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Self-Assembled Pentamers and Hexamers Linked through Quadruple-Hydrogen-Bonded 2-Ureido-4[1*H*]-Pyrimidinones

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Abstract: The preorganization of bifunctional 2-ureido-4-pyrimidinones mediated by either 1,3-substituted adamantane or *meta*-substituted phenylene ring linkers leads to the preferred formation of stable pentameric $(\mathbf{1})_5$ and hexameric $(\mathbf{2})_6$ assemblies, respectively. Despite the high binding constant of the 2-ureido-4-pyrimidinone dimers and the highly preorganized structure of the monomer, the predominant formation of cycles $(\mathbf{1})_5$ and $(\mathbf{2})_6$ in solution occurs only within a specific concentration range.

Keywords: aggregation · gel permeation chromatography · heterocycles · hydrogen bonds · self-assembly

Introduction

The self-assembly of simple fragments into designed cavities and networks mediated by noncovalent, complementary interactions, such as hydrogen bonds or metal centers, constitutes one of the major current goals in supramolecular chemistry.[1–3] Considerable effort has been focused on rosette-like discrete, two-dimensional hydrogen-bonded cyclic assemblies, such as Whitesides and Reinhoudt's cyanuric acid–melamine combinations,[4] carboxylic acid arrays,[5] or cyclic self-assembled tetrameric,[6] pentameric,[7] or hexameric[8] aggregates inspired by the edge-complementarities found in nucleobases.[9]

These examples illustrate the two main requirements for the formation of specific cyclic aggregates:[10,11] a high binding constant and a highly preorganized monomeric subunit. Although the physical basis of cyclic self-assembly is known, a general method of obtaining specific cycles of a given size over a large concentration range remains challenging. In previous work, we described the dimerization of 6-substituted 2-ureido-4[1*H*]-pyrimidinones (UPy's) mediated by a strong donor–donor–acceptor–acceptor (DDAA) linear array of quadruple hydrogen bonds ($K_{ass} = 6 \times 10^7\ \text{M}^{-1}$ in chloroform),[12–14] and we showed that the use of appropriate linker units allows the exclusive formation of cyclic dimers.[15–17] In addition, hexameric cyclic structures based on related quadruple hydrogen bonds have been described by Zimmerman.[18]

Here, we report the self-assembly of **1** and **2**, which are preorganized to give rise to pentameric and hexameric cycles, respectively, mediated by either 20 or 24 hydrogen bonds formed between UPy subunits. A key design feature is the angle between two UPy subunits: around 109° for the adamantyl derivative **1**, and 120° upon use of a *meta*-substituted phenylene spacer for **2** (Figure 1). We also demonstrate that, although these cyclic structures are preferred, they are not the exclusive products, but rather are present in a dynamic pool of other cyclic aggregates.

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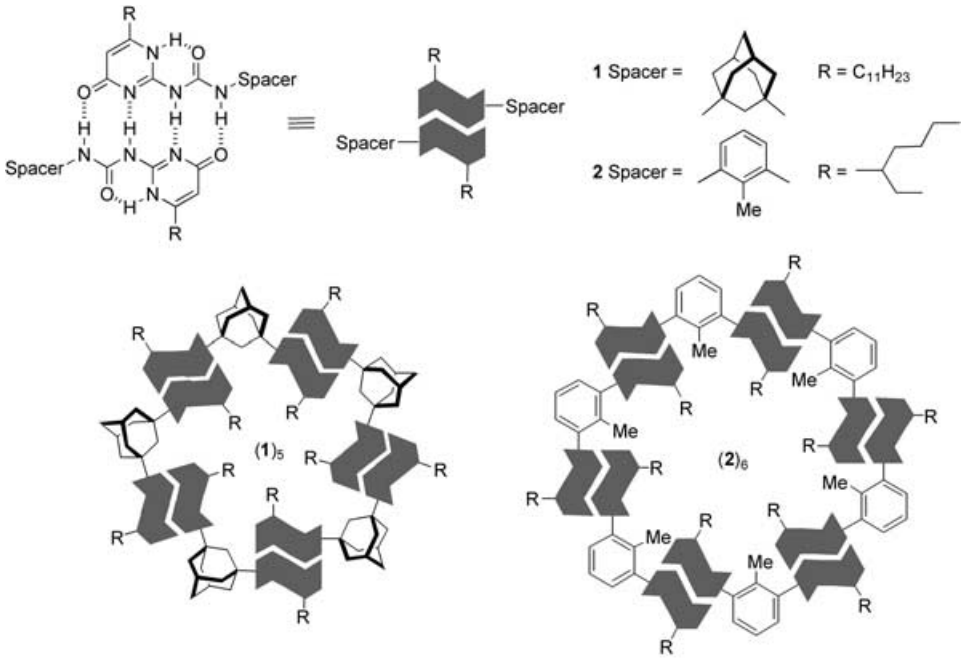


Figure 1. Structures of 1,3-adamantane and 2-methyl-1,3-phenylene bis-ureidopyrimidinones **1** and **2**, and schematic representation of the pentameric $(\mathbf{1})_5$ and hexameric $(\mathbf{2})_6$ assemblies.

