Equilibria of Aminoethanols with Protons and Metal(II) Ions. Part 3.[1,2] L-(+)-*threo*-2-Amino-1-phenylpropane-1,3-diol with Protons and Copper(II) in Aqueous Solution

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The equilibria of L-(+)-*threo*-2-amino-1-phenylpropane-1,3-diol [$H_2L = HO{\cdot}CH(Ph){\cdot}CH(NH_2){\cdot}CH_2OH$] with H^+ and Cu^{II} have been determined potentiometrically at 25 °C and I = 0.1 mol dm^{-3} (K)Cl. The protonation constants are log K_1 = 12.01 and log K_2 = 13.22 for the two hydroxyl groups, and log K_3 = 8.446 for the amine group. With copper(II) the complexes $[Cu(H_2L)]^{2+}$, $[Cu(HL)]^+$, $[Cu(HL)_2]$, $[Cu(OH)(HL)]$, and $[Cu(HL_2)]^-$ are formed. They contain, with the exception of $[Cu(H_2L)]^{2+}$, five-membered chelate rings, with amine nitrogen and hydroxyl oxygen as donor atoms. The crystal structure of the compound $[Cu(HL)_2(OH_2)]{\cdot}4H_2O$, obtained from alkaline solutions, confirms this interpretation.

THE study of a set of compounds containing the aminoethanol moiety, $H_2N{\cdot}CH_2{\cdot}CH(OH){\cdot}X$ ($X = CH_2CO_2H$,[1] CO_2H,[2] CH_2NH_2,[3] or Ph [4,5]), has shown that this moiety is a chelating agent for bivalent metal ions, and that it has a particularly high affinity towards Cu^{2+}. The chelation takes place with ionisation of the hydroxyl group, thus forming five-membered (*NO*) chelate rings.

Formation constants of copper(II) complexes with D- and L-*threo*-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol have also been studied;[6] unfortunately, they were determined in alcoholic solution under undefined conditions of temperature and ionic strength, and are not suitable for comparisons.

Since the aminoethanol group is found in several drugs and natural substances such as some phospholipids and sphingolipids, it is interesting to examine the properties of the aminoethanol compounds, which could mimic the behaviour of natural substances or interfere with them. Here we present the results of a study of the equilibria between protons, copper(II) ions, and L-(+)-*threo*-2-amino-1-phenylpropane-1,3-diol, $H_2L = HO{\cdot}CH(Ph){\cdot}CH(NH_2){\cdot}CH_2OH$ (phenylserinol, pse), a by-product in the industrial preparation of chloroamphenicol.

EXPERIMENTAL

Reagents and Procedure.—An aqueous solution of the compound L-(+)-*threo*-2-amino-1-phenylpropane-1,3-diol (Aldrich, reagent-grade purity) was treated with decolourising charcoal, filtered, concentrated in a Rotavapor, and then left to stand. After some time the compound separated as small colourless crystals, and was filtered off, washed with ethanol and diethyl ether, and dried *in vacuo* over P_4O_{10}, m.p. 114.2 °C (Found: C, 64.5; H, 7.85; N, 8.60. Calc. for $C_9H_{13}NO_2$: C, 64.65; H, 7.85; N, 8.40%). Standard solutions of the reagents were prepared, and the automatic potentiometric measurements carried out, according to the procedures previously described.[7,8] The concentrations of the starting solutions and the pH range of each run are given in Table 1.

In alkaline solution the ligand, in the presence of Cu^{2+}, decomposes slowly into benzaldehyde; thus, some back-titrations with HCl solution were performed. The curves which resulted were superimposable.

RESULTS

The formation function $\bar{n}_H$ = f(pH) of the ligand suggests the existence of three protonation equilibria, the stability constants for which have been refined by the computer program MINIQUAD.[9] Values of the cumulative and stepwise protonation constants were calculated as weighted means of the values obtained in single titrations (Table 2)

TABLE 1

Initial concentrations (10^3 mol dm^{-3}) of ligand (c_L), metal (c_M), and analytical acid (c_H), and pH ranges for titrations of pse with H^+ and Cu^{2+} at 25 °C and I = 0.1 mol dm^{-3} (K)Cl

Expt. no.	Ion	c_L	c_M	c_H	pH
1	H^+	3.709 7		12.143 2	3.00—12.17
2		4.374 3		14.749 1	2.79—12.36
3		4.385 3		15.527 3	2.63—12.35
4		4.370 0		15.464 4	2.85—12.16
5		4.134 1		14.631 6	2.93—12.00
6	Cu^{2+}	4.381 7	1.092 9	14.064 5	3.04—12.14
7		4.383 4	0.546 8	14.419 6	2.90—11.69
8		4.385 0	2.170 0	15.900 0	2.56—11.98
9		4.382 8	1.526 7	15.642 2	2.61—11.92
10		4.380 3	2.168 1	17.101 8	2.40—11.75

