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Tautomeric Transformations and Reactivity of Polyfunctional Hydroxypyrimidines: IV.[1] Effects of Tautomer Structure and Acidity and Solvent Nature on the State of Tautomeric Equilibria in the Series of 5-Nitro Derivatives of 2,4,6-Pyrimidinetrione

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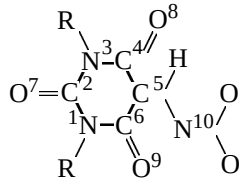
Abstract—Tautomeric equilibria of 5-nitrobarbituric acid and 1,3-dimethyl-5-nitrobarbituric acid were studied by NMR, UV, and IR spectroscopy, as well as by quantum-chemical methods. These compounds were found to exist in the gas phase, in solutions in water and DMSO, and in crystal as the corresponding enol tautomers. In trifluoroacetic and chloroform solutions, an equilibrium mixture of the ketone and enol forms was detected. The parameters determining the state of the tautomeric equilibrium are the total energy of a tautomer, its deprotonation energy, and a component of the latter, which relates to electrostatic interaction between the mobile proton and the rest of the molecule. Proton-donor and proton-acceptor properties of the solvent and 5-nitro-2,4,6-pyrimidinetrione derivatives are the main factors responsible for displacement of the tautomeric equilibrium in solution; electrostatic solvation and tautomer stabilization via hydrogen bonding are less significant.

This work continues our systematic studies on the tautomerism of polyhydroxypyrimidine derivatives. We previously showed that the dynamic tautomeric equilibrium in a molecular system is displaced toward a tautomer possessing the lowest total energy [2]. However, the second factor determining the state of equilibrium in solution is the acidity of tautomers and acid–base properties of the solvent [3]. The third factor is the possible stabilization of tautomeric species via formation of intra- and intermolecular hydrogen bonds [1]. 5-Nitro derivatives of various polyhydroxypyrimidines exhibit antiviral [4] and enzymatic activity [5] and are promising compounds for pharmacology and applied biochemistry [6]. On the other hand, the anomalous behavior of nitro derivatives of β-dicarbonyl compounds in organic reactions [7], as well as their enhanced acidity relative to the other substituted derivatives, requires special investigation. The results of studies of nitro-substituted polyhydroxypyrimidines, specifically of their electronic structure, interactions between substituents in the pyrimidine ring, polyprototropic tautomerism, acid–base properties, intramolecular hydrogen bonding, and hydrogen bonding with solvent molecules [8, 9], have supplemented previously established criteria for the position of equilibrium in tautomeric systems [1–3].

The goal of the present work was to examine tautomeric properties of 5-nitro-2,4,6-pyrimidinetrione (**I**) and 1,3-dimethyl-5-nitro-2,4,6-pyrimidinetrione (**II**). In the framework of this problem we studied the structure of compounds **I** and **II** in the neutral and ionized forms; considered tautomeric transformations involving both neutral molecules and the corresponding anions; examined the acidity and acidifying factors; and analyzed solvent effects (solvation factors). In keeping with the other publications [10], this work was performed as a comparative analysis of the available experimental (spectral) data and the results of theoretical quantum-chemical calculations. Compounds **I** and **II** were synthesized, and their NMR, UV, and IR spectra were recorded, according to [11]. Quantum-chemical calculations were performed at the 3-21+GF level with the aid of GAUSSIAN 94 software package. The following atom numbering was accepted:



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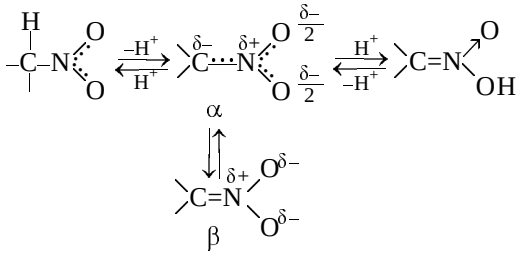
According to published data [12], nitro compounds could give rise to two molecular structures with a common mesomeric anion (Scheme 1). However, in the case of 5-nitrobarbituric acid (**I**), one more enol tautomer should be added, which is formed by proton transfer from C^5 to O^9. As a result, the overall number of possible tautomers (including protonated and deprotonated species) amounts to 9 (Scheme 2). Hereinafter, K stands for ketone, E for enol, Ac for *aci*-nitro form, and A^-, A^{2-}, and A^{3-}, for mono-, di-, and trianion, respectively; H_1^+, H_2^+, and H_3^+ denote different protonated species.

Scheme 1.



