UNIWERSYTET GDAŃSKI
IN MARI VIA CUA
WYDZIAŁ CHEMII
Katedra Chemii Fizycznej
CHEMIA UG

dr Artur Sikorski
Wydział Chemii UG, ul. Wita Stwosza 63, 80-308 Gdańsk, tel. (+48 58) 523 5112, fax (+48 58) 523 5012,
e-mail: artur.sikorski@ug.edu.pl, www.chem.ug.edu.pl

APPENDIX 3B

SELF-PRESENTATION

ARTUR SIKORSKI

UNIVERSITY OF GDANSK
FACULTY OF CHEMISTRY

GDANSK 2016

1. Personal data

Given name and surname: Artur Sikorski

2. Diplomas and scientific degrees

26.06.2001 – M.Sc.; title of M.Sc. Thesis: „Crystal structure and hydrogen-bonding network of (2,4-diamino-6-piperidine)pyrimidine 3-oxide (minoxidil) and its semihydrochloride"

University of Gdansk, Faculty of Chemistry

Supervisor: prof. dr hab. inż. Jerzy Błażejowski

01.03.2006 – Ph.D.; title of Ph.D. Thesis: „Crystal structures of selected 9-carboxyacridine and 10-methyl-9-carboxyacridinium phenyl esters"

University of Gdansk, Faculty of Chemistry

Supervisor: prof. dr hab. inż. Jerzy Błażejowski

3. Information on employment in scientific institutions.

University of Gdansk, Faculty of Chemistry, Department of Physical Chemistry

teaching assistant: 21.10.2005 – 20.10.2006

assistant professor: 21.10.2006 – up to the present

4. List of publications representing scientific achievement as referred in article 16, paragraph 2 of the act of 14 March 2003, The Law on Academic Degrees and Title and Degrees and Title in the Arts (Dz. U., No.65 item 596, with further amendments)

A) Title of scientific achievement:

Multicomponent crystals based on acridines – structure and analysis of intermolecular interactions

B) List of publications included in the scientific achievement:

[H1] Kowalska, K., Trzybiński, D., **Sikorski, A.**✉
Influence of the halogen substituent on the formation of halogen and hydrogen bonding in co-crystals formed from acridine and benzoic acids
CrystEngComm 17(2015) 7199-7212 (IF_{2014}=4,034)

[H2] **Sikorski, A.**✉, Trzybiński, D.
Co-crystals and salts formed from 4-fluorobenzoic acid and heteroaromatic nitrogenous bases
Tetrahedron Letters 54 (2013) 1463-1466 (IF_{2013}=2,391)

[H3] Trzybiński, D., **Sikorski, A.**✉
Solvent-bridged frameworks of hydrogen bonds in crystals of 9-aminoacridinium halides
CrystEngComm 15 (2013) 6808-6818 (IF_{2013}=3,858)

[H4] **Sikorski, A.**✉, Trzybiński, D.
Anion-controlled networks of intermolecular interactions in the crystal structure of 9-aminoacridinium salts
Tetrahedron 67 (2011) 1479-1484 (IF_{2011}=3,025)

[H5] **Sikorski, A.**✉, Trzybiński, D.
The influence of benzoate anion substituents on the crystal packing and hydrogen-bonding network of 9-aminoacridinium salts
Tetrahedron 67 (2011) 2839-2843 (IF_{2011}=3,025)

[H6] **Sikorski, A.**✉, Trzybiński, D.
Networks of intermolecular interactions involving nitro groups in the crystals of three polymorphs of 9-aminoacridinium 2,4-dinitrobenzoate · 2,4-dinitrobenzoic acid
Journal of Molecular Structure 1049 (2013) 90-98 (IF_{2013}=1,599)

[H7] **Sikorski, A.**✉,Trzybiński, D.
Structural insight into the interactions between a cationic dye and an anionic surfactant in crystals of 9-aminoacridinium dodecyl sulfate
Journal of Molecular Structure 1076 (2014) 490-495 (IF_{2014}=1,602)

[H8] **Sikorski, A.**✉, Trzybiński, D.
Synthesis and structural characterization of a cocrystal salt containing acriflavine and 3,5-dinitrobenzoic acid
Tetrahedron Letters 55 (2014) 2253-2255 (IF_{2014}=2,379)

✉ – corresponding author

Total impact factor IF for publications included in the scientific achievement: 21,913 – calculated on the basis of data from the published work (mean IF: 2,739 per article).

Statements regarding the scope of the work performed and the percentage, summary of other research achievements, information about his scientific plans for the future can be found in Appendix 4.

Statements of the co-authors of articles on their individual contribution to the creation of individual articles can be found in Appendix 5.

Multicomponent crystals based on acridines – structure and analysis of intermolecular interactions

Introduction

Acridine derivatives are interesting objects of study, because many of them are active pharmaceutical ingredients. These compounds, mainly aminoacridines, exhibit a broad spectrum of biological activities, such as: antibacterial, antitumour, antiprotozoal, antiprion or antiviral ant other.[1–8] These compounds are also used as dyes and chemiluminescent markers in contemporary clinical analyzes. [9–10] The unique properties of the acridine derivatives are related to their interactions with macromolecules of which the most important example is intercalation.[11–12] In this process, the molecules of acridines, consisting of three fused aromatic rings (including central, heteroaromatic ring involving an endocyclic nitrogen atom) intercalate into the double helix of DNA in such a way that they become located between complementary pairs of nucleobases to form an intercalation complex. The binding of an intercalator with DNA occurs through interaction of π electrons of the intercalator's aromatic systems with the nucleobases molecules, whereas the complex is stabilizing by hydrogen bonds, van der Waals interaction or through electrostatic forces.

One of the major challenges of modern pharmacy is the search of new forms of drugs, in order to reduce the time and cost of processes of their preparation and to improve their pharmacokinetic and pharmacodynamic properties.[13–19] A solution to these problems is possible due to crystal engineering. Crystal engineering is a rapidly developing area of science, whose one of the main objectives is to design and obtain crystals of compounds with a predictable structure and desired properties.[20–24] This applies not only to crystals of medicinal, [13–24] but also to those compounds that may find use in practice, for example such as materials for non-linear optics, ferroelectric and catalytically active materials, and much more.[25–27] Realization of these objectives is possible through getting knowledge and understanding of interactions between individual components of such crystals occurring between different functional groups of molecules forming them, such as: the strong and weak hydrogen bonds and interactions involving the halogen atoms, π electrons of aromatic systems and van der Waals interactions.[14,16–25,28–33] Those interactions lead to aggregation of molecules/ions in the crystals with the formation of characteristic structural motifs (supramolecular synthons).[20–23] Despite extensive studies aimed at obtaining multicomponent crystals, analysis of interactions between different functional groups and synthons that may arise with their participation, predicting the structure of crystals and their properties still remains as a challenging task.[23–24] Main problems are the possibility of varying the orientation of molecules in crystals, inaccuracies in determining the energy of interactions and problems in estimating the contribution of thermodynamic and kinetic factors during crystal growth.[34–35] Therefore, the preliminary design stage of the compounds with the expected structure is to include a small number of functional groups in the molecules order to minimize non-covalent interactions between them. This restricts the potential distribution of molecules in the crystal, and facilitates determining

the influence of structural modifications, for example the presence additional substituents in the molecules, or the influence of solvent molecules (solvates), on the occurrence and repeatability of interactions and synthons forming between different functional groups of these molecules and their packing.

In recent years there has been an increased interest in acridine in the context of designing and obtaining multicomponent crystals (three- or more-component) due to its ability to co-crystallization with other compounds.[36–39] In the case of amino-substituted acridines, the interest it is much smaller, and the main limitations are the difficulties in obtaining high-quality single crystals suitable for X-ray diffraction measurements.

This was the main reason for undertaking my research into this subject.

The planned research included the following tasks: synthesis of multicomponent crystals involving acridines, determination of their structures by single-crystal X-ray diffraction measurements, analysis of the intermolecular interactions in the crystal structures and studies of the spectral and thermal properties of the selected compounds.

Given the nature of the heterocyclic base constituting a component of multi-component crystals, the results are shown for the following three groups:

a) co-crystals formed from acridine and benzoic acids,

b) 9-aminoacridinium salts, and

c) multicomponent crystals involving other acridines.

1. Co-crystals formed by acridine and halobenzoic acids.[H1–H2]

From the point of view of crystallographic studies, acridine is a well-known heterocyclic compound. In the *Cambridge Structural Database* (CSD, version 5.36; update: May 2015) there are deposited to date 175 crystal structures of compounds involving acridines, including 113 crystal structures of organic compounds (with six known polymorphs of acridine). In those structures, there are known crystal structures of multicomponent crystals formed by acridine and carboxylic acids (36 structures deposited in CSD with 11 structures including benzoic acids).[40–45] However, structural investigations into molecular complexes of acridine and halobenzoic acids have not been performed so far. In general, in the CSD database there are relatively few structures of organic crystals, involving molecules/ions of these acids (10, 21, 7 and 4 structures of compounds containing molecules/ions of *ortho*-substituted benzoic acids; 11, 32, 8 and 14 structures of compounds containing molecules/ions of *meta*-substituted benzoic acids, as well as 14, 40, 20 and 11 structures of compounds containing molecules/ions of *para*-substituted benzoic acids with the fluorine, chlorine, bromine and iodine atoms, respectively, including the structures of the acids themselves).

