Synthesis and Complexation Properties of 2-Hydroxy-5-methoxyphenylphosphonic Acid (H₃L¹). Crystal Structure of the [Cu(H₂L¹)₂(H₂O)₂] Complex

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Abstract—2-Hydroxy-5-methoxyphenylphosphonic acid (H₃L¹) and the complex [Cu(H₂L¹)₂(H₂O)₂] were synthesized and characterized by IR spectroscopy, thermogravimetry, and X-ray diffraction analysis. The polyhedron of the copper atom is an axially elongated square bipyramid with oxygen atoms of phenolic and of monodeprotonated phosphonic groups at the base and oxygen atoms of water molecules at the vertices. The protonation constants of the H₃L¹ acid and the stability constants of its Cu²⁺ complexes in water were determined by potentiometric titration. The protonation constants of the acid in water are significantly influenced by the intramolecular hydrogen bond and the methoxy group. The H₃L¹ acid forms complexes CuL⁻ and CuL₂⁴⁻ with Cu²⁺ in water.

Keywords: copper(II) complexes, X-ray diffraction, IR spectroscopy, acid protonation constant, complex stability constant

Organophosphorus compounds are used in many fields of medicine and agriculture and play a significant role in organic synthesis, catalysis, and biochemistry [1–6]. Phosphoryl-substituted phenols are known for their complexing, extraction, and ion-selective properties [7–13]. Among them, 2-hydroxyphenylphosphonic acids occupy a special place, since they are phosphoryl analogues of salicylic acid and can be considered as physiologically active substances (Scheme 1). 2-Hyd-roxy-5-ethylphenylphosphonic acid (H₃L²) and its complex [Cu(H₂L²)₂(H₂O)₂] exhibit analgesic activity [14, 15]. With low toxicity, the analgesic effect of the complex significantly exceeds the effect of analgin. The possibility of using drugs based on complexes of transition metals, such as platinum [16, 17], cobalt(II) [18], manganese(II/IV) [19], nickel(II) [20], and copper(II) [21–25], with organic ligands has been shown. Therefore, the synthesis of new organic compounds and

Scheme 1.

$$H_3L^1 \qquad H_3L^2 \qquad H_3L^3$$
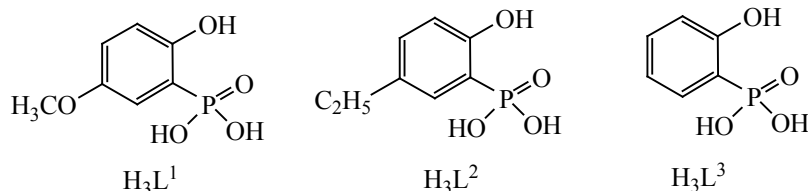
Scheme 2.
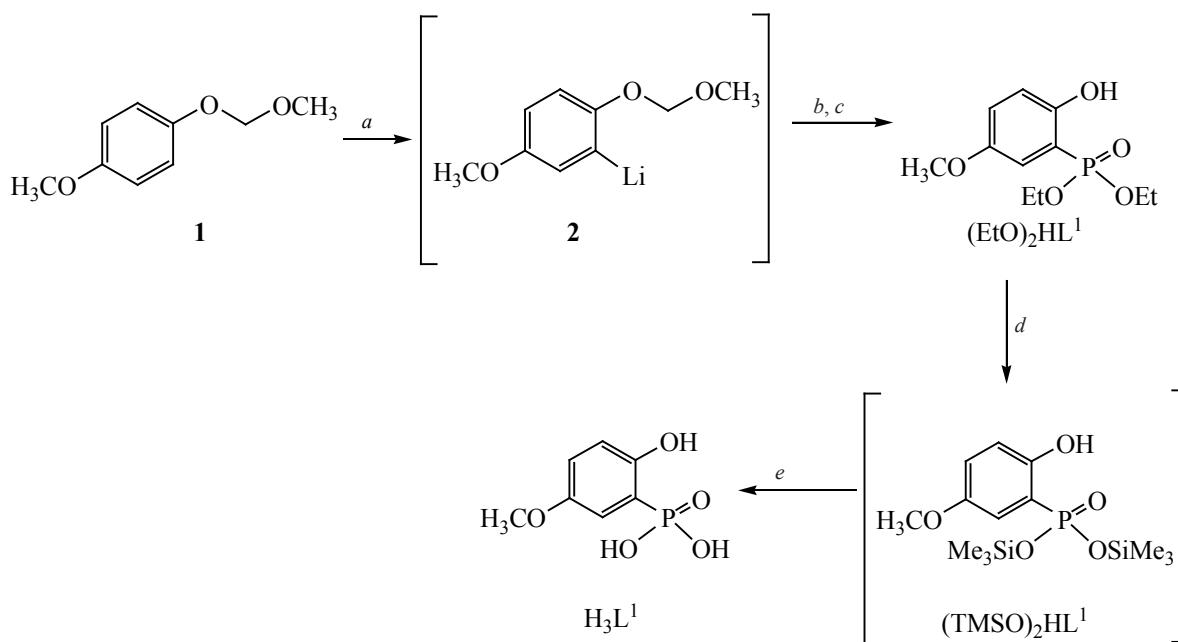
a, BuLi, THF–hexane (3 : 1); b, (EtO)$_2$P(O)Cl, –60°C; c, HCl, EtOH, room temperature; d, Me$_3$SiCl, NaBr, MeCN, 80°C; e, EtOH–H$_2$O (1 : 1), room temperature.

their complexes, which often exhibit higher biological activity than the initial compounds [26–28], is an important area of research.

