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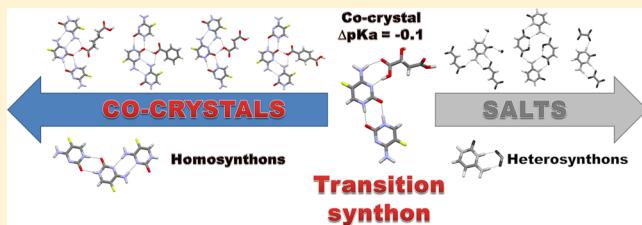
Controlled Synthesis of New 5-Fluorocytosine Cocrystals Based on the pK_a Rule

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S Supporting Information

ABSTRACT: 5-Fluorocytosine (5-FC) was investigated for the controlled synthesis of cocrystals by applying the pK_a rule. Five cocrystals were designed and developed with adipic, succinic, terephthalic, benzoic, and malic acids, all exhibiting negative ΔpK_a values ranging from close to zero up to roughly -1 . The synthesized cocrystals were analyzed by single crystal X-ray diffraction, and the observed supramolecular synthons were compared to the reported structures containing 5-FC. In the first four cocrystals, the intermolecular interactions between adjacent 5-FC molecules form two different homodimers showing $R_2^2(8)$ motifs and assembled via complementary N–H \cdots O and N–H \cdots N hydrogen bonds, respectively. However, in the cocrystal with malic acid ($\Delta pK_a = -0.1$), an intermediate supramolecular synthon pattern between salts and cocrystals is observed. In this crystal packing, the homodimer of 5-FC molecules held by the N–H \cdots O interactions is preserved, but a new heterodimer is formed between 5-FC and the acid molecule, such as the ones observed for 5-FC salts. These differences were analyzed using UNI Force Field Calculations to establish the intermolecular potentials of the synthons. As an application, we synthesized a cocrystal of 5-FC with 5-fluorouracil. This can be considered the first step toward the application of 5-FC for the design of new tailor-made drugs.



1. INTRODUCTION

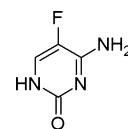
Crystal engineering and supramolecular chemistry are emerging issues in active pharmaceutical ingredients (APIs). Achieving the ability to explore and predict the occurrence of noncovalent interactions among APIs and other molecules, such as solvents, acids, bases, and other substances recognized as safe (GRAS), for the rational design of pharmaceutical products in the solid state, exhibiting improved physical and chemical properties, is a challenge to scientists. Among the solid forms that an API may exhibit, the class of pharmaceutical cocrystals is noteworthy, i.e., solid pharmaceutical compounds containing at least one molecular API and at least one solid nontoxic cocrystal former (usually a GRAS compound) interacting with one another through unique binding interactions; it is a hard task to predict how the API(s) and the coformer(s) will interact to each other. This class has presented increasing interest in the last few years due to its immense ability to form new compounds that do not alter the pharmacological activity of the API but may improve its physical properties, not being restricted to binary compounds, once ternary and quaternary cocrystals may be designed.^{1–7}

By considering that cocrystal formation is not obvious (it is a result of a supramolecular study and synthesis), beyond the fact that pharmaceutical cocrystals have utility (may improve the physical properties of an API) and are considered a novel compound (possesses a new chemical composition and an unpredictable chemical bonding), they are subject to patents. This possibility opens the door to new commercial opportunities for an API, offering to the pharmaceutical

industries the benefits of generating a new and exclusive patent upon a new chemical compound or even of maintaining and extending its exclusivity, by covering, beforehand, new solid forms. In this sense, the patent can encompass not only the initial chemical compound but also its cocrystals through the creation of a solid-form patent portfolio. As advantage, the path to patent a cocrystal can be abbreviated in some aspects, considering that issues such as toxicology and discovery do not need to be extensively evaluated.^{8,9}

5-Fluorocytosine (4-amino-5-fluoro-1,2-dihydropyrimidin-2-one, 5-FC, Scheme 1) was synthesized in 1957 as an

Scheme 1. Molecular Structure of 5-FC



antimetabolite drug to be used as an antitumor agent. It was found to exhibit activity against fungal infections and was released for this use in 1968. By the discovery of its mechanism of action, i.e., conversion into 5-fluorouracil (5-FU) by deamination performed by the enzyme cytosine deaminase (CD)—natural in fungal cells—5-FC is being recently

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Table 1. Crystallographic Data for the 5-FC Solid Forms S, T, A, M, B, and 5-F

Form S	Form A	Form T
$C_4H_4FN_3O$, 1/2 $C_4H_6O_4$	$C_4H_4FN_3O$, 1/2 $C_6H_{10}O_4$	$C_4H_4FN_3O$, 1/2 $C_8H_6O_4$
space group $P\bar{1}$	space group $P\bar{1}$	space group $P\bar{1}$
a (\AA) = 4.9209(3)	a (\AA) = 5.2742(5)	a (\AA) = 3.6265(3)
b (\AA) = 8.6115(5)	b (\AA) = 6.6650(7)	b (\AA) = 9.5274(8)
c (\AA) = 9.4689(6)	c (\AA) = 12.8441(13)	c (\AA) = 13.7902(12)
α ($^\circ$) = 72.466(3)	α ($^\circ$) = 86.411(6)	α ($^\circ$) = 107.812(5)
β ($^\circ$) = 75.129(3)	β ($^\circ$) = 80.757(6)	β ($^\circ$) = 92.036(4)
γ ($^\circ$) = 89.747(3)	γ ($^\circ$) = 71.970(6)	γ ($^\circ$) = 96.844(4)
V (\AA^3) = 368.64(4) \AA^3	V (\AA^3) = 423.72(7) \AA^3	V (\AA^3) = 449.09(7) \AA^3
Z = 2	Z = 2	Z = 2
ρ_{calc} = 1.695 g/cm ³	ρ_{calc} = 1.585 g/cm ³	ρ_{calc} = 1.569 g/cm ³
2572 unique reflns	1624 unique reflns	2602 unique reflns
$R_{(\text{int})}$ = 0.0219	$R_{(\text{int})}$ = 0.0280	$R_{(\text{int})}$ = 0.0302
θ_{max} = 25.00 $^\circ$	θ_{max} = 25.80 $^\circ$	θ_{max} = 27.50 $^\circ$
$R_{1[>2\sigma(I)]}$ = 0.0381	$R_{1[>2\sigma(I)]}$ = 0.0476	$R_{1[>2\sigma(I)]}$ = 0.0449
wR_2 = 0.1153	wR_2 = 0.1322	wR_2 = 0.1131
S = 1.103	S = 1.122	S = 1.078
Form M	Form B	Form 5F
$C_4H_4FN_3O$, $C_4H_6O_5$	$C_4H_4FN_3O$, $C_7H_6O_2$	$C_4H_4FN_3O$, $C_4H_3FN_2O_2$
space group $C2/c$	space group $P2_1/n$	space group $P2_1/c$
a (\AA) = 20.8980(4)	a (\AA) = 9.0565(2)	a (\AA) = 15.0176(3)
b (\AA) = 14.8590(9)	b (\AA) = 5.4318(2)	b (\AA) = 3.5604(1)
c (\AA) = 7.244(1)	c (\AA) = 22.8887(8)	c (\AA) = 27.3113(4)
β ($^\circ$) = 107.178(3)	β ($^\circ$) = 92.870(1)	β ($^\circ$) = 138.282(1)
V (\AA^3) = 2149.1(4) \AA^3	V (\AA^3) = 1124.55(6) \AA^3	V (\AA^3) = 971.78(4) \AA^3
Z = 8	Z = 4	Z = 4
ρ_{calc} = 1.639 g/cm ³	ρ_{calc} = 1.484 g/cm ³	ρ_{calc} = 1.772 g/cm ³
2451 unique reflns	2306 unique reflns	1628 unique reflns
$R_{(\text{int})}$ = 0.0547	$R_{(\text{int})}$ = 0.0252	$R_{(\text{int})}$ = 0.0284
θ_{max} = 27.49 $^\circ$	θ_{max} = 25.242 $^\circ$	θ_{max} = 66.685 $^\circ$
$R_{1[>2\sigma(I)]}$ = 0.0729	$R_{1[>2\sigma(I)]}$ = 0.0482	$R_{1[>2\sigma(I)]}$ = 0.0312
wR_2 = 0.1853	wR_2 = 0.1212	wR_2 = 0.0841
S = 1.010	S = 1.035	S = 1.069

