Hydrogen-Bonded Complexes of Diaminopyridines and Diaminotriazines: Opposite Effect of Acylation on Complex Stabilities

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The association behavior of several 2,4-diamino-*s*-triazines, 2,6-diaminopyridines, and their acylated derivatives with uracil derivatives was studied. In solution ^{1}H-NMR and IR spectroscopy were used, and in the solid state as (co)crystals X-ray diffraction was used. Acylation of 2,6-diaminopyridine leads to an increase of the association constant in $CDCl_3$ of the complexes with *N*-propylthymine from 84 to 440−920 M^{-1}, whereas acylation of diamino-*s*-triazines leads to a dramatic fall in the association constant of the complexes with *N*-propylthymine from 890 to ca. 6 M^{-1}. This phenomenon is related to different conformational preferences of these compounds. The amide groups in bis(acylamino)pyridines prefer a trans conformation, with the carbonyl group anti with respect to the ring nitrogen and coplanar with the aromatic ring. The amides of bis(acylamino)-triazines, however, reside predominantly in a cis conformation. Repulsive secondary electrostatic interactions between the *cis*-amide and uracil carbonyl groups are thought to be responsible for the low association constant of complexes of bis(acylamino)triazines with uracils. The relatively high dimerization constants of bis(acylamino)triazines have been rationalized by the strong tendency to dimerize via quadruple hydrogen bonding.

Introduction

The use of multiple hydrogen bonding for the assembly of supramolecular structures is now a well-established principle.[1] Multiple hydrogen bonding is a particularly good way to achieve recognition because of its strength, directionality, and specificity. In a program aimed at the use of multiple hydrogen bonding for the assembly of supramolecular polymer complexes,[2] we are aiming at a pair of complementary hydrogen-bonding units that offer an optimal balance between synthetic accessibility, strength, and specificity. Ideally, each individual unit would display weak dimerization tendency and the heteroassociation constant would be high.

There are three ways to form a linear array of three hydrogen bonds from a combination of hydrogen-bond donor and acceptor functionalities. A complementary pair frequently encountered in supramolecular chemistry consists of a bis(acylamino)pyridine as the donor−acceptor−donor (DAD) unit and an imide as the acceptor−donor−acceptor (ADA) unit. Examples include complexes of 2,6-bis(acylamino)pyridines with uracils, succinimides, or glutarimides,[3] with association constants in $CDCl_3$ in the range of 50−500 M^{-1}. Recently, the use of melamines,[4] 2,4,6-triaminopyrimidines,[5] (aminoalkyl)-*s*-triazines,[6] and 2,4-diamino-*s*-triazines[7] as DAD groups was also reported. We decided to compare the hydrogen-bonding

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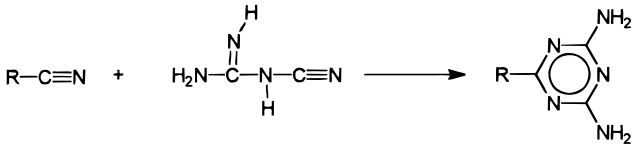
Scheme 1. General Route for the Synthesis of 2,4-Diamino-*s*-triazines



1: R = CH_3
2: R = n-$C_{12}H_{25}$
3: R = CH_2OCH_3
4: R = CH_2OH

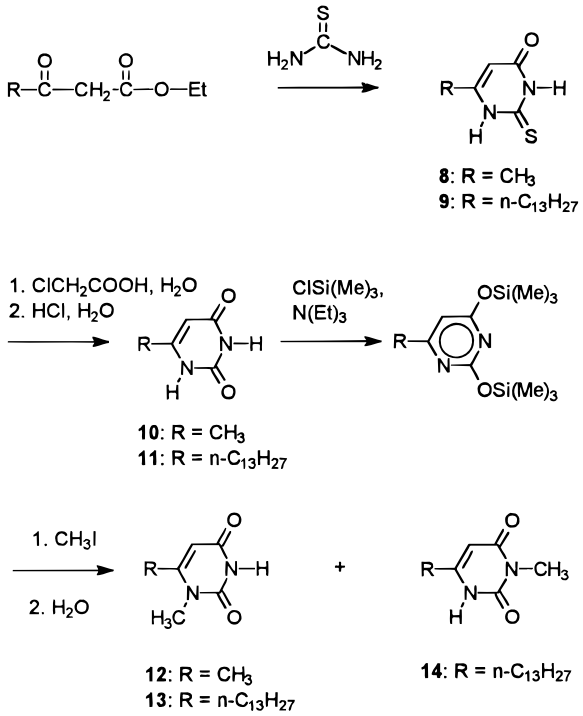
properties of synthetically well-accessible 6-alkyl-2,4-diamino-*s*-triazine derivatives with the well-studied 2,6-diaminopyridine, with special emphasis on the effect of acylation on binding strength with uracils/thymines and dimerization. In the present paper, we describe the results of ^{1}H-NMR titrations of these compounds with uracil/thymine derivatives in $CDCl_3$. The complexation via hydrogen bonding of parent and of acylated diaminotriazines and 2,6-diaminopyridine with uracil derivatives, as well as the amide conformations of acylated compounds in solution, is investigated using IR spectroscopy in chloroform solution. Additional information is gathered from (co)crystallization experiments, which gave access to crystal structures and hence to detailed information about the geometry of the hydrogen bonded complexes. Taking into account the decisive role of amide conformations, the results of the complexation experiments are discussed in the framework of the model of Jorgensen that uses secondary electrostatic interactions to explain differences in strength between arrays of hydrogen bonding groups.[8]

Results

Syntheses. 2,4-Diamino-*s*-triazines **1**−**3** were prepared by condensation of the appropriate nitrile with dicyanodiamide[9] (Scheme 1). 6-(Hydroxymethyl)-2,4-diamino-*s*-triazine (**4**) was prepared according to the method of Sims[10] by protection of glycolonitrile[11] as its butyl vinyl ether, subsequent conversion to the corresponding 2,4-diamino-*s*-triazine, and deprotection with acid.

In general, 2,4-diamino-*s*-triazines are scarcely soluble in chloroform. Attaching a long alkyl chain to the 6-position increases the solubility of 2,4-diamino-*s*-triazines considerably. Acylated 2,4-diamino-*s*-triazines were prepared with the expectation that the amide NH protons would display stronger hydrogen bonding than the parent NH_2 protons. Compound **5** was prepared by boiling diaminotriazine **3** in acetic anhydride;[12] compounds **6** and **7** were prepared using 2 equiv of the appropiate acid chloride in refluxing pyridine. The acylated triazines **5** and **6** readily undergo hydrolysis in water at room temperature.[12c]

Scheme 2. General Route for the Synthesis of Uracil Derivatives

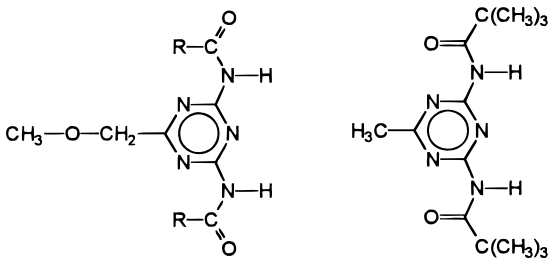


8: R = CH_3
9: R = n-$C_{13}H_{27}$

10: R = CH_3
11: R = n-$C_{13}H_{27}$

12: R = CH_3
13: R = n-$C_{13}H_{27}$

14: R = n-$C_{13}H_{27}$



5: R = CH_3
6: R = n-C_5H_{11}

7

Uracil derivatives **10** and **11** were synthesized from β-keto esters by condensation with thiourea followed by conversion of the thiouracils **8** and **9** to the corresponding uracils with chloroacetic acid[13] (Scheme 2). The limited solubility of 6-tridecyluracil (**11**) in chloroform prevents its use for NMR-complexation experiments. Selective *N*-1-methylation, affording uracil derivatives **12** and **13**, was accomplished by silylation of the uracils **10** and **11**, respectively, followed by reaction with methyl iodide.[14]

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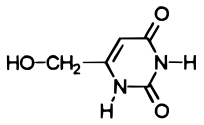
Table 1. Dimerization Constants (K_{dim}) and Complexation-Induced Shift (CIS) Values of NH Protons in Dimers of Diaminotriazine, Diaminopyridine, and Uracil Derivatives

entry	compound	K_{dim} [a] (M^{-1})	CIS (ppm)
1	2,6-bis(hexanoylamino)pyridine (**19**)	0.20	2.9
2	2,4-diamino-6-dodecyl-*s*-triazine (**2**)	2.2	2.37
3	2,4-bis(acetylamino)-6-(methoxymethyl)-*s*-triazine (**5**)	37	2.35
4	2,4-bis(hexanoylamino)-6-(methoxymethyl)-*s*-triazine (**6**)	24	2.33
5	2,4-bis(pivaloylamino)-6-methyl-*s*-triazine (**7**)	1.7	0.76
6	1-*N*-propylthymine (**17**)	4.3	3.40
7	1-*N*-methyl-6-tridecyluracil (**13**)	7.0	3.52
8	3-*N*-methyl-6-tridecyluracil (**14**)	94	3.93

[a] Estimated relative error in K_{dim} is 15%.

