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# Synthesis and spectral properties of alginic acid polymers modified by flavonol fragments

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The article is devoted to the development of a method for the synthesis of polymers based on alginic acid modified with flavonol fragments and the study of the spectral properties of the obtained compounds. The conditions for the direct esterification reaction of alginic acid with 7-hydroxyflavonol and 4'-hydroxyflavonol are described. The reaction demonstrates the regioselectivity: it leads to the formation of ester bridges between the polymer chain and flavonols involving the 7-hydroxy- and 4'-hydroxy groups, while esterification of the 3-hydroxy group of flavonols does not occur. This allows keeping the spectral properties of flavonol fragments, the ability to complex, and intramolecular proton transfer in the excited state. It was shown that the absorption and fluorescence spectra of the modified polymers are similar to the neutral forms of free flavonols. The results obtained will enable the use of flavonol-containing alginate polymers in the gel phase for the detection and accumulation of metal ions, for examination of solvent's polarity, and for medical practice as a depot for the slow release of biologically active flavonoids.

**Keywords**: alginic acid, flavonols, esterification, modified polymers, absorption spectra, fluorescence spectra.

**Синтез і спектральні властивості полімерів альгінової кислоти модифікованих фрагметами флавонолів.** *Д.В. Буханцова, Л.В. Чепелева, Є.С. Гладков, О.Д. Рошаль*

Стаття присвячена розробці методу синтезу полімерів на основі альгінової кислоти модифікованих фрагментами флавонолів і вивченню спектральних властивостей отриманих сполук. Описано умови проведення прямої реакції естерифікації альгінової кислоти 7-гідроксифлавонолом та 4'-гідроксифлавонолом. Реакція має вибірковий характер – приводить до утворення естерних містків полімерній ланцюг – флавонол за рахунок 7-гідрокси- та 4'-гідроксигруп, при цьому естерифікація 3-гідроксигрупи флавонолів не відбувається. Це дозволяє зберігти спектральні властивості флавонольних фрагментів, здатність до комплексоутворення і внутрішньомолекулярного переносу протону у збудженому стані. Було показано, що характеристики спектрів поглинання і флуоресценції модифікованих полімерів подібні до нейтральних форм вільних флавонолів. Отримані результати дозволять використовувати флавонол-вміщуючі альгінові полімери в геліевій фазі для детектування і накопичення іонів металів, для оцінки полярності розчинників, в медичній практиці в якості депо для повільного вивільнення біологічно активних флавоноїдів.

## *1. Introduction*

Alginic acids are a group of biocopolymers of ß-D-mannuronic acid (M) and C-5 epimer-L-guluronic acid (G) [1], common in algae and some exopolysaccharide bacteria. The ratio of elementary units M and G in the polymer chains and the average molecular weights of the polymer molecules depend on the nature of the alginic acid source. For almost 150 years, alginic acid and its salts have found application in medicine [2, 3], medical technology [4], the food industry [5], and cosmetology [6]. Alginic acid has affinity for divalent ions of group II metals, in particular, for ecotoxicant metals – Pb, Cd, Ba, and to a lesser extent for

d-metal ions [7], which allows this polymer to be used as an adsorbent in analytical chemistry.

An important property of alginic acid is its ability to form gels in aqueous solutions. The characteristics of these gels depend on the structure of the macromolecules, which in turn is determined by the raw material from which the alginic acid was isolated. The pK of alginic acid ranges from 3.3 to 3.5, and in an alkaline environment, as the carboxyl groups dissociate, alginic acid transforms from a gel form to a water-soluble form.

The presence of hydroxyl and carboxyl groups in the elementary units of alginic acid opens up extensive possibilities for chemical modification of the polysaccharide [8], which is used to alter its lipophilicity, adsorption capacity, and gel formation ability, as well as to modulate gel parameters. One important method for modifying alginic acid is the esterification of carboxyl groups. The use of direct esterification is limited by the use of strong acids as catalysts, which can lead to partial hydrolysis of polymer chains and a decrease in the molecular weight of the polymer. An alternative method is to obtain esters of long-chain alkyl halides with the tetrabutylammonium salt of alginic acid [9].

