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FULL PAPER

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Bis(2-, 3-, 4-carboxyethylpyridinium) hexafluorosilicates as potential caries prophylactic agents

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Abstract

Interaction of 2-, 3-, 4-carboxyethylpyridines (L1, L2, L3) with fluorosilicic acid results in the corresponding *bis*(pyridinium) hexafluorosilicates **I–III**, characterized by elemental analysis, IR, ^{1}H, ^{19}F nuclear magnetic resonance (NMR), and mass spectrometry, solubility data, and X-ray crystallography. Crystallographic data: *Fdd*2, $Z = 8$, $a = 28.610(2)$ Å, $b = 18.8378(14)$ Å, $c = 7.3236(5)$ Å (**I**); *P*-1, $Z = 1$, $a = 6.2712(4)$ Å, $b = 7.1706(5)$ Å, $c = 10.9721(7)$ Å, $\alpha = 102.514(6)°$, $\beta = 97.037(5)°$, $\gamma = 93.640(6)°$ (**II**); $P2_1/c$, $Z = 2$, $a = 10.0345(6)$ Å, $b = 9.8734(5)$ Å, $c = 9.4704(6)$ Å, $\beta = 94.347(6)°$ (**III**). The dominant intermolecular contacts from the Hirshfeld surface analysis are H···F/F···H, H···H, and H···O/O···H with percentages of 33.3%–34.5%, 26.4%–30.0%, and 16.0%–21.8%. The infrared spectra for **I–III** exhibit stretching vibrations $\nu(N^{+}H)$ at 3300–3050 cm^{-1}; stretching and deformation vibrations ν(SiF) and $\delta(SiF_2)$ for $[SiF_6]^{2-}$ anions are registered near 740 cm^{-1} and in the range of 480–440 cm^{-1}. In the ^{19}F NMR spectra of aqueous solutions of **I–III**, strong singlet signals of the $[SiF_6]^{2-}$ anion were registered at $\delta(F) = -133.35$ ppm (**I**), −131.43 ppm (**II**), −129.02 ppm (**III**) with two satellites due to the spin-spin interaction $^{29}Si–^{19}F$ ($J(^{29}Si–^{19}F) = 107.5$ Hz (**II**), 107.6 Hz (**III**)). **I–III** reveal high solubility in water and dimethyl sulfoxide and very poor solubility in methanol and ethanol. All compounds demonstrate noticeable anticaries activity and absence of hepatotoxic effects, and *bis*(3-carboxyethylpyridinium) hexafluorosilicate **II** displays the highest caries-preventive efficacy, which significantly exceeds values for the reference preparations, NaF and $(NH_4)_2[SiF_6]$.

KEYWORDS
biological activity, crystal structure, hydrogen bonds, pyridinium hexafluorosilicates, solubility

1 | INTRODUCTION

Dental caries, especially in the case of pediatric patients, currently is a cutting-edge problem for the health care system worldwide.[1-3] The fluoride-containing medical preparations dominate in the contemporary list of drugs for treatment and prevention of caries,[4] as their efficacy and safety have been confirmed by results of randomized clinical trials and meta-analysis,[5,6] as well as by many years of practical use.[7-9] For example, in a recently published review[10] authors, based on the analysis of data from epidemiological studies, experiments on animals, and in vitro, dispute the viewpoint discussed in the literature on the neurotoxicity of fluorides for humans at the levels of fluoride concentrations in drinking water, food, and oral hygiene products.[11,12] Of practical importance among the groups of fluorine-containing compounds are ammonium

hexafluorosilicates (AHFS) of general formula $(LH)_2[SiF_6]$ (L = ammonia or N-containing organic bases),[13] which are usually obtained as products of fluorosilicic acid (FSA) utilization. In particular, complex $(NH_4)_2[SiF_6]$ is widely applied as an industrial fluorinating agent, reagent in the processes of modification of zeolite catalysts, and as intermediate in the production of amorphous silicon dioxide.[13] Note that, contrary to the metal hexafluorosilicates $M_2[SiF_6]$, AHFSs are typical supramolecular compounds.[14] From the crystal engineering viewpoint, the crystal structures of salts $(LH)_2[SiF_6]$ (L = N-containing organic bases) are stabilized by the interplay of electrostatic Coulomb and van der Waals interactions, and interionic H-bonds, mainly of NH···F type.[13,15] As shown by Gelmboldt et al.,[13,15,16] the H-bond systems in the solids of AHFSs significantly affect the macroscopic properties of these salts, particularly, their water solubility (WS). The impact of H-bonds on WS can be used for a controlled tuning of this property when creating new materials, in particular, medical preparations.[13] So far, AHFSs are actively studied as new potential anticaries and hyposensitizing agents,[13,17,18] possessing by the prolonged effect of dentin tubule occlusion discovered on the $(NH_4)_2[SiF_6]$ compound.[19,20] In turn, AHFSs, whose cations exhibit antibacterial, anti-inflammatory, and other types of biological activity, demonstrate in experiments an increase in anticaries effect in comparison with the reference drugs, such as NaF, and even $(NH_4)_2[SiF_6]$.[13,18] Our recent findings[21] show that of considerable interest are the AHFSs with substituted pyridinium cations[22,23] since these compounds reveal high WS, acceptable toxicological characteristics, and a wide spectrum of biological activity typical for pyridine ligands.[24-26] In particular, hitherto unknown 2-, 3-, 4-carboxyethylpyridinium hexafluorosilicates, whose cations contain a $-CH_2CH_2COOH$ moiety, as a fragment of a well-known pharmacophore, propionic acid possessing an anti-inflammatory activity, are among the promising anticaries agents.[27]

The aim of this study is to synthesize, study the structure, physicochemical characteristics, and biological activity of isomeric 2-, 3-, 4-carboxyethylpyridinium hexafluorosilicates as potential anticaries agents.

2 | RESULTS AND DISCUSSION

2.1 | Crystal structures

Crystal structure and refinement data for **I–III** are given in Table 1, the hydrogen bonding geometries are summarized in Table 2. Compounds **I–III** have the 2:1 cation/anion ratio and crystallize in the noncentrosymmetric orthorhombic space group *Fdd*2 for **I**, and centrosymmetric space groups, triclinic *P*-1 for **II** and monoclinic $P2_1/c$ for **III** (Table 1). The three-membered formula units for **I–III** are shown in Figure 1. The $[SiF_6]^{2-}$ anions occupy positions on a twofold axis in **I** having the C_2 point group symmetry and on inversion centers in **II** and **III** having the C_i point group symmetry; anions have a distorted octahedral geometry with the Si–F distances ranging within 1.647(3)–1.694(1) Å. Organic cations everywhere occupy general positions and in the same way, as in the reported isomeric *n*-carboxymethylpyridinium hexafluorosilicates[21] the protonation of the pyridine nitrogen atom is indicated by the widened up to 122.1(2)–123.4(3)° C–N–C bond angles in the pyridinium cycles, while neutrality of carboxylic group is supported by differentiation in the C–O distances ranging within 1.172(3)–1.197(4) Å for C═O, and 1.306(3)–1.323(4) Å for C–O(H) bonds. The organic cations have different shapes, twisted one for the 2-carboxyethylpyridinim cation and elongated ones for 3-, 4-carboxyethylpyridinim cations that is originated from the flexibility of the ethyl bridges in the entities and indicated by the $-C-CH_2-CH_2-C-$ torsion angles of −67.6(4)°, −175.9(2)°, and 164.6(2)°, respectively. Furthermore, the pyridinium ring (Py) and carboxylic group (CO_2) are arranged approximately orthogonally in **I** and **II**, and collinearly in **III**, as indicate the corresponding interplanar angles Py/CO_2 of 80.90°, 83.82°, and 17.23° in 2-, 3-, 4-carboxyethylpyridinium cations, respectively; that is contrary to the narrower range of 45.9–48.1° for the *n*-carboxymethylpyridinium homologs.[21] The charged units are held together in the three-membered formula units via a couple of symmetry-related charge-assisted $NH^+\cdots F^-$ hydrogen bonds, N···F distances being of 2.701(2)–2.749(3) Å and supported by adjacent CH···F interactions (Figure 1, Table 2).

The components alternate in **I–III** being linked besides the above-mentioned NH···F hydrogen bonds also by $OH(CO_2H)\cdots F$ hydrogen bonds ranging within 2.588(2)–2.624(2) Å and being the shortest ones in all structures (Table 2). The supramolecular motifs supported by a combination of these strong interactions represent the three-dimensional (3D) H-bonded network in **I** (Figure 2a,b), and double chains in **II** and **III** (Figure 2c,d). The numerous CH···F contacts with the range of C···F distances within 3.002(4)–3.492(3) Å contribute to the effective crystal packing (Table 2). In **I** these CH···F interactions together with NH···F hydrogen bonds combine the components in elegant H-bonded layers parallel to the (1 2 0) plane (Figure 2a) being further interlinked via COOH···F hydrogen bond using the carboxylic tail of the organic cation (Figure 2b).