Based on this knowledge, I synthesized and structurally characterized a series of complexes formed by acridine and: benzoic (compound **1**), 2-fluorobenzoic acid (**2**), 2-chlorobenzoic (**3**), 2-bromobenzoic (**4**), 2-iodobenzoic (**5**); 3-fluorobenzoic (**6**), 3-chlorobenzoic (**7**), 3-bromobenzoic (**8**), 3-iodobenzoic (**9**), 4-fluorobenzoic (**10**) acids. The primary purpose of my research was to determine the influence of the halogen substituent on the formation of intermolecular interactions and crystal packing in the crystals of the compounds investigated.

Single-crystal X-ray diffraction measurements have shown that all the studied complexes are co-crystals, in which a primary structural unit is a heterodimeric synthon, $O_{(acid)}$–H···$N_{(acridine)}$. The molecules of the neighbouring heterodimers are linked by $\pi_{(acridine)}$···$\pi_{(acridine)}$ interactions and $C_{(acridine)}$–H···$O_{(acid)}$=C hydrogen bonds involving hydrogen atoms bound with carbon atoms C8 and/or C9 in the acridine skeleton to form centrosymmetric heterotetramers (Fig. 1). In the co-crystal formed by acridine and benzoic acid (**1**), π–stacking interactions between aromatic rings of the acridine molecule are absent. However, the adjacent tetramers, linked by the $C_{(acridine)}$–H···$O_{(acid)}$ hydrogen bonds and $\pi_{(acid)}$···$\pi_{(acid)}$ interactions, produce layers and the neighbouring layers interact by weak $C_{(acridine)}$–H···$\pi_{(acid)}$ interactions. A similar situation has been noticed in the co-crystal formed by acridine and 4-fluorobenzoic acid (**10**), in which the adjacent tetramers in the layer are linked by the $C_{(acridine)}$–H···F and $C_{(acridine)}$–H···$\pi_{(acid)}$ hydrogen bonds and by the $\pi_{(acid)}$···$\pi_{(acid)}$ interactions. In the crystals of other compounds, in which the neighbouring tetramers interact *via* $\pi_{(acridine)}$···$\pi_{(acridine)}$ interactions, antiparallel ("head-to-tail") oriented acridine molecules are π-stacked, while the neigbouring tetrames form columns. In the co-crystals formed by acridine and *ortho*-halobenzoic acids, apart from the $\pi_{(acridine)}$···$\pi_{(acridine)}$ interactions between acridine molecules, interactions involving halogen atoms are observed ($C_{(acid)}$–H···X (**2**–**5**), $C_{(acridine)}$–H···X (**3**–**4**), F···F (**2**) and I···O–$C_{(carboxy)}$ (**5**)). In the crystals of compounds **2**–**9**, the neighbouring columns of tetramers form layers. In the crystals of complexes formed by acridine and *ortho*-halobenzoic acids, $C_{(acridine)}$–H···X (**2**–**5**), $C_{(acridine)}$–H···$O_{(acid)}$ (**3**–**5**) and $C_{(acridine)}$–H···$\pi_{(acid)}$ (**2**–**4**) interactions occur within these layers, while between the layers, $C_{(acid)}$–H···F, $C_{(acid)}$–H···$O_{(acid)}$, $C_{(acridine)}$–H···$\pi_{(acid)}$ (**2**) and $\pi_{(acid)}$···$\pi_{(acid)}$ (**3**–**5**) interactions take place. In the isostructural crystals of complexes formed by acridine and *meta*-halobenzoic acids (**6**–**9**), the $C_{(acridine)}$–H···$O_{(acid)}$ hydrogen bonds are observed within the layer (a weak $C_{(acridine)}$–H···X hydrogen bond occurs only in the crystal of compound **6**), while between neighbouring layers the $C_{(acridine)}$–H···X, $C_{(acid)}$–H···$X_{(acid)}$, $\pi_{(acid)}$···$\pi_{(acid)}$ interactions and X···O–$C_{(carboxy)}$ halogen bonds are observed.

The melting points of the co-crystals formed by acridine and *ortho*-halobenzoic acids are lower than that of acridine alone and the corresponding benzoic acids, and can be ordered as follows: **4** < **3** < **2** < **5**. Another tendency is seen for co-crystals formed by acridine and *meta*-halobenzoic acids. These compounds have higher melting points than acridine, but lower than the corresponding benzoic acids, and these follow the sequence: **6** < **7** < **8** < **9**. The melting points of compounds **6**–**9** rise with decreasing electronegativities of the halogen atoms and increasing ΔpK_a values (ΔpK_a=$pK_{a(base)}$–$pK_{a(acid)}$). With compounds **2**–**5**, it was shown that the melting points increased with increasing electronegativities of the halogen atoms and decreasing ΔpK_a. An exception is compound **5**, whose melting point is the highest among compounds **2**–**5**, and whose ΔpK_a is one of the largest. The melting point of a co-crystal formed by acridine and benzoic acid (**1**) is one of the lowest, whereas that formed by acridine and 4-fluorobenzoic acid (**10**) melts at a temperature matching that of acridine.

It was found that the melting points of co-crystals formed by acridine and benzoic acids substituted at the *ortho*-/*meta*-possition with a halogen atom depend on intermolecular interactions occurring in the crystals of the title compounds. Thus, the total number and strength of the C–H···O and C–H···π hydrogen bonds in compounds **2**–**5**

are similar to each other. However, the number of all the C–H···X hydrogen bonds decreases with decreasing electronegativities of the halogen atoms and are 6, 4, 4 and 2 for co-crystals **2**–**5**, respectively. In the co-crystal formed by acridine and 2-iodobenzoic acid (**5**), apart from the the already mentioned hydrogen bonds, there is a strong I···O–C halogen bond (the distance *d*(I···O) = 3.26 Å is shorter than the sum of the van der Waals radii of iodine and oxygen atoms, 3.50 Å). In the co-crystal formed by acridine and 2-fluorobenzoic acid (**2**), in which the highest number of C–H···X hydrogen bonds occurs, an additional F···F interaction involving a disordered fluorine atom (the distance *d*(F···F) = 2.81 Å is shorter than the sum of the van der Waals radii of the fluorine atom, 2.94 Å) was identified.

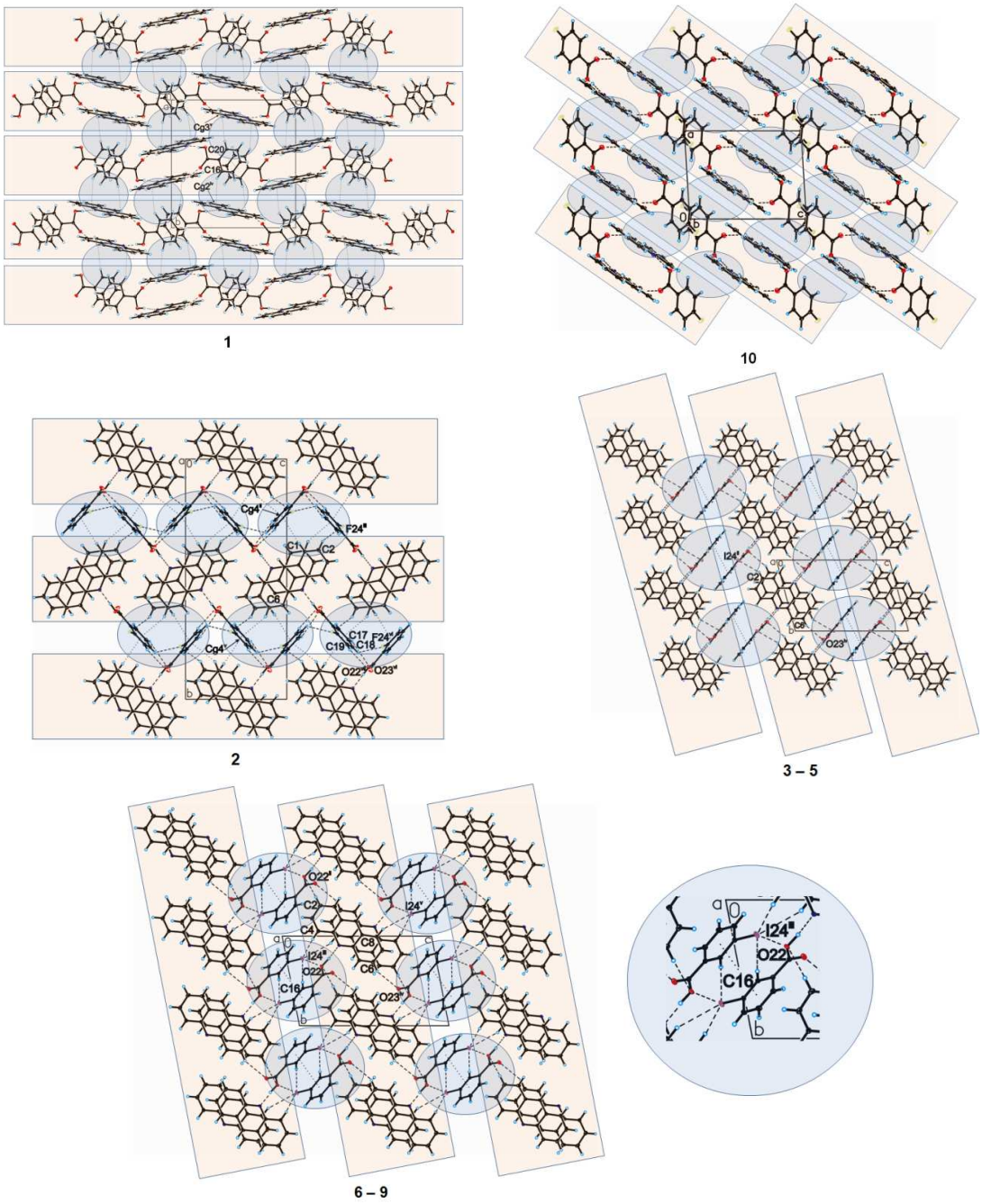


Fig. 1. Crystal packing of co-crystals formed from acridine and benzoic acid (**1**) and monohalogen-substituted benzoic acids (**2–10**).

