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Vanadocene complexes of amino acids bearing functional group in the side chain

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ABSTRACT

Reaction of Cp_2VCl_2 with α-amino acids bearing functional group in the side chain gives *N*,*O*-chelate complexes $[Cp_2V(N,O\text{-aa})]Cl$ (aa = ser, thr, asp, glu, asn, gln, lys, arg). These complexes were studied by spectroscopic methods (ESR, IR and Raman). All prepared complexes contain amino acid ligand bonded *via* oxygen atom of carboxylic group and nitrogen atom of amino group in α-position giving five-membered chelate ring. We have observed that hydroxy, amine, carboxylic, amide and guanidinium groups present in α-amino acid ligand are not able to coordinate to the central vanadium atom.

1. Introduction

Bent metallocene complexes of the formula $[Cp_2M(aa)_x]^{n+}$ ($Cp = \eta^5\text{-}C_5H_5$; M = Ti, V, Mo; aa = amino acid, $x = 1$, 2 and $n = 1$, 2) attract considerable attention due to cytostatic activity of the parent metallocene dichlorides (Cp_2MCl_2) [1–4]. Titanocene dichloride (Cp_2TiCl_2) has reached the phase II of the clinical trials [5,6]. Vanadocene dichloride (Cp_2VCl_2, **1a**) and molybdenocene dichloride (Cp_2MoCl_2) showed *in vitro* activity toward cultured Ehrlich ascites tumor cells as well as *in vivo* activity toward CF1 mice bearing fluid Ehrlich ascites tumors [7–9].

The investigation of the antitumor effect of the metallocene dihalides is currently focused on the interaction with essential α-amino acids, peptides and enzymes. It was found that titanocene dichloride gives monodentate complexes $[Cp_2Ti(O\text{-aa})_2]^{2+}$ with α-amino acids bonded through oxygen of the carboxylic group due to the high oxophilicity of the titanium(IV) [10,11] while in vanadocene and molybdenocene complexes form the *N*,*O*-chelates of the type $[Cp_2M(N,O\text{-aa})]^+$ [12–14]. The equilibrium between *N*,*O*-chelate and complexes with two *O*-bonded amino acids has been described only for vanadocene complexes of the α-amino acids bearing secondary amino groups such as L-proline, *N*-methylglycine or *N*-phenylglycine [15]. Different type of vanadocene complexes was observed in case of sulfur-containing amino acids. In these complexes, depending of pH, six-membered *O*,*S*- and five-membered *N*,*S*- or *N*,*O*-chelate structures were observed [16]. Similar reaction of Cp_2MoCl_2 with cysteine yields $[Cp_2Mo(N,S\text{-cys})]^+$ and complex $[Cp_2Mo(S\text{-cys})_2]$ with two cysteine ligands bonded through sulfur atom [17,18]. The oxygen-bonded complex of the formula $[Cp_2Ti(O\text{-cys})_2]Cl_2$ has been prepared by the reaction of cysteine with Cp_2TiCl_2 in methanol [19]. The interaction of metallocenes with various oligopeptides, enzymes and proteins such as glutathione [18], protein kinase C [20], topoisomerase [20,21] and transferrin [22] were also the subject of several recent studies.

Herein presented study completes our comprehensive investigation of the vanadocene complexes with essential amino acids. It covers derivatives substituted in the cyclopentadienyl rings, complexes of the α-amino acids bearing functional groups in the side chain and new X-ray structures of previously described complexes.

2. Results and discussion

2.1. Synthesis of vanadocene complexes

Vanadocene dichlorides Cp_2VCl_2 (**1a**) and $(MeC_5H_4)_2VCl_2$ (**1b**) were prepared by published method [23,24]. Synthesis of $({}^iPrC_5H_4)_2VCl_2$ (**1c**) was performed according to general route for ring-substituted vanadocene dichlorides starting from ${}^iPrC_5H_4MgCl$ and $V(acac)_3$ [25]. Bis(cyclopentadienyl)vanadium(III) intermediate was not isolated from the reaction mixture and it was subsequently treated with PCl_3 to give desired dichloride **1c**, see Scheme 1.

