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Thermally Responsive Dendrons and Dendrimers Based on Reversible Furan-Maleimide Diels–Alder Adducts

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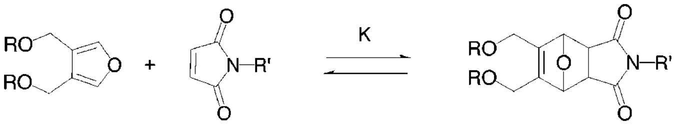
ABSTRACT



Benzyl aryl ether dendrons and dendrimers containing thermally reversible furan-maleimide Diels–Alder adducts were prepared up to the third generation. The covalent cleavage and reassembly of the dendrons and dendrimers were evaluated by ^{1}H NMR.

Dendrimers[1] comprise a family of synthetic macromolecules that are considered to be prime nanometer-scale building blocks for materials that may serve as chemical sensors,[2] molecular recognition devices,[3] chemical delivery systems,[4] separations devices,[5] etc. Recently, the alteration of the structure of novel dendritic architectures through control of covalent and noncovalent interactions and conditions has attracted much attention. Examples include dendritic systems that can be assembled,[6] degraded,[7] and configurationally[8] or conformationally[9] altered. We report here the preparation and initial investigations of thermally cleavable/reassembling dendrons and dendrimers based on furan-maleimide Diels−Alder (DA) reactions. Other examples[10] of dendrimer construction using DA chemistry exist. To our knowledge, this represents the first covalent thermally reversible design strategy in a dendritic system.

Reversible DA reactions between reactive dienes and dienophiles are well studied.[11] In particular, the reaction between substituted furans and maleimides has been fre-

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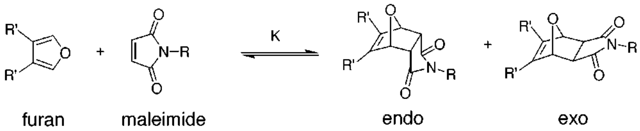
quently utilized in the preparation of thermally responsive polymers.[12] This is primarily due to ease of adduct formation and dissociation. Adduct formation typically occurs at room temperature, and adduct dissociation occurs at elevated temperatures (>90 °C) (Scheme 1).

