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Structural insight into cocrystallization with zwitterionic co-formers: cocrystals of *S*-naproxen†

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The screening of *S*-naproxen, *S*-oxiracetam, *S*-diprophylline, and levetiracetam with a series of essential and nonessential amino acid co-formers has yielded cocrystals only for *S*-naproxen, thus showing that amino acids seem to have a preference for forming cocrystals with compounds containing a carboxyl group. Herein, we report the crystal structures of four *S*-naproxen cocrystals: *S*-naproxen/L-alanine, *S*-naproxen/D-alanine, *S*-naproxen/D-tyrosine, and *S*-naproxen/D-tryptophan monohydrate. All of the described cocrystals show similar structural motifs, *i.e.*, amino acids form head-to-tail chains with strong charge-assisted hydrogen bonding, which are similar to those found in the individual amino acids, with *S*-naproxen molecules grafted on them. According to the systematic search of the Cambridge Structural Database for other cocrystals that involve zwitterionic co-formers, charge-assisted hydrogen bonds between amino acid molecules play an essential role, being present in the majority of structures. The results of this work provide an insight into structural aspects of cocrystallization with zwitterionic co-formers, offer new possibilities for *S*-naproxen pharmaceutical formulations, and can serve as guidelines when developing new cocrystals involving zwitterionic co-formers.

Introduction

Multicomponent crystalline systems have been known for a long time, but only recently the term cocrystal has come into wide use. Over the last decade cocrystals have gained special popularity in pharmaceutics as alternative drug formulations[1–8] as they allow one to tackle issues related to polymorphism,[9] can be formed in compounds that do not easily form salts, offer a certain degree of engineering flexibility,[10–12] may improve biophysical properties[13–15] (such as solubility or dissolution rate), stability,[16] and hygroscopicity[17,18] and make the production process more feasible[19] in comparison with pure active pharmaceutical ingredients (APIs). Despite their growing popularity scientists still argue about the exact definition of a cocrystal; however, they all agree that cocrystals can be defined as "solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts".[20]

Up to now, almost every study concerning these compounds has been oriented towards the development of alternative drug formulations.[1–8] However, cocrystals have a series of specific properties making them potent candidates for the development of solid state applications. Recently, Myerson *et al.* showed how cocrystallization can be used as a purification tool, separating ibuprofen–ketoprofen mixtures.[21] In 2010, Ter Horst *et al.* used cocrystallization as a tool to remove cinnamic acid from water at levels seven times lower than the solubility.[22] They furthermore extended this work by showing how electrochemistry can be combined with cocrystallization for the *in situ* product removal of carboxyl acids.[23]

Although cocrystals of chiral APIs are common, chirality in cocrystals is a relatively unexplored area. Motherwell *et al.* showed how caffeine and theophylline behave differently with respect to DL- and D-tartaric acid.[24] In 2012, Coquerel *et al.* showed how cocrystallization can be used for preferential crystallization.[25] An even fewer number of studies involve cocrystals of two chiral components. Lehmann noted the formation of a diastereomeric pair of cocrystals between proline amide and mandelic acid, using this information to determine the absolute configuration.[26] The enantiospecific behavior in cocrystals

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was noted for the first time in 2008 by Takata *et al.*[27] for the Stanolone/*S*-tartaric acid cocrystal and again in 2011 by Thorey *et al.*,[28] studying the (*R*,*R*)-cyclohexanediol/*R*-tartaric acid cocrystal. The latter used this information to develop an enantiospecific extraction process using supercritical CO_2.[29]

Parallel to Thorey *et al.*, Springuel *et al.* observed this particular behavior when working on levetiracetam,[30] showing an enantiospecific interaction with either *S*-mandelic acid or *S*-tartaric acid.[31] As levetiracetam is produced from a racemic mixture, with the *S*-enantiomer separated using chiral chromatography, they developed a novel chiral resolution technique for compounds which do not or not easily form salts based on enantiospecific cocrystallization in solution. Although the enantiospecific behavior seems to be common to cocrystals, they recently showed naproxen to form a diastereomeric pair of cocrystals with zwitterionic co-formers (D- and L-proline).[32] Ibuprofen, another member of the profen family of APIs, showed the ability to form diastereomeric salts with arginine and lysine amino acids, which found application at the industrial scale.[33]

In the context of these recent findings, we focused on cocrystals formed by *S*-naproxen with various amino acids. Amino acids contain both amino and carboxyl groups, which make them perfect candidates for cocrystallization. Moreover, they are natural to the body, and their use in pharmaceutical cocrystals reduces the risk of negative side effects for human health in comparison with other co-formers and may be even beneficial, improving biophysical properties of APIs. The cocrystals described in this paper can be considered potential candidates for the pharmaceutical industry. Tryptophan-based cocrystals are of special importance; they present a new formulation strategy for naproxen, and aside from the pharmaceutical activity of *S*-naproxen they may be a source of nonessential amino acids. Moreover, the enantiospecific behavior found in the naproxen/tyrosine system opens new horizons for developing chiral resolution techniques based on cocrystallization. From a structural point of view, amino acids are zwitterionic compounds with a strong charge-assisted hydrogen bond network, which might affect the crystallization process.[32,34] Studying their ability to form cocrystals can help to understand how the zwitterionic nature affects cocrystal formation.

Experimental

Materials and methods

S-Naproxen (99%), D-proline (98%), L-valine (98%), D-alanine (98%), L-leucine (98%), D-leucine (98%), L-phenylalanine (98%), D-phenylalanine (98%), L-isoleucine (98%), D-tyrosine (98%), L-methionine (99%), and D-histidine (99%) were purchased from TCI Europe N. V.; *S*-oxiracetam from Angene; levetiracetam from Xiamen Top Health; *S*-diprophylline (99%) from HaOHUA Industry; L-asparagine (≥98%), L-cysteine (97%), L-threonine (≥98%), D-valine (98%), and DL-isoleucine (99%) from Sigma-Aldrich; L-glutamine (99%), D-serine (98%), D-threonine (98%), D-tryptophan (99+%), L-tryptophan (99%), L-proline (99%), L-alanine (99%), D-aspartic acid (99+%), and D-glutamine (98%) from Acros Organics; L-histidine (98+%), DL-serine (99%), L-tyrosine (99%), D-glutamic acid (99+%), L-aspartic acid (98+%), L-glutamic acid (99+%), and D-methionine (99%) from Alfa Aesar; L-serine (98.5–101%) from Fisher Scientific; and D-asparagine from Molekula.

For liquid-assisted grinding, we used methanol and for crystallization, ethanol and distilled water. Methanol (HPLC grade) and ethanol were purchased from VWR International.

All materials were used as received without any further purification.

