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Graphical Abstract

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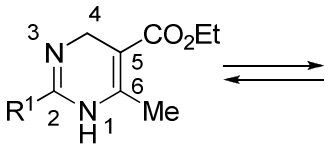
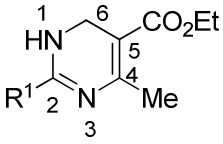
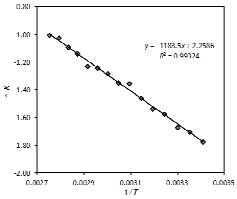


a: 1,4-DP



b: 1,6-DP

1 R^1 = SMe
2 R^1 = OMe
3 R^1 = NMe_2



van't Hoff plot of **1** in DMSO-d_6 (0.012 M)

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Experimental and theoretical studies on thermodynamics and properties of tautomers of 2-substituted 6(4)-methyl-1,4(1,6)-dihydropyrimidine-5-carboxylates

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Abstract: Experimental and theoretical studies on the thermodynamics and properties of 2-substituted 6(4)-methyl-1,4(1,6)-dihydropyrimidine-5-carboxylates were undertaken by ^{1}H NMR measurements and DFT (density functional theory) calculations. The ratios of tautomers **a**/**b** of dihydropyrimidines (DPs) **1**, **2**, and **3** were determined under various conditions to reveal the effects of temperature, solvent, and concentration on the thermodynamic data. The observed results, the free energy differences (ΔG), enthalpy differences (ΔH), and entropy differences (ΔS), are discussed in terms of the molecular structures, dipole moments (DM), and the electrostatic potential maps calculated by the DFT to clarify the nature of the DPs.

1. Introduction

Dihydropyrimidines (DPs) have received much attention from synthetic and medicinal chemists owing to their biological activities and unique physical and chemical characteristics.[1] They exhibit a wide range of activities for possible medicinal applications, such as calcium antagonists,[2] anti-MRSA agents (emmacin),[3] and selective and orally bioavailable inhibitors of Rho kinase (ROCK1).[4] The chemical structure of DPs is ambiguous and complicated owing to tautomerism and the isomerization of double bonds, because DPs theoretically have nine isomeric mixtures including tautomers.[1,5] Tautomerism in the DP system has not been sufficiently investigated to date.[6] A DP is usually observed as a single compound in an NMR spectrum. Namely, a proton transfer from one nitrogen atom to the other is very fast, and the NMR spectrum usually exhibits an average spectrum of two tautomers and so resembles the spectrum of a single compound just like that of an imidazole derivative. Therefore, it is unusual to observe separated isomers of 1,4-DP and 1,6-DP (Fig. 1).

Representative examples demonstrating that both 1,4- and 1,6-tautomers of DPs are sometimes independently observed in ^{1}H NMR spectra are shown in Fig. 2. For instance, Weis and co-workers studied the tautomerism of 6(4)-methyl-2,4(6)-diphenyl-1,4(1,6)-dihydropyrimidine **A** and observed two individual tautomers at –50 °C in a highly diluted $CDCl_3$ solution [0.001–0.003 M (mol L^{-1})].[7] On the other hand, Cho and co-workers synthesized DP derivatives **B** having various 2-substituents and an *o*-nitrophenyl group at the 4(6)-position and observed the individual tautomers of 2-CF_3 and 2-SMe derivatives from 25 °C to 70 °C at higher concentrations (0.007–0.212 M in C_6D_6),[8] although it is generally presumed that tautomers could sometimes be observed at very low temperatures below 0 °C and in highly diluted solutions.[7] They reported in the supporting data that the ratio of individual 1,4- and 1,6-tautomers changes regularly depending on temperature and concentration.[8]

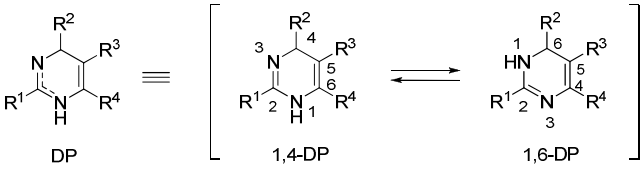

Fig. 1. Tautomerism of dihydropyrimidine.

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Recently, Cho, Nishimura and co-workers reported that individual tautomers of 2-SMe derivative **C** and derivatives **D** were also observed over some ranges of temperatures in DMSO-d_6 and $CDCl_3$ (0.012–0.050 M).[9,10] However, experimental and theoretical studies of the thermodynamics and properties of DPs have not been carried out in detail.

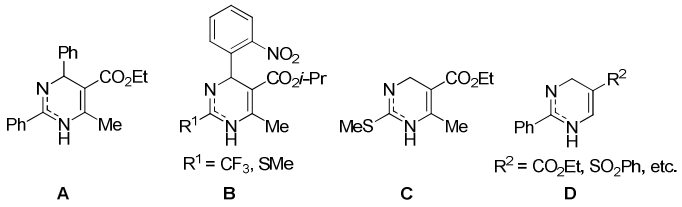


Fig. 2. Examples of dihydropyrimidines observed as their individual tautomers.

Therefore, further ^{1}H NMR studies should be undertaken to clarify the nature of tautomers of novel DPs at various temperatures, in polar or nonpolar solvents, and at several concentrations. In addition, DFT (density functional theory) calculations may prove interesting to explain the cause of the ratio of tautomers regularly changing and to determine their properties.

Hence, we will report experimental results on the regular changes in the ratios of tautomers **a** and **b** of DPs **1**, **2**, and **3** (Fig. 3) under various conditions (temperature, solvent, and concentration) and describe the findings obtained from thermodynamic studies and the properties of several DPs using van't Hoff equations, free energy differences (ΔG), enthalpy differences (ΔH), dipole moments (DM), and electrostatic potential maps.

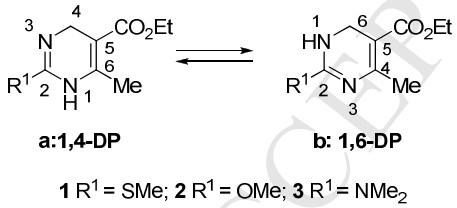
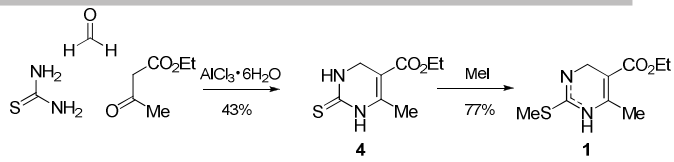


Fig. 3. Chemical structures of dihydropyrimidines **1**–**3** and their tautomers.

