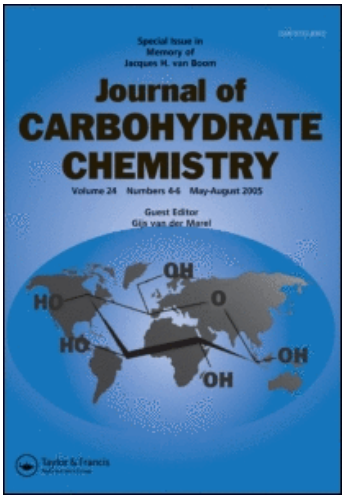

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FROM 3'-KETO-ISOMALTULOSE TO POLYMERS

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ABSTRACT

A new method was developed to prepare polymers with a saccharide in the main chain without blocking and deblocking procedures. The microbial oxidation product of isomaltulose, 3'-keto-isomaltulose, was converted to a diamine by reductive amination. The resulting diamine was employed as a difunctional monomer for direct polyaddition with diisocyanates. The polyureas formed were characterized by IR, ^{13}C NMR, light scattering, and viscosity measurements.

INTRODUCTION

In order to use renewable resources as raw materials for the chemical industry, a new method for preparing polymers with saccharides in the main chain was developed. Through combination of biotechnological and chemical processes, it was possible to attain difunctional derivatives of the polyhydroxy compound isomaltulose without blocking and deblocking procedures.

In an earlier article,[1] we reported on the microbial modification of the disaccharide isomaltulose (α-D-glucopyranosyl-(1'→6)-D-fructofuranose) to 3'-keto-isomaltulose (α-D-*ribo*-hexopyranosyl-3'-ulose-(1'→6)-D-fructofuranose) and described the kinetics and yield of microbial oxidation by resting cells of *Agrobacterium tumefaciens*. Here we present data on reductive amination of 3'-keto-isomaltulose to diamines and subsequent reactions with different difunctional substances to polymers.

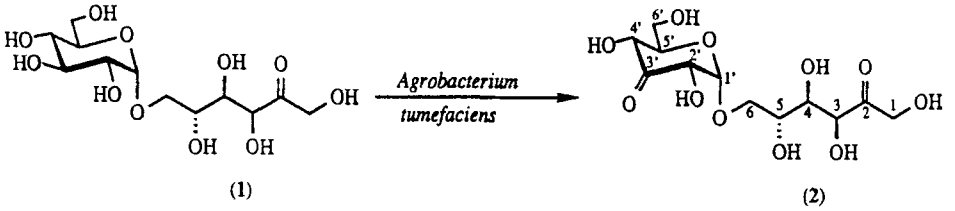
RESULTS AND DISCUSSION

Reductive amination

3'-keto-isomaltulose (**2**), which can be obtained by microbial oxidation of isomaltulose (**1**), formally possesses two carbonyl groups (reducing centers) besides seven hydroxyl groups (Fig. 1), so that reductive amination of (**2**) should lead to a diamine.

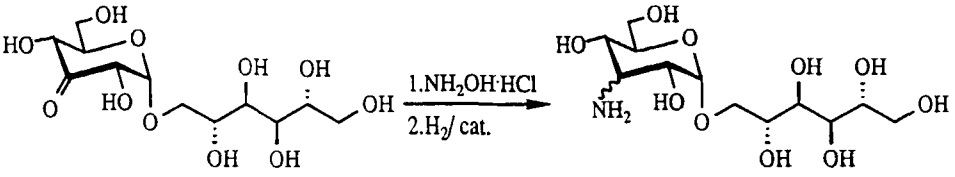
Reductive amination has already been applied to monosaccharides and to some extent to disaccharides.[2-7] Due to alkaline reaction conditions of reductive amination, many side reactions are possible, such as isomerisation, retroaldol-reaction, ß-elimination, HEYNS- and AMADORI-rearrangements and MAILLARD-reactions. Nevertheless, reductive amination of the disaccharide isomaltulose with hydrazine as the aminating reagent yielded isomaltamine (equimolar mixture of α-D-glucopyranosyl-(1→6)-2-amino-2-deoxy-D-mannitol and its sorbitol analog) in a range of about 95 %.[6,7] In contrast, reductive amination of 3'-keto-GPM (α-D-*ribo*-hexopyranosyl-3'-ulose-(1'→6)-D-mannitol, **3**), carried out to examine exclusively the carbonyl-group reactivity of the glycosyl moiety, showed 3'-keto-GPM to be very unstable under these reaction conditions.[8] Best yields were achieved using hydroxylamine-hydrochloride as aminating reagent, and hydrogenating the oxime under hydrogenation conditions used for isomaltulose. After the separation of the reaction mixture on cation exchangers, the product (**4**) was shown by ^{13}C NMR studies to be a mixture of two isomers (Fig. 2).