Screening

Screening was performed by liquid-assisted grinding (10 μL of methanol per ~100 mg of powder mixture with a 1 : 1 ratio) using a Retsch MM400 mixer mill for 90 min at a frequency of 30 Hz. Final powders were analyzed by X-ray powder diffraction (CuKα radiation, λ = 1.5418 Å) using a Siemens D5000 diffractometer; 2θ was scanned from 2 to 50° with a step of 0.02°. When the powder diffraction patterns of the ground materials contained new peaks, different from the peaks of the initial compounds, we assumed formation of a new phase and then tried to crystallize it from solution.

Crystallization

All single-crystals were grown from ethanol–water solution. *S*-Naproxen/L-alanine and *S*-naproxen/D-alanine were crystallized from an ethanol–water solution containing 97 vol% of ethanol and 3 vol% of water.[35] *S*-Naproxen and D- or L-alanine were taken in a ratio of 1 : 1 and put in 1.5 mL of ethanol–water at ~30 °C; solutions were stirred for 3–5 h, filtered, cooled to room temperature and seeded with the cocrystal powder obtained by liquid-assisted grinding. Square-shaped colorless *S*-naproxen/L-alanine or *S*-naproxen/D-alanine cocrystals grew from solutions along with plate-shaped *S*-naproxen crystals. The diffraction patterns calculated from single-crystal diffraction data of those two cocrystals matched their powder diffraction patterns from liquid-assisted grinding.

S-Naproxen/D-tryptophan monohydrate was crystallized by slow evaporation from ethanol–water solution containing 60 wt% of ethanol and 40 wt% of water. *S*-Naproxen and D-tryptophan were taken in the amounts relative to their solubilities (1.54 (ref. 36) and 1.40 (ref. 37) g/100 g, respectively) in this solution.[38] The solution was filtered and left to evaporate slowly at room temperature. Thin needle-shaped crystals of *S*-naproxen/D-tryptophan monohydrate were obtained. *S*-Naproxen and L-tryptophan treated under the same conditions cocrystallize in an unhydrated fine-powder form, similar to that obtained by grinding, as confirmed by X-ray powder diffraction and thermal analysis (see the ESI†).

We were not able to grow crystals of *S*-naproxen/L-tryptophan, unhydrated *S*-naproxen/D-tryptophan, and *S*-naproxen/D-tyrosine cocrystals suitable for single-crystal diffraction analysis.

Structure determination

The structure of *S*-naproxen/L-alanine was solved from single-crystal synchrotron X-ray diffraction data, which were collected using the Swiss-Norwegian Beam Lines BM01A at the European Synchrotron Radiation Facility (ESRF) (Grenoble, France), using a PILATUS 2M hybrid pixel detector at a wavelength of 0.68239 Å and a sample-to-detector distance of 144 mm; the collection mode was ω-scans. The sample was cooled to 100(1) K using an Oxford Cryostream 700 system. The data were converted and integrated using the SNBL toolbox software[39] and the CrysAlisPro software.[40]

The structures of *S*-naproxen/D-alanine and *S*-naproxen/D-tryptophan monohydrate were solved from single-crystal X-ray diffraction data, which were collected using a MAR345 image plate detector using MoKα radiation (Rigaku UltraX 18 rotation anode, Xenocs Fox3D focusing multilayer mirror) at 150(1) K. The data were integrated using the CrysAlisPro software.[40]

The multi-scan absorption correction procedure implemented in the CrysAlisPro software was applied in all of the single-crystal cases. The structures were solved by direct methods using the SHELXS-2013[41] program and refined by full-matrix least squares on $|F|^2$ using SHELXL-2013[41] and the shelXLe shell.[42] Non-hydrogen atoms were refined anisotropically; and hydrogen atoms were either placed on calculated positions in riding mode with temperature factors fixed at 1.2 times U_{eq} of the parent atoms and 1.5 times U_{eq} for methyl groups or were located from the difference Fourier map if the resolution allowed.

The structure of *S*-naproxen/D-tyrosine was solved from powder X-ray diffraction data (for the diffraction data see the ESI†), which were collected using the Swiss-Norwegian beamline BM1A at the European Synchrotron Radiation Facility (ESRF) (Grenoble, France), using a PILATUS 2M hybrid pixel detector at a wavelength of 0.823065 Å and a sample-to-detector distance of 443 mm. These parameters along with image plate tilt angles were calibrated using a standard LaB_6 sample. The two-dimensional diffraction images were integrated using the ESRF Fit2D[43] program. The pattern was indexed using DICVOL04.[44] The $P2_1$ space group was suggested, taking into account systematic absences and considering the chiral nature of molecules in the unit cell. Le Bail fit was done using the FOX[45] program. The structure was solved by global optimization in direct space using the FOX[45] program and refined by the Rietveld method (for Rietveld refinement see Fig. 1) using the Fullprof suite.[46] Molecular models of *S*-naproxen and D-tyrosine were imported from the single-crystal structural models taken from the Cambridge Structural Database (COYRUD12[47] and FAZHET01,[48] respectively). The following groups were made rigid in order to keep a proper planar geometry: carboxylate, a carboxyl group, and benzene rings. The position, orientation and conformation of molecules were optimized. To constrain bond distances and valence angles, 56 distance restraints were applied for interatomic distances and 93 for angles. The background was described by linear interpolation between selected points.

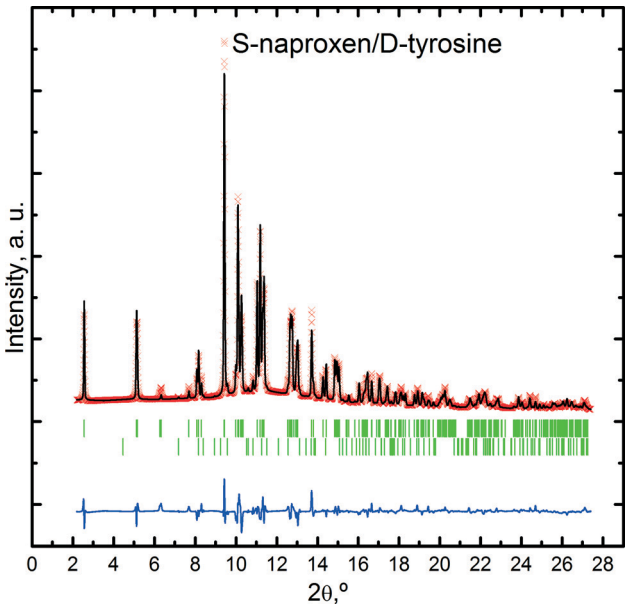


Fig. 1 The Rietveld refinement plot of *S*-naproxen/D-tyrosine. Red crosses and the black line show experimental and calculated data, respectively; the blue line is the difference profile; and green marks indicate Bragg positions.

