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2,4,6-Triaminopyrimidine and Its Associates with Bis(hydroxymethyl)phosphinic Acid. State in Solution, Protolytic, and Complexing Properties

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Abstract—Protolytic and complexing properties of 2,4,6-triaminopyrimidine and its associates with bis (hydroxymethyl)phosphinic acid in aqueous solution were studied using pH measurements, spectrophotometry (298 K), and mathematical simulation of equilibria (CPESSP software). The stability constants of the associates formed in solution were calculated. It was found that the said associates and the nitrogen base in their composition did not form innner-sphere complexes with typical complexing agents like doubly charged cations of *d*-elements and lanthanum(III). 2,4,6-Triaminopyrimidine forms an outer-sphere complex with copper(II) ions to affording tetrachlorocuprate(II) with diprotonated 2,4,6-triaminopyrimidine.

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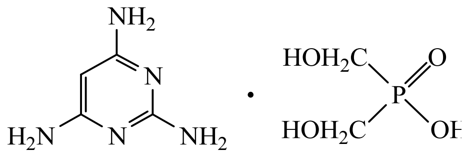
Bis(hydroxymethyl)phosphinic acid is known to form salts possessing a certain biological activity with a number of nitrogen bases, in particular, with the isonicotinic acid hydrazide (tubofen) and melamine (melafen) [1, 2]. Both the nitrogen bases are of heteroaromatic structure. Tubofen is proposed for the treatment of tuberculosis. One of the important practical applications of melamine is due to its role in plant nutrition.

Another preparation [3] includes alongside the bis (hydroxymethyl)phosphinic acid (HA), 2,4,6-triamino-1,3-diazine [2,4,6-triaminopyrimidine (Y)]. This preparation which has been synthesized as a melafen analog, in many cases has an effect similar to melafen [4, 5]. Earlier the acid–base properties have been studied of this acid, melamine, melafen and tubofen, and the behavior of these compounds in the presence of certain metal cations [6, 7].



Y•HA

This paper presents the data on the state of 2,4,6-triaminopyrimidine and its associates with bis(hydroxymethyl)phosphinic acid in aqueous solution and their acid–base and complexing properties. We performed pH-metric titration of aqueous solutions of 2,4,6-triaminopyrimidine at two concentrations (5.05×10^{-3} and 1.01×10^{-2} M). The type of one of the titration curves (curve *2*) is shown in Fig. 1. The protolytic equilibria identified by modeling the scope of experimental data are shown in Table 1.

We found that in addition to the well-known [8, 9] monoprotonated form of 2,4,6-triaminopyrimidine, in the strongly acidic pH range di- and triprotonated species were formed. As seen from the distribution of different forms (Fig. 2), the monoprotonated form of 2,4,6-triaminopyrimidine is predominant in aqueous solution. The found constant of its formation is in good agreement with the published values (Table 1). By analogy with melamine [7], we suggest that the ring nitrogen atom is initially protonated.

The geometry of the 2,4,6-monoprotonated triaminopyrimidine molecule was optimized in the framework of molecular mechanics MM2 [10]. According to calculations, the mono-cation is the most

