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Effect of different α-substituents on the Mannich reaction of copper(II) chelated α-amino acids with formaldehyde and acetamide: X-ray structure of aquabis(3-methylacetamido-5-methyl-oxazolidine-4-carboxylato)-copper(II)

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Abstract

The reactions of a series of bis(α-substituted glycinato)copper(II) complexes, Cu(aa)$_2$, with formaldehyde and acetamide have been carried out. For Cu(aa)$_2$ with an activating α-alkyl or reactive α-hydroxyalkyl substituent, they undergo both aldol-type condensation and Mannich aminomethylation to yield complexes with an oxazolidine-ring and one methylacetamido pendant. The crystal structure of one of these complexes is reported. The Cu(aa)$_2$ with a non-activating α-alkyl substituent is diacetamidomethylated. A proposed mechanism to account for the above differences and an analysis of thermal decomposition data of the two types of complexes are further described.

Keywords: Mannich; Copper(II) complexes; α-Amino acids; Formaldehyde; Acetamide

1. Introduction

The template reactions of metal complexes of amino acids with formaldehyde and various substrates can be considered an ‘inorganic’ Mannich reaction. This has been our long-term interest. One type involves a chelated amino acid as the amine component reacting with formaldehyde and a substrate (benzaldehyde, phenylhydrazone, nitroethane, amide) with active hydrogen [1–3]. Another type involves the reaction of ammonia, formaldehyde and chelated amino acid as a substrate with active hydrogens at the amino nitrogen and carbon centers [4,5], and this latter role of a chelated amino acid is justified based on deuterium exchange and racemization studies [6]. In the first type of Mannich reaction, bis(glycinato)metal(II) complexes, M(gly)$_2$ (**1**), have undergone *N*,*N*-diacetamidomethylation to yield bis[*N*,*N*-di(*N*′-methylacetamido)-glycinato]metal(II), (**2a**) (Scheme 1) [2]. This paper represents a follow-up investigation into the effect of α-alkyl and α-hydroalkyl substituents on the Mannich reaction of copper(II) chelated α-substituted glycine with formaldehyde and acetamide under both acidic and basic reaction media. This investigation has been prompted by our discovery that only the M(gly)$_2$ and those bis(α-aminoacidato)metal(II) complexes with unreactive α-alkyl substituents have undergone the Mannich reaction with formaldehyde and ammonia to yield hexamine-like complexes [4,7]. The synthesized compounds have been characterized by infrared spectroscopy, thermal gravimetric analysis, elemental analysis and X-ray crystallography.

2. Experimental

The acetamide, 37% aqueous formaldehyde (HCHO) solution, amino acids and other reagents were used as

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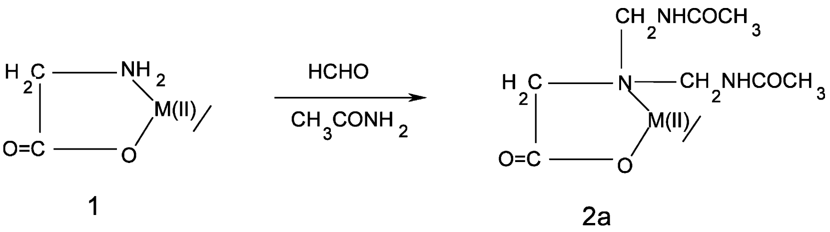


Scheme 1.

supplied. The α-hydroxymethyl-serine was synthesized by a previously reported procedure [8]. The bis(aminoacidato)-copper(II) complexes, $Cu(aa)_2$ (**3**), were prepared as reported previously [9].

2.1. *Physical measurements*

Infrared spectral data of compounds were recorded as KBr discs using a Nicolet-Magna-IR 560 spectrometer in the frequency range 4000–625 cm^{-1}. Elemental analysis was carried out with a Perkin–Elmer 2400. Thermal analysis was performed using a Mettler Toledo Star System on 4–9 mg samples with a heating rate of 30 °C min^{-1} under nitrogen in the temperature range 50–800 °C.

2.2. *Reactions and synthesis*

All reactions of $Cu(aa)_2$, **3** (**3a**, aa = L-ala (L-alaninate); **3b**, aa = C-Φgly (C-phenylglycinate); **3c**, aa = L-threo (L-threoninate); **3d**, aa = L-ser (L-serinate); **3e**, aa = hms (α-hydroxymethyl-serinate)) with formaldehyde and acetamide were carried out in the absence of base (pH ~ 4.0) and in the presence of base (pH ~ 6.0–9.0). Aqueous NaOH or $NaHCO_3$ solution was used to vary the pH. The mole ratio of $Cu(aa)_2$ to acetamide was also varied to see any effect.