The amination product of 3'-keto-isomaltulose under reducing conditions should be a mixture of four isomeric substances (2,3'-diamino-isomalt, namely α-D-3'-amino-3'-deoxy-glucopyranosyl-(1'→6)-D-2-amino-2-deoxy-mannitol (**5a**), α-D-3'-amino-3'-deoxy-allopyranosyl-(1'→6)-D-2-amino-2-deoxy-mannitol (**5b**), α-D-3'-amino-3'-deoxy-glucopyranosyl-(1'→6)-D-2-amino-2-deoxy-sorbitol (**5c**), α-D-3'-amino-3'-deoxy-allopyranosyl-(1'→6)-D-2-amino-2-deoxy-sorbitol (**5d**), Fig. 3). The initial work was done applying the reaction conditions used for isomaltulose.[6,7] In the first step 3'-keto-isomaltulose reacted with hydrazine to form a diimine. Then, the intermediate diimine was hydrogenated on Raney-Nickel with hydrogen under elevated pressure. The results were similar to the reductive amination of 3'-keto-GPM: 3'-keto-isomaltulose was very unstable,



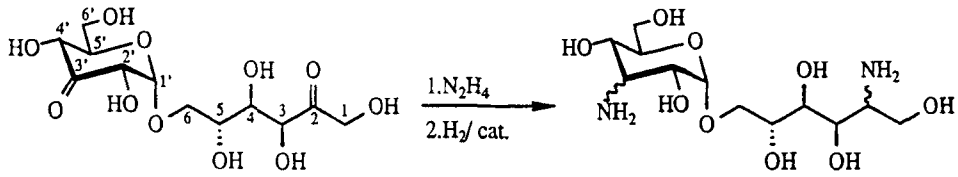
(1) (2)

Fig. 1 Microbial oxidation of isomaltulose (**1**) to 3'-keto-isomaltulose (**2**) (**1** and **2** are shown in their open-chain form to illustrate the ensuing products)



(3) (4)

Fig. 2 Reductive amination of 3'-keto-GPM (**3**) to 3'-amino-GPM (**4**)



(2) (5)

Fig. 3 Reductive amination of 3'-keto-isomaltulose (**2**) to 2,3'-diamino-isomalt (**5**)

decomposition of the saccharide, namely ß-elimination being the main reaction (yield: 4 % diamino-isomalt). Under alkaline conditions cleavage of the glycosidic bond of 3'-keto-isomaltulose is probably preferred because of the conjugating double bonds of the primary product (Fig. 4).

On the basis of these preliminary experiments the reaction conditions of the reductive amination of 3'-keto-isomaltulose were optimized (temperature, hydrogen pressure, amount of catalyst), so that an improvement of diamine yield to approximately

