HEXAFLUOROSILICATES WITH ANTIBACTERIAL ACTIVE GUANIDINE CONTAINING CATIONS

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The present research has studied the spectral data, thermochemical transformations and hydrolysis of hexafluorosilicates with guanidine containing cations \((\text{C}_2\text{H}_5\text{Cl}N\text{O})\text{SiF}_6\) (I) and \((\text{C}_6\text{H}_4\text{N})\text{SiF}_6\text{d}_{1.5}\) (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, mass-spectrometry, thermogravimetric analysis, potentiometry. According to IR spectroscopy data, “onium” hexafluorosilicates I and II have ionic structures. The vibrations of the groups \(\nu(NH)\), \(\nu(NH_2)\) in salts I and II appear as strong absorption bands at 3360-3180 cm\(^{-1}\); \(\delta(NH_2)\) vibrations appear at 1634 and 1637 cm\(^{-1}\). The strong \(\nu(SiF)\) and \(\delta(SiF)\) stretches of \(\text{SiF}_2^–\) anions are observed in their characteristic regions (at 744, 734 and 482 cm\(^{-1}\), respectively). The singlet character of \(\nu(SiF)\) and \(\delta(SiF)\) vibrations indicates the absence of noticeable distortion of symmetry of \(\text{SiF}_2^–\) anion with regard to \(O_6\). The NMR \(^{19}F\) spectra of compounds I and II (in DMSO-d\(_6\) solutions) have one resonance at \(-136,70, -135,09\) ppm (\(\text{SiF}_2^–\)); additional resonance at \(-123,14\) ppm, in the case of II it can be related to the octahedral complex anion \([\text{SiF}_6^2\text{d}(\text{DMCO})]^-\). 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 potassium fluorides, silver diamine fluoride, tin fluoride and potassium monofluorophosphate. The active components of treatment and prevention of dental caries are also antibacterial agents, including high efficient guanidine derivatives (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\(_2\)SiF\(_6\) = 1 : 3). The reaction mixtures were kept at room temperature to evaporate the solvents and obtain colourless crystalline products. The nitrogen content was determined 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.

The IR-absorption spectra were recorded on a Spectruhm BX II FT-IR System spectrophotometer (Perkin-Elmer) (the range was 4000-350 cm\(^{-1}\), the samples were in the form of tablets with KBr). The EI mass spectra were recorded on a MX-1321 spectrophotometer (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 \(^{19}F\) NMR spectra were recorded on a Varian VXR-300 spectrometer (282 MHz, the solvent was DMSO-d\(_6\), with CFCI\(_3\) 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\(_2\)O\(_3\) as a standard).
Wave numbers (cm⁻¹) of the absorption band maxima in IR spectra of chlorhexidine (I) and polyhexamethylene guanidine (II) hexafluorosilicates

| I   | II   | Assignment         |
|-----|------|-------------------|
| 3401 s.br. | 3354 s.br. | v(NH), v(NH₃⁺)   |
| 3207 s.br. | 3187 sh.  | v(SiF)            |
| 2926 sh.  | 2936 s.   | v(CH₃)            |
| 2862 sh.  | 2861 m.   | v(CH₂)            |
| 1690 s.   | 1656 s.   | v(C=O)            |
| 1634 m.   | 1637 sh.  | δ(NH₂)            |
| 1550 m.   | v(CC)      | v(CC)             |
| 1493 m.   | v(Cl₂)     | v(Cl₂)            |
| 1462 m.   | 1473 m.   | δ(CH₂)            |
| 1384 m.br. | v(C₂H₅N)  | δ(NH) + v(CN)     |
| 1249 m.   | v(C₂H₅N)  | v(C₂H₅N)          |
| 1095 s.   | v(Cl₂)     | v(Cl₂)            |
| 1017 s.   | 1026 w.   | v(Cl₂)            |
| 744 s.    | 734 s.    | v(SiF)            |
| 482 m.    | 482 m.    | δ(SiF₂)           |

Note: w = weak, m = medium, s = strong, v = very, sh = shoulder, br = broad.

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 elementary analysis data. Found, %: N – 21.41; Si – 4.50.

For (C₆H₅N₅Cl)_nSiF₆ (I) calculated, %: N – 21.56; Si – 4.32.

Found, %: N – 19.89; Si – 4.22.

For (C₆H₅N₅H)_n(SiF₆)₂ (II) calculated, %: N – 19.70; Si – 4.39.

The mass spectrum EI I: [CIC₂H₅CH₂NH₂]⁺ (m/z = 153, I = 8%), [CIC₂H₅NH₂]⁺ (m/z = 127, I = 100%), [SiF₆]⁻ (m/z = 85, I = 20%), [CIC₂H₅₂⁻]⁺ (m/z = 72, I = 9%), [C₂H₅]⁻ (m/z = 42, I = 6%).

