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Transition metal complexes with oligopeptides: Single crystals and crystal structures

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The coordination chemistry of short chain peptides with transition metals is described in terms of the available crystal structures. Despite of their high interest as synthetic models for metalloproteins, and as building blocks for molecular materials based on the tuneable properties of oligopeptides, single crystal X-ray diffraction studies are scarce. A perusal of the most relevant results in this field allows us to define the main characteristics of oligopeptide-metal interactions, the fundamental problems for the crystallization of these complexes, and some hints to identify future promising approaches to advance in the development of metallopeptide chemistry.

1. Introduction

Metalloproteins are responsible for many essential functions in living entities. From complex multi-electron redox processes[1] to simple structural roles,[2] the purposes are varied and precisely designed.[3] Proteins fold to create a perfect coordination sphere for the right metal, in the desired oxidation state, to perform exclusive tasks that are not easily achieved by purely organic matter. Or vice versa: metal binding allows for the protein to fold properly and deliver the desired function. The understanding and control of the metal-peptide interaction is one of most ambitious biochemical challenges.

These interactions have been typically studied through indirect methods in solution until single crystal X-ray diffraction has become a powerful tool. Even with the argument that solid state structure may differ from the solution phase, the truth is that solid state information has been fundamental to avoid useless discussions. Protein crystallography, though, still depends on single crystal growth, and even with the advanced techniques available, there are several proteins highly improbable to form single crystals, because of its intrinsic instability outside of the living tissues. In order to obtain structural data to support indirect methods, it is of great interest to obtain synthetic analogues. Thus, It would be ideal to reproduce the active site of metalloproteins without the need for the complete protein skeleton.

On second hand, there are also many functions readily performed by proteins and enzymes that would be really useful to mimic in synthetic models for technological applications. Oligopeptide complexes could be also essential in this vein.

Although their high interest, structurally characterized metal complexes with oligopeptides are scarce, whereas there are many metal complexes with amino-acids that have been studied since the beginning of modern coordination chemistry.[4] Furthermore, there is a numerous structural bank of metalloproteins,[5] but few structures solved for oligopeptide complexes.[6] This seems to imply that it is more difficult to grow good quality single crystals from the combination of oligopeptides and metals ions than with metalloproteins containing several thousands of amino acid units. This might appear counterintuitive since small molecule X-ray diffraction and analysis was well established before protein crystallography started to deliver successful stories. It is a very reasonable outcome, though, looking at coordination chemistry principles. Oligopeptides are amphoteric, multidentate, multi-conformational ligands whose solution equilibria have too many degrees of freedom. Crystallization of dynamic systems is rarely an easy task. Furthermore, crystallization is not an equilibrium process, since the less soluble species will crystalize, and not necessarily the thermodynamically favoured. In this sense, the possibility to form insoluble coordination polymers, as a kinetic sink, make difficult the crystallization process.

In this article we have gathered a structural database of transition metal complexes with linear oligopeptides, excluding those obtained with unnatural amino acids, or with the aid of ancillary ligands. We will describe their main structural features and the keys for successful crystallization. As powerful as X-ray diffraction may become, single crystals will always be required, at least in the mid-term future. Along other interesting reviews,[7,8] we intend to highlight the interest of such studies, including some hints about the complex reactivity in these systems, along their great complexity.

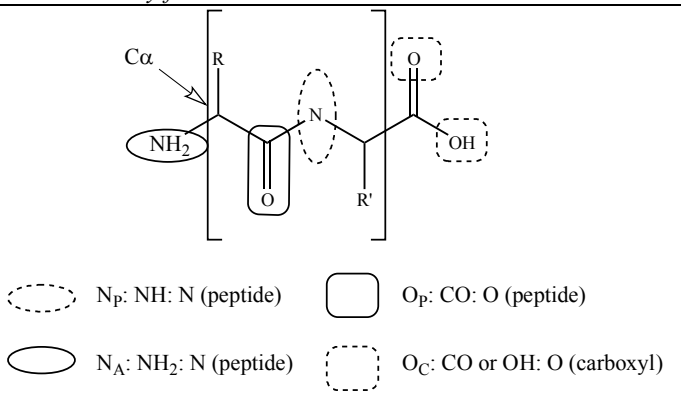
This perspective includes four descriptive sections devoted to: copper(II), due to the particular richness of this chemistry; other first row transition metals; noble transition metals; and metal-oligopeptide frameworks. It concludes with a discussion putting together what we can learn from these works.

Color codes for figures: white (metal), black (C), red (O), blue (N), green (Cl) and yellow (S).

Abbreviations:

Coordinating atoms:	
N_A*: N(amino)*	O_P*: O(peptide)*
N_P*: N(peptide)*	O_C*: O(carboxyl)*
N_{Im}*: N(imidazole)*	O_{Ph}*: O(phenolic ring)*
N_I*: N(imino)*	S_T*: S(thioether)*
Amino acids:	
A: Alanyl	*M: Methionyl*
C: Cysteyl	*P: Prolyl*
E: Glutyl acid	*S: Serine*

F: Phenylalanyl	*T: Threonine*
G: Glycyl	*V: Valyl*
H: Histidyl	*W: Tryptophanyl*
L: Leucyl	*Y: Tyrosyl*
Other molecules:	
Z: Protecting group: phenyl ester	*bpy: 4,4'-bipyridine*
DMSO: Dimethylsulfoxide	*MeOH: Methanol*
EtOH: Ethanol	*Et_2O: Diethyl ether*
DMF: Dimethylformamide	



Scheme 1. General oligopeptide backbone

2. Copper(II)

Copper complexes with oligopeptides have been the most studied by far,[9] where the metal cation always appears in the +2 oxidation state. The versatility of Cu^{2+} to adopt different coordination geometries, its stability in a wide pH range, along its affinity to effectively bind the amide group have probably helped to yield good quality single crystals in different reaction conditions. The complexes can be classified in three different types:

2.1 Glycyl-based oligopeptides

Cu(GG) (**1a**) was one of the first dipeptide metal complexes structurally characterized.[10,11] This blue crystal was obtained by slow evaporation of an equimolar mixture of $CuCO_3$ and the dipeptide in water. The copper atom adopts square-based pyramidal coordination, with the equatorial positions occupied by N_A, N_P, O_C atoms forming two five-membered chelate rings and a water molecule (Fig. 1). A second water molecule is loosely bound in apical position. The Cu-N_P bond (1.87 Å) is shorter than the Cu-N_A bond (2.03 Å) because of deprotonation of the former yields a net negative charge.

