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COMMUNICATION

Simultaneously resolving BINOL and proline using a stoichiometric cocrystal switch.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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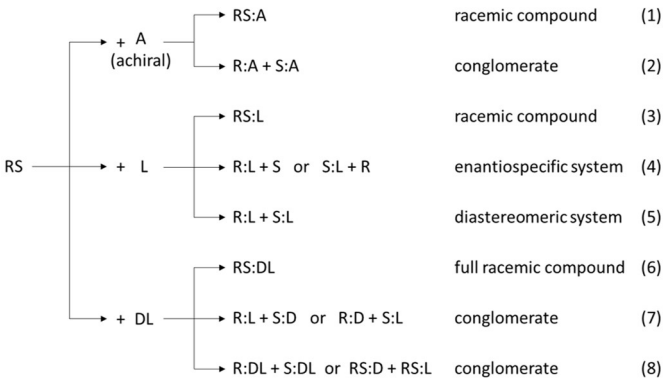
We here highlight the importance of stoichiometry for simultaneous cocrystal resolution. Focusing on combining the racemates of binol and proline, we show that a 1:2 ratio leads to formation of a full racemic compound, whereas a 2:1 ratio, leads to conglomerate formation, with simultaneous resolution of both binol and proline. Playing on stoichiometry, one achieves a reversible switch between the racemic compound and conglomerate. This is the first investigation of such behavior combining two racemates.

Chiral resolution is a major concern for pharmaceutical industry as two enantiomers can show considerable differences in biological activity.[1] While one enantiomer may be beneficial, the other might have a lower, or even adverse effect.[2] Albeit advances in asymmetric synthesis,[3] one of the most common pathways towards enantiopure products remains the synthesis and subsequent resolution of a racemate.[4] Such resolution is commonly performed through chromatography or a crystallization-based process; the latter often less expensive and easier to implement industrially.[5]

Recent advances in the field highlight the potential of multi-component systems as a tool for chiral resolution. In this context, cocrystallization has been shown to be a particularly powerful and diverse tool, with several methodologies successfully introduced in the last decade.[6] Springuel *et al.* set the stage introducing chiral resolution through enantiospecific cocrystallization (Scheme 1, eq. 4), focusing on resolving etiracetam using *S*-mandelic acid.[7] Only the cocrystal with the *S*-enantiomer of the target forms, which emphasizes the difference with respect to diastereomeric salt resolution.[7-12] For some systems, both diastereomeric cocrystals can, however, form, which led to the introduction of a resolution process similar to diastereomeric salt resolution (Scheme 1, eq. 5).[13-18]



Scheme 1 Potential outcomes combining a racemic compound (RS) with an achiral (A), enantiopure (L), or racemic (DL) resolving agent.

Parallel to Harfouche *et al.*,[19] Buol *et al.*[20] showed how to go beyond the use of chiral resolution. Both used achiral coformers to transform a racemic compound into a conglomerate (Scheme 1, eq. 2), which was subsequently resolved through preferential crystallization.[19-24] To obtain a cocrystal conglomerate, we recently showed that one can either play on the nature of the coformer, or, alternatively, on the overall stoichiometry of the system. Changing the amount of $ZnCl_2$ with respect to etiracetam, we were able to switch between a stable conglomerate and a stable racemic compound of this latter.[23] Going beyond the use of achiral coformers, Zhou *et al.*[25] successfully combined two racemic compounds to form a conglomerate (Scheme 1, eq. 7), hereby enabling the two compounds to be resolved simultaneously by preferential crystallization.[25-27] These authors, later showed that the combination of two racemic compounds, however, rarely leads to conglomerate formation, with an overall racemic compound (containing both racemates, Scheme 1, eq. 6) more likely to form.[28] Scheme 1 summarizes potential cocrystallization outcomes between a racemic target and an achiral, enantiopure, or racemic resolving agent.

