Complexes of Doubly Chelating Ligands. Part III.[1] Proton and Copper(II) Complexes of 3,4-Dihydroxyphenylglycine (DOPG)

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The four acid dissociation constants of the 3,4-dihydroxyphenylglycine (DOPG) cation have been determined at 25° ± 0·01° and 1·0M ionic strength (KNO_3) by means of a glass-calomel electrode system. The reactions of the ligand with copper(II) ions were also examined by pH methods; polymer formation and ligand exchange reactions have been observed and the behaviour of this system compared with reactions of related ligands. Stability constants for the copper complexes and for the formation of a tetramer are reported.

CONTINUING our studies of complexes of doubly chelating ligands, we report the results of our investigations of the interactions of 3,4-dihydroxyphenylglycine (DOPG) with hydrogen and copper(II) ions.

Stereochemical considerations are thought to have a large bearing on the identity and strength of the complexes and complex polymers formed when these species involve simultaneous chelation of both sites of the ligand to metal ions; such effects are very apparent in comparisons of the polymerization schemes of DOPG and DOPA [L-β-(3,4-dihydroxyphenyl)alanine]. The two ligands are very similar, but the former has a side chain shorter by one $-CH_2-$ group, and is, therefore, a less flexible molecule which leads to markedly different polymerization reactions.

Definitions of Main Symbols.—Like DOPA, DOPG exists in aqueous solution as the zwitterion, with two independent potential chelating sites, both doubly protonated. Thus the terminology used previously (see Part I,[2] Table 1) is again used to cover most of the equilibrium studies reported here (see also Table 2), apart from the polymerization. In this case K_4^P was defined as the formation constant of a tetramer from the species L^cCuL^cCu. (This method of definition has the advantage that the resulting constant does not directly involve K_1^{Mc} and K_2^{Mc}—which could not be measured—for which values were assumed on the basis of the work on DOPA.)

RESULTS

Acid dissociation constants were determined by normal titration techniques, and an eight-fold concentration range of DOPG was examined. The purity was found to be 99·82 ± 0·04% by titration of the carboxylic acid proton and this was confirmed by titrating 1 : 1 molar ratio mixtures of DOPG: copper(II) ions which liberate four protons per ligand molecule below pH 8·0. Log K_1^H was determined by the back-titration technique previously described.[2] Log K_4^H was obtained directly from the formation curve and the two overlapping constants, log K_3^H and log K_2^H were separated by a computational technique similar to that due to Rossotti *et al.*[3,4a] The results are shown in Table 1.

Titrations with base of 8 : 1, 4 : 1, and 2 : 1 molar ratio DOPG : copper mixtures show that 1 : 1 and 2 : 1 amino-acid-type complexes are initially formed, but at higher pH values an exchange reaction occurs, giving the 2 : 1 catechol-type complex. This behaviour is very similar to that observed with the DOPA–copper systems previously studied[2] and is corroborated by spectral evidence; the systems display spectra similar to that of the glycine–copper system (max at 16 kK) at pH 5, and spectra similar to the catechol–copper system at pH 9 (max at 25 kK).

TABLE 1

Equilibrium constants for the association of proton and copper(II) ions with DOPG at 25° and 1·0M-KNO_3

Reaction		log (equilibrium constant)	Spread	Standard deviation
Proton complexes				
$L^{3-} + H^+ \rightleftharpoons LH^{2-}$	K_1^H	13·64	±0·16	0·09
$LH^{2-} + H^+ \rightleftharpoons LH_2^-$	K_2^H	9·748	±0·005	0·002
$LH_2^- + H^+ \rightleftharpoons LH_3$	K_3^H	8·556	±0·005	0·002
$LH_3 + H^+ \rightleftharpoons LH_4^+$	K_4^H	1·994	±0·012	0·006
Copper(II) complexes: (a) Amino-acid (glycine)-type complexes *				
$Cu + L^a \rightleftharpoons CuL^a$	K_1^{Ma}	6·955	±0·015	0·006
$CuL^a + L^a \rightleftharpoons CuL_2^a$	K_2^{Ma}	5·94	±0·21	0·06
(b) Catechol-type complexes (assumed values [2])				
$Cu + L^c \rightleftharpoons CuL^c$	K_1^{Mc}	13·0		
$CuL^c + L^c \rightleftharpoons CuL_2^c$	K_2^{Mc}	12·0		
Formation constant for tetramer				
$2L^cCuL^cCu \rightleftharpoons (CuL)_4 + 2H^+$	K_4^P	7·88	±0·06	

* At the pH values concerned here $L^a \equiv LH_2^-$, as the catechol-type protons are negligibly ionised.

