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# Self-assembly of 2-(guanidiniocarbonyl)-pyrrole-4-carboxylate in dimethyl sulfoxide: an entropy driven oligomerization

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**Abstract**—The self-assembly of 2-(guanidiniocarbonyl)-pyrrole-4-carboxylate (**2**), which is a heteroditopic zwitterion with self-complementary binding groups, was studied in DMSO. Through intermolecular ion pairing between the carboxylate of one and the guanidinium group of another molecule, **2** forms linear chain like oligomers in solution as can be seen from the corresponding shift changes in the NMR spectrum. Concentration dependent NMR studies at different temperatures allowed us to calculate the corresponding binding constants and thermodynamic parameters for this association process. These data show that the oligomerization is endothermic and therefore an entropy-driven process. The release of ordered solvent molecules into the bulk solution during complexation is hence responsible for the oligomerization. © 2001 Published by Elsevier Science Ltd.

## 1. Introduction

Molecular recognition and especially self-assembly[1–3] can lead to the formation of highly complex and fascinating structures both in the solid state[4–9] and in solution.[10–13] Over the past few years, intense research has been directed towards gaining an understanding of the concepts and principles that govern these processes. Artificial self-assembling systems have been devised, which may prove useful one day in the design of novel materials and nanostructures.[14,15] But especially for polar solvents the design of self-assembling systems is still a challenging task, due to the limited strength of non-covalent interactions in such solvents.[16–18] As the polarity of the surrounding solvent increases, the strength of hydrogen bonds and electrostatic interactions, mainly used for molecular recognition, decreases rapidly, due to the competitive solvation of donor and acceptor sites by the solvent. However, it would be very desirable to have access to self-assembling systems that also function in more polar (i.e. more 'natural') solvents such as DMSO or water.[19–27]

Recently, we introduced a novel class of carboxylate–guanidiniocarbonyl pyrrole zwitterions, which show strong self-association in polar solution.[28,29] For example, the heteroditopic zwitterion **1** forms discrete dimers held together by ion pairing in combination with multiple hydrogen bonds.[30–32] The stability constant for the dimer $\mathbf{1}_2$ in DMSO could be estimated as $K \approx 10^{12}$ $M^{-1}$. Herein, the self-association properties of the regioisomeric zwitterion **2** are reported. In contrast to zwitterion **1**, the two self-complementary binding groups in **2** are not arranged in a U-shaped pattern as necessary for dimerization but rather in a linear way. Therefore, zwitterion **2** cannot form discrete dimers in a head-to-tail orientation due to geometric reasons and hence quite different association properties are expected.

*Keywords*: supramolecular chemistry; molecular recognition; guanidinium cations; zwitterions; oligomerization.

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## 2. Results and discussion

### 2.1. Synthesis

The synthesis of **2** is outlined in Scheme 1. Vilsmeier–Haack formylation[33] of 2-(methoxycarbonyl)-pyrrole (**3**)[34] gave a 2:1 mixture of the corresponding 5 and 4 substituted aldehydes **4a** and **b**, which were separated by chromatography.[35] After oxidation of **4b** with permanganate according to a literature procedure,[34] the acid **5** was treated with guanidinium chloride in sodium methoxide to give the desired zwitterion **2**.

### 2.2. Self-association properties

In contrast to zwitterion **1**, the $^1$H NMR spectrum of **2** does not show any signs of intermolecular association at sub-millimolar concentrations in [$D_6$]DMSO. Whereas the spectrum of **1** clearly showed a strong interaction between the carboxylate group and the guanidiniocarbonyl pyrrole moiety,[28] the spectrum of **2** at this concentration (0.1 mM at 303 K) is consistent with a non-interacting species:[36] a broad signal at $\delta$=8.2 for the 4 guanidinium $NH_2$ protons, a broad signal for the amide NH at $\delta$=11.0, and a singlet at $\delta$=12.7 for the pyrrole NH. However, these shifts are