2.2 | Hirshfeld surface analysis

The Hirshfeld surface analysis[28,29] as a complemented tool to X-ray investigation used for the quantitative assessment of intermolecular interactions occurring within the crystal lattice was implemented in some recent studies for relevant hybrid hexafluorosilicates.[30–32] Herein, for this purpose, the normalized contact distance (d_{norm}) feature of the computed Hirshfeld surface, based on the internal (d_i) and external (d_e) distances, was employed. The corresponding 3D maps of the Hirshfeld surfaces, for **I–III** are shown in Figure 3a,c,e. The regions with intense red color are attributed to the hydrogen bonds. The full interaction contributions (100%) in the crystal packing are provided by resolving the 3D d_{norm} surface into 2D fingerprint plots (Figure 3b,d,f).

TABLE 1 Crystal data and structure refinement parameters for **I–III**

Compound	I	II	III
Empirical formula	$C_{16}H_{20}F_6N_2O_4Si$	$C_{16}H_{20}F_6N_2O_4Si$	$C_{16}H_{20}F_6N_2O_4Si$
Formula weight	446.43	446.43	446.43
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	*Fdd*2	*P*-1	$P2_1/c$
Unit cell dimensions			
a, Å	28.610 (2)	6.2712 (4)	10.0345 (6)
b, Å	18.8378 (14)	7.1706 (5)	9.8734 (5)
c, Å	7.3236 (5)	10.9721 (7)	9.4704 (6)
α, °	90	102.514 (6)	90
β, °	90	97.037 (5)	94.347 (6)
γ, °	90	93.640 (6)	90
V, Å^3	3947.1 (5)	475.98 (6)	935.57 (9)
Z	8	1	2
D (calcd), mg/m^3	1.502	1.557	1.585
μ, mm^{-1}	0.200	0.207	0.210
F(000)	1840	230	460
Reflections collected	2392	2988	3745
Independent reflections	1402 [$R_{(int)}$ = 0.0147]	1866 [$R_{(int)}$ = 0.0115]	1729 [$R_{(int)}$ = 0.0187]
Data/restraints/parameters	1402/3/142	1866/2/141	1729/2/142
Goodness-of-fit on F^2	1.025	1.027	1.055
Final *R* indices [$I > 2\sigma(I)$] R_1, wR_2	0.0318, 0.0767	0.0364, 0.0968	0.0460, 0.1159
R indices (all data), R_1, wR_2	0.0351, 0.0792	0.0410, 0.1002	0.0563, 0.1241
Largest diff. peak/hole, e/Å^3	0.291/−0.256	0.374/−0.241	0.379/−0.326

Figures 4–6 summarize the resolved interactions in structures **I–III**. The analysis of the 2D fingerprint plots of Hirshfeld surfaces reveals that redistribution of weak interactions from structure to structure occurs in narrow intervals. In accordance with the crystallographic data, the meaningful remain H···F/F···H, H···H, H···O/O···H, and H···C/C···H interactions given in descending order. The H···F/F···H cation-anion hydrogen bonds giving an impact of 33.4%–34.5%, manifest as two sharp, symmetric spikes in all crystals. Next meaningful are H···H cation–cation interactions appeared as the scattered points in the middle of the 2D fingerprint plots and comprise 26.4%–30.0%. Next in the population are H···O/O···H contacts comprising 16.0%–21.8%, and manifested as sharp spikes accompanied those ones for H···F contacts in **II** and **III**; C···H/H···C contacts contribute as the longest contacts in the peripheral regions of 2D maps with occupations of 7.0%–10.7%. Otherwise, the C···C interatomic contacts, that prove the occurrence of the π–π contacts between adjacent entities within the investigated crystals, reveal only a meaningless impact of 0.8%–1.8% in all crystals, where intermolecular contacts with H-participation dominate.

2.3 | Selected physicochemical properties

2.3.1 | Solubility in water and organic solvents

Assessment of solubility in water (WS) and organic solvents is a mandatory procedure for all drug candidates.[33] The results of determining the solubility of complexes **I–III** in water, methanol, ethanol (96%), and dimethyl sulfoxide (DMSO) are shown in Figure 7a–c; the WS values (*C*, mol. %) for these and some related pyridinium salts are summarized in Table 3. As it is originated from the data shown in Figure 5, from the standpoint of pharmaceutical criteria[34] hexafluorosilicates can be classified as follows. Compounds **I** and **II** are very easily soluble in water, while **III** is readily soluble in water; otherwise **I–III** are scarcely soluble in methanol, and **I** is very slightly soluble in ethanol (96%); **II** and **III** are practically insoluble in ethanol (96%), while **I**, **II** are readily soluble in DMSO, and **III** is moderately soluble in DMSO. The data summarized in Table 3 show that the WS of compounds **I–III** falls within the range of values typical for hexafluorosilicates

TABLE 2 Hydrogen bonds for **I–III** (Å and °)

D-H···A	d(H···A)	d(D···A)	∠(DHA)	Symmetry transformations used to generate equivalent atoms
I				
N(1)-H(1N1)···F(2)	1.91(2)	2.749 (3)	176 (4)	3/4-*x*, *y*+1/4, *z*-1/4
O(1)-H(1O1)···F(1)	1.77(3)	2.588 (3)	161 (5)	*x*, *y*+1/2, *z*-1/2
C(7)-H(7B)···F(1)	2.54	3.396 (4)	146.6	1/2-*x*, 1/2-*y*, *z*
C(5)-H(5)···F(4)	2.34	3.002 (4)	127.5	3/4-*x*, *y*+1/4, *z*-1/4
C(4)-H(4)···F(2)	2.56	3.327 (4)	139.8	3/4-*x*, *y*+1/4, *z*-5/4
C(2)-H(2)···F(3)	2.59	3.492 (3)	163.6	*x*,*y*,*z*-1
II				
O(1)-H(1O1)···F(3)	1.76(2)	2.604 (2)	163 (3)	*x*-1, *y*, *z*
N(1)-H(1N1)···F(2)	1.85(2)	2.701 (2)	170 (2)	*x*, *y*, *z*-1
C(2)-H(2)···F(3)	2.44	3.240 (2)	144.0	1-*x*, 2-*y*, 1-*z*
C(3)-H(3)···F(1)	2.47	3.072 (2)	122.2	*x*, *y*, *z*-1
C(3)-H(3)···F(1)	2.53	3.269 (2)	137.1	2-*x*, 1-*y*, 1-*z*
C(4)-H(4)···F(2)	2.42	3.270 (2)	152.3	*x*, *y*-1, *z*-1
III				
O(1)-H(1O1)···F(1)	1.75(2)	2.624 (2)	173 (3)	1-*x*, 1-*y*, 1-*z*
N(1)-H(1N1)···F(2)	1.85(2)	2.724 (2)	176 (3)	*x*, *y*, *z*
C(2)-H(2)···O(2)	2.36	3.260 (3)	163.5	1-*x*, *y*+1/2, 3/2-*z*
C(3)-H(3)···F(1)	2.53	3.352 (3)	147.3	*x*, 3/2-*y*, *z*+1/2
C(3)-H(3)···F(3)	2.40	3.177 (3)	140.6	2-*x*,*y*+1/2, 1/2-*z*
C(4)-H(4)···F(2)	2.39	3.177 (3)	142.1	2-*x*, *y*-1/2, 1/2-*z*
C(4)-H(4)···F(3)	2.39	2.992 (3)	122.1	*x*, *y*, *z*

with pyridinium cations containing H-donor substituents, $-CH_2CH_2C(O)OH$ and $-CH_2OH$.

It is known[13,16,36,37] that the WS of hexafluorosilicates with heterocyclic ammonium cations, as well as arylammonium cations, decreases with an increase in a number of strong and medium H-bonds that stabilize the complexes. Gelmboldt,[37] on the basis of qualitative arguments, assumed that it is an effect of H-bonds that have a decisive impact on the WS of the compounds of this type, while an impact of lipophilic–hydrophilic balance is not so important. In Gelmboldt et al.,[38] within the framework of the constructed 2D QSPR models, an analysis of the influence of various physicochemical factors on the WS of AHFSs was carried out, and the results indicate a more modest contribution of the effects of H-bonds to solubility (10%) as compared with the one assumed in Gelmboldt.[37] In this case, the effect of lipophilicity is significantly less (only 3%), and more important are the van der Waals interactions (19%), electrostatic effects (27%), and effects of the cation structure (Dragon's topological indices,[38] 39%).

The detailed characterization of the effect of H-bonds on the WS of hexafluorosilicates carried out in Gelmboldt et al.[38] made it possible to identify structural fragments of ammonium cations that provide negative and positive contributions to solubility. In particular, pyridinium cations, in contrast to pyrimidinium, 1,2,4-triazolium, 1,3,4-thiadiazolium, benzimidazolium analogs, make a positive contribution to solubility. This is consistent with the experimentally determined high hydrophilicity of salts **I–III**, despite the presence of the $-CH_2CH_2C(O)OH$ group in their cations, with a potentially negative (but obviously lower in absolute value) contribution to solubility.