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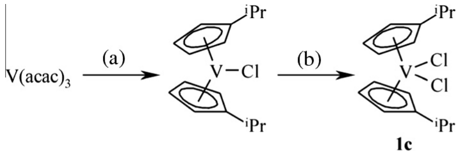


Scheme 1. Synthesis of (^{i}PrC$_5$H$_4$)$_2$VCl$_2$ (**1c**). (a) ^{i}PrC$_5$H$_4$MgCl/THF; (b) PCl$_3$/Et$_2$O.

The α-amino acid complexes were prepared by the reaction of appropriate vanadocene dichloride with α-amino acid in deoxygenated water or in aqueous methanol followed with neutralization by NaOH, see Scheme 2. The cationic species have been precipitated after the addition of large anion salt, such as KPF$_6$ [12,26]. This method and its modifications were previously used for syntheses of [(RC$_5$H$_4$)$_2$V(*N*,*O*-aa)]$^+$ (R = H, Me; aa = gly, ala, val, leu, ile, phe, pro, his, trp), [Cp$_2$V(*O*-pro)$_2$]$^{2+}$, [Cp$_2$V(*O*,*S*-cys)]$^+$ and [Cp$_2$V(*N*,*S*-cys)] [12,15,16,27]. Herein, we present X-ray structures of two complexes belonging to this series [(MeC$_5$H$_4$)$_2$V(*N*,*O*-gly)][PF$_6$] (**2b-PF$_6$**) and [Cp$_2$V(*N*,*O*-ala)][PF$_6$] (**3a-PF$_6$**). This study also covers the synthesis and characterization of vanadocene compounds of the formula [Cp$_2$V(*N*,*O*-aa)]$^+$ with essential α-amino acids bearing functional groups in the side chain such as serine (**4a**), threonine (**5a**), aspartic acid (**6a**), glutamic acid (**7a**), asparagine (**8a**), glutamine (**9a**), lysine (**10a**) and arginine (**11a**) and one congener with substituted cyclopentadienyl rings [(^{i}PrC$_5$H$_4$)$_2$V(*N*,*O*-gly)]$^+$ (**2c**). For the compounds [(^{i}PrC$_5$H$_4$)$_2$V(*N*,*O*-gly)][PF$_6$] (**2c-PF$_6$**), [Cp$_2$V(*N*,*O*-thr)][PF$_6$]·H$_2$O (**5a-PF$_6$·H$_2$O**) and [Cp$_2$V(*N*,*O*-asn)][PF$_6$]·H$_2$O (**8a-PF$_6$·H$_2$O**) the spectroscopic data are also supported by X-ray crystallographic data.

2.2. Spectroscopic characterization

The vibrational spectra of the all studied compounds prove the integrity of bent metallocene moiety and coordination pattern of the α-amino acid. Particularly, the presence of η^5-bonded cyclopentadienyl rings in compounds **4a-Cl–11a-Cl** is evident from CH stretching (IR and Raman: ν_{CH} ~3110 cm^{-1}), symmetrical CC stretch (strong band of “ring breathing” in Raman: ~1135 cm^{-1}) and out-of-plane CH bending (IR: γ_{CH} ~833 cm^{-1}). The Raman spectra of unsubstituted cyclopentadienyl compounds show very strong Raman band at ~285 cm^{-1} that was assigned to ring tilting of bent vanadocene moiety [28]. The coordinated α-amino acids in compounds **2c-Cl** and **4a-Cl–11a-Cl** give characteristic vibration modes of the amine and carboxylic group. The medium bands of N–H stretching [ν_a(NH$_2$) ~3345 cm^{-1}, ν_s(NH$_2$) ~3210 cm^{-1}] and C=O stretching (ν_{CO} ~1640 cm^{-1}) were observed in infrared spectra of these compounds.

