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 Zn(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. 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 Zn(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) (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 Zn(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) 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 and 3. Compound 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) were prepared by mixing different solid ligands with Zn(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 Zn(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 days to give bis (picolinato) Zn(II) complex (4) 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.

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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

<table>
<thead>
<tr>
<th>No.</th>
<th>Zn(II) complex</th>
<th>Reaction conditions</th>
<th>Yield (rec%)</th>
<th>mp (dec. °C)</th>
<th>IR (KBr) cm⁻¹</th>
<th>Elemental analysis (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Kegumt</td>
<td>H₂O</td>
<td>%</td>
<td>(rec%)</td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>4</td>
<td>bis (Picolinato) Zn(OH)₂</td>
<td>Yes</td>
<td>97(84)</td>
<td>222 225</td>
<td>1635(1655)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>37.87(37.79)</td>
</tr>
<tr>
<td>5</td>
<td>bis (Imidazole) Zn(OH)₂</td>
<td>No</td>
<td>98(94)</td>
<td>222 225</td>
<td>1650(1655)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>34.32(34.28)</td>
</tr>
<tr>
<td>6</td>
<td>bis (Maltolato) Zn(OH)₂</td>
<td>No</td>
<td>97(86)</td>
<td>222 225</td>
<td>1650(1655)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>39.89(39.93)</td>
</tr>
<tr>
<td>7</td>
<td>(L-Acetyl-L-cysteinate) Zn(OH)₂</td>
<td>Yes</td>
<td>93(80)</td>
<td>275 280</td>
<td>1620(1620)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>24.67(24.64)</td>
</tr>
<tr>
<td>8</td>
<td>bis (Glycinato) Zn(OH)₂</td>
<td>Yes</td>
<td>91(82)</td>
<td>229 270</td>
<td>1620(1620)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>24.55(24.62)</td>
</tr>
<tr>
<td>9</td>
<td>bis (L-hisalaminato) Zn(OH)₂</td>
<td>Yes</td>
<td>93(85)</td>
<td>230 270</td>
<td>1620(1620)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>26.14(26.20)</td>
</tr>
<tr>
<td>10</td>
<td>bis (L-β-alaninato) Zn(OH)₂</td>
<td>Yes</td>
<td>92(82)</td>
<td>230 270</td>
<td>1620(1620)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>26.14(26.20)</td>
</tr>
<tr>
<td>11</td>
<td>bis (L-phenyl-alaninato) Zn(OH)₂</td>
<td>Yes</td>
<td>90(80)</td>
<td>275 280</td>
<td>1620(1620)</td>
<td>C₂H₂N₂O₂Zn·H₂O</td>
<td>26.14(26.20)</td>
</tr>
</tbody>
</table>

* The values of Zn(II) complexes recrystallized with water.
solid ligands and solid Zn(II) reagents without the use of organic solvents and alkali is high. bis (Mal-
tolato) Zn(II) complex (6)\(^{3,7,8}\) and (N-acetyl-L-
cysteinato) Zn(II) complex (7)\(^9\) (Table 1) have ex-
cellent antidiabetic activity in KK-A\(^+\) 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 pre-
pare 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 ap-
paratus and are uncorrected. IR spectra were record-
ed with a JASCO FT/IR-5300 spectrometer. Elemental
analyses were carried out at the Center for In-
strumental Analysis of Kyoto Pharmaceutical Univer-
sity.

**Crystalline (L-carnosinato) Zn(II) Complex**

(2)\(^2\) A mixture of \(\beta\)-Alanyl-L-histidine (L-car-
nosine) (I) (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,
1430, 1390, 1261, 1230, 1120, 1060, 1000, 983, 660. Anal.
Calcd. for C\(_{36}\)H\(_{57}\)N\(_{13}\)O\(_{12}\)Zn: C, 37.32; H, 4.17; N,

**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 al-
lowed 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 pow-
der, mp >300°C. IR (KBr) cm\(^{-1}\): 3260 (br.), 1600
(br.), 1400, 1250 (br.), 1120, 1050, 980, 660. Anal.
Calcd. for C\(_{36}\)H\(_{57}\)N\(_{13}\)O\(_{12}\)Zn\(\cdot\)2.5H\(_2\)O: 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 tem-
perature 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.). Com-
 pound 4 was recrystallized from water to give 333
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 pow-
der, 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 crys-
tals, 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 crystal-
line 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 pres-
sure 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)

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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REFERENCES