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The peculiar case of Levetiracetam and Etiracetam α-ketoglutaric acid cocrystals: obtaining a stable conglomerate of Etiracetam

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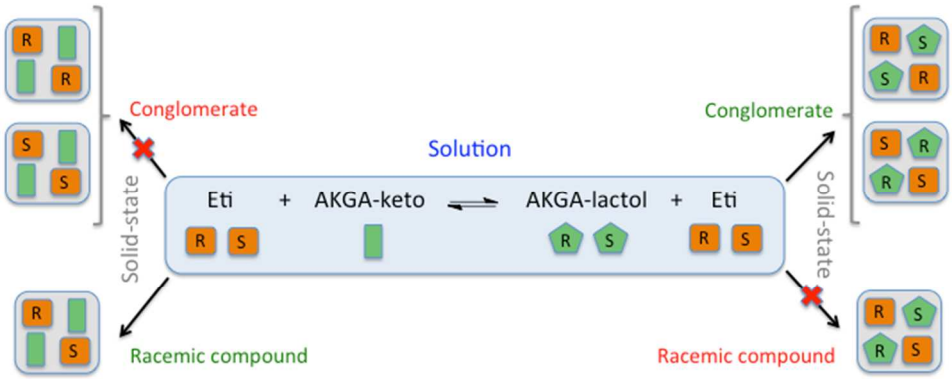
Abstract

In this contribution, we demonstrate that it is possible to obtain the lactol tautomer of alpha-ketoglutaric acid (AKGA) in the solid-state by cocrystallizing it with Leviteracetam, a chiral nootropic drug used to treat epilepsy. Besides, we show that a cocrystal can be isolated with the racemic equivalent of Levetiracetam, Etiracetam (Eti), in which AKGA stays in the keto-form. We also report the existence of a cocrystal conglomerate in the Etiracetam-AKGA system, which is more stable than the racemic cocrystal at room temperature. The existence of a stable conglomerate is put in relation with the enantiospecificity of the Levetiracetam cocrystals, which is likely related to the ability of the Etiracetam enantiomers to stabilize one lactol tautomer at a time in solution, or to promote its formation by H-bonding. By comparing the peculiarities of the system in hand to the general behavior of cocrystallizing chiral systems with and without zwitterionic coformers, we suggest that for a pseudoquaternary cocrystal (made up of two racemate compounds) to exist, the pseudoternary combinations (made up of one racemate and an enantiomer of the second compound) should exist and the enantiomers of the two compounds should form a diastereomeric pair at the binary level, rather than behave enantiospecifically.



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The peculiar case of Levetiracetam and Etiracetam α-ketoglutaric acid cocrystals: obtaining a stable conglomerate of Etiracetam

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Abstract

In this contribution, we demonstrate that it is possible to obtain the lactol tautomer of alpha-ketoglutaric acid (AKGA) in the solid-state by cocrystallizing it with Leviteracetam, a chiral nootropic drug used to treat epilepsy. Besides, we show that a cocrystal can be isolated with the racemic equivalent of Levetiracetam, Etiracetam (Eti), in which AKGA stays in the keto-form. We also report the existence of a cocrystal conglomerate in the Etiracetam-AKGA system, which is more stable than the racemic cocrystal at room temperature. The existence of a stable conglomerate is put in relation with the enantiospecificity of the Levetiracetam cocrystals, which is likely related to the ability of the Etiracetam enantiomers to stabilize one lactol tautomer at a time in solution, or to promote its formation by H-bonding. By comparing the peculiarities of the system in hand to the general behavior of cocrystallizing chiral systems with and without

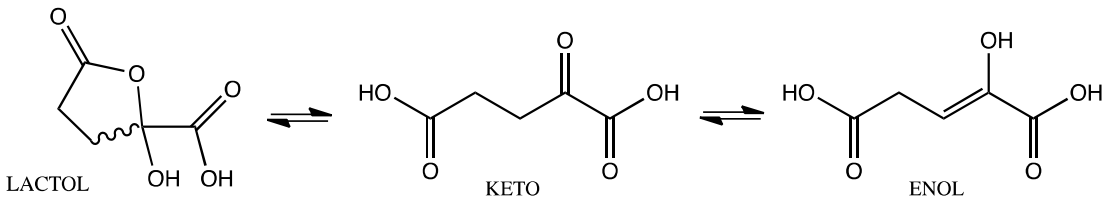
zwitterionic coformers, we suggest that for a pseudoquaternary cocrystal (made up of two racemate compounds) to exist, the pseudoternary combinations (made up of one racemate and an enantiomer of the second compound) should exist and the enantiomers of the two compounds should form a diastereomeric pair at the binary level, rather than behave enantiospecifically.

Introduction

Cocrystals are organic multicomponent crystals containing a stoichiometric ratio of at least two components interacting through directional contacts, and that are not simple solvates or salts (at least one component is non ionized).[1] Cocrystals have been developed extensively in recent years due to their interest in the pharmaceutical industry. Pharmaceutical cocrystals, containing an active pharmaceutical ingredient (API) and one neutral component called coformer, may indeed show very desirable properties in comparison with the isolated drug, such as improved solubility[2] and dissolution rate,[3] but also bioavailability,[4] and handling properties.[5,6] But their potential is not restricted to drug formulation and other applications have been proven, including non-linear optics,[7] and chiral resolution,[8–10] to name but a few.

α-Ketoglutaric acid (AKGA) is a very interesting compound for two reasons. First, it is the substrate of the enzymatic reaction producing L-glutamate.[11] Second, it is involved in three different equilibria in solution[11] due to its double identity.[12] Indeed, it is a α-ketocarboxylic acid and a γ-keto carboxylic acid at the same time and thus shows characteristics of both compounds: being a α-ketocarboxylic acid,[13,14] it is prone to enolization and hydration, while its γ-keto carboxylic acid identity suggests an ability to cyclize into a lactol form (Eq.1). These forms thus coexist in solution, in relative proportions that depend on many factors, including pH and temperature of the solution. This has been the object of several researches.[12] Various NMR

studies[11,12] showed notably that, in aqueous solution, the non-hydrated keto form is predominant and the lactol form inexistant at neutral pH and room temperature, while their percentage have been calculated to be comparable (35% and 30% resp.) at 29°C and pH 0. Besides, their interconversion has been shown to be extremely rapid on the ^{13}C NMR time scale.



Equation 1. Keto-lactol and keto-enol tautomerisms of AKGA in solution.