Direct esterification of alginic acid with high- and low-molecular-weight alcohols is used to increase the polymer's hydrophobicity [10], which, combined with its complexation ability, allows the use of partially modified alginic acid esters for the adsorption of certain metal ions in non-aqueous media. Alginic acid esters with cholesterol, capable of forming stable nanoaggregates, have also been obtained [11].

Esterification of alginic acid with phenolic hydroxyls is ineffective because the phenolic hydroxyl is less nucleophilic than the aliphatic alcoholic hydroxyl. Therefore, this reaction requires strong acids as catalysts and a nonaqueous medium. Nevertheless, the esterification with phenols allows modification of alginic acid, imparting the ability to absorb light in various spectral ranges, fluoresce, selectively adsorb metal ions, and exhibit biological activity. Biodegradation of pharmacophore-modified alginic acid allows the polymer to be used as a drug depot.

Derivatives of 2-phenyl-3-hydroxychromone – flavonols – have all of the above properties. They absorb light in the ultraviolet and violet spectral regions [12], exhibit two-band fluorescence due to excited-state intramolecular proton transfer (ESIPT) [13, 14], form complexes with metal ions [15], and are potent antioxidants and cancerostatics [16]. Thus, alginic acid modified with flavonols can be used as an optical filter for the near UV range, as a source of fluorescence at 420-460 nm and 500-550 nm, as a metallochromic indicator, and as an antioxidant depot.

This article is devoted to the problems of esterification of alginic acid with flavonols and the spectral properties of the resulting polysaccharides.

## 2. Experimental

The degree of purity and structure of the synthesized flavones were established using spectral methods, including $^{1}$H-, $^{13}$C-NMR, and LC-MS.

$^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for $^{1}$H and 126 MHz for $^{13}$C) in DMSO-d6. The signals are given in the δ scale. Mass spectra were recorded on an Agilent 1100 high-performance liquid chromatograph (HPLC) equipped with a diode-array detector and an Agilent LC/MSD SL mass-selective detector, a SUPELCO Ascentis Express C18 chromatographic column 2.7 μm 4.6 mm x 15 cm. Preliminary NMR and LC-MS analysis was provided by Enamine Ltd. (Ukraine).

The UV-vis absorption and fluorescence spectroscopy of flavonols and flavonol-modified alginic acid were performed using an Agilent Cary 3500 spectrophotometer and a FS5 v2 spectrofluorimeter. The spectral measurements were carried out in standard 10 mm cuvettes at 25 °C. DMSO was used as a solvent for spectroscopic investigations to ensure good solubility of the starting flavonols and alginic acid, as well as the final modified polymers.

All solvents and reagents were commercial grade and, if required, purified according to the standard procedures.

### *Synthetic procedures*

7-Hydroxyflavonol (2-phenyl-3,7-dihydroxychromone, 7-HO-HF), 4'-hydroxyflavonol (2-phenyl-3,4'-dihydroxychromone, 4'-HO-HF), and their benzyl-protected precursors – 7-benzyloxyflavonol and 4'-benzyloxyflavonol were synthesized by known methods according to our modified synthetic procedures. The spectral characteristics of the obtained compounds were identical to those described in [17, 18].

Deprotection of 7-benzyloxyflavonol and 4'-benzyloxyflavonol was carried out as follows.

The corresponding benzyl-protected flavonols (3 mmol) were dissolved in THF (40 mL), and 300 mg of Pd/C 10% was added. The mixtures were stirred for 12 h at room temperature under a hydrogen atmosphere. The Pd/C was then filtered off. After the solvent evaporation, the precipitate was washed with 10 ml of hexane and dried.

