Highly Stable Self-Association of 5-(Guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate in DMSO – The Importance of Electrostatic Interactions

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Keywords: Supramolecular chemistry / Self-assembly / Molecular recognition / Guanidinium cations

The zwitterionic compound 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate (**1**) self-assembles to form dimers, which are completely stable in DMSO even at 170 °C or at concentrations of 0.001 mM. This high stability stems from a combination of multiple weak interactions. NMR titrations of 1*H*-pyrrole-2-carboxylate (**5**) with (1*H*-pyrrole-2-carbonyl)-guanidinium (**6**) and [5-(methoxycarbonyl)-1*H*-pyrrole-2-carbonyl]guanidinium (**8**) led to binding constants of $K \approx 10^6$ mol^{-1} in DMSO and $K \approx 10^3$ mol^{-1} in 40% water/DMSO for carboxylate binding by the 2-(guanidiniocarbonyl)pyrrole moiety. The stability constant for the dimer $\mathbf{1}_2$ in DMSO could therefore be estimated as $K \approx 10^{12}$ mol^{-1}. In solution, the self-association process of **1** can be completely disrupted by protonation of the carboxylate group. In the solid state, however, the hydrochloride salt $\mathbf{1}^+$ also exists as a similar but only very weakly hydrogen-bonded dimer.

Introduction

Molecular recognition and especially self-assembly[1] can lead to the formation of highly complex and fascinating structures, as exemplified in nature by the molecular architecture of the tobacco virus, the formation of protein plaques in Alzheimer's disease, or the association of microtubuli during mitosis.[2] 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 also been devised, which may prove useful in the design of novel materials and nanostructures.[1c,3]

Besides metal coordination,[4] most of the work in this field is concerned with weak interactions[5] such as hydrogen bonds, hydrophobic interactions, or π-π stacking interactions, that lead to the assembly of one or more building blocks into more complex structures.[6] Despite the usefulness of this approach, one major drawback of simple hydrogen-bonding interactions, for example, is that their strength decreases rapidly as the polarity of the surrounding solvent increases, owing to the competitive solvation of donor and acceptor sites by the solvent.[7][8] Therefore, most systems described to date show aggregation only in the solid state[9] or in organic solvents such as chloroform.[10] 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.[11] The present paper deals with the synthesis of a very simple, yet efficiently self-associating molecule, which forms highly stable dimers in DMSO, held together by multiple weak interactions. Furthermore, the formation of this dimer can be turned off and on by protonation or deprotonation of the molecule.

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Results and Discussion

It is known that the guanidinium group constitutes a good binding group for oxo anions such as phosphates[12] or carboxylates.[13] Due to the additional electrostatic interaction, such complexes are stronger than their neutral counterparts (i.e. complexes between carboxylic acids and aminopyridines).[14][15] Even so, complexes between guanidinium cations and carboxylates are normally very weak in highly competitive solvents.[16] Only a few systems bind carboxylates in DMSO, methanol, or even water.[13] To achieve strong binding in such polar solvents, additional binding interactions are therefore necessary. Following previous work in this laboratory, 2-(guanidiniocarbonyl)-1*H*-pyrroles were introduced as a new class of receptors for carboxylates (Figure 1), which indeed showed improved binding properties compared to simple acylguanidines. The binding of carboxylates can be increased by a factor of up to 30 compared to the parent acetylguanidinium cation, with binding constants of the order of $K \approx 10^3$ mol^{-1} even in 50% water/DMSO.[17]

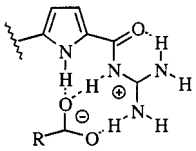

Figure 1. Idealized hydrogen-bonding interactions in the complex between carboxylates and 2-(guanidiniocarbonyl)-1*H*-pyrroles

It was reasoned that by attaching a carboxylate group at the 5-position of the pyrrole ring, a 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate (**1**) would be obtained, which possesses a carboxylate and a complementary binding group within the same molecule and should therefore represent a heteroditopic molecule capable of self-association.[18][19] The pyrrole ring forms a rigid scaffold preventing intramolecular association of the carboxylate and acylguanidinium groups and at the same time places these groups in a U-shaped geometrical arrangement that should

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favour intermolecular association (Figure 2). By virtue of the strong binding interaction between 2-(guanidiniocarbonyl)pyrroles and carboxylates, such self-assembled structures should be stable even in DMSO or water.