The synchrotron X-ray diffraction patterns of unhydrated *S*-naproxen/D-tryptophan and *S*-naproxen/L-tryptophan were measured using the MS-X04SA beam line at the Swiss Light Source (SLS) (PSI, Switzerland) using a 1D microstrip detector MYTHEN II at a wavelength of 0.775045 Å, and the zero shift was −0.0079° (for the diffraction data see the ESI†). The wavelength and zero shift values were calibrated using a standard NIST 640d Si sample. Indexing and Le Bail fit were performed using FOX.[45] The samples were prepared by liquid-assisted grinding in the same manner as for screening, and they showed poor crystallinity resulting in broad peaks, which rendered it difficult to find the structures from these powder data. The most probable space group is $P2_1$; and the unit cell parameters are a = 22.2064(4) Å, b = 10.49608(14) Å, c = 45.2843(10) Å, β = 124.3265(15)° (V = 8716.6(3) Å^3, Z' = 8) for *S*-naproxen/L-tryptophan at room temperature and a = 20.6445(2) Å, b = 11.77119(18) Å, c = 40.7116(6) Å, β = 118.2805(9)° (V = 8712.5(2) Å^3, Z' = 8) for *S*-naproxen/D-tryptophan at 100 K.

The figures were generated using Mercury;[49] the cif files were finalized using the Platon[50] and Encifer[51] programs. Table 1 summarizes the details of crystal data, data collection, and refinement.

Search in the Cambridge Structural Database (CSD)

We used the Cambridge Structural Database[52] (CSD 5.34, last updated May 2013) to study the statistics on amino acids and naproxen as cocrystal formers, *i.e.*, the number of entries for cocrystals that are formed between amino acids and

Table 1 Experimental details

	S-naproxen/L-alanine	*S*-naproxen/D-alanine	*S*-naproxen/D-tryptophan monohydrate	*S*-naproxen/D-tyrosine
Crystal data				
Chemical formula	$C_{14}H_{14}O_3{\cdot}C_3H_7NO_2$	$C_{14}H_{14}O_3{\cdot}C_3H_7NO_2$	$C_{14}H_{14}O_3{\cdot}C_{11}H_{12}N_2O_2{\cdot}H_2O$	$C_{14}H_{14}O_3{\cdot}C_9H_{11}NO_3$
M_r (g mol^{-1})	319.35	319.35	452.49	411.44
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Temperature (K)	100	150	150	295
a (Å)	5.05836 (11)	5.3366 (4)	5.88418 (16)	9.4508 (4)
b (Å)	7.1121 (3)	6.9013 (6)	11.3844 (3)	5.9725 (2)
c (Å)	45.2723 (17)	44.227 (4)	34.6863 (9)	18.9525 (7)
α (°)	90	90	90	90
β (°)	90	90	90	103.814 (2)
γ (°)	90	90	90	90
V (Å^3)	1628.69 (10)	1628.9 (2)	2323.56 (11)	1038.83 (7)
Z	4	4	4	2
Radiation type	Synchrotron, λ = 0.68239 Å	MoKα	MoKα	Synchrotron, λ = 0.823065 Å
Specimen shape, size (mm)	0.15 × 0.13 × 0.02	0.10 × 0.08 × 0.03	0.29 × 0.09 × 0.05	Powder
Data collection				
Diffractometer	Pilatus 2M	MAR345 image plate	MAR345 image plate	Pilatus 2M
Method	Single-crystal	Single-crystal	Single-crystal	Powder
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	14 337, 5462, 5314	6347, 1712, 1424	15 442, 4245, 3244	305[a]
R_{int}	0.034	0.093	0.093	
Refinement				
R factors and goodness of fit	$R[F^2 > 2\sigma(F^2)]$ = 0.050, w$R(F^2)$ = 0.135, S = 1.10	$R[F^2 > 2\sigma(F^2)]$ = 0.083, w$R(F^2)$ = 0.225, S = 1.14	$R[F^2 > 2\sigma(F^2)]$ = 0.046, w$R(F^2)$ = 0.099, S = 1.03	R_{wp} = 5.986, R_{exp} = 0.182, R_{Bragg} = 8.990
No. of reflections/data points	5462	1712	4245	4519
No. of parameters	231	212	314	23
CCDC number	985631	985632	985633	985634

[a] Number of independent reflections.

compounds that contain hydroxyl, carboxyl or amide groups and for cocrystals formed by naproxen with various co-formers. The ConQuest 1.15[52] program was applied to search and retrieve information and the Mercury 3.3[49] software to visualize and explore structural peculiarities of found compounds.

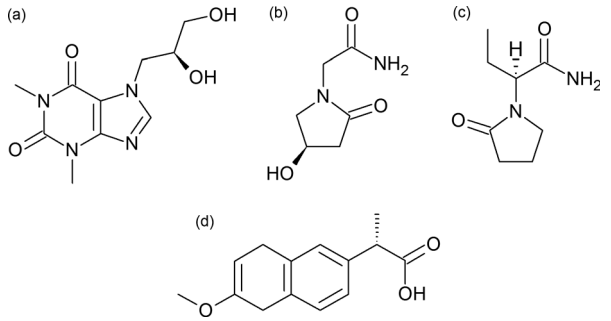
The queries for amino acids with three types of co-formers—containing a carboxyl, hydroxyl or amide group—were built by drawing the general form of an amino acid in the zwitterionic form and a desired group for the co-former linked to any atom and setting the contact type interaction (using the ADD 3D mode) between the centroids of the carboxylate in the amino acid and of the corresponding group in the co-former.

We narrowed the search to non-halogen non-metallic compounds with the heaviest permitted atom being sulfur and with phosphorus and fluorine-containing compounds being excluded; we also omitted compounds with sulfonate and nitrate groups. The following additional filters were applied: 3D coordinates being determined, not polymeric and only organics. The hit lists were additionally checked, only cocrystals containing standard amino acids were included, and all of the irrelevant compounds (including clathrates) were crossed out. Co-formers that contained either both amide and carboxyl groups or both hydroxyl and carboxyl groups were considered carboxyl-type co-formers. The same structures obtained under different conditions were counted as one. Cocrystal solvates and hydrates were also included in the results and counted as individual compounds.

The query to the search for naproxen cocrystals was created by drawing a molecule of naproxen and applying the same filters: 3D coordinates being determined, not polymeric and only organics. Irrelevant entries were deleted from the final hit list.

