Chapter 9
Cadmium(II) Complexes of Amino Acids and Peptides

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Contents

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Abstract Cadmium(II) ions form complexes with all natural amino acids and peptides. The thermodynamic stabilities of the cadmium(II) complexes of the most common amino acids and peptides are generally lower than those of the corresponding zinc(II) complexes, except the complexes of thiolate ligands. The coordination geometry of the cadmium(II) amino acid complexes is generally octahedral with the involvement of the amino and carboxylate groups in metal binding. In the case of simple peptides, both octahedral and tetrahedral complexes can be formed depending on the steric conditions. The terminal amino group and the subsequent carbonyl-O atom are the primary binding sites and there is no example for cadmium(II)-induced peptide amide deprotonation and coordination. The various hydrophobic and polar side chains do not have a significant impact on the structural and thermodynamic parameters of cadmium(II) complexes of amino acids and peptides. β-carboxylate function of aspartic acid and imidazole-N donors of histidyl residues slightly enhance the thermodynamic stability of cadmium(II)-peptide complexes. The most remarkable effects of side chains are, however, connected to the involvement of thiolate residues in cadmium(II) binding. Stability constants of the cadmium(II) complexes of both L-cysteine and its peptides and related ligands are significantly higher than those of the zinc(II) complexes. Thiolate donor functions can be bridging ligands too, resulting in the formation of polynuclear cadmium(II) complexes.

Keywords amino acids • cadmium(II) • peptides • histidine • cysteine • thiolate ligands • stability constants • octahedral complexes • polynuclear complexes

1 Introduction

Cadmium is a d-block element with the electronic configuration $4d^{10}5s^2$. The closed d-shell results in the stabilization of the divalent (+2) oxidation state and up to now stable cadmium compounds have not been prepared in any other form. Cadmium is often referred to as the last member of the 4d (or second row) transition elements, while other textbooks describe cadmium as a member of the zinc group (Zn, Cd, and Hg) and do not consider it as a transition element. This dichotomy is reflected in the chemical properties of the element showing similarities to both transition and p-block metals. The basic chemical properties of cadmium and its major compounds including its complexes have been thoroughly described in the major inorganic and coordination chemistry textbooks. It is not the aim of this compilation to give an overview on the chemistry of cadmium(II) compounds. We will focus only on the major characteristics of cadmium(II) complexes affecting the interactions with amino acids and peptides.

The cadmium(II) ion with its d^{10} configuration shows no preferences for any coordination geometry arising from the crystal field stabilization. Therefore, it displays a variety of coordination geometries based upon the interplay of electrostatic effects, the covalency, and the size factor. Similarly to zinc(II) ion, 4 and 6 are the most common coordination numbers existing in tetrahedral and octahedral complexes, respectively. The ionic radius of cadmium(II) is, however, significantly larger than that of zinc(II) resulting in a high preference for the formation of six-coordinated octahedral species with cadmium(II). The donor atom preferences are also slightly different for the two metal ions. The classification of zinc(II) into the hard-soft categories is rather contradictory because it forms stable complexes with both oxygen and sulfur donor ligands; e.g., see the easy formation of $[Zn(OH)_4]^{2-}$ hydroxo complexes and of the ZnS precipitate. The increased size of cadmium(II) ions enhances its affinity towards sulfur containing ligands which is reflected in the binding mode of cadmium(II) under biological conditions, too. Similar differences can be observed in the hydrolytic reactions of the two metal ions. It is well-known that simple zinc(II) compounds are hydrolyzed even in slightly acidic samples (around pH 6.0) but the hydroxide precipitates are easily dissolved under alkaline conditions. On the contrary, cadmium(II) does not show any amphoteric character. The precipitation of cadmium(II)-hydroxide occurs in slightly basic solution (pH ~ 8.0) but this precipitate does not dissolve even at high pH values.

There is a significant difference in the affinity of the two metal ions towards the complexation with halide ions, too. In a diluted aqueous solution of zinc(II) chloride the octahedral aqua ions $[Zn(H_2O)_6]^{2+}$ are the predominating species, while a significant ratio of chloro complexes are formed with cadmium(II) under the same conditions. The stability constants of the complexes formed with bromide or iodide ions are even higher. The consideration of these differences is especially important during the selection of the appropriate counter ions to adjust the ionic strength for thermodynamic or electrochemical studies or even in the synthesis of cadmium(II) compounds.

