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Acetate Binding within a Supramolecular Network Formed by a Guanidiniocarbonyl Pyrrole Cation in the Solid State

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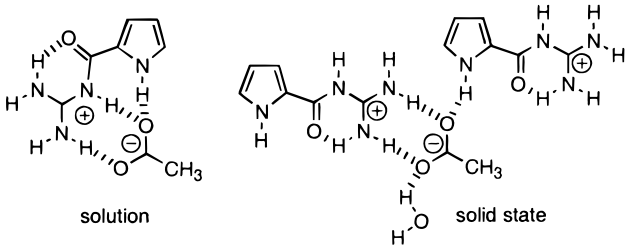
ABSTRACT



The crystal structure of guanidiniocarbonyl pyrrole acetate reveals extended two-dimensional hydrogen bonding networks with embedded anion binding sites. These are formed by the guanidinium moiety of one and the pyrrole NH of another cation in combination with an additional water molecule. Hence, the acetate is bound by the same kind of interactions as those previously found in the solution state complex, but as part of an extended supramolecular hydrogen bonding network and not in form of a discrete 1:1 complex.

Guanidinium cations are well known for the complexation of anions such as phosphates or carboxylates. Not only do the guanidinium ions contained in arginine residues play an important role in enzymes (both for binding and catalysis)[1] but also a large number of sophisticated artificial host systems for the complexation of various anions have been described over the past decade.[2] However, in highly competitive solvents, ion pairing of simple guanidinium cations with anions is still rather weak. Only for the past few years have anion receptors that function in polar solvents such as DMSO, methanol, or water become available, but their design and synthesis remain a challenging task.[3]

To improve the complexation properties, additional binding interactions besides the ion pairing are therefore necessary. Recently, we introduced guanidiniocarbonyl pyrroles, such as **1** (Figure 1), as a new receptor class for carboxylates.[4] These receptors are planar and rather rigid and therefore ideally preorganized for the binding of planar anions such as carboxylates. The increased acidity of the acylguanidinium

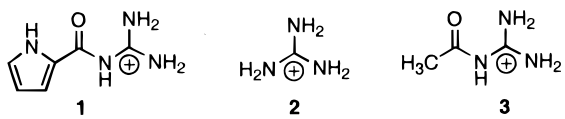


Figure 1. Guanidinium cations **1**−**3**.

(1) (a) Dugas, H. In *Bioorganic Chemistry, A chemical approach to enzyme action*; Springer: New York, 1996. (b) Hannon, C.; Anslyn, E. V. In *Bioorganic Chemistry Frontiers*; Dugas, H., Schmidtchen, F. P., Eds.; Springer: Heidelberg, 1993; p 193.

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group relative to a guanidinium cation favors the formation of ion pairs via hydrogen bonds and hence increases the binding affinity.[5] Additional hydrogen bond donors, such as the pyrrole NH, can further enhance the stability of the complex.

Complex Formation in Solution. Indeed, whereas with the simple guanidinium cation **2** no signs for complexation of acetate in DMSO were detected, its binding by guanidiniocarbonyl pyrrole **1** is so strong that the complexation constant could not be determined accurately ($K > 10^6$ mol^{-1}).[3o] Even in 50% water−DMSO the association constant is still on the order of $K \approx 10^3$ mol^{-1}.[4b] Compared to the parent acetyl guanidinium cation **3**, the association constants for the binding of carboxylates by the pyrrole derivative **1** are about three times larger.[4b]

We have measured the pK_a's of the acetyl and pyrrole acylguanidinium cations **1** and **3** in 10% water in methanol using ammonia as a base.[6] Both cations have essentially the same pK_a value, with the acetyl derivative **3** being even slightly more acidic than **1** (pK_a = 7.9 ± 0.2 for **1** and 7.6 ± 0.2 for **3**). Therefore, the higher association constants for the binding of carboxylates by **1** cannot be due to simple electrostatic effects of the guanidinium moiety. This shows that indeed the pyrrole NH is actively involved in the complexation of the carboxylate, giving rise to the tridentate binding mode schematically shown in Figure 2 (complex **A**).

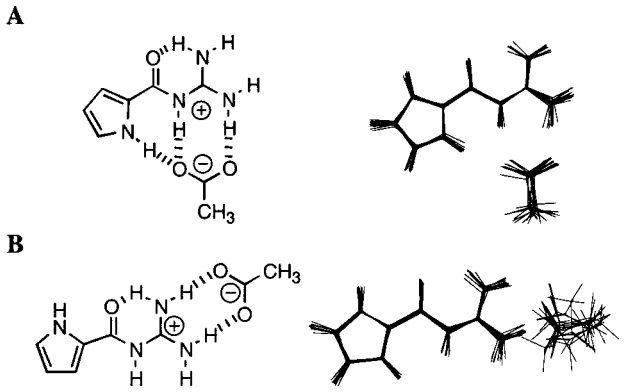

Figure 2. Schematic representation (left) and superposition of 25 calculated structures sampled from a molecular dynamics simulation (50 ps at 300 K) of the tridentate **A** and bidentate **B** complex between **1** and acetate in water (right, Macromodel V6.5,[7] Amber*, GB/SA solvation method).

