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Sulfation of Microcrystalline Cellulose with Sulfamic Acid in N,N-Dimethylformamide and Diglyme

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Sulfation of MCC by sulfamic acid in DMF or diglyme in the presence of urea was studied for the first time. It was established, that the degree of substitution in sulfated MCC was in the range from 1.40 to 1.54. It was shown, that the most effective sulfation of MCC takes place in diglyme. The yield of cellulose sulfate at sulfation MCC in diglyme was 2.5 times higher than the yield for sulfation MCC in N,N-dimethylformamide

Keywords: microcrystalline cellulose, sulfation, sulfamic acid, urea, N,N-dimethylformamide, diglyme, microcrystalline cellulose sulfates.

Introduction

Cellulose sulfates (CS) have a rather wide area of application. Sodium salt of cellulose sulfate is used in the process of fabrics dyeing, as the stabilizer of clay suspensions for drilling oil wells, thickeners, sorbent, ion-exchange material, as a base for cosmetics and perfumes, etc. [1]. Cellulose sulfates possess anticoagulant properties and can be used for prevention and treatment of thromboses. Anticoagulant activity of the CS depends on the degree of substitution and its molecular weight [2, 3]. For sulfation of cellulose various etherifying mixtures on the base of sulfuric acid with aliphatic

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alcohols are used [1]. Another known group of methods is based on cellulose sulfation by sulfur trioxide in *N,N*-dimethylformamide (DMF), pyridine, or in the presence of tertiary amines. In [3, 4] cellulose sulfation by chlorosulfonic acid in liquid sulfur dioxide, dichloroethane, acetic anhydride, DMF and pyridine was studied. Sulfation of microcrystalline cellulose (MCC) by chlorosulfonic acid in dioxane was also studied [5].

Sulfur trioxide, sulfuric and chlorosulfonic acid which are widely used in the sulfation reactions are quite aggressive reagents, and ecology dangerous the use of which requires special equipment that causes technical difficulties. In contrast to the above reagents, the sulfamic acid is a stable, non-hygroscopic crystalline solid. Its acidity is comparable with sulfuric acid. Sulfamic acid is commercially produced by urea interaction with an oleum. In [6] was reported that cellulose is degraded at heating with sulfamic acid, but in the presence of urea, which plays the role of basic catalyst, sulfation occurs more satisfactorily. The sulfation of cellulose which has been previously impregnated with a solution of urea and sulfamic acid in DMF, proceeds more easily [7].

In the present study, for the first time the sulfation of microcrystalline cellulose by sulfamic acid in DMF and dimethyl ether of diethyleneglycol (diglyme) in the presence of urea was investigated.

Experimental

MCC Vivapur® Type 101 from JRS Pharma (Weissenborn, Germany) with an average degree of polymerization (DP) 350, crystallinity index 0,75, and a hemicellulose content of 5.2 % wt. was used as the starting material.

X-ray diffraction scattering analysis was carried out with DRON-3 diffractometer using Cu-K α source ($\lambda=0,154$ nm) in the 2θ range 5–50°.

FTIR analysis was carried out in transmission mode. The mass of sample in matrix KBr was 2 mg. The spectra were recorded with Tensor-27 spectrometer (Bruker, Germany) in range 400–4000 cm⁻¹. Spectral data were processed by program OPUS/YR (version 5.02).

NMR ¹³C spectra were recorded at temperature 25 °C with spectrometer Bruker Avance III 600 MHz using D₂O as reference.

Sulfation of MCC in *N,N*- dimethylformamide

MCC (1.62 g), urea (1.80 g), sulfamic acid (3.40 g) and DMF (40 ml) were placed in a three necked flask (100 ml) equipped with stirrer, thermometer and reflux. The mixture was then boiled on oil bath at vigorous stirring for 1 hour. After that, the reaction mixture was cooled to 15-20 °C, poured into 50 ml of 75 % water-ethanol solution containing 3-4 % sodium hydroxide and stirred until the extinction of ammonia ceasing. The resulting sodium salt of MCC sulfate was separated by filtration, washed with 96 % ethanol, and dried under vacuum. The obtained product was then dissolved in 50-60 ml distilled water, filtered and dialyzed on cellophane against distilled water. After dialysis the aqueous solution of NaCS was concentrated under vacuum until complete removal of water. Yield of sodium salt of MCC sulfate was 0,26 g.

