A Cyclic Hexapeptide Containing L-Proline and 6-Aminopicolinic Acid Subunits Binds Anions in Water**

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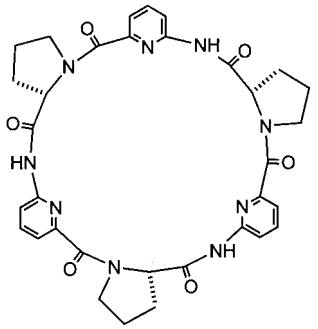
The biological importance of many anions explains why the development of artificial anion receptors is an important area of supramolecular chemistry.[1, 2] Artificial receptors in which the substrate is bound by hydrogen bonds as in natural systems are, however, often only active in nonpolar solvents.[2b] For complexation in water, stronger interactions, such as electrostatic or coordinative interactions, are normally necessary because of the high solvation energy of many anions.[2a] In this article we show that the cyclic hexapeptide **1** is able to bind anions such as halides and sulfates through hydrogen bonds even in aqueous solutions.[3] The anions are held in a cavity that results from the aggregation of two cyclopeptide molecules. This type of complex formation is similar to the guest-induced self-association of a resorcarene derivative recently described by Böhmer and co-workers,[4] and the structure of the complex resembles a molecular capsule.[5] In contrast to real capsules, however, the anion complexes of **1** are not stabilized by additional intermolecular interactions between the two cyclopeptide moieties.



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Compound **1** was synthesized from the two amino acid building blocks Boc-L-proline and 6-aminopicolinic acid benzyl ester, in analogy to the method previously described by us.[6] The picolinic acid derivative was prepared from 6-amino-2-picoline in a four-step synthesis according to known methods.[7]

The X-ray crystal structure analysis of the trihydrate of **1** shows that the conformation of the peptide in the crystal has exact C_3 symmetry. All the protons of the NH groups are arranged on the same side as the nitrogen atoms of the pyridine rings, the tertiary amides adopt the *cis* conformation, and the planes of the aromatic units lie approximately parallel to the C_3 axis of the macrocycle (Figure 1).[8] A water molecule of crystallization is bound to each NH group. In addition to the trihydrate of **1**, we have also obtained, under different conditions, crystals containing nine water molecules per cyclopeptide subunit, as well as crystals containing one acetone and three water molecules.[9] Since the conformation of **1** is practically identical in all these crystals in spite of differing environments (average deviations of the non-hydrogen atoms: 0.31 and 0.49 Å), it is probably the thermodynamically preferred conformation.

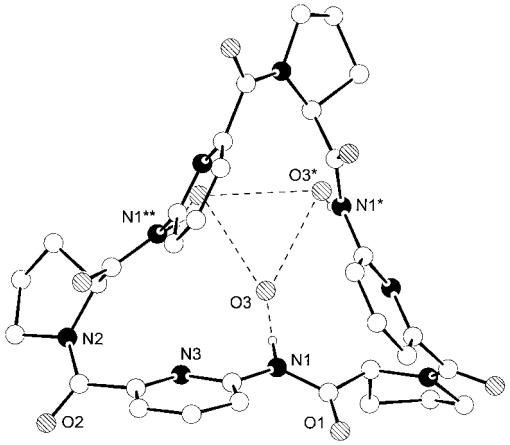

Figure 1. Crystal structure of $\mathbf{1}\cdot 3H_2O$. Selected distances [Å]: N1-O3 2.907(2), O3-O3* 2.930(2), N1-N1* 4.463(2).

NMR spectroscopic investigations show that in polar media, such as [D_6]DMSO or D_2O/CD_3OD mixtures, **1** adopts a conformation which corresponds to that observed in the crystal structure shown in Figure 1. On addition of one equivalent of *n*-butyltrimethylammonium tosylate to a 2 mM solution of **1** in [D_6]DMSO, downfield shifts of 0.77 ppm and 0.47 ppm are observed for the NMR signals of the NH protons and the H(α) protons, respectively. In the case of the corresponding iodide, the shifts of these signals are, respectively, 0.04 and 0.14 ppm. A shift of the cation signals is not observed in either spectrum ($\Delta\delta < 0.001$ ppm). Thus, in contrast to other, structurally similar cyclopeptides, interaction between **1** and ammonium cations cannot be demonstrated.[6] The downfield shift of the NH signals is, however, a typical indication of the involvement of these protons in hydrogen bonds to the anions.[2, 3] We were able to confirm this type of interaction by FT-IR spectroscopy with the tosylate complex of **1** in 1% [D_6]DMSO/$CDCl_3$. Furthermore, NOESY NMR spectroscopic studies showed that the conformation of **1** in the tosylate complex corresponds to that observed for the crystal in the X-ray analysis shown. The shift of the H(α) protons that results from the complexation of the anions

