Calcium complexes of macrocyclic lactams: their structure and calcium induced conformational changes

Agnieszka Szumna,[a] Daniel T. Gryko[a] and Janusz Jurczak *[a,b]

[a] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b] *Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland*

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We have examined the coordination sites of calcium complexes of macrocyclic bislactams and found that macrocyclic lactams are able to form solid complexes with Ca^{2+} ions located inside or outside the cavity depending on the ring's size. The X-ray structures for the complex $[Ca(\mathbf{1})(H_2O)_4](ClO_4)_2$ (**1**–$\mathbf{Ca^{2+}}$) with 20-membered bisamide **1**, where a calcium ion is located inside the cavity, and the complex $[Ca(\mathbf{5})_2(ClO_4)_2]_n$ (**5**–$\mathbf{Ca^{2+}}$) with 15-membered bisamide **5**, where calcium ions are outside the cavity, are reported. Formation of the complex **1**–$\mathbf{Ca^{2+}}$ causes conformational change in the ligand structure. The carbonyl oxygen donor groups change their orientation and rotate, becoming directed inside the cavity. Such a conformational change breaks hydrogen bonds within the ligand structure. An X-ray structure is presented as evidence for such a conformational flip. This confirms an earlier postulation for the structure of a **1**–$\mathbf{Pb^{2+}}$ complex.

Introduction

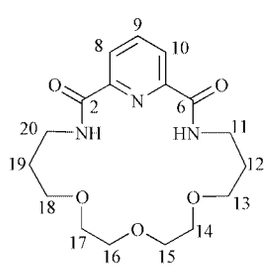
Calcium cations are of special interest, particularly due to their clinical importance.[1] In a variety of analyses of this cation, ion-selective electrodes based on ionophore-impregnated supported liquid membranes are used. Among those carriers neutral acyclic ether-amide based receptors are commercially available and widely used (*e.g.* ETH 129 and ETH 1001). It is well established that introduction of polar amide donors into a complexone plays an important role in the enhancement of the selectivity in cation binding. In particular cations of high charge density are usually favored, leading to the preference for alkaline-earth cations over an alkali metal of the same size.[2] Thus, amide based acyclic or cyclic receptors, which are able to complex alkaline earth metal cations, attract continuing interest.

Similarly, macrocyclic ligands containing additional ethereal oxygen atoms exhibit selectivity toward alkaline earth metal cations.[3] Some structural aspects of Ca^{2+} complexation with macrocyclic tertiary amide-ether based receptors have been reported on the basis of spectral changes and molecular modeling.[4–6]

We are currently interested in the structures of macrocylic secondary amide-ether based receptors with calcium ions. The presence of secondary amide groups makes our ligands more rigid due to the presence of intramolecular hydrogen bonds. CSD searches[7] revealed that there are a few calcium complexes with non-peptide neutral macrocyclic ligands containing at least two secondary amide groups. Examples include the Ca^{2+} complex of a polyamine ligand with secondary amide groups in the side-arm[8] and two polymorphs of rigid aromatic polyamide complexes.[9] In the present paper we report X-ray structures of calcium complexes of secondary amide-based macrocycles containing additional ethereal and pyridine groups. Tsukube *et al.* have demonstrated that while pyridine groups do not possess a great affinity for calcium ions they could, however, be good complexation auxiliaries when present in the side-chain of macrocycles possessing hard base-type atoms such as crown ethers.[10,11] We have examined bislactams that contain pyridine as part of the macrocyclic ring. We have also studied the conformational changes in the ring occurring during complexation.

Discussion

In order to investigate any influence which the ligand structure might have on the complex formation we prepared ligands with similar ring size but different coordination sites: **1**, **2** and **3**. Ligands **4** (with a shorter aliphatic part in the region of the crucial complexing sites) and **5** (small, relatively rigid) were also prepared.[12] Complexation of Ca^{2+} with our ligands in CD_3CN caused, in all cases except **1**, precipitation of the complexes from the solution. Stoichiometry of the solid complexes was



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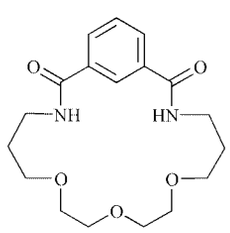

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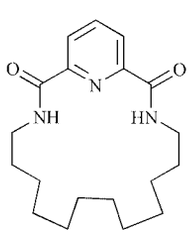

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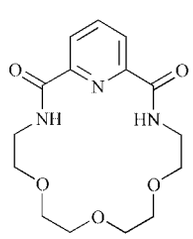

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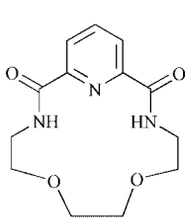

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Table 1 Changes in the amide IR frequencies during Ca^{2+} complexation (KBr, cm^{-1}) and stoichiometry of solid complexes obtained by elemental analyses (EA) for ligands (L)

