DOI: 10.1002/chem.200800860

# Expanding Sapphyrin: Towards Selective Phosphate Binding

**Evgeny A. Katayev,*[a, b] Nikolay V. Boev,[b] Ekaterina Myshkovskaya,[a] Victor N. Khrustalev,[a] and Yu. A. Ustynyuk[b, c]**

**Abstract:** The anion-templated syntheses and binding properties of novel macrocyclic oligopyrrole receptors in which pyrrole rings are linked through amide or imine bonds are described. The efficient synthesis was accomplished by anion-templated [1+1] Schiff-base condensation and acylation macrocyclization reactions. Free receptors and their host–guest complexes with hydrochloric acid, acetic acid, tetrabutylammonium chloride, and hydrogen sulfate were analyzed by single-crystal X-ray diffraction analysis. Stability constants with different tetrabutylammonium salts of inorganic acids were determined by standard $^1$H NMR and UV/Vis titration techniques in [D$_6$]DMSO/0.5% water solution. According to the titration data, receptors containing three pyrrole rings (**10** and **12**) exhibit high affinity ($\log K_a = 5$–$7$) for bifluoride, acetate, and dihydrogen phosphate, and interact weakly with chloride and hydrogen sulfate. The amido-bipyrrole receptors **11** and **13** with four pyrrole rings exhibit $10^4$- and $10^2$-fold selectivity for dihydrogen phosphate, respectively, as inferred from competitive titrations in the presence of tetrabutylammonium acetate.

**Keywords:** host–guest systems · phosphates receptor · pyrroles · receptors · template synthesis

## Introduction

Molecular recognition is an emerging area in modern chemistry that is starting to play a significant role in analytical, organic, inorganic, and medical chemistry.[1–3] The range of targets for molecular recognition has dramatically increased in recent years from simple atomic species to more complex structures such as oligopeptides[4,5] and nucleic acids.[6] The binding of phosphate species is of particular interest due to its ubiquitous role in living organisms.[7] In fact, nearly half of all known proteins interact with partners that contain a phosphate residue. The binding of phosphate is essential to a myriad of biological processes ranging from biosynthesis and metabolism to gene regulation, signal transaction, and antibiotic resistance. In this regard, the development of synthetic receptors for different phosphates should benefit drug discovery.[7]

The general principles of tetrahedral oxoanion recognition have recently been reviewed by us[8] and others.[9,10] At the present time a number of different approaches have been realized for the design of phosphate receptors, among which strategic, high-yielding anion-templated synthesis has attracted particular attention.[11–15] However, many known artificial receptors are unable to distinguish between structurally related anions bearing the same overall charge, for example, acetate and hydrogen sulfate. Some known efficient receptors are based on a combination of coulombic, metal coordination, or hydrogen-bonding interactions, for example, tripodal copper complexes developed by Anslyn[16] and Fabbrizzi[17] and their co-workers with $K_{HPO_4^{2-}}/K_{OAc^-}$, zinc complexes by Gunning[18] and Kim and co-workers[19] with $K_{HPO_4^{2-}}/K_{OAc^-} > 28 > 10$ in water, and protonated sapphyrins described by Sessler and co-workers[20] with a binding constant $K$ (relative to 2 equiv of $OAc^-$) $= 32\,M^{-1}$ in $CD_3OD$, and some other charged organic receptors specifically designed for phosphate binding.[21–23] Neutral receptors are generally less selective mostly due to lower binding affini-

[a] Dr. E. A. Katayev, E. Myshkovskaya, Dr. V. N. Khrustalev
Institute of Organoelement Compounds, Russian Academy of Sciences
Vavilov St., 28, Moscow, 119991 (Russia)
Fax: (+7) 499-135-5085
E-mail: katayev@ineos.ac.ru

[b] Dr. E. A. Katayev, Dr. N. V. Boev, Prof. Y. A. Ustynyuk
Department of Chemistry
M. V. Lomonosov Moscow State University
Leninskie Gory, 1/3, Moscow, 119991 (Russia)

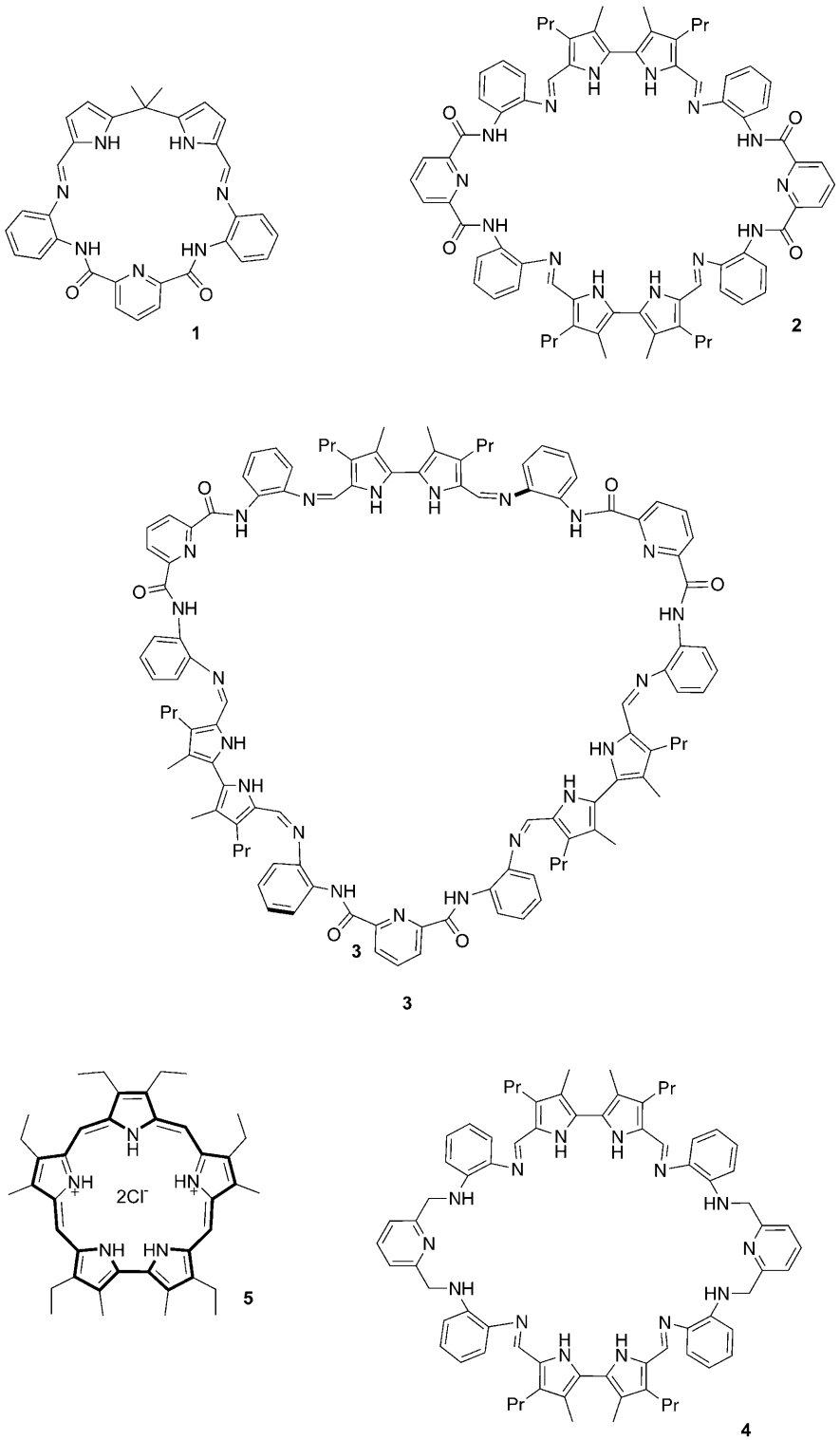
[c] Prof. Y. A. Ustynyuk
Research Center for Magnetic Tomography and Spectroscopy
M. V. Lomonosov Moscow State University
Leninskie Gory, 1, Bldg 73, Moscow, 119991 (Russia)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800860.

