A New Macrocyclic Polylactam-Type Neutral Receptor for Anions − Structural Aspects of Anion Recognition[‡]

Agnieszka Szumna[a] and Janusz Jurczak*[a,b]

Keywords: Amides / Hydrogen bonds / Molecular recognition / Neutral receptors / X-ray diffraction

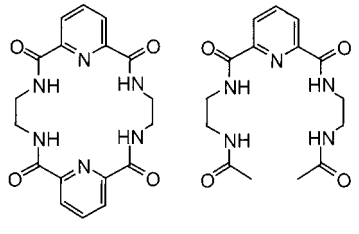
A macrocyclic ligand containing four amide functionalities was synthesised and its complexes with various anions (F^-, Cl^-, AcO^-, $H_2PO_4^-$, and p-$NO_2C_6H_4O^-$) were investigated in solution and in the solid state. NMR titration experiments (carried out in [D_6]DMSO), X-ray studies and electrospray mass spectrometry (ESI MS) were employed for determination of stoichiometry and selectivity. The results in solution indicated predominant formation of 1:1 complexes for all anions studied. However, the existence of a 2:1 complex of **1** with bidentate AcO^- anion as a minor species was also detected. X-ray crystal structure determination provided evidence that the Cl^- anion is too bulky to be included in the cavity of the 18-membered tetralactam ring [K_{ass}(Cl^-; DMSO) = 65 M^{-1}], but that F^- fits well [K_{ass}(F^-; DMSO) = 830 M^{-1}]. The binding mode of AcO^- anion consists of formation of four hydrogen bonds to only one of the carboxylate oxygen atoms (employing the *syn-anti* lone pairs of AcO^-). The selectivity of the receptor towards AcO^- anion [K_{ass}(AcO^-; DMSO) = 2640 M^{-1}] is discussed in terms of a favourable arrangement of hydrogen-bond donors. The limited extent of formation of a 2:1 (**1**/AcO^-) complex is attributed to unfavourable interactions between two receptor molecules.

Introduction

The important current research topic in supramolecular chemistry is the development of synthetic receptors, especially those specific for anions.[1−7] Due to the biomedical and environmental significance of anions,[8] the application of such receptors as membrane transport carriers[9] or sensors[10] is a subject of immediate interest; their application in organic synthesis has also recently been reported. The latter application is exemplified by the work of Crabtree et al.,[11] who used a simple, acyclic anion receptor as a catalyst in a reaction passing through an anionic intermediate. Another, macrocyclic, anion receptor has been used in rotaxane synthesis.[12] The design of neutral ligands, especially for binding guest molecules in polar solvents is a challenging goal, owing to competing solvent effects.[13] One possible means to overcome this drawback would be by incorporation of a number of appropriately arranged binding sites in a receptor structure. Another way, reported recently, involves putting the receptor into a hydrophobic microenvironment.[14] Despite the extensive search for more effective arrangements of binding sites, relatively little is known about the structure of anion complexes with neutral receptors.[15−17] Furthermore, the question of the existence of any preferred coordination environment has still not been answered for some anions.

We resolved to undertake studies on anion-binding properties of amide-type neutral receptors, the complexation modes of anions and the structure of the complexes. Searching for appropriate receptors with conveniently tuneable hydrogen bonds, arranged in convergent manner, we focused our attention on a group of small, relatively rigid macrocycles consisting of −NH−CO− functionalities linked by aromatic and/or short aliphatic subunits. Polylactams of this type can be synthesised by the high-dilution approach[18] or, more conveniently, by macrocyclisation between diesters and diamines in methanol.[19] We had previously found that macrocyclic lactams bearing 2,6-dicarbamoylpyridine moieties have amide hydrogen atoms directed into their cavities, and are able to interact with hydrogen-bond acceptor solvent molecules.[19] There are also some reports on anion binding properties of compounds of such a type [acyclic *N*,*N*-bis(diphenyl)-2,6-pyridinedicarboxyamide,[20] monocyclic[12] and bicyclic,[15] derivatives, for example].

In this paper we would like to report the results of complexation studies of a new, neutral macrocyclic tetralactam



1 **2**

Scheme 1

[‡] Taken in part from the Ph. D. Thesis of A. S.

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
Fax: (internat.) + 48-22/632-6681
E-mail: jurczak@icho.edu.pl
apecak@icho.edu.pl
[b] Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland
Fax: (internat.) + 48-22/632-6681

Supporting information for this article is available on the WWW under http://www.eurjoc.com or from the author.

  1434−193X/01/1121−4031 $ 17.50+.50/0

1 and its acyclic analogue **2** (Scheme 1) with various anions, performed in solution. We also discuss the solid-state structures (X-ray) of some anion complexes in terms of selectivity of the receptor and complex stoichiometry.

Results and Discussion

Complexation of Anions in Solution

In the course of examination of series of compounds, we found that tetralactam **1**, practically insoluble in most of the common solvents (such as $CHCl_3$, MeOH, MeCN, H_2O), can be dissolved in $CDCl_3$ in the presence of various anions (F^-, Cl^-, AcO^-, $H_2PO_4^-$, and p-$O_2NC_6H_4O^-$) present as tetrabutylammonium (TBA) or tetraphenylphosphonium salts. The signals of the amide protons in the ^1H NMR spectra (on addition of 1 equiv. of salt) appear at a very low field ($\delta = 12.3$ for F^-, 10.3 for Cl^-, 10.7 for AcO^-, 10.6 for $H_2PO_4^-$, and $\delta = 10.9$ for p-$O_2NC_6H_4O^-$). Because of solubility requirements, [D_6]DMSO was chosen as a solvent for NMR titration experiments. Association constants for ligand **1** and the anions mentioned above are summarised in Table 1.

Table 1. Association constants K_{ass} (M^{-1}) for **1** (by ^1H NMR titration, [D_6]DMSO, $T = 298$ K)

X^-	R_{vdW} [Å]	pK_a of HX in H_2O	K_{ass} [M^{-1}]	$\Delta\delta_{max}$ (H_{amide})
Cl^-	1.81	−6.1	65 ± 10	0.71
$H_2PO_4^-$	1.58[a]	2.16	1680 ± 110	1.22
F^-	1.46	3.17	830 ± 120	3.00
AcO^-	1.58[a]	4.75	2640 ± 270	1.22
p-$O_2NC_6H_4O^-$	1.58[a]	7.15	67 ± 10	1.23

[a] R_{vdW} for oxygen atom.

For comparison, we synthesised acyclic tetraamide **2** and also studied its binding properties (Table 2). Although **2** has the same binding sites as macrocyclic tetralactam **1**, it interacts with anions much more weakly than **1**.

Table 2. Association constants K_{ass} (M^{-1}) for **2** (by ^1H NMR titration, [D_6]DMSO, $T = 298$ K)

X^-	R_{vdW} [Å]	K_{ass} [M^{-1}]	$\Delta\delta_{max}$ (H_{amide})
F^-	1.46	11±0.6	1.57, 2.30
Cl^-	1.81	12±0.6	0.59, 0.47
AcO^-	1.58[a]	45±0.9	1.25, 1.12

[a] R_{vdW} for oxygen atom.

