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# Piperazine as counter ion for insulin-enhancing anions $[VO_2(dipic\text{-}OH)]^-$: Synthesis, characterization and X-ray crystal structure

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ABSTRACT

The new complex $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$ (**1**), where $H_2$dipic-OH = 4-hydroxypyridine-2,6-dicarboxylic acid and Pipz = piperazine, was synthesized and characterized by elemental analysis, FTIR, $^1$H NMR, $^{13}$C NMR and UV–Vis spectroscopy and single crystal X-ray diffraction. The crystal system is triclinic with space group $P\bar{1}$. In this compound, piperazine is diprotonated and acts as counter ion.



## 1. Introduction

Vanadium has been recognized as an important trace element with relevant biological properties [1–8]. Vanadium in its higher oxidation states has a significant effect on numerous biological processes and has various biological, nutritional, and pharmacological influences, including potential applications in treating diabetes and cancer [5]. Considering the biological properties of vanadium, it can be concluded that the combination of vanadium with organic ligands, which have biological properties in diabetes treatment can lead to the generation of novel improved anti-diabetes agents.

4-Hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid, $H_2$dipic-OH), which obtains from the substitution of dipicolinic acid (2,6-pyridine dicarboxylic acid) with a hydroxyl group in position 4, is used widely in biochemistry, organic chemistry, medical chemistry and even in HIV investigation [9–13]. It forms stable chelates with simple metal ions and can display widely varying coordination behavior, functioning as a multidentate ligand [14–25]. The chelidamic acid ligand with vanadium ions commonly has one or two coordination modes [26]. In one coordination mode and formation of the corresponding $[VO_2(dipic\text{-}OH)]^-$-type complexes, a single planar chelidamic acid ligand binds in the equatorial plane of a vanadium cation and two oxo ligands occupy the remaining sites, thereby forming a square planar or square pyramidal coordination geometry. In the solid state, these complexes are five-coordinate, and the corresponding cations can be either organic or inorganic [27,28]. The $[VO_2(dipic\text{-}OH)]^-$ complex has insulin-enhancing properties and anti-diabetic effects and because counter ions can affect the properties, a suitable counter ion choice could potentially enhance uptake of anions [29–32].

Pharmaceutical piperazine derivatives have participated in ion pair complexation reactions [33], and piperazine itself acts as a good proton accepter and has formed proton transfer compounds with different acids such as dipicolinic acid [34,35]. Moreover, piperazine can be found in some complexes as a discrete cation. In this regard, a large number of compounds containing the piperazine as cation such as $(H_2Pipz)[Pd(dipic)_2]\cdot 2H_2O$, $(H_2Pipz)[Ni(dipic)_2]\cdot 4H_2O$, $(H_2Pipz)[Cu(dipic)_2]\cdot 4H_2O$, $(H_2Pipz)[Mn(dipic)_2]\cdot 6H_2O$, $(H_2Pipz)[Pb(dipic)_2]\cdot 2H_2O$, $(H_2Pipz)[Zn(dipic)_2]\cdot 4H_2O$, $(H_2Pipz)[Hg(dipic)_2]\cdot 6H_2O$ have been constructed [36].

Considering the biological activities of vanadium complexes of pyridinedicarboxylic acids, this work is part of our project dealing with the preparation and characterization of $[VO_2(dipic\text{-}X)]^-$-type

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complexes (dipic = 2,6-pyridinedicarboxylato and X = H, OH, $NH_2$, Cl, Br) with different organic bases as counter ion. We believe that more accurate information about these complexes in the solid state could be helpful in the design and development of new compounds based on the insulin-enhancing anions.

In this paper, we wish to report on the synthesis and full characterization in the solid state of a complex anion $[VO_2(dipic\text{-}OH)]^-$ containing the piperazine as cation and water molecules in the crystal lattice. The complete formula of compound **1** is $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$.

## 2. Experimental

### 2.1. Materials and methods

Piperazine, $H_2$dipic-OH and $VOSO_4$ were purchased from Sigma–Aldrich. Elemental analyses were carried out on a Leco, CHNS-932 elemental analyzer. Fourier transform infrared spectra were recorded on a FT-IR JASCO 680-PLUS spectrometer in the region of 4000–400 $cm^{-1}$ using KBr pellets. $^1H$ NMR and $^{13}C$ NMR spectra were obtained on a Bruker 400 spectrometer. Chemical shifts were reported on the $\delta$ scale relative to TMS. Electronic spectra were obtained using a UV-JASCO-570 spectrometer.

### 2.2. Synthesis of complex $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$ (**1**)

Vanadyl sulfate (217 mg, 1.0 mmol) was dissolved in 30 mL of water. Solid 4-hydroxypyridine-2,6-dicarboxylic acid ($H_2$dipic-OH, 183 mg, 1.0 mmol) then was added. The mixture was stirred at 100 °C until dissolution was complete. Afterward, ethanol (20 ml) and solid piperazin (43 mg, 0.50 mmol) were added to the resulting mixture and was refluxed for 22 h until the light green obtained. After 5 days, colorless crystals suitable for X-ray structural analysis from the title complex, were obtained. Anal. Calc. for $C_{18}H_{22}N_4O_{14}V_2$: C, 34.85; H, 3.58; N, 9.03; V, 16.43. Found: C, 34.80; H, 3.55; N, 8.98; V, 16.39%. $^1H$ NMR (DMSO-$d_6$): $\delta = 3.27$ (s, 8H), 7.33 (s, 4H) ppm. $^{13}C$ NMR (DMSO-$d_6$): $\delta = 40.7$ (−$CH_2$−), 112.4 (C−CH=C), 151.1 (C−COOH), 167.2 (C−OH), 173.0 (−COOH) ppm. IR (KBr): 3420 (s, broad), 3245 (m), 3050 (m), 2818 (m), 2754 (m), 2633 (m), 2519 (m), 1682 (s), 1598 (m), 1380 (s), 1293 (m), 1179 (m), 1133 (m), 1056 (s), 949 (s), 897 (m) 868 (m), 760 (s), 645 (m), 580 (m), 570 (m), 461 (s) $cm^{-1}$. UV–Vis (aqueous solution) (λ, nm): 205, 282.