We synthesized 2-hydroxy-5-methoxyphenylphosphonic acid (H$_3$L^1) and the complex [Cu(H$_2$L^1)$_2$(H$_2$O)$_2$], and determined its structure by X-ray structural analysis. The protonation constants of H$_3$L^1 acid and the stability constants of its complexes with Cu^{2+} in water were determined; the IR spectroscopy and thermogravimetry data are presented.

2-Hydroxyphenylphosphonic acids are rather inaccessible compounds [14, 29–31]. In the synthesis of H$_3$L^1 acid (Scheme 2), we used the technique, which we developed earlier [14]. Its main advantage is the final reaction with *in situ* generated trimethylbromosilane. The reaction proceeds practically without by-products formation.

As the starting compound in the preparation of the organolithium component necessary to create the Ar-P bond, methoxymethyl ether **1** of 4-methoxyphenol was used, which reacts with butyllithium in a mixture

of solvents tetrahydrofuran–hexane (3 : 1) to form [2-(methoxymethoxy)-5-methoxyphenyl]lithium **2**. The (EtO)$_2$HL^1 phosphonate in crystalline form was isolated with a high yield when equivalent amounts of compound **2** and diethyl chlorophosphate reacted *in situ* at –60 ± 5°C with following acid hydrolysis of the methoxymethyl protective group at room temperature. The reaction of (EtO)$_2$HL^1 with trimethyl chlorosilane in the presence of anhydrous sodium bromide in boiling acetonitrile resulted in the formation of bis(trimethylsilyl)-phosphonate (TMSO)$_2$HL^1, which, without isolation, was hydrolyzed at room temperature with a mixture of ethanol and water to form H$_3$L^1 acid. This acid, unlike salicylic acid, is highly soluble in water, which is a key criterion for the selection of compounds promising in the drug development [32, 33].

Crystals of complex [Cu(H$_2$L^1)$_2$(H$_2$O)$_2$] **3** were obtained by the reaction of copper(II) perchlorate with H$_3$L^1 acid. According to the results of the X-ray structural analysis, complex **3** has a centrosymmetric structure (Fig. 1).
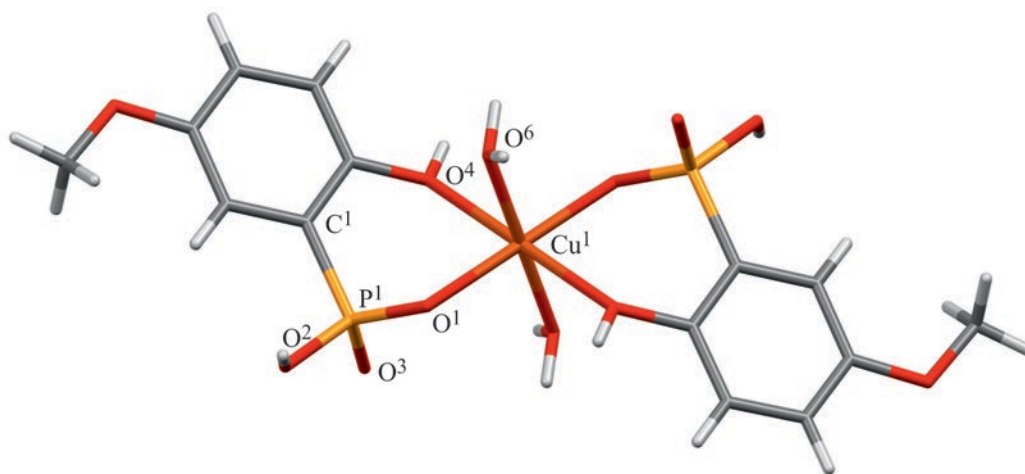
Fig. 1. Structure of the complex $[Cu(H_2L^1)_2(H_2O)_2]$ (**3**). Bond lengths: Cu^1-O^1 1.9601(1), Cu^1-O^4 2.450(2), and Cu^1-O^6 1.9499(17) Å.

Table 1. Main structural data and refinements of the complex **3** structure

Parameter	Value
T, K	296(2)
Syngony	Monoclinic
Space group	$C2/c$
a, Å	30.768(5)
b, Å	4.8551(6)
c, Å	12.6695(16)
β, deg	91.732(6)
V, Å^3	1891.7(5)
Z	4
D_{calc}, g/cm^3	1.776
μ, mm^{-1}	1.388
Crystal size, mm	0.32×0.16×0.06
Interval θ, deg	2.649, 30.001
Reflection index intervals	$-31 \le h \le 41$;
Reflections collected	$-6 \le k \le 6$;
Independent reflections (R_{int})	$-17 \le l \le 16$
Completeness to θ 25.242°, %	8218
Transmission (max, min)	2562, 0.0362
Restrictions/Parameters	99.6%
GOOF	0.746, 0.6405
R_1, wR_2 ($I > 2\sigma(I)$)	0/146
R_1, wR_2 (all data)	0.993
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.0368, 0.0953
R_1, wR_2 (all data)	0.0528, 0.1033
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.543, −0.494

