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Size complementarity in anion recognition by neutral macrocyclic tetraamides ☆

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Abstract—Comparison of the anion binding properties of a series of uncharged macrocyclic tetraamides reveal significant effects of the receptor's size on the strength of its anion complexes. This study allowed for estimation of the optimal size of a macroring for complexation of common anions.
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Anions are of crucial importance in many essential chemical and biological processes and therefore the development of strong and selective artificial anion receptors is of great interest and significance.[1] This is not an easy task, however, because most anions are large, highly solvated and coordinatively saturated species. One way to cope with these difficulties is to make use of the macrocyclic effect. Indeed, in virtually every case studied, macrocyclic anion receptors performed better than their acyclic counterparts.[2–5] Binding properties of macrocyclic receptors depend mainly on the type and arrangement of binding sites, the size and shape of the macroring and its rigidity. Experimental studies on the influence of these factors on anion recognition were focused on highly charged, multiply protonated polyazamacrocycles that bind anions in protic solvents mainly through Coulombic interactions.[6] Hydrogen bonding, being more directional, is also more sensitive to geometric constraints. In spite of this, systematic studies on structure/affinity relationships in uncharged macrocyclic receptors are scarce.[4,5,7]

Therefore, we decided to study the influence of the size of macrorings of hydrogen-bonding receptors on the stability of their anion complexes. Recently, we have shown that macrocyclic tetraamides consisting of 2,6-dicarbamoylpyridine moieties linked with short aliphatic chains form well defined and relatively rigid cavities.[8] Moreover, all the amide hydrogens are directed inwards by intramolecular hydrogen bonding with pyridine nitrogen atoms. Taken together, these features make them ideally suited models for our studies.

We have recently published a full account on the anion binding properties of **1**, the smallest member of the series.[3] Crystallographic studies have shown that the Cl^- anion is too bulky to be included in the cavity of this 18-membered tetraamide. We reasoned that larger tetraamide **2** should accommodate Cl^- more easily resulting in higher affinity for this anion. By the same token, because **1** binds only one oxygen atom of AcO^- in the solid state,[3] we hoped that enlargement of the cavity would allow for simultaneous capture of both oxygens with a concomitant increase of binding constants. An analogous binding mode was observed by Bowman-James and co-workers[9] for the sulfate complex of the 24-membered macrocyclic tetraamide similar to **4**.

Tetraamides **1** and **3**, derived from amines having even numbers of methylene units, can be conveniently synthesised by the macrocyclisation of dimethyl pyridine-2,6-dicarboxylate with an appropriate α,ω-diamine in methanol (Scheme 1).[8]

Due to their very low solubility, they spontaneously separate from the reaction mixture. Extension of this

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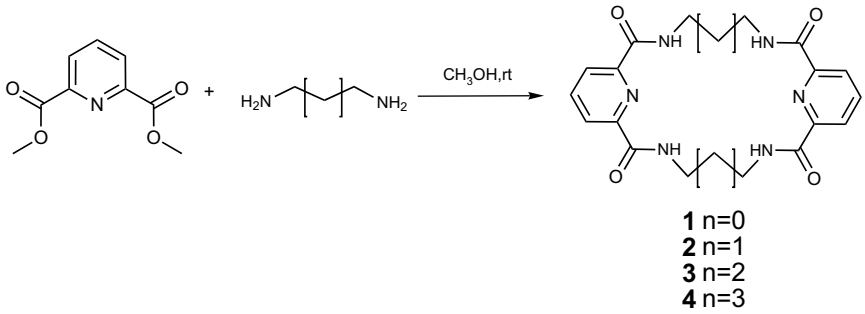


Scheme 1.

method to α,ω-diamines with odd numbers of methylene units was met with severe problems with separation of the desired tetraamide from larger macrocyclic products. Nevertheless, extensive chromatography allowed us to obtain samples of receptors **2** and **4** that were pure enough for anion binding studies.