Sulfation of MCC in diglyme

MCC (1.62 g), urea (1.80 g), sulfamic acid (3.40 g) and diglyme (40 ml) were placed in a three necked flask (100 ml) equipped with stirrer, thermometer and reflux. The procedure of synthesis was the same as in the case of MCC sulfation in *N,N*-dimethylformamide. Yield of sodium salt of MCC sulfate was 0,98 g.

MCC sulfate in the form of the ammonium salt was prepared by diluting the reaction mixture with 70 % ethanol. MCC sulfate in the form of potassium salt was prepared by diluting the reaction mixture with 75 % water-ethanol solution containing 3-4 % potassium hydroxide.

The sulfur content in MCC sulfates was defined by modified method [8] (by burning in oxygen stream with the subsequent absorption of products of burning by hydrogen peroxide and titration by alkali in the presence of the indicator of the methyl red). The average degree of substitution (DS) of MCC sulfates was calculated from the sulfur content according to a formula [4]:

$$DS = \frac{162 \times \omega_S}{3200 - 103 \times \omega_S}$$

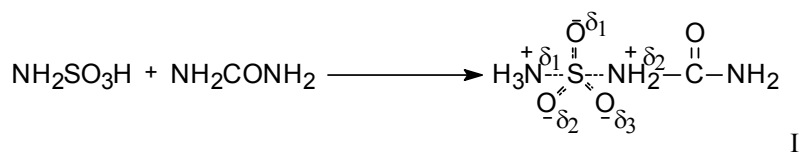
где ω_S – sulfur content (wt. %).

Results and discussion

It is known [6] that the reaction of sulfamic acid with alcohols under heating gives the corresponding ammonium salt with yield about of 22 % wt, according to scheme:



However, yield of the salt can be increased to 70 % by the addition of pyridine to the reaction mixture. The catalytic activity of pyridine, urea, thiourea, acetamide and picoline was compared in the process of sulfation of higher aliphatic alcohols and the most effective catalyst was urea. The higher catalytic activity of urea compared to other additives has also been shown for sulfation of starch, cellulose and other polysaccharides [6]. This was the basis for the use of urea in the sulfation of MCC with sulfamic acid. The mechanism of esterification by sulfamic acid in the presence of urea was explained by formation of a donor-acceptor complex (I), which has high reactivity to sulfation [9]:



Reaction of cellulose sulfation by sulfamic acid in the presence of urea was carried out in boiling solvent at vigorous stirring. Cellulose sulfates were isolated in the form of ammonium, sodium, and potassium salts (Fig. 1).

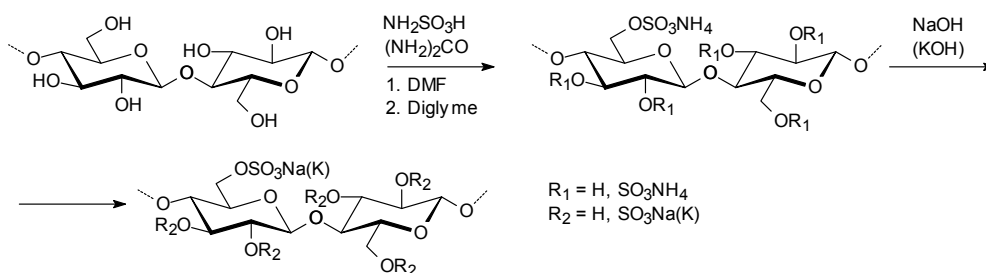


Fig. 1. Scheme of MCC sulfation with sulfamic acid

It was established that the reaction of sulfation of MCC by sulfamic acid in the presence of urea in DMF or diglyme proceeds in a heterogeneous medium. Influence of reaction time on the yield of cellulose sulfates, the sulfur content and the degree of substitution are shown in the Tables 1 and 2.

