The G−C DNA Base Hybrid: Synthesis, Self-Organization and Structural Analysis

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The guanine−cytosine base hybrid **1** is synthesized in five steps from the malononitrile dimer. One face of the molecule possesses the cytosine AAD hydrogen bonding code and the other the guanine DDA code. The expression of this information leads to the self-organization of six molecules of **1** into a hexagonal supermacrocycle in the solid state through the formation of 18 strong hydrogen bonds. This is the first structurally characterized example of a synthetic hexagonal assembly where the molecular program is unambiguous and all of the information required for exclusive rosette formation is contained within hydrogen bonding codes. **1** crystallizes in the very rare, high-symmetry cubic space group $Ia\bar{3}d$, with 96 molecules in the unit cell. The crystal is highly solvated and only ca. 35% occupied by molecules of **1**, with a criss-crossed network of channel voids generated by the overlapping of $\mathbf{1}_6$ hexamers.

Introduction

The pyridopyrimidine **1** is a DNA base hybrid: It incorporates the complementary hydrogen bonding codes of both cytosine (AAD) and guanine (DDA) in the same molecule. Situated at 120° angles to each other, these codes define a molecular program that drives the merger of six molecules of **1** into a hexagonal supermacrocycle (Scheme 1).[1] This was the first example of a structurally characterized, nonnatural molecular aggregate whose subunits possessed information of a standard sufficient to *unambiguously* dictate this particular mode of assembly.[2] Furthermore, the energetics of the association process were maximized by the effectiveness of the nonsymmetric H-bond pattern,[3] such that self-organization could take place in polar solvents (DMF, DMSO), from which crystals of **1** grew. Relevant to this point was concurrent work by Lehn and co-workers,[4] whose study of a closely related molecule provided direct evidence using vapor-pressure osmometry that this hexameric state of aggregation also exists in solution. Later work employing size-exclusion chromatography on yet another similar molecule comes to the same conclusion.[5] We now report the details of the synthesis and structure of **1**.

Results and Discussion

Our initial synthetic approach was built up around the easy availability of 2-bromo-3-cyano-4,6-diaminopyridine **2**,[6] which is derived in one step from malononitrile and already possesses most of the carbon−nitrogen framework of **1**. Reaction of **2** with the NH_2O^- equivalent acetone oxime[7] (Scheme 2) gave the oximino ether **3** in 60% yield, which on hydrolysis produced the isoxazole **4**. This material then underwent smooth hydrogenolysis to the amidinopyridone **5**. Attempts, however, to obtain a pyrido[4,3-*d*]pyrimidine system by reaction of **5** with phosgene or equivalents (diethyl carbonate, ethyl chloroformate, trichloromethyl chloroformate) failed under a range of conditions, possibly due to its limited solubility.

The difficulties inherent in this route led to a reworking of the synthesis, in which a solubilizing group was featured and which avoided the intermediacy of an amidine. Thus, the commercially available (or readily prepared)[8] malononitrile dimer **6** was alkylated by reaction with heptyl bromide in the presence of Hünigs base in 71% yield (Scheme 3). The product **7** could be cyclized with hydrogen bromide to the corresponding bromopyridine **8** in 90% yield and the requisite oxygen functionality introduced by nucleophilic displacement with methoxide. However, direct cyclization of **7** with methoxide[9] was found to be more convenient, even though it gave a mixture of **9** (69%) and its regioisomer **10** (19%). The more nucleophilic 6-amino group of compound **9** had then to be protected in order to elaborate at the 4-nitrogen. Considerable trial-and-error at this point eventually led to the preparation of a methyl carbamate **11** by treatment the dianion of **9** with dimethyl carbonate. The key transformation leading to the bicyclic system **12** was originally accomplished by reaction of **11** with chlorosul-

