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Segment Block Dendrimers via Diels−Alder Cycloaddition

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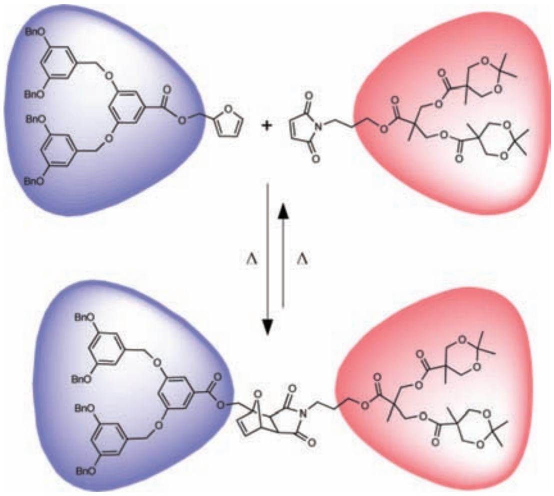
ABSTRACT



Segment block dendrimers consisting of polyester and polyaryl ether dendrons were synthesized using reagent free Diels−Alder cycloaddition reactions. Three generations of furan functionalized polyaryl ether dendrons were reacted with maleimide functionalized polyester dendrons of the same generation to obtain segment block dendrimers in good yields. The thermoreversible nature of these macromolecules was investigated by subjecting them to elevated temperatures in the presence of anthracene as a scavenger diene.

In the past few decades dendrimers[1] have emerged as attractive nanoscale platforms for various applications in areas such as drug delivery,[2] catalysis,[3] formation of enzyme mimics,[4] etc. The fact that they are monodispersed, highly branched, globular structures without defects have made them attractive building blocks in macromolecular chemistry.

While the well-defined multivalent construct of the dendrimer surface itself makes this class of macromolecules unique, the ability to selectively append different functional groups onto the surface renders them multifunctional as opposed to being simply multivalent.

Recent developments have focused on both the efficient surface functionalization of dendrimers and the synthesis of dendrimers with orthogonal reactive groups.[5] Pioneering

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(4) (a) Zimmermann, S. C.; Wendland, M. S.; Rakow, N. A.; Zharov, I.; Suslick, K. S. *Nature* **2002**, *418*, 399–403. (b) Tomalia, D. A.; Huang, B.; Swanson, D. R.; Brothers, H. M., II; Klimash, J. W. *Tetrahedron* **2003**, *59*, 3799–3813.

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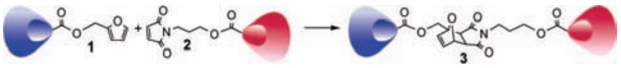
work by Hawker et al. utilized the copper catalyzed [3 + 2] Huisgen-type cycloaddition reaction between an alkyne and an azide to obtain orthogonally functionalizable surface block dendrimers.[6] The facile and favorable nature of this cycloaddition reaction classifies it as a click reaction.[7] Such clean and efficient reactions offer attractive synthetic protocols in macromolecular chemistry. Steric bulk of the macromolecular reactants and difficulty in separation from byproducts generated by undesirable side reactions demand usage of simple, clean, and high-yielding transformations, attributes offered by click reactions.[8] Another alternative click reaction, the Diels−Alder cycloaddition between an electron-rich diene and electron-deficient dienophile has also attracted considerable attention in macromolecular synthesis and transformations.[9,10] While the use of facile cycloaddition reactions is an attractive route for the assembly of reaction components, cycloreversion under elevated temperatures offers disassembly on demand. Reassembly under mild conditions provides a repair mechanism of components.[11]

