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Facile Synthesis of Polyester Dendrimers from Sequential Click Coupling of Asymmetrical Monomers

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Abstract: Polyester dendrimers are attractive for in vivo delivery of bioactive molecules due to their biodegradability, but their synthesis generally requires multistep reactions with intensive purifications. A highly efficient approach to the synthesis of dendrimers by simply "sticking" generation by generation together is achieved by combining kinetic or mechanistic chemoselectivity with *click* reactions between the monomers. In each generation, the targeted molecules are the major reaction product as detected by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). The only separation needed is to remove the little unreacted monomer by simple precipitation or washing. This simple clicklike process without complicated purification is particularly suitable for the synthesis of custom-made polyester dendrimers.

Introduction

Dendrimers, the highly branched macromolecules characterized by precise three-dimensional nanosized molecular structures, provide a perfect nanotechnology platform for numerous applications,[1,2] particularly in pharmaceutics as drug and gene carriers[3−5] because of their internal cavity for drug encapsulation,[6] large numbers of surface functional groups for drug conjugations, and unusually low intrinsic viscosity in solution[7] for easy transport in blood. While many types of dendrimers such as polyamidoamine- (PAMAM-) based dendrimers have been reported as carriers, polyester dendrimers are most attractive[4,5,8] because of their biodegradability, which allows the macromolecules to degrade or hydrolyze into small molecules for exclusion from the body. However, to make these dendrimers useful in practice, researchers must develop more efficient synthesis approaches.

Polyester dendrimers, like other dendrimers, are generally synthesized via the divergent[5,9−12] and convergent[12,13] approaches. Both approaches involve repeated reactions between functional groups A and B in multifunctional monomers A_x and B_y or AB_x. When the A_x and B_y types of monomers are used, a large excess of the reactant must be used in each step to minimize cross-linking.[9] Consequently, a large quantity of unreacted monomer must be removed to isolate the dendrimer. When an AB_x-type monomer is used, the B groups are generally protected to make the A group react solely with the B groups in the prior generation of dendrimer. Deprotection is needed to reactivate the B groups for the subsequent reaction.[14] This protection and deprotection may be incomplete and may have

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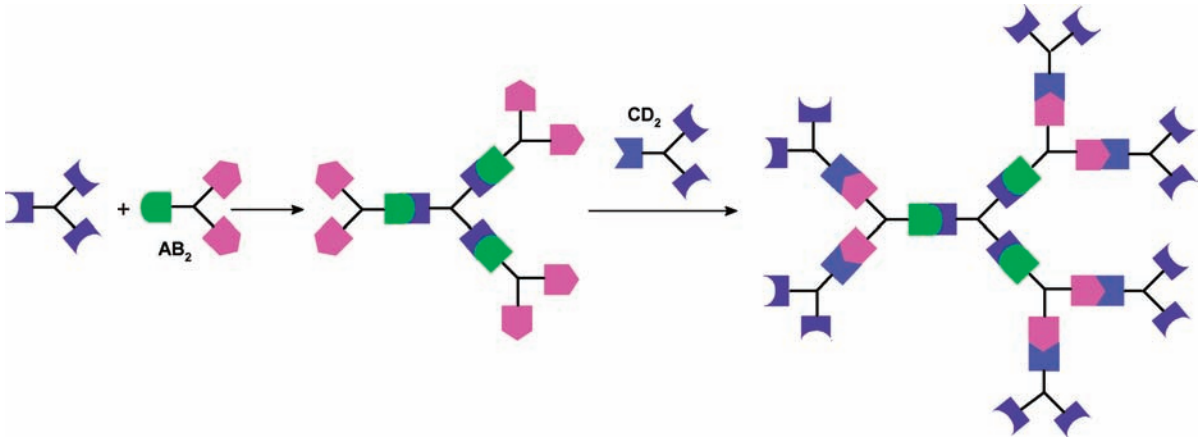
Scheme 1. Sequential Click Coupling of Asymmetrical Monomers for Facile Polyester Dendrimer Synthesis



side reactions, causing defects in the dendrimer structure. For example, the commercially available PAMAM dendrimer is polydispersed, not monodispersed (Figure S1 in Supporting Information).

Various new synthetic methods aiming at enhancing the synthesis efficiency have been developed, including double stage,[14,15] double exponential growth,[16] hypermonomers,[17] and orthogonal coupling.[18] The click reaction—copper(I)-catalyzed regiospecific formation of 1,2,3-triazoles from azides and terminal acetylenes, characterized by complete specificity, quantitative yields, and almost perfect fidelity[19]—has recently been used for efficient synthesis of dendrimers with fewer steps, less purification, and increased overall yields.[20] Very recently, the thiol−ene reaction was found to have the characteristics of the click reaction.[21] Hawker and co-workers[22] demonstrated that it was robust and efficient in dendrimer synthesis.

