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Goto, Kenta

Division of Applied Molecular Chemistry, Institute for Materials Chemistry and Engineering, Kyushu University

Miyahara, Yuji

Department of Chemistry, Graduate School of Sciences, Kyushu University

Shinmyozu, Teruo

Division of Applied Molecular Chemistry, Institute for Materials Chemistry and Engineering, Kyushu University

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A Spherical Molecular Assembly Formed by the Interplay of Hydrophobic and Hydrogen Bonding Interactions. Formation of a Hexameric Ball

Kenta Goto,^{a,*} Yuji Miyahara,^b and Teruo Shinmyozu^a

^a Division of Applied Molecular Chemistry, Institute for Materials Chemistry and Engineering, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.
Tel.: +81 92 642 4350; fax: +81 92 642 2735; E-mail address: g2k@me.com

^b Department of Chemistry, Graduate School of Sciences, Kyushu University

General

All reagents were reagent-grade and used without purification. Methanol was distilled from calcium hydride. Melting points were measured on a Yanaco MP-S3 melting point apparatus and are uncorrected. The NMR spectra were recorded on a Jeol JNM-AL300 spectrometer, operating at 300 and 75 MHz for ^1H and ^{13}C , respectively. The ^{13}C NMR spectra were measured on a Bruker DRX 600 spectrometer at a measurement frequency of 125 MHz. The chemical shifts are given in ppm downfield from the ^1H and ^{13}C signals of tetramethylsilane. The FAB mass spectra were obtained on a Jeol JMS-70 mass spectrometer with *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were performed at the Center of Elementary Analysis affiliated with Faculty of Science, Kyushu University. The FT-IR spectra were recorded on a Nicolet Magna 560 spectrometer. The electrospray ionization mass spectrum was recorded on a Jeol JMS-T100CS AccuTOF spectrometer. The solid-state CPMAS ^{13}C NMR spectra were measured on a Jeol JNM-ECA400 spectrometer at a measurement frequency of 100.5 MHz and a rotation frequency of 10 kHz. The ^{13}C NMR chemical shifts are referenced to the methyl signal ($\delta = 17.36$ ppm) of hexamethylbenzene, which was used as an external standard. The X-ray powder diffraction data were collected on a Rigaku MultiFlex diffractometer over the 2θ range of $5-60^\circ$ with using a copper radiation source.

Synthesis

Scheme 1. Synthesis of 4-isobutylamino-6-oxypyrimidine **1c**.

4-Isobutylamino-6-chloropyrimidine **2**

A solution of 4,6-dichloropyrimidine¹ (10.0 g, 67.1 mmol) in dry MeOH (200 mL) was cooled in an ice-water bath, and then isobutylamine (10.8 g, 0.148 mol) was added dropwise. After 10 min, the bath was removed, and stirring was continued for 6 h at room temperature. After removing the solvent, the residue was partitioned between water (100 mL) and AcOEt (150 mL). The aqueous phase was extracted twice with AcOEt (100 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and evaporated. The

residue was passed through a silica gel column (*n*-hexane/AcOEt = 4:1 (v/v)) to yield the compound **2** (12.4 g, 99%). An analytically pure compound was obtained by Kugelrohr sublimation (78 °C, 5 Pa) as colorless crystals. Mp 120-121.5 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.32 (s, 1H), 6.33 (s, 1H), 5.19 (br s, 1H), 3.10 (br s, 2H), 1.90 (A₃X, *J* = 6.7 Hz, 1H), 0.99 (A₃X, *J* = 6.6 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 163.5, 158.4, 49.1, 28.2, 20.2 (two peaks could not be identified due to broad resonances). IR (KBr): ν 3241, 3101, 3026, 2960, 2871, 1606, 1572, 1458, 1396, 1334, 602, 557, 458, 418 cm⁻¹. FABMS *m/z* (%): 186.12 (100) [C₈H₁₃³⁵CIN₃]⁺, 188.12 (33) [C₈H₁₃³⁷CIN₃]⁺. Anal. Calcd for C₈H₁₂N₃Cl: C, 51.76; H, 6.51; N, 22.63. Found: C, 51.84; H, 6.51; N, 22.64.