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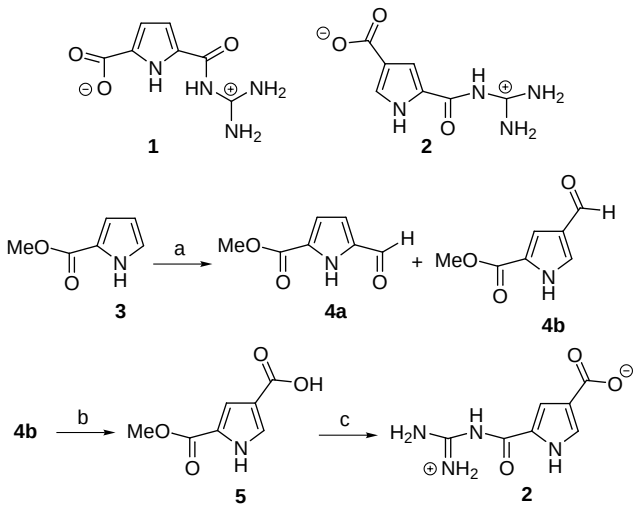



**Scheme 1.** Synthesis of compound **2** (a) $POCl_3$, DMF, $CH_2Cl_2$, chromatography on silica gel (hexane/ethyl acetate 60:40) gave pure **4b** in 24% yield besides 60% of **4a**; (b) $KMnO_4$; acetone/water, 67%; (c) guanidinium chloride (5 equiv.), NaOMe (5 equiv.), MeOH, reflux overnight, 47%.

concentration dependent (Fig. 1). In a 100 mM solution in [D6]DMSO, the signal for the guanidinium $NH_2$ protons has shifted to $\delta$=8.5 and the signal for the amide NH to $\delta$=12.0, respectively. Both signals also become broader.

These results are consistent with the formation of linear aggregates through intermolecular aggregation between the carboxylate group of one molecule and the guanidinium group of another (Fig. 2). As already mentioned above, zwitterion **2** cannot form discrete dimers due to geometric reasons. The rather linear arrangement of the self-complementary binding groups allows only a linear aggregation leading to the formation of chain-like oligomers.[37,38]

To determine the binding constant for this association process, we studied the concentration dependence of the $^1$H NMR spectrum of **2** in [D6]DMSO in the concentration range 1–100 mM following the shift changes of the guanidinium NHs. The signal for the amide NH becomes increasingly broad with increasing concentration (Fig. 1) so that, despite the fact that it shows a larger shift change in total, this signal is less suitable for an accurate quantitative analysis of the oligomerization process. A plot of the observed chemical shift versus concentration gives an

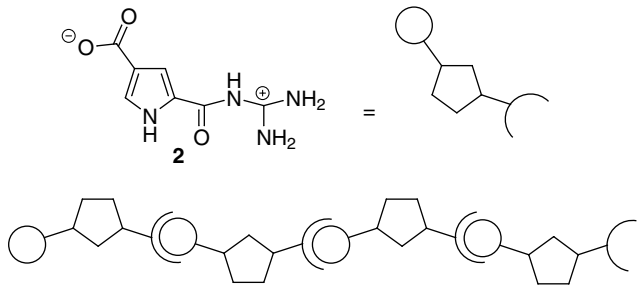



**Figure 2.** Formation of linear aggregates through self-assembly of zwitterion **2**.

isothermic binding curve (Fig. 3), clearly showing that concentration dependent intermolecular association takes place.[39]

As the complexation is fast on the NMR time scale, the observed chemical shift $\delta_{obs}$ is the weighted average of the shifts for the complexed ($\delta_{oligo}$) and the uncomplexed molecule ($\delta_{free}$):[40,41]

$$\delta_{obs} = \delta_{oligo}p + \delta_{free}(1 - p) \quad (1)$$

The parameter $p$ is the fraction of complexed molecules at each concentration. From this value, the number $n$ of aggregated monomers can be estimated according to Eq. (2):[40]

$$n = 1/(1 - p) \quad (2)$$

If one takes the chemical shift of the highest diluted solution (0.1 mM) $\delta_{free}$=8.2 as that of the free, uncomplexed molecule and the extrapolated value from the binding isotherm for high concentrations as that of the complexed molecule within the oligomer ($\delta_{oligo}$=8.7), one can estimate that at a concentration of 100 mM, where the observed chemical shift is $\delta_{obs}$=8.5, an average of 2.5 molecules of **2** are aggregated. This means that in the concentration range studied, dimerization is the main important aggregation process for zwitterion **2** which has to be considered. However, in these dimers only one of the two binding groups of each molecule is used in contrast to the discrete dimers formed by zwitterion **1**. At concentrations above 100 mM, higher oligomers such as trimers or tetramers may also form in significant amounts. Therefore using

