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Synthesis, structure, and complexing properties of macrocyclic receptors for anions*

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Abstract: Understanding of structure–affinity relationships is crucial for rational receptor design, however, such studies for anion receptors are still limited. Therefore, we investigated this issue in the case of amide-based macrocyclic receptors derived from aromatic diacids (i.e., isophthalic and dipicolinic). Using these model compounds, we examined the macrocyclic effect, the influence of intramolecular hydrogen bonds, and the correlation between the ring size and anion affinity. We found that in contrast to what was known for acyclic diamides, macrocyclic isophthalamide receptors bind anions more weakly than their dipicolinic analogs. Comprehensive structural studies revealed that such behavior is due to intramolecular hydrogen bonds present in isophthalamide receptors. Furthermore, we demonstrated how this obstacle can be overcome by the preparation of a hybrid macrocycle based on both building blocks.

Keywords: anion recognition; hydrogen bonds; macrocyclic ligands; receptors; amides.

INTRODUCTION

The supramolecular chemistry of anions is an area of intense current interest owing to the important roles anions play in biological systems [1–6], waste remediation [7], the selective extraction of transition metals [8], and catalysis [9–11]. One of the challenges in this area of supramolecular chemistry is the preparation of anion receptors with high affinity and selectivity for specifically targeted anionic guests. Most of the current scientific research is focused on neutral receptors that bind anions with hydrogen bonds [12–18], since these interactions strongly depend on the direction and distance, hence in principle can assure high selectivity. However, a single hydrogen bond is typically weak, and strong binding can only be achieved by multiple such interactions. This creates new problems, since in order to achieve a perfect complementarity with a target guest it is necessary to arrange the hydrogen-bond donors in a very precise manner within a host structure. For this reason, one of the most important aspects of anion recognition is the understanding of the relationship between ligand structure and its affinity toward anions.

Macrocyclic topology is very effective in gathering many binding sites in close proximity and directing them in a convergent manner [13]. However, investigations of the connection between structure and anion-binding properties of such systems are rare. Therefore, we have undertaken systematic studies of macrocyclic amide receptors for anions. In this report, we present an account of these studies.

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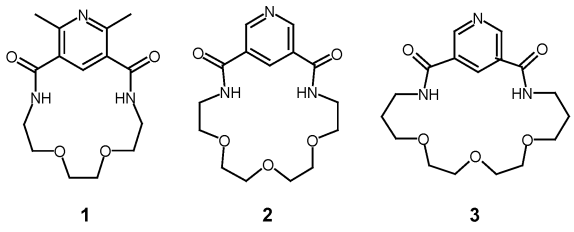
RESULTS AND DISCUSSION

Macrocyclic diamides

Simple acyclic diamides derived from isophthalic acid and 2,6-pyridinedicarboxylic acid (dipicolinic) were reported by Crabtree's group to bind anions strongly in CH_2Cl_2 [19,20]. These results prompted us to prepare macrocyclic receptors based on the aromatic diacids [21,22]. Using our previous experience in the synthesis of coronands [23,24], we prepared compounds **1**–**4** from appropriate esters and polyethyleneamines. However, even in such noncompetitive solvent as dichloromethane, these macrocycles interact with anions very weakly, much weaker than Crabtree's acyclic receptors (e.g., K_a's for Cl^- complexation are <40). It seems that oxygen atoms present in their structure diminish the receptors' affinity toward anions. One possible contributory factor to the weak binding of anions is the intramolecular hydrogen bonds between the ether and amide functionalities, which are disrupted upon anion binding. In addition, the repulsion between the oxygens' lone pairs and the anion will disfavor binding.



On the basis of these findings, we decided to prepare receptor with purely hydrocarbon rim, devoid of oxygen atoms. Although the synthesis was now more challenging, we obtained macrocycle **5** and examined its anion-binding properties [21]. Our initial experiments showed that **5** indeed interacts with anions more strongly than its oxygen-containing analog **4** (Fig. 1). These results demonstrate that although polyether building blocks are often used for the construction of cation binding macrocycles, they are unsuitable for anion receptors.

