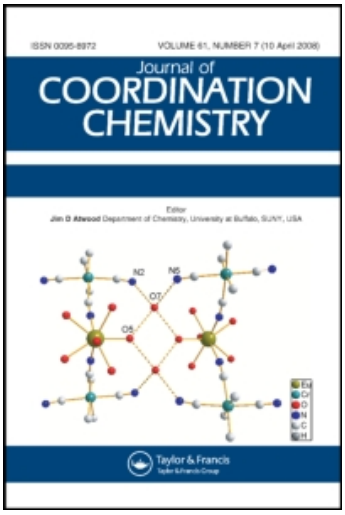

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NMR studies on interactions between diperoxovanadate and picolinamide-like ligands

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To understand the effects of picolinamide-like ligands on reaction equilibrium, a series of picolinamide derivatives were synthesized and the interactions between the diperoxovanadate complex $[OV(O_2)_2L]^-$ ($L = D_2O$ or HOD, abbr. bpV) and picolinamide ligands in solution were explored using multinuclear (^1H, ^{13}C, and ^{51}V) magnetic resonance, COSY, and HSQC in $0.15\,mol\,L^{-1}$ NaCl ionic medium for mimicking physiological conditions. Formation constants among the picolinamide-like ligands are *N*-(1-hydroxypropan-2-yl)-picolinamide ≈ *N*-(2-hydroxypropyl)-picolinamide > *N*-(3-hydroxypropyl)-picolinamide > *N*-propyl-picolinamide. The substituting group influences the equilibrium by electronic effects. The interactions result in a series of new seven-coordinate diperoxovanadate species $[OV(O_2)_2L']^-$ ($L' =$ picolinamide-like ligands).

Keywords: Diperoxovanadate; Picolinamide-like ligands; Interactions; NMR

1. Introduction

Vanadium complexes, particularly vanadates and more recently reported peroxovanadate compounds, have been implicated in many biological processes and therapeutic applications, indicating they are capable of having many important activities [1–4]. A number of well-characterized and stable peroxovanadate complexes display strong insulin-mimetic activity and so they may be developed into new oral drugs for anti-diabetes or tumor suppression [5, 6]. Therefore, it is not surprising that coordination chemistry and biological mechanism of peroxovanadate compounds have received more attention. For example, Orvig *et al.* [7] have synthesized and characterized many vanadium(III, IV, and V) complexes and studied their insulinomimetic activities. Cuin's [8] group synthesized vanadium complexes containing glycolic acid and studied their potential cytotoxic effect. Kwong *et al.* [9] have explored the

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mechanism of reactions of diperoxovanadium(V) compounds at physiological pH and the relevance to their DNA-photocleavage activities. Araujo and Brito [10] have used electromotrive force measurements together with UV-Vis to explore the interactions between vanadium(III and IV) and organic ligands. Tracey *et al.* [11] used nuclear magnetic resonance (NMR) spectroscopy to explore coordination reactions between peroxovanadate complexes and a series of amino acids or peptides. Detailed and thorough potentiometric and ^{51}V NMR spectroscopic investigations of $H^+/H_2VO_4^-/H_2O_2$/ligand systems have been performed by Pettersson *et al.* [12, 13] to propose a model describing the distribution of pentavalent vanadium in human blood [14]. Conte *et al.* [15] studied the NH_4VO_3/H_2O_2/histidine-like ligand systems that imitated the active site of haloperoxidases by using spectroscopy together with density function calculations. Baran also synthesized a series of mixed ligand oxovanadium(V) containing the hydroxylamido ligand (isoelectronic with hydrogen peroxide) and simple amino acids and then studied their vibrational spectra [16]. Similarly, in our previous papers, interactions between peroxovanadate complexes and organic ligands were explored through detailed spectroscopic investigations [17–25].

In this article, we extend our studies to NH_4VO_3/H_2O_2/picolinamide-like ligands to probe the effects of organic ligands on the reaction equilibrium. As an invaluable analytical tool for vanadium(V) species, ^{51}V NMR spectroscopy was utilized, assisted by ^1H, ^{13}C, COSY, and HSQC. Through the combined use of multinuclear and 2-D NMR technologies, the ^1H and ^{13}C NMR spectra of the interaction systems are assigned.

