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New insights into the coordination chemistry of Schiff bases derived from amino acids: Planar [Ni_4] complexes with tyrosine side-chains

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ABSTRACT

Structure and properties of a rare metal complex of the chiral Schiff base ligand derived from *ortho*-vanillin and *L*-tyrosine are presented. This study is a continuation of research on ligands containing biologically compatible moieties. The ligand is also fully characterized in form of a sodium salt, in particular in solution, for the first time. The metal complex contains a unique bowl-shaped [Ni_4] core. Its structure is investigated both in solution (ESI-MS, NMR) and in solid state (X-ray diffraction studies). Under certain conditions the complex can be isolated as crystalline DMF solvate which is studied in solid state.

1. Introduction

Ortho-vanillin is known as a precursor of new magnetic materials, for instance a trinuclear dysprosium complex, that shows SMM behaviour [1] or a heterometallic [Co_2Gd_2] complex [2]. Not only *ortho*-vanillin itself forms materials with highly interesting magnetic properties, but also Schiff-base ligands derived from *ortho*-vanillin are known as precursors of new magnetic materials [3–7].

Introduction of amino acids to such ligands allows for increase in their coordination capabilities, now involving more coordination sites, and in their biological compatibility. Schiff bases containing L-tyrosine and their metal complexes exhibit a variety of interesting properties. Antimicrobial activity against gram-positive and gram-negative bacteria was reported for Schiff bases containing indole-3-carboxaldehyde and their transition metal (Cu, Ni, Co) complexes [8,9]. The metal complexes, in particular those bearing nitrate as counter-ion, showed the highest antimicrobial activity. Cinnamon aldehyde and its derivates used as aldehyde sources lead to Schiff bases, which are potentially antibacterial and antifungal. In some cases their activity was higher compared to the standard reference drugs [10]. A salicylaldehyde-based Schiff base strongly inhibits growth of *E. coli* in the same range like Ampicillin. Measurements of the genes associated with expression of metabolism suggest that the growth is inhibited probably through down-regulation of *cysB* and *tsh* gene leading to an interference in cysteine biosynthetic pathway and to inhibiting the biosynthesis of temperature-sensitive hemagglutinin [11]. The same compound was identified as a potent non-competitive α-glucosidase inhibitor. The free ligand exhibits a higher inhibitory activity compared to its corresponding silver(I) complex [12]. A mononuclear copper(II) complex with a Schiff base derived from 5-bromosalicylaldehyde and *L*-tyrosine mimics ascorbate oxidase activity [13]. Catalytic activity was reported for ruthenium(II) complexes with substituted salicylaldehydes [14], homogenous and heterogeneous binuclear manganese(II) complexes with salicylaldehyde [15] and an encapsulated binuclear manganese(II) complex with salicylaldehyde in zeolite Y [16].

In our previous work we introduced studies of stability and biological properties of a Schiff-base ligand derived from *ortho*-vanillin and *L*-glutamic acid, along with its [Cu_4] complex [17]. The pendant carboxylic group featured by the [Cu_4] complex resulted in its remarkable solubility, also in aqueous solutions and stability in phosphate buffer. We also showed that this ligand system is capable of forming large wheel-like [Ni_{15}] complexes [18].

While for tetranuclear nickel complexes bridged by oxygen

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atoms the cubane-like core is the most common motif, examples with a planar core are rare. In the literature some examples of planar or nearly planar tetranuclear nickel-containing core are known. A complex formed by 1,3-bis(benzoylacetoneimine)-propan-2-ol, a pentadentate Schiff-base ligand, possesses a twisted-chair core [19]. Surrounded by a macrocyclic ligand, a bowl-like complex with a planar core is formed [20]. Further complexes with a planar core, but bridged by acetate and/or methoxo ligands on both sides of the plane, are formed involving other macrocyclic ligands [21,22]. Planar cores bridged outside the plane are formed by non-macrocyclic ligands too [23,24]. The planar core motif can be also found in heptanuclear nickel complexes [25,26].

In this contribution we report on new $[Ni_4]$ complexes of a ligand derived from *L*-tyrosine and *ortho*-vanillin. The structure of the green needle-shaped crystals was confirmed with X-ray diffraction studies and it was found that the central metal ion's coordination sphere is distorted octahedral. Two of metal centers are chelated by three ligand molecules, whereas two solvent molecules complete the coordination sphere of the other two metal ions. The ligand can form complexes in a pentadentate or tridentate manner. The complex units are linked due to intermolecular hydrogen bonds involving the solvent molecules present in the crystal structure. Although the complexes bear aromatic moieties, π-π interactions do not play any role in the crystal structure packing. The ligand has been mentioned in literature, but only herein the first full chemical characterization is provided. The $[Ni_4]$ complexes display a unique planar core and the presence of tyrosine hydroxyl side-chains.

2. Results and discussion

2.1. Synthesis and characterization

The title ligand $\mathbf{H_2L}$ was mentioned in some publications but never full characteristics was reported in spite of the synthetic procedures that yield its monopotassium salt published in 1990 [27] and for the neutral form, but with lack of basic analyses, e. g. NMR and mass spectrometry [28]. The ligand was usually generated *in situ* as precursor of vanadyl complexes used e. g. for modelling of active centers of peroxidases or phosphatases [29–31]. Furthermore, mononuclear vanadium and copper complexes with co-ligands are known [32,33]. It is a Schiff-base derived from *ortho*-vanillin and *L*-tyrosine (Fig. 1).