The 4+2 coordination sphere is usual for Cu^{2+}. The copper atom polyhedron is an axially elongated square bipyramid with oxygen atoms of phenolic and monodeprotonated phosphonic groups at the base and with oxygen atoms of water molecules at the vertices. As a result of the combined action of four hydrogen bonds, a 2D structure is formed (the layers are perpendicular to the a axis, Fig. 2). The structure of similar $[Cu(H_2L^2)_2(H_2O)_2]$ complex of 2-hydroxy-5-ethylphenylphosphonic acid was determined earlier [15]. The molecular structures of the two complexes are the same (accurate to OMe/Et), the parameters of the elementary cells are close [15] (Table 1), and the systems of hydrogen bonds are identical [15] (Table 2), however replacing Et with OMe leads to a noticeable decrease in the unit cell volume (2040 and 1892 Å^3). This change is caused by intermolecular contacts of 3.56 and 4.17 Å in the compexes **3** and $[Cu(H_2L^2)_2(H_2O)_2]$, respectively, between O⋯O (OMe) and C⋯C (CH$_2$Me) atoms connected to each other by the 2_1 axis (Fig. 2). Replacing Et with OMe leads not only to a shift of neighboring complexes relative to each other (Fig. 3a), but also to their half-turn (Fig. 3b).

The assignment of several vibrational frequencies of donor groups in the spectra of H$_3$L^1 acid and $[Cu(H_2L^1)_2(H_2O)_2]$ complex, which allows us to judge the H$_3$L^1 coordination, was carried out taking into account previous spectral studies of H$_3$L^2 and $[Cu(H_2L^2)_2(H_2O)_2]$ [15].

The bands of stretching vibrations ν(C–H), ν(O–H)$_{Ph}$, and ν(O–H)$_P$ in the IR spectrum of H$_3$L^1 acid
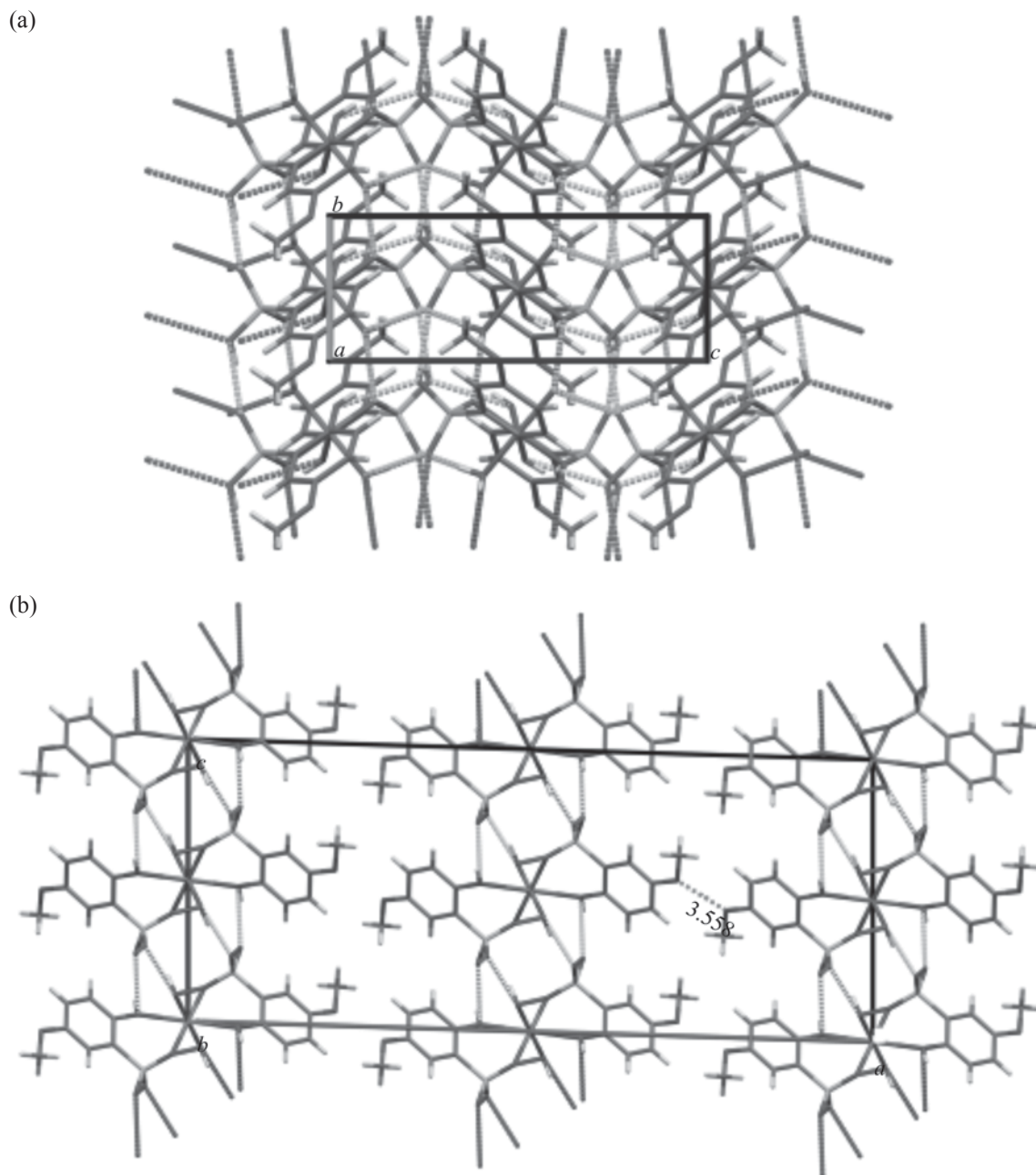
(a)

(b)

Fig. 2. Projections of the complex **3** structure along axes (a) *a* and (b) *b*.

lie in the range of wave numbers 4000–2000 cm^{-1}. The band ν(O–H)$_{Ph}$ is shifted to the low-frequency region up to 3207 cm^{-1} (~3600 cm^{-1} in the spectrum of free phenol), which is caused by the participation of the phenolic group of acid H$_3$L^1 in the formation of hydrogen bonds characteristic of such compounds [34]; the ν(O–H)$_P$ bands are low intensive.

