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N-Hydroxy-α,α'-iminodipropionic and N-Hydroxyiminodiacetic Acid as Complexing Agents and an Example for Selective Coordination of the Vanadyl Ion VO^{2+} in Amavadine

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Abstract

Amavadine is a natural vanadyl complex of the anion of the N-hydroxy-α,α'-iminodipropionic acid. The stability of the complexes of this complexing agent, as well as of some derivatives, with the alkaline earth and 3d divalent cations, as well as with Cd^{2+} and Al^{3+} have been investigated by pH-metric and spectrophotometric methods.

The values of the stability constants show the expected trends for iminodiacetate derivatives. Only with VO^{2+} and the N-hydroxyiminodiacetate derivatives one finds an enormous increase of the stability constants, with formation of the complex $ML_2{}^{2-}$. Calorimetric measurements show that the N-hydroxy group participates in the VO^{2+}–ligand bond. All the other iminodiacetate derivatives give only 1:1 complexes VOL.

Introduction

The accumulation of a given element by a living system is one of the most fascinating phenomenon. Among the metal ions which are involved in such processes, the vanadyl ion is of interest as normally it is not an essential element. One of us has isolated from the poisonous mushroom *Amanita muscaria* a natural vanadium-containing product Amavadine, which contains the anion of the N-hydroxy-α,α'-iminodipropionic acid [1, 2]. Our investigations of the resulting equilibria with this ligand have shown that the enrichment of vanadium can be explained by its selective coordination with respect to that of other metal ions. The complexing agent in question is a derivative of iminodiacetate $HN(CH_2COO^-)_2$ [3], a member of the class of the polyaminopolycarboxylates. An examination of the known stability constants shows that vanadyl and copper(II) form EDTA complexes of a nearly equal stability. This paper reports the stability constants of the anions of the following acids, for which the abbreviations are given in parentheses after the formula: (a) N-hydroxyiminodiacetic acid $HO\text{-}N(CH_2COOH)_2$ (HIDA), (b) N-hydroxy-α,α'-iminodipropionic acid $HO\text{-}N(C(CH_3)H\text{-}COOH)_2$ (HIDP), and (c) imino-α,α'-dipropionic acid $HN(C(CH_3)H\text{-}COOH)_2$ (IDP).

Experimental

Synthesis of the Three Ligands

1. N-hydroxyiminodiacetic acid

(a) Preparation of zinc N-hydroxyiminodiacetate. 6.95 g (0.1 mol) hydroxylamine hydrochloride and 34.7 g (0.25 mol) bromoacetic acid were dissolved in 200 ml of water. The reaction mixture was kept at room temperature and titrated automatically (Impulsomat E 473, Metrohm AG, CH-9100 Herisau) to a pH of 7 using 10% sodium hydroxide solution.

After 6 h the reaction mixture was acidified to a pH of 4 and 21.35 g (0.1 mol) zinc acetate dihydrate added. After standing over night at room temperature the zinc complex of N-hydroxyiminodiacetic acid was collected and dried over P_2O_5. Yield: 12.1 g (56.7 mmol) = 56.7%; white powder, *Fp* > 250 °C. IR (KBr): 3420 (OH), 3240 (NH), 2930 (CH), 1655 and 1580 (CO) cm^{-1}. *Anal.* Calc. for $ZnC_4H_5NO_5$ (212.46): C, 22.61; H, 2.37; N, 6.59; Zn, 30.77. Found: C, 22.59; H, 2.50; N, 6.38; Zn, 29.20%. Zn was determined by dissolving the salt in concentrated nitric acid and titration with EDTA.

(b) Chromatography on ion exchange resin Lewatit S 100. 3.00 g (14.1 mmol of the zinc complex from the above reaction were dissolved in

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25 ml of water by dropwise addition of concentrated hydrochloric acid. The solution was loaded on a column (2.5 × 30 cm) containing the strongly acidic cation exchange resin Lewatit S 100 and eluted with 0.2 N sodium hydroxide solution. The fraction containing the product was concentrated to a volume of 100 ml and freeze-dried. A second run on the same column gave the analytically pure material. Yield: 1.66 g (14.4 mmol) = 81%; white powder, *Fp* 136 °C (dec.). IR (KBr): 3420 (OH), 3240 (NH), 2930 (CH), 1600 (CO), 1585 (COO^- st. asym.), 1420 (COO^- st. sym) cm^{-1}. FD-MS: *m/e* 150 (100% $M+1$), 149 (M^+). *Anal.* Calc. for $C_4H_7NO_5$ (149.10): C, 32.22; H, 4.73; N, 9.39. Found: C, 31.97; H, 4.58; N, 9.14%.

