Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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Online publication date: 29 October 2010

To cite this Article Csokai, Viktor and Bitter, István(2004) 'Unprecedented Cyclizations of Calix[4]arenes with Glycols under the Mitsunobu Protocol. Part 4. An Expedient Route to Thiacalix[4](Aza and Thia)Crowns', Supramolecular Chemistry, 16: 8, 611 — 619
To link to this Article: DOI: 10.1080/10610270412331318818
URL: http://dx.doi.org/10.1080/10610270412331318818

Supramolecular Chemistry, December 2004 Vol. 16 (8), pp. 611–619

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Unprecedented Cyclizations of Calix[4]arenes with Glycols under the Mitsunobu Protocol. Part 4. An Expedient Route to Thiacalix[4](Aza and Thia)Crowns

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Received (in Southampton, UK) 23 August 2004; Accepted 23 September 2004

The Mitsunobu cyclization of *p-t*-butylthiacalix[4]arene with glycols was expanded to oligoethylene glycol analogues composed of O, S and N atoms in the chain. In this way a number of 1,3-thiacalix[4]monocrowns have been synthesized, offering simple and general access to a large variety of crowned thiacalixarenes. The binding properties of some ligands towards transition metal cations have been studied by ^{1}H NMR, UV/Vis spectroscopic and potentiometric methods.

Keywords: Thiacalix[4](O,S,N)crowns; Cyclizations; Glycols; Mitsunobu reaction; Complexation

INTRODUCTION

In the past decade a large number of supermolecules combining the unique properties of calixarenes and crowns have been described [1,2] and applied to analytical and separation chemistry [3,4]. These studies have been expanded to thiacalixcrowns, and recently a series of distally and proximally bridged mono- and bis-crown-5 and -6 ethers have been synthesized and their metal ion complexing abilities assessed [5–9]. A common feature of the synthesis of calixcrowns is the base-promoted cyclization of calixarenes or of the thia analogues with oligoethylene glycol ditosylates [1]. The outcome of the reaction (bridging pattern, regio- and stereocontrol) is strongly dependent on the cyclizing agents and the template effect of the cations of the bases used. Alkali carbonate-mediated ring closures lead to 1,3-bridged calixcrowns in cone or 1,3-alternate conformations and generally require 1–14 days heating of the reactants in MeCN. 1,2-Bridging can be attained with stronger bases (NaH, alkali alcoholates) under milder conditions and shorter times [10,11]. These protocols work with calix[4]arene tetrols where mono- and biscrowns can be selectively obtained. The cyclization of thiacalixarene counterparts, however, cannot be stopped effectively at the mono-stage, only biscrowns are available by this approach [6,9].

Seeking a general method for the synthesis of thiacalixmonocrowns, the Mitsunobu reaction [12–14] was found to fulfil this requirement. In our previous communication the unexpectedly selective diametrical ring closure of *p-t*-butylthiacalix[4]arene (TCA) and the calix[4]arene counterpart (CA) with oligoethylene glycols under Mitsunobu conditions was reported [15]. With the aid of this simple and mild method, 1,3-calix[4]crown-4, -5 and -6 derivatives **I** were accessible in yields of 40–60%, which are comparable to those of the classical templated procedures (Fig. 1[15]).

In light of our results it is surprising that this extremely effective alkylation has not been utilized in calixarene chemistry, apart from two literature examples [16,17]. Even the Mitsunobu cyclization of diphenols with glycols has remained unexplored; only a side reaction between 1,1′-bi-2-naphthol and a 1,3-diol derivative referred to cyclic products [18]. In this paper our earlier results reported briefly for the Mitsunobu cyclizations of calix[4]arenes [15,19] are summarized to provide a reasonable explanation for the mechanism; in addition, the generalization of the method is supported by a number of new examples in the series of thiacalix[4]crowns.

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ISSN 1061-0278 print/ISSN 1029-0478 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10610270412331318818

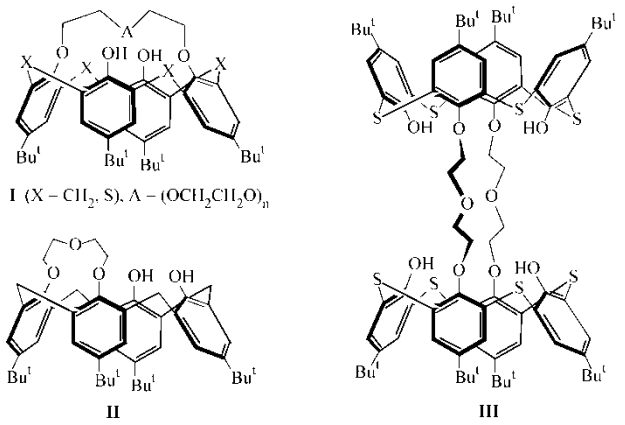


FIGURE 1 Products obtained in the Mitsunobu reaction of calix[4]arenes and oligoethylene glycols .

RESULTS AND DISCUSSION

Our results obtained with glycol homologues [15] suggested that the intra- vs. intermolecular reaction was controlled either by the chain lengths of glycols or by the cavity size of calixarenes (TCA > CA). The role of the latter was reflected by the reactions performed with tri-, tetra- and pentaethylene glycol, respectively. While TCA reacted with each glycol affording 1,3-thiacalix[4](crown-4, -5, -6) derivatives **I** [X = S, A = $(OCH_2CH_2)_{1-3}O$], CA gave the respective crowns **I** [X = CH_2, A = $(OCH_2CH_2)_{1,2}O$] only with tri- and tetraethylene glycol, but failed to cyclize with the longer homologue. Significant difference in the behaviour of TCA and CA was observed towards the short-chain diethylene glycol resulting in dimer **III** vs. 1,2-calix[4]crown-3 **II** (Fig. 1).

