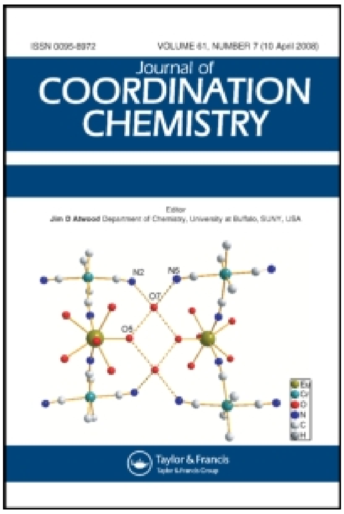

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HYDROXAMIC ACID DERIVATIVES OF PHENYLALANINE, TYROSINE AND 3,4-DIHYDROXYPHENYLALANINE (DOPA) AS LIGANDS

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The systems cobalt(II), zinc(II), nickel(II) and copper(II) with phenylalaninehydroxamic acid (Pheha), tyrosinehydroxamic acid (Tyrha) and 3,4-dihydroxyphenylalaninehydroxamic acid (Dopaha) have been investigated by means of pH-metric, spectrophotometric and e.s.r. methods. Formation constants and assumptions concerning binding modes for complexes in aqueous solution are reported. Effects of the phenyl and hydroxyl groups on complex formation have been evaluated. Because of the phenyl group, the ligands and neutral species have quite poor solubility. Precipitates occur in many of the systems studied. Tyrha forms protonated complexes containing the hydroxy group in the protonated form. Catecholate-type (O,O) chelates can be assumed for copper(II)-Dopaha and zinc(II)-Dopaha above *ca* pH 9.5.

Keywords: Amino acids, hydroxamates, first row complexes, stability constants, spectroscopy

INTRODUCTION

Due to their undoubted biological effects, hydroxamic acid derivatives of amino acids are of great interest.[1,2] At the same time, these compounds are also strong complexing agents. Consequently, clarification of their metal binding properties is of particular importance in terms of biological effects. Over the last few years, several papers have presented data on metal complexes of aminohydroxamic acids.[3–11] However, few publications have appeared concerning complexes of *L*-phenylalaninehydroxamic acid (Pheha), *L*-tyrosinehydroxamic acid (Tyrha) and *L*-3,4-dihydroxyphenylalaninehydroxamic acid (Dopaha).[12,13] This situation is understandable if one considers the poor solubility of these ligands and the even poorer solubility of their neutral complexes. Moreover, Dopaha is very susceptible to atmospheric oxidation, especially under basic conditions.[14] The only reported results on cobalt(II) and copper(II) systems with Pheha[13] merely provides protonation constants for the ligand and stability data for the complexes $[Cu_2(OH)A_2]$ and $[CuA_2]$, since precipitation occurred at an acidic pH. Some protonated complexes were found in the nickel(II)- and copper(II)–Tyrha systems[12] at intermediate pH values (5.5–9.0), with the phenolic hydroxy group in the protonated form. Coordination of the phenolic hydroxy group has not been proposed in any species. It is somewhat surprising that the formation of *bis* complexes in the copper(II)–Tyrha system was found to be quite unfavoured and that dinuclear species, generally formed in copper(II)–aminohydroxamic acid systems, were not found at all.

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Metal complexes of Dopaha have not yet been studied, though Dopaha, which contains the aminohydroxamate and catecholate functions in a single molecule, could serve as a model for metal-binding properties of siderophores.

Accordingly, the aim of the present work was to clarify equilibrium conditions in systems containing cobalt(II), nickel(II), copper(II) and zinc(II) with Pheha, Tyrha and Dopaha, using pH-metric, e.s.r. and spectrophotometric measurements.

EXPERIMENTAL

Pheha, Tyrha and Dopaha were prepared *via* the methyl ester of the amino acids as described in refs. 14 and 15. The purity of the ligands and exact concentrations of stock solutions were determined by Gran's method.[16]

Metal ion solutions were made from the metal chlorides or from zinc(II) oxide (Reanal) by dissolving an appropriate amount in doubly distilled water or in hydrochloric acid of known concentration. Concentrations in the stock solutions were determined gravimetrically *via* precipitation of the appropriate quinolin-8-olate.

