Crystal Structure of Long Alkyl 3-(Thymin-1-yl)propionates: Style of Hydrogen Bonding and Dependence on the Alkyl Chain Length

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Crystal structures of the ester derivatives of thymine having long alkyl chains are described. The crystal structure of the thymine derivative was found to be affected particularly by the carbon number of the alkyl chain. The thymine derivatives having even-numbered alkyl chains formed unusual hydrogen bonds between N3–H and O2 of the thymine base. The interactions between the methyl group and the oxygen were found to play an important role in the crystal structure. The thymine base of the even-numbered alkyl derivatives was surrounded by neighboring molecules with the interactions between the methyl group and the oxygen. Therefore, usual hydrogen bonds between N3–H and O4 were inhibited by steric effects from forming the hydrogen bonds between N3–H and O2.

Thymine in DNA is known to form Watson–Crick type hydrogen bonding with adenine.[1] Hydrogen bonding between nucleic acid bases has been studied for single crystals of nucleic acid base derivatives. The first crystal structure of thymine-adenine pair was reported by Hoogsteen for 1-methylthymine•9-ethyladenine.[2] In this structure, N3–H and O4 of thymine were used for the hydrogen bonding with N7 and NH_2 of adenine. In most crystals for thymine and uracil derivatives, N3–H and O4 are used for hydrogen bonding with adenine derivatives. Adenine-uracil base pair using uracil O2 instead of O4 has been reported in the complex of adenosine•5-bromouridine,[3] as well as in the complex of 9-ethyladenine•5-bromo-1-methyluracil.[4] These hydrogen bonds between N3–H and O2 were formed because the inductive effect of the electronegative bromine atom through the pyrimidine ring tended to make uracil atom O2 more electronegative than uracil atom O4.

Two types of hydrogen bonding are possible for the self-pairing of the thymine bases, as shown in Fig. 1. In type A, the hydrogen bonds are formed between N3–H and O4, which is the same as Watson–Crick type hydrogen bonding in DNA. Type A was reported in the crystals of 1-methylthymine,[5] 1-octylthymines[6,7,8,9] carbamate derivatives of thymine,[10] and others.[11] Type B is the reversed Watson–Crick type hydrogen bonding between N3–H and O2, which was reported for the complexes of 5-bromouridine or 5-bromouracil[3] with adenine derivative. The hydrogen bonding of type B was also reported for thymine monohydrate crystal containing a water molecule that took part in hydrogen bonding.[12] In this structure, O4 was hydrogen-bonded to the water molecule, thus preventing the formation of the hydrogen bonding between N3–H and O4. The same hydrogen bonding between N3–H and O2 of thymines was reported for 1-(2-hydroxyethyl)uracil[13] and 1-{2-[2-(4-hydroxyphenyl) ethylthio]ethyl} thymine.[14] Both compounds contain hydroxy groups that form hydrogen bonds with O4 of the thymine base to prevent the formation of hydrogen bond between thymines using O4.

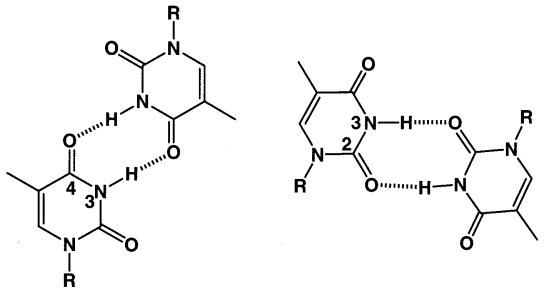
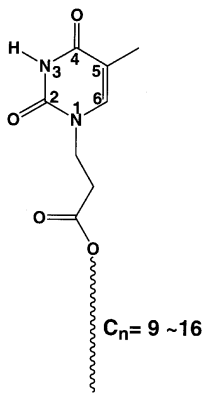


Fig. 1. Two types of hydrogen bonding between the 1-alkylthymines.

Crystal structures of 1-alkylthymines were found to be dependent on the length of alkyl chains and on the solvents used for crystallization. Four kinds of crystal forms were obtained for 1-octylthymines from various solvents, and were found to be closely correlated to photodimerization of thymine base in crystal state. The crystals from ethyl acetate[6] and from acetonitrile[7] gave the photodimers of thymine bases, but the crystals from ethanol[8] and from *N*, *N*-dimethylformamide[9] did not give the photodimer. However, style of hydrogen bonding of these crystals was Type A in Fig. 1.

Ester derivatives of thymine having long alkyl chains (Scheme 1) gave plates for the even-numbered alkyl chains,



Ester Derivatives of Thymine

Scheme 1.

and needles for the odd-numbered alkyl chains. In the case of the decyl derivative, two single crystals were obtained from benzene and ethanol solutions. The reversible photodimerizations of the ester derivatives of thymine having long alkyl chains underwent in solution and in thin solid film,[15] but did not occur in the single crystals. The study of the crystal structure for the ester derivatives of thymine gave new findings of unique crystal structures depending on the carbon numbers of the alkyl chain. Unusual hydrogen bonding of Type B was found between N3–H and O2 of thymine bases for the compounds having even-numbered alkyl chains. This paper deals with crystal structures of the thymine compounds having long alkyl chains linked by ester bonds, where the carbon number (C*n*) is 9 to 16 (Scheme 1). Unusual hydrogen bonds between N3–H and O2 of thymine bases for the thymine compound having even-numbered alkyl chain will be discussed with the conformation of the molecules and the interactions of the molecules in crystal.

