# Strong Dimerization of Ureidopyrimidones via Quadruple Hydrogen Bonding

**Felix H. Beijer,[1] Rint P. Sijbesma,*[,1] Huub Kooijman,[2] Anthony L. Spek,[2] and E. W. Meijer*[,1,3]**

*Contribution from the Laboratory of Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands, and the Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry Padualaan 8, 3584 CH, Utrecht, The Netherlands*

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**Abstract:** 6-Methyl-2-butylureidopyrimidone dimerizes via four hydrogen bonds in the solid state as well as in $CHCl_3$ solution via a donor−donor−acceptor−acceptor (DDAA) array of hydrogen bonding sites in the 4[1H]-pyrimidinone tautomer. An intramolecular hydrogen bond from the pyrimidine NH group to the urea oxygen atom preorganizes the molecules for dimerization. The dimerization constant of the dimer in $CHCl_3$ exceeds $10^6$ $M^{-1}$. In $CHCl_3$ containing DMSO, the dimer is in equilibrium with the monomeric 6[1H]-pyrimidinone tautomer. In 6-phenyl-2-butylureidopyrimidone, the 4[1H]-pyrimidinone tautomer coexists with the pyrimidin-4-ol form, which dimerizes with similar high dimerization constants via four hydrogen bonds in a DADA array. The latter tautomer predominates in derivatives with electronegative 6-substituents, like 6-nitrophenyl- and 6-trifluoromethyl-2-butylureidopyrimidone. Due to its simple preparation and high dimerization constant, the ureidopyrimidone functionality is a useful building block for supramolecular chemistry.

## Introduction

In many synthetic self-assembling structures, the components are held together by arrays of double or triple hydrogen bonds.[4] Due to their strength, directionality, and specificity, arrays of multiple hydrogen bonds are useful building blocks for the reliable assembly of complex structures. This combination of advantageous properties is expected to be particularly pronounced in large arrays of hydrogen bonds. That such arrays indeed form very stable complexes has been shown for receptors for urea,[5] guanines,[6] and barbiturates,[7] for self-assembled receptors,[8] and for cyclic peptides that self-assemble to form nanotubes.[9] However, the use of these arrays is limited by the synthetic efforts required for their preparation. Recently, we reported on the dimerization of acylated triazines[10] and pyrimidines via DADA (donor−acceptor−donor−acceptor) arrays, and on the stabilization of these dimers by intramolecular hydrogen bonds.[11] On the basis of differences in secondary interactions,[12] dimers of DDAA arrays are predicted to be more stable than DADA dimers (Figure 1). In search of stable hydrogen-bonded dimers, we have therefore turned our attention to ureidopyrimidinones **1**.[13]

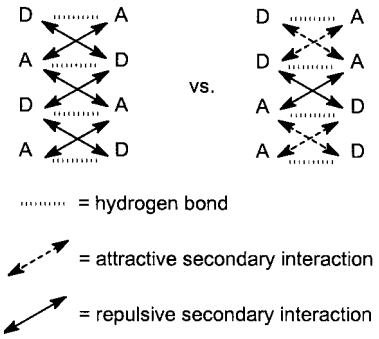


**Figure 1.** Interactions in DADA and DDAA dimers. While both dimers have four primary attractive hydrogen bonds, the DADA dimer has six repulsive secondary interactions, whereas the DDAA dimer has two repulsive and four attractive secondary interactions.

In analogy to parent isocytosines,[14] the 6[1H]-pyrimidinone tautomer (Figure 2) is expected to be the most stable tautomeric form of an isolated 2-ureido-4-pyrimidinone molecule. However, ureidopyrimidinones may actually exist as dimers of 4[1H]-pyrimidinone and pyrimidinol tautomeric forms, since considerable stabilization is expected by dimerization of the linear array of four hydrogen bonds. Notably, both dimerization via

(1) Eindhoven University of Technology.
(2) Bijvoet Center for Biomolecular Research.
(3) To whom correspondence should be addressed.
(4) For a review with many examples of hydrogen-bonded self-assembling complexes, see: Lawrence, D. S.; Jiang, T.; Levitt, M. *Chem. Rev.* **1995**, *95*, 2229.
(5) (a) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. (b) Bell, T. W.; Hou, Z. *Angew. Chem.* **1997**, *109*, 1601; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1536.
(6) Bell, T. W.; Hou, Z.; Zimmerman, S. C.; Thiesen, P. A. *Angew. Chem.* **1995**, *107*, 2321; *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2163.
(7) Geib, S. J.; Hirst, S. C.; Vicent, C.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1283.
(8) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem.* **1993**, *105*, 1820; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699.
(9) Ghadiri, M. R.; Granja, J. R.; Milligan, R. A.; McRee, D. E.; Khazanovich, N. *Nature* **1993**, *366*, 324.
(10) Beijer, F. H.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W.; Kooijman, H.; Spek, A. L. *J. Org. Chem.* **1996**, *61*, 6371.
(11) Beijer, F. H.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem.* **1998**, *110*, 79; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 75.
(12) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008. (b) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810.
(13) The synthesis of several ureidopyrimidones has been reported: (a) Fan, J.; Cheng, C. C. *J. Heterocycl. Chem.* **1993**, *30*, 1273. (b) Urbanski, T.; Serafin, B.; Zylowski, J. *J. Med. Chem.* **1967**, *10*, 521. (c) Kreutzberger, A.; Schimmelpfennig, H. *Arch. Pharm.* **1981**, *314*, 34. (d) Vasilev, G. *Dokl. Bolg. Akad. Nauk* **1990**, *43*, 57.

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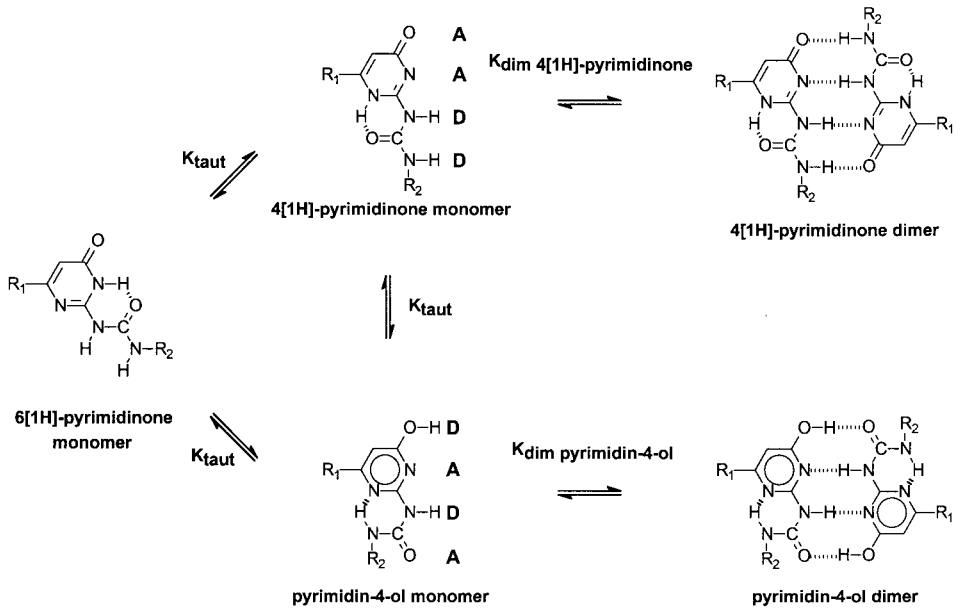
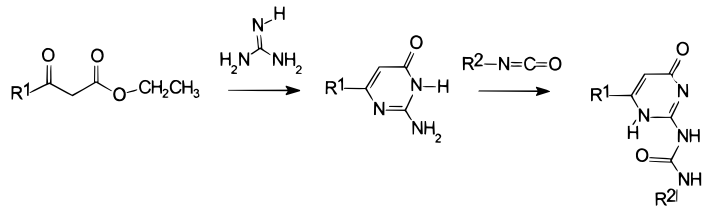



**Figure 2.** Equilibria between tautomeric forms and between monomer and dimer of compounds **1**.

**Scheme 1**



**2a:** $R^1 = CH_3$ **3a:** $R^1 = CH_3$ **1a:** $R^1 = CH_3$, $R^2 = n\text{-}C_4H_9$ (99%)
**1b:** $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$ (21%)

**2b:** $R^1 = n\text{-}C_{13}H_{27}$ **3b:** $R^1 = n\text{-}C_{13}H_{27}$ (36%) **1c:** $R^1 = n\text{-}C_{13}H_{27}$, $R^2 = n\text{-}C_4H_9$ (81%)
**1d:** $R^1 = n\text{-}C_{13}H_{27}$, $R^2 = t\text{-}C_4H_9$ (70%)
**1e:** $R^1 = n\text{-}C_{13}H_{27}$, $R^2 = C_6H_5$ (30%)
**1f:** $R^1 = n\text{-}C_{13}H_{27}$, $R^2 = p\text{-}NO_2\text{-}C_6H_4$ (quant.)
**1g:** $R^1 = n\text{-}C_{13}H_{27}$, $R^2 = p\text{-}NEt_2\text{-}C_6H_4$ (22%)

**2c:** $R^1 = C_6H_5$ **3c:** $R^1 = C_6H_5$ (64%) **1h:** $R^1 = C_6H_5$, $R^2 = n\text{-}C_4H_9$ (82%)
**1i:** $R^1 = C_6H_5$, $R^2 = t\text{-}C_4H_9$ (80%)

**2d:** $R^1 = p\text{-}NO_2\text{-}C_6H_4$ **3d:** $R^1 = p\text{-}NO_2\text{-}C_6H_4$ (30%) **1j:** $R^1 = p\text{-}NO_2\text{-}C_6H_4$, $R^2 = n\text{-}C_{18}H_{37}$ (quant.)

