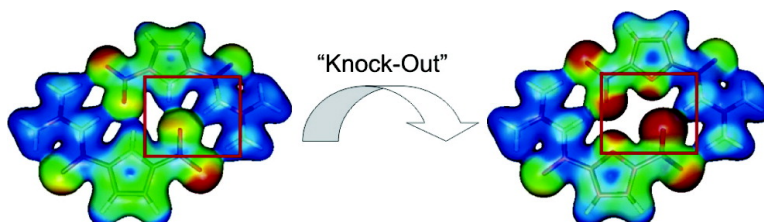


“Knock-Out” Analogues as a Tool to Quantify Supramolecular Processes: A Theoretical Study of Molecular Interactions in Guanidiniocarbonyl Pyrrole Carboxylate Dimers

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“Knock-Out” Analogues as a Tool to Quantify Supramolecular Processes: A Theoretical Study of Molecular Interactions in Guanidiniocarbonyl Pyrrole Carboxylate Dimers

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Abstract: It was recently shown experimentally that 5-(guanidiniocarbonyl)-1H-pyrrole-2-carboxylate **1**, a self-complementary zwitterion, dimerizes even in water with an unprecedented high association constant of $K = 170 \text{ M}^{-1}$ (*J. Am. Chem. Soc.* **2003**, *125*, 452–459). To get an insight into the importance of the various noncovalent binding interactions and of their interplay (electrostatic interactions, hydrogen bonding, cooperative effects), we employ density functional theory to study the stability of several “knock-out” analogues in which single hydrogen bonds within these multiple point binding motif are switched off by replacing N–H hydrogen-donor groups with either methylene groups or an oxygen ether bridge. The influence of a highly polar solvent on the dimer stabilities is also examined. These calculations reproduce the experimental data for zwitterion **1**. A comparison of **1** with the arginine dimer shows that the energy contents of the monomers also significantly influence the dimer stabilities. The analysis of the various “knock-out” analogues reveals as a main conclusion that simple models either based just on hydrogen-bond counting or on the assumption that the charge interaction by itself is the main and dominant factor fail to explain the stability of such self-assembled dimers. Our computations show that the hydrogen-bond network, the electrostatic attraction, and also their mutual interactions are responsible for the high stability of zwitterion **1**.

Introduction

The development of novel building blocks which are capable to self-assemble in polar solutions is one main goal in today's supramolecular chemistry^{1,2} as molecular recognition-directed self-assembly and self-organization can lead to the formation of highly complex and fascinating structures with new and interesting properties.³ However, so far only very few systems show strong self-assembly in polar, especially aqueous solution. For example, purely hydrogen-bonded assemblies possess a considerable association energy only in aprotic solvents of low polarity and are not stable in water due to the competitive solvation of donor and acceptor sites in water.⁴ Therefore, to

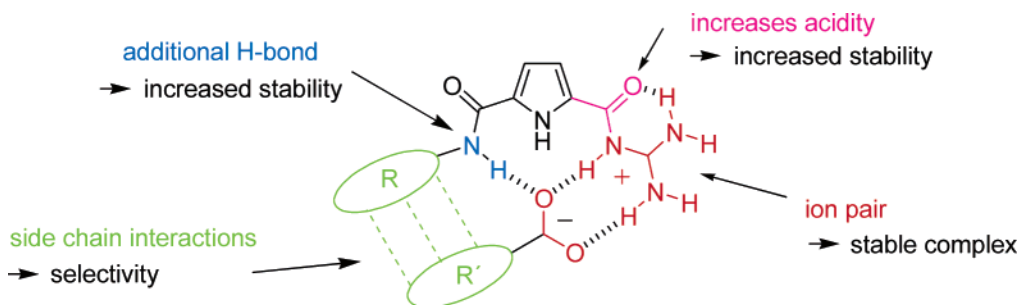
achieve strong self-assembly, hydrogen bonds have to be combined with additional noncovalent interactions such as metal coordination,⁵ salt bridges,⁶ hydrophobic,⁷ or π – π –interactions.^{8,9}

In 1999, Schmuck reported for the first time on a new class of receptor molecules for the binding of carboxylates in aqueous media.¹⁰ These 2-(guanidiniocarbonyl)-1H-pyrroles improve the

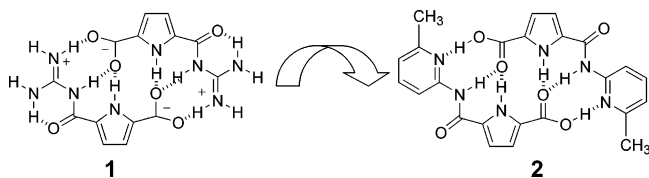
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Scheme 1. Guanidiniocarbonyl Pyrroles Efficiently Bind Carboxylates Even in Aqueous Solvents Due to a Combination of Ion Pair Formation and Additional H Bonds



Scheme 2. Amidopyridine Pyrrole Carboxylic Acids as Neutral “Knock-Out” Analogues of Zwitterionic Guanidiniocarbonyl Pyrrole Carboxylates: Translating the Zwitterionic Dimer **1** into a Neutral Amidopyridine Pyrrole Carboxylic Acid Dimer **2** by “Switching Off” the Ionic Interactions while Keeping the Hydrogen-Bond Network Constant



ion pairing of simple guanidinium cations with oxo anions through a combination of ion pairing and multiple hydrogen bonds (see Scheme 1). Because of the increased acidity of the acyl guanidinium moiety and the additional H bonds, these complexes are much stronger than those of simple guanidinium cations^{11,12} allowing the complexation of carboxylates even in highly polar solvents such as DMSO or water. An experimental comparative thermodynamic study with a series of structurally related guanidiniocarbonyl pyrroles demonstrated that the energetic contributions of the individual noncovalent interactions within this binding motif (the individual hydrogen bonds and the ion pair) are significantly different.^{10b} Besides the ion pairing, mainly the amide NH in position 5 of the pyrrole ring is important for the effective binding of the carboxylate substrate. Further studies showed that also the size and electronic structure of the aromatic ring is important.¹³ Pyrrole systems are superior to the analogous benzene derivatives which in turn show a higher binding affinity than pyridine derivatives, in which the nitrogen lone pair exerts additional repulsive effects on the bound carboxylates.

