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Co-crystals and salts formed from 4-fluorobenzoic acid and heteroaromatic nitrogenous bases

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ABSTRACT

Acridine 4-fluorobenzoic acid (**1**) and 9-aminoacridinium 4-fluorobenzoate monohydrate (**2**) were synthesized and structurally characterized. The single-crystal structure was determined by X-ray diffraction. Analysis of the intermolecular interactions occurring in the crystal packing of both compounds, especially those involving the fluorine atoms, was carried out. The formation of crystalline salts or co-crystals from 4-fluorobenzoic acid was also examined.

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The design and synthesis of multi-component crystalline solids—salts, co-crystals, and their solvates—occupy a special place among the topics of modern crystal engineering.[1–3] This important field of solid state chemistry has developed rapidly since the 1960s, particularly with the arrival of modern crystallographic techniques.[4] There is a strong preference for crystalline forms in the context of medicinal applications, because they tend to be more stable, reproducible, and amenable to purification than other types of solids. Furthermore, such systems often exhibit widely different physicochemical properties compared to their pure components. A co-crystal differs from a crystalline salt in the following way: in a salt, a proton is transferred from the acidic to the basic functionality of the crystallization partner, whereas in a co-crystal no such proton transfer takes place.[5]

Interesting research targets in this field are systems containing the heteroaromatic nitrogenous bases acridine and 9-aminoacridine. This is due to the well-known fact that acridine-based derivatives exhibit biological activity, for example, antibacterial,[6] antiviral,[7] antiprion,[8] antitumor,[9] and antiprotozoal.[10] This medicinal significance, in addition to their ability to react with sufficiently strong carboxylic acids, makes them a natural target for obtaining multi-component crystalline solids. Moreover, knowledge of the nature (salt or co-crystal) of the crystalline products arising from their reaction with acridine-based compounds is important for a better understanding of molecular recognition processes and may help in the preparation of pharmaceuticals. This is particularly interesting in the case of organofluorine compounds, which have applications in medicine[11–13] and crystal engineering, owing to their possible participation in C–H···F, C–F···π, and F···F intermolecular interactions.[14–16]

Here we present the crystal structure of two compounds obtained in reactions of 4-fluorobenzoic acid with acridine (**1**) and 9-aminoacridine (**2**) (Scheme 1), and a detailed analysis of the intermolecular interactions occurring in their crystal packing, with particular emphasis on the interactions involving fluorine atoms. To our knowledge, compound **2** is the first structurally characterized organic salt containing a 4-fluorobenzoate anion (excluding metalloorganic compounds).

Single-crystal X-ray diffraction measurements show that compound **1** crystallizes in the triclinic *P*-1 space group and forms co-crystals with one acridine and one 4-fluorobenzoic acid molecule in the asymmetric unit (Fig. S1a, Table S1).

The bond lengths and angles characterizing the geometry of the acridine skeleton[17] and 4-fluorobenzoic acid molecule[18] are typical of these groups of compounds.

Analysis of the hydrogen bonds in the structure of **1** shows that the 4-fluorobenzoic acid and acridine molecules interact via strong $O_{(carboxy)}$–H···$N_{(acridine)}$ hydrogen bonds [d(O22···N10) = 2.673(3) Å and ∠(O22–H22···N10) = 168(3)°] (Fig. S1a, Table S2). These pairs of molecules are linked to the nearest pairs of molecules by $C_{(acridine)}$–H···$O_{(carboxy)}$ hydrogen bonds [d(C9···O23) = 3.265(3) Å and ∠(C9–H9···O23) = 149°], inverted via the crystallographic inversion center, to form tetramers generating an $R_4^4(18)$ hydrogen