Finally, it is also important to compare the properties of cadmium(II) and mercury(II) ions. For most of the transition elements the chemical properties of the 4d series are rather similar to those of the 5d elements. This is not true for the zinc(II) group elements and the properties of cadmium(II) significantly differ from those of mercury(II). Coordination numbers 2 (linear) and 4 (tetrahedral) are the most preferred arrangements for mercury(II) complexes, while the octahedron is the major stereochemistry of cadmium(II). Moreover, mercury(II) is a typical soft metal ion with an outstanding affinity for the interaction of sulfur or other heavy donor ligands. It has already been mentioned that cadmium(II) ions also prefer the binding of thiolate sulfur atoms but the various nitrogen and oxygen donor ligands are also promising candidates for a stable interaction with this metal ion. As a consequence, all amino acids and peptides are effective ligands for the complexation with cadmium(II) and the differences in the side chain donor functions result in a great variety of the complex formations with these ligands as it will be shown in the next sections.

2 Complexes of Amino Acids and Derivatives

2.1 General Characteristics of Cadmium(II) Complexes of Amino Acids

Cadmium(II) complexes of almost all natural amino acids and numerous amino acid derivatives were studied in the last few decades. The complex formation processes are generally very simple, so in this review the comparison of their stability and structure with those of other metal ions is emphasized. The enhanced stability and high structural variety of the complexes were observed with sulfur-containing amino acids and their derivatives, the characterization of this type of complexes is described in Section 2.3.5.

The stoichiometry and stability constants of the complexes were determined most frequently by means of potentiometric techniques, but these data were very often completed with results of polarography. The structures of complexes were proposed on the basis of the stoichiometry and stability of various species and *via* the analogy to other metal ion complexes. In some cases, the suggested structures of complexes were supported by the use of IR-spectroscopy, ^{113}Cd NMR, and X-ray studies.

The solution studies were performed in the usual concentration range and metal ion to ligand ratios: metal ion concentrations of $5{\cdot}10^{-4}$ to $5{\cdot}10^{-3}$ M give metal ion to ligand ratios of 1:5 to 1:1. The complex formation processes take place in the pH range 5 to 9. The presence of cadmium(II)-amino acid complexes usually cannot be detected in acidic solutions (below pH 5) with the exception of systems containing thiol derivatives. The hydrolysis of cadmium(II) ions takes place in slightly basic solution and the complex formation processes are often not able to prevent the formation of cadmium(II) hydroxide precipitates. The presence of mixed hydroxo complexes is generally not detected.

Cadmium(II) has a high affinity towards halide anions as ligands: the stability of chloro complexes is around one order of magnitude higher than that of the common 3d transition metal ions (e.g., $\log \beta_1 = 1.59$, $\log \beta_2 = 2.25$, $\log \beta_3 = 2.40$ for Cd(II) [1], $\log \beta_1 = 0.73$, $\log \beta_2 = 1.17$, $\log \beta_3 = 1.20$ for Zn(II) [2], and $\log \beta_1 = 0.69$ for Ni(II) [3]). The presence of chloro complexes could not be neglected in diluted solutions, if chloride is the counter anion to adjust the ionic strength. As a consequence, the potentiometric and electrochemical data were generally determined at NO_3^- or ClO_4^- ionic strength. The preparation of $CdCl_2{\cdot}Gly$ and $CdCl_2{\cdot}2Gly$ complexes in the solid state [4] also proves the high affinity of cadmium(II) for chloride.

The stoichiometry and stability constants of cadmium(II)-amino acid complexes are collected in Tables 1 and 2 together with data of the corresponding zinc(II) complexes for comparison.

These data show that, with the exception of thiol derivatives, exlusively CdL and CdL_2 (and CdL_3 or CdHL in some cases) complexes are formed in all cadmium(II)-amino acid systems. The stoichiometries of the zinc(II) and cadmium(II)

Table 1 Stability constants (log β) of complexes formed between Cd(II) or Zn(II) and amino acid systems (I = 0.1–1 M KNO_3/$NaNO_3$, *I = 3 M $NaClO_4$, T = 293–298 K).

