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Synthesis of new chromogenic 2,2′-bithiazoylcalix[4]arenes

Farhana Oueslati, Isabelle Dumazet-Bonnamour* and Roger Lamartine

Laboratoire de Chimie Industrielle, UMR CNRS 5078, Université Claude Bernard-Lyon 1, 43 Bd du 11 novembre 1918, F-69622 Villeurbanne Cedex, France

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Abstract—A new family of calix[4]arenes have been prepared by the incorporation of fluorescent 2,2′-bithiazole (*btz*) units to azocalix[4]arene. From the mono- to the tetrasubstituted *btz* species, five 2,2′-bithiazoylcalix[4]arenes were isolated and fully characterised. NMR analyses show that these compounds are in cone or 1,3-alternate conformations in solution at room temperature.

Calixarenes are a class of phenolic macrocycles extensively used as molecular platforms for the synthesis of highly efficient and selective receptors.[1] Current studies on the synthesis of calixarene derivatives have promised the development of optical sensors,[2] ion-selective electrodes,[3] and spectrofluorometric systems.[4] However, there is still an important need for systems that can exhibit colour changes due to ionic or molecular interactions. Among these works, azocalixarenes have been mainly studied: calixarenes bridging phenylazo moieties on the upper rim[5–7] and lower rim,[8] double azocalixarenes,[9] azocalixcrowns.[10] On the other hand, the incorporation of heterocyclic chelating agents such as for example 2,2′-bipyridine, 2,2′-bithiazole and pyridyl, to the lower rim of calixarene[11–14] have a special interest in the complexation behaviour towards transition metal cations.[15,16]

In the field of our investigations, we are interested in the development of a new class of chromoionophore sensors. Thus the aim of the present work was to build molecular design constituted of calix[4]arene which contain both 2,2′-bithiazole (*btz*) moiety as a metal-binding site and azophenol moiety as coloration site. The incorporation of *btz* subunit has been chosen here due to its potential double-site complexation abilities[16] completed by its properties of fluorescence.[13] This led us to the preparation of five new diazo coupling calix[4]arenes substituted by bithiazole subunits **2**, **3a**, **3b**, **4a**, **4b** (Scheme 1).

p-Tetrakis(phenylazo)-, *p*-tetrakis(nitrophenylazo)-substituted calix[4]arenes,[5] 4,4′-dimethyl-2,2′-bithiazole[17] and 4-bromomethyl-4-methyl-2,2′-bithiazole[13] were synthesised according to the literature. The *btz* subunits were grafted via their 6-position on the lower rim of the azocalixarene platform according to the regioselective *O*-alkylation already describe for heterocyclic substituents.[12,18] The bases were chosen among various alkali metal carbonates ($KHCO_3$, K_2CO_3, Na_2CO_3, Cs_2CO_3) and other bases such as BaO, NaH, versus to their ability to selectively deprotonate phenolic OH groups[19] and try to keep in mind the cone conformation of the starting azocalix[4]arene.

The reaction of **1a** with 4-bromomethyl-4-methyl-2,2′-bithiazole in anhydrous CH_3CN, in the presence of $KHCO_3$, afforded ligand **2**[20] (35% yield). The ligand was found to be, as expected, in the cone conformation in solution at room temperature. Reaction of **1a** with BaO, $Ba(OH)_2{\cdot}8H_2O$ and 4-bromomethyl-4-methyl-2,2′-bithiazole in anhydrous DMF has resulted in the formation of ligand **3a**[20] (64% yield). The same reaction with **1b** gave **3b**[20] (39% yield). ^{1}H NMR spectra of **3a** and **3b** show characteristic one single AB system for the bridging methylene groups, a singlet for the OCH_2-*btz* moieties. In the corresponding ^{13}C NMR spectra, the signal for the bridging methylene groups appears at $\delta = 32.2$ ppm. These results prove that we have a 1,3-distal substitution of the calix[4]arene and clearly indicate a cone conformation.

