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Solid-state chiral resolution mediated by stoichiometry: crystallizing etiracetam with $ZnCl_2$†

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Chiral resolution of racemic etiracetam was achieved *via* co-crystallization with $ZnCl_2$. Depending on the amount of $ZnCl_2$ either a stable racemic compound or a stable conglomerate can be obtained. Excess $ZnCl_2$ triggers the quantitative conversion of the racemate into the conglomerate solid; this unprecedented behaviour was investigated through a racetam/$ZnCl_2$/solvent phase diagram.

Levetiracetam ((*S*)-2-(2-oxopyrrolidin-1-yl)butanamide, *S*-etiracetam) is the active pharmaceutical ingredient (API) of KEPPRA®, an anti-epileptic drug (AED) commercialized by UCB Pharma. Epilepsy is a prevailing chronic neurological disorder or a group of disorders characterized by unprompted seizures which tend to recur.[1] More than 50 million people worldwide are affected by this condition.[2] Levetiracetam is one of the most recent AEDs that has been approved by the Food and Drug Administration.[3]

Etiracetam (Fig. 1) is encountered as a racemic intermediate in the synthesis of levetiracetam (*i.e.* the active *S*-enantiomer of pharmaceutical interest). The *R*-enantiomer contained in the racemic compound does not exert any of the desired biological properties.[4] In order to avoid possible confusion for the reader, in the present article we use the abbreviations *RS*-ETI to indicate etiracetam in its racemic form, *S*-ETI to indicate the active *S*-enantiomer (*i.e.* levetiracetam) and *R*-ETI to indicate the inactive *R*-enantiomer.

Co-crystallization of chiral molecules with organic molecules and inorganic salts has been extensively studied by our groups. The use of solution co-crystallization was proven to be a useful approach for the chiral resolution of racemic mixtures.[5,6] In a similar context, spontaneous chiral resolution upon ionic co-crystal

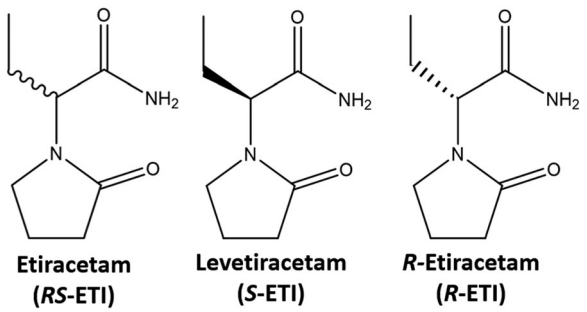

Fig. 1 The chemical structures of etiracetam (*RS*-ETI), levetiracetam (*S*-ETI, the biologically active enantiomer), and the *R*-enantiomer of etiracetam (*R*-ETI).

(ICC)[7–9] formation was discovered by some of us by reacting the amino acid histidine or proline with lithium halides.[10,11] In both cases the Li^+ cations selectively link to molecules of the same chirality, forming enantiopure chains, resulting in a chiral resolution process in the solid state *via* conglomerate formation. A different behaviour was observed for $CaCl_2$, which forms racemic ICCs with DL-histidine,[12] in which each Ca^{2+} is hexacoordinated and interacts with a molecule of D-histidine and a molecule of L-histidine. Thus, it was speculated that one possible reason for chiral preference in lithium ICCs could be the tetrahedral geometry around the lithium cations, which favours the coordination of molecules of the same handedness. In this work we put this hypothesis to test by attempting complexation of enantiopure *S*-etiracetam (levetiracetam) and of racemic *RS*-etiracetam to zinc in the form of their $ZnCl_2$ salts, as zinc is known to favour tetrahedral coordination. Moreover, a ternary phase diagram (TPD) has been constructed as a subset of the more complex *R*-etiracetam:*S*-etiracetam:$ZnCl_2$:EtOH phase diagram, to determine the overall compositions for which the complexes are the only stable phases in EtOH suspension. It will be argued that these phase diagrams could be used to develop a full resolution by entrainment (preferential crystallization),[13,14] focusing on the area where the conglomerate is the only stable phase in suspension.