When an analogous reaction is carried out in basic pH, blue prisms of $K_2[Cu(GG)_2]$ (**1b**) are obtained, where the GG dipeptide stabilizes an octahedral Cu^{2+} ion.[12] The equatorial positions are occupied by N_A and N_P atoms, forming two non planar 5-membered chelate rings (Fig. 1). Two water molecules occupy the elongated axial positions in this distorted octahedron.

Evaporation of an aqueous solution of $CuCl_2$ and the GGG tripeptide yield crystals of [Cu(GGG)Cl] (**2**).[13] In this distorted square-pyramidal geometry, Cu^{2+} is bound to N_A and O_P atoms from the first G residue, to the O_C atom from the second peptide, to a chlorine ion and to a water molecule at the apex of the pyramid (Fig. 2). This complex displays a 5-membered chelating ring between the N_A and the first O_P, with equivalent bond lengths (1.990 Å and 1.987 Å respectively). The second carboxylate O atom in the O_c unit is also loosely bound, (2.8 Å), giving a pseudo-octahedral environment.

The amino group can also participate in a chelate with the deprotonated nitrogen from the amide of the peptide bond as occurs in Na[Cu(GGG)] (**3**).[14] Violet prims of this compound are obtained by slow evaporation of an alkali solution. The copper atoms are 5-coodinated, with the base occupied by a N_A and two deprotonated N_P of one peptide and an O_C atom of a second peptide molecule. The apical position is occupied by a N_p of this second peptide, forming a doubly bridged copper dimer, with a [Cu–N_P–Cu–N_P] square (Fig. 3).

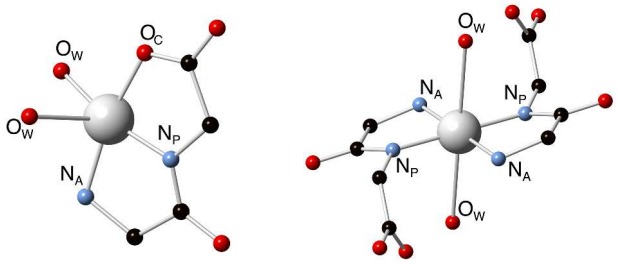


Fig. 1 Coordination around copper(II) in (GG) complexes.

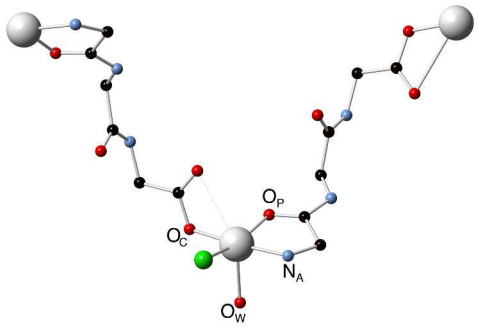


Fig. 2 Coordination around copper(II) in **2**.

Layering with EtOH-acetone a basic solution of $CuCl_2$ and poly-gycyl peptides, single crystals can be obtained, as $Na_2[Cu(GGGG)]$ (**4**)[15] or $Na_2[Cu(GGGGG)]$ (**5**).[16] In both complexes the copper atom presents an approximately square-planar geometry (Fig. 4) with very similar bond lengths and angles (Table 1). As expected, bond lengths follow the trend:[17] Cu-N_A > Cu-N_P. In both compounds, terminal carboxylate units are not coordinating, and the complexes appear as discreet anionic moieties.

2.2 Oligopeptides with weakly coordinating or noncoordinating side chain

The presence of side chain residues has a significant contribution to the crystallization process, even when these residues cannot participate in bonding. Typically, the least soluble complex will be isolated from the solution equilibrium among all possible conformations, and not necessarily the thermodynamic sink.[7,18]

The mixture of $CuSO_4$, $Ba(OH)_2$ and the tripeptide GLY at pH 6-7 yields blue crystals of the $Cu_2(GLY)_2$ (**6**) dimer.[19] There are two crystallographically distinct Cu^{2+} positions. Both adopt square pyramidal geometry with the basal positions occupied by N_A/O_P and N_P/O_C chelates of two peptides (Fig. 5). Each peptide binds two copper cations. The main difference between both metal centres occurs at their apical positions, occupied by

one water molecule, in one case, and by a O_C from a third peptide, forming coordination 1D chains. A close contact[20] occurs between Cu^{2+} and the Y aromatic ring (3.10 ± 0.1 Å between metal and the mean aromatic plane), situated below the basal plane of the square-pyramidal copper coordination, suggesting the presence of weak metal-π interactions.[21] This complex shows chelate angles significantly shorter than expected (114° and 115°), since Freeman[17] had stipulated an average value of 123°. This could be due to steric issues in the crystal.

Table 1 Some relevant crystallographic data for copper(II)-oligopeptide complexes

	Na_2[Cu(GGGG)]	Na_2[Cu(GGGG)]
Bond Lengths (Å)		
Cu-N_A	2.028	2.033
Cu-N_{P1}	1.923	1.913
Cu-N_{P2}	1.912	1.913
Cu-N_{P3}	1.944	1.950
Bond angles (°)		
N_A-Cu-N_{P1}	83.5	84.6
N_{P1}-Cu- N_{P2}	82.8	83.5
N_{P2}-Cu- N_{P3}	84.0	82.9
N_A-Cu-N_{P3}	109.8	109.1

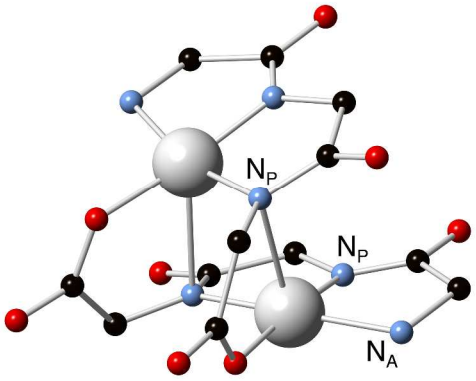


Fig. 3 Coordination around copper(II) in **3**.

