Charge-Separated Modified Nucleobases. On π-Interactions and Hydrogen Bonding of Self-Complementary Cationic and Betainic Uracils

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Depending on the conditions, reaction of 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** with heteroaromatics such as 4-(dimethylamino)pyridine, 4-(pyrrolidin-1-yl)pyridine, pyridine, and 1-methylimidazole, respectively, results in the formation of uracil-6-ylhetarenium salts or cross-conjugated uracilylbetaines, the intramolecular interactions of which are examined. In addition, **1** forms uncharged 1:1 π-stacks with DMAP and PPY, the electronic properties of which are inverted in relation to natural nucleobase−heteroaromatic systems. The geometry of the π-complexes is governed by steric effects as well as by the frontier orbitals of the uracil and the heteroaromatic, whereas the dipole moments are almost completey uncoupled. ^{1}H NMR experiments in DMSO-d_6 at room temperature as well as ESI- and MALDIMS prove *homo*-intramolecular hydrogen bonding of the uracilylhetarenium salts and the uracilylbetaines, respectively. An X-ray single-crystal analysis shows the uracilylbetaine **7** associated with a second molecule via two strong hydrogen bonds, thus forming a centrosymmetric dimer. In contrast to the Watson−Crick pairing mode of natural pyrimidine nucleobases, O(2) and N(3)-H of the uracilylbetaines are involved in hydrogen bonding. This geometry of the dimer **7**=**7** gives rise to a coupling of the semiempirically calculated dipole moments of the monomeric cross-conjugated betaines.

Introduction

Hydrogen bonding, Coulombic and hydrophobic interactions, π-stacking, and metal complexations have been recognized and studied as the main noncovalent forces modulating binding energies that enable molecular recognition in a broad variety of biological systems.[1] In particular, the study of modified nucleobases and related model compounds has become a major challenge in modern bioorganic chemistry because its central goal is a better understanding of degenerative diseases[2] at a molecular level and, as a consequence, gaining new perspectives of drug design.[3] In this context, the presence of charged nucleobases forming mispairs has been discussed[4] and documented by means of X-ray crystallography.[5]

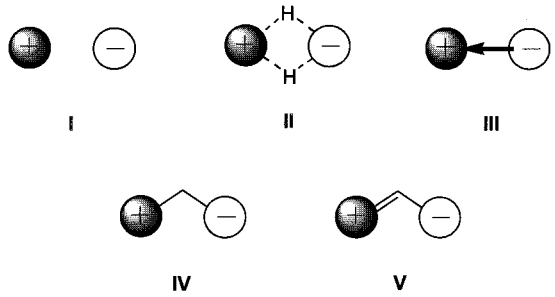

Figure 1. Simplified categorization of charge-separation in organic molecules: individual cations and anions (**I**) and intermolecular interactions in organic salts such as hydrogen bonds (**II**) and CT-interactions (**III**). σ-Bonds joining cations and anions give zwitterions (**IV**), additional π-bonds result in mesomeric betaines (**V**).

Intermolecular forces between cations and anions of a salt **I** (Figure 1) are usually classified in two categories, i.e., nonsaturable directional, induction, and dispersion forces on one hand and hydrogen bonding (**II**) and the

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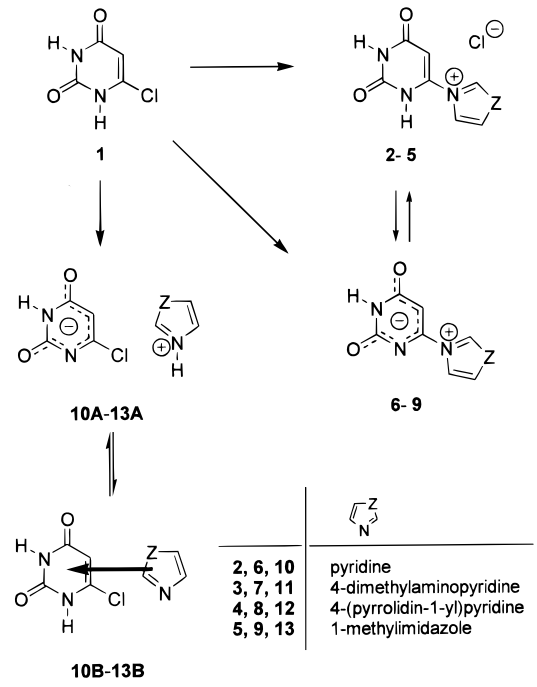
forces of charge transfer or electron pair donor−acceptor forces on the other (**III**).[6] Ion pairs of type **III** have been intensively studied in order to provide insights into the specifity of coenzyme−apoenzyme binding of nicotinamide and proteins[7] or the mutual recognition between proteins and nucleic acids.[8] Zwitterions **IV**, found in a broad variety of biologically interesting molecules such as alkaloids,[9] possess σ-bonds between cationic and anionic parts of molecules. Additional π-bonds between the charged structure elements form mesomeric betaines **V**, the degree of charge separation of which depend on the type of conjugation. Among the four distinct classes of mesomeric betaines,[10] cross-conjugated mesomeric betaines form a class of highly dipolar entities. A stimulus for our work on intermolecular interactions of mesomeric betaines was the conjugated mesomeric betaine 7-methylguanosine (m^7G) that forms the 5′-cap of m-RNA, facilitating the binding of the m-RNA to the ribosom prior to the initiation of translation.[11] The reasons for Nature's selection of a mesomeric betaine at this position remain unclear to date.[10] As a matter of fact, in addition to its biological role in protein biosynthesis, m^7G and its model compounds exhibit several interesting properties, among these self-complementarity at physiological pH[12] and mutagenicity because of induction of base mispairing.[13] Furthermore, m^7G is the main metabolite of the methylation of DNA by carcinogens.[14]

We were interested in model systems that may yield information about the nature of charged or betainic nucleobase−nucleobase or nucleobase−heteroaromatic interactions. This publication describes our surprising results concerning with model systems that combine the electrostatic properties of the categories **I**−**V** (Figure 1) with cationic structure elements of pyridinium coenzymes (NAD^+, $NADPH^+$) and the nucleobase uracil.

We chose the 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** and several heteroaromatics as starting materials (Scheme 1). Depending on the reaction conditions used, cationic (**2**−**5**) or betainic (**6**−**9**) pyrimidine nucleobase derivatives as well as equilibria between salts (**10A**−**13A**) or π-complexes were formed (**10B**−**13B**). Moreover, all forms differ in their arrangements of hydrogen bond donor and acceptor groups, frontier orbital profiles, dipole moments, and basicities. In contrast to the naturally occurring 7-methylguanosine, the dipoles **6**−**9** are members of the class of cross-conjugated mesomeric betaines (CCMB), the positive and negative charges of which are restricted to separate parts of the common π electron system.

