



## Synthesis, structural study and topological analysis of Zn/Aib and Aib-based small peptide complexes (H-Aib-OH = $\alpha$ -aminoisobutyric acid)

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### ARTICLE INFO

#### Article history:

Available online 10 July 2009

Dedicated to Dr. Aris Terzis for his enormous contribution to the advancement of Inorganic Chemistry in Greece through single-crystal X-ray crystallography.

#### Keywords:

$\alpha$ -Aminoisobutyric acid (H-Aib-OH)  
Aminoacid complexes  
Dipeptide complexes  
Tripeptide complexes  
X-ray crystal structures  
Zn(II) complexes

### ABSTRACT

The systematic investigation of the coordination chemistry of  $\alpha$ -aminoisobutyric acid (H-Aib-OH) and Aib-based small peptides is continued. The solid complexes  $[\text{Zn}_3(\text{H-Aib-O})_6] \cdot \text{MeCOOH} \cdot \text{H}_2\text{O}$  (**1**·MeCOOH·H<sub>2</sub>O),  $\{[\text{Zn}(\text{H-Aib-L-Ala-O})_2] \cdot \text{H}_2\text{O}\}_n$  (**2**·H<sub>2</sub>O) and  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4](\text{ClO}_4)_2 \cdot 5.8\text{H}_2\text{O}$  (**3**·5.8H<sub>2</sub>O) have been isolated and characterized by single-crystal X-ray crystallography. In the structure of complex **1**·MeCOOH·H<sub>2</sub>O, three Zn<sup>II</sup> ions and six H-Aib-O<sup>-</sup> ligands have assembled to form a trinuclear cluster. All three Zn<sup>II</sup> centers are in a very distorted trigonal bipyramidal coordination. The trinuclear units assemble through a network of hydrogen bonds to form a 2D framework with a (3.6.3.6) topology, while the lattice acetic acid and water molecule connect the layers to create a 3D framework with a **fcu** topology. Complex **2**·H<sub>2</sub>O is a two-dimensional coordination polymer. The deprotonated dipeptide behaves as a  $\eta^1:\eta^1:\eta^1:\mu_2$  ligand binding one Zn<sup>II</sup> atom through its amino nitrogen and peptide oxygen, and an adjacent Zn<sup>II</sup> atom through one of its carboxylate oxygen. In the crystal lattice, the layers are connected in the third direction through hydrogen bonds and the resulting framework conforms to a **tfa** net. Complex **3**·5.8H<sub>2</sub>O consists of mononuclear  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4]^{2+}$  cations, ClO<sub>4</sub><sup>-</sup> and lattice water molecules. The tripeptide ligands are in their zwitterionic form and coordinate through one of the carboxylate oxygen atom to the metal ion, while they are participating in a network of intra- and intermolecular hydrogen bonds forming a 3D framework that adopts the **bcu** network.

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### 1. Introduction

The metal-aminoacid/peptide interactions is a subject of continuous interest in the fields of bioinorganic and coordination chemistry, molecular biology and solid-state physics. From the bioinorganic point of view, the interest originates mainly from the need of understanding the role of essential metal ions in biological systems, by creating *structural* and *functional* models of the metal sites in metalloenzymes and metalloproteins [1].  $\alpha$ -Aminoacids are excellent metal complexing agents, forming stable chelates through their amino and carboxylate groups. The number of coordination modes grows up from the diversity of the capable for coordination side-chains. Small peptides possess a clearly greater number of functional groups that are potential donor atoms for metal ion complexation. Besides the nitrogen atom of the primary amine group and the oxygen atoms of the carboxylate

group, the carbonyl oxygen atom and the deprotonated nitrogen atom of the peptide bond are implicated in metal ion complexation. The wealth of potential donor atoms on peptides usually gives rise for the formation of single or multiple chelate rings with a metal ion, while in some cases bridging of different metal ions might occur, leading to extended polymeric structures. Several excellent reviews deal with the aminoacid/peptide coordination chemistry focusing mainly on solution studies [2–6]. In addition to the metal coordination, the functional groups that peptides possess can be regarded as potential donor and acceptor atoms for hydrogen bonding. The conformation of the peptides and protein molecules as well as their interaction with each other and with other species in biological systems is largely depending on the formation of hydrogen bonds. Such hydrogen bonding is affected by coordination to metal ions resulting in conformational changes that in turn define a different type of interactions [7]. These intriguing features make aminoacids and peptides and their metal complexes subjects of study in the realm of crystal engineering.

The elucidation of the structural diversity of metal-aminoacid complexes has been documented by early reviews [8–10]. In

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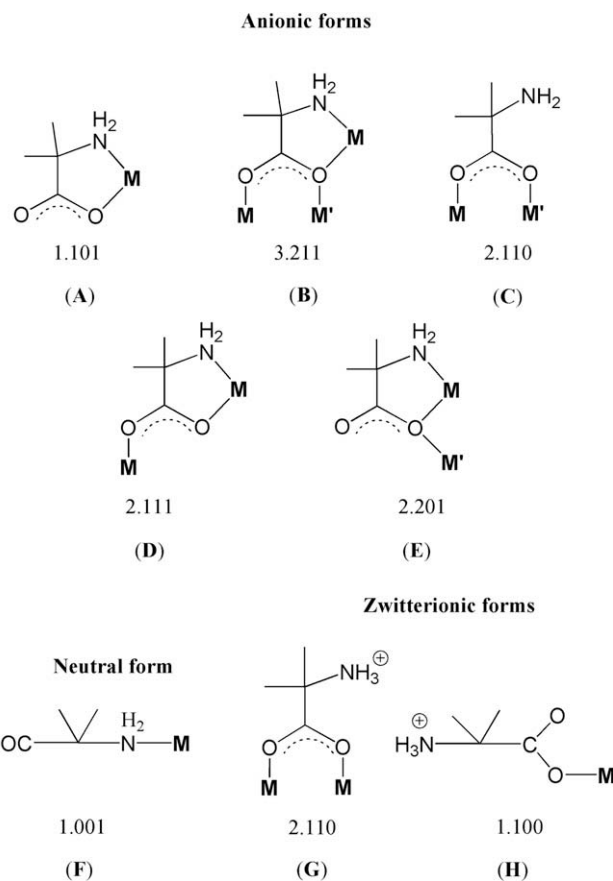
contrast, the structures of metal–oligopeptide complexes are till now scarce, due to the reluctance of the peptide molecules to form crystalline solids. This is specifically valid for the Zn(II)-aminoacid/peptide coordination chemistry. From a careful search in the CCDC base it is evident that crystal structures of Zn(II) complexes with almost all naturally occurring  $\alpha$ -aminoacids have been reported. However, there are less than fifteen structure determinations of Zn(II)/dipeptide complexes, including those containing peptide derivatives or –N and –C protected aminoacid constituents. Among them, only three *binary* Zn(II)/*free-peptide* compounds have been structurally characterized:  $\{[\text{Zn}(\text{H-Gly-Gly-O})_2 \cdot 2\text{H}_2\text{O}]_n\}$  [11a],  $\{[\text{Zn}(\text{H-Gly-L-Thr-O})_2 \cdot 2\text{H}_2\text{O}]_n\}$  [11b] and  $\{[\text{Zn}(\text{H-Gly-His-O})_2 \cdot 7\text{H}_2\text{O}]_n\}$  [11c]; the *ternary* complex  $[\text{Zn}_2(\text{H-Gly-Gly-O})_2(\text{LH}^+)_2](\text{ClO}_4)_4 \cdot 2\text{H}_2\text{O}$  (L = 1-methyl-4(6-amino-2-pyridylmethyl) piperazine) is also known [11d]. Furthermore, in the whole Zn(II)/oligopeptide chemistry, only the crystal structure of the coordination polymer  $\{[\text{Zn}(\text{H-Gly-Gly-Gly-O})(\text{H}_2\text{O})](\text{SO}_4)_{0.5} \cdot 2\text{H}_2\text{O}\}_n$  has been reported so far [11e].

We have initiated a systematic study of the coordination chemistry of  $\alpha$ -aminoisobutyric acid (H-Aib-OH), and dipeptides and tripeptides containing the  $\alpha$ -aminoisobutyryl residue [–HNC(CH<sub>3</sub>)<sub>2</sub>CO–, Aib]. The  $\alpha$ -aminoisobutyric acid (also called  $\alpha$ -methyl-alanine or  $\alpha,\alpha$ -dimethylglycine) is an uncommon natural aminoacid which is commonly found in a family of natural antibiotics produced by microbial sources. As shown by early studies, the replacement of the hydrogen atoms of the C<sub>α</sub> carbon of glycine with methyl groups produces severe restrictions on the conformational freedom of the molecule and, consequently, –Aib– is a strong promoter and stabilizer of folded ( $\beta$ -bends) and 3<sub>10</sub> or  $\alpha$ -helical structures [12]. Our interest in this chemistry is mainly to investigate how the inductive and steric properties of the  $\alpha$ -carbon methyl groups affect the structures of the complexes in the solid state, to test the possibility of creating helical complexes (helicates) or/and one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) coordination polymers or polynuclear aggregates (clusters) and to study the supramolecular assemblies of these species through their hydrogen bonding interactions.

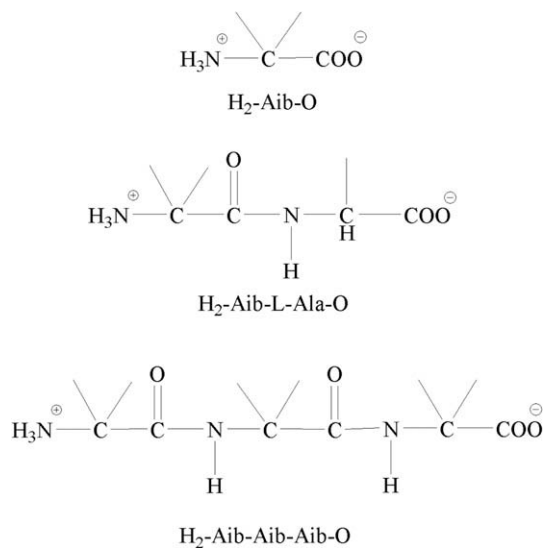
Concerning the coordination chemistry of the free aminoacid (H-Aib-OH), 15 structurally characterized H-Aib-OH/metal ion complexes have been reported. It is impressive that the aminoacid employed in these structures adopts *eight* different coordination modes in its anionic, neutral or zwitterionic forms, as these are illustrated in Scheme 1. The reported metal complexes are listed in Table 1, with the corresponding coordination modes being described using Harris notation [13].

The coordination chemistry of Aib-based dipeptides is poorly explored. In our previous work, the crystal structures of Cu(II) complexes with the dianionic forms of dipeptides H-Aib-Aib-OH [27a], H-Aib-Gly-OH, H-Aib-L-Leu-OH H-Aib-L-Phe-OH [27b], and with the monoanionic and dianionic forms of H-Aib-L-Ala-OH [27c] have been reported. Also, the diorganotin complexes  $[(n\text{-Bu})_2\text{Sn}(\text{H}_{-1}\text{L})]$  where LH = H-Aib-L-Leu-OH and H-Aib-L-Ala-OH, have been structurally characterized and their antibacterial and antiproliferative activities investigated [27d]. Finally, in the coordination chemistry of Aib-based tripeptides, the X-ray crystal structure of the remarkable copper(III) complex  $[\text{Cu}^{\text{III}}(\text{H}_2\text{Aib}_3)] \cdot 2\text{H}_2\text{O} \cdot 1.5\text{NaClO}_4$ , containing the trianion of tri- $\alpha$ -amino-isobutyric acid as ligand, has been determined [28a]. Reduction of this complex by 2,4-di-*tert*-butylphenol gave the dinuclear complex  $[\text{Cu}_2(\text{H}_{-1}\text{Aib}_3)_2]$  [28b].