Slight precipitation occurred in the pH region where the exchange reaction takes place and it was not possible therefore to obtain data of sufficient accuracy to permit the determination of equilibrium constants for the catechol-type complexes. Equilibrium constants for the glycine-type complexes are given in Table 1.

Titrations at a 1 : 1 molar ratio of DOPG to copper showed the liberation of four protons per DOPG molecule below pH 8. As it seems unlikely that olation and hydrolysis reactions occur at these pH values, the reactions which follow the formation of the 1 : 1 amino-acid-type complex must involve polymerization and possibly ligand exchange. The parts of each titration after the removal of two protons

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[1] Part II, J. E. Gorton and R. F. Jameson, preceding paper.

[2] J. E. Gorton and R. F. Jameson, *J. Chem. Soc.* (*A*), 1968, 2615.

[3] F. J. C. Rossotti, H. Rossotti, and L. G. Sillén, *Acta Chem. Scand.*, 1956, **10**, 203.

[4] (*a*) F. J. C. Rossotti and H. Rossotti, 'The Determination of Stability Constants,' McGraw-Hill, London, 1961, p. 99; (*b*) p. 355.

per DOPG were treated by calculating the functions pL′ and $\bar{n}'$

where
$$[L'] = \frac{[CuL_1^a]}{\beta_2^H[H]^2} \qquad (1)$$

$$\bar{n}' = \frac{[H]_T - 2[Cu]_T}{2[Cu]_T} \qquad (2)$$

as was previously done for the DOPA–copper system.[1,2,5] Curves were obtained which intersected precisely at $\bar{n}$ 0·5 and which all had a slope, $(\partial pL/\partial \bar{n})$, greater than that of the simple single formation curve (see Figure 1). It was also noted that the set of curves shows a rather small concentration dependence and that the individual curves are not symmetrical about $\bar{n}$ 0·5.

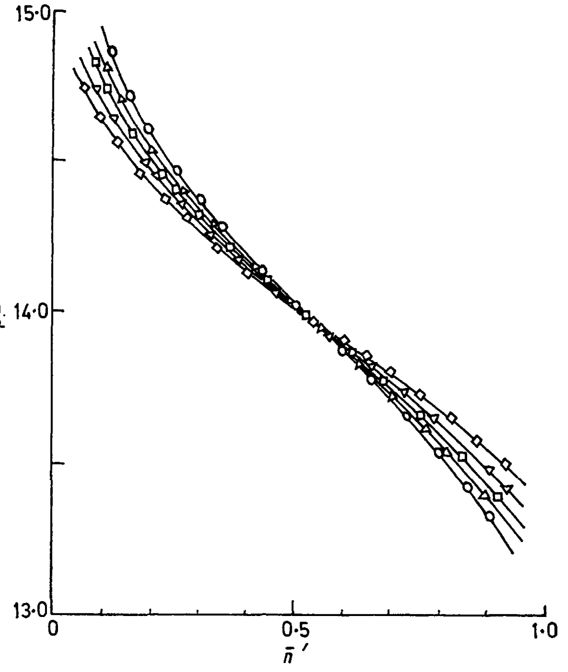

FIGURE 1 Formation curves obtained for 1 : 1 DOPG–Cu(II) solutions: [DOPG] or [Cu]; ◇, $3{\cdot}112 \times 10^{-4}$M, ▽, $6{\cdot}225 \times 10^{-4}$M, □, $1{\cdot}245 \times 10^{-3}$M, △, $2{\cdot}490 \times 10^{-3}$M, ○, $4{\cdot}976 \times 10^{-3}$M