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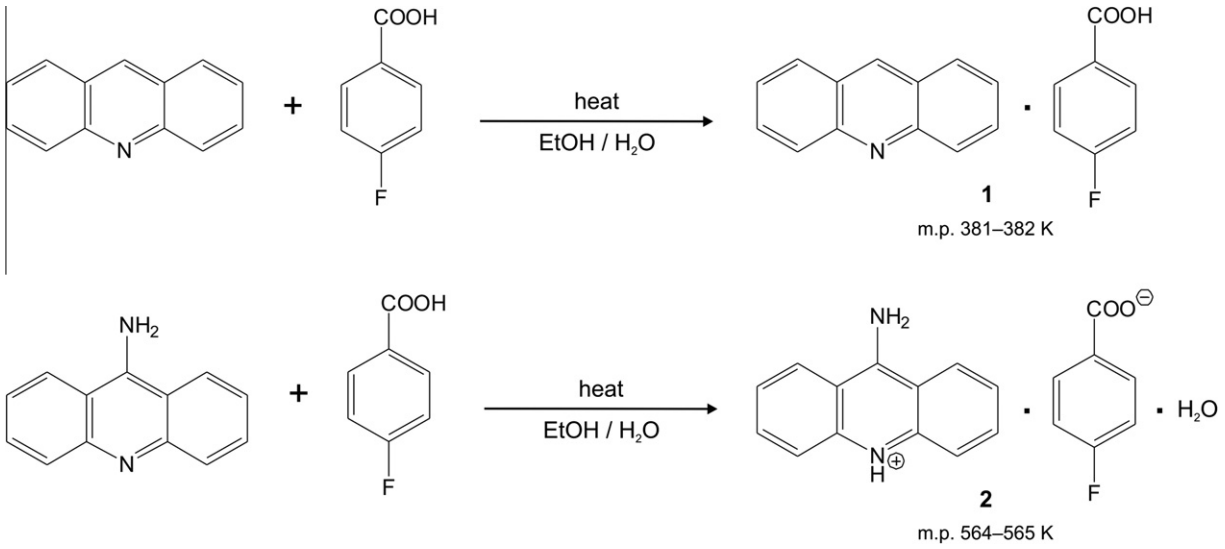

Scheme 1. Synthesis of complexes **1** and **2**.

bond ring motif[19,20] (Fig. S1b, Table S2). The tetramers are also stabilized via π–π interactions between parallel acridine moieties with *centroid*···*centroid* distances (denoted by Cg···Cg) from 3.660(1) to 3.790(1) Å, and with a separation between the mean planes of the acridine skeleton of 3.470(1) Å (Fig. S2, Table S3). The neighboring tetramers are linked via $C_{(acridine)}$–H···F hydrogen bonds [*d*(C4···F24) = 3.225(3) Å and <(C4–H4···F24) = 122°] and π–π interactions between the aromatic rings of the 4-fluorobenzoic acid molecule [*d*(Cg···Cg) = 3.914(1) Å] (the separation between the mean planes of the aromatic rings is 3.494(1) Å) forming chains of rings (Figs. 1 and S2, Tables S2 and S3). The neighboring chains of rings exhibit $C_{(acridine)}$–H···π interactions between the acridine skeleton and the aromatic ring of the 4-fluorobenzoic acid molecule [*d*(H7···Cg4) = 2.88 Å and ∠(C7–H7···Cg4) = 150°] (Fig. 1, Table S2). In the supramolecular architecture, the chains of rings are arranged in layers along the crystallographic *b*-axis (Fig. S2).

Compound **2** forms triclinic crystals (*P*-1 space group) with two 9-aminoacridinium cations, two 4-fluorobenzoate anions and two water molecules in the asymmetric unit, respectively, denoted A and B (Fig. S3, Table S1). The geometric parameters (bond lengths and angles) characterizing the 9-aminoacridinium[21] and 4-fluorobenzoate[22] moieties are typical for these units.

Analysis of the hydrogen bonds in the structure of **2** shows that the ions are linked via $N_{(amino)}$–H···$O_{(carboxy)}$ hydrogen bonds

