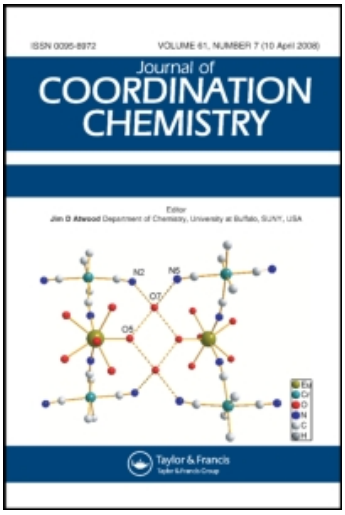

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Copper(II) Complexes of Tyrosine-Containing Di- and Tripeptides

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NOTE

COPPER(II) COMPLEXES OF TYROSINE-CONTAINING DI- AND TRIPEPTIDES

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Tyrosine is a constituent of many neuropeptides, and it may be assumed that it plays a fundamental role in the activity of these compounds. Recent studies on tyrosine-containing oligopeptides has established that the direct participation of the side-chain phenolate groups in metal ion binding depended considerably on the position of the tyrosine in the peptide molecule.[1–5] In this note the stability constants and the binding modes of the proton and copper(II) complexes of *S*-tyrosyl-*S*-tyrosine (TyrTyr) and *S*-tyrosyl-*S*-tyrosyl-*S*-tyrosine (TyrTyrTyr) are presented.

EXPERIMENTAL

The peptides used were Sigma products of puriss quality. The exact concentrations of their solutions were measured by the Gran method.[6] The stability constants of the proton and copper(II) complexes of the ligands were determined by pH-metric titration on a Radiometer pHM84 instrument with a GK23021 combined electrode. To elucidate the binding modes in the complexes formed, electronic spectral studies were made on a Beckman ACTA MIV spectrophotometer. Other details of the experimental work can be found in an earlier publication.[4] The concentration stability constants were calculated from the pH-metric titration curves by means of the PSEQUAD computer program.[7]

RESULTS AND DISCUSSION

The pH-metrically determined acid dissociation constants of the ligands are listed in Table 1. It was earlier unambiguously proved for other Tyr-containing di- and

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TABLE I
Proton dissociation constants for the ligands at 25°C and I = 0.2 mol dm^{-3} (KCl).

	TyrTyr	TyrTyrTyr
pK_{COOH}	3.18±0.02	3.37±0.04
$pK_{NH_3^+}$	7.35±0.01	7.22±0.02
$pK_{OH}(1)$	9.66±0.02	9.56±0.02
$pK_{OH}(2)$	10.52±0.03	9.95±0.05
$pK_{OH}(3)$		10.92±0.05

tripeptides[4,5] that the first two protons dissociate from the terminal $-COOH$ and $-NH_3^+$ groups, and the remaining two or three protons from the side-chain phenolic hydroxy groups. These latter processes overlap each other and thus the pK_{OH} values are a composite of the dissociation microconstants characteristic of the acidities of the individual phenolic hydoxy groups. As a first approach, however, we can assume that the real acidity of each phenolic hydroxy group in TyrTyr and TyrTyrTyr is not affected by the other hydroxy groups and their protonation states, and thus each phenolic hydroxy can be characterised by one group constant.[8] If the above mentioned assumption is valid, then the group constant of the *N*-terminal tyrosine can be taken as equal to the pK_{OH} value for TyrGly (= 9.86),[4] and that of the *C*-terminal tyrosine as equal to that for GlyTyr (= 9.96).[4] By taking into account the relationships between dissociation macroconstants and group constants,[8] we can write

$$K_{OH}(1)(TyrTyr) = K_{OH}(TyrGly) + K_{OH}(GlyTyr) = 10^{-9.86} + 10^{-9.96},$$

$$K_{OH}(1)K_{OH}(2)(TyrTyr) = K_{OH}(TyrGly)K_{OH}(GlyTyr) = 10^{-9.86}10^{-9.96},$$

and we obtain $pK_{OH}(1) = 9.61$ and $pK_{OH}(2) = 10.21$ for TyrTyr, If the same approach is applied to TyrTyrTyr (pK values for the reference compounds are taken from Ref. 5),