Scheme 1



Results and Discussion

Syntheses and Spectrocopic Features of the Cations 2−5 and the Betaines 6−9. Whereas all reported procedures for the synthesis of conjugated hetarenium compounds such as Ortoleva−King-type reactions,[15] in situ anion exchange to the nonnucleophilic tetraphenylborate,[16] modified Finkelstein-type reaction conditions[17] and interception of the leaving group as chlorotrimethylsilane with TMSOTf[18] failed, the nonpolar chlorobenzene (E^T_N = 0.188) was found to be the most suited solvent for the noncatalyzed substitution on 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** by heteroaromatics such as pyridine, 4-(dimethylamino)pyridine (DMAP), 4-(pyrrolidin-1-yl)pyridine (PPY), and 1-methylimidazole (NMI). This finding contrasts to the expectation that polar solvents should accelerate dipolar transition-state reactions which involve considerable charge-separation in the activation step.[6,19] The chlorine displacements, however, proceeds in fair to very good yields to form beige precipitates from which the uracilylhetarenium chlorides **2**−**5** were isolated by recrystallization from water.

Treatment of aqueous solutions of the salts **2**−**5** with Amberlite IRA-400 in its hydroxy form results in the

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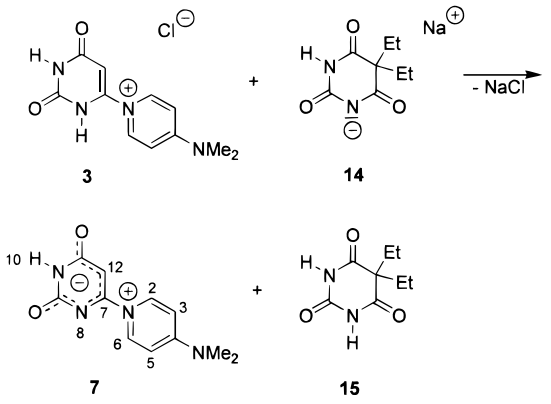
Scheme 2



formation of the mesomeric betaines **6**−**9** in nearly quantitative yield. Alternatively, the cations **2**−**5** can be deprotonated by titration with bases such as sodium 5,5-diethyl-2,4,6-pyrimidinetrionate **14** in ethyl acetate that forms the crystalline 5,5-diethylpyrimidin-2,4,6-trione **15** on protonation[20] (Scheme 2). The titration can well be monitored by ^{1}H NMR spectroscopy, as the signals of 2-H/6-H, 10-H, and 12-H shift characteristically upon betaine formation. As indicated by the NMR titration (Figure 2), no additional deprotonation of the N(10)−H group by **14** forming an anionic species occurs,[21] because even in large excess of the base no additional chemical shift changes of the betaines can be observed.

Remarkably, in contrast to the uracilyl hetarenium salts **2**−**5**, the 12-H protons of the uracil moieties of the mesomeric betaines **6**−**9** and the C-2 of the imidazolium ring of **9** show a coupling constant of $J = 1.3$ Hz, and the α protons of the pyridinium rings split into a dublet of dublets. A HH-COSY-NMR experiment unambiguously proves a coupling of 12-H and 2-H of the imidazolium ring, thus indicating the expected essentially planar conformation in which either proton have a very short distance. This is a result of the charge-separation in the ground state of the cross-conjugated mesomeric betaines, compelling the systems into a conformation with optimal *p* overlap between positive and negative portions of the molecules. From the ^{1}H NMR spectra it is moreover apparent, that the alternative planar conformation of **9** is much less populated in a DMSO-d_6 solution at room temperature, because a coupling of 12-H and 5-H of the imidazolium ring cannot be observed. The structure of the mesomeric betaine **7** was established by X-ray crystallography (vide infra).

Hydrogen Bonding of the Cation 3 and the Betaine 7. As hydrogen bonding is known to be mainly electrostatic in character[22] and of fundamental, functional importance in biological systems, we were interested in studying *homo*-intermolecular associations of the cationic uracils and the highly dipolar mesomeric uracilylbetaines in comparison with the natural nucleobase uracil. We therefore subjected the cation **3** and the betaine **7** to study in DMSO-d_6 solutions in which π-stacking interactions are nil. Due to its proton acceptor capabilities,

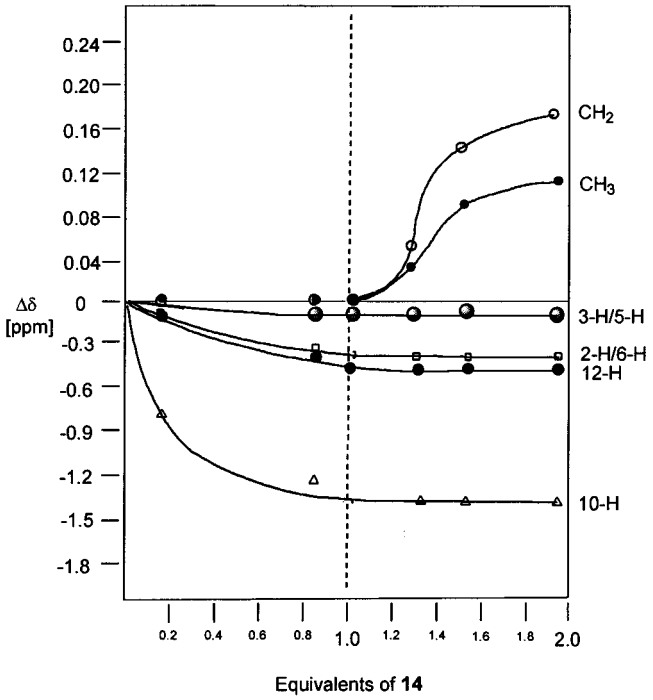


Figure 2. NMR titration of uracil-6-yl hetarenium salt **3** with sodium 5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrionate **14**. For numbering, see Scheme 2.

hydrogen bonding in DMSO is known to be far more similar to interactions in water than in chloroform;[23] however, the latter mentioned solvent offers less competition for hydrogen bond acceptance.[24] Characteristic for the formation of hydrogen bonds, the ^{1}H NMR shifts of the cations **2**−**5** and of the betaines **6**−**9** exhibit a strong concentration dependence. As depicted in Figure 3, dilution of a 2.0 ± 0.25 mM solution of the cationic uracil **3** and a concentrated (5.0 ± 0.25 mM) solution of the betainic uracil **7** in DMSO-d_6 at room temperature, respectively, results in significant upfield shifts of the resonance frequencies, thus proving horizontal interactions between the molecules. The unsubstituted N(8)-H group of the cation **3** gives rise to the formation of higher aggregates, the formation of which is indeed confirmed spectroscopically by deviations from linearity at concentrations >12.0 ± 0.25 mM in DMSO-d_6 at room temperature.[23] In total agreement to this observation, ESI mass spectrometry (which usually reflects conditions in solution or in the gas phase) proves the formation of trimers (vide infra). The ^{1}H NMR resonance frequencies of the associated and of the "monomeric" species **3** and **7** are compared in Table 1.