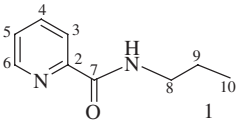
2. Experimental

2.1. *Spectroscopies*

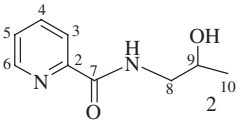
All spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer. DSS [3-(trimethylsilyl)-propanesulfonic acid sodium salt] was used as an internal reference for ^1H and ^{13}C chemical shifts. The ^{51}V chemical shift was measured relative to the external standard $VOCl_3$ with upfield shifts considered negative.

2.2. *Materials and preparations*

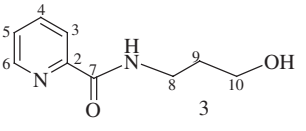
The compounds D_2O, H_2O_2 (30%), NaCl, and NH_4VO_3 were commercial products (Sinopharm Chemical Reagent Company, China) used without purification. The picolinamide-like ligands [*N*-propyl-picolinamide (abbr. Pr-picamide, **1**), *N*-(2-hydroxypropyl)-picolinamide (abbr. 2-PrOH-picamide, **2**), *N*-(3-hydroxypropyl)-picolinamide (abbr. 3-PrOH-picamide, **3**), (*N*-(1-hydroxypropan-2-yl)-picolinamide (abbr. 2-*i*-PrOH-picamide, **4**), scheme 1] were synthesized according to the literature [26]. The ionic medium 0.15 mol L^{-1} NaCl in D_2O solution was used in all NMR experiments. To form the ternary system of NH_4VO_3/H_2O_2/picolinamide-like ligands, NH_4VO_3 and H_2O_2 were first mixed in D_2O to produce $[OV(O_2)_2(D_2O)]^-/[OV(O_2)_2(HOD)]^-$ (abbr. bpV) followed by the addition of **1–4**.



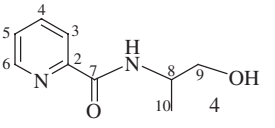
N-propyl-picolinamide



N-(2-hydroxypropyl)-picolinamide



N-(3-hydroxypropyl)-picolinamide



N-(1-hydroxypropan-2-yl)-picolinamide

Scheme 1.

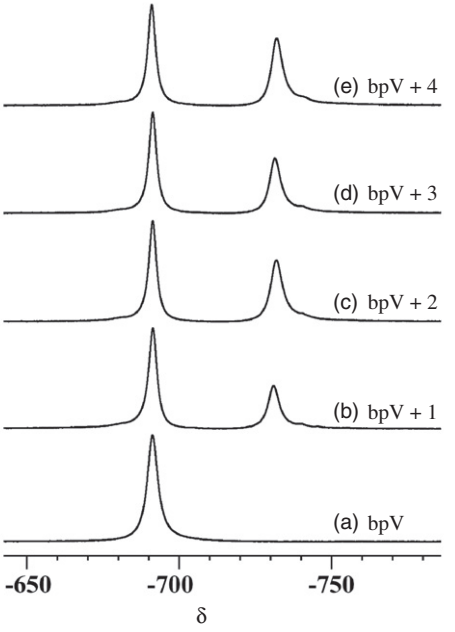


Figure 1. ^{51}V NMR spectra of the interaction systems of NH_4VO_3/H_2O_2/picolinamide-like ligands. The total concentration of vanadate species is $0.2\,mol\,L^{-1}$ and the bpV refers to $[OV(O_2)_2(D_2O)]^-$/$[OV(O_2)_2(HOD)]^-$.