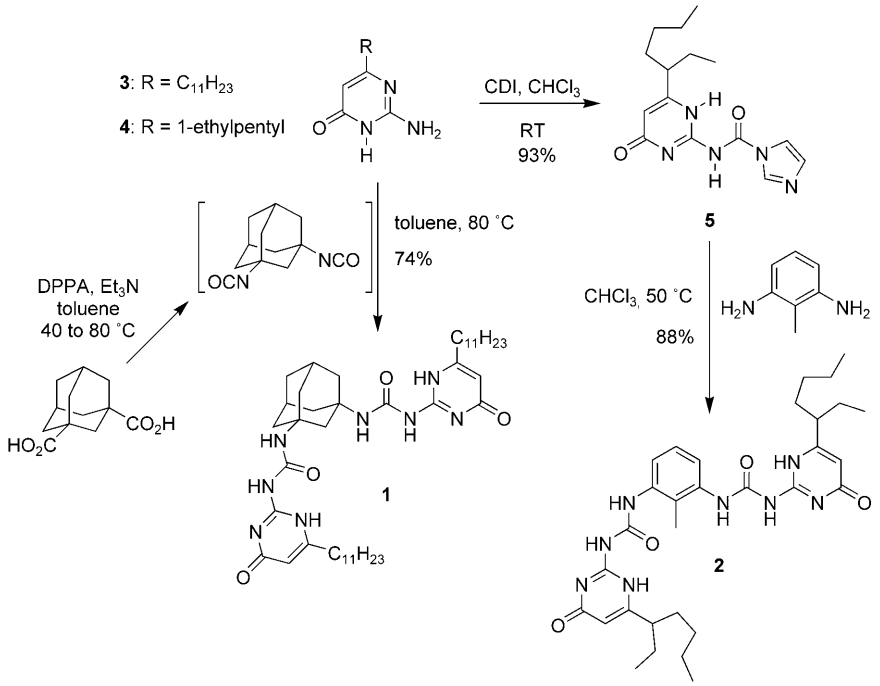
Results and Discussion

By starting from 2-aminopyrimidinone intermediates **3** and **4**, difunctional UPy's **1** and **2** were readily synthesized, as shown in Scheme 1. The corresponding 2-aminopyrimidinones **3** and **4** were prepared by ring-closure of the respective β-ketoesters[19,20] with guanidinium carbonate in refluxing ethanol. Difunctional ureidopyrimidinone **1** was synthesized from **3** and 1,3-adamantane diisocyanate, which can be conveniently generated via a Curtius rearrangement from the corresponding dicarboxylic acid and diphenylphosphorylazide (DPPA).[21] For the formation of **2**, 2-aminopyrimidinone **4** was activated as imidazolide **5** with 1,1′-carbonyldiimidazole (CDI), and then reacted with 2,6-diaminotoluene.[22] Although difunctional UPy's with an aliphatic linker can be conveniently prepared by the isocyanate route, for the less nucleophilic aromatic diamine linkers, the imidazolide route proved superior.

Compounds **1** and **2** were soluble in chloroform, dichloromethane, benzene, or toluene, but almost insoluble in methanol at 30 °C. Remarkably, the viscosity of highly concentrated (>50 mM) solutions of either **1** and **2** in chloroform did not differ markedly from chloroform itself, whereas solutions of comparable concentration containing two UPy's linked through flexible alkyl spacers are very viscous.[14] This indicates that in chloroform, the architecture of **1** and **2** is indeed quite different from a random-coil polymer.

To establish the structure of aggregates **1** and **2**, molecular weight determinations were performed by using complementary methods, such as vapor pressure osmometry (VPO), gel permeation chromatography (GPC), and electrospray ionization mass spectrometry (ESI-MS).

A high intensity signal in the ESI-MS spectrum of **2** was observed at 3554.64 g mol^{-1}, indicating that it forms hexamers even in the presence of HCOOH (Figure 2). The observed molecular weight is in good agreement with the calculated mass of $(\mathbf{2})_6$ (M = 3554.09 g mol^{-1}). Signals for pentamers, tetramers, and so on, are also present in the spectrum.



Scheme 1. Synthesis of difunctional ureidopyrimidinones **1** and **2**.

