

NITRATION OF CARBOXYMETHYLCELLULOSE

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The influence of the conditions of nitration and the structure of the initial carboxymethylcellulose on the depth of conversion and the molecular characteristics of the nitroesters obtained has been investigated. The products obtained after optimization of the hydrophilic-hydrophobic balance with the aim of imparting solubility to them possess a pronounced antianginal action.

One of the promising methods for creating new biologically active substances is the introduction of active groups into the macromolecules of natural polymers, which enables us to obtain a combination of a controlled prolonged action with a low toxicity and good biocompatibility.

It is known [1] that the nitration of cellulose in methylene chloride at a low temperature leads to the formation of nitroesters containing up to 14% of nitrogen. In order to obtain pharmacologically active cellulose derivatives with regulable molecular parameters influencing their biological activity, we have investigated the nitration of carboxymethylcellulose (CMC) and the influence of the conditions of its performance, and also structural and molecular features of the substrate, on the rate of the reaction and the depth of conversion.

The object of investigation was CMC with different degrees of polymerization (DP – 20-500) and with a degree of substitution (DS) in terms of carboxymethyl groups of 0.37-85. The nitration of the CMC specimens was carried out with fuming nitric acid in methylene chloride at temperatures of 3 and 15°C.

With increase in the ratio of HNO₃ to CMC at a constant liquor ratio, the degree of nitration rose (Table 1), which is connected with an increase in the amount of NO₂⁺ ions in the system. A substantial role is also played by the concentration of HNO₃; at a constant ratio of the reactants a decrease in the concentration of the acid from 8 to 2 M was accompanied by a fall in the degree of nitration from 0.30 to 0.15 resulting from a decrease in the number of effective collisions of the NO₂⁺ ions with the hydroxy groups of the substrate.

Since the nitration of CMC takes place heterogeneously, the accessibility of its functional groups for the reagent, which depends on the DP and the DS, exerts a considerable influence on its reactivity. Thus, with a decrease in DS the degree of nitration increased (Fig. 1), since the carboxymethylation of cellulose under heterogeneous conditions takes place in the most accessible section of the macromolecule and, because of this, the rate of subsequent nitration proves to be in inverse dependence on the depth of carboxymethylation.

TABLE 1. Influence of the CMC:HNO₃ Ratio on the Degree of Nitration (liquor ratio 1:150; T = 3°C; DS of the CMC = 80 ± 2; DP of the CMC = 500 ± 30; reaction time 20 min)

Molar ratio, CMC:HNO ₃	Nitrogen content of the reaction product, %	Degree of substitution of the product with NO ₂ groups.
1:3	1.48	4.83
1:5	1.78	5.80
1:10	3.87	12.63
1:20	4.81	15.69
1:30	7.82	25.52
1:50	8.09	26.40
1:100	9.19	29.99
1:200	9.48	30.94
1:300	9.94	32.44

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TABLE 2. Change in the DP of CMC During Nitration (ratio CMC:HNO₃ = 1:500; C_{HNO₃} = 4 M; T = 3°C; DS of the CMC 70±2; DP of the CMC 450±20; DS with nitro groups 31.59)

Reaction time, min;	$[\eta]_{25^{\circ}\text{C}}$ (in methanol).	DP
10	3.70	400
15	3.56	370
30	2.80	300
60	2.42	250
180	2.30	220
300	2.20	200

