HEXAFLUOROSILICATES WITH ANTIBACTERIAL ACTIVE GUANIDINE CONTAINING CATIONS

V.O.Gelmboldt, V.Yu.Anisimov, O.V.Prodan
Odessa National Medical University

Key words: hexafluorosilicates; antibacterial active cations; structure; thermochemical transformations; hydrolysis

The present research has studied the spectral data, thermochemical transformations and hydrolysis of hexafluorosilicates with guanidine containing cations (C\textsubscript{6}H\textsubscript{5}H\textsubscript{3}Cl\textsubscript{4}N\textsubscript{3}+\textsubscript{2}\textsubscript{2}SiF\textsubscript{6} (I) and (C\textsubscript{6}H\textsubscript{5}H\textsubscript{3}N\textsubscript{3}+\textsubscript{2}2\textsubscript{2}SiF\textsubscript{6} (II) for their potential use as caries-preventive and antibacterial agents. Hexafluorosilicates of the composition I and II were separated as crystalline products of interaction of hexafluorosilicic acid with the methanol solutions of chlorhexidine hydrochloride and polyhexamethylene guanidine hydrochloride. The compounds isolated have been characterized by IR, NMR, thermogravimetric analysis, potentiometry. According to IR spectroscopy data, “onium” hexafluorosilicates I and II have ionic structures. The vibrations of the groups v(NH), v(NH\textsubscript{2}) in salts I and II appear as strong absorption bands at 3360-3180 cm\textsuperscript{-1}; s(NH\textsubscript{2}) vibrations appear at 1634 and 1637 cm\textsuperscript{-1}. The strong ν(SiF\textsubscript{6}+) and s(SiF\textsubscript{6}2-) stretches of SiF\textsubscript{6}2- anions are observed in their characteristic regions (at 744, 734 and 482 cm\textsuperscript{-1}, respectively). The singlet character of ν(SiF\textsubscript{6}2-) and s(SiF\textsubscript{6}2-) vibrations indicates the absence of noticeable distortion of symmetry of SiF\textsubscript{6}2-anion with regard to O\textsubscript{6}. The NMR \textsuperscript{19}F spectra of compounds I and II (in DMSO-d\textsubscript{6} solutions) have one resonance at –136,70, –135,09 ppm (SiF\textsubscript{6}2-); additional resonance at –123,14 ppm, in the case of II it can be related to the octahedral complex anion [SiF\textsubscript{6}(DMCO)\textsubscript{2}]\textsuperscript{2-}. The results of thermogravimetric analysis are consistent with a multi-stage thermolysis scheme for hexafluorosilicates I and II. The temperatures of thermolysis beginning of complexes I and II are 270 and 100°C, respectively. The compounds I and II studied are characterized by the predicted tendency to hydrolysis in dilute aqueous solutions with formation of orthosilicic acid and fluoride ions, and it allows considering these salts as potential anticaries agents. The study of the biological activity of these compounds is the subject of further investigations.

In recent years, several research groups consisting of experts from Japan, the United States [10-13] and Armenia [1, 8] demonstrated the possible use of ammonium and amino acids hexafluorosilicates as caries-preventive and hyposensitive agents in dental practice. These results [1, 8, 10-13] allow to consider the “onium” hexafluorosilicates as a promising new class of drugs possessing a number of advantages compared to the conventional agents of fluoride caries therapy such as sodium and sodium monofluorophosphate. The active components of treatment and prevention of dental caries are also antibacterial agents, including high efficient guanidine derivatves (chlorhexidine, polyhexamethylene guanidine hydrochloride, etc.) [9, 13]. In principle, introducing guanidine containing cations possessing the antibacterial action into the composition of hexafluorosilicate allows to obtain compounds for which the caries-preventive effect of the anion is intensified by the bactericidal action of the cation. The aim of this work is the synthesis, the study of the structure and properties of chlorhexidine (CH) and polyhexamethylene guanidine (PHMG) hexafluorosilicates – the first representatives of fluoride-containing salts combined with cations exhibiting the antibacterial activity.

Materials and Methods

The synthesis of hexafluorosilicates was performed by the ion exchange reaction between methanol solutions of the corresponding hydrochloride (HC) (Hangzhou dayangchem Co., Ltd, China) and the solution of 45% fluorosilicic acid (the molar ratio of HC : H\textsubscript{4}SiF\textsubscript{6} = 1 : 3). The reaction mixtures were kept at room temperature to evaporate the solvents and obtain colourless crystalline products. The nitrogen content was determined according to Kjeldahl [5] and the silicon content by the photocolorimetric method [6].

