4,5,6,7-Tetrahydroindazol-3-one Carboxylic Acids. VI. Complexing Behaviour of 5,5-Dicarboxylic Acid with Divalent Metal Ions

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The synthesis and properties of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (HIDA, I), its diammonium, II, and monoammonium salt, III, are described. The concentration stability constants of HIDA with Be^{++}, Mg^{++}, Ca^{++}, Sr^{++}, Ba^{++}, Cu^{++}, Co^{++}, Mn^{++}, Zn^{++}, and Cd^{++} are reported.

The potentiometric titration curves and UV and IR absorption data are recorded.

It was not possible to complete the earlier investigations of 4,5,6,7-tetrahydroindazol-3-one carboxylic acids[1,2] mainly because we were unable to synthesize 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (HIDA, I). We wish now to report the most convenient route for the synthesis of HIDA. The diethyl ester of HIDA was hydrolysed in hydrochloric acid and the hydrochloride converted in aqueous ammonia into diammonium salt (II) and, by a cation exchanger, into diacid I in a nearly quantitative yield. On addition of iodine[3] a benzene solution of diammonium salt II gave the monoammonium salt, III, of diacid I assuming, on the basis of pK values (Table I), a free carboxylic group to be axial.

I   R = R$_1$ = R$_2$ = H
II R = H, R$_1$ = R$_2$ = NH$_4$
III R = R$_2$ = H, R$_1$ = NH$_4$
IV R = Ph, R$_1$ = R$_2$ = H

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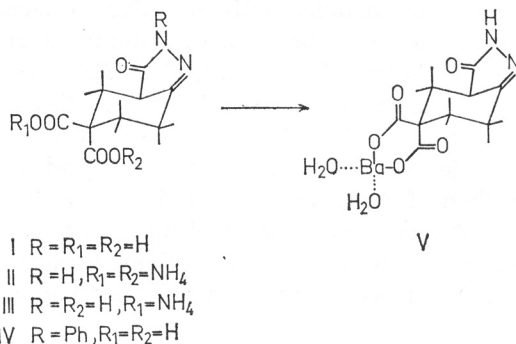
* Taken from the thesis submitted by V. Turjak-Zebić, in partial fulfilment of the requirements for degree of Doctor of Chemistry at the University of Zagreb.

As with 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (FIDA, IV), there was a significant difference in the acidity of the two carboxylic groups (Table I) in HIDA, ΔpK 2.68 (FIDA having ΔpK 2.74). McDaniel and Brown[4] pointed out that apart from electrostatic effects there is a possibility of forming intramolecular hydrogen bonding between carboxylic groups which stabilizes the carboxylate group resulting in an increased tendency for ionization of the first proton and a decreased tendency for ionization of the second.

TABLE I

Apparent pK Values of Indazolone Dicarboxylic Acids at 25⁰ C

Compound	e-COOH (pK_1)	a-COOH (pK_2)	$C \times 10^{-3}$ (M)	H_2O to $O(CH_2CH_2)_2O$ (v/v)
I	5.14	7.82	1.08	1 : 1
	3.72	5.70	1.00	H_2O only
III	—	5.67	1.92	H_2O only
IV	5.05	7.79	1.01	1 : 1
Malonic	4.16	8.20	1.04	1 : 1
acid[2]	2.99	5.62	3.99	H_2O only

The high solubility of HIDA and its diammonium salt II might find particular application in direct complexing with metals. A concentrated aqueous solution of compound II gives a crystalline precipitate with barium which suggests a direct possibility for separating this metal from other alkaline earth metals. The elemental analysis confirms the composition of the precipitate as well as the 1 : 1 ratio of Ba⁺⁺ to ligand. The same structure was proposed for 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (FIDA, IV)--barium complex[2].