ties, for example, urea-based ($K_{H_2PO_4^-}/K_{OAc^-}=28$[24] and $K_{H_2PO_4^-}/K_{OAc^-}=232$[25] in [D$_6$]DMSO), amide-based ($K_{H_2PO_4^-}/K_{OAc^-}=5.7$ in [D$_6$]DMSO),[26] and amido-pyrrole-based receptors ($K_{H_2PO_4^-}/K_{OAc^-}=5$–30 also in [D$_6$]DMSO).[27–29] Our recent investigations of neutral receptors have shown that a combination of hydrogen-bond acceptor (imine or amine) and donor (amide or pyrrole) groups in one receptor with appropriate spatial locations and orientations leads to efficient synthetic receptors for the $H_2PO_4^-$ anion in $CH_3CN$ and DMSO solutions with selectivities in the range of $10^2$–$10^3$, values approaching those of charged receptors (Scheme 1; values of $K_{H_2PO_4^-}/K_{OAc^-}$ are equal to 9, 7.4, and 77 for **1**, **2**, and **4**, and values of $K_{H_2PO_4^-}/K_{HSO_4^-}$ are equal to 5.3, 3, and 0.56, respectively). The introduction of amino groups (receptor **3**) increased the selectivity up to $10^2$–$10^3$ ($K_{H_2PO_4^-}/K_{OAc^-}=250$, $K_{H_2PO_4^-}/K_{HSO_4^-}=25$).[30–32] In our laboratory, solid-phase analysis of oxoanions with receptors containing pyrrolic hydrogen bonds revealed that incorporation of dipyrromethanes into the receptor structure in most cases leads to a selectivity for acetate,[33] whereas the incorporation of 2,2′-bipyrroles leads to a selectivity for phosphate.[32]

With a high phosphate selectivity, sapphyrin has particularly attracted our attention and served as a point of origin for the synthesis of novel receptors. Sapphyrin is a versatile anion-binding agent with remarkable selectivity towards fluoride and phosphate anions in polar media. Analysis of the crystal structures of host–guest complexes leads to the suggestion that the geometry of the coordination sites is complementary only for the fluoride anion and that phosphate selectivity is a result of a high affinity for the phosphate oxygen (see, for example, complexes with $H_3PO_4$, $(C_6H_5O)_2PO(OH)$, $C_6H_5OPO(OH)$,[20] and cAMP).[34] Thus, an expansion of the inner cavity of the receptor with additional coordination sites in appropriate conjunctures is one of the possible ways to introduce geometrical host–guest complementarity and hence improved selectivity. In accord with the above-men-




Scheme 1. Structures of neutral receptors that have proven selective for phosphate anions.

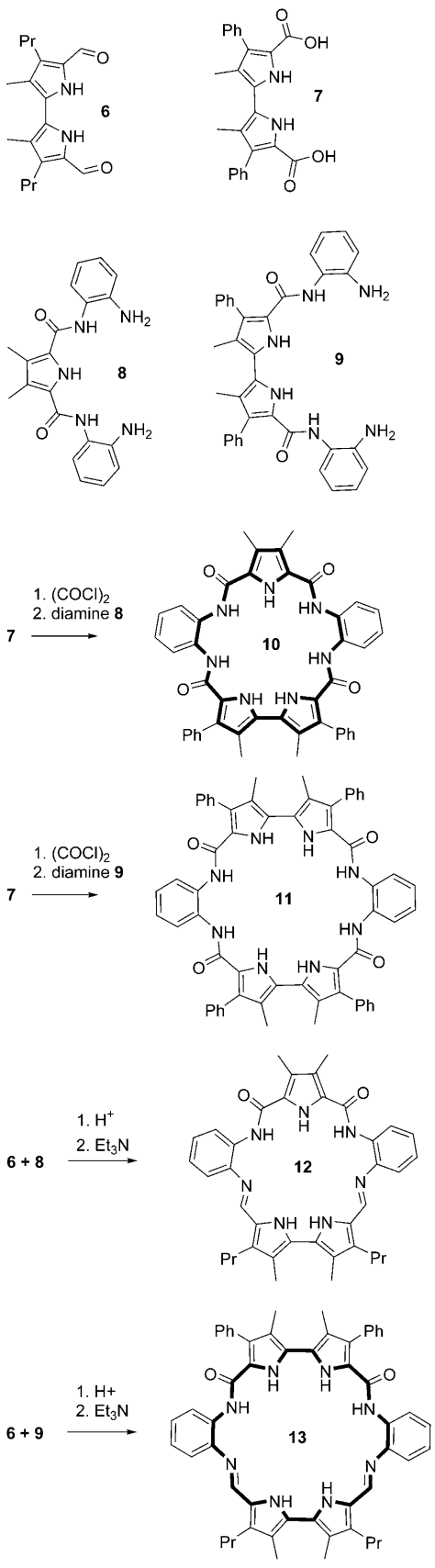
tioned facts, building blocks that contain fragments structurally equivalent to sapphyrin, such as **6**–**9** (Scheme 2), were designed. Note that the proposed receptors, **10**, **12** and **11**, **13**, have similar macrocyclic skeletons to sapphyrin and cyclo[8]pyrrole, respectively (see the bold structures in Scheme 2).

Herein, we describe the anion-templated synthesis and binding properties of novel macrocyclic oligopyrrole receptors in which the pyrrole rings are linked through amide or imine bonds. The receptor synthesis was accomplished by covalent template self-assembly (CTS), successfully used in our laboratory for the synthesis of receptors using template imine[31] and amide[35] bond formation reactions. To show the nature of the host–guest interactions and the influence of geometry, size, and nature of the binding motifs on the overall selectivity of the receptors, we investigated four different macrocyclic ligands. They can be divided into the following two categories: Oligopyrrole amide receptors (**10** and **11**) and oligopyrrole amino-imine receptors (**12** and **13**). Where possible, the host–guest complexes were investigated in the solid state. The anion-binding properties of the receptors were determined by $^1$H NMR and UV/Vis titration techniques.

## Results and Discussion

**Synthesis and structure**: The receptors **10**–**13** were synthesized from dicarbaldehyde **6**, dicarboxylic acid **7**, and the diamine building blocks **8** and **9** (Scheme 2). These compounds were chosen to expand the cavity of sapphyrin with additional amide groups (cf. structure **5** and **10**) and enhance the overall selectivity for oxoanions. Amido-imine receptors **12** and **13** were prepared by acid-catalyzed Schiff-base macrocyclization; a range of inorganic acids, including HCl, $HNO_3$, $H_3PO_4$, $H_2SO_4$, and $CH_3COOH$, were tested to optimize the yield of the reaction. As expected, the smallest macrocycle, **12**, was obtained in similar yields using any of the acids. In accord with our previous investigations, the yield of the imine macrocyclization reaction was in agreement with the affinity of the resulting macrocycles for the anion, which corresponds to the acid used in the reaction.[31] This suggests that **12** does not have a remarkable selectivity towards any particular anion. The condensation of **6** with **9** gave **13** in a high yield only with $H_2SO_4$, $H_3PO_4$, and $HNO_3$. The receptors **10** and **11** were prepared by acylation of the diamines **8** and **9** with a diacyl dichloride derivative of **7**, respectively. In the case of the synthesis of **10** (with a smaller cavity), the chloride anion eliminated during the acylation reaction acts a template in the macrocyclization reaction, which occurs in good yield (46%). However, in the preparation of **11**, tetrabutylammonium dihydrogen phosphate was added as the anion template, which increased the yield from 15 (no template) to 57% (dihydrogen phosphate template).

