

Dimerization of a guanidiniocarbonyl pyrrole cation in DMSO that can be controlled by the counteranion

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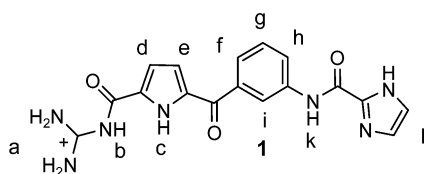
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In the presence of chloride anions cation **1** dimerizes in DMSO with a surprisingly high association constant of $> 10^3 \text{ M}^{-1}$ whereas the addition of picrate disrupts these dimers by formation of even more stable discrete π -stacked ion pairs.

The development of novel building blocks which are capable of self-assembly in polar solutions is one main goal in today's supramolecular chemistry as molecular recognition-directed self-assembly and self-organization can lead to the formation of highly complex and fascinating structures with new and interesting properties.¹ One further appealing aspect in contrast to more traditional covalent systems is that the extent of supramolecular aggregation and hence the properties resulting therefrom can be externally controlled.² However, these processes are still poorly understood. In this context we wish to report here the surprisingly stable self-assembly of a guanidiniocarbonyl pyrrole cation **1** which forms discrete 1:1-dimers in DMSO. However, the dimerization is anion dependent and can be turned off by the addition of picrate anions.

Cation **1** was isolated from the deprotection of the corresponding tBoc protected guanidine as either the picrate or the chloride salt.³ In both cases the isolated salt was the mono-cation. The ¹H NMR spectrum only showed protonation of the guanidinium group which can be clearly seen by the characteristic signal around $\delta = 8.3$ for the four NH₂ protons (Fig. 1). The formation of the monocation is also supported by ESI MS experiments. No signal corresponding to a double protonated form was detected but only a clear signal for the monocation at $m/z = 366$ (M⁺-H, neg. ion mode, DMSO/MeOH solution).

Furthermore, a closer look at the NMR spectrum of the chloride salt revealed that the mono cation self-aggregates: the NMR shifts are concentration dependent (Fig. 1, chloride salt). The ¹H NMR spectrum of **1** at submillimolar concentrations in [D₆]DMSO (0.1 mM at 303 K) is consistent with a non interacting species:⁴ The signal at $\delta = 8.25$ for the four guanidinium NH₂ protons, a signal for the guanidinium amide NH at $\delta = 10.75$ and for the imidazolium amide NH at $\delta = 10.71$ and a singlet at $\delta = 12.86$ for the pyrrole NH. However, these shifts are concentration dependent. In a 50 mM solution in [D₆]DMSO the signal for the guanidinium NH₂ protons has split into two signals and shifted to $\delta = 8.7$ and 8.5. The signal for the imidazolium amide NH has shifted to $\delta = 11.4$, and the signal for the guanidinium amide NH to $\delta = 12.3$, respectively. These concentration-dependent shift changes are indicative of an intermolecular interaction that is more pronounced in more concentrated solutions. As the addition of NaCl to a diluted solution of **1** (0.5 mM) does not cause similar shift changes, interactions of the cation with the chloride anion alone (ion pair formation) can not be the reason. Hence, self-association of the cation **1** must be the origin of the observed shift changes. However, the chloride probably also interacts with these dimers once formed (*vide infra*) thereby reducing their overall charge.



To determine the binding constant for the self-association of cation **1** quantitatively, we studied the concentration dependence of the ¹H NMR spectrum of **1** in the concentration range from 1 to 50 mM.⁵ A plot of the observed chemical shift versus concentration gives an isothermic binding curve (Fig. 2). As the complexation is fast on the NMR time scale, the observed chemical shift δ_{obs} is the

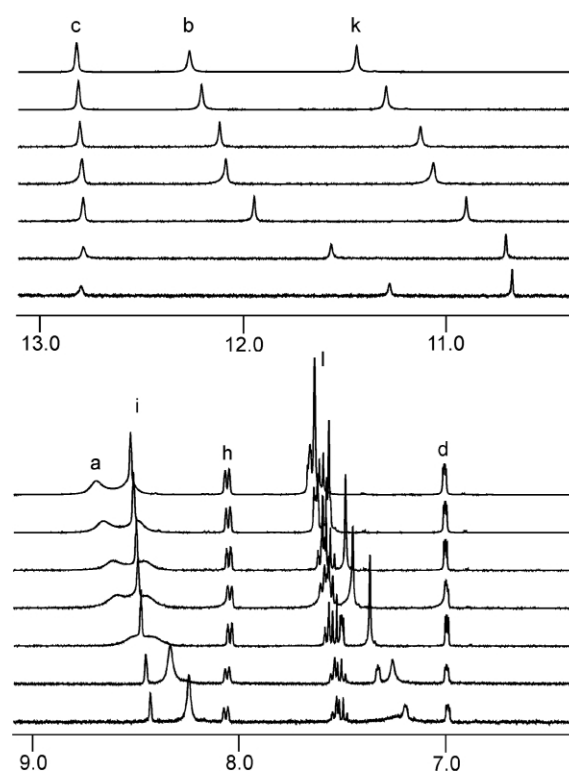


Fig. 1 Parts of the ¹H NMR spectrum (300 MHz, 303 K) of **1** in [D₆]DMSO showing the dimerization induced shift changes (concentrations from bottom to top: 1, 5, 10, 12.5, 15, 25, 50 mM).

