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Exploring the molecular landscape of multicomponent crystals formed by naproxen drug and acridines†

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The cocrystallization of active pharmaceutical ingredient naproxen with some acridines (acridine, 9-aminoacridine, 6,9-diamino-2-ethoxyacridine) has been explored and the conditions under which the crystallization can be carried out have been investigated. While the crystallization of acridine-based molecular crystals was widely studied under solution conditions, solvent-free and/or mechanochemical method potentialities are still unknown. To fill this gap, the cocrystallization of naproxen with the above-mentioned acridines was attempted using different approaches, e.g., by heat treatment of the dry mechanical mixture and by liquid-assisted grinding (LAG), as alternatives to the traditional precipitation by a proper solution. In the first case, the reaction is driven under dry conditions by the temperature and gave no results independently of the temperature used, below or above the melting point of the reactants. In the second case, the reaction is driven by the mechanical action of grinding assisted by a few drops of solvent to facilitate and improve the reaction. This screening allowed obtaining three new molecular crystals for naproxen coupled to acridine and a mono-aminoacridine and solved by single-crystal and powder X-ray diffraction (PXRD). Two host-guest structures were obtained by solution crystallization, while a layered structure was obtained under LAG conditions. Interconversion between molecular crystals formed by the same chemical species was hindered once a molecular crystal was obtained by a specific technique. Hirshfeld and energy framework calculations confirmed the remarkable structural differences between **1a** and **1b** packing and suggested that **1b** is kinetically more stable. Variable-temperature PXRD, DSC and TGA were used to explore the stability of the compounds. 6,9-Diamino-2-ethoxyacridine proved to be too polar and/or too bulky to form crystals with naproxen regardless of the preparation method and the different stoichiometric ratios used. It is noteworthy that LAG allowed the preparation of the naproxen/acridine molecular crystal with a yield higher than 99% under almost solvent-free conditions. DSC indicated the formation of a eutectic between naproxen and acridine, with the possibility of recrystallizing the 1:1 complex also from the melt solution.

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1. Introduction

Crystal engineering is an intensively developing field, and one of its main assumptions is to identify and understand intermolecular interactions in crystals.^{1–4} It allows the design and preparation of new materials based on a repeatable

structural motif (synthons) arising through intermolecular interactions between different functional groups in the molecules. The knowledge on how the synthons assemble is fundamental to obtain multicomponent crystals with the desired, predictable structure as well as the expected properties. However, a change of the stoichiometry of the coformers and an increase in the number of functional groups in the molecules used may lead to unexpected changes in the structural landscape of multicomponent crystals. All these issues are even more important when the synthons are active pharmaceutical ingredients (APIs). In this case, small changes in the molecular formula and/or in the crystal packing might affect the solubility, bioavailability and other properties related to their biological activity. The formulation of APIs is thus one among the key steps when transforming a bioactive molecule into a drug. A common

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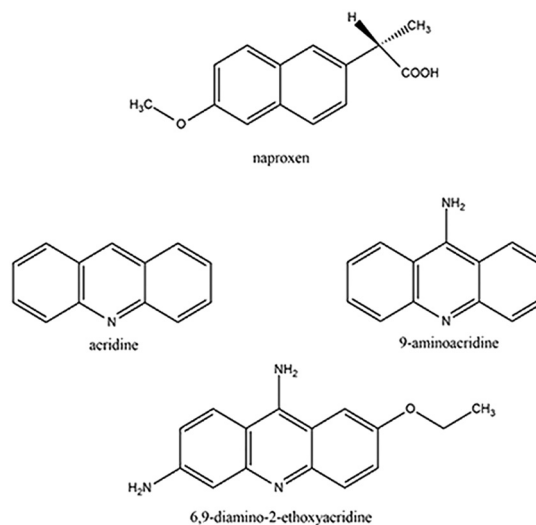
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containing bases, acridines are an interesting object of research. This group of compounds is recognized as APIs because they exhibit anti-cancer, antibacterial, and antiviral properties. Acridines are used as bacteriostatic antiseptic drugs and for various infections and inflammations.^{24–27} The most important property of acridines is their ability to interact with DNA through intercalations.^{28,29} Recently we have presented results regarding the capabilities of different solvents to induce cocrystallization in acridine-based molecular crystals of APIs.³⁰ Some of us demonstrated that, in similar cases, cocrystallization³¹ and solid-state reactions³² can be carried out directly in the solid state under dry conditions with high conversion rates and with the additional advantage of eliminating solvents.³³ In this work, the cocrystallization of naproxen with some acridines is thus attempted by three different approaches: (i) solution methods, (ii) liquid-assisted grinding (LAG), and (iii) solid-state thermal approach, heating the sample just below or above the melting point of the reactants to explore the molecular landscape of the target compounds. While the first case requires large quantities of solvents, in the LAG method, the reaction is driven by the mechanical action of the grinding assisted by a few drops of solvent to facilitate and improve the reaction, as described in ref. 34. In the last case, the reaction is driven by the temperature and by the conditions of autogenous pressure that develops inside the reaction chamber, if a sealed tube is used for the preparation and the temperature is below the reactants' melting points and no eutectic is present. As naproxen counterparts, acridine, 9-aminoacridine, 6,9-diamino-2-ethoxyacridine, depicted in Scheme 1, were chosen because of their complementary biological activities, *i.e.*, NSAID for naproxen and antibacterial and antiviral for acridines. Their combination in a molecular crystal can give synergic powering of their complementary



Scheme 1 Molecular structures of naproxen and acridines reported in the paper (the specific chemical forms used are detailed in the Experimental section).

