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SOLUBILITY AND HYDROLYSIS OF AMMONIUM HEXAFLUOROSILICATES AS POTENTIAL PHARMACEUTICALS (A REVIEW)

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This review analyzes and systemizes results from publications on the solubility and hydrolysis of ammonium hexafluorosilicates (AHFS). These inorganic compounds have a variety of technological applications and have been actively researched as potential anti-caries agents in recent years. The characteristics of AHFS solubility were examined in water, methanol, ethanol (96%), and dimethyl sulfoxide. Existing approaches were discussed to interpret the main trends in changes of salts solubility depending on cation structure. Interionic H-bonds were noted to have a non-trivial negative impact on the water solubility of AHFS. The hydrophobic effect of H-bonds also needed to be considered when searching for new pharmaceutical substances among AHFS. A high, often close to quantitative, degree of hydrolysis of AHFS was found in diluted aqueous solution, resulting in an effective release of fluoride ions with caries-preventive properties.

Keywords: ammonium hexafluorosilicates, anti-caries agents, solubility, hydrolysis, pharmaceuticals.

Introduction

Ammonium hexafluorosilicates (AHFS) are a class of inorganic compounds widely used in modern technological practice and laboratory research [1,2]. In recent years, AHFS have been actively studied as promising anti-caries preventive agents [1−4] because they present certain advantages over traditional fluoride drugs. Dental caries is a serious problem for the health systems of most countries [5,6], and search for new effective and safe means of treatment and prevention of caries remains an urgent task of modern pharmaceutics.

Searching for perspective anti-caries agents among AHFS must include an assessment of physical and chemical characteristics of possible drug candidates, as a mandatory step. A drug candidate must meet certain criteria. In particular, physical and chemical characteristics of potential pharmaceutical drug for oral administration must correspond to Lipinski's empirical rule of five [7,8] and related «drug-like» approaches [9] defining the bioavailability of the candidate drug. The rule of five [7,8] allows evaluating the drug's water solubility (WS), i.e., the main characteristic that needs to be respected for drugs dosage and transport and in anaesthesiology [10]. Another important characteristic of drugs and drug candidates is their hydrolytic instability, which is directly related to the processes of metabolism and to the formation of active intermediates (prodrugs) [11,12]. It is important to emphasize that AHFS are ionic compounds and differ significantly in structure and properties from drugs of organic nature with molecular structure for which were proposed rules [7,8] and transformation schemes [11,12]. The present review attempts to analyze the solubility and hydrolysis characteristics of AHFS as a basis for rational selection of potential pharmaceutical drugs based on the specificity of AHFS structure.

Water solubility

Let us consider existing approaches to rational explanation and *a priori* assessment of solubility characteristics, especially water solubility (WS) of AHFS and how they relate to the rule of five [7,8]. The first was an attempt [13] to link the values of

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AHFS WS with Davis group numbers (GN) (Table 1), used for assessing the hydrophilic-lipophilic balance (HLB) of surface-active compounds [14]. According to ref. [15], GN can characterize, as a first approximation, HLB complexes in a series of compounds of similar composition and structure (in our case ammonium cations in the AHFS composition). According to refs. [14,15], a GN is assigned to each compounds' functional group. The sum of GN according to formula (1) then yields the HLB of a molecule:

$$HLB = \Sigma(\text{hydrophilic GN}) + \Sigma(\text{hydrophobic GN}) + 7. \quad (1)$$

Table 2 presents data on the WS (mol.%) of some AHFS with different aryl(alkyl)ammonium cations and calculated values of HLB salts.

Data from Table 2 show that the concept of Davis group numbers properly reflects (i) the downward trend of AHFS WS with an increase in the lipophilic properties of cations, according to the following series: $C_6H_5NH_3^+$, $C_6H_5CH_2NH_3^+$, $(C_6H_5CH_2)_2NH_2^+$, $(C_6H_5CH_2)_3NH^+$, and (ii) the high salt solubility of $[C(CH_2OH)_3NH_3]_2SiF_6$ with four hydrophilic functional groups. To explain the high WS of $(o\text{-}CH_3OC_6H_4NH_3)_2SiF_6$ salt with the additional hydrophilic fragment $-O-$ (which, however, has the lowest value of GN in the series of hydrophilic groups, Table 1), it seems necessary to involve factors beyond the scope of the model [13,14]. WS values of the salts with functionalized phenylammonium cations $RC_6H_4NH_3^+$ (R=$o\text{-}NO_2$, $o\text{-}$, $n\text{-}COOH$, $n\text{-}SO_2NH_2$) were abnormally low and in disagreement with regard to the model [13]. This group of AFHS contains substituents with marked H-donor/H-acceptor properties, and their low WS can be explained by the relative stabilization of their structures thanks to additional interionic H-bonds (besides H-bonds with $-NH_3^+$ group participation) [13,16]. The same situation apparently occurs for the sulfathiazole salt $(stzH)_2SiF_6$ (C=0.1 mol.%) [17], in which hydrophilic fragments in the phenyl-ammonium cation form strong H-bonds with the anion. The chief merit of attempting to use Davis conception for the interpretation of the data on the water solubility of AHFS [13] is precisely to draw attention to the problem of influence of H-bonds on salts solubility.