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thus stems from the spatial proximity of these protons to the negative charge density of the anions bound to the NH groups of **1**. This shift can be considered as an additional indication of the interaction of the peptide with anions. It allows one to demonstrate anion complexation in protic and, hence, more strongly competitive solvents than DMSO. Thus, even in 80% D_2O/CD_3OD the H(α) signal of the peptide is shifted downfield after addition of, for example, sodium iodide (Figure 2). Investigations of **1** in pure water were not possible because its solubility in water was too low.

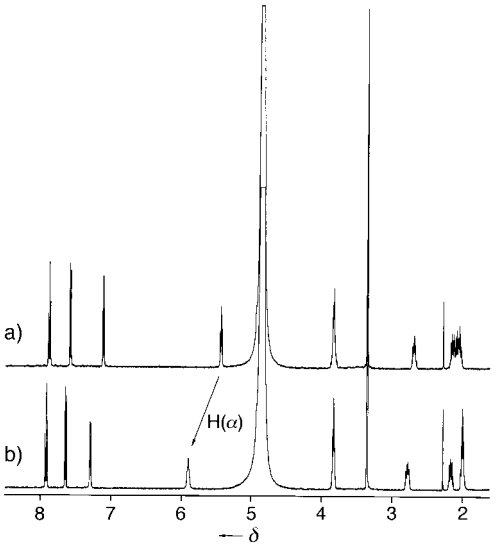

Figure 2. Part of the ^{1}H NMR spectrum of **1** in 80% D_2O/CD_3OD (2 mM) before (a) and after (b) addition of 10 equivalents of NaI.

Apart from iodide, interaction of **1** with chloride, bromide, sulfate, benzenesulfonate, and carbonate in the solvent mixture 80% D_2O/CD_3OD could also be clearly detected by ^{1}H NMR spectroscopy. A weaker interaction was found for the anions HCO_3^-, HPO_4^{2-}, $H_2PO_4^-$, NO_3^-, and OAc^-. Since the complexation of the halides, of sulfate, and sulfonate can be followed in aqueous solutions at pH 7 without addition of buffer, we have initially concentrated our investigations on these anions.

With a Job plot, a 1:1 stoichiometry was determined for the complex between **1** and the sodium salt of benzenesulfonic acid in 80% D_2O/CD_3OD. An NMR titration, in which the position of the signal for the H(α) protons of **1** was followed, gave a stability constant of $44 \pm 5\ M^{-1}$ ($\Delta\delta_{max} = 0.38$ ppm, 298 K) for this complex.[10] In contrast, for the halides and sulfate, it was unexpectedly found that each of these anions is bound by two cyclopeptide molecules. The existence of such 2:1 complexes in solution was confirmed by electrospray ionization mass spectrometry (ESI-MS). All the possible 1:1 and 2:1 halide complexes are, for example, visible next to one another in the ESI-MS spectrum when 0.33 equivalents of each NaCl, NaBr, and NaI are added to a solution of **1** in 80% H_2O/CH_3OH (Figure 3). Since ESI-MS allows the relative complex stability of supramolecular aggregates to be approximately estimated,[11] one can infer from the intensity of the peaks that the stability of the three halide complexes increases

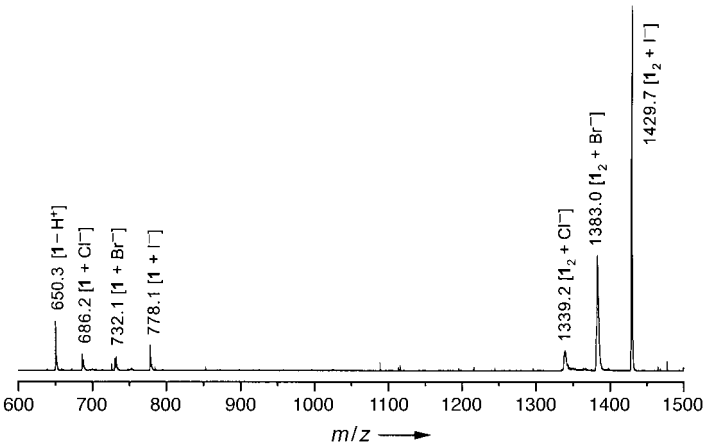

Figure 3. ESI mass spectrum of **1** in 80% H_2O/CH_3OH (100 μM) after addition of 0.33 equivalents of each NaI, NaBr, and NaCl.

