J Incl Phenom Macrocycl Chem (2010) 67:241–246
DOI 10.1007/s10847-009-9697-4

SHORT COMMUNICATION

Electrostatic interaction between cationic calix[4]pyrroles and anionic porphyrins in water

Bhaskar Garg · Tanuja Bisht · Shive Murat Singh Chauhan

Received: 5 October 2009 / Accepted: 29 October 2009 / Published online: 2 December 2009
© Springer Science+Business Media B.V. 2009

Abstract The formation and characterization of molecular assemblies resulting from mixing of solutions of tetracationic calix[4]pyrroles and tetraanionic porphyrins in water are reported. The self-assembly of the complementary building blocks was quantitatively studied by UV–vis, ^{1}H NMR, Fluorescence and ESI–MS. Binding constants calculated by absorption spectroscopic titrations were in the range of 10^3–10^5 M^{-1}. The results indicate that the cationic thiacalix[4]pyrroles show greater binding affinity towards metal free porphyrins than metalloporphyrins under neutral conditions.

Keywords Thiacyclohexanocalix[4]pyrroles · Self-assembly · Ionic interactions · Anionic porphyrins · Absorption spectroscopy

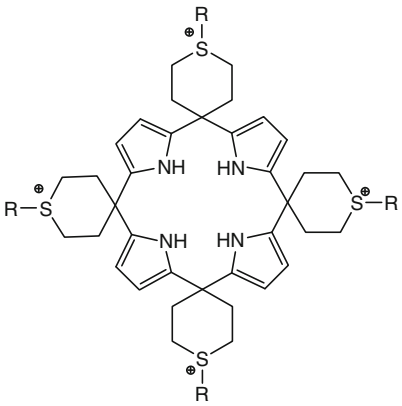
Introduction

In recent years, calix[4]pyrroles, dating from the late 1880s have established in a range of applications under various disciplines of supramolecular chemistry [1–6]. In particular these stable porphyrinogens, structurally related to porphyrins and conformationally to calixarenes have shown considerable potential in the host–guest binding of anions [7]. This anion binding ability has spawned recent efforts to design and synthesize new homologues. In an elegant work, calixpyrrole containing appended carboxylate groups are well documented in self-assembly processes with calixarene, resorcinarene and 5′-guanosine monophosphate [8–10]. More recently, a different strategy has been introduced for the preparation of heteroditopic receptors for anion recognition and fixation that relies on the use of side arm(s) strapping [11, 12]. In all the above mentioned features, H-bonding appears to be the prime interaction type in calixpyrroles as deduced by the sensitivity of complex affinity on the H-bond acceptor strength of the anions. However, a subsidiary interaction mode utilizing electron rich periphery of calixpyrroles for binding metals or neutral molecules through metal–π, π–π stacking, π–H or charge transfer interactions have also been taken into account [13]. Indeed such findings of interest in their own right provide a stimulus to generate calixpyrrole-supramolecular architectures based on novel interactions other than H-bonding.

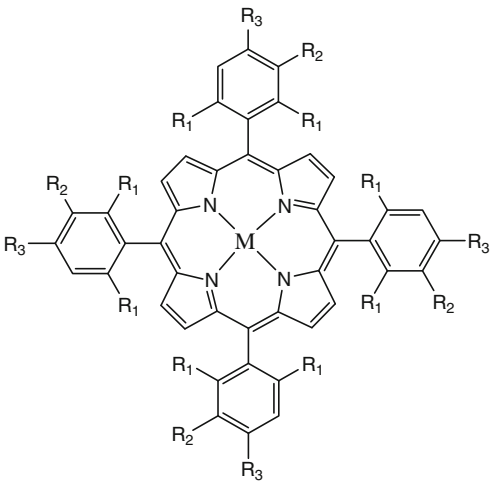
Simple ionic interactions are often employed as an important attractive force in medical, biological and artificial molecular recognition. A large number of supramolecular complexes are based on the assembly of different components making use of electrostatic interactions [14]. Needless to say that to achieve these aims water solubility represents an essential requirement. In recent years, calixarenes and a little bit porphyrin building blocks are frequently used in the formation of water soluble molecular cages through ionic interactions [15–18]. However, to date no reports on calixpyrrole based supramolecular assembly formed mainly through ionic interactions are available in the literature. We anticipated that multiple ionic interactions, based on calixpyrrole and porphyrins would provide a novel class of easily accessible supramolecular complexes. Herein, we report the formation and characterization of molecular assemblies **1.2** that consist of a tetracationic 5,10,15,20-tetraspirocyclohexyl thiacalix[4]pyrroles **1** and a tetraanionic porphyrins **2** (Fig. 1).

