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Chemical Modification of Chitosan. 10.[1] Synthesis of Dendronized Chitosan−Sialic Acid Hybrid Using Convergent Grafting of Preassembled Dendrons Built on Gallic Acid and Tri(ethylene glycol) Backbone

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ABSTRACT: Sialic acid dendrons bearing a focal aldehyde end group were synthesized by a reiterative amide bond strategy. Polyamine-ending trivalent ($G = 1$) and nonavalent ($G = 2$) dendrons having gallic acid as branching unit and tri(ethylene glycol) as spacer arm were prepared and initially attached to a sialic acid *p*-phenylisothiocyanate derivative. The focal aldehyde sialodendrons were then convergently grafted onto the polysaccharide chitosan backbone by reductive amination in 76−80% yields. The degrees of substitution (DS) of the sialodendrimer in the hybrids were 0.13 ($G = 1$) and 0.06 ($G = 2$), which indicates that 87% and 40% of the sialodendrons were attached to the primary amino groups of chitosan. The water solubility of these novel hybrids was further improved by N-succinylation of the remaining amine functionality.

Introduction

Chitin and the deacetylated form, chitosan, are attractive linear amino polysaccharides found in the shell of crustaceans. These abundant biopolymers, composed mainly of poly(β-1,4)-2-acetamido/2-amino-2-deoxy-D-glucopyranose repeating units, constitute valuable biomass resources useful in the preparation of functional biomaterials.[2] Since chitosan itself is nontoxic and biodegradable[2] and shows widespread biological activities,[3] it is an appealing bioactive polymer for further development. Unfortunately, its poor solubility in both organic solvents and aqueous solutions has hampered its widespread development. Recently, this problem has been partly overcome by using counteranions of organic acids.[1b,e]

Alternatively, glycodendrimers[4] are monodispersed and chemically well-defined semi-macromolecules bearing exposed carbohydrate moieties that are finding useful applications as viral and pathogenic cell adhesion inhibitors.[5] Increasing scientific efforts have gone into the design and synthesis of dendrimers.[6] Dendrimers are attractive molecules owing to their multifunctional properties and are useful as scaffold for pharmacophores, neoglycoconjugates, probes, catalysts, and so on.[6] Dendronized polymers, on the other hand, are also attractive because of their rodlike conformation and nanostructures.[7] Although several investigations have been published toward the synthesis of dendronized polymers,[7] there is only scarce reports on dendronized polysaccharide, especially related to chitosan backbone.[1c] We report herein the preparation of chitosan−sialodendrimer hybrids using gallic acid as focal point and tri(ethylene glycol) as spacer arm. The present report complements our previous finding[1c] using poly(amidoamine) (PAMAM) dendrons as scaffold that lacked the capacity for high incorporation of preformed dendrons on chitosan.

Experimental Section

Materials. Chitosan (Flonac C, NHAc = 0.2, DP = 140, FW of unit = 169) was purchased from Kyowa Tecnos Co., Japan. Dialysis membranes (MW 1200 and MW 12 000 cutoff) were purchased from Sigma Co. Aminoacetaldehyde diethyl acetal (**2**) and other reagents were from Aldrich Co. and used without further purification.

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz AMX NMR spectrometer. Proton chemical shifts (δ) are given relative to internal $CHCl_3$ for $CDCl_3$, DMSO for DMSO-d_6, and 3-(trimethylsilyl)propionic-*2,2,3,3*-d_4 acid sodium salt (water-soluble “TMS”, TMSP) for D_2O or 0.5 M DCl in D_2O solution. Carbon chemical shifts are also given relative to $CDCl_3$, DMSO, or TMSP. The degree of polymerization (DP) of original chitosan was determined by GPC using pullulan as standard.

