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Chemoselective ring closure of thiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) via the Mitsunobu reaction

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Abstract—Chemoselective intramolecular ring closure on the phenolic OH groups of *p-tert*-butylthiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) attained under Mitsunobu conditions affords inherently chiral macrocycles capped by carboxamide bridges. Oxazoline or oxazine cyclization products derived from self-condensation of the hydroxyalkylamide moieties were not isolated. In one case the detection of enantiomers was achieved by chiral HPLC.

1. Introduction

The great number of calixarene derivatives is partly ascribed to the regio- and conformation selective reactions developed in the last decades. Among them the partial O-alkylation and acylation of calix[4]arenes (CA) provide important synthetic tools for designing supramolecules of great variety.[1] Similar selective reactions, at least with the same efficiency, have rarely been found in the thiacalixarene chemistry.[2] The lack of regio- and stereoselectivity in the base mediated O-alkylation and acylation reactions of thiacalix[4]arenes (TCA) can be attributed to the substantially fewer differences between the OH acidities[3] and the larger cavity compared with the CA counterpart (the average bond length of the sulfide bridges is ca. 15% larger than that of the methylene bridges).[4,5] Seeking a general method to alleviate this drawback, we have found the Mitsunobu reaction working under neutral conditions provides an extremely useful alternative for O-alkylation. In this way the distal dialkylation and ring closure of TCA with a series of alcohols and glycols have been accomplished with high regioselectivity.[6–9] It is noteworthy that with tri-, tetra-and pentaethylene glycols 1,3-thiacalix[4]-monocrown-4, -5 and -6 derivatives were obtained[7,9] in yields of 40–50%, which cannot be achieved by the classical templated procedure.[10,11] Following our studies with the short chained diethylene glycol and its aza- and thia-analogues, quite different reaction pathways were observed. While thiodiethylene glycol (**a**) gave exclusively dimer **1a**, diethylene glycol (**b**) and *N*-phenyl-iminodiethanol (**c**) afforded the tethered 1,2-monocrowns **2b**,**c** in a competitive intramolecular reaction beside dimers **1b**,**c**[12] (Fig. 1).

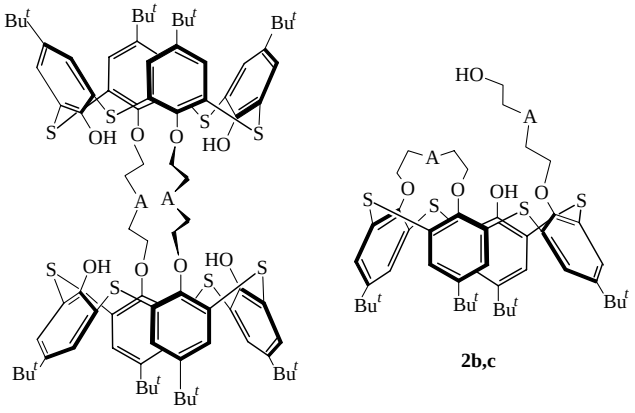

Figure 1. The reaction products of TCA and various diethylene glycols under Mitsunobu condition.

It was surprising that the outcome of the reaction was remarkably influenced by minor differences in the chain length of glycols (**a**>**b**>**c**).

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To obtain further information on how the intra- versus intermolecular cyclization routes of TCA are influenced by the structural features of linkers, thiacalix[4]arene-1,3-bis(*N*-ω-hydroxyalkylamides) with various chain lengths were synthesized and their ability to cyclize under the Mitsunobu protocol was studied. In this model the carboxamide groups not only rigidify the chains, but they provide additional targets for the cyclization. Mitsunobu cyclodehydration of *N*-hydroxyalkylamides affording five,six-membered *O*,*N*-heterocycles by coupling with the oxygen or nitrogen atom of the carboxamide moiety, have been well-documented in the literature. Generally oxazolines and oxazines and even *N*-acylpyrrolidines and piperidines are formed depending on the chain lengths.[13] If this possibility is also taken into consideration, these compounds seemed to be good candidates to study whether the weakly acidic OHs in TCA, or the heteroatoms of the carboxamide groups, or both are attacked under Mitsunobu conditions.

Earlier in the calix[4]arene series we investigated the ring closure of 1,3-bis(ω-chloroalkylamides) **4a**–**c**, using a biphasic phase-transfer catalytic reaction under strongly basic (aq NaOH) conditions. We achieved successful cyclization in the case of **4b** affording the inherently chiral, doubly capped **5b** in high yield.[14] With the shorter-chain **4a** and the longer-chain **4c**, only hydrolysis by-products were formed, cyclic molecules including the alternative oxazoline or dihydro-oxazine derivatives **6** were not detected (Fig. 2). The Mitsunobu reaction of calixarene hydroxyamides **3** have not yet been investigated.