B. Garg · T. Bisht · S. M. S. Chauhan (✉)
Bioorganic Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India
e-mail: smschauhan@chemistry.du.ac.in

Fig. 1 Chemical structures of assembly components, cationic calixpyrrole **1** and anionic porphyrins **2**



1a. R=Me
1b. R=Et



2a. R_1,R_2=H, R_3= SO_3Na,M=2H
2b. R_1,R_2=H, R_3= SO_3Na,M=Zn
2c. R_1=Cl,R_2= SO_3Na, R_3=H, M=2H
2d. 2c. R_1=Cl,R_2= SO_3Na, R_3=H, M=2H

Experimental

General

The absorption spectra were recorded on a Perkin Elmer Lambda 35 UV–vis spectrophotometer. The IR spectra were recorded on Perkin Elmer FT-2000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300, 75 MHz) spectrometer using tetramethylsilane (TMS) as internal standard. The ESI–MS were recorded on LC-TOF (KC-455) mass spectrometer of Waters. Fluorescence spectra were recorded on Shimadzu RF-5301 spectrophotometer. Column chromatography was carried out using silica gel 60–120 mesh and 230–400 mesh of Spectrochem. The solid compounds were dried under vacuum in the presence of P_2O_5. All reagents and chemicals were purchased as analytical grade and were used with out further purification.

Synthesis

Cationic thiacyclohexanocalix[4]pyrrole alkyl sulfonium salts **1a** and **1b** were prepared in quantitative yields by minor modifications of known procedure [19]. Meso-tetrakisthiocyclohexano calix[4]pyrrole methyl sulfonium hexafluorophosphate: Meso-tetrakisthiocyclohexano calix[4]-pyrrole methylsulfonium iodide (200 mg, 0.16 mmol) was dissolved in methanol (5 mL) and excess of potassium hexafluorophosphate was added. The reaction mixture was stirred at ambient temperature for 5 h. After the completion of the reaction, solvent was evaporated in vacuum. The methanol was added to give yellow residue of phosphate salt which was filtered and dried. Yield: 176 mg, 85%; ^1H NMR (300 MHz, D_2O, 298 K): $\delta = 2.50$ (*br*, 28H, CH_2C and CH_3S), 2.99 (*br*, 8H, CH_2S), 3.32 (*br*, 8H, CH_2S), 5.83 (*m*, 8H, β-pyrrole); ESI–MS: 1,323.1842 $[M + Na]^+$ calculated for $C_{40}H_{56}F_{24}N_4NaP_4S_4$. The anionic 5,10,15,20-tetrakis(4′-sulfonatophenyl)porphyrin **2a** was prepared by reaction of pyrrole and benzaldehyde followed by sulfonation with oleum. The 5,10,15,20-tetrakis(2′,6′-dichloro-3′-sulfonatophenyl) porphyrin **2c** was synthesized by condensation of pyrrole and 2,6-dichlorobenzaldehyde in dry chloroform followed by oxidation and subsequent sulfonation. Metallation of **2a** and **2c** with zinc acetate afforded **2b** and **2d** in 85 and 79% yields respectively [20, 21].