$$K_{OH}(1)(TyrTyrTyr) = K_{OH}(TyrGlyGly) + K_{OH}(GlyTyrGly) + K_{OH}(GlyLeuTyr) = 10^{-10.09} + 10^{-9.78} + 10^{-10.30},$$

$$K_{OH}(1)K_{OH}(2)(TyrTyrTyr) = K_{OH}(TyrGlyGly)K_{OH}(GlyTyrGly) + K_{OH}(TyrGlyGly)K_{OH}(GlyLeuTyr) + K_{OH}(GlyTyrGly)K_{OH}(GlyLeuTyr) = 10^{-10.09}10^{-9.78} + 10^{-10.09}10^{-10.33} + 10^{-9.78}10^{-10.30},$$

$$K_{OH}(1)K_{OH}(2)K_{OH}(3)(TyrTyrTyr) = K_{OH}(TyrGlyGly)K_{OH}(GlyTyrGly)K_{OH}(GlyLeuTyr) = 10^{-10.09}10^{-9.78}10^{-10.30}$$

we get pK_{OH} values 9.53, 10.05 and 10.59 for the first, second and third phenolic dissociation processes of TyrTyrTyr. When these calculated data are compared with the experimental ones given in Table I, a reasonably good agreement is obtained with the exception of the last pK_{OH} values. Accordingly, it can be stated that side-chain phenolic functions are fairly separated from one another within the molecules, although some direct interaction (hydrophobic or hydrogen bond) between them cannot be excluded.

The stability constants for the copper(II) complexes were obtained from the pH-metric titration curves by taking into account the speciation models reported earlier for simple di- and tripeptides.[4,5,9] The data are given in Table II. As the pH ranges of metal complex formation and dissociation of the non-coordinated phenolic hydroxy groups are separated from each other, equilibrium constants for the copper(II) complexes of the ligands $(H_2A)^-$ (TyrTyr) and $(H_3A)^-$ (TyrTyrTyr) protonated on the side-chain phenolic hydroxy groups were also calculated. These data too are included in Table II.

TABLE II

Copper(II) complex formation constants (log β_{pqr}) for the ligands at 25°C and I = 0.2 mol dm^{-3} (KCl), $\beta_{pqr} = [M_pA_qH_r]/[M]^p[A]^q[H]^r$.

	TyrTyr		TyrTyrTyr
$[CuAH_2]^+$	25.15±0.11	$[CuAH_3]^+$	34.38±0.12
[CuAH]	21.91±0.05	$[CuAH_2]$	30.01±0.04
$[CuA]^-$	13.04±0.04	$[CuAH]^-$	24.58±0.03
$[CuAH_{-1}]^{2-}$	3.25±0.03	$[CuA]^{2-}$	15.09±0.04
$[CuAH_{-2}]^{3-}$	−7.83±0.01	$[CuAH_{-1}]^{3-}$	4.78±0.04
$[CuA_2H_3]^-$	44.85±0.03	$[CuAH_{-2}]^{4-}$	−6.55±0.05
$[Cu_2A_2]^{2-}$	29.07±0.04		
$[Cu(H_2A)]^+$	4.97	$[Cu(H_3A)]^+$	4.40
$[Cu(H_2AH_{-1})]$	1.73	$[Cu(H_3AH_{-1})]$	−0.42
$[Cu(H_2A)(H_2AH_{-1})]^-$	4.49	$[Cu(H_3AH_{-2})]^-$	−5.85
pK_{CuAH}	8.87	pK_{CuAH}	9.49
pK_{CuA}	9.79	pK_{CuA}	10.21
pK_{CuAH-1}	11.08	pK_{CuAH-1}	11.33

The concentration distribution curves of the complexes formed in the systems studied are depicted in Figure 1. It can be seen from the Figure and the stability data given in Table II, that as with other simple di- and tripeptides,[9] complex formation starts *via* the terminal amino and the peptide-carbonyl groups to form the complexes $[Cu(H_2A)]^+$ or $[Cu(H_3A)]^+$ with an (N,O) bonding mode.

