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Metal Complexes of Amino Acids and Derivatives. V. The Donor Properties of L-Tyrosine[1]

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A convenient method for the preparation of transition metal complexes of L-tyrosine (tyrH) is reported and this has enabled eight complexes of the tyrosinate anion (tyr) to be prepared: $M(tyr)_2(H_2O)_n$ (M = Co, Ni, Cu, Zn; n = 1, 2, 3), $[Cu(tyr)(NO_3)]$, and $Li[Cu(tyr)_3]$. Electronic spectra and magnetic measurements imply that the nickel(II) complex contains the N_2O_4 donor set, and the similarity of the infrared spectra of the other bistyrosinate complexes to the nickel derivative suggests a similar six-coordinate structure. Experiment suggests that upon reacting Lityr with copper(II) nitrate in water the green kinetic product $[Cu(tyr)(NO_3)]$ forms, but on standing this changes to the thermodynamically stable product, $[Cu(tyr)_2]$.

Introduction

There has been some considerable interest recently in the complexes formed between transition metal ions and amino acids which contain catecholic or phenolic side chains. Thus, Gorton and Jameson[2] have investigated the formation of complexes between L-β-(3,4-dihydroxyphenylalanine) (DOPA) and a number of metal ions in solution, and showed that complex formation could occur *via* α-amino acid chelation or deprotonated catecholic -OH groups. Van der Helm and co-workers have X-rayed a number of copper(II) complexes of tyrosine derivatives.[3-5] In bis(glycyl-L-leucyl-L-tyrosinato)copper(II) the dimeric $[Cu_2(glt)_2]$ units exist and there appears to be weak interaction of the copper(II) ions with the aromatic π-system of tyrosine;[3] in bis-(L-phenylalaninato) copper(II) the copper atom is six-cordinate and coordination is *via* the amino and bidentate bridging carboxylate groups;[4] and in bis(L-tyrosinato)copper(II) the coordination around the copper atom is tetragonal pyramidal involving one bidentate ligand and one tridentate (containing a bridging carboxylato group) ligand.[5] Apart from the intrinsic interest in the chemistry of potentially multidentate ligands work in this area has been stimulated by the implication of metal ions in the biological reactions of DOPA and tyrosine. Thus, the autocatalytic oxidation of adrenalin and DOPA by metal ions is well established,[6] and the enzyme tyrosinase contains copper.[7] Tyrosine and DOPA are themselves biologically linked, DOPA being a normal metabolic product of phenylalanine and tyrosine in higher animals.[8,9]

However, despite the importance of this area the work carried out on transition metal complexes of tyrosine (tyrH) has been fragmentary. The X-ray work of Van der Helm on $Cu(tyr)_2$ was preceded by that of Laurie;[10] there has been a brief report of a zinc(II) complex,[11] and some palladium(II)[12] and platinum(II)[13] derivatives have been isolated. In this study we have isolated solid complexes of L-tyrosine with divalent cobalt, nickel, copper, and zinc.

Experimental Section

Initial experiments were performed in order to

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Table I. Some Physical Properties and Analytical Data of the Metal Tyrosine Complexes

Complex	Colour	M.P. (°C)	μ_{eff} (B.M.)	% Carbon Calc.	% Carbon Fd.	% Hydrogen Calc.	% Hydrogen Fd.	% Nitrogen Calc.	% Nitrogen Fd.	% Metal Calc.	% Metal Fd.
$CoL_2(H_2O)$	light pink	250	4.7	49.7	49.5	5.6	5.3	6.4	6.4	13.5	13.5
$CoL_2(H_2O)_2$	dark pink	247	4.8	47.5	47.4	5.4	5.4	6.2	6.1	12.9	13.0
$CoL_2(H_2O)_3$	purple-grey	240	4.8	45.7	46.0	5.4	5.4	5.9	6.0	12.5	12.5
$NiL_2(H_2O)_4$	pale blue	295	3.2	44.1	44.1	5.7	5.4	5.7	5.7	12.0	12.1
$CuL(NO_3)$	green	220	2.1	35.8	36.3	3.3	3.7	9.2	9.5	20.9	21.1
$CuL_2(H_2O)$	blue	250	2.0	49.0	49.0	5.0	4.8	6.3	6.2	14.5	14.3
$LiCuL_3$	blue	281	2.0	53.1	53.8	4.9	5.3	6.7	7.1	10.5	10.4
$ZnL_2(H_2O)_4$	white	263		47.2	46.9	5.2	5.0	5.6	5.4	13.0	13.1

Table II. Some Significant Infrared Absorptions (cm^{-1}) of the Metal Tyrosine Complexes