A similar enhancement in yield was observed previously for the acylation with pyridine-2,6-dicarbonyl dichloride in which the preorganization of **9** upon coordination of dihy-




Scheme 2. Structures of building blocks **6**–**9** and schemes for the synthesis of receptors **10**–**13**.

drogen phosphate is crucial to the formation of the [1+1] acylation product.[35] Interestingly, the benefit of using a template in this reaction was observed only if the concentration of the starting materials was not less than around 2 mM. For all the receptors, we succeeded in obtaining single crystals suitable for X-ray analysis of the receptor in the free form and in some cases as host–guest complexes (see Figures 1–4). Receptors **10** and **12** with three pyrrole rings were crystallized as the tetrabutylammonium chloride and hydrogen chloride salts, respectively. Interestingly, crystals of **10** were grown by slow diffusion of hexane into a mixture of the free receptor and tetrabutylammonium dihydrogen phosphate in chloroform. However, according to the X-ray crystal structure analysis, the receptor contained a chloride anion inside the cavity instead of dihydrogen phosphate. Similarly, crystallization of the free receptor **12** in the same solvent mixture gave the hydrogen chloride salt **12**·HCl. Presumably, both receptors facilitate the hydrolysis of chloroform in the presence of traces of water and chloride complexes are formed as they are more stable in this system. Analysis of the structures of the receptors revealed that amido-imine receptors are more planar than amido receptors, probably due to conjugation in the imino-bipyrrole fragment. As can be clearly seen from Figure 1, the amide ligand **10** is more flexible than the amido-imine ligand **12** and can adjust its structure for chloride complexation. The average $Cl^-\cdots N$ distance is smaller for complex [**10**·$Cl^-$][$TBA^+$] (3.28 Å) than for complex **12**·HCl (3.43 Å), so a higher affinity for chloride by **10** can be expected. The former distance is very close to the Cl···N distance found in a sapphyrin complex, that is, 3.24 Å. The nonplanarity of the receptors can also be evaluated from a comparison of dihedral angles between the N4 and N5 atoms of two pyrrole rings. For **10** this angle is 38° and for **12** it is 28°. Unusual acetate coordination to receptor **12** was found in the complex [**12**·$OAc^-$][$Et_3N^+$], which crystallized upon neutralization with triethylamine of the reaction performed with acetic acid as template (Figure 2). Instead of the coordination of one oxygen atom to the receptor, as in sapphyrins,[36] the 2,5-diamidopyrrole moiety provides NH donor sites for coordination of the second acetate oxygen atom. The ligand has a bent structure to provide strong hydrogen-bonding with the angles O4···H–N4, O3···H–N7, and O3···H–N1 equal to 169, 141, and 175 Å, respectively.

According to the X-ray crystal structure analysis, receptor **11** is a dimer in which two molecules are stabilized by three intermolecular hydrogen bonds between amide oxygen atoms and pyrrole NHs: O4···H–N12 (2.11, 2.903(3) Å, 150°), O5···H–N4 (2.40, 2.961(3) Å, 122°), O7···H–N1 (2.10, 2.877(3) Å, 147°). Molecule **11** is observed to adopt a bowl-like conformation (Figure 3), which is determined by two intramolecular hydrogen bonds: O2···H–N2 (1.96, 2.722(2) Å, 144°), O4···H–N6 (1.99, 2.765(2) Å, 146°) and O5···H–N11 (1.93, 2.697(3) Å, 145°), O7···H–N15 (1.95, 2.729(3) Å, 146°) for the two independent molecules, respectively, in which the amide groups are in *trans* positions. Intramolecular hydrogen-bonding introduces high structural rigidity into the

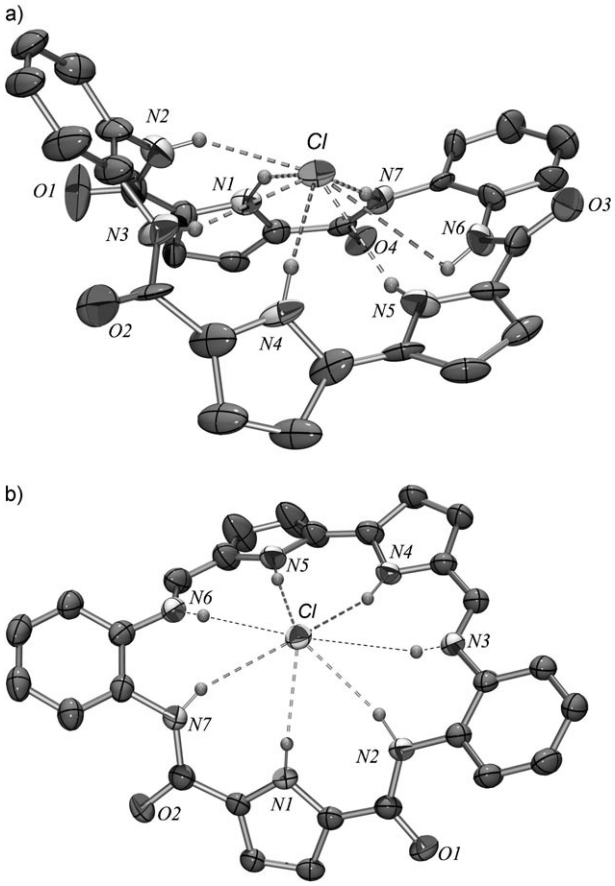



Figure 1. ORTEP-POVray rendered view of the structures of the complex a) [**10**·$Cl^-$][$TBA^+$]·1.25 $CHCl_3$ and b) **12**·HCl·$CHCl_3$·$Et_2O$ as inferred from the single-crystal X-ray structure analysis. The tetrabutylammonium cation for [**10**·$Cl^-$][$TBA^+$]·1.25 $CHCl_3$, exterior hydrogen atoms, and all β substituents on the pyrrole rings, as well as solvent molecules have been removed for clarity.

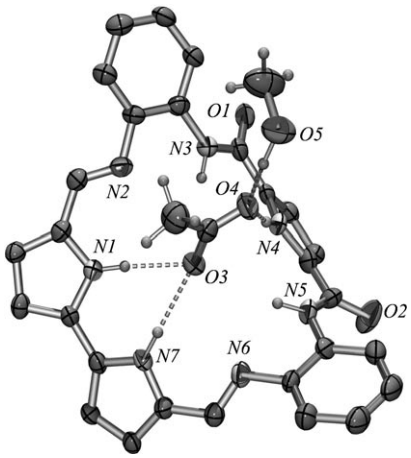



Figure 2. ORTEP-POVray rendered view of the structure of the complex [**12**·$OAc^-$][$Et_3NH^+$]MeOH as inferred from the single- crystal X-ray structure analysis. The triethylammonium cation, exterior hydrogen atoms, and all β substituents on the pyrrole rings have been removed for clarity.

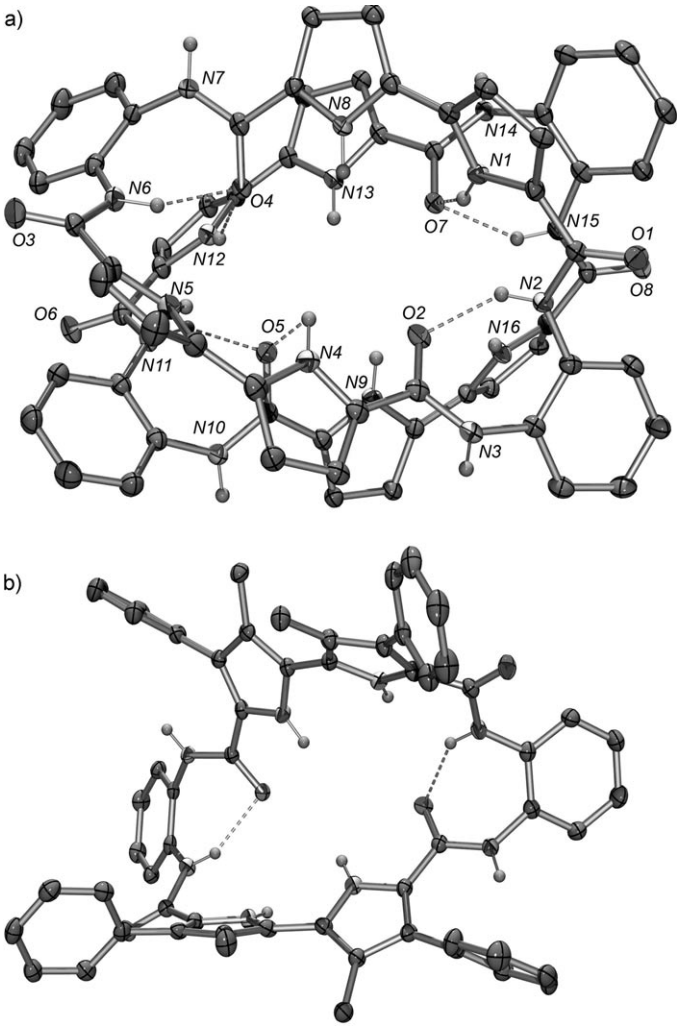



Figure 3. ORTEP-POVray rendered view of a) the structure of the dimer of **11** (without β substituents on the pyrrole rings and exterior hydrogen atoms) and b) the molecule **11** alone (without exterior hydrogen atoms) as inferred from a single-crystal X-ray structure analysis.

