Pergamon

*Tetrahedron* Vol. 50, No. 27, pp. 8103-8116, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00423-4

# Reductive Amination of Aldohexoses with Mono- and Bifunctional Alkyl Amines: Conversion of Carbohydrates into EDTA Type Complexing Agents

**Hendrik Lammers*, Joop A. Peters, and Herman van Bekkum**

Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

**Abstract:** It is shown by $^{1}H$ and $^{13}C$ NMR spectroscopy (1D and 2D) that β-N-propylgalactosylamine (**5a**) is the major species present in an equimolar aqueous solution of D-galactose (**1a**) and propylamine (PA). In equimolar solutions of aldohexoses (**1a-c**) and ethylenediamine (EN) or 1,3-diaminopropane (DAP) in addition to mono- (**9**) and diglycosylamines (**12**) tetra-imidazole (**8**, n=1) and hexahydropyrimidine derivatives (**8**, n=2), respectively, are formed. Hydrogenation of equimolar solutions of aldohexoses (**1a-c**) and primary amines (PA, EN, and DAP) at 100 atm. and 50 °C, using 5% Pt on carbon as the catalyst, gave amino sugars **13-16** in good yields. Carboxymethylation of **14a-b** resulted in sugar based EDTA type complexing agents (**17a-b**) with promising chelating abilities towards Cd(II) and Ca(II) at high pH.

## INTRODUCTION

There are a variety of synthetic pathways leading towards 1-(alkyl)-amino-1-deoxyalditols[1], of which catalytic reductive amination of reducing carbohydrates through the action of a (noble) metal catalyst is the most used one[2-9]. A direct, commercially applied, route to 1-amino-1-deoxy-D-glucitol, is the reductive amination of D-glucose with ammonia using a fixed-bed Ni catalyst[10]. The synthesis of 1-alkylamino-1-deoxy-D-glucitol has been described as a two-step process in which the first step is the formation of the N-alkylglycosylamine which is then hydrogenated in the second step in the presence of a Ni catalyst[11]. Catalytic reductive aminations of several disaccharides have also been reported. Isomaltamine, the equimolar mixture of D-glucopyranosyl-α(1,6)-2-amino-2-deoxy-D-mannitol and its D-glucitol (sorbitol) analog, is obtained by reductive amination with ammonia or hydrazine of isomaltulose, an isomerization product of sucrose, using Raney Ni as the catalyst[12]. 1-Amino-1-deoxyalditols derived from cellobiose, lactose and maltose were synthesized *via* reductive amination with benzylamine and subsequent catalytic removal of the benzyl group at atmospheric pressure[13]. N-alkyllactamines are obtained by a similar two-step proces as mentioned above using either Raney Ni or Pd (10%) on carbon as the catalyst. Higher yields, however, were obtained by reduction with $NaBH_4$[14].

N-alkyl substituted amino sugar derivatives are readily biodegradable and do not cause any skin irritant effects and are therefore being studied as new components for detergents and cosmetics[10]. Further potential applications are as surfactants[15], polymers[16], sweeteners[17] and as liquid crystalline

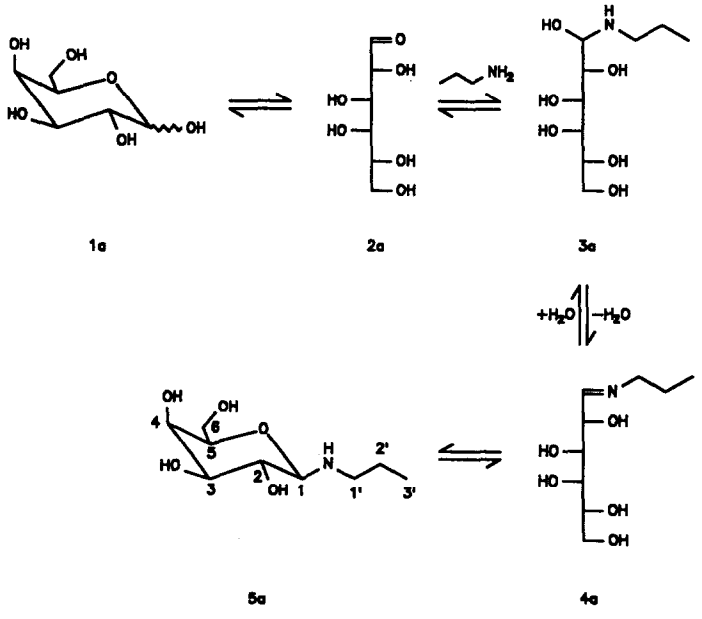
compounds[18].

In this paper we report the reductive amination of the aldohexoses D-galactose (**1a**), D-mannose (**1b**), and D-glucose (**1c**) with propylamine (PA), ethylenediamine (EN) and 1,3-diaminopropane (DAP) through the action of a Pt catalyst. The equilibria and species involved in these reactions are investigated with the aid of $^{1}H$ and $^{13}C$ NMR. The amino sugars obtained by reductive amination with EN are converted into EDTA (ethylenediaminetetraacetate) type complexing agents by carboxymethylation. The Cd(II) and Ca(II) sequestering capacities of the newly synthesized ligands are given.

## RESULTS AND DISCUSSION

*Study of Aqueous Solutions Containing Aldohexoses and Primary Amines*

Upon addition of an equimolar amount of PA to an aqueous solution of an aldohexose, a new set of signals appeared in the $^{13}C$ NMR spectrum next to the signals of the starting compounds. These signals have to be ascribed to an adduct of the amine and the aldohexose. Characteristically this new species has a signal at about 90 ppm and no signal for an imine function ($\delta$ = 150 - 170 ppm). In order to elucidate its structure, the system D-galactose (**1a**)/ PA was studied in more detail. The possible equilibria involved are outlined in Scheme 1.




Scheme 1

The first step is a nucleophilic addition of the primary amine onto the acyclic form (**2a**) yielding the acyclic carbinolamine (**3a**). This latter species can be in equilibrium with the imine (**4a**) and/ or with the N-propylgalactosylamine (**5a**). As no imine is observed, the new species present in solution is either 3a or 5a. In a 0.5 M solution of D-galactose containing an excess of PA ( 5 eq., pH= 11.6) a nearly complete conversion of D-galactose into the new species took place. The $^{13}C$ and $^{1}H$ NMR parameters of this compound are summarized in Table 1.

It is known that free alditols in water prefer a planar carbon chain except when this results in a 1,3 parallel arrangement of two C-O bonds[19,20]. Therefore when carbinolamine **3a** would be present in solution the coupling constants $^{3}J_{3,4}$ and $^{3}J_{4,5}$ would be about 2 and 10 Hz[21], respectively, which is not in agreement with the observed values. Since the $^{3}J_{H,H}$ coupling constants of the carbohydrate moiety closely resemble those of D-galactose[22], it can be concluded that the compound formed is N-propylgalactosylamine (**5a**). The large diaxial $H_1$-$H_2$ coupling constant ($^{3}J_{1,2}$ = 9.2 Hz) shows that we are dealing with the $\beta$-anomer which strongly prefers the $^{4}C_1$ conformation[23].