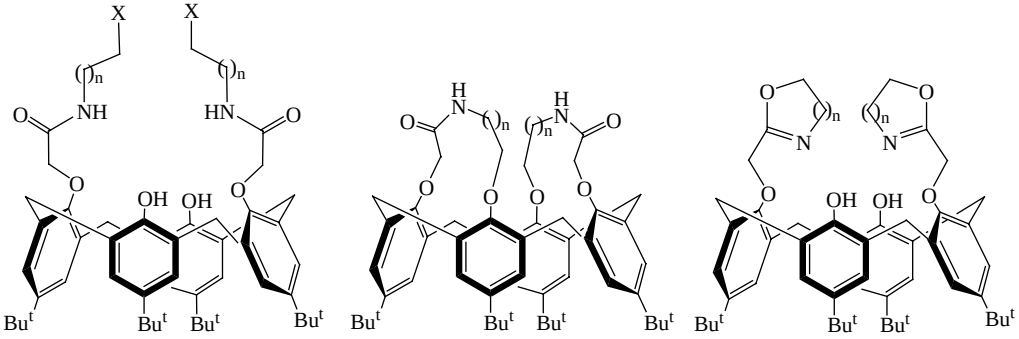
After these preliminary studies we were interested in how the outcome of reaction with the analogous thiacalixarene hydroxyamides would be affected by the larger intramolecular distances between the reacting sites (TCA > CA), and by using a mild and neutral cyclodehydration method.

2. Results and discussion

Starting materials **8**–**10** were prepared by the amination of the respective diesters **7a**–**c** with aminoalcohols as described for the calixarene series.[14] Diesters **7b**,**c** were first synthesized in our laboratory by the selective Mitsunobu alkylation of TCA with ethyl (*S*)-lactate (**7b**) and ethyl (*R*)-mandelate (**7c**), respectively.[6] The base-promoted alkylation of TCA with ethyl bromoacetate reported for the preparation of **7a**[15] was unsatisfactory in our hand (chromatographic separation was required), in turn the Mitsunobu coupling with glycolic acid ethyl ester cleanly afforded the desired **7a** at room temperature. The amination of **7a**,**b** went smoothly with all aminoalcohols, but mandelate **7c** only gave complete conversion with 2-aminoethanol (Scheme 1).

The Mitsunobu reaction was then performed with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in toluene using a molar ratio of **8**–**10**/(TPP/DEAD) = 1:3 at ambient temperature. From compounds **8a**–**c**, **9a**,**b** and **10a** only doubly capped thiacalixarenes **11a**–**c**, **12a**,**b** and **13a** were obtained in acceptable yields, and heterocycles **14**, **15** were not detected (Scheme 1). With hydroxyamide **9c** the reaction did not go to completion even at elevated temperature: a series of spots was seen on the TLC sheet containing the starting **9c**, Ph_3PO, probably singly and doubly cyclized products and others, but we were unable to separate any product in pure form. The success of double cyclization on the phenolic OHs was found to primarily depend on the length of the hydroxyalkyl chain and is not affected by the temperature.

It was notable that the base-promoted cyclization of calix[4]arene chloroalkylamides **4** was much more sensitive to the chain length of the chloroalkyl moiety, because only the propyl derivative **4b** gave cyclic product, suggesting the necessity of the appropriate intramolecular distance between the adjacent phenolate and the electrophilic site.[14] As the diameter of the lower rim in TCA is larger than that of CA (vide supra), consequently the respective intramolecular distances should also be larger. The clean cyclization of **8a**, **9a** and **10a** possessing the same chain lengths as **4a**, therefore contradict this. When the respective calixarene counterparts **3a**–**c** were also subjected to analogous Mitsunobu cyclization at 80 °C, no positive reactions were found: neither doubly capped calixarenes **5** nor heterocycles **6** could be identified. The failure of the former reaction may be due to the weaker acidity of the remaining OHs in distally dialkylated calixarenes as compared to the TCA counterparts,[3] which prevents their further alkylation under Mitsunobu conditions.[8] Perhaps

