Russian Journal of General Chemistry, Vol. 72, No. 6, 2002, pp. 949–956. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 6, 2002, pp. 1015–1023.
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Tautomeric Transformations and Reactivity of Polyfunctional Hydroxypyrimidines: III.[1] Tautomerism of 5-Acyl Derivatives of Hydroxypyrimidines and Formation of H-bonded Complexes with Solvents

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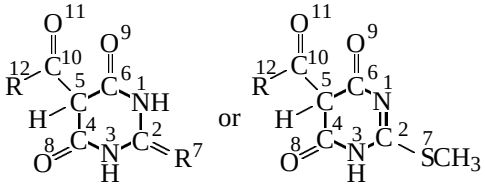
Received June 14, 2000

Abstract—Tautomerism of 5-formyl- and 5-acetyl derivatives of pyrimidine-2,4,6-trione, 2-thioxopyrimidine-4,6-dione, and 4,6-dihidroxy-2-methylthiopyrimidine was studied by NMR, UV, and IR spectroscopy, as well as by quantum chemistry. An equilibrium mixture of *exo*- and *endo*-enols in the neutral state and the presence of the same tautomers in monoanions were found. The energies of intramolecular hydrogen bonds in the gas phase and their changes in going to solutions in water, DMSO, and chloroform were calculated. The energies of intra- and intermolecular hydrogen bonds are close to each other. This fact suggests existence in solutions of two forms: tautomers with intramolecular H bond and H-bonded complexes with the solvents studied, whose formation involves cleavage of the intramolecular H bond. Characteristics of intermolecular hydrogen bonds are determined by the relative proton-donor and proton-acceptor powers of polyhydroxypyrimidines and solvents and are almost independent of the polarity of the medium.

5-Formyl- and 5-acetyl derivatives of polyhydroxypyrimidines can form intramolecular hydrogen bonds, as well as H-bonded complexes with solvents. As shown in [2], polyhydroxypyrimidines are prone to the keto-enol and lactim–lactam tautomerism, but their 5-formyl and 5-acetyl derivatives feature a new type of transformations: formation of *exo*- and *endo*-enol tautomers. It is known that the tautomerism of hydroxypyrimidine is closely associated with the possibility of formation of H-bonded complexes [3]. The aim of the present work was to study the tautomeric equilibrium in 5-formyl- and 5-acetyl derivatives of polyhydroxypyrimidines by NMR, UV, and IR spectroscopy in aqueous, chloroform, and DMSO solutions. This work is a continuation (see [1]) of our research into solvent effects on polyfunctional compounds whose structure is determined not only by the competition of their acidic and basic centers, but also by the possibility of intra- and intermolecular H bonding. Since the position of the tautomeric equilibrium in the polyhydroxypyrimidines studied depends on both their and solvent properties, we compared experimental spectral data with quantum-chemical results for the compounds themselves and their model complexes with solvents. The informative value of such a comparative analysis has been demonstrated in [4].

The objects for study were 5-formylpyrimidine-2,4,6-trione (**A**), 5-acetylpyrimidine-2,4,6-trione (**B**), 5-acetyl-2-thioxopyrimidine-4,6-dione (**C**), 5-acetyl-4,6-dihydroxy-2-methylthiopyrimidine (**D**), and 5-acetyl-4,6-dihydroxy-3-methyl-2-methylthiopyrimidine (**E**). The following atom numbering was applied.



R^7 = O, S; R^{12} = H, CH_3.

Analysis of published data [5] shows that the molecules can exist as the following tautomers: *endo*-enol **I**, *exo*-enol **II**, polycarbonyl structure **III**, and monoanions **IV**–**VII**.

Experimental data. 5-Formylbarbituric acid (**A**), 5-acetylbarbituric acid (**B**), 5-acetyl-2-thiobarbituric acid (**C**), 5-acetyl-4,6-dihydroxy-2-methylthiopyrimidine (**D**), and 5-acetyl-4,6-dihydroxy-3-methyl-2-methylthiopyrimidine (**E**) were synthesized by known procedures [6]. The NMR spectra of all the com-

[1] For communication II, see [1].

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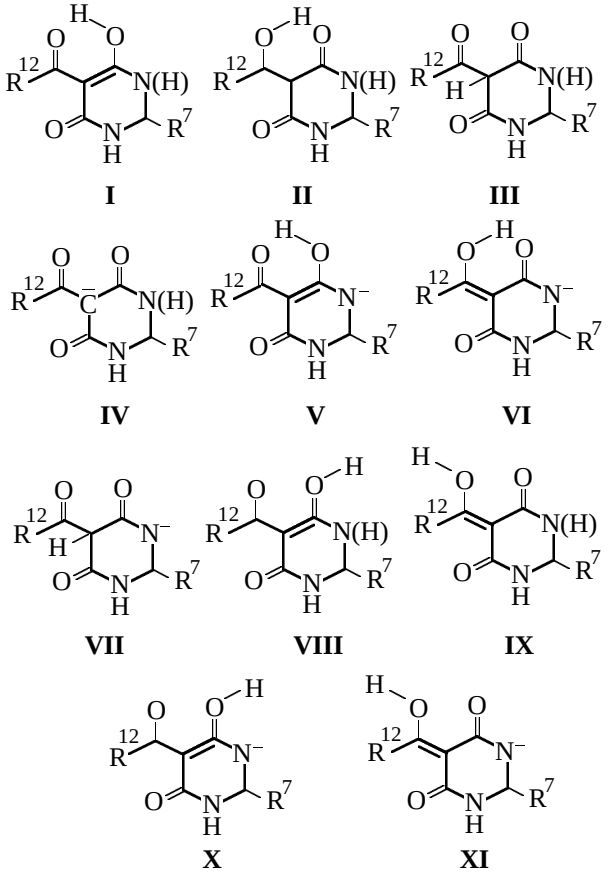