To determine the structure of the associates in the solid state, we tried to crystallize the sparcely soluble uracil derivatives. Single crystals were obtained by slow evaporation of a concentrated solution of the cross-conjugated mesomeric betaine **7** in aqueous HCl. Very surprisingly, no protonation to the cation **3** occurred under these conditions. As a confirmation of the NMR dilution experiments, the X-ray analysis[25] shows the nonplanar betaine

(20) $pK_{a'1}$, $pK_{a'2}$, $pK_{a'3}$ of the conjugate acid: 1.11/7.859/12.74

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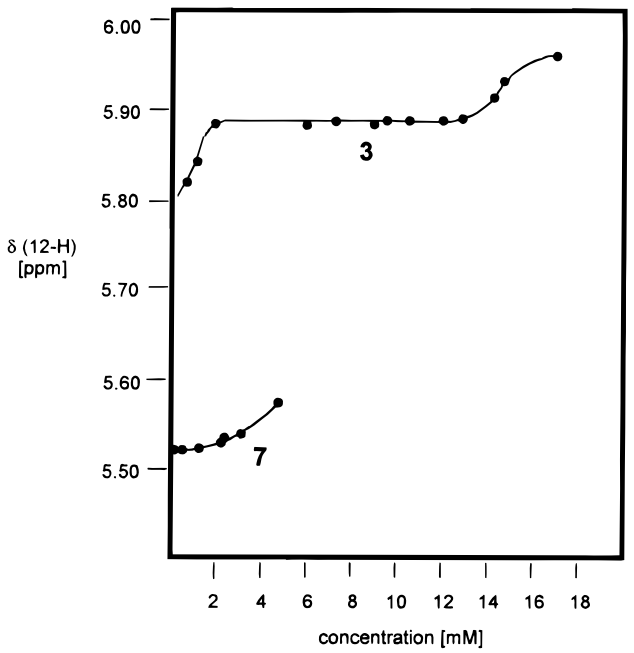

Figure 3. Concentration dependence of the 12-H ^{1}H NMR chemical shifts for the uracilylhetarenium salt **3** and the uracilylbetaine **7** in DMSO-d_6 at 25 °C. The curve of **7** ends at its maximum concentration.

Table 1. ^{1}H NMR Resonance Frequencies of Associated and Monomeric Cation 3 and Betaine 6 in DMSO-d_6 and D_2O at 300 MHz and 25 °C, Respectively[a]

	solvent	concn (mM)	5-H	N(3)-H	2-H/6-H	3-H/5-H	NMe_2
3	DMSO-d_6[b]	<0.9	5.822	10.836	8.550	7.129	3.287
		5.0 ± 0.25[d]	5.972	11.531	8.425	7.173	3.301
3	D_2O[c]	<1.2 ± 0.25	5.934	n.d.[e]	8.230	6.983	3.268
		>66.6[d]	5.883	n.d.	8.125	6.965	3.267
6	DMSO-d_6[b]	<0.3	5.523	9.718	8.795	7.059	3.270
		17.5 ± 0.25[d]	5.534	9.753	8.767	7.051	3.269
6	D_2O[c]	<1.2 ± 0.25	5.900	n.d.	8.275	6.968	3.261
		20.5 ± 0.25[d]	5.791	n.d.	8.244	6.916	3.242

[a] Errors of the NMR values: ±0.0015 ppm. [b] TMS (δ = 0.000 ppm) as internal standard. [c] H_2O (δ = 4.720 ppm) as internal standard. [d] Concentrated solutions; n.d. = not detectable due to deuterium exchange.

7 (Φ = 31°) forming two homo-intermolecular hydrogen bondings to a second molecule, although aqueous solutions are generally unsuited for the formation of hydrogen bonded associates.[23,24] The ORTEP plot of the dimer, which lies upon an inversion center (cf. Supporting Information), is shown in Figure 4. In contrast to the Watson−Crick mode that involves O4 of the pyrimidine nucleobases uracil and thymine, the uracilylbetaine **7** dimerizes through two strong hydrogen bonds between O2 and N3-H of the uracil moiety [spectroscopic numbering: N(8)−H; O(9)]. It is known that the hydrogen bonding acceptor capabilities of the oxygen atoms of pyrimidine bases is determined by their electronegativity, which is obviously inverted in converting the natural uracil into a mesomeric betaine.[5] The hydrogen bonding N(3)−H···O=C(2) forms an angle of 170(1)° and a very short bond distance of 281.87(12) pm [N3−H3 = 87(1) pm; H3···O2 = 196(1) pm; N3···O2 = 281.9(1) pm]. Typical geometrical characteristics of hydrogen bonds in base−base interactions are 177−157° (angles) and average distances of 295 pm.[5]

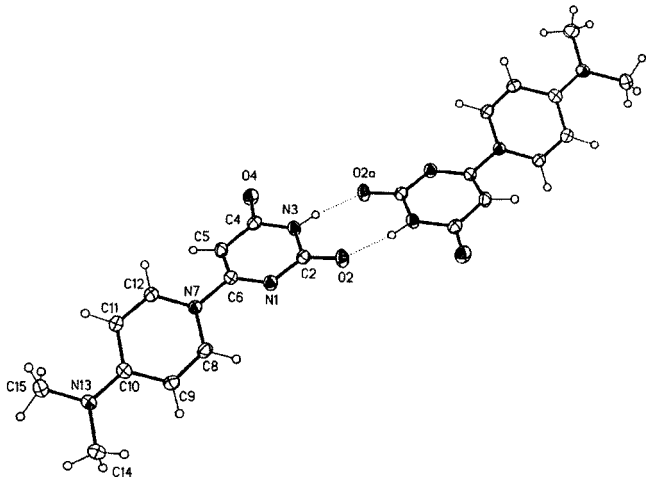

Figure 4. ORTEP-drawing of the hydrogen-bonded dimer of uracilylbetaine **7**. Crystallographic numbering.