2. Results and Discussion

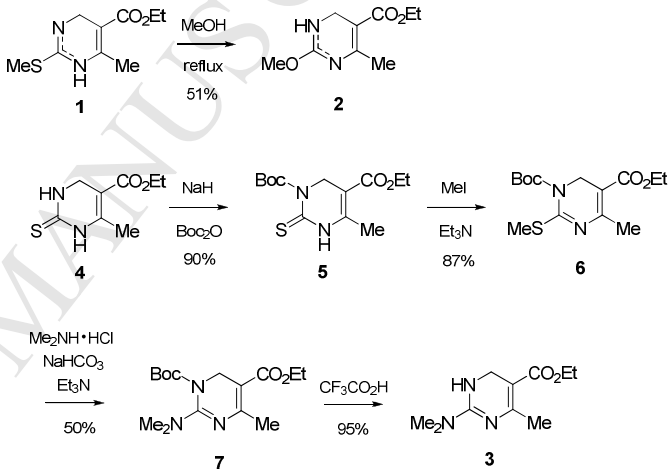
*2.1. Synthesis of DPs **1**, **2**, and **3***

DP **1** was prepared according to a modified procedure based on our previous method.[9] Namely, a three-component Biginelli reaction of thiourea, formaldehyde, and ethyl acetoacetate using aluminum trichloride hexahydrate as a catalyst gave dihydropyrimidine-2-thione **4**. The *S*-methylation reaction of **4** furnished HI salts of **1**, and following basic workup and purification with SiO_2 chromatography gave DP **1**.



Scheme 1. Synthesis of dihydropyrimidine **1**.

DPs **2** and **3** were synthesized as follows (Scheme 2). 2-Methoxy derivative **2** was synthesized in 51% yield by heating **1** in MeOH. 2-Dimethylamino derivative **3** was prepared from **4** in four steps. Regioselective protection with a Boc group (NaH/Boc_2O) afforded **5** in 90% yield, followed by methylation (MeI/Et_3N) to give **6** in 87% yield. Subsequently, the substitution reaction of **6** with dimethylamine hydrochloride under basic condition provided **7** in 50% yield, followed by deprotection of the *N*-Boc group under acidic condition to yield **3** in 95% yield.[9]



Scheme 2. Synthesis of dihydropyrimidines **2** and **3**.

The ^{1}H NMR spectra of SMe-DP **1** and OMe-DP **2** exhibited a mixture of tautomers **a** and **b** at 20 °C (293 K) in DMSO-d_6, respectively. Prior to an NOE study of SMe-DP **1**, the singlet (2.11 ppm) was ascribed to the 6-Me group by the heteronuclear multiple bond coherence (HMBC) correlation between the 6-Me group and 5-carbon (93.9 ppm) (Fig. 4 and Supplementary data Fig. S1). Subsequently, an NOE (2.2%) was observed between the 1-NH proton (9.28 ppm) and the 6-Me group. Thus, the major tautomer was assigned as 1,4-DP. Similarly, an NOE (2.3%) of OMe-DP **2** was found between the 1-NH proton and the 6-Me group, and the major tautomer was assigned to be 1,4-DP; in addition, an NOE (2.6%) was observed between the 1-NH proton and 6-H in the minor tautomer 1,6-DP (Fig. 5). However, in the case of NMe_2-DP **3**, the spectrum suggested a sole isomer, 1,6-DP (Fig. 6). This should not be an average spectrum of 1,4- and 1,6-DP but a single 1,6-tautomer because of the presence of NOE (3.1%) correlations between the NH proton and the NMe protons, and the observed NOE (1.9%) between the NH proton and 6-H (Fig. 6), as well as the results of the theoretical studies described in the later section.

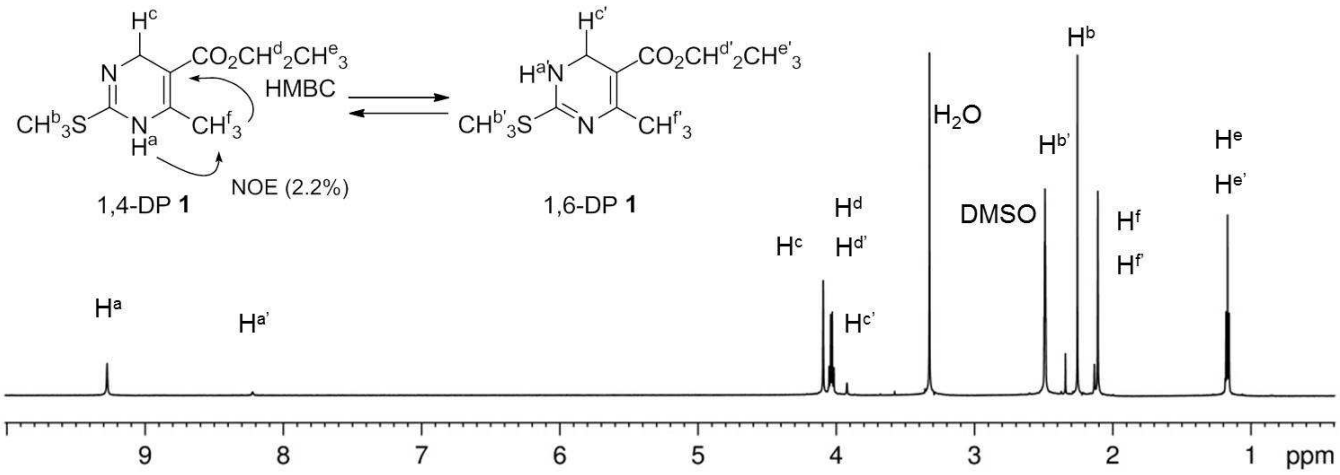


Fig. 4. ^{1}H NMR spectrum of dihydropyrimidine **1** [DMSO-d_6, 0.012 M, 20 °C (293 K)].

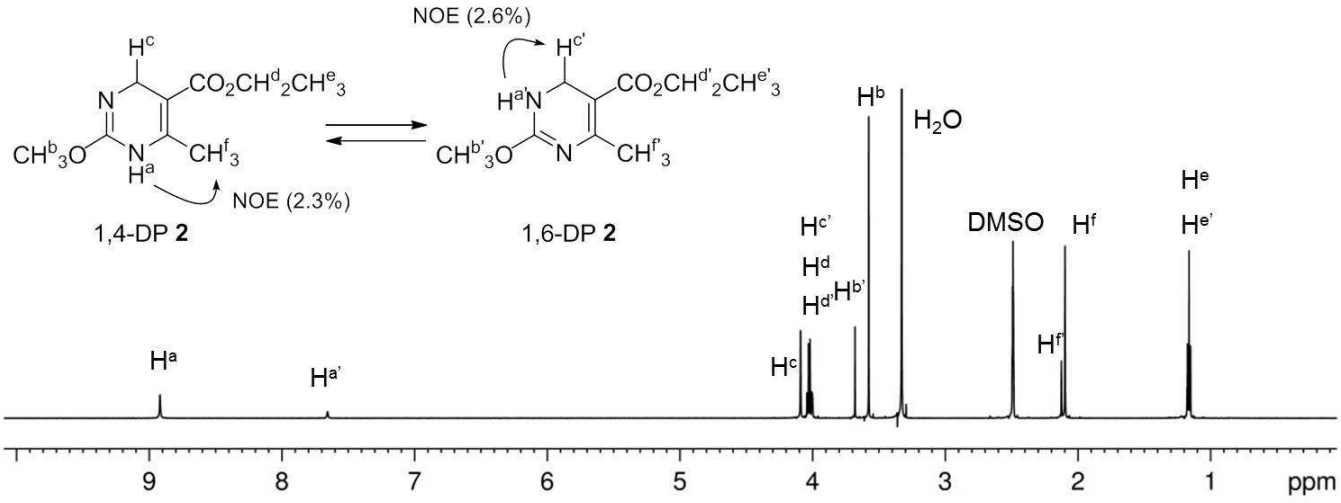


Fig. 5. ^{1}H NMR spectrum of dihydropyrimidine **2** [DMSO-d_6, 0.012 M, 20°C (293 K)].