employed in gene-directed enzyme prodrug therapy (GDEPT) to treat cancer. Concerning pharmacokinetics, toxicity, and drug interactions, 5-FC is a BCS class I drug of small size, high solubility in water, and high permeability (bioavailability of 76% – 89%). It exhibits minor side effects, although hepatotoxicity and bone marrow depression may occur. Nevertheless, normal mammalian cells do not express CD and are resistant to this drug, such that over 90% of it is eliminated unchanged in the urine.^{10–12}

The first crystal structure of 5-FC deposited in the Cambridge Structural Database (CSD)¹³ was a monohydrate reported in 1982.¹⁴ Since then, 30 five crystal structures were reported in the literature, including two polymorphs,¹⁵ six hydrates,^{15–18} four solvates,^{15,17} 10 salts^{19–22} and 13 cocrystals.^{23–25} Nineteen of them crystallize in the monoclinic crystalline system, 12 in the $P2_1/c$ (four hydrates, four salts, one solvate, and three cocrystals), four in the $P2_1/n$ (two salts, one solvate, and one polymorph), two in the Cc (one hydrate and one cocrystal), and one in the $C2/c$ (one cocrystal) space groups. Twelve crystallize in the triclinic $P\bar{1}$ space group (two hydrates, one solvate, and nine cocrystals), and one in the tetragonal $P4_12_12$ space group (polymorph). From these numbers, it is possible to observe that neutral state is predominant for this fluoropyrimidine. Furthermore, it is worth noting that three salts and eight cocrystals have solvents introduced into the crystalline arrangement.^{20–22,24,25}

In our previous work,²² we discussed salt formation by the 5-FC molecules on the basis of a salt/cocrystal continuum study.^{26,27} As a follow-up to these studies, here we discuss the supramolecular synthesis of five cocrystals of 5-FC containing adipic, succinic, benzoic, tereftalic, and malic acids as coformers, aiming to add information to the salt–cocrystal continuum study, to improve understanding of 5-FC drug–receptor interactions and, especially, to understand the controlled synthesis of cocrystals. On the basis of the supramolecular patterns established by these 5-FC cocrystals, we were able to design and synthesize a cocrystal involving two APIs, 5-FC and 5-FU, an antineoplastic drug.

2. EXPERIMENTAL SECTION

All reagents were used without additional purification.

2.1. Cocrystals Supramolecular Synthesis. Stoichiometric amounts of 5-FC (Sigma-Aldrich Brazil) with succinic, adipic, benzoic, terephthalic, and malic acids and 5-FU were employed, using water as the solvent. The solutions were filtered through a 0.45 μm filter (Milipore) and maintained at room temperature, semicovered by Parafilm until complete slow evaporation of the solvent. The resulting crystals were selected for single crystal X-ray diffraction experiments.

2.2. Single Crystal X-ray Structure Determination. The crystallographic data for the cocrystals of 5-FC with adipic, succinic, and terephthalic acids were collected on a Bruker Super-Duo APEX II CCD diffractometer using MoK α radiation (0.71073 \AA). For the cocrystal of 5-FC with 5-FU, Cu K α radiation was used (1.54178 \AA) in

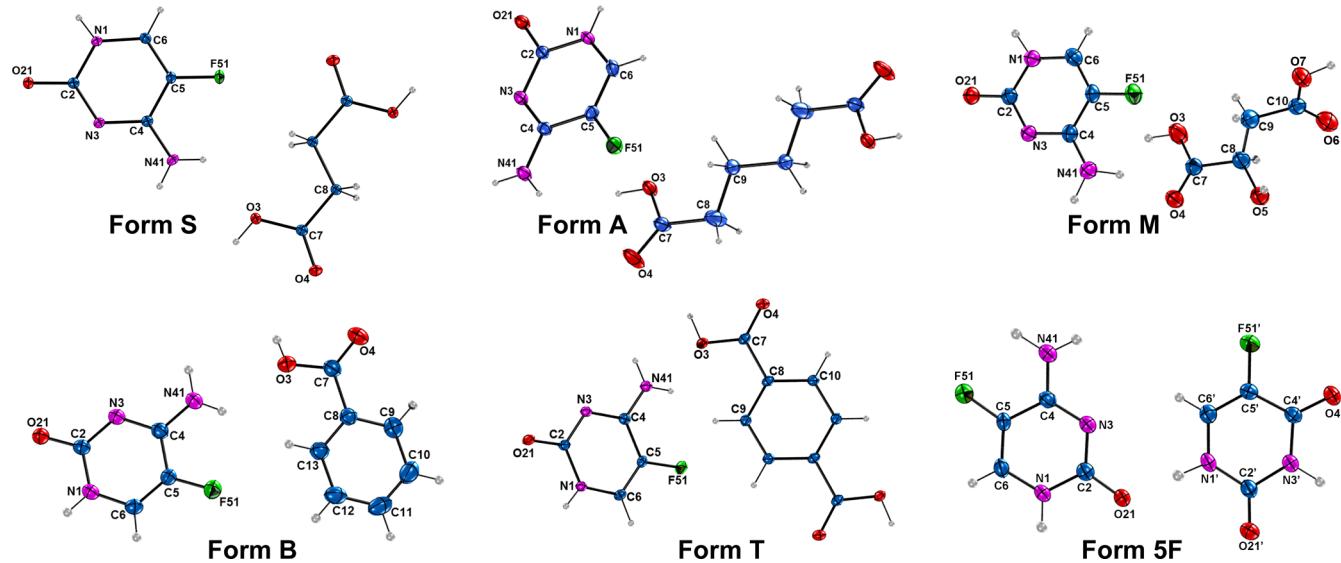


Figure 1. ORTEP-3³⁶ type view of the 5-FC cocrystals. Thermal ellipsoids for forms S, A, and T are at the 50% probability level and for forms M, B, and SF at the 30% probability level. Hydrogen atoms are drawn as spheres of arbitrary radii.

the same equipment. X-ray diffraction data collection (φ scans and ω scans with κ offsets) for the cocrystals of 5-FC with malic and benzoic acids were performed on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on κ -goniostat) using graphite-monochromated MoK α radiation (0.71073 Å). For refinement details^{28–34} see the Supporting Information.

In all cases, the programs MERCURY (version 2.3)³⁵ and ORTEP-3³⁶ were used also within WinGX v1.70.01³² to prepare the crystallographic information file (CIF) and artwork representations for publication.

The CIFs of the three 5-FC cocrystals were deposited in the Cambridge Structural Data Base under the codes CCDC 933072 (cocrystal of 5-FC with adipic acid), CCDC 933073 (cocrystal of 5-FC with succinic acid), CCDC 933074 (cocrystal of 5-FC with terephthalic acid), CCDC 991413 (cocrystal of 5-FC with 5-FU), CCDC 991431 (cocrystal of 5-FC with malic acid) and CCDC 991584 (cocrystal of 5-FC with benzoic acid). Copies of these files may be solicited free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: + 44123–336–033; e-mail: deposit@ccdc.cam.ac.uk or <http://www.ccdc.cam.ac.uk>.