The occurrence of those interactions in the crystal structures of compounds **2** and **5** correspond to the highest melting point of the co-crystals formed by acridine and benzoic acids substituted at the *ortho*- position with a halogen atom. With compounds **6**–**9**, the melting points increase with increasing strength of the X···O–C halogen bond, and the *d*(X···O) distances are larger by about 0.31, 0.13 and 0.05 Å (in compounds **6**–**8**, respectively), and shorter by about 0.03 Å (**9**) than the sum of the van der Waals radii of the X and O atoms. A similar relationship holds also for crystals of benzoic acids substituted by halogen atoms in the *ortho*-/*meta*- position. In crystals of these compounds, the acid molecules are π–stacked, and the C–H···X hydrogen bonds and a X···X halogen bond are observed between these stacks, the strength of these interactions either weakening (hydrogen bonds) or rising (halogen bond) with decreasing electronegativities of the halogen atoms, respectively.

In summary, in the co-crystals formed by acridine and monohalogen-substituted benzoic acids, the primary structural motif is a heterodimeric synthon, $O_{(acid)}$–H···$N_{(acridine)}$. The molecules from the neighbouring heterodimers aggregate through $\pi_{(acridine)}\cdots\pi_{(acridine)}$ interactions and $C_{(acridine)}$–H···$O_{(acid)}$=C hydrogen bonds to form heterotetramer. Such tetramers occur also in other crystal structures of multicomponent crystals of acridine with other mono-substituted benzoic acids.[40–45] An earlier research has shown that the main driving force behind the association of molecules are $\pi_{(acridine)}\cdots\pi_{(acridine)}$ interactions and occurrence of the $C_{(acridine)}$–H···$O_{(acid)}$=C hydrogen bond dependent on the arrangement (offset) of acridine molecules within the tetramer as well as the protonodonor/protonoacceptor properties and position of the substituent in the aromatc ring of acid molecule. In crystals of the analyzed compounds, an interaction with participation of halogen atoms occurs mostly either within the layer (complexes of acridine with *ortho*- and *para*-substituted benzoic acids) or between the layers (complexes of acridine with *meta*-substituted benzoic acids) in which they are arranged as tetramers. In co-crystals formed by acridine and the fluoro-, chloro- and bromo-substituted benzoic acids, an important factor determining the crystal packing are hydrogen bonds involving halogen atoms, while in the case of the complexes of acridine with iodo-substituted benzoic acids – halogen bonds. Those analyses confirm the general observation relating complexes formed by heterocyclic compounds and haloacids.[46–50]

2. 9-Aminoacridinium salts.[H2–H7]

When in 2010 I began studies on multicomponent crystals based on acridines, in the CSD there were deposited only 12 of crystal structures of compounds containing 9-aminoacridine – including 6 crystal structures of organic compounds, such as: 9-aminoacridinium chloride monohydrate (published 1974),[51] 9-aminoacridinium chloride dihydrate (1980),[52] 9-aminoacridine hemihydrate (1983),[53] two complexes of 9-aminoacidine with nitrogenous bases: adenylyl-3'-3'-uridine (1975)[54] and iodocitidylyl-(3'-5')-guanosine (1979),[55] as well as a 9-aminoacridinium salt of sulfadimidine (1988).[56] Actually, in the CSD there are 55 crystal structures of crystals involving 9-aminoacridine, and 27 of them relating to organometallic complexes in which one of the ligands is this compound (research conducted by Z. Derikvand et al.[57–59] and M. Mirzaei et al.[60–62]). My research is a first ever, regular, related to crystal structures

of organic compounds containing 9-aminoacridine. It should be emphasized that among the 28 crystal structures of organic compounds formed by 9-aminoaciridine deposited in the CSD database, as many as 19 are the result of research conducted in the framework of scientific achievement.

The primary purpose the first stage of my research concerning the multicomponent crystals formed by 9-aminoacridine, was to determine the influence of solvent molecules on interactions with participation of endocyclic nitrogen atom/amino group of a cation and halide anions. For this purpose, I synthesized and determined the crystal structure of 9-aminoacridinium: bromide monohydrate (**12**), iodide monohydrate (**13**), chloride methanolate (**14**), bromide methanolate (**15**), iodide methanolate (**16**) and fluoride dihydrate (**17**). At the same time, I synthesized and redetermined the known crystal structures of 9-aminoacridinium chloride monohydrate (**11**) and 9-aminoacridinium chloride dihydrate (**18**) (Fig. 2).

In crystals of the monohydrated 9-aminoacridinium halides (**11**–**13**), the basic structural motif is a centrosymmetric heterotetramer *bis[cation···anion]*, formed by hydrogen bonds between the amino group (–NH_2) of two 9-aminoacridinium cations and two halide anions (X^-), generating a cyclic synthon $[\cdots X^- \cdots H–N–H \cdots]_2$.[63–68] The tetramers are stabilised by weak C–H···X hydrogen bonds involving H-atoms bound with the carbon atoms C1 and/or C8 in the acridinium skeleton (these hydrogen bonds occur in all crystals of 9-aminoacridinium halides solvates and stabilize adducts formed by ions). In the isostructural crystals of 9-aminoacridinium chloride and bromide hydrates (**11**–**12**), tetramers form layers in which antiparallel oriented to each other 9-aminoacridinium cations are involved in interactions between π electrons of aromatic rings ($\pi_{(acridine)} \cdots \pi_{(acridine)}$) to form stacks. Water molecules are built into the layer in such a way that they interact with halide ions from adjacent tetramers through $O_{(water)}–H \cdots X^-$ hydrogen bonds to form centrosymmetric clusters, $[X_2(H_2O)_2]^{2-}$, and participate in the $N^+_{(acridine)}–H \cdots O_{(water)}$ hydrogen bond involving the endocyclic nitrogen atom of the cation. Alternately connected tetramers and clusters form infinite chains within the layer, and between adjacent layers weak $C_{(acridine)}–H \cdots X^-$ hydrogen bonds are observed.

In the crystal of 9-aminoacridinium iodide hydrate (**13**), the tetramers form a corrugated layer. In these layers, it can be seen that 9-aminoacridinium cations are arranged in stacks, in which the neighbouring cations are alternately rotated by an angle of about ± 130° with respect a straight line passing approximately the centre of gravity of the central rings of the acridine skeleton (cations are related *via* a crystallographic glide plane passing through the acridine skeleton). As a consequence, the dominant role in the $\pi_{(acridine)} \cdots \pi_{(acridine)}$ interactions play interactions involving π electrons of the central ring of the 9-aminoacridinium cation. The water molecules are located between the layers in such a way that they interact with halide ions from neighbouring layers *via* $O_{(water)}–H \cdots X^-$ hydrogen bond to form the previously reported centrosymmetric clusters, $[X_2(H_2O)_2]^{2-}$, and participate in the $N^+_{(acridine)}–H \cdots O_{(water)}$ hydrogen bond.

In the isostructural crystals of 9-aminoacridinium chloride and bromide methanolates (**14**–**15**), the ions form centrosymmetric adducts involving the solvent molecule *bis[cation···anion···solvent molecule]*, formed by hydrogen bonds involving –NH_2 groups of two 9-aminoacridinium cations, two halide anions and the -OH groups of two methanol molecules to form a cyclic synthon $[\cdots X^- \cdots H–N–H \cdots O_{(methanol)}–H \cdots]_2$.