The geometric parameters and enthalpies of formation of different tautomers in the gas phase were determined by 3-21+GF quantum-chemical calculations; the validity of this procedure was discussed previously [10, 13]. As follows from the data in Scheme 2 (the enthalpies of formation are given in kJ mol^{-1}), the most energetically favorable among the neutral forms of compound **I** is enol structure E. The energy of formation of ketone K is greater by 5.8 kJ mol^{-1}, and that of *aci*-nitro tautomer Ac, by 17.6 kJ mol^{-1}. Monoanion A^- is stabilized by 288.3 kJ mol^{-1} relative to enol E, and protonation requires 717.1 kJ mol^{-1} and more.

Scheme 2.

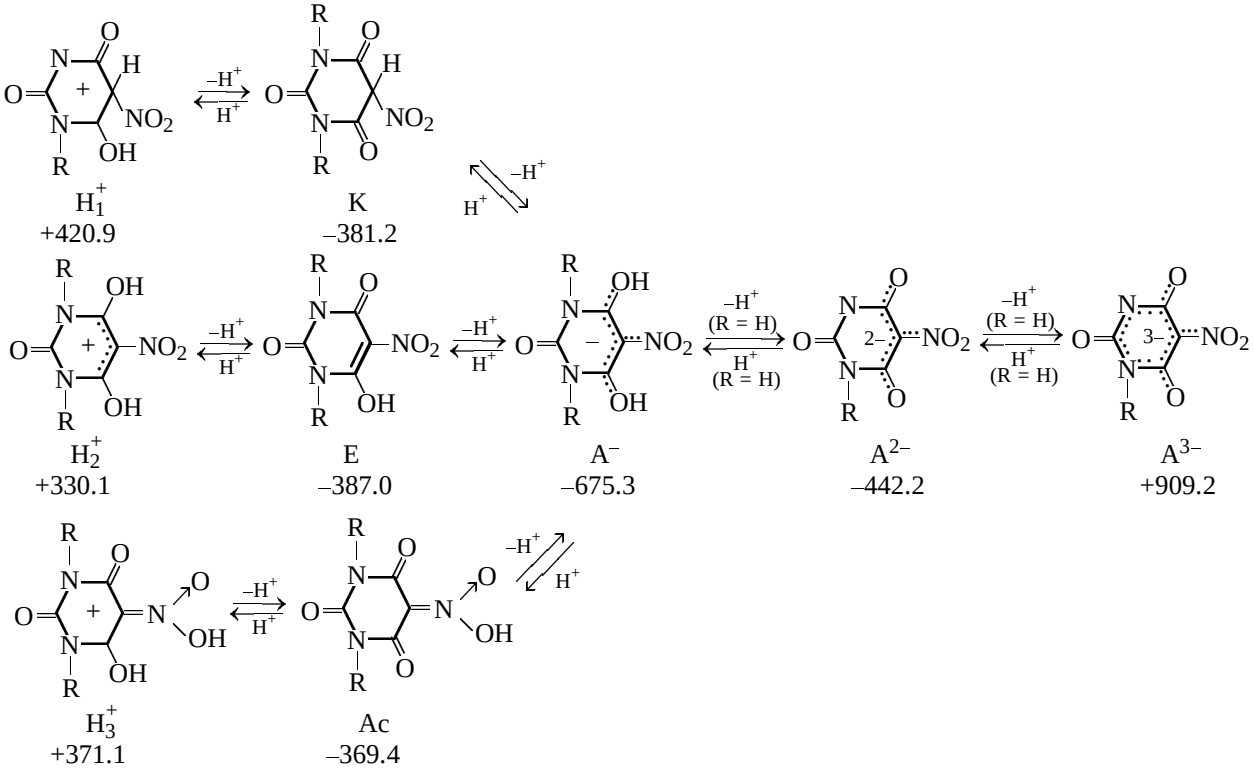


Table 1. Spectral parameters of 5-nitrobarbituric acids **I** and **II** and their ionized forms

Comp. no.	Charge	UV spectrum		Medium	Tautomer	^{1}H NMR spectrum, δ, ppm			^{13}C NMR spectrum, δ_C, ppm				
		λ_{max}, nm	ε			OH	C^5H	$H^{1,3}$	C^2	C^4	C^5	C^6	NCH_3
I	+1	256	7950										
		283	10600										
	0	218	9800	DMSO	E	12.26	–	10.32	150.6	160.5	113.5	160.5	–
		308	13100										
	–1	218	19200	DMSO +	A^-	–	–	10.10	150.5	160.0	113.3	160.0	–
		317.5	10050	NEt_3									
	–2	224	13700										
		333	10900										
	–3	344	14400										
II	+1	261	6800										
		298	13200										
		223	9950	DMSO	E	12.45	–	3.12	151.6	158.1	114.0	158.1	29.0
		315	15200										
	0			$CHCl_3$	E	14.9	–	3.45					
					K	–	9.25	3.18					
				CF^-	E	–	–	3.02	152.0	163.0	109.9	163.0	31.9
				COOH	K	–	9.58	2.57	158.0	171.4	–	171.4	29.4
	–1	223	16400	DMSO +	A^-	–	–	3.18	151.2	158.6	114.1	158.6	27.5
		321	9200	NEt_3									

