Alternate Multiaddition Reactions for the Synthesis of Commodity Dendrimers

Ken'ichi Aoki and Kunihiro Ichimura*
Faculty of Science, Toho University, 2-2-1 Miyama, Funabashi 274-8510
Research Center for Materials with Integrated Properties, Toho University, 2-2-1 Miyama, Funabashi 274-8510

(Received July 13, 2009; CL-090654; E-mail: k-ichimura@sci.toho-u.ac.jp)

A selection rule for the reactivity of monomers to realize a quantity production of dendrimers through alternate multiadditions (AMA) is presented. The prototype of the AMA process was shown by using 2-sulfanylethanol and pentaerythritol tetraacrylate to give a tetraol, which was reacted with 1,1-bis(acryloyloxymethyl)ethyl isocyanate as a branched building block to yield a dendritic octaacrylate. Both additions were repeated for the second generation growth.

The unique properties of dendrimers[1] have led to diverse applications including drug delivery,[2] biomedical purposes,[3] catalysts,[4] optoelectronics,[5] and sensors.[6] It has been a long-awaited subject to achieve their large-scale production, since the majority of the preparative methods are laborious. Click chemistry based on 1,3-dipolar cycloaddition without forming any by-product is attractive,[7] but it is necessary to convert a chlorinated precursor into the corresponding building block bearing azido group for the generation growth. Meanwhile, the one-pot syntheses of dendrimers were reported by employing suitable combinations of reactions.[8] Convenient methods for large-scale synthesis of dendrimers have been recently exploited; the thiol–ene radical addition[9] of thioglycerin as a branched building block, followed by the esterification with an unsaturated carboxylic acid[9b] and the coupling of substitution and deprotection based on the differential reactivity of chlorine atoms of trichlorotriazine.[10] We report here a novel strategy to synthesize commodity dendrimers through the combination of two types of additions without forming any by-product starting from commercially available compounds to achieve the quantity preparation of dendrimers bearing polyols and polyacrylates in a cost-effective way.

Our strategy is based on alternate multiadditions (AMA). Let us consider a couple of difunctional monomers denoted as E_1–E_2 and N_1–N_2 to prepare linear oligomers. E_1 and E_2 are electrophilic, while N_1 and N_2 nucleophilic. In order to accomplish chain lengthening, monomers should fulfill the following requirements. Firstly, E_1 should be reactive with N_1 but not with N_2 at all, whereas E_2 is allowed to react with both N_1 and N_2, in such a way that any cross-talk between the two addition reactions is avoided, as shown in Figure 1a. Secondly, both of the additions involved attain high yields to omit purification processes, leading to the generation growth in a one-pot manner. When R–E_1 as a core molecule reacts with an equimolar amount of N_1–N_2, we obtain specifically R–E_1=N_1–N_2, whereas the double bond stands for the new linkage. The molecule can be converted into R–E_1=N_1–N_2=E_2–E_1 by adding an equimolar amount of the second monomer, E_1–E_2, and E_1 is regenerated at the termini to finish one cycle. If at least one of the monomers is branched and designated as E_2–$(E_1)_2$, the repetition of the reactions results in the generation growth of dendrimers or dendrons, as sketched in Figure 1b.

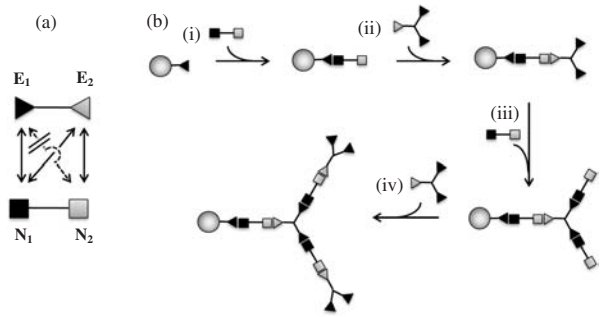

Figure 1. (a) The selection rule of electrophilic (E_1 and E_2) with nucleophilic (N_1 and N_2) substituents. (b) (i) E_1 (closed triangle) of a core molecule adds to N_1 (closed square) of N_1–N_2 to convert the terminus of the product specifically into N_2 (gray square), (ii) which reacts with the trifunctional E_2–$(E_1)_2$. (iii) and (iv) The both additions are repeated for the generation growth.

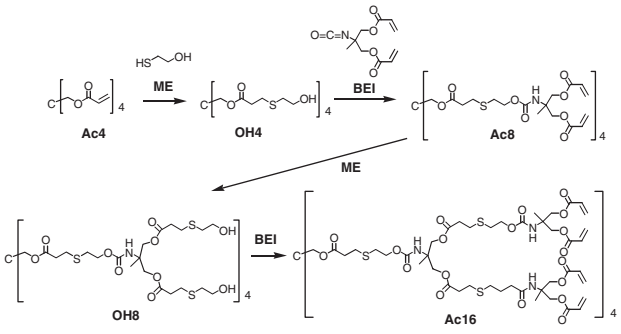

Figure 2. Synthesis of dendrimers through the AMA process starting from commercially available compounds.