In turn, the observed general 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, and the decrease in solubility of these salts in ethanol compared to methanol may reflect the relative "lipophilization" of the medium. Note that a qualitatively similar trend in the change of solubility in the above-mentioned media was found for 2-, 3-, 4-carboxymethylpyridinium[21] and 3-, 4-hydroxymethylpyridinium[22,23] hexafluorosilicates.

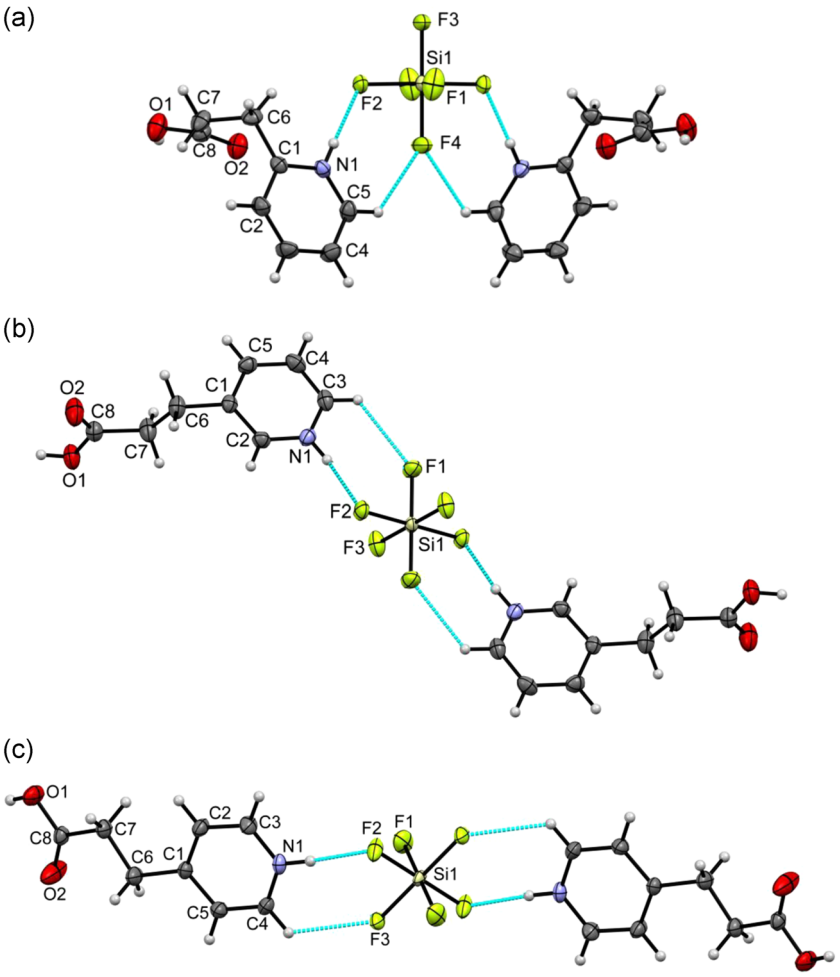

FIGURE 1 Thermal-ellipsoid plot drawings with 30% probabilities for formula units in **I** (a), **II** (b), and **III** (c) with labeling schemes

2.4 | Biological experiments

The results of determining caries prophylactic efficacy (CPE) of fluoride-containing compounds are presented in Table 4. As it follows from the data, the use of gels with AHFS leads to a significant decrease in the number of carious lesions in the next order: $(NH_4)_2[SiF_6]$—by 31.7%, **III**—by 39.0%, **I**—by 41.5%, and **II**—by 51.2% (Figure 8). Thus, all three reported 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 $(NH_4)_2[SiF_6]$.

It is noteworthy to compare the obtained results with the CPE data for compounds $[2\text{-}, 3\text{-}, 4\text{-}HO(O)CCH_2C_5H_4NH]_2[SiF_6]$ (**IV–VI**, respectively),[21] $[3\text{-}HOCH_2C_5H_4NH]_2[SiF_6]\cdot H_2O$ (**VII**), and $[4\text{-}HOCH_2C_5H_4NH]_2[SiF_6]$ (**VIII**).[39] Salts **I–III** and **IV–VI** contain residues of acetic and propionic acids in the forms of cations as pharmacophores with anti-inflammatory activity,[27] while for cations in salts **VII**, **VIII**, according to the PASS forecast no meaningful pharmacological activity significant in the context of caries prevention is expected.[20] The experimental results generally demonstrate higher CPE values of salts **I–III** (the average CPE for **I–III** is 1.5 times higher than the CPE of NaF) and **IV–VI** (the averaged CPE for **IV–VI** is 2.3 times higher than the CPE of NaF) compared to salts **VII** and **VIII** (the average CPE for **VII**, **VIII** exceeds the CPE for NaF by 1.2 times). This, as documented in Gelmboldt et al.,[21] may indicate in favor of an indirect positive contribution of the expected anti-inflammatory effect of cations to the anticaries effect of compounds **I–VI**. However, in an experiment on the carrageenan model of inflammation,[40] the absence of an anti-inflammatory effect for compounds **IV–VI** was found, so the question of possible reasons for the relative increase in the CPE of complexes **IV–VI** remains open.

Table 5 shows the results of determining the activity of phosphatases and the calculated values of the mineralizing index (MI). It is evident that the cariogenic diet (CGD) leads to a significant increase in an AcP activity and a decrease in an AlkP activity so that the pulp MI is four times decreased. The gels with fluoride compounds result in an effective normalization of MI values (Table 5, Figure 9), and when using all drugs, except for complex **III**, MI values exceed the same indicator of the intact group of animals.

The results of determining levels of inflammatory markers (activity of elastase, malondialdehyde [MDA]) in the homogenate of the oral mucosa and the "liver" marker (activity of alanine aminotransferase [ALT] in the serum of rats) are shown in Table 6. As it follows from the data presented, a CGD leads to a significant increase in the level of inflammatory markers, and the use of gels

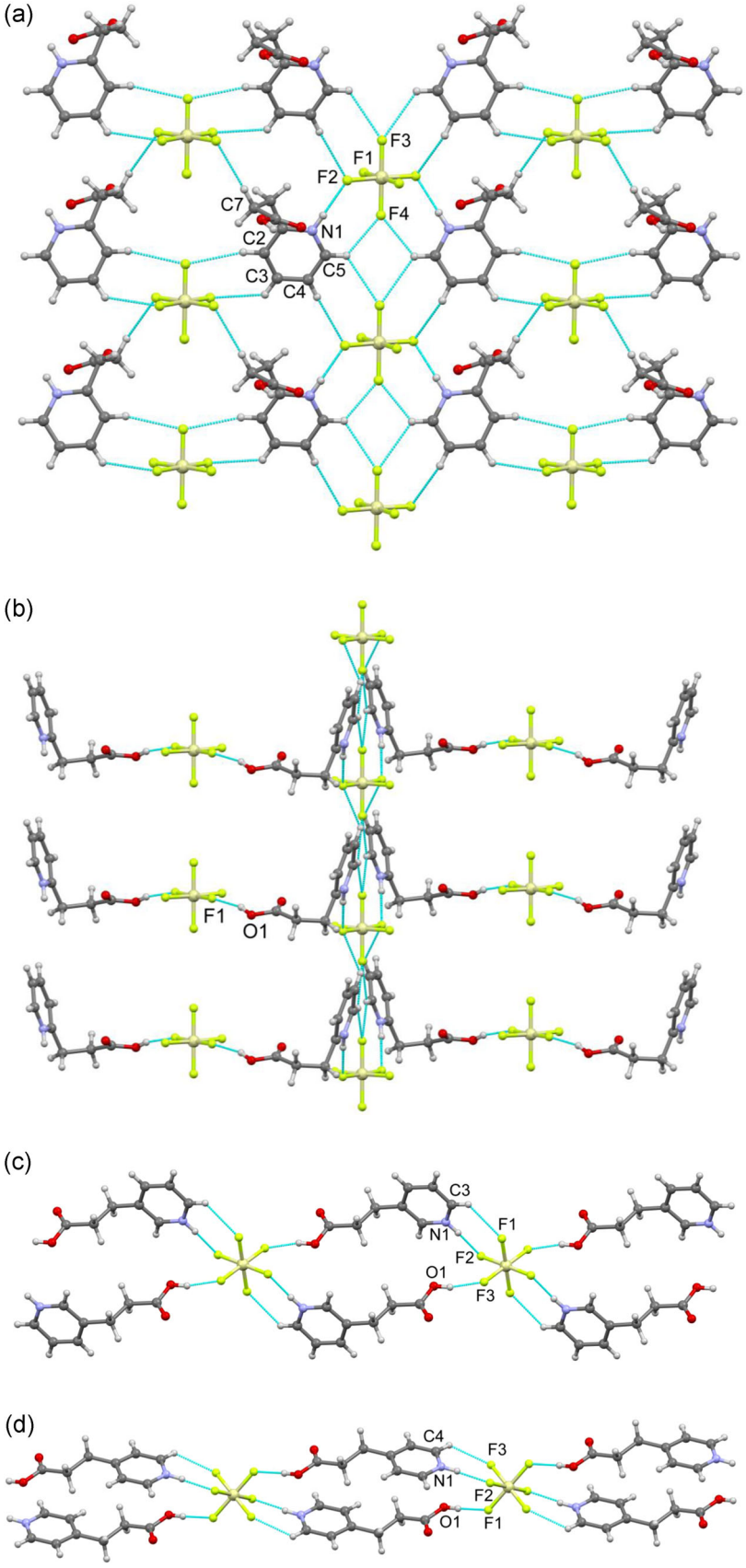

FIGURE 2 Fragments of H-bonded layer (a) and interconnection of these layers (b) in I; H-bonded chains in **II** (c) and **III** (d) with indication of atoms participating in the shortest contacts

