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SYNTHESIS OF NITRO-CONTAINING DERIVATIVES BASED ON MODIFIED CARBOXYMETHYLINULIN

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Abstract

The development of methods for synthesizing new derivatives of polysaccharides remains one of the most interesting areas in the chemistry of high-molecular-weight compounds. In this regard, research on obtaining nitrogen-containing derivatives of polysaccharides is particularly important. In the presented study, the chemical modification of carboxymethylinulin was carried out through periodate oxidation. This approach enables the selective cleavage of vicinal diol groups with the formation of reactive aldehyde functionalities along the polymer chain. Such structural transformations significantly expand the possibilities for subsequent functionalization and targeted introduction of biologically active fragments. In the next stage, low-molecular-weight heterocyclic compounds containing nitro groups in the structure were chemically immobilized to the macromolecules of the oxidized inulin ester. Reaction conditions affecting the structural properties of the synthesized compounds have been found.

Keywords: *polysaccharides, inulin, carboxymethylinulin, oxidation, azomethine bond, heterocyclic compounds*

Introduction

Polysaccharides and their derivatives are widely applied in biotechnology, food, cosmetics, and medicine due to their diverse biological activities, including immunostimulatory, antitumor, and anticoagulant effects (Heinze T., Liebert T., 2001; Balzarini J., 2007). Chemical modification such as the introduction of functional groups or low-molecular-weight fragments enables the development of valuable, low-toxicity drugs with controlled properties and prolonged action. Additionally, polysaccharides can serve as effective carriers, improving targeted drug delivery (Langer R., Peppas N. A., 2003; Dash A. K., Konkimalla S., 2012;

Kamalova D., Khusenov A., Abdullayev O., Rakhmanberdiev G., 2024; Klemm D., Heublein B., Fink H. P., Bohn A., 2005).

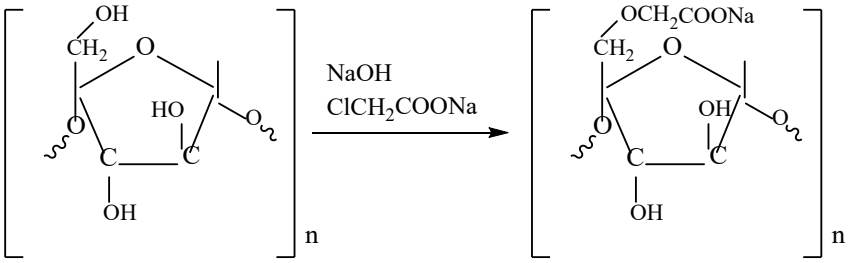
A key research direction is the synthesis of water-soluble polysaccharide derivatives with controlled molecular weight and degree of substitution, which allows regulation of their physicochemical and biological properties. This requires careful control of reaction conditions (pH, temperature, solvents) and functional group reactivity to ensure selective modification and preservation of the polymer structure (Rinaudo M., 2006; Khusenov A.Sh., Zhonuzokov A.Zh., Kamalova D. S., Tilakov Zh.R., Rakhmanberdiev G., 2024; Khusenov A.Sh., Kamalova D. S., Kee N. K., Rakhmanberdiev G., 2024; Liu T., Ren Q. Q., Wang S., Gao J. N., Shen C. C., Zhang S. Y., Wang Y. H., Guan F., 2023). Among polysaccharides, inulin has attracted particular attention due to its biocompatibility, biodegradability, and non-toxicity. Its reactive hydroxyl groups make it a suitable candidate for chemical modification. Modified inulin derivatives can function as drug carriers, hydrogel components, and matrices for biologically active compounds, with tunable solubility and activity (Wang G., Xie L. M., Huang Z. B., Xie J. H., 2023; Khusenov A. Sh., Zhonuzokov A.Zh., Kamalova D. S., Rakhmanberdiev G., 2024).

In this work, carboxymethylinulin derivatives containing nitro-substituted heterocyclic compounds were synthesized and characterized using physicochemical methods to evaluate structural features and property changes.

Materials and methods

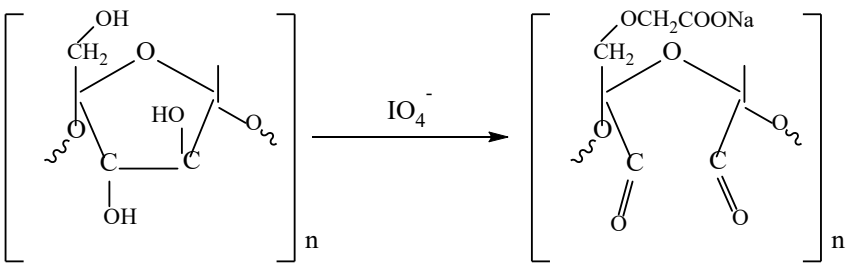
Synthesis of the sodium salt of carboxymethylinulin (Na-CMI). Carboxymethylation of inulin was carried out in isopropanol. Inulin was dispersed for 2 h, then treated with 10% alkali for 1 h. The reaction with sodium chloroacetate (1:3) proceeded at 70 °C for 1.5 h. The product was purified with 96% ethanol and dried at 50–60 °C. The degree of substitution was 30 mol%.