	$\nu(OH)$	$\nu(NH_2)$	$\delta(NH_2)$	$\nu(COO)_{asym}$	$\nu(COO)_{sym}$	$\Delta(COO)$
$CoL_2(H_2O)$	3540m	3350s 3320s 3270s 3200s	**	1590s	1405s	185
$CoL_2(H_2O)_2$	3400br	3200sh	1604s	1586s	1412m	174
$CoL_2(H_2O)_3$	3400br	3200sh	1604s	1586s	1410m	176
$NiL_2(H_2O)_4$	3580s	3350s 3290s	1630s	1595s	1400s	195
$CuLNO_3$ *	3450m,br	3200m	1605s	1590s	1412s	178
$CuL_2(H_2O)$	3403s	3295s,sh 3158m	1600s	1580s	1400s	180
$LiCuL_3$	3405s,sh	3295s,sh 3200s 3150s	1600s	1585s	1400s	185
$ZnL_2(H_2O)_4$	3530m,br	3350m 3320m 3260m 3200m	**	1595s	1410s	185

* band at 1385 cm^{-1} due to NO_3 group; ** band obscured by $\nu(COO)_{asym}$ absorption.

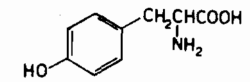
find, if possible, a general method for the preparation of L-tyrosine complexes. Many amino acids will react with metal ions in aqueous solution, but no reaction appeared to occur between solutions of L-tyrosine and metal salts in water, at room temperature or at 70°. A second approach was *via* the reaction of L-tyrosine with lithium hydroxide in water at room temperature; subsequent addition of aqueous metal salt solutions did not appear to lead to complex formation. However, it was found that by heating the $tyrH\text{-}LiOH.H_2O$ solution to 70° for 20 min, followed by addition of the metal salts, complexes formed readily. A general method is:

L-tyrosine (2.0 g) and $LiOH.H_2O$ (0.46 g) were dissolved in water (25 ml) and the solution heated to 70° for 20 min. The metal salt was dissolved in a minimum quantity of water and the solutions mixed with vigorous stirring (for a 1:1 metal:ligand ratio the Lityr solution was added to the metal salt solution, for 1:2 and 1:3 ratios the addition was in reverse). Precipitation was almost instantaneous, but stirring was continued for 5 min. The complexes were filtered, washed with water (25 ml), alcohol (25 ml), and ether (25 ml), and dried *in vacuo* over P_4O_{10}. It was found that lithium hydroxide powder was preferable to sodium hydroxide or potassium hydroxide pellets, as more accurate weighing is possible with the powder.

Carbon, hydrogen, and nitrogen analyses were determined by the Microanalytical Laboratory of this Department. Metal analyses were determined by E.D.T.A. titration.[14] Magnetic measurements were obtained by the Gouy method; infrared spectra were obtained as mulls in Nujol or hexachlorobutadiene or as KBr discs on a Perkin Elmer 621 spectrophotometer; and visible spectra were obtained in the solid state with $BaSO_4$ as dilutant on a Beckman DK2A spectrophotometer.

Results and Discussion

The analytical data suggest that, like many complexes of amino acids, the metal-tyrosine complexes contain, with two exceptions, a number of H_2O molecules. As well as carbon, hydrogen, and nitrogen analyses, metal analyses were performed in order to provide an independent check on the amount of H_2O in the complexes. Table I contains a list of the complexes prepared, together with their colour, melting points, magnetic moments, and analytical data. In all of the complexes it is apparent that the tyrosine moiety complexes as the tyrosinate anion.



tyrH

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Tyrosine can lose a proton in two ways: from the carboxylic acid group or from the phenolic group. It is to be expected that the carboxylic acid group will deprotonate preferentially, especially since the α-amino acid moiety acts as a chelate. In the present study no specific attempt was made to deprotonate the phenolic oxygen and there is no evidence to suggest that it occurred inadvertently. Table II contains the more important infrared absorption frequencies, and assignments were aided by comparison with deuteriated complexes.

$M(tyr)_2(H_2O)_n$ Complexes. It is apparent from a detailed examination of the infrared spectra of these complexes that all the complexes exhibit almost identical spectra, save for the ν(OH) region (this one difference probably reflects the number of coordinated and uncoordinated H_2O molecules). It is reasonable to assume, therefore, that these hydrated complexes possess similar coordination environments, and it is helpful to relate the structures to that of $Ni(tyr)_2 . 4H_4O$.

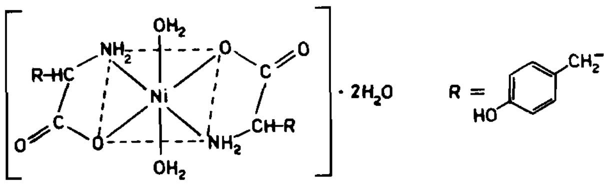
Table III. Solid State Visible Absorption Spectra of the Metal Tyrosine Complexes.