Scheme 1

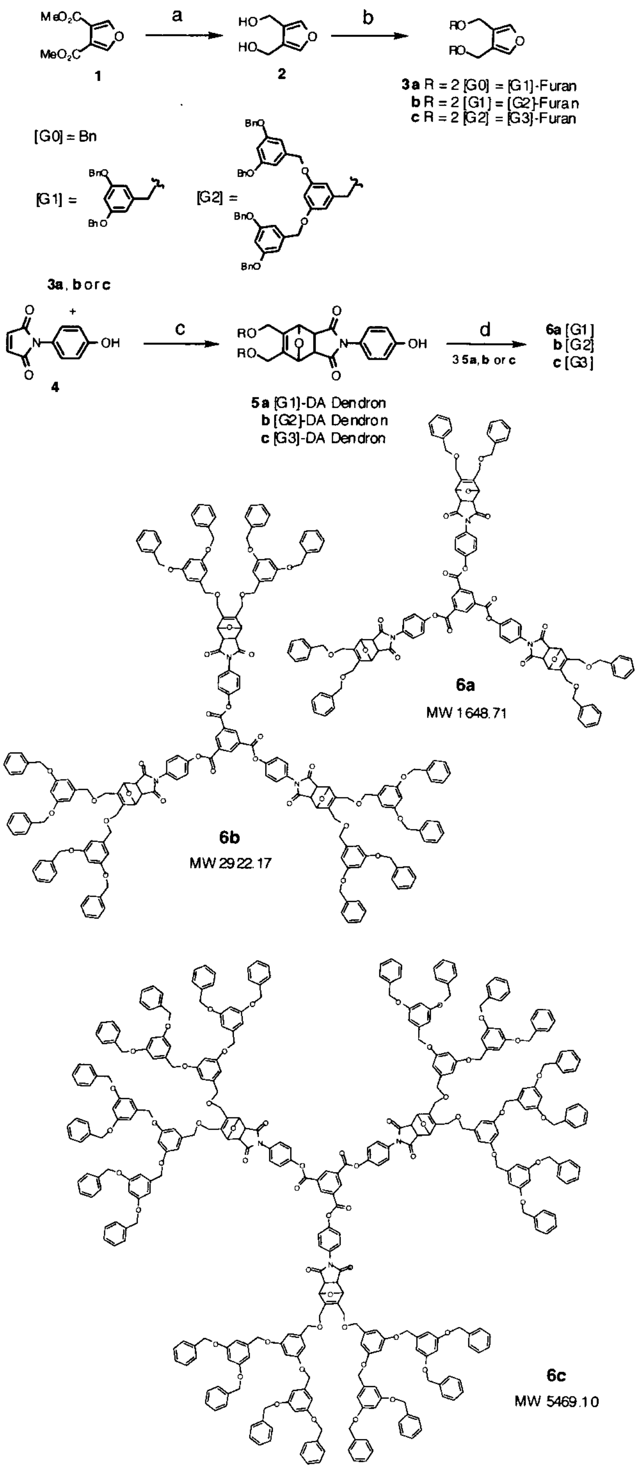


Our convergent approach toward designing thermally responsive dendritic architectures involved preparing dendrons with substituted furan-maleimide DA adducts located at the dendron focal point. We required a disubstituted furan that could serve as an AB_2 monomer and an N-substituted maleimide with a reactive hydroxyl focal point.

AB_2 furan monomer **2**[13] was prepared in one step through $LiAlH_4$ reduction of commercially available dimethyl 3,4-furandicarboxylate (**1**). *N*-(4-Hydroxyphenyl)maleimide[14] (**4**) was chosen as our reactive dienophile (Scheme 2). First through third 3,4-substituted furan dendrons **3a**−**c** were prepared by reaction of **2** with the appropriate dendritic bromide[15] in the presence of NaH in DMF or KH in THF. First through third DA dendrons **5a**−**c** were prepared by reacting the appropriate furan dendron with **4** at either ambient temperature or 65 °C in ether/ethyl acetate solution. First generation **5a** precipitated from the reaction mixture as pure exo isomer, while second and third generation dendrons **5b** and **5c**, respectively, were each obtained as a 33%/66% mixture of endo/exo isomers as determined by ^1H NMR.

First through third generation dendrimers **6a**−**c** were prepared by reaction of 1,3,5-benzenetricarbonyl trichloride central linker with the appropriate DA dendron in the presence of Et_3N in THF. To our delight, thermal isomerization[16] of exo/endo mixtures of second and third generation dendrons and dendrimers gave pure exo isomers after heating **5** and **6** **a**−**c** neat at 65 °C for 48 h.

Scheme 2[a]



[a] Reaction conditions: (a) $LiAlH_4$, Et_2O, 88%; (b) NaH, DMF, and 2 equiv either (i) BnBr, 84% or (ii) [G-1]-Br, 66%; KH, 2 equiv [G-2]-Br, THF, 74%; (c) either Et_2O/EtOAc or EtOAc, rt or 65 °C; (d) benzene-1,3,5-tricarbonyltrichloride, Et_3N, THF, 67%, 87%, and 73%, respectively.

The reversible DA reaction for all dendrons and dendrimers was evaluated by ^1H NMR spectroscopy. NMR samples (DMF-d_7) of identical concentrations[17] of dendrons **5a**−**c** were heated at 110 °C for 48 h. The NMR resonance at δ 9.99, corresponding to the phenolic proton of the DA dendrons, proved diagnostic in determining percent dendron dissociation. As the dendron samples were heated, a new singlet appeared at δ 9.95, corresponding to the phenolic resonance of *N*-(4-hydroxyphenyl)maleimide (**4**) generated during the retro DA reaction. The ratio of these peaks revealed that approximately 40% of dendrons **5a**−**c** had

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[13] **2** and **3a** are known compounds; see: Meissner, R.; Garcias, X.; Mecozzi, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 77.

[14] Compound **4** was prepared according to the literature: Park, J. O.; Jang, S. H. *J. Polym. Sci. Polym. Chem. Ed.* **1992**, *30*, 723−729.