We wish to report here the results of our studies concerning the interaction of Zn(II) and the aminoacid H-Aib-OH, the dipeptide H-Aib-L-Ala-OH and the tripeptide H-Aib-Aib-Aib-OH (Scheme 2). Emphasis is given on the characterization of the products in the solid state.



Scheme 1. The crystallographically established coordination modes of H-Aib-OH using Harris notation [13].



Scheme 2. The ligands used in the present work.

## 2. Experimental

### 2.1. General procedures and physical measurements

All manipulations were performed under aerobic conditions. All chemicals and solvents were purchased from commercial sources and used without further purification. Microanalyses (C, H, N) were performed by the University of Ioannina (Greece) Microanalytical

Service using an EA 1108 Carlo Erba analyzer. Melting points were taken on a Electrothermal 9200 apparatus and are uncorrected. IR spectra (4000–450 cm<sup>-1</sup>) were recorded on a Perkin–Elmer 16 PC FT spectrometer with samples prepared as KBr pellets.

## 2.2. Synthesis of the ligands

### 2.2.1. H-Aib-L-Ala-OH

The dipeptide was prepared in the liquid phase, as described earlier [27c].

### 2.2.2. H-Aib-Aib-Aib-OH

The protected aminoacids Z-Aib-OH and p-TsA-Aib-OBzl were prepared according to the literature [29]. Coupling of Z-Aib-OH with p-TsA-Aib-OBzl via the PyBOP procedure [30], provided Z-Aib-Aib-OBzl [27a]. The dipeptide Z-Aib-Aib-OBzl (0.97 g, 2.5 mmol) was deprotected upon treatment with 2.5 N HBr/CH<sub>3</sub>COOH (25 ml) for 1.5 h at room temperature and the HBr salt was precipitated by trituration with dry ether, washed with dry ether repeatedly and dried over P<sub>2</sub>O<sub>5</sub>/KOH (yield 80%). This salt was dissolved in DMF (4 ml), neutralized with Et<sub>3</sub>N and allowed to react with Z-Aib-OH (0.45 g, 2 mmol) dissolved in DMF (4 ml) and preactivated at 0 °C for 30 min with HOBT (0.45 g, 3.0 mmol) and DCC (0.83 g, 4 mmol). The reaction mixture was stirred for 2 h at 0 °C and overnight at room temperature. The precipitated DCU was filtered and the solvent was removed *in vacuo*. The residue was partitioned in AcOEt–H<sub>2</sub>O. The organic layer was washed alternatively with 5% NaHCO<sub>3</sub> and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent and recrystallization of the product from AcOEt/petroleum ether yielded 0.75 g (75%); mp 138–139 °C; TLC: R<sub>f</sub> 0.65 (single spot) (CHCl<sub>3</sub>/MeOH/AcOEt, 85:10:5), R<sub>f</sub> 0.87 (single spot) (n-BuOH:MeCOOH–H<sub>2</sub>O 3:1:1). The protecting groups were removed by catalytic hydrogenolysis (10% Pd on charcoal) in DMF and the free tripeptide crystallized upon addition of AcOEt–petroleum ether. It was further purified by column chromatography on Sephadex G-10 using AcOH (5%) as the eluent. Yield: 0.33 g (80%); mp 186–187 °C; TLC: 0.40 (single spot) (CHCl<sub>3</sub>/MeOH/AcOEt, 85:10:5), R<sub>f</sub> 0.60 (single spot) (n-BuOH:MeCOOH–H<sub>2</sub>O 3:1:1).

## 2.3. Synthesis of zinc(II) complexes

### 2.3.1. [Zn<sub>3</sub>(H-Aib-O)<sub>6</sub>]·MeCOOH·H<sub>2</sub>O (1-MeCOOH·H<sub>2</sub>O)

H-Aib-OH (0.004 g, 0.04 mmol) was added to a stirred solution of Zn(O<sub>2</sub>CMe)<sub>2</sub>·2H<sub>2</sub>O (0.011 g, 0.05 mmol) in MeOH (5 ml). After the addition of 4–5 drops of H<sub>2</sub>O, the solid soon dissolved. The “pH” of the solution was ~5.5 and adjusted to ~8 with saturated LiOH·H<sub>2</sub>O in MeOH. Colourless crystals of the product (suitable

for crystallographic studies) were obtained from the solution by vapour diffusion with Et<sub>2</sub>O. The crystals were collected by filtration and dried in air. Yield: 57%. The dried solid was analysed as H<sub>2</sub>O-free (1-MeCOOH). *Anal. Calc.* for C<sub>26</sub>H<sub>52</sub>N<sub>6</sub>O<sub>14</sub>Zn<sub>3</sub>: C, 35.9; H, 6.0; N, 9.7. Found: C, 35.8; H, 6.3; N, 9.6%. Selected IR data (KBr, cm<sup>-1</sup>): 3430mb [ν<sub>as</sub>(NH<sub>2</sub>)], 3294mb [ν<sub>s</sub>(NH<sub>2</sub>)], ~3150wb [ν(OH)<sub>acetic acid</sub>], 1655s [ν(C=O)<sub>acetic acid</sub>], 1586s [ν<sub>as</sub>(CO<sub>2</sub>)], 1472m [δ<sub>d</sub>(CH<sub>3</sub>)], 1414mb [ν<sub>s</sub>(CO<sub>2</sub>)], 1385sh [ν<sub>s</sub>(CO<sub>2</sub>)], 1216m, 1098m, 902w, 814m, 692m, 624m.

### 2.3.2. {[Zn(H-Aib-L-Ala-O)]<sub>2</sub>·H<sub>2</sub>O}<sub>n</sub> (2-H<sub>2</sub>O)

To a stirred solution of Zn(O<sub>2</sub>CMe)<sub>2</sub>·2H<sub>2</sub>O (0.013 g, 0.06 mmol) in MeOH (6 ml), the dipeptide H-Aib-L-Ala-OH was added (0.016 g, 0.09 mmol). H<sub>2</sub>O (1 ml) was added and the solid soon dissolved. The “pH” of the solution was ~6. Colourless X-ray quality crystals of the product were obtained from the solution by vapour diffusion with Et<sub>2</sub>O. The crystals were collected by filtration and dried in air. Yield: 60%. The dried solid was analyzed as H<sub>2</sub>O-free (2). *Anal. Calc.* for C<sub>14</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>Zn: C, 40.8; H, 6.4; N, 13.6. Found: C, 41.1; H, 6.3; N, 13.5%. Selected IR data (KBr, cm<sup>-1</sup>): 3400mb [ν<sub>as</sub>(NH<sub>2</sub>)], 3265m [ν<sub>s</sub>(NH)<sub>peptide</sub>], 3236m [ν<sub>s</sub>(NH<sub>2</sub>)], 1646m [ν(C=O)<sub>peptide or amide I</sub>], 1593sb [ν<sub>as</sub>(CO<sub>2</sub>)], 1559m [ν(CN)+δ(NH) or amide II], 1416m [ν<sub>s</sub>(CO<sub>2</sub>)], 1260m [δ(NH+ν(CN) or amide III)].

### 2.3.3. [Zn(H<sub>2</sub>-Aib-Aib-Aib-O)<sub>4</sub>](ClO<sub>4</sub>)<sub>2</sub>·5.8H<sub>2</sub>O (3-5.8H<sub>2</sub>O)

To a stirred solution of Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.011 g, 0.03 mmol) in MeOH (6 ml), the tripeptide H-Aib-Aib-Aib-OH was added (0.016 g, 0.06 mmol). The “pH” of the solution was ~4 and no adjustment was made. Colourless crystals of the product (suitable for crystallographic studies) were obtained from the solution by vapour diffusion with Et<sub>2</sub>O. The crystals were collected by filtration and dried in air. Yield: 55%. The dried solid was analyzed as H<sub>2</sub>O-free (3). *Anal. Calc.* for C<sub>48</sub>H<sub>102</sub>N<sub>12</sub>O<sub>24</sub>Cl<sub>2</sub>Zn: C, 42.2; H, 7.5; N, 12.3. Found: C, 42.3; H, 7.2; N, 12.4%. Selected IR data (KBr, cm<sup>-1</sup>): ~3390sb [ν(OH)<sub>water</sub>], 3254mb [ν(NH)<sub>peptide</sub>], ~3100m [ν(NH<sub>3</sub><sup>+</sup>)], 1654s [ν(C=O)<sub>peptide or amide I</sub>], 1620s [ν<sub>as</sub>(CO<sub>2</sub>)], 1524s [ν(CN) + δ(NH) or amide II], 14586m [δ<sub>d</sub>(CH<sub>3</sub>)], 1430m [ν<sub>s</sub>(CO<sub>2</sub>)], 1284w [δ(NH + ν(CN) or amide III], 1094sb [ν<sub>d</sub>(ClO)], 624m [δ<sub>d</sub>(OCIO)].

## 2.4. X-ray crystallographic studies

Crystals of complexes 1-MeCOOH·H<sub>2</sub>O, 2-H<sub>2</sub>O and 3-5.8H<sub>2</sub>O were mounted in air and covered with epoxy glue. Diffraction measurements were made on a P2<sub>1</sub> Nicolet diffractometer upgraded by Crystal Logic using monochromated Cu radiation. Complete crystal data and parameters for data collection and processing are

**Table 1**

The crystallographically determined Metal/H-Aib-OH complexes.

Compound	Coordination mode <sup>a</sup>	Ref.
[Cu(H-Aib-O) <sub>2</sub> ]	1.101 (A)	[14]
[Ni(H-Aib-O) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]·xH <sub>2</sub> O (x = 2, x = 3)	1.101 (A)	[15a,b]
[Cr(H-Aib-O) <sub>3</sub> ]	1.101 (A)	[16]
[Zn(H-Aib-O) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ][Zn(H-Aib-O) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	1.101 (A)	[17]
<i>trans</i> -[Pt(H-Aib-O) <sub>2</sub> ]	1.101 (A)	[18]
[Pr <sub>2</sub> (H <sub>2</sub> -Aib-O) <sub>4</sub> (H <sub>2</sub> O) <sub>8</sub> ]Cl <sub>6</sub> ·H <sub>2</sub> O	2.110 (G)	[19]
[La <sub>2</sub> (H <sub>2</sub> -Aib-O) <sub>4</sub> (H <sub>2</sub> O) <sub>8</sub> ](ClO <sub>4</sub> ) <sub>6</sub>	2.110 (G)	[19]
[Gd <sub>6</sub> Cu <sub>24</sub> (μ <sub>3</sub> -OH) <sub>30</sub> (H-AibO) <sub>16</sub> (ClO <sub>4</sub> )(H <sub>2</sub> O) <sub>22</sub> ](ClO <sub>4</sub> ) <sub>17</sub> (OH) <sub>2</sub> ·20H <sub>2</sub> O	3.211 (B), 2.110 (C)	[20]
Na[Co(H-Aib-O) <sub>2</sub> (bpy)](ClO <sub>4</sub> ) <sub>2</sub> ·0.5H <sub>2</sub> O (bpy = 2,2'-bipyridine)	1.101 (A)	[21]
[Co(H-Aib-O)(tpa)](ClO <sub>4</sub> ) <sub>2</sub> ·H <sub>2</sub> O (tpa = (2-pyridylmethyl)amine)	1.101 (A)	[22]
[Pt(H-Aib-OH) <sub>2</sub> Cl <sub>2</sub> ]	1.001 (F)	[18]
[Cu(H-Aib-O)(pmdt)]ClO <sub>4</sub> ·H <sub>2</sub> O (pmdt = N,N,N',N',N''-pentamethyldiethylenetriamine)	1.101 (A)	[23]
[Pt(H-Aib-O)Cl(Ph <sub>3</sub> P)]·H <sub>2</sub> O	1.101 (A)	[24]
[Cp <sub>2</sub> Ti(H <sub>2</sub> -Aib-O) <sub>2</sub> ]Cl <sub>2</sub>	1.100 (H)	[25]
[Mn(CO) <sub>3</sub> Mo(CO)(μ <sub>2</sub> -S <sub>2</sub> CPCy <sub>3</sub> )(H-Aib-O)]·CH <sub>2</sub> Cl <sub>2</sub>	2.201 (E)	[26]
[Zn <sub>3</sub> (H-Aib-O) <sub>6</sub> ]·MeCOOH·H <sub>2</sub> O	1.101 (A), 2.111 (D)	this work