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Table 1 Summary of the applied preparation methods and obtained molecular crystals

API	Coformer	Compound	Solution	Dry	LAG
Naproxen	Acridine	1	Single crystals 1α	Mechanical mixture of reactants	Powder 1β
	9-Aminoacridine	2	Single crystals 2α		Mechanical mixture of reactants
	6,9-Diamino-2-ethoxyacridine	—	Mechanical mixture of reactants		Mechanical mixture of reactants

Table 2 Crystal data and structure refinement for **1α**, **2α** and **1β**

Compound	1α (SX)	2α (SX)	1β (PXRD)
Chemical formula	C ₆₇ H ₅₅ N ₃ O ₆	C ₄₁ H ₄₀ N ₂ O ₇	C ₂₇ H ₂₃ NO ₃
Formula weight/g mol ⁻¹	998.14	672.75	409.48
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	17.3435(14)	10.0768(11)	12.6466(4)
<i>b</i> /Å	5.9437(6)	6.2918(5)	29.6246(12)
<i>c</i> /Å	25.672(2)	27.347(3)	5.63596(19)
<i>α</i> /°	90	90	90
<i>β</i> /°	101.975(9)	98.004(11)	90
<i>γ</i> /°	90	90	90
<i>V</i> /Å ³	2588.8(4)	1717.0(3)	2111.52
<i>ρ</i> _{calc} /g cm ⁻³	1.280	1.301	1.288
Final <i>R</i> ₁ value	0.0585	0.0677	<i>R</i> _p = 2.043
Final <i>wR</i> ₂ value	0.0927	0.0843	<i>R</i> _{wp} = 2.635
CCDC number	2168756	2168757	2169121

Crystallization from solution produced single crystals by coupling naproxen to acridine and 9-aminoacridine, while no results were obtained for naproxen/6,9-diamino-2-ethoxyacridine. Single-crystal X-ray diffraction measurements show that compound **1α** crystallizes from solution in the monoclinic *P*2₁ space group as a cocrystal with two naproxen and three acridine molecules in the asymmetric unit (Fig. S1† and Table 2). Compound **2α** crystallizes in the monoclinic *P*2₁ space group as a monohydrate salt cocrystal with one naproxen molecule and anion, one 9-aminoacridinium cation, and one water molecule in the asymmetric unit (Fig. S2† and Table 2). Both **1α** (Fig. 1, top) and **2α** (Fig. 2) show a host-guest-like packing. LAG and dry thermal synthesis were thus performed as described in the Experimental section for all the three acridines and the results are summarized in Table 1. While dry synthesis was unsuccessful in all cases, the LAG approach allowed obtaining a cocrystal of naproxen with acridine (1:1 stoichiometry) (**1β**). In fact, analysis by powder X-ray diffraction (Fig. 3) confirmed that the patterns of the products obtained by LAG (the reactant with a 3:2 naproxen/acridine ratio as in **1α**) did not coincide with those obtained by solution or with the patterns corresponding to the mechanical mixture of the reagents. The new molecular cocrystal appeared with a residual amount of acridine reactant. The LAG procedure was thus repeated with a 1:1 naproxen/acridine reactant ratio and pure **1β** was obtained, within the sensibility limitation of powder diffraction (Table 2). For further confirmation, the reagents were also subjected to the LAG procedure individually to verify that the

products obtained were not mechanical mixtures of molecular crystals of the reagents alone due to the LAG process. In Fig. 3, the PXRD patterns of both molecular crystals **1α** and **1β** of naproxen/acridine cocrystals confirm that their crystal structures are different. To obtain a PXRD pattern suitable for structure solution, a capillary was filled, and a long measurement was carried out to obtain a good resolution. This pattern was used to index and obtain a cell. Then, the structure solution was carried out using the same data based on the available diffraction data; the obtained crystal structure is presented in Fig. 1, bottom. It is worth noting that the product is pure, within the sensitivity limitation of PXRD, as indicated by the Rietveld refinement reported in Fig. 3.

In both molecular crystals **1α** and **1β**, the packing is due to two different driving forces: in the case of the 2:3 molecular crystal **1α**, intermolecular COOH_(naproxen)...N_(acridine) and OH_(naproxen)...N_(acridine) hydrogen bonds and C-H_(naproxen/acridine)...π_(naproxen/acridine) interactions prevail

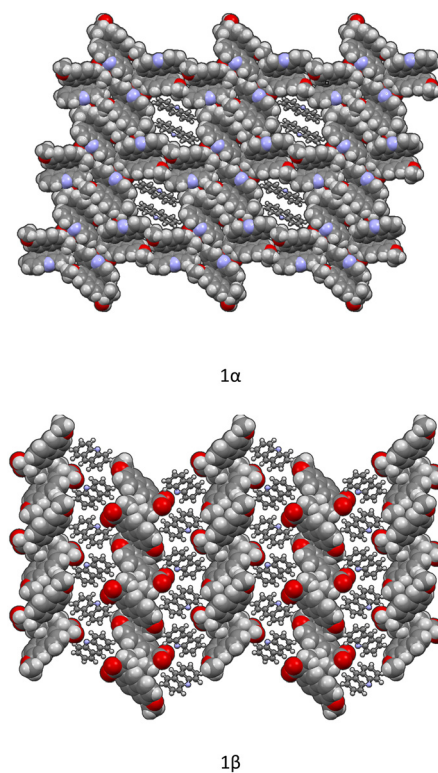
**Fig. 1** Crystal packing of **1α** and **1β**.



Fig. 2 Crystal packing of 2α.