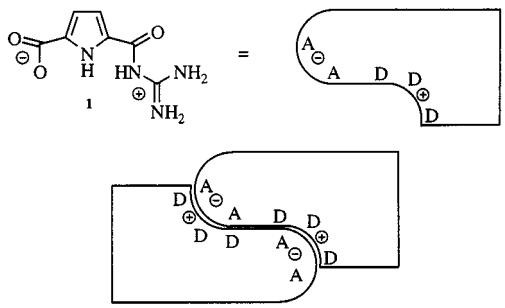
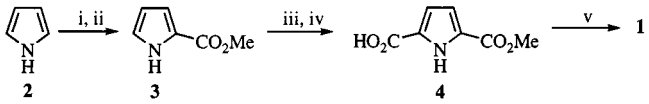


Figure 2. 5-(Guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate (**1**) as a rigid heteroditopic molecule with complementary hydrogen-bond donor (D) and acceptor (A) sites capable of self-assembly

The synthesis of **1** is outlined in Scheme 1. Pyrrole (**2**) was first transformed into 2-(methoxycarbonyl)-1*H*-pyrrole (**3**) by acylation with trichloroacetyl chloride and subsequent cleavage of the trichloroacetyl group with sodium methoxide.[20] Vilsmeier−Haack formylation,[21] followed by oxidation with permanganate, gave 5-(methoxycarbonyl)-1*H*-pyrrole-2-carboxylic acid (**4**).[22] The guanidinylation of this compound was best achieved by refluxing the ester and an excess of guanidinium chloride with sodium methoxide in methanol.[23] Other attempts at carrying out this reaction, e.g. by treating the ester with the free guanidine base, prepared by ion-exchange from the hydrochloride, or by treating activated acid derivatives with guanidine, either failed or gave only very low yields.[24]



Scheme 1. Synthesis of 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate (**1**); reagents and conditions: (i) Cl_3CCOCl, Et_2O, reflux, 30 min., 85%; (ii) 0.1 equiv. NaOMe, MeOH, r.t., 30 min, 63%; (iii) $POCl_3$/DMF, CH_2Cl_2, 0 °C → reflux, 63%; (iv) $KMnO_4$, acetone/water (1:1, v/v), 40 °C, 30 min, 75%; (v) 5 equiv. guanidinium chloride, 5 equiv. NaOMe, MeOH, reflux, 12 h, 72%

The free base of compound **1** can easily be protonated by picric or hydrochloric acid to give the corresponding cationic salts $\mathbf{1}^+$. These salts are readily soluble in methanol or DMSO and can be recrystallized from water. Addition of one equivalent of base, however, leads to deprotonation and formation of the overall neutral compound **1**, which is virtually insoluble in all solvents other than DMSO. Even in DMSO, the maximum achievable concentration is only around 5 mM. Deprotonation of **1** by a second equivalent of base gives the anion $\mathbf{1}^-$, which again is freely soluble in methanol and water.

The ^{1}H-NMR spectrum (Figure 3) of the protonated cation $\mathbf{1}^+$ (picrate salt in [D_6]DMSO) shows the "normal" signals expected for an acylguanidinium cation,[25] i.e. a broad signal at $\delta = 8.2$ for the 4 guanidinium NH_2 protons, a singlet for the pyrrole NH at $\delta = 12.7$, and broad signals for the amide NH and the carboxyl proton at $\delta = 11.1$ and 13.2, respectively. The unsplit signal due to the 4 guanidinium NH protons shows that in DMSO there is no intramolecular hydrogen bonding between these protons and the adjacent carbonyl group. Upon deprotonation, the signals are markedly shifted downfield; the signal due to the guanidinium NH_2 protons splits into two signals (two protons each), appearing at $\delta = 8.1$ and 9.8; the amide NH signal is shifted downfield by nearly 4 ppm and appears at $\delta = 14.8$, and the pyrrole NH signal is shifted by 0.4 ppm and appears at $\delta = 13.1$. Of the pyrrole CH protons, only the 4-H signal shows a minor upfield shift (< 0.2 ppm), probably due to the increased electron density in the heterocycle compared to the cation. Further deprotonation leads to the anion $\mathbf{1}^-$, which shows only very broad, unresolved signals in the NMR spectrum, typical for an acylguanidine.

These results are consistent with the formation of a zwitterion capable of self-association. Compound **1** can exist both in a neutral and a zwitterionic form. The ^{1}H-NMR spectrum of **1** clearly shows that, as expected on the basis of the pK_a values,[26] only the zwitterion is present, as no carboxyl proton but only 4 guanidinium NH_2 proton signals can be seen. In this zwitterionic form, the carboxylate clearly interacts with the 2-(guanidiniocarbonyl)pyrrole group of another molecule as shown in Figure 4. The resonance due to the two guanidinium protons that are not involved in hydrogen bonding to the carboxylate hardly shifts at all (< 0.1 ppm), whereas the signals due to the other two guanidinium protons, the amide NH, and the pyrrole NH, all of which are involved in the complexation process, show significant downfield shifts (up to 3.6 ppm), indicative of hydrogen-bonding interactions. Such a complexation cannot occur *intra*molecularly due to the rigid nature of **1**, thus it has to be concluded that *inter*molecular self-association takes place.