Fortunately, compound **13** is readily soluble in $CHCl_3$. 3-*N*-Methyl-6-tridecyluracil (**14**) was isolated as a minor byproduct (7%) in the synthesis of **13**.

6-(Hydroxymethyl)uracil (**15**) was prepared by reduction of butyl orotate[15] and *N*-1-methylated via the silyl–Hilbert–Johnson reaction to give **16**. *N*-1-propylthymine (**17**) was prepared by direct alkylation of thymine.



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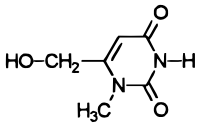
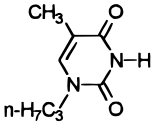
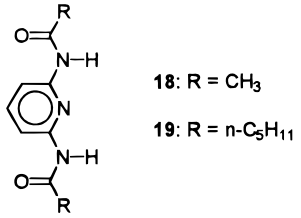


16



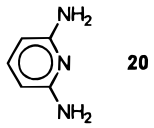
17

Bis(acylamino)pyridines **18** and **19** were prepared from 2,6-diaminopyridine (**20**) by acylation with acetic anhydride and hexanoyl chloride, respectively.



18: R = CH_3

19: R = n-C_5H_{11}



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^{1}H-NMR Titrations. Association constants of hydrogen-bonded complexes may be determined from evaluation of ^{1}H-NMR titration data by computer fitting with nonlinear least-squares methods. Provided the proper binding model is used, this guarantees a more reliable treatment of data than the use of graphical methods. In the present investigation we were specifically interested in dimerization, and we certainly did not want to neglect its effect on the calculated heteroassociation constants. Therefore, dimerization constants were determined separately, and the titration data of heterocomplexation were analyzed using a model that explicitly takes dimerization into account (see the Experimental Section).

Dimerization constants in $CDCl_3$ at 298 K were determined by monitoring the NH proton shift at different concentrations. The results of the ^{1}H-NMR dilution experiments are summarized in Table 1.

The dimerization constants of 2,6-diaminopyridine (**20**) and of 2,6-bis(acetylamino)pyridine (**18**) could not be determined due to their limited solubility. All dimerization constants are low, except those of bis(acylamino)-triazines **5** and **6** and of 3-*N*-methyluracil (**14**).

For all DAD–ADA heterocomplexes studied, a 1:1 stoichiometry was established using Job-plots.[16] The results of the titration experiments, corrected for dimerization of the titrant, are summarized in Table 2. High association constants are observed for the complexes of 2,6-bis(acylamino)pyridines **18** and **19** with uracils **13** and **17**, and for the complexes of diaminotriazine **2** with uracils **13** and **17** intermediate association constants for 2,6-diaminopyridine (**20**) with uracil **17** are observed, whereas a very low association constant is observed for complexes of bis(acylamino)triazines **5**–**7** with uracil **17**. $CDCl_3$ was used as received, since the water content of the chloroform was found to have only a minor effect on binding strength. Upon saturation of $CDCl_3$ with water, association constants dropped by only 0–20%.

Table 2. Association Constants (K_a) and Complexation-Induced Shift (CIS) Values of Complexes of Diaminopyridine and Diaminotriazine Derivatives with (Thio)uracil Derivatives

entry	diaminopyridine or diaminotriazine deriv	*N*-propyl-thymine/ uracil deriv	K_a[a] (M^{-1})	CIS (ppm) of NH proton signal of probe (probe)
1	**20**	**17**	84	1.36 (**20**)
2	**18**	**17**	920	2.86 (**18**)
3	**19**	**17**	436	2.81 (**19**)
4	**19**	**13**	530	2.80 (**19**)
5	**2**	**17**	890	5.65 (**17**)
6	**2**	**13**	750	5.61 (**13**)
7	**5**	**17**	5.7	1.39 (**5**)
8	**6**	**17**	6.4	1.68 (**6**)
9	**7**	**17**	4.7	1.28 (**7**)
10	**2**	**9**	107	3.76 (**9**)
11	**2**	**14**	<2	

[a] Estimated relative error in K_a is 15%.

Table 3. Wavenumbers of NH Stretch Vibrations of Diaminopyridines, Diaminotriazines, and Acylated Derivatives as Free Molecules and in Their Complexes with *N*-propylthymine 17

compd	ν_{NH} (cm^{-1})	ν_{NH} (cm^{-1}) in complex with **17**	ν_{NH} (cm^{-1}) of **17** in complex[a]
2	3424, 3540[b]	3328, 3497[c]	3216
5	3384	[d]	[d]
6	3395	not determined (nd)	nd
7	3424	nd	nd
20	3408, 3508[b]	3339, 3493[c]	3219
18	3422	3275	3215
19	3422	3273	3211

[a] ν_{NH} of free **17**: 3395 cm^{-1}. [b] Symmetric and asymmetric stretch vibrations, respectively. [c] ν_{NH} of hydrogen-bonded NH and of free NH, respectively. [d] Bands due to complex were not observed.

IR Spectroscopy of Bis(acylamino)pyridine and Bis(acylamino)triazines. IR spectra of compounds **2**, **5**–**7**, and **18**–**20** were recorded in dry chloroform solutions at varying concentrations, generally at 50 mM. Wavenumbers of the NH vibrations are reported in Table 3. Bis(acylamino)pyridines **18** and **19** and bis(pivaloylamino)triazine (**7**) show their amide NH stretch vibration at approximately 3422 and 3424 cm^{-1}, respectively, while

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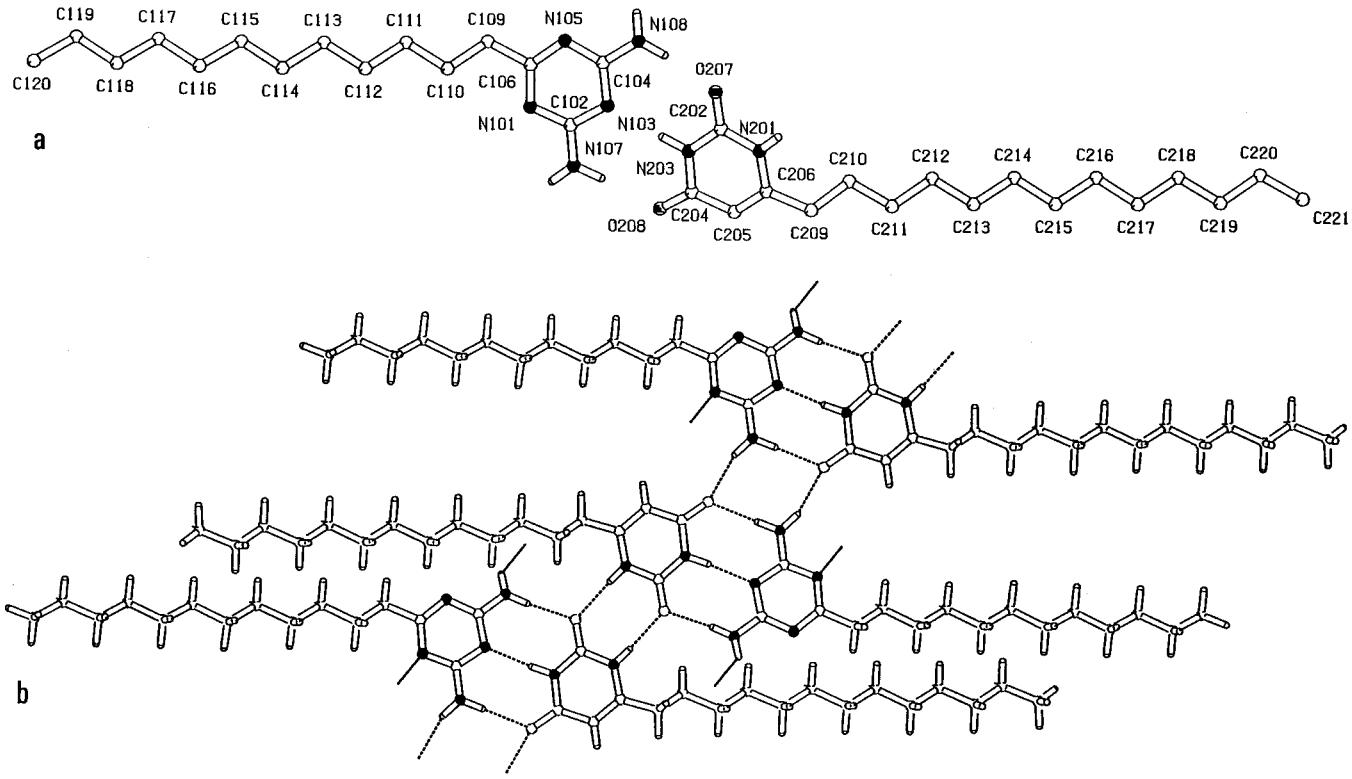