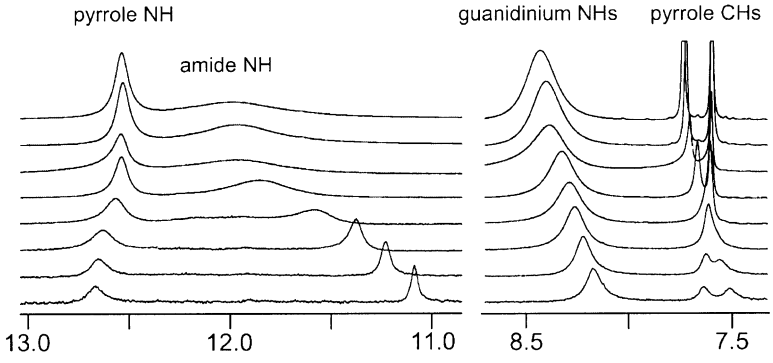



**Figure 1.** Parts of the $^1$H NMR spectrum (300 MHz, 303 K) of **2** in [$D_6$]DMSO showing the complexation induced shift changes of the guanidinium NHs and the amide NH (concentrations from bottom to top: 1, 2.5, 5, 10, 25, 50, 75 and 100 mM).

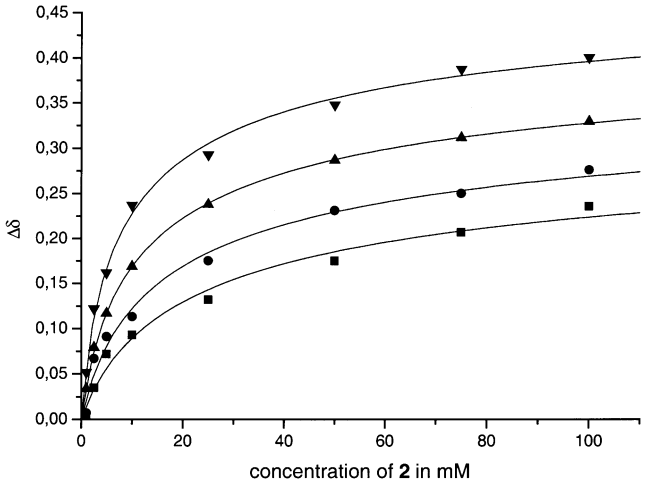


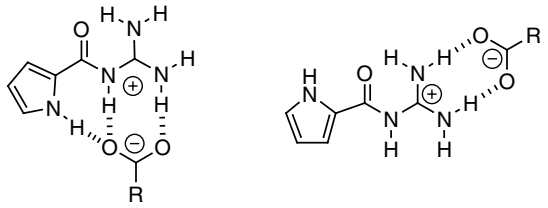

**Figure 3.** Complexation induced shift changes of the guanidinium NHs in **2** in the concentration range 1–100 mM at various temperatures (from bottom to top 303, 323, 343 and 363 K). The solid lines represent the curve fits according to Eq. (3). (300 MHz, [$D_6$]DMSO).

only NMR data from the concentration range $\leq$100 mM, one can calculate the binding constant $K_{ass}$ for the dimerization according to the method of Bangerter and Chan.[42] The observed chemical shift depends then on the total concentration $C$ and the association constant $K_{ass}$ in the following way (Eq. (3)):[43]

$$\delta_{obs} = \delta_{free} + \frac{1 + 4K_{ass}C - \sqrt{1 + 8K_{ass}C}}{4K_{ass}C}(\delta_{oligo} - \delta_{free}) \quad (3)$$

Using a non-linear curve fitting procedure for the data in Fig. 3, the binding constant $K_{ass}$ for the aggregation of zwitterion **2** is calculated to be 22.2 $M^{-1}$ at 303 K. This binding constant is lower by ca. 3 orders of magnitude than the association constants that we found previously for carboxylate binding by the isomeric zwitterion **1** and similar guanidiniocarbonyl pyrroles.[44] This dramatic decrease in binding strength going from **1** to **2** suggests that the binding mode is quite different for these two guanidinium cations.