These synthesis systems, however, still involve intermediate reactions, particularly protection/deprotection steps,[11,12,21−24] which can introduce defects into the dendrimers. Therefore, intensive purifications using, for example, preparative high-performance liquid chromatography (HPLC), have to be conducted to remove the molecules with defects to obtain monodispersed dendrimers. The purifications substantially waste precious precursor dendrimers, especially those already at high generations.

An ideally efficient dendrimer synthesis would be simply sequentially *gluing* asymmetric monomers together (Scheme 1). The monomers AB_x and CD_y are asymmetric in their functional groups' reactivities: A reacting only with D, and B reacting only with C. The A−D and B−C reactions are *click* or close to click reactions involving no intermediate reactions or protection/deprotection. With such a monomer pair, a dendrimer could be synthesized simply by sequentially "sticking" AB_x and CD_y together. The targeted dendrimer molecules would be the only product, thereby requiring minimal purification. This strategy would greatly accelerate the synthesis of the dendrimers. However, such monomer pairs are rare. A sole example is $H_2NN(CH_3)P(S)(OC_6H_4PPh_2)_2$ (AB_2) and $N_3P(S)(OC_6H_4CHO)_2$ (CD_2) demonstrated by Majoral and co-workers.[25,26] The reactions of the NH_2 with the aldehyde and the -PPh_2 with the -N_3 in the monomers were highly efficient and selective.[25] The reactions proceed with neither protection nor deprotection and with quantitative yields. The only byproducts were easily removable H_2O and N_2. The one-pot synthesis produced a phosphorus-containing dendrimer,[25] and an accelerated synthesis could be further achieved by use of AB_5 and CD_5 monomers.[26]

For polyester dendrimers, however, there is no report of such an efficient synthesis. Herein, we demonstrate this "sequential clicking" concept for the synthesis of polyester dendrimers using kinetically and mechanistically chemoselective monomers.

Results and Discussion

Synthesis of Dendrimers from a Kinetically Chemoselective Monomer Pair, MAEA and Cysteamine. The Michael addition reaction of acrylates with amines has few side reactions and requires mild reaction conditions.[28] The reaction can achieve high yields and has been used to synthesize high-molecular-weight poly(β-amino ester)s.[29] By contrast, methacrylates do not react with these amines without catalysts, but they do quantitatively react with thiols.[30] Thus, we designed a pair of kinetically asymmetric monomers, 2-[(methacryloyl)oxy]ethyl acrylate (MAEA) (AB type) and cysteamine (CD_2). They react at the same reaction mechanism, but different reactivities. The acrylate group in the MAEA selectively reacted with the primary and resulting secondary amine groups to produce the core (Scheme 2, A → A-G1). The pendant methacrylate groups then selectively reacted with the thiol group in the CD_2 monomer cysteamine (Scheme 2, A-G1 → A-G1′). Alternately adding the two monomers produced the third and fourth generations of the dendrimers at high overall yields. The overall synthesis strategy is shown in Scheme 2, where 1,4-diaminobutane (A) was used as the core-forming compound.

The Michael reaction of the primary amine with an acrylate was quick and quantitative even at room temperature. The

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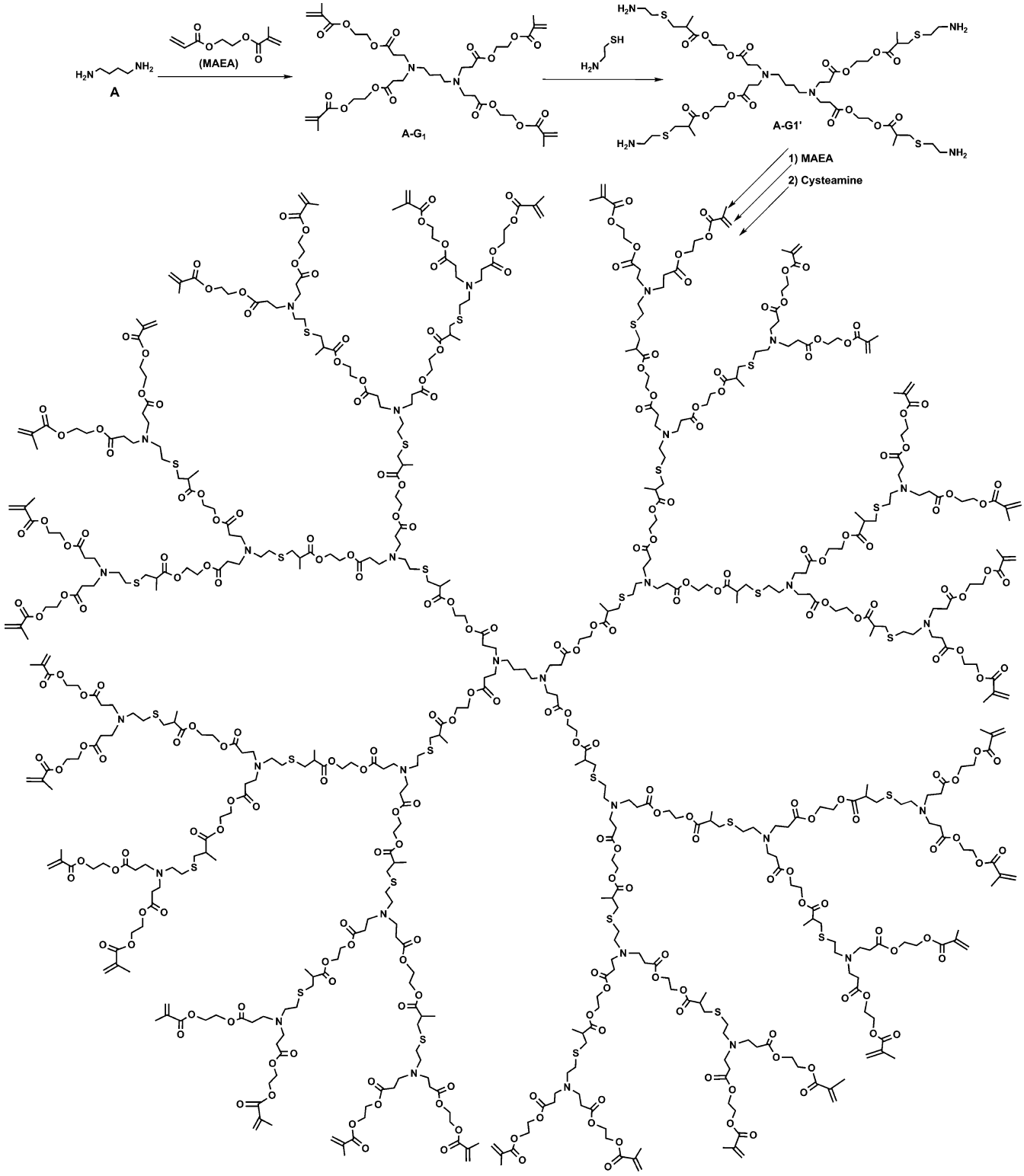
Scheme 2. Dendrimer Synthesis from the Kinetically Selective Monomer Pair MAEA and Cysteamine



