Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3267–3273

TETRAHEDRON

Synthesis and binding studies of new bis-calix[4]arenes containing aromatic and heteroaromatic units

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Received 6 January 2003; revised 12 February 2003; accepted 14 March 2003

Dedicated to Professor Harjit Singh (emeritus scientist) on the occasion of his 65th birthday

Abstract—A series of new bis-calix[4]arenes containing different aromatic and heteroaromatic moieties have been synthesized. The complexing behavior of these bis-calix[4]arenes have been studied towards different metal ions and it has been found that these bis-calix[4]arenes bind silver ions selectively over other metal ions. The complexation has been studied by liquid–liquid extraction and by NMR and IR spectroscopy. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calixarenes, which are easily available from *p-tert*-butylphenol and formaldehyde, are very important in host guest supramolecular chemistry.[1] A variety of sophisticated compounds have been prepared from these starting materials by carrying out the reactions at the phenolic hydroxyl groups[2] or at the *p*-position after the removal of the *p-tert*-butyl groups.[3] The versatility of calix[4]arenes as host molecules suggested that they might serve as potential building blocks for designing more elaborate structures like double calix[4]arenes[3b] which may be constructed through upper rim–upper rim linkage,[4] lower rim–lower rim linkage,[5] upper rim–lower rim linkage or non-covalently generated through hydrogen bonding.[6] Shinkai et al. have reported the synthesis of a series of bis-calix[4]arenes possessing two metal binding sites, each containing four ester or four ether groups.[7–9] Double or triple calix[4]arenes[10] connected through the oxygen atoms have been synthesized by condensing calix[4]arenes 1,3-difunctionalised at the lower rim and different bifunctional reagents such as diacid dichlorides or diamines.[10,11] Double calixarenes linked through one bridge at the lower rim and bearing urea group on the upper rim have also been reported.[12,13] Recently, Rebek et al. reported the synthesis and encapsulation behavior of bis-calix[4]arenes linked by one bridge at the upper rims and bearing urea groups in the same rims.[14] A series of bis-calix[4]arene derivatives linked through their phenolic oxygens with the aid of a single aliphatic or aromatic chain (lower–lower rim fashion) have been obtained by alkylation of 28-hydroxy-25,26,27-tripropoxycalix[4]arenas with α,ω-dibromoalkanes in the presence of NaH,[15] and by condensation of *p-tert*-butylcalix[4]arene with methyl-2,6-bis(bromomethyl)benzoate,[16] 2,6-bis(bromomethyl)-4-methylanisole[17] or with 5,5′-bis(bromomethyl)-2,2′-bipyridine *N*,*N*′-dioxide.[18] Bis- and oligocalix[4]arenes have been obtained by intermolecular metathesis of dialkenylcalix[4]arene derivatives.[19] Recently, Gonzalez et al. reported the synthesis of biscalix[4]arenes by exploiting the potential of 5,11,17,23-tetra-*tert*-butyl 26,28-dihydroxy-25,27-bis(2-isothiocyanoethoxy)calix[4]arene.[20] A series of bis-calix[4]arenes derivatives linked through their upper rims with different aromatic or heteroaromatic units as spacer between them has been reported by Kim et al.[21] However, in all the above mentioned reports there is one limitation or the other like the poor availability of the starting materials, drastic reaction conditions, longer reaction times and poor yields of the products. In a preliminary communication,[22] we reported the synthesis of bis-calix[4]arenes linked through their lower rims and having benzene or phenols as one of the spacers between the calix[4]arene moieties. In the present manuscript we report in detail the synthesis, binding studies and spectral data of these bis-calixarenes and also wish to report the synthesis and evaluation of new bis-calix[4]arenes having thiophene and pyrazole as spacers between the two calix[4]arene rings. To the best of our knowledge the synthesis and extraction ability of bis-calix[4]arenes linked through their lower rims and having pyrazole or thiophene as spacers between the calix[4]arene moieties has not been investigated so far. The N_1–H pyrazole unit introduced in the biscalix[4]arenes can assist in complexation in two different ways. In neutral medium each pyrazole

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Keywords: bis-calix[4]arenes; aromatic and heteroaromatic units; complexation.