In the solid-state, however, the cyclic form has never been isolated for this compound, contrary to certain o-acylbenzoic acids.[15] Indeed, there are only two entries for AKGA in the CSD[16] and in both, AKGA exists in its open-chain form. The first one (refcode COTPAC)[17] is the pure compound structure while the second corresponds to a complex with 1,3-bis((Pyrid-2-ylamino)carbonyl)adamantine (refcode RIZWUS).[18]

In this contribution, we demonstrate that it is possible to obtain the lactol form of AKGA by cocrystallizing it with Leviteracetam (Levi, Figure 1), which is a chiral (S) nootropic drug used to treat epilepsy. Besides, we show that a cocrystal can also be isolated with the racemic equivalent of Levi, Etiracetam (Eti, RS), in which AKGA stays in the keto-form. Last but not least, we found that, depending on the experimental conditions, the racemic mixture (Eti + AKGA) may crystallize as a conglomerate found to be more stable than the racemic cocrystal at room temperature. To the author's best knowledge, this is only the second report of a cocrystal conglomerate; the first one being characterized by Neurohr *et al.* in 2015.[19]

Conglomerates are indeed very rare in comparison with racemic crystals, occurring in only 5-10% of racemic single-component crystallizations.[20] But the probability of finding a

conglomerate is expected to be even smaller in case of cocrystallization, as matching coformers for a given compound are not yet predictable and often implies a high-throughput screening procedure.[5,21–24] Yet, conglomerates are intensely researched as various chiral resolution techniques, including Viedma ripening[25–34] and preferential crystallization,[35–38] are conditioned by their existence.

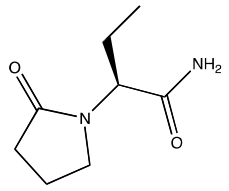


Figure 1. Chemical diagram of (S)-Levi.

Experimental Section

Starting Materials. S-2-(2-oxopyrrolidin-1-yl)butanamide (Levetiracetam) was purchased from Xiamen Top Health Biochem Tech. Co., Ltd. 2-Ketoglutaric acid was purchased from Acros Organics. These materials were used as received, without further purification. (RS)-2-(2-oxopyrrolidin-1-yl)butanamide (Etiracetam) was prepared by racemization of S-2-(2-oxopyrrolidin-1-yl)butanamide. Ten grams of S-2-(2-oxopyrrolidin-1-yl)butanamide together with a catalytic amount (0.05 equiv) of NaOMe was added to 10 mL of MeOH. The solution was kept at reflux under continuous stirring for 24 h and then cooled to room temperature. The compound crystallizes spontaneously. After filtration, the compound was washed twice with MeOH. The recovered compound was used as such. R-2-(2-oxopyrrolidin-1-yl)butanamide cannot be purchased and was therefore obtained from Etiracetam using the chiral resolution procedure described by Springuel et al.[9] A solution containing Etiracetam, R-mandelic acid and acetonitrile in molar percentages of respectively 4.36, 6.63 and 89 mol%, was kept at -10°C and seeded with the cocrystal formed between R-2-(2-oxopyrrolidin-1-yl)butanamide and R-

mandelic acid. Under these conditions, this cocrystal is recovered, as it is the most stable phase in suspension. After filtration, R-2-(2-oxopyrrolidin-1-yl)butanamide was separated from R-mandelic acid with a reverse HPLC system Waters Alliance 2690 equipped with a PDA detector (Waters 2998). A Waters Atlantis T3 column (4.6mm x 50mm x 3.5 _m) has been used with CH_3CN/H_2O 50/50 v/v as dilution solvent. Contrary to its (S)-counterpart, this compound does not show any biological effect and hence does not have any common name. For clarity sake, it will however be referred as (R)-Levi in the following text. Besides, as it was at our disposal in very small quantity, this compound was only used to demonstrate enantiospecicity in the Levi-AKGA system.

Cocrystal Screen. Cocrystals were synthesized by grinding of equimolar mixtures of Levi or Eti and AKGA with or without a drop of solvent (see Table 1). Samples were ground in a RETSCH Mixer Mill MM 400 with a beating frequency of 30 Hertz for at least 10 min (the default grinding time being 90 minutes to ensure complete conversion). The resulting powders were characterized using XRPD. Comparison of the resulting diffraction pattern with the diffraction patterns of the pure phases was used to indicate cocrystal formation. All possible known forms of the pure phases were considered, to avoid confusing cocrystal formation with other phase transformations (e.g. solvate formation, polymorphism).

X-ray Powder Diffraction (XRPD). X-ray diffraction measurements were performed on a Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40 kV and 40 mA and a secondary monochromator allowing selection of the Kα radiation of Cu (λ =1.5418 Å). A scanning range of 2θ values from 2° to 72° at a scan rate of 0.6° min−1 was applied.

Single Crystal Preparation. Single crystals were grown in acetone and/or acetonitrile (one solvent at a time) using an initial non-stoichiometric ratio of both coformers in solution.[22,39,40]

First, suspensions of each component were prepared separately at room temperature. Then, a similar volume of each supernatant solution was filtered and both solutions mixed, such that the resulting solution has a concentration equal to half of the solubilities of each component. Slow evaporating of about half the solvent volume initiated the selective crystallization of the cocrystals with sufficient size.

Single Crystal X-ray Diffraction. Single crystal X-ray diffraction was performed either on a Gemini Ultra R system (4-circle kappa platform, Ruby CCD detector) using Cu Kα radiation (λ = 1.54184 Å) or Mo Kα radiation (λ = 0.71073 Å), or on a Mar345 image plate (Xenocs Fox3D mirrors) using Mo Kα radiation. Cell parameters were estimated from a pre-experiment run and full data sets collected at room temperature. The structures were solved by direct methods with the SHELXS-97 program and then refined on $|F|^2$ using the SHELXL-2014 software.[41] The final reported R_1 value is calculated on |F| for observed reflections (I > 2 sigma(I)). Non-hydrogen atoms were anisotropically refined, and hydrogen atoms were placed at calculated positions and refined in riding mode with isotropic temperature factors fixed at 1.2 times U_{eq} of the parent atoms (1.5 times for methyl groups).

Slurry preparation. Supersaturated solutions of racemic Eti-AKGA 1:1 composition were prepared in two different solvents (acetone and acetonitrile) and using alternatively two different starting materials, for a total of four experiments. In the first two vials (one with each solvent), the suspension was initially composed of Eti-AKGA 1:1 powder obtained by liquid assisted grinding (conglomerate form), while in the last two vials (one with each solvent), the powder resulted from dry grinding of the corresponding mixture (racemic form). These suspensions were left to equilibrate overnight and then seeded with the alternative form (i.e. the form not used as starting material) to test the potential conversion from the starting material to the seeded product,

in case of higher stability of the latter. Suspensions were stirred for one week at room temperature before analyzing the solid phase by XRPD to determine the outcome.

Results

Cocrystal identification

To determine the existence of cocrystals between Levi/Eti and AKGA, liquid assisted grinding (LAG) of the corresponding materials was performed, as this type of experiments has been shown to be among the most effective for cocrystal screening.[42–44] In particular, it enables polymorphism control[6] while avoiding solubility restrictions. The resulting products were analyzed by XRPD and presence of a new phase was detected in both conditions. Then, attempts were made to grow the corresponding single crystals in solution for structural characterization as described in the experimental part. Two novel cocrystal structures were identified. The one with Eti contains AKGA in the keto form while the Levi cocrystal was formed with the lactol AKGA tautomer. Even though cocrystallization has been shown to impact tautomerism,[45] in our case, the result is nevertheless surprising as the lactol tautomer has never been detected up to now in the solid-state.

