C−H···O Interactions as Isofunctional Replacements for N−H···O Interactions − Dimer Formation of Methyl 5-Amidopyrrole-2-carboxylates in the Solid State

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Dedicated to Prof. F.-G. Klärner on the occasion of his 60th birthday

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In the solid state, the chloride salt of methyl 5-amidopyridinium-pyrrole-2-carboxylate (**2**) forms discrete dimers held together by two rather long N–H···O hydrogen bonds in combination with two short C–H···O interactions between the pyridinium C3–H and the ester CO. Structural and thermodynamic evidence is presented which demonstrates that the observed C–H···O hydrogen bonds are indeed important for bonding in these dimers. A comparison with the solid-state structure of the chloride salt of 5-(guanidiniocarbonyl)pyrrole-2-carboxylic acid (**3**), which forms similar dimers to **2**, reveals that the binding geometries for the two C–H···O contacts in **2·2** are identical to those of two N^+–H···O hydrogen bonds in **3·3**. According to theoretical calculations the energy associated with these two C–H···O interactions is also similar to that of the two N^+–H···O hydrogen bonds as both dimers **2·2** and **3·3** have nearly the same calculated interaction energies. Dimer **3·3** is predicted to be only slightly more stable than **2·2**. These data demonstrate that C–H···O interactions can serve as full isofunctional replacements for more conventional N–H···O hydrogen bonds in supramolecular arrangements.

Introduction

Molecular recognition and especially self-assembly can lead to the formation of highly complex and fascinating structures both in solution and in the solid state.[1−3] The search for novel building blocks that self-assemble into well-defined structures is of great importance not only to gain an understanding of the concepts and principles that govern these processes, but also for the design of new molecular materials with tailor-made properties.[4−9] Due to their strength (at least in the solid state) and directionality hydrogen bonds have been extensively used to control the supramolecular structure of solids, giving rise, for example, to linear ribbons, planar networks, or helical structures.[3,10−12] In the last few years it has been more and more recognized that besides conventional N−H···O and O−H···O hydrogen bonds, C−H···O interactions can also play an important role in determining molecular structures. The idea of such C−H···O interactions is rather old,[13] but only recently has their existence and importance as a weak, but forceful, secondary interaction been widely accepted.[14−17] However, the systematic study of their properties has only just begun. This is particularly true for their deliberate use in the field of supramolecular chemistry to direct and control molecular arrangements.[18] In this context, C−H···O interactions are interesting as they can act as a less-polar replacement of more conventional N−H···O interactions. A better understanding of such isofunctional replacements could lead to the development of a whole new class of self-assembling compounds with new exciting properties.[19,20] Herein, we present the crystal structure and a discussion of the binding interactions of self-assembled dimers of the chloride salt of methyl 5-(amidopyridininium)pyrrole-2-carboxylate **2**, in which, compared to the previously reported dimers of the chloride salt of 5-(guanidiniocarbonyl)pyrrole-2-carboxylic acid **3**,[21] two C−H···O bonds are isofunctionally replacing two N−H···O hydrogen bonds.

Results and Discussion

The synthesis of the chloride salt **2·Cl** is outlined in Scheme 1. 5-(Methoxycarbonyl)-1*H*-pyrrole-2-carboxylic acid (**1**)[22] was converted into its acyl chloride with oxalyl chloride in the presence of catalytic amounts of DMF and subsequently coupled with 2-amino-6-methyl pyridine in THF.

Structural Description

The crystal structure of the chloride salt of the methyl ester **2** (recrystallized from water) shows the formation of discrete, completely planar hydrogen-bonded dimers (Figure 1).[23] The two monomers are held together by two rather long N−H···O hydrogen bonds between the pyrrole NH of one molecule and the amide O of the other (N···O distance 3.166 Å). However, in addition to these two conventional hydrogen bonds there are also two C−H···O interactions between the pyridinium C3−H and the carboxyl

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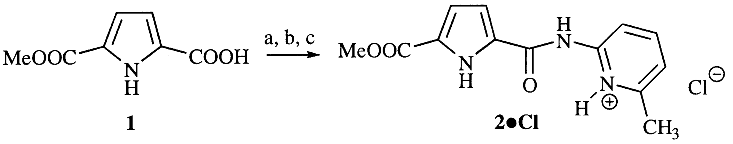


Scheme 1. Reagents and conditions: (a) oxalyl chloride, DMF (cat.), CH_2Cl_2, 40 °C; (b) 2-amino-6-methyl pyridine (2 equiv.), NEt_3, THF, room temp., overnight; (c) HCl, 65% over all steps

CO with a C···O distance of 2.946 Å, a C−H···O distance of 2.215 Å and a C−H−O angle of 135.5°.

