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Original Article

Synthesis and Determination of Partition Coefficients of Zinc Complexes with Clinical Potential application

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Abstract

Zinc sulphate is currently used for treatment of zinc deficiency. Its uptake by the body is poor, necessitating the administration of high doses. This leads to a range of unpleasant side effects. In order to increase the bioavailability of zinc, several zinc complexes have been designed and synthesized using bidentate ligands of hydroxypyranones and hydroxypyridinones. Elemental analysis in each zinc complex was consistent with the formulations of ZnL_2 species L: bidentate ligand) with 1.5 or 7 water molecules per zinc and the water molecules were removed by heating in a vacuum oven to yield anhydrous zinc complexes.

The partition coefficients (K_{part})of the complexes were also determined in 1-octanol/ buffer (at pH 7.40) system by using shake-flask method. It was found that, the complexes with hydroxypyranone ligands possess higher K_{part} values than those with hydroxypyidinone ligands. Therefore, the comparison of the complexes highlights the hydroxypyranone zinc complexes as the most promising candidates for using in zinc deficiency. Since it was anticipated that this type of complexes probably possesses suitable lipophilicity to facilitate their penetration into the gastrointestinal tract.

Keywords: Zinc complexes; Zinc deficiency; Hydroxypyranones; Hydroxypyridinones; Zinc sulfate.

Introduction

Zinc is an essential trace element in man, its major biochemical role being a constituent in a variety of metalloenzyme systems with catalytic, regulatory and structural functions (1,2). The Recommended Dietary Allowance (RDA) of zinc for adults in the U.S. was set at 15 mg per day, an amount normally provided by a balanced diet (3, 4).

Zinc deficiency in humans is common in many developed and developing countries (5). It is noteworthy that although newborn, children, pregnant women and old people are considered as the main risk groups; zinc deficiency may affect the whole population (6). The nutritional causes such as, decreased zinc intake or the consumption of foods with poor zinc content are the most important and common factors in zinc deficiency (7-11). In addition, several syndromes related to metabolic or genetic malfunctions such as malabsorption syndromes, acordermatitis, enteropathica, Crohn's disease, alcoholism, liver cirrhosis, chronic renal disease, sickle cell anemia and gastrointestinal disorders also provoke (determine) zinc deficiency (6, 11-14).

The forms of zinc used as nutritional supplementations or in food fortifications are zinc sulfate, zinc chloride, zinc gluconate, zinc

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oxide, and zinc stearate (1, 15-17). These five zinc salts have been approved as safe by the US Food and Drug Administration (FDA) (1). The total quantity of zinc salts used has notably increased since 1970, and the compounds used the most are zinc sulfate and zinc oxide (1, 15). At present, zinc gluconate has drawn more attention for food fortification or supplementation procedures as a proper zinc compound (6). The main disadvantages of these zinc salts are their unacceptable taste and the resulting nausea and dyspepsia. Uptake of zinc sulfate by the body is poor, therefore the administration of high doses is necessary. This leads to a range of unpleasant side effects, including abdominal pains, nausea, vomiting and severe headaches. Zinc oxide is poorly absorbed, and it precipitates in the nutritional matrix when zinc oxide is used to fortify liquid foods (1, 6, 16-18).

Building on previous work which suggested that chelators such as EDTA increased the bioavailability of zinc (19), together with the fact that a number of 3-hydroxypyran-4-one and 3-hydroxypyridin-4-one derivatives had been found to have a reasonably high affinity for zinc (log β_2 = 10.4 and 12.7 respectively) (20, 21), zinc complexes with these ligands may point to a new form of zinc for oral administration.

Preliminary studies demonstrated that hydroxypyranone derivatives such as 2-methyl-3-hydroxypyran-4-one 1a and 2-ethyl-3-hydroxypyran-4-one 1b and also some derivatives of hydroxypyridinones (1,2-dimethyl-3-hydroxypyridin-4-one 4a and 1-ethyl-2-methyl-3-hydroxypyridin-4-one 4b) possess suitable partition coefficients (k_{part}) (22). Therefore, it was predicted that zinc complexes of these chelating agents have enough lipophilicity to be used as orally active dietary supplements.

In order to design zinc complexes for clinical use it is necessary to select non-toxic ligands. From the toxicity point of view, 1a and 1b are non-toxic and for this reason are widely used as flavour enhancers in food industry (23). Both 3-hydroxypyranone and 3-hydroxypyridinone ligands are rapidly metabolized to glucoronide derivatives, which are excreted in the urine. For instance, urinary recovery studies conducted on 1, 2-dimethyl-3-hydroxypyridin-4-one (L1, 4a) in both rats and men have shown that respectively >44 and >85% of the administered dose is recovered in the urine as the nonchelating 3-O-glucuronide conjugate (Figure 1) (24).

In this work four zinc complexes (6a-d) have been designed and synthesized by using bidentate ligands 1a, 1b, 4a and 4b. The k_{part} values of these complexes between 1-octanol and tris buffer at pH 7.4 have also been determined.

Experimental

All chemicals used in this project were obtained from Aldrich (Gillingham, UK). Melting points are uncorrected. IR spectra were recorded on a perkin-Elmer 1420. ^{1}HNMR spectra were determined with EM-390 (80 MHz). Mass spectra were take using a Vacuum Generaters 16F (35eV). Elemental analyses were performed by micro analytical laboratories (Department of Chemistry, University of Manchester, Manchester M13 9PL, UK).

3-Hydroxypyridin-4-one ligands (4a and 4b) which are not commercially available, were synthesized utilizing the methodology of Harris(25) (Figure 2).

Synthesis of 2-methyl-3-benzyloxypran-4-one (Benzyl maltol)(2).