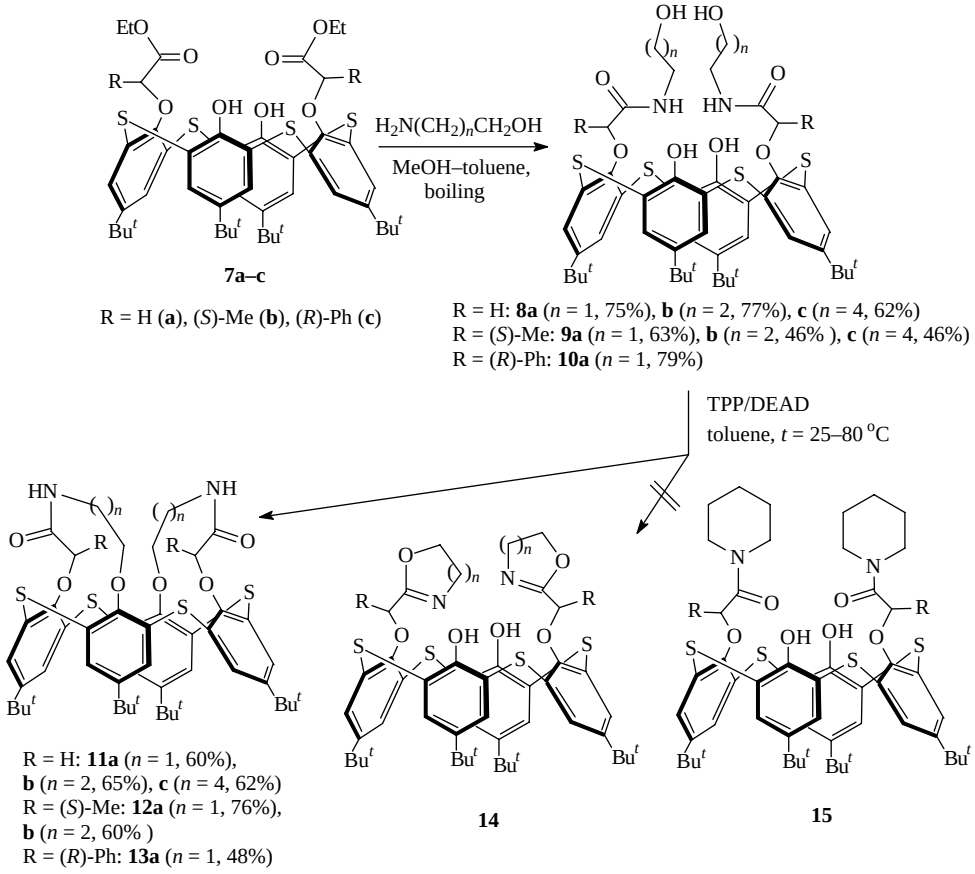


3 (X = OH)
4 (X = Cl)
n = 1(**a**), 2(**b**), 4(**c**)

5b (n = 2)

6a,b

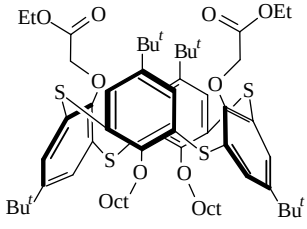
Figure 2. Survey of products obtained or expected in the base-promoted cyclization of **4**.



Scheme 1. Synthesis and Mitsunobu cyclization of *N*-hydroxylkylamides **8**–**10**.

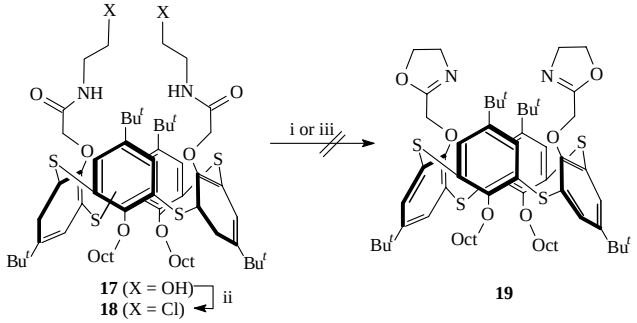
more reactive azodicarboxylate and phosphine coupling agents could help, but so far DIPAD/TPP has been tried without success.

It was rather surprising that the carboxamide groups remained intact, though various *N*-(hydroxyalkyl)amides were reported to undergo different self-cyclizations via the mild Mitsunobu reaction.[13] To check the reactivity of the carboxamide groups, the participation of the phenolic OHs in the cyclization had to be excluded by using an *O*-protected derivative. As the base-promoted O-alkylation of **8a** led to a mixture of 1,3-alt, cone and paco conformers, the highly lipophilic (and soluble) distal 1,3-dioctyloxy-TCA[6] was alkylated with ethyl bromoacetate/Cs_2CO_3 and 1,3-alt diester **16** was obtained.



16

This compound was then treated with 2-aminoethanol resulting in 1,3-alt bisamide **17**, which was subjected to Mitsunobu cyclization. However, we failed to isolate bisoxazoline **19**, only the starting material was recovered (Scheme 2).



Scheme 2. Attempts to cyclize *O*-protected bisamides **17**, **18**. Reagents and conditions: (i) **17**, TPP/DEAD, toluene, 80 °C; (ii) $SOCl_2$, $CHCl_3$, Δ; (iii) **18**, NaOEt, EtOH, Δ.

The bischloro derivative **18** also could not be cyclized to **19** under strongly basic conditions, analogously to the ring closure of *N*-(2-chloroethyl)phenoxyacetamide giving 2-phenoxymethyl-1,3-oxazoline.[16] In contrast, the basic treatment of 1,3-dihydroxy-bis(chloroethoxy)amide derived from **8a** gave selectively again the Mitsunobu product **11a**, thereby providing further evidence for the suppressed reactivity of the carboxamide groups in our models.[†]

[†] To eliminate the adverse effect of the bulky *tert*-butyl groups in the 1,3-alt **17** and **18**, for the referee's suggestion the respective de-*tert*-butylated derivatives were also prepared (as the $AlCl_3$-promoted dealkylation of **17** and **18** was expected to be uncertain due to the reactive endgroups, therefore the same route described for **16** was used) and subjected to Mitsunobu reaction and basic treatment, respectively. However, both trials failed, the expected bisoxazoline could not be achieved.

These experiments revealed that the chemoselectivity in the transformation of thiacalixarene 1,3-bisamides **8–10** to doubly capped **11–13** versus bis(*O*,*N*-heterocycles) **14**, **15** can be attributed to the resistance of the carboxamide groups to self-cyclization, the cause of which is not clear at this point (other approaches to prepare **19** are being tried). The reaction has another interesting aspect as compared with the results obtained with TCA and diethylene glycols, where only single ring closure was attained under the same conditions (see the tethered **2b**,**c** in Fig. 1). We assume the carboxamide NHs of bisamides **8–10** are hydrogen-bonded to the neighbouring phenolic OHs (δNH = 8.5–9.0t, 2H), which in turn, are hydrogen-bonded to the adjacent phenol ether oxygens (δOH = 7.5–8.0s, 2H) keeping the alkyl chains in the vicinity of the nucleophilic sites, thereby facilitating the double cyclization.

