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Synthesis of Carbohydrate-Containing Dendrimers. 5. Preparation of Dendrimers Using Unprotected Carbohydrates

Narayanaswamy Jayaraman and J Fraser Stoddart[1]

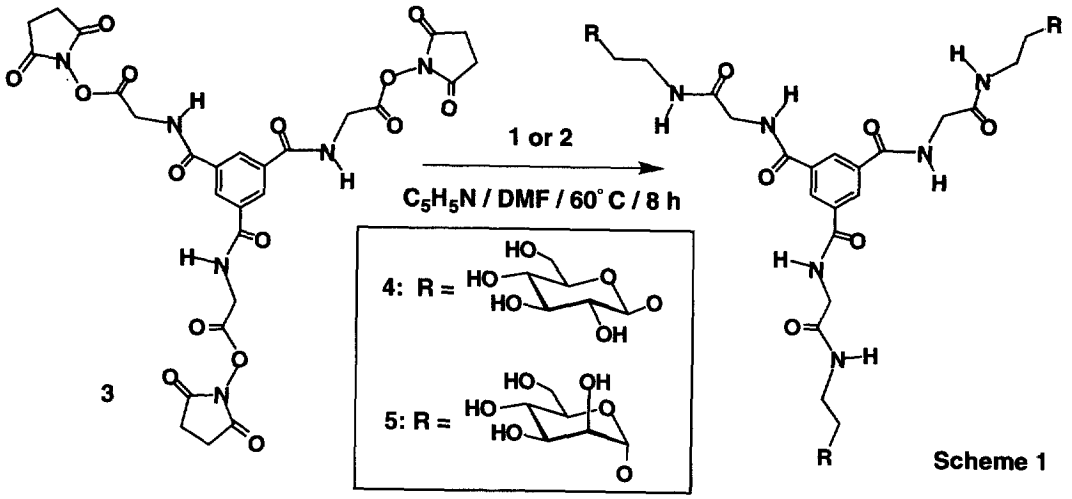
School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Abstract: Carbohydrate-containing dendrimers have been prepared using completely unprotected carbohydrates employing a convergent growth approach. The facile syntheses of lower generation dendrimers, using the amide bond forming methodology, opens up the possibility of obtaining densely-packed glycodendrimers without the need to resort to protecting group manipulations on the saccharide residues. © 1997 Elsevier Science Ltd.

In the reiterative processes that characterise the synthesis of a dendrimer, the number of surface groups increases exponentially as the dendrimer generations advance. The immediate consequences for the physical characteristics of the dendrimer is the evolution of a dendritic structure from one of an open annular shape in the 'lower generation' states to one of a densely-packed, spheroidal shape in the 'higher generation' states.[2] It is now well documented that, when the surface groups are densely packed, dendrimers become capable of acting as hosts for guests.[3]

Recently, we reported on the successful synthesis and characterisation of carbohydrate-containing dendrimers.[4] This research has provided us with a facile entry into new and novel types of dendritic neoglycoconjugate systems. The convergent synthetic approach explored in the syntheses of such dendritic macromolecules has allowed us to obtain high generation dendrimers with very precise molecular sizes and shapes, as well as with complete monodispersities. From the outset, however, we realised that the presence of protecting groups on the saccharide residues could become a limiting factor when attempting to construct a densely-packed dendrimer since the removal of the protecting groups reduces the surface densities of final free carbohydrate-containing dendrimers. In order to circumvent this anticipated limitation upon the growth of such dendrimers, we have focussed on the syntheses of carbohydrate-containing dendrimers wherein the saccharides are totally unprotected during the construction of the dendrimers. Here, we describe the syntheses of some lower generation dendrimers derived from free glucoside- and mannoside-containing dendritic wedges, employing a convergent synthetic strategy.

The feasibility of adopting particular reaction conditions for the formation of amide bonds was explored in the first instance with the model compounds – 2-amino-ethyl β-D-glucopyranoside (**1**) and 2-amino-ethyl α-D-mannopyranoside (**2**). The syntheses of the amino-tethered glycosides **1** and **2** were carried out[5,6] as follows – (i) glycosylation of carbobenzoxy (CBZ) protected 2-amino-ethanol with either benzobromo-D-glucose or -D-mannose, in the presence of $HgBr_2$ and $Hg(CN)_2$, and then (ii) removal of the *O*-benzoyl protecting groups under Zémplen conditions before (iii) the hydrogenolysis of the CBZ-group using Pd/C as a catalyst. Amide bond couplings of the amino-tethered glycosides **1** and **2** were carried out (**Scheme 1**) with a tricarboxylic acid core which was activated to its corresponding *N*-hydroxysuccinimide triester **3**. This triester was obtained by



