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Anion Recognition by Neutral Macrocyclic Amides

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Abstract: Although amides often serve as anchoring groups in natural and synthetic anion receptors, the structure–affinity relationship studies of amide-based macrocyclic receptors are still very limited. Therefore, we decided to investigate the influence of the size of the macroring on the strength and selectivity of anion binding by uncharged, amide-based receptors. With this aim, we synthesized a series of macrocyclic tetraamides derived from 2,6-pyridinedicarboxylic acid and aliphatic α,ω-diamines of different lengths. X-ray analysis shows that all ligands studied adopt expanded conformations in the solid state with the convergent arrangement of all four hydrogen-bond donors. ^{1}H NMR titrations in DMSO solution revealed a significant effect of the ring size on the stability constants of anion complexes; the 20-membered macrocyclic tetraamide **2** is a better anion receptor than its both 18- and 24-membered analogues. This effect cannot be interpreted exclusively in terms of matching between anion diameter and the size of macrocyclic cavity, because **2** forms the most stable complexes with all anions studied, irrespective of their sizes. However, geometric complementarity manifests in extraordinarily high affinity of **2** towards the chloride anion. The results obtained for solutions were interpreted in the light of solid-state structural studies. Taken together, these data suggest that anion binding by this family of macrocycles is governed by competitive interplay between their ability to adjust to a guest, requiring longer aliphatic spacers, and preorganization, calling for shorter spacers. The 20-membered receptor **2** is a good compromise between these factors and, therefore, it was selected as a promising leading structure for further development of anion receptors. Furthermore, the study of an open chain analogue of **2** revealed a substantial macrocyclic effect. X-ray structure of the acyclic model **14** suggests that this may be due to its ill-preorganized conformation, stabilized by two intramolecular hydrogen bonds.

Keywords: amides · anions · hydrogen bonds · macrocyclic ligands

Introduction

Non-covalent interactions with negatively charged species play an important role in many essential chemical and biological processes. Although first studies on anion coordination began as early as in the late 1960s,[1] the real explosion of interest in the field took place in the last decade.[2] This long "induction period" was due to the difficulties arising from inherent properties of anions such as low charge density, coordinative saturation and high solvation energies that make their interactions with receptors relatively weak and a solvent replacement difficult.

The design of anion receptors based solely on hydrogen bonding seems to be particularly challenging,[3] because a typical, single hydrogen-bonding interaction of non-activated amide or alcohol with anion is weak,[4] and the receptors must rely on the concerted action of many such donors. Nevertheless, the interest in this area is rapidly expanding, stimulated by its direct relevance to anion recognition by natural receptors[5] and by the perspective of achieving a good selectivity using interactions that strongly depend on the direction and distance. However, the directionality creates an additional challenge for the researchers, because it is necessary to arrange the hydrogen-bond donors in a very precise manner within a host structure in order to achieve a perfect complementarity to the guest. Despite this sensitivity to geometric constraints, the *systematic* studies on the structure–affinity relationship in uncharged anion receptors are scarce. Instead, a variety of very different structures was described.

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Although it is clear that a convergent displacement of many hydrogen bonds would be beneficial for strong anion binding, it is still far from being obvious how to arrange donors in an optimal, complementary fashion and what selectivity can be achieved this way. Moreover, the following difficulties have to be faced:

- majority of hydrogen-bond donating groups are also hydrogen bond acceptors, creating problems with competing intra- and intermolecular hydrogen bonds.
- majority of hydrogen bond donating groups are large and rigid, what makes it problematic to place them correctly and causes additional synthetic problems.

Nevertheless, a continuous progress in the construction of neutral, hydrogen-bonding receptors is taking place, which is reflected, for example, in the growing popularity of strongly competitive solvents used to evaluate anion binding: DMSO became popular and there were also precedents of significant binding in protic media such as DMSO/water mixtures,[6] methanol[7] and even water.[8] Examples of natural receptors[9] that strongly bind phosphate or sulfate anions in water displaying at the same time excellent selectivity indicate that there is still much room for improvement. Amide groups play an important role in anion binding by these receptors and consequently the study of amide-based receptors appears particularly interesting. Therefore, we focused our attention on macrocyclic amides and resolved to investigate the influence of their structure on the affinity towards anions.

2,6-Pyridinediamides are well known for their strong preference for *syn–syn* conformation of both amide NHs, stemming from hydrogen bonding with the pyridine nitrogen atom and lone pair repulsion in alternative conformations (Figure 1).[10,11] As a result, the whole 2,6-bis(carbamoyl)pyridine fragment is rigid, planar, exhibits a well-defined U-shape and displays two hydrogen bond donating groups in a convergent manner.

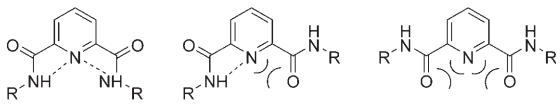


Figure 1.

It is therefore an attractive building block for the construction of supramolecular architectures and was frequently used, for example, to control the three-dimensional folding of molecular strands,[12–14] to induce a turn in the polypeptide chain,[15] in the construction of rotaxanes,[16] catenanes,[17] macrocyclic receptors,[10,18–20] self-assembled macrocyclic boxes,[21] and conformationally-restricted dendrons.[22] Crabtree and co-workers,[23,24] showed that even very simple 2,6-pyridinediamides bound anions strongly and selectively (although in dichloromethane, a particularly undemanding solvent). This discovery encouraged the others to utilize the 2,6-bis(carbamoyl)pyridine unit as an anion binding site for the construction of acyclic fluorescent,[25,26] luminescent,[27] and chromogenic[28] anion sensors. Macrocyclic,[29–32] and macrobicyclic,,[33–36] anion receptors having two and three such units were also described.

Our effort to develop efficient anion receptors began with the synthesis of 18-membered macrocyclic tetraamide **1** (Figure 2).[37] Excellent anion-binding properties of this prototype receptor prompted us to study the influence of the size of macrocyclic tetraamide on its anion binding properties. Therefore, we decided to study a series of receptors consisting of two 2,6-bis(carbamoyl)pyridine moieties linked with aliphatic chains of different lengths (Figure 2). Here we present a full account[38] on the structure and anion binding properties of these receptors.

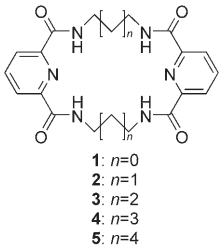
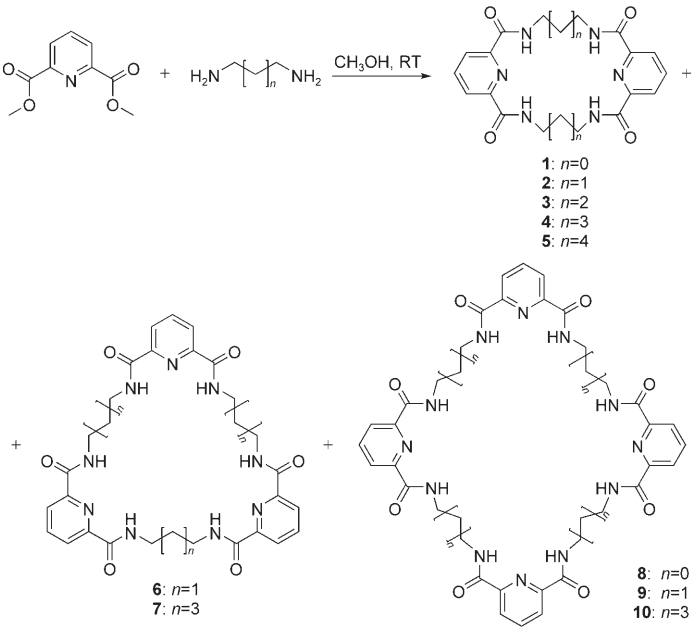


Figure 2.

Results and Discussion

Synthesis of macrocycles: To synthesize the model receptors, the method of macrocyclization consisting in the reaction of α,ω-diamines with α,ω-dicarboxylates was chosen. The scope and limitations of this method were thoroughly studied in our laboratories.[39] The method allows to obtain macrocyclic diamides via the one-to-one ([1+1]) reaction of α,ω-diamine with methyl dicarboxylate in methanol. The yields were particularly high when both the amine and ester components had oxygen or nitrogen atoms β to the reacting groups, like is for example in amino ethers. The method was therefore ideally suited for the synthesis of diaza crowns, an important class of cation receptors. Attempts to use this method for the synthesis of anion receptors required moving beyond its scope: the macrocyclic tetraamides result from a four-component [2+2] reaction, instead of [1+1] and are derived from purely aliphatic amines instead of amino ethers. It was therefore not surprising that the yields were low, ranging around 10% (in case of **3**, **5** and larger tetraamides derived from the amines with an even number of carbon atoms).[40] However, the desired products are usually less soluble than oligomeric by-products and precipitate from the reaction mixture in an almost pure form. This allowed us for a very simple preparation of these tetraamides: it is sufficient to dissolve an equimolar mixture of the suitable amine and dimethyl 2,6-pyridinedicarboxylate in methanol, leave it at ambient temperature for one week and filter off the desired product. The simplicity of the synthesis makes up for the low yields and renders it an attractive method, especially in the case of 18-membered tetraamide **1** derived from 1,2-diaminoethane, that could be obtained in

up to 50% yield.[37] In order to obtain the missing 20-membered macrocycle **2** and 24-membered **4**, we have conducted analogous reactions with the amines having odd number of carbon atoms, 1,3-diaminopropane and 1,5-diaminopentane, respectively (Scheme 1). As previously, the precipitate

