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Diversity of polysaccharide structures designed by aqueous Ugi-multi-compound reaction

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Abstract Carboxymethyl ethers of xylan, cellulose, and pullulan could be efficiently modified applying the Ugi-reaction in the "green" solvent water. Using different components, namely an aldehyde, an amine, and an isonitrile, the reaction led to novel polysaccharide derivatives with peptide-like substituents. The reactions were carried out applying 2-methoxyethylamine and propargyl amine, paraformaldehyde and benzaldehyde as well as *tert*-butylisonitrile at room temperature. The characterization of the products was performed by ^{13}C-NMR spectroscopy. In any case, a high conversion of the carboxyl groups could be realized. The products isolated possessed a lower degree of substitution compared to the starting material, which may result from a hydrolytic cleavage of ether bonds. Nevertheless, the results indicated that carboxymethylated polysaccharides are useful starting materials for new polysaccharide derivatives in a toolbox reaction.

Graphical Abstract
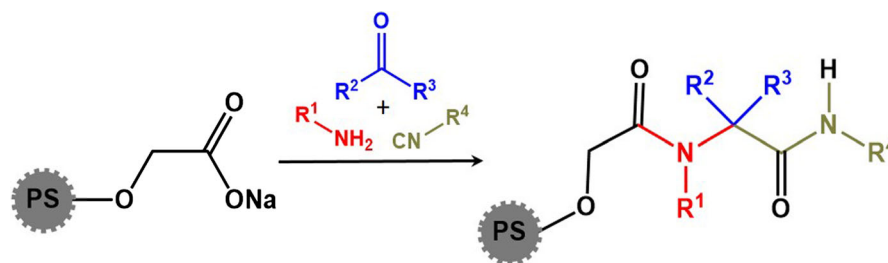
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Introduction

Polysaccharides like cellulose, starch, and xylan are
formed in huge amounts biosynthetically by many
organisms including plant, animals, fungi, algae, and
microorganism. They are renewable resources with a
vast structural diversity (Heinze et al. 2006b). Chem-
ical modifications of polysaccharides using conven-
tional reaction schemes like esterification with organic
acids (Heinze et al. 2006b; Hornig et al. 2009; Schulze
et al. 2016), sulfation (Daus et al. 2011; Gericke et al.
2009; Herrero et al. 2015; Wu et al. 2017), and
sulfoalkylation (Demleitner et al. 1992; Ebringerová
and Pastýr 1988; Vieira et al. 2005; Zhang et al. 2011),
e.g., lead to a broad variety of products with promising
properties useful for many applications. Two-step
reaction paths are also a common path to obtain
polysaccharide-based products with promising prop-
erties. In this context, cellulose tosylates are well-
investigated (Heinze et al. 2006a; Heinze and Rahn
1997; Rahn et al. 1996) useful for nucleophilic
displacement reaction with amines, halides, pseudo-
halides, or others to synthesize novel 6-deoxy-6-
functionalized polysaccharide derivatives (Koschella
and Heinze 2001; Zieger et al. 2015). Another class of
reactive polysaccharide derivative are phenyl carbon-
ates (Elschner et al. 2013a, b) that can be easily
transformed to stabile polysaccharide carbamates by
reaction with a broad variety of amines (Elschner and
Heinze 2015).

Carboxymethylated products of cellulose, starch,
and many other polysaccharides can be easily obtained
under heterogeneous reaction conditions efficiently
yielding one of the most important ionic polysaccha-
ride ether, which possess a myriad of applications
(Heinze 1998; Heinze and Pfeiffer 1999; Heinze et al.
1999; Konduri and Fatehi 2016; Petzold et al.
2006a, b; Tiitu et al. 2006). Although the carboxyl
groups introduced are reactive, there is a limited
number of chemical modifications studied up to now.
Simple methyl esters of carboxymethyl cellulose
(CMC) were synthesized by conversion with dimethyl
sulfate in dimethylsulfoxide (Tezuka et al. 1996).

Furthermore, ethyl ester of carboxymethyl (CM)
polysaccharides were prepared with ethanol using an
autocatalytic process (Sibikina et al. 2004b). Using
additionally amines in this autocatalytic process, the
corresponding amides are generated, however, with
low conversion of 7–50% (Sibikina et al. 2004a, b). It
may be assumed that the chemical modification of
CM-polysaccharides is limited because these biopoly-
mer derivatives are soluble in water only and do not
swell significantly in organic solvents.

In organic chemistry of low-molecular compounds,
isonitrile-based multi-step reactions are an easy and
efficient path to modify carboxylic acid groups
(Dömling 2006; Dömling and Ugi 2000). In this
regard, the Ugi-reaction is of particular interest
because diverse products can be obtained in a single
reaction step (Brauch et al. 2010; Rivera et al. 2012;
Ziyaei Halimehjani and Sharifi 2017). During the
conversion of carboxyl group by Ugi-reaction, a
carbonyl group containing compound, a primary
amine and an isonitrile are included in the reaction.