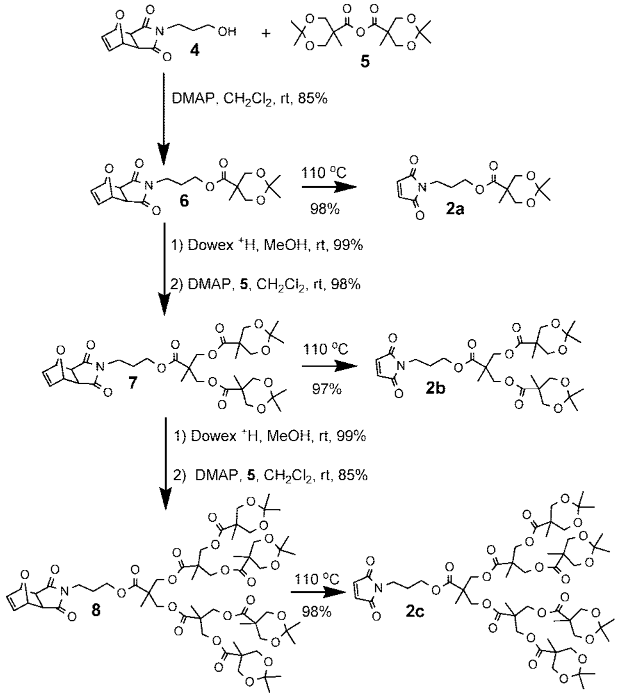
To date, in dendrimer synthesis the Diels−Alder reaction has been utilized to combine identical dendrons to furnish symmetrical dendrimers.[12] Our interest to utilize Diels−Alder-based synthetic strategies in macromolecular synthesis prompted us to evaluate the cycloaddition reaction toward the synthesis of unsymmetrical dendrimers. Herein we report the first example for synthesis of segment block (AB type) dendrimers with Diels−Alder reaction (Scheme 1). The reaction does not require use of metal catalysts and hence the dendrimers formed this way are free of metal impurities which, when present, may cause problems if their biological use is intended.

Scheme 1. General Representation of the Strategy Utilized



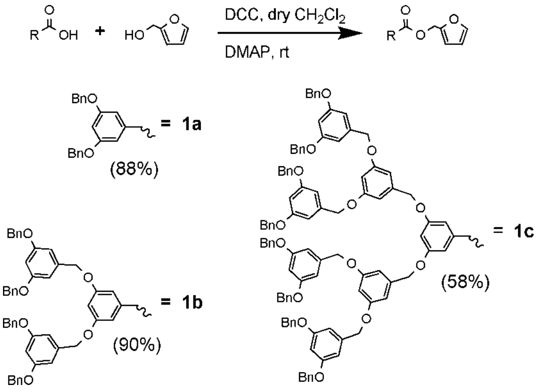
Acetal-protected polyester dendrons were prepared divergently[13] starting with a furan-protected *N*-hydroxypropylmaleimide **4**. Coupling reaction with the anhydride monomer **5** in presence of 4-(dimethylamino)pyridine (DMAP) produced **6**, which upon refluxing in toluene at 110 °C furnished the desired dendron **2a** containing the reactive maleimide group at the focal point (Scheme 2). Second-generation dendron **2b** was obtained by deprotection of the acetal groups in **6**, followed by treatment of thus-obtained diol with anhydride monomer **5** and subsequent rDA reaction by refluxing in toluene. Similar steps were followed to obtain the desired third-generation dendron.

Scheme 2. Divergent Synthesis of Maleimide Functionalized Dendron



Three generations of furan-functionalized polyaryl ether dendrons were prepared by coupling the acid-functionalized Fréchet dendrons[14] with furfuryl alcohol in the presence of DMAP and DCC at ambient temperature. Dendrons were obtained with 88%, 90%, and 58% yields, respectively (Scheme 3).

Scheme 3. Core Modification of Fréchet Dendrons



The reaction of furan-functionalized dendrons **1a**−**c** with dendrons **2a**−**c** in benzene at 85 °C for 24 h afforded the

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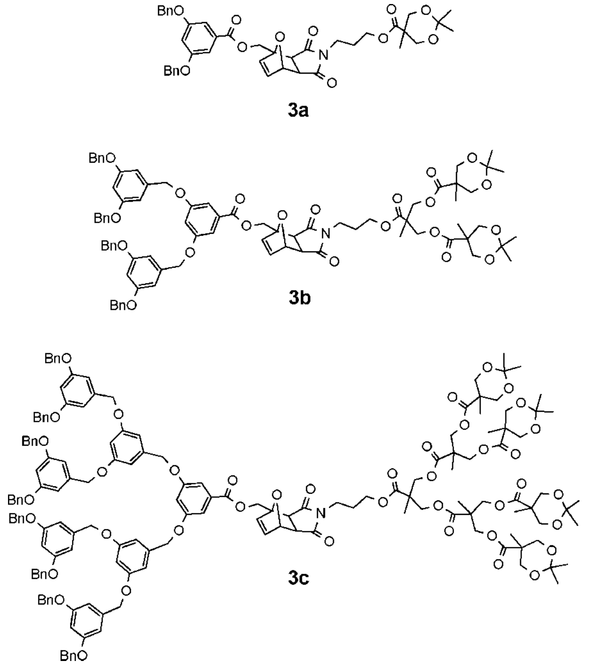
three generations of dendrimers **3a**−**c** in 98%, 76%, and 79%, respectively (Scheme 4). The cycloaddition reactions were very clean transformations, resulting in desired dendrimers after column chromatography.