Figure 1. PLUTON representation of the crystal structure of the cocrystal **2·11**: (a) atom numbering scheme; (b) hydrogen-bonding pattern in the ($1\bar{2}1$) plane.

bis(acylamino)triazines **5** and **6** show their NH stretch vibration band at lower frequencies, at 3384 and 3395 cm^{-1}, respectively.

The complexation behavior of compounds **2**, **5**, and **18**–**20** with *N*-propylthymine (**17**) in chloroform solution was also studied by means of infrared spectroscopy. Wavenumbers of the NH stretch vibrations of the free and of complexed molecules are given in Table 3.

Cocrystallization. To study the specificity of the triple hydrogen bond in complexes of triazines with uracil derivatives, cocrystallization of complementary pairs of triazine and uracil derivatives with additional functionality was investigated. We prepared crystalline complexes of 6-methyltriazine (**1**) with 6-methyluracil (**12**) and with 6-(hydroxymethyl)uracils **15** and **16**, respectively. Cocrystals were also obtained of 6-(hydroxymethyl)triazine (**4**) with 6-(hydroxymethyl)uracil derivatives **15** and **16** and with 6-methyluracil **(10)**, respectively. Cocrystals of 6-dodecyltriazine (**2**) with uracil derivatives **11** and **13** were also obtained. Water or ethanol proved to be the best solvents for cocrystallization. The preference for the formation of 1:1 cocrystals was very pronounced; even when a stoichiometry differing considerably from 1:1 was used, 1:1 cocrystals were formed, sometimes accompanied by crystals of the compound present in excess.

The only exception to the formation of 1:1 cocrystals we observed was the cocrystallization of 2,4-diamino-6-methyl-*s*-triazine (**1)** with 1-*N*-methyl-6-methyluracil (**12**) in a 1:2 stoichiometry, even starting from an equimolar aqueous solution. However, on prolonged standing these 1:2 crystals gradually redissolved while crystals of the 1:1 complex were simultaneously formed. The formation of cocrystals with two different stoichiometries is remarkable for multiple hydrogen-bonded complexes, but has been reported previously.[17]

The crystal structures of 1:1 complexes of triazine **2** with uracil **11** and of triazine **4** with uracil **15** were determined by X-ray diffraction. Figures 1 and 2 show PLUTON[18] drawings of these crystal structures.

X-ray Diffraction of Bis(acylamino)triazine 5. The crystal structure of bis(acetylamino)triazine (**5**) was determined in order to gain a better insight in the conformational differences between bis(acylamino)triazines and bis(acylamino)pyridines. A PLUTON drawing of the crystal structure of **5** is shown in Figure 3.

Discussion

In a certain medium, the strength of a single hydrogen bond is related to the hydrogen-bonding acidity of the donor group and basicity of the acceptor group involved.[19] In complexes held together by multiple hydrogen bonding, additional factors influence the stability of the complex. In a number of papers, Jorgensen and coworkers[8] have shown that the particular arrangement of donor (D) and acceptor (A) groups in an array of hydrogen bonds has a strong influence on complex stability. Repulsive secondary electrostatic interactions between two donor or two acceptor groups were found to be responsible for differences in dimerization strength of imides (ADA array) and lactams (AD array) and for differences in complexation strength of triple hydrogen bonded complexes. For acceptor and donor groups involved in hydrogen bonds, a destabilizing effect of approximately 7 kJ mol^{-1} per secondary interaction is

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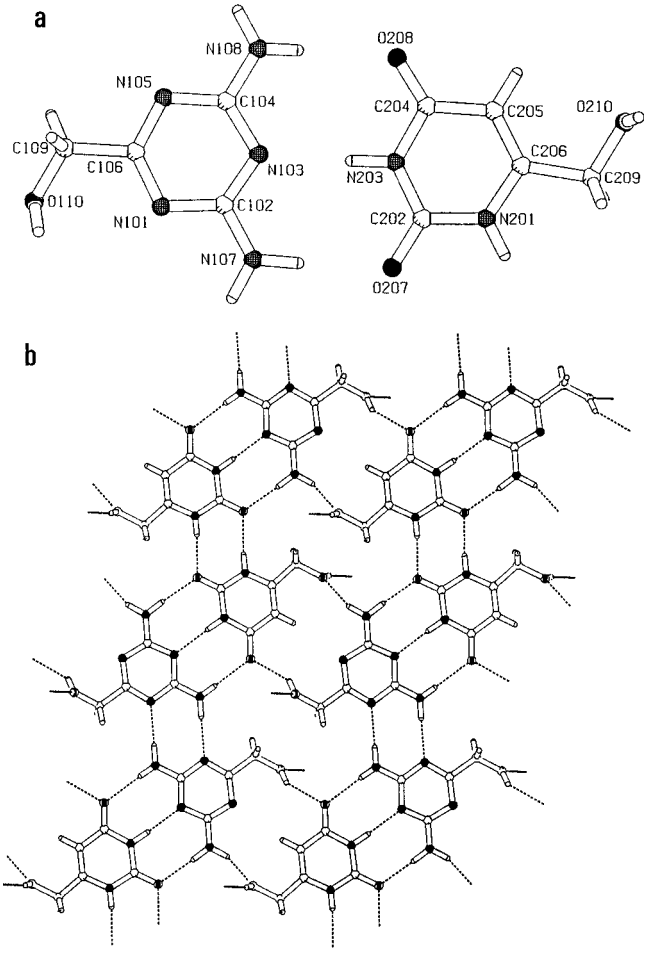

Figure 2. PLUTON representation of the crystal structure of the cocrystal **4·15**: (a) atom numbering scheme; (b) hydrogen-bonding pattern in the [210] direction.

