Microscope and DSC Study of Polymorphism of 1,1′-(1,12-Dodecanediyl)bisthymine

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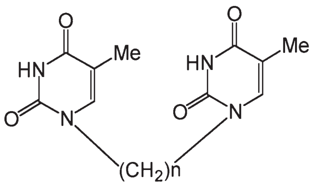
1,1′-(1,12-Dodecanediyl)bisthymine exhibited two distinct types of crystals. One of them was spontaneously transformed into the other under heat treatment. This phenomenon was monitored by DSC and observed under polarizing microscope.

Increasing interest is being shown in the role of hydrogen bond in relation to the development of the crystal engineering that aims at an intended molecular network formation in crystal.[1] Hydrogen bond also plays an important role in the structure formation of molecular assemblies in nature. It is well known that nucleobase forms the hydrogen-bonded assemblies.[2] A dissociation and recombination of the hydrogen bond is of interest in connection with not only the crystal engineering[1] but also a diversity of biological function. However, the detailed research has little been carried out about the dissociation and recombination of the hydrogen bond in solid phase. This paper describes a polymorphism of 1,1′-(1,12-dodecanediyl)bisthymine (**1**) that may be related to the dissociation and recombination of the hydrogen bond.



	n
1	12
2	10
3	5
4	3

A mixture of thymine and 1,12-dibromododecane in the presence of *t*-BuOK in DMF was stirred at room temperature for 15 h. The resulting mixture was evaporated to give a residue, which was submitted to chromatography over silica gel. Elution with ethyl acetate gave 1-(12-bromododecyl)thymine (21%).[3] Further elution with a mixture of ethyl acetate and methanol (9 : 1) afforded a solid mass, which was triturated with ethyl acetate to give the compound (**1**) (mp 148–150 °C) in 13% yield. When **1** was recrystallized from methanol, it precipitated as a crystal (**1a**), which melted at 188–189 °C. On the other hand, a solution of **1** in benzene was allowed to stand at room temperature to give a crystal (**1b**), which melted at 149–150 °C.[4] Even after the formation of different crystals, molecular structure of them was identical because the crystals **1a** and **1b** dissolved together in $CDCl_3$ showed exactly the same NMR chemical shifts. The different crystal formation was also supported by IR spectra of the crystals in KBr. The IR spectrum of **1a** showed two broad bands at 3170 and 3040 cm^{-1} in the range of 3000–3600 cm^{-1} and **1b** in KBr also displayed two broad bands at 3162 and 3032 cm^{-1}. In contrast, **1a** displayed two carbonyl bands at 1691 and 1666 cm^{-1}, while four carbonyl bands at 1709, 1689, 1662, and 1641 cm^{-1} were observed for **1b**.

To estimate the difference in energy for intermolecular interaction, differential scanning calorimeter (DSC) analyses of the crystals were performed.[5] Figure 1 shows the DSC thermogram of **1a** and **1b**. The crystal **1a** had a melting transition at 189 °C (ΔH 105 J/g) as shown in Figure 1-(A). On the other hand, Figure 1-(B) showed three endothermic transitions at 125 °C (ΔH 12 J/g), 150 °C (ΔH 56 J/g), and 189 °C (ΔH 52 J/g) upon the heating of the crystal **1b** at rate of 5 °C/min to 200 °C. Furthermore, a broad exothermic phase transition was found in 150–170 °C (ΔH −48 J/g). The values of ΔH at 189 °C were 42 J/g at rate of 10 °C/min and 28 J/g at rate of 15 °C/min, and therefore were dependent on the heating rate. A polarizing microscopy observation revealed that **1b** once melted at 150 °C, and then experienced a slow transformation into a new crystal (**1c**). When **1b** was heated to 175 °C (Figure 1-(C)) and then cooled to room temperature, the new crystal (**1c**) was isolated. Figure 2 shows the polarizing microscope picture at the formation of **1c** at 160 °C after the melting of **1b**. The crystal **1c** had a simple thermal behavior with only single melting transition temperature at 188 °C (ΔH 103 J/g) (Figure 1-(D)), and the IR spectrum of **1c** in KBr was essentially similar to that of **1a**. Thus it was concluded that the crystal **1c** was identical to **1a**. Furthermore, on the basis of the NMR spectra of **1a** and **1b** in $CDCl_3$, it was confirmed that these crystals did not include the solvents used for recrystallization. This suggests that the different behavior of **1a** and **1b** was not due to solvent inclusion in the crystal.

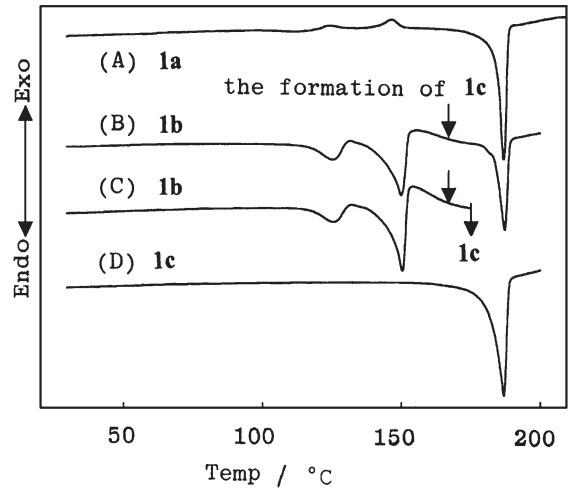


Figure 1. DSC thermogram of **1**, obtained upon heating at rate of 5 °C/min. (A) The crystal **1a** upon heating to 200 °C. (B) The crystal **1b** upon heating to 200 °C. (C) The crystal **1b** upon the heating to 175 °C, giving rise to the crystal **1c**. (D) The crystal **1c** upon heating to 200 °C.