Molecular modelling (Macromodel V 6.0)[27] supports the formation of discrete dimers. Two molecules of **1** can easily form C_2-symmetric dimers $\mathbf{1}_2$ in a head-to-tail orientation. As can be seen in Figure 5, there is a near perfect geometric fit between the complementary groups on each molecule. The planes of the two molecules are slightly tilted (dihedral angle 140°). The hydrogen bonds are all very short (between 169 and 172 pm for the NH−O distances), reflecting the strong interaction between the two molecules.

Due to the apparent high stability of the dimer in DMSO (e.g. concentration and temperature invariance of the shift changes, vide infra) and the insolubility in all other solvents (**1** even precipitates upon addition of 10% water to a 1 mM solution in DMSO), no conditions were found under which the dissociation of the dimer itself could be studied directly by NMR.[28]

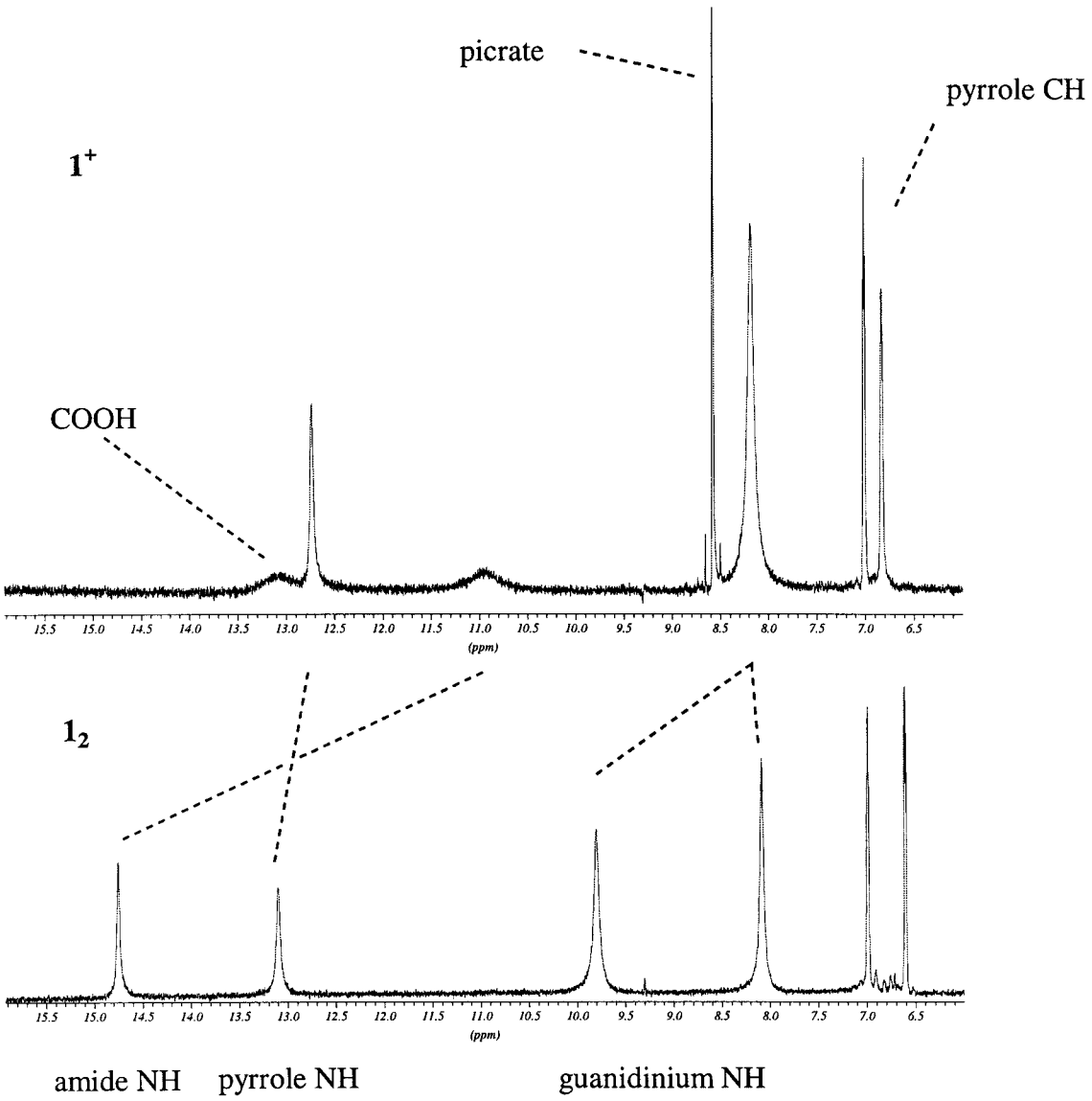


Figure 3. ^{1}H-NMR spectra of the protonated form $\mathbf{1}^+$ and the dimeric zwitterion $\mathbf{1}_2$ (300 MHz, [D$_6$]DMSO)

