A new vanadium (V)-peroxo species in the presence of citric acid

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Abstract
In a pH-specific fashion, V$_2$O$_5$ and citric acid in the absence and presence of H$_2$O$_2$ reacted and afforded, in the presence of NaOH and (C$_6$H$_5$N$_3$)$_2$(CO$_3$)$_2$, two new dinuclear V(V) binary non-peroxo (C$_6$H$_5$N$_3$)$_2$[V$_2$O$_4$(C$_6$H$_5$O$_7$)$_2$]·2H$_2$O (1) and ternary peroxo (C$_6$H$_5$N$_3$)$_4$[V$_2$O$_2$(O$_2$)$_2$(C$_6$H$_5$O$_7$)$_2$]·6H$_2$O (2) species, respectively. Complexes 1 and 2 were characterized by elemental analysis, UV/Visible, FT-IR, NMR (solution and solid state CP-MAS) and Raman spectroscopies, cyclic voltammetry, and X-ray crystallography. Both 1 and 2 are members of the family of dinuclear V(V)-citrate species bearing citrate with a distinct coordination mode and degree of deprotonation, with 2 being the missing link in the family of pH-structural variants of the ternary V(V)-peroxo-citrate system.

Keywords: Vanadium (non)peroxo citrate structure, vanadium picolinate, cell toxicity, insulin mimesis

1. Introduction
Participation of vanadium in abiotic and biological systems has been amply established in the past decades, with research activities aimed at clarifying its role and action [1-3]. Vanadium as an inorganic cofactor has been shown to participate in key metalloenzyme systems [4], such as nitrogenases [5] and haloperoxidases [6]. Concurrently, it has been shown to exhibit bioactivities including antitumorogenicity [7], mitogenicity [8], and inhibition of metabolic enzymes such as phosphoglucomutases and others [9]. Noteworthy, however, has been the association of vanadium with the heterogeneous syndrome of Diabetes mellitus by virtue of its insulin mimetic activity [10].

The physiological effects of vanadium, involving the biologically relevant oxidation states (III, IV and V), are intimately associated with interactions toward physiological substrates of variable molecular mass.

Among such interactions, those corresponding to low molecular mass targets present a particular bioinorganic challenge, perhaps of comparable biological importance to those emerging from high molecular mass biotargets, i.e. peptides and proteins. Understanding such interactions has been one of the most significant goals of vanadium research, specifically targeting the bioavailability and solubility of vanadium species bound to organic substrates. To this end, solution speciation studies [11] projecting fundamental characteristics on binary and ternary vanadium systems, containing physiological as well as biologically relevant ligands, were reported. Among the various ligands studied in the presence of vanadium were hydroxycarboxylate-containing organic ligands, such as citric acid. The latter exists in human plasma (~0.1mM) [12] and is known for its metal ion solubilizing ability and promotion of potential metal ion bioavailability in cellular fluids.
The latter property is a crucial factor in the development of insulin mimetic activity by a synthetic vanadium species. On these grounds, the arisen synthetic studies on binary vanadium-ligand and ternary vanadium-peroxo-ligand systems have over the years provided ample information on a number of dinuclear V(IV and V)-ligand complexes as well as ternary V(V)-peroxo-ligand species [13].

Driven by the need to a) delineate the hitherto incomplete aqueous structural speciation of binary and ternary V(V)-(peroxo)-citrate systems, and b) investigate the insulin mimetic activity of well-defined soluble V(V)-(peroxo)-carboxylate species of distinct structural features and V-oxidation state, synthetic efforts targeting the pH-dependent synthesis and isolation of new binary and ternary vanadium-(peroxo)-citrate complexes were launched in our lab. Hence, we report herein the pH-specific synthesis, isolation, spectroscopic and structural characterization of two new species in the V(V)-(non)peroxo-citrate system.