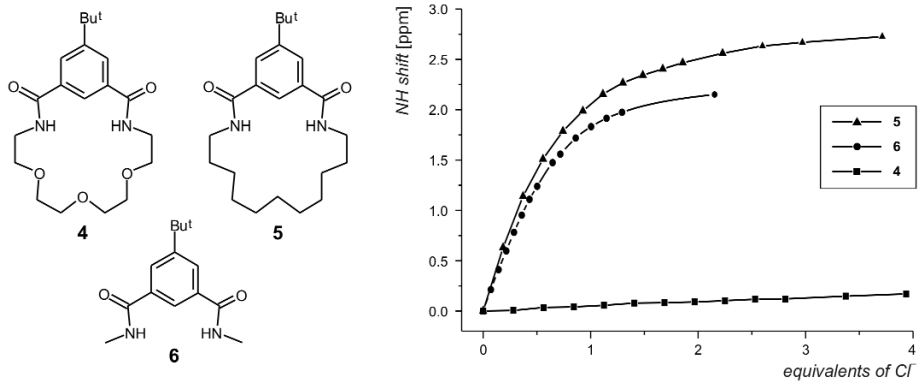


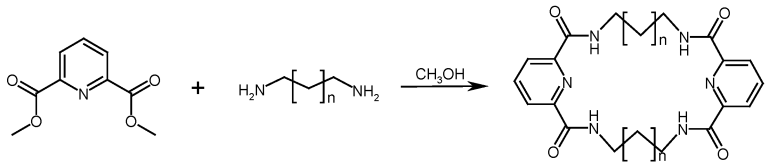
Fig. 1 ^{1}H NMR titration experiments for ligands **4**–**6** with TBACl in $CDCl_3$.

However, we found that macrocycle **5** binds anions with comparable strength to the model acyclic receptor **6** (Fig. 1). The most probable interpretation is that the isophthalic acid moiety is already quite rigid and its incorporation into the macrocyclic structure has little effect on the degree of preorganization of the binding site.

So the question arises, how can the receptor affinity toward anions be improved if a simple macrocyclic effect is insufficient? We approached this problem by multiplication of binding sites in a host molecule and therefore decided to study macrocyclic tetraamides.

Dipicolinic acid-based macrocyclic tetraamides

Application of the synthetic method developed in our group allowed us to obtain a series of macrocylic tetraamides by aminolysis of dipicolinic acid methyl ester with α,ω-diamines of different lengths [25–27]. Using this methodology, we prepared 18-, 20-, 22-, 24-, and 26-membered macrocyclic receptors (**7**–**10**). Although the yields of macrocyclizations were in most cases quite low, this synthetic procedure is particularly straightforward, and, moreover, it also yields interesting higher-order cyclic oligoamides, namely, hexaamides and octaamides [21,28].



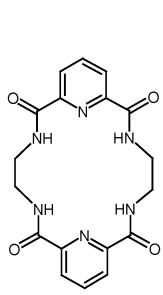
7 n=0, 51 %
8 n=1, 5.6 %
9 n=2, 2 %
10 n=3, 7.5 %

Having prepared our model compounds, we studied their affinity toward anions. Even in highly competitive solvent, dimethylsulfoxide (DMSO), these receptors interact with various anions strongly enough to determine the respective binding constants using ^{1}H NMR titration technique (owing to the small solubility of the ligand **9**, we could not examine its properties in solution).

