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Chiral Resolution of Racemic Ibuprofen Sodium via Diastereomeric Ionic Cocrystallization with Proline

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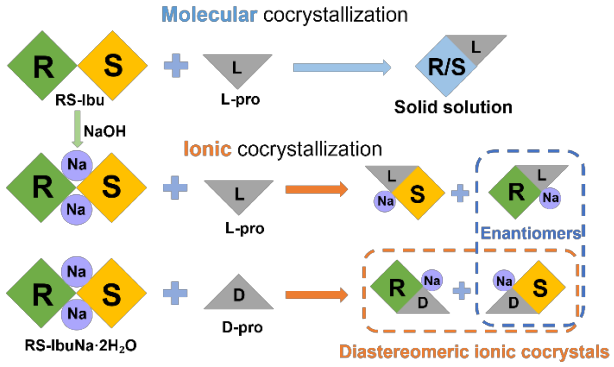
Diasteriomeric ionic cocrystallization is introduced as a novel crystallization-based resolution tool. RS-Ibuprofen sodium is succesfully resolved using proline as a resolution agent, achieving *ee*>90% in a single resolution step. This work, for the first time, demonstrates diastereomeric ionic cocrystallization as a powerful approach to chiral resolution.

Chirality is vital to the pharmacological behaviour of many active pharmaceutical ingredients (APIs), since enantiomers can differ greatly in potency, pharmacokinetics, and safety. Sometimes only one enantiomer provides the desired therapeutic effect while the other may be inactive or even harmful.[1-3] Therefore, new efficient and scalable routes for obtaining enantiopure APIs are crucial.[4] Although various methods such as direct asymmetric synthesis and chromatography have been developed, crystallization-based methods remain among the most commonly used due to their simplicity, low cost, solvent efficiency, and scalability.[5, 6]

Direct preferential crystallization is applicable to those racemates that spontaneously crystallize as conglomerates. Limited to 5-10% of compounds, for most APIs, successful enantiomeric resolution requires transformation into a resolvable form using crystal engineering strategies.[7] For acidic or basic APIs, diastereomeric salt formation is the most widely employed approach; for example, racemic ibuprofen can be resolved by forming diastereomeric salts with enantiopure amines such as phenylethylamine.[8-10] For neutral APIs lacking ionizable functional groups, cocrystallization with chiral coformers provides a viable alternative.[11, 12]

Ionic cocrystals (ICCs), typically defined as solids composed of neutral organic molecules and salts in defined stoichiometric ratios, represent an emerging class of multicomponent crystalline materials with significant potential for chiral resolution.[13] Until now, APIs such as etiracetam, oxiracetam and various amino acids have been successfully resolved by converting them into resolvable ionic cocrystal conglomerates.[14-17] However, this approach remains fundamentally limited by the same constraints that govern conventional preferential crystallization: the spontaneous formation of conglomerates is highly unpredictable and occurs with low probability. Recent developments in crystal engineering have begun to expand the structural landscape of ionic cocrystals. Organic salts such as lithium salicylate, ibuprofen sodium, and diclofenac sodium have been successfully cocrystallized with various neutral and even chiral coformers, opening the possibility of chiral resolution through diastereomeric ionic cocrystal formation.[18-20]

Herein, we report the first example of enantiomeric resolution achieved via diastereomeric ionic cocrystals formation (Fig. 1), as demonstrated by resolution of racemic ibuprofen sodium (RS-IbuNa·2H_2O) with enantiopure D-proline (D-pro). The importance of ionic cocrystallization is highlighted by the fact that ibuprofen itself cannot be resolved using proline, as they combine to give unresolvable solid solutions (Table S1; Fig. S1 and S2, ESI†). Guided by thermodynamics, we successfully resolved the racemate into S-IbuNa·2H_2O achieving an *ee* of as high as 94% in one step.



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Fig. 1 Schematic diagram representing the solid solution and diastereomeric ionic cocrystal pair formation between Ibuprofen and proline.

As direct combination of ibuprofen with proline led to solid solution formation, we explored the well-established propensity of amino acids for ionic cocrystal formation,[21-23] systematically screening RS-IbuNa·2H_2O with a series of amino acids (Table S2, ESI†). The results showed that D-pro and L-pro[§] successfully formed diastereomeric ionic cocrystals with RS-IbuNa·2H_2O, yielding crystallographically distinct solid forms, S-IbuNa-D-pro·2H_2O (S-D·2H_2O) and R-IbuNa-D-pro (R-D[‡]), which were fully characterized (Fig. S3-S7, ESI†). To confirm the diastereomeric nature of these materials and elucidate their molecular packing arrangements, comprehensive structural characterization was undertaken using single crystal X-ray diffraction analysis (Table S3, ESI†). The simulated and experimental powder X-ray diffractionpatterns of S-D·2H_2O and S-L[‡] exhibit excellent agreement with the patterns simulated from the corresponding single crystal structures (Fig. S4, ESI†).

