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AMMONIUM HEXAFLUOROSILICATES AS POTENTIAL ANTI-CARIES AGENTS: INFLUENCES OF CATION EFFECTS ON THE PROPERTIES OF SALTS

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Dental caries is one of the most important socially significant health problems in both industrialized and developing countries [1]. In recent years, a high caries prophylactic efficacy of ammonium hexafluorosilicate $(NH_4)_2SiF_6$ (AHFS) and ammonium hexafluorosilicates with biologically active cations (AHBAC) [2] has been discovered. In the case of AHBAC using, there is a potential possibility of enhancing the anticaries effect of the fluorine-containing anion as a result of the contribution of the effects of cations, for example, anti-inflammatory and antibacterial effects. The purpose of this communication is analysis of the influence of ammonium cation effects on the physicochemical properties and biological activity of ammonium hexafluorosilicates in the context of their potential application as pharmaceutical agents.

It is important to note that, in contrast of hexafluorosilicates of metals cations M_2SiF_6, ammonium salts $(LH)_2SiF_6$ are the typical supramolecular compounds [3]. The specificity of the supramolecular complexes structure is as follows: the structure of salts of anions with cations such as protonated forms of amines are formed both on the bases of electrostatic Coulomb and van der Waals interactions, and with the participation of interionic H-bonds. Fluoride ion is the strongest H-acceptor among the anions, while SiF_6^{2-} anion is the strongest one in the series of complex fluoroanions of *p*-elements: $F^- > SiF_6^{2-} > BF_4^- > PF_6^-$ [4]. According to X-ray diffraction data [2], in the $(LH)_2SiF_6$ structures, mainly strong and medium H-bonds NH···F are realized (distances N···F $\leq$ 3,2 Å [4]), which a priory may indicate a significant contribution of interionic H-interaction NH···F to the total stabilization of ammonium hexafluorosilicates energy. As a consequence, NH···F H-bonds have a significant effect on the structural characteristics and properties of ammonium hexafluorosilicates.

Water solubility. The water solubility (WS) is a fundamental physicochemical characteristic of drugs since the solubility evaluation is a nessasary standart procedure for all drug candidates. As it follows from [2], the introduction of H-donor hydrophylic groups into the pyridinium cations in the row from $(RC_5H_4NH)_2SiF_6$ (R = H, 2-CH_3) to $(R'C_5H_4NH)_2SiF_6$ (R′ = –COOH, –$CONH_2$, –$CONHNH_2$, –$CSNH_2$, –NH_2) is accompanied by significant (in some cases more than an order of magnitude) decrease in the WS of the corresponding hexafluorosilicates. The latter is a consequence of an increase in the number of interionic H-bonds stabilizing the structure of salts, as confirmed by X-ray diffraction data [2]. For a comparative assessment of the interionic H-bonds effect on the solubility of ammonium hexafluorosilicates, the empirical parameter *h* was proposed [2]:

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

where n is the number of short interionic contacts ($D\cdots A \leq 3.2$ Å), $d(D\cdots A)_{av.}$ – is an average donor-acceptor distance in the structure of the complex. The graphical dependence of the solubility values *C* of salts *viz.* parameter *h* is shown in Fig. 1.

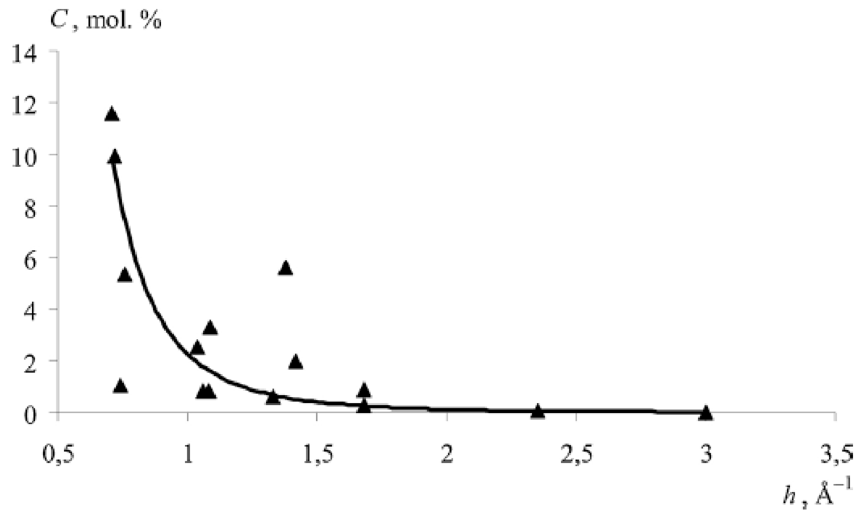

Figure 1. The relationship of the solubility *C* of hexafluorosilicates *viz.* parameter *h*.

So, the WS (mol. %) for hexafluorosilicates of heterocyclic cations tends to an exponential decrease with an increase the number of strong and medium H-bonds in their structures. For example, sharply low solubility value of 2-amino-4,6-dihydroxypyrimidinium hexafluorosilicate $[2\text{-}NH_2\text{-}4,6\text{-}(OH)_2C_4HN_2H]_2SiF_6$ (*C* = 0.002 mol. % [2]) is completely predictable: this salt is stabilized by a system of 18 strong and medium H-bonds NH···F, NH···O, CH···F (*h* = 3). This salt is also characterized by extremely low solubility in non-aqueous solvents – methanol, ethanol (96 %) and dimethyl sulfoxide.

