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Equilibrium Constants of DL-2-amino-4-hydroxybutyric Acid and its Chelates with Divalent Metals

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The equilibrium constants of DL-2-amino-4-hydroxybutyric acid (homoserine = hoser) have been determined potentiometrically; at 25°C ±0.1 and $\mu = 0.1$ M *KCl, they are log* $K_1 = 9.257$ *(1), log* $K_{12} = 2.265$ *(1). The dependence upon ionic strength in the range 0.1—2* M *KCl and upon temperature in the range 5—30°C have been also determined. The thermodynamic functions* $\Delta H_1 = 10.9$ *(4) kcal . mole*$^{-1}$, $\Delta S_1 = 5.9$ *(15) cal . mole*$^{-1}$ *. degree*$^{-1}$ *and* $\Delta H_{12} = 0.3(4)$ *kal . mole*$^{-1}$, $\Delta S_{12} = 11.4$ *(13) cal . mole*$^{-1}$ *. degree*$^{-1}$ *are comparable with those of serine and threonine.*

The ligand forms with metals the complexes: Mn(hoser)$^+$*; Co(hoser)*$^+$*, Co(hoser)*$_2$*; Ni(hoser)*$^+$*, Ni(hoser)*$_2$*, Ni(hoser)*$_3^-$*; Cu (hoser)*$^+$*, Cu(hoser)*$_2$*; Zn(hoser)*$^+$*, Zn(hoser)*$_2$*, Cd(hoser)*$^+$*. The equilibrium constants follow the Irving-Williams series. All the complexes contain very likely pentatomic chelate rings. By comparison with crystal structures of solid complexes and by considering the values of log* K_n/K_{n+1} *some hypotheses are put forward on the structures of the complexes.*

Introduction

DL–2–amino-4–hydroxybutyric acid (homoserine = hoser) is an α-aminoacid and is therefore capable to form pentatomic chelate rings with metals. Such compounds should be analogous to those formed by glycine and by hydrazinecarboxylic acid, thiocarbohydrazide and other ligands studied by us both in the solid state[1,2,3,4] and in solution.[5,6,7]

Experimental Section

Materials. Reagent grade purity substances were employed without further purification. Bidistilled boiled water has been used throughout.

Solutions. A stock solution of hydrochloric acid was prepared and its concentration (0.11 *M*) determined titrimetrically with 2–amino–2–(hydroxymethyl)–1,3–propandiol. A stock solution of KOH (0.29 *M*) was prepared by diluting concentrated KOH (BDH production) by CO_2–free water and its titre checked against potassium hydrogenphtalate. Each equivalent point was determined by Gran's method,[8] the line of best fit being calculated by least squares. The stock solutions of divalent metal chlorides were determined by conventional analytical methods. Each solution to be titrated was prepared by subsequent addition of a weighed amount of homoserine, exact volumes of hydrochloric acid and metal chloride solutions, as much solid potassium chloride as required to keep the ionic strength at the chosen value and water. The initial volume of the aqueous solution was 99.695 ± 0.013 ml in each titration. The total volumes of the titrant KOH solution were 3-5 ml subdivided by a Metrohm pistonburette into 25-40 steps, measured with precision ±0.005 ml.

Potentiometric Measurements. Potentiometric determinations were performed by a digital potentiometer Radiometer PHM52, equipped with G 2025B and G 202C glass electrodes. Calomel electrode sat. KCl was used as reference. Temperature was maintained at the chosen value within ±0.1°C by circulation of thermostated water.

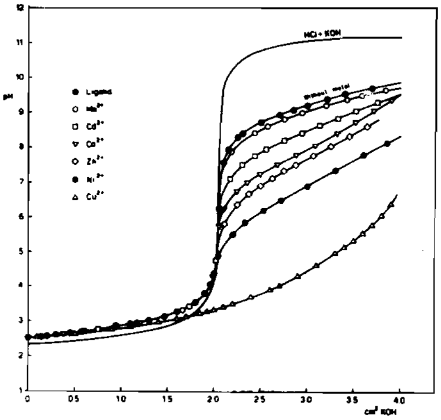

Figure 1. Representation of the titration curves 1, 9, 12, 16, 19, 24 and 27 of Table I.