Replacing Et with OMe leads to noticeable differences in the IR spectra of H$_3$L^1 and H$_3$L^2 acids in the range of

1250–900 cm^{-1}: in the spectrum of H$_3$L^1, compared to the spectrum of H$_3$L^2, there is a significant decrease in the intensity and an increase in the number of bands. The band of average intensity at 1219 cm^{-1}, which is 11 cm^{-1} lower than in the spectrum of H$_3$L^2 [15], can be assigned to stretching vibrations ν(P=O) of the phosphoryl group, the frequency of which is determined by the electronegativity of substituents at the phosphorus atom. According to the assignments made for H$_3$L^2 [15], the band of average

(a)

(b)
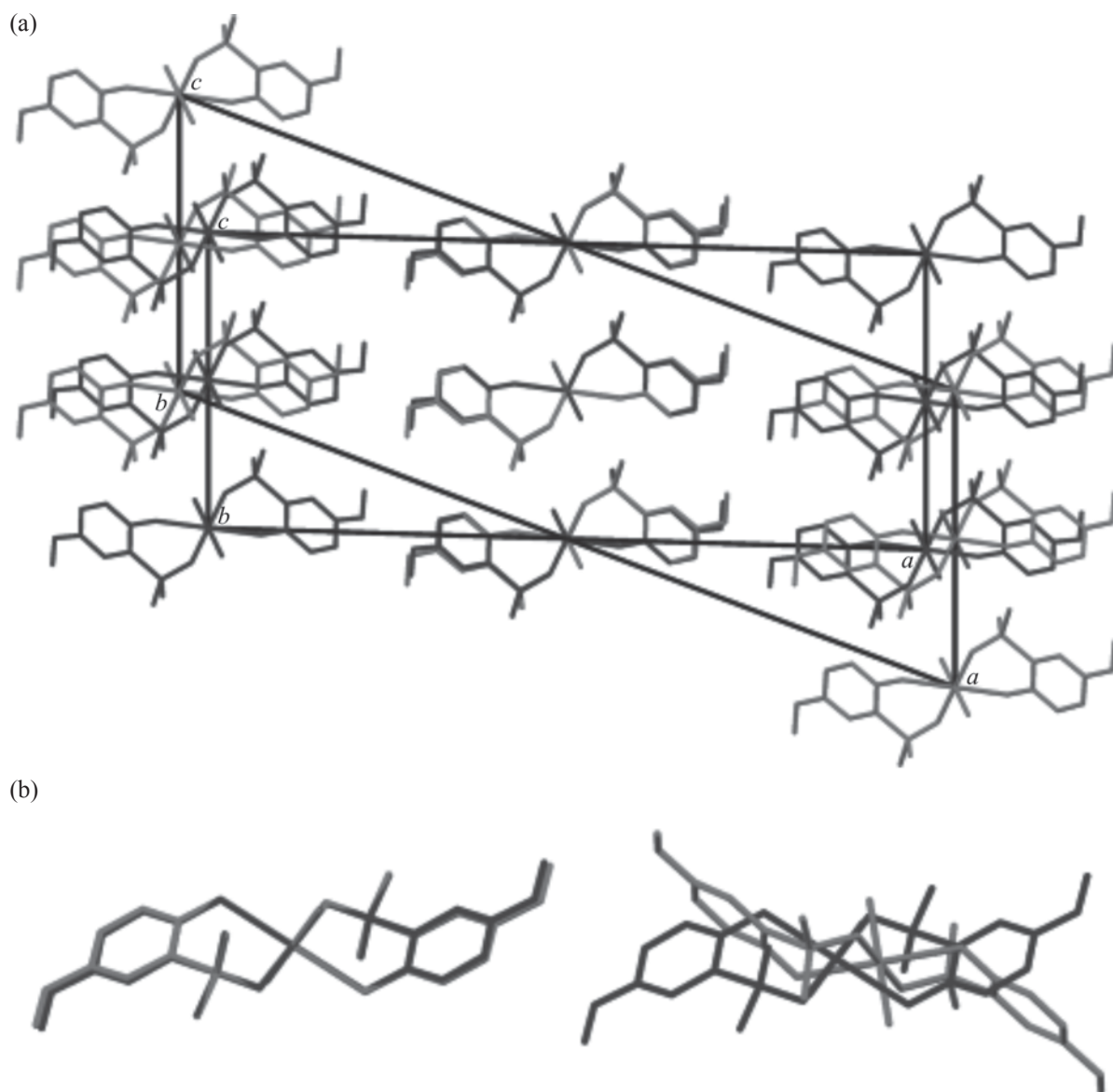
Fig. 3. (a) Comparison of packages of complexes **3** and $[Cu(H_2L^2)_2(H_2O)_2]$ in crystals and (b) mutual arrangement of two pairs of structures formed by complexes **3** (red) and $[Cu(H_2L^2)_2(H_2O)_2]$ (blue). The distances are minimized between Cu, P, and coordinated O atoms of (a) central and (b) left complexes of the two structures.

intensity at 1286 cm^{-1} refers to the ν(Ph–O) absorption of the phenolic fragment. The intense bands at 1026 and 929 cm^{-1} in the H_3L^1 spectrum are caused by δ(POH) and ν(PO) vibrations of the phosphonic fragment.