Furthermore, whereas the XRPD diffractogram of the Levi-AKGA ground material overlapped with the simulated diffractogram obtained from the single crystal, the simulated XRPD diffractogram of the Eti-AKGA cocrystal did not match the XRPD pattern of the ground mixture ((Eti-AKGA_LAG). However, superposition of the diffractograms of Levi-AKGA and the ground mixture Eti-AKGA_LAG revealed identical patterns (Figure 2), indicating the formation of a conglomerate when performing liquid assisted grinding.

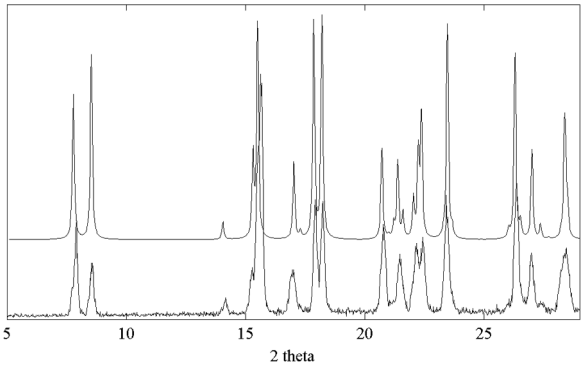


Figure 2. XRPD patterns (up) simulated from the Levi-AKGA single crystal and (down) of ground Eti-AKGA material; the similarity of patterns indicating conglomerate formation.

Dry grinding was also performed on these systems as it is well documented that neat and liquid-assisted grinding may generate different outcomes.[43] In our case, dry grinding of Eti with AKGA indeed led to the racemic compound for which the single crystal was obtained. Neat grinding of the Levi - AKGA mixture however led to the same product as the LAG experiment. This latter observation implies that the tautomeric transformation does not require added solvent to occur in grinding experiments.

Selectivity and stability analyses of the Eti-AKGA system

As a conglomerate was obtained in the case of liquid assisted grinding of Eti-AKGA, while neat grinding led to the formation of the racemic compound, some complementary grinding experiments were performed to assess the kinetics of the system and to evaluate how Eti is dismantled into a conglomerate during liquid assisted grinding (*i.e.* direct transformation, or intermediate transformation into the racemic compound which is then transformed into the conglomerate). For this, the duration of the grinding experiments on Eti - AKGA 1:1 mixtures was varied. Grinding was performed during 4 and 10 min with and without a drop of solvent. It appeared that the conglomerate was totally formed after only 4 min of kneading, while the

conversion of the starting components into the racemic form through dry grinding was not complete at this stage, but well completed after 10 min. In all cases, there were no traces of the reciprocal forms at these smaller grinding times. Both forms are thus rapidly and selectively generated.

To establish the relative stability between the conglomerate and the racemic compound at ambient temperature, slurry experiments[46–49] were carried out. These consist in seeding a suspension of a given composition with all possible phases. The initial suspension progressively evolves toward the most stable phase, following Ostwald's rule of phases. Analysis of the resulting solid phase allows identification of the thermodynamically most stable phase. Solvents with different dielectric constants are often used to vary the solubility profiles and increase the chance of a quick and complete conversion.

In our case, we started by preparing separate suspensions of the conglomerate and the racemic compound in acetone and acetonitrile at room temperature. Each suspension was then seeded with the other solid state (*i.e.* the conglomerate suspension was seeded with the racemic compound, and *vice versa*). Suspensions were then left to equilibrate for a one-week period. In both cases, the solid phase contained only the conglomerate form, indicating the increased stability of the conglomerate over the racemate at room temperature. This was also confirmed by the fact that grinding the racemic compound with a drop of acetonitrile converts it into the conglomerate.

However, their melting points were found to be almost identical (ca. 94°C), suggesting a very slight stability preference in favor of the conglomerate. This situation corresponds to the binary phase diagram shown on Figure 3.

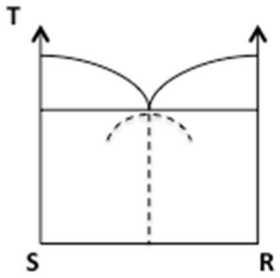


Figure 3. Binary phase diagram of a system characterized by a stable conglomerate (plain curves) and a metastable racemic compound (dash curves).

A summary of all the experiments that were performed in order to characterize the Eti/Levi-AKGA cocrystals can be found in Table 1.

Table 1. Summary of the experimental outcomes of cocrystallization between Eti/Levi and AKGA in various experimental conditions.

Starting materials	**Experiments**	**Conditions** [a]	**Products**	**Solid-state outcomes**
Eti - AKGA 1:1 as solids	Grinding	drop MeCN[b] /MeOH	powder	Conglomerate
	Grinding	dry[c]	powder	Racemic
Eti - AKGA 1:1 in solution	Evaporation	Acetone	Single crystal	Racemic
Conglomerate as supension	Slurry	MeCN/Acetone	powder	Conglomerate
Racemic as supension	Slurry	MeCN/Acetone	powder	Conglomerate

Starting materials	**Experiments**	**Conditions** [a]	**Products**	**Solid-state outcome**
(S)-Levi - AKGA 1:1 solid	Grinding	drop MeCN/MeOH	powder	(S)-Levi_(R)-AKGA
	Grinding	dry	powder	(S)-Levi_(R)-AKGA
(S)-Levi - AKGA 1:1 solution	Evaporation	MeCN/Acetone	Single crystal	(S)-Levi_(R)-AKGA

Starting materials	**Experiments**	**Conditions** [a]	**Products**	**Solid-state outcome**
(R)-Levi - AKGA 1:1 solid	Grinding	drop MeCN	powder	(R)-Levi_(S)-AKGA
	Grinding	dry	powder	(R)-Levi_(S)-AKGA
(R)-Levi - AKGA 1:1 solution	Evaporation	MeCN	Single crystal	(R)-Levi_(S)-AKGA

[a] For all experiments performed in solution or using a drop of solvent, we used one solvent at a time. [b] Complete conversion of the starting components into the conglomerate was achieved after 4 min. [c] Conversion into the racemic form was not complete after 4 min, but well completed after 10 min.

