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Synthesis of new poly(ethylene glycol)-block-poly(ester sulfide) dendrimers

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ABSTRACT

The design and synthesis of novel copolymers that consist of a linear polyoxyethylene block and a dendrimeric poly(ester-sulfide) block with potential applications in drug delivery are described. The dendrimers bear hydroxyl or acrylate functional groups and were prepared via a divergent approach using readily available methoxypoly(ethylene glycol) (mPEG), acryloyl chloride, and 1-thioglycerol as building blocks. All reactions involved occurred efficiently and purification steps consisted of washing the reaction mixture with aqueous solutions and precipitation of the product in diethyl ether.

Dendrimers are globular monodispersed synthetic macromolecules composed of branched repeating units all emanating from a central core. Because dendrimers are prepared in a stepwise fashion, their size and structure can be controlled precisely and their molecular weight distribution is generally very narrow.[1] This is in contrast to traditional polymer synthesis where chain growth is statistical and polydisperse materials are obtained. Dendritic macromolecules have received considerable attention as new polymeric materials for applications in areas such as molecular light harvesting,[2] catalysts,[3] liquid crystals,[4,5] and drug delivery.[6,7] The synthesis of high molecular weight dendrimers normally involves strategies requiring a tedious multistep procedure with repetitive protection–deprotection and extensive purification processes.

Since the initial report on dendrimers by Vogtle[8] in 1978, many different types of dendritic molecules have been reported. Primary among them are poly(amido amine),[9] poly(propylene imine),[8,10] poly(benzaryl ether),[11] poly(ether ester),[12] and linear-dendritic block copolymer comprising poly(ethylene oxide) as the linear block and polylysine,[13] polyamide[14] or polyester[15] as the dendrons. While the synthesis of a vast number of dendrimers has been reported, identification of new monomers and synthesis of new dendrimers remain an active area of research.

To use dendrimers as drug carriers, it is important that the polymers are of high molecular weights, water soluble, biodegradable, and biocompatible. However, the number of reported dendrimers possessing all of the above features is very small. In view of the increasing interest in polymers with such characteristics, here we report the synthesis and characterization of a hybrid block copolymer that consists of an ester-sulfide dendron attached to a hydrophilic poly(ethylene glycol) (PEG) chain. We have employed PEG because it is nontoxic, nonimmunogenic, and is soluble in a variety of organic solvents and aqueous media. Further, the attachment of PEG to other molecules produces conjugates that combine the properties of both the substrate and the polymer.[16]

Scheme 1 illustrates the synthesis of polymers comprising poly(ethylene oxide) as the linear block and a poly(ester-sulfide) as the dendron. In the preparation of this polymer two highly efficient and selective reactions have been employed: (a) reaction of hydroxyl group with acryloyl chloride, and (b) the conjugate addition of a thiol to an α,β-unsaturated ester. The progress of each reaction was followed by NMR spectroscopy by following disappearance or appearance of hydroxyl and acrylic groups to ensure completion of each reaction. In the first step, the reaction of mPEG with acryloyl chloride in the presence of Et_3N in methylene chloride yielded mPEG-acrylate,[17] **1**. In the ^1H NMR spectrum of mPEG-acrylate, the relative integration of the methoxy hydrogens to the acrylate hydrogens (5.90–6.38 ppm) was consistent with a 1:1 mPEG to acrylate ratio. In addition, no observable resonance at 4.56 ppm was observed (diagnostic of terminal –OH for mPEG in DMSO-d_6),[18] meaning that the conversion of mPEG to its corresponding mPEG-acrylate was complete. A Michael reaction between **1** and 1-thioglycerol in water resulted in G1-2OH, **2**. The work-up consisted of extraction of the reaction mixture with methylene chloride, followed by drying of the solution with $MgSO_4$ with subsequent precipitation of **2** in diethyl ether. The ^1H NMR spectrum of **2** showed no trace of the acrylic protons (multiplet at 5.90–6.38 ppm) indicating that the reaction was complete. The complete conversion of **1** to **2** was also confirmed by its ^{13}C NMR, in which no observable residual of carbon–carbon double bond (at 128.12 and 131.56 ppm) could be detected. Reaction of **2** with 4 equiv each of acryloyl chloride and Et_3N was run in methylene chloride which resulted in G1.5-2(acrylate), **3**. The work-up consisted of washing the reaction mixture consecutively with a saturated solution of sodium bicarbonate and brine followed by drying the methylene chloride layer with $MgSO_4$ and

