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2,2'-Bithiazolyl-*p*-*tert*-Butylcalix[4]arene Podands. Synthesis and Fluorescence Properties.

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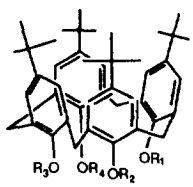
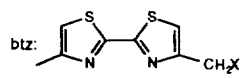
Abstract: Five new conic calix[4]arene-based podands incorporating the fluorescent 2,2'-bithiazole subunit have been synthesised and fully characterised. Comparative fluorescence studies shown a decrease of bithiazole I_{em} from the mono- to the tetra-substituted species. Two intramolecular deactivation processes and a "calixarene effect" have been proposed. Copyright © 1996 Published by Elsevier Science Ltd

In a recent report[1], we have described the synthesis of five conic bipyridyl podands integrating from one to four biheterocyclic subunits, grafted by means of ether linkages on *p*-*tert*-butylcalix[4]arene lower rim. These ligands have been prepared in order to study notably the effects of preorganisation of chelates around the calixarene main axis on their complexing behaviour towards transition metal cations. The preliminary complexation results have allowed the development of similar series incorporating, instead of the previously mentionned bipyridine, other kinds of heterocycles. Among them, beyond its double-site chelating property, the 2,2'-bithiazole (*btz*) has been choosen for its intrinsic blue fluorescence. The latter is known since a long time, like Vitachrom[2], a cellular biomarker, or as optical brightener in polymers[3]. Most of the simply functionnalised species luminesce at 380-400 nm with strong amplification in acidic medium, as well as when incorporated in macrobicyclic cryptate species[4]. We found of interest to study this specific property *vs* preorganisation and concentration around the calixarene lower rim.



A: R_1= R_2= R_3= R_4 = H
1: R_1= btz; R_2= R_3= R_4 = H
2: R_1= R_2 = btz; R_3=R_4 = H
3: R_1= R_3= btz; R_2= R_4 = H
4: R_1= R_2= R_3= btz; R_4 = H
5: R_1= R_2= R_3= R_4 = btz



8: X = H
7: X = O-(*p*-*tert*-But)C_6H_4
6: X = Br

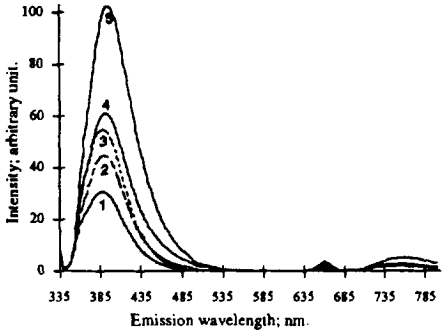
The synthetic strategy developed for this familly of podands was similar, for **1**, **2**, **3** and **5**, to the one described earlier[1]. **4**, instead of following the tiedous two-step process used for its bipyridyl parent, was directly prepared in one step using $BaO/Ba(OH)_2$ as base in DMF, according to Shinkai *et al*[5]. The synthetic procedure for the preparation of 4-bromomethyl-4'-methyl-2,2'-bithiazole **6** was not available in the literature and therefore **6** has been successfully synthesised by carefull radical bromination of the 4,4'-dimethyl-2,2'bithiazole **8**[6] in 35% yield. The usefull Tranaylis/Boeckelheide rearrangement method, as well as SeO_2 oxydation of CH_3 group were unefficient in the present case.

All podands were fully characterised[7], ^1H and ^{13}C-NMR showing notably, according to de Mendoza *et al.*[8], that the cone conformation was retained in all cases. ^1H-NMR studies shown that the calixarene moities, and the O-CH_2 links were similar to each corresponding bipyridyl analogues, indicating a quasi-inexistant influence of the substituants on the macrocyclic frame. In the aromatic parts of the spectra, heterocyclic protons were found as singlets in two main regions, 6.84-7.01 ($\Delta\delta$=0.17 ppm) and 7.30-8.22 ppm ($\Delta\delta$=0.92 ppm). The first series, weakly sensitive to structural changes was attributed to the terminal thiazole rings while the other one, more sensitive, was attributed to the linked units. In **4**, four singlets characterised the heterocycles, two of them integrating for 1 H at 6.84 and 8.22 ppm, corresponding to the central subunit. Mass analyses were performed with electrospray technique, positive mode, giving in all cases base peaks of the sodio-ionised species, accompanied by protonated forms. The respective UV absorption bands of each constituents of ligands were observed separately at 329±2nm for *btz* unit and at 281/288±2 nm for the calix platform. Increments of the ε values at 329 nm followed an approximatively linear relationship *vs* the number of heterocycles, but was accompanied by a slight band broadening.

