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Tetrahedron Letters 46 (2005) 3085–3088
Tetrahedron Letters

A hybrid macrocycle containing benzene and pyridine subunits is a better anion receptor than both its homoaromatic congeners

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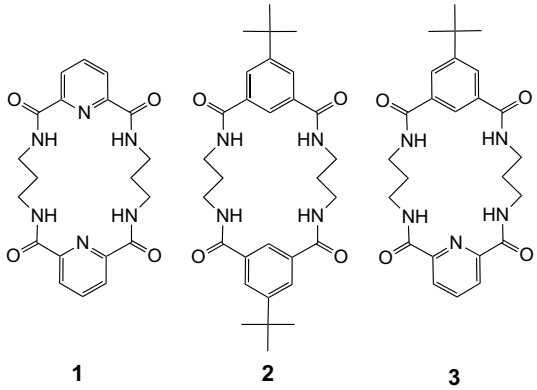
Received 28 December 2004; revised 19 February 2005; accepted 1 March 2005
Available online 16 March 2005

Abstract—The hybrid tetraamide receptor **3** containing both 2,5-diamidopyridine and 1,3-diamidobenzene anion binding units has been synthesized. NOESY spectroscopy revealed that the new receptor is well preorganized for anion complexation, presumably owing to the macrocyclic topology and the rigidity of the 2,5-diamidopyridine unit. Association constants of **3** with several anions are higher than those determined earlier for its homoaromatic congeners **1** and **2**. X-ray crystallographic analysis of the chloride complex of hybrid macrocycle **3** enabled direct comparison of structural aspects of anion recognition by the 2,5-diamidopyridine and 1,3-diamidobenzene moieties.

Amides are frequently used in nature as hydrogen bond donors for anion binding. One prominent example is the antibiotic vancomycin, which is active against Gram-positive bacteria. Three adjacent amide NHs of this natural receptor bind to the terminal COO^- group of its peptide substrate providing the major part of the binding energy.[1] Despite the fact that single $CONH\cdots A^-$ hydrogen bonds are weak and manifest only in non-polar organic solvents,[2] proteins are able to use such multiple interactions to achieve strong and selective binding of anions even in a highly competitive aqueous medium.[3] Accordingly, researchers try to design receptors having a 'high density' of hydrogen bond donating groups properly arranged around the anion.[4] This is not an easy task, however, as documented by numerous examples in the literature, when increasing the amount of hydrogen bond donors led to disappointing results. For example, incorporation of a fourth amide group to the anion binding domain of vancomycin did not improve its affinity for an anionic substrate.[5] The reason was due to the incorrect conformation taken by the fourth amide group which precluded its participation in anion binding. Another common problem in the design of anion receptors is the formation of undesired intramolecular hydrogen bonds—most hydrogen bond donating groups are also hydrogen bond acceptors. Macrocyclic topology is very effective in gathering many binding sites in close proximity and directing them in a convergent manner. Therefore we have undertaken systematic studies of macrocyclic amide receptors for anions.[6] At the beginning we examined a series of macrocyclic tetraamides built from two 2,5-pyridinedicarbamoyl moieties linked by flexible, aliphatic chains of various lengths.[6c] It turned out that the maximum affinity towards model anions was observed for the 20-membered tetraamide **1**.



In trying to construct even better anion receptors, we synthesized tetraamide **2**,[6d] keeping in mind that simple isophthalic acid amides bind anions stronger than their pyridine analogues.[7] However, we found that the

