J|A|C|S
ARTICLES
Published on Web 12/07/2002

Highly Stable Self-Assembly in Water: Ion Pair Driven Dimerization of a Guanidiniocarbonyl Pyrrole Carboxylate Zwitterion

Carsten Schmuck* and Wolfgang Wienand

Contribution from the Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

Received September 10, 2002; E-mail: schmuck@chemie.uni-wuerzburg.de

Abstract: The synthesis of a novel water-soluble guanidiniocarbonyl pyrrole carboxylate zwitterion **2** is described, and its self-association in aqueous solutions is studied. Zwitterion **2** forms extremely stable 1:1 dimers which are held together by an extensive hydrogen bonding network in combination with two mutual interacting ion pairs as could be shown by ESI MS and X-ray structure determination. NMR dilution studies in different highly polar solvents showed that dimerization is fast on the NMR time scale with association constants ranging from an estimated 10^{10} M^{-1} in DMSO to a surprisingly high 170 M^{-1} in water. Hence, zwitterion **2** belongs to the most efficient self-assembling systems solely on the basis of electrostatic interactions reported so far. Furthermore, an amidopyridine pyrrole carboxylic acid **10** was developed as a neutral analogue of zwitterion **2**, which also dimerizes with an essentially identical hydrogen bonding pattern (according to ESI MS and X-ray structure determination) but lacking the ionic interactions. NMR binding studies demonstrated that the solely hydrogen-bonded neutral dimer of **10** is stable only in organic solvents of low polarity ($K > 10^4$ M^{-1} in $CDCl_3$ but <10 M^{-1} in 5% DMSO in $CDCl_3$). The comparison of both systems impressively underlines the importance of ion pair interactions for stable self-association of such H-bonded binding motifs in water.

Introduction

One goal of modern science is to develop "intelligent" materials with tailor-made properties which change and adapt themselves in response to the surroundings. A promising way to develop such materials is the use of supramolecular synthesis.[1,2] In this approach, the self-association of individual molecules is used which depends on reversible noncovalent interactions.[3] This can lead to the formation of complex and highly structured macroscopic assemblies.[4] The properties of such supramolecular aggregates differ significantly from those of the underlying monomers and are determined by the intermolecular forces between the monomers and the resulting three-dimensional superstructure.[5] So far, the vast majority of self-assembling systems both in the solid state[6] and in solution[7,8] rely nearly exclusively on hydrogen bonds due to their directionality and specificity.[9] The main drawback of hydrogen

(1) For general references on supramolecular chemistry, see: (a) Schneider, H. J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley-VCH: Weinheim, 2000. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: Chichester, 2000. (c) Lehn, J.-M. *Supramolecular Chemistry*: *Concepts and Perspectives*; VCH: Weinheim, 1995. (d) Vögtle, F. *Supramolecular Chemistry*; J. Wiley & Sons: Chichester, 1991.

(2) (a) Reinhoudt, D. N.; Crego-Calama, M. *Science* **2002**, *295*, 2403−2407. (b) Menger, F. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4818−4822. (c) Stoddart, F. J.; Tseng, H.-R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4797−4800. (d) Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763−4768. (e) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44.

(3) (a) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312−1319. (b) Bowden, N. B.; Weck, M. M.; Choi, I. S.; Whitesides, G. M. *Acc. Chem. Res.* **2001**, *34*, 231−238. (c) Sharma, C. V. K. *J. Chem. Educ.* **2001**, *78*, 617−622. (d) Rouvray, D. *Chem. Brit.* **2000**, 26−29. (e) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229−2260.

(4) (a) Whitesides, G. M.; Boncheva, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4769−4774. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1155−1196. (c) Lawrence, D. S.; Jiang, T.; Levitt, M. *Chem. Rev.* **1995**, *95*, 2229−2260.

(5) This is especially obvious in the case of supramolecular polymers: (a) Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4363−4369. (b) Sherrington, D. C.; Taskinen, K. A. *Chem. Soc. Rev.* **2001**, *30*, 83−93.

(6) For work on self-assembly in the solid-state, see for example: (a) Bishop, R. *Synlett* **1999**, 1351−1359. (b) Weber, E., Ed. *Design of Organic Solids*, *Top. Curr. Chem.* **1998**, 198. (c) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2328−2345. (d) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: New York, 1989. (e) Wright, J. D. *Molecular Crystals*; Cambridge University Press: Cambridge, 1987. (f) Chin, D. N.; Palmore, T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2115−2132.

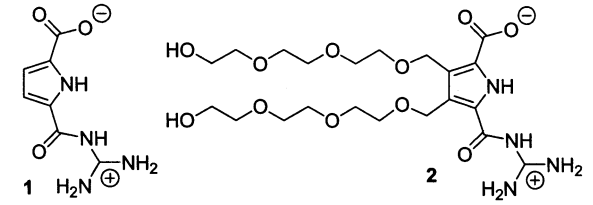
(7) For review articles on hydrogen-bonded self-assembly in organic solvents, see for example: (a) Zimmermann, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, 63−94. (b) Schalley, C. A.; Rebek, J., Jr. Chemical Encapsulation in Self-Assembling Capsules. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; pp 199−210. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286. (d) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (e) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37−44. (f) MacDonald, C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383−2420.

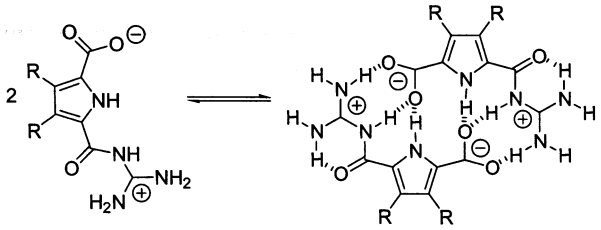
(8) Some recent examples can be found in: (a) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302−10306. (c) Mammen, M.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 12614−12623. (d) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282−4288. (e) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489−8496. (f) Sessler, J. L.; Wang, R. *J. Am. Chem. Soc.* **1996**, *118*, 9808−9809. (g) Heinz, T.; Rudkevich, D. M.; Rebek, J. *Nature* **1998**, *394*, 764−767. (h) Martín, T.; Obst, U.; Rebek, J. *Science* **1998**, *281*, 1842−1845. (i) Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502. (j) Hof, F.; Nuckolls, C.; Craig, S. L.; Martín, T.; Rebek, J. *J. Am. Chem. Soc.* **2000**, *122*, 10991−10996. (k) Rivera, J. M.; Craig, S. L.; Martín, T.; Rebek, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2130−2132.