For fluorescence studies, we first verified that **8**, **7** and **6**, then **1**, **2**, **3**, **4** and **5** displayed the expected

blue fluorescence pattern at *ca* 395 nm after irradiation at their respective absorption bands. For each species, the excitation spectrum was recorded and from the corresponding bands, final emission spectra were obtained. The absence of fluorescence emission for the calixarene platform was also checked in the case of its tetra-methyl ether derivative.

The first experiments have been performed using concentration ranges of 10^{-4}-10^{-5} mol dm^{-3}. At these values, the excitation wavelengths varied from 357 nm for **1** to 366 nm for **5** and the emission relative intensities were totally inconsistent with the number of *btz* units of each podand. This was correlated with a strong intermolecular deactivation generated by a collisional process due to the high experimental concentrations. An ideal concentration range giving for all systems an invariant excitation wavelength was found with **1** and **5** at 330 nm and *ca* 7.0 10^{-6} mol dm^{-3}; it was consistent with **2**, **3** and **4**.



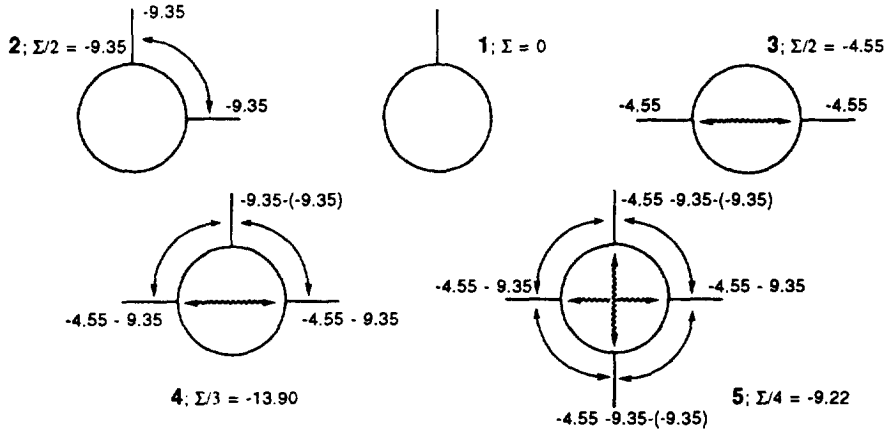
	λ_{em} (nm)	I_{em} (%)	[c]; 10^{-6}M	$I'_{em} = I_{em}.[5]/[c]$	I'_{em} /n btz (%)	loss *per* unit *vs* **1** (%)
5	396	100.0	7.12	100.00	25.00	9.10
4	394	63.0	6.98	64.30	21.40	12.75
3	387	56.0	6.74	59.15	29.60	4.55
2	389	47.0	6.74	49.70	24.80	9.35
1	386	30.7	6.88	34.15	34.15	0.00

Table: Fluorescence properties of bithiazole-containing calix[4]arene podands; 25°C; CH_2Cl_2; I_{exc}: 330 nm.

At this concentration range, the relative fluorescence intensity of **5** was chosen as reference (100%) Emission intensities decreased, as expected, from **5** to **1**. To compare precisely these values, we corrected them, as shown in table, in order to be at the concentration of **5**. Dividing for each podand the corrected emission intensity I'_{em} by the corresponding number of *btz* units shown in fact that the fluorescence intensity per unit (I'_{em}/n btz) decreased from **1** to **5**.

The loss of emission intensity per *btz* unit was calculated *vs* **1** for **2**, **3**, **4** and **5**. Focusing on these values shown that for **3**, in which the two *btz* units are diametrically displayed, the per unit loss is exactly the half of the loss in **5**. For **2**, in which the two *btz* units are close together, the loss is similar to **5**, while it takes the maximum value with **4**.