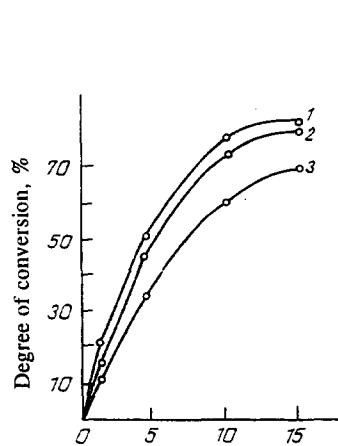


Fig. 1

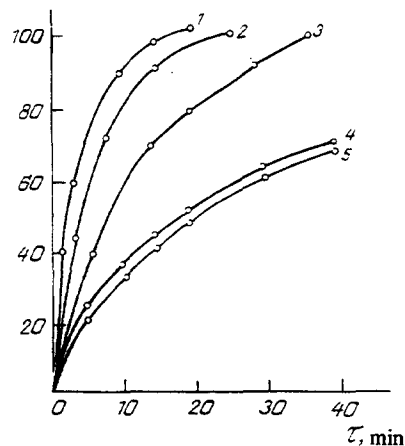


Fig. 2

Fig. 1. Kinetic curves of the nitration of CMC: 1) DS 0.37; DP 1150; 2) DS 37; DP 70; 3) DS 80; DP 70. The ratio CMC:HNO₃ = 1:200; C_{HNO₃} = 5 N; T = 3°C.

Fig. 2. Kinetic curves of the nitration of CNCs with DPs of 500 (1); 300 (2); 130 (3); 60 (4); and 20 (5). Ratio CMC:HNO₃ = 1:200; C_{HNO₃} = 5 M; T = 15°C.

Samples of CMC with different DPs were obtained by hydrolytic splitting [2]. With a decrease in the DP of the initial CMC the rate of nitration fell (Fig. 1). Such a change in the activity was due to substantial differences in the supermolecular structure of the samples investigated and, in particular, to an increase in the degree of crystallinity with a fall in the DP in the course of acid hydrolysis [2].

In all cases, a characteristic feature of the nitration reaction was the existence of an induction period, which increased at lower temperatures. During the first 10-15 min of nitration (Table 2) the DP of the initial CMC changed only slightly, but subsequently there was a far-reaching degradation of the polymeric chain.

Thus, the reactivity of CMC in nitration decreases with an increase in DS and with a fall in DP. This is due to a densification of the structure of the CMC with a rise in the DS and to the decrease in the DP taking place on hydrolytic splitting, accompanied by an increase in the orderedness of the supermolecular structure of the hydrolyzed CMC samples, which leads to hindrance of the diffusion of the NO₂⁺ ions to the reaction centers of the CMC molecules.

The formation of nitroesters of CMC was shown by elemental analysis and IR spectroscopy, and by the change in solubility. The IR spectra of the samples of nitro-CMC showed the absorption bands at 2940 and 2980 cm⁻¹, due to C—H stretching vibrations, that are characteristic for nitroesters. A band at 1765 cm⁻¹ was due to the carbonyl absorption of carboxy groups. These features appeared most clearly in the spectra of samples with the highest possible nitrogen content (10.33%). In contrast to cellulose nitrates, in the IR spectra of the nitro-CMCs the broad band at 1660 cm⁻¹ characteristic

for the nitro group was split, and a narrow band was observed at 1660 cm^{-1} with a shoulder at 1680 cm^{-1} . In all the cellulose nitroesters a band appeared at 1280 cm^{-1} due to the symmetrical stretching vibrations of the nitro groups, and also bands at 840, 750, and 700 cm^{-1} , which are characteristic for them [3].

The features of the nitration of CMC that have been revealed enable us to obtain nitroesters with given characteristics – DP and the DS for nitro groups – which makes it possible to achieve the necessary hydrophilic–hydrophobic balance in the creation of medicinal preparations from them. As pharmacological tests have shown, after solubility had been imparted to them, the CMC nitroesters possessed a pronounced antianginal action [4].

EXPERIMENTAL

CMC according to GOST [State Standard] 5.088-70, types 450 and 530, 70, and 80 were subjected to nitration.

IR spectra were taken on a UR-20 and Specord-75 spectrometers in solution and in KBr tablets [3]. The degree of polymerization of the samples was determined viscosimetrically [5]. The degree of substitution with carboxy groups was determined as described in [6]. The heterogeneous hydrolytic splitting of the CMC was conducted in a mixture of isopropyl alcohol and HCl [2].

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