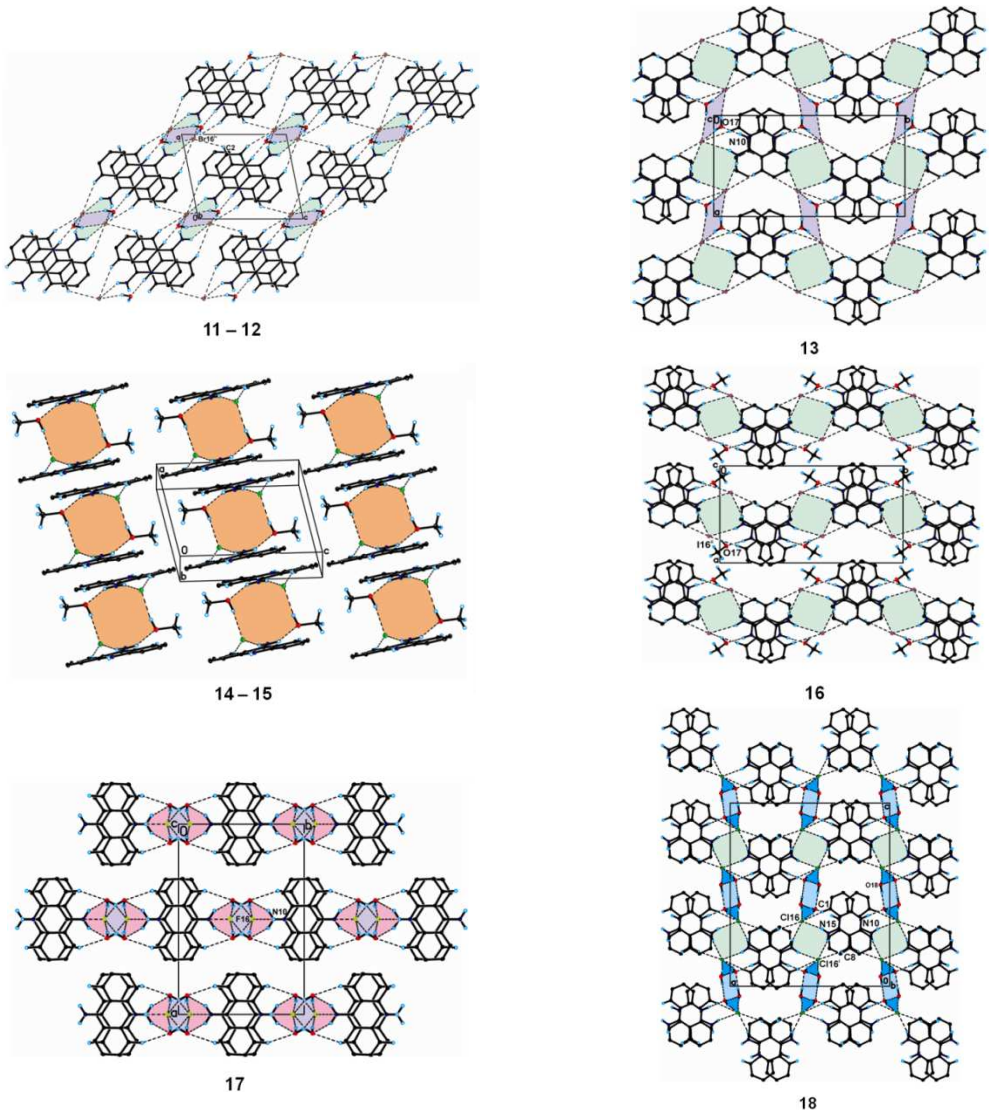


Fig. 2. Crystal packing of 9-aminoacridinium halides solvates (**11**–**18**)
(synthon $[\cdots X^{-}\cdots H{-}N{-}H\cdots]_2$ is highlighted in light green, synthon $[\cdots X^{-}\cdots H{-}N{-}H\cdots O_{(metanol)}{-}H\cdots]_2$ – in orange, synthon $[\cdots F^{-}\cdots H{-}O_{(water)}\cdots H{-}N{-}H\cdots O_{(water)}{-}H\cdots]$ – in pink, clusters $[X_2(H_2O)_2]^{2-}$ – in violet, cluster $(H_2O)_4$ – in light blue, cluster $[Cl_2(H_2O)_4]^{2-}$– in deep blue).

Adjacent adducts are arranged in layers, where the antiparallel oriented 9-aminoacridinium cations are π-stacked and are engaged in the $N^{+}_{(acridine)}{-}H\cdots X^{-}$ hydrogen bonds with halide ions, while between adjacent layers van der Waals interactions occur. The crystal of 9-aminoacridinium iodide methanolate (**16**) has a similar structure to that of isostructural 9-aminoacridinium iodide monohydrate. Replacement of the water molecules with methanol molecules results that the solvent molecules are involved only in hydrogen bonds which are stabilizing layer, $N^{+}_{(acridine)}{-}H\cdots O_{(methanol)}$ as well as $O_{(methanol)}{-}H\cdots I^{-}$, and between adjacent layers van der Waals interactions are observed.

The asymmetric unit of 9-aminoacridinium fluoride dihydrate (**17**) consists of a half-cation of 9-aminoacridinium, half anion of fluoride and one water molecule (N15, C9 H10 N10 atoms of the cation and F^{-} anion occupy a special position in the unit cell – lies on a twofold rotation axis). In a crystal of compound **17** ions form an adduct with C_2 symmetry, involving water molecules [*cation···(solvent molecule)₂···anion]*, through hydrogen bonds between $-NH_2$ groups of two cations, two water molecules and the

fluoride ion to form a cyclic synthon [···F^-···H–$O_{(water)}$···H–N–H···$O_{(water)}$–H···]. Adjacent adducts form layers, where the oriented antiparallel cations are arranged in stacks and are involved in $O_{(water)}$–H···F^- hydrogen bonds. In these layers, water molecules and fluoride ions from the adjacent adducts are involved in the $O_{(water)}$–H···F^- hydrogen bonds to form a centrosymmetric cluster $[X_2(H_2O)_2]^{2-}$, previously observed in crystals of monohydrates. Alternately connected adducts and clusters form infinite tapes within the layers, and between adjacent layers van der Waals interactions are observed.

The crystals of 9-aminoacridinium chloride dihydrate (**18**) has a similar structure to those of the 9-aminoacridinium iodide solvates – the ions are distributed around the twofold rotation axis of symmetry to form heterotetramer *bis[cation···anion]*, and adjacent tetramers are arranged in the form of a corrugated layer. In these layers, 9-aminoacridinium cations of the adjacent columns are not arranged in a parallel manner, as was the case in 9-aminoacridinium iodides, but are arranged at an angle of about 30°. This is due to the fact that the two solvent molecules are built between the layers in such a way as one water molecule is engaged in $N^+_{(acridine)}$–H···$O_{(water)}$ hydrogen bond involving the endocyclic nitrogen atom of the cation ant both water molecules participate in $O_{(water)}$–H···$O_{(water)}$ and $O_{(water)}$–H···Cl^- hydrogen bonds to form a centrosymmetric (H_2O) and $[Cl_2(H_2O)_4]^{2-}$ clusters. Both alternately connected clusters form tapes extending along the layers.

The results of research carried out by differential scanning calorimetry (DSC) and thermogravimetric analysis (TG) indicate a stepwise mass loss associated with the release of solvent molecules. Temperatures at which the solvent molecule is lost are the higher the greater electronegativity of the halide ion and are on the rise in the sequence **13** < **12** < **11** < **17** for the hydrates (for compound **17** refers to the temperature at which the second water molecule is released), and increase in the order **16** < **15** < **14** for methanolates. A similar trend is observed for the melting points of the compounds that are higher for the hydrates than for methanolates (only in the case of the bromides there is an inverse relationship). Furthermore, from the chloride solvates the loss of a water molecule occurs at a temperature lower than that of the methanol molecule, and the opposite trend is observed in the corresponding bromide and iodide solvates.

In summary, when the endocyclic nitrogen atom of the 9-aminoacridinium cation is hydrogen-bonded to the oxygen atom of the solvent molecules, in the crystals of 9-aminoacridinium halide solvates, the *bis[cation···anion]* heterotetramer emerges to form the cyclic synthon $[\cdots X^-\cdots H–N–H\cdots]_2$ (**11**–**13**, **16**, **18**). Alternately, when the endocyclic nitrogen atom is hydrogen-bonded with a halide ion, the $N^+_{(acridine)}$–H···X^- adducts appear with participation of the ion and the solvent molecule: *[cation···anion···solvent molecule]* with cyclic synthon $[\cdots X^-\cdots H–N–H\cdots O_{(methanol)}–H\cdots]_2$ (**14**–**15**) or *[cation···(solvent molecule)$_2$···anion]* to form a cyclic synthon [···X^-···H–$O_{(water)}$···H–N–H···$O_{(water)}$–H···] (**17**). Such synthons are also observed in the crystal structures of halides of other aminoacridines/heterocyclic compounds containing an amino group.[69–79] In crystals of all the compounds investigated, adducts of ions form a layer in which 9-aminoacridinium cations are arranged in stacks through interactions involving π electrons of aromatic systems. When solvent molecules are located within the layer (**11**–**12**, **14**–**15**, **17**) the adjacent 9-aminoacridinium cations in stacks are arranged in a parallel manner and layers is non-corrugated. When solvent molecules are located

within the layer (**13**, **16**, **18**) the adjacent 9-aminoacridinium cations in stacks are alternately rotated by an angle of about ± 130° with respect a straight line passing approximately the centre of gravity of the central rings of the acridine skeleton these layers are corrugated. In the crystals of hydrates a water molecules form clusters involving either halide ions $[X_2(H_2O)_2]^{2-}$ (**11**–**13**, **17**) and $[X_2(H_2O)_4]^{2-}$ (**18**) or a water cluster, $(H_2O)_4$ (**18**). Both in the case of the monohydrates and methanolates, the corrugated layer corresponds to the lowest melting points of the compounds (crystals of 9-aminoacridinium iodides).

The aim of the next step of my research on the multicomponent crystals based on 9-aminoacridine was to determine the influence of the substituent/substituents in the aromatic ring of benzoic acid on interactions involving the endocyclic nitrogen atom/amino group of cation and a carboxylate group of anion. Previous studies on the complexes of amines/amino group-substituted heterocyclic bases with carboxylic acids suggest that in crystals, such complexes can form three types of most common synthons involving these functional groups (Fig. 3).[80–82] Bearing this in mind, I obtained a series of complexes derived from 9-aminoacridine and: benzoic acid (**19**) 4-fluorobenzoic acid, (**20**) 4-chlorobenzoic acid (**21**), 3-chlorobenzoic acid (**22**), 2-hydroxybenzoic acid (**23**) 3-hydroxybenzoic acid (**24**), 1,2-benzenedicarboxylic (phthalic) acid (**25**) and 2,4-dinitrobenzoic acid (**26**–**28**) (Fig. 4). Given that five of the above salt form hydrates (**19**–**21**, **24**–**25**), a further aim was to determine the effect of the presence of water molecules on the interaction between the above-mentioned functional groups present in the crystals of these complexes.