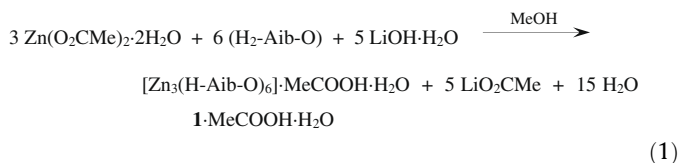
<sup>a</sup> The coordination modes of the ligands are given using Harris notation [13].

reported in Table 2. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range  $22^\circ < 2\theta < 54^\circ$ . Intensity data were recorded using a  $\theta - 2\theta$  scan. Three standard reflections, monitored every 97 reflections, showed less than 3% variation and no decay. Lorenz, polarization and  $\Psi$ -scan absorption corrections were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86 [31] and refined by full-matrix least-squares techniques on  $F^2$  with SHELXL-97 [32]. Further experimental crystallographic details for **1**·MeCOOH·H<sub>2</sub>O:  $2\theta_{\max} = 118^\circ$ ; 472 parameters refined;  $(\Delta/\sigma)_{\max} = 0.052$ ;  $(\Delta\rho)_{\max}/(\Delta\rho)_{\min} = 2.353/-0.772 \text{ e } \text{\AA}^{-3}$ ;  $R_1/wR_2$  (for all data), 0.0777/0.2052. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms, except those of water solvate which were located by difference maps and were refined isotropically. All non-hydrogen atoms were refined anisotropically. Further experimental crystallographic details for **2**·H<sub>2</sub>O:  $2\theta_{\max} = 125^\circ$ ; 279 parameters refined;  $(\Delta/\sigma)_{\max} = 0.003$ ;  $(\Delta\rho)_{\max}/(\Delta\rho)_{\min} = 0.450/-0.339 \text{ e } \text{\AA}^{-3}$ ;  $R_1/wR_2$  (for all data), 0.0307/0.0832. Hydrogen atoms were either located by difference maps and refined isotropically or were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically. Further experimental crystallographic details for **3**·5.8H<sub>2</sub>O:  $2\theta_{\max} = 109.4^\circ$ ; 453 parameters refined;  $(\Delta/\sigma)_{\max} = 0.010$ ;  $(\Delta\rho)_{\max}/(\Delta\rho)_{\min} = 0.722/-0.527 \text{ e } \text{\AA}^{-3}$ ;  $R_1/wR_2$  (for all data), 0.1127/0.2549. All hydrogen atoms were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically, except of water solvate molecules which were refined isotropically.

### 3. Results and discussion

#### 3.1. Brief synthetic comments

Complexes **1**·MeCOOH·H<sub>2</sub>O, **2**·H<sub>2</sub>O and **3**·5.8H<sub>2</sub>O were prepared according to Eqs. (1)–(3), respectively:



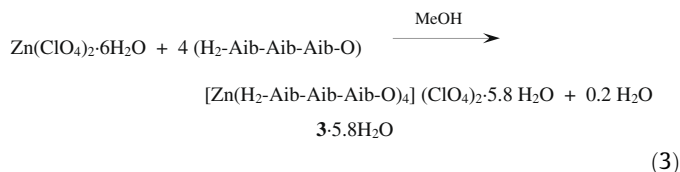
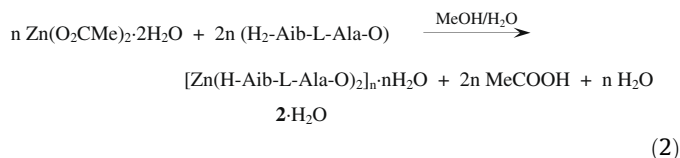
**Table 2**

Crystallographic data for complexes **1**·MeCOOH·H<sub>2</sub>O, **2**·H<sub>2</sub>O and **3**·5.8H<sub>2</sub>O.

Parameter	<b>1</b> ·MeCOOH·H <sub>2</sub> O	<b>2</b> ·H <sub>2</sub> O	<b>3</b> ·5.8H <sub>2</sub> O
Chemical formula	C <sub>26</sub> H <sub>54</sub> N <sub>6</sub> O <sub>15</sub> Zn <sub>3</sub>	C <sub>14</sub> H <sub>28</sub> N <sub>4</sub> O <sub>7</sub> Zn	C <sub>48</sub> H <sub>113.6</sub> Cl <sub>2</sub> N <sub>12</sub> O <sub>29.8</sub> Zn
Formula weight	886.86	429.77	1472.18
Crystal colour, habit	colourless, prismatic	colourless, prismatic	colourless, prismatic
Crystal dimensions (mm)	0.30 × 0.20 × 0.15	0.30 × 0.25 × 0.20	0.25 × 0.20 × 0.15
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	A <sub>1</sub> n <sub>1</sub>	P2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2
a (Å)	18.850(10)	8.2515(8)	13.406(9)
b (Å)	11.752(9)	12.1618(11)	20.140(10)
c (Å)	18.440(10)	10.0928(11)	15.386(7)
α (°)	90.00(3)	90	90
β (°)	93.21	96.161(4)	90
γ (°)	90	90	90
V (Å <sup>3</sup> )	4079(4)	1006.99(17)	4154(4)
Z	4	2	2
T (K)	298	298	298
Radiation, Cu Kα (λ, Å)	1.5418	1.5418	1.5418
ρ <sub>calc</sub> (g cm <sup>-3</sup> )	1.444	1.417	1.177
μ (mm <sup>-1</sup> )	2.632	2.063	1.651
Data collected/unique (R <sub>int</sub> )	5164/5163 (0.0492)	3535/3152 (0.0422)	4891/4531 (0.0810)
Data with I > 2σ(I)	5040	3152	3425
R <sub>1</sub> <sup>a</sup> [I > 2σ(I)]	0.0766	0.0307	0.0867
wR <sub>2</sub> <sup>b</sup> [unique data]	0.2032	0.0832	0.2262

<sup>a</sup>  $R_1 = \sum(|F_o| - |F_c|)/\sum(|F_o|)$ .

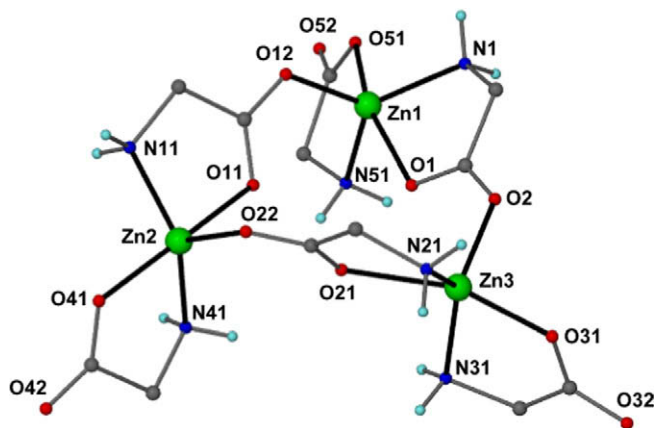
<sup>b</sup>  $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$ .



The use of metal-carboxylates is a common practice in our synthetic procedures in metal-peptide chemistry. The reasons are: (i) carboxylate anions can act as strong bases with consequent deprotonation of the ligands, (ii) the by-products (i.e. MeCO<sub>2</sub>H, PhCO<sub>2</sub>H) can be easily removed from the reaction mixture without contamination of the product, and (iii) a portion of the anions RCO<sub>2</sub><sup>-</sup> can act as ligands with a variety of coordination modes, resulting in the isolation of ternary complexes with interesting and aesthetically pleasant structures.

In fact, the trinuclear complex **1**·MeCOOH·H<sub>2</sub>O was isolated from reaction mixture Zn(O<sub>2</sub>CMe)<sub>2</sub>·2H<sub>2</sub>O/H<sub>2</sub>-Aib-O/LiOH·H<sub>2</sub>O containing a small excess of Zn(II). The stoichiometric metal/ligand molar ratio of 1:2 was avoided in order to prevent the isolation of the known complex [Zn(H-Aib-O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>][Zn(H-Aib-O)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] [17]. On the other hand, the addition of a strong base (LiOH) seems to be necessary for the deprotonation of the amino acid (for H<sub>2</sub>-Aib-O: pK<sub>1</sub> = 2.36, pK<sub>2</sub> = 10.21) and its consequent coordination.

The isolation of complex **2**·H<sub>2</sub>O was initially succeeded by using the 1:1.5 metal:ligand stoichiometry. With the identity of **2**·H<sub>2</sub>O crystallographically established (vide infra), the “correct” stoichiometric ratio, i.e. Zn(II): dipeptide = 1:2, was employed and led to the pure compound in very good yield (60–65%). The same product was also isolated by employing several metal sources (i.e. Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, ZnCl<sub>2</sub>, Zn(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O) in metal:ligand proportions 1:1 or 1:2 and in the presence of LiOH·H<sub>2</sub>O. The fact that all the above synthetic procedures had as a result the isolation of the



**Fig. 1.** The molecular structure of **1**·MeCOOH·H<sub>2</sub>O. The lattice MeCOOH and H<sub>2</sub>O molecules have not been drawn. All methyl groups of the H-Aib-O<sup>-</sup> ligands have been omitted for clarity. Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

same product demonstrates the high stability of the isolated Zn(II)/dipeptide complex **2**·H<sub>2</sub>O.

Our first attempts for the isolation of a Zn(II)/H<sub>2</sub>-Aib-Aib-Aib-O complex were made once more by employing Zn(O<sub>2</sub>CMe)<sub>2</sub>·2H<sub>2</sub>O as the metal source. Indeed, from the 1:2 (metal:ligand) reaction, a crystalline product was isolated, whose solution of the structure revealed the cationic complex [Zn(H<sub>2</sub>-Aib-Aib-Aib-O)<sub>4</sub>] (O<sub>2</sub>CMe)<sub>2</sub>. Unfortunately, the full crystallographic analysis of this complex proved impossible. With the aim to stabilize and isolate the above cationic species, where the tripeptide was in its zwitterionic form (a fact scarce in metal/peptide chemistry), the use of Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O as starting material was the next step. Complex