Herein the ligand $\mathbf{H_2L}$ was synthesized in the form of a disodium salt $\mathbf{Na_2L}$ (Fig. 1) following the procedure recently reported by us for the *L*-glutamic acid derivate [17]. Formation of a disodium salt of the organic ligand is consistent with the elemental analysis results (see SI for more information) and the synthesis procedure (usage of 2 eq NaOH), the ESI(+) mass spectrum shows the molecular peak for $[H_2L{+}H^+]^+$ ($m/z = 316.12$; Fig. S1).

The ^{1}HNMR spectrum in MeOD (Fig. 2) shows all of the expected signals, except for the proton from the phenolic −OH group which is due to a fast exchange with the solvent. Integration of the signal at 3.35 ppm gives a value of 0.57 only instead of the expected integral of 1 due to overlapping of the signal with the solvent peak. The NMR spectra also show residues of diethyl ether which could not be removed.

When the NMR spectrum was recorded in D_2O, additional sets of signals appeared. Similar as previously reported for the ligand derived from *ortho*-vanillin and *L*-glutamic acid [17], $\mathbf{Na_2L}$ (black boxes in Fig. S2) partly decomposes to *ortho*-vanillin (red boxes in Fig. S2) and *L*-tyrosine (blue boxes in Fig. S2). Hereby the signal at 7.15–7.20 ppm with an integral of 1.05 results from overlapping of the signals of the aromatic protons from *ortho*-vanillin and *L*-tyrosine. The signal at 3.08 ppm with an integral of 4.04 results from overlapping of the signals of the methoxy groups from *ortho*-vanillin and $\mathbf{Na_2L}$. The multiplet at 2.96–3.05 ppm with an integral of 1.40 originates from the overlapping of the signals from the ligand and protons of the *L*-tyrosine methylene group. The *ortho*-vanillin/$\mathbf{Na_2L}$ ratio was determined by the integrals which should give 1 in total and showed decomposition of 23%. $\mathbf{Na_2L}$ is soluble in polar solvents such as water and methanol.

The corresponding complex $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ was crystallized from a system where the organic ligand was generated *in situ*. $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ displays molecular peaks under ESI-MS conditions in methanolic solution in both positive ($m/z = 1485.12$) and negative mode ($m/z = 1483.11$) (Figs. S4 and S5). These results indicate the stability of $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ in solution. On drying in vacuum for several hours the color of the solid complex changes slightly to olive green. However, the vacuum-dried and air-dried samples of $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ show identical IR spectra (Fig. 3). These observations additionally confirm a reasonable stability of the complex in solid state. The complex dissolves very well in DMSO resulting in a yellow color of the solution. In methanol $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ is less soluble but the color of the solution is green. $\mathbf{[Ni_4(L)_4]\text{-}MeOH}$ also dissolves in water but formation of colourless to light green residues is observable. Due to the paramagnetic nature of the complex NMR studies are limited, so that it remains unclear if the complex decomposes in water and DMSO.

The DMF solvate of $\mathbf{[Ni_4(L)_4]}$ ($\mathbf{[Ni_4(L)_4]\text{-}DMF}$) is synthesized in the same manner but with addition of DMF at the end (see Experimental section). Synthesis of the complex in a macroscale sample (25 mL; 1 mmol) did not lead to crystals suitable for X-ray analysis. Suitable crystals were obtained from a microscale sample (150 μL; 1/96 mmol). However, the elemental analysis shows a significant increase of nitrogen content compared to the methanol solvate. Comparison of the IR spectra of the DMF and methanol solvate of $\mathbf{[Ni_4(L)_4]}$ reveals a difference in the peaks in the relevant region between 400 cm^{-1} and 1800 cm^{-1} (Fig. 4). This difference is

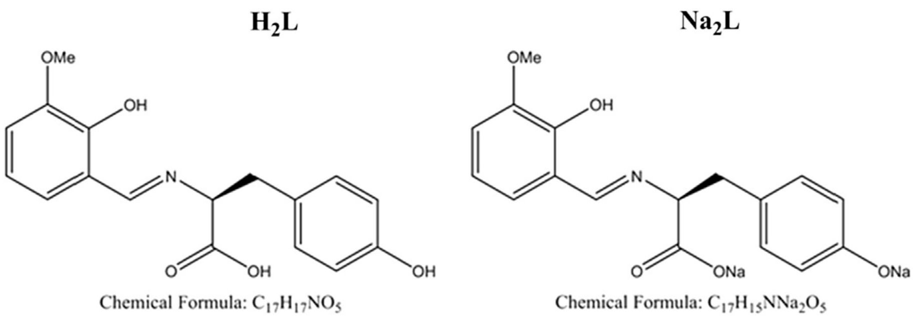

Fig. 1. Structural and chemical formula of the ligand in its neutral form $\mathbf{H_2L}$ and as disodium salt $\mathbf{Na_2L}$.