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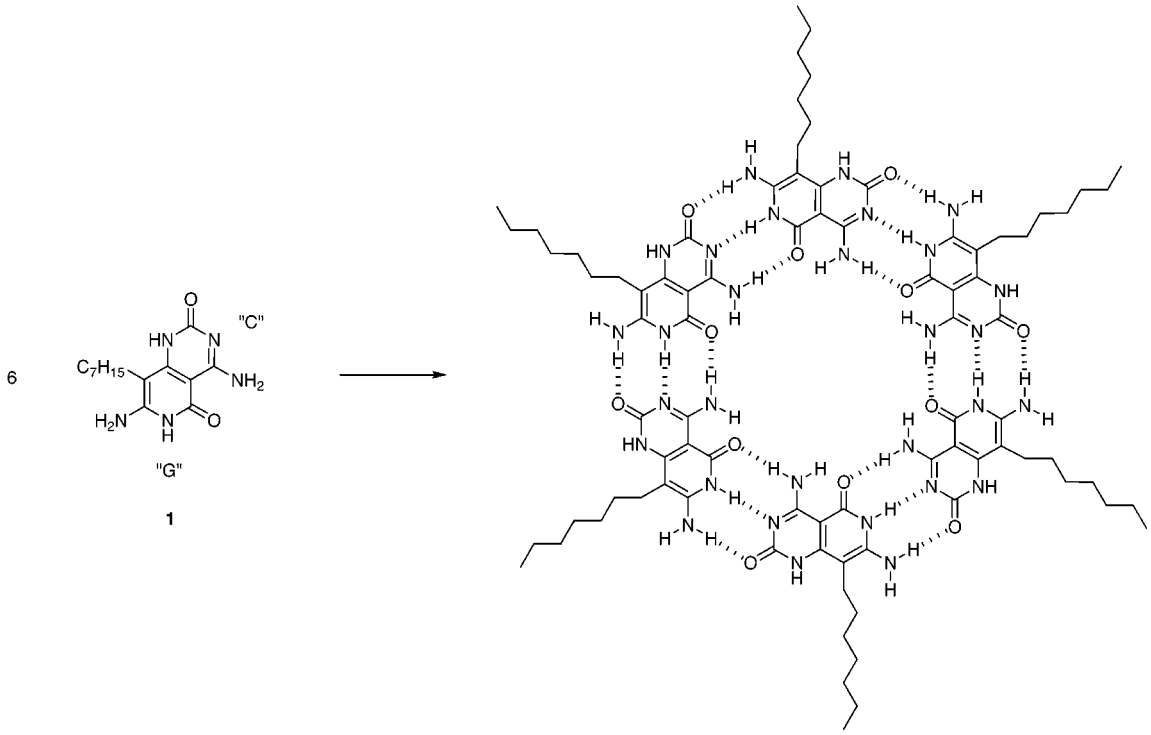
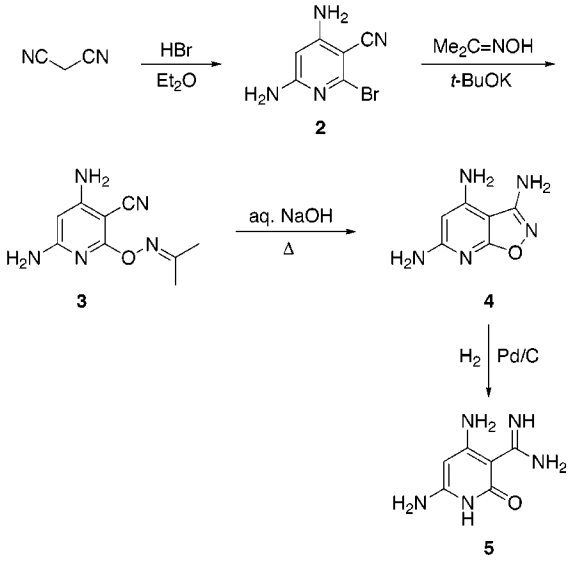
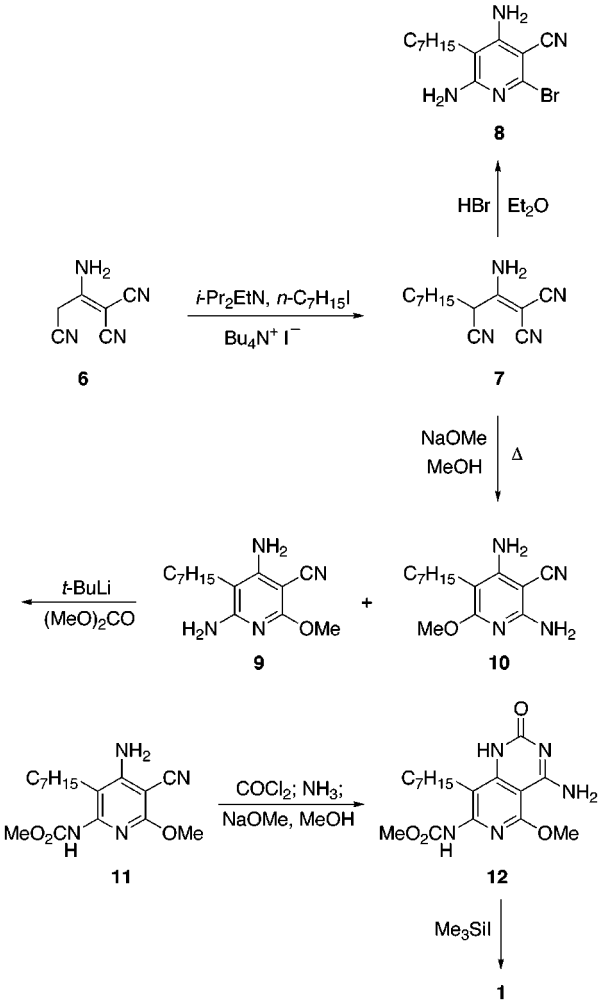
Scheme 1



