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ARTICLE

Co-crystallization of racemic amino acids with ZnCl₂: an investigation of chiral selectivity upon coordination to the metal centre.

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ABSTRACT

The amino acids alanine, valine, proline, isoleucine, serine, asparagine, tyrosine, and threonine in their racemic forms have been reacted with ZnCl₂ in different preparative conditions (grinding and LAG, both manual and ball milling, and co-crystallization from solvent). In most cases relatively stable (from days to months) oils were obtained; only in those cases for which single crystals could grow from oils, structural characterisation was possible via X-ray diffraction. Aim of the work has been the investigation of the occurrence of chiral selectivity upon formation of tetrahedral metal coordination complexes or polymers. It has been shown that the co-crystallization reactions lead, in the majority of cases, to crystals of *racemic*-AA₂ZnCl₂, formed by OD homochiral complexes of formula *L*-AA₂ZnCl₂ and *D*-AA₂ZnCl₂. With the *DL*-amino acid threonine, however, crystals of *meso*-AA₂ZnCl₂ have also been obtained, made of OD heterochiral complexes of formula *D,L*-AA₂ZnCl₂. With *DL*-proline both the known *racemic*- and the new *meso*-AA₂ZnCl₂ solids were obtained. Formation of 1D coordination polymers has been observed in the cases of *DL*-asparagine and *DL*-tyrosine with alternating D and L amino acids along the polymeric chain.

Introduction

Chiral resolution of racemic mixtures has always attracted the interest of chemists.¹⁻⁴ In recent times it has become apparent that the investigation of co-crystals,⁵⁻¹² a branch of the burgeoning field of crystal engineering,^{13,14} also provides a viable route to explore chiral resolution of racemic mixtures. In particular, the use of co-crystallization methods to prepare either molecular¹⁵⁻²² or ionic²³⁻²⁵ co-crystals has been shown to be instrumental to this scope. In the case of molecular crystals this is generally achieved by an approach similar to the one used in diastereomeric salt formation,²⁶ where the racemic acid/base forms two structurally distinct diastereomeric salts with an enantiopure base/acid. Recently, it has been shown that certain metal atoms favouring tetrahedral coordination (such as Zn²⁺, but also the Li⁺ cation) show a marked preference for homochiral coordination by selectively linking chiral molecules of the same handedness in racemic crystals.²⁵ In several cases the homochiral preference has also been found to lead to preferential crystallization of conglomerates over that of

racemic crystals. While chiral selection via co-crystallization of a racemic compound with an enantiopure coformer is predictable, chiral resolution *via* coordination to a metal centre, as in metal containing ionic co-crystals (ICCs), is still less understood. The ICCs formed by the amino acids *DL*-histidine²³ and *DL*-proline²⁴ with lithium halides are good examples. In these ICCs the lithium cations are linked selectively with amino acids of the same handedness, forming either conglomerates or racemic crystals constituted of homochiral chains. The homochiral preference of Li⁺ has been attributed to the tetrahedral geometry around the cation. More recently, this hypothesis was tested by co-crystallization of levetiracetam (*S*-etiracetam) and *DL*-etiracetam with ZnCl₂, since zinc is known to favour tetrahedral coordination.²⁷ The racemic crystal was found to contain enantiopure complexes, which could lead to chiral resolution and reversible racemate-conglomerate transformation by changing the racetam:ZnCl₂ stoichiometric ratio.²⁷

In this paper we report an extension of this technique to the co-crystallization of ZnCl₂ with the amino acids alanine, valine, proline, isoleucine, serine, threonine, asparagine, tyrosine in their racemic forms. The intent was that of exploring the possibility of resolving the racemic mixtures *via* coordination to zinc(II). The eight amino acids listed in Chart 1 yielded solid products in a matter of days or, in some cases, months. It should be pointed out, before proceeding, that co-crystallization is herein used as a tool to explore the chiral preference upon

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formation of the zinc complexes, which could be structurally characterised. The obtained products, except for one notable case (*vide infra*), are not co-crystals but crystals of metal complexes, or – if we were to follow IUPAC recommendations – of coordination entities.*

