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Synthesis of novel chromogenic bi- and tri-functionalized calix[4]arenes

Hatem Halouani, Isabelle Dumazet-Bonnamour* and Roger Lamartine

Laboratoire de Chimie Industrielle, UMR CNRS 5078, Université Claude Bernard-Lyon1, 43 Bd du 11 November 1918, 69622 Villeurbanne Cedex, France

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Abstract—Novel azo-calix[4]arenes have been prepared by the incorporation of both ester and amide groups. Six bis(phenylazo)-*O*-substituted calix[4]arene derivatives were isolated and fully characterized. NMR analyses show that these compounds are in cone conformation in solution at room temperature.

In a recent report,[1] we have described the synthesis of five novel azocalix[4]arenes. By selective *O*-substitution on the lower rim of chromogenic calix[4]arene, 2,2′-bithiazoyl-azocalixarenes were isolated, characterized in order to study their conformation in solution and their complexation properties towards metals. Concerning these last points, when calixarenes are properly functionalized, their conformational mobility is restricted, allowing a well-defined position of functional groups for complexation.[2,3] Furthermore, esters, acetones and amides which have been largely studied as complexation sites on calixarenes, display interesting properties of complexation towards alkaline,[4] alkaline earth[5] lanthanide[6–9] and transition metals,[10–12] due to the convergent location of donor atoms. Moreover, azo groups bring to calixarenes a chromogenic activity.[13,14]

Thus, these studies led us to the preparation of six new bis(azo)calix[4]arenes $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_3}$, $\mathbf{L_4}$, $\mathbf{L_5}$ and $\mathbf{L_6}$ incorporating both ester and amide functions and the examination of their conformation in solution. 4-Nitrophenylazo and phenylazo groups were graft on the upper rim of calixarenes and glycine units on the lower rim providing additional donor atoms.[15]

We have developed a strategy in three steps which permit to obtain the ligands $\mathbf{L_{3-6}}$ incorporating two azo groups on the upper rim and both amide and ester functions on the lower rim of calix[4]arene with a retention of the cone conformation.

The first intermediate $\mathbf{L_0}$,[16] which is a key reactant for the formation of both $\mathbf{L_1}$[17] and $\mathbf{L_2}$,[17] was chosen in order to block the two distal hydroxy groups of calix[4]arene (Scheme 1). Thus, using conventional copulation procedure,[18] $\mathbf{L_1}$ and $\mathbf{L_2}$ can be obtained, respectively in 52 and 40% yields.

Calix[4]arenes tetra-esters $\mathbf{L_3}$[17] and $\mathbf{L_4}$[17] were obtained, respectively by reaction of $\mathbf{L_1}$ and $\mathbf{L_2}$ with the appropriate bromoethylester in presence of Na_2CO_3 as base in acetonitrile at reflux temperature for 72 h in 25.5 and 28% yields. The compounds $\mathbf{L_5}$[17] and $\mathbf{L_6}$[17] were obtained by the same procedure in presence of a catalytic amount of sodium iodide (respectively 33 and 40% yields).

The cone conformation of all ligands were reflected in the characteristic AB system for the methylene groups bridging the aromatic rings in the ^1H and ^{13}C NMR spectrum.[19] In the case of $\mathbf{L_1}$ and $\mathbf{L_2}$, NMR spectrum show the characteristics two AB system at, respectively $\delta = 3.57$, 4.53 ppm and $\delta = 3.36$, 4.86 for Ar-CH_2-Ar groups and one signal at 31.87 and 31.43 for the corresponding carbons, both indicate a cone conformation of $\mathbf{L_1}$ and $\mathbf{L_2}$ probably due to the strong hydrogen bonding between the free phenol hydrogens and the carbonyl groups.[20] In the case of $\mathbf{L_3}$ and $\mathbf{L_4}$, the cone conformation is proven by the presence of two doublets, respectively at $\delta = 3.45$, 5.00 ppm, $J_{AB} = 13.85$ Hz and 3.43, 4.99 ppm, $J_{AB} = 13.75$ Hz for $ArCH_2Ar$ groups and one signal at, respectively $\delta = 31.67$ and 39 ppm of the corresponding carbons, both indicate a cone conformation.

