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Note

Novel dextran derivatives with unconventional structure formed in an efficient one-pot reaction

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ABSTRACT

An efficient one-pot synthesis of new dextran derivatives is described. The functional groups of β-alanine, i.e., the carboxyl- and amine group, are converted independently in one-step by iminium chloride to form products with a single substituent. The dextran N-[(dimethylamino)methylene]-β-alanine ester is formed selectively. The structure of the resulting polymers is unambiguously determined by means of NMR- and FTIR-spectroscopy and elemental analysis.

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1. Introduction

Dextrans, a family of neutral, water soluble α-(1 → 6) linked glucans, are used in medical applications as blood volume expander because of its inherent biocompatibility [1]. To expand the field of applications of these unique and non-toxic biopolymers, chemical modification of the hydroxy groups by etherification [2] or esterification [3] is a very useful tool. In the frame of our studies on chemical modification of polysaccharides including dextrans, iminium chlorides were included in the functionalization of the polymer. Iminium chlorides known as Vilsmeier reagent are formed by the reaction of N,N-dimethyl formamide (DMF) with chlorinating agents like oxalyl chloride or phosphorous trichloride [4]. Iminium chlorides react with various functional groups and have been successfully applied for *in situ* activation of carboxylic acids in esterification reactions [4,5]. Moreover, iminium chlorides react with amines [6] and amides to yield amidines. However, iminium chlorides are not appropriate to activate carboxylic group of amino-Boc-protected α- and β-amino acids. This is due to the decreased electrophilicity of the carbonyl carbon because of the vicinity of the carbamate moiety of the protection group. Moreover, carboxyl protected amino acids (protected glycine) yield diazo-oxo-esters with iminium chlorides in presence of $NaNO_2$ [7]. As expected, in case of unprotected amino acids, a tendency to get oligomers in presence of various activation reagents including iminium chlorides exits [8]. Activation reagents for carboxylic groups are able to oligomerize β-amino acids because the activated group reacts with the amino group of another amino acid molecule, which is expected for iminium chloride as well [5].

In this paper, the reactivity of unprotected amino acids, namely β-alanine in the presence of iminium chloride will be discussed showing that unexpected products can be obtained in an easy way. The structure of the products was clearly evaluated by means of NMR- and FTIR-spectroscopy.

2. Results and discussion

The reaction of amino acids with diimides, i.e., of α-amino acids with 1,1'-carbonyldiimidazole (CDI) and of β-amino acids with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC) was found to yield oligomerized amino acid [8]. On the contrary, the reaction of dextran with β-alanine in the presence of iminium chloride has not been evaluated up to now. The reaction of dextran and β-alanine was conducted as previously reported [3] applying 2 mol iminium chloride per mol β-alanine in order to prevent a

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discrimination of the reaction of one reactive group in favor of the other, i.e., the carboxyl- and the amino groups. Dextran (**1**) was allowed to react with one up to 4 mol reagent per mole repeating unit to study the influence on the degree of substitution (DS, Fig. 1).

The purification of the products (**2a-d**) by dialysis (membrane, molecular weight cut off of 3500 g/mol) followed by lyophilization yielded polymeric products. The structure of the products (**2a-d**) was investigated by a series of NMR spectroscopic experiments. In the ^{13}C-NMR spectrum of sample **2b** (Fig. 2, top), the signals of the modified anhydroglucose unit (AGU) are found in the range of 60–100 ppm. Signals of the carbon atoms 1–6 of the repeating unit appear at 98.5 (C1), 73.9 (C3), 71.9 (C2), 70.6 (C4), 70.2 (C5), and 66.2 ppm (C6). Further signals of unsubstituted C6′ of the end-groups of side-chains are located at 61.1 ppm. Dextran produced by *leuconostoc mesenteroides* possesses a low amount of side-chains of 5% only [9]. The negative signal in the DEPT135-NMR spectrum of sample **2b** (Fig. 2, bottom) at 63.6 ppm could be assigned to C6'$_s$. According to literature, substitution takes places preferably at position 2 of the AGU compared to positions 3 and 4, which have identical reaction rates ($k_2 > k_3 = k_4$) [1]. The difference of reactivity is explained by the vicinity to the anomeric carbon C1. Due to the DS-values of the products obtained, substitution at position 2 can be clearly concluded from the ^{13}C-NMR spectrum. The reaction results in a comparably intensive signal of C2$_s$ at 76.5 ppm. Additionally, signals of adjacent carbons to C2$_s$ at 96.0 ppm (C1$_{C2s}$) and 68.0 ppm (C3$_{C2s}$) confirm derivatization of position 2. The protons associated to these carbon atoms in the ^{1}H,^{13}C-HSQC-NMR spectrum (Fig. S1) couple with the protons of C2$_s$ in the ^{1}H,^{1}H-COSY-NMR spectrum (Fig. S2). According to the obtained spectra regioselectivity at position C2 occurred. However, small amounts of substitution at positions C3 and C4 can not be ruled out and are indicated by the splitting of the signal of C7 at 172.4 ppm. The corresponding signals of C3$_s$ and C4$_s$ are not separated from the stronger signals of the AGU.

