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Complexes of 3,4-Dihydroxyphenyl Derivatives. VI*. Microprocesses of Formation of Proton and Metal Complexes of L-Dopa

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The thermodynamic microquantities of dissociation of L-3,4-dihydroxyphenylalanine (L-dopa) at an ionic strength of 0.2 mol/dm³ (KCl) were determined from the temperature-dependence of microconstants measured with a pH-spectrophotometric method. It was found that the microenthalpies relating to the same donor group depend only slightly on the protonation state of the other group.

In a pH-spectrophotometric study of the manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II)–L-dopa systems the microconstants for the formation of complexes with the same stoichiometric composition but different arrangements of the donor groups were determined. Taking into account the different bonding modes of the species, a quantitative equilibrium description was given for these metal ion–L-dopa systems. It was found that the tendency to rearrangement from L-dopa complexes containing both amino acid-like and pyrocatechol-like bonding to species containing only (O,O) bonds varies with the metal ion: Cu(II) ~ Zn(II) > Co(II) > Mn(II), Ni(II). It was demonstrated that in complexes with the same bonding mode the protonation state of the other group has practically no effect on the deprotonation of donor groups not coordinated to the metal ion.

Introduction

L-3,4-dihydroxyphenylalanine (L-dopa) is of importance from both biochemical and therapeutic aspects. Extensive studies have been made on the proton and metal complexes, in part to obtain a more complete picture of its biological activity and of the optimum possibilities of its application in therapy [1–3], and in part to get new information on the coordination behaviour of ambidentate compounds [4–12].

Detailed data are available on the dissociation processes of L-dopa, which contains four dissociable protons [4, 8, 13]. UV [5, 14] and NMR [15] spectral studies have been performed to determine the dissociation microconstants of the protonated amino group and the first phenolic hydroxy group of the ligand. Data on the other thermodynamic microquantities (microenthalpy, microentropy) have not yet been reported in the literature.

By means of pH-metric investigations in wide pH ranges, the stoichiometric compositions and stability data have been determined for the complexes formed in systems of L-dopa and various metal ions: manganese(II) [10], cobalt(II) [10], nickel(II) [6, 9, 13], copper(II) [4, 5, 8, 13, 16] and zinc(II) [6, 9; 13]. Conclusions as to the binding sites of the metal ion in the complexes have been drawn from the use of different spectral methods: UV-visible [4, 7, 8, 16], CD [16] and ESR [8, 11, 12]. It has been found that coordination *via* the amino acid side-chain is favoured in the case of nickel(II), while *via* the orthophenolic hydroxy groups in the cases of cobalt(II) and zinc(II). Copper(II) forms 'strong' coordinate bonds with both donor group pairs, whereas manganese(II) does not do so with either pair. With all the metal ions, however, species involving a mixed bonding mode are formed, containing both amino acid-type (N,O) and O-phenolate-type (O,O) bonds. Concerning the dependence of the ambidentate nature of L-dopa on the pH, it has been found that the predominant bonding mode at lower pH is generally (N,O) coordination, at higher pH it is (O,O) coordination, while in the intermediate pH interval it is the mixed bonding mode.

UV and visible spectral studies [9, 10] have demonstrated that, as regards the above-mentioned metal ions, rearrangement from the mixed bonding mode into the (O,O) bonding mode occurs only in the cobalt(II), copper(II) and zinc(II)–L-dopa systems, but not in the nickel(II) and manganese(II)–L-dopa systems. Because of the overlapping processes of the rearrangement and the deprotonation of the donor groups not bonded to the metal ions, a given bonding mode can not be ascribed to a given stoichiometric composition. Namely, the species of composition MH_3A_2, which involves the mixed bonding mode, undergoes stepwise deprotonation by different

*Part V, ref. 10.

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pathways, with the intermediate formation of species in which the arrangements of donor groups are different. The equilibria concerning these processes can be characterized by microconstants.

The aim of the present work was to determine the thermodynamic microquantities of dissociation of L-dopa from the temperature-dependence of the pH-spectrophotometrically measured microconstants. Further, by following the formation of the (O,O)-bonded complexes *via* the UV band of the phenolate group, with a similar method we have attempted a complete equilibrium description (including the microprocesses) of the manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II)–L-dopa systems, thereby giving a quantitative characterization of the ambidentate nature of L-dopa too.