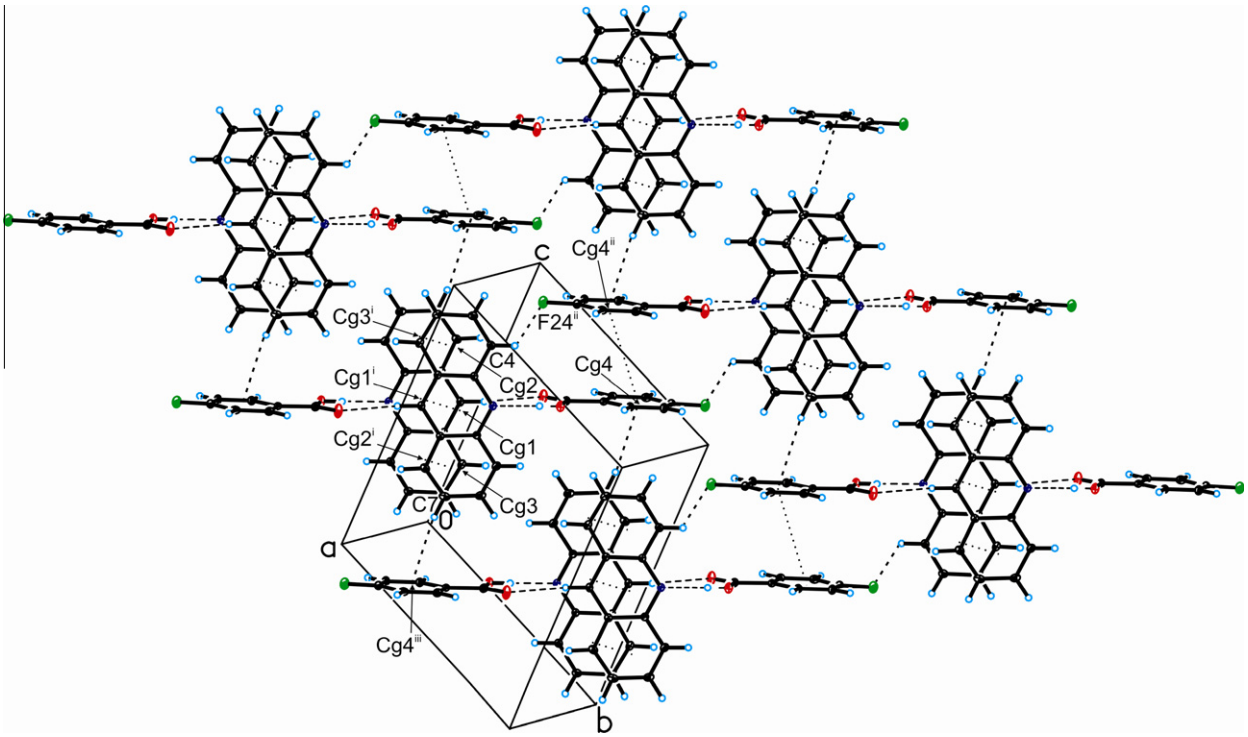

Figure 1. Network of the intermolecular interactions in **1**: O–H···N, C–H···O, C–H···F, and C–H···π hydrogen bonds are represented by dashed lines, and π–π interactions by dotted lines. Symmetry codes: (i) −*x*+1, −*y*+2, −*z*+1; (ii) −*x*+1, −y+1, −*z* +1; (iii) −*x*+2, −*y*+1, −*z*.

[d(N···O) = 2.821(3)–3.132(3) Å and ∠(N–H···O) = 158–162°] to form tetramers (Fig. S3, Table S4). In these tetramers, the amino groups of both 9-aminoacridinium cations and one of the O-atoms from the carboxy groups of both 4-fluorobenzoate anions participate in the hydrogen bonds, producing an $R_2^2(8)$ hydrogen bond ring motif.[19,20] The O23A and O23B atoms from both carboxy groups involved in the formation of the $R_2^2(8)$ hydrogen bond ring motif also take part in the $C_{(acridine)}$–H···$O_{(carboxy)}$ hydrogen bonds [d(C···O) = 3.351(3)–3.370(3) Å and ∠(C–H···O) = 152–166°], which stabilizes these tetramers. In addition, the $N_{(amino)}$–H···$O_{(carboxy)}$ hydrogen bond [d(N15B···O24B) = 3.074(3) Å and ∠(N15B–H15C···O24B) = 119°] is observed (Fig. S3, Table S4). The neighboring tetramers interact directly via $C_{(4\text{-fluorobenzoate})}$–H···$O_{(carboxy)}$ [d(C18A···O23B) = 3.302(4) Å and ∠(C18A–H18A···O23B) = 134°] hydrogen bonds and $C_{(acridine)}$–H···$\pi_{(4\text{-fluorobenzoate})}$ [d(H6A···Cg4B) = 2.96 Å and ∠(C6A–H6A···Cg4B) = 147°] interactions, or are linked indirectly through hydrogen bonds with water molecules as donors/acceptors of H–atoms (Fig. 2, Table S4). Thus, the tetramers inverted via the inversion center are linked by $O_{(water)}$–H···$O_{(carboxy)}$ [d(O···O) = 2.692(3)–2.764(3) Å and ∠(O–H···O) = 169(3)–177(3)°], $O_{(water)}$–H···$O_{(water)}$ [d(O···O) = 2.830(3) Å and ∠(O–H···O) = 163(3)°] and $N_{(acridine)}$–H···$O_{(water)}$ [d(N···O) = 2.731(3)–2.832(3) Å and ∠(N–H···O) = 169–171°] hydrogen bonds, forming layers along the crystallographic (101) plane (Fig. 2, Table S4). In these layers, the acridinium skeletons interact via π–π interactions [d(Cg···Cg) = 3.616(1)–3.830(1) Å with separations from 3.355(1) to 3.495(1) Å], forming infinite π–stacked columns in the BAAB arrangement (Fig. 2, Table S5). In the crystal packing, the layers are connected via C–F···$\pi_{(4\text{-fluorobenzoate})}$ interactions [d(F25A···Cg4B) = 3.583(3) Å and ∠(C19A–F25A···Cg4B) = 96.9(2)°] between 4-fluorobenzoate anions, producing a three-dimensional structure (Fig. S4, Table S6).

