Communications to the Editor

Divergent/Convergent Joint Approach with a Half-Protected Initiator Core To Synthesize Surface-Block Dendrimers

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This paper describes a novel methodology on macromolecular design of block-type dendrimers having a well-defined structure by a divergent/convergent joint approach. The key to block structures is a new method of postremovable half-protection of an initiator core. A *Sugar Ball*[1] family of amphiphilic AB-type surface-block dendrimers was synthesized by using hemispherical building blocks with protected focal functionality.

Block copolymers are, needless to say, one of the most important categories of macromolecules in a variety of aspects such as polymer synthesis, physical property, and applications as functional materials.[2] Although a number of studies related to dendrimers have appeared,[3] few articles on block-type dendrimers have been reported until now.[3,4] The synthetic procedure of block dendrimers has been almost limited in the convergent method.[5] Considering future development of dendrimer-based smart materials, versatile block dendrimer architecture should have significant meaning. Therefore, in this study, we offer the following methodology to elaborate a surface-block dendrimer. Generally, the method is represented as the sequence (a) hemispherical block construction by a divergent-growth procedure with a half-protected initiator core, (b) dual chemical modification of terminal functional groups, (c) deprotection of center cores, and (d) coupling of two hemispherical blocks at their reactive cores in a convergent way.

This divergent/convergent joint approach was actually performed in order to create Sugar Ball derivatives having a surface-block structure. We have recently reported the synthesis of globular artificial glycoconjugate Sugar Balls under a new concept of space regulation of sugar residues,[1] which possess molecular information and cell recognition function.[6] The molecular recognition ability of Sugar Balls has been successfully demonstrated. In the present AB-type block dendrimer design, one block is used as a cell recognition marker, while the other block will be utilized for additional applications.

A novel carbohydrate-based AB-type surface-block dendrimer **9** having an amphiphilic structure was synthesized according to Scheme 1. The surface of the A-block is covered with a sugar layer with hydrophilic property. This block is regarded as a model compound of natural multiantennary oligosaccharides. The surface sector of the B-block provides a hydrophobic part. As a half-protected initiator core, *N*-benzyloxycarbonyl(Z)-protected ethylenediamine **1** was employed.[7] *core*-Z-protected poly(amido amine) (PAMAM) dendrimer-(generation 2.0) **2** was prepared by repeated Michael addition and amide formation reactions according to the literature[3a,8] (for a description of *core* and *surface* (*vide infra*), see ref 9). **2** was divided into two portions. One of the advantages of the present method is that both A and B blocks can be derived from a single hemispherical building block. Hydrophilic *surface*-sugar-substituted PAMAM dendrimer **4** was synthesized by the reaction of *surface*-amino groups of **2** with a 38-fold molar excess *O*-α-D-glucopyranosyl-(1→4)-D-glucono-1,5-lactone (maltono lactone, **3**) in dimethyl sulfoxide at 45 °C for 20 h under a nitrogen atmosphere.[10] Hydrophobic *surface*-phthaloyl block **5** was derived from **2** and phthalic anhydride (50-fold molar excess, in dimethyl sulfoxide at 100 °C for 30 min. Yield, 98%).[11] *core*-Z-protecting groups of **4** and **5** were selectively removed by hydrogenolysis to produce dendritic fragments with a functional core, **6** and **7**, respectively.[12] *core*-Amino hydrophobic block **7** was treated with trichloromethyl chloroformate (TCF) to give **8** having a reactive core of acid chloride.[13] The equimolar reaction between *core*-amino block **6** and *core*-acid chloride-type **8** was undertaken in dimethyl sulfoxide at 45 °C under a dry condition. The progress of the reaction was followed by ^{1}H NMR spectroscopy. AB-type surface-block dendrimer **9** was obtained in 45% yield after purification by preparative size exclusion chromatography (SEC) in dimethyl sulfoxide and a subsequent reprecipitation procedure.[14]

In order to check molecular recognition potential of *surface*-sugar-substituted dendritic fragments, the interaction between **4** and concanavalin A lectin was examined by a UV/vis spectrophotometer.[1a,15] The sugar-bearing hemispherical block of generation 2.0 showed apparent recognition ability toward the protein receptor. This fact suggests that polymers with hemispherical blocks derived from **4** have a capability as cell-recognizable biomedical materials.

Dendritic blocks **6**−**8** are important as building synthons carrying a reactive center core in various dendrimer-based macromolecular designs such as segment-block dendrimers[4a] and block copolymers between dendrimers and linear polymers.[16] In other words, the half-protected initiator core method should be essential in research and development of sophisticated dendritic functional materials, e.g., adhesives, surfactants, and drug delivery systems. For example, **1** will be applicable to a polyamine dendrimer that has been used for a Dendritic Box.[17] Including further extension of the partly protected initiator system, the present architectural principle of AB-type surface-block dendrimer provides numerous applications such as supramolecular self-assembling globular amphiphiles and intelligent nanocapsules having dual binding surface sectors to proteins and DNAs.

