The reaction of 2-aminomethylphenols and their copper(II) complexes with esters of phosphorus acids

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2-Alkyl- and 2-dialkylaminomethylphenols (AMP) with different hydrophobic substituents at the nitrogen atom and their copper(II) complexes (CAMP) react with the esters of phosphorus acids in aqueous solutions of ethanol in two stages: phosphorylated AMP (PAMP) are formed at the first stage and then hydrolyzed to the corresponding acids. The reactivity of AMP and PAMP significantly decreases when the hydrophobicity and steric hindrances of substituents at the nitrogen atom increase. An inverse dependence was found for CAMP.

Key words: 2-aminomethylphenols, copper(II), esters of phosphorus acids; hydrolysis, reactivity, acid-base properties, complex formation.

We have previously shown that 2-dimethyl- and 2-diethylaminomethylphenols (AMP, HL) and their copper(II) complexes (CAMP, CuL_2) are catalysts of the hydrolysis of 4-nitrophenyl esters of phosphorus acids (EPA) in aqueous-ethanol[1,2] and micellar solutions of surfactants.[3—5] The reactions between AMP and EPA proceed in two stages. In the first stage, 4-nitrophenolate is formed by transesterification to give phosphorylated AMP (PAMP). The second stage is the hydrolysis of the latter due to the intramolecular catalysis of the aminomethyl group.[1,3]

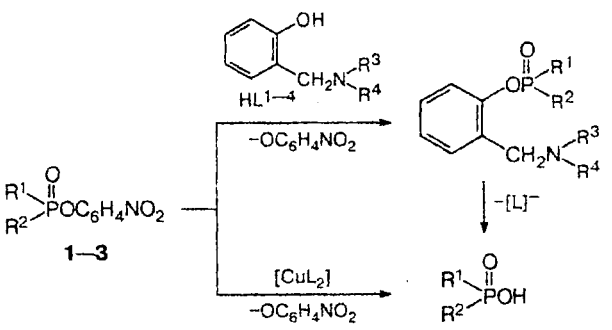
In these media, CAMP is more reactive towards EPA than AMP. The reactivity depends, to a great extent, on the structure and stability (logβ) of complexes that are closely related to the presence of substituents at the nitrogen atom.[1,2,5] It has also been found that the biological activity of AMP, their quaternary ammonium salts, and CAMP are mainly determined by the hydrophobicity of the substituents in the benzene ring and at the nitrogen atom.[6]

In this work, we studied the influence of the hydrophobicity and steric effects of the substituents at the nitrogen atom of AMP (HL^{1-4}) on the reactivity of these compounds towards EPA (**1—3**) in the absence and presence of copper(II) (Scheme 1) and on the acid-base properties of HL^{1-4} and their complexation with copper(II) in aqueous ethanol containing 70 vol.% EtOH.

Experimental

Compounds HL^{1-4} were synthesized by the reaction of phenol, paraform, and the corresponding amine according to the previously described procedure.[7] Substrates **1—3** were prepared by known procedures.[3,8] The other reagents were reagent grade. The acid-base properties of AMP and its complexation with copper(II) were studied by pH-metric titration and spectrophotometry (T = 25±0.05 °C) according to the published procedure.[9] An EV-74 ionomer was used. An ESL-43-07 glass electrode was calibrated in water—ethanol solutions.[10] The ionic strength of the solutions was maintained at a level of μ = 0.1 mol L^{-1} (KNO_3). The electronic absorption spectra of the solutions were recorded on a Specord UV—Vis spectrophotometer. In the study of complex formation between Cu^{II} and HL^{1-4}, we examined the following dependences of absorption (A): (1) on the pH of the solutions (the concentrations were unchanged, $C_{Cu^{2+}} = 5 \cdot 10^{-4}$ mol L^{-1}, $C_{HL} = 1 \cdot 10^{-2}$,

