Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 62–70

Calix[4]azacrowns: self-assembly and effect of chain length and *O*-alkylation on their metal ion-binding properties

Issam Oueslati,[a,*] Pierre Thuéry,[b] Oleksandr Shkurenko,[c] Kinga Suwinska,[c] Jack M. Harrowfield,[d] Rym Abidi[e] and Jacques Vicens[f,*]

[a]*Centro de Química-Física Molecular, Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisboa, Portugal*
[b]*CEA/Saclay, SCM (CNRS URA 331), Bât. 125, 91191 Gif-sur-Yvette, France*
[c]*Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka, 44/52, PL-01 224 Warszawa, Poland*
[d]*Supramolecular Chemistry Laboratory, ISIS/ULP, 8 Allée Gaspard Monge, 67083 Strasbourg Cedex, France*
[e]*Université de Bizerte, 7021 Zarzouna-Bizerte, Tunisia*
[f]*ECPM (CNRS UMR 7512), 25 rue Becquerel, 67087 Strasbourg Cedex 2, France*

Received 20 September 2006; revised 18 October 2006; accepted 19 October 2006
Available online 7 November 2006

Abstract—Both the consequences of 1,3-cyclization of calix[4]arenes by diamide formation, and the effect of 2- and 2,4-alkoxycarbonylmethylation of two 1,3-bridged calix[4]azacrowns on their metal ion-binding capacities have been studied by synthesis of the derivatives in their *cone* conformation and measurement of the stability constants for their complexation in a range of alkaline earth and transition metal cations. In these two cases, the conformation of the ligand in the solid state has been defined in detail by a crystal structure determination. In the first case, a tubular architecture performing methanol channels is displayed, however, in the second case a zigzag architecture generated by a chloroform network connecting calixarene molecules is present. Speciation in solution appears to be limited to the formation of 1:2 and/or 1:1 and/or 2:1 (M–L) complexes, depending on the system, with values of the stability constants determined by absorption spectroscopy in acetonitrile, lying in the ranges log β_{12} ca. 10, log β_{11} ca. 2–5, and log β_{21} ca. 7–9. There is evidence for selectivity toward Cu(II) and for some unexpected anion effects. None of these ligands appear to be an efficient extractant for the metals as their picrate.

1. Introduction

Cu(II) is both a significant environmental pollutant and an essential trace element in biological systems.[1] Its selective coordination is therefore a matter of practical importance as well as of fundamental scientific interest.[2] Calixarenes, and calix[4]arenes in particular, are versatile scaffolds for the construction of selective cation receptors but, while various examples of Cu(II) complexes of calixarenes are known,[3,4] very limited information is available on the degree of selectivity in the metal ion complexation.[4] The family of calix[4]azacrowns involves molecules combining calix[4]arene elements and oxo-azacrown (diamidocrown) units in their framework. One method for their construction is to use polyaminoalkylene chains as bridges between carbonylmethyl substituents already attached to the phenolic oxygen atoms of the calixarene.[5] At least when the resulting amide units are in their neutral form, such compounds should behave as binding ligands through the amide oxygen donor atoms rather than nitrogen atoms.[6,7] The first 1,3-calix[4]azacrowns were prepared by reaction of either 1,3-bis(methoxycarbonylmethyl)calix[4]arene or its corresponding diacyl chloride with the appropriate diamine $NH_2–R–NH_2$ and were shown, in early qualitative studies, to complex divalent [Be(II), Mg(II), Ca(II), Sr(II), and Ba(II)] and trivalent [Sc(III), Y(III), In(III), Gd(III), and Bi(III)] metal cations.[5] Despite the literature now developed,[3g,5,8,9] only rather limited information concerns the metal cation complexation properties of oxo-azacrown calixarene derivatives.[3g,5,9] It is important in such works to use a calixarene in a well-defined conformation and thus it is significant that studies of alkylation of the residual phenolic groups in singly-bridged calix[4]azacrowns[5,8c] have shown that methylation results in a mixture of conformers[5] but that alkylation or acylation involving bulkier groups leads to the predominance of the *pinched-cone* conformer in which the phenyl rings with *O*-alkyl or -acyl substituents lie nearly parallel.[8c,n]

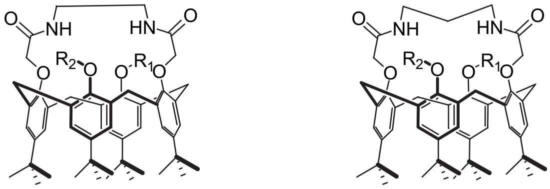
The aim of the present work was to synthesize *O*-alkylated calix[4]azacrowns **2**, **3**, and **5** (Chart 1) in the *cone* conformation in order to compare their ion-binding properties to that of **1** and **4** (Chart 1) toward alkaline earth [Mg(II),

---

Keywords: Calix[4]azacrown; Self-assembly; Channel; Zigzag architecture; Ion-binding; Coordination.

* Corresponding authors. Tel.: +351 21 84 19 206; fax: +351 21 84 64 455 (I.O.); tel.: +33 39 02 42 695; fax: +33 39 02 42 787 (J.V.); e-mail addresses: issam.oueslati@ist.utl.pt; vicens@chimie.u-strasbg.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.047



1, 2, 3
1 $R_1 = R_2 = H$
2 $R_1 = H$, $R_2 = CH_2CO_2CH_3$
3 $R_1 = R_2 = CH_2CO_2CH_3$

4, 5
4 $R_1 = R_2 = H$
5 $R_1 = R_2 = CH_2CO_2CH_3$

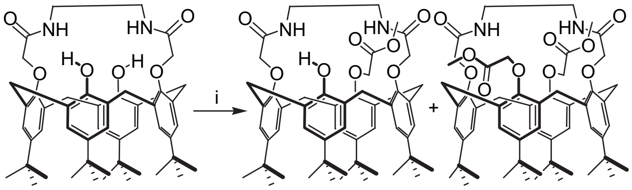
Chart 1. Calixarenes studies in the present work.

Sr(II), and Ba(II)] and transition metal [Co(II), Ni(II), Cu(II), and Zn(II)] ions. The complexation was investigated by UV absorption spectroscopy, while ^1H NMR titrations were conducted to probe the host–guest interaction and the crystal structures of **1** and **4** were elucidated to precisely define the juxtaposition of the donor centers. This study illustrates the consequences of cyclization by diamide formation and *O*-methoxycarbonylmethylation of residual phenolic units on the binding of metal ions. Therefore, we describe herein an unusual self-organization designing nanometer-scale tubes for methanol channels, and the first calixazacrowns to be characterized as selective ionophores for Cu(II).