Pure **5a** could be obtained by reacting D-galactose (**1a**) with 1.1 eq. PA in a minimum amount

Table 1. NMR Data of ß-N-propylgalactosylamine (**5a**) in $D_2O$ at pH 11.6 and 25 °C[a]

Chemical shifts (ppm)

| | 1 | 2 | 3 | 4 | 5 | 6a | 6b | 1'a | 1'b | 2' | 3' |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $^{13}C$[b] | 91.6 | 72.1 | 75.3 | 70.6 | 77.4 | 62.7 | 62.7 | 48.5 | 48.5 | 23.8 | 12.6 |
| $^{1}H$[c] | 3.89 | 3.38 | 3.55 | 3.87 | 3.58 | 3.69 | 3.73 | 2.79 | 2.57 | 1.43 | 0.85 |

H-H coupling constants (Hz)

| | | | |
|---|---|---|---|
| J(1,2) = 9.2 | J(5,6a) = 7.6 | J(1'a,2'a) = 8.7 | J(2',3') = 7.5 |
| J(2,3) = 9.8 | J(5,6b) = 4.3 | J(1'a,2'b) = 6.6 | |
| J(3,4) = 3.7 | J(6a,6b) = -12.0 | J(1'b,2'a) = 6.1 | |
| J(4,5) = 1.2 | J(1'a,1'b) = -11.6 | J(1'b,2'b) = 8.5 | |

[a] obtained from a sample prepared from 0.5 M D-galactose (**1a**) and 2.5 M PA
[b] 100.6 MHz
[c] 400 MHz

of water[24]. After 2h the N-propylgalactosylamine crystallized from the reaction mixture. Dissolution of pure **5a** (0.55 M) resulted, after 1h, in a mixture with the same composition as that obtained when D-galactose (**1a**) and PA (0.55 M) were mixed in equimolar amounts, demonstrating that the thermodynamic equilibrium was reached. When the pH of equimolar mixtures of aldohexoses and primary amines was lowered the molar concentration of the starting aldohexose and primary amine increased. At low pH (<6) a complete hydrolysis to the starting aldohexose and primary amine occurred[25,26].

Since in the solutions studied only **1a** and **5a** were observed, we suppose that the ring opening of these compounds is rate determining in the establishment of the equilibrium. The equilibrium is reached relatively slow starting from **5a**. Therefore, the ring opening of **5a** is probably slower than that of **1a**, which is consistent with the molar ratio **5a**/ **1a** in the equilibrium (see Table 2).

In equimolar solutions of aldohexoses and the bifunctional amines EN or DAP similar species were observed by $^{13}C$ NMR, but in addition to that two other new compounds could be detected. One of them resembled that of the glycosylamines (see e.g. Table 1). The relative intensities of the signals for this compound as a function of the molar ratio aldohexose/ amine suggested that it was the diglycosylamine. In the case of EN this was supported by characteristic signals at 46 and 90 ppm, for the ethylenediamine function and C1, respectively. Because of the $S_2$-symmetry of the diglycosylamine, the methylene groups of the ethylenediamine unit give only a signal at 46 ppm. The $^{13}C$ resonances in the carbohydrate region (60 - 80 ppm) of the diglycosylamine coincide with those of the monoglycosylamine. The diglycosylamines derived from aldohexoses and DAP similarly show characteristic resonances at 30 ($\beta$-$CH_2$), 44 ($\alpha$-$CH_2$), and 90 ppm (C1). The $^{13}C$ resonances in the carbohydrate region of the DAP derived diglycosylamines also coincide with those of the corresponding monoglycosylamines. Diglycosylamines derived from D-glucose and ammonia already have been described, but no spectral data have been reported up to now[27]. In an equimolar solution of D-galactose (**1a**) and DAP the other new species is the major component (see Fig 1). The signals at 39.8 and 35.6 ppm are corresponding to DAP. The resonances with the highest intensities at 73.1, 72.9, 71.8, 71.0, 70.9, 64.8, 45.8, 45.7, and 27.0 ppm indicate the presence of a hexahydropyrimidine derivative (**8a**, n=2; see Scheme 2). Due to the presence of the chiral carbohydrate moiety the $\alpha$-methylene carbons are not equivalent resulting in two resonances (45.8 and 45.7 ppm), the signal for the $\beta$-methylene group of the heterocyclic ring is located at 27.0 ppm The chemical shift of C6 (64.8 ppm) is characteristic for alditol derivatives[22]. In solutions of aldohexoses and EN a similar species is observed, but in a much lower concentration. Consequently the signals were difficult to observe in this case, especially in the carbohydrate region signals do overlap. The C6 resonance at 64 ppm and the (coinciding) $N\underline{C}H_2\underline{C}H_2N$ signals at 46 ppm, however, were easily observed.

On the basis of the species identified, it can be concluded that, for example, the equilibria given in Scheme 2 occur in solutions of D-galactose (**1a**) and EN (n=1) or DAP (n=2). The imine **7a** is formed after elimination of water from the carbinolamine **6a**. Nucleophilic attack of the primary amino

group on the imine C-atom results in the formation of **8a**. The nucleophilic attack of the C5 hydroxyl group results in the galactosylamine **9a**, which is in equilibrium with the digalactosylamine **12a** *via* intermediates **10a** and **11a**.

