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Solid-State Characterization of Enantiomeric and Racemic Hydrated and Anhydrous Zinc-Pidolate Complexes

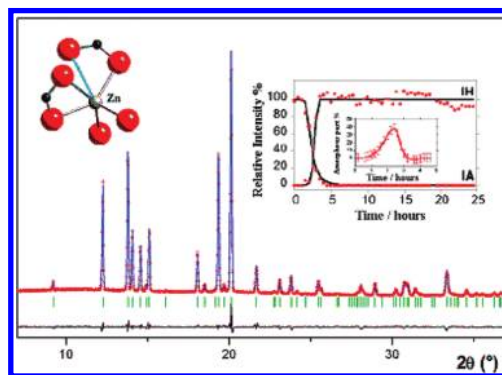
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ABSTRACT: Zn(II) L and DL pidolates diaqua complexes dehydrate at around 407 K, leading to amorphous anhydrous complexes. Only amorphous anhydrous Zn(II) L pidolate was found to crystallize on heating into a crystalline anhydrous phase whose crystal structure was solved from a high resolution X ray powder diffraction pattern. Orthorhombic anhydrous Zn(II) L pidolate exhibits a structure in which (4 + 2) coordinated Zn atoms (with four usual and two additional Zn–O distances of 2.53 and 2.69 Å) and L pidolate ligands alternate so as to form a three dimensional polymerized network. Room temperature rehydration processes under saturating water vapor for amorphous and crystal line anhydrous complexes were found to be different from each other, although they all led back to crystalline diaqua complexes whose relative stabilities were inferred from measurements of their solubilities in water.



INTRODUCTION

Zinc is one of the most important trace elements, as it is essential in metabolism for its functions in body maintenance, growth, and reproduction.^{1,2} Therefore, in the case of deficiency, zinc should be supplemented by means of a form readily assimilated by the living medium. A harmless chiral compound, L pidolic acid, C₅H₇NO₃ (L pyroglutamic acid or 5 oxopyrrolidine 2 carboxylic acid or 5 oxo proline), is often used as a vector of trace elements (Zn, Mn, ...) because it forms coordination compounds that are known to be well reabsorbed when administered in the form of tablets.³

Thus, regulatory considerations demand that zinc pidolate be controlled to make sure that only the L enantiomer derivative is present in the active pharmaceutical ingredient, as zinc pidolates can also be synthesized with racemic DL pidolic acid.

Previous determinations of the crystal structures of the zinc L pidolate enantiomer,⁴ monoclinic C2 (Z = 2), and of the zinc DL pidolate racemate,⁵ monoclinic C2/c (Z = 8), have shown that (i) L pidolic acid exhibits the absolute configuration S and (ii) each zinc atom is tetrahedrally coordinated to four oxygen atoms, of which two are from water molecules and the two others are from the carboxylato groups of two pidolate ligands. Such a 4 fold coordination of Zn(II) with a tetrahedral geometry is usually found in Zn complexes even though hexa and even pentacoordinated Zn(II) have been reported.^{6–9}

Because these structure determinations^{4,5} have disclosed that Zn(II) pidolates usually crystallize so as to form diaqua complexes,

and because powders with a well defined particle size may be obtained by spray drying of aqueous solutions, it should also be controlled how heat and humidity may influence the solid state characteristics of these complexes.

The results of such investigations are reported in the following, together with the crystal structure of anhydrous the Zn(II) L pidolate complex, unexpectedly recrystallized from its amorphous state.

EXPERIMENTAL SECTION

Synthesis. Zinc L pidolate and zinc DL pidolate were prepared by mixing zinc oxide, ZnO, with L or DL pidolic acid (both from Aldrich), respectively, in a 1:2 molar ratio. An excess of distilled water was added at room temperature to these mixtures until complete dissolution. Crystals were grown from slowly evaporated solutions at room temperature.

