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Reactions of a series of bis(α-amino acidato)copper(II) complexes with formaldehyde and benzamide: aldol-type condensation *versus* Mannich aminomethylation

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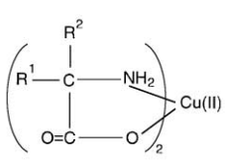
Received 25th March 2002, Accepted 25th June 2002
First published as an Advance Article on the web 2nd August 2002

In the reactions of bis(α-amino acidato)copper(II) with formaldehyde and benzamide, competing processes occur and the preferred pathway depends on the nature and number of the α-carbon substituents of the chelated amino acid, and the pH of the reaction medium. Aldol-type condensation yields complexes with oxazolidine ring(s) while Mannich aminomethylation results in the formation of complexes with *N*-methylbenzamido pendant arm(s). The crystal structure determination of bis(3-methylbenzamido-5-methyloxazolidine-4-carboxylato)copper(II) dihydrate establishes its formation from a combination of both processes, in which aldol condensation occurs first. The chemistry of these reactions is rationalized with a proposed reaction scheme. The synthesized compounds are characterized by infrared spectroscopy and microanalysis.

1 Introduction

Mannich aminomethylation,[1] an organic reaction involving a substrate having active hydrogen, formaldehyde/aldehydes and an amine/ammonia functionality, also encompasses the analogous reaction of metal complexes of amino acids for which the metal amino acetate replaces the amine reagent. This 'inorganic' Mannich reaction involves chelated amino acids reacting as an amine component[2,3] or as a substrate with active hydrogen since the amino protons are labile.[4,5]

To develop further the chemistry of this reaction type, we investigated the reactions of bis(amino acidato)metal(II), $M(aa)_2$, with formaldehyde and amides.[6,7] The first study shows that bis[*N*,*N*-di(*N*-methylacetamido)glycinato]metal(II), M^{II}-$[DMeA\text{-}gly]_2$, were formed from the reactions of bis(glycinato)-metal(II) with formaldehyde and acetamide.[6] Subsequently, we discovered that pH and the nature of the metal(II) cations influences the type of product formed from the reactions of bis(β-alaninato)metal(II), $M(\beta\text{-ala})_2$, with formaldehyde and benzamide.[7] In basic medium, reactions of $Cu(\beta\text{-ala})_2$ yielded bis[*N*-methyl-*N*-(*N*-methylbenzamido)-β-alaninato]copper(II), $Cu^{II}[Me\text{-}MeB\text{-}\beta\text{-ala}]_2$ through both Canizzaro-type methylation and Mannich aminomethylation, while those involving other $M(\beta\text{-ala})_2$ (M = Zn, Ni, Co) resulted in the formation of bis[*N*,*N*-di(*N*-methylbenzamido)-β-alaninato]metal(II) complexes, $M^{II}[DMeA\text{-}\beta\text{-ala}]_2$. In the absence of base, only the $Cu(\beta\text{-ala})_2$ reacted with formaldehyde and benzamide to form $Cu^{II}[DMeA\text{-}\beta\text{-ala}]_2$. To acquire further understanding of this Mannich reaction involving amide, this paper reports the reaction of a series of bis(α-amino acidato)copper(II), $Cu(aa)_2$ **1**, with formaldehyde and benzamide to investigate the effect of pH and different α-substituents of the α-amino acid.



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2 Experimental

Glycine (gly), L-alanine (L-ala), C-phenylglycine (C-ϕgly), L-threonine (L-threo) and L-serine (L-ser) were supplied by Sigma. Hydroxymethylserine (OHMe-ser) was prepared by a previously reported procedure.[8] Benzamide and 37% aqueous formaldehyde solution were obtained from Merck. $Cu(aa)_2$ were prepared as reported previously.[9]

The infrared spectra of the complexes were recorded on a Perkin-Elmer 2000 FT-IR spectrophotometer from 4000–400 cm^{-1} as KBr discs. Elemental analyses were carried out on a Perkin-Elmer 2400 in the School of Chemical Sciences, Universiti Sains Malaysia.

Reaction and synthesis

Each reaction of $Cu(aa)_2$ (aa = gly, L-ala, C-ϕgly, L-ser, L-threo, OHMe-ser) with formaldehyde and benzamide was initially carried out in the absence of base. The pH of the reaction mixtures of subsequent reactions were raised with the addition of aqueous NaOH solution or aqueous $NaHCO_3$. The pH ranges were from pH ≈3.0 to pH ≈10.0. All reactions required the addition of 95% ethanol to help dissolve the benzamide.

Bis[*N*,*N*-di(*N*-methylbenzamido)glycinato]copper(II), 2a. A reaction mixture consisting of *cis*-$Cu(gly)_2 \cdot H_2O$ (0.5 g, 2.4 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (1.2 g, 10 mmol) and 95% ethanol was stirred thoroughly. Within the same day, the resultant solution yielded a blue solid which was filtered off, washed with cold ethanol and finally dried *in vacuo* for 5 h. Yield 1.48 g, 78%. IR (cm^{-1}): 3360, 3288, 3067, 2976, 2944, 1634, 1577, 1545, 1490, 1442, 1421, 1406, 1366, 1332, 1305, 1244, 1192, 1166, 1135, 1080, 1054, 1000, 983, 954, 931, 855, 829, 810, 755, 711, 696, 655, 620, 496, 452, 409. 3360s; ν_{OH}(water) 3302s; ν_{NH}(amide) 3067w; ν_{COO^-}(asym, sym) 1634vs, 1367s. Elemental analysis calculated for $C_{36}H_{36}N_6O_8Cu \cdot 2.5H_2O$: C, 55.42; H, 5.13; N, 10.78. Found: C, 55.37; H, 4.86; N, 10.46%. This complex could be synthesized between pH 3.6 and 9.0. IR spectroscopy shows that the same complex was

formed when *trans*-Cu(gly)$_2$ was used in the reactions. Poor yields were obtained at higher pH values or at higher temperatures (*e.g.* 80 °C, 20% yield).

