9. J. G. Kirkwood, J. Chem. Phys., 2, 51 (1934).
10. D. K. Pimentel and O. L. MacClellan, Hydrogen Bonding [Russian translation], Mir, Moscow (1964), pp. 84.
11. A. I. Kol'tsov, D. Kh. Zheglova, and V. A. Gindin, Khim. Fiz., 3, 810 (1984).
12. G. Klose and E. Uhlemann, Tetrahedron, 22, 1373 (1966).
13. P. Beak, Acc. Chem. Res., 10, 186 (1977).
14. M. Tisler, Synthesis, No. 3, 123 (1973).
15. A. Gordon and R. Ford, The Chemist's Guide [Russian translation], Mir, Moscow (1976), p. 437.
16. T. F. McGrath and R. Levine, J. Am. Chem. Soc., 77, 3656 (1955).
17. N. N. Goldberg and R. Levine, J. Am. Chem. Soc., 74, 5217 (1952).
18. W. C. Guida and D. J. Mathre, J. Org. Chem., 45, 3172 (1980).

TAUTOMERISM OF DERIVATIVES OF AZINES.

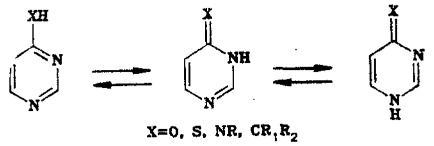
19.* EFFECT OF SOLVENTS ON THE o,p-QUINOID EQUILIBRIA OF THE YLIDENE FORMS OF 4-PYRIMIDINYLCYANOACETIC ACID ESTERS

O. P. Petrenko, I. K. Korobeinicheva,
V. V. Lapachev, and V. P. Mamaev†

UDC 641.623'121'12.0'38.2:
547.853.04

The effect of solvents on the tautomeric equilibria of the ylidene forms of 4-pyrimidinylcyanoacetic acid esters with o- and p-quinoid orientations of the double bonds in the heteroring was determined. The relative stability of the p-quinoid tautomer increased markedly on passing to polar solvents due to nonspecific solvation and the formation of hydrogen bonds.

Annular tautomerism is an important type of tautomeric equilibrium in series of pyrimidine derivatives. In the case of 4-substituted pyrimidines the formation of two NH forms (B and C) with o- and p-quinoid orientations of the double bonds in the heteroring is possible.



Tautomeric equilibia of the B ⇄ C type can be observed for various derivatives of azines. In addition, little study has been devoted to o,p-quinoid tautomeric equilibria, evidently because of the difficulty involved in recording the tautomeric forms. We have previously established [2] that equilibria with the participation of aromatic tautomer A and o-quinoid tautomer B, which is stabilized by an intramolecular hydrogen bond (IHB), are characteristic for substituted 4-pyrimidinylmethanes. "Rare" p-quinoid tautomer C can be stabilized by solvents such as DMSO and HMPT [3, 4], and this makes it possible to investigate the effects of the medium on o,p-quinoid equilibrium B ⇄ C, which is the aim of the present research.

We selected 4-pyrimidinylcyanoacetic acid ester (I) and 2-methyl-4-pyrimidinylcyanoacetic ester (II), for which the observation of tautomeric equilibrium B ⇄ C is not complicated by the presence of tautomer A [4]. The UV spectra of I and II in various solvents are

---

*See [1] for Communication 18.

†Deceased.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 521-524, April, 1988. Original article submitted October 21, 1986; revision submitted April 2, 1987.

0009-3122/88/2404-0430$12.50

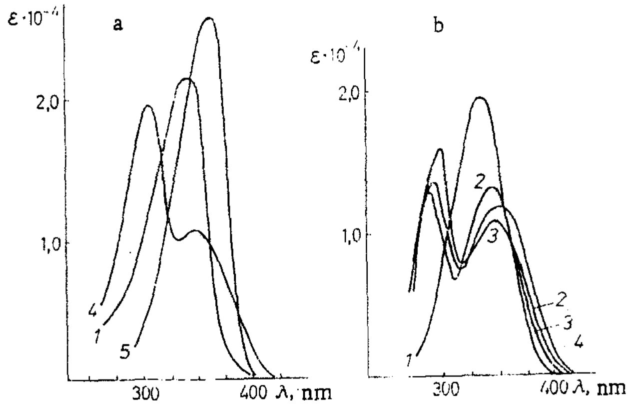


Fig. 1. UV absorption spectra of I (a) and II (b): 1) in DMSO; 2) in CH_3CN; 3) in CH_2Cl_2; 4) in $CHCl_3$; 5) in alcohol (III).