According to the obtained results, the maximum yield of CS was 0.5-0.6 g at sulfation MCC in DMF for 2-3 hours. The sulfur content in the MCC sulfates was 13,6-14,8 %, which corresponds to the degree of substitution of 1,2-1,4 (Table 1). Prolongation of the reaction time more than 3 h resulted in a darkening and decomposition of the reaction mixture, the yield of NaCS also was decreased. Sulfation of MCC in diglyme for 2,0-2,5 h allowed to obtain NaCS with an yield to 1,6 g and a sulfur content of 15.4 %, which corresponds to a degree of substitution 1,4-1,5 (Table 2).

It has been found that at the same reaction time in spite of on the higher boiling point of diglyme (161 °C) as compared to DMF (152 °C), the sulfation of cellulose in diglyme proceeds easier and results in less cellulose degradation than in DMF. The use of diglyme for sulfation allowed to increase the yield of cellulose sulfate by 2.5 times in comparison with DMF.

The increase of temperature of cellulose sulfation reduces the degree of cellulose polymerization regardless of the used method of sulfation [1, 4]. The comparison of XRD patterns of initial MCC and MCC sulfated by sulfamic acid in DMF or diglyme testifies of the disordering of cellulose crystalline structure during sulfation process (Fig. 1).

IR spectra of sulfated MCC (Fig. 4-5) are differ from IR spectrum of the initial MCC (Fig. 3) by the presence of strong absorption bands at 800-805 cm^{-1} (C–O–S) and 1236-1245 cm^{-1} (O=S=O), confirming the introduction of sulfate groups in the structure of cellulose.

It is known [3], that the hydroxyl group at C6 primary carbon atom is predominantly sulfated in a glucopyranose unit of cellulose. The hydroxyl group connected with carbon atom C2 is replaced

Table 1. Sulfation of MCC by sulfamic acid in boiling DMF

Sample №	Reaction time, h	MCC sulfate yield, g	Sulfur content, %	DS
1	1,0	0,26	13,58	1,22
2	2,0	0,51	14,76	1,42
3	3,0	0,64	13,35	1,19
4	4,0	0,63	12,47	1,05

Table 2. Sulfation of MCC by sulfamic acid in boiling diglyme

Sample №	Reaction time, h	MCC sulfate yield, g	Sulfur content, %	DS
1	1,0	0,98	14,00	1,29
2	1,5	1,13	14,42	1,36
3	2,0	1,27	15,17	1,50
4	2,5	1,64	15,41	1,55
5	3,0	1,43	14,64	1,40

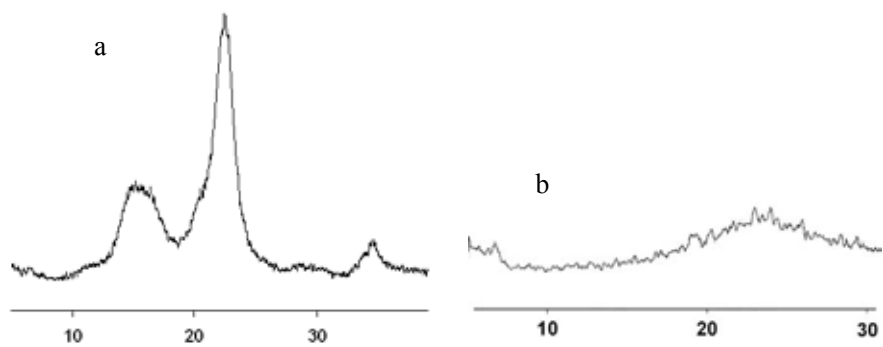


Fig. 2. XRD pattern of initial MCC (a) and sulfated MCC (b)

