Synthesis of a Naphthalimide Functionalized Calix[4]arene; A Host Type Fluorophore for Inclusion Compounds in Organic Medium

IZILDA A. BAGATIN[1], ALEXANDRE T. CRUZ[1], HENRIQUE E. TOMA[1], MÁRIO J. POLITI[1] and GRÉGOIRE J.-F. DEMETS[2],*

[1]Instituto de Química - B12sup. lab 1256/1262-Universidade de São Paulo, Caixa Postal 26077, 05508-000 São Paulo, Brazil; [2]Departamento de Química -F.F.C.L.R.P., Universidade de São Paulo, Av. dos Bandeirantes 3900, 14040-901, Ribeirão Preto, S.P. Brazil

Abstract

This article reports the synthesis and the properties of 5,11,17,23-tetra(t-butyl)-25,27-bis-(ethoxy-1,8-naphthalimide)-26,28-hidroxy-calix[4]arene and the formation of an inclusion compound in organic medium. This functionalized calix[4]arene was conceived as the association of a potential host species with a good fluorophore for optical sensing purposes. Calix[4]-NI as we will call it, maintains its 'cone-pinched' configuration and exhibits typical naphthalimide fluorescence bands in non-polar solvents. Its ability to interact with guest species via hydrogen bonding in its endo-hydrophilic cavity to form inclusion compounds was verified with absorption and fluorescence measurements using N-ethanol-1,8-naphthalimide as guest species, which was projected to fit exactly the host cavity and to interact with its naphthalimide π electrons. For this reason, it was possible to follow the formation of the inclusion compound with electronic spectroscopy.

Introduction

One of the main topics in supramolecular chemistry is molecular recognition, and the possibility to plan molecules able to bind reversibly and selectively with other molecules to form inclusion compounds [1]. A great variety of compounds of the literature are able to accommodate other species, as metallic ions, anions and even larger organic molecules, in their bulk. The most widespread organic structures in the literature for this purpose, known as 'hosts', are certainly the cyclodextrins [2, 3], the crown ethers, the cryptands [4, 5] and the calixarenes [6, 7]. These families of cyclic compounds, present one or more holes or cavities, with different sizes and solvophobicities, which can also contain oxygen, nitrogen or sulphur atoms. These cavities or holes, can thence, be modelled to complex hard or soft acids, polar or non-polar, large or small molecules, by changing their structure and consequently their properties. Furthermore, they can also form hydrogen bonds and present solvophobic interactions with solvent molecules and eventual 'guest' type species [8].

The calixarenes, are well-known macrocyclic compounds, being described earlier by Zinke in the forties and the fifties [9], and by Gutsche some years later [10]. These are extremely useful building blocks for supra-

molecular chemistry because they can be functionalized on their inferior or superior rims, generating a large collection of compounds with very specific functions [11–13]. The phenol-based calix[4]arenes present an hydrophobic cavity on their upper rim and 4 oxygen atoms on their lower hydrophilic rim being, at the same time, a hard base for hard metals complexation and an endo-hydrophilic cavity. These oxygen atoms allow hydrogen bond formation with amines water and alcohols among many others. For this reason, they can be used to elaborate several kinds of chemical sensors for several kinds of large organic and inorganic species [14].

Naphthalimides and naphthalene diimides, on the other hand, are efficient fluorophores having excited states stabilities very sensible to their substituents as well as to the surroundings properties [15]. Changing the nature of the substituents and the solvating environment, affects dramatically their absorption and emission spectra as well as their quantum yields and excited states lifetimes [15]. These molecules are frequently used in fluorescent polymers [16], LASER dyes [17], photodynamic therapy sensitizers, in self-assembled films [18] and many other applications. The association of such fluorophores with ionophore-type host matrices, generates compounds that exhibit specific spectroscopic properties, typical of their association states [19]. This kind of association is the starting point for the tailoring

---

of interaction-specific molecular probes for optical and electrochemical sensors. Vysotsky *et al.* [20] have synthesized naphthalimide modified calixarenes on the upper rim of the cavitand with interesting results. Here, we describe the synthesis of a new calix[4]arene modified with naphthalimides in the bottom rim. Its spectroscopic data have shown strong evidences of the formation of an inclusion compound with *N*-ethanol-1,8-naphthalimide, used as a probe molecule, indicating that the imide functionalized calixarene could be used for optical sensing purposes [21].