Preparation of Dendron Moieties. *3,4,5-Tris(8-azido-3,6-dioxaoctyloxy)benzamidoacetaldehyde Diethyl Acetal (**3**).* 3,4,5-Tris(8-azido-3,6-dioxaoctyloxy)benzoic acid (**1**) was prepared according to previous literature.[8] To a solution of **1** (0.5 mmol) in CH_2Cl_2 (10 mL) was added diisopropylethylamine (DIPEA: 1.5 mmol), aminoacetaldehyde diethyl acetal (**2**) (0.75 mmol), and 1-hydroxybenzotriazole hydrate (HOBt: 0.75 mmol). After stirring at room temperature for 5 min under N_2, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC: 0.75 mmol) was added. After stirring at room temperature for 5 h, the mixture was evaporated, and the resulting residue was purified by silica gel column chromatography using hexane/ethyl acetate (1/1) as eluent to afford **3** (0.39 mmol) in 77% yield. Compound **3:** ^{1}H NMR ($CDCl_3$) δ (ppm) 1.19 (t, $J = 7.1$ Hz, 6 H, CH_3 of OEt), 3.34 (t, 6 H, CH_2N_3), 3.50−3.85 (m, 30 H, OCH_2 and $CONHCH_2$), 4.17 (t, $J = 4.8$ Hz, 6 H, CH_2OAr), 4.57 (t, $J = 5.3$ Hz, 1 H, CH of acetal), 6.35 (t, $J = 5.8$ Hz, 1 H, CONH), 7.00 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm) 14.4 (CH_3 of OEt), 42.5 (CONH−CH_2), 50.6 (CH_2N_3), 63.0 (CH_2 of OEt), 69.1−72.4 (CH_2O), 100.8 (CH of acetal), 107.1, 129.6, 141.5, and 152.5 (Ar), 166.9 (NHCO). FAB-MS (pos): calcd for $C_{31}H_{52}N_{10}O_{12}$ 756, found 757.4 (M + 1, 4.0% base peak).

*3,4,5-Tris(8-amino-3,6-dioxaoctyloxy)benzamidoacetaldehyde Diethyl Acetal (**4**).* To a solution of **3** (0.21 mmol) in EtOH (10 mL) was added 50 mg of 10% palladium on carbon.

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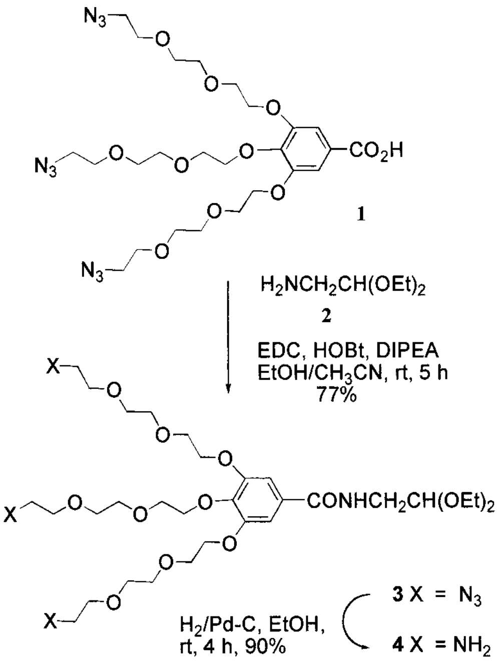
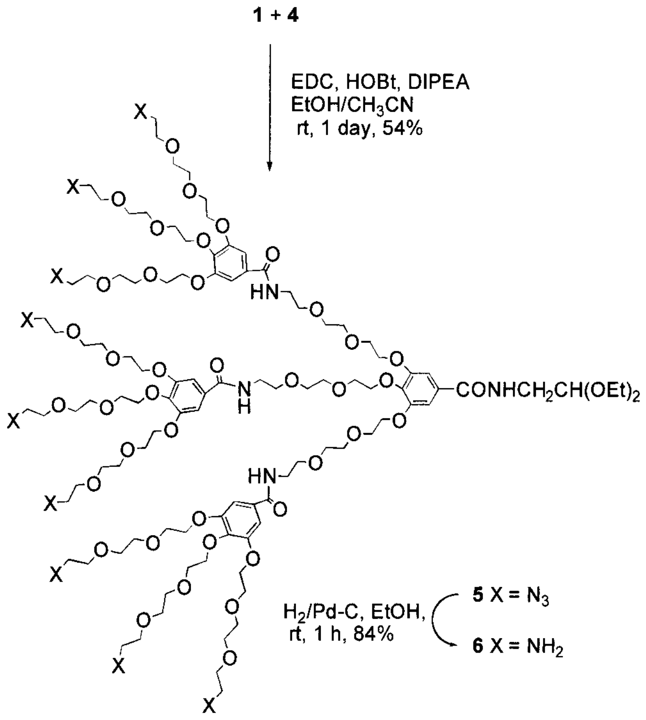
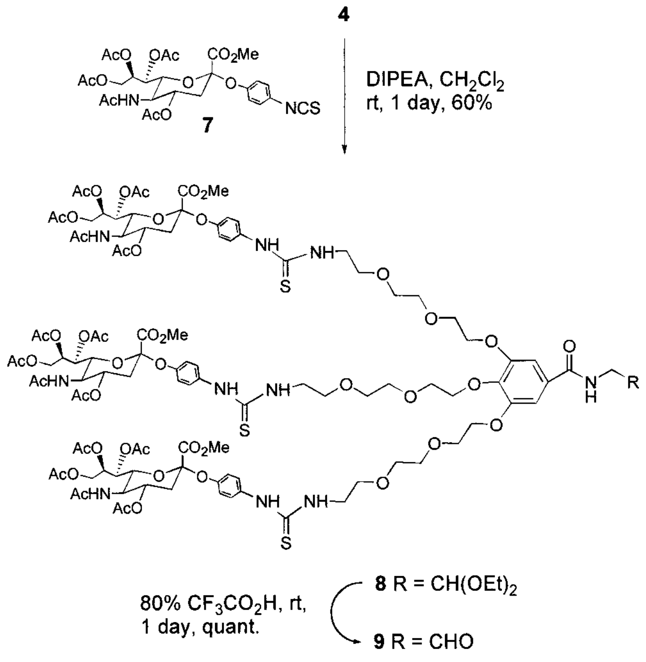
Scheme 1