Scheme 2



Scheme 3



fonyl isocyanate followed by aqueous workup in a disappointing 15% yield.[1] We have now improved the conversion to **12** to a more satisfactory 47% by sequential addition of phosgene, ammonia, and methoxide to **11**. Compound **12** was finally treated with TMS-iodide to simultaneously demask both the 6-amino group and the latent carbonyl function, and the target material **1** was isolated in 73% yield.

Compound **1** was practically insoluble in alcohols, ethers, and halogenated solvents but readily went into dimethyl formamide and dimethyl sulfoxide. Preparation of dilute solutions of **1** at slightly elevated temperatures in either of these solvents, or mixtures thereof, resulted after several hours in the deposition of large, clear crystals of cubic habit that showed no extinction of plane-polarized light. Despite the apparent quality of the crystals, initial attempts to characterize **1** by X-ray diffraction were unsuccessful, and it was only when more powerful techniques were applied that the crystals

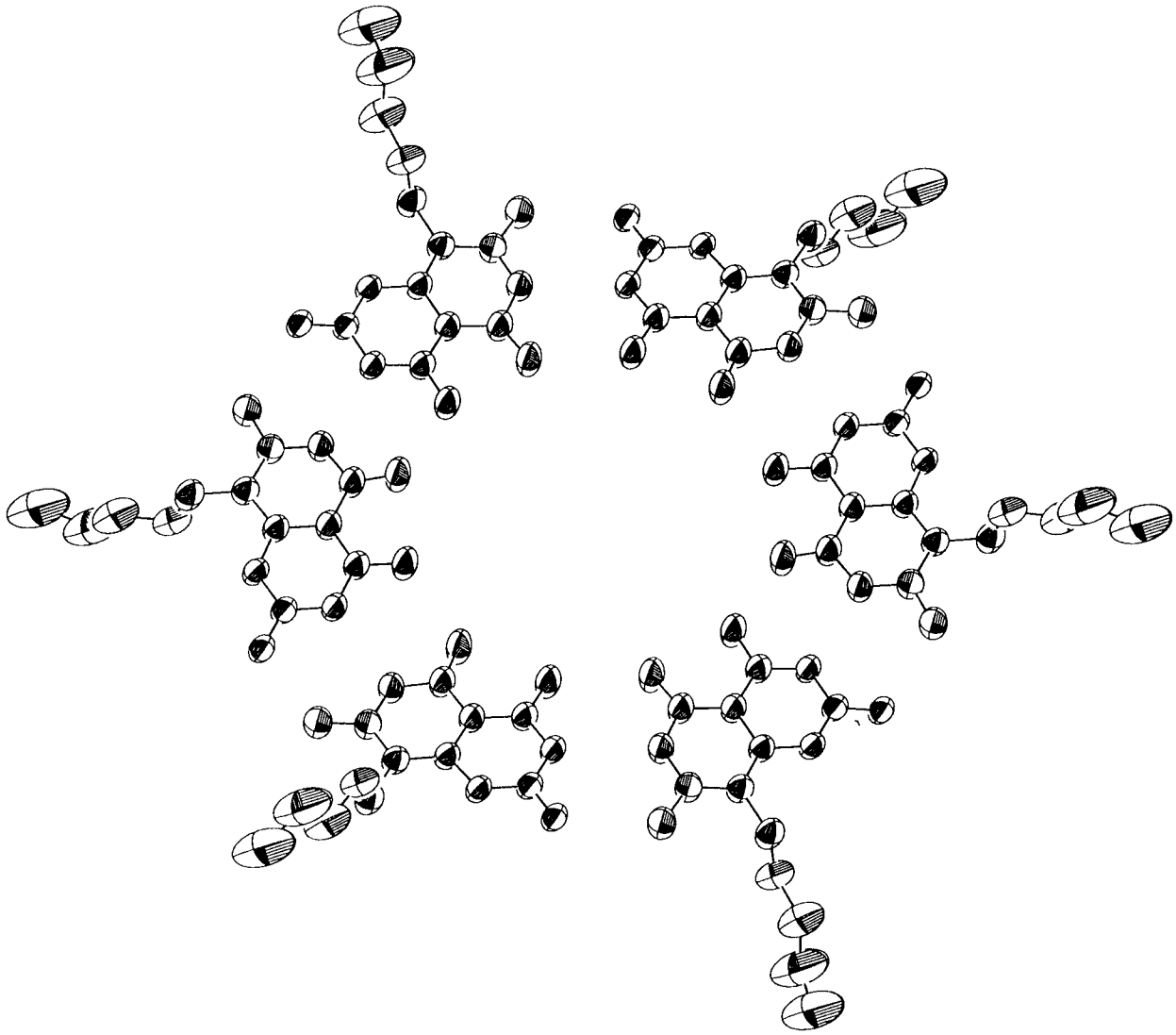


Figure 1. Oblique view of the hexagonal packing of **1** in the crystal.