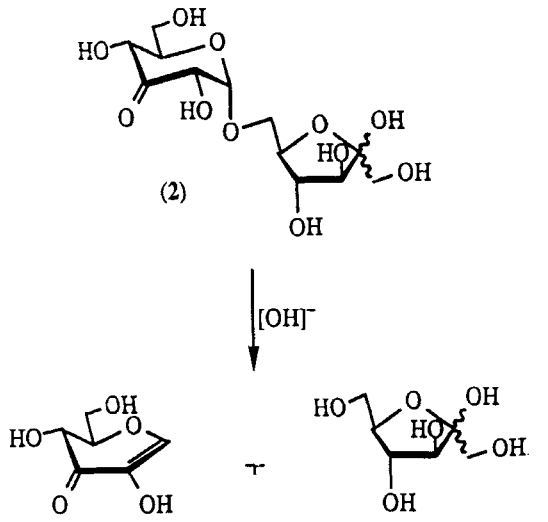


Fig. 4 ß-Elimination of 3'-keto-isomaltulose (**2**) under alkaline conditions

50 % could be reached. As compared to the reductive amination of isomaltulose, double the amount of hydrogenation catalyst was used.

The reaction mixture could be separated by ion exchange chromatography. It was found that cation exchangers, such as Amberlite CG 120-NH_4^+, and dilute aqueous ammonia as eluent were appropriate for separation of aminopolyols.[6] Applying this separation system, three diamino-isomalt fractions could be recovered from the reaction mixture. The diamino-disaccharide structures of the three fractions were proved using ^{13}C NMR and FAB-MS studies. It was found that each of the three fractions contained mixtures of isomeric substances. In the following polymerization reactions, mixtures of these isomers were used to obtain polymers with a sugar moiety in the main chain.

Polymerization reactions

Diamino-isomalt (**5**) is a polyfunctional compound with seven hydroxyl and two amino groups. Because of the higher reactivity of the amino groups, diamino-isomalt should react as a difunctional monomer for direct polycondensation or polyaddition without blocking and deblocking procedures.

Polycondensation of diamino-isomalt together with dicarboxylic acid dichlorides led to polyamides as shown by IR measurements. ^{13}C NMR spectroscopy was also used to clarify the structure but it was not possible to distinguish between amide and ester signals by this method. Nevertheless, esterification as side reaction was detected by IR measurements.[8]

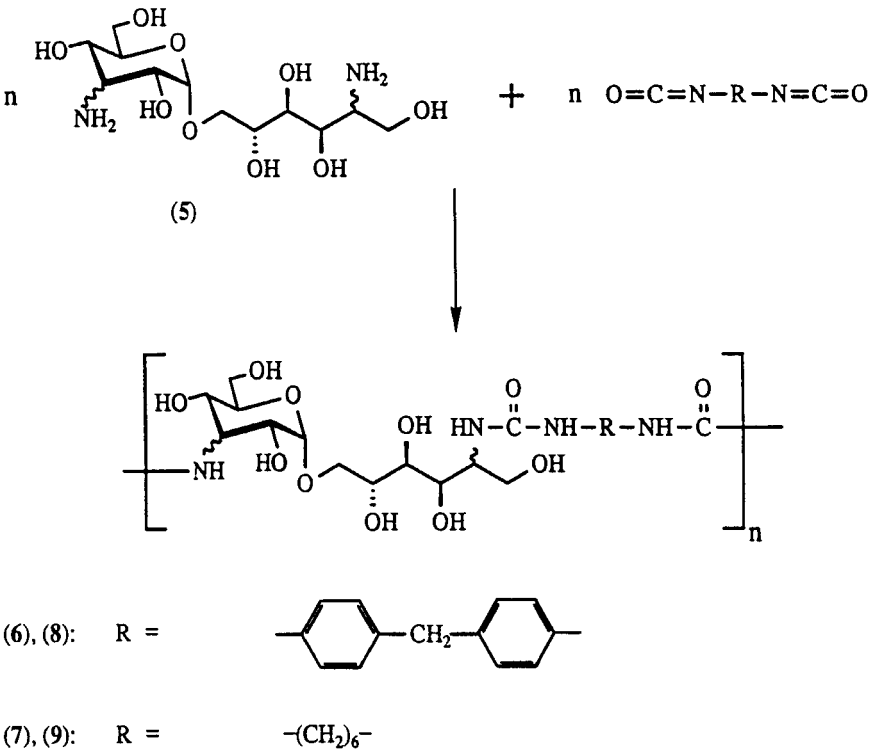


Fig. 5 Polyaddition of diamino-isomalt (**5**) and diisocyanates (**6**,**7**) to polyureas (**8**,**9**)