 10.1021/ja028485+ CCC: $25.00

bonds, however, is their limited strength.[10] The more polar the solvent is, the weaker are the hydrogen bonds because of the increasing competitive solvation of donor and acceptor sites by polar solvent molecules.[11] Therefore, purely hydrogen-bonded assemblies possess a considerable binding energy only in aprotic solvents of low polarity and are not stable in water.[12] However, with respect to any future technological applications, non-water-stable systems can only have a limited use as water is omnipresent in our everyday life. Hence, the long term goal of supramolecular chemistry must be to develop, in addition to the binding motifs accessible so far, new systems that display stable association also in water. This can only be achieved by combining hydrogen bonds with additional noncovalent interactions such as metal coordination,[13] salt bridges,[14] hydrophobic,[15] or $\pi-\pi$ interactions.[16]

In this context, we investigate how additional ionic interactions can be used to enhance the strength of H-bonded self-complementary assemblies. We recently introduced a novel class of guanidiniocarbonyl pyrrole carboxylate zwitterions which show strong self-association not only in organic solvents of low polarity such as chloroform but also in DMSO.[17,18] Depending on the structure of the molecule and the experimental conditions, these zwitterions either dimerize,[19] fold intramolecularly into loops,[20] or form linear supramolecular oligomers.[21] For example, the heteroditopic zwitterion **1** forms extremely stable aggregates in DMSO with an association constant too high to measure by NMR studies. On the basis of theoretical calculations, the formation of 1:1 dimers was postulated. The high stability of these dimers probably stems from a perfectly matching network of six hydrogen bonds further enhanced by the double ion pairing between the carboxylates and the guanidiniocarbonyl pyrrole cations. Unfortunately, the solubility of **1** is limited to DMSO, preventing any further investigations in more polar aqueous solutions. We have now prepared a water-soluble derivative **2** of this zwitterion, which for the first time allowed a *detailed* thermodynamic and structural investigation of this remarkable system. As we will show here, dimerization takes place even in water with a surprisingly high association constant of 170 M^{-1}. Furthermore, a comparison with an appropriate neutral analogue **10**, which is based on an amidopyridine pyrrole−carboxylic acid interaction with the same hydrogen bonding pattern but lacking the charges, allowed one to estimate the energetical contribution of the ion pairs to enhance the binding in DMSO at least by a factor of 10^9 in this specific system.



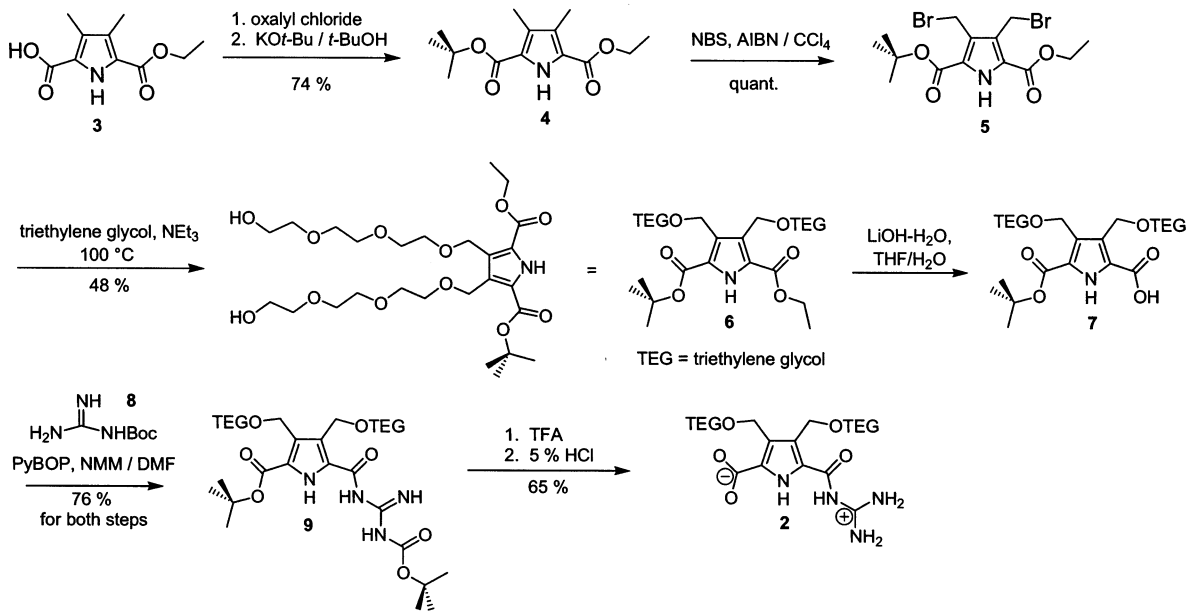


Results and Discussion

Self-Assembly of Zwitterion 2 in Water. (1) Synthesis. To improve the solubility of zwitterion **1** in aqueous solvents, we decided to attach triethylene glycol chains to positions 3 and 4 of the pyrrole ring, which are not involved in the self-assembly process. The synthesis of such a derivative, zwitterion **2**, is outlined in Scheme 1: The acid **3**[22] was converted to its acyl chloride using oxalyl chloride in methylene chloride and reacted with *tert*-butoxide to give the corresponding *tert*-butyl ester **4**. After radical bromination of the methyl groups with NBS[23] to give **5**, the triethylene glycol chains were introduced in the presence of triethylamine at high temperature. The two orthogonal ester functionalities in **6** now allow to selectively hydrolyze the ethyl ester with lithium hydroxide, leaving the *tert*-butyl ester unaffected. The guanidine group was then introduced via a mono *N*-Boc-protected derivative **8**,[24] which