In a first step, the amine and the carbonyl group
form the corresponding imine, which is protonated by
the carboxylic acid. The isonitrile and the carboxylic
acid attack the protonated imine and form an inter-
mediate, which undergo a Mumm-rearrangement to
from a diamide derivative (Brauch et al. 2010). The
mechanism of the Ugi-reaction is given in supporting
information (SI Fig. 1).

In the field of polysaccharides, the Ugi-reaction was
studied to form ionic hydrogels from CMC, hyaluronic
acid, alginic acid, oxidized scleroglucan and pectin
using glutaraldehyde, 1,5-diaminopentane or 1,4-
bis(3-isocyanopropyl)piperazine, i.e. cross-linking of
the polysaccharides derivatives were carried out (Bu
et al. 2005; de Nooy et al. 1999; de Nooy et al. 2000;
Mironov et al. 2013; Shulepov et al. 2016; Werner
et al. 2006). Moreover, Ugi-reaction was also applied
to generate a covalent bond between polysaccharides
and proteins. By deprotonation of cellulose, dextran
and cross-linked agarose with *tert*-butoxide in
dimethylsulfoxide (DMSO) an isonitrile containing
substituent was introduced, which afterwards was used
to generate linkages between polysaccharides and
trypsin or Gly–LeuNH$_2$ (Freeman et al. 1979). The
amino group of trypsin linked to CMC or alginate by
an Ugi-reaction in water (García et al. 2009). Binding
horseradish peroxidase via Ugi-reaction to modified

sodium alginate yielded in a biosensor which showed response towards H_2O_2 (Camacho et al. 2007).

Up to now, there are no investigations of chemical modification of CM-polysaccharides using the Ugi-reaction to synthesize soluble biopolymer derivatives, which could offer a wide field of applications. The aim of this studies was to use common and commercially available carboxymethyl polysaccharides as "platform" to generate new soluble biopolymer derivatives by Ugi-multicomponent reaction and to analyse the structure of the products in detail.

Experimental

Materials

The solvents and reagents were obtained from Sigma-Aldrich Chemie GmbH and were used without further purification. Xylan (M_w 9200 g/mol) from beech wood was provided by Lenzing AG (Lenzing, Austria). Pullulan (M_w 261,000 g/mol) was obtained from TCI Deutschland GmbH (Eschborn, Germany). Carboxymethyl cellulose (M_w 90,000 g/mol) was purchased from Sigma-Aldrich Chemie GmbH. Before use, xylan and pullulan were dried in vacuum at 80 °C for 2 h.

Measurements

NMR spectra of polysaccharide derivatives were recorded at 25 °C in deuterium oxide or DMSO-d_6 (60 mg/ml) with a Brucker Avance 250 MHz spectrometer (^{1}H NMR: 16 scans, ^{13}C NMR: > 10,000 scans). A VARIO EL III CHNS analyzer (Elementaranalysensysteme GmbH) was used for elemental analyses. Size exclusion chromatography (SEC) in DMSO with 0.5 wt% LiBr as solvent (65 °C, flow rate: 0.5 ml/min) was performed on a JASCO system (isocratic pump PU-980, RI-930 refractive index detector) with a Novema 3000 and a Novema 300 column in series. FT-IR spectra were recorded on a Nicolet iS5 spectrometer using translucent KBr tablets containing the solid polysaccharide samples. SEC in water with 0.1 M NaNO$_3$/NaN$_3$ as solvent (30 °C, flow rate: 1.0 ml/min) was performed on a JASCO system (isocratic pump PU-980, RI-2031 Plus refractive index detector) with a PSS SUPREMA guard/

1000/30 column. For both SEC systems pullulan was used as calibration standard.

Carboxymethylation of xylan and pullulan (carboxymethyl xylan **CMX**, typical example)

To a suspension of 30 g (227.3 mmol) xylan in 900 ml isopropanol, 121.2 g (454.5 mmol) of an aqueous solution of NaOH (15%) were added slowly at 25 °C. The reaction mixture was stirred for 1 h at 25 °C and afterwards 26.5 g (227.3 mmol) of sodium monochloroacetate (SMCA) were added. After stirring of the reaction mixture for 5 h at 55 °C, the reaction mixture was filtrated and the solid residue was suspended in 1 L aqueous methanol (80%). After neutralization with dilute acetic acid, the suspension was filtrated and the residue was washed three-times with 1 L of aqueous methanol (80%) and once with 1 L ethanol. The product was dried in vacuum at 40 °C. The degree of substitution was determined by ^{1}H-NMR measurement after hydrolysis of 100 mg polymer in 1.5 ml 25% D$_2$SO$_4$ (in D$_2$O) for 1 h.