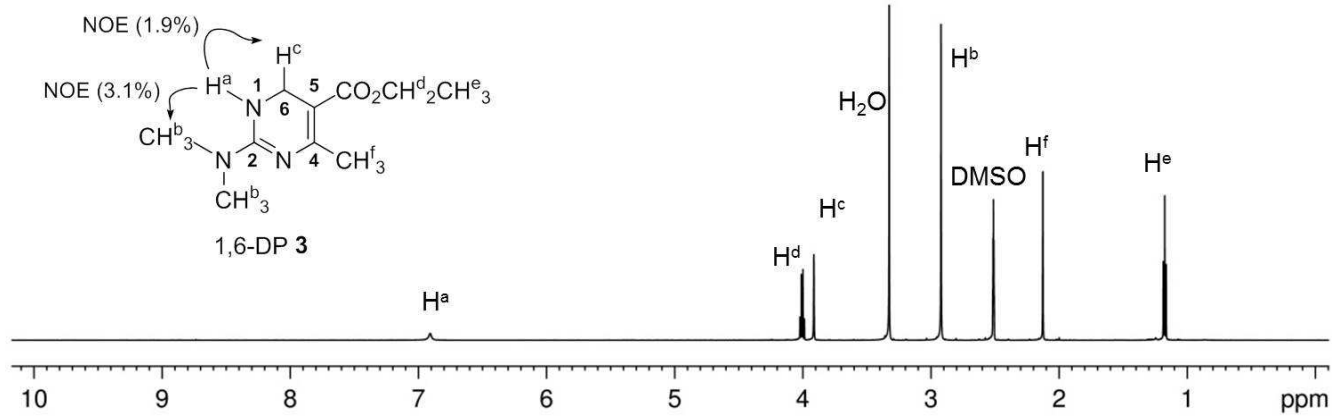


Fig. 6. ^{1}H NMR spectrum of dihydropyrimidine **3** [DMSO-d_6, 0.012 M, 25 °C (298 K)].

Table 1. Ratios of 1,4- and 1,6-tautomers of **1** at various temperatures and concentrations (DMSO-d_6)

Temp.(°C) / (K: kelvin)	Ratio 1,4-DP:1,6-DP		
	0.012 M	0.050 M	0.12 M
20/293	5.92:1.00	6.49:1.00	6.93:1.00
25/298	5.51:1.00	6.18:1.00	6.67:1.00
30/303	5.32:1.00	6.05:1.00	6.29:1.00
35/308	4.83:1.00	5.72:1.00	5.97:1.00
40/313	4.65:1.00	5.38:1.00	5.64:1.00
45/318	4.30:1.00	5.00:1.00	5.30:1.00
50/323	3.87:1.00	4.79:1.00	5.04:1.00
55/328	3.85:1.00	4.48:1.00	4.83:1.00
60/333	3.60:1.00	4.22:1.00	4.73:1.00
65/338	3.47:1.00	4.00:1.00	4.56:1.00
70/343	3.43:1.00	3.85:1.00	4.33:1.00
75/348	3.12:1.00	3.64:1.00	4.02:1.00
80/353	2.99:1.00	3.43:1.00	3.88:1.00
85/358	2.80:1.00	3.19:1.00	3.74:1.00
90/363	2.74:1.00	3.11:1.00	3.55:1.00

Table 2. Ratios of 1,4- and 1,6-tautomers of **2** at various temperatures and concentrations (DMSO-d_6)

Temp.(°C) / (K: kelvin)	Ratio 1,4-DP:1,6-DP		
	0.012 M	0.050 M	0.12 M
20/293	2.74:1.00	2.93:1.00	3.09:1.00
25/298	2.69:1.00	2.86:1.00	3.03:1.00
30/303	2.62:1.00	2.79:1.00	2.91:1.00
35/308	2.57:1.00	2.67:1.00	2.84:1.00
40/313	2.52:1.00	2.60:1.00	2.77:1.00
45/318	2.44:1.00	2.55:1.00	2.68:1.00
50/323	2.37:1.00	2.49:1.00	2.58:1.00
55/328	2.33:1.00	2.37:1.00	2.49:1.00
60/333	2.28:1.00	2.31:1.00	2.42:1.00
65/338	2.22:1.00	2.19:1.00	2.34:1.00
70/343	2.14:1.00	2.13:1.00	2.31:1.00
75/348	2.06:1.00	2.06:1.00	2.23:1.00
80/353	2.00:1.00	1.99:1.00	2.17:1.00
85/358	1.97:1.00	1.90:1.00	2.10:1.00
90/363	1.90:1.00	1.87:1.00	2.05:1.00

2.2. Determination of the population of DP tautomers

The ^{1}H NMR spectra of **1** and **2** were measured at various temperatures in three solvents, such as a polar solvent (DMSO-d_6), a less polar solvent ($CDCl_3$), and a nonpolar solvent (C_6D_6). To investigate the effect of concentration, the measurements were independently performed at three different concentrations (0.012 M, 0.050 M, and 0.12 M in DMSO-d_6 and $CDCl_3$, and 0.0050 M, 0.012 M, and 0.050 M in C_6D_6). All the measurements were carried out under an argon atmosphere in order to prevent oxidation to pyrimidines. The ratios of 1,4- and 1,6-DPs were determined using integrated intensities of their NH signals. The data for **1** and **2** in DMSO-d_6 are provided in Tables 1 and 2, respectively, and the data from the other solvents ($CDCl_3$ and C_6D_6) at three concentrations are given in the supplementary data. The ratios (1,4-DP *vs* 1,6-DP) of **1** and **2** regularly changed as the temperature increased from 20 °C to 90 °C at 0.012 M, 0.050 M, and 0.12 M in DMSO-d_6. For instance, the ratios of the 1,4-DP to 1,6-DP of **1** decreased in 0.012 M DMSO-d_6 from 5.92:1.00 at 20 °C to 2.74:1.00 at 90°C (Table 1). This trend was also observed in the measurements of **1** in $CDCl_3$ and C_6D_6 (Supplementary data). Similarly, the ratios of 1,4-DP to 1,6-DP of **2** in DMSO-d_6 decreased as shown in Table 2, as well as in $CDCl_3$ and C_6D_6 (Supplementary data).

2.3. Thermodynamics of tautomers of DPs from van't Hoff plots

The thermodynamics of tautomerization was analyzed using van't Hoff plots by observing the equilibrium constant K ([1,4-DP]/[1,6-DP]) as a function of temperature T (K). The van't Hoff plots of **1** and **2** in DMSO-d_6 at 0.012 M are shown in Figs. 7 and 8, respectively, as typical cases (other plots are given in the supplementary data). Both plots showed a nearly linear correlation between $1/T$ and ln K, and the enthalpy difference ($\Delta H°$) and entropy difference ($\Delta S°$) were obtained by least squares fitting (experimental section 4.3). The thermodynamic parameters as well as the chemical shifts of the NH protons are compiled in Table 3.