Calculations based on a similar set of polymers to that found in the DOPA–copper system showed that the only way of producing curves of a slope steeper than that of the single ionization curve was to limit the highest order of open-chain polymers formed. This was done by introducing a second closed-chain polymer and using a direct summation to calculate $n[A_{on}]$. However this model of the system did not give a point of $\bar{n} = 0{\cdot}5$ that was concentration independent. Another type of polymer which could give rise to results similar to those obtained is that in which the copper ion is six co-ordinate, having one amino-acid group and two catechol groups chelated to it. In calculations based on these species it was found to be difficult to generate curves of a sufficiently high slope and, although cross-over points could be obtained, their occurrence and position were dependent on the constants used and were thus considered an artefact of the computation. It was concluded that the 1 : 1 amino-acid complex could not be the unit from which the polymers were forming.

It was noted that the DOPG–copper system polymerized in a higher pH region than the DOPA–copper system, and also that, at the higher pH values, an exchange reaction takes place with DOPA and copper to give catechol-type complexes. In this case, therefore, it is possible that the DOPG–copper polymers are formed from catechol-type complex(es) as basic unit(s).

Although the constants for the DOPG–copper exchange reaction have not been measured because of precipitation in these systems, approximate calculations may be made using the values from the DOPA–copper system. It is assumed that metal co-ordination to one ligand site does not affect the constants for the other. The values used for log K_1^{Mc} and log K_2^{Mc} for the formation of these catechol-type complexes were 13·0 and 12·0 respectively. We can then write

$$[L]_T = [CuL^a] + 2[CuL_2^a] + [CuL^c] + 2[L^cCuL^cCu] + \bar{n}^*[L]_T \qquad (3)$$

where the species L^cCuL^cCu is treated as having the same formation constant as L^cCuL^c, the normal 2 : 1 catechol-type complex. In much of the region where polymerization occurs, the concentration of this species (L^cCuL^cCu) is of major importance. The function $\bar{n}^*$ used in this calculation is analogous to the function $Q\bar{n}_Q$ used by Rossotti for a polynuclear complex.[4b,6]

It is convenient to define the function $[OH]_L^*$ (the concentration of base consumed by polymerization, ligand exchange, and the formation of higher complexes) as in equation (4) where the 1 : 1 amino-acid complex is taken as the reference point for $[OH]_L^*$ equal to zero;

$$[OH]_L^* = [CuL_2^a] + [CuL^c] + 3[L^cCuL^cCu] + 2\bar{n}^*[L]_T \qquad (4)$$

note that, in practice, this function is simply twice the function $\bar{n}'[L]_T$ used in the first calculations on this system.

From the equations (3) and (4) we have:

$$2[L]_T(1 - \bar{n}') = 2[CuL^a] + 3[CuL_2^a] + [CuL^c] + [L^cCuL^cCu] \qquad (5)$$

Since the system is 1 : 1 we can ignore $[CuL_2^a]$; and, writing $[CuL^a]$ as X, we can use the known equilibrium constants to convert this equation into a cubic in X as follows:

$$[L^c] = \frac{K_1^HK_2^HX}{[H]^2}$$

$$[CuL^c] = K_1^{Mc}X[L^c] = \frac{K_1^HK_2^HK_1^{Mc}X^2}{[H]^2} = \frac{C_1X^2}{[H]^2}$$

$$[L^cCuL^cCu] = K_1^{Mc}K_2^{Mc}X[L^c]^2 = \frac{(K_1^H)^2(K_2^H)^2K_1^{Mc}K_2^{Mc}X^3}{[H]^4} = \frac{C_2X^3}{[H]^4}$$

So equation (5) becomes

$$2[L]_T(1 - \bar{n}') = 2X + \frac{C_1X^2}{[H]^2} + \frac{C_2X^3}{[H]^4}$$

Solution of this equation gives values $[CuL^a]$, and hence values of $\bar{n}^*$. Plots of $\bar{n}^*$ *vs.* pH give parallel curves, which fit the normal shape formation curve. The spacing between the curves, $\left(\frac{\partial \log [L]_T}{\partial pH}\right)_{\bar{n}^*}$, was found to be regular, and

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[5] R. F. Jameson and W. F. S. Neillie, *J. Inorg. Nuclear Chem.*, 1965, **27**, 2623.