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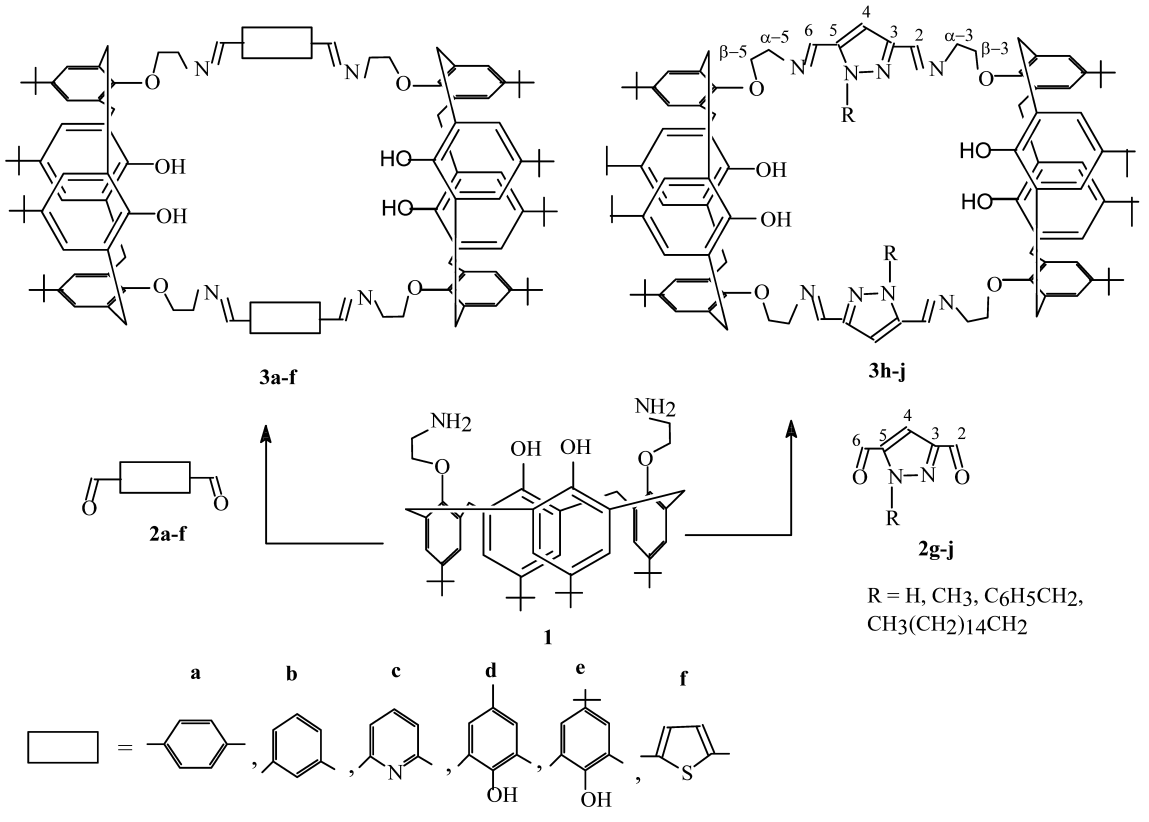
0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00409-5

unit acts as a monodentate ligand; however, in alkaline medium the pyrazole unit is deprotonated, affording a pyrazolate anion which behaves as a exobidentate ligand. In this way, one of us successfully reported the synthesis and study of dinuclear Ag^+, dinuclear and tetranuclear Cu^{2+} and Zn^{2+} complexes formed from a cryptand having 1H–pyrazole moiety.[23] Besides, one of us obtained 26-membered oxaimine, oxaamine, azaimine and polyamine heteroaromatic macrocycles of N_1–H pyrazole able to afford in basic medium dipyrazolate salts, from which dinuclear Zn^{2+} and dinuclear Cu^{2+} complexes have been formed.[24,25] The acid base behavior of these polyamines has also been reported recently.[26] With this background in the synthesis and evaluation of macrocycles and macrobicycles containing the 1H–pyrazole moiety, the present manuscript describes the synthesis and evaluation of novel biscalix[4]arenes having different aromatic and heteroaromatic units as spacers between the two calix[4]arene moieties. The introduction of heterocycles like thiophene pyridine or pyrazole containing soft heteroatoms like sulphur and sp^2 nitrogens can improve the selectivity towards the soft metal ions like silver which find use in cancer immunotherapy and industrial interest in the separation of silver from waste stream effluents and the use of silver complexes in photographic materials.

2. Results and discussion

[2+2] Dipodal condensation of 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis(2-aminoethoxy)-26,28 dihydroxy-calix[4]arene[27] in the cone conformation or cone-1,3-diamine **1** with different bis-aldehydes, **2a**–**j**[26,28] in ethanol gave Schiff base bis-calix[4]arenes (Scheme 1) (except in the condensation of **1** with **2g** where no identifiable product could be isolated) with four imine groups in high yield (85–95%). The high yields of the products were due to the insolubility of the products in ethanol.[29] The structures of these bis-calix[4]-arenes **3a**–**f**, **3h**–**j** were confirmed from their spectroscopic data and analytical data. The IR spectra of **3a**–**f**, **3h**–**j** show a band at 1634–1645 cm^{-1} which indicates the presence of an imine group. There is no band corresponding to the free carbonyl and free amino groups which indicates that the cyclization has taken place. The ^1H NMR spectra of **3a**–**f** are very simple and symmetrical. These spectra show two singlets at δ 0.91–0.95 and at δ 1.27–1.30 which indicates that all these compounds **3a**–**f** are 1,3-bridged. A doublet corresponding to the bridging methylene protons appears at δ 3.25–3.31 (J=12–13 Hz). A distorted triplet corresponding to the NCH_2 protons appears at δ 4.00–4.01 and a multiplet corresponding to bridging $ArCH_2Ar$ and OCH_2 protons appears at δ 4.21–4.27. The singlets corresponding to aromatic protons appear at δ 6.74–6.79, δ 7.00 and δ 7.09, respectively, and a singlet corresponding to imino protons appear at δ 8.35–8.78. Furthermore, the presence of a signal at δ 31.38–31.60 in the ^{13}C NMR spectra confirms that these bis-calix[4]arenes exists in the cone conformation. In the ^1H NMR spectra of **3h**–**j**, the presence of the 1-alkyl substituent breaks the magnetic equivalence of the pyrazole environment. For example in the ^{13}C NMR spectrum of **3h** different signals can be observed for the quaternary carbons labeled as C_3 and C_5 (the pyrazole N=C_3 appear at lower field than C_4=C_5), as well as those of the imine carbons (C_2 more deshielded than C_6). The carbon atoms $C_{\alpha\text{-}5}$ and $C_{\beta\text{-}5}$ which are closer to the pyrazole 1-methyl substituent appear at higher field than $C_{\alpha\text{-}3}$ and $C_{\beta\text{-}3}$ which are closer to the sp^2 nitrogen atom of the