in the order $Cl^- < Br^- < I^-$.[12] In the case of the sulfate complex of **1**, the 2:1 complex $\mathbf{1}_2 \cdot SO_4^{2-}$ can also be identified next to the 1:1 complex in the ESI mass spectrum.

Important information about the structure of these 2:1 complexes was provided by an X-ray crystal structure analysis of the iodide complex (Figure 4).[13] Since suitable crystals of this complex could only be obtained from acetone/hexane/H_2O solution, the observed structure does not necessarily correspond to that of the complex structure in aqueous solution. The fact that 17 water molecules are bound for every four $\mathbf{1}_2 \cdot I^-$ units indicates, however, that water is necessary for the formation of the crystals.[14] Moreover, the two independent iodide complexes in the unit cell have almost identical geometries in spite of differing environments. The iodide anion is located in a cavity between two cyclopeptide molecules,[14] which interlock perfectly like gears, with corresponding planes of two pyridyl–carbonyl–proline units coming together in close contact. The conformation of both peptide subunits corresponds to that of free **1**. Six NH groups point into the cavity and bind the enclosed anion with hydrogen bonds. The coordination geometry of the iodide anion is approximately trigonal prismatic, constrained by the arrangement of the two cyclopeptide moieties to each other. The sodium ions are coordinated to the carbonyl groups of **1**; however, they connect different 2:1 complexes in the crystal, not the two peptide units of a single complex. Intermolecular interactions between both peptide units that cause additional stabilization of the aggregate are not evident, besides those resulting from the binding of the anion.

Molecular modeling studies[15] revealed that sulfate and the smaller halides can also be enclosed in the cavity between the two cyclopeptide units. In the case of the sulfate anion, the calculations showed that hydrogen bonds between the NH groups of both peptides and the oxygen atoms of the sulfate are possible. For partially protonated anions the number of possible hydrogen bonds is reduced, which explains the poorer binding of, for example, HCO_3^-, HPO_4^{2-}, and $H_2PO_4^-$. The steric bulk of the phenyl ring in the benzenesulfonate anion prevents complexation of the anion by a second cyclopeptide so that in this case only a 1:1 complex is possible.

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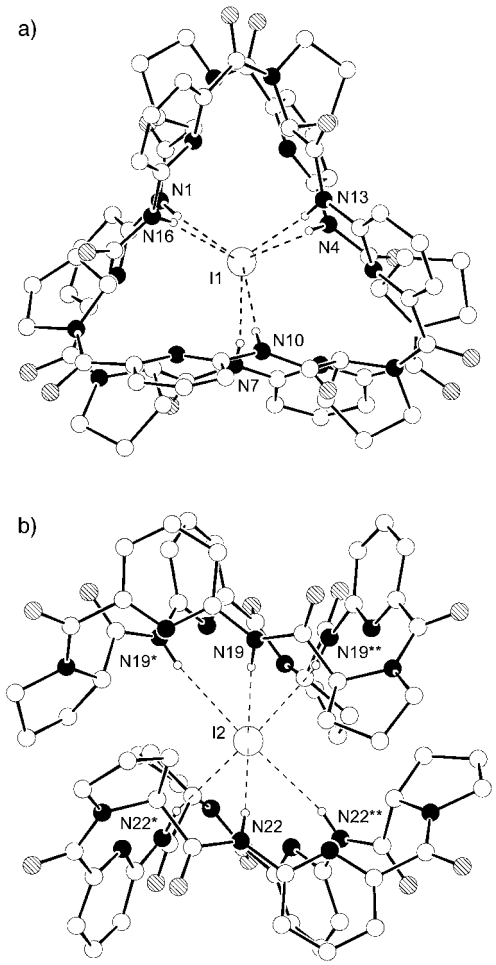

Figure 4. Cross-sections of the crystal structure of $4(\mathbf{1}_2 \cdot I^-) \cdot 4Na^+ \cdot 9C_3H_6O \cdot 17H_2O$: a) view from above, b) view from the side. Selected distances [Å]: I1-N1 3.784(3), I1-N4 3.724(3), I1-N7 3.922(3), I1-N10 3.736(4), I1-N13 3.935(4), I1-N16 3.886(3), N1-N4 4.485(5), N1-N16 5.514(5), I2-N19 3.662(3), I2-N22 3.650(4), N19-N19* 4.564(5), N19-N22 5.196(4).

