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Calix(aza)crowns: synthesis, recognition, and coordination. A mini review

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Abstract—Attaching azacrown bridges on calixarene platform generates calix(aza)crown family. This article reviews synthetic routes for their design and discusses their ion-binding properties by means of coordination and stability constants.

1. Introduction

1.1. The calix(aza)crowns

The importance of calixarenes in the family of host macrocycles is now well established.[1–3] This can be largely attributed to the fact that they are attractive host molecules to which additional binding sites for target guest species are readily added.[2] The reaction between calixarenes and bifunctional reagents can give rise, through bridging, to macrobicyclic molecules. Even more complex species (multimacrocyclic) such as double or triple calixarenes, cavitands, carcerands, etc. can be prepared by similar reactions of both calixarenes and resorcarenes.[4–9]

Since the first report of crown ether derivatives of *p*-*tert*-butylcalix[4]arene in 1983,[10] considerable research has been dedicated to the synthesis of calixcrowns and the study of their molecular and ion recognition in order to use them in catalysis, or in the design of ion selective electrodes and liquid supported membranes.[11–14] Replacement of the *O*-donors of a crown ether by *N*-donors, giving an 'aza-crown', is expected to enhance the binding strength and selectivity toward transition and post-transition metal ions. Thus, it was anticipated that coordinating ability of calixarenes could be extended by the introduction of polyazaethylene bridges, which would favor the formation of complexes with softer cations.[15] The earliest qualitative studies on the ion-binding properties of calix[4](aza)crowns[15] indicated an apparently weak affinity for divalent and trivalent metal ions but only limited further exploration of this issue has been made, despite further ligand syntheses having been developed. 1,3-Bridged calix(aza)crowns, for example, can be obtained in both single-[16–19] and multi-step processes,[15,20,21] and alternative routes are also available to the corresponding 1,2-bridged derivatives through inter- or intramolecular cyclization.[22,23]

1.2. Scope of this review

This review documents current knowledge on the chemistry of calix(aza)crowns, predominantly such derivatives of calix[4]arene. Almost all calix[4]azacrowns known to date contain at least some of their aza-atoms as amide units and thus are not simple azacrowns. Nonetheless, the quantitative data now available concerning their ability to bind metal cations indicate that they are an important and useful class of complexants.

The review starts with an analysis of synthetic routes developed to prepare distal (1,3) and/or proximal (1,2) calix[4]-(aza)crowns, and their O- and/or N-alkylated derivatives. Their conformations are discussed on the basis of NMR spectroscopy in solution and X-ray crystal structure determinations in the solid state. In the next section, their complexation properties are summarized, and their coordination chemistry related again to spectroscopic (UV and ^{1}H NMR) and X-ray studies. Finally, some conclusions and future challenges in the study of metal–calix(aza)crown interactions are discussed.

2. Synthesis of calix(aza)crowns

2.1. Distal calix(aza)crowns

2.1.1. Multi-step synthesis. While direct alkylation of the phenolic oxygen atoms of calix[4]arenes is a well-established method for the synthesis of calix[4]crowns and could in principle be applied to that of calix[4]azacrowns, syntheses of the latter compounds have in fact nearly all been based

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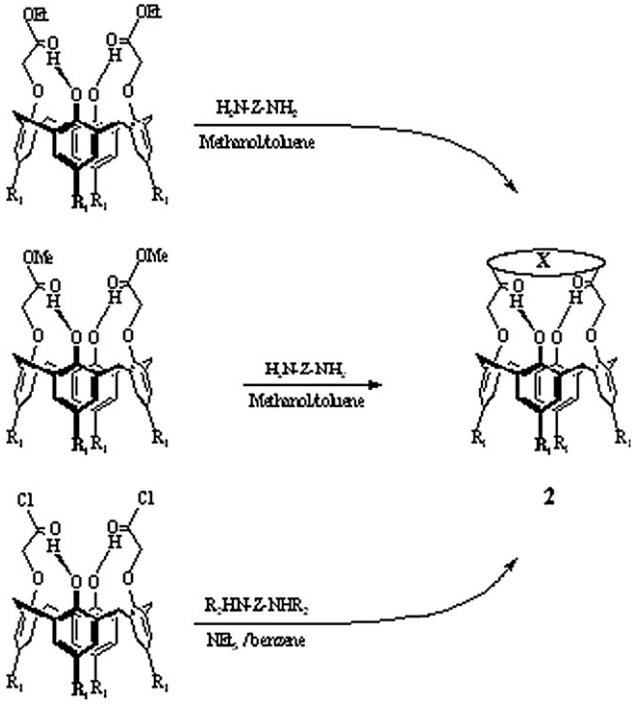
on reactions of derivatives of carboxymethyl ethers of calix[4]arenes. Thus, in reactions which are remarkably uncomplicated by possible polymerization processes, various derivatives of *syn*-1,3-dicarboxymethylcalix[4]arene combine efficiently with linear di- and polyamines to give cyclic diamides.[21,15] The methyl- and ethylester derivatives[20,15] as well as the diacylchloride[21] all give monobridged calix(aza)crowns (Scheme 1). The diacylchloride reacts readily at room temperature in anhydrous benzene with a diamine in the presence of triethylamine base[21] but amidation of the methylester derivative in 1:1 toluene–methanol at room temperature gives higher yields.[15] Further improvement of this method[20] involved elimination of the need for chromatography. Data related to these syntheses are shown in Table 1. Calix[4](aza)crowns obtained from these procedures adopt in solution a cone or distorted cone conformation. While 1,3-calix(aza)crowns with a short connecting chain adopt a symmetrical cone conformation stabilized by strong intramolecular hydrogen bonds, increasing of the chain length causes the bridged aromatic rings to become parallel and the phenolic rings to tilt nearer to coplanarity. The crystal structure of **2a** shows the distorted cone conformation to be associated with intramolecular N–H···O(phenol) hydrogen bonds,[21] whose ^{1}H NMR spectroscopy indicates that they are retained in solution.[20] The divergence of the carbonyl-O atoms from the cavity prevents their involvement in intramolecular H-bonding.[20] The cavity is large enough to encapsulate one dichloromethane molecule. Calixarene **2b** adopts a similar conformation in the solid state and encapsulates one acetonitrile molecule.[31] In contrast, the cone conformation of **2d** is associated with one hydrogen bond between phenolic OH and carbonyl-O and two hydrogen bonds through which a water molecule links the amine NH and another phenolic OH. The water molecule is thereby held within the cavity defined by the crown loop while an acetonitrile molecule is encapsulated in the phenolic cavity.[32] Unlike **2a**,**b**, **2g** adopts a distorted cone conformation stabilized by two intramolecular hydrogen bonds O–H···O between phenolic oxygen and carbonyl oxygen atoms. In this conformation, the inclusion of a small organic molecule inside the calixarene cavity is impossible. Proton NMR studies have revealed that increasing the chain length between the amide centers increases the distortion of calix[4](aza)crown cone conformation.[20]