Scheme 1.

pyrazole. In the ^{1}H NMR spectrum of **3h** three singlets corresponding to *tert*-butyl protons in the ratio 1:1:2 appear at δ 0.80, δ 0.86 and at δ 1.22, two types of doublets (J=12 Hz) corresponding to the equatorial protons of the bridging methylene group appear at δ 3.17 and δ 3.24, two types of triplets (J=8 Hz) corresponding to the NCH_2 protons appear at δ 3.64 and δ 3.94. A multiplet corresponding to axial protons of the bridging methylene group ($ArCH_2Ar$), OCH_2 protons and NCH_2 protons appear at δ 4.05–4.25. The singlets corresponding to aromatic protons appear at δ 6.62, δ 6.70 and at δ 7.19 and the two singlets corresponding to the imino protons appear at δ 8.23 and at δ 8.48. In the ^{13}C NMR spectrum of **3h** the signals corresponding to the methyl carbons of the *tert*-butyl groups appear at δ 30.94 and at δ 31.71 (these signals are unaffected in the DEPT NMR spectrum). The ^{13}C NMR signals corresponding to the bridging methylene groups appear at δ 31.38 and at δ 31.54 and the signals corresponding to the quaternary carbons of the *tert*-butyl groups appear at δ 33.81 and at δ 33.88. The magnetic non-equivalence of the two types of NCH_2 and OCH_2 carbons is clear from the appearance of two types of signals at δ 60.02, 62.22 (NCH_2), 74.65 and at 75.16 (OCH_2) in the ^{13}C NMR spectrum. Likewise the two types of the imino carbons appear at δ 152.87 and δ 157.10. From the ^{1}H NMR and ^{13}C NMR spectra of **3h** it is clear that the molecule has C_2 symmetry and the methyl substituents in the pyrazole ring are in the opposite directions.

The evaluation of the binding efficiencies of the bis-calix[4]arenes **3a**–**f**, **3h**–**j** was carried out by two-phase solvent extraction of metal picrates (Na^+, K^+, Ca^{2+}, Pb^{2+} and Ag^+) into chloroform under neutral conditions. The results are summarized in Table 1. It is clear from the table that when the bridging unit is terephthaloyl or isophthaloyl the percentage extraction of silver is nearly equal (49.52 and 48.56%, respectively). However, when the bridging unit is pyridine, there is almost a 23% increase in percentage extraction of silver. A nearly similar increase in extraction is also observed when the bridging unit is thiophene. This data indicates that the sp^2 nitrogen of pyridine and the sulphur atom of thiophene are coordinating with silver. However, when the bridging unit is *N*-methylpyrazole, there is 33% increase in percentage extraction which indicates that the sp^2 nitrogen of *N*-methylpyrazole is coordinating better than the sp^2 nitrogen of pyridine or sulphur of thiophene which may be due to the geometrically better position of sp^2 nitrogen of *N*-methylpyrazole than sp^2 nitrogen of pyridine or sulphur of thiophene. The percentage increase in extraction when the bridging units are phenols is probably due to exchange of the phenolic hydrogen with the picrate anion at the interface between chloroform and the aqueous layer at pH 7, with the protonated picric then being extracted into the chloroform layer.

We also used a bulk liquid membrane to measure the transport rates of metal ions from an aqueous source phase into an aqueous receiving phase through an organic bulk membrane. The measured transport rates are given in Table 2 and it is clear from these rates that the silver ion is selectively transported by all the bis-calix[4]arenes. This silver ion selectivity may be due to the electrostatic interaction between the metal ion and the four highly preorganized soft-binding sites (imine units) surrounded by ethereal oxygen atoms and donors in the heterocyclic rings. Furthermore, the bis-calix[4]arenes having 3,5-disubstituted-*N*-methylpyrazole or 2,5-disubstituted thiophene as one of the spacers transport silver ions better than those having terephthaloyl[22] (523×10^{-8} mol/24 h) or phenol[22] (745×10^{-8} mol/24 h) as spacers between the two calix[4]-arene moieties. This clearly indicates that the sp^2 nitrogen or the sulphur atoms of the heterocyclic rings are coordinating with the silver ions and thus helping in better transport of silver ions across the apolar membrane. Attempts to obtain suitable crystals for X-ray crystallography were not successful. However, to elucidate the binding mode of these bis-calix[4]arenes with silver picrate under solid–liquid extraction conditions, the ^{1}H NMR(Tables 3 and 4) and IR spectra (Table 5) of their complexes with silver picrate were recorded. Table 3 shows that the complexation of the bis-calix[4]arenes with silver picrate showed different chemical shifts, which indicate that conformational changes take place on complexation with silver ions. The important changes were in the chemical shift of the imino protons and the protons attached to 'N' and 'O' which moved downfield on complexation with silver.