Proposed Cyclization Pathways for the Mitsunobu Reaction of Calix[4]arenes and Glycols

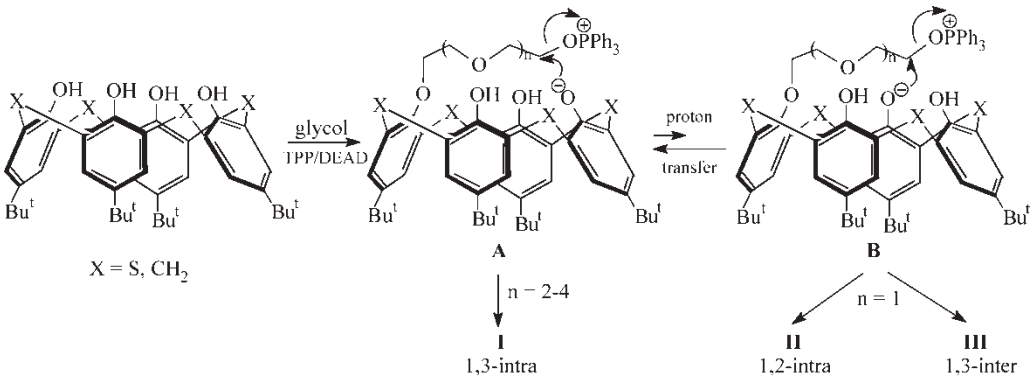
The selective and rapid formation of calix[4]crowns poses two interesting questions. (1) Why and when are the cyclizations preferred to intermolecular couplings? (2) Why do these reactions involving two consecutive steps take place more easily than the 1,3-dialkylation [14] performed with simple alcohols? Both questions can be answered by the considerations outlined in Scheme 1.

We suppose that after the first alkylation step, a betaine-type intermediate **A** is predominantly formed as its phenolate anion is stabilized by two hydrogen bonds of the adjacent OHs. A similar betaine intermediate was detected at −70°C during the selective 3-*O*-alkylation of the endiol moiety in L-ascorbic acid [20]. Intermediate **A** via proton transfer can be equilibrated to a certain extent with the **B** form. When the chain in intermediate **A** is sufficiently long, the terminal electrophilic site is attacked by the distal phenolate resulting in 1,3-ring closure (X = S, CH_2; $n = 2 - 4$). The preference of the intramolecular reaction may be facilitated by the adjacent OH groups keeping the chain in the vicinity of the rim via bifurcated H-bonds with the etheric oxygens. In the case of a short glycolic chain ($n = 1$) where the adjacent phenolate in intermediate **B** (X = CH_2) can still be reached, the intramolecular coupling is also preferred, resulting in 1,2-calix[4]-crown-3 **II**. This term is not fulfilled with the thia counterpart, where intermediate **A** (X = S) is stabilized by self-coupling to afford dimer **III**.

The high rate of cyclizations (0.5–1 h, RT) [15] compared to the 1,3-dialkylation with alcohols (24 h, RT) [14] may be due to the reactive betaine intermediate (it cannot be formed with alcohols), in addition to the intra- vs. intermolecular pathway accompanied by a large entropy loss.

The 'H-bonded template' hypothesis as a governing principle of cyclization was not supported by the reactions performed with calix[4]arene and 1,*n*-diols ($n = 6, 8, 10$), where etheric oxygens as H-bond acceptors in the chain are not available (Fig. 2).

CA and C_6–C_{10} diols possessing comparable chain lengths with the respective oligoethylene glycols gave similar 1,2- or 1,3-bridged products **IV**, **V** and **VI** [19], evidencing that here the regioselectivity is primarily controlled by the fitting between the chain length of the diol and the intramolecular distances of the calix[4]arene OHs. However, the analogous



SCHEME 1 Cyclization pathways of calix[4]arenes and oligoethylene glycols in the Mitsunobu reaction.

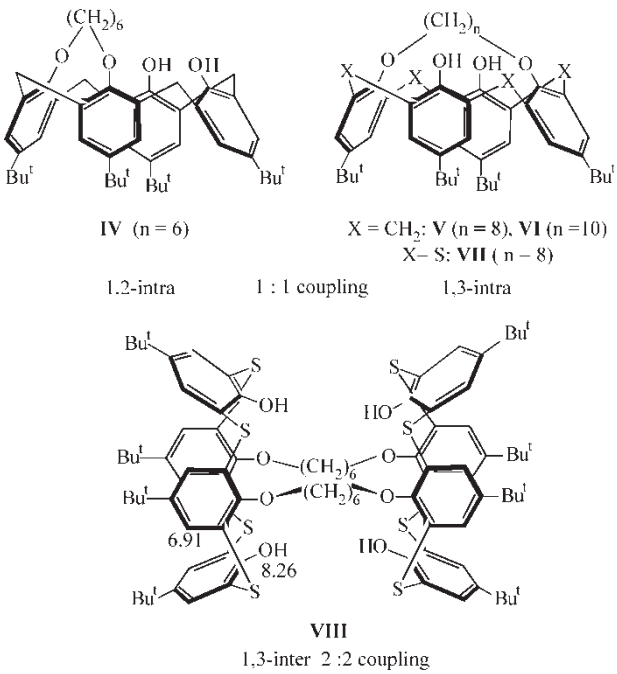


FIGURE 2 Products obtained in the Mitsunobu reaction of calix[4]arenes and 1,*n*-diols [19].

reactions with TCA do not allow straightforward conclusions to be drawn. In this case intra- and intermolecular couplings were taking place simultaneously, affording intractable mixtures. Only a small amount of 1,3-bridged molecule **VII** (22%) and dimer **VIII** (27%) could be separated and identified from the reactions with 1,8-octanediol and 1,6-hexanediol, respectively. These negative results can be attributed either to the lack of the beneficial 'H-bonded template' (which may work with TCA and oligoethylene glycols) or to the inadequate steric arrangements of the reactive sites in the open-chain intermediate of TCA caused by the 15% larger cavity compared to CA.

To collect further data on the reactivity of TCA, the scope of the Mitsunobu cyclizations was expanded to a series of tetra- and pentaethylene glycol analogues with N and S atoms in the chain. As the success of the classical templated ring closures with the ditosylates of aza- and thiaglycols is uncertain, this approach was expected to provide a general access to a wide choice of thiacalix[4]monocrowns.

Synthesis of 1,3-Thiacalix[4](O,S, O,N and O,S,N) Crowns

The reactions were performed at room temperature in toluene with *p*-*t*-butylthiacalix[4]arene **1** using glycols **2**–**9** with the molar ratio of TCA/glycol/(TPP/DEAD) = 1:1.5:(3/3). In all cases monocrowns were obtained exclusively in a fast reaction (0.5–1 h) and in yields of 35–77% (referring to a 1 mmol scale) (Scheme 2).