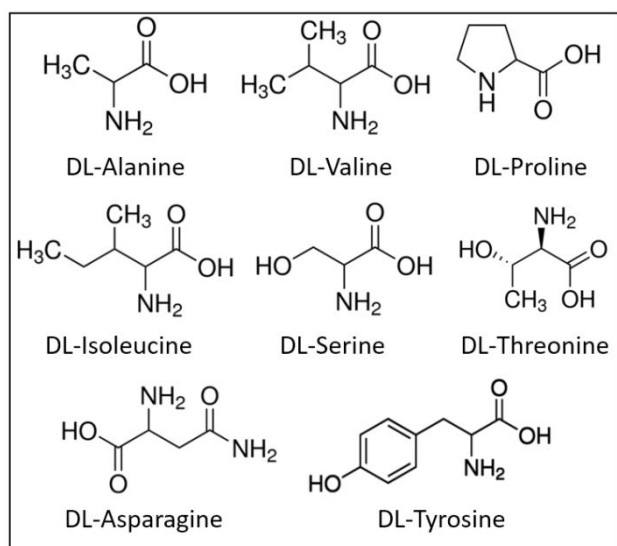
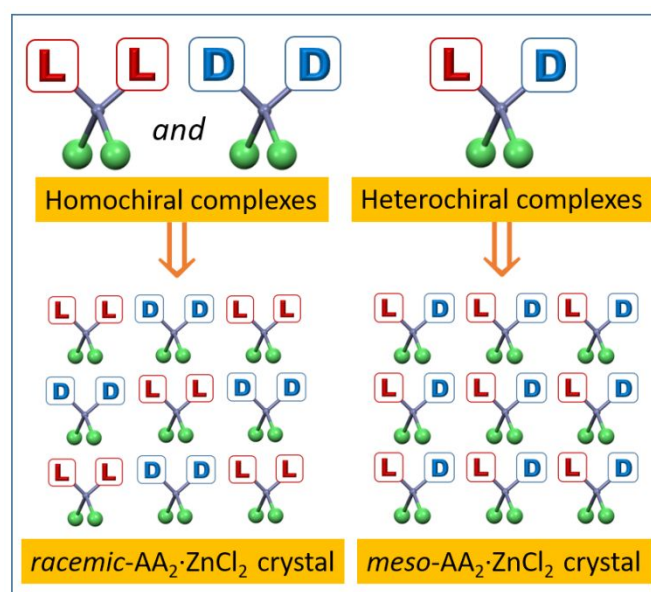


Chart 1. The racemic amino acids yielding solid products upon reaction with ZnCl_2 .

In terms of crystal structures those of $\text{DL-alanine}_2\cdot\text{ZnCl}_2$,²⁸ $\text{DL-valine}_2\cdot\text{ZnCl}_2$,²⁹ and $\text{DL-proline}_2\cdot\text{ZnCl}_2$ ³⁰ had been previously investigated by others. Interestingly, all these compounds show the homochiral choice, i.e. with the Zn^{2+} cation selectively coordinated by amino acids of the same chirality. Needless to say, however, the crystals are racemic and contain both $D\text{-AA}_2\cdot\text{ZnCl}_2$ and $L\text{-AA}_2\cdot\text{ZnCl}_2$ complexes. The heterochiral choice, i.e. molecules containing both D - and L - amino acids, has been observed only for the complexes with threonine and proline, with formation of *meso*-crystalline materials. The two alternative homochiral and heterochiral (*meso*) coordination modes are shown in Scheme 1.

The interactions of zinc(II) with racemic and chiral amino acids have recently been studied by Viedma *et al.*,³¹ who achieved chiral resolution via ball milling of a number of racemic amino acids with a catalytical quantity of ZnO . Coordination modes, stoichiometry and ligands exchange in complexes of zinc(II) with chiral and racemic amino acids, investigated with capillary electrophoresis³² and capillary electrochromatography,³³ also constitute an active field of research in the more general quest of methods to obtain chiral resolution, with possible pharmaceutical implications.³⁴

In the following the preparation modes and structures of the complexes obtained by reaction of the eight amino acids listed in Chart 1 with ZnCl_2 will be described. For sake of clarity and efficacy of comparison we shall refer to them as *racemic*- $\text{AA}_2\cdot\text{ZnCl}_2$ (or $D\text{-AA}_2\cdot\text{ZnCl}_2$ or $L\text{-AA}_2\cdot\text{ZnCl}_2$) and as *catena*- $[(\mu_2\text{-DL-AA})\text{ZnCl}_2]$ complexes rather than as dichlorobis(DL-AA)zinc(II) and dichlorobis(DL-AA)zinc(II) (see Schemes 1 and 2).