Experimental

Preparations of Alkyl 3-(Thymin-1-yl)propionates. Ester derivatives of thymine were prepared by a condensation reaction using dicyclohexylcarbodiimide (DCC). To a pyridine solution (20 ml) of 1-(2-carboxyethyl)thymine (1.5 g, 7.5 mmol)[16,17] and *n*-alkyl alcohol (C_9–C_{16}) (10 mmol), DCC (1.5 g, 7.5 mmol) was added at 0 °C. The solution was stirred for 2 h at 0 °C, and for 2 days at room temperature. The precipitated 1, 3-dicyclohexylurea was removed by filtration. After evaporation of the solvent, the residue was washed twice with ethyl ether and recrystallized from benzene to give the products almost quantitatively. Recrystallization from benzene or ethanol was repeated to give the pure product.

Nonyl 3-(Thymin-1-yl)propionate (ES9). Anal. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.64%. Found: C, 63.18; H, 8.66; N, 8.56%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.75 (1H, s, NH), 7.20 (1H, s, C6–H), 3.88 (2H, t, N–CH_2), 3.98 (2H, t, CO–O–CH_2), 2.74 (2H, t, O–CO–CH_2), 1.81 (3H, s, C5–CH_3), 1.90 (2H, m, COO–C–CH_2), 1.25 (12H, m, CH_2), 0.88 (3H, t, C–CH_3).

Decyl 3-(Thymin-1-yl)propionate (ES10, ES10-2). Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.93; N, 8.28%. Found: C, 63.70; H, 8.83; N, 8.56%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.05 (1H, s, NH), 7.10 (1H, s, C6–H), 4.05 (2H, t, N–CH_2), 4.25 (2H, t, CO–O–CH_2), 3.24 (2H, t, O–CO–CH_2), 2.04 (3H, s, C5-CH_3), 1.80 (2H, m, COO-C-CH_2), 1.40 (14H, m, CH_2), 0.88 (3H, t, C–CH_3).

Undecyl 3-(Thymin-1-yl)propionate (ES11). Anal. Calcd for $C_{19}H_{32}N_2O_4$: C, 64.74; H, 9.15; N, 7.95%. Found: C, 65.00; H, 9.18; N, 7.90%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.70 (1H, s, NH), 7.20 (1H, s, C6–H), 4.05 (2H, t, N–CH_2), 4.25 (2H, t, CO–O–CH_2), 2.78 (2H, t, O–CO–CH_2), 1.96 (3H, s, C5–CH_3), 1.60 (2H, m, COO–C–CH_2), 1.40 (16H, m, CH_2), 0.88 (3H, t, C–CH_3).

Dodecyl 3-(Thymin-1-yl)propionate (ES12). Anal. Calcd for $C_{20}H_{34}N_2O_4$: C, 65.54; H, 9.35; N, 7.64%. Found: C, 65.50; H, 9.41; N, 7.91%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.15 (1H, s, NH), 7.20 (1H, s, C6–H), 3.95 (2H, t, N–CH_2), 4.15 (2H, t, CO–O–CH_2), 2.84 (2H, t, O–CO–CH_2), 2.04 (3H, s, C5–CH_3), 2.40 (2H, m, COO–C–CH_2), 1.40 (18H, m, CH_2), 0.88 (3H, t, C–CH_3).

Tridecyl 3-(Thymin-1-yl)propionate (ES13). Anal. Calcd for $C_{21}H_{36}N_2O_4$: C, 66.28; H, 9.54; N, 7.36%. Found: C, 66.27; H, 9.49; N, 7.37%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.50 (1H, s, NH), 7.11 (1H, s, C6–H), 4.15 (2H, t, N–CH_2), 4.35 (2H, t, CO–O–CH_2), 3.33 (2H, t, O–CO–CH_2), 2.04 (3H, s, C5–CH_3), 2.40 (2H, m, COO–C–CH_2), 1.40 (20H, m, CH_2), 0.95 (3H, t, C–CH_3).

Tetradecyl 3-(Thymin-1-yl)propionate (ES14). Anal. Calcd for $C_{22}H_{38}N_2O_4$: C, 66.97; H, 9.71; N, 7.10%. Found: C, 66.86; H, 9.18; N, 7.21%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.75 (1H, s, NH), 7.24 (1H, s, C6–H), 4.01 (2H, t, N–CH_2), 4.12 (2H, t, CO–O–CH_2), 2.75 (2H, t, O–CO–CH_2), 1.96 (3H, s, C5–CH_3), 2.40(2H, m, COO–C–CH_2), 1.33 (22H, m, CH_2), 0.88 (3H, t, C–CH_3).

Pentadecyl 3-(Thymin-1-yl)propionate (ES15). Anal. Calcd for $C_{23}H_{40}N_2O_4$: C, 67.61; H, 9.87; N, 6.86%. Found: C, 67.47; H, 9.89; N, 7.17%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.05 (1H, s, NH), 7.36 (1H, s, C6–H), 4.01 (2H, t, N–CH_2), 4.22 (2H, t, CO–O–CH_2), 2.75 (2H, t, O–CO–CH_2), 1.87 (3H, s, C5–CH_3), 2.40 (2H, m, COO–C–CH_2), 1.35 (24H, m, CH_2), 1.30 (3H, t, C–CH_3).