Note that even if a stable conglomerate has been found for this system, it appears non-ideal for use in chiral resolutions techniques such as Viedma ripening and preferential crystallization. Indeed, the first method requires the chiral compound to be easily racemizable in solution, which is not the case of Eti enantiomers. Concerning preferential crystallization, Coquerel carefully explained that the existence of an easily isolable metastable racemic compound, which is the case here, drastically reduces the performances of this method. Indeed, the similar stability of the conglomerate and the racemic compound means that the heterochiral and homochiral interactions are competitive in solution, which increases the probability of wrong docking and hinders the process.[35]

Structural analysis

The cocrystals of AKGA found with (S)-/(R)- and (RS)-racetam were structurally characterized through single crystal analysis. Their crystallographic parameters are displayed in Table 2 and followed by a comparative analysis of the main bonding patterns existing in these three cocrystals. Graph-sets were assigned to synthons that were judged to best represent the structures, using Etter's nomenclature.[50]

Table 2. Crystallographic Parameters of the three AKGA cocrystals

Co-crystals	**(RS)-AKGA**	**(S)-AKGA**	**(R)-AKGA**
Structural formula	$(C_8H_{14}N_2O_2)$ $(C_5H_6O_5)$	$(C_8H_{14}N_2O_2)$ $(C_5H_6O_5)$	$(C_8H_{14}N_2O_2)$ $(C_5H_6O_5)$
Formula weight (g/mol)	316,31	316,31	316,31
Space system	triclinic	monoclinic	monoclinic
Space group	*P*-1	$P\,2_1$	$P\,2_1$
a (Å)	5,5195(2)	11,6406(8)	11,7707(15)
b (Å)	11,1809(8)	5,5396(2)	5,5329(4)
c (Å)	13,5104(12)	12,7812(9)	12,706(2)
α (°)	112,193(8)	90	90
β (°)	99,168(5)	115,940(9)	115,831(18)
γ (°)	95,746(5)	90	90

V (Å^3)	750,326	741,152	744,812
Z	2	2	2
R-factor (%)	4,43	6,67	7,34
Density	1,42	1,42	1,42
Radiation	Mo K(α)	Cu K(α)	Mo K(α)
Temperature (K)	150	293	293

Etiracetam- α-ketoglutaric acid (1 :1) ("Eti-AKGA" or "RS-AKGA"). The RS-AKGA co-crystal crystallizes from acetone in a triclinic system with space group *P*-1. The unit cell contains two molecules of Eti and two molecules of AKGA as keto tautomer. An amide-carboxylic acid heterosynthon, described as $R^2_2(8)$, is constituted between the carbamoyl of Eti and the carboxylic acid function of AKGA adjacent to the ketone (Figure 4). In addition, two molecules of Eti and two molecules of AKGA form a tetramer including two hydrogen bonds of the $R^2_2(8)$ heterosynthon mentioned above and two others binding the AKGA ketone to the carbamoyl trans hydrogen of Eti. This tetramer may be characterized by either an "inner" $R^4_4(14)$ ring motif or an "outer" $R^4_4(18)$ ring motif (Figure 4 middle and right), depending on the $R^2_2(8)$ portion included. Finally, the second carboxylic group of AKGA is hydrogen bonded to the carbonyl of the cyclic amide (oxopyrrolidin) of Eti, forming a dimer oriented along the c-axis. However, as there is one extra acceptor in comparison with the total number of donors (two donors on each partner), the second carbonyl of AKGA is not involved in any strong H-bond. Each molecule of the co-crystal is thus involved in four H-bonds.

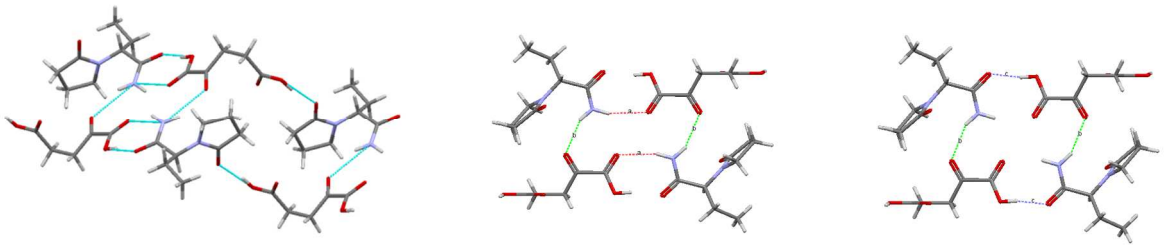


Figure 4. Hydrogen bonds network in RS- AKGA cocrystal showing all types of interactions (left), the inner $R^4_4(14)$ ring (middle) and the outer $R^4_4(18)$ ring motifs (right).

These motifs form stepwise columns directed along the *c*-axis and stacked along *a* and *b*-axes (Figure 5). Columns are two-molecules wide in the *b*-direction, with ethyl groups of Eti molecules pointing outward and facing equivalent groups in neighbouring columns.

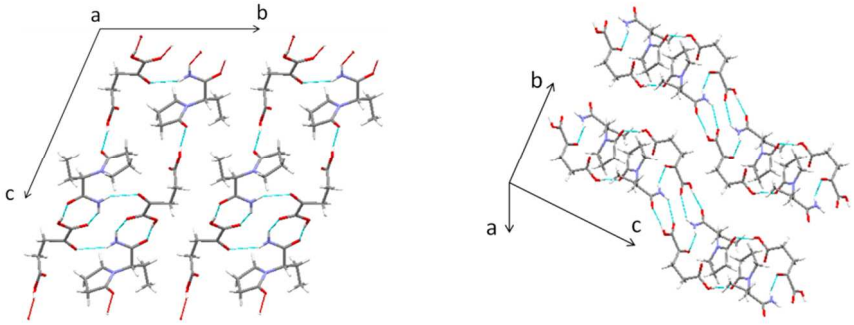


Figure 5. Columnar Stacking in RS- AKGA cocrystal (a) in the *bc*-plane and (b) showing the steps in the columns.

(S)-Levetiracetam- α-ketoglutaric acid (1 :1) ("S-Levi_R-AKGA" or "S-AKGA"). The S-AKGA co-crystal was successfully grown from both acetone and acetonitrile, in a monoclinic system with space group $P2_1$. The unit cell contains two molecules of Levi and two molecules of AKGA in lactol configuration with (R)-chirality exclusively.

Hydrogen bonding patterns in this cocrystal may be described by a $R^2_2(9)$ ring and one $C^2_2(11)$ chain (Figure 6). The ring motif is formed by the carbamoyl (C=O and adjacent H) of a first molecule of Levi with the carboxylic acceptor and adjacent hydroxyl of AKGA. The pyrrolidone carbonyl of a second molecule of Levi then accepts the carboxylic donor of AKGA, which in turn interacts with the trans carbamoyl hydrogen of a third molecule of Levi. This constitutes a chain that involves two parallel molecules of Levi and propagates along the *b*-axis.

Hence, as for the (RS)-AKGA cocrystal, each molecule takes part in four H-bonds. But while all donor and acceptor atoms of Levi are involved in H-bonding, the ester function of AKGA

remains unoccupied. This is due to the bifurcation of the AKGA carboxyl that makes the ester acceptors redundant.