To a solution of 2-methyl-3-hydroxypyran-4-one (1a) (12 g, 0.1 mol) in methanol (100 ml) was added sodium hydroxide (4.4 g, 0.11 mol) dissolved in water (10 ml) followed by benzyl chloride (13.9 g, o.11 mol) and the mixture was refluxed for 6h. After removal of solvent by rotary evaporation, the residue was mixed with water (50 ml) and extracted into dichloromethane (3 × 50 ml). The combined extracts were washed with 5% sodium hydroxide (3 × 150 ml) and then with water (2 × 150 ml). The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield an orange oil which became solid on cooling. Recrystallization form diethyl ether gave the pure product as colourless needles. 17.7 g (82%). mp 52-53ºC, ^{1}H NMR (DMSO-d_6): δ 2.10 (s, 3H, 2-CH_3), 5.10 (s, 2H, O-CH_2-Ph), 7.94(d, 1H, 6-H); MS (EI)): m/z = 216 (M), IR (KBr): 1640 (C=0) cm^{-1}

Anal. CalCd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%. Found: C, 72.31; H, 5.65%.

*Synthesis of 1,2-dimethyl-3-benzyloxypyridin-4-one hydrochloride(3a)***.** To a solution of compound **2** (25g, 0.12 mol) in ethanol (200 ml)/water (200 ml) was added 40% aqueous methylamine (14 g, 0.18 mol) followed by 2N sodium hydroxide solution (10 ml), the mixture was refluxed for 12h. After adjustment to pH=6.4 with HCl, volume was reduced to 200 ml by rotary evaporation prior to addition of water (200 ml) and washing with diethyl ether (400 ml). Subsequent adjustment of the aqueous fraction to pH 7 with 10 N NaOH solution was followed by extraction into dichloromethane (3 × 400 ml), the organic layers after being dried over anhydrous sodium sulphate, filtered and rotary evaporated to give an orange oil. This oil was dissolved in ethanol/hydrochloric acid and rotary evaporated, the resulting white solid was recrystallized from ethanol/diethylether to give a white powder (24.2 g, 76%) mp 206-207ºC.

^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, 2-CH_3), 3.94 (s, 3H, N-CH_3), 5.03 (s, 2H, O-CH_2-Ph), 6.18 (d, 1H, 5-H) 7.25-7.52 (m, 5H, Ph), 7.58 (d, 1H, 6-H); MS (EI)): m/z = 265 (M-HCl).

Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.27; H,6.08; N,5.27; Cl,13.34%. Found: C, 63.15; H, 6.11; N5.21; Cl, 13.43%.

Synthesis of 1,2-dimethyl-3-hydroxypyridin-4-one hydrochloride (4a). Compound 3a (20 g, 0.075 mol) was dissolved in ethanol (270 ml)/ water (30 ml) and subjected to hydrogenolysis in the presence of Pd/C catalyst. Filtration followed by rotary evaporation gave a white solid, recrystallization from ethanol/diethyl ether yielding a white powder (11.6 g, 88%); mp 190-191ºC, ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, 2-CH_3), 4.05 (s, 3H, N-CH_3), 7.4(d, 1H, 5-H) 8.25 (d, 1H, 6-H); MS (EI)): m/z = 139 (M); IR (KBr): 3120 (OH), 1635 (C=0,for free base) cm^{-1}.

Anal. Calcd for $C_7H_{10}NO_2Cl.H_2o$: C, 43.42; H, 6.26; N, 7.24; Cl, 18.31% .Found: C, 43.58; H, 6.18, N, 7.31; Cl, 18.22%.

Synthesis of 1-ethyl- 2-methyl-3-benzyloxypyridin-4-one hydrochloride (3b). The procedure used was as described for synthesis of 1,2-dimethyl-3-benzyloxypyridin-4-one hydrochloride 3a except ethylamine was used in place of methylamine in the reaction mixture. Recrystallization from ethanol/diethyl ether gave the desired product as a white powder in a 84% yield (28.2 g), mp 177-178ºC. ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, N-CH_2CH_3), 2.2 (s, 3H, 2-CH_3), 4.3 (q, 2H, N-CH_2CH_3),5.1 (s, 2H, O-CH_2-Ph), 7.2 (d, 1H, 5-H), 7.3-7.6 (m, 5H, Ph), 8.1 (d, 1H, 6-H); MS (EI)): m/z = 243 (M-HCl); IR (KBR): 1635 (C=0) cm^{-1}.

Anal. Calcd for $C_{15}H_{18}NO_2Cl$: C, 64.40; H, 6.49; N, 5.01; Cl, 12.67%. Found: C, 64.23; H, 6.55; N, 4.96; Cl, 12.59%

Synthesis of 1-ethyl- 2-methyl-3-hydroxypyridin-4-one hydrochloride (4b). The procedure used was as described for synthesis of 1,2-dimethyl-3-hydroxypyridin-4-one hydrochloride 4a except 1-ethyl- 2-methyl-3-benzyloxypyridin-4-one 3b was used in place of 1,2-dimethyl-3-benzyloxypyridin-4-one hydrochloride 3a in the reaction mixture. Recrystallization from ethanol/diethyl ether gave the desired product as a white powder in a 75.2% yield (10.7 g), mp 206-207ºC. ^{1}H NMR (DMSO-d_6): δ 1.4 (t, 3H, N-CH_2CH_3), 2.6 (s, 3H, 2-CH_3), 4.4 (q, 2H, N-CH_2CH_3), 7.4 (d, 1H, 5-H), 8.3 (d, 1H, 6-H); MS (EI)): m/z = 153 (M-HCl); IR (KBR): 1640 (C=0) cm^{-1}.

Anal. Calcd for $C_8H_{12}NO_2Cl$: C, 50.66; H, 6.38; N, 7.39; Cl, 18.70%. Found: C, 50.53; H, 6.44; N, 7.44; Cl, 18.78%.