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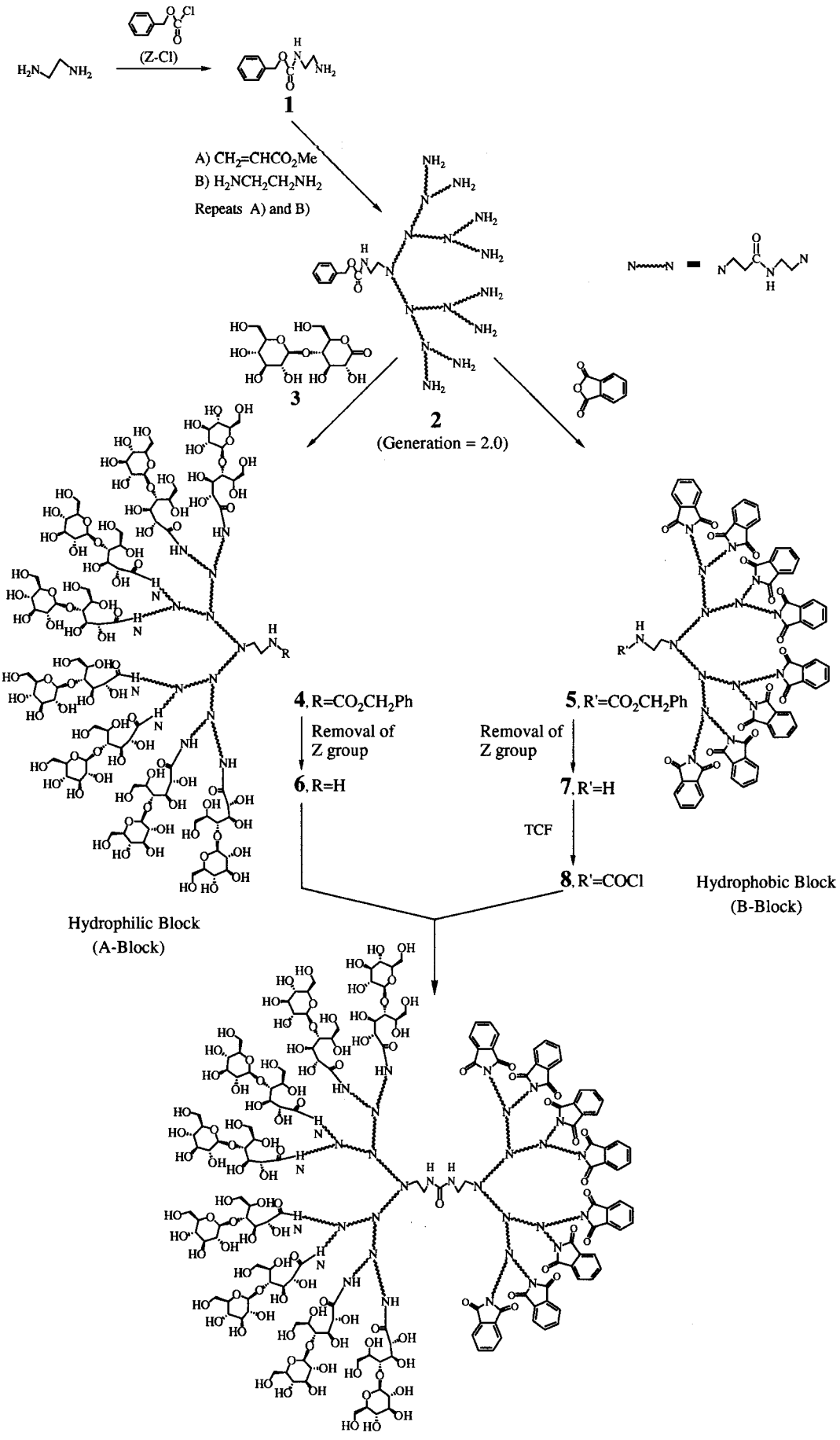
Scheme 1


(Z-Cl)
1
A) CH_2=$CHCO_2Me$
B) $H_2NCH_2CH_2NH_2$
Repeats A) and B)
3
2
(Generation = 2.0)
4, R=CO_2CH_2Ph
5, R'=CO_2CH_2Ph
Removal of Z group
Removal of Z group
6, R=H
7, R'=H
TCF
8, R'=COCl
Hydrophilic Block (A-Block)
Hydrophobic Block (B-Block)
AB-Type Surface-Block Dendrimer
9

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(7) **1** was prepared by the reaction of benzyloxycarbonyl chloride with a 20-fold molar excess of ethylenediamine in methanol with mixing at −50 °C, then raising to −5 °C for 20 h (yield, 66%).

(8) Michael addition between amino compounds, e.g., **1**, and methyl acrylate was carried out in methanol at 40 °C for 120 h. The resulting methyl ester derivatives were allowed to react with ethylenediamine in methanol at 27 °C for 72 h. Each half-generational product was purified by preparative flash-column chromatography using an acetone eluent with addition of methanol gradationally.