2. Results

2.1. Synthesis

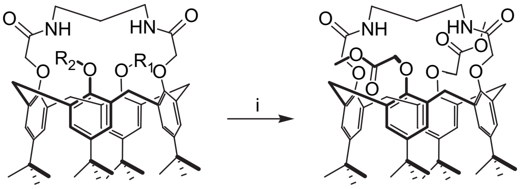
Mono- and di-*O*-substituted derivatives of **1** were prepared according to Scheme 1. Treatment of **1** with $BrCH_2CO_2CH_3$ in the presence of K_2CO_3 in refluxing CH_3CN for 1 day generates mono- and dimethylester derivatives **2** and **3** in 16 and 45% yields, respectively. The products were fully characterized by FTIR, ^1H NMR, mass spectrometry, and elemental analysis, all these evidences supported the conclusion that each isolated species was a single conformer. A problem, which arises in the spectroscopic characterization of calixarenes functionalized in ways, which reduce the molecular symmetry is that simple distinctions of conformers based on the number of ^1H NMR signals observed are no longer possible and the values of coupling constants obtained for calixarenes of known conformation become more important criteria. Thus, critical to the present work was the establishment of the *cone* conformation for compounds **1** and **4** (vide infra) by X-ray crystallography. It is on this basis that all the present materials have been assigned a *cone* conformation. In the particular case of compound **2**, despite its potential conformational lability arising from the presence of one phenolic ring and the presence of at the most (regardless of conformation) a plane of symmetry passing through the 2,4 rings, the methylene-bridge ^1H resonances appear as a single AB system, with J_{AB} (13.5 Hz) very similar to that for the truly equivalent bridging methylene groups in all the other species presently studied. In addition, while a 1:2:1 pattern of *tert*-butyl group resonances should occur regardless of conformation, the fact that the actual resonances are barely resolved into a 1:3 ratio is consistent with a *cone* conformation giving all four substituents a similar environment. Hydrogen bonding of phenolic OH (δ ca. 8.3 ppm) adjacent to ether-O, as observed in the structures of **1** and **4** (vide infra), may explain the preference of **2** for the *cone* conformation.



1 **2** **3**

Scheme 1. Synthetic pathway for *O*-alkylated calixarenes **2** and **3**. (i) $BrCH_2CO_2CH_3/K_2CO_3$/acetonitrile, reflux.

Conditions for the conversion of calixarene **4**, bearing a larger diamidocrown bridge to its bis(methoxycarbonylmethyl) derivative **5**, in 62% yield, are outlined in Scheme 2. While both *cone* and *1,3-alternate* conformers of **5** would give rise to the same number of ^1H resonances in their NMR spectra, again it is on the basis of coupling constant values and the known conformation of **4** that the product is assigned a *cone* conformation.



4 **5**

Scheme 2. Synthetic pathway for *O*-alkylated calixarene **5**. (i) $BrCH_2CO_2CH_3/K_2CO_3$/acetonitrile, reflux.

2.2. Crystal structures of $\mathbf{1 \cdot CH_3CN \cdot CH_3OH}$ and $\mathbf{4 \cdot CH_3CN \cdot CHCl_3}$

As illustrated in Figure 1, the calixarenes in compounds $\mathbf{1}\cdot CH_3CN\cdot CH_3OH$ and $\mathbf{4}\cdot CH_3CN\cdot CHCl_3$ are in a *cone* conformation, with no crystallographic symmetry.

This conformation is stabilized by an intramolecular hydrogen bonding array, which links phenolic protons to ether oxygen atoms and amine protons to phenolic oxygen atoms, thus forcing the amine protons to point inwards. A similar hydrogen bonding pattern has been found in compound $\mathbf{1\cdot CH_2Cl_2}$.[8a] The basal part of the bridge, comprising the two –O–CH_2–CO– groups, defines a mean plane with max. rms deviation of 0.23 Å in **1** and 0.16 Å in **4**, whereas the line defined by the central –$(CH_2)_2$– bond and the plane defined by –$(CH_2)_3$– unit make with the plane defined above angles of 33.1(3) and 64.4(2)°, respectively. The nitrogen atoms link these two planes with one nitrogen on each side of each plane. The torsion angles, which characterize the geometry of the –NH–$(CH_2)_2$–NH– and –NH–$(CH_2)_3$–NH– bridges are, respectively, 91.5(5), 62.0(5), 88.2(5), and 69.6(5), 38.5(6), 46.0(5), 76.5(5)°. The calixarene shape can be characterized by the values of the dihedral angles between the phenolic rings and the mean plane defined by the methylene carbon atoms. The two aromatic rings bound to the bridge appear more 'vertical' [dihedral angles 72.7(1) and 64.5(1)° in **1**, and 68.46(9) and 71.28(9)° in **4**] than the other two ones [53.0(1) and 52.3(1)° in **1**, and 51.2(1)

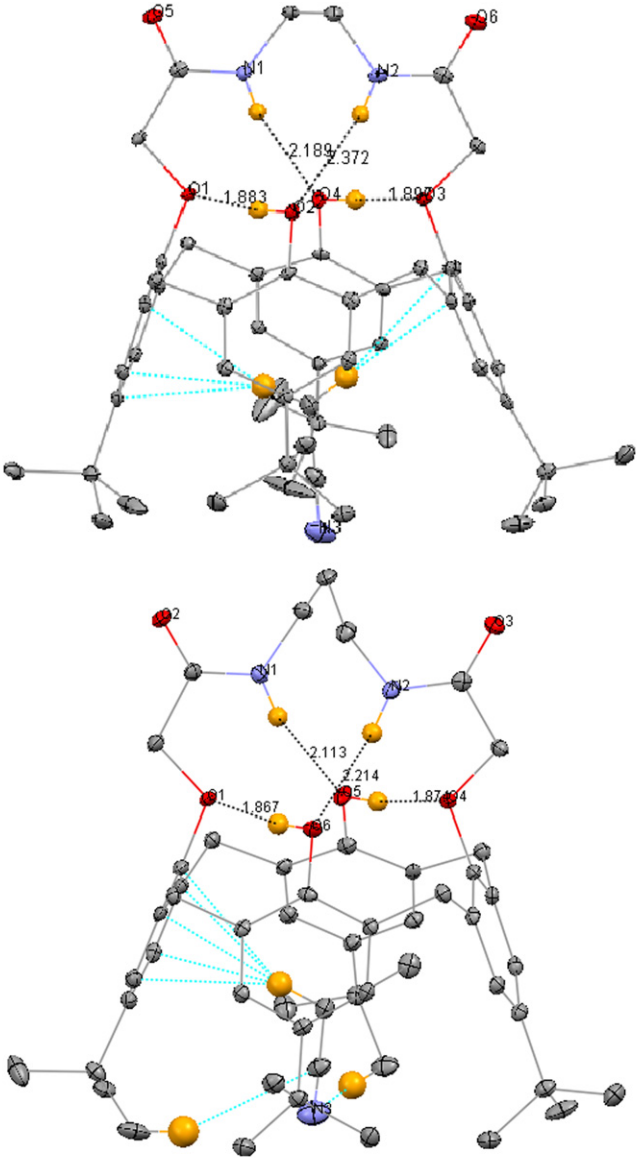


Figure 1. The calixarene molecule, with included CH_3CN, found in the crystal lattice of $\mathbf{1}\cdot CH_3CN\cdot CH_3OH$ (up) and $\mathbf{4}\cdot CH_3CN\cdot CHCl_3$ (down). Carbon-bound hydrogen atoms, methanol, and chloroform molecules omitted, excluding hydrogen atoms involved in electrostatic interactions. Hydrogen bonds shown as black dashed lines. Intermolecular interactions shown as cyan dashed lines. Displacement ellipsoids drawn at the 20% probability level.