Scheme 4. Structures of the Unsymmetrical Dendrimers



3a

3b

3c

These dendrimers possess a bicyclic furan maleimide cycloadduct as a core. The Diels−Alder reaction between a furan and maleimide produces cycloadducts as exo and endo isomers. The endo/exo selectivity of the reaction was determined using ^{1}H NMR spectroscopy as described later. Proton NMR data of the dendrimer shows that the two dendrons are combined together through a bicyclic core. Appearance of new proton resonances corresponding to the bicyclic core at 5.2 and 2.9 ppm and the disappearance of characteristic peaks belonging to the maleimide and furan units at the dendron focal points elucidate the structure of the core (Figure 1).

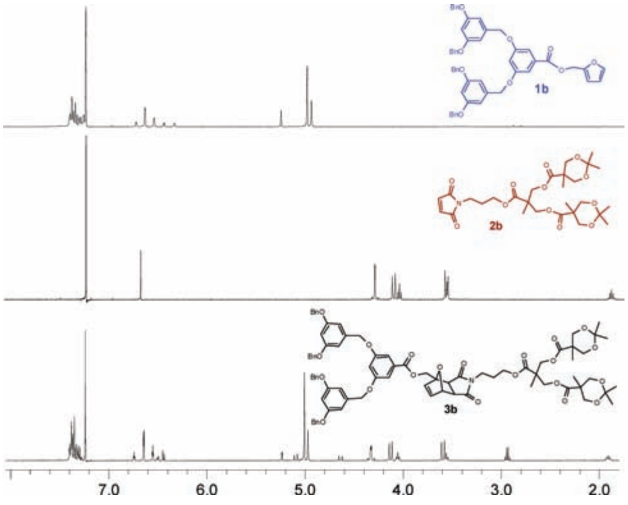


Figure 1. ^{1}H NMR spectra of **1b** and **2b** dendrons and **3b** dendrimer.

Due to the facile thermoreversibility of the endo products relative to the exo adducts, a higher reaction temperature favors formation of exo adducts. In order to investigate effect of temperature on exoendo ratios of the formed products, a series of reactions with first generation dendrons **1a** and **2a** were done at rt, 45, 65, and 85 °C for 24 h. The results suggest that fine-tuning of the reaction temperature plays an important role for the stereoselectivity of the formed product and it is possible to obtain pure exo product at 85 °C for the first generation dendrimers **3a** (Figure 2). However it was not possible to exclusively obtain exo product for the second- and third-generation dendrimers **3b** and **3c**. At this point, a previous literature example was helpful for determining the peaks in the ^{1}H NMR corresponding to exo/endo isomers.[15] For example, in first-generation dendrimer **3a**, the benzoic ester methylene protons in the exo cycloadducts appear as doublets at 5.11 and 4.65 ppm, whereas for the endo-adducts they appear at 5.02 and 4.82 ppm. ^{1}H NMR spectra of the products have shown that the second-generation dendrimer **3b** was obtained with an exo/endo ratio of (91:9), whereas the third-generation dendrimer **3c** was obtained with an exo/

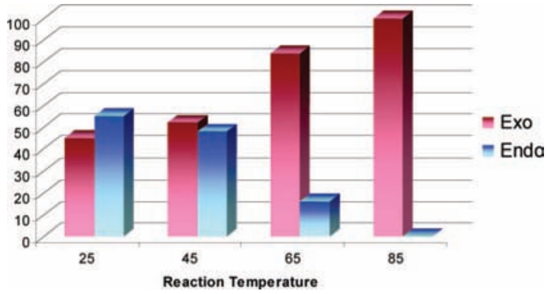


Figure 2. Effect of reaction temperature on stereochemistry of the core of dendrimer **3a**.