In an effort to determine the effect of the polymethylene chains upon the thermal behaviors of bisthymines, the DSC measurements of **2** and **3**[6] were performed. The compounds **2** and

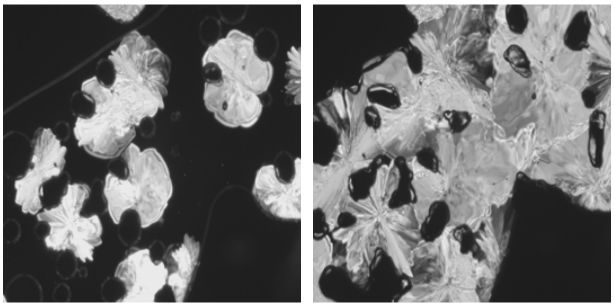
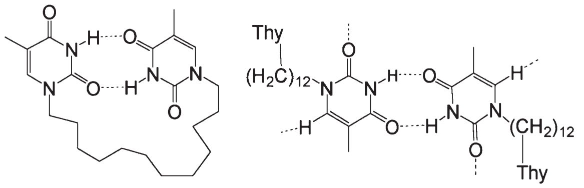

(A) (B)

Figure 2. Optical polarizing micrograph of the formation of the crystal **1c** at 160 °C after the melting of **1b**. (A) Beginning of the formation of **1c** at 2 min after the melting of **1b**. (B) Further growing of **1c** at 10 min after the melting of **1b**.

3 displayed almost single melting transitions at 182 °C (ΔH 109 J/g) and 251 °C (ΔH 110 J/g), respectively. These thermal behaviors were similar to that of the crystal **1a**. However, attempts to prepare crystals of **2** and **3** similar to the crystal **1b** were unsuccessful. The reason why only **1** can exhibit the crystal transformation was of our next interest, especially in the viewpoint that the formation of the crystal **1b** was possibly correlated with the length in the polymethylene chains.

The X-ray analysis of 1,1′-trimethylenebisthymine **(4)** has demonstrated the formation of an intramolecular stacking between the thymine rings and intermolecular hydrogen bonds.[7] A similar intermolecular hydrogen bond structure has been reported on the X-ray analysis of 1-methylthymine.[8] Furthermore, the X-ray analyses of 1-alkylthymines having long alkyl chains have made clear the molecular packing structures.[9] Therefore, it seems reasonable to assume that the crystals **1a** and/or **1b** can hold a certain intermolecular hydrogen bond structure, similar to those of **4**[7] and 1-alkylthymines.[8,9] On the other hand, Kuroda et al. have reported the formation of an intramolecular hydrogen bond structure of bisuridines connected together through long alkyl spacers in chloroform.[10] We also have reported a similar result showing the intramolecular hydrogen bond of 9-[12-(thymin-1-yl)dodecyl]adenine.[3] Taking these facts into consideration, the crystal **1a** or **1b** is reasonably expected to have intramolecular hydrogen bond structure.



Intramolecular hydrogen bond structure **Intermolecular hydrogen bond structure**[11]

In earlier papers[9,12] dealing with the thermal analyses of 1-alkylthymines having long alkyl chains, a pair of endo- and exothermic transitions similar to the thermal behavior of **1b** was found and was discussed from the standpoint of the molecular packing.[9] On the other hand, the thermal transformation of the crystals between **1a** and **1b** was not only monitored by DSC but also observed under polarizing microscope. The reports that described such melt and recrystallization of crystals in solid phase under heat treatment are little known.

The thermal transformation of the crystals from **1b** to **1a** may be explained in terms of the dissociation and recombination of the hydrogen bond in solid phase. Based on the difference in the melting point, we supposed that **1b** was a crystal in which most of thymine moiety formed intramolecular hydrogen bond. Intramolecular hydrogen bond is expected to dissociate at lower temperature than the intermolecular hydrogen bond because of less favorable bond length and/or bondangles.[3,10] After the dissociation of the intramolecular hydrogen bond, the intermolecular hydrogen bond might have formed at temperatures raging from 150 °C to 170 °C where we observed the broad endothermic transition. These speculations will be supported by further investigation that is now in progress.

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References and Notes

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4 The crystal **1b**: ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 2H, NH), 6.97 (s, 2H, Thy-6), 3.69 (t, 4H, $J = 7.2$ Hz), 1.92 (s, 6H, Me), 1.67 (broad quintet, 4H, $J = 7$ Hz), 1.35–1.2 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 164.20, 150.86, 140.38, 110.56, 48.46, 29.34, 29.33, 29.07, 29.06, 26.33, 12.35. HRFABMS *m/z* Calcd for $C_{22}H_{34}N_4O_4$ (M+1) 419.2658, found 419.2657. Found: C, 63.39; H, 8.29; N, 13.21%. Calcd for $C_{22}H_{34}N_4O_4$: C, 63.13; H, 8.19; N, 13.39%.

5 DSC measurements were carried out with a Shimadzu DSC-60. Polarizing microscopy observations were performed under a Nikon Eclipse E600 POL equipped with a hot stage (Tokai Hit ThermoPlate).

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11 The hydrogen bond between the carbonyl group at 2-position and the hydrogen atom at 6-position is shown on the X-ray analyses of **4** and 1-methylthymine.[7,8]

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