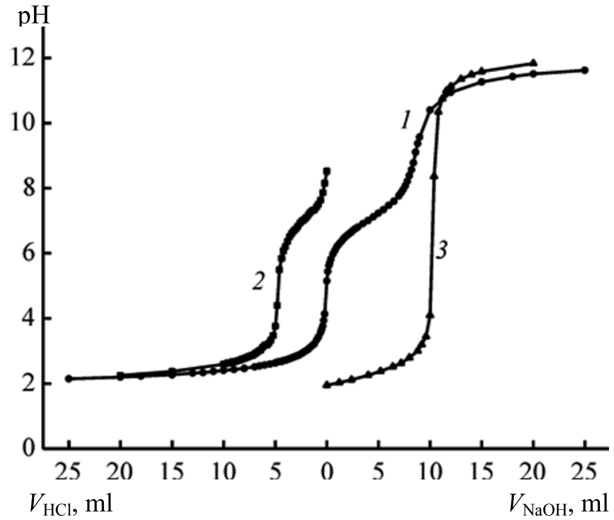


Fig. 1. Curves of pH-metric titration of the associate (HA·Y) solutions ($c_{Y·HA}$ 5.00×10^{-3} M) (*1*), 2,4,6-triaminopyrimidine (c_Y 5.05×10^{-3} M) (*2*) and bis (hydroxymethyl) phosphinic acid (c_{HA} 2.02×10^{-2} M, c_{NaOH} 3.97×10^{-2} M) (*3*) [6]. c_{HCl} 2.0×10^{-2} M, c_{NaOH} 1.0×10^{-2} M.

stable in the form with the protonated nitrogen atom of the heterocycle. The successive protonation constants of 2,4,6-triaminopyrimidine found in the present study are as follows: log k_1 = 6.96, log k_2 = 1.69, and log k_3 = 2.19. The disagreement with the usual succession of protonation constants log k_1 > log k_2 > log k_3 [11] may be, as in the case of melamine [7], due to the change of the protonation center.

Judging from the values of the first protonation constants (log k_1 6.96±0.02), the 2,4,6-triaminopyrimidine containing two nitrogen atoms in the heterocycle is a stronger base than melamine (log k_1 5.11±0.02 [7]) with three heterocyclic nitrogen atoms. This may be due to the electron-withdrawing inductive effect of one additional nitrogen atom in the melamine. The values of the second consecutive constants 1.69 and 1.88, as well as third ones 2.19 and 2.37 are very close in both nitrogen bases.

Table 1. Equilibria in solutions of 2,4,6-triaminopyrimidine

Equilibrium	log *K*	α_{max}	pH_{max}
$Y + H^+ \rightleftarrows [YH]^+$ (1)	6.96±0.02 6.72±0.01 [8] 6.84±0.01 [9]	0.99	4.40
$Y + 2H^+ \rightleftarrows [YH_2]^{2+}$ (2)	8.65±0.17	0.22	1.99
$Y + 3H^+ \rightleftarrows [YH_3]^{3+}$ (3)	10.84±0.12	0.35	1.99

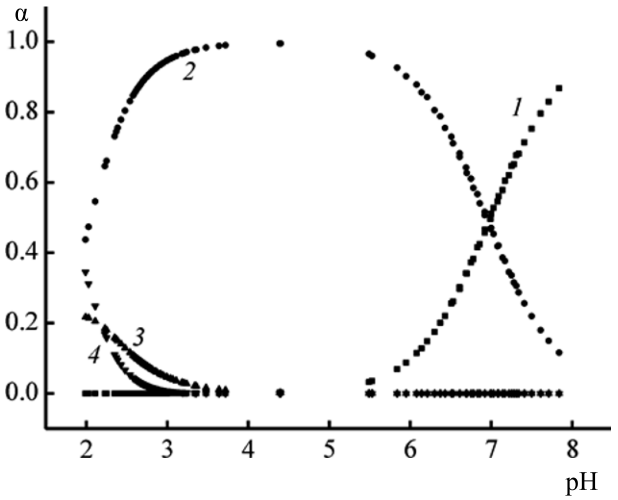


Fig. 2. Distribution of neutral and protonated forms of 2,4,6-triaminopyrimidine in aqueous solution vs. pH. (*1*) Y, (*2*) $(YH)^+$, (*3*) $(YH_2)^{2+}$, (*4*) $(YH_3)^{3+}$.

We also performed the pH-metric titration of the two series of the aqueous solutions of 2,4,6-triaminopyrimidine associates with HA at the concentrations of 5.0×10^{-3} and 1.01×10^{-2} M. One of the titration curves (curve *1*) is shown in Fig. 1 together with the curves of pH-metric titration of 2,4,6-triaminopyrimidine and bis(hydroxymethyl)phosphinic acid (curves *2* and *3*, respectively).