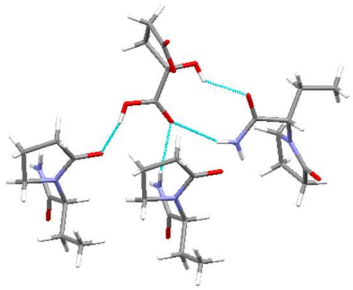


Figure 6. View of main H-bondings in (S)-AKGA cocrystal showing the $R^2_2(9)$ ring motif and the $C^2_2(11)$ chain involving two parallel molecules of Levi.

On the whole, S-AKGA exhibits a columnar stacking. All the hydrogen bonds are located inside the columns, forming a complicated and interlocked network. Columns are directed along the *b*-axis and stacked in the two other directions (Figure 7). In a column, ester groups of AKGA and hydrocarbonated groups of Levi point outward, such that Levi ethyl groups on one column interact with ester or ethyl groups from other columns, holding them together.

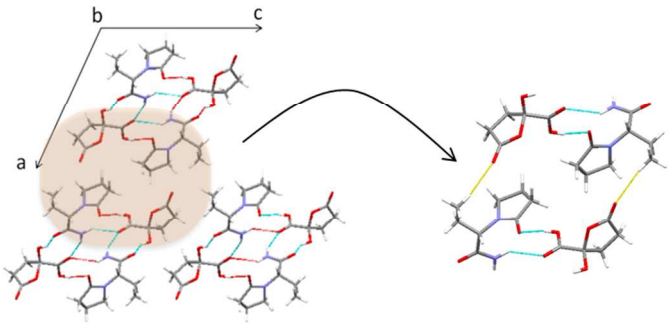


Figure 7. Columnar stacking along *b*-axis in (S)-AKGA cocrystal, showing C-H..O contacts (yellow) between the Levi ethyl and the AKGA ester of different columns.

(R)-Levetiracetam- α-ketoglutaric acid (1 :1) ("R-Levi_S-AKGA" or "R-AKGA"). This cocrystal crystallizes from acetonitrile in a monoclinic system with space group $P2_1$. As it is the

mirror image of the (S)-Levi_(R)-AKGA cocrystal, it differs from this latter by the presence of AKGA in the (S)-enantiomeric lactol form. Structural parameters are almost identical to those of the (S)-Levi cocrystal. Identical hydrogen bonding motif and tridimensional patterns are observed.

Discussion

In view of these observations, three questions arose. First, why was it possible to isolate AKGA in lactol form at the solid state in presence of Levi? Second, why did we not find any traces of a cocrystal form involving (S)/(R)-Levi and AKGA in the keto form? Finally, is there any apparent reason behind the formation of a stable conglomerate in this case? Several elements may be considered to address these questions and will be discussed sequentially.

Lactol formation

A way to rationalize AKGA cyclization in the enantiopure cocrystals consists in paying attention to its mechanism. In particular, one has to consider the two types of factors that influence the intramolecular addition of the carboxyl to the carbonyl, leading to the cyclization.[51] The first type is electronic and refers to the presence of groups adjacent to the ketone and/or the γ-carboxy group that may affect their electro-/nucleo-philic character respectively and/or induce/prevent resonance stabilization. The second type is geometric and concerns the proximity in space of these two functional groups.[52] These factors were illustrated by Jones and Desio to justify the predominance of one isomer (acid or ester) in function of the nature and position of substituents in o-acylbenzoic acids.[15] Similarly, Winston et al.[53] found that for lactones prepared by trichloromethylation of anhydrides, the stability of the lactone form in solution depends on

the distance between acids and trichloromethyl groups in the keto-forms. They also evoked internal rotation preventing coplanarity and ring-chain tautomerism in non-cyclic compounds.

Hence, if AKGA is able to cyclize, it is due to the fact that it possesses a carboxylic acid function in both *alpha* and *gamma* positions of the ketone. Indeed, the one in *alpha* increases the electrophilic character of the ketone while the one in *gamma* makes the 5-membered lactol stable in certain conditions. The reason for the absence of a crystal structure of pure AKGA as lactol may be due to its conformational flexibility. Indeed, there exists several cyclic γ-keto-carboxylic acids crystallized in the ring-form due to their geometrical restrictions.[15,51]

However, when Levi (or its R-equivalent) is added to the solution, it is suspected to selectively stabilize one enantiomer of the lactol form or promote its formation through H-bonding (Figure 8 a and b resp.); which thus influences the corresponding equilibrium. This was already suggested by Valter concerning the solvation effect on γ-aldehydo- and γ-keto-carboxylic acids: "intermolecular hydrogen bonds may play an important part in stabilizing a particular form, the cyclic isomer showing a greater tendency to form such bonds involving both carbonyl and hydroxyl groups".[51] The exact mechanism is nonetheless rather difficult to ascertain as cocrystallization from solution is complex and involves different equilibria,[39,40] and was thus not investigated here.

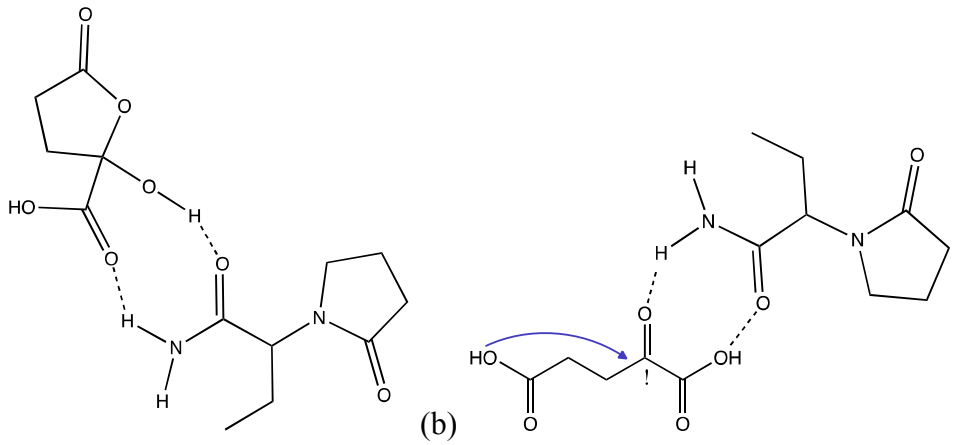


Figure 8. Chemical diagrams showing potential hydrogen bonds occurring in solution that could hypothetically (a) block AKGA in the lactol form or (b) promote its formation by activating the ketone for the intra-molecular attack by the carboxylic acid in *gamma*.

Absence of Levi-AKGA cocrystal with keto-AKGA

Another interesting feature of this work, concerns the fact that thus far we observed no cocrystal of Levi with the keto form of AKGA, whereas this form does appear when cocrystallizing with Eti. It could be that such form exists and that we simply did not encounter it yet. Even though one could argue that this cocrystal should exist under certain conditions, some structural considerations suggest a decreased stability of the potential Levi-AKGA(keto) cocrystal when compared to the existing racemic equivalent.