2. *N-hydroxy-α,α'-iminodipropionic acid*

This was prepared analogously to the procedure previously described from 0.05 mol of $NH_2OH \cdot HCl$ and 0.15 mol of D,L-2-bromopropionic acid by allowing them to react for 24 h at 40 °C. IR (KBr): 3400 (OH), 2995 (CH), and 1750 (CO) cm^{-1}. FD-MS: *m/e* 178 (100% $M+1$) and 177 (M^+). *Anal.* Calc. for $C_6H_{11}NO_5$ (177.16): C, 40.70; H, 6.26; N, 7.91. Found: C, 40.27; H, 6.58; N, 7.68%. Details on the stereochemistry are reported elsewhere [4].

3. *Imino-α,α'-dipropionic acid*

It was prepared as described by Tempé [5]. Yield: 16%, *Fp* 247–250 °C (dec.). *Anal.* Calc. for $C_6H_{11}NO_4$ (161.16): C, 44.72; H, 6.88; N, 8.69. Found: C, 44.41; H, 6.58; N, 8.42%.

Chemicals, Titration Methods and Instrumentations

The pure acids and metal nitrates (p.a., Merck) were used. The solution of $VO(ClO_4)_2$ was obtained dissolving $VOSO_4 \cdot 5H_2O$ in water, adding a stochiometric amount of sodium hydroxide. The precipitated $VO(OH)_2$, after washing with water until the washing water was free of sulphate, was dissolved in diluted $HClO_4$. Solutions stored without special precautions at $[H^+] = 1.5 \times 10^{-2}$ M contain 1–2% of VO_2^+ after some months, which can be eliminated by reduction with SO_2. This oxidation occurs without formation of chloride ions. All solutions were checked by volumetric procedures.

Alkalimetric titrations were employed for the investigation of the equilibria while the hydrogen ion concentrations $[H^+]$ were measured potentiometrically: $pH = -\log[H^+]$ at $I = 0.1$ (KNO_3) and 25 °C with an Orion Research Digital Ionanalyzer Model 801. The results of titrations for different total concentrations of the metal ions (1–4 mM) and of the protonated ligands (1–8 mM) were used for the calculation of the stability constants. The values of the protonation constants of the ligands and the stability constants were calculated by minimization of the weighted protonation and complex formation functions using appropriate programs for the CDC computer at the Rechenzentrum of the ETH [6].

The spectra were measured with a Perkin-Elmer Lambda 5 UV–Vis spectrophotometer with a 3600 data station.

The calorimetric measurements were carried out with an LKB 8700/2 calorimeter by mixing solutions of the neutralized ligands with those of copper(II) and vanadyl(II). In the latter case a small excess of $HClO_4$ is needed to avoid metal hydrolysis. The heat envolved, corrected for the heat of dilution, is due to the formation of the complex and eventually to the strong acid neutralization which allows the calculation of the enthalpies of complex formation from the composition of the solutions. The final solutions were controlled by pH measurements and titrations.

The Investigation of the Equilibria

In general 1:1 and 1:2 complexes ML and ML_2^{2-} are formed [3]. With IDP the vanadyl ion gives a titration curve with two separate buffer regions. Calculations show the formation of complexes with metal/ligand ratio equal to one ML, $MLOH^-$, and $M_2L_2(OH)_2^{2-}$ in accordance with the results of Frausto da Silva *et al.* [7]. After formation of the 1:1 complex, because of its high acidity, deprotonation of ML occurs with formation of $MLOH^-$ and $M_2L_2(OH)_2^{2-}$. An exact analysis of this last region was not carried out as the pH reading is rather unstable and precipitation occurs. In the case of the analogous iminodiacetate, the formation of 1:1 complexes was evidenced by Napoli and Pontelli [8]. In this case the spectra of solutions containing $[VO^{2+}]_t/[IDA]_t = 1:2$ with pH values between 5 and 9 show a slow increase of the optical density at all wave lengths over a period of several days as expected from the formation of hydrolytic products. In the case of the two *N*-hydroxy ligands, 1:2 complexes are formed.