As a representative example, upon complexation of **3a** with silver ions, the strongest interaction takes between the π-electrons of the terephthaloyl moiety and the silver ions as is clear from the downfield shift of the terephthaloyl protons from δ 7.08 to δ 7.84 ppm, ($\Delta\delta$=0.76 ppm). As these aromatic protons are conjugated to the imine nitrogens

Table 1. Solvent extraction results for metal ions using bis-calix[4]arenes **3a**–**f**, **3h**–**j**

Host	Na^+	K^+	Ca^{2+}	Pb^{2+}	Ag^+
3a	2.76	11.86	1.93	20.53	49.52
3b	4.36	3.50	3.88	9.95	48.56
3c	28.03	23.44	17.69	37.48	72.92
3d	45.64	40.48	28.72	38.53	55.26
3e	13.93	10.79	6.76	14.61	66.51
3f	15.02	15.60	17.20	15.00	72.00
3h	9.30	10.00	7.60	10.00	82.00
3i	2.30	2.40	1.60	5.50	37.00
3j	–	–	–	–	58.21

Source phase (aqueous solution of metal picrate, 2 mL), [MPic]=1 mM (except lead picrate which is 0.5 mM); organic phase ($CHCl_3$), 2 mL), (carrier)=0.1 mM. Extractability=(concentration of the extracted metal)/(concentration of the organic ligand)×100%. The data are the average value of three independent determinations.

Table 2. (Transport rates$\times10^8$ mol/24 h) results for metal ions using various bis-calix[4]arenes

Bis-calix[4]arene	Na^+	K^+	Ca^{2+}	Pb^{2+}	Ag^+
3a	136.40	10.60	24.10	182.40	523.00
3b	39.20	46.40	36.90	98.30	966.30
3c	–	–	–	–	1118
3d	32.60	102.40	148.30	86.20	745.00
3e	56.90	62.80	297.90	261.30	1102.00
3f	168.00	84.5	33.54	68.20	2783.00
3h	38.3	11.33	38.10	28.00	2224.00
3i	–	–	–	–	524.00
3j	–	–	–	–	332.00

Transport conditions: source phase (aqueous solution of metal picrates, 3 mL, 0.01 M); membrane phase (chloroform, 15 mL.(carrier)=1.0 mM; i.d. glass vial=20 mm; receiving phase: water 10 mL). The average value of three independent determinations. The experimental value deviate from the reported value by an average of 10%.

Table 3. ^{1}H NMR induced shifts ($\Delta\delta$) of **3a**,**b**, **3d** and **3f** upon complexation with silver picrate in $CDCl_3/CD_3CN$ (9:1)

Host	Protons of the host							
	t-Bu	*t*-Bu	$ArCH_2Ar$	NCH_2	OCH_2	$ArCH_2Ar$	ArH	CH=N
3a	0.95	1.30	3.31	4.00	4.25	4.34	7.08	8.35
3a+Ag	0.91	1.26	3.43	4.40	4.64	4.08	7.84	8.92
$\Delta\delta$	−0.04	−0.04	0.12	0.40	0.39	−0.26	0.76	0.57
3b	0.92	1.28	3.26	4.01	4.20–4.29	4.20–4.29	–	8.41
3b+A	0.88	1.19	3.25	3.90–4.35	3.90–4.35	3.90–4.35	–	8.64
$\Delta\delta$	−0.04	−0.08	−0.01	−0.11−(+0.06)	−0.11−(+0.06)	−0.11−(+0.06)	–	0.23
3d	0.91	1.28	3.25	4.05–4.16	4.05–4.16	4.20	–	8.72
3d+Ag	0.85	1.31	3.30	3.97–4.32	3.97–4.32	3.97–4.32	–	8.70
$\Delta\delta$	−0.06	0.03	0.05	−0.08−(+0.12)	−0.08−(+0.12)	−0.08−(+0.12)	–	−0.02
3f	1.13	1.24	3.31	4.01	4.22	4.28	7.39	8.59
3f+Ag	1.11	1.21	3.37	4.42	4.42	4.19	7.80	8.73
$\Delta\delta$	−0.02	−0.03	0.06	0.41	0.20	−0.09	0.41	0.14