It is assumed that the formation of a crystalline salt or co-crystal can be predicted from the pK_a values of the components participating in the formation of both forms.[23,24] Generally, salt formation requires a difference of about three pK_a units between the conjugate base and the conjugate acid [ΔpK_a >3].[25,26] To explain why 4-fluorobenzoic acid (pK_a = 4.14) forms a crystalline salt or co-crystal, we evaluated the relationship between the formation of these two forms and the ΔpK_a value for compounds **1** and **2**, as well as other known crystal structures containing heteroaromatic nitrogenous bases and 4-fluorobenzoic acid (Table 1).[27,28] Comparison of the acidity of aromatic nitrogenous bases and 4-fluorobenzoic acid shows that co-crystals are formed when the ΔpK_a value is <1.56 (acridine, isonicotinamide), but that when ΔpK_a exceeds this value, crystalline salts (9-aminoacridine) are formed. The ΔpK_a value is 1.56 for the compound containing lamotrigine and 4-fluorobenzoic acid, which crystallizes in two forms (neutral and ionic) co-existing in the asymmetric part of the unit cell. This may suggest that this compound exists in an intermediate state between the formation of co-crystals and salts produced by 4-fluorobenzoic acid.

To conclude, the products of reactions between acridine/9-aminoacridine and 4-fluorobenzoic acid are obtained in two crystalline forms: a co-crystal [acridine and 4-fluorobenzoic acid adduct (**1**)]