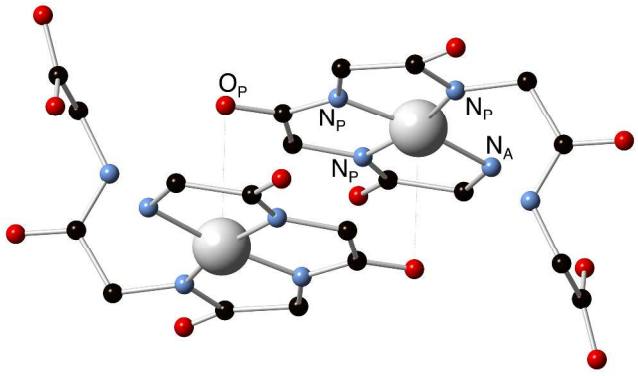


Fig.4. Coordination around copper(II) in **5**.

Slow evaporation of an equimolar mixture of $CuCO_3$ and the GW dipeptide yield crystals of [Cu(GW)] (**7**).[22] In this case, the Cu^{2+} appears in square planar conformation, bound to N_A, N_P, and O_C peptide positions plus a water molecule. (Fig. 6).[23] The basal plane has a slight tetrahedral distortion. The two 5-membered chelate rings formed are sharing a N_P atom with the expected C'-N-C^{α} bond angle of 125°. Weak metal-π interactions appear with the W aromatic ring of an adjacent complex (3.15 Å). The analogous intra-complex interaction is not allowed because the peptide cannot bend enough, as confirmed with a > 3.8 Å metal to aromatic plane distance. This metal-π interaction is not always observed.[24] Cu(LY) (**8**),[25] Cu(LF) (**9**),[26] and Cu(VY) (**10**),[27] synthesised at pH 6-8, show square-pyramidal coordination with the typical basal plane formed by the N_A, N_P, O_C atoms from one peptide and O_C from an adjacent peptide molecule, but with no interaction between the aromatic rings.

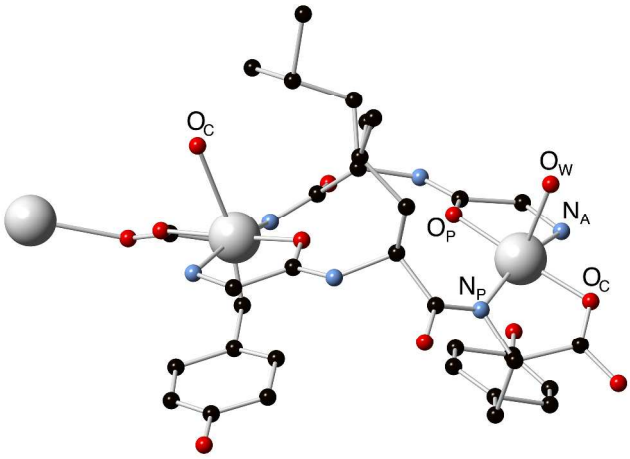


Fig. 5 Coordination around copper(II) in **6**.

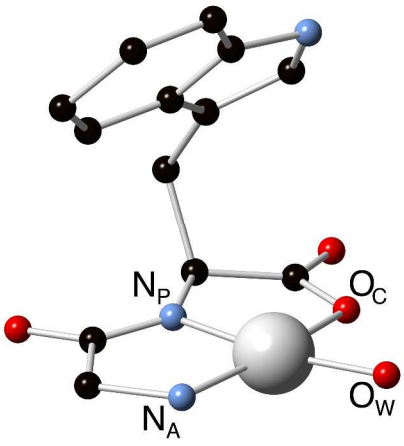


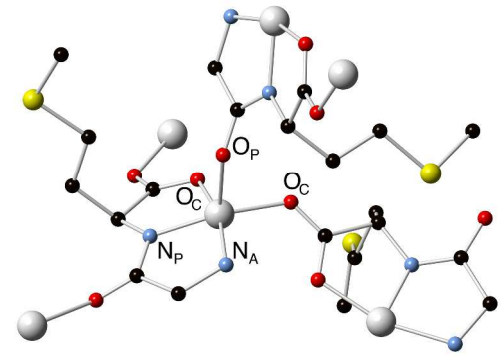
Fig. 6 Coordination around copper(II) in **7**.

Square pyramidal geometry is also found in Cu(GM) (**11**),[28] Cu(MG) (**12**) or Cu(GA) (**13**),[29] as obtained from aqueous solutions near neutrality (Fig 7). In these complexes, the apical position is occupied by a O_P atom of an adjacent peptide. No interaction between the copper atom and the thioether side chain is observed in **11** and **12**, in contrast with others platinum peptides complexes.[30] A close non-bonded C_{β}···O contact with the C_{β} of the A side chain appears in **13**, as a general occurrence in copper dipeptide complexes (Table 2). This short contact restricts the amino acid side chain (C_{α}-C_{β} bond) to a quasi-axial orientation. Thus the C_{β}···O steric strain also

contributes to the distortion or puckering of the chelated dipetide. High puckering angles up to 33º, as in Cu(LY) (**8**); 43-44°, as in Cu(GA) (**13**) and Cu(GM) (**11**); and even 46°, in Cu(VY) (**10**); have been reported.

Table 2. Non-bonding $C_\beta\cdots O$ contacts in copper dipeptide complexes

	$C_\beta\cdots O_P$ O_P in adjacent chelate ring on N_A (Å)	$C_\beta\cdots O_P$ or $C_\beta\cdots O_C$ O_P or O_C in same chelate ring as side chain (Å)
Cu(GA)	3.33	3.00
Cu(GM)	3.37	3.00
Cu(MG)		2.98
Cu(GW)	3.35	3.00
Cu(LY) C_β in L		3.05
Cu(LY) C_β in Y	3.24	2.92
Cu(VY) C_β in V		2.99
Cu(VY) C_β in Y	3.41	3.04
Cu(LF) C_β in L		3.07
Cu(LF) C_β in F	3.33	2.99



