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SYNTHESIS, CRYSTAL STRUCTURES, SOLUBILITY AND BIOLOGICAL ACTIVITY OF 2-, 3-, 4-CARBOXYETHYL PYRIDINIUM HEXAFLUOROSILICATES

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Introduction. The fluoride-containing medical preparations dominate in the contemporary list of drugs for treatment and prevention of caries. Their efficacy and safety have been confirmed by results of clinical trials, as well as by many years of practical use [1, 2]. In recent years, research teams from different countries have identified ammonium hexafluorosilicates as promising caries preventive agents [3].

Aim. The aim of this work is to synthesize, study the structure, spectral characteristics, solubility and biological activity of 2-, 3-, 4-carboxyethylpyridinium hexafluorosilicates as new potential anti-caries agents.

Materials and Methods. H_2SiF_6 (45 %, “pure for analysis”, Reakhim), 2-, 3-,

4-pyridinepropionic acid (L^1, L^2, L^3; 97, 98, 97 %, respectively, Sigma Aldrich), ammonium hexafluorosilicate ("pure for analysis", Reakhim) and sodium fluoride ("pure for analysis", Reakhim) were used without further purification. The salts with the compositions $(L^{1–3}H)_2SiF_6$ (**I-III**, respectively) where obtained by the interaction of corresponding pyridines in methanol solution with fluorosilicic acid in mole ratio L : H_2SiF_6 = 1 : 3.5. The product yield is 98 % in the case of **I**, 99 % in the case of **II** and 95 % in the case of **III**. All compounds were characterized by elemental analysis, IR, NMR ^1H, ^{19}F and mass-spectrometry, solubility data, and X-ray crystallography. Gels containing fluoride preparations NaF, $(NH_4)_2SiF_6$ (AHFS) and **I-III** were prepared on the basis of carboxymethylcellulose gel (sodium salt). The concentration of each drug in the gel corresponded to a fluoride dose of 1.88 mg / kg. The experiments were performed on 35 white Wistar rats (females, 1 month, average live weight 40 ± 1.5 g) distributed into 7 equal groups. Rats of 2-7 groups were kept on Stephan's cariogenic diet (CGD) (sucrose 50 %). All rats of experimental groups (groups 3-7) and control group (group 2) received oral gels with preparations at a dose of 0.3 ml per day for 30 days (excluding Sundays), covering the teeth and gums with gel. After the application, rats were not fed for 1 hour. The details of biological experiments have been described previously [4].

Results and discussion. According to X-ray data, the crystal structures of salts **I-III** are stabilized by the systems of NH·F, OH·F inter-ionic H-bonds and C–H·F contacts (Fig. 1, 2). The $SiF_6^{2–}$ anions in **I-III** have the slightly distorted octahedral geometry with the Si–F distances ranging within 1.647(3)-1.694(1) Å (Fig. 1).

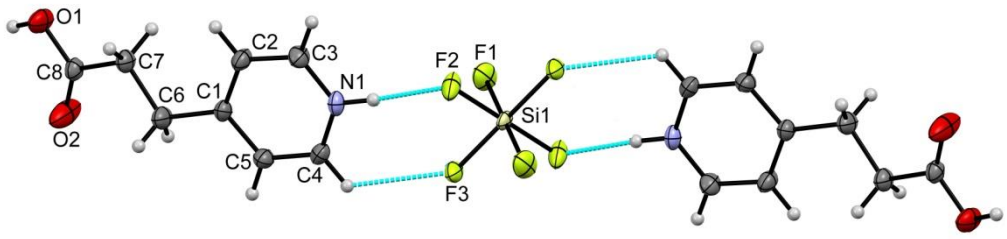

Fig. 1. View of formula unit in III.

Proton transfer to the pyridine N-atom is clearly indicated by the widened C–N–C bond angles in the pyridinium rings falling in the range 122.1(2)-123.4(3)°.