The IR-absorption spectra were recorded on a Spectrun BX II FT-IR System spectrophotometer (Perkin-Elmer) (the range was 4000-350 cm\textsuperscript{-1}, the samples were in the form of tablets with KBr). The EI mass spectra were recorded on a MX-1321 spectrophotometer (a direct introduction of a sample into the source, the energy of ionizing electrons was 70 eV), FAB mass spectra – on a VG 7070 spectrometer (VG Analytical) (desorption of ions from the surface of the liquid phase was performed by a beam of argon atoms with the energy of 8 keV, m-nitrobenzyl alcohol was used as a matrix). The \textsuperscript{19}F NMR spectra were recorded on a Varian VXR-300 spectrometer (282 MHz, the solvent was DMSO-d\textsubscript{6}, with CFCl\textsubscript{3} as a standard, the temperature was 27°C). Thermogravimetric analysis was performed on a Q-1500 D derivatograph of F. Paulik – J. Paulik – L. Erdey’s system (platinum crucibles, samples of 80-100 mg, the temperature range was 20-1000°C, the sample weight heating rate was 10 °/min, Al\textsubscript{2}O\textsubscript{3} as a standard).
The pH values of aqueous solutions of hexafluorosilicates were determined using an EV-74 universal ionomer.

### Results and Discussion

The composition of the compounds isolated has been determined by the elemental analysis data.

For (C₅H₅N)₂Cl(SiF₆)₂ (I) calculated, %: N – 21.56; Si – 4.23.

For (C₅H₅N)₂(N) (SiF₆)₂ (II) calculated, %: N – 19.70; Si – 4.39.

The mass spectrum EI: [CIC₅H₅CH₂N₃H₂]⁺ (m/z = 153, I = 8%, [CIC₅H₅NH₂]⁺ (m/z = 127, I = 100%), [SiF₆]⁻ (m/z = 85, I = 20%), [C₅H₅CH₂]⁺ (m/z = 72, I = 9%), [C₅H₅N]⁺ (m/z = 42, I = 6%).

The mass spectrum FAB: [M₁₆H⁺]⁺ (m/z = 505, I = 2%).

The mass spectrum EI: [NH(C≡NH)NHCH₂⁺]⁺ (m/z = 142, I = 2%, [SiF₆]⁻ (m/z = 85, I = 100%), [C₅H₅CH₂⁺ (m/z = 72, I = 5%), [C₅H₅N]⁺ (m/z = 71, I = 7%), [C₅H₅⁺]⁺ (m/z = 55, I = 7%), [C₅H₅]⁺ (m/z = 42, I = 15%).

Characteristics of IR spectra of compounds I and II are presented in Table 1, with vibration rating carried out using the data in [7]. Stretching ν(NH), ν(N’H₂) and deformation δ(N’H₂) vibrations of cations occur in the areas of 3400-3180 and 1640-1630 cm⁻¹, respectively; a diffused nature of ν(NH) and ν(N’H₂) maxima may indicate the participation of groups =NH and −N’H₂ in H-bonds of NH···F with fluorine atoms of hexafluorosilicates anions. A singlet type of vibration bands ν(SiF₆) and δ(SiF₆) for anions SiF₆²⁻ (identified in characteristic spectral regions I and II at 744, 734 and 482 cm⁻¹, respectively) reflect apparently proximity of the anions structure to the idealized O₆-symmetry.

Low solubility of I and II in chloroform did not allow to carry out the registration of ¹⁹F NMR spectra of salts in the medium of the given solvent. In the ¹⁹F NMR I and II spectra in the solution of dimethyl sulfoxide (DMSO) singlet signals with chemical shifts δF = -136.70-135.09 ppm, respectively, correspond to SiF₆²⁻ anion. Along with SiF₆⁻ anion signal, the signal with δF = -123.14 ppm referred to equatorial fluorine atoms of octahedral anion [SiF₆²⁻(DMSO)]⁻ – the product of SiF₆⁻ anion solvolysis is also recorded in ¹⁹F NMR II spectrum.