Scheme 1. Possible results of the co-crystallization of ZnCl_2 with DL -amino acids: either homochiral or heterochiral $\text{AA}_2\cdot\text{ZnCl}_2$ complexes are obtained, which in turn form *racemic*- and *meso*- $\text{AA}_2\cdot\text{ZnCl}_2$ crystals, respectively.

EXPERIMENTAL PART

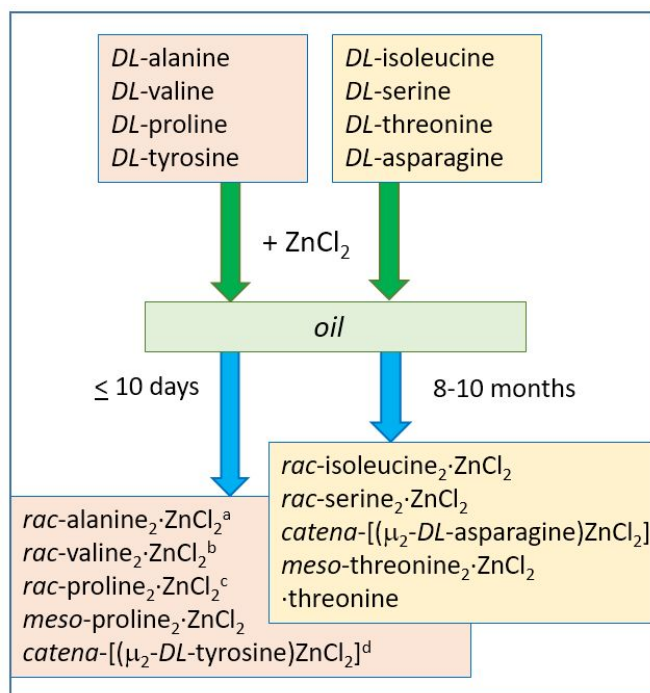
All reagents were purchased either from Merck or TCI Chemical, and used without further purification.

Mechanochemical synthesis

DL -amino acids list in Chart 1 and ZnCl_2 were mixed in a 2:1 stoichiometric ratio via ball milling (0.5 mmol – 0.25 mmol) or manual grinding (agate mortar and pestle). Both methods, with or without the addition of few drops of solvent (kneading or liquid assisted grinding (LAG) conditions^{35, 36} with MeOH , EtOH , H_2O), failed to yield treatable products. In all cases formation of oily “sticky” mixtures was observed, even in the absence of solvent, as ZnCl_2 readily absorbs water from the atmosphere.

Solution synthesis

All the complexes discussed in this paper were instead obtained at room temperature by slow evaporation from undersaturated aqueous solution (2–5 mL) of 1:2 stoichiometric quantities (0.25 mmol – 0.5 mmol) of ZnCl_2 (also ZnBr_2 in the case of proline) and the corresponding amino acids. The evaporation process always resulted in the formation of oil-like products that precipitated as crystalline materials (suitable for X-ray single crystal data collection) after 5–10 days (complexes with alanine, valine, proline, tyrosine), or 8–10 months (complexes with isoleucine, serine, threonine, asparagine) (see Scheme 2). In the case of alanine, valine, proline, threonine, isoleucine and serine attempts with 1:1 stoichiometric ratios invariably yielded the compounds in 1:2 ratio. In the cases of asparagine only a 1:1 product was obtained. In the case of tyrosine a solid product was obtained only if a 4:1 ZnCl_2 :tyrosine stoichiometric ratio was employed.



Scheme 2. Successful co-crystallizations of ZnCl₂ with DL-amino acids. (a) As in ref. 33; (b) as in ref. 34; (c) as in ref. 36 (d) an excess of ZnCl₂ (4:1) was used.

