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Synthesis and spectroscopic properties of porphyrin-(thia)calix[4]arene conjugates

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Abstract—Calix[4]arene diacetate and tetraacetate together with their tetrathia-analogs served as starting compounds for the synthesis of novel porphyrin-calixarene conjugates. The introduction of monoaminotetraphenylporphyrin gave corresponding calixarene derivatives, bearing two or four porphyrin units on the lower calixarene rim. These compounds, immobilized in the *cone* conformation, possess interesting photophysical properties. The absorption and fluorescence emission spectra of the synthesized diporphyrins and tetraporphyrins reveal exciton coupling between the porphyrin units. The flexibility of the amidic bridges accounts for tuning of the degree of porphyrin coupling by the solvent polarity.

1. Introduction

Macrocyclic compounds are widely used in supramolecular chemistry for the construction of various receptors for charged or even neutral molecules. Calix[4]arene **1** represents[1] a unique three-dimensional structure with almost unlimited derivatisation abilities. Thiacalix[4]arene **2** has been described as a new member of the calixarene family.[2] The presence of four sulphur atoms instead of methylene groups imposes many new properties on the thiacalix[4]-arene skeleton when compared with the chemistry of 'classical' calixarenes. Very recently, several reactions[3,4] unknown in classical calix[4]arene chemistry have been described. These features together with easily tuneable shapes of the molecules make (thia)calix[4]arenes ideal candidates for building blocks and/or molecular scaffolds in the design of new sophisticated systems.

Another important family of macrocyclic compounds, the porphyrins, offers[5] useful photoactive and/or electroactive properties suitable for the construction of artificial molecular devices. Therefore, the combination of (thia)-calix[4]arene and porphyrin moieties might lead to novel receptors the function of which is detectable by luminescence spectroscopy. Our purpose was to synthesize new (thia)calix[4]arene-porphyrin conjugates and to study their spectroscopic properties depending on the conditions used (solvent, the presence of cation) to test their ability to serve as fluorescent receptors for alkali metal ions. The design of receptors (outlined in Fig. 1) is based on the fact, that the mutual position of two porphyrin units can be controlled, e.g. by the presence/absence of a metal cation or by changing of the solvent polarity. Under common conditions, the short-range orbital-overlap dependent interactions of the porphyrin units (intramolecular dimerisation) and intramolecular hydrogen bonding between distal diamides of calix[4]arene[6] bring amidic substituents close to each other. Such a potential proximity of the porphyrin units leads to exciton coupling in the excited state[7] and, therefore, to quenching of the fluorescence emission intensity. Upon complexation, the calixarene lower rim can increase the distance between the porphyrin units and reduce exciton interactions. These changes can cause the reappearance of

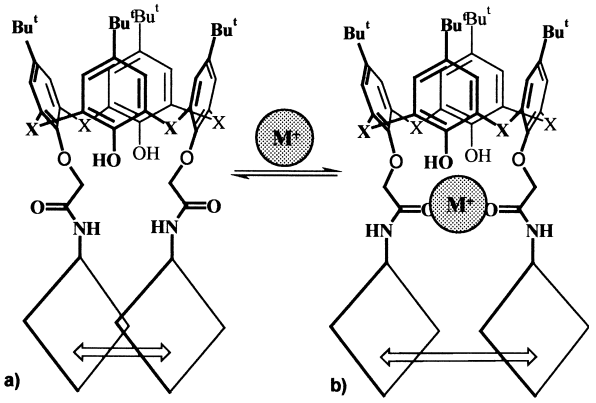

Figure 1. Design of calix–porphyrin receptors.

Keywords: porphyrin; calix[4]arene; thiacalix[4]arene; synthesis; spectroscopic properties.

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the original fluorescence intensity enabling the sensing of the cations by fluorescence spectroscopy.