The ^{1}H and ^{13}C NMR spectra of doubly capped **11–13** are quite complex due to the asymmetric structure. For example **11c** displays one singlet (7.81) and two doublets (7.00, 6.94) for the aromatic protons and two doublets (5.97, 4.08) for the methylene protons in the ArOCH_2CONH moieties. The inherent chirality of these macrocycles was demonstrated by

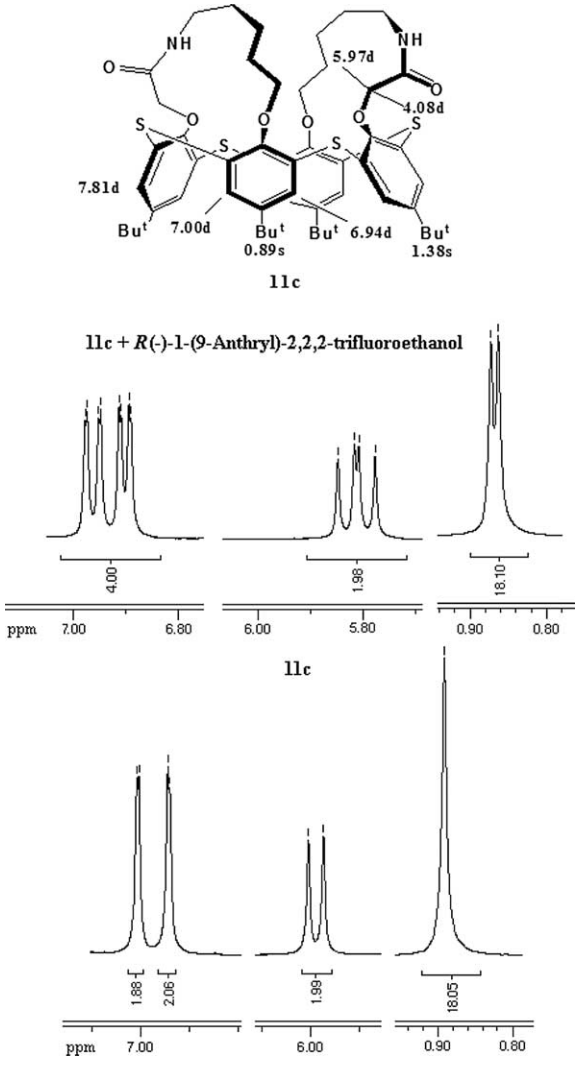


Figure 3. Partial ^{1}H NMR spectra of **11c** in $CDCl_3$ without (lower) and with (upper) Pirkle reagent.

taking the ^{1}H NMR spectrum of **11c** in the presence of Pirkle reagent and the labelled signals were doubled in a 1:1 ratio (Fig. 3).

The enantiomeric resolution of **11c** racemate was attempted by HPLC separation using chiral stationary phases. Earlier, Chiralpak AD column was successfully applied for the separation of **2c**,[12] but in this case it was unsuitable, instead Chiracel OD-H (cellulose tris-(3,5-dimethylphenylcarbamate)) column gave satisfactory resolution for the detection of enantiomers (Fig. 4). Unfortunately, the difference in retention times for the enantiomers (Δt = 2.3 min) did not make their separation feasible on a semi-preparative scale and CD spectra, therefore, were not recorded.

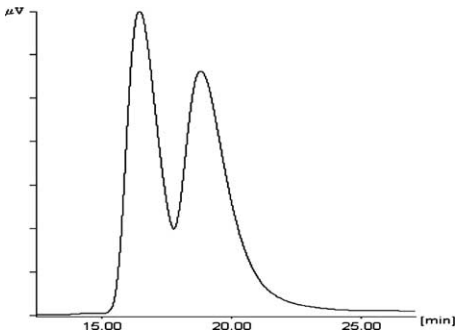


Figure 4. HPLC separation of **11c** on Chiracel OD-H (mobile phase *n*-hexane/2-propanol = 95:5 at 0.5 ml/min).

3. Conclusions

Chemoselective intramolecular ring closure on the phenolic OH groups of *p-tert*-butylthiacalix[4]arene 1,3-bis(*N*-ω-hydroxyalkylamides) was attained under Mitsunobu conditions affording inherently chiral doubly capped derivatives **11–13**. Oxazoline or oxazine cyclization products **14**, **15** derived from self-condensation of the hydroxyalkylamide moieties were not isolated. We pointed out that the chemoselectivity in the transformation of thiacalixarene 1,3-bisamides **8–10** to doubly capped **11–13** versus bis(*O*,*N*-heterocycles) **14**, **15** can be attributed to the markedly decreased reactivity of the carboxamide groups that could not cyclize even in the absence of the competing phenolic OHs.

The new macrocycles were obtained as racemic mixtures as demonstrated by ^{1}H NMR measurement of **11c** carried out in the presence of Pirkle reagent and by the detection of its enantiomers with HPLC using a chiral stationary phase.

4. 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 recorded (frequently in the presence of a mixture of alkali picrates) on a Finigan MAT 8430 instrument (matrix: *m*-NBA, gas: xenon, accelerating voltage: 9 kV). 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. *n*-Hexane and 2-propanol (HPLC grade) were purchased from Merck.