These considerations arise from the analysis of the Eti-/Levi-cocrystals with oxalic acid (OXA) ("RS-OXA" and "S-OXA", refcodes XOGPAM and XOGPEG resp.).[54] OXA and AKGA form similar H-bonding pattern with Eti in their respective cocrystals (Figure 9), due to their structural resemblance. Besides, OXA also successfully cocrystallizes with Levi, giving us an idea of what the Levi-AKGA cocrystal with keto-AKGA would look like. Hence, one could expect conclusions drawn from a (RS)-OXA and (S)-OXA comparison to be reasonably valid for the (RS)- and (S)-AKGA system.

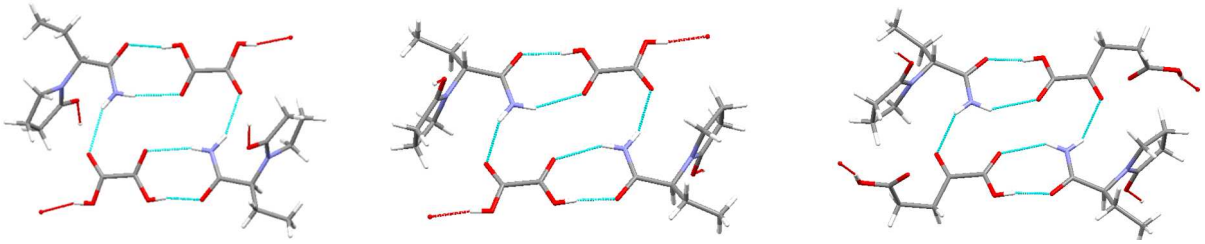


Figure 9. Hydrogen bonding rings in (S)-OXA (left), (RS)-OXA (middle) and (RS)-AKGA (right).

(RS)-OXA and (S)-OXA cocrystals are characterized by identical H-bonding patterns (Figure 9), which results in relatively similar PXRD patterns. But, as the first cocrystal is racemic and the other one chiral, their arrangements must differ in some ways. In fact, the main difference between the two cocrystals lies in the conformation of the racetam. The (S)-OXA cocrystal has twice the number of molecules per asymmetric unit than the (RS)-OXA cocrystal, with the two symmetry-independent molecules of Levi adopting different conformations. In the first conformation, the hydrogen atom on the asymmetric carbon points in the same direction as the oxopyrridin carbonyl ("cis-conformation") while this is contrary in the second conformation ("trans-conformation") (Figure 10). Doing so, the crystal structure of (S)-OXA mimics the centrosymmetric group $P2_1/c$ adopted by the (RS)-OXA cocrystal, with a pseudocenter of inversion relating the two independent molecules of Levi and a pseudo glide plane *c*. This imitation attempt suggests a particularly desirable and thus efficient packing of the racemic crystal.

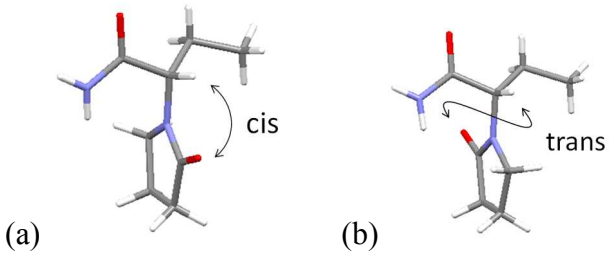
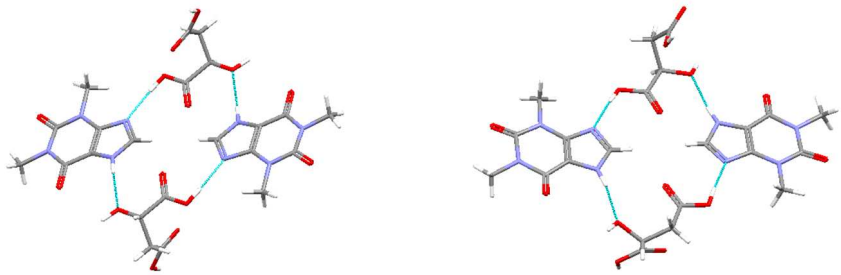


Figure 10. Cis- and trans-conformations of Levi in (S)-OXA cocrystal (left and right resp.).

Besides, among the 17 structures with either (S)-Levi or Eti recorded in the CSD (2015 release) (including the OXA cocrystals), the racetam always adopts the cis-conformation; except in (S)-OXA where both are encountered. The cis-conformation is thus expected to be more stable

than the trans-conformation, as confirmed by their computed single-point energies showing the cis-conformation to be 14 kJ mol $^{-1}$ lower in energy.*

Moreover, the situation is highly similar to the one observed in the structures of the racemic and chiral theophylline – malic acid (tp-ma) cocrystals as described by Friscic *et al.*[55] In this system, the racemic and chiral cocrystals also show similar PXRD patterns and H-bond topologies. Besides, the same $R^4_4(18)$ motif is encountered in the racemic (tp).(DL-ma) cocrystal as in the (RS)-AKGA and (RS)-OXA cocrystals (Figure 10, left). However, as the asymmetric carbon of malic acid molecules is included in the H-bonded ring motif, a conformation change in malic acid molecules is not sufficient to accommodate a chiral space group, as observed for the Levi-OXA cocrystal. In this case, the packing that most mimics the racemic (tp).(DL-ma) cocrystal involves different conformations and different connectivities (*i.e.* the two symmetry-independent molecules of malic acid do not interact with theophylline through the same moieties), which results instead in a $R^4_4(19)$ motif (Figure 11, right). The two conformations were also calculated to have a 15 kJ mol $^{-1}$ energy difference and the presence of the less stable conformer in (tp).(D-ma) was suggested to account for the difference in hydration stabilities and thermal behaviour between the racemic and chiral cocrystals.



* Single point energies were computed using the Gaussian series program with B3LYP/6-31G(d,p) method, and provided a difference of 14.27 kJ mol^{-1} between the two conformations.

Figure 11. $R^4_4(18)$ and $R^4_4(19)$ ring motifs resp. in racemic (left, refcode CIZTAH) and chiral (right, refcode COCDOO) theophylline – malic acid cocrystals.

Hence, one might expect that the conformational features of Levi molecules in the virtual Levi- AKGA(keto) cocrystal would destabilize the overall structure, in comparison with the Eti-AKGA(keto) cocrystal. Indeed, the energetic difference between the two conformations is of the same order of magnitude than the usual stabilization energy of cocrystals estimated by *ab initio* studies.[56–58] And the competition with the Levi- AKGA(lactol) form may make the keto version undetectable.

Besides, this analysis confirms the relevance of considering, for the design of multicomponent crystals, larger synthons than the ones commonly used.[59] In this case, the famous $R^2_2(8)$ motif is indeed little representative of the overall structures while the recurrence of the $R^4_4(18)$ motif in both chiral and racemic cocrystals seems to indicate a very efficient packing and possibly a greater predictive power of this motif.

