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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

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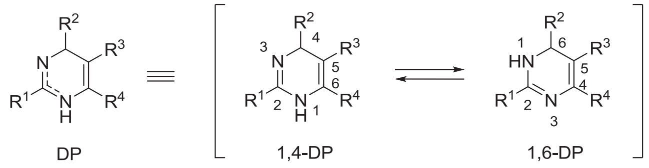


Fig. 1. Tautomerism of dihydropyrimidine.

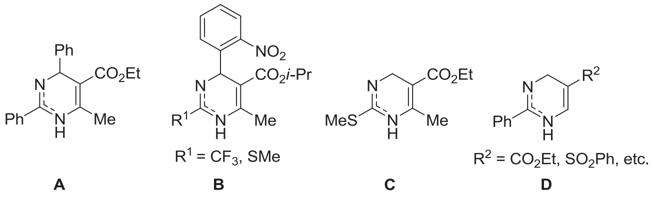


Fig. 2. Examples of dihydropyrimidines observed as their individual tautomers.

1,6-tautomers changes regularly depending on temperature and concentration.[8]

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.

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.

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).

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]

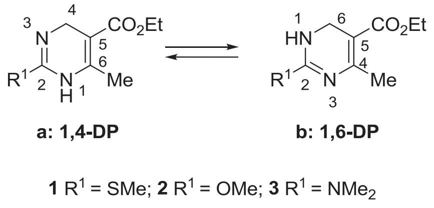
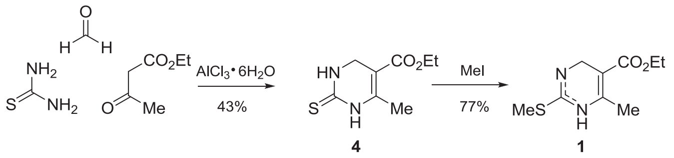
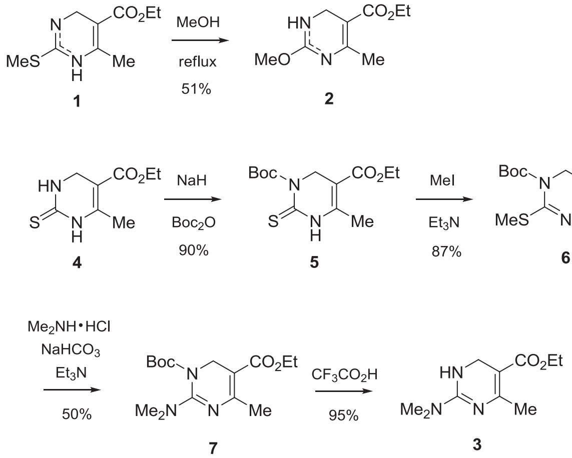


Fig. 3. Chemical structures of dihydropyrimidines **1**–**3** and their tautomers.



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



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 Fig. S1 in Supplementary data). 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.

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,