reaction of the resulting secondary amine with an acrylate became slower due to steric hindrance effect. Heating the reaction solution to 40−70 °C pushed the reaction to completion as confirmed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Magnesium perchlorate (1 equiv) could also catalyze the reaction of the amine with acrylate but not methacrylate. Therefore, adding magnesium perchlorate (1 equiv) as catalyst also could accelerate the reaction (Scheme 2, A → A-G1) to complete at room temperature (data not shown). Under these conditions, the methacrylate in MAEA did not react with the amines at all; therefore, both approaches produced a perfect core structure as confirmed by MALDI-TOF MS spectra. We chose the simple heating method instead of the addition of magnesium perchlorate because it avoided the additional purification step that removed the catalyst solid. In this reaction, a slight excess of MAEA

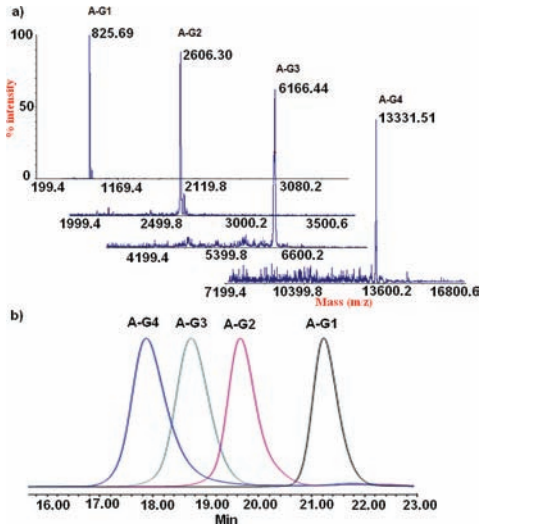


Figure 1. Molecular-weight progress of the dendrimers via the reaction of MAEA and cysteamine with 1,4-diaminobutane as the core, measured by (a) MALDI-TOF MS and (b) GPC. The MALDI-TOF MS spectra were obtained from the reaction solutions without any purification.

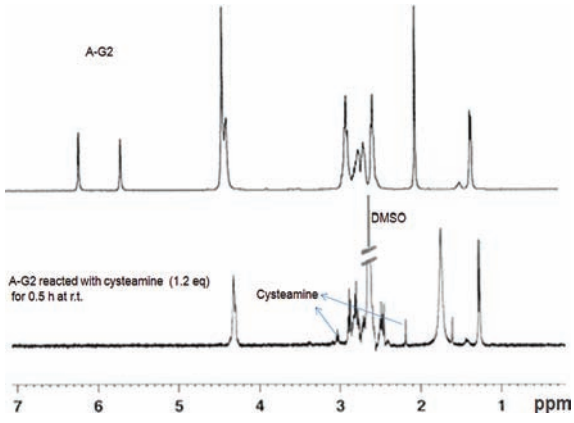


Figure 2. Reaction of the methacrylate-terminated dendrimer with cysteamine (thiol/methacrylate molar ratio of 1.2, room temperature, 0.5 h).