Experimental details

Fluorescence data were obtained on a Photon Technology instrument (PTI), using a 1-cm quartz cell and using $\lambda_{exc} = 333$ nm. Vibrational spectra were carried on a Bomem ABB series. NMR spectra were obtained with a Varian Inova 300 instrument, at room temperature, in $CDCl_3$ solution as internal reference. UV–Vis spectra were recorded on a Shimadzu UV-2401PC spectrophotometer. All solvents (Merck) are analytical grade and were used as received for the synthesis, the dichloromethane (Synth, Brazil) used in titrations, contained a maximum of 0.02% of water. All starting products were used as received from Aldrich for the synthetic procedures. The synthesis of functionalized calix[4]arene (Figure 1) was accomplished from a modification of the literature [22] resulting in two amines attached in 1,3 distal position on a calix[4]arene matrix 1 [23]. $LiAlH_4$ was added to a solution of the correspondent dicyanoethoxycalixarene [24] in dry ether. After 1 h, the excess of $LiAlH_4$ was eliminated using water:NaOH (1:1). The organic phase was washed with water and the solvent was removed under reduced pressure, yielding a white powder (90%). Condensation of these amines
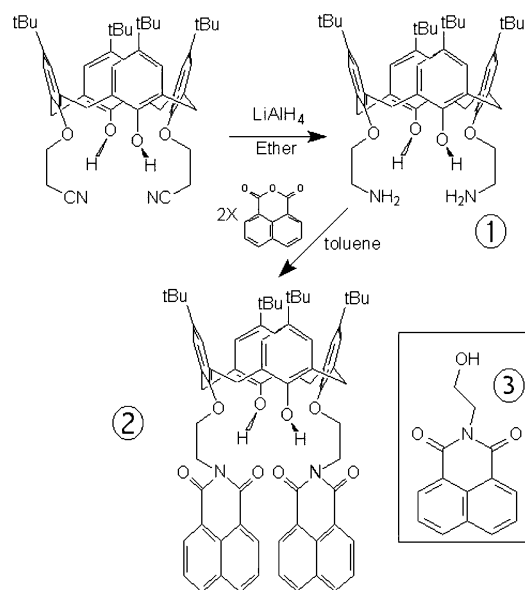
from calixarene 1 with 1,8-naphthalic anhydride in toluene was prepared by reflux for 24 h. The solvent was removed under reduced pressure, yielding a dark yellow powder which was purified by precipitation from hexane yielding a pure, light yellow compound 2 [25] (45%). 1,8-*N*-hydroxy-ethyl-naphthylimide **(3)**, was obtained from 1,8-naphthalic anhydride and ethanolamine, under reflux in dimethylformamide for 24 h yielding brownish crystals (86%), used for inclusion experiments.

Results and discussion

Typical signals of two naphthalimides, bonded to a calixarene unit were observed by ^{1}H NMR. The differences between the two tBu and $ArCH_2Ar$ signals (0.39 and 1.06 ppm, respectively) suggest a 'cone-pinched' conformer for calix[4]arene 2. Assignment of all signals has been performed using two-dimensional NMR techniques (^{1}H-^{1}H COSY and [1]H-^{13}C HETCOR) [26].

The host functionalization can also be verified by vibrational spectroscopy (see Figure 2), once its spectrum shows typical bands of both building blocks. The two imide carbonyl stretching bands appear at 1695 cm^{-1}, for the symmetric mode and at 1664 cm^{-1}, for the asymmetric one, what is typical of alkyl bonded naphthalimides. The band at 1480 cm^{-1} can be assigned to the CH_2–N bonds and figures on the spectrum near from the C–N–C bonds characteristic band, that appears overtoned with Ar–O–CH_2 bands at 1358 cm^{-1}. Another naphthalimide fingerprint is the intensification of the aromatic rings vibration modes, the bands around 779–753 cm^{-1}. The remaining part of the spectrum has calixarenes characteristic modes, the broad band at 3422 cm^{-1}, characteristic for free OH groups, and the bands at 2956, 2902, and 2867 typical for the $\nu^{ass}CH_3$, $\nu^s CH_2$ and $\nu^s CH_3$ modes. In addition to