(Tables S3 and S4†), while in the case of the 1:1 ratio molecular crystal **1β**, there is an overall stabilization of the structure given by π -stacking and intermolecular and the above-mentioned O–H \cdots N hydrogen bonds. In detail, each naproxen is bonded by one H-bond and CH \cdots O interactions

to two different acridine molecules (Table S2†). A T-like interaction and a parallel π – π interaction connect adjacent acridine layers as detailed in Table S3.† Several CH \cdots C longer contacts (mainly involving naproxen methyl groups) complete the packing. Consequently, in the crystal of **1α**, hydrogen-bonded pairs of naproxen and acridine molecules formed the 3D network, with voids filled by the non-hydrogen-bonded acridine molecules. Of course, the host–guest structure cannot be considered a MOF-like compound since the guest cannot be removed without destroying its crystal structure. Conversely, in **1β**, π -stacked columns of acridine molecules and the layered association of naproxen molecules can be observed as previously observed in the molecular crystals of naproxen with proline (1:1) (described by authors as type II).²⁰ A weak CH \cdots O and a strong OH \cdots N hydrogen bond interaction connect the layers of naproxen with those of acridine. This packing was obtained after carefully checking all the possibilities in placing the acridine molecule (that can

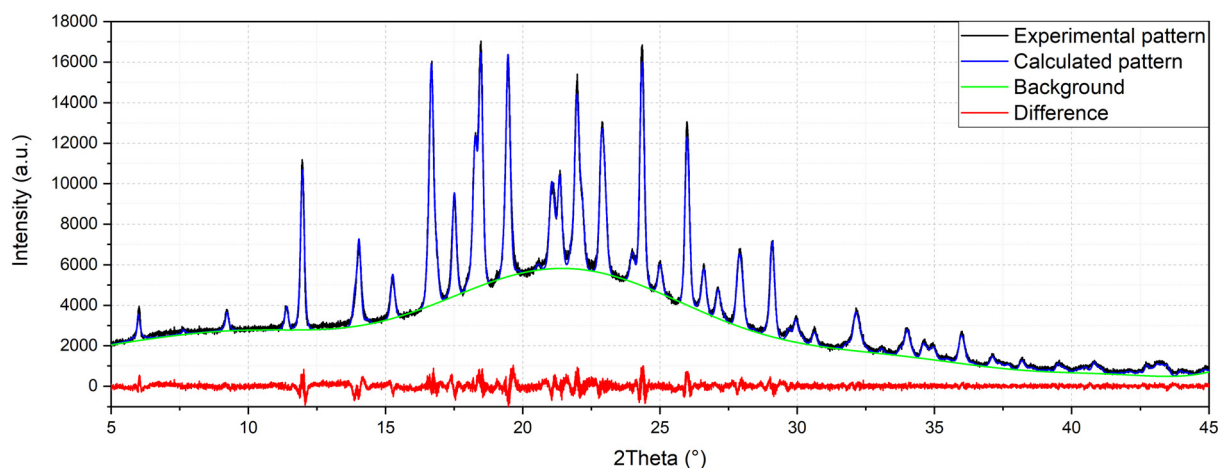
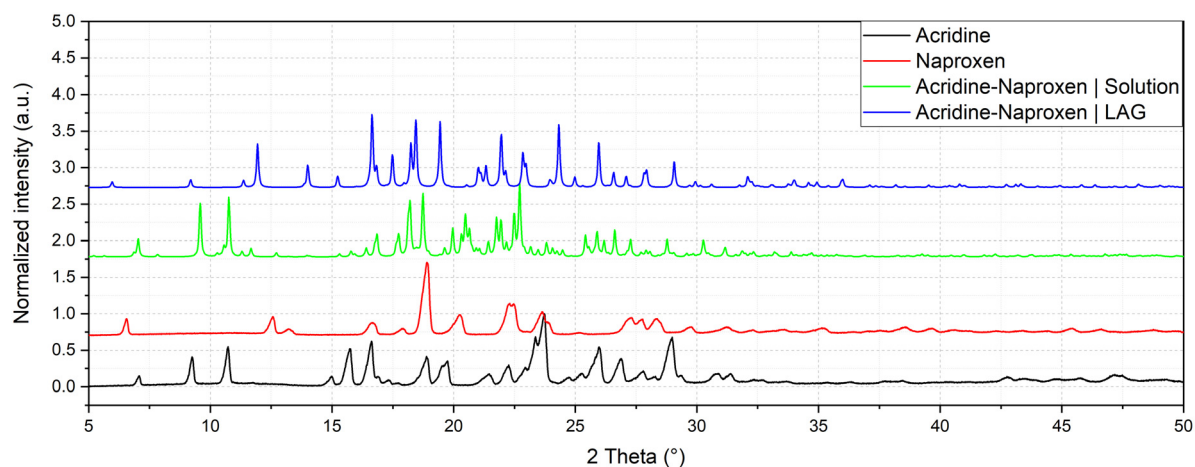


Fig. 3 Comparison of powder patterns of **1α** and **1β** and refinement of crystal structure solved by powder diffraction of **1β** ($R_p = 2.043$, $R_{wp} = 2.635$).



be flipped by 180° without changing the packing) and selecting the correct location of the hydrogen of the hydroxyl.