Keywords: Anion recognition; Anion binding; Macrocyclic receptor.
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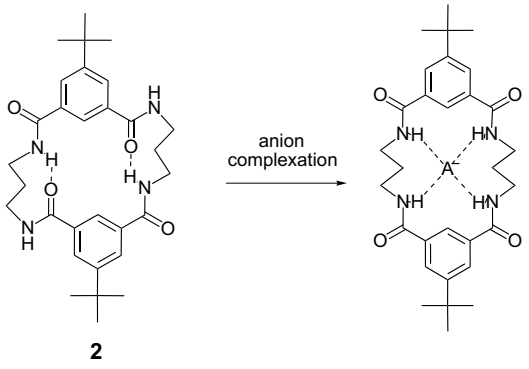
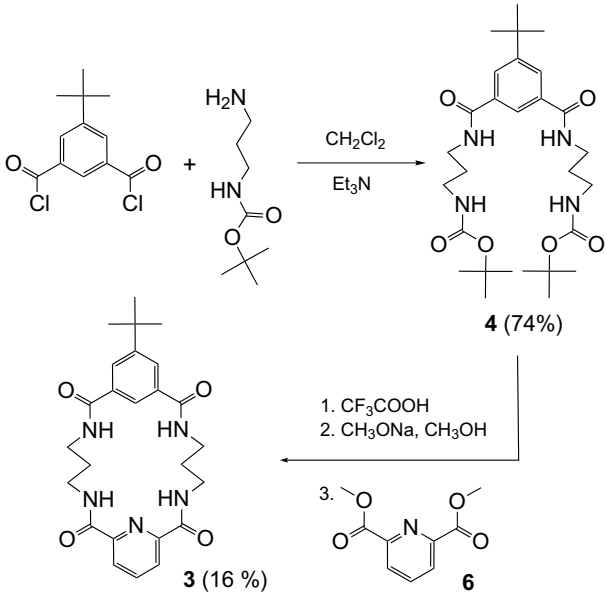
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.03.007



Scheme 1.

isophthalic acid-based macrocyclic tetraamide **2** binds anions more weakly than its pyridine analogue **1**. This is because **2** adopts an unfavourable conformation with two carbonyl oxygens directed towards the centre of the macrocyclic cavity. The conformation is stabilized by two intramolecular hydrogen bonds that have to be broken during anion complexation (Scheme 1).

Receptor **1**, on the other hand, prefers an open conformation with the convergent arrangement of N–H vectors, stabilized by four intramolecular hydrogen bonds to pyridine nitrogen atoms. These bonds, in contrast to those existing in **2**, do not have to be broken upon anion binding. Efforts to combine the benefits of both binding units, namely good preorganization provided by pyridine amides with stronger anion binding by isophthalic amides, led us to design the hybrid macrocycle **3**. We hoped that the pyridine-2,6-dicarbamoyl moiety, locked in the *syn–syn* conformation by two intramolecular bonds, would enforce, through the macroring, the same conformation on the isophthalic unit. The synthesis of receptor **3** was accomplished according to Scheme 2.



Scheme 2. The synthesis of receptor **3**.

The reaction of isophthalic acid chloride with a commercially available monoprotected 1,3-diaminopropane gave a 74% yield of **4**. Deprotection of **4** with trifluoroacetic acid afforded the amine salt **5** which, without any further purification, was dissolved in a methanolic solution of sodium methoxide and the diester **6**. The aminolysis of the diester **6** at room temperature gave a 16% yield of macrocyclic receptor **3**.

The NOESY spectrum of **3** (dissolved in DMSO-d_6) revealed close contacts between the isophthalic amide NH protons and the internal benzene CH protons and pyridine amide NH protons (see Fig. 1 and Supplementary data). Simultaneously, there were no signs of contact between external benzene CH protons and the isophthalic amide NH protons. These observations are in agreement with the desired conformation of the receptor, in which all four amide NH's are directed inwards.

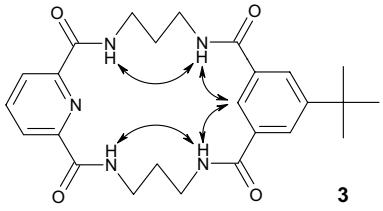


Figure 1. Selected NOE's visible in the NOESY spectrum of receptor **3**.

Anion binding properties of **3** were studied in DMSO-d_6 solutions by ^{1}H NMR titrations (Table 1).[8] In accord with our expectations, the binding constants of the hybrid receptor **3** were higher than the corresponding values obtained for either **1** or **2** under the same conditions.