Experimental

Chemicals and Experimental Conditions

The L-dopa, a Fluka product of puriss. quality, was used without further purification. Metal chloride stock solutions were prepared from compounds of the highest analytical purity; their concentrations were checked gravimetrically *via* the oxinates.

The macro- and microconstants of dissociation of L-dopa were determined by means of pH-spectrophotometric measurements at various temperatures, as described previously [17]. Such titrations were also carried out at 25 °C to determine the microconstants of formation of the metal ion complexes. Samples containing the metal ion, and the ligand were passed in a closed system, with the aid of a peristaltic pump, between the titration vessel and the 1 mm quartz flow cell. The pH was measured at every point of the titration, and the spectra of the solutions were recorded in the region of absorbance of the phenolate group (250–350 nm). Since the ligand tends to undergo autoxidation, efforts were made to exclude air completely. The reproducibility of our measurements was 0.005–0.010 (<2%) absorbance unit, which exceeded the error of the absorbance measurement.

In the samples the ligand concentration was 3×10^{-3} mol/dm^3 and the metal ion/ligand ratio was 1:1, 1:2 or 1:3. The ionic strength was adjusted to 0.2 mol/dm^3 with KCl. Carbonate ion and oxygen-free KOH solution of known concentration (~0.2 mol/dm^3) was used as titrant.

pH was measured with a GK-23013 combined electrode on a Radiometer PHM 64 instrument. Light absorbance was measured with a Beckman ACTA MIV double-beam recording spectrophotometer.

Calculations

The thermodynamic macro- and microquantities relating to the processes of dissociation of L-dopa were calculated as previously [17].

As the first step in obtaining the microconstants of formation of the metal ion complexes, the stability constants and the pH-spectrophotometric titration data were used to calculate (by means of a non-linear least-squares curve-fitting method) the molar absorbances at various wavelengths in the interval 280–315 of the macrospecies* formed in the system. These molar absorbances are the weighted averages of the molar absorbances of the microspecies* (see Fig. 1):

$$\epsilon^{macro} = \Sigma \alpha_i \epsilon_i^{micro} \quad (1)$$

Various assumptions were made for the ϵ_i values and eqn. (1) was written for several wavelengths, and the resulting linear equation system was solved by the least squares method to yield values for the mole ratios (α_i) of the microspecies. The microconstants can be calculated from the following relations:

$$K_1 = k_1 + k_2 + k_3 \quad (2)$$

$$K_1K_2 = k_1k_{12} + k_2k_{23} = k_2k_{21} + k_3k_{32} \quad (3)$$

$$K_3^{-1} = k_{213}^{-1} + k_{321}^{-1} \quad (4)$$

and

$$\alpha_1 = \frac{k_1}{K_1}\ ;\ \alpha_2 = \frac{k_2}{K_1}\ ;\ \alpha_3 = \frac{k_3}{K_1}\ ;\ \alpha_4 = \frac{K_3}{k_{213}}\ ;\ \alpha_5 = \frac{\cdot K_3}{k_{321}} \quad (5)$$

The computations were performed with a programme written in FORTRAN language.

Results and Discussion

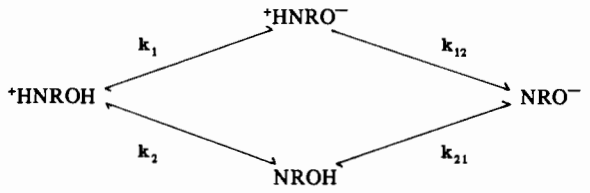
The thermodynamic macro- and microquantities characteristic of the dissociation of the first phenolic hydroxy group and the chain-terminal protonated amino group of L-dopa are listed in Table I. The macroenthalpy values were determined from the temperature-dependence of the pH-metrically obtained macroconstants**, and the microenthalpy data from that of the microconstants obtained by pH-spectrophotometric titration.