Compounds **7a–c**[6] and DEAD[17] were synthesized as described in the literature (CAUTION! DEAD may explode if exposed to shock, friction or heating).

The HPLC measurements were performed on a JASCO liquid chromatograph (pump 1580) with UV spectrophotometric detector (UV-1575) operating at 256 nm. The column (250×4.6 mm) was packed with Chiracel OD-H coated on 5 μm silicagel (Daicel, Tokyo).

4.1. General procedure for the synthesis of thiacalix[4]arene 1,3-bis(ω-hydroxyalkylamides) 8–10

Our early method used for the preparation of the respective calix[4]arene bisamides[14] was adapted. Thus, **7a–c** (1 mmol), aminoalcohol (10 mmol) in toluene–methanol solvent mixture (1/1, 20 ml) were refluxed overnight. The volatiles was then evaporated and the residue was triturated with MeOH to give white solids with sufficient purity.

4.1.1. Compound 8a. Yield: 75%, mp 253–254 °C; ^{1}H NMR δ 8.99 (t, 2H, J=5.5 Hz, N*H*), 7.71 (s, 4H, Ar*H*), 7.61 (s, 2H, O*H*), 7.31 (s, 4H, Ar*H*), 4.77 (s, 4H, ArOCH_2CO), 3.85 (m, 4H, HOCH_2), 3.64 (m, 4H, HNCH_2), 1.32 (s, 18H, Bu^t), 1.00 (s, 18H, Bu^t); ^{13}C NMR δ 169.4 (*C*O), 156.7, 156.2, 149.7, 144.2, 135.6, 135.2, 128.5, 121.3 (Ar), 75.5 (O*C*H$_2$), 62.0 (HO*C*H$_2$), 42.4 (HN*C*H$_2$), 34.6, 34.4 (*C*(CH$_3$)$_3$), 31.5, 31.0 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 923.5 [M+H]$^+$, 945.5 [M+Na]$^+$, 961.5 [M+K]$^+$. Anal. Calcd for $C_{48}H_{62}N_2O_8S_4$ (922.34): C 62.44, H 6.77, N 3.03, S 13.89, found: C 62.32, H 6.82, N 3.11, S 13.71%.

4.1.2. Compound 8b. Yield: 77%, mp 242–243 °C; ^{1}H NMR δ 8.96 (t, 2H, J=5.5 Hz, N*H*), 7.62 (s, 2H, O*H*), 7.71 (s, 4H, Ar*H*), 7.46 (s, 4H, Ar*H*), 4.77 (s, 4H, ArOCH_2CO), 3.74 (t, 4H, J=5.5 Hz, HOCH_2), 3.64 (q, 4H, J=6.0 Hz, HNCH_2), 1.86 (m, 4H, CH_2), 1.31 (s, 18H, Bu^t), 1.09 (s, 18H, Bu^t); ^{13}C NMR δ 169.1 (*C*O), 157.0, 156.4, 150.2, 144.3, 136.0, 135.9, 128.4, 120.9 (Ar), 75.8 (O*C*H$_2$), 59.3 (HO*C*H$_2$), 35.9 (HN*C*H$_2$), 34.7, 34.4 (*C*(CH$_3$)$_3$), 32.4 (*C*H$_2$), 31.5, 31.0 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 951.5 [M+H]$^+$, 973.8 [M+Na]$^+$, 989.5 [M+K]$^+$. Anal. Calcd for $C_{50}H_{66}N_2O_8S_4$ (950.37): C 63.13, H 6.99, N 2.94, S 13.48, found: C 63.28, H 7.02, N 2.81, S 13.27%.

4.1.3. Compound 8c. Yield: 62%, mp 200–202 °C; ^{1}H NMR δ 8.94 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.68 (s, 2H, O*H*), 7.51 (s, 4H, Ar*H*), 4.70 (s, 4H, ArOCH_2CO), 3.54 (t, 4H, J=6.0 Hz, HOCH_2), 3.45 (dt, 4H, J=5.5, 7.5 Hz, HNCH_2), 1.68 (m, 4H, CH_2), 1.58 (m, 4H, CH_2), 1.49 (m, 4H, CH_2), 1.29 (s, 18H, Bu^t), 1.10 (s, 18H, Bu^t); ^{13}C NMR δ 168.1 (*C*O), 157.2, 156.6, 150.3, 144.3, 136.5, 135.8, 128.3, 120.7 (Ar), 76.1 (O*C*H$_2$), 62.4 (HO*C*H$_2$), 39.6 (HN*C*H$_2$), 34.7, 34.4 (*C*(CH$_3$)$_3$), 32.5 (*C*H$_2$), 31.6, 31.1 (C(*C*H$_3$)$_3$), 29.0, 23.2 (*C*H$_2$); FAB-MS *m*/*z* (%): 1007.2 [M+H]$^+$, 1029.2 [M+Na]$^+$, 1045.4 [M+K]$^+$. Anal. Calcd for $C_{54}H_{74}N_2O_8S_4$ (1006.43): C 64.38, H 7.40, N 2.78, S 12.73, found: C 64.21, H 7.47, N 2.83, S 12.85%.