The complex formation leads to a certain decrease of 3207→3190 cm^{-1} in the ν(O–H)$_{Ph}$ frequency. Low-intensity blurred bands with maxima of about 2552 and 2248 cm^{-1} correspond to the ν(O–H)$_P$ vibrations in the spectrum of the complex. In the IR spectrum

of $[Cu(H_2L^1)_2(H_2O)_2]$ complex, a new $\nu(H_2O)$ band, as compared with the spectrum of the free H_3L^1 acid, appears at 3359 cm^{-1}, and a wide low-intensity $\delta(H_2O)$ band appeared nearby 1713 cm^{-1}.

The presence of the OMe donor group leads not only to a decrease in the unit cell volume and a change in the packaging of $[Cu(H_2L^1)_2(H_2O)_2]$ complex, compared to $[Cu(H_2L^2)_2(H_2O)_2]$, but also to a significant decrease in the frequency of the phosphoryl group stretching vibration

Table 2. Lengths and angles of hydrogen bonds in complex **3**

D–H⋯A	d(D–H), Å	d(H⋯A), Å	d(D⋯A), Å	φ(DHA), deg
O^2–H^1⋯O^3 $(x, y+1, z)$	0.77(3)	1.75(3)	2.507(2)	170(3)
O^4–H^2⋯O^2 $(x, -y+1, z+1/2)$	0.70(3)	2.23(3)	2.887(2)	157(3)
O^6–H^3⋯O^1 $(x, y-1, z)$	0.65(3)	2.10(3)	2.728(2)	163(4)
O^6–H^4⋯O^3 $(-x+1, y, -z+1/2)$	0.88(3)	1.85(3)	2.718(3)	165(3)

ν(P=O). In the IR spectrum of $[Cu(H_2L^1)_2(H_2O)_2]$, the ν(P=O) vibrations correspond to the asymmetric band of higher than the average intensity at 1205 cm^{-1}, which is 14 cm^{-1} lower compared to its position in the H_3L^1 spectrum, and is associated with the participation of the phosphoryl oxygen atom in the formation of hydrogen bonds. The formation of hydrogen bonds in $[Cu(H_2L^2)_2(H_2O)_2]$ complex also leads to a decrease in ν(P=O), but it is not so significant (~5 cm^{-1}) [15]. The frequency of the phenolic fragment vibrations ν(Ph–O) in the spectrum of $[Cu(H_2L^1)_2(H_2O)_2]$ complex decreases slightly in comparison with the spectrum of the free H_3L^1 acid, and appears, in our opinion, as an average intensity band at 1257 cm^{-1}. Intense bands near 1020 and 943 cm^{-1} are caused by δ(POH) and ν(PO) vibrations.

In terms of the number, intensity, and position of the main vibrational frequencies, the spectrum of $[Cu(H_2L^1)_2(H_2O)_2]$ complex is identical to the spectrum of $[Cu(H_2L^2)_2(H_2O)_2]$ complex, which points to the isostructurality of these compounds.

Thermogravimetric study of $[Cu(H_2L^1)_2(H_2O)_2]$ complex showed that its multi-stage thermal decomposition begins with the gradual removal of water molecules. On the DTG curve, two corresponding endothermic effects are observed at 76 and 128°C, which could not be separated. Full removal of two water molecules is completed by 151°C (calculated 7.12%, found 7.14%). A further increase in temperature to 400°C leads to a gradual decomposition of the compound.

The protonation constants of H_3L^1 acid were determined by the potentiometric titration method (Table 3). The resulting values of the constants of H_3L^1 and H_3L^2 acids [15] are close to each other, the confidence intervals of the corresponding constants overlap. The value of the second constant log K_2 of H_3L^1, as in the case of H_3L^2, is close to the value of the second constant for unsubstituted 2-hydroxyphenylphosphonic acid

(H_3L^3) (6.19±0.12 (H_3L^1), 6.36±0.37 (H_3L^2) [15], and 6.46 (H_3L^3) [35]). The lower acidity of H_3L^1 and H_3L^2 (log K_3 2.64±0.14 and 3.20±0.74 [15], respectively) compared to H_3L^3 (log K_3 1.66 [35]) may be caused by the presence of donor ethyl and methoxy groups, which affect the ionization of the phosphonic group and change the hydration of acid molecules. Intramolecular hydrogen bonding, characteristic of such compounds and confirmed by the IR spectroscopy data, leads to a decrease in the acidity of the phenolic group in H_3L^1 and H_3L^2 acids (log K_1 11.42±0.08 and 11.58±0.24 [15]) compared with the values of log K_1 10.03 and 10.56 for 3- and 4-hydroxyphenylphosphonic acids, respectively [35].