Relationship between the WS of AHFS with N-containing heterocyclic cations and the characteristics of H-bonds of salts was first established in ref. [18]. The effects of H-bonds on the WS of hexafluorosilicates can be comparatively assessed using the parameter h, defined as:

$$h = n/d(D{\cdots}A)_{av.}, \quad (2)$$

where n is the number of short interionic contacts ($D{\cdots}A \leq 3.2$Å, strong and medium H-bonds according to classification [19]); and $d(D{\cdots}A)_{av.}$ is the average donor-acceptor distance in a complex structure.

Table 3 presents the values of h calculated from X-ray crystallography data for structurally characterized AHFS with pyridinium cations and related cations, containing N-atoms of pyridine type, and the WS values (C, mol.%) of the salts.

The relationship between h and C values is depicted in Fig. 1. The inverse relationship between the values of h and C indicates that the WS of AHFS decreases exponentially with the increase in the value of h; i.e., the increase in the intensity of interionic H-interactions.

Generally, the WS of arylammonium hexafluorosilicates (Table 2) is noticeably lower comparing to heterocyclic cations salts (Table 3), which fits well with the idea of a stabilizing effect of H-bonds. Arylammonium cations have high H-donor capabilities ($-NH_3^+$ group) compared to heterocyclic cations (group NH^+). In particular, as shown by the comparison of the characteristics of $(2\text{-}CH_3C_5H_4NH)_2SiF_6$ (C=11.6 mol.%, h=0.71) and $(2\text{-}CH_3C_6H_4NH_3)_2SiF_6$ (C=1.17 mol.%, h=1.39) salts, an increase in the H-interactions leads to a tenfold decrease in the solubility when passing from the 2-methylpyridinium salt to its 2-methylphenylammonium analogue.

In the absence of structural data, it was proposed [26] to use the parameter h' as a characteristic allowing to evaluate the influence of effects H-bonds on AHFS solubility:

$$h' = N_H/pK_aL, \quad (3)$$

Davis group numbers [14]

Hydrophilic groups	Group number	Lipophilic groups	Group number
$-O-$	1.3	$-CH-$	−0.475
$-COOH$	2.1	$-CH_2-$	−0.475
$-OH$	1.9	$-CH_3$	−0.475
$-NR_4^+$	9.4	$=C-$	−0.475

Ta b l e 2

Solubility of ammonium hexafluorosilicates in water and their hydrophilic-lipophilic balance [13]

Salt	Solubility C, mol.% (25^{0}C)	HLB
$(C_6H_5NH_3)_2SiF_6$	0.75	28.05
$(o\text{-}CH_3C_6H_4NH_3)_2SiF_6$	1.17	28.05
$(o\text{-}CH_3OC_6H_4NH_3)_2SiF_6$	5.67	30.65
$(o\text{-}ClC_6H_4NH_3)_2SiF_6$	0.90	29.00
$(o\text{-}BrC_6H_4NH_3)_2SiF_6$	1.74	29.00
$(o\text{-}O_2NC_6H_4NH_3)_2SiF_6$	0.12	29.00
$(o\text{-}HOOCC_6H_4NH_3)_2SiF_6$	0.49	33.20
$(p\text{-}H_2NO_2SC_6H_4NH_3)_2SiF_6$	0.06	29.00
$(p\text{-}HOOCC_6H_4NH_3)_2SiF_6 \cdot 4H_2O$	0.08	33.20
$(C_6H_5CH_2NH_3)_2SiF_6$	0.30	27.10
$[(C_6H_5CH_2)_2NH_2]_2SiF_6$	0.12	20.14
$[(C_6H_5CH_2)_3NH]_2SiF_6$	0.05	15.70
$[(CH_3)(C_{19}H_{39})NH_2]_2SiF_6$	$1\cdot10^{-4}$	−0.20
$[C(CH_2OH)_3NH_3]_2SiF_6$	3.51	41.35

where N_H is the number of H-donors in cation composition; and pK_aL is the basicity constant of ligand L [27,28] in the composition of the corresponding ammonium cation.