(MAEA/NH = 1.2) was used to accelerate the reaction and to ensure all the secondary amines were reacted. The MALDI-TOF MS spectrum of the reaction solution confirmed that the targeted molecules (MW 825) were the only product in the solution (Figure 1).

A simple washing with hexane removed the remaining MAEA monomer, yielding the pure first generation (A-G1). Subsequently, cysteamine was added to the G1 dendrimer solution and its thiol group reacted with the pendant methacrylate groups. In dimethyl sulfoxide (DMSO), the reaction between the methacrylate and the thiol was very quick, completing in half an hour at room temperature even though cysteamine was initially not very soluble in the solution. The completion of this reaction could be monitored by ^{1}H NMR (Figure 2) in addition to using MALDI-TOF MS spectra. Upon completion, the signal of the methylene group (CH_2=) in the methacrylate disappeared completely. The primary amine in cysteamine could not react with methacrylate. Therefore, a stoichiometric amount of cysteamine could be used. In practice, a slight excess of cysteamine (methacrylate/cysteamine molar ratio of 1/1.2) was again used to accelerate the reaction and ensure complete reaction of all the methacrylate groups. Simply washing the product with brine to remove the unreacted cysteamine produced

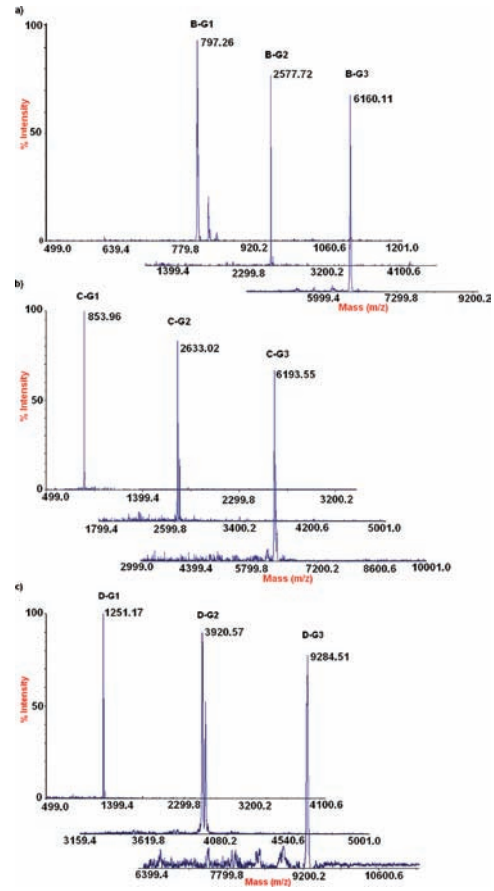


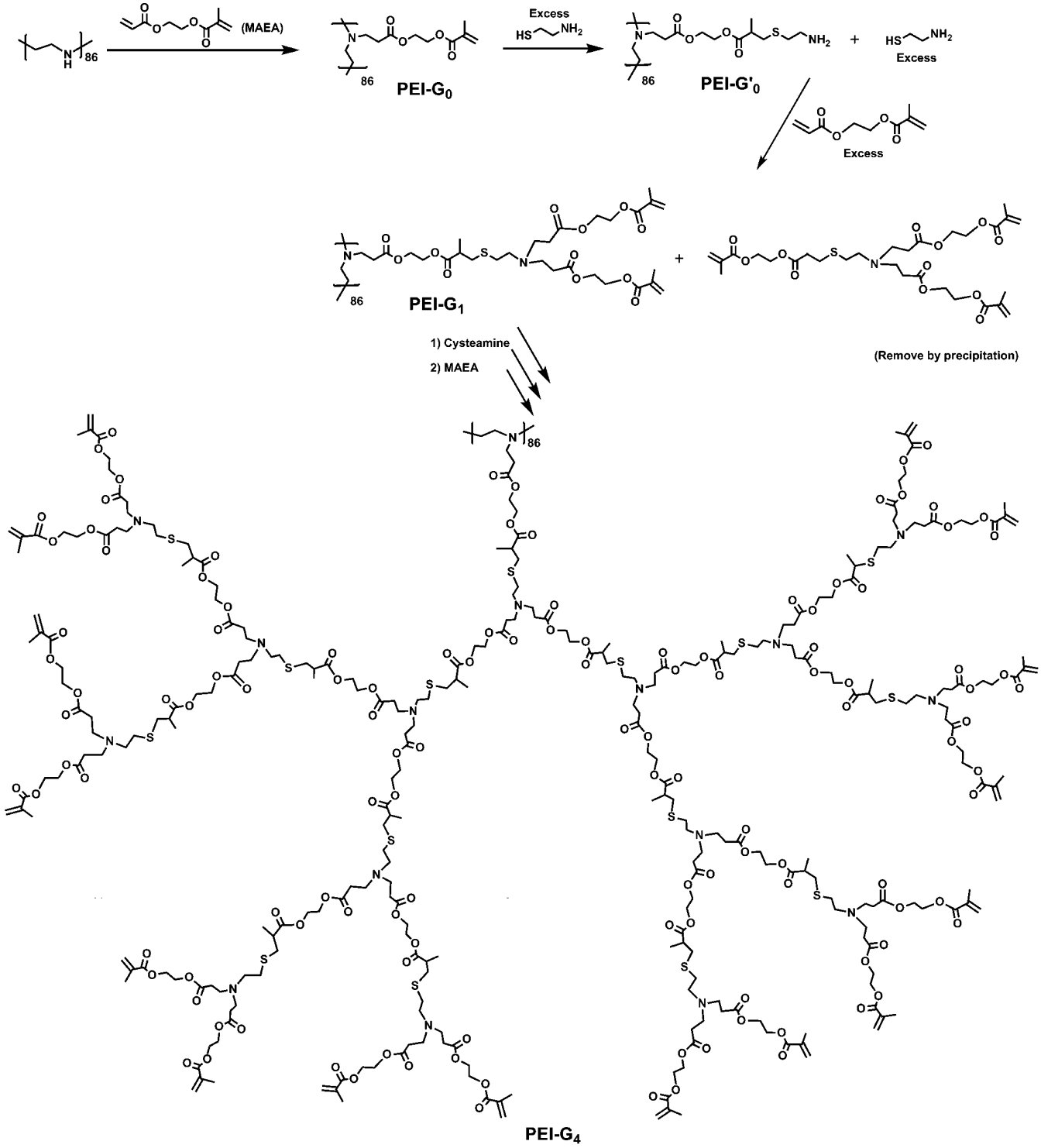
Figure 3. Molecular-weight progress of the dendrimers via the reaction of MAEA and cysteamine with (a) ethylenediamine, (b) 1,6-diaminohexane, and (c) tris(2-ethylamino)amine as the core. The MALDI-TOF MS spectra were obtained from the reaction solutions without any purification.

