NMR and UV Study of 1,1′-(α,ω-Alkanediyl)bis[thymine] and 1,1′-(α,ω-Alkanediyl)bis[uracil]

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Treatment of thymine or uracil with $Br(CH_2)_nBr$ ($n=3$—10) in the presence of *t*-BuOK gave 1,1′-(α,ω-alkanediyl)bis[thymine] or 1,1′-(α,ω-alkanediyl)bis[uracil] together with 1-(ω-bromoalkyl)thymine or 1-(ω-bromoalkyl)uracil. The structures of these products were determined on the basis of the coupling constants between 5- and 3-positions of uracil ring on the ^{1}H NMR spectra. Molecular aggregation of the thymine and uracil rings of these compounds in aqueous solution was studied on the basis of their ^{1}H NMR and UV spectra. A stacking interaction of the two thymine rings linked by shorter polymethylene chains such as trimethylene and tetramenthylene groups was observed.

Nucleic acid bases are stacked one above the other in nucleic acids, but the mechanism of the stacking interaction is still obscure.[1] While the effect of methyl groups on stacking interaction has been noted, the great majority of work has dealt with the effect on stacking of purine bases.[1,2] Little attention has been paid to the effect of methyl groups on stacking of pyrimidine bases, although Leonard et al.[3] compared the hypochromism values of 1,1′-trimethylenebis[thymine] (**1a**) with that of 1,1′-trimethylenebis[uracil] (**3a**), because the stacking interaction between pyrimidine bases is considerably smaller than that between purine bases.[1] However, it may be of importance to compare stacking interaction of thymine with that of uracil in detail in order to elucidate the effect of methyl groups on stacking of pyrimidine bases. The present investigation was undertaken to see if there could be a difference between the stacking interaction of thymine and that of uracil.

^{1}H NMR spectroscopy has been used in order to study the conformational analysis of oligonucleotides. ^{1}H NMR spectra of dinucleotides such as uridilyl-(3′,5′)uridine (UpU) and 2′-deoxythymidilyl-(3′,5′)-2′-deoxythymidine (d-TpT) have been fully studied,[4] but a comparison between stacking of thymine and that of uracil by ^{1}H NMR is not necessarily easy because the measured and calculated association shifts due to the stacking of two pyrimidine bases were reported to be very small compared to those of two purine bases.[5] On the other hand, we reported the relationship between the chemical shifts of purine ring protons of 7,7′-(α,ω-alkanediyl)bis[theophylline][6] or 9,9′-(α,ω-alkanediyl)bis[adenine][7] and the carbon number of the polymethylene chain of the compounds in connection with stacking interaction between the purine rings. So long as the polymethylene chains do not restrict the interaction, the reported method[6,7] may be applicable to a comparison of molecular aggregation of thymine and uracil, although in the earlier paper[6,7] shorter polymethylene chains such as methylene and ethylene groups were reported to restrict the stacking interaction between the two purine rings. In the present paper, 1,1′-(α,ω-alkanediyl)bis[thymine] (**1**) and 1,1′-(α,ω-alkanediyl)bis[uracil] (**3**) were prepared, and relationships between chemical shifts of pyrimidine ring protons of low concentrations of **1** and **3** and the carbon numbers (carbon numbers = 3—10) of the polymethylene chains were studied in detail by means of ^{1}H NMR spectroscopy (Chart 1). The values of the chemical shifts were further compared with those of 1-(ω-bromoalkyl)thymine (**2**) and 1-(ω-bromoalkyl)uracil (**4**). Furthermore, our interest in the effect of methyl groups on stacking interaction led us to reinvestigate the relationship between chemical shifts of uracil ring protons of 1,1′-(α,ω-alkanediyl)bis[3-methyluracil] (**5**), which were prepared as reported in the earlier paper,[6] and the carbon numbers of the polymethylene chains.

In order to detect the base-stacking interaction of nucleic acids and the related compounds, hypochromism (decrease of ultraviolet absorption intensity) has frequently been studied.[1,3] These observations led us to study the UV spectroscopy of **1**, **2**, **3**, and **4** and the hypochromic effect of **1** and **3** by comparison with **2** and **4**, respectively, in an effort to make the comparison of the ^{1}H NMR signals of **1** and **3** more clear.

Results and Discussion

Preparation of 1,1′-(α,ω-Alkanediyl)-bis[thymine] and -bis[uracil]. Some of 1,1′-(α,ω-alkanediyl)bis[thymines] (**1**) and 1,1′-(α,ω-alkanediyl)bis[uracils] (**3**) such as **1a**,[3] **1b**,[8] **1d**,[8] and **3a**[3] had been synthesized by the reaction of thymine with 1-(ω-bromoalkyl)thymine (**2**) or of uracil with 1-(3-bromopropyl)uracil (**4a**). The preparation of **2** and **4** had been reported to be performed by the treatment

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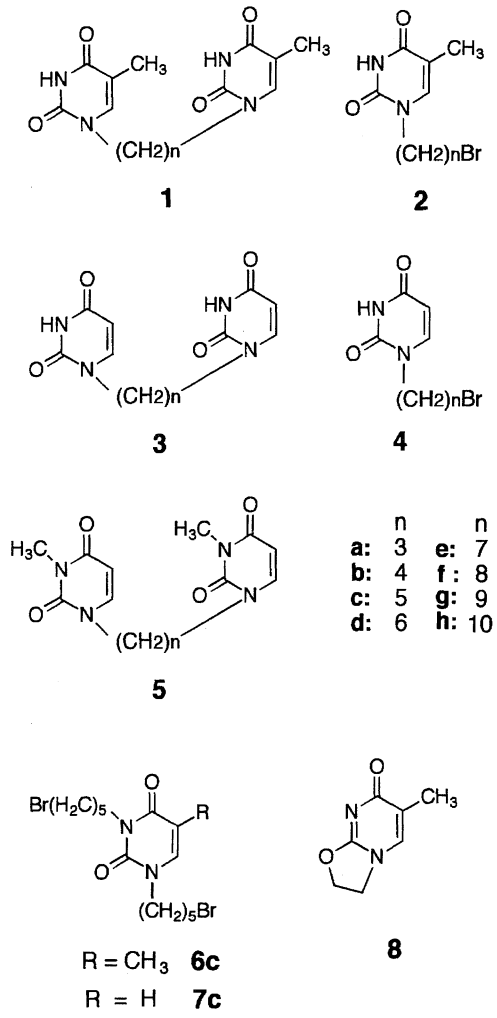

Chart 1.

of 2,4-bis(trimethylsilyloxy)pyrimidines and α,ω-dibromoalkane.[3,8—10] In this paper, a direct method for the preparation of **1** and **3** from thymine and uracil with α,ω-dibromoalkane is presented. That is to say, treatment of thymine or uracil with $Br(CH_2)_nBr$ ($n=3$—10) in the presence of *t*-BuOK in *N*,*N*-dimethylformamide (DMF) resulted in the formation of **1** and **3** together with **2** and **4**, respectively, while similar treatment of thymine and uracil in the presence of bases such as NaH, Cs_2CO_3, K_2CO_3, Na_2CO_3, and CH_3COOK instead of *t*-BuOK did not give **1** and **3**.[11] The reaction of thymine and uracil with *t*-BuOK did not give 3-(ω-bromoalkyl)thymines and -uracils, although small amounts of 1,3-di(5-bromopentyl)thymine (**6c**) and -uracil (**7c**) were isolated from the treatment with $Br(CH_2)_5Br$. In addition, more than 50% of thymine and uracil were recovered in the reaction system. When the carbon number of $Br(CH_2)_nBr$ was 2, the reaction of thymine did not give **1** ($n=2$) and **2** ($n=2$) but gave a cyclic derivative of thymine (**8**). These results are summarized in Table 1.