Scheme 1



1: $R^1 = R^2 = CH_2Cl$; **2**: $R^1 = CH_2Cl$, R^2 = OEt; **3**: $R^1 = R^2$ = OPh
HL^1: R^3 = H, $R^4 = Bu^n$; HL^2: R^3 = H, $R^4 = n\text{-}C_8H_{17}$; HL^3: $R^3 = R^4 = Bu^n$; HL^4: $R^3 = R^4 = n\text{-}C_5H_{11}$

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$2 \cdot 10^{-2}$ mol L^{-1}); (2) on the varied concentration of the ligands ($1 \cdot 10^{-2}$—$3.5 \cdot 10^{-2}$ mol L^{-1}) at unchanged concentrations of copper(II) ($5 \cdot 10^{-4}$ mol L^{-1}) and pH of the solutions (6.5—7); and (3) on the concentration of the complexing reactant ($2.5 \cdot 10^{-4}$—$2 \cdot 10^{-3}$ mol L^{-1}) at unchanged pH values of the solutions and concentrations of the ligands. To maintain the unchanged pH value, we used titrated solutions of HCl and NaOH. Experimental data were processed by the CPESSP program.[11] The reaction kinetics was studied by spectrophotometry and ^{31}P NMR spectrometry under pseudo-first order conditions. In all experiments, the concentration of AMP exceeded the concentration of substrates **1**—**3** by at least an order of magnitude. The concentration of **1** in spectrophotometric measurements was $5 \cdot 10^{-5}$ mol L^{-1}, and those of **2** and **3** in the experiments with ^{31}P NMR monitoring were $3 \cdot 10^{-3}$—$1 \cdot 10^{-2}$ mol L^{-1}. The observed rate constants (k_{obs}) were calculated by a first-order equation using the least-squares method. When the reaction kinetics was studied spectrophotometrically, we monitored the change in the optical density at 400 nm due to the *p*-nitrophenolate ion formed at 25±0.05 °C. ^{31}P NMR spectra were recorded on a Bruker MSL-400 instrument (161.97 MHz) at 308 K. Chemical shifts are presented relative to 85% H_3PO_4. The 1 : 2 copper(II) complexes with HL^{1-4} were prepared similarly to the previously described procedure.[12] ESR spectra were recorded on an SE/X-2544 spectrometer (Radiopan) at 295 K, and the concentration of the complexes was $5 \cdot 10^{-3}$ mol L^{-1}.

Results and Discussion

The study of the reactivity of bifunctional compounds and their metal complexes requires the values of acid-base equilibria and complex formation constants. In aqueous[13] and aqueous-alcohol[14] solutions, the acid-base equilibria of AMP are characterized by two measured constants K_1 and K_2, which correspond to the equilibria

$$H_2L^+ \overset{K_1}{\rightleftharpoons} HL + H^+, \quad (1)$$

$$HL \overset{K_2}{\rightleftharpoons} L^- + H^+, \quad (2)$$

where H_2L^+ is the N-protonated form, HL is the neutral form, and L^- is the phenolate form of AMP. The pK_1 and pK_2 values found are presented in Table 1. In AMP the NR_2 and OH groups interact to form the intramolecular hydrogen bond (IHB)[15] OH...N. The stability of the IHB depends, to a great extent, on the steric effect of the substituents at the nitrogen atom[15] and on the polarity of the medium.[14]

The study of the acid-base properties of AMP in water showed that the IHB exerts a strong effect on the acid-base equilibrium of both functional groups, decreasing the acidity of the phenol group and the basicity of the amine group by 1—2 pK_a units as compared to those of similar phenols and amines,[13,16] and this tendency increases with an increase in the stability of the IHB.