For tetralactam **1**, the highest K_{ass} values were observed for complexation of oxy anions of bidentate type: AcO^- and $H_2PO_4^-$ (Table 1). Surprisingly, K_{ass} was much smaller for the most basic p-nitrophenolate oxy anion. Although we obtained nearly perfect fits of 1:1 binding isotherms to the experimental data in all cases, the possibility of a 2:1 (H/G) complex formation was also considered. This possibility might be reasonable, especially in the case of bidentate anions. However, Job's plots for such complexes (e.g., **1** + AcO^-, see Supporting Information) confirmed the 1:1 binding ratio. It is an interesting observation that maximum chemical shift changes for the amide protons of **1** (complexation-induced shifts, CISs) produced by all oxy anions studied are of almost the same magnitude. This can be explained in terms of similar distances between anion oxygen atoms and amide protons.

We also examined binding abilities toward spherical halide anions. Tetralactam **1** binds F^- anion substantially better than it does Cl^-. This selectivity reflects the hydrogen-bond acceptor strength of the halides [or other related values often used for assessment of the hydrogen bond acceptor strength of an anion: basicity of an anion (pK_a of HX) or the free energy of hydration $\Delta G°_{0,1}$.[21]]. On the other hand, the selectivity is probably strongly influenced by size complementarity between anions and cavity. This problem, as well as other structural requirements for complexation, was addressed with the aid of information obtained from X-ray structure analysis.

Crystal Structure of Ligand 1

The free ligand **1** crystallises as a solvate with two molecules of methanol, which serve as hydrogen bond acceptors (Figure 1). The ligand has a symmetrical, stair-like conformation and so two 2,6-dicarbamoylpyridine groupings exist in an antiparallel relationship. Such an arrangement implies that pairs of amide hydrogen atoms are directed towards opposite sides of the macrocyclic ring, and so two bound MeOH molecules are also located on opposite sides of the macrocycle. The macrocyclic system is stiffened by

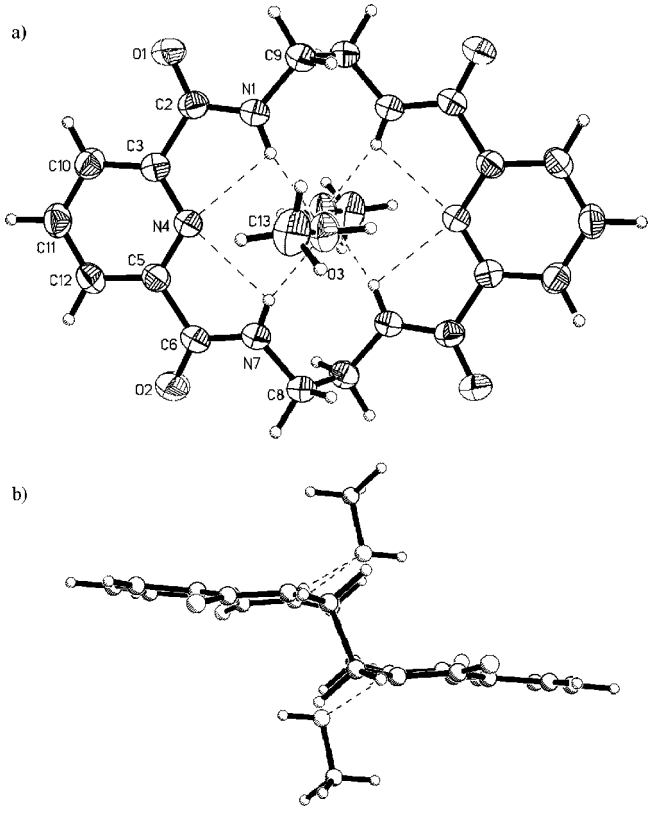


Figure 1. X-ray structure of free ligand **1** (obtained as **1**·2MeOH): a) a view onto the mean plane of macroring; b) side view.

four intramolecular hydrogen bonds ($N-H_{amide}\cdots N_{Py}$, Table 3). The presence of such hydrogen bonds is known to stabilise flat *syn-syn* conformations for compounds containing 2,6-dicarbamoylpyridine moieties.[22−25]

Table 3. Hydrogen-bond geometry for **1**·2MeOH

D−H···A	*d*(H···A) [Å]	*d*(D···A) [Å]	(D−H···A) [°]
N1−H1N···N4	2.31(2)	2.686(2)	105(2)
N7−H7N···N4	2.30(2)	2.690(2)	108(2)
N1−H1N···O3	2.17(3)	2.991(2)	154(2)
N7−H7N···O3	2.25(2)	3.046(2)	156(2)
O3−H10···O1[a]	1.87(3)	2.757(2)	164(3)

[a] (1.5 − *x*, −0.5 + *y*, −*z*).

Crystal Structures of Anion Complexes with Ligand 1

The X-ray structure of complex **1**−**Cl**$^-$ (obtained as **1**·$PPh_4Cl\cdot H_2O\cdot 2.4CH_2Cl_2$, Figure 2) shows that the Cl^- anion is surrounded by five hydrogen-bond donors: four amide NH moieties and a water molecule. As a criterion for hydrogen bonding we adopted the van der Waals approach: $d < R_H + R_X$. Therefore, for H···Cl^- interaction, hydrogen-bond lengths are expected to be less than 3.01 Å (1.20 Å + 1.81 Å).[26] By this criterion, three further CH···Cl^- interactions are apparent (Table 4), and so the total coordination number for the Cl^- anion is eight. It is worthy of mention that the Cl^- anion is not fully included inside the macrocyclic cavity of **1**, but remains outside it (1.9 Å above the mean plane passing through four N_{amide} atoms). The binding of the anion by tetralactam is not symmetrical; two of the four amide hydrogen bonds are considerably shorter than the two others (Figure 2, Table 4).