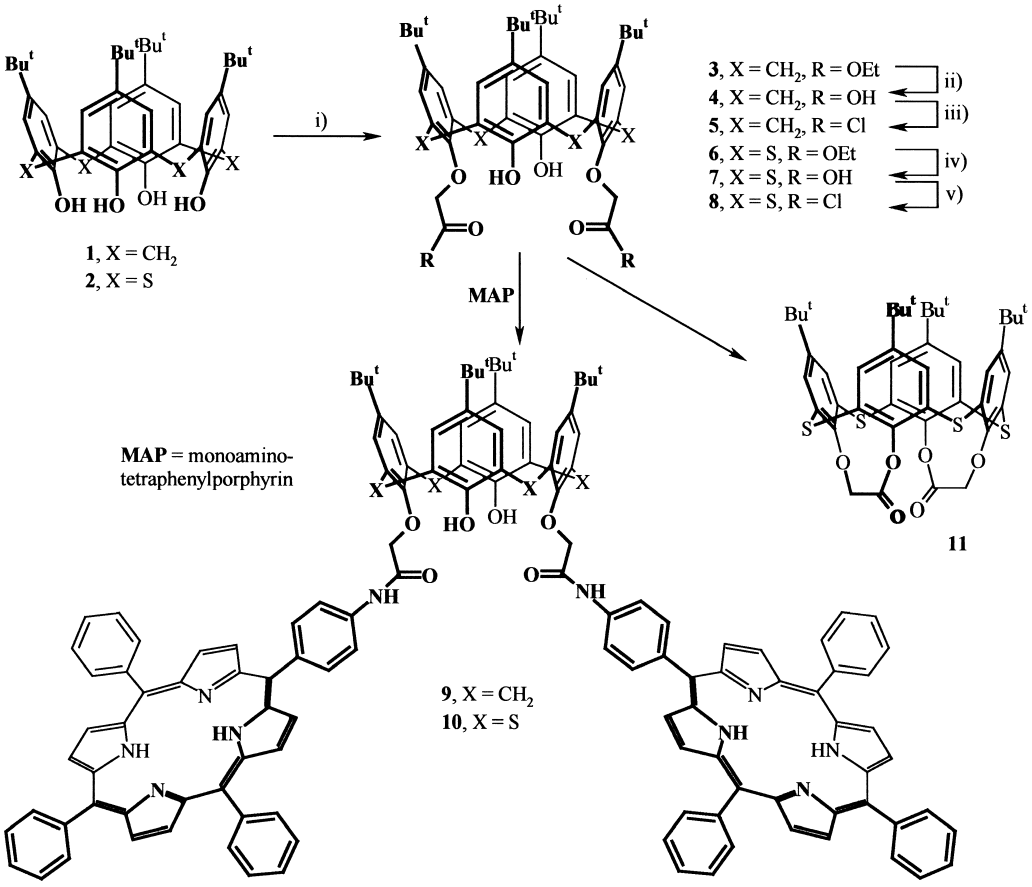
2. Results and discussion

2.1. Synthesis of conjugates

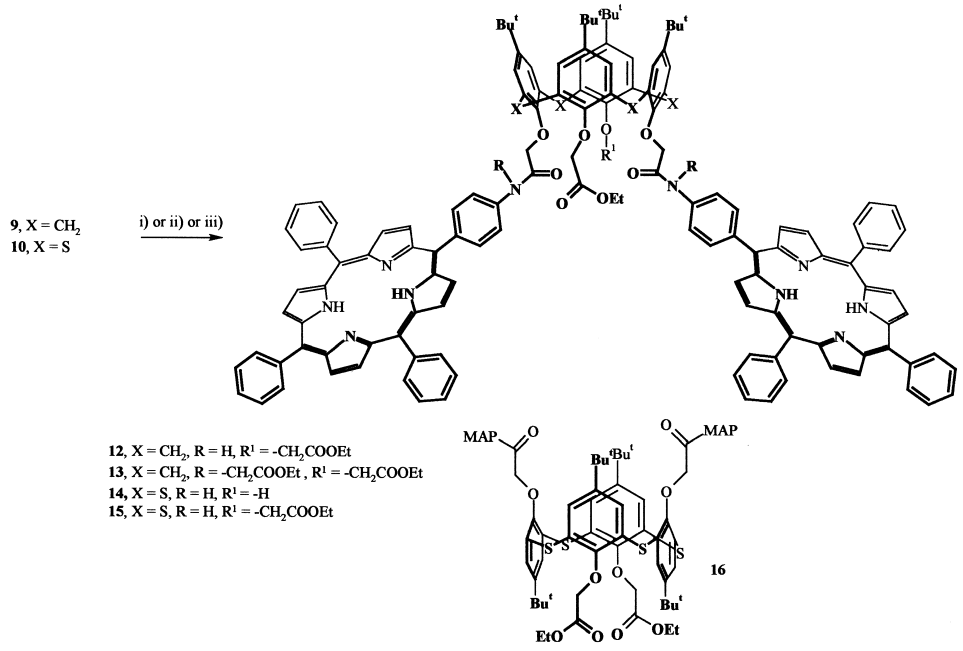
The synthesis started from calixarenes **1** and **2** that were transformed into corresponding diacetates **3** (71% yield) and **6** (51% yield) by alkylation with an excess of ethyl-bromoacetate in refluxing acetone using 1.05 equiv. of K_2CO_3. These esters were hydrolyzed with NaOH in aqueous ethanol under reflux to yield dicarboxylic acids **4** (79% yield) and **7** (98% yield). Diamides **9** and **10** were prepared by two methods: (i) by reacting acyl chlorides **5** and **8** with monoaminoderivative of tetraphenylporphyrin **MAP**, or (ii) by a direct reaction of carboxylic acids **4** and **7** with MAP using dicyclohexyl carbodiimide as a coupling agent. The preparation of chlorides was accomplished by stirring the starting acids with an excess of oxalyl chloride in CCl_4 under reflux. Chloride **5** was obtained in almost quantitative yield and used as a crude compound in the next step due to its presumed instability. Subsequent condensation of **5** with MAP (2.2 equiv., THF, rt) in the presence of base (Et_3N) gave diamide **9** in 30% yield. Surprisingly, the same procedure using thiacalixarene derivative **8** does not lead to diamide **10** but to bis-lactone **11** as a main product. As we have shown recently,[3] chloride **8** reacts in an unexpected manner, never observed in classical calixarene chemistry. Thiacalix[4]arene diamide **10** was prepared by stirring a dichloromethane solution of corresponding diacid **7** with MAP in the presence of DCC for 2 h at room temperature. This procedure gave the expected product **10** in high yield (72%) after isolation by preparative TLC (silica gel). Analogously, diamide **9** was obtained in 78% yield (Scheme 1).

The structure of compound **9** was proved using ^1H NMR spectroscopy. The presence of two doublets of the CH_2 bridging groups (3.71 and 4.51 ppm) with the geminal coupling constant of 13.2 Hz is a clear evidence of a *cone* conformation. Similarly, the spectrum of thiacalixarene derivative **10** with two sets of Bu^t and aromatic singlets reflects the C_{2v} symmetry that is typical for a *cone* conformer. The FAB MS spectra show the molecular peaks $[M+1]^+$ as the most intensive signals (*m/z*: 1990.0 and 2062.9 for **9** and **10**, respectively).

As diamides **9** and **10** exhibited only negligible complexation ability towards alkali metal cations, we attempted to strengthen the complexation by the introduction of two acetate groups. Interestingly, despite the fact that alkylation of the phenolic OH groups with ethyl bromoacetate is a well known reaction in the calixarene chemistry, all our attempts to prepare dialkylated compound **12** have failed. All the



Scheme 1. (i) $BrCH_2COOEt/K_2CO_3$ (1.05 equiv.), acetone, reflux (**3**, 71%; **6** 51%); (ii) NaOH, EtOH/water, reflux (79%); (iii) oxalyl chloride/CCl_4, reflux (quant.); (iv) NaOH, EtOH/water, reflux (98%); (v) oxalyl chloride/CCl_4, reflux (quant.); (vi) aminoporphyrin/Et_3N/THF, rt (**9**, 30%); (vii) DCC/amino-porphyrin/CH_2Cl_2, rt (**4**→**9**, 72%, **7**→**10**, 70%).