It is well known that the alkylation of uracil and thymine can generally occur at N^3 as well as N^1 of the pyrimidine ring,[12] although the selective alkylation at N^1 position is also known.[13] Therefore, it is important to distinguish the difference between the structures of these two isomers at N^1 and at N^3 positions. The structures of the two isomers were differentiated on the basis of coupling constants between H–C^5 and H–N^3 of 1-substituted uracils and those between H–C^6 and H–N^1 of 3-substituted thymines and uracils on the ^{1}H NMR spectra. Figure 1 shows the ^{1}H NMR spectra of uracil, **3a**, **3d**, and **4g**. When the ^{1}H NMR measurements were made in low concentrations of uracil in a mixture of $CDCl_3$ and DMSO-d_6, the signals of H–C^5 and H–C^6 appeared as triple doublets and double doublets, respectively (Fig. 1-A), although the coupling depended on the concentration of uracil and the solvent used (Fig. 1-B, C). Furthermore, it can be seen from the ^{1}H NMR spectra of low concentrations of 3-methylthymine and 1-methyluracil in $CDCl_3$ that the coupling constants between H–C^6 and H–N^1 and between H–C^5 and H–N^3 were 6 Hz and 2 Hz, respectively.[14] The values of the coupling constants were consistent with those reported for the protonated uracil ($J_{1,6}=6.4$ Hz and $J_{3,5}=2.0$ Hz).[15] As can be seen from Fig. 1-D, E, F and Experimental, ^{1}H NMR spectra of low concentrations of **3** and **4** showed the coupling between H–C^5 and H–N^3 ($J_{3,5}=2$ Hz), while ^{1}H NMR spectra of **1**, **2**, **3**, and **4** showed no coupling between H–C^6 and H–N^1. Therefore, one might conclude that **1**—**4** were 1-substituted uracils and thymines, but not 3-substituted ones.

Table 1. Alkylation of Thymine and Uracil with α,ω-Dibromoalkane in the Presence of *t*-BuOK[a)]

	$Br(CH_2)_nBr$	Product
	n	Isolated yield (%)
Thymine	2	**8**/15; thymine/62
	3	**1a**/8; **2a**/22; thymine/53
	4	**1b**/10; **2b**/20; thymine/52
	5	**1c**/16; **2c**/12; **6c**/2; thymine/55
	6	**1d**/22; **2d**/14; thymine/50
	7	**1e**/22; **2e**/11; thymine[b)]
	8	**1f**/24; **2f**/12; thymine/51
	9	**1g**/22; **2g**/10; thymine[b)]
	10	**1h**/23; **2h**/10; thymine/55
Uracil	3	**3a**/5; **4a**/12; uracil/55
	4	**3b**/8; **4b**/11; uracil/52
	5	**3c**/15; **4c**/14; **7c**/2; uracil/57
	6	**3d**/15; **4d**/17; uracil/52
	7	**3e**/17; **4e**/15; uracil[b)]
	9	**3g**/20; **4g**/12; uracil[b)]
	10	**3h**/22; **4h**/10; uracil/57

a) Reaction conditions are shown in Experimental part. b) Yields of thymine and uracil recovered were not determined.

NMR Study: Relationship between the Chemical Shifts and the Carbon Numbers. Figure 2 shows the concentration dependence of the chemical shifts of H-6 of the pyrimidine rings of **1a**, **1b**, and **3a** in D_2O at 27 °C. The measurements were made on solutions ranging in concentrations from 0.05 to 2.0 mmol dm^{-3}. Proton resonances of nucleic acid bases are known to be shifted to higher fields as the solute concentrations are increased because of the self-association,[16] but the differences of the chemical shifts, as can be seen Fig. 2, were within 0.002 ppm over the range

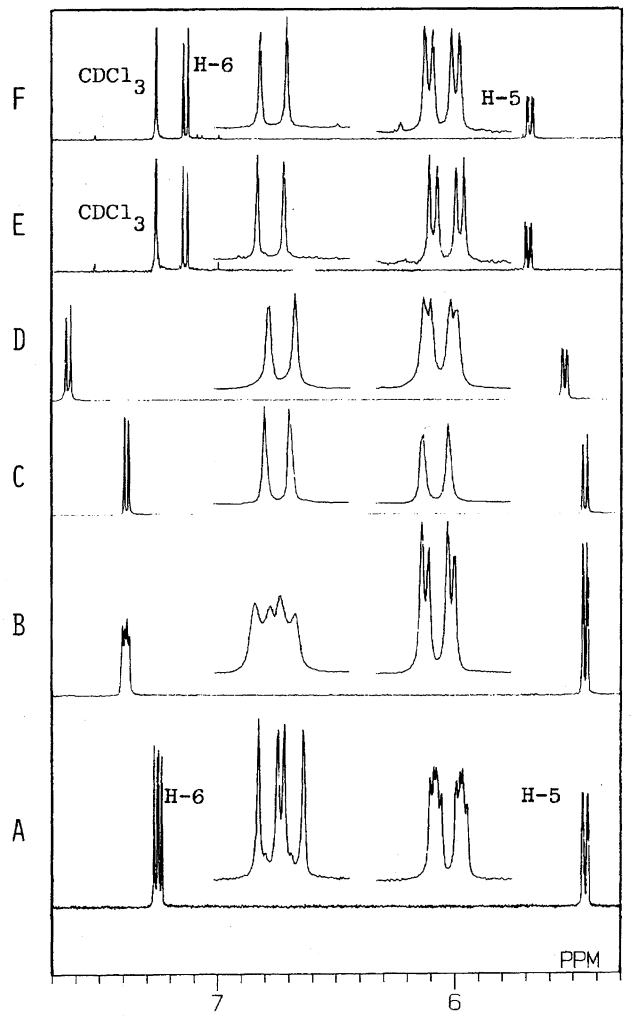

Fig. 1. ^{1}H NMR spectra of uracil, **3a**, **3d**, and **4g**.
A: Uracil (0.5 mg) in a mixture of $CDCl_3$ (0.3 ml) and DMSO-d_6 (0.3 ml). B: Uracil (0.7 mg) in DMSO-d_6 (0.6 ml). C: Uracil (10 mg) in DMSO-d_6 (0.6 ml). D: **3a** (5 mg) in DMSO-d_6 (0.6 ml). E: **3d** (1 mg) in $CDCl_3$ (0.6 ml). F: **4g** (1 mg) in $CDCl_3$ (0.6 ml).

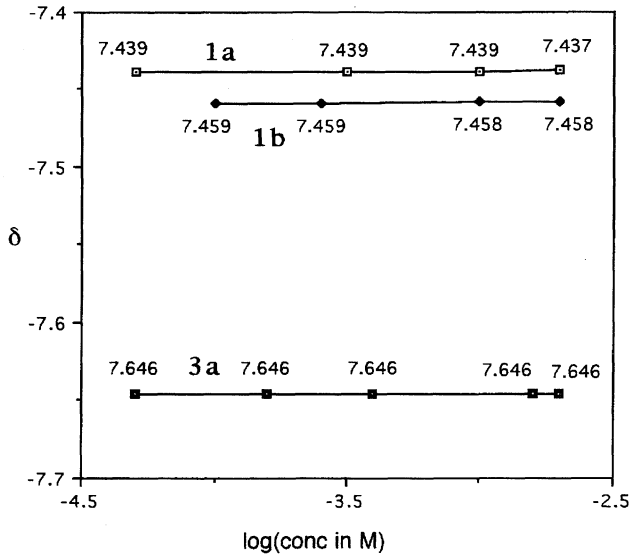

Fig. 2. Relationship between the chemical shifts (δ) of H-6 of the pyrimidine rings of **1a**, **1b**, and **3a** and the concentrations [log (concn in M)] (1 M = 1 mol dm^{-3}) in D_2O at 27 °C.