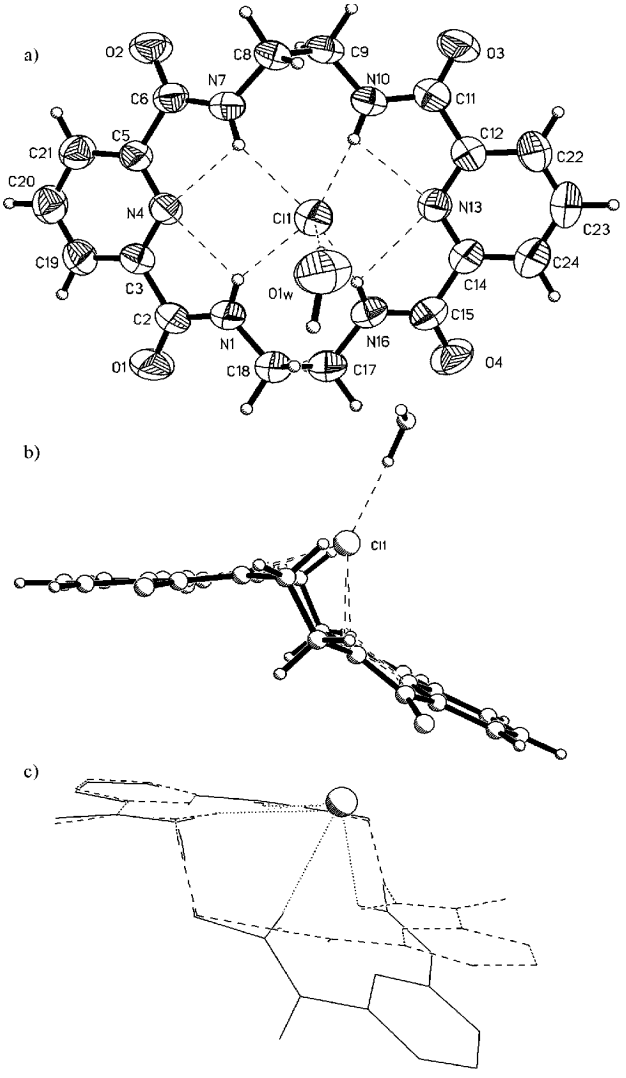


Figure 2. X-ray structure of **1**−**Cl**$^-$ complex (obtained as **1**·$PPh_4Cl\cdot H_2O\cdot 2.4CH_2Cl_2$, counterions and solvent molecules omitted for clarity): a) a view onto the mean plane of macrocycle; b) side view; c) superimposed structures of the free ligand (dashed line) and the complex (solid line)

Table 4. Selected hydrogen bonds in the **1**-**Cl**$^-$ complex.

D−H···A	*d*(H···A) [Å]	*d*(D···A) [Å]	(D−H···A) [°]
N1−H1N···Cl1	2.42(5)	3.210(5)	150(5)
N7−H7N···Cl1	2.40(5)	3.212(4)	151(4)
N10−H10N···Cl1	2.87(6)	3.520(5)	132(5)
N16−H16N···Cl1	2.68(6)	3.424(5)	154(5)
O1W−H1W···Cl1	2.17(2)	3.201(5)	178(8)
C26−H26···Cl1[a]	2.84	3.762(5)	153.0
C35−H35···Cl1[b]	2.95	3.845(5)	150.0
C45−H45···Cl1[c]	2.91	3.789(5)	147.8

[a] (*x*, *y* − 1, *z* − 1). − [b] (*x*, *y* − 1, *z* − 1). − [c] (*x*, *y* − 1, *z* − 1).

Since the Cl^- anion seems to be too large to fit inside the cavity of **1**, we examined the complexation mode for the smaller F^- anion. The anion in complex **1**−**F**$^-$ [obtained as $(\mathbf{1})_{1.5}\cdot PPh_4F\cdot H_2O$, Figure 3] is surrounded by four amide NH moieties and also by a water molecule, which means that, its environment is similar to that of Cl^- in the **1**−**Cl**$^-$ complex, as far as typical hydrogen-bond donors are concerned. No additional interactions within the van der Waals criterion (2.66 Å) were detected. The F^- anion lies slightly above the N_{amide} plane, but the distance (0.9 Å) is much shorter than that for **1**−**Cl**$^-$ (1.9 Å). Additionally, aliphatic chains assist the inclusion of F^- anion in the cavity. In this case, all four hydrogen bonds have similar lengths (Table 5). There is an additional molecule of "uncomplexed ligand" in the complex structure. This "uncomplexed molecule" forms hydrogen bonds with two water molecules and has a conformation identical to that found for the free ligand mentioned above.

In terms of size, the F^- anion has a radius similar to that of a K^+ cation; moreover, the most favourable distances between these ions and their specific ligand binding sites are also similar [2.7−2.9 Å for $K^+\cdots O$, and 2.64 Å for $F^-\cdots N(H)$[27]]. Thus, by simple analogy with cation complexes, the F^- anion should fit best into an 18-membered ring. Recently, Kim et al.[28] have reported results of ab initio calculations for cyclic tetra- and hexapeptides and their anion complexes. According to their calculations, the F^- anion is indeed well fitted for the 18-membered hexapeptide ring, provided that the ring has a conformation with all amide hydrogen atoms directed into the cavity. The F^- anion is then located inside the cavity and bound by all six amide hydrogen atoms. They also reported that, unlike the

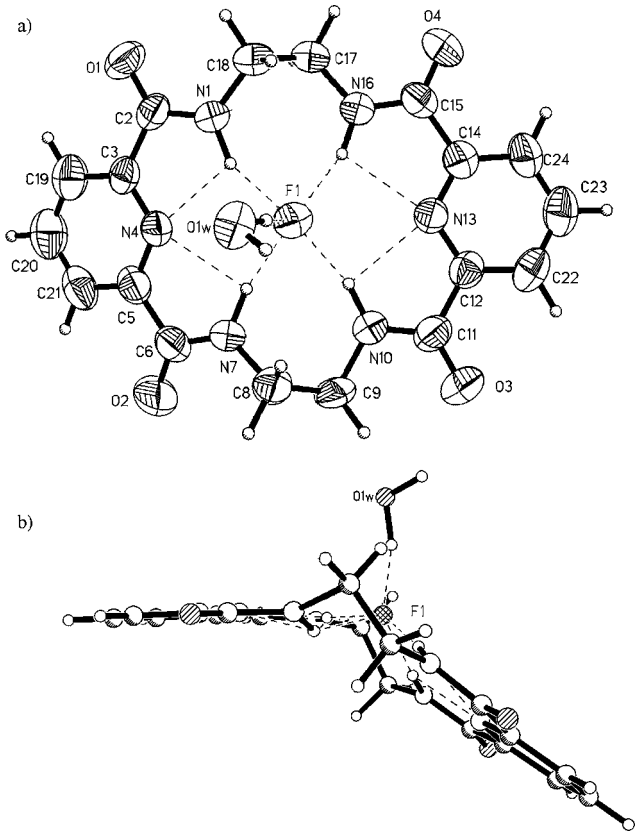


Figure 3. X-ray structure of **1**−**F**$^-$ complex [obtained as (**1**)$_{1.5}$·PPh$_4$F·H$_2$O, counterions omitted for clarity]: a) a view onto the mean plane of macrocycle; b) side view

Table 5. Selected hydrogen bonds in the **1**−**F**$^-$ complex

D−H···A	*d*(H···A) [Å]	*d*(D···A) [Å]	(D−H···A) [°]
N1−H1···F1	1.79	2.745(4)	152.4
N7−H7···F1	1.96	2.825(5)	139.5
N10−H10···F1	1.73	2.742(4)	165.4
N16−H16···F1	1.89	2.881(4)	160.3
O1W−H1W···F1	1.53(2)	2.538(4)	165(3)

F$^-$ anion, Cl$^-$ is positioned above the cavity. Our results provide the first experimental evidence that the F$^-$ anion is complementary to 18-membered polylactam rings, while the Cl$^-$ anion is too large.

