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Anion-Dependent Dimerization of a Guanidiniocarbonyl Pyrrole Cation in DMSO†

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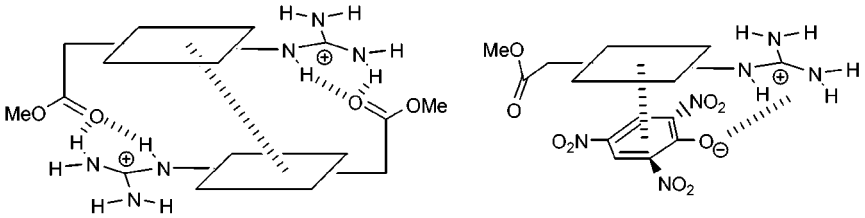
ABSTRACT



With spherical counteranions such as chloride or hexafluorophosphate, the glycine-derived guanidiniocarbonyl pyrrole cation 1 self-assembles into discrete dimers in DMSO, as can be seen by NMR and ESI mass spectral analysis. According to concentration- and temperature-dependent NMR studies, the dimerization is endothermic and therefore entropy driven. Molecular modeling suggests that the dimers are held together by hydrogen bonding in combination with π–π interactions. In the presence of picrate anions, dimerization of cation 1 does not occur, probably due to the formation of π-stacked ion pairs.

Molecular recognition and especially self-assembly[1] can lead to the formation of highly complex and fascinating structures both in the solid state[2] and in solution.[3] The search for novel building blocks that self-assemble into well-defined structures is of great importance not only to gain an understanding of the concepts and principles that govern these processes but also for the design of new molecular materials with tailor-made properties. Especially for polar solvents, the design of self-assembling systems is still a challenging task due to the limited strength of noncovalent interactions in such solvents.[4,5]

Recently, we introduced a novel class of carboxylate guanidiniocarbonyl pyrrole zwitterions which show strong self-association even in polar solution.[6] Depending on the structure of the molecule and the experimental conditions, these zwitterions either fold intramolecularly into loops[6b] or form dimers[6a] or linear polymers.[6c] In all these aggregates,

† Dedicated to Professor Ronald Breslow on the occasion of his 70th birthday.

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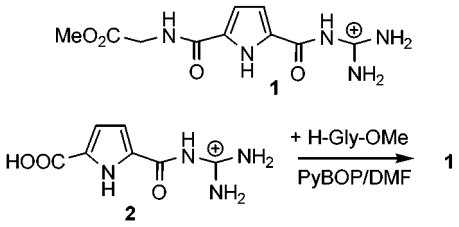
the main binding interaction stems from the ion pairing of the carboxylate with the guanidiniocarbonyl pyrrole cation.[7]

However, such an attractive electrostatic interaction is not necessarily required for self-assembly in polar solvents. Herein, we report that even the simple cationic guanidiniocarbonyl pyrrole cation **1** forms dimers in DMSO. Furthermore, this self-assembly is dependent on the anion present and can be inhibited by picrate.

The synthesis of compound **1** is described in Scheme 1:

Scheme 1. Synthesis of Compound **1**



The previously reported zwitterion **2**[6a] is coupled with glycine methyl ester, using PyBOP in DMF as the coupling reagent. After reaction at room temperature for 16 h and evaporation of the solvent, the product can be precipitated as the chloride or picrate salt by acidification of the crude reaction mixture dissolved in methanol.

In contrast to other guanidiniocarbonyl pyrrole cations, the glycine derivative **1** is only slightly soluble in most organic solvents, such as methanol or THF, which gave a first hint to some unexpected association properties of **1**. This is supported by the ^{1}H NMR spectrum (chloride salt, millimolar concentration in [D$_6$]DMSO), which shows significantly different shifts compared to those of previously reported guanidiniocarbonyl pyrroles (Figure 1):[6−8] The