The selectivity trends displayed by the three macrocycles are similar and typical for most of the hydrogen-bonding receptors: dihydrogen phosphate, acetate, and benzoate are most strongly bound, whereas cyanide, bromide, *p*-nitrophenolate, and hydrogen sulfate anions form weak complexes (Table 1). It is noteworthy that there appears to be no correlation in our data between the basicity of anions and the stability constants of their complexes. For example, the weakest base, bromide ion, forms a stronger complex with **8** than *p*-nitrophenolate does, in spite of basicity weaker by 10 orders of magnitude. Similarly, **8** prefers weakly basic chloride over strongly basic cyanide or *p*-nitrophenolate.

These data present the unique possibility to study the relationship between macroring size and binding properties. The affinity toward anions as a function of macrocycle size shows sharp maximum for the 20-membered macrocycle **8** (Fig. 2). As a result, the ligand **8** is the best receptor for all anions studied. The increase in binding constants was the most pronounced in the case of chloride anion, probably due to geometric complementarity with the 20-membered macrocycle. This complementarity was confirmed by X-ray crystallographic analysis in the solid state (Fig. 2).

Table 1 Binding constants (M^{-1}) for the formation of 1:1 complexes of **7**, **8**, and **10** with various anions in DMSO-d_6 at 298 K.*



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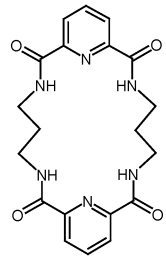

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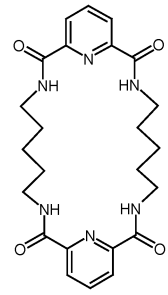


10

Anions	K [M^{-1}]	K [M^{-1}]	K [M^{-1}]
Cl^-	65	1 930	18
Br^-	<5	150	<5
CN^-	50	350	50
p-NO_2PhO^-	70	120	<5
$PhCO_2^-$	200	2 280	300
AcO_2^-	2 640	3 240	310
$H_2PO_4^-$	1 680	7 410	450
HSO_4^-	<5	75	<5

*Determined using ^{1}H NMR titration; TBA salts were used as the source of anions.

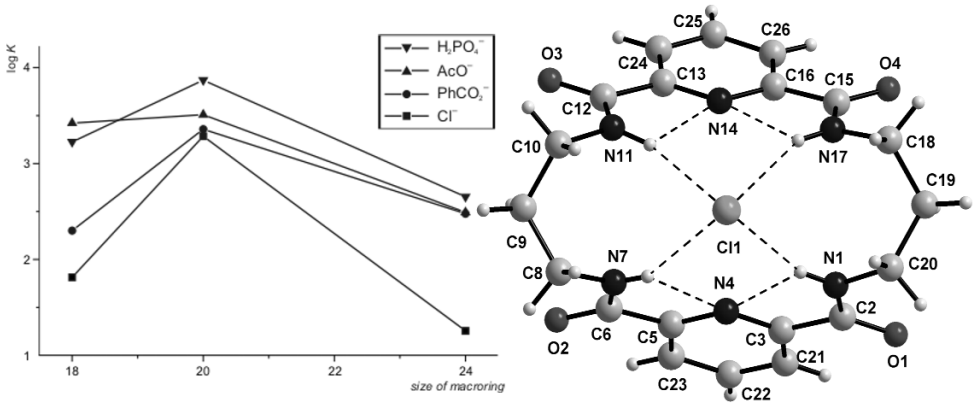
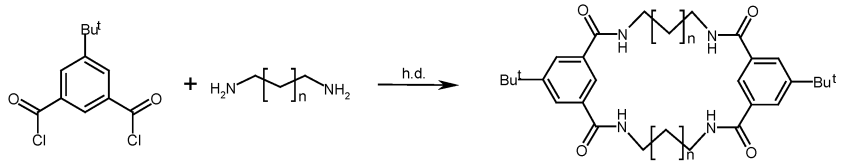


Fig. 2 Plot of the logarithm of the association constant vs. the size of receptor's cavity (left). The crystal structure of the complex **8**·(n-Pr)$_4$NCl (right).