(9) Glusker, J. P. *Top. Curr. Chem.* **1998**, *198*, 1−56.
(10) (a) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997. (b) Israelachvili, J. *Intermolecular & Surface Forces*, 2nd ed.; Academic Press: London, 1992.
(11) (a) For a general comment, see: Gellman, S. H. *Chem. Rev.* **1997**, *97*, 7, 1231−1232. For examples of solvent effects on the strength of H bonds in complexes, see: (b) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080. (c) Ariga, K.; Anslyn, E. V. *J. Org. Chem.* **1992**, *57*, 417−419.
(12) For example, a self-assembled hydrogen-bonded dimer that is stable in $CHCl_3$ but completely dissociates in 70% DMSO in $CHCl_3$ has been reported by: Sessler, J. L.; Wang, R. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1726−1729.
(13) For review articles on metal-templated self-assembly, see: (a) Fujita, M. *Chem. Soc. Rev.* **1998**, *27*, 417−426. (b) Stang, P. J. *Chem. Eur. J.* **1998**, *4*, 19−27. (c) Linton, B.; Hamilton, A. D. *Chem. Rev.* **1997**, *97*, 1669−1681. (d) Stang, P. J.; Olenyuk, B. *Acc. Chem. Res.* **1997**, *30*, 502−518.
(14) For work on capsule formation in polar solvents based on the hetero association of oppositely charged ions, see for example: (a) Grawe, T.; Schrader, T.; Zadmard, R.; Kraft, A. *J. Org. Chem.* **2002**, *67*, 3755−3763. (b) Corbellini, F.; Flammengo, R.; Timmerman, P.; Crego-Calama, M.; Veslius, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 65969−6575. (c) Fiammengo, R.; Timmerman, P.; de Jong, F.; Reinhoudt, D. N. *Chem. Commun.* **2000**, 2313−2314. (d) Hamilin, B.; Jullien, L.; Derouet, C.; Hervé du Penhoat, C.; Berthault, P. *J. Am. Chem. Soc.* **1998**, *120*, 8438−8447. (e) Bok Lee, S.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501−8504.
(15) For examples of recent work on the importance of π-stacking in supramolecular aggregates, see for example: (a) Lahiri, S.; Thompson, J. L.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 11315−11319. (b) Sirish, M.; Schneider, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 5881−5882. (c) Guckian, K. M.; Schweitzer, B. A.; Ren, R. X.-F.; Sheils, C. J.; Tahmassebi, D. C.; Kool, E. T. *J. Am. Chem. Soc.* **2000**, *122*, 2213−2222. (d) Isaacs, L.; Witt, D.; Fettinger, J. C. *Chem. Commun.* **1999**, 2549−2550.
(16) For a recent review on aromatic interactions, see: Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651−669.
(17) Schmuck, C. *Chem. Eur. J.* **2000**, *6*, 709−718.
(18) Review articles on the binding of carboxylates by artificial hosts including guanidinium-based systems: (a) Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841−864. (b) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609−1646. (c) Schmidtchen, F. P. Artificial Anion Hosts: Concepts for Structure and Guest Binding. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997; pp 79−146. (d) Atwood, J. L.; Steed, J. W. Structural and Topological Aspects of Anion Coordination. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997; pp 147−216.
(19) Schmuck, C. *Eur. J. Org. Chem.* **1999**, 2397−2403.
(20) Schmuck, C. *J. Org. Chem.* **2000**, *65*, 2432−2437.
(21) Schmuck, C. *Tetrahedron* **2001**, *57*, 3063−3067.
(22) Synthesis of the starting material 3,4,5-trimethyl-1*H*-pyrrole 2-carboxylic acid ethyl ester: (a) Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1985**, *50*, 5598−5604. (b) Cho, D. H.; Lee, J. H.; Kim, B. H. *J. Org. Chem.* **1999**, *64*, 8048−8050. Oxidation of 3,4,5-trimethyl-1*H*-pyrrole 2-carboxylic acid ethyl ester to acid **3**: (c) Scarsella, M.; Sleiter, G. *Gazz. Chim. Ital.* **1988**, *118*, 757−762. (d) Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1988**, *53*, 2787−2795. (e) Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733−739. (f) Siedel, S. *Liebigs Ann. Chem.* **1943**, *554*, 144−159.
(23) According to a similar approach by: Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 2486−2490.
(24) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136.

Scheme 1. Synthesis of the Water-Soluble Zwitterion **2**



in contrast to the free guanidine base or its diprotected derivatives can be directly coupled with carboxylic acids using PyBOP in DMF.[25] Acidic cleavage of **9** then yielded the desired zwitterion **2**, which is indeed well soluble, both in water and in polar organic solvents such as DMSO.

(2) Dimer Formation. The zwitterion **2** was designed to form dimers via an intermolecular head-to-tail self-assembly of the carboxylate with the guanidiniocarbonyl pyrrole moiety. Accordingly, the ESI mass spectrum of **2** (negative ion mode) not only shows the molecular ion peak at $m/z = 519$ au but also a signal of high intensity at $m/z = 1039$ au which corresponds to a 1:1 dimer (Figure 1), suggesting that dimerization might also occur in solution.[26] No signals for higher aggregates such as trimers or tetramers were found.

The structure of these zwitterionic dimers could be further elucidated by X-ray crystallography. In the solid state, the parent zwitterion **1** forms the anticipated head-to-tail dimers, which are held together by six hydrogen bonds (Figure 2). The hydrogen bond distances between the amide N···O (2.679 Å), the guanidinium N···O (2.854 Å), and the pyrrole N···O (2.731 Å) are all rather short, indicating a strong interaction between these groups. The dimer is completely planar and symmetrical.

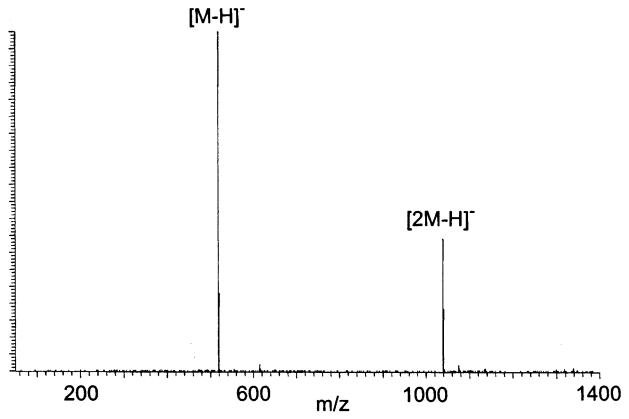


Figure 1. ESI mass spectrum of compound **2** ($m/z = 519$ au) from a solution in methanol showing the formation of a discrete 1:1 dimer at $m/z = 1039$ au.