We here add another tool to the cocrystal-based resolution toolbox, being the first to illustrate how stoichiometry is also of importance, when combining two racemic compounds. We do so, focusing on the binol (1,1'-bi-2-naphthol)-proline system. Hu

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† Electronic Supplementary Information (ESI) available: synthesis, characterization methods, and results. CCDC 2352967-2352968. See DOI: 10.1039/x0xx00000x

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et al.[8] focused on this system to resolve racemic binol using *L*-proline through formation of an enantiospecific 2:1 cocrystal between *S*-binol and *L*-proline (S_2:L). They developed a process where enantiopure *S*-binol (99.98%ee) could be obtained in the solid product, with the *R*-enantiomer (99.88%ee) retrievable from the mother liquor.[8]

In an attempt to identify a conglomerate between the two racemic compounds (scheme 1, eq. 7), we started by investigating the 2:1 combination between racemic binol (*RS*-binol) and racemic proline (*DL*-proline) since the known cocrystal phase is of 2:1 stoichiometry.[8,29] Irrespective of the nature of the solvent, liquid-assisted grinding (LAG) of this 2:1 ratio results in a pattern similar to the S_2:L cocrystal (Figs. 1, S9).

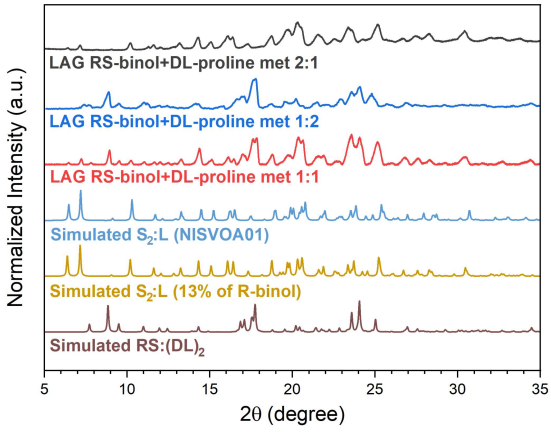


Fig. 1 XRPD patterns of methanol (met) LAG between *RS*-binol and *DL*-proline in a 2:1, 1:2, and 1:1 ratio compared to simulated patterns of S_2:L and RS:$(DL)_2$.

This observation is in alignment with conglomerate formation of the R_2:D+ S_2:L type, which would allow for simultaneous resolution of binol and proline through preferential cocrystallization. Further evidence of conglomerate formation is found comparing the melting of the enantiopure material (onset at 231 °C and ΔH_m of 78.4 kJ.mol^{-1}, Fig. S8), with that of the R_2:D+S_2:L combination (single melting peak with onset at 206 °C and ΔH_m of 71.6 kJ.mol^{-1}, Fig. S7). The difference in enthalpy of melting ($\Delta\Delta H_m$ = -6.8 kJ.mol^{-1}) is typical of a conglomerate system,[20] and the experimental eutectic close to the calculated value of 213°C based on the Schröder-Van Laar equation (see ESI†).[30,31] The binary melting isopleth corresponds to that of a conglomerate (Figs. S5, S6). Single crystal analysis on a crystal obtained from a cooling crystallization from ethanol using a 2.5:1 *RS*-binol to *DL*-proline solution (Fig. S1, ESI†), shows an isostructural compound to the enantiopure S_2:L cocrystal (CSD ref. NISVOA01). However, some disorder is observed due to partial substitution of *S*-binol by *R*-binol molecules (11% according to the XRD data) indicating a partial solid solution for binol. This was confirmed by analyzing a single crystal by HPLC, showing 12% of *R*-Binol (Fig. S4, ESI†). No disorder is observed for the proline molecules. Overall, a conglomerate of the type (S_2:L + R_2:D) is obtained with partial substitution (12-13%) of the binol enantiomer by its counter-enantiomer.

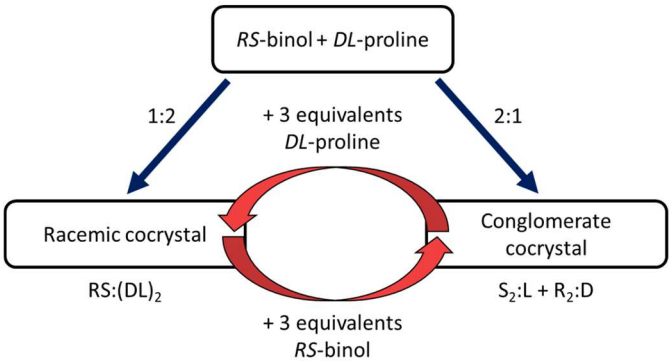
As proline is prone to formation of stoichiometrically diverse cocrystals,[18,32] different ratios between binol and proline were explored (Table 1). Surprisingly, the 1:2 combination (Fig. 1) led to formation of a new solid phase, whereas the 1:1 combination led to a mixture of this phase and the conglomerate discussed above (Table 1).