It is apparent that the calculated[28] dipole moment of the uracilylbetaine **7** (μ = 16.962 D)[31] is by far larger than the dipole moments of known nucleobases, including the betainic RNA-nucleobase 7-methylguanine that we calculated to μ = 9.915 D.[32] It confirms the charge-separation by cross-conjugated positive and negative structure elements of the molecule. As a result of the centrosymmetric arrangement of the hydrogen bonded dimer the dipole moments of the individual molecules are exactly canceled (Figure 5). This observation contrasts to the known dimerization of nucleobases such as the reversed Hoogsteen homopurine base-pair of adenine.[33]

The dimer **7=7**, which is not detectable directly by mass spectrometry due to its net to charge zero, could be observed as sodium adduct [**7=7** + Na]$^+$ both by ESI[34]

(25) X-ray crystal structure analysis of the dimeric uracilylbetaine **7=7**: [$C_{11}H_{12}N_4O_2$], M = 232.25, monoclinic, space group $P2_1/c$ (no. 14), colorless crystals, dimensions 0.60 × 0.25 × 0.20 mm^3, a = 9.6108(5) Å, b = 7.1837(5) Å, c = 15.0309(8) Å, β = 92.474(4)°, V = 1036.78(11) Å^3, D_c = 1.488 Mg m^{-3}, Z = 4, μ(Mo Kα) = 0.107 mm^{-1}, T = 123(2) K, F(000) = 488, 11 883 reflections were collected on a Nonius KappaCCD diffractometer ($2\Theta_{max}$ = 56.6°, $-12 \le h \le 12$, $-9 \le k \le 9$, $-20 \le l \le 20$), 2434 symmetry independent reflections (R_{int} = 0.0302) were used for the structure solution (direct methods)[26] and refinement (full-matrix least-squares on F^2,[27] 160 parameters, 1 restraint), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density and refined using a riding model, H(0) free; wR2 = 0.0939 [R_1 = 0.0342 for 1796$I > 2\sigma(I)$]. An extinction correction was applied.

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(30) Stewart, J. J. P. *QCPE*, No. 455, Department of Chemistry, Bloomington, IN, 1989.
(31) Given is the total moment (Σ), the vectorial sum of the dipole moments on the *x*, *y*, and *z* axes [*x*, C(9)−N(8); *y*, perpendicular to *x* and *z* on C(9); *z*, perpendicular to the *xy*-plane]: 16.941 D, 0.430 D, −0.714 D, respectively.
(32) Given is the total moment (Σ), the vectorial sum of the dipole moments on the *x*, *y*, and *z* axes [*x*, N(1)−C(2) (purine ring numbering); *y*, perpendicular to *x* on N(1); *z*, perpendicular to the *xy*-plane]: 3.542 D, 8.462 D, −0.627 D, respectively. The optimization was verified by a FORCE-calculation; for options used, see ref 28.
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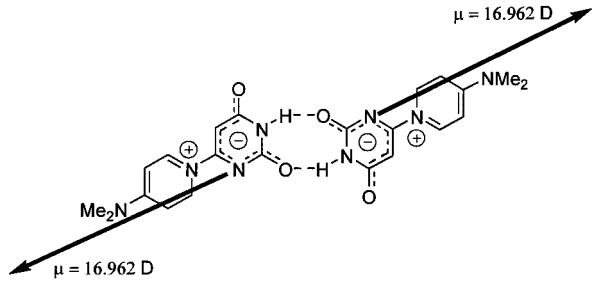
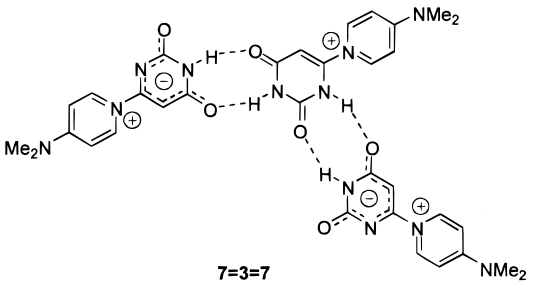


Figure 5. Coupling of the permanent dipole moments of the two individual uracilylbetaine molecules **7** in the hydrogen-bonded centrosymmetric dimer **7═7**. Arrows are the correct size and in the correct direction.

Scheme 3. Possible Structure of the Monocationic Trimer of Two Molecules of Uracilylbetaine 7 and One Molecule of Uracilyl Hetarenium Salt 3 Identified in ESI Mass Spectrometry



and MALDI[35] mass spectrometry. In addition, it was identified in a sample of the cation **3**. The monomeric cation **3** gives peaks at $m/z = 233.32$ under ESI conditions. The sodium adduct of the betaine $[\mathbf{7} + Na]^+$ can be identified by a peak at $m/z = 255.36$. Surprisingly, the dimer **7═7** can be identified as sodium adduct $[\mathbf{7{=}7} + Na]^+$ in both the ESI- and MALDI mass spectra ($m/z = 487.76$). In addition, they form semiprotonated species, detectable at $[\mathbf{7{=}3}]^+$ at $m/z = 465.71$. As noncovalent associates usually are not easily detectable by applying MALDI conditions, these results prove an extraordinary stability of the hydrogen-bonded dimers. As already proved by the NMR dilution experiments, higher aggregates of the cation **3** are identifiable in ESI mass spectrometry at $m/z = 697.272$, a trimeric, monocationic species $[\mathbf{7} + \mathbf{3} + \mathbf{7}]^+$. A plausible structure of this trimer is shown in Scheme 3. In analogy to the results of X-ray crystallography on the betaine **7**, one central molecule of uracil-6-ylhetarenium salt **3** forms two hydrogen bonds through O(2) and N(3)-H. A second betaine molecule **7** is bonded through two additional hydrogen bonds. The spectra give no hints at higher aggregates than trimers.