and 52.0(1)° in **4**]. Therefore, the conformation of **4** is relatively close to that observed in **1**, and the slightly narrower conformation of the cone in **4** being likely due to the larger bridge length. The more nearly 'vertical' rings in the present compound make a dihedral angle of 40.3(2)°, whereas the other two define an angle of 76.9(1)°. The separations between diametrically located ether oxygen atoms $O(1)\cdots O(4)$ 4.530(4) and $O(5)\cdots O(6)$ 3.507(4) Å, and the nitrogen atoms $N(1)\cdots N(2)$ 3.090(4) are comparable to the values 4.484(5), 3.588(4), and 2.904(5) Å in **1**, with the slightly larger $O(1)\cdots O(4)$ and $N(1)\cdots N(2)$ distances in **4** being a result of the larger bridge. Whereas a dichloromethane molecule is included in the cavity of $\mathbf{1\cdot CH_2Cl_2}$,[8a] in the present case an acetonitrile is encapsulated in **1** and **4**, which is a common feature. The later interacts with the calixarene cavity via short contacts, approaching van der Waals distances, analogous to CH-π interaction 2.83 Å in **1** and 2.52 Å in **4**, $N\equiv C\cdots H$–C interaction 2.89(4) Å and $N\cdots H$–C interaction 2.73(4) Å in **4**. The packing of **1** along the *c* axis reveals (cf. Fig. 2) the presence of disconnect vertically aligned channels, every one designs infinite successive hydrophobic ellipsoide cavities delimited, each, by 10 oxygen atoms and four benzene rings belonging to four calixarenes (cf. Fig. 3). Four methanol molecules are encapsulated in each cavity and arranged in an oppositely twofold mode with outdistance separation of 13.50 Å. A particular short contact of 2.84 Å is established between methanol oxygen and carbonyl oxygen O(6) atoms.

On the other hand, the packing of $\mathbf{4}\cdot CH_3CN\cdot CHCl_3$ (Fig. 4) shows successive opposite layers of 17.1 Å describing, each, a zigzag tape generated by a chloroform network connecting calixarene molecules. Every chloroform is attached to two successive calixarenes through $C{=}O\cdots H$–C 2.07(4) Å and $Cl\cdots H$–C 2.86(4) Å. The layers display special short contacts below 3.20 Å achieved by association of each calixarene with two neighboring calixarenes of the opposite layers

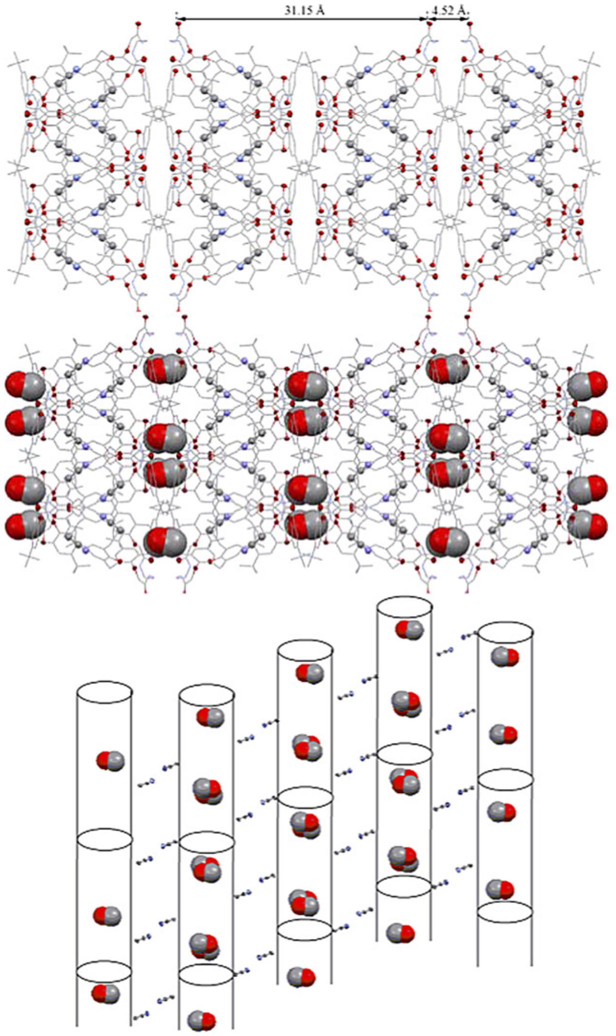


Figure 2. Packing diagram of $\mathbf{1}\cdot CH_3CN\cdot CH_3OH$ along *c* axis illustrating the network of channels (up, methanol omitted) and the incorporation of methanol molecules in the channel-type inter-molecular inclusion complex (middle along *c* axis and down along *b* axis).

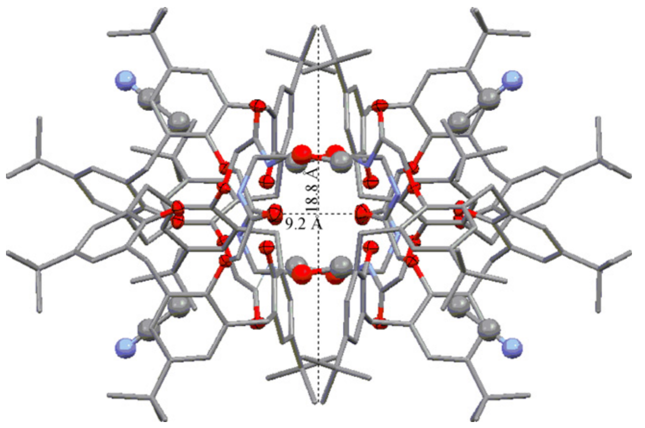


Figure 3. View of a single cavity down the *c* axis illustrating the intra-cavity complexation of four methanol guests.

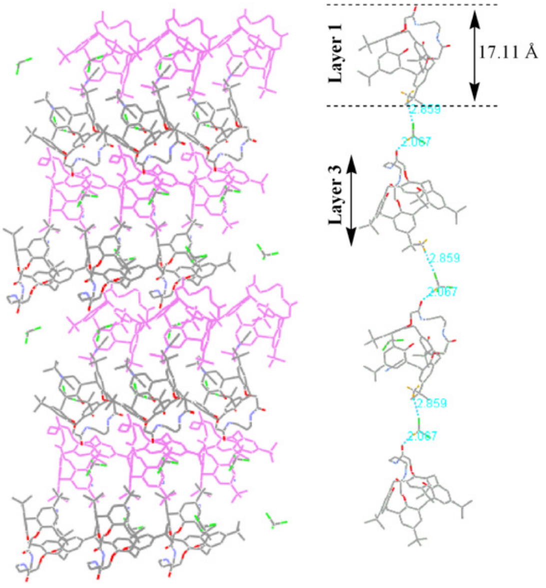


Figure 4. View of the molecular packing (left) and the zigzag architecture of interconnected layers (right).

(cf. Fig. 5). This is drawn by both calixarene–chloroform interactions (2.07 Å, 3.17 Å, and 3.19 Å) shown in green in Figure 5, and calixarene–calixarene interactions sited between azacrown chains, 2.58 Å and 3.21 Å shown in blue, 2.66 Å shown in orange, and 3.08 Å shown in black in Figure 5.