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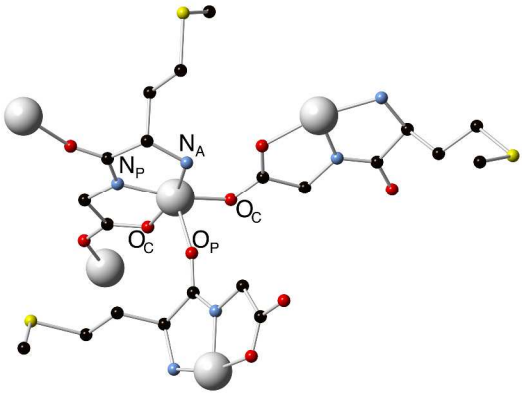

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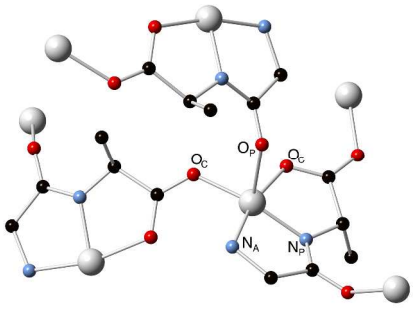


13

Fig. 7. Coordination geometry around copper(II) in **11**, **12** and **13**.

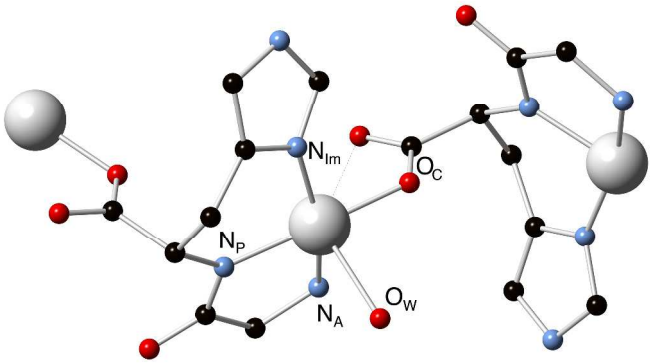


Fig. 8 Coordination geometry around copper)II) in **14**.

It could establish that the changes in the conformation are caused by intermolecular interactions between the chelate and the *peripheral* copper. The puckering increases as the chelate interacts with and additional copper via: one O_C < O_C and O_P < two O_C atoms.

2.3 With oligopeptides with imidazole side chain

Imidazole-N-donor atoms are probably the most common binding sites in metalloproteins. Thus, H-containing peptides offer some unique features in their coordination chemistry. The H side chain can compete with the peptide backbone offering a more flexible 6-membered chelating mode with the adjacent N_P position.

In the Cu(GH)(**14**) complex,[31,32] Cu^{2+} atom has a square-pyramidal geometry, with a N_A, N_P and N^{δ}_{Im} atoms of one peptide and a O_C atom of a second peptide in the basal plane. This is the general trend in all complexes with H-containing peptides. A water molecule occupies the fifth position (Fig. 8). There is a sixth weak bond to the second O_C of the carboxylic unit, as in [Cu(GGG)Cl] (**2**), reminiscent of a pseudo-octahedral environment.

The bond lengths and angles are in the expected range.[33] Only the Cu-N_P (1.99 Å) bond is longer than expected. This could be due to the strain in the chelate ring containing the imidazole group is minimized and the three bonds around the peptide nitrogen remain approximately coplanar.

The GHG tripeptide has yielded several crystal structures with the Cu^{2+} ion, exhibiting the same square pyramidal geometry. In Cu(GHG) (**15a**),[34a] as obtained at pH 4.5, the fifth position is for the other O_C of the same second peptide molecule. In Cu(GHG) (**15b**),[34b] as obtained at neutral pH, contains dimers, since the O_C atoms act as a bridge linking two copper ions. In Cu(GHG) (**15a, 15b**),[35] Cu^{2+} is tetracoordinated, with the four donor atoms organized in a very flattened tetrahedron. All complexes presents Cu-N_P bond shared by a five- and six-membered chelate rings, in agreement with the distances in other similar complexes.[36,37]

In Cu(AH) (**16**)[38] and Cu(YH) (**17**),[39] synthesised at neutral pH, the copper atom is also five-coordinated. In **17** (Fig. 9), the apical direction is occupied by a O_{Ph} atom of a third peptide molecule creating a corrugated 2D coordination network. This distance is significantly long, probably due to steric hindrance due to the close contact between Cu^{2+} and the phenol ring (Cu-C4: 3.59 Å).

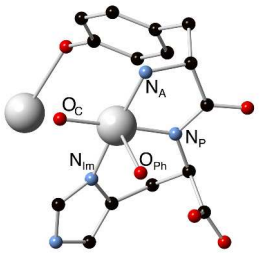


Fig. 9 Coordination geometry around copper(II) in **17**.

3. Other transition metals

3.1 Nickel(II)

Ni^{2+} coordination chemistry with peptides yields blue or yellow complexes depending on the peptide character and reaction conditions. These colours correspond to octahedral (paramagnetic, $S = 1$) or square-planar coordination (diamagnetic, $S = 0$), respectively.[40]

In the green-blue crystals of $Na_2Ni[(GG)_2]$ (**18**), synthesised at pH 10-12, Ni^{2+} atoms are coordinated by two peptides through its N_A, N_P and O_C atoms.[41,42] As in the Cu complexes, previously mentioned in this review, the configuration of the bond at the N_P atoms is trigonal and must be deprotonated.

The yellow crystals of $Na_2Ni[(GGGG)]$ (**19**), synthesised by addition of NaOH to a warmed aqueous solution of $Ni(OH)_2$ and the tetrapeptide, includes a square-planar complex, isomorphous with $Na_2[Cu(GGGG)]$ (**4**). The Ni^{2+} atom is coordinated to a N_A and three deprotonated N_P atoms.[41,43] Bonding distances in the square-planar Ni^{2+} complexes are considerably shorter than in the octahedral complexes, due to the low spin state: O_h (**18**), Ni-N_A: 2.14 Å and Ni- N_P: 1.99 Å; D_4 (**19**), Ni- N_A: 1.92 Å and Ni- N_P: 1.84 Å.

The crystal structure of $[Ni(GC)_2]$ (**20**) was recently reported.[44] These green crystals grow by layering of a pH 8.5 solution of $NiCl_2$ and GC disulfide with MeOH. In the coordination octahedra, two edges are occupied by the N_A / O_P atoms from two peptides, and the open positions are occupied by two O_C atoms from adjacent peptides in a monodentate fashion (Fig. 10). The disulfide bridges are not involved in the coordination.