The reaction of both levetiracetam (*S*-ETI) and etiracetam (*RS*-ETI) with $ZnCl_2$ resulted in the formation of anhydrous

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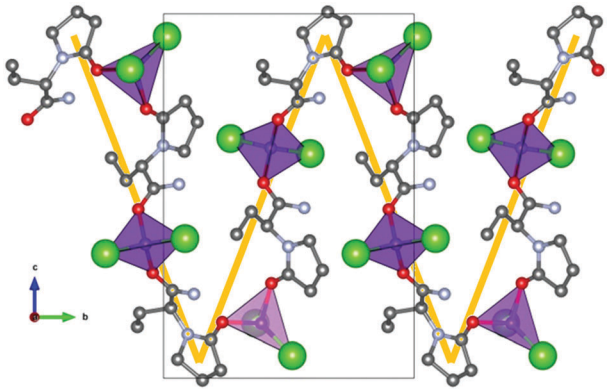
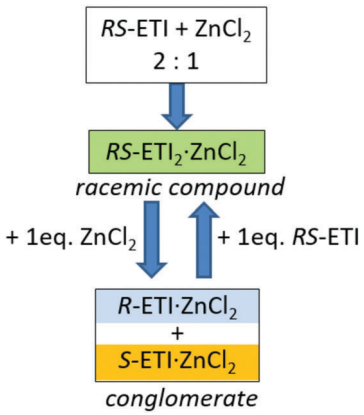


Fig. 2 The infinite zig-zag chain (indicated by the yellow lines) extending in the *bc*-plane in crystalline *S*-ETI·$ZnCl_2$ is formed by $ZnCl_2$ units bridged by *S*-ETI molecules. Hydrogen atoms are omitted for clarity.



Scheme 1 Graphic representation of the *RS*-ETI:$ZnCl_2$ system in the solid state, and the role of stoichiometry in the racemic compound/conglomerate switch mechanism.

complexes (see the ESI†). *S*-ETI·$ZnCl_2$ (Fig. 2) was obtained by crystallization from solution or slurry and by liquid-assisted grinding. A 1 : 1 *S*-ETI : Zn^{2+} stoichiometric ratio is observed with both Zn^{2+} cations, tetrahedrally coordinated by two APIs, which act as bridges between consecutive zinc cations *via* the pyrrolidone and the amido groups (see Fig. 2), and two chloride anions. The zig-zag chains thus formed are held together by hydrogen bonds between the chloride anions and the hydrogen atoms of the amido groups (see Fig. S9, ESI†).

The racemic compound *RS*-etiracetam also combines with $ZnCl_2$ to form the crystalline compound *RS*-ETI_2·$ZnCl_2$ (see Fig. 3). The first difference with *S*-ETI·$ZnCl_2$ can be found in the 2 : 1 stoichiometry, as the crystal contains discrete *RS*-ETI_2·$ZnCl_2$ units. While in *S*-ETI·$ZnCl_2$ both oxygens are involved in the complexation to Zn^{2+}, resulting in infinite 1D chain formation, in *RS*-ETI_2·$ZnCl_2$ only the oxygens of pyrrolidone are bound to Zn^{2+}, and a 0D complex is obtained. The amido groups on etiracetam form typical hydrogen bonded amido rings (see Fig. 3). It is worth pointing out that, in agreement with our working hypothesis, the Zn^{2+} cations selectively bind to molecules of one chirality, forming distinct layers of *R*-ETI_2·$ZnCl_2$ and of *S*-ETI_2·$ZnCl_2$.