It should also be mentioned that co-crystallization of the amino acids glutamine and tryptophan with ZnCl₂ invariably yielded the starting materials, whereas co-crystallization with leucine, phenylalanine, glutamic acid, histidine, lysine and methionine afforded materials that are still oily after more than a year.

Synthesis via slurry

314.09 mg of proline and 185.91 mg of ZnCl₂ (2:1 ratio) were slurried for 60h in closed vials with 2 mL of MeOH, EtOH or water. Afterwards the suspensions were filtered and the obtained solids analysed via X-ray powder diffraction (see Fig. S-4).

X-ray Diffraction from Powder

For phase identification purposes X-ray powder diffraction patterns were collected on a PANalytical X'Pert Pro Automated diffractometer equipped with an X'celerator detector in Bragg-Brentano geometry, using Cu-Kα radiation (λ=1.5418 Å) without monochromator in 3-40° 2θ range (step size 0.033°; time/step: 20 s; Soller slit 0.04 rad, anti-scatter slit: ½, divergence slit: ¼; 40 mA*40kV).

Single Crystal X-ray Diffraction

Single Crystal data were collected at room temperature with an Oxford Diffraction X'Calibur equipped with a graphite monochromator and a CCD detector. Mo-Kα radiation (λ = 0.71073 Å) was used. Unit cell parameters for both complexes discussed herein are reported in Table S-1. The structure was solved by the Intrinsic Phasing methods and refined by least squares methods against F² using SHELXT-2016³⁷ and SHELXL-2018³⁸ with Olex2 interface.³⁹ Non-hydrogen atoms were

refined anisotropically. H_{CH} atoms were added in calculated positions; H_{OH} and H_{NH} atoms were either located from a Fourier map or added in calculated positions and refined riding on their respective carbon, nitrogen or oxygen atoms. The software Mercury 4.3⁴⁰ was used for graphical representations and for powder patterns simulation on the basis of single crystal data. Crystal data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk). CCDC numbers 2005598-2005605.

Results and discussion

OD Homochiral and heterochiral complexes

Synthesis from solution of zinc chloride with racemic alanine and valine yielded the previously known homochiral complexes [refcodes FACREH,²⁸ ACETUX,²⁹ respectively], which crystallize in *racemic*-AA₂ZnCl₂ crystals (see Scheme 1). Similar behaviour has also been observed in our previous work on the co-crystallization of ZnCl₂ with DL-etiracetam.²⁷ Homochiral complexes were also found in the new crystalline *rac*-isoleucine₂·ZnCl₂ and *rac*-serine₂·ZnCl₂ (see Table S-1), with two molecules of the same handedness bound to the same ZnCl₂ unit, as shown in Figure 1.

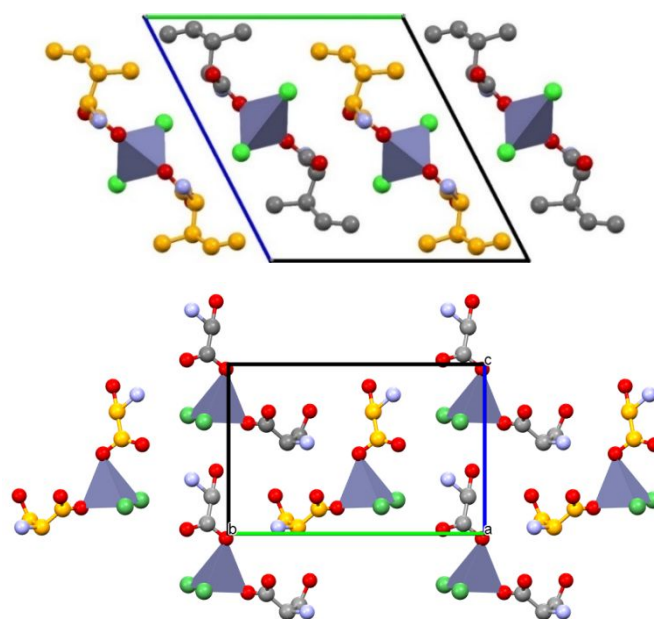


Figure 1. The homochiral complexes in crystalline *rac*-isoleucine₂·ZnCl₂ (top; view in the *bc*-plane) and *rac*-serine₂·ZnCl₂ (bottom; view in the *ab*-plane). H atoms omitted for clarity.

