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Anion induced conformational switch of a macrocyclic amide receptor

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Abstract—Isophthalic acid-based macrocyclic tetraamide **4** shows considerable conformational change during anion binding. In the solid state and in solution the free receptor exists in nonbonding, closed conformation stabilized by two intramolecular hydrogen bonds. Upon anion complexation, the receptor switches to a conformation with convergent arrangement of hydrogen bond donors. The conformational switch is evidenced by 2D NMR and X-ray analyses of the free ligand and its Cl^- complex.
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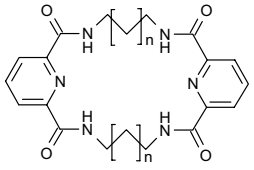
In Nature, conformational changes upon substrate binding, amplified and space propagated, are one of the most commonly used pathways of signal generation. Artificial systems based on that principle utilize mostly cation coordination to trigger molecular shape changes.[1,2] An analogous and complementary approach, based on anion binding[3] by hydrogen bond donating groups, only recently reached the stage of development that allows for its use as a tool in supramolecular chemistry. Therefore there is still a limited number of well-defined anion-triggered shape switching systems.[4–6] Of these some have already been applied for the construction of fluorescent and chromogenic sensors[5] or for controlled translocation of a macrocyclic ring in a rotaxane.[6] In this communication we describe an isophthalic acid-based macrocyclic tetraamide **4** that switches from a highly folded, 'closed' conformation to an open form upon anion binding.

Tetraamide **4** was synthesized during our ongoing project concerning optimization of the structure of macrocyclic amides for anion binding purposes.[7,8] Previously, we have studied anion binding by the series of macrocyclic tetraamides **1**–**3** derived from 2,6-pyridinedicarboxylic acid.[7,8] Macrocyclic amides of this type, owing to the presence of intramolecular hydrogen bonds involving pyridine nitrogen atoms, form well-defined cavities with convergent arrangement of all amide hydrogens and are well preorganized for anion binding.[9] Nevertheless, the electron lone pairs of the pyridine nitrogen atoms interact unfavorably with anions.[10] Therefore we resolved to check whether isophthalic acid-based analogs of **1**–**3** would be better anion receptors. Because 20-membered macrocycle **2** formed more stable complexes with simple anions (Cl^-, AcO^-, $H_2PO_4^-$) than either **1** or **3**,[8] we decided first to study a macrocycle of the same size. To enhance the solubility of isophthalamides in organic solvents we introduced *tert*-butyl groups into the structure, taking advantage of the commercial availability of 5-*tert*-butylisophthalic acid. Receptor **4** thus designed was synthesized according to Scheme 1 in 32% yield.



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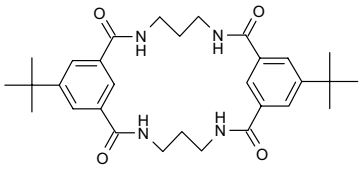
2 n = 1
3 n = 3



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Qualitative observations suggested strong anion binding by **4**: addition of tetrabutylammonium chloride or acetate to the suspension of the receptor in CH_2Cl_2

Keywords: Anion binding; Conformational change; Macrocyclic receptor.
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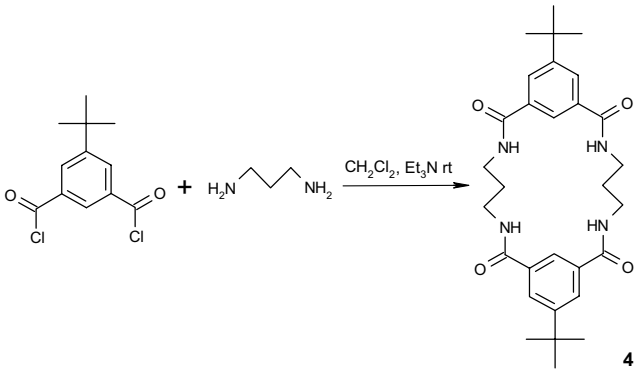


Scheme 1.

caused immediate solubilization of an otherwise insoluble solid. However, the binding constants of receptor **4** with various anions, determined by ^{1}H NMR titrations[11] in DMSO-d_6, turned out to be considerably lower than the values obtained earlier for **2** under analogous conditions (Table 1).