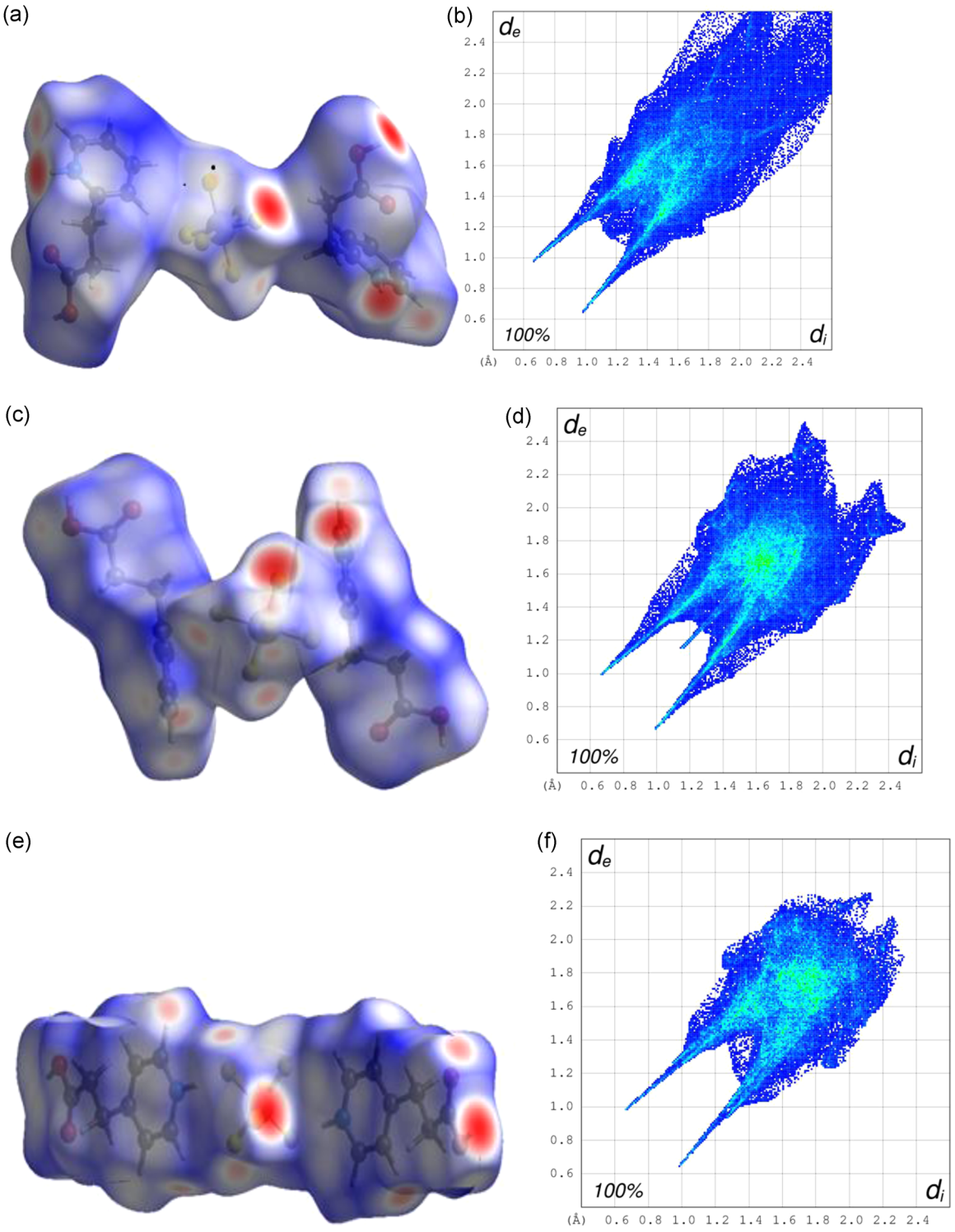

FIGURE 3 Hirshfeld surfaces based on d_{norm} and their full fingerprint plots for **I** (a,b), **II** (c,d), and **III** (d,e)

with fluoride salts, including complexes **I–III**, is accompanied by a reliable normalization of the levels of both inflammatory markers. In turn, the results of determining the ALT activity, whose increase may point toward the development of hepatitis, indicate the absence of hepatotoxic action for all studied compounds. Note that the absence of hepatotoxic effects was also recorded for salts **IV–VIII**,[21,41] as well as for chlorhexidine, polyhexamethylene guanidine, cetylpyridinium, pyridoxine hexafluorosilicates.[42,43] The only known exception is 2-amino-4,6-dihydroxypyrimidinium hexafluorosilicate, the use of which, in contrast to the action of NaF and $(NH_4)_2[SiF_6]$, has led to a significant increase in ALT activity (by 39%).[44]

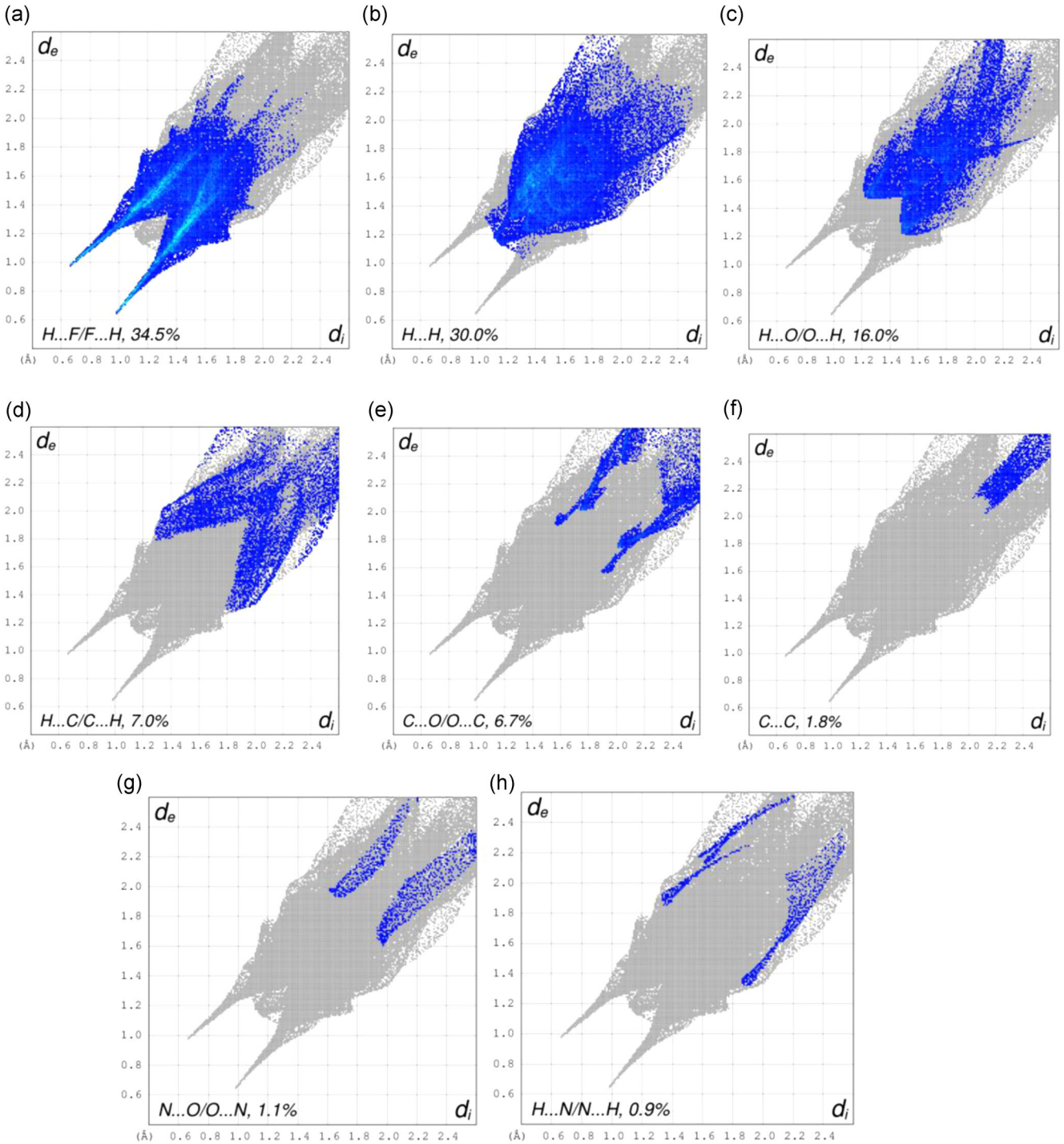

FIGURE 4 Fingerprint plots for **I** resolved in the most well-defined interactions in the descending order, (a) H···F/F···H; (b) H···H; (c) H···O/O···H; (d) H···C/C···H; (e) C···O/O···C; (f) C···C; (g) N···O/O···N; (h) H···N/N···H