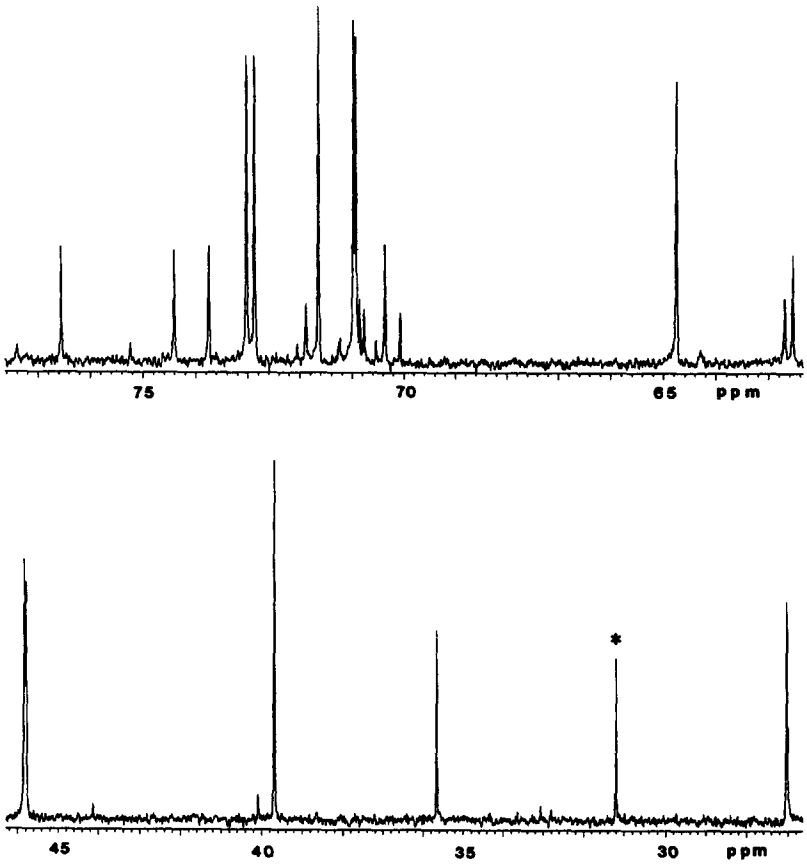
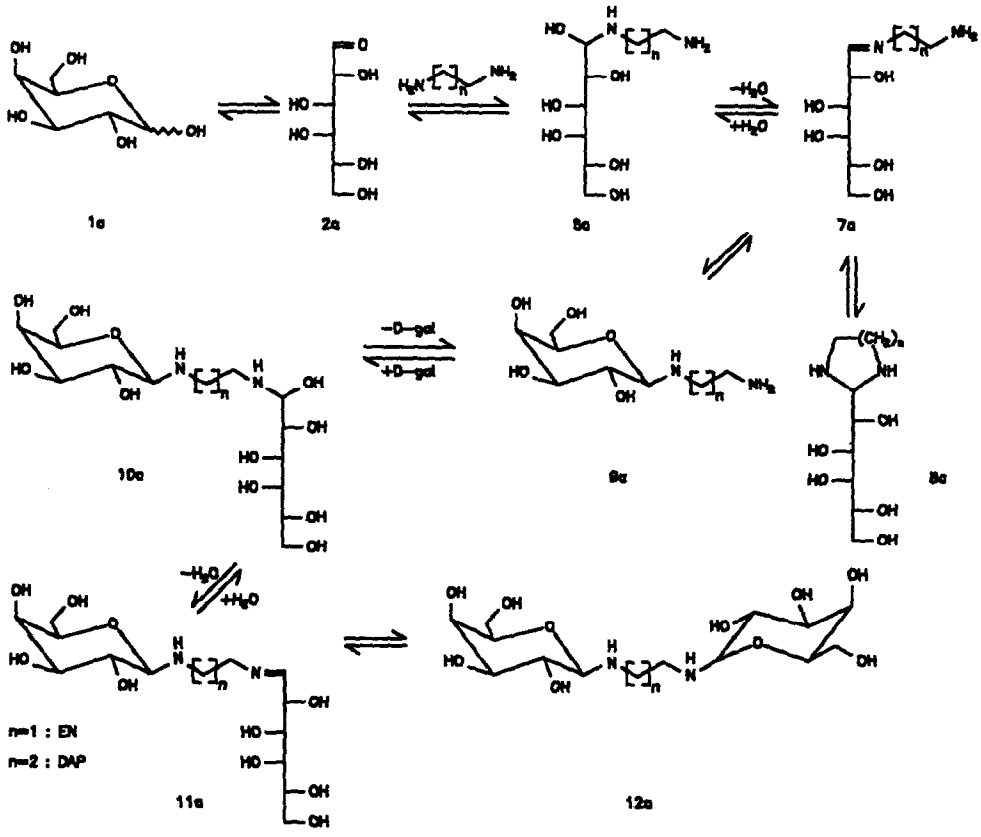



Figure 1. 100.6 MHz $^{13}C$ NMR spectrum of 0.5 M D-galactose (**1a**) and 0.5 M DAP in $D_2O$ at pH 11.7 and 25 °C. * internal standard (t-BuOH).

The equilibria of D-galactose (**1a**) or D-mannose (**1b**) with the primary amines PA, EN, and DAP are established relatively fast (0.5h) compared to those of D-glucose (**1c**) (7h) with these primary amines. At 50 °C the equilibria for D-glucose (**1c**) were reached in 1.5 h. A decrease of the N-glycosylamine concentration occurred after 2h due to non-enzymatic browning[28]. Also in solutions containing D-galactose (**1a**) or D-mannose (**1b**) and primary amines non-enzymatic browning occurred after 2h at 50 °C.




*Scheme 2*

The speciations in aqueous solutions of aldohexoses and mono- and bifunctional amines as determined at pH 11.6 by quantitative $^{13}C$ NMR are summarized in Table 2. The results show that the hexahydropyrimidines (**8a-c**, n=2) are thermodynamically more stable than the tetrahydro-imidazole derivatives (**8a-c**, n=1).

Table 2. Distribution of Aldohexoses and Derivatives in Equimolar Solutions of Aldohexoses and Amines (mol %) at pH 11.6 and at room temperature.

| aldohexose | amine | 1 | 5 | 8 | 9 | 12 |
|---|---|---|---|---|---|---|
| **1a** | PA | 30 | 70 | | | |
| **1a** | EN | 5 | | 10 | 60 | 25 |
| **1a** | DAP | 10 | | 60 | 25 | 5 |
| **1b** | PA | 25 | 75 | | | |
| **1b** | EN | 10 | | 10 | 60 | 20 |
| **1b** | DAP | 10 | | 55 | 25 | 10 |
| **1c** | PA | 25 | 75 | | | |
| **1c** | EN | 15 | | 5 | 60 | 20 |
| **1c** | DAP | 10 | | 30 | 45 | 15 |

*Reductive Amination of Aldohexoses with Mono- and Bifunctional Amines*

All reductive aminations were carried out at 50 °C in aqueous medium (0.55 M based on aldohexose) using 5% platinum supported on carbon as the catalyst using a hydrogen pressure of 100 atm. Similar reaction conditions were applied for the synthesis of dialditylamines *via* hydrogenation of the corresponding aldoximes[29]. Heating of the reaction mixture prior to hydrogenation must be carried out in the absence of catalyst in order to avoid dehydrogenation of the aldohexose towards the corresponding aldonic acid[30]. At temperatures above 50 °C non-enzymatic browning occurred during hydrogenation. From $^{13}C$ NMR data of the hydrogenated products it can be concluded that during the reductive amination there is retention of configuration of the polyhydroxy chain.

The reductive amination of a 0.55 M D-galactose (**1a**) solution with 1 mol equivalent PA was monitored by quantitative $^{13}C$ NMR using dioxane as the internal standard (Figure 2a). The hydrogenation, was started immediately after mixing D-galactose and PA, and was completed within 2 h. Under the reaction conditions applied a considerable amount of D-galactitol is obtained (15 mol %) as a result of the direct hydrogenation of D-galactose. The molar ratio of **13a**/ alditol in the final product is higher than that of **5a**/ **1a** at t= 0, and the hydrogenation rate of **5a** is higher than that of **1a**. Apparently conversion of **1a** into **5a** (see Scheme 1) is relatively fast with respect to the hydrogenation rates.