	CdL	CdL_2	CdL_3	Ref.	ZnL	ZnL_2	ZnL_3	Ref.
Glycine	4.26	7.83	10.51	[6]	5.03	9.23	11.65	[22]
Amino acids with hydrophobic side chains								
α-Alanine	3.96	7.37	9.98	[6]	4.63	8.66		[23]
Valine	3.70	6.90		[8]	4.46	8.24		[23]
Leucine	4.04	7.53		[10]	4.89	9.19		[10]
Isoleucine	3.60	6.79	9.32	[12]	4.49	8.49	10.90	[12]
2-Amino-pentanoic acid	3.73	7.03		[13]	4.42	8.52		[13]
2-Amino-hexanoic acid	3.86	7.33		[13]	4.59	8.93		[13]
β-Alanine	3.60	5.80		[16]	4.14			[23]
Amino acids with polar side chains								
Phenylalanine	3.60	6.79	9.32	[6]	4.43	8.50		[24]
Tryptophan	4.51	8.19		[17]	5.14	9.86		[17]
Arginine	3.27	6.45		[18]	4.19	8.12		[18]
Asparagine*	4.07	7.58	9.61	[19]	5.07	9.43	12.30	[19]
Glutamine*	4.10	7.66		[19]	4.83	9.17	11.84	[25]
Amino acids with O-donor side chains								
Serine[a]	3.77	7.03	9.33	[6]	4.45	8.16		[40]
Threonine	3.90	7.10		[8]	4.74	8.51		[41]
Tyrosine	3.56	6.08		[17]	4.20	8.24		[17]
Aspartic acid[a]	4.68	8.27		[6]	5.69	9.77		[42]
Amino acids with N-donor side chains								
Lysine[b]		7.80		[31]	4.06	7.53		[43]
Ornithine (2,5-diaminopentanoic acid)	3.41	5.82		[32]	3.77	6.44		[44]
Histidine[c]	5.58	9.92		[6]	6.45	12.01		[48]
Histamine[c]	4.78	8.05	10.05	[38]	5.21	10.13		[38]

[a] ZnH_{-1} L: –3.73 (serine), –3.20 (aspartic acid).
[b] ZnHL: 14.72, $ZnHL_2$: 19.67, ZnH_2L_2: 28.85.
[c] CdHL: 11.16 (histidine), 11.53 (histamine).

complexes are very similar, though the formation of mixed hydroxo species was also observed in some cases. The presence of a thiol group in the side chain results in the formation of di- or trinuclear cadmium(II) complexes and the preference for formation of polynuclear species is much higher in cadmium(II)-containing systems than in the presence of zinc(II).

2.2 *Complexes of Amino Acids with Non-coordinating Side Chains*

The stoichiometry and thermodynamic stability constants of cadmium(II) complexes of glycine [5–7] and numerous amino acids containing hydrophobic [6,8–16] and polar [6,17–21] side chains were published. The stability constants of CdL and CdL_2 complexes are usually similar to each other (log β(CdL) ~ 3.6 – 4.1,

log $\beta(CdL_2) \sim 6.8 - 8.2$) and these complexes are around one order of magnitude less stable than the analogous zinc(II) complexes [22–25] (log $\beta(ZnL) \sim 4.4 - 5.2$, log $\beta(ZnL_2) \sim 8.2 - 9.9$). In these complexes metal ions bind to the amino and carboxylate groups forming five-membered chelate rings. This coordination mode was also established for the $CdCl_2 \cdot Gly$ complex in the solid state on the basis of infrared spectra [4]. Although these infrared experiments have shown a monodentate coordination of glycine *via* a carboxylate group in the $CdCl_2 \cdot 2Gly$ complex, the single carboxylate group does not offer an effective binding site for cadmium(II) in solution. This fact is proven by the low stability constant of the cadmium(II)-N-acetyl-glycine complex (log $\beta(CdL) = 1.13$) [26]. Comparison of the stability of Cd(II)-glycinamide [27,28] complexes (log $\beta(CdL) = 2.65$, log $\beta(CdL_2) = 4.88$) with those of the cadmium(II)-glycine systems proves the bidentate coordination of amino acids through the NH_2, COO^- donor set as well, while glycinamide is able to bind the metal ion *via* (NH_2, CO) donor groups resulting in a slightly reduced stability.