Scheme 1. *Synthesis of sodium carboxymethylinulin (Na-CMI)*



Periodic oxidation of Na-CM I. Thoroughly dried 2 g of Na-CMI was dissolved in 100 ml of water. After the polysaccharide was dissolved, 200 ml of acetate buffer (pH 4.5) and 0.2 n of $NaIO_4$ solution were added at a molar ratio of Na-CMI: IO_4^- = = 1:1.5. The mixture was left to mix for 1–5 hours at room temperature. The periodate oxidation reaction was completed by adding 10 ml of ethylene glycol. Upon completion of the reaction, the mixture was dialized against distilled water until a negative reaction for IO_4^- and IO_3^- ions was obtained. The final products isolated by sublimation drying were analyzed using the iodometric titration method.

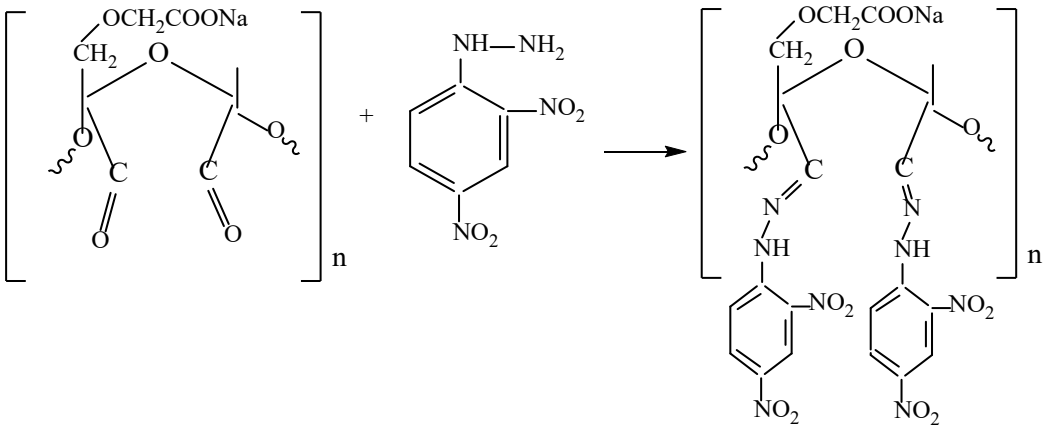
Scheme 2. *Periodate oxidation of Na-CMI to dialdehyde carboxymethylinulin (DACMI)*



Determination of the number of aldehyde groups using the oxime method. A 100 mg sample of dried DACMI was added to 25 mL of freshly prepared hydroxylamine hydrochloride solution (pH 5.0) in a 250 mL flask. After stirring for 1 hour, the released HCl was titrated with 0.1 M NaOH using bromophenol blue. A blank was run in parallel, and the aldehyde content was calculated from the difference in HCl volume (Isogai A., Saito T., 2013).

Chemical modification of Na-CMI dialdehyde with nitro-containing heterocyclic compounds (2,4-dinitrophenylhydrazone). 0.5 g of DACMI was dissolved in 100 mL water, followed by addition of a nucleophilic reagent (pH 3.0–8.5). The reaction proceeded at room temperature for 1 h. The product was purified by dialysis (48 h) and lyophilized.

Scheme 3. *Chemical modification of DACMI with 2,4-dinitrophenylhydrazine (Schiff base formation)*



The molecular weight was determined by gel permeation chromatography (GPC) using an Agilent 1260 Infinity II system equipped with an isocratic pump (G7110B), Prima Lux 1000 Å and Prima Linear S columns, and UV (DAD), RI, MDS, and dual-angle light scattering detectors. The nitrogen content in the samples was determined using an Eura EA (Italy) elemental analyzer.

Results and discussions

Dialdehyde polysaccharide derivatives are commonly used to bind compounds containing primary amino groups. This interaction leads to the formation of azomethine (Schiff base, -C=N-) bonds, which are reversible and relatively hydrolyzable. The process occurs in two stages: first, the formation of a carbinolamine intermediate, followed by its dehydration to form the -C=N- linkage (Liu T., Ren Q. Q., Wang S., Gao J. N., Shen C. C., Zhang S. Y., Wang Y. H., Guan F., 2023; Wang G., Xie L. M., Huang Z. B., Xie J. H., 2023).

The reaction rate depends on substituent effects and pH. Electron-withdrawing groups on the aldehyde accelerate amine addition, while electron-donating groups on amines enhance nucleophilicity. Steric hindrance slows the reaction. The rate-determining step varies with pH: in neutral or slightly acidic media, dehydration is slower, whereas in acidic conditions, amine addition becomes limiting. Excess acidity reduces amine nucleophilicity, overall slowing the reaction.