2.2.1. *Cu(L-ala)*$_2$ *(**3a**) + HCHO + CH*$_3$*CONH*$_2$

For all reaction mixtures containing a **3a**: CH_3CONH_2 mole ratio of 1:4 and in the pH range pH ~ 4.0–9.0, the isolated complexes are bis[*N*-(*N*′-methylacetamido)-L-alaninato]copper(II) (**4a**). At a higher excess of acetamide (1:20), the reaction yielded bis[*N*,*N*-di-(*N*′-methylacetamido)-L-alaninato]copper(II) (**2b**).

Compound **4a**: A reaction mixture consisting of **3a** (1 g, 3.6 mmol), formaldehyde (10 ml, 0.12 mol) and acetamide (0.85 g, 14.4 mmol) was stirred thoroughly. The pH of the blue solution was raised to pH 6.0 by addition of aqueous NaOH solution. On standing for 5 days, the blue solid formed was filtered, washed with cold ethanol and finally dried at 50 °C for 5 h. Yield, 1.39 g (89%). For **4a**: $C_{12}H_{22}N_4O_6Cu \cdot 3H_2O$ required: C, 33.06; H, 6.47; N, 12.85. Found: C, 32.87; H, 6.10; N, 12.49%. IR: 3471, 3286, 3215, 3114, 1665, 1604, 1478, 1451, 1398, 1358, 1296, 1275, 1179, 1114, 1095, 1044, 1003, 907, 845, 776, 746, 679.

For **2b** (yield, 1.31 g (67%)): $C_{18}H_{32}N_6O_8Cu \cdot H_2O$ required: C, 39.89; H, 6.32; N, 15.50. Found: C, 39.68; H, 6.38; N, 15.46%. IR: 3346, 3257, 3054, 1697, 1651, 1621, 1552, 1523, 1474, 1437, 1385, 1367, 1304, 1256, 1174, 1158, 1130, 1094, 1083, 1048, 1012, 991, 901, 866, 810, 693, 673.

2.2.2. *Cu(C-Φgly)*$_2$ *(**3b**) + HCHO + CH*$_3$*CONH*$_2$

The reactions carried out for **3b** were similar to those in 2.11. For all reactions in the pH range ~ 4.0–9.0 and different **3b**: CH_3CONH_2 mole ratios (1:4, 1:10, 1:20, 1:40), only one product was obtained, i.e. bis(3-methylacetamido-4-phenyl-oxazolidine-4′-carboxylato)copper(II) (**5a**).

A reaction mixture consisting of **3b** (0.5 g, 1.25 mmol), acetamide (0.3 g, 5 mmol) and formaldehyde (10 ml, 0.12 mol) was stirred thoroughly and its pH raised to pH 9.0 by addition of NaOH solution. The blue solid, which formed after 3 days, was filtered, washed with cold ethanol and finally dried at 50 °C for 5 h. Yield, 0.36 g (45%). For **5a**, $C_{26}H_{30}N_4O_8Cu \cdot 2.5H_2O$ required: C, 50.61; H, 5.72; N, 9.08. Found: C, 50.72; H, 5.43; N, 8.51%. IR: 3260, 3201, 3070, 1647, 1547, 1500, 1443, 1365, 1342, 1283, 1250, 1117, 1083, 1076, 1000, 967, 933, 752, 698 cm^{-1}.

2.2.3. *Cu(L-threo)*$_2$ *(**3c**) + HCHO + CH*$_3$*CONH*$_2$

At pH 4.0 and a **3c**: CH_3CONH_2 mole ratio of 1:20, the above reaction yielded a blue crystalline product suitable for X-ray crystal structure analysis. This complex is aquabis(3-methylacetamido-5-methyl-oxazolidine-4-carboxylato)copper(II) (**5b**). Yield was 56%.

At a lower mole ratio of **3c**: CH_3CONH_2 and higher pH, two different complexes were recovered and their IR spectra were identical to those of previously synthesized bis(5-methyl-oxazolidine-4-carboxylato)copper(II) (**6a**), and bis(3-hydroxymethyl-5-methyl-oxazolidine-4-carboxylato)copper(II) (**7a**) [10]. The above complex **5b** can also be obtained by reacting **7a** with formaldehyde and acetamide (yield, 41%).