* Corresponding author. Tel.: (33)4.72.44.80.14; fax: (33)4.72.44.84.38; e-mail: i.bonnamour@cdlyon.univ-lyon1.fr

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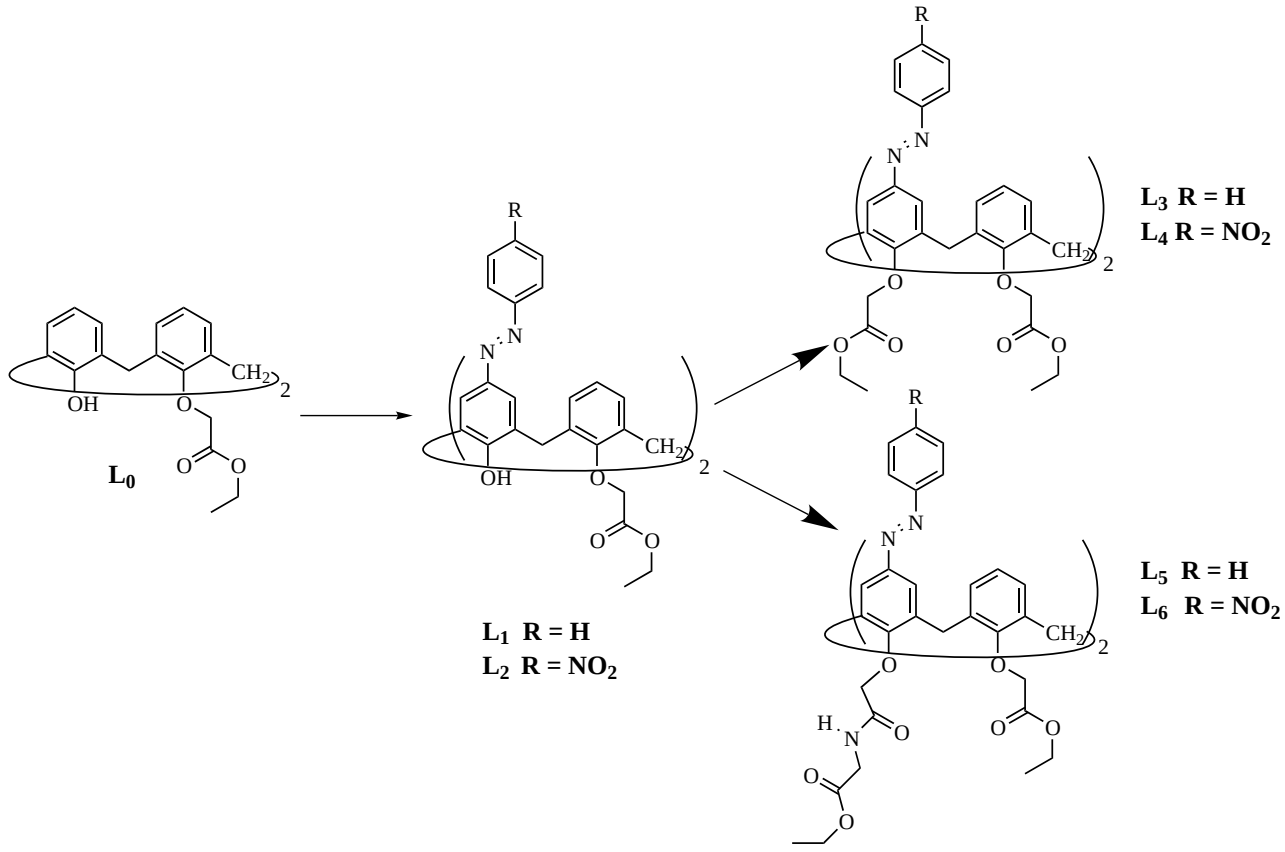

Scheme 1. Synthetic pathway of azocalix[4]arenes amide and ester.