*Synthesis of bis (2-methyl-3-hydroxypyranonato) zinc (II) complex (6a)***.** To a solution of 2-methyl-3-hydroxypyran-4-one 1a (1.26g, 0.01mol) in 6 ml ethanol/1ml water stirring at an elevated temperature was added a solution of zinc chloride (0.68g, 0.005 mol) in 2 ml ethanol/1 ml water. With continous heating/ stirring a solution of sodium hydroxide (0.4 g, 0.01 mol) in 1.5 ml water was added dropwise over a period of 10 min. The reaction mixture was then stored at 4°C for 24 h to give a white precipitate, (1.5 g), recrystallization from 90% ethanol gave hydrated zinc complex (5a) as a white crystalline powder, 1.1 g (64.9%).

Anal. Calcd for $C_{12}H_{10}O_6$ Zn, 1.5 H_2O: C, 42.07; H, 3.83; Zn,19.10%. Found: C, 45.20; H, 3.91; Zn, 18.95%.

The above sample was heated in a vacuum

oven at 100º C for 24 h to give anhydrous bis (2-methyl-3-hydroxypyranonato) zinc (II) complex (**6a**), 0.90 g (89.1%), 275-276º C (dec.), ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 3H, 2-CH_3), 6.5 (d, 1H, 5-H), 8.1 (d, 1H, 6-H); IR (KBr): 1620 (C=0) cm^{-1}

Anal. Calcd for $C_{12}H_{10}O_6Zn$: C, 45.68; H, 3.17; Zn, 20.72%. Found: C, 45.41; H, 3.11; Zn, 20.61%.

Synthesis of bis (2-ethyl-3-hydroxypyranonato) zinc (II) complex (6b). The procedure used was as described for synthesis of bis (2-methyl-3-hydroxypyranonato) zinc (II) complex except 2-ethyl-3-hydroxypyran-4-one (1b) was used in place of 2-methyl-3-hydroxypyran-4-one (1a) in the reaction mixture, recrystallization from 90% ethanol gave hydrated zinc complex (5b) as a white crystalline powder, 1,2 g (64.9%).

Anal. Calcd for $C_{14}H_{14}O_6Zn$, 1.5 H_2O: C, 45.36; H, 4.62; Zn,17.64%. Found: C, 45.24; H, 4.55; Zn, 17.52%.

The above sample was heated in a vacuum oven at 100º C for 24 h to give anhydrous bis (2-ethyl-3-hydroxypyranonato) zinc (II) complex (6b), 0.95 g (84.8%), 270-271º C(dec.), ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, 2-CH_2-CH_3), 2.7 (q, 2H, 2-CH_2-CH_3), 6.4 (d, 1H, 5-H), 8.1 (d, 1H, 6-H); IR (KBr): 1623 (C=0) cm^{-1}

Anal. Calcd for $C_{14}H_{14}O_6Zn$: C, 48.95; H, 4.08; Zn, 19.03%. Found: C, 48.80; H, 4.01; Zn, 18.94%.

Synthesis of bis (1,2-dimethyl-3-hydroxypyridinonato) zinc (II) complex (6c). 1,2-dimethyl-3-hydroxypyridin-4-one hydrochloride (4a; 1.94 g, 0.01 mol) was dissolved in in 6 ml ethanol/1ml water with stirring. The pH of the solution was raised to 7 by dropwise addition of sodium hydroxide solution and then a solution of zinc chloride (0.68g, 0.005 mol) in 2 ml ethanol/1 ml water was added. With continous stirring at 70º C, a solution of sodium hydroxide (0.4 g, 0.01 mol) in 1.5 ml water was added dropwise over a period of 10 min. The reaction mixture was then cooled to yield a white precipitate. Recrystallization from 90% ethanol afforded hydrated zinc complex (**5c**) as a white crystalline solid, 1,44 g (61.5%).

Anal. Calcd for $C_{14}H_{16}N_2O_4Zn$. 7 H_2O: C, 35.94; H, 6.46; N, 5.99; Zn,13.98%. Found: C, 36.40; H, 6.51; N, 5.95; Zn, 13.88%.

The above sample was heated in a vacuum oven at 100º C for 24 h to give anhydrous bis (1,2-dimethyl-3-hydroxypyridinonato) zinc (II) complex (**6c**), 0.90 g (85.7%), 290-291º C(dec.), ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 3H, 2-CH_3), 3.7 (s, 3H, N-CH_3), 6.2 (d, 1H, 5-H), 7.4 (d, 1H, 6-H); IR (KBr): 1605 (C=0) cm^{-1}

Anal. Calcd for $C_{14}H_{14}N_2O_4Zn$: C, 49.23; H, 4.69; N, 8.20; Zn, 19.14%. Found: C, 49.08; H, 4.61; N, 8.25; Zn, 19.22%.

*Synthesis of bis (1-ethyl-2-methyl-3-hydroxypyridinonato) zinc (II) complex (**6d**)*. The procedure used was as described for synthesis of Synthesis of bis (1,2-dimethyl-3-hydroxypyridinonato) zinc (II) complex except 1-ethyl-2-methyl-3-hydroxypyridin-4-one 4b was used in place of 1,2-dimethyl-3-hydroxypyridin-4-one 4a in the reaction mixture. Recrystallization from 90% ethanol gave hydrated zinc complex (5d) as a white crystalline solid, 1,45 g (58.5%).

Anal. Calcd for $C_{16}H_{20}N_2O_4Zn$. 7 H_2O: C, 38.75; H, 6.91; N, 5.65; Zn,13.19%. Found: C, 38.63; H, 6.97; N, 5.60; Zn, 13.29%.

