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# Oxovanadium(IV) Complexes of 1-Hydroxyalkane-1,1-diyldiphosphonic Acids

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Potentiometric and spectroscopic (EPR and UV-VIS) methods were used to study the oxovanadium(IV) complexation with several 1-hydroxyalkane-1,1-diyldiphosphonic acids. Coordination of oxovanadium(IV) to all diphosphonic ligands studied starts at very low pH and formation of the stable monomeric and trinuclear species between pH range 2–9 is observed.

**Key words**: vanadyl complexes, potentiometry, stability constants, oxovanadium(IV), diphosphonates

Phosphonates and aminophosphonates are potent chelating agents for variety of metal ions including Cu(II), Ca(II), Zn(II) and VO(IV) ions [1–3]. Diphosphonic acids bind metals with various ionic radii and form stable complexes with *e.g.*: Na(I), Rb(I), Zn(II), Cu(II), Pb(II), Cd(II) [4–10].

Hydroxyalkilodiphosphonic and alkilodiphosphonic acids are used in medicine as drugs in Paget disease, tumour osteolysis, osteoporosis, in radiodiagnosis as ligands for $^{99m}$Tc [11–14] and as potentially strong chelating agents in metal extraction [15]. Some of them are commercially available drugs *e.g.*: etidronate (Didronel®), pamidronate (Aredian®) and clodronate (Benefos®, Loron®) [11]. Diphosphonic acids have low toxicity, high thermostability and the diphosphonic motif is very resistant against enzymatic degradation. Vanadium is immanent in living systems, although its role is not well understood [16]. Small amounts of vanadium are necessary for development for cells, plants and animals [17–20].

In human body vanadium exists with two major oxidation states: V(V) and V(IV) [21]. In plasma both these oxidation states occur as a result of an equilibrium between two processes – oxidation by oxygen and reduction by endogenous agents, like ascorbate and catecholamines [22]. Vanadate, V(V), transported inside the cell is quickly reduced to oxovanadium(IV) by glutathione [23–24] and stabilized on this valence state by coordination to variety of bio-ligands. The leading role in this process play ligands containing phosphate moieties like nucleoside-phosphates.

Diphosphonic acids can disturb considerably the sensitive administration of vanadium and other metal ions in a human body. Therefore, it is necessary to extend our knowledge about the interactions between diphosphonic ligands and metal ions present in the living systems.

In this work we present the potentiometric and spectroscopic results for oxovanadium(IV) with four 1-hydroxyalkane-1,1-diyldiphosphonic acids $L^1$-$L^4$ (Fig. 1) in solution. The stoichiometries, the stability constants and the bonding modes of the complexes in these systems are presented.

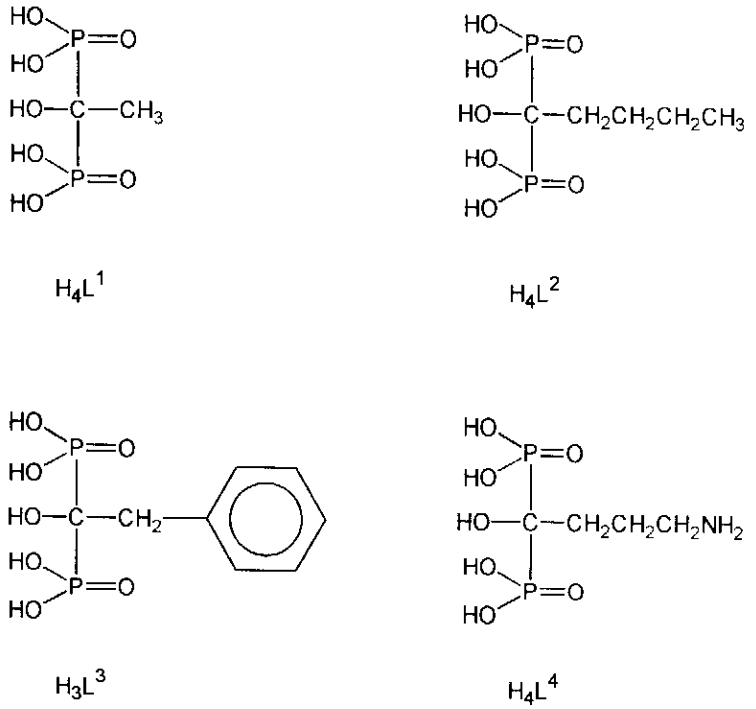



**Figure 1.** 1-Hydroxyalkane-1,1-diyldiphosphonic acids: $H_4L^1$ – 1-hydroxyethane-1,1-diyldiphosphonic acid; $H_4L^2$ – 1-hydroxypentane-1,1-diyldiphosphonic acid; $H_3L^3$ – 1-hydroxy-2-phenylethane-1,1-diyldiphosphonic acid and $H_4L^4$ – 4-amino-1-hydroxybutane-1,1-diyldiphosphonic acid.