**2e:** $R^1 = CF_3$ **3e:** $R^1 = CF_3$ (63%) **1k:** $R^1 = CF_3$, $R^2 = n\text{-}C_4H_9$ (27%)

a DDAA array as well as via a DADA array is possible. In both cases, the linear array of the four hydrogen bonds is preorganized by an intramolecular hydrogen bond, a concept shown previously to enhance the stability of dimers considerably.[11]

Here we report on the formation of exceptionally stable DDAA dimers of a simple ureidopyrimidinone derivative, which is synthesized in one step from commercially available starting materials. The full scope of dimerization of ureido pyrimidones is investigated in a range of derivatives, which dimerize via four hydrogen bonds in either DDAA or DADA dimers.

## Results

**Ureidopyrimidinone Dimers.** 2-Butylureido-4-pyrimidinone **1a** is readily prepared by reaction of commercially available 6-methylisocytosine **3a** with with butyl isocyanate (Scheme 1). Compound **1a** indeed forms quadruply hydrogen-bonded DDAA-dimers, both in the solid state as well in chloroform solution, as is evident from FTIR, X-ray diffraction, and NMR spectroscopy. The crystal structure of **1a** (Figure 3) shows that the molecules are in the 4[1H]-pyrimidinone form. The urea functionality is in a trans−trans conformation, and an intramolecular hydrogen bond is present from the pyrimidine N−H to the urea carbonyl group. This results in a preorganized DDAA array of hydrogen bonding sites, which forms a centrosym-

(14) For studies of tautomerization of isocytosine, see: (a) Stephanian, S. G.; Radchenko, E. D.; Sheina, G. G.; Blagoi, Y. P. *J. Mol. Struct*. **1990**, *216*, 77. (b) Sheina, G. G.; Stephanian, S. G.; Radchenko, E. D.; Blagoi, Y. P. *J. Mol. Struct.* **1987**, *158*, 275. (c) Toledo, L. M.; Musa, K.; Lauher, J. W.; Fowler, F. W. *Chem. Mater*. **1995**, *7*, 1639. (d) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles, Advances in Heterocyclic Chemistry*; Academic Press: New York, 1976. (e) Bühlmann, P.; Badertscher, M.; Simon, W. *Tetrahedron* **1993**, *49*, 595. (f) Bühlmann, P.; Simon, W. *Tetrahedron* **1993**, *49*, 7627.

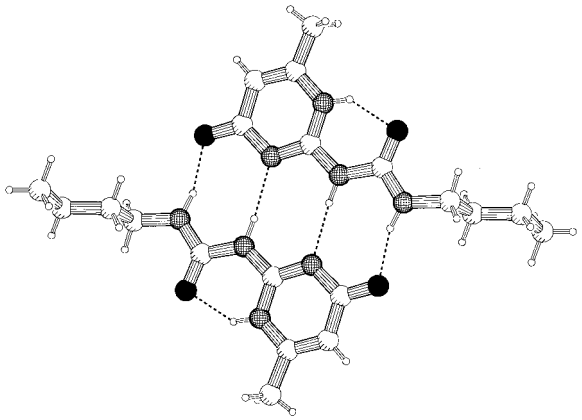


**Figure 3.** PLUTON representation of the dimer geometry of **1a** in the crystal.

metrical dimer. The DDAA array deviates slightly from linearity, the outer N—H···O hydrogen bonds being 0.209 Å shorter than the inner N—H···N hydrogen bonds (Table 1).

Strong similarity of the FTIR spectra of **1a** in the crystal and in $CDCl_3$ solution indicates that the DDAA dimers persist in solution. Bands at 3212 and 3147 $cm^{-1}$ are assigned to hydrogen-bonded NH groups, while bands of free NH groups are not observed. In the $^1H$ NMR spectrum of **1a** in $CDCl_3$ (Figure 4) the NH proton signals are found at 13.15, 11.86, and 10.15 ppm, indicative of extensive hydrogen bonding. Strong intramolecular nuclear Overhauser effects, which were used to assign the NH proton signals, confirm the 4[1H]-pyrimidinone dimer geometry in solution. Upon dilution of a $CDCl_3$ solution of **1a** to $10^{-4}$ M, the NH proton resonances do not shift, nor do any new peaks due to monomeric species appear, putting a lower limit on the dimerization constant of $4.5 \times 10^5$ $M^{-1}$ (for determination of dimerization constants, vide infra).

**Tautomeric Equilibrium between 4[1H]-Pyrimidinone and Pyrimidin-4-ol Dimers.** The scope of the dimerization of the ureidopyrimidinone functionality was investigated in a range of derivatives **1b**−**k**, bearing different substituents at the 6-position and at the terminal urea nitrogen atom. These compounds were prepared as depicted in Scheme 1. Condensation of $\beta$-keto esters **2b**−**e** with guanidine (added as guanidinium carbonate) afforded 6-substituted isocytosines **3b**−**e**. Subsequently, the isocytosine was reacted with the appropriate isocyanate to give the compounds **1b**−**k**. To improve the solubility of 6-phenyl-substituted compounds, compounds **10a**−**d**—which have three dodecyloxy chains on the phenyl group—were prepared via the route depicted in Scheme 2. Ester **4** was hydrolyzed to acid **5** and then converted to acid chloride **6** by refluxing in thionyl chloride.[15] Acid chloride **6** was converted to $\beta$-keto ester **8** via intermediate **7**.[16] $\beta$-Keto ester **8** in turn was reacted with guanidinium carbonate to afford isocytosine **9** and subsequent reaction with the appropriate isocyanate afforded target molecules **10a**−**d**.

Depending on conditions, phenyl-substituted compound **1h** crystallizes from $CHCl_3$ either as needles, or as plates. Single-crystal X-ray analysis of the needles revealed DDAA dimers of the 4[1H]-pyrimidinone tautomer (Figure 5a), similar to the dimer of **1a** (Table 1). Four independent molecules form two independent dimers, without internal crystallographic symmetry. The molecules in the platelike crystals of **1h** were found to exist as pyrimidin-4-ol dimers (Figure 5b). X-ray diffraction on several crystals revealed that at least three crystal modifications had formed, with a similar dimer geometry. In all modifications, the dimers are packed in layers. The main difference between the modifications is the relative position of the layers with respect to each other. The pyrimidinol units are dimerized via a DADA array, which is further stabilized by an intramolecular N—H···N hydrogen bond. The OH···O hydrogen bonds are short (2.58 Å), while the NH···N distance of 2.98 Å is similar to the NH···N distance in the 4[1H]-pyrimidinone dimer (Table 1). FTIR spectra of the two forms of **1h** (see Experimental Section) confirm the presence of strong hydrogen bonds in the crystals of both modifications. In particular the band of the hydrogen-bonded OH group of the pyrimidin-4-ol tautomer is found at low wavenumbers (2500 $cm^{-1}$ ).

The $^1H$ NMR spectrum in $CDCl_3$ of compound **1h** shows two sets of signals. One set of N−H signals at $\delta$ = 13.95, 12.06, 10.23 ppm, is assigned to the 4[1H]-pyrimidinone tautomer, a second set of signals at 13.6, 11.3, and 10.0 ppm, with an abundance of 13%, is assigned to the pyrimidin-4-ol tautomer. The aromatic proton signal of this tautomer resonates 0.5 ppm downfield of the alkylidene signal of the 4[1H]-pyrimidinone tautomer. The presence of the pyrimidin-4-ol tautomer is confirmed by the FTIR spectrum in $CHCl_3$. In toluene-$d_8$, the two tautomers of **1h** are present in approximately equal amounts.

In the $^1H$ NMR spectra of compounds **1**, the aromatic proton signal of the pyrimidin-4-ol tautomer is found 0.3−0.5 ppm downfield from the alkylidene proton signal of the 4[1H]-pyrimidinone tautomer. By using this assignment, the relative amounts of 4[1H]-pyrimidinone and pyrimidinol tautomers of different compounds were determined by integration of peak areas. As is evident from these data (Table 2), the pyrimidinol form is favored[14d] in ureidopyrimidinone derivatives with electron-withdrawing substituents at the 6-position. The highest amount of pyrimidinol tautomer is found in 6-nitrophenyl derivative **1j** (60% enol in $CDCl_3$) and 6-trifluoromethyl derivative **1k** (>99% enol in $CDCl_3$). The electronic substituent effect may be rationalized by the reduced stability of the enone structure in the pyrimidinone when an electron-withdrawing 6-substituent is present, while the hydrogen bond acceptor capability of its carbonyl group is reduced. Comparison of the tautomeric equilibria in compounds **10a**−**d** shows that electron-withdrawing substituents on the ureido group favor the 4[1H]-pyrimidinone tautomer. The different acidities of the NH group adjacent to the substituents are also reflected in the relative exchange rates of N−H signals with $D_2O$. The N−H protons adjacent to the butyl substituent in **10a** or the *p*-di(ethylamino)-phenyl substituent in **10d** exchange slower than corresponding protons adjacent to a phenyl or *p*-nitrophenyl substituents in compounds **10b** and **10c**.

The ratio of 4[1H]-pyrimidinone and pyrimidin-4-ol tautomers of compound **10a** in THF-$d_8$ is concentration-dependent (Figure 6), and the position of the N−H and O−H signals of the pyrimidin-4-ol tautomer shifts upfield upon dilution, while the positions of the 4[1H]-pyrimidinone signals do not shift. These observations suggest that the 4[1H]-pyrimidinone tautomer is dimeric troughout the concentration range studied, whereas the pyrimidin-4-ol dimer dissociates at low concentrations. Hence, the pyrimidin-4-ol tautomer is the most stable form of monomeric **10a** in THF-$d_8$.