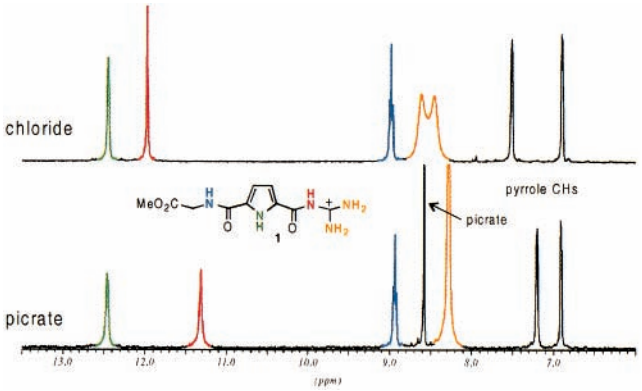


Figure 1. Part of the ^{1}H NMR spectra of compound **1**: whereas the chloride salt (top) forms dimers in solution, the picrate salt (below) does not show any self-association.

signal for the four guanidinium NHs is split into two signals at $\delta = 8.6$ and 8.4, respectively, and the guanidinium amide is shifted downfield from a normal value around $\delta = 11.2$ to $\delta = 12.0$. Furthermore, these shifts are concentration dependent. This clearly indicates that some kind of self-association does take place in this case.[9]

This conclusion is supported by mass spectroscopy. The ESI spectrum of **1** not only shows the molecular ion peak at $m/z = 268$ au but also a signal of equal intensity at $m/z = 535$ au which corresponds to a dimer (Figure 2). No

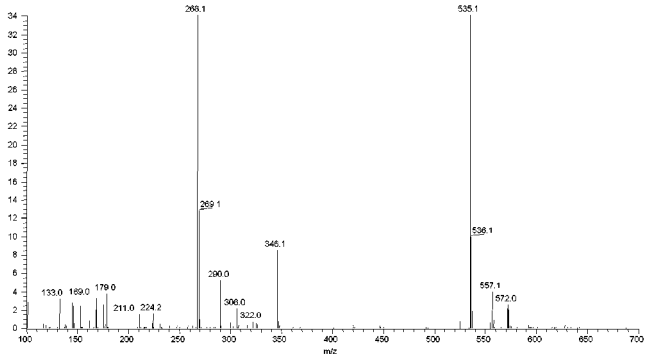


Figure 2. ESI mass spectrum of compound **1** ($m/z = 268$ au) showing the formation of a dimer at $m/z = 535$ au.

significant signals for higher aggregates such as trimers or tetramers were found.

To determine the binding constant for the self-association of compound **1**, we studied the concentration dependence of the ^{1}H NMR spectrum of **1** in the concentration range of 1 to 500 mM.[10] According to the method of Bangerter and Chan,[11,12] the observed chemical shift δ_{obs} depends on the total concentration C and the association constant K_{ass} as expressed by the equation given in Figure 3. We used the signal of the guanidinium amide NH for data analysis, as

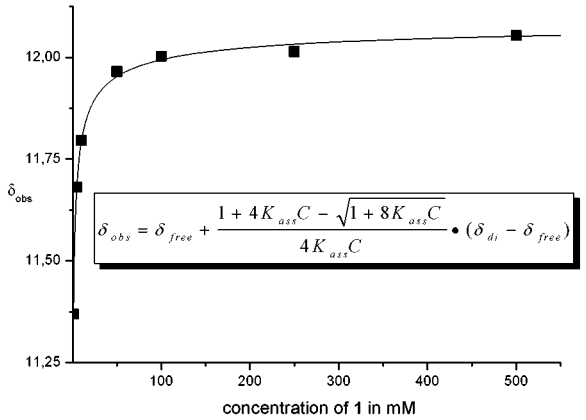


Figure 3. Complexation-induced shift changes of the guanidinium amide NH in **1** in the concentration range from 1 to 500 mM. The solid line represents the curve fit according to the equation shown. (300 MHz, [D6]DMSO).

this NH shows the largest overall shift change upon dilution and hence gives the most accurate results. The chemical shift of the free, uncomplexed molecule δ_{free} as derived from the curve fitting ($\delta = 10.81$) of the data in Figure 3 is in excellent agreement with a value of $\delta = 10.84$ measured for a very highly diluted solution (<0.01 mM) of **1**. Also, the calculated shift within the dimer δ_{di} as extrapolated from the curve fitting of the binding isotherm for high concentrations is essentially identical to the observed shift in the 500 mM sample ($\delta = 12.10$ and 12.05, respectively). This consistency within the data shows that dimerization indeed takes place in solution and that the use of the equation shown in Figure 3 for data analysis is validated.