A careful analysis in the Cambridge Crystal Database displayed a solely subsequent zigzag form to be adopted by calix[4]azacrowns[8k] (cf. Fig. 6) and relatively less rigid, since there is no direct interaction between the zigzag layers as it is observed in the structure of **4**, and the distance between the layers is larger (approximately 4.0 Å against 2.5 Å).

2.3. Complexation of metal ions

The UV absorption spectra of **1**–**5** in acetonitrile are dominated by a structured band between 270 and 290 nm, akin to the observations made for similar calix[4]arenes or monomeric methoxybenzenes.[10] These absorption bands correspond to the π and π* transitions of the aromatic moieties.

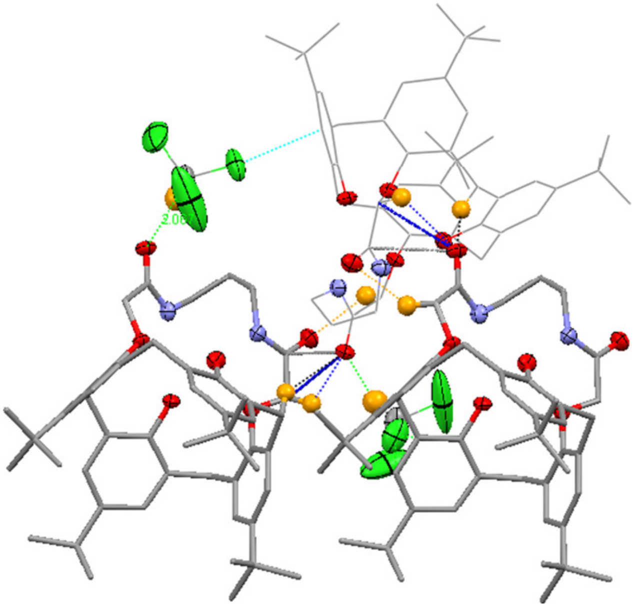


Figure 5. Short contacts displayed between calixarenes of opposite layers. C=O···H–C–O.

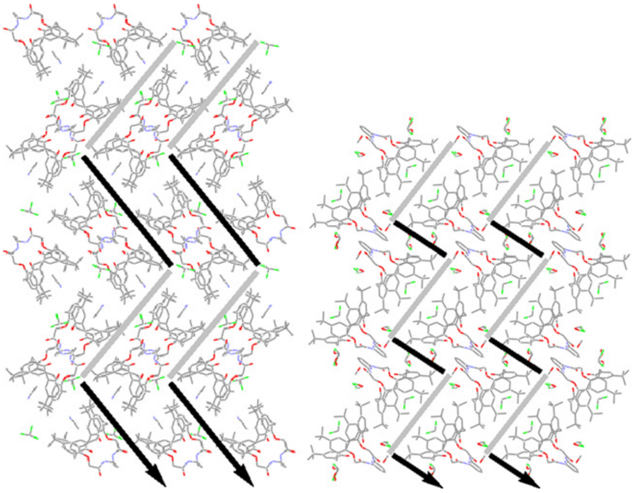


Figure 6. View (left) along the *c* crystal axis of the zigzag layers of **4**, and (right) along the *a* crystal axis of the zigzag structure of a particular calix[4]-azacrown.[8k]

Upon addition of metal perchlorates the spectra, in most cases, show changes (cf. Supplementary data), albeit dependent on the ligand structure. The absence of spectral changes for some examples was taken as indicative of the formation of very weak complexes ($\log \beta_{ij} \leq 1$). In these cases at least for ligands **1** and **4**, however, mass spectrometric studies[5] support the conclusion that negligible changes in the electronic spectrum are indicative of a lack of complexation. These particular ligands in fact appear to be selective for Cu(II), as this was the only metal ion for which spectroscopic changes could be detected, these appearing to result from, in the case of ligand **1**, formation of a 1:1 (M–L) complex ($\log \beta_{11}=4.2$), and, in the case of **4**, formation only of a 2:1 complex ($\log \beta_{21}=6.6$). Molecules **3** and **5** are the only ligands in the present series to interact with alkaline earth metal ions Mg(II) and Sr(II), **3** forms a weak 1:1

complex ($\log \beta_{11}$=1.9) reflected in the need for high metal to ligand ratios to drive the reaction to essential completion, and **5** forms a 2:1 complex ($\log \beta_{21}$=6.5), although Ba(II) does not seem to be complexed.

Complexation of transition metal ions was also limited, there being no spectrophotometric evidence for the interaction of either Ni(II) or Zn(II) with any of the ligands **1**–**5**. Co(II) forms, however, strong complexes with ligands **2** ($\log \beta_{12}$=10.4) and **3** ($\log \beta_{11}$=5.4) and Cu(II) gives complexes with **2**–**5** of stability constants in the order of $\log \beta_{21}$ ca. 6.6−9.2, although the seemingly exclusive formation of single species with the stoichiometries 1:2 or 2:1 could suggest that either the coordination of one cation is very weak or that the spectral changes from [calix] to $[\text{cation}\cdot\text{calix}]^{2+}$ are too small to be fitted. The predominance of Cu(II) complexation is consistent with expectation based on well-established comparisons of M(II) species in the first transition metal series[11] and with earlier observations on calix[4]arene derivatives.[3h,4,12]

2.4. Extraction of metal picrates

Values obtained under standard conditions[13] for the degree of extraction (% E) of alkaline earth and transition metal picrates from water to dichloromethane are all low (cf. Supplementary data), though similar to those reported for calix[4]arenes bearing amide-containing functional groups.[14] This inefficient extraction is possibly a simple reflection of the low stability of the complexes, though the results may also be affected to the hydrolysis of the metal ions under the experimental conditions leading to some extraction of picric acid, a circumstance, which cannot be excluded since we have shown elsewhere for a similar case that exclusive extraction of picric acid may occur.[9a] Thus it would be unwise to attempt any interpretation of the present results in terms of any differences between the metal ions.

3. Discussion

3.1. Calixarene conformation

When **1** is dialkylated by $BrCH_2CO_2Et$ in the presence of K_2CO_3 in acetone[8c] rather than acetonitrile, a mixture of conformers result. This has been attributed[8c] to the imposition of more than one binding mode for K(I) by the amido-crown bridge. The present results indicate that a single templating mode, favoring the *cone* conformation, may apply in acetonitrile, the solvent itself possibly having some direct influence.[15]

It has been widely accepted[10a,16] that the difference between the chemical shifts of the axial (H_{ax}) and equatorial (H_{eq}) methylene protons of the calixarene platform can be used to evaluate the symmetry, in particular the degree of '*pinching*' toward a C_{2v} form, of the *cone* conformation of calixarenes. However, a recent report has shown that this does not hold for bridged calixarenes with structures very similar to the ones investigated in this work.[8d,17] The chemical shift differences of *tert*-butyl and aromatic protons (Ar*H*) of neighboring (proximal) phenyl rings were suggested as more reliable criteria.[8d] For ligands **1**, **2**, and **4** only minor differences (<0.1 ppm) between *tert*-butyl protons or phenyl protons were observed in chloroform-d_1, which points to a conformation, which is effectively close to four-fold symmetry. On the other hand, disubstituted derivatives **3** and **5** show pronounced differences (>0.4 ppm) suggesting, therefore, a strongly '*pinched*' *cone* conformation.

