

# New Preorganized Calix[4]arenes. Part II. Double Schiff-Based Calix[4]arenes Derived from 4,6,10,12,16,18,22,24,25,26,27,28-Dodecamethyl-5,11,17,23-tetrahydroxycalix[4]arene

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**Abstract.** We describe the condensation of an appropriate tetraaldehyde derivative of mesitol calix[4]arene with 1,*n*-diaminoalkanes to afford double Schiff-base calix[4]arene receptors in the 1,3-alternate conformation.

**Key words:** Dinucleating ligand, mesitol calix[4]arene, Schiff base, hydrolysis.

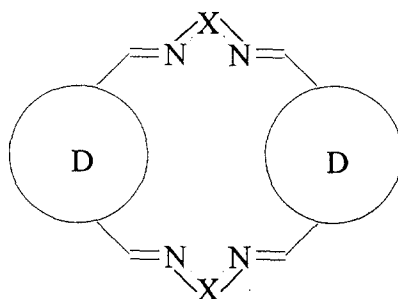
## 1. Introduction

The term compartmental or dinucleating ligands refers to linear or cyclic molecules containing in their framework two binding subunits for metal ions directed so as to form dinuclear complexes in which the arrangement and the distance of the cations held inside the molecular architecture may be controlled through ligand design [1]. They allow the study of cation–cation interactions as well as the fixation of bridging substrates to yield cascade complexes of interest for bioinorganic modelling [1]. In this respect the synthesis and coordination chemistry of macrocyclic Schiff-base ligands has been developing for several years [2]. For example [2+2] condensation reactions between carbonyl compounds and primary diamine derivatives lead to a series of Schiff-base macrocycles in which two Schiff-base units are spaced by pyridine, furan, thiophene, pyrrole, and alkyl or polyethylene glycol chains [3–6].

The present work describes the synthesis and the properties of Schiff-based ligands (5)–(7) in which two Schiff-based units are spaced by a cyclophane. The chosen cyclophane was 4,6,10,12,16,18,22,24,25,26,27,28-dodecamethyl-5,11,17,23-tetrahydroxycalix[4]arene or mesitol-derived calix[4]arene (1) [7] in the fixed 1,3-alternate conformation which presents two sets of *extra-annular* hydroxyl groups

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D = pyridine, furan, thiophene, or pyrrole  
 X = 1,*n*-diamine (alkyl, polyethylene glycol)

suitable for doubly bridging as described for doubly-crowned mesitol-derived calix[4]arene [8].

## 2. Experimental

### 2.1. MATERIAL FOR SYNTHESIS

4,6,10,12,16,18,22,24,25,26,27,28-Dodecamethyl-5,11,17,23-tetrahydroxycalix[4]arene (1) [7] and 2-[(2'-bromo)ethoxy]benzaldehyde (2) [10] were prepared as described in the literature. 1,2-Diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, potassium carbonate, and the solvents were commercial reagents and used without further purification.

### 2.2. ANALYTICAL PROCEDURES

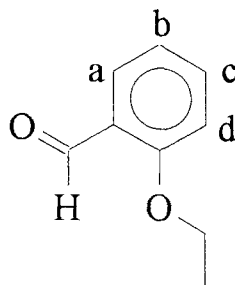
The melting points (mps) were taken on a Büchi 500 apparatus in capillaries sealed under nitrogen. Silica columns were prepared with Kieselgel Merck (Art. 11567). The eluent is specified in the experimental procedures. Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg. The <sup>1</sup>H-NMR spectra were recorded at 200 MHz on a Bruker SY 200 spectrometer. The FAB mass spectra were obtained on a VG-Analytical ZAB HF apparatus.

### 2.3. PREPARATION OF 4,6,10,12,16,18,22,24,25,26,27,28-DODECAMETHYL-5,11,17-TRIS[(2-FORMYLPHENOXYETHYL)OXY]CALIX[4]ARENE (3) AND 4,6,10,12,16,18,22,24,25,26,27,28-DODECAMETHYL-5,11,17,23-TETRAKIS[(2-FORMYLPHENOXYETHYL)OXY]CALIX[4]ARENE (4)

A 250 mL 2-necked round-bottomed flask equipped with a condenser and a dropping funnel was charged with acetonitrile (100 mL), mesitol calix[4]arene (1) (2.377 g; 4.01 mmol), and potassium carbonate (5.533 g; 40.62 mmol). After stirring for 30 min at room temperature, 2-[(2'-bromo)ethoxy]benzaldehyde (2) (1.842 g; 8.01 mmol) dissolved in acetonitrile (20 mL) was added to the mixture.