The peptide-amide(s) of both ligands deprotonate(s) in the acidic pH range. TyrTyr forms an (N,N,O) coordinated complex $[Cu(H_2AH_{-1})]$; its spectral data (λ_{max} = 630 nm, ε = 1200 dm^2 mol^{-1}) indicate the presence of two nitrogen donors in the coordination sphere.[9] TyrTyrTyr loses the two peptide-amide protons in overlapping processes and the complex $[Cu(H_3AH_{-2})]^-$ is formed. The energy of the d-d transition (λ_{max} = 528 nm, ε = 1800 dm^2 mol^{-1}) clearly indicates three nitrogen donors around the copper(II) with an (N,N,N,O) bonding mode.[5,9]

In accordance with expectations,[9] the bis-complex $[Cu(H_2A)(H_2AH_{-1})]^-$ is formed only with TyrTyr. In the case of TyrTyrTyr one ligand molecule can saturate all equatorial binding sites around a copper(II) ion, and thus the coordination of a second ligand molecule is hindered.

At pH > 8, the stepwise deprotonation of the non-coordinated phenolic hydroxy groups takes place in overlapping processes. In the case of TyrTyr this is accompanied by the ionization of a coordinated water molecule; this is strongly hindered with TyrTyrTyr presumably due to the presence of the hydrophobic benzene rings surrounding the metal ion.

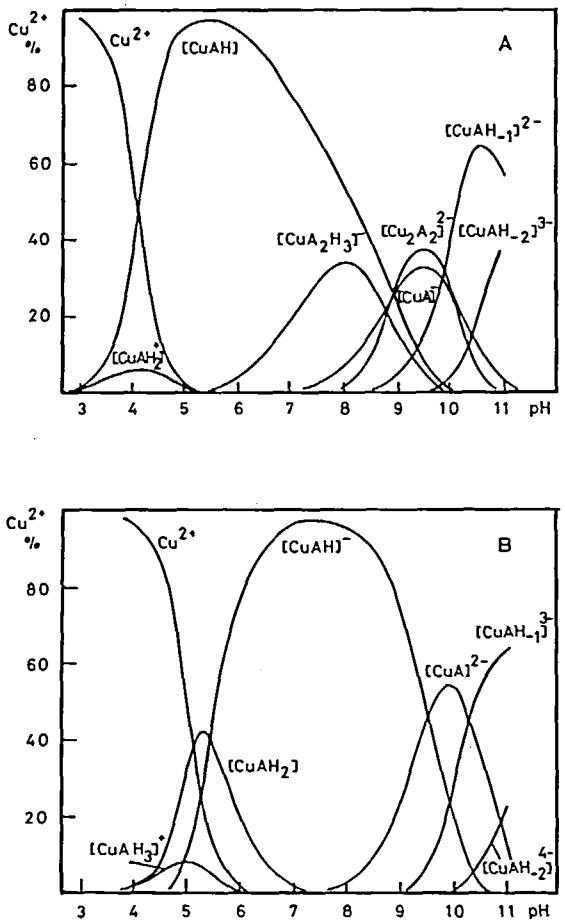

FIGURE 1 Concentration distribution of the complexes formed in the (A) copper(II)-TyrTyr and (B) copper(II)-TyrTyrTyr systems as a function of pH; $C_{Cu} = 0.002$, $C_{ligand} = 0.004$ mol dm^{-3}.

Similarly to other dipeptides containing tyrosine in the *N*-terminal position,[1,2,4] TyrTyr readily forms a dimeric species $[Cu_2A_2]^{2-}$ in which two monomeric species $[Cu(H_2AH_{-1})]$ are linked together by deprotonation *via* *N*-terminal tyrosinate bridges. A charge transfer band at 378 nm ($\varepsilon = 4300$ dm^2 mol^{-1}) is characteristic of a direct copper(II)-phenolate interaction. In the case of TyrTyrTyr, there is no possibility for this dimer formation, due to the development of the very stable (*N,N,N,O*) coordination, which gives a saturated equatorial coordination sphere around the copper(II) ion.

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