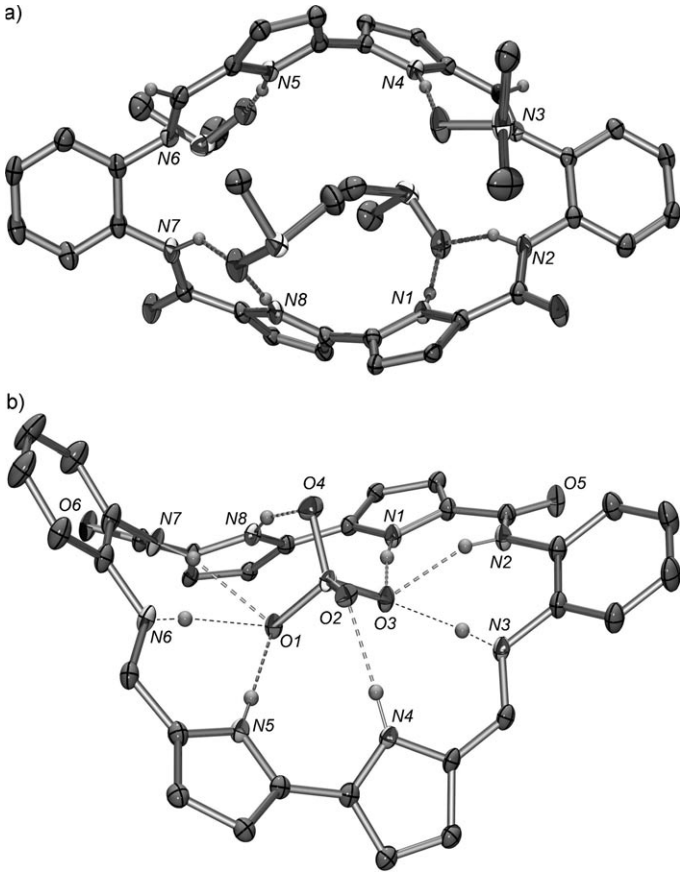



Figure 4. ORTEP-POVray rendered view of the structures of a) **13**·$(DMSO)_4$ and b) **13**·$H_2SO_4$·$2\,CH_2Cl_2$·$0.25\,C_6H_{14}$ as inferred from a single-crystal X-ray structure analysis. The exterior hydrogen atoms, all β substituents on the pyrrole rings, and solvent molecules have been removed for clarity.

receptor and resembles the γ turns often found in cyclic natural peptides. In contrast to the solid phase, in solution no dimerization was observed according to UV/Vis and $^1$H NMR dilution measurements.

The amido-imine macrocycle **13** has a completely different structure. It was crystallized from DMSO (free ligand) and chloroform (with $TBA^+HSO_4^-$), which resulted in the formation of complexes **13**·$(DMSO)_4$ and [**13**·$HSO_4^-$]-[$TBA^+$], respectively (Figure 4). Knowledge of the structures of complexes with geometrically different guests provides an opportunity to assess the conformational flexibility of the receptor. Thus, **13** coordinates to four DMSO molecules, one on each pyrrolic NH donor site, with additional stabilization provided by the amide groups (N2 and N7). The pyrrole rings are rotated in opposite directions so two DMSO molecules are coordinated from one side of the N5–N4–N1–N8 plane and the other two from the other side. It is interesting to follow the changes in the angles between the pyrrole planes and the cavity size upon complexation with tetrabutylammonium hydrogen sulfate. In **13**·$(DMSO)_4$, the dihedral angles between the N4 and N5 pyrroles and the N1 and N8 pyrroles are 61.2 and 55.2°, respectively, and the distances between N1···N4 and N2···N7 are 5.454 and 8.423 Å respectively. In the complex [**13**·$HSO_4^-$][$TBA^+$] the corresponding measurements are 37.3 and 44.6° and 5.901 and 7.290 Å. Thus, upon complexation, the receptor dramatically changes its conformation. The proton coming from the hydrogen sulfate is statistically disordered over two sites at the two nitrogen atoms with equal occupancies. Thus, despite the fact that the sulfate dianion forms only seven hydrogen bonds, its superimposed hydrogen-bonding network resembles that of cyclo[8]pyrrole$H_2^{2+}$·$SO_4^{2-}$ with eight hydrogen bonds reported by Sessler and co-workers[37] Notably, **13** (four pyrrole NH donors, two amide NH donors, and two imine N acceptors) can be considered an analogue of cyclo[8]pyrrole (six pyrrole NH donors and two imine-like N acceptors) in terms of the number and nature of the coordination sites.

**Anion-binding studies**: To investigate the anion-binding properties of these molecules, we performed $^1$H NMR titrations with the tetrabutylammonium salts of inorganic anions in a [D$_6$]DMSO/0.5% water solution (Table 1). The stability constants were determined by using the HYPERNMR and HYPERQUAD 2006 programs.[38] Macrocycle **10** binds fluoride with a 1:2 stoichiometry, whereas **12** binds with a 1:1 stoichiometry according to a Job plot analysis. Fitting of the experimental data reveals multiple equilibria corresponding to $HF_2^-$ binding rather than $F^-$. The unusually high affinity for fluoride can be explained in terms of bifluoride generation in situ upon titration with $TBA^+F^-(H_2O)_3$. Fluoride is known to be a strong base in organic solvents, particularly in the presence of water.[39] As receptor **10** does not have a proton acceptor group, the first binding event will be the binding of two hosts (S) to the $HF_2^-$ anion: $2S + HF_2^- \rightleftarrows S_2HF_2^-$ (1:1 stoichiometry); $S_2HF_2^- + HF_2^- \rightleftarrows S_2(HF_2^-)_2$ (1:2 stoichiometry overall). In contrast, **12** has a proton acceptor group and the first binding event should be protonation of the receptor: $S + HF_2^- \rightleftarrows SHF_2^-$ (2:1 stoichiometry); $SHF_2^- + S \rightleftarrows S_2HF_2^-$ (1:1 stoichiometry overall). Interestingly, both receptors bind acetate and dihydrogen phosphate with a 2:1 stoichiometry with affinities of $10^7\,M^{-1}$ and have a rather low affinity for the hydrogen sulfate anion ($K_a = 43\,M^{-1}$ for **10**). We were unable to determine the $H_2PO_4^-$ binding constant for **10** due to very strong binding and a rather complex equilibrium that could not be described by the proposed models. The equilibrium is also accompanied by a broadening of NMR signals and a downfield shift with $\Delta\delta$ up to 2 ppm. According to the NMR titration data, fluoride, chloride, sulfate, and acetate did not induce changes in the NH donor signals, only a shift of $\Delta\delta =$ 0.4–2 ppm. An exception was receptor **12** with hydrogen sulfate: in addition to the four signals of the NH donor groups, a fifth broad peak appeared after addition of more than one equivalent of hydrogen sulfate. It may be assumed that in DMSO **12** abstracts a proton from hydrogen sulfate concurrent with the binding event. To sum up, the three-pyrrole receptors show an affinity and selectivity for bifluoride, acetate, and dihydrogen phosphate anions. The data were also supported by UV/Vis titration experiments (see the Supporting Information).

