

A New Synthetic Method of Zinc(II) Complexes Based on Mixing

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An environmentally benign new synthetic method of zinc(II) complexes without the use of organic solvents and alkali was developed, and several types of zinc(II) complexes in high yields were prepared by mixing solid ligands with solid $\text{Zn}(\text{OH})_2$ or ZnO .

Key words—zinc(II) complex; mixing; (L-carnosinato) zinc(II) complex; amino acid; heterocyclic ligand

INTRODUCTION

Previously, the preparation of zinc(II) (Zn(II)) complexes required ligands to react with Zn(II) reagents in the presence or absence of alkali in a large quantity of aqueous solution or organic solvents at room temperature or under heating.^{1–17)} However, that method has the disadvantages of increased costs of Zn(II) complexes due to the alkali and large quantity of organic solvents required, along with the undesirable effects on the environment and human health alkali used.

This paper reports a new method to obtain Zn(II) complexes at high yields (more than 90%) by direct mixing of solid ligands and solid $\text{Zn}(\text{OH})_2$ or ZnO with or without the addition of a minimum amount of water without the use of alkali and organic solvents.

RESULTS AND DISCUSSION

Crystalline (L-carnosinato) Zn(II) complex (**2**)^{1,2,18–20)} (generic name, polaprezinc; trade name, Promac), developed first as an agent for the treatment of gastric ulcer and which contains Zn(II), is manufactured in large quantities by the reaction of L-carnosine (β -alanyl-L-histidine) (**1**) and zinc acetate dehydrate with sodium methoxide in a volume of methanol approximately 30-fold the volume of **1**. However, using the mixing method in this study, **2** was easily obtained quantitatively. Specifically, **2** was prepared in 97% yield by drying a well-kneaded pasty mixture of **1** and $\text{Zn}(\text{OH})_2$ with a minimum amount of water at 80–90°C for 5 h to give a white crystalline powder. This pasty mixture was allowed to stand at

room temperature for 2 days and dried under reduced pressure over silicic anhydride at room temperature for 1 day to give amorphous (L-carnosinato) Zn(II) complex (**3**)^{1,3)} as a white powder in 97% yield (Chart 1).

The structures of the **2** and **3** obtained using the mixing method were confirmed by comparison with the IR spectra of previously obtained authentic samples of **2**^{1,2)} and **3**.^{2,3)} Compound **2**^{1,2)} has a characteristically sharp IR spectrum and X-ray powder diffraction pattern when compared with that of **3**, and hence **2** and **3** obtained by the mixing method could be clearly distinguished. Based on these experimental results, the molecular structure of (L-carnosinato) Zn(II) complex is expected to be in the regular crystalline polymer state due to the influence of heat.

Other Zn(II) complexes (**4–11**)^{4–17)} were prepared by mixing different solid ligands with $\text{Zn}(\text{OH})_2$ or ZnO at a 2 : 1 or 1 : 1 molar ratio with or without the addition of a minimum amount of water at room temperature (maximum yield 98%, minimum 90%) (Table 1).

For example, a mixture of picolinic acid (pic) with $\text{Zn}(\text{OH})_2$ or ZnO at a 2 : 1 molar ratio with a minimum amount of water was allowed to stand at room temperature for 2 days, followed by vacuum drying over silicic anhydride at room temperature for 1 day to give bis (picolimate) Zn(II) complex (**4**)^{4,5)} in 95% yield. When this reaction was carried out without water, mixtures of **4** and pic, which were confirmed by comparison with the IR spectra of **4** and pic, were obtained. The mixtures were recrystallized from water and **4** was obtained in 59% yield. It is thought that the mixtures of ligand (acid) and Zn(II) reagent (base) are homogenized by the influence of water