An important factor influencing the degree of substitution of nucleophilic substitution reaction products is the pH of the medium. For each nucleophilic substitution reaction, there is an optimal pH value, i.e., a value or pH region at which the reaction proceeds with maximum speed. To determine the influence of the pH of the medium on the yield and replacement degree of reaction products, the interaction of the nucleophilic reagent with DACMI products was investigated at various pH values. The research results are presented in Table 1. From the presented data, it can be seen that as the pH of the medium increases from 3.0 to 8.0, a gradual decrease in nitrogen content and the degree of DACMI substitution is observed. The maximum values of N (8.5%) and the degree

of substitution (72 mol%) are achieved in an acidic environment (pH 3.0–3.5), indicating the most favorable conditions for the modification reaction to occur.

Table 1. *Influence of pH of the medium on the properties of reaction products based on DACMI*

No.	DACMI oxidation state, mol%	pH of environment	Nitrogen content,%	Degree of substitution, mol%
1.	38	3,0	8,5	72
2.	38	3,5	8,5	72
3.	38	4,0	8,2	70
4.	38	4,5	7,9	65
5.	38	5,0	7,4	61
6.	38	6,0	6,8	54
7.	38	7,0	5,9	43
8.	38	8,0	5,6	39

As pH increases, the reactivity of functional groups likely decreases, which may be related to changes in the protonation degree of active centers and a decrease in the efficiency of reagent interactions. Thus, the acidic medium is optimal for obtaining highly substituted DACMI derivatives with increased nitrogen content.

Table 2. *Influence of the DACMI oxidation state on the composition of reaction products*

No.	DACMI oxidation state, mol%	Nitrogen content,%	Degree of substitution, mol%	Molecular weight, Da
1.	16	4,3	25	3850
2.	23	5,8	41	4230
3.	28	6,5	52	4580
4.	33	8,0	60	4910
5.	38	8,5	72	5200

Figure 1. *Hydrolysis of a sample with a quantitative nitrogen content of 8.5% at pH 2.0*

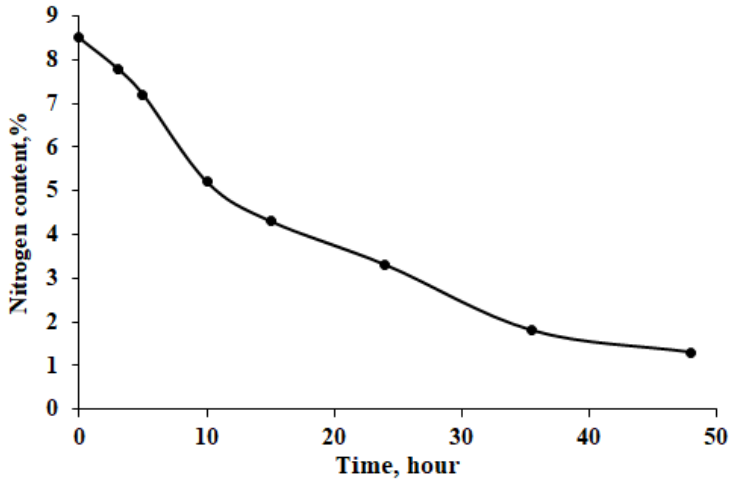


Table 2 shows the dependence of the degree of substitution in the final products on the oxidation state of DACMI.

Table 2 shows that as the oxidation state of Na-CMI increases, the nitrogen content, replacement state, and molecular weight of the reaction products increase. The observed relationship is practically linear in nature, indicating the controllability of the chemical modification process of Na-CMI with varying oxidation states. An increase in nitrogen content indicates the effective introduction of nitrogen-containing functional groups into the macromolecular chain of the polysaccharide, which in turn leads to an increase in the degree of substitution.

To substantiate the formation of covalent azomethine bonds between the low-molecular-weight compound and DACMI, the kinetics of acid hydrolysis of the samples in a buffer medium were studied. The results of this part of the study are presented in **Figure 1.**

The hydrolysis kinetics of a sample with an initial nitrogen content of 8.5% in an acidic medium (pH 2.0) show a rapid initial stage, where nitrogen decreases to ~7–7.4% within the first hours, indicating degradation of labile fragments. Between 5–15 hours, the decrease continues but slows, suggesting transition to more stable, possibly intramolecularly protected groups. After 20 hours, the process becomes gradual, reaching a minimum of ~1.2% by 36–48 hours.

Conclusion

By esterifying inulin under heterogeneous conditions, a carboxymethylinulin sample was obtained. In the next stage, periodic oxidation of inulin ester was carried out, and derivatives with various oxidation states were obtained. The formation of aldehyde groups as a result of oxidation creates active centers that facilitate further covalent bonding reactions. To expand the application range of inulin derivatives, chemical immobilization of heterocyclic compounds into the DACMI structure was performed. The influence of the pH of the medium and the oxidation state of DACMI on the composition of reaction products has been established. Acid hydrolysis has proven that the chemical bonding of the heterocyclic compound with DACMI occurs through labile covalent bonds.

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