Techniques. X ray powder diffraction experiments were performed with a horizontally mounted cylindrical position sensitive detector CPS 120 (Debye–Scherrer geometry, transmission mode) from INEL, and Cu Kα1 radiation (λ = 1.5406 Å). The samples were gently crushed before being introduced into Lindemann glass capillaries with 0.5 mm inner diameter.

Differential scanning calorimetry (DSC) and thermogravimetry (TG) experiments were performed with the DSC 10 cell and the TGA 50

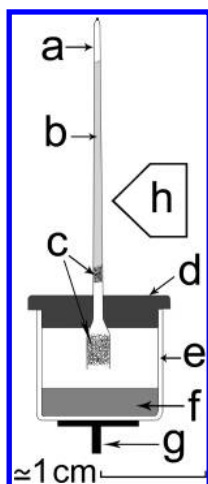


Figure 1. Schematic representation of the device used to study isothermal rehydrations under saturating water vapor: a = vertically mounted Lindemann capillary; b = initially dehydrated specimen; c = silica wool; d = stopper; e = container; f = water; g = to the goniometer head; h = incident X ray beam.

balance of a TA2000 TA Instruments thermal analyzer, respectively. Each experiment with a heating was run with a scanning rate of $2 \text{ K} \cdot \text{min}^{-1}$.

Crystal structure was determined with Materials Studio Modeling 4.1¹⁰ from a high resolution X ray powder diffraction pattern. The pattern was indexed by means of the peak picking option of the software package. Potential solutions for cell parameters and space group were found using the X cell algorithm.¹¹ Then, a Pawley profile fitting procedure¹² was applied to get the best refined cell parameters together with the best fit to the experimental profile. The best distances, angles, and torsions in the molecule were obtained *via* energy minimization calculations using the Compass force field.¹³ Then, a Monte Carlo approach was carried out in the direct space to solve the structure.¹⁴

Solubility Measurements. Crystals of zinc L pidolate and zinc DL pidolate diaqua complexes were allowed to equilibrate for weeks at different temperatures with their saturated aqueous mother liquors in a temperature controlled device. At each temperature, an aliquot was taken from each solution by means of a syringe, weighed (*ms*) and put in a weighed beaker until complete evaporation, and the in beaker dry powder was weighed (*mp*). This allowed solubility values, $s = mp/mw$, to be expressed as a function of the temperature in grams of compound per gram of water ($mw = ms - mp$). The structure of the crystals in equilibrium with their mother liquors was controlled by X ray powder diffraction, which also showed no excess in either of the solid free acids.^{4,5}

Isothermal Rehydration Experiments. The rehydration process of the anhydrous compounds was followed by way of DSC and TG, using previously described homemade adaptations of the DSC and TG cells¹⁵ that allow monitoring DSC and TG isothermal rehydration experiments in a water saturated atmosphere. Rehydration rates were determined at room temperature by X ray powder diffraction. Each capillary tube was mounted on a homemade device (Figure 1) in which, after recording a first pattern as a reference, water was introduced so that the specimen remained in contact with saturating water vapor. Then patterns were recorded at increasing time intervals, until rehydration was complete. To determine the ratio of rehydrated compound (or of remaining anhydrous crystalline solid) as a function of time, time normalized intensities of four well indexed Bragg peaks were summed for each acquisition time, so that a percentage of crystalline solid (still anhydrous or rehydrated) was obtained from a 0–100% intensity scale.

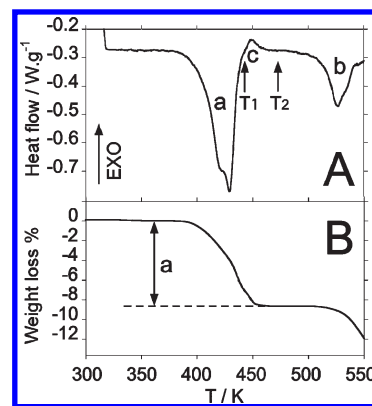


Figure 2. Zn(II) L pidolate diaqua complex: (A) DSC curve ($T_1 = 437 \text{ K}$ and $T_2 = 473 \text{ K}$; peak numbering is used in the text); (B) TGA signal (heating rate: $5 \text{ K} \cdot \text{min}^{-1}$).