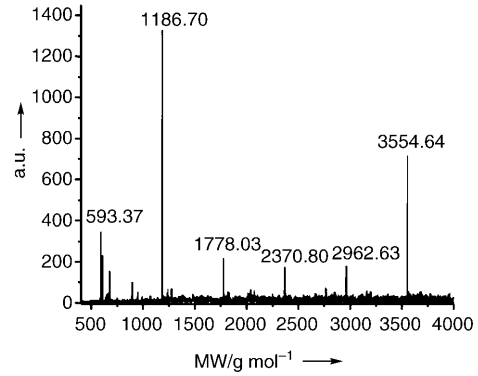


Figure 2. Deconvoluted ESI-MS spectrum of **2** in THF/HCOOH (1:0.05 v/v).

The positive-ion mode FAB-MS spectrum of **1** revealed a peak at $m/z = 750$, which corresponds to the monomer (calculated = 749), however, peaks with higher m/z were not present. VPO measurements of **1** (35 °C, benzil as standard, $CHCl_3$) showed an increase of the average molecular weight up to a value of 3715 ± 206 g mol^{-1} within the range $c_{mon} =$ 22.5–36 mM (Table 1). At higher concentrations, this value remained almost unchanged (3755 ± 275 g mol^{-1}, $c_{mon} = 53$–111 mM). VPO measurements were also performed for **2** within a concentration range of 0–20 mM, and revealed an average molecular weight of 5977 g mol^{-1}, which corresponds to a higher-order aggregate.

Table 1. VPO measurements of **1** in $CHCl_3$ at 35 °C (benzil as standard).

c_{mon} [mM]	Average MW [g mol^{-1}]
3–15	2576
6–30	2952
22.5–36	3715
53–111	3755

In the case of **1**, GPC measurements ($CHCl_3$, polystyrenes as standards) showed an increase in the average molecular weight as the concentration of the sample was raised. At $c_{mon} = 1$ mM, a broad and tailed peak with a low molecular weight of 1742 g mol^{-1} was observed, whereas at $c_{mon} = 5$ mM, a tailed peak with a molecular weight of 3786 g mol^{-1} (calculated MW = 3745 g mol^{-1} for pentamer) was seen (Figure 3a). Because of the uncertainties in using polystyrenes as standard, a tris-ureidocalix[6]arene dimer $(\mathbf{6})_2$[23] was selected as a comparator compound that had a similar overall shape as $(\mathbf{1})_5$. Compound $(\mathbf{6})_2$ exhibited a molecular weight of 2656 g mol^{-1} (calculated MW = 2473 g mol^{-1}) (Figure 3c). The values obtained by conducting VPO and GPC at higher concentrations (> 40 mM) fully agree with those calculated for the proposed pentameric structure, and suggest that **1** self-assembles preferentially into pentamers, as predicted. For **2** (MW = 592.3 g mol^{-1}), the GPC performed at $c_{mon} =$ 2.5 mM revealed a tailed peak (Figure 3b), which corresponds to a rather low molecular weight of 1480 g mol^{-1}, obtained by using polystyrene calibration. For both **1** and **2**,

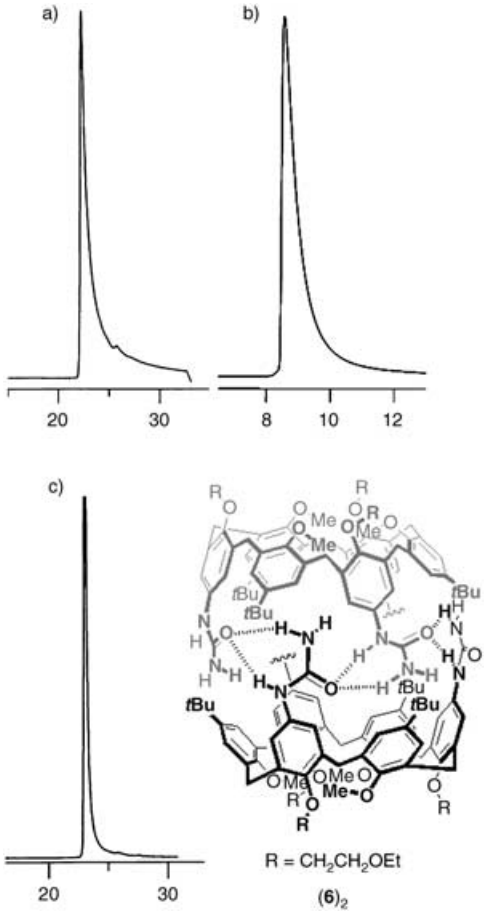


Figure 3. GPC chromatograms of a) $(\mathbf{1})_5$ (5 mM); b) $(\mathbf{2})_6$ (2.5 mM); c) $(\mathbf{6})_2$ (5 mM) in $CHCl_3$.

the GPC trace features a distinct peak with some tailing, indicating that defined architectures are formed at these concentrations, and not random-coil polymers, which would show very broad and undefined GPC traces.