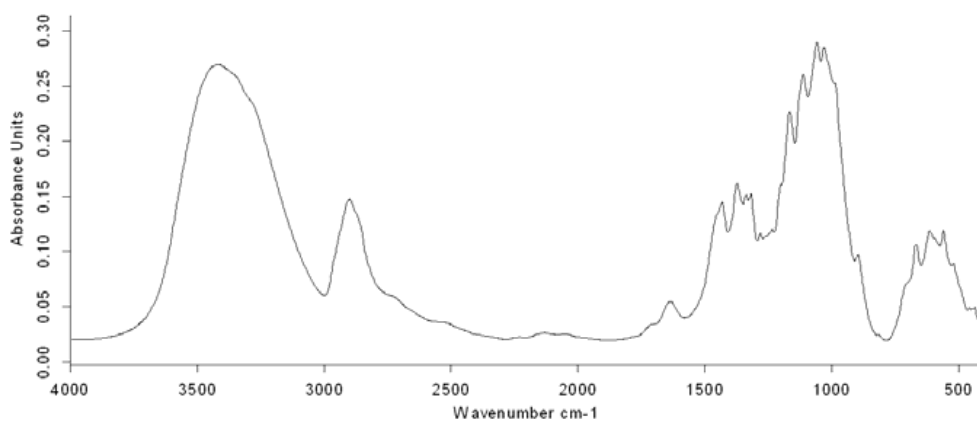


Fig. 3. FTIR spectrum of initial MCC

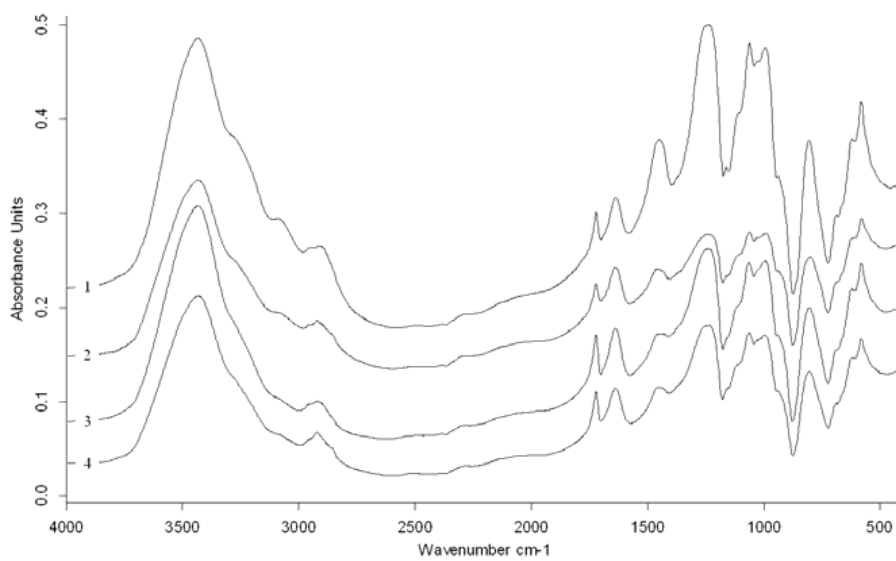


Fig. 4. FTIR spectra of MCC sulfated in DMF: 1 – 1 h., 2 – 2 h., 3 – 3 h., 4 – 4 h

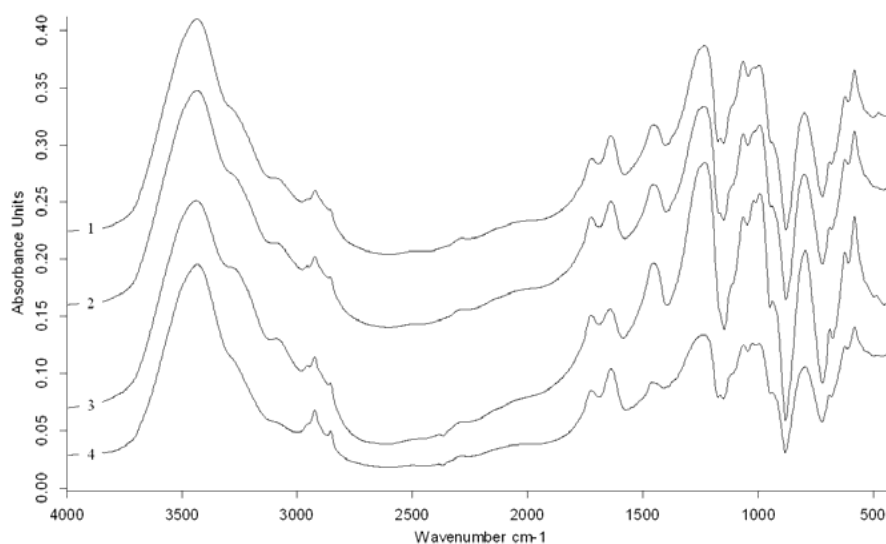


Fig. 5. FTIR spectra of MCC sulfated in diglyme: 1 – 1,0 h., 2 – 1,5 h., 3 – 2,0 h., 4 – 2,5 h