Complex	Band Maxima (cm^{-1})
$CoL_2(H_2O)$	8,330, 19,610, 27,030
$CoL_2(H_2O)_2$	8,264, 19,380, 27,030(sh)
$CoL_2(H_2O)_3$	8,264, 19,800
$NiL_2(H_2O)_4$	9,524, 11,110, 17,090, 29,410
$CuL(NO_3)$	14,710, 25,000
$CuL_2(H_2O)$	16,860, 23,530
$LiCuL_3$	16,780, 28,570

Table IV.

Complex	Ligating Atoms	Absorption Maxima ($cm^{-1} \times 10^{-3}$)				Ref.
$[Ni(H_2O)_6]^{2+}$	6 O	8.5	13.5	15.4	25.3	16
$[Ni(en)_3]^{2+}$	6 N	11.2	12.4	18.35	29.0	16
$[Ni(glycinate)_3]^-$	3 N, 3 O	10.1	13.1	16.6	27.6	16
$[Ni(tyr)_2(H_2O)_2] . 2H_2O$	2 N, 4 O	9.5	11.1	17.1	29.4	This work

The pale blue $Ni(tyr)_2 . 4H_2O$ complex has a magnetic moment quite typical of octahedral Ni^{II} complexes, $\mu_{eff} = 3.2$ B.M. (Table I), and its solid reflectance spectrum, Table III, is indicative of high-spin octahedral Ni^{II}, and is indeed similar to many other hydrated Ni^{II} amino acid complexes.[15] Table IV compares the visible spectral maxima of $Ni(tyr)_2 . 4H_2O$ with those of some other nickel(II) complexes containing oxygen and nitrogen donors. The energy of the ligand field band is an additive property resulting from the donors used (Jørgensen's rule of average environment[17]). The most plausible structure for $Ni(tyr)_2(H_2O)_4$ is



From this structure, containing 2N,4O donors, the predicted energy of the ligand field band would be

$$[(\nu_1 \text{ for } Ni(H_2O)_6{}^{2+}) \times \frac{4}{6}] + [(\nu_1 \text{ for } Ni(en)_3{}^{2+}) \times \frac{2}{6}]$$

$$= 5{,}700 + 3{,}700 \text{ cm}^{-1}$$

$$= 9{,}400 \text{ cm}^{-1}$$

Since ν_1 actually observed is 9,524 cm^{-1}, then this is good evidence for the type of structure postulated (note, the *trans*-structure is most likely, but a *cis*-structure is also possible).

It may thus be concluded that the hydrated bis-(tyrosinato)-complexes of cobalt(II), nickel(II), copper(II), and zinc(II), have essentially octahedral configurations.

Three cobalt(II) complexes were isolated from the reaction between $Co(H_2O)_6(NO_3)_2$ and lithium tyrosinate:

$$Co^{2+} + 2tyr^- \xrightarrow{H_2O} \text{immediate pink ppt. } Co(tyr)_2(H_2O)_2$$

$$\xrightarrow[15 \text{ min}]{\text{stir}} \text{purple ppt. } Co(tyr)_2(H_2O)_3 \qquad \xrightarrow[10 \text{ min}]{\text{stir}} \text{pink ppt. } Co(tyr)_2(H_2O)$$

In all, this reaction was attempted twelve times, and in each case compounds with almost identical analyses and infrared and visible spectra were obtained for the three types of complex. Warming the reaction mixture did speed up the colour changes. It was originally thought that these differences were due to the formation of oxygen-adduct complexes, as these are well-established in Co-amino acid species.[18,19] However, there was no evidence of Co^{III} derivatives; and despite the striking colour changes the visible spectra are almost identical (Table III).

$Cu(tyr)NO_3$ and $LiCu(tyr)_3$. Although several attempts were made to produce species such as $Ni(tyr)^+$ and $Ni(tyr)_3^-$ only the 1:2 adduct could be isolated. However, all three copper(II) complexes were obtained. The green $[Cu(tyr)(NO_3)]$ complex contains a coordinated nitrato group as evidenced by a strong band at 1385 cm^{-1} in the infrared spectrum.[18] If

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the green complex is not isolated from the original reaction mixture, but allowed to stand, it becomes blue [Cu(tyr)$_2$] after only a few minutes, suggesting that the kinetic product is the 1:1 adduct but the thermodynamically stable product is the blue 1:2 complex. As it appears that the NO_3^- group is monodentate in this complex it may well be that the α-amino acid group is tridentate and contains a bridging carboxylate ligand.

The infrared spectrum of the tris-tyrosinate complex, Li[Cu(tyr)$_3$], is very similar to that of Cu(tyr)$_2$(H$_2$O)$_2$ and indicates that the ligand is probably bidentate in the former resulting in a CuN_3O_3 coordination environment.