Scheme 1. Different routes for the synthesis of 1,3-monobridged calix[4](aza)crowns.

Some true calix[4]azacrown species have been derived from the reaction of a calix[4]arene dialdehyde with various polyamines followed by borohydride reduction but only the anion-binding properties of the protonated forms have been investigated.[33]

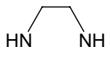
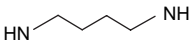
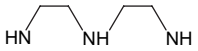
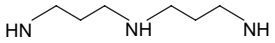
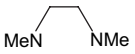
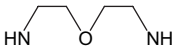
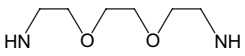
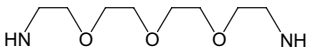
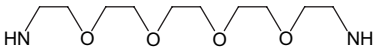
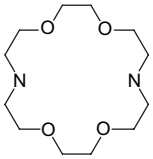
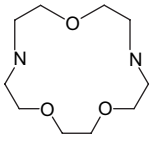
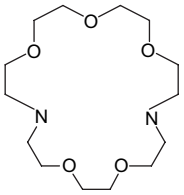
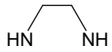
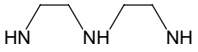
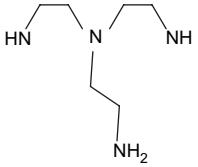
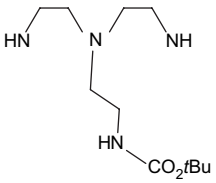
2.1.2. One-step synthesis. Although the final step of the diamide-producing reactions described above is efficient, it must of course be preceded by several steps to produce the calixarene reactant.[15,20,21] An inverse procedure in which a phenolic calixarene is dialkylated by a chloracetylamide derivative of a polyamine has been shown to provide a high-yielding, one-step pathway to calix[4] and [6](aza)-crowns (Scheme 2).[16,17,34]

In general, the higher degree of functionality and the conformational flexibility of calix[6]arenes makes their synthetic chemistry more difficult than that of calix[4]arenes.[35]

However, the first 1,4-bridged *p-tert*-butylcalix[6]arene, produced by acylation of the parent calixarene with succinoyl chloride,[36] was found to have greatly diminished conformational flexibility. Subsequently, 1,4-,[37–40] 1,2-, and 1,3-bridged[41–44] azacrown derivatives of *p-tert*-butylcalix[6]arene were synthesized by similar reactions (Scheme 3),[18] enabling it to be shown that while one bridge simply reduces the flexibility of the ring, double bridging produces effective immobilization.[18,44] The high observed yields of calixarene **5** were, therefore, explained by the fact that phenolic oxygen in position 5 is least shielded from attack, and the oxygen on position 4 is appropriately oriented for bridging. These two calix[6](aza)crowns (**4** and **5**) showed selective extraction of both elongated $Et_2NH_2^+$ and spherical Li^+. However, **5** seems to be more preorganized than **4** for cation complexation.[18]

1,3-4,5-Doubly diamide-bridged *p-tert*-butylcalix[6]arene shows a certain selectivity for Li^+,[18] whereas cone and 1,2,3-alternate stereoisomers of calix[6]-4-dialkoxy-2,3-5,6-bis-crown-4 show a high Cs^+/Na^+ selectivity.[45] The first example of polytopic system with various ionophoric sites,[17] *p-tert*-butylcalix[6]-1,4-crown-4-2,6-dioxo-diaza-crown-4 (Scheme 4) containing hard and soft sites was prepared in 32% yield starting from *p-tert*-butylcalix[6]arene onto which was introduced a poly(oxyethylene) chain followed by a poly(azaethylene) chain. The study of the extraction of alkaline and transition metal picrates by ligand **6** showed Cs^+ and Ni^{2+} selectivity. Whereas Cs^+ selectivity was ascribed to its binding within the cavity and to the large poly(oxyethylene) loop, Ni^{2+} selectivity was explained by the contribution of soft sites in the smaller azacrown loop.[17]

Table 1. Different bridged chains

2	R_1	X	Reaction time (day)	Yield (%)	Melting Point (°C)
a	^{t}Bu		3	90	>300
b	^{t}Bu		2–3	82	194–200
c	^{t}Bu		2–3	—	—
d	^{t}Bu		2–3	63	183–185
e	^{t}Bu		2–3	74	255–256
f	^{t}Bu		7	17	155–157
g	^{t}Bu		1/2	21	308–320
h	^{t}Bu		1/2	32	275–276
i	^{t}Bu		1/2	22	242–244
j	^{t}Bu		1/2	35	235–236
k	^{t}Bu		1/2	31	208–213
l	^{t}Bu		1/2	52	300
m	^{t}Bu		1/2	34	215
n	^{t}Bu		1/2	19	278–280
o	H		2–3	89	351–352
p	H		2–3	87	>380
q	H		2–3	82	264–265
r	H		2	93	250–252
r′	H		4 h	75	248–249

