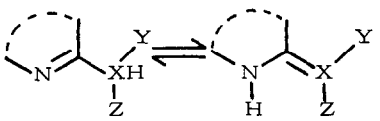
Tetrahedron Letters No. 33, pp 3055 - 3058. 0040-4039/78/0808-3055$02.00/0

TAUTOMERISM IN THE PYRIMIDYLMETHANE SYSTEMS

V.V.Lapachov*, O.A.Zagulayeva, S.F.Bichkov, V.P.Mamaev
Institute of Organic Chemistry, Siberian Division of the
Academy of Science, Novosibirsk 90, USSR.

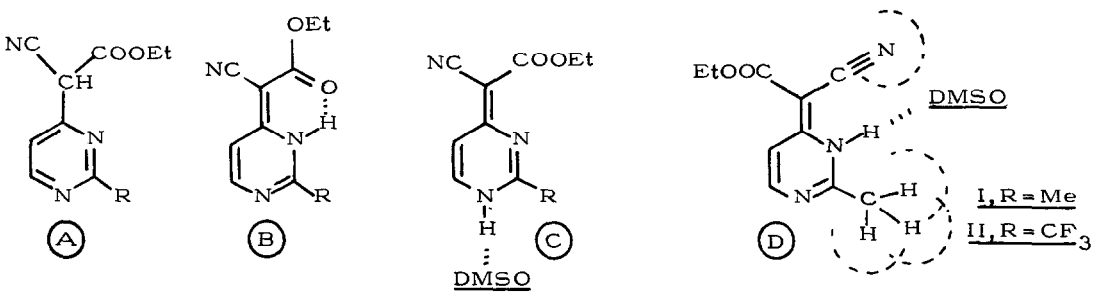
Experimental evidence concerning tautomerism in the azahetarylmethane system (Scheme 1, X=C) is very limited in spite of the fact that it could be a convenient model for the investigation of the general regularities of tautomerism of the type a⇌b. Fundamental importance of such tautomerism has been recently emphasized by Elguero and Katritzky in their excellent monograph[1]. It has been found earlier[2] that both tautomers A and B exist in $CHCl_3$ and CCl_4 solution in the case of pyrimidyl-4-malonic ester derivatives. In the course of further studies we have now obtained and isolated the ortho- and para-quinoid type pyrimidylidene tautomers of pyrimidyl-4-methanes and studied their equilibrium in solution. We have also observed the first example of pyrimidine-pyrimidylidene tautomeric equilibrium in the pyrimidyl-2-methane system.

Scheme 1
X = O,N,S,C...
Y,Z - substituents or electron pairs



a b

The first "ortho-para" equilibria studied were those involving compounds I and II, because the presence of the third tautomer A does not complicate the picture in this particular case. NMR reveals tautomer B as the only one present in $CHCl_3$ and CCl_4 solutions of compounds I and II (δ_{NH} of chelated proton = 14-15 ppm). We believed that



tautomer C would be favoured by aprotic bipolar solvents (DMSO, HMPA) due to efficient disruption of the H-bonding in tautomer B, on one hand, and to stabilisation of tautomer C by strong intermolecular H-bonding, on the other. A similar stabilization of tautomer D would have to overcome strong steric hindrance, and its formation therefore does not seem probable. Addition of DMSO to solution of I in CCl_4 brings about new signals in the PMR spectrum (Fig. 1), the intensity of which increases with increasing concentration of DMSO and decreases with increasing concentration of CCl_4. These signals are not due to the tautomeric form A because they are not accompanied by signals of methine protons. In spite of the strong acidity of I, no anionic form is involved in this equilibrium, as suggested by UV spectra. The considerable shift of signals of ring protons and of the Me-group protons is indicative of a rearrangement of the heterocyclic π-electron system and suggests the presence of tautomer C rather than D, because such shifts for D should be much smaller. The formation of tautomer C in this equilibrium was confirmed by consideration of the ^{13}C NMR chemical shifts of the ring carbon atoms in terms of the known dependence of chemical shifts on electron density[3]. The proton-decoupled spectrum of I in $CDCl_3$ contains signals of C-5 and C-6 at 110 and 151 ppm, respectively (Fig. 1). This assignment was confirmed by selective proton decoupling experiments. It is also in accord with the values of electron densities for model compound B (Fig. 1) calculated by CNDO/2 or PPP methods ($q_5 > q_6$). As suggested by these calculations, tautomers C and D should differ considerably: disruption of the intramolecular H-bonding leading to D would not result (unlike the situation with C) in a great change of the distribution of electron density at C-5 and C-6. This change caused by formation of tautomer C, on the other hand, should be very great, especially at C-6, and the signal should strongly shift