Scheme 2. (i) $BrCH_2COOEt/Na_2CO_3$ (excess), acetone, reflux (**14**, 32%); (ii) $BrCH_2COOEt/KI/K_2CO_3$ (excess), DMF, rt (**13**, 67%); (iii) $BrCH_2COOEt/NaI/Na_2CO_3$ (excess), DMF, rt (**15**, 30% and **16**, 43%).

reaction conditions used (K_2CO_3 or Na_2CO_3/acetone, K_2CO_3 or Na_2CO_3/DMF, NaH/DMF) led to a very complex reaction mixture and only the unusual tetraacetate derivative **13** was isolated and fully characterized. We found that compound **9** is transformed to **13** in 67% yield using $BrCH_2COOEt$, K_2CO_3/DMF system and a catalytic amount of KI. The ^1H NMR spectrum confirms the C_{2v} symmetry of **12**. The presence of the ester groups is supported by two separated methyl signals of these groups (triplets at 1.47 and 1.54 ppm) together with three individual singlets of $-OCH_2CO-$ at 4.62, 4.83 and 4.91 ppm. The FAB MS spectrum shows the $[M+Na]^+$ peak at *m/z* 2357.5 (Scheme 2).

The same alkylation reaction of thia-analog **10** resulted in dialkylated products. Alkylation with ethyl bromoacetate/Na_2CO_3 in refluxing acetone for five days led to monoester **14** in 32% yield. Using DMF as a solvent in $BrCH_2COOEt/K_2CO_3$/DMF/KI system gave a mixture of two main products **15** and **16**. The products were isolated by column chromatography on silica gel and identified as diesters.

Generally, the conformational analysis of thiacalix[4]arene derivatives is not a trivial task. The absence of the CH_2 bridges means it is necessary to apply more complicated NMR methods. The splitting patterns of diesters **15** and **16** ^1H NMR are similar indicating either a *1,3-alternate* or a *cone* conformation in $CDCl_3$. To distinguish between the two conformers, a one-dimensional DPFGSE-NOE experiment[9] was carried out. Due to the slow molecular motion of these compounds (molecular weight >2000), we were in the negative NOE regime and recorded negative NOE enhancements. The strong NOE coupling between the ester and amide groups and no interaction between the ester groups and calixarene aromatic rings in **15** indicate the *cone* conformation. On the other hand, the *1,3-alternate* conformation of **16** was unambiguously proven by the finding of NOE interactions between the ester groups and aromatic protons of the rings bearing porphyrins and between the amide groups and aromatic protons of the rings bearing acetate groups (Fig. 2).

In contrast to **16** in the *1,3-alternate* conformation, the ^1H NMR spectrum of the *cone* conformer of **15** revealed a different signal pattern. The resonances of the aromatic protons of the rings bearing porphyrins or acetates in compound **15** differ significantly (7.21, 7.87 ppm), while the chemical shifts of the corresponding resonances in **16** are almost the same (7.65, 7.68 ppm). This leads us to an assumption that compound **15** adopts a less symmetrical *pinched cone* conformation,[8] where two opposite phenyl rings face each other in the cavity and two flattened rings are oriented outside the cavity.

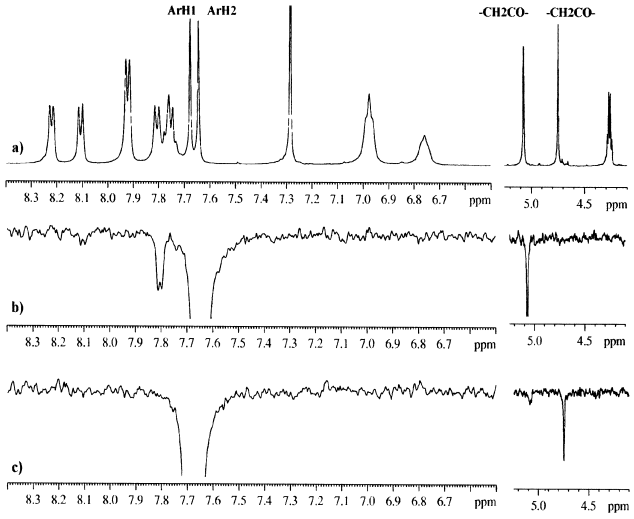


Figure 2. DPFGSE-NOE spectra of **16** (a) partial ^1H NMR spectrum, (b) ArH2 irradiated, (c) ArH1 irradiated.

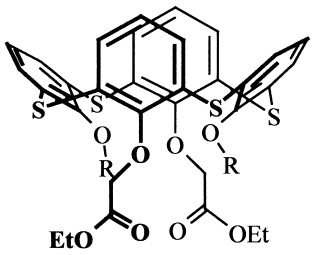


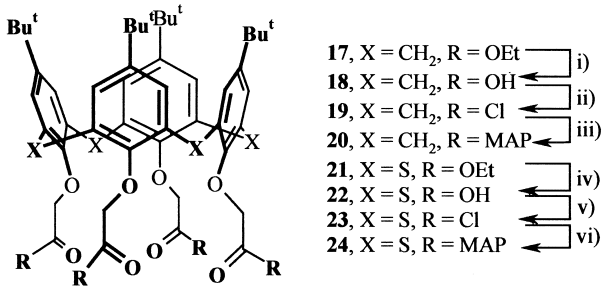
Figure 3. Proposed preferred structure of compound **15**.

To specify the rings bearing the porphyrin units, a complete assignment based on COSY, ^{13}C NMR, $^{1}H-^{13}C$ HMQC and HMBC experiments was carried out. The key evidence was obtained from the HMBC experiment affording $^{1}H-^{13}C$ two and three bond correlations. The cross-peaks of the methylene protons with corresponding carbonyl and C1 carbons (aromatic carbon bearing oxygen atom) determined that the aromatic rings with less shielded protons (7.87 ppm) bear the porphyrins and the rings with more shielded protons (7.21 ppm) bear the acetate groups. These results indicate that the rings facing each other have the acetate groups on the lower rim, while the flattened rings oriented outside the cavity are linked to the porphyrin units (Fig. 3).

