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The fixation of linear *versus* loop-type peptidic structures by metal coordination: the coordination chemistry of Val–Val- and Val–Val–Val-bridged dicatechol ligands

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The Val–Val-bridged dicatechol ligand L^1-H_4 forms triply-bridged dinuclear complexes with titanium(IV) ions, while the more flexible Val–Val–Val derivative L^2-H_4 leads to mixtures of complexes containing species with a cyclic arrangement of the ligand; with [*cis*-MoO_2]$^{2+}$ on the other hand, a well-defined macrocycle [(L^2)MoO_2]$^{2-}$ is formed which possesses a loop-type structure in the peptidic part of the ligand.

Molecular recognition is an essential ability of proteins and controls the selective interaction with other proteins, DNA, or membranes or the binding of substrates. Different peptidic microstructures play different roles in the molecular recognition processes. Therefore, the stabilization of small sheet, helix or turn/loop microstructures is an important challenge to investigate in the special structural or binding features of isolated small moieties of big protein structures.[1] In several cases metal coordination was used to stabilize structures of peptides. Helix bundles or α-helical domains can be stabilized by coordination of metal ions to peptide side chains or to artificial ligands which are attached to the peptide. Typical ligand units which were used for the coordination to the metals are crown ether or bipyridine moieties.[2] Just recently a single turn of an α-helix was stabilized in solution by binding of a Pd-complex fragment to a His–Ala–Ala–Ala–His pentapeptide.[3]

In this paper we describe the coordination chemistry of a dipeptide- (Val–Val) $\mathbf{L^1}$-H_4 and of a tripeptide- (Val–Val–Val) bridged $\mathbf{L^2}$-H_4 dicatechol ligand (Fig. 1) in which the ligands are able to adopt either a stretched (sheet-type) or a bent (loop type) arrangement. The Val–Val- and Val–Val–Val-spacers were choosen as sterically highly demanding peptides which possess a restricted conformational flexibility.[4]

Mixing of the Val–Val-bridged ligand $\mathbf{L^1}$-H_4 (3 equiv.) with $TiO(acac)_2$ (2 equiv.) and K_2CO_3 (2 equiv.) in methanol results in the formation of a red material which is purified by filtration over Sephadex LH 20 with methanol as solvent. NMR spectroscopy in methanol-d_4 of the product shows a spectrum which cannot be interpreted. This indicates that not only one defined product is formed but that a mixture of different species is present. However, negative ESI-MS reveals that a mixture of different isomers of helicate-type[5] triple-stranded dinuclear complexes $K_4[(\mu\text{-}\mathbf{L^1})_3Ti_2]$ is obtained {*m*/*z* = 1620, $K_3[(\mathbf{L^1})_3Ti_2]^-$; 790.5, $K_2[(\mathbf{L^1})_3Ti_2]^{2-}$; 514, $K[(\mathbf{L^1})_3Ti_2]^{3-}$; in addition, peaks are observed with one potassium substituted by a sodium cation or a proton}. Owing to the directionality (N-*versus* C-terminus) and the chirality at the ligand and at the metal, up to eight different regio- and stereo-isomers of triple-stranded dinuclear complexes can be formed. After two weeks at room temperature the NMR spectrum in methanol-d_4 gets simpler and one dominating isomer of $K_4[(\mathbf{L^1})_3Ti_2]$ can be detected besides broad resonances which are probably due to the presence of minor isomers (Fig. 2, top). Only one set of signals is observed for the three ligands $\mathbf{L^1}$ of the main isomer, showing C_3 symmetry with a parallel orientation of all three ligand strands (**A**). This means that all three ligands bind with their N-terminal catechol to one of the titanium(IV) ions and with the ligand unit bound to the C-terminus to the other.[6] Besides the signals of aromatic protons [δ 7.14 (dd), 6.56 (t), 6.49 (dd), 6.45 (dd), 6.38 (t), 6.32 (dd)] characteristic doublets are observed for the two α-CH moieties at δ 4.46 and 4.31 and for the diastereotopic protons in the benzylic position at δ 4.34 and 4.06. The resonances of the ^{i}Pr groups are observed at δ 2.14, 1.99, 1.75 (3 × m) and 0.85, 0.82, 0.69, and 0.60 (4 × d).

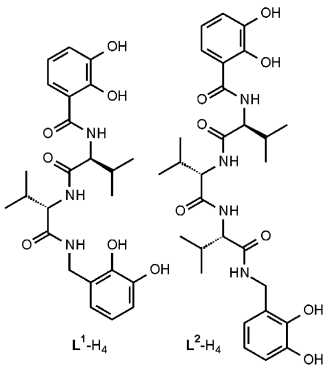

Fig. 1 Ligands $\mathbf{L^1}$-H_4 and $\mathbf{L^2}$-H_4.