the perfect amine-functionalized first generation (A-G1′ in Scheme 2). Repeating these two steps produced the desirable generations of the dendrimer (Scheme 2).

Figure 1a shows the MALDI-TOF MS spectra of the reaction solutions. Clearly, the spectrum of the reaction solution in each generation had the targeted dendrimer peak in agreement with its calculated molecular weight (see Supporting Information for all the spectra). There was no signal or very weak signal(s) of incomplete molecules. For example, the reaction solution in the synthesis of the third-generation dendrimer had the targeted molecular weight peak at 6166.44, which was in good agreement with the calculated value of 6166.52 (Figure 1a). The spectra of the amine-functionalized dendrimers (Supporting Information) were somewhat complicated, but the dendrimers of the subsequent generations with terminal methacrylates showed monodispersity, indicating that the amine-terminated dendrimers were also monodispersed and the multiple peaks in their spectra were caused by chelation of the primary amines with multiple Na^+ and K^+ cations during the MALDI-TOF MS measurements. Thus, the reaction solution contained mainly the targeted molecules and a small amount of the unreacted small-molecule monomers that were used to accelerate the reactions.

The purification of the dendrimer in each step was as simple as removing the remaining monomers. The small amount of excess MAEA was removed by simply washing the product with hexane. The slight excess of cysteamine in the amine-terminated dendrimers was removed by washing its dichloromethane solution with cold brine. Figure 1 shows the

Scheme 3. Synthesis of Dendronized PEI by a One Pot per Generation Method from MAEA and Cysteamine



molecular-weight progression of the dendrimers with the increased generations with 1,4-diaminobutane as the core. The steady increase of the molecular weight was monitored by gel-permeation chromatography (GPC) (Figure 1b). The fourth-generation dendrimer, containing 32 terminal methacryloyl groups, was easily obtained by alternately adding the two monomers and using the simple purifications as described above.

It should be noted that the primary amine-terminated dendrimers easily undergo aminolysis of their ester groups during storage, and thus they should be used soon once made. However, the methacrylate-terminated dendrimers are stable in the presence of radical inhibitors and can be stored for a long time. When the amine-terminated dendrimers are needed, we simply add cysteamine and let it react for half an hour, and then they are ready to use. Furthermore, by reacting the primary amine-terminated dendrimers with 2-(*N,N*-dimethylamino)ethyl acrylate, they can also be converted to tertiary amine-terminated dendrimers, which became quite stable. This result will be reported elsewhere very soon.

Similarly, the dendrimers with ethylenediamine, 1,6-diaminohexane, and tris(2-aminoethyl)amine as the core were also

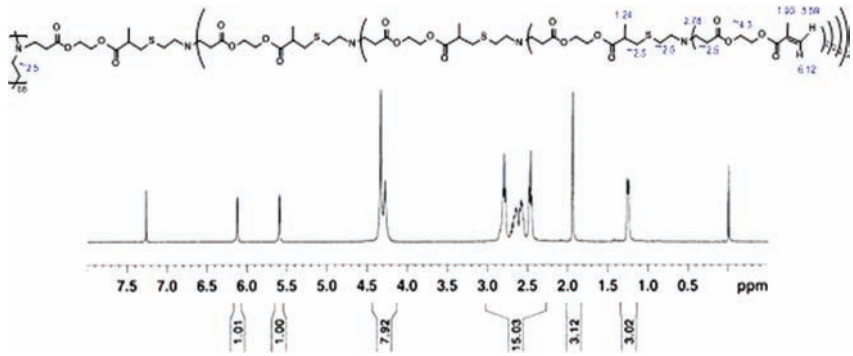


Figure 4. ^{1}H NMR spectrum of PEI-G4 (in $CDCl_3$). (The numbers in the structure are the estimated chemical shifts of the protons.)

synthesized easily by the same reactions (Figure 3 and Supporting Information).