The X-ray crystal structure of tetraamide **4** and its chloride complex shed some light on the reasons for this unexpected behavior. The free ligand adopts a highly twisted conformation in the solid state, stabilized by two intramolecular NH···O$_{amide}$ hydrogen bonds (Fig. 1). Amide groups of both, symmetrically equivalent isophthalic moieties are in a *syn–anti* relationship, that is, two N–H bonds of the same isophthalic moiety point in opposite directions. The macrocyclic cavity in such a conformation is closed, and the molecule can form only weak, external complexes with anions, via single hydrogen bonds.

In DMSO-d_6 solution, ^{1}H and ^{13}C NMR spectra suggest that **4** exists in a more symmetrical conformation, since only 1/4 of the maximum number of signals are visible. However, 2D NOESY spectra reveal NOEs between amide NH protons and both internal and external CH protons of the benzene ring (Fig. 3a). This means that there is a considerable proportion of both *syn*- and *anti*-positioned amide hydrogen atoms in an averaged conformation and suggests that the conformation observed in the solid state predominates also in solution.

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

Anion	2	4
Cl^-	1930[b]	378
Br^-	150	20
AcO^-	3240[b]	3130
$H_2PO_4^-$	7410[b]	[c]
HSO_4^-	75[b]	<5

[a] Errors are estimated to be <10%. Tetrabutylammonium salts were used as anion sources.
[b] Values from Ref. 8.
[c] The data does not fit satisfactorily to a simple 1:1 binding model.

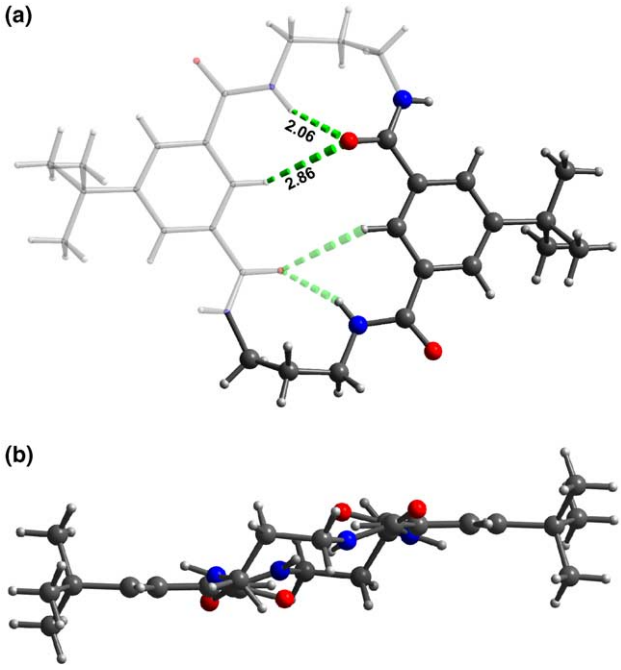


Figure 1. Crystal structure of **4**. (a) Top view. (b) Side view. Distances are given in Å.

The symmetry observed in the 1D NMR spectra must be therefore due to rapid interconversion between two equivalent, unsymmetrical conformations. This dynamic

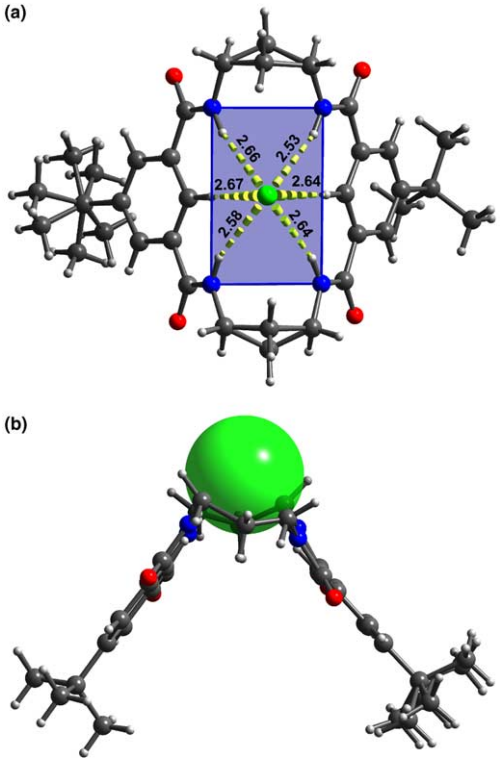


Figure 2. Crystal structure of **4** × Ph_4PCl. (a) Top view. Distances are given in Å. (b) Side view. Cl^- sphere reflects its van der Waals radius. Part of the disorder was removed for clarity.

process is fast on the NMR time scale even at −70 °C (in DMF-d_7).