Different bases such as NaH, Na_2CO_3 and K_2CO_3 were tested to prepare **4** in cone conformation.[21] But in each case we have obtained a mixture of mono-, di-, tri- and tetrasubstituted species from which these compounds

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

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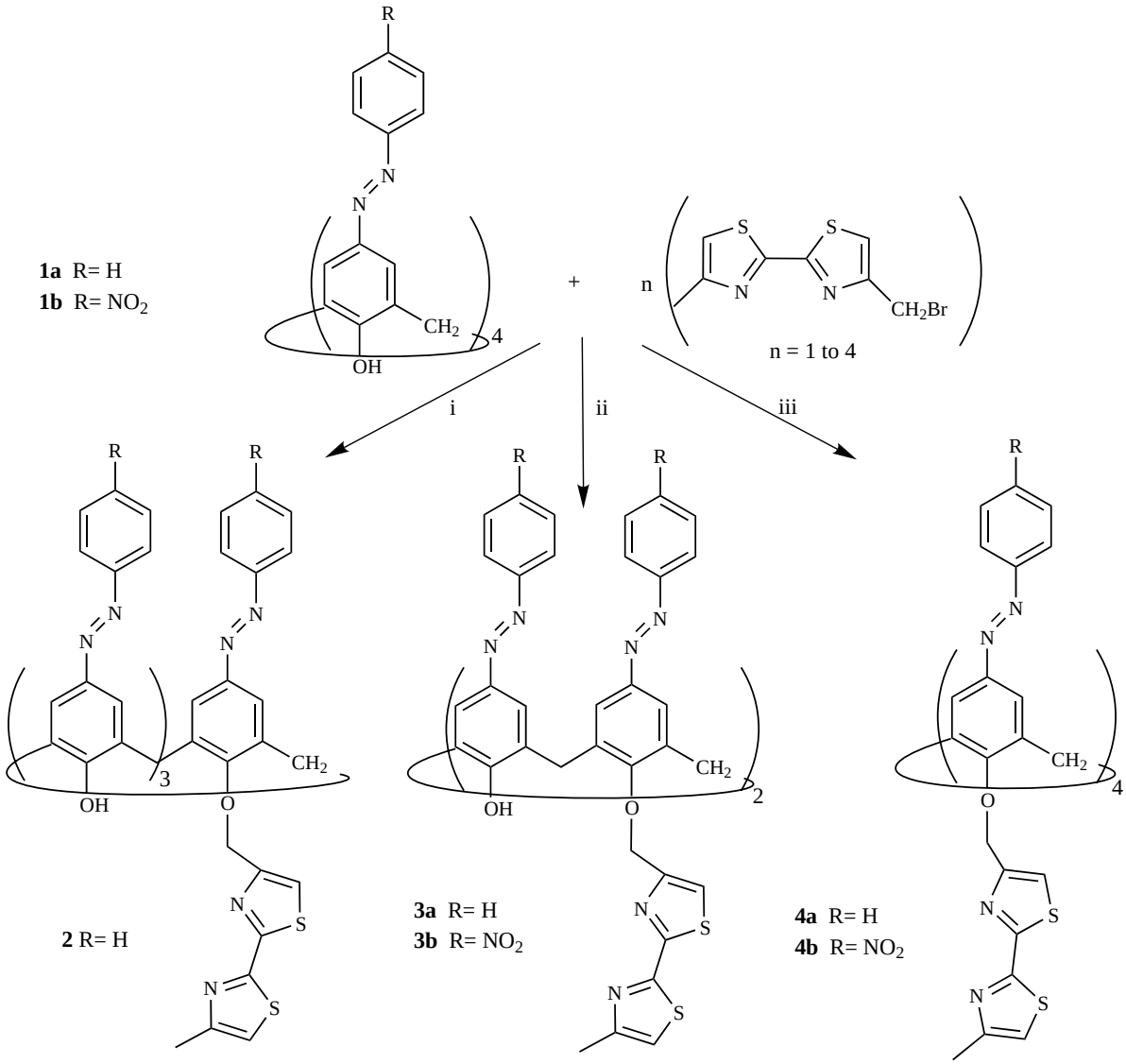

Scheme 1. *Reagents and conditions*: (i) $KHCO_3$ (2.1 equiv.), CH_3CN, 28 h, 35%; (ii) BaO (3 equiv.), $Ba(OH)_2{\cdot}8H_2O$ (3 equiv.), DMF, 48 h, 64% (**3a**); BaO (6 equiv.), $Ba(OH)_2{\cdot}8H_2O$ (6 equiv.), DMF, 3 days, 39% (**3b**); (iii) Cs_2CO_3 (10 equiv. (**4a**)), (12 equiv. (**4b**)), acetone, 2 days, 60% (**4a**), 35% (**4b**).