The results of simulation of the experimental data for these associates are shown in Table 2, the distribution of species, in Fig. 3. As can be seen, the components of the associate interact with each other, just as in the cases of melafen and tubofen solutions, forming a formally uncharged tight species of 1:1 composition [Eq. (4)] and anionic associate of 1:1 composition [Eq. (6)]. An anion of the same 1:2 composition [Eq. (5)] was found in the case of tubofen. The (HA·Y) species dominates in the solution in the

Table 2. Equilibria in aqueous solutions of the associate (HA·Y)

Equilibrium	log *K*	α_{max}	pH_{max}
$HA + Y \rightleftarrows [HA·Y]$ (4)	7.49±0.01	0.77	3.07
$HA + 2Y \rightleftarrows [A·Y_2]^- + H^+$ (5)	2.85±0.06	0.30	9.91
$HA + Y \rightleftarrows [A·Y]^- + H^+$ (6)	–0.18±0.04	0.24	10.90

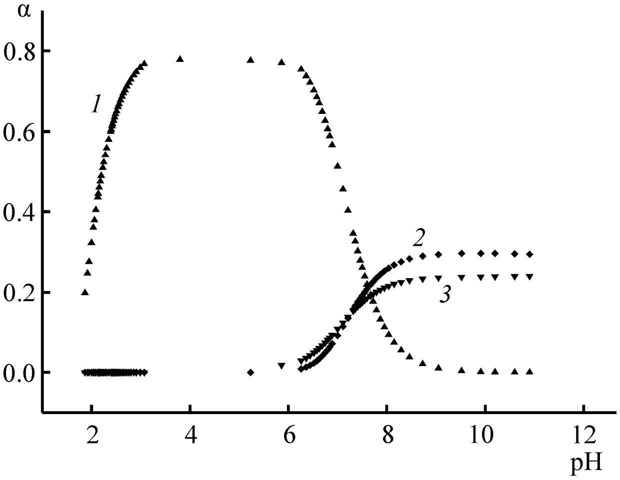


Fig. 3. Distribution of “neutral” and the ionized forms of the associate (HA·Y) in aqueous solution vs. pH: (*1*) (HA·Y), (*2*) $(A\cdot Y_2)^-$, (*3*) $(A\cdot Y)^-$.

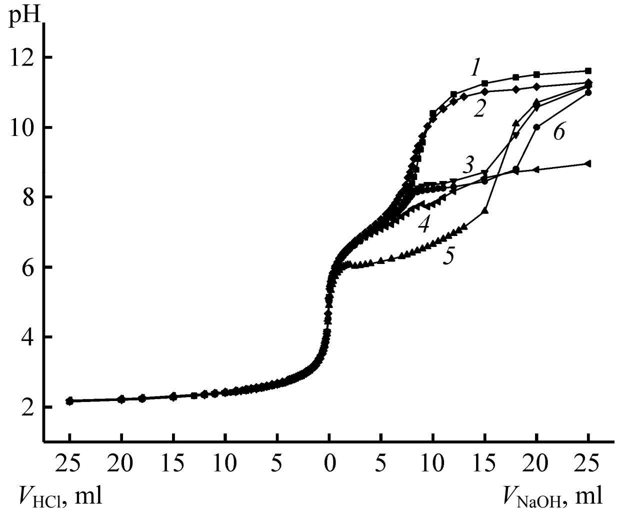
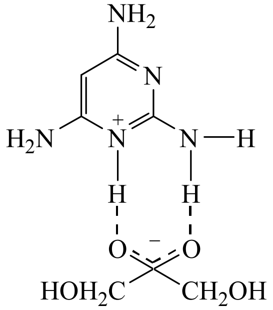


Fig. 4. Curves of pH-metric titration of solutions of the associate (HA·Y) ($c_{Y\cdot HA}$ 5.00×10^{-3} M) in the absence (*1*) and in the presence of complexing agents (c_M 2.5×10^{-3} M) (*2*) Mg(II), (*3*) Co(II), (*4*) La(III), (*5*) Cu(II), (*6*) Ni(II). 2.0×10^{-2} M, c_{NaOH} 1.0×10^{-2} M.

pH range from 2 to 7.5. The forces responsible for the association of bis(hydroxymethyl)phosphinic acid with 2,4,6-triaminopyrimidine are apparently of the types of hydrogen bonding and electrostatic interactions. The possible structure of the associate is presented in the following scheme:



This structure has been suggested in the literature [8] for the ion pair formed by monoprotonated 2,4-diaminopyrimidine with a phosphate ion.