As can be seen from the data in Table 1, the basicity of the amino group of HL^{1-5} in a 70% (v/v) ethanol—water solution and in water[13] decreases on going from 2-alkyl- to 2-dialkylaminomethylphenols similarly to the decrease in the basicity on going from secondary to tertiary aliphatic amines.[17] This agrees with the fact that 2-alkyl- and 2-dialkylaminomethylphenols do not obey a single dependence between the stability of the IHB and steric constants.[15]

Table 1. pK_a and reaction rate constants k_2 of the neutral forms of AMP with **1** (pH 8.25, 25 °C) in a water—ethanol solution (70 vol.%)

Compound	pK_1	pK_2	k_2/L mol^{-1} s^{-1}
HL^1	8.45±0.02	10.85±0.08	61±2
HL^2	8.55±0.06	9.12±0.18	19±1
HL^3	7.31±0.04	9.80±0.2	4.1±0.2
HL^4	7.33±0.04	8.88±0.06	2.3±0.1
HL^{5*}	7.45±0.01	10.85±0.08	3.6±0.1

* 2-Diethylaminomethylphenol.[11]

By contrast, the acidity of the phenol group of AMP in the solvent under study, as compared to water,[13] increases with an increase in the steric effect of the substituents at the N atom in all studied AMP (see Table 1). This is a consequence of a superposition of several factors. The main factors are a decrease in the stability of the IHB in 70% ethanol and stabilization of the phenolate ion with an increase in the volume of the substituents at the N atom, similarly to what occurs in the gas phase.[17] The processing of the experimental data $A = f(pH)$, $A = f(C_{AMP})$, and $A = f(C_{Cu^{2+}})$ showed that two 1 : 1 and 1 : 2 mononuclear complexes (equilibria (3) and (4)) and one binuclear complex (equilibria (5) or (6) for HL^1) form in the solutions:

$$Cu^{2+} + H_2L^+ \overset{K_3}{\rightleftharpoons} [CuL]^+ + 2\,H^+, \quad (3)$$

$$Cu^{2+} + 2\,H_2L^+ \overset{K_4}{\rightleftharpoons} [CuL_2] + 4\,H^+, \quad (4)$$

$$2\,Cu^{2+} + 4\,H_2L^+ \overset{K_5}{\rightleftharpoons} [Cu_2(HL)_3L]^{3+} + 5\,H^+, \quad (5)$$

$$2\,Cu^{2+} + 4\,H_2L^+ \overset{K_6}{\rightleftharpoons} [Cu_2(HL)_4]^{4+} + 4\,H^+. \quad (6)$$

The equilibrium constants of the complexation reactions, their combined confidence intervals, and the stability constants of the complexes calculated by Eqs. (7)—(10) are presented in Table 2. In addition, the pH_{max} values corresponding to the maximum molar fraction of the complexes (α_{max}) are also collected in Table 2.

$$\log\{\beta([CuL]^+)\} = \log K_3 + pK_1 + pK_2, \quad (7)$$

$$\log\{\beta([CuL_2])\} = \log K_4 + 2pK_1 + 2pK_2, \quad (8)$$

$$\log\{\beta([Cu_2(HL)_3L]^{3-})\} = \log K_5 + 4pK_1 + pK_2 , \quad (9)$$

$$\log\{\beta([Cu_2(HL)_4]^{4+})\} = \log K_6 + 4pK_1 . \quad (10)$$

The sharp decrease in the stability constants of the 1 : 1 and 1 : 2 complexes of HL^4 is probably explained by the monodentate coordination of the ambidentate ligand: either the phenolate or amino group participates in complex formation. If both modes of coordination are approximately equiprobable, the complex species $[CuL^4]^+$ is present in isomeric forms.[18] The increased stability of the $[CuL^2]^+$ complex as compared to that of $[CuL^1]^+$ may be related to a higher hydrophobicity of the C_8H_{17} group, *i.e.*, to a less polar microenvironment of the chelate node that models a nonaqueous solution. However, when the second ligand is coordinated, the ratio of the stability constants of the $[CuL^1_2]$ and $[CuL^2_2]$ complexes reverse due to steric hindrances.[18]