3 | CONCLUSIONS

In conclusion, the products of interaction of methanolic solutions of 2-, 3-, 4-carboxyethylpyridines with an excess of 45% hydrofluorosilicic acid are the corresponding AHFS **I–III**, isolated in 95%–99% yields. The crystal structures of salts are sustained by the interplay of strong NH···F, OH···F interionic H-bonds and C–H···F contacts; the involvement of all fluorine atoms in a plethora of intermolecular interactions of different strength leads to a minor redistribution of bond lengths in octahedral $[SiF_6]^{2-}$ anions. The solubility of hexafluorosilicates varies widely from high in water (0.08%–1.33 mol. %) and DMSO to extremely low in alcohols and decreases in the following order: **I** > **II** > **III**. According to biological experiments, all three hexafluorosilicates exhibit

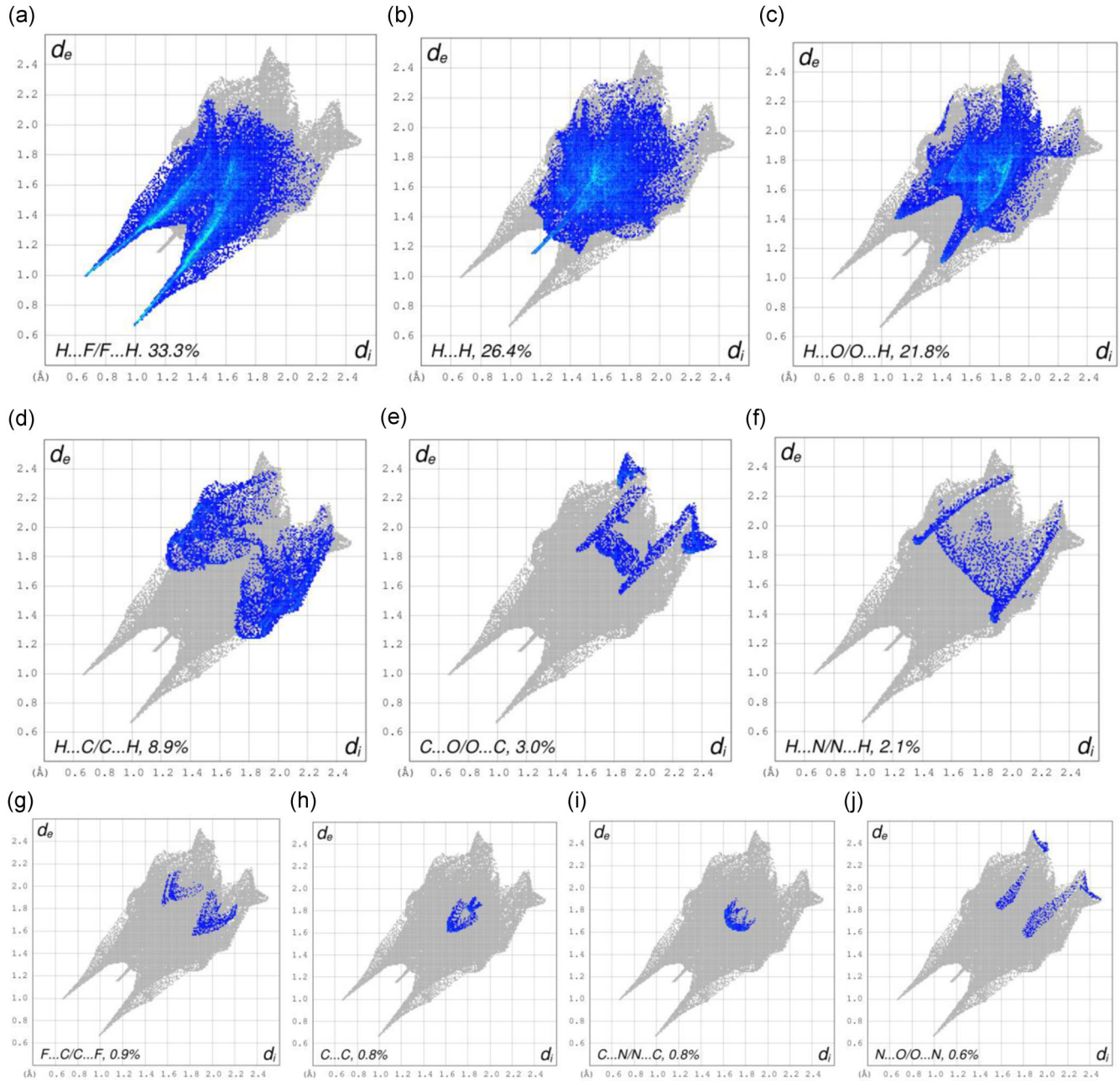

FIGURE 5 Fingerprint plots for **II** resolved in the most well-defined interactions in the descending order, (a) H···F/F···H; (b) H···H; (c) H···O/O···H; (d) H···C/C···H; (e) C···O/O···C; (f) H···N/N···H; (g) F···C/C···F; (h) C···C; (i) C···N/N···C; (j) N···O/O···N

noticeable anticaries activity with the simultaneous significant improvement in the biochemical parameters of the dental pulp and the absence of hepatotoxic effects. The salt of 3-carboxyethylpyridinium hexafluorosilicate **II** exhibits the highest caries-preventive efficacy, which exceeds the analogous indicators for the reference drugs, NaF and $(NH_4)_2[SiF_6]$, by 1.75 and 1.62 times, respectively. Among the studied hexafluorosilicates, complex **II** provides the most effective increase in the MI, which was four times reduced as a result of caries, so that the final MI value exceeds the given index for the intact group. The presented results of studying the physicochemical properties and biological activity of 3-carboxyethylpyridinium hexafluorosilicate make it possible to consider this compound as a promising object for further pharmacological research as a potential caries prophylactic agent.

4 | EXPERIMENTAL

4.1 | Materials

H_2SiF_6 (45%, "pure for analysis"; Reakhim, Russian Federation, CAS Number 16961-83-4), 2-pyridinepropionic acid (97%; Sigma Aldrich, CAS Number 15197-75-8), 3-pyridinepropionic acid (98%, Sigma