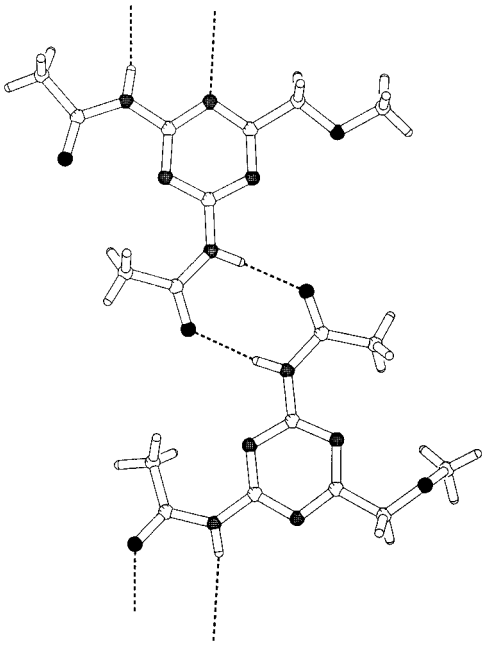

Figure 3. PLUTON representation of the hydrogen-bonding pattern in the crystal structure of 2,4-bis(acetylamino)-6-(methoxymethyl)-*s*-triazine (**5**).

derived from calculations. If the groups responsible for the secondary interaction are not involved in hydrogen bonding, e.g., two spectator oxygens in an imide dimer,

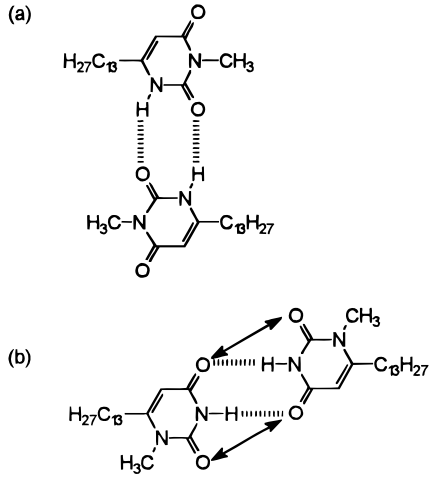

Figure 4. (a) Centrosymmetric dimer geometry of 3-*N*-methyl-6-tridecyluracil (**14**). (b) One of three possible dimer geometries of 3-*N*-methyl-6-tridecyluracil (**13**). Additional repulsive electrostatic interactions are indicated by double-headed arrows.

this value is estimated to be approximately 11 kJ mol^{-1}.[20] These effects provide useful guidelines to interpret the remarkable differences in complex stability we observe for complexes of uracil derivatives with pyridines, triazines, and their acylated derivatives in chloroform solution. It is equally useful to explain the relative magnitude of dimerization constants of these compounds.

Dimerization of Uracil Derivatives. Nonmethylated uracil derivatives possess a lactam-like DA array and an imide-like ADA array. These compounds can dimerize via hydrogen bonding in five different geometries,[21] and can form oligomers or polymers if the two arrays are simultaneously involved in hydrogen bonding. The latter fact is undoubtedly responsible for the low solubility of nonsubstituted uracil derivatives in chloroform. 1-Methyl-6-tridecyluracil (**13**) can dimerize via its ADA array in three geometries, but in 3-alkyl derivative **14** only one dimer geometry remains possible. A much higher dimerization constant is found for **14** than for **13** (Table 1, entries 7 and 8). This observation is in complete agreement with the difference in dimerization constants of imides and lactams reported by Jorgensen[8] and Burrows.[20] These effects were explained through repulsive electrostatic interactions between carbonyl oxygen atoms. We propose that similar effects are contributing to the difference in dimerization constants of **13** and **14**. In the centrosymmetric dimer of **14** (Figure 4a) there are two repulsive secondary interactions, whereas in all three possible dimer geometries of **13**, due to two spectator oxygens, there are two *additional* repulsive interactions (depicted by double-headed arrows in Figure 4b). Consequently, the dimerization of **14** is more favorable than the dimerization of **13**.

Comparison of Diaminotriazines and (Acylated) Diaminopyridines. Dimerization and Complexation with *N*-Propylthymine and Uracil Derivatives. The ^{1}H-NMR data in Table 1 show that dimerization constants are low for diaminotriazine **2** and bis(hexanoylamino)pyridine (**19**). The dimerization constant of 2,6-diaminopyridine could not be determined, but

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from infrared spectra of this compound in chloroform solution it was estimated to be very low.[22] The dimerization constants of bis(acylamino)triazines, except that of the sterically hindered bis(pivaloylamino) derivative **7**, are higher by 1 order of magnitude.

2,6-Diaminopyridine (**20**) forms a 1:1 complex with *N*-propylthymine (**17**), which has an association constant of 84 M^{-1}. Upon acetylation of the amino groups, the association constant increases to 920 M^{-1}.[23] This increase presumably results from the increased acidity of the amide protons as compared to the amino protons in **20**. The amino protons of diaminotriazines are considerably more acidic and, consequently, are better hydrogen bond donors then the amino protons of aminopyridines. Inspection of Table 2, entry 5, indeed shows that *N*-propylthymine (**17**) forms a complex with triazine **2**, which has a much higher association constant (K_a = 890 M^{-1}) than the complex with diaminopyridine (Table 2, entry 1: K_a = 84 M^{-1}) and has strength comparable to that of the complex of 2,6-bis(acetylamino)pyridine (**18**) with *N*-propylthymine **17** (Table 2, entry 2). Substituents on the uracil/thymine, or on bis(acylamino)pyridine, strongly affect the association constant of the complexes but barely affect the chemically induced shift of the protons in the complexes (compare Table 2, entries 2 and 3 with 4, and entry 5 with 6). The association constants we measured are comparable to literature values of complexation of triazines with uracils [7b,c] and with flavine derivatives.[3n]

Inspection of Table 3 shows that diaminotriazine **2**, 2,6-diaminopyridine (**20**), and bis(acylamino)pyridines **18** and **19** all form complexes with *N*-propylthymine (**17**) in chloroform solution. Complexation induces a decrease of the wavenumber of the NH stretch vibration of *N*-propylthymine (**17**) of 179, 176, 180, and 184 cm^{-1}, respectively. Due to the electron-withdrawing nature of the triazine ring, the asymmetric and symmetric NH_2 stretch vibrations in diaminotriazine **2** are found at higher wavenumbers than in diaminopyridine **20**.[24] In the complex with *N*-propylthymine (**17**), the asymmetric and symmetric NH_2 stretch vibrations in compound **2** are shifted to lower wavenumbers by approximately 43 and 96 cm^{-1}, respectively, whereas the corresponding vibrations in diaminopyridine **20** are shifted by only 15 and 69 cm^{-1} upon complexation. Upon complexation, the wavenumbers of the (single) NH stretch of bis(acylamino)pyridine **18** and **19** decrease by 147 and 149 cm^{-1}, respectively. From these data it is concluded that *N*-propylthymine (**17**) forms stronger hydrogen bonds with **18**, **19**, and **2** than with **20**, in line with the association constants determined by NMR titrations.

The lack of association of **2** with **14** (K_a < 2 M^{-1}) is not unexpected because a triple hydrogen-bonded complex cannot be formed and steric interactions with the alkyl substituent of **14** cannot be avoided in a complex involving two hydrogen bonds.

Complexation of **2** with thiouracil **9** is weaker than with uracil **13** because the sulfur atom is a weaker hydrogen bond acceptor. Unfortunately, association constants of triazines with *N*-1-unsubstituted uracil derivatives could not be determined due to the low solubility of the latter.

Persistence of the Triazine−Uracil Triple Hydrogen-Bonding Motif in the Solid State. To obtain unambiguous information about the hydrogen bonding in cocrystals, several crystal structures of diaminotriazine−uracil cocrystals were determined by X-ray diffraction. As depicted in Figure 1, the triazine and uracil molecules in the 1:1 cocrystal of **2** with **11** are triply hydrogen bonded, and infinite sheets are formed by four additional hydrogen bonding interactions: (i) uracil dimerization via N201−O207, (ii) triazine dimerization via N108−N105, (iii) triazine N107 to uracil−hydroxymethyl O210, and (iv) triazine−hydroxymethyl O110 to uracil O208. These sheets, spaced by 3.1845(5) Å, are connected via single hydrogen bonds of uracil−hydroxymethyl O210 to triazine−hydroxymethyl O110.

In the cocrystal of **4** with **15**, uracil and triazine are also triply hydrogen bonded, but the ring planes are twisted by 14.79(13)° around the central, almost linear, N203−N103 axis (vide infra). As depicted in Figure 2, an infinite ribbon is formed by dimerization of uracil via N201−O207 hydrogen bonds and formation of a quadruplet consisting of two triazine- and two uracil molecules. Torsion of the triply hydrogen-bonded complex allows the remaining triazine NH to be hydrogen bonded to a triazine ring nitrogen in another ribbon, resulting in sheets covered with apolar chains on both sides. These sheets point with their apolar regions to each other.