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[1] A. Braibanti, A.M. Manotti Lanfredi, A. Tiripicchio, and F. Bigoli, *Acta Cryst.*, B26, 806 (1970)

[2] A. Braibanti, A. Tiripicchio, A.M. Manotti Lanfredi, and M. Camellini, *Acta Cryst.*, 23, 248 (1967).

[3] A. Braibanti, A.M. Manotti Lanfredi, A. Tiripicchio, and F. Bigoli, *Acta Cryst.*, B25, 100 (1969).

[4] A. Braibanti, A. Tiripicchio, and A.M. Manotti Lanfredi, *Zeit. Kristallogr.*, *124*, 335 (1967).

[5] A. Braibanti, E. Leporati, F. Dallavalle, and M.A. Pellinghelli, *Inorg. Chim. Acta*, 2, 449 (1968).

[6] A. Braibanti, F. Dallavalle, and E. Leporati, *Inorg. Chim. Acta*, 3, 459 (1969).

[7] A. Braibanti, E. Leporati, and F. Dallavalle, *Inorg. Chim. Acta*, 4, 529 (1970.

[8] G. Gran, *Analyst*, 77, 661 (1952).

Table I. Initial concentrations(m*M*),$-\log[H^+]$ and $\bar{n}$ ranges for the titrations.

Curve	Ion	MCl_2	hoser	T_H	$-\log[H^+]$	$\bar{n}$
1	H^+		0.46330	0.92658	2.522-9.666	
2			0.24286	0.48580	2.737-9.806	
3			0.59232	1.18471	2.448-9.613	
4			0.37163	0.74334	2.578-9.843	
5	Ni^{2+}	0.10607	0.42124	0.84254	2.558-9.808	0.0-2.4
6		0.10281	0.51409	1.02822	2.485-9.661	0.0-2.2
7		0.13463	0.40387	0.80773	2.566-9.799	0.0-2.0
8		0.30892	0.30884	0.61774	2.664-7.448	0.0-1.0
9		0.22173	0.46330	0.92660	2.517-10.239	0.0-2.0
10	Co^{2+}	0.24726	0.24789	0.49586	2.720-8.839	0.0-1.0
11		0.11589	0.34830	0.69668	2.608-9.901	0.0-1.7
12		0.22404	0.46328	0.92658	2.519-9.446	0.0-1.6
13		0.10745	0.53755	1.07489	2.465-9.252	0.0-1.8
14	Cu^{2+}	0.18053	0.54154	1.08315	2.449-9.564	0.0-1.8
15		0.29995	0.29994	0.59991	2.634-6.461	0.0-1.2
16		0.23165	0.46330	0.92660	2.507-10.386	0.0-1.7
17		0.09352	0.37390	0.74771	2.573-9.301	0.0-1.9
18	Mn^{2+}	0.10875	0.54565	1.09137	2.458-9.517	0.0-0.6
19		0.22735	0.46330	0.92658	2.515-9.292	0.0-0.6
20		0.11860	0.35903	0.71796	2.603-7.451	0.0-0.3
21		0.09389	0.39513	0.79030	2.569-9.377	0.0-0.5
22	Zn^{2+}	0.24424	0.24439	0.84019	2.318-7.593	0.0-0.7
23		0.11987	0.36027	1.32385	2.605-7.925	0.0-1.6
24		0.23157	0.46330	1.02820	2.412-7.681	0.0-1.5
25		0.11689	0.52328	1.00443	2.509-8.766	0.0-1.7
26	Cd^{2+}	0.32667	0.32634	0.77828	2.470-8.537	0.0-0.4
27		0.23062	0.46330	0.93390	2.304-9.042	0.0-0.6
28		0.11757	0.35266	0.71720	2.591-9.674	0.0-0.6
29		0.10852	0.43602	0.87518	2.527-9.864	0.0-0.6

The concentration ranges for each titration are reported in Table I. Typical titration curves are drawn in Figure 1.