Because of the poor solubility of the ligands, their maximum concentrations in samples for pH-metric titrations were as follows: Pheha and Tyrha *ca* $2.5.10^{-3}$ mol dm^{-3}, Dopaha $5.5.10^{-3}$ mol dm^{-3}. The metal–ligand ratios were adjusted in the range 1:1–1:5 and titrations were made with samples at five or six different ratios. Ionic strength was adjusted to 0.2 mol dm^{-3} with KCl. Titrations were carried out with carbonate-free KOH solutions of known concentrations (*ca* 0.2 mol dm^{-3}). All measurements with Dopaha were performed under an argon atmosphere in a closed system so that air was excluded completely.

A Radiometer PHM 84 pH meter with an ABU 13 burette and a GK 2421C combined electrode was used. The electrode system was calibrated by the method of Irving *et al.*[17] so that the pH meter readings could be converted into hydrogen ion concentrations. The calculations were performed with the aid of the PSEQUAD computer program.[18]

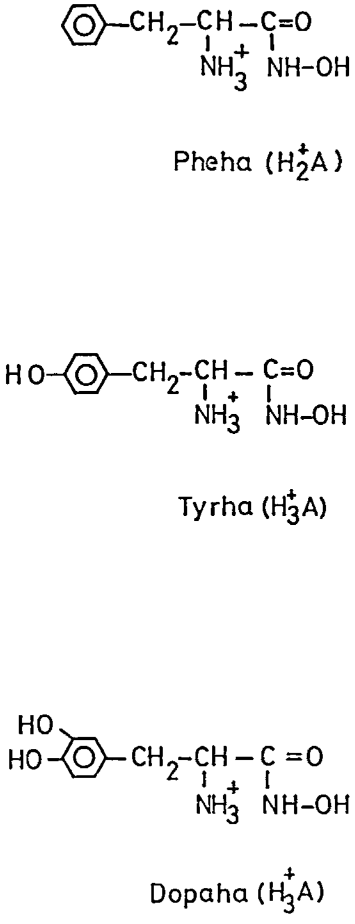
The absorption spectra were recorded on a Varian DMS100 double-beam recording spectrophotometer over the range 350–800 nm. The metal–ligand ratio in the samples was *ca* 1:3. E.s.r. measurements on the copper(II)–Dopaha and copper(II)–Tyrha systems were made at liquid nitrogen temperatures on a JES-ME-3F spectrometer.

RESULTS AND DISCUSSION

Proton complexes

The fully protonated forms of the ligands are shown in Scheme 1.

Two protons can be released from Pheha (from the amino and hydroxamic acid groups), three from Tyrha (from the phenolic hydroxy group in addition to the above) and three from Dopaha in the measured pH region. One of the phenolic hydroxy groups of Dopaha does not release its proton up to *ca* pH 12.5. (The corresponding pK value of Dopa is 13.4[19].) Refined pK values are listed in Table I. Our data relating to Pheha and Tyrha are in fairly good agreement with those of Leporati.[12,13] However, a knowledge only of the data in Table I is not enough for the acid-base characterization of these ligands. It was proved in the case of Dopa[20]



Scheme 1

and tyrosine[21] that dissociation steps of the phenolic hydroxy and $-NH_3^+$ groups overlap (in Tyrha, the $-NH_3^+$ group is more acidic than the phenolic hydroxy, but in Dopa one of the phenolic hydroxy groups is more acidic than the ammonium group). Moreover, in the hydroxamic acid derivatives, the acidity of the hydroxamic acid groups is comparable with the above.[22] This means that the microscopic acid dissociation constants must be determined to clarify the acid-base properties of Pheha, Tyrha and Dopaha, but this was beyond the scope of the present work.

TABLE I
Macroscopic dissociation constants for Pheha, Tyrha and Dopaha; T = 25°C; I = 0.2 mol dm^{-3} (KCl).

