TERNARY MIXED-LIGAND COPPER(II) COMPLEXES WITH CHIRAL AMINOPHOSPHONIC ACIDS AND AMINO ACIDS

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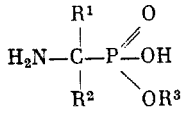
Ternary mixed-ligand complexes of divalent copper, where one ligand is an α-aminoalkylphosphonic acid (APA) and the second ligand is L-phenylalanine, L-tyrosine, or L-dihydroxyphenylalanine, are studied by potentiometric titration in aqueous medium at 25°C and μ = 0.1. A maximum in the formation of the ternary complexes is exhibited at pH 7-8. The log K_{st} for the complexes formed and the statistical parameters characterizing the ternary complexes Δlog K and log X are determined. The effect of substituents on the α-carbon atom of the α-APA and of hydroxy groups on the phenyl substituent of the α-amino acids on the nature of the distribution of the complexes formed is studied.

Recently, the conditions for forming ternary mixed-ligand complexes in systems containing a metal ion and two different ligands, one of which is an amino acid, have received much attention [1-3]. These studies are especially interesting from the viewpoint of modeling processes occurring on a chromatographic column in liquid ligand-exchange chromatography [4, 5]. Besides this, mixed-ligand copper(II) complexes with optically active and racemic α-amino acids are physiologically active [6].

Phosphorus analogs of amino acids, aminoalkylphosphonic acids, containing a phosphonate group instead of the carboxylate have been found in plants and animals [7]. The ability of the phosphonate group to compete with the carboxylate in formation of ternary mixed-ligand compounds was demonstrated for the example of oxyethylenediphosphonic acid [8].

The present work studies the features of forming ternary complexes of α-aminoalkylphosphonic acids (APA) in solutions where the complex-forming ion is Cu^{2+} and the second ligands are various naturally occurring amino acids. Optically active APA of the general formula below were studied



$R^1 = Me$, $R^2 = Et$, $R^3 = H$ (H_2L^I); $R^1 = H$, $R^2 = Ph$, $R^3 = H$(H_3L^{II}); $R^1 = Me$, $R^2 = Ph$, $R^3 = H$ (H_2L^{III}); $R^1 = Me$, $R^2 = Et$, $R^3 = Et$ (HL^{IV}).

EXPERIMENTAL

The L-isomers of amino acids (analytically pure) were used. The APA were prepared by the method of [9] in optically active form. The acid concentration in all experiments was $(2\text{-}3)\cdot10^{-3}$ M. The initial $Cu(NO_3)_2$ solution was standardized by complexometric titration. A carbonate-free KOH solution was titrated with a 0.1 M standard HCl solution.

Potentiometric titration was carried out on a Radiometer PHM-82 autotitrator at 25°C and constant ionic strength of μ = 0.1 (KCl) in an Ar atmosphere. The region studied was pH 3-10.

The acid constants of ligands and stability constants of binary complexes with Cu^{2+}, which are necessary for calculation of the stability constant of the ternary complexes, were measured by us for APA and taken from the literature for glycine (Gly), phenylalanine (Phe), tyrosine (Tyr), and dihydroxyphenylalanine (Dopa). These are given in Table 1. The formation

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TABLE 1. Dissociation Constants of Amino Acids and Optically Active APA and Stability Constants of Their Copper Complexes [25°C, μ = 0.1 M (KCl)]

Ligand	$pK^{HL}_{H_2L}$	pK^{H}_{HL}	$\log \beta^{Cu}_{CuLH}$	$\log \beta^{Cu}_{CuL}$	$\log \beta^{Cu}_{CuL_2}$	Reference
L-Glycine		9,84	–	8,25	15,63	[11]
L-Phenylalanine		8,94	–	7,93	14,83	[4]
L-Tyrosine	9,03	10,14	17,99	10,64	15,36	[12]
L-Dopa	8,84	9,77	17,25	–	18,67	[13]
H_2L^{I}	5,90	10,13	–	8,3	14,77	*
H_2L^{II}	5,62	9,25	–	8,1	14,89	*
H_2L^{III}	6,04	9,59	–	8,5	15,30	*
HL^{IV}		8,61	–	5,0	9,60	*

*This work.

TABLE 2. Stability Constants for Ternary Mixed-ligand CuAB Complexes (μ = 0.1 M, 25°C)

Ligand		$\lg \beta^{Cu}_{CuAB}$	$\Delta \log K$	$\log X$
A	B			
Gly	Phe	15,48	−0,67	0,53
Gly	H_2L^{III}	15,76	−1,01	0,59
H_2L^{II}	H_2L^{III}	15,67	−0,93	1,15
HL^{IV}	H_2L^{III}	14,13	+0,63	3,36

constants of ternary complexes were calculated on a Nord-10 computer using a program published earlier [10].