[6] F. J. C. Rossotti and H. Rossotti, *Acta Chem. Scand.*, 1957, **10**, 957.

indeed if we assume it to be equal to −2 at $\bar{n}^*$ 0·5, a set of theoretical curves is obtained which is in good agreement with the experimental data (Figure 2). The curves correspond to, and may be adequately described by, a dimerization reaction involving the loss of one proton per monomer unit.[7] The only species available in appreciable concentration and capable of such a dimerization is L^{c}CuL^{c}Cu. It seems, therefore, that the function $\bar{n}^*$ represents the formation of one species only: $(CuL)_4$, see Figure 3, and that this is the highest order polymer formed.

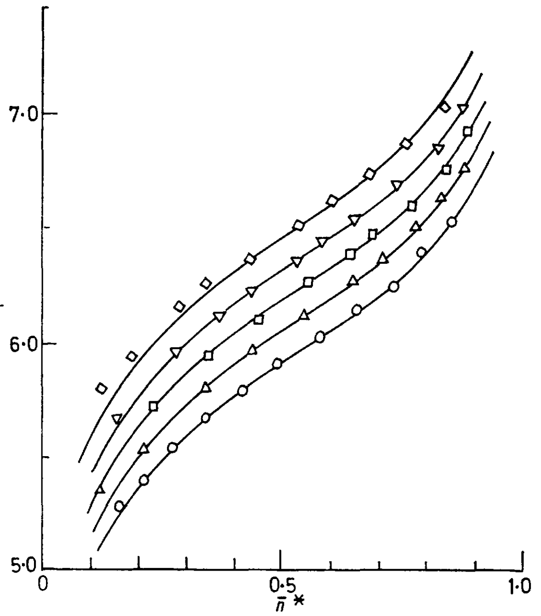
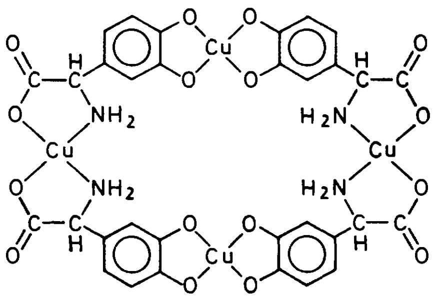


FIGURE 2 Formation of DOPG–Cu(II) tetramer, theoretical parallel curves with points calculated from experimental data. [DOPG] or [Cu]; ◇, 3·112 × 10^{-4}M, ▽, 6·225 × 10^{-4}M, □, 1·245 × 10^{-3}M, △, 2·490 × 10^{-3}M, ○, 4·976 × 10^{-3}M



Cu_4L_4

FIGURE 3 Probable DOPG–Cu(II) tetramer (the *cis*-configuration of the glycine rings is not a stereochemical requirement)

In order to calculate the ' dimerization ' constant for the formation of $(CuL)_4$ from L^{c}CuL^{c}Cu, the curves were replotted to give a set of coincident curves (after Olin [8]), and the ' best-fit ' curve through the complete data used. The log constant was found to be 7·88 ± 0·06.

DISCUSSION

The values found for the acid dissociation constants and for the normal 1 : 1 and 2 : 1 copper complexes correlate well with many literature values for such interactions, confirming our identification of K_2^H with ionization of a phenolic proton, and K_3^H with that of the amine proton. The value of log K_4^H is appreciably lower than the ionization constant of the carboxylic acid proton in DOPA and other amino-acids. We note a similar phenomenon in the set of analogous substituted acetic acids; the phenyl group seems to have little effect on the ionization of the carboxylic acid proton except when it is attached to the α carbon atom (see Table 2).