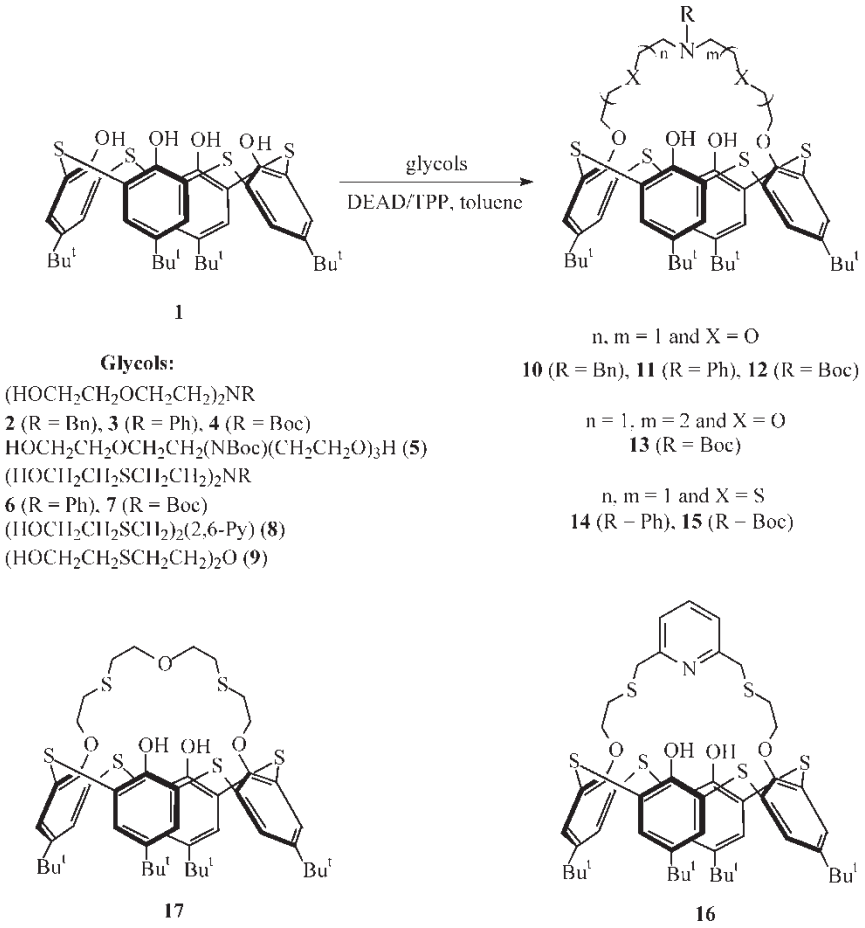
As expected, all monocrowns exist in cone conformation as described previously for the analogues **I** [15]. The C_{2v} symmetry of compounds **10**, **11**, **14**, **16** and **17** is reflected by the simple ^{1}H NMR spectra exhibiting one OH, two ArH and two Bu^t signals. The N-Boc derivatives **12**, **13** and **15** display more complicated signal patterns because of the restricted rotation of the Boc group, in addition to the disymmetric azacrown ring in **13**. It should be noted that the majority of these crowns are unprecedented even in calix[4]arene chemistry.

Several thiacalix[4]crowns prepared in this work were subjected to O-alkylations to obtain ionophores in 1,3-alt conformation and to improve the lipophilicities. Both features were thought to be advantageous for potential analytical applications. Thus, ligands **11**, **14** and **17** were propylated under basic conditions (PrI/Cs_2CO_3, MeCN, 80°C) to afford 1,3-alt **18**–**20**. The alkylation of **16** was carried out with *n*-octanol under the Mitsunobu protocol to avoid the quaternization of the pyridine moiety. Ligand **21** also exists in the 1,3-alt conformation as shown earlier for all tetraalkylated thiacalixarenes prepared by the Mitsunobu reaction [14] (Scheme 3).

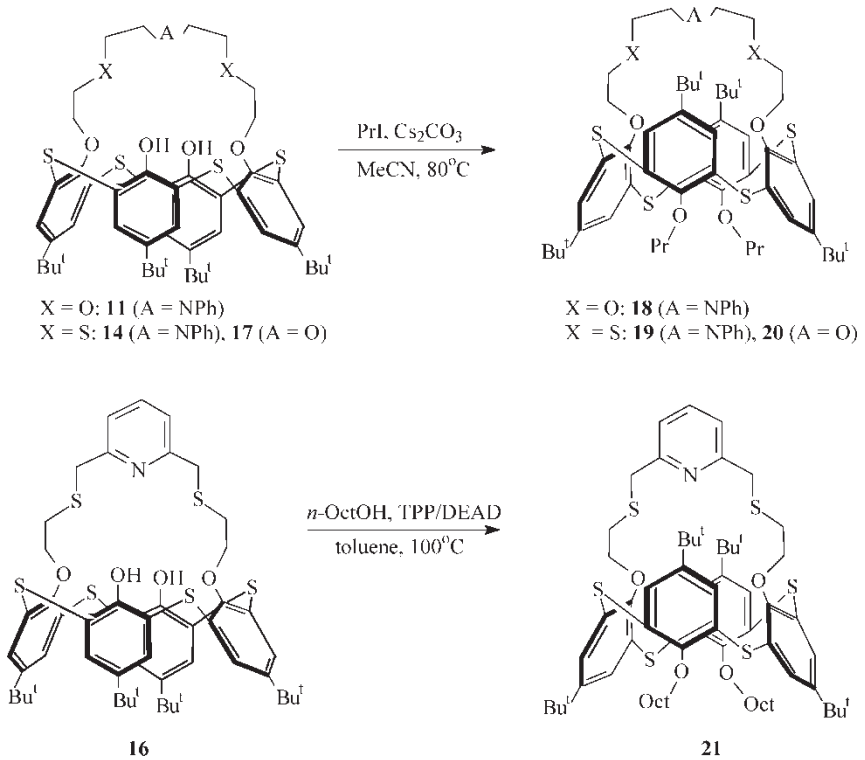
Preliminary Complexation Studies

The O_3S_2 and O_2S_2N macrocyclic ligands were expected to bind soft cations, such as Ag^+, Zn^{2+}, Hg^{2+}, Cd^{2+}, Cu^{2+}, etc. Therefore, the cation binding properties of ionophores **20** and **21** were investigated by ^{1}H NMR in $CDCl_3$. Upon addition of $AgBF_4$ the OCH_2 and SCH_2 signals of **20** were shifted downfield by 0.5–0.8 ppm. More extensive downfield shifts were found in the spectrum of **21** when $Zn(ClO_4)_2$ was added (Fig. 3). These changes are indicative of complex formation.

As part of our ongoing programme to synthesize chromoionophores for developing optical sensors, we have studied the optical properties of different chromophore groups (2,4-dinitrophenylazo, pyridinium, indophenol) introduced into various calix[4]arenes including bridged derivatives [21–24]. Ligands **18** (O_4N_1) and **19** ($O_2S_2N_1$) seemed to be suitable to supply the 4-nitrophenylazo signalling group in the anilino moiety (Scheme 4). Although the de-*t*-butylated chromogenic and fluorogenic 1,3-alt-calix[4]azacrown-5 counterparts in MeCN solution were reported to give optical responses to alkali cations [25–28], the visible spectrum of our analogous **22** scarcely changed upon addition of alkali salts. We do not believe that the steric hindrance of the *t*-butyl groups is responsible for the lack of complexation [6,7], but that the larger intramolecular distance between the distal



SCHEME 2 Synthesis of thiacalix[4]crowns containing various hetero atoms in the ring under the Mitsunobu protocol.