3.2. The consequences of cyclization by diamide formation

Without deprotonation at N, amides, RCONHR′, usually behave as O-donor ligands[6] and, since the present studies have been performed in neutral media, it would be anticipated that the ligands **1**–**5** would behave as multidentate O-donor species. Further, as structural studies show that in complexes of the podands tris- and tetrakis(diethylamidocarbonylmethyl)-*p*-*tert*-butylcalix[4]arene and tetrakis(dibutylamidocarbonylmethyl)-*p*-*tert*-butylcalix[4]arene ('calix[4] tri- and tetramide') there is a stronger interaction with carbonyl-O than with phenolic-O atoms,[3a,18] it is to be expected that preferential binding to carbonyl-O might occur in **1**–**5**. Modeling at the MM2 level, as well as the crystal structure determination for **1** and **4** (cf. Figs. 1 and 7) shows, however, that the carbonyl units of the diamide bridge tend to be divergent from the calixarene cavity, so that with the exception of a metal, which may bind only to four phenolic-O atoms or, which may produce gross distortions of the ligand structure, **1** and **4** might be expected to act at best as bidentate species toward 'externally' bound metal ions. This may explain both their weakness as ligands toward the metals presently studied and why Cu(II), as the metal expected to form the most stable species, is, in some cases, the only metal for which complex formation can be detected. Thus, similar to

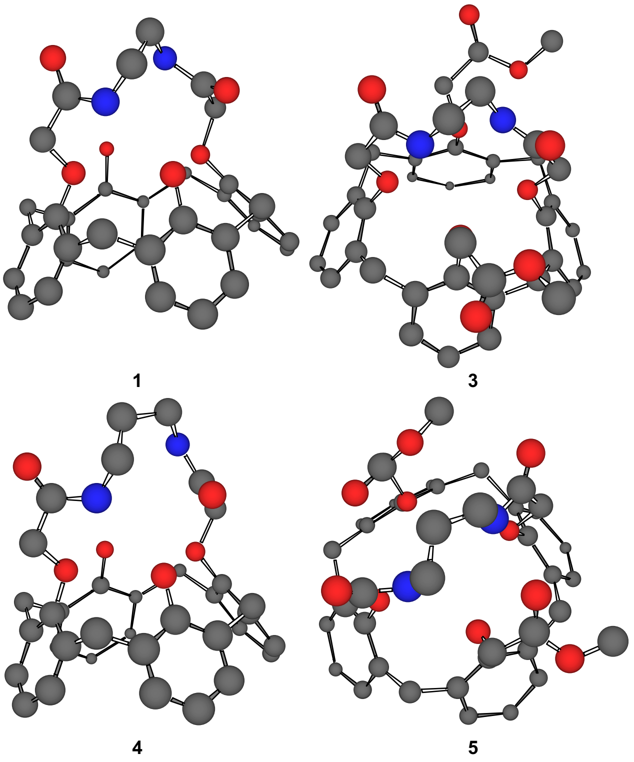

1 3
4 5

Figure 7. Energy minimized structures of calixarenes **1**, **3**–**5**.

what has been observed with some primary amide ligands.[11b,e] Such an effect can be evaluated when comparing the complexing behaviors of **1** and **4** to that of 1,3-diethylester-*p*-*tert*-butylcalix[4]arene, which is known to complex alkaline earth (log β_{11} ca. 3.3 – 5.2) and transition metal ions.[19] In the solid state, the lateral bridging of *p*-*tert*-butylcalix[4]arene with ethylene diamide chain generates self-organized nanotubes adequate to act as channels for small molecules, methanol in the case of **1**.

3.3. Effect of *O*-methoxycarbonylmethylation of residual phenolic units

In acetonitrile, dialkylation (ligand **3**) leads to detectable complexation of Mg(II) and Sr(II) (as 1:1 species). The introduction of two methylester functions on **1** abolishes intramolecular hydrogen bonds OH····O and may bring more flexibility to **3**, facilitating its rearrangement to bind the cations, as well as providing additional O-donor sites as part of chelating arms. The low stabilities observed may reflect an external localization of the cation and the participation of solvent molecules in its coordination sphere, viz., simple unidentate or bidentate binding of the calixarene to the metal. While O-donors of the methoxycarbonylmethyl arms could presumably be oriented toward the cavity center, this may well be inhibited by the diamidocrown bridge. The small ^{1}H NMR chemical shift changes observed on titration of **3** with Sr(ClO$_4$)$_2$ in a 1:1 mixture CD$_3$CN–CDCl$_3$ (cf. Table 1) are consistent with the low stability constant determined in acetonitrile and the most marked downfield shift, that of the NH protons, is consistent with simple binding via amide carbonyl-O atoms. Further, no spectroscopic evidence (cf. Supplementary data) of any marked conformational change induced by complexation suggests an external localization of Sr(II). Such a coordination mode may also be evoked with Mg(II).

The apparently relatively strong interaction of Co(II) with **2** and **3** may be a reflection of the ease, compared at least to Ni(II) and Cu(II), with which Co(II) adopts a tetrahedral coordination geometry and, which may even allow it to enter the calixarene cavity. Modeling shows that such inclusion is possible for **3** with two ester carbonyl-O and two phenolic ether-O (of the cyclic unit) atoms bound to Co(II). A 1:2 species, as is apparently formed with **2**, might involve inclusion with one donor coming from a second calixarene molecule but, of course, could also concern a simpler species involving 'external', bidentate coordination of the two calixarene molecules. The seeming failure of these ligands to interact with Zn(II), given the stability of the Co(II) species and the common observation of similar complexation behavior of the two metal ions,[3g,h,11a,c,d] could originate from the small differences in size and oxophilicity, which may give rise to marked differences in the case of a ligand where entry to the central cavity is inhibited by the diamide 'strap'.

3.4. Effect of chain length

Albeit the incorporation of one methylene group on the bridge influences slightly the calixarene conformation, self-assembly of **1** and **4** is deeply affected, thus ranging from a tubular architecture to a zigzag one. The achievement of mono-O-alkylation of **1**, which is not attainable for **4**, could result from the obstruction of the second OH by the shorter bridge, since the reaction takes longer (24 h for **1** vs 8 h for **4**).

In the absence of the podand methylester groups, the lengthening of the bridging chain by the insertion of a single methylene group does not significantly enhance the complexation capacity of the ligand toward the chosen metals. This is consistent with previously reported results showing that substitution of amide nitrogen atoms with groups of similar electronic properties leads to similar complexation profiles.[20]

The unusual observation for both **4** and **5** where complexation is detectable, a 1:1 species cannot be detected whereas a 2:1 can, may be explicable if perchlorate anion is also bound in the 1:1 species and acts as a bridge to facilitate binding ('positive cooperativity') of the second metal ion. Such a phenomenon has already been observed with some dinuclear macrocyclic cryptates, crown ethers, and hexaazamacrocyles with metal ions and is termed 'cascade' complex formation.[21] Structural and IR studies of Ca(II) perchlorate complexes formed with bislactam (macrocyclic bisamide) ligands confirm the participation of ClO_4^- anions in complexation via NH$_{amide}$···O hydrogen bonds.[6c] Besides, supramolecular positive cooperativity has been described in detail predominately in connection with metal ion coordination and organic systems.[22] The greater length of the bridge in **4** and **5** may result in a lesser obstruction of the calixarene cavity by the methylene groups, though at least for ligand **4**, the possibility that metal ion-binding is associated with a conformational change of the calixarene entity cannot be excluded. Once again, study of changes in the ^{1}H NMR spectrum of the ligand, here **5**, as Sr(ClO$_4$)$_2$ is added (cf. Table 2 and Supplementary data) shows that the most marked