and so it may simply be that binding of Ag^+ to the nitrogens induces this downfield shift. There may not be any cation–π interaction. The next strong interaction takes place between the sp^2 imino nitrogens and the silver ions as the imino protons shift significantly downfield from δ 8.35 to δ 8.92 ppm, ($\Delta\delta$=0.57 ppm). This clearly shows that the imino nitrogens are also coordinating with the silver ions. Evidence in support of this coordination also comes from the IR spectrum where the absorption band corresponding to the C=N group shifts from 1644 to 1634 cm^{-1}. Further, the chemical shift of NCH_2 and OCH_2 protons also move considerably downfield from δ 4.00 to δ 4.40 ppm, ($\Delta\delta$=0.40 ppm) and from δ 4.25 to δ 4.64 ppm, ($\Delta\delta$=0.39 ppm), respectively. From these observations it is clear that the silver ions interact more strongly with the central part of the bis-calix[4]arene **3a**. The chemical shifts of the aromatic protons of the phenolic rings and the protons of the *tert*-butyl group were not affected much. Another point to note is the changes in the chemical shift of the bridging methylene protons upon complexation, the higher field resonance ascribable to the equatorial protons shifted to a downfield position ($\Delta\delta$=0.12 ppm). That at lower field is ascribable to the axial protons, moved upfield ($\Delta\delta$=−0.26 ppm). The difference in the chemical shift of the bridging methylene protons is generally decreased compared with the free host. This might be due to *endo* rotation of the calix-crown, forming a somewhat flattened calixarene framework upon complex formation. The difference in chemical shifts of the bridging methylene protons is known to decrease with a minor increase in flatness of the calix[4]arene backbone.[30] Similar complexing behavior is observed for bis-calix[4]arenes **3f** (binding constant 100 M^{-1} as determined by EQNMR[31]). Upon complexation with the silver ions, the resonances of the host **3f** changed significantly particularly the resonances of the central part of the bis-calix[4]arene **3f** (Table 3). The imino protons, protons of the thiophene ring and protons of the NCH_2 group are deshielded upon complexation. The most marked downfield shifts seem to be those experienced by the thiophene protons followed by the imino protons. The ligand therefore uses its soft binding sites in order to complex the silver ions. Likewise bis-calix[4]arene **3h** shows significant changes in the chemical shifts of the protons of **3h** on complexation with silver picrate (Table 4). The binding constant as determined by EQNMR was found to be 462 M^{-1}.[31] With bis-calix[4]arenes like **3b** and **3d** the changes in the chemical shifts of the protons of **3b** and **3d** on complexation with silver ions are somewhat less pronounced.

Table 4. ^{1}H NMR induced shifts ($\Delta\delta$, ppm) of imino protons of **3h** upon complexation with silver picrate in $CDCl_3/CD_3CN$ (9:1)

Host	CH=N (H_6)	CH=N (H_2)
3h	8.25	8.56
3h+Ag	8.65	8.76
$\Delta\delta$	0.40	0.20

Table 5 shows that there are considerable changes in the IR absorption band of the imine moiety on complexation of these bis-calix[4]arenes with silver picrate. The IR absorption band due to the imine moiety shifts to lower frequency on complexation with the silver picrate which indicates that the coordination takes place through the imine nitrogen.

In conclusion, new Schiff-base bis-calix[4]arenes were synthesized with thiophene and pyrazole as spacer between the two calixarene rings. Complexation studies by two-phase solvent extraction, transport studies and by ^{1}H NMR indicate that the bis-calix[4]arenes complexes selectively with silver in comparison to other metal ions. This silver ion selectivity is due to the electrostatic interaction between the metal ions and the aza crown cavity composed of oxygen, nitrogen and sulphur atoms as donors.

Table 5. Shifts in the IR frequency (cm^{-1}) of the imine moiety of **3a–f** upon complexation with silver picrate in $CDCl_3/CD_3CN$ (9:1)

Host	IR frequency of the imine moiety		
	Free ligand	Complex	$\Delta\nu$ (cm^{-1})
3a	1644	1634	10
3b	1647	1608	39
3c	1650	1629	21
3d	1638	1634	04
3e	1638	1634	04
3f	1644	1610	34
3h	1647	1610	37

3. Experimental

Most of the solvents and all the reagents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as solvent. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using xenon (6 kV, 10 mA) as the FAB gas. Some of the FAB mass spectra were done at University of Sheffield, UK. Infrared spectra were recorded on a Pye Unicam SP3-300 infrared spectrophotometer. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Melting points were determined in capillaries and are uncorrected. C, H and N analysis were done at Central Drug Research Institute, Luknow (India).

3.1. General procedure for the synthesis of bis-calix[4]arenes 3a–j

To a solution of 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,27-bis(2-aminoethoxy)-26,28 dihydroxycalix[4]arene[27] **1** (0.734 g, 1.00 mmol) dissolved in 50 mL of ethanol was added a solution of dialdehyde **2a–f**,**h–j** (1.00 mmol) dissolved in 50 mL of ethanol. The mixture was stirred/refluxed for 4–24 h in ethanol. A solid separated which was filtered, washed, and recrystallized from dichloromethane and methanol and dried under vacuum.