Previously,[12] we have shown by ESR the presence of the N_2O_2 coordination node, which is tetrahedrally distorted depending on the steric properties of substituents at the N atom, for the copper(II) complex with AMP with a copper : ligand ratio of 1 : 2. The parameters of the ESR spectra of solutions of copper(II) HL^{1-4} complexes in toluene and ethanol are presented in Table 3. The magnetic parameters of solutions of $[CuL^{1-4}_2]$ in toluene indicate that the first coordination sphere of the $[CuL^{1,2}_2]$ complexes is closer in shape to a planar square than that of $[CuL^{3,4}_2]$, *i.e.*, in the case of $[CuL^{1,2}_2]$, the reactants approach each other more easily. The influence of the volume of the substituents is also pronounced when toluene is replaced by an electron-donating solvent such as ethanol. In the case of $[CuL^{1,2}_2]$, coordination with ethanol considerably increases the *g* factor (2.105 and 2.111, respectively), whereas for the $[CuL^{3,4}_2]$ complexes with a higher tetrahedral distortion, the parameters of the ESR spectra in both solvents slightly differ. The latter indicates a higher conformational stability[12] of the first coordination sphere of the $[CuL^{3,4}_2]$ complexes as compared to $[CuL^{1,2}_2]$.

Table 2. Equilibrium constants of the complex formation of copper(II) with AMP (*K*), stability constants of the complexes (logβ), and bimolecular reaction rate constants (k_2^K/L mol^{-1} s^{-1}) of the complexes with **1** in an aqueous-ethanol solution (70 vol.%) at 25 °C, μ = 0.1 mol L^{-1} (KNO_3)

Complex	$-\log K$	$\log\beta$	pH_{max}	α_{max} (%)	k_2^K
	2-Butylaminomethylphenol				
$[CuL]^+$	9.67±0.04	8.93	6.29	64.91	—
$[CuL_2]$	21.16±0.15	16.04	>9.25	99.99	96±3
$[Cu(HL)_4]^{4+}$	12.75±0.07	21.05	5.89	41.00	—
	2-Octylaminomethylphenol				
$[CuL]^+$	7.00±0.11	10.67	5.43	88.87	—
$[CuL_2]$	20.67±0.15	14.67	>9.46	98.31	1100±100
$[Cu_2(HL)L]^{3+}$	13.28±0.34	30.04	7.35	88.36	30±1
	2-Dibutylaminomethylphenol				
$[CuL]^+$	7.14±0.16	9.955	6.44	70.19	—
$[CuL_2]$	18.64±0.16	15.54	>8.57	99.76	35±3
$[Cu_2(HL)_3L]^{3+}$	15.87±0.17	23.15	6.63	1.82	—
	2-Dipentylaminomethylphenol				
$[CuL]^+$	12.43±0.42	3.78	7.61	10.44	—
$[CuL_2]$	24.60±0.36	7.82	>8.39	95.20	180±15
$[Cu(HL)_3L]^{3+}$	23.06±0.16	15.14	6.91	76.39	—
	2-Diethylaminomethylphenol				
$[CuL]^+$	11.95±0.02	6.35	7.10	32.38	—
$[CuL_2]$	23.87±0.02	12.73	>8.70	98.90	161±12

Table 3. Parameters of the ESR spectra of solutions of the copper(II) complexes with AMP in toluene (*A*) and ethanol (*B*)

Complex	g_{iso}		A_{iso}	
	A	*B*	*A*	*B*
CuL^1_2	2.105	2.111	89	82
CuL^2_2	2.105	2.111	89	82
CuL^3_2	2.110	2.110	75	77
CuL^4_2	2.111	2.109	75	77

The found dependences of the observed rate constants k_{obs} of the first-order reaction of HL^{1-4} with **1** on the concentration of AMP at pH 8.25 are linear. The second-order rate constants k_2 for the neutral forms of HL^{1-4} were calculated by the formula