Results and discussion

In this paper, we focus on studying *S*-naproxen cocrystals with both essential and nonessential amino acids and, in this context, the ability of amino acids to form cocrystals with other types of co-formers. For this reason four different reference compounds were selected (Scheme 1): *S*-naproxen, as it contains a carboxyl group and is shown to form cocrystals with amino acids;[32] levetiracetam, as this molecule is shown to be a potent cocrystal former containing two amide functionalities;[31] *S*-oxiracetam, another compound of the racetam family, which besides the two amide functionalities also contains a hydroxyl group and forms cocrystals as well;[17] and diprophylline, a xanthine derivative, which is structurally related to caffeine and theophylline, both of which are frequently used in cocrystallization studies.[53–56] Liquid-assisted grinding of these active pharmaceutical ingredients (APIs)



Scheme 1 Structural formulas of (a) *S*-diprophylline, (b) *S*-oxiracetam, (c) levetiracetam, and (d) *S*-naproxen.

with a series of amino acids showed that only *S*-naproxen was capable of forming cocrystals (see the ESI†). Although levetiracetam and oxiracetam have already been shown to be prone to cocrystal formation,[17,31] they do not seem to respond well to amino-acid co-formers, nor does diprophylline. Based on the structural formulas in Scheme 1 and the screening results, amino acids seem to have a preference for forming cocrystals with compounds containing a carboxyl group.

Herein, we report and analyze the structures of four novel *S*-naproxen cocrystals: three structures that involve alanine and tyrosine, nonessential amino acids, and one structure that involves tryptophan, an essential amino acid. The structural analysis of obtained cocrystals is followed by the discussion of the results of the CSD search.

S-Naproxen/L-alanine and *S*-naproxen/D-alanine

The asymmetric unit of *S*-naproxen/L-alanine contains one molecule of *S*-naproxen in the neutral form and one molecule of L-alanine in the zwitterionic form, which are linked *via* a N1–H1···O1 hydrogen bond formed between a positively charged amino group of L-alanine and a carboxyl group of *S*-naproxen (Fig. 2g). The molecules of L-alanine form infinite head-to-tail $C_1^1(5)$ chains in the [100] direction—the structural motif, typical for crystalline amino acids,[57–59]—due to hydrogen bonding between a positively charged amino group of one amino acid (tail) and a carboxylate (head) of an adjacent molecule. Chains connect to one another *via* N1–H1C···O5 hydrogen bonds, forming a folded sheet parallel to the (001) plane (Fig. 2a, d). Each L-alanine molecule links two molecules of *S*-naproxen, sharing each of them with an adjacent L-alanine molecule from a neighboring head-to-tail chain: the first naproxen molecule attaches to the amino acid sheet from one side by a N1–H1A···O1 hydrogen bond, and the second naproxen molecule attaches to the sheet from the opposite side by a O2–H2···O4 hydrogen bond. Both hydrogen bonds involve the carboxyl acid group of *S*-naproxen and either a charged amino group or a carboxylate of L-alanine. Overall,

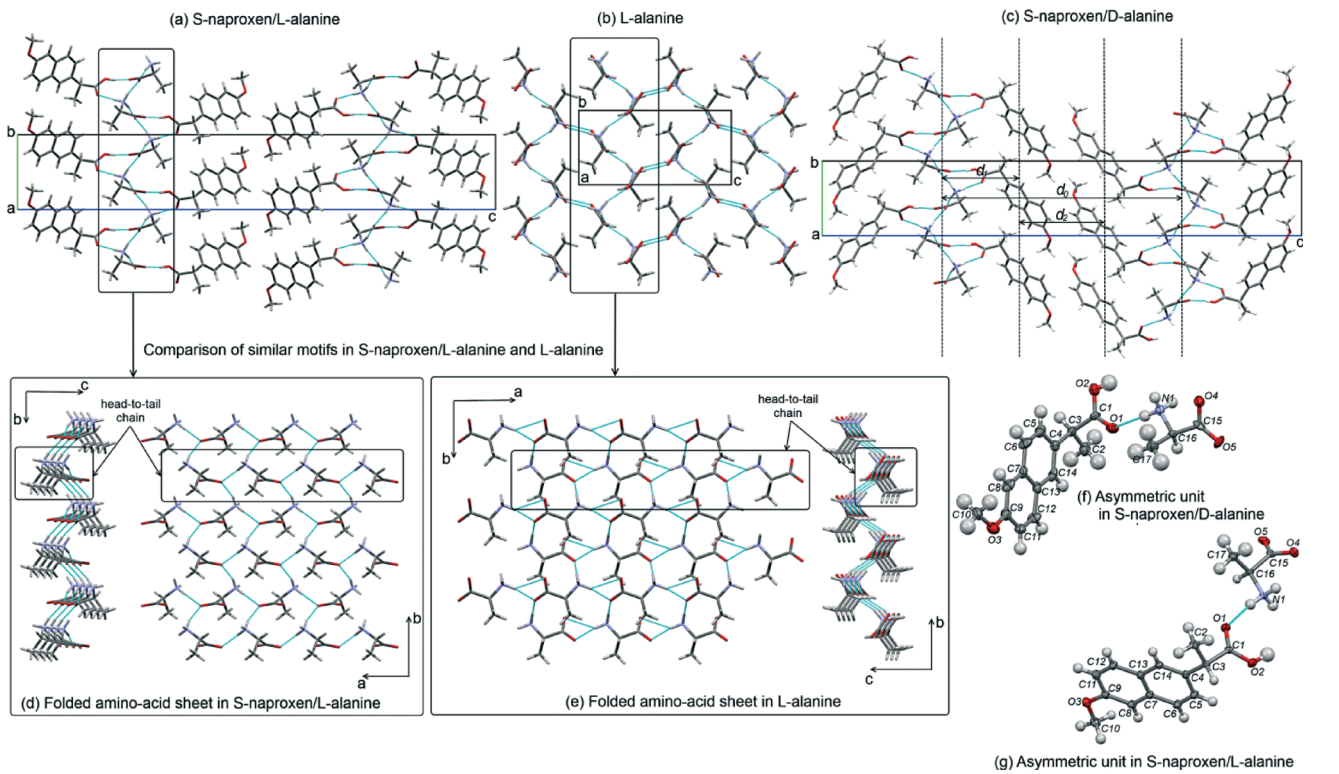


Fig. 2 Crystal packing of the (a) *S*-naproxen/L-alanine cocrystal, (b) L-alanine (rectangular regions in (a) and (b) confine a folded amino-acid sheet), and (c) *S*-naproxen/D-alanine (distances d_0, d_1, and d_2 are explained in the text); the folded amino-acid sheet in (d) *S*-naproxen/L-alanine and (e) L-alanine (in *bc* and *ab* projections, naproxen molecules are omitted for clarity); and displacement ellipsoid plots showing the atom numbering scheme and 50% probability displacement ellipsoids of (f) *S*-naproxen/D-alanine and (g) *S*-naproxen/L-alanine.

we can describe the structure as composed of "sandwich-like" motifs; each motif consists of a folded amino acid sheet ("core") surrounded by *S*-naproxen molecules from both sides. Amino acids within a sheet are linked by strong N–H···O charge-assisted hydrogen bonds; no hydrogen bonding appears between *S*-naproxen molecules themselves. "Sandwich-like" motifs join one another by weak interactions (therefore the structure is characterized by a 2D hydrogen bond network) (Fig. 2a, d).

