The effect of substituents (CH_3 and NH_2) in positions 4 and 6 on the acid-base properties of 2(1*H*)-pyrimidinethiones

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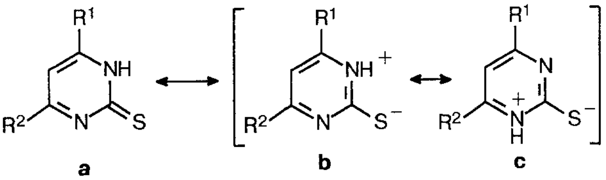
The acid-base properties of 4,6-dimethyl- and 4,6-diamino-2(1*H*)-pyrimidinethiones (**1** and **2**) were investigated by potentiometric titration. Dissociation of **1** and protonation of its anion occur in two steps, the first of which affords the deprotonated dimer $[HA_2]^-$. The relative stability of the dimer depends on the nature of the solvent. The effect of kinetic factors on the acid-base behavior of **1** was elucidated by comparing the results of potentiometric titrations carried out under various kinetic conditions. It was concluded that the difference between the acid-base properties of **1** and **2** results from the electron-donating effect of the amino groups.

Key words: acidity; basicity; 2(1*H*)-pyrimidinethiones.

Thio derivatives of nitrogen-containing bases are widely used in analytical chemistry for qualitative and quantitative determination of ions of several transition and nontransition metals.[1] Pyrimidinethiones can exist as two tautomers: the thione form (**a**) and the thiol form. According to *ab initio* calculations by the SCF method, the energy of the thiol form is 33 kJ mol^{-1} lower than the corresponding value for the thione form, which is in agreement with the data of IR spectra recorded in an inert gas matrix.[2] However, in the crystalline state, the thione form is stabilized due to intermolecular hydrogen bonds.[2] In polar solvents, the thione form also prevails.[3] In addition, for thio derivatives of nitrogen-containing heterocyclic compounds, unlike the corresponding oxo derivatives, the contributions of bipolar structures **b** and **c** are more significant (see Ref. 4).



It might be expected that the existence of a tautomeric equilibrium would exert an effect on the dependence of the acid-base properties of the thio derivatives of nitrogen-containing heterocycles on the nature of the solvent and on substituents R^1 and R^2. The goal of the present work has been to study the acid-base properties of 4,6-dimethyl- and 4,6-diamino-2(1*H*)-pyrimidinethiones (**1** and **2**, respectively) in various organic solvent—water mixtures.

Experimental

Compounds **1** and **2** and their sodium salts were prepared by the known procedures.[5,6] The products were purified by recrystallization, and the solvents, DMSO, DMF, and methanol, were distilled according to the standard procedures.[7] The activity of protons was determined on an I-130 pH-meter with an accuracy of 0.05 pH units. The pH-meter was adjusted using standard aqueous buffer solutions. To determine the pH of organic solvent—water solutions, the electrode was preliminarily steeped in the corresponding organic solvent—water mixture of the specified composition for 24 h. The pH values of organic solvent—water solutions were determined from the relationship:

$$pH = (pH)_{meas} - \Delta pH,$$

where pH, the pH value experimentally determined in a mixed solvent, and ΔpH, the value reflecting the difference between the activity of protons in water and in the organic solvent—water mixture, were estimated according to the previously described procedure.[8] Potentiometric titration was carried out in two kinetic modes: 1) titration with varying volume, in which the pH value was recorded within 1—2 min after addition of the titrant; 2) titration with constant volume, in which the pH values were recorded within several hours after preparation of solutions with various amounts of the titrant. Quantum-chemical calculations were carried out by the MNDO—PM3[9] method with full optimization of the geometry using the AMPAC program. The UV spectra were recorded on a Specord M-40 instrument.