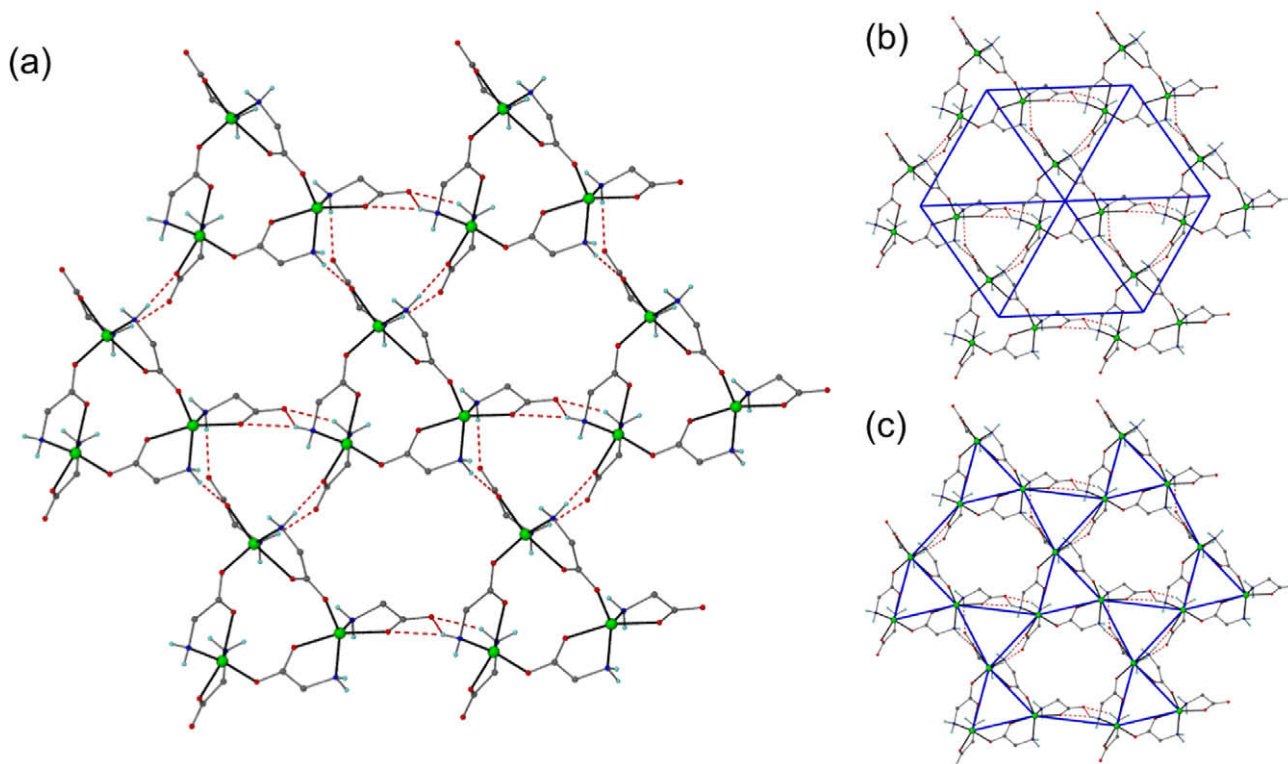
**3**·5.8H<sub>2</sub>O was then isolated employing the “wrong” (1:2) or the “correct” (1:4) metal:ligand ratio.

### 3.2. Description of structures

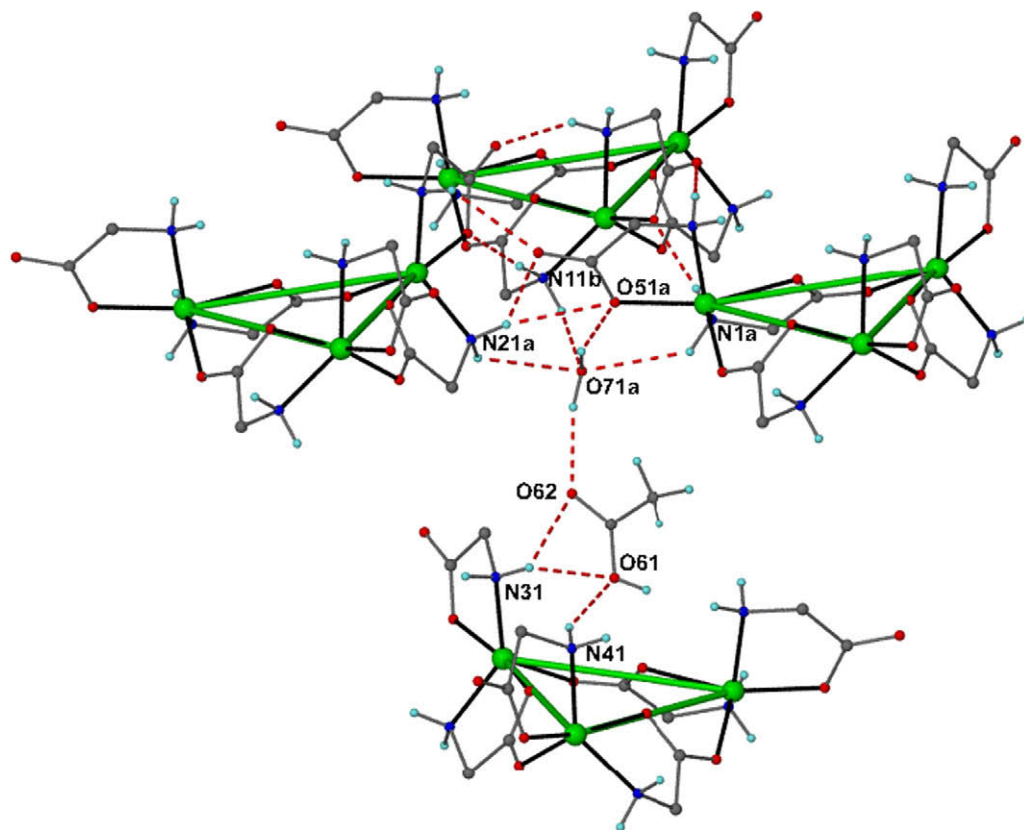
The molecular structures of complexes **1**·MeCOOH·H<sub>2</sub>O, **2**·H<sub>2</sub>O, and **3**·5.8H<sub>2</sub>O are shown in Figs. 1, 5 and 9, respectively. Aspects of the crystal structures are shown in Figs. 2–4 (**1**·MeCOOH·H<sub>2</sub>O), 6–8 (**2**·H<sub>2</sub>O), and 10 and 11 (**3**·5.8H<sub>2</sub>O). Selected interatomic distances and angles are listed in Tables 3, 5 and 6 for **1**·MeCOOH·H<sub>2</sub>O, **2**·H<sub>2</sub>O, and **3**·5.8H<sub>2</sub>O, respectively, while important hydrogen bonding interactions are presented in Tables 4 (for **1**·MeCOOH·H<sub>2</sub>O), and 7 (for **3**·5.8H<sub>2</sub>O).

Complex **1**·MeCOOH·H<sub>2</sub>O crystallizes in the monoclinic space group *An*. Its crystal structure consists of trinuclear [Zn<sub>3</sub>(H-Aib-O)<sub>6</sub>] units and of lattice MeCOOH and H<sub>2</sub>O molecules. One H-Aib-O<sup>-</sup> ligand chelates to each of the three Zn<sup>II</sup> atoms through its amino nitrogen atom and one of the carboxylate oxygen atoms, while each of the remaining three anions chelates to each Zn<sup>II</sup> atom and bridges a neighboring metal ion through the second carboxylate oxygen atom. The carboxylate bridging interaction is of the *syn, anti* type (Fig. 1).

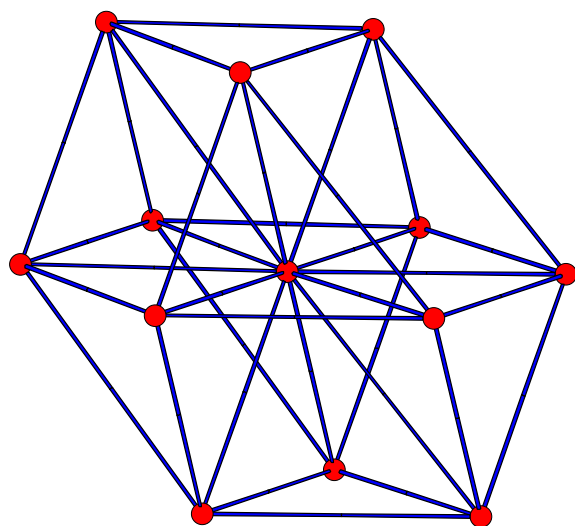
Thus, three of the six H-Aib-O<sup>-</sup> anions behave as η<sup>1</sup>:η<sup>1</sup> ligands or in a 1.101 mode [13], while the other three α-aminoisobutyrate anions behave as η<sup>1</sup>:η<sup>1</sup>:η<sup>1</sup>:μ<sub>2</sub> ligand or in a 2.111 mode (Scheme 1). Each metal center is five-coordinate with an O<sub>3</sub>N<sub>2</sub> environment. On the basis of the angular criterion τ, as defined by Addison et al. (τ = 1.00 for an ideal trigonal bipyramid and τ = 0.00 for an ideal square pyramid) [33], the coordination polyhedra around all three Zn atoms lie almost between the two geometrical shapes, with a slight inclination towards the trigonal bipyramidal (τ = 0.55, 0.56 and 0.54 for Zn(1), Zn(2) and Zn(3), respectively). The principal axes and angles for the three trigonal bipyramidal Zn<sup>II</sup> atoms are O(1)–Zn(1)–O(51) 160.3(3)°, O(11)–Zn(2)–O(41) 164.1(3)° and



**Fig. 2.** The 2D hydrogen bonded framework of **1**·MeCOOH·H<sub>2</sub>O (a) that conforms to a (3,6)-net (b) or to a (3,6.3,6)-net (c). All methyl groups of the H-Aib-O<sup>-</sup> ligands have been omitted for clarity. Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. The blue lines in (b) and (c) are guides for the eye and draw the underline nets. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** The hydrogen bonding interactions between the layers in  $[Zn_3(-H-Aib-O)_6] \cdot MeCOOH \cdot H_2O$ . All methyl groups of the H-Aib- $O^-$  ligands have been omitted for clarity. Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. The green lines are guides for the eye and draw the trinuclear units. Symmetry codes: a  $0.5 + x, 1.5 - y, z$ ; b  $0.5 + x, 1 - y, 0.5 + z$ . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

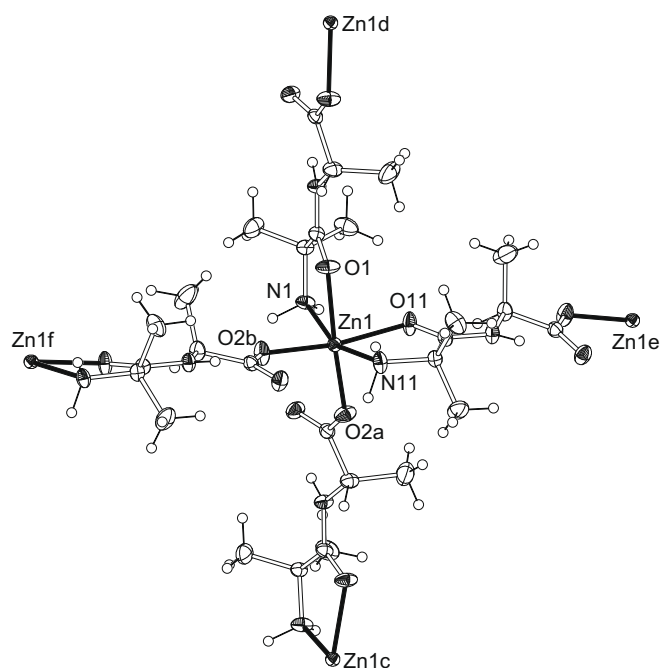


**Fig. 4.** The 3D 12-connected hydrogen bonded fcu net in  $1 \cdot MeCOOH \cdot H_2O$ . The red circles represent the center of gravity of the trinuclear units.

$O(21)-Zn(3)-O(31)$   $159.2(3)^\circ$  (Table 3). The  $Zn(1) \cdots Zn(2)$  and  $Zn(1) \cdots Zn(3)$  and  $Zn(2) \cdots Zn(3)$  separations are 5.335, 5.351, and 5.317 Å, respectively.

All twelve values of the C–O carboxylate bonds of the organic ligands lie in the range 1.219–1.292 Å (mean value 1.26 Å), which is referred as the range (1.20–1.33 Å, mean value 1.245 Å) of C–O bond lengths of  $\alpha$ -aminoacids in all metal complexes [34].

In complex  $1 \cdot MeCOOH \cdot H_2O$ , the aminoacid moiety obviously presents quite different conformation (which is defined by the  $\phi$



**Fig. 5.** ORTEP plot (30% probability) of the coordination environment around the central atom in  $2 \cdot H_2O$  and the connectivity of the 2D polymer. Symmetry codes: a  $2 - x, 0.5 + y, -z$ ; b  $1 - x, 0.5 + y, 1 - z$ ; c  $2 - x, 0.5 + y, -z$ ; d  $1 - x, -0.5 + y, 1 - z$ ; e  $2 - x, -0.5 + y, -z$ ; f  $1 - x, 0.5 + y, 1 - z$ .