***π*-Interactions of the Cation 3 and the Betaine 7.** Stacking of protonated pyrimidine bases has not been observed to now, suggesting that charged pyrimidines tend to unstack.[5] In contrast to this, vertical stacking interactions of the uracilylcation **3** as well as of the uracilylbetaine **7** can unambiguously be determined by NMR dilution experiments in D_2O. Water is the most suited medium for studying π-interactions, because hydrogen bonding is nearly completely suppressed in this solvent.[24] We conducted ^1H NMR measurements versus concentration and observed a movement of the resonances to lower frequencies with increasing concentration. This is a consequence of diamagnetic ring current moments caused by vertical overlapping of the molecules exerting shielding upon protons of neighboring associating bases.[24] From the slopes of the lines—presented in Figure 6—it is apparent that the betaine **7** exerts stronger π-interactions on neighboring molecules than the cation **3**.

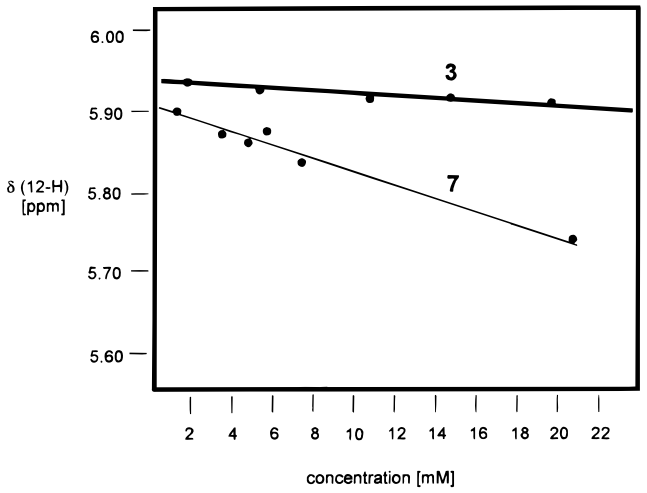


Figure 6. ^1H NMR versus concentration measurement of the uracilylcation **3** and the mesomeric betaine **7** in D_2O at 25 °C. The negative slopes are due to π-stacking of the bases.

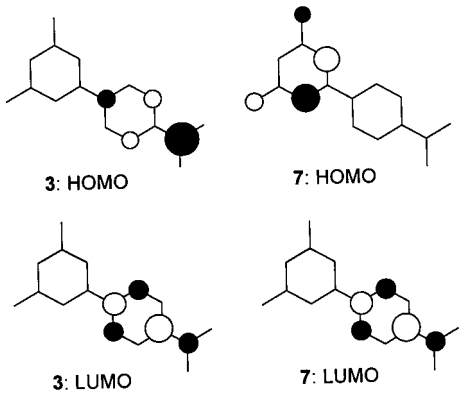


Figure 7. PM3-calculated frontier orbitals of the uracil-6-ylhetarenium salt **3** and the uracilylbetaine **7**.

A balance between hydrophobic forces,[36] frontier orbital interactions,[8] van der Waals−steric interactions,[24] permanent and dipole−induced dipole moments,[24] and electrostatic attracting forces that involve fixed partial atomic charges and asymmetric σ and π electron distributions[37] seems to be important in vertical base stacking. As a consequence, it is not unambiguous to draw any conclusions on the geometries of the aggregates in solution. Furthermore, it is known that the π-stacks build up and break down rapidly on the NMR time scale so that average shift values of all topological variants are observed.[23] As a matter of fact, however, the HOMOs of the uracilylcation **3** and the mesomeric betaine **7** differ significantly. The results of the PM3 calculation[28] are presented in Figure 7. The HOMO as well as the LUMO of the uracilyl hetarenium salt **3** are essentially located

(35) Karas, M.; Hillenkamp, F. *Anal. Chem.* **1988**, *60*, 2299.

(36) Davis, A. M.; Teague, S. J. *Angew. Chem.* **1999**, *111*, 778; *Angew. Chem., Int. Ed.* **1999**, *38*, 736.

(37) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.

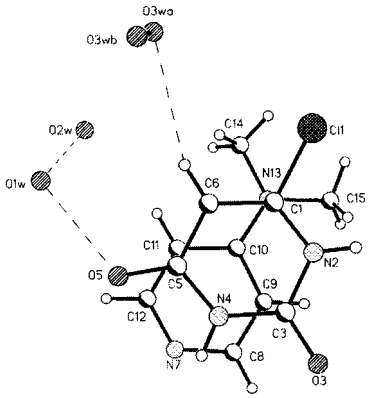


Figure 8. Drawing of the π-complex of 6-chlorouracil **1** and DMAP. Crystallographic numbering.

in the pyridinium ring. In addition, the calculation leads to a most stable conformation of **3** with the pyrimidine and pyridine rings twisted by 115° from planarity. In contrast to this, the HOMO of the mesomeric betaine **7**, the most stable conformation of which is the planar one, has its largest coefficients in the pyrimidine moiety so that the π-acceptor and π-donor substructures are located in separate parts of the molecule. Anticipated, on examining the π-interactions of the starting materials of the betaine **7**, 6-chlorouracil **1**, and DMAP, we found completely reversed donor/acceptor properties (see below).

As already discussed, on crystallization from an aqueous solution the betaine **7** as well as the cation **3** destacks forming hydrogen-bonded dimers of the betaine **7**═**7**. In the elemental cell, no π-interactions between the betaine molecules are detectable.

Noncovalent Interactions of 6-Chloropyrimidine-2,4(1*H*,3*H*)-dione and Heteroaromatics. In sharp contrast to the reaction conditions mentioned above, stirring the 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** with 4-(dimethylamino)pyridine (DMAP) and 4-(pyrrolidin-1-yl)pyridine (PPY), respectively, in various solvents such as water, ethanol, ethyl acetate, or acetonitrile results in stable 1:1 compounds **11** and **12** (Scheme 1) composed of noncovalently associated uracils and heteroaromatics. Attempts to replace DMAP and PPY by pyridine (pK_a 5.23) or 1-methylimidazole (pK_a' 7.13), however, failed, as the starting material **1** containing small nonstoichiometric amounts of the heteroaromatics was finally recovered.

To elucidate the structure of these complexes in view of the biological importance of modified nucleobase−heteroaromatic interactions, we performed an X-ray single-crystal analysis[38] as well as NMR measurements in DMSO-d_6. Monoclinic single crystals were obtained by slow evaporation of a concentrated solution of 6-chlorouracil **1** and DMAP at 8 °C. Surprisingly, despite the considerable acidity of the uracil derivative [pK'_{a1} (H_2O) = 5.67] and the basicity of the DMAP [pK_a = 9.75] the ORTEP drawing (Figure 8) shows two *uncharged* molecules that crystallize in stacks. Obviously, the neutralization in the solid state is compensated in favor of electronic interactions. Thus, deprotonation of the π-acceptor 6-chlorouracil forming the 6-uracilate anion would cause an increasing LUMO energy, and—on the other hand—protonation of the π-donor DMAP forming $DMAPH^+$ would induce a decreasing of the HOMO energy.