On the basis of this new recognition motif a self-complementary zwitterion **1** (Scheme 2) has been developed that forms extremely stable dimers as could be shown by X-ray, ESI-MS, and NMR solution studies.¹⁴ The association constant is approximately $K > 10^{10} \text{ M}^{-1}$ in DMSO and still surprisingly

high ($K = 170 \text{ M}^{-1}$, $\Delta G \approx -15 \text{ kJ/mol}$) in water. Therefore compound **1** is one of the most efficient self-assembling systems relying solely on electrostatic interactions reported so far. Hence, an interesting question is which of the multiple binding interactions present in this dimer is mainly responsible for its unique binding properties? We could already show experimentally by comparison with a neutral amidopyridine pyrrole analogue that the charge interaction within the ion pair is crucial for its high stability. The neutral binding motif in this “knock-out” analogue **2** has the same H-bond pattern like dimer **1** as could be shown by X-ray analysis. Nevertheless, the dimerization is several orders of magnitude less efficient. Whereas **2** dimerizes in chloroform with $K > 10^4 \text{ M}^{-1}$, already the addition of >5% DMSO completely disrupts these dimers due to the competitive solvation of the H-bond donor by the polar solvent.

On the basis of these data, one could assume that the main important factor being responsible for the high stability of zwitterion **1** is simply the charge interaction. However, already a single guanidiniocarbonyl pyrrole/carboxylate ion pair is much stronger than simple salt bridges between carboxylates and ammonium ions or even the parent guanidinium cation. Therefore, one has to account for the various H-bonds, their number and strength, the properties of the actual ion pair, and further secondary electrostatic and cooperative effects. To design even better self-assembling systems for future applications (e.g., for supramolecular polymers), a detailed understanding of the importance of these various noncovalent interactions and their mutual interplay is needed. However, experimentally this is difficult to achieve as only the overall association energy can be determined. It is impossible to dissect these data into individual contributions of single interactions. The comparison of structurally closely related “knock-out” analogues is one way address this problem and to obtain at least semiquantitative data (as shown above for zwitterion **1** and its neutral analogue **2**). However, very often the most interesting “knock-out” analogues cannot be made synthetically or might not even be stable molecules at all. Computational determination of their stabilities does not encounter any of these problems, and indeed high-level theoretical approaches have already proven quite useful to analyze supramolecular systems in general.¹⁵ This approach is therefore used here to study in detail the various noncovalent interactions and factors that might be responsible for the high stability of zwitterion **1**.

In the present paper, we calculate dissociation energies of a systematically varied series of “knock-out” analogues by means of density functional approaches. This should give an insight

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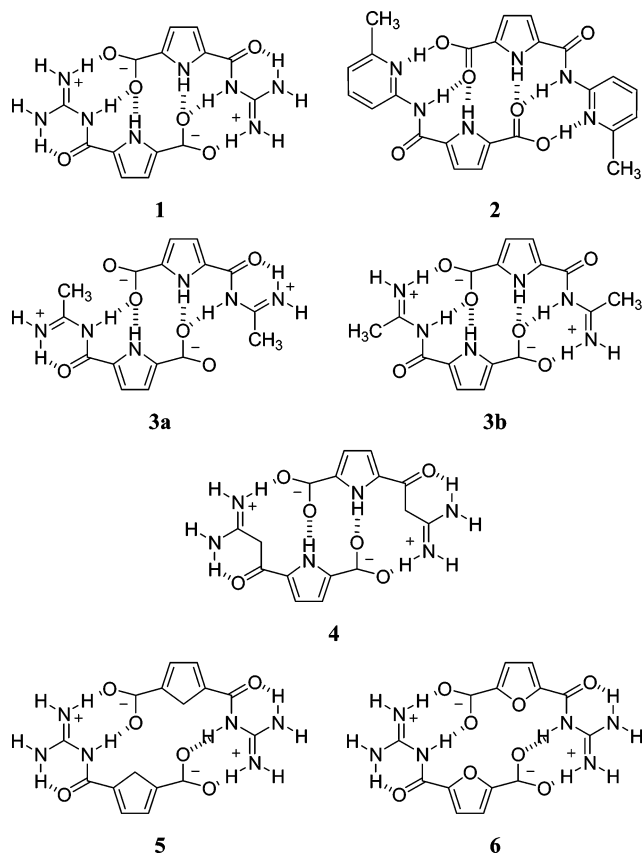
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Chart 1. Guanidiniocarbonyl Pyrrole Carboxylate Dimer (**1**), Amidopyridine Pyrrole Carboxylic Acid Dimer (**2**), Methyl Derivative (**3a**, **3b**), Amidine Derivative (**4**), Cyclopentadienyl Derivative (**5**), and Furan Derivative (**6**)



into the strengths of the individual hydrogen bonds within these complex binding motifs which probably vary for every donor site. Additionally, it should elucidate the importance of cooperative effects (e.g., secondary interactions), which can be expected to be as important as already seen for the guanine cytosine pairing.¹⁶

The compounds used in this study are shown in Chart 1. In each of these analogues, one of the several noncovalent interactions present in **1** is switched off. The amidopyridine dimer **2**, which was also already studied experimentally, has the same H-bond pattern but no charge interactions. The “knock-out” analogues **3a**, **4**, **5**, and **6** are again zwitterionic, but the individual N–H hydrogen-bond donor sites are replaced by either methylene groups as in the methyl (**3a**), amidine (**4**), and cyclopentadienyl (**5**) derivatives or by an oxygen atom (in the furan derivative **6**). Dimer **3b** is obtained from **3a** by an internal

rotation. It possesses the same hydrogen pattern as **1** and was included to study the influence of a methylation of the amidinium unit on the stability. For arginine such effects were found to stabilize the zwitterionic species with respect to the neutral one (vide infra).¹⁷ For these later “knock-out” analogues **3–6**, no experimental data are available, and at least for **3a** and **5**, this is probably impossible to achieve due to their conformational (**3a**) and tautomeric (**5**) instability.

Theoretical Methods

The geometry optimizations of all compounds were performed with the TURBOMOLE program package¹⁸ at the BLYP/TZVPP level of theory^{19–21} using the RI approximation.²² For the zwitterionic species, extra diffuse functions were added to the negatively charged carboxylate oxygens in order to describe the diffuse shape of the valence orbitals properly. The TZVPP basis set was enlarged by 1s and 1p primitive uncontracted basis functions with an exponential coefficient of 0.068, whereas for the auxiliary basis sets the exponent was doubled (0.136). Dissociation energies were calculated including the counterpoise correction according to Boys and Bernardi.²³

In most computations the influence of a solvent is dissected in several parts.²⁴ In the present paper, the so-called electrostatic contributions (often also abbreviated as electrostatic component of solvation) were estimated using the COSMO^{25a} approach as implemented in TURBOMOLE^{25b} with a dielectric constant of $\epsilon = 78$ to simulate a waterlike solvent. Since the COSMO implementation in TURBOMOLE only takes electrostatic contributions of the solvent into account, the nonelectrostatic effects²⁴ were estimated by single-point calculations (BLYP/6-31++G(d,p))²⁶ on the optimized structures in water employing the Gaussian03 program package²⁷ implementation of the COSMO.