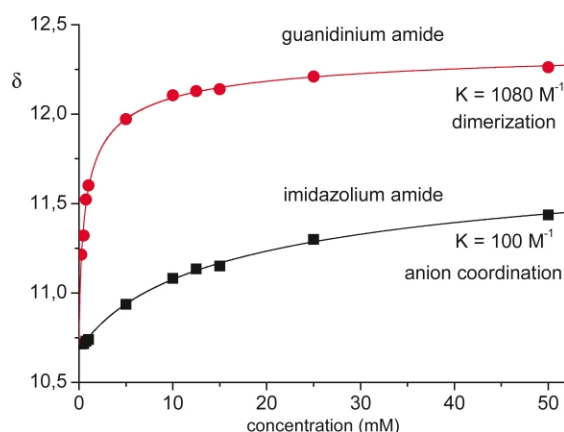


Fig. 2 Binding isotherms for the guanidinium (red) and the imidazolium amide (black) of **1**. The solid lines show the curve fitting for a 1:1-dimerization.

weighted average of the shifts for the complexed (δ_{dimer}) and the uncomplexed molecule (δ_{free}). According to the method of Bangerter and Chan,⁶ for a dimerization equilibrium the observed chemical shift δ_{obs} depends on the total concentration C and the association constant K_{dim} as expressed by the following equation:

$$\delta_{\text{obs}} = \delta_{\text{free}} + \frac{1 + 4K_{\text{dim}}C - \sqrt{1 + 8K_{\text{dim}}C}}{4K_{\text{dim}}C} (\delta_{\text{dimer}} - \delta_{\text{free}}) \quad (1)$$

The association constant for the dimerization of cation **1** is calculated to be $K_{\text{dim}} = 1080 \text{ M}^{-1}$ at 298 K using *e.g.* the shift changes of the guanidinium amide NH^b or the guanidinium NH_s^a. However, the shift change of the imidazolium amide NH^k represents a second and weaker association process with $K \approx 100 \text{ M}^{-1}$, most probably reflecting anion coordination.

To gain further insight into the binding interactions, we performed molecular modelling calculations. A Monte Carlo simulation (Macromodel 8.0,⁷ Amber⁸, water solvation) supports this view that the dimer is held together by a combination of hydrogen bonds and π -stacking interactions (Fig. 3). The CO of the imidazolium amide is hydrogen bonded by the guanidinium amide NH^b and the pyrrole NH^c. The guanidinium NH^as interact with the imidazolium nitrogen. Furthermore π -stacking⁸ or hydrophobic interactions between the two guanidiniocarbonyl pyrrole moieties and the benzene and imidazolium rings, respectively, probably further stabilize the complex. At least one anion is probably bound on the backside of this dimer by interactions with the amide NH^k and the imidazolium NH as reflected by the weak shift changes of these signals.

Interestingly, the self-aggregation of **1** can be switched off by the addition of picrate anions to a solution of the chloride, as can be seen for example by a highfield shift of the guanidinium amide NH signal upon addition of picrate to a solution of the chloride. Obviously, an intermolecular interaction between cation **1** and picrate disrupts the dimers. This is supported by an inspection of the nmr spectrum of the picrate salt of **1**. Diluted samples have the same chemical shifts as samples of the chloride salt indicating the presence of non-interacting monomers. With increasing concentration complexation induced shift changes are observed, which however are remarkably different from those observed for the chloride salt. For example, the limiting shift of the guanidinium amide NH at high concentrations is $\delta = 11.8$ instead of 12.3 for the chloride and the guanidinium NH₂ signal is not split into two and shifts to $\delta = 8.4$ only. The signal for the picrate anion also shows a downfield shift change indicating its participation in the complexation event. Hence, these shift changes reflect not the dimerization of **1** but its interaction with the picrate counter anion. Probably, the electron deficient picrate anion forms a stable π -stacked ion pair with the guanidiniocarbonyl pyrrole cation **1**

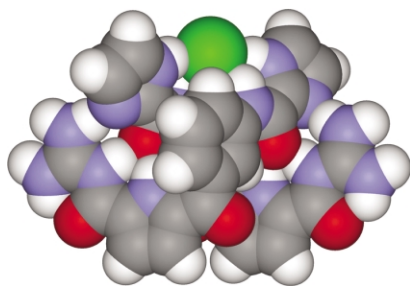


Fig. 3 Proposed structure for the dimer **1-1** with an associated chloride anion (green).

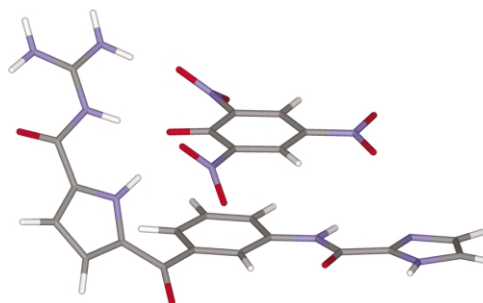


Fig. 4 Calculated structure of ion pair between picrate and **1**.

preventing its dimerization.⁹ The calculated structure for this ion pair is shown in Fig. 4. The picrate anion interacts with the positively charged guanidinium moiety, whereas the electron deficient aromatic ring of the picrate π -stacks with the electron-rich benzene ring of **1**. A quantitative analysis of the guanidinium amide NH shift from the dilution data provides a binding constant for this ion pair formation of $K_{\text{ion}} = 2400 \text{ M}^{-1}$ at 298 K. Hence, ion pair formation is more than twice as stable than the dimerization of **1** by itself.

In conclusion, we have presented here an anion-switchable self-aggregation of a cationic guanidiniocarbonyl pyrrole in DMSO. The understanding of such supramolecular processes may lay the basis for a more rational design of switchable self-aggregating systems in the future.

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