That dimer formation also takes place in solution can be seen in the NMR spectrum (Figure 3). Significant downfield shifts are observed for the NH protons in the zwitterion **2** in comparison to reference compounds which are not capable of self-assembly.[17,27] In DMSO-d_6, for example, the signal for the guanidinium amide NH is shifted to $\delta = 14.5$ from an anticipated value of approximately $\delta \approx 11$, and the signal for

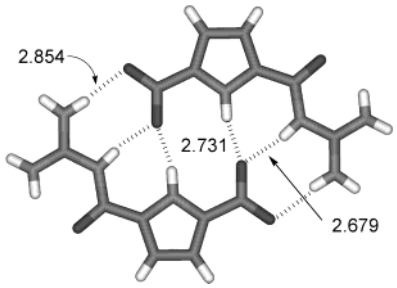


Figure 2. Crystal structure and selected hydrogen bond distances (Å) for dimer **1·1**.

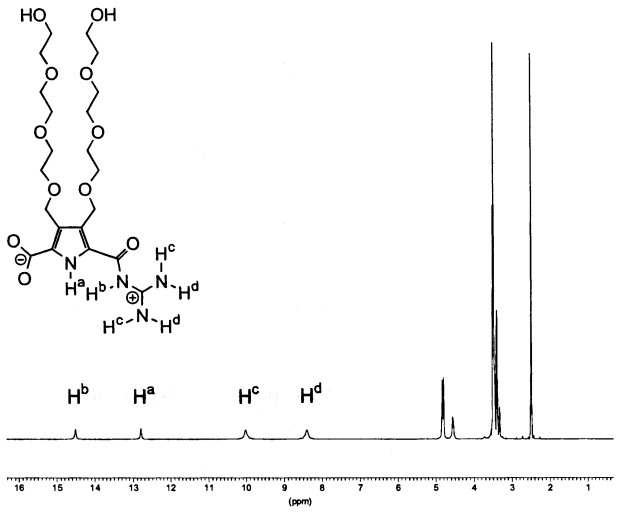


Figure 3. ^{1}H NMR spectrum of zwitterion **2** in DMSO-d_6 demonstrating the exclusive presence of dimers as can be seen from the split signals for protons NH^c and NH^d and downfield shifted signals for NH^a and NH^b.[29]

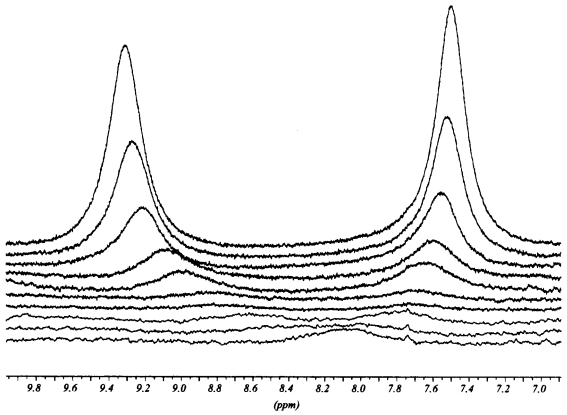


Figure 4. Part of the ^{1}H NMR spectrum of **2** in 2.5% DMSO-d_6 in water showing the complexation-induced shift changes of the guanidinium NHs (concentrations from bottom to top: 1, 2, 3, 4, 5, 7, 12, 17, and 22 mM).

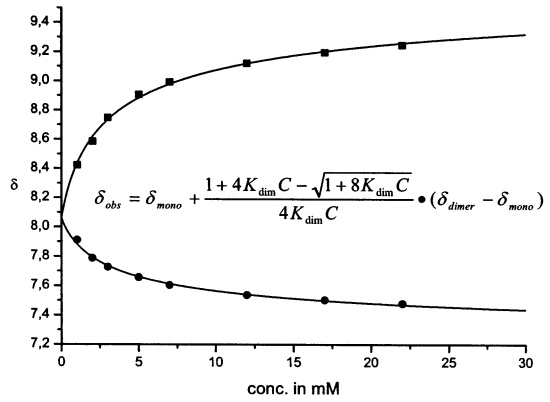


Figure 5. Complexation-induced shift changes of the two guanidinium NH signals in **2** in the concentration range from 0 to 25 mM in 2.5% DMSO in water. The solid line represents the curve fittings according to the equation shown.

the four guanidinium NH_2 protons is split into two signals, appearing at $\delta = 8.4$ and 10.0, respectively, as expected for the complexation of a carboxylate by a guanidiniocarbonyl pyrrole cation.[17,27] The ^{1}H NMR spectrum of **2** clearly shows that, as expected from the pK_a values,[17,28] only the zwitterion is present in solution as no carboxyl proton but four guanidinium NH_2 protons can be seen. Furthermore, these dimers are remarkably stable. Up to 50% water in DMSO-d_6, the signal for the guanidinium NH_2 groups of a 1 mM solution in the ^{1}H NMR spectrum is still split into two signals with chemical shifts of $\delta = 7.9$ and 9.0, respectively, indicating that the dimer is by far the predominant species. Even in water, concentration-dependent shift changes in the NMR spectrum can still be observed.

(3) Solvent-Dependent Binding Studies. To determine the binding constant for the self-association of compound **2** quantitatively,[30] we studied the concentration dependence of the ^{1}H NMR spectrum of **2** in the concentration range from 1 to 25 mM in 2.5% DMSO-d_6 in water. The two signals of the guanidinium NH_2 protons were used for data analysis. Whereas in the dimer these four protons give rise to two individual signals (see above) indicating the complexation of the carboxylate by the guanidinium cation, in the uncomplexed monomer only one signal is observed. Hence, with decreasing substrate concentration and beginning dissociation of the dimer, the two signals approach each other to finally coalesce to one signal as expected for the free monomer (Figure 4). The guanidinium amide NH could not be followed in this case, although the largest complexation-induced shift change appears here.[19] Because of the use of H_2O and water presaturation in the NMR experiment, this signal was not observable probably because of fast exchange processes with the solvent. Only in highly concentrated solutions was a broad signal at $\delta = 14.6$ detected, which, however, is exactly the expected shift for this proton within the dimer.[19]