All optimized structures were characterized by harmonic frequency analysis employing either analytical derivatives (RI-DFT/BLYP/TZVP) for gas-phase structures as implemented in TURBOMOLE or numerical derivatives (RIDFT/BLYP/TZVPP) for solvated structures using the SNF program, respectively.²⁸ Thermodynamic corrections for the gas phase were obtained with TURBOMOLE employing the standard

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approach.²⁹ Thermodynamic corrections in solution were obtained by frequency calculations with the SNF program of the TURBOMOLE suite employing the COSMO approach with $\epsilon = 78$.²⁸ For the computation of entropy effects resulting from the translation motion (ΔS_{trans}), this implementation uses the standard formula for gas phase.²⁹ However, this approximation overestimates the absolute values. As a consequence, the stability of dimer formation is underestimated as discussed recently.^{30,31} Let us take **2** as an example: By employment of the approximation of Williams and co-workers³⁰ to estimate ΔS_{trans} for a solvent, the absolute value for $T\Delta S$ obtained with the standard formula decreases by about 20 kJ/mol. Despite this influence, we refrained from considering this effect due to the following reasons: Within the approximation of Williams and co-workers differences between compounds arise only due to their masses, i.e., only a small fraction of the various effects are included. As a consequence mainly the absolute values change, but the differences between the various compounds studied here stay more or less constant.

As expected,³² test calculations employing various functionals and the MP2 approach³³ showed that the BLYP functional underestimates the dissociation energies. Nevertheless it gives geometrical parameters which are virtually identical to those obtained with the B3LYP functional. The latter predicted a stronger binding. Therefore we computed improved stabilities for solvent conditions employing the B3LYP functional based on previously optimized BLYP geometries. The thermodynamic corrections are also taken from BLYP calculations. Since we are more interested in solvent data, the BLYP functional was employed for gas-phase calculations throughout.

Coupled-cluster computations^{32,34} indicate that also B3LYP often underestimates dissociation energies for hydrogen bonds. Consequently, its predictions may be looked upon as lower bounds for the dissociation energies. The computed differences between the various knock-out analogues, however, should possess a considerably higher accuracy since the binding situations are quite similar. More information can be taken from the Supporting Information.

To get a deeper insight into the variations appearing in our series of model compounds, the electrostatic potentials of all compounds for both the gas phase and the solvent have been calculated to visualize variations in the electronic distributions and molecular interactions of guanidiniocarbonyl pyrrole carboxylate **1** and its knock-out analogues **2–6**. For these computations, the Gaussian03 program package²⁷ was used.

Results and Discussions

Geometries. Table 1 summarizes selected computed geometrical parameters, whereas Table 2 compares computed and measured distances of the bonds described in Chart 2. Table 2 contains data for compounds **1** and **2** for which X-ray data are available. The complete geometrical arrangement can be taken from the Supporting Information. For all covalent bonds, computed and measured structural parameter agree in the expected range (± 0.02 Å). Measured and computed distances

Table 1. Hydrogen Bond Lengths in **1–6** (BLYP/TZVPP; Solvent Calculations Performed with COSMO)^a

bond	1		2		3	
	gas phase	solvent	gas phase	solvent	gas phase	solvent
1	1.68	1.86	1.58	1.69	1.79	1.81
2	1.77	1.72	1.85	1.88	1.82	1.86
2^b	1.83		1.83		1.79	
3a			1.58	1.76	1.76	1.78
3b	1.65	1.81	1.60	1.70	1.79	1.80
4	1.52	1.77			1.80	1.90
5	1.63	1.84	1.61	1.76		
6	1.54	1.74	1.62	1.77		

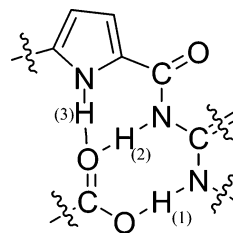
^a Numbering of bonds according to Chart 2. ^b With fixed C_s symmetry.

Table 2. Heteroatomic C...N Distances Obtained from X-ray Studies^a and Calculations (BLYP/TZVPP/gas phase)

bond	1		2		3	
	X-ray	theoretical	X-ray	theoretical	X-ray	theoretical
1	2.85	2.75	2.68	2.65	2.73	2.77
2	2.62	2.80	2.72	2.88	2.73	2.81

^a The amidopyridine pyrrole carboxylic acid dimer **2** was synthesized with hexyloxymethyl groups in positions 3 and 4 of the pyrrole ring.¹⁴

Chart 2. Numbering of the Intermolecular Bonds in the Dimers



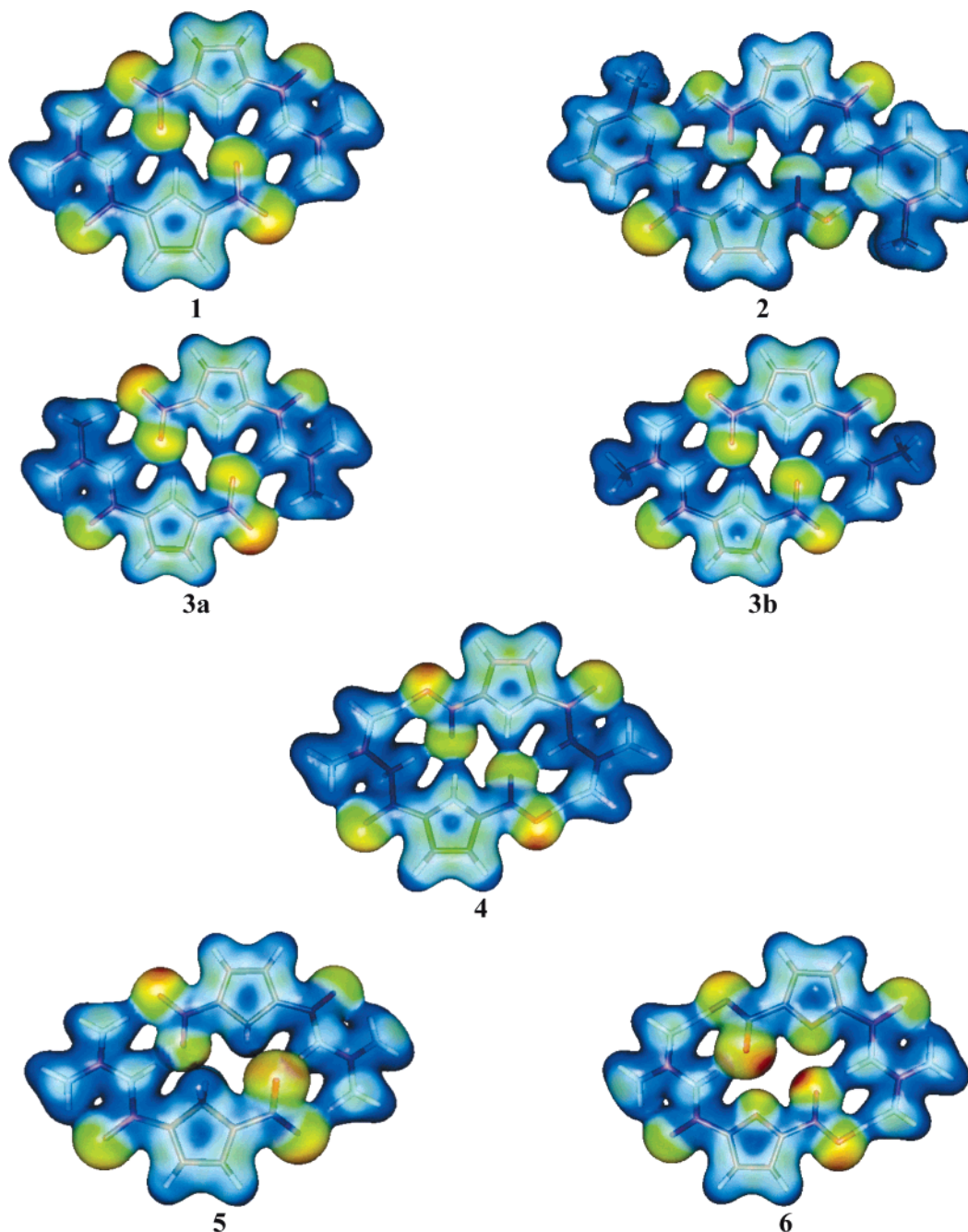
between the heavy centers of bonds 1–3 (Chart 3 and Table 3) agree to about 0.1 Å. The larger deviations are expected due to the weakness of the bonds and crystal effects.