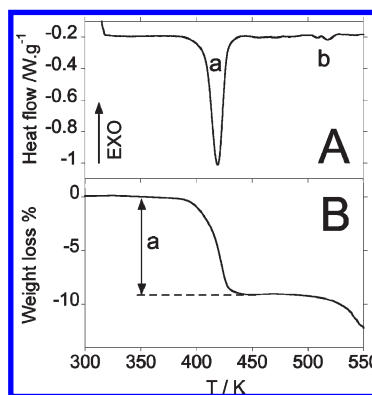


Figure 3. Zn(II) DL pidolate diaqua complex: (A) DSC curve (peak numbering is used in the text); (B) TGA signal (heating rate: $5 \text{ K} \cdot \text{min}^{-1}$).

RESULTS AND DISCUSSION

Crystallographic Characterization. Crystals of the two aqua complexes grown at room temperature were gently crushed into powders for characterization by X ray powder diffraction. The patterns recorded with long exposure times (12–24 h) were found to be virtually the same as the profiles calculated according to the crystal structures^{4,5} (see Supporting Information, Figure S1), in which no unindexed peak is observed. By the way, it may be mentioned that such results rule out the hypothesis according to which the equimolar mixture of enantiomorphous solids might crystallize, as a result of a spontaneous resolution, while evaporating solutions prepared with racemic DL pidolic acid.

Dehydration Behavior. DSC and TGA experiments showed that, on heating, the two zinc pidolate diaqua complexes lose endothermally water up to 8.7% and 9.1% in weight, respectively (peaks a and weight losses a in Figures 2 and 3). This agrees with the theoretical value (10%), calculated assuming 2 mol of water per mole of aqua complex. Dehydration related data (onset and end temperatures, dehydration enthalpies) for the two diaqua complexes are compiled in Table 1.

These dehydration enthalpies compare well with or even virtually match literature values, ranging from 112 to $149 \text{ kJ} \cdot \text{mol}^{-1}$ at about 373 K , found on heating other aqua complexes of various atoms: Mg (149 and $136 \text{ kJ} \cdot \text{mol}^{-1}$),^{16,17} Mn ($112 \text{ kJ} \cdot \text{mol}^{-1}$), Co ($115 \text{ kJ} \cdot \text{mol}^{-1}$), Ni ($119 \text{ kJ} \cdot \text{mol}^{-1}$) and Zn ($124 \text{ kJ} \cdot \text{mol}^{-1}$),¹⁶ or Cu ($114.47 \text{ kJ} \cdot \text{mol}^{-1}$).¹⁸

Table 1. Temperatures and Dehydration Enthalpies for Zn(II) L-Pidolate and Zn(II) DL-Pidolate Aquacomplexes, as Determined from Peak a in Parts A and B, respectively, of Figure 3

dehydration	Zn(II) L-pidolate	Zn(II) DL-pidolate
onset temperature (K)	(405 ± 1)	(409 ± 1)
end temperature (K)	(435 ± 1)	(419 ± 1)
enthalpy (kJ·mol ⁻¹)	(114 ± 3)	(126 ± 11)

On further heating, the two anhydrous complexes underwent decompositions, both starting exothermally at about 510 K (onset of peaks b in Figures 2 and 3), as indicated by the brown color of the residues. However, in the meanwhile, only the anhydrous L-pidolate complex exhibited an exothermic peak (-11 ± 1 kJ·mol⁻¹) at 440 K (onset) (peak c in Figure 2), i.e. just after the end of the dehydration related peak and far below decomposition. It was ascribed to the crystallization of the amorphous anhydrous Zn(II) L-pidolate complex into a new phase after X ray diffraction analyses were performed on specimens quenched to room temperature from 437 and 473 K (T_1 and T_2 in Figure 2, respectively). To try to obtain information on the molecular packing of this unexpected phase, its crystal structure was determined, as reported in the following.