Hexadecyl 3-(Thymin-1-yl)propionate (ES16). Anal. Calcd for $C_{24}H_{42}N_2O_4$: C, 68.21; H, 10.02; N, 6.63%. Found: C, 68.41; H, 10.14; N, 6.58%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.75 (1H, s, NH), 7.44 (1H, s, C6–H), 4.01 (2H, t, N–CH_2), 4.22 (2H, t, CO–O–CH_2), 2.85 (2H, t, O–CO–CH_2), 1.92 (3H, s, C5–CH_3), 2.40 (2H, m, COO–C–CH_2), 1.35 (24H, m, CH_2), 1.30 (3H, t, C–CH_3)

Instruments. ^{1}H-NMR Spectra were recorded with a JEOL GSX270. A Seiko I&E DSC6200 series performed differential scanning calorimetric (DSC) measurements. The IR spectra of the crystals were measured for KBr pellets on a JASCO IR-810. X-ray powder diffraction patterns were measured by a Rigaku X-ray diffractometer RINT 2000 with Cu-$K\alpha$ radiation.

Crystal Structure Analysis. Data of X-ray diffraction for alkyl 3-(thymin-1-yl)propionates were collected by a Rigaku RAXIS-CS imaging plate two-dimensional area detector using graphite-monochromatized Mo-$K\alpha$ radiation (λ = 0.71070 Å). All the crystallographic calculations were performed by using TEXSAN software package of the Molecular Structure Corporation. The crystal structures were solved by the direct methods (shelxs97) and refined by the full-matrix least squares. The positions of hydrogen atoms attached to nitrogen atoms were obtained

from the difference Fourier syntheses. All non-hydrogen atoms and hydrogen atoms were refined anisotropically and isotropically, respectively. The crystal data of six thymine derivatives are shown in Table 1.

Results and Discussion

Crystal Structure of Alkyl 3-(Thymin-1-yl)propionate Crystallized from Benzene. Plates of decyl (**ES10**) and dodecyl (**ES12**) 3-(thymin-1-yl)-propionates, and needles of nonyl (**ES9**), undecyl (**ES11**), and tridecyl (**ES13**) 3-(thymin-1-yl)propionates were obtained from benzene solution. Figure 2a shows the molecular packing of **ES10**. The crystal structure of **ES10** was the same as the structure of another ester derivative having even-numbered alkyl chain (**ES12**), except for the length of the *b* axis. Figure 2b shows the molecular packing of **ES11**, which was the same as the structures of the compounds having odd-numbered alkyl chains (**ES9**, **ES11**, and **ES13**) except for the length of the *b* axis. These structures show bilayer structures of the polar thymine bases and the nonpolar alkyl chains. For both structures, thymine bases were connected with the hydrogen bonding.

The values of the axis in Table 1 are plotted against the carbon number of the alkyl chain in Fig. 3. The lengths of *a* axis for even-numbered alkyl chains are shorter than the values for odd-numbered alkyl chains. On the other hands, the lengths of *c* axis for even-numbered alkyl chains are longer than the values for odd-numbered alkyl chains. In the case of the *b* axis, however, the lengths increased with increase of the carbon number. The absorption bands assigned to C=O stretching vibration of thymine bases in IR spectra were found to depend on the carbon number of the alkyl chain. The ratios in IR spectra, 1660 cm^{-1}/1680 cm^{-1}, of the crystals having even-numbered alkyl chains were higher than those of the compounds with odd-numbered alkyl chains (Fig. 3). The dependence on the carbon number of the alkyl chain observed in the IR spectra should be caused by the style of hydrogen bonds between thymines, because 1660 cm^{-1} was assigned to C4=O, and 1680 cm^{-1} was assigned to C2=O stretching vibrations.[18]

The difference of the crystal structure between **ES10** and **ES11** may be due to intermolecular interactions in crystals. Figure 4 shows three neighboring molecules in crystal for **ES10** and **ES11**. In **ES10**, the alkyl chains were symmetrically arranged, and the distances between the chains were 4.18 Å and 5.52 Å. The distance between the terminal methyl group of the alkyl chain (molecule **2**) and the 5-methyl of thymine in another molecule (molecule **1**) was short (3.81 Å), suggesting significant van der Waals force between these two methyl groups. When the carbon number was even, the terminal meth-

Table 1. Crystal Data of Ester Derivatives of Thymine

Compound	**ES 9**	**ES10**	**ES10-2**	**ES11**	**ES12**	**ES13**
Solvent	benzene	benzene	ethanol	benzene	benzene	benzene
Crysstal dimension	0.4×0.3×0.1	0.7×0.3×0.1	0.7×0.05×0.05	0.5×0.08×0.08	0.5×0.3×0.05	0.8×0.1×0.02
Formula	$C_{17}H_{28}N_2O_4$	$C_{18}H_{30}N_2O_4$	$C_{18}H_{30}N_2O_4$	$C_{19}H_{32}N_2O_4$	$C_{20}H_{34}N_2O_4$	$C_{21}H_{36}N_2O_4$
Fw	324.42	338.45	338.45	352.47	366.50	380.53
Crystal shape	needle	plate	needle	needle	plate	needle
Crystal system	triclinic	triclinic	triclinic	triclinic	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a/Å	9.695(5)	7.828(5)	19.122(3)	9.711(3)	7.806(3)	9.71(3)
b/Å	19.65(4)	20.59(1)	21.59(2)	21.66(1)	22.79(2)	23.83(4)
c/Å	4.818(2)	6.189(2)	4.679(5)	4.829(1)	6.213(5)	4.87(3)
α/°	91.92(8)	91.44(4)	90.84(5)	91.97(3)	92.47(3)	93.9(3)
β/°	101.83(4)	97.00(5)	92.9(1)	101.73(2)	96.92(4)	102.1(4)
γ/°	86.32(8)	83.98(6)	96.17(9)	94.49(3)	85.32(5)	96.3(2)
V/$Å^3$	896(1)	984.7(9)	1917(3)	990.4(6)	1092(1)	1092(7)
Z	2	2	4	2	2	2
D_{calc}/g cm^{-3}	1.2	1.14	1.17	1.18	1.11	1.16
F(000)	352.0	368.0	736.0	384.0	400.0	416.0
μ/cm^{-1}	0.85	0.80	0.82	0.82	0.77	0.79
No. of reflns measd	1553	2323	2377	3040	2097	3716
No. of reflns used ($I > 3.00\ \sigma(I)$)	1500	2301	2352	3017	2072	3637
No. of parameters	320	338	673	354	372	389
R[a)]	0.115	0.075	0.097	0.079	0.079	0.105
R_W[b)]	0.093	0.095	0.097	0.084	0.097	0.100
GOF	2.60	2.44	6.28	2.58	5.68	
Max/min peaks in final difference map/*e* $Å^{-3}$	0.34, −0.40	0.29, −0.23	0.36, −0.46	0.53, −0.36	0.28, −0.28	
Temp/°C	−50	room	room	−50	−50	room