The investigation of interactions of HIDA with alkaline earth metals by potentiometric titration, for instance with Sr⁺⁺ (Fig. 1), clearly shows the formation of metal-ligand species. The data of potentiometric titrations in the presence of divalent metals Be⁺⁺, Mg⁺⁺, Cu⁺⁺, Co⁺⁺, Mn⁺⁺, Zn⁺⁺, Cd⁺⁺ within the 3.5 to 7.0 pH range confirms the complexing properties of HIDA. The concentration stability constants for the 2 : 1 molar ratio (ligand-metal) were determined by the Bjerrum method[5] at ñ = 0.5, and for the 1 : 10 ratio according to the method of Schwarzenbach and Ackermann[6] in water-dioxane (1 : 1, v/v) (Table II). The concentration stability constants of protonated complexes were also determined by the method of Schwarzenbach and Ackermann[6] and it might be expressed according to our earlier paper[2] by the following equation:

$$K_{k_1}^{M} = \frac{[MH_2A^+]}{[M^{2+}][H_2A^-]}$$

Except for the Cd⁺⁺-HIDA complex, both approaches gave the same or very

similar results for the concentration stability constants (log $K_{k_2}^M$), which are defined as:

$$K_{k_2}^M = \frac{[MHA]}{[M^{2+}][HA^{2-}]}$$

The stability constant for Cd^{++}-HIDA complex was not calculated with the desired accuracy because of the rapid precipitation which occurs at pH 5.5. Table II shows that Mg^{++} has the lowest value for the stability constant within the group of alkaline earth metals. The stability constants of HIDA with transition metals follows Irving-Williams' order[7], $i. e.$ Zn < Cu > Co > Mn. Because of hydrolysis, it is not possible to determine by this method the stability constants for Be^{++} and Cu^{++} at the 1 : 10 ratio. For the evaluation of stability constants (log $K_{k_2}^M$), the potentiometric titration curves for HIDA-Sr^{++} (Fig. 1), — Mn^{++} (Fig. 2), and —Zn^{++} (Fig. 3) interactions are illustrated as the most typical.

The calculations of $K_{k_2}^M$, shown in Table II, for 2 : 1 molar ratio ligand to metal, might be achieved from degree of formation, ñ, for HIDA-metal
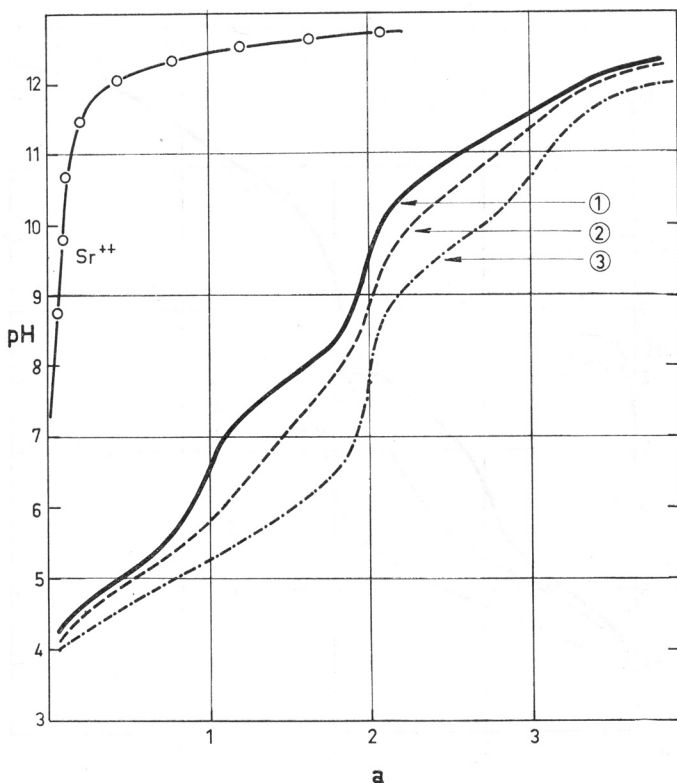

Fig. 1. Potentiometric titration of 1) HIDA, 2) HIDA-Sr^{++} system at molar ratios 2 : 1, 3) 1 : 10. Abscissa a = moles of NaOH added per mole of HIDA. Curves 1—3 refer to the systems that are 1×10^{-3} M in HIDA.