Ternary systems were studied at a ratio of $C_{Cu}:C_A:C_B = 1:1:1$. The stability constants were expressed as

$$\beta_{nsqp} = \frac{C\,[Cu_nA_sB_qH_p]}{C^n_{Cu}C_A{}^sC_B{}^qC_H{}^p}$$

where A and B are ligands. Hydrolysis of compounds was minimal and was not considered in the calculations.

RESULTS AND DISCUSSION

The following systems were studied by pH titration to compare the ability of APA and amino acids to form ternary mixed-ligand complexes

$$Cu—Phe—Gly\ (I)\quad Cu—H_2L^{III}—Gly\ (II)$$
$$Cu—H_2L^{II}—H_2L^{III}\ (III)\quad Cu—H_2L^{III}—HL^{IV}\ (IV)\,.$$

The calculated complexation constants are given in Table 2. The quantities $\Delta \log K$ and $\log X$ were used as a quantitative stability characteristic of the ternary complex in comparison to the binary (containing ligands of one type) [11]. The parameter $\Delta \log K$ characterizes the equilibrium.

$$CuA + CuB \rightleftarrows CuAB + Cu$$

and is expressed by the equation

$$\Delta \log K = \log \beta^{Cu}_{CuAB} - \log \beta^{Cu}_{CuA} - \log \beta^{Cu}_{CuB}\,.$$

The parameter $\log X$ characterizes the disproportionation

$$CuA_2 + CuB_2 \rightleftarrows 2\ CuAB$$

and is expressed by the equation

$$\log X = 2 \log \beta^{Cu}_{CuAB} - (\log \beta^{Cu}_{CuA_2} + \log \beta^{Cu}_{CuB_2})\,.$$

The logarithms of the ternary complex stability constants are of the same order, differing only for the ternary complex in system (IV), which has the lowest stability constant and the highest log X. This is consistent with a mixed-ligand ternary complex in system (IV) being formed preferentially over binary complexes. A maximum in formation of ternary complexes for the APA and the amino acids is reached at the physiological range of pH 7-8 (Fig. 1a). This suggests possible existence of similar systems in living organisms.

The APA and their acidic esters can act as one or two ligands in ternary copper(II) complexes. The higher log X parameter in comparison to the ternary complexes of amino acids indicates more favorable conditions for forming ternary complexes with APA.

Three amino acids in L-form, Phe, Tyr, and Dopa, which are found in copper-containing hydroxylase [14], were selected for establishing the effect of ligand structure on the formation of the ternary complexes. Table 3 gives stability constants for the $Cu_nA_sB_qH_p$ complexes, as well as $\Delta\log K_{1110}$ and $\log X_{1110}$ parameters calculated from [10].

Two types of mixed-ligand complexes of compositions 1110 and 1111 form for the systems APA–Cu–Tyr (Fig. 1b). The protonated ternary complex formed in the range pH 7-8 almost suppresses formation of all remaining types of complexes. Protons are titrated as the pH increases and the 1110 complex reaches maximum concentration near pH 10. Formation of other complexes in this pH range is suppressed.

From [13], Phe and Tyr are known to coordinate through the amino and carboxylate groups. Coordination through the hydroxyl group of Tyr is less probable, although the increased stability constant of the ternary Tyr complexes in comparison to Phe suggests that a fully ionized Tyr can act as a tridentate ligand in complexes with APA and copper(II).

The stability of mixed APA complexes decreases in the order $H_2L^{I} > H_2L^{III} > H_2L^{II}$, having a minimum for the acidic ester of APA HL^{IV}. At pH 8, the ternary complex with HL^{IV} precipitates.

The fact that deprotonation of the second phenol group (pK ~ 13) of catechol ligands is not observed in the absence of Cu^{2+} was considered in studying the APA–Cu–Dopa systems. Potentiometric measurements at such a high pH value do not give accurate results. The second phenol group was not considered to dissociate under the experimental conditions.

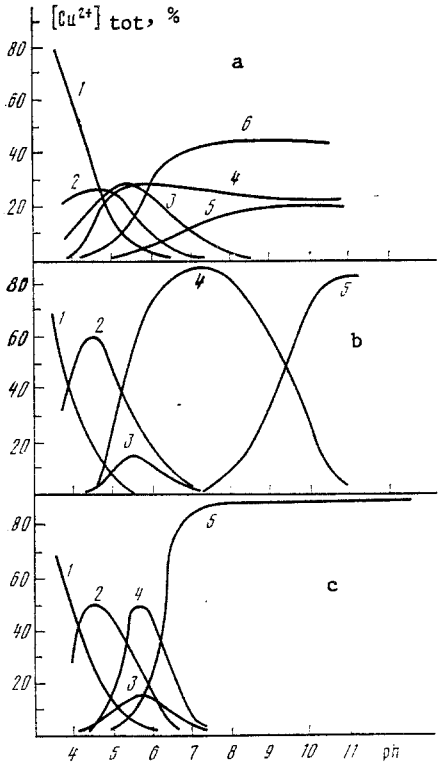

Fig. 1. Concentration distribution of species formed (as percent of total copper present) as a function of pH in the systems Cu(II)–phenylalanine (HA)–APA (H_2B) (a); Cu(II)–tyrosine (H_2A)–APA (H_2B) (b); Cu(II)–Dopa (H_2A)–APA (H_2B) (c). For a: 1) Cu; 2) CuA; 3) CuB; 4) CuA_2; 5) CuB_2; and 6) CuAB. For b, c: 1) Cu; 2) CuAH; 3) CuB; 4) CuABH; and 5) CuAB. CuABH, CuA_2, and CuB_2 are less than 5%.