(15) Palmans, A. R. A.; Vekemans, J. A. J. M.; Fischer, H.; Hikmet, R. A.; Meijer, E. W. *Chem. Eur. J.* **1997**, *3*, 300.

(16) (a) Perkin, W. H.; Weizmann, C. *J. Chem. Soc.* **1906**, *89 II*, 1655. (b) Bradley, W.; Robinson, R. *J. Chem. Soc.* **1928**, 1548. (c) Hunsdiecker, H. *Berichte* **1942**, *75*, 1190. (d) Günthard, H. H.; Heinemann, S. D.; Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 1147.

**Table 1.** Bond Distances (Å) and X−H−X Angles (deg) in the Crystal Structures of **1a** and of the 4[1H]-Pyrimidinone and Pyrimidin-4-ol Tautomers of **1h**

| | N−H···N | | X−H···O | | |
|---|---|---|---|---|---|
| compound | distance | angle | distance[a] | angle | hydrogen bond length difference |
| **1a** | 2.966(3) | 175(3) | 2.757(3) | 163(3) | 0.209 |
| 4[1H]-pyrimidinone **1h**[b] | 2.95(1) | 172(6) | 2.78(5) | 166(3) | ∼0.17 |
| pyrimidin-4-ol **1h**[c] | 2.98(1) | 173(4) | 2.58(1) | 169(3) | ∼0.40 |

[a] X = N in **1a** and 4[1H]-pyrimidinone tautomer of **1h**; X = O in pyrimidin-4-ol tautomer of **1h**. [b] Average values of the four independent molecules in the crystal. [c] Average of six values from two crystallographically nonequivalent molecules in each of the three pyrimidin-4-ol polymorphs.

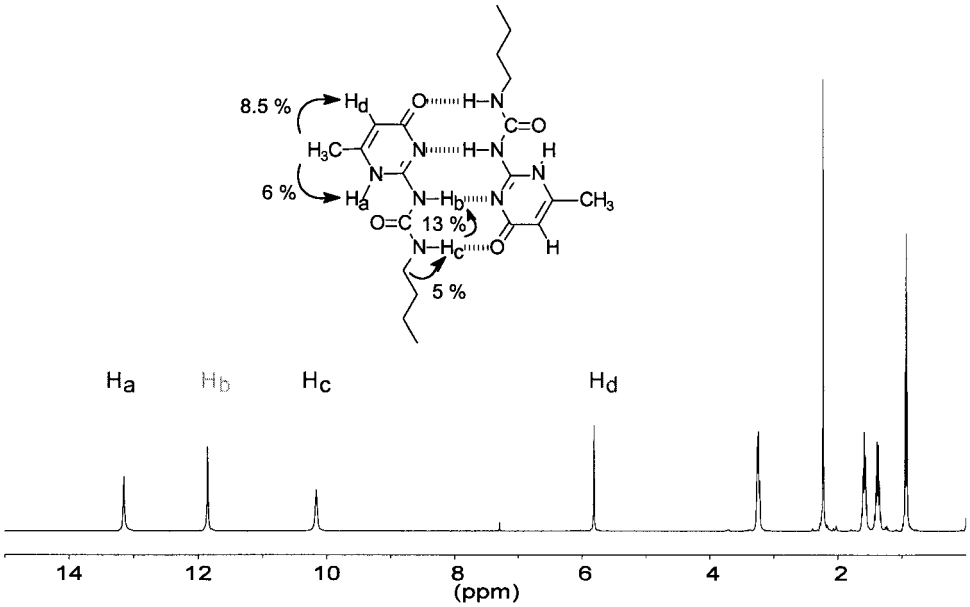
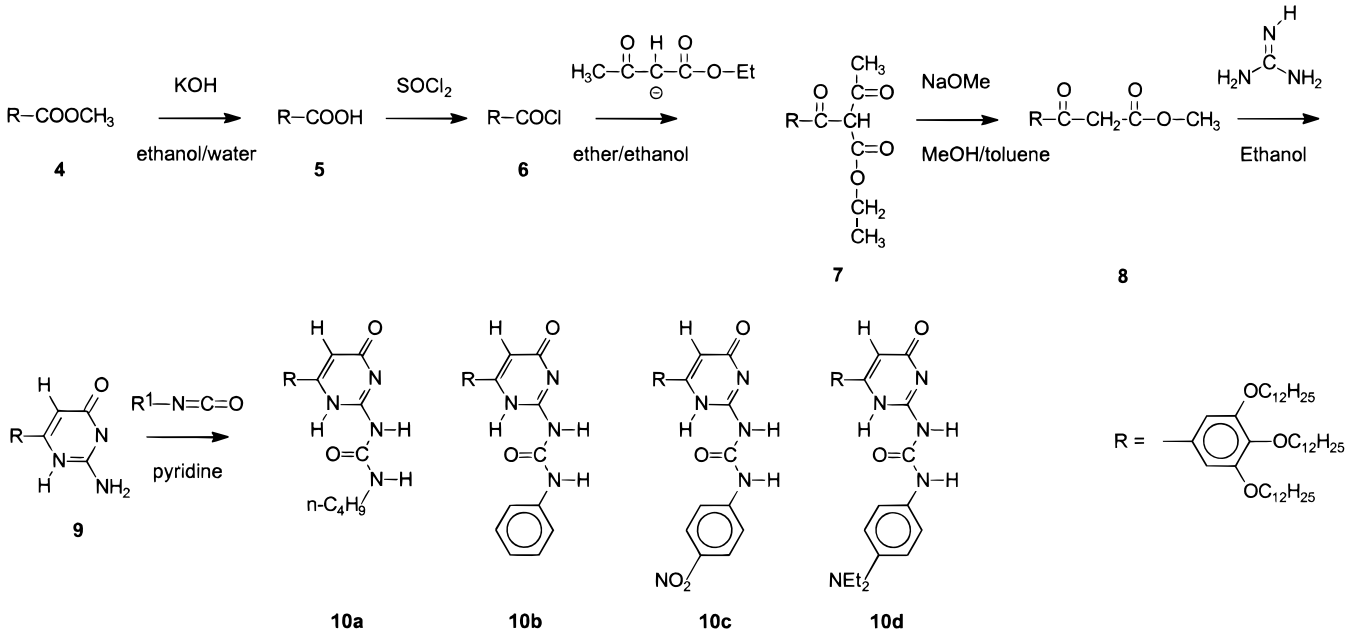



**Figure 4.** $^1$H NMR spectrum of **1a** in $CDCl_3$. Nuclear Overhauser effects between protons are indicated with arrows.

**Scheme 2**




**Dimerization Constants.** Strong dimerization of compounds **1** in $CDCl_3$ prevented us from using the concentration dependence of the $^1$H NMR spectrum for determination of the dimerization constant. As was discussed above, dilution of **1a** in chloroform did not result in perceivable dissociation. Dilution of trifluoromethyl derivative **1k**, which exists exclusively as dimers of the pyrimidin-4-ol tautomer in chloroform, to $10^{-4}$ M does also not result in perceivable dissociation. Dilution of a $CDCl_3$ solution of compound **1i**—which is present as a 1:1 mixture of 4[1H]-pyrimidinone and pyrimidin-4-ol dimers—to $10^{-4}$ $M^{-1}$ does not affect the ratio of 4[1H]-pyrimidinone to pyrimidin-4-ol signals. A conservative estimate of less than

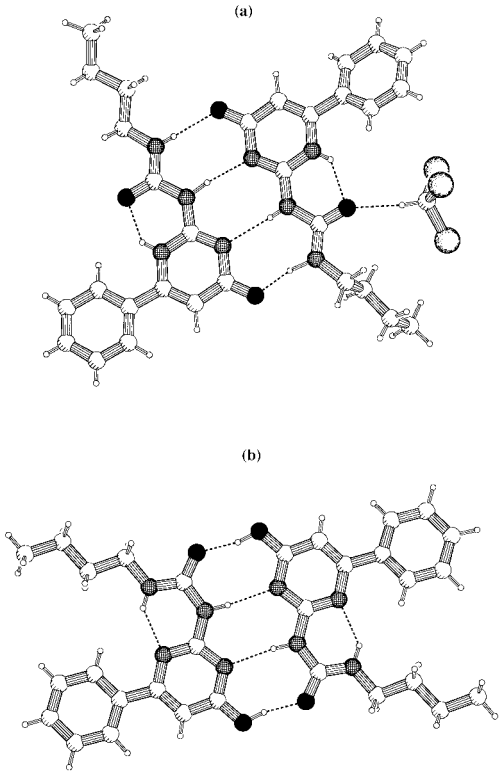
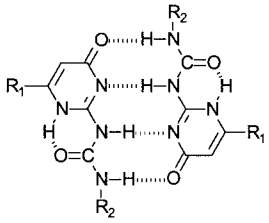
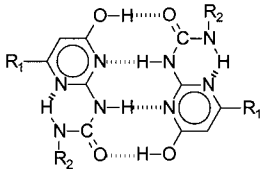



**Figure 5.** (a) Dimer geometry of the molecules of **1h** in the 4[1H]-pyrimidinone tautomer in the needle-shaped crystal and (b) dimer geometry of the molecules of **1h** in the pyrimidin-4-ol tautomer in the plate-shaped crystals.