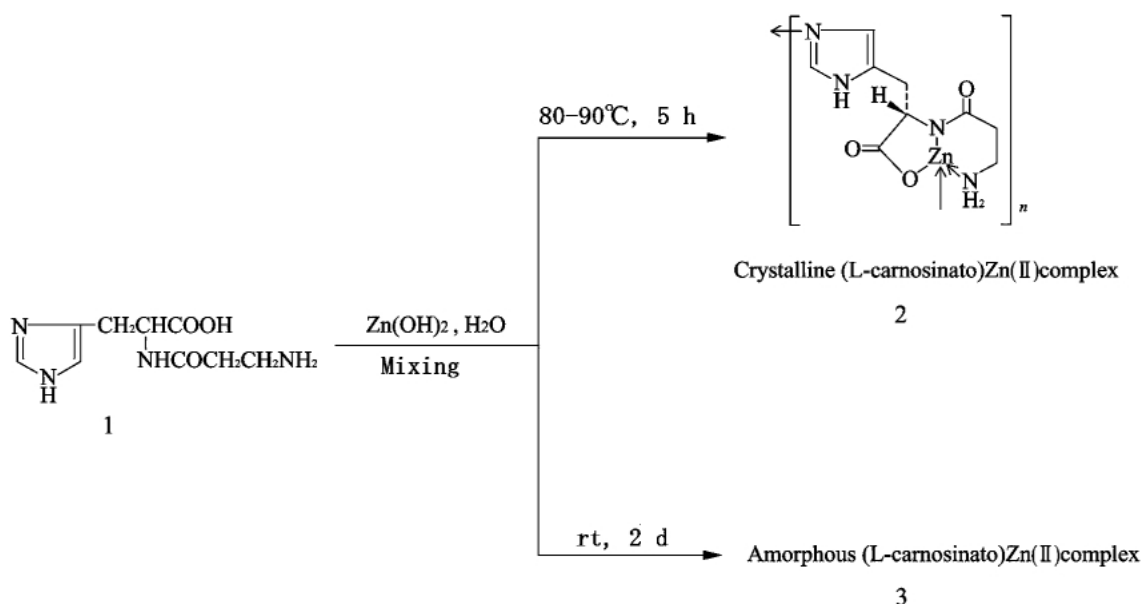


Chart 1

Table 1. Synthetic Data on Zn (II) Complexes (4–11)

No.	Zn (II) complex	Reaction conditions		Yield (rec*) %	mp (dec. °C) (rec*)	IR (KBr) cm ⁻¹ C=O (rec*)	Formula	Elemental analysis (%)			Ref.
		Reagent	H ₂ O					Calcd. [C H N]	Found (rec*) C H N		
4	bis (Picolinato)	Zn (OH) ₂	Yes	97 (84)	222–225 (225–227)	1635 (1635)	C ₁₂ H ₈ N ₂ O ₄ Zn·4H ₂ O	37.87 (37.79)	4.25 (4.20)	7.26 (7.37)	4, 5
		Zn (OH) ₂	No	(59)	(225–227)	(1635)	[37.76 4.22 7.34]	(37.83)	(4.30)	(7.31)	4, 5
		ZnO	Yes	90	222–225	1635		37.86	4.26	7.29	
5	bis (Imidazolato)	Zn (OH) ₂	No	98	>300	1600	C ₆ H ₆ N ₄ Zn·0.5H ₂ O	34.32	3.37	26.71	6
		ZnO	No	94	>300	1600	[34.5 3.38 26.86]	34.39	3.23	26.60	
6	bis (Maltolato)	Zn (OH) ₂	No	97 (86)	144–150 (144–150)	1615 (1615)	C ₁₂ H ₁₀ O ₆ Zn·2.5H ₂ O	39.89 (39.93)	4.24 (4.17)		5, 7, 8
7	(N-Acetyl-L cysteinato)	ZnO (OH) ₂	Yes	93 (80)	275–280 (277–282)	1620 (1620)	C ₅ H ₇ N ₃ O ₃ Zn·H ₂ O	24.67 (24.64)	3.81 (3.77)	5.76 (5.70)	9
8	bis (Glycinato)	Zn (OH) ₂	Yes	91 (82)	>300	1600 (1600)	C ₄ H ₈ N ₂ O ₄ Zn·H ₂ O	20.69 (20.72)	4.41 (4.37)	11.97 (12.05)	10–13
9	bis (L-α-alaninato)	Zn (OH) ₂	Yes	93 (85)	>300	1610 (1610)	C ₆ H ₁₂ N ₂ O ₄ Zn·H ₂ O	27.61 (27.68)	5.47 (5.49)	10.84 (10.73)	13, 14
10	bis (L-β-alaninato)	Zn (OH) ₂	Yes	92	230 (vicinity)	1620	C ₆ H ₁₂ N ₂ O ₄ Zn·2H ₂ O	26.14	5.71	9.98	15
		ZnO	No	90	230 (vicinity)	1620	[25.96 5.80 10.09]	26.22	5.65	9.91	
11	bis (L-phenyl- alaninato)	Zn (OH) ₂	Yes	90	275–280	1625	C ₁₈ H ₂₀ N ₂ O ₄ Zn·2H ₂ O	50.41	5.74	6.43	16, 17
							[50.30 5.62 6.51]				