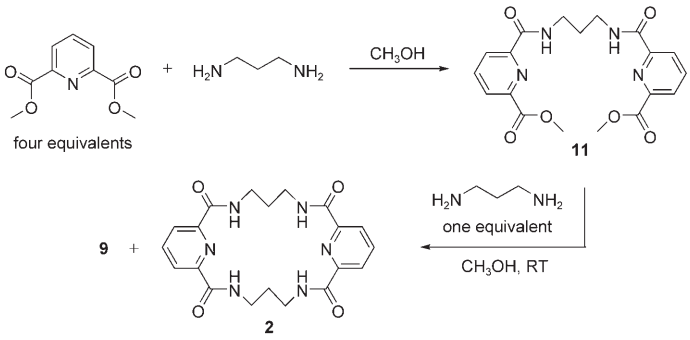


Scheme 1. Synthesis of macrocyclic tetraamides, hexaamides and octaamides.

formed also in the reaction with 1,3-diaminopropane; this time, however, it contained mainly 30-membered hexaamide **6** (7.7% yield) and 40-membered macrocyclic octaamide **9** (6.2% yield). For macrocycles of this size, there is always an uncertainty concerning their structures: is it a single macrocycle or maybe a catenane from two tetraamides? These doubts were dispelled by an X-ray single crystal analysis of the chloride complex of **9**. It revealed that **9** is indeed a 40-membered octaamide and that there are two chloride anions inside its huge cavity. Simultaneous binding of two anions was previously observed by us for its 36-membered analogue **8**.[41] This extraordinary phenomenon will be described in detail in a separate paper. Also the compound **6** is a potentially interesting anion receptor: a similar hexaamide of the same ring size has been shown to bind $CaCl_3^-$ anions in the solid state.[42] The one-pot synthesis described here opens an easy access to these interesting receptors. Extensive chromatography of the filtrate from the same reaction afforded the desired macrocyclic tetraamide **2**, although in low yield (5.6%).

Analogous products were also obtained by the reaction of dimethyl 2,6-pyridinedicarboxylate with 1,5-diaminopentane: 24-membered tetraamide **4** (7.5%), 36-membered hexaamide **7** (6.4%) and 48-membered octaamide **10** (2.4%). They are more soluble than their analogues **2**, **6** and **9**, and, consequently, the precipitate that forms in the reaction mixture consists only of unidentified, probably polymeric, products.

Summing up, in the case of α,ω-diamines having odd numbers of methylene units, our synthetic procedure for macrocyclic tetraamides met severe problems concerning separation of the desired tetraamides from the larger macrocyclic products. However, these difficulties, as well as low yields, were compensated by the fact that every such reaction afforded three interesting macrocycles, being potential anion receptors: a tetraamide (**2**: 5.6%, **4**: 7.5%), a hexaamide (**6**: 7.7%, **7**: 6.4%) and an octaamide (**9**: 6.2%, **10**: 2.3%). Taking into account the low cost of substrates, it appears that the major drawback of the method is not its low yield, but rather a cumbersome separation of the reaction products. This difficulty may be overcome by separating the synthesis into two steps (Scheme 2). In the first step, 1,3-diaminopropane reacts with four equivalents of dimethyl 2,6-pyridinedicarboxylate affording several linear oligomeric



Scheme 2. Stepwise synthesis of the macrocyclic tetraamide **2**.

amidoesters, that can be easily separated by column chromatography ([2+1] product **11**, 46% yield based on 1,3-diaminopropane). In the second step, amidoester **11** reacts with one equivalent of amine in a [1+1] fashion giving considerably higher yields of the desired macrocyclic products: tetraamide **2** (21%) and octaamide **9** (17%). Moreover, separation of the reaction mixture is easier, because some macrocyclic products, for example hexaamide, are absent. Accordingly, octaamide **9** precipitates directly from the reaction mixture in an almost pure form. This stepwise approach allows for the synthesis of unsymmetrical macrocycles derived from two different amines.

X-ray studies of ligands: Receptors **1**, **3** and **5** have been already characterized structurally.[37,40] To complete the structural analysis of the whole series of "homologous" macrocycles **1**–**5**, we performed the X-ray crystal structure determination for **2** and **4**.

Diffraction-grade single crystals of **2** were obtained by slow diffusion of Et_2O into a solution of **2** in CH_2Cl_2/CH_3OH 9:1. Single crystals of **4** grew during our efforts to obtain cyanide complex, after slow evaporation of the ethanolic solution of the ligand and tetrabutylammonium cyanide. All five macrorings adopt very similar, centrosymmetric, expanded, stair-like conformation (Figure 3). The pyri-

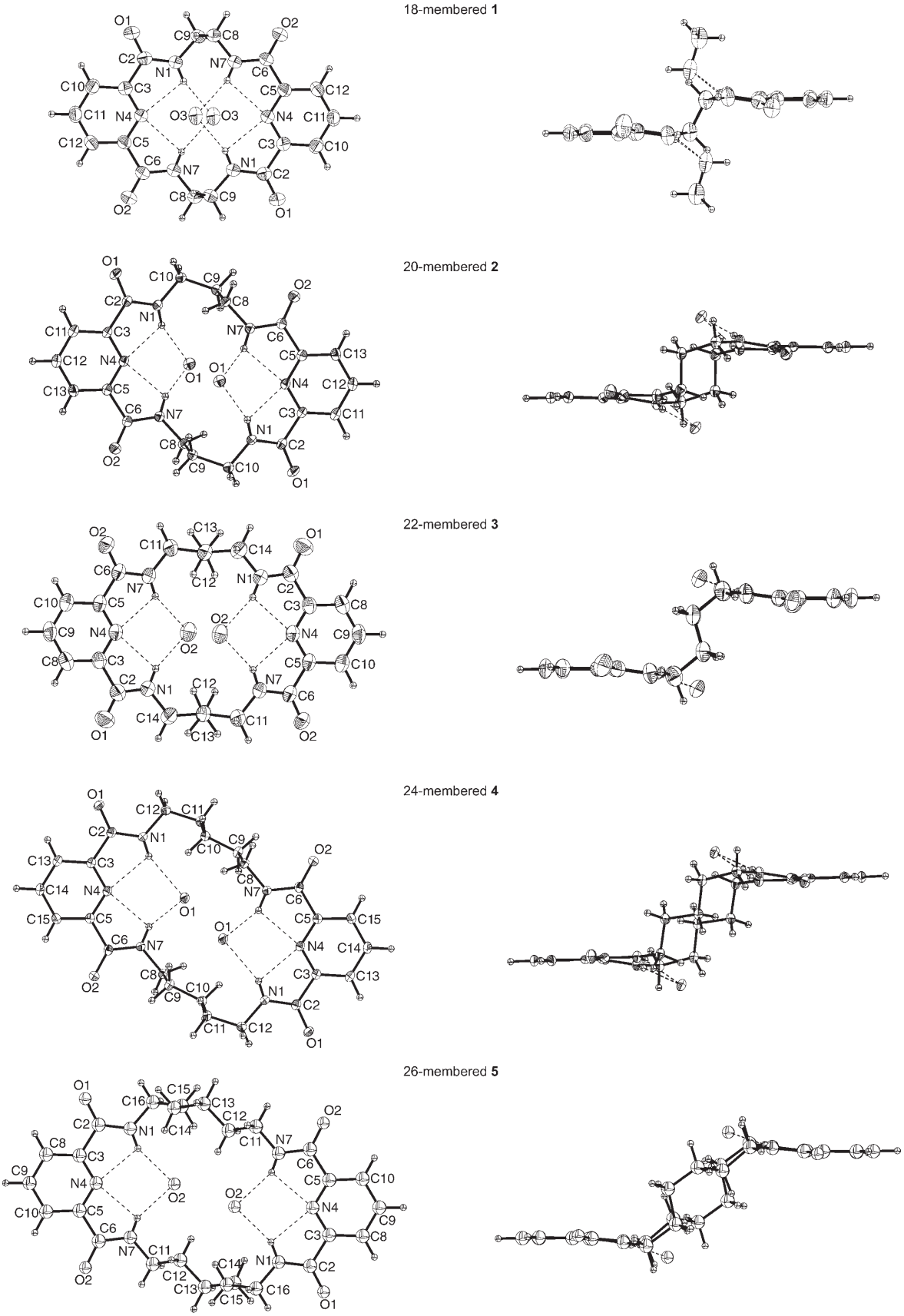


Figure 3. Comparison of the X-ray structures of macrocyclic receptors **1**–**5**. (ORTEP plots, displacement ellipsoids scaled to 50% probability level).

dine rings of each receptor are antiparallel to each other and the distance *h* between their planes (the height of the stairs) is given in Table 1. The amide hydrogens are arranged in a convergent manner by intramolecular $NH_{amide}\cdots N_{py}$ interactions and the amide groups are almost coplanar with adjacent pyridine rings (dihedral angles vary from 2.8 to 12.3°). Aliphatic chains linking two such rigid 2,6-bis(carbamoyl)pyridine planes are in an extended, unstrained conformation, with most torsion angles close to optimal antiperiplanar or synclinal conformations. Exceptions are found in linkers having odd number of methylene groups (**2** and **4**) where one of torsion angles is deviated by about 30° from the ideal value. The cavity dimensions, approximated by the distances between symmetrically related amide nitrogen atoms (diagonals of parallelogram), are collected in Table 1.

Table 1. Distances characterizing the cavity sizes of receptors **1**–**5**.

Receptor	*h* [Å]	Diagonals [Å]
1	1.47	5.45×5.50
2	2.15	5.18×6.82
3	2.85	6.72×6.73
4	3.14	6.37×9.18
5	3.69	8.12×9.19

In each ligand structure, each pair of the amide hydrogen atoms binds one oxygen acceptor: hydroxy group of methanol molecule (in the crystal of **1**) or carbonyl oxygen of neighboring molecule (all other examples). Noteworthy, due to the stair-like conformation of the molecule, two pairs of the amide hydrogens interact with two different acceptors. This leads to a similar packing mode for compounds **2–5**: each macrocycle is surrounded by four perpendicular, symmetry related ones, being hydrogen bonded to them. Two of these neighbors (from above and below) act as hydrogen bond acceptors, while the remaining two as donors (from both sides).