4-Isobutylamino-6-methoxypyrimidine **3**

A three-necked flask was equipped with a nitrogen gas inlet, dropping funnel and reflux condenser with the top attached to a CaSO₄ drying tube. The apparatus was dried with a heat gun under nitrogen flow. In the flask, sodium methoxide (14.7 g, 0.272 mol) was dissolved in dry MeOH (180 mL) under nitrogen. To the clear solution, pyrimidine **2** (7.68 g, 41.4 mmol) was added in one portion. The mixture was refluxed for 12 h. After cooling, the mixture was concentrated under reduced pressure. The residue was partitioned between water (100 mL) and ether (100 mL). The aqueous phase was extracted with ether (100 mL). The organic phase was dried over Na₂SO₄, filtered and evaporated. The obtained material was freeze-dried to give the product **3**, which was purified by sublimation (63 °C, 5 Pa) to give the compound **3** (6.69 g, 89%) as a white solid. Mp 41-42 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.23 (s, 1H), 5.62 (s, 1H), 4.94 (s, 1H), 3.91 (s, 3H), 3.02 (A₂X, *J* = 6.3 Hz, 2H), 1.88 (A₃X, *J* = 6.7 Hz, 1H), 0.98 (A₃X, *J* = 6.6 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 170.3, 164.3, 157.7, 84.3, 53.5, 49.4, 28.1, 20.3. IR (KBr): ν 3248, 3098, 3008, 2955, 2930, 2905, 2871, 1612, 1548, 1509, 1478, 1442, 1398, 1358, 1335, 1305, 638, 589, 557, 473 cm⁻¹. FABMS *m/z*: 182.18 ([M+H]⁺, C₉H₁₆N₃O). Anal. Calcd for C₉H₁₅N₃O: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.85; H, 8.37; N, 23.04.

4-Isobutylamino-6-oxypyrimidine **1c**

A solution of pyrimidine **3** (5.43 g, 30.0 mmol) in 9 N HCl (300 mL) was refluxed for 1 h. After removing the solvent, the residue was dried in vacuo using a KOH trap. Then the product was dissolved in water (20 mL) and neutralized by aqueous NaOH. The liberated material was collected by suction filtration to give the product **1c** (2.35 g, 47%). Recrystallization from water with charcoal treatment gave colorless prisms containing 0.25 molecule of water. Anhydrous **1c** was obtained by drying at 120 °C in vacuo. Mp 222.5-223.5 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.39 (s, 1H), 7.78 (s, 1H), 6.98 (t, *J* =

5.7 Hz, 1H), 4.90 (s, 1H), 2.85 (br s, 2H), 1.78 (A₃X, *J* = 6.7 Hz, 1H), 0.87 (A₃X, *J* = 6.8 Hz, 6H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 162.9, 161.8, 149.0, 83.0, 48.6, 27.4, 20.1. CPMAS ¹³C NMR (100.5 MHz): [α crystals] δ 165.8, 163.0, 149.5, 85.0, 50.6, 26.0, 21.4; [β crystals] δ 167.3, 165.8, 164.6, 163.0, 84.9, 84.4, 51.4, 28.9, 26.0, 21.4. IR (KBr): ν 3249, 3102, 3049, 2958, 2870, 2795, 2664, 1651, 1632, 1572, 1543, 1468, 1406, 1389, 1362, 1342, 1304, 592, 556, 512, 461 cm⁻¹. FABMS *m/z*: 168.16 ([M+H]⁺, C₈H₁₄N₃O). Anal. Calcd for C₈H₁₃N₃O·0.25H₂O: C, 55.96; H, 7.92; N, 24.47. Found: C, 55.84; H, 7.90; N, 24.35. Anal. Calcd for C₈H₁₃N₃O: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.43; H, 7.81; N, 25.06.

X-ray crystallography

Crystal preparation

The α and β crystals were prepared in the following way. The compound **1c** was dissolved in boiling nitrobenzene, and the solution was incubated at 35 °C. When the concentration of **1c** was at 0.024 M, β crystals were predominantly formed, while above 0.033 M both α and β crystals formed. The light β crystals, which floated near the surface, were scooped up and separated from the heavier α crystals.