yielded to analysis. Because crystals of **1** rapidly desolvated on exposure to air and did not withstand freezing, data had to be collected at room temperature on samples mounted in sealed capillaries. Reflections could not be resolved using a basic, sequential crystallographic protocol. The use, however, of an area detector and rotating anode Cu Kα radiation source did give a good dataset to the maximum resolution available (1.66 Å), which, although not sufficient to solve the structure, indicated a very large unit cell with $a = 47$ Å and $V > 100\,000$ Å^3. A solution was ultimately derived from data collected using a synchrotron radiation source, and the result confirmed the predicted hexagonal mode of assembly (Figure 1). Six molecules of **1** thus converge into a ring fixed by 18 strong H-bonds as dictated by the G−C pairing codes, with distances O···N (outer) 2.80, N···N 2.91, and O···N (inner) 2.91 Å. The molecule crystallizes in the very rare cubic space group $Ia\bar{3}d$ (number 230), in which only two other organic structures have been reported.[10] There are 96 molecules of **1** in the unit cell, with a single molecule of **1** in the asymmetric unit and 96-fold symmetry in the crystal.

An additional feature of the structure is that the hexamers coincide with one another to describe channels that extend through the crystal parallel to the body diagonals. The view of the unit cell down [111] in Figure 2, which shows how each 10.5 Å channel is surrounded by six triangular voids in a Star of David type arrangement, about the periphery of which another six channels occur. Although these features can be clearly identified in Figure 2, distinguishing individual hexamers is complicated by the fact that each is rotated 24° relative to the one above it. The alkyl chains of neighboring subunits protrude 2.7 Å above and below the hexamer plane in an alternating pattern of $\bar{3}$ symmetry. The mobility of these groups is marked and increases progressively with distance from the rigid aromatic core, such that discrete positions for the two terminal carbons could not be found. The $\mathbf{1}_6$ units do not "stack" in the traditional sense but are separated by about 20 Å along the channel axis. The calculated density of the crystal is remarkably low (0.479 g cm^{-3}), indicating that ca. 65% of the cell is "unoccupied". Since the presence of only 0.7 solvent molecules (DMSO in this case) per molecule of **1** could be modeled on the