Table 6. Selected hydrogen bonds in the **1**−**AcO**$^-$**(TBA)** complex

D−H···A	*d*(H···A) [Å]	*d*(D···A) [Å]	(D−H···A) [°]
N1−H1···O5	2.05	3.030(9)	157.5
N7−H7···O5	2.08	3.065(9)	158.5
N10−H10···O5	2.18	3.044(9)	140.1
N16−H16···O5	2.16	2.987(8)	135.8

Careful analysis of the complexation geometry indicates that the four amide donor sites in the **1**−**F**$^-$ complex are tetrahedrally distorted, in contrast to the complexes of other anions. For **1**−**Cl**$^-$ and **1**−**AcO**$^-$ complexes (discussed in detail below), the deviations of the fourth N_{amide} from the plane defined by three remaining N_{amide} moieties

Table 7. Selected hydrogen bonds in the **1**−**AcO**$^-$**(TMA)** complex

D−H···A	*d*(H···A) [Å]	*d*(D···A) [Å]	(D−H···A) [°]
N1−H1···O5	2.00	2.894(8)	145.8
N7−H7···O5	2.03	2.936(9)	148.5
N10−H10···O5	2.04	3.015(9)	162.0
N16−H16···O5	2.04	3.030(8)	166.8
O1W−H1W···O6	1.847(8)	2.70(1)	179.6(9)

are less than 0.15 Å; all amide nitrogen atoms are thus almost in the plane, while the deviation from the above plane in the case of **1**−**F**$^-$ is 0.74 Å. There has been considerable discussion about the existence of any preferred coordination environment for halide anions, and a vast variety of geometries have been obtained for interactions with positively charged species.[29−31] For interactions with neutral ligands, a few results suggest tetrahedral geometry.[32,33] Conformations of ligand **1** offering fully tetrahedral arrangements of binding sites do not seem to be possible. In our results, however, such a tendency can be seen in the case of F$^-$ anion complexation.

The X-ray structure of the **1**−**AcO**$^-$**(TBA)** complex [obtained as (**1**)$_2$·(*n*Bu)$_4$NAcO, Figure 4] indicates that the

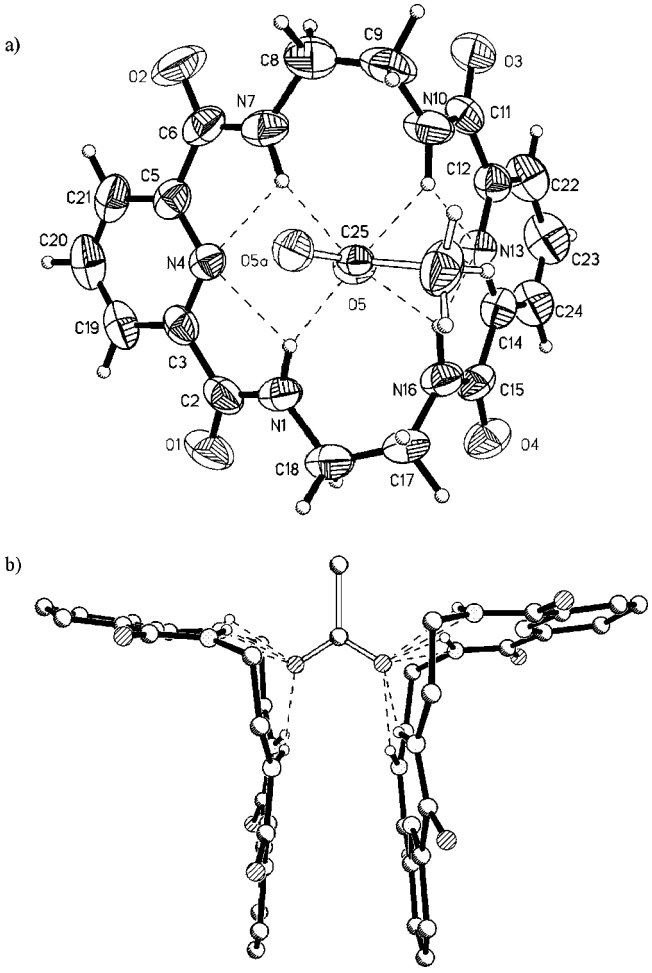


Figure 4. X-ray structure of **1**−**AcO**$^-$**(TBA)** complex (obtained as (**1**)$_2$·(*n*Bu)$_4$NAcO, counterions omitted for clarity): a) a view onto the mean plane of macrocycle; b) side view

solid complex has a binding stoichiometry (2:1) different from that in the solution state. Only one of the acetate oxygen atoms is bound to one macrocyclic cavity, using four hydrogen bonds. All four hydrogen bonds are of similar lengths. At first, we considered the chelate effect of binding both acetate oxygen atoms to one macrocyclic cavity as the reason for selectivity towards the AcO^- anion,[34] but the X-ray structure of **1−AcO⁻(TBA)** revealed that this is not the case. In order to confirm this observation, we obtained the crystalline complex with another counterion: Me_4N^+[**1−AcO⁻(TMA)**]. Figure 5 shows the X-ray structure of the **1−AcO⁻(TMA)** complex. The structure shows that binding here also involves only one of the acetate oxygen atoms to the macrocyclic cavity. The other one is engaged in hydrogen bonding to the water molecule.

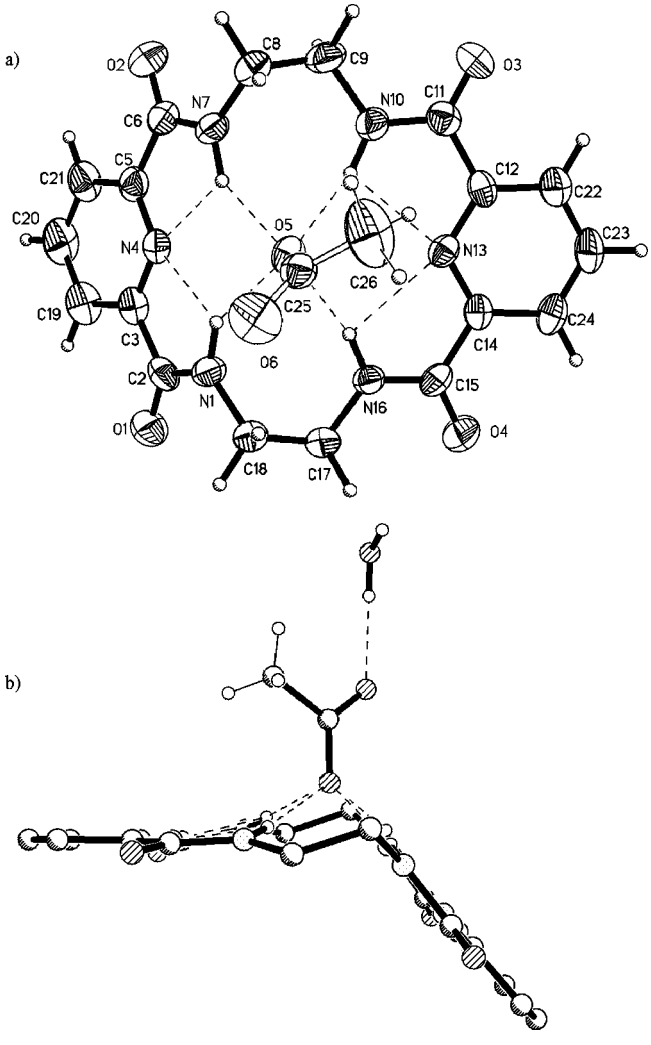


Figure 5. X-ray structure of **1−AcO⁻(TMA)** complex [obtained as **1**·$Me_4NAcO·2H_2O$, counterions and solvent molecules omitted for clarity): a) a view onto the mean plane of macroring; b) side view