Figure 1. Synthetic route for the obtention of Calix[4]-NI. Inset: 1,8-*N*-hydroxy-ethyl-naphthylimide structure.
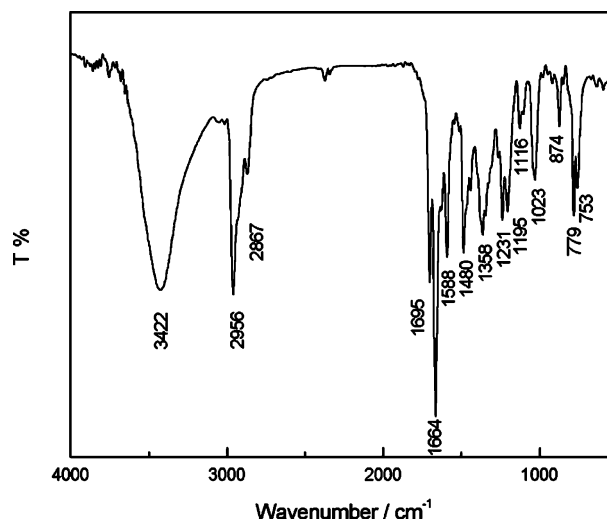

Figure 2. Vibrational spectrum of Calix[4]-NI, film over KBr.

these bands, it is also possible to see ν C $=$ C modes at 1588 and CH$_2$-N modes around 1480 cm^{-1}, associated to the band at 1023 cm^{-1} that seems to be related to the C–O–C bonds modes. [27].

The electronic spectrum (see Figure 3) of the naphthalimide modified calix[4]arene shows four bands at 281, 290, 332 and 347 nm ($\varepsilon = 13200$, 14200, 26700 and 24100 cm^{-1} mol^{-1} dm^3) and a shoulder at 320 nm ($\varepsilon = 18150$ cm^{-1} mol^{-1} dm^3 after deconv.), respectively. The first two bands are assigned to $\pi \rightarrow \pi^*$ transitions in the calix[4]arene moiety and is also present in the absorption spectrum of the starting calixarene amine precursor (1) at 283 and 290 nm (not shown). The three other bands are typical from naphthalimides, and are associated to their vibronic structured $\pi \rightarrow \pi^*$ transitions. The sub-units chromophores are practically unaffected by the surroundings, and the Calix[4]-NI absorption spectrum looks like the sum of its constituents spectra. This is probably due to the distance of two carbons that separates the naphthalimide rings from the macrocycle, impeding any interaction. The proximity of the naphthalic rings, however, should favour some kind of stacking, but the rings are not supposed to be in a co-facial arrangement, as a consequence of a Jahn–Teller-type effect and this feature does not affect the absorption spectrum. The emission spectrum is the mirror image of the absorption one, except for the calixarene's bands, that do not appear. The emission bands arise basically from the naphthalimide moieties of the molecule, having a major S1$\rightarrow$S0 transition at 380 nm with vibronic structure at 362, 376 and 395 nm. The fluorescence emission presents a low quantum yields ($\Phi_f = 0.02$ in toluene).

In order to evaluate calix[4]arene host properties towards inclusion chemistry, a probe molecule was synthesized with specific guest characteristics: 1,8-N-hydroxy-ethyl-naphthylimide (3). This probe has the same length, and exactly the same aromatic structure
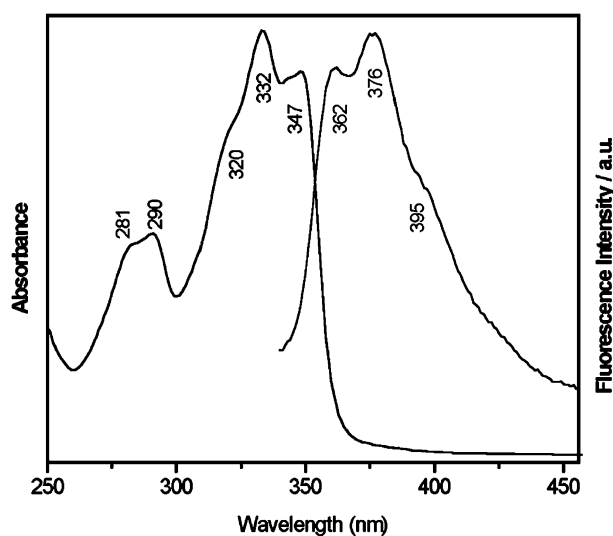

Figure 3. Absorption and emission spectra of calix[4]-NI in CH$_2$Cl$_2$ ($\lambda_{\text{exc}} = 333$ nm).

than the lower rim imidic substituents. It was conceived this way in order to facilitate the interaction between the naphthalic rings, our main chromophore. This molecule has a hydroxyl group that can be oriented, in non-polar medium, to the macrocycle's endo-hydrophilic cavity direction, to form hydrogen bonds. Besides this, the probe also contains a naphthalimide, separated by an ethyl segment, corresponding to the distance (3.9 Å) that separates the naphthalimides from the calixarene matrix. The presence of that naphthalic ring can originate a stacked structure with host's rings, generating a π-type interaction, an excellent spectral signal for inclusion.