TABLE 2

Protonation constants of L-(+)-*threo*-2-amino-1-phenylpropane-1,3-diol (pse) and related compounds at 25 °C. Standard deviations are given in parentheses

Cumulative constants [a] of pse

log β_{011} = 12.01(2), log β_{021} = 25.28(6), log β_{031} = 33.732(65)

	Stepwise constants			
Group \ Ligand	pse	DL-2-Amino-1-phenylethanol [b]	DL-4-Amino-3-hydroxybutanoic acid [c]	DL-3-Amino-2-hydroxypropanoic acid [d]
OH, log K_1	12.01 (2) [e]			
OH, log K_2	13.22 (2) [f]	11.90	13.0 ± 0.1	13.2 ± 0.1
NH_3^+, log K_3	8.446 (3)	8.79	9.487(11)	9.139 (21)

$-\log K_w = 13.756$

[a] $\beta_{0qr} = [H_qL_r]/[H]^q[L]^r$. [b] Ref. 4. [c] Ref. 1. [d] Ref. 2. [e] Range: ±0.05. [f] Range: ±0.04.

The titration curves of the protonated ligand, $[H_3L]^+$, in the presence or in the absence of Co^{2+}, Ni^{2+}, and Zn^{2+} do not differ significantly from each other. In contrast, the curve in the presence of Cu^{2+} is clearly different from that of the ligand and the equivalence point of the NH_3^+ group is shifted with respect to that of the protonated ligand alone (Figure 1). The shifts, Δ in mmol of K[OH], are twice the number of mmol of copper(II) present. This behaviour is compatible with two alternative couples of reactions (1), (2) and (1′), (2′), with a net gain of two protons in both cases. Equilibria (1) and (1′) refer to the deprotonation of NH_3^+, equilibrium (2) involves the ionisation of NH_3^+ and of both OH groups, and equation (2′) involves the ionisation of

$$\text{ligand only} \quad [H_3L]^+ \rightleftharpoons H_2L + H^+ \qquad (1)$$

$$\text{ligand + metal} \quad Cu^{2+} + [H_3L]^+ \rightleftharpoons [CuL] + 3H^+ \qquad (2)$$

$$\text{ligand only} \quad 2[H_3L]^+ \rightleftharpoons 2H_2L + 2H^+ \qquad (1')$$

$$\text{ligand + metal} \quad Cu^{2+} + 2[H_3L]^+ \rightleftharpoons [Cu(HL)_2] + 4H^+ \qquad (2')$$

NH_3^+ and one OH, probably that adjacent to the phenyl group.

The formation functions $\bar{n}$, calculated on the assumption that the complexes were unprotonated, roughly indicate the possible existence of complexes with metal to ligand ratios of 1 : 1 and 1 : 2, but their irregular features suggest the presence of protonated or dimeric complexes. Various models were consequently tested in the refinement using the program MINIQUAD. No dimeric species could be confirmed, whereas the 'hydrogenated' species $[Cu(H_2L)]^{2+}$, $[Cu(HL)]^+$, $[Cu(HL)_2]$, $[Cu(OH)(HL)]$, $[Cu(HL_2)]^-$ were suggested. The species $[Cu(HL_2)]^-$ is however uncertain.

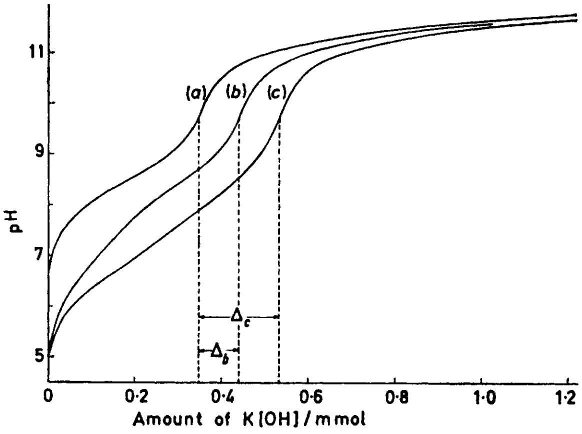

FIGURE 1 Titration curves of pse in the absence and in the presence of Cu^{2+}: (*a*) pse, (*b*) pse : Cu^{2+} = 8 : 1, (*c*) pse : Cu^{2+} = 8 : 2 at a constant concentration of pse (0.350 82 mmol). Δ_b and Δ_c are shifts of the equivalence points in solutions (*b*) and (*c*), respectively

The program was applied separately to each titration, as was the case in the refinement of the glycinate–proton–nickel(II) system.[8] This method of refinement permits the identification of experimental errors specific to each titration. Values of the cumulative formation constants (Table 3) and of the stepwise equilibrium constants (Table 4) were obtained as weighted means of the values in single titrations.