The shift of carbonyl carbon of the starting β-alanine (C7) from 179.2 ppm [10] to 172. ppm indicates formation of an ester bond at positon 2 of the AGU, peaks at 171.8 and 171.7 indicate formation of an ester bond at positions 3 and 4, thus affirming regioselectivity of the esterification. The peak of the α-carbon atom (C8) appears at 34.9 ppm, independent of functionalization, while the β-carbon atom (C9) is shifted to 42.7 ppm, when compared to β-alanine. This indicates a change of electronic environment due to derivatization of the amino group. These signals can be easily assigned due to the negative orientation in the DEPT135-NMR spectrum of sample **2b** (Fig. 2, bottom). The signal at 156.7 ppm results from a methine carbon (C10), as is evidenced by the polarity of the signal in the DEPT135-NMR spectrum. The high ppm-value of the signal rules out a methyl group, which show the same polarity like methine groups in the DEPT135-NMR spectrum. The ^{1}H,^{13}C-HSQC-NMR spectrum shows that the proton at 8.14 ppm belongs to this carbon. This proton couples in the ^{1}H,^{13}C-HBMC-NMR spectrum with the carbons of the two methyl groups at 43.4 ppm and 35.2 ppm (Fig. 3) and, moreover, is in correlation over three bonds with the methylene group of C9. However, the β-protons of the β-alanine moiety couple with the carbonyl carbon (C7) and the methine carbon (C10) over three bonds. The α-protons of C8 couple over two bonds with the carbonyl carbon C7.

From these results, it clearly appears that condensation products of β-alanine of different molecular weights were not formed at the dextran backbone by esterification as may be expected. Instead a clearly defined *N,N*-dimethyl formamidine containing one β-alanine residue only have been synthesized, which are linked by an ester bond to the biopolymer backbone as shown in Fig. 1 (bottom). The carbon atoms of the methyl groups at 43.6 and 36.2 ppm have

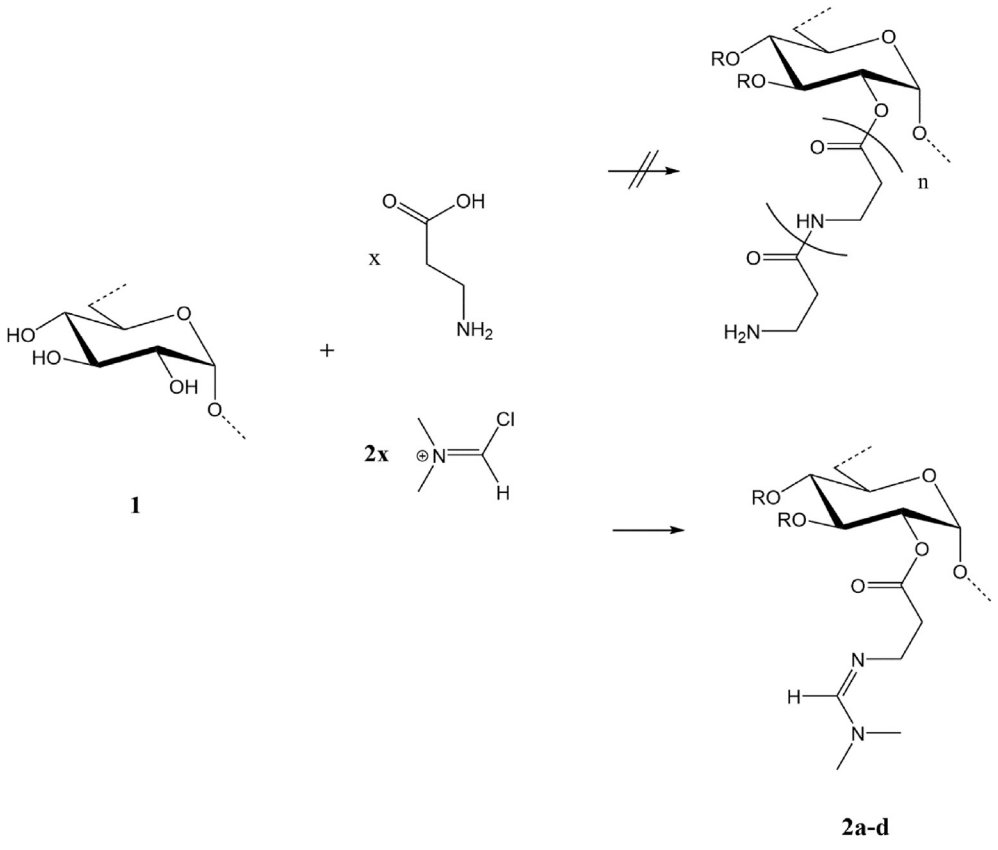

Fig. 1. Reaction pathway and structure of resulting products **2a-d** (R indicates that minor esterification at positions 3 or/and 4 is not excluded).

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