Another interesting way to prepare polymers of diamino-isomalt is the polyaddition. Preliminary tests showed that side reactions occurred to a minor extent only. Therefore, diisocyanates together with diamino-isomalt were found to be suitable compounds to get polyureas (**8**, **9**) with saccharides in the main chain (Fig. 5). Similar reactions were reported by Kurita et al., who converted mono- and diaminated monosaccharides, and unsubstituted disaccharides with two primary hydroxyl groups with diisocyanates into poly(urea-urethane)s, polyureas and polyurethanes.[9-14]

With diamino-isomalt as the saccharide monomer for polyaddition, side reactions at the hydroxyl groups are possible in spite of the higher affinity of the amino groups for the diisocyanates. To avoid this urethane formation and the following crosslinking of the polymer chains, equimolar amounts of diisocyanate and diamine were applied. Moreover, polyaddition was carried out at low temperatures in the aprotic polar solvent *N,N*-dimethylacetamide (DMAc) to increase the selectivity of the isocyanate groups towards the amino groups of the saccharide compound[14] and to avoid urethane formation. IR and

Table 1 Characteristics of the polyureas **8** and **9**

polymer (diisocyanate; T)	dn/dc[a]	M_w[b] [g/mol]	P_w[c]	$[\eta]$[d] [mL/g]
8a (**6**; 0°C/5°C)	0.153	3.13×10^5	1057	22.0
8b (**6**; -5°C/0°C)	0.145	1.04×10^4 *	35	13.3
9a (**7**; 0°C/5°C)	0.107	8.74×10^5	3427	9.3
9b (**7**; -5°C/0°C)	0.114	1.10×10^4 *	43	9.6

a. refractive index increment (25 °C)
b. weight average molecular weight
c. weight average degree of polymerization
d. intrinsic viscosity (25 °C)

* molecular weight was measured by the low-angle light scattering method

^{13}C NMR studies confirmed the expected chemical structure of the polyureas: Characteristic signals of the -NH-CO-NH- group at 1640 and 1560 cm^{-1} can be distinguished from the urethane group at 1695 and 1538 cm^{-1}.[15] Besides the urea group, the structural characteristics of the applied monomers (signals of aliphatic respectively aromatic groups and saccharides) were detectable, whereas signals of a urethane group did not appear in the IR spectrum.

The polymers were also characterized by light scattering and viscosity measurements. The weight-average molecular weight M_w was found to be 1.0×10^4 to 8.7×10^5 g/mol depending on the diisocyanate used and the reaction temperature (-5 °C to 5 °C).

Higher temperatures during polyaddition led to much higher molecular weight products. Viscosity measurements showed the difference in the intrinsic viscosities to be small in spite of the high differences in molecular weights of the polymers (tab. 1). These observations indicate that urethane formation probably did occur to some extent followed by wide-meshed crosslinking of the polymer chains. Signals of these crosslinking-reactions could not be detected by IR-spectroscopy so that their part was probably very low (i. e. < 1%[16]).

EXPERIMENTAL

General procedures. Solvents were removed by concentration *in vacuo* using an evaporator at 30-40 °C. ^{13}C NMR spectra were recorded in D_2O or DMSO solution with

a BRUKER AM-300 NMR spectrometer (external TMS). Values are given in parts per million (ppm) downfield from the external standard. Infrared (IR) spectra were recorded with a UNICAM SP 1100 spectrometer (PYE UNICAM LTD). FAB mass spectra were taken with a FINNIGAN MAT 8430 spectrometer. The compounds were ionized by fast atom bombardment (FAB) with glycerol as the liquid matrix.