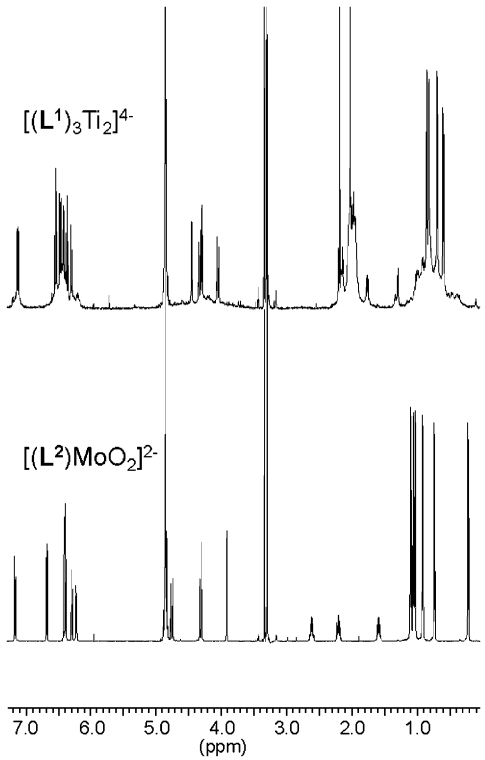

Fig. 2 ^{1}H NMR spectra of the 'stretched' triple-stranded titanium(IV) complex $[(\mathbf{L^1})_3Ti_2]^{4-}$ (top) and the mononuclear molybdenum(VI) dioxo complex $[(\mathbf{L^2})MoO_2]^{2-}$ (bottom) in methanol-d_4.

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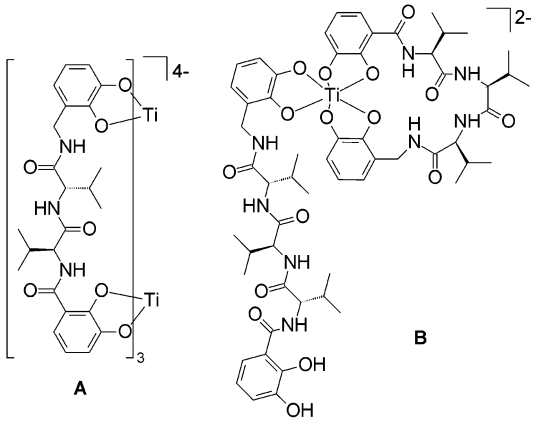
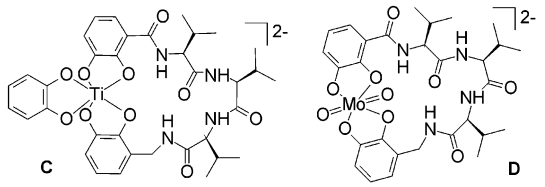


Introducing the longer and thus more flexible Val–Val–Val-bridged derivative $\mathbf{L^2}$-H_4 into coordination studies with titanium(IV) ions again leads to the formation of triple-stranded dinuclear complexes $K_4[(\mathbf{L^2})_3Ti_2]$ (similar to **A**). The compounds can be observed by negative ESI-MS spectrometry {*e.g.* *m/z* = 931.5, $KNa[(\mathbf{L^2})_3Ti_2]^{2-}$; 923.5, $Na_2[(\mathbf{L^2})_3Ti_2]^{2-}$, 613.3, $K[(\mathbf{L^2})_3Ti_2]^{3-}$; 608, $Na[(\mathbf{L^2})_3Ti_2]^{3-}$; 450.25, $[(\mathbf{L^2})_3Ti_2]^{4-}$; Na-cations were probably introduced during Sephadex filtration}. In addition, peaks can be observed by mass spectrometry at *m/z* = 1210/593 $\{Na[(\mathbf{L^2})(\mathbf{L^2}\text{-}H_2)Ti]^-/[(\mathbf{L^2})(\mathbf{L^2}\text{-}H_2)Ti]^{2-}\}$ which are assigned to mononuclear species with one tetradentate and one bidentate ligand (**B**). The bidentate ligand strand possesses one uncoordinated catechol unit dangling around. The observation of a species **B** makes the presence of a complex with only one bridging and two terminal ligands $[(\mathbf{L^2})Ti(\mu\text{-}\mathbf{L^2})Ti(\mathbf{L^2})]^{4-}$ most probable in the mixture.[7] This single-bridged complex possesses the same molar mass as the corresponding triple-stranded isomer $[(\mu\text{-}\mathbf{L^2})_3Ti_2]^{4-}$. Unfortunately NMR spectroscopy is not useful for the characterization of the mixture.