The ^{1}H NMR spectra of either **1** or **2** in $CDCl_3$ revealed large downfield shifts for the urea NH protons, at $\delta = 11.69$/9.60 and 12.48/11.83 ppm, respectively, which is consistent with the presence of four DDAA hydrogen bonds in the associated compound. The chelated NH at position C-1 was observed at $\delta = 13.19$ and 13.11 ppm for **1** and **2**, respectively. None of these signals shifted upon dilution, although at lower concentrations (< 19 mM and < 5 mM for **1** and **2**, respectively), a new set of signals was observed. This suggests that association of **1** and **2** depends on the concentration, and implies the existence of equilibria between cyclic structures of different sizes at lower concentrations (Figure 4).

Pentamer $(\mathbf{1})_5$ was further studied in mixtures of $CDCl_3$ and [D$_6$]DMSO, which is a strong hydrogen-bond acceptor (Figure 5). The aggregate was fully dissociated at $\chi_{DMSO} >$ 0.28 (Figure 6). In the ^{1}H NMR spectra, only two species were observed, which were assigned to pentameric and monomeric compounds. The apparent association constant was determined by integration at $\chi_{DMSO} = 0.11$ ($K^*_{ass} = 1.2 \times 10^9$ M^{-1}) and at $\chi_{DMSO} = 0.17$ ($K^*_{ass} = 1.0 \times 10^8$ M^{-1}).[24]

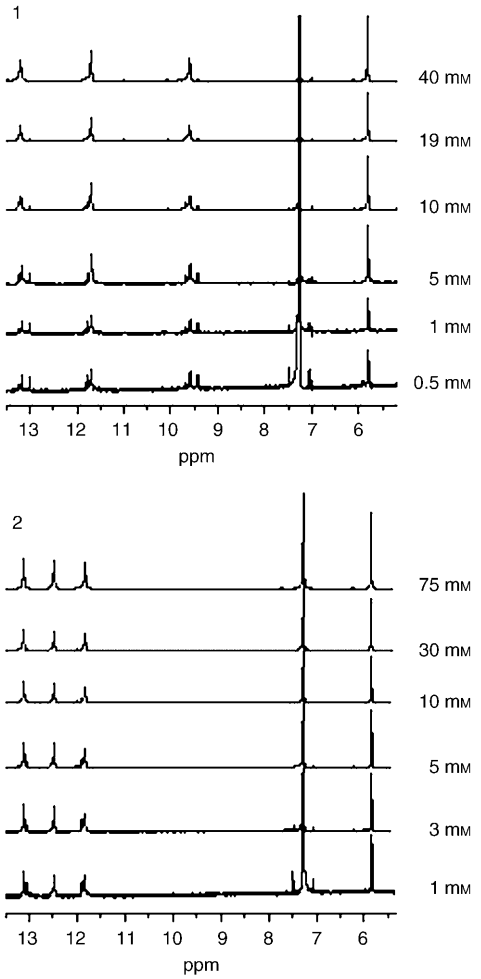


Figure 4. ^{1}H NMR spectra ($CDCl_3$, 500 MHz, 20.5 °C) of **1** and **2** at different concentrations.

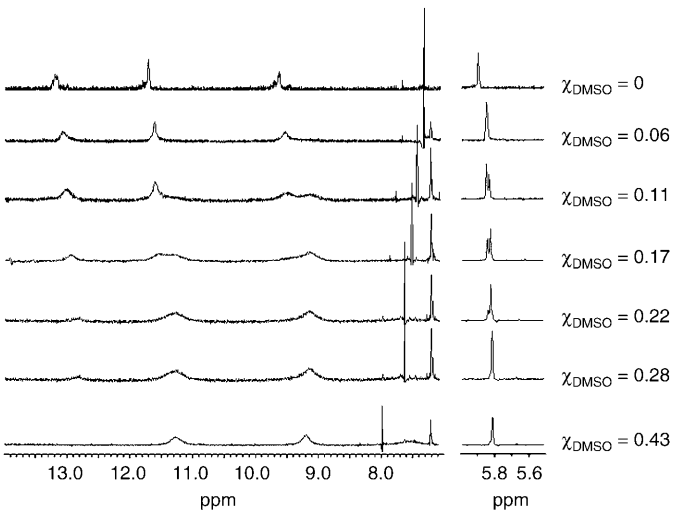


Figure 5. ^{1}H NMR spectra (300 MHz) of $(\mathbf{1})_5$ in mixtures of $CDCl_3$/[D_6]DMSO.

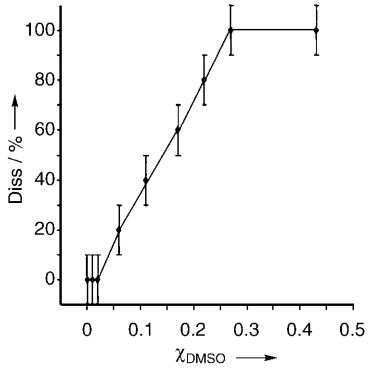


Figure 6. Plot of the % of dissociation versus solvent composition for aggregate $(\mathbf{1})_5$ in a $CDCl_3$/[D_6]DMSO mixture (the lines connecting the data do not reflect a mathematical function and serve only to guide the eye).