(*continued*)

Table 1. (*continued*)

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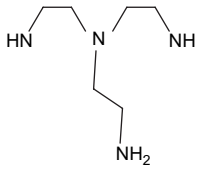
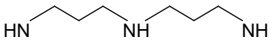
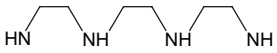
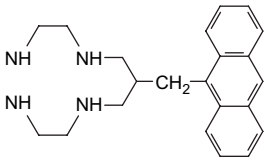
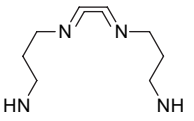
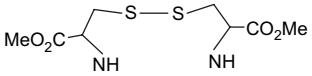
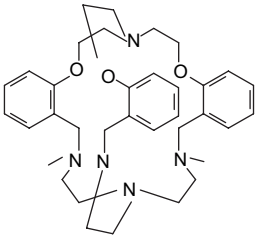
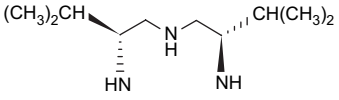
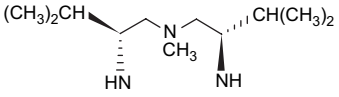
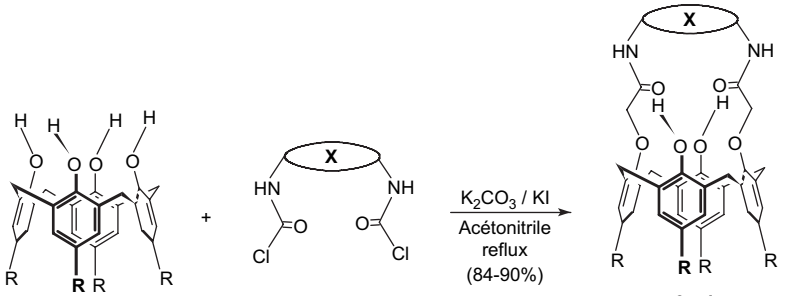
r″	^{t}Bu		3	56	262–264
s	H		2–3	81	272–274
t	H		2–3	49	203–205
u	H		10	14	155–156
v	H		8	13	—
w	^{t}Bu		—	28	—
x	^{t}Bu		1	55	130
y	^{t}Bu		2	12	218–220
z	^{t}Bu		2	25	180–182

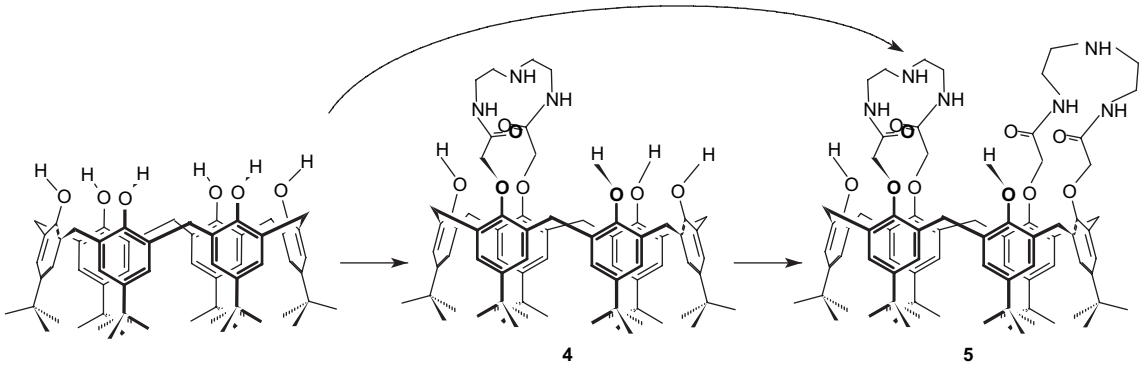
Source: **2a**,**b**,**d–f** Ostaszewski et al.,[15] **2b**,**g–n** Böhmer et al.,[21] **2c**,**o–t** Bitter et al.,[24,20] **2r″** Bond et al.,[25] **2u** Unob et al.,[26] **2v** Grunder et al.,[27] **2w** Hu et al.,[28] **2x** Bandyopadhyay et al.,[29] **2y**,**z** He et al.[30]



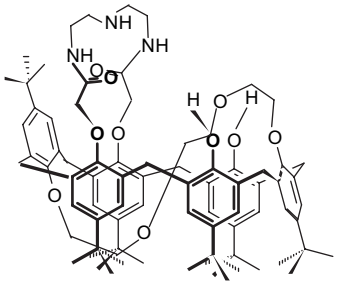
3a R = H, X = CH_2CH_2 **3b** R = *t*Bu, X = CH_2CH_2

3c R = H, X = *o*-C_6H_4 **3d** R = *t*Bu, X = *o*-C_6H_4

Scheme 2. Direct synthesis of calix[4](aza)crowns **3a–d**.



Scheme 3. Direct synthesis of calix[6]-bis-(aza)crowns.[18]



Scheme 4. Doubly bridged *p-tert*-butylcalix[6]arene **6**.[17]

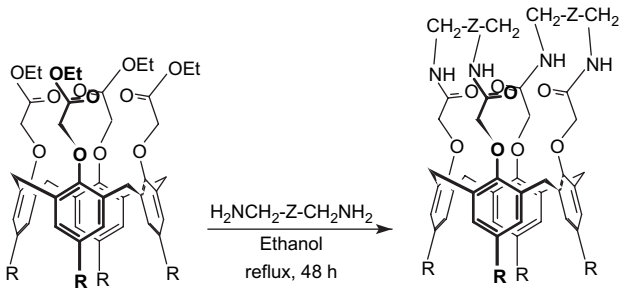
2.2. Proximal calix(aza)crowns

2.2.1. Intermolecular cyclization. Using relatively short polyamines, 1,2-3,4-doubly-bridged calix[4]-bis-azacrowns can be obtained by using tetrakis(alkoxycarbonylmethyl)-calix[4]arenes as reactant. Initially it was shown that the tetraethoxycarbonyl compound reacted with a large excess (calix–diamine 1:20) of the diamine in anhydrous methanol for over two days at room temperature (Scheme 5)[23] but the procedure was later improved by using the methoxycarbonyl reactant and methanol–toluene (1:1) as solvent (Scheme 6).[46]