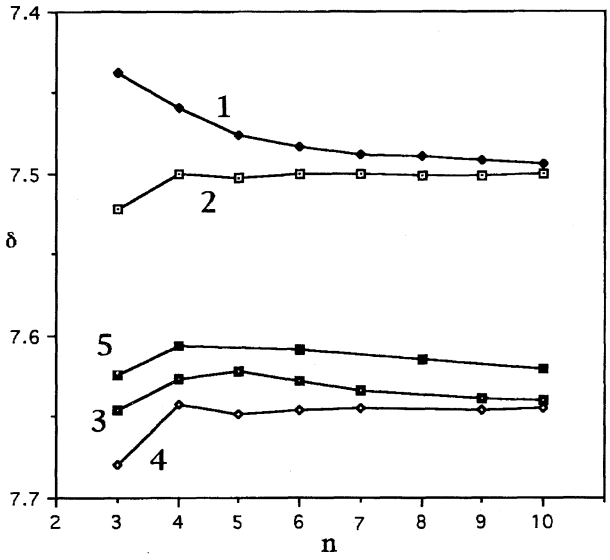

Fig. 3. Relationship between the chemical shifts (δ) of H-6 of the pyrimidine rings of **1**—**5** and the carbon numbers (n) of the polymethylene chains in D_2O at 27 °C. The ^{1}H NMR spectra of **1**—**5** were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm.

of the concentrations from 0.05 to 2.0 mmol dm^{-3}. Therefore, self-association of **1** and **3** may be neglected at the concentrations measured in this study (in aqueous solutions: < 1.0 mmol dm^{-3}), and interaction between two pyrimidine rings linked with the polymethylene chains in **1** and **3** was expected to be observed by means of ^{1}H NMR spectroscopy.

The ^{1}H NMR spectroscopy of the low concentrations of **1**, **2**, **3**, **4**, and **5** was investigated in aqueous solutions and organic solvents at 27 °C (in the case of the measurement in D_2O: 27 and 50 °C). In aqueous solutions, the concentrations of **1**, **3**, and **5** were less than 1.0 mmol dm^{-3} and those of **2** and **4** were less than 1.2 mmol dm^{-3}. In organic solvents, the concentrations of **1**, **3**, and **5** were less than 2.0 mmol dm^{-3}. These results are summarized in Table 2.

Figure 3 shows the relationship between the chemical shifts of H-6 of thymine ring of **1** and **2** and of uracil ring of **3**, **4**, and **5** in D_2O at 27 °C and the carbon numbers of the polymethylene chains. The signals of H-6 of **1** were shifted to a higher field when the carbon numbers are 3 and 4, whereas those of **2**, **3**, **4**, and **5** were reversely shifted to a lower field when the carbon number is 3. The chemical shift difference $\Delta\delta_{1a,1c}$ ($\Delta\delta_{1a,1c} = \delta_{1c} - \delta_{1a}$) which was determined by the comparison of the chemical shift of **1a** ($n = 3$) with that of **1c** ($n = 5$) was +0.037 ppm and $\Delta\delta_{1c,1h}$ ($\Delta\delta_{1c,1h} = \delta_{1h} - \delta_{1c}$) was +0.018 ppm. On the other hand, $\Delta\delta_{3a,3c}$ ($\Delta\delta_{3a,3c} = \delta_{3c} - \delta_{3a}$) was −0.024 ppm and $\Delta\delta_{3c,3h}$ ($\Delta\delta_{3c,3h} = \delta_{3h} - \delta_{3c}$) was +0.018 ppm. On the basis of these data, it seemed reasonable to assume that the molecular aggregation of the two thymine rings of **1a** and **1b** was different

Table 2. Chemical Shifts of the Protons at 6- and 5-Positions and Methyl Group of **1**, **2**, **3**, **4**, and **5**

	Solvent		Chemical shift/δ[a]							
			a ($n=3$)	**b** ($n=4$)	**c** ($n=5$)	**d** ($n=6$)	**e** ($n=7$)	**f** ($n=8$)	**g** ($n=9$)	**h** ($n=10$)
1	D_2O	H-6	7.437	7.459	7.476	7.483	7.488	7.489	7.492	7.494
		Me	1.841	1.870	1.877	1.879	1.880	1.880	1.880	1.880
	D_2O, 50 °C	H-6	7.416	7.442	7.450	7.458	7.462	7.465	—	7.472
		Me	1.846	1.870	1.874	1.878	1.879	1.880	—	1.881
	pD 1.0[b]	H-6	7.425	7.448	7.455	7.467	7.471	7.475	7.478	7.482
		Me	1.825	1.850	1.855	1.860	1.861	1.861	1.862	1.862
	CD_3OD	H-6	7.432	7.424	7.412	7.413	7.414	—	7.414	7.414
		Me	1.860	1.863	1.865	1.865	1.866	—	1.866	1.866
	DMSO	H-6	7.516	7.518	7.510	7.513	7.512	—	—	7.513
		Me	1.742	1.745	1.745	1.746	1.746	—	—	1.746
	CF_3COOD	H-6	7.538	7.470	7.454	7.448	7.449	7.448	7.448	—
		Me	2.073	2.075	2.075	2.074	2.075	2.075	2.075	—
2	D_2O	H-6	7.522	7.501	7.503	7.500	7.500	7.501	7.501	7.500
		Me	1.890	1.889	1.889	1.886	1.887	1.887	1.887	1.886
3	D_2O	H-6	7.646	7.627	7.622	7.628	7.634	—	7.639	7.640
		H-5	5.832	5.825	5.820	5.822	5.825	—	5.825	5.824
	D_2, 50 °C	H-6	7.629	7.613	7.606	7.613	7.619	—	7.624	7.624
		H-5	5.835	5.829	5.825	5.827	5.830	—	5.830	5.828
	pD 1.0[b]	H-6	7.633	7.616	7.611	7.618	7.622	—	7.627	—
		H-5	5.815	5.810	5.801	5.803	5.806	—	5.808	—
	CD_3OD	H-6	7.602	7.575	7.563	7.563	7.563	—	7.563	7.564
		H-5	5.649	5.639	5.635	5.636	5.635	—	5.635	5.635
	DMSO	H-6	7.674	7.636	7.630	7.630	7.631	—	7.631	—
		H-5	5.547	5.529	5.530	5.530	5.531	—	5.530	—
4	D_2O	H-6	7.680	7.642	7.648	7.646	7.644	—	7.646	7.646
		H-5	5.839	5.836	5.832	5.830	5.829	—	5.828	5.828
5	D_2O	H-6	7.624	7.606	—	7.609	—	7.615	—	7.620
		H-5	5.889	5.887	—	5.881	—	5.887	—	5.889
	D_2O, 50 °C	H-6	7.604	7.591	—	7.595	—	7.600	—	7.605
		H-5	5.890	5.889	—	5.884	—	5.888	—	5.890
	pD 1.0[b]	H-6	7.612	7.594	—	7.597	—	7.602	—	7.608
		H-5	5.872	5.870	—	5.865	—	5.870	—	5.872
	CD_3OD	H-6	7.600	7.572	—	7.563	—	7.563	—	7.563
		H-5	5.736	5.726	—	5.719	—	5.719	—	5.719

a) The ^{1}H NMR spectra of **1**—**5** were measured at least twice and the chemical shifts were reproduced within ±0.003 ppm. Unless otherwise stated, the measurement were carried out at 27 °C. b) The buffer solution at pD 1.0.

from that of two uracil rings of **3a** and **3b**, while the relationship between two thymine rings of **1c**—**h** was similar to that between two uracil rings of **3c**—**h** when the carbon numbers are more than 5. The chemical shift difference $\Delta\delta_{\mathbf{1a,1c}}$ (+0.037 ppm) is roughly consistent with the calculated association shifts $\Delta\delta$ due to the stacking of two thymine rings.[5b,5c] Therefore, the shift to a higher field of **1a** and **1b** may be interpreted in terms of stacking interaction between two thymine bases.