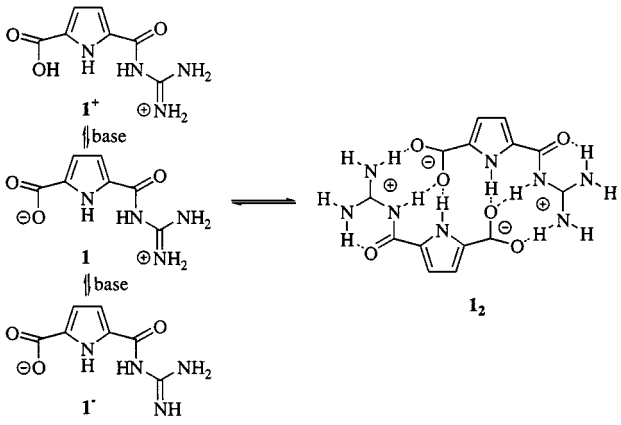


Figure 4. Association of **1** to give the dimer $\mathbf{1}_2$, held together by a network of multiple weak interactions; this dimerization is only possible in the zwitterion **1**; neither the cation $\mathbf{1}^+$ nor the anion $\mathbf{1}^-$ can form a similarly stable complex

However, the association constant for the dimer, with its two equivalent binding sites, can be estimated if the binding energy for one such interaction is known. NMR titrations of 1*H*-pyrrole-2-carboxylate (as the NMe_4^+ salt) (**5**) with 2-(guanidiniocarbonyl)pyrrole picrate (**6**) and [5-(methoxycarbonyl)-1*H*-pyrrole-2-carbonyl]guanidinium chloride (**8**), obtained from **1** by esterification of the acyl chloride with methanol (Scheme 2), were performed. The interactions in the complex of **5** with **6** correspond to one of the two binding sites in the dimer. In the complex between **5** and **8**, there is an additional hydrogen-bonding interaction. In both cases, the observed complexation-induced shift changes are the same as those observed for the zwitterion **1**. The binding constants for the complexes of **5** with **6** and **8** were calculated using a non-linear least-squares fitting procedure with a 1:1 association model in each case (Table 1). In DMSO, there is a linear increase in the chemical shift change until a molar ratio of 1:1 is reached (Figure 6),

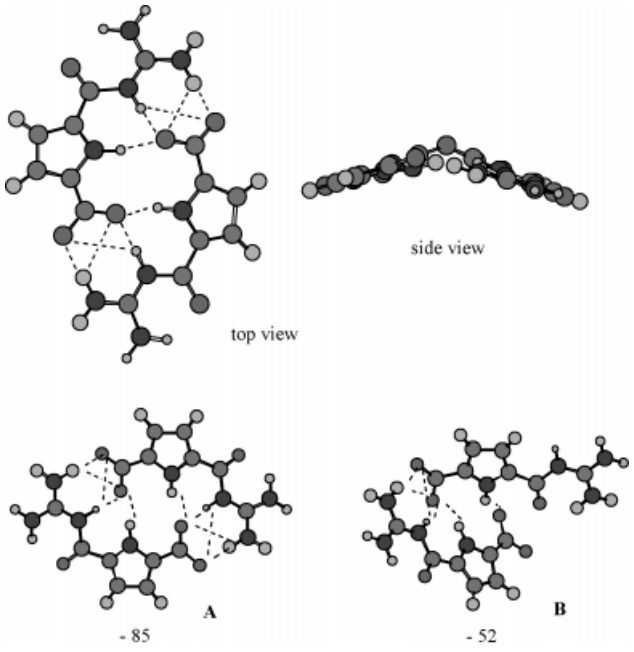
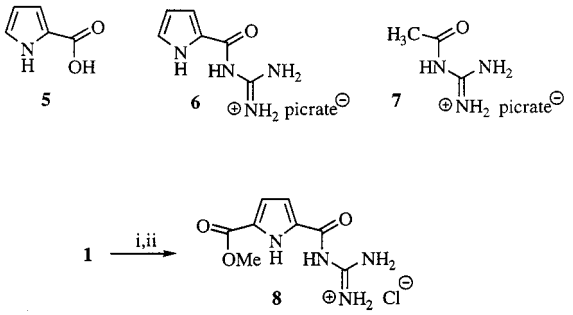