Diffraction-grade single crystals of **2** were obtained by slow diffusion of Et_2O into a solution of **2** in 9:1 CH_2Cl_2/CH_3OH solvent mixture. Both the conformation of the receptor and crystal packing were very similar to the previously published structures of **1** and **3** (Fig. 1).[8]

The macroring is in a centrosymmetric, expanded conformation. All the amide hydrogens are arranged in a convergent manner by intramolecular $NH_{amide}\cdots N_{py}$ interactions and are also involved in intermolecular hydrogen bonding with amide oxygens of neighbouring molecules. It should be stressed that, due to the stair-like conformation of the molecule, the two pairs of amide hydrogens interact with two different acceptors.

It follows that simultaneous formation of four hydrogen bonds to the same acceptor must be accompanied by a conformational change. Such an adjustment of the structure of **2** is enabled by its flexible aliphatic linkers, as illustrated by the crystal structure of its complex with acetonitrile (Fig. 2).

High quality single crystals of this solvate were obtained during our efforts to grow crystals of the acetate complex of **2**, by slow evaporation of a solution of **2** and tetrabutylammonium acetate in acetonitrile. In the

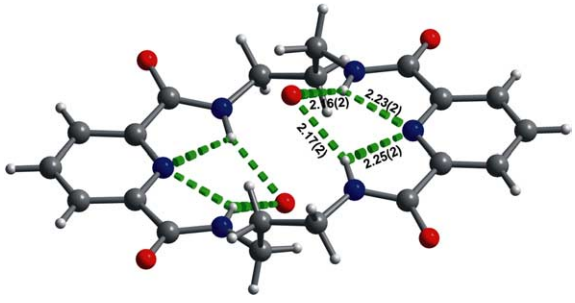


Figure 1. Crystal structure of **2**. Lengths of intramolecular $NH\cdots N_{py}$ and intermolecular $NH\cdots O_{amide}$ hydrogen bonds are given in angstrom.

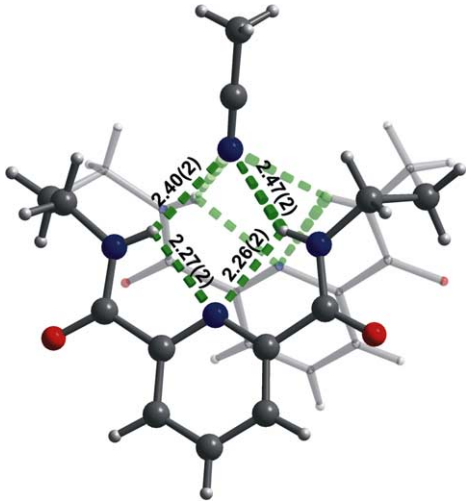


Figure 2. Crystal structure of **2**×CH_3CN. Lengths of intramolecular $NH\cdots N_{py}$ and intermolecular $CH_3CN\cdots HN$ hydrogen bonds are given in angstrom.

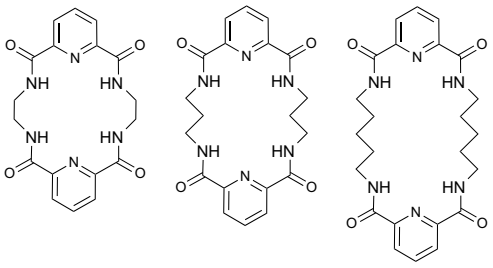
crystal structure, **2** adopts a highly bent conformation that allows for simultaneous formation of four hydrogen bonds to the same molecule of acetonitrile.

The stability constants of receptors **2** and **4** with various anions were determined by ^1H NMR titrations in DMSO-d_6 solution (Table 1, for details see Supplementary material). The low solubility of compound **3**, although facilitated its synthesis, prevented evaluation of its anion complexation properties.

It is immediately apparent from Table 1 and Figure 3 that the 20-membered macrocyclic tetraamide **2** is the best receptor for all the anions studied.