Synthesis of Dendronized Linear Poly(ethylenimine) by a One Pot Per Generation Method. The facile synthesis of dendrimers from the MAEA−cysteamine monomer pair was further demonstrated by a one pot per generation method for the synthesis of a dendronized polymer from linear poly(ethylenimine) (LPEI, Scheme 3). LPEI was first reacted with MAEA to produce the methacrylate-functionalized PEI (PEI-G0). Cysteamine (1.2/1 to the methacrylate groups) was added to the PEI-G0. Within half an hour, the reaction was complete and produced the amine-functionalized PEI-G0 (PEI-G0′). Without removing the slight excess of cysteamine, a slight excess of MAEA relative to the amines in the PEI-G0′ as well as the amine and thiol groups in unreacted cysteamine was added to the solution. The reaction was allowed to proceed until all the primary amines in the PEI-G0′ were consumed, as monitored by ^{1}H NMR spectra. Because of the asymmetric activity of the monomers, the excess of cysteamine used to push the reaction did not cause any gel formation, unlike the symmetric monomers that can cause gelation.[31] The product solution contained the targeted first-generation dendronized PEI (PEI-G1) and some small molecules resulting from cysteamine reacted with three molecules of MAEA. Precipitation in ether easily removed the small molecules and pure PEI-G1 was obtained with a 90% yield. Repeating this step produced dendronized PEI with higher generations of dendrons. The completeness of the reaction was monitored by the intensities of the methyl groups in the reacted−unreacted methacrylate groups in the ^{1}H NMR spectra. For example, the perfect PEI-G4 should have 16 methyl groups in the pendant methacrylates and 15 methyl groups in the reacted methacrylate with a theoretical ratio of 1.07. The ratio calculated from the NMR spectrum is 1.033 (Figure 4), suggesting that the PEI-G4 is very close (96.5%) to the perfect structure.

GPC traces showed that the PEI-G*x* gradually shifted to the high molecular weight region (Figure 5). There was no trace of the small molecules, which would appear at around 21 min. This indicates that the small molecules were completely removed by precipitation. The polydispersity of the polymer was around 1.2, close to that of the starting LPEI. The measured molecular weights of the PEI with the dendron generations from G0 to G4 were very close to their calculated values when measured via GPC equipped with a laser light scattering detector. For example, the measured molecular weight of the dendronized PEI-G4 was 556K, close to its theoretical value of 592K. This result is in agreement with the NMR spectrum result showing complete reaction in each step (Figure 4).

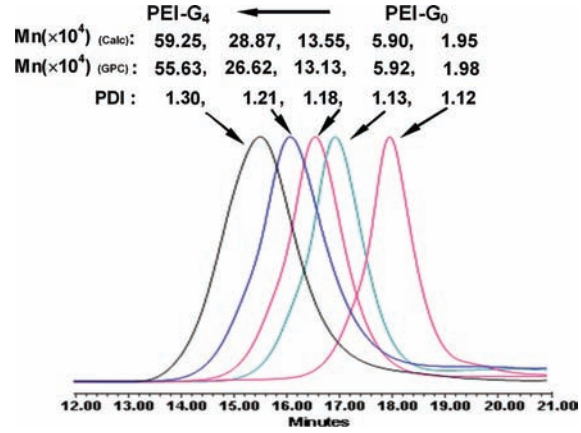


Figure 5. Molecular-weight progress and GPC curves from G0 to G4 of the dendronized PEI synthesized by the one pot per generation method.