Anion binding in solution: The addition of anions, in the form of tetrabutylammonium (TBA) salts, to the DMSO solutions of each receptor caused significant downfield shifts of amide signals in ^{1}H NMR spectra, indicating N-H···A$^-$ hydrogen-bonding interactions and also fast equilibrium between complexed and free forms of ligands. Typical titration curves are shown in Figure 4.

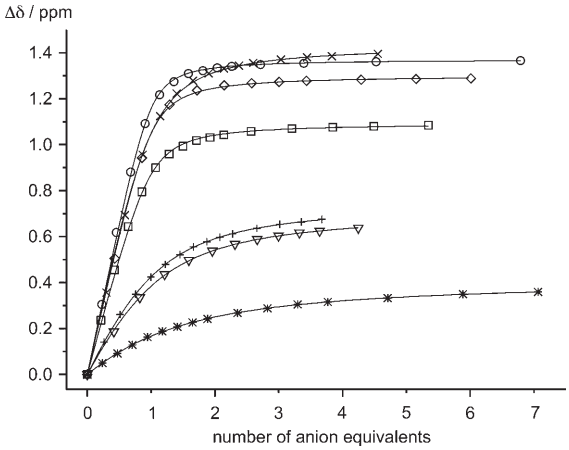
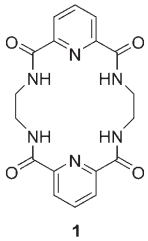
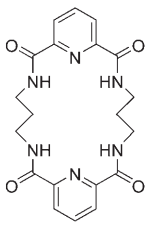
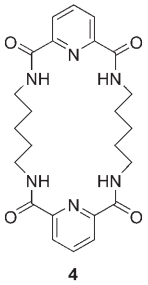


Figure 4. ^{1}H NMR titration curves of ligand **2** with various anions; × $PhCOO^-$, ○ $H_2PO_4^-$, ◇ AcO^-, □ Cl^-, + Br^-, ▽ CN^-, * HSO_4^-.

Standard nonlinear analysis of the data thus obtained afforded 1:1 stability constants of receptors **1**, **2** and **4**, collected in Table 2.[43] The solubility of receptor **3** in DMSO was too low to allow for determination of its stability constants.

The selectivity trends displayed by the three receptors are similar and common for hydrogen-bonding receptors: hydrogen phosphate, acetate and benzoate are most strongly bound, whereas cyanide, bromide, *p*-nitrophenolate and hydrogen sulfate anions form weak complexes. Noteworthy, there is no correlation in our data between the basicity of anions (expressed in terms of pK_a measured in DMSO) and the stability constants of their complexes.[45] For example, the weakest base, bromide ion, forms a stronger complex with **2** than *p*-nitrophenolate does, in spite of basicity weaker by ten orders of magnitude. Similarly, **2** prefers

Table 2. Binding constants [M^{-1}] for the formation of 1:1 complexes of **1**, **2**, and **4** with various anions in [D_6]DMSO at 298 K.[a]

Anion X^-	 **1**	 **2**	 **4**	pK_a HX in DMSO[b]	Gas-phase basicity[c] [kJ mol^{-1}]	$\Delta G^{0,1}$[d] [kJ mol^{-1}]
Cl^-	65[e]	1930	18	1.8	1373	29
Br^-	<5	150	<5	0.9	1332	30
CN^-	52	349	51	12.9	1438	34
$PhCOO^-$	202	2283	301	11.1	1394	39
AcO^-	2640[e]	3240	310	12.6	1427	32
$H_2PO_4^-$	1680[e]	7410	450	–	1351	32
p-O_2N-Ph-O^-	67[e]	123	<5	10.8	1343	25
HSO_4^-	<5	75	<5	–	1251	25

[a] Errors are estimated to be < 10%. Tetrabutylammonium salts were used as anion sources. [b] Taken from ref. [2h]. [c] Standard free enthalpy of protonation in the gas phase, taken from ref. [44]. [d] Standard free enthalpy of the gas phase reaction: $X^- + H_2O \rightleftarrows [X^-\cdot H_2O]$. Values from ref. [2h]. [e] Values from ref. [37].

weakly basic chloride over strongly basic cyanide or *p*-nitrophenolate. Since the differences of the solvation energies of X^- and HX may limit the adequacy of pK_a values as a measure of hydrogen bond acceptor strengths, gas phase basicities or the free energies of anion hydration by single water molecule ($\Delta G^0_{0,1}$) were put forward as a better measure of intrinsic anion properties.[46] Here, however, the correlations are also very poor, what is not surprising considering solvation effects and the possible influence of host–guest geometric complementarity on the complex stability.

The above-mentioned geometric complementarity is most probably responsible for the striking effect of the receptor size on affinity towards Cl^-: enlargement of the macrocycle from the 18-membered ring in **1** to the 20-membered ring in **2**, resulted in a 30-fold increase in the respective binding constant, whereas further enlargement by four methylene units (in **4**) causes reduction of affinity towards Cl^- by two orders of magnitude. Remarkably, the 20-membered receptor **2** binds Cl^- almost as strongly as benzoate anion.

Similar but smaller effects can be seen for other anions (Figure 5); as a result, receptor **2** is the best receptor for all anions under the study. This in turn implies that the size match between anion and cavity of the receptor does not account solely for the observed selectivity. For instance, the cavity of the largest receptor **4** matches the size of hydrogen phosphate and carboxylate anions better than receptor **2**, but respective complexes are weaker. Apparently, anion binding ability of our receptors results from their intrinsic proprieties, most probably flexibility and rigidity. Whereas the smallest receptor **1** has too short aliphatic linkers to allow for comfortable adjustment to all anionic guests except fluoride, the largest receptor **4** is too floppy and presumably pays large entropic penalty for complexation. Evidently, the three methylene groups in the aliphatic linkers of receptor **2** are a good compromise between contradictory requirements of adaptability and preorganization.

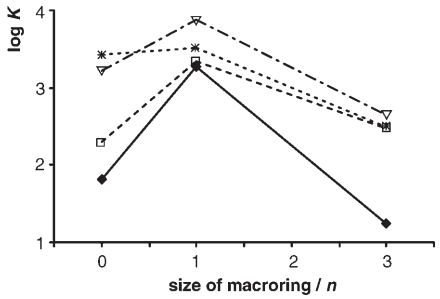


Figure 5. Plot of the logarithm of the association constant versus the size of receptor's cavity; ▽ $H_2PO_4^-$, * AcO^-, □ $PhCOO^-$, ◆ Cl^-.

The picture emerging from the above data is strikingly similar to what is well-known for simple crown ethers and alkali metal cations, where K^+ is preferred over all other cations by a range of crowns irrespective of ring size, and the strongest binding of all cations is observed for [18]crown-6 irrespective of cation size.[47]

To test the importance of size complementarity in anion recognition by our receptors, it would be valuable to compare affinity of **1** and **2** towards fluoride and chloride anions. Previous structural studies[37] have shown that 18-membered cavity of receptor **1** was too small to accommodate Cl^-, whereas F^- fitted well. Accordingly, F^- is bound more strongly than chloride. In this case, however, geometric fit and hydrogen bond accepting ability work in concert and it is impossible to judge their relative importance. More significant would be the comparison of $K(F^-)$ and $K(Cl^-)$ for **2**, but unfortunately $K(F^-)$ is not an easily accessible value. First of all, it is difficult to prepare fluoride solution of exactly known concentration. Commercially available tetrabutylammonium fluoride is a hydrate having an unspecified water content, and drying it results in decomposition by Hoffman elimination.[48] Our attempts to dissolve weighed amounts of potassium or sodium fluoride in DMSO with the aid of [2.2.2]cryptate were unsuccessful, although the method worked well in acetonitrile.[49] Finally, we performed NMR titrations of ligands **1**, **2** and **4** using the solution of tetrabutylammonium fluoride hydrate and estimated its concentration by integration of NMR spectra with respect to ligands. At the beginning of each titration, the amide NH signals broadened significantly, but narrowed again as the amount of F^- approached two equivalents. Near this point, the NH signals of **1** and **2** split into doublets ($J \approx 43$ Hz) as a result of H–F coupling, and stopped shifting. The tentative

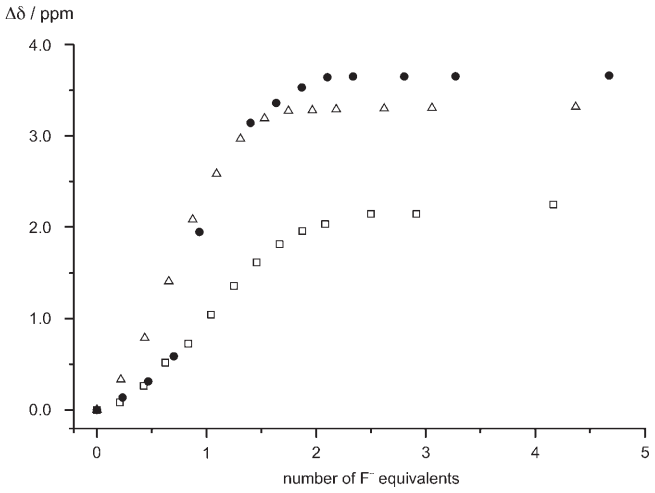


Figure 6. ^1H NMR titration curves of ligands **1** (△), **2** (□) and **4** (●) with fluoride anion.

assignment of the positions of these broad signals led to S-shaped titration curves shown in the Figure 6.