Spectroscopic measurements were carried on in several mixtures of the calixarene host and the guest probe. The formation of aggregates or inclusion compounds is not evident at first glance, once the two naphthalimidic chromophores (host and guest's) have identical spectra, except obviously for their molar extinction coefficients, with maxima at 334, 348 nm and a shoulder at 318 nm, respectively. The formation of aggregates could be deduced from non-linearity of absorbance/emission *versus* concentration plots (not shown). Considering three individual samples A, B, and C. The first one containing only the host species, the second one containing only the guest one and the third containing a mixture of both. The last contains the same amounts of host and guest species than A and B samples. The theoretical absorbance of a simple mixture, without any kind of interaction between the chromophores, should correspond to the sum of the individual species, guest and host, absorbance according to the following expression:

$$A_{\text{tot}} = A_{\text{G}} + A_{\text{H}}; \quad \text{for } b = 1 \text{ in A } = \varepsilon \cdot b \cdot C,$$

where C is the concentration and b is the optical path (Beer–Lambert). For the mixture of a 2.26×10^{-5} mol dm^{-3} host solution with a 8.36×10^{-6} mol dm^{-3} guest solution sample, one would obtain:

$$A_{334} = (10690 \times 2.26\text{E}^{-5}) + (26700 \times 8.36\text{E}^{-6})$$
$$= 0.464$$

The measured absorbance is much greater, reaching 0.691 absorbance unit, as shown in Figure 4. In the same figure one can also observe the sum of A and B spectra.

This intensification of the absorption band suggests an interaction between imidic rings, but it is surely not due to the calixarene nor the guest species alone. There is a third species in solution, with different molar absorptivity than both component species.

Three situations could justify this non linear behaviour. The first of all, would be the formation of guest aggregates in solution, where it would interact somehow with himself, but no concentration effect for N-ethanol-1,8-naphthalimide spectra was verified by the authors. The second, would be the formation of intramolecular
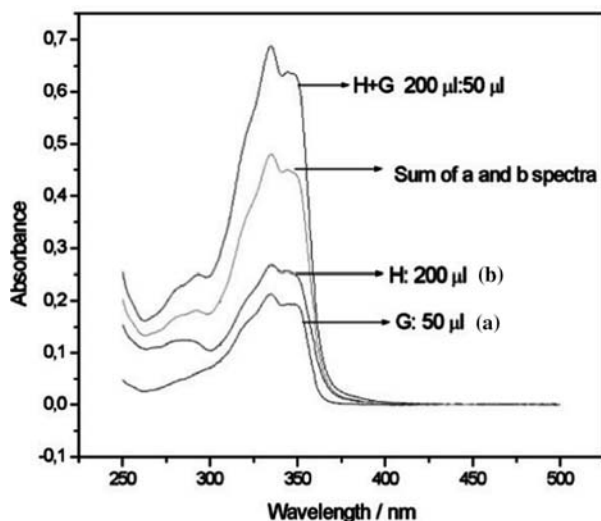
Figure 4. Absorption spectra of the host species (H), the guest one (G) the sum of both spectra and the spectrum of the inclusion compound (H + G).

Figure 6. Benesi–Hildebrand plots for a mixture of host and guest species for a 1:1 stoichiometry. (Squares = 347 nm, balls = 337 nm; H = host species).

hydrogen bonds, binding the terminal OH groups to carbonylic oxygens, affecting the properties of the π-π* transitions, as verified with similar guest's amine by Pardo and cols. This wasńt verified for these concentrations in CH_2Cl_2 as well. The third and last one, would be effectively the formation of an inclusion compound.