Thus, we can assume that binding of AcO^- anion by ligand **1** indeed operates through only one of the carboxylate oxygen atoms. The 1:1 binding stoichiometry, observed in the solution, can be explained by the very low value of the 2:1 binding constant. This is probably due to unfavourable interactions between two receptor molecules, or interaction of the second carboxylate oxygen atom with traces of water present even in the dried [D_6]DMSO.

The selectivity of the receptor toward AcO^- and $H_2PO_4^-$ anions can be considered in terms of entropy factors and/or the binding geometry. Figure 6a shows experimental hydrogen-bond density around the AcO^- anion, generated by IsoStar.[35] The map shows four maxima around the carboxylate group, consistent with the directions of the carboxylate group's lone pairs. We compared this map with the crystal structure of complex **1−AcO⁻(TBA)**; the positions of the amide hydrogen atoms suit the maxima very well (Figure 6b). It is an interesting observation that tetralactam **1** binds the AcO^- anion using its *syn-anti* lone pairs, while another mode of binding, namely *syn-syn*, is usually postulated for urea-type receptors. Gandour[36] showed that *syn* lone pairs of carboxylate anions are $> 10^4$ times more basic than *anti* lone pairs; a carboxylate group *syn* lone pair is hence catalytically more active in biologically active systems than the *anti* lone pair.[37] On the other hand, it has also been reported that the stereoelectronic preferences for catalysis by carboxylate groups do not translate into stereoelectronic preferences for hydrogen bond formation.[38] From our data it is evident that the K_{ass} value observed for association of AcO^- anions with tetralactam **1** is not lower than that for interaction with monourea receptors.

Conformational Changes During Complexation

Even though the 18-membered macrocycle of **1** seems to be relatively rigid, due to four intramolecular hydrogen bonds, X-ray structural studies indicate that the ligand undergoes conformational changes upon complexation. In all cases, these changes involve the torsion angles of the aliphatic part. Thus, the flat *syn-syn* relationships of the two 2,6-dicarbamoylpyridine moieties and intramolecular hydrogen bonds are preserved, but their mutual arrangement is changed. The dihedral angle between the two pyridine rings ("bending") is 0° for the free ligand, 23° for **1−Cl⁻**, and 38° for **1−F⁻**. The bending is the greatest for **1−AcO⁻** complexes (95° for TBA and 48° for TMA counterion). Such conformational changes enable all amide hydrogen atoms to be directed towards the same side of the macrocycle, in contrast to the situation in the free ligand (cf. Figure 2c).

Electrospray Mass Spectrometry Studies

Since the introduction in 1988 of electrospray ionisation mass spectrometry (ESI MS) as a tool for investigation of biomolecules, this technique has also become successfully used for examination of noncovalent associations,[39,40] since the ionisation process is gentle enough to allow reasonable preservation of noncovalent interactions in the gas phase. Although the electrospray ionisation process involves a great change in the bulk solution environment, because of solvent evaporation, some features of the original equilibrium of the solution may be retained in the types and distribution of species in the gas phase. This direct method,

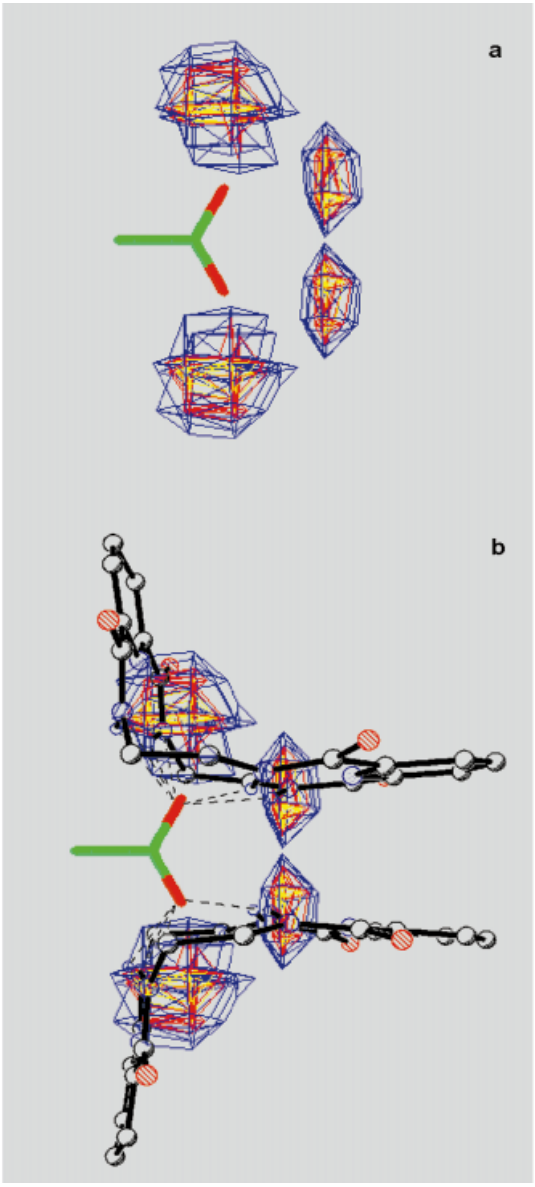


Figure 6. a) IsoStar presentation of hydrogen bond density (positions of hydrogen atoms) around the AcO^- anion; b) superposition of the map and the **1**−**AcO⁻(TBA)** complex