Results and discussion

Ionic interaction studies

UV–vis spectroscopy

The two building blocks are readily soluble in water. 2.5 mL solution of porphyrin **2** (2×10^{-6} M) in water were taken in quartz cell and titrated with an increasing volume of **1** (1×10^{-5}–30×10^{-4} M) in water. The aggregation of porphyrin was not observed at this concentration range. Stepwise addition of **1a–1b** to **2a–2d** results in pronounced UV–vis spectral changes. Figure 2 shows that the intensity of the Soret band, corresponding B transition of porphyrin **2a** at 413 nm decreases gradually upon increasing the concentration of **1a**, with a well defined isobestic point at 448 nm. In all the cases, 1:1 stoichiometry was determined for **1.2** assemblies by method of continuous variation. The apparent binding

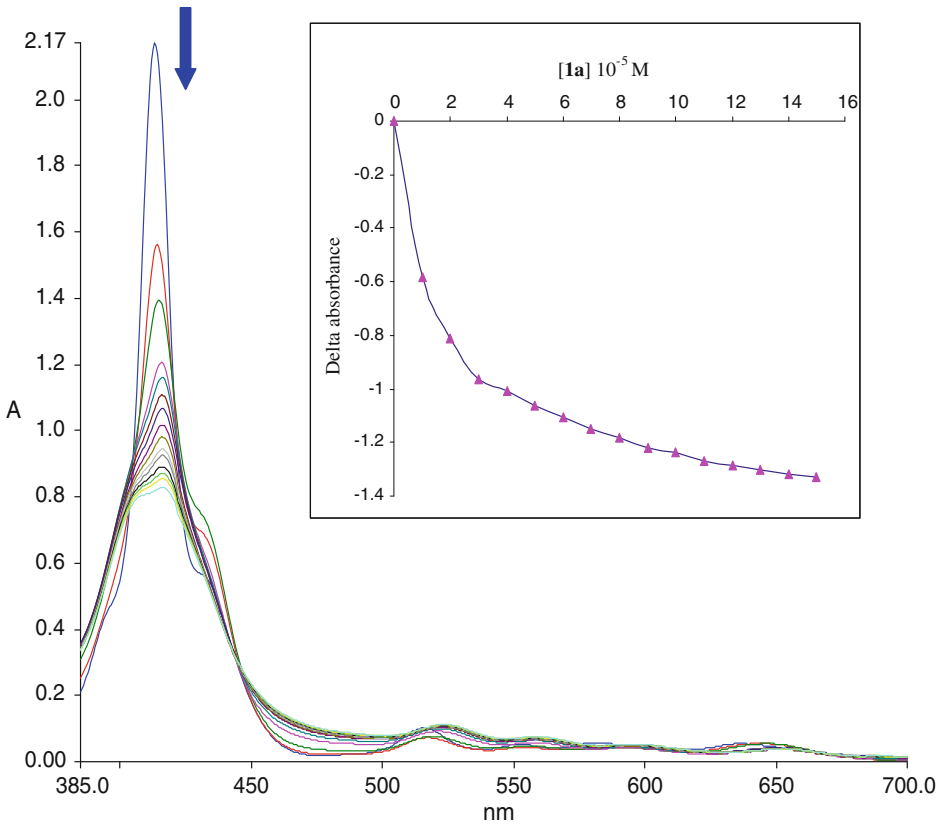


Fig. 2 UV–vis spectra of **2a** (2.0×10^{-6}) in water upon addition of **1a** (1×10^{-5}–1.6×10^{-4}); *inset*: the changes at 413 nm (Soret band) as a function of **1a**

Table 1 Binding constants (K_{ass}) for assembly between cationic thiacalix[4]pyrrole (**1a** and **1b**) and anionic porphyrins (**2a–2d**) at 22 °C