Diffusion ordered ^{1}H NMR spectroscopy (DOSY) measurements have been applied for the characterization of supramolecular aggregates and have provided useful information about the size of these aggregates.[25–27] We performed DOSY experiments on solutions of **1** and **2** in $CDCl_3$ at different concentrations, using heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin as internal standard (Figure 7). In

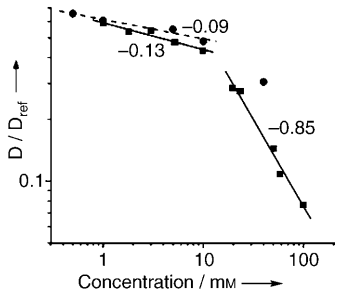


Figure 7. Concentration-dependent diffusion ^{1}H NMR spectroscopy measurements of **1** (-----) and **2** (——) in $CDCl_3$ at room temperature (heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin was used as an internal standard).

the case of **2**, two concentration regimes can be distinguished in a double logarithmic plot of the relative diffusion coefficient versus the concentration. In the high concentration region (>10 mM), the relative diffusion coefficient decreases with an exponent $\alpha_D = -0.85$ in chloroform, whereas in the lower concentration region, the relative diffusion coefficient hardly decreases as the concentration increases ($\alpha_D = -0.13$). Compound **1** also revealed a low exponent ($\alpha_D = -0.09$) at lower concentrations (<10 mM). The presence of two concentration regimes for **2** suggests that at concentrations above 10 mM, the hexamers of **2** aggregate into higher-molecular-weight structures. Furthermore, the relative diffusion coefficient of **2** for concentrations >1 mM is smaller than the diffusion coefficient of **1**. Therefore, at concentrations greater than 1 mM, aggregates of compound **2** have a

higher molecular weight than those of **1**, which is in agreement with VPO measurements.

It is difficult to estimate accurately the overall shapes of the cyclic aggregates described here, as the inner R groups are much too large to be accommodated inside flat, rosette-like structures. Furthermore, the need to avoid eclipsed conformations around the adamantane linker in **1**, as well as the presence of an inner methyl group in **2**, clearly allude to nonplanar-, tubular-, or bowled-shaped conformations. Likely model structures are shown in Figure 8, and suggest that $(\mathbf{2})_6$ could have a tendency to form stacked hexameric cycles.

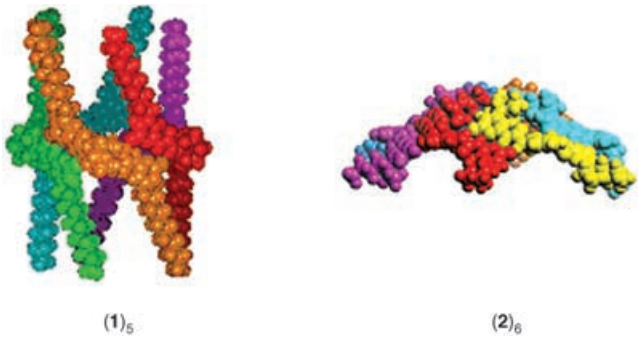


Figure 8. Front view representations of energy-minimized pentameric $(\mathbf{1})_5$ and hexameric $(\mathbf{2})_6$ assemblies.

Conclusion

Difunctional 2-ureido-4-pyrimidinones can be easily preorganized by means of either a 1,3-substituted adamantane linker or a *meta*-substituted phenylene ring to form pentameric and hexameric assemblies. The concentration range, within which the formation of cycles $(\mathbf{1})_5$ and $(\mathbf{2})_6$ is preferred, is determined by dissociation at low concentrations and the formation of higher-molecular-weight species at high concentrations. These results show that the formation of defined aggregates in solution is a dynamic process, in which the aggregates of interest are part of a mixed population, and are the predominant species under only certain conditions. The higher stability of hexamer $(\mathbf{2})_6$ relative to pentamer $(\mathbf{1})_5$ may be ascribed to its, presumably, more flattened structure, which allows hierarchical aggregation into higher-order-molecular-weight oligomers, as revealed by VPO and ^{1}H NMR diffusion measurements. To further elucidate the architecture of these aggregates, we are currently studying structures in solution at higher concentrations (>10 mM).