TABLE 2

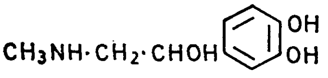
Proton association constants of ligands related to DOPG

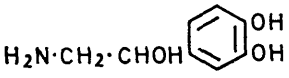
Ligand	log constant		Temp.	Ionic strength (Molality + salt)	Ref.
	K_1	K_2			
Glycine	9·76	2·43	20°	1·0 $NaClO_4$	*a*
Glycine	9·77	2·39	25	→0	*b*
Alanine	9·79	2·49	20	1·0 $NaClO_4$	*c*
Valine	9·59	2·38	20	1·0 $NaClO_4$	*d*
β-Phenylalanine	9·18	2·21	20	1·0 $NaClO_4$	*c*
β-Phenylalanine	9·31	2·20	25	→0	*b*
Acetic acid	5·014		25	3·0 $NaClO_4$	*e*
Propionic acid	5·161		25	3·0 $NaClO_4$	*e*
Phenylacetic acid	4·557		25	3·0 $NaClO_4$	*f*
Phenylacetic acid	4·25		30	0·1 $NaClO_4$	*g*
Phenylpropionic acid	4·56		30	0·1 $NaClO_4$	*g*
		K_4^H			
DOPA		2·31	25	1·0 KNO_3	2
DOPG		1·994	25	1·0 KNO_3	This work

[a] D. D. Perrin, *J. Chem. Soc.*, 1958, 3120. [b] K. P. Anderson, W. O. Greenhalgh, and R. M. Izatt, *Inorg. Chem.*, 1966, **5**, 2106. [c] D. D. Perrin, *J. Chem. Soc.*, 1958, 3125. [d] D. D. Perrin, *J. Chem. Soc.*, 1959, 290. [e] D. L. Martin and F. J. C. Rossotti, *Proc. Chem. Soc.*, 1959, 60. [f] J. D. E. Carson and F. J. C. Rossotti, unpublished results in *Chem. Soc. Special Publ.*, No. 17, 1964. [g] V. T. Athavale, L. H. Prabhu, and D. G. Vartak, *J. Inorg. Nuclear Chem.*, 1966, **28**, 1237.

In comparison with the polymerization of the DOPA–copper system we note that in the DOPG case closed-ring dimerization does not occur; a difference attributable to the lower flexibility of the side-chain of this catecholamine. Moreover our attempts to develop a more universally applicable set of master variables for use in such polymer systems were frustrated by the uniqueness of the set of polymers formed by this ligand; and our computational approach, in order to be rigorous, had to be far more specialised than we would normally wish.

It is of considerable interest that one of us (R. F. J.) in a study of the interaction of copper(II) with adrenaline and noradrenaline [1] was led to propose similar tetramers to those met with in the DOPG–copper(II) system.





EXPERIMENTAL

The apparatus used for titrations has been described previously; [2] the accuracy of the thermostat was improved to better than ±0·01°. (Volumetric glassware was, as previously, calibrated at the temperature at which it was used.)

[7] L. G. Sillén, *Acta Chem. Scand.*, 1954, **8**, 318.

[8] A. Olin, *Acta Chem. Scand.*, 1957, **11**, 1445.

The potassium nitrate and copper salts used were AnalaR, and stock solutions of the latter were analysed for copper by the salicylaldoxime method.[9]

DOPG was made from veratraldehyde by means of a Strecker reaction followed by a Zeisel ether-cleavage reaction:

$$\mathrm{C_6H_3(OMe)_2{\cdot}CHO + NH_4Cl + NaCN \xrightarrow{H_2O\text{–}MeOH} C_6H_3(OMe)_2{\cdot}CH(CN){\cdot}NH_2,HCl}$$

$$\Big\downarrow \text{Reflux, 6M-HCl aq}$$

$$\mathrm{C_6H_3(OMe)_2{\cdot}CH(CO_2H){\cdot}NH_2,HCl}$$

$$\mathrm{C_6H_3(OH)_2{\cdot}CH(CO_2H){\cdot}NH_2,HI \xleftarrow[\text{HI aq } (d\ 1{\cdot}5)]{\text{Reflux}}}$$

The hydriodide was converted into the hydrochloride by passing it, in HCl solution, through an anion-exchange column in the chloride form; this salt was recrystallized twice from acetone–HCl–water as white microcrystals; these were washed with acetone and ether and the solvents were removed by pumping at 10^{-5} mmHg for 2 h.

A Unicam SP 700 spectrophotometer was used. Data were processed on the Elliott 4130 computer at the University.

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[1/1148 *Received, July 5th,* 1971]

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[9] A. I. Vogel, ' A Textbook of Quantitative Inorganic Analysis,' Longmans, London, 1967, 3rd edn., p. 497.