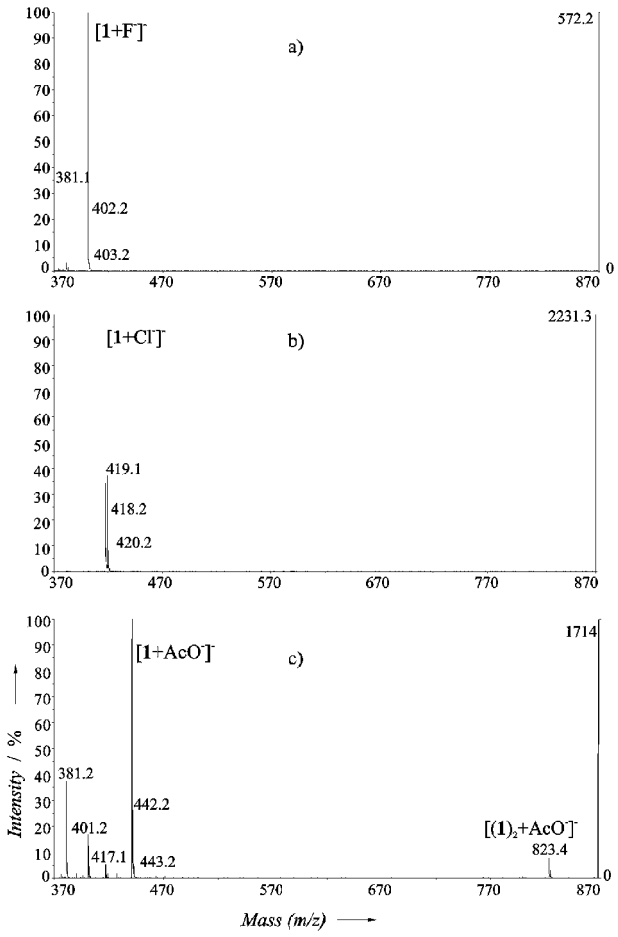


Figure 7. ESI MS spectra (negative ion mode, declustering potential 40 V) of 1:1 mixtures of **1** (3.3×10^{-3} M in $CHCl_3$) and: a) $(n\text{Bu})_4\text{NF}$; b) $(n\text{Bu})_4\text{NCl}$; c) $(n\text{Bu})_4\text{NAcO}$

based on molecular mass determination, seems to be particularly suited to confirmation of stoichiometries of complexes. Applications of ESI MS for determination of supramolecular complexes have so far involved highly stable metal complexes[39] or hydrogen-bonded assemblies encapsulating organic cations,[41−43] but have not yet been applied to hydrogen-bonded anion complexes of neutral ligands. We therefore decided to examine electrospray mass spectrometry as a potential tool for detection of anion complexes. Molecular peaks of anion complexes can easily be observed in the negative ion ESI MS (Figure 7). The main peak in each spectrum corresponds to the formation of a 1:1 anion complex (m/z = 401 for $[\mathbf{1} + F^-]^-$, 417 for $[\mathbf{1} + Cl^-]^-$, and 441 for $[\mathbf{1} + AcO^-]^-$). However, only in the case of **1** + AcO^- was an additional peak associated with a 2:1 complex ($[(\mathbf{1})_2 + AcO^-]^-$ at m/z = 832) also observed (intensity ca. 10% of that of the 1:1 complex). Thus, the ESI MS method confirms the predominant formation of 1:1 complexes in the solution for all anions studied. It also shows the existence of a 2:1 complex of **1** with AcO^-, but as a minor species. The results are in agreement with our conclusions from X-ray studies, as well as those based on NMR experiments.

Conclusion

In summary, we have found that the simple neutral 18-membered tetralactam **1** exhibits pronounced affinity towards anions. The size of the cavity seems to determine binding selectivity: the Cl^- anion is too bulky to be included in the cavity, whereas the smaller F^- anion fits well. The best binding, however, was observed for the AcO^- anion. X-ray structures of both obtained AcO^- complexes of **1** show that four hydrogen bonds are formed with only one of the carboxylate oxygen atoms, but that the binding geometry is very favourable. Additionally, we have shown that ESI MS offers a rapid and elegant method to evaluate the major noncovalent species present in solution. The com-

bination of all these methods gives a more complete picture of the structures of anion complexes and complexation phenomena.

Experimental Section

3,6,14,17,23,24-Hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8(24),9,11,19,21-hexaene-2,7,13,18-tetraone (1):[44] Dimethyl 2,6-pyridinedicarboxylate (200 mg, 1.02 mmol) and 1,2-diaminoethane (61 mg, 1.02 mmol) were mixed in methanol (10 mL) and left for 7 d, after which the precipitated crystals were collected, washed with methanol and dried overnight under vacuum at 70 °C. Compound **1** was obtained as **1**·2MeOH (116 mg, 51%). Additional drying was required to remove solvent. M.p. 315−325 °C (subl.; ref.[44] m.p. 318−325 °C). − ^{1}H NMR (200 mhz, [D$_6$]DMSO): δ = 9.45 (br. s, 4 H), 8.20 (*m*, 6 H), 3.60 (br. s, 8 H), 3.15 (*s*, MeOH). − ^{13}C NMR (50 mhz, [D$_6$]DMSO): δ = 163.1, 148.7, 139.6, 124.3, 39.1. − IR (KBr): $\tilde{\nu}_{max}$ = 3374, 3272, 2940, 1666, 1540, 1452, 1314, 1338, 1175, 1086, 1015, 915, 849, 746, 685, 647 cm^{-1}. − HR MS (LSIMS): *m*/*z* calcd. for $C_{18}H_{19}N_6O_4$ [M + H]$^+$ 383.1468; found 383.1468. − $C_{20}H_{26}N_6O_4$ (**1**·2MeOH): calcd. C 53.8, H 5.9, N 18.8; found C 53.6, H 6.0, N 18.8.

***N*,*N*′-Bis[2-(acetylamino)ethyl]pyridine-2,6-dicarboxamide (2):** Dimethyl 2,6-pyridinedicarboxylate (1.02 mmol; 200 mg) and an excess of 1,2-diaminoethane (5.13 mmol; 308 mg) were mixed in methanol (10 mL) and stirred for 2 h. The solvents were removed by coevaporation several times with CH_2Cl_2 and dried under vacuum, in order to remove excess 1,2-diaminoethane. The solid (hygroscopic) was dissolved in CH_2Cl_2 (10 mL) and 400 mg (5.80 mmol) of pyridine was added. The mixture was cooled to 0 °C and acetic anhydride (2.2 mmol; 0.16 mL) was added dropwise whilst stirring. Stirring was continued for 2 h at room temperature. The solution was concentrated and purified by column chromatography (CH_2Cl_2/MeOH, 85:15) to afford a white powder, which was crystallised from *i*PrOH/Et$_2$O (317 mg; 94%). M.p. 202−206 °C. − ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 9.45 (br. s, 2 H), 8.19 (m, 5 H), 3.4-3.2 (m, 8 H), 1.84 (s, 6 H). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 170.1, 163.2, 148.5, 139.5, 124.0, 39.3, 38.2, 22.6. − IR (KBr): $\tilde{\nu}_{max}$ = 3430, 3313, 3105, 2939, 2856, 1643, 1569, 1541, 1438, 1373, 1304, 1230, 1177, 1117, 739, 676, 64, 609 cm^{-1}. − HR MS (LSIMS): *m*/*z* calcd. for $C_{15}H_{22}N_5O_4$ [M + H]$^+$ 336.1672; found 336.1682. − $C_{15}H_{23}N_5O_5$ (**2**·H$_2$O): calcd. C 51.0, H 6.6, N 19.8; found C 51.1, H 6.8, N 19.8.