	Pheha	Tyrha	Dopaha
pK_1	6.91(1)	6.81(1)	6.94(1)
pK_2	9.08(2)	8.90(1)	8.78(1)
pK_3		9.91(2)	9.61(2)

Metal complexes

A comparison of the experimental results with those for α-alaninehydroxamic acid[9] (used as reference data) revealed a great difference in solubility conditions. Whereas the solubility of the metal complexes formed with α-alaninehydroxamic acid is quite good, in the systems containing Pheha or Dopaha (except for nickel(II)–Dopaha), and also with zinc(II)– and cobalt(II)–Tyrha, precipitation occurred in the pH region where neutral (or polynuclear) complexes were formed. In copper(II)–Pheha and –Dopaha, where the precipitates dissolved at relatively low pH (*ca* 5.5–6.0), it was possible to obtain experimental data after the dissolution. In such cases, two samples were made with the same concentration, but the metal ion was added to one of them only after the pH had been increased to a value where precipitation no longer occurred.

TABLE II

Stability data (log β or pK) for complexes present in the metal ion–Pheha, –Tyrha and –Dopaha systems; T = 25°C; I = 0.2 mol dm^{-3} (KCl).

Metal ion	Species	log β			
		Pheha	Tyrha	Dopaha	Aha*
Co(II)	[MAH_2]		minor	20.97(5)	
	[MAH]	11.82(2)	14.41(6)	14.51(2)	12.12
	[MA]	5.05(2)			4.74
	[MA_2H_2]		28.55(6)	28.76(5)	
	[MA_2]	9.75(5)			
Zn(II)	[MAH_2]		20.8(3)	21.19(5)	
	[MAH]	11.69(3)	14.28(5)	14.90(3)	12.27
	[MA]	4.84(5)			5.29
	[MA_2H_2]		29.2(4)	28.9(2)	
	[MA_2]	9.5(2)			
Ni(II)	[MAH]		16.01(9)	16.25(7)	
	[MA]	6.53(3)			6.76
	[MA_2H_2]		33.94(4)	33.08(9)	
	[MA_2H]		24.69(9)	25.02(9)	
	[MA_2]	13.89(7)	15.12(8)	16.28(8)	14.13
	[MA_2H_{-1}]		5.15(8)		5.47
Cu(II)	[MAH]		19.78(9)	19.81(2)	
	[MA]	10.7(8)			10.89
	[M_2A_2H]		39.4(2)	(prec)	
	[MA_2H_2]		39.17(5)	(prec)	
	[MA_2H]		30.07(9)		
	[MA_2]	(prec)	20.21(9)		19.87
	[MA_2H_{-1}]		9.94(8)		9.98
	$pK^{MA_2H_2}_{MA_2H}$			8.32	
	$pK^{MA_2H}_{MA_2}$			9.10	
	$pK^{MA_2}_{MA_2H_{-1}}$	9.85		9.35	
	$pK^{MA_2H_{-1}}_{MA_2H_{-2}}$			10.37	

* Constants for metal(II)-α-alaninehydroxamate complexes[9] are used as reference data.

The pH-metric titration curves were evaluated by assuming all feasible models. Models that provided the best fit and refined formation constants together with data previously published[9] for metal ion–α-alaninehydroxamic acid systems are given in Table II.

As can be seen in Table II, a number of protonated complexes are formed, especially with Tyrha and Dopaha. A comparison with appropriate data for α-alaninehydroxamic acid[9] shows that in most of the protonated complexes the phenolic hydroxy groups contain the dissociable protons.

Table II gives only the stepwise pK values for complexes formed in the copper(II)–Pheha and copper(II)–Dopaha systems after dissolution of precipitates. Taking all experimental findings and results together, the following conclusions can be drawn.

The measurable pH range is quite narrow in the systems containing zinc(II) or cobalt(II). Complex formation starts at *ca* pH 5.5–6.0 and a precipitate appears at *ca* pH 7.0–7.5. This pH is practically the same for different metal–ligand ratios. These findings suggest that the precipitation is caused primarily by the poor solubility of neutral complexes and not by the hydrolysis of metal ions. The precipitates dissolve at or above *ca* pH 10 in all of the systems except zinc(II)–Dopaha, where it does so at *ca* pH 9.5. In the former systems, the dissolution may be caused by the formation of complex(es) with non-zero charge and/or hydroxo complex(es). In the latter system, a change in binding mode may occur. It has been proved[23] for zinc(II)–Dopa that the zinc(II) ion prefers the catechol-like (O,O) chelate at high pH, and this is most probably the case with zinc(II)–Dopaha as well.