Experimental study of 5-nitro derivatives in the gas phase is very difficult; therefore, we examined the structure of compounds **I** and **II** in solution in water, DMSO, chloroform, and trifluoroacetic acid and also in crystal. Published data on the structure of 5-nitrobarbituric acid are contradictory. Hantzsch and Vogt [14] and Mihal and Nutiu [15] maintained the existence of equilibrium between the enol and *aci*-nitro forms. Cernatasch et al. [16] concluded that anion A^- is formed by proton abstraction from C^5, i.e., via ionization of keto structure K. In the present work we have found that spectral parameters of 5-nitro- and 1,3-dimethyl-5-nitrobarbituric acids are similar. This means that their structures are also similar. Compounds **I** and **II** are very strong acids; their pK_a values in water are –2.6 and –2.0, respectively. They exist as neutral species only in sulfuric acid solutions with a concentration of more than 60%.

The results of spectral studies (Table 1) indicate the absence of *aci*-nitro tautomer Ac. In the ^{13}C NMR spectra of the two nitro derivatives, the C^5 signal (δ_C 113.5 ppm) appears in in a stronger field than the corresponding signal of 5-nitrosobarbituric (violuric) acid having a C^5=N moiety (δ_C 138.6 ppm) [11]. On the other hand, a signal in the region of δ_C 113.5 ppm is typical of vinyl group containing a strong electron-acceptor substituent [17]. Moreover, the spectrum of a solution in DMSO contains a signal assignable to C–OH group, whose position is very sensitive to the presence of water in the solvent (Table 1). No signals from other tautomers were detected in the spectra recorded from DMSO solutions, in agreement with the data of [18]. The generally accepted test for *aci*-nitro compounds, i.e., the same color of the *aci* form and the anion [14], was also negative in the case of nitrobarbituric acids. Solutions containing only neutral species of **I** and **II** are colorless, while solutions containing their anionic forms are yellow.

Further evidence for the above conclusion was obtained by analysis of the IR spectra of 5-nitrobarbituric acid (**I**) in 70% H_2SO_4 (Fig. 1). In the region 1550–1800 cm^{-1} we observed three well-defined absorption bands (unlike 5-nitrosobarbituric acid which gives only one band in that region [11]). The most intense band is located below 1600 cm^{-1}, and it may be assigned to antisymmetric stretching vibrations of the proper nitro group rather than of C=N bond [19]. The band at 1650 cm^{-1} belongs to vibrations of multiple bonds in the O=C–C=C–OH sequence. Thus, the IR spectra of 5-nitrobarbituric acid in solution rule out tautomer Ac.

We also examined the IR spectra of crystalline

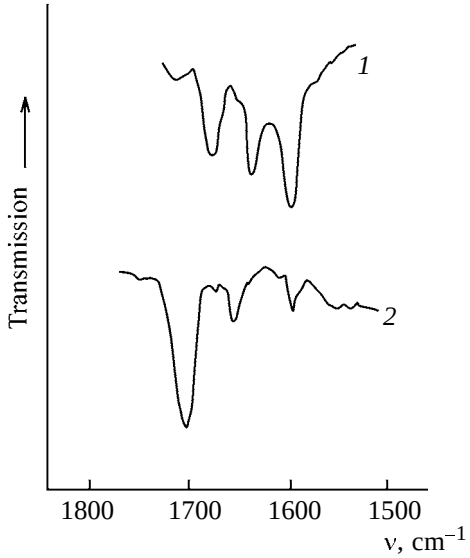


Fig. 1. IR spectra of (*1*) 2-nitrobarbituric acid and (*2*) 5-nitrosobarbituric acid in 70% H_2SO_4.