The chosen solution minimizes the agreement factor and gives more reliable interactions and intermolecular contacts without geometrical warnings. On the other hand, the crystal structure of **2a** may be considered as a 3D network formed by monoanionic dimers of the naproxen molecule and anion with π -stacked 9-aminoacridinium cations located in the cavities formed by the network, similarly to **1a**. To date, no molecular crystals belonging to this family are available; however different structures of molecular crystals of naproxen and acridine with other molecules are present within the CCDC database. In this broad landscape of structures, molecular crystals can be found crystallizing with similar cell parameters and with equivalent space groups. For example, naproxen crystallizes according to space group $P2_1$ with (*S*)-1-phenylethylammonium, as reported by Rossi *et al.*,⁴⁷ with a needle crystal habit, as in the case of the single crystal presented in this work. Naproxen also crystallizes in space group $P2_12_12_1$ with (1*S*,2*S*)-*trans*-1-aminobenz[*f*]indan-2-ol,⁴⁸ but with a very different arrangement of the asymmetric unit, *i.e.*, without an alternation between the two molecules in the structure. Acridine also has similar molecular crystal structures reported in the CCDC, such as that of Bao *et al.*⁴⁹ with space group $P2_1$, or with $P2_12_12_1$, reported by Rajkumar *et al.*⁵⁰

The same procedure used to obtain **1b** was applied to compound **2** and (hypothetical) **3** but no results were obtained, as can be seen from the PXRD data reported in Fig. 4. It can be concluded that compound **2** (with a monoamino acridine) has only one stable molecular crystal with the host-guest hydrate structure, while hypothetical compound **3** (with a diamino acridine) cannot be obtained, probably because of the higher polarity of the diamino acridine and/or its steric hindrance is not suitable for a host-guest-like or layered structures such as **1a** and **1b**, respectively.

3.2. Exploring the landscape of cocrystals of naproxen with acridines with different molecular ratios

The presence of two molecular crystals of naproxen with acridine raises questions on which is the more stable one and on their possible interconversion. To shed light on this point, single crystals of **1a** obtained by solution precipitation were subjected to the LAG procedure under *in situ* PXRD conditions: surprisingly, after this procedure, **1a** did not produce **1b** (Fig. 5, top), suggesting that **1a** should be the more stable compound, able to resist the harsh mechanochemical treatment. Only a degradation of the structure of **1a** (obtained from solution crystallization) is visible after applying the LAG procedure. The main peak of compound **1a** (8° in Fig. 5, top) remained after the treatments and the main peaks (indicated by asterisks) of **1b** do not appear. After the failure of conversion of **1a** to **1b** by LAG, the opposite experiment was attempted. **1b** formerly

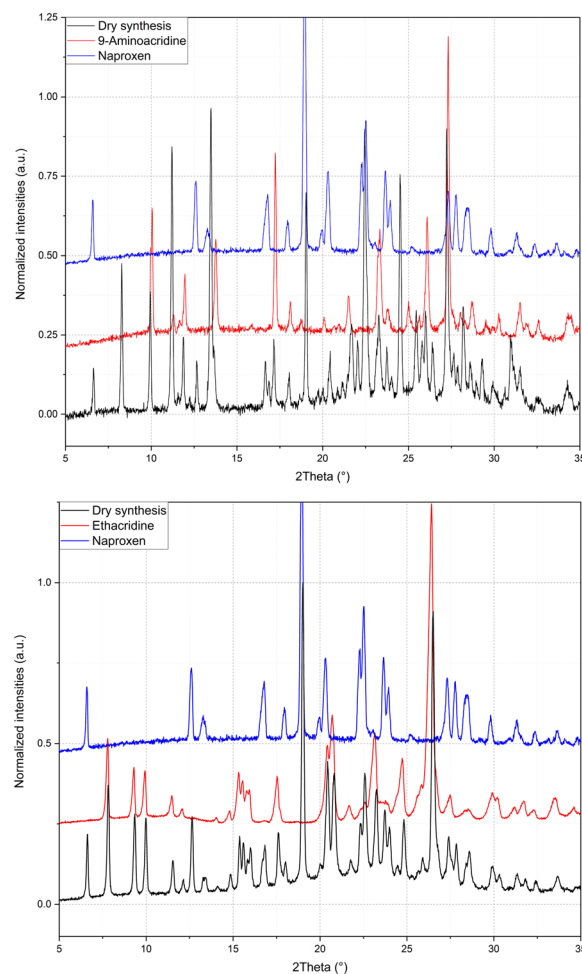


Fig. 4 Refinement of LAG of **2** and **3** as mechanical mixture.

obtained by LAG was dissolved and crystallized from solution with the same procedure used to obtain **1a** using water, ethanol and a 50:50 mixture as solvent. Even more surprisingly, solution crystallization of **1b** did not produce **1a** but still **1b** as indicated by the refinement in Fig. 5, bottom. Clearly, the interconversion between **1a** and **1b** seems unfeasible, suggesting a similar stability between the two cocrystals and/or a very high energy barrier between the two. Also, the different stoichiometry might play a role in hindering their interconversion, which was not observed despite several attempts (Fig. 5 represents only one of several experiments).

To further understand the driving forces of the crystal packing and estimate which compound is more stable between **1a** and **1b**, Hirshfeld surface analysis and energy framework calculations were carried out. Fig. 6 presents a crystal structure model of **1a** viewed along the *b*-axis, showing Hirshfeld surfaces with *d*-norm plotted, and the fingerprint plots for each individual molecule in **1a** are reported. Acridine molecules are labelled with “a” and naproxen molecules with “n”.

By looking at the Hirshfeld surfaces and fingerprint plots of **1a** the presence of two short contact OH...N hydrogen bonds





Fig. 5 Refinement of **1α** after LAG (top) and solution crystallization of **1β** after full dissolution (bottom).

can be readily seen between Mol_1 and Mol_2_n and a slightly shorter one between Mol_4_a and Mol_5_n. Mol_1_a and Mol_2_n also share an O \cdots H interaction, while Mol_5_n has an O \cdots H interaction with a symmetry equivalent molecule. The more symmetrical plot of Mol_3_a evidences a predominance of interactions with symmetry equivalent molecules. There is no evidence by looking at both the Hirshfeld surfaces and fingerprint plots of π - π interactions (C \cdots C).