The above sample was heated in a vacuum oven at 100º C for 24 h to give anhydrous bis (1-ethyl-2-methyl-3-hydroxypyridinonato) zinc (II) complex (**6d**), 0.96 g (88.9%),

275-276º C(dec.), ^{1}H NMR (DMSO-d_6): δ 1,3 (t,3H, N-CH_2CH_3), 2.4 (s, 3H, 2-CH_3), 4.00 (q, 3H, N-CH_2CH_3), 6.3 (d, 1H, 5-H), 7.4 (d, 1H, 6-H); IR (KBr): 1610 (C=0) cm^{-1}

Anal. Calcd for $C_{16}H_{20}N_2O_4Zn$: C, 52.00; H, 5.41; N, 7.58; Zn, 17.69%. Found: C, 52.11; H, 5.35; N, 7.51; Zn, 17.75%.

Determination of partition coefficients using the shake slask method. Partition coefficients (K_{part}) of the ligands used in the present study were determined using the shake flask method as previously described (22). The shake slask method technique was also used to determine the K_{part} values of the zinc complexes of the bidentate ligands. The two phases used in determination were tris buffer (50 mM, pH 7.4, prepared using distilled water) and 1-octanol, each of which was pre-equilibrated with the other phase before use

(because the solubility of water in 1-octanol is 2.3 M (26).

A solution of complexes with concentration of 10^{-4} M was prepared in tris buffer and the absorbance of solution was measured in the ultraviolet region of a wavelength of approximately 305 nm using the buffer as a blank. A known volume (normally 10- 50 ml) sample of the solution was stirred vigorously with a suitable volume of 1- octanol in a glass vessel for 1 h. The two layers were separated by centrifugation for 5 minutes. An aliquot of the aqueous layers was then carefully removed using a glass Pasteur pipette ensuring that the sample was not contaminated with 1-octanol. The absorbance of the sample was measured as above and the partition coefficient was then calculated using the following formula:

$$K_{part} = \frac{A_1 - A_2}{A_2} \times \frac{V_w}{V_0} \qquad \text{(Eq 1)}$$

Where

A_1 = Absorbance reading in the aqueous layer before partitioning.

A_2 = Absorbance reading in the aqueous after partitioning.

V_0 = Volume of 1-octanol layer used in partitioning

V_v = Volume of aqueous layer used in partitioning

For each sample, the experiment was repeated at least four times which led to calculation of a mean K_{part} value and standard deviation (Table 1).

Results and Discussion

Synthesis of the selected ligands

The bidentate ligands of 2-methyl-3-hydroxypyran-4-one 1a and 2-ethyl-3-hydroxypyran-4-one 1b are commercially available. The general methodology (25) adopted for the synthesis of ligands 4a and 4b, is summarized in figure 2. The bidentate ligand 1a was benzylated to give compound 2. Reaction of compound 2 with methylamine or ethylamine, gave the benzylated pyridinones 3a and 3b, which were subsequently subjected to catalytic hydrogenation to remove the protecting group, yielding the corresponding bidentate chelators 4a and 4b as hydrochloride salts.

Conversion of 2-methyl-3-hydroxypyran-4-one to the corresponding 2-methyl-3-hydroxy pyridin-4-ones can be achieved without protection

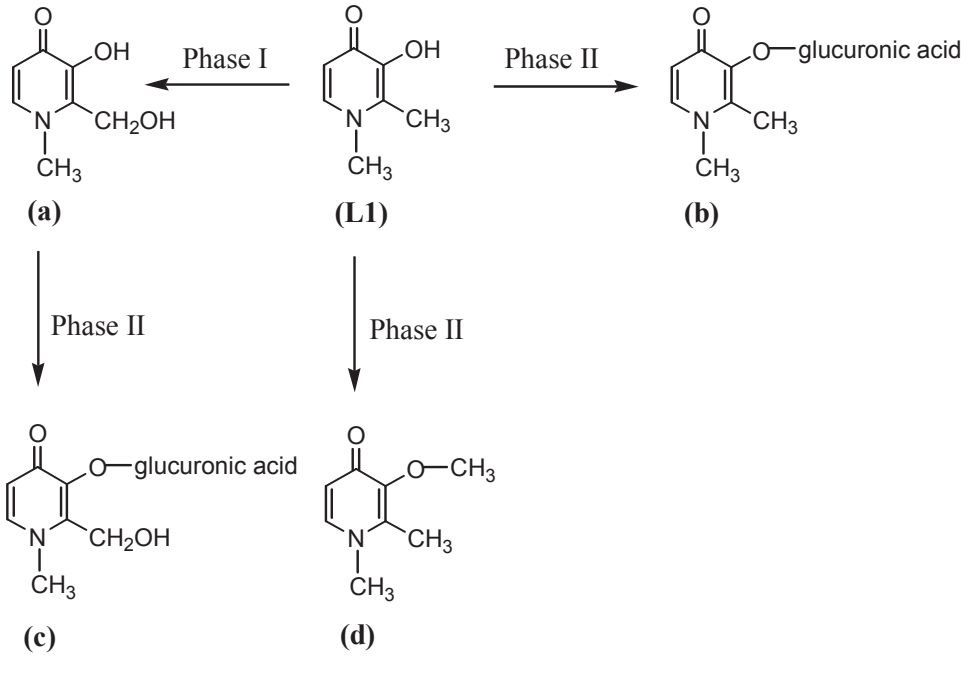
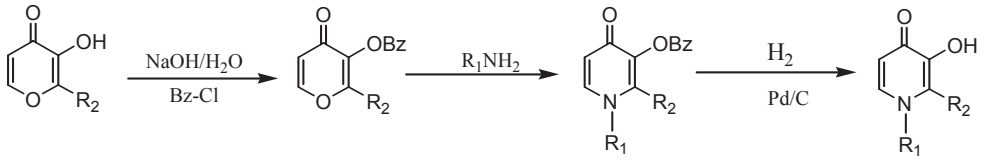


Figure 1. Metabolism of compound 1,2-dimethyl-3-hydroxypyridin-4-one (**L1**) in man/rat; **b** is major metabolite in both species.