In accordance with this scheme, in the ^{1}H NMR spectrum one observes large complexation-induced downfield shifts of all those receptor NHs, which participate in the proposed binding (up to 4.0 ppm in DMSO).[4]

This binding motif requires a receptor conformation in which the partially positively charged pyrrole NH points in the same direction as the positively charged guanidinium NHs in contrast to the more extended conformation found in the alternative bidentate complex **B**. According to theoretical calculations, especially in polar solvents, both these conformations have essentially the same energy. Molecular dynamics calculations also show that the proposed tridentate binding mode is by far energetically more favorable than any other possible complex structure (Figure 2). The tridentate complex **A** is rather rigid and 19 kJ mol^{-1} more stable than the bidentate complex **B**, in which the acetate group has a rather high flexibility and does not seem to have any preference for a distinct binding geometry.

Solid State Structure. Crystals of guanidiniocarbonyl pyrrole acetate, suitable for structure determination by X-ray diffraction,[8] were obtained from water−methanol solutions upon evaporation of the solvent. The guanidiniocarbonyl pyrrole cation **1** is completely planar and, in contrast to the situation found in solution, exists in the extended conformation in which the pyrrole NH points away from the guanidinium NHs (similar to complex **B** in Figure 2). The acetate is bound by the guanidinium NHs in the same bidentate hydrogen bonding fashion as known from simple guanidinium salts (Figure 3).[9] The bond lengths are remarkably short (O- - -HN distance 1.928 and 1.822 Å, respectively), reflecting the high stability of these hydrogen bonds. In addition to this ion pairing, the carboxylate group is simultaneously hydrogen bonded to the pyrrole NH of another guanidiniocarbonyl pyrrole molecule (O- - -HN distance 2.079 Å) on the one side and to one water molecule (O- - -HO distance 1.824 Å) on the other side. The remaining two guanidinium NHs, not involved in binding of the carboxylate, form hydrogen bonds to another water molecule, so that every donor and acceptor site of both the acetate and **1** are finally fully hydrogen bonded.

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(6) Schmuck, C.; Koenig, B. Unpublished results.

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(8) Nonius KappaCCD diffractometer (20 °C), Mo Kα radiation, $2\theta_{max} = 56°$; structure determination by direct methods (SHELXS-97, SHELXL-97). $C_8H_{12}N_4O_3 \cdot H_2O$, triclinic, space group *P*-1, $a = 8.360(1)$, $b = 8.462(1)$, and $c = 8.558(1)$ Å, $\alpha = 103.18(1)$, $\beta = 105.09(1)$, and $\chi = 93.46(1)°$, $V = 546.51(12)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.354$ g cm^{-3}, $\mu = 0.110$ mm^{-1}, 4483 data measured, 2504 independent reflections ($R_{int} = 0.0210$), $R_1 = 0.0366$, $R_w = 0.0960$ (based on refinement of 2069 observed reflections with $I > 2\sigma$ and 201 variable parameters). The final difference density was less than 0.177 e Å^{-3}.

(9) (a) Atwood, J. L.; Steed, J. W. Structural and Topological Aspects of Anion Coordination, in ref 2c, pp 147−216. (b) Muller, G.; Riede, J.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516−1517. See also ref 3n.