In the structure of *S*-naproxen/D-alanine, molecules arrange in the same manner as in *S*-naproxen/L-alanine. D-Alanine molecules form head-to-tail chains, linked in folded sheets, each surrounded by *S*-naproxen molecules, thereby yielding "sandwich-like" motifs (Fig. 2c, f). The hydrogen bond network is similar to that observed in *S*-naproxen/D-alanine with minor differences in the hydrogen bond distances (see the ESI†). The distance between the planes passing through the centers of two neighboring "sandwich-like" motifs, d_0 (each plane was constructed by first calculating centroids for amino acid molecules from two neighboring "sandwich-like" motifs and then drawing a surface through them; all other planes were constructed in the same manner from centroids of corresponding molecules), in *S*-naproxen/L-alanine slightly exceeds the corresponding value observed for *S*-naproxen/D-alanine: 22.636 Å against 22.114 Å, respectively, and in agreement with a slightly longer *c* parameter in *S*-naproxen/L-alanine: 45.2723(17) Å against 44.227(4) Å, respectively (for distance notations see Fig. 2c). Within a head-to-tail chain, amino acid molecules lie closer to one another in *S*-naproxen/L-alanine than in *S*-naproxen/D-alanine [the *D*–*A* distances are 2.838(2) Å and 2.933(7) Å, respectively] and, correspondingly, the *a* parameter in *S*-naproxen/L-alanine is shorter [5.05836(11) Å against 5.3366(4) Å]. The distance, d_1, between the planes passing through *S*-naproxen molecules and the amino acid "core" within a "sandwich-like" fragment remains similar in both structures: 7.198 Å in *S*-naproxen/L-alanine and 7.121 Å in *S*-naproxen/D-alanine; whereas the distance, d_2, between the layers formed by *S*-naproxen from two neighboring "sandwich-like" fragments is longer in *S*-naproxen/L-alanine than in *S*-naproxen/D-alanine: 8.240 Å against 7.198 Å, since *S*-naproxen molecules in *S*-naproxen/D-alanine pack in a more tilted manner relative to the *c* axis than in *S*-naproxen/L-alanine, allowing a closer packing. However, those packing differences hardly influence the packing indices (Kitaigorodskii type) of these two structures, which have almost the same values: 68.9% (the percent of filled space) in *S*-naproxen/L-alanine against 68.7% in *S*-naproxen/D-alanine.

The motifs that amino acid molecules form in the *S*-naproxen/D-alanine and *S*-naproxen/L-alanine cocrystals resemble those observed in the crystal structures of the individual amino acids, L-alanine and D-alanine. In L-alanine (LALNIN53[60]), we distinguish three types of N–H···O hydrogen bonds: 1) between molecules within a $C_1^2(6)$ infinite head-to-tail chain; 2) between infinite chains linked in folded sheets; and 3) between folded sheets (Fig. 2b, e). The L-alanine molecules in the cocrystal behave similarly, *i.e.*, they form head-to-tail amino acid chains that form a folded sheet, like mentioned in 1) and 2). Molecules within a chain in the individual amino acids are linked through bifurcated N–H···O hydrogen bonds; whereas in *S*-naproxen/L-alanine and *S*-naproxen/D-alanine cocrystals, the amine function forms a hydrogen bond with only one oxygen atom of the carboxylate group, while another oxygen serves as an acceptor in the O–H···O hydrogen bond with *S*-naproxen (Fig. 2d, e) This similarity in the arrangement of amino acids within a folded sheet in the cocrystals and the original amino acids highlights the important role of the strong charge-assisted amino acid hydrogen bonds.

According to the fingerprint plots generated from the Hirshfeld surfaces[61] for *S*-naproxen in the *S*-naproxen/D-alanine and *S*-naproxen/L-alanine cocrystals, the main differences observed between these diastereomeric pairs are the presence of π–π stacking interactions (region 1 in Fig. 3a, 4.8% of all of the interactions) and a decreased percentage of C–H···π interactions in *S*-naproxen/L-alanine (19.6% against 27.4%) (Fig. 3). These differences agree well with the structural peculiarities. In *S*-naproxen/L-alanine, *S*-naproxen molecules arrange so as to allow interactions between the benzene rings, whereas in *S*-naproxen/D-alanine, these are shifted relative to one another, increasing the percentage of C–H···π interactions but completely reducing π–π interactions (Fig. 3c, d).

S-Naproxen/D-tryptophan monohydrate

The asymmetric unit of *S*-naproxen/D-tryptophan monohydrate contains one molecule of *S*-naproxen in the neutral form that links one molecule of D-tryptophan in the zwitterionic form *via* a N1–H1A···O1 hydrogen bond and one water molecule *via*

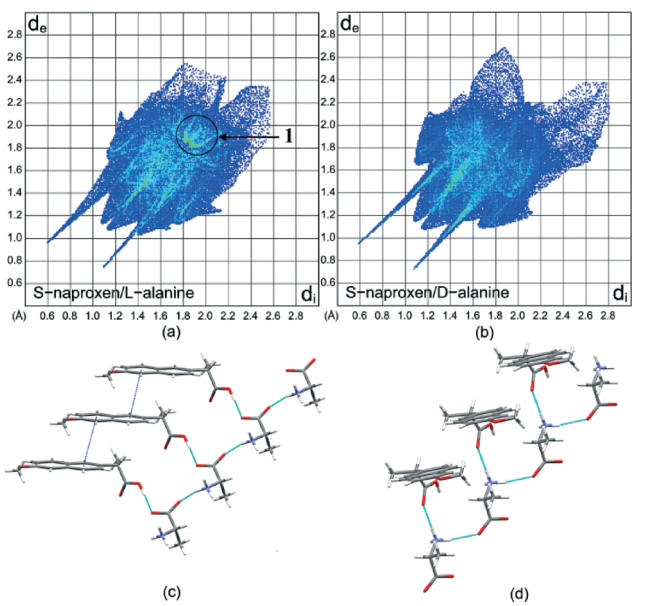


Fig. 3 Two dimensional fingerprint plots of *S*-naproxen in (a) *S*-naproxen/L-alanine and (b) *S*-naproxen/D-alanine and structural fragments of (c) *S*-naproxen/L-alanine (dotted blue lines indicate π–π interactions) and (d) *S*-naproxen/D-alanine.