The complexes of Cu^{2+} and VO^{2+} with HIDP and HIDA were already formed in the mixtures to be titrated, thus other methods were used. For instance, in the case of HIDP with copper(II), a 2 mM solution in both components has a pH value near to 2.4, with a degree of complex formation of 0.96 ± 0.03, the uncertainty being mainly due to the pH error. The small amounts of the non-complexed components, representing only 4 ± 3% of the total concentrations, are affected by a large error, thus making K_1 unreliable. In presence of protonated tris(-β-aminoethyl) amine (H_3TREN^{3+} [3]) by addition of strong base, the 1:1 ML copper(II) complex is converted to the complex $CuTREN^{2+}$. The exchange and the desired stability constants are calculated from the experimental data – added volume of strong base and pH value of the obtained solution – in the appropriate buffer region. No mixed ligand complexes were detected.

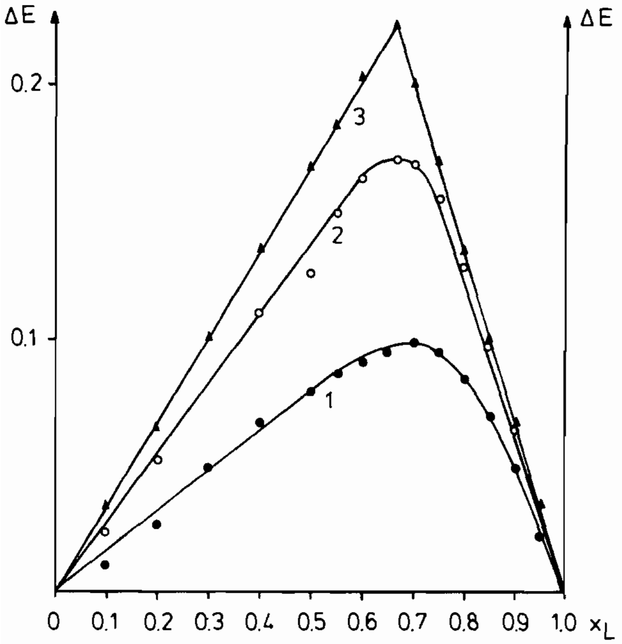


Fig. 1. Optical density ΔE at 560 nm, corrected for the VO^{2+} excess, due to complex formation of VO^{2+} with HIDA for solutions with $[VO^{2+}]_t + [HIDA]_t = 25$ mM and variable $X_L = [HIDA]_t/([VO^{2+}]_t)$, in presence of different amounts of perchloric acid (1, 1 M; 2, 0.5 M; 3, 0.1 M).

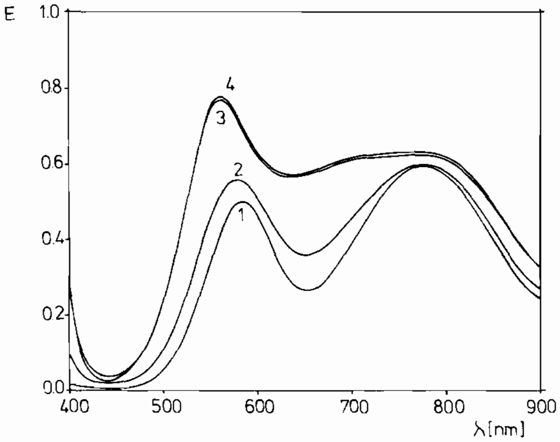


Fig. 2. Ligand exchange between $VOEDTA^{2-}$ and HIDP at pH = 7 in presence of 0.2 M phosphate buffer. Spectra of solutions with: 1, 5 mM VO^{2+}, 10 mM EDTA; 2, 5 mM VO^{2+}, 10 mM EDTA and 15 mM HIDP after 2 h from the mixing, 3, the same as 2 but after 33 d; 4, 5 mM VO^{2+}, 15 mM HIDP. 5 cm cells.