While co-crystallization of alanine and valine with zinc chloride was unsurprising, proline yielded intriguing results. The first reaction of zinc chloride with DL-proline resulted in the growth from oil, after ca. 10 days, of large crystals containing the heterochiral complex shown in Fig. 2 (top), i.e. a *meso*-

proline₂·ZnCl₂. As this proved to be a different result from that reported previously for *rac*-proline₂·ZnCl₂,³⁰ a slurry experiment was performed starting from the reagents (see Experimental): *rac*-proline₂·ZnCl₂ was obtained, thus suggesting a higher stability for this form with respect to the *meso* one. The reaction was then repeated in solution, in order to obtain a larger amount of *meso* crystalline material, but this time – and in all subsequent attempts – *meso*-proline₂·ZnCl₂ could never be prepared again. For sake of comparison between the single crystals of the racemic form and the bulk product, new data was collected at room temperature for *rac*-proline₂·ZnCl₂ (see Table S-1). A comparison between the two forms of proline₂·ZnCl₂ is reported in Figure 2.

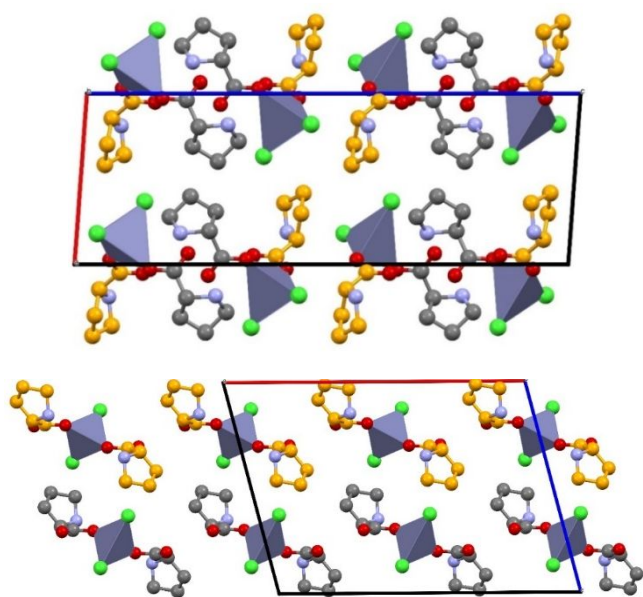


Figure 2. Comparison between crystal packings at room temperature for *meso*-proline₂·ZnCl₂ (top) and *rac*-proline₂·ZnCl₂ (bottom). H atoms omitted for clarity.

In order to understand the unusual behaviour of proline, we explored the possibility of obtaining the *meso*-form using zinc bromide, given that enantiopure *L*-proline₂·ZnBr₂⁴¹ is isomorphous with *L*-proline₂·ZnCl₂.⁴² The product of the solution co-crystallization, however, turned out to be *rac*-proline₂·ZnBr₂, isomorphous with the ZnCl₂ analogue (see Table S-1).

At variance with the trend of homochiral preference shown by the 2:1 complexes (with the notable exception of *meso*-proline₂·ZnCl₂) a heterochiral complex with zinc chloride were obtained also upon co-crystallization with racemic threonine. In this case, the resulting solid can be described as a co-crystal of *meso*-threonine₂·ZnCl₂ with threonine itself, as an additional molecule of threonine is brought in the crystal and it is not involved in coordination to the zinc cation (see Figure 3). *Meso*-threonine₂·ZnCl₂·threonine is therefore a *bona fide* co-crystal of an organic molecule and of a metal complex.