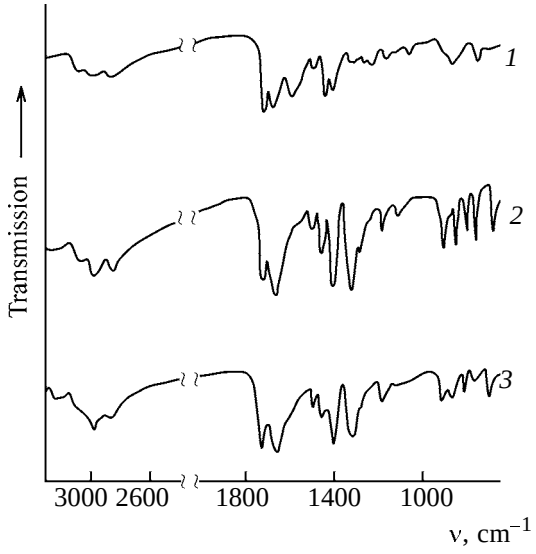


Fig. 2. IR spectra of crystalline (*1*) 5-nitrobarbituric acid, (*2*) its potassium salt, and (*3*) 5-nitrobarbituric acid trihydrate.

samples of acids **I** and **II**, as well as of their deuterated analogs and salts (Fig. 2). When the spectra were recorded from films on KBr plates or from pellets with KBr, we always obtained spectra of potassium salts rather than neutral forms. Salts were not formed when samples were prepared as suspensions in mineral oil applied to NaCl plates. The IR spectra of crystalline 5-nitrobarbituric acid and its 1,3-dimethyl derivative contained bands at 1550–1570 cm^{-1}, which did not change their position on deuteration. These bands correspond to antisymmetric stretching vibrations of the nitro group involved in strong hydrogen bond [20]. The symmetric vibration frequency (ν_s 1325 cm^{-1}) of the nitro group in compound **I** is lower while the antisymmetric vibration frequency (ν_{as} 1560 cm^{-1}) is higher than the corresponding frequencies for 5-nitrouracil (ν_s 1350, ν_{as} 1515 cm^{-1} [21]). In the region 1580–1700 cm^{-1} we observed two broad absorption bands which have a composite nature. They arise mainly from vibrations of the C=O and C=C bonds in the $O=C^4–C^5=C^6–OH$ fragment. Small shifts of these bands in the spectra of deuterated species of **I** and **II** (from 1680–1700 to 1655–1670 and from 1580–1650 to 1550–1670 cm^{-1}) indicate a contribution of the hydroxy group and reflect change in the hydrogen bond strength upon replacement of hydrogen by deuterium. Absorption bands located above 1710 cm^{-1} correspond to vibrations of the $C^2=O$ carbonyl group. Unlike compound **II**, in the spectrum of **I** this band appears as a doublet which is defined especially clearly in the spectrum of the deuterated analog. The presence of the doublet band in that region is consistent with the presence of another doublet at 1402/1432 cm^{-1}, which is absent in the spectra of the deuterated sample and 1,3-dimethyl derivative **II**; therefore, the doublet at 1402/1432 cm^{-1} was assigned to bending vibrations of the NH groups. These data suggest existence of two kinds of NH groups in molecules **I** in crystal, as should be the case of the enol tautomer. The presence of a hydroxy group in molecules of acids **I** and **II** follows from the occurrence of a diffuse band in the region 2500–3300 cm^{-1} and absorption at 1050 and 1150 cm^{-1} (bending vibrations) which are lacking in the spectra of their deuterated analogs and salts. Thus, the IR spectra indicated an enol structure of acids **I** and **II** in crystal. Figure 2 shows that the IR spectrum of 5-nitrobarbituric acid trihydrate is analogous to the spectrum of its potassium salt. This means that compound **I** undergoes ionization due to the presence of crystallization water, i.e., formation of anion A^- (as in the potassium salt) rather than of *aci*-nitro form [22]. The different N–O bond lengths (1.288 and 1.221 Å) in the nitro group of 5-nitrobarbituric acid trihydrate are explained by specific location of the anion and hydroxonium ion in a crystal unit cell [23]. Therefore, this difference cannot be interpreted in favor of the *aci*-nitro structure which was erroneously assigned on the basis of the X-ray diffraction data [24]. As we already noted, the change in the total energy in going from tautomer K to E or Ac is not large. This suggests the possibility for dynamic tautomeric equilibrium and existence of a mixture of tautomers. However, no more than one tautomer was detected experimentally in crystal and

Table 2. Energies of deprotonation of nitro derivatives (ΔE_{deprot}) and their components (ΔE_1, ΔE_2, ΔE_3), kJ mol^{-1}; 3-21+GF calculation