According to the available X-ray data, compounds **1** and **2** exhibit a planar structure. In contrast, geometry optimizations in the gas phase or polar solvent give slightly bended geometries but the bending potential is extremely flat. For **1**, the planar geometry, which represents a local minimum, lays only about 1 kJ/mol higher than the bended structure. For **2**, the energy difference is only 2 kJ/mol. The differences are so small that π - π stacking interaction within the crystal can explain the difference between experiment and theory. Additionally, already dynamic effects (large amplitude bending motion) are expected to lead to averaged planar geometries in X-ray experiments and in solution.

Our calculations show that from the “knock-out” derivatives only the methyl derivatives **3a** and **3b** have a planar geometry. The geometries of the other compounds are more or less distorted due to steric or electronic effects. In Charts 3 and 4, which contain the electrostatic potentials, the distortions are best seen in the slight rotations of the carboxylate groups out of planarity. The optimization of the amidine derivative **4** revealed two conformers, differing only in the relative orientation of the methylene units within the dimer and resembling therefore in a side view a “boat” and a “chair” conformer, whereof the latter is about 5 kJ/mol more stable in the gas phase. In the cyclopentadienyl derivative **5**, a hydrogen atom of the methylene group of the ring system points toward the carboxylate group, so that the cyclopentadienyl rings are forced into an up and down orientation. Also for the knock-out analogues **3a** and **4**

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Chart 3. Electrostatic Potential (Contour Value = 0.02) Mapped on the Electron Density (Contour Value = 0.015) of the Dimers 1–6 in the Gas Phase



the geometry optimizations lead to structures in which one of the hydrogen atoms of the methyl (**3**) or methylene (**4**) group is directed toward the carboxylate group. The distances are between 2.01 and 2.13 Å pointing to small attractive interactions. The distortions within the furan derivative **6** result from the electronic repulsion of the oxygen lone pairs of the furan oxygen and the carboxylate oxygen. This is expected to be a similar effect as observed experimentally for the pyridine derivatives.¹³

The calculated hydrogen-bond lengths for **1** in the gas phase and polar solvent show that solvent effects influence the individual bonds differently (Table 1). As expected the influence decreases going from the outer (bond 1, Chart 2) to the inner bond (bond 3, Chart 2). Bond 1, representing the second shortest one for the gas phase (1.68 Å), increases by 26% and becomes

the longest bond in a polar solvent (1.86 Å). Bond 2 is elongated by about 0.1 Å (7%) but still remains the shortest bond. The influence of the inner bond is negligible (0.02 Å or 1%). By comparison of the hydrogen bond lengths of **2** obtained for the gas phase with the values calculated using the COSMO approach, the inner H bond is only slightly longer in solvent than in a vacuum. The largest change in a magnitude of about 0.05 Å can be observed for the outer bond, but in contrast to the zwitterionic dimer **1**, the H-bond length now decreases a little upon solvation. This does not indicate increased bond strength but results from larger bending angles (see Supporting Information).

Energies. The calculated dissociation energies for gas phase and solvent for all compounds **1–6** are given in Table 3. Table

Table 3. Contributions to the Total Dissociation Energies (All Values Given in kJ mol⁻¹)

	1	2	3a	3b	4	5	6
	Gas Phase						
ΔE_{elec}^a	+438/+464	-/-	+340/-	+443/-	+364/-	+364/-	+345/-
ΔE_{elec}^b	+158/+170	+116/-					
$\Delta H^{\text{corr } c}$	-9	-10	-11	-11	-21	-11	-6
$T\Delta S^{\text{corr } d}$	+85	+61	+72	+74	+68	+80	+67
ΔG^e	+344/+370	-/-	+256/-	+358/-	+275/-	+273/-	+272/-
ΔG^f	+64/+76	+45/-					
Solvent ($\epsilon = 78$)							
ΔE_{elec}^g	+108	+48	+64	+111	+55	+64	+51
$\Delta E(\text{n.e.})^h$	+9	+3	+6	+9	+4	+5	+4
$\Delta H^{\text{corr } c}$	+1	-6	-3	-4	-4	+1	+2
$T\Delta S^{\text{corr } d}$	+62	+62	+66	+50	+59	+58	+56
ΔG^i	+56	-17	+1	+66	-3	+13	-2

^a Dissociation energy with respect to the zwitterionic monomers. The left value gives the BLYP result. For the right value the B3LYP functional was employed. ^b Dissociation energy with respect to the neutral monomers. The left value gives the BLYP functional results, for the right value the B3LYP functional was employed. ^c Correction to the free dissociation energies to obtain the enthalpy term (BLYP computations). ^d Correction to the free dissociation energies arising due to the entropy term ($T = 298$ K, BLYP computations). ^e Free dissociation energies $\Delta G = \Delta E + \Delta H^{\text{corr}} - T\Delta S^{\text{corr}}$ with respect to the zwitterionic monomers. The left value gives the dissociation energy obtained with the BLYP functional; the right value gives the dissociation energy computed with the B3LYP functional. ^f Free dissociation energies $\Delta G = \Delta E + \Delta H^{\text{corr}} - T\Delta S^{\text{corr}}$ with respect to the neutral monomers assuming that the thermodynamic correction are similar to those computed for the dissociation into the zwitterionic monomers. The left value gives the dissociation energy obtained with the BLYP functional; the right value gives the results of the B3LYP functional. ^g Dissociation energies with respect to the lowest lying monomers. These represent the zwitterionic forms for **1** and **3–6**, while it is the neutral monomer for **2**. The B3LYP functional was employed in combination with BLYP geometries. ^h Corrections to the free dissociation energies arising due to the nonelectrostatic interactions (free energy of cavity, dispersion–repulsion interaction between solute and solvent). The calculations were performed with GAUSSIAN03 (BLYP computations). ⁱ Free dissociation energies $\Delta G = \Delta E_{\text{elec}} + E(\text{n.e.}) + \Delta H^{\text{corr}} - T\Delta S^{\text{corr}}$. Thermodynamic corrections are obtained with the BLYP functional.