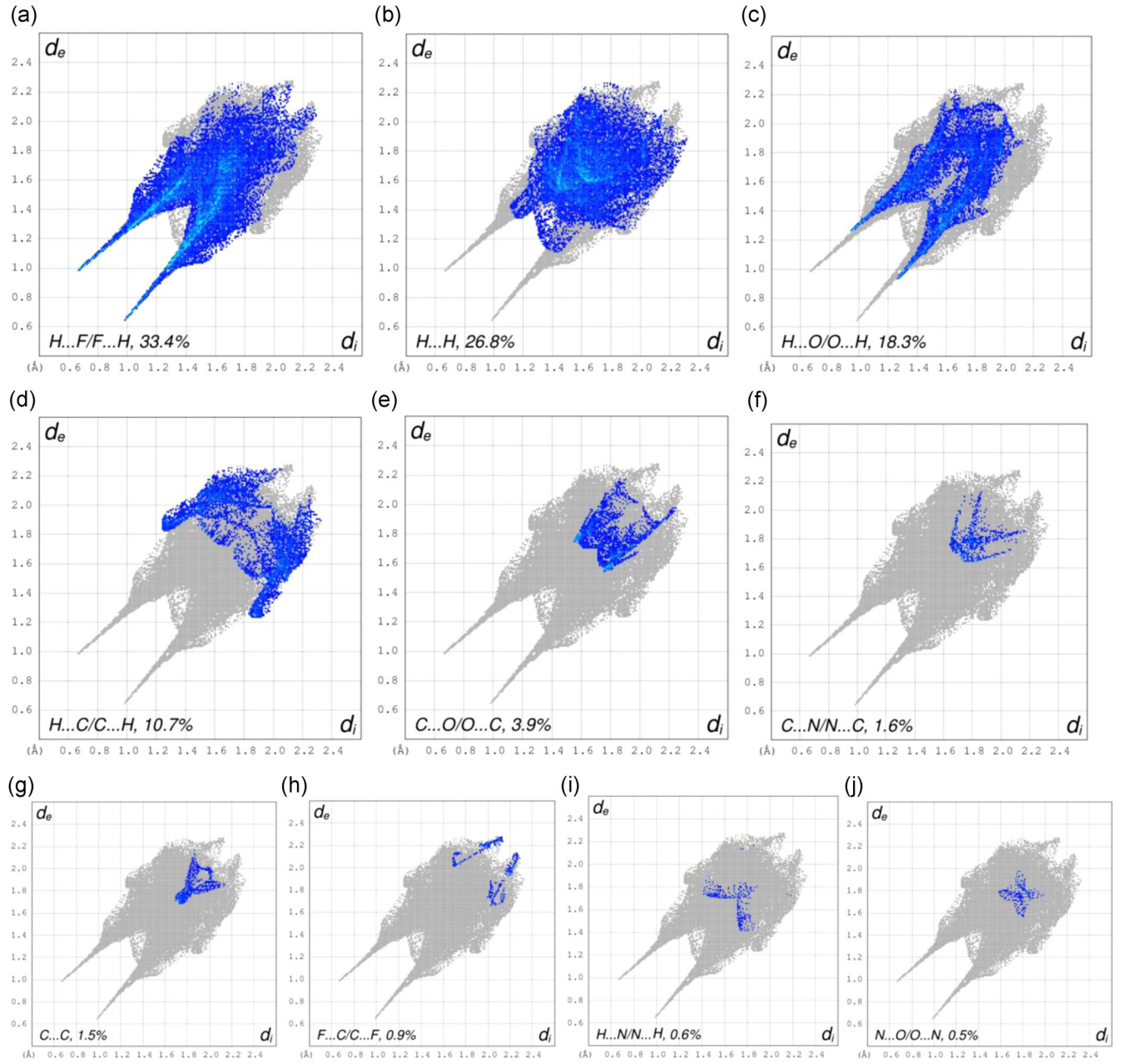

FIGURE 6 Fingerprint plots for **III** resolved in the most well-defined interactions in the descending order, (a) H···F/F···H; (b) H···H; (c) H···O/O···H; (d) H···C/C···H; (e) C···O/O···C; (f) H···N/N···H; (g) F···C/C···F; (h) C···C; (i) C···N/N···C; (j) N···O/O···N

Aldrich, CAS Number 3724-19-4), 4-pyridinepropionic acid (97%; Sigma Aldrich, CAS Number 6318-43-0), AHFS ("pure for analysis"; Reakhim, Russian Federation, CAS Number 16919-19-0) and sodium fluoride (CAS Number 7681-49-4) were used without further purification.

4.2 | Instrumentation

The infrared (IR)-absorption spectra were recorded on a spectrophotometer Spectrum BX II FT-IR System (Perkin-Elmer) (range: 4000–350 cm^{-1}, samples as tablets with KBr). ^{1}H, ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on Varian MercuryPlus spectrometer (^{1}H 301.55 MHz, ^{19}F 188.14 MHz, TMS, $CFCl_3$ as standards). The electron ionization (EI) mass spectra were registered on a spectrometer MX-1321 (direct input of a sample in a source, energy of ionizing electrons 70 eV). The fast atom bombardment (FAB) mass spectra were registered on a spectrometer VG 7070 (VG Analytical) (desorption of ions from the surface of a liquid phase was performed by a beam of argon atoms with the energy of 8 keV, glycerol was used as a matrix). The isothermal conditions of experiments on detection of solubility of hexafluorosilicates ($t = 25 \pm 0.2$°C) were provided with the help of an ultra-thermostat U15. The solubility in water and organic solvents (methanol, ethanol 96%, DMSO) was determined in accordance with the requirements of Jouyban.[33]

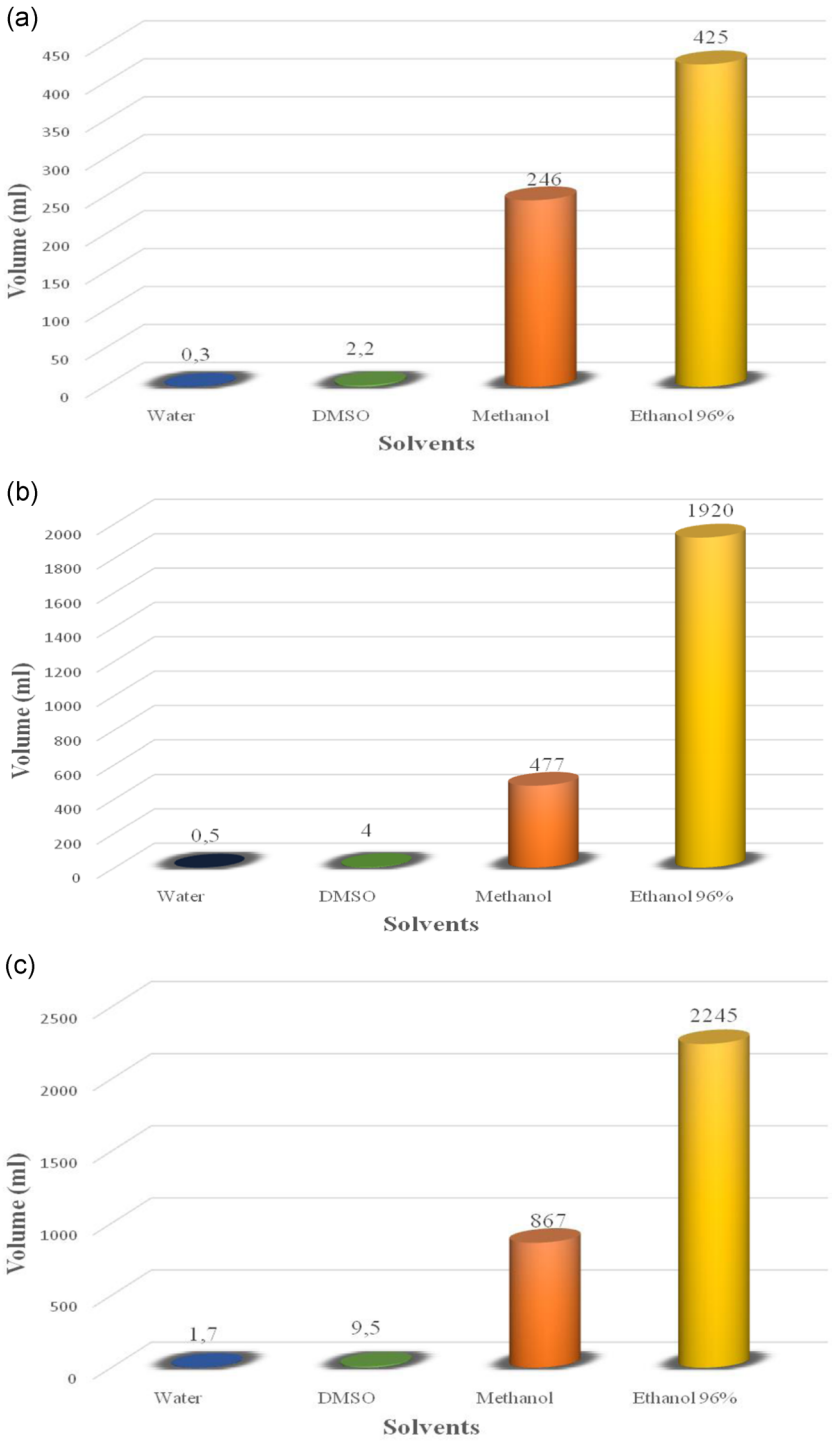

FIGURE 7 Solubility of 2-, 3-, 4-carboxyethylpyridinium hexafluorosilicates (a–c, m = 100 mg) in water and organic solvents. DMSO, dimethyl sulfoxide

4.3 | Synthesis of compounds I–III

4.3.1 | Synthesis of bis(2-carboxyethylpyridinium) hexafluorosilicate (**I**)

2-Pyridinepropionic acid (L^1; 3,045 g, ~0.02 mol) was dissolved in warm methanol (150 ml) and to the obtained solution the FSA (45%, ~0.07 mol, molar ratio L^1:FSA = 1:3.5) was added. A reaction mixture stored at ambient conditions before the beginning of crystallization of the reaction product (4.42 g, yield 98%). Colorless transparent crystals with the composition $(L^1H)_2[SiF_6]$ (**I**). Anal. found, %: C 42.53, H 5.12, Si 6.14, N 6.33, F 25.29. Calcd. for $C_{16}H_{20}F_6N_2O_4Si$: C 42.85, H 4.94, Si 6.29, N 6.28, F 25.53. Mass spectrum EI: $[ML^1]^{+\bullet}$ (m/z = 151, I = 6%), $[ML^1–CO_2–H]^+$ (m/z = 106, I = 100%), $[SiF_3]^+$ (m/z = 85, I = 21%). Mass spectrum FAB: $[ML^1+H]^{+\bullet}$ (m/z = 152, I = 57%), $[ML^1]^{+\bullet}$ (m/z = 151, I = 2%). IR-spectrum (cm^{-1}): 3382, 3325, 3252, 3174, 3159, 3125, 3113, 3073 [$\nu(N^+H)$, ν(CH)], 1733, 1700 [ν(C=O), δ