Molecular assembly	pH	Solvent[a]	Binding constant K_{ass} (M^{-1})
2a.1a	7.0	H_2O	5.28×10^5
2a.1b	7.0	H_2O	3.29×10^5
2b.1a	7.0	H_2O	2.92×10^4
2c.1a	7.0	H_2O	1.95×10^3
2d.1a	7.0	H_2O	3.3×10^2
2b.1a	9.2	H_2O	3.81×10^3
2b.1a	4.0	H_2O	n.d.[b]
2a.1a	7.0	MeOH:H_2O	1.24×10^4
2a.1a	7.0	DMSO	n.d.[b]
2a.1a	7.0	MeOH	7.96×10^3

Determined by absorption spectroscopic titrations

[a] All pH solutions were prepared in phosphate buffer

[b] Not determined. Errors are less than ±18%

constants for assembly $K_{1.2}$ were determined by quantitative absorption spectroscopic titrations [22] and are summarized in Table 1. It is clear that binding constants $K_{\mathbf{1.2a}} > K_{\mathbf{1.2b}}$ i.e. metal free porphyrins strongly bind with calix[4]pyrroles. Presumably, it is due to greater flexibility of metal free porphyrins that should allow a more optimal interaction between two moieties. Moreover, $K_{\mathbf{1.2a}} > K_{\mathbf{1.2c}}$; it is explicable on account of steric reasons. In the case of **2a**, the sulfonato groups are at 4-position while in **2c** the negative centers are at more hindered 3-position, the negative charge on sulfonato groups of **2a** is easily available for positive centers of calix[4]pyrroles **1a** for effective interaction. The results emerges that a change of the alkyl chain at the sulfur has almost no effect on the strength of the ion pair complex.

Solvent, salt and pH effect

The stability of molecular assemblies **1.2** was examined in different polar solvents (H_2O, MeOH, MeOH:H_2O 1:1, DMSO). The UV–vis experiments revealed that water is most suitable for assembly formation in which aggregates hold together very strongly. In polar aprotic solvent like DMSO, the spectral changes were not sufficient to determine binding constants. The ^{1}H NMR spectroscopy essentially confirmed this, when titrations of **2a** didn't show any noticeable spectral changes even upon addition of excess of **1a**. This indicates a different solvation shell around the porphyrin upon complex formation.

The assembly formation between **1** and **2** was also studied at different pH. At pH 9.2, the titrations of **2b** with **1a** showed a constant decrease as well as significant broadening in the Soret band (Fig. 3). Consistent and reproducible results were obtained with **2d**. On the contrary, the UV–vis spectral changes could not be rationalized under