The polymers were characterized by means of viscosimetry and light scattering measurements. Viscosity was determined with an UBBELOHDE-viscosimeter, using DMF as solvent. The weight-average molecular weight (M_W) was determined in a *N,N*-dimethylformamide solution by wide angle light scattering, using a modified photo-gonio-diffusiometer from SOFICA (LE MESNIL-SAINT-DENIS, F) or a KMX-6 low angle laser light scattering photometer (CHROMATIX, USA). The scattering intensities were measured with a He-Ne-laser at a wavelength of 633 nm (vertical polarized) and at a temperature of 298 K. Using the SOFICA instrument, evaluation was done by the double extrapolation method of Zimm. The refractive index measurements were carried out with a BRICE-PHOENIX-refractometer at a wavelength of 633 nm (vertical polarized) and at a temperature of 298 K.

3'-Keto-isomaltulose (2) and **3'-keto-GPM (3).** These substances were prepared by microbial oxidation of isomaltulose (product **2**) or glucopyranosyl-mannitol (product **3**) described earlier.[1]

3'-Amino-3'-deoxy-GPM (4). Hydroxylamine hydrochloride (10.0 g, 0.15 mol) was dissolved in distilled H_2O (200 mL) and the pH value was adjusted to 6 with 10% sodium hydroxide. A solution of 3'-keto-GPM (**3**, 10.0 g, 0.03 mol) in distilled H_2O (50 mL) was added. The mixture was stirred at room temperature while keeping the pH at 6 by titration with 1 N NaOH. After 17 h, the solution was transferred to a 750 mL high-pressure autoclave together with moist Raney-Nickel (4 g). The mixture was hydrogenated 72 h under 15 MPa of hydrogen pressure at 50 °C with stirring at 1000 rpm. The autoclave was depressurized and the catalyst filtered off. The solution was passed through an ion-exchange column to remove the Na^+ ions (packing: Amberlite CG 120 II-NH_4^+) and then the product was isolated by ion-exchange chromatography (separation conditions: column size 0.015 x 1.0 m; packing: Amberlite CG 120 II-NH_4^+; eluent: 0.25 % NH_4OH); yield: 3.6 g (36 %); F 1 (isomeric mixture A/B, ratio approx. 4:1) ^{13}C NMR (75.5 MHz/D_2O) δ 99.3(C1'), 70.6/70.7(C6, A/B*), 64.0(C1, A/B), 61.5(C6', A/B), 54.5/55.2*(C3', A/B*), 71.5/70.0/69.9/69.7/68.6*/ 67.7/67.6/67.2*/66.9*/65.9(C2-5,2',4',5', A/B*); FAB-MS (pos., matrix glycerol) *m/z* 344$(M+H)^+$, 366$(M+Na)^+$, 687$(2M+H)^+$, 162$(fragment+H)^+$.

Anal. Calcd for $C_{12}H_{25}NO_{10}$: C 41.98; H 7.28; N 4.07. Found: C 42.08; H 6.72; N 4.05.