3. RESULTS

3.1. Structure Determination. We adopt the following nomenclature for the cocrystals depicted herein: form S (cocrystal of 5-FC with succinic acid), form T (cocrystal of 5-FC with terephthalic acid), form B (cocrystal of 5-FC with benzoic acid), form M (cocrystal of 5-FC with malic acid), form A (cocrystal of 5-FC with adipic acid), and form SF (cocrystal of 5-FC with 5-FU). Table 1 exhibits the crystallographic data for the structures.

3.2. Structural Description. A detailed description of the structures is depicted below. The main hydrogen-bond metrics for each cocrystal are listed in Table S1 (Supporting Information). In Figure 1, an ORTEP-3³⁶ view of the asymmetric unit of each cocrystal is shown. The structure and data for form SF will be depicted in a separate section.

Cocrystal of 5-FC with Succinic Acid. The asymmetric unit of form S (Figure 1) exhibits one 5-FC molecule as well as a succinic acid, the latter sitting on a crystallographic inversion center giving just half of this molecule per asymmetric unit. Bifurcated hydrogen bonds (N41–H41A···O3 and O3–H3···O21) occur among the acid and two 5-FC molecules (Figure

2a). These interactions lead the 5-FC molecules to interact with each other forming a $R_2^2(8)$ motif^{37a,b} (Figure 2a) assembled via complementary N41–H41···N3 hydrogen bonds and also promote the formation of a nonclassical C6–H6···O4 (bond

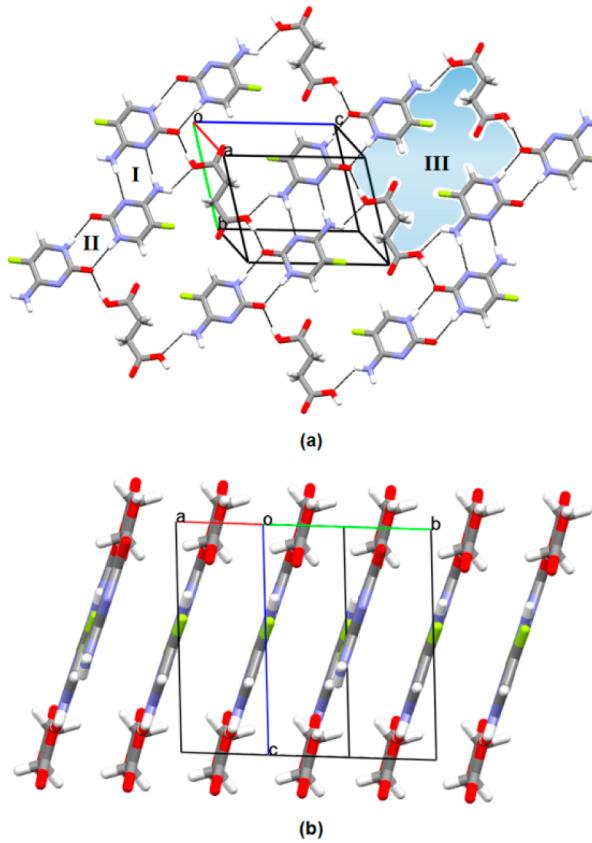


Figure 2. (a) Crystal packing diagram of form S. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motif^{37a,b} involving the N–H···N 5-FC homodimers, (II) to the $R_2^2(8)$ motif^{37a,b} involving the N–H···O 5-FC homodimers, and (III) to the $R_4^4(40)$ motif,^{37a,b} (b) three-dimensional hydrogen-bonded network of form S.

length of 2.071 Å) one. A second $R_2^2(8)$ motif is observed between the 5-FC molecules, involving complementary N1–H1···O21 hydrogen bonds, leading to the formation of 1-D tapes which run parallel on both sides of the acid molecule. This arrangement of the molecules in the crystal lattice gives rise to the formation of cavities with graph set $R_6^4(40)$ and constitutes flat layers offset stacked along [121]. The stacking of the layers (Figure 2b) is kept only by van der Waals contacts, of the types C···O, C···F, and C···N, which results in an interlayer separation of approximately 3.20 Å to one another (van der Waals radii³⁸ for C = 1.70 Å, N = 1.55 Å, O = 1.52 Å and F = 1.47 Å).

Cocrystal of 5-FC with Adipic Acid. The asymmetric unit of form A (Figure 1) also exhibits one molecule of 5-FC and half adipic acid since, as mentioned previously, it is sitting on an inversion center. The crystal packing preserve similar intermolecular interaction patterns such as the ones found for form S (Figure 3a): two $R_2^2(8)$ motifs, constituted via complementary N41–H41···N3 and N1–H1···O21 hydrogen bonds between 5-FC molecules and a bifurcated (N41–

H41A···O3 and O3–H3···O21) interaction between 5-FC molecule and both carboxyl groups of the acid, also resulting in the formation of the nonclassical C6–H6···O4 (bond length of 2.109 Å) intermolecular interaction plus a C8–H8···F51 (bond length of 2.444 Å) one. In this way, the forms S and A exhibit a similar arrangement of the molecules in the crystal lattice. However, as a result of the increase in the length of the carbon chain in the adipic acid, the cavity formed (Figure 3a) possess a graph set of $R_6^4(48)$, and the layers are not as flat as the ones observed in form S once the adipic acid adopts a zigzag conformation in its carbon chain. The layers are offset stacked along [120], and beyond the van der Waals contacts holding these layers together, there is a nonclassical C9–H9A···F51 (bond length of 2.419 Å) hydrogen bond (Figure 3b).

Cocrystal of 5-FC with Terephthalic Acid. The asymmetric unit of form T (Figure 1) exhibits one 5-FC and half terephthalic acid molecule, for the acid is placed on an inversion center as in forms S and A. As observed in forms S and A, the two 5-FC ring motifs (Figure 4a) and the two 5-FC–acid hydrogen bonds (Figure 4a) plus the nonclassical C6–H6···O4 (bond length of 2.201 Å) are preserved in form T. As a consequence of the close packing, a nonclassical C10–H10···F51 (bond length of 2.491 Å) intermolecular interaction overcome. Form

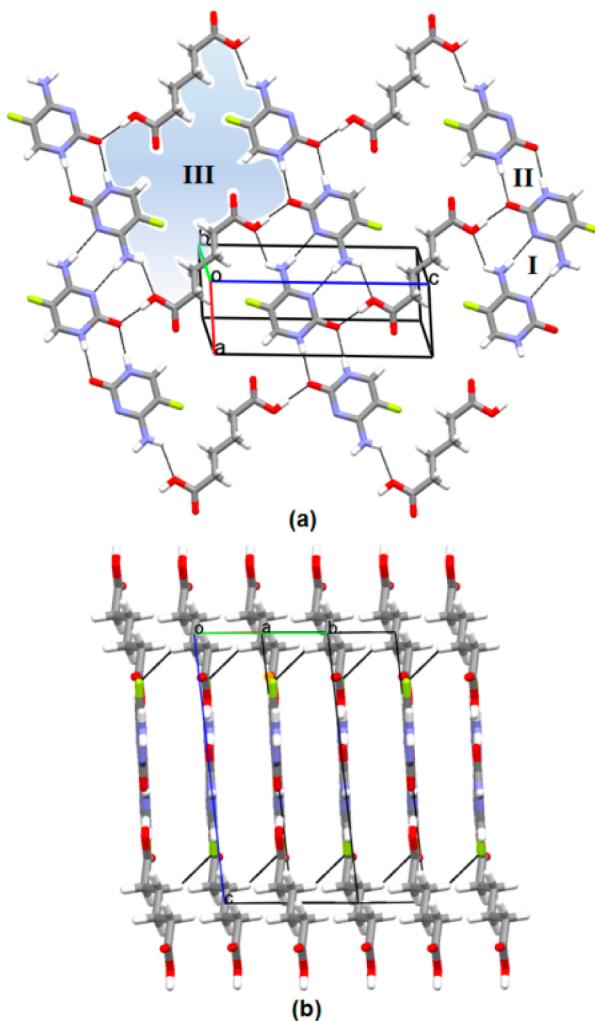


Figure 3. (a) Crystal packing diagram of form A. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motif^{37a,b} involving the N–H···N 5-FC homodimers, (II) to the $R_2^2(8)$ motif^{37a,b} involving the N–H···O 5-FC homodimers, and (III) to the $R_6^4(48)$ motif^{37a,b} (b) three-dimensional hydrogen-bonded network of form A.

