

SYNTHESIS, CRYSTAL STRUCTURE, AND SOME PROPERTIES OF 4-HYDROXYMETHYLPYRIDINIUM HEXAFLUOROSILICATE

V. O. Gelmboldt^{1*}, I. O. Shyshkin¹,
M. S. Fonari^{2**}, and V. Kh. Kravtsov²

Hexafluorosilicate with the composition (LH)₂SiF₆ (**I**), (L = 4-hydroxymethylpyridine) is isolated as the interaction product of an L methanol solution and 45% hydrofluorosilicic acid (L:H₂SiF₆ = 1:3). In the crystal structure of **I** the cations and anions are linked by NH⁺⋯F (N⁺⋯F of 2.809(2) Å, 2.824(2) Å) and OH⁺⋯F (O⁺⋯F of 2.7036(18) Å) H bonds; the geometry of the SiF₆²⁻ anion is a distorted octahedron (Si–F distances 1.6780(11)-1.6877(11) Å). In the IR spectrum of **I** the absorption bands of the main vibrations are identified; the solubility of **I** in water and some organic solvents and the degree of hydrolysis of the salt in a 1·10⁻⁴ M aqueous solution are determined.

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In recent years, ammonium hexafluorosilicates have been the objects of extensive studies as novel promising anticaries and hyposensitive agents [1-6]. The specificity of the anticaries action of these compounds is the effect of prolonged occlusion of open dentin tubules by the calcium fluoride precipitate found by the example of ammonium hexafluorosilicate (AHFS): the precipitation is catalyzed by a soluble form of silicon dioxide formed during the AHFS hydrolysis in saliva medium [1, 7]. Hexafluorosilicates with biologically active ammonium cations, in particular, pyridinium cations, should be specially mentioned among possible candidates for anticaries drugs. Pyridine derivatives exhibit a wide spectrum of the pharmacological activity [8], including antibacterial, and can enhance the anticaries effect of the fluoride component. In this work, 4-hydroxymethylpyridinium hexafluorosilicate is synthesized and its structure and physicochemical characteristics as a potential anticaries agent are studied.

EXPERIMENTAL

Synthesis. Commercial hydrofluorosilicic acid (HFSA, 45%, analytical grade) and 4-hydroxymethylpyridine (Sigma Aldrich, 99%) were used in the work. 4-Hydroxymethylpyridine (L 5.46 g, 0.05 mol) was dissolved in warm methanol (150 mL) and a 45% HFSA solution (45 mL, molar ratio L:HFSA = 1:3) was added to the resulting solution. The reaction

¹Odessa National Medical University, Odessa, Ukraine; *vgelmboldt@te.net.ua. ²Institute of Applied Physics, Chisinau, Republic of Moldova; **fonari.xray@phys.asm.md. Original article submitted January 25, 2019; revised January 25, 2019; accepted February 13, 2019.

mixture was subjected to spontaneous evaporation at room temperature. We obtained 8.56 g of a colorless crystalline product whose composition was determined from the elemental analysis data. For (LH)₂SiF₆ **I** calculated, %: Si 7.73, N 7.73; found, %: Si 7.91, N 7.58.

An attempt to synthesize 2-, 3-hydroxymethylpyridinium hexafluorosilicates by the analogous procedure was not successful, apparently due to a substantial decrease in the basicity when moving from 4-hydroxymethylpyridine to its 2- and 3-substituted isomers [9].

The EI mass spectrum was recorded on a MX-1311 spectrometer (direct injection of the sample into the source, the electron ionization energy of 70 eV).

The mass spectrum of **I**: [ML]⁺ (*m/z* = 109, *I* = 100%), [SiF₃]⁺ (*m/z* = 85, *I* = 75%), [ML–HCO]⁺ (*m/z* = 80, *I* = 77%).

The IR absorption spectrum was recorded on a Spectrum BX II FT-IR System (Perkin-Elmer) spectrophotometer (4000–350 cm⁻¹ region, KBr pellet sample).

The IR spectrum of **I** (cm⁻¹): 3211, 3157, 3102, 3044, 3030 [ν(OH), ν(N⁺H), ν(CH)], 2930 [ν_{as}(CH₂)], 2818 [ν_s(CH₂)], 1640 [δ(CNH), δ(COH)], 1606, 1508 [ν_{ring}], 797 [ρ(CH₂)], 738 [ν(SiF)], 482, 423, 403 [δ(SiF₂)].