Diamino-isomalt (5). 3'-Keto-isomaltulose (**2**, 20 g, 0.06 mol) was dissolved in distilled H_2O (250 mL) and a 99 % hydrazinium hydrate solution (23.5 mL, 0.48 mol) was added. After the solution was stirred for 17 h at room temperature it was transferred to a 750 mL high-pressure autoclave together with moist Raney-Nickel (24 g). The mixture was hydrogenated 24 h under 15 MPa of hydrogen pressure at 50 °C while stirring at 1000 rpm.The autoclave was depressurized and the catalyst filtered off. The solution was concentrated and three fractions of isomeric diamino-isomalt (F1-3) were separated from the reaction mixture by ion-exchange chromatography (separation conditions: column size 0.05 x 1.0 m; packing: Amberlite CG 120 II-NH_4^+; eluent: 0.5 % NH_4OH); yield: F1 3.22 g (16 %), F2 4.27 g (21 %), F3 2.84 g (14%); F 1 (isomeric mixture A/B) ^{13}C NMR (75.5 MHz/D_2O) δ 100.8/100.7*(C1', A/B*), 70.1/69.2*(C6, A/B*), 63.2-61.4(C1,6', A/B), 54.2-52.7(C2,3', A/B), 74.4-64.9(C3-5, 2',4',5',A/B); FAB-MS (pos., matrix glycerol) *m/z* 343$(M+H)^+$, 435$(M+glycerol+H)^+$, 685$(2M+H)^+$, 162(fragment A+H)$^+$, 182(fragment B+H)$^+$; F 2 (isomeric mixture A/B) ^{13}C NMR (75.5 MHz/D_2O) δ 99.5/101.0*(C1', A/B*), 70.6/69.9*(C6, A/B*), 63.9/62.7/61.9/61.6(C1,6', A/B), 55.2/54.4/53.9/53.6(C2,3', A/B), 72.1-65.2(C3-5,2',4',5', A/B); FAB-MS (pos., matrix glycerol) *m/z* 343$(M+H)^+$, 387$(M+2Na-H)^+$, 435$(M+glycerol+H)^+$, 685$(2M+H)^+$, 162(fragment A+H)$^+$, 182 (fragment B+H)$^+$; F 3 (isomeric mixture A/B) ^{13}C NMR (75.5 MHz/D_2O) δ 99.4/ 99.2*(C1', A/B*), 70.3(C6, A/B), 64.1/61.5*(C1, A/B*), 61.4*/61.2(C6', A/B*), 55.5/55.4*/55.2/54.5*(C2,3', A/B*), 71.8/69.7/68.6/68.3/67.2/66.9/72.0*/69.7*/68.5*/ 67.7*/67.5*/65.9*(C3-5,2',4',5', A/B*); FAB-MS (pos., matrix glycerol) *m/z* 343$(M+H)^+$, 365$(M+Na)^+$, 387$(M+2Na-H)^+$, 685 $(2M+H)^+$, 162(fragment A+H)$^+$, 182(fragment B+H)$^+$.

Polyureas (8) and (9). Polymerization was carried out in a nitrogen atmosphere with stirring. A typical example (polyurea **8a**) is as follows. A dispersion of diamino-isomalt (**5**, 2.0 g, 6 mmol) in *N,N*-dimethylacetamide (DMAc, 45 mL) was stirred for 1 h and then cooled to 0 °C. 4,4'-diisocyanatodiphenylmethane (**6**, 1.5 g, 6 mmol), dissolved in DMAc (5 mL), was added dropwise. The mixture was stirred for 2 hours at 0 °C and 48 h at 5 °C. Then it was poured into diethylether. The precipitated polymer was collected, washed with diethylether and dried *in vacuo*; yield: 3.39 g (97 %); ^{13}C NMR (75.5 MHz/d_6DMSO)(**8a**) δ 157.0/156.2/155.7/155.6 (C=O), 138.6/138.5/ 1138.4/138.2,134.5/ 134.4/134.2, 129.1/128.9, 118.3/118.1/118.0/ 117.7 (aryl-C), 100.2/98.3 (C1'), 72.1-60.5 (C1,3,4,5,6,2',4',5',6'), 53.4/53.1/52.4/ 51.9 (C2,3'); IR(KBr)(**8a**) 3360 cm^{-1} (OH,NH), 2930 cm^{-1} (CH_2), 1600 cm^{-1} (C=C), 1660 cm^{-1} (amide-I), 1545 cm^{-1} (amide-II), 1510 cm^{-1} (C=C), 1035 cm^{-1} (C-O, saccharide), 815 cm^{-1} (CH), 760 cm^{-1} (C=C); ^{13}C NMR (75.5 MHz/d_6DMSO)(**9**) δ 160.5/159.4/159.0/158.8/158.3 (C=O), 99.8/98.3 (C1'),72.0-60.6 (C1,3,4,5,6,2', 4',5',6'), 53.9/53.3/52.6/52.4 (C2,3'), 30.0/26.3 (CH_2); IR(KBr)(**9**) 3400

cm^{-1} (OH,NH), 2950/2880 cm^{-1} (CH_2), 1640 cm^{-1} (amide-I), 1570 cm^{-1} (amide-II), 1270 cm^{-1} (CH_2), 1050 cm^{-1} (C-O, saccharide), 770 cm^{-1} (CH_2).

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