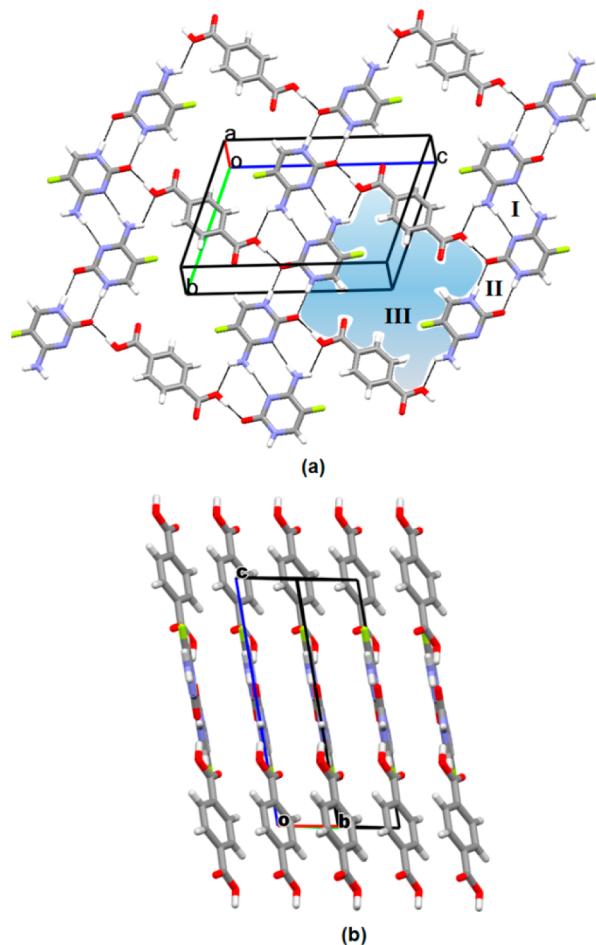


Figure 4. (a) Crystal packing diagram of form T. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motif^{37a,b} involving the N–H···N 5-FC homodimers, (II) to the $R_2^2(8)$ motif^{37a,b} involving the N–H···O 5-FC homodimers, and (III) to the $R_6^4(44)$ motif^{37a,b} (b) three-dimensional hydrogen-bonded network of form T.

T also exhibits a similar layered pattern stacked along [110]. The cavities (Figure 4a) formed in this crystalline arrangement adopts a ring graph-set with the $R_6^4(44)$ notation, smaller than the one found in form A. Although both 5-FC and terephthalic acid molecules adopt a planar conformation, they are not aligned in the same plane (Figure 4b). The angle between the plane passing through the non-hydrogen atoms of the 5-FC molecules and the one passing through the terephthalic acid is $26.66(2)^\circ$. The terephthalic molecules are stacked as the 5-FC ones, in a fashion that $\pi\cdots\pi$ interactions take place (centroid–centroid distance equal to $3.6265(3)\text{\AA}$ for both molecules), being mainly responsible for the maintenance of form T crystalline packing.

Cocrystal of 5-FC with Benzoic Acid. The asymmetric unit of form B (Figure 1) exhibits one molecule of 5-FC and one of benzoic acid. The arrangement of the 5-FC molecules follows the same pattern observed for form T, with the two 5-FC ring motifs^{37a,b} (Figure 5a) and the two 5-FC–acid hydrogen bonds preserved as is the nonclassical C6–H6···O4 (bond length of 2.071\AA). The 1-D tapes of the 5-FC molecules are surrounded by benzoic acid molecules forming stacked layers sustained only by van der Waals contacts with an interlayer separation of approximately 5.432\AA (Figure 5b). The neighboring layers are twisted 74.25° with respect to each other, forming a herringbone pattern. This supramolecular pattern arises from unconventional hydrogen bonds (Table S1 in the Supporting Information) involving fluorine atoms of the 5-FC and carbon atoms (C11 and C13) of the benzoic acid molecules (Figure 5a). As is observed in form T, the benzoic acid molecules are not exactly placed on the same plane of the 1-D tape. However, the angle between the mean plane defined by the non-hydrogen atoms of the 5-FC and the non-hydrogen atoms of the benzoic acid molecule is smaller in form B than in form T, assuming a value of 20.43° .

Cocrystal of 5-FC with Malic Acid. The asymmetric unit of form M (Figure 1) exhibits one 5-FC and one molecule of malic acid. In contrast to the other forms, form M preserves only the $R_2^2(8)$ motif accessed via complementary N1–H1···O21 hydrogen bonds among the 5-FC molecules, like that observed in the other cocrystals (Figure 6a). However, a second $R_2^2(8)$ motif is inherent of form M and arises from the interactions of 5-FC molecules with surrounding malic acid molecules (O3–H3···N3 and N41–H41B···O4), constituting a heterodimer (Figure 6a). Additional hydrogen bonds (N41–H41A···O5 and O7–H7···O21) lead to the formation of flat layers stacked along the *c* axis and of a cavity represented by the $R_6^4(36)$ graph-set notation^{37a,b} (Figure 6a). The layers are held together via O5–H5···O6 hydrogen bonds involving the malic acid molecules and also via $\pi\cdots\pi$ interactions (centroid–centroid distance equal to $3.495(9)\text{\AA}$) between the rings of the 5-FC molecules (Figure 6b).

4. DISCUSSION

We have conducted cocrystallization experiments with 5-FC and five dicarboxylic acids presenting the following pK_a values: 4.43 (adipic acid), 4.21 (benzoic acid), 4.16 (succinic acid), 3.52 (terephthalic acid) and 3.40 (malic acid). These acids were chosen in an attempt to evaluate the extent of proton transfer to the 5-FC molecules, based on the pK_a rule,^{26,27,39} contributing to the study of the salt/cocrystal continuum and providing information related to the capability of predicting and controlling the synthesis of compounds containing the fluoropyrimidine group.

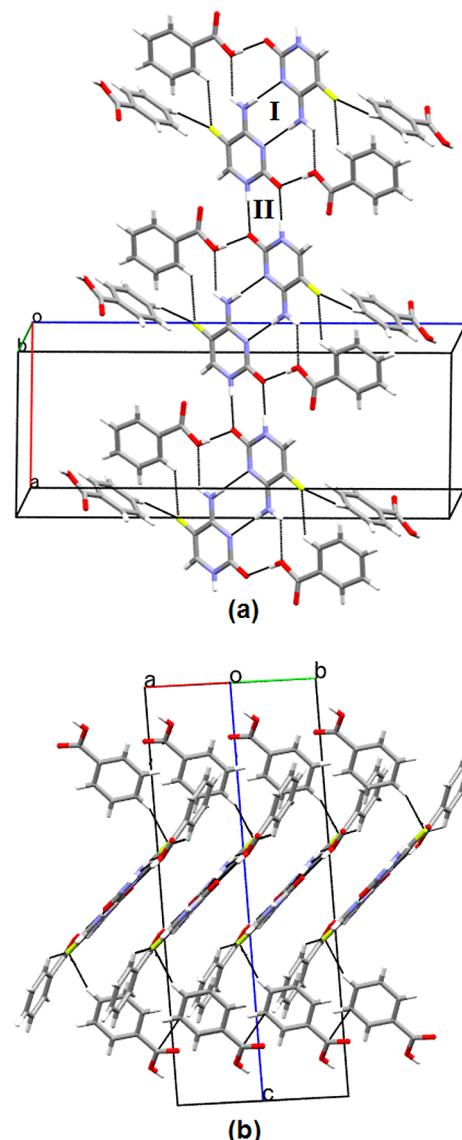


Figure 5. (a) Crystal packing diagram of form B. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motif^{37a,b} involving the N–H···N 5-FC homodimers and (II) $R_2^2(8)$ motif^{37a,b} involving the N–H···O 5-FC homodimers, (b) three-dimensional hydrogen-bonded network of form B.