3 also contains the computed thermodynamic corrections leading to the dimerization enthalpies and dimerization free energies. The electrostatic potentials mapped on isosurfaces of electron densities of all compounds are given in Charts 3 (gas phase) and 4 (polar solvent). The electrostatic potentials of the monomers can be taken from the Supporting Information.

The Zwitterionic Dimer (1). For the gas phase, the dissociation energy (ΔE_{elec}) of zwitterion **1** with respect to the zwitterionic monomers is calculated to +464 kJ/mol (B3LYP/TZVPP). This value is surprisingly high compared to other guanidinium/carboxylate-based ion pairs, for example, the arginine dimer.^{17,35} Arginine possesses a high affinity to form an abundant number of clusters when electrosprayed into gas phase.³⁶ Theoretical studies³⁵ predict that zwitterionic dimers are formed, which are stabilized by two guanidinium-carboxylate salt bridges. The dissociation energy of the zwitterionic structure was calculated to 199 kJ/mol by Goddard III and co-workers.³⁵ Hence, with respect to its zwitterionic monomers, dimer **1** is more than twice as stable as the zwitterionic arginine dimer with respect to its zwitterionic monomers. A closer look at the

dissociation channels reveals however that the possible reason for this extraordinary stability of dimer **1** lies more within the energy content of the corresponding monomers than the actual binding interactions within the dimers. Figure 1 summarizes the computed values for **1** and for the arginine dimer.¹⁷

The dissociation energies mentioned above refer to the dissociation into two zwitterionic monomers. However, in the gas phase, isolated zwitterions are normally energetically less stable than the corresponding neutral monomers. The stability of such zwitterionic monomers is significantly depending on the possibility of internal charge interactions. For example, for arginine the neutral monomer is still more stable than the zwitterion, but the energy difference between both forms is rather small (about 5 kJ/mol).^{35,37} Because of the flexibility of the molecule, an effective intramolecular charge interactions between the carboxylate and the guanidinium cation is possible, stabilizing the zwitterionic form. Methylation of the arginine³⁵ or the presence of an electric field³⁸ is already sufficient to make the zwitterionic form the absolute minimum. Similar effects were recently found for guanidiniocarbonyl pyrrole/carboxylate zwitterions with flexible linkers of varying chain length between both ionic groups. It was shown that the stability of the zwitterionic form depends on the length of the linker.³⁹ Only those zwitterions in which the linker is long enough to allow internal charge interactions are zwitterionic in the gas phase. For the smaller ones the neutral form is more stable.

For zwitterion **1** no internal charge stabilization is possible due to the rigidity of the molecule. In accordance with this, we compute an energy difference of 136 kJ/mol between the zwitterionic and the neutral monomer of **1** (Figure 1, left-hand side). Hence, the energy difference is 1 order of magnitude larger than for arginine (Figure 1, right-hand side). For the dimers, however, even in the gas phase the zwitterionic form represents the minimum structure. The neutral dimer structures obtained through a double-proton transfer from the guanidinium to the carboxylate groups also represent local minima on the hyper surface but are less stable. For **1**, B3LYP/TZVPP predicts the neutral structure to be 22 kJ/mol above the zwitterionic structure. For the arginine dimer, the difference between the neutral and the zwitterionic structure is computed to be 56 kJ/mol.³⁵ As the guanidinium group in arginine ($\text{p}K_{\text{a}} = 13.5$) is about 6 orders of magnitude less acidic than the acyl guanidinium group in **1** ($\text{p}K_{\text{a}} = 7–8$), proton transfer in **1** is expected to be easier as reflected by these data.

The energetically most favorable dissociation channel should therefore lead from the zwitterionic dimers to the neutral monomers. If one considers this process, compound **1** and the arginine dimer become equally stable. For dimer **1**, we compute a dissociation energy of 192 kJ/mol, while Goddard III and co-workers³⁵ give a value of 189 kJ/mol for the arginine dimer (Figure 1). If one compares the dissociation of the less stable neutral dimers into its neutral monomers, the arginine dimer possesses a dissociation energy of about 133 kJ/mol, whereas for **1**, we find a dissociation energy of 170 kJ/mol, respectively. The difference in the dissociation energies of both neutral