Scheme 2



Scheme 3



Hydrogen was constantly bubbled through the solution at room temperature. After 4 h, the catalyst was removed by filtration, and the filtrate was evaporated under vacuum to dryness. The crude product **4** (0.19 mmol, 90% yield) was used in the next step without further purification. Compound **4**: ^{1}H NMR ($CDCl_3$) δ 1.14 (m, 6 H, CH_3 of OEt), 2.69 (br, 6 H, NH_2), 2.80 (t, J = 4.6 Hz, 6 H, CH_2NH$_2$), 3.45−3.80 (m, 30 H, OCH_2 and CONHCH_2), 4.16 (t, J = 5.1 Hz, 6 H, CH_2OAr), 4.59 (t, J = 5.3 Hz, 1 H, CH of acetal), 7.06 (s, 2 H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.7 (CH$_3$ of OEt), 41.3 (CH$_2$NH$_2$), 42.6 (CONH−CH$_2$), 62.7 (CH$_2$ of OEt), 69.0−72.6 (CH$_2$O), 100.7 (CH of acetal), 107.4, 129.9, 140.9, and 152.3 (Ar), 166.3 (NHCO). FAB-MS (pos): calcd for $C_{31}H_{58}N_4O_{12}$ 678, found 679.2 (M + 1, 1.0% base peak).

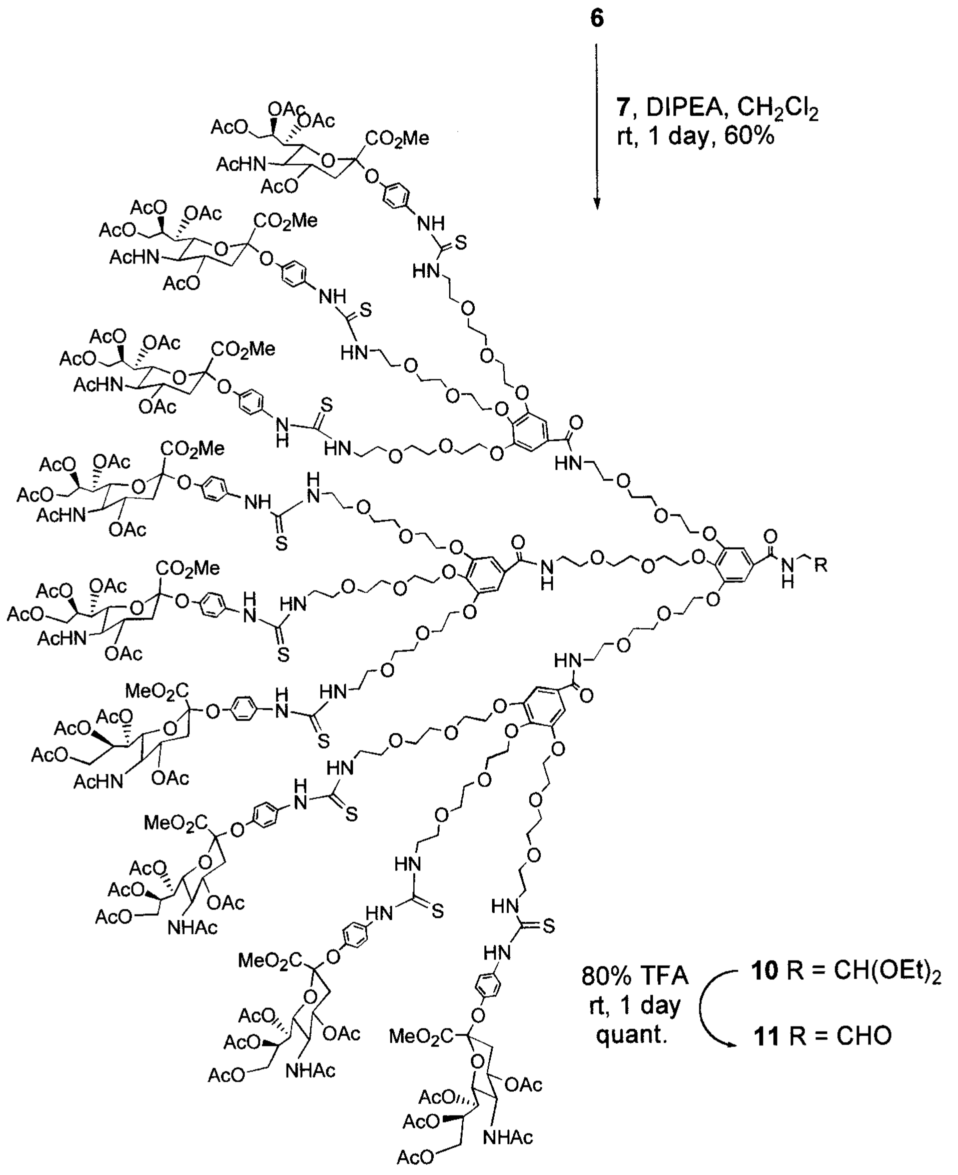
*3,4,5-Tris{8-[3,4,5-tri-(8-azido-3,6-dioxaoctyloxy)benzamido]-3,6-dioxaoctyloxy}benzamidoacetaldehyde Diethyl Acetal (***5***).* To a solution of amine **4** (0.36 mmol) in EtOH/CH_3CN (1/1: 20 mL) was added DIPEA (1.8 mmol), **1** (1.3 mmol: 1.2 equiv/NH$_2$), and HOBt (1.8 mmol). After stirring at room temperature for 5 min under N_2, EDC (1.8 mmol) was added. After stirring at room temperature for 1 day, the mixture was evaporated, and the crude product was purified by silica gel column chromatography using hexane/ethyl acetate (1/1) to afford **5** (0.194 mmol) in 54% yield. Data for **5**: ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.1 Hz, 6 H, CH_3 of OEt), 3.34 (t, 18 H, CH_2N$_3$), 3.50−3.85 (m, OCH_2 and CONHCH_2), 4.17 and 4.30 (m, 24 H, CH_2OAr), 7.27 (m, 8 H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH$_3$ of OEt), 50.6 (CH$_2$N$_3$), 61.6 (CH$_2$ of OEt), 68.3−72.7 (CH$_2$), 106.0, 109.0, 110.8, 125.3, 143.7, and 152.3 (Ar), 165.7 and 166.0 (NHCO).