L	$\nu(C{=}O)_L$	$\nu(C{=}O)_{L\text{-}Ca}$	$\nu(N{-}H)_L$	$\nu(N{-}H)_{L\text{-}Ca}$	$\Delta\nu(C{=}O)$	$\Delta\nu(N{-}H)$	EA
1	1671.6	1657.9	1528.0	1555.8	−13.7	+27.8	$[Ca(\mathbf{1})(H_2O)_4](ClO_4)_2$
2	1658.3	1633.8	1553.3	1550.8	−24.5	−2.5	$Ca(ClO_4)_2{\cdot}2(\mathbf{2})$
	1634.6				−0.8		
3	1679.7	1656.9	1533.9	1550.3	−22.9	+16.4	$Ca(ClO_4)_2{\cdot}2(\mathbf{3}){\cdot}2H_2O$
	1654.7				−2.2		
4	1676.7	1668.6	1539.6	1555.6	−10.1	+16.0	$[Ca(\mathbf{4})_2(NCCH_3)_2]_n(ClO_4)_2$ [a]
4	1676.7	1615.8	1539.6	1553.0	−60.9	+13.4	$Ca(Pic)_2{\cdot}2(\mathbf{4}){\cdot}2H_2O$
		1655.5			−20.7		
5	1680.1	1662.6	1534.8	1552.0	−17.5	+17.2	$[Ca(\mathbf{5})_2(ClO_4)_2]_n$

[a] On the basis of a very recent crystallographic result.

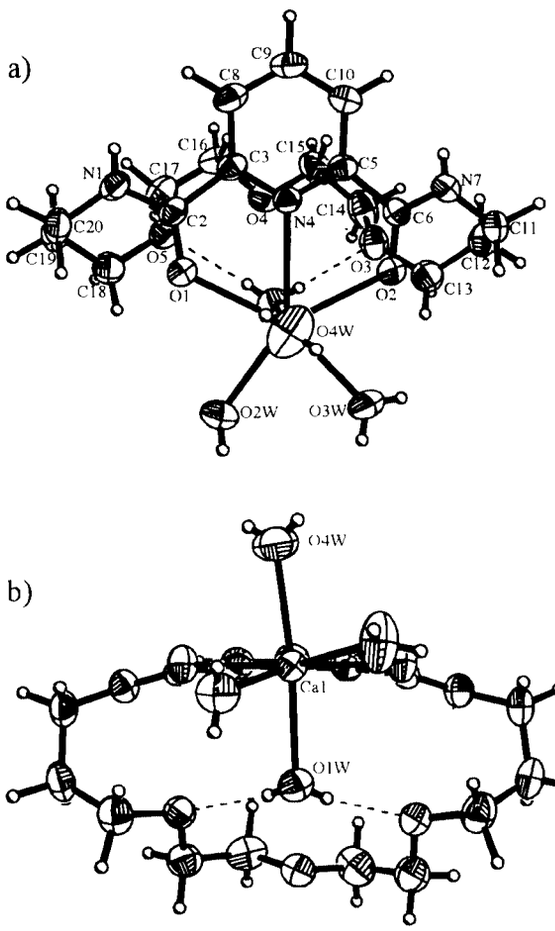

Fig. 1 Calcium complex of **1**. A view a) perpendicular and b) parallel to the mean plane passing through the pyridine ring. Ca(1)–O(1) 2.401(2), Ca(1)–O(2) 2.431(2), Ca(1)–N(4) 2.512(2), Ca(1)–O(1W) 2.358(3), Ca(1)–O(2W) 2.400(3), Ca(1)–O(3W) 2.345(3), Ca(1)–O(4W) 2.339(3) Å. Geometry of hydrogen bonds in the second coordination sphere: O(1W)–H(1WA) 0.74(5) Å, O(1W)···O(3) 2.871(4) Å, O(1W)–H(1WA)···O(3) 2.13(5) Å, 171(5)°; O(1W)–H(1WB) 0.72(5) Å, O(1W)···O(5) 2.881(4) Å, O(1W)–H(1WB)···O(5) 2.16(5) Å, 171(5)°.

determined from elemental analyses. Only ligand **1** forms a 1 : 1 (**1** : Ca^{2+}) complex; the others form 2 : 1 complexes (L : Ca^{2+}). In some cases water molecules are present in the structures (Table 1). From the above findings we can state that formation of the stable solid complexes of bislactams requires the presence only of the amide groups, since we obtained complexes of **2** (without N_{Py}) and **3** (without ethereal oxygen atoms).

X-Ray study

In all known cases ligands containing a 2,6-dicarbamoylpyridine moiety have intramolecular hydrogen bonds between NH_{amide} and the pyridine nitrogen atom. We reported the same observation for ligands **1**,[13] **4** and **5**.[12] Such a conformation seems to be well stabilized and only the presence of a competitive hydrogen bond acceptor can destroy this arrangement.