Yield: 36.6 g (178.1 mmol modified AXU) **CMX** (78% of the theoretical yield); DS = 0.93.

Elemental analysis found (calculated): C%: 40.05 (40.1), H%: 5.1 (3.86).

^{13}C-NMR (101 MHz; D$_2$O; 298 K): δ [ppm] = 181.71, 181.23, 180.55 (C=O), 104.48 (C1), 84,90, 82.99, 79.02, 76.56, 75.67 (C2–C4), 73.87 (*CH$_2$*COONa), 65.61 (C5).

Ugi-reaction with CM-polysaccharides (**2a**, typical example)

For preparation of Ugi-derivatives, 0.5 g (2.42 mmol) of **CMX** were dissolved in 25 ml water. The pH value of the solution was adjusted to 1 with conc. hydrochloric acid. 0.203 g (6.75 mmol) paraformaldehyde and 0.51 g (6.75 mmol) 2-methoxyethylamine were added. The pH value of the reactions mixture is increased sa result of the addition of the amine. A pH value above 5 should be adjusted. The reaction mixture was stirred for 30 min at room temperature. After addition of 0.56 g (6.75 mmol) *tert*-butyl isonitrile, the mixture was allowed to react for 20 h at room temperature under stirring. The mixture was poured into 200 ml acetone. The precipitate formed was removed by filtration and washed three times with 100 ml acetone. The crude product was dissolved in

20 ml water, dialyzed against water, and finally freeze dried. The DS was determined by elemental analysis applying the following equation.

$$DS = \frac{\frac{\% \, N}{100\%} \cdot M_{AGU} - 2M_N}{2M_N - \frac{\% \, N}{100\%} \cdot (M_{substituent} - M_H)} \qquad (1)$$

Product **2a**: DS = 0.68, Yield: 0.30 g (1.05 mmol modified AXU) (43% of the theoretical yield).

Elemental analysis found (calculated): C%: 50.50 (52.37), H%: 7.52 (7.20), N%: 6.62 (6.66).

^{13}C-NMR (101 MHz; D$_2$O; 298 K): δ [ppm] = 175.49 (C12), 172.16, 171.25 (C7), 104.49 (C1), 84,55, 79.16, 76.51, 75.59 (C2–C4), 72.38 (C9), 65.75 (C5), 61.41, 61.04 (C10), 54.42, 54.23 (C6), 23.53, 23.06 (C13), 50.63 (C11), 49.92 (C15), 30.72 (C14).

Results and discussion

Carboxymethylation of polysaccharides

As illustrated in Fig. 1, the carboxymethylation of the polysaccharides were carried out heterogeneously with sodium monochloroacetate (SMCA) in an alkaline medium using aqueous sodium hydroxide (15%) and isopropanol as slurry medium, i.e. in the conventional synthesis path (Heinze 1998; Petzold et al. 2006b). As known, the sodium hydroxide activated the hydroxyl groups of the polysaccharide to increase their nucleophilicity. The activated hydroxyl group attacked the SMCA by a S$_N$2 reaction to form the corresponding CM-polysaccharide derivative (Konduri and Fatehi 2016; Petzold et al. 2006b). While the CMC was commercial available, the carboxmethyl xylan (CMX) and the carboxymethyl pullulan (CMP) had to synthesized. The CMC possessed a DS of carboxymethyl groups (DS$_{CM}$) of 0.96. Xylan converted with a equimolecular amount of SMCA and a twofold molar excess of aqueous NaOH gave a CMX with a DS$_{CM}$ of 0.93. In the case of pullulan, a twofold molar excess of SMCA and aqueous NaOH was used. The CMP received possessed a DS$_{CM}$ of 1.17.

^{13}C-NMR spectra of CMX and CMP clearly showed the signal of the carbonyl carbon of the carboxymethyl group at typical chemical shift of 181.2 ppm (Fig. 2). The methylene group of the CM-substituent was observed at 73.9 ppm. The signal belonging to position 1 of the CMP appeared as a broad peak at a chemical shift 100 ppm (Fig. 2a). For CMP, the anhydroglucose unit (AGU) can be assigned to signals between 83 and 73 ppm. The peaks at 68.4 and 63.8 ppm were assigned to the different positions 6 of the pullulan backbone. In case of CMX, the ^{13}C-NMR signal related to position 1 appeared at 104.5 ppm. The further signals assigned to the anhydroxylose unit (AXU) were found in the range of 86 to 74 ppm. Position 5 of the CMX was related to the signal at 65.7 ppm (Fig. 2b).