The association constant for the dimerization of compound **1** is calculated to be 673 M^{-1} at 298 K. Using the shift changes of the guanidinium NH_2 or the pyrrole C3H, one obtains similar values, but the regression analysis is less accurate. The data for the shift change of the amino acid amide NH however do not fit this dimerization model. Hence, this shift change seems to originate not from the dimerization but from another (second and much weaker) association process, probably anion coordination. This value of 673 M^{-1} for the dimerization of **1** is surprisingly high for a cationic species in such a highly polar solvent as DMSO and suggests that the binding within the dimer is probably not just only due to hydrogen bonding. To gain further insight into the binding interactions, we studied the temperature dependence of the dimerization constant.

With increasing temperature, the association constant increases from 673 M^{-1} at 298 K to 1581 M^{-1} at 348 K. Hence, the dimerization is an endothermic process driven by entropy.[13] From a van't Hoff plot (Figure 4) of the

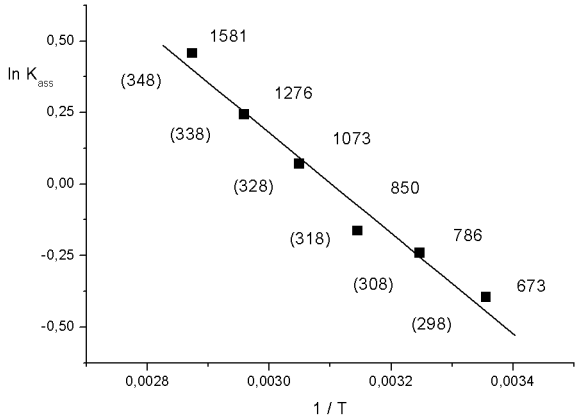


Figure 4. Van't Hoff plot for the dimerization of **1** in the temperature range from 298 to 348 K (values above the line are dimerization constants K_{ass} in M^{-1}, values in parentheses are temperatures in K).

calculated binding data, the thermodynamic parameters for the dimerization of **1** in DMSO can be obtained: $\Delta H = +14.6$ kJ mol^{-1} and $\Delta S = +45.2$ J mol^{-1} K^{-1}. These data suggest that in addition to conventional hydrogen bonding, which is enthalpy controlled in general, $\pi-\pi$ stacking between the two heterocyclic rings or hydrophobic interactions might also be important.[14]

Although it is quite clear from the NMR and mass spectral data that cation **1** dimerizes even in polar solutions, the explicit structure of the dimers cannot be deduced from these experiments. Therefore, to learn more about the conformation of **1** in solution we performed ROESY NMR measurements in DMSO (Figure 5) under conditions where it can be

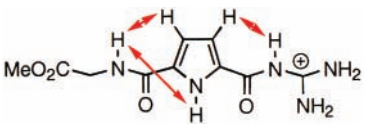


Figure 5. Key NOEs in **1** as obtained from a ROESY experiment under conditions where **1** is mostly dimeric (500 MHz, [D_6]DMSO, 100 mM, 298 K).

assumed from the chemical shift of the guanidinium amide ($\delta = 11.96$) that **1** is mostly dimeric.

On the basis of these NOE findings, the guanidinioncarbonyl group seems to be in an orientation where the carbonyl oxygen points in the same direction as the pyrrol NH, since the guanidinium amide gives only a NOE with the pyrrole CH but not with the pyrrole NH. The orientation of the amino acid amide group cannot be assigned from the ROESY experiment since we see both a NOE with the pyrrole NH and CH. Interestingly, the methylene group does not show any NOE with the pyrrole, although this is the case in a more dilute sample, in which **1** is mostly monomeric. This suggests that in the dimer **1** exists in a rather extended conformation in which the methylene group is too far away from the pyrrole ring to give rise to a NOE.