The data reveal that, as a consequence of the overlapping processes the macroquantities differ considerably from the corresponding thermodynamic data for pyrocatechol [18] (pK = 9.20; ΔH = 34.5 kJ/mol; ΔS = 60.3 J/mol degree) and phenylalanine

*Similarly to the terms macroconstant and microconstant, we use the nomenclature macrospecies and microspecies to differentiate between complex species characterized by a given stoichiometric composition and complex species characterized by a given bonding mode at a given stoichiometric composition.

**Direct calorimetric measurement of the macroenthalpies did not prove successful, for atmospheric oxygen could not be completely excluded during measurement, and accordingly the ligand underwent partial oxidation.

TABLE I. The Thermodynamic Macro- and Microquantities for Dissociation of L-dopa.



$$H_2A \xrightleftharpoons{K_1} HA \xrightleftharpoons{K_2} A$$

t = 25 °C; I = 0.2 mol/dm^3 (KCl)

	1[a]	2[a]	21[a]	12[a]
pk	8.98	9.19	9.42	9.63
Δh (kJ/mol)	33.6	44.7	34.1	45.2
Δs (J/K mol)	59	25	65	18

	1[a]	2[a]
pK	8.80	9.83
ΔH (kJ/mol)	37.7	41.0
ΔS (J/K mol)	41.4	50.0

[a]Subscripts identifying the dissociation processes.

[19] (pK = 9.06; ΔH = 44.8 kJ/mol; ΔS = 22.6 J/mol degree). At the same time, taking into account the inductive effect of the other group, the microquantities do exhibit good agreement with these reference values. It may also be stated that the dissociation microenthalpies relating to the same donor group depend slightly on the state of protonation of the other group ($\Delta h_1 \sim \Delta h_{21}$ and $\Delta h_2 \sim \Delta h_{12}$), and consequently this causes a change primarily in the entropy factor. This observation is in accordance with our earlier results on tyrosine derivatives [17].

Reference is made here only to the findings concerning the compositions of the complexes formed in the metal ion–L-dopa systems, their stability data, and the binding sites of the metal ions in these species [4–10, 16]. Our attention is restricted merely to an investigation of the microprocesses describing the stepwise deprotonation of the species MH_3A_2 containing a mixed bonding mode. These microprocesses of deprotonation, taking place by different pathways, are illustrated in Fig. 1.

Our earlier investigations [9, 10] indicated that rearrangement into the purely (O,O)-bonded complex is practically negligible up to pH ~ 11 in the nickel(II) and manganese(II)–L-dopa systems, and thus the above scheme can be simplified appreciably, as the formation of species 3, 5 and 6 need not be reckoned with. On the other hand, in the cobalt(II),