We supposed that at these relatively high dilutions, only an intramolecular deactivation process occurs, involving energy transfers between proximal and/or distal heterocycles as speculated in scheme 1.



Scheme 1: Hypothesis on intramolecular fluorescence deactivation in podands **1** to **5** (values in %).

Two types of through-space deactivation processes may be proposed, one occuring across the calixarene main axis (cases of **3**, **4** and **5**), the other one being lateral (cases of **2**, **4** and **5**). The deactivation process can not occur in **1**. Reference loss per unit have been formated from **2** and **3** and have been reported in **4** and **5**. We supposed that in **4**, the intermediate *btz* unit is playing as a simple lateral relay between the two opposed ones and was thus discarded from calculations; this afforded a loss per unit of 13.9%, close to the experimental value. Applying in **5** the same hypothesis on two opposed *btz* units gave an averaged loss per unit of 9.22%, similar to measurement. This implies nevertheless a discrimination between *btz* units during the light collection process which should be shared out over all the molecular electronic system.

We noted that at the same concentration, **1** fluoresces 18 times less than **8** and 6 times less than **7** which was synthesised[7] in order to study the influence of the phenoxy group on *btz* fluorescence. These last results indicate that this group is strongly deactivating (**7** *vs* **8**), but that an additional calixarene effect must be expected (**7** *vs* **1**). The influence of the free OH groups of **1** can be suspected in this sense but the *tetra* ether **5** shows inversely, *vs* **1**, a decrease of *btz* emission of *ca* 9%.

Addition of stoechiometric amount or excess of *p-tert*-butylphenol to **7** did not produce any extinction, indicating thus that, excepted intervention of an intramolecular regio-controlled effect, the OH groups do not interfere with the fluorescent heterocycles. The sus-mentionned calixarene effect was estimated at *ca* 84% from **7** and **1** and was recovered in the other podands.

Fluorescence enhancement and quenching of compounds **8** - **1** are presently under investigation.

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7. *General*: M.p., uncorrected. IR in KBr pellets, 1/ν in cm^{-1} (attribution). UV in CH_2Cl_2, ν in nm, (ε in $mol.dm^{-3}.cm^{-1}$). ^1H and ^{13}C-NMR in $CDCl_3$ + TMS, Bruker AC200 or AM300 (chemical shifts in ppm, J in Hz). Mass spectrometry: electrospray technique, positive mode. Elemental analyses performed at Ecole de Chimie, Montpellier. Fluorescence measurements were performed at 25°C on a Kontron SFM 25 spectrofluorimeter; Xenon lamp, PM R212. **6**: NBS (0.830 g, 4.59 mmol), **8** (1 g, 5.1 mmol) and CCl_4 (75 ml) were heated at 80°C during 0.5 h. After addition of benzoyl peroxide (0.1 g) the mixture was stirred during 2 h. in presence of light. After cooling, the N-succinimide formed was filtered off and the filtrate evapored to dryness. Chromatography (SiO_2, CH_2Cl_2) followed by cristallisation in hexane afforded pure **6** (0.49 g, 35%). White powder. M.p. 99°C. IR: 3100-3060(C-H stretch.); 2800-3000(CH_3, stretch.); 1500(C=C); 1400(C-S); 1210(CH_2-Br); 980, 880, 770, 670(C-H). UV: 331(15300). ^1H-NMR: 2.51(s, *Me*); 4.61(s, C*H*$_2$Br); 7.01(s, Ar*H*); 7.38(s, Ar*H*). ^{13}C-NMR: 17.27(*Me*); 26.80(*C*H_2Br); 116.3, 119.6(C(H), btz); 153.5, 154.5, 160.2, 162.2(C(2), C(2'), C(5), C(5'), btz). ES-MS: 276([M + H]$^+$), 195([M - Br]$^+$). $C_8H_7N_2S_2Br$ (275.19): *calc.* C 34.92, H 2.56, N 10.2, S 23.3; *found*: C 35.08, H 2.42, N 9.75, S 22.92.