In the earlier paper,[7] we reported the pH-dependence of the chemical shifts of adenine ring protons of 9,9′-(α,ω-alkanediyl)bis[adenine]. In order to study the pH dependence in the interaction of thymine and of uracil, the relationship between the chemical shifts of pyrimidine ring protons of **1**, **3**, and **5** and the carbon numbers of the polymethylene chains was examined in KCl–HCl buffer solution at pD 1.0[17] at 27 °C. The relationship of **1**, **3**, and **5** was further investigated in organic solvents such as CD_3OD, DMSO-d_6, and CF_3COOD. Figure 4 shows the relationship between the chemical shifts of H-6 of **1**, **3**, and **5** and the carbon numbers in D_2O at 50 °C, in the buffer solution at pD 1.0 at 27 °C, and in organic solvents at 27 °C. The relations of **1** in D_2O at 50 °C and in the buffer solution at pD 1.0 were similar to that of **1** in D_2O at 27 °C (Fig. 3), while the signals of **1** in organic solvents were not shifted to a higher field when the carbon numbers are 3 and 4.

Figure 5 shows the relationship between the chemicals shifts of methyl group of **1** and **2** and the carbon numbers in aqueous solutions and in organic solvents. The only signals of methyl group of **1a** and **1b** in D_2O and the buffer solution at pD 1.0 were shifted to a higher field. The chemical shift difference $\Delta\delta_{\mathbf{1a,1c}}$ ($\Delta\delta_{\mathbf{1a,1c}} = \delta_{\mathbf{1c}} - \delta_{\mathbf{1a}}$) which was de-

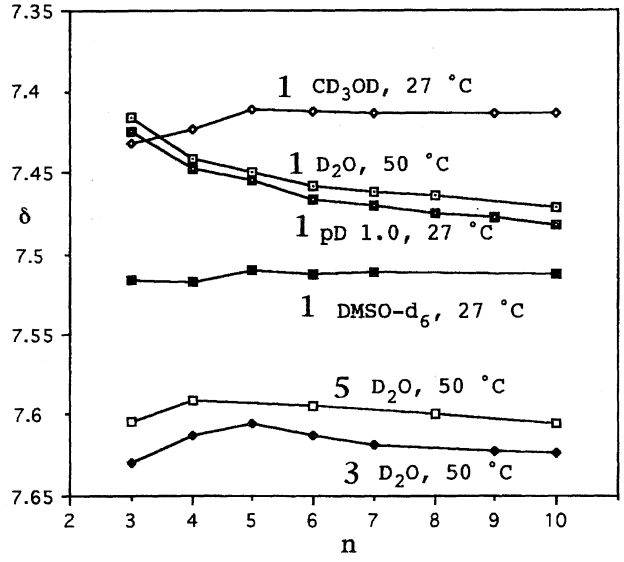

Fig. 4. Relationship between the chemical shifts of H-6 of **1**, **3**, and **5** and the carbon numbers of the polymethylene chains in D_2O at 50 °C, in the buffer solution at pD 1.0 at 27 °C, and in organic solvents at 27 °C. The ^1H NMR spectra of **1**, **3**, and **5** were measured at least twice and the chemical shifts were reproduced within ±0.003 ppm.

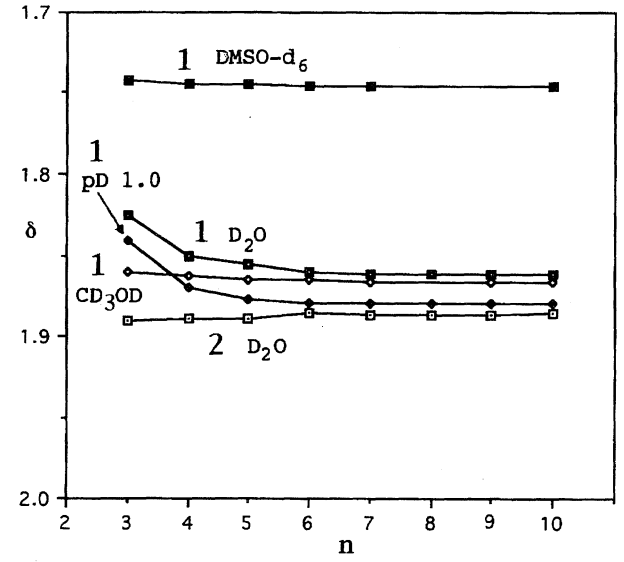

Fig. 5. Relationship between the chemical shifts of methyl group of the thymine ring of **1** and **2** and the carbon numbers of the polymethylene chains in D_2O, the buffer solution at pD 1.0, and organic solvents at 27 °C. The ^1H NMR spectra of **1** and **2** were measured at least twice and the chemical shifts were reproduced within ±0.003 ppm.

termined by the comparison of the chemical shift of methyl group of **1a** (n=3) with that of **1c** (n=5) in D_2O at 27 °C was +0.036 ppm and $\Delta\delta_{1c,1h}$ ($\Delta\delta_{1c,1h} = \delta_{1h} - \delta_{1c}$) was +0.003 ppm (Table 2). On the other hand, the chemical shift difference $\Delta\delta_{1a,1c}$ ($\Delta\delta_{1a,1c} = \delta_{1c} - \delta_{1a}$) in CD_3OD was +0.005 ppm and $\Delta\delta_{1c,1h}$ ($\Delta\delta_{1c,1h} = \delta_{1h} - \delta_{1c}$) was +0.001 ppm. The chemical shift difference $\Delta\delta_{1a,1c}$ (+0.036 ppm) is roughly consistent with the calculated association shifts $\Delta\delta$ due to the stacking of two thymine rings.[5b,5c]

Figure 6 shows the relationship of the chemical shifts of H-5 of **3** and **5** and the carbon numbers in aqueous solutions and in organic solvents. As can be seen from Fig. 6, the signals of H-5 of **3** and **5** were not shifted to a higher field with a decrease of the carbon numbers in not only organic solvents but also aqueous solutions. On the basis of the data of Table 2 and Figs. 3, 4, 5, and 6, we concluded that only the signals of the thymine ring protons of **1a** (n=3) and **1b** (n=4) were shifted to a higher field and water was essential for the shifts to a higher field.

UV Study: Hypochromicity. From a consideration of these ^1H NMR data, it seemed reasonable to assume that there was a stacking interaction between two thymine rings of **1a** and **1b** in aqueous solutions, but the interaction was not observed between two uracil rings of **3a** and **3b**. However, the shifts of **1a** and **1b** were not pronounced, compared with those between two adenine rings of bis[adenine].[7] Therefore, in the present investigation, another search, namely hypochromism, was made for the comparison between stacking interactions of **1** and **3**.

Table 3 shows electronic absorption data of **1**, **2**, **3**, and **4** in water. A bathochromic shift was observed in the absorption maxima of **1** as the carbon numbers of the polymethylene chains of **1** were increased, while the shift of **3** was smaller than that of **1**. The hypochromicity values (h/%)[18] of **1** and **3** were obtained by comparing their molecular absorptivity with those of **2** and **4**, respectively, although the hypochromism values of **1a** (7.0) and of **3a** (1.2) had been reported by comparing their oscillator strength with those of 1-propylthymine and of 1-propyluracil.[4] The hypochromicity of **1a** by comparison with **2a** was 11, while that of **3a** by

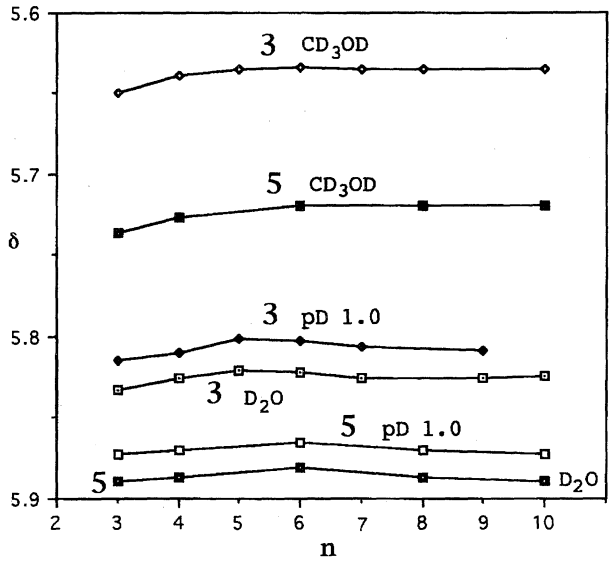

Fig. 6. Relationship of the chemical shifts of H-5 of **3** and **5** and the carbon numbers of the polymethylene chains in D_2O, the buffer solution at pD 1.0, and CD_3OD at 27 °C. The ^1H NMR spectra of **3** and **5** were measured at least twice and the chemical shifts were reproduced within ±0.003 ppm.