As the pK_a value for the 5-FC is 3.26, then the respective values of ΔpK_a ($pK_{\text{acid}} - pK_{\text{base}}$) for adipic, benzoic, succinic, terephthalic, and malic acids are -1.16 , -0.95 , -0.9 , -0.26 , and -0.14 ranging from close to zero to more negative values. According to Bhogala et al.,²⁷ for negative values of ΔpK_a a cocrystal formation is expected. One method of verifying successful cocrystal formation is to calculate the C–O bond length differences of the carboxyl groups in the acid molecule, $\Delta D_{\text{C}-\text{O}}$. If this variation is small ($<0.03\text{\AA}$), then a salt is formed. If, however, this difference is higher than 0.08\AA , then a cocrystal is formed. For all the structures depicted here, the $\Delta D_{\text{C}-\text{O}}$ values are above 0.08\AA (form S = $0.117(1)\text{\AA}$, form A = $0.119(3)\text{\AA}$, form T = $0.114(2)\text{\AA}$, form B = $0.121(2)\text{\AA}$, and form M = $0.109(5)\text{\AA}$), which means that the C–O distances are not symmetrical, as in the carboxylate anions, evidencing cocrystal formation.

4.1. Supramolecular Analysis. In our previous manuscript,²² we synthesized three 5-FC salts also using as coformers

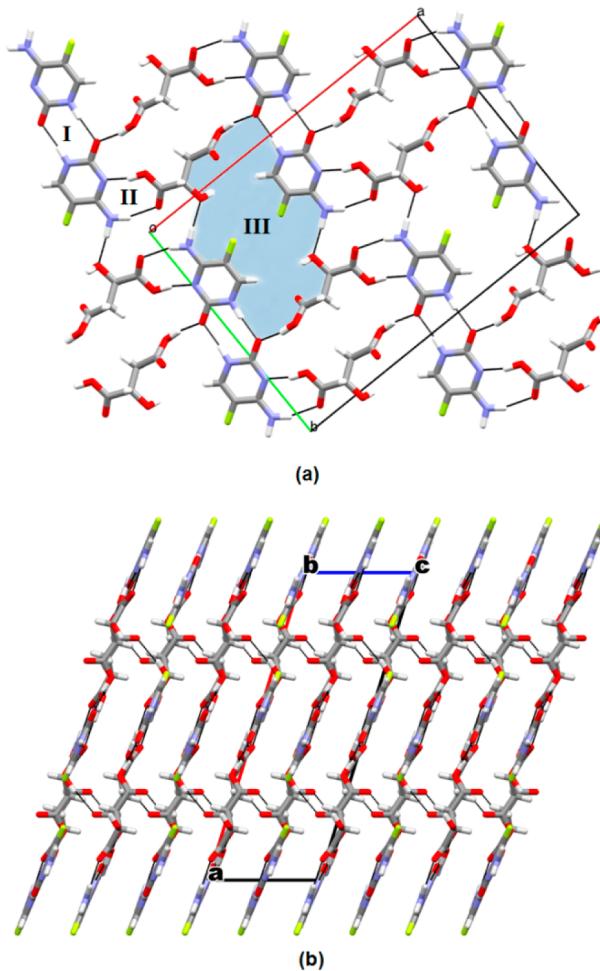


Figure 6. (a) Crystal packing diagram of form M. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motif^{37a,b} involving the N–H...O 5-FC homodimers, (II) to the $R_2^2(8)$ motif^{37a,b} involving the N–H...O and O–H...N 5-FC heterodimer, and (III) to the $R_6^4(36)$ motif,^{37a,b} (b) three-dimensional hydrogen-bonded network of form M.

dicarboxylic acids: fumaric, maleic, and oxalic. The structures were obtained from the continuum to the salt part of the spectrum, according to the ΔpK_a rule, where the ΔpK_a value ranged between 0 and positive values. Due to the complementarity among the carboxylic group and the functional groups present in the 5-FC molecules, all the salts exhibited the same $R_2^2(8)$ motif, constituting heterodimers, via N41–H41A...O4 and N3⁺–H3...O3⁻ hydrogen bonds. The same supramolecular synthon was observed for the salicylate of 5-FC, reported by Portalone and Colapietro in 2007.²⁰ On the other hand, when we go to the other side of the spectrum, i.e., when weaker dicarboxylic acids are used as coformers, changes occur in the ionicity of the 5-FC molecule and new supramolecular synthons overcome. According to Mukherjee and Desiraju,⁴⁰ cocrystal formation is usually expected to occur when heterosynthons are formed over homosynthons. However, for the cocrystals of 5-FC with succinic, adipic, benzoic, and terephthalic acids, instead of heterodimers we observe homodimers occurring among the 5-FC molecules accessed through complementary N41–H41...N3 and N1–H1...O21 hydrogen bonds. Nevertheless, for a ΔpK_a very close to 0 (“cutoff” among cocrystals and salts for this fluoropyrimidine), as in form M ($\Delta pK_a = -0.1$), a supramolecular transition

synthon is observed. In this cocrystal, the crystal packing still preserves the heterodimer observed in the salts, except for the fact that no proton transfer is observed, but also exhibits the N1–H1...O21 homodimer among the 5-FC molecules. For this homodimer, which is common in all cocrystals, the 5-FC carbonyl bond lengths go from 1.265 to 1.249 Å. These values are significantly higher than the ones found for the 5-FC salts (1.232 to 1.219 Å). It is clear that this feature is the result of the protonation where the charge redistribution implies on a reduction of the carbonyl bond lengths, which, in turn, does not favor the geometric requirements for the formation of the synthon needed for the establishment of the homodimers present in the cocrystals. However, the geometric features of the form M show intermediate values for the carbonyl bond lengths, suggesting a partial charge redistribution that may lead to a hybrid salt/cocrystal specie. Indeed, this form shows the salts heterodimer synthon, even without protonation, possibly due the intermediate strength of malic acid ($pK_a = 3.40$). This transition state becomes clearer when a correlation plot between the variations of the C–O bond lengths in the carboxylic fragments (ΔD_{C-O}) of the coformers and the variations of the C–N bond lengths (ΔD_{C-N}) of the imidic fragments of the 5FC ring is carried out (Figure 7). It is worth

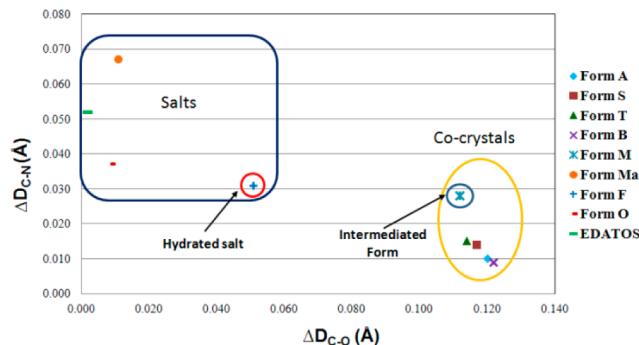


Figure 7. Correlation between the C–N bond length differences, ΔD_{C-N} , of the imidic group of 5-FC ring vs the C–O bond length differences of the carboxylic fragments, ΔD_{C-O} , evidencing the intermediary interface between salts/cocrystals of form M. The forms Ma, F, O, and EDATOS refer to the salts of 5-FC with maleic, fumaric, oxalic, and salicylic acids.^{19,22}

mentioning that the fumarate salt of 5-FC²² (form F) is hydrated, and the presence of water molecules in its crystal packing result in changes in the intermolecular interaction patterns leading to a different behavior of the 5-FC intramolecular bond lengths approximating its ΔD_{C-N} values to the ones found for form M.