Comp. no.	Tautomer (pK_a)[a]	ΔE_{deprot}	E_1	$-\Delta E_2$	$-\Delta E_3$
I	K	1248	2503	1106	144
	E (–2.6)	1254	2230	917	56
	Ac	1236	2233	936	57
III	K	1248	2575	1199	129
	E (0.98)	1256	2303	967	70
	Ac	1239	2311	976	86
IV	K (–2.0)	1304	2534	1100	126
	E	1285	2267	912	66
	Ac	1279	2272	925	64
V	K	1293	2559	1091	171
	E (0.8)	1316	2290	912	57
	Ac	1282	2303	952	64
VI	K (5.1)	1384	2579	1001	193
	E	1369	2303	860	72
	Ac	1425	2290	828	40
VII	K	1284	2499	1078	133
	E (7.2)	1378	2236	800	55
	Ac	1289	2341	994	62
VIII	K (10.2)	1498[b]	2701	1046	184
	Ac	1375	2316	875	69
IX	K (~15)	1569[c]	2689	1078	76
	Ac	1239	2221	956	27

[a] In parentheses are given the experimental pK_a values for the really existing tautomer. [b] Experimental data [28]. [c] Data of [29].

solutions in DMSO and water. Obviously, it is necessary to search for additional parameters which could describe the compounds under study.

A factor responsible for prevalence of one or another tautomer in a tautomeric system is its acidity. The relations between the structure and gas-phase acidity have been studied insufficiently. An attempt to analyze structural and electronic effects of substituents (including nitro group) was made in [13]. In keeping with the above stated, 5-nitrobarbituric acid is an OH acid; its deprotonation implies proton abstraction from the enol form. Eigen [25] analyzed factors determining the strength of protic acids based on different elements and concluded that OH acids should be much stronger than the respective CH acids. On the other hand, the predominant tautomer in a tautomeric system is that possessing a weaker acidity. In our case, this is keto tautomer K (CH acid), which contradicts the experimental data. In order to resolve this contradiction, we calculated the gas-phase acidity of 5-nitrobarbituric acid **I** by quantum-chemical methods. According to [26], the calculated gas-phase deprotonation energy (ΔE_{deprot}) was arbitrarily divided into three components: (1) electrostatic energy of proton abstraction from the "acidic" bond, the rest of the molecule remaining unperturbed (ΔE_1); (2) energy of electronic relaxation (ΔE_2) of the emerged molecular residue and formation of a "virtual" anion with the same geometric parameters as those of the initial molecule; and (3) energy (ΔE_3) corresponding to displacement of the nuclei in going from the virtual to real anion. The formulas for the calculation of ΔE_{deprot}, ΔE_1, ΔE_2, and ΔE_3 were given in [27]. The data in Table 2 show that the parameter directly characterizing the gas-phase acidity, e.g., deprotonation energy ΔE_{deprot}, was the greatest just for enol structure *E* and that the lowest ΔE_{deprot} was found for the *aci*-nitro form. This means that the *aci*-nitro tatomer is the most energetically favorable acid and that the enol form is the least favorable while the ketone structure occupies an intermediate place. The validity of our theoretical results was checked by calculating an extended series of nitro-substituted carbonyl compounds, including 2-nitrodimedone (**III**), 2-nitro-1,3-indanedione (**IV**), 2-nitroperinaphthindan-1,3-dione (**V**), nitroacetone (**VI**), *o*-nitrophenol (**VII**), and also nitromethane (**VIII**) and nitroethylene (**IX**) (Table 2). In all cases, the highest deprotonation energy was found for the predominant tautomer. Therefore, ΔE_{deprot} may be accepted as an additional parameter indicating prevalence of one or another tautomer in a tautomeric system.

On the other hand, the contribution of ΔE_1 to ΔE_{deprot} is much greater than those of ΔE_2 and ΔE_3. The component ΔE_1 (as the electrostatic potential of a molecule at the point corresponding to the proton being abstracted, taken with the opposite sign [27]) should reflect only electrostatic interaction between the acidic proton and molecular residue, i.e., the effect of electrostatic field. This is confirmed by the data of Laidig and Streitwieser [30] who found that ΔE_1 correlates with the sum of the σ_I constants of all substituents at the bond being deprotonated. Insofar as the values of ΔE_1 for the examined nitro compounds considerably exceed the other energy components, we can state that electrostatic interactions constitute the main factor determining the ΔE_{deprot} value. The component ΔE_1 is large for tautomer K, whereas ΔE_1 values for enol E and *aci* form Ac differ only slightly. Therefore, the acidic proton is bound most strongly with the molecular residue of just tautomer K. Nevertheless, analysis of the charge distribution in different structures gives no unambiguous criterion allowing tautomers K, E, and Ac to be

Table 3. Energies of intra- (E_{intra}) and intermolecular hydrogen bonds (E_{inter}) in associates with the solvent, total energies of keto–enol equilibrium (ΔE_t), and their corrected values [37] (ΔE_t^{corr}) for 5-nitrobarbituric acid, kJ mol^{-1}; 3-21+GF calculation