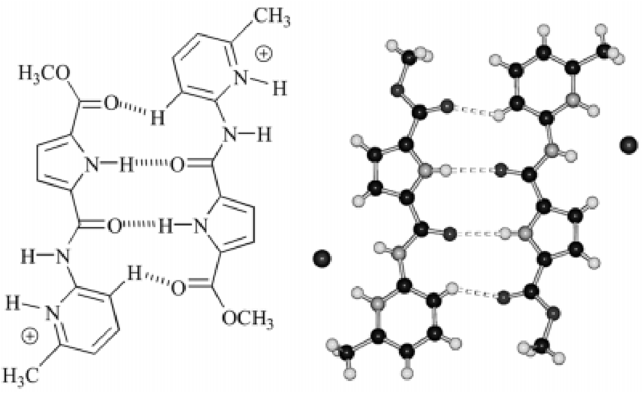


Figure 1. Schematic representation (left) and crystal structure (right) of dimer **2·2** (as the chloride salt)

Normally, C−H···O interactions are found between polarized CH groups, such as acceptor substituted acetylenes, the C2−H in imidazolium cations or the C^{α}−H in amino acids. The C···O separations are typically ≥3 Å and the C−H···O distances for strong interactions around 2.3 Å. The binding energies are thought to be ≤2−3 kcal/mol.[14,15,24] Therefore, the C−H···O interaction found in **2·2** with a C···O distance of 2.946 Å is quite short.[25] The bond angle of 135.5° is rather small as short C−H···O bonds tend to be more linear, with C−H−O angles around 160−150°. Although C−H···O bonds are geometrically more flexible than conventional hydrogen bonds, their directionality typically becomes softer only at longer H···O distances.[15] However, this bond angle is still within the limits found for strong interactions. A more linear bond in **2·2** is probably not possible due to geometric constraints resulting from the crystal packing arrangement.

Within the crystal, the dimers **2·2** are arranged in two dimensional planar layers with no specific interaction between the individual planes. Of interest is the binding situation of the chloride anions. They are embedded within the layers and are hydrogen bonded by the pyridinium NH, the amide NH and the pyrrole C4−H of one molecule (see Figure 1) and the pyridinium C5−H of another (see Figure 2). Hence, each anion binding site is composed of two N−H···Cl and two C−H···Cl hydrogen bonds. These latter interactions have C···Cl distances of 3.715 and 3.580 Å, respectively.

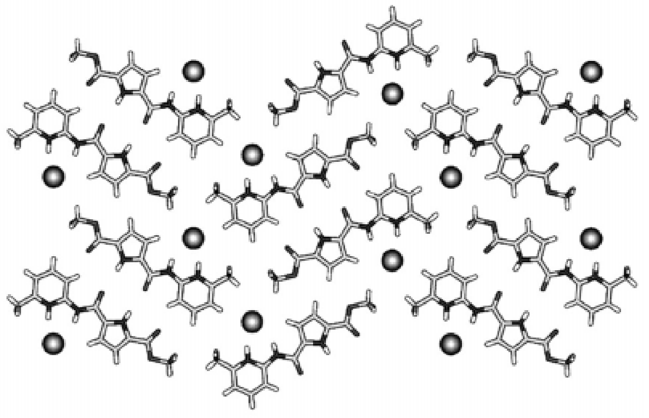
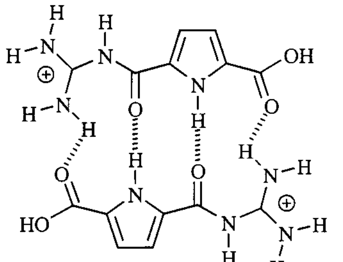


Figure 2. Packing diagram of **2·Cl** in the solid state

Interestingly, the structure of the dimer **2·2** is remarkably similar to the X-ray structure of the chloride salt of guanidiniocarbonyl pyrrole acid (**3**) described previously (Figure 3).[21] In both dimers each molecule forms hydrogen bonds through the carboxyl CO, the pyrrole NH, the amide CO and an additional hydrogen bond donor site X−H in the amide moiety: the guanidinium NH in **3** and the pyridinium C3−H in **2**, respectively. In both dimers the four intermolecular contacts have nearly identical distances within ±0.03 Å (see Figure 3). The chloride anions are also bonded in a similar manner.