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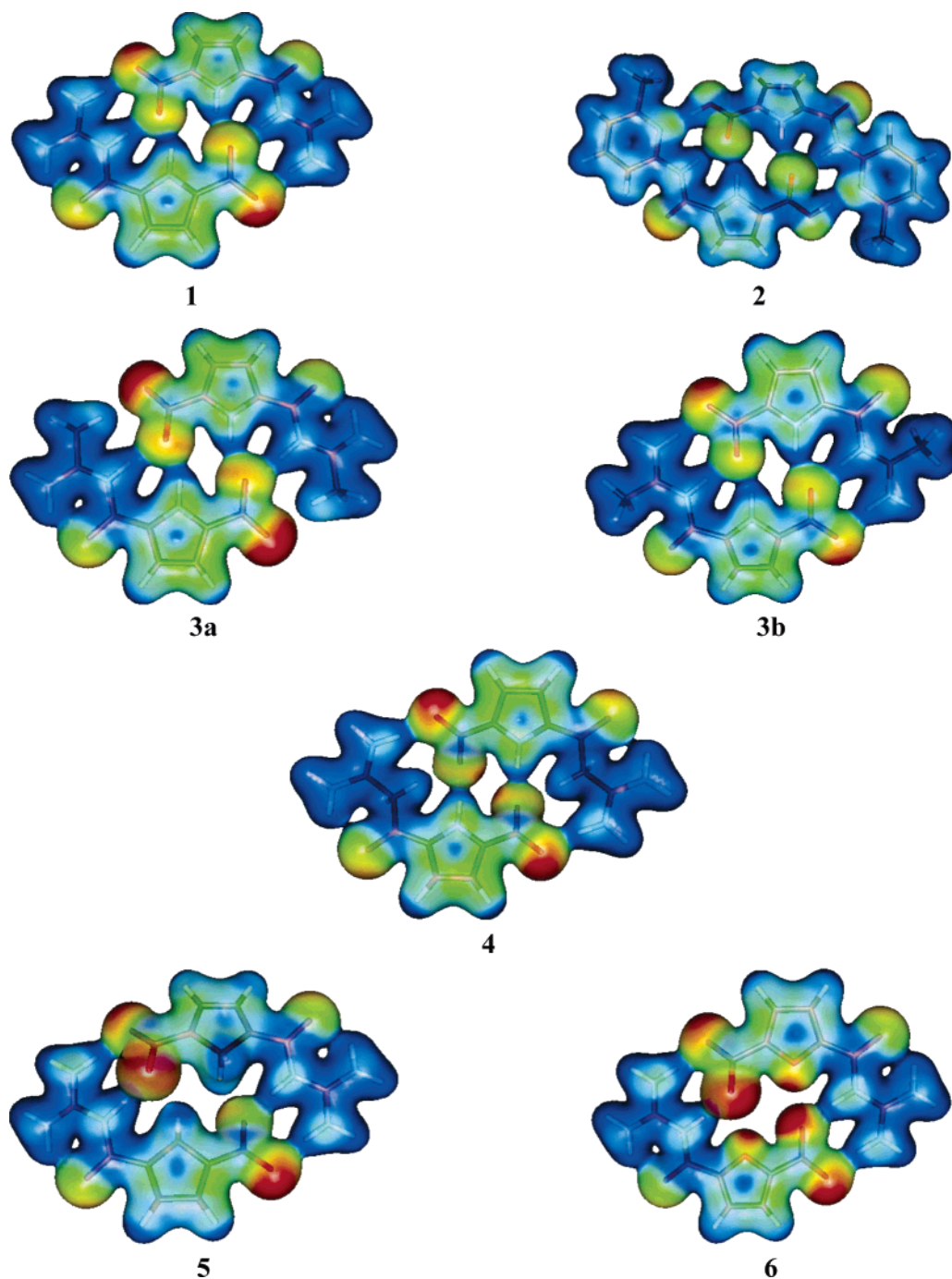
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Chart 4. Electrostatic Potential (Contour Value = 0.02) Mapped on the Electron Density (Contour Value = 0.015) of the Dimers 1–6 in Solvent



structures is reasonable since **1** is stabilized by two additional hydrogen bonds between the pyrrole N–H unit and the carbonyl oxygen of the carboxylic acid.

A dimerization free energy of about $\Delta G = +76$ kJ/mol is calculated for the energetically most favorable dissociation of the zwitterionic dimer **1** into the neutral monomers using the same thermodynamic corrections as calculated for the dissociation into two zwitterions ($\Delta G = +370$ kJ/mol). However, in an attempt to dissociate **1** in the gas phase using IRMPD-MS techniques only fragmentation due to covalent bond rupture was observed.⁴⁰ By assumption that such bond rupture needs energies

in the range of a normal covalent bond (>250 kJ/mol), this experimental outcome indicates that dissociation of zwitterionic dimer **1** requires more energy than expected based on the calculated stabilities of both the dimer and monomers. But this dissociation channel requires a double proton transfer. Obviously, this imposes a large energy barrier onto the dissociation.

As expected for electrostatic interactions, solvation by a polar solvent drastically affects the stability of dimer **1**. In general, the stability of salt bridges is influenced by the polarity of the solvent⁴¹ or microsolvation.⁴² In contrast to the situation in gas phase, for a polar solvent the zwitterionic form now represents the global minimum for both the monomer and the dimer.^{14,43}

(40) Schmuck, C.; Schäfer, M., unpublished results.

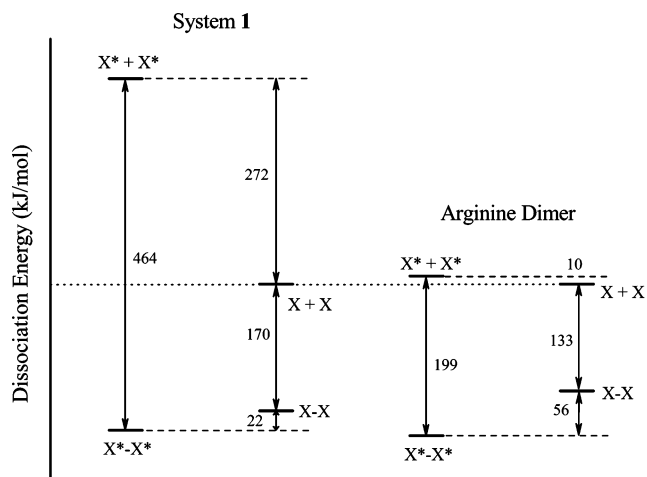


Figure 1. Left: reaction diagram of **1** in the gas phase (B3LYP/TZVPP//BLYP/TZVPP). Right: reaction diagram of arginine in the gas phase (B3LYP/6-31G**).³⁴ The neutral form of a monomer is abbreviated as X, whereas X* denotes the zwitterionic analogue.

Therefore, the dissociation channel that has to be considered now leads from zwitterionic dimer **1** directly to the zwitterionic monomers. The dissociation energy of **1** to the zwitterionic monomers is reduced to +108 kJ/mol in water (~23% of the gas-phase value), which translates into a dissociation free energy of $\Delta G = +56$ kJ/mol. This is quite reasonable compared to the experimental value of $\Delta G \approx +15$ kJ/mol measured from NMR dilution studies. In comparison of these data, one has to take into account that our theoretical approach computes dissociation free energies for one single dimer of **1** in the solvent. The experimental values are however measured at millimolar concentrations. As the ionic strength (salt concentration) of the solution has a tremendous destabilizing effect on the stability of salt bridges, it is not surprising that the experimental value is smaller than the calculated one. For example, Schneider assigns an upper limit of dissociation energies of $\Delta G \approx 8$ kJ/mol to single organic ion pairs in an indefinite dilute solution,⁴⁴ but at millimolar concentrations the corresponding association constants of these ion pairs are more than a factor of 1000 smaller! Gallivan and Dougherty came to a similar conclusion on the basis of a theoretical characterization of the methylammonium–acetate dimer.^{15g} The computed and measured data underline that similar to the situation in gas phase also for water as solvent dimer **1** is much more stable than other organic zwitterionic dimers. For regular organic zwitterionic dimers, a stability of $\Delta G \leq 16$ kJ/mol would be expected based on Schneider’s evaluation of literature data. Hence, our dimer **1** is at least three times more stable. Similar to the situation found in the gas-phase part of this larger stability results probably again

from the higher energy content of the rigid monomers of **1** compared to more flexible zwitterions. The instability of the zwitterionic monomer caused by its lack of intramolecular charge stabilization seems to emerge as an interesting principle for the realization of highly stable electrostatically driven self-assembly.