$$k_2 = k_{obs}/(C_0 \cdot \alpha),$$

where C_0 is the total AMP concentration, and α is the fraction of the neutral HL^{1-4} form at a specific pH calculated using the equilibrium constants K_1 and K_2. The dependences of the molar distribution of different forms of HL^1 and HL^3 on the pH of solution are presented as an example in Fig. 1. The fraction of the phenolate form at a certain pH for HL^{1-4} is <0.1. Hence, in the calculation of k_2 its contribution was neglected. As can be seen from the data in Table 1, the reactivity of HL sharply decreases with increase in the hydrophobicity and steric effects of the substituents at the N atom. On going from HL^1 to HL^2, k_2 decreases by ~3 times, and in the case of HL^1 and HL^3, *i.e.*, when a second substituent (Bu^n) is introduced, it decreases by 15 times. However, further increase in the length of the hydrocarbon groups in HL^{3-5} insignificantly decreases the reactivity of these compounds. Analysis of the influence of the hydrophobicity of the substituents at the N atom (the scale of π constants of substituents)[19] (see Table 2) and parameters E_N, which characterize the steric accessibility of the N atom,[20] on k_2 shows that for $HL^{1,2}$ an increase in the hydrophobicity results in a decrease in the reactivity of these compounds, and for HL^{3-5} it has almost no effect on the reactivity. In the last case, the E_N values weakly change. It is most likely that both factors (the influence of the π constants of the substituents and the E_N values) are superimposed when the second alkyl substituent is introduced, which sharply decreases the reactivity of HL^{3-5} as compared to $HL^{1,2}$.

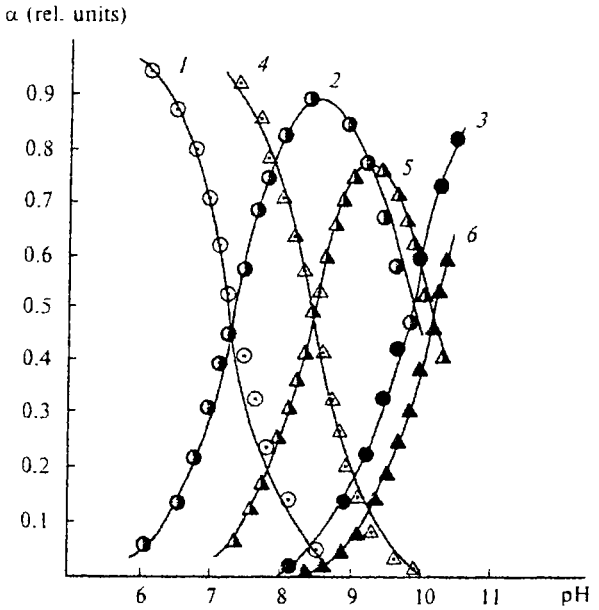

Fig. 1. Molar distribution of the ionized forms of the compounds HL^3 (*1—3*) and HL^1 (*4—6*) *vs.* the pH of their solutions in aqueous ethanol (70 vol.%) at $C_{AMP} = 1 \cdot 10^{-2}$ mol L^{-1}: *1* and *3*, HL^+; *2* and *5*, HL; and *3* and *6*, L^-.