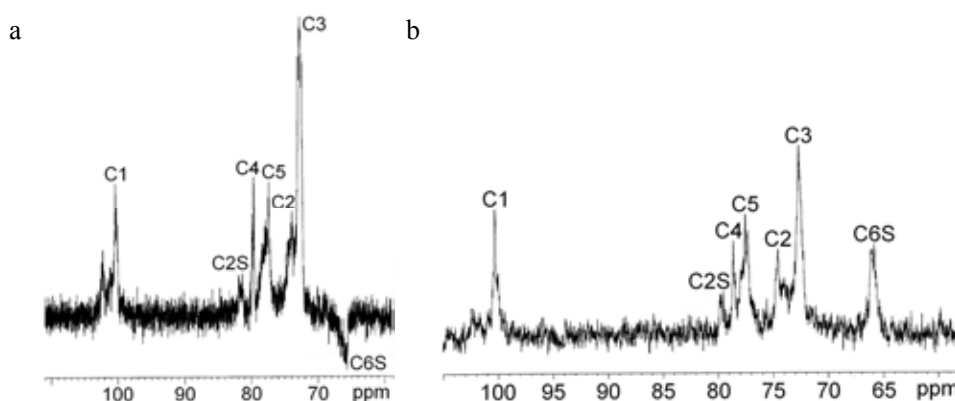


Рис. 6. ^{13}C NMR spectra of MCC sulfated in DMF (a) and in diglyme (b)

with difficulty. The hydroxyl group at C3 carbon atom is replaced only under hard conditions, which leads to a high depolymerization of cellulose [3]. According to ^{13}C NMR [3, 10] the chemical shifts corresponding to carbon atoms C1 – C6 in glucopyranose units of cellulose are observed at 102, 74, 73, 79, 77 and 66 ppm, respectively. The introduction of sulfate groups to MCC affected the chemical shifts of carbon atoms to lower magnetic field.

Studying of ^{13}C NMR spectrum of the obtained cellulose sulfates (Fig. 6) showed that the signal of carbon atom C6 completely moved to 66 ppm. It means that all of the hydroxyl groups at carbon atoms C6 were substituted on sulfate groups. Appearance of a signal of the carbon atom C2 in the field of 80-82 ppm indicates that the hydroxyl groups at the C2 sulfated partially. Similar results were reported by the authors of work [3], in which MCC was sulfated by chlorosulfonic acid in DMF. No shift of a signal of atom C3 was observed. This indicates the absence of sulfate group at C3 atom at sulfated MCC.

Conclusions

Sulfation of MCC by sulfamic acid in DMF or diglyme in the presence of urea was studied at the first time. It was established, that the degree of substitution of sulfated MCC reaches to 1.40-1.54. The most effective sulfation of MCC takes place in diglyme. The yield of MCC sulfate prepared in diglyme was by 2.5 times higher than the yield of MCC sulfate obtained in N,N-dimethylformamide

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**Сульфатирование
микrokристаллической целлюлозы
сульфаминовой кислотой
в N,N-диметилформамиде и диглиме**

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Изучено сульфатирование МКЦ сульфаминовой кислотой в присутствии мочевины в ДМФА и диглиме. Установлено, что степень замещения серы в полученных сульфатах МКЦ составляет от 1,40 до 1,54. Показано, что наиболее эффективно происходит сульфатирование МКЦ в диглиме, при этом выход сульфата МКЦ возрастает в 2,5 раза по сравнению с сульфатированием МКЦ в N,N-диметилформамиде.

Ключевые слова: микrokристаллическая целлюлоза, сульфатирование, сульфаминовая кислота, мочевина, N,N-диметилформамид, диглим, сульфат микrokристаллической целлюлозы.