For **5b**, $C_{16}H_{26}N_4O_8Cu \cdot H_2O$ required: C, 39.71; H, 5.83; N, 11.58. Found: C, 39.61; H, 5.67; N, 11.67%. IR: 3429, 3356, 3072, 1687, 1636, 1540, 1458, 1404, 1361, 1305, 1276, 1171, 1130, 1072, 1061, 1022, 968, 949, 927, 890, 856, 806, 744, 668 cm^{-1}.

2.2.4. Cu(L-ser)$_2$ (3d) + HCHO + CH_3CONH_2

At pH 7.0 and a **3d**: CH_3CONH_2 mole ratio of 1:4, the reaction yielded bis(3-methylacetamido-oxazolidine-4-carboxylato)copper(II) (**5c**) (Yield, 11%). In a non-base reaction involving a lower mole ratio of **3d**: CH_3CONH_2, **6b** was the complex recovered while in basic reactions above pH 7, **8** was the only complex isolated. The IR spectrum of **6b** was identical to bis(oxazolidine-4-carboxylato)copper(II) previously synthesized from the reaction of Cu(L-ser)$_2$ and formaldehyde in the absence of base [7]. The complex **8** has an IR spectrum identical to the copper(II) complex of dihydro-1H,3H,5H-oxazolo[3,4-c]oxazole-7a-carboxylic acid [11].

For **5c**, $C_{14}H_{22}N_4O_8Cu \cdot 2H_2O$ required: C, 35.33; H, 5.51; N, 11.77. Found: C, 35.60; H, 5.67; N, 11.52%. IR: 3241, 3065, 2905, 1636, 1563, 1450, 1379, 1333, 1303, 1278, 1166, 1115, 1090, 1076, 1057, 1008, 984, 937, 877, 854, 805, 761, 735, 703, 668.

2.2.5. Cu(hms)$_2$ (3e) + HCHO + CH_3CONH_2

All reactions involving bis(α-hydroxymethyl-serinato)copper(II) (**3e**), yielded a complex which has an IR spectrum identical to that of **8** obtained in 2.14. This complex is, therefore, the same as **8**.

IR of **8**: 3421, 2900, 2901, 1639, 1544, 1474, 1284, 1185, 1112, 1091, 1007, 967, 929, 806, 757, 665.

2.3. X-ray crystallography

The diffraction data for **5b** was collected on a Siemens P4 diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 298 K. The structure was solved by direct methods [12] and refined using full-matrix least-squares [13].

Crystal data is listed in Table 1. Selected bond lengths and angles are listed in Table 2.

Table 1
Crystallographic data for **5b**

Empirical formula	$C_{16}H_{28}N_4O_9Cu$
Formula weight	484.0
Temperature (K)	298
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	9.397(2)
b (Å)	7.073(2)
c (Å)	15.946(4)
β (°)	102.240(10)
V (Å^3)	1035.8(4)
Z	2
D_{calc} (Mg m^{-3})	1.552
Absorption coefficient (mm^{-1})	1.111
F (000)	506
Crystal size (mm)	0.2 × 0.3 × 0.5
θ Range for data collection (°)	1.5–27.5
Total reflections collected	3190
Independent/observed reflections ($F > 4.0\sigma(F)$)	2777/2661
Data/restraints/parameter	3190/0/278
Goodness-of-fit on F^2	0.92
Final R indices ($F > 4.0\sigma(F)$)	$R_1 = 0.0378$, $wR_2 = 0.0424$

Table 2
Selected bond lengths (Å) and angles (°) for **5b**

Bond lengths			
Cu–N1	2.048(3)	Cu–O1	1.930(3)
Cu–N3	2.021(3)	Cu–O5	1.928(3)
Cu–O1w	2.392(4)	Cu–O4	3.140(3)
Bond angles			
N1–Cu–N3	160.8(1)	N1–Cu–O1	85.5(1)
N3–Cu–O1	90.2(1)	N1–Cu–O5	100.9(1)
N3–Cu–O1w	85.3(1)	O1–Cu–O5	172.0(1)
N1–Cu–O1w	95.0(1)	N3–Cu–O1w	103.3(1)
O1–Cu–O1w	85.9(1)	O5–Cu–O1w	88.7(1)
O4–Cu–N3	86.0(1)	O4–Cu–O5	68.5(1)
O4–Cu–O1	117.9(1)	O4–Cu–N1	79.6(1)
O4–Cu–O1w	154.7(1)		