(9) By the conventional nomenclature, positions at an initiating end and a terminal end of the linear polymer are denoted as α and ω, respectively. In this nomenclature, positions of a center core and terminal branches are determined with respect to divergent and convergent methods in dendrimer synthesis, that is, α and ω for the former method and ω and α for the latter method, respectively. Thus, in dendrimer chemistry, the authors propose terms *core-* and *surface-*, which indicate the positions of a center core and terminal branches straightforwardly. While the term of reactive focal point is well-known, this does not cover the nonreactive center core of globular dendrimer.

(10) **4** was purified by dialysis against water using a cellulose tube (Spectrum Medical Industries, Inc., MW cutoff 1000) (yield, 34%).

(11) *core*-Benzyloxycarbonyl-*surface*-perphthaloylpoly(amido amine) dendrimer **5** ($G = 2.0$): IR (KBr) 3100 (ν_{C-H}), 2950 (ν_{C-H}), 1780, 1720 ($\nu_{C=O,}$ imide), 1640 ($\nu_{C=O}$, amide), 1560 (δ_{N-H}, amide), 750, 720 (δ_{C-H}, amide) cm^{-1}; ^1H NMR ($(CD_3)_2$-SO, TMS, 27 °C, 270 MHz) δ 8.10 (br, NH), 7.86−7.53 (m, CH of phthalimide), 7.33 (m, aromatic CH of Z), 5.02 (s, CH_2 of Z), 3.64 (m, CH_2 adjacent to phthalimide nitrogen), 3.26 (m, $NHCH_2$ of PAMAM), 3.05 (m, $NHCH_2CH_2N$ of PAMAM), 2.45 (m, NCH_2CH_2CONH and CH_2CONH of PAMAM); ^{13}C NMR ($(CD_3)_2SO$, TMS, 27 °C, 100 MHz) δ 170.8 (C═O, amide), 168.4 (C═O, phthalimide), 156.3 (C═O, Z), 138.4 (quaternary aromatic carbon of Z), 134.2−122.8 (aromatic carbon), 65.4 (CH_2 of Z), 51.2 ($NHCH_2CH_2N$ of PAMAM), 49.1 (NCH_2CH_2CONH of PAMAM), 37.3 ($NHCH_2CH_2N$ of PAMAM), 30.9 (CH_2CONH of PAMAM).

(12) **4** was treated with hydrogen in the presence of a Pd/C catalyst in a 50/50 mixture of methanol and water at 27 °C to give **6** (yield, 72%). Similar deprotection of the Z group of **5** was conducted with H_2/Pd−C in methanol at 27 °C (**7**, 84% yield). Removal of the Z group was also conducted by using a trifluoroacetic acid solution containing 7 wt % of thioanisole at 27 °C.

(13) Reaction conditions: in chloroform at 45 °C under nitrogen. **8** was purified by repeated reprecipitations (chloroform (solvent)/diethyl ether (nonsolvent) under dry conditions.

(14) *surface-block*-Permaltobionamido/perphthaloylpoly(amido amine) dendrimer **9** ($G = 2.0$): M_w/M_n (SEC, 27 °C, Me_2-SO), 1.01; IR (KBr) 3650−3100 (ν_{N-H} and ν_{O-H}), 3100 (ν_{C-H}), 2950 (ν_{C-H}), 1780, 1720 ($\nu_{C=O}$, imide), 1645 ($\nu_{C=O}$, amide), 1635 ($\nu_{C=O}$, urea), 1550 (δ_{N-H}) cm^{-1}; ^1H NMR ($(CD_3)_2SO$, TMS, 27 °C, 400 MHz) δ 8.10, 8.04, 8.01 (br, NH), 7.91−7.69 (m, CH of phthalimide), 4.95−3.32 (m, sugar residue), 3.23 (m, $NHCH_2$ of PAMAM), 3.00 (m, $NHCH_2CH_2N$ of PAMAM), 2.41 (m, NCH_2CH_2CONH and CH_2CONH of PAMAM); ^{13}C NMR ($(CD_3)_2SO$, TMS, 27 °C, 100 MHz) δ 174.1 (C═O of maltobionamide), 170.9 (C═O, amide), 168.2 (C═O, phthalimide), 153.2 (C═O, urea), 134.2−122.9 (aromatic carbon), 100.6 (anomeric carbon), 73.2, 73.1, 72.2, 72.0, 71.9, 71.5, 70.7, 69.8 (other carbons derived from maltono lactone), 51.8 ($NHCH_2CH_2N$ of PAMAM), 48.5 (NCH_2CH_2CONH of PAMAM), 38.1 ($NHCH_2CH_2N$ of PAMAM), 31.3 (CH_2CONH of PAMAM).

(15) Precipitation studies were carried out by mixing equivolume phosphate buffer solutions (pH 7.4) of concanavalin A (Con A, Sigma Chemical Co., 6 mg/mL) and **4**. Turbidity was estimated by a UV/vis spectrophotometer. Solutions of **4** (2.0, 1.0, and 0.5 mg/mL) were added to the Con A solutions, and absorbance values were 0.01, 0.21, and 0.44, respectively, after incubation at 25 °C for 20 min. Precipitation is caused by the formation of cross-linking between Con A and glucose residues of antennary synthetic glycoconjugate **4**.

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