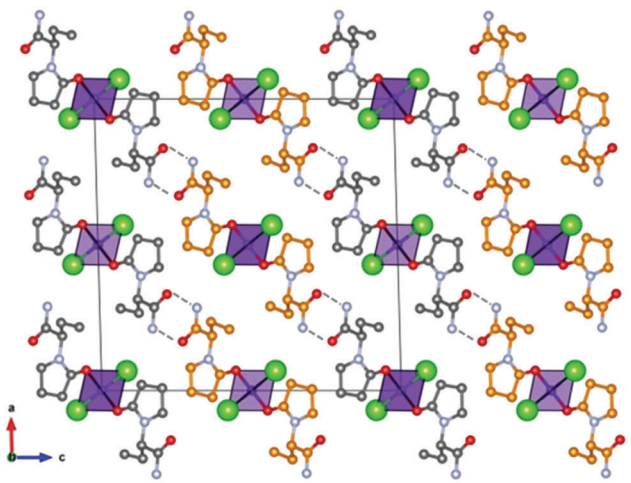


Fig. 3 Crystalline *RS*-ETI_2·$ZnCl_2$: hydrogen bonds between the amido groups of the etiracetam molecules of opposite chirality (colored in grey and orange for clarity). "Orange" and "grey" layers of *R*-ETI_2·$ZnCl_2$ and *S*-ETI_2·$ZnCl_2$ can be seen in projection, parallel to the *a*-axis.

In order to explore the effect of varying the stoichiometric ratios, a series of experiments was performed for both levetiracetam and etiracetam with $ZnCl_2$. In the case of levetiracetam, irrespective of the *S*-ETI : $ZnCl_2$ stoichiometric ratio, a 1 : 1 compound with the formula *S*-ETI·$ZnCl_2$ was invariably obtained, together with unreacted starting material. In the case of etiracetam, in contrast, increasing the amount of $ZnCl_2$ with respect to etiracetam (from a 2 : 1 to 1 : 1 ratio) not only affected the stoichiometry of the product, but also caused the disruption of the racemic compound, followed by reconstruction of both the enantiopure aggregates, leading to the formation of the stable conglomerate *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ (see Scheme 1). To the best of these authors' knowledge, this is the first time that stoichiometry is used as a switch between a racemic compound and a conglomerate.

Different combinations of *RS*-ETI, *S*-ETI and $ZnCl_2$ lead to the solid-state ternary phase diagram reported in Fig. 4, built experimentally *via* multiple LAG experiments.[15,16] Starting with a mixture of *RS*-ETI (1 equiv.) and *S*-ETI (1 equiv.), addition of 0.5 equivalent of $ZnCl_2$ (orange-dotted line) results in the formation of racemic *RS*-ETI_2·$ZnCl_2$. When further 0.5 equivalent of $ZnCl_2$ is added, half of *S*-ETI reacts and correspondingly forms 0.5 equivalent of *S*-ETI·$ZnCl_2$. The third addition of 0.5 equivalent (for a total of 1.5 equiv.) of $ZnCl_2$ causes complete reaction of *S*-ETI, and the solid obtained is a mixture of racemic *RS*-ETI_2·$ZnCl_2$ (1 equiv.) and enantiopure *S*-ETI·$ZnCl_2$ (1 equiv.). The last addition of $ZnCl_2$ (0.5 equiv.) dismantles the racemic compound *RS*-ETI_2·$ZnCl_2$ into the enantiopure counterparts: the final solid mixture will then contain 0.5 equiv. of *R*-ETI·$ZnCl_2$ and 1.5 equiv. of *S*-ETI·$ZnCl_2$. Fig. 4 also indicates which combinations can be expected to be stable in suspension when a solvent is added to the system.

The experimental isoplethal section of the *R*-ETI:*S*-ETI:$ZnCl_2$:EtOH isobaric and isothermal quaternary phase diagram (see Fig. 5 and Fig. S16, ESI†) shows how, by changing the amount of $ZnCl_2$ in solution, both the racemic compound *RS*-ETI_2·$ZnCl_2$