3.1.1. Compound 3a. Bridging unit: terephthaldialdehyde (yield 95%); refluxed for 10 h; white solid; mp: 260–262°C; IR (KBr): 1644 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (s, 36H, $C(CH_3)_3$), 1.30 (s, 36H, $C(CH_3)_3$), 3.31 (d, J=15 Hz, 8H, $ArCH_2Ar$), 4.00 (t, J=5 Hz, 8H, NCH_2), 4.25 (t, J=5 Hz, 8H, OCH_2), 4.34 (d, J=15 Hz, 8H, $ArCH_2Ar$), 6.75 (s, 8H, ArH), 7.05 (s, 8H, ArH), 7.25 (s, 4H, ArOH), 7.8 (s, 8H, ArH), 8.35 (s, 4H, HC=N); ^{13}C NMR ($CDCl_3$): δ 31.02 ($C(CH_3)_3$), 31.71 ($C(CH_3)_3$), 33.81 (quaternary carbon), 60.64 (NCH_2), 75.24 (OCH_2), 125.01 (ArC),125.48 (ArC), 127.95 (ArC),128.61 (ArC), 132.54 (ArC), 138.20 (ArC), 141.29 (ArC), 149.93 (ArC) 150.74 (ArC), 163.09 (CH=N); FAB-MS (m/z): 1664 (M$^+$). Anal. calcd for $C_{112}H_{136}O_8N_4$: C, 80.76; H, 8.17; N, 3.33. Found: C, 80.39; H, 7.87; N, 3.41.

3.1.2. Compound 3b. Bridging unit: isophthaldialdehyde (yield 85%); refluxed for 10 h; white solid; mp: 250°C; IR (KBr): 1647 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (s, 36H, $C(CH_3)_3$), 1.28 (s, 36H, $C(CH_3)_3$), 3.26 (d, J=15 Hz, 8H, $ArCH_2Ar$), 4.01 (t, J=5 Hz, 8H, NCH_2), 4.20–4.29 (m, 16H, OCH_2, $ArCH_2Ar$), 6.75 (s, 8H, ArH), 7.01 (s, 8H, ArH), 7.18 (s, 4H, ArOH), 7.32 (t, J=6 Hz, 2H, ArH), 7.85 (d, J=6 Hz, 4H, ArH), 8.02 (s, 2H, ArH), 8.41 (s, 4H, HC=N); ^{13}C NMR ($CDCl_3$): 30.98 ($C(CH_3)_3$), 31.60 ($ArCH_2Ar$), 31.71 ($C(CH_3)_3$), 33.85, (quaternary carbon), 60.20 (NCH_2), 75.00 (OCH_2), 124.90 (ArC), 125.41 (ArC), 127.76 (ArC), 128.64 (ArC), 129.86 (ArC), 132.36 (ArC), 136.44 (ArC), 141.03 (ArC), 146.77 (ArC), 149.71 (ArC), 150.66 (ArC), 150.59 (ArC), 159.50 (CH=N); FAB-MS (m/z): 1664 (M$^+$). Anal. calcd for $C_{112}H_{136}O_8N_4$: C, 80.76; H, 8.17; N, 3.33. Found: C, 80.96; H, 8.51; N, 3.66.

3.1.3. Compound 3c. Bridging unit: pyridine (yield 85%); stirred for 3 h; white solid; mp: 242–244°C; IR (KBr): 1650 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (s, 36H, $C(CH_3)_3$), 1.28 (s, 36H, $C(CH_3)_3$), 3.26 (d, J=12 Hz, 8H, $ArCH_2Ar$), 4.13–4.16 (m, 16H, NCH_2, OCH_2), 4.23 (d, J=12 Hz, 8H, $ArCH_2Ar$), 6.79 (s, 8H, ArH), 7.02 (s, 8H, ArH), 7.32 (s, 4H, ArOH), 7.57 (t, J=5.8 Hz, 2H, PyH), 7.97 (d, J=8 Hz, 4H, PyH), 8.74 (s, 4H, HC=N); ^{13}C NMR ($CDCl_3$): 30.98 ($C(CH_3)_3$), 31.57 ($ArCH_2Ar$), 31.75 ($C(CH_3)_3$), 33.81 (quaternary carbon), 33.88 (quaternary carbon), 60.42 (NCH_2), 74.90 (OCH_2), 122.54 (ArC), 124.90 (ArC), 125.45 (ArC),127.62 (ArC), 132.58 (ArC), 136.80 (ArC), 141.18 (ArC), 146.91 (ArC), 149.56 (ArC), 150.74 (ArC), 154.30 (ArC), 164.30 (CH=N); FAB-MS (m/z): 1666 (M$^+$). Anal. calcd for $C_{110}H_{134}O_8N_6$: C, 79.23; H, 8.04; N, 5.04. Found: C, 79.03; H, 7.85; N, 4.89.

3.1.4. Compound 3d. Bridging unit: 4-methylphenol (yield 90%); stirred for 1 h; white solid; mp: 222–224°C; IR (KBr): 1638 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (s, 36H, $C(CH_3)_3$), 1.28 (s, 36H, $C(CH_3)_3$), 1.78 (s, 6H, CH_3), 3.25 (d, J=12 Hz, 8H, $ArCH_2Ar$), 4.05–4.14 (m, 16H, NCH_2, OCH_2), 4.20 (m, 8H, $ArCH_2Ar$), 6.74 (s, 8H, ArH), 7.02 (s, 8H, ArH), 7.08 (s, 4H, ArH), 7.27 (br, s, 4H, ArOH), 8.72 (s, 4H, HC=N); ^{13}C NMR ($CDCl_3$): 19.55 (CH_3), 30.98 ($C(CH_3)_3$), 31.75 ($C(CH_3)_3$), 33.81 (quaternary carbon), 60.20 (NCH_2), 74.97 (OCH_2), 124.90 (ArC), 125.48 (ArC), 127.84 (ArC), 132.50 (ArC), 141.03 (ArC), 146.91 (ArC), 149.63 (ArC), 150.70 (ArC), 159.00 (CH=N); FAB-MS: (m/z): 1724 (M$^+$). Anal. calcd for $C_{114}H_{140}O_{10}N_4$: C, 79.35; H, 8.12; N, 3.24. Found: C, 78.94; H, 7.96; N, 3.02.