The most important interactions in **1β** shown by Hirshfeld surface analysis (Fig. 7) are the OH \cdots N hydrogen bond between acridine and naproxen, separated by a short contact distance (2.08 Å) clearly evidenced by plotting d -norm on the surfaces (Fig. 7, bottom), and the presence of π - π stacking between acridine molecules. The fingerprint plots are shown in the top part of Fig. 7 for acridine (Mol_1_a) and naproxen (Mol_2_n). The fingerprint plot features are labelled according to the interaction; the first atom is the one inside the surface. The hydrogen bond is clearly shown by a spike in both plots, indicating a short-range contact between the N atom in acridine and the OH group in naproxen, while the

π - π interaction (C \cdots C) is found at longer distances and occurs between acridine molecules. This feature is clearly visible only in the acridine plot, represented by a green symmetrical spot at 1.8 Å on both axes, indicating a contact distance of about 3.6 Å.

From the analysis of the Hirshfeld surfaces and fingerprint plots of **2α** (Fig. S9 and S10, respectively, in the ESI†) it appears that the shorter interactions are hydrogen bonds, the one between the water molecule and Mol_1_a (9-aminoacridinium). Other hydrogen bonds are formed between the naproxen moieties and water, while N \cdots H interactions are long range and can be seen in the fingerprint plot only after filtering (Fig. S10,† bottom). It is also worth noting the formation of π - π interactions between 9-acridinium molecules (Mol_1_a) evidenced by a green spot in the fingerprint plot as in **1β**.

The energy frameworks were also calculated for all structures. In Fig. 8 the energy frameworks for the coulombic interactions are reported showing that in **1α** the stronger interactions (thicker tubes in the picture) form a crossed



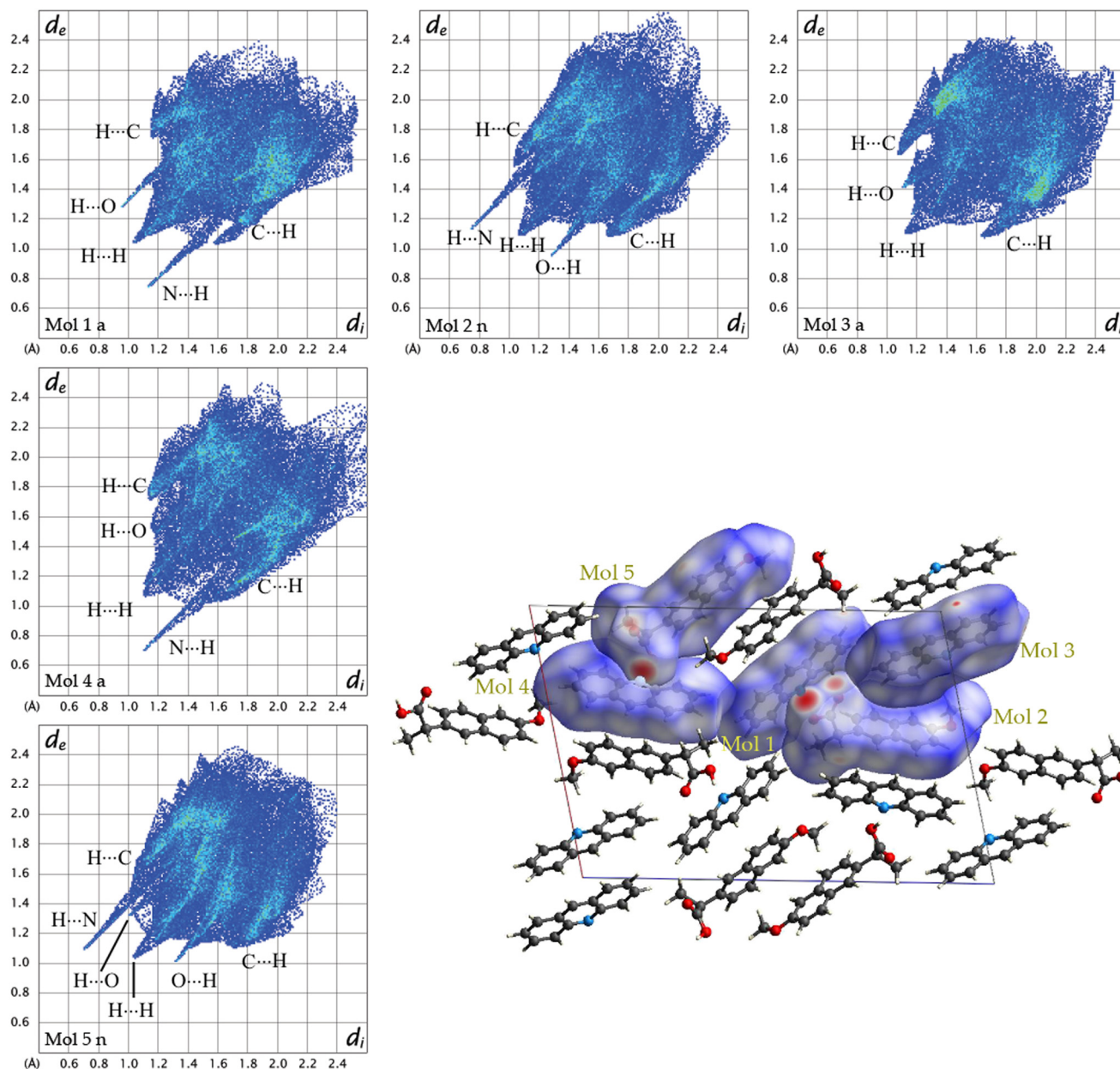


Fig. 6 Fingerprint plots for each symmetry-independent molecule in 1a and crystal structure model of 1a viewed along the *b*-axis showing Hirshfeld surfaces with *d*-norm plotted.

pattern, while in **1β** the interactions are almost parallel, forming a layered structure. Remarkable differences can be seen also in the dispersion interactions, forming a honeycomb-like motif in **1α** viewed along the *b*-axis, while a square motif is observed for **1β**. In this structure, along the *b*-axis the packing is stabilised mainly by coulombic forces, while dispersion forces are stronger in the perpendicular directions. Therefore, the layers are kept together by π - π interactions while the interaction between the layers is polar (*i.e.* hydrogen bonds).