Table 1. ^{1}H NMR chemical shift changes (ppm) of **3** with the addition of Sr(ClO$_4$)$_2$ in a 1:1 mixture CD$_3$CN–CDCl$_3$ at 298 K, [**3**]=10^{-3} M

Sr(II)/L[a]	N*H*	Ar*H*	ArOC*H*$_2$-ester	*H*$_{ax}$	ArOC*H*$_2$-amide	COOC*H*$_3$	C(C*H*$_3$)$_3$
0	8.20	7.25	4.54	4.53	4.28	3.71	1.21
0.5	+0.07	−0.01	−0.03	−0.04	0	−0.02	−0.02
1	+0.12	−0.01	−0.03	−0.05	+0.01	−0.02	−0.02
1.5	+0.16	−0.01	−0.03	−0.05	+0.03	−0.02	−0.02
2	+0.18	−0.01	−0.03	−0.06	+0.04	−0.02	−0.03
2.5	+0.21	0	−0.03	−0.06	+0.04	−0.01	−0.03
3	+0.24	0	−0.03	−0.06	+0.05	−0.01	−0.03
3.5	+0.27	0	−0.03	−0.07	+0.06	−0.01	−0.03
8.5	+0.34	0	−0.04	−0.08	+0.08	0	−0.03

[a] Mole ratio.

Table 2. ^{1}H NMR chemical shift changes (ppm) of **5** with the addition of $Sr(ClO_4)_2$ in a 1:1 mixture CD_3CN–$CDCl_3$ at 298 K, [**5**]=10^{-3} M

Sr(II)/L[a]	NH	Ar*H*	ArOC*H*$_2$-ester	H_{ax}	ArOC*H*$_2$-amide	COOC*H*$_3$	C(C*H*$_3$)$_3$
0	8.26	7.25	4.51	4.53	4.31	3.71	1.22
0.5	+0.09	−0.01	−0.03	−0.04	+0.02	−0.02	−0.02
1	+0.16	−0.01	−0.03	−0.05	+0.04	−0.01	−0.02
1.5	+0.21	−0.01	−0.03	−0.06	+0.05	−0.01	−0.02
2	+0.26	0	−0.02	−0.06	+0.06	0	−0.02
2.5	+0.29	0	−0.02	−0.07	+0.07	0	−0.02
3	+0.32	0	−0.02	−0.07	+0.07	0	−0.02
3.5	+0.35	+0.01	−0.02	−0.07	+0.08	0	−0.02
9.5	+0.45	+0.01	−0.02	−0.07	+0.08	0	−0.03

[a] Mole ratio.

downfield shift involves the NH protons. This could be indicative of a form of coordination as simple as unidentate binding of an amide carbonyl-O atom (and rapid exchange of the metal ion between both sites) and would explain why stability constant values are low for some metals.

4. Conclusions

Sulfonated calixarenes show the capacity to design water and ion channels, however, calixazacrown **1** exhibits similar aptitude to form in the solid state channels for small molecules, methanol in our issue, which is the first example of encapsulation of organic molecules within an organized network of calixarene cavities.

Although readily obtained in their *cone* conformation by the appropriate choice of reaction solvent, phenolic-*O*-alkylated calix[4]azacrowns appear to be relatively poor ligands for at least alkaline earth and first-row transition metal ions. This may be a consequence of the divergent orientation of the O-donor entities in the amide links of the crown bridge as well as of the interference of the bridge in the attainment of a convergent arrangement of O-donor atoms in the flexible phenolic-O substituents. When binding does occur, unexpected complex ion stoichiometries arise and this may be indicative of some specific interaction between the calixarenes and perchlorate anion. This is an issue, which may be resolved by current work aimed at the crystallization of the complexes for structure determinations. Nonetheless, this selectivity could promote the design of novel fluorescent chemosensors for Cu(II) based on the excitation of the aromatic units of **1** and **4**. The latter approach is currently under consideration.

5. Experimental

5.1. General

Reagents, characterization techniques, infra-red spectra, physical measurements, and crystallographic data collections are described in the Supplementary data.

5.2. Synthesis

5.2.1. Preparation of 2-mono- (2) and 2,4-bis(methoxycarbonylmethyl) (3) derivatives of 1,3-[ethylene-bis-(aminocarbonylmethoxy)]-*p*-*tert*-butylcalix[4]arene (1). Calixarene **1** (2.004 g, 2.50 mmol), K_2CO_3 (0.370 g, 2.67 mmol), and CH_3CN (110 mL) were stirred for 1 h at rt under N_2. Then $BrCH_2CO_2CH_3$ (0.687 g, 4.49 mmol) was added. After refluxing for 1 day, the solvents were evaporated to dryness. The residue was dissolved in CH_2Cl_2 and acidified with 1 M HCl. The organic layer was dried (Na_2SO_4) and the residue was precipitated with CH_3OH to give **2** (0.341 g, 0.396 mmol) and **3** (1.060 g, 1.136 mmol) as white solids after column separation with 90/10 CH_2Cl_2–acetone.

Compound **2**. Mp >270 °C. R_f=0.26 (90/10 CH_2Cl_2–acetone). ν_{max} (KBr) 3373 (OH), 1763 (ester C=O), 1691 (amide C=O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H/ppm 8.51 (t, 2H), 8.22 (s, 1H), 7.15 (d, *J*=1.7 Hz, 2H), 7.08 (s, 2H), 7.07 (s, 2H), 6.97 (d, *J*=1.7 Hz, 2H), 4.66 (d, *J*=16.1 Hz, 2H), 4.65 (d, *J*=13.5 Hz, 2H), 4.62 (s, 2H), 4.26 (d, *J*=13.8 Hz, 2H), 4.07 (d, *J*=13.5 Hz, 2H), 3.78 (s, 3H), 3.62 (br s, 4H), 3.41 (d, *J*=13.5 Hz, 4H), 1.25 (s, 9H), 1.16 (s, 27H). FAB(+) MS *m/z* 861.5 (M$^+$). Anal. Calcd for $C_{53}H_{68}N_2O_8\cdot 2CH_3OH\cdot 2CH_2Cl_2$: C, 62.52; H, 7.36. Found C, 62.32; H, 7.60. Yield 16%.

Compound **3**. Mp >270 °C. R_f=0.20 (90/10 CH_2Cl_2–acetone). ν_{max} (KBr) 3443 (NH), 1764 (ester C=O), 1687 (amide C=O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H/ppm 8.20 (t, 2H), 7.12 (s, 4H), 6.72 (s, 4H), 4.41 (s, 4H), 4.40 (d, *J*=12.5 Hz, 4H), 4.20 (s, 4H), 3.70 (s, 6H), 3.55 (m, 4H), 3.21 (d, *J*=12.5 Hz, 4H), 1.24 (s, 18H), 0.84 (s, 18H). FAB(+) MS *m/z* 933.7 (M$^+$). Anal. Calcd for $C_{56}H_{72}N_2O_{10}\cdot CH_3COCH_3$: C, 71.47; H, 7.94. Found C, 71.36; H, 8.02. Yield 45%.