In both crystal structures, the triazine is paired via its DAD array with the ADA array of a uracil derivative, confirming our observation from complexation experiments in chloroform solution that this is the dominant interaction between diaminotriazines and uracils. Other hydrogen bonds are present in the cocrystal, but they rather seem to represent *additional* interactions.[25] In the cocrystal of **2** and **11**, the N107−O207 and N108−O208 distances are 2.954(3) and 2.958(3) Å, respectively, both with an angle of 178(3)° in the hydrogen bond, while the N203−N103 distance is 2.911(3) Å with an angle of 176(3)°. The values for the cocrystal of **4** and **15** are 2.885(3) Å for the N203−N103 distance with an angle of 176(3)°, while the outer hydrogen bonds are somewhat longer (N−O distances are 2.953(3) and 2.966(3) Å) and in one case bent (angle of 175(3)° and 159(3)°), because of the twist in the complex. These distances and angles are comparable to those in cocrystals of bis(acylamino)-pyridine derivatives with imides.[26]

Opposite Effect of Acylation on the Stability of Diaminopyridine and Diaminotriazine Complexes. Dimerization and Complexation with *N*-Propylthymine. The association constant of the complex of diaminopyridine (**20**) with *N*-propylthymine (**17**) increases approximately 10-fold upon acylation of the amino groups. A corresponding increase in association constant upon acylation of diaminotriazines was expected. However, when a diaminotriazine was acetylated, the association constant of the complexes with *N*-propylthymine dramatically dropped to approximately 6 M^{-1} (Table 2, entries 5, 7, and 8). Infrared spectroscopy also shows that *N*-propylthymine and 2,4-bis(acetylamino)triazine **5** do not form a stable complex in chloroform (Table 3).

Initially, we were quite puzzled by these unexpected results. In acylated triazines, the reduced basicity of the

(22) A 50 mM solution of **18** does not show any sign of dimerization.

(23) This value is somewhat higher than the association constant of 450 M^{-1} found for the complex of bis(hexanoylamino)pyridine with *N*-propylthymine.

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(25) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.

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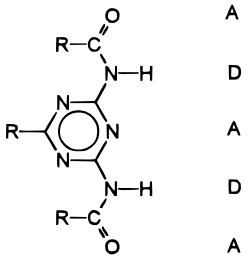

Figure 5. ADADA array of a bis(acylamino)triazine with cis-amide groups.

ring nitrogen atoms alone fails to explain the differences, because bis(acylamino)pyridines, where a similar reduction in basicity is expected, do not show this effect. The spectroscopic and X-ray data discussed below led us to believe that the differences result from the formation of a linear ADADA array of five hydrogen bonding sites when the amides in bis(acylamino)triazines are in a *cis* conformation (Figure 5).

Whereas in bis(acylamino)pyridines the *trans* conformation is the most stable conformation,[27] in bis(acylamino)triazines the *cis* conformation might predominate because electrostatic repulsion between the amide oxygen atom and one of the nitrogen atoms in the triazine ring cannot be avoided when the amide is *trans*. In both types of molecules, it is expected that the amide group is more or less coplanar with the aromatic ring because of resonance stabilization. A search of the Cambridge structural database for (acylamino)pyridines, −pyrimidines, and −triazines confirmed this hypothesis. The search yielded eight structures of bis(acylamino)-pyridines,[28] having amides exclusively in the *trans* conformation, with the carbonyl *anti* to the ring nitrogen atom. In the only two structures of 2-(acylamino)-pyrimidines in the database, the amide has a *cis* conformation.[29] Remarkably, one of these crystal structures features a linear array of four alternating donor and acceptor groups, incorporated in a quadruple hydrogen-bonded centrosymmetric dimer.

In the X-ray structure of bis(acylamino)triazine **5** (Figure 3), the unit cell contains four crystallographically inequivalent amide groups in two independent molecules. Three of these amide groups are in a *cis* conformation, while one of them is *trans* oriented. Whereas the *trans* amides in (acylamino)pyridines are usually coplanar with the pyridine ring, the trans amide in **5** is rotated 8.97(8)° out of the plane of the triazine ring, presumably to reduce electrostatic repulsion between the carbonyl group and the ring nitrogen atom.

Although the crystallographic data suggest a preference for *cis* amides in the nonsterically hindered bis(acetylamino)triazine **5** and in 2-(acetylamino)-4-aminopyrimidine derivative[29] in the solid state, they do not give information on the occurrence of this conformation in solution. Therefore, we decided to record infrared spectra of bis(acylamino)triazines and bis(acylamino)pyridines in dilute chloroform solution.

In the IR spectra of *N*-arylamides in dilute $CHCl_3$ or CCl_4 solution, in which the amides are predominantly

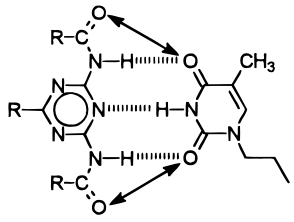

Figure 6. Proposed geometry of the complex of *N*-propylthymine (**17**) and bis(acetylamino)triazine **5**. Additional repulsive electrostatic interactions are indicated by double-headed arrows.

trans, the NH stretch vibration of the *trans* form appears at higher wavenumbers than that of the *cis* form.[30] In the infrared spectrum of bis(acetylamino)- or bis(hexanoylamino)pyridine at 50 mM in dry $CHCl_3$, we find a single band at 3422 cm^{-1}, strongly suggesting that the amide groups are predominantly in the *trans* conformation.[27]

In bis(acylamino)triazines **5** and **6**, however, single bands at 3383 and 3395 cm^{-1}, respectively, are found for the NH stretch vibration in dilute chloroform solution (5 mM[31]). In bis(pivaloylamino)triazine **7,** in which the conformation of the amide groups is *trans* for steric reasons, this band is found at 3424 cm^{-1}.[32] Comparison of these wavenumbers with the NH stretch vibration wavenumbers of *cis* and *trans* conformers of acetanilide in CCl_4 solution (3402 and 3446 cm^{-1}, respectively)[30] strongly suggests that amide groups in **5** and **6** are predominantly *cis* in solution. Due to the *cis* conformation of the amide groups, these compounds feature a linear ADADA array of *five* hydrogen bonding sites, in noticeable contrast with the DAD array in 2,6-bis(acylamino)pyridines.

The formation of a linear ADADA array has two important consequences for the complexation behavior of bis(acylamino)triazines:

(i) The amide oxygen atoms in bis(acylamino)triazines create additional repulsive interactions in complexes with ADA systems, thus decreasing the binding strength with uracil derivatives.[33] These interactions are indicated by double-headed arrows in Figure 6.

(ii) Dimerization constants of bis(acylamino)triazines are much higher than dimerization constants of bis(acylamino)pyridines. The ADADA array of bis(acylamino)triazines allows dimerization to a complex that is held together by four hydrogen bonds, showing the geometry depicted in Figure 7.[34]

Conclusions

2,4-Diamino-*s*-triazines form complexes with uracil derivatives that are as strongly associated as complexes

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(31) It is essential to record at this low concentration, as at higher concentrations dimerization is observed (seen by the appearance of broad peaks at 3251 and 3192 cm^{-1}).

(32) The (50 mM) solution of compound **7** contained (crystal) water (seen in the infrared spectrum at 3667 cm^{-1}), but this could be removed by rigorously drying the solution over calcium chloride. The wavenumber of the NH stretch of the dried solution is used (3424 cm^{-1}); the value for the solution containing water is 3433 cm^{-1}.

(33) Although the amide groups of **7** are in a *trans* amide conformation, complexation with *N*-propylthymine is weak (K_a = 4.7 L·mol^{-1}). This observation is in accordance with the observation of Feibus[3a] that bis(pivaloylamino)pyridines do not form complexes with imides, presumably due to steric hindrance.

(34) An alternative dimer geometry, which is found in the crystal structure of **5**, is expected to be significantly less stable in solution because it is held together by two instead of four hydrogen bonds.