X-ray diffraction data collections and structure solution

The X-ray data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71069 Å). The structure was solved using the direct method technique (SIR 97) and a full-matrix least squares refinement based on *F*². All non-hydrogen atoms were refined anisotropically, while the hydrogen atoms, all found in the difference Fourier map, were isotropically refined. The details of the X-ray analysis for the crystals of **1c** (quarter hydrated, α and β) have been deposited as CCDC 724430, 724431 and 724432 can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk) or at http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data

1c·0.25H₂O: 4(C₈H₁₃ON₃)·H₂O, *M_r* = 686.86, monoclinic, *C*2/c (no. 15), *a* = 14.8158(4), *b* = 18.4200(4), *c* = 13.7700(3) Å, β = 104.7611(3)°, *U* = 3633.9(1) Å³, *Z* = 4, *T* = 113 K, *D_c* = 1.255 g cm⁻³, μ(Mo Kα) = 0.00 cm⁻¹, 2θ_{max} = 55.0°, 17039 reflections were collected, of which 4172 were unique, 330 parameters, GOF = 1.07, *R*₁ = 0.043 (*I* > 2(σ)*I*), *wR*₂ = 0.125 (*I* > 2(σ)*I*), residual electron density: 0.51 and -0.57 eÅ⁻³. CCDC 724430.

1c (α form): $\text{C}_8\text{H}_{13}\text{ON}_3$, $M_r = 167.21$, triclinic, $P\bar{1}$ (no. 2), $a = 4.8006(2)$, $b = 8.3974(4)$, $c = 11.4115(4)$ Å, $\alpha = 68.879(3)^\circ$, $\beta = 87.276(1)^\circ$, $\gamma = 83.736(3)^\circ$, $U = 426.54(3)$ Å³, $Z = 2$, $T = 113$ K, $D_c = 1.302$ g cm⁻³, $\mu(\text{Mo K}\alpha) = 0.90$ cm⁻¹, $2\theta_{\text{max}} = 55.0^\circ$, 3683 reflections were collected, of which 1888 were unique, 161 parameters, GOF = 1.62, $R_1 = 0.042$ ($I > 2(\sigma)I$), $wR_2 = 0.134$ ($I > 2(\sigma)I$), residual electron density: 0.34 and -0.16 eÅ⁻³. CCDC 724431.

1c (β form): $\text{C}_8\text{H}_{13}\text{ON}_3$, $M_r = 167.21$, triclinic, $P\bar{1}$ (no. 2), $a = 11.1904(5)$, $b = 11.9041(3)$, $c = 12.6406(5)$ Å, $\alpha = 109.066(1)^\circ$, $\beta = 105.254(2)^\circ$, $\gamma = 110.408(1)^\circ$, $U = 1349.78(10)$ Å³, $Z = 6$, $T = 113$ K, $D_c = 1.234$ g cm⁻³, $\mu(\text{Mo K}\alpha) = 0.85$ cm⁻¹, $2\theta_{\text{max}} = 55.0^\circ$, 11749 reflections were collected, of which 5950 were unique, 481 parameters, GOF = 1.66, $R_1 = 0.045$ ($I > 2(\sigma)I$), $wR_2 = 0.148$ ($I > 2(\sigma)I$), residual electron density: 0.43 and -0.41 eÅ⁻³. CCDC 724432.

Pulsed field gradient NMR

Diffusion experiments were recorded on a Jeol JNM-ECA 600 NMR spectrometer equipped with a pulse field gradient probe (TH5ATFG2). The pulse sequence was based on the stimulated echo and incorporated bipolar gradient pulses and a longitudinal eddy current delay. The sine gradient pulse was applied by varying the gradient strength from 0.01 to 0.9 T m⁻¹. The ratio of the echo intensity between the presence (I) and the absence (I_0) of the a pulsed gradient is given by^{2,3}

$$\ln(I/I_0) = -\gamma^2 D \delta^2 g^2 (4\Delta - \delta) / \pi^2 \quad (1)$$

where δ is the duration of the field gradient with magnitude g , γ is the gyromagnetic ratio, D is the diffusion coefficient, and Δ is the separation between the two gradient pulses. The δ was in the range of 0.36–1.4 ms. The Δ was 100 ms and 200 ms for a 0.10 M and a 5.0×10^{-3} M solution of **1c**, respectively. For a 5.0×10^{-3} M solution of dichloropyrimidine, the Δ used was 300 ms. The decay curve was obtained by plotting the signal intensity as a function of the gradient strength. The resulting decay was analyzed by fitting to eq. (1) using a nonlinear least-square method implemented in the NMR software of Delta, Jeol. The reported diffusion coefficient is the mean of at least three measurements.

Determination of the solubility of the α and β crystals in nitrobenzene

Each of the separated crystals of **1c** was powdered and ca. 10 mg was put in nitrobenzene (2 mL) at the specific thermostated temperature until saturation (18 h; an equilibrium was confirmed by several experiments) with the crystals present in excess. After filtering off the undissolved crystals, 0.60 mL of the solution was taken and diluted with 40 mL of *n*-hexane to precipitate the crystals. The crystals were collected at the bottom of a test tube by centrifugation, and the supernatant solvents were removed. After washing by 3 cycles of *n*-hexane addition, centrifugation and removal of the supernatant liquid, the residual crystals were dried. However, since the amount of crystals so obtained was minute, and even a trace of residual nitrobenzene could not be ignored, the amount of crystals was determined by HPLC in the following manner.