The only exception is HSO_4^-, which shows the highest affinity for **1**, possibly due to additional stabilization of its complexes by a $^-O_3SO–H\cdots N_{py}$ hydrogen bond. Qualitatively, all the receptors display the same selectivity: $H_2PO_4^- > PhCOO^- > Cl^- > Br^- > HSO_4^-$ which is not surprising, given their similar structures. Nevertheless, they do show some individual character; for example **1** displays exceptionally strong affinity towards chloride versus the much more basic benzoate, whereas **2** and **3** prefer benzoate. Apparently, the change of aromatic ring in the receptor scaffold from pyridine to

Table 1. Stability constants (M^{-1}) for the formation of 1:1 complexes of **1**, **2** and **3** with various anions in DMSO-d_6 at 298 K[a]

Anion	1	2	3
Cl^-	1930[b]	378[c]	2148
Br^-	150[c]	20[c]	175
$PhCOO^-$	2283[b]	601	3612
$H_2PO_4^-$	7410[b]	— [c,d]	>8000
HSO_4^-	75[b]	<5	51

[a] Errors are estimated to be <10%. Tetrabutylammonium salts were used as anion sources.
[b] Values from Ref. 6c.
[c] Values from Ref. 6d.
[d] The data does not fit satisfactorily to a simple 1:1 binding model.

Table 2. Stability constants (M^{-1}) for the formation of 1:1 complexes of **1**, **2** and **3** with various anions in DMSO-d_6 + 5% H_2O at 298 K[a]

Anion	1	2	3
Cl^-	373	98	555
$PhCOO^-$	292	169	666
$H_2PO_4^-$	575	1320	2680

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

benzene affects not only the binding strength, but also the selectivity. Similar effects were also observed for simple acyclic diamides by Crabtree and co-workers[7] (isophthalamides vs diamidopyridines) and by Gale and co-workers[9] (diamidopyrroles vs diamidofurans).

The high stability constants measured for hydrogenphosphate, benzoate and chloride complexes of **1**, **2** and **3** in DMSO solution prompted us to investigate an even more challenging medium—a DMSO–water mixture (95:5 v/v). The results are collected in Table 2.

Despite the presence of several hundred equivalents of H_2O, all three tetraamides formed remarkably stable complexes with the anions. Nevertheless, the hybrid receptor **3** was clearly superior to **1** and **2**, even more so than in pure DMSO. Particularly impressive was the stability constant of the hydrogenphosphate—**3** complex: $K = 2680\ M^{-1}$. Although these limited data do not allow for firm generalizations, it seems pyridine receptor **1** is the most sensitive to the presence of water. This was probably why, in the presence of water, receptor **2** turned out to be better than **1** with respect to hydrogenphosphate binding.[10] Conversely, the anion binding properties of isophthalamide-containing receptors **2** and **3** seemed to be less affected by addition of water. Another interesting effect of water addition is the reversal of the chloride/benzoate selectivity of **1** in favour of the less basic chloride anion.

On the basis of the results summarized in Tables 1 and 2, we conclude, that the isophthalamide moiety is indeed a better anion binding unit than 2,6-dicarbamoylpyridine, displaying slightly different selectivity. The X-ray crystal structure analysis of a chloride complex of the hybrid receptor **3** provides a unique opportunity for the direct comparison of the structural aspects of anion binding by both building blocks. Diffraction-grade single crystals of $\mathbf{3} \times TBACl \times 0.5C_2H_4Cl_2$ were obtained by slow diffusion of diethyl ether into the solution of **3** and tetrabutylammonium chloride (TBACl) in 1,2-dichloroethane. As expected, the chloride anion is held within the macrocyclic cavity by four $NH\cdots Cl^-$ hydrogen bonds and one $CH_{arom}\cdots Cl^-$ interaction (Fig. 2). Interestingly, the anion resides slightly closer to the pyridine amides (mean $N_{amide}\cdots Cl^-$ distance is 3.27 Å) than to the isophthalic amides (mean $N_{amide}\cdots Cl^-$ distance is 3.34 Å) suggesting a higher hydrogen bond donating ability of the former. This is somewhat surprising at first, because the pyridine appended amide NH's are already engaged in hydrogen bonds with another acceptor, that is, pyridine nitrogen atom N14. However, closer inspection of the structure reveals that this is