Doubly bridged calix[4]arenes **7**–**12** adopt the cone conformation in solution. The crystal structure of **7** shows the molecule to be in a pinched cone conformation with two carbonyl oxygen atoms of one bridge pointing inside the cavity and the two others pointing outside. Intermolecular NH···O (carbonyl oxygen) H-bonding creates a long chain supramolecule of **7**.[23] Model construction (MM2) for compound **11** shows that two of the carbonyl groups are divergently oriented with respect to the cavity defined by the tripodal loops but the third is oriented convergently to a degree, which could allow its interaction with the residual phenolic group (Fig. 1). An X-ray structural study confirms this feature and shows that the carbonyl-O atom turning inside the cavity is indeed hydrogen bonded to phenolic oxygen. Its associated NH unit, divergently oriented, is involved in intermolecular H-bonding.[46]

Given the fact that diaminolysis of tetraethoxycarbonylmethylcalix[4]arene by monoamines (RNH_2) takes place on opposite (1,3) ester groups,[47] double proximal bridging can be explained if, first, two opposite ethylester groups react intermolecularly with separate diamine molecules, then each terminal amine group reacts intramolecularly with the nearer remaining ethylester groups.

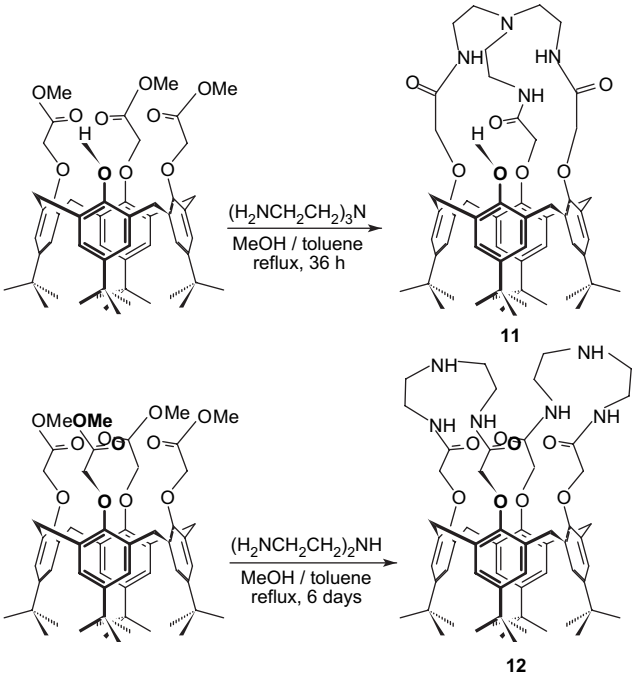
2.2.2. Intramolecular cyclization. In 1998,[22] the first report was made on the synthesis, via intramolecular cyclization, of calix[4]arenes bearing two proximal carboxamide bridges



7 R = *t*Bu, Z = -
9 R = H, Z = -

8 R = *t*Bu, Z = $CH_2CH_2NHCH_2CH_2$
10 R = H, Z = CH_2

Scheme 5. Synthesis of calix[4]-1,2-3,4-bis-azacrowns **7**–**10**.[23]



11

12

Scheme 6. Synthesis of calix[4]-1,2-1,3- and -1,2-3,4-bis-azacrowns **11** and **12**.[46]

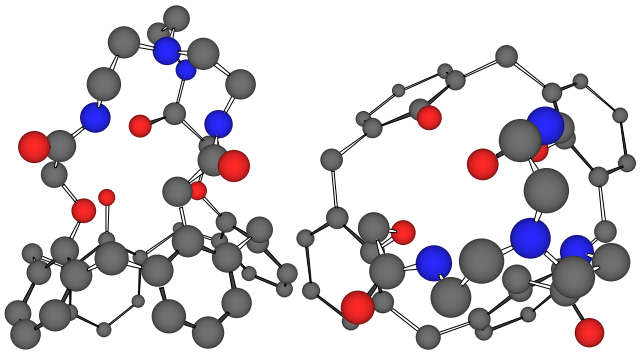


Figure 1. Energy minimized structure for calixarene **11**.

(Scheme 7). While 1,2-calix(bis)crowns[48] may be obtained by intramolecular cyclization with flexible poly(oxyethylene) chains of 5, 8, and 11 linked atoms, intramolecular cyclization with poly(azaethylene) chains depends on chain length and takes place only for seven-atom chains.[22]

In 1995, Beer et al.[49] reported the synthesis and coordination chemistry of novel heteroditopic calixarenes bearing benzo-15-crown-5 units attached to the lower rim via amide functions. Here, the calixarene phenolic oxygen atoms do not form part of the crown, so the molecules cannot be termed 'calixcrowns' but an extension of this chemistry based on reactive bis(isothiocyanate) and chloracetyl derivatives of calix[4]arene and final intramolecular ring closure reactions has enabled the synthesis of true calix[4]thiacrowns and thia-azacrowns.[50]