4.1.4. Compound 9a. Yield: 63%, mp 248–250 °C; ^{1}H NMR δ 8.75 (t, 2H, J=5.5 Hz, N*H*), 7.71 (s, 4H, Ar*H*), 7.64 (s, 2H, O*H*), 7.20 (d, 4H, J=2.5 Hz, Ar*H*), 7.16 (d, 4H, J=2.5 Hz, Ar*H*), 4.76 (q, 2H, J=7.0 Hz, ArO(CH$_3$)C*H*CO), 3.85 (m, 4H, HOCH_2), 3.67 (m, 2H, HNCH_2), 3.60 (m, 2H, HNCH_2), 1.60 (d, 6H, J=7.0 Hz, CH_3), 1.35 (s, 18H, Bu^t), 0.92 (s, 18H, Bu^t); ^{13}C NMR δ 172.2 (*C*O), 155.7, 154.7, 149.1, 143.9, 135.3, 135.1, 134.8, 133.6, 129.2, 128.5, 122.1, 121.5 (Ar), 83.9 (ArO*C*HCO), 62.4 (HO*C*H$_2$), 42.3 (HN*C*H$_2$), 34.4, 34.4 (*C*(CH$_3$)$_3$), 31.6, 30.9 (C(*C*H$_3$)$_3$), 17.7 (CH$_3$); FAB-MS *m*/*z* (%): 951.5 [M+H]$^+$, 974.5 [M+Na]$^+$, 989.5 [M+K]$^+$. Anal. Calcd for $C_{50}H_{66}N_2O_8S_4$ (950.37): C 63.13, H 6.99, N 2.94, S 13.48, found: C 62.85, H 7.05, N 2.83, S 13.20%.

4.1.5. Compound 9b. Yield: 46%, mp 240–244 °C; ^{1}H NMR δ 8.94 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.57 (s, 2H, O*H*), 7.32 (d, 2H, J=2.0 Hz, Ar*H*), 7.27 (d, 2H, J=2.0 Hz, Ar*H*), 4.83 (q, 2H, J=6.5 Hz, ArO(CH$_3$)C*H*CO), 3.71 (t, 4H, J=5.5 Hz, HOCH_2), 3.67 (dt, 2H, J=6.0, 7.0 Hz, HNCH_2), 3.48 (dt, 2H, J=6.0, 7.0 Hz, HNCH_2), 1.83 (m, 4H, CH_2), 1.60 (d, 6H, J=6.5 Hz, CH_3), 1.32 (s, 18H, Bu^t), 0.98 (s, 18H, Bu^t); ^{13}C NMR δ 172.4 (*C*O), 156.0, 154.8, 149.5, 144.1, 135.6, 135.6, 135.1, 134.4, 129.0, 128.7, 121.7, 121.1 (Ar), 83.6 (ArO*C*HCO), 59.4 (HO*C*H$_2$), 36.1 (HN*C*H$_2$), 34.5, 34.4 (*C*(CH$_3$)$_3$), 32.2 (*C*H$_2$), 31.6, 30.9 (C(*C*H$_3$)$_3$) 17.7 (CH$_3$); FAB-MS *m*/*z* (%): 979.6 [M+H]$^+$, 1001.5 [M+Na]$^+$, 1017.6 [M+K]$^+$. Anal. Calcd for $C_{52}H_{70}N_2O_8S_4$ (978.40): C 63.77, H 7.20, N 2.86, S 13.10, found: C 63.68, H 7.14, N 2.91, S 13.05%.

4.1.6. Compound 9c. Yield: 46%, mp 188–192 °C; ^{1}H NMR δ 8.81 (t, 2H, J=5.5 Hz, N*H*), 7.69 (s, 4H, Ar*H*), 7.64 (s, 2H, O*H*), 7.35 (d, 4H, J=12.5 Hz, Ar*H*), 4.93 (q, 2H, J=7.0 Hz, ArO(CH$_3$)C*H*CO), 3.51 (t, 4H, J=6 Hz, HOCH_2), 3.46 (dt, 2H, J=6.0, 7.5 Hz, HNCH_2), 3.38 (dt, 2H, J=6.0, 7.5 Hz, HNCH_2), 1.66 (m, 8H, CH_2), 1.54 (d, 6H, J=7.0 Hz, CH_3), 1.46 (m, 4H, CH$_2$), 1.32 (s, 18H, Bu^t), 0.99 (s, 18H, Bu^t); ^{13}C NMR δ 171.4 (*C*O), 156.2, 154.7, 149.5, 144.1, 135.9, 135.5, 134.9, 129.0, 128.9, 128.6, 121.7, 121.0 (Ar), 83.3 (ArO*C*HCO), 62.5 (HO*C*H$_2$), 39.8 (HN*C*H$_2$), 34.5, 34.4 (*C*(CH$_3$)$_3$), 32.4 (*C*H$_2$), 31.6, 31.1 (C(*C*H$_3$)$_3$) 29.0, 23.2 (*C*H$_2$), 17.5 (CH$_3$); FAB-MS *m*/*z* (%): 1035.3 [M+H]$^+$. Anal. Calcd for $C_{56}H_{78}N_2O_8S_4$ (1034.46): C 64.95, H 7.59, N 2.71, S 12.39, found: C 65.12, H 7.52, N 2.84, S 12.30%.