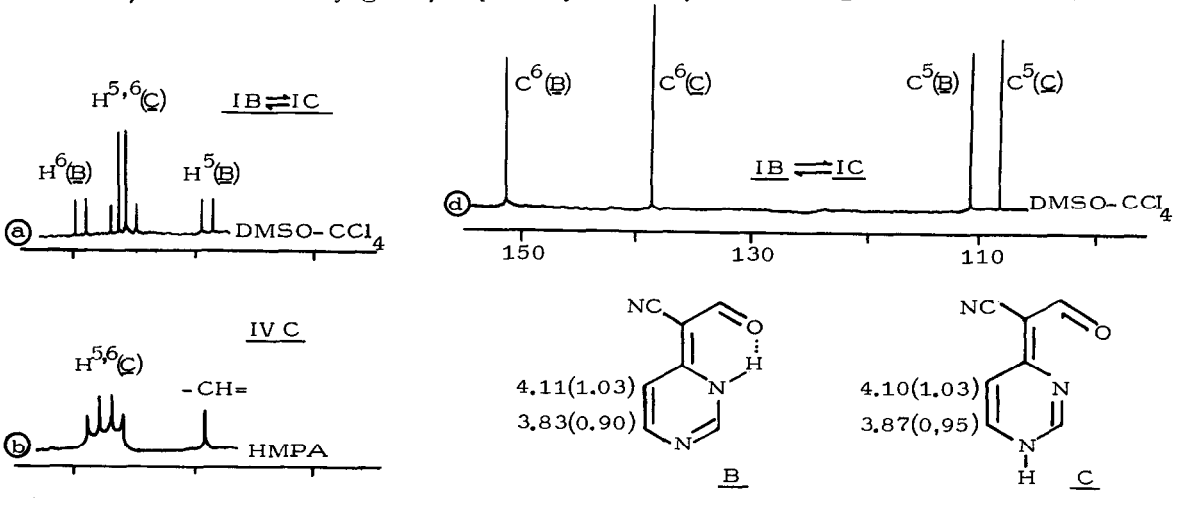


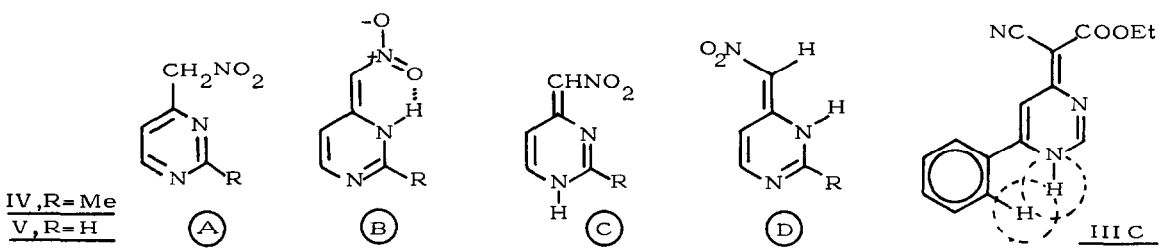
Fig. 1 a, b, c - the spectra of the pyrimidylidene tautomers I(B+C), IV C, IV B; d - the ^{13}C-NMR signals of C-5, C-6 atoms of tautomers IB, IC and the values of ($\sigma+\pi$)- and π-electron densities (in brackets) calculated by CNDO/2 [4] and PPP [5] methods, respectively.

upfield. The latter effect is observed in fact experimentally (Fig. 1 d).

Thus, both ^{1}H and ^{13}C NMR spectra strongly suggest that in the presence of DMSO there exists an equilibrium of pyrimidylidene tautomers with ortho- and para-quinoid position of double bonds. Compound II behaves similarly: addition of DMSO induces reversible transformation to para-quinoid form IIC, although the great acidity, which increases the rate of the exchange B⇌C, increases also the width of the PMR signals. A characteristic consequence of transformation to para-quinoid form IC and IIC is the decrease of the distance between signals of 5-H and 6-H protons ($\Delta\delta H^{5,6}$) and transformation of the spin system from AX-pattern (ortho-form B) to AB-pattern (para-form C).

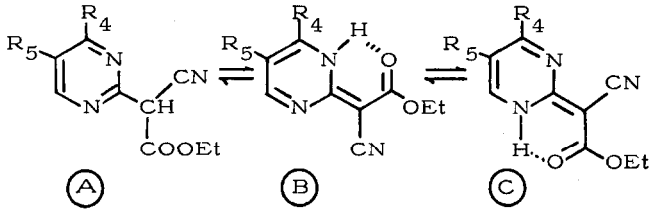
We succeeded to isolate each of this forms. The ortho-quinoid tautomer B may be obtained by evaporation of $CHCl_3$ solution of I. However, if a few drops of DMSO is added before, the compound which precipitates in the course of evaporation is the para-quinoid tautomer IC. The two products have different melting points (IB - 130°, IC - 160°) and very different solubilities: the compound IB is readily and rapidly soluble in pure $CHCl_3$, whereas to dissolve IC it necessary to boil it in $CHCl_3$ for several hours! IR spectroscopy revealed that dissolution (as well as melting) of IC involves complete isomerization C⟶B. The NH band ortho-tautomers IB, IIB is weak and may be identified by deuteration ($\nu_{NH} = 3100\,cm^{-1}$, $\nu_{ND} = 2300\,cm^{-1}$), whereas the para-quinoid tautomers IC, IIC have a very strong NH band at 2800-3300 cm^{-1}, which is characteristic of compounds of such structure[6]. It is noteworthy that the sterically hindered tautomer C of the compound III may not be obtained either in solution, or in solid state. This fact is regarded as additional evidence in favour of the structures of the above discussed tautomeric forms.