1 **2** **3** **4**

a: $R_2 = CH_3$ (Maltol)
b: $R_2 = C_2H_5$ (Ethyl maltol)

a: $R_1 = R_2 = CH_3$
b: $R_1 = C_2H_5$, $R_2 = CH_3$

a: $R_1 = R_2 = CH_3$ (L1)
b: $R_1 = C_2H_5$, $R_2 = CH_3$

Figure 2. Synthesis of 3- hyddroxypyridin-4-ones (**4a**-**b**).

of the 3-hydroxyl group (27). However, the yield of this synthetic route is less than 40% (28).

The synthetic procedure of the zinc complexes

Zinc forms three different complexes with mono-protonated bidentate ligands (LH) such as hydroxypyridinones and hydroxypyranones, ZnL^+, ZnL_2 and ZnL_3^-, (Figures 3 and 4) (29, 30). Only the non-charged ZnL_2 complex is likely to permeate membranes by simple diffusion and therefore conditions were selected in this study to optimize the formation of this neutral compound. Using speciation plots it is also possible to determine the optimum conditions for synthesis of other species (Figure 4).

The developed synthetic procedure was centered on the fact that at pH 7 the 2:1 complex (ZnL_2) predominates (Figure 4), and this species has low solubility in aqueous ethanol. In this study, four zinc-complexes have been designed and synthesized in good yield by the direct reaction of above bidentate ligands (1a, 1b, 4a and 4b) with zinc chloride (Figure 5). Neutral condition was used for the synthesis of the complexes. Elemental analysis in each complex was consistent with the formulations of ZnL_2 species; however, the complexes were very hygroscopic, forming reproducibly analyzable hydrates. The complexes of 5a and 5b are lightly hydrated, with only 1.5 water molecules per zinc. In contrast, both complexes of 5c and 5d are heavily hydrated, with 7 water molecules per zinc (Figure 5). The water molecules were removed in vacuum oven at 100º C for 24 h to yield anhydrous zinc complexes of bis (2-methyl-3-hydroxypyranonato) zinc (II) (6a), bis (2-ethyl-3-hydroxypyranonato) zinc (II) (6b), bis (1,2-dimethyl-3- hydroxypyridinonato) zinc (II) (6c) and bis (1-ethyl-2-methyl-3-hydroxypyridinonato) zinc (II) (6d) (Figure 5). The complexes are all nonvolatile, decomposing above 290 ˚C and are soluble in water at neutral pH.

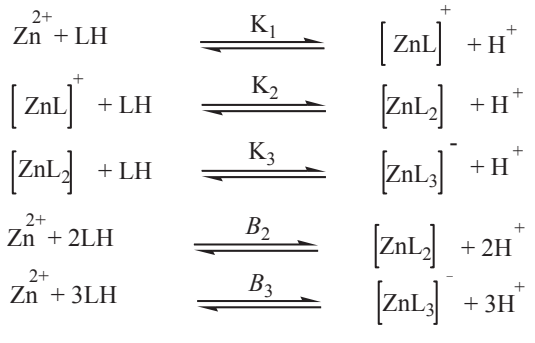


Figure 3. Complex formation of zinc with bidentate hydroxypyridinones and hydroxypyranones (LH). log β_2 = log K_1 + log K_2 ; log β_3 = log K_1 + log K_2+ log K_3. The affinity constants for the interaction between zinc ion and 2-metyl-3-hydroxypyran-4-one (**1a**) are log K_1, 5.62; log K_2, 4.82; log K_3, 8.73 (29). The affinity constants zinc ion with 1,2-dimethyl-3-hydroxypyridin-4-one (**1b**) are log K_1, 6.35; log K_2, 6.38; log K_3, 5.38 (30).

The K_{part} values of zinc complexes

The complexes covered a range of K_{part} values of 0.01-0.15. Among the zinc complexes reported in this study, complex 6a possesses the highest partition coefficients (0.15, Table 1).The zinc complexes of 6c and 6d are more hydrophilic (possess lower K_{part} values) than 6a and 6b (Table 1). This trend also holds for their ligands. A likely explanation for this observation is the change in the balance of the relative contribution of the canonical forms of 7 and 8 (Figure 6). For hydroxypyridinone ligands which possess N-alkyl groups, the resonance from **7** is stabilized due to electron donation of alkyl group R_1. Such stabilization is not possible with the hydroxypyranone ligands (forms of 9 and 10). Thus the dipole of the N-alkyl hydroxypyridinones (4a-b) is predicted

Table 1. The pK_a values of ligands (**1a-b** and **4a-b**) together with their partition coefficients and K_{part} values of zinc complexes (**6a-d)** between 1-octanol and tris buffer at pH 7.4. Number of determinations = 4.

Ligand	Pk_{a1}	Pk_{a2}	K_{part} of Ligand	Zn-Complex	K_{part} of Zn-Complex
1a	-	8.51	0.5 ± 0.03	6a	0.06 ± 0.006
1b	-	8.58	0.9 ± 0.05	6b	0.16 ± 0.02
4a	3.68	9.77	0.18 ± 0.01	6c	0.01 ± 0.005
4b	3.81	9.93	0.6 ± 0.04	6d	0.03 ± 0.004

to be larger and hence more hydrophilic than that of the hydroxypyranone ligands (1a-b). Zinc complexes are more hydrophilic than their corresponding free ligands (Table 1). Interestingly, this trend hold for those iron (III) complexes which the K_{part} values of their free ligands are lower than 3 (31).