The collected crystals were dissolved in methanol and mixed with a fixed amount of dimethyl isophthalate (DMIP) as an internal standard, and the solution was diluted to 10 mL to give DMIP in a concentration of 4.40×10^{-4} M. The HPLC analyses of the solutions were performed on a Hitachi EZChrom Elite/LaChrom system equipped with an analytical column (Nacalai Tesque, Cosmosil 5C18-AR-II, 20×250 mm). The mobile phase was 30% aqueous MeOH at a flow rate of 5 mL min^{-1} . In order to make the HPLC peak areas correspond to the amount of **1c**, a calibration line was prepared using standard solutions containing the accurately weighed **1c** and DMIP in 30% aqueous MeOH in the concentration range of $0.20\text{--}9.70 \times 10^{-4}$ M and 1.10×10^{-3} M, respectively. An example of the chromatogram of a standard solution is shown in Figure S7 (retention time of **1c** and DMIP were 12.6 and 27.3 min, respectively). The concentration of **1c** in the sample solution was estimated by comparison with the calibration line for **1c** prepared by plotting the ratio of the peak area of **1c** to that of the DMIP versus the ratio of the concentration of **1c** to that of DMIP. However, when the solubility of **1c** was increased at higher temperatures, the ratio to DMIP became too large, and another calibration line, obtained by plotting the peak area against the concentration of **1c**, was used instead (the linearity in the concentration region used was confirmed to be high: a correlation coefficient $R_2 > 0.998$, Figure S8). The resultant chromatographic data are summarized in Table S1.

Reference

- (1) Hull, R. *J. Chem. Soc.* **1951**, 2214.
- (2) Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *42*, 288-292.
- (3) Price, W. S.; Kuchel, P. W. *J. Magn. Reson.* **1991**, *94*, 133-139.

Figure S1. Photomicrograph of the polymorphic crystals of **1c**: (a) α crystals and (b) β crystals.

Figure S2. Variations in the distances of hydrogen bonds for the linear tape structures: (a) **1a**, (b) **1b**·2H₂O, (c) **1c**·0.25H₂O and (d) **1c**.

Figure S3. FT-IR spectra of **1c**. (a) α and (b) β crystals.

Figure S4. Perspective view of the hexameric ball-like assembly of **1c** in the β crystals. Dashed lines represent the hydrogen bonding.

Figure S5. Electrospray ionization mass spectrum of **1c** in ethanol (1×10^{-4} M).

Figure S6. Powder XRD patterns of **1c**. Simulated powder patterns of the polymorphic (a) the plate and (b) the trapezoid crystals calculated from their crystallographic data. Observed powder XRD patterns of the crystal separated. (c) α crystals, (d) β crystals, and (e) crystals obtained by recrystallization from MeOH.

Figure S7. Representative chromatogram of **1c** with dimethyl isophthalate (DMIP) in 30% aqueous MeOH.

Figure S8. (a) The calibration line obtained by plotting the ratios of the peak areas as a function of concentration ratio of **1c** to dimethyl isophthalate (DMIP) used as the internal standard. (b) The calibration line for **1c** obtained by plotting the peak area versus the known concentration of **1c**.

Table S1. Chromatographic profiles of the analytes containing **1c** and DMIP.

Crystal form	Temperature [°C]	Peak area of 1c [$\times 10^6$]	Peak area of DMIP [$\times 10^6$]	Area ratio (1c :DMIP)	Concentration of 1c [M]
α	15	2.995	8.114	0.369	6.1×10^{-5} ^a
	25	6.936	7.757	0.894	5.9×10^{-4} ^a
	37	92.90	6.998	13.3	8.2×10^{-3} ^b
	47	169.8	7.367	23.1	3.0×10^{-2} ^b
β	15	1.675	8.019	0.209	3.4×10^{-5} ^a
	25	1.573	8.141	0.193	1.3×10^{-4} ^a
	37	57.80	7.722	7.49	5.0×10^{-3} ^b
	47	116.0	6.076	19.1	2.0×10^{-2} ^b

^a Calculated from the calibration line on the left side. ^b Calculated from the calibration line on the right side.