All the calculations were made on the computer CDC CYBER 70/76 of the Consorzio Interuniversitario dell'Italia Nord-Orientale, Bologna. A complete list of the experimental data is available as Supplementary Publication No. SUP 22397 (13 pp.).*

DISCUSSION

Protonation Equilibria.—The protonation constants of the two hydroxyl groups of pse can be determined only approximately due to the levelling effect of the strong base $[OH]^-$, and to other factors in alkaline solutions. These two stepwise constants have values which vary in a way opposite to that expected for successive constants in polyprotic acids. Nevertheless, the order log K_1 = 12.01 < log K_2 = 13.22 has been confirmed by several experiments and computer trials. Some caution is required in attributing precise chemical meaning to log K_1 and log K_2. At any rate, log K_2 corresponds to the values obtained for hydroxyl groups of other compounds, namely DL-4-amino-3-hydroxybutanoic acid (log K 13.0)[1] and DL-3-amino-2-hydroxypropanoic acid (log K 13.2).[2]

TABLE 3

Comparison of cumulative formation constants[a] of Cu^{II} with different aminoethanol derivatives at 25 °C. Standard deviations are given in parentheses

	(A)[b]	(B)[c]	(C)[d]	(D)[e]
log β_{121}	29.73 (2)			24.120 (53)
log β_{111}	23.54 (1)			
log β_{101}	16.13 (6)	9.50	12.961 (43)	
log β_{122}	44.54 (13)			
log β_{202}			28.696 (70)	34.568 (22)
log β_{102}		15.50	18.856 (21)	19.462 (124)
log β_{112}	32.56 (25)			

[a] $\beta_{pqr} = [M_pH_qL_r]/[M]^p[H]^q[L]^r$. [b] (A) = L-(+)-*threo*-2-amino-1-phenylpropane-1,3-diol (H_2L). [c] (B) = DL-2-Amino-1-phenylethanol (HL), ref. 5. [d] (C) = DL-4-Amino-3-hydroxybutanoic acid (H_2L), ref. 1. [e] (D) = DL-3-Amino-2-hydroxypropanoic acid (H_2L), ref. 2.

TABLE 4

Comparison of stepwise stability constants of Cu^{II} with different aminoethanol derivatives at 25 °C. Standard deviations are given in parentheses

Ligand *	Reaction	log K
(A)	$Cu^{2+} + [HL]^- \rightleftharpoons [Cu(HL)]^+$	11.53 (1)
(B)	$Cu^{2+} + L^- \rightleftharpoons [CuL]^+$	9.50
(C)	$Cu^{2+} + L^{2-} \rightleftharpoons [CuL]$	12.961
(D)		
(A)	$[Cu(HL)]^+ + [HL]^- \rightleftharpoons [Cu(HL)]_2$	8.99 (17)
(B)	$[CuL]^+ + L^- \rightleftharpoons [CuL_2]$	6.0
(C)	$[CuL] + L^{2-} \rightleftharpoons [CuL_2]^{2-}$	5.895
(D)		
(A)	$Cu^{2+} + 2[HL]^- \rightleftharpoons [Cu(HL)_2]$	20.54 (13)
(B)	$Cu^{2+} + 2L^- \rightleftharpoons [CuL_2]$	15.50
(C)	$Cu^{2+} + 2L^{2-} \rightleftharpoons [CuL_2]^{2-}$	18.856
(D)	$Cu^{2+} + 2L^{2-} \rightleftharpoons [CuL_2]^{2-}$	19.462

* See footnotes *b*—*e* in Table 3.

The protonation constant of the amine group of pse (log K_3 8.446) is in good agreement with that of DL-2-amino-1-phenylethanol (log K 8.79).[4] The value calculated according to Barlin and Perrin[10] is log K = 8.11.

Copper(II) *Complexes.*—The complexes actually formed are $[Cu(H_2L)]^{2+}$, $[Cu(HL)]^+$, $[Cu(HL)_2]$, $[CuL]$ or $[Cu(OH)(HL)]$, and $[Cu(HL_2)]^-$. The constant of the hydrolysis product, $[Cu_2(OH)_2]^{2+}$, has been fixed throughout the calculations at $^*\beta_{22} = 2.5 \times 10^{-11}$ mol dm^{-3};[11] the fraction of hydrolysed species never exceeded 6.4% of the total Cu^{II}. A typical distribution diagram is shown in Figure 2.