presented in Fig. 1. In the case of solutions in $CHCl_3$, in which the tautomeric equilibrium is shifted completely to favor tautomer B [4], two absorption bands at ∿300 and 350 nm are observed in the spectra of I and II. In DMSO I and II exist primarily in p-quinoid tautomeric form C [4], and absorption bands with λ_{max} 339 (I) and 324 mm (II) are observed for them (Fig. 1). 1-Methyl-1,4-dihydro-4-pyrimidinylidenecyanoacetic acid ester (III), which models the p-quinoid tautomeric form of I, also has similar absorption (Fig. 1). When both tautomeric forms exist in equilibrium, their absorption bands are partially superimposed. In this connection the percentage of p-quinoid tautomer IIB in various solvents was determined from the absorption at 390 nm, where absorption of p-quinoid tautomer IIC is absent (see Fig. 1b). The molecular coefficient of extinction of tautomer B was found from the spectrum of II in $CHCl_3$, in which only tautomer B exists. To verify the reliability of this method of evaluation we determined the percentage of tautomer IIB in CCl_4–DMSO (1:4) from the absorption at 390 nm in the UV spectrum and from the PMR spectrum. The close percentages of tautomer B found by these methods (68% and 70%, respectively) make it possible to use UV spectroscopy to study the effect of solvents on the o,p-quinoid tautomeric equilibrium. An isobestic point is observed in recording the UV spectra of I and II in mixtures with various ratios of CCl_4 and DMF; this confirms the existence in equilibrium of only two tautomeric forms and indicates the low sensitivity of the position and form of the long-wave absorption bands with respect to the character of the solvent. It has been shown [3, 4] that the relative stability of the p-quinoid tautomer increases in DMSO and HMPT, which are capable of forming hydrogen bonds as proton acceptors. The role of nonspecific solvation, the contribution of which may be particularly significant, remained unclear. A theoretical evaluation of the effect of nonspecific solvation shows (Fig. 2) that the p-quinoid tautomer can be stabilized not only by hydrogen bonds but also by polar solvents. We evaluated the effect of the polarity of the solvent on the position of the tautomeric equilibrium within the framework of the Gerner model [5]. This approach, which takes into account interaction of the dissolved molecule with the solvations, makes it possible to evaluate the relative energies of solvation of the heterocyclic tautomers [6]. The results of calculations of the differences in the energies of solvation of the o,p-quinoid tautomers of 4-hydroxypyrimidine and 4-pyrimidinylacetaldehyde by the CNDO/2 method taking into account Germer solvation are presented in Fig. 2 in graphical form. In conformity with the calculations tautomer C, regardless of the type of side fragment that undergoes tautomerization, is stabilized with an increase in the polarity of the solvent to a greater degree than tautomer B. This makes it possible to assume that observation of the p-quinoid tautomer is also possible in polar solvents for which the ability to form hydrogen bonds is not great.

To verify the results of the calculations we determined the position of the tautomeric equilibrium by UV spectroscopy for II in solvents that have little capacity for specific solvation (Figs. 1 and 3). We observed that whereas only tautomer B is observed in CCl_4 and $CHCl_3$ [3, 4], tautomer C also is present in equilibrium in CH_2Cl_2, dichloroethane, and CH_3CN (Table 1, Fig. 3). This is indicated by the gradual decrease in this series of the absorption in the UV spectrum at 390 nm. Thus stabilization of the p-quinoid tautomer only through nonspecific solvation in polar solvents is possible.