The solubility of **I** in water and organic solvents (methanol, ethanol, dimethyl sulfoxide (DMSO)) was determined in line with the requirements of [10]. Isothermal conditions (*T* = 25 ± 0.2 °C) were provided using an U15 ultra thermostat.

A soluble form of silicon dioxide (orthosilicic acid) in the hydrolysis products of **I** was identified by photocolourimetry [11] based on the ability of silicic acid to form complex yellow silicomolybdic acid with molybdate ions (ammonium molybdate (NH₄)₂MoO₄ was the reagent) in acidic medium. The measurements were made at a wavelength of 380 nm on a KFK-3 spectrophotometer. The degree of hydrolysis α was calculated by the formula α = C_{Si hydr}/C_{Si total}, where C_{Si hydr} is the silicon concentration found in the hydrolysis products of hexafluorosilicate in the form of silicic acid; C_{Si total} is the calculated total silicon concentration in the salt solution.

Single crystal XRD. The structural data for compound **I** were obtained on an Xcalibur E diffractometer (room temperature, Eos two-dimensional CCD detector, graphite monochromator, MoK_α radiation).

The crystals of **I** are triclinic (C₁₂H₁₆F₆N₂O₂Si, *M* = 362.36): *a* = 7.0069(6) Å, *b* = 7.2565(6) Å, *c* = 7.9672(7) Å, α = 95.998(7)°, β = 101.503(7)°, γ = 109.940(7)°, *V* = 366.56(6) Å³, space group *P*-1, *Z* = 1, ρ_{calc} = 1.641 g/cm³, μ = 0.238 mm⁻¹, *F*(000) = 186. In total, 2270 reflections were recorded, including 1330 independent. The final refinement results are as follows: *R*₁ = 0.0374, *wR*₂ = 0.0907 for 1088 reflections with *I* > 2σ(*I*); *R*₁ = 0.0503, *wR*₂ = 0.0993 for all reflections. The structure was solved and refined using the SHELX97 software [12]. All non-hydrogen atoms were refined in the anisotropic approximation. Hydrogen atoms in ammonium and hydroxy groups were determined from Fourier difference maps and refined in the isotropic approximation. Selected bond lengths and bond angles for **I** are given in Table 1; geometric parameters of H bonds are given in Table 2. Crystallographic data for compound **I** have been deposited with the Cambridge Structural Database (CIF file CCDC No. 1892519, deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

TABLE 1. Interatomic Distances and Bond Angles in Compound **I**

Bond length	<i>d</i> , Å	Angle	ω, deg
Si(1)–F(2)	1.6780(11)	F(3)–Si(1)–F(1)	89.72(6)
Si(1)–F(3)	1.6795(12)	F(2)–Si(1)–F(3)	90.03(7)
Si(1)–F(1)	1.6877(11)	F(2)–Si(1)–F(1)	89.00(6)
O(1)–C(6)	1.401(3)	C(4)–N(1)–C(3)	122.24(18)
N(1)–C(4)	1.323(3)	N(1)–C(4)–C(5)	120.2(2)
N(1)–C(3)	1.339(3)	O(1)–C(6)–C(1)	111.19(18)

TABLE 2. Hydrogen Bonds in Compound **I**

Donor–H···Acceptor	H···A, Å	D···A, Å	∠DHA, deg	Symmetry transformation for acceptor
O(1)–H(1)···F(3)	1.885(6)	2.7036(18)	177(3)	$x, 1+y, z$
N(1)–H(1A)···F(1)	2.085(15)	2.824(2)	143(2)	$2-x, 1-y, 1-z$
N(1)–H(1A)···F(2)	2.049(14)	2.809(2)	146(2)	$2-x, 1-y, 1-z$
C(2)–H(2)···F(3)	2.53	3.283(3)	138.4	x, y, z
C(3)–H(3)···O(1)	2.39	3.220(3)	149.1	$x, y-1, z$
C(4)–H(4)···F(1)	2.35	3.239(3)	158.8	$x, 1+y, 1+z$
C(5)–H(5)···F(2)	2.40	3.177(2)	141.4	$2-x, 2-y, 1-z$
C(6)–H(6B)···F(3)	2.56	3.352(2)	138.8	$1-x, 1-y, -z$

RESULTS AND DISCUSSION

Compound **I** crystallizes in the centrosymmetric space group $P-1$ of the triclinic system. The ionic crystal is formed of pyridinium LH^+ cations and SiF_6^{2-} anions in the 2:1 ratio linked by the system of $\text{NH}\cdots\text{F}$ and $\text{OH}\cdots\text{F}$ hydrogen bonds and the $\text{CH}\cdots\text{F}$ and $\text{CH}\cdots\text{O}$ contacts (Fig. 1, Table 2).