Results and Discussion

The acid-base properties of compounds **1** and **2** and their sodium salts (**3** and **4**, respectively) were studied by

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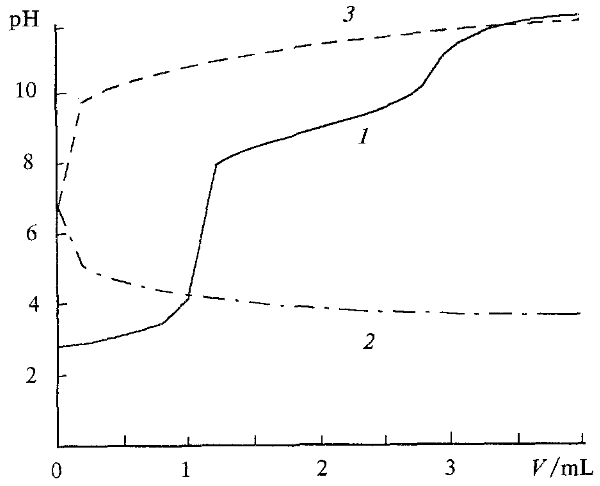


Fig. 1. Potentiometric titration of **1**: $C_1 = 0.007$ *M*, $C_{KOH} = 0.042$ *M* (*1*); **2**: $C_2 = 0.003$ *M*, $C_{HCl} = 0.016$ *M* (*2*); $C_2 = 0.003$ *M*, $C_{KOH} = 0.016$ *M* (*3*).

potentiometric titration with varying volume in water—DMF (I) and water—methanol (II) solvent mixtures in which the proportion of the organic component was 80 % (v/v). The curves of the potentiometric titration of compounds **1** and **2** and their sodium salts, **3** and **4**, in solvent I are presented in Figs. 1 and 2. Mathematical processing of the data of the potentiometric titration of **1** and **3** using the CPESSP program[10] indicates that the two jumps on the titration curves are due to the occurrence of equilibria (1) and (2).

$$2HA \rightleftharpoons [HA_2]^- + H^+ \qquad (1)$$

$$[HA_2]^- \rightleftharpoons 2A^- + H^+ \qquad (2)$$

Thus, both dissociation of **1** and the protonation of its anion occur in two steps, and the first step affords a deprotonated dimer of the composition $[HA_2]^-$. Below are presented the types of bonding (**d**—**f**) that are possible in this dimer according to quantum-chemical calculations.

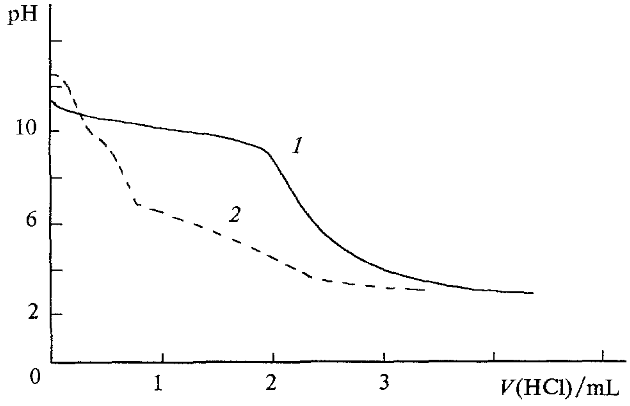
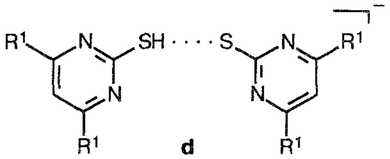
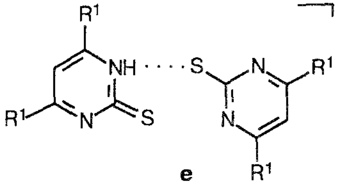


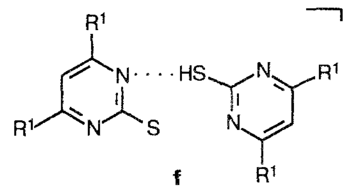
Fig. 2. Potentiometric titration of **3** ($C_3 = 0.008$ *M*) (*1*) and of **4** ($C_4 = 0.003$ *M*) (*2*) at $C_{HCl} = 0.032$ *M*.



d



e



f

The calculations of the energies of formation of forms **d**—**f** using the AMPAC program in the PM3 parametrization[9] indicate that the deprotonated dimers correspond to the minima on the potential energy surface and that in the gas phase they are more stable than the original species by 28, 20, and 7 kcal mol^{-1}, respectively. Since the π—π^*-absorption peak typical of the C=S group[11] is exhibited over the whole region of the potentiometric titration and its intensity decreases as the pH value increases (Fig. 3), form **e** should be the most probable for the $[HA_2]^-$ dimer.