Table 3. Electronic Absorption Data of **1**, **2**, **3**, and **4** and Hypochromicity in Water[a)]

	1 and **3** λ_{max}/nm (ε)			**2** and **4** λ_{max}/nm (ε)		Hypochromicity h/%[b)]
1a:	269.6	(17190)	**2a:**	272.4	(9700)	11[c)]
1b:	270.8	(18510)	**2b:**	273.0	(9880)	6
1c:	271.4	(18280)	**2c:**	273.0	(9850)	7
1d:	272.6	(18670)	**2d:**	273.2	(9920)	6
1e:	273.0	(18920)	**2e:**	273.4	(9880)	4
3a:	266.8	(19680)	**4a:**	266.6	(10100)	3[d)]
3b:	267.0	(19810)	**4b:**	267.4	(10190)	3
3c:	267.0	(19770)	**4c:**	267.4	(10330)	4
3d:	267.6	(19820)	**4d:**	267.4	(10070)	2
3e:	267.6	(19840)	**4e:**	267.8	(10030)	1

a) The spectra of **1**—**4** in water were measured at least five times and the average values of the absorption maxima were reported. b) The values of the hypochromicity (h/%) were determined by the following equation: $h/\% = 100 \times (1 - \varepsilon_A/2\varepsilon_B)$; ε_A is the molecular absorptivity of **1** or **3**, and ε_B is that of **2** or **4**. c) The reported hypochromism value of **1a** by comparing the oscillator strength with 1-propylthymine was 7.0.[3)] d) The reported hypochromism value of **3a** by comparison with 1-propyluracil was 1.2.[3)]

comparison with **4a** was 3. The results of the studies on the hypochromism may lend some support to the conclusion to be drawn from the NMR data.

Discussion. When ^{1}H NMR spectra of **1**, **3**, and **5** are measured in low concentrations similar to those used in UV measurements, only the interaction between the intramolecular pyrimidine rings may be observed. If there is a stacking interaction between two pyrimidine rings and the linkers do not restrict the interaction, the interaction is expected to be correlated with the length of the linkers (polymethylene chains). Therefore, it appeared of interest to investigate the relationship between the chemical shifts of pyrimidine ring protons and the carbon numbers of the polymethylene chains in order to compare molecular aggregations of **1**, **3**, and **5**.

The X-ray analysis of **1a** showed the stacking of the intramolecular thymine rings as shown in Chart 2-A.[19)] Although the hypochromism of **1a** in aqueous solution was known to be larger than that of **3a**,[3)] little attention has been paid to a detailed comparison of the stacking interaction of thymine with that of uracil in aqueous solution. It may be concluded from the results of this investigation that there is a clear difference between molecular aggregation of the intramolecular thymine rings of **1a**, **b** and that of the intramolecular uracil rings of **3a**, **b**. The upfield shifts of

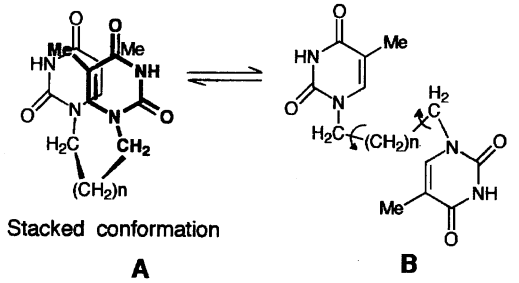

Chart 2.

the thymine ring signals of **1a**, **b** with shorter polymethylene chains may correspond to an increase of population of stacked conformers as compared with a random conformational motion of the polymethylene chains (Chart 2-B). UV hypochromism confirmed the formation of stacked conformers of **1a** but provided little significant information regarding the stacked conformation. From a consideration of the upfield shifts of H-6 and methyl group on ^{1}H NMR of **1a**, **b**, the stacked conformation may be explained in terms of a structure similar to that elucidated by the X-ray analysis of **1a**[19)] (Chart 2-A). On the other hand, the relationship between the signals of thymine ring protons of **1c**—**h** with longer polymethylene chains ($n \geq 5$) and the carbon numbers was similar to that of **3c**—**h**. The results may indicate that the effect of 5-methyl group on stacking interaction of the intramolecular pyrimidine rings was not observed in the case of **1c**—**h** with longer polymethylene chains ($n \geq 5$).

The comparison between **1a**, **b** and **3a**, **b** is looked upon as the effect of 5-methyl group in uracil ring on stacking interaction. However, the signals of the uracil ring protons of **5a**, **b** were little influenced by the introduction of N^3-methyl group into uracil ring, compared with those of **3a**, **b**. Taking into account the proposed stacked conformation (Chart 2-A), the 5-methyl group of the pyrimidine ring contributes to the stacking, but the N^3-methyl group seems to contribute little to the stacking. The results may be of interest in connection with the mechanism of stacking interaction.

Experimental

The melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were obtained with a JEOL GSX400 spectrometer. Chemical shifts are reported as ppm (δ) downfield from tetramethylsilane in organic solvents or from sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 in D_2O. The electronic absorption spectra in water (Wako pure water) were recorded on a Shimadzu UV-160A spectrometer. The elemental analyses were performed by the Analytical Center of Kyoto University. The preparation of 1,1′-(α,ω-alkanediyl)bis[3-methyluracil] (**5**) was previously reported.[6)]

Alkylation of Thymine and Uracil. Into a solution of thymine or uracil (10 mmol) in DMF (150 ml), *t*-BuOK (10 mmol) and Br-$(CH_2)_n$Br (n = 3—10; 10 mmol) were added. The mixture was stirred at room temperature for 40 h. The resulting mixture was evaporated to give a residue which was submitted to chromatography over silica gel. By elution of a mixture of ethyl acetate and hexane, 1-(ω-bromoalkyl)thymine (**2**) or 1-(ω-bromoalkyl)uracil (**4**) was obtained. When Br$(CH_2)_5$Br was used, small amounts of 1,3-di(5-bromopentyl)thymine (**6c**) and 1,3-di(5-bromopentyl)-uracil (**7c**) were isolated. Further elution with a mixture of ethyl acetate and methanol gave 1,1′-(α,ω-alkanediyl)bis[thymine] (**1**) or 1,1′-(α,ω-alkanediyl)bis[uracil] (**3**). Treatment of thymine with Br$(CH_2)_2$Br gave **8** but did not give **1** (n = 2) and **2** (n = 2). The spectral data of **1**, **2**, **3**, **4**, **6c**, **7c**, and **8** are given below.

1,1′-(1,3-Propanediyl)bis[thymine] (1a): Mp >300 °C (lit,[3)] 330—332 °C); ^{1}H NMR (DMSO-d_6) δ = 11.21 (s, 2H, NH), 7.52 (s, 2H), 3.65 (t, 4H, J = 7.2 Hz), 1.90 (quintet, 2H, J = 7.2 Hz), 1.74 (s, 6H); ^{13}C NMR (DMSO-d_6) δ = 164.17, 150.82, 141.14, 108.46, 44.73, 27.78, 11.83.