In an attempt to understand which changes occur in the 5-FC molecule and consequently the specific supramolecular patterns formed, the UNI Force Field Calculations, a tool of the Mercury crystallography package,^{41,42} was used to establish and compare the intermolecular potentials of the main interactions. It is important to highlight that the purpose of this application is to display those interactions between molecules which are most significant in energetic terms without performing the computationally expensive lattice energy calculations. This study allowed us to determine that in most of the cases the potentials of the complementary N1H1...O21 hydrogen bonds are the strongest ranging between -9.1 to -7.6 kcal/mol, with the exception of form T and form M. Since this homodimer was recurrent in all the cocrystals of 5-FC, this synthon can be

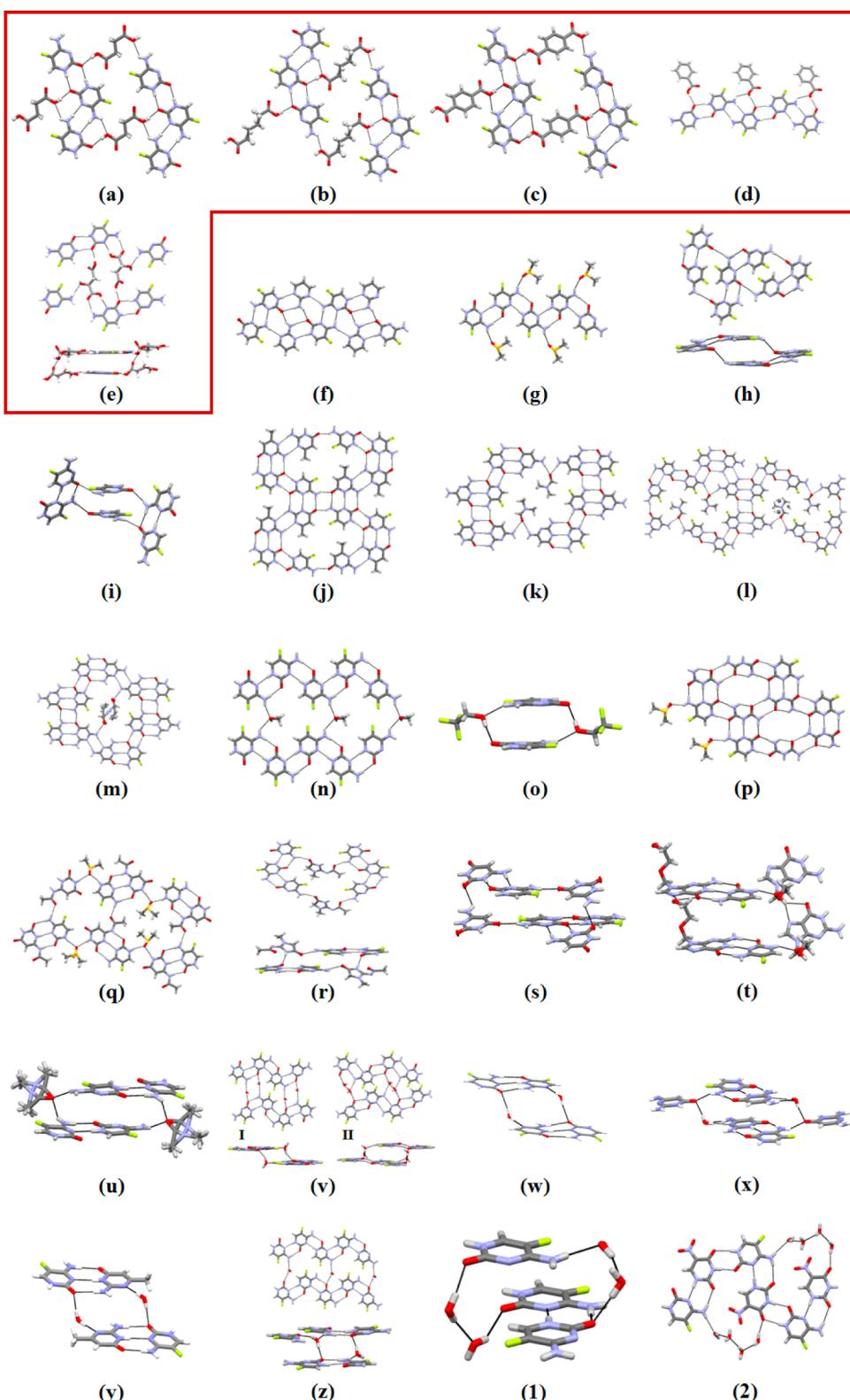


Figure 8. Comparison of the supramolecular structure of different 5-FC solid forms containing just neutral 5-FC molecules: (a) form S, (b) form A, (c) form T, (d) form B, (e) form M, (f) cocrystal under refcode MECTUL,²⁴ (g) solvate under refcode DUKWAI,¹⁷ (h) polymorph under refcode MEBQEQQ1,¹⁵ (i) polymorph under refcode MEBQEQQ1,¹⁵ (j) cocrystal under refcode MECXID,²⁵ (k) cocrystal under refcode MECVUN,²⁴ (l) cocrystal under refcode MECWAU²⁴ and (m) cocrystal under refcode MECWEY,²⁴ (n) solvate under refcode MEBQOA,¹⁵ (o) solvate under refcode MEBQIU,¹⁵ (p) cocrystal under refcode MECWUO,²⁵ (q) cocrystal under refcode MECXEZ,²⁵ (r) cocrystal under refcode MECVEX,²⁴ (s) cocrystal under refcode MECVIB,²⁴ (t) cocrystal under refcode MECWOL²⁴ (u) solvate under refcode DUKWEM,¹⁷ (v) hydrates of 5-FC (I) under refcodes BIRMEU,¹⁴ BIRMEU01,¹⁶ BIRMEU02,¹⁵ and (II) under refcode BIRMEU03¹⁵ (w) hydrate under refcode PANLAS,¹⁸ (x) hydrated cocrystal under refcode MECVOH,²⁴ (y) hydrated cocrystal under refcode MECXOJ²⁵ (z) hydrate under refcode DUKWIQ¹⁷ (1) hydrate under refcode MEBQUG¹⁵ and (2) hydrated cocrystal under refcode GATMUL.²³

Table 2. Distribution of the Main Supramolecular Synths Observed for the Different 5-FC Solid Forms Containing Just Neutral 5-FC

structure ^a	N-H···O, N-H···N		N-H···O		N-H···N		C≡G-like base pairing		planar cavity	tubular cavity	5-FC ribbons
	homo	hetero	homo	hetero	homo	hetero	homo	hetero			
a			✓		✓				✓		✓
b			✓		✓				✓		✓
c			✓		✓				✓		✓
d			✓		✓					✓	✓
e			✓		✓				✓	✓	
f		✓				✓					
g	✓										
h	✓									✓	
i	✓									✓	
j			✓				✓		✓		
k			✓				✓		✓		
l	✓		✓				✓		✓		
m			✓				✓		✓		
n	✓							✓			✓
o	✓									✓	✓
p				✓			✓		✓		
q							✓		✓		
r	✓							✓		✓	
s		✓	✓							✓	
t							✓		✓		
u	✓						✓		✓		✓
v(I)	✓									✓	
v(II)			✓		✓					✓	
w							✓			✓	
x							✓			✓	
y							✓			✓	
z	✓							✓		✓	
1	✓									✓	
2		✓			✓				✓		