The non-enzymatic browning, as mentioned earlier, is observable after 2 h at 50 °C. At higher reaction temperatures considerable browning was observed, which was expected since it is known that the rate of non-enzymatic browning has an exponential dependence on the temperature[28].

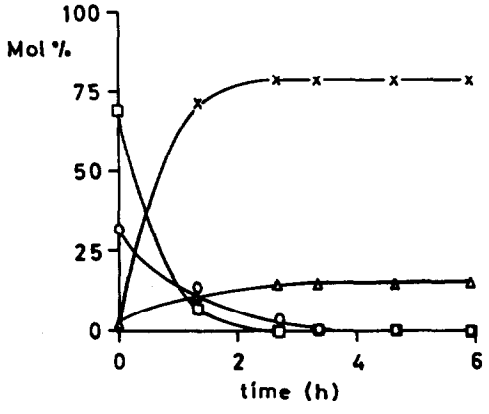



Figure 2a

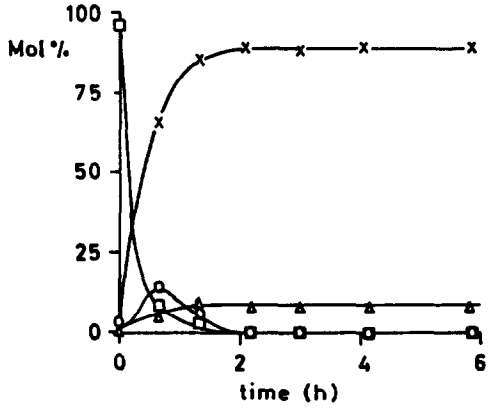
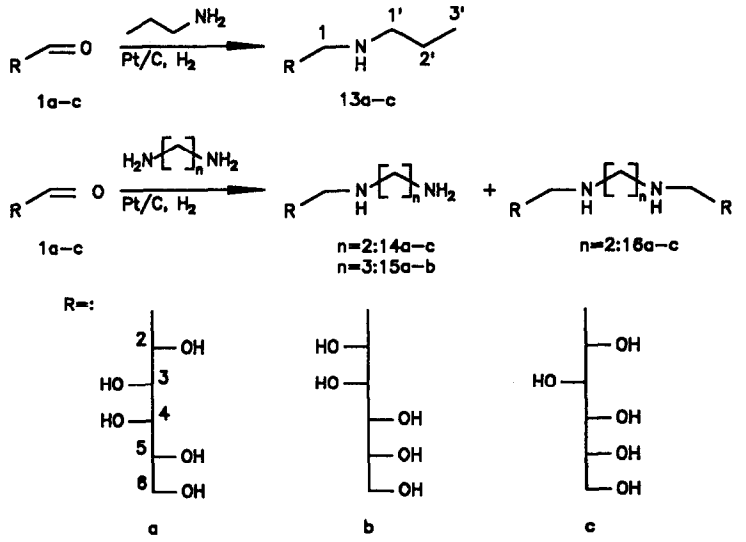



Figure 2b

Product distribution of the hydrogenation of an equimolar mixture (0.55 M) D-galactose (**1a**) and propylamine (Figure 2a) and of a 0.55 M solution N-propyl-galactosylamine (**5**) (Figure 2b); (□ N-propylgalactosylamine (**5**);o D-galactose (**1a**); × 1-Deoxy-1-(propylamino)-D-galactitol (**13a**); ▵ D-galactitol).

The hydrogenation of a 0.55 M solution of **5a** in water was also followed by quantitative $^{13}C$ NMR (Figure 2b). During hydrogenation the concentration of **1a** initially increases due to the hydrolysis of **5a** and a relatively low hydrogenation rate of **1a**. The hydrolysis of **5a**, however, is rather slow resulting in a higher molar ratio **5a**/**1a** at the initial stage of the hydrogenation in comparison with the above described reaction starting from an equimolar sugar/amine solution, and consequently the molar ratio of **13a**/ galactitol in the final product is higher in this case. This behaviour is in agreement with the conclusion of the speciation studies on solutions of **1a** and PA, that ring opening of **5a** is relatively slow with respect to that of **1a**.



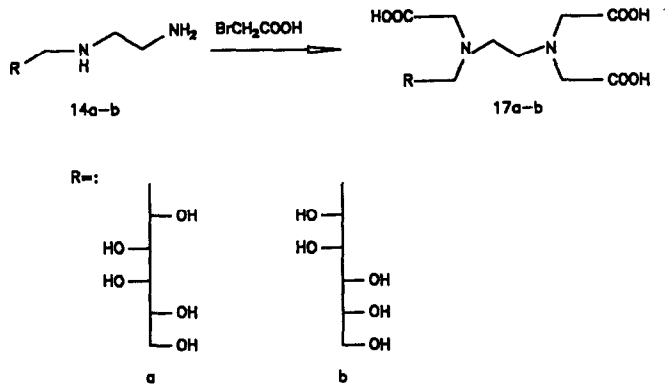

Scheme 3

The reductive amination of **1a-c** with 1 mol equivalent PA gave the corresponding amino sugars **13a-c** in good yields (70%), when a 5-fold excess of amine was used higher yields (85%) were obtained (Scheme 3). Using 1 mol equivalent EN in the reductive amination resulted in mixtures of mono- and diadducts (and alditol). The monoadducts **14a-c** and diadducts **16a-c** were obtained in yields of 55%, and 15%, respectively. All compounds were isolated as white solids except **14c** which was obtained as a syrup from which sorbitol could not be removed. The ratio mono-/diglycosylamine in the starting solutions of aldohexoses and EN closely resembles the ratio mono-/diadduct in the hydrogenated products. Since the equilibration of D-glucose with EN is rather slow (7h at 25 °C), hydrogenation must start after the equilibration is completed. Hydrogenation before equilibrium is reached results in different product compositions and lower yields of the amino sugars. The product composition can be altered in favour of the monoadduct by application of 5 mol equivalents of EN. This resulted in higher yields (75%) of

**14a-c**, compound **14c** was still obtained as a syrup containing sorbitol. The amino sugars **15a** and **15b** were obtained in 50% yield by reductive amination of D-galactose (**1a**), and D-mannose (**1b**), respectively with 5 mol equivalents DAP.

*Cadmium(II) and Calcium(II) Sequestering Capacities of the Compounds* **14a-b** *and their Carboxymethylated Adducts* **17a-b**

The monoadducts **14a-b** were carboxymethylated using bromoacetate with a yield of 45% (Scheme 4). The thus obtained compounds **17a-b** are EDTA type complexing agents in which one of the acetate groups is substituted by a sugar moiety. In Table 3 the Cd(II) and Ca(II) sequestering capacities (CdSC and CaSC, respectively) of the ligands **14a-b**, **15a-b**, and **17a-b** and EDTA at pH 11.6 are presented.