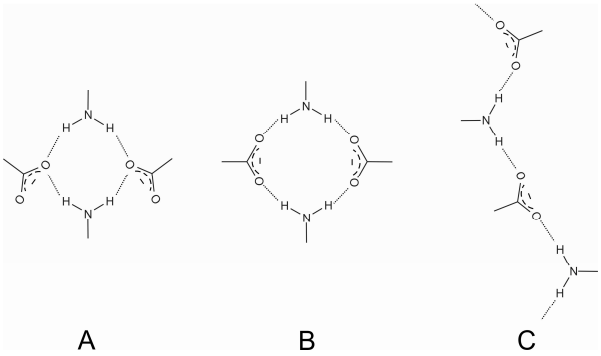


Fig. 3. Three types of most common synthons observed between amines/amino group and carboxylate group.

In the isostructural crystals of 9-aminoacridinium benzoate (**19**) and 4-fluorobenzoate (**20**) monohydrates, the primary structural motif is a *bis[cation···anion]*, formed by hydrogen bonding between the $-NH_2$ groups of two symmetrical independent 9-aminoacridinium cations and one oxygen atom of the $-COO^-$ groups of two symmetrical independent benzoate anions to forms cyclic synthon $[\cdots O^-\cdots H-N-H\cdots]_2$ (synthon A). Tetramers are also stabilized by weak $C_{(acridine)}-H\cdots O^-$ hydrogen bonds involving hydrogen atoms bonded to carbon atoms C1 and/or C8 of acridine skeleton (as in a case 9-aminoacridinium halide solvates, these interactions take place in all the 9-aminoacridinium benzoate crystals and stabilize the formed adducts of ions). The water molecules are involved in the $O_{(water)}-H\cdots O^-_{(carboxy)}$ hydrogen bonds with oxygen atoms of the $-COO^-$ groups of anions not participating in hydrogen bonds with the amino group and the $O_{(water)}-H\cdots O_{(water)}$ hydrogen bonds, resulting in short tapes connecting two

adjacent tetramers. These adducts form a layer in which 9-aminoacridinium cations are π-stacked in the sequence BAAB while water molecules are involved in the $N^{+}_{(acridine)}–H\cdots O_{(water)}$ hydrogen bond and the adjacent layers interact *via* weak $C_{(acridine)}–H\cdots\pi_{(acid)}$ (**19**–**20**) and $C_{(acid)}–F\cdots\pi_{(acid)}$ (**20**) interactions (Fig. 4).

In the crystal of 9-aminoacridinium 4-chlorobenzoate monohydrate (**21**), the cation and anion interact through the $N_{(amino)}–H\cdots O^{-}_{(carboxy)}$ hydrogen bond to form a heterotetramer *bis[cation···anion]*. However, unlike compounds **19**–**20**, the $–NH_2$ group of the cation is engaged in the hydrogen bonds involving both oxygen atoms of the $–COO^{-}$ anion to form a cyclic synthon $[\cdots(O\cdots C\cdots O)^{-}\cdots H–N–H\cdots]_2$ (synthon B). In the crystal of compound **21**, adjacent tetramers form a layer in which antiparallel oriented 9-aminoacridinium cations are arranged in stacks. Water molecules are incorporated into the layers in such a way that they interact with oxygen atoms of the group -COO- of anions from adjacent heterotetramer through the $O_{(water)}–H\cdots O^{-}_{(carboxy)}$, hydrogen bond to form a cluster $[(O\cdots C\cdots O)_2(H_2O)_2]^{2-}$, and participate in the $N^{+}_{(acridine)}–H\cdots O_{(water)}$ hydrogen bond involving the endocyclic nitrogen atom of the cation. Alternately connected tetramers and clusters form tapes within the layer, and between adjacent layers the weak $C_{(acridine)}–H\cdots Cl$ hydrogen bonds are observed.

In a crystal of 9-aminoacridinium 3-chlorobenzoate (**22**), a centrosymmetric heteroheterotetramer *bis[cation···anion]* is present as a result of a hydrogen bonds $N_{(amino)}–H\cdots O^{-}_{(carboxy)}$, to form a cyclic synthon $[\cdots O^{-}\cdots H–N–H\cdots]_2$ (synthon A), previously observed in the crystals of compounds **19**–**20**. However, only one cation and one anion is observed in the in the asymmetric unit, and adjacent tetramers are arranged in corrugated layers. In these layers, 9-aminoacridinium cations form stacks previously observed in the crystal structures of 9-aminoacridinium iodide solvates. In these layers, the endocyclic nitrogen atom is involved in the $N^{+}_{(acridine)}–H\cdots O^{-}_{(carboxy)}$ hydrogen bond with participation of oxygen atom of the carboxylate group not engaged in the hydrogen bonds involving the amino group, while van der Waals interactions between adjacent layers are observed. A similar structure has a crystal of 9-aminoacridinium 2-hydroxybenzoate (**23**), wherein as a result of multiplication of the molecules in the asymmetric unit, the ions formed two centrosymmetric heterotetramers *bis[cation···anion]*, in each attended by one cation and one anion of the asymmetric unit (in contrast to the crystals of compounds **19** and **20**, in which two cations and two anions of the asymmetric unit form a heterotetramer). Interestingly, although compound **23** crystallized in the triclinic space group, the heterotetramers formed a corrugated layer – previously seen only in the crystals of 9-aminoacridine salts crystallizing in the monoclinic (**13**, **16**, **22**) and orthorhombic (**18**) space groups. In these layers, 9-aminoacridinium cations are arranged in stacks with the sequence AB and between adjacent layers weak $C_{(acid)}–H\cdots O_{(hydroxy)}$ hydrogen bonds are observed.

Interesting results were obtained during attempted preparation of the 9-aminoacridinium 3-hydroxybenzoate salt (**24**). Namely, instead of the expected product, a mixed salt was obtained crystallizing in the monoclinic $P\,\bar{1}$ space group with two 9-aminoacridinium cations, one 3-hydroxybenzoate anion, one chloride anion, and two water molecules in the asymmetric unit. Search of the CSD databases has shown that it is the first ever described in the literature organic structure of a mixed salt formed by 9-aminoacridine.