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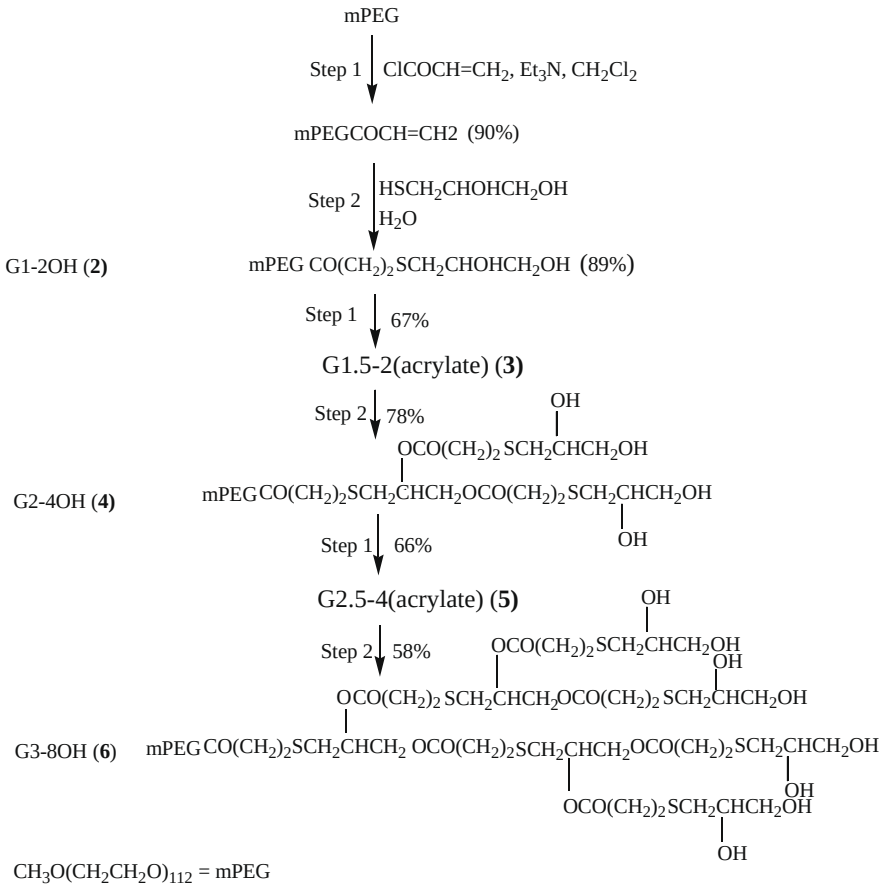

Scheme 1. Synthesis of mPEG-block-poly(ester sulfide) dendrimer.

precipitation in diethyl ether to give **3. 3** was then reacted with 25 equiv of 1-thioglycerol in water to give G2-4OH, **4**. Work-up and analysis were the same as those for the synthesis of **2**. Similarly, G2.5-(acrylate)4, **5**, was synthesized from the reaction of **4** with 12 equiv each of acryloyl chloride and Et_3N in methylene chloride. Reaction of **5** with about 59 equiv of 1-thioglycerol in water yielded G3-8OH, **6**.