Such a shape suggests multiple equilibria resulting from formation of complexes of different stoichiometries. In this case, however, this was simply due to partial coalescence of the NH signals of free and complexed ligands. Using higher field spectrometer (400 instead of 200 MHz), we were able

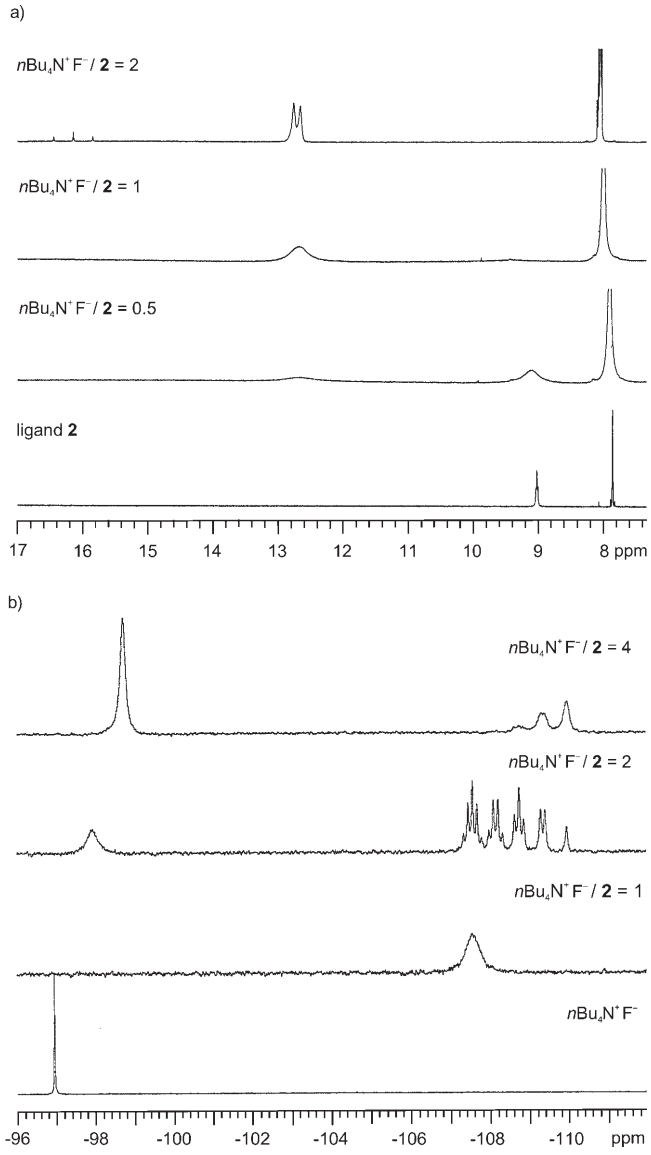


Figure 7. a) ^{1}H NMR and b) ^{19}F NMR spectra of ligand **2** with $nBu_4N^+F^-$ recorded at different F^- to ligand ratio in $[D_6]$DMSO.

to separate these signals in the case of **2** (Figure 7a), partly in **1**, but still not **4**. Unfortunately, broadening of NH signals and progressing deuterium exchange precluded quantitative determination of binding constants.

^{19}F NMR spectra recorded at different F^- to ligand ratio provided direct insight into the solution structures of species involved, owing to ^{1}H–^{19}F couplings through hydrogen bonds[50] (Figure 7b).

The signal of the free fluoride anion at −97.0 ppm disappears after addition of one equivalent of the ligand, and the signal of complexed fluoride appears at −92.2 ppm for **1**·F^-, −107.6 ppm for **2**·F^-, and −108.0 ppm for **4**·F^-. At 2:1 F^--to-ligand ratio, separate signals of free and complexed fluoride are visible, indicating slow exchange; furthermore, in the case of **1**·F^- and **2**·F^- the signal of encapsulated F^- is a well-resolved quintet ($J \approx 43$ Hz); this indicates coupling of the fluoride nucleus with all four NH protons of each ligand. Moreover, four new signals are also apparent: quartet, triplet, doublet and singlet, with the same coupling constants. These originate from fluoride encapsulated within partially deuterated ligands, lacking one, two, three or all four protons, respectively (^{2}H–^{19}F coupling constants are about seven times smaller than ^{1}H–^{19}F and could not be observed in these relatively broad multiplets). The shift of fluoride signal caused by each proton-to-deuterium exchange is similar and large enough (0.55 ppm in **1** and 0.59 ppm in **2**) that these multiplets do not overlap. These spectra constitute a direct evidence that, in the DMSO solutions, the fluoride anion is encapsulated inside the macrocyclic cavities of tetraamides **1** and **2** by four NH···F^- hydrogen bonds. Furthermore, the observation of separate signals only from F^- and 1:1 complexes strongly suggests that other complexes are not present in detectable amounts under these conditions. This is a non-trivial information, because the reverse might be expected from the inspection of the titration curves from Figure 6, where the saturation point is reached after addition of nearly two equivalents of fluoride and also because multiplets in fluorine spectra appear only in the presence of excess of fluoride. Perhaps the stability constants of fluoride complexes are not large enough and therefore the excess of the anion is required to achieve 100% complexation of receptors.

Larger excess of fluoride (4:1 anion-to-ligand ratio) results in significant deprotonation of all ligands with concomitant formation of bifluoride anions HF_2^- and DF_2^-, evidenced by a characteristic triplet in ^{1}H NMR spectra (HF_2^-: t, 16.14 ppm, $J = 120$ Hz) and doublet or triplet, respectively, in ^{19}F NMR spectra (HF_2^-: d, −142.2 ppm, $J = 120$ Hz, DF_2^-: t, −142.7 ppm, $J = 18$ Hz).[51] Consequently, deuterium exchange with the $[D_6]$DMSO solvent speeds up and multiplets in fluorine spectra gradually disappear.

Similar observations made recently by Bowman-James and co-workers[36] for hexaamide cryptands **12** and **13** (Figure 8) allow for interesting comparison. First, ^{1}H–^{19}F coupling constants measured for bicyclic receptors (27 Hz for **12** and 14 Hz for **13**) were smaller than for our tetraamides (43 Hz) suggesting weaker N-H···F^- hydrogen bonds. This decrease in the strength of each single hydrogen bond is clearly related to the increasing total number of hydrogen bonds, rising from four for our tetraamides, to six in **12**, and 9 in **13** (including three C-H···F^- hydrogen bonds). Second, deuterium exchange is much slower in bicyclic receptors **12** and **13**, achieving equilibrium requires heating to 150 °C for 1 h, whereas monocyclic tetraamides **1**, **2** and **4** are deuterated after a few hours at room temperature. The chemical structure of these two

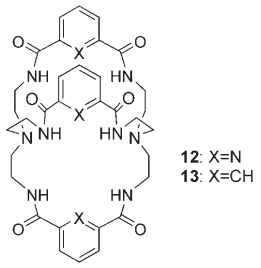


Figure 8. Bicyclic receptors studied by Bowman-James and co-workers.[36]

types of receptors is similar and suggests similar thermodynamic acidity, therefore we ascribe their different behavior to different topologies: proton abstraction from the cage compounds **12** and **13** is apparently slower.

However, a large excess of fluoride was able to deprotonate our ligands to a significant extent, as judged by the increase of bifluoride signal in ^{19}F NMR spectra, whereas no such observation was mentioned by Bowman-James and coworkers.[36] So, the question whether the difference in the rate of fluoride-facilitated deuterium exchange between macrocyclic and macrobicyclic receptors is purely kinetic or has also some thermodynamic origin requires further investigation.[52]

X-ray studies of anion complexes of macrocyclic receptors: Structural studies of anion complexes in the solid state provide a valuable insight into binding modes and coordination geometries, that may help in the interpretation of the solution-phase results. Therefore, we have made a considerable effort to obtain crystals of anion complexes of **2** and **4** suitable for X-ray analysis.

Complexes of 20-membered ligand 2: Careful layering of hexane onto the solution of tetrabutylammonium chloride and tetraamide **2** in CH_2Cl_2 afforded, after a few days, long needles of the chloride complex of **2**. Unfortunately, poor quality of these crystals did not allow for satisfactory refinement of their structure. Therefore, we used tetrapropylammonium cations as less flexible counterions, and obtained, under the same conditions, the X-ray quality crystals of the desired complex. All our efforts to grow crystals of the acetate complex of **2** were unsuccessful, but slow evaporation of a solution of **2** and tetrabutylammonium acetate in acetonitrile gave high quality single crystals of **2**·CH_3CN. Solid state structures of both complexes are very similar (Figure 9).

Each guest forms four, almost equal hydrogen bonds with all four amide hydrogen atoms of the ligand. In order to provide convergent hydrogen bonds to the same acceptor, the macrocycle adopts a highly bent shape, with an angle between the pyridine ring planes of 55.3 and 49.4°, respectively. Both guests sit on the top of the ligand, 1.81 Å (Cl^-) and 1.68 Å (CH_3CN) above the mean plane of four amide nitrogens. The chloride anion is bound only from the bottom (if a weak, 2.82 Å, intermolecular contact to the aliphatic hydrogen atom of neighboring macrocycle is neglected) and, therefore, its coordination sphere may be described as pyramidal. This is in contrast to what was found for chloride and fluoride complexes of a smaller, 18-membered macrocycle **1**, where both anions are coordinated by one water molecule from the side opposite to the receptor.