7: From *p-tert*-butylphenol (0.055 g, 0.364 mmol), **6** (0.1 g, 0.364 mmol) and K_2CO_3 (0.055 g, 0.364 mmol) in dry acetone, 24 h at reflux. Treated with H_2O (30 ml), extracted with ether (20 ml) and recrystallised from methanol. 0.07 g, 56%. UV: 280 (sh, 2000); 326 (12000). ^1H-NMR: 1.30(s, *Me*$_3$C); 1.65(s, *Me*-btz); 2.51(s; OC*H*$_2$-btz); 6.99(s, btz*H*); 7.33(d, J=8.7, 2 Ar*H*); 7.40(s, btz*H*).

1: From **A** (0.3 g, 0.405 mmol), **6** (0.111 g, 0.405 mmol) and $NaHCO_3$ (0.034 g, 0.405 mmol) in refluxing MeCN (30 ml); 28 h. Purification: SiO_2, CH_2Cl_2/MeOH, 99:1. White powder (0.243 g, 71%). M.p. 204-206°C. IR: 3300(OH, br, strech.); 3100-3040(Me-btz, stretch.); 1500(C=C); 1400(C-S), 980, 880(btzC-H). UV: 281(sh, 10000), 288(11000), 329(16000).^1H-NMR: 1.20(s, 2 *Me*$_3$C); 1.21(s, 2 *Me*$_3$C); 2.51(s, *Me*-btz); 3.42, 4.24('q', AB, J_{AB}=13, 2 Ar-C*H*$_2$-Ar); 3.42,4.43('q', AB, J_{AB}=13.5, 2 Ar-C*H*$_2$-Ar); 5.36(s, OC*H*$_2$-btz); 6.97(d, J= 2.5, 2 Ar*H*); 6.98(s,btz*H*); 7.03(s, 2 Ar*H*); 7.06(d, J=2, 2 Ar*H*); 7.10(s, 2 Ar*H*); 7.92(s, btz*H*); 9.30(s, 2 O*H*), 10.06(s, O*H*). ^{13}C-NMR: 17.14(*Me*-btz); 31.23,

31.49(*Me*$_3$C); 32.27, 32.97(Ar-*C*H$_2$-Ar); 33.91, 33.99, 34.26(Me$_3$*C*); 73.52(O*C*H$_2$-btz); 116.10, 119.61(C(H), btz); 125.63, 125.72, 126.55(*Ar*H); 127.47, 128.01, 128.24, 133.54, 143.12, 143.62, 147.70, 148.42, 149.35(C_o, C_p, C_i, Ar); 152.75, 154.34, 160.43, 161.98(C(2), C(2'), C(5), C(5'), btz). ES-MS: 865.5([M + Na]$^+$); 844.5([M + H]$^+$). $C_{52}H_{62}O_4N_2S_2$ (843.19): *calc.* C 74.07, H 7.41, O 7.59, N 3.32; *found*: C 74.08, H 7.43, O 7.78, N 3.41.