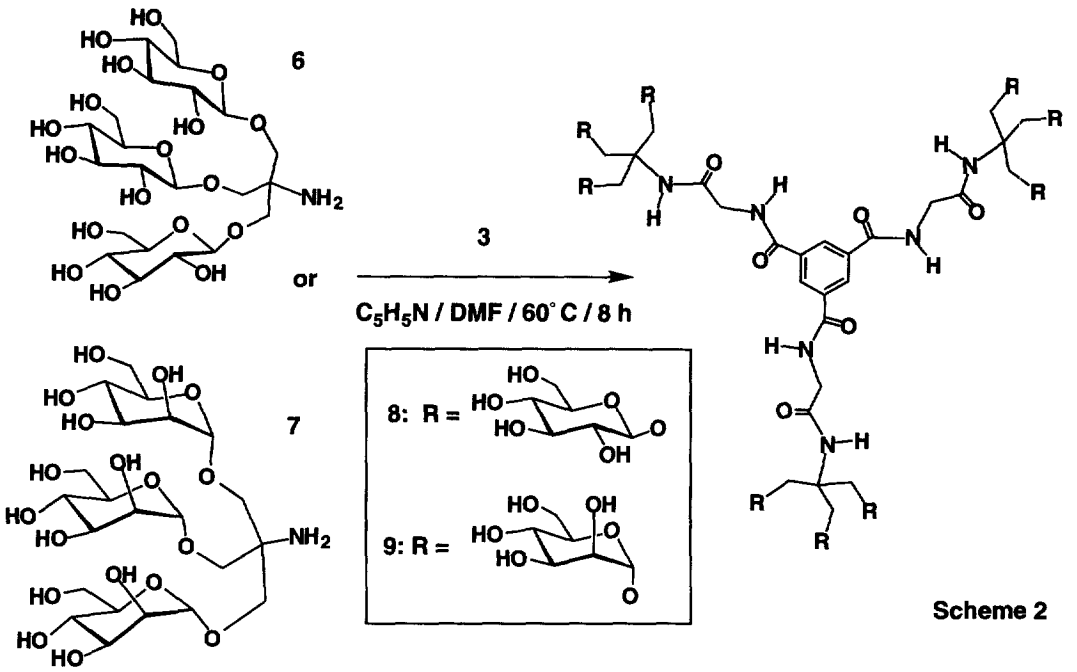
Scheme 1

the reaction of benzene-1,3,5-carbamido-*N,N,N*-tris(acetic acid)[4a] with *N*-hydroxysuccinimide in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC).[7] A typical amide bond forming reaction of **3** with the amino-tethered glycosides was carried out as follows. The reaction mixture, containing the *N*-hydroxysuccinimide triester **3** and the amine (4.5 mol equiv) in DMF/C_5H_5N (9:1), was stirred at 60°C under a nitrogen blanket for 12 h, before being cooled to room temperature. Solvents were then evaporated and the resulting residue was dissolved in the minimum amount of H_2O. The aqueous solution was extracted successively with Et_2O and EtOAc to remove the by-products, before the aqueous solution was concentrated under vacuum to obtain the desired carbohydrate-containing dendrimer, which was purified by GPC using H_2O as the eluant. Thus, the dendrimers **4** and **5**, bearing β-D-glucopyranosyl and α-D-mannopyranosyl residues at their peripheries were obtained[8] in 60 and 57% yields, respectively.

The branched dendritic glycosides, derived from tris(hydroxymethyl)amino-methane (TRIS), have been identified by us[4] previously as suitable building blocks for dendrimer construction. The TRIS-glycoside derivatives **6** and **7** were prepared following a similar protocol to that employed for the synthesis of the 2-amino-ethyl glycosides **1** and **2**, except that the glycosylations were carried out using AgO_2CCF_3 as the promoter.[9] Amide bond formation between the amino-tethered TRIS-glycosides **6** and **7** and the *N*-hydroxy-succinimide triester **3** afforded (**Scheme 2**) the glucoside and mannoside dendrimers **8** and **9**, respectively, each containing nine monosaccharide residues. The efficiency of this reaction is underlined by the formation of the dendrimers as the major products.[10]

The dendrimers were all fully characterised using the usual techniques: MALDI-TOF-MS demonstrated clearly the formation of the desired products while the ^1H and ^{13}C NMR spectra exhibited sharp and well-resolved resonances for all the required protons and carbon atoms, respectively.

The experimental results described here demonstrate that the reduced reactivities of the focal point amine functionalities in dendritic wedges, resulting from steric inhibition caused by the presence of protecting groups on saccharides, can be circumvented. The absence of any protecting groups on the peripheral glycoside units using this synthetic methodology[11] should be of considerable use in the preparation of large densely-packed carbohydrate-containing dendrimers.