a) $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. b) $R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)]^{1/2}$.

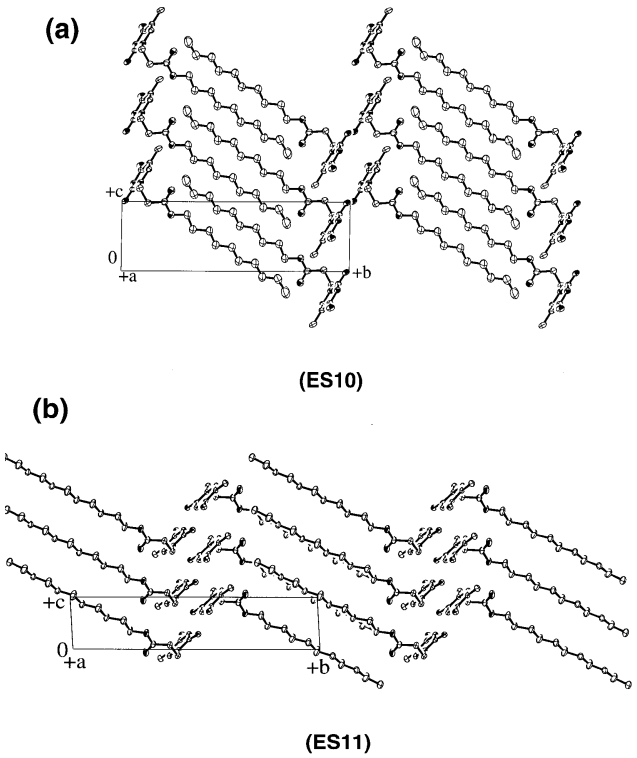


Fig. 2. Crystal structures of Alkyl 3-(thymin-1-yl)propionates viewed along *a* axis. (a) decyl 3-(thymin-1-yl)propionate (**ES10**), and (b) undecyl 3-(thymin-1-yl)propionate (**ES11**).

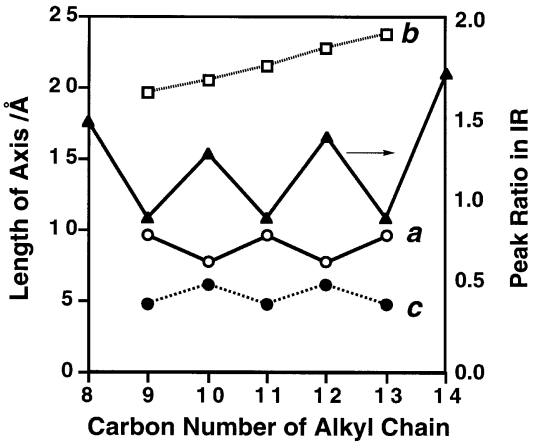


Fig. 3. Length of axis in Table 1 and ratios of IR spectra against carbon number of the alkyl chain. Peak ratios of IR spectra (1660 cm^{-1}/1680 cm^{-1}) (KBr pellet of crystals).

yl group was directed outside, and interacted with 5-methyl of thymine base. The distance between the 5-methyl of the thymine (molecule **1**) and the ether oxygen of the third molecules (molecule **3**) was also short (3.89 Å). Therefore, the moving of the thymine group was strictly inhibited by the interactions of the 5-methyl group with the ether oxygen and the terminal methyl group.

In the case of the crystals having odd-numbered alkyl chains

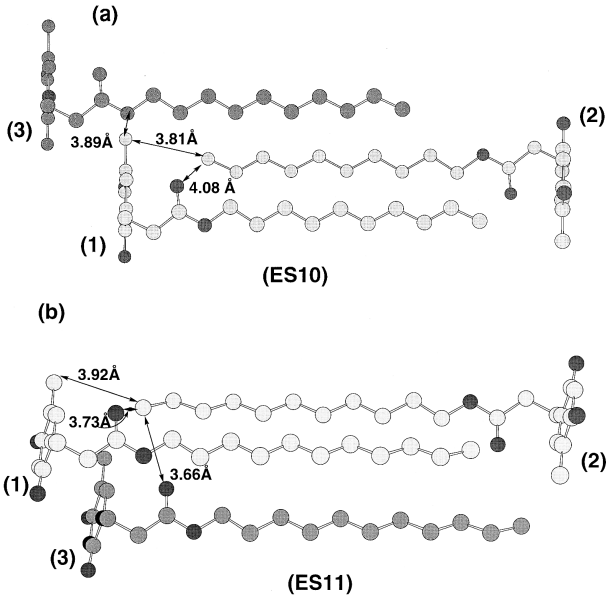


Fig. 4. The packing of neighboring three molecules for (a) **ES10** and (b) **ES11**.