I **II** **III**

IV **V** **VI**

VII **VIII** **IX**

X **XI**

R^7 = O, S, SCH_3; R^{12} = H, CH_3.

pounds in water, chloroform, and DMSO were obtained by the procedures in [7]. It was shown that ^1H and ^{13}C NMR spectroscopies are an effective tool for studying the *endo*-enol–*exo*-enol tautometic equilibrium. The contents of *endo*-enol **I** [*P*(**I**)] and *exo*-enol **II** [*P*(**II**)] were estimated from the observed chemical shift (δ_{obs}) of the tautomeric mixture and the chemical shifts for pure *endo*-enol [δ(**I**)] or *exo*-enol forms [δ(**II**)], using the following formula [6]:

$$P(\mathbf{I}) = [\delta_{obs} - \delta(\mathbf{II})]/[\delta(\mathbf{I}) - \delta(\mathbf{II})].$$

Here δ(**I**) and δ(**II**) are the chemical shifts expected for pure tautomers **I** and **II**. According to published data for cyclic β-dicarbonyl compounds, the signal of the carbonyl C^{10} atom is at δ(**I**) 202 ppm, and the signal of the C^{10} atom double-bonded with C^5 and bearing a hydroxy group, at δ(**II**) 168 ppm [7, 8]. Characteristic spectral features of neutral and anionic forms of polyhydroxypyrimidines we described in [6]; account was also taken of data in [9]. The IR spectra were obtained for solid samples as described [10].

Table 1 lists NMR and UV spectral data for solutions. The UV spectra of neutral molecules both in aqueous solutions and in alcohols and dioxane contain a strong band at 280–300 nm, which points to a strongly conjugated system, lacking in polycarbonyl tautomer **III** and characteristic of enol forms **I** and **II**. The enol forms, according IR spectral data, remains prevailing in the crystal state, as judged from the observation of a series of strong bands at 1500–1640 cm^{-1}, characterstic of conjugated carbonyl groups, a diffuse band at 2500–3000 cm^{-1}, as well as well-defined bands at 1150–1200 cm^{-1}, characteristic of H-bonded hydroxy groups. The ^1H and ^{13}C NMR spectra reveal presence of tautomers **I** and **II** and lack of structure **III**. However, the sharp difference in the signals of associated proton and C^{10} in 5-formyl and 5-acetyl derivatives suggests different *endo/exo*-enol ratios in these derivatives. The contents of tautomers **I** and **II**, estimated from the NMR spectra, as well as the tautometic equilibrium constants pK_t = –log [**II**]/[**I**] are listed in Table 2. As seen, the prevailing tautomer in 5-formylbarbituric acid is *exo*-enol **II**, 5-acetylbarbituric and 5-acetyl-2-thiobarbituric acids prefer *endo*-enol form **I** (*endo/exo*-enol ratio ca. 1.7 : 1), while in 2-methylthio derivatives **G** and **E** *endo/exo*-enol ratio is ca. 7 : 1.

In going to monoanions, as seen from data in Table 1, the UV spectra acquire one more absorption maximum at 240–260 nm, and the long-wave band in the spectra of acetyl derivatives gets weaker, while in the spectra of formyl derivatives, stroger (which gives further evidence for the existence of different tautomers in the neutral state). According to [11], the short-wave maximum relates to the electron transition between molecular orbitals of the overall conjugated system, and the long-wave maximum, to the electron transition from the β-dicarbonyl system to the acetyl carbonyl group.

The ^1H and ^{13}C NMR spectra of the anions of acetyl derivatives, too, correspond to tautomer **IV**, since they contain NH proton signals, and the C^4 and C^6 signals coalesce to form a single narrow signal. The coincidence of the C^4 and C^6 signals in the NMR spectra of the monoanions of acetyl derivatives (Table 1) points to a low multiplicity of the bond between the acetyl group and the pyrimidine ring. The same conclusion follows from the fact that the C^{10} signal is near 200 ppm, i.e. in the region characteristic of ketone carbonyl signals [7]. At the same time, the broadened signals of the pyrimidine NH protons appear to imply involvement of these protons in the lactim–lactam tautomerism and, consequently, formation of *endo*-enol **V** and *exo*-enol **VI**.