## EXPERIMENTAL

***Chemicals***: Ligands were synthesized as described earlier [15,25–27]. Vanadyl sulphate trihydrate was used as obtained from Aldrich with purity 99.99+ %. All other reagents were of analytical grade.

***Potentiometric measurements:*** The stability constants were determined by pH-metric titrations of 2–3 $cm^3$ samples at 25°C. The hydroxydiphosphonic acid concentration in each sample was $1.5\times10^{-3}$ mol $dm^{-3}$ and metal to ligand ion ratio was 0:1 and 1:2. The ionic strength ($I$) was adjusted to 0.1 mol $dm^{-3}$ with $KNO_3$. Argon was bubbled through solutions to remove oxygen. The titration were performed with carbonate-free 0.1 mol $dm^{-3}$ NaOH standard solution under argon atmosphere over pH range 2.3–11 for ligand and 2.3–9.5 for metal:ligand systems. Potentiometric measurements were made with a MOLSPIN 1000 titration system and micro-combined glass-silver/silver chloride electrode (Russell) calibrated in hydrogen ion concentration using $HNO_3$ [28]. The concentration stability constants $\beta_{prs} = [M_pH_rL_q]/[M]^p[H]^r[L]^q$ were calculated with the SUPERQUAD computer program [29].

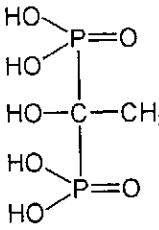
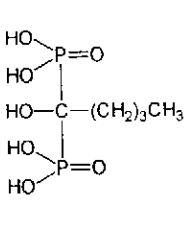
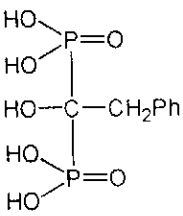
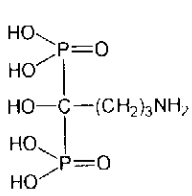
***Spectroscopic measurements:*** Absorption spectra was recorded with a BECKMAN DU-650 spectrophotometer. The EPR spectra were recorded on a BRUKER ESP 300E spectrometer at X-band (9.3 GHz) at liquid nitrogen in 1:2 ethanodiol–water solutions. The metal to ligand concentration ratios were 1:2 or 1:5 and the metal concentration was $3\times10^{-3}$ mol $dm^{-3}$.

## RESULTS AND DISCUSSION

The diphosphonic acids $L^1$ and $L^2$ contain four dissociable protons at two phosphonic groups ($H_4L$). In the case of $L^3$ ligand the first protonation site with log K = 11.6 [3] is over our pH measurement range, and we treated this ligand as $H_3L$. The last ligand – $L^4$ has four protons at phosphonic moieties and one additional on the amino group ($-NH_3^+$). The log K of the first protonation constant is about 12 [3], and could not be determined precisely. In this case we treated this ligand as $H_4L$. Alcoholic hydroxyl proton is not able to deprotonate below pH 13.

Protonation constants of diphosphonic acids differ considerably from those of monophosphonic acids. The strong electrostatic interaction between the two highly negative phosphonic moieties increase the basicity of the other phosphonic group. The monophosphonic acids have two protonation constants with log $K_{HL} \approx 5$–7 and log $K_{H_2L} \approx 1$–2 [2,30–32]. In diphosphonic acids the protonation constants of the first phosphonic group are similar to these values, while in the second phosphonic moiety the first protonation constant is very basic with log $K_{HL} \approx 10$–11 (Table 1).