We have shown before that in the case of **1**, the carboxylate group is bound in a tridentate fashion by one of the guanidinium NHs, the amide NH and the pyrrole NH (Scheme 2).[28] However, in the case of **2**, we do not see any significant complexation induced downfield shift of the pyrrole NH in the NMR spectrum even at high concentrations. Also the observed maximum shift changes for both the amide and the guanidinium NHs are much less pronounced than in **1**, in which, for example, the amide NH shifts nearly 4 ppm to $\delta$=15.7, respectively. From these results one can conclude that in the zwitterion **2**, the carboxylate group is bound only in a bidentate way by the two H atoms of the guanidinium moiety as also shown in Scheme 2. Such a bidentate binding mode is energetically less stable than the tridentate one.[45] Hence, the binding mode in the linear oligomers of **2** resembles that of a simple guanidinium cation and not a guanidiniocarbonyl pyrrole. And indeed the binding constant of 22.2 $M^{-1}$ is in good



**Scheme 2.** Tridentate (left) versus bidentate (right) binding mode in complexes between guanidiniocarbonyl pyrroles and carboxylates.

agreement with those of other literature data, which have given association constants for anion binding by simple guanidinium cations in DMSO ranging from $10^1$ to $10^3$ $M^{-1}$.[30,46–49]

## 2.3. Temperature dependance

We have also studied the association process of zwitterion **2** at different temperatures from 303 to 363 K using the NMR dilution experiment described above following the complexation induced shift change of the guanidinium NH. The obtained binding curves are shown in Fig. 3. Non-linear regression analysis using the dimerization model (Eq. (3)) gave satisfactory curve fits in all cases. Interestingly, the association constant increases with increasing temperature from 22.2 $M^{-1}$ at 303 K to 70.5 $M^{-1}$ at 363 K. From a van't Hoff plot of the calculated binding constants, the thermodynamic parameters for the oligomerization process of zwitterion **2** in DMSO can be obtained (Fig. 4).

These data show that the association of **2**, at least in the temperature range studied, is endothermic ($\Delta H$= 17.6 kJ $mol^{-1}$) and therefore driven by entropy ($\Delta S$= 83.4 J $K^{-1}$ $mol^{-1}$). Similar endothermic binding events have been reported previously for the binding of anions such as sulfate to ditopic guanidinium cations in polar solvents[46,50] or for the formation of 'softball' dimers in chloroform.[51] The formation of salt bridges and hydrogen bonds between a donor and acceptor requires first a desolvation of the corresponding binding sites. In highly

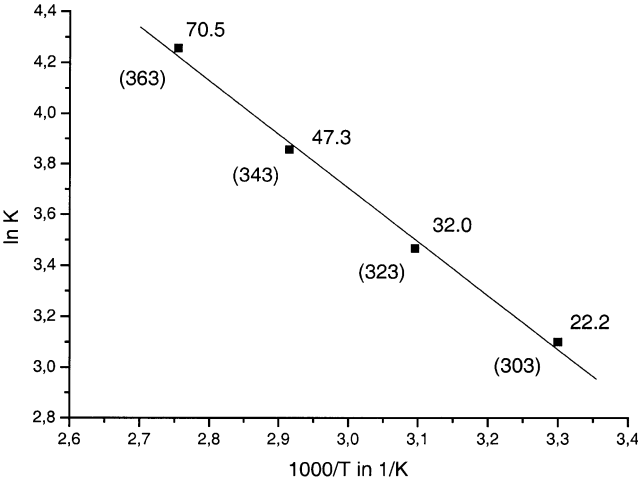



**Figure 4.** van't Hoff plot for the oligomerization of **2** in the temperature range 303–363 K (values above the line are aggregation constants $K_{ass}$ in $M^{-1}$, values in parentheses are temperatures in K).

polar solvents, such as DMSO ($\epsilon$=49, $\mu$=3.96 D), the energy necessary for this desolvation can obviously be larger than the energy gain resulting from the following noncovalent interaction between donor and acceptor, making the overall process endothermic. However, the release of ordered solvent molecules from the binding sites increases the entropy of the system, so that the binding event is still energetically favorable.[52]

## 3. Conclusions

In summary, it was shown here by concentration and temperature dependent NMR studies that zwitterion **2** forms linear aggregates in an endothermic and therefore entropy driven process. This underlines the importance of solvation effects for effective host–guest binding in polar solvents. It is therefore necessary for the future design of stable supramolecular arrangements to not only concentrate on enthalpic contributions but also on the role the solvent plays for the overall binding.

## 4. Experimental

### 4.1. General remarks

Solvents were dried and distilled under argon before use. All other reagents were used as obtained from either Aldrich or Fluka. All experiments were run in oven dried glass ware under argon unless otherwise stated. Products were dried in high vacuum ($10^{-3}$ mbar) over phosphorus pentoxide at room temperature overnight. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM300 spectrometer. Shifts are reported relative to the deuterated solvents. Elemental analysis was carried out with an Elementar Vario EL.

