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Stereospecificity in vanadium Schiff base complexes: Formation, crystallization and epimerization processes

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ABSTRACT

The structures of two stereoisomers of the chiral anion $[VO_2(N\text{-salicylidene-isoleucinato})]^-$ possessing three centers of chirality, the vanadium atom (configuration *A*/*C*) and the isoleucine moiety (configuration *R*/*S* on *alpha* and *beta* carbons), are presented. The absolute configuration of all available stereoisomers, *CSS*, *ARR*, *CSR* and *ARS*, was determined by electronic circular dichroism (ECD), which allows distinguishing between diastereomers, and by vibrational circular dichroism (VCD) capable of differentiating between all four stereoisomers. The comparison of experimental VCD and infrared (IR) spectra with simulated spectra for band assignment revealed the IR spectra of the diastereomers differing significantly in the C – H stretching region of the aromatic part in the molecule. Crystallization from binary systems composed of equal ratio of two stereoisomers of isoleucine, unveiled the lower solubility of *CSS* and *ARR* stereoisomers, while a longer crystallization time of the *CSR* and *ARS* stereoisomers allowed proceeding the vanadium-catalyzed epimerization, leading to the subsequent presence of the *CSS* and *ARR* stereoisomers in the product obtained.

1. Introduction

Oxidovanadium complexes of tridentate Schiff bases and ligands providing similar coordination mode for the vanadium atom attract continuous research interest for their application in the catalysis of oxidative reactions [1–9]. The reactivity of such complexes is closely related to the role of the metal center in vanadium haloperoxidases [10–14] which are able to catalyze different halogenation reactions. In particular, special interest is focused on the asymmetric oxidations of prochiral sulfides and alkenes to the corresponding chiral sulfoxides and epoxides [1,15–17]. However, the structural variability and chemical reactivity of vanadium Schiff base complexes give rise to a wider range of their biochemical applications, such as insulin mimetics [18], modeling of supramolecular interactions in vanadium haloperoxidases [19,20] and probing the chirality at the metal centre, which is discussed in this paper. Vanadium compounds exhibit many biological functions [21,22] including the binding and cleavage of DNA achievable by several vanadyl ($V^{IV}O^{2+}$) [23,24] and peroxido (V^{V}) complexes [25,26] as well as vanadium Schiff base complexes [27–29], that results in some cases in anticancer activity [23,24]. Recently it has been shown that this type of interaction may significantly be influenced by the chirality of the vanadium complex [30]. Furthermore, as chirality is an extremely important property for biological systems and upon considering the known examples of different biological activity of enantiomers [31], the chirality of potential biologically active vanadium complexes should be always discussed.

As a result of the geometry of Schiff bases used commonly for the synthesis of corresponding vanadium complexes (Fig. 1a), a chiral complex of vanadium is formed upon complexation, yielding two enantiomers possessing a stereogenic center at the vanadium atom (Fig. 1b).

A structure search in the Cambridge Crystallographic Data Centre (CCDC) [32] provided over 300 hits of octahedral and tetragonal pyramidal complexes of vanadium with Schiff bases or closely related ligands, while having the geometry depicted in Fig. 1b. Unfortunately, little attention has been devoted to the study of the metal centered chirality in vanadium Schiff base complexes so far, although some stereospecific aspects of such complexes have been already described [33–37]. In this paper we report on the chirality of vanadium Schiff base complexes derived from isoleucine. Isoleucine belongs to the branched-chain amino acids (valine, leucine, isoleucine), and possessing two stereogenic centers it occurs in the form of four stereoisomers (Fig. 2). Among these forms, the L-isomer dominates in biological systems. It was found that isoleucine increases the glucose uptake in an insulin independent manner [38]. The hypoglycemic effect of isoleucine involves an increased muscle glucose uptake and a whole body glucose oxidation [39]. L-*allo*-isoleucine is formed in human body in trace amounts by a mechanism not yet explained quite well; however, based on studies with ^{13}C-labeled isoleucine the proposed mechanism includes in vivo retransamination of 3-methyl-2-oxopenanoate, the byproduct of