Combining expressions (4) and (6) gives the equilibrium (7)

$$(A\cdot Y)^- + H^+ \rightleftarrows (HA\cdot Y) \qquad (7)$$

with the constant log K_{13} = 7.67 exceeding the formation constant of the 2,4,6-triaminopyrimidine monoprotonated form $(YH)^+$, log K_1 6.96 (Table 1). In other words, the associate (HA·Y) holds proton somewhat stronger than the base itself.

At the introduction to the associate solution of copper(II), or cobalt(II), or nickel(II), no visible change in color was observed. The titration curves of the associate (HA·Y) in the presence of the above complexing agents and La(III) coincide with the titration curve of the substance in the pH range from 2 to 6 (Fig. 4). At the titration such solutions with alkali the precipitate, most likely, consists of the hydrolysis products of the metal ions. Under the experimental conditions the value of the solubility product of magnesium hydroxide [12] is not reached, and therefore the titration curves of the associate (HA·Y) with and without magnesium salts are practically identical. Thus, the associate (HA·Y), like melafen, does not form inner-sphere complexes with the considered metal cations.

In the case of 2,4,6-triaminopyrimidine solutions, the introduction of metal cations results in a slight decrease in pH (Fig. 5). Particularly large differences are observed in the solutions containing copper(II). Mathematical modeling of the experimental data showed that copper(II) does not form complexes with assumed composition of 1:1 and 1:2 with 2,4,6-triaminopyrimidine. An adequate description can be achieved with the introduction into the stoichiometry matrix of the stage of copper(II) hydrolysis, as in the case of melamine.

Figure 6 shows the absorption spectra of solutions of 2,4,6-triaminopyrimidine in the absence and the presence of copper(II). The introduction of copper(II) does not shift the absorption bands in the UV region,

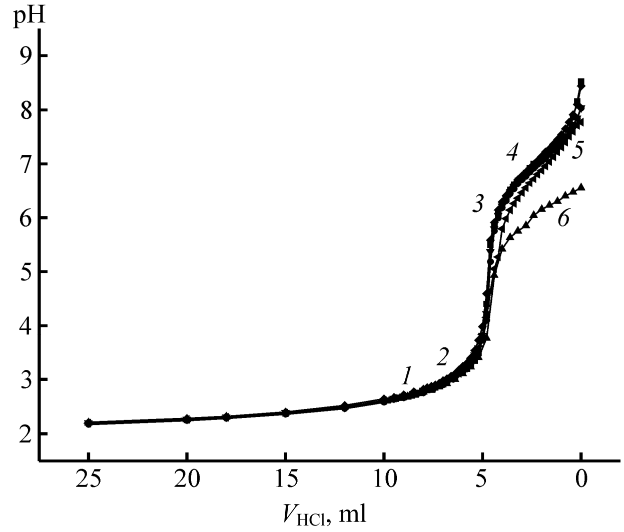


Fig. 5. Curves of pH-metric titration of solutions of 2,4,6-triaminopyrimidine (c_Y 5.0×10^{-3} M) in the absence (*1*) and in the presence of complexing agents [c_M 2.5×10^{-3} M]: (*2*) Mg(II), (*3*) Ni(II), (*4*) Cp(II)), (*5*) La(III), (*6*) Cu(II). c_{HCl} 2.0×10^{-2} M.