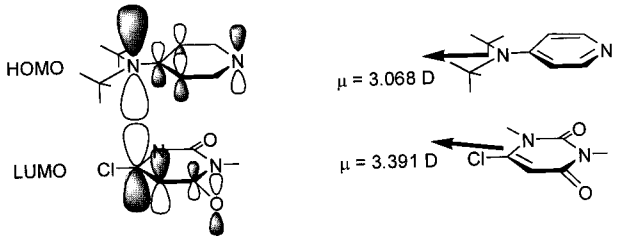


Figure 9. Left: HOMO of the π-donor DMAP, LUMO of the π-acceptor 6-chlorouracil **1**. Right: Permanent dipole moments of DMAP and 6-chlorouracil **1** (arrows in correct scale and direction).

The orientation of the molecules in the π-complex is obviously governed by frontier orbital interactions as well as by steric effects as the main factors. Thus, the steric interaction between the methyl groups of the NMe_2 group of DMAP and the chlorine atom of the uracil is small due to a nearly symmetric arrangement. As evidenced by X-ray crystallography, in known nucleobase−nucleobase or nucleobase−heteroaromatic π-stacking complexes heteroatoms such as O, N, or Cl usually overlap with polarizable regions of the delocalized systems.[1]

In contrast to these findings, the chlorine atom of the π-complex **11B**, however, is *not* superimposed over the π-electron sextet of the DMAP. On the contrary, it is located at the farthest distance from all atoms of the heteroaromatic. Characteristic for $\pi-\pi$ interactions between the HOMO of the donor and the LUMO of the acceptor molecules,[8] the distance between the C(4) of DMAP (crystallographic numbering in Figure 6: C10) and C(6) of the 6-chlorouracil (crystallographic numbering: C1) in the complex is significantly smaller (334.2 pm) than a typical van der Waals distance (340 pm).[5,8] The PM3-calculated HOMO/LUMO profile shows that the largest coefficients of the LUMO of the acceptor 6-chlorouracil is indeed essentially located at C(6), whereas the largest coefficients of the HOMO of the donor molecule DMAP are calculated at C(4) (Figure 9).[28] The absence of suited substituents might be the reason for the finding that pyridine and 1-methylimidazol do not form stable complexes with 6-chlorouracil **1**. In contrast to the adenine/tryptophan system, the dipole moments of **1** and DMAP are not responsible for the relative orientation of the molecules in the complex as they are almost completely uncoupled.

The elemental cell shows discrete charge-transfer pairs and several hydrogen bondings (Figure 10). One of these is measured between the acidic NH group of the uracil and the basic nitrogen atom of DMAP. Other hydrogen bonds are found to the water of hydration present in the crystal. 6-Chlorouracil **1** obviously does not form hydrogen bonds via the Watson−Crick positions.

(38) X-ray crystal structure analysis of the π-complex: [$C_4H_3ClN_2O_2$ − $C_7H_{10}N_2$ − 3 H_2O], M = 322.75, monoclinic, space group $C2/c$ (no. 15), colorless crystals, dimensions 0.25 × 0.18 × 0.08 mm^3, a = 13.7642(12) Å, b = 29.511(2) Å, c = 8.7659(8) Å, β = 118.130(3)°, V = 3140.1(5) Å^3, D_c = 1.365 Mg m^{-3}, Z = 8, μ(Mo Kα) = 0.269 mm^{-1}, T = 123(2) K, F(000) = 1360, 16052 reflections were collected on a Nonius KappaCCD diffractometer ($2\Theta_{max}$ = 56.8°, $-18 \le h \le 18$, $-36 \le k \le 36$, $-11 \le l \le 11$), 3718 symmetry independent reflections (R_{int} = 0.0560) were used for the structure solution (direct methods)[26] and refinement (full-matrix least-squares on F^2,[27] 181 parameters, 0 restraints), non-hydrogen atoms were refined anisotropically, H atoms were localized by difference electron density and refined using a riding model, wR2 = 0.3805 [R_1 = 0.1061 for 1790I > 2σ(I)]. One water molecule is disordered. The water molecules were refined isotropically without H-atoms which could not be localized.

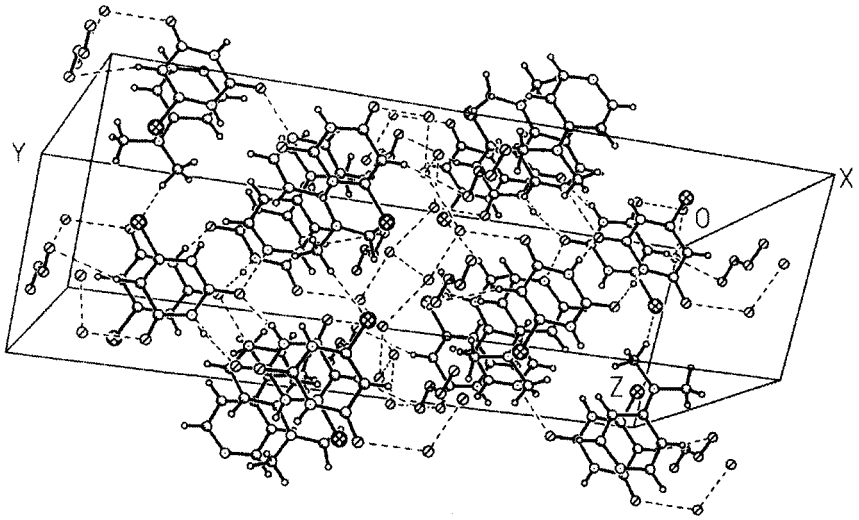


Figure 10. Elemental cell of the π-complex of 6-chlorouracil **1** and DMAP.

As could be expected, in DMSO-d_6 partial neutralization of the 1:1 pair of 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** and DMAP and 4-(pyrrolidin-1-yl)pyridine, respectively, occurs. The observed ^{1}H NMR chemical shifts correspond to average values between the neutral compounds **1** and the heteroaromatic on one hand, and the pyridinium uracilates **11A** and **12A** on the other (cf. Scheme 1).

