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THE FACTORS AFFECTING POSSIBILITY OF OBSERVATION OF ANNULAR TAUTOMERISM IN DIHYDROPYRIMIDINE SYSTEMS

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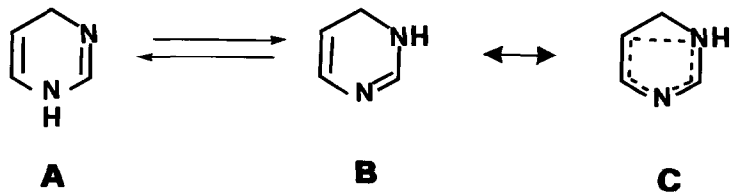
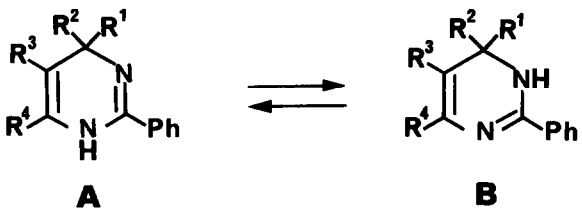
Summary: The amount of water in the solvent, microconcentration of H^+ ions in the solution, paramagnetic impurities, concentration dependence, have remarkable effects on the ability of observing tautomerism in dihydropyrimidines.

Dihydropyrimidines easily convertible to pyrimidines possess important antioxidant, membranotropic and pharmacological properties.[1] The chemistry of dihydropyrimidines in virtually unknown because of the widely accepted opinion regarding the instability of these compounds and the absence of convenient isolation and purification methods. In addition to this, there is a lack of data on the stabilization - destabilization effects of substituents on these ring systems. Moreover, the question concerning the structure and relative stabilization of the tautomeric 1,4- and 1,6-dihydropyrimidines is open. The majority of articles dealing with 1,4- and 1,6-dihydropyrimidines describe the tautomeric compounds in one of the possible forms, usually form B, without any discussion of the tautomerism.[2] Other publications suggest either complete delocalization C[3] or a time average of rapidly interchanging tautomers A and B.[4]



Scheme I

We have undertaken a systematic study of dihydropyrimidines and recently reported a preliminary account of the observation of each individual tautomer I_A and I_B of 6-methyl-2,4-diphenyldihydropyrimidine (I) in DMSO and HMP solutions.[5]



A ⇌ B

I. $R_1=R_3=H$ $R_2=Ph$ $R_4=Me$
II. $R_1=R_2=R_4=Me$ $R_3=H$
III. $R_1=H$ $R_3=R_4=Me$ $R_2=Ph$
IV. $R_1=R_3=R_4=H$ $R_2=Ph$
V. $R_1=R_3=H$ $R_2=2$-furyl $R_4=Me$
VI. $R_1=R_3=H$ $R_2=2$-thienyl $R_4=Me$
VII. $R_1=R_4=Me$ $R_3=R_2=Ph$

Scheme II

Furthermore it was shown[6] that in the solid state compound I exists in the 1,4-dihydroform (I_A) and by comparison of the spectral (IR, UV, NMR) data it became possible to make definitive structural assignments of both tautomers.

Recently van der Plas et al.[4b] and Girke[4c] have also studied the behaviour of a variety of dihydropyrimidines, but attempts to obtain the NMR spectra in deuteriochloroform of each of the tautomers failed even at -88°C. It should be noted that our experiments confirm this, where in $CDCl_3$ solutions only average spectra were detected.

The transfer of the proton between two heteroatoms is usually a rapid (in NMR time scale) process.[7] It may be expected that on using an aprotic dipolar solvent (DMSO, HMP) a decrease in the rate of tautomerism takes place, because of strong intermolecular H-bonding with the solvent, allowing the observation of the individual tautomers. In the course of our NMR studies on the tautomerism of I_A and I_B in DMSO-d_6 solution we noted that the tautomerism was affected by the following factors:

1. The amount of H_2O in the solvent. This was confirmed by the addition of small amounts of water to a sample, where slow exchange had been observed previously and this caused an increase in the rate of proton exchange as indicated by the broadening of the H^4 and H^5 signals of both tautomers and a decrease in the separation of these signals.

2. Microconcentrations of H^+ ions in the solution. The rate of exchange was greatly accelerated by the addition catalytic amounts of H^+, in each case an "average" spectrum was obtained.