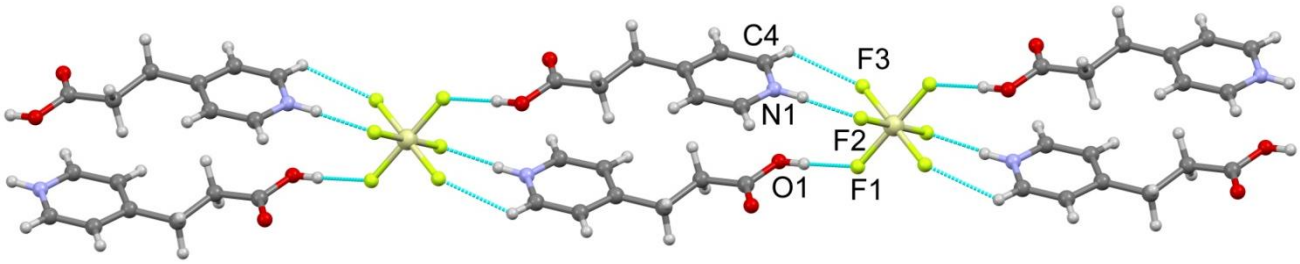

Fig. 2. Fragment of H-bonded chains in III.

In IR spectra for **I-III** deformation vibration $\delta(SiF_2)$ for the anion in the form of doublet were registered in the range 480-440 cm^{-1}. The multiple character of the $\delta(SiF_2)$ vibrations were in agreement with the X-ray data indicating the distortion of the octahedral geometry of the SiF_6^{2-} anions in **I-III** due to inter-ionic H-bonds. The ^{19}F NMR spectra of aqueous solutions **I-III** show the single resonance at –133.35, –131.43, –129.02 ppm respectively accompanied by two silicon satellites with coupling constant $J(^{29}Si–^{19}F)$ = 107.5 Hz (**II**) and 107.6 Hz (**III**).

Assessment of solubility in water and organic solvents is a mandatory procedure for all drug candidates. The solubility of salts **I-III** varies widely from high in water (1.33, 0.08, 0.24 mol %, respectively) and DMSO to extremely low in alcohols – methanol and ethanol (96 %) (Fig. 3), and decreases in the following order: **I** > **II** > **III**.

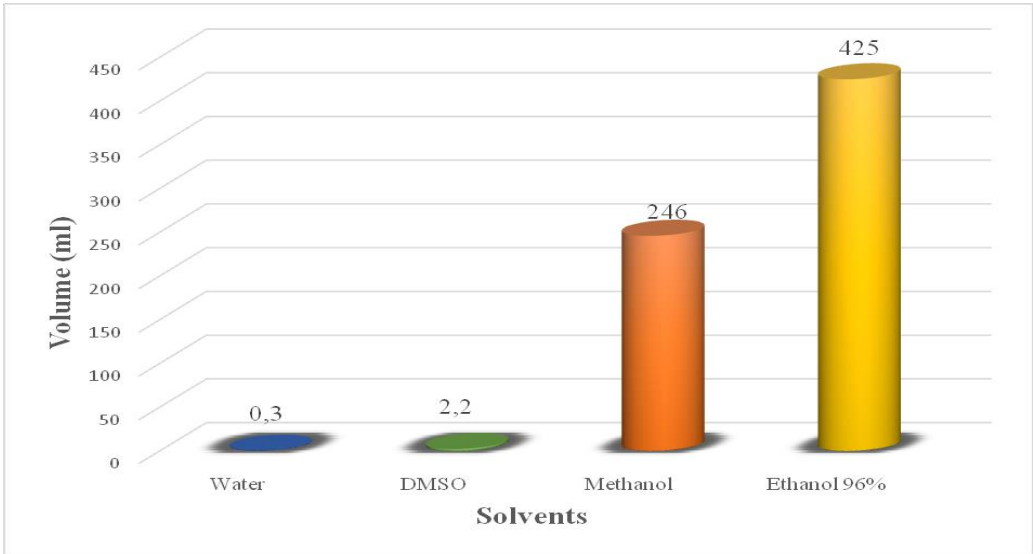

Fig. 3. Solubility of hexafluorosilicate I (m = 100 mg)

in water and organic solvents

The observed tendency towards a significant decrease in solubility of ionic

complexes **I-III** upon going from solutions in highly polar water and DMSO solvents to less polar alcoholic media is generally quite expected. Note that a qualitatively similar trend in the change of solubility in the above-mentioned media was found for 2-, 3-, 4-carboxymethylpyridinium hexafluorosilicates [4].