$= Zn-N-C^{\alpha}-C'$  and  $\psi = N-C^{\alpha}-C'-O$  dihedral angles) from the minimum energy conformation, as calculated theoretically, which is

**Table 3**  
Selected bond distances (Å), angles (°) and dihedral angles for complex **1**·MeCOOH·H<sub>2</sub>O.

Distances			
Zn(1)–O(1)	2.1888(7)	Zn(2)–N(11)	2.004(10)
Zn(1)–O(12)	1.989(7)	Zn(2)–N(41)	1.987(9)
Zn(1)–O(51)	2.069(7)	Zn(3)–O(2)	1.980(7)
Zn(1)–N(1)	2.029(8)	Zn(3)–O(21)	2.210(6)
Zn(1)–N(51)	2.025(8)	Zn(3)–O(31)	2.033(7)
Zn(2)–O(11)	2.244(6)	Zn(3)–N(21)	1.985(8)
Zn(2)–O(22)	2.001(6)	Zn(3)–N(31)	2.009(8)
Zn(2)–O(41)	2.030(8)		
Angles			
O(1)–Zn(1)–O(12)	97.5(3)	O(41)–Zn(2)–O(22)	101.2(3)
O(1)–Zn(1)–O(51)	160.2(3)	O(41)–Zn(2)–N(11)	102.2(4)
O(1)–Zn(1)–N(1)	77.6(3)	O(41)–Zn(2)–N(41)	80.0(4)
O(1)–Zn(1)–N(51)	90.0(3)	N(11)–Zn(2)–O(22)	109.6(3)
O(51)–Zn(1)–O(12)	102.3(3)	N(11)–Zn(2)–N(41)	130.3(4)
O(51)–Zn(1)–N(1)	93.9(3)	O(2)–Zn(3)–O(21)	100.4(3)
O(51)–Zn(1)–N(51)	81.1(3)	O(2)–Zn(3)–O(31)	100.4(3)
N(1)–Zn(1)–O(12)	116.6(3)	O(2)–Zn(3)–N(21)	111.5(3)
N(1)–Zn(1)–N(51)	127.5(3)	O(2)–Zn(3)–N(31)	121.4(4)
N(51)–Zn(1)–O(12)	115.5(3)	O(21)–Zn(3)–O(31)	159.2(3)
O(11)–Zn(2)–O(22)	94.0(3)	O(21)–Zn(3)–N(21)	76.3(3)
O(11)–Zn(2)–O(41)	164.1(3)	O(210)–Zn(3)–N(31)	88.0(3)
O(11)–Zn(2)–N(11)	76.6(3)	O(31)–Zn(3)–N(21)	96.4(4)
O(11)–Zn(2)–N(41)	88.6(3)	O(31)–Zn(3)–N(31)	80.8(3)
O(22)–Zn(2)–N(41)	118.8(4)	N(21)–Zn(3)–N(31)	126.7(3)
Dihedral angles (°) for the aminoacid moieties			
Zn(1)–N(1)–C(2)–C(1)	( $\phi_1$ ) 26.86	Zn(3)–N(31)–C(32)–C(31)	( $\phi_4$ ) 31.17
N(1)–C(2)–C(1)–O(1)	( $\psi_1$ ) –14.54	N(31)–C(32)–C(31)–O(31)	( $\psi_4$ ) –21.44
Zn(2)–N(11)–C(12)–C(11)	( $\phi_2$ ) 29.26	Zn(2)–N(41)–C(42)–C(41)	( $\phi_5$ ) 28.88
N(11)–C(12)–C(1)–O(11)	( $\psi_2$ ) –11.37	N(41)–C(42)–C(41)–O(41)	( $\psi_5$ ) –24.31
Zn(3)–N(21)–C(22)–C(21)	( $\phi_3$ ) 26.58	Zn(1)–N(51)–C(52)–C(51)	( $\phi_6$ ) 33.77
N(21)–C(22)–C(21)–O(21)	( $\psi_3$ ) –15.82	N(51)–C(52)–C(51)–O(51)	( $\psi_6$ ) –27.36

**Table 4**  
Dimensions of the unique hydrogen bonds (distances in Å and angles in °) for **1**·MeCOOH·H<sub>2</sub>O.

D <sup>a</sup> –H...A <sup>b</sup>	H...A <sup>b</sup>	D <sup>a</sup> ...A <sup>b</sup>	∠D <sup>a</sup> H A <sup>b</sup>
N1–H1A...O41 [x, 1/2 + y, 1/2 + z]	2.00	2.896(12)	172
N11–H11A...O31 [x, 1/2 + y, –1/2 + z]	2.04	2.938(12)	178
N21–H21A...O51 [x, –1 + y, z]	2.52	3.397(10)	165
N21–H21A...O52 [x, –1 + y, z]	2.14	2.874(11)	138
N31–H31A...O52 [x, –1 + y, z]	2.43	3.106(12)	132
N41–H41A...O32 [x, 1/2 + y, –1/2 + z]	2.01	2.832(16)	150
N51–H51A...O42 [x, 1/2 + y, 1/2 + z]	2.12	2.951(15)	154
N1–H1B...O71	2.51	3.205(13)	134
N11–H11B...O71 [x, –1/2 + y, –1/2 + z]	2.34	3.131(12)	146
N21–H21B...O71 [x, –1 + y, z]	2.55	3.127(12)	122
N31–H31B...O61	2.53	3.381(11)	158
N31–H31B...O62	2.35	3.106(12)	142
N41–H41B...O61	2.19	2.992(12)	148
O71–H71B...O62 [–1/2 + x, 3/2 – y, z]	1.97	2.805(13)	165
O71–H71A...O51	2.11	2.922(12)	157

<sup>a</sup> D, donor atom.<sup>b</sup> A, acceptor atom.

also that commonly observed for  $\alpha$ -aminoisobutyric acid residues in peptide crystal structures [12,18]. This conformation, characterized by  $\phi$  and  $\psi$  values of about  $-60^\circ$ ,  $-30^\circ$  (or the centrosymmetric  $60^\circ$ ,  $30^\circ$ ) falls in the helical region of the  $\phi$ – $\psi$  map [35]. In the parent complex, in which the aminoacid anion coordinates in a chelate mode, the observed conformation is folded with values for the  $\phi$  and  $\psi$  dihedral angles in the region of  $26.58^\circ$  to  $33.77^\circ$  and  $-11.37^\circ$  to  $-27.36^\circ$ , respectively.

The trinuclear units assemble through seven hydrogen bonds (and their symmetry related) that involve the  $-NH_2$  groups and some of both the coordinated and uncoordinated carboxylate O atoms (Table 4) to form a 2D hydrogen bonded framework

(Fig. 2) that conforms to a regular net of a (3,6) topology running parallel to the *bc* plane (Fig. 2a). Due to the size and the shape of the trinuclear complexes which serve as 6-connected nodes within the 2D (3,6) framework, half of the triangular cavities around a trinuclear node are bigger than the others and look like hexagons. The hexagonal cavities could also be envisaged by considering each metal as a 4-connected node. In this perspective, the resulting network is a semi-regular net with (3.6.3.6) topology (kagome net) (Fig. 2c) [36].

The lattice acetic acid and water molecules sit within the layers and connect them to create a 3D hydrogen bonded framework with a  $3^{24}.4^{36}.5^6$  topology (**fcu**) [37,38]. The acetic acid molecule sits above the trinuclear unit and is hydrogen bonded to it through three hydrogen bonds [N31–H31B...O61, N31–H31B...O62 and O71–H71B...O62] (Fig. 3). The water molecule sits above a small trigonal cavity and is hydrogen bonded to the three trinuclear units [N1–H1B...O71, N11–H11B...O71, N21–H21B...O71 and O71–H71A...O51] that form the trigonal cavity, while it is also hydrogen bonded to the acetic acid molecule [O71–H71B...O62] (Fig. 3). In this arrangement each trinuclear unit is connected via the MeCOOH and the H<sub>2</sub>O molecules to six trinuclear units belonging to two neighboring layers above and below the main layer's plane. In this arrangement each trinuclear unit connects to six other trinuclear units that belong to the same (3,6)-layer and to six trinuclear units that belong to neighboring layers, giving rise to a 12-connected 3D network with **fcu** topology (Fig. 4).

Complex **1**·MeCOOH·H<sub>2</sub>O is the ninth member of crystallographically established binary H-Aib-OH/metal ion complexes (Table 1), and three of its ligands adopt the new coordination mode [2.111], as is seen in Scheme 1.

Concerning the structurally characterized Zn(II)/ $\alpha$ -aminoacid binary complexes we have to mention the following: (a) The crystal structures of binary complexes of Zn(II) with almost all the natural

**Table 5**  
Selected bond distances (Å) and angles (°) for complex **2**·H<sub>2</sub>O<sup>a</sup>.

<i>Distances</i>			
Zn(1)–O(1)	2.258(2)	Zn(1d)–O(2)	2.083(2)
Zn(1)–N(1)	2.086(3)	Zn(1e)–O(12)	2.026(2)
Zn(1)–O(11)	2.181(2)	C(4)–O(1)	1.252(3)
Zn(1)–N(11)	2.116(3)	C(4)–N(2)	1.320(4)
Zn(1)–O(2a)	2.026(2)	C(7)–O(2)	1.249(3)
Zn(1)–O(2b)	2.083(2)	C(7)–O(3)	1.244(3)
<i>Angles</i>			
O(2a)–Zn(1)–O(2b)	98.21(11)	O(2a)–Zn(1)–O(1)	176.43(10)
O(2a)–Zn(1)–N(1)	106.74(9)	O(2b)–Zn(1)–O(1)	84.44(9)
O(2b)–Zn(1)–N(1)	87.50(10)	N(1)–Zn(1)–O(1)	75.69(9)
O(2a)–Zn(1)–N(11)	89.20(10)	N(11)–Zn(1)–O(1)	87.81(10)
O(2b)–Zn(1)–N(11)	104.58(9)	O(11)–Zn(1)–O(1)	87.29(10)
N(1)–Zn(1)–N(11)	158.62(12)	N(1)–C(1)–C(4)	108.3(2)
O(2a)–Zn(1)–O(11)	90.12(10)	N(2)–C(5)–C(7)	111.1(2)
O(2b)–Zn(1)–O(11)	171.61(11)	C(1)–C(4)–N(2)	117.9(2)
N(1)–Zn(1)–O(11)	89.13(10)	C(1)–C(4)–O(1)	120.7(2)
N(11)–Zn(1)–O(11)	76.41(9)	C(1)–C(4)–N(2)	121.3(2)
<i>Hydrogen bonds</i>			
D <sup>b</sup> –H···A <sup>c</sup>	H···A <sup>c</sup>	D <sup>b</sup> ···A <sup>c</sup>	<D <sup>b</sup> HA <sup>c</sup>
Ow1–Hw1A···O3 [2–x, 1/2+y, 1–z]	2.19(6)	3.011(4)	135(4)
Ow1–Hw1A···O13 [2–x, 1/2+y, –z]	2.17(6)	3.004(4)	136(4)
Ow1–Hw1B···O1 [1+x, y, z]	2.11(6)	2.949(3)	169(6)
N1–Hn1A···Ow1	2.27(6)	3.083(4)	168(4)
N2–Hn2···O13 [x, y, 1+z]	2.21(3)	3.076(3)	174(3)
N12–Hn12···O3 [x, y, –1+z]	2.02(3)	2.875(3)	164(3)
N12–Hn12···O13	2.32(3)	2.711(3)	107(3)

<sup>a</sup> Symmetry transformations used to generate equivalent atoms: a = 2 – x, 0.5 + y, –z; b = 1 – x, 0.5 + y, 1 – z; d = 1 – x, –0.5 + y, 1 – z; e = 2 – x, 0.5 + y, z.