For each entry, the $\Delta H°$ and $\Delta S°$ values are positive. This means that 1,4-DP is enthalpically favorable to 1,6-DP, and that the conversion from 1,4-DP to 1,6-DP results in an increase in molecular freedom in solution. The positive $\Delta G°$ values (namely $K < 1$) mean that 1,4-DP is more abundant than 1,6-DP at 298 K. Under the same conditions, the $\Delta G°$ value of **1** is always larger than that of **2** (e.g., 4.24 and 2.48 kJ mol^{-1} for **1** and **2**, respectively, in DMSO-d_6 at 0.012 M). The $\Delta G°$ values decrease, namely the population of 1,4-DP increases, in the order DMSO-d_6, $CDCl_3$, and C_6D_6 at the same concentration for each compound. There are small effects of concentration on the tautomer population: the population of the 1,4-isomer constantly increases with increasing concentration except for **1** in C_6D_6. These results will be discussed later with the aid of theoretical calculations.

2.4. DFT calculations of DP tautomers

In order to obtain further insight into the experimental results, we carried out DFT calculations for the two tautomers of DPs **8**–**12** (Fig. 9). Compounds **9**–**11** are model compounds of **1**–**3**, respectively, where the ethyl group in the ester moiety is replaced by a methyl group for simplification.[11] Substituent-free derivative **8** and CF_3-substituted derivative **12** (an analog of **B**: $R^1 = CF_3$ in Fig. 2) were also treated as a series of compounds, although the synthesis of the corresponding ethyl esters was unsuccessful. The structures of the two tautomers were optimized at the M06-2X/6-31G(d) level, because this function tended to give reliable thermochemical parameters for common organic compounds.[12] The thermodynamic parameters were obtained by a frequency analysis of each energy-minimum structure.

*2.4.1. Calculations of tautomers of **8***

The structural optimization of **8a** and **8b** gave one energy-minimum structure each, as shown in Fig. 10. In the optimized structures of **8a** and **8b**, the six-membered rings are almost planar regardless of the positions of the double bonds. The two compounds have similar conformations with respect to the ester moiety: the plane consisting of the COO moiety is coplanar with the six-membered ring so as to the carbonyl oxygen atom is away from the ring methyl group. These structural features are common in the X-ray structures of the other 1,4-DP and 1,6-DP derivatives.[9, 13]

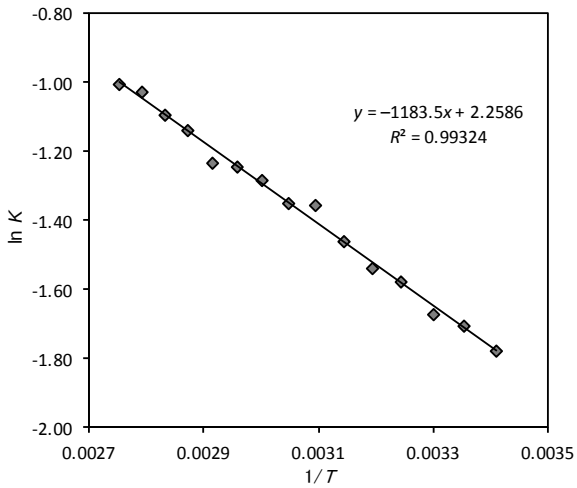


Fig. 7. van't Hoff plot of **1** in DMSO-d_6 (0.012 M).

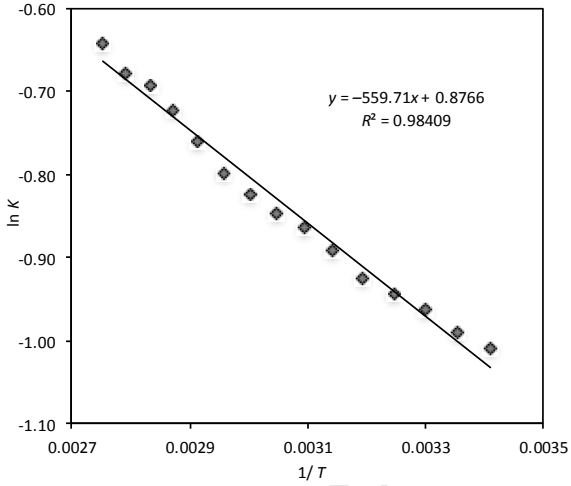


Fig. 8. van't Hoff plot of **2** in DMSO-d_6 (0.012 M).

Table 3. Effects of solvents and concentration on thermodynamic parameters for tautomerization of **1** and **2**. [a]

Compound	Solvent [b]	Concentration (mol L^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J mol^{-1} K^{-1})	$\Delta G°$ [c] (kJ mol^{-1})	K_{298} [c]	δNH [d] 1,4-DP	δNH [d] 1,6-DP
1	DMSO-d_6	0.012	9.84 ± 0.49	18.8 ± 1.5	4.24	0.180	9.25	8.20
1	DMSO-d_6	0.050	9.70 ± 0.49	17.2 ± 1.6	4.59	0.157	9.25	8.20
1	DMSO-d_6	0.12	8.43 ± 0.32	12.6 ± 1.0	4.69	0.151	9.25	8.19
1	$CDCl_3$	0.012	7.38 ± 0.57	13.7 ± 1.9	3.31	0.263	5.89	5.16
1	$CDCl_3$	0.050	7.25 ± 0.51	12.5 ± 1.7	3.51	0.242	6.00	5.24
1	$CDCl_3$	0.12	7.93 ± 0.39	13.2 ± 1.3	4.00	0.199	6.15	5.37
1	C_6D_6	0.0050	5.12 ± 0.32	8.5 ± 1.1	2.59	0.351	5.03	3.77
1	C_6D_6	0.012	4.79 ± 0.36	7.5 ± 1.2	2.55	0.357	5.06	3.79
1	C_6D_6	0.050	3.84 ± 0.28	3.3 ± 0.9	2.85	0.316	5.23	– [e]
2	DMSO-d_6	0.012	4.65 ± 0.35	7.3 ± 1.1	2.48	0.368	8.89	7.63
2	DMSO-d_6	0.050	5.87 ± 0.41	10.8 ± 1.3	2.64	0.344	8.89	7.63
2	DMSO-d_6	0.12	5.31 ± 0.19	8.6 ± 0.6	2.75	0.330	8.89	7.63
2	$CDCl_3$	0.012	4.91 ± 0.44	9.2 ± 1.5	2.16	0.419	5.60	4.71
2	$CDCl_3$	0.050	4.47 ± 0.25	7.1 ± 0.9	2.35	0.387	5.67	4.77
2	$CDCl_3$	0.12	4.86 ± 0.46	7.3 ± 1.6	2.69	0.338	5.79	4.87
2	C_6D_6	0.0050	1.56 ± 0.10	2.4 ± 0.4	0.86	0.707	4.79	3.54
2	C_6D_6	0.012	1.50 ± 0.05	2.1 ± 0.2	0.89	0.699	4.80	3.56
2	C_6D_6	0.050	2.06 ± 0.13	3.8 ± 0.5	0.92	0.691	4.93	3.69

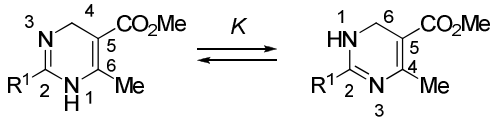
a. Symbol ° refers to the standard condition (298 K, 1 atm).

b. See footnote of Table 6 for dielectric constants of these solvents.

c. Calculated according to the equations of $\Delta G° = \Delta H° - T\Delta S°$ and $\Delta G° = -RT\ln K$ (298 K).

d. At 298 K.

e. Overlapped with other signals.