From the calculation of pairwise interactions, the lattice energy was calculated for each independent molecule. For structure **1β** the sum of energies for the acridine molecule

was found to be about -90 kJ mol^{-1} , while for naproxen it was -108 kJ mol^{-1} . For structure **1α** the energies for the acridine molecules resulted to be -100 , -82 and -97 kJ mol^{-1} for Mol_1_a, Mol_3_a and Mol_4_a, respectively (avg. -93 kJ mol^{-1}), while the energies for the naproxen molecules are -122 kJ mol^{-1} for Mol_2_n and -125 kJ mol^{-1} for Mol_5_n (avg. -124 kJ mol^{-1}). Therefore, the average energy for acridine molecules was found to be similar in the two structures, while naproxen appears to be more stable in **1α**. These data, keeping in mind the different stoichiometry, allow estimating the lattice energies to be -263 and -198 kJ mol^{-1} for **1α** and **1β**, respectively, suggesting that **1α** is the thermodynamically stable cocrystal.



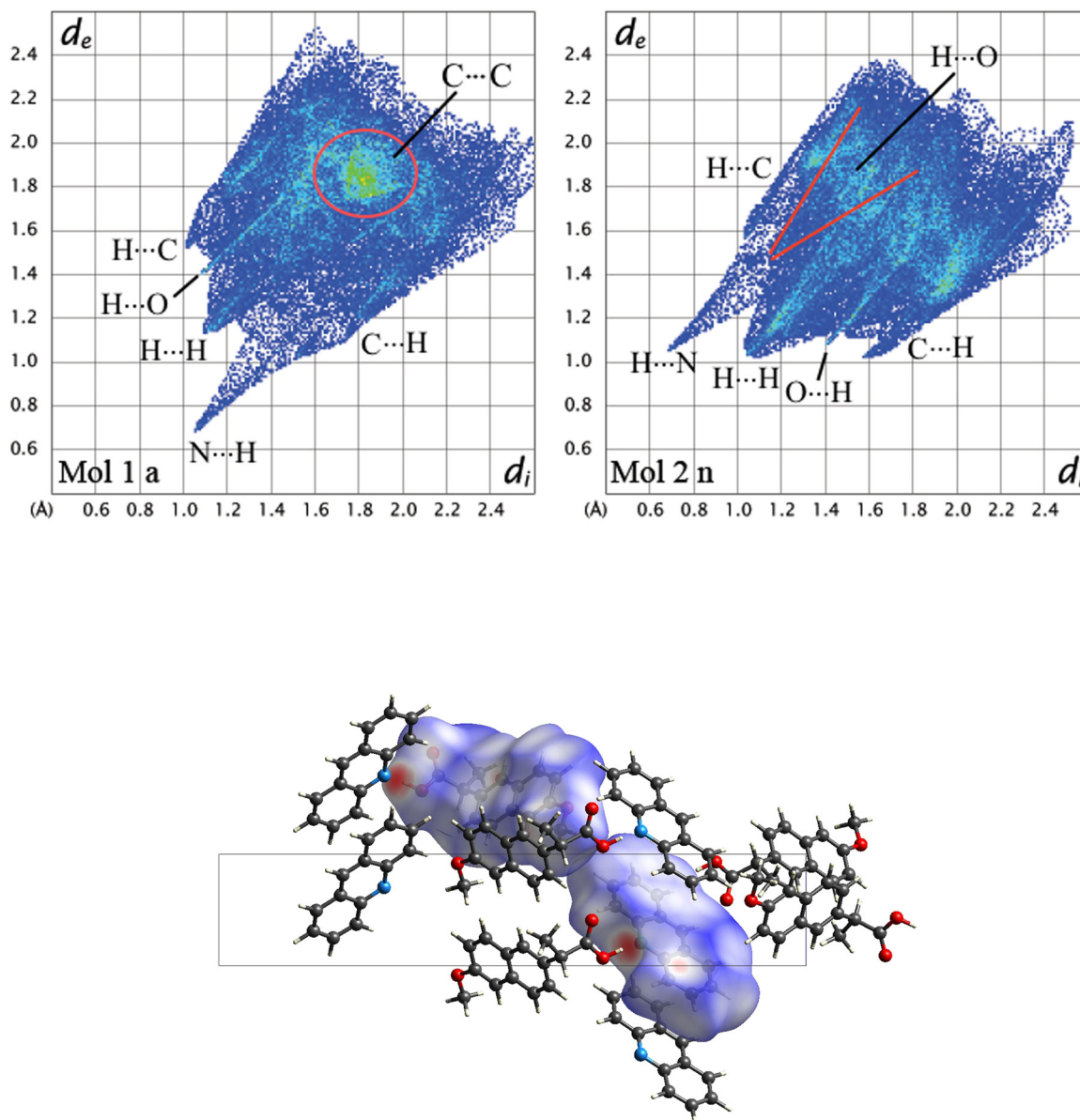


Fig. 7 (Top) Fingerprint plots for acridine (Mol_1_a) and naproxen (Mol_2_n) in **1β** and (bottom) the crystal structure model of **1β** viewed along the *a*-axis showing Hirshfeld surfaces with *d*-norm plotted. Some molecules were omitted for clarity.