(**ES11**) (Fig. 4b), two alkyl chains were parallel with the distances of 4.12 Å and 5.62 Å. The nearest atoms of the terminal methyl group of the alkyl chain (molecule **2**) were the carbonyl oxygens in molecule **1** (3.73 Å) and in molecule **3** (3.66 Å). The distance between the terminal methyl group of molecule **2** and the 5-methyl of the thymine for molecule **1** (3.92 Å) was slightly longer than that of **ES10**.

The style of hydrogen bonding between thymines for the ester derivatives of the even-numbered alkyl chains (**ES10**, and **ES12**) was different from the style for the compound with the odd-numbered alkyl chains (**ES9**, **ES11**, and **ES13**). Figure 5 shows the hydrogen bonding pairs of the ester derivatives of thymine for **ES10** and **ES11**. In the crystals of **ES11** (Fig. 5b) and of the odd-numbered alkyl chain derivatives, the hydrogen bonding was formed between N3–H and O4, which was the usual hydrogen bonding observed in DNA (type A in Fig. 1). On the contrary, the hydrogen bonding for **ES10** and **ES12** was formed between N3–H and O2 (Fig. 5a) which was type B in Fig. 1. The lengths of the hydrogen bond, however, were 2.8 Å for both crystals. Watson–Crick type hydrogen bonding of thymine base (type A) is more stable than reversed Watson–Crick type hydrogen bonding (type B), because the basicity of O4 is higher than the basicity of O2[19] and the first protonation occurs at O4 of uracil.[20] The hydrogen bonding at O4 in preference to O2 was also shown for thymine monohydrate crystals[12] and 1-(2-hydroxyethyl)uracil[13] where water or the hydroxy group formed the hydrogen bonds with O4 instead of O2. The unstable hydrogen bonds in **ES10** may be formed by blocking of O4 by steric hindrance , because no hydroxy group is contained in **ES10**.

The conformations of the molecules in crystal were studied for **ES10** and **ES11**. As shown in Fig. 5a for **ES10**, the alkyl chain was perpendicular to the face of thymine ring (93°) and the face of the alkyl chain was directed to N1 of the thymine

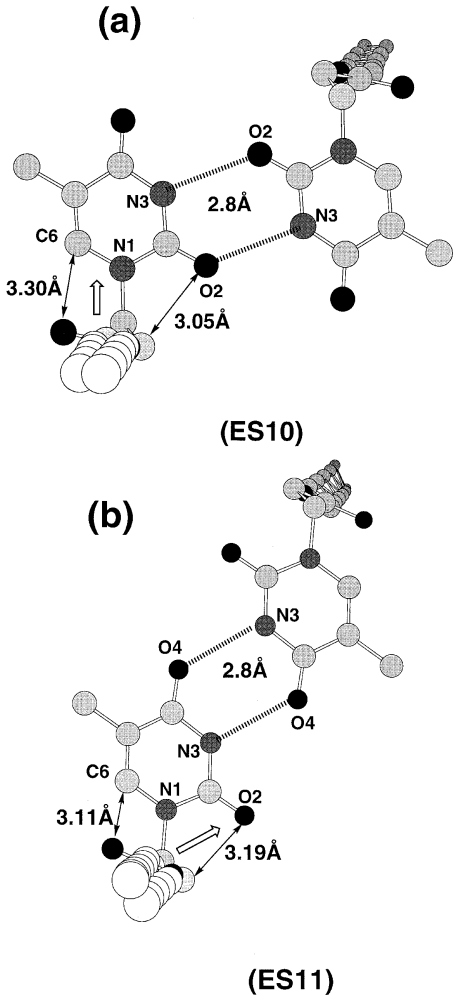


Fig. 5. Hydrogen bonding pairs for (a) **ES10** and (b) **ES11**.

base. The carbonyl oxygen of the ester was located near C6 of thymine base at the distance of 3.30 Å. On the other hand, the carbonyl oxygen of thymine (O2) was located near the α-methylene of the ester group (3.05 Å). For the ester derivatives having odd-numbered alkyl chains (**ES9**, **ES11**, and **ES13**), on the other hand, the alkyl chain was twisted and faced to O2 of thymine ring, and was inclined 100° from the face of thymine base (Fig. 5b). In Fig. 5b, the carbonyl oxygen of the ester was located near C6 of thymine (3.11 Å), and the carbonyl oxygen of thymine (O2) was located near the α-methylene of the ester group (3.19 Å). The reason for the verticality of the alkyl chain from the thymine ring may be the interaction between the ester group and the thymine base.

Stacking of the nucleic acid bases is one more important interaction in the structure of DNA. Stacking interactions of the thymine bases in crystals are shown for **ES10** and **ES11** in Fig. 6. Both **ES10** (Fig. 6a) and **ES11** (Fig. 6b) had the same style of stacking interactions of *anti* conformation, where bonds of O4–C4–N3–C2 overlapped each other in antiparallel orientation with 3.2 Å spacing, while the style of hydrogen bonding was different for these crystals. Type B hydrogen bonding in **ES10** may be stabilized by the stacking interaction of the

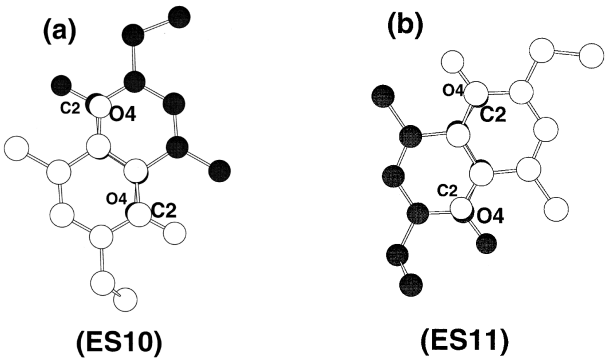


Fig. 6. Stacking of thymine bases in (a) **ES10** and (b) **ES11**.

thymine bases.