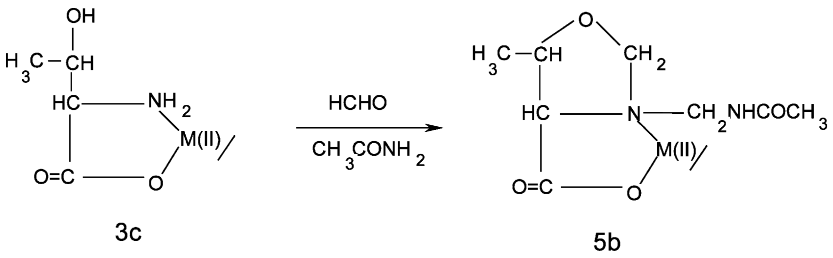
3. Results and discussion

3.1. Structure of 5b

The reaction of Cu(L-threo)$_2$ (**3c**), with formaldehyde and a high excess of acetamide in the absence of base results in the formation of **5b** (Scheme 2). The two L-threoninate moieties are chelated to the copper atom via their amino nitrogen and carboxylate oxygen atoms in a *trans*-configuration (Fig. 1). The fifth coordination site is occupied by a water molecule. The carbonyl oxygen atom of one methylacetamido fragment interacts strongly with the copper atom (Cu–O4, 3.140(3) Å). Thus, the coordination geometry about the copper atom can be considered a severely distorted octahedron [14].

Hydrogen bonding links each **5b** molecule with adjacent molecules in the lattice into an inter-linking network. The atoms involved in each molecule are N2 (amide proton of one methylacetamido fragment), N4 and O8 (amide proton and carbonyl oxygen atoms of the second methylacetamido fragment) and O1w (both protons of the coordinated water molecule). The hydrogen bonding data are listed in Table 3.

The methylacetamido fragments established the occurrence of Mannich aminomethylation between Cu-(L-threo)$_2$, formaldehyde and acetamide. The non-hydrogen atoms in each fragment (deviations from least-



Scheme 2.

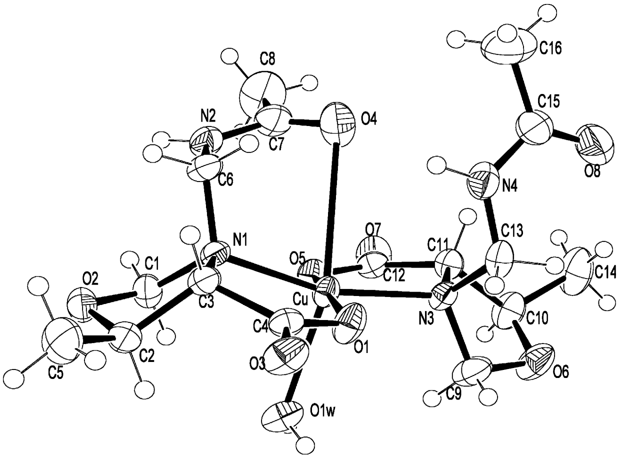


Fig. 1. ORTEP drawing of **5b**.

squares best plane for fitted atoms are O4(−0.0076), C7(0.0081), C8(0.0079), N2(−0.0234) and C6(0.0151 Å) with rms deviation of 0.0139 Å; and deviations for the other best plane are O8(−0.0031), C15(0.0170), C16 (−0.0135), N4(0.0124) and C13(−0.0128 Å) with rms deviation of 0.0126 Å; dihedral angle between the two planes is 72.71°) are still quite co-planar. The carbonyl carbon in each methylacetamido fragment (C7 and C15) uses sp^2 hybridization for bonding but the trigonal angles (e.g. N2–C7–C8, 114.8(4)°; N2–C7–O4, 122.6(4)°; O4–C7–C8, 122.5(5)°)) deviates from the ideal angle of 120° due to difference in valence bond electron pair repulsion (double–single bond repulsion > single–single bond repulsion). The angles about the amide nitrogen (their sum equals 360°) and its co-planarity with atoms bonded to it suggests use of sp^2 hybridization as in the above carbonyl carbon. The short amide nitrogen–carbonyl carbon bond (1.369(6) and 1.349(5) Å) supports partial pπ–pπ interaction. Even the nitrogen atom in the relatively flattened aza-capped ligand of cobalt complexes exhibits a shift towards sp^2 hybridization in bonding with three methylene-bridging carbon atoms, and here the mean N–C bond length is relatively longer (1.440 and 1.430(7) Å) [15,16]. This amide bond is, nevertheless, longer than 1.3351(1) Å for the corresponding bond in acetamide [17] and the imine C=N bond of 1.274(3) Å in *mer*-(ethylenediamine)[*N*-((5,6-dihydro-5,5-bis(hydroxymethyl)-1,3-oxazin-4-yl)carbonyl)glycinato]nitrocobalt(III) trihydrate [18]. In contrast, the bond angles about the amino nitrogen atom of each threoninate moiety shows use of typical sp^3 hybridized nitrogen orbitals for bonding and its N–C bonds average 1.495(5) Å.