3.1.5. Compound 3e. Bridging unit: 4-*tert*-butylphenol (yield 90%); stirred for 2 h; white solid; mp: 240°C (dec.); IR (KBr): 1638 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (s, 36H, $C(CH_3)_3$), 1.00 (s, 18H, $C(CH_3)_3$), 1.27 (s, 36H, $C(CH_3)_3$), 3.24 (d, J=12 Hz, 8H, $ArCH_2Ar$), 4.03–4.34 (br, m, 24H, NCH_2, OCH_2, $ArCH_2Ar$), 6.76 (s, 8H, ArH), 6.99 (s, 8H, ArH), 7.18 (s, 4H, ArH), 7.64 (br, s, 4H, ArOH), 8.78 (s, 4H, HC=N); ^{13}C NMR ($CDCl_3$): 30.98 ($C(CH_3)_3$), 31.60 ($ArCH_2Ar$), 31.71 ($C(CH_3)_3$), 33.85 (quaternary carbon), 60.20 (NCH_2), 75.00 (OCH_2), 124.90 (ArC),125.41 (ArC), 127.76 (ArC),128.64 (ArC), 129.86 (ArC), 132.36 (ArC), 136.44 (ArC), 141.03 (ArC), 146.77 (ArC), 149.71 (ArC), 150.66 (ArC), 150.59 (ArC), 159.50 (CH=N); FAB-MS: (m/z): 1808 (M$^+$). Anal. calcd for $C_{120}H_{152}O_{10}N_4$: C, 79.64; H, 8.40; N, 3.09. Found: C, 80.07; H, 8.73; N, 2.80.

3.1.6. Compound 3f. Bridging unit: thiophene (yield 90%); refluxed for 10 h; white solid; mp: 248°C (dec.); IR (KBr): 1644 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (s, 36H, $C(CH_3)_3$), 1.27 (s, 36H, $C(CH_3)_3$), 3.26 (d, J=11 Hz, 8H, $ArCH_2Ar$), 3.99 (distorted t, 8H, NCH_2), 4.21–4.27 (m, 16H, $ArCH_2Ar$, OCH_2), 6.74 (s, 8H, ArH), 6.98 (s, 8H, ArH), 7.00 (s, ArOH), 7.25 (s, 2H, ArH), 8.52 (s, 4H, CH=N); FAB-MS (m/z): 1676 (M$^+$). Anal. calcd for $C_{108}H_{132}O_8N_4S_2$: C, 77.32; H, 7.37; N, 3.34. Found: C, 77.71; H, 7.63; N, 3.01.

3.1.7. Compound 3h. Bridging unit: *N*-methylpyrazole (yield 85%); refluxed for 20 h; white solid; mp: 276°C(dec.); IR (KBr): 1647 cm^{-1} (–C=N); ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.80 (s, 18H, C(CH$_3$)$_3$), 0.86 (s, 18H, C(CH$_3$)$_3$), 1.22 (s, 36H, C(CH$_3$)$_3$), 3.17, 3.24 (d, J=13 Hz, 8H, ArCH$_2$Ar), 3.64 (t, J=8 Hz, 4H, $H_2C_{\alpha\text{-}5}$), 3.94 (t, J=8 Hz, 4H, $H_2C_{\alpha\text{-}3}$), 4.05–4.25 (m, 22H, ArCH$_2$Ar, $H_2C_{\beta\text{-}5}$, $H_2C_{\beta\text{-}3}$, NCH$_3$), 6.62 (s, 8H, ArH), 6.70 (s, 8H, ArH), 6.97 (s, 4H, ArOH), 7.19 (s, 2H, H_4), 8.23 (s, 2H, H_6), 8.48 (s, 2H, H_2). ^{13}C NMR (CDCl$_3$): 30.94 31.38 (C(CH$_3$)$_3$), 31.54, 31.71 (ArCH$_2$Ar), 33.81, 33.88 (quaternary carbon), 39.95 (NCH$_3$), 60.02 ($C_{\alpha\text{-}5}$), 62.22 ($C_{\alpha\text{-}3}$), 74.65 ($C_{\beta\text{-}5}$), 75.16 ($C_{\beta\text{-}3}$), 109.24, (C_4), 124.86 (ArC), 125.08 (ArC), 125.37 (ArC), 127.43 (ArC), 128.02 (ArC), 132.21 (ArC), 132.39 (ArC), 139.56 (ArC), 141.33 (C_5), 146.66 (C_3), 147.10 (ArC), 148.53 (ArC), 149.52 (ArC), 149.78 (ArC), 150.59 (ArC), 152.87 (N=C_6),157.10 (N=C_2); FAB-MS (*m/z*): 1672 (M$^+$). Anal. calcd for $C_{108}H_{136}O_8N_8$: C, 77.51; H, 8.13; N, 6.69. Found: C, 77.99; H, 8.37; N, 6.43.