The reactants were refluxed for 8 h. The same quantities of potassium carbonate and (2) dissolved in acetonitrile (20 mL) were then added, and the reaction mixture was refluxed for 20 additional days. After cooling to room temperature the solvents were evaporated to dryness under reduced pressure. The residue was suspended in chloroform (500 mL) and neutralized with 1N hydrochloric acid (200 mL). The organic layer was dried over sodium sulfate and filtered. Precipitation occurred upon addition of methanol-acetone during removal of the solvents. The solid was chromatographed on silica with a mixture of 95 : 5 dichloromethane–ethyl acetate. 4,6,10,12,16,18,22,24,25,26,27,28-Dodecamethyl-5,11,17,23-tetrakis[(2-formylphenoxyethyl)oxy]calix[4]arene (4) (1.239 g) was eluted first and isolated as a white solid (mp 285–286°C). Yield 26%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 10.60 (s, 4H, CHO), 7.87 (d, 4H, *J*<sub>H–H</sub> = 10 Hz, ArHa), 7.57 (t, 4H, *J*<sub>H–H</sub> = 10 Hz, ArHb), 7.10–7.03 (m, 8H, ArHc and ArHd), 4.54–4.07 (m, 16H, OCH<sub>2</sub>CH<sub>2</sub>O), 3.92 (s, 8H, ArCH<sub>2</sub>Ar), 2.39 (s, 24H, *extra-annular* CH<sub>3</sub>), 1.12 (s, 12H, *intra-annular* CH<sub>3</sub>). MS FAB positive: 1185.3. Elemental analysis for C<sub>76</sub>H<sub>80</sub>O<sub>12</sub>·CH<sub>3</sub>OH *calcd.* C 75.96, H 6.95. *Found* C 75.72, H 6.93.

4,6,10,12,16,18,22,24,25,26,27,28-Dodecamethyl-5,11,17-tris[(2-formylphenoxyethyl)oxy]calix[4]arene (3) (0.333 g) was isolated as a white solid (mp 238–239°C). Yield 8%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 10.60 (s, 3H, CHO), 7.88 (d, 3H *J*<sub>H–H</sub> = 10 Hz, ArHa), 7.58 (t, 3H, *J*<sub>H–H</sub> = 10 Hz, ArHb), 7.07–7.03 (m, 6H, ArHc and ArHd), 4.43–4.10 (m, 12H, OCH<sub>2</sub>CH<sub>2</sub>O), 3.93 (s, 8H, ArCH<sub>2</sub>Ar), 2.38 (s, 18H, *extra-annular* CH<sub>3</sub>), 1.13 (s, 12H, *intra-annular* CH<sub>3</sub>). MS FAB positive: 1036.2. Elemental analysis for C<sub>67</sub>H<sub>72</sub>O<sub>10</sub>·CH<sub>3</sub>OH *calcd.* C 76.38, H 7.16. *Found* C 76.97, H 7.07.



#### 2.4. PREPARATION OF DOUBLE-SCHIFF-BASE MESITOL-DERIVED CALIX[4]ARENES (5)–(7)

A typical procedure is given for the preparation of double-Schiff-base mesitol-derived calix[4]arene (7): a 500 mL 2-necked round-bottomed flask equipped with a condenser and dropping funnel was charged with acetonitrile (100 mL), chloroform (100 mL), and the tetraaldehyde calix[4]arene (4) (237 mg, 0.20 mmol). After dissolution of the reacting mixture, 1,3-diaminobutane (48 mg, 0.54 mmol) dissolved in acetonitrile (30 mL) was dropped in over 1 h. The contents were

refluxed for 24 h. Then the solvents were removed under reduced pressure, and the solid residue was recrystallized from dichloromethane–diethylether. Pure Schiff-base calix[4]arene (**7**) (242 mg, yield 94%) was filtered off by suction. Mp > 310°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.84 (s, 4H, CHN), 7.95 (d, 4H,  $J_{\text{H-H}} = 8$  Hz, Ha), 7.37 (t, 4H,  $J_{\text{H-H}} = 8$  Hz, Hb), 7.03–6.91 (m, 8H, Hc and Hd), 4.38–3.97 (m, 32H,  $\text{OCH}_2\text{CH}_2\text{O}$  and  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 3.95 (s, 8H,  $\text{ArCH}_2\text{Ar}$ ), 2.41 (s, 24H, *extra-annular*  $\text{CH}_3$ ), 1.16 (s, 12H, *intra-annular*  $\text{CH}_3$ ). MS FAB positive: 1289.5. Elemental analysis *calcd.* for  $\text{C}_{84}\text{H}_{96}\text{O}_8\text{N}_4$  C 78.23 H 7.50. *Found* C 78.29 H 7.58.