Structure of 5-formyl- and 5-acetyl derivatives in the gas phase. Relation between characteristics of

Table 1. Spectral characteristics of 5-formylbarbituric acid (**A**), 5-acetylbarbituric acid (**B**), 5-acetyl-2-thiobarbituric acid (**C**), 5-acetyl-4,6-dihydroxy-2-methylpyrimidine (**D**), and 5-acetyl-4,6-dihydroxy-3-methyl-2-methylthiopyrimidine (**E**)

Compound	Charge	UV spectrum		^{1}H NMR spectrum, δ, ppm				^{13}C NMR spectrum, δ_C, ppm			
		λ_{max}, nm	ε	solvent	$H^{1(3)}$	R^{12}	OH	C^4	C^5	C^6	C^{10}
A	0	274	12 000	$CDCl_3$	3.32	8.65	13.9	160.3	98.9	167.5	177.4
				DMSO	3.10	8.52	13.2	160.4[a]	99.5	163.4[a]	176.4
	–1	244	5600	DMSO[b]	3.20	8.45	–	164.3	95.2	164.3	186.9
		280	17 000								
B	0	276	17900	$CDCl_3$	3.38 3.32	2.70	17.2	160.6	95.4	169.1	1975.6
				DMSO	3.20	2.60	17.2	165.2[a]	95.8	165.2[a]	194.9
	–1	250	9200	DMSO[b]	3.12	2.55	–	164.9	95.9	164.9	195.0
		277	14 400								
C	0	306	25400	DMSO	12.0	2.46	17.0	165.0[a]	96.2	165.0[a]	195.8
	–1	254	4250	DMSO[b]	11.0[a]	2.30	–	163.2	97.3	163.2	194.4
		299	17 900								
D	0	251	5400	DMSO	12.0	2.55	16.0[a]	174.5[a]	98.2	174.5	202.9
		303	17 000								
	–1	235	11 400	DMSO[b]	9.7[a]	2.35	–	172.4	98.4	172.4	201.7
		296	10 100								
E	0	252	5000	DMSO	3.3	2.65	16.0[a]	172.0	97.3	170.6	203.4
		304	17 500								
	–1	296	10 450	DMSO[b]	3.25	2.35	–	169.7	99.2	162.6	197.8

[a] Broad signal. [b] DMSO-d_6 + triethylamine.

Table 2. Constants of the *endo*–*exo*-enol tautomeric equilibrium (pK_t) and experimental and calculated dissociation constants (pK_a) of tautomers **I** and **II** of polyhydroxypyrimidine derivatives

Compound	pK_t	Content, %		pK_a	pK_a(**I**)	pK_a(**II**)
		I	**II**			
A	–0.51	23.8	76.2	2.35	1.73	2.26
B	0.22	62.5	37.5	4.62	4.42	4.20
C	0.29	66.0	34.0	2.70	2.52	2.23
D	0.84	87.5	12.5	5.50	5.44	4.60
E	0.91	89.0	11.0	6.00	5.95	5.04

intramolecular hydrogen bond and position of tautomeric equilibrium in hydroxypyrimidines in the absence of solvents have never been studied [12]. Gas-phase characteristics were obtained by quantum-chemical calculations. As follows from published data, semiempirical calculation schemes both provide reliable results and allow one to span a wide range of structures and their associates [13]. Like Millefiori and Millefiori [14], we consider AM1 results for polyhydroxypyrimidine derivatives fairly fitting experiment. However, to avoid errors intrinsic in the AM1 scheme, we also performed PM3 calculations. The geometries of the structures were fully optimized, no symmetry constraints were imposed, and local minima and transition states on the potential energy surface were identified by analysis of the matrix of force constants. The calculations were performed using GAMESS [15]. It was found that, regardless of the fact that the AM1 and PM3 geometries differ considerably, the relative energies obtained by these two methods are mutually consistent.

In accordance with [2, 16], apart from *endo*- and *exo*-enol structures **I** and **II**, we calculated all possible tautomers of the compounds studied for the neutral and anionic states. Table 3 lists the enthalpies of formation (AM1 and PM3) of tautomers **I**–**VII**. It can be seen that the enthalpies of formation of enol tautomers are higher than that of keto tautomer **III**. The difference in the enthalpies of formation of tautomers **I** and **II** for all the compounds studied is much smaller than the respective value for keto tautomer **III** and enol **I** or **II**. Consequently, according to the theoretical criteria for real tautomeric processes [2], the keto-enol tautomerism in the hydroxypyrimidine fragment of 5-formyl and 5-acetyl derivatives is

Table 3. Enthalpies of formation of tautomeric structures **I**–**VII** of polyhydroxypyrimidines **A**–**D**, calculated by the AM1 and PM3 methods, kcal/mol