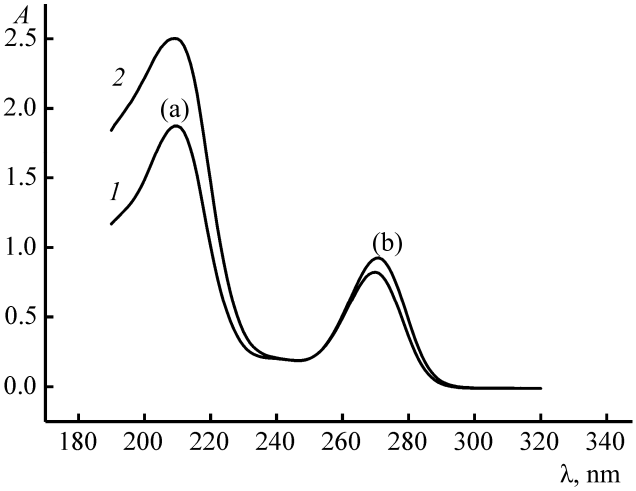
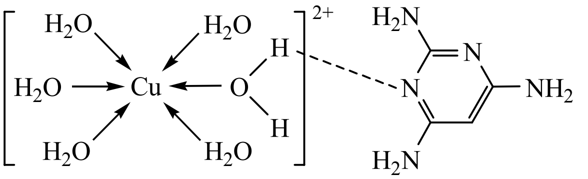
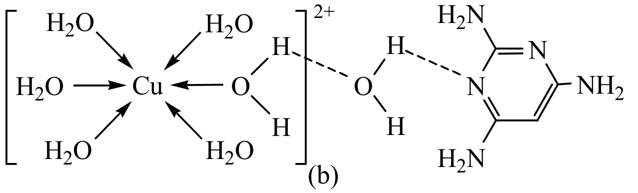


Fig. 6. Absorption spectra of solutions of 2,4,6-triaminopyrimidine in the absence (*1*) and in the presence of copper (II) (*2*). (*1*) c_Y 6.4×10^{-5}, (*2*) c_Y 6.4×10^{-5} M, $[Cu^{2+}]$ = 3.87×10^{-5} M. (*1*) λ_{max} = 210 nm, *A* = 1.874, ε_{210} = 2.93×104 (a); λ_{max} = 270 nm, *A* = 0.824, ε_{270} = 1.29×10^4(b); (*2*) λ_{max} = 211 nm, *A* = 2.503 (a), λ_{max} = 271 nm, *A* = 0.926 (b).

but increases the absorption intensity at both wavelengths. A low intensity (ε_{780} = 16 l mol^{-1} cm^{-1}) and stretched band in the wavelength range 600–850 nm practically coincides with the absorption band of copper(II) aqua complex, as in the case of melamine solutions containing copper(II). Such changes in the UV spectrum of 2,4,6-triaminopyrimidine with the introduction of copper (II) and the absence of changes in the visible spectrum may indicate the outer-sphere complexation [13]. It can be assumed that the molecules of 2,4,6-triaminopyrimidine (outer-sphere) and water in the inner coordination sphere of the copper(II) aqua complexes are either directly connected through hydrogen bonds (a) or an additional water molecule is involved in joining the inner and outer coordination spheres (b).



(a)



(b)

The absorption spectrum of the associate (HA·Y) solution is very similar to the absorption spectrum of 2,4,6-triaminopyrimidine, namely, it also contains two absorption bands in the UV region, somewhat shifted to longer wavelengths: 214 vs. 210 nm for the first band, and 272 and 270 for the second one. The intensity of the first absorption band of the associate (HA·Y) is reduced ($\varepsilon_{210} = 2.93\times10^4$ and $\varepsilon_{214} = 2.42\times10^4$) compared to that of 2,4,6-triaminopyrimidine, and the second is increased ($\varepsilon_{270} = 1.29\times10^4$ and $\varepsilon_{272} = 1.42\times10^4$).

On the introduction of copper(II) the position of the absorption band is little changed (Fig. 7), as in the case of 2,4,6-triaminopyrimidine. The absorption intensity of the first band increases (ΔA_1 = 0.690, while in the system with 2,4,6-triaminopyrimidine ΔA_1 = 0.629). Further, while in the system with 2,4,6-triaminopyrimidine the increase in the intensity of the second absorption band at λ_{max} = 270 is ΔA_2 = 0.102, in the system the associate (HA·Y)–copper(II) the intensity of the second band remains unchanged. Hence, the involvement of the associate (HA·Y) itsef in the outer-sphere interaction with copper(II) is not excluded.