*7-Hydroxyflavonol*. $^{1}$H NMR (500 MHz, DMSO-$d_6$), δ, ppm: 10.80 (bs, 1H), 9.36 (bs, 1H), 8.16 (d, $J$ = 7.5 Hz, 2H), 7.95 (dd, $J$ = 9.2, 3.0 Hz, 1H), 7.54 (t, $J$ = 7.6 Hz, 2H), 7.46 (t, $J$ = 7.3 Hz, 1H), 6.98 – 6.89 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$), δ, ppm: 172.8, 163.0, 157.0, 144.6, 139.0, 131.9, 129.9, 128.9, 127.8, 127.0, 115.4, 114.7, 102.4. Mass spectrum, $m/z$ ($I_{rel}$, %): 255.0 $[M+H]^+$ (100). Parameters were identical to those described in [18].

*4'-Hydroxyflavonol*. $^{1}$H NMR (500 MHz, DMSO-d6), δ, ppm: 10.08 (s, 1H), 9.33 (s, 1H), 8.10 (t, J = 7.7 Hz, 3H), 7.79–7.72 (m,2H), 7.44 (s, 1H), 6.93 (d, J = 8.3 Hz, 2H). 13C NMR (126 MHz,DMSO-d6), d, ppm: 172.5, 159.1, 154.4, 146.1, 137.8, 133.3, 129.5, 124.7, 124.4, 122.0, 121.3, 118.2, 115.4. Mass spectrum, $m/z$ ($I_{rel}$, %): 253.0 $[M-H]^-$ (100). Parameters were identical to those described in [17].

The synthesis of hydrogels modified by 7-hydroxyflavonol and 4'-hydroxyflavonol was carried out according to two general procedures discussed in the next section.

Method A. To a suspension of ~ 2 mmol of alginic acid (from brown algae) and 4 mmol of corresponding flavonol in DMSO (30 mL), 6 mL of concentrated HCl was added. The reaction mixture was stirred at 80°C for 24 hours. After cooling, 30 mL of water was added to the reaction mixture, and after 15 minutes of vigorous stirring, the mixture was left until the phases were completely separated. The upper phase of the solvent was carefully decanted. The washing procedure was repeated three times. After washing, the obtained gel was dried from water by azeotropic distillation with acetonitrile (3 times). The resulting hydrogel was further used without additional purification.

Method B. To a suspension of ~ 2 mmol of alginic acid (from brown algae) and 4 mmol of 4'-OH-HF or 7-OH-HF in dioxane (20 mL) was added 5 mL of concentrated HCl, and the reaction mixture was stirred at 80 °C for 24 hours. After cooling, the solvents were removed in vacuo. The remaining water was removed by azeotropic distillation with acetonitrile (30 mL, 3 times). The resulting hydrogel was washed with chloroform (20 mL, 3 times), and finally, the solvents were removed in vacuo.

## 3. Results and discussion

### Synthesis of flavonols and flavonol esters of alginic acid

Most of the spectral properties of flavonols are due to the presence of a 3-hydroxy group. The introduction of this group leads to:

- a shift in the flavone absorption band from 315-325 nm to 350-365 nm and the appearance of a yellow color in these compounds;
- proton transfer from the hydroxyl group to the carbonyl group in the excited state and the formation of a phototautomer, which causes the appearance of a second long-wavelength band in the fluorescence spectra;
- the ability to form chelate complexes with metal ions.

Therefore, maintaining the free 3-hydroxy group during esterification is necessary for modified alginic acid to keep spectral and complexing properties similar to those of free flavonols. We studied the options for binding flavonols to the polymer matrix through additional 7- and 4'-hydroxy groups.

7-hydroxy- and 4'-hydroxyflavonols were synthesized in four steps (Figure 1) by protecting the *para*-hydroxy groups of the corresponding acetophenone and aldehyde with benzyl moieties, subsequent condensation of these reagents to form 2-hydroxychalcone, oxidative

Table 1. Chemical structure, solvents and yield of target flavonols.

| Flavonol | 7 ($R_1$)* | 4' ($R_2$)* | Solvent | Yield, % | Prototype |
|---|---|---|---|---|---|
| 4'-BnO-HF | H | BnO | MeOH | 80 | [17] |
| 7-BnO-HF | BnO | H | MeOH | 63 | [18] |
| 4'-HO-HF | H | OH | THF | 73 | [17,19] |
| 7-HO-HF | OH | H | THF | 88 | [18,19] |

* $R_1$ and $R_2$ are shown in Figure 1.