Hydrogenation of **5** was performed under the same conditions described above for **4** and gave **6** in 84% yield. Data for **6**: ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6 H, CH_3 of OEt), 2.50 (br, 18 H, NH_2), 2.80 (m, 18 H, CH_2NH$_2$), 3.40−3.85 (m, OCH_2 and CONHCH_2), 4.15 and 4.30 (m, 24 H, CH_2OAr), 7.20−7.25 (m, 8 H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH$_3$ of OEt), 41.5 (CH$_2$-NH$_2$), 41.6 (CONH−CH$_2$), 61.4 (CH$_2$ of OEt), 67.7−73.3 (CH$_2$), 104.02, 108.7, 111.4, 125.4, 152.0, and 152.5 (Ar), 165.8, 166.0, and 166.6 (NHCO).

Preparation of Sialodendrimer. *p*-Isothiocyanatophenyl α-sialoside (**7**) was prepared from acetochloroneuraminic acid and *p*-nitrophenol according to published data.[9] To a solution of amine **4** (0.3 mmol) in CH_2Cl_2 (10 mL) was added DIPEA (1.2 mmol) and **7** (1.0 mmol: 1.1 equiv/NH$_2$). After stirring at room temperature for 1 day, the mixture was evaporated to dryness. The residue was dissolved in MeOH (5 mL) and the mixture dialyzed against MeOH/H_2O (2/1) with dialysis membrane (MW 1200 cutoff) for 2 days. The resulting solution was evaporated to dryness to give trivalent α-sialodendrimer acetal **8** (G = 1) in 60% yield.

Data for **8**: ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6 H, CH_3 of OEt), 1.8−2.1 (m, 45 H, OAc and NHAc of Neu5Ac), 2.75 (br, 3 H, H-3ax of Neu5Ac), 3.40−3.80 (m, OCH_2, CONHCH_2, and CO$_2$-Me of Neu5Ac), 4.10 (m, 6 H, CH_2OAr), 4.20−5.30 (H-4, 7, 8, 9 of Neu5Ac), 7.00−7.50 (m, 14 H, Ar), 7.80 (br, NHC(S)NHAr), 9.80 (brs, NHC(S)NHAr). ^{13}C NMR ($CDCl_3$) δ 15.3 (CH$_3$ of OEt), 20.7 and 20.9 (OAc), 23.0 (NHAc), 39.0 (C-3 of Neu5Ac), 41.6 (CONH-CH$_2$), 44.1 (CH$_2$−NHCS), 47.8 (C-5 of Neu5Ac), 53.1 (CO$_2$$Me$), 61.0 ($CH_2$ of OEt), 62.2 (C-9 of Neu5Ac), 66.8−73.5 (CH$_2$ and C-4, 6, 8 of Neu5Ac), 99.4 (CH of acetal), 106.0, 123.9, 137.6, and 151.8 (Ar), 167.1−171.9 (NHCO), 181.5 (C=S).