As noted in ref. [26], the parameter h' retains the meaning of h to a certain extent: the values of n (number of H-bonds) and N_H change symbatically, as well as d(D⋯A)$_{av.}$ and pK_aL (the growth of pK_aL is accompanied by the decrease of H-donor capacity of cations, and, as a consequence, the increase of D⋯A distances).

The values of WS AHFS, as well as N_H and h' are presented in Table 4, while Figure 2 shows the relationship between C and h' values.
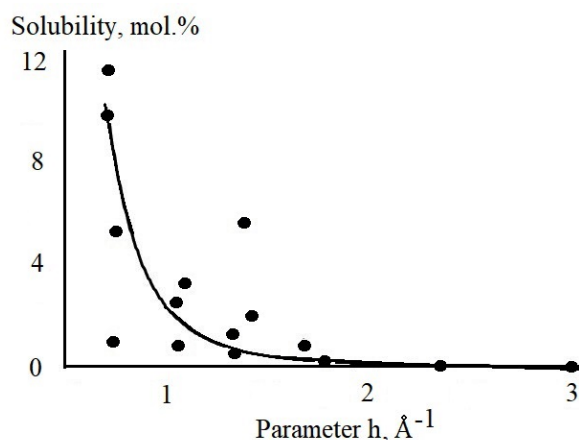

Fig. 1. The relationship between the solubility C and parameter h of ammonium hexafluorosilicates ([1], with modification)

As in the case of C and h values interconnection, the values of C and h' show an inverse relationship and the corresponding graphical representations have a similar form. It should be noted that equations for h and h' parameters include the number of potential H-donors (or H-bonds) as one of the «drug-like» criteria of the rule of five [7,8] proposed in publications [18,26]. The growth of these characteristics is accompanied by a decrease in the values of WS of corresponding AHFS.

Ta b l e 3

Solubility of hexafluorosilicates of N-heterocyclic cations in water and value of *h* parameter

Compound	C, mol.% (25^{0}C)	h, Å^{-1}	References
$[2\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	0.82	1.06	[20]
$[3\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	1.02	0.74	[20]
$[4\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	0.58	1.33	[20]
$(2\text{-}CH_3C_5H_3NH)_2SiF_6$	11.60	0.71	[21]
$[2,6\text{-}(CH_3)_2C_5H_3NH]_2SiF_6$	9.90	0.72	[21]
$[2\text{-}HO(O)CC_5H_4NH]_2SiF_6$	5.33	0.76	[18]
$[3\text{-}HO(O)CC_5H_4NH]_2SiF_6$	3.33	1.09	[18]
$[4\text{-}HO(O)CC_5H_4NH]_2SiF_6$	0.80	1.08	[16]
$(2\text{-}H_2NC_5H_4NH)_2SiF_6$	5.60	1.38	[18]
$[2,6\text{-}(H_2N)_2C_5H_3NH]_2SiF_6$	0.06	2.35	[18]
$(2\text{-}Br\text{-}6\text{-}CH_3C_5H_3NH)_2SiF_6 \cdot H_2O$	2.01	1.42	[22]
$[2,6\text{-}(HOCH_2)_2C_5H_3NH]_2SiF_6$	2.52	1.04	[22]
$[5\text{-}OH\text{-}6\text{-}CH_3\text{-}3,4\text{-}(HOCH_2)_2C_5HNH]_2SiF_6$	0.89	1.68	[22]
$(4\text{-}HOCH_2C_5H_4NH)_2SiF_6$	1.30	1.33	[23]
$[2\text{-}NH_2\text{-}4,6\text{-}(OH)_2C_4HN_2H]_2SiF_6$	0.002	3.0	[24]
$(C_2H_6N_5)_2SiF_6{}^*$	0.28	1.78	[25]

Note: * − $(C_2H_6N_5)^+$ stands for 3,5-diamino-1,2,4-triazolium cation
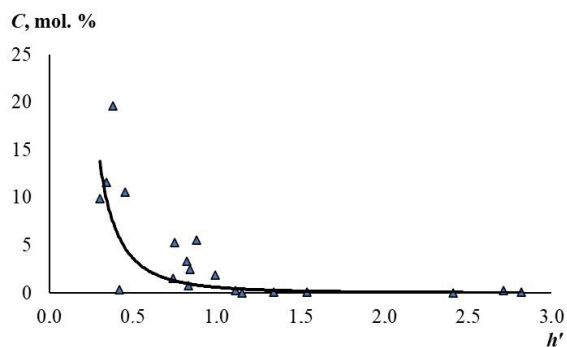
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Fig. 2. The relationship of the solubility C of ammonium hexafluorosilicates vs. parameter h' [26]

The next step towards identifying factors determining WS of AHFS and role of H-bonds in regulating the WS of such salts was made in the work [29]. To describe and forecast the AHFS WS, suitable 2D QSPR models were used [29], constructed using Simplex representation of molecular structure method (SiRMS) [30]. It should be pointed out that until now only two following publications have studied the WS of ammonium salts within QSPR models: ionic liquids, piperidine and pyrrolidine salts [31], and salts of benzyl ammonium [32]. However, the role of H-bonds effects in such systems was not discussed. Results of the analysis [29] of influence of various physical and chemical factors on salts WS are given in Table 5.