The next step towards elucidating the factors that determine the WS of AHBAC was the construction of adequate 2D QSPR models for describing and prediction the WS of these compounds [5]. All models were developed using structural descriptors calculated by the SiRMS method, based on the simplex representation of the molecular structure and Dragon descriptors. All QSAR models were obtained using the partial least squares method. Model M1 has examined the influence of various physicochemical and structural factors on the WS of the studied compounds. The interpretation results are consistent with the qualitative data of previous experimental works [2]. The nontrivial nature of the H-bond effect ("hydrophobic effect") was also shown. Model M2 could predict the solubility of new compounds of the studied type with satisfactory accuracy (coefficient of determination $R^2_{test} = 0.72$). Relationship between observed and predicted values of Log(WSol) for the test set within the consensus model is presented in Fig. 2.

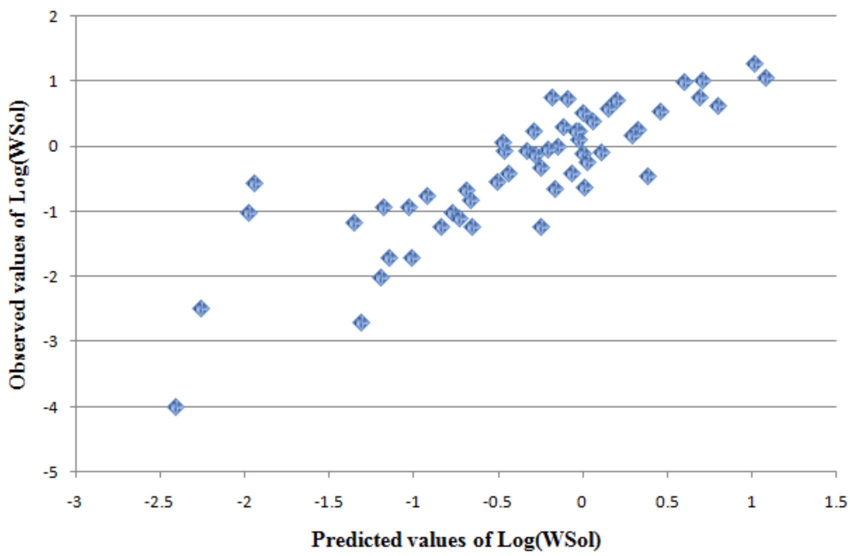

Figure 2. Observed vs predicted diagram of Log(WSol) for test set (model M2).

Hydrolysis. The hydrolytic unstability of ammonium hexafluorosilicates is an important prerequisit for the use of AHFS and AHBAC as caries profilactic agents. The hydrolysis of the salts $(LH)_2SiF_6$ can be described by general schemes:

$$SiF_6^{2-} + 4H_2O \rightleftarrows Si(OH)_4 + 6F^- + 4H^+, \qquad (2)$$

$$LH^+ + H_2O \rightleftarrows L + H_3O^+. \qquad (3)$$

The shift of equation (2) to the right is accompanied by the released of fluoride ions, which form with the Ca^{2+} cations a precipitate of calcium fluoride CaF_2:

$$Ca^{2+} + 2F^- \rightarrow CaF_2. \qquad (4)$$

The latter ensures the occlusion of dentine tubule. As noted in [6], the acidic nature of the studied $(LH)_2SiF_6$ solutions of various concentration (pH 2.2 – 3.4, as a result of salt hydrolysis by anion (2) and cation (3)) leads to etching of the dentine surface and its coating with stable layer of CaF_2 sediment.

In [2], the degree of hydrolysis of several ammonium hexafluorosilicates in $1{\cdot}10^{-4}$ M aqueous solutions was determined by analyzing the content of the silicon dioxide soluble form in the products of hydrolysis. The degree of hydrolysis α of all studied salts in dilute aqueous solutions (simulating the behavior of AHBAC in the saliva environment) is consistently high and in some cases reaches practically quantitative values (α = 80.5 – 99.8 %). It was hypothesized that the hydrolysis of ammonium hexafluorosilicates could be stimulated by the weakening the part of the Si–F bonds in the SiF_6^{2-} anion due to the effects of H-bonding [2].

Thermal stability. The thermal stability (TS) is an important physicochemical characteristic of drugs; TS is closely connected with the period and storage conditions of pharmaceutical substances [7]. Differential scunning calorimetry and thermogravimetric analysis (TGA) are commonly used to study the TS of drugs. In the case of TGA, the TS is estimated from the temperature of the onset of thermolysis, at which a decrease in the mass of the test substance is observed. According to TGA data, the onset thermolysis temperatures t_0 (°C) in the series of ammonium hexafluorosilicates with pyridinium cations $(RC_5H_4NH)_2SiF_6$ (R = 2-CH_3, 2-HOOC, 3-HOOC, 4-HOOC, 4-H_3NHNOC, 2-H_2N) and $(R_2C_5H_3NH)_2SiF_6$ (R_2 = 2,6-$(CH_3)_2$, 2,6-$(H_2N)_2$) are symbatically correlate with the values of the parametr *h* (Fig. 3).