3·3

	2•2	3•3
pyrNH---O	2.313	2.345
angle	174.5	173.3
X-H---O	2.215	2.236
angle	135.5	125.4

Figure 3. Schematic representation and selected hydrogen bond distances (Å) and angles (deg) for dimer **3·3** relative to dimer **2·2**

As the two inner N−H···O hydrogen bonds are rather long in both dimers (N···O distances >3 Å), it seems reasonable that the two outer hydrogen bonds also play an important role in the structure determination. This is not surprising in the case of compound **3**, as a cationic NH^+ group is an even better hydrogen bonding donor than a neutral one. However, the structure of dimer **2·2** shows that even a C−H···O hydrogen bond seems to be at least as

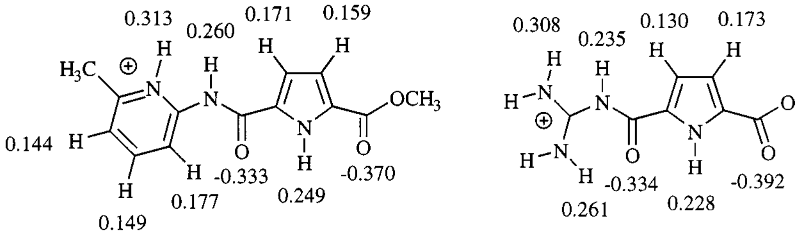


Figure 4. Calculated charge distribution in the dimers **2·2** and **3·3** (AM1) (only one monomer of each dimer is shown)

strong and can isofunctionally replace the guanidinium N−H···O hydrogen bond in **3·3**. Hence, the C−H···O bond is not just an unimportant bystander in **2·2** but probably an important structure-determining interaction.[26]

Computational Evaluation of Binding Interactions

Unfortunately, neither **2** nor **3** show self-assembly in solution. Being charged salts, both compounds are insoluble in nonpolar organic solvents such as dichloromethane. In more polar solvents, however, the bonding in the dimers is disrupted by competing solvation of the donor and acceptor sites by the solvent and, consequently, no signs of any intermolecular association can be seen in the NMR spectrum, for example. We therefore turned to theoretical calculations to gain further insight into the importance of the various binding interactions present in **2·2** and **3·3**.

The charge distributions calculated with semiempirical methods (Figure 4) are very similar for both compounds and clearly show that, indeed, in **2** the C3−H of the pyridinium ring carries the largest positive charge of all the CHs in the molecule (+0.177), therefore making it especially suitable for C−H···O interactions, although it is not as highly charged as the guanidinium NH in **3** (+0.261). As can be seen from this charge distribution, the "back sides" of **2** and **3** are composed of only positively charged NHs or CHs and are therefore ideally suited for the anion binding, whereas the "front sides" form very similar alternating patterns of donor (NH and CH) and acceptor sites (CO) as needed for dimerization.

It has been pointed out that due to secondary interactions between the donor and acceptor sites an alternating hydrogen bonding pattern ADAD/DADA should, in general, be less stable than hydrogen bonding motifs with AAAA/DDDD interactions.[27] This prediction has been experimentally verified for various self-assembling neutral heteroaromatic molecules in chloroform.[28] However, in the case of the dimers **2·2** and **3·3**, such destabilizing secondary interactions are less important as both monomers are charged species and hence possess significant molecular dipoles which align in a favourable way in the observed complex.[29] The associated large stabilizing dipole−dipole interaction is independent from the arrangement of donor and acceptor sites in the hydrogen bonding motif and probably also stabilizes the dimeric structure to a significant extent.[30]

To establish the contributions of the C−H···O hydrogen bonds to the binding energy in dimer **2·2** with respect to the N^+−H···O hydrogen bonds in dimer **3·3**, a series of single-point energy calculations were performed. Interaction energies resulting from the four X−H···O contacts within the dimers were computed as the difference in energy between the dimer, on the one hand, and the sum of two isolated monomers, on the other hand.[31] As input geometries the atomic coordinates from the crystal structures were used. According to AM1 calculations the interaction energies within the dimers are −6.1 kcal·mol^{-1} for **2·2** and −11.8 kcal·mol^{-1} for **3·3**, which are, taking the error margin of such calculations into account, very close to each other. PM3 calculations give slightly smaller but still similar energies of −0.3 and −4.6 kcal·mol^{-1}, respectively. This means that dimer **3·3** with its two N^+−H···O hydrogen bonds is only slightly more stable than dimer **2·2** with its two C−H···O hydrogen bonds! To confirm this unexpected findings, we also performed a preliminary ab initio calculation using the 6−31*+ basis set. Again, the calculated interaction energies are very close to each other: −7.2 kcal·mol^{-1} for **2·2** and −13.8 kcal·mol^{-1} for **3·3**.