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(10) (a) Gacal, B.; Durmaz, H.; Tasdelen, M. A.; Hizal, G.; Tunca, U.; Yagci, Y.; Demirel, A. L. *Macromolecules* **2006**, *39*, 5330–5336. (b) Gheneim, R.; Perez-Berumen, C.; Gandini, A. *Macromolecules* **2002**, *35*, 7246–7253. (c) Gousse, C.; Gandini, A.; Hodge, P. *Macromolecules* **1998**, *31*, 314–321. (d) Dispinar, T.; Sanyal, R.; Sanyal, A. *J. Polym. Sci. Part A: Polym. Chem.* **2007**, *45*, 4545–4551.

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endo ratio of (87:13). But, thermal treatment, as described later, allows one to obtain dendrimers with exo bridged cores.

To simplify the access to pure exo isomer of dendrimers **3b** and **3c**, we added a furan-functionalized Merrifield resin to scavenge any remaining maleimide dendron that was difficult to separate from the desired dendrimer using chromatographic techniques. This thermal treatment of mixture of endo/exo adducts with the scavenger resin at 50 °C also enables one to exclusively obtain exo bridged dendrimer. The resulting exo dendrimers were further characterized by GPC (Figure 3) giving narrow polydispersity values as expected; however, the molecular weights were far from the exact values due to the globular shape of the dendrimers.

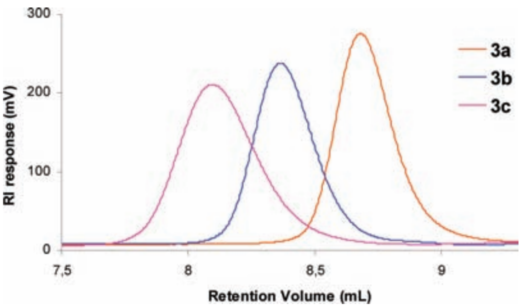

Figure 3. GPC results for the dendrimers **3a**−**c**.

In order to demonstrate the thermoreversibility property of the dendrimers formed, dendrimer **3b** was refluxed in toluene in the presence of anthracene. Anthracene was added as a scavenger diene to prevent reassembly of the released maleimide and furan dendrons.

Cycloaddition with anthracene under these conditions produces an adduct that is nonreversible. Disappearance of the peak at 2.94 ppm proves that the dendrimer **3b** has disassembled completely. ^{1}H NMR data shows that the peaks corresponding to **1b** were recovered completely. Furthermore absence of a singlet at 6.64 ppm and formation of the new multiplet at 3.16 ppm indicates that maleimide has completely reacted with the anthracene molecule (Figure 4).

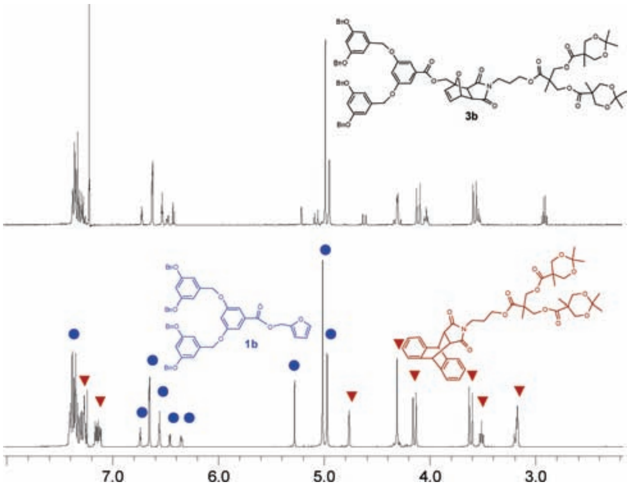

Figure 4. ^{1}H NMR spectra of second-generation dendrimer (**3b**) and the retro-Diels−Alder products.

To sum up, a general strategy for the combination of dendrons to obtain dendrimers in good yield has been developed using a reagent-free thermal cycloaddition reaction. Further work along these lines to obtain dendron−polymer conjugates are currently in progress and will be reported in due course.

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Supporting Information Available: Complete details of the synthesis and characterizations of the dendrons **1a**−**c**, **2a**−**c**, and dendrimers **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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