The synthesis of conjugates bearing four porphyrin units started from corresponding tetraesters **17** and **21** that were prepared by the alkylation of **1** and **2** with an excess of ethyl-bromoacetate/K_2CO_3 in refluxing acetone. These esters were hydrolyzed with KOH in aqueous ethanol under reflux to yield tetracarboxylic acids **18** (95% yield) and **22** (94% yield). Subsequent reaction with oxalyl chloride in CCl_4 gave corresponding acyl chlorides **19** and **23** that were used without purification for the next step. Final condensation of chlorides with MAP (5 equiv.) was carried out in THF at room temperature in the presence of base (Et_3N). Pure tetraamides **20** and **24** were obtained after chromatographic separation on a silica gel column in 45 and 71% yields, respectively (Scheme 3).

2.2. Spectroscopic properties

The absorption spectra of **9**, **10**, **20** and **24** are shown in Fig. 4. In the region above 500 nm the Q-bands have similar shape and the molar absorption coefficients (see Section 3) are roughly twice (**9**, **10**) and four times (**20**, **24**) as large as those for 5,10,15,20-tetraphenylporphyrin (TPP). This additivity indicates that the electronic structure of the



Scheme 3. (i) NaOH, EtOH/water, reflux (79%); (ii) oxalyl chloride/CCl_4, reflux (quant.); (iii) MAP/Et_3N, THF, rt (30%).

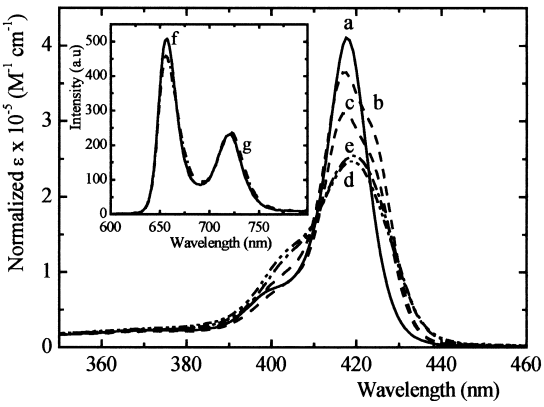


Figure 4. Absorption spectra of (a) TPP, (b) **9**, (c) **10**, (d) **20** and (e) **24** in CH_2Cl_2 per porphyrin unit. Inset: fluorescence emission spectra of (f) TPP and (g) **9** in CH_2Cl_2 excited at 516 nm, matching absorbance $A_{516}=0.078\pm0.002$ in 1 cm cell.

porphyrin units in the first excited singlet state is close to that of TPP. However, the Soret bands (Fig. 4) are broader compared to that of TPP at 418 nm and are split into two components separated by 9 and 17 nm for **9**, **10** and **20**, **24**, respectively. In addition, the molar absorption coefficients per porphyrin at the Soret maxima decrease with the increasing number of the porphyrin units. A shoulder at about 400 nm is due to the vibrational B(0,1) transition. The presence of the methylene or sulphur calixarene bridges does not affect the absorption spectra indicating that the observed spectral splitting is caused by intramolecular exciton coupling between the porphyrin units in the second excited singlet state and that the calixarene moiety behaves as a bridging unit keeping the porphyrins close enough to effect short-range exciton coupling. Similarly, the compound **15** with alkylated free phenolic OH groups exhibits the same spectral behavior as the parent compound **10**. According to the molecular exciton model[7] a spectral red shift is attributed to a head-to-tail alignment of the interacting chromophores and a blue-shifted band is due to a face-to-face alignment. The observed split Soret bands are typical for an oblique alignment of the porphyrin units. Such alignment exhibits exciton splitting of 10–20 nm[7] and the strong dependence of the relative intensities of the respective bands on the dihedral angle. The compounds **13** and **16** have no splitting of the Soret band indicating very weak interaction between the porphyrin units. This can be attributed to the steric restrictions imposed by two N-acetates or *tert*-butyls between the arms bearing the interacting

Table 1. Emission peaks λ_{max} and the fluorescence quantum yields Φ_f of the porphyrins in CH_2Cl_2 and MeOH

Porphyrin	CH_2Cl_2		MeOH	
	λ_{max} (nm)	Φ_f[a]	λ_{max} (nm)	Φ_f[a]
TPP	656, 721	0.11[b]	655, 719	0.10
9	656, 721	0.11	655, 719	0.10
10	656, 721	0.11	656, 720	0.09
15	654, 720	0.11	654, 719	0.09
16	656, 721	0.10	657, 721	0.08
20	657, 723	0.10	661, 724	0.07
24	658, 723	0.11	659, 725	0.02

[a] Estimated error 10%.
[b] Φ_f of TPP taken as a standard.[10]

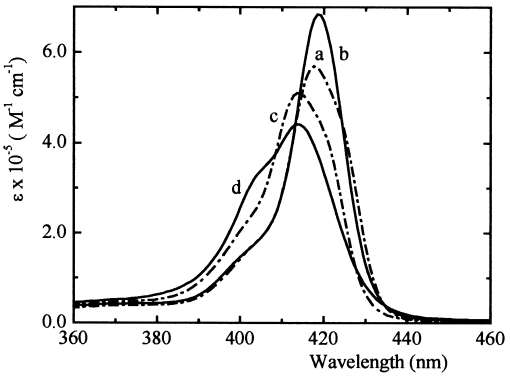


Figure 5. Absorption spectra in the Soret region of **15** and **16** in CH_2Cl_2 (a) and (b) and methanol (c) and (d).

porphyrins. In CH_2Cl_2, the fluorescence emission bands do not shift and the fluorescence quantum yields are the same for all compounds (Fig. 4, Table 1) in agreement with the absorption spectra where the Q-bands are unchanged.

The splitting of the Soret bands is strongly solvent dependent reflecting spatial flexibility of the alignment of the porphyrin units. A broadening of the Soret band (compare, e.g. Fig. 5(b) and (d) for **16**) indicates stronger exciton coupling in more polar solvents such as methanol or acetonitrile. More effective exciton coupling in methanol is also evidenced by the dramatic decrease of the fluorescence quantum yields (Table 1). Thiacalix[4]arenes appear to be more sensitive to the solvent polarity than calix[4]arenes.