<sup>b</sup> D, donor atom.

<sup>c</sup> A, acceptor atom.

$\alpha$ -aminoacids have been reported. (b) The majority of these compounds are monomeric or coordination polymers with only few exceptions, where the Zn(II)/aminoacid coordination results in a cluster formation. These are: [Zn(Iva)<sub>2</sub>]<sub>2</sub>·2H<sub>2</sub>O (Iva = isovaline), which is described as a 1D coordination polymer or as a cyclic trimer [39], [Zn(Iva)<sub>2</sub>]<sub>2</sub>·3.25H<sub>2</sub>O in which six [Zn(Iva)<sub>2</sub>] moieties form the discrete cyclic complex [Zn<sub>6</sub>(Iva)<sub>12</sub>] [39], and the organometallic tetranuclear cluster [EtZn( $\alpha,\alpha$ -Ph<sub>2</sub>Gly)]<sub>4</sub>·CH<sub>3</sub>CN ( $\alpha,\alpha$ -Ph<sub>2</sub>Gly =  $\alpha,\alpha$ -diphenylglycine) [40]. At this point, a remarkable feature has to be noted: All three aminoacids, i.e. H-Aib-OH, H-Iva-OH

and H-Ph<sub>2</sub>Gly-OH, are closely related to each other. So, -Iva- is formally derived from -Aib- by replacing a methyl group by an ethyl group, and -Ph<sub>2</sub>Gly- by replacing the two methyl groups by two phenyl groups. The dialkylation of the  $\alpha$ -carbon, which sterically restricts the conformational freedom of the aminoacid and causes a bent around C<sup>a</sup> atom, seems to favor cluster formation.

Complex **2**·H<sub>2</sub>O crystallizes in the monoclinic space group P2<sub>1</sub>. The Zn<sup>II</sup> atom and the anionic peptide H-Aib-L-Ala-O<sup>-</sup> ligands have assembled to create a two-dimensional (2D) square grid framework laying parallel to the 1 0 1 plane (Figs. 5 and 6). The Zn<sup>II</sup>

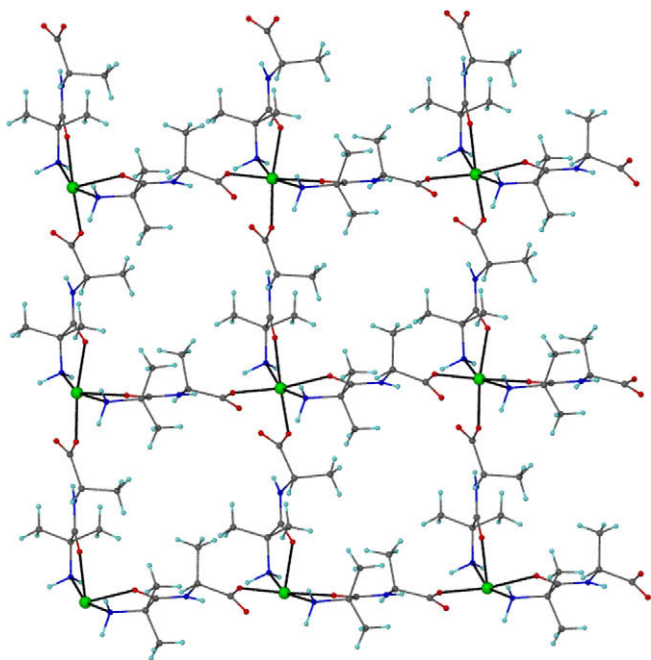
**Table 6**  
Selected bond distances (Å) and angles (°) for complex **3**·5.8H<sub>2</sub>O<sup>a</sup>.

<i>Distances</i>			
Zn–O(1)	1.968(6)	C(9)–O(4)	1.2369(13)
Zn–O(1a)	1.968(6)	C(9)–N(2)	1.307(15)
Zn–O(11)	1.974(6)	C(5)–O(3)	1.222(13)
Zn–O(11a)	1.974(6)	C(5)–N(1)	1.315(13)
C(1)–O(1)	1.284(12)	C(29)–O(14)	1.195(11)
C(1)–O(2)	1.236(11)	C(29)–N(12)	1.344(13)
C(21)–O(11)	1.262(12)	C(25)–O(13)	1.226(12)
C(21)–O(12)	1.231(12)	C(220)–N(11)	1.453(12)
<i>Angles</i>			
O(1)–Zn–O(1a)	108.2(4)	N(3)–C(10)–C(9)	105.5(9)
O(1)–Zn–O(11a)	119.7(3)	N(2)–C(6)–C(5)	110.6(9)
O(1)–Zn–O(11)	101.5(3)	N(1)–C(2)–C(1)	106.6(8)
O(1a)–Zn–O(11a)	101.5(3)	N(13)–C(30)–C(29)	104.8(7)
O(1a)–Zn–O(11)	119.7(3)	N(12)–C(26)–C(25)	112.3(9)
O(11a)–Zn–O(11)	107.3(4)	N(11)–C(22)–C(21)	107.9(8)
<i>Dihedral angles of the peptide ligand</i>			
N(3)–C(10)–C(9)–N(2)	( $\psi_1$ ) = –172.76	N(13)–C(30)–C(29)–N(12)	( $\psi_1$ ) = –174.51
C(9)–N(2)–C(6)–C(5)	( $\phi_2$ ) = –56.89	C(29)–N(12)–C(26)–C(25)	( $\phi_2$ ) = –62.64
N(2)–C(6)–C(5)–N(1)	( $\psi_2$ ) = –32.82	N(12)–C(26)–C(25)–N(11)	( $\psi_2$ ) = –22.67
C(5)–N(1)–C(2)–C(1)	( $\phi_3$ ) = –172.02	C(25)–N(11)–C(22)–C(21)	( $\phi_3$ ) = –175.20
N(1)–C(2)–C(1)–O(1)	( $\psi_3$ ) = 6.83	N(11)–C(22)–C(21)–O(11)	( $\psi_3$ ) = –3.53
N(1)–C(2)–C(1)–O(2)	( $\psi'_3$ ) = –179.13	N(11)–C(22)–C(21)–O(12)	( $\psi'_3$ ) = 174.57

<sup>a</sup> Symmetry transformations used to generate equivalent atoms: a = –x, –y, z.



atom is in a distorted octahedral  $N_2O_4$  environment. Two dipeptide monoanions bind one  $Zn^{II}$  atom *via* their amino nitrogens [N(1), N(11)] and peptide oxygens [O(1), O(11)], with the oxygen atoms in a *cis* orientation and the nitrogen atoms in a *trans* orientation, and two adjacent  $Zn^{II}$  atoms each through one of their carboxylate oxygens, adopting the  $\eta^1:\eta^1:\eta^1:\mu_2$  or 2.11010 [13] coordination mode. Two monodentate carboxylate oxygen atoms from the C-terminal group of two other H-Aib-L-Ala- $O^-$  ligands in *cis* orientation complete the octahedral environment around the  $Zn^{II}$  atom.



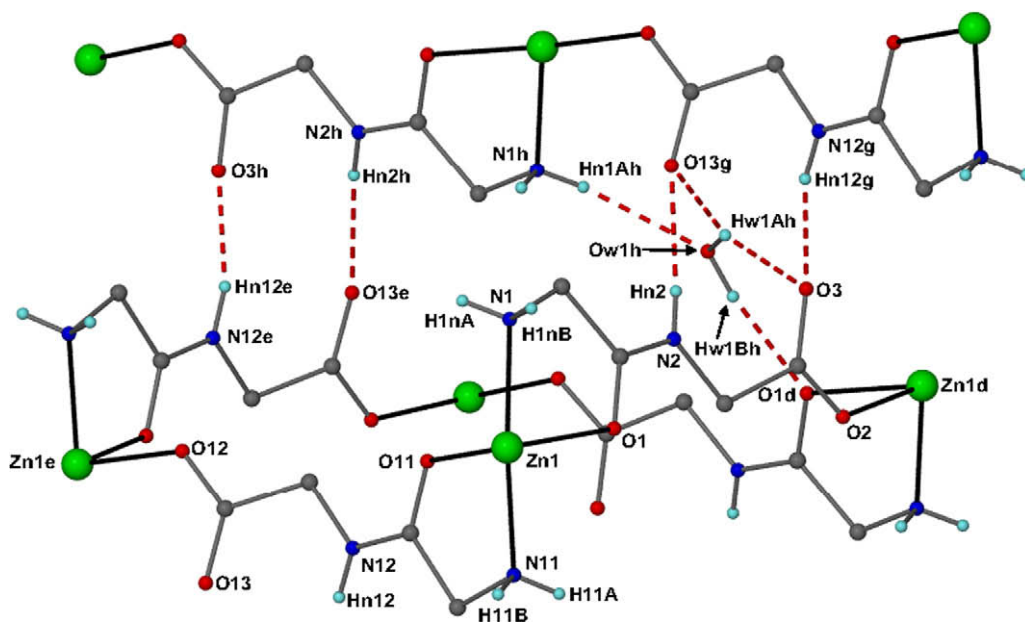
**Fig. 6.** Perspective view of the 2D layer in  $2\text{-H}_2\text{O}$ . Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The 2D layers are parallel and stacked off set in such a way that the  $Zn^{II}$  atoms of one layer are placed above the square cavities of the next layer. The layers are connected in the third dimension through two complementary hydrogen bonds (and their symmetry related) that involve the amidic N-H group and the uncoordinated carboxylate O atom [N2–Hn2 $\cdots$ O13 and N12–Hn12 $\cdots$ O3] (Fig. 7). In this arrangement, each  $Zn^{II}$  atom serves as a 4-connected node, by being the vertex of the square grid [(4,4)-net], while each dipeptide ligand might be regarded as a 3-connected node by bridging two  $Zn^{II}$  atoms within the same layer and connecting an H-Aib-L-Ala- $O^-$  ligand of a neighbouring net through the two complementary hydrogen bonds. The resulting framework conforms to a **tfa** net (Fig. 8) [38,41]. The solvate  $\text{H}_2\text{O}$  molecules complement this hydrogen bonding pattern by forming a bifurcated hydrogen bond with the two carboxylate O atoms [Ow1–Hw1A $\cdots$ O3 and Ow1–Hw1A $\cdots$ O13] that form the double hydrogen bond bridge between the layers, connecting a neighbouring coordinated carbonyl O atom [Ow1–Hw1B $\cdots$ O1], while accepting a hydrogen bond from a N-H group of the N terminal side [N1–Hn1A $\cdots$ Ow1] (Fig. 7).

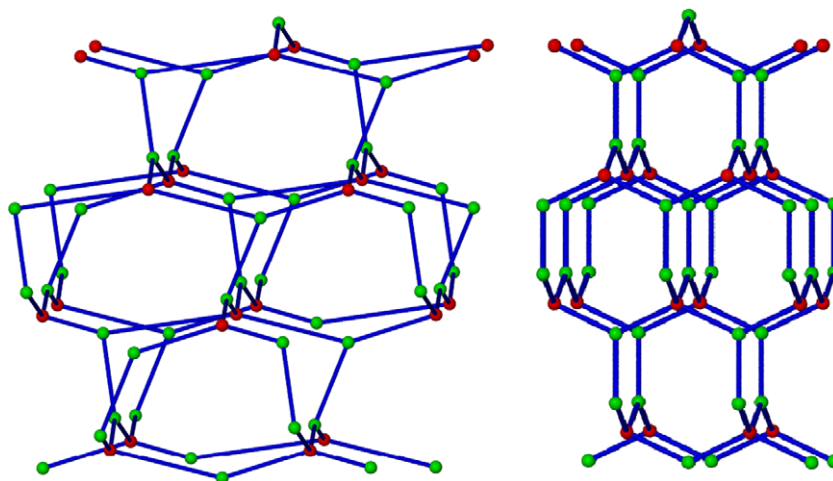
Complex  $2\text{-H}_2\text{O}$  is the fourth member of a small family of structurally characterized *binary*  $Zn^{II}$ /free dipeptide complexes (see Section 1 [11a–c], in all of which the dipeptide anions adopt the same  $N_{\text{amine}}, O_{\text{peptide}}, O_{\text{carboxylate}}$  coordination mode.