Scheme 4



Acetal **8** (0.13 mmol) was dissolved in aqueous 80% CF_3CO_2H (TFA, 3 mL). After stirring at room temperature for 1 day, the solution was evaporated to dryness to afford aldehyde **9** in quantitative yield. Data for **9:** ^{1}H NMR (DMSO-d_6) δ 1.8–2.0 (m, 45 H, OAc and NHAc of Neu5Ac), 2.60 (br, 3 H, H-3ax of Neu5Ac), 3.40–4.30 (m, OCH_2 and Neu5Ac), 7.00–7.60 (m, 14 H, Ar), 7.80 (br, N*H*C(S)NHAr), 9.80 (brs, NHC(S)N*H*Ar).

The nonavalent α-sialodendrimer acetal **10** ($G = 2$) was obtained 60% yield, and aldehyde **11** ($G = 2$) was also obtained quantitatively in a similar manner as above. Data for **10:** ^{1}H NMR (DMSO-d_6) δ 1.30 (m, 6 H, CH_3 of OEt), 1.7–2.05 (m, 45 H, OAc and NHAc of Neu5Ac), 2.57 (br, 3 H, H-3ax of Neu5Ac), 3.20–4.00 (m, OCH_2, $CONHCH_2$, and CO_2Me of Neu5Ac), 4.10 (m, 6 H, CH_2OAr), 4.20–5.20 (H-4, 7, 8, 9 of Neu5Ac), 7.00–7.60 (m, 14 H, Ar), 7.90 (br, N*H*C(S)NHAr), 9.80 (brs, NHC(S)N*H*Ar). ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3 of OEt), 20.2–20.8 (OAc), 22.3, and 22.6 (NHAc), 43.7 (CH_2–NHCS), 50.0 (C-5 of Neu5Ac), 53.0 (CO_2Me), 61.0 (CH_2 of OEt), 62.2 (C-9 of Neu5Ac), 66.8–73.5 (CH_2 and C-4, 6, 8 of Neu5Ac), 98.0 (CH of acetal), 108.0, 124.0, 137.5, and 151.8 (Ar), 168.0–171.7 (NH*C*O), 180.2 (C=S). Data for **11:** ^{1}H NMR (DMSO-d_6) δ 1.8–2.0 (m, 45 H, OAc and NHAc of Neu5Ac), 2.60 (br, 3 H, H-3ax of Neu5Ac), 3.40–4.60 (m, OCH_2 and Neu5Ac), 7.00–7.60 (m, 14 H, Ar), 7.80 (br, N*H*C(S)NHAr), 9.80 (brs, NHC(S)N*H*Ar).