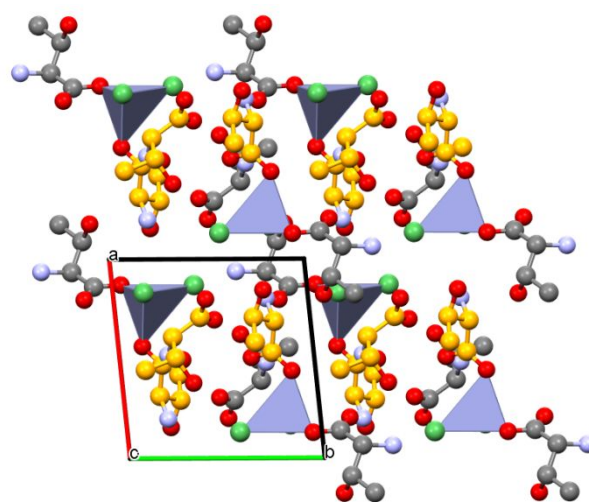


Figure 3. View in the crystallographic *ab*-plane of crystalline *meso*-threonine₂·ZnCl₂·threonine, containing racemic threonine in addition to the heterochiral zinc(II) complexes. H atoms omitted for clarity.

1D coordination polymers

Co-crystallization of zinc chloride with racemic asparagine and tyrosine resulted in the formation of compounds in 1:1 stoichiometric ratio of formula *catena*-[(μ₂-*DL*-asparagine)ZnCl₂] and *catena*-[(μ₂-*DL*-tyrosine)ZnCl₂]. Figures 4 and 5 show the solid state structures of the two crystalline materials characterised by infinite 1D chains. In both cases the chains are formed via *D*- and *L*-amino acid molecules alternatively bridging the ZnCl₂ units. However, the two compounds differ in the coordination mode of the amino acids to zinc(II). In the asparagine coordination polymer one oxygen atom of the carboxylate group and the oxygen atom of the amido C=O bridge two zinc centres, as is it shown in Fig. 4.

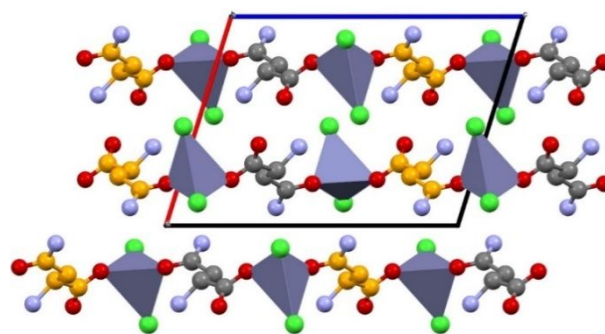


Figure 4. The 1D coordination polymer in crystals of *catena*-[(μ₂-*DL*-asparagine)ZnCl₂]. Note that amino acids of opposite chirality alternate along the chain.

In the tyrosine coordination polymer both oxygen atoms of the

same carboxylate group are involved in the coordination to zinc chloride moieties, as it can be seen in Fig. 5.

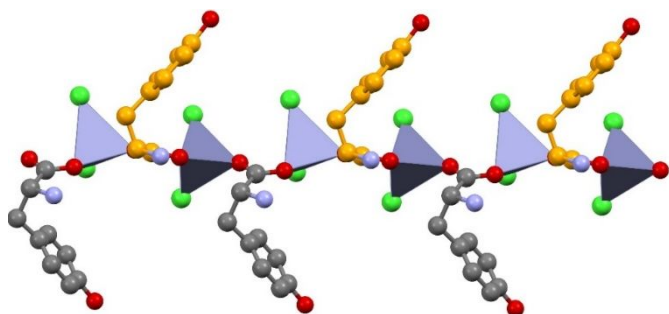


Figure 5. *catena-[(μ₂-DL-tyrosine)ZnCl₂]*. Note how both oxygens of tyrosine carboxylate participate in coordination to the Zn²⁺ cations.