The protonation center in the LH^+ cation is the nitrogen atom of the pyridine ring. The protonation of the nitrogen atom in LH^+ manifests itself in an increase in the $\text{C}(4)\text{--N}(1)\text{--C}(3)$ angle in the heterocycle to $122.24(18)^\circ$, which agrees with the literature data for this cation [13] and substantially larger than that in the neutral molecule of unprotonated 4-hydroxymethylpyridine [14]. The geometry of the SiF_6^{2-} anion in **I** is a distorted octahedron: the Si–F bond lengths are in a range 1.6780(11)–1.6877(11) Å. The difference in the Si–F bond lengths is explained by the involvement of fluorine atoms of the anions in H bonds of different strength with H-donor moieties of the cations.

In the three-term formula unit $(\text{LH})_2\text{SiF}_6$ the hexafluorosilicate anion is located in the inversion center; the organic cation occupies a general position, being practically in the anion plane determined by fluorine atoms Si(1), F(1), and F(2) (Fig. 1). The NH group is involved in the bifurcated hydrogen bond with these two fluorine atoms. The shortest intermolecular contact in the crystal is the $\text{O}\text{--H}\cdots\text{F}(3)$ hydrogen bond (Table 2) involving a hydroxyl group of the cation. These strong interactions link the neighboring formula units into ribbons along the crystallographic $[0\ 1\ -1]$ direction in the crystal. The cations related by the inversion center are arranged in a ribbon in parallel planes; the distance between the centroids of pyridine rings of the cations is 3.632 Å and the distance between their mean planes is 3.359 Å, indicating the $\pi\cdots\pi$ stacking interaction between these moieties (Fig. 2).

The $\text{CH}\cdots\text{F}$ and $\text{CH}\cdots\text{O}$ contacts (Table 2), involving aromatic hydrogen atoms, link the neighboring ribbons into layers parallel to the bc plane in the crystal (Fig. 3). There are only weak $\text{C}(6)\text{--H}\cdots\text{F}(3)$ interactions involving the methylene hydrogen atom between the layers (Table 2).

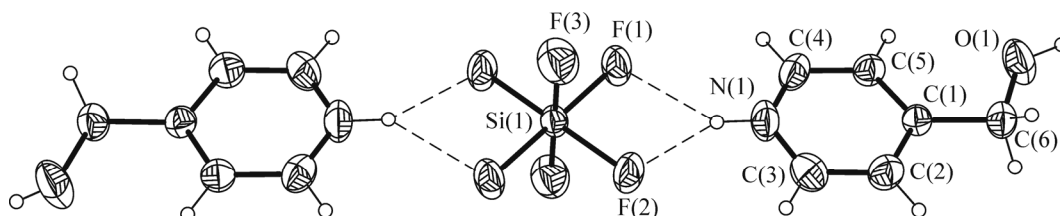


Fig. 1. Formula unit of compound **I** with thermal ellipsoids, hydrogen bonds, and numbering of basic atoms. Thermal ellipsoids are shown at the 50% probability level.

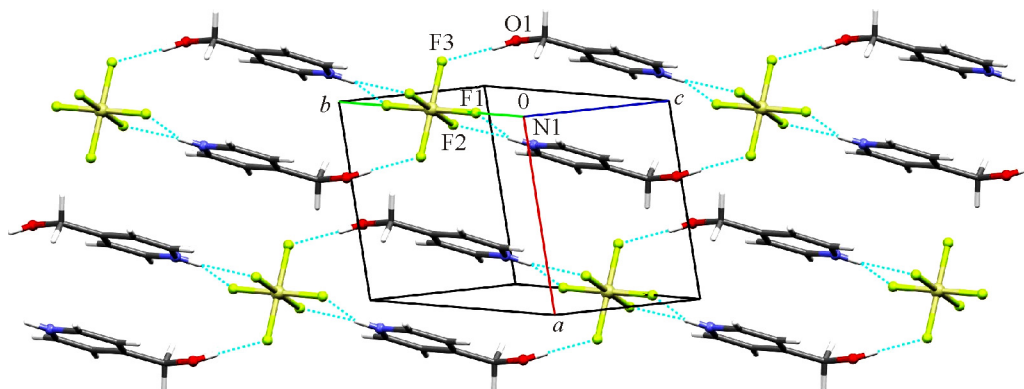


Fig. 2. Fragment of packing in compound **I** showing the arrangement of the structural components into ribbons.