The inclusion of 1,8-*N*-hydroxy-ethyl-naphthalimide (G) into calixarene's **2** cavity (H) in CH_2Cl_2 solution, was clearer evidenced by the variation of the fluorescence spectra as function of host–guest concentrations (Figure 5). The experiment was realized preparing equimolar solutions of H and G species and mixing them to constant volume in different ratios H/G. The determination of the inclusion compound's stoichiometry can be estimated with the continuous variation method [28], where the sum of the individual concentrations of the H and G species was kept constant ($[H]_t + [G]_t = M_t$) at 1×10^{-5} mol dm^{-3} as the sum of the components concentrations, and the ratio $r = [G]_t/([G]_t + [H]_t)$ varied from 0 to 1. Plotting the
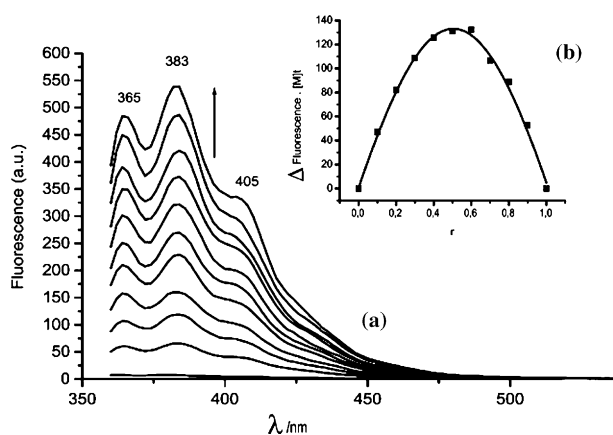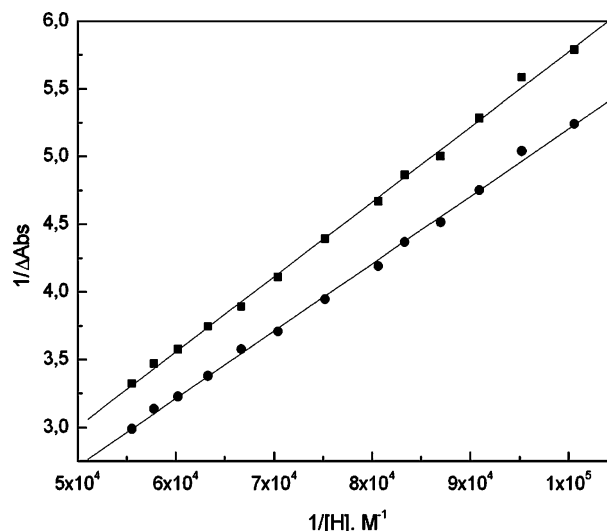

Figure 5. Emission job plot of the inclusion compound formation between Calix[4]NI and the 1,8-*N*-hydroxy-ethyl-naphthalimide probe molecule .

observed fluorescence variation (ΔFluorescence). [M_t] as a function of **r** leads to the Job plot presented in Figure 5b, showing a maximum at **r** = 0.5 and a symmetrical bell shape, indicating that the inclusion compound has 1:1 stoichiometry and that no other compound seems to be present. It is known that dichloromethane can interact with calixarenes, but this kind of interaction would not involve any chromophore and would not be noticeable in this context.

Using Benasi–Hilldebrand type plots (Figure 6) for a one to one stoichiometry [29], it is possible to obtain the formation constant of the complex from the intercept/ slope ratio. This constant was calculated at 2 wavelengths, 334 and 347 nm using very low initial host concentrations (1.6×10^{-7} mol dm^{-3}). The values are respectively 3.5×10^3 and 3.79×10^3 M^{-1}, leading to a medium value of 3.64×10^3 M^{-1}, showing that the association is very high.

The kinetics of the inclusion reaction seems to be very fast, and no further spectral variation was observed at longer periods of time, after mixing both compounds. The inclusion compound appears to be very stable. According to these results, an inclusion compound is being formed, and its ε should be around 37,200 cm^{-1} mol^{-1} dm^{-3}, what would be reasonable for a molecule containing 3 naphthalic rings.

Conclusion

It was shown, in the present study, that it is possible to associate the properties of naphthalic imides and calixarene's generating a compound with inclusion host and fluorophore characteristics. This compound shows spectral variations with the insertion in its endo-hydrophilic cavity of guest species able to interact with its aromatic system. Guest selectivity and experiments as well as the

synthesis of a double calix[4]-NI analogue, with two calix[4]arenes bonded by naphthalene diimides are being carried out in our laboratory.