A plot of the observed chemical shifts versus concentration gives two isothermic binding curves (Figure 5), which can both be used for a quantitative analysis of the dimerization process according to the method of Bangerter and Chan.[31] 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 equation given in Figure 5. Using a nonlinear curve fitting procedure for the two data sets, we calculated the binding constant K_{dim} for the dimerization of zwitterion **2** in 2.5% DMSO-d_6 in water to be 170 and 182 M^{-1}, respectively. The excellent agreement of these two values within the experimental error underlines the consistency of the data. Also, the chemical shift of the free monomer δ_{mono} as derived from the curve fittings ($\delta = 8.04$ and 8.09, respectively) is in excellent agreement with the value of $\delta = 8.06$ measured for a highly diluted solution (<0.1 mM) of **2**. Also, the calculated shift δ_{dimer} for the guanidinium NH involved in the binding of the carboxylate within the dimer as extrapolated from the curve fitting for high concentrations is essentially identical to the observed shift in pure DMSO-d_6 where only dimer is present ($\delta = 9.9$ and 10.0, respectively). The binding constant of zwitterion **2** has the same value of around 170 M^{-1} also in 5 and 10% DMSO-d_6 in water (data given in the Supporting Information). Hence, at such high water content, the stability constant seems to be unaffected by small changes in the solvent composition, implying that the dimer is still intact with $K_{dim} \approx 170$ M^{-1} even in pure water.[32] This association constant is surprisingly high taking into account that there are no additional hydrophobic or $\pi-\pi$ interactions that could stabilize these aggregates in water, as the zwitterions are orientated within the

(25) Schmuck, C.; Geiger, L.; Schwegmann, M. 2001, unpublished results.
(26) As neither in the positive ion mode nor for the unsubstituted parent zwitterion **1** could any signals be detected in the ESI mass spectrum, deprotonation probably takes place at the terminal OH group of one of the triethylene glycol chains in the case **2**. Hence, the binding motif itself is not affected by this deprotonation.
(27) Dixon, R. D.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1992**, *114*, 365−366.
(28) Guanidiniocarbonyl pyrroles have pK_a values of 7−8 (ref 17); therefore, they are 2 orders of magnitude less acidic than pyrrole carboxylic acid with a pK_a of 4.6.
(29) The assignment of proton H^c and H^d was based on the assumption that rotation around the amide $CONH^b-C$ bond is fast on the NMR time scale, whereas rotation around the $C-NH_2$ bonds is slow. This is plausible as the amide nitrogen NH^b is less nucleophilic than the other two nitrogens $NH^{c/d}$ and therefore less capable to stabilize the guanidinium cation as its electron density is lower. See also ref 27.
(30) (a) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: Weinheim, 1990; pp 123−144. (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.
(31) (a) Bangerter, B. W.; Chan, S. I. *J. Am. Chem. Soc.* **1969**, *91*, 3910−3921. (b) Davis, J. C., Jr.; Deb, K. K. *Adv. Magn. Reson.* **1970**, *4*, 201−270. For a general discussion of chain-association equilibria studies by NMR, see: (c) LaPlanche, L. A.; Thompson, H. B.; Rogers, M. T. *J. Phys. Chem.* **1965**, *69*, 1482−1488.
(32) With a DMSO concentration of <2.5%, the properties of the solvent mixture are hardly affected by its presence as the more polar component (water) is already present in a large excess. Therefore, it is not expected that an additional increase of the water content from 97.5 to 100% further affects the stability of the supramolecular aggregate.

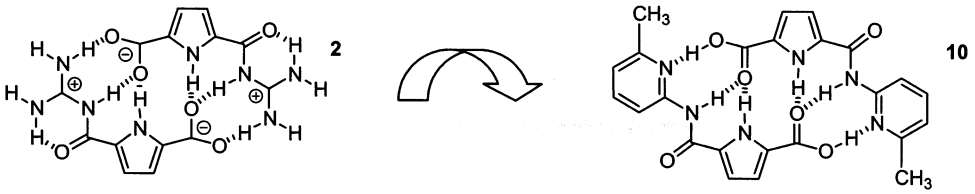
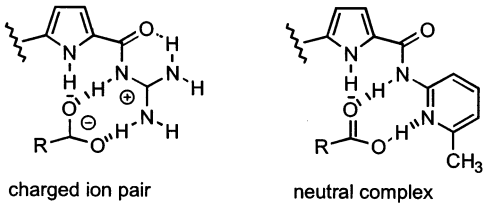


Figure 6. Amidopyridine pyrrole carboxylic acids as neutral counterparts of zwitterionic guanidiniocarbonyl pyrrole carboxylates: Translating the zwitterionic dimer **2·2** into a neutral amidopyridine pyrrole carboxylic acid dimer **10·10** by "switching off" the ionic interactions while keeping the hydrogen bond network constant.

dimer in an edge-on manner and the aromatic surfaces of the two molecules are not in contact with each other. Therefore, with a stability of about 170 M^{-1} in water, zwitterion **2** belongs to the most efficient self-complementary binding motifs reported so far, which rely solely on electrostatic interactions (i.e., ion pairs and H-bonds).

The association constant for dimer **2** is astonishingly high as compared to those of other ion pair interactions in aqueous solvents. For example, the lactate-guanidinium ion pair has a stability of only 6 M^{-1} in water on the basis of spectrapolarimetry measurements.[33] Ion pairs formed between dicarboxylates and diammonium cations were shown to have a stability of $K = 20-50$ M^{-1} at millimolar concentrations in water,[34] even though in some of these cases additional aromatic interactions still overlap with ion pair formation. On the basis of a statistical analysis of a variety of data of organic and inorganic ions, a single salt bridge was assigned a stability of 5 kJ mol^{-1} in water, which corresponds to an association constant of $K = 7$ M^{-1}.[35] The formation of two ion pairs is then expected to provide around 10 kJ mol^{-1} or $K \approx 50$ M^{-1} in water. Especially as guanidinium cations normally form weaker ion pairs as compared to other cations such as ammonium due to the greater extent of charge delocalization,[36] the stability of the zwitterionic dimer **2** is around 1 order of magnitude larger than expected. This might be a hint for a positive cooperativity in this case: Upon dimer formation, the initially large dipoles of both zwitterions are nearly completely canceled due to the mutual interaction of both ion pairs. Hence, these secondary electrostatic interactions,[37] which cannot occur in the case of the hetero association of a dication with a dianion, are probably responsible for the much larger dimerization constant of **2** relative to associations of two oppositely charged species.