Isophthalic acid-based macrocyclic tetraamides

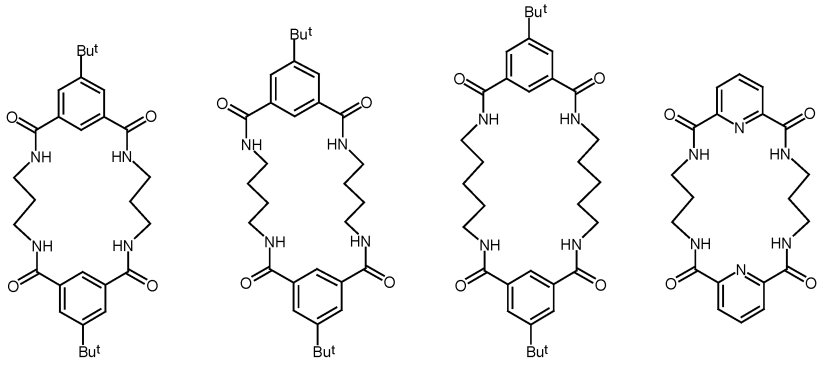
We continued our studies of macrocyclic receptors with a family of ligands based on 5-*tert*-butylisophthalic acid [29,30]. Owing to the low reactivity of isophthalic esters, we could not employ aminolysis for macrocyclization, so instead we used isophthalic acid chloride and a high-dilution technique. The product derived from 1,2-diaminoethane (**11**) turned out to be hardly soluble in most solvent, and therefore we were unable to obtain it in a pure form.



11 n=0, -
12 n=1, 32 %
13 n=2, 15 %
14 n=3, 11 %

^{1}H NMR spectroscopic binding studies in DMSO-d_6 solution revealed that this class of receptors shows similar selectivity to the previous series based on pyridine subunit (Table 2). The strongest interaction is observed for oxo-anions: acetate, benzoate, and dihydrogen phosphate. Furthermore, the 20-membered ligand **12** is once again the best receptor in all studied cases.

Table 2 Binding constants (M^{-1}) for the formation of 1:1 complexes of **12**, **13**, **14**, and **8** with various anions in DMSO-d_6 at 298 K.*



	12	**13**	**14**	**8**
Anions	K [M^{-1}]	K [M^{-1}]	K [M^{-1}]	K [M^{-1}]
Cl^-	380	300	50	1 930
Br^-	20	20	7	150
$PhCO_2^-$	600	300	80	2 280
AcO_2^-	3 130	550	205	3 240
$H_2PO_4^-$		573		7 410
HSO_4^-	<5			75

*Determined using ^{1}H NMR titration; TBA salts were used as the source of anions.

These observations confirmed that the preference for oxo-anions is characteristic of macrocyclic tetraamides derived from aromatic diacids and α,ω-diamines. In both examined series of ligands, starting from 20-membered receptor, monotonic decrease of the binding affinity with increasing macrocycle size is clearly observed for all anions tested, irrespective of their size. Thus, the size match between an anion and the cavity of the receptor does not solely determine the observed selectivity. Extensive structural analysis of macrocycles **7**–**14** and their complexes allowed us to understand these results [26,29]. In all complexes observed, anions are not encapsulated but perch on ligands, hence there is no reason for the size correlation. It seems most likely that the three methylene groups in the aliphatic linkers of

receptors **8** and **12** are a good compromise between contradictory requirements of adaptability and preorganization.

Why do isophthalamide-based receptors bind anions weaker than pyridine-based receptors?

According to Crabtree et al. [19,20], isophthalamides are much more potent anion receptors than 2,6-pyridine diamides, in which the electron pair of the pyridine nitrogen atom competes with anions for hydrogen bonding with the amide *NH* groups. According to an alternative view, higher anion affinity of isophthalamides may be attributed to additional favorable interaction with aromatic *CH* protons at the 2-position. Surprisingly however, our macrocyclic isophthalamides (**12**–**14**) turned out to be weaker anionophores than their pyridine analogs (**7**–**10**). Similar observations were made by Bowman-James [31] on the 24-membered macrocyclic receptors and were ascribed to worse preorganization of the isophthalamide receptors. Our comprehensive structural studies provided better insight into origins of these phenomena.