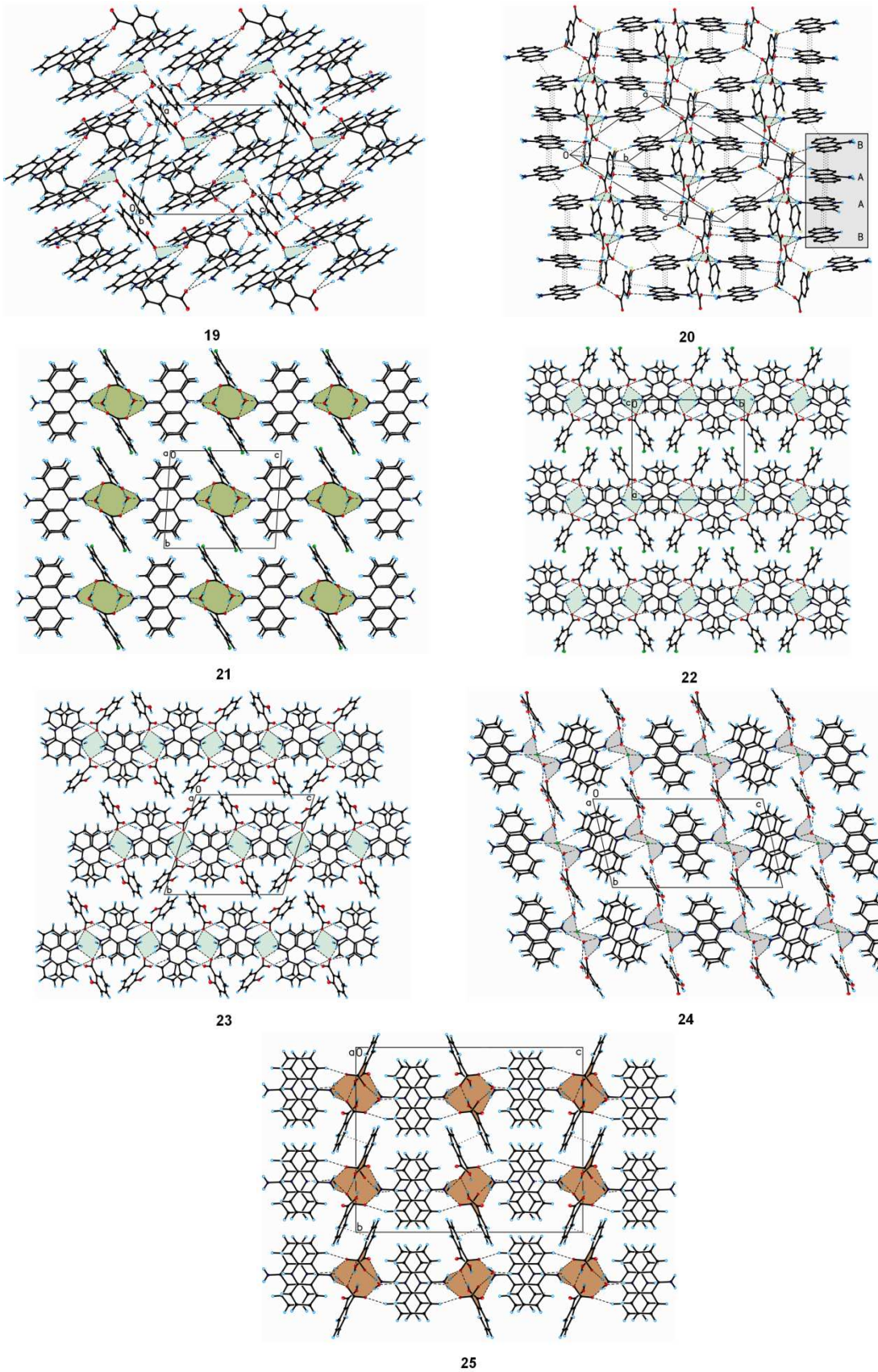


Fig. 4. Crystal packing of 9-aminoacridinium benzoates (**19**–**25**) (synthon [···O⁻···H–N–H···]$_2$ is highlighted in light green, synthon [···(O═C═O)⁻···H–N–H···]$_2$ – in deep green, synthon [···O⁻···H–N–H···Cl⁻···H–O$_{(water)}$···H–N–H···O$_{(water)}$–H···] – in grey, synthon [···(O═C═O)⁻···H–N–H···O⁻–C–C–C–C=O···H–N–H···]– in brown).

In the crystal of compound **24**, a dominant role is played by hydrogen bond involving hydroxyl and carboxylate groups, $O_{(hydroxy)}–H\cdots O^-_{(carboxy)}$, between 3-hydroxybenzoate anions which form chains. Considering the structure of the crystal of compound **24** in the context of interaction between the amino and carboxylate groups, it can be seen that the ions form a non-centrosymmetric adduct involving solvent molecules, *bis[cation···anion···solvent molecule]*. In this adduct, the $–NH_2$ group of one of the cations is involved in $N_{(amino)}–H\cdots O_{(water)}$ hydrogen bonds with two water molecules, and the $–NH_2$ group of the other cation is engaged in the $O_{(water)}–H\cdots O^-_{(carboxy)}$ and $O_{(water)}–H\cdots Cl^-$ hydrogen bonds with the chloride anion and oxygen atom of 3-hydroxybenzoate anion. The aforementioned water molecules and anions interact *via* $O_{(water)}–H\cdots Cl^-$ oraz $O_{(water)}–H\cdots O^-_{(carboxy)}$ hydrogen bonds, and this resulting in the formation of the cyclic synthon $[\cdots O^-\cdots H–N–H\cdots Cl^-\cdots H–O_{(water)}\cdots H–N–H\cdots O_{(water)}–H\cdots]$. Ions of the neighbouring adducts are involved in the $N^+_{(acridine)}–H\cdots Cl^-$, $O_{(water)}–H\cdots O_{(hydroxy)}$ hydrogen bonds and the already mentioned $O_{(hydroxy)}–H\cdots O^-_{(karboxy)}$ hydrogen bond to form layers. In these layers, antiparallel oriented 9-aminoacridinium cations are arranged in stacks in such a way that each of the cations of the asymmetric unit forms a separate stack and cations from adjacent stacks are arranged at an angle of approximately 20°. Between the layers, a $O_{(water)}–H\cdots O^-_{(carboxy)}$ hydrogen bond occurs with participation of one hydrogen atom of the water molecule and the oxygen atom of the carboxylate anion groups involved in hydrogen bonding with the hydroxyl group.

In the crystal of a monohydrated salt derived from 9-aminoacridine and 1,2-benzenedicarboxylic acid (phthalic acid) (**25**), the dominant role plays the $O_{(carboxy)}–H\cdots O^-_{(carboxy)}$ hydrogen bond with participation of the carboxyl and carboxylate groups of the anions which form chains. Ions arranged around the twofold screw axis form heterotetramers *bis[cation···anion]*, but their formation occurs through hydrogen bonding involving the amino group of the cation and the protonated and deprotonated carboxy groups of anion, and this resulting in the formation of the cyclic synthon $[\cdots(O\cdots C\cdots O)^-\cdots H–N–H\cdots O^-–C–C–C–C=O\cdots H–N–H\cdots]$. The above-mentioned $O_{(carboxy)}–H\cdots O^-_{(carboxy)}$ hydrogen bond is observed within tetramer and between neighbouring tetramers and as a result adjacent tetramers form tape. The water molecule stabilizes the tape *via* $O_{(water)}–H\cdots O^-_{(carboxy)}$ hydrogen bonds and participates in hydrogen bonding with the endocyclic nitrogen atom, $N^+_{(acridine)}–H\cdots O_{(water)}$, connecting adjacent tapes into a layer. In these layer, antiparallel oriented 9-aminoacridinium cations are arranged in stacks, and cations of adjacent stacks are arranged at an angle of approximately 54°, and between adjacent layers are $\pi_{(acid)}\cdots\pi_{(acid)}$ interactions.

Interesting are also the results of research on a salt formed by 9-aminoacridine and 2,4-dinitrobenzoic acid. This compound forms three polymorphs, which crystallize in the monoclinic $P2_1/n$ space group (polymorph I – compound **26**), and the triclinic $P\bar{1}$ space group (polymorphs II – compound **27** – and III – compound **28**). All polymorphs are co-crystals of the salt, in crystals whose asymmetric unit consists of the 9-aminoacridinium cation, a 2,4-dinitrobenzoate anion and a 2,4-dinitrobenzoic acid molecule. In the crystals of all polymorphs, the molecule and the 2,4-dinitrobenzoic acid anion are linked *via* the $O_{(carboxy)}–H\cdots O^-_{(carboxy)}$ hydrogen bond to form a negatively-charged dimer. However, these dimers have a different structure resulting from differences in mutual arrangement of the functional groups of the molecule and the

2,4-dinitrobenzoic acid anion in the crystals of polymorphs I–III. A closer examination of the CSD database has shown that there are only 15 structures of organic crystals formed by 2,4-dinitrobenzoic acid (including the structure of the acid itself), thus the structures of three polymorphs of the compound investigated were the first ever in which the negatively-charged dimers of 2,4-dinitrobenzoic acid have been identified.

In the crystals of all polymorphs of the co-crystal salt formed by 9-aminoacridine and 2,4-dinitrobenzoic acid, the cation and the 2,4-dinitrobenzoic acid dimer are linked *via* $N_{(acridine)}–H\cdots O^-_{(carboxy)}$ hydrogen bond. However, only in the crystals of polymorph II, in this hydrogen bond is engaged the same O-atom of the carboxy group which acts in the $O_{(carboxy)}–H\cdots O^-_{(carboxy)}$ hydrogen bond in the dimer. There are also hydrogen bonds with participation of the amino group of the the 9-aminoacridinium cation. In the crystal of polymorph III, the $–NH_2$ group of the 9-aminoacridinium cation is engaged in the hydrogen bonds with oxygen atoms of the carboxy and carboxylate groups of the dimer to produce a cyclic heterotrimeric synthon [···O⁻···H–O–C=O···H–N–H···].