Crystal Structure of Anhydrous Zn(II) L-Pidolate. The crystal structure of anhydrous Zn(II) L-pidolate was determined using the high resolution pattern recorded at room temperature. The space group and cell parameters best reproducing the diffraction pattern were found to be orthorhombic space group $P2_12_12_1$ ($Z = 4$) with parameters $a = 14.4202(5)$ Å, $b = 12.8149(4)$ Å, and $c = 6.6909(2)$ Å. For the calculations, the asymmetric unit was assumed to be made of three parts: Zn alone and two organic ligands, both assumed to be L-pidolates. Each ligand was placed in the unit cell as a rigid body together with its symmetry related homologues, but with the dihedral angle of the CO₂ group allowed to adjust freely. Seventeen degrees of freedom were used: nine translations, six rotations, and two dihedral angles of the CO₂ group, until reaching the best agreement between calculated and experimental powder patterns. A final Rietveld refinement (including Pawley refined parameters, rigid body molecular units, and preferred orientations) converged to a final R_{wp} value of 6.66% (Figure 4).

Atom coordinates, selected bond distances, and selected bond angles can be found as part of the Supporting Information (Tables S1, S2, and S3, respectively). The X ray crystallographic file (CIF) is available at www.ccdc.cam.ac.uk/data_request/cif with deposition number CCDC 815084.

The crystal structure shows that recrystallization of the anhydrous amorphous Zn(II) L-pidolate complex is accompanied with polymerization and with some change in the coordination of the zinc atom. As shown in Figure 5A, the zinc atom has six near O neighbors, of which four (O1, O3, O6, O7) form a distorted tetrahedron with usual Zn—O short distances of about 2 Å, close to the value of 2.099 Å listed by Shannon.¹⁹ Two additional atoms (O8 and O2, at 2.53 and 2.69 Å from Zn, respectively) complete the distorted octahedral geometry of the (4 + 2) coordination shell, i.e. different from the 4 fold coordination observed in the diaqua complexes.^{4,5} It is worth mentioning that similar Zn—O long distances have been found in “small molecule” crystal structures (2.687 Å,⁶ 2.547 Å,²⁰ 2.422 Å,²¹ for instance) and that theoretical insights into the coordination sphere of the Zn active

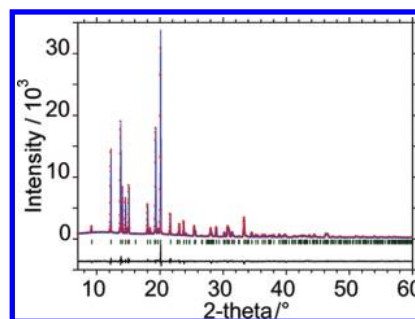


Figure 4. Final Rietveld refinement of the room temperature X ray diffraction pattern for the crystalline Zn(II) L-pidolate anhydrous complex: hollow circles (red) = experimental pattern; lines (blue) = calculated pattern; vertical bars (green) = peak positions. The difference line (black) (observed minus calculated) is shown at the bottom of the figure.

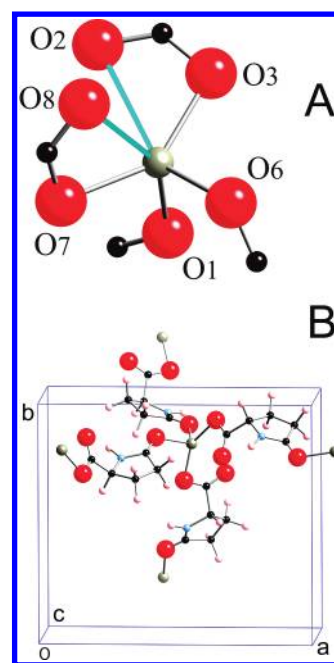


Figure 5. Orthorhombic anhydrous Zn(II) L-pidolate: (A) distorted (4 + 2) octahedral environment of the zinc atom with four shorter (gray) and two longer (light blue) Zn—O distances; (B) unit cell within which each zinc atom is linked to four L-pidolate ligands (gray = Zn; black = C; blue = N; pink = H; red = O).