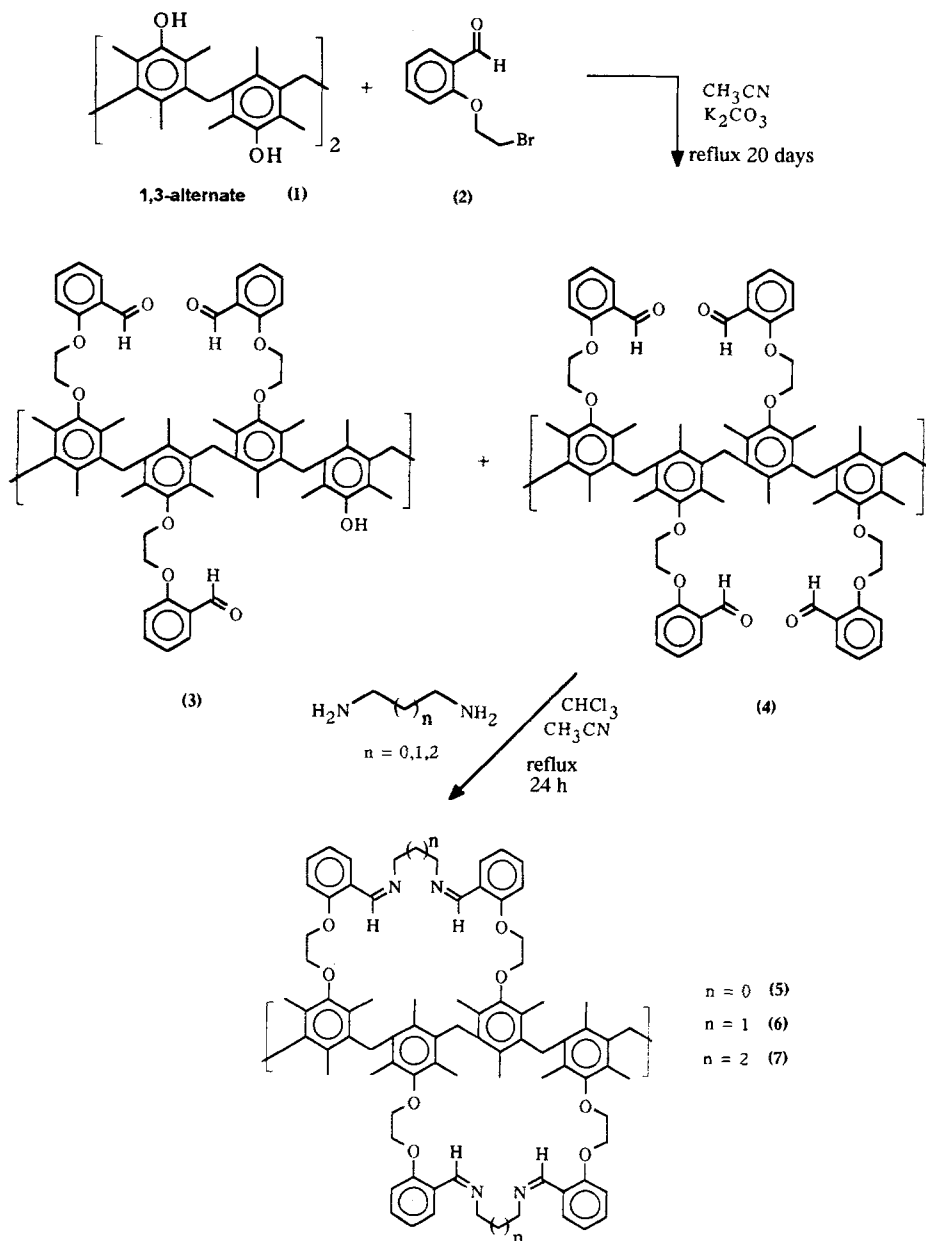
Physical data for (**5**): mp > 310°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.87 (s, 4H, CHN), 8.03 (d, 4H,  $J_{\text{H-H}} = 8$  Hz, Ha), 7.40 (t, 4H,  $J_{\text{H-H}} = 8$  Hz, Hb), 7.06–6.95 (m, 8H, Hc and Hd), 4.45–3.88 (m, 24H,  $\text{OCH}_2\text{CH}_2\text{O}$  and  $\text{NCH}_2\text{CH}_2\text{N}$ ), 3.90 (s, 8H,  $\text{ArCH}_2\text{Ar}$ ), 2.30 (s, 24H, *extra-annular*  $\text{CH}_3$ ), 1.09 (s, 12H, *intra-annular*  $\text{CH}_3$ ). MS FAB positive: 1234.5. Elemental analysis *calcd.* for  $\text{C}_{80}\text{H}_{88}\text{O}_8\text{N}_4 \cdot \text{CH}_2\text{Cl}_2$  C 73.79 H 6.88. *Found* C 73.80 H 6.60. Yield 72%.