Although the computed interaction energies are very similar, it is not trivial to establish the relative contributions of individual interactions to the overall binding process. As the two inner N−H···O bonds are more or less identical in **2·2** and **3·3** as far as charge distribution, bonding geometry or chemical microenvironment is concerned (Figure 3 and 4), it seems reasonable to assume that they also provide the same binding energy in both dimers. As the overall calculated binding energy for **3·3** is only slightly larger than for **2·2**, this means that the energetical contribution from the two C−H···O interactions in **2·2** is only slightly smaller than that of the two outer N^+−H···O interactions in **3·3**. This is in good agreement with the slightly smaller electrostatic charge of the CH in **2** relative to the NH in **3**. Hence, the C−H···O bond in **2·2** is indeed isofunctionally replacing the N−H···O in **3·3**. Not only are the binding geometries the same but the binding energies are also very similar.

Conclusion

We have presented here structural and thermodynamic evidence to demonstrate that within self-assembled dimers of 5-amidopyrrole-2-carboxylates, C−H···O hydrogen bonds can serve as full isofunctional replacements for more traditional N−H···O bonds. The comparison of two X-ray structures revealed the ability of C−H···O contacts to control supramolecular arrangements in the same way as N−H···O bonds. Semiempirical and ab initio calculations showed that the binding energy associated with these C−H···O bonds is only slightly smaller than for the system with the N^+−H···O bonds. These findings might open the way to a more deliberate use of such unconventional binding interactions for the design of supramolecular arrangements.

Experimental Section

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

2-[2-Carbonyl-5-(methoxycarbonyl)-1*H*-pyrrole]amino-6-methyl Pyridinium Chloride (2·Cl): Compound **1** (676 mg, 4 mmol) was suspended in dry CH_2Cl_2 (20 mL). Dry DMF (3 drops) and oxalyl chloride (1102 mg, 8 mmol, 2 equiv.) were then added and the reaction mixture was refluxed for 4 h. After removal of the solvent under reduced pressure, the acyl chloride was dissolved in THF (20 mL) and slowly added to a solution of 2-amino-6-methyl pyridine (864 mg, 8 mmol) and triethylamine (3 mL, 22 mmol) in THF (20 mL). After stirring the suspension overnight, the solvents were removed under vacuum and the resulting residue taken up in water (10 mL). The pH was adjusted to 8 with $NaHCO_3$ and the resulting brown precipitate was extracted into ether (20 mL). The ether phase was reextracted with dilute hydrochloric acid (20 mL, 5%) and, after removal of the water, the crude hydrochloride salt was obtained, which was recrystallized from water to yield a pink solid (767 mg, 65%). − ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.51$ (s, 3 H, pyridine Me), 3.82 (s, 3 H, ester Me), 6.88 (d, 1 H, pyrrole CH), 7.16 (d, 1 H, pyrrole CH), 7.19 (d, 1 H, pyridine CH), 7.93 (t, 1 H, pyridine CH), 8.14 (d, 1 H, pyridine CH), 11.35 (s, 1 H, amide NH), 12.73 (s, 1 H, pyrrole NH). The pyridinium NH gives a very broad signal around $\delta = 6.5$, probably due to fast exchange with traces of water in the solvent. − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 22.1$ (CH_3), 51.9 (CH_3), 112.4, 115.3, 115.5, 119.8, 138.7 (all CH), 126.4, 129.7, 150.0, 154.4, 158.3, 160.5 (all quat. C). − $C_{13}H_{13}N_3O_3 \cdot HCl$ (295.07): calcd. C 52.87, H 4.78, N 14.24; found C 52.68, H 4.80, N 14.16.

Molecular Modelling: All calculations described in this paper were performed on an SGI O_2 workstation with the software packages Cerius^2 V. 4.0 (Molecular Simulations, Inc., San Diego, CA, 1999) for semiempirical AM1 and PM3 calculations and Jaguar V3.5 (Schrödinger, Inc., Portland, OR, 1998) for ab initio calculations. All calculations were done as single-point energy calculations using the atomic coordinates obtained from the X-ray structure determination for dimers **2·2** and **3·3**, including the chloride anions. The corresponding monomer data were obtained by deleting one of the two molecules in the dimer structures.

X-ray Crystallographic Study of 2·Cl: Nonius KappaCCD diffractometer (20 °C), Mo-K_α radiation, $2\Theta_{max} = 56°$; structure determination by direct methods (SHELXS-97, SHELXL-97). $C_{13}H_{14}ClN_3O_3$, monoclinic, space group $C2/c$, $a = 13.581(1)$, $b = 31.129(1)$, $c = 6.952(1)$ Å, $\beta = 109.35(1)$, $V = 2773.0(5)$ Å^3, $Z = 8$, $\rho_{calcd.} = 1.417$ g cm^{-3}, $\mu = 0.286$ mm^{-1}, 2575 data measured, $R_1 = 0.0580$, $R_w = 0.1064$ [based on refinement of 1798 observed reflections with $I > 2\sigma(I)$ and 238 variable parameters]. The final difference density was less than 0.209 eÅ^{-3}.

Acknowledgments

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