Mixing of hot hydrochloric acid solutions of copper chloride(II) and 2,4,6-triaminopyrimidine results in the precipitation of yellow-brown crystals. Their composition, according to the elemental analysis, corresponds to the formula C_4H_9CuCl, or (YH_2) $[CuCl_4]$. This compound is apparently the outer-sphere complex. Indeed, copper(II) is known to form four mononuclear complexes with chloride ions of the composition from 1:1 to 1:4 [14]. In the acidic environment, 2,4,6-triaminopyrimidine is protonated and can be an effective cationic counterion in the formation of compounds poorly soluble in water.

A complex of similar composition, (HAmpyr)$_2$CuCl$_4$ [along with such as (HAmpyr)CuCl$_3$·H$_2$O, (HAmpyr)$_2$Cu$_2$Cl$_6$, where HAmpyr$^+$ is 2-aminopyrimidinium] is known for 2-aminopyrimidine [15]. These compounds have been investigated by various methods: thermal analysis, IR spectroscopy, ESR, and magnetic susceptibility measuring. Analysis of the results allowed a conclusion [15] on the outer-sphere coordination of 2-aminopyrimidine. The compounds of this type, as noted in [16], are interesting as the first examples of ionic coordination compounds among the aminoheterocycles with cationic N-bases.

The melamine cations in some cases behave like the 2,4,6-triaminopyrimidinium cations. Thus, a complex of lead(II) with melamine and pyridine-2,6-dicarboxylic acid has been synthesized and studied in the solid state [17], containing the outer-sphere molecules of melamine and melamine cations.

We failed to isolate a compound of copper(II) with the associate (HA·Y). Pouring together hot hydrochloric acid solutions of the associate (HA·Y) and copper(II) chloride does not result in precipitation, in contrast to a similar procedure with 2,4,6-triaminopyrimidine. The solutions remained transparent during a week, and had a bright green color inherent in the strong hydrochloric acid solution of copper(II) chloride.

EXPERIMENTAL

The study was performed by methods of pH-titration and spectrophotometry. The pH of solutions was measured on a pH meter pH-673 M with a glass electrode ELS 43-07 as indicator electrode and a saturated silver chloride electrode as a reference. The electron absorption spectra of solutions taken relative to water were registered on a Lambda 35 101N6112101 (Perkin-Elmer UV WinLab) and a SPEKOL 11 spectrophotometers in quartz cells (thickness of the absorbing layer 1 cm).

Solutions of 2,4,6-triaminopyrimidine (reagent from Lancaster) and of the associate (HA·Y) were prepared by precise weighing. The studies were carried out with aqueous solutions. Ionic strength of solutions was created by their components, since the introduction of the supporting electrolyte decreases the solubility of compounds and can influence the processes of association in solution. Working solutions of the carbonate-free sodium hydroxide, hydrochloric acid, copper(II), lanthanum(III), and cobalt(II) nitrates and nickel(II) and magnesium(II) sulfates were prepared from the reagents of the chemically pure grade. The concentration of working solutions was established by volumetric analysis.