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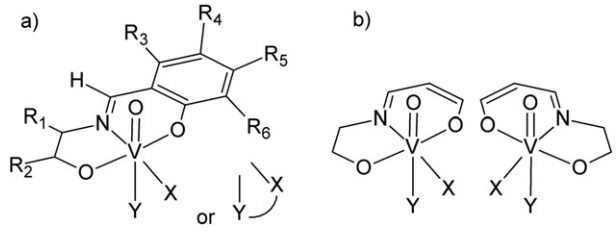

Fig. 1. General formula of the vanadium(IV or V) Schiff base complexes (a) and the corresponding enantiomers (b). In principle, Schiff bases with different donor sets or tridentate ligands with different side chains but the same coordination geometry around the vanadium enforce the chirality at the vanadium atom as well. The X position is frequently occupied by an oxido ligand (= O) or alcoholate (–O–R′), the Y position is free (tetragonal pyramidal geometry) or occupied by N or O donor atom. The formation of a chelate ring at these positions is often observed. The configuration on the vanadium atom (b) is assigned depending on whether clockwise (*C*) or anticlockwise (*A*) sequence of the priority numbers of the ligating atoms is found in the chelate ring [37].

L-isoleucine transamination, demonstrating that the carbon skeleton of L-*allo*-isoleucine is derived from L-isoleucine [40]. The maple syrup urine disease (MSUD) is a recessive deficiency of the branched-chain-ketoacids dehydrogenase complex involved in the metabolism of the branched-chain amino acids. MSUD manifests itself with neonates by their feeding intolerance failure to thrive, and may lead to irreversible mental retardation and possible death if left untreated. The concentration of L-*allo*-isoleucine above 5 μM in blood plasma is currently the most sensitive diagnostic marker for MSUD [41].

Here we provide structures of two new stereoisomers of the complex $[VO_2(N\text{-salicylidene-isoleucinato})]^-$ which complete the comprehensive information about the chirality of this type of vanadium complexes [42] and we show that the unequivocal determination of the absolute configuration of the complexes done by X-ray structure analysis as well as electronic and vibrational circular dichroism (ECD and VCD) completed by the NMR data and infrared spectroscopy (IR) may bring fruitful results to the study of vanadium-centered chirality. This complex anion possesses three stereogenic centers: the vanadium atom (configuration *A* or *C*), the *alpha* and *beta* carbons of the isoleucine moiety (configuration *R* or *S* on both carbon atoms), so the total number of stereoisomers theoretically possible is 8: *ASS*, *ASR*, *ARS*, *ARR*, *CSS*, *CSR*, *CRS* and *CRR*.

2. Experimental

2.1. General information and materials

All reagents and solvents were obtained from commercial sources and used without further purification. V_2O_5 was prepared by thermal decomposition of NH_4VO_3. Elemental analyses (C, H, N) were performed on a Vario MIKRO cube (Elementar). Vanadium(V) was determined volumetrically by titration with $FeSO_4$ using diphenylamine as indicator. Solid state IR spectra were recorded on Thermo Scientific Nicolet 6700 FT IR spectrometer in Nujol (400–1800 cm^{-1}) and Fluorolube (2000–3500 cm^{-1}) mulls. The ^1H NMR spectra were recorded with a Varian Mercury plus instrument (300 MHz for ^1H). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. The ^{51}V NMR spectra of 2×10^{-3} M solutions in acetonitrile were registered at 278 K on a Varian Mercury Plus 600 MHz spectrometer operating at 157.88 MHz (^{51}V) in 5 mm tubes. Chemical shifts (δ) are given in ppm relative to $VOCl_3$ as external standard ($\delta = 0$ ppm). Solution VCD spectra were recorded on a Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution equipped with the Bruker PMA 50 VCD sidebench module, using a data collection time of 6 h. CD_3CN solution samples were placed in a 100 μm path length BaF_2 cell. All spectra were corrected for background effects by solvent subtraction. ECD spectra were recorded on a JASCO J-815 CD spectrometer in CH_3CN solutions with a 1 cm cell.