3.2 Zinc(II)

Only one Zn^{2+}-oligopeptide complex has been reported. The structure of $[Zn(GGG)(H_2O)_4]\cdot½(SO_4)$ (**21**),[45] recrystallized by layering an aqueous solution of ZnSO4, $Ba(OH)_2$ and the tripeptide with Et_2O, is similar to Cu(GGG)Cl (**2**)[13] with the chlorine ion replaced by a water molecule in this case. The Zn^{2+} centres are coordinated by one N_A/O_P chelate 5-membered ring, two O_C atoms from an adjacent peptide, and two water molecules.

3.3 Cobalt(III)

One of the first Co^{3+} complexes structurally characterized was the salt $NH_4[Co(GG)_2]$ (**22**).[46] In this compound the Co^{3+} anion presents a distorted octahedral conformation, as coordinated to N_A, N_P and O_C atoms of two peptides. This complex can be obtained by oxygenation of a basic solution containing Co^{2+} and the GG peptide.[47]

Acidification of $[Co(GG)_2]^-$ solutions with perchloric acid leads to the formation of the equivalent cationic complex $[Co(GG)_2]^+$ (**23**) by a rapid and reversible protonation of the O_P atoms.[47]**Error! Bookmark not defined.** The Co^{3+} ion keeps the same coordination, with longer C-O_P (from 1.26 to 1.36 Å) and shorter C-N_P bond lengths (from 1.31 to 1.25Å) than in anionic complexes. This suggests that protonation increases the donor character of C-N bond but decreases the C-O bond. These structural differences are support that the only coherent protonation occurs at the O_P atoms and also with the O_P atom makes hydrogen-bond with the O_C of the adjacent peptide molecule.

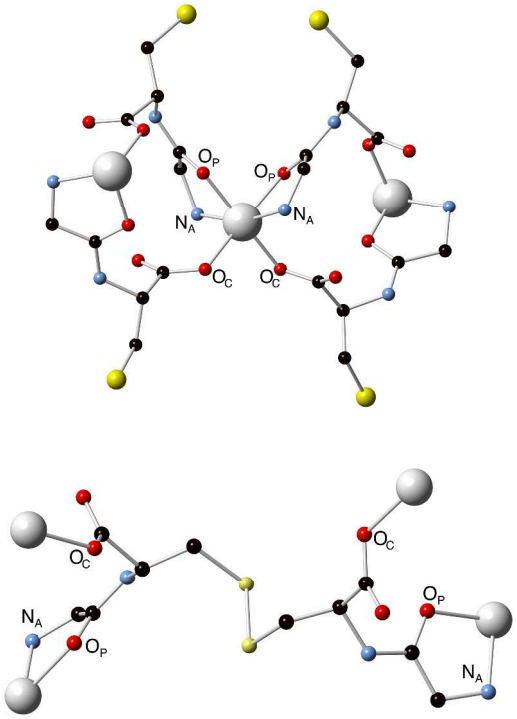


Fig. 10 Coordination geometry around nickel(II) (top) and connectivity through the disulfide bridges (bottom) in **20.**

4. Noble transition metals

4.1 Platinum(II)

Platinum-based drugs represented by cisplatin, carboplatin and oxaliplatin have become fundamental components of standard chemotherapy regiments, and are widely used in antitumor therapy.[48,49] However Pt-protein and Pt-peptide interactions produce concentration-dependent toxicities as side effects, what limits their use.[50] Therefore, there is a great interest in the development new Pt complexes.[51] Pt^{2+} has been used in the preparation of heavy-atom derivatives for protein structure analysis.[7,17,52] However, the number of of Pt-oligopeptide crystal structures available is very low.

As a "soft" metal, Pt^{2+} prefers sulphur and nitrogen coordination with amino acids, peptides and proteins. It is also able to promote deprotonation and coordination of the peptide amide group. Counterions/solvent ligands remain coordinated in all single crystals available.

[Pt(GM)Cl] (**24**)[53,54] was recrystallized in diluted HCl, after heating an equimolar aqueous solution of K_2PtCl_4 and dipeptide. Pt^{2+} ions, in typical square planar geometry, are coordinated by N_A, N_P and S_T atoms to form adjacent five- and

six-membered chelate rings, with a Cl^- anion in the fourth position. The S_T atom is an additional chiral centre in this complex. The Pt-N_P bond (1.98 Å) is shorter than Pt-N_A bond (2.07 Å).

In 1999 Shi et al. studied three platinum complexes with three different oligopeptides:[55] $[Pt(MG)Cl_2]$ (Fig. 11, **25**): prepared in the same synthetic conditions than [Pt(GM)Cl]; [Pt(PG)(DMSO)Cl](**26**): obtained by slow evaporation of a DMSO solution of the reagents; and [Pt(GH)Cl](Fig. 11, **27**): obtained in basic pH, and recrystallized in neutral pH.

In **25**, two Cl^- ions remain attached to the metal centre, with a N_A and a S_T completing the planar square. Again, a new chiral centre is generated at the S_T atom. This complex is the first example where no peptide group is coordinated to Pt^{2+}. It could be postulated that the first bond formed is the Pt-S, followed by the N_A coordination. The participation of N_P or O_P atoms at would yield a seven-membered chelate ring, entropically unfavourable.