Believing that aprotic bipolar solvents must favour the formation of the para-quinoid tautomer also in case of other tautomeric pyrimidyl-4-methanes, we investigated the tautomerism of pyrimidyl-4-nitromethanes IV-V. It will be mentioned that tautomerism of pyrimidine-4-nitromethane has been observed by Feuer and Laurence[6] who suggested the para-quinoid structure for the pyrimidylidene tautomer. To study this compound we used PMR Fourier-spectroscopy because of low solubility. We found that the structure of this compound also depends on solvent. In $CDCl_3$ the distance between the signals of 5-H and 6-H ($\Delta\delta H^{5,6}$) is equal to 1.4 ppm, which is close to the value observed for the ortho-quinoid form IB (1.2 ppm). Addition of DMSO which stabilizes form C brings about changes in the PMR spectrum similar to those characteristic of the above discussed transformation IB⟶IC: the chemical shift difference between the signals of the protons



5-H and 6-H becomes smaller and approaches 0.4 ppm (AX⟶AB). Use of more polar solvent (HMPA) does not change this difference suggesting that DMSO shifts the equilibrium to the para-quinoid tautomer IV C. The pyrimidyl-4-nitromethane V, like IV, is present in $CHCl_3$ as the pyrimidine form V A with a small admixture (≈5%) of the ortho-quinoid form B. The latter form exhibits 5-H and 6-H at practically the same chemical shift (within 0.1 ppm) as found in IV B, and $\Delta\delta H^{5,6}$ is exactly the same (1.4 ppm). However, 3% solution of V in DMSO exhibits $\Delta\delta H^{5,6}$ 0.8 ppm which is two times greater than that expected for the para-quinoid tautomer V C ($\Delta\delta H^{5,6}$ = 0.4 ppm in IV C). This is indicative of a rapid equilibrium of V C with the ortho-quinoid tautomer V D, the content of which may be estimated by the expression: %V D = (0.8 ppm − 0.4 ppm)·100/(1.4 ppm − 0.4 ppm) = 40%. The lower stability of form C in the case of IV is most probably due to the steric hindrance of the Me-group inhibiting the stabilizing effect of H-bonding with solvent. Thus, the pyrimidyl-4-methanes investigated in the present studies exist in the presence of DMSO as pyrimidine form A, ortho-quinoid form B and para-quinoid form C. The tautomeric equilibrium between these forms (especially between the pyrimidylidene tautomers B and C) strongly depends on solvent and is more complicated than that suggested by Feuer and Laurence[6].

In conclusion we would like to report for the first time an example of pyrimidine-pyrimidylidene equilibrium in the substituted pyrimidyl-2-methane series.



VI-XI: R_4 = H
R_5 = H (VI), Me (VII), Br (VIII), Cl (IX), OMe (X), NMe_2 (XI)

XII-XIV: R_5 = H
R_4 = Me (XII), Ph (XIII), OMe (XIV)

The content of form A increases in the sequence VI, VII < VIII, IX < X, XI (from ≈ 1% to 30-40% in $CHCl_3$). In the case of 4-substituted XII-XIV, form C is also present in the equilibrium due to assymmetry of the system. Transfer of a proton between two hetero-atoms is usually a rapid process[1], but the transformation B⇌C appears to be slow owing to intramolecular H-bond. This fact emphasizes once more the convenience of the above compounds as models for the investigation of equilibria of type a⇌b (Scheme 1).

References

1. J. Elguero, C. Marzin, A. R. Katritzky, P. Linda, "The Tautomerism of Heterocycles", N.Y., Acad. Press, 1976.
2. V.V. Lapachov, O.A. Zagulayeva, V.P. Mamaev, Khim. Geterotsicl. Soedin., 395 (1977).
3. G.J. Martin, M.L. Martin, S. Odiot, Organic Magnetic Resonance, 7, 2, (1976).
4. J.A. Pople, G.A. Segal, J. Chem. Phys., 44, 3289 (1966).
5. R. Pariser, R.G. Parr, ibid., 21, 466 (1953); J.A. Pople, Trans. Faraday Soc., 49, 1375 (1953).
6. H. Feuer, J.P. Lawrence, J. Org. Chem., 37, 3662 (1972).

(Received in UK 31 May 1978; accepted for publication 15 June 1978)