The comparison of the X-ray crystal structures of receptor **2** and its chloride complex demonstrate the large extent to which the ligand can change its conformation in order to maximize binding with a guest. The angle between pyridine ring planes is reduced from 180° in the free ligand to 55.3°

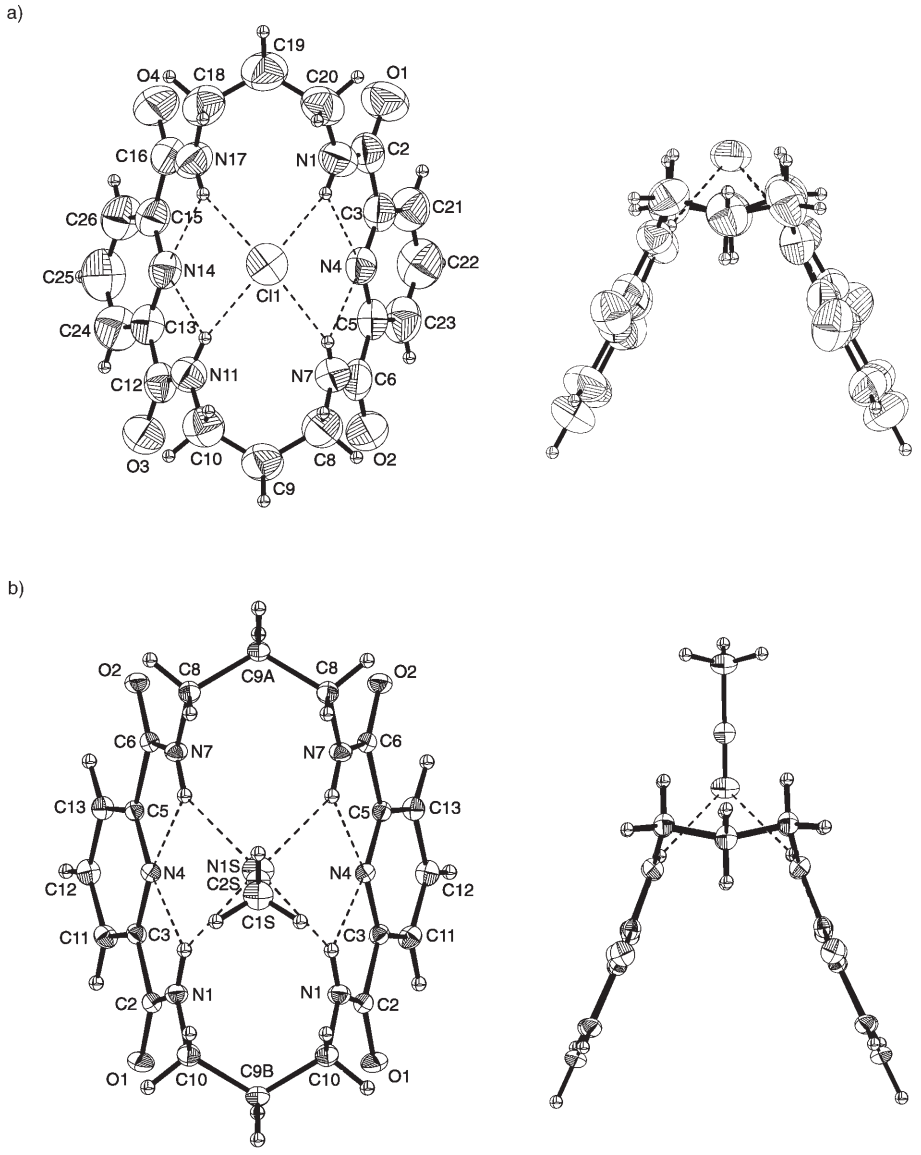


Figure 9. ORTEP view of the molecular structure of a) **2**·$(n\mathrm{Pr})_4N^+Cl^-$, b) **2**·CH_3CN. Displacement ellipsoids are scaled to the 50% probability level. Dashed lines are indicative of hydrogen-bonding interactions.

upon Cl^- binding, much more than in smaller macrocycle **1**—from 180° to 157.4°. This supports our hypothesis that the better efficacy of receptor **2** results from its better adaptability. It is also worth to note that even small chloride anion is not truly encapsulated by the receptor **2**, as it sits above the plane of highly bent macrocycle. The same must be true for larger anions, and this accounts for minor role of size complementarity in anion recognition by receptor **2**.

The large differences between the solid-state structures of the free ligand **2** and its complexes pose a question whether such conformational changes during anion binding take place in solution too. Whereas the structure of chloride complex in solution is probably well represented by the solid state structure, the privileged conformation of the free ligand is more ambiguous—it may either resemble the crystal structure of free ligand with two DMSO molecules on opposite sides as hydrogen bond acceptors, or may be similar to that found in the acetonitrile complex, with one DMSO molecule in place of CH_3CN. DMSO is a strong hydrogen bond acceptor and, therefore, such specific interactions between the receptor and solvent are probable. If the second possibility is true, anion binding would consist in a simple guest exchange with little conformational change of the host. It points to a possible double role of DMSO, which strongly competes with anion binding, but probably also preorganizes the receptor. Unfortunately, it is difficult to get experimental insight into such dynamic phenomena in solution due to the low solubility and high symmetry of our ligands, as well as high rate of these processes, leading to averaged, but broadened NMR spectra. Boudon and Wipff[53] used Monte Carlo simulations to show that specific interactions with water molecules help to preorganize polyammonium macrocycle toward anion binding.

In our opinion, the crystal structures of chloride and acetonitrile complexes of **2** provide valuable inspiration for future designs. Almost parallel mutual disposition of two pyridine rings of **2** in these structures is reminiscent of calixarene in 1,3-alternate conformation. Taking into account the well-known binding capabilities of calixarenes, it is worth to consider the possibility of simultaneous, cooperative binding of two guests by such receptors, equipped with appropriate functionalities. Examination of the crystal structures of above complexes from this point of view reveals that the gaps between the pyridine rings are filled by aliphatic groups. For example, in the chloride complex, receptor molecules lie side by side, forming a grove filled by aliphatic chains of tetrapropylammonium cations.

Chloride complex of 24-membered ligand 4: Vapor diffusion of diethyl ether into the solution of macrocyclic tetraamide **4** and tetrabutylammonium chloride in 1,2-dichloroethane gave monocrystals of the complex **4**·TBA^+Cl^-·2.61 H_2O. The X-ray analysis shows that there are two guests in the receptor's cavity: a chloride anion and a water molecule (Figure 10).

Each guest lies nearly in the plane of one 2,6-pyridinedicarbamoyl unit, chelated by two amide groups. The two guests are connected by almost perfectly linear O-H···Cl^- hydrogen bond (O-H···Cl angle 177.2°, H···Cl distance 2.30 Å). The last, fourth hydrogen bond comes to Cl^- from another water molecule, which resides in the cavity of the symmetrically related receptor. This gives rise to the formation of hydrogen bonded, centrosymmetric dimer, in which rhombic $(Cl^-)_2(H_2O)_2$ cluster bridge the two molecules of **4**. Such chloride water cluster is a common motif in the solid state.[41,54,55]

Thus, the 24-membered macrocycle is clearly too large for a single chloride anion. Nevertheless, the study of such geometrically mismatched systems may give an interesting insight into means, by which they adapt in order to maximize

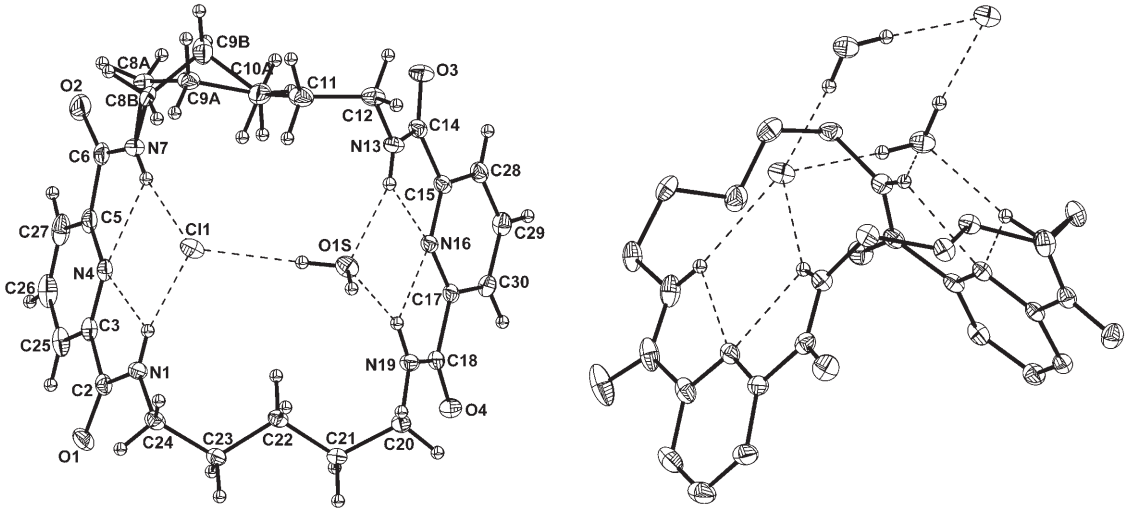
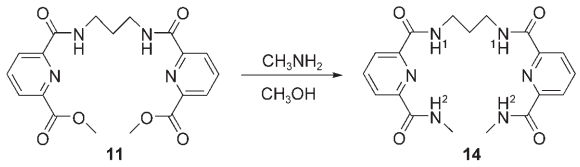


Figure 10. ORTEP view of the molecular structure of **4**·TBA^+Cl^-·2.61 H_2O. Left figure: top view. Right figure: rhombic cluster of two water molecules and two Cl^- ions joining two symmetrically equivalent macrocyclic receptors (only bottom one is shown) Hydrogen atoms and part of disorder have been removed for clarity. (Displacement ellipsoids are scaled to the 50% probability level. Dashed lines are indicative of hydrogen-bonding interactions).

the number of noncovalent interactions. The sterically mismatching cation complexes of crown ethers have been already studied from this perspective.[56] The present structure highlights the role of water molecules, that may fill the gaps between small guests and too large hosts. It is worth to remind here that we were unable to observe the well-defined multiplets in the ^{19}F NMR spectra of $\mathbf{4}\cdot F^-$. It might be due to the involvement of water molecules in the solution structure of this fluoride complex. Considering a very strong interaction of water with anions (especially fluoride), it seems reasonable to deliberately construct hosts able to accommodate target anion together with a fraction of its hydration sphere. Indeed, Burns and co-workers have shown recently that anion complexation in a competitive solvent may be enhanced when a solvent molecule is incorporated into the binding motif.[57] Such a new strategy for the design of anion receptors may be useful in applications like the transport of anions through lipophilic channels or membranes, were stripping off the solvation shell gives rise to high energy barrier.[58] The chloride complex of **4** may be a prototype receptor of this class.

