Unusual Encapsulation of Two Anions in the Cavity of Neutral Macrocyclic Octalactam

Preliminary Communication

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A new neutral anion receptor – macrocyclic octalactam **2**, possessing a large 36-membered ring, was synthesized, and its unusual property of encapsulation of two Cl^- ions and two H_2O molecules in the cavity was confirmed by X-ray crystallography (see *Figure*). The octalactam, consisting of four 2,6-dicarbamoylpyridine and four ethylene moieties, exhibits a symmetrical, fully expanded conformation in the complex $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-}$ (obtained as $\mathbf{2}\cdot 2\ Bu_4NCl\cdot 4\ H_2O\cdot 2\ CH_2Cl_2$). Inside the cavity, encapsulated species – two Cl^- ions and two H_2O molecules – are connected to each other by H-bonds. This kind of complex-in-complex system is formed by means of twenty intra-ring H-bonds and additionally four from the 'outside' H_2O molecules. Considering size and symmetry, it can be stated that the planar $(H_2O\cdot Cl^-)_2$ dimer fits well into the cavity of octalactam **2**. The ligand has an optimal arrangement of binding sites to form H-bonds to every corner of the dimer.

Introduction. – Anion recognition, as compared with cation binding, is a relatively new and less-explored area in the field of supramolecular chemistry [1]. First examples of anion receptors comprised multicharged polyammonium hosts [2], and this research direction is still being explored [3]. Despite the strong binding by charged hosts, there are disadvantages in the use of cations as anion-complexing agents: first, the nondirectional nature of electrostatic forces, and second, the competition for binding by the existing counter anions. Therefore, neutral receptors, which usually act by more directional interactions, like H-bonding or various *Lewis* acid/base interactions, offer wider possibilities for selectivity. Also, for some applications, like membrane transport, the neutral hosts exhibit much better properties because of their more lipophilic nature, as found in naturally occurring systems. Hence, synthetic neutral receptors for anion guests are of great interest. Among receptors that employ H-bond interactions for anion recognition, examples involve amides [4], ureas [5], alcohols [6], and calix[4]pyrroles [7]. The design of macrocyclic receptors for this purpose is challenging, since anions are relatively large and, therefore, require receptors of considerably greater size than cations (*e.g.*, one of the smallest anions, F^-, is comparable in ionic radius to K^+).

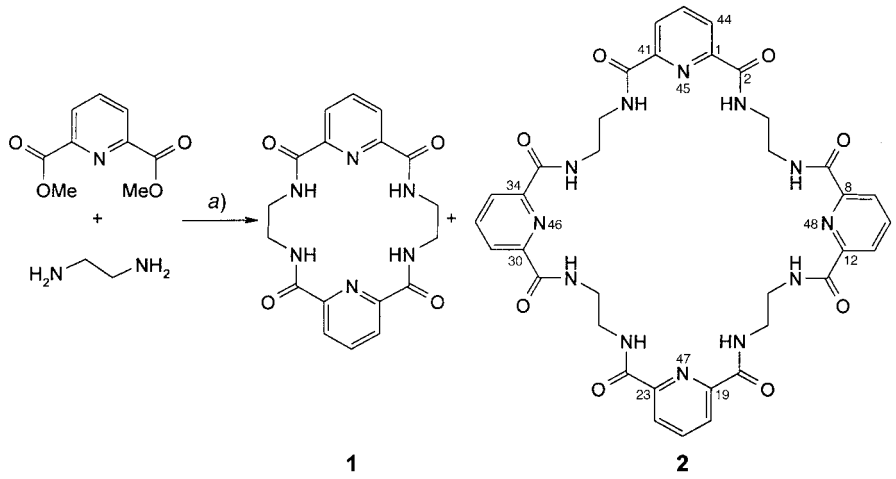
Currently, work in our group is aimed at designing synthetic amide-type neutral anions hosts and searching for more efficient arrangements of H-bond donor sites for this purpose. The relationship between host-guest complementarity (size, spatial arrangement of binding sites) and selectivity is well-established for cation receptors [8] but is much less well-defined for anion guests, mainly due to the limited amount of

structural information that is available so far. Another reason could be the less-pronounced trend of anions to be in a preferred coordination environment, especially for the H-bond interaction type. For some anions, like those with well-defined electron lone pairs, the directionality of interaction with H-bond donors has already been documented [9]; for others, like halides, the discussion on the preferred coordination environment is still ongoing [10].