As shown in Table 5, the contribution of Dragon's topological indices comes first (39%), this factor characterizing branching of the cation structure. As for the other factors, electrostatic interactions are expected to be in second place (27%) and van der Waals interactions (19%) in the third. Lipophilicity, quite unexpectedly, makes a very modest contribution (3%), whereas the contribution of H-bonds effects is more significant (10%). However, the observed value is clearly inferior to the expectations of works [18,26], that assumed a dominant contribution of H-bonds effects in AHFS solubility.

The detailed analysis of the influence of H-bonds on WS of AHFS [29] led to the identification of structural fragments of cations that provide a negative contribution to water solubility. It was shown that inclusion of pyridinium and anilinium cations of $-SO_2NH_2$, $-CONH_2$, $-NH_2$, $-COOH$, and $-OH$ functional groups, capable of forming strong H-bonds, had a negative influence on WS (Fig. 3,a). A similar hydrophobic effect is provided by heterocyclic pyrimidinium cations, 1,2,4-triazolium, 1,3,4-thiadiazole, and benzimidazolium, containing two or three nitrogen atoms inside/in the cycle (Fig. 3,b).

As noted in ref. [29], results of calculation and qualitative evaluation [18,26] are in good agreement. In particular, the presence of heterocyclic cations in the structure along with N^+H-fragment of one or two N-atoms lead to additional interionic H-interaction

Table 4

Solubility of hexafluorosilicates of N-heterocylic cations in water and N_H and $h2$ values

Compound[*]	C, mol.% (25^{0}C)	N_H	h'	References
$(C_5H_5NH)_2SiF_6$	19.60	2	0.38	[18]
$(2-CH_3C_5H_4NH)_2SiF_6$	11.60	2	0.34	[21]
$[2,6-(CH_3)_2C_5H_3NH]_2SiF_6$	9.90	2	0.30	[21]
$[2,6-(HOCH_2)_2C_5H_3NH]_2SiF_6$	2.52	4	0.84	[22]
$[2-HO(O)CC_5H_4NH]_2SiF_6$	5.33	4	0.75	[18]
$[3-HO(O)CC_5H_4NH]_2SiF_6$	3.33	4	0.82	[18]
$[4-HO(O)CC_5H_4NH]_2SiF_6$	0,80	4	0.83	[16]
$(BIAH)_2SiF_6$	1.53	4	0.74	[26]
$(2-H_2NC_5H_4NH)_2SiF_6$	5.60	6	0.88	[18]
$(3-H_2NC_5H_4NH)_2SiF_6$	1.86	6	0.99	[18]
$[2-C_2H_5-4-H_2N(S)CC_5H_3NH]_2SiF_6$	0.10	6	1.34	[16]
$[2,5-(HOOC)_2C_5H_3NH]_2SiF_6$	0.07	6	2.82	[16]
$[2,6-(HOOC)_2C_5H_3NH]_2SiF_6$	0.02	6	2.41	[16]
$(ABIAH)_2SiF_6$	0.23	8	1.11	[26]
$(AMTDH)_2SiF_6$	0.01	8	1.15	[26]
$[2,6-(H_2N)_2C_5H_3NH]_2SiF_6$	0.06	10	1.54	[18]
$(C_2H_6N_5)_2SiF_6$	0.28	12	2.71	[25]