SCHEME 3 Alkylations of thiacalix[4]crowns under different conditions.

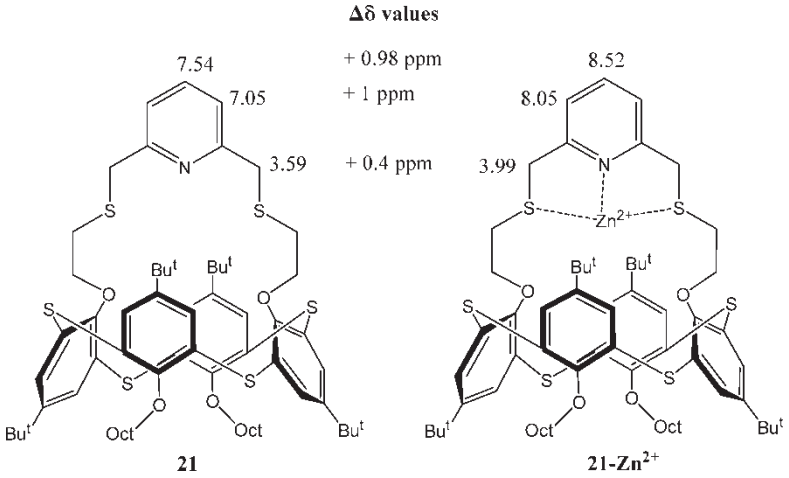


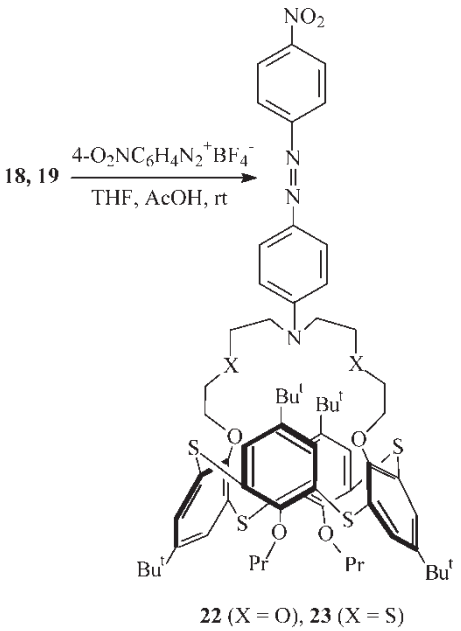
FIGURE 3 ^{1}H NMR shifts of **21** (in $CDCl_3$) on addition of $Zn(ClO_4)_2$.

pillar positions in thiacalix[4]crowns than that in the analogous calix[4]crowns is responsible. This structural feature results in a less flexible crown ring of **22**, which is still capable of capturing alkali cation, but instead it penetrates into the cavity where it is stabilized by π-cation interaction. Thus, the cation will be too far from the nitrogen atom of the azacrown ring, and consequently the visible spectrum remains unaffected.

By contrast, the O_2S_2N ligand **23** containing soft sulfur atoms in the vicinity of the signalling group responded to several transition metal cations in acetone solution. The absorption maximum at 456 nm was not affected by Cd^{2+} and Cu^{2+} ions (in the latter case the absorbance was markedly decreased), but upon addition of Ag^+ and Hg^{2+} salts, 20 and 16 nm hypsochromic shifts were observed. The most significant optical changes were found in the presence of Zn^{2+} ions, resulting in absorption maxima at 522 and 546 nm (Fig. 4). The large bathochromic shifts, visible to the naked eye, require further quantitative measurements to obtain deeper insight into the binding process.

As the preliminary qualitative experiments revealed the distinct binding properties of the O_2S_2N crown-5 ionophores, a PVC membrane electrode was fabricated from the most lipophilic ligand **21** and the ion-selectivities were determined by potentiometric transduction. In contrast to the strong binding of Zn^{2+} detected by NMR measurements in solution (Fig. 3), the liquid membrane electrode based on **21** exhibited Cu^{2+} selectivity (Table I).

The potentiometric data clearly show an excellent Cu^{2+} selectivity over a series of mono- and divalent cations, except for Pb^{2+}. Further studies including a complete electroanalytical evaluation are currently under way in our laboratory.



SCHEME 4 Thiacalixcrown chromoionophores with O_4N and O_2S_2N binding sites.

CONCLUSIONS

The regioselectivity of the Mitsunobu cyclization of *p-t*-butylcalix[4]arenes with oligoethylene glycols has been studied and a mechanistic pathway was suggested to describe the outcome of the reaction. The scope of this ring closure was expanded to a series of aza and thia analogues, and a number of novel 1,3-thiacalix[4]aza- and thia-crowns were synthesized. The method provides a new, rapid and easy method to access to crowned thiacalixarenes. Part of the macrocycles was further transformed to ionophores (with or without chromogenic function) and preliminary binding studies were carried out to estimate the ion-sensing properties by ^{1}H NMR, UV/Vis spectroscopic and potentiometric methods.

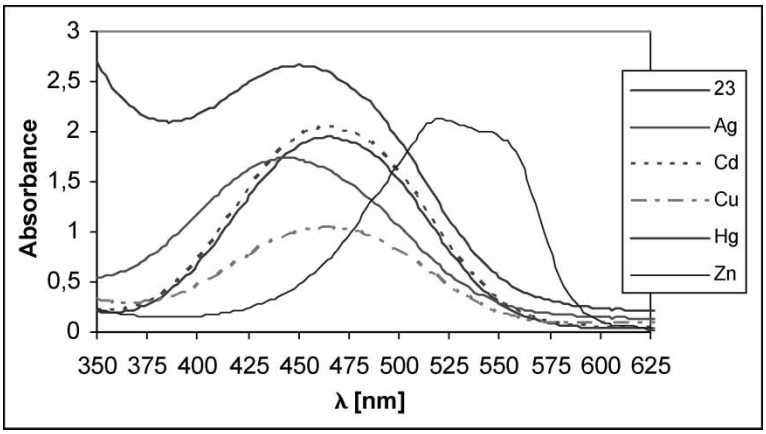


FIGURE 4 Optical responses of **23** to transition metal salts in acetone, $[L] = 5 \times 10^{-5}$ M, $[M^+] = 5 \times 10^{-3}$ M.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500/125 MHz on a Bruker Avance DRX-500 spectrometer. FAB mass spectra were obtained (frequently in the presence of a mixture of alkali picrates) on a Finnigan MAT 8430 spectrometer (ion source temperature: 25°C, matrix: *m*-nitrobenzyl alcohol, gas: xenon, accelerating voltage: 9 kV). UV/VIS spectra of the chromoionophores were recorded on a HP 8452A spectrophotometer. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade and used without further purification.