The kinetics of the reactions of HL^1 and HL^3 with substrates **2** and **3** was also studied by ^{31}P NMR. The signals in the ^{31}P NMR spectra were identified by comparison of their chemical shifts with those of the signals from the reaction products that model hydrolysis, aminolysis, and transesterification. The changes in the intensity of the ^{31}P NMR signals in the course of the reaction of HL^1 ($C_{AMP} = 1.63 \cdot 10^{-1}$ mol L^{-1}) with substrate **3** ($C_3 = 9.8 \cdot 10^{-3}$ mol L^{-1}) at 35 °C and pH 9.2 are presented in Fig. 2. Analysis of the change in the ^{31}P NMR spectra during the reaction of **3** with HL^1 showed that at the first stage, along with a decrease in the intensity of the signal from substrate **3** (δ_P −19.2), the intensity of the signal from PAMP increases (δ_P −18.3). The hydrolysis of the intermediate product at the second stage results in the appearance of two signals corresponding to diphenyl phosphate (δ_P −11.2) and phenyl(2-butylaminomethyldiphenyl) phosphate (δ_P −10.6). The observed rate constants of transesterification (consumption of substrate **3** and formation of PAMP) calculated from the change in the intensity of the ^{31}P NMR signals are $3.7 \cdot 10^{-3}$ and $4.0 \cdot 10^{-3}$ s^{-1}, respectively, that of the hydrolysis of the intermediate product is $1.5 \cdot 10^{-3}$ s^{-1}, and those of the formation of the acids are $7 \cdot 10^{-4}$ and $1.0 \cdot 10^{-3}$ s^{-1}, respectively. Similar dependences have been obtained by us previously[3] for the reaction of 2-dimethylaminomethylphenol (HL^6) with **3**, which indicates an identical mechanism of the reactions of 2-alkyl- and 2-alkylaminomethylphenols with EPA. However, in the case of HL^6, the rate of PAMP hydrolysis is an order of magnitude lower than the rate of its formation, whereas for HL^1 it is lower by ~3 times only. The same ratio of transesterification to hydrolysis rates was found for the reactions (pH 9.2, 35 °C) of 2-butyl- and 2-dibutylaminomethylphenol ($C_{AMP} = 7 \cdot 10^{-2}$ mol L^{-1}) with substrate **2** ($C_2 = 5 \cdot 10^{-3}$ mol L^{-1}, δ_P 16.7), in which the hydrolysis of the intermediate product (δ_P 16.45) results in the formation of the acid (δ_P 13.3). For the reaction of **2** with HL^1, k_{obs} of the first stage is equal to $2 \cdot 10^{-3}$ s^{-1}, and that of the second stage is $6 \cdot 10^{-4}$ s^{-1}. In the case of HL^3, k_{obs} of the first stage is $1.2 \cdot 10^{-3}$ s^{-1}, and that of the second stage is $1 \cdot 10^{-4}$ s^{-1}. The hydrolysis of PAMP is due to the intramolecular catalysis by the aminomethyl group that occurs *via* the general basic or nucleophilic mechanism.[3] It is known that reactions of nucleophilic catalysis,[21] in particular, intramolecular nucleophilic catalysis,[22] are more sensitive to steric hindrances than reactions of general basic catalysis. The observed changes in the rates of PAMP hydrolysis when the substituents at the N atom change can favor the nucleophilic mechanism of intramolecular catalysis.

The pH dependences of k_{obs} of the reactions of $HL^{1,2}$ and $HL^{3,4}$ with **1** in the absence and presence of copper(II) are shown in Figs. 3 and 4. The molar distribution of the copper(II) complexes with HL^2 at different pH of the solutions is presented in Fig. 5. As can be seen from the data in Table 2, the pH regions in which $[CuL]^+$ and the binuclear complexes are accumulated (pH 5.5—7.5) almost coincide, except for the HL^2 ligand (see Fig. 5). At these pH, k_{obs} are low (see Figs. 3 and 4), *i.e.*, the sharp increase in k_{obs} in the region of pH > 7.5 is related to the accumulation and effect of the $[CuL_2]$ complexes, whose bimolecular rate constants k_2^K