The thymine bases of **ES10** could not form the stable hydrogen bonds of type A, and formed unstable hydrogen bonds of type B. The reason may be blocking of O4 of the thymine base by steric hindrance. Figure 7 shows the backside view of Fig. 4a for **ES10**. Around the 5-methyl of thymine (molecule **1**), the ether oxygen (3.89 Å) and the O2 (3.73 Å) of molecule **3**, and the terminal methyl group (3.81 Å) of close-neighboring molecules **2** are closely located. In addition, the α-methylene of the ester group (molecule **4**) is located near the O4 (3.42 Å) of molecule **1**. In this molecular arrangement for **ES10**, the only possible hydrogen bonds of thymine bases are between N3–H and O2 (type B), because the hydrogen bonds between N3–H and O4 (type A) is inhibited by steric hindrance.

Crystal Structure of Decyl 3-(Thymin-1-yl)-propionate Crystallized from Ethanol. From ethanol solution, needles of decyl 3-(thymin-1-yl)propionate (**ES10-2**) were obtained. Powder X-ray diffraction and DSC of the decyl derivative indicated that **ES10-2** was the polymorphic crystal of **ES10** from benzene solution. DSC of the plates (**ES10**) showed one endothermic peak at 89.4 °C, but two endothermic peaks at 80.4 °C

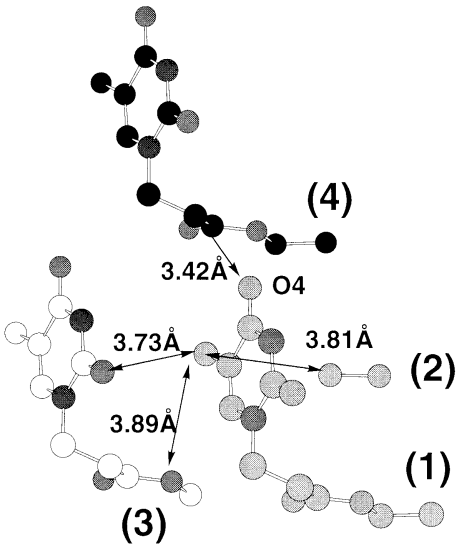


Fig. 7. Packing of molecules around the thymine base in **ES10**.

and 89.3 °C, and one exothermic peak at 82.1 °C were observed for **ES10-2**. The DSC data indicated that the unstable crystal of **ES10-2** melt at 80.4 °C, and transformed to the stable crystal having a melting point of 89.3 °C. The stable crystal should be the crystal **ES10** that had almost the same melting point of 89.4 °C. Powder X-ray diffraction of the crystals (Fig. 8) supported the transformation of the crystal form from **ES10-2** to **ES10**. Annealing of **ES10-2** (**a** in Fig. 8) at 85 °C for 10 min gave the pattern **b** which was almost the same as the peaks of **ES10** (**c** in Fig. 8). The investigation of the crystal structure for the unstable **ES10-2** may give useful information for stable **ES10** having unusual hydrogen bonds.

The crystal structure of **ES10-2** is shown in Fig. 9, where both the interaction of the alkyl chain and the hydrogen bonding of the thymines are different from the plates (**ES10**, Fig. 2a). Though the structure of **ES10-2** was a bilayer structure of alkyl chains and thymine bases, the association of the alkyl chain was not uniform as viewed along the *a* axis (Fig. 9a). The alkyl chains arranged in zigzag and not parallel orientation. The arrangement of alkyl chains in **ES10-2** suggests a weak interaction between the alkyl chains that makes the crystal unstable. The crystal structure of **ES10-2** consists of two independent molecules forming a racemic pair. Figure 10 shows two kinds of conformations (**I** and **II**) in crystal. The hydrogen bonds of the thymine bases in this crystal were formed between O4 and N3–H (type A in Fig. 1); that is the same as the case of derivatives with odd-numbered alkyl chain (Fig. 5b). Transformation of **ES10-2** to **ES10** observed by DSC and Powder X-ray diffraction means the change of hydrogen bonding style from type A to type B.

One base pair **I** (Fig. 10a) shows similar conformation to **ES11** (Fig. 5b), where the alkyl chain is perpendicular to the thymine ring. The alkyl chains of the other base pair **II** (Fig. 10b), however, were in extended conformation. In Fig. 11, the angles of the alkyl chains from the thymine ring for three base pairs (**ES10**, **ES10-2I**, and **ES 10-2II**) are compared by picking up from Fig. 5a, 10a, and 10b. The highest angle was **ES10-2II** (138°), and the lowest angle was **ES10** (93°). However, the angles of the 2-carboxyethyl group from thymine were similar for three pairs because of the interactions between the carbonyl group of the ester and C6 of thymine base, and between the carbonyl group of C2 of thymine base and the α-methylene of the ester group (Fig. 5). A higher angle of the alkyl chains from the thymine ring for **ES10-2** should result in loose interaction of the molecules to form stable hydrogen bonds of type A.