Experimental Section

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 and 75 MHz, respectively. The chemical shifts are reported in ppm relative to tetramethylsilane. IR spectra were obtained in the range from 400 to 4000 cm^{-1} (2.5% pellets in KBr). The ESI mass spectra were recorded in water/methanol = 1:1. In MALDI measurements 2,5-dihydroxybenzoic acid was used as matrix. All chemicals, except for nondeuterated solvents, were purchased from Aldrich Chemical Co. and were used as received. Limited solubilities in common deuterated solvents prevented us from measuring some ^{13}C NMR spectra. All new compounds were dried at 80 °C prior to combustion analysis and measurements of the UV spectra. However, in accordance with known hetarenium compounds[13a,b,26] and X-ray crystallographic results (cf. Figure 8), some compounds crystallize with considerable amounts of water. The water of hydration indicated in the formulas give the best fit to the values obtained. Insufficient solubilities of the betaines **6**−**9** in water, MeOH, MeCN, and CH_2Cl_2 (<0.8 mg/50 mL solvent) prevented us from determining log ϵ, because the substances precipitated from the solutions. In these cases, qualitative measurements of highly diluted solutions were performed.

General Procedure for the Preparation of the Uracilylpyridinium Chlorides 2−**5.** Stirred suspensions of 0.73 g (5.0 mmol) of 6-chloro-2,4(1*H*,3*H*)-pyrimidinedione **1** and the heteroaromatic in 150 mL of chlorobenzene were heated at reflux temperature over a period of 3 h. After cooling, the precipitates were filtered off, washed with 30 mL of dichloromethane, and recrystallized. Details are given below.

1-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium Chloride (2). A 1.95 g (25.0 mmol) portion of pyridine was used. Recrystallization of the crude reaction product from ethanol/water/hydrochloric acid (10:5:1) gave a beige-colored solid: yield 0.83 g (73%); mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 6.26 (s, 1H), 8.36 (dd, J = 7.7/6.5 Hz, 2H), 8.90 (m, 1H), 9.36 (dd, J = 6.5/1.3 Hz, 2H), 11.64 (s, broad, 1H); ^{13}C NMR (DMSO-d_6) δ 97.9, 127.8, 144.2, 149.5, 150.4, 150.5, 163.2; IR 1728.6, 1677.8 cm^{-1}; UV λ_{max}(H_2O) (log ϵ) 334.10 (4.324), 256.50 (3.876), 220.20 (3.975) nm; FABMS *m*/*z* 190.5 (M^+; 100), 41.2 (100). Anal. Calcd for $C_9H_8ClN_3O_2 \cdot 0.25H_2O$: C, 46.97; H, 3.72; N, 18.25. Found: C, 46.69; H, 3.46; N, 17.94.

4-(Dimethylamino)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium Chloride (3). A 0.61 g (5.0 mmol) portion of DMAP was used. Recrystallization from ethanol formed a beige solid: yield 0.55 g (41%); mp > 300 °C; ^{1}H NMR (concentrated solution in DMSO-d_6) δ 3.30 (s, 6H), 5.97 (s, 1H, H/D exchangeable), 7.17 (d, J = 8.1 Hz, 2H), 8.42 (d, J = 8.1 Hz, 2H), 11.53 (s, 1H, H/D-exchangeable); ^{13}C NMR (DMSO-d_6) δ 40.3, 94.5, 107.2, 139.5, 150.1, 151.0, 156.8, 163.6; IR 1722.3, 1651.9 cm^{-1}; UV λ_{max}(H_2O) (log ϵ) 294.5 (4.312), 213.3 (4.158) nm; λ_{max}(CH_2Cl_2) 280.00 nm; λ_{max}(MeCN) 308.10 nm; λ_{max}(MeOH) 305.70 nm; FABMS *m*/*z* 233.5 (54, M^+). Anal. Calcd for $C_{11}H_{13}ClN_4O_2 \cdot H_2O$: C, 46.08; H, 5.27; N, 19.54. Found: C, 45.47; H, 5.38; N, 19.92.

4-(Pyrrolidin-1-yl)-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)pyridinium Chloride (4). A 0.74 g (5 mmol) portion of 4-(pyrrolidin-1-yl)pyridine was used. Recrystallization from aqueous ethanol furnished a nearly colorless solid: yield 0.86 g (59%); mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 2.02 (m, 4H), 3.61 (m, 4H), 5.86 (s, 1H), 6.99 (d, J = 7.8 Hz, 2H), 8.50 (d, J = 7.8 Hz, 2H), 11.02 (s, broad, 1H); ^{13}C NMR not measured due to insufficient solubility; IR 1719.3, 1650.2 cm^{-1}; UV (H_2O) λ_{max} (log ϵ) 320.6 (4.228), 213.9 (4.040) nm; FABMS *m*/*z* 259.5 (M^+; 43), 149.3 (PPY; 100). Anal. Calcd $C_{13}H_{15}ClN_4O_2$: C, 52.97; H, 5.13; N, 19.00. Found: C, 53.37; H, 5.33; N, 18.84.

3-Methyl-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl)imidazolium Chloride (5). A suspension of 0.63 g (4.37 mmol) of chlorouracil **1** and 0.72 g (8.74 mmol) of 1-methylimidazole in 30 mL of chlorobenzene was heated at reflux temperature over a period of 7 h. After cooling, the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethyl acetate/ethanol (5:1 vol/vol) to give a colorless solid: yield 0.59 g (59%); mp 282−286 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.94 (s, 3H), 6.05 (s, 1H), 7.94 (m, 1H), 8.18 (m, 1H), 9.85 (s, 1H), 11.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.4, 92.8, 120.6, 124.3, 137.0, 144.9, 151.3, 163.5; IR 1733.1, 1663.1 cm^{-1}; UV λ_{max}(H_2O) (log ϵ) 299.8 (3.789), 211.6 (4.112) nm; λ_{max}(MeOH) 273.71, ca. 295 nm (shoulder); λ_{max}(MeCN) 259.33, 313.29 nm; λ_{max}(CH_2Cl_2) 255.50 nm; FABMS *m*/*z* 193.4 (30, M^+). Anal. Calcd for $C_8H_9ClN_4O_2 \cdot 2H_2O$: C, 41.21; H, 4.11; N, 24.03. Found: C, 41.17; H, 4.22; N, 23.78.