The presence of an oxazolidine ring for each threoninate moiety confirmed the aldol-type reaction between **3c** and formaldehyde. Both rings have envelope conformation and are *cis* with respect to the N1–O1–N3–O5 plane. The above two methylacetamido fragments are *cis* to each other but on the opposite side of this plane; each methylacetamido fragment is adjacent to its own oxazolidine ring.

3.2. Chemistry of Cu(aa)$_2$+HCHO+CH$_3$CONH$_2$

The above structural determination has established that Cu(L-threo)$_2$ (**3c**), has undergone both Mannich aminomethylation and aldol-type condensation with formaldehyde and acetamide to yield the **5b** (refer Section 2). The former reaction type yields the methylacetamido fragments while the latter gives rise to the oxazolidine rings. Higher excess of acetamide and acidic pH favors formation of this complex. However, the isolated complexes of reactions at higher pH values and

Table 3
Hydrogen bonding distances and angles for **5b**

D–H	Distance (Å) D–H	Distance (Å) H···A	Angle (°) DHA	Distance (Å) D···A	A	Symmetry operation
N2–H2A	0.900	2.149	147.14(3)	2.945(4)	O8	a: $x+1, y, z$
N4–H4A	0.900	2.299	151.14(4)	3.118(5)	O7	b: $x, y+1, z$
O1w–H1wA	0.750	2.142	164.42(4)	2.872(5)	O3	c: $-x+2, y-1/2, -z$
O1w–H1wB	0.911	1.933	178.22(3)	2.843(4)	O3	d: $x, y-1, z$

lower mole ratios of **3c**: CH_3CONH_2 are oxazolidine-type complexes, suggesting failure of acetamide to take part in the reaction.

Similar findings are obtained with the reactions of Cu(L-ser)$_2$ (**3d**). Like L-threonine, the L-serine has a α-hydroxyalkyl substituent. At pH 7.0 and **3d**: CH_3CONH_2 mole ratio of 1:4, the reaction has yielded a complex whose IR spectrum shows a peak at 3065 cm^{-1} indicating the presence of acetamide >NH in the chelated ligand moiety. Such peaks are found in the IR spectra of the above **5b** and **2a** [2]. Thus, substitution of one of the amide protons of acetamide and its coupling with the amino nitrogen of the chelated amino acid via the formaldehyde-derived methylene bridge causes a lowering in IR frequency (υ_sNH) of the amide from 3380 to 3190 cm^{-1} ($\upsilon_s NH_2$) to 3065 cm^{-1} [19]. A triplet in the 1200–1060 cm^{-1} IR spectral region shows characteristic vibrations due to an oxazolidine ring system [20,21]. The microanalytical result supports the postulated formula of the complex as similar to the above **5b**, and as such this complex is similarly labeled as **5c**. Both these similar complexes are depicted as **5** ($R^1 = H$ and CH_3 for L-ser and L-threo, respectively) in Scheme 3.

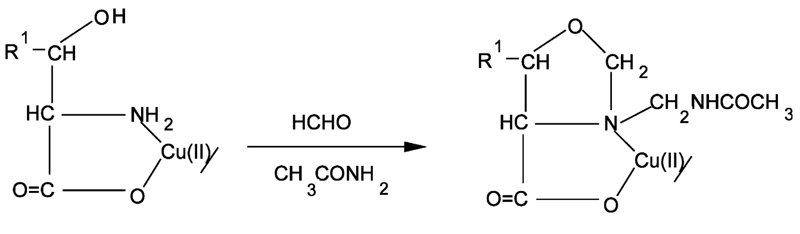
For all reactions involving Cu(hms)$_2$ (**3e**), which has two α-hydroxymethyl substituents, the isolated product formed in each case is **8** (Scheme 4) and this shows that the acetamide failed to react with **3e** and thus no Mannich aminomethylation has occurred.