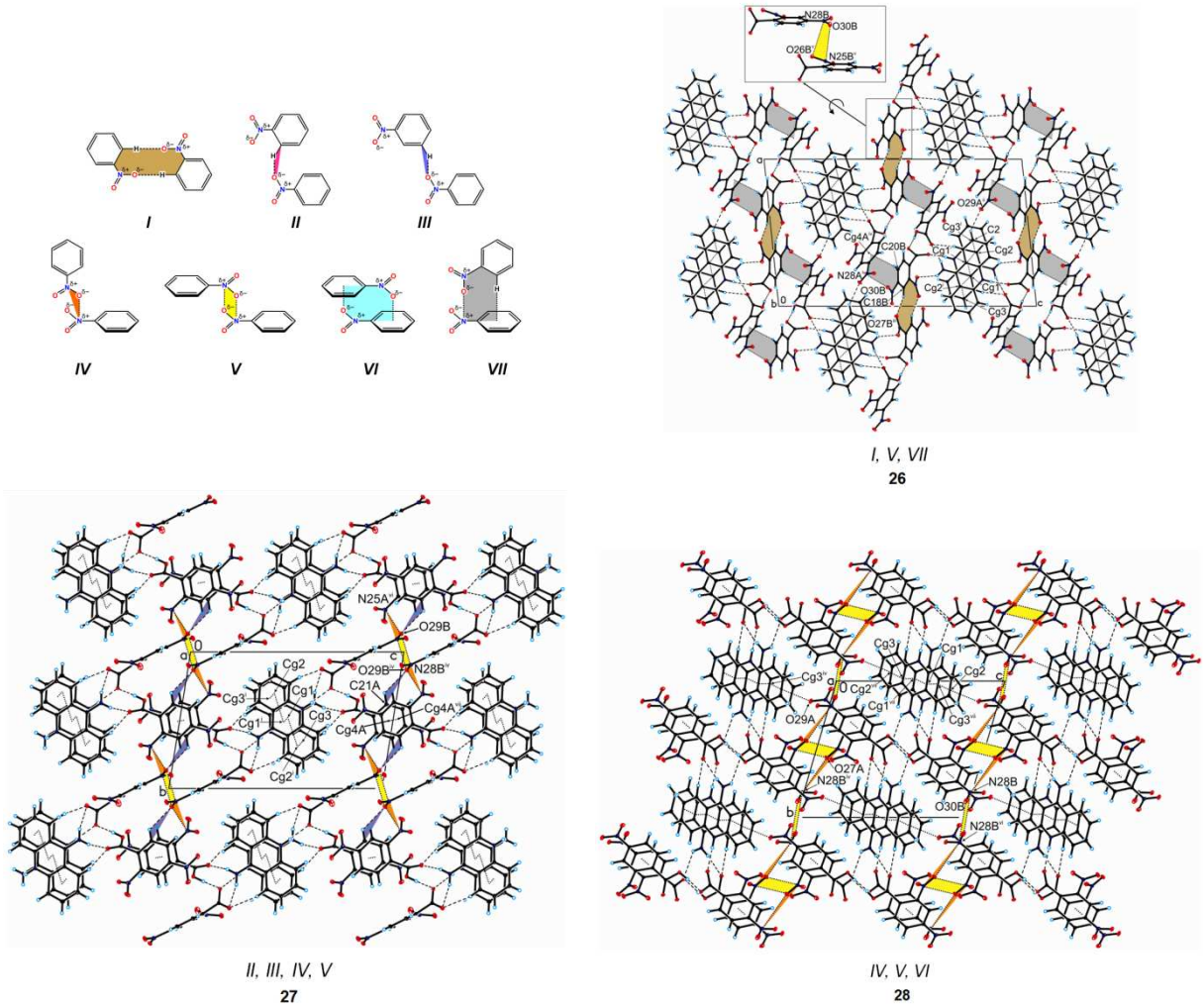


Fig. 5. Crystal packing of three polymorphs of the co-crystal salt formed by 9-aminoacridine and 2,4-dinitrobenzoic acid (**26**–**28**).

The heterotrimeric synthon has also been identified in the crystal of polymorph I, in which one H-atom of the amino group of cation participates in the $N_{(amino)}–H\cdots O_{(carboxy)}=C$ hydrogen bond with oxygen atom of the carboxy group of acid

molecule, while the other is involved in $N_{(amino)}$–H···$O_{(nitro)}$ hydrogen bond with oxygen atom of the *ortho*-nitro group of the 2,4-dinitrobenzate anion. In the case of polymorph II, the $-NH_2$ group of the cation is engaged in the $N_{(amino)}$–H···$O_{(carboxy)}$=C and $N_{(amino)}$–H···$O^-_{(carboxy)}$ hydrogen bonds in which two dimers of the acid. Moreover, apart from above-mentioned interactions, the 9-aminoacridine cation and the 2,4-dinitrobenzoic acid dimer interact *via* $C_{(acridine)}$–H···$O_{(nitro)}$ hydrogen bonds (polymorph I) and N–O···$\pi_{(acridine)}$ interactions (polymorph III) with participation of the *para*-nitro group of the 2,4-dinitrobenzoic acid molecule. In the crystals of all polymorphs, the neighbouring 9-aminoacridine cations interact by π–stacking interactions, whereas the neighbouring dimers of 2,4-dinitrobenzoic acid are linked *via* $\pi_{(acid)}$···$\pi_{(acid)}$ interactions (polymorphs II and III) and the following seven types of interactions involving nitroarene fragments of ions/molecules of acid: $C_{(acid)}$–H···$O_{(nitro)}$ (type *I*), N–O···$N_{(nitro)}$ (type *V*) and $C_{(acid)}$–H···$\pi_{(acid)}$ and N–O···$N_{(nitro)}$ (type *VII*) in polymorph I; $C_{(acid)}$–H···$O_{(nitro)}$ (type *II* and type *III*) and N–O···$N_{(nitro)}$ (type *IV* and type *V*) in polymorph II and N–O···$N_{(nitro)}$ (type *IV* and type *V*) and N–O···$\pi_{(acid)}$ (type *VI*) in polymorph III (Fig. 5). In the crystals of polymorphs I and II, dimers of 2,4-dinitrobenzoic acid form corrugated layers between which π-stacked 9-aminoacridine cations are arranged, while in the crystal of the polymorph form III, the dimers form a porous organic framework in voids of which the π-stacked 9-aminoacridine cations are located.

In summary, from my research it follows that in the crystals of 9-aminoacridinium the heterotetramers are formed by hydrogen bonds involving the amino group and either one (**19**–**20**, **22**–**23**) or two (**21**) oxygen atoms of the carboxylate anion or oxygen atoms of carboxyl and carboxylate groups of anion (**24**). Synthons corresponding to these interactions also occur in the crystal structure of other complexes containing amines/amino-substituted heterocyclic compounds and aromatic carboxylic acids.[37,63,80–90] If in the crystals of the compounds a water molecule is present (**19**–**21, 24**–**25**), it locates itself within the non-corrugated layer formed by adducts of the ions, and takes part in $N^+_{(acridine)}$–H···$O_{(water)}$ hydrogen bond with the endocyclic nitrogen atom, and in $O_{(water)}$–H···$O^-_{(carboxy)}$ hydrogen bond with carboxylate/carboxy groups. Only in the crystal of mixed salt (**25**), the water molecules participates in hydrogen bonding with amino group $N_{(amino)}$–H···$O_{(water)}$ and with ions, $O_{(water)}$–H···X^-, whereas the endocyclic nitrogen atom is engaged in $N_{(acridine)}$–H···Cl^- hydrogen bond with chloride ion. If there is no water molecules (**22**–**23**), one of the oxygen atom of the carboxylate group is involved in hydrogen bonding with the amino group, $N_{(amino)}$–H···$O^-_{(carboxy)}$ **,** and the other in hydrogen bond with the endocyclic nitrogen atom, $N^+_{(acridine)}$–H···$O^-_{(carboxy)}$, to form a corrugated layer of tetramers. An additional protonodonor group on the aromatic ring of benzoic acid, may (**24**–**25**), but need not (**23**) be competitive with the amino group in the context of interaction with oxygen atoms of the carboxylate anion. The presence of the negatively-charged dimers of the acid in the crystals of three polymorphs of the co-crystal salt formed by 9-aminocridine and 2,4-dinitrobenzoic acid (26–28) causes that the ions do not form heterotetramers via hydrogen bonds with participation of the amino groups and carboxyl/carboxylate groups, and that the nitro groups may interact with the amino group of the 9-aminoacridine cation.

The aim of the next stage of my research was to obtain crystals formed by 9-aminoacridine and phospholipids, main components of the lipid membranes. Understanding the structures of these compounds could provide preliminary information about expected interaction of 9-aminoacridine with cell membranes. Unfortunately, I failed to obtain crystals of such systems, which would be suitable for structural studies. Alternatively, I carried out successful attempts to obtain the salts derived from 9-aminoacridine and sodium dodecyl sulfate – a surfactant used in physicochemical studies as a simple model of the negatively-charged lipid membrane. A closer examination of the CSD database has shown that there are only 12 crystal structures of salts that contain a dodecyl sulfate anion, and the crystal structure of the title compound is the first ever to contain the anion and a cationic organic dye.

In the crystal of 9-aminoacridinium dodecyl sulfate (**29**), 9-aminoacridinium cations are arranged in stacks previously identified in the crystals of 9-aminoacridinium salts, where corrugated layers of tetramers are observed, whereas the neighbouring dodecyl sulfate anions interact *via* weak C–H···$O_{(sulfate)}$ hydrogen bonds and van der Waals interactions to form monolayers. The surface of the monolayer is corrugated and a shallow groove and a deep groove could be spotted on it (Fig. 6). On surface of these monolayer, we can distinguish a "shallow groove", and a "deep groove". Π–stacked 9-aminoacridinium cations are located on the surface of the monolayers formed by the anions, in such a way that in the shallow groove the ions interact with dodecyl sulfate ions *via* $N_{(amino)}$–H···$O^-_{(sulfate)}$ hydrogen bonds. In turn, there is a $N_{(acridine)}$–H···$O^-_{(sulfate)}$ hydrogen bond between the cations and anions in the shallow groove. In the context of interactions between the amino and sulfate groups, it could be found that the 9-aminoacridinium cations of the neighbouring stacks and the dodecyl sulfate anions of the neighbouring monolayers formed a centrosymmetric cyclic tetrameric synthon $[\cdots O^- \cdots H–N–H \cdots]_2$, – typical of the hydrogen bonds between the amino and sulfate/sulfonate groups.[91–93] An analysis of arrangement of dodecyl sulfate in 12 crystal structures deposited in the CSD database shows that the monolayers occur in two salts, whereas bilayers are present in the crystals of seven compounds. Mixed anionic-cationic monolayers occur in the crystals of two compounds, whereas in the crystal structure of one compound the layers are missing. Analysis of parameters characterizing the crystal packing of the dodecyl sulfate anions[94] shows that in the title compound the average surface area occupied by a single dodecyl sulfate anion in a crystallographic plane parallel to the layer surface formed by these ions is 0.30 nm^2, whereas the average surface charge density of sulfate groups in this plane is 1.67 e^-/nm^2. For comparison, in the crystal structures deposited in the CSD, these values fall in the ranges of 0.22–0.23 nm^2