In microcalorimetric investigations a small endothermic effect was found for the complex formation between **1** and NaI.[12] The formation of hydrogen bonds between the peptide and the iodide anion is apparently not able to compensate for the energy necessary for the desolvation of host and guest. Thus, entropic reasons must be mainly responsible for the anion complexation by **1**, that is, the release of solvent molecules from the solvation shells of the anion and the cyclopeptide. Similar effects have already been described for other anion receptors in polar solvents.[16]

Our investigations show that the peptide **1** can be used to complex anions in aqueous solution. As a result of the particular binding mechanism of **1**, the anion loses its solvent shell during formation of the complex and is shielded from the surrounding solvent in the complex. The interactions between the receptor and substrate are thereby strengthened. Peptide **1** is thus able to imitate principles that play an important role during the recognition of anions by natural receptors.

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[9] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156896 – 156899 ($\mathbf{1} \cdot 3H_2O$, $\mathbf{1} \cdot C_3H_6O \cdot 3H_2O$, $\mathbf{1} \cdot 9H_2O$, and $4(\mathbf{1}_2 \cdot I^-) \cdot 4Na^+ \cdot 9C_3H_6O \cdot 17H_2O$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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[13] Crystal data for $4(\mathbf{1}_2 \cdot I^-) \cdot 4Na^+ \cdot 9C_3H_6O \cdot 17H_2O$:[9] Colorless crystals from acetone/hexane/H_2O, $4((C_{33}H_{33}N_9O_6)_2 \cdot I^-) \cdot 4Na^+ \cdot 9C_3H_6O \cdot 17H_2O$, $M_r = 6642.01$, trigonal, space group $P3$ (No. 143), $a = 27.4212(1)$, $c = 12.7273(1)$ Å, $V = 8287.81(8)$ Å^3, $T = 100$ K, $Z = 1$, $\rho_{calcd} = 1.33$ g cm^{-3}, $\mu = 0.468$ mm^{-1}, crystal size $0.315 \times 0.30 \times 0.13$ mm, Nonius KappaCCD diffractometer, $Mo_{K\alpha}$ radiation, $1.05 < \theta < 32.59^\circ$, 51733 measured reflections, 36424 independent and 31610 with $I > 2\sigma(I)$, programs SHELXS-97 and SHELXL-97; both programs from G. M. Sheldrick, University of Göttingen, **1997**; 1308 parameters, $R1 = 0.057$, $wR2$ (all data) $= 0.157$, $(\Delta/\sigma)_{max} = 0.002$, hydrogen atoms on water molecules not calculated, max./min. residual electron density 1.307/ – 1.303 e Å^{-3}.

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[14] The complete structure of $4(\mathbf{1}_2\cdot I^-)\cdot 4Na^+\cdot 9C_3H_6O\cdot 17H_2O$ is a catemer. The main motif is the $\mathbf{1}_2\cdot I^-$ unit. There are two independent $\mathbf{1}_2\cdot I^-$ units in the unit cell and both have very similar conformations. Sodium ions and solvent molecules surround these groups, but in contrast to the anions, there are two types of sodium ions in the structure. One is pentacoordinated. Three coordination sites are occupied by carbonyl groups of neighboring cyclopeptides, one by the oxygen atom of a bound acetone molecule, and the remaining coordination site is occupied by a water molecule. This cation has a trigonal bipyramidal coordination geometry. The other sodium ion is merely tetrahedrally coordinated. Again three coordination sites are occupied by carbonyl groups of neighboring cyclopeptides and on the remaining coordination site sits a water molecule. In addition, there are two independent uncoordinated acetone molecules and five independent water molecules in the asymmetric unit.