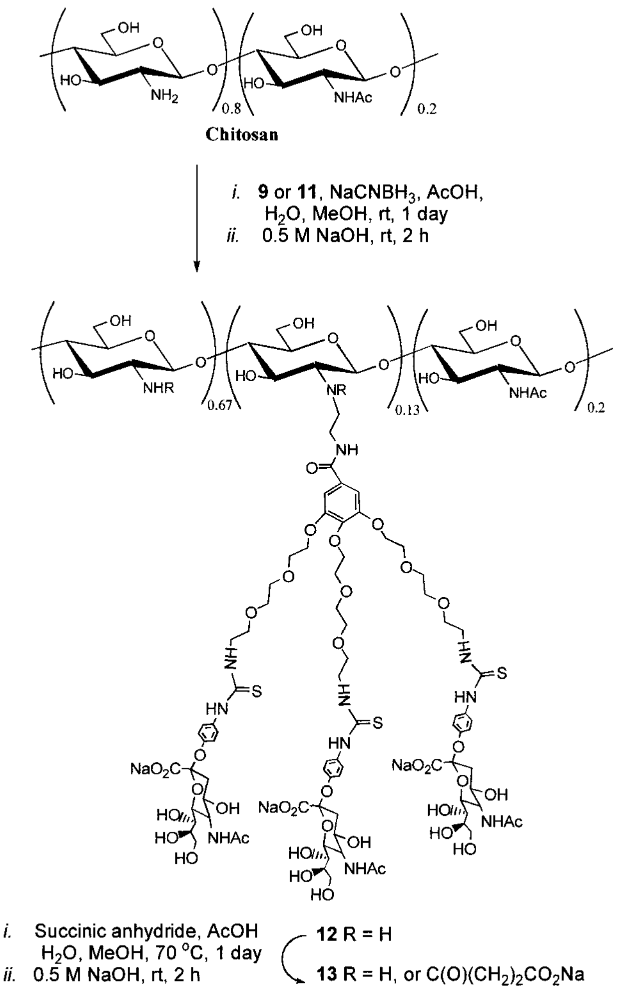
Preparation of Sialodendrimer–Chitosan Hybrids. A typical procedure is as follows: To a solution of chitosan (200 mg: 1.18 mmol of hexosamine residue) in water (10 mL) and MeOH (30 mL) containing AcOH (30 mg) was added aldehyde **9** (0.18 mmol, 0.15 equiv/hexosamine residue) in MeOH (10 mL). After stirring at room temperature for 1 h, $NaCNBH_3$ (2.4 mmol) was added, and the solution was continuously stirred at room temperature for 1 day. The reaction mixture was evaporated to dryness and immediately treated with 0.5 M NaOH at room temperature for 2 h. Dialysis against distilled water and lyophilization gave trivalent chitosan–sialodendrimer hybrid ($G = 1$) **12** (370 mg, 76%). Data for **12** (DS = 0.13): ^{1}H NMR (0.5 M DCl/D_2O) δ 1.95–2.12 (m, 2.16 H, NHAc and H-3ax of Neu5Ac), 2.88 (br, 0.39 H, H-3eq of Neu5Ac), 3.26 (brs, 0.67 H, H-2 of unsubstituted GlcN), 3.4–5.0 (m, CH_2 of dendrimer, *C*H and CH_2 of chitosan and Neu5Ac backbone), 7.30–7.60 (m, 1.82 H, Ar). ^{13}C NMR (0.5 M DCl/D_2O) δ 25.0 (NHAc), 43.6 (C-3 of Neu5Ac), 58.7 (C-5 of Neu5Ac and C-2 of chitosan), 62.9 (C-6 of chitosan), 65.5 (C-9 of Neu5Ac), 71.0–74.8 (CH_2 of dendrimer, C-4, 6, 7, 8 of Neu5Ac and C-3 of chitosan), 77.6 (C-5 of chitosan), 79.4 (C-4 of chitosan), 100.3 (C-1 of chitosan), 104.1 (C-2 of Neu5Ac), 127.7, 140.3, 140.7, and 154.7 (Ar), 174.1–178.1 (C=O).

Nonavalent chitosan–sialodendrimer hybrid ($G = 2$) **14** was also obtained in a similar manner as above (80%). Data for **14** (DS = 0.06): ^{1}H NMR (0.5 M DCl/D_2O) δ 1.94 (br, 0.54 H, H-3ax of Neu5Ac), 2.00–2.12 (m, 2.22 H, NHAc), 2.88 (br, 0.54 H, H-3eq of Neu5Ac), 3.26 (brs, 0.74 H, H-2 of unsubstituted

GlcN), 3.4−5.0 (m, CH_2 of dendrimer, CH and CH_2 of chitosan and Neu5Ac backbone), 7.00−7.60 (m, 2.64 H, Ar). ^{13}C NMR (0.5 M DCl/D_2O) δ 25.0 (NHAc of chitosan and Neu5Ac), 42.5 (C-3 of Neu5Ac), 54.6 (C-5 of Neu5Ac), 58.8 (C-2 of chitosan), 63.0 (C-6 of chitosan), 65.6 (C-9 of Neu5Ac), 70.8−74.7 (CH_2 of dendrimer, C-4, 6, 7, 8 of Neu5Ac and C-3 of chitosan), 77.8 (C-5 of chitosan), 79.5 (C-4 of chitosan), 100.4 (C-1 of chitosan), 104.3 (C-2 of Neu5Ac), 127.9, 140.3, and 154.7 (Ar), 174.2−178.0 ($C{=}O$). The DS of sialodendrimer was estimated by ^{1}H NMR from the peak ratio at δ 3.26 (H-2 of unsubstituted GlcN) and 7.3−7.6 (Ar). The DS estimated from the ratio at δ 2.88 (H-3eq of Neu5Ac) and 3.26 (H-2) also confirmed the result.