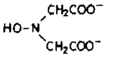
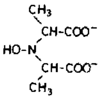
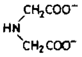
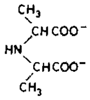
In the case of vanadyl ion, the alkalimetric titrations show no dissociation of the proton of the *N*-hydroxy group of the 1:2 vanadyl complexes until pH > 7 where slow complex decomposition occurs. Addition of strong acid to these complexes shows that protonation takes place only below pH = 1, in 1 M perchlorate solution ($HClO_4 + NaClO_4$). The p*K* value of the acid ML_2H^- is estimated to be equal to 0 ± 0.2. For the further protonation with formation of ML_2H_2, from statistical considerations, a p*K* value of −0.6 is expected.

The vanadyl complexes with HIDA and HIDP were investigated by spectrophotometric methods. It seems that in both cases, under the experimental conditions used also for solutions with equimolar amounts of the two components, only the 1:2 complexes ML_2^{2-} are formed. At pH values below 1, a decrease of the optical density due to ML_2^{2-} is observed. The constant β_2 can be obtained assuming that by addition of strong acid, decomposition according to the corresponding equilibrium occurs (Fig. 1). The values of ΔE for low X_L, being corrected for the large absorptivity of VO^{2+}, are affected by a large error. One obtains $\beta_2 = 10^{21.9 \pm 0.3}$ (HIDA) and $\beta_2 = 10^{23.4 \pm 0.5}$ (HIDP) for $I = 1$ ($NaClO_4$), the large error being due to the fact that only 50 and 20% respectively of each complex dissociates in 1 M $HClO_4$ whereas also partial complex protonation occurs. These values would be larger if the complexes VOL_2^{2-} were to dissociate in two separate steps giving VOL and VO^{2+}; however, the results from spectra of solutions with different vanadyl ion to ligand mol ratios are against this possibility. Both VOL_2^{2-} complexes are stable in presence of an EDTA excess in solutions which range from strongly acidic to pH 7 when the exchange begins. Higher pH values cannot be used as the solutions are not stable. Since the concentration of $VOEDTA^{2-}$ in the equilibrated solution is never larger than 5% of the total vanadyl ion concentration (Fig. 2), only the lower limiting value of the stability constant for VOL_2^{2-} can be given $\beta_2 \geqslant 10^{21.3}$, in agreement with the value from measurements in acidic solutions.

Among the constants obtained only those of VO^{2+} with HIDA and HIDP are so odd that one feels they need checking. A direct comparison of the constants of VO^{2+} and Cu^{2+} for the same ligand can be done by exchange equilibria between the two complexes, as their concentrations can be detected by spectrophotometric measurements. From the constants obtained one expects that solutions equimolar in Cu^{2+}, VO^{2+}, and ligand, the latter cation should be mainly bound. The concentrations of the different species in the equilibrated solutions agree within experimental errors with those calculated. On the contrary, using IDA and IDP, because of normal stability sequence, the copper complex CuL prevails.

In order to explain the formation of 1:2 complexes with iminodiacetate derivatives, we have also investigated the complex formation with glycine. The stability constants for these complexes are given in the literature [9] but a check of the measurements shows that complex formation and metal hydrolysis take place simultaneously. In the presence of a tenfold excess of glycine, a small fraction of the vanadyl

TABLE I. Logarithms of the Protonation Constants $K_{p,\mathrm{H}}(=[\mathrm{H}_p\mathrm{L}]/[\mathrm{H}][\mathrm{H}_{p-1}\mathrm{L}])$ of Iminodiacetate Derivatives L^{2-} and of the Stability Constants $K_n(=[\mathrm{ML}_n]/[\mathrm{ML}_{n-1}][\mathrm{L}])$ of their Complexes with Different Metal Ions. In Parentheses Three Times the Standard Deviation in the Last Figure(s)