Acknowledgements

References

1. J.M. Lehn: *Supramolecular Chemistry, Concepts and Perspectives,* VCH: Weinheim, Germany (1995).
2. J.C. Netto-Ferreira, V. Wintgens, L.F. Vieira Ferreira, A.R. Garcia, L.M. Ilharco, and M.J. Lemos: *J. Photochem. Photobiol. A* **132**, 209 (2000).
3. S. Brochsztain, M.A. Rodrigues, and M.J. Politi: *J. Photochem. Photobiol. A* **107**, 195 (1997).
4. P. Bandyopadhyay and P.K. Bharadwaj: *Synlett* Dec. 1331 (1998).
5. R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb, and J.J. Christensen: *Chem. Rev.* **85**, 271 (1985).
6. A. Specht, M. Goeldner, J. Wirz and L.Peng: *Synlett* **S1**, 981, (1999).
7. I.A. Bagatin and H.E. Toma: *New J. Chem.* **24**, 841 (2000).
8. P.D. Beer and P.A. Gale: *Angew. Chem. Int. Ed.* **40**, 486 (2001).
9. A. Zinke, R. Kretz, E. Leggewie, and K. Hössinger: *Monatsh. Chem.* **83**(5), 1213 (1953).
10. C.D. Gutsche: Calixarenes. In J.F. Stoddart (ed.), *Monographs in Supramolecular Chemistry*, Royal Society of Chemistry, Cambridge (1989).
11. Y. Okada, M. Mizutani, F. Ishii, and J. Nishimura: *Synlett,* **1**, 41 (2000).
12. P. Tongraung, N.Chantarasiri, and T. Tuntulani: *Tetrahedron Lett.* **44**, 29 (2003).
13. K. Tantrakarn, C. Ratanatawanate, T. Pinsuk, O. Chailapakul, and T. Tuntulani: *Tetrahedron Lett.* **44**, 33 (2003).
14. Y. Kubo: *Synlett* **2**, 161 (1999).
15. (a) T.C. Barros, G.R. Molinari, P. Berci Filho, V.G. Toscano, and M.J. Politi: *J. Photochem. Photobiol. A.* **76**, 55 (1993); (b) P. Berci Filho, V.G. Toscano, and M.J. Politi: *J. Photochem. Photobiol. A.* **43**, 51 (1988); (c) F.L.C.A. Ceneviva, V.G. Toscano, O. Santos, M.J. Politi, G. Newmann, and P. Berci Filho: *J. Photochem. Photobiol. A* **58**, 289 (1991); (d) T.C. Barros, P. Berci Filho, V.G. Toscano, and M.J. Politi: *J. Photochem. Photobiol. A* **89**, 141 (1995); (e) A. Pardo, J.M.L. Poyato, E. Martin, J.J. Camacho, and D. Reyman: *J. Photochem. Photobiol. A* **46**, 323 (1989); (f) A. Pardo, E. Martin, J.M.L. Poyato, J.J. Camacho, M.F. Braña and J.M. Castellano: *J. Photochem. Photobiol. A* **41**, 69 (1987); (g) P. Berci Filho, F.H. Quina, M.J. Gehelen, M.J. Politi, M.G. Neumann, and T.C. Barros: *J. Photochem. Photobiol. A* **92**, 155 (1995).
16. I. Grabchev and V. Bojinov: *Polym. Degrad. Stabil.* **70**, 147 (2000).
17. A. Pardo, E. Martin, J.M.L. Poyato, and J.J. Camacho: *J. Photochem. Photobiol. A* 48, 259 (1989).
18. M.A. Rodrigues, G.J.-F. Demets, M.J. Politi, and S. Brochsztain: *J. Mater. Chem.* **12**, 1250 (2002).
19. F. Cosnard and V. Wintgens: *Tetrahedron Lett.* **39**, 2751 (1998).
20. M.O. Vysotsky, V. Bo1hmer, F. Wu1rthner, C.-C. You, and K. Rissanen: *Org. Lett.* **4**(17), 2901 (2002).