**Table 2.** Relative Amounts 4[1H]-Pyrimidinone and Pyrimidin-4-ol Tautomers in $CDCl_3$ and Toluene-$d_8$[a]



4[1H]-pyrimidinone



pyrimidin-4-ol

| | | | % 4[1H]-pyrimidinone | |
|---|---|---|---|---|
| compound | $R^1$ | $R^2$ | in $CDCl_3$ | in toluene-$d_8$ |
| **1a** | $CH_3$ | *n*-$C_4H_9$ | >99 | insoluble |
| **1b** | $CH_3$ | *t*-$C_4H_9$ | 97 | |
| **1c** | $C_{13}H_{27}$ | *n*-$C_4H_9$ | >99 | 87 |
| **1d** | $C_{13}H_{27}$ | *t*-$C_4H_9$ | 96.5 | 76 |
| **1e** | $C_{13}H_{27}$ | $C_6H_5$ | >99 | 98 |
| **1f** | $C_{13}H_{27}$ | *p*-$NO_2C_6H_5$ | >99 | insoluble |
| **1g** | $C_{13}H_{27}$ | *p*-$NEt_2C_6H_5$ | >99 | 97 |
| **1h** | $C_6H_5$ | *n*-$C_4H_9$ | 87 | 42 |
| **1i** | $C_6H_5$ | *t*-$C_4H_9$ | 50 | 44 |
| **1j** | *p*-$NO_2C_6H_5$ | *n*-$C_{18}H_{37}$ | 40 | insoluble |
| **1k** | $CF_3$ | *n*-$C_4H_9$ | <1 | |
| **10a** | $C_6H_2(OC_{12}H_{25})_3$ | *n*-$C_4H_9$ | 87 | 57 |
| **10b** | $C_6H_2(OC_{12}H_{25})_3$ | $C_{6H5}$ | 93 | 77 |
| **10c** | $C_6H_2(OC_{12}H_{25})_3$ | *p*-$NO_2C_6H_5$ | >99 | >99 |
| **10d** | $C_6H_2(OC_{12}H_{25})_3$ | *p*-$NEt_2C_6H_5$ | 85 | 51 |

[a] Ratios were identical at low (±1 mM) and high (>50 mM) concentration. For compounds **1f** and **1j**, only spectra at low concentration were taken in $CDCl_3$.

10% dissociation at $10^{-4}$ $M^{-1}$ results in a lower limit of $4.5 \times 10^5$ $M^{-1}$ for the dimerization constant of both pyrimidin-4-ol and 4[1H]-pyrimidinone tautomers of **1a, 1k,** and **1i**.

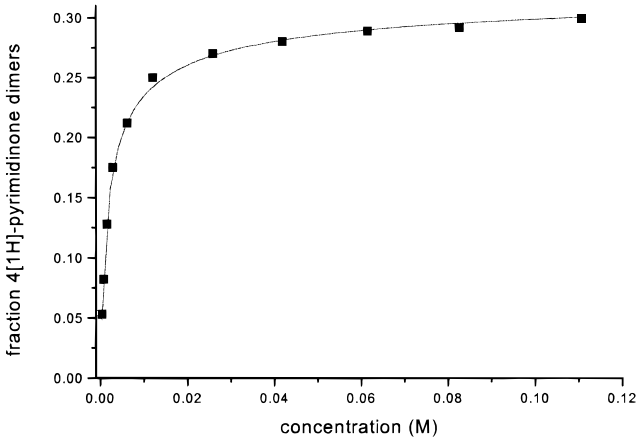



**Figure 6.** Plot of the fraction of 4[1H]-pyrimidinone tautomer vs concentration in solutions of **10a** in THF-$d_8$. The solid line serves to guide the eye.

Dimerization of compounds **1** was studied in mixtures of $CDCl_3$ with DMSO-$d_6$, a strong hydrogen bond acceptor solvent. We found that in these solvent mixtures the dimers of the 4[1H]-pyrimidinone tautomer of **1a** (NH signals at 13.95, 12.06, and 10.23 ppm), are in equilibrium with a second tautomer, which is the only tautomer present in pure DMSO-$d_6$. This tautomer has one hydrogen-bonded NH proton at 11.4 ppm and two non-hydrogen-bonded NH protons at 9.4 and 7.2 ppm. The signals are assigned to a presumably monomeric 6[1H]-pyrimidinone tautomeric form (Figure 2). The assignment is confirmed by the observation that 6-phenyl-2-*tert*-butylureido derivative **1i**, which exists as a 1:1 mixture of 4[1H]-pyrimidinone and pyrimidin-4-ol dimers in pure $CDCl_3$, coexists with the third tautomer in $CDCl_3$/DMSO-$d_6$ mixtures. The NH peak positions agree best with the conformation of the 6[1H]-pyrimidinone tautomer as drawn in Figure 2, with an intramolecular hydrogen-bonded pyrimidone NH group and two non-hydrogen-bonded ureido NH groups.

The $^1$H NMR spectrum of trifluoromethyl derivative **1k**—entirely in the pyrimidin-4-ol dimeric form in pure chloroform—also shows a second set of signals in $CDCl_3$/DMSO-$d_6$ mixtures, which were assigned to the 6[1H]-pyrimidinone tautomer. The ratio between the dimeric forms and the 6[1H]-pyrimidinone tautomer varies upon dilution in a $CDCl_3$/DMSO-$d_6$ mixture of constant composition.

Complex dimerization constants, $K_{dim*}$, were assigned to the equilibria of **1a** and **1k**; the constants are based on the dimerization constant ($K_{dim}$) and the tautomeric equilibrium constant ($K_{taut}$). In a given solvent mixture, the ratio $K_{dim*}$ of dimeric tautomer (the 4[1H]-pyrimidinone tautomer of **1a** and the pyrimidin-4-ol tautomer of **1k**, respectively) to the square of the concentration of 6[1H]-pyrimidinone tautomer has a constant value within experimental error. This implies a dimer—monomer relationship, with the 6[1H]-pyrimidinone tautomer as the most stable form of monomeric **1** in $CDCl_3$/DMSO-$d_6$ mixtures (see Discussion).

The values of $K_{dim*}$ of compounds **1a** and **1k** were determined in several $CDCl_3$/DMSO-$d_6$ mixtures with the objective of extrapolating the values to a value in pure $CDCl_3$.

A plot of log $K_{dim*}$ vs solvent composition is strongly curved (Figure 7), rendering extrapolation to a $K$ value in pure chloroform impossible without a quantitative model for fitting the relation between dimerization constant and solvent composition. The solvent dependence of $K_{dim*}$ is particularly strong at low concentrations of DMSO-$d_6$.

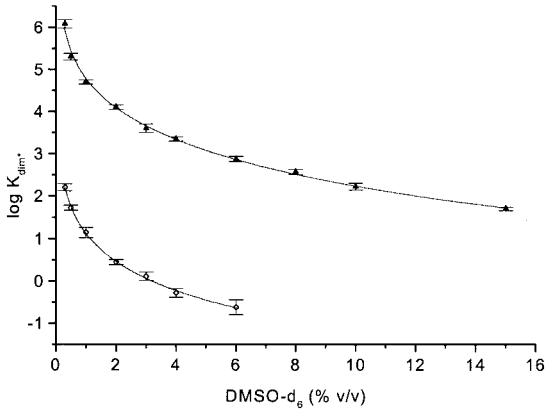



**Figure 7.** Plot of log $K_{dim*}$ vs solvent composition of compounds **1a** (▲) and **1k** (◇) in $CDCl_3$/DMSO-$d_6$ mixtures; solid lines serve to guide the eye.

Nevertheless, from inspection of Figure 7, the conclusion can be drawn that the complex dimerization constant $K_{dim*}$ of 6-methylisocytosine derivative **1a** in pure chloroform significantly exceeds $10^6$ $M^{-1}$, and that $K_{dim*}$ of 6-trifluoromethylisocytosine derivative **1k**—present as a DADA dimer of a pyrimidin-4-ol tautomer—is lower than that of **1a** by roughly 4 orders of magnitude in $CDCl_3$/DMSO-$d_6$ mixtures.

## Discussion

In solution, three different tautomeric forms of 2-ureido-4-pyrimidinone derivatives are observed, which are proposed to be related by the equilibria shown in Figure 2. The equilibrium constants are dependent on substituent, solvent, and concentration. Two of the tautomers strongly dimerize via quadruple hydrogen bonds. For application as a supramolecular building block, a high dimerization constant is advantageous, and for a predictable recognition process a single tautomer should be present in solution. In chloroform, 6-alkyl derivatives of ureidopyrimidinone like **1a** and trifluoromethyl derivative **1k** meet these requirements.

As can be seen from Figure 2, the $K_{dim*}$ values that were used as an expression for the complex dimerization constant of **1a** and **1k** in $CDCl_3$/DMSO-$d_6$ mixtures, are equivalent to the product of the $K_{dim}$ of a single tautomer and the square of the tautomeric equilibrium constant $K_{taut}$. As in $CDCl_3$/DMSO-$d_6$ mixtures the latter constant is smaller than one (nearly all monomer is in the 6[1H]-pyrimidinone form), the actual $K_{dim}$ values of the pure tautomers are higher than $K_{dim*}$.

On the basis of an empirical evaluation, Schneider[17] has predicted association constants for the DADA and DDAA dimers of $3.1 \times 10^2$ and $3.6 \times 10^6$ $M^{-1}$ in chloroform. The values of $K_{dim*}$ observed for the DADA and DDAA arrays of 2-ureido-4-pyrimidinone derivatives led us to infer that the $K_{dim}$ values are higher than predicted by Schneider. The value found for $K_{dim*}$ of the pyrimidin-4-ol tautomer ($>4.5 \times 10^5$ $M^{-1}$) with a DADA array exceeds the predicted $K_{dim}$ value (310 $M^{-1}$ for DADA arrays) by at least 32 kJ $mol^{-1}$. The high stability of pyrimidin-4-ol dimers may be attributed to a combination of two effects. First, the DADA array is preorganized by an intramolecular hydrogen bond. In a recent paper,[11] we have shown that this strongly increases dimerization constants of multiple hydrogen-bonded dimers. Second, the dimers of the pyrimidin-4-ol tautomer contain a strong O—H···O═C hydrogen bond, whereas the free energy relationships of Schneider are entirely based on N—H···N and N—H···O═C hydrogen bonds.