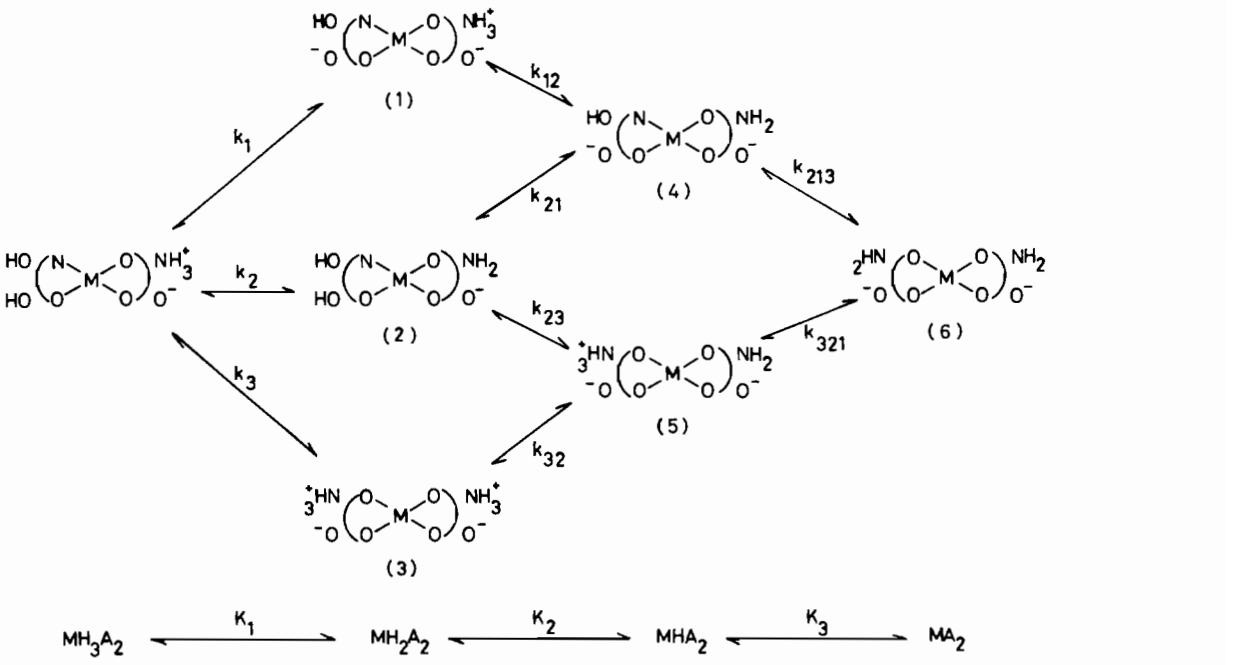


Fig. 1. Microprocesses of deprotonation of the species MH_3A_2 formed in the metal ion–L-dopa systems.

zinc(II) and copper(II)–L-dopa systems the deprotonation processes take place in accordance with the outlined scheme. These considerations were not applied to the case of copper(II) in our previous work [8].

In the same way as for the microprocesses of dissociation of the ligand [14], the microconstants for these part-processes were determined by following the formation of the complexes containing (O,O) bonds *via* the UV band of the phenolate groups. Figure 2 presents pH-spectrophotometric titration curves at a given wavelength for the metal ion–L-dopa systems.

To determine the microconstants, by simultaneous evaluation of the pH-spectrophotometric data obtained at various metal ion/ligand ratios, first the molar absorbances of the macrospecies relating to a given stoichiometric composition were calculated at different wavelengths. In the pH range of formation of the complexes which partially or completely contain (O,O) bonds, a significant, readily evaluated spectral change may be observed in a relatively narrow wavelength interval. Hence, the molar absorbances of the macrospecies at definite wavelengths were calculated only in the interval 290–305 nm. As an illustration, Fig. 3 shows data obtained for the copper(II)–L-dopa system.

The molar absorbances of the macrospecies are the sums of the molar absorbances of the microspecies with the same stoichiometric composition, weighted in accordance with their mole ratios. Hence taking into account the processes in Fig. 1 the following equations may be written:

$$\epsilon_{MH_2A_2} = \alpha_1\epsilon_1 + \alpha_2\epsilon_2 + \alpha_3\epsilon_3 \qquad (6)$$

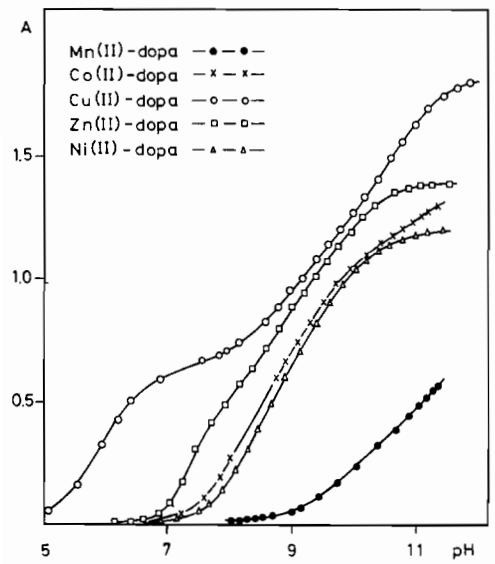


Fig. 2. pH-spectrophotometric curves of the metal ion–L-dopa systems at 301 nm, at a metal ion/ligand ratio of 1:2.