The only favoured complexes for the "nitrogen-philic" nickel(II) ion are planar, most probably the well-known aminohydroxamate-type *bis* complexes,[3,7,9] in which the metal ion is coordinated by 4N donors of the two ligands (amino and hydroxamate nitrogens). Complex formation starts at *ca* pH 5.5, and at practically the same pH the samples turn yellow. Precipitation occurs only with Pheha. This precipitate exists in the pH range *ca* 6–9 where the neutral complex $[NiA_2]$ is formed (see Table II). Most probably the formation of $[NiA_2H_{-1}]^-$ (its formation is well known with simple aminohydroxamic acids[3,7,9]) leads to dissolution of the precipitate at *ca* pH 9.

The stepwise deprotonation constants from the overall stability data (Table II) for the different protonated *bis*-complexes formed in the nickel(II)–Tyrha and nickel(II)–Dopaha systems give the pK values below.

Ni(II)-Tyrha: $pK^{NiA_2H_2}_{NiA_2H} = 8.69$; $pK^{NiA_2H_2}_{NiA_2H} = 9.56$; $pK^{NiA_2H_2}_{NiA_2H}{}_{-1} = 9.97$;

Ni(II)-Dopaha: $pK^{NiA_2H_2}_{NiA_2H} = 8.06$; $pK^{NiA_2H}_{NiA_2} = 8.75$;

No data for $[NiA_2]$ deprotonation in case of nickel(II)–Dopaha are provided, because we could not fully avoid oxidation of the ligand in basic solution, where $[NiA_2H_{-1}]^-$ should be formed. The difference of *ca* 0.6 between the two data sets for the nickel(II)–Dopaha system relates to the deprotonation of two separate donor groups with the same basicity. This means that the uncoordinated phenolic hydroxy groups (one each from both Dopaha moieties) lose their protons in the corresponding processes. In the case of Tyrha, the deprotonation of the less acidic phenolic hydroxy groups may overlap with the deprotonation of a coordination hydroxamate group.

There was quite a large variation in colour in the copper(II)-containing systems. The solutions were pale blue at *ca* pH 3 and turned green at around pH 4, where precipitation occurred in the copper(II)–Pheha and copper(II)–Dopaha systems.

The precipitate dissolved at *ca* pH 5.5–6.0, to give a violet solution (λ_{max} ~ 530 nm). The colour also turned violet at the same pH in the copper(II)–Tyrha system. No further change in colour was observed in any system up to pH 9. Above this pH the λ_{max} shifts from *ca* 530 nm to *ca* 500 nm in the copper(II)–Tyrha and copper(II)–Pheha systems, but in the copper(II)–Dopaha, the colour changed from violet to greenish-yellow.

In addition to pH-metric and spectrophotometric studies e.s.r. measurements were also performed on the copper(II)–Tyrha and copper(II)–Dopaha systems (in frozen samples (77K) containing 5–10% methanol, there was no precipitation even in the copper(II)–Dopaha system). Some e.s.r. parameters are listed in Table III.

TABLE III

E.s.r. parameters calculated for the copper(II)–Tyrha and copper(II)–Dopaha systems.

Ligand	pH	$g_\parallel$	$A_\parallel$ (G)
Tyrha	4.02	2.43	115
		2.34	154
	5.06	2.19	203
	6.33	2.19	202
	8.33	2.19	203
	10.62	2.19	203
Dopaha	3.94	2.43	111
		2.33	162
	4.58	2.19	201
	5.60	2.19	203
	7.95	2.19	202
	9.53	2.19	202
	10.43	2.18	204
		2.29	186
	10.8	2.19	204
		2.29	184

As can be seen from the Table, two e.s.r.-active species are present in both systems at pH *ca* 4. The $g_\parallel$ and $A_\parallel$ parameters show that one of them should be the aquated copper(II) ion while the other is a $Cu(N_2O_2)$-type complex.[6]

The e.s.r. results strongly suggest the coordination of 4N atoms only at *ca* pH 5. Upon increasing the pH from 5 to *ca* 11, the e.s.r. parameters remain unchanged for copper(II)–Tyrha, but for copper(II)–Dopaha a new species starts to form above pH *ca* 9.5 with less than 4N in equatorial positions.