Calculations

The protonation constants have been calculated using the program LGST prepared by Vacca;[9] this program minimizes the sum of squares of the residuals $\Sigma(\nu_c-\nu_o)^2$ where ν_c and ν_o are the calculated and measured volumes of the titrant KOH solution at each point. The program has been completed by us with an analysis of variance applied to the distribution of the residuals as function of ν_o, in order to ascertain if the distribution is, or is not, normal with mean $\bar{m}=0$. The formation constants of the complexes have been refined using the program GAUSS Z prepared by Tobias.[10] This program minimizes the function $\Sigma(\bar{n}_c-\bar{n}_o)^2$; also this program has been completed by an analysis of the distribution of $(\bar{n}_c-\bar{n}_o)$ as function of $\bar{n}_o$. All the calculations have been performed on the computer CDC 6600 of Consorzio Interuniversitario dell'Italia Nord-Orientale, Bologna.

Discussion

Protonation Equilibria. The HO–group does not possess either acidic or basic properties, at least in the solution considered. This is confirmed also by the behaviour of homoserine with varying ionic strength, which is perfectly analogous to htat of non-hydroxyaminoacids. The protonation constants at different

Table II.[a] Protonation constants of homoserine at different ionic strengths at 25°C.

$\mu(M)$ KCl	$\log K_1$ observed	$\log K_1$ calculated[b]	$\log K_{12}$ observed	$\log K_{12}$ calculated[c]
0.034	9.301(1)	9.294	2.230(1)	2.237
0.100	9.257(1)	9.274	2.265(1)	2.247
0.250	9.275(2)	9.264	2.250(2)	2.264
0.500	9.272(2)	9.275	2.290(2)	2.290
1.000	9.335(3)	9.333	2.348(3)	2.342
1.500	9.406(2)	9.412	2.391(1)	2.396
2.000	9.502(2)	9.501	2.452(2)	2.452

[a] In each Table the e.s.d.'s are reported in parenthesis in units of the last decimal digit. [b] Values calculated from the equation (1). [c] Values calculated from the equation (2).

Table III. Dependence of the protonation constants of homoserine upon temperature. Ionic strength, μ = 0.1 *M* KCl.

Temperature t°C	$\log K_1$ observed	$\log K_1$ calculated[a]	$\log K_{12}$ observed	$\log K_{12}$ calculated[a]
5°	9.843(3)	9.846	2.258(3)	2.246
10°	9.712(3)	9.685	2.210(4)	2.240
15°	9.506(1)	9.533	2.239(3)	2.238
20°	9.379(2)	9.388	2.253(3)	2.238
25°	9.257(1)	9.251	2.265(1)	2.241
30°	9.127(1)	9.120	2.223(1)	2.246

[a] Values calculated from the equation (3).

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(9) A. Vacca, private communication.
(10) R.S. Tobias and M. Yasuda, *Inorg. Chem.*, *2*, 1307 (1963).

Table IV. Thermodynamic functions for protonation equilibria of homoserine, serine and threonine.

Compound	ΔH_1 kcal - mole^{-1}	ΔS_1 cal · degree^{-1} · mole^{-1}	ΔH_{12} kcal . mole^{-1}	ΔS_{12} cal · degree^{-1} · mole^{-1}
glycine [a]	—10.55	9.05	—0.95	7.56
serine [a]	—10.35	7.41	—1.32	5.57
homoserine [b]	—10.9(4)	5.9(15)	0.3(4)	11.4(13)
threonine [c]	—10.04(10)	8.0	—1.36(10)	5.0

[a] μ = 0.0 potentiometric method (13,14). [b] μ = 0.1 *M* KCl potentiometric method (present work). [c] μ = 0.0 calorimetric method (15).

Table V. Formation constants of homoserine complexes with divalent metals compared with those of serine and threonine. t = 25°C and μ = 0.1 *M* KCl.

Metal	Constant	Homoserine	Serine [a]	Threonine [a]
Mn^{2+}	log K_1	2.468(11)	2.51 [b]	2.59 [b]
Co^{2+}	log K_1	4.300(21)	4.33	4.43
	log K_2	3.512(18)	3.33	3.41
Ni^{2+}	log K_1	5.403(9)	5.42	5.51
	log K_2	4.519(9)	4.34	4.43
	log K_3	2.6	—	—
Cu^{2+}	log K_1	7.930(11)	7.89	8.06
	log K_2	6.491(16)	6.51	6.63
Zn^{2+}	log K_1	4.454(17)	4.66	4.74
	log K_2	3.522(19)	3.72	3.77
Cd^{2+}	log K_1	3.694(27)	—	—