For the compounds $\mathbf{L_5}$ and $\mathbf{L_6}$, the NMR spectrum confirmed the presence for an expanded AB system at, respectively $\delta = 3.51$, 4.77 ppm, $J_{AB} = 14.13$ Hz and $\delta = 3.48$, 4.78 ppm, $J_{AB} = 14.0$ Hz for $ArCH_2Ar$ groups and one signal at, respectively $\delta = 31.76$ and 31.67 ppm of the corresponding carbons.

The infrared analysis of $\mathbf{L_1}$ and $\mathbf{L_2}$ shows a broad absorption at 3390 cm^{-1}, revealing intramolecular hydrogen bonding. This correlates with a 'cone' conformation, where the remaining phenolic hydrogen are at a suitable distance from the vicinal oxygens.

In conclusion, we have developed a convenient method which permits to graft selectively both azo groups on the upper rim and ester or amide functions on the lower rim of calix[4]arene. These new compounds offer the advantage to be colored, in cone conformation and bi-, tri-functionalized. Further investigations in metal complexation field are under way.

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17. *General*: Solvents were purified and dried by standard methods prior to use. All reactions were carried out under nitrogen. Column chromatography was performed with silica gel 60 (0.040–0.063 mm) from Merck. Melting points were recorded on an Electrothermal 9100 capillary apparatus and were uncorrected. Infrared was performed on a Mattson 5000 FT apparatus (ν in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Brucker AM 300 (300.13 and 75 MHz), ($CDCl_3$, TMS as internal standard, chemical shifts in ppm, J in Hertz). Mass spectra were obtained by electrospray technique (positive mode). Infra-red spectra were performed on a Spectrum One Perkin–Elmer apparatus (ν in cm^{-1}).

General procedure for the syntheses of bis(phenylazo- and 4-nitrophenylazo)-substituted bis(ester)-calix[4]arene L_1 and L_2. Calix[4]arenes, substituted on the upper rim by bis(phenylazo and 4-nitrophenylazo) and on the lower rim by bis(ester) groups, were synthesized according to the following method: 25,27-di(ethoxycarbonylmethoxy)-26,28 (di-hydroxy) calix[4]arene $\mathbf{L_o}$ (2 g, 3.37 mmol) and the BF_4^- salt benzenediazoniums or *p*-nitrobenzene diazoniums (8.42 mmol) were dissolved in THF (100 ml). The reaction was initiated by the addition of pyridine (5 ml) to the cooled THF solution at 0°C. After 48 h the mixture was evaporated to dryness. The residue was dissolved in minimum pyridine. The addition of methanol has given an orange precipitate which was recovered by filtration and washed with methanol.

5,17-Bis(phenylazo)-26,28-dihydroxy-25,27-di(ethoxy carbonylmethoxy)calix[4]arene L_1 was purified by chromatography column on silica gel (ethyl acetate/hexane; 4:6 (v/v)) to yield $\mathbf{L_1}$ as an orange solid (1.4 g, 52%). Mp: 248–249°C. ^1H NMR ($CDCl_3$) $\delta=8.29$ (s, 2H, OH), 7.85 (d, 4H, $J=7.17$ Hz, H-diazo), 7.75 (s, 4H, H-diazo), 7.50–7.39 (m, 6H, H-diazo), 7.02 (d, 4H, $J=7.53$ Hz, H_{Ar}), 6.78 (t, 2H, $J=7.53$ Hz, H_{Ar}), 4.74 (s, 4H, OCH_2CO), 4.53, 3.57 ('q', AB, $J_{AB}=13.17$ Hz, $ArCH_2Ar$), 4.37 (q, 4H, $J=7.14$ Hz, OCH_2CH_3), 1.36 (t, 6H, $J=7.17$ Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) $\delta=$ 169.16 (CO), 156.93, 153.43, 152.65, 146.09, 132.91, 130.36, 130.02, 129.40, 128.87, 126.30, 124.30, 122.76 (C_{Ar}), 72.90 (OCH_2CO), 61.99 (OCH_2CH_3), 31.87 ($ArCH_2Ar$), 14.58 (OCH_2CH_3). ES-MS m/z: 805.3 $[M+H]^+$ (calcd. 805.9), 827.3 $[M+Na]^+$ (calcd. 827.9). IR: 3381.7 (OH), 2981.5 (C_{Ar}-H), 2929.6 (CH_2, CH_3), 1749.9 (CO), 1473.1, 1461.3, 1441.5 (C=C, N=N).