As evidenced by X-ray and NMR studies the molecule is not well suited for convergent anion binding. The question therefore arises whether anion complexation inside the cavity can be strong enough to compete with the two intramolecular hydrogen bonds and compensate for the cost of a necessary conformational change. The X-ray structure of the chloride complex $\mathbf{4}\times Cl^-$ ($\mathbf{4}\times PPh_4Cl$) undoubtedly proves that the anion can indeed open the macrocyclic cavity breaking two intramolecular hydrogen bonds and switch the macrocycle to a completely different conformation (Fig. 2). The Cl^- anion in the complex forms four hydrogen bonds with amide hydrogen atoms and also lies in close proximity to both internal aromatic protons suggesting additional favorable interactions. We note also that the amide groups are almost co-planar with the benzene rings. This is in contrast with the structure of the free ligand **4** and also most known structures of benzamides and isophthalamides, in which these groups are usually tilted with respect to the adjacent benzene ring due to steric repulsion between the amide proton and aromatic hydrogen atoms in the *ortho*-position.[12] Side views reveal another significant difference between the two structures: whereas the free receptor is roughly planar (Fig. 1b), it adopts a V-shape in the complex, with an angle between the arms of 79° (Fig. 2b).

To probe the structure of anion complexes in solution, NMR studies were conducted. Titration of a DMSO-d_6 solutions of **4** with tetrabutylammonium fluoride, chloride, acetate, or hydrogenphosphate caused considerable downfield shifts of the amide NH and internal aromatic CH signals, whereas external aromatic protons were virtually untouched. This proves that the complexation/decomplexation process is fast on the NMR time scale and furthermore suggests that all these anions are encapsulated inside the macrocyclic cavity and that the complex structure is analogous to that observed in the solid state. The magnitudes of the downfield shifts of the internal aromatic CH signals (0.55 ppm for Cl^-, 0.43 for AcO^-, 0.69 for $H_2PO_4^-$) are particularly impressive; such large values point to quite strong non-classical CH···anion hydrogen bonding interactions.[13]

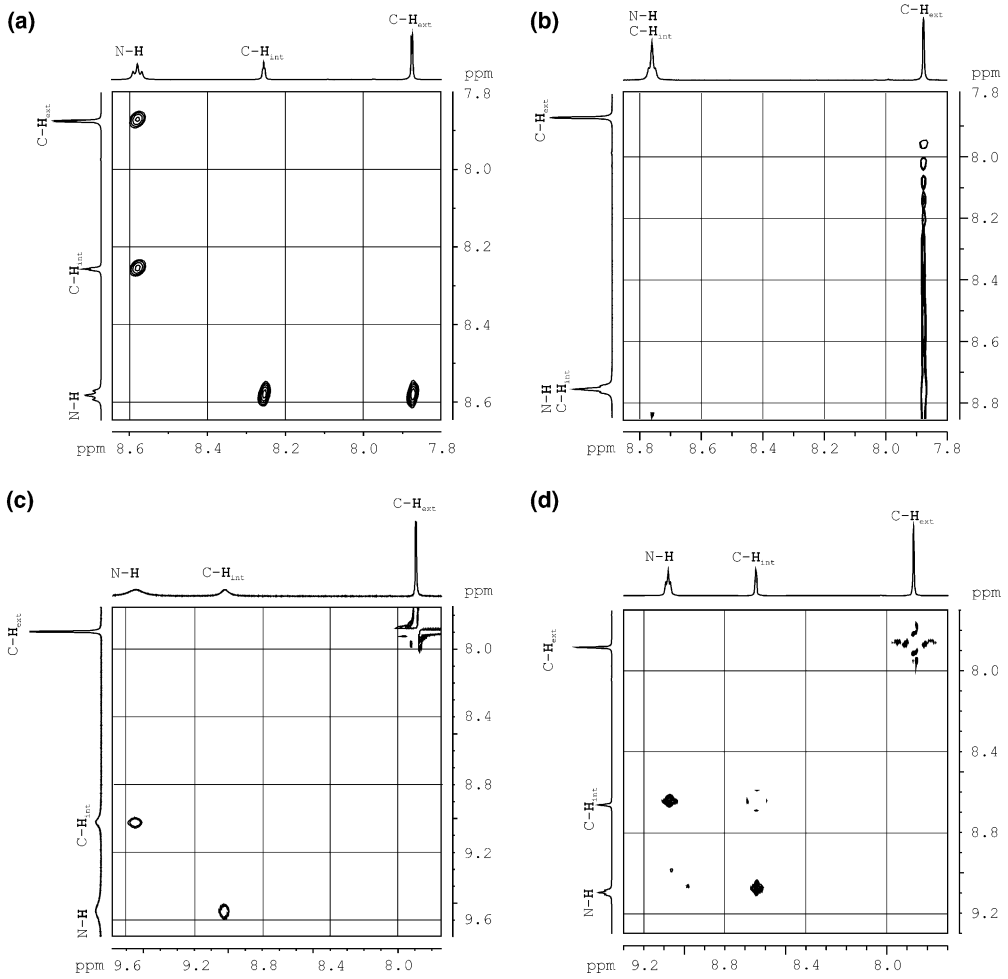
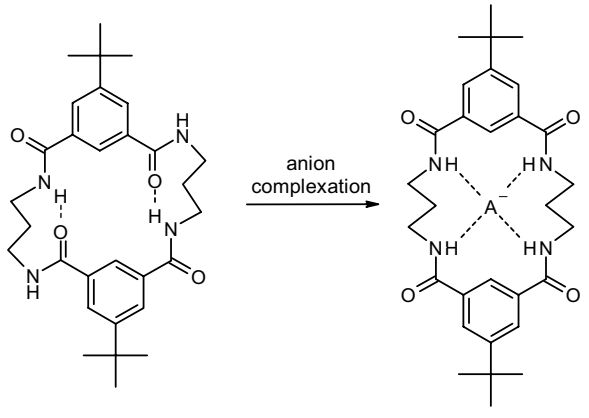