Bis[{*N*-hydroxymethyl-*N*-(*N*-methylbenzamido)}glycinato]-copper(II), 3a. By using a Cu(gly) to $C_6H_5CONH_2$ mol ratio of 1 : 1, the above reaction (in the absence of a base) led to the isolation of **3a** in ≈60% yield: a reaction mixture consisting of Cu(gly)$_2$ (0.5 g, 2.4 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (0.3 g, 2.5 mmol) and 95% ethanol was stirred thoroughly. The solution was filtered and allowed to stand at room temperature. A light blue solid which was formed within the same day, was filtered off, washed with cold ethanol and dried *in vacuo* for 5 h. Yield 0.86 g, 61%. IR(cm^{-1}): 3301, 3067, 2974, 2945, 1633, 1577, 1547, 1491, 1439, 1424, 1378, 1333, 1310, 1246, 1161, 1139, 1082, 1048, 1013, 964, 952, 928, 859, 830, 810, 754, 708, 654, 622, 498, 465, 410. ν_{OH}(water) 3301s; ν_{NH}(amide) 3067w; ν_{COO^-}(asym, sym) 1633vs, 1378s. Elemental analysis calculated for $C_{22}H_{26}N_4O_8Cu\cdot 3H_2O$: C, 44.63; H, 5.41; N, 9.47. Found: C, 44.77; H, 5.09; N, 9.27%.

Bis[*N*,*N*-di(*N*-methylbenzamido)-L-alaninato]copper(II), 2b. A mixture of Cu(L-ala)$_2$ (0.5 g, 2.1 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (0.5 g, 4.1 mmol) and 95% ethanol was stirred thoroughly and filtered. (filtrate pH ≈4). After 1 day, a blue solid had formed. It was filtered off, washed with ethanol and dried *in vacuo* for 5 h. Yield 1.38 g, 75%. IR(cm^{-1}): 3851, 3413, 3266, 3066, 2941, 1630, 1603, 1578, 1548, 1492, 1464, 1446, 1383, 1351, 1314, 1157, 1133, 1078, 1047, 998, 949, 875, 839, 806, 779, 707, 618, 522, 460. ν_{OH}(water) 3413s; ν_{NH}(amide) 3066w; ν_{COO^-}(asym, sym) 1630vs, 1383s. Elemental analysis calculated for $C_{38}H_{40}N_6O_8Cu\cdot 6H_2O$: C, 51.84; H, 5.95; N, 9.55. Found: C, 51.87; H, 5.38; N, 9.79%. Poor yields (< 10%) of **2b** were obtained at higher pH values. Optimum yield (50–75%) for **2b** was obtained in the pH range 5.5–6.0 and with a Cu(L-ala)$_2$ to benzamide mole ratio > 1 : 2.

Bis(4-methyl-oxazolidine-4-carboxylato)copper(II), 4a. A mixture of Cu(L-ala)$_2$ (1 g, 4.2 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (1 g, 8.2 mmol) and 95% ethanol was stirred thoroughly and filtered. The filtrate was heated in a water bath at 80 °C. A blue solid formed after 2 weeks and was filtered off, washed with ethanol and dried *in vacuo* for 5 h. Yield 0.12g, 14%. IR(cm^{-1}): 3734, 3461, 3176, 2992, 2919, 2877, 1634, 1606, 1575, 1494, 1457, 1398, 1380, 1366, 1259, 1197, 1184, 1157, 1115, 1077, 1047, 1013, 944, 924, 825, 789, 766, 722, 585, 483. ν_{OH}(water) 3461s; ν_{NH}(amino) 3176s; ν_{COO^-}(asym, sym) 1607vs, 1398s; ν(triplet, oxazolidine) 1184, 1115, 1077s. This complex has an IR spectrum identical to that of bis(4-methyl-oxazolidine-4-carboxylato)-copper(II) synthesized previously.[10] Elemental analysis calculated for $C_{10}H_{16}N_2O_6Cu\cdot 2H_2O$: C, 33.38; H, 5.56; N, 7.79. Found: C, 33.77; H, 5.25; N, 7.47%. In the pH range 9.0–10.0, a mixture of **4a** (≈10% yield) and **2b** (≈1–2% yield) was obtained.

Bis(3-methylbenzamidooxazolidine-4-carboxylato)copper(II), 5a. A mixture of Cu(L-ser)$_2$ (0.5 g, 1.6 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (0.5 g, 4 mmol) and 95% ethanol was stirred thoroughly. The blue solid which formed after 9 days was filtered off, washed with cold ethanol and dried *in vacuo* for 5 h. (Copper was also deposited.) Yield 0.28 g, 31%. IR(cm^{-1}: 3598, 3435, 3222, 3060, 2878, 1646, 1578, 1539, 1487, 1452, 1397, 1376, 1315, 1291, 1215, 1185, 1154, 1115, 1089, 1059, 1041, 999, 969, 950, 927, 850, 797, 760, 711, 590, 557, 499. ν_{OH}(water) 3435s; ν_{NH}(amide) 3060w; ν_{COO^-}(asym, sym) 1646vs, 1376s; ν(triplet, oxazolidine) 1185, 1154, 1059s. Elemental analysis calculated for $C_{24}H_{26}N_4O_8Cu\cdot 0.5H_2O$: C, 50.48; H, 4.77; N, 9.81. Found: C, 50.31 7; H, 4.53; N, 9.91%. This complex was formed between pH ≈4 and 9.