TCA **1** [29] and DEAD [30] were synthesized as described in the literature. (Caution! DEAD may explode if exposed to shock, friction or heating.) Glycols **2** [31], **3** [32] and **4**–**9** [33] were prepared according to the literature or by analogy. The synthesis and structure determination of compounds **I**–**III** and **IV**–**VIII** are available in our recent communications [15,19].

General Procedure for the Synthesis of Thiacalixcrowns 10–17

To the stirred mixture of **1** (0.72 g, 1 mmol), TPP (0.8 g, 3 mmol) and glycols **2**–**9** (1.5 mmol) in 20 mL toluene, a 40% toluene solution of DEAD (1.3 mL, 3 mmol) was added at room temperature and allowed to react for 0.5–1 h. The solvent was then removed under reduced pressure and the residue was triturated with MeOH to remove by-products. The insoluble portion was then purified by chromatography on silica with hexane:EtOAc 9:1 eluent to give white solids.

TABLE I Potentiometric selectivities ($\log K_{M^+/Cu^{2+}}$) of ligand **21** measured in a PVC membrane electrode

Na^+	NH_4^+	Ca^{2+}	Mg^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
−3.44	−2.59	−4.01	−3.23	−3.01	−1.42	−0.17

Plasticizer: *o*-NPOE, lipophilic additive: K-tetrakis(*p*-chlorophenyl)borate (70 mol%), $[M^+] = 10^{-1}$–10^{-4} M, pH 5.0.

N-Benzyl-(O_4N)crown **10** (30%), mp 138–142°C; ^{1}H NMR: δ 8.07 (s, 2H, O*H*), 7.68 (s, 4H, Ar*H*), 7.36 (m, 2H, Ar*H*), 7.23 (m, 3H, Ar*H*), 6.92 (s, 4H, Ar*H*), 4.72 (t, 4H, OCH_2), 4.06 (t, 4H, OCH_2), 3.83 (t, 4H, OCH_2), 3.73 (s, 2H, NCH_2Ar), 2.92 (t, 4H, NCH_2), 1.34 (s, 18H, Bu^t), 0.77 (s, 18H, Bu^t); ^{13}C NMR: δ 155.9, 155.7, 147.7, 142.3, 136.3, 134.6, 132.5, 129.1, 128.7, 128.1, 126.8, 122.1, 120.5, (Ar), 73.3, 69.8, 69.7 (O*C*H$_2$), 61.1 (N*C*H$_2$Ar), 53.2 (N*C*H$_2$), 34.4, 34.2 (*C*(CH$_3$)$_3$), 31.7, 31.0 (C(*C*H$_3$)$_3$); anal. calcd. for $C_{55}H_{69}NO_6S_4$ (968.39): C, 68.22; H, 7.18; N, 1.45; S, 13.24, found: C, 67.93; H, 7.11; N, 1.40; S, 13.17%.

N-Phenyl-(O_4N)crown **11** (45%), mp 236–238°C; ^{1}H NMR: δ 8.14 (s, 2H, O*H*), 7.70 (s, 4H, Ar*H*), 7.20 (bs, 2H, Ar*H*), 6.97 (s, 4H, Ar*H*), 6.75 (bs, 2H, Ar*H*), 6.65 (bs, 1H, Ar*H*), 4.73 (bs, 4H, OCH_2), 4.09 (bs, 4H, OCH_2), 3.93 (bs, 4H, OCH_2), 3.75 (bs, 4H, NCH_2), 1.37 (s, 18H, Bu^t), 0.81 (s, 18H, Bu^t); ^{13}C NMR: δ 156.0, 155.7, 148.0, 142.5, 134.8, 132.7, 129.3, 129.2, 122.2, 115.9, 111.7 (Ar), 74.0, 70.0, 69.2 (O*C*H$_2$), 51.4 (N*C*H$_2$), 34.5, 34.3 (*C*(CH$_3$)$_3$), 31.9, 31.1 (C(*C*H$_3$)$_3$); anal. calcd. for $C_{54}H_{67}NO_6S_4$ (954.36): C, 67.96; H, 7.08; N, 1.47; S, 13.44, found: C, 67.75; H, 7.04; N, 1.42; S, 13.28%.

N-Boc-(O_4N)crown **12** (35%), mp 150–155°C; ^{1}H NMR: δ 8.11 (s, 2H, O*H*), 7.83 (s, 4H, Ar*H*), 6.97 (s, 2H, Ar*H*), 6.88 (s, 2H, Ar*H*), 4.69 (bs, 4H, OCH_2), 4.04 (bs, 4H, OCH_2), 3.81 (bs, 4H, OCH_2), 3.56 (bs, 4H, NCH_2), 1.44 (s, 9H, OBu^t), 1.34 (s, 18H, Bu^t), 0.80 (s, 9H, Bu^t) 0.75 (s, 9H, Bu^t); ^{13}C NMR: δ 156.0, (*C*O), 155.8, 155.5, 148.1, 147.8, 142.5, 136.4, 134.9, 134.6, 133, 132.4, 129.4, 129.2, 122.4, 122.0 (Ar), 79.8 (OC(CH$_3$)$_3$), 74.0, 73.4, 70.5, 70.3, 70.0, 69.8 (O*C*H$_2$), 48.8, 48.7 (N*C*H$_2$), 34.5 (OC(*C*H$_3$)$_3$), 34.4, 34.3 (*C*(CH$_3$)$_3$), 31.9, 31.6, 31.1, 28.8 (C(*C*H$_3$)$_3$); FAB-MS m/z (%): 999.4 $[M + Na]^+$, anal. calcd. for $C_{53}H_{71}NO_8S_4$ (978.38): C, 65.06; H, 7.31; N, 1.43; S, 13.11, found: C, 64.89; H, 7.29; N, 1.47; S, 13.02%.