Self-Assembly of a Neutral Amidopyridine Analogue. (1) Concept. Another factor probably contributing to the high stability of dimer **2·2** is the additional presence of the directed H-bond pattern overlapping with the ionic interactions. Unfortunately, it is impossible to experimentally determine the binding energy of an individual bond or type of interaction within an array of several noncovalent interactions as only the overall stability can be measured. One approach to arrive at a quantitative value for the energetical contribution of an individual interaction is therefore to compare the stability of isostructural analogues which differ in their binding sites just by the specific interaction in question. In this context, an amidopyridine analogue **10** can be used to determine the importance of the hydrogen bonds for the dimerization of zwitterion **2** (Figure 6). Amidopyridines are known to bind carboxylic acids via a neutral bidentate H-bonded interaction with $K \approx 10^2-10^3$ M^{-1} in organic solvents[18a,38] and can therefore serve as an appropriate neutral analogue of the ionic guanidinium−carboxylate interaction with a "switched off" ion pairing but still an essentially identical hydrogen bond pattern.

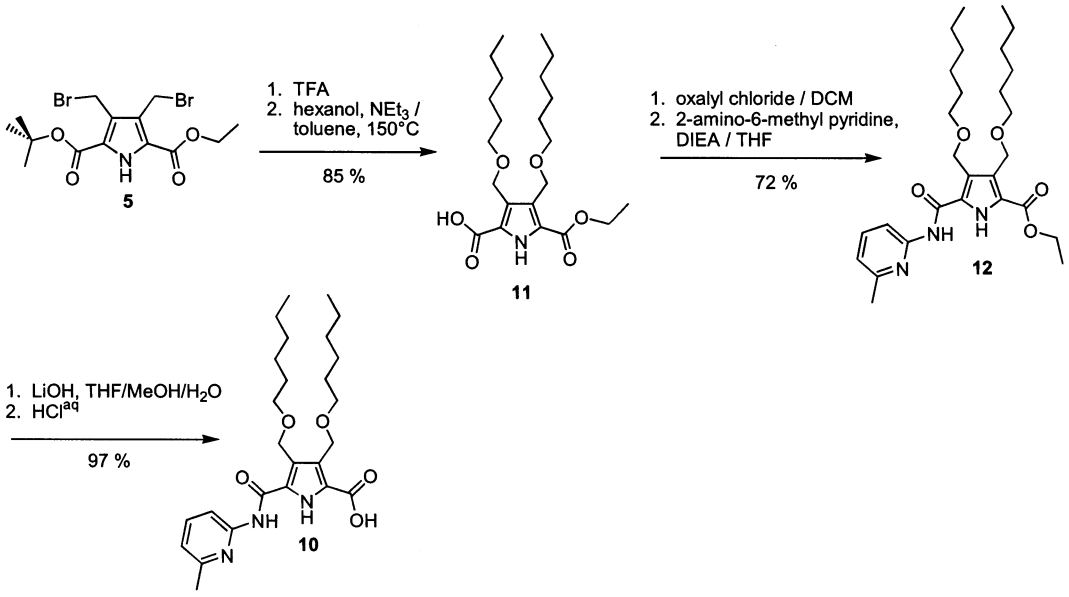


By replacing the positively charged guanidinium moiety in **2** by such an amidopyridine group, the neutral, but still self-complementary, compound **10** was identified as an appropriate analogue of zwitterion **2** for a comparative thermodynamic study. Both systems are shown in Figure 6 illustrating the guanidiniocarbonyl pyrrole carboxylate dimer and its "translation" into a neutral amidopyridine pyrrole-carboxylic acid dimer by "switching off" the ionic interactions while keeping the hydrogen bond network constant. A comparison of the stability of these two dimers should then allow one to quantify the thermodynamic contribution of the H-bonds and the ion pairs separately.

(2) Synthesis. Preliminary studies with an unsubstituted amidopyridine pyrrole carboxylic acid had indicated that the parent compound itself was not well soluble in organic solvents. On the basis of the known binding strength of the amidopyridine-carboxylic acid complexes, we did not expect these dimers to be stable in solvents more polar than DMSO, but instead we intended to study its self-association in chloroform/DMSO mixtures. Hence, solubility in organic solvents was required. Therefore, the hexyl substituted amidopyridine analogue **10** was synthesized following a strategy similar to that for the zwitterion **2** (Scheme 2). In this case, hexyl instead of triethylene glycol chains were chosen to ensure solubility in organic solvents. The hexyl chains were introduced by reacting the dibromide,

(33) Horvath, P.; Gergely, A.; Noszal, B. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1419−1422.
(34) Hossain, M. A.; Schneider, H.-J. *Chem. Eur. J.* **1999**, *5*, 1284−1290.
(35) Schneider, H.-J. *Chem. Soc. Rev.* **1994**, *22*, 227−234.
(36) Dietrich, B.; Fryles, D. L.; Fryles, T. M.; Lehn, J.-M. *Helv. Chim. Acta* **1979**, *62*, 2763−2787.
(37) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008−2010. (b) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 2810−2819.
(38) For a review article, see: (a) Galàn, A.; deMendoza, J. *Top. Curr. Chem.* **1995**, *175*, 101−132. Selected examples: (b) Goswami, S.; Ghosh, K.; Dasgupta, S. *Tetrahedron* **1996**, *52*, 12223−12232. (c) König, B.; Möller, O.; Bubenitschek, P. *J. Org. Chem.* **1995**, *60*, 4291−4293. (d) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314−5315. (e) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394. (f) Etter, M. C.; Adsmond, D. A. *J. Chem. Soc., Chem. Commun.* **1990**, 589−590.

Scheme 2. Synthesis of the Neutral Analogue, the Amidopyridine Pyrrole Carboxylic Acid **10**



obtained from **5** after cleavage of the *tert*-butyl ester group with TFA, with hexanol in the presence of triethylamine in toluene at elevated temperatures. The carboxylic acid **11** was then converted to its acyl chloride using oxalyl chloride in methylene chloride and reacted with 2-amino-6-methyl pyridine to give ester **12**. Hydrolysis of the ethyl ester with lithium hydroxide and neutralization with HCl then yielded the final product, the neutral amidopyridine analogue **10**. Because of the attached hexyl chains, **10** is well soluble in chloroform and other organic solvents.