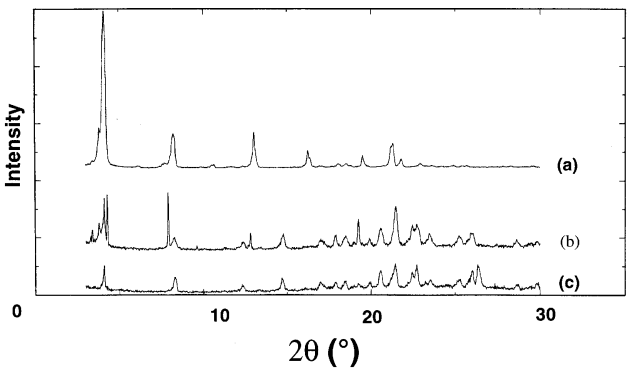


Fig. 8. Powder X-ray diffractions. (a) **ES10-2**, (b) after annealing of **ES10-2** at 85 °C for 10 min, and (c) **ES10**.

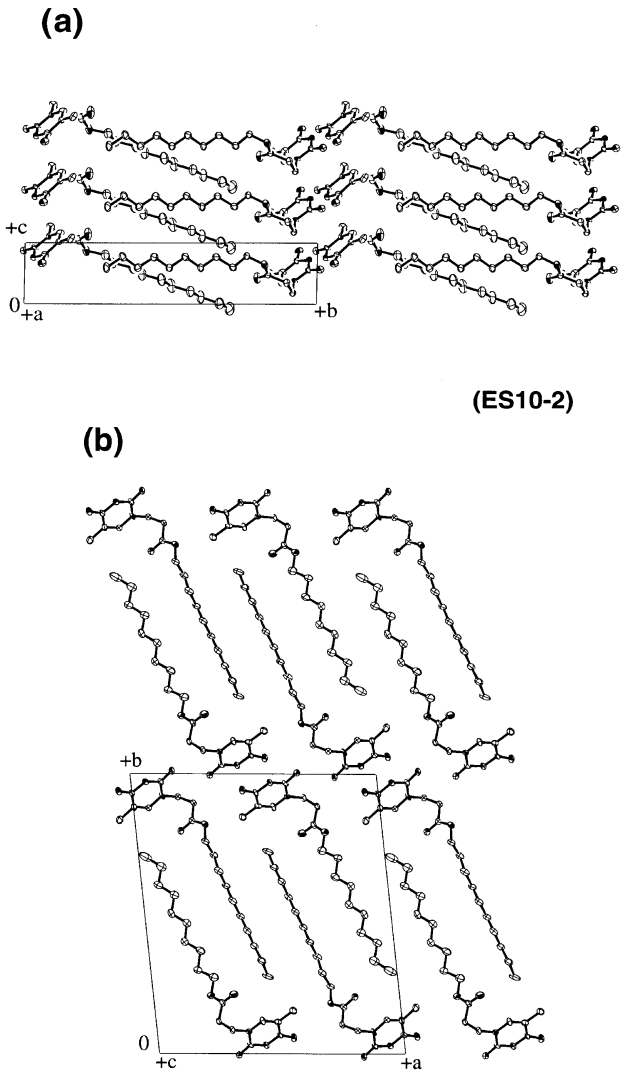


Fig. 9. Crystal structure of needles of decyl 3-(thymin-1-yl)-propionate (**ES10-2**) viewed along (a) *a* and (b) *c* axis.

Loose interaction of the alkyl chain is shown in Fig. 12 for two neighboring molecules of **ES10-2**. Two alkyl chains (**I** and **II**) were not parallel but crossing, suggesting no interaction between these the alkyl chains. The nearest atom of the terminal methyl group of the alkyl chain (**II**) was the carbonyl oxygen of the ester group in another molecule **I** (3.85 Å). The distance between the methyl group of the thymine and the terminal methyl group of the alkyl chain in **ES10-2** was 4.02 Å, which was longer than the value of **ES10** (3.81 Å). Therefore, the main interaction between **I** and **II** is the interaction between the terminal methyl group of the alkyl chain and the carbonyl oxygen of the ester group. The interaction of the methyl group with the carbonyl oxygen may be the important interaction that was also found in **ES11** (Fig. 4b). The instability of the crystal **ES10-2**