Here, we present a new host, the neutral macrocyclic octalactam **2**, which has unusual inclusion properties toward Cl^- ions, and we discuss the interactions in terms of complementarity (size, symmetry) and host preorganization.

Results and Discussion. – The macrocyclization reaction of dimethyl pyridine-2,6-dicarboxylate and ethane-1,2-diamine gave the tetralactam **1** [11][12]. We have previously reported the anion-binding properties of this ligand [11]. Modification of the reaction conditions by the addition of 5 equiv. of tetrabutylammonium hexafluorophosphate gave **1** (52%) as a major product, besides octalactam **2** (4%) as a minor one (*Scheme*).

Scheme



a) $c = 0.1$M, MeOH, 5 equiv. of $Bu_4N(PF_6)$, 14 days.

We were interested in the interaction of this huge macrocycle **2** with anions. Upon cocrystallization of octalactam **2** with Bu_4NCl, we obtained a complex $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-}$ of the composition $\mathbf{2} \cdot 2\,Bu_4NCl \cdot 4\,H_2O \cdot 2\,CH_2Cl_2$. Unexpectedly, X-ray crystallography showed that octalactam **2** has an unusual ability to bind two Cl^- ions and two H_2O molecules in the cavity (see *Fig.*). Two additional H_2O molecules are positioned outside the cavity.

Binding of two ions of the same charge in a limited space, as in the cavity, is energetically very unfavorable due to repulsive electrostatic forces. Obviously, the exceptional situation exists for anions acting as H-bond donors and acceptors simultaneously (*e.g.* $H_2PO_4^-$, HSO_4^-), which can even show a positive cooperativity effect in binding two anions [13]. However, for anions without H-bond-donating ability, examples that exhibit this phenomenon are rare. The encapsulation of two nitrate ions