8 R^1 = H
9 R^1 = SMe
10 R^1 = OMe
11 R^1 = NMe_2
12 R^1 = CF_3

Fig 9. Chemical structures of dihydropyrimidines **8**–**12** for DFT calculations.

Table 4. Calculated data for the optimized structures of tautomers **8a** and **8b** at M06-2X/6-31G(d) level. [a]

	E° (au)	*H*° (au)	*G*° (au)	μ (D)[b]
8a	–532.481181	–532.295543	–532.344546	5.25
8b	–532.481439	–532.295693	–532.345024	1.70
8b–8a	–0.000257 (–0.68)[c]	–0.000150 (–0.39)[c]	–0.000478 (–1.25)[c]	

[a] In au (atomic unit) unless otherwise noted. 1 au = 2625.50 kJ mol^{-1}.

[b] Dipole moment in debye (D), 1 D = 3.33564×10^{-30} C m.

[c] In kJ mol^{-1}.

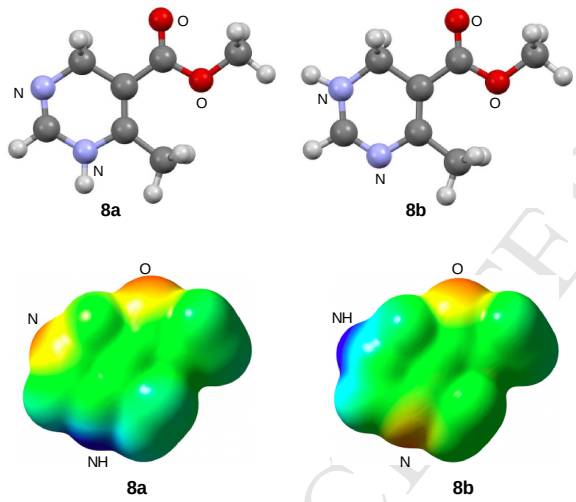


Fig. 10. Calculated structures of **8a** and **8b** at M06-2X/6-31G(d) level and their electrostatic potential maps (red: electron-rich, blue: electron-deficient).

The thermodynamic parameters and dipole moments of optimized **8a** and **8b** are listed in Table 4. The data indicate that **8b** is slightly more stable than **8a**; the energy differences are 0.39 kJ mol^{-1} in *H*° and 1.25 kJ mol^{-1} in *G*°. The comparable stabilities of the two tautomers of the parent DP were predicted in a previous theoretical study.[14] From the free energy difference (ΔG°), the equilibrium constant K_{298} ([**8b**]/[**8a**]) was calculated to be 1.66 (Table 5). The thermodynamic preference for 1,6-DP **8b** is attributable to the extended conjugation along the three double bonds. The calculated dipole moments mean that **8a** (5.25 D) is much more polar than **8b** (1.70 D). Qualitatively, this difference can be explained by the dipole moments of the two polar C=O and C=N double bonds. In 1,4-DP **8a**, the dipole moments direct in nearly the same direction to enhance the net dipole moment. On the other hand, the two dipole moments cancel out to some extent in 1,6-DP **8b**. The difference in molecular polarity can be confirmed from the electrostatic maps in Fig. 10. In the two compounds, electron-rich regions are distributed around the carbonyl oxygen atom and sp^2 nitrogen atom, and electron-deficient regions are distributed around NH moiety. This feature is well understood in terms of the resonance structures shown in Fig. 11 where the C=O and NH moieties contribute negative and positive charges, respectively.

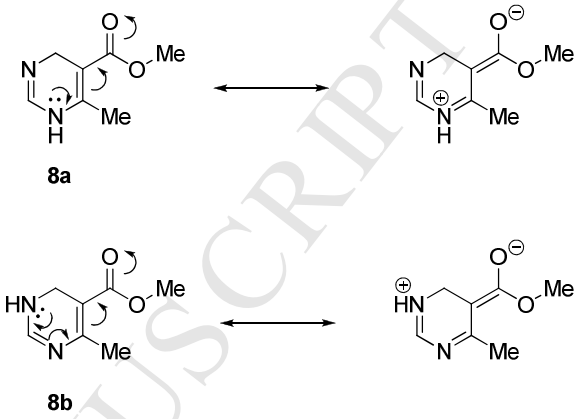


Fig.11. Resonance structures of **8a** and **8b.**

2.4.2. Calculations for 2-substituted derivatives

Similar calculations were also carried out for the 2-substituted derivatives **9**–**12**. For **9** and **10**, we calculated structures from the conformers shown in Fig. 12 that differ in the conformation of the OMe or SMe group. We obtained two energy-minimum structures of **9a** and **9b**, where the Me group in the SMe group is nearly coplanar with the attached C=N bond in either *syn* or *anti* conformation. The *syn* forms, 1,4-DP *syn*-**9a** and 1,6-DP *syn*-**9b**, are much more stable than the corresponding *anti* forms, 1,4-DP *anti*-**9a** and 1,6-DP *anti*-**9b**, in the two tautomers. Therefore, we can ignore the presence of the *anti* forms under ordinary conditions. The *anti* forms are destabilized by the steric interaction between the Me group and the adjacent NH group. For the methoxy derivatives **10**, only *syn* forms were obtained as energy-minimum structures. Although **10b** gave two structures that differ in the conformation of the six-membered ring, only the stable one is considered in the following discussion.

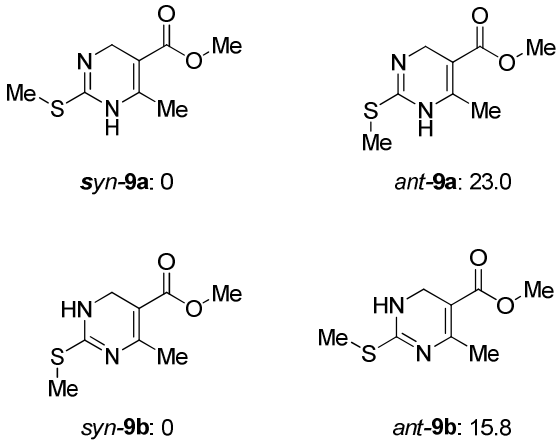


Fig. 12. Two energy-minimum conformers of **9a** and **9b**. Values are relative energies to the *syn* forms in kJ mol^{-1}.