Scheme 4

The monoadducts **14a-b** are poor Ca(II) sequestrants, attachment of the acetate groups increases their

Table 3. Cadmium(II) and Calcium(II) Sequestering Capacities in mg/gram (mol/mol) Ligand at pH 11.6 and at room temperature.

| ligand | CdSC | CaSC |
|---|---|---|
| **14a** | 224 (0.4) | 20 (0.1) |
| **14b** | 279 (0.7) | 8 (0.04) |
| **15a** | 82 (0.2) | 10 (0.05) |
| **15b** | 68 (0.1) | 15 (0.08) |
| **17a** | 225 (0.9) | 90 (1.0) |
| **17b** | 226 (0.9) | 86 (1.0) |
| EDTA | 342 (1.0) | 142 (1.3) |

Ca(II) sequestering abilities significantly. The ligands **14a-b** possess good CdCS abilities, the attachment of acetate groups did not improve the Cd(II) complexing abilities as much as with the sequestering capacities of the hard Ca(II)[31] cation. The CaSC of **15a-b** are comparable with those of ligands **14a-b**. The CdSC of **15a-b** are significantly lower than those of **14a-b**. The decrease in complex stability of the Cd(II) complexes caused by increase of the chelate ring size from five- to six-membered can be ascribed to an enthalpy effect[32]. The strong CdSC and CaSC of the sugar-based EDTA type ligands **17a-b** can be ascribed to additional coordination of one of the hydroxyl groups of the polyhydroxy chain besides the coordination of the nitrogen-atoms and carboxylate groups. Further studies on the structures of these complexes are in progress[33].

## CONCLUSIONS

The major species present in equimolar aqueous solutions (0.55 M) of aldohexoses and PA or EN are the N-alkylglycosylamines, with DAP as the amine hexahydropyrimidines are predominant. Hydrogenation of the aqueous solutions with the primary amines (PA, EN, and DAP) at 50 °C and 100 atm. $H_2$, using a 5% Pt on carbon catalyst, gave the desired amino sugars in good yields. The amino sugars **14a-b** obtained by reductive amination of **1a-b** with EN can be carboxymethylated to give the sugar based EDTA type complexing agents **17a-b**, which show promising Cd(II) and Ca(II) sequestering properties at high pH.

## EXPERIMENTAL SECTION

The $^{13}C$ NMR spectra were recorded at 50.3 MHz with a Nicolet NT-200 WB NMR spectrometer or at 100.6 MHz with a Varian VXR-400 S NMR spectrometer with $D_2O/H_2O$ (4:1 v/v) as the solvent and t-butanol as the internal reference ($\delta$ (ppm): 31.2 (methyl)). The quantitative $^{13}C$ NMR spectra were recorded with 45° flip angle, an acquisition delay of 30 s, 32 K datapoints with $^1H$ decoupling during the acquisition only. Product ratios were determined by deconvolution of the $^{13}C$ signals using Lorentzian line shapes. $^1H$ NMR spectra were recorded using the Varian VXR-400 S NMR spectrometer with $D_2O/H_2O$ (4:1 v/v) as the solvent and t-butanol as internal reference ($\delta$ (ppm); 1.20. The complete $^1H$ and $^{13}C$ NMR analysis of **5a** was carried out by means of $^1H$ homonuclear correlation spectroscopy, $^1H$-$^{13}C$ chemical shift correlation spectroscopy (HETCOR) and selective proton decoupling experiments. With J-resolved 2D NMR the $^3J_{H\text{-}H}$ coupling constants (first order systems) could be determined. FAB mass spectra were obtained with a VG 70-250 SE mass spectrometer.

The starting materials were all purchased from Janssen Chimica. The hydrogenations were carried out in a 300 ml Hastelloy C276 autoclave model 4562, manufactured by Parr. The autoclave was equipped with a motor-driven impeller stirrer, a sampling device and a temperature programming system (M 4841 Parr). The aldohexose/ amine solutions were thermostatted at 50 °C by a water bath before transferring to the autoclave. The catalyst (5% Pt/C) was added and the mixtures were hydrogenated

for 12 h at 100 atm. $H_2$ and 50 °C. After hydrogenation the catalyst was filtered off, the solvent and amine were removed by evaporation. Purification of the reaction product was carried out by recrystallization. When using DAP, the amine could not removed by evaporation. The products derived from DAP crystallized upon addition of MeOH to the crude reaction mixture after removal of the solvent. The quantitative $^{13}C$ NMR analyses have been carried out with 3 ml samples taken at certain intervals. From the samples the catalyst was removed by centrifugation, 0.8 ml $D_2O$ was added and then the $^{13}C$ NMR spectrum was measured. Dioxane was used as internal standard ($\delta$ (ppm): 66.6. The pH values given are direct meter readings.

Metal-ion sequestering capacities were determined according to a procedure used by AKZO Chemical Research Center Deventer[34] or according to Mehltretter *et al*[35]. Cadmium(II) and calcium(II) sequestering capacities, at ambient temperature, were determined by adding a solution of Cd(II) or Ca(II) chloride to a solution containing approximately 100 mg ligand. The CdSC and CaSC were determined at pH 11.6 using NaOH/ $Na_2CO_3$ as indicator. As endpoint of a titration the first turbidity that not disappeared within 30 seconds was taken. The estimated errors in the metal-ion sequestering capacities are 20%.

*1-Deoxy-1-(propylamino)-D-galactitol* (**13a**). To a mixture of 15 g (83 mmol) D-galactose (**1a**) and 24.6 g (417 mmol) PA dissolved in 150 ml $H_2O$ 2 g catalyst were added. Recrystallization of the hydrogenated mixture from MeOH/$H_2O$ (9/1) and drying *in vacuo* yielded 15.8 g (85%) pure **13a**. $^1H$ NMR (pH = 10.7): $\delta$ (ppm) 3.98 (ddd, 1H, H2, $J_{21a}$ =8.7 Hz, $J_{21b}$ =4.2 Hz, $J_{23}$ =1.6 Hz); 3.92 (m, 1H, H5, $J_{54}$ =1.4 Hz, $J_{56}$ =6.7 Hz); 3.65 (d, 2H, H6); 3.62 (dd, 1H, H4, $J_{43}$= 9.3 Hz); 3.54 (dd, 1H, H3); 2.75 (dd, 1H, H1a, $J_{1a1b}$= -12.7 Hz); 2.67 (dd, 1H, H1b); 2.55 (m, 2H, H1', $J_{1'a1'b}$= -11.7 Hz); 1.45 (m, 2H, H2', $J_{2'3'}$= 7.3 Hz); 0.88 (t, 3H, H3'). $^{13}C$ NMR (pH = 11.6): $\delta$ (ppm) 72.4, 71,7, 71.0 (C3, C4, C5); 69.9 (C6); 52.9, 51.9 (C1, C1'); 23.3 (C2'); 12.6 (C3'). FAB-MS (glycerol matrix): m/z 224 (M + $H^+$).