Figure 5. Calculated structure of the dimer $\mathbf{1}_2$ in water; energies of two different conformers of the dimer $\mathbf{1}_2$ relative to two non-interacting monomers **1** (according to molecular dynamics calculations; in kJ mol^{-1})



Scheme 2. Compounds which are not capable of self-assembly; reagents and conditions for the synthesis of [5-(methoxycarbonyl)-1*H*-pyrrole-2-carbonyl]guanidinium (**8**): (i) 1.1 equiv. $(COCl)_2$, DMF (cat.), CH_2Cl_2, reflux 2 h; (ii) MeOH, r.t., 10 h, 44% over both steps

Table 1. Binding constants of carboxylate **5** with cations **6**, **7**, and **8**[a]

Cation	Solvent	K [mol^{-1}]
6	DMSO	ca. 10^6
7	H_2O/DMSO	150
8	DMSO	ca. 10^6
8	H_2O/DMSO	4140

[a] Measured by NMR titration at 25 °C; [**5**] = 1 mM in [D_6]DMSO or 40% H_2O/[D_6]DMSO.

clearly indicating the 1:1 stoichiometry of the binding interaction. The binding constants for both complexes **5**/**6** and **5**/**8** are $K \approx 10^6$ mol^{-1}. Using this binding constant for the complexation of a carboxylate group by an acylguanidinium pyrrole group and assuming that the association energies for the two binding sites in the dimer $\mathbf{1}_2$ are identical,

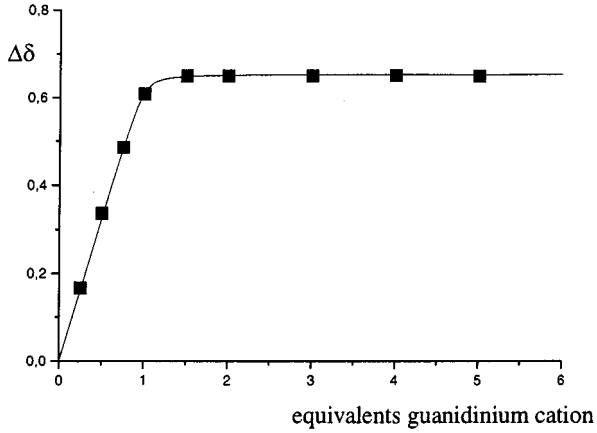


Figure 6. NMR titration curve of carboxylate **5** (1 mM) with guanidinium cation **6** in [D_6]DMSO

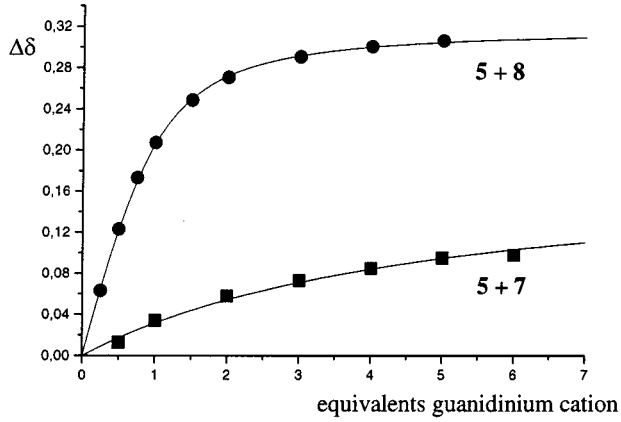


Figure 7. NMR titration curves of carboxylate **5** (1 mM) with guanidinium cations **7** and **8** in 40% water/DMSO

as is suggested by the findings of molecular modelling studies (vide infra), the dimerization constant for **1** in DMSO can be estimated as $K \approx 10^{12}$ mol^{-1}. Hence, it is not surprising that under the conditions accessible by NMR, no indications of any break-up of the dimer could be seen. Even in 40% water/DMSO, the binding constant for the complex of **5** with **8** is still $K = 4.1 \times 10^3$ mol^{-1} (Table 1).