Comp. no.	A		B		C		D	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
I	–134.1	–157.2	–139.1	–163.5	–83.2	–92.1	–80.0	–98.3
II	–139.6	–158.5	–145.1	–165.2	–89.0	–93.8	–81.5	–95.3
III	–129.6	–150.0	–137.8	–159.6	–79.6	–84.5	–72.6	–88.3
IV	–190.7	–213.0	–193.8	–216.2	–143.4	–155.0	–127.0	–148.6
V	–182.8	–211.6	–186.3	–217.0	–137.6	–154.1	–128.1	–155.1
VI	–172.3	–198.9	–176.1	–204.7	–129.3	–144.2	–120.1	–145.7
VII	–169.6	–195.8	–175.8	–202.6	–127.9	–142.1	–120.6	–144.7

hardly probable. The low probability of the lactim–lactam tautomerism follows from the fact that the formation of a dienol with O^9–H and O^{11}–H groups and dissociated N^1–H bond raises the energy by 20 kcal/mol and more. The energetically favorable tautomer of monoanions is tautomer **IV** containing C^6=O and C^{10}=O bonds and dissociated heteroring C^5–H bond. However, the close enthalpies of formation of enols **V**, **VI** and **IV** point to a considerable probability of the lactam–lactim tautomerism in monoanions. The keto-enol equilibrium involving anion **VII** is energetically disfavored (Table 3). An exception is the monoanion of 5-acetyl-4,6-dihydroxy-2-methylthiopyrimidine (**D**) whose polycarbonyl structure **IV** has a higher enthalpy of formation than enol. This fact can be considered evidence in favor of a high probability of the lactim–lactam tautomerism in the monoanions of polyhydroxypyrimidines: Since 2-methylthio derivatives have no hydrogen atom on N^1, lactam structure **IV** proves to be less favored than lactim structures **V** and **VI**. Consequently, the calculations predict the energetic preference of the *endo*–*exo*-enol equilibrium both in molecules and in monoanions, which fully agrees with experimental data.

In keeping with [17], as a measure of the H-bond energy (E_H) in *endo*-enols we took the difference in the enthalpies of formation of tautomers **VIII** and **I**, and in *exo*-enols, the respective difference for tautomers **IX** and **II**. Similarly, the H-bond energies in monoanions are estimated through the differences in the enthalpies of formation of tautomers **X** and **V** for *endo*-, and of tautomers **XI** and **VI**, for *exo*-enols. Table 4 lists the relative energies of *endo*- and *exo*-enol tautomers and the energies of the corresponding H bonds for neutral forms. Table 5 lists the respective values for monoanions. Analysis of the resulting data shows that the intramolecular H bonds in *endo*- and *exo*-enols are nonequivalent, but the E_{intra} values for these tautomers range from 0 to 0.8 kcal/mol in neutral molecules (except for 2-methylthio derivative **D**). In monoanions, the E_{intra} range is 0.4–12.1 kcal/mol. The H-bond lengths in neutral *endo*-enols are, on average, 1.9217 Å, in *exo*-enols, 1.9450 Å, and in monoanions, 1.9172 and 1.8924 Å, respectively. Consequently, anions have shortened internuclear distances between H-bonded atoms, which is consistent with reduced energies of the structures and enlargement of their conjugation system [2]. The enthalpies of formation were recounted into the corresponding dissociation constants to find that pK_a(**I**) – pK_a(**II**) for neutral molecules is 0.004 and for monoanions, 0.007. Consequently, the two tautomers are close in acidity. Further conclusion is that the potential energy surfaces of both isolated molecules and monoanions have local minima both for *endo*- and *endo*-enols. These minima differ from each other, but, as judged from the calculated energies, geometries, electron density distributions, and some other parameters, the difference is inconsiderable. Consequently, the system in hand close in its properties to systems with very strong, low-barrier hydrogen bonds [18]. The above findings also provide evidence showing that the dynamic *endo*–*exo*-enol tautomeric equilibrium really exists [19].

Solvent effects. We experimentally established that the electronic spectra of nonionized derivatives of barbituric acids in water, alcohol, and dioxane are similar. As seen from Table 1, the chemical shifts of the C^{10}, C^5, C^2, and NH signals in the NMR spectra of these compounds in DMSO and chloroform almost coincide. Consequently, solvents exert no effect on the position of the tautomeric equilibrium (earlier the same effect was observed in [7]). Assuming similar pK_t values (for the *endo*–*exo*-enol equilibrium) in different solvents, we estimated, from the pK_t values of the compounds in DMSO and the respective pK_a

Table 4. Differences in the enthalpies of formation (ΔH_t) of *endo*- (**I**) and *exo*-enols (**II**) of polyhydroxypyrimidines **A**–**D**, energies of their intramolecular H bonds (E_{intraH}), and energies of intermolecular H bonds in solvation complexes (E_{interH}), calculated by the AM1 and PM3 methods, kcal/mol

Compound	ΔH_t[a]		$-E_{intra}$H(**I**)		$-E_{intraH}$(**II**)		$-E_{interH}$(**I**)		$-E_{interH}$(**II**)	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
A	–5.5	–1.3	9.8	13.8	9.9	10.3	–	–	–	–
A + $2H_2O$	–4.7	–0.5	5.9	10.8	8.4	5.3	13.5	6.2	14.3	6.6
A + DMSO	–4.0	–0.7	1.6	3.7	3.6	3.2	5.2	1.9	6.7	2.5
A + $CHCl_3$	–4.9	–1.0	11.7	15.4	11.7	11.0	1.9	1.6	2.5	1.9
B	–6.0	–2.1	10.4	4.6	9.7	9.9	–	–	–	–
B + 2 H_2O	1.0	0.5	5.8	5.8	3.4	6.7	14.2	4.8	7.2	3.2
B + DMSO	4.1	1.3	2.1	0.8	3.5	3.6	6.4	2.4	4.5	1.6
B + $CHCl_3$	5.7	1.5	11.3	3.2	10.0	10.4	2.5	2.2	2.2	1.6
C	–5.8	–1.7	10.2	16.7	9.4	9.4	–	–	–	–
C + 2 H_2O	0.9	0.3	5.7	3.8	2.5	4.4	14.2	4.7	7.5	3.3
C + DMSO	4.2	1.1	1.6	0.7	3.4	3.0	6.6	2.8	5.0	2.2
C + $CHCl_3$	5.6	1.4	11.2	1.9	9.6	9.8	2.4	1.9	2.2	1.6
D	–1.5	3.0	0.7	6.9	10.3	9.2	–	–	–	–
D + 2 H_2O	1.4	5.5	1.9	1.1	2.5	5.7	16.0	5.7	13.1	3.2
D + DMSO	0.3	5.0	2.8	1.1	5.2	1.2	6.8	4.6	5.0	2.6
D + $CHCl_3$	0.3	2.8	5.3	4.0	10.8	10.7	4.9	2.8	3.7	3.0