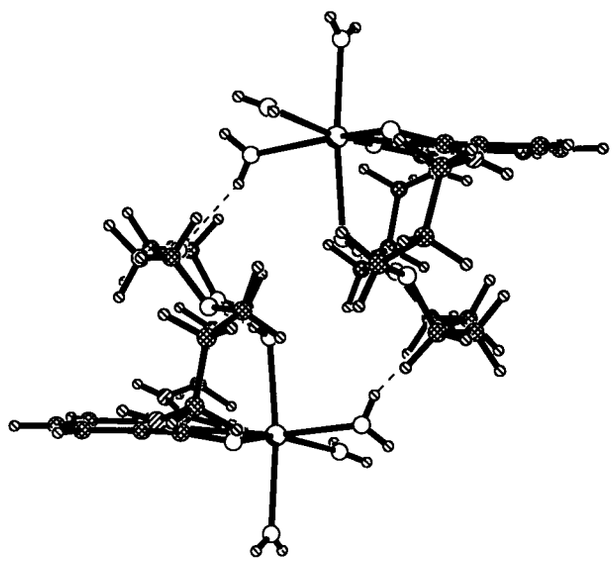

Fig. 2 Supramolecular dimers formed by **1**·Ca^{2+}·H_2O species. Hydrogen bond geometry: O(2W)–H(2WA) 0.75(5) Å, O(2W)···O(4)(2 − x, 1 − y, −z) 2.15(6) Å, O(2W)–H(2WA)···O(4)(2 − x, 1 − y, −z) 2.874(4) Å, 160(5)°.

We were able to obtain good quality crystals for **1**–Ca^{2+} and **5**–Ca^{2+}. Fig. 1 shows the calcium complex of **1**. The calcium ion is 7-coordinated. Coordination involves both carbonyl oxygen atoms, pyridine nitrogen atom and four water molecules. This coordination mode is possible only if both of the ligand's intramolecular hydrogen bonds are broken. Thus the conformation of the whole macrocyclic ring in the complex must be considerably different from conformations reported earlier for the free macrocycle. The complex has a structure where the macrocyclic ring is no longer co-planar with the pyridine ring, as was observed in the free ligand and other ligands of similar structure. The macrocyclic ring is somewhat perpendicular (the angle between the pyridine ring and the mean plane passing through the rest of the macrocyclic ring is 26° for the free ligand and 112° for the complex). The methylene hydrogen atoms from C(15) and C(16) approach the pyridine aromatic ring (the distance is 3.4 Å). The O(1W) water molecule seems to have a special function for this conformation. It connects the ethereal moiety of the macrocyclic ring with the calcium ion. The water molecule is involved in Ca^{2+} coordination and forms simultaneously two symmetrical hydrogen bonds in the second coordination sphere.[14] Hydrogen bonding seems to influence its geometric parameters of coordination (see following section). Another water molecule O(2W) connects supramolecular species into dimers (Fig. 2). ClO_4^- anions remain uncomplexed. They form a network of hydrogen bonds with NH groups and

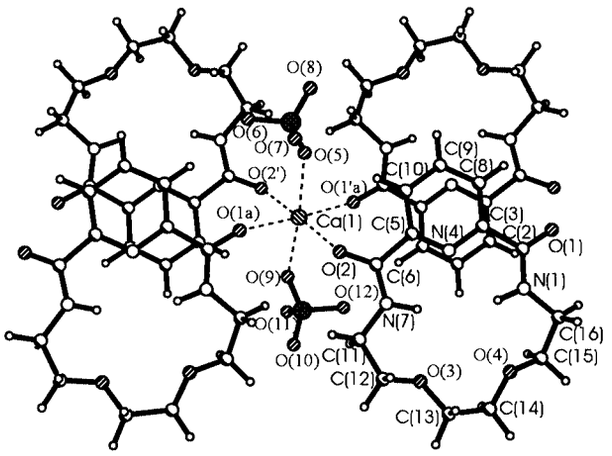

Fig. 3 Polymeric complex **5**–Ca^{2+}. Ca(1)–O(1′) (x, $1 + y$, z) 2.266(6), Ca(1)–O(2′) 2.273(7), Ca(1)–O(9) 2.326(9), Ca(1)–O(1) (x, $-1 + y$, z) 2.333(6), Ca(1)–O(2) 2.342(7), Ca(1)–O(5) 2.351(8) Å.