Judging by the thermogravimetric analysis data the thermal decomposition of compound I is accompanied by elimination of 2 moles of HF in the gas phase (the endothermic effect on the curves of DTG and DTA at t₀ = 270°C, tmax = 300°C; Δmcalc = 8.3%, Δmexp = 6.2%), 1 mole of SiF₆²⁻ (the endothermic effect at t₀ = 350°C, tmax = 400°C; Δmcalc = 33.3%, Δmexp = 22.2%), degradation products of CH and their oxidation (endothermic and exothermic effects at t₀ = 440°C, tmax = 480°C and t₀ = 690°C, tmax = 750°C, respectively). The evident excess of the value of the weight loss I experimentally determined compared to the calculated value in the case of SiF₆ removal effect may be due to the superposition of CH expansion effect. The total weight loss of the sample I is 93.3%.

Complex II is differentiated by lower thermal resistance than complex I. Thermolysis II begins at 100°C, on DTA and DTG curves a series of endothermic effects is fixed at tmax = 120, 170, 200, 270, 340, 480°C and exothermic effect at tmax = 660°C. The total weight loss of sample II is 98.3%. The proximity of the thermal stability II and PHMG HC studied earlier by the pyrolysis mass spectrometry method should be noted [4].

Attempt to determine the extent of hydrolysis of compounds I and II at 1×10⁻⁴ M of the aqueous solution using the spectrophotometric method [3, 6] based on the ability of orthosilicic acid – the product hydrolysis – to form a yellow-coloured silico-molybdic complex with ions MoO₄²⁻ failed due to intense opalescence of solutions. But the fact of hydrolysis of SiF₆⁻ ion according to the scheme (1) is confirmed by the expected development of a yellow coloration of the solution after addition of (NH₄)₂MoO₄:

\[
\text{SiF}_6^{2-} + 4\text{H}_2\text{O} \rightarrow \text{Si(OH)}_4 + 6\text{F}^- + 4\text{H}^+. \quad (1)
\]

The results of pH determination of diluted aqueous solutions of salts (Table 2) indicate the hydrolytic instability of compounds I and II: pH values are in the “acidic” region and close to the corresponding values for the aqueous solutions of pyridinium hexafluorosilicates [2].
CONCLUSIONS
The synthesis has been performed, the spectral characteristics and physico-chemical properties have been studied, and the conclusion has been made about the probable structure of hexafluorosilicates of chlorhexidine and polyhexamethylene guanidine as potential caries-preventive and antibacterial agents. Evaluation of the biological activity of the compounds obtained will be the subject of our further research.

REFERENCES
2. Анисимов В.Ю., Гельмбольт В.О., Кузьмин В.Е. и др. // Одесский мед. журн. – 2013. – №1. – С. 6-10.
методами ИК-, ЯМР $^{19}$F-, масс-спектроскопии, термогравиметрического анализа, потенциометрии. Согласно данным ИК-спектроскопии «оньевые» гексафторосиликаты I и II имеют ионное строение. Колебания $v$(NH), $v$(N-H$^+$) в спектрах I и II проявляются в виде интенсивных полос поглощения при 3360-3180 см$^{-1}$; колебания $\delta$(N-H$^+$) – при 1634 и 1637 см$^{-1}$. Интенсивные полосы колебаний $v$(SiF) и $\delta$(SiF$^-$) ионов SiF$_6^{2-}$ наблюдаются в характерных областях спектров при 744, 734 и 482 см$^{-1}$ соответственно. Синглетный характер колебаний $v$(SiF) и $\delta$(SiF$^-$) указывает на отсутствие заметных искажений геометрии ионов SiF$_6^{2-}$ относительно O$_h$-симметрии. В спектрах ЯМР $^{19}$F растворов солей I и II в DMSO-d$_6$ ионам SiF$_6^{2-}$ соответствуют резонансные сигналы с химическими сдвигами $-$136,70, $-$135,09 м.д.; дополнительный резонансный сигнал при $-$123,14 м.д. в спектре II может относиться к октаэдрическому комплексному аниону [SiF$_5$(DMSO)]$^-$.

Результаты термогравиметрического анализа согласуются с многоступенчатой схемой термолиза I и II. Температуры начала термолиза комплексов I и II составляют 270 и 100 °C соответственно. Соединения I и II характеризуются ожидаемой склонностью к гидролизу в разбавленных водных растворах с образованием щелочи SiF$_4$ или фторид-ионов, что позволяет рассматривать указанные соли в качестве потенциальных антикариесных агентов. Изучение биологической активности полученных соединений будет предметом наших дальнейших исследований.