Synthesis, crystal structures, properties and caries prevention efficiency of 2-, 3-, 4-carboxymethylpyridinium hexafluorosilicates

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ABSTRACT

Three pyridinium hexafluorosilicates with the compositions $(LH)_2[SiF_6]$ (**I, II, III**, where L = 2-, 3-, 4-carboxymethylpyridine) were obtained as crystalline solids upon interaction of hexafluorosilicic acid with isomeric carboxymethylpyridines. All compounds were characterized by elemental analysis, IR, NMR ^{19}F and mass-spectrometry, solubility data, and X-ray crystallography. The binary ionic solids are stabilized by the interplay of intermolecular interactions including strong charge assisted and conventional hydrogen bonds of the NH···F, and OH···O types along with CH···F contacts and π–π stacking interactions. The different supramolecular motifs in **I-III** are dictated by the different arrangement of the principal binding sites in the isomeric carboxymethylpyridines. The relationship between the salts structure and solubility data is discussed. All hexafluorosilicates reduce the depth and the number of dental caries, and provide efficiency of caries prevention up to 45%.

1. Introduction

Nowadays, the tooth decay is one of the most common diseases [1], while for the childhood this pathology ranks first among chronic diseases and has a pandemic character. In the arsenal of treatment and prevention of caries, the key positions occupy inorganic fluorides, including sodium and potassium fluorides, tin difluoride, sodium monofluorophosphate, and silver diammine fluoride, $[Ag(NH_3)_2]F$ (SDF) [2]. In recent years, researchers from Japan and the USA have announced ammonium hexafluorosilicate, $(NH_4)_2[SiF_6]$ (AHF) as a promising caries preventive agent [3–9]. Unlike SDF, AHF does not cause staining of hard tooth tissues [10] and provides acid resistance of tooth enamel and dentin [3], prolonged occlusion of tubul dentin [4], and increases the crystallinity of tooth enamel [5,6]. The specificity of the action of AHF as a caries prophylactic and hyposensitive agent is as follows: in saliva (biological fluid) environment, AHF is hydrolyzed to form a soluble form of silica which catalyzes the precipitation of a mixture of fluorapatite and calcium fluoride [4,7], and the formation of the crystalline precipitate stable in saliva. In principle, the effectiveness of the anti-caries action of salts with the $[SiF_6]^{2-}$ anion can be increased by using hexafluorosilicates with biologically active "onium" cations. In this case, it becomes possible to enhance the caries-preventive action of the fluoride component as a result of specific (pharmacological, physicochemical) cation effects [11]. In particular, the search for new

potential anti-caries agents in the series of hexafluorosilicates whose cations exhibit bactericidal and anti-inflammatory activity is important in a complex of measures in the treatment and prevention of caries [12,13].

This contribution is addressed to the synthesis, study of the structure, properties and caries prevention effect of 2-, 3-, 4-carboxymethylpyridinium hexafluorosilicates, whose organic cations are expected to exhibit anti-inflammatory activity based on the PASS-prognosis [14].

2. Results and discussion

2.1. Crystal structures

All compounds were obtained by interaction of relevant N-base with hexafluorosilicic acid in aqueous solution. Crystal structure and refinement data for **I–III** are given in Table 1, hydrogen bonding geometry is summarized in Table 2. The formula units for **I-III** are shown in Fig. 1. Compounds **I–III** have the 1:2 acid : base ratio and crystallize in the monoclinic centrosymmetric space groups $P2_1/n$ (**I**), $P2_1/c$ (**II**), and $I2/a$ (**III**) with the $[SiF_6]^{2-}$ anion occupying positions on inversion centers in **I**, **II** and on a two-fold axis in **III**. On the molecular level, the changes in the geometry of components are identical to those previously reported for the related hexafluorosilicates, since the proton

Table 1
Crystal data and structure refinement parameters for **I-III**.

Compound	I	II	III
Empirical formula	$(C_{14}H_{16}N_2O_4)SiF_6$	$(C_{14}H_{16}N_2O_4)SiF_6$	$(C_{14}H_{16}N_2O_4)SiF_6$
Formula weight	418.38	418.38	418.38
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$I2/a$
Unit cell dimensions			
a, Å	7.3852(7)	7.8540(9)	13.5599(8)
b, Å	14.5692(10)	13.4503(14)	7.5462(5)
c, Å	8.3778(8)	7.7836(9)	17.1896(11)
β,°	113.869(12)	92.697(10)	109.959(7)
Volume, Å³	824.33(14)	821.33(15)	1653.3(2)
Z	2	2	4
$D_{\text{(calc)}}$ Mg/m³	1.686	1.692	1.681
μ, mm-1	0.233	0.234	0.232
$F(000)$	428	428	856
Reflections collected	2616	3651	2677
Independent reflections	1447	1455	1529
	[R(int) = 0.0226]	[R(int) = 0.0229]	[R(int) = 0.0167]
Data/restraints/ parameters	1447/0/133	1455/0/132	1529/0/131
Goodness-of-fit on F^2	1.044	1.004	1.040
Final R indices [$I > 2\sigma(I)$] R_1, wR_2	0.0367, 0.0878	0.0608, 0.1576	0.0358, 0.0854
R indices (all data) R_1, wR_2	0.0457, 0.0931	0.0714, 0.1648	0.0469, 0.0919

transfer to the pyridine nitrogen atom is clearly indicated by the widened C−N−C bond angles in the aromatic rings falling in the range 121.8(2)–123.6(4)°. The unionized character of the carboxylic group is proven by differentiation of the C−O distances adjusting the values of 1.190(3)–1.193(4) Å for C=O, and 1.312(2)–1.325(2) Å for C−O(H) bonds, and involvement of these groups in the O−H⋯F hydrogen bonds. The hexafluorosilicate anion in the structures has the geometry of the distorted octahedron with the Si–F distances running from 1.655(1) till 1.695(1) Å. Three isomeric carboxymethylpyridinium cations have angular geometry with the dihedral angle between the pyridinium core and carboxylic group adjusting the values 47.4° in **I**, 45.9° in **II**, and 48.1° in **III**. The ionic species are held together in the

three-membered formula units *via* a couple of charge-assisted $NH^{+}\cdots F^{-}$ hydrogen bonds, N⋯F distances varying in the range 2.683(2)- 2.825(4) Å (Fig. 2, Table 2).