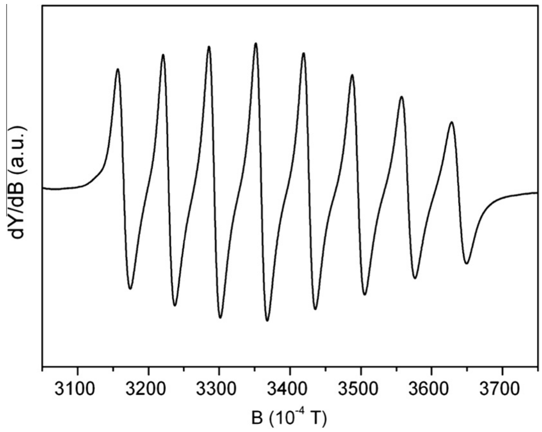
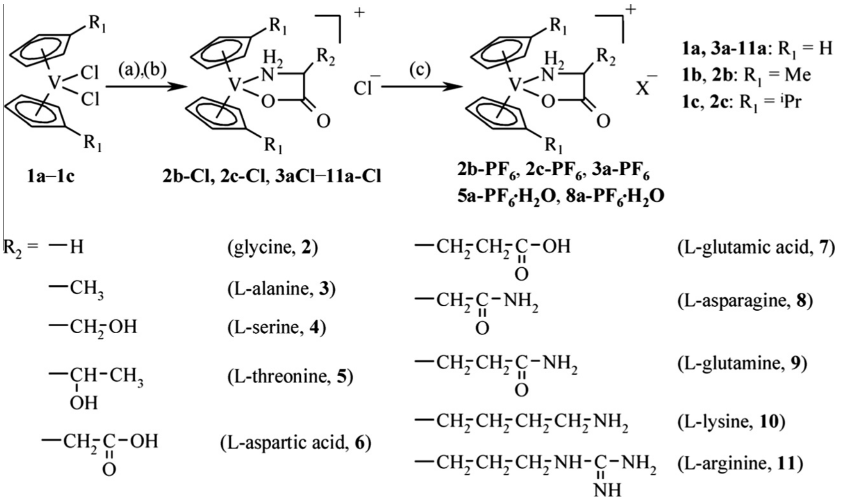


Fig. 1. Representative EPR spectrum of methanolic solution of **2c-Cl** at 9.45 GHz.

Methanolic or aqueous solutions of **2b-Cl**, **2c-Cl** and **3a-Cl–11a-Cl** give simple eight-line EPR spectra proving the presence of only one paramagnetic species, see Fig. 1. Observed |A_{iso}| values for all studied complexes were found in very narrow range 62.1–62.9 × 10^{-4} cm^{-1}. The g_{iso} values (1.985–1.988) are also independent on the substituent in the side chain (see Table 1). Both EPR parameters are virtually identical to those observed for previous series of the *N*,*O*-chelate complexes [Cp$_2$V(*N*,*O*-aa)]$^+$ [12,15,16,27,29]. This observation proves that the amino acid ligand in all studied compounds **2a–11a** is *N*,*O*-bonded giving five-membered chelate complex and secondary functional groups of amino acid do not interact with the vanadium center. As expected, the exchange of counter ion does not affect the central metal and has only neglectable effect on the EPR parameters.

2.3. Mass spectrometry

Vanadocene complexes of the α-amino acids containing function group in the side chain (**4a-Cl–11a-Cl**) were studied by mass spectrometry. The base peaks of the first-order positive-ion ESI mass spectra were assigned to corresponding [M–Cl]$^+$ ions. The



Scheme 2. Synthesis of the amino acid complexes: (a) water (for **1a** and **1b**) or aqueous methanol (for **1c**); (b) 1 equiv. of amino acid, 1 equiv. of NaOH; (c) aqueous solution of KPF$_6$.