* The values of Zn (II) complexes recrystallized with water.

molecules generated during the mixing reaction, thereby allowing the mixing reaction to proceed. The minimum amount of water added was assumed to act like a catalyst.

These Zn (II) complexes, listed in Table 1, were all already known, and thus their structures were confirmed by comparison of their IR spectra and melting points (mp) with those of established Zn(II) complexes. Further, water-soluble Zn (II) complexes (4,

6, 7, and 9) that were purified by means of recrystallization from water had IR spectra completely identical with those of the original Zn (II) complexes used for purification; their mp and elemental analysis values were also essentially the same. The purities and physical properties of the Zn (II) complexes prepared by mixing were essentially unchanged before and after purification. Consequently, it appears that the quality of the Zn (II) complexes prepared by direct mixing of

solid ligands and solid Zn(II) reagents without the use of organic solvents and alkali is high. bis (Maltoato) Zn(II) complex (6)^{5,7,8)} and (*N*-acetyl-L-cysteinato) Zn(II) complex (7)⁹⁾ (Table 1) have excellent antidiabetic activity in KK-A^y mice with type II diabetes mellitus.

This new mixing method is easy and useful for the synthesis of Zn(II) complexes and has environmental and human health advantages. It is planned to prepare other metal complexes using this mixing method.

CONCLUSION

Zn(II) complexes were prepared in high yields by directly mixing solid ligands with Zn(OH)₂ or ZnO.

EXPERIMENTAL

Materials and Methods Zn(OH)₂ was used as obtained from Kisida Chemical Industries (Japan). Other reagents were purchased from Wako Pure Chemical Industries (Japan). All reagents were used without further purification. Melting points were measured with a Yamagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-5300 spectrometer. Elemental analyses were carried out at the Center for Instrumental Analysis of Kyoto Pharmaceutical University.

Crystalline (L-carnosinato) Zn(II) Complex (2)^{1,2)} A mixture of β-Alanyl-L-histidine (L-carnosine) (1) (566 mg, 2.5 mmol), Zn(OH)₂ (248 mg, 2.5 mmol), and water (0.8 ml) was ground using an agate mortar and pestle at room temperature, and the pasty mixture was dried for 5 h at 80–90°C to give 2 (705 mg, yield 97%) as a white crystalline powder, mp > 300°C. IR (KBr) cm⁻¹: 3290, 1625, 1562, 1480, 1390, 1261, 1230, 1120, 1060, 1000, 983, 660. *Anal.* Calcd. for C₉H₁₂N₄O₃Zn: C, 37.32; H, 4.17; N, 19.34. Found: C, 37.26; H, 4.24; N, 19.26.

Amorphous (L-carnosinato) Zn(II) Complex (3)^{2,3)} a) 1 (566 mg, 2.5 mmol) and Zn(OH)₂ (248 mg, 2.5 mmol) were mixed with water (0.8 ml) at room temperature, and the pasty mixture was allowed to stand at room temperature for 5 days, and dried under reduced pressure at room temperature for 2 days to give 3 (827 mg, yield 97%) as a white powder, mp > 300°C. IR (KBr) cm⁻¹: 3260 (br.), 1600 (br.), 1400, 1250 (br.), 1120, 1050, 980, 660. *Anal.* Calcd. for C₉H₁₂N₄O₃Zn · 2.5H₂O: C, 32.30; H, 5.11; N, 16.74 Found: C, 32.50; H, 4.98; N, 16.65.