NMR Titrations: (*n*Bu)$_4$NX salts (X = F, Cl, AcO, H$_2$PO$_4$) were purchased from Aldrich, (*n*Bu)$_4$N(*p*-O$_2$NPhO$^-$) was prepared according to a literature procedure.[45] Titrations were run at ca. 7 mM concentrations, with aliquots of a 0.2 M (*n*Bu)$_4$NX salt solution added. [D$_6$]DMSO was dried over molecular sieves (4 Å), salts were dried overnight (70 °C) under vacuum prior to the experiments. All solutions during experiments were stored under argon. Usually, 20 data points were recorded. The CurveExpert computer program

Table 8. Crystal data and structure refinement for **1**, **1**−**Cl**$^-$, **1**−**F**$^-$, **1**−**AcO**$^-$**(TBA)** and **1**−**AcO**$^-$**(TMA)**

Identification code	**1**	**1**−**Cl**$^-$	**1**−**F**$^-$	**1**−**AcO**$^-$**(TBA)**	**1**−**AcO**$^-$**(TMA)**
Empirical formula	$C_{20}H_{26}N_6O_6$	$C_{44.45}H_{44.90}Cl_{5.90}N_6O_5P$	$C_{51}H_{49}F_1N_9O_7P$	$C_{54}H_{75}N_{13}O_{10}$	$C_{24}H_{37}N_7O_8$
Molecular mass	446.46	983.29	949.96	1066.27	551.61
T [K]	293(2)	293(2)	293(2)	293(2)	293(2)
λ [Å]	1.54178	1.54178	1.54178	1.54178	1.54178
Crystal system	monoclinic	triclinic	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/a$	$P\bar{1}$	$P2_1/n$	*Pbcn*	$P2_1/n$
a [Å]	8.7872(4)	12.653(3)	15.578(3)	19.115(1),	13.084(2)
b [Å]	13.3584(6)	14.221(3)	14.332(3)	17.010(2),	10.800(2)
c [Å]	9.2462(4)	14.393(3)	21.548(4)	17.675(1)	20.163(4)
α [°]	90.0	102.15(3)	90	90	90
β [°]	98.120(4)	100.16(3)	103.46(3)	90	91.665(13)
γ [°]	90.0	103.54(3)	90	90	90
V [Å^3]	1074.46(8)	2391.1(9)	4678.7(2)	5747.2(9)	2848.0(9)
Z	2	2	4	4	4
$\rho_{calcd.}$ [Mg·m^{-3}]	1.380	1.366	1.349	1.232	1.286
μ [mm^{-1}]	0.871	3.955	1.084	0.709	0.818
F(000)	472	1018	1992	2280	1176
θ_{max} [°]	73.84	73.15	74.15	64.86	64.73
Index ranges	$0 \le h \le 10$, $16 \le k \le 0$, $11 \le l \le 11$	$-15 \le h \le 15$, $-17 \le k \le 17$, $-17 \le l \le 0$	$-19 \le h \le 18$, $-17 \le k \le 0$, $0 \le l \le 26$	$-21 \le h \le 0$, $-19 \le k \le 0$, $0 \le l \le 20$	$0 \le h \le 15$, $-12 \le k \le 0$, $-23 \le l \le 22$
Reflections collected/unique [R_{int}]	1898/1773 [R_{int} = 0.0202]	6001/5756 [R_{int} = 0.0217]	5215/5063 [R_{int} = 0.0177]	2091/2064 [R_{int} = 0.00]	2441/2342 [R_{int} = 0.0388]
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restr./param.	1773/0/169	5756/11/631	5063/2/650	2064/37/327	2342/4/358
GooF	0.758	1.073	0.915	1.070	1.096
R indices [$I > 2\sigma(I)$]	*R*1 = 0.0391 *w*R2 = 0.1260	*R*1 = 0.0689 *w*R2 = 0.1704	*R*1 = 0.0561 *w*R2 = 0.1474	*R*1 = 0.0755 *w*R2 = 0.2010	*R*1 = 0.0967 *w*R2 = 0.2582
R indices [all data]	*R*1 = 0.0402, *w*R2 = 0.1280	*R*1 = 0.0725 *w*R2 = 0.1750	*R*1 = 0.0601 *w*R2 = 0.1529	*R*1 = 0.0799 *w*R2 = 0.2066	*R*1 = 0.1172 *w*R2 = 0.2823
$\Delta\rho_{max}/\Delta\rho_{min.}$ [e·Å^{-3}]	0.165/−0.201	0.341/−0.413	0.201/−0.220	0. 409/−0.241	0.242/−0.348
Decay (%)	0%	6.7%	17.1%	0%	0%

was used for curve fitting. For 1:1 complexation the following Equation was used, where $\Delta\delta$ = chemical shift change at given point (ppm), $[L]_0$ = total concentration of ligand (mol dm^{-3}), $[G]_0$ = total concentration of guest at the given point (mol dm^{-3}), K_{ass} = association constant (parameter, mol^{-1} dm^3), $\Delta\delta_{max}$ = maximum chemical shift change (parameter, ppm).

$$\Delta\delta = \frac{([L]_0 + [G]_0 + \frac{1}{K_{ass}} - (\sqrt{(([L]_0 + [G]_0 + \frac{1}{K_{ass}})^2 - 4[G]_0[L]_0)))\Delta\delta_{max}}{2[L]_0}$$

In the case of simultaneous formation of 1:1 and 2:1 complexes, data fitting was carried out using Marquardt's method.[46] Equilibrium concentrations were calculated using the EQUIL procedure.[47] NMR shifts corresponding to host−guest binding for higher complexes were evaluated according to the method described in ref.[48] The results indicate that it is impossible to obtain reasonable fitting parameters for the model if assuming the existence of 1:1 and 2:1 complexes.

ESI Mass Spectrometry: ESI-TOF measurements were performed with a MARINER apparatus (PerSeptive Biosystems Inc.). Samples were prepared by addition of 1 equiv. of **1** to a solution of the $(n\text{Bu})_4\text{NX}$ salt in $CHCl_3$ (c = 3 mM).

X-ray Crystallographic Study: Crystal data and details of the crystal structure determinations are presented in Table 8. The intensity data were collected using an Enraf−Nonius CAD-4 diffractometer, using the ω/2θ mode. Data were corrected for decay, Lorentz and polarisation effects. The program used to solve structures was SHELXS86.[49] The program used to refine the structures and to prepare materials for publication was SHELXL97.[50] Carbon atoms in the $(n\text{Bu})_4\text{N}^+$ ion in **1−AcO⁻(TBA)** complex were refined isotropically, due to disorder and poor data/parameter ratio. All remaining non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were calculated and refined as riding model, except for the amide and methanol H atoms in **1** and **1−Cl⁻**, which were located from Fourier map and refined freely. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-160526 (**1**), -160527 (**1−Cl⁻**), -160528 (**1−F⁻**), -160529 [**1−AcO⁻(TBA)**] and -160530 [**1−AcO⁻(TMA)**]. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was supported by the State Committee for Scientific Research (Project 3T09A 127 15) and by the Polish Science Foundation. We would like to thank Dr. Marcin Palys for providing data-fitting procedures for simultaneous formation of 1:1 and 2:1 complexes.