Table 1. Anion affinities ($\log K_{11}$) for the receptors **10**–**13** determined from $^1$H NMR titrations carried out at 298 K in [D$_6$]DMSO/0.5 water solution.

| Anion/Receptor | **10** | **12** | **11** | **13** |
|---|---|---|---|---|
| $H_2F^-$ | $\log K_{11} = 5.70(5)$<br>$\log K_{12} = 5.23(4)$ | $\log K_{21} = 5.50(3)$<br>$\log K_{11} = 2.22(4)$ | n.d.[a] | n.d.[a] |
| $Cl^-$ | 2.38(2) | 1.97(1) | 1.63(8) | 0.89(1) |
| $CH_3COO^-$ | c.e.[a] $\log K_{21} > 7$ | c.e.[a] $\log K_{21} > 7$ | $\log K_{11} = 3.54(6)$<br>$\log K_{12} = 2.09(5)$ | 3.07(4) |
| $NO_3^-$ | n.d.[a] | n.d.[a] | n.d.[a] | n.d.[a] |
| $HSO_4^-$ | 1.64(6) | $< 1$ | 1.84(7) | 2.18(1) |
| $H_2PO_4^-$ | c.e.[a] | $\log K_{21} = 7.44(5)$<br>$\log K_{11} = 2.21(4)$ | $> 4$[b] | 2.44(4)[b] |

[a] n.d. = no apparent binding seen, as reflected in the lack of observable change in the $^1$H NMR spectrum upon anion addition; c.e. = complex equilibrium, that could not be fitted by any binding model or the errors was very large. [b] Binding constants determined from competitive experiments in the presence of two equivalents of tetrabutylammonium acetate.

In the initial titration experiments with the larger receptors **11** and **13**, we were only able to calculate the binding constants with tetrabutylammonium chloride, acetate, and hydrogen sulfate (Table 1). Recall that the template synthesis of **13** was also efficient in the presence of nitric acid. However, according to the $^1$H NMR and UV/Vis titration experiments, no apparent binding was observed with tetrabutylammonium nitrate. The binding stoichiometry of acetate complexation showed that the presence of more NH donor binding sites in **11** resulted in a 1:2 host–guest interaction, whereas for **13** a 1:1 stoichiometry was observed (Table 1). Complexation of dihydrogen phosphate by **11** and **13** was very strong and was observed in the $^1$H NMR titration as changes in both the integral intensities and the shifts of the peaks. However, the binding curves calculated on the basis of these data were found to be phase-transition-like curves that did not allow us to calculate the binding constants. The same difficulties were encountered in the UV/Vis titration experiments. The phase-transition curve is characteristic of a host with multiple binding sites or with highly cooperative binding.[40] Thus, we suggest that upon addition of the phosphate, the affinity of the receptor causes aggregation processes both before and after the saturation point of 1:1 ligand/phosphate. Interesting binding trends were also noted through the changes of the $^1$H NMR titration spectra of **11** and **13** upon addition of tetrabutylammonium acetate or dihydrogen phosphate. In the $^1$H NMR spectrum of **11** there were only two signals at $\delta = 11.69$(4H) and 9.17-(4H) ppm arising from the amide and pyrrolic NHs. After the addition of 2 equiv of acetate, four additional peaks appeared, six in total, at $\delta = 13.74$, 12.95, 12.45, 11.38, 10.51, and 10.20 ppm. This means that the coordination of two acetates stabilizes the unsymmetrical conformation of the free receptor. Similarly, after addition of 1 equiv of dihydrogen phosphate, six signals were observed at $\delta = 13.84$, 11.69, 11.52, 10.75, 10.28, and 9.22 ppm. However, the addition of more $TBAH_2PO_4$ reduced the number of signals to two (at $\delta = 13.84$ and 11.52 ppm). We thus suggest that **11** has two binding sites for $XO_2$ (e.g., acetate) complexation, but can adjust its binding sites around $XO_4$ species with high geometrical complementarity. In contrast, upon titration of receptor **13** with acetate only four (pyrrole and amide) signals were observed to be shifted downfield. When $TBAH_2PO_4$ was added to **13**, the number of signals decreased to two, probably due to fast proton exchange on the NMR timescale caused by imine protonation. To determine the desired binding constants for $TBAH_2PO_4$ and TBAOAc we used a competitive titration method[41] that we had successfully applied in recent work on acetate-selective receptors.[33] The macrocycles were mixed with 2 equiv of tetrabutylammoni-

um acetate to saturate all the binding sites and subsequently titrated with tetrabutylammonium dihydrogen phosphate. In all cases (for **10**, **11**, and **13**) changes in integral intensities were observed rather than shifts of the peaks. In other words, the integral intensities of the peaks of the acetate complex gradually decreased as the peaks of the phosphate complex increased (Figure 5). We were not able to fit the binding curve for **10** with any appropriate model, however, **11** and **13** were fitted with a 1:1 model and relative binding constants of $K_a > 10^4$ and 275 $M^{-1}$, respectively, were determined (Figure 5). Thus, in our studies, receptor **11** with eight NH donor binding sites (amide and pyrrolic NHs) was the most selective for the dihydrogen phosphate anion in [$D_6$]DMSO/0.5 % water solution.

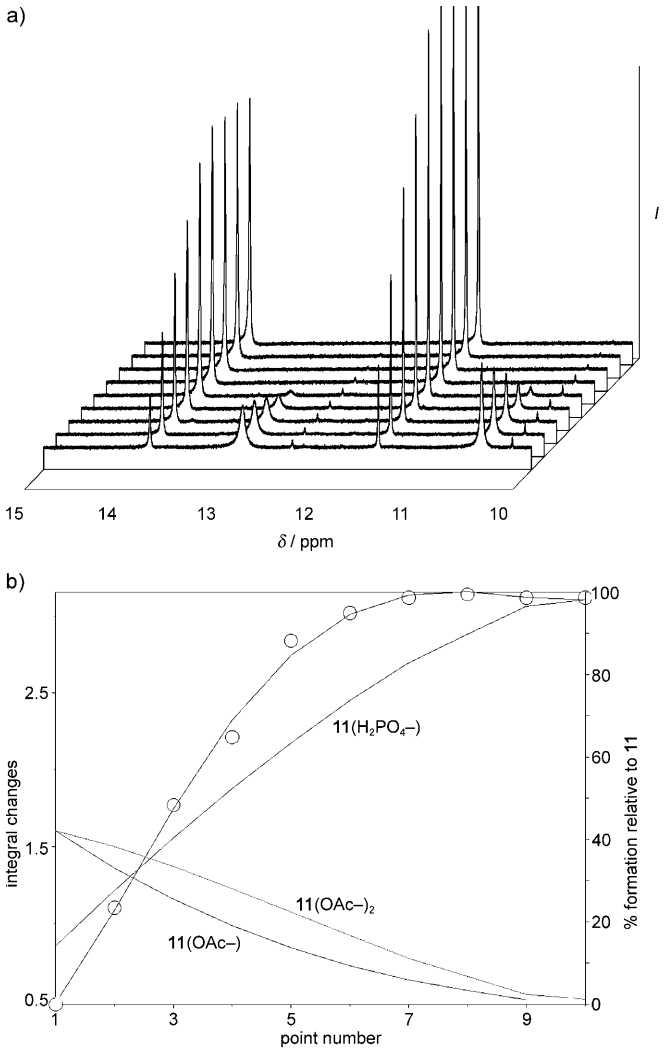



Figure 5. a) Integral changes for **11**+2 TBAOAc upon addition of (from the bottom) 0.28, 0.41, 0.53, 0.64, 0.75, 0.86, 0.95, 1.16, and 1.37 equivalents of $TBAH_2PO_4$. In the graph b, ○ denote experimental data and the curves theoretical data generated by the fitting of experimental data points using the HYPERNMR 2006 computer program.[38]