Medium	E_{intra}[a]		E_{inter}				ΔE_t	ΔE_t^{corr}
	E	Ac	K	E	Ac	A^-		
Gas	36.4	2.5	–	–	–	–	6.3	5.0
H_2O	31.8	4.2	51.6	57.3	52.7	89.5	11.7	8.3
DMSO	7.9	9.2	34.1	40.6	29.7	36.4	12.6	9.1
$CHCl_3$	33.5	0.5	0.1	9.6	6.7	25.5	15.9	12.1
CF_3COOH	36.8	9.6	35.4	41.8	36.4	71.1	12.6	10.7

[a] Calculated according to [31].

distinguished. Thus the energy component ΔE_1 (rather than charges on particular atoms) may be used to characterize the acidity of a specific tautomer.

The component ΔE_3 reflects variation of geometric parameters of the molecular framework. The absolute value of ΔE_3 for tautomer K of all the examined compounds (Table 2) is greater by a factor of ~2–3 than those calculated for E and Ac. Therefore, regardless of the substituent at the acidic bond, the transition from the sp^3-hybridized carbon atom in tautomer K to ~sp^2-hybridized carbon atom in anion anionu A^- is accompanied by evolution of a greater energy than that released on deprotonation of the hydroxy group in tautomer E or nitro group in *aci*-nito tautomer Ac. This means that ΔE_3 is determined mainly by variation of the *s*-character of the hybride molecular orbital localized on the carbon or oxygen atom. It should be noted that ΔE_2 changes only slightly both within the series of compounds **I**–**IX** and in going from one tautomer to another, indicating a weak effect of the substituent and geometric parameters on electron density relaxation upon ionization.

Tautomers E and Ac of 5-nitrobarbituric acid could give rise to formation of intramolecular hydrogen bond. As follows from the results of calculations (Table 3), the energy of hydrogen bond in the enol form is much greater than in the *aci*-nitro form. Presumably, tautomer E is additionally stabilized via intramolecular hydrogen bonding, as compared to the *aci*-nitro form.

Solvation effects and their influence on liquid-phase acidity were estimated on a quantitative level using the basis-line method [13, 26, 27]. The basis straight line was plotted from the experimental data on gas-phase (ΔE_{deprot}) and liquid-phase acidities ($\Delta G = 2.3RT\mathrm{p}K_a$) of hydrocarbons which give rise to planar highly delocalized anions. This is necessary to ensure approximate equality between the energies of solvation of molecules and the corresponding anions. The effect of solvation is estimated from the deviation of points from the basis straight line. Figure 3 shows that the points for compounds **IV**–**VII** fall onto the basis-line. However, the points for 5-nitrobarbituric acids **I** and **II** and 2-nitrodimedone **III** are characterized by negative deviations from the basis-line. This pattern is explained by stronger solvation of their molecules as compared to the anions derived therefrom [13]. Relatively weak solvation of charged species should be related to high degree of delocalization of the negative charge. According to the calculations, the effective charge on the oxygen atoms in the nitro group in tautomer E of compounds **I** and **II** changes only slightly as a result of deprotonation (from –0.36 to –0.42 *e*). For comparison, the corresponding value for nitromethane (**VIII**) increases from –0.29 (tautomer K) to –0.61 *e*, and for nitroethylene, from –0.27 (tautomer K) to –0.55 *e*. The charges on N^{10} (nitro group), C^5, and C^6 in compounds **I** and **II** almost do not change upon ionization: the differences are, respectively, –0.01, –0.05, and +0.02 *e*. Taking into account the relatively small charge variations, no appreciable change in the electrostatic solvation energy should be observed even in polar solvents (such as H_2O and DMSO). Therefore, specific solvation may be the reason for the negative deviations of points for compounds **I**–**III** from the basis straight line (Fig. 3). On the other hand, these deviations cannot be assigned only to the fact that 5-nitrobarbituric acids **I** and **II** and 2-nitrodimedone (**III**) exist in the enol form [32] (i.e., they are OH acids), for both *o*-nitrophenol (**VII**) and 2-nitroperinaphthindane-1,3-dione (**V**) also have enol structure in protic solvents [33].