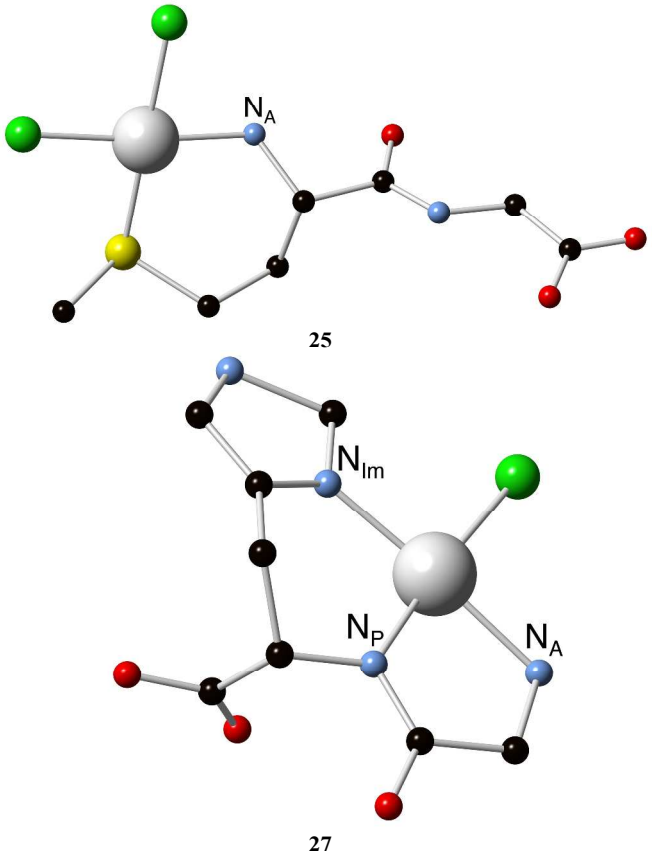


Fig. 11 Coordination geometry around platinum(II) in **25** and **27**.

In **26**, the dipeptide binds through N_I and N_P atoms. A DMSO solvent molecule and Cl^- atom remain *trans* to the dipeptide positions. A five-membered N,N'-chelate ring is created with an usual puckered 'envelope' conformation, in which the N_I is at the 'flap' vertex. N_I is a new chiral centre.

In **27**, the asymmetric unit contains two independent [Pt(GH)Cl] complexes, that only differ at the orientation of the carboxyl groups. The peptides act as a *N,N',N''*-tridentate ligands through the N_A, N_P and N^{δ}_{Im} atoms to forms five and six-membered chelate rings. A Cl^- atom occupies the fourth position in the square.

4.2 Palladium(II)

Palladium exhibits analogous chemistry to Pt, also promoting the deprotonation and coordination of the peptide amide group.[56] Pd^{2+} tends to form stable square planar, diamagnetic complexes with dipeptides through its N_A, N_P and O_C atoms.[57] However, in presence of coordinating side chain residues, such as M[58] or H,[59] the O_C atom is replaced by an S_T or a N_{Im}, increasing the stability of the complex. This is observed, for example, in [Pd(GM)]Cl (**28**),[60] [Pd(GH)Cl] (**29**)[61,62] or [Pd(GGH)] (**30**),[63] where Pd^{2+} is coordinated by N_A, N_P and S_T or N^{δ}_{Im}, respectively. The fourth position is occupied by a Cl^- atom in the dipeptide complexes, and by a N_P atom in the tripeptide one.

The bond distances in all complexes are typical, following the Pd-N_A > Pd-N_P trend. In the tripeptide, the shortest angles in the square-planar geometry around the metal are the corresponding to the atoms belonging to the five-membered chelate ring.

4.3 Gold(III)

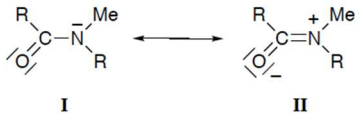
Gold has been explored for its antitumor potential.[64] As Pt complexes, Au^{3+} compounds are able to bind DNA which may account for their cytotoxic activity.[65,66] Au^{3+} has the same d^8 electronic configuration as Pt^{2+} and both preferentially form square-planar complexes.[67] One of the key problems that hampered the development of Au^{3+} complexes for medical application is their low stability under physiological conditions.[68] The stability can be enhanced by chelating ligands, such as pyridine,[69] bypiridine, porphyrin[71] and cyclometalated structures.71 In these complexes, Au^{3+} is coordinated by at least two chelating nitrogen donors, which lowers the redox potential of the metal center. The crystal structure of Au^{3+}-peptide complexes has been recently reviewed.[8]

The pH plays an important role in the crystallization. The same reaction yields a binary complex [Au(GH)Cl]Cl (**31**) (Figure 12) at pH 2, and a cyclic tetramer $[Au(GH)_4]$ (**32**) at pH 6-7.72 In both complexes, Au^{3+} presents square-planar coordination geometry and is coordinated to N_A, N_P and N^{δ}_{Im} atoms, with the fourth position occupied by Cl^- in **31** and by a deprotonated N^{ε}_{Im} in **32**. Thus, the imidazole ring acts as bridge linking two gold units. A longer Au-N_A bond (1.999 Å) when compare with the monomer complex (1.94 Å) is attributed to the larger *trans* effect influence of N^{ε}_{Im}. The formation of cyclic tetramer at neutral pH is exclusive of Au^{3+} chemistry. Analogous polynuclear species with other metals appear only in alkali conditions.[73]

[Au(GGH)]Cl(**33**), synthesised at pH 2.4, shows analogous coordination features to **32**, completing the $Au3^+$ square geometry with a second N_P atom of the GH peptide bond.[74] The C=O distance is slightly shorter and the OC-N slightly longer than in the free peptide. This is contrary to the tendency displayed in complexes with divalent metals. This should be related to the stronger electron-withdrawing effect of gold(III), what might favour the resonance form I (Scheme 2). The same tendency is observed for Cu^{3+} due to its strong Cu-N bonds.[75]

Two novel Au^{3+} complexes were obtained at pH 1.5 by addition of HNO_3 to an aqueous mixture of $H[AuCl_4]$ and a dipeptide:[76] $[Au(GH)Cl]NO_3$ (**34**) and $[Au(AH)Cl]NO_3$ (**35**). The dipeptides coordinate through N_A, N_P and N^{δ}_{Im}, with Cl^- completing the square. The five-membered G or A rings present significant deviation from planarity due to intermolecular interactions in the solid. Moreover, the square-planar coordination around Au^{3+} is completed to an elongated pseudo-octahedron by Au···Cl interactions with neighbouring complexes, mediated by

the counter-anions. These interactions lead to the formation of chains in **34** or ladder motifs **35**. These ladder motifs were also found in crystals of **34** obtained by serendipity as a dehydrated salt.



Scheme 2

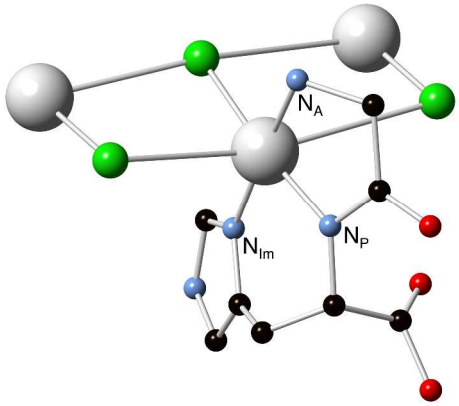


Fig. 12. Coordination geometry around gold(III) in **31**.