1,1′-(1,4-Butanediyl)bis[thymine] (1b): Mp >300 °C (lit,[8] >320 °C); ^{1}H NMR (DMSO-d_6) δ = 11.19 (s, 2H, NH), 7.52 (s, 2H), 3.63 (broad, 4H), 1.75 (s, 6H), 1.55 (broad, 4H); ^{13}C NMR (DMSO-d_6) δ = 164.17, 150.81, 141.32, 108.37, 46.62, 25.30, 11.83.

1,1′-(1,5-Pentanediyl)bis[thymine] (1c): Mp 250—252 °C (hygroscopic); ^{1}H NMR (DMSO-d_6) δ = 11.19 (s, 2H, NH), 7.51 (s, 2H), 3.60 (t, 4H, J = 7.2 Hz), 1.75 (s, 6H), 1.58 (quintet, 4H, J = 7.2 Hz), 1.22 (broad quintet, 2H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ = 164.52, 151.08, 141.65, 108.63, 47.17, 28.26, 22.90, 12.13. Found: C, 54.41; H, 6.53; N, 16.82%. Calcd for $C_{15}H_{20}N_4O_4 \cdot 1/2H_2O$: C, 54.70; H, 6.43; N, 17.01%.

1,1′-(1,6-Hexanediyl)bis[thymine] (1d): Mp 232—234 °C (lit,[8] 236—237 °C); ^{1}H NMR (DMSO-d_6) δ = 11.19 (s, 2H, NH), 7.51 (s, 2H), 3.60 (t, 4H, J = 7.2 Hz), 1.75 (s, 6H), 1.56 (broad quintet, 4H, J = 7.2 Hz), 1.26 (broad quintet, 4H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ = 164.20, 150.77, 141.30, 108.30, 46.89, 28.23, 25.33, 11.81.

1,1′-(1,7-Heptanediyl)bis[thymine] (1e): Mp 208—210 °C; ^{1}H NMR ($CDCl_3$) δ = 8.58 (s, 2H, NH), 6.97 (q, 2H, J = 1 Hz), 3.69 (t, 4H, J = 7.2 Hz), 1.93 (d, 6H, J = 1 Hz), 1.68 (quintet, 4H, J = 7.2 Hz), 1.33—1.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ = 164.01, 150.78, 140.30, 110.69, 48.35, 28.96, 28.67, 26.17, 12.34. Found: C, 58.36, H, 6.96; N, 15.85%. Calcd for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.09%.

1,1′-(1,8-Octanediyl)bis[thymine] (1f): Mp 188—190 °C; ^{1}H NMR ($CDCl_3$) δ = 8.64 (s, 2H, NH), 6.97 (q, 2H, J = 1 Hz), 3.68 (t, 4H, J = 7.2 Hz), 1.93 (d, 6H, J = 1 Hz), 1.67 (quintet, 4H, J = 7.2 Hz), 1.34—1.30 (m, 8H); ^{13}C NMR ($CDCl_3$) δ = 164.06, 150.78, 140.35, 110.64, 48.42, 29.01, 28.88, 26.21, 12.33. Found: C, 59.31; H, 7.26; N, 15.00%. Calcd for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.23; N, 15.46%.

1,1′-(1,9-Nonanediyl)bis[thymine] (1g): Mp 195—196 °C; ^{1}H NMR ($CDCl_3$) δ = 8.55 (s, 2H, NH), 6.97 (q, 2H, J = 1Hz), 3.68 (t, 4H, J = 7.2 Hz),1.93 (d, 6H, J = 1 Hz), 1.67 (broad quintet, 4H, J = 7.2 Hz), 1.35—1.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ = 164.07, 150.76, 140.38, 110.60, 48.48, 29.13, 29.04, 28.94, 26.28, 12.33. Found: C, 60.34; H, 7.39, N, 14.61%. Calcd for $C_{19}H_{28}N_4O_4$: C, 60.62; H, 7.50; N, 14.88%.

1,1′-(1,10-Decanediyl)bis[thymine] (1h): Mp 181—182 °C; ^{1}H NMR ($CDCl_3$) δ = 8.52 (s, 2H, NH), 6.97 (q, 2H, J = 1 Hz), 3.68 (t, 4H, J = 7.2 Hz), 1.92 (d, 6H, J = 1 Hz), 1.67 (broad quintet, 4H, J = 7.2 Hz), 1.34—1.27 (m, 12H); ^{13}C NMR ($CDCl_3$) δ = 164.03, 150.74, 140.38, 110.57, 48.52, 29.21, 29.05, 29.02, 26.32, 12.34. Found: C, 61.41; H, 7.73; N, 14.48%. Calcd for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74; N, 14.35%.

1-(3-Bromopropyl)thymine (2a): Mp 135—136 °C (lit,[3] 136—138 °C; lit,[9] 136 °C): ^{1}H NMR ($CDCl_3$) δ = 8.64 (s, 1H, NH), 7.06 (q, 1H, J = 1 Hz), 3.88 (t, 2H, J = 6.8 Hz), 3.44 (t, 2H, J = 6.4 Hz), 2.27 (tt, 2H, J = 6.8 and 6.4 Hz), 1.93 (d, 3H, J = 1 Hz); ^{13}C NMR ($CDCl_3$) δ = 163.93, 150.75, 140.60, 110.89, 47.27, 31.20, 29.78, 12.32.

1-(4-Bromobutyl)thymine (2b): Mp 134—135 °C (lit,[8] 134—135 °C lit,[9] 124—126 °C); ^{1}H NMR ($CDCl_3$) δ = 8.91 (s, 1H, NH), 6.98 (q, 1H, J = 1 Hz), 3.75 (t, 2H, J = 6.8 Hz), 3.45 (t, 2H, J = 6.4 Hz), 1.93 (d, 3H, J = 1 Hz), 1.93—1.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ = 164.16, 150.95, 140.01, 111.06, 47.43, 32.66, 29.29, 27.72, 12.35.

1-(5-Bromopentyl)thymine (2c): Mp 101—102 °C(lit,[9] 102—104 °C); ^{1}H NMR ($CDCl_3$) δ = 8.88 (s, 1H, NH), 6.98 (q, 1H, J = 1 Hz), 3.71 (t, 2H, J = 7.2 Hz), 3.42 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.91 (quintet, 2H, J = 7 Hz), 1.72 (quintet, 2H, J = 7 Hz), 1.50 (quintet, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ = 164.11, 150.82, 140.27, 110.77, 48.30, 33.26, 32.05, 28.21, 24.91, 12.33.

1-(6-Bromohexyl)thymine (2d): Mp 109—110 °C (lit,[3] 111—113 °C; lit,[10] 112—113.5 °C; ^{1}H NMR ($CDCl_3$) δ = 8.66 (s, 1H, NH), 6.98 (q, 1H, J = 1 Hz), 3.70 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.87 (quintet, 2H, J = 6.8 Hz), 1.70 (quintet, 2H, J = 7.2 Hz), 1.49 (quintet, 2H, J = 7 Hz), 1.37 (quintet, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ = 164.06, 150.77, 140.30, 110.70, 48.37, 33.60, 32.45, 28.93, 27.65, 25.57, 12.34.

1-(7-Bromoheptyl)thymine (2e): Mp 107—108 °C; ^{1}H NMR ($CDCl_3$) δ = 8.68 (s, 1H, NH), 6.97 (q, 1H, J = 1 Hz), 3.69 (t, 2H, J = 7.2 Hz), 3.40 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.86 (quintet, 2H, J = 7.2 Hz), 1.69 (broad quintet, 2H, J = 7 Hz), 1.45 (broad quintet, 2H, J = 7 Hz), 1.40—1.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ = 164.07, 150.78, 140.31, 110.64, 48.46, 33.77, 32.58, 28.99, 28.30, 27.93, 26.25, 12.33. Found: C, 47.42; H, 6.34; N, 9.28%. Calcd for $C_{12}H_{19}N_2O_2Br$: C, 47.54; H, 6.32; N, 9.24%.