*1-Deoxy-1-(propylamino)-D-mannitol* (**13b**). The procedure described for **13a** was followed. From 15 g (83 mmol) D-mannose (**1b**) 15.3 g (82 %) pure **13b** was obtained. $^1H$ NMR (pH = 10.5): $\delta$ (ppm) 3.81 (dd, 1H, H6a, $J_{6a5}$ =2.4 Hz, $J_{6a,6b}$ =-11.6 Hz); 3.78-3.66 (m, 4H, H2, H3, H4, H5); 3.61 (dd, 1H, H6b, $J_{6b5}$ =5.9 Hz); 2.87 (dd, 1H, H1a, $J_{1a2}$ =4.0 Hz, $J_{1a1b}$ =-12.7 Hz); 2.62 (dd, 1H, H1b, $J_{1b2}$ =8.3 Hz); 2.54-2.50 (m, 2H, H1'); 1.46 (m, 2H, H2', $J_{2'3'}$ =7.3 Hz); 0.88 (t, 3H, H3'). $^{13}C$ NMR (pH = 10.4): $\delta$ (ppm) 72.9, 72.4, 70.9 (C3, C4, C5); 70.4 (C2); 64.8 (C6); 52.5, 51.8 (C1, C1'); 22.7 (C2'); 12.4 (C3'). FAB-MS (glycerol matrix): 224 (M + $H^+$).

*1-Deoxy-1-(propylamino)-D-glucitol* (**13c**). The procedure described for **13a** was followed. From 15 g (83 mmol) D-glucose (**1c**) 14.8 g (80%) pure **13c** was obtained. $^1H$ NMR (pH = 10.6): $\delta$ (ppm) 3.85 (ddd, 1H, H2, $J_{21a}$ =3.7 Hz, $J_{21b}$ =8.1 Hz, $J_{23}$ =6.0 Hz); 3.78 (dd, 1H, H6a, $J_{6a6b}$ =-11.7 Hz, $J_{6a5}$ =2.9 Hz); 3.72 (m, 1H, H5, $J_{56b}$ =6.3 Hz, $J_{54}$ =8.1 Hz); 3.70 (dd, 1H, H3, $J_{34}$ =2.1 Hz); 3.60 (dd, 1H, H6b); 3.59 (dd, 1H, H4); 2.70 (dd, 1H, H1a, $J_{1a1b}$ =-12.7 Hz); 2.61 (dd, 1H, H1b); 2.54 (dt, 1H, H1'a, $J_{1'a1'b}$ =-11.7 Hz, $J_{1'a2'}$ =7.3 Hz); 2.49 (dt, 1H, H1'b, $J_{1'b2'}$ =7.3 Hz); 1.45 (m, 2H, H2', $J_{2'3'}$ =7.3 Hz); 0.88 (t, 3H, H3'). $^{13}C$ NMR (pH = 11.6): $\delta$ (ppm) 72.6 (broad, C3, C4, C5); 72.4 (C2); 64.4 (C6); 51.9, 51.8 (C1, C1'); 23.2 (C2'); 12.5 (C3'). FAB-MS (glycerol matrix): 224 (M + $H^+$).

*1-(2-Aminoethylamino)-1-deoxy-D-galactitol* (**14a**). To a mixture of 10 g (55 mmol) D-galactose (**1a**) and 16.7 g (278 mmol) EN dissolved in 100 ml $H_2O$ 1.5 g catalyst was added. Recrystallization of the hydrogenated mixture from MeOH/$H_2O$ (1/1) and drying *in vacuo* yielded 9.3 g (75 %) pure **14a**. $^1H$ NMR (pH = 10.5): $\delta$ (ppm) 3.97 (ddd, 1H, H2, $J_{21a}$ =4.2 Hz, $J_{21b}$ =8.8 Hz, $J_{23}$ =1.5 Hz); 3.92 (dt, 1H,

H5, $J_{56}$ =6.0 Hz, $J_{54}$ =1.5 Hz); 3.63 (d, 2H, H6); 3.61 (dd, 1H, H4, $J_{34}$ =9.3 Hz); 3.54 (dd, 1H, H3); 2.77 (dd, 1H, H1a, $J_{1a1b}$ =-12.6 Hz); 2.66 (dd, 1H, H1b); 2.74-2.60 (m, 4H, H1', H2'). $^{13}$C NMR (pH = 11.7): $\delta$ (ppm) 72.5, 71.8, 71.1 (C3, C4, C5); 70.0 (C2); 64.8 (C6); 53.0 (C1); 52.0 (C1'); 41.4 (C2'). FAB-MS (glycerol matrix): 225 (M + $H^+$).

*1-(2-Aminoethylamino)-1-deoxy-D-mannitol* (**14b**). The procedure for **14a** was followed. From 10 g (55 mmol) D-mannose (**1b**) 9.0 g (72 %) pure **14b** was obtained. $^1$H NMR (pH = 10.5): $\delta$ (ppm) 3.81 (dd, 1H, H6a, $J_{6a5}$ =2.5 Hz, $J_{6a6b}$ =-11.6 Hz); 3.75 (m, 1H, H2, $J_{21a}$ =3.7 Hz, $J_{21b}$ =8.3 Hz); 3.70 (m, 3H, H3, H4, H5); 3.61 (dd, 1H, H6b, $J_{6b5}$ =5.6 Hz); 2.90 (dd, 1H, H1a, $J_{1a1b}$ =-12.7 Hz); 2.64 (dd, 1H, H1b); 2.78-2.66 (m, 4H, H1', H2'). $^{13}$C NMR (pH = 11.4): $\delta$ (ppm) 72.9, 72.4, 70.9 (C3, C4, C5); 70.8 (C2); 52.8 (C1); 51.4 (C1'); 41.1 (C2'). FAB-MS (glycerol matrix): 225 (M + $H^+$).

*1-(2-Aminoethylamino)-1-deoxy-D-glucitol* (**14c**). The procedure for **14a** was followed. From 10 g (55 mmol) D-glucose (**1c**) 9.0 g of a mixture containing **14c** and sorbitol was obtained as a syrup. Estimated yield of 70% based on quantitative $^{13}$C NMR. $^{13}$C NMR (pH = 11.4): $\delta$ (ppm) 72.7 (broad, C3, C4, C5); 72.5 (C2); 64.4 (C6); 52.0, 51.9 (C1, C1'); 41.4 (C2').