Table 1 Outcome (based on XRPD analysis) of LAG experiments using different ratios of binol vs proline.

stoichiometric ratio	Solvent		
	Methanol	Ethanol	Acetonitrile
RS+DL (2:1)	S_2:L+R_2:D	S_2:L+R_2:D	S_2:L+R_2:D
RS+DL (1:2)	RS:$(DL)_2$	RS:$(DL)_2$	RS:$(DL)_2$
RS+DL (1:1)	cg + rac	cg + rac	cg + rac

cg = conglomerate (S_2:L+R_2:D), rac = racemic compound (RS:$(DL)_2$)

LAG results are solvent independent (Fig. S9, ESI†), ruling out potential solvate formation. Single crystal analysis confirmed that the new phase obtained in the 1:2 grinding belongs to a racemic 1:2 cocrystal of the RS:$(DL)_2$ type (Fig. S2, ESI†), with the simulated pattern matching the experimental LAG pattern (Fig. 1). Not unexpectedly, the 1:1 LAG experiments, lead to a mixture of this 1:2 racemic phase and the 2:1 conglomerate phase (see Fig. 1). This led us to introduce a stoichiometric switch to convert from a racemic to a conglomerate cocrystal or *vice versa*. We showed experimentally that addition of 3 equivalents of *RS*-binol to the RS:$(DL)_2$ racemic compound followed by another LAG cycle leads to the stable S_2:L + R_2:D conglomerate, whereas adding 3 equivalents of *RS*-proline to this latter followed by LAG leads back to the stable racemic compound (scheme 2, Fig. S10).



Scheme 2 Illustration presenting the stoichiometrically dependent outcome of *RS*-binol and *DL*-proline cocrystallization, as well as the conversion potential between the S_2:L + R_2:D conglomerate and RS:$(DL)_2$ racemic compound.

Fascinatingly, the binol-proline system therefore not only allows for conglomerate formation between two racemic compounds[25] but also yields a stoichiometric switch allowing the transformation from a stable racemic compound to a conglomerate by tuning the stoichiometry of the system.[23] To the best of our knowledge this is the first evidence of such a system.

As recently shown by our group, conglomerate cocrystal formation involving two racemic compounds can lead to simultaneous resolution of both compounds through a single preferential crystallization process.[19,20] To identify robust process conditions, ideally the full phase diagram (*R* and *S* binol, *D* and *L* proline, and solvent) is constructed. However, carefully