The structural data of zinc complexes

The $\nu_{c=o}$,C=O stretching frequencies (cm^{-1}), in complexes are significantly lower than $\nu_{c=o}$ in the corresponding ligands. These variations in $\nu_{c=o}$ ($\Delta\nu_{c=o}$), indicated that all complexes were successfully synthesized (Table 2). In fact, the formation of complexes are associated with the formation of some new metal- oxygen bonds (Zn-O=C). The presence of new bonds causes an increase in the C=O bond order which leads to drive the C=O stretching frequencies down. For instance, the bond lengths of C=O in free ligand of 4a and in chelate rings of its corresponding zinc complex (5c) are 1.276Å and 1.293 Å respectively (Figure 7) (32). All the hydrated zinc complexes showed broad water O-H stretches in the region 2500-3400 cm^{-1} which were disappeared in anhydrous zinc complexes (6c-d). Below 800 some new bonds appeared, and these were tentatively assigned as metal-oxygen bond formation (ν_{M-O}).

The structure of zinc complexes

The majority of zinc complexes are four-, five- and six-coordinate, and coordination number five is the most common. Four- and six-coordinate complexes are tetrahedral (hybrid orbital: sp^3) and octahedral (hybrid orbital: sp^3d^2) respectively. Five-coordinate complexes are known in square-pyramidal and trigonal-bipyramidal configurations (hybrid orbital: sp^3d) (Figure 8).

There are some zinc complexes with bidentate ligands, such as $Zn(acac)_2(H_2O)$ [acac is acetyl acetate] and Zn(dimethyl-3-oxopentanedioate)$_2(H_2O)_2$, in which one and two H_2O molecules are coordinated to zinc ion as fifth and sixth coordination site respectively (32).. In other words, in this type of complexes, zinc occurs in both five- and six-coordination (Figure 8). As mentioned before, all synthesized zinc complexes of 5a-d, are hydrated. It is possible that in our zinc complexes like above complexes, one or two water molecules coordinated to the zinc. Indeed, the structures of only two hydrated complexes of 5a and 5c were determined by x-ray diffraction technique (32). It was reported that the zinc in hydrated complex of **5c** ($ZnL_2.7H_2O$) is five coordinated, with a distorted square-pyramidal geometry around the zinc ion. The structure of this complex, [Zn(1,2-dimethyl-3-hydroxypyridinonato)$_2(H_2O)$].$6H_2$O is shown in figure 9. Figure 9 shows how the water molecules containing O*, effectively block the sixth coordination site at the zinc without themselves interacting with the zinc. The structure of complex 5a ($ZnL_2.1.5H_2O$) is also shown in figure 10. The overall structure can be viewed as layers of ABA sandwiches, i.e…ABA…ABA…, with layers A consisting of

Table 2. The $\nu_{c=o}$ values **(stretching frequencies, cm^{-1})** of hydroxypyranone (**1a-b**) and hydroxypyridinone(**4a-b**) ligands and their corresponding zinc complexes (**6c-d**) ($\Delta\nu_{c=o}$ = variations in C=O stretching frequencies).

Ligand	$\nu_{c=o}$ of Ligand (cm^{-1})	Zn-Complex	$\nu_{c=o}$ of Zn-Complex (cm^{-1})	$\Delta\nu_{c=o}$
1a	1640	6a	1620	20
1b	1645	6b	1623	22
4a	1635	6c	1605	30
4b	1640	6d	1610	30

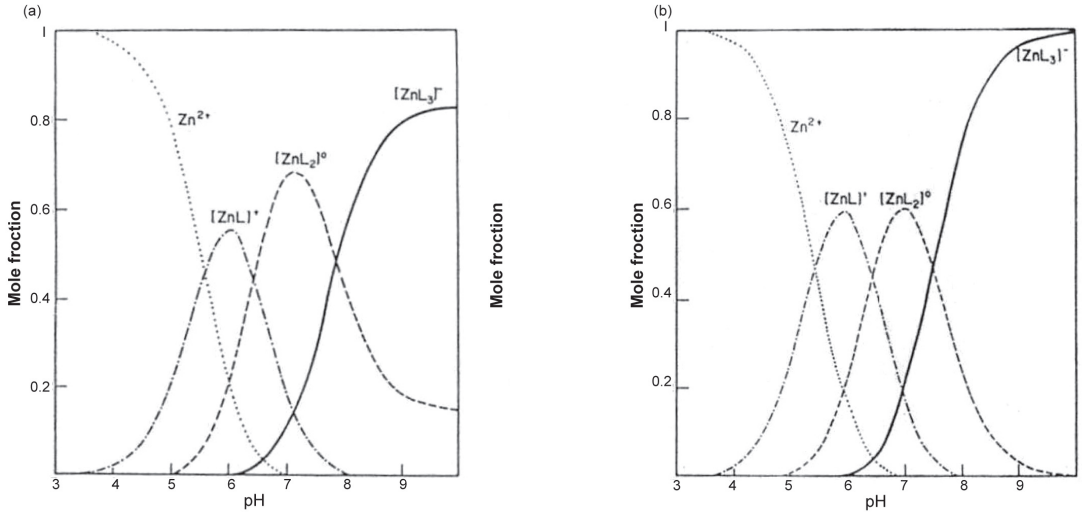


Figure 4. The pH dependence of speciation plots for zinc bidentate ligands. (a) zinc: 2-ethyl-3-hydroxypyran-4-one (1: 20), [Zn] = 5×10^{-4} M; (b) zinc: 1,2-dimethyl-3-hydroxypyridin-4-one (1: 10), [Zn] = 5×10^{-4} M

$$Zn^{2+} + 2LH + 2OH^- + (x\text{-}2)\,H_2O \longrightarrow ZnL_2 .xH_2O$$

LH:
2-Methyl-3-hydroxypyranone (**1a**)

2-Eethyl-3-hydroxypyranone (**1b**)