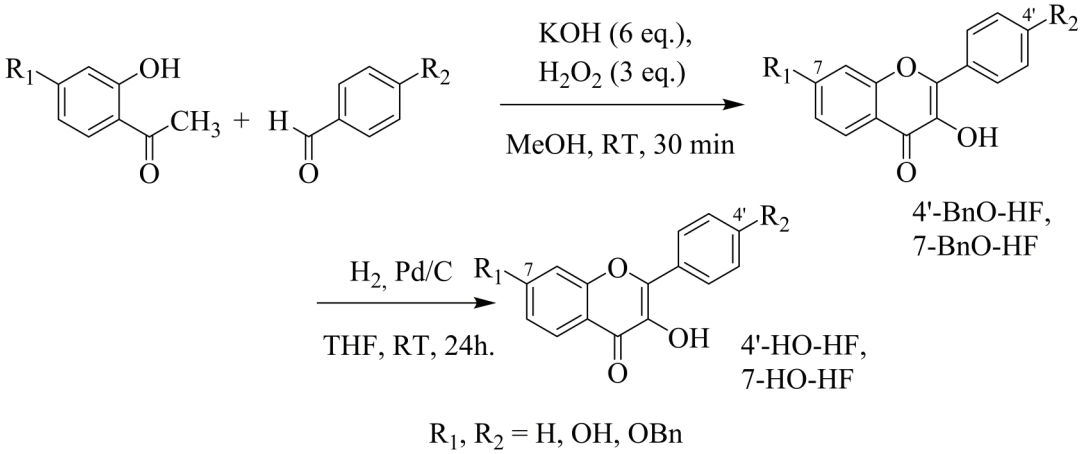


Fig. 1. Scheme for the synthesis of 7-hydroxy- and 4'-methoxyflavonols.

Algar-Flynn-Oyamada cyclization, followed by removal of the protecting groups. The basis was taken from our previously developed methods for the synthesis of flavonols [17, 18]. To increase the flavonol yield, the methods were further modified and optimized.

Some refined synthesis conditions and characteristics of the obtained compounds are given in the experimental section. The application of modified parameters led to a significant increase in the yield of the target compounds (Table 1) compared to previously used synthesis methods.

Previous studies of the acidity of hydroxyl groups in polyhydroxyflavonols have shown that the most acidic are hydroxyl groups at positions C4' and C7. In contrast, the $pK_a$ of the 3-hydroxy group is an order of magnitude higher [20, 21]. Given the nucleophile mechanism of the esterification reaction, the 3-hydroxy group should react first. However, taking into account that the 3-hydroxy group is bound to the carbonyl group via an intramolecular hydrogen bond and undergoes steric hindrances from the side benzene ring, its reactivity is substantially weaker. This allows for the selective alkylation or acylation of 4'- and 7-hydroxy groups without affecting the 3-hydroxy group [22]. This also makes it possible to carry out the selective esterification of flavonols with alginic acid, cross-linking the polymer and flavonols only through the 4'- and 7-hydroxy groups, and excluding cross-linking through the 3-hydroxy group.

The scheme of binding of flavonols to the polymer matrix via additional 7- and 4'-hydroxy groups is shown in Figure 2.

Taking into account the relatively low thermal stability of both alginic acid and the starting flavonols, mild reaction conditions were used. Based on [23, 24], we used the solvent systems DMSO-water and dioxane-water, which yielded a satisfactory result. Further optimization of the synthesis enabled us to select the solvent composition and find the best reaction conditions that ensure the maximum yield of the target esters (Table 2). A concentrated aqueous HCl solution was used as a catalyst. The reaction was carried out by heating stoichiometric amounts of the starting compounds in a mixture of DMSO and water 5:1 v/v or dioxane and water for 24 hours at 80 °C. The conversion degree was monitored by TLC for the presence of the starting flavonol in the reaction mixture (eluent: chloroform). The dependence of the degree of esterification on the medium temperature and the solvent system used is given in Table 2.