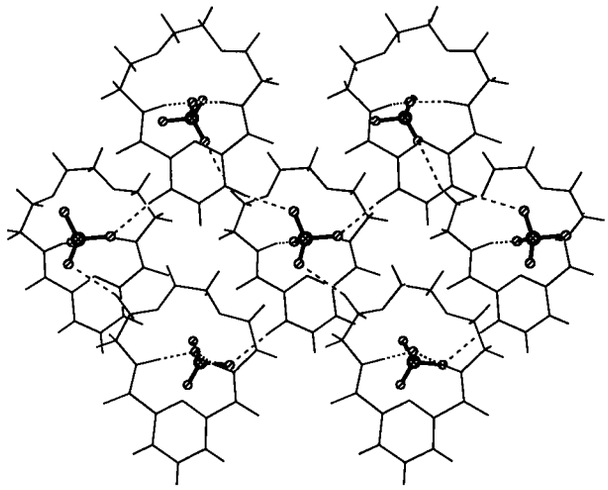

Fig. 4 The crystal packing of **5**–Ca^{2+}. ClO_4^{2-} counterions are hydrogen bonded just over the macrocyclic cavities. Geometry of hydrogen bonds, d(D–H), d(D···A), d(H···A) (Å), angle D–H···A (°): N(1)–H(1)···O(11)($-x + 1$, $2 - y$, $z + 0.5$) 1.00, 2.31, 3.04(2), 129.5°; N(7)–H(7)···O(11) ($-x + 1$, $2 - y$, $z + 0.5$) 1.00, 2.65, 3.49(3), 142.6°; N(1′)–H(1′)···O(7)($-x + 0.5$, $y - 0.5$, $z - 0.5$) 1.00, 2.49, 3.22(2), 130.3°; N(7′)–H(7′)···O(7)($-x + 0.5$, $y - 0.5$, $z - 0.5$) 1.00, 2.39, 3.28(2), 148.6°; C(8)–H(8)···O(6)(x, $1 + y$, z) 1.00, 2.46, 3.43(2), 164.0°; C(15)–H(15B)···O(8)($0.5 + x$, $2.5 - y$, z) 1.05, 2.49, 3.495(18), 159.9°.

water molecules (d(D–H), d(D···A), d(H···A) (Å), angle D–H···A (°): N(1)–H(1N)···O(8) 0.79(4), 2.33(4), 3.047(5), 152(4)°; N(7)–H(7N)···O(7)($2 - x$, $1 - x$, $1 - x$) 0.79(4), 2.38(4), 3.120(5), 156(3)°; O(2W)–H(2WB)···O(11)($2 - x$, $-y$, $-z$) 0.80(5), 2.16(5), 2.917(4), 157(5)°; O(3W)–H(3WA)···O(13)($2 - x$, $-y$, $-z$) 0.73(6), 2.11(6), 2.812(5), 163(6)°; O(3W)–H(3WB)···O(12) 0.78(7), 2.23(7), 2.996(6), 166(6)°; O(4W)–H(4WA)···O(6)(x, $y - 1$, z) 0.68(6), 2.27(6), 2.945(6), 172(7)°; O(4W)–H(4WB)···O(7)($1 - x$, $1 - y$, $1 - z$) 0.73(6), 2.36(6), 3.024(6), 153(6)°).

Despite the inner complex of **1**–Ca^{2+}, ligand **5** forms a stable complex with a Ca^{2+} ion located completely outside the cavity. The environment of the Ca^{2+} cation is shown in Fig. 3. The Ca^{2+} ion is 6-coordinated: with four carbonyl groups of four different lactam molecules and two oxygen atoms from ClO_4^- counterions. This coordination number is most frequent in simple peptides. However α-chelating peptides can produce 7 or 8 coordination numbers (the **1**–Ca^{2+} complex is also 7-coordinated).[15] Such a coordination implies stacking of the pyridine rings. The distance between parallel rings is in the range of 3.37–3.48 Å (the angle between them is 2.5°). This complex has proved to be polymeric and infinite chains are formed in such a way that every bislactam molecule coordinates two different calcium ions using its two carbonyl oxygen atoms.

In this case the ligand seems to better interact with the anions. While Ca^{2+} ions are bound outside, ClO_4^- anions are hydrogen bonded directly over the cavity (Fig. 4). Two $NH_{amide}\cdots O$ hydrogen bonds bind the anion to the macrocyclic ring. Each ClO_4^- anion thus has one oxygen atom coordinated to the calcium ion and another one hydrogen bonded.

Geometry of water molecules

In both structures water molecules seem to function as a "glue". Einspahr and Bugg have investigated the geometry of water–calcium interactions.[16] According to their classification all water molecules found in the structure of the complex **1**–Ca^{2+} are class I water molecules. They have found that the calcium ion tends to lie near the plane bisecting the water molecule and that two parameters are characteristic for that position: firstly φ (dihedral angle between the plane defined by the water dipole, the Ca–O vector and the plane of the water molecule) and secondly θ (the angle between the Ca–O vector and the water-dipole vector). Thus φ angles tend to be 90° and the θ angle 0°.

O(1W) shows considerable deviation from the expected value for θ (Table 2). This could be attributed to simultaneous hydrogen bonding in the second coordination sphere. Water hydrogen atoms are directed towards ethereal oxygen atoms forming highly directional hydrogen bonds. In a barium complex reported by Costes *et al.*,[17] a water molecule is hydrogen bonded in a similar way. It also shows a big value for the θ angle (50°).

Table 2 Geometry of water molecules in **1**–Ca^{2+}

	φ/°	θ/°
O(1W)	86.1	47.0
O(2W)	89.3	30.9
O(3W)	44.3	8.1
O(4W)	48.7	5.7

IR study

IR spectra recorded for solid complexes (in KBr) revealed that complexation of all bislactam macrocycles was accompanied by a shift to lower frequency of the carbonyl stretching band (Table 1). Variation of the same magnitude has been observed for alkaline-earth complexes with linear amides.[18] These results indicate that the carbonyl oxygen atoms are involved in the coordination.