The calculated energies of **8**–**12** are compiled in Table 5, where only relative energies of 1,4-DP and 1,6-DP are given. The free energy differences increase in the order of **11**(NMe_2) << **10**(OMe) < **8**(H) ≈ **9**(SMe) < **12**(CF_3). The value of **11** is large and negative, meaning that most molecules should exist as 1,6-DP in equilibrium. In contrast, the positive value of **12** means that 1,6-DP is less stable than 1,4-DP. These results mean that electron donating groups tend to stabilize 1,6-DP relative to 1,4-DP. In 1,6-DP, the substituent at the 2-position is bonded to a terminal carbon of the three conjugated double bonds. Therefore, the electron donating group should result in stabilization by resonance, as shown as the resonance structures of **11b** in Fig. 13. The dipole moment of 1,4-DP is larger than that of its tautomer 1,6-DP in all the substituted derivatives as discussed for **8**. As for 1,6-DP, the dipole moment of **11b** (4.41 D) is much larger than those of the other derivatives (1.42–1.99 D). This feature also supports the significant contribution of the charge-separated resonance structure mentioned previously. In fact, the NMe_2 nitrogen atom is nearly planar in the optimized structure of **11b**, where the single bonds in the conjugated moiety are significantly shorter than the corresponding bonds of **11a** (Fig. 14). For example, the Me_2N–C single bond of **11b** is shorter by 0.033 Å than that of **11a**.

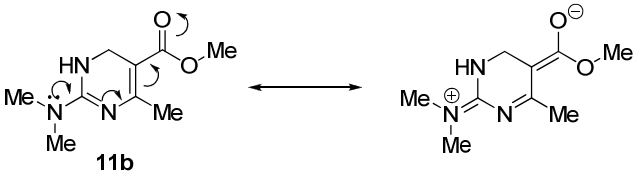


Fig. 13. Resonance structures of **11b**.

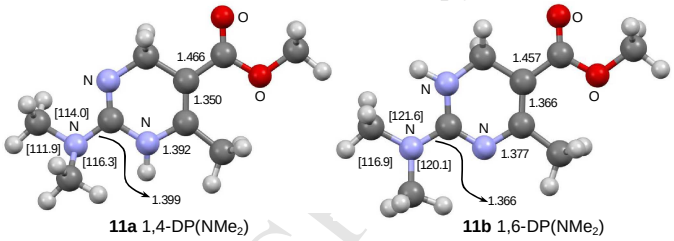


Fig. 14. Calculated structures of **11a** and **11b**. Selected bond lengths (Å) and bond angles [°]

Table 5. Thermodynamic data and dipole moments of 2-substituted DP derivatives **8**–**12** calculated at M06-2X/6-31G(d) level. [a]

	ΔE (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta G°$ (kJ mol^{-1})	K_{298}([**b**]/[**a**])	μ (D) [b]		σ_p^0 [c]
					a	**b**	
8	–0.68	–0.39	–1.25	1.66	5.25	1.70	0.00
9	–2.84	–3.00	–1.21	1.63	3.44	1.42	0.12
10	–6.47	–5.89	–3.52	2.46	3.98	1.99	–0.10
11	–13.6	–13.6	–16.3	714	4.76	4.41	–0.43
12	1.28	1.69	2.18	0.41	4.98	1.59	0.51

[a] Energies are relative values, **b**(1,6-DP)–**a**(1,4-DP), in kJ mol^{-1}. Negative and positive values mean the preference of 1,6-DP and 1,4-DP, respectively.

[b] Dipole moment in debye (D), 1 D = 3.33564×10^{-30} C m.

[c] Hammett constants of the 2-substituents (Ref. 15).

Table 6. Solvent effects on standard free energy differences ($\Delta G°$) and standard enthalpy differences ($\Delta H°$) of 2-substituted DP derivatives **8**–**12** calculated at M06-2X/6-31G(d) level in kJ mol^{-1} [a]

Solvent	ε [b]	**8**		**9**		**10**		**11**		**12**	
		$\Delta H°$	$\Delta G°$	$\Delta H°$	$\Delta G°$	$\Delta H°$	$\Delta G°$	$\Delta H°$	$\Delta G°$	$\Delta H°$	$\Delta G°$
vacuum	1	–0.39	–1.25	–3.00	–1.21	–5.89	–3.52	–13.6	–16.3	1.69	2.18
C_6H_6	2.27	0.68	–0.80	–1.85	0.16	–5.10	–4.60	–15.6	–18.6	2.46	1.96
$CHCl_3$	4.71	1.56	0.00	–0.86	1.25	–4.36	–4.77	–16.5	–19.2	2.87	2.71
THF	7.58	2.00	0.50	–0.45	1.04	–3.99	–4.58	–16.7	–19.1	3.07	2.86
Acetone	20.5	2.60	1.30	0.08	0.74	–3.48	–3.83	–17.0	–18.7	3.33	3.00
DMSO	46.8	2.83	1.63	0.27	0.68	–3.30	–3.53	–17.1	–18.5	3.42	3.00

[a] Relative values, **b**(1,6-DP)–**a**(1,4-DP).

[b] Dielectric constants as parameters for solvent polarity.

2.4.3. Solvent effects

In order to consider solvent effects, the calculations were performed by adopting the polarizable continuum model (PCM).[16] The structures and energies of two tautomers of **8**–**12** (only stable conformers for **10** and **11**) were calculated with the parameters for benzene, chloroform, THF, acetone, and DMSO. The calculated free energy and enthalpy differences between the two tautomers are listed in Table 6. For **8**, the $\Delta G°$ values slightly increase with increasing solvent polarity. The positive value in DMSO means that 1,4-DP is more stable than 1,6-DP, contrary to the value in vacuum. This tendency means that the polar 1,4-DP tautomer is more stabilized by solvation in polar solvents than the 1,6-DP tautomer. A similar tendency was observed for **12**, even though the solvent effect was rather small. The solvent effects on the free energy differences were irregular for compounds **9**, **10**, and **11**: the value in $CHCl_3$ was maximum for **9** while the values were minimum for **10** and **11**. In contrast, the $\Delta H°$ values change regularly with solvent polarity. Polar solvents tend to stabilize 1,4-DP relative to 1,6-DP for **8**–**10**, and **12**, and vice versa for **11**. The irregular changes in the relative free energies are attributed to entropy factors, although it is not straightforward to understand this tendency from available data.