General Procedure for the Synthesis of the Cross-Conjugated Mesomeric Betaines 6−**9.** A 150 mL portion of the anion-exchange resin Amberlite IRA-400 was filled into a column without frit (height: 16 cm, diameter 3 cm) and washed with 2 L of water. Then, 150 mL of an 8% aqueous solution of sodium hydroxide was added and remained in the column for 45 min. The sodium hydroxide was then rinsed out with water until pH 7 was reached. Then, samples of 400 mg

of the uracilylhetarenium salts **2**−**5** in 40 mL of water, respectively, were given on the resin. A flow rate of one drop per second was adjusted. The elutes were concentrated in vacuo and cooled to 8 °C overnight. The resulting precipitates were filtered off and dried in vacuo.

6-Pyridinio-2,4(1*H*,3*H*)-pyrimidinedionate (6): yield 0.32 g (96%); mp > 193 °C dec; ^{1}H NMR (DMSO-d_6) δ 5.74 (d, J = 1.2 Hz, 1H), 8.18 (dd, J = 7.2/1.5 Hz, 2H), 8.74 (m, 1H), 9.46 (dd, J = 7.2/1.2 Hz, 2H), 10.09 (s, broad, 1H); ^{13}C NMR (DMSO-d_6) δ 89.8, 127.7, 142.1, 148.5, 156.0, 158.0, 165.7; IR 1654.2 cm^{-1}; UV λ_{max}(H_2O) 334.30, 256.70, 220.20 nm; FABMS *m*/*z* 190.4 ($M^+ + 1$; 36), 41.2 (100). Anal. Calcd for $C_9H_7N_3O_2 \cdot 4H_2O$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.30; H, 3.86; N, 16.21.

6-(4-(Dimethylamino)pyridinio)-2,4(1*H*,3*H*)-pyrimidinedionate (7). The general procedure gave a beige-colored solid: yield 0.34 g (94%); mp > 300 °C; ^{1}H NMR δ 3.53 (s, 6H), 5.53 (s, 1H), 7.05 (d, J = 8.1 Hz, 2H), 8.76 (d, J = 8.1 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR not measured because of insufficient solubility; IR 1640.2, 1573.6 cm^{-1}; UV (H_2O) λ_{max} 316.4, 214.7 nm; FABMS *m*/*z* 231.5 (1; M^+), 43.2 (100). Anal. Calcd for $C_{11}H_{12}N_4O_2 \cdot 3H_2O$: C, 46.14; H, 6.33; N, 19.57. Found: C, 45.45; H, 5.44; N, 19.34.

6-[4-(Pyrrolidin-1-yl)pyridinio]-2,4(1*H*,3*H*)-pyrimidinedionate (8). The general procedure gave a beige-colored solid: yield 0.33 g (94%); mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 2.02 (m, 4H), 3.61 (m, 4H), 5.51 (d, J = 1.3 Hz, 1H), 6.89 (d, J = 7.9 Hz, 2H), 8.75 (d, J = 7.9 Hz, 2H), 9.75 (s, broad, 1H); ^{13}C NMR (DMSO-d_6) δ 24.6, 48.7, 83.0, 107.7, 137.5, 154.2, 158.3, 159.3, 167.0; IR 1634.2, 1566.7 cm^{-1}; UV (H_2O) λ_{max} 320.4, 214.7 nm; FABMS *m*/*z* 259.7 (1, $M^+ + 1$), 31.2 (100). Anal. Calcd for $C_{13}H_{14}N_4O_2 \cdot 3H_2O$: C, 49.99; H, 6.45; N, 17.94. Found: C, 49.25; H, 6.41; N, 17.34.

6-(3-Methylimidazolio)-2,4(1*H*,3*H*)-pyrimidinedionate (9): yield 0.30 g (98%); mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 5.60 (d, J = 1.2 Hz, 1H), 7.81 (m, 1H), 8.24 (m, 1H), 9.75 (s, broad, 2H); ^{13}C NMR (DMSO-d_6) δ 36.0, 82.5, 118.4, 124.1, 135.1, 154.7, 158.4, 166.8; IR 1662.8, 1635.2 cm^{-1}; FABMS *m*/*z* 193.4 (27; $M^+ + 1$), 55.2 (100). Anal. Calcd for $C_8H_8N_4O_2 \cdot 4H_2O$: C, 36.36; H, 6.10; N, 21.20. Found: C, 35.86; H, 3.99; N, 20.56.

Crystallization of the π-Complex of 4-(Dimethylamino)pyridine and 6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione (11B). A 146 mg (1.0 mmol) portion of 6-chloropyrimidine-2,4-(1*H*,3*H*)-dione **1** and 122 mg (1.0 mmol) of 4-(dimethylamino)-pyridine were dissolved in water and crystallized at 8 °C: yield 220 mg (82%) of large colorless crystals; mp > 155 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 6H), 5.30 (s, 1H), 6.75 (d, J = 6.9 Hz, 2H), 8.16 (d, J = 6.9 Hz, 2H), 10.25 (s, 1H, broad); ^{13}C NMR (DMSO-d_6) δ 40.2, 95.8, 107.0, 143.9, 153.6, 154.5, 155.4, 164.2; IR 1650.3, 1557.4 cm^{-1}; FABMS *m*/*z* 147.2 (**1**, 1), 123.2 ($DMAPH^+$, 100). Anal. Calcd for $C_{11}H_{13}ClN_4O_2 \cdot 1.5H_2O$: C, 44.67; H, 5.45; N, 18.94. Found: C, 44.42; H, 5.44; N, 18.96.

Crystallization of the π-Complex of 4-(Pyrrolidin-1-yl)pyridine and 6-Chloro-2,4(1*H*,3*H*)-pyrimidinedione (12B). A 146 mg (1.0 mmol) portion of 6-chloropyrimidine-2,4-(1*H*,3*H*)-dione **1** and 148 mg (1.0 mmol) of 4-(pyrrolidin-1-yl)-pyridine were dissolved in water and crystallized at 8 °C: yield 297 mg (91%); mp > 159 °C dec; ^{1}H NMR δ 1.97 (m, 4H), 3.41 (m, 4H), 5.30 (s, 1H), 6.67 (d, J = 6.7 Hz, 2H), 8.12 (d, J = 6.7 Hz, 2H), 10.35 (s, 1H); IR 1656.0, 1550.5 cm^{-1}; UV (H_2O) λ_{max} 282.4, 212.7 nm; FABMS *m*/*z* 149.4 (PPY, 100), 147.4 (**1**, 7). Anal. Calcd for $C_{13}H_{15}ClN_4O_2$ (294.7409)$\cdot H_2O$: C, 49.92; H, 5.48; N, 17.91. Found: C, 49.67; H, 5.13; N, 17.55.

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Supporting Information Available: Summary of data collection and structure solution and refinement details of **7** and **11B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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