(17) Sartorius, J.; Schneider, H.-J. *Chem. Eur. J.* **1996**, *2*, 1446.

Only a lower limit can be given for the dimerization constant of the DDAA system of **1a** in chloroform, because the complex $K_{dim*}$ values in a mixed-solvent system could not be extrapolated to pure chloroform. The results show that the dimerization constant is at least of the same order of magnitude as predicted by Schneider ($3.6 \times 10^6$ $M^{-1}$). The actual value may be higher, because $K_{dim*}$ (which is smaller than $K_{dim}$) is already $1.2 \times 10^6$ in $CDCl_3$ containing 0.3% v/v DMSO-$d_6$, while it is strongly dependent on the presence of small amounts of DMSO.

## Conclusions

We have shown that a novel building block for self-assembly, ureidopyrimidinone, is readily synthesized, and forms exceptionally stable dimers via quadruple hydrogen bonds, with dimerization constants exceeding $10^6$ $M^{-1}$ in $CDCl_3$. The tautomeric form of the compound changes from keto to enol when electron-withdrawing substituents are introduced at the 6-position, thus affording two discrete self-complementary hydrogen-bonding units with DDAA and DADA arrays, respectively. The dimerization constant of the enol form of **1a** is very much higher than predicted in the literature for dimers of DADA arrays. Derivatives with *n*-alkyl substituents at both the ureido group and at the 6-position are excusively present as 4[1H]-pyrimidinone tautomers.

The ready availability of compounds with high dimerization strength and predictable tautomerism opens the way to supramolecular architectures such as supramolecular polymers with a high degree of polymerization, which is the subject of a recent paper by us.[18]

## Experimental Section

**General Methods.** Chemicals, including $\beta$-keto esters **2c**, **2d**, **2e,** and methylisocytosine **3a** were purchased from Acros Chimica, Fluka, or Aldrich and used as received unless otherwise stated. All reactions were carried out under an atmosphere of dry nitrogen unless otherwise stated. Solvents were of technical grade unless otherwise stated. Anhydrous THF and diethyl ether were obtained by distillation from sodium/potassium/benzophenone; 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 spectrometer. Chemical shifts are given in parts per million (ppm) relative to TMS. For the $^1$H NMR titrations, deuteriochloroform was used as received. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Dry chloroform for the infrared experiments in solution 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, for lower concentrations a 1 mm cell was used. Melting points were determined on a Jenaval THMS 600 melting point microscope and are uncorrected. Liquid crystalline materials are characterized by their isotropization temperatures $T_i$.

**Determination of $K_{dim*}$.** In each solvent mixture, integrated peak areas of appropriate $^1$H NMR signals at 2—10 different concentrations of **1a** or **1k** were measured. $K_{dim*}$ was assigned the average value of the intensity ratio $(I_{\text{dimeric tautomer}})/(I_{\text{monomeric tautomer}})^2$. For compound **1a**, the sharp $CH_3$ signals were used, allowing integration down to $10^{-5}$ M with an estimated relative error of 20%. For compound **1k**, the broader N—H signals were used. The relative error is estimated to be 40%.

**X-ray Crystal Structure Analyses.** Pertinent data for the structure determinations are collected in tabular form in the Supporting Information.

All data were collected on an Enraf-Nonius CAD4T diffractometer on rotating anode ($\omega$ scan, $T$ = 150 K, Mo K$\alpha$ radiation, graphite

(18) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601.

monochromator, $\lambda = 0.710\ 73$ Å). Accurate unit-cell parameters and an orientation matrix were determined by least-squares fitting of the setting angles of 25 well-centered reflections (SET4).[19] The unit-cell parameters were checked for the presence of higher lattice symmetry.[20] Data were corrected for *Lp* effects and for the observed linear decay of the reference reflections. Structures were solved with SHELXS96[21] and refined on $F^2$ using SHELXL96.[22] No observance criterion was applied during refinement on $F^2$. The hydrogen atoms of **1h** (pyrimidinone tautomer) were included in the refinement on calculated positions; the hydrogen atoms of all other structures were located on a difference Fourier map and their coordinates were included as parameters in the refinement. The non-hydrogen atoms of all structures were refined with anisotropic thermal parameters. The hydrogen atoms were refined with a fixed isotropic displacement parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms. Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[23] Geometrical calculations and illustrations were performed with PLATON;[24] all calculations were performed on a DEC station 5000 cluster.

***N*-[(butylamino)carbonyl]-6-methylisocytosine (1a).** A suspension of 6-methylisocytosine **3a**, (6.20 g, 0.050 mol) and butyl isocyanate (10 mL, 0.090 mol) in dry pyridine (200 mL) was heated under reflux for 2 h, giving a clear solution. Cooling induced the formation of crystals. Acetone was added (200 mL), and the resulting microcrystalline powder was filtered. Recrystallization from ethanol/chloroform 9:1 v/v gave analytically pure **1a** (3.30 g, 0.0197 mol, 99%), mp 225 °C with sublimation. X-ray-quality crystals were obtained by slow evaporation of a dichloromethane solution to air. $^1$H NMR ($CDCl_3$) $\delta$: 13.15 (s, 1H), 11.85 (s, 1H), 10.16 (s, 1H), 5.81(s, 1H), 3.24 (dd, 2H), 2.23 (s, 3H), 1.58 (m, 2H), 1.37 (m, 2H), 0.94 (tr, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$: 173.0, 156.5, 154.7, 148.1, 106.6, 39.7, 31.5, 20.1, 18.9, 13.7. IR (KBr) $\nu$: (dimeric 4[1H]-pyrimidinone) 3215, 3147, 3036, 2954, 2916, 2870, 1704, 1665, 1583, 1528, 1252 cm$^{-1}$. Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.57; H, 7.36; N, 25.18.

***N*-[(*tert*-Butylamino)carbonyl]-6-methylisocytosine (1b).** A suspension of 6-methylisocytosine **3a**, (1.24 g, 0.010 mol) and *tert*-butyl isocyanate (1.7 mL, 0.015 mol) in dry pyridine (25 mL) was heated under reflux for 4 h, giving a clear solution. Cooling induced the formation of crystals. Acetone was added (50 mL), and the resulting powder was filtered. Recrystallization from acetone/chloroform 1:1 v/v gave analytically pure **1b** (0.46 g, 21%), mp 203−204 °C (dec). $^1$H NMR ($CDCl_3$) $\delta$: 13.14 (s, 1H), 11.73 (s, 1H), 9.53 (s, 1H), 5.81 (s, 1H), 2.22 (s, 3H), 1.43 (s, 9H). $^{13}$C NMR ($CDCl_3$) $\delta$: 172.8, 155.8, 154.9, 147.9, 106.7, 51.3, 28.8, 18.9. IR (KBr) $\nu$: (dimeric 4[1H]-pyrimidinone) 3212, 2970, 1698, 1674, 1636, 1586, 1521, 1265 cm$^{-1}$. Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.76; H, 7.29; N, 25.04.

**6-Tridecylisocytosine (3b).** Crude $\beta$-keto ester **2b**[11] (136.1 g, containing 0.29 mol of keto ester) in ethanol (220 mL) was heated under reflux with guanidinium carbonate (30.6 g, 0.17 mol) overnight. The resulting clear, yellow solution was partially evaporated, and then cooled, inducing precipitation of a white powder. Addition of hexane (500 mL) and then water (500 mL) resulted in the precipitation of more white powder, which was filtered off, and washed thoroughly with water and acetone. Crystallization from ethanol gave pure **3b** as tiny plates (39.7 g, 36%), mp 181 °C. $^1$H NMR (DMSO-$d_6$) $\delta$: 10.57 (s, 1H), 6−7 (br, 2H), 5.36 (s, 1H), 2.24 (t, 2H), 1.55 (t, 2H), 1.26 (m, 20 H), 0.86 (t, 3H). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 171.8, 162.7, 155.0, 99.2, 36.1, 30.4, 28.1 (multiple peaks), 26.6 (multiple peaks), 21.1, 12.6. IR (KBr) $\nu$: 3365, 3146, 2920, 2850, 2713, 1662, 1634, 1553, 1468, 1400 cm$^{-1}$. Anal. Calcd for $C_{17}H_{31}N_3O$: C, 69.58; H, 10.65; N, 14.32. Found: C, 69.74; H, 10.80; N, 14.00.

***N*-[(Butylamino)carbonyl]-6-tridecylisocytosine (1c).** A solution of 6-tridecylisocytosine, **3b** (10.22 g, 0.036 mol), and butyl isocyanate (6.8 mL, 0.060 mol) in dry pyridine (200 mL) was heated under reflux for 2h. After cooling, the solution was evaporated to dryness. Treatment of the residue in hot acetone with active carbon and crystallization afforded analytically pure **1c** as tiny needles (11.6 g, 82%), mp 118 °C. $^1$H NMR ($CDCl_3$) $\delta$: 13.18 (s, 1H), 11.88 (s, 1H0, 10.17 (s, 1H), 5.82 (s, 1H), 3.24 (q, 2H), 2.45 (t, 2H), 1.62 (m, 4H), 1.31 (m, 22 H), 0.90 (m, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$: 174, 157, 155, 152, 106, 41, 33, 32, 30 (multiple peaks), 24, 21, 15, 14. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3203, 3130, 3012, 2955, 2920, 2849, 2498, 1666, 1610, 1557, 1453, 1318 cm$^{-1}$. Anal. Calcd for $C_{22}H_{41}N_4O_2$: C, 67.31; H, 10.27; N, 14.35. Found: C, 67.31; H, 10.41; N, 14.35.