The next two series of reactions involve the complexes Cu(C-Φgly)$_2$ (**3b**) and Cu(L-ala)$_2$ (**3a**), both of which are α-substituted chelated glycines with one α-alkyl substituent. All reactions involving **3b** yielded the same complex, **5a** which has an IR spectrum with these features: (i) typical carboxylate asymmetric and symmetric stretching frequencies at ~1600 and ~1400 cm^{-1}, (ii) a peak attributed to an amide fragment at 3070 cm^{-1}, and (iii) a typical triplet attributed to the presence of an oxazolidine system in the region 1200–1050 cm^{-1}. These spectral data and the microanalysis result support our postulation that **5a** is bis(3-methylacetamido-4-phenyl-oxazolidine-4′-carboxylato)copper(II) and its structure is depicted in Scheme 5.

For the reactions of **3a**, the complex formed depends on the **3a**: CH_3CONH_2 mole ratio. When the mole ratio is 1:4, the isolated complex shows an IR peak at 3114 cm^{-1}, indicating the presence of an amino proton. However, the weak peak at about 3060 or 3070 cm^{-1} is not observed and is probably masked due to overlapping with the stronger absorption of the amino >NH. Similarity of the IR spectrum with those of complexes which are formed from the Mannich aminomethylation of Cu(aa)$_2$ with formaldehyde and acetamide, and the microanalytical result supports our postulate that it is bis[*N*-(*N*′-methylacetamido-L-alaninato]copper(II) (**4a**). At a higher mole ratio of **3a**: CH_3CONH_2, the complex is postulated to be bis[*N*,*N*-di(*N*′-methylacetamido)-L-alaninato]copper(II) (**2b**) based on IR spectral evidence (such as a peak at 3054 cm^{-1} due to amide and the absence of an amino nitrogen peak) and the microanalytical result. In both cases (Scheme 6), only Mannich aminomethylation has been found to occur and this is in contrast with those other reactions involving Cu(L-threo)$_2$ (**3c**), Cu(L-ser)$_2$ (**3a**) and Cu(C-Φgly)$_2$ (**3b**) where both Mannich aminomethylation and aldol-type reactions have taken place.

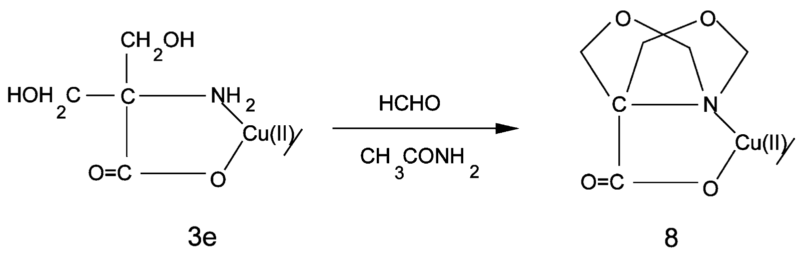
The following mechanism is postulated to account for the effect of a different α-carbon substituent of the Cu(aa)$_2$ on its reaction with formaldehyde and acetamide (Scheme 7).

In both aldol-type and Mannich aminomethylation reactions of chelated amino acids, the initial steps lead to the presumed formation of an exo-imine intermediate (**9**). Nevertheless, similar imine intermediates have been isolated and it is known that the imine carbon atom is partially activated towards attack by nucleophiles [18,22]. The oxygen atom of the α-hydroxyalkyl substituent in Cu(aa)$_2$ is nucleophilic, and so is the acetamide and its conjugate base [23]. Thus, the α-hydroxyalkyl group of Cu(L-threo)$_2$ or Cu(L-ser)$_2$ or Cu(C-Φgly)$_2$ competes with the acetamide for the imine function, and two reaction pathways, **I** and **II**, are possible. As the reactions of Cu(hms)$_2$ with formaldehyde and acetamide under all conditions investigated yield only the bis(oxazolidine)-type complex **8**, the hydroxymethyl groups have successfully competed with the acetamide and it is reasonable to conclude that the α-hydroxyalkyl oxygen atom in those Cu(aa)$_2$ complexes with an α-hydroxyalkyl substituent is more reactive and nucleophilic. Further evidence is adduced from the close resemblance of **5b** (**5**: R = H, $R^1 = CH_3$)