5,17-Bis(4-nitrophenylazo)-26,28-dihydroxy-25,27-di(ethoxy-carbonylmethoxy)-calix[4]arene L_2 was purified by chromatography on silica gel (ethyl acetate/hexane; 4:6 (v/v)) to yield $\mathbf{L_2}$ as a red solid (1.6 g, 40%). Mp: 247–248°C. ^1H NMR (C_5D_5N) $\delta=9.26$ (brs, 2H, OH), 8.41 (d, 4H, $J=7.14$ Hz, H-diazo), 8.24 (s, 4H, H_{Ar}), 8.10 (d, 4H, $J=6.96$ Hz, H-diazo), 7.04 (d, 4H, $J=7.74$ Hz, H_{Ar}), 6.49 (t, 2H, $J=7.53$ Hz, H_{Ar}), 4.98 (s, 4H, OCH_2CO), 4.86, 3.36 ('q', AB, $J_{AB}=12.99$ Hz, $ArCH_2Ar$), 4.28 (q, 4H, $J=7.17$ Hz, OCH_2CH_3), 1.19 (t, 6H, $J=7.14$ Hz, OCH_2CH_3); ^{13}C NMR (C_5D_5N) $\delta=169.15$ (CO), 158.58, 156.34, 152.95, 148.23, 146.28, 132.69, 129.81, 125.83, 125.40, 125.01, 123.59, 123.12 (C_{Ar}), 72.82 (OCH_2CO), 61.39 (OCH_2CH_3), 31.43 ($ArCH_2Ar$), 13.90 (OCH_2CH_3). ES-MS m/z: 917.2 $[M+Na]^+$ (calcd. 917.9). IR: 3389.6 (OH), 2982.1, 2933.5 (C-H), 1740.6 (CO), 1588.2, 1519.2, 1473.5, 1427.5 (OH, H_{Ar}, C=C).

General procedure for the synthesis of bis(phenylazo or 4-nitrophenylazo)-substituted tetra (ester)calix[4]arenes L_3 and L_4. A solution of L_1 or L_2 (0.249 mmol) and Na_2CO_3 (0.996 mmol) were stirred for 2 h under nitrogen in dry acetonitrile (20 ml) at reflux temperature. After the addition of ethyl bromoacetate (1 mmol), the mixture was heated under reflux for 72 h. After filtration, the solvent was removed in vacuum, the residue was taken up in CH_2Cl_2 (20 ml) and washed with a saturated aqueous ammonium chloride solution (2×10 ml) and water (20 ml). After evaporation of the solvent, the solid residue was submitted to the column chromatography (silica gel, ethyl acetate:hexane; 2:8 (v/v)).