[a] $\Delta H_t = \Delta_f H$(**II**) – $\Delta_f H$(**I**).

Table 5. Differences in the enthalpies of formation (ΔH_t) of the monoanions of *endo*- (**I**) and *exo*-enols (**II**) of polyhydroxypyrimidines **A**–**D**, energies of their intramolecular H bonds (E_{intraH}), and energies of intermolecular H bonds in solvation complexes (E_{interH}), calculated by the AM1 and PM3 methods, kcal/mol

Compound	ΔH_t[a]		$-E_{intraH}$(**V**)		$-E_{intraH}$(**VI**)		$-E_{interH}$(**V**)		$-E_{interH}$(**VI**)	
	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3	AM1	PM3
A	10.5	12.7	3.5	5.4	15.6	17.7	–	–	–	–
A + $2H_2O$	5.9	9.6	2.1	5.4	21.0	23.2	16.8	11.6	21.4	14.7
A + DMSO	4.5	8.4	4.0	5.6	15.7	26.8	2.6	6.3	8.6	10.6
A + $CHCl_3$	8.0	9.4	6.4	3.0	23.6	20.3	5.9	7.5	8.4	10.8
B	10.2	12.3	4.3	7.2	15.5	16.9	–	–	–	–
B + 2 H_2O	6.2	12.1	2.2	9.2	11.7	23.5	17.4	13.9	21.4	14.1
B + DMSO	4.1	8.3	3.6	7.6	18.5	17.3	2.5	6.5	8.6	10.5
B + $CHCl_3$	7.8	7.0	6.1	1.9	4.7	24.2	6.2	5.6	8.6	10.9
C	8.3	9.9	5.4	6.2	5.0	14.2	–	–	–	–
C + 2 H_2O	6.3	7.7	8.0	8.4	8.2	23.5	16.4	13.4	18.4	15.6
C + DMSO	2.7	7.8	6.6	2.4	5.2	15.6	2.0	5.4	7.6	7.5
C + $CHCl_3$	6.4	10.1	5.7	7.6	4.0	2.1	5.6	4.7	7.5	4.5
D	8.0	9.4	5.0	7.1	11.2	14.0	–	–	–	–
D + $2H_2O$	7.4	10.9	2.0	4.5	7.0	11.0	17.4	10.2	18.0	8.8
D + DMSO	7.1	8.0	2.6	4.4	18.9	17.5	6.4	6.0	7.3	7.4
D + $CHCl_3$	5.9	7.6	5.4	5.6	13.0	19.6	6.2	7.9	8.3	9.7

[a] $\Delta H_t = \Delta_f H$(**VI**) – $\Delta_f H$(**V**).

values in H_2O [3], pK_a(**I**) and pK_a(**II**) for *endo*-enol **I** and *exo*-enol **II**. The calculation procedure is described in [6]. The resulting pK_a(**I**) and pK_a(**II**) values are given in Table 2. Comparison of the pK_a values with data for 1,3-dimethylbarbituric acid (pK_a 2.88), 2-thiobarbituric acid (pK_a 2.1), and 4,6-dihydroxy-2-methylthiopyrimidine (pK_a 3.1) shows that the formyl substituent enhances the acidity of the polyhydroxypyrimidine fragment, while the acetyl substituent weakens it. As a result, formyl derivatives prefer the *exo*-enol form, while acetyl derivatives, the *endo*-enol form. Therewith, the properties of the nitrogen containing fragment of the pyrimidine ring are also affected. For instance, since the acetyl substituent weakens the acidity of the pyrimidine β-dicarbonyl system, 2-methylthio derivative **D** has no zwitter-ionic forms, unlike 4,6-dihydroxy-2-methylthiopyrimidine [6].