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TABLE II

Concentration Stability Constants of Metal Complexes at 25⁰ C in 50% v/v water-dioxane mixture

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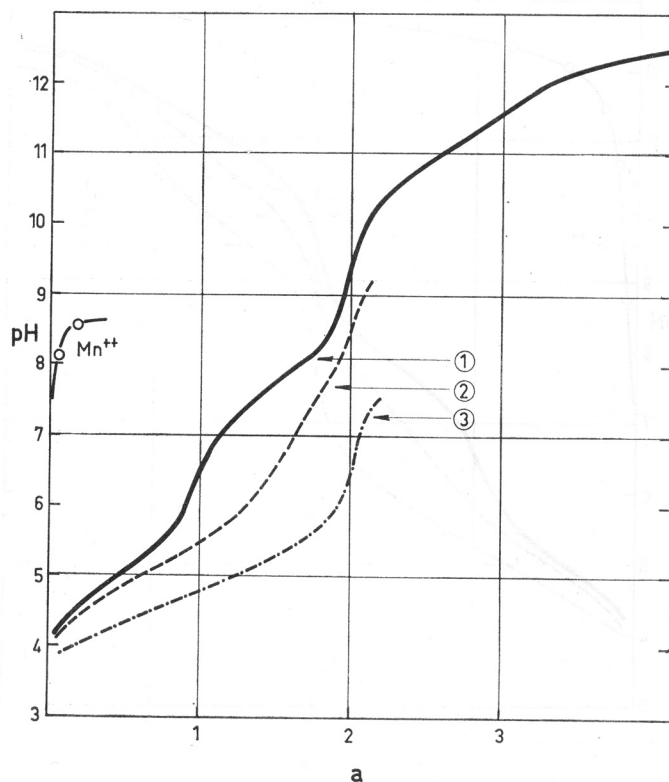| Metal ion	HIDA to metal ratio		
	molar ratio 2 : 1	molar ratio 1 : 10	
	$\log K_{k_2}^{M}$	$\log K_{k_2}^{M}$	$\log K_{k_1}^{M}$
Be⁺⁺	8.85	—	—
Mg⁺⁺	4.33	4.27	2.15
Ca⁺⁺	4.73	4.63	2.38
Sr⁺⁺	4.57	4.41	2.30
Ba⁺⁺	4.58	4.46	2.30
Cu⁺⁺	8.45	—	—
Co⁺⁺	5.50	5.31	2.59
Mn⁺⁺	5.27	5.26	2.53
Zn⁺⁺	5.91	5.62	2.63
Cd⁺⁺	∼ 5.2	5.91	2.91

Fig. 2. Potentiometric titration of 1) HIDA, 2) HIDA-Mn⁺⁺ system at molar ratios 2 : 1, 3) 1 : 10. Abscissa a = moles of NaOH added per mole of HIDA. Curves 1—3 refer to the systems that are 1×10^{-3} *M* in HIDA.

a
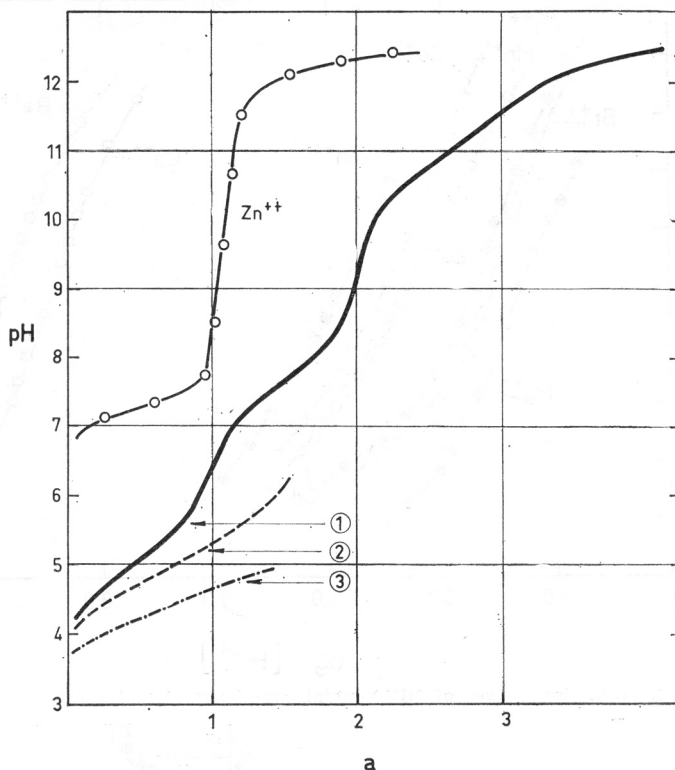
Fig. 3. Potentiometric titration of 1) HIDA, 2) HIDA-Zn++ system at molar ratios 2 : 1, 3) 1 : 10. Abscissa a = moles of NaOH added per mole of HIDA. Curves 1—3 refer to the systems that are 1×10^{-3} M in HIDA.