5.2.2. Preparation of 2,4-bis(methoxycarbonylmethyl) (5) derivative of 1,3-[propylene-bis(aminocarbonylmethoxy)]-*p*-*tert*-butylcalix[4]arene (4). Calixarene **4** (0.800 g, 1.00 mmol), K_2CO_3 (0.553 g, 4.00 mmol), and CH_3CN (50 mL) were stirred for 1 h at rt under N_2. Then $BrCH_2CO_2CH_3$ (0.635 g, 4.14 mmol) was added. After refluxing for 8 h, the solvents were evaporated to dryness. The residue was dissolved in CH_2Cl_2 and acidified with 1 M HCl. The organic layer was dried (Na_2SO_4) and the residue was precipitated with CH_3OH to give **5** (0.585 g, 0.618 mmol) as white solid. Mp >270 °C. R_f=0.43 (75/25 CH_2Cl_2–acetone). ν_{max} (KBr) 3444 (NH), 1765 (ester C=O), 1681 (amide C=O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H/ppm 8.26 (t, *J*=5.5 Hz, 2H), 7.16 (s, 4H), 6.62 (s, 4H), 4.56 (s, 4H), 4.50 (s, 4H), 4.47 (d, *J*=13.9 Hz, 4H), 3.79 (s, 6H), 3.52 (m, *J*=6.4 Hz, 4H), 3.28 (d, *J*=13.9 Hz, 4H), 2.24 (q, 2H), 1.33 (s, 18H), 0.85 (s, 18H). FAB(+) MS *m/z* 947.8 (M$^+$). Anal. Calcd for

$C_{57}H_{74}N_2O_{10}$: C, 72.28; H, 7.87. Found C, 72.12; H, 7.99. Yield 62%.

5.3. X-ray crystal data for 1 and 4

Crystal data and refinement details for **1**·CH_3CN·CH_3OH. $C_{53}H_{71}N_3O_7$, M=862.13, monoclinic, space group $C2/c$, a=35.499(1), b=11.8598(2), c=25.6668(8) Å, β=15.288(1), V=9770.5(4) Å^3, Z=8, D_c=1.172 g cm^{-3}, μ=0.077 mm^{-1}, F(000)=3728. Refinement of 601 parameters on 6923 independent reflections out of 42440 measured reflections (R_{int}=0.037) led to R=0.081, wR=0.192, and S=1.13. Crystal data and refinement details for **4**·CH_3CN·$CHCl_3$. $C_{54}H_{70}Cl_3N_3O_6$, M=963.48, orthorhombic, space group $Pna2_1$, a=12.6378(2), b=33.1849(13), c=12.6464(5) Å, V=5303.7(3) Å^3, Z=4, D_c=1.207 g cm^{-3}, μ=0.223 mm^{-1}, F(000)=2056. Refinement of 608 parameters on 7285 independent reflections out of 25830 measured reflections (R_{int}=0.054) led to R=0.056, wR=0.157, and S=1.07. Crystallographic data for the structures of **1** and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 621387 and CCDC 621388. Copies of data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.047.

References and notes

1. (a) Holm, R. H.; Kennepohl, P.; Solomon, E. I. *Chem. Rev.* **1996**, *96*, 2239–2314; (b) Harrison, M. D.; Dameron, C. T. *J. Biochem. Mol. Toxicol.* **1999**, *13*, 93–106.
2. (a) Fallis, I. A. *Annu. Rep. Prog. Chem., Sect. A* **2002**, *98*, 321–368; (b) Cronin, L. *Annu. Rep. Prog. Chem., Sect. A* **2003**, *99*, 289–347.
3. (a) Alemi, A. A.; Shaabani, B. *Acta Chim. Slov.* **2000**, *47*, 363–369; (b) Arena, G.; Contino, A.; Longo, E.; Sciotto, D.; Sgarlata, C.; Spoto, G. *Tetrahedron Lett.* **2003**, *44*, 5415–5418; (c) Asfari, Z.; Harrowfield, J. M.; Thuéry, P.; Nierlich, M.; Vicens, J. E. *Aust. J. Chem.* **1999**, *52*, 403–407; (d) Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 1273–1283; (e) Hamdi, A.; Abidi, R.; Trabelsi Ayadi, M.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 3595–3598; (f) Le Clainche, L.; Giorgi, M.; Reinaud, O. *Inorg. Chem.* **2000**, *39*, 3436–3437; (g) Oueslati, I.; Abidi, R.; Thuéry, P.; Vicens, J. *J. Inclusion Phenom.* **2003**, *47*, 173–178; (h) Tuntulani, T.; Thavornyutikarn, P.; Poompradub, S.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron* **2002**, *58*, 10277–10285.
4. (a) Cao, Y.-D.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2003**, *44*, 4751–4755; (b) Liu, J.-M.; Zheng, Q.-Y.; Yang, J.-L.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2002**, *43*, 9209–9212; (c) Liu, J.-M.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Inclusion Phenom.* **2005**, *51*, 165–171.
5. Ostaszewski, R.; Stevens, T. W.; Verboom, W.; Reinhoudt, D. N.; Kaspersen, F. M. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 294–298.
6. (a) Fabbrizzi, L.; Kaden, T. A.; Perotti, A.; Seghi, B.; Siegfried, L. *Inorg. Chem.* **1986**, *25*, 321–327; (b) Gryko, D. T.; Piatek, P.; Pecak, A.; Palys, M.; Jurczak, J. *Tetrahedron* **1998**, *54*, 7505–7516; (c) Szumna, A.; Gryko, D. T.; Jurczak, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1553–1558; (d) Malval, J.-P.; Lapouyade, R. *Helv. Chim. Acta* **2001**, *84*, 2439–2451; (e) Pessoa, J. C.; Correia, I.; Kiss, T.; Jakusch, T.; Castro, M. M. C. A.; Geraldes, C. F. G. C. *J. Chem. Soc., Dalton Trans.* **2002**, 4440–4450.
7. Clement, O.; Rapko, B. M.; Hay, B. P. *Coord. Chem. Rev.* **1998**, *170*, 203–243.
8. (a) Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Phillips, J.; Williams, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1521–1527; (b) Beer, P. D.; Drew, M. G.; Knubley, R. J.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 3117–3132; (c) Bitter, I.; Grün, A.; Tóth, G.; Balázs, B.; Tõke, L. *Tetrahedron* **1997**, *53*, 9799–9812; (d) Bitter, I.; Grün, A.; Tóth, G.; Balázs, B.; Horváth, G.; Tõke, L. *Tetrahedron* **1998**, *54*, 3857–3870; (e) Unob, F.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1998**, *39*, 2951–2954; (f) Bandyopadhyay, P.; Bharadwaj, P. K. *Synlett* **1998**, 1331–1332; (g) Wu, Y.; Shen, X.-P.; Duan, C.-Y.; Liu, Y.-J.; Xu, Z. *Tetrahedron Lett.* **1999**, *40*, 5749–5752; (h) Chen, C.-F.; Zheng, Q.-Y.; Huang, Z.-T. *Synthesis* **1999**, *1*, 69–71; (i) Hu, X.; Chan, A. S. C.; Han, X.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **1999**, *40*, 7115–7118; (j) Grunder, M.; Dozol, J.-F.; Asfari, Z.; Vicens, J. *J. Radioanal. Nucl. Chem.* **1999**, *241*, 59–67; (k) Beer, P. D.; Drew, M. G. B.; Gradwell, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 511–519; (l) Balázs, B.; Tóth, G.; Horváth, G.; Grün, A.; Csokai, V.; Töke, L. *Eur. J. Org. Chem.* **2001**, *42*, 61–71; (m) He, Y.; Xiao, Y.; Meng, L.; Zeng, Z.; Wu, X.; Wu, C.-T. *Tetrahedron Lett.* **2002**, *43*, 6249–6253; (n) Benevelli, F.; Klinowski, J.; Bitter, I.; Grün, A.; Balázs, B.; Tóth, G. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1187–1192; (o) Mohammed-Ziegler, I.; Poór, B.; Kubinyi, M.; Grofcsik, A.; Grün, A.; Bitter, I. *J. Mol. Struct.* **2003**, *650*, 39–44.
9. (a) Oueslati, I.; Abidi, R.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Harrowfield, J.; Vicens, J. *Tetrahedron Lett.* **2000**, *41*, 8263–8267; (b) Abidi, R.; Oueslati, I.; Amri, H.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 1685–1689; (c) Banthia, S.; Samanta, A. *Org. Biomol. Chem.* **2005**, *3*, 1428–1434; (d) Lee, J. Y.; Kim, S. K.; Jung, J. H.; Kim, J. S. *J. Org. Chem.* **2005**, *70*, 1463–1466; (e) Oueslati, I.; Sá Ferreira, R. A.; Carlos, L. D.; Baleizão, C.; Berberan-Santos, M. N.; de Castro, B.; Vicens, J.; Pischel, U. *Inorg. Chem.* **2006**, *46*, 2652–2660.
10. (a) de María Ramírez, F.; Charbonnière, L.; Muller, G.; Scopelliti, R.; Bünzli, J.-C. G. *J. Chem. Soc., Dalton Trans.* **2001**, 3205–3213; (b) Prodi, L.; Bolletta, F.; Montalti, M.; Zaccheroni, N.; Casnati, A.; Sansone, F.; Ungaro, R. *New J. Chem.* **2000**, *24*, 155–158.
11. (a) Arnaud-Neu, F.; Fuangswasdi, S.; Maubert, B.; Nelson, J.; McKee, V. *Inorg. Chem.* **2000**, *39*, 573–579; (b) Beltramello, M.; Gatos, M.; Mancin, F.; Tecilla, P.; Tonellato, U. *Tetrahedron Lett.* **2001**, *42*, 9143–9146; (c) Bencini, A.; Bianchi, A.; Garcia-Espana, E.; Micheloni, M.; Paoletti, P. *Inorg. Chem.* **1989**, 2480–2482; (d) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721–2085; (e) Krämer, R. *Angew. Chem., Int. Ed.* **1998**, *37*,