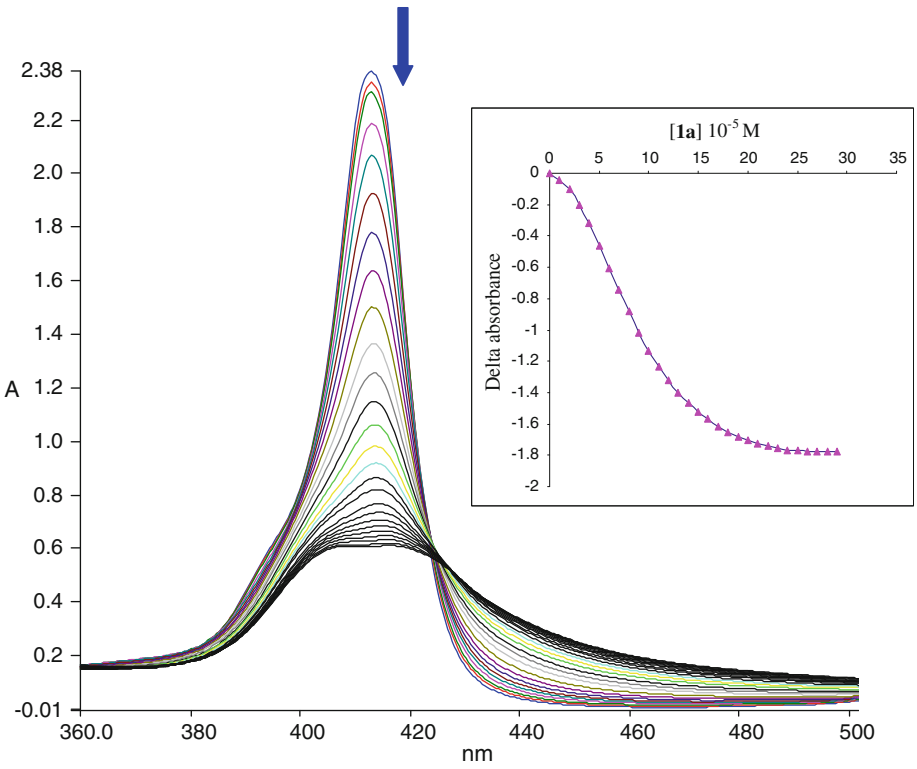


Fig. 3 UV–vis spectra of **2b** (2.0×10^{-6}) in water upon addition of **1a** (1×10^{-5}–4×10^{-4}) at pH 9.2; *inset*: the changes at 413 nm (Soret band) as a function of **1a**

acidic conditions. Indeed, at pH 4, the metal free porphyrin **2a** itself showed significant bathochromic shifting of ~25 nm due to self-aggregation, a characteristic of anionic porphyrins. Furthermore, gradual addition of **1a** to the solution of **2a** resulted fine splitting in the Soret band with new maxima's located at 417 and 438 nm at the end point of titration. The results indicate that neutral condition is most suitable for ionic interaction.

Fluorescence spectroscopy

In order to correlate the results, obtained by UV–vis spectroscopy, the titration of porphyrins (**2a–2d**, 2.0×10^{-6} M) with **1a** was performed by fluorescence spectroscopy. Taken into account of the heavy atom effect of **1a** on fluorescence spectra, the counter anion was replaced with hexafluorophosphate, most suitable for spectrofluorometry. On gradual addition of **1a** into solution of **2a**, the characteristic peak at 643 nm quenches with significant broadening. A clear hump at 668 nm was detected at the end point of the titration. The binding constants calculated by fluorescence spectroscopy were in good agreement with that of UV–vis spectroscopy.

ESI–MS spectrometry

The additional evidence for the formation of molecular assemblies **1.2** was also obtained with ESI–MS by mixing equimolar solutions (5×10^{-5} M) of **1** and **2**. For instance, the positive ion mode ESI–MS spectrum of assembly **1a.2a** in CH_3OH showed two peaks at m/z = 1,673.3 Da [**1a.2a**-3Na-4I$^-$]$^+$ and 1,696.3 Da [**1a.2a**-2Na-4I$^-$]$^{2+}$ for singly and doubly charged species respectively (Fig. 4). In addition, the spectrum shows one major peak at m/z = 931.4 Da corresponding to porphyrin **2a** [**2a** + H$^+$-4Na]$^+$ with the lost four sodium groups under the mass spectroscopic conditions. Other small peaks at m/z = 720.0 Da [**1a**-4I$^-$], 675.0 and 422.5 Da were recognized for intact thiacalix[4]pyrrole, [**1a**-$(CH_3)_3$–$(NO_3)_4$]$^+$ and [**1a**-$(NO_3)_2$]$^{2+}$ respectively. The absence of signals of trimers and tetramers, etc. indicates that the signals correspond to an assembly and not to associates.

^{1}H NMR spectroscopy

The ^{1}H NMR titrations of **2** with **1** (1×10^{-4} M each) in CD_3OD/D_2O mixture exhibited significant spectral changes (Fig. 5). In case of **1a.2a**, the largest shift changes were observed for the $H_{o\text{-sulfo}}$ ($\Delta\delta = 0.77$ ppm) and $H_{m\text{-sulfo}}$ ($\Delta\delta = 0.58$ ppm) H-atoms of the aromatic system with significant broadening. The largest downfield shift for $H_{o\text{-sulfo}}$ is supposed to be as a consequence of their close proximity to the cationic groups of **1a**. However, no changes were observed for the β-pyrrolic protons of **2a**. In contrast, the signals of the cyclohexyl protons of **1a** underwent a noticeable upfield shift ($\Delta\delta_{cyclohexyl} \geq$