(Dihydro-1*H*,3*H*,5*H*-oxazolo[3,4-*c*]oxazole-7a-carboxylato)-copper(II), 6a. When the reactions of Cu(L-ser)$_2$ with formaldehyde and benzamide were conducted at pH > 10, the compound obtained has an IR spectrum identical to that of **6a** reported previously.[11] This complex is also formed when the reactions of Cu(OHMe-ser)$_2$ with formaldehyde and benzamide were carried out in the absence or presence of base (pH range ≈3.0–9.5) and a high yield was obtained for each reaction (≈80%). A mixture of Cu(OHMe-ser)$_2$ (0.1 g, 0.3 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (0.08 g, 0.64 mmol) and 95% ethanol was stirred thoroughly. The pH of the resultant solution was raised to pH 7.5 by addition of aqueous NaOH solution. The solution was filtered and upon standing at room temperature yielded a blue crystalline solid after a day. This was filtered off, washed with ethanol and dried *in vacuo* for 5 h. Yield, 0.09 g, 79%. IR(cm^{-1}): 3429, 2904, 2868, 1638, 1611, 1540, 1510, 1491, 1474, 1381, 1283, 1240, 1191, 1183, 1144, 1120, 1111, 1183, 1090, 1058, 1007, 965, 929, 904, 818, 806, 775, 756, 666, 553, 492, 435. ν_{COO^-}(asym, sym) 1638vs, 1381s; ν(triplet, oxazolidine) 1183, 1090, 1058s. Elemental analysis calculated for $C_{12}H_{16}N_2O_8Cu$: C, 37.95; H, 4.22; N, 7.38. Found: C, 38.37; H, 4.27; N, 7.08%.

Bis(3-methylbenzamido-5-methyloxazolidine-4-carboxylato)-copper(II), 5b. A mixture of Cu(L-threo)$_2$ (0.6 g, 2 mmol), formaldehyde (10 ml, 0.12 mol), benzamide (0.5 g, 4 mmol) and 95% ethanol was stirred thoroughly. Blue crystalline needles formed after 3 days and were filtered off, washed with cold ethanol and dried *in vacuo* for 5 h. Yield: 0.46 g, 37%. IR(cm^{-1}): 3579, 3434, 3225, 3064, 2982, 2928, 1623, 1666, 1576, 1546, 1522, 1489, 1455, 1385, 1361, 1335, 1315, 1291, 1276, 1260, 1170, 1124, 1079, 1068, 967, 936, 899, 882, 862, 799, 842, 762, 719, 691, 560, 510, 484, 428. ν_{OH}(water), 3579; ν_{NH}(amide) 3064w; ν_{COO^-}(asym, sym) 1623vs, 1385s; ν(triplet, oxazolidine) 1170, 1124, 1079s. Elemental analysis calculated for $C_{26}H_{30}N_4O_8Cu\cdot 2H_2O$: C, 49.88; H, 5.47; N, 8.95. Found: C, 50.10; H, 5.42; N, 8.67%. This complex could be synthesized between pH ≈ 4 and 8.0, but the yield was less than 40% for each reaction. At pH > 8.0, lower yields (< 25%) were obtained, decomposition occurred and copper was deposited.

Bis[*N*,*N*-di(*N*-methylbenzamido)-C-phenylglycinato]copper(II), 2c. A mixture of Cu(C-φgly)$_2$ 0.5 g, 1.4 mmol), formaldehyde (10 ml, 0.13 mol), benzamide (0.6 g, 2.8 mmol) and 95% ethanol was stirred thoroughly. The pH of the solution was raised to pH 6.0 with NaOH solution. The light blue solid, which formed after one day, was washed with ethanol and dried *in vacuo* for 5 h. Yield: 0.62 g, 44%. IR(cm^{-1}): 3510, 3400, 3235, 3063, 1665, 1647, 1626, 1603, 1576, 1553, 1524, 1490, 1452, 1421, 1367, 1306, 1186, 1162, 1119, 1080, 1054, 1033, 975, 948, 910, 984, 824, 784, 753, 693, 643, 605, 508. ν_{OH}(water) 3400; ν_{NH}(amide) 3063w; ν_{COO^-}(asym, sym) 1626vs, 1367. Elemental analysis calculated for $C_{48}H_{44}N_6O_8Cu\cdot 6H_2O$: C, 57.39; H, 5.62; N, 8.37. Found: C, 57.88; H, 5.20; N, 8.45%. This complex was formed between pH ≈3.0 and 8.0, and the yield ranges from 36–50%. At pH > 8, lower yields (< 25%) were obtained. At pH ≈ 9, bis(4-phenyloxazolidine-4′-carboxylato)copper(II), **4b**, was isolated as evidenced by its infrared spectrum.[10]