5,17-Bis(phenylazo)-25,26,27,28-tetra(ethoxycarbonylmethoxy)calix[4]arene L_3 (0.062 g, 25.5%). Mp: 173–174°C. ^1H NMR ($CDCl_3$) $\delta=7.89$ (d, 4H, $J=7.89$ Hz, H-diazo), 7.69 (s, 4H, H_{Ar}), 7.52–7.46 (m, 6H, H-diazo), 6.45 (brs, 6H, H_{Ar}), 5.04 (s, 4H, OCH_2CO), 5.00, 3.45 ('q', AB, $J_{AB}=13.85$ Hz, $ArCH_2Ar$), 4.62 (s, 4H, OCH_2CO), 4.31 (q, 4H, $J=7.14$ Hz, OCH_2CH_3), 4.26 (q, 4H, $J=6.96$ Hz, OCH_2CH_3), 1.36 (t, 6H, $J=7.17$ Hz, OCH_2CH_3), 1.33 (t, 6H, $J=7.14$ Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) $\delta=$ 170.64, 169.87 (CO), 160.07, 155.32, 153.27, 148.55, 137.27, 133.15, 130.84, 129.43, 128.81, 124.27, 123.79, 122.99 (C_{Ar}), 72.15, 71.56 (OCH_2CO), 61.96, 54.98 (OCH_2CH_3), 31.97 and 31.67 ($ArCH_2Ar$), 14.66 and 14.61 (OCH_2CH_3). ES-MS m/z: 977.3 $[M+H]^+$ (calcd. 978.08), 999.4 $[M+Na]^+$ (calcd. 1000.07). IR: 2985.1 (C_{Ar}-H), 2933.4 (CH_2, CH_3), 1756.2 (CO), 1587.7, 1459.5, 1441.8 (H_{Ar}, N=N, C=C).

5,17-Bis(4-nitrophenylazo)-25,26,27,28-tetra(ethoxycarbonylmethoxy)calix[4]-arene L_4. (0.075 g, 28.2%). Mp: 104–106°C. ^1H NMR ($CDCl_3$) $\delta=8.27$ (d, 4H, $J=6.96$ Hz, H-diazo), 7.88 (d, 4H, $J=7.17$ Hz, H-diazo), 7.57 (s, 4H, H_{Ar}), 6.54 (brs, 6H, H_{Ar}), 4.99, 3.43 ('q', AB, $J_{AB}=13.75$ Hz, $ArCH_2Ar$), 4.97 (s, 4H, OCH_2CO), 4.65 (s, 4H, OCH_2CO), 4.25 (q, 4H, $J=7.14$ Hz, OCH_2CH_3), 4.23 (q, 4H, $J=7.14$ Hz, OCH_2CH_3), 1.33 (t, 6H, $J=7.14$ Hz, OCH_2CH_3), 1.30 (t, 6H, $J=7.35$ Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) $\delta=170.33$, 170.06 (CO), 160.98, 156.23, 155.64, 148.62, 148.45, 137.11, 133.49, 129.04, 124.95, 124.77, 123.85, 123.47 (C_{Ar}), 72.03, 71.64 (OCH_2CO), 61.21, 61.13 (OCH_2CH_3), 31.96 ($ArCH_2Ar$), 14.64, 14.60 (OCH_2CH_3). ES-MS m/z: 1067.2 $[M+H]^+$ (Calcd. 1068.08), 1089.1 $[M+Na]^+$ (calcd. 1090.06). IR: 2981.9

(C_{Ar}-H), 2931.7 (CH_2, CH_3), 1753.8 (CO), 1735.1 (CO), 1607.4, 1589.0, 1523.1, 1461.8, 1444.0 (H_{Ar}, C=C, N=N).

General procedure for the synthesis of L_5 and L_6. A mixture of L_1 or L_2 (0.25 mmol), anhydrous sodium carbonate (0.265 g, 2.5 mmol), *N*-(chloroacetyl) glycine ethylester (1.75 mmol) and sodium iodide (catalytic amount) in acetonitrile (35 ml) were refluxed for 72 h. The solvent was then evaporated and the residue was taken up in CH_2Cl_2 (30 ml), washed with a saturated aqueous ammonium chloride solution (2×15 ml) and water (2×15 ml). After evaporation of the solvent the product was triturated with MeOH and filtered off and dried to give pure L_5 or L_6 as a red solid.