The results of determining caries prophylactic efficacy (CPE) of fluorine-containing compounds are shown in Fig. 4. The CPE values demonstrate that fluoride-containing compounds significantly decreased the number of carious lesions in the order: NaF – by 29.3 %, AHFS – by 31.7 %, **I** – by 41.5 %, **II** – by 51.2 %, **III** – 39.0 %. All three compounds **I-III** demonstrate higher CPE values compared to the reference drugs, and the CPE for the leader compound **II** is 1.75 times higher than that value for NaF, and 1.62 times higher than that value for AHFS.

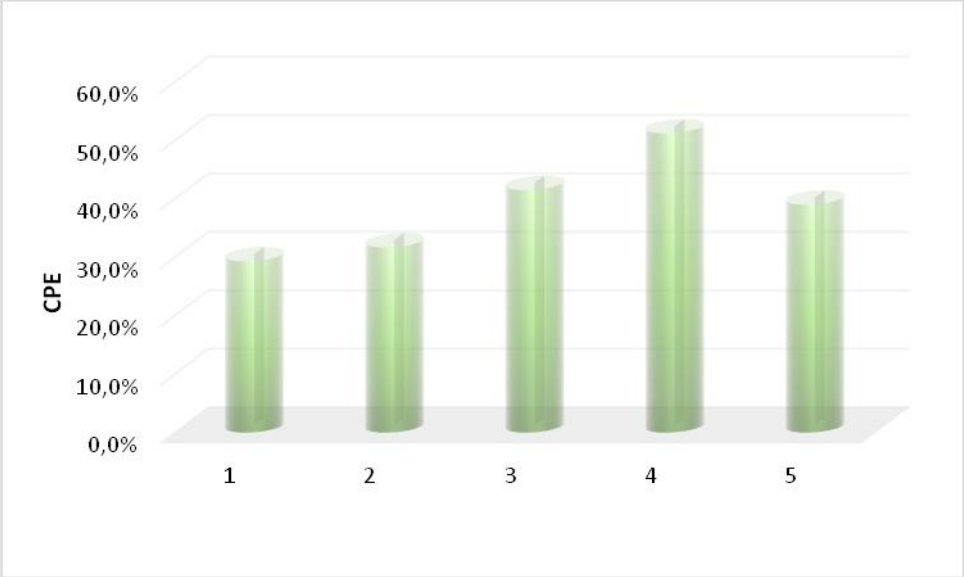

Fig. 4. Caries preventive efficiency of fluorine-containing compounds: 1 – CGD + gel-NaF, 2 – CGD + gel-AHFS, 3 – CGD + gel-I, 4 – CGD + gel-II, 5 – CGD + gel-III

The results of determination of alanine aminotransferase (ALT) activity (Fig.5), whose increased level in serum may indicate the development of hepatitis, demonstrated a lack of hepatotoxic effect for all studied compounds.