(3) Dimer Formation. The neutral analogue **10** does not show any signs at all for a dimerization in DMSO, not to mention in even more polar aqueous solvent mixtures. The signals for the various protons in the ^{1}H NMR spectrum in DMSO-d_6 appear at the normal values expected for these functional groups:[38] the amide NH at $\delta = 10.8$, the pyrrole NH at $\delta = 12.1$, and the carboxylic acid proton at $\delta = 13.0$, respectively. These shifts also confirm that **10** as expected exists in solution in the form of the neutral amidopyridine carboxylic acid tautomer shown and not as the pyridinium carboxylate zwitterion resulting from an intramolecular proton transfer. However, ESI MS experiments (positive ion mode) confirmed the general ability of **10** to self-assemble via the formation of 1:1 dimers. In the ESI mass spectrum (Figure 7), next to the signal for the monomer at $m/z = 474$ au, a signal for a dimer at $m/z = 969$ au is found. This dimer is mainly present in the form of its sodium adduct 2M + Na and not as the protonated dimer. This suggests that upon protonation, which probably occurs at the pyridine nitrogen, the binding motif is disrupted; hence, no dimer is formed. The same happens upon deprotonation of the carboxylic acid groups, and accordingly no dimer formation is observed in the negative ion mode.

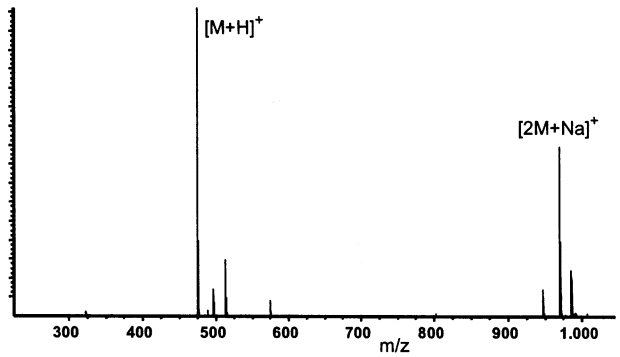


Figure 7. ESI mass spectrum of compound **10** ($m/z = 474$ au) showing the formation of a dimer at $m/z = 969$ au for 2M + Na.

In the solid state, **10** also forms discrete 1:1 dimers, which are completely planar and held together by six hydrogen bonds (Figure 10, green structure). The hydrogen bond distances between the amide N···O (2.762 Å), pyridine N···O (2.701 Å), and pyrrole N···O (2.728 Å) are again rather short, suggesting a strong interaction between the donor and acceptor sites in the solid state. However, in solution, these dimers are held together rather weakly and already dissociate in DMSO. Yet in the less polar solvent chloroform, dimerization takes place very efficiently as indicated by large concentration-dependent downfield shifts of the NH protons. For example, the signal for the amide NH shifts from $\delta = 10.8$ at 0.1 mM to $\delta = 12.4$ in a 100 mM solution. A nonlinear curve fitting of this shift change provides a value of $>10^4$ M^{-1} for the association constant, showing that dimerization in pure chloroform is nearly too strong to determine it accurately by NMR. Yet already the addition of only 10% DMSO almost completely disrupts the dimers.

(4) Solvent-Dependent Binding Studies. We therefore studied the solvent dependence of the dimerization constant of **10** quantitatively using various chloroform/DMSO mixtures in the range from 0 to 5% DMSO-d_6 following the complexation-induced shift changes of the amide and the pyrrole NH (Figure 8). Both signals show significant downfield shifts with increasing concentration of the substrate in solution. The signal for the carboxylic acid proton is rather broad and can only be observed in the more concentrated solutions. The data obtained from the nonlinear curve fitting of the binding isotherms are summarized in Figure 9. For each solvent mixture, the data sets for both the pyrrole and the amide NH provide essentially the same dimerization constants within the experimental error. Furthermore, the calculated values of $\delta \approx 10.8$ for the free amide NH in the monomer and of $\delta \approx 12.4$ for the H-bonded amide

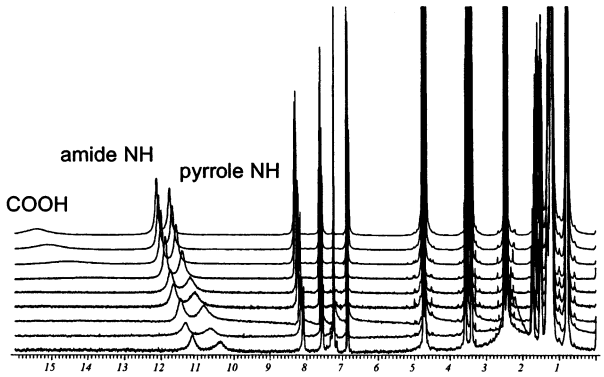


Figure 8. ^{1}H NMR spectrum of **10** in 2.5% DMSO-d_6 in $CDCl_3$ showing the complexation-induced shift changes of the amide and pyrrole NHs (concentrations from bottom to top: 5, 10, 20, 30, 40, 100, 200, 300, and 400 mM).

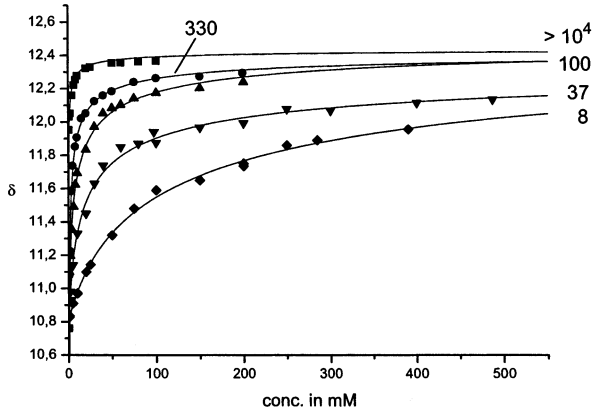


Figure 9. Complexation-induced shift changes of the amide NH signal in **10** in the concentration range from 0 to 500 mM in different solvent mixtures (from top to bottom: 0, 0.5, 1, 2.5, and 5% DMSO-d_6 in $CDCl_3$). The solid lines represent the curve fittings according to the equation shown in Figure 5. The numbers are the calculated dimerization constants obtained from these fits (in M^{-1}).