3. Results and discussion

3.1. *^{51}V NMR studies on the interaction systems*

The starting sample is a mixture of NH_4VO_3 and H_2O_2 with 1 : 5 molar ratio and $0.2\,mol\,L^{-1}$ vanadate concentration in D_2O. Its ^{51}V NMR spectrum has a strong peak at -692 ppm, shown in figure 1, which was assigned to $[OV(O_2)_2(D_2O)]^-$/$[OV(O_2)_2(HOD)]^-$ (abbr. bpV) according to previous reports [18–23]. When the same molar quantity of picolinamide-like ligands was added to the peroxovanadate solutions,

the area of bpV peak decreased and a new peak appeared at −730 ppm for *N*-propyl-picolinamide {assigned to $[OV(O_2)_2(Pr\text{-picamide})]^-$}, −731 ppm for *N*-(3-hydroxypropyl)-picolinamide {assigned to $[OV(O_2)_2(3\text{-PrOH-picamide})]^-$}, and −732 ppm for *N*-(2-hydroxypropyl)-picolinamide {assigned to $[OV(O_2)_2(2\text{-PrOH-picamide})]^-$} or (*N*-(1-hydroxypropan-2-yl)-picolinamide {assigned to $[OV(O_2)_2(2\text{-}i\text{-PrOH-picamide})]^-$}, respectively. Because the ligands are all derivatives of picolinamide, the resulting oxovanadate species have similar chemical shifts [27]. Judged from the difference of the ratio of bpV peak areas before and after the reaction, different ligands have different equilibrium constants. Based on equation (1)

$$\mathrm{bpV} + \mathrm{L}' = \mathrm{bpV(L')} \tag{1}$$

the equilibrium constant of different reactions could be calculated from the following equation:

$$K = [\mathrm{bpV(L')}]/[\mathrm{L}'][\mathrm{bpV}] \tag{2}$$

where L′ = picolinamide-like ligands. As a result, the equilibrium constants are 4.1, 8.4, 7.2, and 8.7 mol L^{-1} for **1**, **2**, **3**, and **4**, respectively. Therefore, based on equilibrium constants, the order of interaction strength of picolinamide-like ligands with diperoxovanadate is deduced to be 2-*i*-PrOH-picamide ≈ 2-PrOH-picamide > 3-PrOH-picamide > Pr-picamide.

3.2. *Assignments of ^{1}H and ^{13}C NMR data of the interaction systems*

In the interaction systems, some peaks in the pyridine ring either overlapped with each other or have close chemical shifts. This made assignments of the ^{1}H and ^{13}C NMR spectra difficult. Therefore, we used 2-D NMR spectra to make the assignments, shown in figure 2 (the NH_4VO_3/H_2O_2/3-PrOH-picamide system was used as an example).

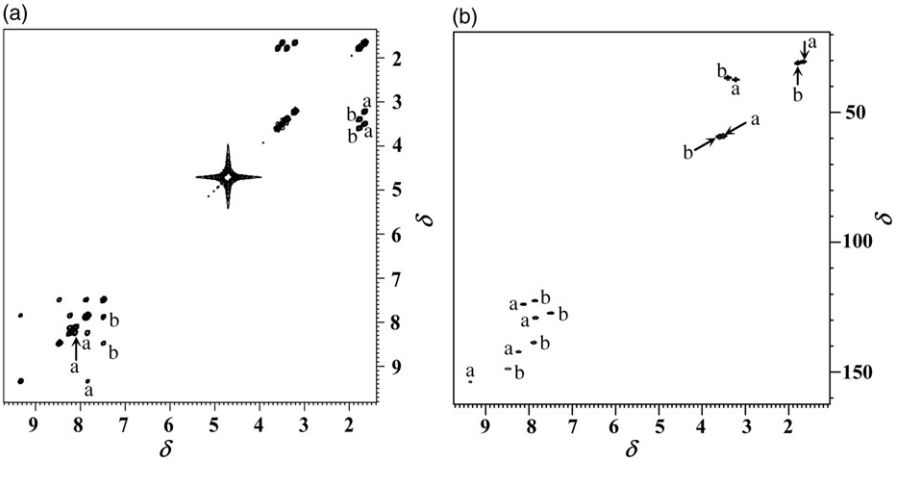


Figure 2. COSY (a) and HSQC (b) spectra of NH_4VO_3/H_2O_2/3-PrOH-picamide with 1 : 5 : 1 molar ratio in D_2O solution. The total concentration of vanadate species is 0.2 mol L^{-1}. a: coordinated ligands; b: free ligands.