Another striking effect is the sharp maximum of affinity towards Cl^- as a function of receptor size. Enlargement of the size of the macrocyclic ring from 18 to 20 resulted in a 30-fold increase in the respective binding constant, whereas further enlargement by four methylene units causes reduction of affinity towards Cl^- by two orders of magnitude. This suggests a very good size complementarity between chloride and 20-membered tetraamide **2**. Similar, but smaller effects can be seen for binding constants of oxyanions; as a consequence, receptor **2** binds chloride anions almost as strongly as benzoate,

Table 1. Binding constants (M^{-1}) for the formation of 1:1 complexes of **1**, **2** and **4** with various anions in DMSO-d_6 at 298 K[a]



Anion	1	2	4
Cl^-	65[b]	1930	18
$PhCOO^-$	202	2283	301
AcO^-	2640[b]	3240	310
$H_2PO_4^-$	1680[b]	7410	450
HSO_4^-	<5	75	<5

[a] Errors are estimated to be <10%. Tetrabutylammonium salts were used as anion sources.
[b] Values from Ref. 3.

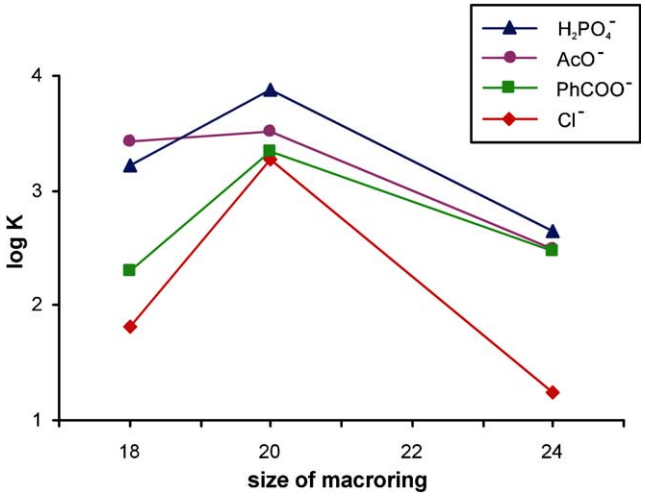


Figure 3. Plot of the logarithm of the association constant versus the size of receptor.

despite Cl^- being several orders of magnitude weaker in basicity.

The similarly large difference in basicity and hydrogen bond acceptor ability between dihydrogenphosphate and hydrogensulfate is not counterbalanced by geometric effects. As a result, all three receptors bind $H_2PO_4^-$ at least two orders of magnitude more strongly than HSO_4^-. This behaviour is often found for receptors based on hydrogen bonding.

The 24-membered macrocycle **4** is large enough to accommodate the two oxygen atoms of phosphate, sulfate or carboxylate anions. Therefore, we expected strong interactions between the receptor and these anions. However, the binding constants of receptor **4** with carboxylate, phosphate and sulfate anions are relatively small. This suggests that in all these cases, only one oxygen atom of the anion is involved in binding with the receptor.

The hypothesis for the monodentate binding mode of oxyanions with tetraamides **1**–**4** also explains why the effect of ring size on binding constants with spherical chloride is qualitatively the same as on the binding constants with acetate, phosphate and sulfate. From the receptor viewpoint, all these oxyanions are represented by one oxygen atom and resemble spherical chloride anions. In contrast to oxyanions, however, Cl^- can enter the receptor cavities more deeply and this better geometrical fit is responsible for the more pronounced changes in affinity.

These preliminary results are very promising. It is evident that the correct choice of the size of uncharged macrocyclic receptors is essential for strong anion binding. The effect is quite pronounced despite the relatively high conformational flexibility of our model receptors. Although size complementarity between Cl^- and receptor **2** was insufficient to overcome the basicity differences between chloride and much more basic oxyanions such as acetate or hydrogenphosphate, it is still possible that 20-membered macrocyclic tetraamide **2** does not perfectly match the size of the chloride anion. Further tuning of the receptor size or the introduction of more rigid spacers in place of polymethylene chains may further improve its selectivity. Work towards this end is in progress in our laboratory.

Supplementary material

Experimental procedures, characterization data for compounds **2** and **4**, details concerning determination of binding constants and X-ray crystal data for **2** and **2**$\times CH_3CN$ are available.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229349 and CCDC 229350. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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