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Array of fluorescent chemosensors for the molecular recognition of halide anions on the basis of the stereoisomers of thiacalix[4]arene tetranaphthylamides

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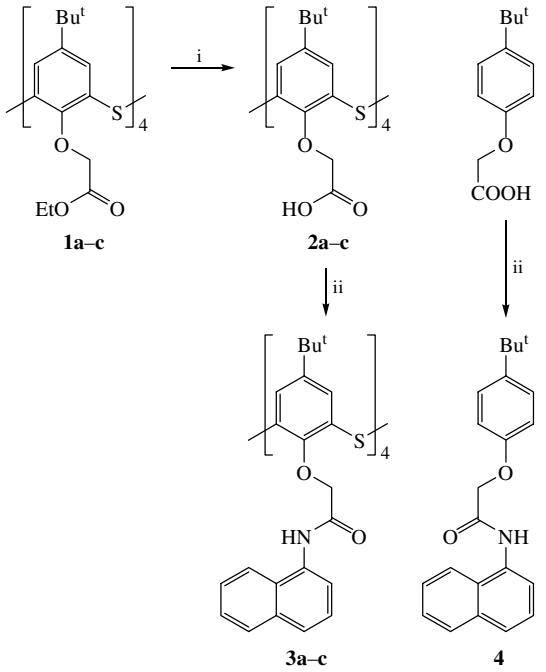
Three macrocyclic dye-labelled receptors were synthesised and structurally characterised.

The design of fluorescent molecular sensors is of importance in analytical chemistry, clinical biochemistry, medicine and environmental chemistry. Dye-labeled molecular sensors are generally composed of a fluorescent dye and a binding site connected to a suitable molecular platform, and are incorporated with a signaling mode for the fluorophore in response to the event at the binding site.[1–3] Calixarenes and thiacalixarenes have been successfully used for the design of anion hosts.[4,5] In particular, calix[4]arenes bearing amide substituents are capable of anion recognition because of analyte coordination to amide hydrogens.[6,7]



Scheme 1 *Reagents and conditions*: i, LiOH, THF/H_2O; ii, $SOCl_2$, reflux, 1 h, then NEt_3, 1-aminonaphthalene, CH_2Cl_2.

Miyano *et al.*[8] reported on the facile one-pot synthesis of three tetraester stereoisomers: *cone* **1a**, *partial cone* **1b**, 1,3-*alternate* **1c**, providing direct synthetic route to stereoisomers of tetrasubstituted at the lower rim thiacalix[4]arenes. It was shown that receptor properties of tetra-*O*-alkylated thiacalix[4]arenes towards a number of substrates (cations, anions and neutral molecules) depend on their conformation.[9] Thus, an array of sensors for different analytes could be constructed on the basis of tetrasubstituted thiacalix[4]arene stereoisomers, readily available by a two-stage synthesis from parent macrocycles **1a–c**.

Here, we report on the synthesis and structure characterization of three new fluorescent molecular sensors (stereoisomers **3a–c** of the tetranaphthylamide derivative of thiacalix[4]arene and the study of their receptor properties towards halide anions. Monomer naphthylamide **4** was synthesised in order to compare its binding properties with those of compounds **3a–c**.

Tetraesters **1a–c** were quantitatively hydrolysed to tetraacids **2a–c** by LiOH in aqueous THF followed by conversion to their acid chlorides and then were treated with 1-aminonaphthalene in the presence of triethylamine to give corresponding tetranaphthylamides **3a–c** (Scheme 1).† Overall yields are 79, 86 and 72% for compounds **3a**, **3b** and **3c**, respectively. Model compound **4** was obtained in a similar way from (4-*tert*-butylphenoxy)acetic acid.