1-(8-Bromooctyl)thymine (2f): Mp 96—97 °C (lit,[10] 96—96.5 °C); ^{1}H NMR ($CDCl_3$) δ = 8.90 (s, 1H, NH), 6.98 (q, 1H, J = 1 Hz), 3.69 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.85 (quintet, 2H, J = 7.2 Hz), 1.68 (broad quintet, 2H, J = 7 Hz), 1.43 (broad quintet, 2H, J = 7 Hz), 1.37—1.30 (broad, 6H); ^{13}C NMR ($CDCl_3$) δ = 164.61, 151.08, 140.45, 110.60, 48.51, 33.91, 32.68, 29.04, 28.96, 28.53, 27.99, 26.30, 12.33.

1-(9-Bromononyl)thymine (2g): Mp 104—105 °C; ^{1}H NMR ($CDCl_3$) δ = 8.13 (s, 1H, NH), 6.99 (q, 1H, J = 1 Hz), 3.68 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.85 (quintet, 2H, J = 7.2 Hz), 1.67 (broad quintet, 2H, J = 7 Hz), 1.43 (broad quintet, 2H, J = 7 Hz), 1.37—1.28 (broad, 8H); ^{13}C NMR ($CDCl_3$) δ = 164.27, 150.90, 140.37, 110.57, 48.53, 33.96, 32.74, 29.21, 29.08, 29.06, 28.61, 28.07, 26.38, 12.33. Found: C, 50.90; H, 7.23; N, 8.50%. Calcd for $C_{14}H_{23}N_2O_2Br$: C, 50.76; H, 7.00; N, 8.46%.

1-(10-Bromodecyl)thymine (2h): Mp 93—94 °C (lit,[10] 92—94 °C); ^{1}H NMR ($CDCl_3$) δ = 9.00 (s, 1H, NH), 6.98 (q, 1H, J = 1 Hz), 3.69 (t, 2H, J = 7.2 Hz), 3.41 (t, 2H, J = 6.8 Hz), 1.93 (d, 3H, J = 1 Hz), 1.85 (quintet, 2H, J = 7.2 Hz), 1.67 (broad quintet, 2H, J = 7 Hz), 1.42 (broad quintet, 2H, J = 7 Hz), 1.37—1.27 (broad, 10H); ^{13}C NMR ($CDCl_3$) δ = 164.24, 150.86, 140.39, 110.54, 48.55, 34.01, 32.79, 29.30, 29.29, 29.13, 29.10, 28.68, 28.11, 26.41, 12.33.

1,1′-(1,3-Propanediyl)bis[uracil] (3a): Mp 280—285 °C (lit,[3] 287—293 °C); ^{1}H NMR (DMSO-d_6) δ = 11.22 (broad, 2H, NH), 7.67 (d, 2H, J = 8 Hz), 5.55 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.69 (t, 4H, J = 7.2 Hz), 1.90 (quintet, 2H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ = 163.63, 150.89, 145.40, 100.92, 44.85, 27.94.

1,1′-(1,4-Butanediyl)bis[uracil] (3b): Mp >300 °C; ^{1}H NMR (DMSO-d_6) δ = 11.20 (broad, 2H, NH), 7.64 (d, 2H, J = 8 Hz), 5.53 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.66 (broad, 4H), 1.55 (broad, 4H); ^{13}C NMR (DMSO-d_6) δ = 163.66, 150.86, 145.57, 100.77, 46.93, 25.26. Found: C, 48.36; H, 5.18; N, 18.27%. Calcd for $C_{12}H_{14}N_4O_4 \cdot H_2O$: C, 48.65; H, 5.44; N, 18.90%.

1,1′-(1,5-Pentanediyl)bis[uracil] (3c): Mp 246—248 °C; ^{1}H NMR (DMSO-d_6) δ = 11.21 (broad, 2H, NH), 7.63 (d, 2H, J = 8 Hz), 5.53 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.64 (t, 4H, J = 7.2 Hz), 1.59 (broad quintet, 4H, J = 7.2 Hz), 1.22 (broad quintet, 2H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ = 163.60, 150.81, 145.54, 100.67, 47.11, 27.88, 22.51. Found: C, 53.14; H, 5.43; N, 19.18%. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17%.

1,1′-(1,6-Hexanediyl)bis[uracil] (3d): Mp 242—245 °C; ^{1}H NMR (DMSO-d_6) δ = 11.18 (broad, 2H, NH), 7.63 (d, 2H, J = 8 Hz), 5.53 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.63 (t, 4H, J = 7.2 Hz), 1.60—1.50 (broad, 4H), 1.30—1.20 (broad, 4H); ^{13}C NMR (DMSO-d_6)

δ = 163.61, 150.81, 145.53, 100.67, 47.18, 28.21, 25.30. Found: C, 54.58; H, 5.95; N, 17.78%. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29%.

1,1′-(1,7-Heptanediyl)bis[uracil] (3e): Mp 227—230 °C; ^{1}H NMR ($CDCl_3$) δ = 8.82 (d, 2H, J = 2 Hz), 7.15 (d, 2H, J = 8 Hz), 5.70 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.72 (t, 4H, J = 7 Hz), 1.75—1.60 (m, 4H), 1.45—1.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ=163.49, 150.75, 144.35, 102.22, 48.67, 28.86, 28.53, 26.08. Found: C, 55.32; H, 6.22; N, 17.38%. Calcd for $C_{15}H_{20}N_4O_4 \cdot 1/2H_2O$: C, 54.70; H, 6.43; N, 17.01%.

1,1′-(1,9-Nonanediyl)bis[uracil] (3g): Mp 158—160 °C; ^{1}H NMR ($CDCl_3$) δ = 8.77 (broad, 2H, NH), 7.15 (d, 2H, J = 8 Hz), 5.70 (dd, 2H, J = 8 Hz, J = 2 Hz), 3.72 (t, 4H, J = 7.2 Hz), 1.68 (quintet, 4H, J=7.2 Hz), 1.4—1.25 (m, 10H); ^{13}C NMR ($CDCl_3$) δ = 163.53, 150.73, 144.39, 102.12, 48.81, 29.07, 28.96, 28.86, 26.21. Found: C, 58.87; H, 7.16; N, 16.38%. Calcd for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.09%.

1,1′-(1,10-Decanediyl)bis[uracil] (3h): Mp 158—159 °C; ^{1}H NMR ($CDCl_3$) δ = 8.30 (broad, 2H, NH), 7.14 (d, 2H, J = 8 Hz), 5.69 (dd, 4H, J = 8 Hz, J = 2 Hz), 3.72 (t, 4H, J = 7.2 Hz), 1.68 (quintet, 4H, J=7.2 Hz), 1.4—1.25 (m, 12H); ^{13}C NMR ($CDCl_3$) δ = 163.41, 150.67, 144.39, 102.09, 48.85, 29.13, 28.96, 28.94, 26.24. Found: C, 59.48; H, 7.13; N, 15.33%. Calcd for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.23; N, 15.46%.

1-(3-Bromopropyl)uracil (4a): Mp 88—89 °C (lit,[9] 85—87 °C); ^{1}H NMR ($CDCl_3$) δ = 9.23 (broad, 1H, NH), 7.26 (d, 1H, J = 8 Hz), 5.73 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.92 (t, 2H, J = 6.4 Hz), 3.44 (t, 2H, J = 6.4 Hz), 2.28 (quintet, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ = 163.56, 150.82, 144.71, 102.37, 47.52, 31.04, 29.69.

1-(4-Bromobutyl)uracil (4b): Mp 95—96 °C (lit,[9] 95—96 °C); ^{1}H NMR δ = 9.15 (broad, 1H, NH), 7.17 (d, 1H, J = 8 Hz), 5.73 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.78 (t, 2H, J = 6.4 Hz), 3.45 (t, 2H, J = 6.4 Hz), 1.95—1.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ = 163.56, 150.84, 144.08, 102.53, 47.79, 32.55, 29.26, 27.70.