## Conclusion

In this work we have developed novel receptors with binding cavities analogous to the expanded porphyrins sapphyrin and cyclo[8]pyrrole but with the pyrrole rings linked by amide and amine bonds rather than through direct linkages. Their easy and efficient synthesis was accomplished by using anion-templated [1+1] Schiff condensation and acylation macrocyclization reactions. Their stability constants with different tetrabutylammonium salts of inorganic acids were determined by standard $^1$H NMR and UV/Vis titration techniques in DMSO. According to the titration data, the receptors that contain three pyrrole rings exhibit high affinities ($\log K_a = 5$–7) for bifluoride, acetate, and dihydrogen phosphate, but interact weakly with chloride and hydrogen sulfate. Receptors **11** and **13**, which contain four pyrrole rings, exhibit unprecedented affinity and selectivity for dihydrogen phosphate. The determined binding constants were even higher than those for known charged or metal-containing receptors in DMSO solution.[8] The shapes of the binding curves produced from peak shifts or integral changes upon titration with tetrabutylammonium dihydrogen phosphate suggest that the binding event is accompanied by a host–guest aggregation process. This is in agreement with sapphyrin behavior and apparently is an integral feature of NH donor receptors possessing high affinity. Competitive experiments in which **11** and two equivalents of acetate anion were titrated against dihydrogen phosphate allowed us to determine a relative binding constant of $\log K_a = > 4$. Moreover, the selectivity of receptor **11** is higher by at least three orders of magnitude in comparison with analogue **13**, which bears two imine bonds. Analysis of the X-ray data of the free receptor **11** revealed that, in the solid state, it forms inter- and intramolecular hydrogen bonds. All these facts support the proposition that the geometry of **11** is highly complementary to the dihydrogen phosphate anion. The results of this work have shown that a combination of suitable coordination sites (or binding motifs) in a complementary geometry to the target anion and the rigidity of the structure stabilized by rigid ether linkers (e.g., in **13**) or hydrogen-bonding (e.g., in **11**) can lead to highly selective receptors for dihydrogen phosphate. Such receptors possess a unique property to encapsulate the phosphate and form a hydrophobic shell, and hence are of great interest as phosphate carriers across membranes. They also offer good prospects for the investigation and development of, among others, selective nucleotides and phosphorylated amino acids as receptors and biomimetic catalysts, for example, in phosphodiester hydrolysis. Work in this area is underway.

## Experimental Section

**General methods**: All solvents and starting materials were of reagent grade quality and purchased commercially unless noted otherwise. The tetrabutylammonium (TBA) salts were dried under high vacuum prior to use. NMR spectra were recorded on a Bruker Avance 400 MHz spec-

trometer and referenced to the solvent peak. Column chromatography was performed on 60 Å (230–400 mesh) silica gel. 3,3′-Dimethyl-4,4′-diphenyl-2,2′-bipyrrole-5,5′-dicarbonyl dichloride was prepared by a similar method to that described by Sessler and co-workers[29] and was used immediately. Compounds **6**[31] and **7–9**[42] were prepared as described earlier.

**Titration conditions**: For NMR titrations, stock solutions of the host molecule to be studied were prepared in [D$_6$]DMSO/0.5% water solution, with the final concentrations being in the range of $(1.3–1.7)\times10^{-3}$ mol L$^{-1}$ for **10–13**. Stock solutions of the guest were prepared by dissolving 4–8 equiv of the TBA salts of the anions in question in 1 mL of the host stock solution ($1\times10^{-2}$ mol L$^{-1}$). The general procedure for the UV/Vis binding studies involved the preparation of stock solutions with concentrations 100-fold more dilute than those used for the NMR experiments, sequential addition of the titrant (anionic guest) to a 1 mL sample of the host stock solution in the spectrometric cell, and monitoring of the changes in the spectral features. The total number of data points in both NMR and UV/Vis experiments was between 10 and 40, depending on the stoichiometry of the complexation; for a presumed 1:1 complex 10–15 data points were usually measured. The data points were then collated and combined to produce plots that, in turn, were processed by the HYPERNMR and HYPERQUAD computer programs.[38]

**X-ray diffraction analysis**: Data were collected on Bruker APEX II and SMART 1K diffractometers equipped with CCD area detectors using graphite-monochromated Mo$_{K\alpha}$ radiation ($\lambda=0.71073$ Å). Data reduction was performed by using SAINTPlus (v. 6.01 and 6.2).[43] Crystallographic data are presented in Table 2. The structures were solved by direct methods and refined by full-matrix least-squares on $F^2$ with anisotropic displacement parameters for the non-hydrogen atoms. The hydrogen atoms on carbon were refined in ideal positions with isotropic displacement parameters set to $1.2U_{eq}$ of the attached atom ($1.5U_{eq}$ for the methyl hydrogen atoms). The hydrogen atoms bound to the nitrogen atoms were observed in the $\Delta F$ maps and refined with fixed positions and isotropic displacement parameters. In some cases, where noted, the contribution to the scattering by solvent molecules was removed by the use of the utility SQUEEZE in PLATON98.[44] All calculations were carried out by use of the SHELXTL PLUS program (PC Versions 5.10 and 6.12).[45]

CCDC-685341, CCDC-685342, CCDC-685343, CCDC-685344, CCDC-685345, and CCDC-685346 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.

**Receptor 10**: A freshly prepared solution of 3,3′-dimethyl-4,4′-diphenyl-2,2′-bipyrrole-5,5′-dicarbonyl dichloride (144 mg in 20 mL THF) was added dropwise over 10 min to a THF solution (50 mL) containing $N^2$,$N^5$-bis(2-aminophenyl)-3,4-dimethyl-1H-pyrrole-2,5-dicarboxamide (**8**) (100 mg, 0.275 mmol) and pyridine (410 mg). The solution was stirred for 24 h at RT and evaporated under reduced pressure. The residue was dissolved in a MeOH/$CH_2Cl_2$ mixture (5:95, v/v) and filtered through a small plug of silica. The filtrate was evaporated and recrystallized from MeOH to yield 92 mg of **10** as a white powder (46%). $^1$H NMR (600 MHz, [D$_6$]DMSO): $\delta=11.87$ (s, 1H), 11.78 (s, 2H), 9.42 (s, 2H), 9.30 (s, 2H), 7.93 (d, $J=7.2$ Hz, 2H), 7.55 (d, $J=7.2$ Hz, 2H), 7.30 (m, 8H), 7.27 (m, 2H), 7.17 (m, 4H), 2.35 (s, 6H), 1.91 ppm (s, 6H); $^{13}$C NMR (600 MHz, [D$_6$]DMSO): $\delta=160.1$, 158.7, 135.3, 132.54, 129.9, 129.3, 127.4, 126.3, 125.9, 125.6, 124.4, 124.1, 124.0, 123.5, 123.0, 122.7, 122.4, 119.0, 10.3, 10.0 ppm; ESI-MS(+): $m/z$: 728 $[M]^+$; elemental analysis calcd (%) for $C_{44}H_{37}N_7O_4$: C 72.61, H 5.12, N 13.47; found: C 72.54, H 4.89, N 13.42.