**Table 1.** Stability constants of the proton (log K) and oxovanadium(IV) complexes (log β) of 1-hydroxyalkane-1,1-diyldiphosphonic acids at 25°C and $I$ = 0.1 mol dm$^{-3}$ ($KNO_3$).

| Species |  |  |  |  |
|---|---|---|---|---|
| | $H_4L^1$ | $H_4L^2$ | $H_3L^3$ | $H_4L^4$ |
| log K ($NH_2$) | – | – | – | ≈ 12[a] |
| log K ($PO_3^{2-}$) | 10.86(1) | 10.72(1) | > 11.5[a] | 10.79(1) |
| log K ($PO_3^{2-}$) | 6.83(1) | 6.91(1) | 6.73(1) | 6.36(1) |
| log K ($PO_3H^-$) | 2.65(1) | 2.74(1) | 2.64(1) | 2.38(1) |
| log K ($PO_3H$ ) | ≈ 1 | ≈ 1 | ≈ 1 | ≈ 1 |
| log K (HL) | 10.86(1) | 10.72(1) | 6.73(1) | 10.79(1) |
| log K ($H_2L$) | 6.83(1) | 6.91(1) | 2.64(1) | 6.36(1) |
| log K ($H_3L$) | 2.65(1) | 2.74(1) | ≈ 1 | 2.38(1) |
| log K ($H_4L$) | ≈ 1 | ≈ 1 | – | ≈ 1 |
| log β [VOHL] | 18.56(2) | 18.23(2) | – | 17.41(3) |
| log β [VOL] | – | – | 7.02(1) | – |
| log β [$(VO)_3L_3$] | 53.25(3) | 51.52(5) | – | 50.17(4) |
| log β [$(VO)_3H_{-3}L_3$] | – | – | 18.02(2) | – |

[a]data from [3].

1-Hydroxyalkane-1,1-diyldiphosphonic acids coordinate to VO(IV) ions well below pH 2.5. Both potentiometric and spectroscopic data indicate that at pH range 2.3–9 the two complex species are formed (Fig. 2). The first of them the monomeric VOHL ($L^1$, $L^2$, $L^4$) or VOL ($L^3$) is observed clearly at pH range 2–3.6 with $g_{||}$ =

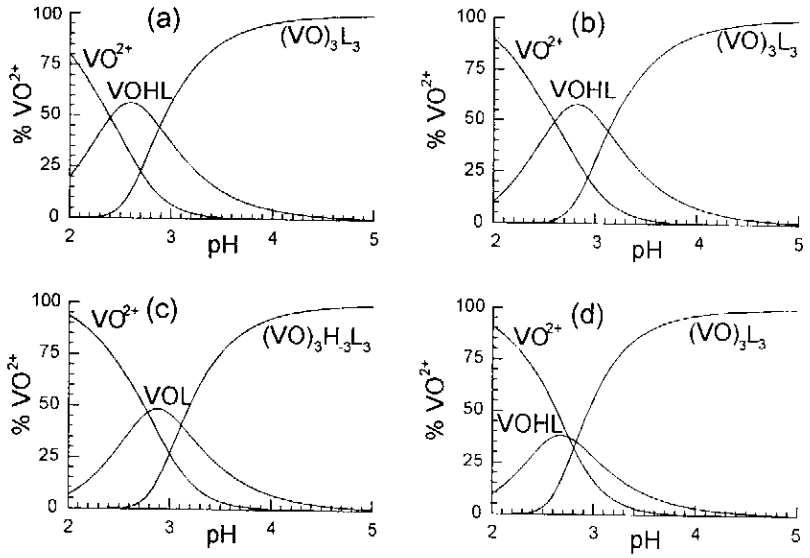



**Figure 2.** Species distribution curves for the: (a) $VO^{2+}$–$H_4L^1$, (b) $VO^{2+}$–$H_4L^2$, (c) $VO^{2+}$–$H_3L^3$, (d) $VO^{2+}$–$H_4L^4$ systems; metal concentration 1 mmol $dm^{-3}$, ligand concentration 2 mmol $dm^{-3}$.