Structure determination of 5b

The 21,658 room-temperature intensities for a selected crystal of size 0.50 × 0.46 × 0.28 mm were collected to $\theta = 29.17°$ at 293 K on a Siemens CCD area-detector diffractometer that was equipped with Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods and refined on F^2 to $R = 0.053$ for 5277 ($I \geq 2\sigma(I)$) reflections.[12] The carbon- and nitrogen-bound hydrogen atoms were generated geometrically; the water hydrogen atoms were found by the HYDROGEN option[13] in the WinGX suite,[14] but these were not refined. The structure is

Table 1 Selected bond distances (Å) and angles (°) for **5b**

Cu(1)–O(1)	1.953(2)	Cu(1)–N(1)	2.046(3)
Cu(1)–N(3)	2.060(3)	Cu(1)–O(4)	2.293(3)
Cu(1)–O(5)	1.950(2)	Cu(1) ··· O(8)^{i}	3.379(4)
O(1)–Cu(1)–O(4)	99.3(1)	O(1)–Cu(1)–O(5)	163.6(1)
O(1)–Cu(1)–N(1)	84.9(1)	O(1)–Cu(1)–N(3)	96.5(1)
O(4)–Cu(1)–O(5)	96.8(1)	O(4)–Cu(1)–N(1)	88.7(1)
O(4)–Cu(1)–N(3)	92.3(1)	O(5)–Cu(1)–N(1)	93.1(1)
O(5)–Cu(1)–N(3)	85.3(1)	N(1)–Cu(1)–N(3)	178.2(1)

Symmetry transformation: i: $1 - x$, $\frac{1}{2} + y$, $1\frac{1}{2} - z$.

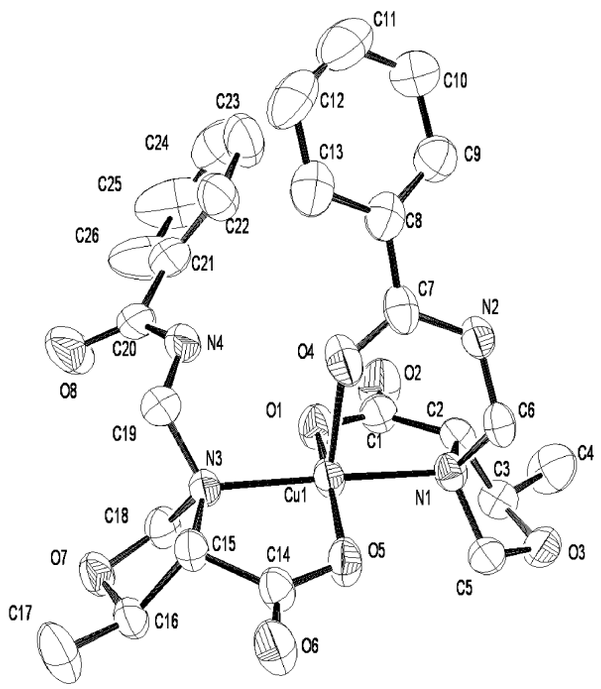


Fig. 1 Molecular structure of **5b** showing all non-hydrogen atoms at 50% probability level and the atom numbering scheme. The two lattice water molecules are not shown.

illustrated as an ORTEP plot[15] in Fig. 1. Selected bond lengths and angles are given in Table 1.

Crystal data/refinement data. $C_{26}H_{34}N_4O_{10}Cu$, M = 626.11, orthorhombic, $P2_12_12_1$, a = 12.2944(2), b = 12.4471(1), c = 19.7477(3) Å, ρ = 1.376 g cm^{-3}, V = 3021.98(7) Å^3, Z = 4, μ = 0.781 mm^{-1}, N = 21 658, N_o ($I \geq 2\sigma(I)$) = 5277, R = 0.053, R_w = 0.123.

CCDC reference number 180977.

See http://www.rsc.org/suppdata/dt/b2/b202955c/ for crystallographic data in CIF or other electronic format.

3 Results and discussion

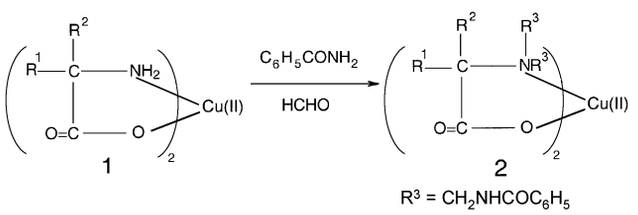
Chemistry of $Cu(aa)_2$ + HCHO + $C_6H_5CONH_2$ reactions

In the Mannich aminomethylation of chelated amino acids by formaldehyde and a third substrate, there exists possible competition from aldol-type condensation. This is because chelated α-amino acids with α-hydroxyalkyl substituents have undergone aldol-type condensation with formaldehyde alone, in the absence of base, to yield complexes containing oxazolidine rings.[11,16,17] However, $M(gly)_2$ and chelated α-alkyl substituents need a base to react similarly to yield such oxazolidine-containing complexes.[10,16–19]

In the present investigation, the series of $Cu(aa)_2$ **1** can thus be grouped into two categories: the first group comprises $Cu(gly)_2$, $Cu(L\text{-}ala)_2$ and $Cu(C\text{-}\phi gly)_2$, in which the latter two are α-alkyl substituted copper(II) chelated glycine; and the second set comprises $Cu(L\text{-}ser)_2$, $Cu(L\text{-}threo)_2$ and $Cu(OHMe\text{-}ser)_2$ complexes which are α-hydroxyalkyl substituted copper(II) chelated glycine.