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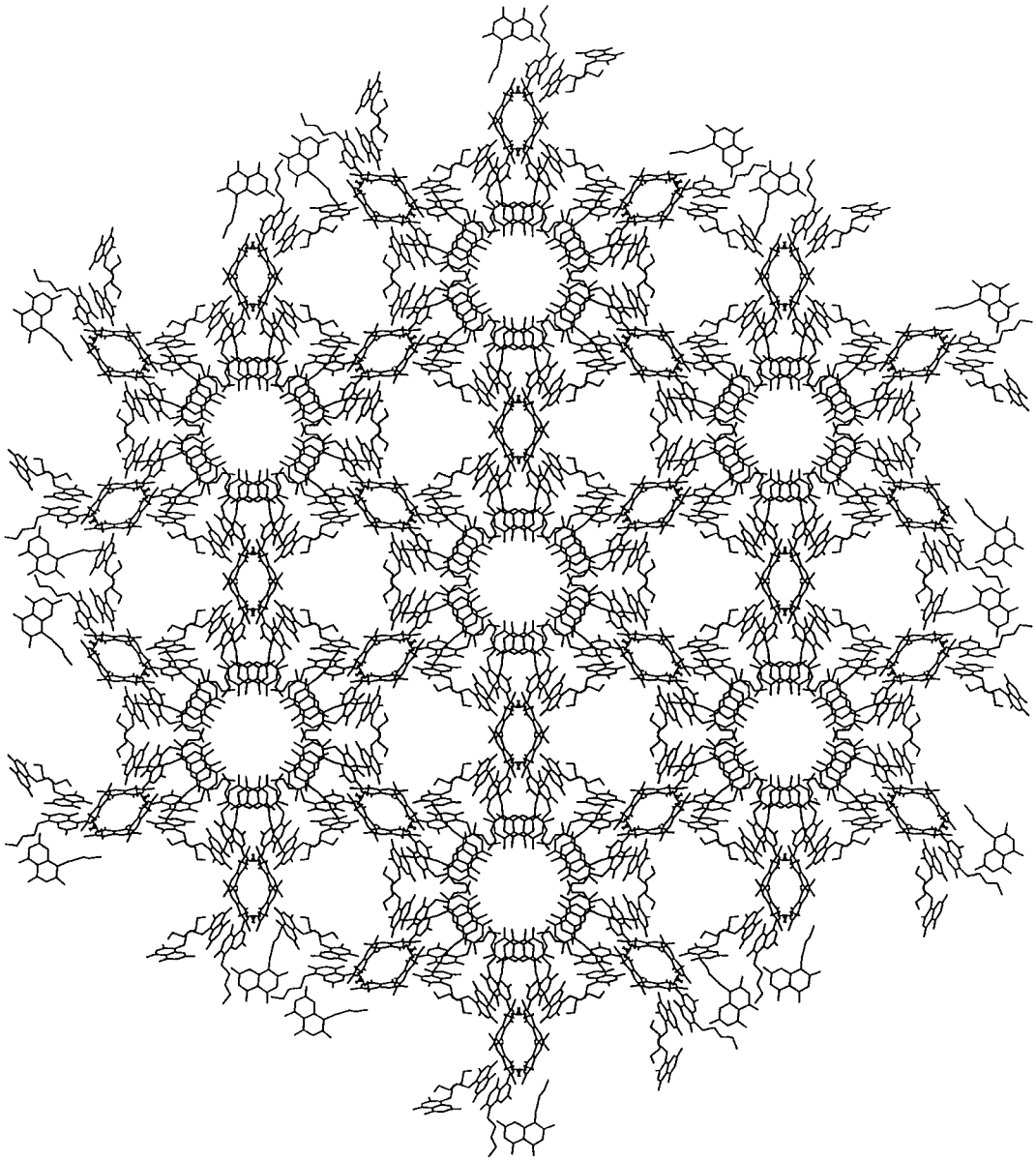

Figure 2. A view of the cell of **1** down a body diagonal.

data, the remainder of the space is apparently filled by highly disordered (or liquid) solvent. The vacancies in the structure raise the intriguing prospect of cocrystallizing **1** with species complementary to the channel voids, particularly polymeric materials (peptides, saccharides), which should act to reinforce the assembly and thereby also improve the physical integrity of the crystals.

In conclusion, the adaptation of reciprocal DNA-base codes in G−C hybrid molecule **1** to self-organization processes leads to the first structurally characterized example of an unambiguous hexagonal mode of assembly. The robustness of the assembly provides an unparalleled means of creating hexagonal order on the molecular scale. Current efforts on our part in this area include the organization of sterically demanding substituents in the periphery of $\mathbf{1}_6$ in an attempt to force the subunits from planarity. This would introduce a "screw defect" into the ring resulting in an H-bonded polymer with helical secondary structure. The previously mentioned issue of the host properties of the zeolite-like lattice of **1** is also under investigation, and progress along these lines will be reported in due course.

Experimental Section

3-Cyano-4,6-diamino-2-isopropylidineaminooxypyridine (3). Potassium *tert*-butoxide (1.21 g, 10.8 mmol) was added to a solution of acetone oxime (765 mg, 10.5 mmol) in dry DMF (20 mL) under nitrogen. The suspension was stirred for 1 h at room temperature, and then 2-bromo-3-cyano-4,6-diaminopyridine **2** (2.13 g, 10.0 mmol) in dry DMF (10 mL) was added and the resulting red-orange solution stirred for 20 h at 60 °C. Saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL) were added, and the solution was then neutralized with 2 M HCl. After extraction with chloroform (×4), the combined organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed (3:7 acetone/CH_2Cl_2) to give starting material **2** (420 mg) and product **3** (1.24 g, 60%) as pale yellow solid: ^{1}H NMR (250 MHz; DMSO-d_6) δ 1.94 (3 H, s), 1.98 (3 H, s), 5.37 (1 H, s), 6.27 (2 H, br s), 6.39 (2 H, br s); ^{13}C NMR (100 MHz; DMSO-d_6) δ 16.1, 21.2, 67.3, 83.6, 158.1, 160.7, 161.1, 165.5. Anal. Calcd for $C_9H_{11}N_5O$: C, 52.7; H, 5.4; N, 34.1. Found: C, 52.5; H, 5.6; N, 34.2.