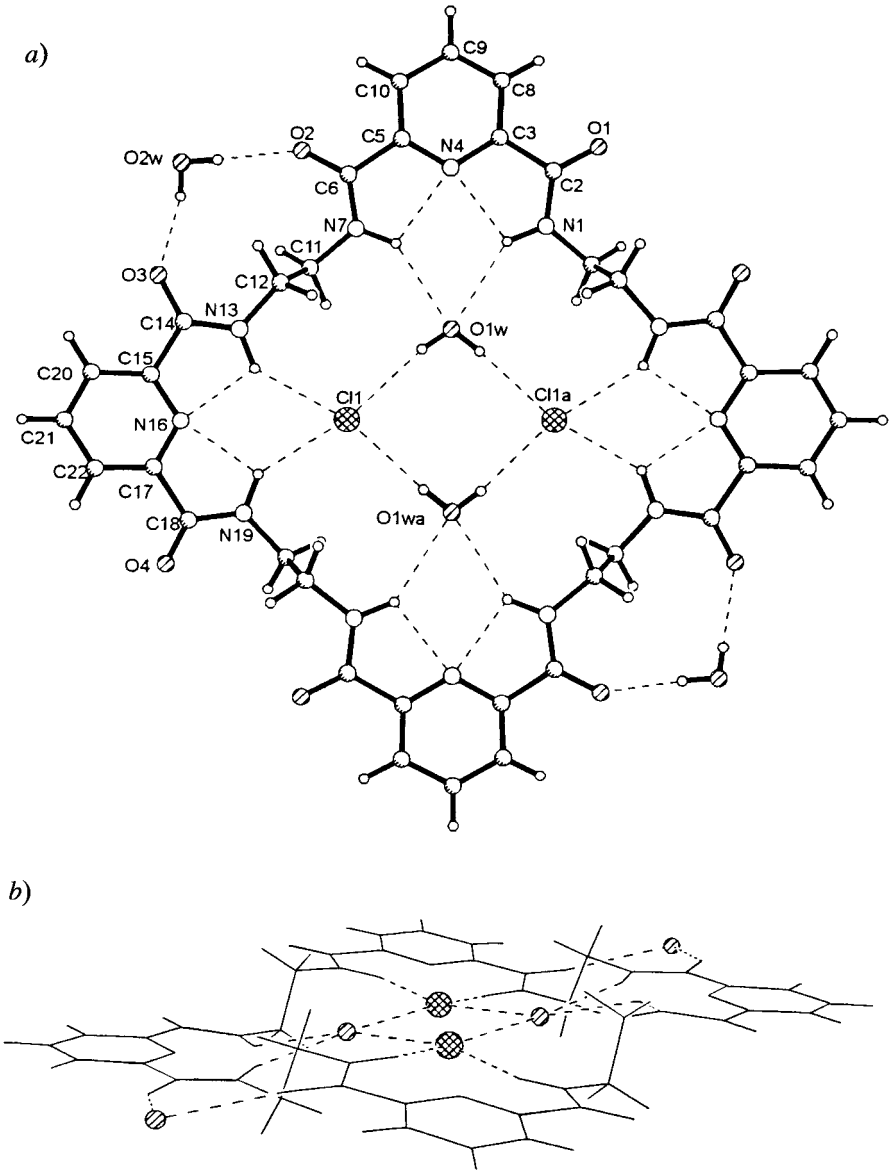


Figure. a) *X-Ray structure of the* $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-} \cdot 2\ H_2O$ *complex, obtained as* $\mathbf{2} \cdot 2\ Bu_4NCl \cdot 4\ H_2O \cdot 2\ CH_2Cl_2$. b) *Stair-like conformation of* $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-} \cdot 2\ H_2O$. Solvent molecules CH_2Cl_2/Bu_4N^+ counterions are omitted for clarity. Arbitrary numbering. Operator for the symmetry related part of molecule: $-x+1, -y+1, -z$.

in the cavity has been observed in the case of multicharged bicyclic polyammonium receptors [14]. For neutral receptors, such an encapsulation is even more difficult to realize, because ion-dipole interactions (*e.g.* H-bonds) are generally weaker than ion-ion electrostatic interactions. Thus, numerous favorable interactions are required to

overcome electrostatic repulsion. To the best of our knowledge, the phenomenon of binding two anions without H-bonding donating ability by neutral hosts has been observed only for a macrobicyclic cyclophane host as reported by *Anslyn* and co-workers [15]. Nevertheless, in that case, two Cl^- ions reside in different monocyclic cavities. The distance between the Cl^- ions is 5.52 Å, and they are separated by H_2O and MeCN molecules.

In our case, the distance between the two complexed Cl^- ions is much smaller (4.88 Å), and these anions reside in the same monocyclic cavity. Two H_2O molecules additionally bridge the two bound Cl^- ions to each other, forming a kind of complex-in-complex system. The stability of this arrangement is probably due to the presence of these organizing H_2O molecules. Searching the CSD database [16] for such chloride-water clusters, we found that a planar, pseudo-square $(H_2O\text{-}Cl^-)_2$ dimer is a very common motif in the solid state [17]. The average geometry of this cluster (atom-atom distances) surveyed from CSD is very similar to that observed in the $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-}$ complex, which means that the dimer is not significantly altered during encapsulation within the macrocyclic ligand. It is also worth mentioning that the ligand has an optimal arrangement of binding sites to form H-bonds to every corner of the dimer. Thus, considering size and symmetry, it can be stated that the $(H_2O\text{-}Cl^-)_2$ dimer fits well in the 36-membered ring of **2**.