The p*K* values of equilibria (1) and (2) for compound **1** and its sodium salt **3** are noticeably different judging by the data of the "quick" potentiometric titration with varying volume, and are almost identical according to the "slow" titration with constant volume (Table 1). The time dependence is observed only for the results of the titration of compound **3**. In view of the fact that the greatest negative charge on anion **3** is localized at the sulfur atom (Fig. 4), one may assume that under the conditions of "quick" titration with varying volume, the experimentally determined p*K* value of equilibrium (1) corresponds to the formation of dimers with structures **d** and **f**, which are converted in the course of time into the more stable dimer **e**. This is supported by the fact that the constant of dimer formation determined from the data from the "slow" titration is greater than the corresponding value determined from the "quick" titration (see Table 1). At the same time, the $[HA_2]^-$ dimer formed in the dissociation of **1** has structure **e**. In water (solvent III), the constants of equilibria (1) and (2) for compounds **1** and **3** are identical (see Table 1).

We also determined the corresponding constants for **1** in a water—DMSO (80 % (v/v)) solvent mixture (IV)

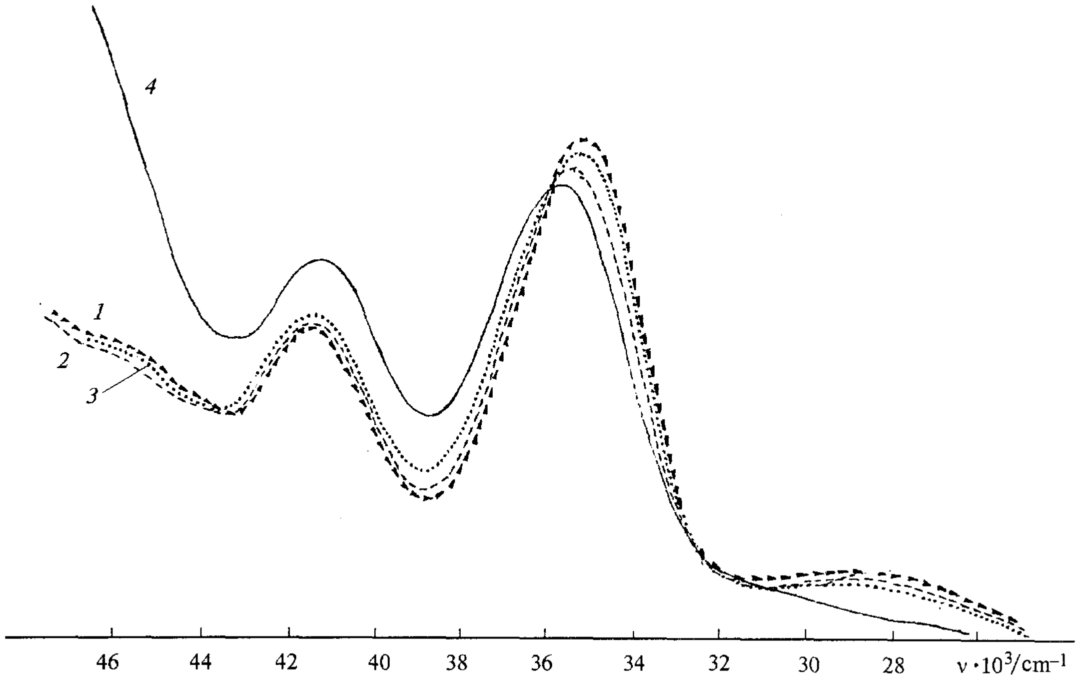


Fig. 3. The UV spectra of solutions of **1** in methanol at pH 2.6 (*1*); 4.2 (*2*); 6.5 (*3*) and 11.0 (*4*) (C = 0.001 *M*).

(see Table 1). Figure 5 presents the curves of the distribution of forms of **1** having various degrees of deprotonation *vs.* pH in solvents I—IV. These data imply that in solvent IV, the $[HA_2]^-$ dimer possesses the highest stability and in water it has the lowest stability.