interactions according to the earlier work[2]. Formation curves for all the metal-ligand systems investigated are shown in Fig. 4.

The value of K_M^{ZH} for 1 : 10 molar ratio ligand to metal can be computed according to Schwarzenbach and Ackermann[6] by constructing diagrams analogous to that shown, as an example, in Fig. 5.

The small but advantageous difference in the stability constants for calcium and strontium, suggested an investigation of the action of HIDA and FIDA for the elimination of radioactive strontium from biological systems. Preliminary investigations had already suggested their application in the treatment of contaminated organisms.

The qualitative investigation of the interactions of 4,5,6,7-tetrahydroindazol-3-one monocarboxylic acids (4-, 5-, and 7-carboxy isomers)[3] with the alkaline earth metals by means of potentiometric titration, in the pH range of enol formation shows the order of the stability of the complexes as Ca > Sr > Ba. The best complexing ligand was found to be a 4-carboxy isomer. The fact that ethyl esters of the monoacids do not interact with metal ions in the pH range of the enol form corroborates the conclusion that for this type of complexing a free carboxylic acid group is required. It may also be noted that 2-phenyl derivatives of these isomers enter into interactions at lower pH values.
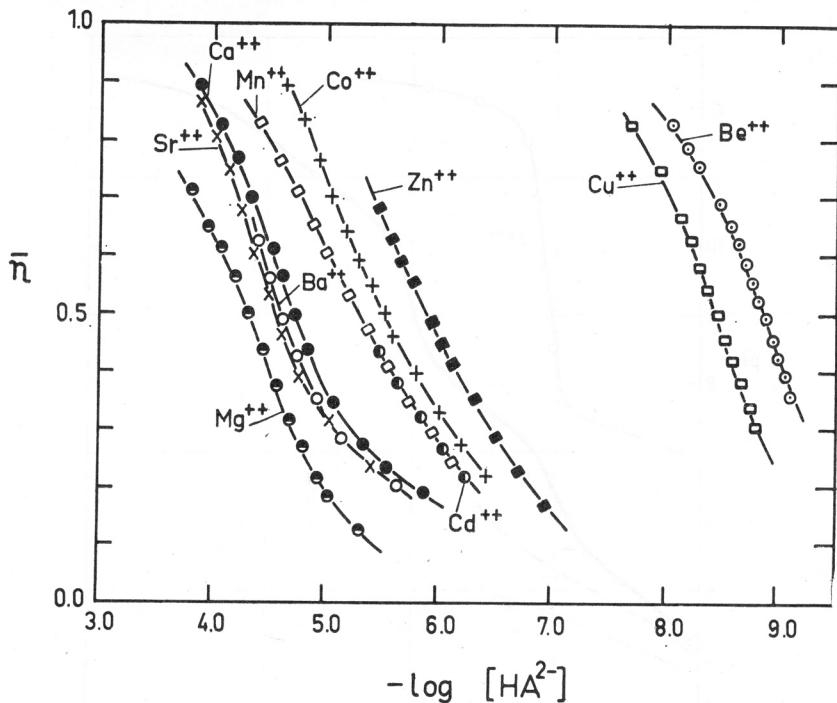
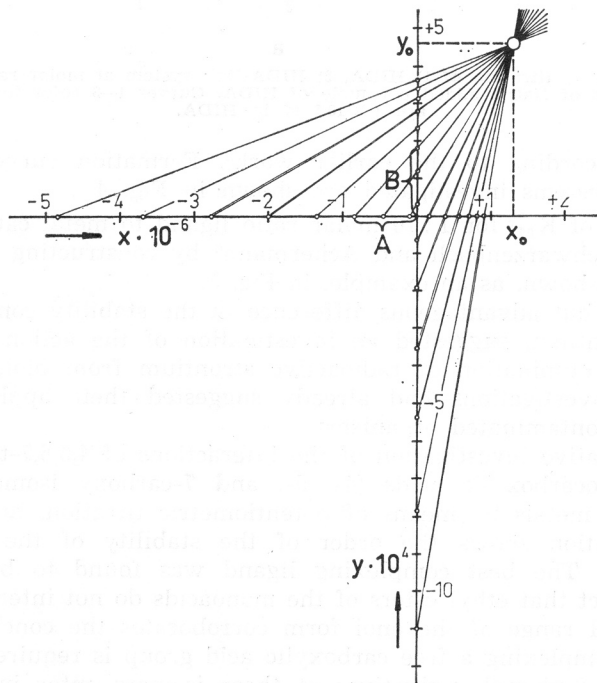Fig. 4. Formation curves of HIDA-metal complexes at molar ratios 2 : 1.