Molecular modeling, solution NMR studies, and X-ray crystallography unanimously show that pyridine-containing ligands favor convergent conformation with all four amide hydrogens directed toward the center of each macrocycle (Fig. 3). This increased preorganization means that all hydrogen bond donors are readily available for the interaction with an anion. On the contrary, isophthalic acid-based macrocycles prefer to adopt a conformation with two intramolecular NH···O=C hydrogen bonds between the two opposite isophthalamide moieties (Fig. 3). These two bonds need to be broken during anion complexation, and thus disfavor binding. This conformational change is accomplished by the rotation of amide groups from the *syn–anti* relative orientation to the *syn–syn* one. Although simple isophthalamides undergo similar conformational change [32], it is not accompanied by the breakage of intramolecular hydrogen bonds. That is why, although simple acyclic isophthalamides are better anion receptors than pyridine diamides, the contrary is true for our macrocyclic tetraamides.

The above results illustrate an intrinsic disadvantage of amide-based anion receptors. The amide group consists of hydrogen bond donor (NH) and hydrogen bond acceptor (C=O) which can easily participate in intramolecular hydrogen bonds that obstruct efficient anion binding.

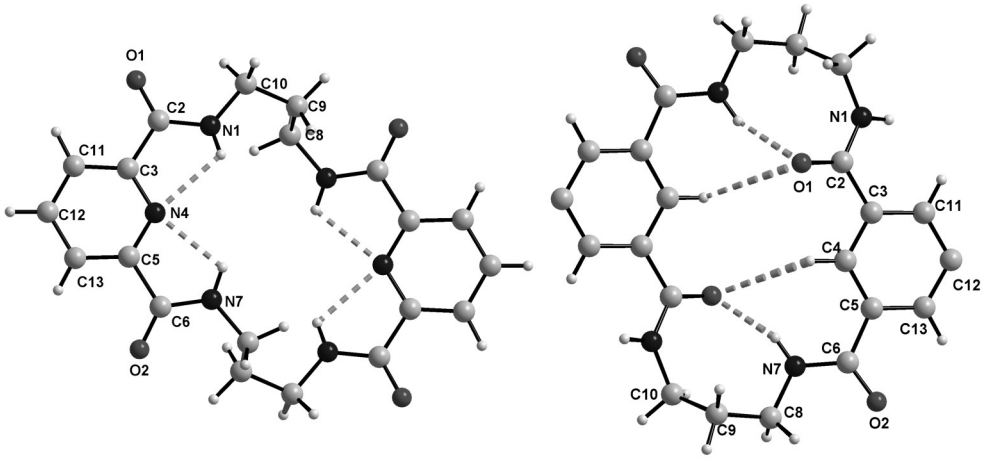
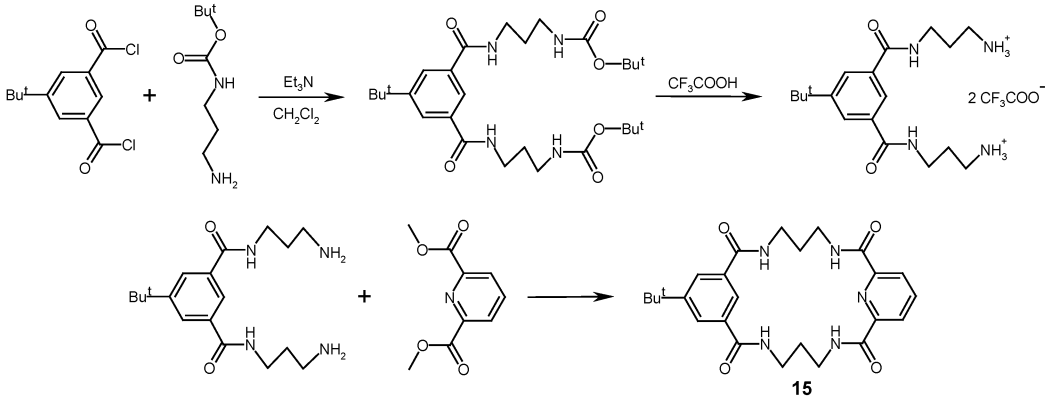