Participation of ClO_4^- anions in complexation is often discussed[5,6] on the basis of multiplicity of the IR band at 1100 cm^{-1}. The 'isolated' perchlorate anion has a T_d symmetry and shows a ν(Cl–O) single band.[19] In all our cases those bands show a high degree of multiplicity, which seems to indicate that the geometry of ClO_4^- is distorted from tetrahedral by metal coordination. Our results indicate that it is unwise to speculate on this participation, since even for **1**–Ca^{2+}, where X-ray study excluded participation of this anion in coordination to the calcium ion, this band shows a high degree of multiplicity.

NMR studies

Complexation was investigated by preparing 0.1 M solutions of the isolated solid complexes in appropriate solvents. For ligand **1** spectra were recorded in CD_3CN by addition of 2 equiv. of $Ca(ClO_4)_2$. Further addition of the salt did not change the spectra. In this case besides ^1H and ^{13}C spectra, a ^{15}N NMR spectrum was also obtained.

Complexation caused a downfield shift of ^{13}C NMR carbonyl signals. This is in agreement with a general effect of complexation proceeding *via* carbonyl oxygen atoms.

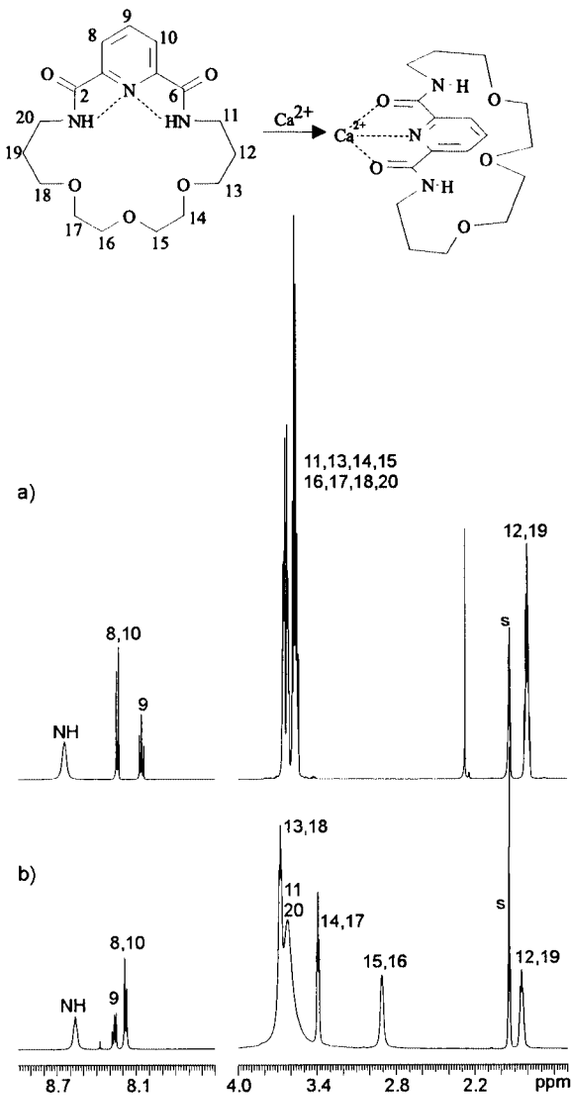

Fig. 5 Changes to the ^{1}H NMR spectrum of **1** (CD_3CN) upon complexation and signals' assignment: a) free ligand **1**, $c = 0.1$ M; b) **1**–Ca^{2+}, 2 equiv. of $Ca(ClO_4)_2$ were added in order to achieve >95% complexation.