Isoxazolo[5,4-*b*]pyridine-3,4,6-triamine (4). Compound **3** (2.90 g, 14.1 mmol) was added to 0.5 M aqueous NaOH (200 mL), and the suspension was heated at 90 °C for 30 h under nitrogen. The reaction mixture was neutralized with 6 M HCl,

saturated with NaCl, and extracted with 1:1 ethyl acetate/methanol (×3). The aqueous layer was evaporated and the residue triturated with hot 1:1 acetone/methanol. The organic extracts were combined, the solvent was evaporated, and the crude product was preabsorbed onto silica gel. Chromatography (12:1 → 3:1 EtOAc/MeOH) gave 3-cyano-4,6-diamino-2-pyridone (710 mg, 33%)[11] and the product **4** (670 mg, 29%) as a pale yellow solid: ^{1}H NMR (250 MHz; DMSO-d_6) δ 5.35 (1 H, s), 5.81 (2 H, s), 5.96 (2 H, s), 6.26 (2 H, s); ^{13}C NMR (67.8 MHz; DMSO-d_6) δ 84.8, 86.1, 151.1, 157.8, 161.7, 172.1. Anal. Calcd for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.5; H, 4.5; N, 42.6.

4,6-Diamino-2-pyridone-3-carboxamidine (5). To a solution of compound **4** (100 mg, 0.60 mmol) in methanol (20 mL) was added 10% Pd on activated charcoal (40 mg). The mixture was degassed by flushing with hydrogen (×3) and stirred at room temperature over hydrogen for 24 h. The reaction was filtered and the solvent evaporated to give **5** (94 mg, 93%): ^{1}H NMR (250 MHz; DMSO-d_6) δ 4.96 (1 H, s), 6.42 (2 H, br s), 8.01 (6 H, br s); ^{13}C NMR (67.8 MHz; DMSO-d_6) δ 78.2, 84.4, 152.2, 160.6, 164.1, 164.4; *m*/*z* (CI/NH_3) 168 (M + H, 100).

2-Amino-1,1,3-tricyano-1-decene (7). Diisopropylethylamine (5.5 mL, 4.1 g, 31.6 mmol) was added to a solution of 2-amino-1,1,3-tricyanopropene **6**[8] (1.995 g, 15.1 mmol) in DME (50 mL) and the solution stirred at room temperature for 40 min. 1-Bromoheptane (10.0 mL, 11.4 g, 63.6 mmol) and tetrabutylammonium iodide (0.33 g, 0.89 mmol) were added, and the suspension was heated at reflux for 110 h with light excluded. The mixture was cooled to room temperature, and the precipitated ammonium salt was filtered off and washed with ethyl acetate (×5). The solvent was evaporated and the residue partitioned between hydrochloric acid (0.4 M, 100 mL) and dichloromethane (50 mL). The aqueous layer was extracted with additional dichloromethane (×4), the combined organic extract dried ($MgSO_4$), and the solvent evaporated to give a black oil. Chromatography (0 → 100% ether in hexanes) gave **7** (2.459 g, 71%) as a pale orange solid: mp 70.5−71.5 °C (from EtOH/H_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.90 (3 H, *t*, *J* 6.9), 1.29−1.41 (8 H, m), 1.50−1.61 (2 H, m), 1.95−2.02 (2 H, m), 3.98 (1 H, t, *J* 7.4), 6.42 (1 H, br s), 6.81 (1 H, br s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 14.0, 22.5, 26.8, 28.5, 28.7, 31.5, 32.9, 35.8, 54.6, 112.7, 113.1, 116.0, 167.8. Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.8; H, 7.9; N, 24.3. Found: C, 67.7; H, 8.1; N, 24.2.

4,6-Diamino-2-bromo-3-cyano-5-heptylpyridine (8). Hydrogen bromide was bubbled into a solution of **7** (0.128 g, 0.56 mmol) in diethyl ether (45 mL) over a period of 2 h.[6] Initially, the mixture was kept at 0 °C but as the reaction proceeded it was allowed to gradually warm to room temperature. Saturated $NaHCO_3$ (10 mL) was carefully added, followed by solid sodium carbonate, until no further gas evolution was observed. The aqueous layer was separated and extracted with ethyl acetate (×3), the combined organic extract dried (Na_2CO_3), and the solvent evaporated to give a yellow oil. Chromatography (0 → 15% ethyl acetate in CH_2Cl_2) gave **8** (0.155 g, 90%) as a white solid: mp 143−143.5 °C (from MeOH/H_2O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (3 H, t, *J* 6.9), 1.27−1.38 (8 H, m), 1.50 (2 H, quintet, *J* 7.8), 2.27 (2 H, t, *J* 7.8), 4.80 (2 H, s), 5.02 (2 H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 14.0, 22.5, 24.7, 26.5, 29.1, 29.8, 31.7, 89.6, 99.4, 116.6, 140.8, 154.0, 157.9. Anal. Calcd for $C_{13}H_{19}BrN_4$: C, 50.2; H, 6.2; N, 18.0. Found: C, 50.2; H, 6.2; N, 17.9.