N-Succinylation of primary amino groups in hybrids (**12, 14**) was performed according to the previous literature.[1a,d,10] Hybrid (**14**: 140 mg) was dispersed in H_2O (20 mL) and MeOH (60 mL) containing AcOH (100 mg). Succinic anhydride (3.0 mmol) was added in excess and stirred at 70 °C. After 1 day, the mixture was concentrated to ca. 10 mL, 1.0 M NaOH (10 mL) was then added, and the mixture (in 0.5 M NaOH) was stirred at room temperature. After 2 h, the mixture was dialyzed (H_2O) for 2 days and lyophilized to afford water-soluble N-succinylated hybrid (**15**: 140 mg) in 90% yield. Data for **15** (DS of dendrimer = 0.06, DS of succinyl group = 0.60): ^{1}H NMR (D_2O) δ 1.89 (brt, J = 11.7 Hz, 0.54 H, H-3ax of Neu5Ac), 2.10 (s, 1.62 H, NHAc of Neu5Ac), 2.13 (s, 0.60 H, NHAc), 2.54 (br, 1.20 H, NHC(O)−CH_2 of *N*-succinyl group), 2.62 (br, 1.20 H, CH_2−CO_2Na of *N*-succinyl), 2.93 (H-3eq of Neu5Ac), 3.4−4.6 (m, CH_2 of dendrimer, CH and CH_2 of chitosan and Neu5Ac backbone), 7.00−7.60 (m, 2.64 H, Ar). ^{13}C NMR (D_2O) δ 25.0 (NHAc of Neu5Ac), 25.1 (NHAc of chitosan), 35.5 and 35.8 (CH_2 of succinyl), 43.8 (C-3 of Neu5Ac), 54.6 (C-5 of Neu5Ac), 58.1−59.1 (C-2 of chitosan), 63.1−63.4 (C-6 of chitosan), 65.5 (C-9 of Neu5Ac), 71.2−75.1 (CH_2 of dendrimer, C-4, 6, 7, 8 of Neu5Ac and C-3 of chitosan), 77.7 (C-5 of chitosan), 80.6 (C-4 of chitosan), 100.4 (C-1 of chitosan), 104.3 (C-2 of Neu5Ac), 126.2, 127.6, 139.4, and 154.1 (Ar), 176.2−179.2 (NH*C*O), 183.9 (CO_2Na). The DS of succinyl group was estimated by ^{1}H NMR from the peak ratio at δ 1.89 (H-3ax of Neu5Ac: 0.54 H) and at δ 2.54−2.62 (CH_2 of *N*-succinyl group). Although a part of water-insoluble materials was found in N-succinylated hybrid **13** (90%), the corresponding signals of *N*-succinyl group were observed in ^{1}H NMR (D_2O) at δ 2.54 (br, NHC(O)−CH_2) and 2.62 (br, CH_2−CO_2Na).