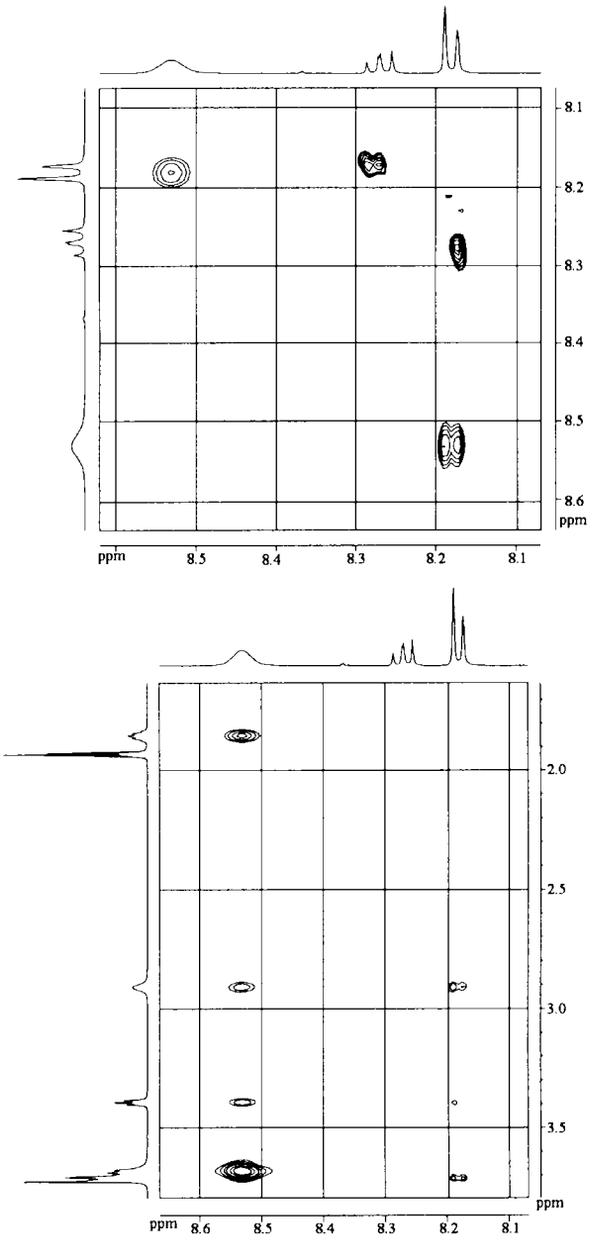

Fig. 6 Partial NOESY spectrum of **1**–Ca^{2+} (in CD_3CN, at 25 °C, mixing time 300 ms, ligand concentration 0.1 M, 2 equiv. of $Ca(ClO_4)_2$ added).

An ^{1}H-NMR-shift titration for **1** with $Ca(ClO_4)_2$ was carried out. It showed a nearly perfect nonlinear least-squares fit for a 1 : 1 (**1** : Ca^{2+}) stoichiometric model, as was also observed in the solid state. For complex **1**–Ca^{2+} there are indications that the structure in solution could resemble the solid state structure. Fig. 5 presents changes in the ^{1}H NMR spectra upon complexation and the signal assignment. It shows that H(8)/H(10) and H(9) protons change their relative position. This indicates that the carbonyl oxygen atoms flip towards the cavity. Chemical shifts for the methylene H(15)/H(16) and H(14)/H(17) protons also change considerably during complexation by −0.68 and −0.20 ppm, respectively. Such an upfield shift could be caused by their positioning under the aromatic ring (as in the crystal structure).

Additional evidence comes from the NOESY spectrum. It shows an NOE effect between the aromatic H(8)/H(10) and NH protons (absent in the ligand's spectrum) (Fig. 6). This is possible only if amide hydrogen atoms are positioned outside the cavity. The NOE effect is also observed between the aromatic H(8)/H(10) and methylene H(15)/H(16) protons. Proximity of those groups, positioned on the opposite sides of the molecule in the free ligand, is possible only if the conformation is similar to those observed in the solid state.

For the complex of $Ca(ClO_4)_2$ with 18-membered bislactam **4**, possessing the same coordination sites, there is no upfield shift for any methylene proton. Very small changes in chemical shifts for the pyridine protons also indicate that the ring does not undergo considerable conformational changes. In order to investigate this further we also obtained the complex of ligand **4** with calcium picrate. Although this precipitated from CD_3CN solution, it was soluble enough to record a ^{1}H NMR spectrum. Methylene protons and pyridine protons, as in the perchlorate complex, do not change considerably, which indicates that the 18-membered ligand does not change its conformation in order to complex calcium inside the cavity. A ^{13}C NMR titration of **4** with $Ca(ClO_4)_2$ was carried out since changes in the ^{1}H NMR spectra were too small, but it gave titration curves that cannot be fitted to simple models like 1 : 1 or 2 : 1.

Comparison to Pb^{2+} complex, ^{15}N NMR study

In our earlier work concerning a Pb^{2+} complex of bislactam **1** we postulated from spectroscopic experiments, including NOE and ^{15}N NMR, conformational changes in the ligand structure which occurred upon complexation.[13] However we were unable to obtain crystals in order to obtain X-ray data. The ^{1}H NMR

spectra resulted in the same direction and the magnitude of chemical shifts as in the present case (*i.e.* change of the relative position of H(8)/H(10) and H(9) signals and upfield shift of some methylene protons). We postulated that carbonyl oxygen atoms change their position and flip towards the cavity in this complex too.

In the case of Pb^{2+} complexation we observed by ^{15}N NMR a deshielding effect (+7.1 ppm) on N_{py}, which is opposite to the commonly observed effect of complexation on N_{py}.[20] We have proved that N_{py} is crucial for Pb^{2+} complexation so the chemical shift changes are the result of two components: the deshielding effect upon hydrogen bond breaking (which should be the larger component) and shielding effect of the complexation.

In the present case we also observed a very small deshielding effect (1.0 ppm) in ^{15}N NMR, which mainly indicates that in this situation, where multiple hydrogen bonds are present, ^{15}N NMR chemical shifts for N_{py} are not a good measure for determining participation of that atom in complexation.

The other signal, N_{am}, is downfield shifted in the ^{15}N NMR spectrum for Pb^{2+} complex (+18.1 ppm). In the present case we also observed a +12.5 ppm shift. This is in agreement with the commonly observed effect of the complexation through an amide oxygen atom (deshielding).