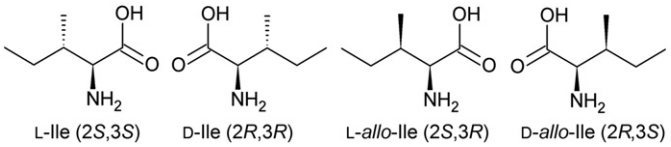

Fig. 2. Stereoisomers of isoleucine.

2.2. X-ray diffraction

Diffraction data were collected using a Kappa Apex II (Bruker) diffractometer equipped with a Cryostream Cooler (Oxford Cryosystems). Data were collected using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) and were corrected for radiation absorption and polarization effects by methods incorporated in the diffractometer software. The phase problem was solved by direct methods (SHELXS97 [43]) and refined by full-matrix least-squares based on F^2 (SHELXL97 [43]). All non-hydrogen atoms were refined with no restraints and with anisotropic displacement parameters. Hydrogen atoms were included in idealized positions and refined as riding atoms. Geometric data were obtained with a recent version of the PLATON [44] program. Graphics were obtained with DIAMOND [45].

2.3. Computational details

All the calculations were carried out using the Gaussian09, Revision A.02 [46] software package. The molecular structures of nine conformers for given complex anion have been optimized at the DFT (density functional theory) level with the B3PW91 [47–49] hybrid functional both in vacuo and within the solvent environment using tight convergence criteria and an ultrafine integration grid. We have employed the all-electron Wachters+f (14s11p6d3f)/[8s6p4d1f] basis set [50,51] for the vanadium atom together with the 6-31++G(d, p) basis sets [52,53] for the remaining atoms. The polarizable continuum model (PCM) in its integral-equation formalism (IEF-PCM) [54,55] with default parameters has been used to simulate the acetonitrile solution. Subsequent calculations of harmonic vibrational frequencies, infrared absorption intensities (IR) and rotational strengths (VCD) were carried out for the optimized structures. The presented simulated Boltzmann-averaged VCD spectra were calculated at the B3PW91 level using the PCM solvent model. Normalized Boltzmann factors (equilibrium populations) of 9 conformers of the stereoisomers built up by rotation of the *sec*-isobutyl and/or ethyl groups by 120° were estimated according to their calculated ΔG values at T = 298.15 K. Experimental IR bands were compared with the scaled gas-phase vibrational frequencies obtained only for the conformers presented in the crystal structures (Fig. 3). The simulated VCD and IR spectra have been plotted using Lorentzian band shapes with 4 cm^{-1} and 1 cm^{-1} bandwidths respectively and with frequencies scaled by 0.9669 [56]. Further computational details and comments are covered in [42].

2.4. Syntheses

All stereoisomers were prepared following the synthesis protocol described in [42]. Briefly: Salicylaldehyde (0.531 mL, 5 mmol) in tert-butanol (3 mL) was added to a solution of the amino acid (0.645 g, 5 mmol) dissolved in acetone (3 mL) and tetrabutylammonium hydroxide (3.6 mL of 40% w/w solution, 5 mmol) and the solution was stirred for 1 h. After V_2O_5 (0.45 g, 2.5 mmol) was dissolved in tetrabutylammonium hydroxide (3.6 mL of 40% w/w solution, 5 mmol) at room temperature the resulting colorless solution was added to the solution of a Schiff base and the solution was stirred for 15 min. To the orange solution 3 mL of distilled water was added. Pale yellow crystals of corresponding complex appear after 1–2 days. Anal. (%) Cald. for $C_{29}H_{51}N_2O_5V$: C 63.35, H 9.2, N 5.01, V 9.12.

$(NBu_4)[VO_2(N\text{-salicylidene-D-isoleucinato})]$ *ARR*: Anal. (%) Found: C 63.37, H 9.22, N 5.09, V 9.23. ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.36 (dt, J = 16.93 Hz, 1.51 Hz, 1H) 7.31 (dd, J = 8.93 Hz, 1.2 Hz, 1H), 6.96 (d, J = 8.23 Hz, 1H), 6.74 (t, J =