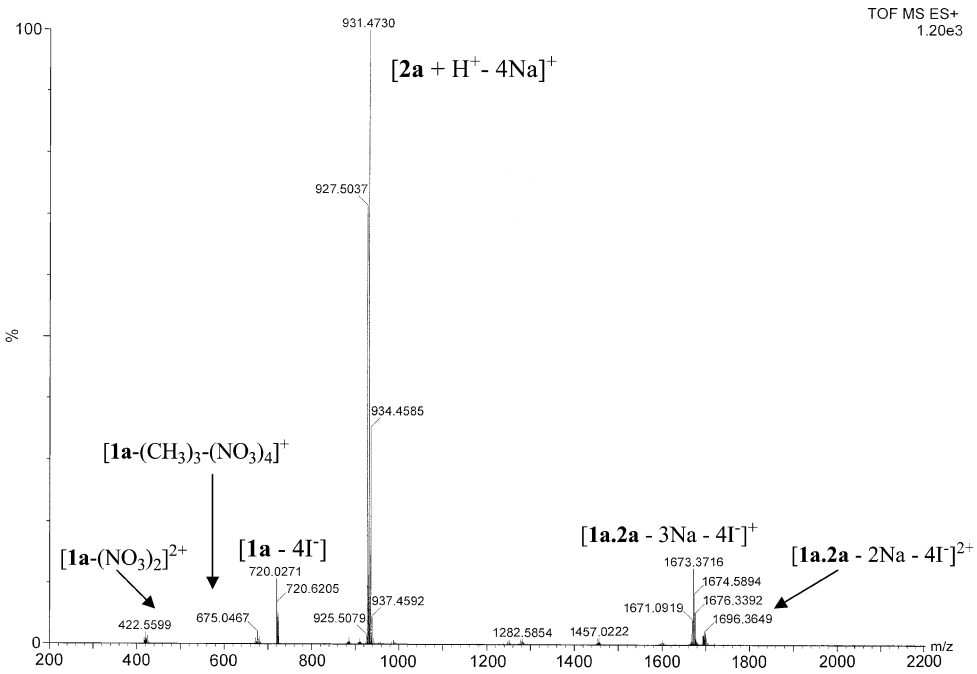


Fig. 4 ESI-MS spectra of 1:1 complex of cationic thiacalix[4]pyrrole **1a** and anionic porphyrin **2a** in MeOH