could not be isolated. Only Cs_2CO_3 gave selectively tetrasubstituted compounds in good yield and in an 1,3-alternate conformation as excepted with this kind of base.[22] Thus, compounds **4a**[20] and **4b**[20] were prepared by reaction of Cs_2CO_3 with azocalix[4]arenes (**1a** and **1b**) and 4-bromomethyl-4-methyl-2,2′-bithiazole. Their ^1H NMR spectra show one singlet corresponding to the bridging methylene group, one singlet assigned to the OCH_2-*btz* moieties and one singlet corresponding to the aromatic protons of the calixarene. Their ^{13}C NMR spectra show that the bridging methylene groups appear as one singlet at $\delta = 37.83$ and 36.53 ppm, respectively. These spectra clearly indicate an 1,3-alternate conformation[23] of these tetrasubstituted calix[4]arenes in solution at room temperature.

The present paper describe for the first time the syntheses of calixarenes both in cone and 1,3-alternate conformations bearing both azo and bithiazoyl groups. Application to these new compounds in the field of complexation and fluorescence properties are presently under investigation.

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20. 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. UV measurements were recorded on a Shimadzu UV-2401 PC spectrophotometer, λ_{max} in nm. Infrared was performed on a Mattson 5000 FT apparatus (ν in cm^{-1}, ξ in mol dm^{-3} cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300.13 and 75 MHz), ($CDCl_3$, TMS as internal standard, chemical shifts in ppm, J in Hz). Mass spectra were obtained by the electrospray technique (positive mode). Elemental analyses were performed at S.C.A., CNRS, Solaize, France.

Compound 2: **1a** (0.20 g, 0.212 mmol) and $KHCO_3$ (0.045 g, 0.445 mmol) were stirred in refluxing CH_3CN (20 ml) under nitrogen for 1 h. A solution of 4-bromomethyl-4-methyl-2,2′-bithiazole (0.148 g, 0.538 mmol) in CH_3CN (7 ml) was added dropwise and reflux continued for 28 h. After evaporation to dryness, the residue was dissolved in CH_2Cl_2 (50 ml) and extracted with water (2×20 ml). The organic phase was dried over Na_2SO_4 and removed by evaporation. The product was purified by a chromatography column on silica gel (CH_2Cl_2/petroleum ether/CH_3CN, 50/74/26) to give red powder (0.071 g, 35%). Mp: 233–234°C. ^1H NMR: 2.56 (s, 3H, CH_3-*btz*); 3.75, 4.47 ('q', AB, $J_{AB}=13$, 4H, Ar-CH_2-Ar); 3.80, 4.66 ('q', AB, $J_{AB}=13.3$, 4H, Ar-CH_2-Ar); 5.46 (s, 2H, O-CH_2-*btz*); 6.57 (s, 2H, H-*btz*); 7.28 (t, 8H, H_m-diazo); 7.42 (t, 4H, H_p-diazo); 7.68 (d, $J=8.8$, 8H, H_o-diazo); 7.25 (s, 8H, ArH); 9.46 (s, 2H, OH); 9.55 (s, 1H, OH). ^{13}C NMR: 17.41 (CH_3-*btz*); 32.31, 32.51 (Ar-CH_2-Ar); 69.45 (OCH_2-*btz*); 116.91, 120.85 (C(H)-*btz*); 154.81, 146.70, 145.48, 145.19, 143.12, 131.63, 131.60, 130.55, 129.48, 126.27, 124.11, 123.21, 123.01, 122.57, 120.84, 122.87 (C_{Ar}); 163.69, 159.22, 154.83, 152.95 (C_{btz}). UV: 349 (72500), 266 (56700). ES-MS m/z: 1056.31 $[M+Na]^+$ (calcd 1056.1), 1035.1 $[M+H]^+$ (calcd 1035.3). Anal. calcd for $C_{60}H_{46}N_{10}O_4S_2$ (1034.1): C, 70.77; H, 6.61; N, 13.00; O, 9.82. Found: C, 70.57; H, 6.55; N, 12.99; O, 9.89. IR: 3310 (OH), 3126–3043 (CH_3-*btz*), 1582.6, 1474.3, 1444.2, 1424.5 (C=C, N=N), 1432 (C–S), 976, 884 (*btz*C–H).

