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LETTERS TO THE EDITOR

Sulfation of Alginic Acid with Chlorosulfonic Acid in the Formamide–1,2-Dichloroethane Medium

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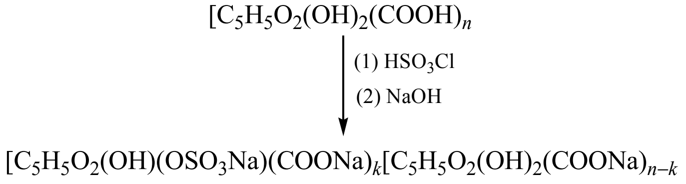
For the sulfation of polysaccharides solutions of sulfur trioxide in inert solvents and its complexes with different compounds are widely used [1]. However, the low stability of SO_3 creates technical difficulties in its application, therefore the search for the methods of sulfation of polysaccharides with chlorosulfonic acid is very promising.

In recent years the importance of alginic acid in various industries increased [2], but its sulfuric esters were poorly studied. The literature describes a method of alginic acid sulfation with chlorosulfonic acid in pyridine [2]. However, the presence of toxic pyridine, which is difficult to be removed, in food and drugs is inadmissible. Therefore, the aim of our study is to investigate the possibility of using the previously suggested method of dextran sulfation with chlorosulfonic acid in the 1,2-dichloroethane–formamide [3] for the sulfation of alginic acid.

Chemical modification of alginic acid was carried out by the scheme.



$$[C_5H_5O_2(OH)_2(COOH)]_n \xrightarrow[(2)\ NaOH]{(1)\ HSO_3Cl} [C_5H_5O_2(OH)(OSO_3Na)(COONa)]_k[C_5H_5O_2(OH)_2(COONa)]_{n-k}$$

The sulfation of alginic acid with chlorosulfonic acid was carried out by a method developed for dextran [3].

The sodium salt of alginic acid sulfate is a fine powder of white or light beige color, soluble in water and alkaline aqueous solutions, poorly soluble in acidic aqueous solutions, insoluble in alcohols and other organic solvents.

The solubility of sodium alginate sulfate in water and acid solutions depends strongly on the number of sulfo groups in the sample. When the content of sulfo groups is more than 0.4 mol per 1 mol of monosaccharide fragment, it is readily soluble in the acid aqueous solutions.

In the IR spectra of the sodium salt of alginic acid sulfate there are the absorption bands in the range of 1240–1265 cm^{-1} attributable to the stretching vibrations ν(S=O), which are absent in the spectra of the original alginic acid. In addition, there are the absorption bands at 1619–1624 cm^{-1} and in some cases at 1725–1732 cm^{-1} belonging to the stretching vibrations of carboxylate ion and carboxy group [ν(C=O)], which is formed at the hydrolysis of the salts in the stage of the product separation [4].

The obtained samples of the sulfated alginic acid were characterized by the degree of sulfation (C_s), the number of sulfo groups in the monomer unit of the polysaccharide, which was determined by the acid hydrolysis of the sulfate groups [5].

As it turned out, alginic acid, like dextran, but rather slower, forms a homogeneous reaction mixture. At the same time it is partially dissolved in formamide, which facilitates its sulfation and isolation of the product. When this procedure was used for the sulfation of aubazidan, starch and cellulose, which are not soluble in this medium, much worse results ($C_s \sim 0.1$) were obtained.

The IR spectra of the sulfated alginic acid samples contain the absorption bands in the range of 1685–1690 cm^{-1}, which are absent in the spectra of the samples obtained using a solution of sulfur trioxide in dichloroethane. In this regard, the nitrogen content in the sulfation products of alginic acid was deter-mined by a modified Nessler method [6], and the acyl group content, by the hydroxame reaction [7].

All the samples of the sulfated alginic acid were found to contain nitrogen, and most of them give positive hydroxamic reaction. Their purification via the multiple precipitating from the aqueous alkali and dialysis gave no positive results. In this regard, we can assume that the sulfation of alginic acid with chlorosulfonic acid in a dichloroethane–formamide mixture leads to the formation of complex compounds that contain nitrogen in addition to sulfo groups. The only source of nitrogen in the reaction mixture is formamide, which easily decomposes to release ammonia. In this regard, we attempted to replace formamide with the more stable *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide. The sulfation and analysis of the products were performed as described above.

The first experiments on alginic acid sulfation in the presence of dimethylformamide and dimethylacetamide showed that the side reactions were absent. The resulting samples did not contain nitrogen, and did not give a positive hydroxamic reaction. In their IR spectra the absorption bands of the extra functional groups were not detected. However, when using DMF, the sulfation degree of the polysaccharide samples obtained under the identical conditions varied from 0.09 to 0.33, while in the case of dimethylacetamide it did not exceed 0.07. Probably, the reason of the process instability is that the different sulfating species (SO_3, HSO_3^+, and SO_3 complex with dimethylformamide) are involved into the reaction. The formation of these species depends on the reaction rate of DMF with chlorosulfonic acid. As described above, all of the species mentioned above can take part in the reaction.

The result obviously depends on the concentration of different species in a given moment, i.e. on the rate of mixing the reagents, stirring, polymer swelling, etc. To test this assumption we changed the sequence of the reagents addition: chlorosulfonic acid was mixed with DMF at different molar ratio before adding to the polysaccharide.

As expected, the use of sulfating mixture containing an excess of DMF led to the stabilization of the reaction results, but with a very low sulfation degree (0.01–0.05). This can be ascribed to the participation in the reaction mainly of SO_3 complex with dimethylformamide and its low activity. When the sulfonating mixture contains an excess of chlorosulfonic acid, in addition to the complex other more active species are involved into the reaction, and the number of sulfo groups in the polymer increases to 0.15.

Due to the fact that by the replacement of formamide with dimethylformamide and dimethylacetamide the desired results were not achieved, the sulfation of alginic acid was carried out by the previously proposed method with formamide followed by the samples purification. To purify the sulfated alginic acid it was dissolved in 0.1 N sodium hydroxide solution and left for 24 h, then the reaction mixture was centrifuged to separate a precipitate and subjected to dialysis. The resulting solution was concentrated, the polysaccharide was precipitated, washed with alcohol, and dried in a vacuum at 61°C.

The IR spectra of the purified sulfated alginic acid contain the absorption bands characteristic of alginic acid and sulfo groups. The absorption bands in the range of 1685–1690 cm^{-1} disappeared [4]. The resulting samples did not contain nitrogen that indicate the high purification degree of the polymer. The sulfonation degree of the samples, treated with alkali, increased slightly, which also indicates an increase in the purity of the polysaccharide.

Thus, the sulfation of alginic acid with chlorosulfonic acid in a formamide–1,2-dichloroethane system followed by purification of the reaction products in alkaline solution allows the preparation of samples with the sulfation degree of the polysaccharide up to 0.57 with a minimal content of the undesired functional groups. The replacement of formamide with *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide prevents the side reactions and provides pure samples of sulfated alginic acid, but the sulfation degree of the polysaccharide is very small.

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