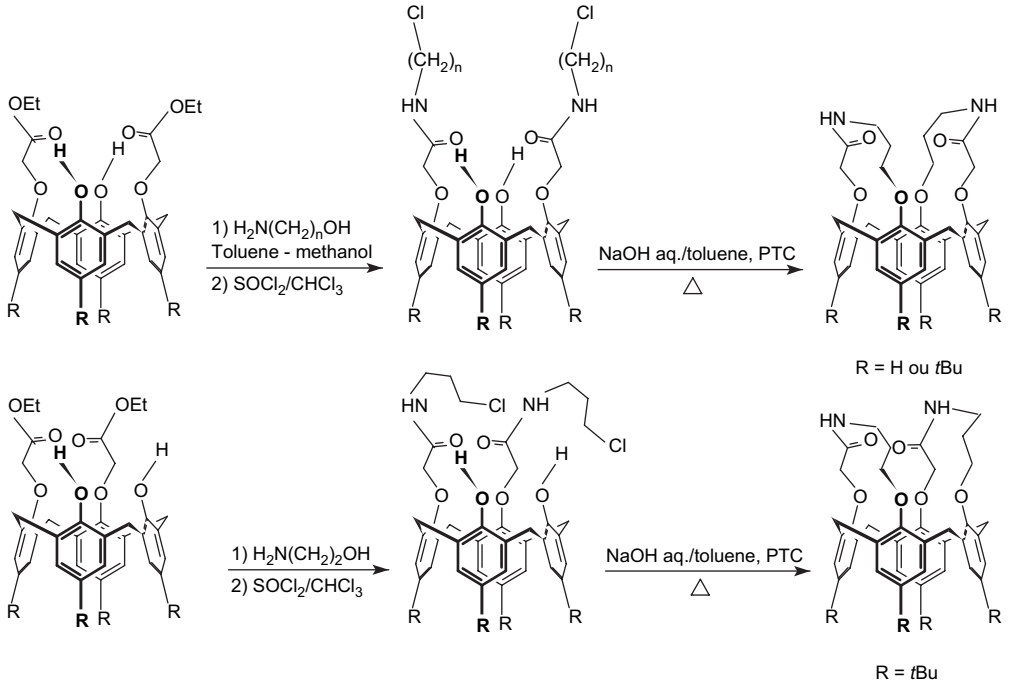
2.3. O-Alkylated calix(aza)crowns

A series of O-alkylated calix(aza)crowns was prepared to study the effect of alkylation of phenolic OH groups on calixarene conicity (Scheme 8)[15,20,31] and to see[20] if the two free phenolic OH or NH in the chain could selectively be alkylated with the retention of the initial calix(aza)crown cone conformation. Methylation of the two free OH in fact leads to a mixture of cone, partial-cone, and 1,3-alternate conformers[15] but alkylation or acylation with bulkier groups stabilizes the distorted cone conformer in which the alkoxy-substituted rings are essentially parallel.[20,31,51] Selective O-alkylation of 1,3-bridged calix[4](aza)crowns supporting amine or ether groups on the chain could be run, via an indirect route, by amidation of convenient acid chloride and methylester derivatives of *p-tert*-butylcalix[4]arene (Scheme 9).[46,15,32]

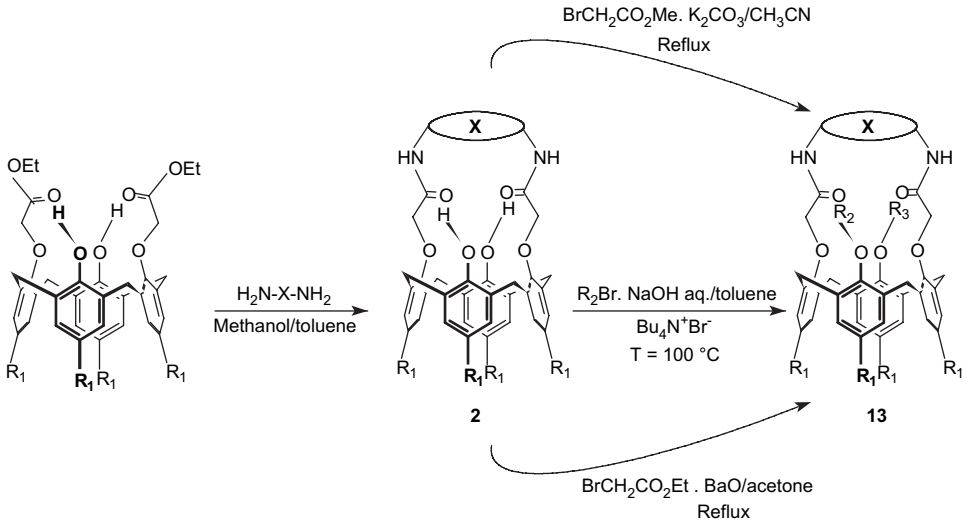
The selective N-alkylation of calixarene **2q** with *N*-bromoethyl-4-aminophthalimide was possible in the presence of K_2CO_3 in acetonitrile (giving compound **2q′**).[53] However, selective N-alkylation of calixarene **2d** failed. Reacting **2d** with CH_3I in similar condition leads to substitution of all labile protons by methyl groups. The product **17** (Scheme 10) has a cone conformation.[32]

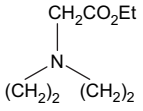
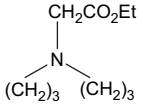
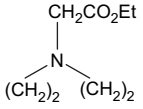
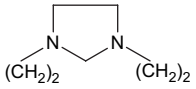
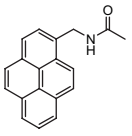
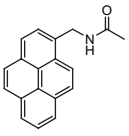
3. Ion-binding properties of calix(aza)crowns

Many macrocyclic receptors possess a hydrophilic cavity in which an ionic substrate like a metal ion can nest and be shielded from the environment by a lipophilic envelope.[54,55] Accordingly, they can mediate cation transfer from an aqueous medium to a lipophilic phase and considerable interest has been attached to their use as synthetic models to mimic the ionophoric properties of natural antibiotics toward alkali and alkaline earth cations. An exhaustive review of thermodynamic data for ion–macrocycle interactions is available[56] and Cram[57] has defined the importance of preorganization and complementarity in