The energy frameworks for **2α** are shown in Fig. S11 and S12 in the ESI.† Coulombic energy is shown in Fig. S11;† the attractive interactions are shown in red while repulsive forces are in yellow. The water molecule is involved in the stronger attractive interaction involving the 9-aminoacridinium and naproxen molecules, while repulsion occurs between the aromatic rings and the deprotonated naproxen. The layered motif of the packing is driven by the presence of parallel dispersion forces like in **1β** (see Fig. S12,† view along the *a*-axis). The key role of the water molecule in the crystal packing of **2α** could be the reason why both thermal dry synthesis and LAG were unsuccessful in obtaining a second cocrystal, as in the case of compound **1**.

Finally, to experimentally assess which compound is more stable between **1α** and **1β** and further explore the thermal

behaviour of reactants and products, TGA and DSC analysis of the mechanical mixture of acridine and naproxen and of the cocrystal in their various forms was investigated. TGA was carried out from 40 to 600 °C and the profiles are in Fig. S3.† The maximum of the loss degradation slope profile is at 241 °C for **1α** and at 283 °C for **1β**, clearly suggesting that **1β** is the more stable cocrystal. This indication is apparently contradictory with respect to energy framework calculations, and it could in principle be ascribed to the limitations of this theoretical approach. Another hypothesis could be that the stability of **1β** is due to kinetic reasons. DSC was also measured from 40 to 160 (in the case of acridine when the samples melt at around 105°) or 180 °C (in the case of 9-aminoacridine to reach full melting) and the results are reported in the ESI.† The heating/cooling ramp was cycled to



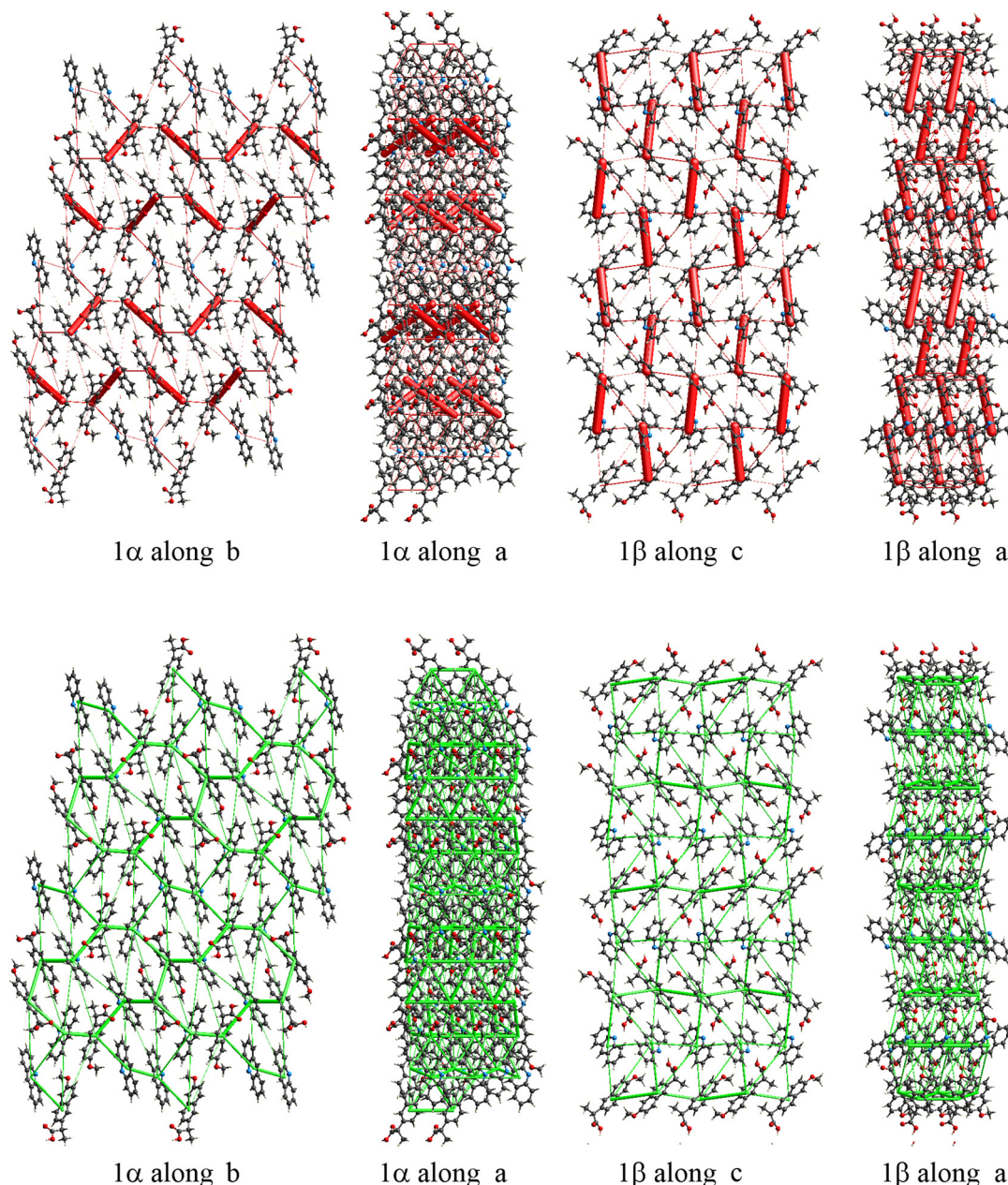


Fig. 8 Energy framework plot of coulomb interactions in red (top) and dispersion interactions in green (bottom) for structure **1α** and **1β**.