Owing to their intrinsic chirality, S-D·2H_2O and S-L[‡] (equivalent to R-D) crystallized in the Sohncke space groups $P2_1$ and $P1$, respectively. For S-D·2H_2O, the Na(I) centres exhibit a distorted octahedral coordination environment (Coordination Number, CN=6) defined by multiple carboxylate oxygen atoms from D-pro zwitterions and ibuprofenates (Fig. 2a). The zwitterionic D-pro occupies a bidentate bridging coordination mode through their carboxylate group, linking adjacent Na(I) centres and promoting the formation of a repeating Na-O-C-O motif along the *b*-axis. The ibuprofenate also connects to a Na(I) centre via two oxygen atoms from its carboxylate group (bidentate chelating). In addition, two water molecules are coordinated to each Na(I) centre, thereby stabilizing the overall coordination geometry. The combined bridging modes of the two ligands generate a continuous, infinitely extended helical one-dimensional coordination chain. The hydrophobic aromatic rings and isobutyl substituents of ibuprofenates extend from the sides of the chain, occupying their peripheral regions. The overall crystal packing is governed by the parallel alignment of the one-dimensional Na-carboxylate chains through the hydrophobic interaction between ibuprofenates (Fig. 2b).

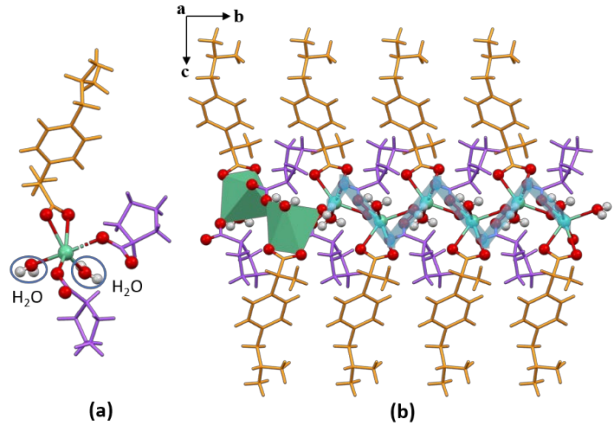


Fig. 2 Structure of S-D·2H_2O: (a) the Na(I) coordination environment; (b) crystal packing. S-ibuprofenates are depicted in yellow, oxygen atoms in red, sodium atoms in green, D-pro zwitterions in purple.

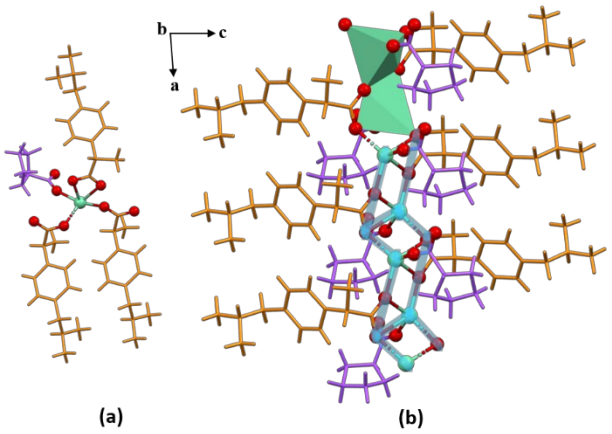


Fig. 3 Structure of S-L: (a) the Na(I) coordination environment; (b) crystal packing. S-ibuprofenates are depicted in yellow, oxygen atoms in red, sodium atoms in green, L-pro zwitterions in purple.

In the case of S-L (or R-D), the Na(I) centres adopt a distorted square pyramidal coordination environment (CN=5) different from that in S-D·2H_2O (Fig. 3a). Without coordinating water molecules, the coordination mode of the ibuprofenate alters to a tetradentate bridging type. Consequently, the ibuprofenate replaces L-pro zwitterion as bridging ligand, linking adjacent Na(I) centres through a repeating Na-O-C-O motif along the a-axis. The L-pro zwitterion connects to the Na(I) centre via one oxygen atom from its carboxylate group (monodentate), with its pyrrolidine ring projecting outward from the chain axis. The hydrophobic groups of ibuprofenates project from both sides of the chain, occupying the lateral regions of the ladder-like framework (Fig. 3b).

To identify promising solvents for the resolution of the diastereomeric ionic cocrystal pair, screening experiments were performed using an equimolar mixture of RS-IbuNa·2H_2O and D-pro suspended in various solvents. A binary solvent of IPA/Hex (10:90, v/v) was chosen for further investigation, since PXRD analysis of the solid phase harvested from the suspension confirmed the formation of the diastereomeric ionic cocrystal pair in this solvent system (Table S4, ESI†). An isoplethal ternary phase diagram between RS-IbuNa·2H_2O, D-pro and IPA/Hex (10:90, v/v) was subsequently established, enabling identification of the thermodynamically stable equilibrium states associated with different compositions at 25 ℃ (Table S5, ESI†). Chiral resolution can be achieved based on this diagram.[24, 25]