Taking these NOE constraints into account, we performed molecular mechanics calculations (Macromodel V. 6.5,[15] Amber* force field, GB/SA water solvation treatment). The

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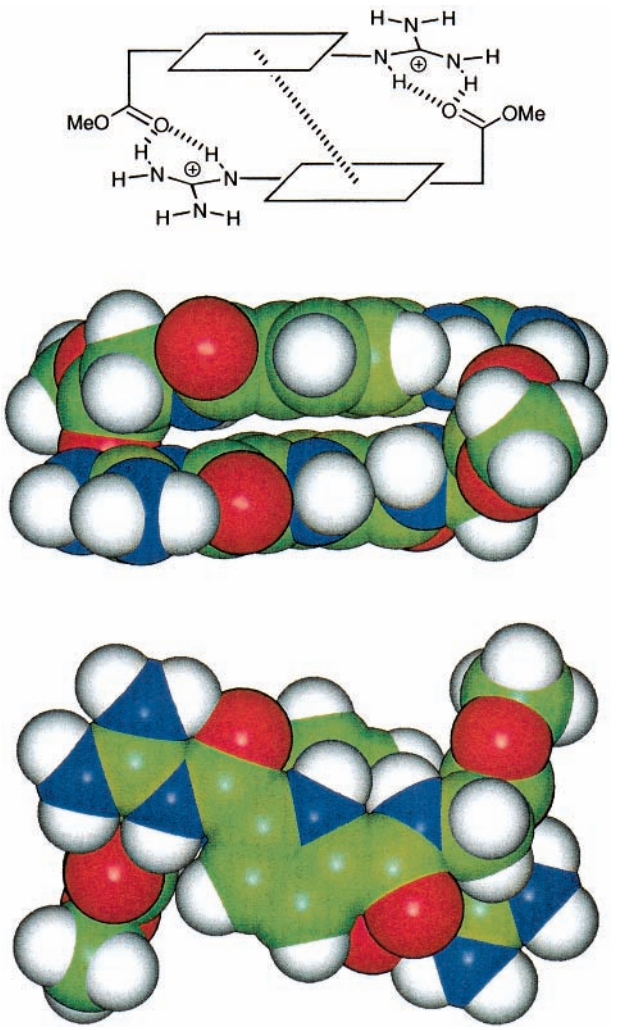

Figure 6. Proposed structure for dimeric **1**, based on NOE constraints and molecular mechanics calculations (top, schematic representation; middle, CPK model side view; bottom, CPK model top view).

resulting structure is shown in Figure 6. The carbonyl oxygen of the ester group is hydrogen bonded by the guanidinium amide NH and one of the guanidiniocarbonyl NH_2 hydrogens. The planar aromatic parts of the two molecules are π-stacked. The amino acid amide NH is not involved in the dimerization process but probably might be used for anion coordination. In this sense, the structure is in good agreement with all the observed experimental data, e.g., the different shift changes of the various NHs, the NOE derived conformation, or the entropy driven association probably resulting from the π-stacking.

That π-stacking is indeed important for dimerization[16] can also be seen from the fact that when picrate is used as the anion instead of chloride or hexafluorophosphate, the self-association is completely disrupted. The ^{1}H NMR spectrum of the picrate salt of **1** (Figure 1) does not show any signs of dimerization but rather resembles the spectrum of a normal guanidiniocarbonyl pyrrole: an unsplit signal for the guanidinium NHs around $\delta = 8.3$ and a signal around $\delta = 11.2$ for the guanidinium amide NH. Obviously, in this case the electron deficient picrate anion forms a π-stacked ion pair with the guanidiniocarbonyl pyrrole cation preventing dimerization (Figure 7).

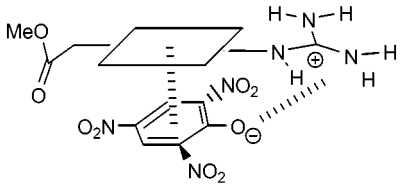

Figure 7. Formation of a π-stacked ion pair between the picrate anion and **1** prevents dimerization.

In conclusion, we have shown here by the use of NMR titration experiments and mass spectral data that cation **1** self-assembles in DMSO by an entropy-controlled process forming π-stacked dimers. These dimers are only stable if the counteranion is not capable of competing with the π-stacking interaction (e.g., chloride). Otherwise, as in the presence of picrate anions, π-stacked ion pairs are formed instead. On the basis of these findings, the design of larger self-assembled molecular boxes, whose formation can be controlled by the anion present, should also be possible.

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