Ligand L^{2-}				 [6]	
Temperature (°C)		25	25	20	25
Ionic strength		0.1(KNO$_3$)	0.1(KNO$_3$)	0.1(KNO$_3$)	0.1(KNO$_3$)
H^{+a}	$\log K_{1,\mathrm{H}}$	5.041(20)	5.649(20)	9.45	9.39(2)
	$\log K_{2,\mathrm{H}}$	2.952(30)	2.515(30)		2.58(5)
Ca^{2+}	$\log K_1$	3.0(1)	2.7(1)	2.6	2.0(1)
Co^{2+}	$\log K_1$	5.44(5)	4.72(10)	6.97	6.4(1)
	$\log K_2$	4.00(5)	4.0(1)	5.34	4.9(1)
Ni^{2+}	$\log K_1$	6.4(1)	5.7(1)	8.19	7.6(1)
	$\log K_2$	4.65(10)	5.0(1)	6.11	5.9(1)
Cu^{2+b}	$\log K_1$	8.45(10)^c	9.2(1)^c	10.63	10.6(2)
	$\log K_2$	4.10(5)	3.45(10)	6.05	4.4(1)
Zn^{2+}	$\log K_1$	5.5(1)	5.05(10)	7.27	6.6(1)
	$\log K_2$	3.96(1)	4.05(10)	5.33	4.5(1)
Cd^{2+}	$\log K_1$	4.94(10)	4.5(1)	5.73	5.4(1)
	$\log K_2$	4.2(1)	4.0(1)	4.46	4.3(1)
VO^{2+d}	$\log K_1$			9.0[7]	9.4(2)
	$\log \beta_2{}^e$	21.9(3)	23.4(5)		
Al^{3+}	$\log K_1$	5.1(1)	5.9(1)		

^{a}In 1 M NaClO$_4$ for HIDA: $\log K_{1,\mathrm{H}} = 4.80(2)$, $\log K_{2,\mathrm{H}} = 2.88(4)$ and $\log K_{3,\mathrm{H}} = 0.8(2)$; for HIDP: $\log K_{1,\mathrm{H}} = 5.47(2)$, $\log K_{2,\mathrm{H}} = 2.54(5)$ and $\log K_{3,\mathrm{H}} = 1.0(2)$. ^{b}p$K$ of CuL: 7.5(1) (HIDA), 8.22(1) (HIDP); pK of $\mathrm{CuL_2}^{2-}$: 8.28(10) (HIDA). ^{c}Ligand exchange with TREN. ^{d}For glycine with VO^{2+}: $\log K_1 \leq 6.6$, $\log \beta_2 \leq 11.9$. ^{e}$I = 1(\mathrm{NaClO_4})$.

ions are complexed giving $K_1 \leqslant 10^{6.6}$. $\beta_2 \leqslant 10^{11.9}$ is obtained taking $K_1/K_2 = 10^{1.3}$, *i.e.* the value for copper(II) with glycine.

Results

A comparison of the logarithm of the stability constants obtained with those of iminodiacetate from the literature is given in Table I. A paper [7] giving equilibrium constants for the three acids under investigation with nickel(II), copper(II), and vanadyl VO^{2+} appeared while our work was in progress. Their values are in good agreement with ours with the exception of those of VO^{2+} with HIDA and HIDP. A solution of $\mathrm{VOL_2}^{2-}$ (L = HIDA or HIDP) shows the same spectrum in the pH range from 7 to 1, indicating that alkalimetric titrations cannot give reliable constants as the above complex remains unchanged in the pH range. Furthermore, the presence of $\mathrm{SO_4}^{2-}$ in their mixtures, resulting from use of $\mathrm{VOSO_4}$ solutions with tenfold excess of $\mathrm{H_2SO_4}$, is not favourable. This anion is partially protonated below pH = 3 (pK of $\mathrm{HSO_4}^- \approx 2$ at $I = 0.1$) and its deprotonation can simulate complex formation (which is already accomplished). For this reason, we continued our efforts in order to obtain reliable results.

For some copper complexes with the two *N*-hydroxy ligands, the pK values are given (Table I, footnote (b)): they are comparable in magnitude with those of iminodiacetate derivatives [3]. In the case of HIDP and HIDA, the pK values are also given for the ionic strength 1 (NaClO$_4$) in footnote (a), because the decomposition of their vanadyl complexes has been investigated in this medium.