**Receptor 11**: A freshly prepared solution of 3,3′-dimethyl-4,4′-diphenyl-2,2′-bipyrrole-5,5′-dicarbonyl dichloride (144 mg, 0.33 mmol in 20 mL THF) was added dropwise over 10 min to a THF solution (50 mL) containing $N^2$,$N^5$-bis(2-aminophenyl)-3,3′-dimethyl-4,4′-diphenyl-2,2′-bipyr-

Table 2. Crystallographic data for the investigated complexes.

| | **10**·[Cl$^-$][TBA$^+$]·1.25 $CHCl_3$ | **11**·1.875 $CH_2Cl_2$·0.5 $C_5H_{12}$ | [**12**H$^+$][Cl$^-$]·$CHCl_3$·$Et_2O$ | **12**·[$Et_3NH^+$][$OAc^-$]·$CH_3OH$ | **13**·4$(CH_3)_2SO$ | [**13**H$^+$][TBA$^+$][$SO_4^{2-}$]·2 $CH_2Cl_2$·0.25 $C_6H_{14}$ |
|---|---|---|---|---|---|---|
| empirical formula | $C_{61.25}H_{74.25}Cl_{4.75}N_8O_4$ | $C_{64.375}H_{57.75}Cl_{3.75}N_8O_4$ | $C_{43}H_{53}Cl_4N_7O_3$ | $C_{47}H_{64}N_8O_5$ | $C_{62}H_{76}N_8O_6S_4$ | $C_{73.5}H_{96.5}Cl_4N_9O_6S$ |
| formula mass | 1154.92 | 1140.37 | 857.72 | 821.06 | 1157.55 | 1375.96 |
| crystal size [mm] | 0.30×0.25×0.25 | 0.30×0.25×0.20 | 0.18×0.15×0.12 | 0.21×0.18×0.15 | 0.24×0.21×0.15 | 0.30×0.25×0.20 |
| diffractometer | SMART 1K | SMART 1K | SMART 1K | APEX II | SMART 1K | APEX II |
| temperature [K] | 120 | 100 | 120 | 100 | 120 | 100 |
| crystal system | monoclinic | triclinic | monoclinic | monoclinic | monoclinic | monoclinic |
| space group | $C2/c$ | $P\bar{1}$ | $P2_1/c$ | $P2_1/c$ | $P2_1/n$ | $P2_1/n$ |
| $a$ [Å] | 34.288(8) | 16.8233(14) | 13.699(5) | 15.456(2) | 16.1783(12) | 15.4448(12) |
| $b$ [Å] | 18.950(5) | 18.3589(16) | 17.068(5) | 17.708(3) | 21.7496(15) | 21.4657(17) |
| $c$ [Å] | 26.151(6) | 22.7384(19) | 20.866(6) | 18.047(3) | 18.3369(13) | 24.1556(19) |
| $\alpha$ [°] | 90 | 67.581(5) | 90 | 90 | 90 | 90 |
| $\beta$ [°] | 130.299(3) | 71.641(5) | 104.593(5) | 114.096(3) | 104.211(1) | 103.401(2) |
| $\gamma$ [°] | 90 | 72.564(5) | 90 | 90 | 90 | 90 |
| $V$ [Å$^3$] | 12960(6) | 6031.3(9) | 4721(3) | 4508.9(12) | 6254.8(8) | 7790.3(11) |
| $Z$ | 8 | 4 | 4 | 4 | 4 | 4 |
| $\rho_{calcd}$ [g cm$^{-3}$] | 1.184 | 1.256 | 1.207 | 1.210 | 1.229 | 1.173 |
| $F(000)$ | 4884 | 2383 | 1808 | 1768 | 2464 | 2930 |
| $\mu$ [mm$^{-1}$] | 0.263 | 0.239 | 0.294 | 0.080 | 0.207 | 0.232 |
| $\theta$ range [°] | 2.04–23.01 | 1.30–26.23 | 1.95–25.03 | 1.85–25.02 | 1.87–26.06 | 1.65–27.00 |
| index range | $-37\le h\le37$ | $-20\le h\le20$ | $-16\le h\le16$ | $-18\le h\le18$ | $-19\le h\le19$ | $-19\le h\le19$ |
| | $-20\le k\le20$ | $-22\le k\le22$ | $-20\le k\le20$ | $-21\le k\le21$ | $-26\le k\le26$ | $-27\le k\le27$ |
| | $-28\le l\le28$ | $-28\le l\le28$ | $-24\le l\le24$ | $-21\le l\le21$ | $-22\le l\le22$ | $-30\le l\le30$ |
| refl. collected | 42445 | 58090 | 32459 | 38414 | 44508 | 105078 |
| independent | 8925 | 23940 | 8071 | 7818 | 12252 | 16750 |
| refl. | [$R_{int}$=0.092] | [$R_{int}$=0.049] | [$R_{int}$=0.073] | [$R_{int}$=0.069] | [$R_{int}$=0.058] | [$R_{int}$=0.038] |
| no. of rflns with $I>2\sigma(I)$ | 2850 | 14876 | 4318 | 3369 | 8389 | 13226 |
| $R_1$ [$I>2\sigma(I)$] | 0.111 | 0.062 | 0.074 | 0.092 | 0.056 | 0.056 |
| $wR_2$ (all data) | 0.277 | 0.158 | 0.189 | 0.215 | 0.160 | 0.143 |
| data/restraints/parameters | 8925/57/713 | 23940/18/1287 | 8071/11/431 | 7818/32/538 | 12252/0/735 | 16750/12/783 |
| GOF on $F^2$ | 1.041 | 1.018 | 1.004 | 1.009 | 1.002 | 1.001 |
| largest diff. peak/hole [e Å$^{-3}$] | 0.783/−0.398 | 0.490/−0.604 | 0.568/−0.663 | 0.536/−0.581 | 0.370/−0.390 | 0.899/−0.732 |

role-5,5′-dicarboxamide (**9**) (160 mg, 0.275 mmol), pyridine (410 mg), and $TBAH_2PO_4$ (112 mg, 0.33 mmol). The solution was stirred for 24 h at RT and evaporated under reduced pressure. The residue was dissolved in a $MeOH/CH_2Cl_2$ mixture (5:95 v/v) and filtered through a small plug of silica. The filtrate was evaporated and recrystallized from $MeOH/CH_2Cl_2$ to yield 148 mg of **11** as a white powder (57%). $^1$H NMR (600 MHz, [D$_6$]DMSO): $\delta = 11.69$ (s, 4H), 9.19 (s, 4H), 7.37 (m, 24H), 7.00 (m, 4H), 1.91 ppm (s, 12H); $^{13}$C NMR (600 MHz, [D6]DMSO): $\delta = 160.5$, 142.1, 135.5, 130.7, 128.61, 127.2, 126.0, 125.3, 123.8, 123.0, 118.0, 116.7, 11.24 ppm; ESI-MS (+): $m/z$: 945 $[M]^+$; elemental analysis calcd (%) for $C_{60}H_{48}N_8O_4$: C 76.25, H 5.12, N 11.86; found C, 76.20, H 5.10, N 11.83.

**Receptor 12**: HCl (38%, 0.1 mL) was added to a mixture of diamine **8** (363 mg, 1 mmol) and dialdehyde **6** (300 mg, 1 mmol) in MeOH (50 mL). On heating the solution at reflux for 20 min, its color changed to orange-red. An excess of triethylamine was added to this boiling solution and the mixture was cooled to 0°C. The resulting precipitate was filtered off and recrystallized from MeOH to yield 463 mg (74%) of a yellow powder. $^1$H NMR (600 MHz, [D$_6$]DMSO): $\delta = 11.84$ (s, 1H), 10.88 (s, 2H), 9.48 (s, 2H), 8.55 (s, 2H), 7.88 (m, 2H), 7.42 (m, 2H), 7.15 (m, 4H), 3.32 (m, 4H), 2.69(m, 4H), 2.20 (s, 6H), 2.06 (s, 6H), 1.56(m, 4H), 0.97 ppm (t, $J = 12$ Hz, 6H); $^{13}$C NMR (600 MHz, [D$_6$]DMSO): $\delta = 10.0$, 11.1, 13.8, 24.4, 25.4, 45.7, 116.6, 117.6, 123.7, 124.5, 125.0, 125.9, 126.4, 128.7, 131.7, 132.8, 141.8, 145.2, 160.1 ppm; ESI-MS(+): $m/z$: 627 $[M]^+$; elemental analysis calcd (%) for $C_{38}H_{41}N_7O_2$: C 72.70, H 6.58, N 15.62; found: C 72.46, H 6.67, N 15.53.