It is also worth noting that the calculated charges unambiguously indicate a considerable contribution of

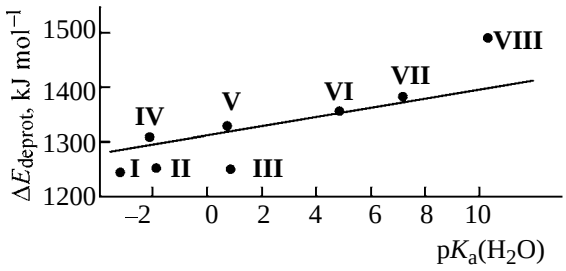


Fig. 3. Corelation between the energies of deprotonation of nitro derivatives **I**–**III** (ΔE_{deprot}) and their dissociation constants (pK_a). The basis-line was plotted according to the data of [13].

mezomeric form α to the structure of anions derived from nitrobarbituric acids **I** and **II** (Scheme 1): in the barbituric acid anion, the charge on C^5 is –0.54 *e*, while in the anions of nitro derivatives **I** and **II**, despite the presence of the strong electron-acceptor nitro group, the charge on C^5 is equal to –0.49 *e*. In support of the above stated, delocalization of the negative charge over the entire structure, including the nitro group, was experimentally found in monoanions A^- of both compounds **I** and **II**. The IR spectra of anions A^- lack bands corresponding to stretching vibrations of the nitro group, and solutions containing these anions are colored. The ^{13}C and ^1H NMR spectra of anion A^- and the neutral form differ insignificantly (Table 1), which suggests small variation of charges on deprotonation. On the other hand, experimental data, namely the symmetric absorption patterns in the electronic and vibrational spectra of the monoanion (A^-) and dianion (A^{2-}) of 5-nitrobarbituric acid, indicate the absence of tautomerism involving proton transfer from ring nitrogen atoms.

The state of keto–enol equilibrium is described by the equilibrium constant K_t = [E]/[K]. According to the NMR spectra, no tautomeric equilibrium is observed in water, dioxane, and DMSO. However, the spectra of 1,3-dimethyl-5-nitrobarbituric acid (**II**) in chloroform contain signals from CH_3N groups belonging to different tautomers. The calculated fraction of tautomer K is 10%, and pK_t = –0.95. The concentration of tautomer K of compound **II** in trifluoroacetic acid is 61%; pK_t = 0.19. According to Mauer [34] and Kabachnik [35], the pK_t value found for one solvent can be recalculated for another medium provided that the parameter ψ_S is known; this parameter characterizes the relative enolizing power of the solvents. From the data of [3] we found that ψ_S for trifluoroacetic acid relative to chloroform is ~1.1, for chloroform relative to DMSO, ~1.1, and for DMSO relative to water, ~0.3. Therefore, the pK_t value for compound **II** in DMSO is -2.1 ± 0.15, and in water, -2.4 ± 0.15.

We also analyzed the effect of various solvation factors on the state of tautomeric equilibrium in terms of the supermolecular approach [36] which primarily takes into account specific solvation. The effects of continuous polar medium and electrostatic solvation were taken into consideration by correcting the results of supermolecular calculations with the aid of SCI-PCM scheme incorporated into GAUSSIAN 94 [37]. This scheme implies that a species of a solute is placed in a cavity corresponding to a set of overlapping spherical atoms with definite van der Waals radii. The potential on the surface of the cavity is calculated by numerical differentiation with account taken of the dielectric constant of the solvent. The interaction between the solute species and the field is assumed to be self-consistent. The results (Table 3) showed no regular variation in ΔE_t in going from the enol to ketone tautomer in the series of solvents water, DMSO, chloroform, and trifluoroacetic acid. The ΔE_t values corrected according to scheme [37] are lower than those determined without taking into account electrostatic field of the solvent; however, they do not fit the pK_t series as well.

We estimated the solvation effect due to intermolecular hydrogen bonding (E_{IHB}) and determined the energies of intermolecular bonds in 5-nitrobarbituric acid associates with the examined solvents (Table 3). As might be expected, the highest energy of intermolecular bonds was found for aqueous solution, and the lowest energy was typical to aprotic and weakly polar chloroform. Intermediate (and very similar) E_{IHB} values were obtained for DMSO and trifluoroacetic acid. Figure 4 illustrates the results of analysis of the solvation effect arising from proton-donor and proton-acceptor properties of the solvent. The ΔE_{solv} values were calculated as the difference between the proton affinity and deprotonation energy of solvent molecules. The resulting pK_t–ΔE_{solv} dependence is almost linear; this indicates the determining role of acid–base properties of the solvent in the state of keto–enol equilibrium for the compounds under study.