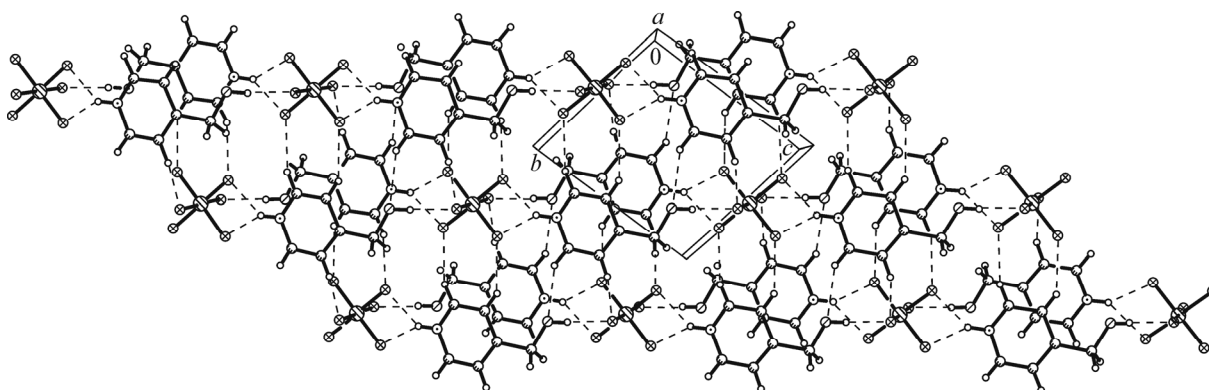


Fig. 3. Arrangement of ribbons into a layer in the structure of **I** in the projection on the *bc* plane.

The intense absorption bands at 738 cm^{-1} [$\nu(\text{SiF})$] and 482 cm^{-1} , 423 cm^{-1} , 403 (shoulder) cm^{-1} [$\delta(\text{SiF}_2)$] in the IR spectrum of **I** are assigned to the SiF_6^{2-} anion vibrations. According to [15], for the isolated SiF_6^{2-} ion with the O_h symmetry, two vibrations are active in the IR spectrum: ν_3 ($\nu(\text{SiF})$, at 740 cm^{-1}) and ν_4 ($\delta(\text{SiF}_2)$, at 480 cm^{-1}). From the single crystal XRD data it follows that the anion symmetry in the structure of **I** corresponds to the C_i group due to the effects of H bonds. According to the DFT calculation results for the $[\text{NH}_3(\text{CH}_2)_4\text{NH}_3]\text{SiF}_6$ complex [16], a decrease in the anion symmetry $O_h \rightarrow C_i$ should result in a split of the degenerate vibration ν_4 into three components. This conclusion agrees with the spectral characteristics of **I**.

It is known [17] that water solubility is a principal characteristic of drugs; the estimation of solubility in water and organic solvents is mandatory for all candidates for medicines. Fig. 4 depicts the solubility results for **I** in water, methanol, ethanol, and DMSO. From the obtained data and in accordance with the requirements from [10], complex **I** is very readily soluble in water, readily soluble in DMSO, and poorly soluble in methanol and ethanol (96%).

Previously, in [18, 19], it was shown that water solubility of pyridinium hexafluorosilicates and salts of the related heterocyclic cations with the pyridine-type N atoms antibatically correlated with the number of strong and medium H bonds (or the number of H-donors) in the structures of hexafluorosilicates. To estimate the influence of H bonds on the physicochemical characteristics of salts the parameter h was proposed

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

where n is the number of strong and medium H bonds ($\text{D}\cdots\text{A} \leq 3.2\text{ \AA}$ [20]); $d(\text{D}\cdots\text{A})_{\text{av}}$ is the average donor–acceptor distance in the structure of the complex. Table 3 reports the determined water solubility of **I**, the known solubility data for related salts with heterocyclic cations [4, 5, 18, 19], and the parameter h calculated from the single crystal XRD data. Note that the solubility value for **I** agrees with the correlation [18, 19] reflecting the relative stabilization of the salt structure (and, accordingly, a decrease in its solubility) with an increase in the parameter h .