Compound 3a: **1a** (0.113 g, 0.135 mmol), $Ba(OH)_2{\cdot}8H_2O$ (0.127 g, 0.405 mmol) and BaO (0.062 g, 0.405 mmol) were mixed in dry DMF (5 ml) under nitrogen for 24 h at room temperature. After addition of 4-bromomethyl-4-methyl-2,2′-bithiazole (0.111 g, 0.405 mmol), the mixture was stirred at room temperature for 48 h. Then water (25 ml) was added to this solution and the resulting precipitate was filtered off, washed with water (25 ml) and then dissolved in CH_2Cl_2. The residue was extracted with water and dried over Na_2SO_4. The product was recrystallised with CH_2Cl_2/MeOH (99/1) affording a red powder (0.073 g, 64%). Mp: 245–246°C. ^1H NMR: 2.55 (s, 6H, CH_3-*btz*); 3.91, 4.79 ('q', AB, $J_{AB}=13.5$, 8H, Ar-CH_2-Ar); 5.34 (s, 4H, OCH_2-*btz*); 6.99 (s, 2H, H-*btz*); 7.45 (t, 8H, H_m-diazo); 7.53 (t, 4H, H_p-diazo); 7.71 (d, $J=8.7$, 8H, H_o-diazo); 7.89 (s, 8H, ArH); 7.81 (s, 2H, OH); 8.32 (s, 2H, H-*btz*). ^{13}C NMR: 17.15 (CH_3-*btz*); 32.21 (Ar-CH_2-Ar); 74.13 (OCH_2-*btz*); 117.50, 120.04 (C(H)-*btz*); 123.37, 124.00, 124.32, 125.28, 129.27, 129.64, 134.37, 135.67, 136.00, 150.41, 154.85, 153.46 (C_{Ar}); 152.87, 153.52, 160.67, 162.77 (C_{btz}). UV: 334 (83400), 228 (66800). ES-MS m/z: 1250.31 $[M+Na]^+$ (calcd 1250.6), 1229.31 $[M+H]^+$ (calcd 1229.5). Anal. calcd for $C_{68}H_{52}N_{12}O_4S_4$ (1228.31): C, 66.43; H, 4.26; N, 13.67; O, 5.21; S, 10.43. Found: C, 66.48; H, 4.32; N, 13.61; O, 5.28; S, 10.39. IR: 3306 (stretching, OH), 3112–3054 (CH_3-*btz*), 1593.7, 1543.1, 1487.4, 1439.0 (C=C, N=N), 1420 (C–S), 975, 878 (*btz*C–H).

Compound 3b: **1b** (0.110 g, 0.135 mmol), $Ba(OH)_2{\cdot}8H_2O$ (0.254 g, 0.810 mmol) and BaO (0.124 g, 0.810 mmol) were mixed in dry DMF (10 ml) under nitrogen for 24 h at room temperature. After addition of 4-bromomethyl-4-methyl-2,2′-bithiazole (0.116 g, 0.405 mmol), the mixture was stirred at room temperature for 3 days. The product was recrystallised from CH_2Cl_2/MeOH (97/3) affording a red powder (0.043 g, 39%). Mp: 248–250°C. ^1H NMR: 2.53 (s, 6H, CH_3-*btz*); 3.71, 4.55 ('q', AB, $J_{AB}=13.3$, 8H, Ar-CH_2-Ar); 5.15 (s, 4H, OCH_2-*btz*); 6.76 (s, 2H, H-*btz*); 7.72 (d, $J=8.8$, 8H, H_m-diazo); 7.76 (d, $J=8.6$, 8H, H_o-diazo); 7.81 (s, 8H, ArH); 7.88 (s, 2H, OH); 8.41 (s, 2H, H-*btz*). ^{13}C NMR: 17.64 (CH_3-*btz*); 32.24 (Ar-CH_2-Ar); 76.36 (OCH_2-*btz*); 115.50, 119.64 (C(H)-*btz*); 123.58, 124.54, 127.56, 129.72, 132.74, 135.45, 135.72, 135.98, 144.64, 149.72, 151.28, 153.67 (C_{Ar}); 152.52, 154.24, 159.63, 160.87 (C_{btz}). UV: 340 (81600), 288 (63500). ES-MS m/z: 1408.25 $[M+Na]^+$ (calcd 1408.4), 1431.52 $[M+H]^+$ (calcd 1431.8). Anal. calcd for $C_{68}H_{48}N_{16}O_{12}S_4$

(1408.25): C, 57.95; H, 3.43; N, 15.90; O, 13.62; S, 9.10. Found: C, 58.06; H, 3.58; N, 15.76; O, 13.36; S, 9.47. IR: 3310 (stretching, OH), 3141–3065 (CH_3-*btz*), 1581.4, 1459.5, 1431.1 (C=C, N=N), 1425 (C–S), 987, 882 (*btz*C–H).