Fig. 5. Graphical determination of the stability constants for HIDA-Sr⁺⁺ system at molar ratio 1 : 10. The meaning of x and y is the same as in ref. 6.

Melting points, uncorrected, were taken on a Kofler hot stage. UV spectra were measured in water with a Beckmann model DU-2 ultraviolet spectrophotometer. The IR spectra were recorded in potassium bromide pellets using a Perkin-Elmer Infracord model 137.

Conditions and Apparatus for the Determination of Dissociation and Stability Constants

The instrument and the conditions used for the potentiometric titration and determination of pK values and stability constants were the same as those described in the earlier paper[2].

Materials

The purities of the indazolone carboxylic acids and their corresponding ethyl esters were found to be at least 99 per cent by potentiometric titrations and elemental analyses.

Analytical grade $Be(NO_3)_2 \cdot 3 H_2O$ purchased from Merck was used to make up a stock solution. It was standardized by a gravimetric method as BeO.

Analytical grade $Mg(NO_3)_2 \cdot 6 H_2O$, $Mn(NO_3)_2 \cdot 6 H_2O$, and $ZnCl_2$ purchased from Hopkin and Williams and $Cd(NO_3)_2 \cdot 4 H_2O$ from Merck were used to make up stock solutions. The solutions were standardized by a standard complexometric method[8] with Eriochrome Black T as an indicator.

Analytical grade $CoCl_2 \cdot 6 H_2O$ solution, purchased from Merck, was standardized by a complexometric method with Murexide as an indicator.

Analytical grade $Ca(NO_3)_2 \cdot 4 H_2O$ and $Ba(NO_3)_2$ purchased from Merck and $Sr(NO_3)_2$ from Hopkin and Williams were used to make up stock solutions. The solutions were standardized by an ion exchange method[9]. A solution of salt was passed through the cation exchange resin (hydrogen form of Dowex 50-x). The filtrate and washings of salt solutions containing HNO_3 were titrated with 0.1 N NaOH against methyl orange.

Analytical grade of $Cu(NO_3)_2 \cdot 3 H_2O$ solution purchased from B. D. H., was standardized by an electrogravimetric method[10] and stabilized with perchloric acid.

Diammonium salt of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (II)

Diethyl 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (250 mg., 0.9 mmole) in 15% hydrochloric acid (30 ml.) was refluxed for 1 hour. The solution was evaporated to dryness under reduced pressure. The residual solid was dissolved in water (2 ml.) and treated with concentrated ammonium hydroxide to a slight alkaline reaction. This alkaline solution was evaporated to dryness and dissolved in water. A crystalline product separated on addition of ethanol. Yield 165 mg. (92%). Crystallization from water-ethanol gave the analytical sample as microcrystals, m. p. 254—256°.