[a] μ = 0.2 *M* KNO_3 (16); [b] at 15°C (16).

ionic strengths are quoted in Table II. The values obtained (Figure 2) show a trend perfectly analogous to that of glycine;[11] they can be represented by the empirical relations:

$$\log K_1 = 9.338 — 0.292\mu^{1/2} + 0.285\mu + 0.002\mu^{3/2} \quad (1)$$

$$\log K_{12} = 2.228 + 0.042\mu^{1/2} + 0.047\mu + 0.025\mu^{3/2} \quad (2)$$

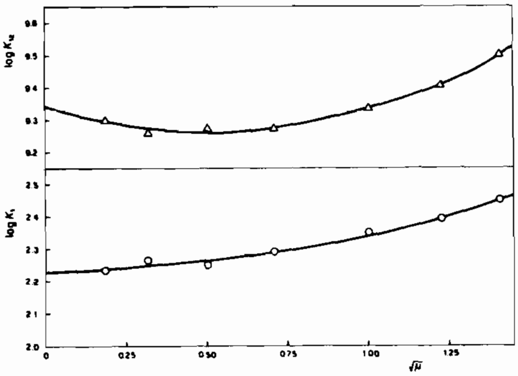

Figure 2. Dependence of the protonation constants of homoserine on ionic strength at 25°C. Curves have been calculated by equations (1) and (2).

The dependence of the protonation constants upon temperature (Table III) is represented by a relation proposed by Pitzer:[12]

$$\log K = \frac{A}{T} - B + 20 \log T \quad (3)$$

with $A_1 = 4965.6$, $B_1 = -56.892$ and

$A_{12} = 2521.4$, $B_{12} = -55.705$

where the indices refer to K_1 and K_{12} respectively, with standard deviation σ (log K_1) = 0.01 and σ (log K_{12}) =

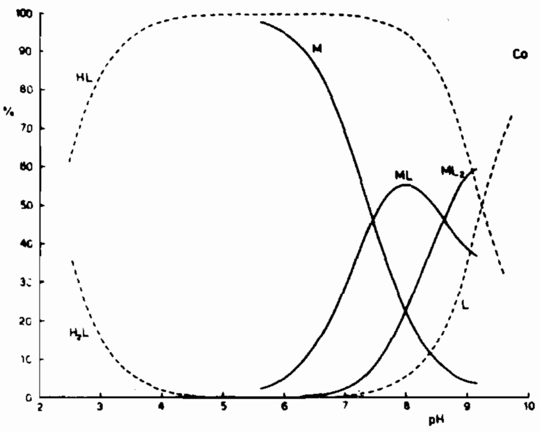

Figure 3. Representative distribution diagram for Co-hoser system. The percentages have been calculated from the data of curve 12 in Table I. Broken lines show species not containing metal and the percentages relative to total ligand have been calculated from the data of curve 1 in Table I.

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(11) E.J. King, *J. Am. Chem. Soc.*, *67*, 2178 (1945).
(12) K.S. Pitzer, *J. Am. Chem. Soc.*, *56*, 2365 (1937).
(13) E.J. King, *J. Am. Chem. Soc.*, *73*, 155 (1951).
(14) P.K. Smith, A.T. Gorham, and E.R.B. Smith, *J. Biol. Chem.*, *144*, 737 (1942).
(15) R.M. Izatt, J.J. Christensen, and V. Kothari, *Inorg. Chem.*, *3*, 1565 (1964).

0.009. The thermodynamic functions at 25°C have been calculated by differentiating (3) with respect to temperature and then compared with values obtained for other aminoacids in Table IV.

Metal Complexes Equilibria. The analysis and refinement of the formation constants of the complexes formed by hoser with Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} show that the following complexes are formed:

$Mn(hoser)^+$
$Co(hoser)^+$, $Co(hoser)_2$
$Ni(hoser)^+$, $Ni(hoser)_2$, $Ni(hoser)_3^-$
$Cu(hoser)^+$, $Cu(hoser)_2$
$Zn(hoser)^+$, $Zn(hoser)_2$
$Cd(hoser)^+$

Representative distribution functions are presented for Co^{2+} (Figure 3), Ni^{2+} (Figure 4), Cu^{2+} (Figure 5).