Note: [*] − BIA, ABIA and AMTD stand for benzimidazole, 2-aminobenzimidazole and 2-amino-5-mercapto-1,3,4-thiadiazole, respectively.
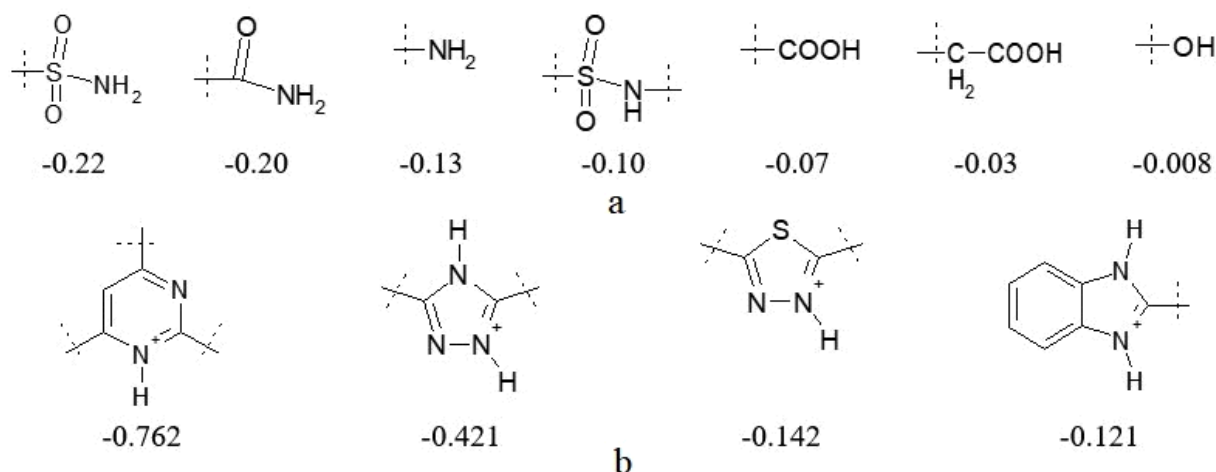
Fig. 3. Relative influence of some substituting groups/substituents (a) and N+-containing heterocyclic fragments (b) on the water solubility of ammonium hexafluorosilicates

of NH···F and NH···N, providing additional contribution to the AHFS structure stabilization. It also leads to reduction of WS of corresponding salt.

This situation is well illustrated by the example of 3,5-diamino-1,2,4-triazolium salt having the composition $(C_2H_6N_5)_2SiF_6$ (Tables 3 and 4), in whose structure all three N-atoms of the cycle (two H-donors and one H-acceptor) together with two $-NH_2$ groups are included in the H-bonds NH···F and NH···N [25]. Accordingly, a low WS is expected for the $(C_2H_6N_5)_2SiF_6$ salt, which is confirmed experimentally (0.28 mol.%).

One general remark is appropriate here. The negative influence of interionic H-bonds on WS AHFS, as established in works [18,26,29], is far from being trivial. The generally accepted point of view is that the presence of hydrophilic groups in organic compounds, playing the role of donors and/or acceptors of H-bonds, favors WS of compounds [33−36]. This conclusion is appropriate and logical in relation to the molecular structure of compounds. However, the situation is exactly the opposite in case of ionic AHFS with organic cations.

Table 5

Assessment of the relative impact of various factors on water solubility of ammonium hexafluorosilicates

Physical and chemical factors	Relative impact, %
Dragon's topological indices	39
electrostatic interactions	29
Van der Waals attraction	13
Van der Waals repulsion	6
donor/acceptor of H-bond	10
lipophilicity	3
atom type	2

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Solubility in organic solvents

Organic solvents (OS) are widely used in the pharmaceutical industry as a reaction medium, in process of separation and purification of synthesis products, for cleaning of technological equipment [37] and in the processes of sublimation dehydration of pharmaceutical products [38−40]. Furthermore, OS (in particular, ethanol) are used for the manufacture of various liquid dosage forms [41]. The results of studies [42,43] give an idea of the main trends in changes in the solubility of some AHFS with heterocyclic cations in media of such widespread OS as aliphatic alcohols (methanol, ethanol) and dimethyl sulfoxide (DMSO) compared to data for WS. The objects of study [42] were 2-, 3-, 4-carboxymethylpyridinium, 2-amino-4,6-dihydroxypyrimidinium and octenidine hexafluorosilicates (I−V, accordingly), while the objects of study were 2-, 3-, 4-carboxyethylpyridinium hexafluorosilicates (VI−VIII, accordingly).

Data on solubility of ammonium hexafluorosilicates in water, methanol, ethanol and DMSO are presented in Table 6. Values of 2-carboxyethylpyridinium hexafluorosilicate solubility are shown in Fig. 4 as an example.

According to data given in Table 6, a general decreasing trend in solubility is observed for salts I−III and VI−VIII with structurally similar substituted pyridinium cations in the order of solvents «water−methanol−ethanol», which may be a consequence of «lipophilization» (decrease in hydrophilicity) of the solvents [45]. Noteworthy analogies exist in the dissolving power of water, the ideal solvent for ionic compounds [46], and DMSO towards the studied AHFS. With exception of compounds of IV and V,