Macrocyclic effect: Having established that the 20-membered macrocyclic tetraamide **2** is the most effective anion receptor, we were interested whether its macrocyclic topology was really indispensable for its effectiveness. To answer this question, we resolved to synthesize the model acyclic tetraamide **14** and compare its anion binding properties with **2**. It may be argued that **14** consists of two rigid fragments that are well-preorganized for anion binding by intramolecular hydrogen bonds, and therefore should not suffer very much from the lack of macrocyclic topology. The open-chain model receptor **14** was obtained in 91% yield from amidoester **11** (Scheme 3).



Scheme 3.

The results of ^1H NMR titrations are collected in Table 3. Binding constants for the three anions studied are at least 20 times smaller for the acyclic receptor **14**, despite its partially rigid structure.

To throw some light on the possible structural basis of this large macrocyclic effect, we performed the X-ray analyses of **14** (Figure 11) and its chloride complex (Figure 12). Both crystals grew from the same crystalisation, during slow diffusion of hexanes into the solution of **14** and TBACl in 1,2-dichloroethane.

In the structure of $\mathbf{14}\cdot 2H_2O$ there are two independent molecules of the ligand in the unit cell, both having a similar zig-zag shape stabilized by intramolecular NH···O=C hydrogen bonds (Figure 11).

Table 3. Binding constants [M^{-1}] for the formation of 1:1 complexes of **2** and **14** with various anions in [D_6]DMSO at 298 K.[a]

Anion	**2**	**14**	
		NH^1	NH^2
Cl^-	1931	45	45
AcO^-	3241	163	160
$H_2PO_4^-$	7409	346	223

[a] Errors are estimated to be < 10%. Tetrabutylammonium salts were used as anion sources.

In both molecules, one 2,6-bis(carbamoyl)pyridine fragment chelates the carbonyl oxygen atom of the other, which in turn binds a water molecule. If a similar conformation predominates in solution too, the receptor may either bind an anion with only two hydrogen bonds, like the water molecule in the crystal, or undergo a major conformational change, accompanied with the breaking of two intramolecular hydrogen bonds, to bind an anion with all four amide groups. No matter which possibility is realized, the net energy gain in the complexation process comes from the formation of just two new hydrogen bonds, instead of four, like in the macrocyclic tetraamide **2**. Thus, apart from increased flexibility, also the competition from intramolecular hydrogen bonds may account for much worse anion binding properties of acyclic versus macrocyclic receptor.

The X-ray structure of **14** suggests also a plausible explanation for poor results of macrocyclizations leading to **2** as contrasted to those leading to **1**. The linear triamide, precursor of **2**, may fold in a way similar to **14**, adopting conformation that hampers macrocyclization. Such disadvantageous conformation would be difficult to attain by analogous intermediate, precursor of **1**, having a shorter linker. Accordingly, **1** is obtained in 50% yield, whereas **2** in only 5.6%.

However, the NMR spectra of **14**, taken at room temperature in DMSO solution, show an equivalence of both 2,6-bis(carbamoyl)pyridine moieties. It means that either the molecule adopts a more symmetrical conformation in solution than in the solid state, or there is a fast equilibrium between equivalent, folded conformations leading to time-averaged spectra.

The X-ray analysis of the crystal structure of the chloride complex of acyclic tetraamide **14** reveals that the ligand wraps around anion to form four N-H···Cl^- hydrogen bonds (Figure 12). The coordination sphere of the anion is completed by one water molecule from the bottom and a tetrabutylammonium cation from the top forming C-H···Cl^- hydrogen bond. The conformation of the ligand **14** in the complex is very different from that of the free **14**, demonstrating flexibility of the tetraamide lacking macrocyclic topology.

Although significant energetic cost of structural reorganization necessary for anion binding is probably responsible for low binding constants of **14** in solution, the unconstrained acyclic tetraamide **14** can better adjust to the anionic guest than macrocyclic **2**, producing presumably more favorable arrangement in the solid state. Thus X-ray structures of

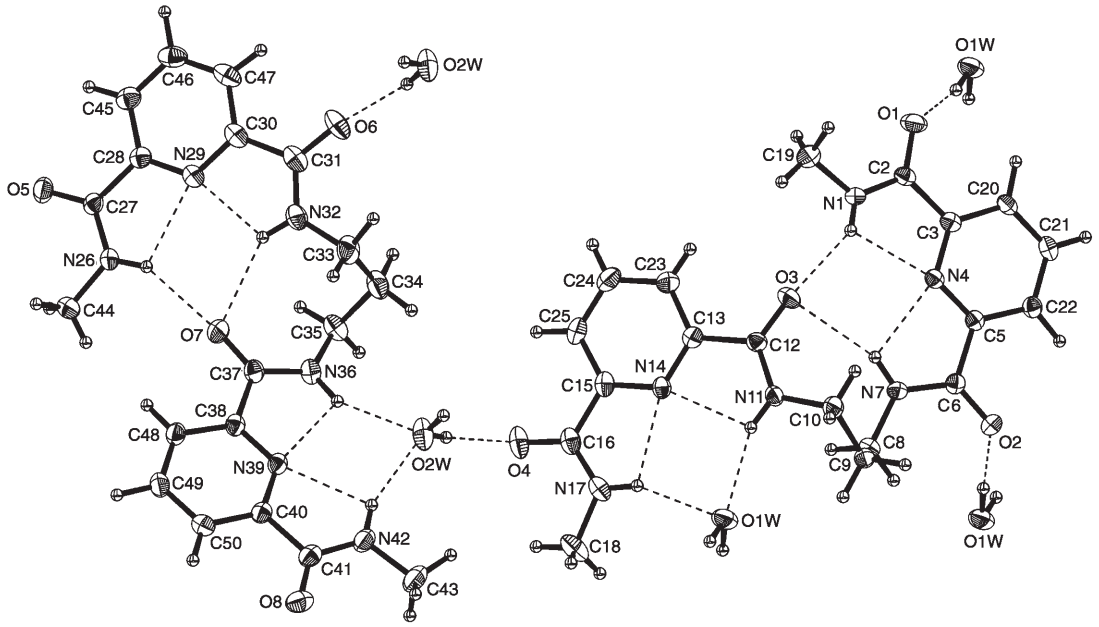


Figure 11. ORTEP view of the molecular structure of acyclic receptor **14** showing two nonequivalent, but similar, molecules and the network of hydrogen bonds (dashed lines). Displacement ellipsoids are scaled to the 50% probability level.

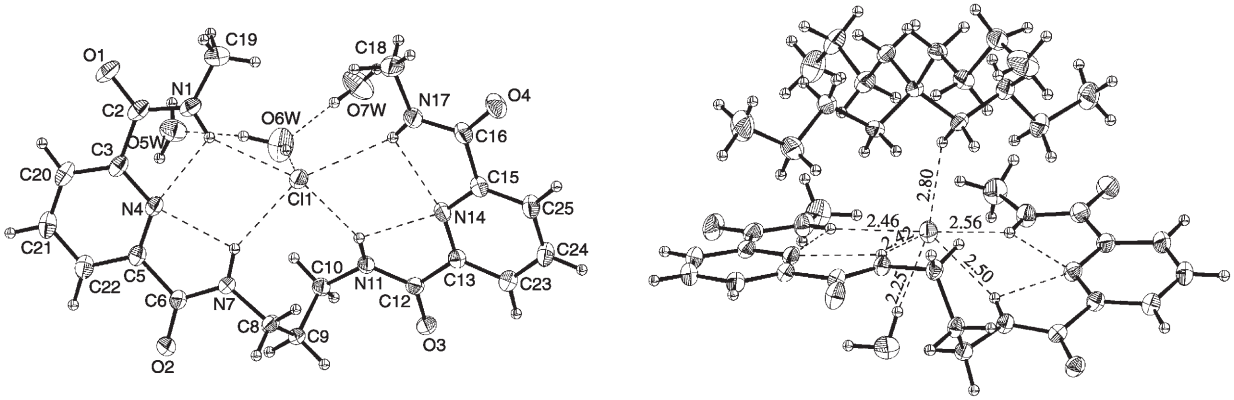


Figure 12. ORTEP view of the molecular structure of **14**·$TBA^+Cl^-\cdot 3H_2O$. Left: numbering scheme. Right: coordination sphere of the chloride anion. Dashed lines indicate hydrogen-bonding interactions. Displacement ellipsoids are scaled to the 50% probability level.

anion complexes of the acyclic model **14** may provide valuable hints for the construction of the second-generation anion receptors. First, the distance between the amide nitrogens connected by the linker is 3.67 Å in the chloride complex of **14**, what is much shorter than the distance (5.61 Å) between the terminal amide nitrogens. This suggests that in the macrocyclic receptor **2** at least one linker should be longer, having four or five carbon atoms. Second, this reminds that even perfectly tailored macrocyclic receptors leave apical positions empty and it would be advantageous to equip it with pendant arms having, for example, hydroxy groups able to provide additional binding.

Conclusion

A family of neutral, macrocyclic, tetraamide receptors of different ring sizes was obtained without using the high dilution methodology. Hexaamides **6** and **7** as well as octaamides **9** and **10**, also interesting as potential anion receptors, were isolated as major synthetic by-products. The structure and anion binding properties of this family of tetraamides were studied using the X-ray diffraction analyses and the solution-phase affinity measurements. The study revealed a significant effect of the receptor size on its anion-binding ability. Each anion, irrespective of its size or shape, binds most strongly to the 20-membered macrocycle **2**. Apparently, the size complementarity between an anion and the receptor's cavity plays a secondary role here and does not determine the mutual affinity. More likely, anion binding abili-

ty of our receptors depends on their flexibility, and receptor **2** is a good compromise between contradictory requirements of adaptability and preorganization. Nevertheless, the geometric fit manifests in exceptionally strong complexation of Cl^- by receptor **2**.