***N*-[(*tert*-Butylamino)carbonyl]-6-tridecylisocytosine (1d).** A solution of 6-tridecylisocytosine, **3b** (0.56 g, 2 mmol) and *tert*-butyl isocyanate (0.3 mL, 2.6 mmol) in dry pyridine (10 mL) was heated under reflux for 2 h. After cooling, the suspension was diluted with acetone, and the precipitated powder was filtered. Crystallization from acetone gave pure **1c** as needles (0.55 g, 70%), mp 117.3−117.9 °C. $^1$H NMR ($CDCl_3$) $\delta$: 13.22 (s, 1H), 11.72 (s, 1H0, 9.57 (s, 1H), 5.81 (s, 1H), 2.45 (t, 2H), 1.63 (m, 2H), 1.42 and 1.31 (m, 29H), 0.88 (t, 3H); furthermore 3.5% of pyrimidin-4-ol tautomer: 13.5 (s, 1H), 11.0 (s, 1H), 10.0 (s, 1H), 6.1 (s, 1H), 2,6 (m, 2H), other peaks overlap with peaks of main tautomer. $^{13}$C NMR ($CDCl_3$) $\delta$: 173.0, 155.9, 155.0, 152.1, 105.7, 51.2, 32.6, 31.7, 29.6, 29.6, 29.4 (multiple peaks), 29.3, 29.2, 29.0, 28.8, 26.9, 22.7, 14.1. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3224, 3133, 2922, 2850, 2490, 1664, 1612, 1560, 1458, 1330 cm$^{-1}$. Anal. Calcd for $C_{22}H_{41}N_4O_2$: C, 67.31; H, 10.27; N, 14.35. Found: C, 67.57; H, 10.36; N, 14.30.

***N*-[(Phenylamino)carbonyl]-6-tridecylisocytosine (1e).** A solution of 6-tridecylisocytosine, **3b**, (2.93 g, 0.010 mol) and phenyl isocyanate (2.1 mL, 0.018 mol) in dry pyridine (50 mL) was heated under reflux for 2 h. After cooling, the suspension was diluted with acetone and the resulting powder was filtered. Crystallization from acetone/chloroform 2:1 v/v afforded analytically pure **1e** (1.25 g, 30%), mp 155−156 °C. $^1$H NMR ($CDCl_3$) $\delta$: 13.0 (s, 1H), 12.21 and 12.19 (2*m, 1H), 7.70 (d, 2H), 7.34 (t, 2H), 7.09 (t, 1H), 5.83 (s, 1H), 2.30 (t, 2H), 1.53 (m, 2H), 1.26 (m, br, 20 H), 0.88 (t, 3H). $^{13}$C NMR ($CDCl_3$) $\delta$: 173.0, 154.6, 152.8, 142.0, 138.2, 128.9, 123.9, 120.6, 106.0, 32.5, 32.0, 29.6, 29.6, (multiple peaks), 29.4, 29.4, 29.2, 28.8, 26.6, 22.7, 14.1. IR (KBr) $\nu$: (4[1H]-pyrimidinone tautomer) 3133, 3022, 2910, 2850, 1701, 1660, 1580, 1500 cm$^{-1}$. Anal. Calcd for $C_{24}H_{36}N_4O_2$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.97; H, 8.99; N, 13.49.

***N*-[[(*p*-Nitrophenyl)amino]carbonyl]-6-tridecylisocytosine (1f).** A solution of 6-tridecylisocytosine, **3b**, (0.44 g, 1.5 mmol) and *p*-nitrophenyl isocyanate (0.27 g, 1.6 mmol) in dry pyridine (20 mL) was heated under reflux overnight. The resulting suspension was evaporated to dryness, and the yellow powder was extracted with hot toluene. Crystallization from acetic acid afforded analytically pure **1f**, mp 234.5−237.5 °C. $^1$H NMR ($CDCl_3$, 55 °C, saturated at low concentration) $\delta$: 12.83 (s, 1H), 12.7 (s, br, 1H), 12.36 (s, br, 1H), 8.20 (d, 2H), 7.94 (d, 2H), 5.99 (s, 1H), 2.56 (t, 2H), 1.71 (s, 2H), 1.27 (s, br, 20 H), 0.88 (t, 3H). IR (KBr) $\nu$: (4[1H]-pyrimidinone tautomer) 3067, 2920, 2850, 2750, 1712, 1656, 1625, 1574, 1511, 1500, 1334, 1240 cm$^{-1}$. Anal. Calcd for $C_{24}H_{35}N_5O_4$: C, 63.00; H, 7.71; N, 15.31. Found: C, 62.65; H, 7.63; N, 15.49.

***N*-[[[*p*-(diethylamino)phenyl]amino]carbonyl]-6-tridecylisocytosine (1g).** A solution of 6-tridecyl-isocytosine, **3b** (2.93 g, 10 mmol), and *p*-(diethylamino)phenyl isocyanate[25] (3.0 g, 15 mmol) in dry pyridine (20 mL) was heated under reflux for 4 h. Water was added to the cooled solution, resulting in precipitation of a brown gum, which was crystallized from acetone/water/ethanol 20:10:1 v/v/v with treatment with active carbon. Recrystallization from acetone/ethanol 1:1 v/v gave analytically pure **1g** (1.04 g, 22%), mp 76−90 °C. $^1$H NMR ($CDCl_3$) $\delta$: 13.09 (s, 1H), 12.12 (s, 1H), 11.97 (s, 1H), 7.49 (d, 2H), 6.67 (d,

(19) de Boer, J. L.; Duisenberg, A. J. M. *Acta Crystallogr.* **1984**, *A40*, C-410.
(20) Spek, A. L. *J. Appl. Crystallogr.* **1988**, *21*, 578.
(21) Sheldrick, G. M. *SHELXS96 Program for crystal structure determination*; University of Göttingen: Germany, 1996.
(22) Sheldrick, G. M. *SHELXL96 Program for crystal structure refinement*; University of Göttingen: Germany, 1996.
(23) Wilson, A. J. C., Ed. *International Tables for Crystallography*, Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Volume C.
(24) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C-34.
(25) Benn, M. H.; Creighton, A. M.; Owen, L. N.; White, G. R. *J. Chem. Soc.* **1961**, 2365.

2H), 5.75 (s, 1H), 3.32 (m, 4H), 2.19 (m, 2H), 1.48 (m, 2H), 1.24 (m, br, 20 H), 1.14 (tr, 3H), 0.88 (t, 3H). $^{13}$C NMR ($CDCl_3$): 173.0, 154.6, 152.5, 144.8, 126.8, 122.5, 112.7, 105.6, 44.6, 32.3, 31.7, 29.6−29.2 (multiple peaks), 28.7, 26.5, 22.6, 14.1, 12.5. IR (KBr) $\nu$: (4[1H]-pyrimidinone tautomer) 3128, 3030, 2923, 2851, 1698, 1663, 1616, 1587, 1512, 1326, 1243 cm$^{-1}$. Anal. Calcd for $C_{28}H_{45}N_5O_2$: C, 69.53; H, 9.38; N, 14.48. Found: C, 69.99; H, 9.56; N, 14.33.

**6-Phenylisocytosine (3c).** A mixture of ethyl benzoylacetate **2c** (19.2 g, 0.10 mol) and guanidinium carbonate (9.09 g, 0.05 mol) in absolute ethanol (100 mL) was heated overnight. After cooling, the precipitated white powder was filtered off, and washed thoroughly with ethanol, water, and acetone. Drying gave pure **3c** (12.02 g, 64%), mp 312 °C. $^1$H NMR (DMSO-$d_6$, 115 °C): 10.84 (br, 1H), 7.9 (m, 2H), 7.43 (m, 3H), 6.62 (br, 2H), 6.11 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 162.8, 162.2, 155.2, 137.1, 128.9, 127.4, 125.9, 97.4. IR (KBr) $\nu$: 3350, 3087, 2956, 1658, 1502, 1476, 1380 cm$^{-1}$. Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.05; H, 4.85; N, 22.52.

***N*-[(Butylamino)carbonyl]-6-phenylisocytosine (1h).** A suspension of 6-phenylisocytosine **3c** (1.93 g, 10 mmol) and butyl isocyanate (1.7 mL, 15 mmol) in dry pyridine (40 mL) was heated under reflux for 4 h. After cooling, acetone was added, and the precipitated white powder was filtered off. Crystallization from ethanol/chloroform 1:1 v/v gave analytically pure **1h** (2.34 g, 82%), mp 245 °C (pyrimidin-4-ol tautomer). $^1$H NMR ($CDCl_3$) $\delta$: 13.92 (s, 1H), 12.04 (s, 1H), 10.21, s, 1H), 7.67 (m, 2H), 7.54 (m, 3H), 6.35 (s, 1H), 3.30 (m, 2H), 1.65 (q, 2H), 1.42 (q, 2H), 0.88 (t, 3H); 14% of pyrimidin-4-ol tautomer at 13.6 (2, 1H), 11.3 (s, 1H), 10.0 (s, 1H), 6.7 (m, 2H), 3.5−3.4 (m, 2H), other peaks obscured by signals of main tautomer. $^{13}$C NMR ($CDCl_3$) $\delta$: 173.2, 157.0, 155.4, 148.8, 131.4, 129.6, 125.8, 104.4, 40.0, 31.6, 20.2, 13.9; pyrimidin-4-ol tautomer at 157.0, 137.0, 130.7, 128.9, 126.9, 39.9, 31.8, other peaks obscured by signals of main tautomer. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3208, 3134, 3025, 2955, 2930, 2870, 2502, 1657, 1612, 1556, 1441, 1328 cm$^{-1}$. (4[1H]-pyrimidinone tautomer) 3202, 3133, 3010, 2958, 2871, 1692, 1656, 1588, 1528, 1255 cm$^{-1}$ Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.10; H, 6.41; N, 19.34.