Anal. $C_9H_{16}N_4O_5$ (260.25) calc'd.: C 41.53; H 6.20; N 21.53%
found: C 41.69; H 5.99; N 21.53%

UV spectrum: λ_{max} 264.5 nm, log ε 3.926, and λ_{min} 218.5 nm, log ε 3.370.
IR spectrum: 3.34(m), 3.55(m), 6.22(m), 6.49(s), 7.03(m), 7.73(m), 7.82(s), 8.18(w), 8.89(w), 10.02(vw), 11.08(vw), 12.83(m) μm.

4,5,6,7-Tetrahydroindazol-3-one-5,5-dicarboxylic acid (I)

Diammonium salt of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (II, 1 g., 385 mmole) in water (1 l.) was passed through a column of Amberlite IR-120 (10 ml.) and evaporated to a crystalline product. Yield 815 mg. (93.5%). For analysis it was recrystallized from water as a colourless plates, m. p. 252—256° (change at 185—195°).

Anal. $C_9H_{10}N_2O_5$ (226.19) calc'd.: C 47.79; H 4.46; N 12.39%
found: C 47.98; H 4.65; N 12.32%

Neutralization equivalent calc'd.: 226.19 and 113.1; found: 229.4 and 112.9.

UV spectrum: λ_{max} 246.5 nm, log ε 3.787, and λ_{min} 218 nm, log ε 3.418.
IR spectrum: 3.18(m), 3.41(m), 5.89(s), 6.14(m), 6.31(s), 6.49(m), 7.54(s), 7.71(s), 8.74(m), 12.81(vw) μm.

Monoammonium salt of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (III)

To a suspension of diammonium salt of 4,5,6,7-tetrahydroindazol-3-one-5,5-di-carboxylic acid (II, 100 mg., 0.38 mmole) in anhydrous benzene (60 ml.) an excess of iodine (500 mg., 1.97 mmole) was added. The mixture was stirred at room tempe-rature for 1 hour and then evaporated to dryness under reduced pressure. To the residue water was added and extracted with ether. On addition of ethanol to the water layer an amorphous precipitate (20 mg.) separated and from mother liquor a crystalline product (40 mg.) was obtained by adding ether. Crystallization from ethanol-ether gave the analytical sample as colourless needles, m.p. 208—210⁰ (decomp.).

Anal. $C_9H_{13}N_3O_5$ (243.22) calc'd.: N 17.28⁰/₀
found: N 17.36⁰/₀

IR spectrum: 2.78(w), 3.22(s), 5.86(m), 6.36(s), 6.56(s), 7.16(s), 7.94(s), 8.86(m), 12.14(m), 12.30(m), 13.96(vw) μm.

Barium complex of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (V)

Diammonium salt of 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (II, 52 mg., 0.2 mmole) dissolved in the minimal amount of water was treated with 0.1 M solution of barium nitrate (2 ml., 0.2 mmole). The mixture was stirred and a crystalline product separated. After standing at room temperature the microcrystals were filtered off, washed with water and dried. Yield 71 mg., (89.6⁰/₀).

Anal. $C_9H_8N_2O_5$ Ba · 2 H_2O (397.56)
calc'd.: C 27.19; H 3.04; N 7.05; Ba 34.55⁰/₀
found: C 26.52; H 3.35; N 6.89; Ba 35.48⁰/₀

IR spectrum: 2.89(w), 3.84(w), 3.55(w), 6.29(s), 6.44(s), 7.04(m), 7.19(w), 7.54(m), 11.52(w), 12.36(m) μm.

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4,5,6,7-Tetrahidroindazol-3-on karbonske kiseline. VI. Stvaranje kompleksa 5,5-dikarbonske kiseline s dvovalentnim metalnim ionima

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Opisana su svojstva i sinteza 4,5,6,7-tetrahidroindazol-3-on-5,5-dikarbonske kiseline (HIDA, I) i njene diamonium- II i monoamonium-soli III.

Određene su koncentracijske konstante stabilnosti HIDA-a s Be^{++}, Mg^{++}, Ca^{++}, Sr^{++}, Ba^{++}, Cu^{++}, Co^{++}, Mn^{++}, Zn^{++} i Cd^{++}.

Priloženi su podaci o potenciometrijskim titracijama, ultraljubičastim i infracrvenim apsorpcijskim spektrima.

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