Synthesis of calix[4]arenes bearing benzothiazolyl, benzoxazolyl and benzoimidazolyl heterocycles

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A novel series of calix[4]arenes bearing benzothiazole, benzoxazole, and benzoimidazole groups were obtained by the reaction of the corresponding 2-mercaptoheterocycle with 5,11,17,23-tetra-*tert*-butyl-25,27-bis[2-(chloroacetamido) ethoxy]-26,28-di-hydroxycalix[4]arene and structurally characterised by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analyses. From their analytical data, it was found these compounds had cone conformations.

Keywords: calix[4]arenes, chloroacetamide, benzothiazole, benzoxazole, benzoimidazole

Calixarenes are a class of cyclooligomers composed of phenolic units connected by methylene bridges, formed via a phenol–formaldehyde condensation.[1] They exist in a cup-like shape with a defined upper and lower rim and a central annulus. By functionally modification it is possible to prepare various derivatives. They have been widely used in the last two decades as building blocks for the synthesis of receptors for cations, anions and neutral molecules[2-5] and they are connected to multiple systems (cyclodextrines, porphyrines, aminoacids, sugars, *etc*). Currently, selective recognition and sensing of cations and anions by artificial receptors have attracted a considerable research interest in terms of their potential applications in various areas.[6,7] Indeed, a large number of calixarene derivatives containing pendant ether, amide, ketone, ester and crown ethers have been employed in studies of ISEs (ion-selective electrodes) sensitive to alkaline and alkaline earth metal cations.[8,9] But only a few reports are concerned with calixarenes as carriers sensitive to transition metal ions in the ionophore-based ISEs. One approach is to construct tweezer-like receptor molecules which are sensisitive to transition metal ions by incorporating nitrogen or sulfur atoms into the lower rim of calix[4]arenes. Reinhoudt[10] and Zeng[11,12] found that this type of calix[4]arene derivative as an ionophore in ISEs exhibits a good Ag^+-selectivity against most interfering ions such as alkali metal, alkaline earth metal, lead and transition metal ions. Recently, some of the heterocyclic groups, such as a piridyl, bipiridyl, bithiazolyl, benzothiazolyl, and dihydrothiazoly,[13] have been introduced into the calixarenes both at their lower and upper rims.

Continuing the development of our research on asymmetric and symmetric calix[4]arenas,[14,15] we recently have described the effective synthesis of a variety of *bis*-thiourea bridged chiral calix[4]arenes bearing optically pure α,β-amino alcohol groups.[16]

Results and discussion

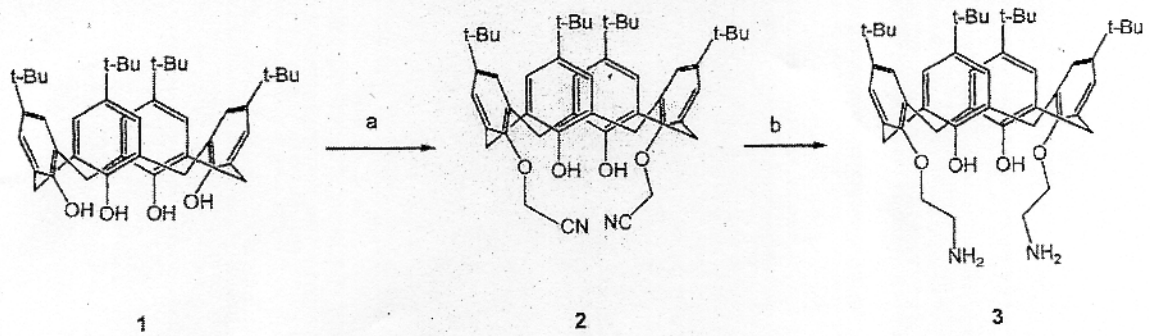
As the starting material, 25,27-bis(2-aminoethoxy)calix[4] arene (**3**) was chosen. This is readily obtained in two steps from *p-tert*-butylcalix[4]arene (**1**), by reaction with bromoacetonitrile and reduction of the cyano function with $LiAlH_4$[17] (Scheme 1).

We have previously described the effective transformation of the amino functions of compound **3** into corresponding chloroacetamido groups **4** as a potential gateway to the preparation of different calix[4]arenes derivatives.[18] Treatment of **3** with chloroacetic anhydride, using ethyl acetate as solvent, led to dichloroacetamide derivative **4** in high yield (84%). The two arms of compound **4** were efficiently linked by treatment with the corresponding 2-mercaptoheterocycle and sodium bicarbonate in refluxing acetonitrile, yielding the calixarene derivatives **5**–**7** in good yields (Scheme 2). The structures of compounds **5**–**7** were established by IR radiation, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The spectroscopic data for compounds **5**–**7** evidenced a cone conformation. Considering **5** as a reference compound the signals (^{1}H NMR, $CDCl_3$) for the methylene bridge protons of the calix[4]arene skeleton appeared as two doublets at 4.05 and 3.17 ppm (J = 13.0 Hz), the difference in the chemical shift of about 1.10 ppm, indicates that this compound exists in the cone conformation in solution. Moreover, in the ^{13}C NMR data, the signal peak of the methylene carbons of $ArCH_2Ar$ appeared at about 32.0 ppm according to Mendoza's rule,[19] which is also consistent with the cone conformation.