The thermodynamic data of complex formation are summarized in Table II. In the case of Cu^{2+} and HIDP, because of the low value for K_2, hydrolysis does not allow the exact determination of the corresponding enthalpy. In the case of vanadyl aqua ion, no enthalpy data for complex formation have been hitherto obtained by calorimetric measurements.

Discussion

The basicity of the nitrogen atom of a ligand $\mathrm{NHR_1R_2}$ is strongly decreased by substitution of the bound hydrogen atom with a hydroxyl group. This is

TABLE II. Thermodynamic Data for the Reaction: $M^{2+} + nL^{\mu-} \rightarrow ML_n^{(n\mu-2)-}$ at 25 °C and I = 0.1(KNO$_3$)

Complex	n	Cu^{2+}			VO^{2+}		
		ΔG_n (kJ/mol)	ΔH_n (kJ/mol)	ΔS_n (J/(mol K))	ΔG_n (kJ/mol)	ΔH_n (kJ/mol)	ΔS_n (J/(mol K))
$M(EDTA)^{2-}$	1	−106.7(5)[a]	−34.0(5)[a]	244(3)[a]	−106.7(5)	−10.5(5)	326(3)
$M(HIDA)_2{}^{2-}$	2	−71.3(10)	−21.5(5)	168(5)	−124.7(15)[b]	−56.5(5)	229(7)
$M(HIDP)_2{}^{2-}$	2	–	–	–	−133.2(25)[b]	−60.2(5)	245(10)

In parentheses three times the standard deviation in the last figure(s). [a]From ref. 10. [b]The approximate values for I = 1(NaClO$_4$) are used.

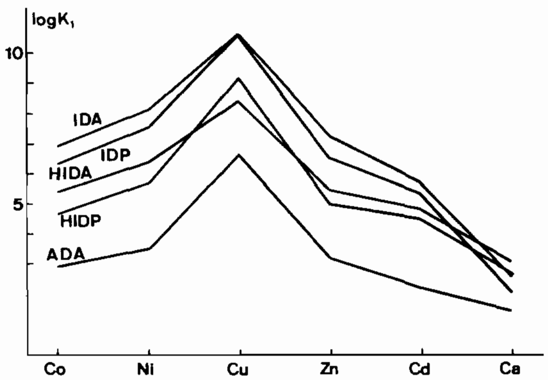


Fig. 3. The logarithm of the stability constant K_1 of divalent cations with some iminodiacetate ligands.

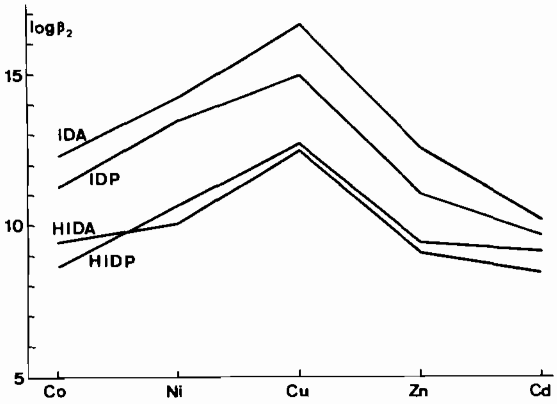


Fig. 4. The logarithm of the overall stability constant β_2 of divalent cations with some iminodiacetate ligands.