Complex  $3\text{-}5.8\text{-H}_2\text{O}$  crystallizes in the orthorhombic space group  $P2_12_12_1$ . Its molecular structure consists of mononuclear complex cations  $[Zn(\text{H}_2\text{Aib-Aib-O})_4]^{2+}$ ,  $\text{ClO}_4^-$  anions and lattice water molecules. The  $Zn^{II}$  atom lies in a distorted tetrahedral environment surrounded by four (two crystallographically independent) tripeptide ligands. Each tripeptide is in its zwitterionic form and coordinated to the metal ion through one of its carboxylate oxygen atoms, while the protonated  $\text{NH}_3^+$  group forms an intramolecular hydrogen bond [N3–Hn3A $\cdots$ O12 and N13–Hn13A $\cdots$ O2] with the uncoordinated carboxylate oxygen atom of a neighbouring ligand (Fig. 9).

This “head-to tail” sequence, in which the terminal amine and carboxylate groups are brought in proximity, is also observed in the crystal structure of the free tripeptide ( $\text{H}_2\text{-Aib-Aib-Aib-O}$ )- $2\text{H}_2\text{O}$  [42]. A comparison of the values of important parameters



**Fig. 7.** The hydrogen bonding between the square grid layers and the solvate  $\text{H}_2\text{O}$  molecule in  $2\text{-H}_2\text{O}$ . Color code as in Fig. 6. Many H and C atoms have been omitted for clarity. Symmetry codes same as in Fig. 5 and h  $2-x$ ,  $-0.5+y$ ,  $1-z$ ; g  $x, y, 1+z$ . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 8.** The real (left) and ideal (right) **tfa** network that  $2\text{-H}_2\text{O}$  adopts (see text for details). Color code: Zn = red, H-Aib-Ala- $\text{O}^-$  = green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the coordinated and free peptide skeleton can give us a measure of the difference in conformation upon complexation of the ligand. The values of N-C $\alpha$ -C $\beta$  angles are not significantly affected by metal ion coordination, the major difference being the value of the second -Aib- residue [N(2)-C(6)-C(5) = 110.6 $^\circ$ /N(12)-C(26)-C(25) = 112.3 $^\circ$ ], which is larger in the complex than the corresponding value of free peptide (107.1 $^\circ$ ). Also, small to negligible deviations of the values of C-O and C-N peptide bonds are observed for the free and coordinated tripeptide. The two carboxylate C-O bonds in the free peptide (both of which are involved in hydrogen bonds) (C-O1 = 1.248(3) Å, C-O2 = 1.256(3) Å), are elongated (C(1)-O(1) = 1.284(12) Å, C(21)-O(11) = 1.262(12) Å) and shortened (C(1)-O(2) = 1.236(11) Å, C(21)-O(12) = 1.231(12) Å) after com-

plexation. The planarity of the peptide bonds is retained in the free and complexed tripeptide, as it results from the sum of the angles around the peptide carbon atom (359.5–360.0 $^\circ$ ). A better description of the peptide backbone conformation is possible by comparing the values of the dihedral angles, ( $\phi$ ,  $\psi$ ) for each residue in the structures of the free and complexed tripeptide. For the first and the third residues these values do not differ essentially for the two forms ( $\psi_1 = 180^\circ$ ,  $\phi_3 = 178.4^\circ$ ,  $\psi_3 = 4.6^\circ$  for the free peptide [42],  $\psi_1 = -172.76^\circ$  and  $-174.51^\circ$ ,  $\phi_3 = -172.02^\circ$  and  $-175.20^\circ$ ,  $\psi_3 = 6.83^\circ$  and  $-3.53^\circ$  for the complex) and these residues are in an extended conformation. A significant difference appears in the values of the second residue ( $\phi_2 = 52.9^\circ$ ,  $\psi_2 = -141.5^\circ$  for the free ligand,  $\phi_2 = -56.89^\circ$  and  $-62.64^\circ$ ,  $\psi_2 = -32.82^\circ$  and  $-22.67^\circ$  for the complexed peptide). The above values indicate a more folded conformation which lies in the limits of the helical region ( $\phi = \pm 60$ ,  $\psi = \pm 30$ ) of the  $\phi$ - $\psi$  map [35].

Each tripeptide ligand is connected to two other tripeptide ligands belonging to two neighboring  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4]^{2+}$  complexes through two hydrogen bonds [N3-Hn3B $\cdots$ O3b and N13-Hn13B $\cdots$ O13c; b  $-0.5 + x$ ,  $0.5 - y$ ,  $1 - z$ ; c  $0.5 + x$ ,  $0.5 - y$ ,  $-z$ ] that involve the protonated  $-\text{NH}_3^+$  group and one of the carbonyl O atoms (Table 7). In this arrangement each  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4]^{2+}$  cation is connected to eight neighbouring complexes forming a 3D hydrogen-bonded framework (Fig. 10) that adopts the **bcu** network [38] (Fig. 11) with the Zn<sup>II</sup> atoms being the nodes of the 8-connected net.

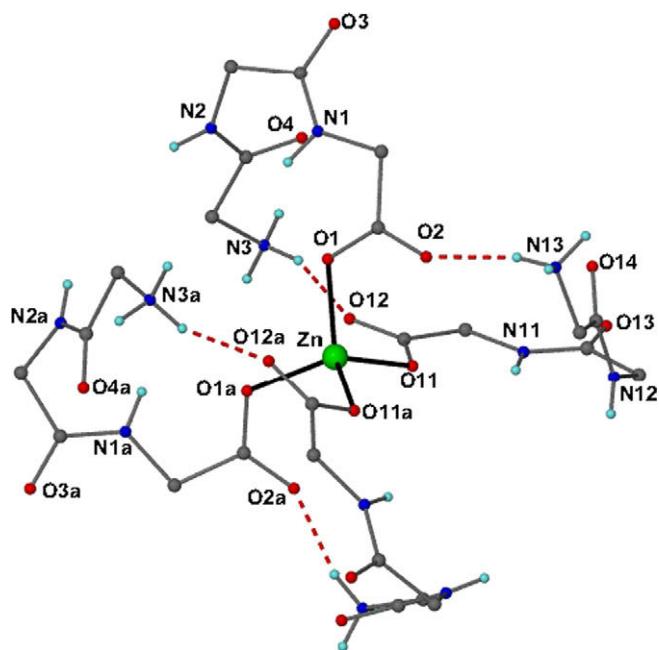
**Table 7**

Dimensions of the unique hydrogen bonds (distances in Å and angles in  $^\circ$ ) for  $3.5.8\text{H}_2\text{O}$ .

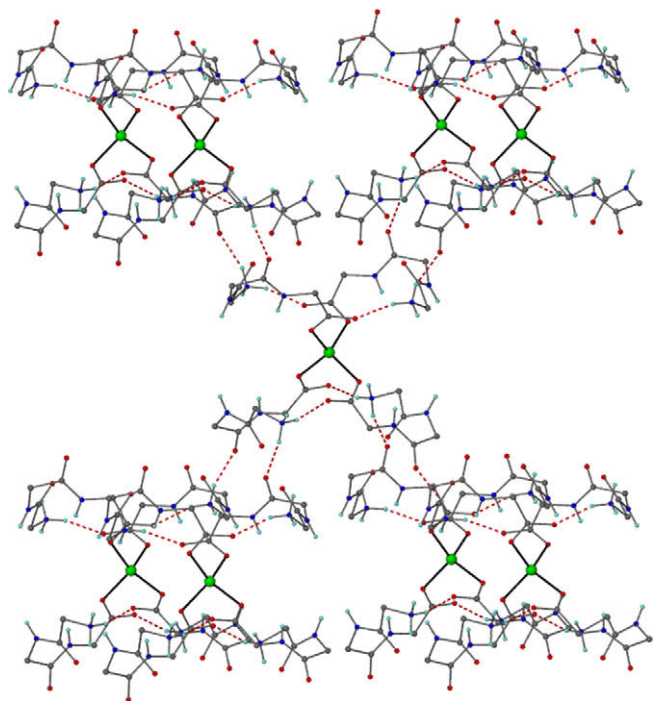
D <sup>a</sup> -H $\cdots$ A <sup>b</sup>	H $\cdots$ A <sup>b</sup>	D <sup>a</sup> $\cdots$ A <sup>b</sup>	$\angle$ D <sup>a</sup> HA <sup>b</sup>
N3-Hn3A $\cdots$ O12	1.93	2.784(12)	160
N13-Hn13A $\cdots$ O2	1.90	2.769(11)	164
N3-Hn3B $\cdots$ O3 [-0.5 + x, 0.5 - y, 1 - z]	1.94	2.788(13)	158
N13-Hn13B $\cdots$ O13 [0.5 + x, 0.5 - y, -z]	1.99	2.832(11)	157
N2-Hn2 $\cdots$ O21	2.27	3.127(11)	171
N3-Hn3C $\cdots$ Ow1 [-1 + x, y, z]	1.85	2.73(2)	172
N12-Hn12 $\cdots$ O24 [x, y, -1 + z]	2.21	2.98(2)	150
N12-Hn12 $\cdots$ O22 [-x, -y, -1 + z]	2.19	2.95(2)	146
N13-H13B $\cdots$ O13 [1/2 + x, 1/2 - y, -z]	1.99	2.832(11)	157
N13-H13C $\cdots$ O31 [1 - x, -y, z]	2.09	2.97(3)	169

<sup>a</sup> D, donor atom.

<sup>b</sup> A, acceptor atom.



**Fig. 9.** The coordination environment around the central atom in  $3.5.8\text{H}_2\text{O}$  and the intramolecular hydrogen bonding. All methyl groups of the side chains of the tripeptide ligands and the  $\text{H}_2\text{O}$  solvate molecules have been omitted for clarity. Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. Symmetry code: a  $-x$ ,  $-y$ ,  $z$ . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 10.** The hydrogen bonding between the  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4]^{2+}$  cations in  $\mathbf{3}\cdot\mathbf{5.8H}_2\text{O}$ . All methyl groups of the side chains of the tripeptide ligands have been omitted for clarity. Color code: Zn = green, O = red, N = blue, C = grey, H = cyan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Alternatively, if we regard each tripeptide ligand as a 3-connected node due to its hydrogen bonding to two other tripeptide ligands and the coordination to the  $\text{Zn}^{\text{II}}$  atom, which can now be regarded as a 4-connected node, the resulting network is a 3,4-connected net with a Schläfli symbol  $(8^3)_4\cdot 8^6$  (topological type: **sqc185**) [43] (Fig. 11).

