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A NOVEL TAUTOMERISM IN ALKYL DIHYDROPYRIMIDINES : OBSERVATION OF TAUTOMERISM BY H-D EXCHANGE OF 2- AND/OR 4-METHYL PROTONS OF DIHYDROPYRIMIDINES IN CD_3OD

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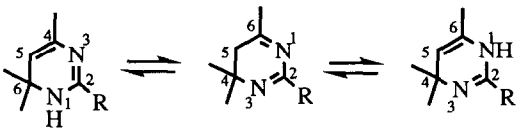
Summary : A novel tautomerism was found in dihydropyrimidines such as 2-amino-4,6,6-trimethyldihydropyrimidine **1** and 2,4,6,6-tetramethyldihydropyrimidine **2** by the observation of H-D exchange on both 4-methyl protons of **1** and 2,4-dimethyl protons of **2** by the treatment of **1** and **2** with CD_3OD in the absence of base under mild conditions.

The structural study of dihydropyrimidines has been virtually delayed because of the instability and the difficulty for purification of these dihydropyrimidines.[1-3] Recently, intensive studies on the tautomerism of dihydropyrimidines have been studied by the ^1H NMR observation of tautomers of good model compounds in $CDCl_3$ solution,[4] by the X-ray crystallographic study in the solid state,[5] and by the both synthesis and the spectral observation of 2-substituted dihydropyrimidines in $CDCl_3$.[6] In a solid state, one isomer of 1,4-dihydropyrimidine **5** has been reported to exist.[5] In general, tautomeric mixtures of 1,6-dihydropyrimidine **3**, 4,5-dihydropyrimidine **4**, and 1,4-dihydropyrimidine **5** exist in aprotic organic solvents.



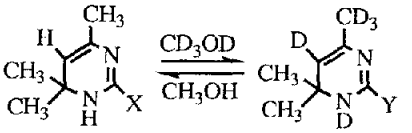
3 **4** **5**

However, all these tautomerisms in the ring system(**3** ⇌ **4** ⇌ **5**) have been performed in aprotic solvents such as $CDCl_3$ or DMSO-d_6 or in solid state.

Earlier, we reported synthesis and characterization of 2-aminodihydropyrimidine derivatives.[7] It was observed that 2-aminodihydropyrimidines are readily isomerized in protic solvents such as water, methanol, and ethanol.[8] Weis demonstrated that the ratio of **5** to **3** is higher in more polar aprotic solvents.[2] In the polar protic solvent system, the conjugated double bond of **3** may convert to the unconjugative isomer,**5**, in water or in methanol.

Attempts to purify 2-amino-4,6,6-trimethyldihydropyrimidine by recrystallizations with aqueous methanol or with water were failed because these compounds are readily isomerized in protic solvent of water or methanol.[9] We have now found that H-D

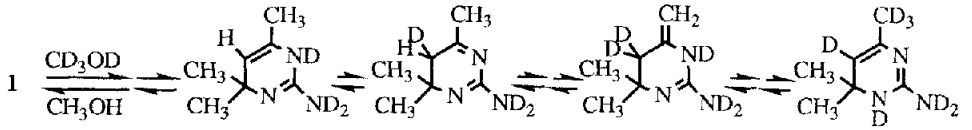
exchanges on the vinyl proton and 4-methyl protons of **1** and 2-methyl protons of **2** occur readily by treatment with CD_3OD at room temperature in 3 h and that H-D exchanges on vinyl and 4-methyl protons of **2** occur at 80 °C for 9 h.



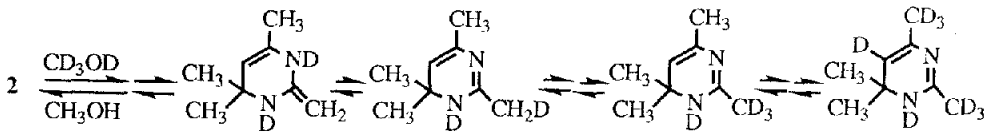
1 : X = NH_2 **1'** : Y = ND_2
2 : X = CH_3 **2'** : Y = CD_3

In experiment, the dihydropyrimidine **1** was dissolved in CD_3OD with stirring. From time to time, ^1H NMR spectra of the sample were taken to see the H-D exchanges. After stirring for 3 h, the complete H-D exchanges of the vinyl proton at 5 position and methyl protons at 4 position were observed by ^1H NMR spectrum : the peaks corresponding to vinyl and 4-methyl protons disappeared completely. The mass spectrum of **1'** shows the deuterated single molecular peaks(MS, 70 eV, M^+: 146(1.3)). On the other hand, the deuterated **1'** was dissolved in CH_3OH and after 9 h at room temperature the solution was concentrated to give a colorless solid. the solid obtained by concentration was found to be identical with **1** by means of ^1H NMR,[10,a] IR and mass spectrum(MS, 70 eV , M^+: 139(8.0)). In the case of **2**, the methyl peak at 2-position disappeared at room temperature after 3h in CD_3OD. On the other hand, peaks for the vinyl proton at 5- position and the methyl protons at 4-position disappeared after heating at 80 °C for 9 h converting to **2'**. The deuterated **2'** was converted to **2** after refluxing in CH_3OH for ca. 10 h. The conversion of **2'** to **2** was also confirmed by ^1H NMR[10,b] and mass spectrum.