In principle, the self-association could also lead to the formation of oligomeric chain-like structures instead of discrete dimers. Two such possible structures are shown in Figure 8, in which the zwitterions are either arranged in a zigzag (type B) or in a linear way (type C). However, the complex of **5** with the unsubstituted acetylguanidinium cation **7** has a binding constant $K = 1.5 \times 10^2$ mol^{-1} (in 40% water/DMSO), which is 30 times lower than that with **8**. This energetic disadvantage of simple 2-point binding makes the formation of oligomers $\mathbf{1}_n$ of type C less likely than dimers $\mathbf{1}_2$. Formation of linear oligomers of type C would only allow the same 2-point interaction with the carboxylate as seen in the complex with **7** (Figure 8). In comparison with the formation of such oligomeric chains, the dimer would therefore be expected to have a binding constant some 900 times higher. In the zigzag like oligomer of type B the same three point binding is present as in the dimer $\mathbf{1}_2$. In prin-

ciple, the concentration dependence of the ^{1}H-NMR spectrum should allow a distinction to be made between dimerization and oligomerization. With decreasing concentration, the formation of oligomers becomes more and more unfavorable relative to the formation of discrete dimers. In the concentration range from 5 mM to as low as 0.001 mM in [D_6]DMSO, the ^{1}H-NMR spectrum of the zwitterion **1** does not change. Moreover, even at 170 °C, no indications of any breaking-up of the aggregates were found, further highlighting their very high stability. Taking all data into account, it seems likely that in the self-association process of the zwitterion **1** no oligomers but exclusively discrete dimers are formed.[29]

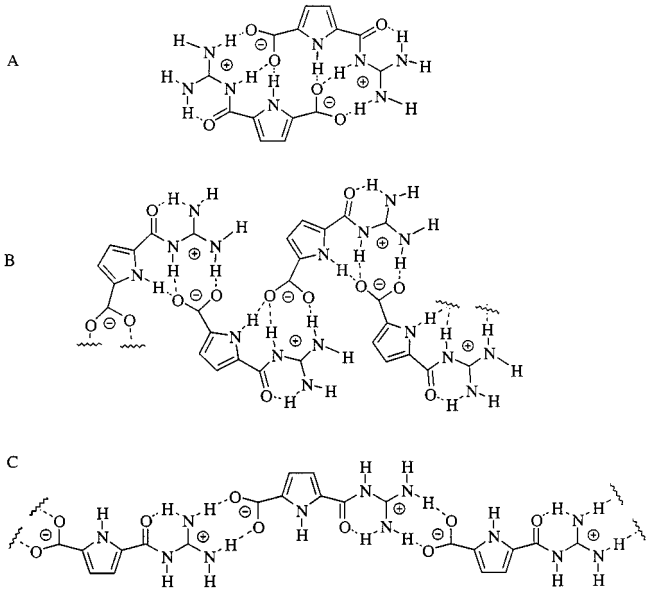


Figure 8. Three possible alternatives for the self-association of zwitterion **1**: discrete dimers (A) and oligomer chains (B and C)

A major part of the binding energy of the dimer $\mathbf{1}_2$ is probably associated with the ion pairing between the carboxylate group and the guanidinium moity; this is one reason why protonation of the carboxylate groups disrupts the dimer. Addition of the carboxylic acid **5** to guanidinium cation **6** or **8** in DMSO at millimolar concentrations does not lead to any shift changes in the NMR spectra, which implies that the binding constant for this type of interaction must be < 100 mol^{-1}. The carboxylate is therefore bound with a binding constant at least three times higher than that for binding of the acid.

The cation $\mathbf{1}^+$ does not self-assemble in polar solution. However, the X-ray crystal structure of the hydrochloride salt $\mathbf{1}^+$ (Figure 9)[30] shows the existence of a very weakly bound dimer $(\mathbf{1}^+)_2$ in the solid state, held together by 4 intermolecular hydrogen-bonding interactions. These hydrogen bonds are all very long (O−H distances 223 and 235 pm, respectively), reflecting the weak nature of the complex. The protonation or deprotonation of the carboxylate group in the zwitterion **1** therefore provides a means of turning the self-association off or on.

To gain further insight into the stability of such structures, we performed molecular mechanics calculations on

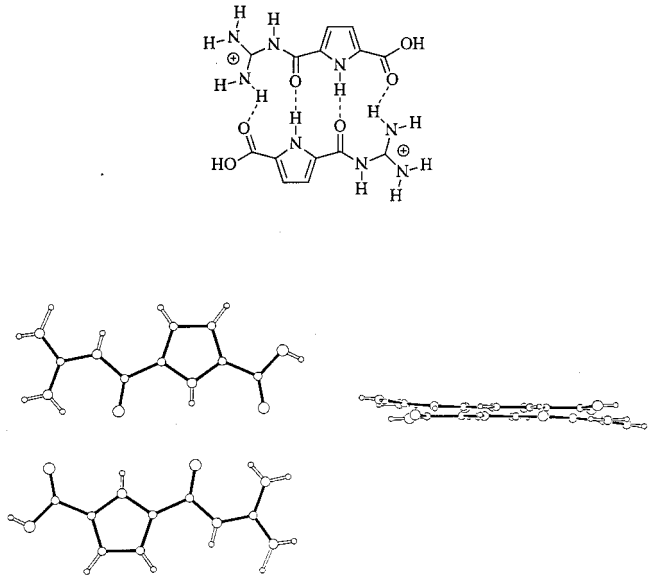


Figure 9. X-ray crystal structure of $\mathbf{1}^+$ (chloride salt); above: schematic representation; below: top view (left), and side view (right) (chloride anions and water molecules have been omitted for the sake of clarity)