TABLE 3. Stability Constants for Ternary Mixed-ligand $Cu_nA_sB_qH_p$ Complexes of APA and Amino Acids (25°C, μ = 0.1 M, KCl)

Ligand	Constant	*L*-Phe	*L*-Tyr	*L*-Dopa
H_2L^I	$\log \beta_{1110}$	15,78	18,35	18,98
	$\log \beta_{1111}$	–	25,28	24,98
	$\Delta \log K$	−0,59	−0,59	
	$\log X$	1,96	6,57	4,52
H_2L^{II}	$\log \beta_{1110}$	15,18	16,50	18,74
	$\log \beta_{1111}$	19,5(4)	25.67	24,88
	$\Delta \log K$	−0,85	−2,24	–
	$\log X$	0,64	2,75	3,92
H_2L^{III}	$\log \beta_{1110}$	15,76	16,64	19,73
	$\log \beta_{1111}$	20,2(2)	26,00	25,67
	$\Delta \log K$	−0,67	−2,50	–
	$\log X$	1,39	2,62	5,49
HL^{IV}	$\log \beta_{1110}$	12,92	13,92	18,01
	$\log \beta_{1111}$	–	22,20	23,22
	$\Delta \log K$	−0,01	−1,69	–
	$\log X$	1,51	2,94	9.89

Dopa is known to act as either an amino acid or a catechol ligand in binary complexes [15]. Two formation constants for ternary complexes of 1110 and 1111 composition were obtained from the calculations. The stability constant of the protonated Dopa complex is several times lower than the corresponding constant for Tyr. This indicates destabilization of the ternary APA and Dopa complex by a second undissociated phenol group.

On the other hand, the stability of deprotonated complexes of Dopa, APA, and copper(II) of 1110 composition significantly surpasses the values for Phe and Tyr. Figure 1c shows that the complex of 1110 composition is predominantly formed near pH 7. Dopa can be assumed to coordinate to copper through the amine and carboxylate groups near pH 5. At high pH values, Tyr can coordinate through hydroxyl groups. The maximum stability of ternary complexes with Dopa occurs for APA with an ethyl substituent on the carbon atom (H_2L^I).

The behavior of the monobasic acidic ester APA HL^{IV} is interesting. Ternary complexes of it with Dopa have lower stability than for the remaining APA. The high value of log X indicates that formation of ternary complexes of the HL^{IV} acid with the amino acids studied is more preferred.

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LITERATURE CITED

1. H. Sigel, Angew. Chem. Int. Ed., 14, No. 6, 394 (1975).
2. P. R. Reddy and M. Rao, Polyhedron, 4, No. 9, 1603 (1985).
3. Ya. D. Fridman, S. V. Alikeeva, N. V. Dolashova, and T. G. Nemal'tseva, Zh. Neorg. Khim., 31, No. 5, 1232 (1986).
4. G. Brookes and L. D. Pettit, J. Chem. Soc. Dalton Trans., 1918 (1977).
5. J. L. Ulanovsci, A. A. Kurganov, and V. A. Davankov, Inorg. Chim. Acta, 104, 63 (1985).
6. L. F. Chapurina, I. A. D'yakon, S. V. Doku, and S. S. Budnikov, Problems of Modern Bioinorganic Chemistry [in Russian], Nauka, Novosibirsk (1986), p. 228.
7. Yu. E. Vel'tishchev, É. A. Yur'eva, A. N. Kudrin, et al., Khim.-Farm. Zh., No. 3, 282 (1983).
8. R. R. Amirov and Z. A. Saprykova, Zh. Obshch. Khim., 57, No. 7, 1526 (1987).
9. S. V. Rogozhin, V. A. Davankov, and Yu. P. Belov, Izv. Akad. Nauk SSSR, Ser. Khim., 955 (1973).
10. V. P. Novikov, T. I. Ignat'eva, and O. A. Raevskii, Zh. Neorg. Khim., 31, No. 6, 1474 (1986).
11. H. Sigel and R. Griesser, Helv. Chim. Acta, 50, 1842 (1967).
12. L. D. Pettit and J. L. M. Swash, J. Chem. Soc. Dalton Trans., 486 (1982).
13. G. Daniele, P. Amico, and G. Ostacoli, Ann. Chim. (Rome), 74, 105 (1984).
14. D. Metzler, Biochemistry, Vol. 2, Academic Press, New York (1977).
15. V. K. Patel and P. K. Bhattacharya, J. Inorg. Biochem., 12, 169 (1984).