1,2-Dimetyl-3-hydroxypyridinone (**4a**)

1-Ethyl-2-methyl-3-hydroxypyridinone (**4b**)

x=1.5:
Hydrated (**1a**)-Zn(II) complex (**5a**)

Hydrated (**1b**)-Zn(II) complex (**5b**)

x=7:
Hydrated (**4a**)-Zn(II) complex (**5c**)

Hydrated (**4b**)-Zn(II) complex (**5d**)

$$ZnL_2 .xH_2O \xrightarrow[100\ ^oC]{\text{Vacuum oven}} ZnL_2 + xH_2O$$

Bis (2-methyl-3- hydroxypyranonato) Zn(II)(**6a**)

Bis (2-ethyl-3- hydroxypyranonato) Zn(II)(**6b**)

Bis(1,2-dimethyl-3- hydroxypyridinonato) Zn(II) (**6c**)

Bis(1-ethyl-2-methyl-3- hydroxypyridinonato) Zn(II) (**6d**)

Figure 5. Synthesis of zinc complexes using bidentate ligands.

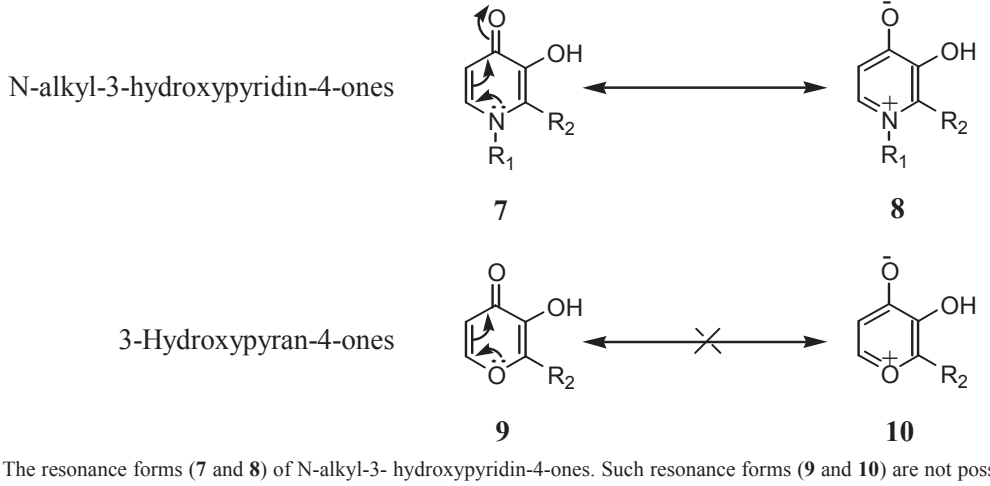


Figure 6. The resonance forms (**7** and **8**) of N-alkyl-3- hydroxypyridin-4-ones. Such resonance forms (**9** and **10**) are not possible with 3- hydroxypyran-4-ones.

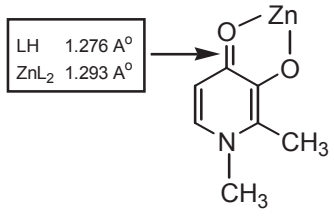


Figure 7. Comparison of C=O bond distances in the free ligand (LH) of 1,2-dimethyl-3-hydroxypyridin-4-one (**4a**) and in the chelate rings of its corresponding zinc complex (ZnL2) of **5c**.

five-coordinated zinc complexes [Zn(2-methyl-3-hydroxypyranonato)$_2$(H_2O)], layers B of the six-coordinate complexes [Zn(2-methyl-3-hyd roxypyranonato)$_2$(H_2O)$_2$]. The five-coordinate zinc ion (Zn1) in layers A is in an approximately square-pyramidal coordination environment where as, the six-coordinate zinc ion (Zn2) in layers B is in octahedral coordination geometry. The two 2-methyl-3-hydroxypyranonato ligands (also two H_2O molecules) of complex [Zn(2-methyl-3-hydroxypyranonato)$_2$(H_2O)$_2$] in layers B are effectively in the trans configuration to each other in the planar Zn(2-methyl-3-hydroxypyranonato)$_2$ unit in the octahedral species (32). It is clear that both hydrated 3-hydroxypyranone and 3- hydroxypyridinone complexes are extensively hydrogen bonded. The hydrogen bonding usually involves water-water and water- ligand intractions (Figures 9 and 10). As mentioned before, both hydrated complexes of 5c and 5d (3- hydroxypyridinone complexes) are heavily hydrated with seven water molecules per zinc ion. As it has been shown in figure 9, only one water molecule is coordinated to zinc ion in complex 5c. The rest of water molecules are hydrogen bonded to each other or bonded to donor oxygen atoms of ligands. In contrast, our zinc 3-hydroxypyranone complexes (hydrated complexes of 5a and 5b) are lightly hydrated, with only 1.5 water molecules per zinc. All these water molecules in complex 5a are coordinated to zinc ions (Figure 10). The water in the five-coordinated zinc units is hydrogen bonded to ligand oxygen in adjacent six-coordinated zinc units; the water in the latter is also coordinated to ligands in the former (32).