2.3. Complexation study

The complexation behavior of the porphyrin–calixarene conjugates was studied by UV–VIS and ^{1}H NMR spectroscopy. The absorption and fluorescence spectra of the conjugates do not change upon addition of Li^+, Na^+ and K^+ as studied in CH_2Cl_2, methanol and acetonitrile. In ^{1}H NMR, no significant changes attributable to the complexation were observed after addition of alkali metal picrates to the solution of dihydroxy derivatives **9** and **10** in a $CDCl_3/CD_3OD$ 4:1 v/v mixture. It is well-known[1] that calix[4]arene tetraesters or tetraamides have a pre-organized cavity on the lower rim that considerably increases the affinity for cations. Surprisingly, both tetraamides **20** and **24** appear to be very poor complexation agents towards alkali metal cations. The broadening of the ^{1}H NMR signals excluded determination of the complexation constants. Evidently, the steric restrictions imposed by four bulky porphyrin units on the lower rim hinder the pre-organization needed (C_4 symmetry). A dynamic NMR study of tetraamide **24** (CD_2Cl_2) revealed the broadening of the signals at low temperatures which indicates an additional dynamic process. This can be ascribed to the C_{2v}–$C_{2v'}$ interconversion between the two pinched cone conformations. While the aromatic region of the spectrum remains very broad at the lowest accessible temperature (−80°C), the signal of the *tert* butyl groups is clearly separated into two singlets ($\Delta\nu \cong 200$ Hz) with a coalescence temperature approx. −60°C. This temperature is much higher than that of corresponding tetraacetate **21** where a similar process was not observed till −90°C. The pinched cone conformation does not support cation complexation.

In conclusion, novel (thia)calixarenes with the porphyrin units on the lower rim have been prepared. Our results indicate that the porphyrin units attached to the lower rim of the calixarene *cone* are flexible, however, the steric hindrance imposed by the porphyrin units renders the conjugates with a low tendency to bind alkali metal cations. On the other hand, the flexibility of (thia)calixarene–porphyrin conjugates could be a desired behavior for the design of novel receptors. The work on more elaborate receptors is underway.

3. Experimental

3.1. General

Melting points are uncorrected and were determined using a Boetius Block apparatus. ^{1}H NMR spectra were recorded on a Varian Gemini 300 and a Bruker AMX3 400 spectrometers using tetramethyl silane as an internal standard. The assignment and NOE experiments were carried out on a Bruker DRX 500 Avance spectrometer. ^{1}H NMR spectra were measured with a spectral width 7500 Hz, data size 32K, the recycle time 3.1 s, and 16 scans. ^{13}C NMR spectra were measured with a spectral width 26.5 kHz, data size 32K, the recycle time 2.6 s, and 3000 scans. The spin systems were identified by 2D COSY (128 t_1-increments of 1024 data points,16 scans, spectral width 3000 Hz), ^{1}H–^{13}C HMQC (128 t_1 increments, spectral widths 3000 Hz in ^{1}H and 23.7 kHz in ^{13}C dimensions, respectively, 16 scans, the delay for polarization transfer 3.5 ms), ^{1}H–^{13}C HMBC (128 t_1 increments, spectral widths 3000 Hz in ^{1}H and 23.7 kHz in ^{13}C dimensions, respectively, 128 scans, the delay for polarization transfer 60 ms). 1D ^{1}H DPFGSE-NOE experiment[9] was performed using selective q3-gaussian-cascade of 79.2 ms, the mixing time was 2 s. Typical $\pi/2$-pulses were 9.5 μs for ^{1}H, and 12 μs for ^{13}C. FAB MS were measured on ZAB-EQ VG analytical spectrometer. Absorption and fluorescence spectra were measured on a Philips PU 8720 spectrophotometer and on a Perkin–Elmer LS 50B luminescence spectrophotometer, respectively. Absorbance titrations were conducted with concentrated stock solutions of $LiClO_4$, $NaClO_4$ and $KClO_4$ in methanol. The salts were dried in a vacuum oven before the preparation of the solutions. All emission spectra were corrected for the characteristics of the detection monochromator and photomultiplier.[11] The absorbances were adjusted to the same value (<0.08/1 cm) at the excitation wavelength at the $Q_y(1,0)$ absorption band (516 nm). Then, the fluorescence quantum yields Φ_f were obtained by comparison of the integrated area under the emission spectra of the compounds and TPP[10] in CH_2Cl_2 (Φ_f=0.11) using refractive index correction.[12]

Compounds **3**,[13] **6**,[14] **17**[15] and **21**[8] were prepared according to procedures known by the reaction of **1** and **2** with ethyl bromoacetate in boiling acetone in the presence of Na_2CO_3 or K_2CO_3. Corresponding diacid **4** and tetraacid **18** were prepared by the hydrolysis of starting esters using NaOH in boiling aqueous ethanol,[16] while the thiacalix[4]arene

derivatives **7** and **22** were obtained by the same procedure[14] using KOH.

3.1.1. Synthesis of derivative 9. *Method A*. A mixture of diacid **4**[16] (17 mg; 2.24×10^{-2} mmol) and $(COCl)_2$ (39 μl; 0.44 mmol) in 5 ml of anhydrous CH_2Cl_2 was stirred under reflux for 3 h. The solvent was distilled off, the residue was dissolved in anhydrous CH_2Cl_2 (5 ml) and the solvent was again evaporated under reduced pressure. This procedure was repeated twice to remove all traces of oxalyl chloride. The resulting solid (acyl chloride **5**) was then dried in a high vacuum for 1 h. The solid was dissolved in 5 ml of dry THF and this solution was added dropwise at room temperature to a stirred solution of MAP[17] (30 mg; 4.76×10^{-2}) and Et_3N (31 μl; 0.22 mmol) in 5 ml of dry THF. The reaction mixture was stirred for 1 h and the solvent was removed in a reduced pressure. The residue was dissolved in $CHCl_3$ (20 ml) and washed with water (20 ml). The separated organic layer was dried over $MgSO_4$. After the evaporation of solvent, the crude product was purified by column chromatography on silica gel using $CHCl_3$/petroleum ether (5:1) as an eluent to give the product **9** as a purple powder (13 mg, 30%). Mp >350°C (ethyl acetate). ^{1}H NMR ($CDCl_3$): δ −2.81 (s, 4H, NH por.), 1.20 (s, 18H, Bu^t), 1.34 (s, 18H, Bu^t), 3.71 (d, *J*=13.2 Hz, 4H, Ar*CH*$_2$Ar eq.), 4.51 (d, *J*=13.2 Hz, 4H, Ar*CH*$_2$Ar ax.), 4.96 (s, 4H, O*CH*$_2$CO), 7.16 (s, 4H, H-arom), 7.24 (s, 4H, H-arom), 7.71 (m, 20H, C*H* por.), 8.17 (m, 10H, C*H* por.), 8.30 (m, 8H, C*H* por.), 8.80 (s, 8H, *CH* por.), 8.84 (s, 2H, Ar*OH*), 8.88 (d, *J*=4.8 Hz, 4H, *CH* por.), 9.17 (d, *J*=4.8 Hz, 4H, *CH* por.), 11.11 (s, 2H, *NH*CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.09, 31.63, 32.70, 34.06, 34.36, 75.11, 117.67, 119.82, 119.87, 120.03, 126.03, 126.57, 126.71, 127.29, 127.54, 132.57, 134.48, 135.03, 137.71, 138.46, 142.24, 142.28, 143.89, 148.55, 149.17, 149.49, 165.95. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1689 (C═O), 3320 (OH, NH). EA calcd for $C_{136}H_{118}N_{10}O_6$: C, 82.15; H, 5.98; N, 7.04. Found: C, 82.58; H, 6.24; N, 7.34. FAB MS *m/z* (rel. int.) 1990 $[M+1]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 417 (730), 516 (37.9), 551 (17.9), 591 (11.5), 646 (8.6).