Scheme 5

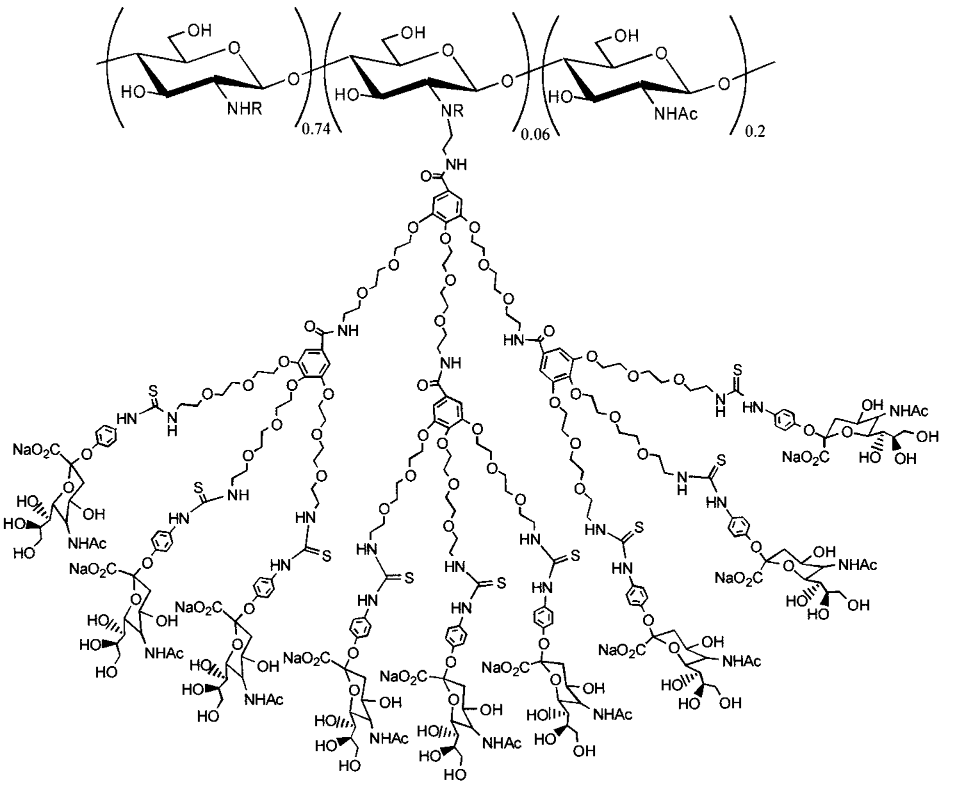


Results and Discussion

3,4,5-Trihydroxybenzoic acid (gallic acid)-based sialodendrons were synthesized using commercially available tri(ethylene glycol) as a spacer arm. The latter was chosen to ensure advantageous water solubility of the resulting hybrid and to counteract the hydrophobic effect of the aromatic gallic acid used as focal backbone. As shown in Scheme 1, the terminal carboxyl group of known precursor **1**[8] was modified into focal acetal-protected **3** by simple coupling with commercially available aminoacetaldehyde diethyl acetal (**2**) in good yield (77%) using carbodiimide (EDC) and hydroxybenzotriazole, followed by hydrogenation of the azide groups to afford trivalent amine **4** in 90% yield. To build up the next generation of dendron backbone (Scheme 2), the coupling of **4** with 3.6 equiv (1.2 equiv/NH_2) of acid **1** and hydrogenation sequence were carried out as described above for **3** to give a nonavalent amine **6** in moderate yields (**5**: 54%; **6**: 84%). Trivalent sialodendrimer acetal (**8**) was prepared with amine **4** and peracetylated *p*-isocyanatophenyl α-sialoside (**7**) (3.3 equiv, 1.1 equiv/ NH_2) at room temperature for 1 day (Scheme 3). Although the purification of **8** (FW = 2451) by silica gel column was difficult owing to its high molecular weight, crude **8** was successfully separated from the remaining sialoside **7** (FW = 627) by dialysis (MW 1200 cutoff)[9] with a mixed solvent of MeOH/H_2O (2/1) and gave pure **8** in 60% yield. The hydrolysis of acetal **8** was carried out with aqueous 80% CF_3CO_2H at room temperature for 1 day to provide aldehyde **9**.[1c] Noteworthy is the fact that the O-sialoside linkage has resisted the hydrolysis step owing to the presence of the ester protecting groups which confer higher stability to the molecule. As shown in Scheme 4, the protected nonavalent sialodendron acetal **10** (FW = 7956) was also successfully prepared and purified in 60% yield and provided aldehyde **11** under the same trifluoroacetolysis conditions (80%). The extent of coupling could be readily established using a negative ninhydrin test and the exact integration of NMR signals.

Scheme 5 shows the efficient reductive amination of trivalent sialodendrimer aldehyde **9** and chitosan with $NaCNBH_3$ according to the previous literature.[1a,c,d] The aldehyde **9** (0.15 equiv/hexosamine residue) was successfully attached to the chitosan backbone and gave trivalent chitosan−sialodendrimer hybrid (G = 1) **12** in 76% yield. The degree of substitution (DS) of hybrid **12** was shown to be 0.13 by NMR, which indicates that 87% of aldehyde **9** reacted to the primary amino group of chitosan. The nonavalent chitosan−sialodendrimer hybrid (G = 2, Scheme 6) **14** was also successfully prepared with aldehyde **11** (0.15 equiv) in 80% yield. The DS of hybrid (G = 2) was 0.06, and only 40% of aldehyde **11** could be attached to chitosan. The lower reactivity in G = 2 would be due to the steric hindrance of the higher molecular weight aldehyde **11** (MW = 7866), compared with aldehyde **9** (MW = 2361). Both hybrids **12** and **14**, obtained after protecting group hydrolysis (0.5 M NaOH,

Scheme 6



i. Succinic anhydride, AcOH H_2O, MeOH, 70 °C, 1 day
ii. 0.5 M NaOH, rt, 2 h

14 R = H
15 R = H, or $C(O)(CH_2)_2CO_2Na$

rt, 2 h), were only slightly soluble in neutral water and thus would not be useful in biological evaluation. To further improve their water solubility, the remaining unmodified amino groups of the chitosan backbone were succinylated with excess succinic anhydride (i: AcOH, H_2O, MeOH, 70 °C, 1 day; ii: 0.5 M NaOH, rt, 2 h, then dialyzed and lyophilized) to give freely water-soluble N-succinylated hybrids **13** and **15** in 90% yields.

In conclusion, water-soluble dendronized chitosan–sialic acid hybrids were successfully prepared using gallic acid as focal point and tri(ethylene glycol) as spacer arm. Further biological evaluation of these promising hybrids is being investigated toward the inhibition of viral pathogens including the flu virus.[5]

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References and Notes

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