2.5. Comparison with the experimental data

The calculated results for a series of compounds were compared with the experimental results of **1**–**3**. The fact that NMe_2 compound **3** exists only as 1,6-DP is consistent with the calculation for **11**, in which 1,6-DP is much more stable than 1,4-DP (>18 kJ mol^{-1} in solution). The calculations for **9** showed that 1,6-DP was more stable than 1,4-DP in vacuum and vice versa in solution. This trend means that polar 1,4-DP is stabilized by solvation in solution compared with 1,6-DP. In fact, the observed entropy differences are large and positive especially in polar DMSO, and these values mean effective solvation for 1,4-DP molecules. The observed free energy differences for **1** were not always reproduced by the theoretical calculations for **9**, where the calculated values are smaller by 2–4 kJ mol^{-1} than the observed values in the three solvents. These differences between the experimental and theoretical data are larger for the OMe compounds (ca. 5 kJ mol^{-1} for **2** and **10**) than for the SMe compounds (**1** and **9**). These inconsistencies suggest that factors stabilizing 1,4-DP should be underestimated or not be considered in the theoretical calculations. This is attributable to the limitations of the PCM method that lacks specific solvation effects such as hydrogen bonds. Intermolecular interactions should be important in these molecules, which have polar moieties as well as hydrogen bond donor and acceptor moieties.[13]

Weis *et al.* pointed out that DP derivatives form oligomers or complexes with solvent molecules via hydrogen bonds in solutions.[7] The chemical shift of the NH protons is a good indication of the formation of hydrogen bonds. The data of **1** and **2** in Table 3 show that the deshielding of the NH protons in polar aprotic DMSO-d_6 (ca. δ 9) is due to strong hydrogen bond with solvent molecules at any concentration. If each molecule behaves independently as solvated species, the concentration effect on the tautomer ratios should be absent. The presence of the small concentration effect indicates the presence of interactions between solvated species or changes in the solvation state so as to stabilize the polar 1,4-DP at high concentrations. In $CDCl_3$ and C_6D_6, the chemical shifts of the NH protons (δ 4.8–6.0) are smaller than those in DMSO-d_6, and they increase with increasing concentration. The latter phenomenon can be explained by intermolecular interactions: namely, the populations of monomer, dimer, and possibly higher oligomers depend on the concentration. The underestimation of the stability of 1,4-DP mentioned is also attributable to intermolecular interactions because this polar tautomer should form strong hydrogen bonds in solution. These treatments are too difficult in conventional theoretical calculations to reproduce the observed thermodynamic data quantitatively.

3. Conclusion

Experimental and theoretical studies on the thermodynamics and properties of 2-substituted 6(4)-methyl-1,4(1,6)-dihydropyrimidine-5-carboxylates were undertaken by ^{1}H NMR measurements and DFT calculations. For **1** and **2**, the ^{1}H NMR spectra revealed the presence of two tautomers, and the major and minor tautomers were assigned to 1,4-DPs and 1,6-DPs based on the NOE experiments. The ratios of the two tautomers regularly changed depending on the temperature, solvent, and concentration. In contrast, the NMe_2 compound existed solely as 1,6-DP. The observed tautomer ratios at various temperatures were analyzed using van't Hoff plots to give the enthalpy differences ($\Delta H°$), entropy differences ($\Delta S°$), and free energy differences ($\Delta G°$) for tautomerization of 1 and 2, where 1,4-DP was found to be enthalpically favored and entropically disfavored relative to 1,6-DP. In general, 1,4-DP was the major tautomer and its population increased at low temperatures, in polar solvents, and at high concentrations.

The structures and properties of these tautomers were investigated by DFT calculations of analogous derivatives **8**–**12** having various 2-substituents. The calculated thermodynamic data revealed the effects of 2-substituents on the tautomer ratios, and explained well the predominance of 1,6-DP for the NMe_2 compound. The calculated large dipole moments of 1,4-DPs were consistent with the preference for this polar tautomer in polar solvents due to solvation. The theoretical calculations tended to underestimate the stability of 1,4-DPs relative to 1,6-DPs. This finding as well as the presence of concentration effects is attributable to strong hydrogen bonds of 1,4-DP molecules with other substrate and solvent molecules. Further calculations with precise solvation models will reveal the role of these intermolecular interactions in determining the thermodynamic characteristics.

Few experimental and theoretical studies on the tautomerism have been carried out so far and our works may provide useful information to researchers in the near future who will study the tautomerism of dihydropyrimidines, imidazoles and other tautomeric heterocycles.

4. Experimental section

4.1. General

Melting points were determined on Yanaco micro melting point apparatus and uncorrected. IR spectra were measured on SHIMADZU FTIR-8300 spectrometer. ^{1}H NMR spectra were recorded on a Varian Mercury (300, 400 MHz) or a Bruker AVANCE III 600 (600 MHz) with tetramethylsilane (0 ppm), CD_3OD (3.30 ppm), DMSO-d_6 (2.49 ppm), or C_6D_6 (7.15 ppm), as an internal standard. The abbreviations of signal patterns are follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a Varian Mercury (75, 100 MHz) or a Bruker AVANCE III 600 (150 MHz) with CD_3OD (49.0 ppm) or DMSO-d_6 (39.7 ppm) as an internal

standard. Mass spectra were recorded on a JMS-DX303, JMS-700 or JMS-T100GC spectrometer. Flash column chromatography was performed on silica gel 60N (Kanto, 40-60 μm) using indicated solvent. Reactions and fractions of chromatography were monitored by employing pre-coated silica gel 60 F_{254} plates (Merck).

*4.2. Synthesis of compounds **1**–**4***

*4.2.1. Ethyl 6-methyl-2-(methylthio)-1,4-dihydropyrimidine-5-carboxylate and ethyl 4-methyl-2-(methylthio)-1,6-dihydropyrimidine-5-carboxylate (**1**)*

A mixture of thiourea (1.98 g, 26.0 mmol), 37% formaldehyde aqueous solution (1.62 g, 20.0 mmol), ethyl acetoacetate (2.60 mL, 20.6 mmol), and aluminum trichloride hexahydrate (483 mg, 2.00 mmol) in EtOH (40 mL) was heated at reflux for 6 h. After cooled in ice bath for 1 h, the precipitate was collected by filtration. The filtrate was washed with EtOH, and dried to give the dihydropyrimidine-2-thione **4** (1.74 g, 8.69 mmol, 43%). ^{1}H NMR (DMSO-d_6) δ: 1.18 (3H, t, J = 7.2 Hz), 2.16 (3H, s), 3.87 (2H, s), 4.06 (2H, q, J = 7.2 Hz), 8.96 (1H, s), 9.95 (1H, s). To a suspension of **4** (1.74 g, 8.69 mmol) in MeOH (17 mL) was added MeI (1.40 mL, 22.5 mmol) at rt, and the reaction mixture was heated at reflux for 3 h. $CHCl_3$ (30 mL) and saturated $NaHCO_3$ aqueous solution (15 mL) were added, and the organic layer was separated. The organic materials were extracted with $CHCl_3$ (30 mL), and combined organic layers were washed with brine (10 mL), and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [CH_2Cl_2-EtOAc (10:1 to 1.5:1)] to give **1** (1.44 g, 6.72 mmol, 77%) as a pale yellow solid. Mp 113–115 ºC (n-hexane-$CHCl_3$); IR (KBr) cm^{-1}: 3318, 1668, 1647, 1171; ^{1}H NMR (0.012 M, 20°C in DMSO-d_6) δ: 1.17 (3H^e and 3H$^{e'}$, t, J = 7.2 Hz), 2.11 (3H^f, s), 2.13 (3H$^{f'}$, s), 2.26 (3H^b, s), 2.35 (3H$^{b'}$, s), 3.92 (2H$^{c'}$, s), 4.04 (2H^d and 2H$^{d'}$, q, J = 7.2 Hz), 4.10 (2H^c, s), 8.22 (1H$^{a'}$, s), 9.27 (1H^a, s); ^{13}C NMR (average spectrum of tautomers in CD_3OD) δ: 13.4, 14.7, 18.1, 46.7, 60.9, 96.9, 150.1 (br), 157.6 (br), 168.2; HRMS-EI (m/z): [M^+] calcd for $C_9H_{14}N_2O_2S$, 214.0776; found, 214.0770.