To ascertain the contribution of specific solvation to stabilization of the p-quinoid tautomer we determined the tautomeric equilibrium constants in dipolar solvents (DMSO, DMF) and for mixtures of them with CCl_4. The development of the p-quinoid tautomer was recorded by UV spectroscopy with the addition of 5-10% DMF, DMSO, or N-methylpyrrolidone to CCl_4. The presence of trace amounts of the p-quinoid tautomeric form of II in CCl_4 + 5% d_6-DMSO was

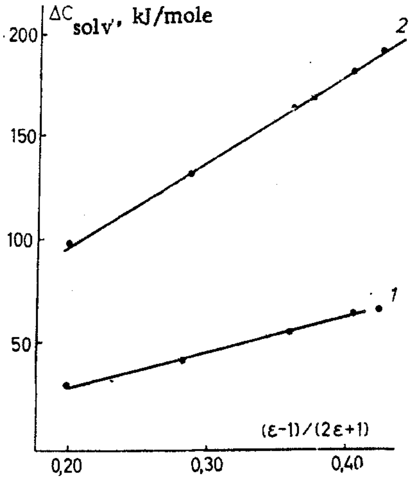


Fig. 2

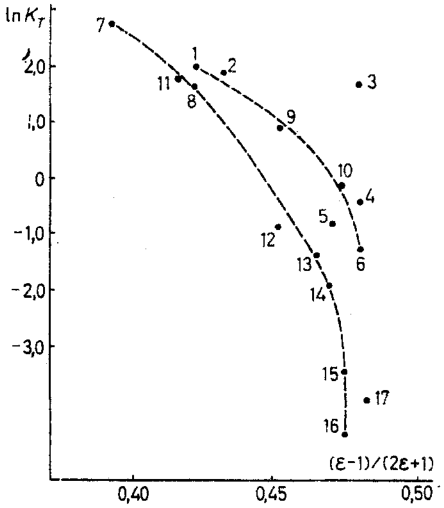


Fig. 3

Fig. 2. Differences in the energies of solvation of ylidene tautomers B and C ($\Delta G_{solv} = G^{C}_{solv} - G^{B}_{solv}$) of 4-hydroxy-pyrimidine (1) and 4-pyrimidinylacetaldehyde (2) calculated by the CNDO/2 method taking into account Germer solvation.

Fig. 3. ln K_T (B/C) values of II. The numbers correspond to the numbering of the solvents in Table 1.

confirmed by PMR data [4]. The polarity of the mixture increased with an increase in the concentration of the aprotic dipolar solvent, and stabilization of tautomer C was observed. However, a linear relationship between the ln K_T value and the polarity function in the Kirkwood–Onsager equation Y = (ε − 1)/(2ε + 1) [7] is not observed (Fig. 2); this is evidently associated with the effects of specific solvation. The strong contribution of specific solvation to the increase in the stability of tautomer C in polar solvents is also indicated by the difference in the tautomeric equilibrium in CH_3CN, CH_3OH, DMF, and DMSO, for which the Y values are close (0.477–0.484) (Table 1, Fig. 3). Whereas 45% tautomer B is present in acetonitrile for II, 20% B is present in DMF and 5% B is present in DMSO. Judging from these values, for solvents such as DMSO and DMF the contributions of specific and nonspecific solvation are comparable and act in the direction of stabilization of p-quinoid tautomer C.

In addition to stabilization of the p-quinoid tautomer by solvents that are capable of forming hydrogen bonds of the proton-acceptor type, one observes an increase in the relative stability of tautomer C also through specific solvation in solvents that are proton donors. Thus, the precentage of tautomer C in methanol is substantially higher than in acetonitrile (Table 1). The addition of 0.5% water, which has an even greater ability to form hydrogen bonds, to solutions of II in CH_3OH and CH_3CN leads to further stabilization of tautomer C: in aqueous methanol solution the tautomeric equilibrium is shifted completely to favor tautomer C, whereas in aqueous acetonitrile solution the percentage of tautomer C increases by 40% as compared with the solution of CH_3CN. This effect cannot be associated with an increase in the polarity of the solvent, since Y changes by only 0.001–0.002 when water is added.

TABLE 1. Constants of the Tautomeric Equilibrium of II

No.	Solvent	K_T (B/C)	No.	Solvent	K_T (B/C)	No.	Solvent	K_T (B/C)
1	CH_2Cl_2	7,3	7	CCl_4— DMF, 9:1	15,3	13	CCl_4— NMP, 4 : 6	0,23
2	Dichloroethane	6,2	8	CCl_4— DMF, 8 : 2	6,0	14	CCl_4— NMP, 2 : 8	0,15
3	CH_3CN	5,6	9	CCl_4— DMF, 6 : 4	2,2	15	CCl_4— NMP, 15 : 9	0,03
4	CH_3CN+0,5% H_2O	0,82	10	CCl_4— DMF, 2 : 8	0,82	16	CCl_4— NMP	0,01
5	CH_3OH	0,45	11	CCl_4— NMP,* 8 : 2	6,7	17	DMSO	0,02
6	DMF	0,25	12	CCl_4— NMP, 6 : 4	0,43			

---

*NMP is N-methylpyrrolidone.