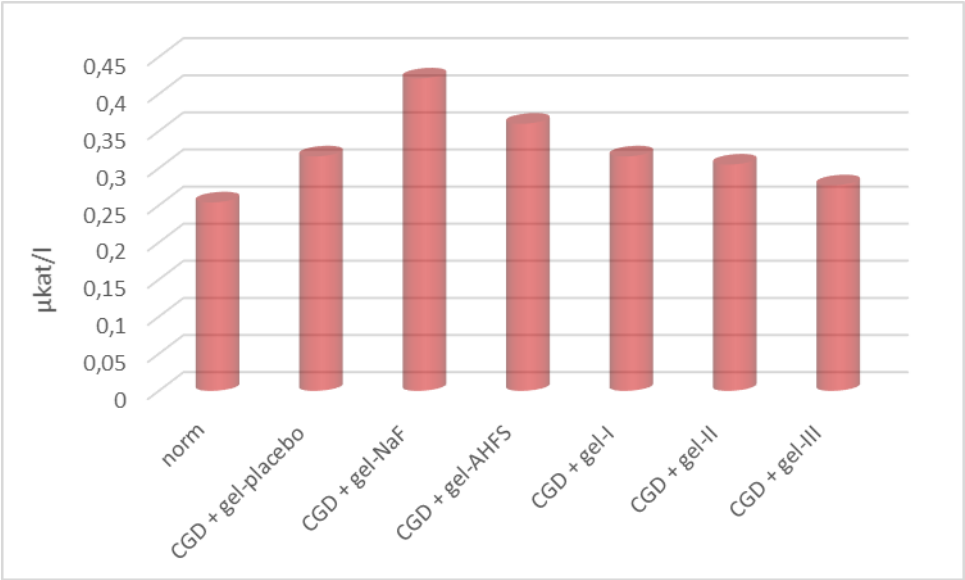

Fig. 5. ALT level under the influence of fluorine-containing compounds: 1 – normal, 2 – CGD + gel-placebo, 3 – CGD + gel-NaF, 4 – CGD + gel-AHFS, 5 – CGD + gel-I, 6 – CGD + gel-II, 7 – CGD + gel-III

A cariogenic diet leads to significant increase in the level of inflammatory markers (activity of elastase, malondialdehyde), and the use of gels with fluoride-containing salts, including complexes **I-III**, is accompanied by a reliable normalization of the levels of both inflammatory markers (Fig. 6).

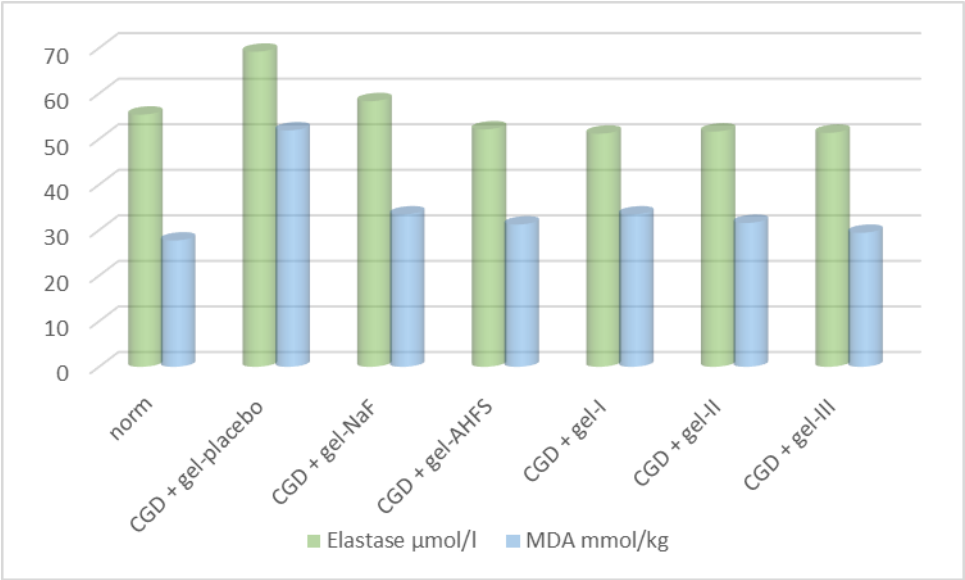

Fig. 6. The level of inflammation markers under the influence of fluorine-containing compounds: 1 – normal, 2 – CGD + gel-placebo, 3 – CGD + gel-NaF, 4 – CGD + gel-AHFS, 5 – CGD + gel-I, 6 – CGD + gel-II, 7 – CGD + gel-III

Conclusions. Three hexafluorosilicates with the compositions $(L^{1–3}H)_2[SiF_6]$ (**I**, **II**, **III**) were obtained as crystalline solids in a good yield (95-99 %) upon interaction of hexafluorosilicic acid with isomeric 2-, 3-, 4-carboxyethylpyridines ($L^{1–3}$). The crystal structures **I-III** are stabilized by the NH·F, OH·F inter-ionic H-bonds and C–H·F contacts. The studied compounds are characterized by high solubility in water and DMSO, and very poor solubility in methanol and ethanol (96%). The results of the determination of the caries prophylactic efficacy of salts in experiments on rats showed that compound **II** exhibits maximum efficiency (51.2 %, 1.75 times exceeding the same index for NaF) with the simultaneous significant improvement in the biochemical parameters of dental pulp and the absence of hepatotoxic effects.

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