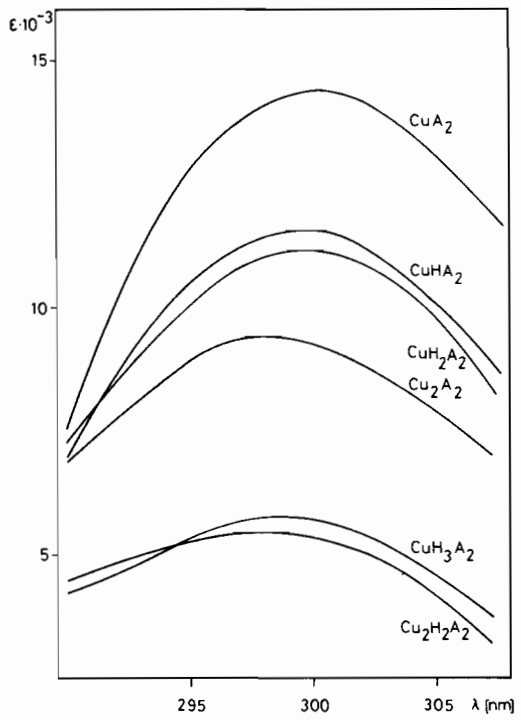


Fig. 3. Molar absorbance of complexes containing (O,O) bonds in the copper(II)–L-dopa system, as a function of wavelength.

$$\epsilon_{MHA_2} = \alpha_4\epsilon_4 + \alpha_5\epsilon_5 \qquad (7)$$

As concerns the ϵ values of the microspecies, a similar assumption to that used in the case of the microprocesses of dissociation of the ligand may be made [14, 17]. Namely the molar absorbances of complexes containing the same bonding mode are independent of the protonation degree of the amino groups not bonded to the metal ion, *i.e.*

$$\epsilon_2 = \epsilon_{MH_3A_2};\ \epsilon_3 = \epsilon_5 = \epsilon_{MA_2};\ \epsilon_1 = \epsilon_4$$

These equalities have been confirmed by the spectral characteristics of the metal complexes of 3,4-dihydroxyphenylethylamine (dopamine), which is capable only of (O,O) coordination. Thus, in the pH interval where only the complexes $M(HA)_2$, MHA_2 and MA_2 exist, which contain partly or completely deprotonated amino groups, no spectral change can be observed in the UV range. This supports the validity of the equality $\epsilon_3 = \epsilon_5 = \epsilon_{MA_2}$ for the metal ion–L-dopa system.

The approximate equality of the values of ϵ_1 and ϵ_4 was concluded from a spectral study of metal ion–dopamine–tyrosine mixed ligand systems. From the pH-spectrophotometric titration data we calculated the molar absorbances of the mixed ligand complexes $MABH_2$ (both the phenolic hydroxy group of the tyrosine and the chain-terminal amino group of the dopamine are protonated) and MAB

(both of these donor groups are deprotonated). It was found that the proportionality $\epsilon_{MAB}/\epsilon_{MABH_2} = 1.43 \pm 0.02$ holds between the molar absorbances of the two species at the same wavelength in the interval 290–310 nm. The values of ϵ_1 and ϵ_4 were estimated on the basis of this proportionality, in the knowledge of the $\epsilon_{MH_3A_2}$ values for the metal ion–L-dopa systems. The corresponding data obtained for the copper(II)–ligand systems are given in Fig. 4.

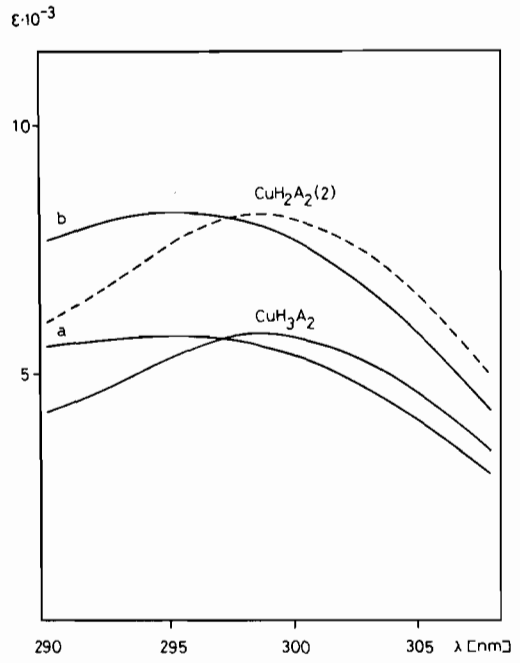


Fig. 4. Molar absorbances of the complexes $CuABH_2$ (a) and CuAB (b) in the copper(II)–tyrosine–dopamine system, the complex CuH_3A_2 in the copper(II)–L-dopa system, and the molar absorbance calculated from these for the microspecies of composition CuH_2A_2 (1), as a function of wavelength.