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First O–H–N Hydrogen Bond with a Centered Proton Obtained by Thermally Induced Proton Migration**

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There is great current interest in the strongest types of hydrogen bonds, both in the chemical and the biological fields.[1] In contrast to "normal" and weak hydrogen bonds, which are primarily electrostatic $X^{\delta-}$–$H^{\delta+}\cdots Y^{\delta-}$ interactions,[2, 3] very strong hydrogen bonds have a quasi-covalent character.[4] In such a three-center four-electron bond X–H–Y, the H atom is involved in two partial covalent bonds of comparable bond orders. Very strong hydrogen bonds are stable in solution and in crystals, but have also been proposed to occur in intermediates of chemical[5] and enzymatic[6] reactions. In particular the latter proposal has led to heated and controversial discussions.[7] Very strong homonuclear hydrogen bonds (X–H–X) are experimentally well accessible, and numerous examples of centered or almost centered geometries have been reliably found by neutron diffraction experiments.[8] For heteronuclear hydrogen bonds, the structural information is much poorer. There are a few examples of X-ray crystal structures with O–H–N bonds in which the H atom has at least similar distances to O and N,[9, 10] but accuracies are poor, and not a single case was found as yet in neutron diffraction studies.[11] We now have been able to produce for the first time an exactly centered O–H–N hydrogen bond and characterize it by neutron diffraction. To achieve this goal, we used the effect of thermally induced proton migration, which we monitored by variable-temperature time-of-flight Laue neutron diffraction.

A good model system to study very short O–H–N hydrogen bonds are adducts of pentachlorophenol (PCP) with pyridine bases.[12, 13] The pK_a values of PCP and pyridine are similar, and suitable substitutions at the pyridine ring allow fine tuning of its pK_a value to match the one of PCP in an optimal way.[14] In a series of X-ray crystal structures, substituted pyridine · PCP complexes were found to crystallize as formally molecular or ionic adducts linked by hydrogen bonds $O–H\cdots N$ or $O^-\cdots H–N^+$, respectively, depending on the base selected.[15] The shortest hydrogen bond was found in crystalline 4-MePy · PCP (4-MePy = 4-methylpyridine), in which the $O\cdots N$ distance is 2.515(4) Å at 80 K,[10] and the H atom is situated approximately midway between the O and N atoms (Table 1). However, X-ray diffraction does not allow to determine the position of the H atom with an accuracy that is sufficient for a quantitative discussion.

To characterize the hydrogen bond in 4-MePy · PCP reliably, we determined the crystal structure by means of neutron diffraction (ND) at 20 K. The extremely short hydrogen bond ($O\cdots N$ 2.506(2) Å) has the center of gravity of the vibrating proton slightly off-center in the direction of the N atom (N–H 1.206(6), O–H 1.309(7) Å, N–H–O 170.4(6)°, Table 1). This represents by far the shortest O–H–N hydrogen bond for which ND data has been obtained. The most interesting observation, however, came as a complete surprise to us, and emerges from comparison with the X-ray crystal structures at room temperature[16] and at 80 K.[10] The overall crystal

Table 1. Geometrical parameters of the hydrogen bond in 4-MePy · PCP.

T [K]	O–H [Å]	H–N [Å]	Δ(X–H) [Å]	$O\cdots N$ [Å]	O–H–N [°]
RT, X-ray[16]	1.09(6)	1.47(6)	–	2.552(4)	170(5)
200	1.228(11)	1.306(11)	– 0.078(11)	2.525(4)	170.5(10)
150	1.229(11)	1.300(11)	– 0.071(11)	2.519(4)	169.6(10)
125	1.241(10)	1.288(10)	– 0.047(10)	2.519(4)	169.6(10)
100	1.258(8)	1.265(8)	– 0.007(8)	2.513(3)	170.1(8)
80	1.266(8)	1.255(8)	0.011(8)	2.513(3)	170.9(8)
80, X-ray[10]	1.22(4)	1.29(4)	–	2.515(4)	176(5)
60	1.275(10)	1.249(10)	0.026(10)	2.515(4)	170.9(10)
45	1.279(8)	1.242(8)	0.037(8)	2.513(3)	170.8(8)
20[a]	1.309(7)	1.206(6)	0.103(7)	2.506(2)	170.4(6)

[a] Measured on a different crystal than that at the other temperatures.

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