This last mode of coordination is not common: a search in the CSD for complexes of zinc(II) halogenides with amino acids returned only another example (refcode IMEPAT), involving zinc iodide and glycine.⁴⁷

Concluding remarks

In this paper we have reported the results of a series of complexation reactions between amino acids in racemic DL form and ZnCl₂. To prepare the crystalline materials we have adopted a crystal engineering approach based on co-crystallization methods (mechanochemical mixing, slurry, as well as crystallization from solution) previously used by us and many others to explore the formation of hybrid organic-inorganic crystalline solids. The aim of this work, as stated in the Introduction, was that of ascertaining whether the homochiral preference observed previously in the co-crystallization of few racemic compounds with metals such as zinc and lithium that favour tetrahedral coordination was a general phenomenon. To this end, the amino acids alanine, valine, proline, isoleucine, serine, asparagine, tyrosine, and threonine in their DL racemic forms have been reacted with ZnCl₂ in different modes. Crystal structures have been determined in all cases where solid crystalline materials could be obtained, sometimes after a considerable length of time. As a matter of fact, irrespective of the mode of preparation, whether manual grinding or ball milling in neat or *kneading* mode, or crystallization from water solutions, the reactions yielded rather untreatable oily materials that produced crystals after very slow evaporation of the solvent in a matter of days. In some cases, crystals were obtained only after several months. Single crystal structures were determined for the compounds listed in Table 2.

The overall picture that emerges from this comparative study is intriguing. There is indeed a clear indication that, when the stoichiometric ratio amino acid/metal cation is 2:1, the Zn²⁺ centre favours complexation with two molecules of amino acid of the same handedness, i.e. homochiral preference is observed (Fig. S-1). Since the complexes crystallize in achiral,

centrosymmetric, space groups, the homochiral complexation implies that complexes of DD and LL are present in racemic mixture in the crystals. It is worth pointing out that, contrary to what observed in the cases of the ionic co-crystals of proline and histidine with LiX salts (X= Cl, Br, I) there is no separation of the DD and LL complexes into separate crystals, i.e. conglomerates have not (as yet) been observed.

As mentioned above, the proline₂ZnCl₂ case is somewhat special since it is the only case for which both a *rac*- and a *meso*-form (Fig. S-2) of the complex have been isolated and characterised, albeit in a serendipitous way. One would tend to apply to the formation of the *meso*-form in a co-crystallization experiment reasoning analogous to that used to explain formation of metastable (kinetic) crystal forms that, once the stable form has been obtained, can no longer be isolated in the same lab.⁴³⁻⁴⁵ With only one example, this is admittedly very speculative. The fact that DL-proline₂ZnBr₂ is also in the *rac*-form being isostructural and isomorphous with DL-proline₂ZnCl₂ does only confirm that the homochiral preference is undoubtedly preferred.

Another case of heterochiral complexation at the 0D level is represented by the peculiar co-crystal of *meso*-threonine₂ZnCl₂threonine (Fig. S-2). Whether this particular material ought to be regarded as an “accident” of the complex interplay of kinetics and thermodynamics in the construction of a (meta)stable crystalline material or could open the door to exploring the possibility of forming co-crystals or mixed crystals of stable amino acid complexes of Zn with other amino acids also calls for further investigations.

The other interesting outcome of this work is that the 1:1 complexes with asparagine and tyrosine form 1D coordination polymers, whereby the two amino acids are able to act as bidentate divergent ligands. In these cases the *D*- and *L*-amino acids alternate along the 1D polymer so that no chiral preference or segregation is observed (see Fig. S-3).

In summary, this work lends further support to the idea that the clustering of chiral molecules around a tetrahedral centre prefers, with all due exceptions, coordination of amino acids of the same chirality. The difference in relative stability of homo- and hetero-chiral complexes ought to be very small since, at least in the case of proline, and also, although in a fairly different crystalline environment, in the case of threonine, also complexes carrying amino acid of opposite chirality have been observed. We also note that, contrary to what observed in the ionic co-crystals with LiX (X=Cl, Br, I) of proline and histidine, no conglomerate formation has been thus far observed, i.e. the chiral preference shown in the coordination of alanine, valine, proline (in the *racemic* case), isoleucine and serine to zinc(II) remains “confined” to formation of homochiral 0D-complexes in racemic crystals.

We plan to approach the relationship between molecular and crystal structures of *homo*- and *heterochiral* complexes with the aid of computational tools. Also we plan to investigate the behaviour of these systems in non-stoichiometric conditions, i.e. by using non racemic compositions to see if there is way to alter the complexation and crystallization kinetics.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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