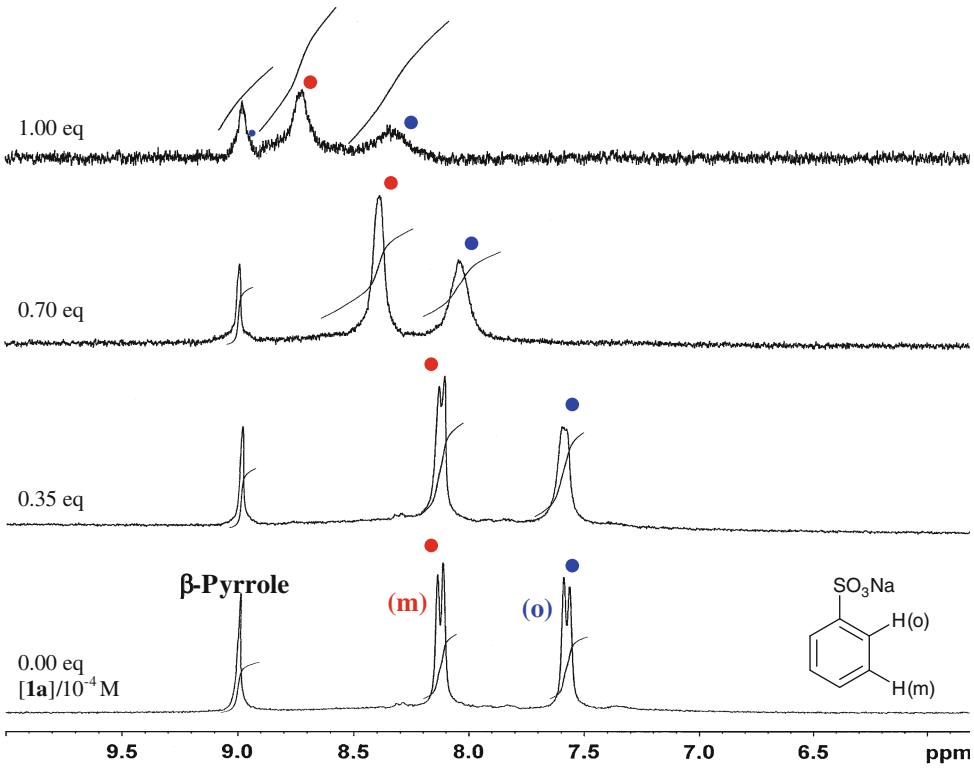


Fig. 5 Selected region of ^{1}H NMR titrations of anionic porphyrin **2a** (1×10^{-4} M) with cationic calix[4]pyrrole **1a** (1×10^{-4} M) in CD_3OD/D_2O

0.10 ppm). A similar upfield shift was also recognized for the β-pyrrolic protons of **1a** ($\Delta\delta_{\beta\text{-pyrrolic}} = 0.05$ ppm). The titration experiments revealed that till a 1:1 ratio is attained, all **1a** is bound. This is concluded from the negligible changes in the shifts of sulfonato protons which further confirmed the 1:1 stoichiometry between two complementary building blocks.

Conclusions

We have introduced a simple strategy for the formation of new type of molecular assemblies. In the present study, the assembly process is based on ionic interactions; the tetrasulfonium alkyl functionalized calix[4]pyrroles readily associate with the anionic porphyrins as confirmed by

different spectroscopic techniques. These findings have opened new way for the use of calix[4]pyrroles as molecular receptors or drug delivery systems in physiological media. The encapsulation of different drugs as guest molecules is now under investigation based on this strategy.

Acknowledgments The authors are thankful to the Department of Science and Technology (DST) for project number SR/S1/OC-54/2003, Council of Scientific and Industrial Research (CSIR) and University of Delhi, New Delhi for financial assistance.