study the reversibility of the process (Fig. S4†). While acridine and naproxen melt at 107 and 153 °C, respectively, their mechanical mixture melts as a eutectic at about 100 °C. A double DSC peak is observed for both the mechanical mixture and **1β**, indicating two steps in the eutectic formation. The high temperature and more intense peak is attributed to the melting, while the first DSC peak can be ascribed to a metastable phase. It must be noticed that a double DSC peak is not unusual in a molecular complex²¹ where a monotropic phase transformation of a metastable form is supposed to explain the low temperature DSC signal. The liquid mixture obtained by heating the mechanical mixture and **1β** up to 160 °C was cooled and solidified

without any DSC peak, suggesting the formation of amorphous solid materials. To confirm the DSC data, variable temperature PXRD was carried out on the **1β** molecular adduct at the same temperature range of DSC (Fig. S7,† left). The crystalline compounds show peaks until 118 °C, and above this temperature their disappearance suggests the melting, confirmed by imaging data. On cooling to RT from 160 °C, the formation of an amorphous solid is confirmed by XRD (Fig. S7,† right). Surprisingly, after heating **1β** just above the eutectic temperature (120°) and cooling to 40 °C, crystalline **1β** is again formed, similarly to the solution crystallization after solubilizing **1β** instead. At this temperature, couples of acridine and naproxen are probably



with respect to the crystallization after solubilizing the reactants separately (**1α** crystallizes). Moreover, it must be noted that **1β** from solution shows a habit (long needles in the optical microscope) different from that of **1β** obtained from LAG (powder made up of small crystallites) as can be seen by the preferred orientation evident in the pattern of recrystallized **1β** in Fig. 5, bottom. Except for preferred orientations, this “needle form” showed the same powder pattern of the LAG-obtained sample, confirming the same crystal structure despite the different morphology. This seeding effect of a molecular crystal (**1β**) prevailing, although it does not appear to be the more thermodynamically stable one, is rare but not new and observed also in famous case studies as those depicted as “the disappearing polymorph” summarized in review some years ago.⁵¹ However, in the present case, the different stoichiometries and solvation degrees of **1α** and **1β** can also be other explanations of the impossibility of the mutual interconversion between the two forms.

Concerning the number of molecular crystals obtained using the reactant in Scheme 1, it can be concluded that a clear trend from acridine (two molecular crystals), 9-aminoacridine (one molecular crystal) and 6,9-diamino-2-ethoxyacridine (no cocrystal) is evident. Such results suggest that only compounds with a limited number of polar side chains can be used as cocrystals with naproxen. When the affinity is higher as in the case of **1**, a eutectic is formed upon heating and the 1:1 compound (**1β**) can be obtained by the LAG method, besides the host/guest compound (**1α**). When the affinity is smaller, as in the case of **2**, the eutectic is formed only upon cooling of the melt, but the cooling



causes crystallization of the same reactant and the 1:1 layered phase equivalent to **1β** cannot be obtained. Only the host/guest structure (**2α**) can be obtained by solution crystallization. With a bulkier and more polar counterpart (6,9-diamino-2-ethoxyacridine in Scheme 1) no crystallization is observed by any preparation technique. In this case the DSC profile of the mechanical mixture gave contradictory results: a eutectic partial melting is observed at 120 °C (6,9-diamino-2-ethoxyacridine lactate melts at 245°), then a large bump around 140° but a net sharp peak is observed at 175 °C, just some degrees above the naproxen MP (165 °C), followed by amorphous solidification under cooling. These results are not much different from the acridine/naproxen couple, but in this case not one among the three methods used allowed obtaining a crystalline molecular complex despite the affinity observed in the melt state by DSC. The unsuccessful attempt could be due to the use of its common and stable lactate form.

Conclusions

A total of three cocrystals of naproxen with acridines, comprising two cocrystals with a different stoichiometry, were obtained: two through the reaction carried out in solution and one carried out by the LAG procedure. The efficacy of LAG as a means of exploring stoichiometric diversity in molecular cocrystals was confirmed in this study.

Three new crystal structures were obtained, one of them solved by powder diffraction data. The crystallization from solution allowed obtaining solvated 3:2 and 2:1 host–guest structures for **1α** and **2**. Conversely, LAG allowed obtaining a 1:1 layered head-to-tail crystal structure (**1β**) with a yield larger than 99% under almost dry conditions. Surprisingly, the two molecular cocrystals of naproxen with acridine cannot be converted from one to the other, probably because of the different stoichiometry and complex equilibria between reactants and products, governed by contrasting thermodynamic and kinetic effects, favouring **1α** and **1β**, respectively. Interestingly, during the review of the present article, a very recent publication reported that mechanochemistry resulted in a unique way to expand the crystal landscape of dexamethasone to obtain kinetically stable cocrystals with benzenediols (catechol and resorcinol).⁵²

The **1β** form was experimentally found to be more stable than **1α**, as indicated by TGA and DSC measurements, in contrast to energy framework calculations. DSC also allowed identification of eutectic melting and amorphous solidification in the case of acridine/naproxen mechanical mixtures and cocrystals. Conversely, aminoacridine and naproxen melt separately and then crystallize as a mixture of the reactants with a eutectic solidification. As a final consideration, increasingly substituted acridines are less prone to cocrystallize with naproxen, with acridine showing two molecular cocrystals, 9-aminoacridine showing one molecular cocrystal, and

6,9-diamino-2-ethoxyacridine giving no cocrystals, independently of the adopted preparation procedure.

Conflicts of interest

The authors declare no conflict of interest.

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