Table 1. The pK* values of equilibria (1), (2), (3) and (4) from the data of potentiometric titration of **1** and **2** and their sodium salts **3** and **4**, in the following solvents: water—80 % (v/v) DMF (I), water—80 % (v/v) MeOH (II), water (III), water—80 % (v/v) DMSO (IV)

pK	Solvent	**1**	**3**	**2**	**4**
p$K_{(1)}$	I	2.4	6.5		9.2
	II	1.5	6.7		10.2
	II**	1.6	1.7		
	III	5.1	5.1		
	IV	0.94			
p$K_{(2)}$	I	8.0	11.7		8.4
	II	11.1	10.7		8.2
	II**	11.4	11.5		
	III	10.7	10.6		
	IV	12.5			
p$K_{(3)}$	I			5.0	5.0
	II			5.0	5.0
p$K_{(4)}$	I			11.0	
	II			10.9	
	II**				10.9

* The accuracy of the determination was at least 0.1 pK units.

** pK values determined from the data of potentiometric titration with constant volume.

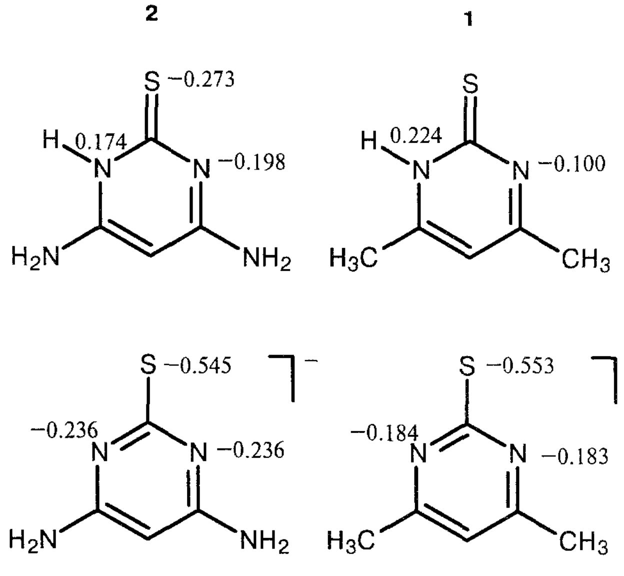


Fig. 4. The charge distribution in molecules **1** and **2** and their anions.

The titration curve of compound **4** exhibits three jumps. The first and the second jumps are due to equilibria (1) and (2), and the third jump is caused by equilibrium (3), which indicates that the basicity of compound **4** is substantially higher than that of **3** (see Table 1).