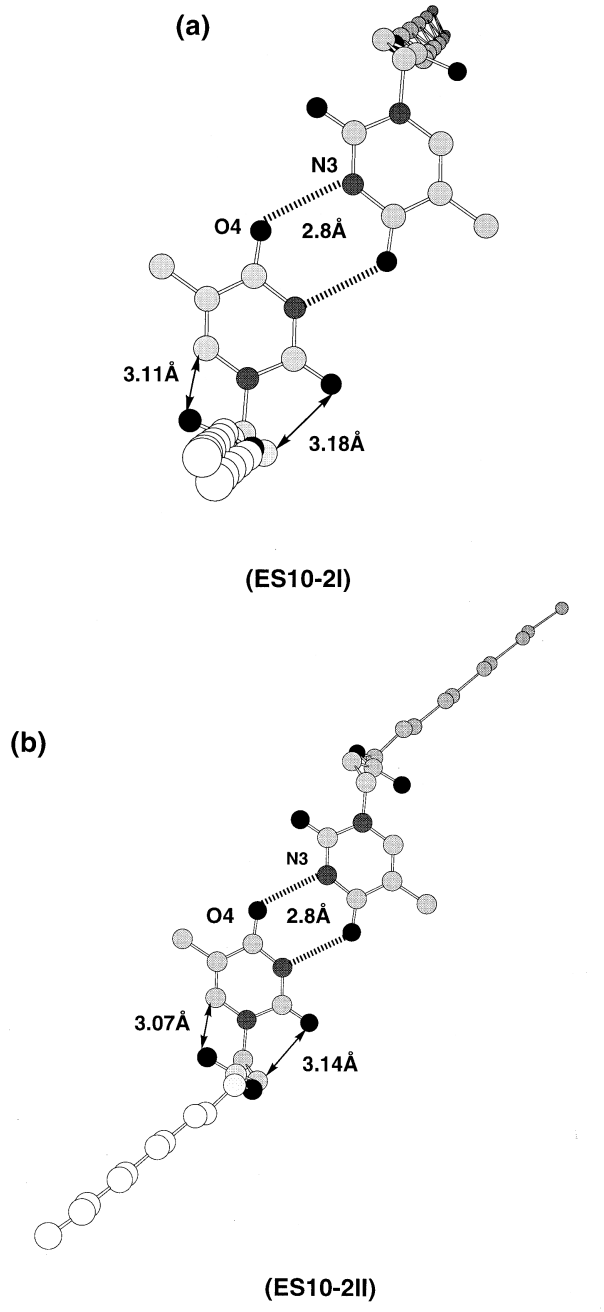


Fig. 10. Hydrogen bonding pairs for **ES10-2**. (a) **ES10-2I**, and (b) **ES10-2II**.

suggested by the DSC data should be caused by a weak interaction of alkyl chains, because the distance of the hydrogen bonds between thymine bases (2.8 Å, Fig. 10) was the same as the distance for **ES10** (Fig. 5), and the stacking interaction of the thymine bases of **ES10-2** was similar to the stacking in **ES10** (Fig. 6). Then, the unstable alkyl chains of **ES10-2I** and **II** melt at 80.4 °C, and the angle of the alkyl chain from thymine ring become 93° from 138° (Fig. 11) to give the stable conformation of **ES10** which melts at 89.3 °C. The transformation of the hydrogen bonding from type A to type B should occur during melting of the alkyl chains.

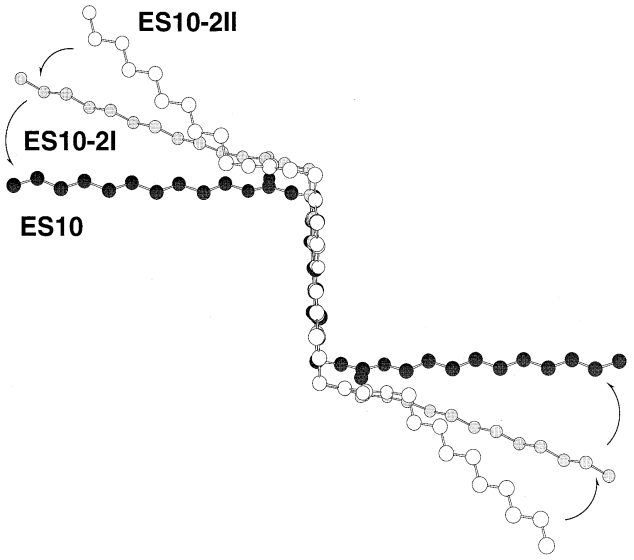


Fig. 11. Three kinds of base pairs for **ES10**, **ES10-2I**, and **ES10-2II**.

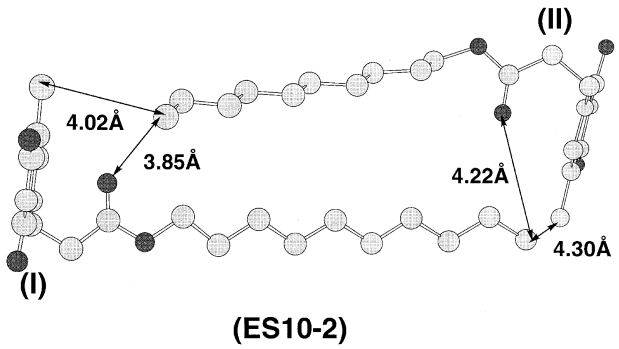


Fig. 12. The packing of two molecules (**I** and **II**) for **ES10-2**.

Conclusion

Crystal structures of the ester derivative of thymine were found to be affected particularly by the carbon number of the alkyl chains. For the derivatives having even-numbered alkyl chains, unusual hydrogen bondings between N3–H and O2 (type B) were observed. However, usual hydrogen bondings between N3–H and O4 (type A) of the thymine bases were observed for the derivatives having odd-numbered alkyl chains and the polymorphic crystal of the decyl derivative (**ES10-2**). The interaction of the methyl group with oxygen was found to play an important role in the crystal structure of the thymine compounds. For the derivatives of the odd-numbered alkyl chains and the unstable polymorhlic crystal of the decyl derivative, the terminal methyl group of the alkyl chain interacted with the carbonyl oxygen of the ester group. Then, the thymine base was relatively free to form the stable hydrogen bonds between N3–H and O4 (type A). On the other hand, for the derivatives of the even-numbered alkyl chains, the terminal methyl group interacted only weakly with the carbonyl oxygen of the ester group because the methyl group was directed outside. In

this case, the 5-methyl group of thymine bases interacted with O2 and the carbonyl oxygen of the neighboring molecules. This arrangement of molecules results in the blocking of O4 of thymine base to form unstable hydrogen bonds between N3–H and O2 (type B).

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