References

1. Gale, P.A., Anzenbacher Jr, P., Sessler, J.L.: Calixpyrroles II. Coord. Chem. Rev. **222**, 57–102 (2001)
2. Jain, V.K., Mandalia, H.C.: The chemistry of calixpyrrole. Heterocycles **71**, 1261–1314 (2007)
3. Aydogan, A., Coady, D.J., Kuk Kim, S., Akar, A., Bielawski, C.W., Marquez, M., Sessler, J.L.: Poly(methyl methacrylate)s with pendant calixpyrroles and crown ethers: polymeric extractants for potassium halides. Angew. Chem., Int. Ed. **47**, 9648–9652 (2008)
4. Jain, V.K., Mandalia, H.C., Gupte, H.S., Vyas, D.J.: Azocalix[4]pyrrole Amberlite XAD-2: new polymeric chelating resins for the extraction, preconcentration and sequential separation of Cu(II), Zn(II) and Cd(II) in natural water samples. Talanta **79**, 1331–1340 (2009)
5. Blangy, V., Heiss, C., Khlebnikov, V., Letondor, C., Stoeckli-Evans, H., Neier, R.: Synthesis, structure, and complexation properties of partially and completely reduced meso-octamethylporphyrinogens (calix[4]pyrroles). Angew. Chem., Int. Ed. **48**, 1688–1691 (2009)
6. Fisher, M.G., Gale, P.A., Hiscock, J.R., Hursthouse, M.B., Light, M.E., Schmidtchen, F.P., Tonga, C.C.: 1,2,3-Triazole-strapped calix[4]pyrrole: a new membrane transporter for chloride. Chem. Commun. 3017–3019 (2009)
7. Anzenbacher, P. Jr, Nishiyabu, R., Palacios, M.A.: N-confused calix[4]pyrroles. Coord. Chem. Rev. **250**, 2929–2938 (2006) and references there in
8. Arai, S., Ishihaa, S., Takeoka, S., Ohkawa, H., Shibue, T., Nishide, H.: Stability of porphyrin-calix[4]arene complexes analyzed by electrospray ionization mass spectrometry. Rapid Commun. Mass Spectrom. **18**, 2065–2068 (2004)
9. Sessler, J.L., Andrievsky, A., Gale, P.A., Lynch, V.: Anion binding: self-assembly of polypyrrolic macrocycles. Angew. Chem., Int. Ed. **35**, 2782–2785 (1996)
10. Sessler, J.L., Král, V., Shishkanova, T.V., Gale, P.A.: Cytosine substituted calix[4]pyrroles: neutral receptors for 5′-guanosine monophosphate. PNAS **99**, 4848–4853 (2002)
11. Lee, C.-H., Miyaji, H., Yoona, D.-W., Sessler, J.L.: Strapped and other topographically nonplanar calixpyrrole analogues. Improved anion receptors. Chem. Commun. 24–34 (2008)
12. Panda, P.K., Lee, C.-H.: Metalloporphyrin capped calix[4]pyrroles: hetero-ditopic receptor models for anion recognition and ligand fixation. J. Org. Chem. **70**, 3148–3156 (2005)
13. He, X., Hu, S., Liu, K., Guo, Y., Xu, J., Shao, S.: Oxidized bis(indolyl)methane: a simple and efficient chromogenic-sensing molecule based on the proton transfer signaling mode. Org. Lett. **8**, 333–336 (2006)
14. Oshovsky, G.V., Reinhoudt, D.N., Verboom, W.: Supramolecular chemistry in water. Angew. Chem., Int. Ed. **46**, 2366–2393 (2007) and references there in
15. Fiammengo, R., Timmerman, P., Huskens, J., Versluis, K., Heck, A.J.R., Reinhoudt, D.N.: Non-covalent synthesis of calix[4]arene-capped porphyrins in polar solvents via ionic interactions. Tetrahedron **58**, 757–764 (2002)
16. Corbellini, F., Costanzo, L.D., Crego-Calama, M., Geremia, S., Reinhoudt, D.N.: Guest encapsulation in a water-soluble molecular capsule based on ionic interactions. J. Am. Chem. Soc. **125**, 9946–9947 (2003)
17. Corbellini, F., Knegtel, R.M.A., Grootenhuis, P.D.J., Crego-Calama, M., Reinhoudt, D.N.: Water-soluble molecular capsules: self-assembly and binding properties. Chem. Eur. J. **11**, 298–307 (2005)
18. Oshovsky, G.V., Reinhoudt, D.N., Verboom, W.: The underestimated role of counter ions in electrostatic self-assembly: [1 + 1] Cavitand-calix[4]arene capsules based on azinium–sulfonate interactions. Eur. J. Org. Chem. 2810–2816 (2006)
19. Valik, M., Kra′l, V., Herdtwecka, E., Schmidtchen, F.P.: Sulfoniumcalixpyrrole: the decoration of a calix[4]pyrrole host with positive charges boosts affinity and selectivity of anion binding in DMSO solvent. New J. Chem. **31**, 703–710 (2007)
20. Chauhan, S.M.S., Kumar, A., Srinivas, K.A.: Oxidation of thiols with molecular oxygen catalyzed by cobalt(II) phthalocyanines in ionic liquids. Chem. Commun. 2348–2349 (2003)
21. Lindsey, J.S., Wagner, R.W.: Investigation of the synthesis of ortho-substituted tetraphenylporphyrins. J. Org. Chem. **54**, 828–836 (1989)
22. Connors, K.A.: Binding Constants. Wiley, New York (1987)