Ugi-reaction of carboxymethyl polysaccharides

To investigate appropriate conditions of the Ugi-reaction of CM-polysaccharides, *tert*-butylisonitrile, paraformaldehyde, and 2-methoxyethylamin were used. Due to the lower degree of polymerization, CMX was chosen for the experiments to get a higher resolution of the NMR spectra of the corresponding products. According to the reaction mechanism, a proton is needed for the Ugi-reaction. Therefore, CH$_2$COONa was converted into the acid form (CH$_2$COOH) by addition of hydrochloric acid (Fig. 3).

To get a complete conversion of carboxymethyl moieties, the influence of excess of the amine, aldehyde, and isonitrile was studied and the pH value of medium were changed. The following pH values were only the values after acidifying the CM-polysaccharide solutions. Through the excess of the amine the Ugi reaction itself was performed at pH values from 5 to 7. Otherwise a hydrolyses of the isonitrile is possible. In the first set of experiments, a molar excess of 1.2 mol of the amine, aldehyde, and isonitrile to carboxylic group at a starting pH value of 3.5 were applied. The product obtained showed typical but small signals of the corresponding Ugi-product in the ^{13}C-NMR spectrum. At a starting pH of 1 and a molar excess of 1.2 mol per mol acid group, no reaction occurred. In Fig. 4, the ^{13}C-NMR spectra of the products obtained using a molar excess of 3 mol amine, aldehyde, and isonitrile per mol acid group are shown. At a starting pH of 3.5, the signals of the Ugi-product were clearly visible, but the reaction was incomplete (Fig. 4b). Based on this result, the starting pH value was decreased to 1. The ^{13}C-NMR spectrum of the product obtained showed a complete conversion of the carboxy groups (Fig. 4c). Both signals of the carboxymethyl moiety at 181.2 and 73.9 ppm disappeared, on the one hand. On the other hand, two new

Fig. 1 Scheme of the carboxymethylation of xylan (**a**), cellulose (**b**) and pullulan (**c**) under heterogeneous reaction conditions
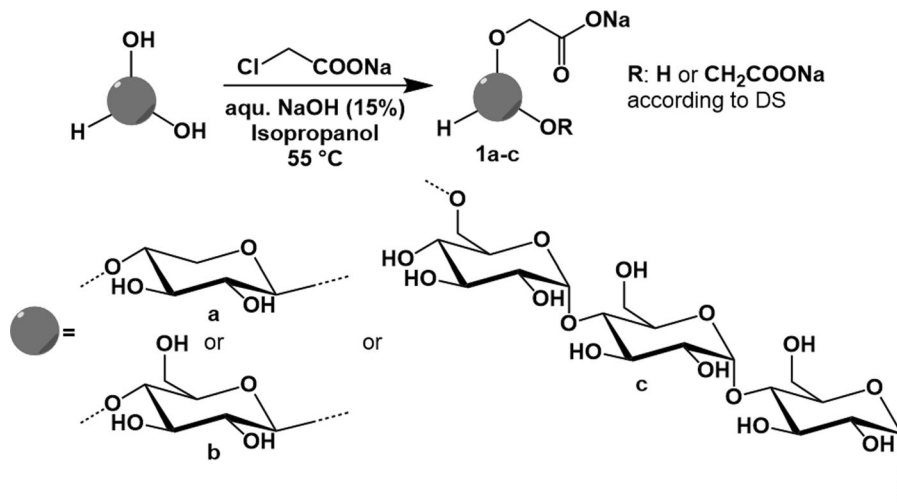

Fig. 2 ^{13}C-NMR spectra of **a** carboxymethyl pullulan (CMP) with a degree of substitution (DS) of 1.17 and **b** carboxymethyl xylan (CMX) with a DS of 0.93, recorded in D$_2$O at 25 °C
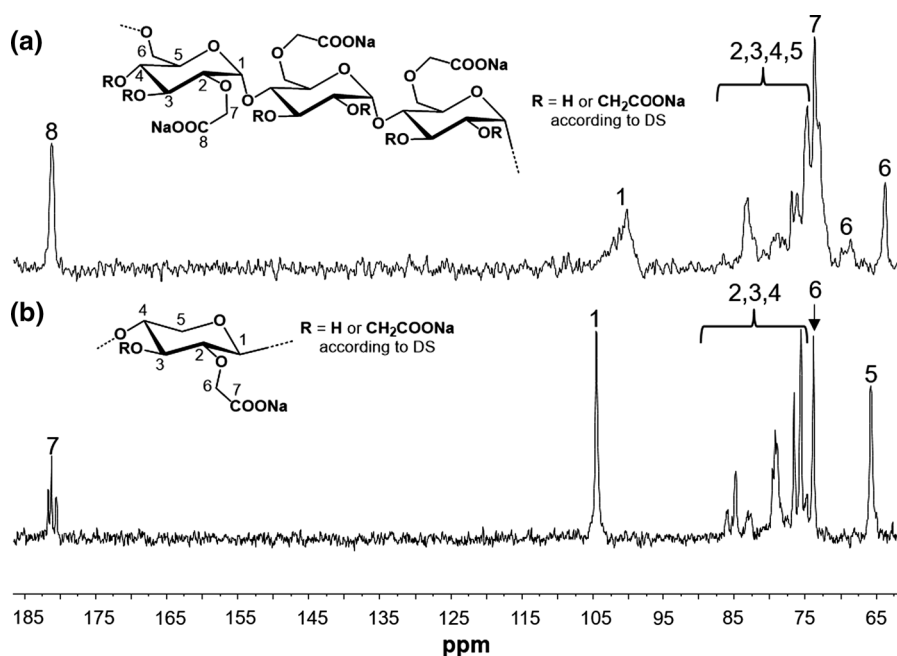
signals occurred at 175.5 and 172.2 ppm, which can be assigned to the carbonyl atoms of the two amide moieties of the structure formed by the Ugi-reaction. In addition to the signals of the AGX between 84.6 and 75.6 ppm, peak at 72.4 ppm occurred, which can be assigned to the position 8 of the new substituent. At a chemical shift of 65.8 ppm, the signal of position 5 appeared. The methyl group at position 10 yield a peak at 61.2 ppm in the ^{13}C-NMR spectrum. The methylene groups of the carboxymethyl groups was shifted to 53.1 ppm. The small signal at 52.1 ppm can be