Comparative analysis shows that the experimental (Tables 1, 2) and calculated (Tables 4, 5) lead to different conclusions concerning the position of the *endo*–*exo*-enol equilibrium. Gas-phase (calculated) data are known to differ from liquid-phase because of solvent effects. To gain insight into the solvent effects on the molecules and monoanions studied, we performed, like in [1], supermolecular calculations of solvent–solute complexes [20]. For solvents we took H_2O, chloroform, and DMSO, which differ in polarity and proton-donor and proton-acceptor properties. As found in [21], derivatives of barbituric acid in these media form variable-composition associates with solvent molecules, both via nonbonded interactions and via H bonding. Our supermolecular calculations showed that solvent molecules, forming H-bonded structures, fit into *endo*-enols **I** and **V** between H–O^9 and O^{11} with cleavage of the intramolecular hydrogen bonds H···O^{11} and into *exo*-enols **II** and **VI**, between H–O^{11} and O^9 with cleavage of the intramolecular hydrogen bonds H···O^9. Solvent molecules coordinate with solute molecules or anions via intermolecular H bonding. The number of solvent molecules required for calculated data to fit experiment is small (like in [4]). Calculations of some hydroxypyrimidine complexes with one H_2O molecule have been reported [22]. However, such associates, according to Jorgensen's concept [23] of more intricate H interactions in hydration shells of molecules [24] than in the model one barbituric acid molecule–one H_2O molecule, cannot model the effect of water as solvent. Therefore, like in [25], we performed calculations with two H_2O molecules. The calculation with one chloroform or DMSO is correct, since the second solvent molecule here cannot form, for steric reasons, H bonds between O^9 and O^{11}. The superomolecular calculations were performed by the AM1 and PM3 methods without symmetry constraints and with identification of local minima and transition states on the potential energy surface.

As can be seen (Tables 4, 5), in the presence of solvents the energy gaps between the *endo*- and *exo*-enols change. Thus, in full agreement with experiment, 5-formylbarbituric acid (**A**) in solutions should prefer *exo*-enol form **II**, while 5-acetyl derivatives, *endo*-enol form **I**. In monoanions, both formyl and acetyl derivatives should prefer tautomer **V**.

The energies of intramolecular hydrogen bonds in the presence of solvents were calculated. It is shown E_{intraH} in the latter case changes compared with those for isolated molecules. It can be stated that the E_{intraH} of both the tautomers of nonionized derivatives decrease. For aqueous solutions of monoanions, E_{intraH} increase in the *exo*-enol of 5-formyl- and 5-acetyl-2-thiobarbituric acid and decrease in the *endo*-enols of all the derivatives. Dimethyl sulfoxide generally similarly change E_{intraH}. The comparatively low-polarity chloroform, as a rule, strengthens the hydrogen bond (except for the monoanion of the *exo*-enol).

It is expedient to consider the total energies of H bonding with solvents, i.e. the energies of intermolecular hydrogen bonds (E_{interH}). The E_{interH} values were calculated as differences between the enthalpies of formation of the complex involving one molecule of a barbituric acid derivative and one molecule of a solvent and the enthalpies of formation of isolated molecules of the barbituric acid derivatives and solvent. For instance, the formula for calculating E_{interH} for tautomer **I** is as follows:

$$E_{interH} = \Delta_f H(\text{complex}) - \Delta_f H(\mathbf{I}) - \Delta_f H(\text{solvent}).$$

Here $\Delta_f H$(complex) is the enthalpy of formation of the complex barbituric acid derivative–solvent, $\Delta_f H$(**I**) if the enthalpy of formation of tautomer **I**, and $\Delta_f H$(solvent) is the enthalpy of formation of two mol of H_2O or one mol of chloroform or DMSO.

Data in Tables 4 and 5 show that, first, both methods give mutually consistent E_{interH} values. Second, the total energy of H bonding E_{interH} is the highest for H_2O, for DMSO it is lower by a factor 2–3, and for chloroform it is even lower. Third, E_{interH} vary only slightly for different derivatives and tautomers. Fourth, in going to monoanions the energy increases only slightly (1–4 kcal/mol), and the largest increase is characteristic of chloroform.

Analysis of solvation energies most commonly involves their separation into electrostatic and specific

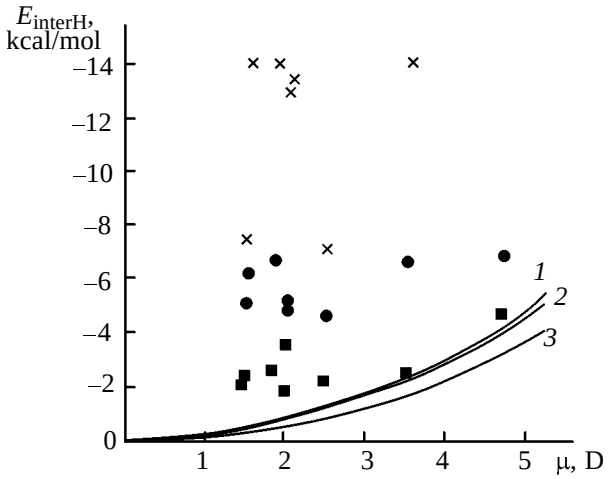

Fig. 1. Comparison of the total energy of H bonding E_{interH} in solvation complexes with (crosses) H_2O, (circles) DMSO, and (squares) $CHCl_3$ and (*1*–*3*) the electrostatic contribution on the dipole moment μ of solute. Solvent: (*1*) H_2O, (*2*) DMSO, and (*3*) $CHCl_3$.