Experimental Section

General: Toluene was dried before use by employing the standard method. All reactions were performed under an argon or nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR spectra were recorded by using Varian Mercury Vx 400 NMR, Varian Inova 500, Bruker AMX-300 and DRX-500 spectrometers. Chemical shifts (δ) are given in ppm downfield from TMS. ^{1}H NMR diffusion measurements were performed by using the BPPSTE pulse sequence and were evaluated by using the Varian DOSY software incorporated in VNMR. Elemental analyses were obtained by using a Perkin–Elmer 2400 series II CHNS/O analyzer. Infrared (IR) spectra were recorded by using a Perkin–Elmer Spectrum One FT-IR spectrometer with a Universal ATR Sampling Accessory, and an FT-IR Bruker IFS60v spectrometer. Mass spectrometry was conducted by using a PE-Sciex API 300 spectrometer for the electrospray ionization (ESI) method, a PerSeptive Biosystems Voyager-DE PRO spectrometer for the MALDI-TOF technique, and a VG AutoSpec spectrometer for the fast atom bombardment (FAB) method. Melting points were determined by using a Gallenkamp apparatus and a Jenaval polarization microscope with a Linkam THMS 600 hot stage, and are uncorrected. Vapor pressure osmometry (VPO) was measured in an Osmomat 070 cell unit with an Osmomat 070/090 control unit-B. The instrument was operated at 35 °C with ethanol-free chloroform as solvent. Calibration was achieved by using benzil standards that were prepared gravimetrically, and the solvent zero was periodically checked for instrument drift. The samples were also prepared gravimetrically. GC/MS measurements were performed by using a Shimadzu GCMS-QP5000 with a Zebron ZB-5 column. Gel permeation chromatography (GPC) was performed with a sampling rate of 2 Hz by using a Shimadzu FCV-10 AL VP with SCL-10 A System Controller, LC-10 AD VP Liquid Chromatograph, DGU-14 A Degasser, SIL-10 A Auto injector, and SPD-10 AV UV/Vis Detector, or by using three on-line PLgel columns of 10^4, 10^3, and 500 Å, consecutively (MW range 500 000–50 Da), in $CHCl_3$ with polystyrenes as standards.

Ethyl 3-oxotetradecanoate: A suspension of NaH (60% on dispersion oil, 3.55 g, 88.7 mmol) and diethyl carbonate (8 mL, 65.9 mmol) in dry THF (55 mL) was refluxed under an argon atmosphere. A solution of 2-tridecanone (5.68 g, 28.6 mmol) in 10 mL of dry THF was then added dropwise over 2 h and the mixture was refluxed overnight. The dense suspension was carefully poured into a mixture of saturated aqueous NH_4Cl, 5% aqueous HCl, and ice, and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, then dried ($MgSO_4$), and concentrated to dryness. The crude was purified by performing column chromatography on silica gel (hexane/Et_2O, 9:1) to afford the product in 78% yield as yellowish oil. The end product was a mixture of ~20% enol and ~80% keto (as determined by performing ^{1}H NMR spectroscopy); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 12.12$ (s, 1H; (CO)CH=(*COH*)OCH_2 enol), 4.68 (s, 1H; (CO)*CH*(COH)OCH_2 enol), 4.19 (q, ^3J(H,H) = 7.3 Hz, 2H; CH_2O), 3.42 (s, 2H; (CO)CH_2(CO)), 2.52 (t, ^3J(H,H) = 7.0 Hz, 2H; CH_2CO), 1.58 (m, 2H; CH_2), 1.26 (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 1.25 (brs, 18H; CH_2), 0.87 ppm (t, ^3J(H,H) = 6.6 Hz, 3H; CH_3); ^{13}C NMR (25 MHz, $CDCl_3$): $\delta = 202.6$, 166.9, 60.9, 48.9, 42.7, 29.4, 29.2, 29.1, 28.8, 23.2, 22.4, 13.8 ppm; MS (FAB): *m*/*z* (%): 271.3 (100) [M^++H].

Ethyl 5-ethyl-3-oxononanoate: This compound was synthesized according to the literature procedure[20] and was obtained in 92% yield as slightly yellow oil. The end product was a mixture of ~20% enol and ~80% keto (as determined by performing ^{1}H NMR spectroscopy); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.05$ (s, 1H; (CO)CH=(CO*H*)OCH_2 enol), 4.97 (s, 1H; (CO)*CH*=(COH) enol), 4.17 (q, ^3J(H,H) = 7.3 Hz, 2H; OCH_2), 3.43 (s, 2H; (CO)CH_2(CO)), 2.49 (m, 1H; $(CH_2)_2$*CH*(CO)), 1.94 (m, 1H; $(CH_2)_2$*CH*(C=O) enol), 1.70–1.20 (m, 18H; CH_2, CH_3), 0.88 ppm (m, 6H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 206.3$, 181.3, 172.7, 167.1, 89.5, 61.1, 59.8, 53.9, 48.4, 47.5, 32.1, 30.4, 29.5, 29.3, 25.7, 24.1, 22.7, 22.6, 14.0, 11.8, 11.5 ppm; FT-IR (ATR): $\tilde{\nu} = 739$, 803, 843, 948, 1031, 1095, 1151, 1226, 1304, 1368, 1422, 1463, 1625, 1646, 1712, 1746, 2862, 2875, 2934 cm^{-1}; >99% pure, as determined by performing GC-MS: *m*/*z* (%): 215 [M^++H], 214 [M^+].