*1-(3-Aminopropylamino)-1-deoxy-D-galactitol* (**15a**). To a mixture of 10 g (55 mmol) D-galactose (**1a**) and 20.6 g (278 mmol) DAP 1.5 g catalyst was added. Removal of the solvent and subsequent addition of MeOH to the remaining solution resulted in the precipitation of **15a**. After filtration and drying *in vacuo* 6.0 g (45%) pure **8a** was obtained. $^1$H NMR (pH = 10.4): $\delta$ (ppm) 3.97 (dd, 1H, H2, $J_{21a}$ =8.7 Hz, $J_{21b}$ =4.0 Hz, $J_{23}$ =1.4 Hz); 3.92 (m, 1H, H5, $J_{56}$ =6.6 Hz, $J_{54}$ =1.2 Hz); 3.65 (d, 2H, H6); 3.61 (dd, 1H, H4, $J_{43}$ =9.3 Hz); 3.55 (dd, 1H, H3); 2.76 (dd, 1H, H1a, $J_{1a1b}$ =-12.5 Hz); 2.67 (dd, 1H, H1b); 2.62 (m, 4H, H1', H3'); 1.61 (m, 2H, H2'). $^{13}$C NMR (pH = 11.4): $\delta$ (ppm) 72.5, 71.8, 71.1 (C5, C4, C3); 70.0 (C2); 64.8 (C6); 53.0, 47.7, 40.1 (C1, C1', C3'); 32.7 (C2'). FAB-MS (glycerol matrix): 239 (M + $H^+$).

*1-(3-Aminopropylamino)-1-deoxy-D-mannitol* (**15b**). The procedure described for **15a** was followed. From 10 g (55mmol) D-mannose (**1b**) 6.4 g (48%) pure **15b** was obtained. $^1$H NMR (pH = 10.6): $\delta$ (ppm) 3.80 (dd, 1H, H6a, $J_{6a5}$ =2.6 Hz, $J_{6a6b}$ =-11.9); 3.82-3.66 (m, 4H, H2, H3, H4, H5); 3.61 (dd, 1H, H6b, $J_{6b5}$ =5.8 Hz); 2.87 (dd, 1H, H1a, $J_{1a2}$ =3.8 Hz, $J_{1a1b}$ =-12.5 Hz); 2.63 (dd, 1H, H1b, $J_{1b2}$ = 8.1 Hz); 2.67-2.57 (m, 4H, H1', H3'); 1.66-1.54 (m, 2H, H2'). $^{13}$C NMR (pH = 11.4): $\delta$ (ppm) 73.0, 72.4, 71.0 (C3, C4, C5); 70.9 (C2); 64.8 (C6); 52.8, 47.7, 40.2 (C1, C1', C3'); 32.9 (C2'). FAB-MS (glycerol matrix): 239 (M + $H^+$).

*N,N'-ethylenedi-(1-imino-1-deoxy-D-galactitol)* (**16a**). To a mixture of 10 g (55 mmol) D-galactose (**1a**) and 3.33 g (55 mmol) EN 1.5 g catalyst was added. Recrystallization of the hydrogenated mixture from MeOH and drying *in vacuo* yielded 1.62 g (15%) pure **16a**. $^1$H NMR (pH = 10.3): $\delta$ (ppm) 3.99 (ddd, 2H, H2, $J_{21a}$ =8.8 Hz, $J_{21b}$ =4.1 Hz, $J_{23}$ =1.6 Hz); 3.92 (dt, 2H, H5, $J_{56}$ =6.0 Hz, $J_{54}$ =1.6 Hz); 3.64 (d, 4H, H6); 3.62 (dd, 2H, H4, $J_{43}$ =9.4 Hz); 3.55 (dd, 2H, H3); 2.80 (dd, 2H, H1a, $J_{1a1b}$ =-12.6 Hz); 2.68 (dd, 2H, H1b); 2.80-2.70 (m, 4H, H1'). $^{13}$C NMR (pH = 11.2): $\delta$ (ppm) 72.5, 71.8, 71.1 (C3, C4, C5); 70.0 (C2); 64.8 (C6); 53.0, 49.1 (C1, C1'). FAB-MS (glycerol matrix): 389 (M + $H^+$).

*N,N'-ethylenedi-(1-imino-1-deoxy-D-mannitol)* (**16b**). The procedure for **16a** was followed. From 10 g D-mannose (**1b**) 1.2 g (11%) pure **16b** was obtained. $^1$H NMR (pH = 10.2): $\delta$ (ppm) 3.81 (dd, 2H, H6a, $J_{6a5}$ =2.7 Hz, $J_{6a6b}$ =-11.8 Hz); 3.78-3.68 (m, 8H, H2, H3, H4, H5); 3.62 (dd, 2H, H6b, $J_{6b5}$ =5.6 Hz); 2.94 (dd, 2H, H1a, $J_{1a2}$ =3.5 Hz, $J_{1a1b}$ =-12.6 Hz); 2.85-2.75 (m, 4H, H1'); 2.68 (dd, 2H, H1b, $J_{1b2}$ =8.3 Hz). $^{13}$C NMR (pH = 11.3): $\delta$ (ppm) 72.9, 72.3, 70.9 (C3, C4, C5); 70.6 (C2); 64.8 (C6); 52.9, 48.9 (C1, C1'). FAB-MS (glycerol matrix): 389 (M + $H^+$).

*N,N'-ethylenedi-(1-imino-1-deoxy-D-glucitol)* (**16c**). The procedure for **16a** was followed. From 10 g (55

mmol) D-glucose (**1c**) 1.1 g (10%) pure **16c** was obtained. $^1$H NMR (pH = 10.3): δ (ppm) 3.87 (ddd, 2H, H2, $J_{21a}$ =3.7 Hz, $J_{21b}$ =8.5 Hz, $J_{23}$ =2.1 Hz); 3.78 (dd, 2H, H6a, $J_{6a6b}$ =-11.7 Hz, $J_{6a5}$ =3.0 Hz); 3.73 (dd, 2H, H5, $J_{56b}$ =6.2 Hz, $J_{54}$ =8.1 Hz); 3.71 (dd, 2H, H3, $J_{34}$ =2.1 Hz); 3.60 (dd, 2H, H6b); 3.59 (dd, 2H, H4); 2.76 (dd, 2H, H1a, $J_{1a1b}$ =-12.6 Hz); 2.70-2.75 (m, 4H, H1'); 2.68 (dd, 2H, H1b). $^{13}$C NMR (pH = 11.4): δ (ppm) 72.6, 72.5 (C3, C4, C5); 72.3 (C2); 52.0, 49.1 (C1, C1'). FAB-MS (glycerol matrix): 389 (M + $H^+$).

*1-Deoxy-1-(2-aminoethylamino)-D-galactitol-N-triacetate* (**17a**). In 40 ml $H_2O$ 2 g (9 mmol) **14a** and 7.45 g (54mmol) bromoacetic acid were dissolved. The pH was raised to 11 with LiOH. The reaction mixture was heated for 5 h at 90 °C. The reaction mixture was concentrated *in vacuo* and fractionated on a Dowex 50W ($H^+$) cation exchange column. A gradient was applied from 0 to 0.7 M $NH_4OH$. The fractions were concentrated, 1.74 g (43 %) pure **17a** was obtained. $^{13}$C NMR (pH = 1.5): δ (ppm) 172.3, 172.2 (-$CH_2$<u>C</u>OOH); 71.9, 71.6, 70.9 (C3, C4, C5); 67.3 (C2); 64.8 (C6); 59.6 (-$CH_2$<u>C</u>OOH); 58.9 (2 x $CH_2$<u>C</u>OOH); 58.1, 53.1, 52.8, (C1, C1', C2'). FAB-MS (glycerol matrix): 399 (M + $H^+$).