### 2.3. X-ray crystal structure determination of complex **1**

The crystallographic data for complex **1** were collected at room temperature on a Bruker Smart Apex II single-crystal diffractometer working with monochromatic Mo Kα radiation and equipped with an area detector. The crystal structure was solved by direct methods with SHELXS-97 and refined against $F^2$ with SHELXL-97 [37], with anisotropic thermal parameters for all non-hydrogen atoms. Idealized geometries were assigned to the hydrogen atoms except the hydrogen atoms of the water molecule, which have been found in the ΔF map and refined isotropically. Details of the X-ray data collection are reported in Table 1.

**Table 1**
Main crystallographic parameters of complex $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$.

| | |
|---|---|
| Formula | $C_{18}H_{22}N_4O_{16}V_2$ |
| Molecular weight | 652.28 |
| Crystal system | Triclinic |
| Space group | $P\bar{1}$ |
| $a$ (Å) | 7.4407(5) |
| $b$ (Å) | 8.3151(6) |
| $c$ (Å) | 11.4899(8) |
| $\alpha$ (°) | 97.9480(10) |
| $\beta$ (°) | 96.4230(10) |
| $\gamma$ (°) | 115.3870(10) |
| Volume (Å$^3$) | 624.32(8) |
| $Z$ | 1 |
| $D_{calc}$ (g cm$^{-3}$) | 1.735 |
| μ(cm$^{-1}$) | 0.836 |
| F(000) | 332 |
| $\theta_{max}$ (°) | 30.57 |
| Reflections collected | 10130 |
| Independent reflections | 3812 |
| Reflections observed | 3403 |
| $R$(int) | 0.0248 |
| Refined parameters | 332 |
| Final $R_1$[a], $wR_2$[b] (Obs. data) | 0.0321, 0.0871 |
| Final $R_1$[a], $wR_2$[b] (all data) | 0.0365, 0.0904 |
| Goodness-of-fit on $F^2$ | 1.158 |
| Largest peak/hole [e cm$^{-3}$] | −0.22/0.39 |

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$.
[b] $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]$.

## 3. Results and discussion

### 3.1. Synthesis and characterization

The reaction of $VOSO_4$ with $H_2$dipic-OH and piperazin in mixture of water and ethanol were carried out at reflux condition, and colorless crystals **1** were obtained by the slow evaporation of the solvent at room temperature (Scheme 1).

The solid-state properties of $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$ were examined by infrared spectroscopy. IR spectrum of complex **1** shows strong, broad and branched bands at 2519–3420 $cm^{-1}$ due to the O–H stretching vibrations of the crystallization water molecules, aliphatic C–H's of piperazinium, aromatic C–H's of pyridine ring and $NH_2^+$ stretching vibrations of piperazinium. The strong bands at 1682 and 1380 $cm^{-1}$ corresponds to the asymmetric and symmetric stretching of carboxyl groups, respectively [38]. The complex also shows a sharp and strong bond at 948 $cm^{-1}$ due to V=O symmetric stretching and two bands at 897 and 867 $cm^{-1}$, which are assigned to V=O asymmetric stretching absorptions. Furthermore, this complex showed one strong band at 1056 $cm^{-1}$, which is attributed to the C–O (hydroxy) vibration of dipic-OH ligand. The IR spectrum of $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$ shows a very similar spectral pattern with that of five-coordinate complexes reported $[VO_2(dipic\text{-}OH)]^-$ [27,28] except for the characteristic modes of the cations. This fact indicates similar coordination environments in these compounds as confirmed by crystal structural data.

The $^1H$ and $^{13}C$ NMR spectroscopies were applied as a tool for structure determination of the **1**. $^1H$ NMR spectrum complex **1** shows two characteristic sets of resonances from which the one at 3.27 ppm is assigned to methylene protons on the piperazin [34] and another one at 7.33 ppm corresponds to $(dipic\text{-}OH)^{2-}$ protons [27] (Fig. 1). Free ligand, $H_2$dipic-OH, has a resonance at 7.54 ppm in DMSO-$d_6$ (Fig. S1). The resonance at 7.33 ppm is shifted up-filed from the non-coordinated ligand at 7.54 ppm, indicating that these protons are more shielded upon coordination. The broad and low intense resonance at 9–10 ppm is assigned to hydroxyl protons on the $(dipic\text{-}OH)^{2-}$ ligand. The $^{13}C$ NMR spectrum this complex consists of five distinct resonances at 40.7, 112.4, 151.1, 167.2 and 173.0 ppm (Fig. S2). The first peak at 40.78 ppm is assigned to piperazinum ion [34] and the four latest are related to $(dipic\text{-}OH)^{2-}$.

For the oxovanadium(V) compounds, no d–d bands are expected because they have a 3 $d^0$ configuration and there are no d electrons [39]. The electronic spectrum of the complex, $[H_2Pipz][VO_2(dipic\text{-}OH)]_2\cdot 2H_2O$, was recorded in the 190–400 nm region in water, ethanol, methanol, DMF and DMSO (Fig. S3). In water,