Method B. A solution of **4** (130 mg; 0.17 mmol) and dicyclohexyl carbodiimide (141 mg; 6.82 mmol) in CH_2Cl_2 (10 ml) was stirred for 10 min and then MAP (215 mg; 0.34 mmol) was added. The reaction mixture was then stirred for 2 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in $CHCl_3$ (50 ml) and washed with water (30 ml). The organic layer was dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel using $CHCl_3$/petroleum ether (5:1) mixture as an eluent to yield the product **9**, identical with the above-obtained sample (264 mg, 78%).

3.1.2. Synthesis of derivative 10. Analogously to the synthesis of **9** (Method B) starting from **7** (150 mg; 0.18 mmol) and DCC (141 mg; 0.682 mmol) product **10** was obtained as a purple powder after column chromatography on silica gel using $CHCl_3$/petroleum ether (4:1) mixture as an eluent (270 mg, 72%). Mp >350°C ($CHCl_3$/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.74 (s, 4H, NH por.), 1.28 (s, 18H, Bu^t), 1.37 (s, 18H, Bu^t), 5.11 (s, 4H, OCH_2CO), 7.74 (m, 20H, CH por.), 7.78 (s, 4H, H-arom), 7.86 (s, 4H, H-arom), 8.20 (m, 10H, CH por.), 8.34 (s, 8H, CH por.), 8.84 (s, 8H, CH por.), 8.94 (d, *J*=4.8 Hz, 4H, CH por.), 9.28 (d, *J*=4.8 Hz, 4H, CH por.), 9.51 (s, 2H, ArOH), 11.13 (s, 2H, NHCO). EA calcd for $C_{132}H_{110}N_{10}O_6S_4$: C, 76.94; H, 5.38; N, 6.80; Found: C, 77.39; H, 5.71; N, 7.13. FAB MS *m/z* (rel. int.) 2062.9 $[M+1]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 417 (620), 516 (31.3), 551 (14.5), 591 (9.1), 647 (7.3).

3.1.3. Synthesis of derivative 13. A mixture of **9** (100 mg, 5.03×10^{-2} mmol) and K_2CO_3 (70 mg, 0.503 mmol) in anhydrous DMF (10 ml) was stirred for 30 min. Thereafter ethyl bromoacetate (56 μl, 0.51 mmol) and a catalytic amount of KI were added and the reaction mixture was stirred for 4 days at room temperature. DMF was removed in vacuo and the residue was stirred overnight in a $CHCl_3$/water mixture (30 ml/30 ml). The organic layer was dried over $MgSO_4$ and evaporated under a reduced pressure. The residue was purified by column chromatography using $CHCl_3$/acetone (2:1) mixture with 2% Et_3N as an eluent to give the pure product as purple micro crystals (72 mg, 67%). Mp 263–265°C ($CHCl_3$/ethanol). ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.78 (s, 4H, NH por.), 1.16 (s, 18H, Bu^t), 1.20 (s 18H, Bu^t), 1.47 (t, *J*=7.3 Hz, 6H, OCH_2CH_3), 1.54 (t, *J*=7.3 Hz, 6H, OCH_2CH_3), 3.50 (d, *J*=11.7 Hz, 4H, Ar*CH*$_2$Ar), 4.43 (q, *J*=7.0 Hz, 4H, O*CH*$_2$CH$_3$), 4.50 (d, *J*=11.7 Hz, 4H, Ar*CH*$_2$Ar), 4.62 (s, 4H, *CH*$_2$CO), 4.67 (q, *J*=7.0 Hz, 4H, O*CH*$_2$CH$_3$), 4.83 (s, 4H, *CH*$_2$CO), 4.91 (s, 4H, *CH*$_2$CO), 7.19 (s, 8H, H-arom), 7.78 (m, 16H, H-arom), 7.89 (d, *J*=8.1 Hz, 4H, H-arom), 4.52 (d, *J*=5.9 Hz, 8H, H-arom), 8.34 (d, *J*=7.7 Hz, 4H, H-arom), 8.79 (d, *J*=7.7 Hz, 4H, H-arom), 8.86 (brs, 16H, H-arom), 8.94 (m, 2H, H-arom). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.46, 29.69, 30.11, 31.32, 34.22, 36.94, 51.85, 61.83, 61.97, 73.52, 74.45, 117.79, 120.45, 120.74, 125.83, 125.98, 126.16, 126.49, 126.73, 127.83, 134.57, 136.36, 139.97, 142.03, 148.37, 150.09, 150.56, 169.17, 170.40, 171.24. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1749, 1676 (C═O), 3322 (NH). EA calcd for $C_{152}H_{142}N_{10}O_{14}$: C, 78.26; H, 6.14; N, 6.00; Found: C, 78.51; H, 6.47; N, 6.33. FAB MS *m/z* (rel. int.) 2357.5 $[M+Na]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 419 (650), 516 (25.3), 550 (11.8), 590 (7.7), 645 (5.5).