b) A mixture of 4 (113 mg, 0.5 mmol), ZnO (81 mg, 0.5 mmol), and water (0.25 ml) was allowed to stand at room temperature for 8 days to give 3 (150 mg, yield 90%) as a white powder, mp > 300°C. The IR spectrum was the same as that in method a).

bis (Picolinato) Zn(II) Complex (4)^{4,5)} a) A mixture of pic (615 mg, 5 mmol), Zn(OH)₂ (248 mg, 2.5 mmol), and water (0.3 ml) was mixed using an agate mortar and pestle at room temperature for 5 min. The mixture was allowed to stand at room temperature for 2 days, followed by vacuum drying over silicic anhydride in a desiccator at room temperature for 1 day to give 4 (929 mg, yield 97%) as a white crystalline powder, mp 222–225°C (dec.). Compound 4 was recrystallized from water to give 833 mg (yield 87%) of 4 as colorless crystals, mp 225–227°C (dec.).

b) A mixture of pic (123 mg, 1 mmol) and Zn(OH)₂ (49.7 mg, 0.5 mmol) was ground to a fine powder using a mortar and pestle. The mixture was allowed to stand at room temperature for 2 days and then dried *in vacuo* at room temperature for 2 days to give a mixture of 4 and pic as a white crystalline powder, mp 100–105°C (dec.). The IR spectrum was almost identical to that of the mixture of equal amounts of pic and 4. The mixture was purified from water to give 4 (111 mg, yield 59%) as colorless crystals, mp 225–227°C (dec.). The IR spectrum was the same as that obtained in method a).

c) Compound 4 was obtained in a manner similar to method a) from pic (615 mg, 5 mmol) and ZnO (202 mg, 2.5 mmol) with water (0.6 ml) [844 mg, yield 90%, mp 222–225°C (dec.) as a white crystalline powder]. The IR spectrum was the same as that obtained in method a).

bis (Imidazolato) Zn(II) Complex (5)⁶⁾ a) Imidazole (340 mg, 5 mmol) and Zn(OH)₂ (248 mg, 2.5 mmol) were mixed well in an agate mortar with an agate pestle at room temperature for 2 min. The mixture first became pasty and solidified after 5 min. The solid was allowed to stand at room temperature for 2 days, and then it was dried under reduced pressure over silicic anhydride in a desiccator at room temperature overnight to give 5 (510 mg, yield 98%) as colorless crystals, mp > 300°C.

b) A mixture of imidazole (136 mg, 2 mmol) and ZnO (81 mg, 1 mmol) was allowed to stand at room temperature for 3 days, and dried *in vacuo* at room temperature overnight to give 5 (200 mg, yield 94%)

as a white crystalline powder, mp > 300°C. The IR spectrum was the same as that obtained in method a).

(N-Acetyl-L-cysteinato) Zn(II) Complex (7)⁹⁾
A mixture of *N*-acetyl-L-cysteine (407 mg, 2.5 mmol), Zn(OH)₂ (248 mg, 2.5 mmol) and water (0.15 ml) was treated in a manner similar to method a) of 4 to give 7 (570 mg, yield 93%) as a white crystalline powder, mp 275–280°C (dec.). After 7 was dissolved in water (10 ml), the solution was concentrated to approximately 1 ml under reduced pressure at 50°C, and ethanol (15 ml) was added to the residue to give 490 mg (yield 80%) of 7 as white crystals, mp 277–282°C (dec.). The IR spectrum was the same as that obtained in the method described above.

bis (Maltolato) Zn(II) Complex (6)^{5,7,8)}, bis (glycinato) Zn(II) Complex (8)^{10–13)}, bis (L- α -alaninato) Zn(II) Complex (9)^{13,14)}, bis (L- β -alaninato) Zn(II) Complex (10)¹⁵⁾, and bis (L-phenylalaninato) Zn(II) Complex (11)^{16,17)}
These Zn(II) complexes were prepared in a manner similar to method a), b), or c) of 4 using the corresponding ligands (2.5 mmol) and Zn(OH)₂ or ZnO (1.25 mmol) as a white crystalline powder (the Zn(II) complexes recrystallized by water; colorless crystals) (see Table 1).

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