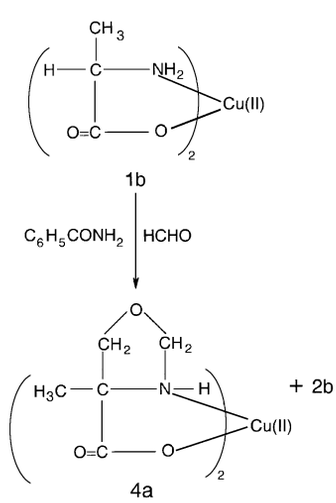
All the related synthesized complexes **2a**, **2b**, **2c**, **3a**, **5a**, and **5b**, obtained from the reactions of various $Cu(aa)_2$ with formaldehyde and benzamide, exhibit typical coordinated carboxylate asymmetric and symmetric stretching frequencies at ≈1600 cm^{-1} and ≈1400 cm^{-1} respectively. Peaks attributed to Cu–N stretching between 500 and 400 cm^{-1} observed for unreacted chelated amino acids are similarly observed for the above complexes.[20] Their infrared spectra also possess an amide NH peak at ≈3060 cm^{-1}, which is similarly observed for (i) $M^{II}[DMeA\text{-}gly]_2$ complexes[6] and (ii) $Cu^{II}[Me\text{-}MeB\text{-}\beta\text{-}ala]_2$ and $M^{II}[DMeB\text{-}\beta\text{-}ala]_2$ complexes.[7] These IR data indicate that the above series of complexes are the result of the reactions of their corresponding chelated amino acids, $Cu(aa)_2$, with formaldehyde and benzamide. Furthermore, microanalytical data supports the postulated formulae of these complexes.

The first series of $Cu(aa)_2$, comprising $Cu(gly)_2$ **1a** ($R^1 = R^2 =$ H), $Cu(L\text{-}ala)_2$ **1b** (R^1 = H, $R^2 = CH_3$), and $Cu(C\text{-}\phi gly)_2$ **1c** (R^1 = H, $R^2 = C_6H_5$), reacted with formaldehyde and benzamide to give **2a**, **2b** and **2c** respectively (Scheme 1). Their infrared



Scheme 1

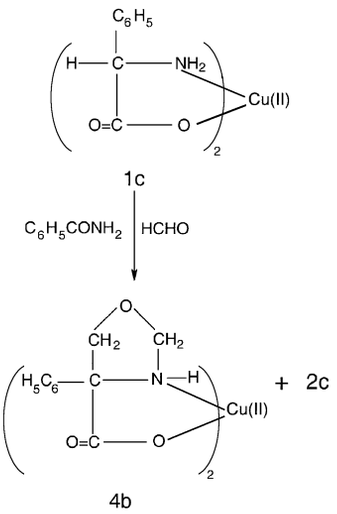
spectra also has an absence of the amino proton peak at ≈3160 cm^{-1} and this indicates both amino protons have been substituted. Hence, **1a**, **1b** and **1c** are postulated to have undergone *N*,*N*-diaminomethylation to yield two *N*-methylbenzamido substituents. These complexes are shown as **2**. Nevertheless, the oxazolidine-containing complex **4a** is also recovered together with **2b** from the reactions of $Cu(L\text{-}ala)_2$ with formaldehyde and benzamide at pH 9.0–10.0 (Scheme 2); similarly, **4b** was formed



Scheme 2

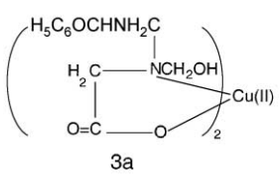
from the corresponding reactions of $Cu(C\text{-}\phi gly)_2$ at pH ≈ 9 (Scheme 3).

In one of the reactions of $Cu(gly)_2$ **1a** with formaldehyde and benzamide (see Experimental section), we managed to isolate an intermediate complex bis[{*N*-hydroxymethyl-*N*-(*N*-methylbenzamido)}glycinato]copper(II) **3a**. In its infrared spectrum, there is an absence of the peak at ≈3160 cm^{-1}; this shows the absence of amino protons and that both amino protons of **1a**

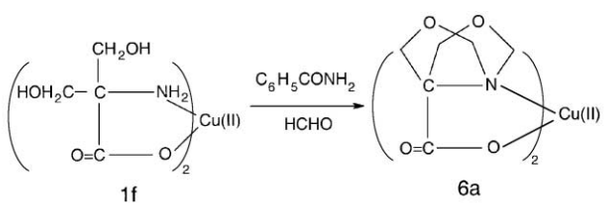


Scheme 3

have been substituted. An amide peak at 3067 cm^{-1} confirms the formation of at least one *N*-methylbenzamido substituent. Elemental analysis supports the postulated *N*-hydroxymethylation and Mannich aminomethylation of **1a**. The isolation of **3a** supports our contention that **2** has to be formed from this complex and thus lend support to the reaction mechanism to be outlined latter.