Conclusions

Calcium complexes of macrocylic bisamide ligands form very easily. In contrast to Pb^{2+} complexes, they do not require participation of pyridine nitrogen or ethereal oxygen atoms but only amide oxygen atoms. Bislactam **1** with a 20-membered ring is able to include a calcium ion inside the cavity and change its conformation, even though this requires the breaking of intramolecular hydrogen bonds. Rings smaller than 20-members form 2 : 1 ($L : Ca^{2+}$) species with calcium ions completely outside the cavity.

Experimental

General

FT-IR spectra were recorded on a Perkin-Elmer Spectrum 2000 spectrometer in KBr discs. NMR spectra were recorded on a Bruker 200 and Varian UNITY+500 spectrometer.

Syntheses of ligands

The following compounds were prepared as we described earlier: **1**, **4**, **5**,[12] **2**, **3**.[13]

Syntheses of complexes

General. Complexes were prepared by mixing equimolar 0.1 M solutions of lactams in acetonitrile and $Ca(ClO_4)_2$ in acetonitrile. Solutions were left to evaporate to *ca.* half of a previous volume. The resulting crystals were collected, washed and dried under vacuum at about 352 K overnight. Elemental analyses and IR spectra were recorded.

$[Ca(1)(H_2O)_4](ClO_4)_2$ (1–Ca^{2+}). See general procedure. Good quality crystals for X-ray analyses were obtained after evaporation of *ca.* 2/3 of solvent, mp 215–217 °C (123–125 °C solvent release). ^1H NMR (500 MHz, CD_3CN): δ 8.563 (2H, br t, NH), 8.265 (1H, t, J = 7.0 Hz, H9), 8.180 (2H, d, J = 8.0 Hz, H8, H10), 3.679 (4H, t, J = 5.0 Hz, H13), 3.625 (4H, br s, H11), 3.393 (4H, t, J = 4.2 Hz, H14, H17), 2.907 (4H, br s, H15, H16), 1.845 (4H, t, J = 5.0 Hz, H12, H19); ^{13}C NMR (125 MHz, CD_3CN): δ 167.3, 149.6, 141.9, 125.2, 70.6, 70.3, 68.5, 40.3, 27.4. ^{15}N NMR (CD_3CN, ref. nitromethane, HSQC[21] and HMQC[22] experiments, respectively): −260.9 (N_{amide}, d, $J^1_{N,H}$ = 93.7 Hz), −89.5 (N_{py}). IR ν_{max}(KBr)/cm^{-1} 3494, 3386, 2948, 1657, 1556, 1462, 1324, 1276, 1140, 1069, 981, 714, 628.

$Ca(ClO_4)_2 \cdot 2(2)$ (2–Ca^{2+}). Both components **2** and $Ca(ClO_4)_2$ were separately dissolved in 1 : 1 $CHCl_3$–CH_3CN and the solutions were mixed. Crystals precipitated after about 1 hour, mp > 300 °C (decomp.). IR ν_{max}(KBr)/cm^{-1} 3349, 3105, 2925, 2873, 1634, 1551, 1443, 1346, 1309, 1091, 993, 824, 731, 622; Anal. calc. for $C_{36}H_{52}N_4O_{18}Ca_1Cl_2$: C, 46.01, H, 5.58, N, 5.96; found: C, 46.03, H, 5.90, N, 5.91%.

$Ca(ClO_4)_2 \cdot 2(3) \cdot 2H_2O$ (3–Ca^{2+}). To a solution of **3** in $CHCl_3$ an equimolar solution of $Ca(ClO_4)_2$ in CH_3CN was added. Complex precipitated immediately, mp > 300 °C (decomp.). IR ν_{max}(KBr)/cm^{-1} 3338, 3089, 2931, 2857, 1657, 1550, 1450, 1317, 1245, 1161, 1146, 1118, 1048, 1000, 938, 846, 729, 681, 622; Anal. calc. for $C_{38}H_{62}N_6O_{14}Ca_1Cl_2$: C, 48.68, H, 6.66, N, 8.96; found: C, 48.71, H, 6.77, N, 9.07%.

Ligand 4. ^1H NMR (200 MHz, CD_3CN–$CDCl_3$ 1 : 1): δ 9.03 (2H, br, NH), 8.209 (1H, d, J = 8.4 Hz, H8(or H10)), 8.207 (1H, J = 7.0 Hz, H8(or H10)), 7.998 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.0 Hz, H9), 3.601 (12H, m); ^{13}C NMR (50 MHz, CD_3CN–$CDCl_3$ 1 : 1): δ 164.2, 149.9, 140.0, 125.5, 71.6, 71.3, 71.1, 39.9.

$[Ca(4)_2(NCCH_3)_2]_n \cdot (ClO_4)_2$ (4–Ca^{2+}). See general procedure. Complex precipitated immediately, mp > 300 °C (decomp.). ^1H NMR (200 MHz, CD_3CN–$CDCl_3$ 1 : 1): δ 9.51 (2H, br, NH), AB_2: 8.28 (1H, J = 6.2 Hz, H9), 8.24 (2H, J = 6.2 Hz, H8, H10), 3.67 (12H, m); ^{13}C NMR (50 MHz, CD_3CN–$CDCl_3$ 1 : 1): δ 165.2, 148.6, 140.9, 126.8, 70.9, 70.6(2C), 40.5; IR ν_{max}(KBr)/cm^{-1} 3456, 3341, 2906, 1669, 1556, 1448, 1355, 1249, 1180, 1121, 1107, 1090, 1002, 950, 843, 746, 684, 654, 628. Colorless crystals underwent partial destruction on drying (solvent release), thus elemental analysis was not satisfactory.