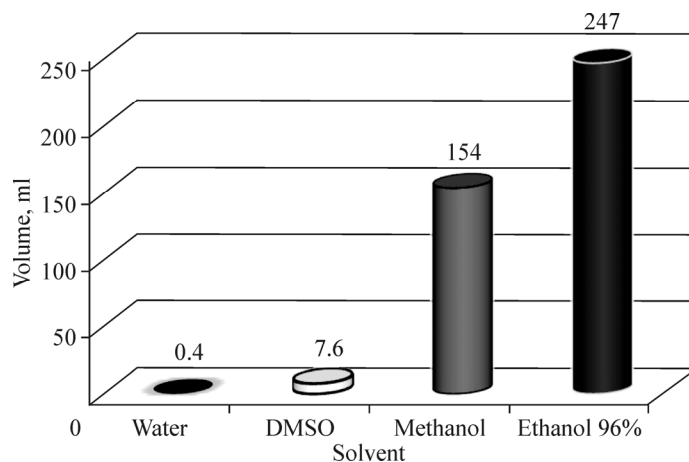


Fig. 4. Solubility of 4-hydroxymethylpyridinium hexafluorosilicate ($m = 100$ mg) in water and organic solvents.

TABLE 3. Water Solubility (mol%) of Hexafluorosilicates and h Values

Complex	Solubility, mol.%, 25 °C	h , Å ⁻¹
(2-HOCH ₂ C ₅ H ₄ NH) ₂ SiF ₆ (I)	1.33	1.30
(2-CH ₃ C ₅ H ₃ NH) ₂ SiF ₆	11.60	0.71 [21]
[2,6-(CH ₃) ₂ C ₅ H ₃ NH] ₂ SiF ₆	9.90	0.72 [21]
[3-HO(O)CCH ₂ C ₅ H ₄ NH] ₂ SiF ₆	1.02	0.74 [5]
[2,6-(HOCH ₂) ₂ C ₅ H ₃ NH] ₂ SiF ₆	2.52	1.04 [4]
[2-HO(O)CCH ₂ C ₅ H ₄ NH] ₂ SiF ₆	0.82	1.06 [5]
[4-HO(O)CCH ₂ C ₅ H ₄ NH] ₂ SiF ₆	0.58	1.33 [5]
(2-H ₂ NC ₅ H ₄ NH) ₂ SiF ₆	5.60	1.38 [18]
(2-Br-6-CH ₃ C ₅ H ₃ NH) ₂ SiF ₆ ·H ₂ O	2.01	1.42 [4]
[5-OH-6-CH ₃ -3,4-(HOCH ₂) ₂ C ₅ HNH] ₂ SiF ₆	0.89	1.68 [4]
(C ₂ H ₆ N ₅) ₂ SiF ₆	0.28	1.78 [22]
[2,6-(H ₂ N) ₂ C ₅ H ₃ NH] ₂ SiF ₆	0.06	2.35 [18]
[2-NH ₂ -4,6-(OH) ₂ C ₄ HN ₂ H] ₂ SiF ₆	0.002	3.0 [6]

Notes. (C₂H₆N₅)⁺ is the cation on 3,5-diamino-1,2,4-triazolium. [2-NH₂-4,6-(OH)₂C₄HN₂H]⁺ is the cation of 2-amino-4,6-dihydroxypyrimidinium.

The calculated degree of hydrolysis α of salt **I** in the $1 \cdot 10^{-4}$ M aqueous solution by general scheme (2) is expectedly high, being 87.3%



which indicates a high degree of SiF₆²⁻ ion conversion in diluted solutions with the formation of silicon dioxide and the release of fluoride ions. The latter is important in the context of clarifying the prospects for using **I** as a carioprophylactic agent.

Therefore, the interaction product of 4-hydroxymethylpyridine with hydrofluorosilicic acid is respective ammonium hexafluorosilicate, whose crystal structure is stabilized by NH \cdots F and OH \cdots F hydrogen bonds. The effects of H bonds result in a decrease in the SiF₆²⁻ anion symmetry in the structure to C_v, which is reflected in the complication of the IR spectrum of the salt in the region of anion bending vibrations. The salt is featured by high water solubility and almost quantitative hydrolysis occurs in diluted aqueous solutions. The discussed features in the behavior of 4-hydroxymethylpyridinium

hexafluorosilicate in aqueous solutions allow us to conclude about the feasibility of further research of its biological activity as a potential caries-prophylactic agent.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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