The stepwise stability constants characterizing the formation of ML_2 complexes and the log (K_1/K_2) values describing the preference for binding of the second ligand to the metal ion correspond to the statistical values, similarly to those of the zinc(II) complexes. For all cadmium(II)- and zinc(II)-phenylalanine and -arginine systems the log (K_1/K_2) values are lower than statistically expected (0.6) suggesting that the binding of the second ligand is favored. This can be explained by the stacking of aromatic rings of phenylalanine in the ML_2 complexes. Similar trends can be observed in the case of the cadmium(II)- and zinc(II)-arginine systems due to a secondary interaction between the polar side chains. The distance between the amino and carboxylate groups is larger in the β-alanine molecule and the simultaneous coordination of the two terminal groups to the metal ion results in six-membered chelate rings decreasing the stability of mono- and bis(ligand) cadmium(II) complexes and increasing the log (K_1/K_2) value.

The octahedral geometry of cadmium(II) complexes also allows the formation of tris(ligand) complexes. Because of steric requirements the presence of ML_3 complexes was suggested only in the case of glycine and for some other amino acids containing small side chain residues. Indeed, the formation of all three cadmium(II)-glycine species was detected by means of ^{113}Cd NMR measurements [29]. These observations strongly support the existence of an octahedral coordination geometry of cadmium(II) in its common amino acid complexes.

2.3 *Complexes of Amino Acids with Coordinating Side Chains*

The O- and/or N-atoms in the side chains of amino acids can be potential binding sites for metal ions depending on the position of the donor atoms and the hard-soft character of the metal ion. Taking into account the soft character of cadmium(II) a negligible effect of O donor side chains can be expected, while the N donor atoms may have an enhanced ability to take part in the complex formation processes.

The characterization of complexes of various amino acids containing –OH (serine, threonine, tyrosine) [6,8,17,30] or –COOH groups (aspartic and glutamic acids) [6] and $–NH_2$ (lysine, ornithine) [31,32] or imidazole N (histidine, histamine) [3,6,33–38] has been published.

2.3.1 Complexes of Amino Acids with O-Donor Side Chains

The stoichiometry and stability constants of the complexes in Table 1 reflect that the presence of an –OH group in the side chain does not affect the metal binding ability of amino acids, not even the –OH group in a chelatable position (serine, threonine) takes part in metal ion binding. A slight enhancement of stability can be detected, however, for aspartic acid, where the tridentate coordination of the ligand is suggested. The coordination of side chain carboxylate groups was found in the solid complex of $Cd(AspH)NO_3$ and Cd(Asp) [39]. The coordination of the (NH_2,α-COO^-) set was detected in the Cd(Asp) species, nevertheless, the crystal structure of the $Cd(AspH)NO_3$ complex shows a two-dimensional polymer in which each cadmium is coordinated to oxygen donor atoms of carboxylate groups and a nitrate anion, the amino group is protonated and the aspartic acid molecules act as bridging ligands. The metal center is seven-coordinated with distorted octahedral geometry. It is worth to compare these data with those of lead(II), which has a similar soft character, and both types of analogous solid complexes were prepared. The metal ion is bound to the same donor atoms in these species, but the metal center in the $Pb(AspH)NO_3$ complex is six-coordinated with regular octahedral geometry.

A similar trend of stability constants can be observed for the corresponding zinc(II) complexes [17,40–42]. The binding of the extra carboxylate group of aspartic acid results in an increased stability. At the same time, similarly to the amino acids containing non-coordinating side chains, these amino acids also form more stable complexes with zinc(II) compared to cadmium(II). The steric effects of bulky side chains or the tridentate binding of the ligands prevent the formation of tris complexes in all cadmium(II)- and zinc(II)-containing systems with the exception of the cadmium(II)-serine system.