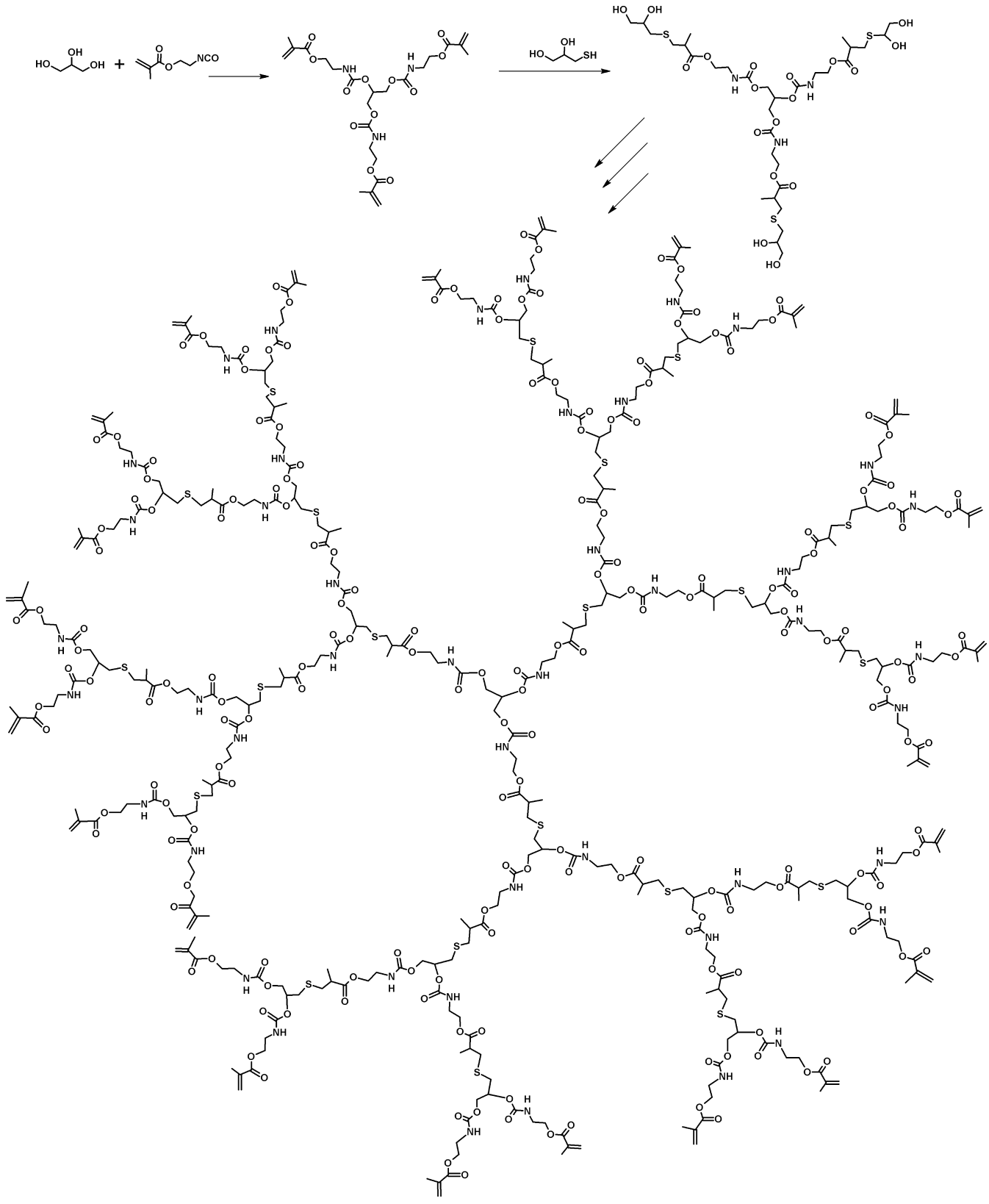
Dendrimer Synthesis from a Mechanistically Chemoselective Monomer Pair. An alternative to kinetic chemoselectivity of the functional groups in a monomer is mechanistic chemoselectivity. In this case, the groups react in different mechanisms. For example, isocyanates readily react with alcohols with high yields in a mechanism different from the Michael addition reaction.[32] We designed a pair of mechanistically asymmetric monomers for the dendrimer synthesis, 1-thioglycerol and 2-isocyanatoethyl methacrylate (IEMA). This synthesis strategy is shown in Scheme 4.

The core was formed by the reaction of glycerol with IEMA. This reaction was very fast and exothermic in DMSO but mild in dichloromethane at room temperature. A slight excess of IEMA (IEMA/OH = 1.02) was used to drive the reaction to completion and form the core [G1]-methacrylate$_3$. 1-Thioglycerol was then added and its thiol reacted with the methacrylates, producing the hydroxyl-terminated first-generation (G1′) dendrimer.

Alternating addition of IEMA and 1-thioglycerol produced higher generations of the dendrimers. Both reactions were carried out at room temperature. Triethylamine was used as the catalyst to accelerate the reactions of hydroxy with isocyanate and thiol with methacrylate groups. At each step, a slight excess of monomer was added to ensure complete conversion of the dendrimer to the next generation.

Figure 6 shows the MALDI-TOF MS spectra of the reaction solutions in each step. Again, the Na^+, K^+ adducts of the targeted dendrimer molecules were the main product in each step. For instance, the reaction solution in the synthesis of the third generation contained only molecular ions at 4342 and 4358 (Figure 6), which agreed well with the molecular weights of the adducts of the targeted mole-

Scheme 4. Dendrimer Synthesis via Sequential Clicking of Mechanistically Selective Monomers IEMA and 1-Thioglycerol



cules (4320) with Na^+ and K^+. Thus, Figure 6 also suggests that the conversion of the prior-generation dendrimer in each step was close to 100%. Their GPC spectra further confirmed the molecular-weight progress of this series of dendrimers.