The above topological analysis is rather oversimplified, giving the connectivity of the  $[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4]^{2+}$  cation in the lat-

**Table 8**

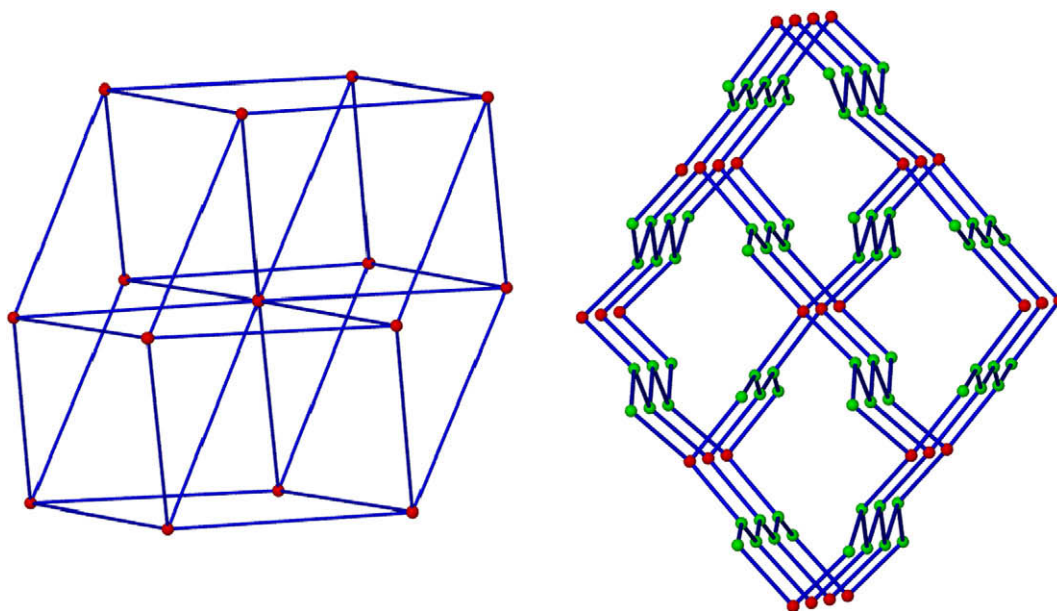
The crystallographically established coordination modes of tripeptides in the binary  $\text{M}^{n+}$ /free-tripeptide complexes, in their zwitterionic, mono-, di- and trianionic forms.

Compound	Coordination mode <sup>a</sup>	Ref.
$[\text{Fe}_3(\mu_3\text{-O})(\text{H}_2\text{-Gly-Gly-Gly-O})_6(\text{H}_2\text{O}_3)(\text{ClO}_4)_7\text{-HClO}_4\cdot\text{H}_2\text{O}]_n$	2.1100000 ( <b>A</b> )	[44]
$\{[\text{Mo}_4\text{O}_{12}(\text{H}_2\text{-Gly-Gly-Gly-O})_2]\cdot 9\text{H}_2\text{O}\}_n$	2.1100000 ( <b>A</b> )	[45]
$[\text{Zn}(\text{H}_2\text{-Aib-Aib-Aib-O})_4](\text{ClO}_4)_2\cdot 5.8\text{H}_2\text{O}$	1.1000000 ( <b>B</b> )	This work
$[\text{Cd}(\text{H-Gly-Gly-Gly-O})_2\cdot\text{H}_2\text{O}]_n$	3.1100100 ( <b>C</b> )	[46]
$\{[\text{Zn}(\text{H-Gly-Gly-Gly-O})(\text{H}_2\text{O})](\text{SO}_4)_{0.5}\cdot 2\text{H}_2\text{O}\}_n$	2.1010100 ( <b>D</b> )	[11e]
$[\text{Cd}(\text{H-Ala-Ala-Ala-O})_2]_n$	2.1010100 ( <b>D</b> )	[46]
$\{[\text{Eu}(\text{H-Gly-Gly-Gly-O})_3(\text{H}_2\text{O})_4](\text{ClO}_4)_3\cdot\text{H}_2\text{O}\}_n$	3.1111000 ( <b>E</b> )	[47]
$[\text{Cu}(\text{H-Gly-Leu-Tyr-O})_2]\cdot 8\text{H}_2\text{O}\cdot\text{Et}_2\text{O}$	2.1010101 ( <b>F</b> )	[48]
$[\text{Cu}(\text{H-Aib-H}_1\text{-Aib-Aib-O})_2\cdot 0.5(\text{H}_2\text{O})]\cdot\text{CH}_3\text{CN}\cdot 7\text{H}_2\text{O}$	2.1100110 ( <b>G</b> )	[28b]
$\text{Na}_2[\text{Cu}_2(\text{H-Gly-H}_1\text{Gly-H}_1\text{Gly-O})_2]\cdot 2\text{H}_2\text{O}$	2.1000111 ( <b>H</b> )	[49]
$\text{Na}[\text{Cu}^{\text{III}}(\text{H-Aib-H}_1\text{Aib-H}_1\text{Aib-O})](\text{ClO}_4)\cdot 2\text{H}_2\text{O}$	1.1000111 ( <b>I</b> )	[28a]

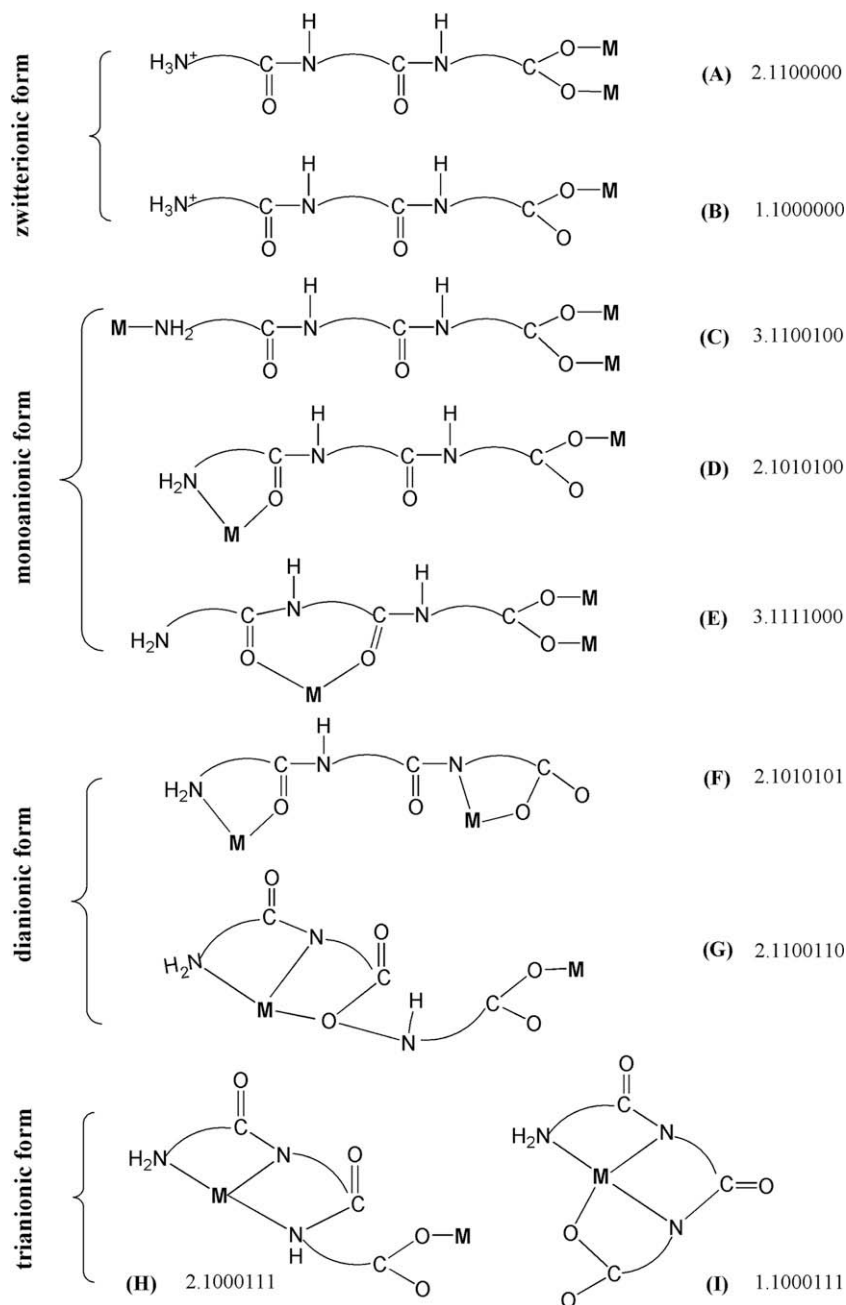
<sup>a</sup> The coordination modes of the ligands are given using Harris notation [13].

tice through the intermolecular hydrogen bonds that form between the coordinated tripeptide ligands, but ignoring the  $\text{ClO}_4^-$  and the lattice water molecules. The presence of the  $\text{ClO}_4^-$  (one of which is disordered) ions and the lattice water molecules (also disordered) which participate in the formation of several hydrogen bonds with the tripeptide ligands and with each other, complicate the resulting three-dimensional framework making the topological analysis difficult, if not impossible.

The monodentate carboxylate coordination of the zwitterionic form of the peptide ligand, as it is observed in complex  $\mathbf{3}\cdot\mathbf{5.8H}_2\text{O}$ , is very scarce in the metal/peptide coordination chemistry. In fact, there are 16 crystal structures of binary  $\text{M}^{n+}$ /free tripeptide complexes deposited at CCDC (May 2009). We note a very interesting feature: In the 10 structures (after the exclusion of the tripeptides with coordinated side chains), the tripeptide ligands adopt *eight* different coordination modes (Table 8, Scheme 3); the coordination mode of the tripeptide ligand in  $\mathbf{3}\cdot\mathbf{5.8H}_2\text{O}$  is novel. In the remarkable complexes  $[\text{Fe}_3(\mu_3\text{-O})(\text{H}_2\text{-Gly-Gly-Gly-O})_6(\text{H}_2\text{O})_3]^{7+}$  [44] and  $\{[\text{Mo}_4\text{O}_{12}(\text{H}_2\text{-Gly-Gly-O})_2]\cdot 9\text{H}_2\text{O}\}_n$  [45], the tripeptide is in its zwitterionic form and bridges two metal ions through the bidentate bridging carboxylate group.



**Fig. 11.** The 8-connected **bcu** net (left) and the 3,4-connected **sqc185** net (right) in the crystal structure of  $\mathbf{3}\cdot\mathbf{5.8H}_2\text{O}$ .



**Scheme 3.** The coordination modes of tripeptides in the *binary*  $M^{n+}/\text{free-tripeptide}$  complexes (without coordination of their side chains), in their zwitterionic, mono-, di- and trianionic forms. The coordination modes are given using Harris notation [13].

#### 4. Concluding comments and perspectives

The present work extends the body of results that emphasize the ability of  $\alpha$ -aminoisobutyric acid and  $\alpha$ -aminoisobutyric acid-based peptides to form new structural types in 3d-metal chemistry. The use of H-Aib-OH, H-Aib-*L*-Ala-OH and H-Aib-Aib-Aib-OH in reactions with  $Zn^{II}$  sources has provided access to complexes **1**, **2** and **3**, respectively. Complex **1** is the second, structurally characterized  $Zn^{II}$  complex containing any form of H-Aib-OH and proves the ability of the monoanionic ligand to give non-hydroxo/oxo triangular clusters; the 2.111 ligand mode is observed for the first time in the coordination chemistry of this amino acid. Complex **2** is the first structurally characterized  $Zn^{II}$  complex of any form of H-Aib-*L*-Ala-OH and constitutes a welcome new addi-

tion to the family of complexes that adopt the **tfa** network. Compound **3** is a novel example of a complex containing a monodentate tripeptide ligand; of structural interest is also the **bcu** network observed as a result of hydrogen bonding.

Clearly,  $Zn^{II}/\alpha$ -aminoisobutyric acid-based peptide chemistry warrants further expansion to other di- and tripeptides. With complexes **2** and **3** as stimuli, we are also exploring synthetic methods for isolating  $Zn^{II}$  complexes involving the dianionic form of H-Aib-*L*-Ala-OH and the various anionic forms of H-Aib-Aib-Aib-OH as ligands. Finally, analogues of **1–3** with the other Group 12 metals, i.e.  $Cd^{II}$  and  $Hg^{II}$ , are not known to date, and it is currently not evident whether the preparation and stability of such mononuclear, trinuclear and polymeric complexes are dependent on the nature of the metal ion; work along this line is in progress in our group.

## Supplementary data

CCDC 738622, 738623 and 738624 contains the supplementary crystallographic data for **1**·MeCOOH·H<sub>2</sub>O, **2**·H<sub>2</sub>O and **3**·5.8H<sub>2</sub>O. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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