apparent by comparing the protonation constants $K_{1,H}$ of ammonia NH_3 ($10^{9.3}$) with that of hydroxylamine NH_2OH ($10^{6.2}$), as well as those given in Table I. Because of the correlation between log $K_{1,H}$ of a ligand L and its stability constants with a given metal ion [3], it is also expected that these latter quantities should decrease with the log $K_{1,H}$ values. This relationship for log K_1 and log β_2 is shown in Figs. 3 and 4, respectively, where adjacent points for the same ligand are connected with straight lines. In addition to the data of the cations investigated, the cortion to the data of the cations investigated, the corresponding values for iminodiacetate (IDA, $K_{1,H} = 10^{9.45}$ [10]) and aniline-*N*,*N*′-diacetate (ADA, $K_{1,H} = 10^{4.96}$ [3]) are also depicted in both figures. It appears that the values of log K_1 for the hydroxy substituted ligands are lower than those of the more basic iminodiacetate but much larger than those of the ligand with similar $K_{1,H}$ value, *i.e.* aniline-*N*,*N*′-diacetate, indicating that these N atoms are better donors than would be expected on the basis of their basicities. These changes are practically parallel for all cations considered from Co^{2+} to Ca^{2+} for log K_1 and from Co^{2+} to Cd^{2+} for log β_2. Only some log K_1 (CuHIDP, CuIDP) and log β_2 ($Cd(IDP)_2{}^{2-}$) values show an evident deviation with respect to those for the other cations but this is never larger than two units. The reasons for such discrepancies can sometimes be found by examining the thermodynamic data for complex formation. This could not be done in this case because of inadequate data basis.

The data of vanadyl ion with the two hydroxy ligands cannot be fully compared with those of the other iminodiacetate derivatives, since in the former case only β_2, in the latter case only K_1 is known. A comparison can be made using Cu^{2+} as reference, as in this last case both constants K_1 and β_2 are known. K_1 always is lower than the corresponding values for copper(II) (with IDP: log K_1 (Cu^{2+}) = 10.6 and log K_1 (VO^{2+}) = 9.4), whereas for the hydroxy ligands β_2 with VO^{2+} is ten orders of magnitude larger than that with Cu^{2+} (with HIDP: log β_2 (Cu^{2+}) = 12.65 and log β_2 (VO^{2+}) = 23.4). Because of these large differences in behaviour with similar ligands and the much larger β_2 for the *N*-hydroxy ligands, one can speak, in this last case, of a selective coordination of vanadyl ion, thus explaining the formation of amavadine.

Since among the iminodiacetate derivatives only those with a *N*-hydroxy group bind VO^{2+} selectively, the further participation of that coordinating group seems plausible. Our efforts to obtain single crystals of such complexes, suitable for X-ray structure determination, were unsuccessful. Quite recently, a publication described the structure of a vanadium

2,2′-bipyridine (bip) complex (Hbip)(H[$VO(O_2)_2$-bip]$_2$)$\cdot 0.5H_2O_2 \cdot 5.5H_2O$ [11], in which the vanadium atom has a pentagonal bipyramidal arrangement of the donor atoms; the peroxo O atoms and one N atom from bip form the pentagonal plane while the vanadyl O atom and the other N atom occupy the apical positions. Furthermore, V(V) mixed hydroxylamine complexes, in which both N and O ligand atoms are coordinated are known [12–15].

The interpretation of the thermodynamic data of Cu^{2+} and VO^{2+} of Table II is also in favour of the further participation of the *N*-hydroxy group. Indeed, going from $M(EDTA)^{2-}$ to $M(HIDA)_2{}^{2-}$ and $M(HIDP)_2{}^{2-}$, a different trend of the values of the functions ΔH and ΔS is observed. For the coordinated copper(II), their changes are those normally observed for similar ligands [10]. As iminodiacetate with lower basicity, HIDA gives a ΔH increase from −34 to −21.5 kJ/mol whereas ΔS decreases from 244 to 168 J/(mol K) for the larger number of reacting species. For a vanadyl ion showing the same coordination, a parallel change of the functions is expected. This is only approximately true for the entropy ΔS. The large increase in exothermicity can only be explained by that of the metal–ligand bond strength, due to the *N*-hydroxy group.

Thus, VO^{2+} forms very strong complexes with the *N*-hydroxyiminodiacetate ligands taking advantage of the hydroxy group. The preference by VO^{2+} for oxygen to nitrogen as donor atom can be expected as this cation in aqueous solution does not bind NH_3 and forms only very weak complexes with ethylenediamine while with oxalate its complexes are more stable than those with Cu^{2+}. On the basis of the actual knowledges about the coordination chemistry of VO^{2+} it is difficult to explain our results. Further investigation with analogous ligands are planned in order to clarify this selectivity and the unexpected stability sequence $K_1 < K_2$.

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