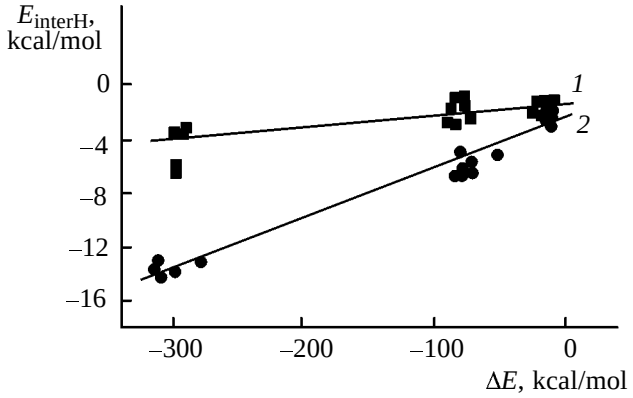

Fig. 2. Dependence of the total energy of H bonding E_{interH} in solvation complexes of the ΔE value measuring the proton-donor and proton-acceptor properties of solvents and solutes. Calculation method: (*1*) PM3 and (*2*) AM1.

contributions [26]. Figure 1 shows the dependence of solvation on the dipole moments of solutes. The curves were plotted in terms of the reactive field model and Onsager's formula [27] for solutions of the compounds studied in water, DMSO, and chloroform. These curves relate to a "pure" contribution of electrostatic solvation. The points corresponding to E_{interH} lie much higher, implying a considerable contribution of the energies of H bonds into the energies of formation of solvation complexes. However, the magnitude of deviation of points from calculated curves (Fig. 1) includes not only the energy of intermolecular H bonding, but also, according to [28], changes of this energy under the action of a polar solvent. The energy of formation of intermolecular H bond in the gas phase is associated with proton donation from polyhydroxypyrimidine [for instance, in tautomer **I**, from O^9] and proton acception from solvent. Simultaneously, all the solvents studied donate their proton, while polyhydroxypyrimidine accepts it by a neighboring functional group [in structure **I** it is O^{11}]. Consequently, E_{interH} should depend on the difference in the deprotonation energy (E_{deprot}) and the proton affinity (E_{H^+}) of both solute and solvent. In the present work we calculated both E_{deprot} and E_{H^+} and correlated E_{interH} with ΔE calculated by the following formula:

$$\Delta E = E_{deprot}(\text{tautomer}) - E_{H^+}(\text{tautomer}) - E_{deprot}(\text{solvent}) + E_{H^+}(\text{solvent}).$$

The resulting correlations are as follows (see also Fig. 2).

AM1 method

E_{interH}(**I, II**) = 0.0375ΔE – 2.21; *r* 0.943, *s* 2.3, *n* 20,

E_{interH}(**V**) = 0.0385ΔE – 13.29; *r* 0.961, *s* 1.5, *n* 12,

E_{interH}(**VI**) = 0.0340ΔE – 15.05; *r* 0.974, *s* 1.9, *n* 12.

PM3 method

E_{interH}(**I, II**) = 0.0092ΔE – 1.53; *r* 0.926, *s* 3.0, *n* 20,

E_{interH}(**V**) = 0.0125ΔE – 8.83; *r* 0.982, *s* 1.3, *n* 12,

E_{interH}(**VI**) = 0.0194ΔE – 12.97; *r* 0.955, *s* 2.9, *n* 12.

These correlations show that the solvation of H bonding, measured bu with solvents is mostly determined by the proton-donor and proton-acceptor properties of tautomers and solvents, while the effect of electrostatic solvation and the polarity of the medium on E_{interH} is much weaker.

The above findings led us to conclude that in the molecules of polydentate 5-formyl and 5-acetyl polyhydroxypyrimidine derivatives both in solutions and the gas phase undergo no other tautomerism than *endo*–*exo*-enol. In monoanions, in addition, the lactam–lactim tautomerism was also revealed. It was found that in solutions two types of structures can coexist: structures involving intramolecular H bonds, as well as solvation H complexes in which the latter bonds are cleaved, because the energies of intramolecular H bonds and of solvation intermolecular H bonding are close to each other. We also established that in solutions the *endo*-*exo*-enol equilibrium in

5-acetyl derivatives is shifted, compared to the gas phase, to the *endo* tautomer.