Considering the above-presented results of calculations of the effects of nonspecific solvation of the o- and p-quinoid tautomers of 4-hydroxypyridine (Fig. 2) one might expect a monotypic effect of the polarity of the solvent on the $B \rightleftarrows C$ tautomerism of hydroxy and methyl derivatives. The p-quinoid tautomer should be stabilized to a greater degree with an increase in the polarity of the solvent, regardless of the type of side fragment. The previously described [8] shift of the tautomeric equilibrium of 2-methyl-4-hydroxypyrimidine to favor the p-quinoid tautomer on passing from solutions in hexane to water is in agreement with this conclusion.

Thus in the case of pyrimidinylcyanoacetic acid esters we have demonstrated an increase in the relative stability of the tautomer with a p-quinoid orientation of the double bonds in the heteroring by polar solvents through nonspecific solvation and also by proton-acceptor and proton-donor solvents that are capable of specific solvation.

EXPERIMENTAL

The UV spectra of solutions of I-III ($1 \cdot 10^{-4}$ M) were recorded at 20°C with a Beckmann DU-8 spectrophotometer. For II $\varepsilon = 3600 \pm 100$ cm/mole-liter at 390 nm. The PMR spectra were recorded with a Bruker WP 200 spectrometer. The solvents were purified by the method in [9]. The quantum-chemical calculations by the CNDO/2 method were made by means of the program in [10] with a BÉSM-6 computer from the GPVTs of the Siberian Branch of the Academy of Sciences of the USSR. The geometry of the molecules was selected in accordance with [11].

The synthesis of I and II was previously described in [3, 12]. The authors thank O. A. Zagulyaeva for providing us with a sample of III.

The ε values for the mixtures of solvents were found on the basis of the volume-per-unit additivity of the dielectric permeability [13].

LITERATURE CITED

1. I. Ya. Mainagashev, O. P. Petrenko, V. V. Kapachev, M. A. Fedotov, I. K. Korobeinicheva, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 4, 514 (1988).
2. V. V. Lapachev, O. A. Zagulyaeva, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 3, 395 (1977).
3. V. V. Lapachev, O. A. Zagulyaeva, and V. P. Mamaev, Dokl. Akad. Nauk SSSR, 238, 113 (1977).
4. V. V. Lapachev, O. A. Zagulyaeva, S. F. Bichkov, and V. P. Mamaev, Tetrahedron Lett., No. 33, 3055 (1978).
5. H. A. Germer, Theor. Chim. Acta, 35, 273 (1974).
6. O. P. Petrenko, V. V. Lapachev, I. K. Korobeinicheva, and V. P. Mamaev, Khim. Geterotsokl. Soedin., No. 12, 1668 (1987).
7. H. Reichard, Solvents in Organic Chemistry [Russian translation], Khimiya, Leningrad (1973), p. 67.
8. T. Kitagawa, S. Mizukami, and E. Hirai, Bull. Chem. Soc. Jpn., 26, 1403 (1978).
9. A. Gordon and R. Ford, The Chemist's Guide [Russian translation], Mir, Moscow (1976), p. 437.
10. L. G. Gorb and I. A. Abronin, CNINDO/Solv. SFKP-49. Informational Materials of the SFKP of the Siberian Branch of the Academy of Sciences of the USSR at the IKhKiG of the Siberian Branch of the Academy of Sciences of the USSR [in Russian], Vol. 2, Novosibirsk (1985).
11. S. Furberg and J. Solbakk, Acta Chem. Scand., 24, 3230 (1970).
12. O. A. Zagulyaeva, O. A. Grigorkina, V. I. Mamatyuk, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 3, 397 (1982).
13. Yu. Ya. Fialkov, I. I. Zhitomirskii, and Yu. L. Tarasenko, The Physical Chemistry of Nonaqueous Solutions [in Russian], Khimiya, Moscow (1973), p. 54.