2: From **A** (0.2 g, 0.27 mmol), **6** (0.163 g, 0.594 mmol) and NaH (0.053 g, 1.35 mmol) in anhydrous DMF (6 ml) at r.t., 2 h. Purification: SiO_2, CH_2Cl_2/MeOH, 98:2. White powder (0.08 g, 29%). M.p. 170°C. IR: 3300(OH, br, stretch.); 3100, 3040(Me-btz, stretch.); 1500(C=C); 1400(C-S); 980, 880(btzC-H). UV: 284(sh, 9200), 294(10800), 329(27000). ^{1}H-NMR: 1.14(s, 2 *Me*$_3$C); 1.19(s, 2 *Me*$_3$C); 2.47(s, 2 *Me*-btz); 3.28, 3.38(3 1/2AB, J_{AB}=13, 4H of Ar-C*H*$_2$-Ar); 4.20(1/2AB, J_{AB}=13, 2 H of Ar-C*H*$_2$-Ar); 4.37 (1/2AB, J_{AB}=13, 1 H of Ar-C*H*$_2$-Ar); 4.57(1/2AB, J_{AB}=13, 1 H of Ar-C*H*$_2$-Ar); 5.01, 5.35('q', AB, J_{AB}=12, 2 OC*H*$_2$-btz); 6.94(d, J=2, 4 Ar*H*); 6.95(s, 2 btz*H*); 7.01(d, J= 2, 2 Ar*H*); 7.03(d, J= 2, 2 Ar*H*); 7.78(s, 2 btz*H*); 8.97(s, 2 O*H*). ^{13}C-NMR: 17.16(*Me*-btz); 31.09(Ar-*C*H$_2$-Ar); 31.30, 31.56(*Me*$_3$C); 32.50, 32.78(Ar-*C*H$_2$-Ar); 33.91, 34.13(Me$_3$*C*); 73.09(O*C*H$_2$-btz); 115.85, 119.58(C(H), btz); 124.64, 125.33, 125.45, 126.16(*Ar*H); 127.70, 128.56, 133.23, 133.87, 142.42, 146.96, 149.04, 151.33(C_o, C_p, C_i, Ar); 153.76, 154.28, 160.53, 161.50(C(2), C(2'), C(5), C(5'), btz). ES-MS: 1076.4([M + K]$^+$); 1060.5([M + Na]$^+$); 1038.5([M + H]$^+$). $C_{60}H_{68}O_4N_4S_4$ (1037.46): *calc.* C 69.46, H 6.60, O 6.17, N 5.40; *found*: C 69.30, H 6.53, O 6.16, N 5.38.

3: From **A** (0.5 g, 0.675 mmol), **6** (0.390 g, 1.418 mmol) and K_2CO_3 (0.2g, 1.418 mmol) in refluxing MeCN (50 ml), 25 h. Purification: SiO_2, CH_2Cl_2/MeOH, 98:2. White powder (0.595 g, 85%). M.p. 165-166°C. IR: 3300(OH, br, stretch.); 3100, 3040(Me-btz, stretch.); 1500(C=C); 1400(C-S), 980, 880(btzC-H). UV: 286(sh, 11000); 290(14000); 328(31500). ^{1}H-NMR: 0.94(s, 2 *Me*$_3$C); 1.29(s, 2 *Me*$_3$C); 2.54(s, 2 *Me*-btz); 3.34, 4.32 ('q', AB, J_{AB}=13, 4 Ar-C*H*$_2$-Ar); 5.27(s, 2 OC*H*$_2$-btz); 6.81(s, 4 Ar*H*); 6.99(s, 2 btz*H*); 7.08(s, 4 Ar*H*); 7.24(s, 2 O*H*); 8.05(s, 2 btz*H*). ^{13}C-NMR: 17.29(*Me*-btz); 30.96(*Me*$_3$C); 31.55(Ar-*C*H$_2$-Ar); 31.70(*Me*$_3$C); 33.85, 33.96(Me$_3$*C*); 74.09(O*C*H$_2$-btz); 115.78, 117.58(C(H), btz); 125.12, 125.66(*Ar*H); 127.66, 132.49, 141.77, 147.42, 149.42, 150.53(C_o, C_p, C_i, Ar); 154.19, 154.37, 160.49, 161.76(C(2), C(2'), C(5), C(5'), btz). ES-MS: 1075.5([M + K]$^+$); 1059.5([M + Na]$^+$); 1038.5([M +H]$^+$). $C_{60}H_{68}O_4N_4S_4$ (1037.46): *calc.* C 69.46, H 6.60, O 6.17, N 5.40; *found*: C 69.31, H 6.48, O 6.52, N 5.80.