A comparison of esterification methods revealed that using DMSO (Method A) poses difficulties in purifying the final modified polymers

Table 2. Optimization of esterification reaction conditions using 4'-HO-HF and alginic acid.

| Temperature, °C | 60 | 80 | 100 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| Method | A | A | A | B | B | B |
| Solvent system | DMSO - $H_2O$ | | | Dioxane - $H_2O$ | | |
| Esterification completeness, % | 45 | 78 | 81 | 61 | 85 | 85 |

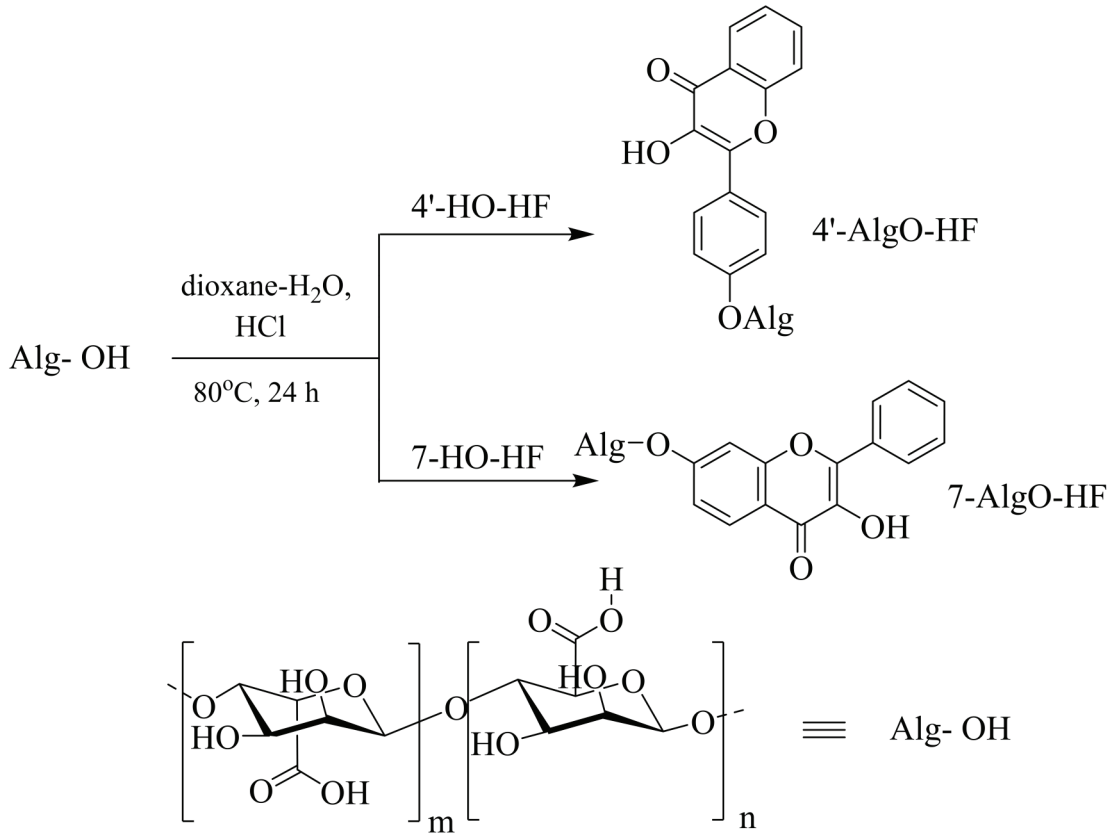


Fig. 2. Scheme of grafting flavonols to the elementary units of alginic acid.

from solvent traces. However, using a dioxane-water mixture (Method B) produces clean and dry final products.

***Spectral properties of alginic acid esters***

Depending on the flavonol grafting method to the alginic acid units, two types of polymers were obtained. Using 4'-hydroxyflavonol, the flavonol-alginate ester 4'-AlgO-HF was obtained (Figure 2), whereas esterification of alginic acid with 7-hydroxyflavone resulted in the formation of the ester 7-AlgO-HF. The spectral properties of the resulting esters were compared with those of the corresponding free flavonols.