With respect to the gas phase (Chart 3) the electrostatic potential computed for a polar solvent (Chart 4) shows a considerably higher polarization. The electrostatic potentials reflect nicely the strong binding interaction between both monomers.

The Neutral Analogue (2). The calculated dimer dissociation energies (gas phase $\Delta E_{\text{elec}} = +116$ kJ/mol, $\Delta G = +45$ kJ/mol; polar solvent $\Delta E_{\text{elec}} = +48$ kJ/mol, $\Delta G = -17$ kJ/mol) are much smaller compared to the zwitterionic dimer **1** reflecting the great importance of charge interactions within this kind of dimers. The influence of the solvent on **2** (reduction by about 60%) is weaker than on the zwitterion **1** for which a reduction by about 80% is calculated. Such an effect is generally found if salt bridges are compared to neutral hydrogen bonds. Even though the electronic dissociation energy is still negative, a positive free energy of dimerization ΔG is computed in water showing that the hydrogen binding interactions within the dimer are not sufficient to compete with solvation. In polar solvents the neutral analogue **2** is therefore predicted to exist only in form of monomers, which was indeed experimentally observed.¹⁴ For the neutral dimer **2** the polarization upon solvation reflected by the electrostatic potential is less pronounced than for **1** (Charts 3 and 4).

Knock-Out Analogues 3–6: “Switching Off” Single Hydrogen Bonds. From the comparison of the stabilities of **1** and its neutral analogue **2** one could conclude that the main and most important factor responsible for the different stabilities is the zwitterionic nature of **1** and hence the resulting coulomb interaction between the monomers. However, that this interpretation is premature can be seen by taking a look at the knock-out analogues **3a**, **4**, **5**, and **6**. These are all zwitterionic species with extensive charge interactions between the monomers (see Charts 3 and 4 for the electrostatic potentials) but different hydrogen-binding schemes compared to **1**. Despite their zwitterionic nature, the calculated stabilities are much lower than for the parent zwitterion **1**. In the gas phase, the dissociation energies with respect to the zwitterionic monomers of the dimers **3a**, **4**, **5**, and **6** lie between +340 and +364 kJ/mol corresponding to about 80% of the value for the zwitterion **1** (BLYP computations).⁴⁵ Solvation reduces their dissociation energies to about +48 to +64 kJ/mol, which are only about half of the corresponding dissociation energy of **1** (B3LYP calculations). This clearly demonstrates that the mere charge interaction is not enough to explain the stability of dimer **1**. The strength of the ion pair must be also influenced by the exact nature of hydrogen bond network.

But the computed dissociation energies of **3–6** indicate that a second simple model based on just counting the number of formal hydrogen bonds within the binding motifs is not sufficient

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 (43) Attempts to find a local minimum for the neutral structure of dimer **1** in a polar solvent (COSMO calculation) failed. All optimizations starting from neutral geometries (proton attached to the carboxylate groups) transformed into zwitterionic structures without any barrier. Geometrical structures with fixed O–H distances (~1.044 Å) lie about 150 kJ/mol above the zwitterionic structure.
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(45) As for **1**, the lowest dissociation channel of these knock-out analogues in the gas phase would lead to the neutral monomers. We are, however, mainly interested in a comparison of the various binding schemes and in the results obtained for a polar solvent. Therefore, we will only compare the dissociation energies with respect to the zwitterionic monomers both in the gas phase and in water.

either. If one neglects the weaker C–H \cdots O $^-$ bonds, the knock-out analogues except **3b** all possess four instead of six formal hydrogen bonds in dimer **1**. On the basis of the number of H bonds, one would expect dissociation energies of about +300 kJ/mol for the gas phase and about +70 kJ/mol for a polar solvent (~66% of stability of dimer **1**). On one hand, the computed dissociation energies between +340 and +364 kJ/mol for the gas phase show that here the missing of two H bonds relative to **1** is somehow compensated, i.e., the dimers are more stable than expected on the basis of this simple model. On the other hand, for a polar environment the dissociation energy decreases above average with respect to the number of H bonds. With dissociation energies of about +48 to +64 kJ/mol, the dimers are less stable than expected. Part of this finding can be probably explained by the effect that in the gas phase especially anionic groups have an extremely high energy content and benefit from any kind of molecular interaction, which allows a larger polarization of the negative charge.⁴⁶ This stabilizing effect is more or less independent from the exact chemical nature of the monomer and its binding motif. Therefore, the relative importance of any other noncovalent interaction (such as H bonds or even ion pairs) for the stability of the dimers is reduced in the gas phase. In a polar solution, however, the anion is already stabilized by the solvent molecules. Hence, the relative importance of additional or missing H bonds increases.

As both simple models (number of coulomb interactions and number of H bonds) fail to predict the stability of these zwitterionic dimers, a more sophisticated insight into the various noncovalent interactions and their mutual interplay is needed. An estimate of the importance of the individual hydrogen bonds and of cooperative effects can be obtained by comparing the dissociation energies of **3a**, **3b**, **4**, **5**, and **6**. Within this series, compound **3b** possesses the same hydrogen-bond pattern as **1** and the same kind of charge interactions. Therefore, its dissociation energies in gas phase (+443 kJ/mol) and polar solvent (+111 kJ/mol) are more or less identical to those of **1**.

As mentioned before all the other “knock-out” analogues, **3a–6** have a different H-binding pattern and all lead to a drastically reduced stability of the dimers compared to **1** (and **3b**). But even though their number of formal H bonds is identical, their stabilities differ significantly. This is most likely due to the different nature of the H bonds and additional secondary electrostatic effects. For example, in dimers **3a** and **4**, each carboxylate is bound by one neutral H bond (from the pyrrole NH) and one ionic H bond (from the amidinium or guanidinium moiety, respectively), whereas in dimers **5** and **6**, both H bonds are ionic. Furthermore, dimer **3a** exhibits bidentated hydrogen bonds to the inner carboxylate oxygen and the outer oxygen is not bound at all, whereas in dimers **4–6** both oxygens are hydrogen bonded.