^aComparison of the supramolecular structure of different 5-FC solid forms containing just neutral 5-FC molecules: (a) form S, (b) form A, (c) form T, (d) form B, (e) form M, (f) cocrystal under refcode MECTUL,²⁴ (g) solvate under refcode DUKWAI,¹⁷ (h) polymorph under refcode MEBQEQQ¹⁵ (i) polymorph under refcode MEBQEQQ1,¹⁵ (j) cocrystal under refcode MECXID,²⁵ (k) cocrystal under refcode MECVUN,²⁴ (l) cocrystal under refcode MECWAU²⁴ and (m) cocrystal under refcode MECWEY,²⁵ (n) solvate under refcode MEBQOA,¹⁵ (o) solvate under refcode MEBQIU,¹⁵ (p) cocrystal under refcode MECWUO,²⁵ (q) cocrystal under refcode MECXEZ,²⁵ (r) cocrystal under refcode MECVEX,²⁴ (s) cocrystal under refcode MECVB,²⁴ (t) cocrystal under refcode MECWOI,²⁴ (u) solvate under refcode DUKWEM,¹⁷ (v) hydrates of 5-FC (I) under refcodes BIRMEU,¹⁴ BIRMEU01,¹⁶ BIRMEU02,¹⁵ and (II) under refcode BIRMEU03,¹⁵ (w) hydrate under refcode PANLAS,¹⁸ (x) hydrated cocrystal under refcode MECVOH,²⁴ (y) hydrated cocrystal under refcode MECXOJ,²⁵ (z) hydrate under refcode DUKWIQ,¹⁷ (1) hydrate under refcode MEBQUG¹⁵ and (2) hydrated cocrystal under refcode GATMUL.²³

considered a key piece in the assembly of the cocrystal packing. On the other hand, the complementary N41–H41···N3 hydrogen bonds (present in the forms A, S, T, and B) show smaller potential values ranging between -5.5 to -4.9 kcal/mol. As previously discussed, form M represents an intermediate state in the border of the salt–cocrystal continuum. Instead of the N41–H41···N3 hydrogen bonds present in the homodimers, we observed interactions occurring among the 5-FC molecule and the malic acid one (N41–H41B···O4 and O3–H3···N3), this heterosynthon being typical of the organic acid salts.^{19,22} The potential value of this synthon for form M is -9.7 kcal/mol, and this one is the highest potential observed for all interactions present in this crystalline form, showing that stronger acids have the ability of competing for these interactions, thus replacing the weaker N–H···N ones.

In addition, the study of the intermolecular potentials also allows us to evaluate the strength of the $\pi\cdots\pi$ interactions between the layers formed by the 5-FC-acids units. These interactions have potentials ranging from -9.6 to -4.9 kcal/

mol, agreeing in all the cases with the proximity of the layers in the 3D supramolecular arrangements. A correlation is observed between the energy of these interactions and the distance of the layers. form M, which displays the closest distance between the layers, also exhibits a high potential (-8.2 kcal/mol) for the $\pi\cdots\pi$ interactions, whereas the highest potential observed to the $\pi\cdots\pi$ interactions was between terephthalic acid units of form T (-9.6 kcal/mol). All the potentials calculated are summarized in Tables A7, B7...E77 (see the Supporting Information, Sections A–E).

Extending our supramolecular study for the neutral 5-FC molecules, a comparative analysis was performed on the basis of all the crystalline structures already reported containing 5FC molecules. Polymorphs, solvates, and cocrystals, plus mixtures of them, such as solvated cocrystals, were also considered. 5-FC is a rigid molecule and presents three potential patterns of hydrogen bonding sites, two acceptor–donor involving the atoms O21–N1 and N3–N41 (ON and NN, respectively), and one acceptor–acceptor–donor involving the atoms O21–N3–

N41 (ONN). Tutughamiarso and co-workers¹⁷ showed that the 5-FC molecule, when neutral, tends to interact to one another by self-complementary homodimers, constituting planar or tubular 5-FC ribbons. These homodimers, as observed in the cocrystals depicted here, are essentially composed by one N–H···O and one N–H···N (ON/NN), or by two N–H···O (ON/ON), or even by two N–H···N (NN/NN) intermolecular interactions. Complementing this claim, Figure 8 exhibits a schematic drawing of the classical intermolecular interactions of each reported structure considering the whole supramolecular architecture adopted by the 5-FC molecules under the different crystalline arrangements. It shows that not only ribbons are observed, but also planar and/or tubular cavities, mainly due to the intrinsic geometry of the ON, NN, ONN hydrogen bonding sites. Furthermore, Table 2 exhibits a statistical analysis of the distribution of the main supramolecular synthons observed for the 5-FC molecule, including homo- and heterodimers involving the three main hydrogen bonding sites (ON/ON, ON/NN and NN/NN) plus the formation of homo- and heterotrimers with hydrogen bonding patterns similar to the C≡G Watson and Crick base pairing.

According to Table 2, the 5-FC molecule tends to form ON/NN, ON/ON, and NN/NN homodimers. Tutughamiarso and co-workers¹⁷ observed the particular NN/NN homodimer formation only in the hydrate under refcode BIRMEU03,¹⁵ reporting later a cocrystal of 5-FC under refcode MECTUL²⁴ also exhibiting this pattern of NN/NN homodimer formation. The forms S, T, A, and B, however, exhibit the same ribbon formation that occurs for the hydrate under refcode BIRMEU03,¹⁵ i.e., ON/ON and NN/NN $R_2^2(8)$ motifs^{37a,b} per 5-FC molecule, while in the 5-FC cocrystal under refcode MECTUL²⁴ the free ON site of the 5-FC molecule is intercepted by the formation of a ON/NN heterodimer with the coformer molecule. In addition, two ON/NN (refcodes MECVIB²⁴ and e GATMUL²³) and two ON/ON heterodimers (refcodes MECWUO²⁵ and GATMUL²³) are observed. However, no NN/NN heterodimer was reported until the present.

On the other hand, for the ONN C≡G-like base pairing, the tendency is the formation of heterosynthons with a total of nine structures. Only in one hydrate (refcode PANLAS¹⁸) the C≡G-like base pairing is observed between the 5-FC molecules. By analyzing the crystalline packing of the 5-FC cocrystal under refcode MECTUL²⁴ (see Figure 8f), the occurrence of one ON/NN heterodimer disrupts the 5-FC ribbon formation. Although homoribbons (i.e., ribbons constituted only by 5-FC molecules) are prevalent in most of the crystalline structures, 12 of them exhibit heteroribbons and all refer to cocrystals (2 cocrystals and 10 solvated cocrystals).