The high acidity of the 4'- and 7-hydroxy groups of flavonols ensures their partial dissociation in polar nucleophilic solvents such as DMSO or water. Therefore, the absorption spectra of flavonols in such media exhibit not only the absorption bands of the neutral forms but also weak bands of anions. Unsubstituted flavonols can also dissociate in polar solvents to form an anion; however, given the lower acidity of the 3-hydroxy group, the anion can be present in solutions at trace levels, usually in the presence of traces of bases.

Figure 3a shows the normalized absorption spectra of free 4'-hydroxyflavonol and the alginate ester of flavonol – 4'-AlgO-HF. As shown in the figure, the spectral curves of flavonol and modified alginic acid coincide in the short-wavelength range of the spectrum. The absorption spectra of neutral flavonol and flavonol-alginate have identical maxima at 318 and 359 nm. The spectra of free 4'-hydroxyflavonol contain an additional long-wavelength band at 435 nm, the intensity of which increases with the addition of bases to the solvent and disappears with the addition of acids. This absorption band is attributed to the anionic form of 4'-HO-HF, which is formed by the dissociation of flavonol in polar nucleophilic solvents.

In the 4'-AlgO-HF spectra, the anion absorption band is absent, indicating the disappearance of the 4'-hydroxy group upon formation of an ester bridge with alginic acid. As shown in [25], substitution of the 3-hydroxy group proton must lead to a hypsochromic shift of the flavonol absorption bands. The absence of such a shift indicates that esterification does not affect the

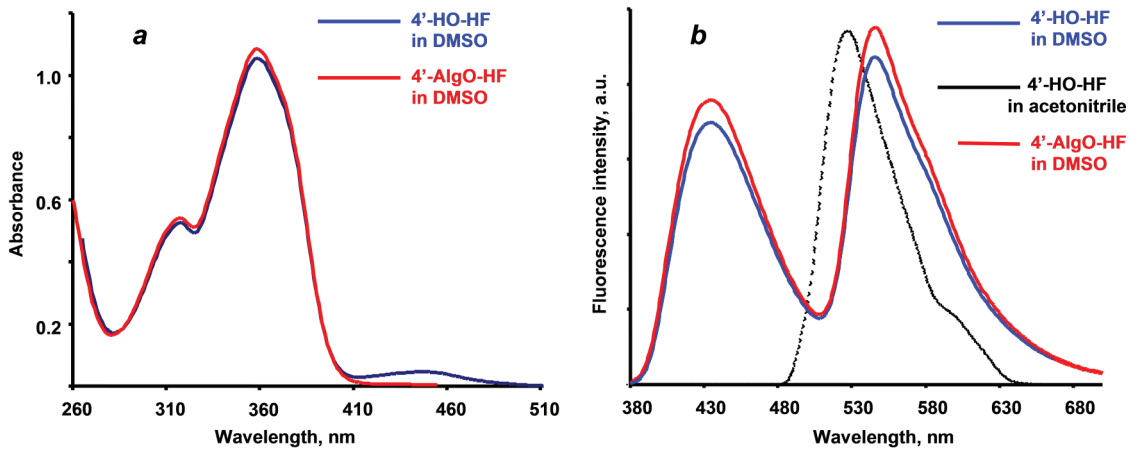


Figure 3. Absorption and fluorescence spectra of 4'-HO-HF and 4'-AlgO-HF

3-hydroxy group, and the latter does not form bridging bonds with the polymer molecule.

The most important feature of flavonols is the excited-state intramolecular proton transfer (ESIPT), which leads to the appearance of long-wavelength fluorescence due to the phototautomer (T*) formed. Usually, the rate of the ESIPT process is much higher than the rate of radiation deactivation of the initial form (N*). That is why, most often, flavonol fluorescence spectra exhibit only one long-wavelength emission band of T* with a large Stokes shift >9500 $cm^{-1}$. So, the spectrum of 4'-HO-HF in acetonitrile depicted in Figure 3b demonstrates only one emission band.