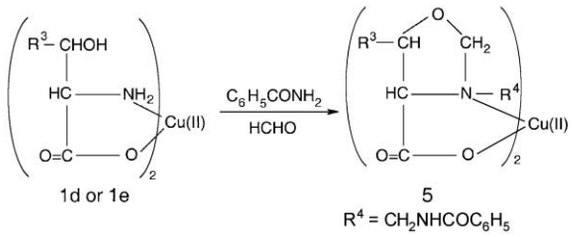


In contrast, the second series of $Cu(aa)_2$ **1**, consisting of $Cu(L\text{-ser})_2$ **1d** (R^1 = H, R^2 = CH_2OH), $Cu(L\text{-threo})_2$ **1e**, $Cu(OHMe\text{-ser})_2$ **1f**, yielded different types of complexes. Under all pH values investigated **1f** (which has two α-hydroxymethyl substituents) merely reacted with formaldehyde, *i.e.* it has undergone an aldol-type condensation, to yield **6a** which contains two oxazolidine rings; no Mannich reaction has occurred (Scheme 4). The $Cu(L\text{-ser})_2$ **1d** reacted with formaldehyde and



Scheme 4

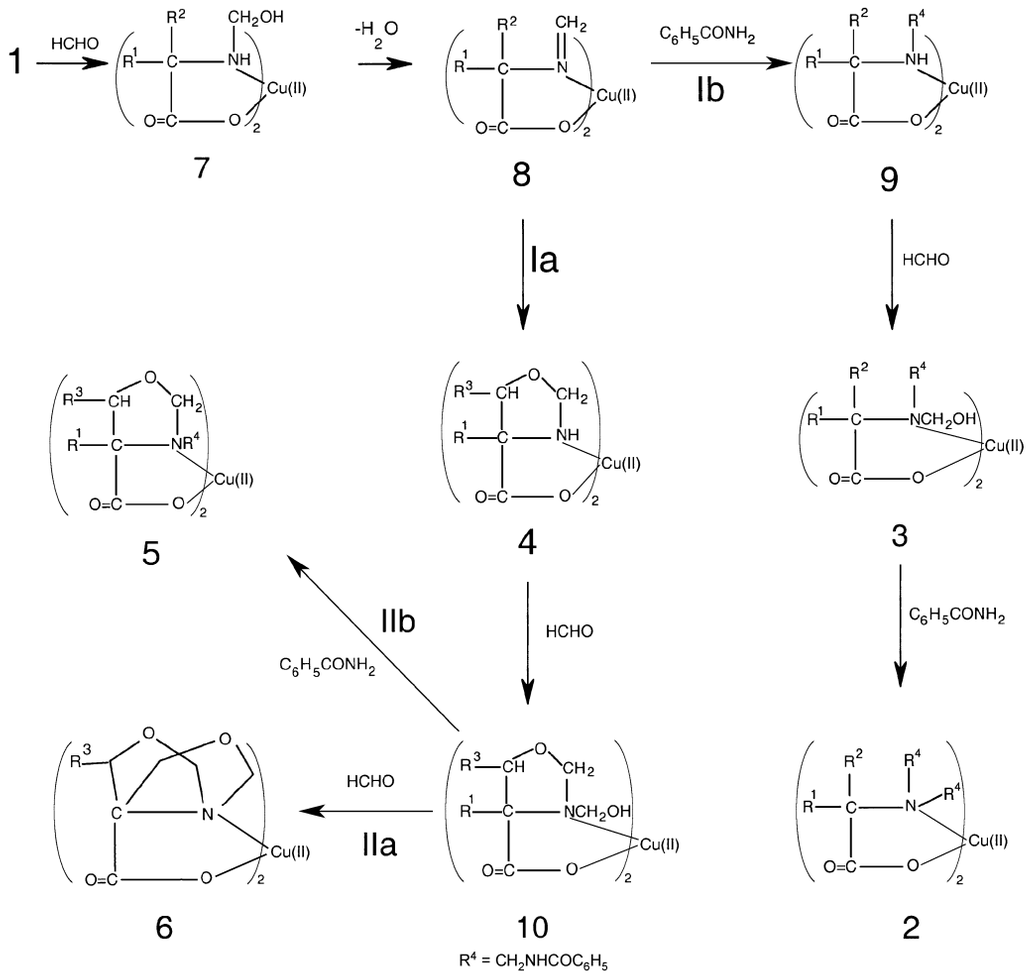
benzamide to produce the complex **5a** which has an infrared spectrum showing an amide NH peak (3060 cm^{-1}) and a triplet in the 1200–1050 cm^{-1} region characteristic of an oxazolidine ring system.[16,19,21] This suggests that **5a** has one *N*-methylbenzamido pendant arm and one oxazolidine ring per chelated serine moiety. Microanalytical results support the postulated structure. The infrared spectrum of **5b** obtained from the reaction of $Cu(L\text{-threo})_2$ **1e**, formaldehyde and benzamide shows similar features, *i.e.* the amide and oxazolidine peaks. The structures of both reaction products are therefore similar. The crystal structure determination of **5b** (Fig. 1) confirms the postulated structure. Thus, **5a** and **5b** are depicted as structure **5** in Scheme 5. Finally, for the reactions of **1d** at pH > 10, the recovery of only **6a**, a bis(oxazolidine) complex, shows that aldol-type condensation occurs without Mannich aminomethylation.