Thus the results of the present study led us to the following conclusions:

(1) 5-Nitro derivatives of 2,4,6-pyrimidinetrione in the gas phase, crystalline state, and solutions in water (where dissociation of acids **I** and **II** is suppressed) and DMSO exist in the enol form. No other tautomers were detected;

(2) In trifluoroacetic acid and chloroform, equilibrium mixtures of the enol and ketone forms are present;

(3) The state of the keto–enol equilibrium is determined by the total energies of tautomers, their deprotonation energies, and the component of the latter which reflects electrostatic interaction of the acidic poton and the molecular residue;

(4) The main factor responsible for displacement of the tautomeric equilibrium in solution is proton-donor and proton-acceptor properties of the solvents and 5-nitro derivatives of 2,4,6-pyrimidinetrione rather than the ability of the medium to stabilize one or another tautomer via electrostatic solvation or intermolecular hydrogen bonding.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on RYa-2309 (90 MHz) and Bruker H-200 spectrometers (200 MHz) from solutions in DMSO-d_6, $CDCl_3$, D_2O, and CF_3COOD; hexamethyldisiloxane was used as internal reference. The spectra of the ionized forms were obtained in DMSO and H_2O in the presence of a necessary amount of triethylamine as base. The high-resolution ^{13}C NMR spectra of solid samples were run on a Bruker CXP-100 spectrometer (25 MHz) using the standard magic-angle spinning and polarization-transfer technique [17]. The solvents used for spectral measurements were purified and dried by the procedures described in [38]. The electronic absorption spectra were recorded on an SF-46 spectrophotometer at 20°C from solutions with a concentration of 10^{-4} to 10^{-5} M (1-cm quartz cells). The IR spectra were measured on IKS-29 and Bruker-113 instruments. Solid samples were examined as KBr pellets and suspensions in mineral oil on KBr and NaCl plates. The spectra of solutions in sulfuric acid were recorded using polyethylene cells. Deuterated analogs of acids **I** and **II** were prepared by double recrystallization from D_2O and CD_3OD, followed by drying under reduced pressure.

The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates using chloroform–acetone (1 : 1), ethyl acetate, chloroform, and isopropyl alcohol–water (4 : 1) as eluent. Also, NMR and UV spectroscopy and elemental analysis were used. The melting points were determined by the capillary method. The ionization constants were measured by potentiometric titration using a pH-673 ionometer (water, 20°C, constant ionic strength; accuracy 0.05 pH units). Each titration was repeated at least three times if the deviation of the ionization constant from the average value did not exceed 5%. The constants were calculated following the standard procedure [39]. The dissociation constants of strong acids ($pK_a < 3$), weak acids ($pK_a > 10$), and poorly soluble compounds were determined by spectrophotometry [40]. Solutions of sulfuric acid (up to a concentration of 100%) were used in the spectrophotometric determination of pK_a in the range from 1.0 to 12.0. A portion of a stock solution of a compound was diluted with an appropriate buffer or sulfuric acid solution. In all cases, the pH value was checked using a pH-meter, and the acid concentration was refined by acid–base titration. For each ionization step, an isosbestic point was observed in the corresponding series of the UV spectra, and the spectral changes were reversible. Sulfuric acid solutions were characterized by the acidity function H_a [41]. The acidity constants (pK_a) of strong acids were calculated by the Yates–MacClelland method [42] using the general equation $\log I = -mH_a + pK_a$, where I is the optical density. When the acidity function H_a was used to calculate pK_a, the slope m varied within the range 0.88–1.1, indicating that the use of H_a is appropriate for characterization of protolytic equilibria in the series of 5-nitro-2,4,6-pyrimidinetrione derivatives.

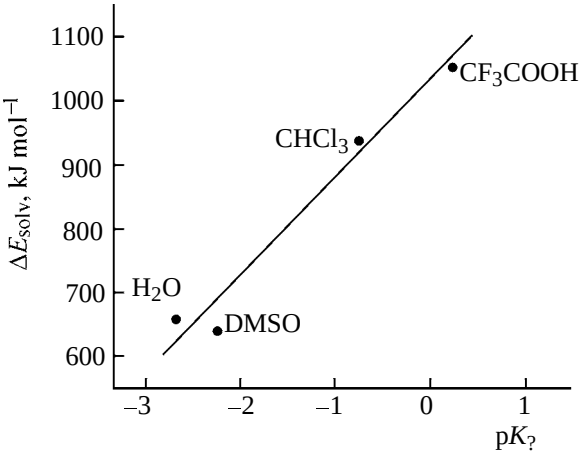


Fig. 4. Correlation between the keto–enol equilibrium constants (pK_t) of 5-nitro derivatives and proton-donor and protono-acceptor properties of solvents (ΔE_{solv}, calculated as the difference between the proton affinity and deprotonation energy of solvent molecules by the 3-21+GF method).

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