We selected the combinations of SH and OH groups as nucleophilic substituents (N_1 and N_2) and acrylate and NCO groups as electrophiles (E_1 and E_2) to fulfill the requirements.[11] We employed 2-sulfanylethanol (ME) as a spacer E_1–E_2, 1,1-bis(acryloyloxymethyl)ethyl isocyanate (BEI) as a branched E_2–$(E_1)_2$ and pentaerythritol tetraacrylate (Ac4) as a core molecules (R–$(E_1)_4$). Note that they are commercially available and used as received. The first step shown in Figure 2 consists of the Michael addition of Ac4 with a 4 molar amount of ME to give the branched tetra-ol (OH4) in THF containing triethylamine (TEA) as a catalyst.[12] As shown in Figure 3 (spectra a and b), the acrylate peaks of Ac4 at ca. 5.9, 6.1, and 6.4 ppm disappeared entirely, accompanied by the appearance of a signal due to CH_2–OH at 3.68 ppm. The product was isolated after the removal of the solvent to confirm the structure by means of MALDI-TOF/MS.[12] A single parent peak due to the sodium-additive form of OH4 appeared at m/z 667. The second step was the ure-

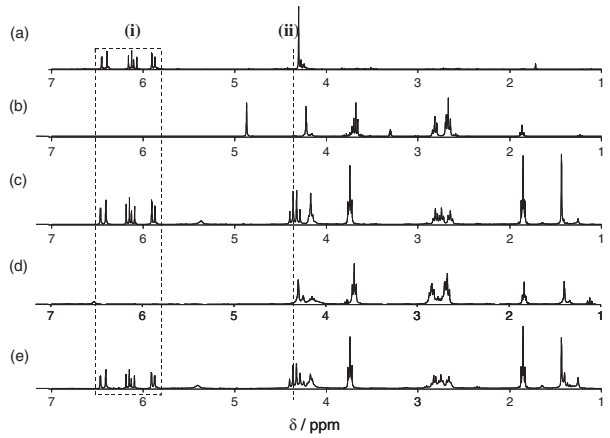

Figure 3. ^{1}H NMR spectra of (a) Ac4, (b) OH4, (c) A8c, (d) OH8, and (e) Ac16 as crude products. The dotted square (i) and line (ii) show the signals of the acrylate and $SHCH_2C\mathit{H}_2$–OH.

thane formation between the OH groups of OH4 and a 4 equiv of BEI in THF under reflux in the presence of dibutyltin dilaurate as a catalyst and cupferon as a polymerization inhibitor to give the dendritic octaacrylate (Ac8). A new signal at ca. 4.3 ppm due to $C\mathit{H}_2$–OCONH appeared as a couple of doublets instead of the perfect disappearance of the $C\mathit{H}_2$–OH signal, as displayed in the spectrum c in Figure 3. The structure of Ac8 was also supported by the MALDI-TOF/MS exhibiting two peaks at m/z 1643 and 1659 assigned to the sodium- and the potassium-additive forms of Ac8, respectively.[12] THF remained even after the prolonged treatment under a reduced pressure, implying the entrapment of THF in Ac8 chains. Subsequently, the yield of crude product exceeded 100%.

The second cycle was achieved in a similar manner by using 8 equiv of ME to react with Ac8 to afford the octa-ol (OH8) quantitatively. Whereas no peak signal due to acrylate was observable, the signals of $C\mathit{H}_2$–OH were observed at 3.68 ppm (the spectrum d in Figure 3). A MALDI-TOF/MS displayed a single peak at m/z 2268 due to the sodium-additive form of OH8.[12] OH8 was treated subsequently with an 8 equiv of BEI to give Ac16. The molecular structure was supported by the thorough disappearance of the proton signals due to $C\mathit{H}_2$–OH (the spectrum e in Figure 3). A MALDI-TOF/MS exhibited a parent peak at m/z 4180 corresponding to the sodium-additive form of Ac16.[12] A ^{1}H NMR spectrum showed that THF is not thoroughly removed again so that the yield of a crude product exceeded 100%.

