



# Preparation and characterization of amidated derivatives of alginic acid



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## ABSTRACT

Alginic acid is a suitable material for modification to prepare new derivatives because of presence of its carboxyl groups. The high content of carboxyl groups over the entire length of its chain renders it an easily modifiable material with a possibility of achieving a high degree of substitution in the prepared derivatives. The salt of alginic acid (sodium alginate) is readily commercially available and is widely used in many branches of chemistry. Alginic acid was thus selected as the substrate for amidation. The amidation used two-steps: methyl esterification followed by amino-de-alkoxylation. The aim of this study was to prepare highly substituted derivatives with different polysaccharide chain characteristics. As such, the alginic acid was modified by the two-step amidation based on the esterification of the alginic acid carboxyl groups by reaction with methanol and further amino-de-alkoxylation (aminolysis) of the obtained methyl ester with amidation reagents (*n*-alkylamines, hydrazine and hydroxylamine). The purity and substitution degree of the prepared derivatives were monitored by vibration spectroscopic methods (FTIR and FT Raman) and organic elemental analysis. These analytical methods confirmed the preparation of highly or moderately substituted *N*-alkylamides, hydrazide and hydroxamic acid of alginic acid.

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## 1. Introduction

The use of polysaccharides and their derivatives in industry is significant. The preparation of polysaccharide derivatives is a good way to alter the properties of the initial polysaccharide to prepare materials with better properties. Polysaccharides represent a wide range of materials with broad possibilities for chemical modification. Alginate is a very interesting polysaccharide from this point of view.

Alginate, carrageenan and agar are some of the most important representatives of seaweed polysaccharides. Algin is a name for alginic acid **1** (Fig. 1) and its salts, alginates **1a** (Fig. 1) [1]. Alginates are linear unbranched copolymers of  $\beta$ -D-mannuronic acid **M** (Fig. 1) and  $\alpha$ -L-guluronic acid **G** (Fig. 1) bound by glycosidic linkages (1  $\rightarrow$  4) [2,3]. The molar mass of sodium alginate ranges from

10,000 to 600,000. The number of  $\beta$ -D-mannuronic acid units **m** (Fig. 1) and  $\alpha$ -L-guluronic acid units **n** (Fig. 1) depends on the algal species, the age of the plant and the type of tissue from which the alginates are extracted. Alginates are found in brown algae (*Phaeophyceae*), for example, in *Sargassum muticum*, *Mycrocystis pyrifera*, *Ascophyllum nodosum*, and *Laminaria hyperborea*. Alginic acid and derivatives have been detected in the bulb of *Pancreaticum maritimum* [1,4]. Alginates are isolated and commercially available in their sodium salt form, from which alginic acid can be obtained by washing with hydrochloric acid. Alginic acid is a polyuronic acid containing carboxyl groups in the C-6 position [5]. Alginates of alkali metals, ammonium salts, amine salts and magnesium salts are soluble, while the calcium salts are insoluble. The solubility depends on pH, ionic strength and type of ion. Alginates are stable under neutral conditions and at higher temperatures. Alginates are used as thickeners, stabilizers and emulsifiers to improve the consistency of products. Alginates are also used for gel-forming properties [1,6]. Alginates have various industrial applications; they are used to adjust viscosity, as stabilizers or thickeners and are capable of producing films and can be applied as binder materials. Alginates are used mainly in the food industry for their ability to form thermostable gels, in textile printing, in the production of ceramics, for welding wire and in the pharmaceutical industry for

**Abbreviations:** CMC, carboxymethylcellulose; DA, degree of amidation; DM, degree of methylation (methyl esterification); DMF, *N,N*-Dimethylformamide; FT, fourier transform; FTIR, fourier transform infrared spectroscopy; MCC, monocarboxy cellulose.

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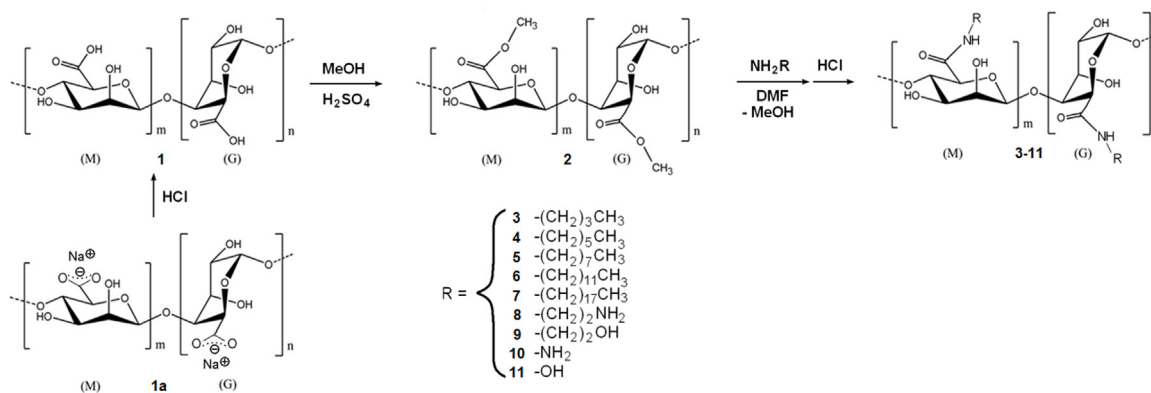