Both components, that are three isomeric carboxymethylpyridinium cations with the different arrangement of the principal binding centers, and $[SiF_6]^{2-}$ anions mediate in the crystals. Each cation bridges two anions acting besides the above mentioned NH⋯F H-bonds also *via* COOH⋯F H-bonds, for which the O⋯F distances fall in the range 2.583(3) − 2.6525(18) Å, while each anion binds four cations. These motifs are realized as three-dimensional H-bonded network in **I**, one-dimensional double tapes in **II**, and two-dimensional layers in **III** (Fig. 2). No stacking interactions have been observed in **I**. The π-π stacking patterns between the partially overlapping cations are different in **II** and **III**: in **II** such interactions are realized in the forms of infinitive stacks between cations that belong to the adjacent chains (Cg⋯Cg = 3.977 Å), while in **III** they act within the centrosymmetric dimers (Cg⋯Cg = 3.798 Å) that are generated due to the double-fold interpenetration of the H-bonded layers. The numerous CH⋯F contacts with the range of C⋯F distances within 3.088(5) − 3.516(4) Å contribute to the effective crystal packing as concluded from the high Kitaigorodskii index values of 74, 74.1 and 73.9 for **I-III**, and is confirmed by the close values of crystal densities in **I-III** (Table 1).

2.2. Selected physico-chemical properties

2.2.1. Solubility in water

The water solubility is a fundamental physico-chemical characteristic of drugs [15] since the solubility evaluation is a necessary standard procedure for all drug candidates. The relationship between the solubility C (mol. %) and the structure of pyridinium hexafluorosilicates was reported [16,17], and the parameter h was proposed as a structural characteristic of salts:

$$h = n/d(\text{D}\cdots\text{A})_{\text{av.,}} \qquad (1)$$

In eq. (1) n is the number of strong and medium H-bonds (D⋯A ≤ 3.2 Å [18]), $d(\text{D}\cdots\text{A})_{\text{av.}}$ is an average donor-acceptor distance in the complex structure. Table 3 summarizes the solubility of salts **I-III** and of the other previously studied pyridinium hexafluorosilicates [16,17], as well as the values of h parameter. As it follows from Table 3, the solubility data for compounds **I-III** fit well into the previously observed tendency to an exponential decrease in the solubility of salts of pyridinium cations with an increase the number of H-bonds (an

Table 2
Hydrogen bonds for **I-III** [Å and °].

D-H⋯A	d(D-H)	d(H⋯A)	d(D⋯A)	∠(DHA)	Symmetry transformations used to generate equivalent atoms:
I					
N(1) − H(1N1)⋯F(1)	0.93(3)	1.75(3)	2.683(2)	176(2)	3/2-x, y + 1/2, 1/2-z
O(1) − H(1O1)⋯F(2)	0.86(3)	1.74(3)	2.600(2)	171(3)	x, y, z
C(2) − H(2A)⋯F(3)	0.97	2.45	3.279(3)	143.7	x + 1/2, 1/2-y, z + 1/2
C(6) − H(6)⋯F(2)	0.93	2.48	3.191(3)	133.6	3/2-x, y + 1/2, 3/2-z
C(7) − H(7)⋯O(2)	0.93	2.38	3.283(3)	163.4	3/2-x, y + 1/2, 3/2-z
II					
O(1) − H(1O1)⋯F(1)	0.85(5)	1.74(5)	2.583(3)	171(5)	x, y, z
N(1) − H(1N1)⋯F(2)	0.85(5)	2.03(5)	2.825(4)	155(5)	-x, 2-y, 1-z
C(2) − H(2A)⋯F(1)	0.97	2.52	3.146(4)	122.5	1-x, 2-y, 1-z
C(2) − H(2A)⋯F(3)	0.97	2.55	3.516(4)	177.6	1-x, 2-y, 1-z
C(2) − H(2B)⋯F(3)	0.97	2.38	3.305(4)	158.8	1-x, y-1/2, 1/2-z
C(6) − H(6)⋯F(3)	0.93	2.50	3.088(5)	121.7	−x, 2-y, 1-z
III					
N(1) − H(1N1)⋯F(2)	0.92(3)	1.78(3)	2.692(2)	176(3)	1-x, y + 1/2, 1/2-z
O(1) − H(1O1)⋯F(1)	0.89(3)	1.77(3)	2.6525(18)	173(3)	x + 1, y, z
C(2) − H(2A)⋯F(2)	0.97	2.53	3.282(2)	133.9	1-x,-y,-z
C(2) − H(2B)⋯F(1)	0.97	2.59	3.291(3)	129.3	1-x, 1-y, −z
C(5) − H(5)⋯F(3)	0.93	2.46	3.118(2)	127.5	1-x, y + 1/2, 1/2-z
C(5) − H(5)⋯O(2)	0.93	2.45	3.069(3)	124.4	x-1/2, 1-y, z
C(6) − H(6)⋯O(1)	0.93	2.59	3.298(3)	133.1	x, 1/2-y, z + 1/2