assigned to the quaternary C-atom of the *tert*-butyl group (position 13). At chemical shifts of 49.9 and 50.6 ppm, two signals appeared that could be assigned to position 9 and 11. The methyl groups of the *tert*-butyl group (positon 14) led to a signal at 30.7 ppm.

Elemental analysis of product **2a** indicated a DS$_{Ugi}$ of 0.68, which revealed a transformation of 73% of the CM moieties. Nevertheless, there were no remaining carboxyl groups in the sample, which indicated a complete formation of the novel polymeric structure based on CMX. Compared to the starting CMX, lower
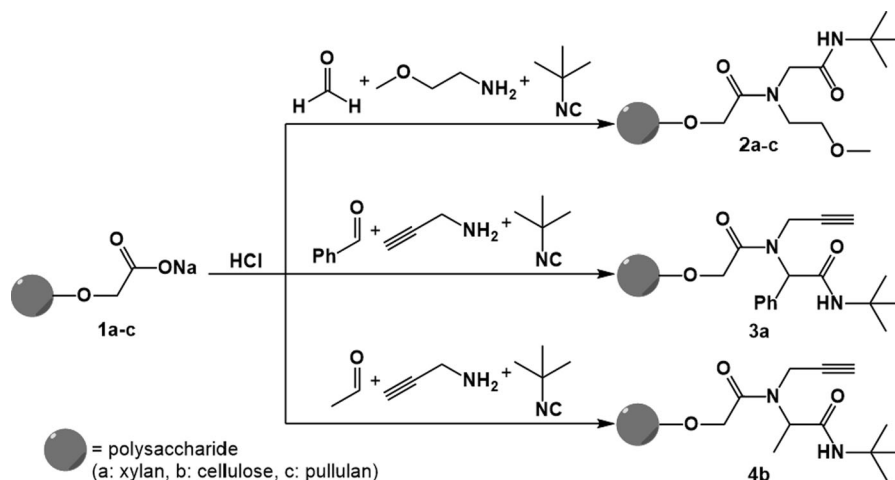
Fig. 3 Scheme of Ugi-reactions of CM-polysaccharides with *tert*-butylisonitrile, different aldehydes, and different amines

Fig. 4 ^{13}C-NMR spectra of starting carboxymethyl xylan (CMX) **1a** with a degree of substitution (DS$_{CM}$) of 0.93 (**a**) and Ugi-products obtained by conversion of **1a** with a molar excess of 3 mol 2-methyoxyethylamine, paraformaldehyde, and *tert*-butyl isonitrile per mol AXU at a starting pH value of 3.5 (**b**) and at a starting pH value of 1 (**c**, DS$_{Ugi}$ 0.68), recorded in D$_2$O at 25 °C
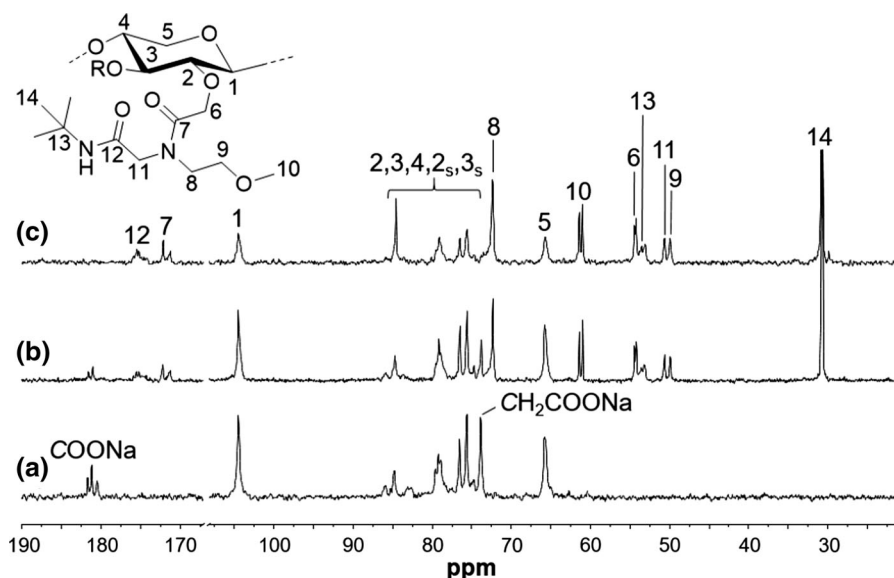
DS is explained by some splitting of ether moieties under the acidic conditions of the reaction.

