61.1 (CO*C*(CH_3)$_2$CO), 107.0 (fr-CH), 133.3 and 137.3 (olefin), 156.7 (fr-Cq), 201.4 and 202.5 (CO); EI-MS: *m*/*z*: 712 $[M^{+\bullet}]$. **9**: 155 mg, 14 %, m.p. 128–130 °C from EtOH. ^{1}H NMR: $\delta = 1.33$ (br s, 24 H, CH_3), 1.40 (br s, 12 H, CH_3), 6.10 (s, 2 H, fr), 6.29 and 6.33 (AB system, $J_{AB} = 12.1$ Hz, 4 H, olefin), 6.51 (br s, 6 H, olefin); EI-MS: *m*/*z*: 728 $[M^{+\bullet}]$.

Reduction of the eneketones **4**, **7**, **8**: An excess of Zn powder was added to a warm solution of the eneketones in glacial acetic acid (ca. 30 mg mL^{-1}). After cooling, the mixture was filtered, diluted with water, and extracted with $CHCl_3$. The combined organic extracts were washed ($NaHCO_3$ aq), dried ($MgSO_4$), and concentrated to give the saturated ketones in quantitative yield.

10: m.p. 200–201 °C from EtOH. ^{1}H NMR: $\delta = 1.42$ (s, 36 H, CH_3), 2.43 (s, 24 H, CH_2), 6.17 (d, 6 H, fr); ^{13}C NMR: $\delta = 23.4$ (CH_3), 31.8(CH_2), 48.1 (*C*(CH_3)$_2$), 106.8 (CH(fr)), 157.4 (Cq(fr)), 210.0 (CO); EI-MS: *m*/*z*: 702 $[M^{+\bullet}]$.

8: m.p. 151–152 °C from EtOH. ^{1}H NMR: $\delta = 1.37$ (s, 12 H, CO*C*(CH_3)$_2$-CO), 1.43 (s, 24 H, CO*C*(CH_3)$_2$-fr), 2.52–2.67 (m, 16 H, CH_2), 6.19 (fr); ^{13}C NMR: $\delta = 21.5$ (COC(CH_3)$_2$CO-), 23.3 (COC(CH_3)$_2$-fr), 31.9 and 32.0 (CH_2), 48.6 (CO*C*(CH_3)$_2$-fr), 62.0 (CO*C*(CH_3)$_2$CO-), 106.6 (CH(fr)), 157.6 (Cq(fr)), 209.8 (CO); EI-MS: *m*/*z*: 720 $[M^{+\bullet}]$.

Received: October 25, 1999 [Z 14183]

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[13] The X-ray structure of **5** has also been determined and will be reported elsewhere.

[14] Crystal data for **6**: $C_{42}H_{54}N_6 \cdot H_2O \cdot EtOH$, $M_r = 707.0$, monoclinic, space group $P2_1/n$ (no. 14), $a = 14.913(1)$, $b = 16.974(1)$, $c = 16.477(2)$ Å, $\beta = 107.00(1)°$, $V = 3988.4(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.177$ g cm^{-3}, $\mu(\mathrm{Cu}_{K\alpha}) = 5.67$ cm^{-1}, $F(000) = 1536$, $T = 183$ K, clear platelike needles, crystal dimensions 0.57 × 0.43 × 0.07 mm^3, Siemens P4/RA diffractometer, ω-scans, 6247 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give $R_1 = 0.045$, $wR_2 = 0.108$ for 5155 independent observed reflections $[|F_o| > 4\sigma(|F_o|), 2\theta \leq 124°]$ and 518 parameters.

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[16] Crystal data for **11**: $C_{42}H_{51}N_3O_3$, $M_r = 645.9$, triclinic, space group $P\bar{1}$ (no. 2), $a = 11.582(1)$, $b = 12.600(1)$, $c = 13.766(1)$ Å, $\alpha = 94.13(1)$, $\beta = 109.02(1)$, $\gamma = 96.17(1)°$, $V = 1875.9(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.143$ g cm^{-3}, $\mu(\mathrm{Cu}_{K\alpha}) = 5.59$ cm^{-1}, $F(000) = 696$, $T = 293$ K, clear rhomboids, crystal dimensions 0.53 × 0.33 × 0.28 mm^3, Siemens P4/RA diffractometer, ω-scans, 5555 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full matrix least-squares based on F^2 to give $R_1 = 0.054$, $wR_2 = 0.143$ for 4472 independent observed reflections $[|F_o| > 4\sigma(|F_o|), 2\theta \leq 120°]$ and 446 parameters. The alternating siting of the furan and pyrrole rings was established in part by the unambiguous locating and successful refinement of the hydrogen atoms on the pyrrole rings. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136389 (**6**) and -136390 (**11**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[17] Studies conducted by us after the submission of this manuscript have confirmed this prediction (G. Cafeo, F. H. Kohnke, G. L. La Torre, A. J. P. White, D. J. Williams, unpublished results).

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