In complexes like **B** a bent ('loop-type') conformation has to be adopted by the small peptidic unit of the ligand strand. It would be most interesting to stabilize such loop-type structures in well-defined, pure coordination compounds.[8]

In a first experiment we performed the reaction of ligand $\mathbf{L^2}$-H_4 (1 equiv.) with $TiO(acac)_2$ (1 equiv.) in the presence of catechol and obtained a complex which for the major component of the mixture showed a simple ^1H NMR spectrum, indicating the presence of the mixed mononuclear complex $K_2[(\mathbf{L^2})(catecholate)Ti]$ (**C**). Characteristic signals are observed at δ 5.06, 4.26, 4.01 (3 × α-CH), 4.65, 4.14 (2 × diastereotopic H in benzylic position), 2.57, 2.22, 1.99 (3 × CH-^{i}Pr), 1.09, 1.07, 1.01, 0.87, 0.76 and 0.28 (6 × CH_3-^{i}Pr). The highfield shift of the methyl group at 0.28 ppm is characteristic for a loop-type arrangement of the 'peptide' (*vide infra*). However, FAB-MS showed that the ligand heterorecognition[9] during complex formation from a mixture of $\mathbf{L^2}$-H_4 and catechol is not perfect. Besides the major product $K_2[(\mathbf{L^2})(catechol)Ti]$ several other complexes {*e.g.* $K_4[(\mathbf{L^2})_3Ti_2]$} are formed.



To specifically obtain pure and well-defined mononuclear complexes in which a single peptide loop is stabilized, we switched the metal complex fragment so that only one ligand-strand binds with both catechol binding sites to the same metal ion. As an appropriate metal complex fragment we choose the *cis*-MoO_2-unit.[10] The short Val–Val-bridged ligand $\mathbf{L^1}$ does not form a defined mononuclear complex with the *cis*-MoO_2-moiety, but a mixture of oligomers. The reason for this is probably the steric hindrance of the bulky Val–Val-spacer of the short dipeptide, preventing a tight peptide loop.

On the other hand, reaction of *cis*-$O_2Mo(acac)_2$ with the longer tripeptide-bridged ligand $\mathbf{L^2}$-H_4 in the presence of K_2CO_3 in methanol followed by filtration over Sephadex LH 20 yields an orange solid. Negative ion ESI-MS reveals the presence of the mononuclear coordination compound $K_2[(\mathbf{L^2})MoO_2]$ {**D**, *m/z* = 737, $K[(\mathbf{L^2})MoO_2]^-$; 699, $H[(\mathbf{L^2})MoO_2]^-$; 349, $[(\mathbf{L^2})MoO_2]^{2-}$}. One nicely resolved set of signals is observed by NMR (Fig. 2, bottom). The ^1H NMR spectrum shows signals at δ 7.18 (dd), 6.69 (dd), 6.41 (m, 2 H), 6.31 (dd), 6.24 (dd) [aromatic protons] and at δ 4.85 (α-CH), 4.77, 4.32 (2 diastereotopic protons in the benzylic position), 4.31, 3.93 (2 × α-CH), 2.61, 2.20, 1.58 (3 × CH-^{i}Pr), 1.09, 1.05, 1.03, 0.91, 0.73, and 0.21 (6 × CH_3-^{i}Pr). At δ 0.21 an unusual shift is observed for one of the diastereotopic methyl groups of the N-terminal valine-unit of $K_2[(\mathbf{L^2})MoO_2]$. This shows that this group is located close to one of the aromatic moieties of the ligand as it also was observed for $K_2[(\mathbf{L^2})$(catecholate)Ti]. The formation of the macrocyclic complex $K_2[(\mathbf{L^2})MoO_2]$ proceeds highly diastereoselectively and the configuration at the metal is induced by the chiral tripeptide-bridged ligand strand $\mathbf{L^2}$ {$\alpha_{[D]}$ = +50; methanol, 296 K, *c* = 0.14}.

In this paper we have described the coordination chemistry of dicatechol ligands with short peptides as spacers. The preferred conformation of geometrically constrained ligands with bulky amino acids as building blocks can control the specificity of the complex formation in coordination studies with titanium(IV) ions. Either the selective formation of one 'stretched' triple-stranded dinuclear complex with a linear arrangement of the ligands (ligand $\mathbf{L^1}$) or the unspecific formation of mixtures of complexes (ligand $\mathbf{L^2}$) can be observed. On the other hand, metal complex fragments like *cis*-MoO_2 which bind both catechol units of the long and thus flexible ligand strand $\mathbf{L^2}$ can be used to obtain macrocyclic complexes. Here the metal complex fragment acts as a clip and stabilizes a peptidic loop structure.

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