Fig. 3 Crystal structure of ligands **8** (left) and **12** (right), Bu^t groups omitted for clarity.

The hybrid macrocyclic tetraamide

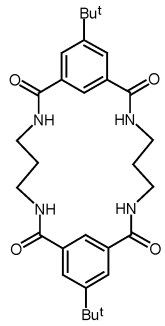
The anion binding of our macrocyclic, isophthalamide-based receptors has been shown to be hampered by their poor preorganization, therefore our next aim was to force isophthalamide subunit to adopt the *syn–syn* conformation. To achieve this goal we decided to use dipicolinic acid moiety as an organizing element. Amides derived from dipicolinic acid are known for their strong preference for the *syn–syn* conformation, whereas isophthalamides easily adapt either *syn–anti* or *syn–syn* conformations. We hoped that the pyridine-2,6-dicarbamoyl moiety would enforce, through the macroring, the same conformation on the isophthalic unit. To check this hypothesis, we prepared hybrid macrocycle **15** consisting of both pyridine and phenyl moieties [33].



15

Anion-binding studies in DMSO-d_6 confirmed our expectations (Table 3). The hybrid receptor **15** binds anions stronger than its homoaromatic analogs **8** and **12**. The increase of binding strength is most striking when compared to isopthalamide-based ligand **12**, at the same time ligand **12** and hybrid macrocycle **15** have similar relative selectivities. To summarize, our design of hybrid receptor **15** has overcome two problems that appear in isophthalic receptors **12**–**14**—firstly, the wrong conformation of the isophthalic moieties, and secondly, the existence of competing intramolecular hydrogen bonds.

Table 3 Binding constants (M^{-1}) for the formation of 1:1 complexes of **12**, **15**, and **8** with various anions in DMSO-d_6 at 298 K.*



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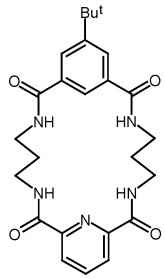

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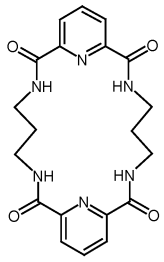


8

Anions	K [M^{-1}]	K [M^{-1}]	K [M^{-1}]
Cl^-	380	2 150	1 930
Br^-	20	175	150
$PhCO_2^-$	600	3 610	2 280
$H_2PO_4^-$		>8 000	7 410

*Determined using ^{1}H NMR titration; TBA salts were used as the source of anions.

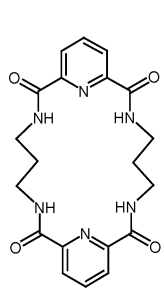
The macrocyclic effect

The idea behind preparation of macrocyclic tetramides was to multiplicate binding sites in order to increase ligands' affinity toward anions. This goal was undoubtedly achieved since binding constants for both types of receptors were more than two orders of magnitude higher than for simple models—acyclic diamides based on the same building blocks (e.g., K_a in DMSO for complex formation between TBA benzoate and dipicolinic acid butyl amide is ~6, while for isophthalamide ~10 [32]).