In addition to the reaction of the CM-polysaccharides discussed above, the Ugi-reaction was studied with CMC and CMP applying same reagents, namely 2-methoxyethylamine, paraformaldehyde, and *tert*-butylisonitrile applying the aqueous reaction system with a pH value of 1 and an excess of the amine, aldehyde, and isonitrile of 3 mol per mol AGU (Table 1). The Ugi-product **2b** obtained with CMC (DS$_{CM}$ 0.96) possesses a DS$_{Ugi}$ of 0.57. Starting with CMP (DS$_{CM}$ 1.17), a Ugi-product **2c** could be synthesized with a DS$_{Ugi}$ of 0.92.

Figure 5 shows the ^{13}C-NMR spectra of the CM-cellulose based product **2b** and the CM-pullulan based product **2c**. The spectra clearly indicated the successful conversion due to the fact that in both cases no signals of the carboxymethyl moiety were visible, on one hand. On the other hand, carbonyl groups of the Ugi-product could be assigned to signals at 174.9 ppm and 171.7 ppm. The further signals of the new substituent appeared, comparable to the xylan product **2a**, at 72.4, 61.3, 54.2, 53.4, 50.8, 49.9, and 30.7 ppm.
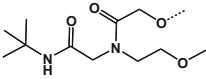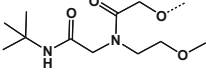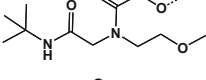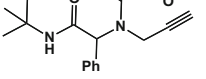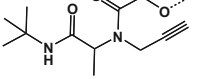
The Ugi-reaction of CM polysaccharides was additionally studied with further amines and aldehydes. CMX was converted with benzaldehyde and

propargylamine. The corresponding xylan derivative **3a** isolated possess a DS$_{Ugi}$ of 0.83. **3a** showed two typical signals in the ^{13}C-NMR spectrum at 174.2 and 170.9 ppm that were assigned to the two carbonyl groups 12 and 7 (Fig. 6a). Furthermore, the quaternary C-atom of the phenyl moiety was assigned to the signal at 138.2 ppm. The C-atoms of phenyl groups yield signals with a chemical shift of 131.2 ppm. In addition to the signals of the AXU, the quaternary C-atom (9) of the propargyl moiety had a chemical shift of 82.1 ppm. The methylene C-atom of the propargyl moiety resulted in a signal at 36.1 ppm. Signals at 61.8 ppm and 31.2 ppm resulted from the *tert*-butyl group. The methylene groups of the carboxymethyl moiety appeared at a chemical shift of 53.1 ppm. Using propargylamine, acetaldehyde, and *tert*-butylisonitrile, the CMC (DS$_{CM}$ 0.96) was yielded cellulose derivative **4b** with a DS$_{Ugi}$ of 0.26. ^{13}C-NMR spectroscopy proofed the successful conversion (Fig. 6b). Both carbonyl carbons were related to signals at 180.1 and 174.4 ppm. The signals of the triple bond vanished under the signals of the AGU in the range from 70.2 to 86.4 ppm. At a chemical shift of 64.5 ppm, a signal appeared that was assigned to chiral carbon 12 of the substituent. The quaternary

C-atom of the *tert*-butyl moiety could be assigned to a signal at 57.7 ppm. In this case, the methylene groups of the carboxymethyl moiety appeared at a chemical shift of 53.1 ppm as well. The methylene C-atom of the propargyl moiety was assigned to a signal at 36.1 ppm, too. Furthermore, the signal of the methyl groups of the acetaldehyde moiety was assigned to a signal at 17.5 ppm. The double peaks observed in all ^{13}C-NMR spectra of Ugi-products could be explained by the tautomeric character of the amide bond (Hammaker and Gugler 1965). The infrared (IR)-spectroscopy of the products obtained showed a clear shift of the carbonyl signal of the carboxylate from 1600 to 1670 cm^{-1} of the amide group (SI Fig 2-4). Furthermore, the signals of the ether bond between 1040 and 1100 cm^{1} were present, which proof that the substituents were linked to the polymer backbone. This finding indicated additionally the success of the chemical modification.