*4.2.2. Ethyl 2-methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylate and ethyl 2-methoxy-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**2**)*

A solution of **1** (447 mg, 2.09 mmol) in MeOH (10 mL) was heated at reflux for 3 h. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography [CH_2Cl_2-MeOH (50:1 to 20:1)] to give **2** (213 g, 1.07 mmol, 51%) as a colorless solid. Mp 89–90 ºC (not recrystallized because of its instability); IR (KBr) cm^{-1}: 2988, 1699, 1510, 1229, 1089; ^{1}H NMR (0.012 M, 20°C in DMSO-d_6) δ: 1.16 (3H^e, t, J = 7.2 Hz), 1.17 (3H$^{e'}$, t, J = 7.2 Hz), 2.10 (3H^f, s), 2.13 (3H$^{f'}$, s), 3.58 (3H^b, s), 3.68 (3H$^{b'}$, s), 4.00 (2H$^{c'}$, s), 4.03 (2H^d and 2H$^{d'}$, q, J = 7.2 Hz), 4.09 (2H^c, d, J = 0.6 Hz), 7.66 (1H$^{a'}$, s), 8.92 (1H^a, s); ^{13}C NMR (average spectrum of tautomers in CD_3OD) δ: 14.7, 18.4, 45.8, 54.3, 60.8, 96.8, 151.5 (br), 155.2 (br), 168.3; HRMS-CI (m/z): [$(M+H)^+$] calcd for $C_9H_{15}N_2O_3$, 199.1083; found, 199.1074.

*4.2.3. Ethyl 2-(dimethylamino)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (**3**)*

Dihydropyrimidine **3** was prepared from **4** for four steps according to the procedure in reference 9. A mixture of **6** (200 mg, 0.636 mmol), dimethylamine hydrochloride (156 mg, 1.91 mmol), sodium hydrogen carbonate (160 mg, 1.91 mmol), and acetic acid (36 μL, 0.629 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 63 h. To complete the reaction, dimethylamine hydrochloride (156 mg, 1.91 mmol), and triethylamine (0.270 mL, 1.94 mmol) were added, and the reaction mixture was heated at reflux for 9 h. EtOAc (15 mL) and saturated $NaHCO_3$ aqueous solution (5 mL) were added, and the organic layer was separated. The organic layer was washed with brine (5 mL), and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography [n-hexane-EtOAc (5:1 to 1:1)] to give **7** (99.4 mg, 0.319 mmol, 50%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.2 Hz), 1.47 (9H, s), 2.34 (3H, s), 2.98 (3H, brs), 3.15 (3H, brs), 3.42 (1H, brs), 4.18 (2H, q, J = 7.2 Hz), 5.07 (1H, brs). To a solution of **7** (99.0 mg, 0.318 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.5 mL, 6.53 mmol) at rt. The reaction mixture was stirred at rt for 44 h, and 1 M NaOH aqueous solution (10 mL) and EtOAc (15 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give **3** (63.8 mg, 0.302 mmol, 95%) as colorless crystals. Analytical sample of **3** was obtained by recrystallization (n-hexane-EtOAc). Mp 69–72 ºC; IR (KBr) cm^{-1}: 3505, 2985, 1670, 1601, 1507, 1204, 1089; ^{1}H NMR (DMSO-d_6) δ: 1.15 (3H, t, J = 7.2 Hz), 2.10 (3H, s), 2.90 (6H, s), 3.89 (2H, s), 3.98 (2H, q, J = 7.2 Hz), 6.86 (1H, s); ^{13}C NMR (DMSO-d_6) δ: 14.9, 23.2, 37.5, 41.4, 60.3, 95.4, 157.8, 162.3, 168.9; HRMS-CI (m/z): [M^+] calcd for $C_{10}H_{17}N_3O_2$, 211.1321; found, 211.1323. Exact structure assignment of **3** as a sole isomer (1,6-isomer) was made using NOE experiment: the NOE (3.1%) was observed between 2-NMe_2 protons (2.90 ppm) and 1-NH proton (7.14 ppm), and the NOE (1.9%) was observed 6-CH_2 protons (3.89 ppm) and 1-NH proton (7.14 ppm). As such, its structure was determined to be 1,6-isomer (Fig. 6).

4.3. Thermodynamic Analysis.

An NMR sample at 0.050 M was prepared by dissolution of 7.0 mg of **1** in 0.65 mL of DMSO-d_6, $CDCl_3$ C_6D_6. or CD_3OD. For $CDCl_3$, the solvent was passed through a short alumina before use to remove acidic impurities. The solution and the sample tube were purged by argon gas before the measurement. NMR samples at other concentrations and those of **2** were similarly prepared. The ^{1}H NMR spectra were measured at variable temperatures (0–90 °C, 5° intervals). After the thermometer reached the set temperature, the sample was kept at the conditions for at least 10 min before the measurement. The populations of the two tautomers were determined by the intensities of NMR signals due to NH protons. The errors in the population ratios in Tables 1, 2, and S1–S4 were estimated to be within 3%. It was confirmed that the ratios were not affected by using DMSO-d_6 dried over MS 4A. In CD_3OD, the exchange between the two tautomes was so fast on the NMR time scale that only averaged signals were observed.

The observed equilibrium constants (K = [1,4-DP]/[1,6-DP]) and the temperatures (T/K) were used for the van't Hoff plot:

$$\ln K = -\Delta H°/RT + \Delta S°/R ,$$

where $-\Delta H°$ is the standard enthalpy difference, $-\Delta S°$ is the standard entropy difference, and R is the gas constant. The free energy differences $\Delta G°$ were calculated by the equation of $\Delta G° = -RT\ln K$ or $\Delta G° = \Delta H° - T\Delta S°$. The original data and the thermodynamic parameters are shown in Table 3 and Tables in Supplementary data.

4.4. DFT calculations

Calculations were carried out with Gaussian 09W[17] program on a Windows computer. The structures were optimized by the hybrid DFT method at the M06/6-31G(d) level. The frequency analysis gave no imaginary frequency for each energy-minimum structure, and gave thermodynamic parameters. The calculations of each energy minimum structure in several solvents were carried out by the PCM SCRF method [18] at the same level. The PCM using the integral equation formalism variant (IEFPCM[19]) is the default of the SCRF method. The detailed data of the calculations are shown in Tables and Figures in Supplementary data.

Acknowledgments

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Supplementary Material

^{1}H spectra of all compounds, HMBC spectrum of DP **1**, van't Hoff plots of **1** and **2** in various solvents, and the detailed data of the calculations are available, and the data can be found online at xxxxxx. Scientific articles: