Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4788

www.rsc.org/obc

PAPER

Solid-phase synthesis and acidolytic degradation of sterically congested oligoether dendrons†

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Received 23rd February 2012, Accepted 27th April 2012
DOI: 10.1039/c2ob25691f

Up to third-generation sterically crowded polyether dendrons were prepared on a solid support, using a novel building block derived from dimethyl 5-hydroxyisophthalate *via* *O*-allylation/Claisen rearrangement key steps. These dendrons underwent smooth disassembly to monomers, when subjected to acidic solution. The reason for this decomposition was traced to the increased electron density of the aromatic rings of the new monomers that destabilizes the bonds connecting the building blocks.

Introduction

In the past two decades an impressive variety of dendritic molecules were prepared and investigated for a broad range of applications.[1] These molecules were mostly prepared in solution, while only a relatively small portion of the dendritic compounds were assembled on an insoluble matrix or post-synthetically attached to solid supports.[2,3] While, in general, the structure and properties of monomeric units usually strongly affect the properties of the dendritic molecules assembled from these modules, in the case of dendronized solid supports these features of the branched monomers strongly affect not only the properties of the dendritic fragment, but also those of the whole matrix–dendron composite material. The strongest influence is that of the terminal units decorating the dendritic periphery, as we demonstrated in the past for polyether dendrons on cross-linked polystyrene.[4] However, the structure and properties of the inner parts of the dendrons can also impart important features on the properties and functioning of the entire construct. For instance, we observed the influence of the coordinating heteroatoms in the dendritic backbone of supported catalysts on the outcome of the Heck reaction.[5]

While this was a purely electronic effect, steric effects in the dendritic backbone of dendronized supports are also an intriguing possibility. In this regard, the questions that we asked ourselves are whether it is possible to construct dendrons on solid support from sterically congested monomers, what would be the properties of such dendrons and how will such a dendritic design affect the properties and functioning of the new support? Herein we report the synthesis of a sterically crowded building unit for polyether dendrons, the assembly of such dendrons on polystyrene support and the unexpected decomposition of the new dendrons in acidic solution.

Results and discussion

So far the majority of dendritic motifs used in insoluble support–dendron composites were the easily accessible "privileged" structures, such as PAMAM, polylysine or polyurea dendrons.[6–8] While in a number of cases steric hindrance of the dendrons was reported (usually as a factor obstructing their effective synthesis), it did not originate from the monomeric unit structure, but rather emerged during the dendron assembly.[9] Due to the extensive experience in solid-phase synthesis of polyether dendrons gathered in our group in the past decade,[4,10] we decided to design and prepare a sterically congested monomeric unit that will enable assembly of dendrons based on this motif. Though soluble polyether dendrons, mostly of the Fréchet-type, are used frequently for a variety of applications,[11] polyether-dendronized supports are relatively scarce.[4,10,12]

A literature search concluded that incorporation of substituents in the *ortho*-to-hydroxyl positions in 5-hydroxyisophthalates, which we used previously as a monomer in the polyether dendron synthesis,[4,10c] can be accomplished in an efficient and selective manner only for allyl substituents *via* the Claisen rearrangement reaction.[13,14] The bis-allylated compound **1** was obtained from dimethyl 5-hydroxyisophthalate by a stepwise introduction of two allylic groups in the *ortho*-to-hydroxyl positions of dimethyl 5-hydroxyisophthalate *via* the *O*-allylation/Claisen rearrangement sequence performed twice (Scheme 1).[14a–f] The synthesis can be carried out in a highly efficient and practical way. The *O*-allylation reactions afford allyl ether intermediates in excellent yield and high purity, so that in the next steps they could be used after a short workup without further purification. Moreover, there is usually no need for extensive purification after the first Claisen rearrangement, since

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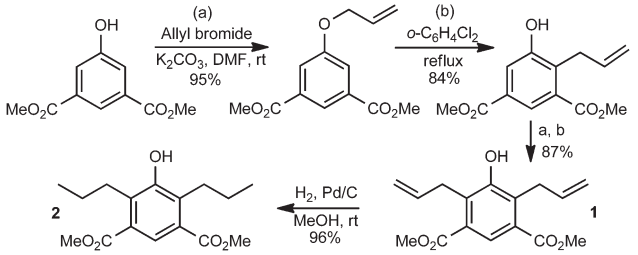
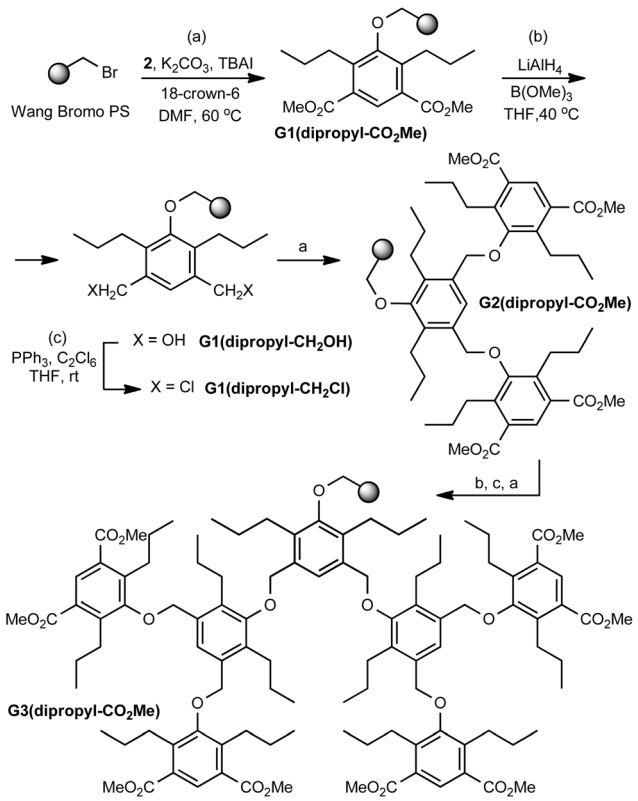
†Electronic supplementary information (ESI) available: NMR spectra. See DOI: 10.1039/c2ob25691f



Scheme 1 Synthesis of the branched building blocks.



Scheme 2 Synthesis of dendrons on solid support.

partial solvent removal usually leads to spontaneous crystallization of the pure product as a colorless solid.[15] Chromatographic purification must be carried out only after the second Claisen rearrangement, yielding compound **1**.

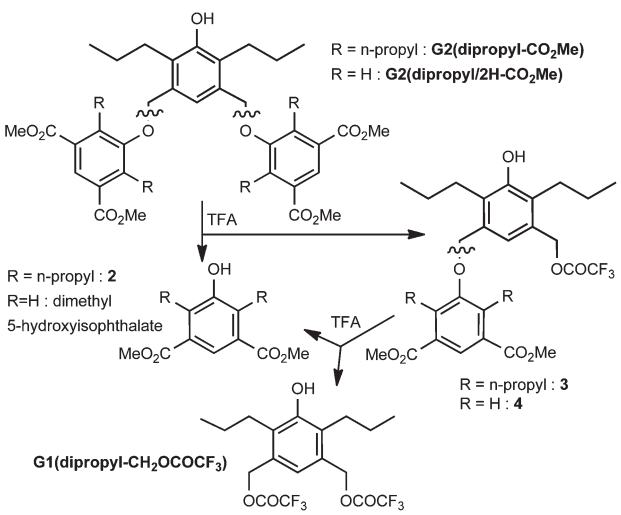
In order to avoid unwanted side reactions of the allylic substituents during the dendron-building procedures, we decided to continue working with *n*-propyl substituted monomer **2**, which was obtained *via* hydrogenation of **1** in excellent yield and purity after a simple workup (Scheme 1).[14b,e]

The synthetic route to the dendron preparation followed the one reported in the past for the assembly of polyether dendrons from the hydroxyisophthalate units without the propyl substituents (Scheme 2).[10c] It included immobilization of **2** *via* nucleophilic substitution, followed by the reduction with $LiBH_4$ and, then, activation of the hydroxybenzyl arms, used for the dendrimer growth, by the chlorodehydroxylation reaction with PPh_3 and C_2Cl_6. The replacement of the LiH base by a more "user-friendly" K_2CO_3 at the substitution step was the only alteration to the reported procedures. In this manner we succeeded in building the first to third generation structures **G1(dipropyl-X)–G3(dipropyl-X)** (X = CO_2Me, CH_2OH or CH_2Cl).

Gel phase ^{13}C NMR spectroscopy of the resins was used to monitor the synthetic transformations, while the structure and purity of the dendrimers were determined *via* the TFA-induced cleavage, followed by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR measurements of the dendrons of the first generation demonstrated excellent conversion and purity of each of the steps, based on the following characteristic changes. The reduction step was accompanied by the disappearance of the carboxymethyl signal at 4.00 ppm and the appearance of the CH_2OCOCF_3 signals (under the cleavage conditions the alcohols gradually undergo trifluoroacetylation) at 5.44 ppm; the latter disappeared upon chlorodehydroxylation, being replaced by the CH_2Cl signal at 4.62 ppm.

The ^{1}H NMR measurements of the cleaved second and third generation dendrons revealed that under acidic conditions these molecules are being disassembled gradually to the monomeric building blocks (*e.g.* Scheme 3, R = *n*-propyl). This was somewhat surprising, since similar dendrons built from dimethyl 5-hydroxyisophthalate (which lacks propyl substituents) are stable under equivalent conditions.[4,10c]

The observed phenomenon does not represent a synthetic problem, since we intend to use the intact matrix–dendron composite support. However, it somewhat complicated the characterization. Accordingly, the analysis of each synthetic step followed the complete disassembly of the dendron and was based on the total loading of the monomeric units and the proportion between their different variants. These measurements demonstrated excellent conversion and purity of each of the synthetic steps forming the second and third generation dendrons. The characteristic changes in the aromatic region of the ^{1}H NMR spectrum, observed upon the decomposition described in Scheme 3, are demonstrated in Fig. 1. Thus, the disassembly of intact **G2(dipropyl-CO_2Me)** was accompanied by the disappearance of the aromatic signals at 8.17 and 7.64 ppm and the appearance of the signal of **2** at 7.95 ppm and the signals of **3** at 8.17 and 7.33 ppm (Fig. 1a–b). The subsequent disassembly of **3** was accompanied by the disappearance of its aromatic signals and



Scheme 3 Post-cleavage acidolytic degradation of dendrons.

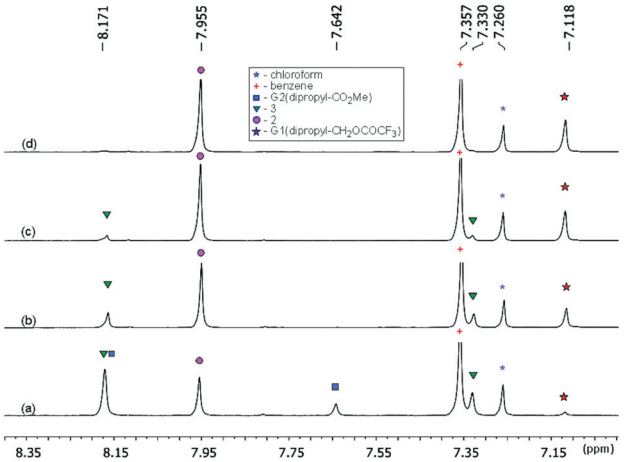


Fig. 1 The aromatic part of the ^{1}H NMR spectra of **G2(dipropyl-CO$_2$Me)** in the cleavage solution (TFA–$CDCl_3$, 1 : 1) after (a) 0.5 h; (b) 2.5 h; (c) 5 h; (d) 7.5 h.

the appearance of the **G1(dipropyl-CH$_2$OCOCF$_3$)** signal at 7.12 ppm in addition to the increase in the intensity of the signal of **2** at 7.95 ppm.

The introduction of the propyl substituents on the dendron-forming modules could affect the dendron stability under acidic conditions in a number of possible ways. The stabilization of the benzyl cations in the respective *ortho*/*para* positions makes the benzylic carbon–oxygen bond more labile and may facilitate its cleavage. Alternatively, the increase in the electron density on the propylated aromatic rings raises the basicity of phenol oxygen, facilitates its protonation and thus may increase the rate of the bond cleavage. Finally, the steric strain may destabilize the dendritic structure.

In order to distinguish between these mechanistic explanations of the dendrimer degradation, we synthesized two additional second-generation dendritic molecules (Fig. 2). One of the dendrons was built starting with the dipropylated building block **2** as the first generation module, while the second generation was assembled using dimethyl 5-hydroxyisophthalate (**G2(dipropyl/2H-CO$_2$Me)**). The use of these two building blocks in the construction of the second dendron was in the opposite order (**G2(2H/dipropyl-CO$_2$Me)**). In this way each of the dendrons expressed only one of the electronic factors, which might be responsible for the **G*n*(dipropyl)** dendrons' disassembly. If the stabilization of the benzylic cations by the *ortho*- and *para*-positioned propyls is the main reason for the instability of the **G*n*(dipropyl)** ($n > 1$) dendrons in the TFA solution, then the "mixed" dendron **G2(dipropyl/2H-CO$_2$Me)** will be also decomposed in this solution. However, if the increase in the basicity of the phenol oxygen induced by the propyl substituents contributes to the instability of **G*n*(dipropyl)** in the acidic solution, then we may expect that the second "mixed" dendron (**G2(2H/dipropyl-CO$_2$Me)**) will be decomposed upon acidic treatment. The disassembly of both "mixed" dendrons will proceed slower than that of **G2(dipropyl-CO$_2$Me)**, if at all, in the case that the steric strain is the main reason for the phenomenon. In the latter case, one may expect that the more sterically congested dendron **G2(2H/dipropyl-CO$_2$Me)** will undergo the decomposition faster than **G2(dipropyl/2H-CO$_2$Me)**.

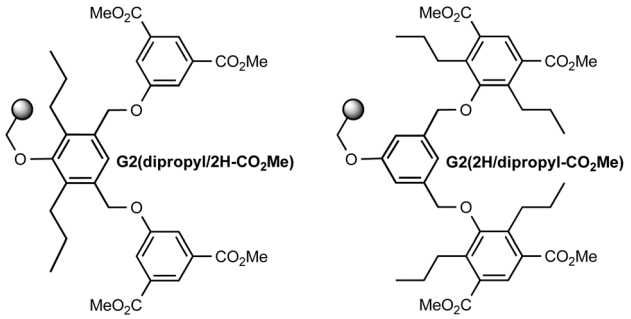


Fig. 2 "Mixed" second generation dendrons.

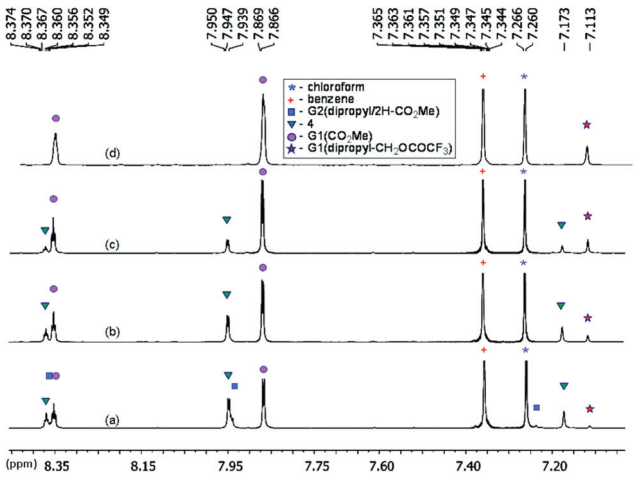


Fig. 3 The aromatic part of the ^{1}H NMR spectra of **G2(dipropyl/2H-CO$_2$Me)** in the cleavage solution (TFA–$CDCl_3$, 1 : 1) after (a) 1 h; (b) 2.5 h; (c) 7.5 h; (d) 24 h.

Both dendrons were analyzed by a series of ^{1}H NMR measurements in the 1 : 1 TFA–$CDCl_3$ cleavage solution, which revealed that only the **G2(dipropyl/2H-CO$_2$Me)** dendron was decomposed under the acidolytic conditions (Scheme 3 (R = H)), while **G2(2H/dipropyl-CO$_2$Me)** remained as an intact structure in this solution, even after 72 h. This behavior proves that the major factor contributing to the sensitivity of the **G*n*(dipropyl)** ($n > 1$) dendrons to acid is the stabilization of the benzylic cations by the *ortho*- and *para*-positioned propyl substituents.

The characteristic changes in the aromatic region of the ^{1}H NMR spectrum, observed upon the degradation of **G2(dipropyl/2H-CO$_2$Me)**, are demonstrated in Fig. 3. The disassembly of intact **G2(dipropyl/2H-CO$_2$Me)** was accompanied by the disappearance of the aromatic signals at 8.36, 7.94 and 7.24 ppm and the appearance of the dimethyl 5-hydroxyisophthalate (**G1(CO$_2$Me)**) signals at 8.35 and 7.87 ppm and the signals of **4** at 8.37, 7.95 and 7.17 ppm (Fig. 3a–b). The subsequent decomposition of **4** was accompanied by the disappearance of its aromatic signals and the appearance of the **G1(dipropyl-CH$_2$OCOCF$_3$)** signal at 7.11 ppm, as well as the increase in the intensity of the signals of **G1(CO$_2$Me)** at 8.35 and 7.87 ppm.

Processing of the raw NMR monitoring data of the decomposition of the second generation dendrons in the 1 : 1 TFA–$CDCl_3$

solution is summarized in the charts in Fig. 4a–b. Though it is difficult to compare the rates of the conversion of the intact dendrons **G2(dipropyl-CO_2Me)** and **G2(dipropyl/2H-CO_2Me)** into the partially disassembled dendrons **3** and **4**, respectively, due to the partial overlap of the signals of the two-arm and one-arm structures and the fast reaction rate, the subsequent decomposition of the one-arm **G2** structures is notably faster for compound **3** (k_{obs} 0.44 h^{-1} for **3** and 0.19 h^{-1} for **4**).[16] In order to carefully monitor the first disassembly process, we performed a series of ^{1}H NMR measurements in the less acidic 1 : 9 TFA–$CDCl_3$ solvent mixture. The characteristic changes in the aromatic region of the ^{1}H NMR spectrum, observed upon the degradation of both dendrons in this solvent mixture, were similar to those depicted in Fig. 1 and 3,[17] but occurred at a slower rate. Processing of these data (Fig. 4c–d) proved that **G2(dipropyl-CO_2Me)** undergoes decomposition significantly faster than **G2-(dipropyl/2H-CO_2Me)** (k_{obs} values of 0.19 h^{-1} and 0.076 h^{-1} respectively).[18] It is likely that these differences, as well as those between the decomposition rates of **3** and **4**, are caused by the increased phenol–oxygen basicity induced by the propyl substituents and/or higher steric strain in the case of the **G2(dipropyl-CO_2Me)** dendron and compound **3**, whereas these properties by themselves are not sufficient to induce acidolytic degradation.