2.3.2 Complexes of Amino Acids with N-Donor Side Chains

Lysine and ornithine contain an additional terminal amino group in the side chain. The simultaneous binding of these amino groups with the (NH_2,COO^-) donor set to the metal ion would result in the formation of eight- or seven-membered chelate rings, respectively, which are not favored by transition metal ions. Similarly to other metal ions, the presence of the side chain amino group does not have a significant impact on the thermodynamic stability of these cadmium(II) complexes [31,32,43,44]. There are, however, significant differences in the preferred stoichiometry of the complexes because the non-coordinated amino groups remain protonated below pH 9.0.

The imidazole-nitrogen donor of histidine is one of the most important binding sites for transition metal ions in biological systems. The N(3) atom itself can be a metal binding site which is reflected in the significant complex formation processes in the lead(II) or copper(II) 4-methylimidazole and N-acetyl-histidine-amide systems [45,46]; yet, a much lower affinity of these ligands is observed towards cadmium(II) [45,47]. The presence of the terminal amino group in histidine or histamine, however, enhances the coordination ability of the ligands forming stable six-membered chelate rings. As a consequence, a higher thermodynamic stability of the cadmium(II)-histamine and -histidine complexes was observed compared to other amino acids, or similarly, compared to other metal ions like Cu(II), Ni(II) or Zn(II) [48]. Nevertheless, the stability order follows the same trend as was mentioned for other amino acids: log β(Cd(II) complexes) < log β(Zn(II) complexes). On the other hand, similarly to other metal ions, a tridentate coordination of histidine was suggested, which is reflected in the stability order: log β(Cd(II)(histamine)$_{1,2}$) < log β(Cd(II)(histidine)$_{1,2}$) [6]. The stoichiometry and stability of the complexes were determined using potentiometry [3,6,33–36] or polarography [37]; the tridentate coordination of the ligand and the regular octahedral geometry of the complexes were further supported by means of cyclic voltammetry [49] and IR multiple photon dissociation spectroscopy [50]. In the latter experiments, the structures of Cd(Cl)(HHis), CdL and Cd(HHis)$_2$ species have been determined in the gas phase and the data were completed by quantum mechanical calculations. The results indicated that histidine coordinates to the metal in a charge-solvated tridentate form in the Cd(Cl)(HHis) complex and has a similar tridentate configuration with a deprotonated carboxylic acid terminus in the CdL complex.

2.3.3 Complexes of Amino Acids Containing Sulfur Donor Atoms

The sulfur atom with its soft character can be an important binding site for cadmium(II). Methionine and cysteine (or cystine) are proteinogenic amino acids containing sulfur donor atoms in the side chain in different chemical environments, namely as thioether and thiol (or disulfide) groups, respectively. In addition to their cadmium(II) and zinc(II) complexes [6,51–53] those of numerous amino acid derivatives containing thioether (S-methyl-cysteine) [6] and thiol groups (D-penicillamine, N-acetyl-cysteine, cysteine-methylester, N-acetyl-D-penicillamine, N-2-mercaptopropanoyl-glycine, 2-mercaptosuccinic acid) [27,54–59] were studied. The thermodynamic stability constants of cadmium(II) and zinc(II) complexes of sulfur-containing ligands are collected in Table 2.

2.3.4 Complexes of Thioether Ligands

In both, the cadmium(II) S-methyl-cysteine and methionine systems, mono-, bis-, and tris(ligand) complexes are formed corresponding to the six-coordinated octahedral geometry of cadmium(II). Although the corresponding zinc(II) complexes

Table 2 Stability constants (log β) of complexes formed by Cd(II) or Zn(II) and sulfur-containing ligand systems (I = 0.1–1 M KNO_3/$NaNO_3$, T = 293–298 K).

	CdL	CdL_2	CdL_3	Cd_2L_3	Cd_3L_4	Ref.	ZnL	ZnL_2	ZnHL	Zn_2L_3	Zn_3L_4	Ref.
Amino acids with a sulfur-containing side chain												
S-Methyl-cysteine	3.79	7.04	9.63			[6]	4.46	8.52				[54]
Methionine	3.65	6.76	9.08			[6]	4.38	8.35				[53]
Cysteine[a,b]	12.82	21.71	27.52	40.41		[52]	8.20	12.05	14.76	29.20	42.11	[51]
D-Penicillamine[a,b]	11.53	19.64			50.22	[27]	9.66	19.39	14.80			[51]
N-Acetyl-cysteine[b,c]	7.05	13.49	17.41		35.53	[27]	4.90	11.48				[55]
Cysteine-methylester[b,c]	8.51	16.41	19.28	29.52		[27]	8.21	15.91	11.90			[56]
N-Acetyl-D-penicillamine	7.53	14.11	17.44		35.99	[27]	6.85	14.03				[57]
N-2-Mercaptopropanoyl-glycine	6.83	12.78	16.71		33.01	[27]	5.72	10.45				[58]
2-Mercaptosuccinic acid	10.05	13.51			41.59	[27]	8.24	14.56				[59]

[a] Zn_3HL_4: 49.01 (cysteine), ZnH_2L_2: 29.93 (cysteine), 30.65 (D-penicillamine).
[b] $ZnHL_2$: 24.43 (cysteine), 25.23 (D-penicillamine), 18.39 (N-acetyl-cysteine), 20.76 (cysteine-methylester).
[c] ZnH_{-1} L: 2,71 (N-acetyl-cysteine), 0.41 (cysteine-methylester).

are more stable, the formation of ZnL_3 complexes was not detected. Taking into account the different pK values of the terminal amino groups of amino acids, the relative stability of the complexes can be evaluated by the comparison of the the log β_1 – pK(NH_3^+) values: glycine: –5.30 ~ methionine: –5.41 < S-methyl-cysteine: –4.93. The higher value for S-methyl-cysteine reflects the enhancement of the stability of the cadmium(II) complex of this ligand, which could be explained by the participation of the thioether sulfur atom in metal binding. The tridentate coordination of the ligand results in the formation of two five-membered chelate rings. The contribution of the thioether moiety to metal binding is, however, rather weak and cannot prevent formation of the tris(ligand) complex. Moreover, the same effect cannot be observed for methionine due to the larger distance between thioether and amino/carboxylate groups.

2.3.5 Complexes of Cysteine and Derivatives

The investigation of the complexes of cysteine and a series of amino acid derivatives containing thiol groups gave the possibility to compare the coordination ability of these ligands and assess the trend of stability of the complexes which coordinate to different donor groups. In L-cysteine and D-penicillamine three potential donor groups (NH_2, S^-, COO^-) are present, while in the N-acetyl-cysteine, N-acetyl-D-penicillamine, N-2-mercapto-propanoyl-glycine and 2-mercapto-succinic acid the (S^-,COO^-/CO) and in cysteine-methylester the (NH_2,S^-) donor sets serve as the metal binding sites. All data reveal the significantly enhanced stability of cadmium(II) complexes with these thiolate ligands. The stability of complexes follows the trend: N-2-mercapto-propanoyl-glycine ~ N-acetyl-cysteine ~ N-acetyl-D-penicillamine < cysteine-methylester < 2-mercapto-succinic acid < D-penicillamine ~ L-cysteine. The highest stability constants for D-penicillamine and L-cysteine prove the tridentate coordination of these ligands with (N,S,O) binding mode and this coordination mode is preferred compared to the tridentate (N,O,O) coordination of 2-mercapto-succinic acid. Thiol sulfur donor atoms of cysteine and penicillamine are in chelating position with both amino (five-membered) and carboxylate groups (six-membered) and this tridentate coordination mode is much more favored for binding to cadmium(II) than that of bidentate coordination of the common amino acids. Moreover, the coordination of thiol sulfur atoms together with the carboxylate or/and amino groups results in the enhanced stability of cadmium(II) complexes as compared to those of zinc(II) or nickel(II) [51]. It can be concluded that the thiol group is a more effective binding site for cadmium(II) than for the other two metal ions.