The whole system is stabilized by twenty intra-ring H-bonds and additionally by four H-bonds from the 'outside' H_2O molecules. The macrocycle has a symmetrical, fully expanded, stair-like conformation (*Fig. 1, b*). Eight of the intra-ring H-bonds are intramolecular NH(amide)$\cdots$N(py) interactions, which are known to stabilize a flat *syn-syn* conformation for compounds containing 2,6-dicarbamoylpyridine moieties [18][19]. We can suppose that, as a result, the macrocycle is made rigid and has amide H-atoms arranged in a convergent manner, and is, thereby, preorganized for anion binding. Contrarily, acyclic [18] and macrocyclic [20] amides containing isophthaloyl moieties are known to prefer a *syn-anti* conformation and thus a divergent arrangement of the NH(amide). However, the presence of the pyridine lone pair in such an arrangement is considered unfavorable, and consequently, is thought to be the reason for a significant decrease in affinity toward anions of the receptors containing pyridine, as compared with their isophthaloyl analogues [4c]. One can expect that this unfavorable interaction can cause elongation of H-bonds to Cl^- or a rise of the anion out of the pyridine-ring mean plane. However, this seems not to be the case, or is not pronounced, at least in the structure of complex $[(Cl)_2(\mathbf{2})(H_2O)_2]^{2-}$. The anion lies in the plane of the pyridine ring and is linked by short H-bonds [21].

Conclusions. – It is clear that the 36-membered ring of octalactam **2**, considering size and symmetry, is suitable for complexation of the planar $(H_2O\text{-}Cl^-)_2$ assembly by forming H-bonds to every corner of the dimer. It must be mentioned that the apparent disadvantage of the presence of the 2,6-dicarbamoylpyridine moiety as a building block of anion receptors, namely the presence of the pyridine lone pair which can cause repulsion of anions, may be very desirable since it forces amide H-atoms to be arranged in a convergent manner. This arrangement is the more important the bigger the macrocycle is, and probably is the reason why the huge macrocycle does not adopt a collapsed conformation.

Experimental Part

3,6,14,17,25,28,36,39,45,46,47,48-Dodecaazapentacyclo[39.3.1.1^{18,12}.1^{19,23}.1^{30,34}]octatetraconta-1(45),8,10,12(48),-19,21,23(47),30,32,34(46),41,43-dodecaene-2,7,13,18,24,29,35,40-octone (**2**). Dimethylpyridine-2,6-dicarboxylate (200 mg, 1.02 mmol), ethane-1,2-diamine (61 mg, 1.02 mmol), and $Bu_4N(PF_6)$ (2.3 g, 5 equiv.) were mixed in MeOH (10 ml) and left for 14 days. Then the precipitate (containing a mixture **1**/**2**) was collected. For anal. purposes, the mixture was chromatographed ($MeOH/CH_2Cl_2$ 95:5): 8 mg (*ca.* 4%) of **2**. Due to the limited solubility of **2**, no NMR spectra could be recorded. However, a satisfactory ESI-MS (neg.-ion mode) was obtained (*m*/*z* 799.3 (100, $[\mathbf{2}+Cl^-]^-$) see *Supplementary Material*[1]).

For the co-crystallization with Bu_4NCl, we used the sample enriched in **2**. The enriched sample was prepared from the precipitate containing a mixture of **1**/**2**. The mixture was treated with $MeOH/CH_2Cl_2$ 1:1 and then filtered. The filtrate was enriched in **2**. The procedure was repeated several times.