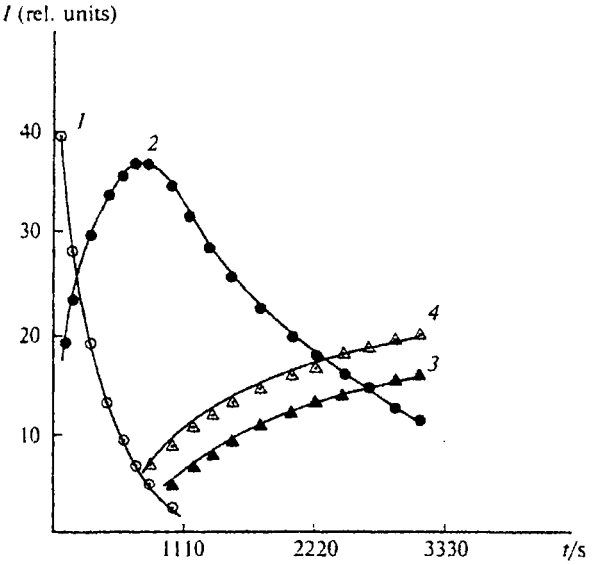

Fig. 2. Changes in the intensities of the ^{31}P NMR signals during the reaction of **3** ($C_3 = 9.8 \cdot 10^{-3}$ mol L^{-1}) with HL^1 ($C_{AMP} = 1.63 \cdot 10^{-1}$ mol L^{-1}) in a water—ethanol solution (70 vol.%) at 35 °C and pH 9.2. Chemical shifts (δ_P): −19.2 (*1*), −18.3 (*2*), −11.2 (*3*), and −10.6 (*4*).

are presented in Table 1. The constant k_2^K was calculated by the formula

$$k_2^K = (k_{obs} - k_{obs,AMP})/C_0\alpha$$

in the pH region where $\alpha > 0.5$, C_0 is the total concentration of copper(II), and $k_{obs,AMP}$ is the observed reaction rate constant of the corresponding ligand (AMP) at the specific pH.

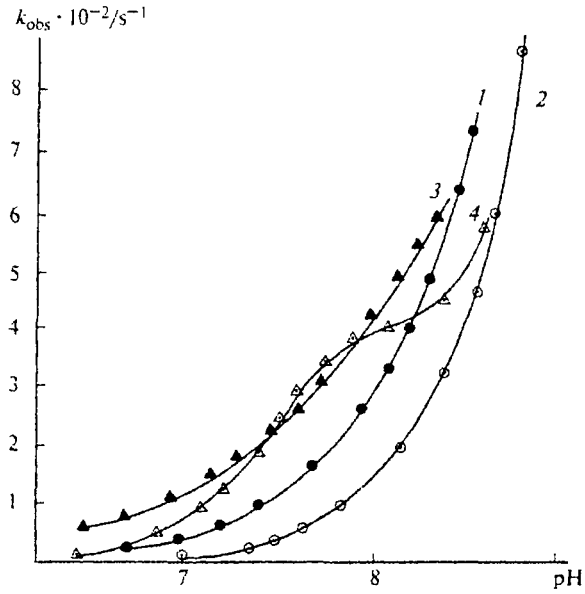

Fig. 3. Observed reaction rate constants (k_{obs}) of substrate **1** with AMP HL^1 (*1*, *3*) and HL^2 (*2*, *4*) ($C_{AMP} = 2.7 \cdot 10^{-3}$ mol L^{-1}) in the absence (*1*, *2*) and presence (*3*, *4*) of copper(II) ($C_{Cu^{2+}} = 1.1 \cdot 10^{-4}$ mol L^{-1}) as functions of the pH in aqueous ethanol (70 vol.%) at 25 °C.

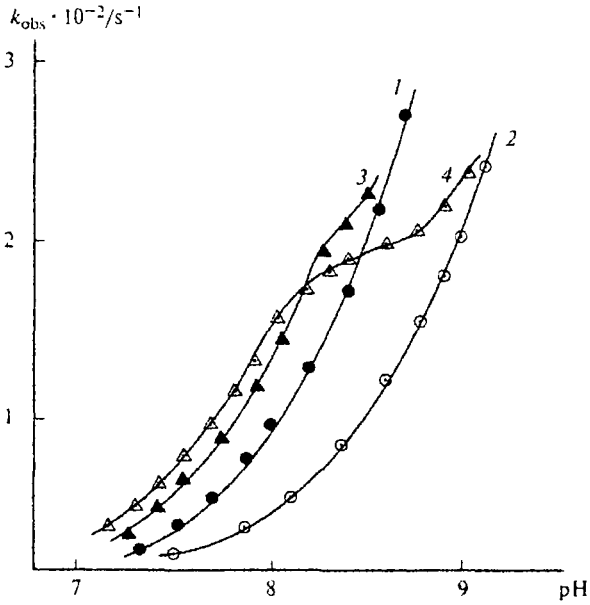

Fig. 4. Observed reaction rate constants (k_{obs}) of substrate **1** with AMP HL^3 (*1*, *3*) and HL^4 (*2*, *4*) ($C_{AMP} = 2.7 \cdot 10^{-3}$ mol L^{-1}) in the absence (*1*, *2*) and presence (*3*, *4*) of copper(II) ($C_{Cu^{2+}} = 1.1 \cdot 10^{-4}$ mol L^{-1}) as functions of the pH in aqueous ethanol (70 vol.%) at 25 °C.