$$[H_2A]^+ \rightleftharpoons HA + H^+ \qquad (3)$$

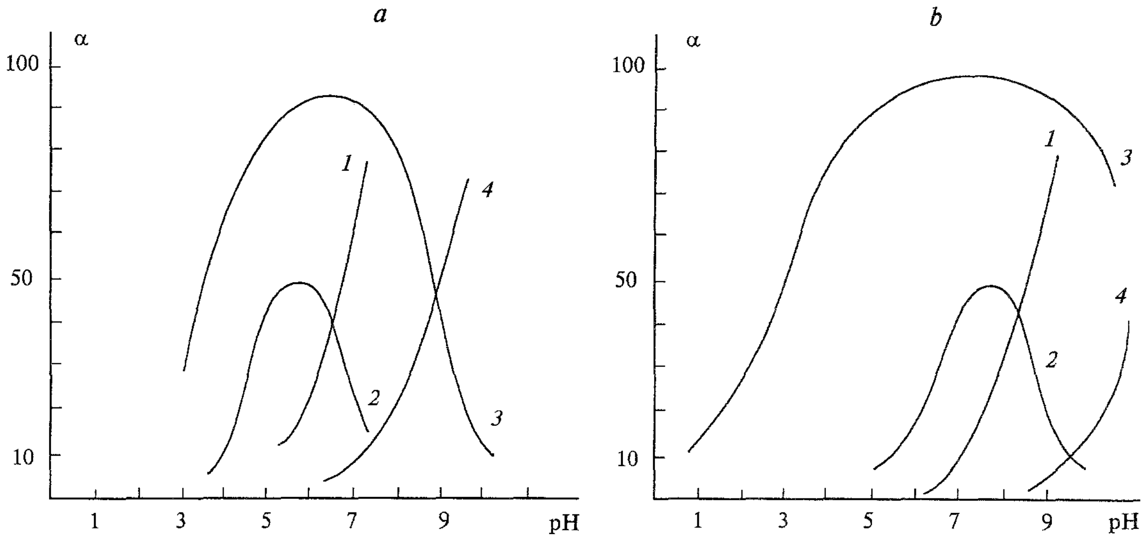


Fig. 5. Distribution of forms of compound **1** with various degrees of protonation as a function of pH in solvents I—IV; *a*: *1* — A^-(I); *2* — $[HA_2]^-$(I); *3* — $[HA_2]^-$(II); *4* — A^-(II); *b*: *1* — A^-(III); *2* — $[HA_2]^-$(III); *3* — $[HA_2]^-$(IV); *4* — A^-(IV).

According to the data from the "quick" titration, protonation of the anion occurs in two steps (see Table 1), the first of which yields the deprotonated dimer (equilibrium (1)), in conformity with the previous suggestion that the anion is protonated initially at the sulfur atom to give dimers **d** and **f**, whereas under the conditions of "slow" titration, the anion is protonated according to Eq. (4) (see Table 1).

$$HA \rightleftharpoons A^- + H^+ \qquad (4)$$

The shape of the titration curve of compound **2** differs substantially from those of compounds **1**, **3**, and **4**. This shape of the titration curve is typical of bipolar systems. The bipolar form exists at pH 4—9 (see Fig. 2).

The charge distribution in compound **2** (see Fig. 4) illustrates the electron-donating effect of the amino groups, which noticeably increase the negative charge at the nitrogen atoms of the ring and slightly increase it at the sulfur atom, resulting in a considerable decrease in the acidity of **2**. Consequently, owing to the contribution of the bipolar structure, the thione form of **2** is markedly stabilized, equilibrium (1) is not realized during titration of **2**, and its dissociation occurs according to Scheme (4).

Thus, on the basis of potentiometric titration, we found that the dissociation of **1** gives both the A^- anion and the $[HA_2]^-$ deprotonated dimer, whose relative stabilities depend on the nature of the solvent. By comparing the results of potentiometric titration of compounds **3** and **4** under various conditions, the effect of the kinetic factors on the acid-base properties was identified. It was also shown that the differences between the acid-base properties of compounds **2** and **1** result from the substantial stabilization of the bipolar form due to the electron-donating effect of the amino groups.

References

1. F. Umland, A. Janssen, D. Thierig, and G. Wünsch, *Theorie und Praktische Anwendung von Komplexbildern*, Akademische Verlagsgesellshaft, Frankfurt am Main, 1971.
2. M. J. Nowak, H. Rostowska, L. Lapinski, J. Leszczynski, and J. S. Kwiatkowski, *Spectrochim. Acta*, 1991, **47A**, 339.
3. J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1951, 1004.
4. B. Stanovnik and M. Tisler, *Arzneimittel-Forsch.*, 1964, **14**, 1004.
5. R. R. Hunt, J. F. McOmic, and E. R. Sager, *J. Chem. Soc.*, 1959, 525.
6. V. M. Berezovskii and A. M. Yurkevich, *Zh. Obshch. Khim.*, 1962, **32**, 1655 [*J. Gen. Chem. USSR,* 1962, **32** (Engl. Transl.)].
7. A. J. Gordon and R. A. Ford, *The Chemist's Companion*, Wiley Intersci., New York—London, 1972, Chapt. 7. III.
8. V. V. Aleksandrov, *Kislotnost' nevodnykh rastvorov* [*Acidity of Nonaqueous Solutions*], Vishcha Shkola, Khar'kov, 1982 (in Russian).
9. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.
10. Yu. I. Sal'nikov, A. N. Glebov, and F. V. Devyatov, *Poliyadernye kompleksy v rastvorakh* [*Polynuclear Complexes in Solutions*], Kazan' State University Publ., Kazan', 1989 (in Russian).
11. A. V. Sverdlova, *Elektronnye spektry v organicheskoi khimii* [*Electronic Spectra in Organic Chemistry*], Khimiya, Leningrad, 1973 (in Russian).

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