TABLE 3 Water solubility of pyridinium hexafluorosilicates

Compound	Solubility, mol. %, 25°C	References
I	1.33	Present work
II	0.08	Present work
III	0.24	Present work
$[2\text{-}HO(O)CCH_2C_5H_4NH]_2[SiF_6]$	0.82	[21]
$[3\text{-}HO(O)CCH_2C_5H_4NH]_2[SiF_6]$	1.02	[21]
$[4\text{-}HO(O)CCH_2C_5H_4NH]_2[SiF_6]$	0.58	[21]
$(3\text{-}HOCH_2C_5H_4NH)_2[SiF_6]\cdot H_2O$	1.55	[23]
$(4\text{-}HOCH_2C_5H_4NH)_2[SiF_6]$	1.33	[22]
$[2,6\text{-}(HOCH_2)_2C_5H_3NH]_2[SiF_6]$	2.52	[35]
$[2\text{-}CH_3\text{-}3\text{-}OH\text{-}4,5\text{-}(HOCH_2)C_5HNH]_2[SiF_6]$	0.89	[35]

TABLE 4 Caries preventive efficiency (CPE) of fluorine-containing compounds

No.	Groups	Number of carious lesions	Depth of carious lesions	CPE (%)
1	Norm	6.4 ± 0.3	7.0 ± 0.3	–
2	CGD + gel-placebo	8.2 ± 0.4 $p < .002$	8.5 ± 0.4 $p < .02$	–
3	CGD + gel-NaF	5.8 ± 0.4 $p > 0.25$ $p_1 < 0.002$	6.4 ± 0.6 $p > 0.4$ $p_1 < 0.01$	29.3
4	CGD + gel-$(NH_4)_2[SiF_6]$	5.6 ± 0.7 $p > 0.3$ $p_1 < 0.02$ $p_2 > 0.6$	6.9 ± 0.2 $p > 0.8$ $p_1 < 0.002$ $p_2 > 0.4$	31.7
5	CGD + gel-**I**	4.8 ± 0.4 $p < 0.01$ $p_1 < 0.002$ $p_2 > 0.2$	5.4 ± 0.6 $p < 0.02$ $p_1 < 0.01$ $p_2 > 0.25$	41.5
6	CGD + gel-**II**	4.0 ± 0.5 $p < 0.002$ $p_1 < 0.002$ $p_2 < 0.02$	4.1 ± 0.6 $p < 0.002$ $p_1 < 0.01$ $p_2 < 0.01$	51.2
7	CGD + gel-**III**	5.0 ± 0.3 $p < 0.01$ $p_1 < 0.001$ $p_2 > 0.1$	5.4 ± 0.4 $p < 0.02$ $p_1 < 0.01$ $p_2 > 0.2$	39.0

Note: p—in comparison with group 1; p_1—in comparison with group 2; p_2—in comparison with Group 3.
Abbreviation: CGD, cariogenic diet.

(CN^+H)], 739 [ν(SiF)], 482, 471 [$\delta(SiF_2)$], 405 [δ(CNC)]. ^{1}H NMR (301.55 MHz, D_2O) δ ppm 2.73 (t, J = 7.1 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 7.67 (t, J = 6.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 8.27 (t, J = 7.9 Hz, 1H), 8.41 (d, J = 5.9 Hz, 1H). ^{19}F NMR (188.14 MHz, D_2O): δ = −133.35 ppm (s, SiF_6^{2-}).

4.3.2 | Synthesis of bis(3-carboxyethylpyridinium) hexafluorosilicate (**II**)

3-Pyridinepropionic acid (L^2; 3.003 g, ~0.02 mol) was dissolved in warm methanol (150 ml) and to the obtained solution the FSA (45%, ~0.07 mol, molar ratio L^2:FSA = 1:3.5) was added. A reaction mixture stored at ambient conditions before the beginning of crystallization of the reaction product (4.46 g, yield 99%). Colorless transparent crystals with the composition $(L^2H)_2[SiF_6]$ (**II**). Anal. found, %: C 42.61, H 4.75, Si 6.36, N 6.13, F 25.81. Calcd. for $C_{16}H_{20}F_6N_2O_4Si$: C 42.85, H 4.94, Si 6.29, N 6.28, F 25.53. Mass spectrum EI: $[ML^2]^{+\bullet}$ (m/z = 151, I = 36%), $[ML^2\text{–}CO_2\text{–}H]^+$ (m/z = 106, I = 52%), $[SiF_3]^+$ (m/z = 85, I = 40%). Mass spectrum FAB: $[ML^2+H]^{+\bullet}$ (m/z = 152, I = 58%), $[ML^2]^{+\bullet}$ (m/z = 151, I = 1%). IR-spectrum (cm^{-1}): 3238, 3183, 3127, 3114, 3091, 3076, 3061, 3026 [ν(N^+H), ν(CH)], 1724, 1686, 1635 [ν(C═O), δ(CN^+H)], 740 [ν(SiF)], 482, 445 [$\delta(SiF_2)$], 405 [δ(CNC)]. ^{1}H NMR (301.55 MHz, D_2O) δ ppm 2.67 (t, J =7.3 Hz, 1H), 2.99 (t, J = 7.1 Hz, 1H), 7.83 (t, J = 7.0 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.53 (s, 1H). ^{19}F NMR (188.14 MHz, D_2O): δ = −131.43 ppm (s, SiF_6^{2-}), $J(Si^{29}\text{–}F^{19})$ = 107.5 Hz.

4.3.3 | Synthesis of bis(4-carboxyethylpyridinium) hexafluorosilicate (**III**)

4-Pyridinepropionic acid (L^3; 3.021 g, ~0.02 mol) was dissolved in warm methanol (150 ml) and to the obtained solution the FSA (45%, ~0.07 mol, molar ratio L^2:FSA = 1:3.5) was added. A reaction mixture stored at ambient conditions before the beginning of crystallization of the reaction product (4.22 g, yield 95%). Beige transparent crystals with the composition $(L^3H)_2[SiF_6]$ (**III**). Anal. found, %: C 43.12, H 4.67, Si 6.44, N 6.31, F 25.11. Calcd. for $C_{16}H_{20}F_6N_2O_4Si$: C 42.85, H 4.94, Si 6.29, N 6.28, F 25.53. Mass spectrum EI: $[ML^3]^{+\bullet}$ (m/z = 151, I = 75%), $[ML^3\text{–}CO_2\text{–}H]^+$ (m/z = 106, I = 94%), $[ML^3\text{–}CO_2\text{–}2H]^{+\bullet}$ (m/z = 105, I = 100%), $[SiF_3]^+$ (m/z = 85, I = 67%). Mass spectrum FAB: $[ML^3+H]^{+\bullet}$ (m/z = 152, I = 25%), $[ML^3]^{+\bullet}$ (m/z = 151, I = 3%). IR-spectrum (cm^{-1}): 3185, 3129, 3096, 3081 [ν(N^+H), ν(CH)], 1711, 1636 [ν(C═O), δ(CN^+H)], 740 [ν(SiF)], 482, 453 [$\delta(SiF_2)$]. ^{1}H NMR (301.55 MHz, D_2O): δ ppm 2.70 (m, 2H), 3.04 (m, J = 7.0, 2H), 7.77 (d, J = 5.1 Hz, 2H), 8.48 (d, J = 5.5 Hz, 2H). ^{19}F NMR (188.14 MHz, D_2O): δ = −129.02 ppm (s, SiF_6^{2-}), $J(Si^{29}\text{–}F^{19})$ = 107.6 Hz.

4.4 | X-ray structure determination for I–III

Single crystal X-ray diffraction analysis was performed on an Xcalibur E diffractometer (room temperature, two-coordinate Eos CCD detector, graphite monochromator, MoKα radiation). Structure solution and refinement were performed using the SHELX97

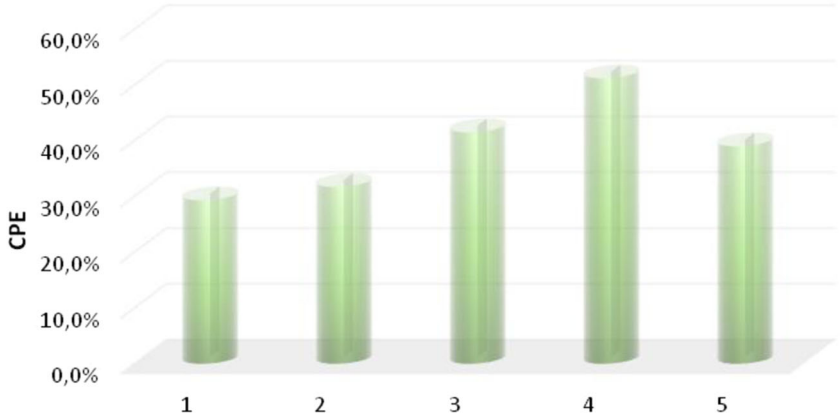

FIGURE 8 Caries preventive efficiency of fluoride-containing compounds: 1—CGD + gel-NaF, 2—CGD + gel-$(NH_4)_2[SiF_6]$, 3—CGD + gel-**I**, 4—CGD + gel-**II**, 5—CGD + gel-**III**.
CGD, cariogenic diet