Scheme 5

Scheme 6 is proposed to help rationalize the various results obtained. $Cu(aa)_2$ complex, **1**, is easily *N*-hydroxymethylated by formaldehyde in basic and non-basic media[5,7,21] to yield a *N*-hydroxymethyl derivative, **7** (a carbinolamine). Subsequent elimination of a water molecule results in the formation of an *exo*-imine intermediate, **8**. Similar imine intermediates have been isolated and the imine carbon atom is known to be partially activated towards attack by nucleophiles.[22] Benzamide is weakly acidic ($pK_a \approx 14.5$); both itself and its conjugate base are nucleophilic.[23] The oxygen atom of the α-hydroxyalkyl substituent of $Cu(aa)_2$ is also nucleophilic due to lone pairs of electrons. As a consequence, two competing processes occur and the ensuing reaction of **8** can proceed along two different pathways, **Ia** and **Ib**. When R^2 is a hydroxyalkyl substituent [**1** is then $Cu(L\text{-ser})_2$ **1d**, $Cu(L\text{-threo})_2$ **1e** or $Cu(OHMe\text{-ser})_2$ **1f**], pathway **Ia** is preferred and the oxazolidine ring in complex **4** is formed from the cycloaddition of the α-hydroxyalkyl substituent of **8** to its own imine. When R^2 is a proton or an alkyl substituent [**1** is **1a**, **1b** or **1c**], the reaction proceeds along pathway **Ib** where the deprotonated benzamide attacks each imine group to yield the *N*-methylbenzamido derivative **9**. Pathways **Ia** and **Ib** can be viewed as an intramolecular cyclization and intermolecular condensation pathway respectively. Subsequently, both **9** and **4** are again *N*-hydroxymethylated by formaldehyde and an iminium intermediate with an uncoordinated nitrogen is believed to be formed prior to further reaction.[7] The second *N*-methylbenzamido substituent in **2** is thus formed from **9** in a manner similar to that reported for the formation of $M^{II}[DMeB\text{-}\beta\text{-}ala]_2$ from the reaction of $M(\beta\text{-}ala)_2$ with formaldehyde and benzamide.[7] Though the iminium intermediate has not been isolated, iminium salts have been utilized as Mannich reagents in aminomethylation of various substrates.[24] However, under suitable conditions (*e.g.* sufficiently high pH), the intermediate **8** for $Cu(L\text{-ala})_2$ **1b** seems to undergo parallel reactions to yield both the aldol condensation complex **4** and the Mannich aminomethylation complex **2**. The formation of both oxazolidine-complexes **4a** (**4**, R^1 = H, R^3 = CH_3) and **4b** (**4**, R^1 = phenyl, R^2 = H) at higher pH necessitates the prior α-hydroxymethylation of $Cu(L\text{-ala})_2$ **1b** and $Cu(C\text{-}\phi gly)_2$ **1c** by formaldehyde *via* abstraction of an α-carbon proton by base; this is consistent with earlier studies of $M(L\text{-ala})_2$ reactions with formaldehyde.[10]

For $Cu(L\text{-threo})_2$ **1e** reactions, the intermediate **10a** (R^1 = H, R^3 = CH_3) undergoes further reaction with benzamide to give the final complex **5b** (R^1 = H, R^3 = CH_3); an intermediate **10a** (R^1 = H, R^3 = CH_3 in **10**) has previously been isolated.[21] Complex **10a** (synthesized by directly reacting **1e** with formaldehyde), when treated with formaldehyde and benzamide in a separate reaction, yields the same product **5b**; this result supports the proposed formation of **5b** from **10a**. For the $Cu(L\text{-ser})_2$ **1d** reactions, the subsequent reaction of **10b** (R^1 = R^3 = H in **10**) can proceed along pathway **IIa** or **IIb**, depending on pH. At pH > 10, pathway **IIa** is preferred and the bis(oxozolidine)copper(II) complex, **6a** (R^3 = H in **6**), is formed. No such competitive reaction has been observed for the reactions involving **1e**; this can be explained on the basis of the inability of the base to abstract the α-carbon proton in **10** (R^1 = H, R^3 = CH_3) and thereby allow α-hydroxymethylation by formaldehyde.



Scheme 6

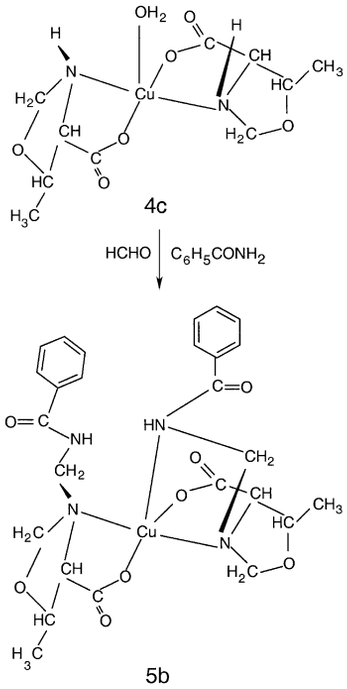
In the above overall reaction scheme, both series of reaction steps (i) **1** ⟶ **7** ⟶ **8** ⟶ **4** and (ii) **4** ⟶ **10** ⟶ **6**, which yield oxazolidine-containing complexes, constitute aldol-type condensation. The other series of reaction steps (iii) **1** ⟶ **7** ⟶ **8** ⟶ **9**, (iv) **9** ⟶ **3** ⟶ **2** and (v) **4** ⟶ **10** ⟶ **5**, which yield complexes with *N*-methylbenzamido substituents, constitute Mannich aminomethylation. As such, the present findings have shown that both the nature of the α-carbon substituent of the $Cu(aa)_2$ and the pH predisposes the choice of reaction pathway – aldol-type condensation or Mannich aminomethylation. For the special case involving $Cu(OHMe\text{-}ser)_2$ **1f**, the isolation of only **6a** shows aldol condensation is the preferred reaction and both α-hydroxymethyl substituents in **1f** have successfully competed with the benzamide and this result supports our proposal that **5** is formed *via* an initial aldol condensation and a subsequent Mannich aminomethylation.