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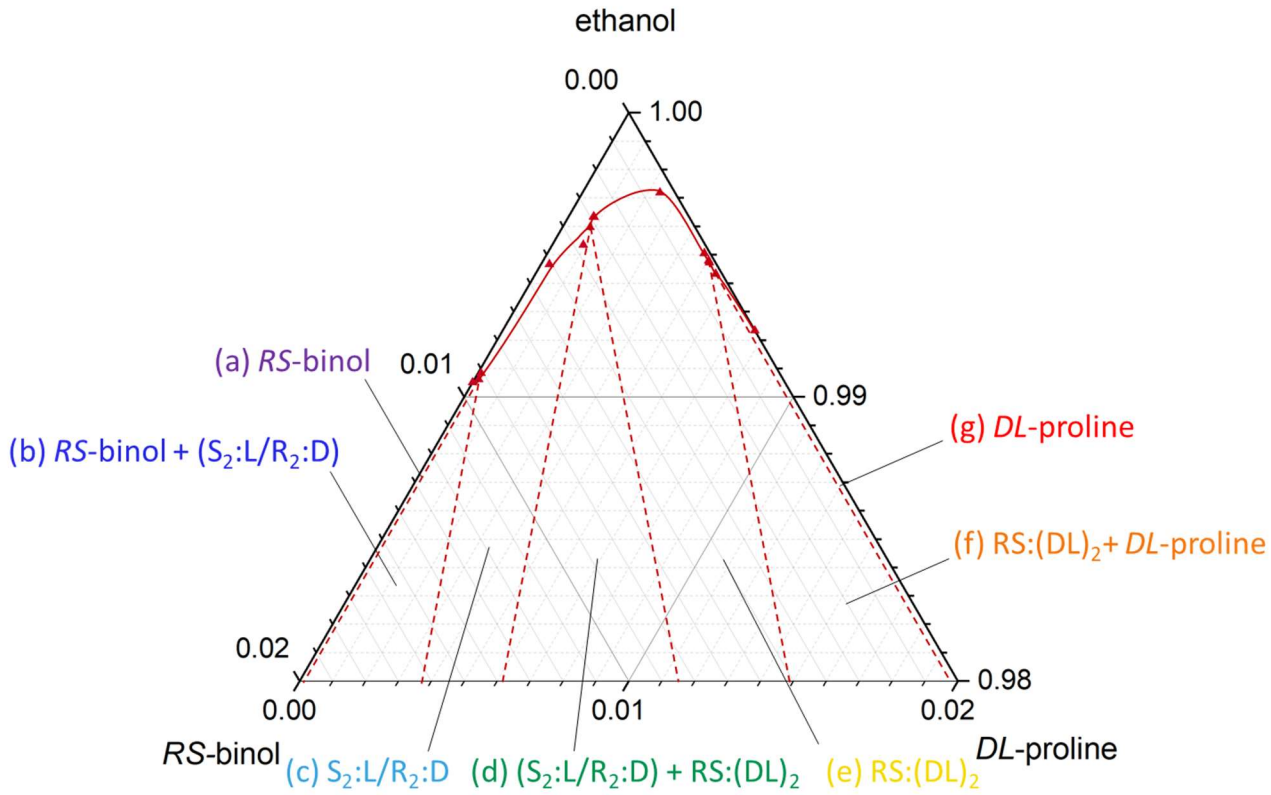

Fig. 2 Isopleth (mole fraction) between *RS*-binol, *DL*-proline, and ethanol at a temperature of 20°C.

chosen isopleth sections of this diagram are sufficient for the development of an initial process. As we start from two racemates, we decided to construct an isopleth maintaining racemic compositions of both compounds, using ethanol as a solvent and working at 20°C.

The molar isopleth (Figs. 2, S12) is constructed on a series of slurry experiments varying the ratio of both racemic compounds. The resulting solid phase was identified by XRPD, whereas the composition of supernatant was determined combining NMR measurements with a gravimetric approach (see ESI† for details). Taking a fixed amount of solvent (e.g. 98%), going from left to right through the diagram, one not unexpectedly successively encounters the regions where (a) *RS*-binol, (b) a mixture of *RS*-binol and the conglomerate S_2:L/R_2:D, (c) the conglomerate S_2:L/R_2:D, (d) a mixture of the conglomerate S_2:L/R_2:D and the racemic compound RS:$(DL)_2$, (e) the racemic compound RS:$(DL)_2$, (f) a mixture of the racemic compound RS:$(DL)_2$ and *DL*-proline, and (g) *DL*-proline are stable in suspension. The red triangles highlight the composition of the supernatant, and therefore correspond to solubility lines. As shown by this diagram, the conglomerate is found to be stable in suspensions working with mixtures enriched in *RS*-binol, whereas enriched *DL*-proline mixtures lead to the racemic compound RS:$(DL)_2$. Once again, altering the stoichiometry will allow switching between a stable conglomerate and a stable racemic compound. The region where the conglomerate is the only stable suspension in solution, can be used to develop a future simultaneous resolution of both compounds through preferential cocrystallization.[25]

In this work, we are the first to showcase a stoichiometric switch between a stable conglomerate and a stable racemic compound involving two racemates. Careful control of stoichiometry and amount of solvent allows obtaining a stable conglomerate in suspension, which offers the potential for future simultaneous resolution of both compounds using a preferential cocrystallization approach.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Authors would like to thank the FNRS for their support (PDR T.0262.20 ; CDR J.0168.22). Postdoctoral scholarship for SS was provided by Vidyasirimedhi Institute of Science and Technology.

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