4.1.7. Compound 10a. Yield: 79%, mp 240–242 °C; ^{1}H NMR δ 8.99 (t, 2H, J=5.5 Hz, N*H*), 7.65 (d, 2H, J=2.5 Hz, Ar*H*), 7.63 (d, 2H, J=2.5 Hz, Ar*H*), 7.56 (s, 2H, O*H*), 7.31–7.41 (m, 10H, Ar*H*), 7.09 (d, 2H, J=2.5 Hz, Ar*H*), 6.90 (d, 2H, J=2.5 Hz, Ar*H*), 4.76 (s, 2H, ArOPhC*H*CO), 3.85–3.94 (m, 4H, HOCH_2), 3.71 (m, 4H, HNCH_2), 1.32 (s, 18H, Bu^t), 0.81 (s, 18H, Bu^t); ^{13}C NMR δ 170.4 (*C*O), 155.6, 154.5, 148.8, 143.8, 135.0, 134.9, 134.8, 134.4, 133.3, 130.0, 129.6, 128.8, 128.1, 122.7, 121.5 (Ar), 89.3 (ArO*C*HCO), 62.2 (HO*C*H$_2$), 42.4 (HN*C*H$_2$), 34.4, 34.3 (*C*(CH$_3$)$_3$), 31.6, 30.8 (C(*C*H$_3$)$_3$); FAB-MS *m*/*z* (%): 1075.6 [M+H]$^+$, 1098.6 [M+Na]$^+$, 1113.8 [M+K]$^+$. Anal. Calcd for $C_{60}H_{70}N_2O_8S_4$ (1074.40): C 67.01, H 6.56, N 2.60, S 11.93, found: C 67.16, H 6.49, N 2.46, S 11.80%.

4.2. General procedure for the synthesis of doubly capped thiacalix[4]arenes 11–13

To the mixture of **8–10** (1 mmol) and TPP (0.79 g, 3 mmol) in toluene (20 ml), 40% toluene solution of DEAD (1.30 ml,

3 mmol) was dropped under stirring at ambient temperature and allowed to react overnight. The suspension was then evaporated to dryness and the residue was triturated with MeOH to give **11–13** as white solids in substantially pure form. Compounds **11a**,**b** were sparingly soluble in $CDCl_3$ and DMSO-d_6, which prevented the measurement of suitable NMR spectra.

4.2.1. Compound 11a. Yield: 60%, mp>360 °C; IR (KBr) 3390, 3342 (NH), 2963, 2872 (CH_2), 1684 (amide CO), 1561, 1440, 1384, 1270, 1090, 1035 cm^{-1}; FAB-MS *m/z* (%): 887.8 $[M+H]^+$(91). Anal. Calcd for $C_{48}H_{58}N_2O_6S_4$ (886.32): C 64.98, H 6.59, N 3.16, S 14.46, found: C 65.10, H 6.52, N 3.32, S 14.27%.

4.2.2. Compound 11b. Yield: 65%, mp>360 °C; IR (KBr) 3392, 3340 (NH), 2961, 2870 (CH_2), 1684 (amide CO), 1560, 1439, 1384, 1271, 1094, 1030 cm^{-1}; FAB-MS *m/z* (%): 916.0 $[M+H]^+$(100). Anal. Calcd for $C_{50}H_{62}N_2O_6S_4$ (914.35): C 65.61, H 6.83, N 3.06, S 14.01, found: C 65.47, H 6.77, N 3.02, S 14.17%.

4.2.3. Compound 11c. Yield: 62%, mp 340–342 °C; IR (KBr): 3390, 3334 (NH), 2962, 2871 (CH_2), 1677 (amide CO), 1543, 1444, 1382, 1268, 1093, 1027 cm^{-1}; ^1H NMR δ 8.40 (t, 2H, $J=5.8$ Hz, N*H*), 7.79 (s, 4H, Ar*H*), 6.99 (d, 2H, $J=2.5$ Hz, Ar*H*), 6.93 (d, 2H, $J=2.4$ Hz, Ar*H*), 5.97 (d, 2H, $J=15.5$ Hz, ArOCH_2CO), 4.08 (d, 2H, $J=15.5$ Hz, ArOCH_2CO), 4.01 (dt, 2H, $J=8.7$, 3.4 Hz, NCH_2), 3.80 (tt, 2H, $J=3.0$, 3.0 Hz, NCH_2), 3.62 (tdd, 2H, $J=11.1$, 8.9, 2.2 Hz, OCH_2), 3.35 (tt, 2H, $J=9.0$, 3.0 Hz, OCH_2), 2.14 (m, 2H, CH_2), 2.13 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.36 (s, 18H, Bu^t), 0.87 (s, 18H, Bu^t); ^{13}C NMR δ 169.0, 161.0, 156.8, 147.2, 147.1, 137.3, 137.1, 133.7, 131.9, 130.2, 129.1, 128.7, 128.5 (Ar), 74.9, 78.4 (OCH_2), 36.3 (HNCH_2), 34.4, 34.1 ($C(CH_3)_3$), 31.4, 30.9 (C(CH_3)$_3$), 26.3, 20.5 (CH_2); FAB-MS *m/z* (%): 971.3 $[M+H]^+$(62). Anal. Calcd for $C_{54}H_{70}N_2O_6S_4$ (970.41): C 66.77, H 7.26, N 2.88, S 13.20, found: C 66.91, H 7.32, N 2.96, S 13.04%.