A very important condition for the ESIPT occurring is the presence of the intramolecular hydrogen bond between the proton-donating 3-hydroxy group and the proton-accepting carbonyl group. When this bond is broken, the fluorescence spectrum exhibits only the band of the form N*, having a significantly lower Stokes shift than that of the phototautomer.

Table 3. Spectral properties of free flavonols and their alginates.

| Flavonol | Solvent | $\lambda_{abs}$, nm | $\nu_{abs}$, $cm^{-1}$ | $\lambda_{fl}$, nm* | $\nu_{fl}$, $cm^{-1}$ | $\Delta\nu_{St}$, $cm^{-1}$ | Form† |
|---|---|---|---|---|---|---|---|
| 4'-HO-HF | acetonitrile | 350 | 28570 | 530 | 18865 | 9705 | T* |
| | DMSO | 359 | 27855 | 435 | 22990 | 4865 | N* |
| | | 318 | 31445 | 547 | 18280 | 9575 | T* |
| | | 435 | 22990 | 485 | 20620 | 2370 | A* |
| 4'-AlgO-HF | DMSO | 359 | 27855 | 435 | 22990 | 4865 | N* |
| | | 318 | 31445 | 546 | 18315 | 9570 | T* |
| 7-HO-HF | acetonitrile | 341 | 29325 | 532 | 18800 | 10525 | T* |
| | DMSO | 342 | 29240 | 402 | 24875 | 4365 | N* |
| | | 325 | 30770 | 545 | 18350 | 10890 | T* |
| | | 413 | 24215 | 485** | 20620 | 3595 | A* |
| 7-AlgO-HF | DMSO | 342 | 29240 | 402 | 24875 | 4365 | N* |
| | | 325 | 30770 | 545 | 18350 | 10890 | T* |

* The fluorescence of 4'-HO-HF and 4'-AlgO-HF is excited at 360 nm, fluorescence of 7-HO-HF and 7-AlgO-HF is excited at 340 nm.

** The fluorescence of anions is excited at 420 nm.

† Protolytic forms of flavonols in the excited state: N* – neutral (starting) form, T* – phototautomer form, A* – anionic form.

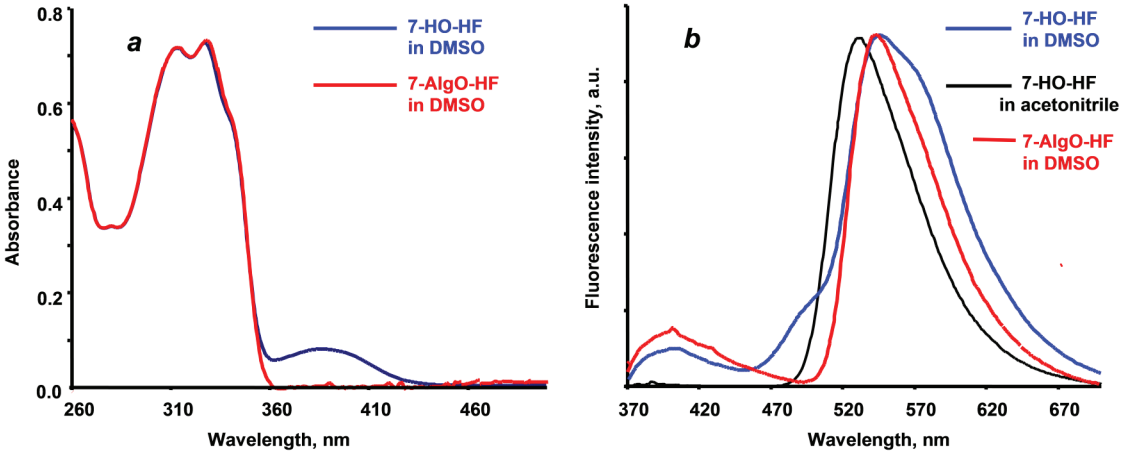


Fig. 4. Absorption and fluorescence spectra of 7-HO-HF and 7-AlgO-HF

As shown in Figure 3b, the fluorescence spectrum of 4'-HO-HF in DMSO exhibits both bands – N* and T*, which indicate the existence of the competition between the intramolecular hydrogen bond and the intermolecular hydrogen bond connecting the flavonol 3-hydroxy group and the sulfoxide group of the solvent.