3.1.4. Synthesis of derivative 14. Na_2CO_3 (32 mg; 0.302 mmol) and $BrCH_2COOEt$ (34 μl; 0.306 mmol) were added to a solution of **10** (63 mg; 3.06×10^{-2} mmol) in anhydrous acetone and the reaction mixture was refluxed for 5 days. The solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (15 ml) and washed with water (20 ml). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by preparative TLC using CH_2Cl_2/ethyl acetate/petroleum ether mixture (1:1:12) as an eluent to give 22 mg of the title compound (32%) as a purple powder. Mp 236–239°C ($CHCl_3$/MeOH). ^{1}H NMR (300 MHz $CDCl_3$) δ: −2.87 (s, 4H, *NH* por.), 1.00 (t, *J*=7.3 Hz, 3H, OCH_2CH_3), 1.15 (s, 18H, Bu^t), 1.18 (s, 9H, Bu^t), 1.31 (s, 9H, Bu^t), 4.43 (q, *J*=7.3 Hz, 2H, O*CH*$_2$CH$_3$), 5.00 (d, *J*=15.4 Hz, 2H, O*CH*$_2$CONH), 5.05 (s, 2H, O*CH*$_2$COOEt), 5.45 (d, *J*=15.4 Hz, 2H, O*CH*$_2$CONH), 7.4 (brs, 8H, H-arom), 7.48 (m, 8H, H-arom), 7.68 (s, 2H, H-arom), 7.75 (m, 8H,

H-arom), 7.84 (d, *J*=7.0 Hz, 4H, H-arom), 8.23 (m, 16H, H-arom), 8.52 (d, *J*=4.8 Hz, 4H, H-arom), 8.68 (d, *J*=4.0 Hz, 4H, H-arom), 8.79 (m, 4H, H-arom), 8.87 (m, 4H, H-arom), 10.51 (s, 1H, CO*NH*). FAB MS *m/z* (rel. int.) 2147.7 $[M+H]^+$ (100).

3.1.5. Synthesis of derivative 15 and 16. To a solution of **10** (150 mg; 7.28×10^{-2} mmol) in anhydrous DMF (20 ml), $BrCH_2COOEt$ (81 μl, 0.73 mmol), Na_2CO_3 (78 mg, 0.73 mmol) and NaI (10 mg, 6.67×10^{-2}) were added and the reaction mixture was stirred for 7 days at room temperature. DMF was removed under reduced pressure, the residue was dissolved in $CHCl_3/H_2O$ (50 ml/100 ml) mixture and stirred overnight. The organic layer was separated, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel using CH_2Cl_2/Et_3N (100:1) to give two conformations of the product: *1,3 alternate* **16** (70 mg, 43%) and *cone* **15** (48 mg, 30%).

*Compound **15***. Mp 271–275°C ($CHCl_3$/MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: −2.75 (s, 4H, NH por.), 1.06 (s, 18H, Bu^t), 1.09 (t, *J*=7.1 Hz, 6H, OCH_2CH_3), 1.42 (s, 18H, Bu^t), 4.17 (q, *J*=7.1 Hz, 4H, OCH_2CH_3), 5.00 (s, 4H, OCH_2COOEt), 5.70 (s, 4H, OCH_2CONH), 7.21 (s, 4H, H-arom), 7.64 (t, *J*=7.4 Hz, 8H, CH por.), 7.71 (t, *J*=7.4 Hz, 4H, CH por.), 7.79 (m, 6H, CH por.), 7.87 (s, 4H, H-arom), 8.09 (d, *J*=7.1 Hz, 8H, CH por.), 8.25 (d, *J*=6.6 Hz, 4H, CH por.), 8.28 (d, *J*=8.2 Hz, 4H, CH por.), 8.39 (d, *J*=8.2 Hz, 4H, CH por.), 8.77 (d, *J*=4.4 Hz, 4H, CH por.), 8.81 (d, *J*=4.4 Hz, 4H, CH por.), 8.85 (d, *J*=4.3 Hz, 4H, CH por.), 8.94 (d, *J*=4.3 Hz, 4H, CH por.), 11.15 (s, 2H, *NH*CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.01, 29.70, 30.99, 31.35, 34.22, 34.41, 72.61, 74.72, 119.86, 119.96, 120.01, 120.06, 126.52, 126.65, 127.54, 127.64, 128.20, 128.26, 133.22, 134.44, 134.55, 135.06, 136.73, 137.80, 138.42, 142.07, 142.21, 147.11, 147.63, 156.46, 159.25, 168.16, 168.99. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1751, 1679 (C═O), 3295 (NH). EA calcd for $C_{140}H_{122}N_{10}O_{10}S_4$: C, 75.31; H, 5.51; N, 6.27; Found: C, 74.81; H, 5.47; N, 5.91. FAB MS *m/z* (rel. int.) 2233.0 $[M+1]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 418 (670), 516 (30.7), 550 (13.3), 591 (9.1), 646 (6.8).

*Compound **16***. Mp 243–245°C ($CHCl_3$/MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ: −2.69 (s, 4H, *NH* por.), 1.26 (s, 18H, Bu^t), 1.27 (t, *J*=7.1 Hz, 6H, OCH_2CH_3) 1.36 (s, 18H, Bu^t), 4.27 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 4.74 (s, 4H, OCH_2COOEt), 5.08 (s, 4H, OCH_2CONH), 6.76 (brs, 4H, CH por.), 6.98 (brs, 8H, CH por.), 7.65 (s, 4H, H-arom), 7.68 (s, 4H, H-arom), 7.78 (m, 6H, CH por), 7.81 (d, *J*=8.0 Hz, 4H, CH por.), 7.92 (d, *J*=7.3 Hz, 8H, CH por.), 8.11 (d, *J*=8.0 Hz, 4H, CH por.), 8.22 (d, *J*=6.6 Hz, 4H, CH por.), 8.68 (d, *J*=4.0 Hz, 4H, CH por.), 8.75 (d, *J*=4.2 Hz, 4H, CH por.), 8.81 (d, *J*=4.2 Hz, 4H, CH por.), 8.85 (d, *J*=4.3 Hz, 4H, CH por.), 9.17 (brs, 2H, *NH*CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.19, 29.70, 30.97, 31.35, 34.54, 60.71, 65.93, 117.97, 119.49, 120.06, 126.05, 126.63, 127.02, 127.66, 128.41, 128.76, 132.87, 133.99, 134.53, 134.89, 137.36, 138.51, 141.85, 142.21, 147.54, 147.92, 155.81, 156.66, 166.74, 167.62. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1770, 1685 (C═O), 3286 (NH). EA calcd for $C_{140}H_{122}N_{10}O_{10}S_4$: C, 75.31; H, 5.51; N, 6.27; Found: C, 74.88; H, 5.27; N, 5.95. FAB MS *m/z* (rel. int.) 2233.0 $[M+H]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$) in parentheses: 419 (690), 516 (30.4), 551 (16.2), 591 (9.3), 647 (7.0).