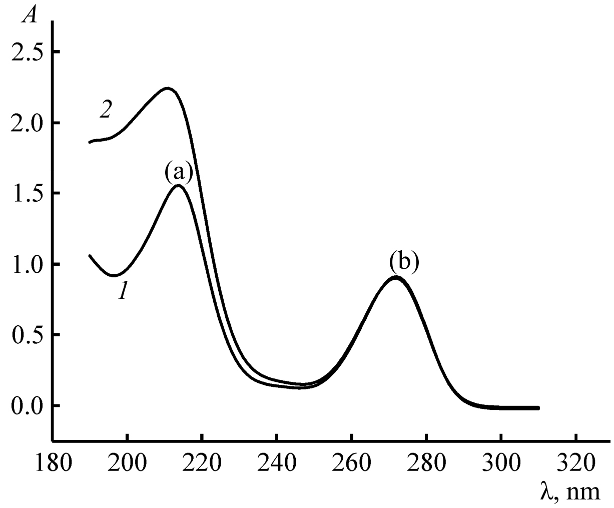


Fig. 7. The absorption spectra of the associate (HA·Y) solutions in the absence (*1*) and in the presence of copper(II) (*2*). Concentration, M: $c_{\mathrm{Y\cdot HA}} = 6.4\times10^{-5}$, $[\mathrm{Cu}^{2+}] = 3.9\times10^{-5}$; (*1*) $\lambda_{\max} = 214$ nm, $A = 1.55$, $\varepsilon = 2.42\times10^4$ (a), $\lambda_{\max} = 272$ nm, $A = 0.91$, $\varepsilon = 1.42\times10^4$ (b); (*2*) $\lambda_{\max} = 211$ nm, $A = 2.24$ (a), $\lambda_{\max} = 272$ nm, $A = 0.90$ (b).

During the experiment the solutions of 2,4,6-triaminopyrimidine were titrated pH-metrically with the solution of hydrochloric acid, and the associate (HA·Y) solutions, with the solutions of acids and alkalis. The titration with the continuous introduction of a titrant was performed in a thermally controlled glass cell (298 K). In the study of the complexation reactions, the titrated solutions contained additionally copper(II), nickel(II), cobalt(II), magnesium(II), or lanthanum(III). The titrated solutions were stirred with a magnetic stirrer.

Reproducible values of glass electrode potentials were reached in 2–3 min. However, we increased this time considerably for the studied compounds in the region close to the equivalence point. In these cases, the pH was measured 10 min after the addition of another portion of the titrant.

The experimental data, as in [7], were treated with the CPESSP software [18]. The reliability of selected models is described by the factors F and R [19, 20]. The average deviations of experimental data from the calculated (R-factor [20]) was less than 0.05 (5%).

The geometry of the molecule of monoprotonated 2,4,6-triaminopyrimidine was optimized by the method of molecular mechanics MM2 (software package ChemOffice 12.0) [10].

Synthesis of the associate (HA·Y). To a suspension of 2.68 g (0.02 mol) of 2,4,6-triaminopyrimidine in 30 ml of methanol at 50–55ºC was added dropwise with vigorous stirring 3.2 g (0.025 mol, 15% excess with respect to the 2,4,6-triaminopyrimidine) of bis-(hydroxymethyl)phosphinic acid in 25 ml of water-free methanol. The mixture was stirred for 30 min, the precipitate was filtered off and dried in a vacuum of a water-jet pump at 50ºC. Yield 4.1 g (76%), mp 187–188ºC. Found, %: C 28.66; H 5.57; N 27.34; P 12,57. $C_6H_{14}N_5O_4P$. Calculated, %: C 28.68; H 5.58; N 27.89; P 12.35. M 251. ^{31}P NMR spectrum (H_2O), δ, ppm: 35.9.

Synthesis of (YH_2) [$CuCl_4$]. Equimolar amounts of 2,4,6-triaminopyrimidine (1.88×10^{-3} mol, 0.2359 g) and copper(II) chloride dihydrate (1.88×10^{-3} mol, 0.3214 g) were dissolved separately in a minimum volume of hot solution of 6 M HCl. Then the solution of the copper(II) salt was poured to the solution of 2,4,6-triaminopyrimidine. From the resulting green solution upon the natural evaporation gradually precipitated needles of yellow-green color. After complete evaporation of liquid the air-dried product was weighed and analyzed. Yield 0.5978 g (95.4%). Found, %: C 15.01; H 2.14; Cl 39.12; Cu 19.06; N 20.72;. $C_4H_9Cl_4CuN_5$. Calculated, %: C 14.43; H 2.71; Cl 42.70; Cu 19.11; N 21.05;. M 332.5.

The copper content in the sample (m, g) after dissolving the sample in concentrated solution of ammonia was determined by spectrophotometry using a calibration curve constructed on the standard solutions. Conditions of preparation of standard solutions are the same as in the synthesis of the sample. The calibration function for $\lambda = 630$ nm is of the form: $A - (0.037 \pm 0.005) = (39.06 \pm 0.62)m$, $r = 0.99975$.

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