In the knowledge of the ϵ values in eqns. (6) and (7), the mole fractions of the species with the various bonding modes could subsequently be calculated by means of the linear least squares method (assumption 1).

As already mentioned, rearrangement to species containing only (O,O) bonds is practically negligible in the nickel(II)–L-dopa system. Thus, the calculation becomes simplified to a task analogous to that for the microprocesses of dissociation of the ligand. Having the molar absorbance data, for NiH_3A_2, NiH_2A_2 and $NiHA_2$ the mole ratios were obtained by solution of the eqn. (8)

$$\epsilon_{MH_2A_2} = \epsilon_{MH_3A_2}\alpha_2 + \epsilon_{MHA_2}(1 - \alpha_2) \qquad (8)$$

written for several wavelengths by the least squares method.

In the manganese(II)–L-dopa system the fully protonated, mixed bonding mode complex MnH_3A_2 is not formed, and hence the related values $\epsilon_{MH_3A_2} = \epsilon_2$ and α_2 are unknowns. In the equation system written for several wavelengths, therefore, the number of unknowns is always larger by one than the number of equations. Consequently, the values of ϵ_2 at the various wavelengths were estimated from the spectral data for the metal ion–dopamine–tyrosine system as described previously, and the mole ratios were then calculated in the manner used for the nickel(II)–L-dopa system.

Estimation of the ϵ_1 and ϵ_4 values *via* the metal ion–dopamine–tyrosine model system yields only approximations, accordingly we attempted to find the unknown mole fractions using other considerations. It was assumed that, in complexes with the same bonding mode, because of the great distance between the donor groups not bonded to the metal ion and also since the steric arrangement is unfavourable for direct interaction, the change in the protonation of the amino groups does not influence the deprotonation constants (assumption 2). Hence, the following equalities may be written:

$$k_1 = k_{21};\ k_2 = k_{12};\ \text{and}\ k_{32} = 4k_{321}$$

The validity of the equality $k_{32} = 4k_{321}$ seems to be supported by the fact that this assumption holds approximately for the stepwise deprotonation constants of the complex MH_2A_2 in the metal ion–catecholamine systems [20, 21]. The assumptions of the equalities $k_1 = k_{21}$ and $k_2 = k_{12}$ were based on the results for the nickel(II)–L-dopa system, where there equalities are reasonably well satisfied (see Table III).

The mole ratios calculated with the two different assumptions are listed in Table II.

The appropriate microconstants were obtained from the α values as described in the calculations section. These results, together with the equilibrium data derived from them, are listed in Table III. To check the validity of the assumptions, the experimental titration curves were recalculated with the resulting microconstants and with the molar absorbances of the microspecies. The dA (average) values characterizing the goodness of the fit are also given in Table III.

The data in Table III reveal that the fit obtained with assumption 2 is somewhat poorer than that in the case of assumption 1. Nevertheless, in both cases the reproducibility of the spectrophotometric measurements is good. The change in the protonation state of the other group therefore has probably only a slight effect on the deprotonation microconstants of complexes with the same bonding mode, and results in a spectral change of only approximately the same magnitude as that of the error in the method.

The errors in the mole ratios resulted in differences of ±0.01–0.1 log unit in the microconstants.

TABLE II. The Mole Ratios for Micro-Species Formed in the Metal(II)–Dopa Systems. t = 25 °C; I = 0.2 mol/dm^3 KCl.