Encapsulation of fluoride anion by tetraamide receptors **1** and **2** in DMSO solution was confirmed by the observation of through-hydrogen-bond coupling between F^- and amide NH protons in ^{19}F and ^1H NMR spectra. Despite the mismatch between the size of the F^- and cavity of 24-membered receptor **4**, no complexes of different than 1:1 stoichiometry were detected, possibly due to the intervention of a water molecule, able to fill the gap between the large receptor and small guest anion.

The comparison of X-ray crystal structures of receptor **2** and its chloride complex demonstrated the large extent to which the ligand can change its conformation in order to adapt to a guest. This anion-induced conformational change is much larger than that previously described for smaller macrocycle **1**, and thus supports our hypothesis, that better efficacy of receptor **2** results from its better adaptability. The crystallographic studies of the chloride complex of **2** revealed also that even small chloride anion is not truly encapsulated by the receptor, as it sits above the plane of highly bent macrocycle. This accounts for minor role of size complementarity in anion recognition by receptors **1** and **2**.

The macrocyclic topology of the receptor **2** is crucial for its effectiveness, as revealed by comparison with its acyclic analogue **14**. This was explained by the X-ray crystallographic analysis, that showed the free ligand **14** in ill-preorganized conformation, stabilized by two intramolecular hydrogen bonds. These hydrogen bonds have to be broken during anion binding and, therefore, compete directly with the latter process.

The receptor **2** is therefore proposed as the best candidate for further modifications. Some possible improvements leading hopefully to better selectivity towards Cl^- were suggested on the basis of X-ray analysis. They include introduction of pendant arms bearing additional hydrogen bond donating groups able to occupy axial positions of the chloride anion, and slight enlargement of the receptor's cavity by elongating one aliphatic linker by one or two methylene units. In view of these emerging directions of research, we have developed a more convenient two-step synthesis of **2**, which furthermore allows to obtain unsymmetrical receptors, having two different linkers. Considering the recent report[59] on the significantly improved anion-binding properties of tetrathioamide derived from **1** in comparison with the parent compound, we expect even better properties of the thioanalogues of **2**.

Experimental Section

Instrumentation and methods: NMR spectra were measured on Varian Gemini 200 (^1H: 200 MHz, ^{13}C: 50 MHz) or Varian Mercury 400 (^1H: 400 MHz, ^{19}F: 376.4 MHz). Chemical shifts are given in ppm with the solvent signals taken as internal standards (except for fluorine spectra, where $CFCl_3$ was used as internal standard); coupling constants are in hertz. ESI mass spectra were obtained with a Mariner (ESI TOF) and API 365 (ESI 3Q) mass spectrometers with methanol as the spray solvent. Melting points are uncorrected.

Syntheses: All precursors for the syntheses were obtained from Aldrich or Fluka and were used as purchased. Dimethyl 2,6-pyridinedicarboxylate was obtained by esterification of 2,6-pyridinedicarboxylic acid according to excellent literature procedure.[60] TLC was carried out on Merck silica gel 60 F_{254} aluminium plates; for column chromatography, Merck silica gel 60 with a mesh size of 63–100 μm was used. Macrocycles under study gave unsatisfactory elemental analyses due to solvent molecules encapsulated in the crystals. This phenomenon is well known and, even after prolonged heating in high vacuum, the solvents can still be detected in the NMR spectra. The isotope patterns obtained by ESI-MS spectra are, however, consistent with those calculated on the basis of natural isotope abundances and thus confirm the elemental composition.

Reaction of dimethyl 2,6-pyridinedicarboxylate with 1,3-diaminopropane: Dimethyl 2,6-pyridinedicarboxylate (3.903 g, 20 mmol) and 1,3-diaminopropane (1.482 g, 20 mmol) were dissolved in methanol (200 mL) and left at room temperature over a period of 7 d.

Isolation of 6 and 9: The precipitate containing hexaamide **6** and octaamide **9** was filtered, washed with methanol and subjected to chromatography on a silica gel (200 g) column eluted with 6% CH_3OH in CH_2Cl_2. Pure **6** was obtained together with slightly contaminated **9**. Octaamide **9** was further purified on 100 equivalents of silica gel by using first 6–9% mixtures of methanol and ethyl acetate (to remove less polar impurities) and than 10% methanol in CH_2Cl_2 to wash out the desired product.

Hexaamide 6: Yield: 318 mg, 7.7%; m.p. >350°C; ^1H NMR (200 MHz, [D$_6$]DMSO): $\delta = 9.45$ (t, $J = 6.0$ Hz, 6H; NH), 8.17 (m, 9H; $CH_{arom.}$), 3.46 (q, $J = 6.6$ Hz, 12H, CH_2), 1.89 (quintet, $J = 6.6$ Hz, 6H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 162.9$ (4°), 148.6 (4°), 139.4 (3°), 124.1 (3°), 36.2 (2°), 30.4 (2°); HR MS (ESI): *m/z*: calcd for $C_{30}H_{33}N_9O_6Na$: 638.2452, found: 638.2459 $[M+Na]^+$.

Octaamide 9: Yield: 255 mg, 6.2%; m.p. >350°C; ^1H NMR (200 MHz, [D$_6$]DMSO): $\delta = 9.43$ (t, $J = 6.3$ Hz, 8H; NH), 8.18 (m, 12H; $CH_{arom.}$), 3.43 (br m, 16H; CH_2), 1.82 (br m, 8H; CH_2); ^{13}C NMR: due to the low solubility of **9** the spectrum was unachievable; HR MS (ESI): *m/z*: calcd for $C_{40}H_{44}N_{12}O_8Na$: 843.3297, found: 843.3323 $[M+Na]^+$.

Isolation of 2: The filtrate from above reaction mixture was evaporated to dryness, and the remaining was purified by chromatography on a silica gel (100 g) column by using gradient elution with mixtures of CH_2Cl_2 and CH_3OH (7→10%). All fractions containing **2** were combined and chromatographed again on 100 equivalents of silica gel using 6–7% mixtures of methanol and ethyl acetate to give **2** (230 mg, 5.6%). M.p. >350°C; ^1H NMR (200 MHz, [D$_6$]DMSO): $\delta = 8.96$ (t, $J = 5.6$, 4H; NH), 7.86 (m, 6H; $CH_{arom.}$), 3.54 (br m, 8H; CH_2), 2.05 (br m, 4H, CH_2); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 162.5$ (4°), 148.2 (4°), 138.8 (3°), 123.3 (3°), 39.2 (2°), 26.2 (2°); HR MS (ESI): *m/z*: calcd for $C_{20}H_{22}N_6O_4Na$: 433.1595, found: 433.1617 $[M+Na]^+$.

Reaction of dimethyl 2,6-pyridinedicarboxylate with 1,5-diaminopentane: Dimethyl 2,6-pyridinedicarboxylate (3.903 g, 20 mmol) and 1,5-diaminopentane (2.044 g, 20 mmol) were dissolved in methanol (200 mL) and left at room temperature for at least one weak. After this time the precipitate was filtered off and the filtrate was evaporated to dryness. The residue was purified by chromatography on a silica gel (250 g) column using 5% CH_3OH in CH_2Cl_2. The separation process was followed by TLC (plates were developed twice in ethyl acetate/methanol 9:1). Tetraamide **4** (350 mg, 7.5%) was obtained together with a mixture of hexaamide **7** and octaamide **10** (ca. 600 mg). These two compounds were separated on a second column, using silica gel (200 g) and 5% CH_3OH in CH_2Cl_2 as an eluent. Pure hexaamide **7** (299 mg, 6.4%) and octaamide **10** (110 mg, 2.4%) were obtained together with an unseparated mixture of these compounds (185 mg).

Tetramide 4: M.p. >350°C; ^1H NMR (200 MHz, [D$_6$]DMSO): $\delta = 9.31$ (t, J = 5.6, 4H; NH), 8.07 (m, 6H, $CH_{arom.}$), 3.42–3.23 (br m, 8H; CH_2), 1.64 (br m, 8H; CH_2), 1.39 (br m, 4H; CH_2); ^{13}C NMR (50 MHz, [D$_6$]DMSO):

δ=163.0 (4°), 148.5 (4°), 139.3 (3°), 123.8 (3°), 39.1 (2°), 28.4 (2°), 23.9 (2°); HR MS (ESI): *m*/*z*: calcd for $C_{24}H_{30}N_6O_4Na$: 489.2221, found: 489.2241 $[M+Na]^+$.

Hexaamide 7: M.p. 342–345 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ= 9.26 (t, J=6.0 Hz, 6H; NH), 8.15 (m, 9H; $CH_{arom.}$), 3.37 (m, 12H, overlapping with water signal; CH_2), 1.62 (m, 12H), 1.40 (m, 6H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ=162.9 (4°), 148.7 (4°), 139.4 (3°), 124.0 (3°), 38.8 (2°), 29.3 (2°), 24.1 (2°); HR MS (ESI): *m*/*z*: calcd for $C_{36}H_{45}N_9O_6Na$: 722.3385, found: 722.3393 $[M+Na]^+$.

Octaamide 10: M.p. 303–306 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ= 9.27 (t, J=6.0 Hz, 8H; NH), 8.12 (m, 12H, $CH_{arom.}$), 3.44–3.24 (br m, 16H), 1.59 (br m, 16H), 1.36 (br m, 8H); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ=163.0 (4°), 148.7 (4°), 139.3 (3°), 124.0 (3°), 38.8 (2°), 29.2 (2°), 24.1 (2°); MS (ESI): *m*/*z*: calcd for $C_{48}H_{60}N_{12}O_8$: 955, found: 955.5 $[M+Na]^+$.