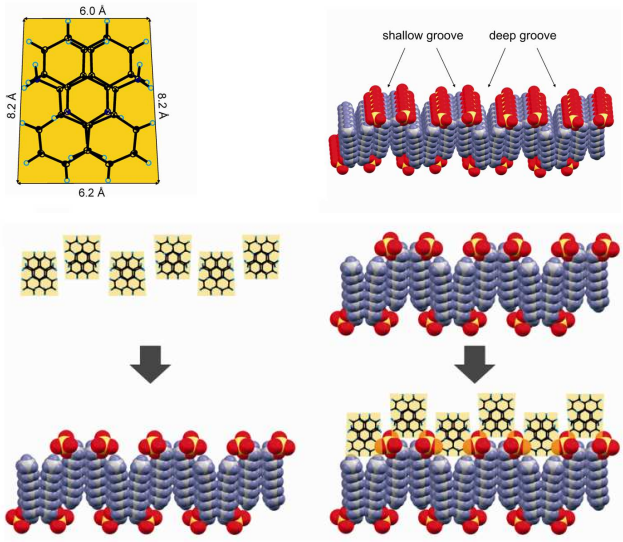
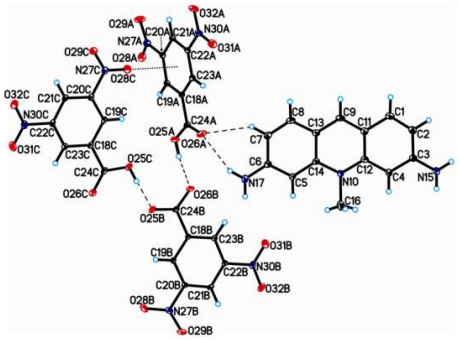


Fig. 6. Crystal packing of compound **29**.

and 2.17–2.27 e^-/nm^2 and of 0.27–0.42 nm^2 and 2.51–3.97 e^-/nm^2 for compounds in which monolayers and bilayers of the dodecyl sulfate anions are being formed, respectively.

In summary, the arrangement of dodecyl sulfate anions in the crystal of 9-aminoacridinium dodecyl sulfate represents a new type of self-assembled monolayers of dodecyl sulfate in the crystals and has not been reported so far in other structures containing this anion. The large average surface area occupied by a single dodecyl sulfate anion, and the low average surface charge density of the sulfate groups in a crystallographic plane parallel to the layer surface is associated with the surface matching of monolayer of anionic surfactant and π-stacked 9-aminoacridinium cations. An analysis of the interactions occurring between ions in the crystal structure of compound **29** may be helpful for understanding interactions of aminoacridines in the biological systems and for designing surfactant - dye systems containing other acridines.

3. Multicomponent crystals involving other acridines.[H8]



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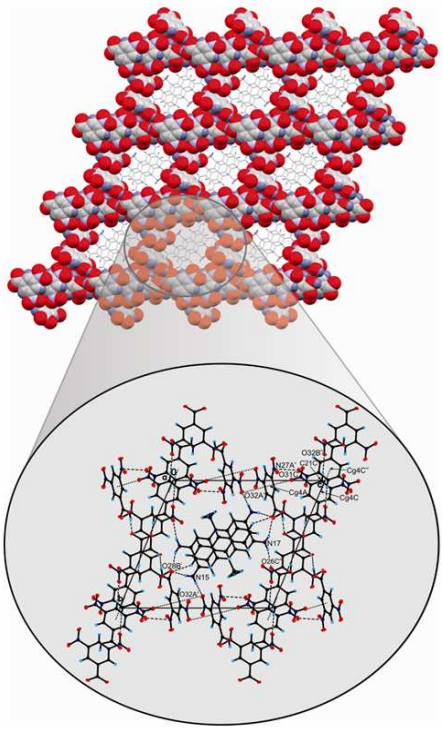

Fig. 7. Crystal packing of compund **30**.

The upshot of research during the last decades has demonstrated that we are now familiar with structures of multicomponent crystals based on different aminoacridines, such as those containing 9-aminoacridine, proflavine[95–96] and acridine orange.[97–98] To date, however, there have been no reports on the crystal structures of acridines, compounds important from the biological activity point of view. This conclusion refers also to acriflavine (3,6-diamino-10-methylacridinium chloride), a compound exhibiting interesting properties, such as antibacterial, antitumour and antiamoebic activities.[99–101] Therefore, I tried to obtain the crystals derived from acriflavine and a variety of mono- and di-substituted benzoic acids. As a result of over 100 syntheses, I obtained the crystals only in one case. It was a compound formed by acriflavine and 3,5-dinitrobenzoic acid (**30**). Single-crystal X-ray diffraction measurements have shown that the compound **30** is a co-crystal of a salt which forms triclinic crystals ($P\bar{1}$ space group) with one cation of acriflavine, one 3,5-dinitrobenzoate anion and teo 3,5-dinitrobenzoic acid molecules in the asymmetric unit (Fig. 7). In the crystal of compound **30**, the molecules and anion of 3,5-dinitrobenzoic acid form a negatively-charged trimer *via* $O_{(carboxy)}–H\cdots O_{(carboxy)}$ hydrogen bonds. The structure of the trimer is stabilized

by N–O···$\pi_{(acid)}$ interactions occurring between both molecules of 3,5-dinitrobenzoic acid. The neighbouring trimers are further linked *via* interactions involving nitroarene fragments: $C_{(acid)}$–H···$O_{(nitro)}$, N–O···$\pi_{(acid)}$, N–O···$N_{(nitro)}$ and $\pi_{(acid)}$···$\pi_{(acid)}$. As a result of all these interactions, a porous organic frameworks can be formed by the molecules and anion of 3,5-dinitrobenzoic acid in the voids of which antiparallel oriented π-stacked acriflavine cations are located. These columns are linked to the porous organic framework of the acid by $N_{(amino)}$–H···O hydrogen bonds. Interestingly, only one amino group of the acriflavine cation is engaged in the $N_{(amino)}$–H···$O_{(carboxy)}$=C hydrogen bond with carboxy groups of 3,5-dinitrobenzoic acid molecules to produce a cyclic $[\cdots H–N–H\cdots O=C–O–H\cdots(O\cdots C\cdots O)^{-}\cdots H–O–C=O\cdots]_2$ synthon, while the other $–NH_2$ group interacts *via* $N_{(amino)}$–H···$O_{(nitro)}$ with the nitro groups.

In summary, examination of the CSD database has shown that this is the first ever crystal structure of a compound containing the acriflavinium cation, as determined by X-ray diffraction method. The structure of the title compound is also interesting from the supramolecular chemistry point of view. This is because in the CSD database, there are deposited the crystal structure of one complex only, in which the negatively-charged 3,5-dinitrobenzoic acid trimer appears.[102] Moreover, based on structural investigations of compounds **26**–**28** and **30** and inspection of the CSD database it can be concluded that an aromatic carboxylic acid substituted with nitro groups might have been a "convenient" component for the preparation of multicomponent crystals based on acridines, also in the case of acridines whose crystal structure has not yet been determined.

Summary

An outstanding achievement resulting from implementation of my research is the synthesis of 30 multicomponent crystals based on acridines, determination of their crystal structure using a single-crystal X-ray diffraction method, and a detailed analysis of intermolecular interactions occurring between individual components of the compounds obtained.

Specific achievements resulting from the implementation of my research are described below.

1. Synthesis of ten co-crystals formed by acridine and benzoic acids(**1**–**10**), determination of their crystal structures, exploration of the influence of the halogen substituents in the aromatic ring of benzoic acid on the formation of intermolecular interactions in the crystals, and determination of the influence of those interactions on the melting points of the compounds investigated **[H1]**, **[H2]**.

2. Synthesis of eight solvates of 9-aminoacridinium halides (**11**–**18**), determination of their crystal structures, determination of the influence of the solvent molecules on the interactions between ions in the crystals, and determination of thermal stability of the compounds investigated **[H3]**.

3. Synthesis of seven salts derived from 9-aminoacridine and mono-substituted benzoic acids (**19**–**25**), determination of their crystal structures and exploration of the influence

of the substituent in the aromatic ring of benzoic acid on interactions between ions in the crystals of the compounds investigated **[H2]**, **[H4]**, **[H5]**.

4. Synthesis of three polymorphs of a co-crystal of a salt derived from 9-aminoacridine and 2,4-dinitrobenzoic acid (**26**–**28**), determination of their crystal structures, identification and analysis of intermolecular interactions, especially those involving the nitro groups, occurring in the crystals of the compounds investigated **[H6]**.

5. Synthesis of 9-aminoacridinium dodecyl sulfate (**29**), determination of its crystal structure, analysis of intermolecular interactions between ions occurring in the crystal and analysis of parameters characterizing the packing of the dodecyl sulfate anions in the crystal of compound investigated **[H7]**.

6. Synthesis of a multicomponent crystal formed by acriflavine and 3,5-dinitrobenzoic acid (**30**), determination of its crystal structure, and identification and analysis of intermolecular interactions occurring in the crystal of the compound investigated **[H8]**.

Investigations conducted within the framework of scientific achievement are important from the cognitive point of view and enrich the knowledge of the synthesis, structure and properties of complexes containing acridine. They also a source of information about interactions between acridines and other compounds containing different functional group. This is important for an understanding the specific properties of acridine derivatives related to their ability to interact with macromolecules in biological systems. This research may also be of practical importance, from the crystal engineering point of view, in the context of design of new crystalline materials based on acridine derivatives.

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Artur Sikorski