Fig. 4 shows an enlarged view of the upper region of the full isoplethal ternary phase diagram (Fig. S8, ESI†). In regions where excess amounts of RS-IbuNa·2H_2O are used, this phase combined with both diastereomers is, as expected, the stable phase in suspension, depicted by the black triangles. On the opposite side of the diagram, where D-pro is present in excess, this phase remains stable in suspension along with both diastereomers (black circles). Between these zones, a narrow zone is obtained (yellow squares), where both diastereomeric solids S-D·2H_2O and R-D are the only stable phases in suspension, with no residual starting material remaining. To favour the presence of only one of the diastereomers in

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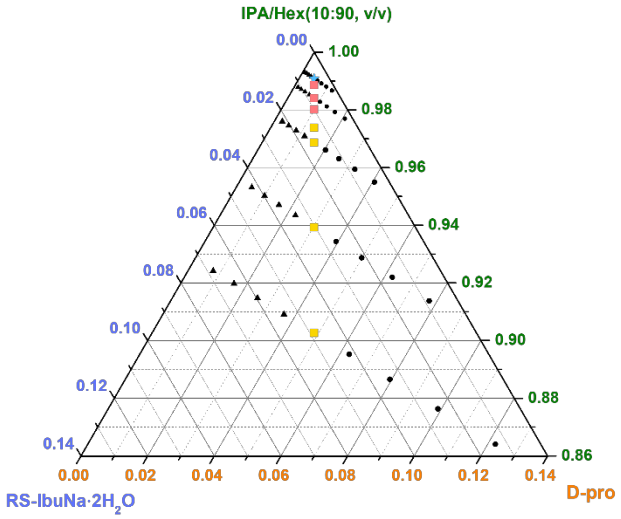


Fig. 4 Isoplethal ternary phase diagram (mole fraction) between RS-IbuNa·2H_2O, D-pro and IPA/Hex (10:90, v/v). Zones show thermodynamically stable suspensions of RS-IbuNa·2H_2O and both diastereomers (black triangles), suspensions of D-Pro and both diastereomers (black circles), suspensions of both diastereomers S-D·2H_2O+R-D (yellow squares), and suspensions of S-D·2H_2O (red square), as well as the liquid phase zone (blue star).

suspension, increased amounts of solvent were used with the aim of reaching a region where only one of the two diastereomers remains in suspension (upper region of the diagram). Starting from the central region of the diagram and increasing the amount of solvent, R-D progressively disappears from the recovered solids, ultimately yielding crystalline material composed solely of S-D·2H_2O (red squares). Upon further increasing the amount of solvent, all components dissolve, as shown by the liquid-phase region (blue star).

As shown by the isoplethal phase diagram, the narrow region in which both diastereomers form without concomitant crystallization of the starting materials occurs at equimolar ratio of RS-IbuNa·2H_2O to D-pro. Focusing on the zone where S-D·2H_2O is the only stable phase in suspension, we successfully resolved RS-IbuNa·2H_2O with all recovered powders exhibiting an *ee*>90%, the best result reaching an *ee* of 95.80%, highlighting the potential of this resolution technique (Table S6, Fig. S9, ESI†). When scaling up the resolution experiment, the obtained solid phase showed an *ee* of 90.06% (Fig. S10, ESI†). Compared with previously reported methods, such as diastereomeric salt formation between ibuprofenand chiral amines or membrane-based separation techniques, the *ee* obtained after a single operation is markedly higher using the technique introduced here (Table S7, ESI†).

The common-ion effect previously observed in ionic cocrystal systems can be leveraged here to induce efficient dissociation of ibuprofen sodium and proline.[26] Upon dissolving the Na^+-containing ionic cocrystal in a NaCl solution, the presence of Na^+ cations immediately shifts the dissolution equilibrium, resulting in the rapid crystallization of ibuprofen sodium, while proline remains in solution. Performing this procedure on the powder recovered from the scale-up experiment, PXRD analysis unambiguously shows the isolated solid to be S-IbuNa·2H_2O, with a recovery yield of 72.58% and an *ee* of 93.50% (Fig. S11, ESI†).

In summary, this work represents the first report of chiral resolution through diastereomeric ionic cocrystallization. Compared with the rare and unpredictable conglomerate systems, this approach offers significantly greater applicability. We successfully resolved RS-IbuNa·2H_2O using proline as a resolving agent. Guided by thermodynamics, S-D·2H_2O was obtained in a single resolution step with an *ee* exceeding 90%. Moreover, a strong common-ion effect enables rapid cocrystal dissociation to S-IbuNa·2H_2O. Overall, this work not only demonstrates an efficient strategy for the chiral resolution of RS-IbuNa·2H_2O, but also establishes diastereomeric ionic cocrystallization as a practical and promising tool for the stereoselective purification of chiral APIs.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: synthesis, characterization methods, and results. See DOI: https://doi.org/xxxx/xxxxxxxxxx.
CCDC number 2530249-2530250 contain the supplementary crystallographic data for this paper.

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Conflicts of interest

There are no conflicts to declare. Notes and references

§ Both D-pro and L-pro can resolve RS-IbuNa·2H_2O, with D-pro selectively targeting S-IbuNa·2H_2O and L-pro selectively targeting R-IbuNa·2H_2O.
‡ R-D and S-L are enantiomerically related, with identical scalar properties.

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