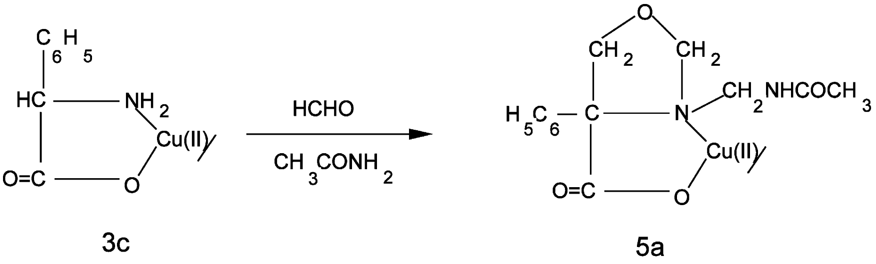


3d **5**

Scheme 3.



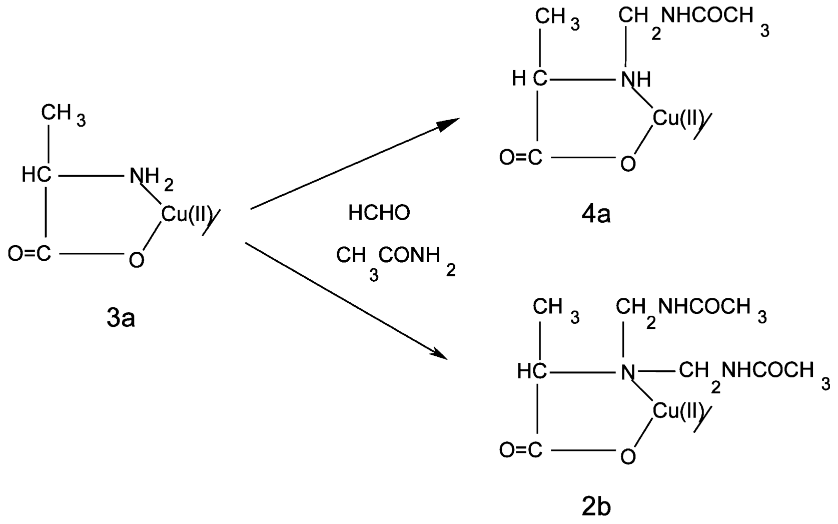
Scheme 4.



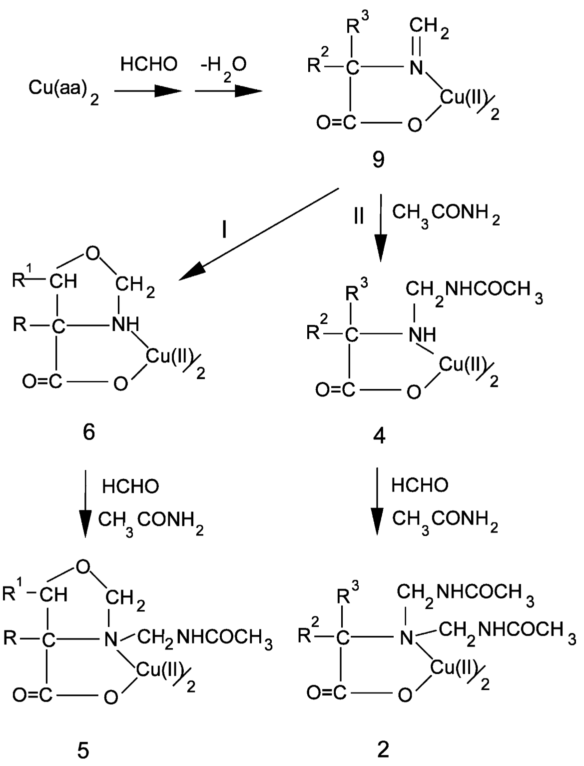
Scheme 5.

structure to that of **6a** (**6**: R = H, $R^1 = CH_3$) [10]. In the former, the *N*-methylacetamido substituent of each threonine moiety is orientated upwards while its oxazolidine ring, having an envelope conformation, bends downwards in relation to the N_2O_2 plane. The single amino proton and oxazolidine ring of each threonine moiety in **6a** are similarly orientated. The *N*-methylacetamido group apparently substitutes the amino proton of the threonine moiety in **6a** stereospecifically. In spite of the absence of more direct evidence, it is more plausible to suggest that complex **5** is formed from **6** instead of via **4**. Additional evidence for this intermediate **6** comes from reacting bis(3-hydroxymethyl-5-methyl-oxazolidine-4-carboxylato)copper(II) (**7a**), with formaldehyde and acetamide. The complex **5a** is obtained from this reaction and also from the reaction of bis(L-threoninato)-copper(II) (**3c**), with formaldehyde and acetamide. As **7a** is obtained from the reaction of **3c** with formaldehyde alone, this additional result provides evidence for formation of **5b** from **3c** through the *N*-hydroxymethylated derivative of the intermediate **6** ($R' = CH_3$, R = H).