The H-D exchanges of methyl protons of **1** and **2** are probably originated from the enamine tautomerism (**4a** ≒ **4a'** ≒ **4a"**, **4b** ≒ **4b'** ≒ **4b"**) as shown below.



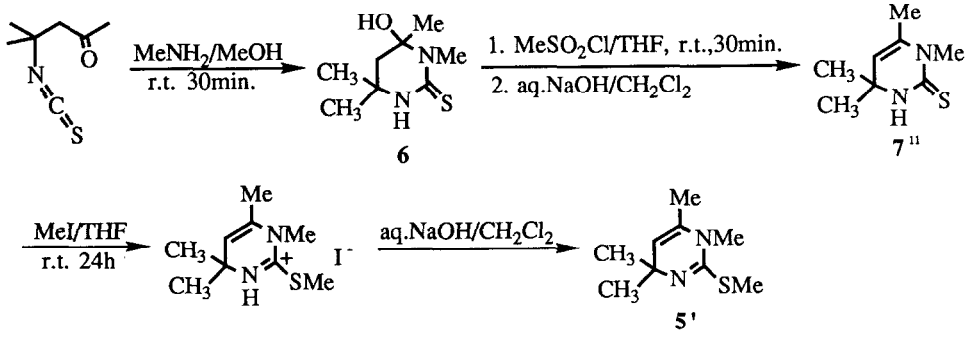
4a **4a'** **4a"**



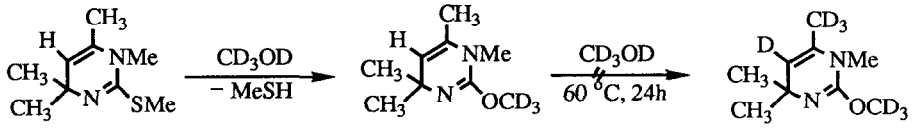
4b **4b'** **4b"**

In order to see possibility of H-D exchange on 4-methyl group in blocked tautomerism system (**5'**), 1,4,4,6-Tetramethyl-2-methylthio-1,4-dihydropyrimidine **5'**

whose N at 1-position substituted with methyl group would be a good model compound to examine whether H-D exchange is proceeded via enamine tautomerism or not, was synthesized as follows.



When **5'** was heated in CD_3OD, methanethiol was evolved with its peculiar smell and the peak for methylthio group was replaced by the peak for methoxy group in ^1H NMR spectrum. But the vinyl proton and methyl protons at 4-position were not exchanged with deuteriums after reflux in CD_3OD for 24h.



It has been well known that dihydropyrimidines are readily converted to the corresponding pyrimidines by their aromatizations.[12] Thus, it is valuable and noteworthy that the easy H-D exchanges of the methyl groups in **1** and **2** are applicable to introduce the deuterated methyl groups on 2- and/or 4-positions in pyrimidines.[13] And it is the first time to find out a tautomerism between a dihydropyrimidine ring and the substitutied alkyl groups.

Acknowledgment: Financial support for this work was gratefully obtained from KAIST and Ministry of Science and Technology.

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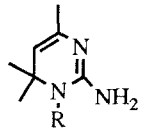
8. Decrease of intensity(%) at 250 nm were observed by UV absorption after 15 minutes from the sampling.



R	H_2O %	MeOH %	EtOH %	i-PrOH %	t-BuOH %
H	-[a]	57	14	1.5	~0
Me	60	48	24	3	~0
Et	53	49	27	3	~0

a; too fast to detect the decrease of the absorbance

9. Recrystallization of 2-amino-4,6,6-trimethyldihydropyrimidine with aqueous methanol or with water gave impurities of isomers : Repeated recrystallizations afforded formation of more impurities.
10. ^{1}H NMR(DMSO-d_6, δ), a) ; 4.37(s, C=CH), 1.63(s, C=CMe), 1.20(s, CMe_2), b) ; 4.06(s, C=CH), 1.63(s, N=CMe), 1.33(s. CMe_2).
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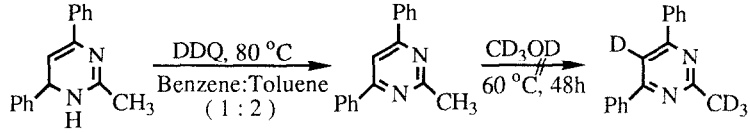
13. The H-D exchanges of proton at 5-position and methyl protons of 2-methyl-4,6-diphenylpyrimidine do not occur in CD_3OD at 60 °C for 48h. Thus, it is easier to prepare 5-deutero-2-trideuteromethyl-4,6-diphenylpyrimidine, and then to get the deuterated pyrimidine by its aromatization. 2-Methyl-4,6-diphenylpyrimidine was actually obtained in 72 % yield by heating 2-methyl-4,6-diphenyl-1,6-dihydro-pyrimidine with DDQ(2,3-dichloro-5,6-dicyano-1,4- benzoquinone) at ca. 100 °C for 3 h.



72 %

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