Table 6

Solubility of ammonium hexafluorosilicates in water, methanol, ethanol and dimethyl sulfoxide

| Compound	Solvent	Data on solubility of 100 mg substance powder / volume of solvent, ml (25^0C)	Solubility [44]
I	water	dissolved in 0.6 ml solvent	freely soluble
	methanol	dissolved in 110 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 185 ml solvent	very slightly soluble
	DMSO	dissolved in 11.5 ml solvent	slightly soluble
II	water	dissolved in 0.4 ml solvent	freely soluble
	methanol	dissolved in 136 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 151 ml solvent	very slightly soluble
	DMSO	dissolved in 13 ml solvent	slightly soluble
III	water	dissolved in 0.7 ml solvent	freely soluble
	methanol	dissolved in 216 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 197 ml solvent	very slightly soluble
	DMSO	dissolved in 14 ml solvent	slightly soluble
IV*	water	dissolved in 110 ml solvent	very slightly soluble
	methanol	dissolved in 650 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 359 ml solvent	very slightly soluble
	DMSO	dissolved in 470 ml solvent	very slightly soluble
V	water	dissolved in 76 ml solvent	slightly soluble
	methanol	dissolved in 1 ml solvent	freely soluble
	ethanol (96%)	dissolved in 3.5 ml solvent	sparingly soluble
	DMSO	dissolved in 392 ml solvent	very slightly soluble
VI	water	dissolved in 0.3 ml solvent	freely soluble
	methanol	dissolved in 246 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 425 ml solvent	very slightly soluble
	DMSO	dissolved in 2.2 ml solvent	soluble
VII	water	dissolved in 0.5 ml solvent	freely soluble
	methanol	dissolved in 477 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 1920 ml solvent	very slightly soluble
	DMSO	dissolved in 4 ml solvent	sparingly soluble
VIII	water	dissolved in 2.2 ml solvent	sparingly soluble
	methanol	dissolved in 867 ml solvent	very slightly soluble
	ethanol (96%)	dissolved in 2245 ml solvent	very slightly soluble
	DMSO	dissolved in 9.5 ml solvent	very slightly soluble

Note: * − in case of slightly soluble, 50 mg of compound IV were used.

the high solubility values of ionic AHFS in DMSO are explained by the high polar nature of this solvent (dipole moment is equal to 3.96 D [47]), which also has an extremely high solvation ability (Gutmann's donor number DN=29.8 [47]). In its turn, the very low solubility of the pyrimidinium salt **IV** in all used media is the result of a powerful structure stabilizing effect of **IV** due to the collective action of the system of 20 H-bonds of various types [24].

Hydrolysis

When discussing the processes of AHFS hydrolysis, it should be noted that the hydrolytic instability of the SiF_6^{2-} anion is a prerequisite for the use of AHFS as anti-caries agents, and of H_2SiF_6 and Na_2SiF_6 compounds in municipal programs for fluoridation of potable water as a method of caries prevention [48,49]. According to data [1,21,48,50], hydrolysis of AHFS with composition $(LH)_2SiF_6$ (where L=NH₃, organic base) is described by the following general reaction schemes:

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

$$LH^+ + H_2O \overrightarrow{\leftarrow} L + H_3O^+. \qquad (5)$$
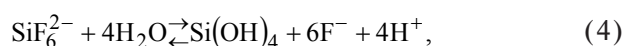
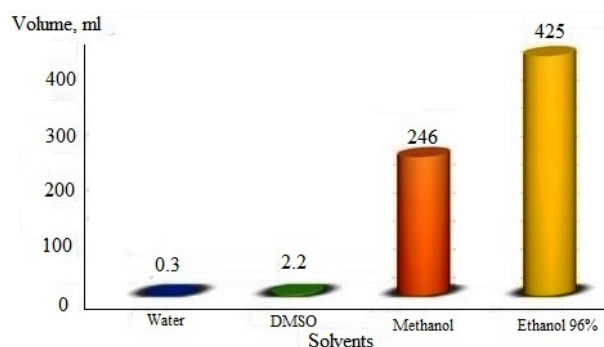Thus, hydrolysis processes of both anion (4) and cation (5) lead to a shift in the pH of solutions to

Fig. 4. Solubility of 2-carboxyethylpyridinium of hexafluorosilicate (m=100 mg) in water and organic solvents

more acidic values. Table 7 provides pH-metry data for $1 \cdot 10^{-3}$ M aqueous solutions of AHFS with different heterocyclic cations.

Based on data given in Table 6, pH values are quite conservative to changes in the nature of the cation and are in the range of 2.95−3.35. According to ref. [53], a narrow range of pH values (2.2−3.4) is also found for aqueous solutions of $(NH_4)_2SiF_6$ of various concentrations. However, no correlation was found between solution pH and hexafluorosilicate concentration.

Results of determination of degree of hydrolysis (α, in %) for diluted $1 \cdot 10^{-4}$ M water solutions of AHFS are presented in Table 8.