Amidoester 11: A solution of sodium methoxide was prepared by dissolving sodium metal (0.7 g, 30 mmol) in methanol (100 mL). In this solution a dimethyl 2,6-pyridinedicarboxylate (7.807 g, 40 mmol) and 1,3-diaminopropane (0.743 g, 10 mmol) was dissolved. After one week at room temperature the solvent was removed on vacuum evaporator, and the remaining mixture was separated on silica gel (300 g) using CH_2Cl_2/CH_3OH 98:2 as an eluent. The unreacted substrate (2.080 g, 26.6%) and amidoester **11** (1.850 g, 46.2% based on amine) were obtained after the purification. M.p. 118–121 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ=8.73 (t, J=6.0 Hz, 2H; NH), 8.26–8.10 (m, 6H; $CH_{arom.}$), 3.92 (s, 6H; CH_3), 3.40 (q, J=6.4 Hz, 4H; CH_2), 1.81 (quintet, J=6.6 Hz, 2H; CH_2); ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ=164.6, 163.2, 150.3, 146.4, 139.2, 127.0, 125.1, 52.6, 36.8, 29.3; HR MS (ESI): *m*/*z*: calcd for $C_{19}H_{20}N_4O_6Na$: 423.1275, found: 423.1260 $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{20}N_4O_6$ (400.39): C 57.00, H 5.03, N 13.99; found: C 56.73, H 5.14, N 13.82.

Tetraamide 14: Methylamine (0.50 mL 8 M solution in ethanol, 4 mmol) was added to the solution of amideoester **11** (0.400 g, 1 mmol) in methanol (10 mL). After one week the solvent was evaporated and the product purified on a chromatographic column from silica gel (30 g) using 3% methanol in dichloromethane as an eluent (382 mg, 90.6%). M.p. 213–214 °C; ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ=9.47 (t, J=6.1 Hz, 2H; NH), 9.26 (q, J=5.5 Hz, 2H; NH), 8.18 (m, 6H; $CH_{arom.}$), 3.46 (q, J= 6.2 Hz, 4H; CH_2), 2.90 (d, J=4.8 Hz, 6H; CH_3), 1.89 (quintet, J=6.6 Hz,

Table 4. Crystallographic data for new structures.

Identification code	**2**	**4**	**2**·CH_3CN	**2**·Cl^-	**4**·Cl^-	**14**	**14**·Cl^-
empirical formula	$C_{20}H_{22}N_6O_4$	$C_{24}H_{30}N_6O_4$	$C_{22}H_{25}N_7O_4$	$C_{32}H_{50}ClN_7O_4$	$C_{40}H_{71.22}ClN_7O_{6.61}$	$C_{38}H_{48}N_{12}O_{10}$	$C_{35}H_{64}ClN_7O_7$
M_w	410.43	466.54	451.50	632.24	791.47	832.88	730.38
T [K]	120(2)	100(2)	120(2)	293(2)	100(2)	120(2) K	120(2)
λ [Å]	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073 Å	0.71073
crystal system	monoclinic	monoclinic	orthorhombic	monoclinic	triclinic	triclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	*Pnma*	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a [Å]	10.077(2)	11.0917(10)	17.711(4)	12.7159(18)	11.6383(6)	7.1976(14)	9.933(2)
b [Å]	10.042(2)	10.6950(8)	13.595(3)	17.4208(19)	13.0528(8)	12.281(3)	19.408(4)
c [Å]	9.6014(19)	10.2747(8)	9.2556(19)	17.196(2)	15.1161(8)	22.685(5)	21.660(4)
α [°]	90	90	90	90	84.214(5)	88.61(3)	90
β [°]	100.67(3)	110.970(8)	90	108.992(12)	76.575(5)	87.35(3)	90.54(3)
γ [°]	90	90	90	90	75.233(5)	82.60(3)	90
V [Å^3]	954.9(3)	1138.12(16)	2228.5(8)	3601.9(8)	2157.7(2)	1986.1(7)	4175.4(14)
Z	2	2	4	4	2	2	4
ρ_{calcd} [g cm^{-3}]	1.427	1.361	1.346	1.166	1.218	1.393	1.162
μ [mm^{-1}]	0.103	0.095	0.096	0.149	0.142	0.103	0.142
F(000)	432	496	952	1360	860	880	1584
crystal size [mm]	0.52×0.50×0.02	0.54×0.28×0.09	0.57×0.34×0.17	0.12×0.16×0.90	0.79×0.13×0.11	0.68×0.24×0.13	0.73×0.25×0.11
range of θ [°]	3.37 to 29.99	2.85 to 28.74	2.66 to 30.00	2.76 to 28.79	2.77 to 30.00	3.15 to 28.76	3.29 to 32.50
index ranges	$-14\le h\le 13$ $-13\le k\le 14$ $-13\le l\le 12$	$-14\le h\le 14$ $-14\le k\le 14$ $-13\le l\le 13$	$-24\le h\le 24$ $-19\le k\le 19$ $-13\le l\le 13$	$-16\le h\le 16$ $-22\le k\le 23$ $-21\le l\le 22$	$-16\le h\le 16$ $-18\le k\le 18$ $-21\le l\le 21$	$-8\le h\le 9$ $-16\le k\le 16$ $-30\le l\le 30$	$-12\le h\le 14$ $-28\le k\le 29$ $-28\le l\le 32$
reflns (collected/unique)	15584/2755 [R(int)=0.0377]	20919/2840 [R(int)=0.0312]	49451/3366 [R(int)=0.0348]	31993/8811 [R(int)=0.0951]	76064/12561 [R(int)=0.0658]	18339/9299 [R(int)=0.0237]	57540/13669 [R(int)=0.0440]
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	full-matrix least squares on F^2	full-matrix least squares on F^2
data/restr./param.	2755/0/181	2840/0/215	3366/0/213	8811/18/416	12561/15/780	9299/0/723	13669/0/686
GooF	1.124	1.042	1.050	0.861	1.022	1.050	0.964
R indices [$I>2\sigma(I)$]							
R1	0.0595	0.0397	0.0436	0.0650	0.0576	0.0475	0.0544
wR2	0.1737	0.0991	0.1175	0.1582	0.1500	0.1342	0.1440
R indices (all data)							
R1	0.0685	0.0611	0.0476	0.2308	0.0857	0.0656	0.0874
wR2	0.1874	0.1181	0.1221	0.2312	0.1746	0.1591	0.1709
extinction coefficient	0.002(6)	0.008(3)	0.0111(14)	0.0031(8)	0.0083(18)	0.0023(12)	0.0009(5)
$\Delta\rho_{max}/\rho_{min}$ [e Å^{-3}]	0.615/−0.360	0.366/−0.316	0.471/−0.246	0.342/−0.255	0.989/−0.584	0.377/−0.274	0.672/−0.367

2H; CH_2); ^{13}C NMR (50 MHz, [D_6]DMSO): $\delta = 163.4$, 163.2, 148.6, 148.5, 139.4, 123.9, 36.6, 29.8, 25.8; HR MS (ESI): m/z: calcd for $C_{19}H_{22}N_6O_4Na$: 421.1595, found: 421.1609 $[M+Na]^+$; elemental analysis calcd (%) for $C_{19}H_{22}N_6O_4$ (398.42): C 57.28, H 5.57, N 21.09; found: C 56.96, H 5.71, N 20.84.

^{1}H NMR titrations: All salts and ligands were pre-dried under high vacuum at 60 °C. [D_6]DMSO of 99.9 % isotopic purity, purchased from ARMAR AG, was used as received. Varian Gemini 200 spectrometer was used for titration experiments (^{1}H: 200 MHz).

A 2.6 −17 mM solution of a ligand (0.45–0.60 mL) was titrated in NMR tubes with 10–40 μL aliquots of a solution of respective tetrabutylammonium salt (50–160 mM). The shifts of the proton signals were monitored and 12–16 data points were recorded. Association constants were calculated from changes in chemical shifts in ligands' amide hydrogens. Nonlinear curve fit for simple 1:1 binding model was carried out with the Origin program. Association constants K and asymptotic change in chemical shift $\Delta\delta_{max}$ were set as free parameters for fitting. Dilution of a ligand was taken into account in the following equation:

$$\Delta\delta = \frac{\Delta\delta_{max}\left(\frac{VL}{V+X} + \frac{AX}{V+X} + \frac{1}{K} - \sqrt{\left(\frac{VL}{V+X} + \frac{AX}{V+X} + \frac{1}{K}\right)^2 - 4\left(\frac{VL}{V+X}\right)\left(\frac{AX}{V+X}\right)}\right)}{\frac{2VL}{V+X}}$$

where $\Delta\delta$ is the chemical shift change at given point (ppm); $\Delta\delta_{max}$, the asymptotic, maximum change in chemical shift (parameter, ppm); X, the amount of an anion salt solution added to the NMR tube (mL); L, the initial concentration of a ligand solution (mol dm^{-3}); A, the concentration of an anion salt solution (TBAX, mol dm^{-3}); V, the initial volume of a ligand solution in the NMR tube (mL); K, the association constant (parameter, mol^{-1} dm^3).

X-ray crystallographic study: The X-ray measurements were undertaken in the Crystallographic Unit of the Physical Chemistry Lab. at the Chemistry Department of the University of Warsaw. Crystal data and details of the crystal structure determinations are presented in Table 4. The intensity data were collected by using Kuma KM4CCD diffractometer, using the omega scan mode. Data were corrected for decay, Lorentz and polarization effects. The structure was solved by direct methods[61] and refined using SHELXL.[62] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were found from a difference density map and refined without any constraints.

CCDC-229349 (**2**), -264724 (**4**), -264726 (**14**), -264723 (**2**·Cl$^-$), -229350 (**2**·CH_3CN), -264725 (**4**·Cl$^-$), -264727 (**14**·Cl$^-$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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