site of the farnesyltransferase metalloenzyme led to the conclusion that it could involve Zn—O interactions with distances as long as 2.40–2.60 Å.²² In the present case, the pidolato groups are attached to the zinc atoms not only by their carboxylato groups, as they do in the molecular diaqua complexes,^{4,5} but also by their C=O groups, so that a L-pidolato group bridges two Zn atoms, thus forming a 3 dimensional polymeric network in which each zinc atom is surrounded by four pidolato groups, as shown in Figure 5B.

X-ray Diffraction Patterns of Amorphous Anhydrous Zn(II) L- and DL-Pidolates. Amorphous phases obtained by heating the crystalline aquacomplexes until complete dehydration through thermogravimetry experiments were quenched at room temperature and subjected to X ray diffraction as soon as obtained. Preliminary X ray diffraction patterns with short

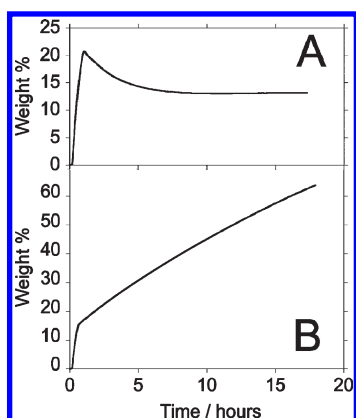


Figure 6. Examples of isothermal rehydration TGA curves: (A) water uptake and recrystallization with subsequent water release; (B) water uptake with dissolution and then dilution to infinite with no recrystallization.

exposure times (about 1 h) showed very close patterns (see Supporting Information, Figures S2A and S2B). Thus, a new series of data was collected from specimens in sealed capillaries within about 6 (DL complex) and 12 h (L complex). Again, close patterns were recorded (see Supporting Information Figures S2C and S2D), both showing two broad peaks at about 10.4° and 20.7° (in 2θ), which correspond to distances d of about 4.2 and 8.2 Å, respectively. Although the purpose of such experiments was not to determine the structure factors of these amorphous phases and the subsequent pair correlation functions, it may be assumed that these phases locally resemble each other closely. Since these amorphous phases are obtained from crystalline powders dehydrated in the solid state, it can be hypothesized that they are made of micro (or nano) crystallites whose diffraction patterns can be compared to the ideal pattern of orthorhombic anhydrous Zn(II) L pidolate made of very small crystallites. Such a pattern was calculated, following the Scherrer equation,²³ using the particle size option of the program CrystaDiffract.²⁴ Reducing the mean crystallite dimension to $0.0015\text{--}0.002\text{ }\mu\text{m}$ resulted in the pattern shown in the Supporting Information (Figure S2), differing from both experimental patterns by a broad peak at about 14° instead of 10.4° (2θ). This indicates that the two amorphous phases exhibit very close local orders, which are both different from the local order in the crystalline anhydrous Zn(II) L pidolate. It may thus be likely inferred that (i) amorphous anhydrous Zn(II) DL pidolate is made of an equimolar mixture of D and L amorphous complexes (that should exhibit the same diffraction pattern), (ii) recrystallization of the anhydrous amorphous enantiomer is reconstructive, and (iii) symmetry and/or entropy related barriers prevent crystallization of the racemic anhydrous amorphous complex.

Rehydration Behavior. How the three anhydrous complexes (amorphous and crystalline Zn(II) L pidolates and amorphous Zn(II) DL pidolate) rehydrate at room temperature was followed as a function of time by isothermal gravimetry, differential calorimetry, and X ray diffraction experiments. In every case, rehydration was monitored under a water vapor saturated atmosphere.

Whichever the complex, isothermal gravimetry showed two kinds of behaviors (Figure 6).