The complex $[Cu(H_2L)]^{2+}$ can be seen as a simple amine complex. This is confirmed by the value of the equilibrium constant log $K\{Cu^{2+} + H_2L \rightleftharpoons [Cu(H_2L)]^{2+}\}$ = 4.45 which is comparable with that of

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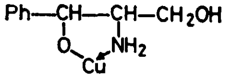
* For details see Notices to Authors No. 7, *J.C.S. Dalton*, 1978, Index issue.

ammonia (log K 4.16).[12] The complexes $[Cu(HL)]^+$ and $[Cu(HL)_2]$ can be assigned five-membered chelate rings,



as indicated by the crystal structure of the solid complex $[Cu(HL)_2(OH_2)]\cdot4H_2O$ [13] where the Cu^{II} has a distorted square-pyramid co-ordination, with an oxygen atom of a water molecule in the apical position. The species [CuL] or [Cu(OH)(HL)] and $[Cu(HL_2)]^-$ also belong to this type of chelate complex but differ in the dissociation of the second OH group of the ligand or in the dissociation of the co-ordinated water, as shown below.

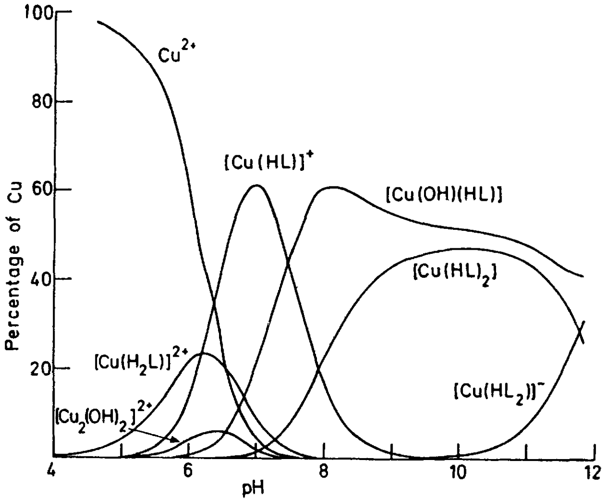


FIGURE 2 Typical distribution diagram for the Cu^{2+}–pse system. Data from experiment (8) (Table 1)

The stepwise formation constants of $[Cu(HL)]^+$ and $[Cu(HL)_2]$ can be compared with those of other aminoethanols (Table 4). The value log $K = 11.53$ can be compared with log $K = 9.50$ for DL-2-amino-1-phenylethanol [5] and log $K = 12.961$ for DL-4-amino-3-hydroxybutanoic acid.[1] The second partial formation constant, log $K = 8.99$, is larger than log $K = 6.0$ for DL-2-amino-1-phenylethanol [5] and log $K = 5.895$ for DL-4-amino-3-hydroxybutanoic acid.[1] It seems therefore that the binding of the second ligand is favoured in pse with respect to other ethanolates, but here also the steric conditions should be taken into account because the present compound is not racemic.

The species [CuL] and $[Cu(HL_2)]^-$ deserve special comment. The former can be also written as [Cu(OH)(HL)], thus indicating the dissociation of one co-ordinated water molecule. In fact, log K $\{[Cu(OH)(HL)] + H^+ \rightleftharpoons [Cu(HL)(OH_2)]^+\} = 7.42$ falls in the range 7.5 ± 0.3 assigned by Martell *et al.*[14] to such processes. The species $[Cu(HL_2)]^-$ seems to be derived from $[Cu(HL)_2]$ by deprotonation of one of the two hydroxyl groups. The value log $K\{[Cu(HL_2)]^- + H^+ \rightleftharpoons [Cu(HL)_2]\} = 11.98$ falls in the range of the constants of the hydroxyl groups of the ligand.

Spectroscopic Properties.—Solutions of pse and Cu^{2+} show at pH *ca.* 7.8 a change of colour from blue to violet. The absorption spectrum indicates that one maximum shifts from 660 nm at pH *ca.* 6.5 to 600 nm at pH *ca.* 8.5 and at the same time a shoulder appears at *ca.* 530 nm.

The reflectance spectrum of solid $[Cu(HL)_2(OH_2)]\cdot4H_2O$ shows a maximum at *ca.* 510 nm with a shoulder at *ca.* 590 nm, and apparently corresponds to the spectra of the solutions at high pH. This is in agreement with the spectroscopic behaviour of solutions of Cu^{2+} and DL-4-amino-3-hydroxybutanoic acid [1] and of Cu^{2+} with DL-3-amino-3-hydroxypropanoic acid,[2] and also with the behaviour of the copper(II) complex of glycylglycyl-L-histidine-N-methylamide ($\lambda_{max.}$ 525 nm).[15]

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