The reaction of Cu(C-Φgly)$_2$ with formaldehyde and acetamide, in forming complex **5a** (**5**: $R = C_6H_5$, $R^1 =$ H) depicted by the general structure **5**, shows chemical similarity to those reactions of Cu(L-threo)$_2$ and Cu-(L-ser)$_2$. Unlike the α-hydroxyalkyl, the C-phenyl substituent is not reactive towards the imine complex **9**. However, it activates the α-carbon of Cu(C-Φgly)$_2$ and allows α-hydroxymethylation by formaldehyde. As



Scheme 6.



Scheme 7.

such, an oxazolidine ring is formed (from condensation of this hydroxymethyl group with the imine) together with the *N*-methylacetamido susbtituent in **5a**.

In contrast, Cu(L-ala)$_2$ has undergone diaminomethylation (specifically, diacetamidomethylation) to yield the bis(*N*-methylacetamido) complex **2b** (**2**: $R^2 = H$, $R^3 = CH_3$). Like the C-phenyl group, the α-methyl substituent in Cu(L-ala)$_2$ is unreactive. Unlike the C-phenyl group, this α-methyl substituent is deactivating and as a consequence α-hydroxymethylation by formaldehyde does not occur. The reactive center is at the amino nitrogen and **2b** is formed from **4a** (**4**: $R^2 = H$, $R^3 = CH_3$) reacting with more formaldehyde and acetamide.

The above results and discussion lead to the conclusion that the α-substituent affects the type of complex formed from the reaction of chelated α-aminoacid with formaldehyde and acetamide. Cu(aa)$_2$ with reactive α-hydroxyalkyl or activating α-substituent undergoes both Mannich aminomethylation and aldol-type reactions. Chelated amino acids with unreactive α-substituents, as is the case with Cu(L-ala)$_2$, under appropriate conditions are mono- or diacetamidomethylated by formaldehyde and acetamide.

3.3. Thermal analysis of complexes

The complexes obtained from the reactions of Cu(aa)$_2$ with formaldehyde and acetamide, as explained in the Section 3, are of two types (Table 4). The thermal decomposition of these complexes seems to parallel these two categories. The first group, comprising **5a**, **5b** and **5c** has one decomposition peak, at which about 45–60% of the complex is lost as gaseous products. The second group, comprising **2a**, **4a** and **2b**, has two or more decomposition peaks. The first decomposition step for all complexes is above 100 °C. Except for **4a**, the TGA–DTA data do not show expulsion of lattice water, implying coordination or strong or multiple hydrogen bonding of these water molecules. For **4a**, the first decomposition involves expulsion of two water molecules (calculated: 8.2%; found: 7.8%); the high decomposition temperature at 146.2 °C suggests a hydrogen bonding effect.

4. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Data Center, CCDC No. 186851. Copy of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Table 4
Thermal decomposition data of complexes of Cu(aa)$_2$+HCHO+CH$_3$CONH$_2$

	Complex	Formula	Decomposition temperature (°C) (wt.% loss)	Residue (%)
1	**2a**	$C_{16}H_{28}N_6O_8Cu\cdot 2H_2O$	119.8 (12.7), 217.3 (50.1), 266.4 (15.9), 570.1 (7.4)	14.3
2	**4a**	$C_{12}H_{22}N_4O_6Cu\cdot 3H_2O$	146.2 (7.8), 194.4 (41.0), 241.4 (29.4)	21.8
3	**2b**	$C_{18}H_{32}N_6O_8Cu\cdot H_2O$	194.8 (49.5), 245.3 (14.0)	20.4
4	**5c**	$C_{14}H_{22}N_4O_8Cu\cdot 2H_2O$	208.4 (59.8)	40.2
5	**5a**	$C_{26}H_{30}N_4O_8Cu\cdot 2.5H_2O$	195.9 (46.1)	20.6
6	**5b**	$C_{16}H_{26}N_4O_8Cu\cdot H_2O$	188.9 (67.6), 475.0, 690.0 (15.8)	15.6

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