The species distribution diagram for H_3L^1 acid depending on pH is shown in Fig. 4. At a physiological pH value of 7.4, the HL^{2-} anion predominates in water, as also in H_3L^2 acid [15]. In the pH range from 3 to 5.5, the acid is mainly in the form of H_2L^- anion.
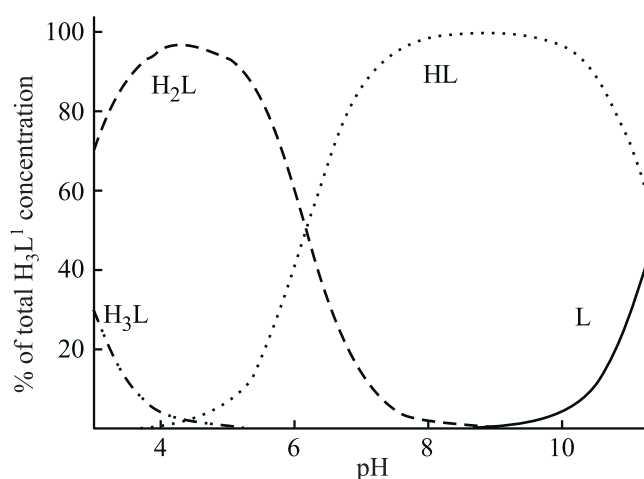
Fig. 4. Species distribution diagram for H_3L^1 acid as a function of pH in water at 298 K, ionic strength 0.1 M, and analytical concentration 2.0 mM. For simplicity, charges are not included in the formulas of acid anions.

Table 3. Stepwise and total protonation constants of H_3L^1 acid in water at 298 K and ionic strength 0.1 M KCl[a]

i	Equilibrium	$\log K_i \pm sd$ [b]	Equilibrium	$\log \beta_i \pm sd$ [c]
1	L + H = HL	11.42±0.08	L + H = HL	11.42±0.08
2	HL + H = H$_2$L	6.19±0.12	L + 2H = H$_2$L	17.60±0.09
3	H$_2$L + H = H$_3$L	2.64±0.14	L + 3H = H$_3$L	20.24±0.11

[a] Here and further for simplicity of equilibria representation, charges of chemical species are not specified: instead of $H^+ + L^{3-} = HL^{2-}$, H + L = HL is given, etc.

[b] $\log K_i$ and sd are stepwise equilibrium constants and their standard deviations calculated from the results of several titrations and calculations (see the experimental part) using error propagation rule and standard deviations for the total equilibrium constants $\log \beta_i$.

[c] $\log \beta_i$ and sd are total equilibrium constants and their standard deviations calculated using the program CHEMEQUI.

Table 4. Stepwise and total stability constants of Cu^{2+} complexes with H_3L^1 acid in water at 298 K and ionic strength 0.1 M KCl

i	Equilibrium	$\log K_i \pm sd$	Equilibrium	$\log \beta_i \pm sd$
1	Cu + L = CuL	8.34±0.02	Cu + L = CuL	8.34±0.02
2	CuL + L = CuL$_2$	7.88±0.20	Cu + 2L = CuL$_2$	16.21±0.19
3	CuL + OH = Cu(OH)L	5.02±0.11	Cu + L + OH = Cu(OH)L	13.35±0.11
4	CuL$_2$ + OH = Cu(OH)L$_2$	2.94±0.20	Cu + 2L + OH = Cu(OH)L$_2$	19.16±0.06

Stability constants of copper(II) complexes with deprotonated forms of H_3L^1 acid were determined by the potentiometry method using the CHEMEQUI program (Table 4). According to the species distribution diagram
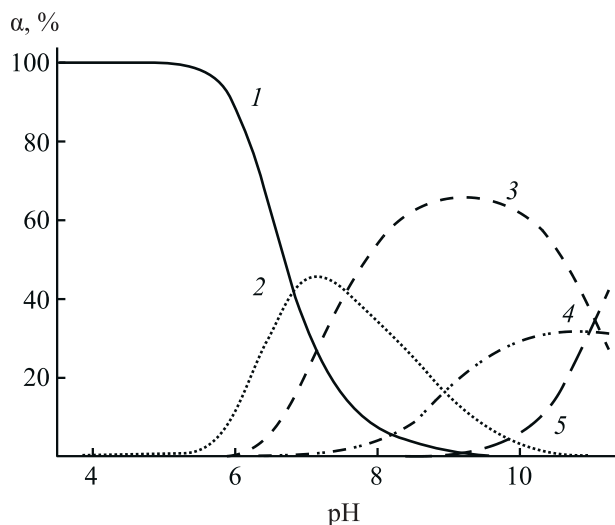
Fig. 5. Species distribution diagram for the Cu^{2+} complexes with H_3L^1 acid as a function of pH in water at 298 K, ionic strength 0.1 M, and initial concentrations of reagents 0.49 (H_3L^1) and 0.24 (Cu^{2+}) mM. Percentage α of equilibrium ion concentrations relative to the total Cu^{2+} concentration: (1) Cu^{2+}, (2) CuL^-, (3) CuL_2^{4-}, (4) $CuL(OH)^{2-}$, and (5) $CuL_2(OH)^{5-}$.

for the Cu^{2+} complexes with H_3L^1 acid (Fig. 5), the complex of the composition Cu : L = 1 : 2 is formed in solution. The complex of the composition 1 : 1 is formed in a much smaller amount (similar to the complex formation of Cu^{2+} with H_3L^2 acid [15]).