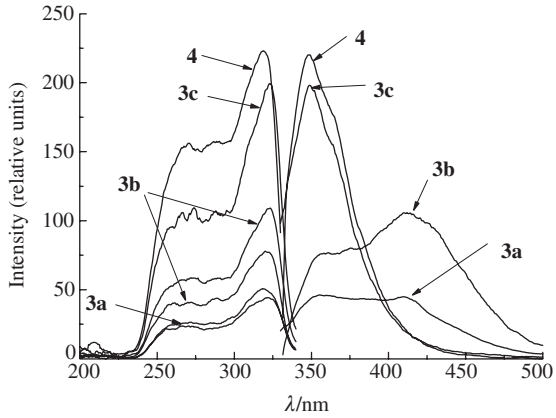


Figure 1 Emission (excitation wavelength 320 nm) and excitation spectra of compounds **3a–c** and **4** Emission was monitored at $\lambda = 350$ nm for excitation spectra of **3c** and **4**; for each of compounds **3a** and **3b** two excitation spectra are presented, monitored at $\lambda = 350$ nm and $\lambda = 410$ nm.

Fluorescent properties of compounds **3a–c** and **4** were studied in chloroform solutions under air-equilibrated conditions. Excitation spectra of compounds **3a–c** are identical with that of compound **4** and possess a maximum at 320 nm, related to the excitation of the naphthalene unit. Emission spectra of low-molecular-weight naphthylamide **4** and 1,3-*alternate* stereoisomer **3c** possess a maximum at 350 nm, which corresponds to the fluorescence of the naphthalene unit. The emission spectra of compounds **3a** and **3b** possess two maxima at 350 and 410 nm. Excitation spectra corresponding to both emission bands

† *General procedure for the synthesis of compounds* **2a–c**. Tetraester **1a–c** (1.00 g, 0.95 mmol) was dissolved in THF (20 ml); then, a solution of $LiOH·H_2O$ (0.54 g, 13.0 mmol) in water (14 ml) was added. The reaction mixture was incubated at room temperature with vigorous stirring until completion of reaction by TLC. Then, the reaction mixture was concentrated at a reduced pressure, a 2 M aqueous HCl (10 ml) was added; the white precipitate was collected by filtration, washed with water (3×20 ml) and dried *in vacuo* to yield corresponding tetraacid **2a–c**. ^{1}H NMR spectra and mp of compounds **2a–c** are identical to literature data.[2]