Conglomerate increased stability

The last point of this analysis concerns the existence of a conglomerate in this system and the origin of its higher stability.

A racemic solution may crystallize, by decreasing order of probability, as a racemic compound, a conglomerate or a solid solution. In a racemic compound, both enantiomers are present in the same quantity in the crystal lattice. In a conglomerate, the two enantiomers crystallize independently (*i.e.* they form homochiral crystals). In a solid solution for various compositions, both enantiomers are distributed at random in the same crystal network. Solid solution formation is rare for organic compounds and will not be considered in the following discussion.

Conglomerates are statistically disadvantaged in comparison with racemic compounds for two reasons.[60] The first one is thermodynamic. There are simply less packing arrangements available to accommodate chiral crystals. In consequence, as nicely expressed by Brock *et al.*, "it seems likely that the best of many possible racemic packing arrangements is to be preferred to the best of fewer possible chiral arrangements". The second reason concerns the crystallization kinetics. In a racemic solution, the rate of formation of chiral crystals is reduced in comparison with the nucleation of racemic crystals. Indeed, only half of the molecules (the "right" enantiomer) that come in contact with an existing chiral cluster will be suited for its development, whereas molecules of both enantiomers will find a matching site on the racemic clusters. This contrasts with polymorphism, for which less stable forms are usually kinetically favored, as poorer arrangements may be generated more easily. Conglomerates are thus often thermodynamically penalized and not really preferred kinetically either.

Conglomerates are thus expected to spontaneously occur only when their stability is favorable or when the energy difference between the racemic compound and the conglomerate is relatively small. This may be the case when the two structures display a high level of packing similarities, such as homochiral columns or layers, and thus comparable densities.

This is however, not what happens in the system described here. Indeed, the racemic compound and the conglomerate found for this system differ by the nature of AKGA tautomer and are thus not directly related neither structurally, nor energetically. In fact, it is preferable to virtually separate this system (Eti and AKGA) into two systems (Figure 12): one with AKGA in the keto form on one hand and one with AKGA in the lactol form on the other. In each system, the observed form (*i.e.* racemic compound or conglomerate) is more stable than the other possible outcome to such extent that the latter is not formed. The greater stability of the racemic

compound in the first system involving a keto-AKGA has indeed been suggested in the previous section and is likely due to the reduced stability of the hypothetical enantiopure crystals involving keto-AKGA. Concerning the second system (lactol-AKGA), we shall refer to our earlier work on enantiospecificity.

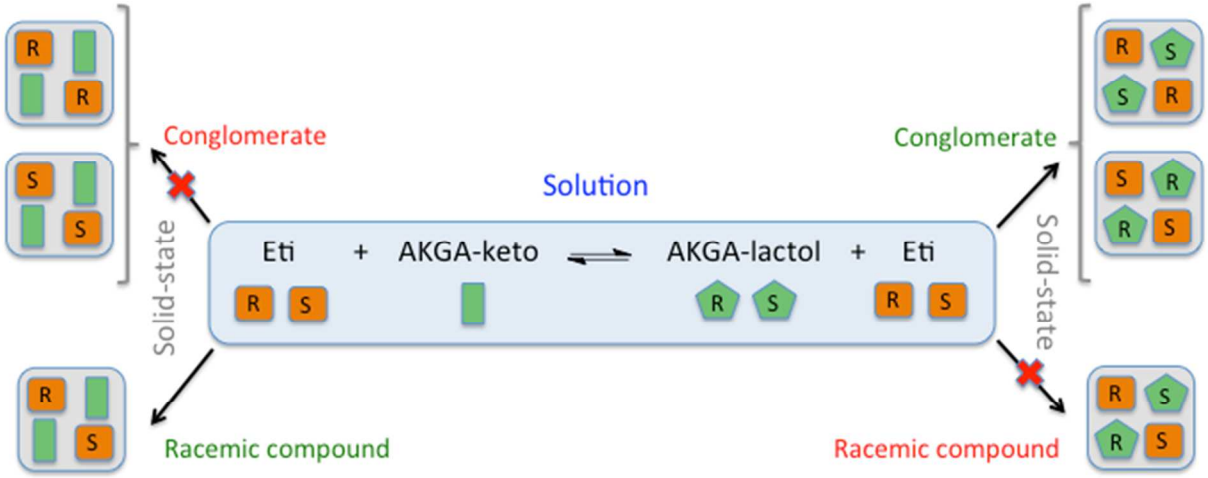


Figure 12. Schematic representation of the two virtual systems featuring Eti and AKGA in solution, and their respective outcomes in the solid-state.

Two optically active compounds cocrystallize enantiospecifically when only one of the two enantiomers of the first pair (RS) cocrystallizes with an enantiomer of the second pair (distinguished as DL). This behaviour is represented by the binary level of situation A in Table 3 and may be opposed to the formation of diastereomeric pairs, which involves both enantiomers cocrystallizing with the chiral coformer (binary level of situation B in Table 3). A recent contribution showed that enantiospecific cocrystallization is frequent between two optically active compounds in contrast with chiral salts, which usually form diastereomeric pairs.[61]

To explain this difference between cocrystals and salts, Springuel and coworkers[61] invoked the very weak stabilization energy of cocrystals with respect to salts. Indeed, it has been estimated by *ab initio* calculations that the energy difference between a cocrystal and its separate

components is often inferior to 10 kJ/mol (which is similar to the energy difference between polymorphs),[56–58] while the stabilization free energy may amount to 400 kJ/mol in case of salt formation. For that matter, cocrystals are very sensitive to minor changes in secondary interactions (π-stacking, Van der Waals contacts...), as the one induced by a change of chirality, even when similar H-bonding occurs. Systems involving zwitterionic coformers lie in-between, as charge-assisted interactions are stronger than conventional H-bonds, but weaker than ionic interactions. In practice, they usually form diastereomeric pairs as well.[62] But one could also evoke the position of the chiral center with respect to the functional groups potentially interacting, to account for cocrystal enantiospecificity. For example, H-bonding motifs including the chiral center or close to it may be more sensitive to the steric profile of the coformer and be allowed with only one of its two enantiomers.

These authors also studied cocrystallization between racemic compounds and in particular the likelihood of forming pseudoternary (*i.e.* one racemic compound with one chiral coformer) and pseudoquaternary (*i.e.* two racemic compounds) cocrystals.[10] They analyzed nine different systems forming at least one binary cocrystal, either in an enantiospecic manner (7/9) or as a diastereomeric pair (2/9). Among these, they found only two pseudoternary cocrystals and one pseudoquaternary cocrystal. The system forming a pseudoquaternary cocrystal (Eti with methylsuccinic acid) is also one of the two systems for which a ternary cocrystal is formed, as well as for which a diastereomeric pair is observed. In other words, a pseudoquaternary cocrystal was encountered only when all the binary and ternary combinations were also successful (Table 3, situation B).