compound **1** in water. A conformational docking study revealed the proposed dimeric structure $\mathbf{1}_2$ to be the energy minimum, with any other possible orientation of the two molecules being at least 20 kJ mol^{-1} less stable (Figure 5). Also of interest was the structure **B**, in which the relative orientation of the two molecules is such that only one of the two carboxylates and acylguanidinium groups interact while the others are pointing away from each other and are solvated only by water. The binding site in this conformer possesses a similar geometry to that in **A** (similar hydrogen-bonding distances, though there is a more pronounced tilt). The relative energy is more or less half-way between the energies of the two non-interacting molecules and that of the fully complexed dimer $\mathbf{1}_2$. As expected for a rigid molecule, the binding energies for the two binding sites are identical. Figure 10 shows a superposition of complex

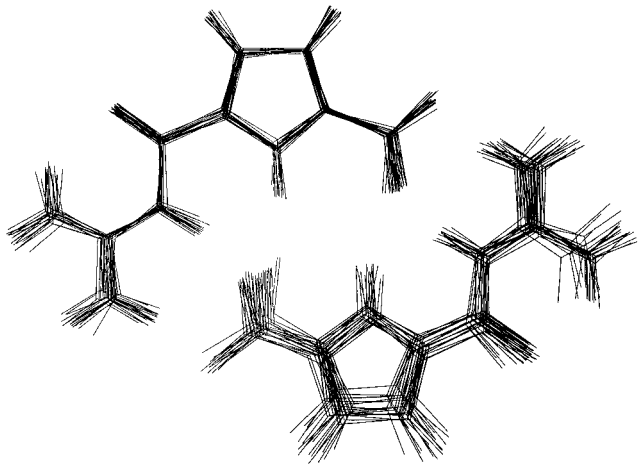


Figure 10. Superposition of 50 structures of the dimer $\mathbf{1}_2$ in water, sampled from a molecular dynamics calculation over 100 ps at 300 K

structures sampled over a period of 100 ps at 300 K in water, as generated by a molecular dynamics calculation. The complex barely changes its structure, with not one of the binding interactions being even temporarily broken over time. This again clearly reflects the high stability of the dimer. More detailed studies aimed at further elaborating the importance of the various binding interactions are currently in progress.

Conclusions

The design of systems that self-assemble in highly polar solvents remains a difficult task, owing to the weak nature of non-covalent intermolecular forces in such solvents. It has been shown herein that by using multiple weak interactions, a new self-associating molecule **1** can be constructed that forms a highly stable dimer $\mathbf{1}_2$ in DMSO, with an estimated stability constant $K \approx 10^{12}$ mol^{-1}. This hitherto unexplored binding motif can also be used for the complexation of other oxo anions in water/DMSO. This might prove useful for the design of switchable molecular devices, functional oxo anion receptors, or self-assembling polymers. Relevant work is currently in progress.

Experimental Section

General Remarks: Solvents were dried and distilled under argon prior to use according to standard procedures. All other reagents were used as obtained from either Aldrich or Fluka. All experiments were performed in oven-dried glassware under argon unless otherwise stated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM300 spectrometer. Shifts are reported relative to the deuterated solvents. Elemental analysis was carried out with an Elemtar Vario EL.

5-(Guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate (1): The ester **4**[22] (2.0 g, 12 mmol) and guanidinium hydrochloride (5.7 g, 60 mmol) were added to a solution of sodium methoxide, prepared from sodium (1.3 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 thoroughly with methanol to afford a white solid (1.7 g, 72%). In order to obtain the picrate salt, **1** was dissolved in aqueous picric acid solution; after filtration of the hot solution, the product crystallized as yellow needles. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.84 (d, 1 H, pyrrole CH), 7.01 (s, 1 H, pyrrole CH), 8.16 (br. s, 4 H, guanidinium NH$_2$), 8.58 (s, 2 H, picrate), 11.07 (br. s, 1 H, amide NH), 12.74 (s, 1 H, pyrrole NH), 13.16 (br. s, 1 H, acid NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 115.26 (CH), 115.84 (CH), 124.36 (quat. C), 125.39 (CH), 127.05, 132.5, 142.06, 155.05, 159.53, 160.99 (all quat. C). − $C_{13}H_{11}N_7O_{10}\cdot H_2O$ (443.1): calcd. C 35.02, H 2.93, N 22.12; found C 35.37, H 3.03, N 22.40.