5. Metal-peptide frameworks (MPFs)

Metal organic frameworks (MOFs) are porous crystalline solids with low density and exceptional porosity, useful for a wide range of potential uses including gas storage,[77] separations,[78] and catalysis.[79] These materials are constructed metal cations connected by multitopic organic linkers.[80,81] In addition to permanent porosity, open metal sites can be generated by thermal removal of coordinating solvent molecules retained in the pore, adding active sites.[80,82-84] MOFs based in biomolecules, as amino acids[85] or nucleobases,[86] have attracted much interest for biological and medical applications.[87,88] In this sense, oligopeptides offer many attractive advantages as linkers: exhibiting a great variety of metal-binding modes, structural flexibility, intrinsic chirality, and strong hydrogen bonding capabilities, essential to construct stable "secondary" structures. In addition, their side chains can be selected to control MPFs chemical features. These possibilities have not been exploited yet, since MPFs have only been systematically obtained very recently.

The first MPFs were reported by Takayama and coworkers.[89] $[Zn(GG)_2]$ (**36**), synthesised at pH 6, presents distorted octahedral Zn^{2+} coordination with the equatorial positions occupied by N_A/O_P 5-membered chelate rings of two peptides. The axial positions are occupied by two O_C atoms of two additional peptides, building a 3D polymer. In $[Cd(GG)_2]$ (**37**), obtained at pH 9, the dipeptides act as tridentate ligands coordinating three Cd^{2+} ions through their O_C and N_A atoms. As a result, each Cd^{2+} atom is linked to six neighbouring cations through four peptide linkers, forming a unique 3-D polymer.

In $[Cd(GE)_2]$ (**38**) and $[Pb(GE)_2]ClO_4$ (**39**)[90] the M^{2+} centres are surrounded by four O_C and two water molecules. No nitrogen atom is involved. In the Pb^{2+} complex, O_C acts as μ_3-coordinated forming a 2D network. The 3D polymeric structure is built through water bridges.

In $Cd(AA)_2$ (**40**) and $Cd(AT)_2$ (**41**),[91] the dipeptides form 2D square lattices with the octahedral metal centers. Each dipeptide adopts three bridging modes: i) long: with monodentate N_A and O_C; ii) mid-range: bidentate N_A/O_P and monodentate O_C; iii) short: double chelate, N_A/O_P and O_C/O_C. In $Cd(AA)^2$ the layers are strongly hydrogen bonded.

$Cd(GGG)_2$ (**42**) and $Cd(AAA)_2$ (**43**)[91] are formed by complex 3D networks where each Cd^{2+} ion is coordinated through apical N_A, and equatorial O_C atoms. The rest of O_C positions propagate the growth of the structure.

MPFs have been also obtained with copper. $[Cu(ZVVE)(NH_4)_2]$ (**44**)[92] presents a 2-D substructure interconnected via hydrogen bonding and π-π stacking from the Z units between the layers creating a 1D channel and two different pore sizes. $[Cu_4(GA)_4(H_2O)_4(bpy)_2]$ (**45**)[93] and $[Cu_4(GL)_4(H_2O)_4(bpy)_2]$ (**46**)[94] are formed by tetranuclear complexes linked through 4,4'-bipyridine (bpy), in a similar fashion than typical MOFs, such as MOF-5.[95] In both complexes, Cu^{2+} is coordinated to N_A, N_P and O_C atoms and to the bpy ligands.

The majority of MPFs reported up to day use Zn^{2+} as interlinking metal cation.[87,96] One of the most remarkable examples is $[Zn(GA)_2]$ (**47**).[97] The tetrahedral Zn^{2+} sites are coordinated to four peptides through two N_A and two O_C atoms. Each peptide acts as μ_2-linker between two Zn ions creating coordination layers (Figure 13). The layers are aligned through hydrogen bonds to create a 3D network with square-shaped pores. The adaptable porosity of this complex, due to the flexibility of the peptides, makes the crystal structure to close the pore space after desorption/reabsorption of solvent molecules. Recently, Rosseinsky *et al.*[98] have studied the structural response of the MPFs to the conformational changes in the peptide backbone of the isostructural $[Zn(GS)_2]$ (**48**) and $Zn[(GS)_{0.75}(GT)_{0.25}]_2$ (**49**). In these materials, the guest molecules determine the orientation of the S hydroxyl groups. After desolvation, a cooperative single-crystal-to-single-crystal rearrangement could be monitored, from an open/solvated to a close/desolvated state, with the loss of hydrogen bonding interactions. Despite of this, the closed state retains the overall metal-to-peptide connectivity. The crystal transformation is enabled by the torsional flexibility of GS dipeptide that folds to occupy the empty space, with a new host-host interaction, arises between the S hydroxyl group and a C_O group of a neighbour peptide.

Zn^{2+} ions adopt also tetrahedral coordination in the carnosine-based MPF[99] (carnosine is the natural peptide β-AH). This is the second example, after $[Au(GH)_4]$ (**32**), where the imidazole group is deprotonated, forming infinite N^{δ}_{Im}-Zn-N^{Y}_{Im} chains. A N_A and a O_C atoms from two different adjacent peptides complete the coordination, in this 4:4 motif. The intra and intermolecular hydrogen bonding aligns the layers forming 1D square-shape pores which present permanent porosity after removal of solvent DMF in a structural flexible framework.

In $[Zn(GT)_2]$ (**50**),[100] Zn^{2+} ions display octahedral geometry, coordinated by two O_C/N_A chelate 5-membered rings and two O_A from adjacent peptides, forming a square 2D network (Figure 14). As in $[Zn(GA)_2]$ (**47**), the layers stack defining a 1D channel occupied by guests molecules. The presence of the hydroxyl group (O_H) of the threonine side chain creates additional hydrogen bonding inter and intralayer reinforcing the stability of the solid. In this case, the crystallinity is retained upon solvent removal, creating a "classic" rigid porous open framework.