N-Boc-(O_5N)crown **13** (77%), mp 220–221°C; ^{1}H NMR: δ 8.14 (s, 2H, O*H*), 7.69 (s, 4H, Ar*H*), 7.05 (s, 1H, Ar*H*), 6.93 (d, 2H, $J = 11.5$, Ar*H*), 6.84 (s, 1H, Ar*H*), 4.88 (bs, 1H, OCH_2), 4.81 (bs, 2H, OCH_2), 4.69 (bs, 1H, OCH_2), 4.13 (bs, 2H, OCH_2), 4.07 (bs, 2H, OCH_2), 3.85 (bs, 4H, OCH_2), 3.75 (bs, 1H, OCH_2), 3.72 (bs, 1H, OCH_2), 3.68 (bs, 2H, NCH_2), 3.61 (bs, 2H, OCH_2), 3.52 (bs, 2H, NCH_2), 1.47 (s, 9H, OBu^t), 1.35 (s, 18H, Bu^t); 0.90 (s, 3H, Bu^t), 0.80 and 0.81 (s, 6 + 6H, Bu^t), 0.73 (s, 3H, Bu^t); ^{13}C NMR: δ; 156.3, (*C*O), 156.1, 155.9, 148.7, 148.3, 148.2, 147.8, 142.9, 142.8, 135.4, 135.1, 135.0, 134.8, 133.8, 133.1, 133.0, 132.3, 129.9, 129.6, 129.5, 129.3, 123.0, 122.7, 122.5, 122.2 (Ar), 80.0, 79.9 (O*C*(CH$_3$)$_3$), 74.9, 73.8, 73.4, 72.9, 71.3, 70.7, 70.5, 70.1 (O*C*H$_2$), 49.3, 49.1, 48.9, 48.6 (N*C*H$_2$), 34.8, 34.7, 34.6, (*C*(CH$_3$)$_3$), 32.2, 31.4, 29.2 (C(*C*H$_3$)$_3$); FAB-MS m/z (%): 1042.8 $[M + Na]^+$, 1059.5 $[M + K]^+$, 1106.1 $[M + Rb]^+$, anal. calcd. for $C_{55}H_{75}NO_9S_4$ (1022.44): C, 64.61; H, 7.39; N, 1.37; S, 12.54, found: C, 64.45; H, 7.38; N, 1.32; S, 12.42%.

N-Phenyl-(O_2S_2N)crown **14** (54%), mp 220–222°C; ^{1}H NMR: δ 7.92 (s, 2H, O*H*), 7.67 (s, 4H, Ar*H*), 7.14 (bs, 2H, Ar*H*), 6.96 (s, 4H, Ar*H*), 6.74 (bs, 2H, Ar*H*), 6.65 (bs, 1H, Ar*H*), 4.69 (bs, 4H, OCH_2), 3.76 (bs, 4H, NCH_2), 3.27 (t, 4H, $J = 6.0$, SCH_2), 3.07 (bs, 4H, SCH_2), 1.35 (s, 18H, Bu^t), 0.81 (s, 18H, Bu^t); ^{13}C NMR: δ 156.2, 156.1, 148.5, 143.1, 135.0, 133.2, 129.7, 129.4, 122.5, 113.0, 112.9 (Ar), 75.8 (O*C*H$_2$), 52.6 (N*C*H$_2$), 34.9, 34.7 (*C*(CH$_3$)$_3$), 33.0, 32.2 (S*C*H$_2$), 31.9, 31.5 (C(*C*H$_3$)$_3$); anal. calcd. for $C_{54}H_{67}NO_4S_6$ (986.49): C, 65.75; H, 6.85; N, 1.42; S, 19.50, found: C, 65.49; H, 6.93; N, 1.38; S, 19.43%.

N-Boc-(O_2S_2N)crown **15** (69%), mp 147–149°C; ^{1}H NMR: δ 7.94 (s, 2H, O*H*), 7.67 (s, 4H, Ar*H*), 7.06 (s, 2H, Ar*H*), 6.85 (s, 2H, Ar*H*), 4.75 (bs, 2H, OCH_2), 4.60 (bs, 2H, OCH_2), 3.64 (bs, 4H, SCH_2), 3.22 (bs, 4H, SCH_2), 3.00 (t, 4H, $J = 6.4$, NCH_2), 1.41 (s, 9H, Bu^t), 1.34 (s, 18H, Bu^t), 0.87 (s, 9H, Bu^t) 0.73 (s, 9H, Bu^t); ^{13}C NMR: δ 154.4 (*C*O), 154.3, 153.8, 141.3, 133.5, 132.9, 132.2, 130.6, 127.9, 127.2, 122.0, 121.5 (Ar), 78.6 (O*C*(CH$_3$)$_3$), 73.2, 72.8 (O*C*H$_2$), 47.9, 47.3 (N*C*H$_2$), 33.1 (*C*(CH$_3$)$_3$), 32.8, 31.2, 31.0, 30.6 (S*C*H$_2$), 30.4, 29.7, 27.3 (C(*C*H$_3$)$_3$); anal. calcd. for $C_{53}H_{71}NO_6S_6$ (1010.51): C, 63.00; H, 7.08; N, 1.39; S, 19.04, found: C, 62.78; H, 7.02; N, 1.33; S, 18.92%.

Pyridino(O_2S_2)crown **16** (57%), mp 132–133°C; ^{1}H NMR: δ 7.92 (s, 2H, O*H*), 7.67 (s, 4H, Ar*H*), 7.54 (t, 1H, $J = 7.65$, Py*H*), 7.23 (d, 2H, $J = 8.4$, Py*H*), 6.95 (s, 4H, Ar*H*), 4.86 (t, 4H, $J = 7.35$, OCH_2), 3.99 (s, 4H, 2,6-PyCH_2S), 3.28 (t, 4H, $J = 7.35$, SCH_2), 1.34 (s, 18H, Bu^t), 0.78 (s, 18H, Bu^t); ^{13}C NMR: δ 158.7, 156.1, 156.0, 148.4, 143.1, 138.0, 134.8, 133.2, 129.6, 122.6, 121.6 (Ar), 72.6 (O*C*H$_2$), 37.6 (Py*C*H$_2$S), 34.9, 34.7 (*C*(CH$_3$)$_3$), 32.2, 31.4 (C(*C*H$_3$)$_3$), 30.7 (S*C*H$_2$); FAB-MS m/z (%): 944.3 $[M + H]^+$, 966.3 $[M + Na]^+$, 982.2 $[M + K]^+$; anal. calcd. for $C_{51}H_{61}NO_4S_6$ (944.40): C, 64.86; H, 6.51; N, 1.48; S, 20.37, found: C, 64.68; H, 6.60; N, 1.41; S, 20.25%.