3. Paramagnetic impurities in solution also accelerate the rate of exchange.

4. Concentration dependence. The concentration dependence of the sample plays an extremely important role in our ability to detect tautomerism. For example it was shown that in ^{1}H-NMR the observation of the tautomers was possible only at 0.001-0.003 M concentrations.

The fact that in $CDCl_3$ only "average" spectra were observed may be attributed to both the lack of hydrogen bonding stabilization of the tautomers as well as minute amounts of acid which are usually present in this solvent. However, when the spectra were determined on a dilute sample (0.001 M) in $CDCl_3$ initially filtered through alumina in order to remove traces of acid, at low temperature (-50°C) and degasing with argon the tautomerism was observed (see Table).

Table. NMR spectra of 6-methyl-2,4-diphenyldihydropyrimidine (270 MHz, δ,TMS)

	I_A			I_B[8]			Average				
Solvent	H_A^4	H_A^5	NH_A	H_B^4	H_B^5	NH_B	H_X^4	H_X^5	NH_X	CH_3	Ratio
HMPA	5.26	4.27	9.35	5.20	4.77	8.90	-	-	-	-	2:1
DMSO-d_6	5.26	4.39	8.56	5.21	4.87	8.05	5.24	4.59	8.36	1.79	3:2 (7:5)[§]
$CDCl_3$*	5.33	4.53	6.13	5.33	4.83	5.53	5.34	4.70	-	1.90	3:4 (17:13)[§]
Acetone-d_6	5.30	4.47	-	5.30	4.89	-	5.30	4.62	-	1.82	3:2 (27:17)[§]

*Spectra of tautomers in $CDCl_3$ obtained at -50°C.

[§]Ratio calculated from formulae A:B = $\Delta(\delta H_X^5 - \delta H_A^5) : \Delta(\delta H_B^5 - \delta H_X^5)$

The equilibrium position is strongly solvent dependent. The infrared spectra of a series of these compounds (Scheme II) were of particular interest. They showed a minimum of three important absorption bands 1550-1620 (C=C), 1600-1700 (C=N) and 3200-3500 (N-H) cm^{-1}. But characteristic absorptions in the 1600-1700 cm^{-1} region of the IR spectra provided an excellent tool for differentiation of the tautomers. It has been consistantly observed in a large number of newly prepared compounds that the band assigned to the C=C-NH-C=N fragment of the 1,4-tautomers appears at a higher frequency by Δ 30-60 cm^{-1} than the corresponding band for the C=C-N=C-NH fragment of 1,6-tautomer (for example I_A- 1700 cm^{-1} and I_B-1648 cm^{-1}). Intensity of these peaks correlates well with the ratio of tautomers in solution.

The validity of our interpretation of the IR and NMR data in the assignment of the tautomers available was further demonstrated by the structure elucidation of dihydropyrimidine II obtained by Silversmith.[4a] Although no definitive structure had been proposed earlier for this compound, we assigned its structure to the 1,6-tautomer on the basis of its IR band at 1652 cm^{-1}, when compared to the IR spectra of I_A and I_B. This was indeed confirmed by x-ray analysis.[9] Moreover, when the NMR spectrum of this compound was measured in DMSO-d_6, while taking into account the above mentioned precautions both tautomers could be clearly observed.[10]

Thus it can be concluded that the rate of proton exchange in dihydropyrimidine systems is sufficiently slow, and that it is possible to observe this equilibrium on an NMR time scale. It is to be expected that these compounds should serve as reliable models for the investigation of tautomerism of other cyclic amidines.

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7. J. Elguero, C. Marzin, A.R. Katritzky and P. Linda, "The Tautomerism of Heterocycles", N.Y., Acad. Press, 1976.
8. The correct nomenclature of structure I_B is 4-methyl-2,6-diphenyl-1,6-dihydropyrimidine; we have numbered it as shown only for the sake of convenient comparison of tautomers I_A and I_B.
9. A. Weis and F. Frolow, to be published.
10. ^{1}H-NMR (270 MHz, DMSO-d_6, δ, ppm): II_A 1.18 [C-$(CH_3)_2$], 1.74 (C=C-CH_3), 4.23 (H^5) 7.30-7.85 (Arom.), 8.38 (NH; II_B 1.18 [C-$(CH_3)_2$] , 1.74 (C=C-CH_3), 4.63 (H^5), 7.30-7.85 (Arom. + NH). Ratio II_A:II_B = 9:11.

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