Table 3. Some possible interactions between two racemates (RS and DL) or the different combinations of their enantiomers.

	Binary	Ternary	Quaternary
A	*Enantiospecific* R + D → RD R + L → /	R + DL → /	RS + DL → /
B	*Diastereomeric* R + D → RD R + L → RL	R + DL → RDL D + RS → DRS	RS + DL → RSDL

To rationalize this behaviour, one may proceed in stages. Ternary cocrystals are expected to be less likely with a chiral coformer than with an achiral one,[54] as the pseudoternary cocrystal RDL cannot adopt a centrosymmetric packing. This is the contrary in case of an achiral coformer A as for this latter the pseudoternary cocrystal ARS has high chances to display such an arrangement. Besides, pseudoternary cocrystallization would be more likely when one enantiomer of the first pair doesn't have a strong preference for an enantiomer of the second pair (*i.e.* when there is no enantiospecific cocrystallization at the binary level) and rather forms satisfactory interactions with both enantiomers. Hence the occurrence of pseudoternary cocrystals may suggest a preponderant role of the interactions in these systems and less strict requirements on packing. In these flexible systems, pseudoquaternary cocrystals are thus expected to be more likely as well.

This could explain why there is no racemic cocrystal of Eti with AKGA-lactol. Indeed, AKGA is chiral in the lactol form and the corresponding racemic cocrystal could thus be considered as a pseudoquaternary cocrystal. Yet there are no pseudoternary cocrystals in this system, as this would imply for either Eti to crystallize with one of the lactol forms of AKGA or Levi with both lactol forms of AKGA, which is not observed. Furthermore, one can also consider that the binary combinations are enantiospecific, as Levi prefers to crystallize with the R-form of AKGA (and reciprocally for the (R)-Levi); even if in practice the enantiomers of AKGA-lactol were not introduced separately but created in situ. In fact, enantiospecificity in this case is probably due to the cyclization mechanism of AKGA. All these outcomes are summarized in Table 4.

Table 4. Crystalline outcomes of the different combinations of enantiomers of Eti and AKGA-lactol.

Binary	Ternary	Quaternary
Enantiospecific	Eti + (R)-AKGA ➔ /	Eti + (RS)-AKGA ➔ /
(S)-Levi + (R)-AKGA ➔ (S)-Levi_(R)-AKGA	Eti + (S)-AKGA ➔ /	
(S)-Levi + (S)-AKGA ➔ /	(S)-Levi + (RS)-AKGA ➔ /	

Even though this analysis is based on a very limited number of cocrystallizing systems, it can be placed in parallel with systems involving zwitterionic coformers that easily form diastereomeric pairs and which in consequence easily generate all higher order combinations.[63]

Hence the fact that a conglomerate has been easily isolated in this system should be put in relation to the ability of AKGA to cyclize in solution and likely to the ability of the enantiomers of Eti to stabilize the lactol tautomer. Even though the peculiarities of this system are not very likely to occur for many other systems, they do show that formation of a conglomerate through cocrystallization is a possibility.

Besides, the conglomerate being more stable than the racemic compound should also be taken with care, as the ring-chain tautomerism equilibrium has been proven to depend on the temperature, nature of the solvent and pH. The stability ranking and the ease of formation of the conglomerate with respect to the racemic cocrystal may therefore be affected by varying these parameters. A full study allowing for a comprehensive rationalization of this phenomenon goes however beyond the scope of this work.

Conclusion

In this contribution, we report three novel cocrystal structures involving AKGA and (S)-/(R)-Levi or (RS)-Eti. Surprisingly, the Levi cocrystals are formed with the lactol tautomer of AKGA, which has never been isolated in the solid-state up to now. These cocrystals may be generated by neat or liquid-assisted grinding; indicating that solvent is not required for the tautomeric equilibrium to take place. On the contrary, the presence of Levi in the medium is suspected to influence the equilibrium by selectively stabilizing one enantiomer of the lactol form at a time (depending on the nature of the Levi enantiomer) or promote its formation by H-bonding.

Concerning the Eti-AKGA system, it was established that two forms may be selectively isolated, depending on the experimental conditions. The first one is a racemic cocrystal, in which AKGA is present as the keto form and the second one is a cocrystal conglomerate, which corresponds to a physical mixture of the two (S)-/(R)-Levi - (R)-/(S)-AKGA(lactol) cocrystals, and which was proven to be more stable than the racemic compound at ambient temperature.

By comparison with two other related systems, it was suggested that the absence of any Levi-AKGA cocrystal with the keto tautomer of AKGA is due to the presence of an unfavorable conformation of the racetam molecules in the potential cocrystal, which should significantly reduce its stability in comparison with the existing racemic compound.

Finally, the existence of a stable conglomerate in this system was put in relation with the chiral nature of the AKGA lactol form and the enantiospecificity of the Levi cocrystals, which is likely related to the ability of the Eti enantiomers to stabilize the lactol tautomer in solution. In particular, it was suggested that for a pseudoquaternary cocrystal (*i.e.* cocrystal made up of two racemate compounds) to exist, the pseudoternary combinations (*i.e.* cocrystal made up of one racemate and an enantiomer of the second compound) should be isolable and the enantiomers of

the two compounds should form a diastereomeric pair at the binary level, rather than behave enantiospecifically.

Supporting information. Structures described in this contribution have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers 1482522 (R-Levi_S-AKGA), 1482523 (S-Levi_R-AKGA) and 1482524 (Eti_AKGA). DSC curves corresponding to the two cocrystal forms obtained from the racemic Eti-AKGA mixture (the racemic compound and the conglomerate) are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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The peculiar case of Levetiracetam and Etiracetam α-ketoglutaric acid cocrystals: obtaining a stable conglomerate of Etiracetam

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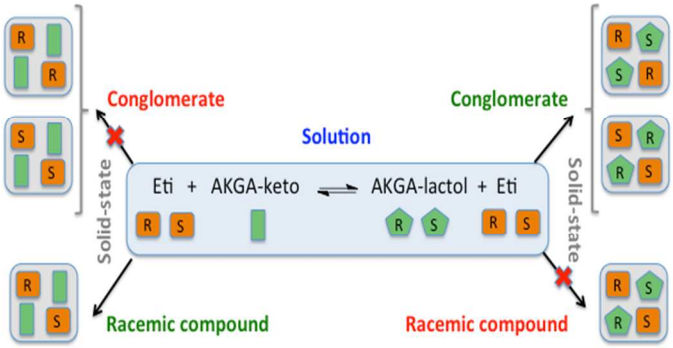

It is possible to obtain the lactol tautomer of alpha-ketoglutaric acid (AKGA) in the solid-state by cocrystallizing it with Leviteracetam, a chiral nootropic drug. Besides, using AKGA and the racemic counterpart of Levetiracetam, Etiracetam (Eti), one can selectively isolate a racemic cocrystal or a cocrystal conglomerate, the latter being more stable than the former at room temperature.