4.2.4. Compound 12a. Yield: 76%, mp>360 °C; ^1H NMR δ 8.94 (dd, 2H, $J=10.8$, 1.7 Hz, N*H*), 7.84 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.79 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.21 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.18 (d, 2H, $J=2.4$ Hz, Ar*H*), 4.59 (q, 2H, $J=6.7$ Hz, ArOC*H*CH$_3$), 4.28 (dd, 2H, $J=8.4$, 4.4 Hz, OCH_2), 4.14 (ddd, 2H, $J=13.7$, 11.0, 4.1 Hz, NHCH_2), 3.85 (ddd, 2H, $J=11.6$, 8.5, 4.3 Hz, OCH_2), 3.62 (dddd, 2H, $J=13.7$, 11.7, 4.4, 2.0 Hz, NHCH_2), 1.73 (d, 6H, $J=6.9$ Hz, CH_3), 1.33 (s, 18H, Bu^t), 0.89 (s, 18H, Bu^t); ^{13}C NMR δ 175.3 (*C*O), 160.5, 155.9, 148.4, 146.1, 137.7, 136.8, 134.3, 134.1, 133.0, 130.0, 129.1, 124.6 (Ar), 83.5 (O*C*H), 74.1 (O*C*H$_2$), 38.0 (NH*C*H$_2$), 34.5, 34.0 ($C(CH_3)_3$), 31.4, 30.0 (C(CH_3)$_3$), 19.6 (CH_3); FAB-MS *m/z* (%): 915.4 $[M+H]^+$. Anal. Calcd for $C_{50}H_{62}N_2O_6S_4$ (914.35): C 65.61, H 6.83, N 3.06, S 14.01, found: C 65.37, H 6.77, N 3.02, S 14.17%.

4.2.5. Compound 12b. Yield: 60%, mp>360 °C; ^1H NMR δ 8.95 (dd, 2H, $J=6.1$, 2.3 Hz, N*H*), 7.80 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.79 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.37 (d, 2H, $J=2.1$ Hz, Ar*H*), 7.31 (d, 2H, $J=2.1$ Hz, Ar*H*), 4.79 (dd, 2H, $J=9.6$, 7.0 Hz, OCH_2), 4.42 (q, 2H, $J=6.7$ Hz, ArOC*H*CH$_3$), 3.95 (ddd, 2H, $J=10.2$, 6.6, 3.7 Hz, NHCH_2), 3.92 (t, 2H, $J=8.8$ Hz, OCH_2), 3.40 (m, 2H, HNCH_2), 2.45 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 1.69 (d, 6H, $J=6.7$ Hz, CH_3), 1.31 (s, 18H, Bu^t), 0.96 (s, 18H, Bu^t); ^{13}C NMR δ 172.2 (*C*O), 161.1, 156.4, 147.8, 147.4, 137.7, 136.8, 134.7, 134.4, 131.0, 129.8, 129.6, 129.3 (Ar), 83.9 (O*C*H), 79.0 (O*C*H$_2$), 40.6 (NH*C*H$_2$), 34.4, 34.1 ($C(CH_3)_3$), 31.4, 30.9 (C(CH_3)$_3$), 28.0 (CH_2), 17.7 (CH_3); FAB-MS *m/z* (%): 943.4 $[M+H]^+$. Anal. Calcd for $C_{52}H_{66}N_2O_6S_4$ (942.38): C 66.21, H 7.05, N 2.97, S 13.60, found: C 66.08, H 6.92, N 3.12, S 13.77%.

4.2.6. Compound 13a. Yield: 48%, mp 320–324 °C; ^1H NMR δ 8.25 (dd, 2H, $J=10.9$, 1.8 Hz, N*H*), 7.89 (d, 4H, $J=7.6$ Hz, Ar*H*), 7.85 (s, 4H, Ar*H*), 7.42 (t, 4H, $J=7.6$ Hz, Ar*H*), 7.35 (t, 2H, $J=7.4$ Hz, Ar*H*), 7.23 (d, 2H, $J=2.4$ Hz, Ar*H*), 7.14 (d, 2H, $J=2.4$ Hz, Ar*H*), 5.54 (s, 2H, ArOPhC*H*CO), 4.36 (dd, 2H, $J=8.5$, 4.4 Hz, ArOCH_2), 4.17 (ddd, 2H, $J=14.0$, 11.1, 4.0 Hz, HNCH_2), 4.00 (ddd, 2H, $J=11.9$, 8.6, 4.1 Hz, ArOCH_2), 3.72 (dddd, 2H, $J=14.1$, 11.9, 4.0, 2.5 Hz, HNCH_2), 1.35 (s, 18H, Bu^t), 0.88 (s, 18H, Bu^t); ^{13}C NMR δ 172.9 (*C*O), 160.5, 155.9, 148.4, 146.2, 137.9, 137.0, 136.9, 134.2, 134.1, 133.0, 129.9, 128.8, 128.4, 128.3, 126.6, 124.1 (Ar), 87.8 (ArO*C*HCO), 74.3 (ArO*C*H$_2$), 38.2 (HN*C*H$_2$), 34.5, 34.0 ($C(CH_3)_3$), 31.4, 30.8 (C(CH_3)$_3$); FAB-MS *m/z* (%): 1039.5 $[M+H]^+$. Anal. Calcd for $C_{60}H_{66}N_2O_6S_4$ (1038.38): C 69.33, H 6.40, N 2.70, S 12.34, found: C 69.42, H 6.49, N 2.83, S 12.20%.

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