NH within the dimer are in perfect agreement with the corresponding shifts measured in pure DMSO (only monomer) and for a saturated solution in pure chloroform (only dimer).

As the data in Figure 9 show, already the addition of only small amounts of DMSO-d_6 has a dramatic effect on the stability of the neutral dimers of **10**: The association constant drops by a factor of more than 30 from $>10^4$ M^{-1} in pure $CHCl_3$ to only 330 M^{-1} in 0.5% DMSO in chloroform. Increasing the amount of DMSO in the mixture even more leads to a still further, although smaller, decrease. In 1% DMSO in chloroform, the association constant is $K_{dim} = 100$ M^{-1}, in 2.5% DMSO it is 37 M^{-1}, and in 5% DMSO it is 8 M^{-1}, respectively. Hence, the self-assembly of **10** is hardly any more detectable by NMR in mixtures with more than 5% DMSO.

At such low concentrations of <5% DMSO, the bulk properties of chloroform are barely affected.[39] Therefore, these data show that a specific direct molecular interaction between the binding sites of the amidopyridine **10** and DMSO is probably disrupting the dimerization. A content of 0.5% DMSO already corresponds to a concentration of ca. 65 mM, which is of the same order of magnitude as the concentration of the amidopyridine **10** used in these dilution experiments. DMSO is an extremely good H-bond acceptor; its electron donor capacity is even higher than that of water.[40] Hence, DMSO can effectively replace the amidopyridine group from the carboxylic acid, thereby inhibiting the self-association. This also explains why the effect of DMSO on the binding strength levels off with increasing concentrations as more than a 1:1 interaction is not needed. Any more added DMSO only affects the bulk properties of the solvent mixture such as the dielectric constant. This still has an effect, for example, on coulomb or dipole−dipole interactions, but that is much less dramatic than the direct specific interaction of DMSO with the H-bonding donor sites.

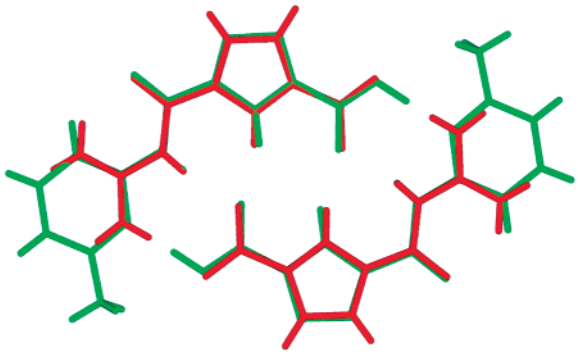


Figure 10. Overlay of the X-ray structures of the zwitterionic dimer **1·1** (red) and its neutral analogue, the amidopyridine dimer **10·10** (green), demonstrating the isostructural H-bond pattern in both compounds (for **10**, the hexyl side chains were omitted for clarity).

Comparison of Zwitterion 2 with Its Neutral Analogue 10: The Importance of the Ion Pairs. These data show that the zwitterionic dimer **2** with its extra charges is remarkably more stable than its neutral analogue **10**. Whereas the former dimerizes even in water with $K_{dim} = 170$ M^{-1}, the latter forms stable aggregates only in chloroform solutions. As a comparison of the X-ray structures shows, both systems are structurally essentially identical as far as the positions of the H-bond donors and acceptors are concerned (Figure 10).

The hydrogen bonding patterns are almost perfectly superimposable with all N···O distances differing by less than 5%. Therefore, in a first approximation it can be assumed that the interaction energies provided by these H-bonds are similar. Hence, any difference in the complex stabilities then must arise from the additional ion pairs, which are not present in the neutral analogue **10** but only in the zwitterion **2**. However, due to the remarkably large difference in the stability of both systems, it was not possible to measure their self-association under exactly the same experimental conditions (e.g., solvent compositions, respectively). Yet still the contribution of the ion pairs can be at least estimated by extrapolating the measured stability constants of both systems to pure DMSO. The upper limit for the stability of the neutral dimer in DMSO is <10 M^{-1}, the value measured in 5% DMSO in chloroform. However, the zwitterionic dimer is too stable to analyze in pure DMSO. Already the interaction of acetate or 2-pyrrole carboxylate with a guanidiniocarbonyl pyrrole cation has an association constant of 5×10^3 M^{-1} in 40% water in DMSO and of $>10^5$ M^{-1} in pure DMSO.[19] The zwitterionic dimer, which contains this interaction twice, has therefore at least a stability twice this value

(39) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990.

(40) Bianchi, A. Thermodynamics of Anion Complexation. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: New York, 1997; pp 217−276.

in pure DMSO. Using a lower estimate of 10^{10} M^{-1} for its dimerization constant, this means that the ion pairs and their mutual interaction within the dimer enhance the stability of this system in DMSO by a factor of at least 10^9 over the simple hydrogen bonding.

Conclusion

In conclusion, we have presented extensive experimental evidence based on ESI MS, X-ray, and NMR data for the formation of a zwitterionic dimer **2·2** even in water. These dimers, which are held together solely by electrostatic interactions (ion pairs in combination with H-bonds), have an astonishingly high stability of 170 M^{-1} in water, making them one of the most efficient self-complementary supramolecular systems reported so far. By comparison with the stability of a neutral amidopyridine analogue **10**, it could be shown that the ion pairs and their mutual interaction within the dimer are mainly responsible for its large stability. Such highly efficient binding motifs as in **2**, which form stable supramolecular assemblies even in water, might be useful for the realization of water-stable supramolecular materials in the future.

Acknowledgment. Financial support from the Fonds der Chemischen Industrie (Kekulé-Fellowship for W.W.) and the Deutsche Forschungsgemeinschaft is gratefully acknowledged. The authors thank Michael Schwegmann and Dr. Johann Lex for the X-ray analysis, Dr. Mathias Schäfer for the ESI-MS analysis, Dr. Hans Schmickler for the NMR assignments, and Prof. Dr. Albrecht Berkessel for his general support (all University of Cologne).

Supporting Information Available: (1) Experimental section, (2) crystallographic information files (CIF), (3) NMR assignments of **2** and **10**, and (4) NMR data for the dilution studies of **2** and **10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028485+