	Mn(II)	Co(II)		Ni(II)	Cu(II)		Zn(II)	
		Assumption 1	Assumption 2		Assumption 1	Assumption 2	Assumption 1	Assumption 2
α_1	0.76 ± 0.07	0.62 ± 0.09	0.69 ± 0.01	0.77 ± 0.03	0.41 ± 0.04	0.36 ± 0.03	0.42 ± 0.06	0.37 ± 0.05
α_2	0.24 ± 0.03	0.26 ± 0.05	0.21 ± 0.01	0.23 ± 0.02	0.08 ± 0.01	0.11 ± 0.01	0.09 ± 0.02	0.09 ± 0.01
α_3		0.13 ± 0.01	0.10 ± 0.01		0.51 ± 0.02	0.54 ± 0.02	0.50 ± 0.04	0.53 ± 0.05
α_4		0.87 ± 0.02	0.85 ± 0.02		0.45 ± 0.01	0.45 ± 0.01	0.42 ± 0.01	0.42 ± 0.03
α_5		0.13 ± 0.02	0.15 ± 0.01		0.55 ± 0.01	0.55 ± 0.01	0.58 ± 0.01	0.59 ± 0.03

TABLE III. The Microconstants and Derived Equilibrium Constants Characterizing the $MH_3A_2 \rightarrow MA_2$ Deprotonation Processes in the Metal(II)–Dopa Systems. t = 25 °C; I = 0.2 mol/dm^3 KCl.

	Mn(II)	Co(II)		Ni(II)	Cu(II)		Zn(II)	
		Assumption 1	Assumption 2		Assumption 1	Assumption 2	Assumption 1	Assumption 2
pk_1		9.17 ± 0.07	9.12 ± 0.01	9.11 ± 0.02	8.87 ± 0.04	8.92 ± 0.03	8.97 ± 0.06	9.02 ∓ 0.06
pk_2		9.54 ± 0.10	9.64 ± 0.02	9.65 ± 0.03	9.57 ± 0.05	9.41 ± 0.01	9.63 ± 0.10	9.61 ± 0.01
pk_3		9.85 ± 0.15	9.96 ± 0.07		8.76 ± 0.02	8.74 ± 0.01	8.88 ± 0.05	8.87 ± 0.05
pK_1		8.96		9.00	8.47		8.59	
pk_{12}	9.55 ± 0.04	9.58 ± 0.08	9.64 ± 0.02	9.54 ± 0.02	9.46 ± 0.04	9.41 ± 0.01	9.65 ± 0.07	9.61 ± 0.01
pk_{21}	9.07 ± 0.03	9.21 ± 0.05	9.12 ± 0.01	9.03 ± 0.03	8.76 ± 0.04	8.92 ± 0.03	8.89 ± 0.06	9.02 ± 0.06
pk_{23}		10.02 ± 0.08	9.89 ± 0.03		8.67 ± 0.03	8.83 ± 0.01	8.75 ± 0.05	8.87 ± 0.03
pk_{32}		9.71 ± 0.06	9.56 ± 0.03		9.48 ± 0.04	9.49 ± 0.01	9.60 ± 0.04	9.61 ± 0.03
pK_2	9.67	9.73		9.66	9.51		9.65	
pk_{213}		10.94 ± 0.01	10.93 ± 0.01		10.00 ± 0.01	10.00 ± 0.01	10.06 ± 0.01	10.06 ± 0.03
pk_{321}		10.13 ± 0.05	10.16 ± 0.04		10.09 ± 0.01	10.09 ± 0.01	10.20 ± 0.01	10.21 ± 0.03
pK_3	11.32	11.0		11.47	10.35		10.44	
dA average	0.0048	0.0102	0.0112	0.0076	0.0071	0.0085	0.0089	0.0102
k_1/k_2	3.02 ± 0.53	2.34 ± 1.12	3.28 ± 0.26	3.47 ± 0.42	5.01 ± 0.94	3.1 ± 0.29	4.57 ± 1.41	3.89 ± 0.58
pk_2-pk_{12}		−0.04	0.0	0.11	0.11	0.0	−0.02	0.0
pk_1-pk_{21}		−0.04	0.0	0.08	0.09	0.0	0.08	0.0
pk_{321}-pk_{32}		0.42	0.6		0.61	0.6	0.6	0.6
log $k_{rearr.}$		2.46	2.47		3.40	3.40	3.34	3.34

The reliability of the constants was therefore also checked as follows. The macroconstants determined pH-metrically were kept unchanged, while the microconstants were varied with a maximum error of ±0.1 log unit and the pH-spectrophotometric titration curves were recalculated. As a demonstration Fig. 5 shows the curves obtained for the zinc(II)–L-dopa system.