Although, without X-ray diffraction data we are unable to determine precisely the coordination geometry around the zinc ion in both hydrated and anhydrous complexes but:

1- Based on the elemental analysis along with

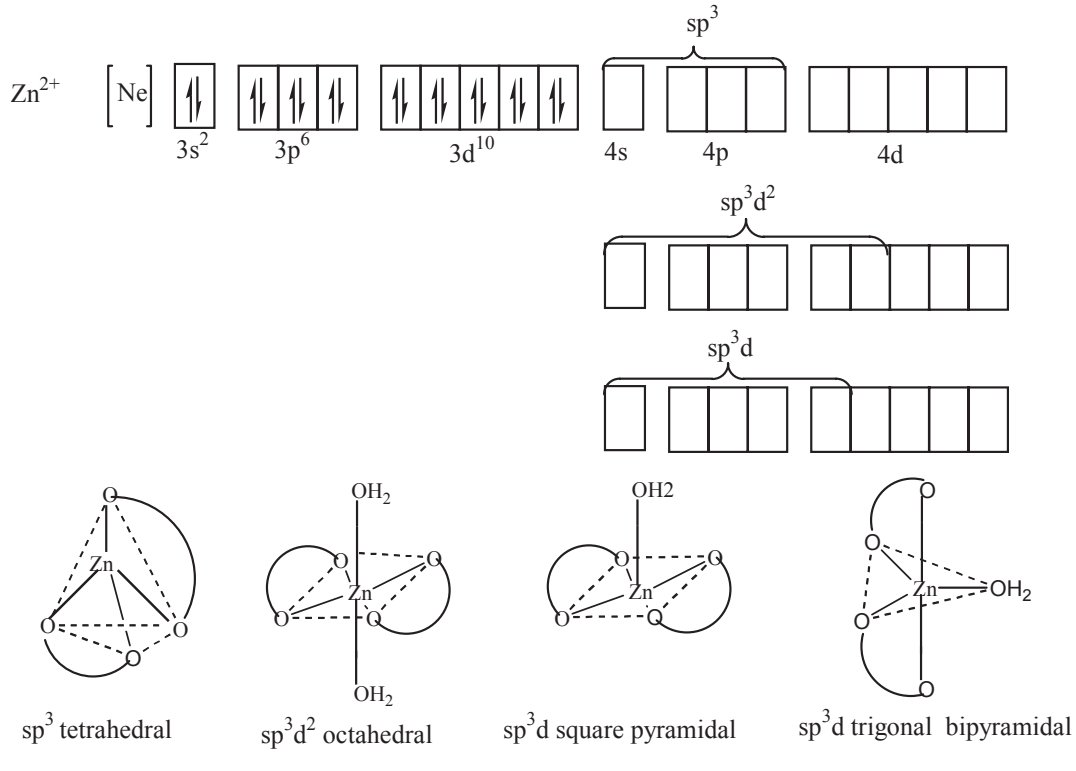


Figure 8. Hybrid orbitals and geometries of zinc complexes with bidentate ligands and water molecules.

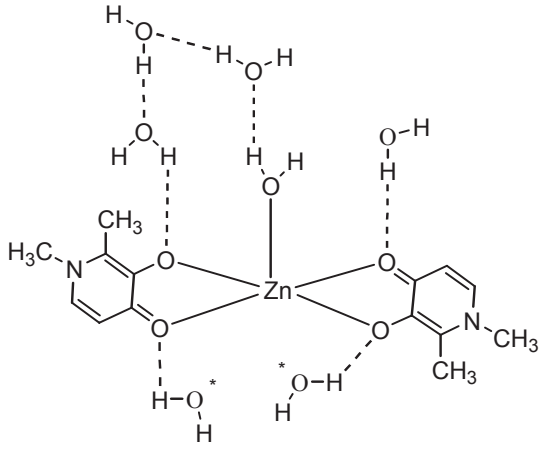


Figure 9. The molecular structure of hydrated 1,2-dimethyl-3-hydroxypyridin-4-one- zinc complex (**5c**).

X-ray diffraction data (which was only reported for two hydrated zinc complexes of 5a and 5c) it was anticipated that, hydrated zinc complexes of 5b and 5d have also been successfully synthesized and their structures could be the same as the structure of 5a and 5c respectively

2- The structural data (such as IR, elemental analysis and pysico-chemical properties) show that the anhydrous complexes (6a-c) have also been synthesized and hence the structure of this type of complexes could be as a tetrahedral configuration (sp^3 hybrid).

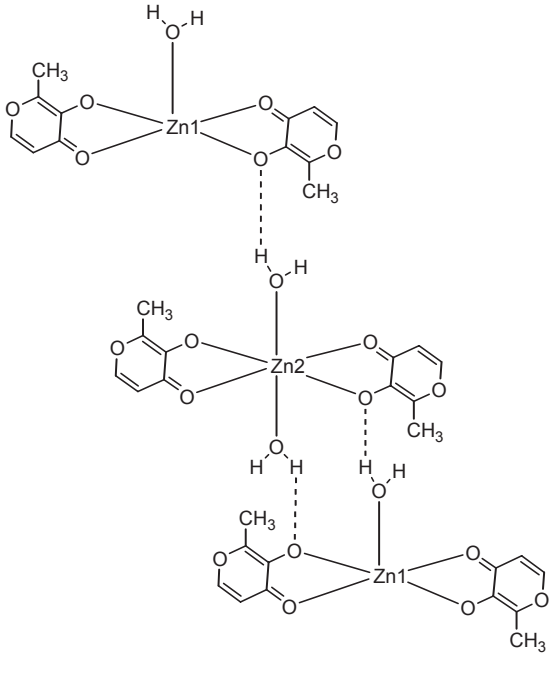


Figure 10. The molecular structure of hydrated 3-hydroxypyran-4-one- zinc complex (**5a**).

Conclusion

Elemental analysis in each zinc complex was consistent with the formulations of ZnL_2 species with 1.5 or 7 water molecules per zinc and the water molecules were removed by heating in a vacuum oven to yield anhydrous zinc complexes (ZnL_2). The complexes with hydroxypyranone ligands possess higher K_{part} values than those with hydroxypyidinone ligands. The comparison of the complexes highlight the hydroxypyranone zinc complexes (especially 6b with K_{part} value of 0.15) as the most promising candidates for zinc deficiency. It was anticipated this type of complexes apparently possesses suitable K_{part} values to facilitate their penetration into the gastrointestinal tract.

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