Scheme 2

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References and Footnotes

1. Address for correspondence after October 1, 1997: Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90095-1569, USA.
2. For authoritative reviews and a monograph on dendrimers, see: a) D.A. Tomalia, H.D. Durst, in *Top. Curr. Chem.* **1993**, *165*, 193-313; b) J.M.J. Fréchet, *Science*, **1994**, *263*, 1710-1715; c) G.R. Newkome, C.N. Moorefield, F. Vögtle, *Dendritic Molecules. Concepts, Syntheses, Perspectives*, VCH, Weinheim, **1996**.
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5. Preparation of **1** and **2**: 2-(*N*-Benzyloxycarbonyl amino)ethanol was glycosylated either with benzobromo-D-glucose (in the case of **1**) or with benzobromo-D-mannose (in the case of **2**) in CH_2Cl_2 in the presence of $HgBr_2$ and $Hg(CN)_2$ for ~24 h. The reaction mixture was filtered, washed with 1 M aqueous KI solution, saturated aqueous $NaHCO_3$ solution, and finally with H_2O. The organic phase was dried ($MgSO_4$) and the solvents were removed *in vacuo* to obtain (>90%) the protected glycosides. The *O*-benzoyl protecting groups were removed first of all using 0.1M NaOMe/MeOH solution for 12 h, followed by neutralisation of the reaction mixture with Amberlite (H^+ form) ion-exchange resin. Solvents were then removed and the resulting residue was dissolved in a minimum amount of H_2O and extracted with Et_2O and the H_2O layer was concentrated to dryness. The CBZ-group was then removed by hydrogenolysis over 10% Pd-C in EtOH/H_2O (1:1) for ~15 h to obtain the free amino group tethered glycosides **1** and **2** as glassy solids (overall yields >70%).
6. Selected spectroscopic data for **1**: ^{13}C NMR (75.5 MHz, 304 K, D_2O): δ 42.5 (CH_2NH_2), 63.3 (C-6), 71.9 (O-CH_2), 72.3 (C-4), 75.8 (C-2), 78.3 (C-3), 78.6 (C-5), and 105.0 (C-1). For **2**: ^{13}C NMR (75.5 MHz, 304 K, D_2O): δ 42.3 (CH_2NH_2), 63.6 (C-6), 69.1 (O-CH_2), 69.4 (C-4), 72.6 (C-2), 73.2 (C-3), 75.5 (C-5), and 102.6 (C-1).
7. The reaction mixture of benzene-1,3,5-carbamido-*N,N,N*-tris(acetic acid) [4a], *N*-hydroxysuccinimide (4.5 molar equivalents) and EDC (4.5 molar equivalents) in CH_2Cl_2-DMF (9:1) was stirred at room temperature for 15 h. The solvents were evaporated and the resulting residue was triturated with Et_2O and CH_2Cl_2, before being dried thoroughly to obtain the *N*-hydroxysuccinimide triester **3** in 74% yield.
8. Selected spectroscopic data for **4**: ^{13}C NMR (125.5 MHz, 304 K, D_2O): δ 41.9 (CH_2NH), 45.8 ($COCH_2NH$), 63.3 (C-6), 70.9 (O-CH_2), 72.2 (C-4), 75.7 (C-2), 78.2 (C-3), 78.5 (C-5), 104.9 (C-1), 132.2, 136.6 (aromatic), and 171.4, 174.0 (CONH). For **5**: ^{13}C NMR (75.5 MHz, 304 K, D_2O): δ 41.7 (CH_2NH), 45.9 ($COCH_2NH$), 63.6 (C-6), 68.5 (O-CH_2), 69.4 (C-4), 72.7 (C-2), 73.1 (C-3), 75.5 (C-5), 102.3 (C-1), 132.3, 136.7 (aromatic), and 171.4, 174.1 (CONH).
9. The synthesis of TRIS-mannoside derivative **7** was carried out using a procedure analogous to that described for the corresponding TRIS-glucoside derivative **6**. See ref. [4a]. Selected spectroscopic data for **7**: ^{13}C NMR (75.5 MHz, D_2O): δ 56.5 (C(quat)), 63.5 (C-6), 69.5 (C-4), 71.5 (CH_2C(quat)), 72.5 (C-2), 73.2 (C-3), 75.5 (C-5), and 102.9 (C-1).
10. The spectroscopic data for the glucoside dendrimer **8** is in agreement with that for the same compound prepared by removing the protecting groups in the final step of a synthesis involving protecting groups. See ref. [4a]. Selected spectroscopic data for **9**: ^{13}C NMR (75.5 MHz, D_2O): δ 42.4 ($COCH_2NH$), 56.5 (C(quat)), 63.6 (C-6), 68.6 (CH_2C(quat)), 69.5 (C-4), 72.6 (C-2), 73.3 (C-3), 75.7 (C-5), 103.0 (C-1), 133.5, 138.0 (aromatic), and 170.2, 174.1 (CONH).
11. Recently, the use of unprotected carbohydrates to modify pre-formed dendrimer (PAMAM) structures, with thiourea bridges, has been reported. See: C. Kieburg, T.K. Lindhorst, *Tetrahedron Lett.* **1997**, *38*, 3885–3888.

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