Inorganica Chimica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Vanadate complexes of 3-hydroxy-1,2-dimethyl-pyridinone: Speciation, structure and redox properties

Tamás Jakusch [a,*], Éva A. Enyedy [a], Károly Kozma [a], Zsófia Paár [a], Attila Bényei [b], Tamás Kiss [a,c,*]

[a] Department of Inorganic and Analytical Chemistry, University of Szeged, Dóm tér 7, H-6720 Szeged, Hungary
[b] Institute of Chemistry, Laboratory for X-ray Diffraction, University of Debrecen, Egyetem tér 1, Debrecen H-4032, Hungary
[c] HAS-USZ Bioinorganic Chemistry Research Group, Dóm tér 7, H-6720 Szeged, Hungary

ARTICLE INFO

Article history:
Received 9 October 2013
Received in revised form 20 December 2013
Accepted 30 December 2013
Available online xxxx

Keywords:
Vanadate complexes
3-Hydroxy-1,2-dimethyl-pyridinone
Speciation
^{51}V NMR
Redox properties

ABSTRACT

Several articles were published about the vanadate–3-hydroxy-1,2-dimethyl-pyridinone (Hdhp) system, however, the results are contradictory and not complete: pH-potentiometry and ^{51}V NMR spectroscopy were used to clarify this complicated system. The eleven peaks in the spectra at different chemical shifts were assigned to ten stoichiometrically different compounds; four of them are new, never identified or assigned before. Besides the simple mono- (in two different protonation states) and bis complexes (in three different protonation states) a tris complex, three dinuclear and a trinuclear complex were found based on the ^{51}V NMR spectra measured at different pH values and various metal ion concentrations and metal-to-ligand ratios. As a joint evaluation of the two methods, overall stability constants were calculated for all species.

X-ray structure of the potassium salt of the bis complex, $[V(V)O_2(dhp)_2]$ was also determined. The trans effect of the oxido-oxygens results in maltolato-type coordination of the ligand instead of the catecholate-like chelation.

The redox properties of $[V(V)O_2(dhp)_2]$ and some other prodrug vanadium(V) bis complexes were investigated by spectrophotometry in aqueous solution via their reduction by glutathione (GSH) and L-ascorbic acid (ASC) under strictly anaerobic conditions and by cyclic voltammetry at physiological pH. The reduction was found to be much faster by ASC in all cases as compared with GSH and the reaction rate of the reduction of $[V(V)O_2(dhp)_2]$ was prominently high most probably due to the formation of the significantly higher stability of the corresponding vanadium(IV) complex.

1. Introduction

Numerous vanadium(IV) and (V) complexes showed significant antidiabetic activity in preclinical *in vitro* and *in vivo* studies [1–4]. One of them the bis(ethylmaltolato)oxovanadium(IV) (BEOV) complex has entered into Phase IIa trial [5]. The active vanadium species exhibit *ca.* 30–70% of the activity of insulin *in vitro*, and generally the efficacy of the V(IV) salt and especially complexes exceeds the originally tested V(V) salts [5, 6]. However the V(V)-compounds tend to be less toxic than V(IV)-complexes, and in general there is no significant correlation between vanadium oxidation state and the insulin-mimetic efficacy [3].

Up to now the most effective hypoglycemic drug candidates are the orally available charge-neutral bis complexes of V(IV) formed with bidentate ligands. The advantage of these metal complexes over the inorganic oxovanadium(IV) salts is their increased bioavailability and thus enhanced pharmaceutical efficacy. According to the stability of this type of complexes, they are usually not stable enough at the pH of the gastric juice resulting in unfavorable uptake, however, that can be bypassed by means of proper drug formulation such as encapsulation methods [7]. Based on the dosage range data of the clinical trials and the absorption properties of BEOV *ca.* 20 μM is estimated as the maximum concentration of vanadium attainable in the human blood serum during the treatment of diabetes mellitus [8]. This kind of vanadium complexes shows facile interconversion between the oxidation states (IV and V) and biologically relevant reducing agents such as L-ascorbic acid (ASC, $10–80 \times 10^{-6}$ mol dm^{-3}), cysteine (33×10^{-6} mol dm^{-3}), glutathione (GSH, 4×10^{-6} mol dm^{-3}), uric acid ($200–400 \times 10^{-6}$ mol dm^{-3}), alpha-tocopherol ($20–30 \times 10^{-6}$ mol dm^{-3}) *etc.* and the dissolved oxygen ensure that both V(IV) and V(V) species are relevant under serum conditions [9].

It was pointed out in our previous works that vanadium in oxidation state IV and V is bound mostly to serum transferrin in the therapeutically relevant concentration range and the original

* Corresponding authors. Address: HAS-USZ Bioinorganic Chemistry Research Group, Dóm tér 7, H-6720 Szeged, Hungary. Tel.: +36 62 544 337 (T. Kiss).
E-mail addresses: jakusch@chem.u-szeged.hu (T. Jakusch), kiss@chem.u-szeged.hu (T. Kiss).

0020-1693/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2013.12.034