Figure 3. NOESY spectra of **4** and its anion complexes in DMSO solutions: (a) free ligand **4**, (b) **4** + 1.1 equiv of TBACI, (c) **4** + 1.7 equiv of TBAF, (d) **4** + 1.1 equiv of TBAAcO.

Also there is an unusually small effect of Cl^- binding on amide signal shifts. This is most probably due to the fact that the amide protons had already been engaged in intramolecular hydrogen bonding before complexation. Further evidence concerning the conformation of ligand **4** in anion complexes comes from the 2D NOESY spectra (Fig. 3). In the case of the chloride complex of **4** (**4** + 1.1 equiv of TBACl in DMSO-d_6) incidental signal overlapping of amide protons and internal aromatic CH protons precluded observation of the NOE between them. However, in accordance with the proposed structure, no effect could be detected between the amide and the external aromatic protons. In the ^1H NMR spectra of fluoride and acetate complexes of **4** all aromatic and amide signals were clearly distinguishable and NOE were observed between amide NH protons and internal aromatic CH protons. At the same time, no effect was detected between the amide protons and the external aromatic protons. These spectra indicate that in the presence of anions the *syn–syn* conformation of the isophthalic moieties largely predominates. Taken together, it is evident that anion induced conformational change took place and consequently all amide NHs point toward the cavity (Scheme 2).

Summing up, simple isophthalamides may exist as a mixture of three possible conformers: *syn–syn*, *syn–anti*, and *anti–anti*. In the case of tetraamide **4** however, macrocyclic topology and intramolecular hydrogen bonds impose additional constraints to the system and lock both isophthalic units in a *syn–anti* conformation. We have shown here that anion binding is able to break these two intramolecular hydrogen bonds and switch both isophthalic moieties into a *syn–syn* conformation leading to a completely different shape for the entire molecule. Analogous behavior was previously observed for amides derived from 2,6-pyridinedicarboxylic acid. They may be switched from the preferred *syn–syn* conformation to an *anti–anti* conformation through either cation binding[14] or protonation.[15] This second method was used to reversibly switch acyclic oligoamides of this type between linear and helical forms.[15] We hope that the above analogy between cation and anion controlled conformational regulation will promote further fruitful applications of anions as effectors in supramolecular switching devices.



Scheme 2.

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Supplementary data

The synthetic procedure and characterization data for compound **4**; details concerning determination of binding constants and X-ray crystal data for **4** and **4** × Ph_4PCl 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 246610 and 246611. 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]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.135.

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