(O_3S_2)crown **17** (62%), mp 224–226°C; ^{1}H NMR δ 7.91 (s, 2H, O*H*), 7.60 (s, 4H, Ar*H*), 6.86 (s, 4H, Ar*H*), 4.69 (t, 4H, $J = 7.63$, OCH_2), 3.70 (t, 4H, $J = 4.85$, OCH_2), 3.31 (t, 4H, $J = 7.65$, SCH_2), 2.88 (t, 4H, $J = 4.75$, SCH_2), 1.27 (s, 18H, Bu^t), 0.71 (s, 18H, Bu^t); ^{13}C NMR: δ 155.8, 155.7, 148.1, 142.7, 134.5, 132.7, 129.1, 122.3 (Ar), 73.6, 71.8 (O*C*H$_2$), 34.5, 34.3 (*C*(CH$_3$)$_3$), 32.4, 32.0 (S*C*H$_2$), 31.8, 31.1 (C(*C*H$_3$)$_3$); FAB-MS m/z (%): 910 $[M + H]^+$, 933 $[M + Na]^+$, 949.8 $[M + K]^+$; anal. calcd. for $C_{48}H_{62}O_5S_6$ (911.37): C, 63.26; H, 6.86; S, 21.11, found: C, 63.05; H, 6.90; S, 21.05%.

Alkylation of Thiacalixcrowns 11, 14, 16 and 17

Base-promoted Propylation of 11, 14 and 17

The mixture of **11**, **14** or **17** (0.5 mmol), Cs_2CO_3 (3.25 g, 10 mmol) and PrI (0.35 g, 2 mmol) in MeCN (20 mL) was stirred under reflux for 48–72 h. The inorganic materials were then filtered off, the filtrate was evaporated to dryness and the residue was extracted with $CHCl_3$, washed with dilute aq. HCl, water and dried. The products were purified by column chromatography on silica eluting with hexane:EtOAc 9:1 to give white solids.

N-Phenyl-dipropyl(O_4N)crown **18** (77%), mp 248–250°C; ^{1}H NMR: δ 7.38 (s, 4H, Ar*H*), 7.29 (s, 4H, Ar*H*), 7.17 (t, 2H, $J = 7.8$, Ar*H*), 6.66 (t, 1H, $J = 7.2$, Ar*H*), 6.59 (t, 2H, $J = 7.2$, Ar*H*), 3.90 (t, 4H, $J = 5.9$, OCH_2), 3.65 (t, 4H, $J = 7.9$, OCH_2), 3.43 (t, 4H, $J = 5.6$, OCH_2), 3.29 (t, 4H, $J = 5.6$, OCH_2), 3.19 (t, 4H, $J = 5.9$, NCH_2), 1.26 (s, 18H, Bu^t), 1.23 (s, 18H, Bu^t), 0.76 (br, 4H, CH_2), 0.62 (t, 6H, $J = 7.3$, CH_3); ^{13}C NMR: δ 157.8, 155.6, 147.5, 146.0, 145.5, 129.2, 128.9, 128.8, 127.4, 125.7, 116.3, 112.8 (Ar), 70.6, 70.0, 69.9, 69.3 (O*C*H$_2$), 50.4 (N*C*H$_2$), 34.6, 34.5 (*C*(CH$_3$)$_3$), 31.7, 31.5 (C(*C*H$_3$)$_3$), 21.7 (*C*H$_2$), 10.3 (*C*H$_3$); FAB-MS m/z (%): 1037.9 $[M + H]^+$ (26), 1059.9 $[M + Na]^+$ (51), 1074.9 $[M + K]^+$ (14); anal. calcd. for $C_{60}H_{79}NO_6S_4$ (1038.53): C, 69.39; H, 7.67; N, 1.35; S, 12.35, found: C, 69.14; H, 7.71; N, 1.32; S, 12.25%.

N-Phenyl-dipropyl(O_2S_2N)crown **19** (80%), mp 276–278°C; ^{1}H NMR: δ 7.38 (s, 4H, Ar*H*), 7.36 (s, 4H, Ar*H*), 7.26 (t, 2H, $J = 7.5$, Ar*H*), 6.74 (t, 1H, $J = 6.5$, Ar*H*), 6.64 (t, 2H, $J = 7.5$, Ar*H*), 4.04 (t, 4H, $J = 8.5$, OCH_2), 3.76 (t, 4H, $J = 7.5$, OCH_2), 3.26 (br, 4H, NCH_2), 2.59 (br, 4H, SCH_2), 2.23 (t, 4H, $J = 8.0$, SCH_2), 1.36 (s, 18H, Bu^t), 1.31 (s, 18H, Bu^t), 0.86 (br, 4H, CH_2), 0.64 (t, 6H, $J = 7.0$, CH_3); ^{13}C NMR: δ 156.8, 147.2, 146.5, 146.3, 130.1, 129.1, 128.7, 127.8, 126.1, 116.8, 111.4 (Ar), 70.4, 67.1 (O*C*H$_2$), 51.0 (N*C*H$_2$), 35.1, 34.9 (*C*(CH$_3$)$_3$), 32.4, 31.9 (S*C*H$_2$), 31.7, 31.5 (C(*C*H$_3$)$_3$), 22.4 (*C*H$_2$), 10.7 (*C*H$_3$); FAB-MS m/z: 1070.4 $[M + H]^+$; anal. calcd. for $C_{60}H_{79}NO_4S_6$ (1070.65): C, 67.31; H, 7.44; N, 1.31; S, 17.97, found: C, 67.07; H, 7.42; N, 1.25; S, 17.89%.

Dipropyl(O_3S_2)crown **20** (90%), mp 306–308°C; ^{1}H NMR: δ 7.31 (s, 4H, Ar*H*), 7.30 (s, 4H, Ar*H*), 3.90

(t, 4H, $J = 8.15$, OCH_2), 3.73 (t, 4H, $J = 7.48$, OCH_2), 3.46 (br, 4H, OCH_2), 2.50 (br, 4H, SCH_2), 2.20 (t, 4H, $J = 8.18$, SCH_2), 1.34 (s, 18H, Bu^t), 1.26 (s, 18H, Bu^t), 0.86 (br, 4H, CH_2), 0.59 (t, 6H, $J = 7.28$, CH_3); ^{13}C NMR: δ 155.2, 154.9, 144.5, 144.2, 126.7, 126.2, 126.0, 124.8, (Ar), 72.7, 68.5, 66.3 (OCH_2), 33.3, 33.1 (*C*(CH$_3$)$_3$), 32.7, 31.9 (SCH_2), 30.4, 30.1 (C(*C*H$_3$)$_3$), 20.6 (*C*H$_2$), 8.9 (*C*H$_3$); FAB-MS m/z: 993.8 $[M + H]^+$; anal. calcd. for $C_{54}H_{74}O_5S_6$ (995.54): C, 65.15; H, 7.49; S, 19.32, found: C. 64,90; H, 7.41; S, 19.24%.