The first of the stability constants $\log K_1$ 8.34±0.02 and $\log K_2$ 7.88±0.20 of the CuL^- and CuL_2^{4-} complexes appeared to be significantly lower than the corresponding constants of Cu^{2+} complexes with salicylic acid ($\log K_1$ 10.83 and $\log K_2$ 8.05 [36, 37]) and lower than those with H_3L^2 acid ($\log K_1$ 8.91±0.06 and $\log K_2$ 8.39±0.08 [15]). This seems to be caused by the fact that, according to structural data, the phenolic oxygen of H_3L^1 and H_3L^2 acids practically does not participate in the complex formation {the length of the Cu–OPh bonds of 2.450(2) and 2.448(3) Å [15] is significantly longer than the length of the Cu–OP(O)(OH)Ph bond 1.960(1) and 1.967(3) Å [15], respectively} in contrast to 4-methoxysalicylic acid {the Cu–OPh bond length 1.899 Å and that of Cu–OC(O)Ph 1.889 Å [38]}. The differences in the stability of the CuL and CuL$_2$ complexes of H_3L^1 and H_3L^2 acids can be explained by the influence of the methoxy group (H_3L^1) and ethyl substituent (H_3L^2), which changes the free energy of acid hydration and the phosphonic group acidity.

Thus, we synthesized 2-hydroxy-5-methoxyphenyl-phosphonic acid (H_3L^1) with a sufficiently high yield, which allowed us to prepare trial batches of this compound necessary for biological research. For the first time the obtained complex $[Cu(H_2L^1)_2(H_2O)_2]$ was characterized by the methods of X-ray structural analysis, IR spectroscopy, and thermogravimetry. The protonation constants of the acid in water are significantly influenced by the intramolecular hydrogen bond and the methoxy group. The H_3L^1 acid, as well as the 2-hydroxy-5-ethylphenylphosphonic acid (H_3L^2), forms with Cu^{2+} water-soluble CuL^- and CuL_2^{4-} complexes. Since the results of biological studies have shown that $[Cu(H_2L^2)_2(H_2O)_2]$ complex has a high analgesic activity [15], our planned studies of biological activity of $[Cu(H_2L^1)_2(H_2O)_2]$ complex are very promising.

EXPERIMENTAL

All reactions involving [2-(methoxymethoxy)-5-methoxyphenyl]lithium **2** were carried out in a dry argon atmosphere. The ^1H and ^{31}P NMR spectra were recorded on a Bruker SHR-200 spectrometer. Melting temperatures were measured on a Boetius PHMK 05 device. Elemental analysis was performed on a C, H, N analyzer (Carlo Erba Strumentazione) and an IRIS Advantage (Thermo Jarrell Ash) atomic emission spectrometer with inductively coupled plasma. The IR absorption spectra were recorded in the range of 4000-550 cm^{-1} by the FTIR spectroscopy method on a Nexsus Nicolet spectrometer. Thermogravimetric studies were carried out on a SDT Q600 derivatograph in the temperature range 20–600°C at a heating rate of 4 deg/min in argon current.

Diethyl ether of 2-hydroxy-5-methoxyphenyl-phosphonic acid [(EtO)$_2$HL^1]. To a solution of [2-(me-thoxymethoxy)-5-methoxyphenyl]lithium **2** obtained by the reaction of 40 mL of 2.5 N solution of *n*-butyllithium in hexane with 21.5 g (130 mmol) of 4-methoxyphenol methoxymethyl ether **1** [39, 40] in 130 mL of THF, 22 g (130 mmol) of diethylchlorophosphate was added at –60±5°. Then the temperature of the reaction mixture was raised to 20°C. The mixture was stirred for 1.5 h, and the solvent was removed in vacuum. To the residue, 100 mL of saturated KH_2PO_4 solution was added, extraction with CHCl$_3$ (2×50 mL) was carried out, the extract was washed with water (3×50 mL), dried with Na_2SO_4, and the solvent was removed in vacuum. To the residue, 100 mL of an 1 : 1 mixture of concentrated HCl and EtOH, was added and left overnight, then poured into

300 mL of water, and extracted with CHCl$_3$ (3×50 mL). The extract was washed with water (3×50 mL), dried with Na_2SO_4, and the residue was distilled in vacuum. Yield 26.30 g (78%), bp 134–136°C (1 mmHg), mp 58–60°C (heptane). ^1H NMR spectrum (DMSO-d_6–CCl$_4$, 1 : 3), δ, ppm: 1.32 t (6H, 2OCH$_2$CH$_3$, $^3J_{HH}$ 7.0 Hz), 3.74 s (3H, ArOCH$_3$), 4.05 m (4H, 2OCH$_2$CH$_3$), 6.85 m (2H$_{Ar}$), 6.89 m (1H$_{Ar}$), 9.67 s (1H, OH). $^{31}P\{^1H\}$ NMR spectrum DMSO-d_6–CCl$_4$, 1 : 3): δ$_P$ 21.61 ppm. Found, %: C 50.88; H 6.19; P 11.95. C$_{11}$H$_{17}$O$_5$P. Calculated, %: C 50.77; H 6.59; P 11.90.

2-Hydroxy-5-methoxyphenylphosphonic acid (H$_3$L^1). To a solution of 1.50 g (5.8 mmol) of (EtO)$_2$HL^1 ether in 15 mL of anhydrous acetonitrile, 1.18 g (11.6 mol) of NaBr and 1.28 g (11.9 mmol) of Me$_3$SiCl were added. The reaction mass was boiled for 6 h. The hot solution was filtered, the solvent was evaporated. The residue was dissolved in 20 mL of aqueous ethanol (1 : 1), kept for 12 h at room temperature, and the solvent was evaporated in vacuum. To the residue, 10 mL of CH$_2$Cl$_2$ was added, the precipitate was filtered and dried in vacuum (12 h, 10 mmHg). Yield 0.8 g (67 %), mp 148–149°C (mp 158–159°C [29]). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.70 s (3H, CH$_3$OAr), 6.88 m (3H$_{Ar}$). $^{31}P\{^1H\}$ spectrum (DMSO-d_6): δ$_P$ 16.83 ppm. Found, %: C 41.54; H 4.63; P 15.01. C$_7$H$_9$O$_5$P. Calculated, %: C 41.19; H 4.44; P 15.17.