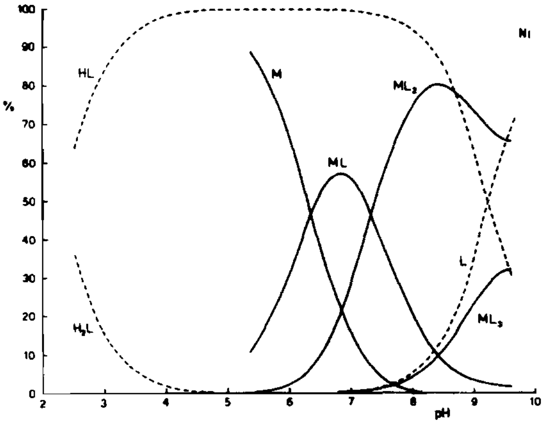


Figure 4. Representative distribution diagram for Ni-hoser system. The percentages have been calculated from the data of curve 5 in Table I. Broken lines show species not containing metal and the percentages relative to total ligand have been calculated from the data of curve 1 in Table I.

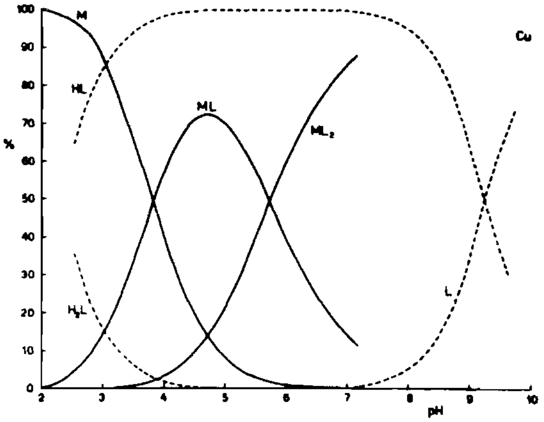
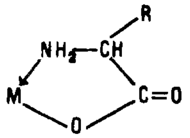


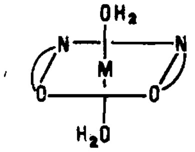
Figure 5. Representative distribution diagram for Cu-hoser system. The percentages have been calculated from the data of curve 16 in Table I. Broken lines show specie not containing metal and the percentages relative to total ligand have been calculated from the data of curve 1 in Table I.

The refined constants are reported in Table V and compared with corresponding constants of serine[16] and threonine.[16] The results for the three ligands agree fairly well.

Each ligand molecule can be assumed to be bound in such a way to form pentatomic chelate rings

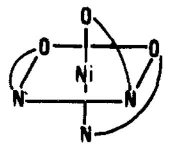


The succession of log K_1 values is in accordance with Irving-Williams series. The absence of complexes higher than those 1:1 for Mn^{2+} and Cd^{2+} can be due to the radii of these ions, which are large in comparison with the aperture N . . . . . O of the entering molecule; «biting» by the chelating ligand of the ion would require an extra energy, not available for the second ligand molecule. The small differences in log K_1/K_2 for Co^{2+} (log $K_1/K_2=0.79$) for Ni^{2+} (log $K_1/K_2=0.88$) and for Zn^{2+} (log $K_1/K_2=0.93$) suggest that all complexes $M(hoser)_2$ possess the same structure, and by comparison with the analogous ligand serine, the *cis*(O),*cis*(N),*trans*(OH_2) structure found for



bis(L–serinate)nickel dihydrate by X-rays,[17] could be assigned to them. The higher value for Cu^{2+}, log $K_1/K_2=1.44$, could be explained either by Jahn-Teller effect or even by a different arrangement of the ligand. The introduction of the third molecule in the complex implies in any way a rearrangement of the ligands and this could explain both the high value of log $K_2/K_3=1.92$ for Ni^{2+} and the difficulty to get $M(hoser)_3^-$ complexes with Cu^{2+}, Co^{2+}, and Zn^{2+}.

A *cis*–octahedral structure



can be assumed for $Ni(hoser)_3^-$ by analogy with *tris*-(hydrazinecarboxylato–N',O)niccolate(II) anion.[4]

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(16) E.V. Raju and H.B. Mathur, *J. Inorg. Nucl. Chem.*, 30, 2181 (1968).
(17) D. Van der Helm and M.B. Hossain, *Acta Cryst.*, B25, 457 (1969).