Novel Poly(ethylene glycol) Dendrimers for Drug Delivery Applications

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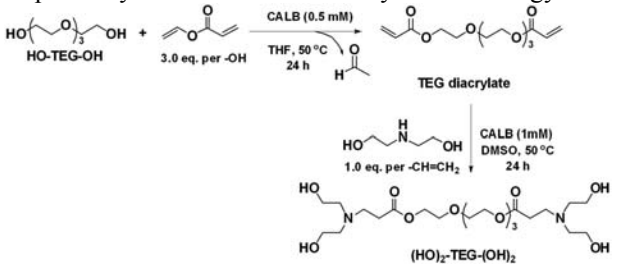
Statement of Purpose: Dendrimers have extensively been applied in novel drug delivery systems, due to the advantages of well-defined molecular weight, multivalent surfaces, and high drug carrying capacity.[1] However, the synthesis of dendrimers remains an expensive and difficult process with a complex mixture of products, resulting in stochastic conjugation of both targeting ligands and drugs.[2] Poly(ethylene glycol) (PEG) dendrimers[3] are outstanding candidates for targeted drug delivery, because of a unique combination of properties including water solubility, non-toxicity and limited recognition by the immune system.[4] Recently, we reported the enzyme-catalyzed functionalization of macromolecules, with unparalled chemo- and region-selectivity as well as environmentally friendly reaction conditions.[5] Our goal is to synthesize novel dendrimer drug carriers with well-defined structures using enzymatic catalysis. This paper reports the synthesis and characterization of the dendrimer core.

Materials and Methods: Lipase B from *Candida antarctica* immobilized on microporous acrylic resin (CALB, Sigma), tetraethylene glycol (HO-TEG-OH, 99 %, Aldrich), diethanolamine (99.5 %, Aldrich), vinyl acrylate (VA, Monomer-Polymer Dejac Inc), and dimethyl sulfoxide (Anhydrous, 99.9 %, Sigma) were used as received. Tetrahydrofuran (Fisher Scientific) were distilled from Sodium and Benzophenone (Aldrich), respectively. Scheme 1 shows the synthetic strategy.



Scheme 1. Synthesis of $(HO)_2$-TEG-$(OH)_2$ by transesterification and Michael addition using CALB.

VA (3 eq. per –OH) was added into the HO-TEG-OH solution in THF containing 0.5 mM CALB. The reaction mixture was stirred for 24 h at 50 °C. After the reaction, the mixture was filtered to remove the enzyme and the THF was replaced with DMSO. In the second step, diethanolamine (1 eq. per acrylate) and CALB was added into the TEG diacrylate solution and the reaction mixture was stirred for 24 h at 50 °C. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 NMR spectrometer at 300 and 75 MHz, respectively. Dimethyl sulfoxide-d_6 [Chemical Isotope Laboratories, (D, 99.9%)] was used as the solvent. Electrospray ionization mass spectrometry (ESI-MS) was used to verify the expected structures.

Results: Figure 1. shows the NMR spectra of the products. In the spectrum of the TEG-diacrylate, the integration ratios of the vinyl [δ=5.8 (3), δ= 6.2 (2), and δ=6.3 (1)], and methylene protons [δ=4.2 (4)] were 1:1:1:2 as expected (Figure 1-(A)). After the Michael addition, the vinyl protons from the acrylate groups disappeared and new signals corresponding to the protons of OH end groups appeared at δ=4.2 ppm with good agreement of integration ratios (Figure 1-(B)). ^{13}C NMR and ESI-MS verified the expected structures. The reactions proceeded quantitatively with no side reactions.

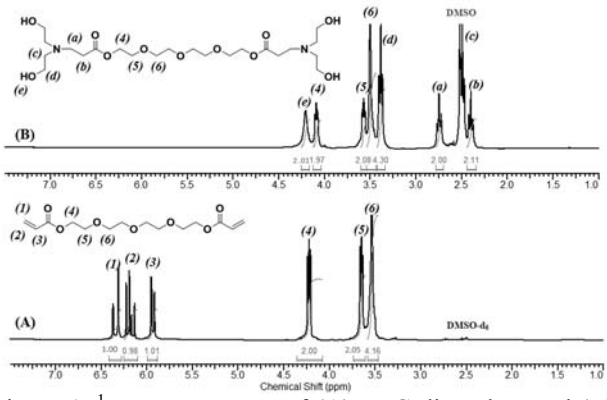


Figure 1. ^{1}H NMR spectra of (A) TEG diacrylate and (B) $(HO)_2$-TEG-$(OH)_2$.

Conclusions: In conclusion, TEG diacrylate was quantitatively prepared by CALB-catalyzed transesterification of vinyl acrylate with HO-TEG-OH. Then the TEG diacrylate was effectively reacted with diethanolamine to generate $(HO)_2$-TEG-$(OH)_2$ by enzyme-catalyzed Michael addition. The structure of the products was confirmed by NMR and ESI-MS. This method offers effective strategies of TEG and PEG dendrimer building with enzymatic catalysis, which can be applied to drug delivery systems.

Reference:

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