X-Ray Analysis of Tetrabutylammonium Bis[μ-(aqua-)κH:κH′)] [μ-3,6,14,17,25,28,36,45,46,47,48-dodecaazapentacyclo[39.3.1.1^{18,12}.1^{19,23}.1^{30,34}]octatetraconta-1(45),8,10,12(48),19,21,23(47),30,32,34(46),41,43-dodecaene-2,7,13,18,24,29,35,40-octone-κH^6,κH^{14}:κH^{28},κH^{36}]dichlorate(2−) Dichloromethane Water (2:1:2:2) ($(Bu_4N)_2[(Cl_2)(\mathbf{2})(H_2O)_2]\cdot 2\,CH_2Cl_2\cdot 2\,H_2O$). Crystals suitable for X-ray analysis were obtained from the sample enriched in **2**. The sample was solubilized in CH_2Cl_2 upon the addition of Bu_4NCl. The soln. was filtered, and a layer of hexane was carefully put on the top. Crystals appeared after 4 days on the former border of layers. Crystal size $0.21\times 0.35\times 0.56$ mm. X-Ray single-crystal diffraction was carried out on a *Enraf-Nonius-CAD4* diffractometer (CAD4-EXPRESS program [22]) with Cu-K_α radiation (1.54178 Å) and the $\omega/2\theta$ scanning mode. The standard reflections were measured every 50 min, and a maximum of 68% of decay was detected. Data were corrected for decay and *Lorentz* and polarization effects. The program used to solve the structure was SHELXS86 [23]. The program used to refine the structure and to prepare materials for publication was SHELXL97 [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 water H-atoms, which are located from *Fourier* map and refined with restrained O−H distances. Formula $C_{70}H_{120}Cl_6N_{14}O_{12}$ ($\mathbf{2}\cdot 2\,Bu_4NCl\cdot 4\,H_2O\cdot 2\,CH_2Cl_2$), M 1562.50; triclinic, $a=13.599(3)$, $b=13.627(3)$, $c=13.792(3)$ Å, $\alpha=100.95(3)$, $\beta=106.21(3)$, $\gamma=112.10(3)^\circ$, $V=2145.3(8)$ Å^{-3}, space group *P*-1, $Z=1$, $D_x=1.209$ Mg m^{-3}; $\mu(CuK_\alpha)=2.325$ mm^{-1}; 7595 reflections measured, 4863 observed ($I>2\sigma(I)$), 7251 unique reflections ($R_{int}=0.0293$), which were used in all calculations. Data/restraints/parameters 7251/6/478. Final $R=0.1306$, $wR=0.2389$ ($I>2\sigma(I)$), $s=1.245$. Residual electron density 0.379 and −0.402 e Å^{-3}. For the geometry of the H-bonds, see the *Table*.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-164973. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21 EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table. *Geometry of Hydrogen Bonds in the Crystal Structure of [(Cl)$_2$(**2**)(H$_2$O)]$^{2-}$.* For numbering, see the *Figure*.

D−H···A	*d* (H···A) [Å]	*d* (D···A) [Å]	(D−H···A) [°]
N(1)−H(1)···O(1W)	2.66	3.388(9)	143.9
N(7)−H(7)···O(1W)	2.57	3.308(9)	144.6
N(13)−H(13)···C(11)	2.60	3.328(5)	142.2
N(19)−H(19)···C(11)	2.63	3.369(6)	144.4
N(1)−H(1)···N(4)	2.26	2.668(7)	108.9
N(7)−H(7)···N(4)	2.27	2.660(7)	108.0
N(13)−H(13)···N(16)	2.25	2.661(7)	109.4
N(19)−H(19)···N(16)	2.25	2.672(7)	110.2
O(1W)−H(1WA)···C(11)	2.43(3)	3.267(7)	168(6)
O(1W)−H(1WB)···C(11)(1 − *x*, 1 − *y*, − *z*)	2.47(2)	3.306(7)	173(9)
O(2W)−H(2WB)···O(2)	2.10(7)	2.846(9)	147(12)
O(2W)−H(2WB)···O(3)	1.97(5)	2.796(10)	163(15)

[1]) Available upon request from the authors.

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