Studies of selective ionophore behaviour for these calixarenes derivatives are in progress.

Conclusions

We have efficiently synthesised three new calix[4]arenes bearing benzothiazolyl, benzoxazolyl and benzoimidazolyl



1 **2** **3**

Scheme 1 (a) $BrCH_2CN$, K_2CO_3, CH_3CN, reflux, 8 h; (b) $LiAlH_4$, THF anh., 0°C.

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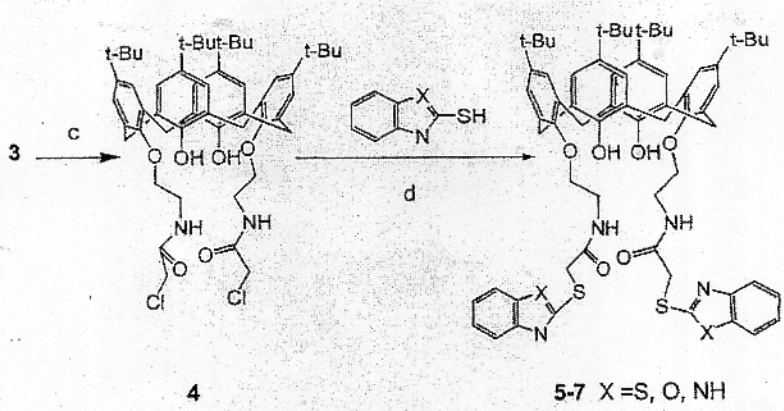

4 5-7 X =S, O, NH

Scheme 2 (c) $(ClAc)_2$, AcOEt, rt, 1h; (d) $NaHCO_3$, reflux, 6h.

heterocycles, introducing an infrequent $-SCH_2-(C=O)-NH$ feature as bridge between the calixarene and the heterocycle. We expected to enhance sensitivity towards transition metals incorporating both nitrogen and sulfur atoms.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. Spectra were recorded using the following instruments: IR, FT-IR Bruker IFS 55; ^1H and ^{13}C NMR, Bruker DRX-400 (400 and 100 MHz), using tetramethylsilane as internal reference. Microanalyses were determinated using Fisons EA 1108 analyser and were performed in CEPEDEQ (Centro Para el Desarrollo de la Química), Facultad de Ciencias Químicas y Farmaceuticas, Universidad de Chile. Mass spectra (MALDI-TOF) were obtained on a Bruker mod. AUTOFLEX spectrometer, using HCCA/DSO as matrix in Centro de Instrumentación Científica de La Universidad de Granada, España. Column chromatography was performed on Merck silica gel 60, 230-400 mesh, and TLC on Merck silica gel G.

5,11,17,23-Tetra-t-butyl-25,27-bis[2-(chloroacetamido)ethoxy]-26,28-di-hydroxycalix[4]arene **(4):** To a solution of 2 (0.2 g, 0.27 mmol) in AcOEt (15 ml) chloroacetic anhydride (0.10 g, 0.60 mmol) was added. The reaction was kept at room temperature, and monitorated by TLC (AcOEt) until complete disappearance of **2** (1 h). The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution (2 × 15 ml). The organic phase was dried ($MgSO_4$) and the solvent evaporated under reduced pressure, giving a crude product that was purified by a short column chromatography (CH_2Cl_2/hexane 2:1), giving **4** (0.22 g, 84%) as a solid: m.p. 246–247°C. IR (KBr): ν = 3422, 1665, 1541, 1485, 1362, 1202 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 (br s, 2 H: 2 NH), 8.11 (s, 2 H, 2 OH), 7.05, 6.95 (2 s, 8 H: Ar), 4.20 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 4.12 (t, *J* = 4.7 Hz, 4 H: 2 OCH_2), 4.11 (s, 4 H: 2 CH_2Cl), 3.97 (m, 4 H: 2 CH_2NH), 3.39 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 1.26, 1.07 (s, 36 H: 4 Me_3C). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9 (CO), 149.8, 148.6, 148.1, 142.6, 132.9, 127.6, 126.1, 125.6 (Ar), 75.1 (OCH_2), 42.7 ($NHCH_2$), 40.0 (CH_2Cl), 34.2, 33.9 (Me_3C), 32.1 ($ArCH_2Ar$), 31.7, 31.1(Me_3C) $C_{52}H_{68}Cl_2N_2O_6$ (888.0): calcd. C 70.3, H 7.7, N 3.2: found C 70.2, H 8.0, N 2.9.

General procedure for the synthesis of calix[4]arenes **5–7**

To a solution of **4** (0.10 g, 0.122 mmol) in acetonitrile (5 ml) 2-mercaptobenzothiazole (0.268 mmol) and $NaHCO_3$ (50 mg) were added. The reaction mixture was refluxed by 6 h. Filtration and evaporation under reduced pressure gave a crude product that was triturated with ethyl acetate/hexane (1:1).