21. A. Brecht and G. Gauglitz: *Sensors Actuators B* 38 (1997).
22. [5,11,17,23-tetra(*tert*-butyl)-25,27-diaminoetoxy)-26,28-(di-hydroxycalix[4]arene)] (1) $-^1$H NMR (299.95 MHz): δ(CDCl$_3$) = 7.20 (s,OH, 2H), 7.05 and 6.99 (2s, *m*-ArH, 4H each), 4.33 and 3.38 (2d, spin AB system, 4H each, ^2J = 12.9 Hz), 4.08 (t, OCH_2CH$_2$NH$_2$, 4H, ^3J = 6 Hz), 3.15 (t, OCH$_2$CH_2NH$_2$, 4H, ^3J = 6 Hz), 2.4 (bs, NH$_2$, 4H), 1.25 and 1.12 (2s, ^{t}Bu, 18H each). ^{13}C{^{1}H}NMR (75.42 MHz): δ(CDCl$_3$) = 150.07–127.67 (Cq, rings), 125.79 and 125.32 (CH), 78.81 (OCH$_2$CH$_2$NH$_2$), 42.73 (OCH$_2$CH$_2$NH$_2$), 34.00 (Cq, C(CH$_3$)$_3$), 32.01 (CH$_2$, spin AB system), 31.56 and 31.11 (CH$_3$, ^{t}Bu). Anal. calc. For C$_{48}$H$_{66}$O$_4$N$_2\cdot$2H$_2$O: C 74.8, H 9.1, N 3.6; found: C 75.0, H 8.4, N 3.5.
23. E.M. Georgiev, N. Wolf, and D.M.Roundhill: *Polyhedron* **16**, 1581 (1997).
24. E.M. Collins, M.A. McKervey, E. Madigan, M.B. Moran, M. Owens, G. Ferguson, and S.J. Harris: *J. Chem. Soc. Perkin Trans.* 3137 (1991).
25. [5,11,17,23-tetra(*tert*-butil)-25,27-bis(1,8-*N*-etoxy-naphthalimide-)-26,28 (dihydroxy)calix[4]arene) (2) $-$ ^{1}H NMR (299.95 MHz): δ(CDCl$_3$) = 8.70 (d, 3-CH, 4H, ^3J = 7.2 Hz), 8.19 (d, 1-CH, 4H, ^3J = 8.4 Hz), 7.78 (t, 2-CH, 4H, ^3J = 7.6 Hz), 6.99 and 6.71 (2s, *m*-ArH, 4H), 6.85 (s, OH, 2H), 4.95 (t, OCH$_2$CH_2N, 4H, ^3J = 7.2 Hz), 4.35 and 3.29 (2d, spin AB system, 4H each, ^2J = 13.2 Hz), 4.30 (t, OCH_2CH$_2$N, 4H, ^3J = 7.0 Hz), 1.28 and 0.89 (2s, ^{t}Bu, 18H each). ^{13}C{^{1}H} NMR (75.42 MHz): δ(CDCl$_3$) = 164.14 (Cq, C=O), 150.63–141.03 (Cq, rings), 133.88 and 132.25 (CH, naphthalene), 131.35 and 126.90 (Cq, calixarene), 127.83 (CH, naphthalene), 125.40 and 124.86 (CH, calixarene), 122.66 (Cq, naphthalene), 71.96 (OCH$_2$CH$_2$N), 39.47 (OCH$_2$CH$_2$N), 33.75 (Cq, C(CH$_3$)$_3$), 31.38 (CH$_2$, spin AB system), 31.71 and 30.94 (CH$_3$, ^{t}Bu). Anal. calc. C:76,7,H:7,1,N:4,7 calc.C:72,76, H:7,4, N:4,85.
26. (a) C.D. Gutsche: Calixarenes. In J.F. Stoddart (ed.), *Monographs in Supramolecular Chemistry,* Royal Society of Chemistry, Cambridge, (1989). ref. 10; (b) C.D. Gutsche: Calixarenes Revisited. In J.F. Stoddart (ed.), *Monographs in Supramolecular Chemistry,* Royal Society of Chemistry, Cambridge, (1998); (c) Calixarenes: Z. Asfari, V. Böhmer, J. Harrowfield, and J. Vicens, (eds.), Kluwer Academic Publishers, Dordrecht (2001).
27. C.M. Lee and W.D. Kumler: *J. Org. Chem.,* **27**(6), 2055 (1962).
28. (a) Y. Dotsikas, E. Kontopanou, C. Allagiannis, and Y.L. Loukas: *J. Pharm. Biomed. Anal.* **23**, 997 (2000); (b) F. Djedïni, S.Z. Lin, B. Perly, and D. Wouessidjewe: *J. Pharm. Sci.* **79**, 643 (1990).
29. K.A. Connors: *Binding Constants*, Jonh Wiley & Sons, New York (1987).