As follows from data in Table 7, the degree of hydrolysisof the studied salts, α, is relatively high in

diluted aqueous solutions. In some cases, it reaches almost quantitative values and does not reveal any connection with cations nature. The observed high degree of SiF_6^{2-} anions conversion into silicon dioxide (silicic acid) in diluted aqueous solutions of AHFS is accompanied, according to scheme (4), by the effective release of fluoride ions, which are the source of the caries-preventive effect due to the following reaction occurring in the oral cavity:

$$Ca^{2+} + 2F^- \rightarrow CaF_2\downarrow. \qquad (6)$$

The formation of calcium fluoride precipitate provides occlusion of dentin tubules. As mentioned in ref. [53], the acidic nature of the studied solutions of $(NH_4)_2SiF_6$ with various salt concentration leads to etching of the dentin surface and its coating with a stable layer of CaF_2 precipitate.

It is known [1,18,21,22,55,56] that in AHFS structures the inclusion of fluorine atoms of SiF_6^{2-} anion into H-bonds of different strength with cations' H-donor centers is accompanied by a noticeable redistribution of the Si−F bond lengths. As a rule, fluorine atoms included in the strongest bonds X−H⋯F (where X=N, O) form the longest (weakest) Si−F bonds. Therefore, it is possible that reaction of AHFS hydrolysis with braking-up of Si−F bonds could be stimulated by weakening of some Si−F anion connections at the expense of H-bonding [57].

With hydrolysis process of SiF_6^{2-} anion, a practically important feature of AHFS is the ability to

Table 7

Values of pH of hexafluorosilicates water solutions with different heterocyclic cations

Compound*	pH of $1 \cdot 10^{-3}$ M solution (25^0C)**	References
$(C_5H_5NH)_2SiF_6$	3.20	[18]
$(2-CH_3C_5H_4NH)_2SiF_6$	3.27	[18]
$(2-H_2NC_5H_4NH)_2SiF_6$	3.30	[18]
$(3-H_2NC_5H_4NH)_2SiF_6$	3.35	[18]
$(4-H_2NC_5H_4NH)_2SiF_6 \cdot H_2O$	3.09	[18]
$[2,6-(H_2N)_2C_5H_3NH]_2SiF_6$	3.33	[18]
$[2-HO(O)CC_5H_4NH]_2SiF_6$	2.95	[51]
$[3-HO(O)CC_5H_4NH]_2SiF_6$	3.00	[51]
$[4-HO(O)CC_5H_4NH]_2SiF_6$	2.96	[51]
$[2-C_2H_5-4-H_2N(S)CC_5H_3NH]_2SiF_6$	3.31	[52]
$[2-C_3H_7-4-H_2N(S)CC_5H_3NH]_2SiF_6$	3.30	[52]
$[4-H_3NHN(O)CC_5H_4NH]SiF_6$	3.23	[18]
$(C_2H_6N_5)_2SiF_6$	3.33	[24]
$(C_{21}H_{38}N)_2SiF_6$	3.25	[51]
$(2,2'-DipyH_2)SiF_6$	3.05	[51]
$(4,4'-DipyH_2)SiF_6$	3.15	[51]

Notes: * − $(C_{21}H_{38}N)^+$ means cetylpyridinium cation; ** − hydrolysis time is 10 min [51].

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Table 8

Degree of hydrolysis for ammonium hexafluorosilicates in $1 \cdot 10^{-4}$ M aqueous solutions

Compound	α, % $(25^0C)^*$	References
$(NH_4)_2SiF_6$	95.6	[50]
$(3\text{-}HOCH_2C_5H_4NH)_2SiF_6 \cdot H_2O$	91.6	[53]
$(4\text{-}HOCH_2C_5H_4NH)_2SiF_6$	87.3	[53]
$[2\text{-}HO(O)CC_5H_4NH]_2SiF_6$	89.0	[50]
$[3\text{-}HO(O)CC_5H_4NH]_2SiF_6$	99.8	[50]
$[4\text{-}HO(O)CC_5H_4NH]_2SiF_6$	95.4	[50]
$[2\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	80.5	[20]
$[3\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	88.5	[20]
$[4\text{-}HO(O)CCH_2C_5H_4NH]_2SiF_6$	85.3	[20]
$[2,6\text{-}(HOCH_2)_2C_5H_3NH]_2SiF_6$	96.7	[22]
$[2\text{-}CH_3\text{-}3\text{-}OH\text{-}4,5\text{-}(HOCH_2)C_5HNH]_2SiF_6$	98.0	[22]
$(2\text{-}Br\text{-}6\text{-}CH_3C_5H_3NH)_2SiF_6 \cdot H_2O$	93.5	[22]

Note: * — hydrolysis time is 10 min [51].

cause the effect of prolonged occlusion of open dentin tubules by calcium fluoride precipitate. This feature was observed [53,58] in experiments using $(NH_4)_2SiF_6$, synthetic saliva and dentin discs obtained from caries-free human molars. Let us recall that, according to numerous studies [59–64], silicon dioxide and silicates are kind of catalysts initiating the precipitation of calcium phosphate (apatite) from simulated biological fluids and synthetic saliva. In the case of use of $(NH_4)_2SiF_6$, silicon dioxide (silicic acid) formed according to the scheme (4) is included in the sediment composition on the dentin surface and causes the formation of new portions of sediment, which, based upon EDXA data analysis, is a mixture of fluorinated apatite and calcium fluoride [53].