In the first case (Figure 6A), anhydrous specimens first took water up to 20% in weight and then released water until reaching final values of about 13%, somewhat greater than the value of 10% that should be found in a dry diaqua complex. Such an excess

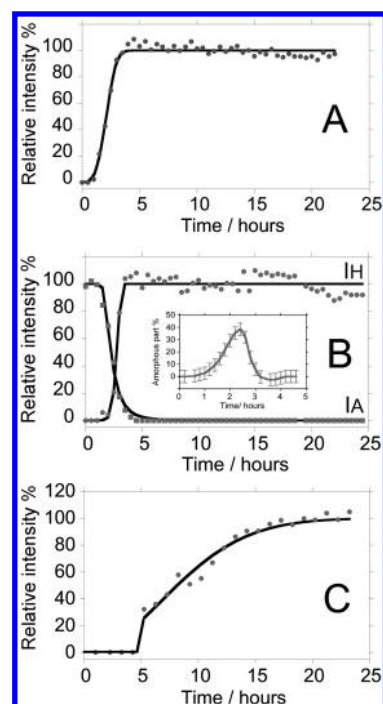


Figure 7. Isothermal rehydration X ray diffraction experiments: (A) formation of diaqua Zn(II) L pidolate from anhydrous amorphous Zn(II) L pidolate; (B) transformation of anhydrous crystalline Zn(II) L pidolate into diaqua Zn(II) L pidolate; (inset) amount of the transitory amorphous part forming while anhydrous crystalline zinc L pidolate rehydrates, estimated by $100 - (I_A + I_H)$, in which I_A and I_H are the normalized intensities of four Bragg peaks of patterns A (crystalline anhydrous complex) and H (crystalline diaqua complex), respectively (error bars: fixed value of ± 5); (C) formation of diaqua Zn(II) DL pidolate from anhydrous amorphous Zn(II) DL pidolate.

of absorbed water is likely due to the humidity conditions (near saturation) within which wet crystalline diaqua complexes form at the end of the water uptake.

In the second case, i.e. when no crystallization into a diaqua complex is observed, specimens took water indefinitely up to complete dissolution and to infinite dilution, as exemplified in Figure 6B by the mass vs time curve obtained with a specimen of a racemic anhydrous complex. This case was encountered only while running isothermal gravimetry experiments, but no convincing explanation was found for why it was only observed in these experiments.

When the rehydration process is followed by X ray diffraction as a function of time (Figure 7), it appears clearly that the anhydrous amorphous and the anhydrous crystalline L pidolate complexes rehydrate within about 4 h (parts A and B, respectively, of Figure 7). Relative intensities vs time were fitted, using the Avrami's model,²⁵ to equations of the form $RI(\%) = 100[1 - \exp(-at^k)]$, in which RI stands for relative intensity (%), t for time in hours, and a and k for adjustable parameters whose values are listed in Table 2.

The ratio of times for 75% and 25% of transformation of the anhydrous form into the rehydrated one is calculated for the two transformations. In both cases, it comes to a value of about 1.5, which defines polyhedral growth with the same rate of transformation in the three directions. On the contrary, another rehydration behavior is observed with the racemic anhydrous complex (Figure 7C), whose complete rehydration into the crystalline

Table 2. Calculated Values of Parameters a and k in the Equation $RI(\%) = 100[1 - \exp(-at^k)]$ Describing the Isothermal Formation of Zn(II) Diaqua Complexes from Amorphous and Crystalline Anhydrous Complexes and the Concomitant Decay of Anhydrous Crystalline Zn(II) L Pidolate

formation of Zn(II) pidolate diaqua complexes from:	a	k
anhydrous amorphous L-pidolate	0.0489	3.5366
anhydrous crystalline L-pidolate	$2.10 \cdot 10^{-5}$	10.2287
(decay of anhydrous crystalline Zn(II) L-pidolate)	18.576	-4.05594
anhydrous amorphous DL-pidolate	0.0124	1.9164

diaqua complex occurs within about 25 h. The Avrami's model (Table 2) gives a ratio of 2.3, i.e. a frontier value between two types of behavior: a platelike growth (two dimensional transformation) and a linear growth (transformation along one direction). It is worth pointing out (see Figure 7C) that rehydration starts after a 5 h induction period at the end of which 30% of the diaqua complex forms rapidly.