TABLE 5 The effect of fluoride-containing compounds on the activity of phosphatases and the mineralizing index of the pulp of teeth of rats treated with CGD

No.	Groups	Alkaline phosphatase activity (μkat/kg)	Acid phosphatase activity (μkat/kg)	Mineralizing index
1	Norm	2.63 ± 0.10	36.22 ± 0.18	72.61 ± 4.82
2	CGD + gel-placebo	1.26 ± 0.09 $p < 0.002$	68.32 ± 0.28 $p < 0.001$	18.44 ± 1.05 $p < 0.001$
3	CGD + gel-NaF	2.23 ± 0.09 $p < 0.002$ $p_1 < 0.02$	26.53 ± 0.18 $p < 0.001$ $p_1 < 0.001$	84.06 ± 5.86 $p > 0.2$ $p_1 < 0.001$
4	CGD + gel-$(NH_4)_2[SiF_6]$	2.50 ± 0.08 $p > 0.3$ $p_1 < 0.001$ $p_2 < 0.02$	24.65 ± 0.16 $p < 0.001$ $p_1 < 0.001$ $p_2 < 0.001$	101.42 ± 5.84 $p < 0.002$ $p_1 < 0.001$ $p_2 < 0.05$
5	CGD + gel-**I**	2.63 ± 0.08 $p > 0.8$ $p_1 < 0.001$ $p_2 < 0.002$	35.39 ± 0.23 $p < 0.01$ $p_1 < 0.001$ $p_2 < 0.002$	74.31 ± 5.25 $p > 0.2$ $p_1 < 0.001$ $p_2 > 0.2$
6	CGD + gel-**II**	2.52 ± 0.09 $p > 0.4$ $p_1 < 0.001$ $p_2 < 0.02$	29.73 ± 0.16 p < 0.001 $p_1 < 0.001$ $p_2 < 0.002$	84.76 ± 6.32 p > 0.2 $p_1 < 0.001$ $p_2 > 0.8$
7	CGD + gel-**III**	2.52 ± 0.10 $p > 0.8$ $p_1 < 0.001$ $p_2 < 0.03$	36.39 ± 0.12 $p > 0.5$ $p_1 < 0.001$ $p_2 < 0.002$	69.25 ± 4.37 $p > 0.5$ $p_1 < 0.001$ $p_2 < 0.05$

Note: p—in comparison with Group 1; p_1—in comparison with Group 2; p_2—in comparison with Group 3.
Abbreviation: CGD, cariogenic diet.

software package.[45] All nonhydrogen atoms were refined in the anisotropic approximation. The N,O-bound hydrogen atoms were found from difference Fourier maps and refined in the isotropic approximation. The figures were produced using MERCURY.[46]

The crystallographic data for compounds **I–III** (CIF file) have been deposited with the Cambridge Structural Database CCDC deposition numbers 2143185-2143187. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk

4.5 | Biological activity

Gels that contain fluoride preparations NaF, $(NH_4)_2[SiF_6]$ and **I–III** were prepared on the basis of carboxymethylcellulose gel (sodium salt).[42] The concentration of drugs in the gel corresponded to a fluoride dose of 1.88 mg/kg.

Animal studies were carried out in compliance with the provisions of the European Convention for the Protection of Animals used for Experimental and Other Scientific Purposes.[47] The experiments were performed on 35 white Wistar rats (females, 1 month, average live weight 40 ± 1.5 g) distributed into seven equal groups (Table 3). Rats of 2–7 groups were kept on Stephan's CGD (sucrose 50%).[48] 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/day for 30 days (excluding Sundays), covering the teeth and gums with gel. After the application, rats were not fed for 1 h.

Euthanization of animals was performed on the 31st day of the experiment under thiopental anesthesia (20 mg/kg) by total blood-letting of their heart.

A serum of blood was obtained in which the activity of alanine ALT was determined.[49]

The activity of alkaline phosphatase (AlkP) and acid phosphatase (AcP)[50] was determined in the homogenate of pulp extracted from the incisors; in the homogenate of the oral mucosa, the activity of elastase and the level of MDA[51] were determined.

The MI was calculated as the AlkP/AcP ratio.[52]

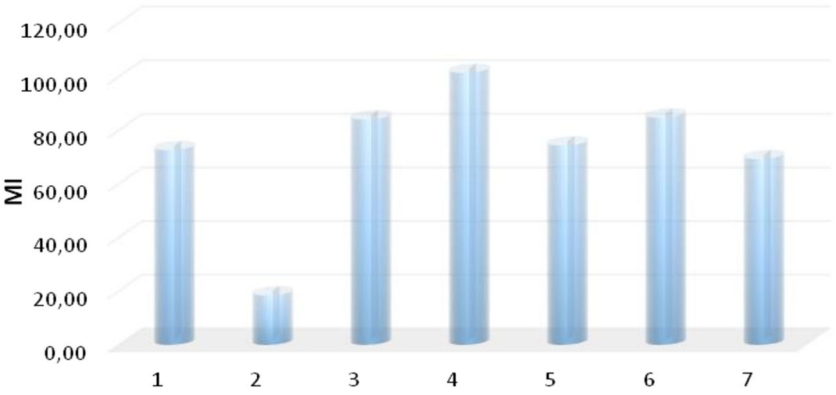

FIGURE 9 Influence of fluoride-containing compounds on mineralizing pulp index of the teeth of rats receiving a cariogenic diet (CGD): 1—intact, 2—CGD + gel-placebo, 3—CGD + gel-NaF, 4—CGD + gel-$(NH_4)_2[SiF_6]$, 5—CGD + gel-**I**, 6—CGD + gel-**II**, 7—CGD + gel-**III**

TABLE 6 Influence of fluoride-containing compounds on the level of inflammatory markers (homogenate of the oral mucosa) and ALT (blood serum) activity in rats treated with cariogenic diet

No.	Groups	Elastase activity (μkat/kg)	MDA content (μmol/kg)	Alanine aminotransferase activity (μkat/L)
1	Norm	55.38 ± 3.62	27.74 ± 1.10	0.254 ± 0.005
2	CGD + gel-placebo	69.19 ± 2.83 $p < 0.002$	51.92 ± 2.32 $p < 0.001$	0.316 ± 0.002 $p < 0.001$
3	CGD + gel-NaF	58.33 ± 3.3 $p > 0.8$ $p_1 < 0.02$	33.46 ± 1.22 $p < 0.001$ $p_1 < 0.001$	0.421 ± 0.007 $p < 0.001$ $p_1 < 0.001$
4	CGD + gel-$(NH_4)_2[SiF_6]$	52.14 ± 1.45 $p > 0.8$ $p_1 < 0.001$ $p_2 > 0.1$	31.25 ± 1.56 p > 0.1 $p_1 < 0.001$ $p_2 > 0.2$	0.360 ± 0.009 $p < 0.001$ $p_1 < 0.001$ $p_2 < 0.001$
5	CGD + gel-**I**	51.19 ± 3.12 p > 0.8 $p_1 < 0.001$ $p_2 > 0.2$	33.46 ± 1.87 $p < 0.02$ $p_1 < 0.001$ $p_2 > 0.8$	0.316 ± 0.001 $p < 0.001$ $p_1 > 0.8$ $p_2 < 0.001$
6	CGD + gel-**II**	51.66 ± 2.50 $p > 0.8$ $p_1 < 0.001$ $p_2 > 0.2$	31.59 ± 1.65 $p > 0.1$ $p_1 < 0.001$ $p_2 > 0.4$	0.305 ± 0.001 $p < 0.001$ $p_1 < 0.02$ $p_2 < 0.001$
7	CGD + gel-**III**	51.38 ± 1.62 $p > 0.8$ $p_1 < 0.001$ $p_2 > 0.1$	29.43 ± 1.05 $p > 0.3$ $p_1 < 0.001$ $p_2 < 0.005$	0.277 ± 0.008 $p < 0.001$ $p_1 < 0.001$ $p_2 < 0.001$

Note: p—in comparison with Group 1; p_1—in comparison with Group 2; p_2—in comparison with Group 3.
Abbreviation: ALT, aminotransferase; CGD, cariogenic diet.

The jaws were dissected and the number and depth of carious lesions of the teeth were counted.[53] CPE was calculated using the formula: CPE = $[(A - B)/A] \times 100\%$, where A is the number of carious lesions in rats receiving CGD, B is the number of carious lesions in rats receiving CGD + fluoride.

The results of the studies were subjected to a standard statogram, the arithmetic mean (M), the arithmetic mean error ($\pm m$) were calculated. A comparison of the indices in the groups was made according to Student's t-test. For significant differences, data were taken with $p < 0.05$.[54]

4.6 | Computations

The Hirshfeld surfaces are mapped with d_{norm}, and 2D fingerprint plots presented in this paper were generated using CrystalExplorer 2.1.[28,29]

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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