Fig. 1. Preparation of the *N*-alkylamide, hydrazide and hydroxamic acid derivatives of alginic acid.

the production of bandages and dental impression materials and to encapsulate cells and enzymes. The encapsulated cells are then protected against mechanical stress, while metabolites and nutrients can diffuse through the semipermeable capsule. New materials such as alginate-based polyurethanes have excellent mechanical properties and have potential use in vascular applications [7,8]. They can be used to encapsulate cells and drugs. Research has shown that the unique physicochemical properties of alginate may be successfully employed for medical applications. These properties depend on the type, isolation properties, pH and concentration of the alginate. It is possible to prepare products with high stability, biocompatibility and antimicrobial properties [9]. The use of alginates is considerable in medical as well as in biotechnology and pharmaceutical applications [3].

The area of alginate application is very wide, and it is possible to extend the field of application even further by the modification of alginate. The presence of its carboxyl groups makes alginate more chemically reactive than other polysaccharides. Modification of these carboxyl groups makes it possible to prepare new derivatives of this polysaccharide. In our previous work, we described the preparation of amidated derivatives of monocarboxy cellulose (MCC) and carboxymethylcellulose (CMC) [10,11]. These polymers are derivatives of cellulose. The presence of the carboxyl or carboxymethyl groups was important to prepare their amidated derivatives. Therefore, cellulose was first modified by oxidation or carboxymethylation. This modification process is eliminated when working with alginate. To modify alginate, it is only necessary to isolate it. This process of isolation has been described in the literature [3]. The carboxyl groups present in alginate are a great advantage. The present work is focused on the preparation of alginic acid derivatives by amidation. A two-step process including the esterification of carboxyl groups with methanol and further amino-de-alkoxylation (aminolysis) of the obtained methyl ester with seven selected primary amines, hydrazine and hydroxylamine was used for modification [10]. The content of carboxyl groups is much higher in alginic acid than in MCC and CMC containing uronic carboxyl groups or *O*-carboxymethyl groups at the C-6 position. Therefore, alginate was selected as a substrate for amidation with the goal of preparing more substituted products.

*N*-Alkylamides of polysaccharides are interesting to lower cholesterol and fat levels [12–16]. Certain *N*-octadecylamide polysaccharide derivatives were tested in another of our studies [17] as lipid sorbents. It was found that these cellulose derivatives have a high affinity to cholesterol and thus can be used as cholesterol lowering agents. Hydroxamic acids  $R_1\text{-(C=O)-NH-OH}$  have a high binding affinity to a variety of transition metal ions, notably iron(III) [18]. They have a considerable range of biological activity and do not exhibit toxicity. Hydroxamic acids are important bioli-

gands and participate in many biological processes including the transport of metal ions and the inhibition of metalloenzymes. Some goals when studying them are to determine their hypothetical effects in various diseases such as cancer, malaria, and tuberculosis. They have antifungal properties, and they have also been found to play a role in therapy focused on cardiovascular diseases, HIV and poisoning [19]. They have strong chelating properties and produce effective complexes with metal ions [20,21]. Hydrazides  $R\text{-(C=O)-NH-NH}_2$  belong to a group of organic compounds that are characterized by a covalent bond between the two nitrogens *N*-*N*. Hydrazides have not been as widely applied in organic synthesis as hydroxamic acids, but some of these compounds do exhibit significant biological activity. In recent years, investigations of hydrazides and their derivatives have led to results showing such varied biological activities as antibacterial, antifungal, analgesic, chemotherapeutic activity and anti-inflammatory effects. Hydrazides play an important role in inorganic chemistry, where they easily form stable complexes with most transition metal ions. Some of these compounds can inhibit enzymes and are interesting in pharmaceutical applications [22].

## 2. Materials and methods

### 2.1. Materials and reagents

The sodium salt of alginic acid (sodium alginate) (**1a**) was obtained in a dry, powder form from ROTH GmbH (Karlsruhe, Germany); alginic acid (**1**) was prepared by washing this sodium alginate with acidified ethanol (1:1 mixture of ethanol and  $4\text{ mol L}^{-1}$  HCl), pure ethanol and acetone and finally dried in air. Five *n*-alkylamines (*n*-butylamine, *n*-hexylamine, *n*-octylamine, *n*-dodecylamine and *n*-octadecylamine), ethylenediamine, ethanolamine, hydrazine hydrochloride and hydroxylamide hydrochloride were purchased from Sigma-Aldrich (Prague, Czech Republic). *N,N*-Dimethylformamide, ethanol and acetone were purchased from Lach-Ner (Neratovice, Czech Republic). Sodium alginate, alginic acid and the prepared derivatives are shown in Fig. 1.

### 2.2. Preparation procedures

#### 2.2.1. Preparation of the methyl ester of alginic acid

Alginic acid was esterified with methanol in the presence of sulfuric acid [4]. Alginic acid (**1**) (1 g) was suspended in 200 mL of methanol containing 1 mL of concentrated 96% sulfuric acid. The reaction was carried out under heterogenous conditions with stirring at  $60^\circ\text{C}$  for 72 h. The solid reaction product (**2**) was filtered, washed with ethanol and acetone, and then dried in air. An alterna-

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