5,17-Bis(phenylazo)-26,28-bis{[(ethoxycarbonyl) methylcarbamoyl]methoxy} - 25,27 - di(ethoxycarbonylmethoxy) calix[4]arene L_5 (0.09 g, 33%). Mp: 92–94°C. ^{1}H NMR ($CDCl_3$) δ=8.28 (t, 2H, J=6.24 Hz, $HNCH_2$), 7.86 (d, 4H, J=7.14 Hz, H-diazo), 7.64 (s, 4H, H_{Ar}), 7.46–7.43 (m, 6H, H-diazo), 6.47 (t, 2H, J=6.21 Hz, H_{Ar}), 6.40 (d, 4H, J=6.78 Hz, H_{Ar}), 4.92 (s, 4H, OCH_2CO), 4.77, 3.51 ('q', AB, J_{AB}=14.13 Hz, $ArCH_2Ar$), 4.54 (s, 4H, OCH_2CO), 4.29–4.16 (m, 12H, $HNCH_2CO$ and OCH_2CH_3), 1.32 (t, 6H, J=7.17 Hz, OCH_2CH_3), 1.30 (t, 6H, J=6.96 Hz, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ= 171.09, 170.00, 169.89 (CO), 160.68, 154.98, 153.07, 148.48, 135.93, 132.85, 131.07, 129.44, 129.39, 124.62, 123.05 (C_{Ar}), 74.48, 72.91 (OCH_2CO), 61.84, 61.61 (OCH_2CH_3), 40.94, 31.76 ($ArCH_2Ar$), 14.55 (OCH_2CH_3). ES-MS *m*/*z*: 1091.2 $[M+H]^+$ (calcd. 1092.19), 1113.3 $[M+Na]^+$ (calcd. 1114.17). IR: 3395.3 (NH), 2964, 2932.8 (C-H), 1741.7, 1680.3 (CO), 1583.4, 1531.9, 1461.7, 1434.3 (H_{Ar}, C=C).

5,17 - Bis(4 - nitrophenylazo) - 26,28 - bis{[(ethoxycarbonyl)-methylcarbamoyl] - methoxy} - 25,27 - di(ethoxycarbonylmethoxy)calix[4]arene L_6 (0.12 g, 40.6%). Mp: 108–110°C. ^{1}H NMR ($CDCl_3$) δ=8.30 (t, 2H, J=6.3 Hz, $HNCH_2$), 8.19 (d, 4H, J=9.03 Hz, H-diazo), 7.81 (d, 4H, J=9.06, H-diazo), 7.44 (s, 4H, H_{Ar}), 6.62 (brm, 6H, H_{Ar}), 4.97 (s, 4H, OCH_2), 4.78, 3.48 ('q', AB, J_{AB}=14.10 Hz, $ArCH_2Ar$), 4.64 (s, 4H, OCH_2), 4.24–4.15 (m, 12H, CH_2NH and OCH_2CH_3), 1.30 (t, 6H, J=7.17, OCH_2CH_3), 1.29 (t, 6H, J=6.96, OCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ=170.80, 170.43, 169.61 (CO), 160.78, 155.91, 155.66, 148.47, 135.88, 133.43, 129.70, 124.89, 124.84, 124.51, 123.49 (C_{Ar}), 74.41, 72.65 (OCH_2CO), 61.73, 61.65 (OCH_2CH_3), 41.03 (NCH_2CO), 31.67 ($ArCH_2Ar$), 14.56, 14.49 (OCH_2CH_3). ES-MS *m*/*z*: 1181.2 $[M+H]^+$ (calcd. 1182.18), 1203.2 $[M+Na]^+$ (calcd. 1204.16). IR: 3386.5 (N-H), 2981.2 (C-H), 1740.4, 1679.9 (CO), 1588.4, 1522.7, 1462.6, 1441.4 (H_{Ar}, C=C).

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