Physical data for (**6**): mp > 310°C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.84 (s, 4H, CHN), 7.95 (d, 4H,  $J_{\text{H-H}} = 8$  Hz, Ha), 7.37 (t, 4H,  $J_{\text{H-H}} = 8$  Hz, Hb), 7.03–6.91 (m, 8H, Hc and Hd), 4.38–3.97 (m, 28H,  $\text{OCH}_2\text{CH}_2\text{O}$  and  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 3.95 (s, 8H,  $\text{ArCH}_2\text{Ar}$ ), 2.41 (s, 24H, *extra-annular*  $\text{CH}_3$ ), 1.16 (s, 12H, *intra-annular*  $\text{CH}_3$ ). MS FAB positive: 1262.2. Elemental analysis *calcd.* for  $\text{C}_{82}\text{H}_{92}\text{O}_8\text{N}_4$  C 78.06 H 7.35. *Found* C 78.06 H 7.45. Yield 70%.

### 3. Results and Discussion

The synthesis of (**5**)–(**7**) were conducted according to Scheme 1. In the first step 1,3-alternate mesitol calix[4]arene (**1**) was refluxed with 8 eq. of 2-[(2'-bromo)ethoxy]benzaldehyde (**2**) during 20 days in acetonitrile in the presence of 20 eq. of potassium carbonate. After precipitation the crude mixture was chromatographed on silica with a mixture of dichloromethane–ethyl acetate as eluent to afford pure (**3**) (mp 238–239°C; yield 8%) and (**4**) (mp 285–286°C; yield 26%). Tetrabenzaldehyde (**4**) was then treated with ca. 2.5 eq. of 1,*n*-diaminoalkane ( $n = 2, 3$  or 4 or  $n = 0, 1, 2$  in Scheme 1) in a 1 : 1 mixture of acetonitrile–chloroform under reflux for 24 h. After evaporation of the solvents the crude mixture was precipitated with dichloromethane–diethylether to afford pure double-Schiff-base mesitol-derived calix[4]arenes (**5**) ( $n = 2$ , yield 72%), (**6**) ( $n = 3$ , yield 70%) and (**7**) ( $n = 4$ , yield 94%).

Products (**3**)–(**7**) were characterized by  $^1\text{H-NMR}$  spectroscopy, fast atom bombardment mass spectroscopy, and element analysis (see Experimental Section). Tri- and tetraaldehyde calix[4]arene (**3**) and (**4**) and double-Schiff-base mesitol-derived calix[4]arenes (**5**)–(**7**) were deduced to be in 1,3-alternate conformation due to the presence of singlets at 3.92, 3.92, 3.90, 3.97, and 3.95 ppm for the  $\text{Ar}-\text{CH}_2-\text{Ar}$  resonance in their  $^1\text{H-NMR}$  spectra, matching with mesitol-derived calix[4]arene **1** which presents a singlet at 3.94 ppm for these protons [9].



Scheme 1.

Calixarene (7) was observed to be more soluble than (5) and (6), and preliminary studies of reaction with metal cations were run with calixarene (7). Unfortunately, addition of 2 eq. of europium triflate to a  $10^{-2}$  M solution of calixarene (7) in chloroform- $d_1$  provoked hydrolysis of the imino functions, and one observed the formation of tetraaldehyde (4). Even when less than 2 eq. of europium triflate was

used, only the formation of tetraaldehyde (**4**) occurred, leading to the conclusion that intermediates of hydrolyzed (**7**) cannot be observed. Nevertheless the hydrolysis implies a preliminary complexation of the Eu cation by the nitrogen atoms, leading to an activation of the imino functions and catalyzing the nucleophilic attack of the water molecules. This fact is reminiscent of an *autoaccelerative* reaction observed by Shinkai and coworkers in the diazo coupling of calix[4]arene [9]. Addition of an excess of barium triflate or perchlorate under similar conditions did not show any change in the shifts in the  $^1\text{H-NMR}$  spectrum of (**7**), in agreement with a low complexation as already described for a very similar Schiff-based *p-tert*-butyl-calix[4]arene [10].

Further synthetic work and studies of cation binding with hydrogenated double-Schiff-base calix[4]arene (**5**)–(**7**) are in progress.

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