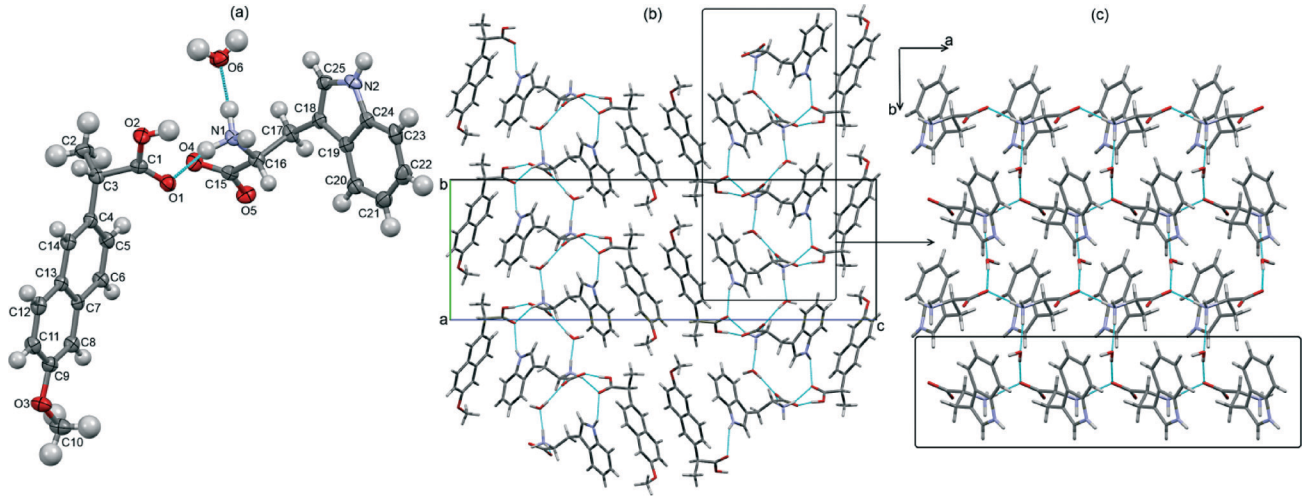


Fig. 4 (a) The displacement ellipsoid plot showing the atom numbering scheme and 50% probability displacement ellipsoids of *S*-naproxen/D-tryptophan monohydrate; (b) crystal packing of *S*-naproxen/D-tryptophan monohydrate, the rectangular region confines the structural fragment formed by amino-acid head-to-tail chains and water molecules; the same fragment is shown in (c) in the *ab* projection (the rectangular region in (c) contours one of the head-to-tail chains).

N1–H1B···O6 (Fig. 4a). The general structural motif is similar to that observed in *S*-naproxen/L-alanine and *S*-naproxen/D-alanine cocrystals, *i.e.*, "sandwich-like" fragments that connect to one another by weak interactions (Fig. 4b). D-Tryptophan molecules form C_1^1 (5) head-to-tail chains through N1–H1C···O5 charge-assisted hydrogen bonds between a positively charged amino group and a carboxylate in the [100] direction (Fig. 4b, c). In contrast to the above-described structures of *S*-naproxen/L-alanine and *S*-naproxen/D-alanine, head-to-tail chains in *S*-naproxen/D-tryptophan monohydrate do not join one another directly but rather *via* water molecules and *S*-naproxen, *i.e.*, water molecules enter the space between two neighboring head-to-tail amino acid chains, forming a N1–H1B···O6 bond with an amino acid molecule from one chain and O6–H6B···O5 with an amino acid from the neighboring chain (Fig. 4c). The carboxyl group of *S*-naproxen links three molecules of D-tryptophan: two from the same chain by N1–H1A···O1 (as an acceptor) and O2–H2···O4 (as a donor) hydrogen bonds and one from the neighboring chain *via* a N2–H2D···O1 bond with the cyclic N–H group. Thus, the "sandwich-like" motif in *S*-naproxen/D-tryptophan monohydrate consists of an amino-acid layer, parallel to the (001) plane and composed of infinite head-to-tail chains linked *via* water and *S*-naproxen molecules grafted on it from both sides (Fig. 4b).

We failed to find a structure for D-tryptophan (the CSD reports the structure of D-tryptophan, DEZHIZ,[62] but only the unit cell parameters are available without atomic coordinates). The reported structure of L-tryptophan[63] shows a rather complex head-to-tail N–H···O hydrogen bonding (Z' = 16). Tryptophan in the cocrystal keeps its ability to form infinite head-to-tail chains.

S-Naproxen/D-tyrosine

The asymmetric unit of *S*-naproxen/D-tyrosine contains one molecule of *S*-naproxen in the neutral form that links one molecule of D-tyrosine in the zwitterionic form *via* a O2–H2···O4 hydrogen bond (Fig. 5). We clearly see the essential role of charge-assisted hydrogen bonds between amino acid molecules, *i.e.*, D-tyrosine in the cocrystal tends to form infinite C_1^1 (5) head-to-tail chains in the [010] direction with molecules linked *via* N1–H1C···O4 hydrogen bonds; these chains look exactly the same as in individual D-tyrosine (Fig. 6). Owing to the presence of a hydroxyl group attached to the benzene ring, two complementary head-to-tail chains link one another through O6–H6A···O5 and N1–H1B···O6 bonds, forming a "tube" in the [010] direction (Fig. 6c, d). Each amino acid in the tube connects one *S*-naproxen molecule by O2–H2···O4 hydrogen bonds. The tubes stack on one another *via* N1–H1A···O5 hydrogen bonds along the *c* axis, thereby forming an amino acid "core" that attaches *S*-naproxen otherwise not linked by hydrogen bonds (Fig. 6a). Thus, the structure of *S*-naproxen/D-tyrosine can be still considered in terms of "sandwich-like" motifs, which, in contrast to the above-discussed structures, connect to one another in a

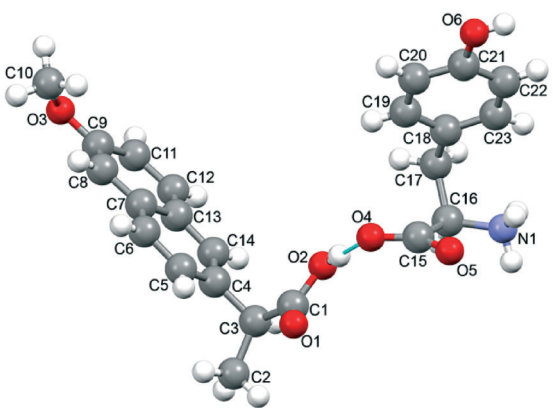


Fig. 5 The asymmetric unit cell in *S*-naproxen/D-tyrosine (numbering scheme).