3-Cyano-4,6-diamino-5-heptyl-2-methoxypyridine (9) and 5-Cyano-4,6-diamino-3-heptyl-2-methoxypyridine (10). Trinitrile **7** (0.474 g, 2.06 mmol) was added to a methanolic solution of sodium methoxide prepared from sodium (0.41 g, 18 mmol) and methanol (10 mL), and the reaction was heated at reflux for 37 h.[9] The solution was cooled to room temperature and the solvent evaporated. Water (20 mL) was added and the mixture extracted with dichloromethane (×3). The combined organic extract was dried ($MgSO_4$) and the solvent evaporated to give a white solid. Chromatography (0 → 40% ether in hexanes) provided, in order of elution, compound **10** (0.104 g, 19%) and compound **9** (0.370 g, 69%).

9: mp 62.5−63.5 °C (from EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.88 (3 H, t, *J* 6.9), 1.15−1.40 (8 H, br m), 1.48 (2 H, quintet, *J* 7.7), 2.25 (2 H, t, *J* 7.8), 3.87 (3 H, s), 4.56 (2 H, br s), 4.62 (2 H, br s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 14.0, 22.6, 24.7, 27.3, 29.2, 29.8, 31.8, 53.5, 71.7, 94.6, 116.5, 155.1, 157.1, 163.8. Anal. Calcd for $C_{14}H_{22}N_4O$: C, 64.1; H, 8.5; N, 21.4. Found: C, 64.1; H, 8.6; N, 21.5.

10: mp 134.5−135 °C (from EtOAc/hexanes); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.88 (3 H, t, *J* 7.0), 1.20−1.32 (8 H, br m), 1.40 (2 H, m), 2.33 (2 H, t, *J* 7.6), 3.83 (3 H, s), 4.53 (2 H, br s), 4.76 (2 H, br s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 14.1, 22.6, 23.0, 28.2, 29.2, 29.5, 31.8, 53.6, 70.7, 96.5, 117.1, 154.4, 157.9, 164.0. Anal. Calcd for $C_{14}H_{22}N_4O$: C, 64.1; H, 8.5; N, 21.4. Found: C, 64.3; H, 8.7; N, 21.3.

4-Amino-3-cyano-5-heptyl-2-methoxy-6-[(methoxycarbonyl)amino]pyridine (11). *tert*-Butyllithium (1.7 M in pentanes, 4.0 mL, 6.8 mmol) was added dropwise to a stirred suspension of **9** (0.786 g, 3.00 mmol) in DME (40 mL) at −78 °C, during which time the reaction became homogeneous. The mixture was allowed to warm to room temperature over a period of 1 h, and dimethyl carbonate (5.0 mL, 5.3 g, 59 mmol) was added. The reaction was then stirred at room temperature for 19 h. All volatiles were removed under reduced pressure, aqueous $NaHCO_3$ (2%, 50 mL) was added, and the mixture was extracted with dichloromethane (×5). The combined organic extract was dried ($MgSO_4$) and the solvent evaporated to give a pale yellow solid. Chromatography (0 → 50% ethyl acetate in hexanes) gave **11** (0.829 g, 86%) as a white solid: mp 118−121 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.89 (3 H, t, *J* 7.0), 1.28−1.32 (8 H, m), 1.48 (2 H, quintet, *J* 7.3), 2.39 (2 H, t, *J* 7.9), 3.79 (3 H, s), 3.94 (3 H, s), 4.92 (2 H, br s), 6.62 (1 H, br s); ^{13}C NMR (100 MHz; DMSO-d_6) δ 13.8, 22.0, 23.7, 27.3, 28.4, 28.5, 31.1, 51.7, 53.3, 75.1, 109.2, 115.1, 148.8, 154.2, 157.9, 162.0. Anal. Calcd for $C_{16}H_{24}N_4O_3$: C, 60.0; H, 7.6; N, 17.5. Found: C, 60.0; H, 7.8; N, 17.7.