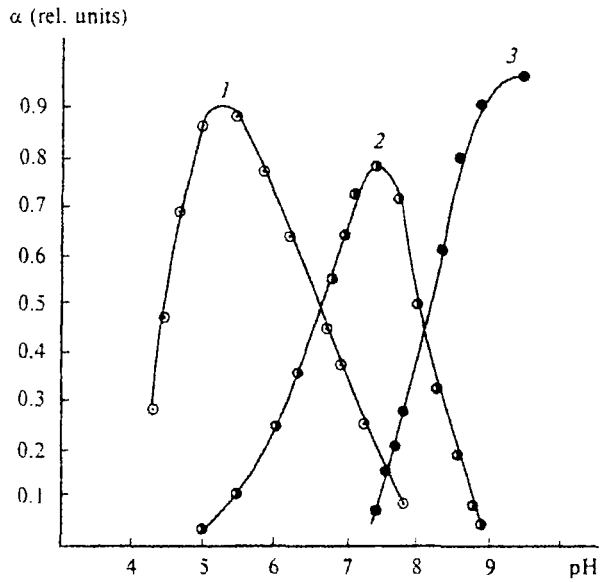

Fig. 5. Molar distribution of the HL^2 complexes with copper(II) as functions of the pH in aqueous ethanol (70 vol.%) at $C_{AMP} = 1 \cdot 10^{-2}$, $C_{Cu^{2+}} = 5 \cdot 10^{-4}$ mol L^{-1}: *1*, $[CuL]^+$, *2*, $[Cu_2(HL)_3L]^{3+}$, and *3*, $[CuL_2]$.

As can be seen in Table 2, an increase in the stability of the $[CuL_2]$ complexes (logβ) results in a decrease in their reactivity, similarly to the correlation found by us for $[CuL^5_2]$ when the composition of an aqueous-organic solvent changed.[2] However, a distinct mathematical correlation is observed in the last case, whereas no quantitative dependence $\log k_2 = f(\log\beta)$ is observed when the structure of the ligand changes. As for the hydrophobicity factor, an increase in the π constants of the substituents in $HL^{1,2}$ and $HL^{3,4}$ results in a decrease in the reactivity, whereas in the case of $[CuL^{1,2}_2]$ and $[CuL^{3,4}_2]$, it results, by contrast, in an increase (see Table 2). Probably, this behavior is related to the fact that the hydrophobic environment of the coordination node favors a stronger binding of molecule **1** with the substrate, which is indicated by the more pronounced plateau (see Figs. 3 and 4) for $[CuL^{2,4}_2]$ as compared to $[CuL^{1,3}_2]$. The $[CuL^{2,4}_2]$ complexes exceed in reactivity the HL^2 and HL^4 ligands by 60 and 90 times, respectively. The high reactivity of the $[CuL^2_2]$ complex ($k_2 = 1100$ L mol^{-1} s^{-1}) is explained by a favorable combination of several factors. In addition to the hydrophobic environment of the coordination node, the $[CuL^2_2]$ complex has a geometry close to a planar square (see Table 3), which facilitates the coordination with the substrate to the axial positions. The formation of adducts of the complexes with the substrates is indicated by a broadening of the lines in the ESR spectra of solutions of the $[CuL^{1-4}_2]$ complexes in the presence of **3** in toluene. The decrease in the intensity of the ESR signals of the complexes that achieves 50% at the com-

plex : substrate ratio of 1 : 1 can be related[1,12] to the partial decomposition of the $[CuL_2]$ complexes after the end of the reaction and an increase in the acidity of the medium.

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