4: **A** (0.2 g, 0.27 mmol), Ba(OH)$_2$; 8H$_2$O, (0.255 g, 0.81 mmol) and BaO (0.124 g, 0.81 mmol) were mixed in dry DMF (5 ml) under N_2 during 1 h. After addition of **6** (0.233 g, 0.81 mmol), the mixture was stirred at r.t. during 25 h. The excess of NaH was carefully hydrolyzed by addition of MeOH (0.5 ml) followed by H_2O (40 ml). The resulting precipitate was filtered off, rinsed with H_2O, then dissolved in CH_2Cl_2 and dried (Na_2SO_4). Purification on SiO_2 (CH_2Cl_2/MeOH, 98:2) afforded pure **4**. White powder (0.205 g, 62%). M.p. 161°C. IR: 3300(OH, br, stretch.); 3100-3050(Me-btz); 1500(C=C); 1400(C-S); 980,880(btzC-H). UV: 284(11000); 294(sh, 15000); 329(44000). ^{1}H-NMR: 0.85(s, 2 *Me*$_3$C); 1.32(s, *Me*$_3$C); 1.34(s, *Me*$_3$C); 2.44(s, 2 *Me*-btz); 2.47(s, *Me*-btz); 3.15, 4.43('q', AB, J*AB*=13, 2 Ar-C*H*$_2$-Ar); 3.23, 4.32('q', AB, J_{AB}=13, 2 Ar-C*H*2-Ar); 4.81, 4.93('q', AB, J_{AB}=12, 2 OC*H*$_2$-btz); 5.14(s, OC*H*$_2$-btz); 6.40(s, O*H*); 6.57(d, J=2, 2 Ar*H*); 6.65(d, J=2, 2 Ar*H*); 6.84(s, btz*H*); 6.91(s, 2 btz*H*); 7.06(s, 2 Ar*H*); 7.15(s, 2 Ar*H*); 7.3(s, 2 btz*H*); 8.22(s, btz*H*). ^{13}C-NMR: 17.11, 17.20(*Me*-btz); 30.91(Ar-*C*H$_2$-Ar); 31.02, 31.56(*Me*$_3$C); 31.69(Ar-*C*H$_2$-Ar); 31.76(*Me*$_3$C); 33.76, 33.87, 34.18(Me$_3$*C*); 72.08, 72.66(O*C*H$_2$-btz); 114.98, 115.83, 119.19, 120.16(C(H), btz); 125.10, 125.68(*Ar*H); 128.46, 132.03, 132.68, 135.73, 141.49, 145.87, 146.22, 150.67, 150.78(C_o, C_p, C_i, Ar); 152.94, 153.89, 153.92, 153.99, 154.41, 159.11, 160.53, 160.97, 161.21(C(2), C(2'), C(5), C(5'), btz). ES-MS: 1253.5([M + Na]$^+$); 1232.3([M + H]$^+$). $C_{68}H_{74}O_4N_6S_6$ (1231.73): *calc.* C 66.31, H 6.06, N 6.82, O 5.19; *found*: C 66.50, H 6.00, N 6.81, O 5.38.

5: From **A** (0.2 g, 0.27mmol), **6** (0.3g, 1.09 mmol) and NaH (0.165g, 2.7 mmol) in dry DMF (5 ml), r.t., 2 h. Purification: SiO_2, CH_2Cl_2/MeOH, 97:3. White powder (0.165g, 43%). M.p. 186°C. IR: 3100-3040(Me-btz, stretch.); 1500(C=C); 1400(C-S); 980, 880(btzC-H). UV: 285(sh, 11000); 326 (52000). ^{1}H-NMR: 1.07(s, 4 *Me*$_3$C); 2.46(s, 4 *Me*-btz); 2.98, 4.40('q', AB, J_{AB}=12.5, 4 Ar-C*H*$_2$-Ar); 5.07(s, 4 OC*H*$_2$-btz); 6.79(s, 8 Ar*H*); 6.89(s, 4 btz*H*); 7.50(s, 4 btz*H*). ^{13}C-NMR: 17.14(*Me*-btz); 31.08(Ar-*C*H$_2$Ar); 31.42(*Me*$_3$C); 33.87(Me$_3$*C*); 71.67(O*C*H$_2$-btz); 115.61,119.73 (C(H), btz); 125.14 (*Ar*H); 133.97, 145.00, 152.38(C_o, *Cp*, C_i, Ar); 153.92, 154.95, 160.53, 160.91 (C(2), C(2'), C(5), C(5'), btz). ES-MS: 1448.5([M + Na]$^+$); 1427.5([M + H]$^+$). $C_{76}H_{80}O_4N_8S_8$ (1426.01): *calc.* C 64.01, H 5.65, O 4.49, N 7.86; *found*: C 64.04, H 5.63, O 4.77, N 7.71.

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