A comparison of the results for copper(II)–Pheha, –Tyrha and –Dopaha with those for copper(II)–α-alaninehydroxamic acid[9] indicates fairly good agreement in the bonding mode of the species. However, there are also some differences. The formation of $[Cu_2A_2H]$ (or, in the case of Pheha, $[Cu_2A_2H_{-1}]$), which involves a mixed binding mode *via* the amino and hydroxamate nitrogens and the hydroxamate oxygens,[9] is somehow suppressed for the present ligands. This is proved by the e.s.r. measurements. Namely, there was no totally e.s.r.-silent pH region in the present systems as there was for alaninehydroxamic acid,[9] while there was a significant decrease in the intensity of the spectra only in the pH range *ca* 4.5–5.5. Steric hindrance due to the phenyl ring may lead to formation of the binuclear species being unfavoured. Good agreement is observed between the abovementioned findings and species distribution diagrams calculated from pH-metric results. Concentration distribution curves relating to copper(II)–Tyrha systems where precipitation has not occurred are shown in Figure 1.

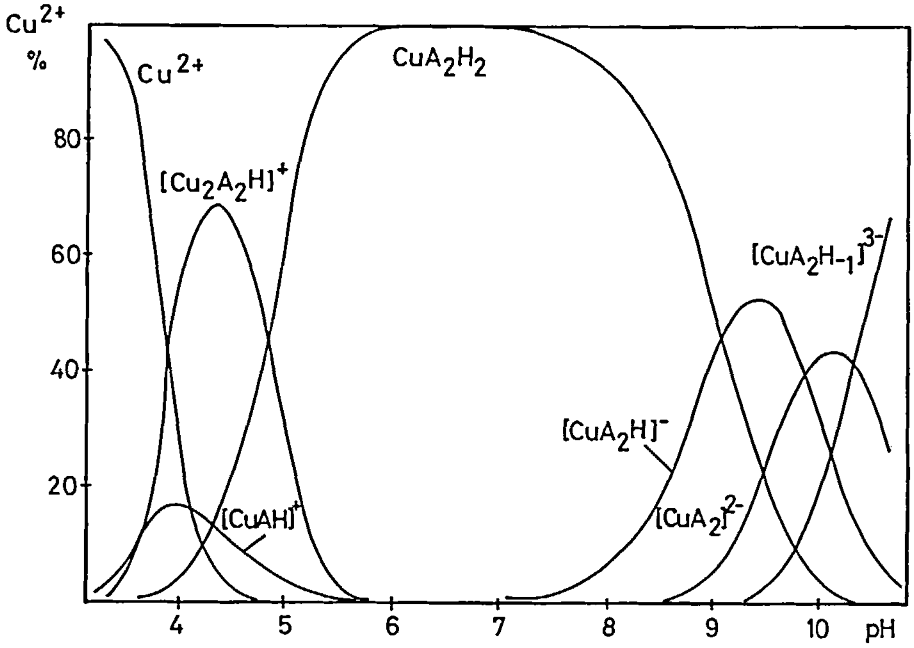


FIGURE 1. Concentration distribution curves for complexes present in the copper(II)–Tyrha system. Concentrations (mol dm^{-3}): Tyrha, 2.5.10^{-3}; copper(II), 8.10^{-4}

In the copper(II)–Dopaha system, the e.s.r. and spectrophotometric results strongly suggest the formation of a "chatecholate type" chelate above pH 9.5. A comparison of our findings with the results for copper(II)–Dopa[19] shows that formation of the (O,O) chelate occurs at a much lower pH for Dopa than for Dopaha. This indicates that the copper(II) ion is in a more stable environment when surrounded by aminohydroxamate groups than in the case of aminoacids.

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