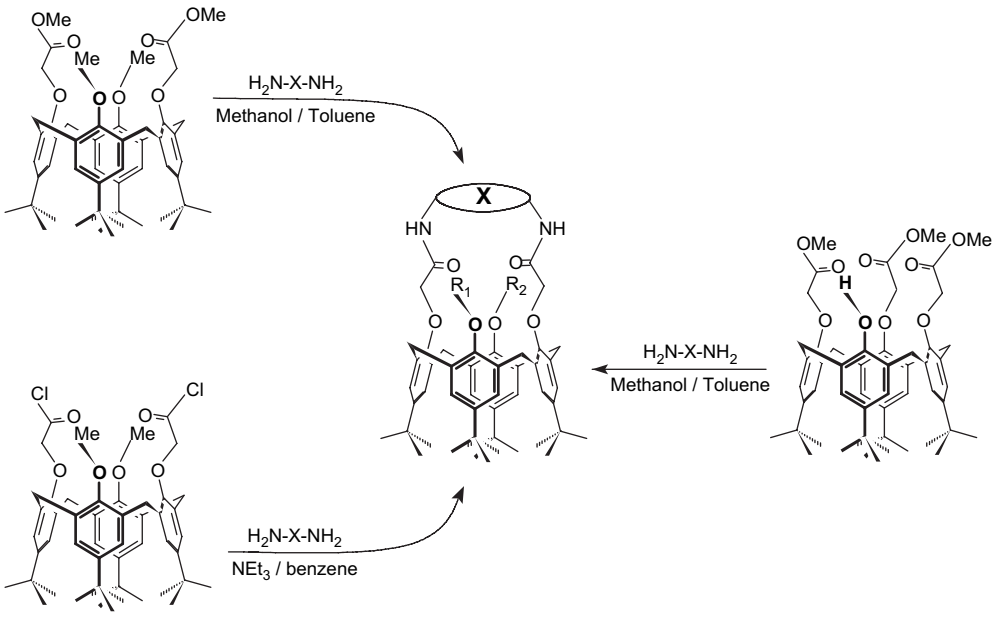
Scheme 7. Synthesis of doubly carboxamide bridged calix[4]arenes via intramolecular cyclization.[22]



13	R_1	X	R_2	R_3
a	*t*Bu	CH_2CH_2	Me	Me
b	*t*Bu	CH_2CH_2	Pr	Pr
c	*t*Bu	CH_2CH_2	Bu	Bu
d	*t*Bu	CH_2CH_2	i-Bu	i-Bu
e	*t*Bu	CH_2CH_2	CH_2CO_2Me	H
f	*t*Bu	CH_2CH_2	CH_2CO_2Me	CH_2CO_2Me
g	*t*Bu	$CH_2CH_2CH_2$	Bu	Bu
h	*t*Bu	$CH_2CH_2CH_2$	CH_2CO_2Me	CH_2CO_2Me
i	*t*Bu	$CH_2CH_2CH_2CH_2$	Bu	Bu
j	*t*Bu		H	H
k	*t*Bu		H	H
l	H	CH_2CH_2	CH_2CO_2Et	CH_2CO_2Et
m	H		H	H
n	H		H	H
o	H	$CH_2CH_2NH\ CH_2CH_2$		

Scheme 8. General synthesis of O-alkylated calix[4](aza)crowns.[20,31,52]

determining the stability of cation complexes. The principle of preorganization states that 'the smaller the changes in organization of host, guest, and solvent required for complexation, the stronger will be the binding'. The complementarity principle defining the structural recognition within the supramolecular assembly states that 'to complex,



14 X = $CH_2CH_2(OCH_2CH_2)_2$, $R_1 = R_2 = Me$

15 X = $CH_2CH_2NHCH_2CH_2$, $R_1 = R_2 = Me$

16 X = $CH_2CH_2NHCH_2CH_2$, $R_1 = H$, $R_2 = CH_2CO_2Me$

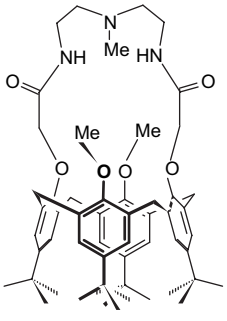
Scheme 9. Synthesis of selective O-alkylated calix[4](aza)crowns.[15,32,46]

hosts must have binding sites that cooperatively contact and attract the binding sites of guests without generating strong nonbonded repulsions'.

Since the first qualitative assessment of the ion-binding properties of calix[4](aza)crowns toward metal cations,[15] a number of works have been devoted to quantitative characterization of this interaction.[31,32,46,52,53,58–61] The calix(aza)crowns **2a**, **2d**, **2e**, **2f**, and **2i** show low affinity for M(II) (Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and M(III) (Ce^{3+}, Y^{3+}, In^{3+}, Gd^{3+}, Bi^{3+}) species,[15] and a survey[62–65] of the ion-binding properties of some secondary amide derivatives of calix[4]arene revealed their inefficiency in alkali and alkaline earth metal ion extraction. However, it might be anticipated that binding of transition metal cations could be enhanced by the incorporation of true amine-N donor atoms within the ligand structure.[66–69] The basicity of amide-N is reduced by involvement of the lone pair in double bonding to C, which simultaneously enhances the basicity at O, so that without deprotonation at N, amides RCONHR′ usually behave as *O*-donor ligands.[70–75] Quantitative data for the binding and extraction of both alkaline earth and transition metal complexes of calix(aza)crowns in which both amide- and amine-N donors are present have been interpreted in relation to accompanying spectroscopic and structural measurements[31,59] as outlined below.

3.1. Extraction

Calix[4](aza)crowns supporting carboxamide functions are apparently inefficient in extracting alkaline earth and transition metal picrates from water into dichloromethane (Fig. 2).[31,59] However, although commonly chosen as substrates for extraction studies, metal picrates are an inappropriate choice in systems where basicity of the ligand may lead to metal ion hydrolysis and ultimate extraction of picrate ion by the protonated ligand rather than of the metal picrate by the neutral ligand. The apparently greater extraction



17

Scheme 10. Structure of **17**.