2-Amino-6-undecylpyrimidin-4(1*H*)-one (3): A suspension of guanidinium carbonate (2.01 g, 11.1 mmol) and ethyl 3-oxo-tetradecanoate (6.04 g, 22.3 mmol) in EtOH (60 mL) was refluxed overnight. After cooling to room temperature, the white precipitate was filtered off and washed with EtOH. The solvent of the filtrate was evaporated at reduced pressure and the residue was triturated with Et_2O to give a white solid that was

collected by filtration. Both solids were dried under vacuum, affording **3** as a white solid in 86% yield; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 10.61$ (brs, 1H; NH), 6.44 (brs, 2H; NH$_2$), 5.35 (s, 1H; (CO)*CH*=C), 2.20 (t, ^3J(H,H) = 7.6 Hz, 2H; CH$_2$), 1.50 (m, 2H; CH$_2$), 1.22 (brs, 16H; CH$_2$), 0.84 ppm (t, ^3J(H,H) = 6.4 Hz, 3H; CH$_3$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 170.0$, 163.0, 155.7, 99.7, 37.2, 31.4, 29.1, 29.0, 28.8, 28.7, 27.6, 22.2, 14.0 ppm; MS (FAB): *m*/*z* (%): 266.3 (100) [*M*$^+$+H]; elemental analysis calcd (%) for $C_{15}H_{27}N_3O$ (265.2): C 67.88, H 10.25, N 15.83; found: C 68.02, H 10.53, N 15.30.

2-Amino-6-(heptan-3-yl)pyrimidin-4(1*H*)-one (4): Ethyl 5-ethyl-3-oxononanoate (50 g, 0.23 mol) in ethanol (400 mL) was boiled with guanidinium carbonate (46.31 g, 0.26 mol) overnight. The resultant clear, yellow solution was evaporated under vacuum and then 400 mL of $CHCl_3$ was added. The organic layer was washed with saturated aqueous $NaHCO_3$ (2×200 mL), brine (200 mL), and then dried over Na_2SO_4. The organic layer was reduced to around 75 mL by evaporation and this solution was slowly added to pentane (500 mL) under vigorous stirring, forming a precipitate. The precipitate was filtered off and washed thoroughly with pentane. Compound **4** was obtained in 70% yield as a white powder. M.p. 163°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.00$ (brs, 2H; NH$_2$), 5.63 (s, 1H; (CO)CH=C), 2.23 (m, 1H; (CH$_2$)$_2$*CH*C), 1.58 (m, 4H; CH$_2$), 1.30 (m, 4H; CH$_2$), 0.84 ppm (m, 6H; CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.6, 165.5, 156.5, 101.3, 47.0, 33.1, 29.4, 26.6, 22.5, 13.8, 11.7 ppm; FTR-IR (ATR): $\tilde{\nu} = 824$, 839, 980, 1099, 1178, 1225, 1378, 1463, 1636, 2859, 3329, 2873, 2929, 2958, 3152 cm^{-1}; MS (direct insertion probe-electron ionization, DIP-EI): *m*/*z*: 209 [*M*$^+$], 194, 166, 153, 138, 125.

***N*-[6-(Heptan-3-yl)-1,4-dihydro-4-oxopyrimidin-2-yl]-1*H*-imidazole-1-carboxamide (5)**: A solution of **4** (4 g, 19.14 mmol) and 1,1′-carbonyldiimidazole (CDI) (4.03 g, 24.88 mmol) in 20 mL of $CHCl_3$ was stirred for 3 h under nitrogen at room temperature. Then, 50 mL of $CHCl_3$ was added to the reaction mixture and the organic layer was washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4. The organic layer was evaporated under vacuum, affording **5** in 93% yield as a light yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.85$ (s, 1H; NCH=N), 7.65 (s, 1H; (CO)N*CH*=CH), 7.07 (s, 1H; (CO)NCH=*CH*), 5.83 (s, 1H; (CO)*CH*=C), 2.55 (m, 1H; (CH$_2$)$_2$*CH*C), 1.75 (m, 4H; CH$_2$), 1.32 (m, 4H; CH$_2$), 0.95 (t, 3H; CH$_3$), 0.92 ppm (t, 3H; CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.3$, 160.3, 157.3, 128.4, 117.3, 103.7, 45.4, 32.7, 29.2, 26.5, 22.4, 13.8, 11.5 ppm; FTR-IR (ATR): $\tilde{\nu} = 754$, 790, 823, 833, 857, 912, 952, 989, 1004, 1023, 1067, 1092, 1175, 1221, 1277, 1311, 1375, 1418, 1466, 1600, 1626, 1691, 1706, 1916, 2661, 2860, 2932, 2959, 3149 cm^{-1}; MS (DIP-EI): *m*/*z*: 235 [*M*$^+$−Im], 210 [*M*$^+$+H−COIm], 206, 192, 179, 164 153, 138.