The ternary species appears to be the missing link in the family of V(V)-(peroxo)-citrate pH-structural variants, structurally characterized thus far. In view of the distinct structural features borne by the presented species, binary V(III), V(IV) and V(V) as well as ternary V(V) O- and O,N-containing relevant compounds were tested in vitro cell cultures to assess their toxicity and insulin mimetic activity, thus associating their nature and composition with biochemical attributes of biologically active vanadium.

2. Materials and Methods

All experiments were carried out under aerobic conditions. Nanopure quality water was used for all reactions. V₂O₅, citric acid, and H₂O₂ 30% were purchased from Aldrich. Sodium hydroxide and guanidinium carbonate were supplied by Fluka.

3. Results and Discussion

The overall stoichiometric reaction leading to complex 1 is shown schematically below:

\[
\text{pH} \approx 6.5 \\
\text{V}_2\text{O}_5 + 2 \text{HOOC-CH}_2-\text{COOH} + 6 \text{OH}^- \\
[\text{V}_2\text{O}_4\text{C}_6\text{H}_5\text{O}_7]^{6-} + 7 \text{H}_2\text{O}
\]

In an alternative approach, the addition of hydrogen peroxide to the reaction mixture in a molar ratio of V:H₂O₂ 1:5 expedited the reaction and led to the same non-peroxo structural variant compound 1. The identity of the crystalline product as 1 was attested to by elemental analysis, FT-IR and X-ray unit cell determination for one of the single crystals.

The (CH₆N₃)₄[V₂O₄(C₆H₅O₇)₂]·6H₂O (2) complex was synthesized from simple reagents in aqueous solutions. In a typical reaction, V₂O₅ reacted with citric acid in the presence of NaOH and guanidinium carbonate at pH ~7.0. Addition of dilute H₂O₂ solution in a molar ratio V:H₂O₂ 1:16 (vide infra) promoted efficiently the peroxidation reaction of V(V). The overall stoichiometric reaction leading to complex 2 is shown schematically below:

\[
\text{pH} \approx 7.0 \\
\text{V}_2\text{O}_5 + 2 \text{HOOC-CH}_2-\text{COOH} + 2 \text{H}_2\text{O}_2 + 4 \text{OH}^- \\
[\text{V}_2\text{O}_2\text{O}_2\text{C}_6\text{H}_5\text{O}_7]^{4-} + 7 \text{H}_2\text{O}
\]

Ethanol, added as a precipitating solvent to the reaction mixture in both reactions described above, afforded yellow (1) and red (2) crystalline materials, the analytical composition of which was consistent with the formulation of 1 and 2, respectively (vide supra). Positive identification of the crystalline products was achieved by spectroscopic methods and X-ray crystallography for one of the isolated single crystals from 1 and 2.
Both complexes are stable, in the crystalline form, in the air, for fairly long periods of time. Complex 1 is readily dissolved in water in contrast to complex 2, which exhibits low solubility in water. Both species are insoluble in dimethyl sulfoxide (DMSO), N,N'-dimethylformamide (DMF), acetonitrile, alcohols (CH₃OH, i-PrOH), and dichloromethane at room temperature even after heating up of the respective solutions.

4. Conclusions
The synthetic structural speciation approach, targeting pH-specific reactivity of the binary and ternary systems of V(V) with citrate and hydrogen peroxide, led efficiently to the isolation, spectroscopic and structural characterization of two new species, one binary complex 1 and one ternary species 2. Both complexes confirm a) the pH-dependent nature of the deprotonation state of citrates bound to a universally stable V₂O₂ core assembly, and b) the influence of the employed reaction conditions upon the formation of the coordination sphere of V(V) in both binary and ternary species. Compound 2 presents the missing link in a triad of pH-dependent structural variants [V₂O₃(O₂)₄(C₆H₇O₇)]ₙ⁻ (n=6, p=2; n=5, p=4; n=4, p=6), thus projecting the complex yet well-defined speciation components of the ternary V(V)-peroxo-citrate system. Synthetic and biological work in the direction of elucidating the distinct role and involvement of such factors, enabling vanadium to promote insulin mimetic effects, are further perused in our labs.

References