By considering the cavity formation, two exceptions arise, one referring to the cocrystal under refcode MECTUL²⁴ (Figure 8f), where flat layers are stacked by van der Waals contacts and one referring to the solvate under refcode DUKWAI¹⁷ (Figure 8g), for which small cavities are observed only when the nonclassical C–H···O and C–H···F intermolecular interactions between the dimethyl sulfoxide and 5-FC molecules are considered. Both reported polymorphs of 5-FC exhibit tubular patterns (Figure 8h, (i), constituting $R_4^4(24)$ and $R_6^4(26)$ motifs, involving four and six 5-FC molecules, respectively. Forms S, A, and T (Figure 8a–c) exhibit similar cavities, differing only in their size ($R_6^4(40)$, $R_6^4(48)$, $R_6^4(44)$, for forms S, A, and T, respectively), proportional to the size and the geometry of each acid molecule. Figure 8h exhibits the last

planar cavity, $R_7^6(44)$, involving only solid coformers, concerning the cocrystal under refcode MECXID.²⁵ When solvents are involved in the interactions, they lead to planar and tubular cavities, for which it is not possible to establish a specific pattern for these ternary systems. In particular, the cocrystal under refcode MECVEX²⁴ (Figure 8r) and the hydrate under refcode DUKWIQ¹⁷ (Figure 8z) display cavities of both tubular and planar types. It is worth mentioning that the planar cavities of the methanol solvate under refcode MEBQOA¹⁵ (Figure 8(l)), of the cocrystal under refcode MECVEX²⁴ (Figure 8r) and of the hydrate under refcode DUKWIQ¹⁷ (Figure 8z), are similar to the one formed in forms S, A, and T. This shows that the recurrent supramolecular synthon observed for the cocrystals depicted herein is not restricted to the use of carboxylic acids as coformers. In this way, it could be expected that new structures containing 5-FC molecule can be designed and developed as new tailor-made drugs.

4.2. Cocrystal of 5-FC and 5-FU. 5-Fluorouracil, 5-fluoro-2,4-(1H,3H)-pyrimidinedione, is an antineoplastic API rationally designed by Heidelberger and co-workers in 1957.⁴³ It is used for the treatment of superficial skin carcinomas as a cream formulation and as injections in the treatment of various cancers, including, among others, gastrointestinal, head and neck, breast, colorectal, and ovarian. 5-FU is a synthetic pyrimidine analogue and is probably the most widely used, being of great interest in the clinical and experimental chemotherapy among the developed analogues of purine and pyrimidine, as it is structurally similar to natural bases. Nevertheless, only a fraction of the administered amount of this API becomes available in the systemic circulation after oral administration due to its poor water solubility.^{44–46} Indeed, oral delivery of antineoplastic APIs is considered a challenge due their physical and chemical properties and physiological barriers.⁴⁷

As an illustration of a controlled rational supramolecular synthesis of new solid forms of a given API using 5-FC as coformer, we designed a cocrystal of 5-FC and 5-FU (form SF, $pK_a = 8.0$).⁴⁴ It is clear that the 5-FU was our first molecule of choice for this example due to its structural similarities with 5-FC. The cocrystallization experiment was developed according to the pK_a rule and a cocrystal was expected ($\Delta pK_a = -4.74$). The aim of this particular experiment was to design a new solid form of 5-FU with enhanced physical and chemical properties that could enable this API to be orally administered together with 5-FC, which in turn exhibits high solubility and bioavailability profiles.¹⁰ However, the solubility properties of form SF-5FU are still under investigation.

The asymmetric unit of form SF (see Figure 1) exhibits one molecule of 5-FC and one of 5-FU. The main intermolecular interactions responsible for maintaining the crystalline arrangement of this cocrystal are of the types N–H···O and N–H···F (see Table S1 in the Supporting Information section), including the formation of homodimers of 5-FC (I, in Figure 9a), homodimers of 5-FU (II, in Figure 9a) and intermolecular interactions among the 5-FC and 5-FU molecules (Figure 9a). Nonclassical intermolecular interactions are also present, as a result of the close packing: C6–H6···F51 (bond distance of 2.467 Å), C6'–H6'···F51' (bond distance of 2.354 Å), C6'–H6'···N3 (bond distance of 2.639 Å), and C6–H6···O21' (bond distance of 2.553 Å). The crystal packing of form SF is composed of flat tapes in which the dimers are interspersed. These tapes are stacked constituting columns with a parallel

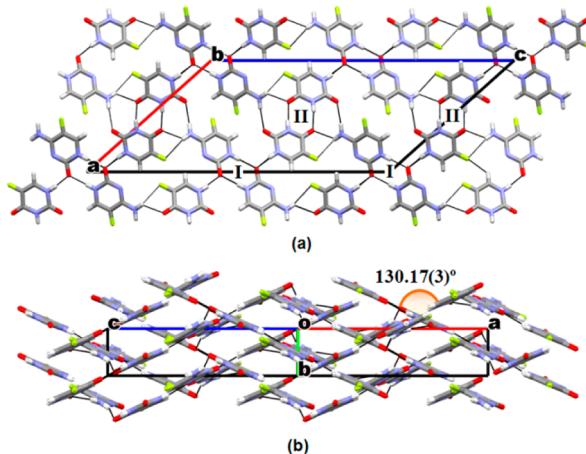


Figure 9. (a) Crystal packing diagram of form 5f. Black dashed lines indicate hydrogen bonds, (I) refers to the $R_2^2(8)$ motifs^{37a,b} involving the N–H···O homodimers occurring among 5-FC molecules and (II) correspond to $R_2^2(8)$ motifs^{37a,b} involving the N–H···O homodimers occurring among 5-FU molecules, (b) three-dimensional hydrogen-bonded network of form 5f.

displaced arrangement (displacement angle of 23.2°), maintained by $\pi\cdots\pi$ interactions ($5\text{-FC}_{\pi\cdots\pi} = 3.5604(9)$ Å and $5\text{-FU}_{\pi\cdots\pi} = 3.5603(9)$ Å). Adjacent tapes (and consequently adjacent columns) exhibit two directions of growth and are connected to one another by intermolecular interactions between the molecules of 5-FC and 5-FU, forming a dihedral angle of 130.17(3)° (Figure 9b).

5. CONCLUSION

The 5-FC cocrystals with succinic, adipic, benzoic, and tereftalic acids were obtained following the tendency of the pK_a rule and have revealed a similar hydrogen-bonding pattern, leading to 5-FC ribbons, stabilized by two $R_2^2(8)$ motifs, characterized by complementary homodimeric N–H···N (NN/NN) and N–H···O (ON/ON) interactions, which was found to be a feature of cocrystals containing this fluoropyrimidine molecules. Analyzing the supramolecular characteristics of the four 5-FC cocrystals (together with some similar structures reported in the literature), it was observed that the 5-FC molecule tends to form ON/NN, ON/ON, and NN/NN homodimers, ONN C≡G-like base pairing heterotrimers, and both tubular and planar cavities. Nevertheless, when the cocrystallization experiment was conducted with malic acid, where the $\Delta pK_a = -0.1$, a supramolecular transition synthon was observed, in which the N–H···O homodimeric synthon present in the cocrystals remains, but a new heterodimeric synthon, characterized by complementary N–H···O hydrogen bonds between the 5-FC molecule and the malic acid, emerged. This last synthon was found in the 5-FC organic salts, obtained even from very small positive ΔpK_a values (such as for the fumarate of 5-FC where $\Delta pK_a = 0.23$). The discovery of this transition synthon indicates that the 5-FC molecule is a suitable candidate for the design and development of cocrystallization experiments based on crystal engineering techniques, once its behavior could be, until the present, well predicted by the pK_a rule. To check our hypothesis, we conducted a cocrystallization experiment of 5-FC with the antineoplastic drug 5-FU, aiming to obtain a cocrystal once the system exhibits a $\Delta pK_a = -3.0$. The success of this experiment points to a new path to apply 5-

FC as a coformer in new controlled crystallization experiments for the development of new tailor-made drugs.

■ ASSOCIATED CONTENT

■ Supporting Information

Crystallographic data of the 5-FC, calculated potentials. This material is available free of charge via the Internet at: <http://pubs.acs.org/>.

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Notes

The authors declare no competing financial interest.

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