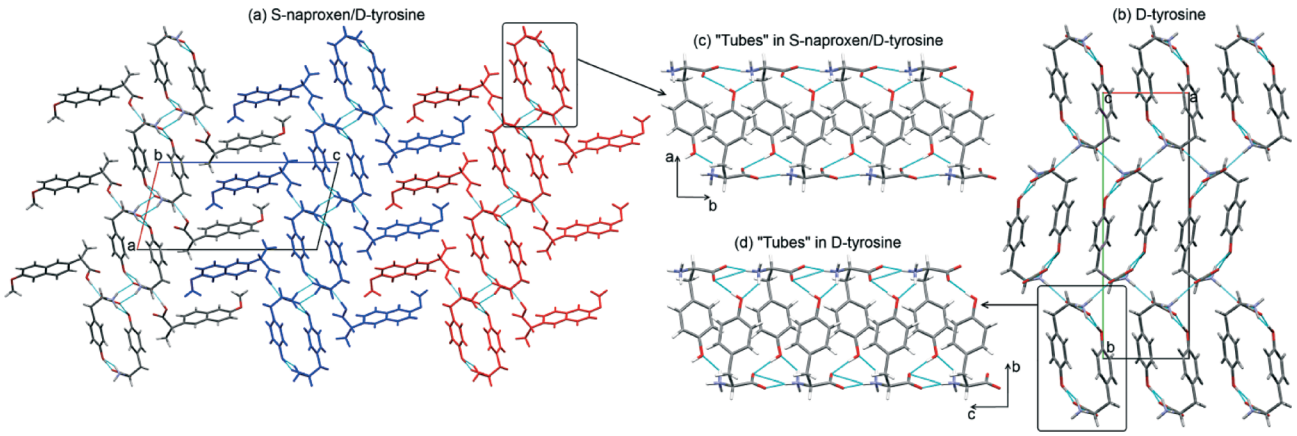


Fig. 6 (a) Structural fragments of *S*-naproxen/D-tyrosine (red and blue color – two neighboring "sandwich-like" motifs stacked to one another in a "zip-like" manner); (b) structural fragments of D-tyrosine (rectangular regions in (a) and (b) highlight a similar motif, "tubes", formed by amino acid molecules in the cocrystal and the individual amino acid); (c) the "tube" motif in *S*-naproxen/D-tyrosine along the *b* axis; and (d) the "tube" motif in D-tyrosine along the *c* axis.

"zip-like" manner by weak interactions (see Fig. 6a, two neighboring "sandwich-like" fragments are colored red and blue).

Comparison with known structures from the CSD

So far we showed that amino acid co-formers have a tendency to form cocrystals with compounds that contain a carboxyl acid group, and furthermore, we showed that even within these compounds, the main hydrogen bonding patterns found in the amino acid co-former are maintained, with the neutral API grafted onto these elements.

To verify these observations with respect to the literature, a systematic Cambridge Structural Database search was performed. The CSD reports only two naproxen-amino acid compounds; in both cases, the amino acid is *S*-arginine which cocrystallizes with *S*- and *R*-naproxen (the refcodes are JASHOB[64] and QANPEB,[64] respectively); the compounds formed are salts: a proton moves from the carboxyl group of naproxen to the amino group of *S*-arginine. Thus, naproxen becomes negatively charged, whereas *S*-arginine becomes positively charged. Tilborg *et al.* described four other cocrystals: *S*-naproxen/D-proline, *S*-naproxen/L-proline, L-proline/*RS*-naproxen, and DL-proline/*RS*-naproxen (FEVZOX, FEVZUD, BEXGUI, and BEYTUW, respectively), in which no proton transfer occurs between the co-formers – *S*-naproxen molecules are in the neutral form, and proline is zwitterionic.[32] To our knowledge, no other cocrystals formed by naproxen and amino acids have been reported. The structural motifs observed in all of the above mentioned structures containing proline or arginine are similar to those found in our cocrystals: "sandwich-like" fragments which link one another by weak interactions and are composed of an amino-acid "core" with naproxen molecules attached from both sides.

Although *S*-arginine in the aforementioned salts preserves head-to-tail linking, the molecules form dimers rather than infinite head-to-tail chains found in *S*-arginine (TAQBIY[65]).

In *S*-naproxen/L-proline and *S*-naproxen/D-proline cocrystals, proline molecules form infinite head-to-tail chains, which connect to one another in a zig-zag manner forming a folded sheet to which naproxen molecules attach from both sides, yielding "sandwich-like" motifs, therefore showing head-to-tail linking similar to the individual L-proline crystals. The other two published cocrystals from the naproxen–proline family are hydrates and show slightly different hydrogen bonding patterns between amino acids, with water molecules playing an essential role. In L-proline/*RS*-naproxen monohydrate, water "glues" separate amino acid molecules not directly linked by hydrogen bonding. In DL-proline/*RS*-naproxen, water chains join infinite amino acid head-to-tail zig-zag chains to one another. Those kinds of interactions with water are typical for proline—in its individual crystal hydrates, water serves as a "glue" between separate head-to-tail chains.

Thus, from the above-considered crystal structures of cocrystals, amino acids seem to form a "platform" which then "guides" the arrangement of *S*-naproxen molecules. Although this simplified situation seems to hold for naproxen, this is no longer the case when considering other amino-acid cocrystals.

To understand how the discussed amino acids behave with respect to other compounds, we performed a systematic CSD search (excluding all halogen-containing compounds). We failed to find any cocrystals for D-tyrosine, so we considered only cocrystals formed by tryptophan, alanine, arginine, and proline. Multicomponent systems show greater structural complexity than compounds in their individual forms, since different types of molecules in one crystal lattice mutually influence one another (conformations, torsion angles, packing, *etc.*). This brings along difficulties in identifying similar structural motifs. Thus, when comparing several cocrystals/salts, we rather mention similar structural trends than identical structural motifs. We analyzed 51 cocrystals/salts formed by alanine, tryptophan, proline, and arginine (formed by alanine: CAPKEL,[66] AHERAG,[67] BEYVAD,[68] BOQTEG,[69] IMEGIR,[70]

IROVAM,[71] NELPUP,[72] PAVYIW,[73] XUGMER,[74] and YEJYIV;[75] by tryptophan: HAGBOG,[76] LAQXIM,[77] NUQHIR,[78] TPTPCM,[79] TRYPTB, and UGITAG;[80] by proline: NASGIG,[81] NAZGOM,[81] NAZGUS,[81] NAZHAZ,[81] EXIBOC,[82] GIVROS,[83] IHUMAZ,[84] LABZUJ,[85] OLIZAL,[86] POCKHAY10,[87] QIJYIR,[67] VESCUS,[88] ZEZHIV,[89] and NISVOA01;[90] and by arginine: ADAVIK,[91] EWINAZ,[92] GOLFOC,[93] JASHOB,[64] LARASC20,[94] MUPNUG,[95] MUPPAO,[95] NOSXAU,[96] NOSXEY,[96] OFIWUW,[97] ORUXEF,[98] QAMXEI,[99] QAMXIM,[99] QANPEB,[64] RIFXAG,[100] RIFXEK,[100] TEFLUL,[101] TEFMAS,[101] TIDCAK,[102] YOWDET,[103] and YOWDIX[103]). The comparison of structural motifs found in those structures reveals that amino acids tend to form infinite head-to-tail chains owing to N–H···O charge-assisted hydrogen bonding between their amino and carboxylate groups; this motif occurs in the majority of analyzed structures; chains do not necessarily connect to one another—they can be linked through an intermediate, *i.e.*, co-former or solvent molecules (when we deal with cocrystal hydrates or solvates). However, in some structures, amino acid molecules form only dimers or form hydrogen bonds only with co-former molecules but not with each other. A number of structures show "sandwich-like" motifs, as we observed for the naproxen cocrystals, but the "core" formed by amino acid molecules is not necessarily composed of similar motifs as those observed in individual amino acids. It would therefore not be entirely accurate to state that the interactions between amino acids remain identical in the cocrystals, as the nature of the second cocrystal former can significantly affect the cocrystallization process.