772–773; (f) Xu, Z.; Xiao, Y.; Qian, X.; Cui, J.; Cui, D. *Org. Lett.* **2005**, *7*, 889–892.

12. McKervey, M. A.; Schwing-Weill, M.-J.; Arnaud-Neu, F. *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., McNicol, D. D., Vögtle, F., Eds.; Elsevier Science: Oxford, 1996; p 537.
13. Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Ogden, M. I. *Inorg. Chim. Acta* **1996**, *246*, 133–141.
14. Buncel, E.; Shin, H. S.; Bannard, R. A. B.; Purdon, J. G.; Cox, B. G. *Talanta* **1984**, *31*, 585–592.
15. (a) Shinkai, S.; Iwamoto, K.; Araki, K.; Matsuda, T. *Chem. Lett.* **1990**, 1263–1266; (b) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1611–1613; (c) de Mendoza, J.; Prados, P.; Campillo, N.; Nieto, P. M.; Sáchez, C.; Fayet, J. P.; Vertut, M. C.; Jaime, C.; Elguero, J. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 367; (d) Oueslati, I.; Abidi, R.; Amri, H.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Harrowfield, J.; Vicens, J. *Tetrahedron Lett.* **2000**, *41*, 8439–8443.
16. (a) Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1996**, *61*, 2564–2568; (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: London, 1998; (c) Danil de Namor, A. F.; Jafou, O. *J. Phys. Chem. B* **2001**, *105*, 8018–8027; (d) Solovyov, A.; Cherenok, S.; Tsymbal, I.; Failla, S.; Consiglio, G. A.; Finocchiaro, P.; Kalchenko, V. *Heteroat. Chem.* **2001**, *12*, 58–67; (e) Danil de Namor, A. F.; Aparicio-Aragon, W. B.; Goitia, M. T.; Casal, A. R. *Supramol. Chem.* **2004**, *16*, 423–433; (f) Danil de Namor, A. F.; Chahine, A.; Castellano, E. F.; Piro, O. E. *J. Phys. Chem. B* **2004**, *108*, 11384–11392.
17. Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron* **1995**, *51*, 7951–7958.
18. (a) Arnaud-Neu, F.; Barrett, G.; Corry, D.; Cremin, S.; Ferguson, G.; Gallagher, J. F.; Harris, J. J.; McKervey, M. A.; Schwing-Weill, M.-J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 575–580; (b) Ogden, M. I.; Skelton, B. W.; White, A. *J. Chem. Soc., Dalton Trans.* **2001**, 3073–3077.
19. (a) Baklouti, L.; Abidi, R.; Vicens, J.; Asfari, Z.; Harrowfield, J.; Rokbani, R. *J. Inclusion Phenom.* **2002**, *42*, 197–201; (b) Baklouti, L. Ph.D. Thesis, University of Tunis ElManar, 2002.
20. Arnaud-Neu, F.; Barrett, G.; Fanni, S.; Marrs, D.; McGregor, W.; McKervey, M. A.; Schwing-Weill, M.-J.; Vetrogon, V.; Wechsler, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 453–461.
21. (a) Lehn, J.-M. *Pure Appl. Chem.* **1980**, *52*, 2441–2459; (b) Li, F.; Delgado, R.; Félix, V. *Eur. J. Inorg. Chem.* **2005**, 4550–4561; (c) Lu, T.; Zhuang, X.; Li, Y.; Chen, S. *J. Am. Chem. Soc.* **2004**, *126*, 4760–4761; (d) Chen, J.-A.; Lai, J.-L.; Lee, G. H.; Wang, Y.; Su, J. K.; Yeh, H.-C.; Lin, W.-Y.; Leung, M.-K. *Org. Lett.* **2001**, *3*, 3999–4002.
22. (a) Hamacek, J.; Borkovec, M.; Piguet, C. *Chem.—Eur. J.* **2005**, *11*, 5217–5226; (b) Ruben, M.; Rjo, J.; Romero-Salguero, F. J.; Uppadine, L. H.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3644–3662; (c) Rekharsky, M. V.; Yamamura, H.; Kawai, M.; Osaka, I.; Arakawa, R.; Sato, A.; Ko, Y. H.; Selvapalam, N.; Kim, K.; Inoue, Y. *Org. Lett.* **2006**, *8*, 815–818.