The other characteristic feature of the thiol donor group in cadmium complexes is the formation of oligomeric structures. The existence of Cd_2L_3 was detected in the cadmium(II)-cysteine and -cysteine-methylester system,

while trinuclear Cd_3L_4 species are present for the other thiol derivatives. Similar structures were determined for nickel(II) and zinc(II) [51]. The suggested structure of these complexes contains two or three metal ions connected *via* sulfur bridges. The formation of oligomeric species is the most common in the case of cadmium(II)-containing systems, and these complexes are usually present in the slightly acidic or neutral pH range in equimolar solutions. Increasing the excess of ligand and/or pH makes the formation of CdL_2 and CdL_3 species preferable. The use of polarographic techniques established the formation of polynuclear species as well [27].

Most of the earlier studies on the cadmium(II) complexes of L-cysteine and derivatives have been performed in rather diluted solutions and the tridentate chelating form of the ligand predominated under these conditions. In the last few years the structures of the complexes formed in more concentrated samples or in the solid state were determined by means of X-ray diffraction, ^{113}Cd NMR, Raman, IR, EXAFS, and XANES spectroscopic methods [60–62]. The complexes $[Cd(HCys)_2 \cdot H_2O]$ and $[Cd(HCys)_2 \cdot H_2O] \cdot H_3O^+ClO_4^-$ were prepared from acidic solution and the combined application of various spectroscopic techniques revealed that the cysteine amino group is protonated and not involved in bonding. The existence of CdS_4 and CdS_3O structural units with single thiolate (Cd-S-Cd) bridges were identified, although a minor amount of central Cd(II) with $CdS_3O_{2/3}$ and CdS_4O coordination environments cannot be ruled out. ^{113}Cd NMR measurements were carried out in cadmium(II)-cysteine, -penicillamine, and -N-acetyl-cysteine solutions at two orders of magnitude higher concentration (0.2–2.0 M) than the one used for the potentiometric measurements. Around physiological pH and in the presence of high excess of ligand the complexes are almost exclusively sulfur-coordinated as [Cd(S-cysteinate)$_4$], while the deprotonation of the ammonium groups promotes chelate formation, and the presence of complexes with CdS_3N coordination was also supposed. Similarly to the cadmium(II)-cysteine system the tetrathiolate complex is the major species in the cadmium(II)-N-acetyl-cysteine solution under similar circumstances ([ligand] = 1.0 M, high excess of ligand). Oligomeric complexes with CdS_3O_3, CdS_3O, and CdS_4 coordination sites and a single thiolate bridge between cadmium(II) ions were also detected at a 1:2 metal to ligand ratio.

For the corresponding penicillamine systems, however, the Cd(penicillamine)$_3$ complexes were found to be the dominating species with a CdS_3(N/O) coordination mode around pH 7.5. The increase of pH resulted in the formation of complexes with mixed coordinated CdS_2(N)(N/O) metal centers. These findings are in good agreement with previous conclusions that D-penicillamine has a reduced affinity to form polynuclear complexes. On the basis of these studies it was concluded [61] that the differences between cysteine and penicillamine as metal binding ligands can explain why cysteine-rich metallothioneines are capable of capturing cadmium(II) ions, while penicillamine can be a useful molecule for the treatment of the toxic effects of mercury(II) and lead(II) exposure and is not efficient against cadmium(II) poisoning.

Abbreviations and Definitions

Ac	acetyl
Ala	alanine
Asn	asparagine
Asp	aspartic acid
BSA	bovine serum albumin
CD	circular dichroism
Cys	cysteine
DFT	density functional theory
ESI-MS	electrospray ionization mass spectrometry
EXAFS	extended X-ray absorption fine structure
Gln	glutamine
Glu	glutamic acid
Gly	glycine
His	histidine
HSA	human serum albumin
Ile	isoleucine
IR	infrared
L	general ligand
L-carnosine	β-alanyl-L-histidine
Leu	leucine
Lys	lysine
NMR	nuclear magnetic resonance
PC	phytochelatin
Phe	phenylalanine
Pro	proline
PSA	porcine serum albumin
ROS	reactive oxygen species
Sar	sarcosine = N-methylglycine
Thr	threonine
Val	valine
XANES	X-ray absorption near-edge structure

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