Deposition of new crystals was observed even when the studied the dentin samples were immersed into synthetic saliva for 24 hours [58]. Considering works [60–64], it can be assumed that the scheme of prolonged occlusion of dentinal tubules under the action of acidic solutions of ammonium hexafluorosilicate is based on the absorption of Ca^{2+}, F^- and PO_4^{3-} ions on silanol groups $\equiv Si-OH$ of the dentin surface enriched with silicon dioxide, followed by crystallization of fluorapatite and calcium fluoride as a result of local oversaturation.

Conclusions

Significant progress has been made in the study of solubility and hydrolytic instability of AHFS, two important factors in the context of their potential use as pharmaceuticals. It has been shown that, due to the high H-acceptor abilities of SiF_6^{2-} anion [19] system, H-bonds in supramolecular structures of AHFS significantly influence structural characteristics and macroscopic properties of salts [1,2,26,65,66]. In particular, the discovered «hydrophobic» influence of

H-bonds on AHFS solubility [13,18] and the identified relationships «cation structure vs. solubility» [18,26,29] can be used to predict changes in aqueous solubility of AHFS when creating new pharmaceutical substances. Analogies have been established in the dissolving ability of the water, the most effective solvent for ionic compounds, and dipolar aprotic DMSO in relation to the studied AHFS [42,43]. It has been suggested that ammonium cations can stimulate the development of AHFS hydrolysis process because of the weakening of some $Si-F$ bonds due to the H-bonding effects. Obviously, one of the promising new aspects of studying the properties of AHFS is to clarify how the mediums' nature influences the antibacterial activity of these salts against the multi-resistant strains of bacteria [67]. The first encouraging results have been already obtained in this direction [68].

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РОЗЧИННІСТЬ І ГІДРОЛІЗ АМОНІЄВИХ ГЕКСАФТОРОСИЛІКАТІВ ЯК ПОТЕНЦІЙНИХ ЛІКАРСЬКИХ ПРЕПАРАТІВ (ОГЛЯД ЛІТЕРАТУРИ)

В.О. Гельмбольдт

В огляді проаналізовано та узагальнено результати публікацій, присвячених вивченню розчинності та гідролізу амонієвих гексафторосилікатів (АГФС). Зазначені неорганічні сполуки мають різноманітні галузі технологічного застосування, а останніми роками стали об'єктом активних досліджень як потенційні антикарієсні агенти. Розглянуто характеристики розчинності АГФС у воді, метанолі, етанолі (96%), диметилсульфоксиді; обговорено існуючі підходи до інтерпретації основних тенденцій у зміні розчинності солей залежно від будови катіона. Відзначено нетривіальний характер негативного впливу міжіонних Н-зв'язків на розчинність у воді АГФС, а також необхідність урахування гідрофобного ефекту Н-зв'язків при здійсненні пошуку нових фармацевтичних субстанцій серед АГФС. Констатовано високий, часто близький до кількісного, ступінь гідролізу АГФС у розведених водних розчинах, який забезпечує ефективне вивільнення фторид-іонів − джерела карієс-профілактичного ефекту.

Ключові слова: амонієвих гексафторосилікати; антикарієсні агенти; розчинність; гідроліз; лікарські препарати.

SOLUBILITY AND HYDROLYSIS OF AMMONIUM HEXAFLUOROSILICATES AS POTENTIAL PHARMACEUTICALS (A REVIEW)

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This review analyzes and systemizes results from publications on the solubility and hydrolysis of ammonium hexafluorosilicates (AHFS). These inorganic compounds have a variety of technological applications and have been actively researched as potential anti-caries agents in recent years. The characteristics of AHFS solubility were examined in water, methanol, ethanol (96%), and dimethyl sulfoxide. Existing approaches were discussed to interpret the main trends in changes of salts solubility depending on cation structure. Interionic H-bonds were noted to have a non-trivial negative impact on the water solubility of AHFS. The hydrophobic effect of H-bonds also needed to be considered when searching for new pharmaceutical substances among AHFS. A high, often close to quantitative, degree of hydrolysis of AHFS was found in diluted aqueous solution, resulting in an effective release of fluoride ions with caries-preventive properties.

Keywords: ammonium hexafluorosilicates; anti-caries agents; solubility; hydrolysis; pharmaceuticals.

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