Mitsunobu Alkylation of 16 with n-Octanol

To a stirred mixture of **16** (0.47 g, 0.5 mmol), TPP (0.53 g, 2 mmol) and *n*-octanol (0.52 g, 4 mmol) in 20 mL toluene, a 40% toluene solution of DEAD (0.9 mL, 2 mmol) was added at room temperature and allowed to react at 80°C for 6 h. The solvent was then removed under reduced pressure and the residue was triturated with MeOH. The insoluble solid was filtered off and chromatographed on silica with hexane:EtOAc 9:1 eluent to give **21** as a white solid.

Dioctyl-pyridino(O_2S_2)crown **21** (50%), mp 224–225°C, ^{1}H NMR: δ 7.54 (t, 1H, $J = 7.5$, Py*H*), 7.28 (s, 4H, Ar*H*), 7.26 (s, 4H, Ar*H*), 7.05 (d, 2H, $J = 7.5$, Py*H*), 3.91 (t, 4H, $J = 8.5$, OCH_2), 3.75 (t, 4H, $J = 8.5$, SCH_2), 3.59 (s, 4H, 2,6-Py-SCH_2), 2.11 (t, 4H, $J = 8.8$, OCH_2), 1.27 (s, 18H, Bu^t), 1.17 (s, 18H, Bu^t), 1.20–1.04 (m, 24H, CH_2), 0.87 (t, 6H, $J = 7.0$, CH_3); ^{13}C NMR: δ 159.0, 156.4, 156.3, 146.2, 145.9, 137.7, 127.9, 127.5, 126.8, 126.1, 121.2 (Ar), 68.5 (Py*C*H$_2$S), 66.5, 66.4 (OCH_2), 39.1 (SCH_2), 34.6, 34.5 (*C*(CH$_3$)$_3$), 32.2 (CH_2), 31.9, 31.7 (C(*C*H$_3$)$_3$), 30.8, 29.0, 26.2, 23.0 (CH_2), 14.5 (*C*H$_3$); FAB-MS m/z: 1168.1 $[M + H]^+$; anal. calcd. for $C_{67}H_{93}NO_4S_6$ (1168.84): C, 68.85; H, 8.02; N, 1.20; S, 16.46, found: C, 68.62; H, 8.08; N, 1.15; S, 16.31%.

Synthesis of Chromoionophores 22 and 23

To a THF (15 mL) solution of **18** or **19** (0.5 mmol) were added 2–3 drops of AcOH and *p*-nitrophenyldiazonium tetrafluoroborate (0.12 g, 0.5 mmol) at ambient temperature and the mixture allowed to react for 2 h. The solvent was then removed under reduced pressure, the residue was dissolved in $CHCl_3$, washed with water and dried. After evaporation to dryness the crude material was washed thoroughly with MeOH to give **24** and **25** as orange–red solids in essentially pure form.

Compound **22** (78%), mp 296–298°C; ^{1}H NMR: δ 8.33 (d, 2H, $J = 8.5$, NO_2ArH_o), 7.92 (d, 2H, $J = 8.0$, NO_2ArH_m), 7.85 (d, 2H, $J = 8.5$, N_2ArH_o), 7.40 (s, 4H, Ar*H*), 7.27 (s, 4H, Ar*H*), 6.71 (d, 2H, $J = 8.5$, N_2ArH_m), 3.94 (t, 4H, $J = 5.5$, OCH_2), 3.64 (t, 4H, $J = 7.5$, OCH_2), 3.41 (br, 8H, OCH_2), 3.29 (t, 4H, $J = 5.5$, NCH_2), 1.26 (s, 18H, Bu^t), 1.23 (s, 18H, Bu^t), 0.75 (br, 4H, $J = 7.0$, CH_2), 0.63 (t, 6H, $J = 7.0$, CH_3); ^{13}C NMR: δ 158.5, 156.0, 146.3, 146.0, 129.7, 129.5, 127.8, 126.5, 126.1, 125.1, 123.0, 112.4 (Ar), 71.1, 70.7, 70.4, 70.1 (OCH_2), 51.6 (NCH_2), 35.0, 34.9 (*C*(CH$_3$)$_3$), 32.1, 31.9 (C(*C*H$_3$)$_3$), 22.0 (*C*H$_2$), 10.6 (*C*H$_3$); FAB-MS m/z: 1186.8 $[M + H]^+$; anal. calcd. for $C_{66}H_{82}N_4O_8S_4$ (1187.64): C, 66.75; H, 6.96; N, 4.72; S, 10.80, found: C, 66.49; H, 7.02; N, 4.66; S, 10.70%.

Compound **23** (74%), mp 268–270°C; ^{1}H NMR: δ 8.34 (d, 2H, $J = 8.5$, NO_2ArH_o), 7.92 (d, 2 + 2H, $J = 8.5$, NO_2ArH_m, N_2ArH_o), 7.35 (s, 4H, Ar*H*), 7.34 (s, 4H, Ar*H*), 6.71 (d, 2H, $J = 8.5$, N_2ArH_m), 4.02 (t, 4H, $J = 8.0$, OCH_2), 3.73 (t, 4H, $J = 7.0$, OCH_2), 3.34 (br, 4H, NCH_2), 2.61 (br, 4H, SCH_2), 2.22 (t, 4H, $J = 8.0$, SCH_2), 1.34 (s, 18H, Bu^t), 1.29 (s, 18H, Bu^t), 0.83 (br, 4H, CH_2), 0.62 (t, 6H, $J = 7.0$, CH_3); ^{13}C NMR: δ 156.9, 156.8, 156.7, 150.8, 148.0, 146.4, 144.5, 128.7, 127.9, 127.7, 126.8, 126.0, 125.1, 123.2, 11.4 (Ar), 70.4, 67.1 (OCH_2), 51.2 (NCH_2), 35.1, 35.0 (*C*(CH$_3$)$_3$), 32.4, 31.9 (C(*C*H$_3$)$_3$), 31.6, 30.3 (SCH_2), 22.4 (*C*H$_2$), 10.7 (*C*H$_3$); FAB-MS m/z: 1219.4 $[M + H]^+$; anal. calcd. for $C_{66}H_{82}N_4O_6S_6$ (1219.76): C, 64.99; H, 6.78; N, 4.59; S, 15.77, found: C, 64.72; H, 6.69; N, 4.52; S, 15.60%.

Acknowledgements

Financial support from the Hungarian Scientific Research Foundation (OTKA No. T 046055) is gratefully acknowledged. We thank Professor Klára Tóth for the electroanalytical measurements. V.Cs. thanks the József Varga Foundation for a fellowship.

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