General procedure for the synthesis of compounds **3a–c**. A solution of tetraacid **2a–c** (1.00 g, 1.05 mmol) in $SOCl_2$ (10 ml, 140 mmol) was stirred at reflux for 1 h. Then, an excess of thionyl chloride was removed under a reduced pressure, the resulting chloroanhydride was dried under reduced pressure for 1 h at 85 °C. Chloroanhydride was transferred by 30 ml of dichloromethane into a flask containing a solution of 1-aminonaphthalene (1.00 g, 7.02 mmol) and NEt_3 (1.24 ml, 9.00 mmol) in 20 ml of dichloromethane. The reaction mixture was stirred under nitrogen at ambient temperature overnight. The reaction mixture was washed with 2 M aqueous HCl (10 ml), the aqueous layer was separated, washed with 3×20 ml dichloromethane, the combined organic layers were dried over 3 Å molecular sieves. The pure product was obtained by column chromatography (SiO_2) and eluted by dichloromethane–ethanol.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis[(*N-*naphthalen-1-ylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone)* **3a**. Yield 1.21 g (79%); mp 145–146.5 °C. IR (ν/cm^{-1}): 1266 (COC), 1683 (C=O), 2962 (Ar–H), 3296 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.18 (s, 36H, Bu^t), 5.08 (s, 8H, OCH_2CO), 7.09–7.12 (m, 4H, Ar), 7.21–7.26 (m, 8H, Ar), 7.30–7.32 (m, 4H, Ar), 7.45–7.52 (m, 12H, Ar), 7.61–7.62 (m, 4H, Ar), 7.74–7.76 (m, 4H, Ar), 9.41 (br. s, 4H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.1, 34.4, 75.1, 121.7, 122.4, 125.5, 125.7, 126.2, 126.4, 127.9, 128.2, 128.3, 131.3, 133.9, 135.2, 147.8, 157.4, 167.3. MALDI-TOF MS (matrix, 4-nitroaniline), *m/z*: 1475 $[M + Na]^+$. Found (%): C, 72.40; H, 5.98; N, 3.87; S, 8.88. Calc. for $C_{88}H_{84}N_4O_8S_4$ (%): C, 72.70; H, 5.82; N, 3.85; S, 8.82.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis[(*N-*naphthalen-1-ylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (partial cone)* **3b**. Yield 1.32 g (86%); mp 159–160.5 °C. IR (ν/cm^{-1}): 1266 (COC), 1653 (C=O), 2959 (Ar–H), 3261 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.99 (s, 18H, Bu^t), 1.23 (s, 9H, Bu^t), 1.38 (s, 9H, Bu^t), 4.41 (d, 2H, OCH_2CO, $^2J_{HH}$ 14.8 Hz), 4.81 (s, 2H, OCH_2CO), 5.14 (s, 2H, OCH_2CO), 5.25 (d, 2H, OCH_2CO, $^2J_{HH}$ 14.8 Hz), 6.86–6.88 (m, 2H, Ar), 6.98–7.00 (m, 2H, Ar), 7.15–7.18 (m, 2H, Ar), 7.20–7.27 (m, 7H, Ar), 7.37–7.42 (m, 2H, Ar), 7.46–7.47 (m, 2H, Ar), 7.50–7.55 (m, 4H, Ar), 7.58 (d, 2H, Ar, $^4J_{HH}$ 1.9 Hz), 7.60–7.65 (m, 3H, Ar), 7.77 (s, 2H, Ar), 7.79–7.81 (m, 2H, Ar), 7.89–7.91 (m, 3H, Ar), 7.97–7.99 (m, 3H, Ar), 8.45 (br. s, 1H, NH), 9.69 (br. s, 2H, NH), 10.22 (br. s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.9, 31.0, 31.4, 34.2, 34.4, 34.5, 70.4, 73.2, 73.9, 120.5, 120.7, 121.9, 122.1, 122.5, 122.7, 125.2, 125.3 (two overlapping peaks), 125.4, 125.6, 125.7 (two overlapping peaks), 126.1, 126.2, 126.4, 126.5 (two overlapping peaks), 126.6, 126.7, 126.9, 127.1, 128.1 (two overlapping peaks), 128.2 (two overlapping peaks), 128.6, 128.7, 130.7, 131.6 (two overlapping peaks), 133.2, 133.8, 134.0, 134.4, 135.2, 135.9, 136.2, 146.8, 147.7, 148.0, 155.5, 157.6, 159.0, 167.0, 167.4, 167.6. MALDI-TOF MS (matrix, 4-nitroaniline), *m/z*: 1475 $[M + Na]^+$. Found (%): C, 72.03; H, 6.15; N, 3.84; S, 9.05. Calc. for $C_{88}H_{84}N_4O_8S_4·EtOH$ (%): C, 72,07; H, 6,05; N, 3,74; S, 8,55.

5,11,17,23-Tetra-tert-*butyl-25,26,27,28-tetrakis[(*N-*naphthalen-1-ylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate)* **3c**. Yield 1.11 g (79%); mp 148.5–150 °C. IR (ν/cm^{-1}): 1264 (COC), 1682 (C=O), 2955 (Ar–H), 3284 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.83 (s, 36H, Bu^t), 4.26 (s, 8H, OCH_2CO), 7.52–7.56 (m, 12H, Ar), 7.60 (s, 8H, Ar), 7.79–7.81 (m, 4H, Ar), 7.83–7.84 (m, 4H, Ar), 7.91–7.93 (m, 4H, Ar), 7.97–7.99 (m, 4H, Ar), 9.63 (br. s, 4H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.5, 34.1, 71.9, 121.8, 121.9, 125.5, 126.1, 126.4, 126.5, 127.9, 128.1, 128.7, 131.9, 132.9, 134.3, 148.6, 156.7, 167.2. MALDI-TOF MS (matrix, 4-nitroaniline), *m/z*: 1475 $[M + Na]^+$. Found (%): C, 72.27; H, 6.10; N, 3.83; S, 8.39. Calc. for $C_{88}H_{84}N_4O_8S_4·EtOH$ (%): C, 72.07; H, 6.05; N, 3.74; S, 8.55.