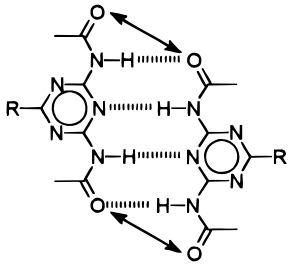

Figure 7. Proposed dimer geometry of bis(acylamino)triazines with a quadruple hydrogen bond.

of bis(acylamino)pyridines with uracils. 6-Substituted triazines are synthetically more accessible than 4-substituted bis(acylamino)pyridine derivatives; therefore, 2,4-diamino-*s*-triazine and uracil represent a convenient couple for supramolecular chemistry. Both units are synthesized in a comparable fashion by simple condensation reactions of nitriles, esters, or β-keto esters, and both units are functionalized in the same fashion with a substituent at the 6-position. The reliability of the triple hydrogen bond as the dominant organizing interaction has been shown by its persistence in cocrystals of triazines and uracils in the presence of additional hydrogen-bonding groups.

The linear ADADA array we propose for acylated diaminotriazines is not suitable for the formation of complexes with imides, but (acylamino)triazines may be used for the construction of self-complementary complexes via four hydrogen bonds. The interesting possibility to achieve very strong dimerization of self-complementary groups via quadruple hydrogen bonding is currently under investigation.

Experimental Section

General Methods. Chemicals were purchased from Acros Chimica, Fluka, or Aldrich and used as received unless otherwise stated. Compounds **1**, **8**, **10**, and **12** were synthesized analogously to described methods and gave satisfactory analyses. *N*-1-propylthymine (**17**) was prepared according to a literature procedure.[35] 2,6-Bis(acylamino)pyridine derivatives **18** and **19** were prepared analogously to literature procedures.[36] All reactions were carried out under an atmosphere of dry nitrogen, and solvents were of technical grade, unless otherwise stated. Anhydrous THF and diethyl ether were obtained by distillation from sodium/potassium/benzophenone, and analytical grade pyridine, ethanol, and 2-propanol were dried over 4 Å molecular sieves. NMR-spectra were recorded on a Varian Gemini 300 or a Bruker AC400. Chemical shifts are given in ppm relative to TMS for proton and carbon spectra. For the ^{1}H-NMR titrations, deuteriochloroform was used as received. IR-spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Dry chloroform for the infrared experiments was obtained by purification of analytical grade chloroform by several extractions with water, followed by drying over calcium chloride for 2 h and distillation under an atmosphere of dry nitrogen. Spectra at concentrations higher than 5 mM were taken in a 0.1 mm NaCl cell and at lower concentrations in a 1 mm cell. Melting points were determined on a Jenaval THMS 600 melting point microscope and are uncorrected.

Binding Experiments. ^{1}H-NMR titration experiments were performed following the guidelines of Derenleau[37] and Carta *et al.*[38] Dimerization and association constants were evaluated using a nonlinear least-squares fitting procedure. When one of the components in a complex showed significant dimerization, a binding model was adopted in the fitting of the association constant that uses the previously determined dimerization constant and its CIS value as fixed parameters.

Cocrystallizations. Unless otherwise stated, cocrystals were obtained by recrystallization from excess hot water by slow cooling, followed by slow evaporation in air. Cocrystals of 2,4-diamino-6-dodecyl-*s*-triazine and 6-tridecyluracil were obtained by slow evaporation of an ethanol:water:dichloromethane 8:1:1 (v:v:v) solution. Cocrystals of 2,4-diamino-6-dodecyl-*s*-triazine and 1-*N*-methyl-6-tridecyluracil were obtained by dissolving both components in warm aqueous ethanol, followed by slow cooling and evaporation of solvent in air.

Single-Crystal X-ray Structure Determination of 5 and of the Complexes of 2 with 11 and 4 with 15. Crystals suitable for X-ray structure determination were mounted on a Lindemann-glass capillary and transferred to an Enraf-Nonius CAD4-T diffractometer on a rotating anode (Mo Kα radiation, graphite monochromator, $\lambda = 0.710\ 73$ Å, $T = 150$ K). Data were corrected for Lorentz-polarization effects and for linear instability in the periodically measured reference reflections, but not for absorption. The unit-cell parameters were checked for the presence of higher lattice symmetry.[39] The structures were solved by automated direct methods (SHELXS-86[40]). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-93[41]). No observance criterion was applied during refinement. All hydrogen atoms were located on different Fourier maps; their coordinates were included as parameters in the refinement. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were refined with a fixed isotropic thermal parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms.

Crystal data for compound **5** are as follows: $C_9H_{13}N_5O_3$, $M_r = 239.23$, colorless plate-shaped crystal ($0.05 \times 0.2 \times 0.7$ mm), triclinic, space group $P\bar{1}$ with $a = 8.7289(8)$ Å, $b = 10.9012(7)$ Å, $c = 11.5137(7)$ Å, $\alpha = 95.915(5)°$, $\beta = 93.588(6)°$, $\gamma = 93.153(6)°$, $V = 1085.54(14)$ Å^3, $Z = 4$, $D_c = 1.464$ g·cm^{-3}, μ(Mo Kα) = 1.1 cm^{-1}, 8465 reflections measured ($1.78° < \theta < 27.50°$), 4985 independent ($R_{int} = 0.033$), final $wR2 = 0.106$, $R1 = 0.043$ (for 3791 $F_o > 4\sigma(F_o)$), $S = 1.04$ for 385 parameters. No residual density outside −0.26 and 0.24 e Å^{-3}.

Crystal data for complex **2·11** are as follows: $C_4H_7N_5O$·$C_5H_6N_2O_3$, $M_r = 283.24$, colorless block-shaped crystal ($0.3 \times 0.5 \times 0.7$ mm), triclinic, space group $P\bar{1}$ with $a = 6.9057(6)$ Å, $b = 9.0323(8)$ Å, $c = 10.0639(8)$ Å, $\alpha = 73.793(7)°$, $\beta = 72.431(7)°$, $\gamma = 80.202(7)°$, $V = 572.13(10)$ Å^3, $Z = 2$, $D_c = 1.644$ g.cm^{-3}, μ(Mo Kα) = 1.3 cm^{-1}, 5391 reflections measured ($2.19° < \theta < 27.50°$), 2610 independent ($R_{int} = 0.078$), final $wR2 = 0.137$, $R1 = 0.052$ (for 1479$F_o > 4\sigma(F_o)$), $S = 1.01$ for 220 parameters. No residual density outside −0.27 and 0.32 e Å^{-3}.

Crystal data for complex **4·15** are as follows: $C_{15}H_{29}N_5$·$C_{17}H_{30}N_2O_2$, $M_r = 573.87$, colorless plate-shaped crystal crystal ($0.02 \times 0.6 \times 1.0$ mm), triclinic, space group $P\bar{1}$ with $a = 6.7134(13)$ Å, $b = 7.7297(7)$ Å, $c = 31.988(3)$ Å, $\alpha = 93.917(7)°$, $\beta = 91.894(11)°$, $\gamma = 93.704(12)°$, $V = 1651.4(4)$ Å^3, $Z = 2$, $D_c = 1.154$ g·cm^{-3}, μ(Mo Kα) = 0.7 cm^{-1}, 12414 reflections measured ($0.64° < \theta < 27.50°$), 7576 independent ($R_{int} = 0.064$), final $wR2 = 0.174$, $R1 = 0.071$ (for 3332 $F_0 > 4\sigma(F_0)$), $S = 1.02$ for 547 parameters. No residual density outside −0.25 and 0.24 e Å^{-3}.

The authors have deposited all atomic coordinates, thermal parameters, and bond lengths and angles of the crystal

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structures of **5** and of the complexes **2·11** and **4·15** at the Cambridge Crystallographic Data Centre. These data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IE2, U.K.

2,4-Diamino-6-dodecyl-*s*-triazine (2). Tridecanenitrile (20.3 g, 0.104 mol) was heated under reflux overnight with dicyanodiamide (9.18 g, 0.109 mol) and potassium hydroxide (1.77 g, 0.031 mol) in dry 2-propanol (120 mL). After cooling to ambient temperature, ice−water was added and the resultant white precipitate filtered. The solid was crystallized from water:ethanol 1:1 (v:v), yielding large colorless plates (70%). These crystals appeared to contain the product and starting material in a 1:1 ratio.[42] Dissolving the solid in warm methanol and subsequent addition of a large amount of hexane caused **2** to precipitate as tiny needles. Repeating this procedure gave pure **2** (8.72 g, 30%), mp 121.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.12 (br, 4H), 2.48 (t, 3H), 1.69 (m, 2 H), 1.26 (m, 18 H), 0.88 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ: 179.7, 167.1, 38.8, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 27.9, 22.7, 14.1. IR (KBr) ν: 3493, 3452, 3394, 3315, 3144, 2916, 2850, 1628, 1550, 1433 cm^{-1}. Anal. calcd for $C_{15}H_{29}N_5$: C, 64.48; H, 10.46; N, 25.06. Found: C, 64.09; H, 10.59; N, 24.88.