As far as the rehydration behavior of the anhydrous crystalline L pidolate complex is concerned, it can also be observed (Figure 7B) that the emergence of the crystalline diaqua complex and the vanishing of the anhydrous crystalline complex do not follow the same rate, since the crossing point of the two curves occurs when 35% of the diaqua complex is formed. In other words, this indicates that the decrease of the content in the crystalline anhydrous complex goes faster than the increase of the content in the crystalline diaqua complex: it can be seen in Figure 7B that, when about 50% of the anhydrous crystalline complex has disappeared, only about 20% has been converted to the crystalline diaqua complex. Thus, X ray diffraction experiments show that an amorphous phase transitorily forms up to 30–40% of the sample (see the inset in Figure 7B) while the anhydrous crystalline complex hydrates into the crystalline diaqua complex.

Rehydration, as characterized by isothermal calorimetry for each three compounds, is accompanied by two main effects (see Figure 8): first a broad exothermic peak d and then an endothermic effect f (tentatively delimited by a gray area) that superimposes to peak d. In the case of the amorphous and crystalline anhydrous complexes (curves A and B, respectively), the exothermic effect f is greater than the endothermic effect d, i.e. different from the case of the amorphous racemic complex (curve C), with which an endothermic shift of the baseline is recorded.

In addition, for each (amorphous and crystalline) anhydrous L pidolate complex, a narrow exothermic peak (peak e in Figure 8A and B), which is not seen for the racemic complex (Figure 8C), superimposes just after the maximum of the main exothermic effect d. Since the crystalline complex amorphizes (at least partly) while rehydration occurs, such an additional effect can be ascribed to the change from the amorphous state into the final crystalline diaqua complex. Why such an effect is not recorded while the amorphous anhydrous racemic complex rehydrates under the same conditions remains open to question.

Anyway, it may tentatively be assumed that the exothermic (d) and the endothermic (f) effects are respectively related to the uptake and the subsequent release of water that accompany the transformation of anhydrous complexes into crystalline diaqua complexes (see the TGA curve in Figure 6A). In addition, summing the rehydration related thermal effects as a whole results

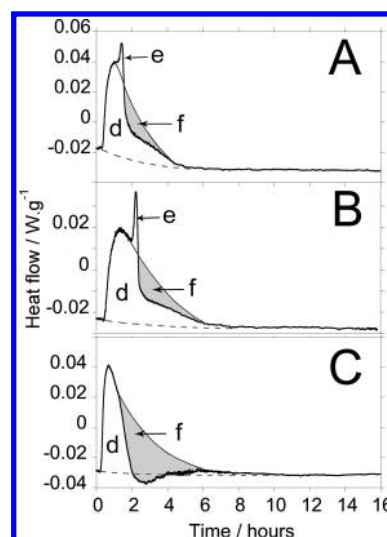


Figure 8. Isothermal rehydration DSC experiments (exo up): (A) anhydrous amorphous Zn(II) L pidolate; (B) anhydrous crystalline Zn(II) L pidolate; (C) anhydrous amorphous Zn(II) DL pidolate.

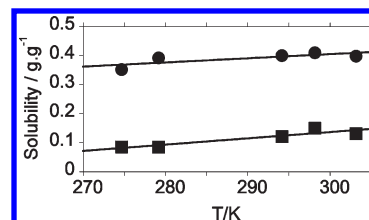


Figure 9. Solubility curves (in grams of diaqua complex per gram of water) versus temperature (in K) for Zn(II) DL pidolate (filled circles) and Zn(II) L pidolate (filled squares) diaqua complexes.

in enthalpy change values of $-120 \text{ kJ} \cdot \text{mol}^{-1}$ for the transformation of anhydrous amorphous L and DL complexes into diaqua complexes and of $-110 \text{ kJ} \cdot \text{mol}^{-1}$ only when the anhydrous crystalline L complex hydrates into the diaqua L complex. The difference ($-10 \text{ kJ} \cdot \text{mol}^{-1}$) is virtually the same as the difference previously found ($-11 \text{ kJ} \cdot \text{mol}^{-1}$) for peak c in Figure 2 ascribed to the crystallization of the amorphous anhydrous L complex.