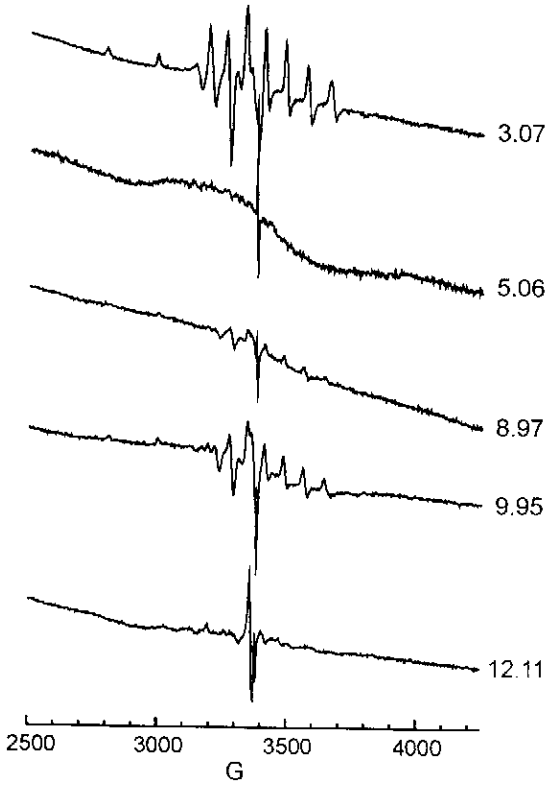



**Figure 3.** EPR spectra at 120 K of VO(IV):$L^1$ system in 1:2 ethanodiol–water solutions with varying pH; VO(IV) concentration 3 mmol $dm^{-3}$ and metal to ligand ratio 1:5.

1.937–1.940 and $A_{||} = 171–181 \times 10^{-4}$ cm$^{-1}$. Between pH 4 and 9 the EPR spectra become broad (Fig. 3). The broadening of the EPR spectrum as well as the absorption spectra support calculations of the potentiometric titration curves suggesting the formation of the trimeric species $(VO)_3L_3$ ($L^1$, $L^2$, $L^4$) or $(VO)_3H_{-3}L_3$ ($L^3$) [33,34].

In very basic solution above pH 10 the new EPR spectra with $g_{||} = 1.940$ and $A_{||} = 174 \times 10^{-4}$ cm$^{-1}$ are detected. This may suggest the formation of the monomeric $VOL_2$ ($L^1$, $L^2$, $L^4$) or $VOH_{-2}L_2$ ($L^3$) $2 \times (PO_3^{2-}, PO_3^{2-})$ species. The strong oxidation process of $VO^{2+}$(IV) to V(V) observed above pH 9 has not allowed, however, to support the formation of these complexes by the potentiometric titrations.

**Table 2.** Spectroscopic parameters for oxovanadium(IV) complexes formed by 1-hydroxyalkane-1,1-diyldiphosphonic acids.

| Ligand | Species | EPR | | Donor set | UV-Vis |
|---|---|---|---|---|---|
| | | $g_{||}$ | $A_{||}$/cm$^{-1}$ × 10$^{-4}$ | | $\lambda_{max}$ /nm (ε/dm$^3$ mol$^{-1}$ cm$^{-1}$) |
| $H_4L^1$ | [VOHL] | 1.937 | 181 | $PO_3^{2-}$, $PO_3H^-$ | 623s(7), 827(21) |
| | $[(VO)_3L_3]$ | unresolved | | | 370s(13), 619(10), 850(19) |
| $H_4L^2$ | [VOHL] | 1.940 | 178 | $PO_3^{2-}$, $PO_3H^-$ | 622s(9), 810(25) |
| | $[(VO)_3L_3]$ | unresolved | | | 370s(10), 620(7), 850(18) |
| $H_3L^3$ | [VOL] | 1.939 | 171 | $PO_3^{2-}$, $PO_3H^-$ | 623s(9), 821(23) |
| | $[(VO)_3H_{-3}L_3]$ | unresolved | | | 370s(15), 620(9), 845(20) |
| $H_4L^4$ | [VOHL] | 1.938 | 179 | $PO_3^{2-}$, $PO_3H^-$ | 622s(8), 812(23) |
| | $[(VO)_3L_3]$ | unresolved | | | 370s(7), 620(7), 855(18) |

s – shoulder.

Although all ligands studied have shown similar coordination abilities towards VO(IV) ion, the small but distinct steric effects of alkane side-chains are observed. *E.g.* the monomeric and trimeric species of the $L^1$ then $L^3$ ligand are formed at lower pH when compared to the other two ligands.

All diphosphonates are very potent chelating agents for vanadyl ions already in acidic solutions. The most effective complex is the trimeric species dominating over the large pH range.

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