5,11,17,23-Tetra-tert-butyl-25,27-bis-{2-[2-benzothiazol-2-ylsulfanyl)acetamido]ethoxy}-26,28-dihydroxycalix[4]arene **(5):** Yield: 85%; m.p. 227–229°C. IR (KBr): ν = 3480, 1657, 1561, 1484, 1361, 1207 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.60 (t, 2 H: 2 NH), 8.15 (s, 2 H, 2 OH),7.78, 7.66 (2 d, 2 H, *J* = 7.80 Hz), 7.37, 7.27 (2 t, 2H, *J* = 7.80 Hz) 6.91, 6.43 (2 s, 8 H: Ar), 4. 21 (s, CH_2S, 4H), 4.05 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 4.01–3.98 (m, 4 H: 2 OCH_2), 3.93–3.89 (m, 4 H: 2 CH_2NH), 3.17 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 1.23, 1.05 (s, 36 H: 4 Me_3C). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (CONH), 152.8, 149.6, 148.6, 147.9, 142.5, 135.7, 133.0, 127.7 126.0, 125.9, 125.4, 121.6, 121.1 (Ar), 75.3 (OCH_2), 40.0 ($NHCH_2$), 34.1, 33.9 (Me_3C), 32.0 ($ArCH_2Ar$), 31.6, 31.1(Me_3C); MS (MALDI-TOF) $C_{66}H_{76}N_4O_6S_4$: calcd for $[M + Na]^+$ 1171.453; found 1171.430; calcd for $[M+K]^+$ 1187.423; found 1187.414; $C_{66}H_{76}N_4O_6S_4$ (1149,7): calcd. C 68.9, H 6.7, N 4.9, S 11,2: found C 69.1, H 7.0, N 4.9, S 10,8.

5,11,17,23-Tetra-tert-butyl-25,27-bis-{2-[2-benzoxazol-2-ylsulfanyl) acetamido]ethoxy}-26,28-dihydroxycalix[4]arene **(6)**: Yield: 80%; m.p. 220–222°C. IR (KBr) (yield: 85%): ν = 3480, 1655, 1522, 1480, 1364, 1200 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (t, 2 H: 2 NH), 8.45 (s, 2 H, 2 OH),7.64, 7.44 (2 d, 2 H, *J* = 7.80 Hz), 7.37–7.9 (2 t, 2 H, *J* = 7.80 Hz) 7.09 (s, 8 H: Ar), 4. 31 (s, CH_2S, 4H), 4.25 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 4.16 (m, 4 H: 2 OCH_2), 4.08 (m, 4 H: 2 CH_2NH), 3.40 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 1.35, 1.22 (s, 36 H: 4 Me_3C). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6 (CONH), 164.0, 152.1, 149.1, 148.5, 148.4, 143.0, 141.6, 138.1, 133.3, 127.8 126.0, 125.5, 125.4, 124.1, 118.5, 116.4, 110.11(Ar), 75.5 (OCH_2), 40.1 ($NHCH_2$), 35.8 (CH_2), 32.0 ($ArCH_2Ar$), 31.6 (Me_3C), 31.5, 31.1(Me_3C) $C_{66}H_{76}N_4O_8S_2$ (1117.6): calcd. C 70,93, H 6.87, N 5.01, S 5.74: found C 71.1, H 7.0, N 4.8, S 5.8.

5,11,17,23-Tetra-tert-butyl-25,27-bis-{2-[2-benzoimidazol-2-ylsulfanyl)acetamido]ethoxy}-26,28-dihydroxycalix[4]arene **(7)**: Yield: 78%; m.p.216–218°C. IR (KBr) ν = 3460, 1654, 1512, 1485, 1361, 1206 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.54 (s, 2 H, NH), 8.67 (t, 2 H: 2 NH), 8.48 (s, 2 H, 2 OH), 7.40 (2 d, 4H), 7.37, 7.27 (2 t, 4 H) 7.12 (s, 8 H: Ar), 4. 17 (s, CH_2S, 4H), 4.0 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 3.98–3.88 (m, 8 H: 2 OCH_2CH_2NH), 3.10 (d, *J* = 13.0 Hz, 4 H: ArCH_2Ar), 1.16, 1.11 (s, 36 H: 4 Me_3C). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (CONH), 152.8, 149.6, 148.6, 147.9, 142.5, 135.7, 133.0, 127.7 126.0, 125.9, 125.4, 121.6, 121.1 (Ar), 75.3 (OCH_2), 40.0 ($NHCH_2$), 34.1 33.9 (Me_3C), 32.0 ($ArCH_2Ar$), 31.6, 31.1(Me_3C); MS (MALDI-TOF) $C_{66}H_{78}N_6O_6S_2$: calcd for $[M + Na]^+$ 1137.606; found 1137.609; calcd for $[M + K]^+$ 1153.579; found 1153.572; $C_{66}H_{78}N_6O_6S_2$ (1115.6): calcd. C 71.05, H 7.06, N 7.53, S 5.75: found C 71.25, H 7.15, N 7.8, S 5.8.

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