Description of the crystal structure of 5b

This complex **5b** (Fig. 1, Table 1) is formed from the reaction of $Cu(\text{L-threo})_2$ with formaldehyde and benzamide. Each threonine moiety has an oxazolidine ring and one *N*-methylbenzamido substituent. The oxazolidine ring arises from an aldol-type condensation of the threonine moiety with formaldehyde as has been found to occur in the reaction of $Cu(\text{L-threo})_2$ with formaldehyde alone.[21] The *N*-methylbenzamido substituent is formed from a Mannich reaction between the threonine moiety, formaldehyde and benzamide.

The structure of **5b** bears close resemblance to that of bis(5-methyloxazolidine-4-carboxylato)copper(II) dihydrate,[21] **4c**. In the latter, the single amino proton in 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 *N*-methylbenzamido substituent and the oxazolidine ring of each threonine moiety in **5b** are likewise similarly orientated. This suggests that **4c** is formed first and it then reacts with more formaldehyde and benzamide to yield **5b** (Scheme 7); in this postulated sequence, the reaction occurs on the same side as the amino proton and the *N*-methylbenzamido group substitutes the amino proton of the threonine moiety in **4c**, *i.e.* the substitution is stereospecific. A similar conclusion is suggested in the *N*-hydroxymethylation of chelated amino acids.[25] Further evidence for this postulated pathway **1e** ⟶ **4c** ⟶ **10a** ⟶ **5b** and this stereospecificity is obtained when two separate reactions, (i) **4c** with formaldehyde and benzamide and (ii) **10a** with formaldehyde, yield the same complex **5b**.

The copper atom in **5b** is five-coordinate in a distorted square pyramidal geometry (81% along the trigonal bipyramidal–square pyramid Berry pseudorotation pathway). The two anionic ligands chelate through their carboxyl oxygen and tertiary nitrogen atoms such that the N_2O_2 donor atoms forming the basal plane (which is non-planar with a mean deviation of 0.120 Å) has a *trans*-configuration. Characteristically, the copper atom lies 0.157 Å out of the N_2O_2 basal plane in the direction of the apical atom (apical bond length, 2.293(3) Å). The benzamido oxygen atom of the second anion interacts with an adjacent molecule [Cu ⋯ O = 3.379(4) Å] to furnish a linear chain along the *c*-axis of the orthorhombic unit cell as shown in Fig. 2. Steric repulsion prevents further approach of this benzamido oxygen atom and hexa-coordination for copper is not achieved. The N3–Cu1–N1 basal angle (178.2°) could have been straightened due to steric interaction as such angles



Scheme 7

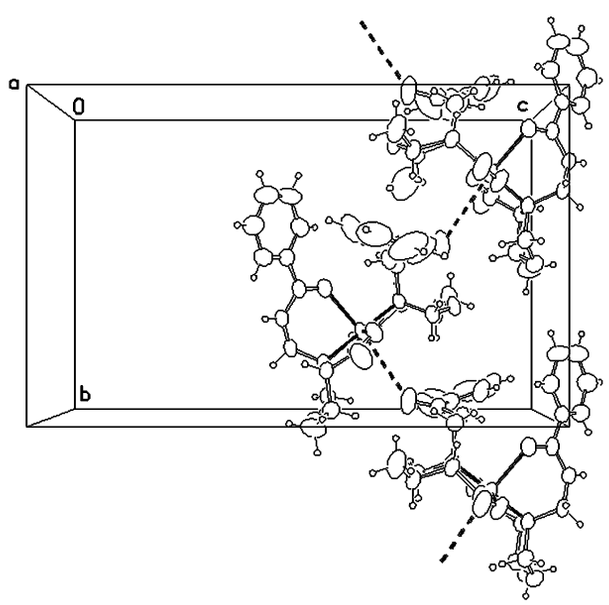


Fig. 2 Diagram showing the polymeric nature of the **5b** molecules.

in other bis(oxazolidine)copper(II) complexes [11,21] are more bent (165.8, 161.6°).

4 Conclusion

Competing processes occur in the reactions of $Cu(aa)_2$ with formaldehyde and benzamide. The nature of the α-carbon substituent of the chelated amino acid and the pH determine the preferred pathway. For $Cu^{II}[OHMe\text{-}ser]_2$, the two α-hydroxymethyl substituents successfully competed with the benzamide to yield the intramolecular aldol condensation complex, a bis(oxazolidine)copper(II). For $Cu(aa)_2$ with one reactive α-hydroxyalkyl substituent per amino acid moiety, aldol condensation occurs first prior to Mannich aminomethylation and the resultant complexes posses an oxazolidine ring and an *N*-methylbenzamido pendant arm. In contrast, $Cu(gly)_2$ and those complexes with unreactive α-alkyl substituent, are *N*,*N*-diaminomethylated to yield the di(*N*-methylbenzamido)-substituted complexes. However, higher pH can result in α-hydroxymethylation by formaldehyde and thus hinder Mannich aminomethylation.

Acknowledgements

We thank Tunku Abdul Rahman College (01–1404), the Universiti Sains Malaysia (304/PKIMIA/63306) and University of Malaya (PJP 0717/2002A) for supporting this work. The X-ray diffraction measurements were carried out by Professor Hoong Kun Fun of the School of Physics, Universiti Sains Malaysia.

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