2,4-Diamino-6-(methoxymethyl)-*s*-triazine (3). A mixture of dicyanodiamide (31.0 g, 0.37 mol), methoxyacetonitrile[43] (29.2 mL, 0.34 mol), and potassium hydroxide (5.70 g, 0.084 mol) in dry 2-propanol (240 mL) was heated under reflux overnight. After being cooled to 0 °C, the resulting white precipitate was filtered and washed with cold water (crude yield 50.5 g, 88%). An analytical sample was prepared by recrystallization from hot water, giving colorless plates. Only after thorough drying at 50 °C in vacuo was satisfactory elemental analysis of **3** obtained, mp 258−260 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.95, 6.75 (br, 4H), 4.05 (s, 2H), 3.29 (s, 3H). ^{13}C-NMR (DMSO-d_6) δ: 174.6, 167.3, 74.2, 58.5. IR (KBr) ν: 3385, 3333, 3231, 3146, 1667, 1638, 1546, 1469 cm^{-1}. Anal. Calcd for $C_5H_9N_5O$: C, 38.71; H, 5.85; N, 45.14. Found: C, 39.06; H, 5.77; N, 45.50.

2,4-Bis(acetylamino)-6-(methoxymethyl)-*s*-triazine (5). To 2,4-diamino-6-(methoxymethyl)-*s*-triazine (**3**) (8.55 g, 0.050 mol) was added acetic anhydride (50 mL) (no reaction occurred). After boiling for 15 min under reflux, the suspension turned into a clear solution, and then reflux was continued for 2 h. After cooling, most of the acetic anhydride was removed in vacuo. Diethyl ether was added, and the resultant suspension was filtered and washed thoroughly with diethyl ether. After drying at 50 °C in vacuo, crude **5** was obtained (8.14 g, 68%). An analytical sample of **5**, as suitable X-ray quality crystals, was prepared by recrystallization from hot ethyl acetate after treatment with activated carbon, mp 165−166 °C. ^{1}H-NMR ($CDCl_3$) δ: 9.67 (br, 2H), 4.54 (s, 2H), 3.53 (s, 3H), 2.56 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ: 178.8, 172.6, 164.4, 74.4, 60.0, 26.5. IR (KBr) ν: 3477, 3294, 3162, 2932, 1737, 1688, 1589, 1496, 1298 cm^{-1}. Anal. Calcd for $C_9H_{13}N_5O_3$: C, 45.19; H, 5.48; N, 29.27. Found: C, 45.24; H, 5.31; N, 29.16.

2,4-Bis(hexanoylamino)-6-(methoxymethyl)-*s*-triazine (6). To a suspension of 2,4-diamino-6-(methoxymethyl)-*s*-triazine (8.55 g, 0.050 mol) in boiling dry pyridine (35 mL) was added hexanoyl chloride (14 mL, 0.102 mol) slowly. After 20 min of reflux a clear solution had formed that was then cooled to ambient temperature. Addition of ethyl acetate (100 mL) gave a suspension that was filtered. The filtrate was evaporated, and the residue was dissolved in dichloromethane. The solution was washed with dilute sodium bicarbonate solution and with water, dried over sodium sulfate, filtered, and concentrated to ca. 50 mL. Addition of a large amount of hexane caused **6** to precipitate slowly. The product was filtered and washed with hexane, and the precipitation procedure was repeated. Drying in vacuo gave pure **6** (12.91 g, 74%). An analytical sample was prepared by dissolution in hot ethyl acetate, treatment with activated carbon, and filtration. Adding hexane caused the product to precipitate as white grains, mp 82−83 °C. ^{1}H-NMR ($CDCl_3$) δ: 9.91 (br, 2H), 4.50 (s, 2H), 3.50 (s, 3H), 2.83 (t, 4H), 1.68 (m, 4H), 1.30 (m, 8H), 0.88 (t, 6H). ^{13}C-NMR ($CDCl_3$) δ: 178.8, 175.5, 164.4, 74.4, 59.9, 38.4, 31.9, 24.9, 22.9, 14.4. IR (KBr) ν: 3252, 3201, 3145, 2955, 2928, 2871, 1736, 1891, 1583, 1485, 1381, 1322 cm^{-1}. Anal. Calcd for $C_{17}H_{29}N_5O_3$: C, 58.10; H, 8.32; N, 19.93. Found: C, 57.89; H, 8.40; N, 19.70.

2,4-Bis(pivaloylamino)-6-methyl-*s*-triazine (7). To a suspension of 2,4-diamino-6-methyl-*s*-triazine (6.26 g, 0.050 mol) in boiling dry pyridine (110 mL) was added pivaloyl chloride (2.6 mL, 0.102 mol) slowly via a syringe. After being boiled under reflux for 75 min, the clear solution was poured into ice−water, and the resultant precipitate was filtered and dissolved in dichloromethane. The dichloromethane phase was extracted with water, dried over sodium sulfate, filtered, and partially evaporated. Addition of a large amount of hexane caused the product to precipitate as off-white crystals (9.65 g, 66%). Recrystallization from hot ethanol:water 1:3 (v:v) yielded crystals of the hydrate of **7**, mp (of the anhydrate) 221−222 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (br, 2 H), 2.58 (s, 3H), 1.32 (s, 18 H). ^{13}C-NMR ($CDCl_3$) δ: 179.2, 176.3, 163.9, 40.5, 27.1, 25.8. IR (KBr) ν: 3477, 3263, 2975, 1708, 1588, 1487, 1397, 1360 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_5O_2\cdot 0.5H_2O$: C, 55.61; H, 8.00; N, 23.16. Found: C, 55.56; H, 7.83; N, 23.24.

6-Tridecylthiouracil (9) (preparation analogous to the method of Gershon).[44] Ethyl 3-oxopalmitate was prepared using the method of Huckin.[45] To 60% sodium hydride (4.42 g, 0.11 mol) in dry THF (250 mL) was added at 0 °C ethyl acetoacetate (13.0 g, 0.10 mol). After 15 min of stirring at this temperature, 1.6 M *n*-butyllithium in hexane (65.6 mL, 0.105 mol) was added dropwise with a syringe at the same temperature. After the mixture was stirred for 15 min at 0 °C, dodecyl bromide (27.6 g, 0.11 mol) was added. Then the temperature was allowed to rise to rt during 30 min, whereupon the mixture was poured into acidified ice−water and extracted several times with diethyl ether. The combined diethyl ether layers were washed with water, dried over sodium sulfate, and evaporated to dryness to yield a yellow oil (33.77 g). NMR showed the oil to consist of ethyl 3-oxopalmitoate and unreacted dodecyl bromide in a ∼3:2 ratio (yield 67%). The crude product was used without purification.

Freshly cut sodium (2.17 g, 0.094 mol) was dissolved in dry ethanol (94 mL). To the solution were added subsequently thiourea (5.0 g, 0.066 mol) and crude ethyl 3-oxopalmitoate (23.7 g, ca. 0.047 mol) at once. After reflux overnight, the solution was cooled to ambient temperature and acidified with dilute hydrochloric acid. After removal of most of the solvent in vacuo, the product was filtered off. Crystallization from ethanol gave pure **9** (8.39 g, 57%). An analytical sample was prepared by recrystallization from water:ethanol 4:1(v:v), mp 154−155 °C. ^{1}H-NMR (DMSO-d_6) δ: 12.34 and 12.00 (br, 2 H), 5.66 (s, 1H), 2.32 (t, 2H), 1.31 (m, 2H), 1.21 (m, 20 H), 0.82 (t, 3H). ^{13}C-NMR (DMSO-d_6) δ: 176.4, 161.4, 103.2, 31.7, 29.4, 29.3, 29.1 (overlapping peaks), 29.0, 28.7, 27.6, 22.5, 14.3. IR (KBr) ν: 3058, 2955, 2918, 2849, 1662, 1639, 1585 cm^{-1}. Anal. Calcd for $C_{17}H_{30}N_2OS$: C, 65.76; H, 9.74; N, 9.02. Found: C, 65.89; H, 9.78; N, 9.06.