(1*H*-Pyrrole-2-carbonyl)guanidinium (5): To a solution of sodium methoxide, prepared from sodium (1.3 g, 56.5 mmol) and dry methanol (50 mL), the ester **3**[20] (1.4 g, 11.5 mmol) and guanidinium hydrochloride (5.5 g, 57.6 mmol) were added and the reaction mixture was refluxed for about 12 h. The solvent was then evaporated, the residue was taken up in water (20 mL), and the resulting solution was acidified with hydrochloric acid. The white precipitate formed was filtered off, washed with cold water, and redissolved in aqueous sodium hydroxide. Upon addition of picric acid, the picrate salt precipitated, which was filtered off and recrystallized from ethanol to give orange needles (2.28 g, 52%). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.28 (dt, 1 H, pyrrole CH), 7.04 (m, 1 H, pyrrole CH), 7.20 (m, 1 H, pyrrole CH), 8.11 (br. s, 4 H, guanidinium NH$_2$), 8.58 (s, 2 H, picrate), 10.71 (br. s, 1 H, amide NH), 12.20 (s, 1 H, pyrrole NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 110.55 (CH), 115.22 (CH), 123.34 (quat. C), 125.41 (CH), 127.09 (CH), 142.04, 155.29, 159.83, 161.01 (all quat. C). − $C_6H_7N_4O\cdot$picrate (381.1): calcd. C 37.79, H 2.91, N 25.72; found C 37.72, H 3.01, N 25.82.

[5-(Methoxycarbonyl)-1*H*-pyrrole-2-carbonyl]guanidinium (8): Compound **1** (644 mg, 3.3 mmol) was suspended in dry THF (20 mL), dry DMF (3 drops) and oxalyl chloride (835 mg, 6.6 mmol, 2 equiv.) were added, and the reaction mixture was refluxed for 4 h. To the slightly yellow suspension, methanol (20 mL) was then added dropwise at room temperature. After stirring for about 12 h, the white precipitate formed was filtered off, washed with ice-cold methanol, and dried over phosphorus(V) oxide. After recrystallization from water, white needles were obtained (360 mg, 44%). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.82 (s, 3 H, Me), 6.88 (d, 1 H, pyrrole CH), 7.51 (s, 1 H, pyrrole CH), 8.30−8.70 (two broad overlapping singlets, 4 H, guanidinium NH$_2$), 12.19 (br. s, 1 H, amide NH), 12.87 (s, 1 H, pyrrole NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 52.03 (CH$_3$), 115.69 (CH), 116.19 (CH), 128.09 (quat. C), 155.78, 159.84, 160.28 (all quat. C). − $C_8H_{11}ClN_4O_3$ (246.0): calcd. C 39.02, H 4.51, N 22.76; found C 38.69, H 4.48, N 22.97.

Molecular Modelling: All calculations described in this paper were performed on an SGI O$_2$ workstation using the software package Macromodel 6.0.[27] Conformational searches were performed with at least 1000 steps until the minimum structure had been found several times. Molecular dynamics calculations were carried out using a constant temperature bath at 300 K, with 1.5 fs time steps and 100 ps total time. The Amber* force field and the GB/SA water solvation model implemented in Macromodel were used in all studies.

X-ray Crystallographic Study of 1·HCl: Nonius KappaCCD diffractometer (20 °C), Mo-K_α radiation, $2\Theta_{max}$ = 56°; structure determination by direct methods (SHELXS-86, SHELXL-93). $C_7H_9ClN_4O_3\cdot 2\ H_2O$, monoclinic, space group $P21/n$, a = 4.779(1), b = 27.868(1), c = 10.654(1) Å, β = 112.39(1)°, V = 1311.9(3) Å^3, Z = 4, $\rho_{calcd.}$ = 1.360 g cm^{-3}, μ = 3.07 cm^{-1}, 2268 independent reflections, of which 2113 with $I > 0$ were used; R = 0.0813, R_w = 0.1256. The final difference density was less than 0.309 eÅ^{-3}.

NMR Titrations: All NMR titrations were carried out by adding aliquots of a 10 mM solution of the guanidinium salt to a 1 mM solution of the carboxylate and recording the chemical shifts after each addition. Dilution was taken into account when analyzing the data. For each titration, 6−8 measurements were made. Where possible, different NMR signals of the carboxylate were used to calculate the binding constants. For the titrations in water, presaturation of the water signal was used.

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