A typical procedure for the synthesis of compounds **5** and **6** follows. Under a nitrogen atmosphere, to a cold (5 °C) solution of **4** (4.10 g, 0.75 mmol) and Et_3N (0.91 g, 9.03 mmol) in methylene chloride (100 mL) acryloyl chloride (0.82 g, 9.03 mmol) was added slowly (over 10 min). The reaction mixture was stirred overnight at room temperature. The reaction mixture was treated as described for **3**. Dendrimer **5** (2.35 g, 0.42 mmol) was dissolved in water (150 mL, degassed by bubbling nitrogen through it for 10 min) containing 0.15 g of sodium bicarbonate to which 1-thioglycerol (2.69 g, 24.88 mmol) was added and the mixture stirred for 3 h while nitrogen bubbling continued. The reaction mixture was saturated with sodium chloride and extracted with CH_2Cl_2 (3×20 mL) and the combined CH_2Cl_2 layers were dried over $MgSO_4$. The volume of dried CH_2Cl_2 solution was reduced to 5 mL and the product was precipitated by addition to ice-cold dry diethyl ether (150 mL). The products **5** and **6** were analyzed by NMR.[19] Polymer **6** (G3-8OH) was further characterized by MALDI-TOF mass spectrometry.[19] From Figure 1, the molecular weight found from MALDI-TOF spectrum agrees well with the calculated value suggesting the presence of very few defects in the structure of the polymer. Further, the calculated carbon, hydrogen, and sulfur analyses were in reasonable agreement with those found experimentally.[19]

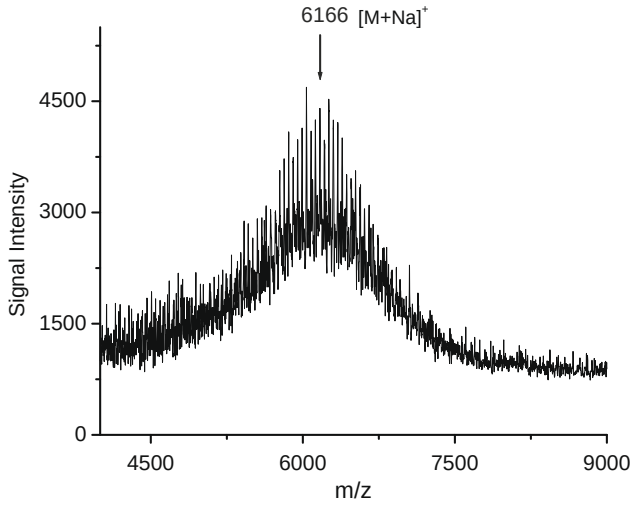

Figure 1. Maldi-TOF mass spectrum of **6**.

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19. G2.5-4 (acrylate), **5**: IR (Nujol): ν (cm^{-1}): 1734; ^1H NMR (400 MHz, DMSO-d_6): δ 2.59–2.95 (m, –OC**H**$_2$C**H**$_2$SC**H**$_2$–, 18H), 3.23 (s, methoxy), 3.50 (s, PEG backbone), 4.11–4.45 (m, C**H**$_2$OCO, 8H), 5.06–5.13 (m, –C**H**OCO–, 3H), 5.19–5.25 (m, –C**H**=C**H**$_2$, 12H); ^{13}C NMR (100.55 MHz, DMSO-d_6): δ 27.30, 27.40, 31.89, 34.74, 34.82, 34.93, 46.29, 58.72, 64.13, 64.47, 68.91, 70.27, 70.47, 71.18, 71.97, 128.50, 128.62, 132.78, 132.93, 165.50, 165.76, 171.49, 171.74, 172.06. G3-8OH, **6**: IR (thin film): ν (cm^{-1}): 1735; ^1H NMR (400 MHz, DMSO-d_6) for **6**: δ 2.40–2.81 (m, –OCOC***H***$_2$C***H***$_2$SC***H***$_2$–, 42H), 3.23 (s, methoxy), 3.50 (s, PEG backbone), 4.00–4.30 (m, –C***H***$_2$OCO–, 8H), 4.51 (m, –CH$_2$O***H***, 4 H), 4.70 (m, –CHO***H***, 4H), 5.06 (m, –C***H***OCO–, 3H); ^{13}C NMR (100.55 MHz, DMSO-d_6): δ 27.40, 27.76, 34.99, 35.19, 35.81, 58.72, 64.12, 65.15, 68.90, 70.22, 70.46, 70.69, 71.95, 72.16, 171.51, 171.65, 171.78, 171.93, 172.08. Anal. Calcd for $C_{269}H_{526}O_{135}S_7$: C, 52.57; H, 8.63; S, 3.65. Found: C, 51.88; H, 8.63; S, 3.55. Calcd: $[M+Na]^+$ ($C_{269}H_{526}O_{135}S_7$) m/z = 6169 found: MALDI-TOF MS: $[M+Na]^+$ m/z = 6166.