The fluorescence spectra of DMSO solutions of modified alginic acid 4'-AlgO-HF are identical to the spectra of 4'-HO-HF. This allows us to conclude that esterification at the 3-hydroxy group does not occur, and equilibrium between intra- and intermolecular hydrogen bonds in flavonol fragments of modified alginic acid does not differ from that in free flavonol. Thus, flavonol-containing alginic acid keeps all the spectral properties of the modifying fragment.

The spectra of concentrated 4'-AlgO-HF solutions measured under excitation at 420 nm demonstrate a trace fluorescence of the anion at 485 nm. This indicates a negligible amount of free 4'-hydroxyflavonol in the gel not removed after 4'-AlgO-HF washing. It can be assumed that free flavonol is retained in alginic acid due to the formation of intermolecular hydrogen bonds with hydroxyl groups of polysaccharide units.

The spectral parameters of 4'-HO-HF and 4'-AlgO-HF are listed in Table 3.

Figure 4a shows the spectra of free 7-HO-HF and its ester with alginic acid – 7-AlgO-HF. The spectrum of free 7-hydroxyflavonol differs from that of 4'-HO-HF: the absorption bands of the neutral molecule 7-HO-HF are located closer to each other, overlap, and merge into a broad complex band. Also in DMSO solutions, dissociation of the 7-hydroxy group occurs, which leads to the appearance of a long-wavelength band of the C7-anion at 413 nm. In a polar weakly nucleophilic solvent – acetonitrile, the anionic form is not formed.

The absorption spectrum of 7-AlgO-HF is similar to that of 7-HO-HF, but does not contain an anion band, which indicates complete binding of flavonol molecules to alginic acid through 7-hydroxy groups.

The fluorescence spectrum of 7-HO-HF (Figure 4b) has a complex structure. When excited at 320 nm, in the fluorescence spectrum, in addition to the short-wave emission band of the original form N* at 400-405 nm and a band of the phototautomeric form T*, there are shoulders corresponding to the emission bands of the anion A* at 485 nm and the anion-tautomer at 575 nm. The latter protolytic form of 7-HO-HF was discovered and described in [18].

The spectrum of 7-AlgO-HF contains only two emission bands - N* and T*. The anionic and anion-tautomeric forms are formed in the excited state only in the presence of a 7-hydroxy group, which is absent in the obtained alginic acid esters. The weak emission band of the anion form was found in the fluorescence spectra of concentrated 7-AlgO-HF solutions upon excitation at 420 nm. This indicates the presence of trace amounts of 7-HO-HF bound with alginic acid via intermolecular hydrogen bonds.

As in the case of 4'-AlgO-HF, modification of alginic acid with 7-hydroxyflavonol results in a polymer that retains all the spectral properties of the grafted flavonol.

## 4. Conclusions

The presented results allow us to draw two important conclusions. First, the possibility of obtaining alginic acid modified with flavonol fragments has been demonstrated. Taking into account the ability of alginic acid to undergo

enzymatic hydrolysis – both the cleavage of the polysaccharide chain into individual units and the decomposition of esters with the formation of free flavonols, the obtained modified polymers can be used as implants that will serve as a depot for the gradual release of compounds with antioxidant, anti-inflammatory, and cancerostatic properties.

An important feature of the obtained polymers is that the spectral properties of solutions of alginic acid with grafted flavonols are almost identical to those of free flavonols in solutions. In this case, the properties of the polymers do not depend on the method of grafting flavonol fragments. The only difference of 4'-AlgO-HF and 7-AlgO-HF from free flavonols is the absence of anionic forms in polar nucleophilic solvents due to the conversion of "anchor" hydroxyl groups into ester fragments.

The similarity of spectral properties allows the use of modified alginic polymers in gel form, in the same way as free flavonols, to assess the polarity of the medium, and as metallofluorochrome indicators. The advantage of using gels is that they do not mix with the solvent, allowing dynamic binding and accumulation of metal ions with fluorescent control.

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