Complex [Cu(H$_2$L^1)$_2$(H$_2$O)$_2$] (3) was obtained by the reaction of equimolar amounts of H$_3$L^1 and Cu(ClO$_4$)$_2$·6H$_2$O in water. Varying the ratio of reagents and performing the reaction in the presence of 1 eq. of NaOH did not affect the yield and composition of the resulting compound. The light blue crystals for the X-ray structural analysis were obtained by slow evaporation of the solution. The complex is slightly soluble in low-polar organic solvents and readily soluble in ethanol, DMFA, and DMSO. Found, %: C 33.43; H 4.14. C$_{14}$H$_{20}$CuO$_{12}$P$_2$. Calculated, %: C 33.26; H 3.96.

**Potentiometric titration** with the aim of determining the protonation constants of H$_3$L^1 acid and the stability constants of its complexes with copper(II) perchlorate was performed according to the method [41], using an OP-300 Radelkis potentiometer. To study the complex formation, chemically-pure grade copper(II) perchlorate hexahydrate was used.

Solutions of H$_3$L^1 acid were titrated with a standard 0.1 M NaOH solution at 298± 0.1 K and ionic strength 0.1 M with KCl. Three titrations including 41–60 points were performed in the pH range from 2.9 to 11.5; the

initial analytical H_3L^1 concentration in the experiments was 0.96, 1.62, and 2.00 mmol/L. The values of the H_3L^1 protonation constants were obtained with the help of the CHEMEQUI program freely available on the server [42], using four algorithms EQ, SIMPLEX, MONTE-CARLO [43], and GENETIC ALGORITHM [44], which significantly increase the reliability of the calculated constants and reduce the influence of the detected correlations between the logarithms of the constants for these experiments. The average values of the protonation constants of H_3L^1 acid were determined from eight estimates of the constants obtained using two best titrations and four calculation algorithms. In all calculations of the constants, Hamilton's R-factor (HRF) and the determination coefficient (R^2_{det}) were used as criteria for the agreement of the assumed set of equilibrium reactions in solution with experimental data [41]. For H_3L^1 acid, the HRF factor ranged from 0.62 to 1.11%, and the R^2_{det} coefficient ranged from 0.9990 to 0.9997.

Titration of H_3L^1 acid solutions with $Cu(ClO_4)_2$ was performed under similar conditions in the pH range from 3.4 to 11.3. The copper(II) cation forms stable hydroxides in water [44], therefore estimates of the complexation constants of Cu^{2+} with the acids under study were performed both taking into account the copper(II) hydrolysis reactions and without taking them into account. The stability constants of log β_n for hydroxocomplexes in water, –6.29 and –13.10, for n = 1 and 2 in equilibria (1), respectively, were used in the calculations [44].

$$Cu^{2+} + nH_2O = Cu^{2+}(OH^-)_n + nH^+ , n = 1, 2. \quad (1)$$
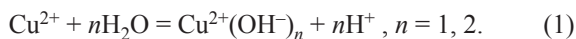
In the both variants, as in the calculation of the complexation constants of H_3L^2 with $Cu(ClO_4)_2$ [15], close values of constants with overlapping intervals of their standard deviations were obtained. The stability constants of copper(II) perchlorate complexes with H_3L^1 were estimated on the basis of three titrations, including from 47 to 52 points, with the analytical concentrations of acid and salt for each experiment of 0.62 and 0.31, 0.54 and 0.28, 0.49 and 0.24 mmol/L, respectively. The complexation constants of H_3L^1 with $Cu(ClO_4)_2$ were estimated using the CHEMEQUI program [42, 43] and four of its algorithms. The HRF factor varied from 0.56 to 0.80%, and the R^2_{det} coefficient – from 0.9994 to 0.9997. Thus, according to three titrations and four algorithms, 12 estimates of the constants were performed, according

to which their average values were calculated. Sharply deviating values were excluded according to Thomson's rule [45]. In the calculations of the constants of Cu^{2+} complex formation with protonated forms of the $H_nL^{(3-n)-}$ (n = 0, 1, 2) ligand, the acid protonation constants were not varied, they were taken as earlier estimated in the previous three titrations of the initial acid.

The X-ray diffraction analysis of compound $[Cu(H_2L^1)_2(H_2O)_2]$ **3** was performed at the Center for Collective Use of N.S. Kurnakov Institute of General and Inorganic Chemistry of the Russian Academy of Sciences on a Bruker SMART APEX3 diffractometer [$\lambda(MoK_\alpha)$ with a graphite monochromator] [46]. Absorption was taken into account by the semi-empirical equivalent method using the SADABS program [47]. The structure was determined by a combination of the direct method and Fourier syntheses. Hydrogen atoms were partially localized from the Fourier difference synthesis (O-H), and partially calculated from geometric considerations (C–H). The structure was refined by a full-matrix anisotropic-isotropic least squares method (H atoms bound to O atoms). All calculations were performed using the SHELXS and SHELXL programs [48]. The experimental data for complex **3** were deposited in the Cambridge Structural Data Bank (CCDC 2102671).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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