$Ca(Pic)_2 \cdot 2(4) \cdot 2H_2O$. See general procedure. Complex precipitated immediately, mp 106–109 °C. ^1H NMR (200 MHz, CD_3CN): δ 9.06 (2H, br, NH), 8.74 (2H, s, pic), 8.24 (2H, d, J = 7.6 Hz, H8, H10), 8.09 (1H, J = 7.6 Hz, H9), 3.61 (12H, m); ^{13}C NMR (50 MHz, CD_3CN): δ 164.1, 149.8, 140.2, 127.2, 125.4, 71.3, 71.0, 70.9, 39.9. IR ν_{max}(KBr)/cm^{-1} 3435, 3090, 2876, 1655, 1639, 1616, 1553, 1496, 1448, 1431, 1365, 1321, 1271, 1165, 1094, 1001, 943, 915, 846, 790, 746, 712, 687, 647; Anal. calc. for $C_{42}H_{50}N_{12}O_{24}Ca_1$: C, 42.71, H, 4.27, N, 14.26; found: C, 42.68, H, 4.25, N, 14.35%.

$[Ca(5)_2(ClO_4)_2]_n$ (5–Ca^{2+}). See general procedure. Complex precipitated immediately. Good quality crystals for X-ray analyses were obtained from the filtrate, mp 124–126 °C. IR ν_{max}(KBr)/cm^{-1} 3372, 3087, 2876, 1663, 1552, 1453, 1355, 1248, 1135, 1100, 1049, 1002, 860, 726, 686, 626; Anal. calc. for $C_{26}H_{34}N_6O_{16}Ca_1Cl_2$: C, 39.15, H, 4.30, N, 10.54; found: C: 39.09, H, 4.43, N, 10.51%.

^1H NMR titration

A 0.022 mol dm^{-1} solution of **1** was prepared in CD_3CN. The initial ^1H NMR spectrum was recorded and aliquots of $Ca(ClO_4)_2$ solution (0.138 mol dm^{-3} in CD_3CN) were added by microsyringe (10 μl portions). A plot of displacements in chemical shift was subjected to analysis by curve fitting (computer CurveExpert program). Typically 16 data points were recorded. The stability constant for the 1 : 1 model was calculated (2.4×10^2 M^{-1} at 297 K) on the basis of changes in the chemical shifts (for aromatic, CH_2 and NH protons) and was in agreement within experimental error (*ca.* 10%).

For **4** a ^{13}C NMR titration in CD_3CN was carried out, since the changes in the ^1H NMR spectrum were too small. Total receptor concentration was 0.052 M. The titration curve does not fit well to simple models like 1 : 1 and 2 : 1 ($L : Ca^{2+}$).

X-Ray structure determinations

X-Ray single-crystal diffraction experiments (see Table 3) were

Table 3 Experimental data for the X-ray diffraction studies

Identification code	**1**–Ca^{2+}	**5**–Ca^{2+}
Empirical formula	$C_{17}H_{33}CaCl_2N_3O_{17}$	$C_{26}H_{34}CaCl_2N_6O_{16}$
M	662.44	797.57
Crystal system	Triclinic	Orthorhombic
Space group	$P\bar{1}$	$Pna2_1$
Unit cell dimensions		
a/Å	10.4979(5)	23.1803(15)
b/Å	11.9658(6)	10.1436(3)
c/Å	13.9671(9)	14.6585(7)
α/°	63.975(5)	90
β/°	68.452(4)	90
γ/°	70.444(2)	90
V/Å^3	1434.4(1)	3446.7(3)
T/K	293(2)	293(2)
Z	2	4
μ(Cu-Kα)/mm^{-1}	4.325	3.719
Reflections coll./unique	5498/5498	2545/2545
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0561$, $wR2 = 0.1381$	$R1 = 0.0743$, $wR2 = 0.1730$
R indices (all data)	$R1 = 0.0561$, $wR2 = 0.1381$	$R1 = 0.0859$, $wR2 = 0.1971$

carried out on an Enraf-Nonius CAD-4 diffractometer. Psi-scan absorption corrections were applied for both calculations. The program used to solve structures was SHELXS86 (Sheldrick, 1990).[23] The program used to refine the structures and to prepare materials for publication was SHELXL97 (Sheldrick, 1997).[24] All non-H atoms were refined with anisotropic displacement parameters. H atoms were refined in isotropic approximation. All H atoms were calculated and refined as riding model except for the amide and water H-atoms for **1**–Ca^{2+}, which were located from the Fourier map and refined freely.

CCDC reference number 188/244. See http://www.rsc.org/suppdata/p2/b0/b000966k/ for crystallographic files in .cif format.

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