3.1.6. Synthesis of derivative 20. A solution of **18**[16] (30 mg, 3.4×10^{-2} mmol) and $(COCl)_2$ (0.3 ml, 3.4 mmol) in anhydrous CCl_4 (5 ml) was refluxed for 4 h. The solvent was removed in vacuum and the residue was dissolved in anhydrous CH_2Cl_2 (5 ml). The CH_2Cl_2 was distilled off again. This procedure was repeated twice. The resulting acyl chloride **19** was then dried in high vacuo for 1 h. The crude product was dissolved in 5 ml of anhydrous THF and this solution was added dropwise to a mixture of MAP (107 mg, 0.17 mmol) and Et_3N (38 μl, 0.27 mmol) in anhydrous THF (5 ml). The reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in $CHCl_3$ (30 ml) and washed with water (20 ml). The separated organic layer was dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel using $CHCl_3$/petroleum ether (3:1) mixture containing 2% of Et_3N as an eluent to yield the product as a purple powder (50 mg, 45%). Mp >350°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.91 (s, 8H, *NH* por.), 1.27 (s, 36H, Bu^t), 3.64 (d, *J*=13.19 Hz, 4H, CH_2 eq.), 5.05 (d, *J*=13.19 Hz, 4H, CH_2 ax.), 5.13 (s, 8H, CH_2CO), 7.08 (brs, 16H, CH por.), 7.23 (s, 8H, H-arom), 7.63 (brs, 8H, CH por.), 7.75 (s, 24H, CH por.), 8.19 (d, *J*=4.03 Hz, 16H, H por.), 8.29 (brs, 8H, H por.), 8.62 (brs, 8H, H por.), 8.71 (brs, 8H, H por.), 8.76 (d, *J*=4.03 Hz, 16H, H por.), 10.00 (s, 4H, *NH*CO). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.46, 34.27, 73.55, 119.134, 119.84, 126.06, 126.60, 127.08, 127.58, 132.82, 134.02, 134.47, 135.32, 136.72, 137.21, 141.61, 142.16, 146.20, 168.32. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1681 (C═O), 3321 (NH). EA calcd for $C_{228}H_{180}N_{20}O_8$: C, 82.29; H, 5.45; N, 8.42; Found: C, 81.81; H, 5.17; N, 8.11. FAB MS *m/z* (rel. int.) 3326.6 $[M+1]^+$ (100). UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 419 (990), 517 (63.7), 552 (30.9), 591 (19.5), 648 (16.4).

3.1.7. Synthesis of derivative 24. A solution of **22** (30 mg, 3.15×10^{-2} mmol) and oxalyl chloride (0.3 ml, 3.4 mmol) in anhydrous CCl_4 (5 ml) was refluxed for 4 h. The solvent was distilled off, the residue was dissolved in anhydrous CH_2Cl_2 (5 ml) and the solvent was distilled off again. After drying in high vacuo for 1 h the acyl chloride **23** was dissolved in 5 ml of absolute THF and the resulting solution was added to a solution of MAP (100 mg, 0.16 mmol) and Et_3N (38 μl, 0.27 mmol) in anhydrous THF (5 ml). The reaction mixture was stirred for 2 h at room temperature. THF was removed in vacuo, the residue was dissolved in $CHCl_3$ (30 ml) and washed with water (20 ml). The organic layer was dried over $MgSO_4$. The crude reaction mixture was purified by column chromatography on silica gel using petroleum ether/$CHCl_3$/ethyl acetate (4:1:1) with 2% Et_3N as an eluent to yield the product as a purple powder (65 mg, 71%). Mp >350°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: −2.89 (s, 8H, NH por.), 1.31 (s, 36H, Bu^t), 5.69 (s, 8H, CH_2CO), 7.09 (t, *J*=6.96 Hz, 8H, H-arom), 7.21 (t, *J*=6.22 Hz, 4H, H-arom), 7.70 (m, 44H, H-arom), 8.18 (d, *J*=5.13 Hz, 8H, H-arom), 8.26 (d, *J*=8.42 Hz, 8H, H-arom), 8.36 (d, *J*=4.40 Hz, 8H, H-arom), 8.49 (d, *J*=8.42 Hz, 8H,

H-arom), 8.65 (d, J=4.76 Hz, 8H, H-arom), 8.76 (d, J=4.76 Hz, 8H, H-arom), 8.82 (d, J=4.76 Hz, 8H, H-arom), 10.36 (s, 4H, *NH*CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.26, 34.55, 75.83, 118.80, 119.51, 119.79, 119.88, 126.08, 126.61, 127.08, 127.58, 127.93, 134.10, 134.51, 135.39, 137.32, 138.83, 141.74, 142.27, 148.21, 158.15, 167.28. IR ($CHCl_3$) ν_{max} (cm^{-1}): 1690 (C=O), 3320 (NH). EA calcd for $C_{224}H_{172}N_{20}O_8S_4$: C, 79.13; H, 5.10; N, 8.24; Found: C, 78.81; H, 5.17; N, 8.01. UV–VIS (CH_2Cl_2) λ_{max} (nm), ε ($mM^{-1}\,cm^{-1}$): 419 (1 020), 517 (62.2), 552 (29.9), 592 (19.0), 648 (15.7).

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