**Receptor 13**: Concentrated nitric acid (0.2 mL) was added to a solution of diamine **9** (581 mg, 1 mmol) and dialdehyde **6** (300 mg, 1 mmol) in MeOH (70 mL) at reflux. The solution was heated at reflux for a further 20 min. An excess triethylamine was added to this boiling solution and the mixture was cooled to 0°C. The resulting precipitate was filtered off and recrystallized from MeOH to yield 515 mg (61%) of a yellow powder. $^1$H NMR (600 MHz, [D$_6$]DMSO): $\delta = 11.57$ (s, 2H), 11.35 (s, 2H), 9.12 (s, 2H), 8.47 (s, 2H), 8.47 (s, 2H), 7.08–7.40 (m, 18H), 2.67 (m, 4H), 1.91 (s, 6H), 1.85 (s, 6H), 1.15 (m, 4H), 0.93 ppm (t, $J = 12$ Hz, 6H); $^{13}$C NMR (600 MHz, [D$_6$]DMSO): $\delta = 10.3$, 18.4, 55.9, 118.5, 122.1, 123.3, 124.3, 125.0, 126.2, 127.4, 129.4, 130.2, 130.4, 135.0, 158.7 ppm; ESI-MS (+): $m/z$: 845 $[M]^+$; elemental analysis calcd (%) for $C_{54}H_{52}N_8O_2$: C 76.75, H 6.20, N 13.26, found: C 76.80, H 6.37, N 13.21.

## Acknowledgements

This work was supported by the Russian Academy of Sciences, program "Chemistry and Physico-Chemistry of Supramolecular Systems and Atomic Clusters", and the Russian Foundation for Basic Research. We would like to thank Yu. A. Pirogov (Research Center for Magnetic Tomography and Spectroscopy) for helpful discussions.

[1] J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151–160.
[2] J. L. Sessler, P. A. Gale, W.-S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, **2006**.
[3] K. Severin, *Top. Organomet. Chem.* **2006**, *17*, 123–142.
[4] S. Stadlbauer, A. Riechers, A. Späth, B. König, *Chem. Eur. J.* **2007**, *13*, 2536–2541.
[5] C. Schmuck, *Angew. Chem.* **2007**, *119*, 5932–5935; *Angew. Chem. Int. Ed.* **2007**, *46*, 5830–5833;
[6] M. J. Hannon, *Chem. Soc. Rev.* **2007**, *36*, 280–295.
[7] A. K. H. Hirsch, F. R. Fischer, F. Diederich, *Angew. Chem.* **2007**, *119*, 342–357; *Angew. Chem. Int. Ed.* **2007**, *46*, 338–352.
[8] E. A. Katayev, Y. A. Ustynyuk, J. L. Sessler, *Coord. Chem. Rev.* **2006**, *250*, 3004–3037.
[9] S. O. Kang, M. A. Hossain, K. Bowman-James, *Coord. Chem. Rev.* **2006**, *250*, 3038–3052.
[10] S. Kubik, C. Reyheller, S. Stüwe, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 137–187.
[11] M. D. Lankshear, P. D. Beer, *Acc. Chem. Res.* **2007**, *40*, 657–668.
[12] M. D. Lankshear, P. D. Beer, *Coord. Chem. Rev.* **2006**, *250*, 3142–3160.
[13] P. A. Gale, R. Quesada, *Coord. Chem. Rev.* **2006**, *250*, 3219–3244.
[14] T. J. Wedge, M. F. Hawthorne, *Coord. Chem. Rev.* **2003**, *240*, 111–128.
[15] M. Bru, I. Alfonso, M. I. Burguete, S. V. Luis, *Angew. Chem.* **2006**, *118*, 6301–6305; *Angew. Chem. Int. Ed.* **2006**, *45*, 6155–6159.
[16] S. L. Tobey, B. D. Jones, E. V. Anslyn, *J. Am. Chem. Soc.* **2003**, *125*, 4026–4027.
[17] M. Allevi, M. Bonizzoni, L. Fabbrizzi, *Chem. Eur. J.* **2007**, *13*, 3787–3795.
[18] P. T. Gunning, *Org. Biomol. Chem.* **2005**, *3*, 3877–3879.
[19] M. S. Han, D. H. Kim, *Angew. Chem.* **2002**, *114*, 3963–3965; *Angew. Chem. Int. Ed.* **2002**, *41*, 3809–3811.
[20] V. Král, H. Furuta, K. Shreder, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1996**, *118*, 1595–1607.
[21] S. K. Kim, N. J. Singh, S. J. Kim, H. G. Kim, J. K. Kim, J. W. Lee, K. S. Kim, J. Yoon, *Org. Lett.* **2003**, *5*, 2083–2086.
[22] J. Y. Kwon, N. J. Singh, H. N. Kim, S. K. Kim, K. S. Kim, J. Yoon, *J. Am. Chem. Soc.* **2004**, *126*, 8892–8893.
[23] P. Schiessl, F. P. Schmidtchen, *J. Org. Chem.* **1994**, *59*, 509–511.
[24] P. S. Lakshminarayanan, I. Ravikumar, E. Suresh, P. Ghosh, *Chem. Commun.* **2007**, 5214–5216.
[25] A. N. Leung, D. A. Degenhardt, P. Bühlmann, *Tetrahedron* **2008**, *64*, 2530–2536.
[26] J.-H. Liao, C.-T. Chen, J.-M. Fang, *Org. Lett.* **2002**, *4*, 561–564.
[27] I. E. D. Vega, S. Camiolo, P. A. Gale, M. B. Hursthouse, M. E. Light, *Chem. Commun.* **2003**, 1686–1687.
[28] I. E. D. Vega, P. A. Gale, M. B. Hursthouse, M. E. Light, *Org. Biomol. Chem.* **2004**, *2*, 2935–2941.
[29] A. Andrievsky, F. Ahuis, J. L. Sessler, F. Vögtle, D. Gudat, M. Moini, *J. Am. Chem. Soc.* **1998**, *120*, 9712–9713.
[30] J. L. Sessler, E. Katayev, G. D. Pantos, Y. A. Ustynyuk, *Chem. Commun.* **2004**, 1276–1277.
[31] E. A. Katayev, G. D. Pantos, M. D. Reshetova, V. N. Khrustalev, V. M. Lynch, Y. A. Ustynyuk, J. L. Sessler, *Angew. Chem.* **2005**, *117*, 7552–7556; *Angew. Chem. Int. Ed.* **2005**, *44*, 7386–7390.
[32] E. A. Katayev, J. L. Sessler, V. N. Khrustalev, Y. A. Ustynyuk, *J. Org. Chem.* **2007**, *72*, 7244–7252.
[33] E. A. Katayev, N. V. Boev, V. N. Khrustalev, Y. A. Ustynyuk, I. G. Tananaev, J. L. Sessler, *J. Org. Chem.* **2007**, *72*, 2886–2896.
[34] B. L. Iverson, K. Shreder, V. Král, P. Sansom, V. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1996**, *118*, 1608–1616.
[35] E. A. Katayev, E. N. Myshkovskaya, N. V. Boev, V. N. Khrustalev, *Supramol Chem.* **2008**, DOI: 10.1080/10610270701561342.
[36] J. L. Sessler, J. M. Davis, *Acc. Chem. Res.* **2001**, *34*, 989–997.
[37] D. Seidel, V. Lynch, J. L. Sessler, *Angew. Chem.* **2002**, *114*, 1480–1483; *Angew. Chem. Int. Ed.* **2002**, *41*, 1422–1425.
[38] P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739–1753.
[39] S. O. Kang, R. A. Begum, K. Bowman-James, *Angew. Chem.* **2006**, *118*, 8048–8061; *Angew. Chem. Int. Ed.* **2006**, *45*, 7882–7894.
[40] K. A. Connors, *Binding constants*, Wiley, New York, **1987**.
[41] B. J. Whitlock, H. W. Whitlock, *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.
[42] N. V. Boev, Y. A. Ustynyuk, *Russ. J. Org. Chem.* **2007**, *43*, 297–304.
[43] Bruker SAINTPlus, Data Reduction and Correction Program, v. 6.01, Bruker AXS, Madison, WI, **1998**.
[44] PLATON, A Multipurpose Crystallographic Tool, A. L. Spek, Utrecht University, The Netherlands, **1998**.
[45] SHELXTL, v. 5.10, Structure Determination Software Suite, G. M. Sheldrick, Bruker AXS, Madison, WI, **1998**.

Received: May 6, 2008
Published online: September 9, 2008