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

The mass spectrum EI II: [NH(C=NH)NH(CH₃)₂]+ (m/z = 142, I = 2%), [SiF₆]⁻ (m/z = 85, I = 100%), [C₂H₅]⁻ (m/z = 72, I = 5%), [C₂H₅CH₃]⁻ (m/z = 71, I = 7%), [C₂H₅CH₃]⁻ (m/z = 55, I = 7%), [C₂H₅CH₃]⁻ (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 v(NH), v(NH₃⁺) and deformation δ(NH₂) vibrations of cations occur in the areas of 3400-3180 and 1640-1630 cm⁻¹, respectively; a diffused nature of v(NH) and v(NH₃⁺) maxima may indicate the participation of groups =NH and –N₂H₂ in H-bonds of NH···F with fluorine atoms of hexafluorosilicates anions. A singlet type of vibration bands v(SiF) and δ(SiF₂) 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 δᵣ = -136.70-135.09 ppm, respectively, correspond to SiF₆²⁻ anion. Along with SiF₆²⁻ anion signal, the signal with δᵣ = -123.14 ppm referred to equatorial fluorine atoms of octahedral anion [SiF₆(DMSO)]⁻ – the product of SiF₆²⁻ 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 tₒ = 270°C, tᵣ = 300°C; Δmₐᵢₓₛ = 8.3%, Δmₖᵦₑᵢₓ = 6.2%), 1 mole of SiF₆⁻ (the endothermic effect at tₒ = 350°C, tᵣ = 400°C; Δmₐᵢₓₛ = 33.3%, Δmₖᵦₑᵢₓ = 22.2%), degradation products of CH and their oxidation (endothermic and exothermic effects at tₒ = 440°C, tᵣ = 480°C and tₒ = 690°C, tᵣ = 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 tᵣ = 120, 170, 200, 270, 340, 480°C and exothermic effect at tᵣ = 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 1×10⁻⁵ 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 SiF₆²⁻ ion according to the scheme (1) is confirmed by the expected development of a yellow coloration of the solution after addition of (NH₄)₂MoO₄:

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

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].
ГЕКСАФТОРОСИЛІКАТИ З ГУАНІДИНОВМІСНИМИ КАТИОНАМИ, ЩО ВИЯВЛЯЮТЬ АНТИБАКТЕРІАЛНУ АКТИВНІСТЬ
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Ключові слова: гексафторосилікати; бактерицидні катіони; будова; термомічні перетворення; гідросилікати; бактерицидні катіони

Гексафторосилікати – це комплексы, які можуть містити бактерицидні катіони та використовуватися для захисту від бактеріальних захворювань. Вивчення біологічної активності цих сполук є предметом наших подальших досліджень.

Видалені сполуки складу I та II охарактеризовані методами ІЧ-, ЯМР, мас-спектроскопії, термогравіметричного аналізу, потенціометрії. Згідно з даними ІЧ-спектроскопії «енієві» гексафторосилікати I та II мають іонну будову. Коливання ν(SiF₂⁻) у спектрах I і II відповідно становлять 3360-3180 см⁻¹ і 3360-3180 см⁻¹. Результати термогравіметричного аналізу узгоджуються з багатоступінчастою схемою термогравіметричного аналізу I та II. Температура початку термогравіметричного аналізу I та II складають 270 і 100°C відповідно. Сполуки I і II характеризуються охідкою склінності до гідролізу в розведених водних розчинах з утворенням ортокремнієвої кислоти і фторид-іонів, що дозволяє розглядає зазначені солі в якості потенційних антикарієсних агентів.

ГЕКСАФТОРОСИЛІКАТИ С ГУАНІДИНОВСОДЕРЖАЩИМИ КАТИОНАМИ, ПРОЯВЛЯЮЩИМИ АНТИБАКТЕРИАЛЬНУ АКТИВНОСТЬ
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Ключевые слова: гексафторосилкаты; бактерицидные катионы; строение; термомеханические превращения; гидролиз

С использованием реакции ионного обмена между гидрохлоридами хлоргексидина (полигексаметилиленгуанидина) и кремнефторводородной кислотой в среде метанола синтезированы гексафторосилкаты соответствующих гуанидиносодержащих катионов (C₂H₅ClN₂)SiF₆²⁻ (I) и (C₂H₅N₂)SiF₆²⁻ (II), представляющие интерес в качестве потенциальных бактерицидных и антакариесных агентов. Выделенные соединения состава I и II охарактеризованы...
методами ИК-, ЯМР $^{19}$F-, масс-спектроскопии, термогравиметрического анализа, потенциометрии. Согласно данным ИК-спектроскопии «онивые» гексафторосиликаты I и II имеют ионное строение. Колебания $\nu$(NH), $\nu$(N$^+$H$_2$) в спектрах I и II проявляются в виде интенсивных полос поглощения при 3360-3180 см$^{-1}$; колебания $\delta$(N$^+$H$_2$) – при 1634 и 1637 см$^{-1}$. Интенсивные полосы колебаний $\nu$(SiF) и $\delta$(SiF$_2^-$) аннонов SiF$_6^{2-}$ наблюдается в характеристических областях спектров при 744, 734 и 482 см$^{-1}$ соответственно. Синглетный характер колебаний $\nu$(SiF) и $\delta$(SiF$_2^-$) указывает на отсутствие заметных искажений геометрии аннонов SiF$_6^{2-}$ относительно $O_h$-симметрии. В спектрах ЯМР $^{19}$F растворов солей I и II в ДМСО-д$_6$ анноном 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 аннону [SiF$_5$(ДМСО)]$^-$, Результаты термогравиметрического анализа согласуются с многоступенчатой схемой термолиза I и II. Температуры начала термолиза комплексов I и II составляют 270 и 100°С соответственно. Соединения I и II характеризуются ожидаемой склонностью к гидролизу в разбавленных водных растворах с образованием ортокремниевой кислоты и фторид-ионов, что позволяет рассматривать указанные соли в качестве потенциальных антикариесных агентов. Изучение биологической активности полученных соединений будет предметом наших дальнейших исследований.