In the COSY, the 5-H in coordinated ligands almost overlapped with the 3-H and 4-H in pyridine ring of the free ligand. Based on assignments of 1-D NMR and COSY spectra, we assigned the ^{13}C NMR spectral peaks. In figure 2, there are two groups of picolinamide-like ligand peaks in both the ^{1}H and ^{13}C NMR spectra, respectively. One group was assigned to the coordinated picolinamide (mark as component a), that is, the ligand of the new species formed in the interaction system, and the other group was assigned to free picolinamide (mark as component b). Through the combined use of multinuclear and 2-D NMR, the ^{1}H and ^{13}C NMR spectral assignments of the interaction systems of bpV ($0.2\,mol\,L^{-1}$) and picolinamide-like ligands with 1 : 1 molar ratio in sodium chloride/deuterium oxide solution are listed in Supplementary Material. According to the chemical shifts and/or the relative areas of the ^{1}H, ^{13}C, and ^{51}V peaks, we suggest that the newly formed species $[OV(O_2)_2L']^-$ (L′ = picolinamide-like ligands) is seven-coordinate because of the following reasons: (1) A V–N bond is formed as shown by experimental results [18]; (2) The chemical shift of $[OV(O_2)_2L']^-$ is more upfield than that of $[OV(O_2)_2(Py)]^-$ [20]; this means there is another group contributing electron density to the metal center besides nitrogen. It is possible that the carbonyl oxygen in picolinamide is chelated to the center metal.

3.3. *Reaction modes of the interaction systems*

Some early studies by Margerum [28] indicated binding of metal to peptidyl group is pH dependent, the carbonyl group first prior to deprotonation of the amide. The increase in pH results in bond rearrangement and binding of the metal to the deprotonated amide. However, as the molar ratio of the interaction systems NH_4VO_3/H_2O_2/picolinamide-like ligands is 1 : 5 : 1, the system is weakly acidic. Based on Pettersson's work [29], the hydrogen of N–H is still in the amide group. The crystal structure of the peroxovanadate-containing picolinamide [27] shows carbonyl oxygen coordinates to V in addition to nitrogen in the pyridine when the ligand is picolinamide-like. The charge distribution of the amide group shown in figure 3 makes the carbonyl oxygen negatively charged and amino nitrogen positively charged [22] when coordinated to metal. Therefore, the more negatively charged the carbonyl oxygen is, the stronger the coordination ability of the ligand. As propyl is a weak electron-donating group and hydroxyl is a stronger electron-withdrawing group, the amino nitrogen is less positively charged in *N*-propyl-picolinamide compared with other picolinamide-like ligands in the interaction systems, implying less negative charge resides on the carbonyl oxygen. Therefore, the reactivity of *N*-propyl-picolinamide is lowest towards bpV. For *N*-(1-hydroxy-propan-2-yl)-picolinamide or *N*-(2-hydroxypropyl)-picolinamide, the hydroxyl position in the *N*-substituted group is nearer than that of *N*-(3-hydroxypropyl)-picolinamide, so the electron-withdrawing effect is stronger. According to the hydroxyl position and the electron effect of the ligands, the order of reaction of

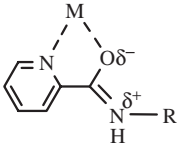


Figure 3. Charge distribution of the amide group in organic ligands when coordinated to the metal center.

the picolinamide-like ligands with $[OV(O_2)_2(D_2O)]^-/[OV(O_2)_2(HOD)]^-$ is: *N*-(1-hydroxypropan-2-yl)-picolinamide ≈ *N*-(2-hydroxypropyl)-picolinamide > *N*-(3-hydroxypropyl)-picolinamide > *N*-propyl-picolinamide.

4. Conclusions

In this article, a series of picolinamide-like ligands was interacted with NH_4VO_3/H_2O_2/picolinamide-like ligands under physiological conditions and studied by NMR. The coordination capability among the ligands is *N*-(1-hydroxypropan-2-yl)-picolinamide ≈ *N*-(2-hydroxypropyl)-icolinamide > *N*-(3-hydroxypropyl)-picolinamide > *N*-propyl-picolinamide. The newly formed peroxovanadate species is seven-coordinate and electron effect plays a key role in the reaction equilibrium.

Supplementary material

Assignments of ^1H and ^{13}C NMR spectra of the interaction systems of NH_4VO_3/H_2O_2/picolinamide-like ligands.

Acknowledgements

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