***N*-[(*tert*-Butylamino)carbonyl]-6-phenylisocytosine (1i).** A suspension of 6-phenylisocytosine **2c** (0.98 g, 5 mmol) and *tert*-butyl isocyanate (0.86 mL, 7.5 mmol) in dry pyridine (20 mL) was heated under reflux for 2 h. After cooling, acetone was added, and the white crystals were filtered off (1.14 g, 80%), mp 259 °C (dec). $^1$H NMR ($CDCl_3$) $\delta$: (equimolar ratio of pyrimidin-4-ol and 4[1H]-pyrimidinone tautomer) 14.03 (br, 0.5H), 13.79 (s, 0.5H), 11.90 (s, 0.5 H) and 11.12 (s, 0.5 H), 10.02 (s, 0.5 H) and 9.60 (br, 0.5H), 7.90 (1H), 7.67 (1H), 7.54 and 7.49 (3H), 6.70 (br, 0.5H), 6.36 (s, 0.5H), 1.47 (s, 9H). $^{13}$C NMR ($CDCl_3$) $\delta$: 158, 148.6, 136.8, 131.4, 130.7, 129.6, 128.7, 126.9, 125.7, 104.4, 98, 51.4, 51.1, 29.1, 29.8. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3214, 3138, 3030, 2974, 2502, 1658, 1609, 1560 cm$^{-1}$. Anal. Calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.40; H, 6.46; N, 19.67.

**6-(*p*-Nitrophenyl)isocytosine (3d).** A mixture of ethyl *p*-nitrobenzoylacetate, **2d** (11.86 g, 0.05 mol), and guanidinium carbonate (4.86 g, 0.027 mol) in absolute ethanol (50 mL) was heated overnight. After cooling, the dark yellow powder was filtered off and washed thoroughly with acetone, water, and ethanol. The dark yellow-brown powder was triturated at reflux temperature with water/ethanol 1:1 v/v (1 L) resulting in partial solution, then cooled, to afford yellow microneedles. This procedure was repeated twice and then the nice yellow microneedles in suspension were decanted and filtered from a brown residue. Drying the needles gave pure **2d** (3.49 g, 30%), mp >300 °C (dec). $^1$H NMR (DMSO-$d_6$) $\delta$: 11.05 (s, 1H), 8.28 (d, 2H), 8.21 (d, 2H), 6.78 (br, 2H), 6.30 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 163.3, 161.0, 156.0, 148.1, 143.5, 127.9, 123.5, 99.6. IR (KBr) $\nu$: 3440, 3286, 3167, 3116, 2966, 1662, 1611, 1544, 1345 cm$^{-1}$. Anal. Calcd for $C_{10}H_8N_4O_3$: C, 51.60; H, 3.71; N, 24.07. Found: C, 51.33; H, 3.91; N, 24.44.

***N*-[(Octadecylamino)carbonyl]-6-(*p*-nitrophenyl)isocytosine (1j).** A suspension of 6-(*p*-nitrophenyl)isocytosine, **3d** (0.92 g, 4 mmol), and octadecyl isocyanate (2.36 g, 8 mmol) in dry pyridine (15 mL) was heated under reflux for 4 h. After cooling, acetone was added, and the powder was filtered off (2.16 g, 105%). An analytical sample was prepared by trituration with hot acetic acid, mp 271−283 °C (dec). $^1$H NMR ($CDCl_3$, 60 °C) 4[1H]-pyrimidinone tautomer (40%): 14.35, 12.10, 10.10, 8.4, 8.05, 6.44, pyrimidin-4-ol tautomer (60%): 13.93, 11.32, 9.74, 8.4, 6.80. Not assigned: 3.5, 3.3, and 3.1 (m, $CH_2$−N), 1.7−1.0 ($CH_2$), 0.9 ($CH_3$). $^{13}$C NMR (DMSO-$d_6$, 110 °C): 161.2, 158.7, 154.0, 151.8, 148.2, 142.2, 127.3, 122.8, 103.5, 30.6, 29.4, 28.7 (multiple peaks), 25.7, 21.2, 12.9. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3228, 3136, 3091, 3024, 2953, 2919, 2849, 2516, 1665, 1618, 1567, 1533, 1456, 1348, 1331 cm$^{-1}$. Anal. Calcd for $C_{29}H_{45}N_5O_4$: C, 66.00; H, 8.59; N, 13.27. Found: C, 65.94; H, 8.79; N, 12.81.

**6-(Trifluoromethyl)isocytosine**[26] **(3e).** A mixture of ethyl trifluoroacetoacetate, **2e**, (9.2 g, 0.05 mol) and guanidinium carbonate (4.68 g, 0.026 mol) in absolute ethanol (50 mL) was heated under reflux overnight. After cooling, water (100 mL) was added. The solvent was partially removed by evaporation, resulting in precipitation of pure **3e** (5.63 g, 63%). Sublimation at 220−240 °C yields large crystals, which melt at 289 °C (Lit.[26] mp 282 °C). $^1$H NMR (DMSO-$d_6$): 9−12 (br, 1H), 6.99 (br, 2H), 5.90 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): 162.9, 157.2, 153.0 (q), 120.8 (q), 98.5. IR (KBr) $\nu$: 3456, 3330, 3166, 2938, 2767, 1678, 1644, 1496, 1446 cm$^{-1}$. Anal. Calcd for $C_5H_4N_3OF_3$: C, 33.53; H, 2.25; N, 23.46. Found: C, 32.05; H, 2.73; N, 24.04.

***N*-[(Butylamino)carbonyl]-6-(trifluoromethyl)isocytosine (1k).** A suspension of 6-(trifluoromethyl)isocytosine, **3e** (1.79 g, 10 mmol), and butyl isocyanate (1.0 mL, 18 mmol) in dry pyridine (25 mL) was heated under reflux for 4 h. After cooling, the solution was evaporated to dryness, and the resulting powder was crystallized from acetone with treatment with active carbon. Cooling to 0 °C resulted in the formation of white crystals (0.74 g, 27%), mp 178.3−185.5. $^1$H NMR ($CDCl_3$) $\delta$: 14.30 (s, 1H), 11.14 (s, 1H), 9.30 (s, 1H), 6.64 (s, 1H), 3.38 (m, 2H), 1.58 (m, 2H), 1.43 (m, 2H), 0.97 (t, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 60 °C) $\delta$: 172.6, 157.8, 156.4, 155.5 (q), quartet at (124.4, 121.6, 118.9, 116.2), 100.1, 40.0, 31.3, 19.9, 13.5 ppm. IR (KBr) $\nu$: (pyrimidin-4-ol tautomer) 3263, 3150, 3115, 3052, 2969, 2937, 2864, (2594, 2529, 2466, 2398), 1673, 1622, 1563, 1477, 1453, 1340, 1268, 1196, 1143 cm$^{-1}$. Anal. Calcd for $C_{10}H_{13}N_4O_2F_3$: C, 43.17; H, 4.71; N, 20.14. Found: C, 43.54; H, 4.89; N, 20.23.

**Methyl 3,4,5-Tris(dodecyloxy)benzoylacetate (8).** To a solution of ethyl acetoacetate (10.93 g, 0.084 mol) in dry ether (68 mL) was added a solution of sodium ethoxide (0.0808 mol) in absolute ethanol (40 mL), while the temperature was maintained below 5 °C by cooling with an ice−salt bath. At the same temperature, crude acid chloride **6**[15] (0.040 mol) in dry ether (100 mL) was added dropwise, and the resulting thick suspension was stirred overnight at room temperature. The suspension was poured into dilute sulfuric acid, and dichloromethane was added. The layers were separated, and the aqueous layer was extracted with dichloromethane. Further workup of the combined organic phases included washing with a dilute sodium hydrogen carbonate solution (twice), dilute hydrochloric acid (twice), and water (three times), drying over sodium sulfate, filtration, and evaporation to dryness. The resulting white solid (crude **7**) was dissolved in dry toluene (20 mL), and a solution of sodium methoxide (0.06 mol) in methanol (70 mL) was added slowly. The suspension was heated to reflux to achieve complete dissolution and then stirred overnight at room temperature. The solution was poured into ice-cold dilute sulfuric acid, and the aqueous phase was extracted with ether/hexane. The combined organic phases were consecutively extracted with dilute hydrochloric acid (twice), sodium hydrogen carbonate solution (twice), and finally with water (three times). The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. Two repetitive recrystallizations from 2-propanol afforded **8** (20.58 g, 70%), of sufficient for purity (>98%) for further synthesis. An analytically pure sample was obtained by column chromatography with hexane/ethyl acetate 5:1 v/v, followed by crystallization from 2-propanol. $T_i$ = 46 °C. $^1$H NMR ($CDCl_3$): 7.17 (s, 2H), 4.03 (m, 6H), 3.75 (s, 3H), 1.8−1.7 (m, 6H), 1.47 (m, 6H), 1.28 (m, 48H), 0.88 (t, 9H). $^{13}$C NMR ($CDCl_3$) $\delta$: 191.0, 167.9, 152.9, 143.4, 130.7, 107.2, 73.5, 69.2, 69.1, 52.3, 45.6, 31.8, 30.3, 29.6−29.2 (multiple peaks), 26.0, 29.95, 22.6, 14.0 ppm. IR (KBr) $\nu$: 2919, 2849, 1744, 1725, 1677, 1583, 1468, 1429, 1341, 1121 cm$^{-1}$. Anal. Calcd for $C_{46}H_{80}O_6$: C, 75.78; H, 11.06. Found: C, 75.63; H, 10.91.

(26) Giner-Sorolla, A.; Bendich, A. *J. Am. Chem. Soc.* **1958**, *80*, 5744.