*1-Deoxy-1-(2-aminoethylamino)-D-mannitol-N-triacetate* (**17b**). The procedure described for **10a** was followed. From 2 g (**14b**) (9 mmol) 1.76 g (44%) pure **17b** was obtained. $^{13}$C NMR (pH = 1.6): δ (ppm) 176.3, 176.0 (-$CH_2$<u>C</u>OOH); 72.7, 72.4, 70.6, (C3, C4, C5); 68.1 (C2); 64.8 (C6); 59.8 (-<u>C</u>$H_2$COOH); 59.0 (-<u>C</u>$H_2$COOH); 58.2, 53.2, 52.6, (C1, C1', C2'). FAB-MS (glycerol matrix): 399 (M + $H^+$).

## ACKNOWLEDGEMENTS

This investigation was carried out with support of the Dutch National Innovation Program Carbohydrates. We are grateful to AKZO Corporate Research for their financial support and fruitful discussions. Mr. A. Sinnema is thanked for recording part of the NMR spectra, Mrs. A. H. Knol-Kalkman for measuring the FAB mass spectra, and Mr. E. Wurtz for carrying out the hydrogenation experiments. Dr. L. Maat is thanked for his contribution in naming several compounds.

## REFERENCES

1. Long, J.W.; Bollenback, G.N. *Methods in Carbohydrate Chemistry*, Vol. II; Whistler, R.L.; Wolfrom, M.L., Eds.; Academic Press, **1963**, 79-83.
2. Ling, A.R.; Nanji, D.R. *J. Chem. Soc.* **1922**, 121, 1682-1688.
3. Flint, R.B.; Salzberg, P.L. *US Pat.* 2,016,962, **1974**; *Chem. Abstr.* **1935**, 29, 8007.
4. Wayne, W.; Adkins, H. *J. Am. Chem. Soc.* **1940**, 62, 3314-3316.
5. Holly, F.W.; Peel, E.W.; Mozingo, R.; Folkers, K. *J. Am. Chem. Soc.* **1950**, 72, 5416-5418.
6. Kagan, F.; Rebenstorf, M.A.; Heinzelman, R.v. *J. Am. Chem. Soc.* **1957**, 79, 3541-3544.
7. Lemieux, R.U. *US Pat.* 2,830,983, **1958**; *Chem. Abstr.* **1958**, 52, 14668.
8. Tronchet, J.M.J.; Baehler, B.; Zumwald, J.-B. *Helv. Chim. Acta* **1977**, 60, 1932-1934.
9. Larkin, J.M.; Yeakey, E.L.; Watts, Jr. L.W. *US Pat.* 4,540,821, **1985**; *Chem. Abstr.* **1985**, 104, 110120
10. Kelkenberg, H. *Tens. Surf. Det.* **1988**, 25, 8-13.
11. Shumate, R.E.; Burdsall, D.C.; Scheibel, J.J.; Connor, D.S. *WO Pat.* 08687, **1992**; *Chem. Abstr.* **1992**, 117, 215006b.
12. Klein, J.; Behrens, W.; Kunz, M. *EP* 225,033, **1987**; *Chem. Abstr.* **1989**, 110, 95711j.

13. Christiansen-Brams, I.; Meldal, M.; Bock, K. *J. Carbohydr. Chem.* **1992**, 11, 813-835.
14. Latgé, P.; Rico, I.; Lattes, A.; Godefroy, L. *FR Pat.* 2,661,413, **1991**; *Chem. Abstr.* **1992**, 116, 194795v.
15. Koch, H.; Beck, R.; Röper, H. *Starch* **1993**, 45, 2-7.
16. Klein, J.; Kunz, M.; Kowalczyk, J. *Makromol. Chem.* **1990**, 191, 517-528.
17. Ellis, J.W.; Malehorn, S.H.; Browning, L.M.; Heischmidt, T.A. *J. Carbohydr. Chem.* **1992**, 11, 761-778.
18. Jeffrey, G.A.; Wingert, L.M. *Liq. Crystals* **1992**, 12, 179-202.
19. Schnarr, G.W.; Vyas, D.M.; Szarek, W.A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 496-502.
20. Angyal, S.J.; Le Fur, R. *Carbohydr. Res.* **1980**, 84, 201-209.
21. Hawkes, G.E.; Lewis, D. *J. Chem. Soc. Perkin Trans.* II **1984**, 2073-2078.
22. Bock, K.; Thogersen, H. *Annu. Rep. NMR Spectrosc.* **1982**, 13, 2-57.
23. Paulsen, H.; Gyorgydeak, Z.; Friedman, M. *Chem. Ber.* **1974**, 107, 1590-1613.
24. Votoček, E.; Valentin, F. *Collect Czech. Chem. Commun.* **1934**, 6, 77-96.
25. Ellis, G.P.; Honeyman, J. *Adv. Carbohydr. Chem.*, Vol. 10; Wolfrom, M.L., Ed.; Academic Press, **1955**, Chapter 2, 95-168.
26. Capon, B. *Chem. Rev.* **1969**, 69, 407-498.
27. Mitts, E.; Hixon, R.M., *J. Am. Chem. Soc.* **1944**, 66, 483-486.
28. Leal, F.; Schleicher, E. *Angew. Chem. Int. Ed. Eng.* **1990**, 29, 565-594.
29. van Haveren, J.; Lammers, H.; Peters, J.A.; Batelaan, J.G.; van Bekkum, H. *Carbohydr. Res.* **1993**, 243, 259-271.
30. de Wit, G.; de Vlieger, J.J.; Kock-van Dalen, A.C.; Heus, R.; Laroy, R.; van Hengstum, J.; Kieboom, A.P.G.; van Bekkum, H. *Carbohydr. Res.* **1981**, 91, 125-138.
31. Hancock, R.D.; Martell, A.E. *Chem. Rev.* **1989**, 89, 1875-1914.
32. Hancock, R.D. *J. Chem. Educ.* **1992**, 8, 615-621.
33. Lammers, H.; van Bekkum, H.; Peters J.A., to be published.
34. Bekendam, G. (AKZO Chemical Research Center Deventer) *personal communication.*
35. Mehltretter, C.L.; Alexander, B.H.; Rist, C.E. *Ind. Eng. Chem.* **1953**, 45, 2782-2784.

(*Received in UK* 4 *March* 1994; *revised* 12 *May* 1994; *accepted* 13 *May* 1994)