1-(5-Bromopentyl)uracil (4c): Mp 80—81 °C (lit,[9] 57—59 °C); ^{1}H NMR ($CDCl_3$) δ = 9.54 (broad, 1H, NH), 7.16 (d, 1H, J = 8 Hz), 5.72 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.75 (t, 2H, J = 7 Hz), 3.42 (t, 2H, J = 7 Hz), 1.91 (quintet, 2H, J = 7 Hz), 1.73 (quintet, 2H, J = 7 Hz), 1.51 (quintet, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ = 164.30, 150.98, 144.45, 101.94, 48.32, 33.20, 31.77, 27.87, 24.63. Found: C, 41.61; H, 4.99; N, 10.79%. Calcd for $C_9H_{13}N_2O_2Br$: C, 41.40; H, 5.02; N, 10.73%.

1-(6-Bromohexyl)uracil (4d): Mp 76—77 °C; ^{1}H NMR ($CDCl_3$) δ = 10.06 (broad, 1H, NH), 7.19 (d, 1H, J = 8 Hz), 5.72 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.74 (t, 2H, J = 7 Hz), 3.41 (t, 2H, J = 7 Hz), 1.87 (quintet, 2H, J = 7 Hz), 1.72 (quintet, 2H, J = 7 Hz), 1.49 (quintet, 2H, J = 7 Hz), 1.36 (quintet, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ = 164.23, 151.13, 144.47, 102.21, 48.66, 33.62, 32.43, 28.86, 27.62, 25.53. Found: C, 43.57; H, 5.40; N, 10.13%. Calcd for $C_{10}H_{15}N_2O_2Br$: C, 43.65; H, 5.49; N, 10.18%.

1-(7-Bromoheptyl)uracil (4e): Mp 78—79 °C; ^{1}H NMR ($CDCl_3$) δ = 10.34 (broad, 1H, NH), 7.23 (d, 1H, J = 8 Hz), 5.73 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.74 (t, 2H, J = 7 Hz), 3.41 (t, 2H, J = 7 Hz), 1.85 (quintet, 2H, J = 7 Hz), 1.70 (quintet, 2H, J = 7 Hz), 1.50—1.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ = 164.52, 151.21, 144.67, 102.09, 48.74, 33.91, 32.53, 28.86, 28.23, 27.88, 26.16. Found: C, 45.62; H, 6.18; N, 9.80%. Calcd for $C_{11}H_{17}N_2O_2Br$: C, 45.69; H, 5.93; N, 9.69%.

1-(9-Bromononyl)uracil (4g): Mp 87—88 °C; ^{1}H NMR ($CDCl_3$) δ = 8.41 (d, 1H, J = 2 Hz, NH), 7.14 (d, 1H, J = 8 Hz), 5.69 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.72 (t, 2H, J = 7 Hz), 3.41 (t, 2H, J = 7 Hz), 1.85 (quintet, 2H, J = 7 Hz), 1.69 (quintet, 2H, J = 7 Hz), 1.43 (quintet, 2H, J = 7 Hz), 1.35—1.25 (m, 8H); ^{13}C NMR ($CDCl_3$) δ = 163.95, 150.91, 144.36, 102.04, 48.79, 33.92, 32.65, 29.12, 28.95, 28.94, 28.52, 27.98, 26.27. Found: C, 49.13; H, 6.58; N, 8.75%. Calcd for $C_{13}H_{21}N_2O_2Br$: C, 49.22; H, 6.67; N, 8.83%.

1-(10-Bromodecyl)uracil (4h): Mp 76—77 °C; ^{1}H NMR ($CDCl_3$) δ = 8.68 (d, 1H, J = 2 Hz, NH), 7.14 (d, 1H, J = 8 Hz), 5.69 (dd, 1H, J = 8 Hz, J = 2 Hz), 3.72 (t, 2H, J = 7 Hz), 3.41 (t, 2H, J = 7 Hz), 1.85 (quintet, 2H, J = 7 Hz), 1.68 (quintet, 2H, J = 7 Hz), 1.42 (quintet, 2H, J = 7 Hz), 1.35—1.25 (m, 10H); ^{13}C NMR ($CDCl_3$) δ = 163.89, 150.89, 144.43, 102.09, 48.89, 34.03, 32.78, 29.29, 29.27, 29.10, 29.03, 28.67, 28.10, 26.38. Found: C, 51.25; H, 7.00; N, 8.57%. Calcd for $C_{14}H_{23}N_2O_2Br$: C, 50.76; H, 7.00; N, 8.46%.

1,3-Di(5-bromopentyl)thymine (6c): Oil; ^{1}H NMR ($CDCl_3$) δ = 6.99 (s, 1H), 3.95 (t, 2H, J = 7 Hz), 3.73 (t, 2H, J = 7 Hz), 3.42 (t, 2H, J = 7 Hz), 3.41 (t, 2H, J = 7 Hz), 1.91 (quintet, 4H, J = 7 Hz), 1.72 (quintet, 2H, J = 7 Hz), 1.66 (quintet, 2H, J = 7 Hz), 1.50 (quintet, 4H, J = 7 Hz), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 163.70, 151.34, 138.32, 109.81, 49.21, 41.04, 33.66, 33.34, 32.29, 32.04, 28.18, 26.63, 25.45, 24.95, 13.04.

1,3-Di(5-bromopentyl)uracil (7c): Oil; ^{1}H NMR ($CDCl_3$) δ = 7.18 (d, 1H, J = 8 Hz), 5.71 (d, 1H, J = 8 Hz), 3.93 (t, 2H, J = 7 Hz), 3.76 (t, 2H, J = 7 Hz), 3.43 (t, 2H, J = 7 Hz), 3.42 (t, 2H, J = 7 Hz), 1.91 (quintet, 2H, J = 7 Hz), 1.90 (quintet, 2H, J = 7 Hz), 1.74 (quintet, 2H, J = 7 Hz), 1.66 (quintet, 2H, J = 7 Hz), 1.50 (quintet, 2H, J = 7 Hz), 1.49 (quintet, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ = 162.88, 151.30, 142.20, 101.52, 49.46, 40.73, 33.66, 33.32, 32.23, 31.97, 28.07, 26.54, 25.36, 24.89.

2,3-Dihydro-6-methyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (8): Mp 250—254 °C (lit,[20a] > 300°C); ^{1}H NMR (DMSO-d_6) δ = 7.62 (s, 1H), 4.64 (t, 2H, J = 8 Hz), 4.19 (t, 2H, J = 8 Hz), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6) δ = 171.60, 160.51, 133.96, 115.61, 66.52, 46.15, 13.47. The structure of **8** was further confirmed by the reaction of **8** with HBr in MeOH[20b] to give 1-(2-bromoethyl)-thymine (**2**) (n = 2) (51% yield): Mp 200—202 °C (lit,[20b] 209—210 °C); ^{1}H NMR (DMSO-d_6) δ = 11.32 (s, 1H), 7.56 (s, 1H), 4.02 (t, 2H, J = 6.4 Hz), 3.70 (t, 2H, J = 6.4 Hz), 1.76 (s, 3H); ^{13}C NMR (DMSO-d_6) δ = 164.12, 150.70, 141.38, 108.17, 48.46, 30.51, 11.83.

^{1}H NMR Study in Aqueous Solution. Each sample of **1**, **3**, and **5** was added into D_2O or the buffer solution at pD 1.0 (1.0 ml) containing the reference. After the mixture was heated and then cooled by standing in air, an insoluble material was removed by filtration. The concentrations of sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 as the reference were 0.6 mmol dm^{-3} in D_2O and 0.8 mmol dm^{-3} in the buffer solution at pD 1.0. The value of pD of the buffer solution was determined by means of a pH meter and was uncorrected. The ^{1}H NMR spectra were obtained from accumulation of 40—2000 times and observed over a range of 6002.4 Hz, corresponding to 32768 data points.

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