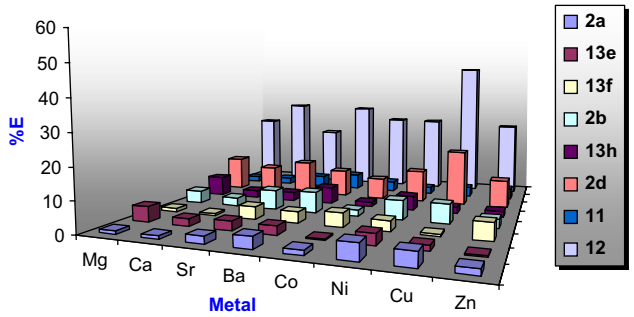


Figure 2. Extend of alkaline earth and transition metal cation extraction.

by **12** than by **2d**, for example, is probably a consequence of this effect.[32] Consistent with this, dichromate ion, which would be hydrolyzed to hydrogen chromate in neutral water, is efficiently extracted from water into dichloromethane by calixarene **2i**.[76]

3.2. Complexation

Complexation data for alkaline earth and transition metal ions are shown in Table 2.[31,59] Values for calixarenes **11** and **12** are reported here for the first time. The inefficient extraction of alkaline earth and transition metal ions appears to be a simple reflection of their poor ligating ability, which is, in turn, assigned to the fact that the carbonyl units of the diamide bridge units tend to be divergent from the calixarene cavity, so that these ligands might be expected to act at best as bidentate *O*-donor species toward 'externally' bound metal ions. The low stability constant values for calixarenes **2a**,**b** and **13e**,**f**,**h** (Table 2) and the small spectroscopic changes observed for calixarenes **13f**,**h** suggest an external binding mode but with a few solvent molecules displaced from the metal cation. NH proton signals are those most affected by the approach of the metal, therefore consistent with simple binding via amide carbonyl-O atoms.

Ligands **2a**,**b** show selectivity toward Cu(II), though this is associated with an unexpected stoichiometry (M_2L), which may be indicative of some specific interaction between the calixarenes and perchlorate anion. It is possible that perchlorate anion bound in the 1:1 species to the calixarene via $NH_{amide}\cdots O$ hydrogen bonds acts as a bridge to facilitate binding ('positive cooperativity') of the second metal ion in a 'cascade' complex formation.[31] An analogous situation is known to arise where the ligand *o*-methylenepyridine-4-(dimethylamino)benzamide (DMABA-MP) shows Cu(II) selectivity for ML_2 stoichiometry.[73]

The lengthening of the bridging chain by insertion of a single methylene group does not significantly enhance the complexation capacity of the ligand toward these metal ions, but facilitates the formation of M_2L species (Fig. 3).

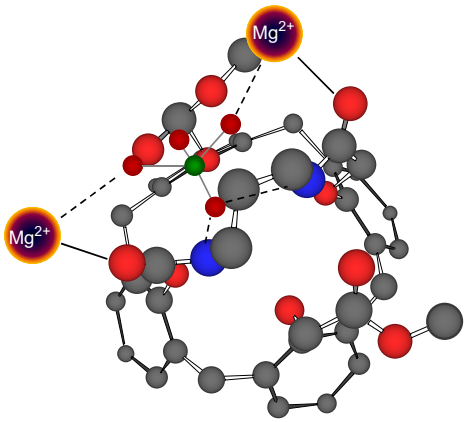


Figure 3. Possible structure of $\mathbf{Mg_2}\cdot\mathbf{13f}$ complex through ClO_4^- bridge.

The presence of secondary *N*-donor atoms, as in calixarene **2d**, is expected to enhance the binding of transition metal ions, even though such donors are relatively weak unless incorporated into a chelating ligand. Depending upon the ligand conformation and *N*-donor configuration, N,O chelation is certainly possible in **2d** but a structural study of the Mg(II) complex showed it to be a coordination polymer, with **2d** acting as a bis(unidentate) bridging ligand (Fig. 4).[59]

This structure indicates that **2d** may act as no more than a simple unidentate ligand in solution, which would explain the low stability of the Ba(II) complex (log β_{11}=3.03). With Co(II), Ni(II), and Zn(II), it is possible that the amino group is involved in chelate formation as established crystallographically for the Cu(II) complex of ML_2 stoichiometry.[25] The same stoichiometry, associated with amide-O and amine-N chelation, was deduced on the basis of ^{1}H NMR studies of the Zn(II) complex formed by extraction into $CHCl_3$.

Table 2. Stability constant (log β_{ij}) values for alkaline earth and transition metal complexes in acetonitrile at 20 °C[31,52,53,59]

Compounds	M/L	log β_{ij}						
		Mg^{2+}	Sr^{2+}	Ba^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
2a	1:1	[a]	[a]	[a]	[a]	[a]	4.20	[a]
13e	1:2	[a]	[a]	[a]	10.40	[a]	7.14	[a]
	2:1							
13f	1:1	1.92	2.29	[a]	5.37	[a]	9.19	[a]
	2:1							
2b	2:1	[a]	[a]	[a]	[a]	[a]	6.61	[a]
13h	2:1	6.50	6.63	[a]	[a]	[a]	7.16	[a]
13o	1:1	—	—	—	6.69	—	—	—
2d	1:1	5.13	10.04	3.03	10.30	11.01	7.63	11.04
	1:2							
	2:1							
2q′	1:1	—	—	—	—	3.23	5.20	4.39
11[b]	1:1	5.33	11.09	[a]	4.01	4.83	4.58	5.15
	1:2							
12[b]	1:1	10.83	9.63	13.23	9.68	10.46	4.27	9.71
	1:2							
	1:3							
	2:1							

[a] No complexation.
[b] Unpublished data.