Let us first compare dimers **3a** and **4**. In the gas phase, the dissociation energy of **4** is 29 kJ/mol higher than the dissociation energy of **3**. Binding of both oxygens by one H bond each is obviously more efficient than two H bonds to the same oxygen atom. However, for a polar solvent this trend is reversed. Upon

solvation the stability of dimer **4** drops to 13% of the gas-phase value, whereas the one of **3a** decreases to about 17%. As a consequence, in a polar environment dimer **3a** is predicted to possess a higher dissociation energy than dimer **4** (+64 vs +55 kJ/mol). This reflects the stronger impact of solvation on the solvent-exposed hydrogen bond (bond 1), which is present in dimer **4** but not **3a**. This effect could already be seen in the variation of the bond distances of the parent zwitterion **1** (Table 1). For **3a** and **4**, additional C–H \cdots O $^-$ C interactions have to be considered. On the basis of computations for CH₄ \cdots Cl (~10 kJ/mol),⁴⁷ we estimate these effects to about 10 kJ/mol for the gas phase and about 2–3 kJ/mol in a polar solvent.^{48,49} Higher values than for CH₄ \cdots Cl could be assumed since the neighbored guanidinium group increases the acidity of the CH₃ or CH₂ group. A smaller value could be estimated since the charge of the carboxylate group is smeared over the whole unit. This effect will be enhanced by the interactions between the guanidinium group and the carboxylate group. In all respect the C–H \cdots O $^-$ C interactions can be considered to be much smaller than the effects discussed above.

Surprisingly, for gas phase the calculations for the cyclopentadienyl derivative **5** predict a dissociation energy of +364 kJ/mol, which is equal to the amidine derivative **4**. One would expect a higher dissociation energy for **5** than for **4** since the H-bond pattern of **5** contains two ionic H bonds instead of one neutral and one ionic one for **4**, and furthermore, the binding motif of **5** allows attractive secondary interactions. Additionally, **5** could be stabilized by an attractive interaction between the CH₂ group of the cyclopentadienyl unit and the carboxylate group. Obviously, this possible advantage is probably canceled out to some extent by other factors. One possibility could be geometric strain in **5**. Additionally the C–H \cdots O $^-$ C interactions could be decreased since the charge of the carboxylate group is smeared out as discussed for **4**. For a polar environment, **5** (decreased to 16% of the dissociation energy in gas phase) becomes more stable than knock-out analogues **4** and **6** as expected for its binding motif with two ionic H bonds and no further destabilizing secondary interactions. “Knock-out” analogue **3a** has a similar stability in water as **5**, despite its less efficient binding motif. This again probably reflects the fact that the influence of the solvent on the stability of the various H bonds depends on their accessibility.

The furan derivative **6** exhibits the same H-bond pattern with two ionic H bonds as the cyclopentadienyl derivative **5** and could have been expected to be equally stable. However, although the outer hydrogen bond is even shorter than in **5**, repulsive secondary electrostatic effects connected with oxygen lone pairs of the furan oxygen and the bound carboxylate reduces the dissociation energies about 19 kJ/mol in the gas phase and 13 kJ/mol in a polar solvent, respectively. This repulsive interaction, which is also nicely reflected from the electrostatic potentials of **6** (Charts 3 and 4), makes dimer **6** even slightly less stable than the neutral analogue **2**.

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(48) The decrease assumes that the CH₄ \cdots Cl interaction similarly behaves upon solvation than all other effects.

(49) The major contribution to ΔS is the changes in translation and rotation resulting from the formation of one single dimer from two independent monomers. This part of ΔS , however, is not influenced by the solvent. Its effect on the already smaller absolute dissociation energies in solvent is therefore more pronounced.

The discussion so far was restricted to the mere electronic dissociation energies to analyze the intrinsic stabilities of the various binding motifs. Thermodynamic contributions leading from dissociation energies to the corresponding enthalpies and free energies considerably reduce the stability of all dimers (Table 3) with respect to their monomers. In the gas phase, the reduction is about 25%. For a polar solvent the relative importance of the corrections is considerably stronger due to smaller absolute dissociation energies.⁴⁹ As shown in Table 3 within a polar solvent the absolute values of the $T\Delta S$ term vary between 50 and 66 kJ/mol. The variations in ΔS among the series arrive mainly from the contributions of vibration (ΔS_{vib}), while the corrections due to translation and rotation are very similar (see Supporting Information). One could expect that the variations mainly correlate with the magnitude of the binding interaction between the monomers since as a result of this binding various low-lying bending vibrations of the monomers are hindered considerably. However, such a correlation is not found as most prominently shown by a comparison between **1** and **3b**. The dissociation energies of both compounds are very similar, but their $T\Delta S$ terms differ by 11 kJ/mol (~20%). This may result from the rigidity of the molecules studied here. The size of $T\Delta S$ is therefore probably determined by the reorganization of the whole electronic structure upon dimerization. The sum of the resulting subtle changes in all monomer bonds leading to various slight changes in many vibrations then determines the changes in ΔS_{vib} . It is important to note that even the thermodynamic corrections change the trend in the predicted stabilities to some small extent. However, considering the theoretical approximations, differences smaller than 5 kJ/mol are too small for sound predictions.

On the basis of the computed ΔG values, we see that besides **1** and **3b** only dimer **5** is expected to form stable dimers in water. For all other analogues the dimerization in water is endergonic. And even for dimer **5** the dissociation free energy is rather small ($\Delta G = +13$ kJ/mol for a hypothetical infinite dilute solution), probably not allowing its experimental detection due to the salt effect mentioned above, which will further decrease the stability in macroscopic samples. Apart from the fact that **5** due to its tautomeric instability can never be studied experimentally.

Conclusions

In the present study, we investigate the molecular interactions in 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate by comput-

ing various “knock-out” analogues in which single hydrogen bonds are switched off. The influence of a polar solvent is also tested. Our computations clearly show that simple models fail to predict the stability of the knock-out analogues.

Our analysis of the “knock-out” analogues indicates that the following interactions seem to be important: (a) charge interactions within ionic hydrogen binding networks are significantly more stable than simple point charge interactions, (b) additional neutral H bonds further stabilize the dimer but less efficiently than the ionic ones, (c) solvation affects H bonds differently depending on their accessibility, and (d) secondary electrostatic interactions further modulate the stability.

The comparison of 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate dimer with the arginine dimer in the gas phase revealed a final important effect: The zwitterionic monomer of 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate has a considerably higher energy content than the zwitterionic form of arginine. The strong stabilization of the latter arises from the interaction of the charged ends, which is prevented in 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate due to its stiffness. Transferring this knowledge to the situation in a polar medium the high stability of the 5-(guanidiniocarbonyl)-1*H*-pyrrole-2-carboxylate dimer (e.g., in comparison to arginine) seems to result also from the monomers, which are less stabilized. This finding suggests a new approach for the optimization of supramolecular self-assembly. To have a strong dimerization affinity, the monomers should be as rich in energy as possible, i.e., this principle does not only focus on the number and strengths of the bonds in the dimers but tries to enforce this effect by thermodynamically high lying monomers.

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Supporting Information Available: Detailed energy tables and geometries for structures **1–6**, electrostatic potentials of the monomers in gas phase and solvent, as well as a full author list for refs 18 and 27. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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