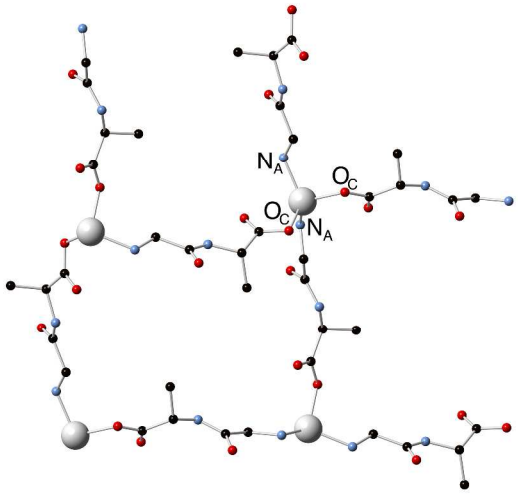


Fig. 13 Coordination geometry around zinc(II) in the 2D coordination layers in **47**.

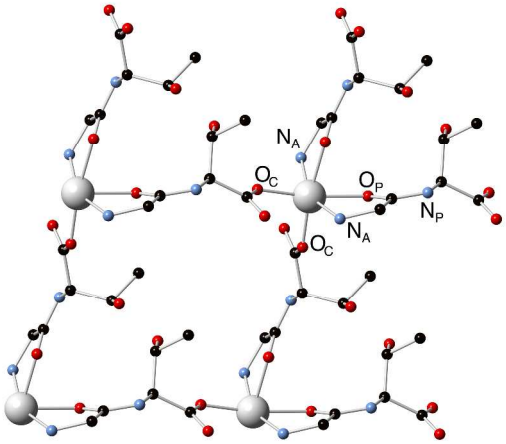


Fig. 14 Coordination geometry around zinc(II) in the 2D coordination layers in **50**.

6. Discussion

New alternative crystallization techniques are clearly needed to successfully crystallize metal-oligopeptide complexes. As we have described, slow evaporation under pH control has been the almost exclusive approach used in the last decades. One remarkable exception is the use of solvothermal methods. In this case, the drawback of oligopeptides as multidentate ligands able to yield insoluble coordination polymers was taken as an advantage for the discovery of chiral and flexible metal organic frameworks. Thus, the rich chemistry and functionalities of oligopeptides open numerous possibilities to develop solid state materials, beyond biologically relevant motifs.

Characterization of molecular entities in the solid state will need of additional strategies. Crystallization is an out of equilibrium process and not necessarily the most stable complex will form part of the solid, but the least soluble. Thus, slow evaporation, or layering with organic solvents, are good crystallization techniques only in solutions with major dominant products, i.e. when the complexes in solution have long lifetimes. Crystals of oligopeptides with metal cations inert to ligand substitution (noble heavy metals or Co^{3+}, for example) have been "easily" obtained, whereas single crystals are rare with labile cations, such as Zn^{2+}. The unique ability of Cu^{2+} to adopt different geometries, mixing strong and weak metal-to-ligand contacts makes it a very good case of study. The same oligopeptides yield different compounds, with respect to local coordination and packing, slightly varying the reaction conditions.

Another important aspect is the multiple protonation sites. At very low pH, oligopeptide cations are poor ligands for first row transition metal cations. Most complexes obtained in acid media contain soft metals, able to promote further deprotonation, to generate anionic oligopeptides even in these conditions. In neutral or basic conditions, some metals are easily oxidized in water to high valence species, yielding the corresponding oxides. This is probably the main reason why no single crystals of Mn^{2+}, Fe^{2+} or Co^{2+} have been obtained. In the latter case, Co^{3+} complexes are isolated, because it becomes highly inert when oxidized as part of a complex, avoiding further decomposition and oxide formation.

Neutral pH synthesis and crystallization would be preferred especially in the search for biologically relevant species. We can suggest some synthetic alternatives to expand the series of metal-oligopeptide complexes: i) Strict control over pH during the reaction and crystallization process. At neutral pH the oligopeptide/metal reaction can easily modify the proton concentration, displacing equilibrium. The use of external pH control, or buffers, could be very valuable on this regard. ii) Air-free synthesis and crystallization. Air is the main oxidant in these reactions, and air free conditions have not been explored. iii) Longer oligopeptide chains. Although increasing complexity, the longer chains would allow the oligopeptides to bend, forming additional intramolecular bonds which could enhanced stability. iv) Chiral counterions. Chiral matching would help crystal growth. The popularity of polyglycyl peptides can be understood due to the lack of optical activity of this amino acid. Of course, being the smallest building unit is also important to avoid structural disorder. All these strategies are being studied in our labs.

Regarding oligopeptide coordination modes, the chemistry is dominated by the stability of 5-membered chelate rings involving the N_A/N_P, and to a lesser extent N_A/O_C, from a terminal amino or carboxyl group with the neighbouring peptide moiety. The combination of both modes yields a tridentate $N_A/N_P/O_C$ ligand, with enhanced stability. Amino acid side chains rarely participate, with the remarkable exception being histidine, which becomes a preferential coordination site through the imidazole group, displacing the backbone positions.

Conclusion

After decades of oligopeptide coordination chemistry, not so many successful stories have been reported regarding structural characterization. This is particularly surprising when compared, for example, with the protein crystallography database. Although it can be argued that metalloproteins bare more interest, the numerous efforts from coordination chemists, forced to use characterization methods in solution,[101] reveal that crystal growth represents a maximum challenge. Oligopeptides are multidentate, flexible, amphoteric, chiral ligands. Thus, the solution equilibria and intermolecular interactions that determine the packing in the solid state are much more complex than in metalloproteins, where the metal site is perfectly defined and stable in the tertiary structure. The formation of insoluble and, many times, intractable coordination polymers that crush out from solution is one of the major handicaps to obtain good quality single crystals.

Still, with the solid support peptide synthesis allowing to obtaining any desirable peptide chain in length and composition, the oligopeptide coordination chemistry challenge could exploit its initial drawbacks to obtain polynuclear, flexible, chiral complexes, with tailor-made functions. Few ligands can match the possibilities of oligopeptides for biochemical assays, but also for applications in molecular materials, in the search for magnetic and/or optical features.

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ToC:
The crystal structures of metal complexes with oligopeptides are reviewed, highlighting crystallization strategies and main binding modes.