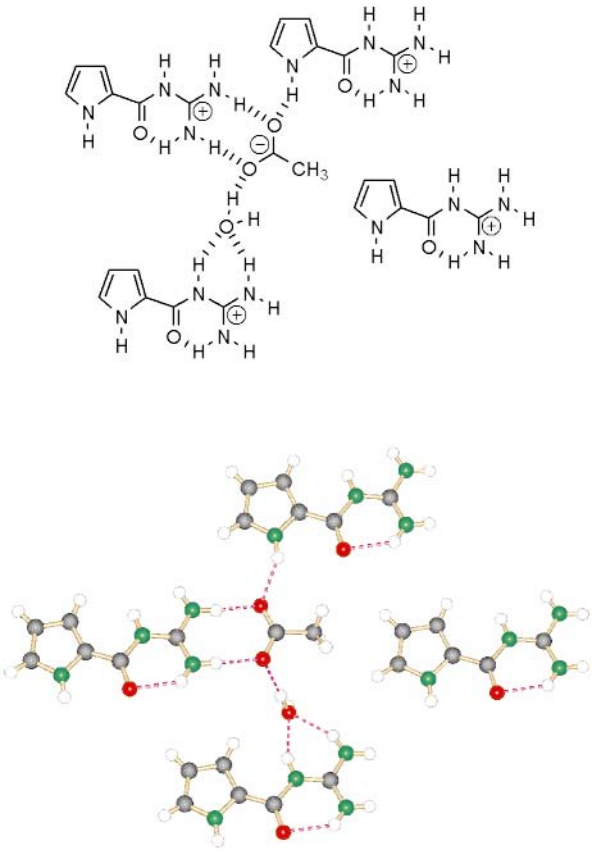

Figure 3. Schematic representation (above) and part of the crystal structure of guanidiniocarbonyl pyrrole acetate (below), showing the acetate binding site (dashed lines represent hydrogen bonds).

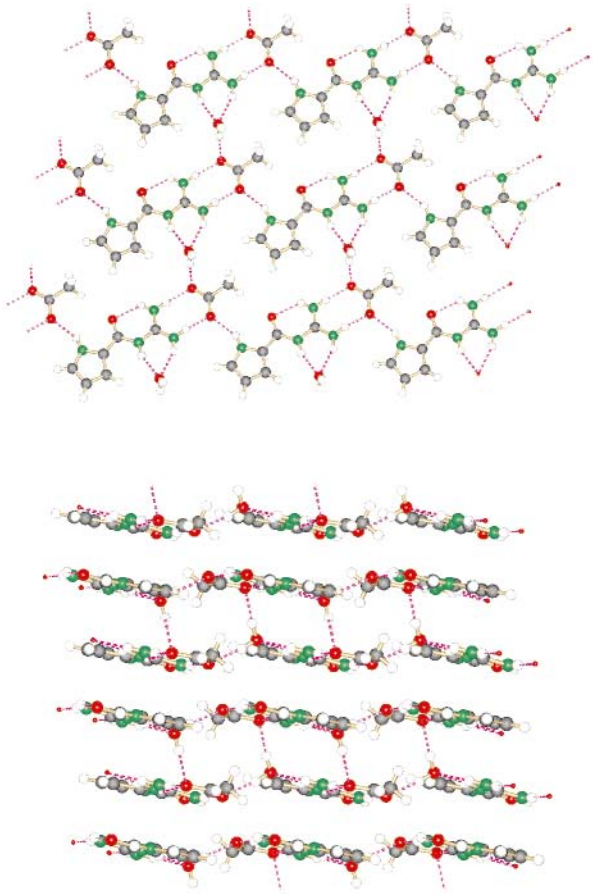

Figure 4. Packing arrangement of guanidiniocarbonyl pyrrole acetate in the solid state (above, top view; below, side view).

Though the receptor conformation in the solid state is different, the overall binding environment is similar to the situation found in solution: Each receptor molecule uses both the guanidinium NHs and the pyrrole NH for the binding of a carboxylate. For the carboxylate, we find bidentate ion pairing of both oxygens to the guanidinium moiety, an additional hydrogen bond from a pyrrole NH to one oxygen with the other oxygen atom being exposed to the solvent. The major difference is that in the solid state the pyrrole NH binding interaction is provided not by the same but by a second receptor molecule. The role of the water molecule, found in the crystal structure, is to mimic the solvent at the open sides of both the carboxylate and the receptor.

The nonpolar methyl group of the acetate is in close van der Waals contact to the nonpolar pyrrole ring of a third receptor molecule. Hence, all possible binding interactions of both the acetate and the guanidiniocarbonyl pyrrole, namely, polar electrostatic interactions on the one side of the molecule and nonpolar van der Waals contacts on the other, are used. Thereby, extended two-dimensional, planar networks are formed (Figure 4). Two such layers are held together by hydrogen bonds between the water molecules of one layer and the carboxylate groups of the other. Between these pairs of hydrogen bonded layers there are only weak interactions provided by π-stacking. Such a layered structure is probably not possible with the tridentate binding motif found in solution. Therefore, the solid state structure differs from the solution structure, though the general binding characteristics are conserved.

In summary, we have reported here the crystal structure of guanidiniocarbonyl pyrrole acetate. In contrast to the situation observed in solution, no discrete complexes are present in the solid state, but rather the acetate is embedded in an extended two-dimensional hydrogen bonding network. However, each individual anion binding site is constituted by exactly the same kind of binding interactions also present in the bimolecular complex in solution. Therefore, both structures are remarkably similar and are in this sense “the same and not the same”.

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Supporting Information Available: Detailed X-ray structural information on the guanidiniocarbonyl pyrrole acetate. This material is available free of charge via the Internet at http://pubs.acs.org.

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