Considering the problems of SEC of polyelectrolytes like CM-polysaccharides, i.e., the determination of a too high molar mass, some conclusions regarding acid hydrolysis of the polysaccharide chain can be made. Nevertheless, the values of the degree of polymerization (DP) of the Ugi-products (Table 1)

Table 1 Results of Ugi-reaction of carboxymethyl xylan (CMX), carboxymethyl cellulose (CMC), and carboxymethyl pullulan (CMP) of different degree of substitution (DS$_{CM}$)

No.	CM-PS	DS$_{CM}$	DP$_{CM}$	Substituent	DS$_{Ugi}$	DP$_{Ugi}$	Solubility			
							H$_2$O	DMSO	DMF	DMAc
2a	CMX	0.93	102		0.68	26	+	+	+	+
2b	CMC	0.96	293		0.57	123	+	+	+	+
2c	CMP	1.17	332		0.92	384	+	+	+	+
3a	CMX	0.93	102		0.83	21	−	+	+	+
4b	CMC	0.96	293		0.26	153	+	(+)	−	−

DMSO dimethyl sulfoxide, *DMF* N,N-dimethylformamide, *DMAc* N,N-dimethylacetamide, +: soluble, −: insoluble, (+): swollen

Fig. 5 ^{13}C-NMR spectra of Ugi-products of carboxymethyl cellulose (CMC, **a**) and carboxymethyl pullulan (CMP, **b**) obtained after conversion with 2-methoxyethylamine, paraformaldehyde and *tert*-butylisonitrile, recorded at 25 °C in D$_2$O
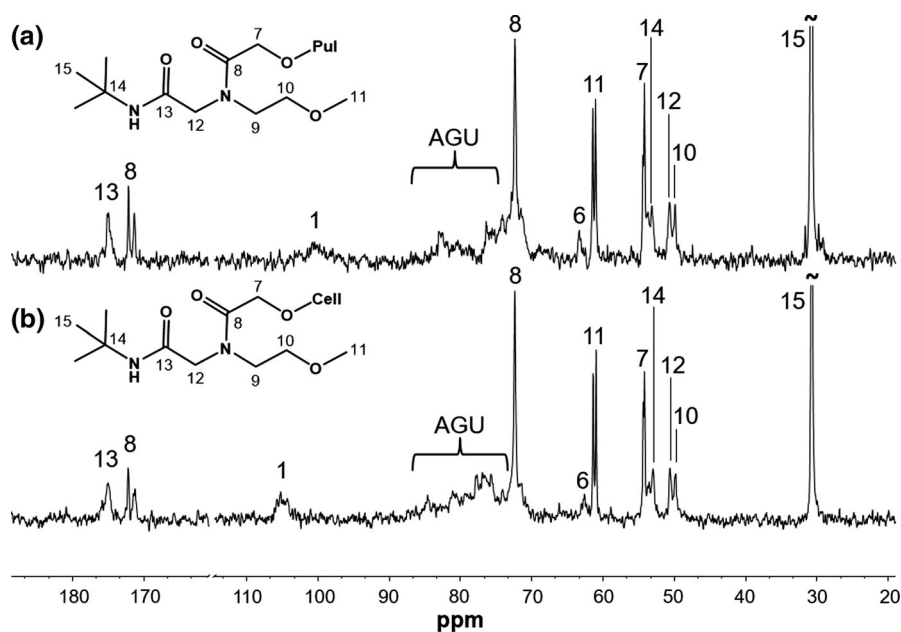
Fig. 6 ^{13}C-NMR spectra of Ugi-products by conversion of carboxymethyl xylan (CMX, **a**) with benzaldehyde, propargylamine and *tert*-butylisonitrile and of carboxymethyl cellulose (CMC, **b**) with acetaldehyde, propargylamine, and *tert*-butylisonitrile, recorded at 25 °C in D$_2$O
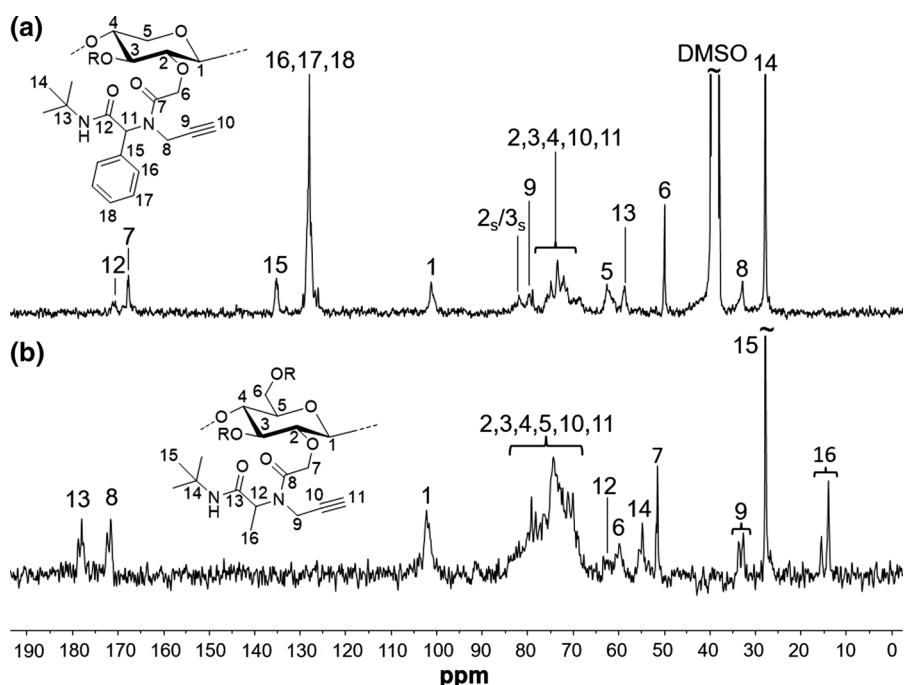
indicates that polymer degradation occurs under reaction conditions used.