Bis-1,3-adamantylureidopyrimidinone (1): A suspension of 1,3-adamantane dicarboxylic acid (400 mg, 1.783 mmol) and Et_3N (0.54 mL, 3.91 mmol) in dry toluene (12 mL) was stirred under an argon atmosphere until complete dissolution. Diphenylphosphoryl azide (DPPA) (0.88 mL, 4.083 mmol) was added and the mixture was heated at 40°C for 1 h and at 80°C for another 4 h. Finally, **3** (1.06 g, 3.994 mmol) was added and the mixture was stirred at 80°C for 16 h. The reaction mixture was evaporated and the residue was triturated with cold MeOH to yield **1** as a white solid in 74% yield. M.p. 184–185°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 13.19$ (s, 2H; *NH*C=N), 11.69 (s, 2H; C*NH*(CO)NHAr), 9.60 (s, 2H; CNH(CO)*NH*Ar), 5.79 (s, 2H; (CO)*CH*=C), 2.44 (s, 4H; CH$_2$, CH), 2.27 (s, 4H; CH$_2$, CH), 1.87 (s, 4H; CH$_2$, CH), 1.62 (s, 10H; CH$_2$, CH), 1.24 (s, 32H; CH$_2$, CH), 0.86 ppm (t, ^3J(H,H) = 6.4 Hz, 6H; CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C): $\delta = 173.0$, 155.6, 154.9, 152.2, 105.7, 53.3, 40.3, 32.6, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.9, 26.9, 22.7, 14.1 ppm; IR (KBr): $\tilde{\nu} = 1660$, 1694, 2853, 2924, 3217 cm^{-1}; MS (FAB): *m*/*z* (%): 772 (2) [*M*$^+$+Na], 750 (4) [*M*$^+$+H], 484 (13) [*M*$^+$−pyrim], 458 (12) [*M*$^+$−COPyrim]; HRMS *m*/*z*: calcd for $C_{42}H_{69}N_8O_4$ [*M*$^+$+H]: 749.5441; found: 749.5447.

Bis-*meta*-phenyleneureidopyrimidinone (2): Compound **5** (2.60 g, 8.58 mmol) was added to a solution of 2,6-diaminotoluene dihydrochloride (0.73 g, 3.73 mmol) and Et_3N (1.0 mL, 7.83 mmol) in 10 mL of $CHCl_3$, and this solution was stirred for 3 h under nitrogen at 50°C. $CHCl_3$ (50 mL) was added to the reaction mixture and the organic layer was washed with 1N HCl (20 mL) and brine (20 mL), then dried over Na_2SO_4. The organic layer was reduced to about 10 mL by evaporation under vacuum. This concentrated solution was slowly added to 50 mL of MeOH under vigorous stirring, which resulted in a precipitate. The precipitate was filtered off, and washed thoroughly with MeOH, affording **2** in 88% yield as a white powder. M.p. 186°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 13.12$ (s, 2H; *NH*C=N), 12.48 (s, 2H; C*NH*(CO)NHAr), 11.83 (s, 2H; CNH(CO)*NH*Ar), 7.26 (m, 3H; Ar*H*), 5.86 (s, 2H; (CO)*CH*=C), 2.37 (s, 3H; ArCH$_3$), 2.30 (m, 2H; (CH$_2$)$_2$*CH*C), 1.70–1.60 (m, 8H; CH$_2$), 1.36–1.27 (m, 8H; CH$_2$), 0.93 ppm (m, 12H; CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.0$, 161.5, 152.9, 152.3, 134.8, 132.3, 132.0, 122.4, 105.4, 45.8, 40.9, 32.6, 30.9, 29.1, 26.4, 22.3, 19.9, 13.6, 13.5, 12.4, 11.2 ppm; FTR-IR (ATR): $\tilde{\nu} = 709$, 835, 877, 785, 1134, 1185, 1267, 1314, 1392, 1447, 1527, 1551, 1591, 1612, 1692, 2599, 2871, 2931, 2959, 3039, 3158 cm^{-1}; MS (ESI): *m*/*z*: 593.4 [*M*$^+$+H]; elemental analysis calcd (%) for $C_{31}H_{44}N_8O_4$ (592.3): C 62.80, H 7.49, N 18.91; found: C 62.61, H 7.15, N 18.70.

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