3.1.8. Compound 3i. Bridging unit: *N*-benzylpyrazole (yield 70%); refluxed for 20 h; white solid; mp: 210–212°C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.88 (s, 18H, C(CH$_3$)$_3$), 0.94 (s, 18H, C(CH$_3$)$_3$), 1.30 (s, 18H, C(CH$_3$)$_3$), 1.33 (s, 18H, C(CH$_3$)$_3$), 3.22–3.30 (m, 8H, ArCH$_2$Ar), 3.83–4.26 (m, 24H, ArCH$_2$Ar, $H_2C_{\alpha\text{-}5}$, $H_2C_{\alpha\text{-}5\text{-}3}$, $H_2C_{\beta\text{-}5}$, $H_2C_{\beta\text{-}3}$), 5.84, 5.91 (s, 4H, C$_6$H$_5$CH$_2$), 6.68 (s, 8H, ArH), 6.77 (s, 8H, ArH), 7.01 (s, 8H, ArH), 7.03 (s, 2H, ArH), 7.30 (s, 10H, ArH), 8.20, 8.32, 8.45 and 8.58 (s, 4H, H_6, H_2); FAB-MS (*m/z*): 1824 (M$^+$). Anal. calcd for $C_{120}H_{144}O_8N_8$: C, 78.34; H, 7.39; N, 6.14. Found: C, 78.69; H, 7.61; N, 5.91.

3.1.9. Compound 3j. Bridging unit: *N*-hexadecylpyrazole (yield 70%); refluxed for 20 h; white solid; mp: 212°C; ^{1}H NMR (200 Hz, CDCl$_3$): δ 0.88 (s, 18H, C(CH$_3$)$_3$), 0.93 (s, 18H, C(CH$_3$)$_3$), 1.27 (s, 18H, C(CH$_3$)$_3$), 1.30 (s, 18H, C(CH$_3$)$_3$), 3.21–3.35, (m, 8H, ArCH$_2$Ar), 3.73–4.97 (m, 24H, ArCH$_2$Ar, $H_2C_{\alpha\text{-}5}$, $H_2C_{\alpha\text{-}3}$, $H_2C_{\beta\text{-}5}$, $H_2C_{\beta\text{-}3}$), 6.69 (s, 8H, ArH), 6.78 (s, 8H, ArH), 7.03 (s, 2H, H_4), 8.30 (s, 2H, H_6), 8.58 (s, 2H, H_2); FAB-MS (*m/z*): 2092 (M$^+$). Anal. calcd for $C_{138}H_{196}O_8N_8$: C, 79.15; H, 9.36; N, 5.35. Found: C, 79.60; H, 9.67; N, 4.98.

3.2. Extraction measurements

For the extraction experiments, metal picrate solutions (0.01 mol dm^{-3}) were prepared in deionized distilled water. The solutions of the bis-calixarenes (0.01 mol dm^{-1}) were prepared in chloroform (AR grade).

An aqueous solution (2 mL) of metal picrate (0.01 mol dm^{-3}) and a chloroform solution (2 mL) of the bis-calixarene (0.01 mol dm^{-3}) were shaken in a glass tube closed with a stopper for 10 min and kept at 27±1°C for 5 h. An aliquot of the chloroform layer (1 mL) was withdrawn with a syringe and diluted with acetonitrile to 10 mL. The UV absorptions were measured against CHCl$_3$/CH$_3$CN (1:9) solution at 374 nm. Extraction of the metal picrate was calculated as the percentage of the metal picrate extracted in the chloroform layer and the values reported here are the mean of the three independent measurements which were within ±2% error (Table 1).

3.3. Transport measurements

The transport experiments were carried out in a cylindrical glass cell consisting of outer and inner jackets by using (i) metal picrate (0.01 mol dm^{-3}) in water (3 mL) in the inner phase; (ii) water (10 mL) in the outer phase; (iii) ligand (0.001 mmol dm^{-3}) in a chloroform layer (15 mL) with stirring at 27±1°C. After stirring for 6 h the amount of picrate transported in the outer aqueous phase was determined from UV absorptions at 355 nm. Each value is a mean of three independent experiments which are within ±10% error (Table 2). Blank experiments were also carried out in the absence of the bis-calix[4]arenes in order to determine the leakage of the metal picrates. Under the conditions given for transport experiments, in the absence of the bis-calix[4]arenes, metal picrates were not transported to the receiving phase except in the case of Pb^{2+} picrate, which shows significant transport and hence the results for the bis-calix[4]arene induced transport of the Pb^{2+} are not reliable.

Acknowledgements

The authors are thankful to CSIR (New Delhi) for financial support (project no. 01/1652(EMR-II), Professor C. A. Hunter (University of Sheffield, UK) for FAB mass and Miss Meena Sharma for recording NMR spectra.

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