Noting the facile reactivity of SH with acrylate, Ac8 and Ac16 were subjected to reaction with naphthalene-2-thiol to afford the corresponding 2-naphthylsulfanyl-terminated derivatives (N8 and N16). The purpose was twofold. The first was to determine the purity of the dendrimers after chromatographic separation. The second was to confirm the reasonable chemical modification of the polyacrylate dendrimers. The gel-permeation chromatography analysis revealed that purified N8 exhibits $M_w = 2701$ and $M_w/M_n = 1.04$ whereas the theoretical M_w is 2903, supporting that Ac8 is sufficiently monodispersed. On the other hand, M_w and M_w/M_n of N16 with theoretical $M_w = 6724$ was 5519 and 1.06, respectively, suggesting that the purity of Ac16 is slightly reduced.

The results shown above support the validity of our strategy approaching the quantity production of dendrimers without weight loss. We believe that the dendrimers shown here play a role as commodity chemicals and precursors in developing functional dendrimers by tailor-made chemical modification, followed by final purification. In addition, Ac8 and Ac16 are of practical significance as UV-curable materials because of the enhanced photosensitivity and low polymerization shrinkage, and the results will be reported elsewhere.

References and Notes

1 a) J. M. Fréchet, D. A. Tomalia, *Dendrimers and Other Dendritic Polymers*, John Wiley & Sons, Ltd., **2001**. b) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendrimers and Dendrons, Concepts, Synthesis, Applications*, John Wiley & Sons, **2001**. c) U. Boas, J. B. Christensen, P. M. H. Heegaard, *J. Mater. Chem.* **2006**, *16*, 3785.

2 a) M. J. Cloninger, *Curr. Opin. Chem. Biol.* **2002**, *6*, 742. b) C. C. Lee, J. A. MacKay, J. M. J. Fréchet, F. C. Szoka, *Nat. Biotechnol.* **2005**, *23*, 1517. c) Y. Cheng, Z. Xu, M. Ma, T. Xu, *J. Pharm. Sci.* **2008**, *97*, 123.

3 a) N. Nishiyama, W.-D. Jang, K. Kataoka, *New J. Chem.* **2007**, *31*, 1074. b) M. Guillot-Nieckowski, S. Eisler, F. Diederich, *New J. Chem.* **2007**, *31*, 1111. c) S. Langereis, A. Dirksen, T. M. Hackeng, M. H. P. van Genderen, E. W. Meijer, *New J. Chem.* **2007**, *31*, 1152. d) M. W. Grinstaff, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 383.

4 E. de Jesús, J. C. Flores, *Ind. Eng. Chem. Res.* **2008**, *47*, 7968.

5 a) C.-K. Song, B.-W. Koo, C.-K. Kim, *Jpn. J. Appl. Phys.* **2002**, *41*, 2735. b) S.-C. Lo, P. L. Burn, *Chem. Rev.* **2007**, *107*, 1097. c) P. L. Burn, S.-C. Lo, I. D. W. Samuel, *Adv. Mater.* **2007**, *19*, 1675.

6 a) D. Astruc, C. Ornelas, J. Ruiz, *Acc. Chem. Res.* **2008**, *41*, 841. b) S.-H. Hwang, C. D. Shreiner, C. N. Moorefield, G. R. Newkome, *New J. Chem.* **2007**, *31*, 1192.

7 a) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. b) J. A. Johnson, M. G. Finn, J. T. Koberstein, N. J. Turro, *Macromol. Rapid Commun.* **2008**, *29*, 1052.

8 a) S. P. Rannard, N. J. Davis, *J. Am. Chem. Soc.* **2000**, *122*, 11729. b) M. Okaniwa, K. Takeuchi, M. Asai, M. Ueda, *Macromolecules* **2002**, *35*, 6232. c) F. Koç, M. Wyszogrodzka, P. Eilbracht, R. Haag, *J. Org. Chem.* **2005**, *70*, 2021. d) C. Ornelas, J. R. Aranzaes, E. Cloutet, D. Astruc, *Org. Lett.* **2006**, *8*, 2751.

9 a) L. M. Campos, I. Meinel, R. G. Guino, M. Schierhorn, N. Gupta, G. D. Stucky, C. J. Hawker, *Adv. Mater.* **2008**, *20*, 3728. b) K. L. Killops, L. M. Campos, C. J. Hawker, *J. Am. Chem. Soc.* **2008**, *130*, 5062. c) L. M. Campos, K. L. Killops, R. Sakai, J. M. J. Paulusse, D. Damiron, E. Drockenmuller, B. W. Messmore, C. J. Hawker, *Macromolecules* **2008**, *41*, 7063.

10 A. Chouai, E. E. Simanek, *J. Org. Chem.* **2008**, *73*, 2357.

11 Preliminary reports: a) K. Aoki, R. Sakurai, K. Ichimura, *J. Photopolym. Sci. Technol.* **2007**, *20*, 277. b) K. Aoki, K. Ichimura, *J. Photopolym. Sci. Technol.* **2008**, *21*, 75.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) September 19, 2009; doi:10.1246/cl.2009.990