[1] P. D. Beer, P. A. Gale, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 487−516.
[2] P. A. Gale, *Coord. Chem. Rev.* **2000**, *199*, 181−233.
[3] T. S. Snowden, E. V. Anslyn, *Curr. Opin. Chem. Biol.* **1999**, *3*, 740−746.
[4] V. Kral, O. Rusin, T. Shishkanova, R. Volf, P. Matejka, K. Volka, *Chem. Listy* **1999**, *93*, 546−553.
[5] P. D. Beer, *Acc. Chem. Res.* **1998**, *31*, 71−80.
[6] M. M. G. Antonisse, D. N. Reinhoudt, *Chem. Commun.* **1998**, 443.
[7] F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609−1646.
[8] C. F. Mason, *Biology of Freshwater Pollution*, 2nd ed., Longman, Harlow, **1991**.
[9] V. Kral, J. L. Sessler, *Tetrahedron* **1995**, *51*, 539−554.
[10] P. Bühlmann, E. Pretsch, E. Bakker, *Chem. Rev.* **1998**, *98*, 1593−1687.
[11] K. Kavallieratos, R. H. Crabtree, *Chem. Commun.* **1999**, 2109−2110.
[12] G. M. Hübner, J. Gläser, C. Seel, F. Vögtle, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 383−386; *Angew. Chem.* **1999**, *111*, 395−398.
[13] T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080.
[14] T. Hayashita, T. Ondodera, R. Kato, S. Nishizawa, N. Teramae, *Chem. Commun.* **2000**, 755−756.
[15] A. P. Bisson, V. M. Lynch, M.-K. C. Monahan, E. V. Anslyn, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2340−2342; *Angew. Chem.* **1997**, *109*, 2435−2437.
[16] Y. H. Kim, J. Calabrese, C. M. McEwen, *J. Am. Chem. Soc.* **1996**, *118*, 1545−1546.
[17] P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141.
[18] B. Dietrich, J. -M. Lehn, J. -P. Sauvage, *Tetrahedron Lett.* **1969**, *10*, 2885−2888.
[19] D. T. Gryko, P. Piatek, A. Pecak, M. Palys, J. Jurczak, *Tetrahedron* **1998**, *54*, 7505−7516.
[20] K. Kavallieratos, C. M. Bertao, R. H. Crabtree, *J. Org. Chem.* **1999**, *64*, 1675−1683.
[21] The example of using $\Delta G°_{0,1}$ for interpretation of selectivity results: P. Bühlmann, S. Nishizawa, K. P. Xiao, Y. Umezawa, *Tetrahedron* **1997**, *53*, 1647−1654.
[22] C. A. Hunter, D. A. Purvis, *Angew. Chem., Int. Ed. Engl.* **1992**, *104*, 792−795; *Angew. Chem.* **1992**, 779.
[23] Y. Hamuro, J. Geibs, A. D. Hamilton, *J. Am. Chem. Soc.* **1996**, *118*, 7529−7541.
[24] Formation of M^{2+} complexes can cause flipping this conformation: A. Szumna, D. T. Gryko, J. Jurczak, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1553−1558.
[25] D. T. Gryko, P. Piatek, A. Pecak, W. Kozminski, J. Jurczak, *Supramol. Chem.* **2000**, 229−235.
[26] R. S. Rowland, R. Taylor, *J. Phys. Chem.* **1996**, *100*, 7384−7391.
[27] T. Steiner, *Acta Crystallogr., Sect. B* **1998**, *54*, 465−463.
[28] K. S. Kim, C. Cui, S. J. Cho, *J. Phys. Chem. B* **1998**, *102*, 461−463.
[29] C. A. Ilioudis, K. S. B. Hancock, D. G. Georganopoulou, J. W. Steed, *New. J. Chem.* **2000**, *24*, 787−798; and references therein.
[30] B. Dietrich, J. Guilhem, J.-M. Lehn, C. Pascard, E. Sonveaux, *Helv. Chim. Acta* **1984**, *67*, 91.
[31] B. Dietrich, B. Dilworth, J.-M. Lehn, J.-P. Souchez, M. Cesario, J. Guilhem, C. Pascard, *Helv. Chim. Acta* **1996**, *79*, 569−587.
[32] For interaction with urea-type molecules: N. A. Mc.Donald, E. M. Duffy, W. L. Jorgensen, *J. Am. Chem. Soc.* **1998**, *120*, 5104−5111.
[33] Tetrahedral arrangement of the complexation sites is also postulated as a reason of the high K_{ass} value with F^-: A. Andrievsky, F. Ahuis, J. L. Sessler, F. Vögtle, D. Gudat, M. Moini, *J. Am. Chem. Soc.* **1998**, *120*, 9712−9713.
[34] Comparing K_{ass} with available literature data we found that it has a similar magnitude as for calix-4-arene substituted with two urea groups (the authors postulate binding using four hydrogen atoms to both caboxylate oxygen atoms and additional C−H···π interactions): A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro, D. N. Reinhoudt, *Gazz. Chim. Ital.* **1996**, *126*, 99−106.

[35] I. J. Bruno, J. C. Cole, J. P. M. Lommerse, R. S. Rowland, R. Taylor, M. L. Verdonk, *J. Computer Aided Mol. Des.* **1997**, *11*, 525−537.
[36] R. D. Gandour, *Biorg. Chem.* **1981**, *10*, 169−176.
[37] A. Fersht, *Enzyme Structure and Mechanism*, 2nd ed., W. H. Freeman, New York, **1985**, chapter 15.
[38] C. H. Görbitz, M. C. Etter, J. Am. Chem. Soc. 1992, *1* **14**, 627−631.
[39] M. Przybylski, M. O. Glocker, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 806−826; *Angew. Chem.* **1996**, *108*, 878−899.
[40] J. S. Brodbelt, *Int. J. Mass Specrom.* **2000**, *200*, 57−69 and references therein.
[41] C. A. Schalley, T. Martin, U. Obst, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 2133−2138.
[42] C. A. Schalley, R. K. Castellano, M. S. Brody, D. M. Rudkevich, G. Siuzdak, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4568−4579.
[43] C. A. Schalley, J. M. Rivera, T. Martin, J. Santamaria, G. Siuzdak, J. Rebek, Jr., *Eur. J. Org. Chem.* **1999**, 1325−1331.
[44] E. Weber, F. Vögtle, *Justus Liebigs Ann. Chem.* **1976**, 891−915.
[45] P. A. Gale, L. J. Twyman, C. I. Handlin, J. L. Sessler, *Chem. Commun.* **1999**, 1851−1852.
[46] W. H. Press, S. A. Teukolsky, W. T. Vetterling, B. P. Flannery, *Numerical Recipes in C*, Cambridge University Press, Cambridge, **1992**.
[47] M. Bos, H. Q. J. Meershoek, *Anal. Chim. Acta* **1972**, *61*, 185−199
[48] A. P. Bisson, C. A. Hunter, J. C. Morales, K. Young, *Chem. Eur. J.* **1998**, 845−851.
[49] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
[50] G. M. Sheldrick, *SHELXL97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, **1997**.

Received June 6, 2001
[O01271]