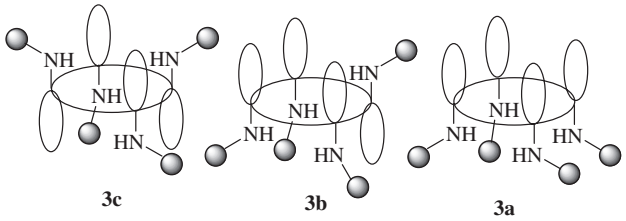


Figure 2 Schematic structures of compounds **3a–c**. Ellipses stand for benzene rings and gray balls, for naphthalene units.

showed that the origin of the bands is naphthalene fragment fluorescence (Figure 1).

Difference in emission spectra of macrocyclic compounds **3a–c** is caused by the chemical environment of fluorogenic groups in these stereoisomers (Figure 2). In compounds **3a** (*cone*) and **3b** (*partial cone*), four or three naphthalene groups are located on the same side of a macrocyclic ring and thus emission at 410 nm could be assigned to the formation of an excimer between two naphthalene moieties.[10] The ratio of fluorescence intensities at 350 and 410 nm for compounds **3a** and **3b** did not change in the test concentration range (10^{-3}–10^{-5} M). Therefore, the excimer formation is an intramolecular process. In compound **3c** (1,3-*alternate*), pendant naphthyl groups are isolated from each other by bulky *tert*-butyl residues and benzene rings of the macrocycle; thus, the only emission band of an isolated naphthalene unit is present in the fluorescence spectrum of compound **3c**.

Binding properties of compounds **3a–c** and **4** towards halide anions with respect to fluorescence changes were tested using a 500-fold excess of tetrabutylammonium halide in chloroform solution (Figure 3). Influence of halide anions on the fluorescence spectra of compounds **3a–c** is different.

For I^-, which is a well known quenching heavy anion,[11] a decrease of fluorescence intensity is observed in emission spectra of all macrocyclic receptors **3a–c** and model compound **4** upon addition of Bu_4NI.

Monomer emission in the fluorescence spectrum of compound **3c** is deteriorated in the presence of the fluoride anion, while addition of chloride and bromide anions does not cause changes in the emission spectrum. This is presumably caused by steric hindrance of amide moieties, shielded by neighbouring Bu^t groups and benzene rings of the parent macrocycle, so bulkier ions (Cl^- and Br^-) are not bound. Interestingly, calix[4]-arene amide in 1,3-*alternate* conformation is also selective for the fluoride anion.[4]

A monomer emission band (350 nm) in the fluorescence spectrum of *cone* stereoisomer **3a** is greatly increased in the case of interaction with F^- and, to a lesser extent, Cl^-.

Partial cone conformer **3b** gives two different responses: enhancement of monomer emission and deterioration of excimer emission for F^- and Cl^-, and a decrease of the excimer emission band for Br^-.

Fluorescence spectrum of model compound **4** remains unchanged upon addition of halide anions (except for unspecific quenching by the iodide anion); thus, a macrocyclic effect occurs through the introduction of naphthylamide moieties into a thiacalix[4]arene platform.

Thus, the study of receptor properties of fluorescent sensors showed that 1,3-*alternate* stereoisomer **3c** recognises F^-; *cone* stereoisomer **3a** gives specific responses to F^- and Cl^-, while