4-Amino-8-heptyl-5-methoxy-7-[(methoxycarbonyl)-amino)]pyrido[4,3-*d*]pyrimidin-2(1*H*)-one (12). A solution of **11** (0.160 g, 0.50 mmol) in a mixture of toluene (5.0 mL), dichloromethane (2.0 mL), and triethylamine (1.0 mL) was added dropwise to a 20% solution of phosgene in toluene (2.5 mL, 5.0 mmol). The mixture was stirred for 3 h, and then ammonia gas was bubbled through for 30 min. The resulting suspension was left stirring under an ammonia atmosphere for 16 h. Water (15 mL) and ethyl acetate (15 mL) were then added, and the aqueous layer was separated and extracted with ethyl acetate (×4). The combined extracts were washed with brine (50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The dry residue was dissolved in 0.2 M sodium methoxide in MeOH (5 mL), and the solution was stirred for 4 h. The solvent was evaporated, and the solid was partitioned between saturated aqueous $NaHCO_3$ (25 mL) and chloroform (15 mL). The aqueous layer was separated and extracted with chloroform (×4), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. Purification was achieved by preabsorption (MeOH) onto silica gel followed by chromatography twice (25 → 50% ethyl acetate/CH_2Cl_2, then 0 → 20% methanol in dichloromethane) to give **12** (0.085 g, 47%) as a white solid: mp 165 °C dec; ^{1}H NMR (400 MHz; DMSO-d_6) δ 0.85 (3 H, t, *J* 6.8), 1.15−1.35 (10 H, br m), 2.64 (2 H, m), 3.65 (3 H, s), 3.94 (3 H, s), 7.64 (1 H, br s), 8.02 (1 H, br s), 9.44 (1 H, br s), 10.25 (1 H, br s); ^{13}C NMR (100 MHz; DMSO-d_6) δ 13.8, 22.0, 22.9, 28.2, 28.3, 28.5, 31.2, 51.7, 53.9, 90.6, 109.2, 148.6, 151.0, 154.2, 155.8, 157.7, 162.5; HRMS (FAB) found *m*/*z* 364.2002 (M + H), $C_{17}H_{26}N_5O_4$ requires 364.1985.

4,7-Diamino-8-heptyl-1*H*,6*H*-pyrido[4,3-*d*]pyrimidine-2,5-dione (1). Chlorotrimethylsilane (0.30 mL, 0.26 g, 2.4 mmol) was added to a stirred suspension of **12** (0.146 g, 0.40 mmol) and sodium iodide (0.60 g, 4.0 mmol) in acetonitrile (30 mL), and the mixture was heated at reflux for 42 h with light excluded. The reaction was cooled to 0 °C, and a solution of $NaHCO_3$ (0.5 g) and sodium thiosulfate pentahydrate (1.0 g)

(11) Junek, H.; Uray, G.; Kotzent, A.; Kastner, G. *Monatsh. Chem.* **1985**, *116*, 1199.

in water (25 mL) was added. The mixture was allowed to warm to room temperature with stirring, and the precipitated product was filtered and dried under vacuum to give **1** (0.085 g, 73%) as a pale yellow solid: mp 160 °C dec (from 4:1 DMF/DMSO); ^{1}H NMR (400 MHz; DMSO-d_6) δ 0.85 (3 H, t, J 6.6), 1.24 (10 H, br m), 2.37 (2 H, br m), 6.75 (2 H, br s), 7.46 (1 H, br s), 8.84 (1 H, br s), 9.57 (1 H, br s), 11.37 (1 H, br s); ^{13}C NMR (100 MHz; DMSO-d_6) δ 13.8, 21.3, 21.9, 28.2, 28.8, 31.3, 85.2, 86.0, 151.6, 152.8, 156.7, 162.1, 165.0; HRMS (FAB) found m/z 292.1778 (M + H), $C_{14}H_{22}N_5O_2$ requires 292.1774.

Crystallization of 1. All manipulations were performed under a nitrogen atmosphere. Crude **1** (ca. 6−8 mg) was placed in a glass tube, and dry DMF or DMSO (ca. 2 mL) was added. The mixture was warmed carefully until it became homogeneous and then filtered through glass wool into a second tube. The filtrate was again warmed until it became homogeneous before being allowed to cool undisturbed to room temperature. After several hours, a crop of translucent crystals of cubic morphology was observed. Freshly grown crystals mounted in glass capillaries yielded good quality diffraction patterns with a rotating anode source, although the quality deteriorated markedly in the course of a few days. Attempts at rapid cooling of the crystals to cryogenic temperatures dramatically reduced the resolution of the diffraction pattern and introduced severe mosaicity coupled with powder rings of "crystallized" solvent. A complete dataset collected using synchrotron radiation and a 30 cm MAR imaging plate permitted structure solution by direct methods as described.[1] Several attempts to model partially occupied DMSO molecules in the remaining electron density were carried out. In the final structure, the remaining peaks were modeled as two partially occupied, restrained DMSO molecules. This resulted in final conventional R values of 0.1462 for 4134 $F_o > 4\sigma(F_o)$ and 0.1643 for all 5725 data and a difference map with no feature above 0.29 e Å^{-3}.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **5**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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