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[17] Dendron concentration was 9.62 × 10^{-2} M.

dissociated to maleimide **4** and furan dendron **3** after 1 h of heating, at which point equilibrium was established and no further changes were observed by NMR. Similarly, the reassembling of dendrons **5a**−**c** was evaluated by heating the samples at 65 °C. As anticipated, the reassembly process was much slower; approximately 82% dendron formed after 5 days. Concentration of **5a**−**c** and heating (65 °C, 48 h) regenerated dendrons **5a**−**c** completely as observed by ^{1}H NMR (Figure 1).

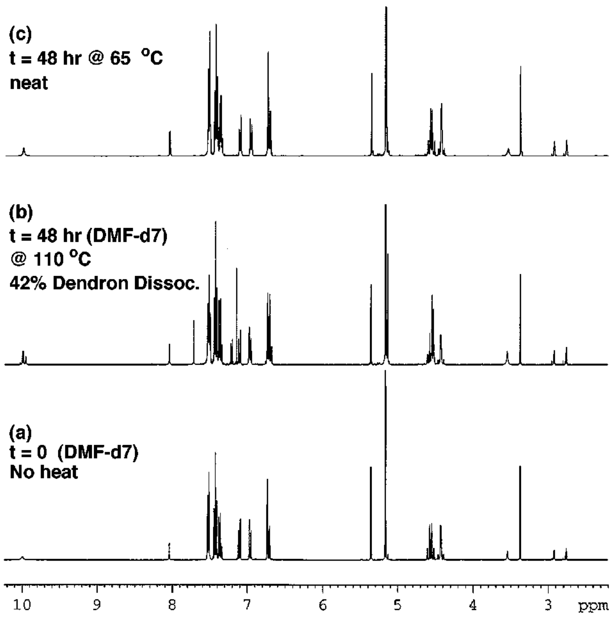

Figure 1. ^{1}H NMR spectra (DMF-d_7) of [G-2]-DA dendron **5a** (a) before heating, (b) after heating (110 °C) for 48 h (42% dissociation), and (c) after concentration and heating (65 °C) for 48 h (100% dendron).

Identical NMR experiments were performed with dendrimers **6a**−**c**.[18] Dissociation of **6a**−**c** was clearly evident; however, degradation of the samples occurred upon prolonged heating (110 °C) in DMF-d_7. This is presumably due to amine generated through partial thermal decomposition of DMF and subsequent reaction with the esterified dendritic core. Michael addition[19] through amine attack upon free maleimide is less likely since no degradation is observed in dendrons **5a**−**c**.

Similar NMR experiments were performed in DMSO-d_6 with substantially less dendrimer degradation. Dendrimers **6a**−**c** again readily dissociated at 110 °C. The extent of dendrimer dissociation cannot be calculated accurately, as three DA adducts are present. Fortunately, percent furan dendron formed could be calculated through comparison of characteristic ^{1}H NMR resonances.[20] First, second, and third generation dendrimers yielded 80%, 70%, and 86% furan dendron, respectively, after heating for 24 h. The dendrimer reassembly process was examined after concentration and heating at 65 °C for 48 h. ^{1}H NMR revealed complete reassembly of first generation dendrimer **6a** (exo). Reassembly was incomplete for second generation **6b** and third generation **6c** with 58% and 80% dendron, respectively, still present. Incomplete reassembly of **6b** and **6c** may be due to a combination of steric and entropic influences.

The present work represents the first examples of thermally cleavable/reassembling dendrons and dendrimers via the reversible DA reaction between furan and maleimide. We hope to demonstrate application as chemical delivery and/or encapsulant systems in our future studies.

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Supporting Information Available: Synthetic details and characterization data for all compounds reported and dendrimer molecular weight determination by GPC. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Dendrimer concentration was 1.05 × 10^{-2} M.

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(20) Percent furan dendron formed was calculated through a ratio of peaks (δ 9.06) corresponding to the three protons of the central core with (a) the singlet (δ 4.39) corresponding to four methylene protons of the [G-1] furan dendron (for [G-1] dendrimer) or (b) the singlet (δ 5.02) corresponding to eight benzyl protons of the [G-2] or [G-3] furan dendron (for [G-2] and [G-3] dendrimers).