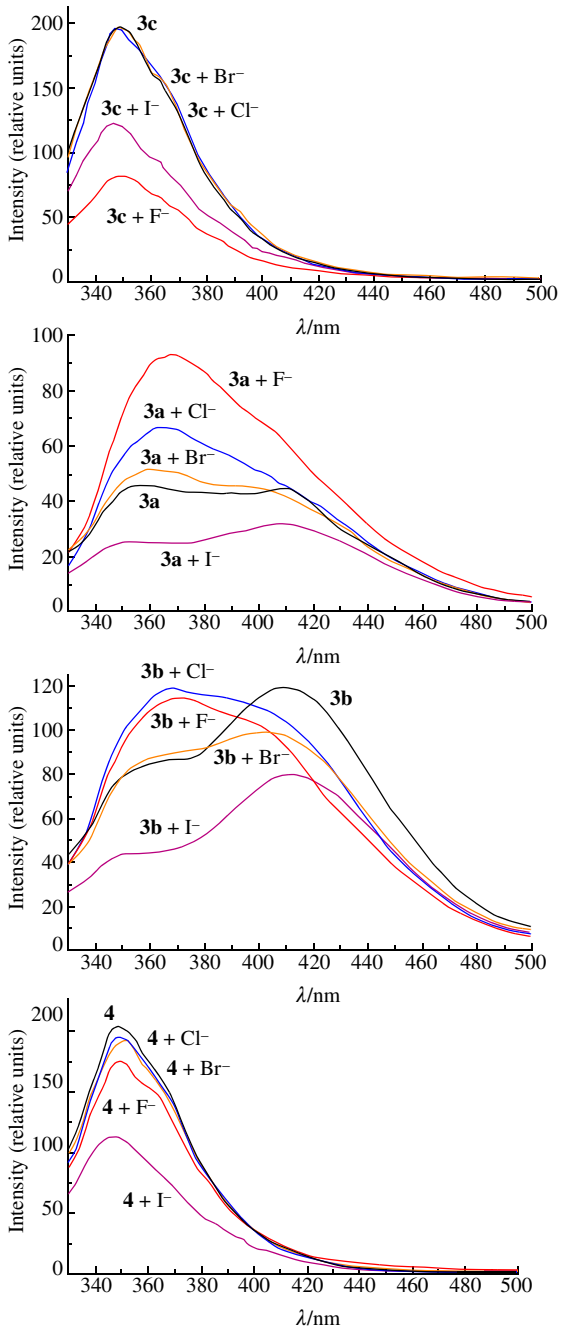


Figure 3 Changes of fluorescence spectra upon addition of Bu_4N halides ($CHCl_3$, $c_{ligand} = 10^{-4}$ M for compounds **3a–c**, $c_4 = 4\times10^{-4}$ M, $c_{Bu_4NX} = 0.05$ M). $\lambda_{ex} = 320$ nm.

partial cone conformer **3b** could discriminate F^- and Cl^- from Br^-. Thus, thiacalix[4]arene tetranaphthylamides **3a–c** could be utilised in fluorescent sensor array construction for halide anion recognition within a physiological (millimolar) range of concentrations, which is important in both chemical analysis and life sciences. Ratiometric sensors for halide anions may be created on the basis of *cone* **3a** and *partial cone* **3b** stereoisomers because of intramolecular excimer formation.

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2-(4-tert-*Butylphenoxy)*-N-*naphthalen-1-ylacetamide* **4**. Yield 0.62 g (77%); mp 178–180 °C. IR (ν/cm^{-1}): 1267 (COC), 1666 (C=O), 2963 (Ar–H), 3251 (NH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (s, 36H, Bu^t), 4.76 (s, 8H, OCH_2CO), 7.00–7.03 (m, 2H, Ar), 7.39–7.42 (m, 2H, Ar), 7.48–7.51 (m, 3H, Ar), 7.71–7.74 (m, 2H, Ar) 7.86–7.88 (m, 1H, Ar), 8.05–8.07 (m, 1H, Ar), 8.78 (br. s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.5, 34.2, 67.9, 114.3, 120.2, 120.4, 125.8, 126.0, 126.1, 126.5, 126.8, 128.8 (two overlapping peaks), 131.2, 134.1, 145.4, 154.8, 167.0. MS (ESI), *m*/*z*: 334.20 $[M + H]^+$. Found (%): C, 78.95; H, 7.14; N, 4.61. Calc. for $C_{22}H_{23}NO_2$ (%): C, 79.25; H, 6.95; N, 4.20.

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