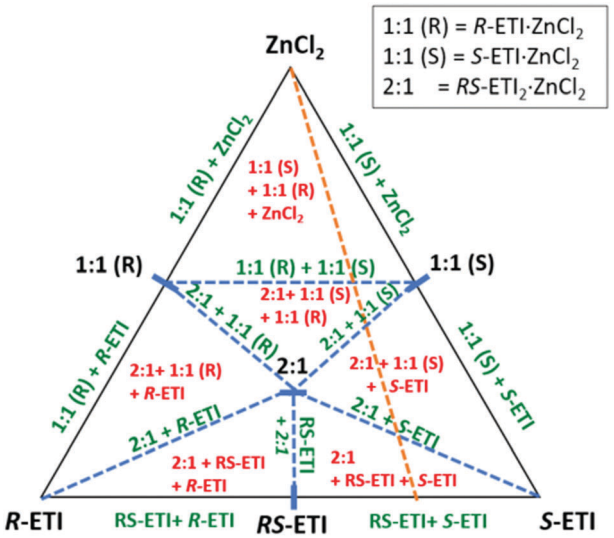


Fig. 4 Ternary solid-state phase diagram for *R*-ETI, *S*-ETI and $ZnCL_2$, showing the thermodynamic solid-state outcome for different combinations of the three components. Pure phases are indicated in black, mixtures of two solid phases in green, and mixtures of three solid phases in red. [To make the diagram easier to read, we use here stoichiometric ratios to indicate the compounds with $ZnCl_2$; thus *R*-ETI·$ZnCl_2$, *S*-ETI·$ZnCl_2$ and *RS*-ETI_2·$ZnCl_2$ are represented with 1 : 1 (*R*), 1 : 1 (*S*) and 2 : 1, respectively.]

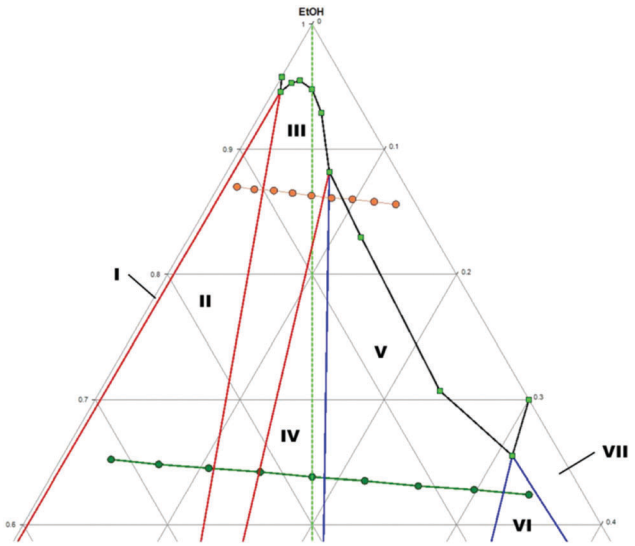


Fig. 5 Enlarged portion of the isoplethal section of the *R*-ETI:*S*-ETI:$ZnCl_2$: ethanol isothermal and isobaric phase diagram at 298 K (mol%). The orange and green dotted points are the experimental starting conditions used to create this diagram (for the full version see Fig. S16, ESI†).

and the conglomerate *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ can be found as thermodynamically stable suspensions. The TPD shows (i) three biphasic regions (**I** = *RS*-ETI + L; **III** = *RS*-ETI_2·$ZnCl_2$ + L; **VII** = $ZnCl_2$ + L), (ii) two triphasic regions (**II** = *RS*-ETI_2·$ZnCl_2$ + *RS*-ETI + L; **V** = *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ + L), and (iii) two quadriphasic regions (**IV** = *RS*-ETI_2·$ZnCl_2$ + *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ + L; **VI** = $ZnCl_2$ + *R*-ETI·$ZnCl_2$ + *S*-ETI·$ZnCl_2$ + L); L is the liquid phase. By targeting the biphasic region **III**, where the racemic compound is stable in suspension, the latter can be isolated through solution crystallization. In region **V** the conglomerate is the stable phase in suspension. Overall, solution data confirm the possibility of using different amounts of $ZnCl_2$ to switch, in suspension, from a thermodynamically stable racemic compound to a thermodynamically stable conglomerate.

In summary, we have reported for the first time that by varying the stoichiometric ratio it is possible to ''switch'' reversibly from a stable racemic compound to a conglomerate. As the conglomerate is accessible in suspension, a resolution process by entrainment could be developed for this system. Furthermore, the results reported above strengthen the fact that co-crystallization with metal ions favouring tetrahedral coordination can be successfully used to achieve chiral selectivity and conglomerate formation from racemic compounds.

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Conflicts of interest

There are no conflicts to declare.

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