



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).

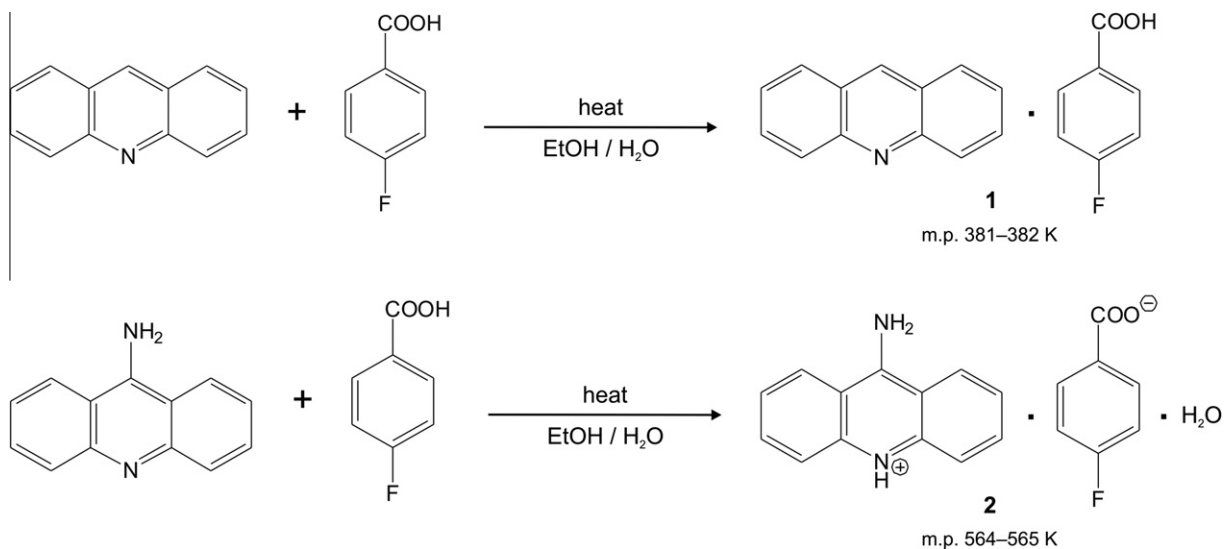
Single-crystal X-ray diffraction measurements show that compound **1** crystallizes in the triclinic *P*-1 space group and forms co-crystals with one acridine and one 4-fluorobenzoic acid molecule in the asymmetric unit (Fig. S1a, Table S1).

The bond lengths and angles characterizing the geometry of the acridine skeleton¹⁷ and 4-fluorobenzoic acid molecule¹⁸ 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 [$d(\text{O}22\cdots\text{N}10) = 2.673(3) \text{ \AA}$ and $\angle(\text{O}22\text{--H}22\cdots\text{N}10) = 168(3)^\circ$] (Fig. S1a, Table S2). These pairs of molecules are linked to the nearest pairs of molecules by C_(acridine)–H···O_(carboxy) hydrogen bonds [$d(\text{C}9\cdots\text{O}23) = 3.265(3) \text{ \AA}$ and $\angle(\text{C}9\text{--H}9\cdots\text{O}23) = 149^\circ$], inverted via the crystallographic inversion center, to form tetramers generating an R₄¹(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 $C_{(\text{acridine})}\text{-H}\cdots\text{F}$ hydrogen bonds [$d(\text{C4}\cdots\text{F24}) = 3.225(3)$ Å and $\angle(\text{C4-H4}\cdots\text{F24}) = 122^\circ$] and π - π interactions between the aromatic rings of the 4-fluorobenzoic acid molecule [$d(\text{Cg}\cdots\text{Cg}) = 3.914(1)$ 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 $C_{(\text{acridine})}\text{-H}\cdots\pi$ interactions between the acridine

skeleton and the aromatic ring of the 4-fluorobenzoic acid molecule [$d(\text{H7}\cdots\text{Cg4}) = 2.88$ Å and $\angle(\text{C7-H7}\cdots\text{Cg4}) = 150^\circ$] (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-aminoacridinium²¹ and 4-fluorobenzoate²² moieties are typical for these units.

Analysis of the hydrogen bonds in the structure of **2** shows that the ions are linked via $N_{(\text{amino})}\text{-H}\cdots\text{O}_{(\text{carboxy})}$ hydrogen bonds

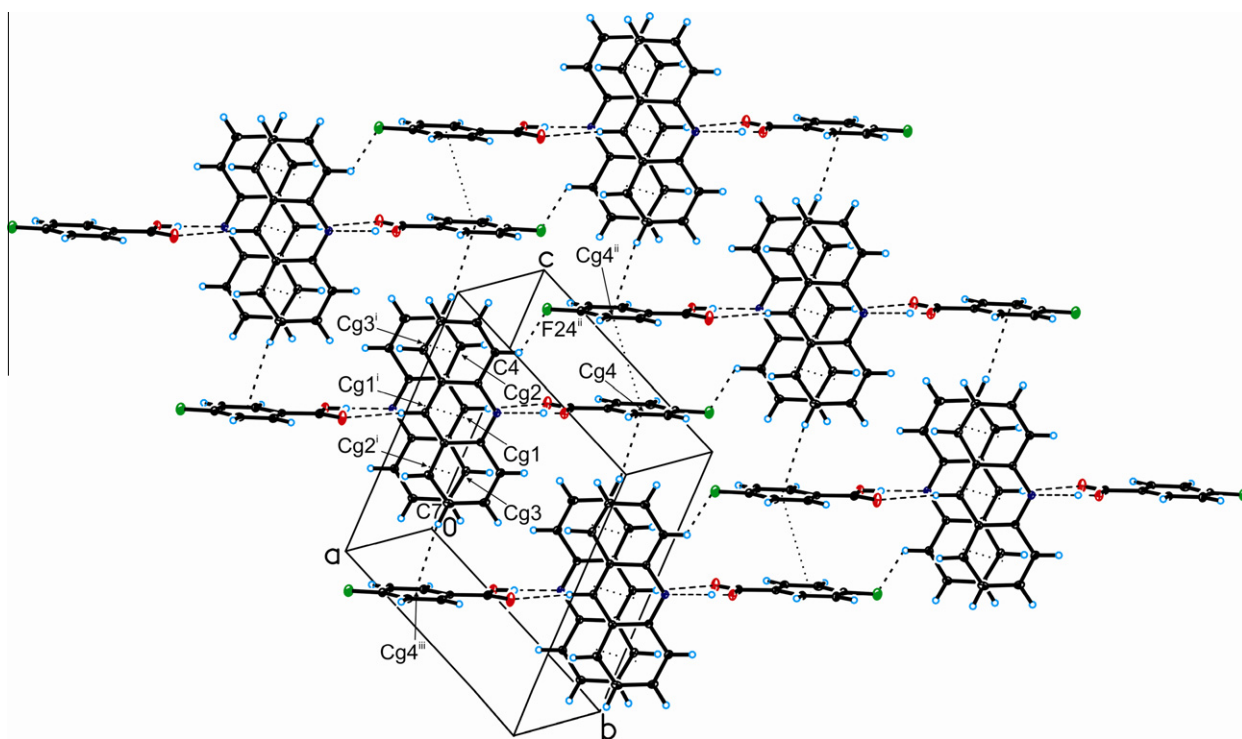


Figure 1. Network of the intermolecular interactions in **1**: O-H···N, C-H···O, C-H···F, and C-H··· π hydrogen bonds are represented by dashed lines, and π - π interactions by dotted lines. Symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $-x+2, -y+1, -z$.

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