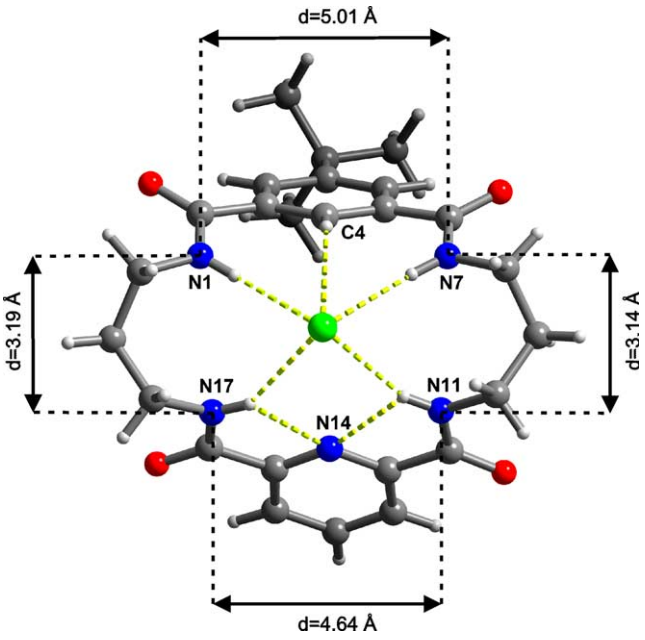


Figure 2. Top view of the crystal structure of $\mathbf{3} \times TBACl \times 0.5C_2H_4Cl_2$.

probably a simple geometric effect. The isophthalamide moiety has wider outspread amide arms than 2,6-pyridinediamide (the distance between amide nitrogens is 0.37 Å longer) and therefore the anion has to approach the benzene ring more closely in order to form comparably short $NH\cdots Cl^-$ hydrogen bonds. As a result, the distance between the chloride anion and the benzene C4 carbon atom (3.56 Å) is shorter than that to the pyridine nitrogen atom N14 (3.70 Å). The chloride anion probably cannot further shorten its contacts with the isophthalic amide protons because of steric crowding with the internal aromatic CH proton, even though the benzene ring reduces this hindrance by bending aside by about 25° with respect to the appended amide groups. (Such tilting is also typical for the structures of free isophthalamides and arises from steric repulsion between amide protons and aromatic hydrogen atoms in the *ortho* position.)[11] The close contact between the chloride anion and internal aromatic CH proton ($CH\cdots Cl^-$ 2.73 Å) manifests in the solution ^1H NMR spectra as a very high anion induced chemical shift change of the corresponding signal, $\Delta\delta_{max}(Cl^-) = 0.80$ ppm. Similar shifts have been observed in the case of other anion complexes: $\Delta\delta_{max}(Br^-) = 0.66$ ppm, $\Delta\delta_{max}(PhCOO^-) = 1.06$ ppm, $\Delta\delta_{max}(H_2PO_4^-) = 0.77$ ppm). Such large downfield shifts are usually interpreted as indicative of $CH_{arom}\cdots A^-$ bonding interactions.[12]

In conclusion, intramolecular hydrogen bonds present in the structures of receptors may be divided into two main categories: those that have to be broken upon substrate binding, and therefore are in direct competition with the binding, as in receptor **2,** and those that survive complexation, like the $CON–H\cdots N_{py}$ interactions in receptors **1** and **3**. Whereas hydrogen bonds falling into the first category are detrimental to strong binding, as in

the case of **2**, interactions of the second type can be useful. As an example, we have shown that the 2,5-diamidopyridine moiety could force, via the macroring, another anion binding unit to adopt a convergent conformation of its hydrogen bond donors. Thus, we have prepared hybrid receptor **3** which overcomes the two problems appearing in the purely isophthalic receptor **2**—the wrong conformation of the isophthalic moieties and the existence of competing intramolecular hydrogen bonds. Gratifyingly, **3** shows high affinity to the anions tested even in a very strongly competitive DMSO–water mixture.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 250961. 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

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.007. Synthetic procedures and characterization data for compounds **3** and **4** and details concerning determination of the binding constants are available.

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10. As revealed by NOE spectra, isophthalamide receptor **2** in a DMSO–H_2O (95:5 v/v) mixture still exists as an intramolecularly hydrogen bonded conformation as depicted in Scheme 1. Nevertheless, in the presence of water, breaking of hydrogen bonds, as necessary for anion binding, may be easier.
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