**6-[3,4,5-Tris(dodecyloxy)phenyl]isocytosine (9).** A solution of methyl 3,4,5-tris(dodecyloxy)benzoylacetate, **8** (5.86 g, 0.008 mol), and guanidinium carbonate (0.87 g, 0.0048 mol) in absolute ethanol (30 mL) was heated under reflux overnight. The solution was evaporated to dryness and the residue was dissolved in dichloromethane (300 mL). The solution was extracted with water several times, and dried over sodium sulfate. Ethanol was added (200 mL), and the solution was heated under reflux, treated with active carbon, and filtered. Slow addition of water to the colorless filtrate, and slow reduction of the volume by evaporation resulted in the precipitation of pure **9** (3.2 g, 54%), $T_i$ = 130 °C. $^1$H NMR ($CDCl_3$): 12.35 (br, 1H), 7.11 (s, 2H), 6.16 (s, 1H), 5.88 (br, 2H), 4.01 (s, 6H), 1.8−1.7 (m, 6H). 1.48 (m, 6H), 1.26 (m, br, 48H), 0.88 (t, 9H). $^{13}$C NMR ($CDCl_3$) $\delta$: 159.8, 154.0, 153.8, 151.4, 142.7, 123.6, 105.8, 100.4, 73.7, 70.0, 31.9, 30.5, 29.7−29.5 (multiple peaks), 29.3, 26.2, 26.1, 22.6, 13.9 ppm. IR (KBr) $\nu$: 3155, 2922, 2851, 1654, 1467, 1119 cm$^{-1}$. Anal. Calcd for $C_{46}H_{80}N_3O_4$: C, 74.75; H, 10.91; N, 5.68. Found: C, 74.67; H, 10.91; N, 5.73.

***N*-[(Butylamino)carbonyl]-6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (10a).** A solution of 6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (**9**) (1.70 g, 0.0023 mol) and butyl isocyanate (0.73 mL, 0.0065 mol) in dry pyridine (20 mL) was heated under reflux for 3 h. The solution was evaporated to dryness, and the residue was codistilled with toluene. The resultant dark yellow gum was dissolved in hot hexane, and the resultant solution was treated with sodium dihydrogen phosphate with a few drops water, dried over sodium sulfate, treated with active carbon, and then filtered through Celite. Evaporation gave a yellowish gum, which was dissolved in hot dichloromethane/acetone 1:1 v/v. Cooling and slow evaporation in air resulted in the precipitation of white microneedles (1.09 g, 56%), $T_i$ = 131 °C. $^1$H NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 13.9, (s, 1H), 12.04 (s, 1H), 10.19 (s, 1H), 6.82 (s, 2H), 6.25 (s, 1H), 4.02 (m, 6H), 3.29 (m, 2H), 1.84 (m, 6H), 1.75 (m, 2H), 1.63 (m, 2H), 1.42 (m, 6H), 1.27 (m, br, 48H), 0.94 (m, 3H), 0.88 (m, 9H); [pyrimidin-4-ol tautomer (13%)] 13.62 (s, 1H), 11.38 (s, 1H), 10.00 (s, 1H), 7.05 (s, 2H), 6.62 (s, 1H), 3.42 (m, br, 2H), other peaks overlap with peaks of main tautomer. $^{13}$C NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 173.3, 156.7, 155.0, 153.8, 149.1, 140.9, 125.9, 104.1, 103.6, 73.6, 69.3, 39.8, 31.9, 31.5, 30.3, 29.7−29.2 (multiple peaks), 26.0, 22.7, 20.2, 14.1, 13.8. IR (KBr) $\nu$: 3226, 3132, 3020, 2952, 2920, 2850, 1694, 1639, 1608, 1336, 1121 cm$^{-1}$. Anal. Calcd for $C_{51}H_{90}N_4O_5$: C, 72.99; H, 10.81; N, 6.68. Found: C, 73.19; H, 11.12; N, 6.94.

***N*-[(Phenylamino)carbonyl]-6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (10b).** A solution of 6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine, **9** (0.37 g, 0.50 mmol), and phenyl isocyanate (0.22 mL, 2.0 mmol) in dry pyridine (5 mL) was heated under reflux for 3 h. The solution was cooled to room temperature, acetone was added, and the white powder was filtered off. Crystallization from ethanol gave analytically pure **10b** as a white powder (0.03 g, 7%), $T_i$ = 235−240 °C. $^1$H NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 13.77 (s, 1H), 12.39 (s, 1H), 12.24 (s, 1H), 7.72 (d, 2H), 7.28 (d, 2H), 7.06 (t, 1H), 6.60 (s, 2H), 6.32 (s, 1H), 4.0 (m, 6H), 1.84 (m, 4H), 1.73 (m, 2H), 1.47 (m, 6H), 1.26 (m, 48H), 1.15 (t, 4H), 0.88 (t, 9H); [pyrimidin-4-ol tautomer (7%)] 13.25 (s, 1H), 12.40 (s, 1H), 11.49 (s, 1H), 7.55 (br, 2H), 6.66 (s, 1H), other peaks overlap with peaks of main tautomer. $^{13}$C NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 173.2, 154.9, 154.7, 153.8, 149.1, 141.1, 138.2, 128.7, 125.5, 123.7, 120.4, 104.0, 103.8, 73.6, 69.3, 31.9, 30.3, 29.8−29.3 (multiple peaks), 26.1, 22.7, 14.1. IR (KBr) $\nu$: 3205, 3128, 3060, 2919, 2050, 1691, 1646, 1590, 1567, 1499, 1329, 1258, 1120 cm$^{-1}$. Anal. Calcd for $C_{53}H_{86}N_4O_5 \cdot H_2O$: C, 72.6; H, 10.1; N, 6.4. Found: C, 72.85; H, 10.09; N, 6.18.

***N*-[[(*p*-Nitrophenyl)amino]carbonyl]-6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (10c).** A solution of 6-[3,4,5-tris(dodecyloxy)phenyl]-isocytosine (**9**) (0.37 g, 0.50 mmol) and *p*-nitrophenyl isocyanate (0.16 g, 1.0 mmol) in dry pyridine (5 mL) was heated under reflux for 3 h. After cooling, acetone was added, and the resultant white powder was filtered. The powder was dissolved in hot chloroform/acetone 1:1 v/v, treated hot with active charcoal, and filtered hot. Cooling resulted in the precipitation of pure **10c** as a white powder, which was filtered (0.23 g, 51%), $T_i$ = 261 °C (dec). $^1$H NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 13.51 (s, 1H), 12.85 (s, 1H), 12.46 (s, 1H), 8.09 (d, 2H), 7.88 (d, 2H), 6.74 (d, 2H), 6.29 (s, 1H), 4.00 (m, 6H), 1.83 (m, 4H), 1.78 (m, 2H), 1.49 (m, 6H), 1.27 (m, br, 48H), 0.88 (t, 9H). $^{13}$C NMR ($CDCl_3$ 50 °C) $\delta$: 172.9, 154.9, 154.5, 154.1, 149.1, 144.5, 143.4, 142.4, 124.5, 124.3, 119.4, 104.3, 103.4, 73.8, 69.8, 32.0, 30.5, 29.8−29.4 (multiple peaks), 26.2, 26.2, 22.7, 14.0. IR (KBr) $\nu$: 3052, 2955, 2920, 2849, 1701, 1649, 1629, 1582, 1567, 1512, 1498, 1332, 1264, 1226 cm$^{-1}$. Anal. Calcd for $C_{53}H_{85}N_5O_7$: C, 70.40; H, 9.47; N, 7.74. Found: C, 70.51; H, 9.50; N, 7.72.

***N*-[[[*p*-(Diethylamino)phenyl]amino]carbonyl]-6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (10d).** A solution of 6-[3,4,5-tris(dodecyloxy)phenyl]isocytosine (**9**) (0.37 g, 0.50 mmol) and *p*-(diethylamino)-phenyl isocyanate (0.19 g, 1.0 mmol) in dry pyridine (5 mL) was heated under reflux for 3 h. The solution was cooled to room temperature, acetone was added, and the white powder was filtered off. Dissolution of the powder in hot dichloromethane/acetone mixture and slow evaporation of the solution resulted in the precipitation of **10d** as a creamy-white powder (0.28 g, 60%), $T_i$ = 134.5−135 °C. $^1$H NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 13.83 (s, 1H), 12.34 (s, 1H), 11.91 (s, 1H), 7.51 (d, 2H), 6.84 (s, 2H), 6.68 (d, 2H), 6.33 (s, 1H), 4.0 (m, 6H), 3.33 (dd, 4H), 1.84 (m, 4H), 1.73 (m, 2H), 1.47 (m, 6H), 1.26 (m, 48 H), 1.15 (t, 4H), 0.88 (t, 9H); [pyrimidin-4-ol tautomer (15%)] 13.45 (s, 1H), 12.04 (s, 1H), 11.49 (s, 1H), 7.38 (d, 2H), 7.13 (s, 2H), 6.65 (s, 1H), other peaks overlap with peaks of main tautomer. $^{13}$C NMR ($CDCl_3$) $\delta$: (4[1H]-pyrimidinone tautomer) 173.3, 155.0, 154.6, 153.8, 153.5, 149.1, 144.9, 141.0, 126.8, 125.9, 122.4, 112.7, 112.3, 105.4, 104.1, 103.8, 73.6, 69.3, 44.6, 44.5, 31.9, 30.4, 30.3, 29.7−29.2 (multiple peaks), 26.1, 26.0, 22.7, 14.1, 12.5. IR (KBr) $\nu$: 3215, 3128, 2923, 2852, 2500, 1691, 1643, 1606, 1514, 1332, 1257, 1229, 1118 cm$^{-1}$. Anal. Calcd for $C_{57}H_{95}N_5O_5$: C, 73.58; H, 10.29; N, 7.53. Found: C, 73.91; H, 10.39; N, 7.54.

**Supporting Information Available:** Further details of the structure determinations, including atomic coordinates, bond lengths and angles and thermal parameters (1 page, print/PDF). See any current masthead page for ordering information and Internet access instructions.

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