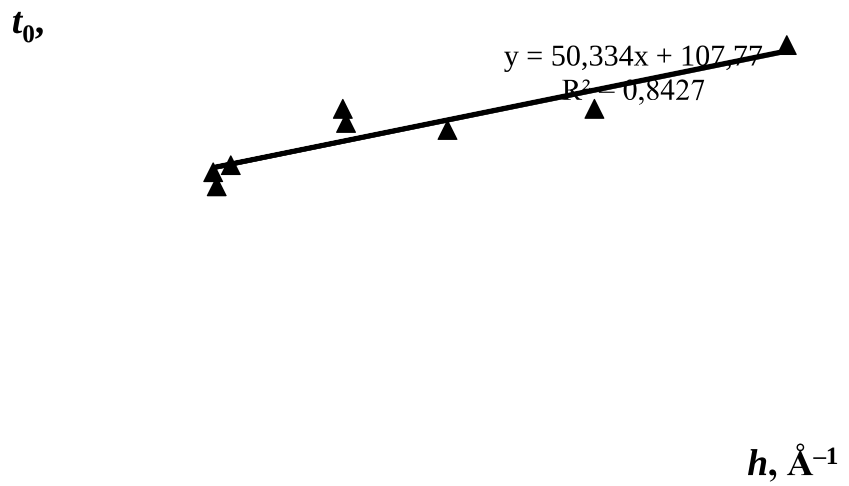

Figure 3. The relationship of the onset thermolysis temperature *viz.* parameter *h*.

The TS of the complexes guite predictable increases with an increase in the number of interionic H-bonds.

Biological activity. According to the results of a systematic study of caries prophylactic efficacy (CPE) of a number of AHBAC with various types of cations [2, 8-11] when sodium fluoride and AHFS are used as reference drugs, the following general trend is observed:

$$CPE_{AHBAC} \geq CPE_{AHFS} > CPE_{NaF}. \qquad (5)$$

The right side of inequality (5) reflects the differences in the dynamics of the CaF_2 precipitate formation process when using AHFS and NaF, while the left side may indicate a certain contribution of the pharmacological effect of the ammonium cation to the anticaries action of hexafluorosilicate. For example, the CPE, determined in animal experiments (Wistar white rats) for a series of compounds NaF, AHFS, $(L^{1-3}H)_2SiF_6$ (L^{1-3} = 2-, 3-, 4-$HOOCCH_2C_5H_4N$, **I** – **III**), is 9.1, 27.7, 6.8, 11.4 and 45.5 %, respectively [9]. Thus, **III** shows the maximum CPE 5 times exceeding the indicated figure for NaF. It is interesting to note that the PASS forecast data for these compounds demonstrate the maximum likelihood of anti-inflammatory activity for the 3-isomer [2]. However, an attempt to experimentally evaluate the anti-inflammatory activity of compounds **I** – **III** in a carrageenan model of inflammation did not lead to identification of this type of activity. In a series of similar AHBAC $(L^{4-6}H)_2SiF_6$ (L^{4-6} = 2-, 3-, 4-$HOOCC_5H_4N$, **IV** – **VI**) the salt of 4-substituted isomer **VI** also exhibits the maximum CPE [10]; however, the differences in the anticaries activity of these compounds and reference salts are not so significant. Thus, CPE of the salt **VI** is 1.9 times higher than that for NaF. According to the results of PASS analysis [8], for isomeric pyridinecarboxylic acids L^{4-6} a high probability of stimulation of salivation activity is expected. The CPE for octenidine hexafluorosilicate $(C_{36}H_{62}N_4)SiF_6$ (**VII**) with bactericidal cation and AHFS is almost the same (36,4 %) and exceed the corresponding value for NaF by 1.7 times [11]. Salt **VII** has a noticeably more significant periodontal efficiency (54.7 %), which may be the result of the contribution of the cation bactericidal effect.

Conclusions. Ammonium hexafluorosilicates have a supramolecular structure based on strong interionic H-bonds NH···F. The high H-acceptor ability of the SiF_6^{2-} anion leads to a noticeable influence of the H-bond effects on such macroscopic properties of ammonium hexafluorosilicates as water solubility and thermal stability, which can be used for a controlled change in those properties when creating new potential medicinal substances. QSPR model was developed with satisfactory predictive ability for virtual screening of the water solubility of new ammonium hexafluorosilicates. The hydrolytic unstability of ammonium hexafluorosilicates could be stimulated by the weakening of some Si–F bonds in the SiF_6^{2-} anion due to the H-bonds effects. The relationship between the pharmacological activity of the cation and the anticaries action of hexafluorosilicates is found in the form of an increase in the CPE of AHBAC in comparison with a similar characteristic of AHFS. The influence of the biological activity of the cation on the CPE of AHBAC has a complex nature and is not reduced to the action of one dominant type of activity.

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