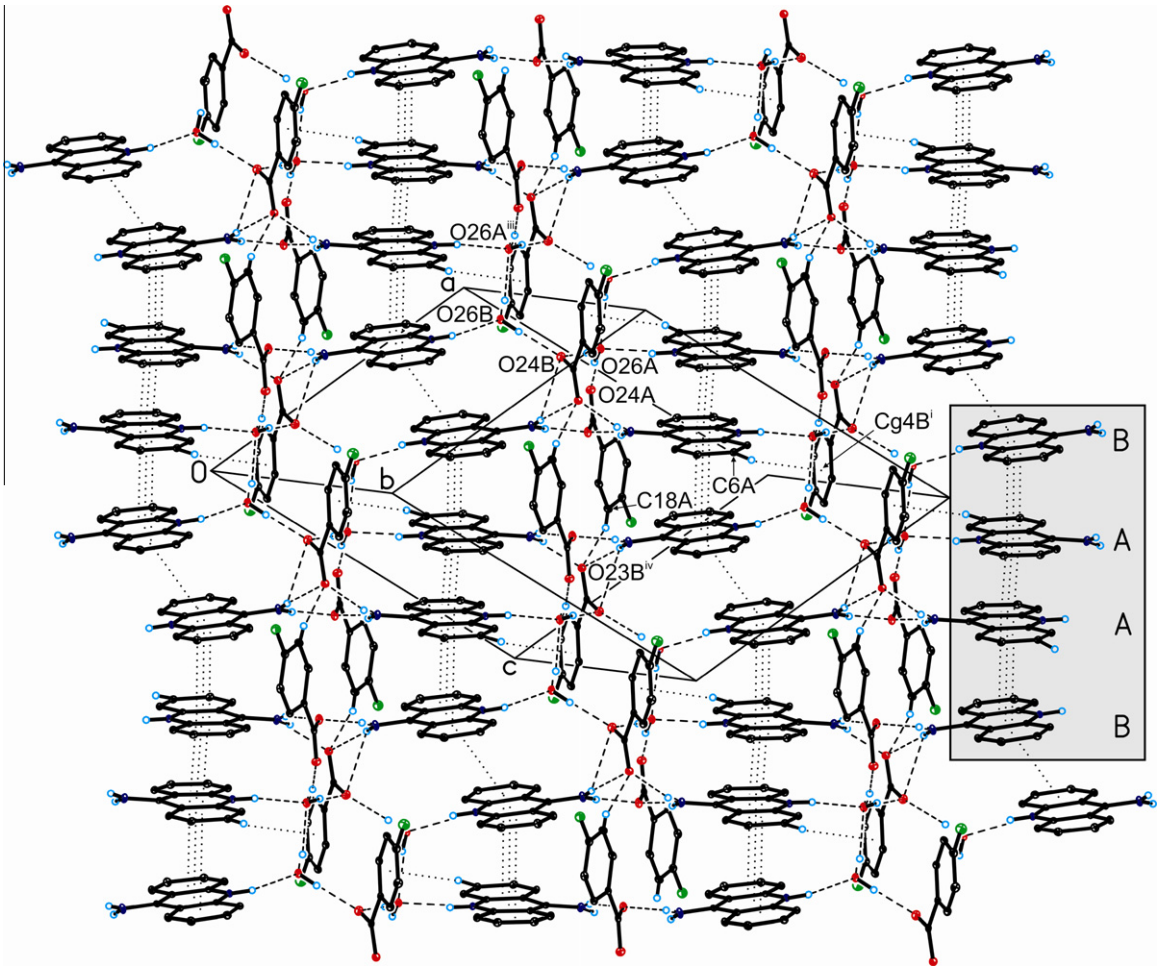

Figure 2. Network of intermolecular interactions in **2**: N–H···O, O–H···O, and C–H···O hydrogen bonds are represented by dashed lines, and C–H···π and π–π interactions by dotted lines (H atoms not involved in these interactions have been omitted). Symmetry codes: (i) −x+2, −y+1, −z+1; (iii) −x+2, −y+1, −z; (iv) −x+1, −y+1, −z+1.

Table 1
Acidity of complexes of heteroaromatic nitrogenous bases and 4-fluorobenzoic acid

Compound	pK_a	ΔpK_a[a]	Crystalline form	References
Acridine	5.60	1.46	Co-crystal	This work
9-Aminoacridine	9.90	5.76	Salt	This work
Isonicotinamide	3.67	-0.47	Co-crystal	27
Lamotrigine	5.70	1.56	Co-crystal and salt	28

[a] The pK_a value of 4-fluorobenzoic acid is 4.14.

and a solvated salt [9-aminoacridinium 4-fluorobenzoate monohydrate (**2**)]. In the crystal packing, the molecules or ions interact via O–H···O, O–H···N, N–H···O and C–H···O hydrogen bonds, forming tetramers and producing $R_4^4(18)$ and $R_2^2(8)$ hydrogen bond ring motifs in **1** and **2**, respectively. Apart from the C–H···π and π–π interactions observed in the packing of both compounds, the crystal lattices are stabilized by interactions involving fluorine. These interactions link the neighboring tetramers, which leads to the formation of chains of molecules (C–H···F hydrogen bonds in **1**), or connects the layers into a three-dimensional network (C–F···π interactions in **2**). The formation of crystalline salts and co-crystals between 4-fluorobenzoic acid and aromatic nitrogenous bases depends on the ΔpK_a value (for the co-crystal, ΔpK_a <1.56) between the individual components of the crystals.

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Supplementary data

Crystallographic data for the structures reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 891079 (**1**) and 891080 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data (experimental procedures, Figures and Tables) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.026. These data include MOL files and InChiKeys of the most important compounds described in this article.

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