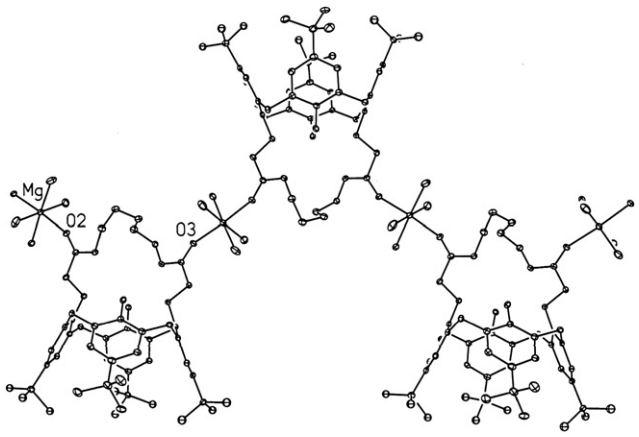


Figure 4. Position of the **Mg·2d** polymer found in the crystal.[59]

Semiquantitative studies revealed that, while **2a** and **2d** do not complex Be(II), the larger chelating unit present in **2f** does result in binding, possibly reflecting the preference of a small cation for larger chelate rings.[15]

Both FABMS and ^{1}H NMR measurements indicate that methylation of the free hydroxyl groups of 1,3-calix[4]azacrowns leads to weaker alkaline earth transition metal and rare earth complexes.[15,32] Since MeO is a better ligating function than free OH in neutral medium, the dramatic decrease of complexation may be assigned to a change in calixarene conformation.[15] The further methylation of amine-N (compound **17**) enhances the complexation of transition metal ions.[32] Alkylation of free hydroxyl groups by the introduction of two methoxycarbonylmethyl functions on **2a** abolishes intramolecular hydrogen bonds OH···O and may bring more flexibility to the molecule **13f**, thus facilitating its rearrangement to bind cations. Modeling shows that the inclusion of one Co(II) is possible for **13f** with two ester carbonyl-O and two phenolic ether-O (of the cyclic unit) atoms bound to Co. An ML_2 species, as is apparently formed with **13e**, 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 effect of adding a third azacrown bridge, as in compound **11**, is to favor 1:1 stoichiometry for transition metal complexes. This may be consistent with the contribution of the second proximal carbonyl-O atom to transition metal coordination. Alkaline earth ions (Mg^{2+}, Sr^{2+}) may, however, retain unidentate binding to one carbonyl-O atom as with calixarene **2d**. A calix[4]arene supporting two proximal azacrowns (compound **12**) forms ML_2 complexes with Mg(II), Sr(II), Co(II), and Ni(II) with stability constant values ranging from 9.6 to 10.8 log units. MM2 modeling of the free molecule **12** shows that different conformations may be adopted where the amide-O atoms may be considered divergent from the cavity (Fig. 5 right) or where at least two can be oriented so as to make intramolecular H-bonding possible (Fig. 5 left). The latter arrangement, also observed in the structure of **7**,[23] could allow the formation of ML_2 species. Positive FABMS experiments[46] revealed the presence of ML and M_2L (M=Co(II), Ni(II), Zn(II)) complexes

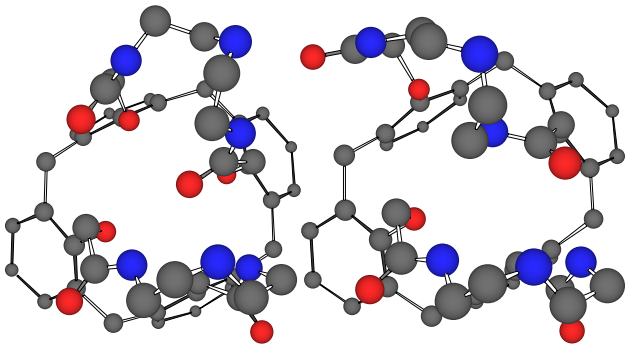


Figure 5. Energy minimized structures for compound **12**.

with **12**, an analysis supported by UV and ^{1}H NMR measurements on the Zn(II) complex. For the complexation of calix[4]azacrowns **11** and 1**2** by lanthanide ions [Eu(III), Tb(III), Nd(III), Er(III), La(III)],[60] the binding constants were found to be reasonably high ($\log \beta_{11}$ ca. 5–6 and $\log \beta_{12}$ ca. 10; except for La-**11**: $\log \beta_{12}$ ca. 8). ^{1}H NMR studies yielded insights into the coordination mode of the lanthanide ions. While for ligand **11** complexation outside the ionophoric cavity is assumed, the more flexible ligand **12** should be able to accommodate the lanthanide ion inside the cavity. Fluorescence measurements of the π,π^*-excited singlet state of the aromatic moieties of the calixarene platform revealed opposite behavior of the two calix[4]-azacrowns. In the case of ligand **11** the involvement of the amine nitrogen in the complexation resulted, via blocking of PET, in fluorescence enhancement upon addition of a lanthanide. In contrast, complexes with ligand **12** showed fluorescence quenching with respect to the free ligand, most likely due to lanthanide–chromophore interactions, e.g., heavy-atom-induced intersystem crossing. Further, the potential of both ligands as organic antenna chromophores for the energy transfer sensitization of luminescent excited states of lanthanides was demonstrated. Particularly efficient (Φ_{lum}=12%) and long-lived (τ_{lum}=2.60 ms) luminescence was observed for Tb-**12**. This has been rationalized based on an efficient energy transfer and shielding of the lanthanide from quenching effects of the chemical environment. The favorable emission characteristics of this complex suggest a promising application as a luminescent label. Generally, sensitization of Eu(III) luminescence was less favorable, which can be traced back to the involvement of a CT state and quenching by NH oscillators. For Nd(III) the successful sensitization of NIR luminescence was observed, which is quite astonishing, taking into account its easy deactivation by CH oscillators and the anticipated poor matching in energy between the calixarene triplet state and Nd(III) excited state.

4. Conclusions and future developments

The known characteristics of metal complexes of calix(aza)-crowns summarized herein indicate that these ligands are certainly worthy of more extensive investigation. Of particular interest for use with transition metal ions would be the reduction of the amide units in presently known systems to give true polyaza macrocycles.

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