Compound 4a: **1a** (0.122 g, 0.145 mmol) and Cs_2CO_3 (0.47 g, 1.45 mmol) in acetone (25 ml) was stirred under nitrogen at 60°C. 4-Bromomethyl-4-methyl-2,2′-bithiazole (0.24 g, 0.872 mmol) was added after 1 h. The reaction was cooled to room temperature after 2 days. The solvent was removed and the residue was dissolved in CH_2Cl_2 and the resulting precipitate was filtered off on Celite®. The filtrate was concentrated by evaporation. Then MeOH was added to the residue and the precipitate was filtered off, affording a red powder (0.075 g, 60%). Mp: 258–259°C. ^{1}H NMR: 2.46 (s, 12H, CH_3-*btz*); 4.08 (s, 8H, Ar-CH_2-Ar); 5.09 (s, 8H, OCH_2-*btz*); 6.53 (s, 4H, H-*btz*); 6.90 (s, 4H, H-*btz*), 7.19 (t, 4H, H_p-diazo); 7.22 (t, 8H, H_m-diazo); 7.43–7.45 (d, $J=8.4$, 8H, H_o-diazo); 7.508 (s, 8H, ArH). ^{13}C NMR: 17.05 (CH_3-*btz*); 37.83 (Ar-CH_2-Ar); 69.06 (OCH_2-*btz*); 116.29, 119.58 (C(H)-*btz*); 123.13, 125.42, 129.15, 130.48, 135.37, 135.66, 149.81, 153.68 (C_{Ar}); 153.55, 154.5, 159.12, 161.55 (C_{btz}). UV: 334 (99600), 277 (62100). ES-MS *m*/*z*: 1640.3 $[M+Na]^+$ (calcd 1639.4), 1617.3 $[M+H]^+$ (calcd 1617.6). Anal. calcd for $C_{84}H_{64}N_{16}O_4S_8$ (1616.31): C, 62.35; H, 3.99; N, 13.85; O, 3.96; S, 15.85. Found: C, 62.56; H, 3.91; N, 13.89; O, 3.87; S, 15.76. IR: 3125–3070 (CH_3-*btz*), 1584, 1469, 1448 (N=N, C=C). 1418 (C–S), 975, 884 (*btz*C–H).

Compound 4b: **1b** (0.125 g, 0.073 mmol), 4-bromomethyl-4-methyl-2,2′-bithiazole (0.120 g, 0.437 mmol) and Cs_2CO_3 (0.285 g, 0.875 mmol) in refluxing acetone (20 ml) for 48 h. Purification: recrystallisation in CH_2Cl_2/MeOH (2/3) affording a orange powder (0.088 g, 35%). Mp: 256–258°C. ^{1}H NMR: 2.44 (s, 12H, CH_3-*btz*); 4.05 (s, 8H, Ar-CH_2-Ar); 5.03 (s, 8H, OCH_2-*btz*); 6.30 (s, 4H, H-*btz*); 6.90 (s, 4H, H-*btz*); 7.52 (s, 8H, ArH); 7.43 (d, $J=8.7$, 8H, H_m-diazo); 7.96 (d, $J=8.7$, 8H, H_o-diazo). ^{13}C NMR: 17.05 (CH_3-*btz*); 36.53 (Ar-CH_2-Ar); 69.06 (OCH_2-*btz*); 118.92, 120.55 (C(H)-*btz*); 123.17, 126.39, 129.85, 134.54, 135.26, 144.88, 149.29, 153.8 (C_{Ar}); 152.11, 152.77, 158.62, 161.28 (C_{btz}). UV: 343 (96300), 279(62400). ES-MS *m*/*z*: 1796.25 $[M^+]$ (calcd 1796.5). Anal. calcd for $C_{84}H_{60}N_{20}O_{12}S_8$ (1796.25): C, 56.11; H, 3.36; N, 15.58; O, 10.68; S, 14.27. Found: C, 56.23; H, 3.42; N, 15.47; O, 10.71; S, 14.23. IR: 3130–3020 (CH_3-*btz*), 1500 (C=C), 1450 (N=N), 1434 (C–S), 973, 887 (*btz*C–H).

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