REFERENCES

1. Slesarev, V.I. and Popov, A.S., *Zh. Obshch. Khim.*, 2000, vol. 70, no. 4, p. 660.
2. Slesarev, V.I. and Popov, A.S., *Zh. Obshch. Khim.*, 1999, vol. 69, no. 6, p. 1027.
3. Smets, J., Destexhe, A., Adamowicz, L., and Maes, G., *J. Phys. Chem. A*, 1998, vol. 102, no. 42, p. 8157.
4. Zhanpeisov, N.U. and Lesczynski, S., *Int. J. Quantum Chem.*, 1998, vol. 69, no. 1, p. 37.
5. Ivin, B.A., Slesarev, V.I., Smorygo, N.A., Tsereteli, I.Yu., and Sochilin, E.G., *Zh. Org. Khim.*, 1970, vol. 6, no. 6, p. 1313; Buckingham, D.A., Clarc, C.R., McKeown, R.H., and Wong, O., *J. Am. Chem. Soc.*, 1987, vol. 109, no. 2, p. 446; Tate, J.V., Tinnerman, N.W., Jurevics, V., Jeskey, H., and Biehl, E.R., *J. Heterocycl. Chem.*, 1986, vol. 23, no. 1, p. 9.
6. Slesarev, V.I., Popov, A.S., and Okun, V.M., *Targets Heterocycl. Systems*, 1998, vol. 2, p. 309.
7. Gindin, V.A., *Yadernyi magnitnyi rezonans v organicheskoi khimii* (Nuclear Magnetic Resonance in Organic Chemistry), Leningrad: Leningr. Gos. Univ., 1974, no. 1, p. 132.
8. Ascenso, J., Candiode, M., Vaz, T.A., and Frausto da Silva, J.J.R., *Inorg. Nucl. Chem.*, 1981, vol. 43, p. 1255; Kelly-Rowley, A.M., Lynch, V.M., and Auslyn, E.V., *J. Am. Chem. Soc.*, 1995, vol. 117, no. 12, p. 3438.
9. Wilcox, C.S. and Frontiers, A.D., *Supramolecular Organic Chemistry and Photochemistry*, Scheider, H.J. and Durr, H., Eds., Weinheim: VCH, 1990.
10. Bideau, J.-P., Huong, P.V., and Toure, T., *Acta Crystallogr., Sect. B*, 1976, vol. 32, p. 481.
11. Gren, E.Ya. and Vanag, G.Ya., *Teor. Eksp. Khim.*, 1966, vol. 2, no. 3, p. 302.
12. Chandra, A.K., Nguyen, M.T., and Zcegers-Huys kens, T., *J. Phys. Chem. A*, 1998, vol. 102, no. 29, p. 6010.
13. Morpurgo, S., Bossa, M., and Morpurgo, G.O., *Theochem*, 1998, no. 429, p. 71.
14. Millefiori, S. and Millefiori, A., *J. Heterocycl. Chem.*, 1989, vol. 26, no. 3, p. 639.
15. Schmidt, M.W., Baldridge, K.K., Boatz, J.A., Elbert, S.T., Gordon, M.S., Jensen, J.H., Koseki, S., Matsunaga, N., Nguyen, K.A., Su, S.J., and Windus, T.L., *J. Comput. Chem.*, 1993, vol. 14, no. 8, p. 1347.
16. Gilli, P., Vertolasi, V., Ferretti, V., and Gilli, G., *J. Am. Chem. Soc.*, 1994, vol. 116, no. 2, p. 909.
17. McAllister, M.A., *Can. J. Chem.*, 1997, vol. 75, no. 7, p. 1195.
18. Hibert, F. and Emsley, J., *Adv. Phys. Org. Chem.*, 1990, vol. 26, no. 1, p. 255.
19. Minkin, V.I., Olekhnovich, L.P., and Zhdanov, Yu.A., *Molekulyarnyi dizain tautomernykh system* (Molecular Design of Tautomeric Systems), Rostov-on-Don: Rostov. Gos. Univ., 1977.
20. Simkin, B.Ya. and Sheikhet, I.I., *Kvantovo-khimicheskaya i statisticheskaya teoriya rastvorov. Vychislitel'nye metody i ikh primenenie* (Quantum-Chemical and Statistical Theory of Solutions. Computational Methods and Their Applications), Moscow: Khimiya, 1989; Schneider, B., Cohen, D., and Berman, H.M., *Biopolymers*, 1992, vol. 32, no. 3, p. 725.
21. Chang, S.K. and Hamilton, A.D., *J. Am. Chem. Soc.*, 1988, vol. 110, no. 5, p. 1318; Tecilla, P., Dixon, R.P., Slobodkin, G., Alavi, D.S., Waldeck, D.H., and Hamilton, A.D., *J. Am. Chem. Soc.*, 1990, vol. 112, no. 15, p. 9408.
22. Ngyuen, M.T., Chandra, A.K., and Zeegers-Huyskens, Th., *J. Chem. Soc., Faraday Trans.*, 1998, vol. 94, no. 16, p. 1277.
23. Jorgensen, W.L. and Pranata, J., *J. Am. Chem. Soc.*, 1990, vol. 112, no. 4, p. 2008; Jorgensen, W.L. and Severance, D.L., *J. Am. Chem. Soc.*, 1991, vol. 113, no. 1, p. 207.
24. Savage, H.J., Elliot, C.J., Freeman, C.M., and Finney, J.L., *J. Chem. Soc., Faraday Trans.*, 1993, vol. 89, no. 17, p. 2609.
25. Ghomi, M., Aamouche, A., Cadioli, B., Berthier, G., Grajcar, L., and Baron, M.H., *J. Mol. Struct.*, 1997, no. 390, p. 11.
26. Burger, K., *Solvation, Ionic and Complex Formation Reactions in Non-Aqueous Solvents*, Amsterdam: Elsevier, 1983.
27. Smirnova, N.A., *Molekulyarnye teorii rastvorov* (Molecular Theories of Solutions), Leningrad: Khimiya, 1984.
28. Jorg, S., Grago, R.S., and Adams, J., *J. Chem. Soc., Perkin Trans. 2*, 1997, no. 2, p. 2431.