Relative Stabilities. Because enantiomeric and racemic zinc pidolate diaqua complexes dehydrate and decompose, thus preventing observation of melting, no information on their relative stabilities can be inferred from inequality in their melting points. Nevertheless, the relative stabilities of enantiomeric and racemic diaqua complexes may be inferred from density inequalities as well as solubility inequalities.²⁶ The L diaqua complex exhibits a specific volume smaller than that of the DL diaqua complex (342 and $347 \text{ Å}^3/\text{molecule}$, respectively), and the small difference in the specific volume might indicate that the stability of the L aquacomplex is greater than that of the DL aquacomplex. This is confirmed by the solubility of the DL aquacomplex (0.40 g per gram of water at 298 K), which is about 3 times higher than that for the L aquacomplex (0.13 g per gram of water at 298 K) (Figure 9). According to Jacques et al.,²⁶ such a great difference in solubility should imply a large difference in the melting points of the L and DL diaqua complexes. Then, the melting point of the DL diaqua complex should be lower than that of the L (or D) diaqua complex, assuming that the lower the melting point, the higher the solubility.

CONCLUDING REMARKS

Enantiomeric and racemic Zn(II) pidolate diaqua complexes dehydrate on heating, turning into amorphous or crystalline anhydrous phases that are persistent for only a few hours under ordinary atmospheric humidity conditions.

As far as rehydration and recrystallization of the anhydrous complexes are concerned, it is shown that anhydrous amorphous Zn(II) L and DL pidolates differ in mechanisms of both rehydration and recrystallization. Only the amorphous anhydrous L complex recrystallized into a crystalline anhydrous phase whose crystal structure was solved, thus showing a new (4 + 2) coordination of Zn(II) with an intermediate geometry between distorted tetrahedron and octahedron. Such a case, which is another example of the versatility of the Zn atom coordination, does not persist and turns back to the 4 fold tetrahedral coordination in the presence of water vapor. However, why the anhydrous amorphous DL complex did not recrystallize under the same conditions remains open to question, even if the diffraction patterns of the two amorphous anhydrous solids were found to be very close, which indicates close or virtually identical local orders. It might thus tentatively be suggested that long range ordering (i.e., spontaneous recrystallization) of the amorphous polymeric enantiomer was favored for three complementary reasons: (i) no mirror plane, (ii) no entropy of mixing ($R \ln 2$), and thus (iii) no energy barrier ($R \cdot T \cdot \ln 2 = 1.7 \text{ kJ} \cdot \text{mol}^{-1}$ at 298 K) that might be high enough so as to prevent reconstruction from the amorphous racemic phase into a racemic crystalline anhydrous complex.

As far as the manufacturing and pharmaceutical aspects of the supplementation in zinc through anhydrous pidolates as active pharmaceutical ingredients are concerned, the following may be inferred:

- If anhydrous Zn(II) pidolates were to be obtained by spray drying, they should turn into hydrated phases while standing under ordinary atmospheric conditions.
- If anhydrous Zn(II) pidolates were to be compressed into tablets after mixing with molecular hydrates as excipients, exchange of water molecules might likely occur, at least partly, so as to change the coordination of the zinc atom into its less distorted 4 fold coordination, accompanied with a subsequent change in the conformation of the pidolato ligand. In addition, the process should be accompanied with localized volume changes that could weaken or even shatter the tablets in question.
- Although L enantiomers are usually preferred by manufacturers, for they are recommended by regulatory agencies, it may be remarked that the 3 times greater solubility of the racemic diaqua complex with respect to that of the L enantiomer diaqua complex might favor a better bioavailability through the racemic complex.

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