Usually, the Ugi-products synthesized possessed a lower DS value compared to the starting carboxymethylated polysaccharide. That result could be explained by an assisted acid cleavage of the ether bond at the backbone of the polysaccharide. An assisting effect of a neighbouring amide moieties may be assumed, which facilitated a hydrolysis of an ether bond as discussed in the literature (Arcelli et al. 2001, 2004; Calvaresi et al. 2008). The assisted cleavage of ether bonds is described to occur by a formation of a five-member ring after protonation of the oxygen atom of the ether bond. In case of the Ugi-

products, no five-member ring could be formed, but in a similar reaction mechanism a six membered ring may be postulated. Due to the fact that the assisted mechanism could not be exactly applied, a partial cleavage of ether bonds took place only. The results led to the conclusion that the pullulan derivative **2c** was the most stable regarding the cleavage of ether bonds. Xylan derivative **2a** possessed a slightly higher extent of hydrolysis. Whereas the cellulose derivative **2b** lost most of the ether substituents. Especially cellulose derivative **4b** underwent the highest extent of hydrolysis of ether bonds. These results indicated that the stability of the resulting ether bonds depends on the structure of the polysaccharide, which is well known, and on the substituent. It may be assumed that the different structure (conformation) of CM-polysaccharides influences the accessibility of the ether bonds that will be investigated in further studies. To investigate the ether cleavage, the conversion of CMC to product **4b** was done again. The DS of the product of first experiment was 0.26 and those of the second reaction was 0.24. Consequently, the ether cleavage occurred with a comparable extent and the Ugi-reaction yield to reproducible results.

The polysaccharide derivatives synthesized by conversion of the carboxymethyl groups of CM polysaccharides with paraformaldehyde, 2-methoxyethylamine, and *tert*-butylisonitrile (samples **2a**-**c**) were soluble in water and organic solvents including dimethylsulfoxide, *N,N*-dimethylacetamide, and *N,N*-dimethylformamide. Due to the hydrophobic phenyl group in the substituent, xylan derivative **3a** possessed solubility in the organic solvents only. Whereas the cellulose derivative **4b** exhibited solubility in water only due to the low DS value of 0.26.

Conclusion

The Ugi-multicomponent reaction is very useful to convert carboxymethyl moieties of CM-polysaccharides selectively with aldehydes, amins, and isonitriles in water. During the conversion, a cleavage of ether bonds may occur yielding a decrease in the number of CM-substituents was observed. However, the studies exhibit a new path to generate substituents with a high structural diversity starting from well-established CM-polysaccharides. Whereby the Ugi-reaction offers the possibility to use CM-polysaccharides as synthetic platform in polysaccharide chemistry. Using the Ugi-reaction, the preparation of a broad variety of polysaccharide derivatives can be expected because diverse reactive compounds can be applied. In principle, it is possible to introduce up to three reactive and orthogonal moieties in a single substituent, because every component, i.e., the isonitrile, the amine, and the aldehyde, could include a reactive moiety for further reactions. Such reactions are under investigation. Beside the CM-polysaccharides, further polysaccharides containing carboxyl groups, like alginates and pectin, seem to be suitable starting materials for the Ugi-reaction to generate soluble derivatives. This structural diversity could offer new avenues in the field of conjugation of one or more biomolecules as well as simultaneously binding of dyes to the polysaccharide backbone. In this regard, the studies about the Ugi-reaction with oligo- and polysaccharides will be expanded.

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