We suggest that the first factor responsible for the formation of a cocrystal with an amino acid co-former is the strength of the hydrogen bonds formed between a co-former and an amino acid; if these bonds are competitive in strength with strong charge-assisted N–H···O bonds between zwitterionic molecules, one observes unlinked amino acid molecules that form hydrogen bonds only with a co-former but not with each other. In this context, the presence of functional groups in a co-former prone to hydrogen bonding has a crucial role on the final cocrystal structure. The second factor is the size of the co-former. If the co-former is bulky, it will influence the packing significantly, and hereby, affect the structural arrangement of the amino acids.

Overall, if a compound forms weak hydrogen bonds with a selected amino acid, then one can expect motifs that resemble those found in individual amino acid crystals, but if the compound molecules themselves form strong hydrogen bonds with amino acid molecules, such similar patterns might not be seen. Thus, as we saw in the case of naproxen, only one functional group allows formation of hydrogen bonds, which is not enough to counterbalance strong charge-assisted hydrogen bonds between amino acid molecules, and these latter keep forming hydrogen bond motifs, similar to those observed in individual amino acids. However, the arrangement of naproxen molecules around those amino-acid motifs is determined by bulky naproxen which tends to pack in a stacking manner on each side of the amino acid "core".

This conclusion agrees well with the results of screening. We found cocrystals only for naproxen, which contains a carboxyl group prone to hydrogen bonding, but not for the other APIs that contain hydroxyl and/or amide groups with weaker hydrogen bonding potential. The search of the Cambridge Structural Database showed that amino acids form many cocrystals with compounds that contain a carboxyl group but only a few with compounds that contain only a hydroxyl or amide group (95, 21, and 2 entries, respectively), which also confirms the above-mentioned key factors in cocrystal formation.

Among the 21 compounds formed by amino acids with hydroxyl-containing compounds, only three types of co-formers were found: picric acid, squaric acid, and (2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(4-ethylbenzyl)-phenyl)-6-hydroxymethyl-tetrahydro-2*H*-pyran-3,4,5-triol; in the first two cases, the compounds were salts (*i.e.*, proton transfer occurred between an amino acid and a co-former) and for the latter, cocrystals (*i.e.*, no proton transfer). Searching for amide-containing co-formers gave only two entries, both contain nitrogen in the cycle. In the group of carboxyl-containing compounds, the most studied co-formers were oxalic, maleic, tartaric, and mandelic acids (23, 14, 11, and 9 entries, respectively). All of the compounds with oxalic and maleic acids were salts, whereas among the rest of compound, both salts and cocrystals existed.

The results of the CSD search highlight the complexity of multicomponent systems, illustrating well the ability of the studied molecules to form both cocrystals and salts, which is referred to in the literature as the salt–cocrystal continuum[104] (see the ESI†).

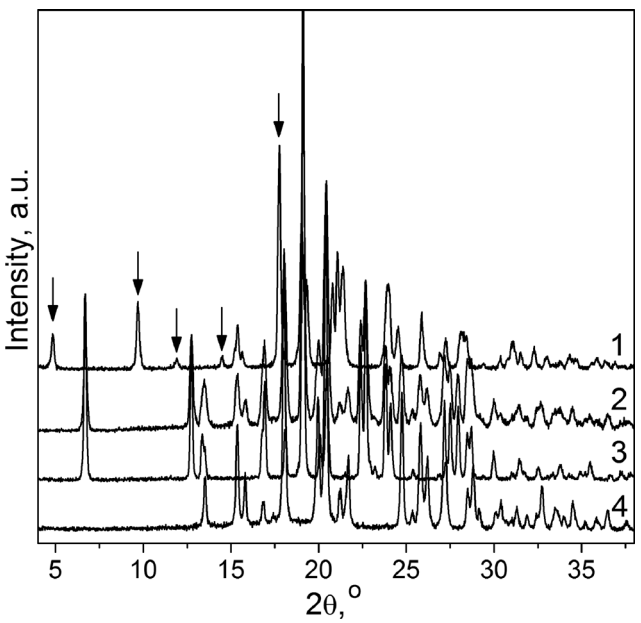


Fig. 7 Diffraction patterns (CuKα radiation) of (1) *S*-naproxen ground with D-tyrosine (liquid-assisted grinding shows the formation of a new phase, several new peaks which are indicated with arrows), (2) *S*-naproxen ground with L-tyrosine, (3) *S*-naproxen, and (4) L- or D-tyrosine.

Finally, we would like to note the importance of chirality in cocrystal formation. A selected compound of a particular chirality might form a cocrystal with one chiral co-former but not with its mirror image. We observed such an enantiospecific behavior in the *S*-naproxen/tyrosine system, *i.e.*, *S*-naproxen cocrystallized with D- but not with L-tyrosine. Fig. 7 shows that, after grinding, *S*-naproxen and D-tyrosine yielded a new phase, whereas *S*-naproxen and L-tyrosine remained a physical mixture. This observation can be used to construct an effective resolution of racemic naproxen using enantiospecific cocrystallization in solution.

Conclusions

Zwitterionic co-formers are characterized by the presence of strong charge-assisted hydrogen bonds, which lead to great structural complexity in cocrystals, highlighting the relative importance of all hydrogen bonding interactions, and especially, between an amino acid co-former and a target compound—the latter has to be strong enough to counterbalance potentially strong charge-assisted hydrogen bonds that exist in the crystal lattices of individual amino acids. Due to this fact, amino acids are effective in the case of carboxyl acids but fail when dealing with other studied compounds. As we saw from the examples with naproxen, amino acids can preserve motifs similar to those observed in their individual crystals. This observation can be helpful when solving structures from powder data or performing theoretical simulations.

Although amino acids seem to form diastereomeric cocrystal pairs more often, the *S*-naproxen/tyrosine system behaves enantiospecifically. Thus, since amino acids play a crucial role in the body, the possibility of an enantiospecific behavior is an interesting issue to bear in mind when dealing with biological aspects. Another promising application of enantiospecific systems is enantiomeric resolution of racemic drugs in pharmaceutical industry based on cocrystal engineering principles.[30] Moreover, to our knowledge, this cocrystal is the very first reported cocrystal found for tyrosine. We successfully solved its structure from synchrotron X-ray powder diffraction data, thus providing another example of how powerful structure determination techniques from powder data are.

Acknowledgements

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