**4.1.1. Methyl 4-(formyl)-1*H*-pyrrole-2-carboxylate (4b).** Phosphoryl chloride (60.7 g, 396 mmol) was added within 15 min to ice cold DMF (28.9 g, 396 mmol). The reaction mixture was allowed to warm to room temperature, diluted with $CH_2Cl_2$ (200 mL) and cooled again to 0°C. A solution of ester **3**[34] (45.0 g, 360 mmol) in $CH_2Cl_2$ (200 mL) was added dropwise within 1 h, while the temperature was kept at 0°C. After the addition was complete, the reaction mixture was refluxed for 30 min under vigorous stirring, cooled to 10°C and hydrolyzed with a solution of sodium acetate (162.0 g) in water (500 mL). The phases were separated and the aqueous phase was extracted three times with diethyl ether (200 mL). The combined organic extracts were washed with a saturated sodium carbonate solution until no further $CO_2$ evolved and dried with solid sodium carbonate. The solvent was removed under reduced pressure and the oily, orange residue was purified by chromatography (silica gel, hexane/ethyl acetate 60:40) to yield **4a** (33.0 g, 216 mmol, 60%) and **4b** (13.5 g, 88 mmol, 24%) both as slightly yellow solids.

**4a**. $^1$H NMR (300 MHz, [D$_6$]DMSO) $\delta$=3.87 (s, 3H, methyl), 7.29 (m, 1H, pyrrole CH), 7.56 (m, 1H, pyrrole CH), 9.82 (s, 1H, CHO), 10.06 (s, 1H, pyrrole NH). $^{13}$C NMR (75.5 MHz, [D$_6$]DMSO) $\delta$=52.0 (q, methyl), 114.2 (d, pyrrole C3), 124.8 (s, pyrrole C2), 127.6 (s, pyrrole C4), 128.6 (d, pyrrole C5), 161.3 (s, ester C), 185.6 (s, CHO).

**4b**. $^1$H NMR (300 MHz, [D$_6$]DMSO) $\delta$=3.90 (s, 3H, methyl), 6.91 (m, 2H, pyrrole CH), 9.65 (s, 1H, CHO), 9.96 (s, 1H, pyrrole NH). $^{13}$C NMR (75.5 MHz, [D$_6$]DMSO) $\delta$=52.2 (q, methyl), 115.7 (d, pyrrole C4), 119.7 (d, pyrrole C3), 128.1 (s, pyrrole C2), 134.5 (s, pyrrole C5), 160.8 (s, ester C), 180.3 (s, 1C, CHO).

**4.1.2. 2-(Guanidiniocarbonyl)-1*H*-pyrrole-4-carboxylate (2).** The ester **5**[34] (2.00 g, 12 mmol) and guanidinium hydrochloride (5.70 g, 60 mmol) were added to a solution of sodium methoxide, prepared from sodium (1.29 g, 56 mmol) in methanol (50 mL). The reaction mixture was refluxed for 12 h and then the solvent was evaporated. The oily residue was dissolved in water (50 mL). Upon acidification with concentrated hydrochloric acid, the crude product precipitated, which was filtered off and washed with water and a small portion of ice cold methanol to afford a white solid (1.10 g, 47%). $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$=7.61 (d, 1H, pyrrole CH), 7.79 (s, 1H, pyrrole CH), 8.21 (brs, 4H, guanidinium $NH_2$), 11.02 (brs, 1H, amide NH), 12.03 (s, 1H, pyrrole NH). $^{13}$C NMR (75.5 MHz, [D$_6$]DMSO): $\delta$=115.38 (CH), 116.24 (CH), 127.45, 131.25, 155.23, 159.61, 161.18 (all quat. C). $C_{13}H_{11}N_7O_{10}\cdot 1H_2O$ (picrate salt, 443.08): calcd: C, 35.02; H, 2.93; N, 22.12; found: C, 35.25; H, 3.15; N, 22.36.

### 4.2. NMR experiments

Solutions of zwitterion **2** with varying concentrations were obtained by diluting aliquots of a 100 mM stock solution with [D6]DMSO to a total volume of 600 μl. The chemical shifts were recorded (Bruker AM300 spectrometer) for each sample at increasing temperatures starting from 303 K in intervals of 20 degrees. After changing the temperature, an equilibration time of 5 min was allowed for each sample before recording the spectrum.

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