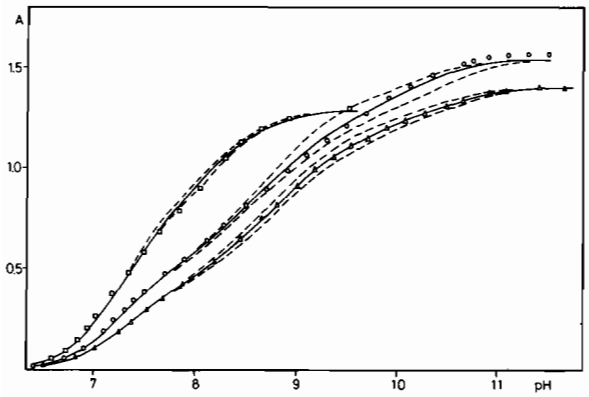


Fig. 5. pH-spectrophotometric titration curves of the zinc(II)–L-dopa system at 300 nm, at various metal ion/ligand ratios: 1:1 – □ –; 1:2 – ○ –; 1:3 – △ –. The continuous line is the curve recalculated with the constants given in Table III. The dashed line is the curve recalculated with the maximum error in the constants (see text).

It can be seen in Fig. 5 that the fit of the curves recalculated in this way is substantially poorer; the value characterizing the goodness of the fit is considerably larger than the reproducibility of the measurements. Therefore, the calculated error in the constants appears to be realistic.

Besides the constant characterizing the rearrangement from the mixed bonding mode to the (O,O) bonding mode, the constants k_3, k_{23} and k_{213} include the appropriate deprotonation microconstants and also the dissociation constant of the second phenolic hydroxy group: $pK_4 = 13.4 \pm 0.2$ [9]. From these data the equilibrium constant for the rearrangement alone, $k_{rearr.}$, was calculated *via* the relation

$$k_{rearr.} = \frac{[(O,O)M(O,O)]^{2-}}{[(O,O)M(N,O)]^{2-}} = \frac{k_{321}k_{32}k_3}{k_1k_2K_4} = \frac{k_{321}k_{23}}{k_1K_4} = \frac{k_{213}}{K_4}$$

The resulting data are listed in the last row of Table III. It is noteworthy that, in their tendency, these data directly characterizing the ambidentate nature of L-dopa agree well with the equilibrium constants of the processes

$$MAB + B \rightleftharpoons MB_2 + A$$

describing the similar 'rearrangements' in the mixed ligand systems metal ion–alanine (A)–pyrocatechol (B); the logarithms of these are: Mn(II) = 2.60, Co(II) = 2.96, Ni(II) = 1.64, Cu(II) = 4.15 and Zn(II) = 3.83. The differences between these latter values and the constant $k_{rearr.}$ may originate from the effect of the L-dopa side-chain or from the error in the value of pK_4.

The pk_3, pk_{23} and pk_{213} values calculated with the aid of the 'rearrangement' constants of the metal ion–alanine–pyrocatechol systems were used to recalculate the concentration distributions in the manganese(II) and nickel(II)–L-dopa systems, and it was found that up to pH 11.0 the concentration of the 1:2 complexes containing only (O,O) bonds does not attain 5% in either system. This confirms our assumption that the 1:2 complexes do indeed remain in the mixed bonding mode in the pH interval in question in these two systems.

For the complexes with the same bonding mode, the differences $pk_2 - pk_{12}$, $pk_1 - pk_{21}$ and $pk_{321} - pk_{32}$, which express the effect of the 'other group', are nearly zero; it may thus be stated that this effect is merely a slight one. These donor groups are indeed too far from one another for the effect of the electron density change occurring due to the deprotonation of one of the donor groups to appear in the other donor group, either directly, or indirectly, through the carbon chain or a solvent molecule(s). In fact, this has the result that the relative acidity of the donor groups not bonded to the metal ion differs appreciably from that of the free ligand ($k_1/k_2 = 1.62$), while at the same time it is a nearly constant value independently of the metal ion.

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