6-Tridecyluracil (11). 6-Tridecylthiouracil (4.10 g, 0.013 mol) and chloroacetic acid (2.49 g, 0.026 mol) were heated under reflux in water (26 mL) in air during 6 h, whereafter a clear water layer with a floating pasty oil was obtained. After concentrated hydrochloric acid (6.5 mL) was added , reflux was continued overnight to yield a clear liquid containing crystals. After the liquid was cooled in an ice bath, the crystals were filtered off and recrystallized from chloroform and then from ethanol:water 4:1 (v:v) to yield **11** as tiny white needles, (3.25 g, 85%, mp 172−173.5 °C). ^{1}H-NMR (DMSO-d_6) δ: 10.88 and 10.78 (br, 2H), 5.30 (s, 1H), 2.24 (t, 2H), 1.51 (m, 2 H), 1.22 (m, 20 H), 0.83 (t, 3H). ^{13}C-NMR (DMSO-d_6) δ: 165.0, 157.2, 152.0, 98.2, 32.0, 31.8, 29 (overlapping peaks), 27.6, 22.1, 13.9. IR (KBr) ν: 2954, 2920, 2847, 1740, 1650 cm^{-1}. Anal. calcd

(42) Addition of acetonitrile to a deuteriochloroform solution of pure 2,4-diamino-6-dodecyl-*s*-triazine does not result in any proton shifts.

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for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.60; H, 10.44; N, 9.22.

1-*N*-Methyl-6-tridecyluracil (13). 2,4-Bis[(trimethylsilyl)oxy]-6-tridecylpyrimidine was prepared as described for 2,4-bis[(trimethylsilyl)oxy]-6-[[(trimethylsilyl)oxy]methyl]-pyrimidine (vide infra). The crude product was distilled quickly with the aid of a burner (79%, bp 205 °C, 0.8 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 6.09 (s, 1H), 2.48 (t, 2H), 1.59 (m, 2H), 1.21−1.18 (m, 20 H), 0.81 (t, 3 H), 0.31 (s, 18 H). ^{13}C-NMR ($CDCl_3$) δ: 174.5, 170.1, 163.1, 102.2, 32.6, 31.7, 29.6, 29.5, 29.4 (overlapping peaks), 29.3, 28.5, 22.7, 14.1, 0.4.

The 2,4-bis[(trimethylsilyl)oxy]-6-tridecylpyrimidine (3.79 g, 0.008 64 mol) was set aside with freshly distilled methyl iodide (10 mL) in the dark. After a period of 2 weeks, ethanol was added and the methyl iodide evaporated in vacuo into a cold trap. Dilute hydrochloric acid was added and the product filtered. The product was dissolved in chloroform, and the chloroform solution was successively extracted with dilute hydrochloric acid, dilute potassium permanganate solution in dilute acid, sodium sulfite solution, dilute hydrochloric acid, and water. The chloroform layer was dried over sodium sulfate, filtered, and diluted with hexane. Partial evaporation of the solvent gave a white precipitate, which was filtered off. Recrystallization from water:ethanol 1:1 (v:v) and then ethanol gave analytically pure **13** as tiny white needles (1.84 g, 54% based on uracil **11**, mp 138.6−139.8 °C). ^{1}H-NMR ($CDCl_3$) δ: 10.19 (br, 1H), 5.50 (s, 2H), 3.31 (s, 3H), 2.40 (t, 2H), 1.52 (m, 2H), 1.33 (m, 2H), 1.19 (m, 8 H), 0.81 (t, 3H). ^{13}C-NMR ($CDCl_3$) δ: 163.3, 157.6, 152.2, 100.6, 32.6, 31.8, 30.3, 29.5 (overlapping peaks), 29.4, 29.3, 29.2, 29.1, 28.9, 27.0, 22.5, 14.0. IR (KBr) ν: 3176, 3044, 2953, 2922, 2848, 1717, 1679 cm^{-1}. Anal. Calcd for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46; N, 9.08. Found: C, 70.38; H, 10.78; N, 8.99.

Column chromatography (silica, $CHCl_3$:MeOH 200:3 v/v) of the mother liquor of the crystallization of **13** afforded another crop of pure **13** (0.31 g, 9% based on uracil **11**) (R_f = 0.20) and a small amount of 3-*N*-methyl-6-tridecyluracil (**14**) (0.25 g, 7% based on uracil **11**, mp 147.0−147.4 °C) (R_f = 0.30). ^{1}H-NMR ($CDCl_3$) δ: 10.61 (br, 1H), 5.59 (s, 2H), 3.30 (s, 3H), 2.39 (t, 2H), 1.64 (m, 2H), 1.32 (m, 2H), 1.25 (m, 18H), 0.87 (t, 3H). ^{13}C-NMR ($CDCl_3$): δ = 163.7, 153.8, 153.5, 99.2, 32.6, 31.8, 29.6 (overlapping peaks), 29.5, 29.4, 29.3, 29.1, 28.9, 27.0, 26.8, 22.6, 14.0. IR (KBr) ν: 3420, 2919, 2850, 1738, 1637, 1598 cm^{-1}. MS: *m/e* 308.30 ($M^{\cdot+}$, 4.6). Anal. Calcd for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46; N, 9.08. Found: C, 70.92; H, 10.41; N, 8.68.

1-*N*-Methyl-6-(hydroxymethyl)uracil (16). To a suspension of 6-(hydroxymethyl)uracil[15] (9.95 g, 0.070 mol) in dry THF (500 mL) were added trimethylsilyl chloride (28 mL, 0.22 mol) at once and dry triethylamine (22 mL, 0.22 mol) in THF (200 mL) dropwise (analogous to the method of Nishimura).[46] After being stirred overnight, the suspension was filtered (under nitrogen) and the white cake was thoroughly extracted with dry THF. The filtrate was evaporated to dryness, and the residual yellow oil was distilled (23.72 g, 95%, bp 109 °C, 0.05 mmHg). The product, 2,4-bis[(trimethylsilyl)oxy]-6-[[(trimethylsilyl)oxy]methyl]pyrimidine, is extremely sensitive to moisture. ^{1}H-NMR ($CDCl_3$) δ: 6.21 (s, 1H), 4.23 (s, 2H), 0.25 (s, 18H), 0.02 (s, 9H). ^{13}C-NMR ($CDCl_3$) δ: 174.1, 171.2, 163.1, 100.2, 64.9, 0.8, 0.8, 0.2.

To the distilled 2,4-bis(trimethylsiloxy)-6-methylpyrimidine (23.7 g, 0.066 mol) was added freshly distilled methyl iodide (ca. 100 mL), under an atmosphere of dry nitrogen. After the solution was left to stand in the dark for 2 weeks, 1 M hydrochloric acid (300 mL) was added. After the mixture was stirred for 1 h, methyl iodide was distilled off under reduced pressure into a cold trap. The water layer was extracted repeatedly with diethyl ether to remove the yellow color, neutralized to pH = 7, and evaporated to ca. 200 mL. Cooling to 0 °C gave pure **16** as nice crystals (5.49 g, 53%, mp 235−237 °C, slight dec starting at 230 °C). Another 20% yield of **16** was obtained by evaporation of the mother liquor to dryness, extraction of the residual solid with hot DMSO, evaporation to dryness, and finally crystallization from water. ^{1}H-NMR (DMSO-d_6) δ: 5.70 (br, 1H), 5.60 (s, 1H), 4.33 (s, 2H), 3.19 (s, 3H) ppm. ^{13}C-NMR (DMSO-d_6) δ: 163.2, 158.1, 152.2, 98.3, 59.3, 29.3 ppm. IR (KBr) ν: 3286, 3174, 3045, 1714, 1674 cm^{-1}. Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.43; H, 5.41; N, 17.95.

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Supporting Information Available: NMR-spectra of compound **14** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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