However, the question arises which factor contributes more to the observed binding constant: the macrocyclic effect or the presence of two additional amide groups? This question is especially interesting in the case of dipicolinic acid derivatives which consist of two rigid fragments that are already well preorganized for anion binding, and therefore should not suffer very much from the lack of macrocyclic topology. To investigate this question, we prepared two model acyclic tetraamides **16** and **17** based on building blocks previously studied [26,29]. Their binding properties were examined in DMSO-d_6, and the stability constants are shown in Table 4. Both acyclic ligands **16** and **17** bind anions very weakly, their binding constants are about 20 times smaller than these of macrocyclic receptors **8** and **12**.

These results show the importance of macrocyclic effect, though its strength is hard to explain. Structural analysis of acyclic ligand **16** shows that its twisted conformation is stabilized by two intramolecular hydrogen bonds, which have to be broken during complexation [26]. However, both isophthalamide-based receptors **12** and **17** are locked with intramolecular hydrogen bonds, so observed differences in binding affinity origin only from the "flexibility" of the acyclic ligand. It could be assumed that in the case of these receptors, the macrocyclic effect should be less pronounced, however, we observed comparable macrocyclic effects for both pairs of receptors.

Table 4 Binding constants (M^{-1}) for the formation of 1:1 complexes of macrocycles **8**, **12**, and their acyclic models **16**, **17** with various anions in DMSO-d_6 at 298 K.*



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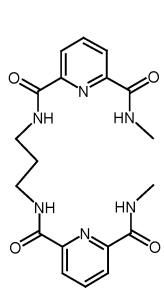

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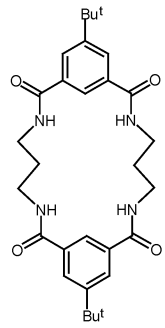

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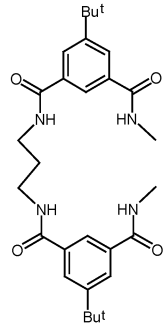

17

Anions	**8** K [M^{-1}]	**16** K [M^{-1}]	**12** K [M^{-1}]	**17** K [M^{-1}]
Cl^-	1 930	45	380	14
Br^-	150		20	2
AcO_2^-	3 240	160	3 130	130
$H_2PO_4^-$	7 410	350		60

*Determined using ^{1}H NMR titration; TBA salts were used as the source of anions.

CONCLUSION

During our comprehensive studies of macrocyclic amide-based receptors derived from dipicolinic and isophthalic acids, we have had an unique opportunity to resolve the relationship between structure of the ligands and their affinity toward anions. For better understanding of complexation phenomena, we used various techniques of structural analysis, namely, molecular modeling for gas-phase, 2D NMR studies in solution, and X-ray crystallographic analysis for solid state. Not only does it give us insight into anion recognition, but also stimulated us to design and prepare more efficient receptors.

Investigation of macrocyclic bisamides showed limitation of macrocyclic effect and demonstrated how the presence of ethereal oxygen atoms can hamper anion binding. It also prompted us to prepare the macrocyclic tetraamides.

Synthesis of the whole family of macrocyclic tetraamides allowed us to examine the correlation between the macroring size and binding constants. The study revealed a significant effect of the receptor size on anion-binding ability. Each anion, irrespective of its size or shape, binds most strongly to the 20-membered macrocycles. Apparently, the size complementarity between an anion and the receptor cavity plays a secondary role here and does not determine the mutual affinity. More likely, the anion-binding ability of our receptors depends on their flexibility. Nevertheless, the geometric fit manifests in exceptionally strong complexation of Cl^- by the receptor **8**.

Isophthalamide moieties present in macrocycles **12**–**14** adopt a self-complementary *syn–anti* conformation and form two strong intramolecular hydrogen bonds, which close the macrocyclic cavity and lower anion-binding affinity. To lock isophthalamide subunit in the *syn–syn* conformation and prevent it from participation in intramolecular hydrogen bonds we prepared hybrid macrocycle **15**. The hybrid ligand **15** is the best receptor studied and demonstrates how understanding of structural aspects of complexation phenomena can lead to increased efficiency.

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