Purification of the dendrimers in each step was also extremely simple, requiring only the removal of the slight excess of monomers used to accelerate the reaction. The methacrylate-terminated dendrimers were precipitated in hexane to remove excess IEMA, and the hydroxyl-terminated dendrimers were

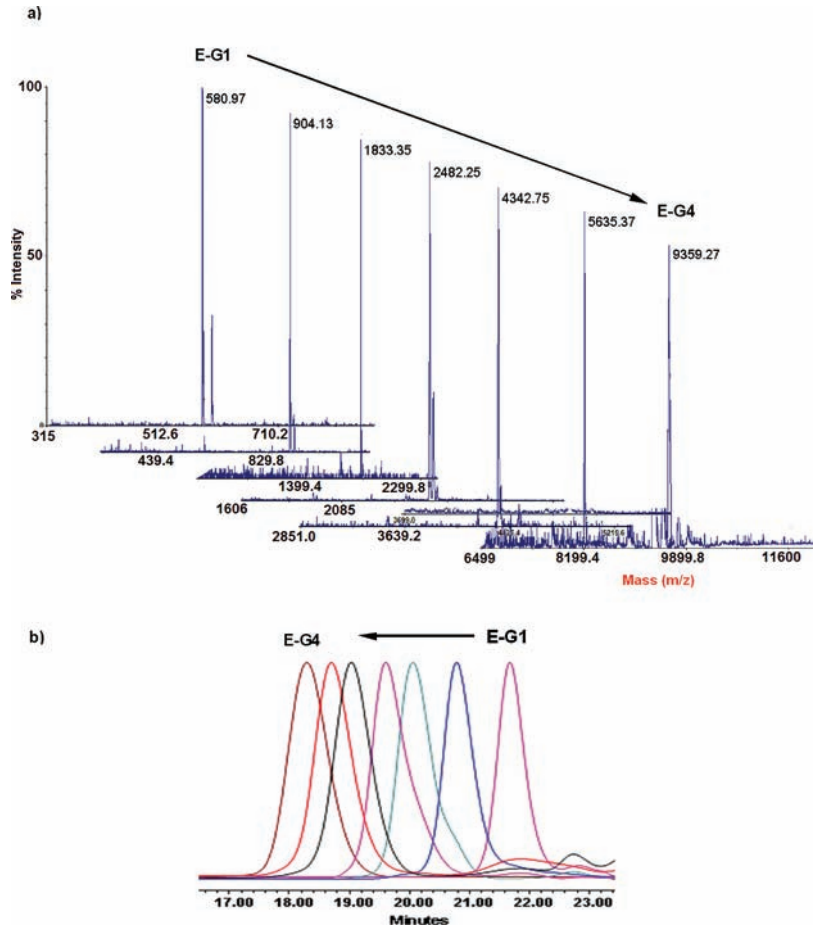


Figure 6. Molecular-weight progress of the dendrimers via the reaction of IEMA and 1-thioglycerol with glycerol (E) as the core, measured by (a) MALDI-TOF MS and (b) GPC. The MALDI-TOF spectra were obtained from the reaction solutions without any purification.

precipitated in diethyl ether to remove unreacted 1-thioglycerol. In six steps, the fourth-generation dendrimers with perfect structures and 24 hydroxy ($G4_{-OH24}$) or methacrylate ($G4_{-methacrylate24}$) groups were obtained.

Conclusion

In conclusion, using simple and readily available monomers, we demonstrated a highly efficient approach to synthesis of polyester dendrimers by combining kinetic or mechanistic chemoselectivity and click reactions between the monomers. Chemoselectivity allows the use of amounts of monomers close to the stoichiometric ratio and avoids the formation of byproducts. The click reactions ensure that all the reaction groups in the prior-generation dendrimer react with the monomer so that only the targeted molecules of the subsequent-generation dendrimer are produced. This not only greatly simplifies the purification process, which is only to remove unreacted monomers, but also avoids wasting the precious dendrimer precursors. Thus, the combination of chemoselectivity and *click* reactions makes it possible to simply "stick" generations together. This *sequential coupling* process without complicated purifications may allow researchers to synthesize their own custom-made dendrimers. The dendrimers with pendant methacrylate or amine groups can be easily used for conjugations of drugs. Most attractively, these dendrimers are degradable, which is critical

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for in vivo applications. The degradability can be used to tailor the dendrimer's DNA affinity. For example, the dendrimer D-G2′ with terminal primary amines can form complexes with DNA but can release the DNA after 6 h at pH 7.4 and 37 °C due to its degradation (Figure S31 in Supporting Information). This is useful for controlled release of DNA for gene delivery. Furthermore, we found that the degradability of the polyester dendrimers could be tailored by their pendant groups. The dendrimers with terminal tertiary amines hydrolyze more slowly. Further development of this method for accelerated synthesis and the applications of the dendrimers in in vivo gene and drug delivery as well as magnetic resonance imaging are currently under investigation, and these results will be reported elsewhere very soon.

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Supporting Information Available: Experimental procedures, characterization,and MALDI-TOF MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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