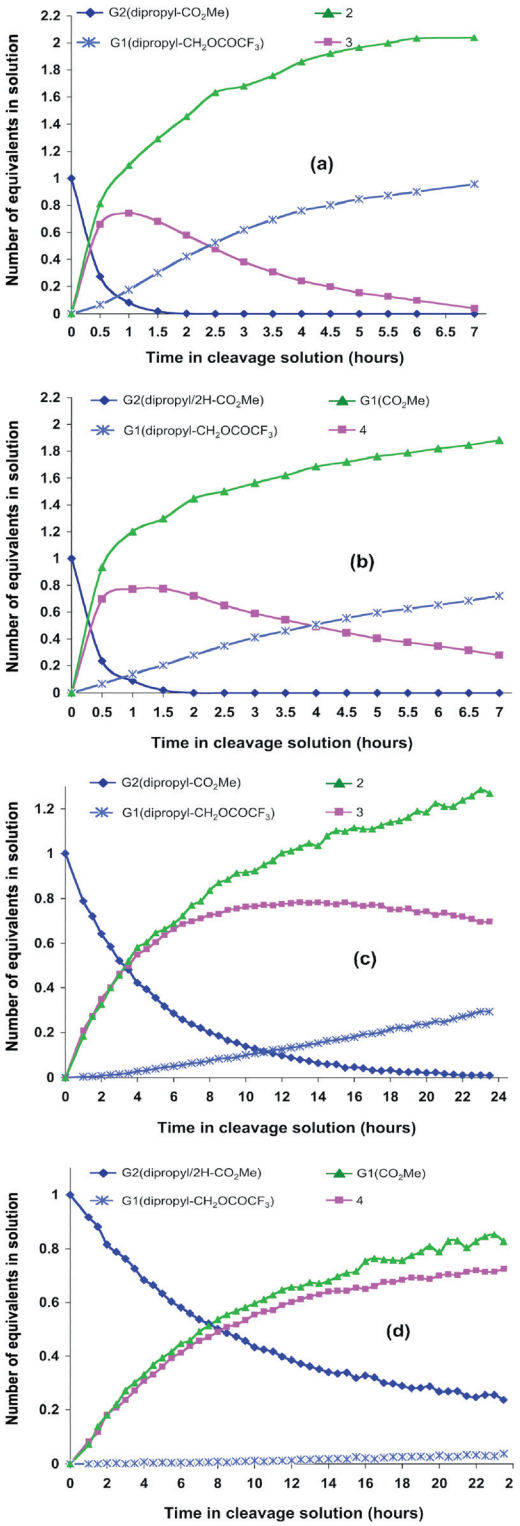


Fig. 4 Monitoring of the disassembly of (a) **G2(dipropyl-CO_2Me)** in TFA–$CDCl_3$, 1 : 1; (b) **G2(dipropyl/2H-CO_2Me)** in TFA–$CDCl_3$, 1 : 1; (c) **G2(dipropyl-CO_2Me)** in TFA–$CDCl_3$, 1 : 9; (d) **G2(dipropyl/2H-CO_2Me)** in TFA–$CDCl_3$, 1 : 9.

Experimental

General

All reactions were conducted under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. THF was dried over, and distilled from, sodium metal with benzophenone as the indicator. Dichloromethane was dried over, and distilled from, CaH_2.

Wang bromo polystyrene resin is 1% crosslinked divinylbenzene–styrene copolymer, 100–200 mesh, with loading 0.90 mmol g^{-1} and was purchased from Novabiochem.

^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.62 MHz) spectra were recorded on Bruker AVANCE-200 and AVANCE-400 spectrometers, in $CDCl_3$ or $CDCl_3$–TFA 1 : 1, with residual $CHCl_3$ (^{1}H, 7.26 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm) as an internal standard. Gel-phase ^{13}C NMR (100.62 MHz) spectra were recorded in benzene-d_6 on a Bruker AVANCE-400 instrument using the solvent as an internal standard (^{13}C, 126.0 ppm).

Column chromatography was performed using silica gel 60 (particle size 0.04–0.06 mm).

For solid-phase synthesis, yields were determined using the ^{1}H NMR spectra of TFA–$CDCl_3$ (1 : 1, v/v) cleavage solutions with 11 mM C_6H_6 (7.36 ppm) as an internal standard. Alcohols were fully converted to TFA esters under these conditions. For MALDI measurements, dendrons were cleaved by TFA–$CDCl_3$ (1 : 9, v/v) for 15 min and the solvents were evaporated immediately after filtration.

Synthesis in solution

Typical *O*-allylation procedure: synthesis of dimethyl 5-(allyloxy)isophthalate.[13] Allyl bromide (4.12 ml, 47.6 mmol, 2 equiv.) was slowly added to a stirred solution of dimethyl 5-hydroxyisophthalate (5.00 g, 23.8 mmol, 1 equiv.) and K_2CO_3 (4.93 g, 35.7 mmol, 1.5 equiv.) in dry DMF (44 ml). The slurry was stirred at room temperature for 19 h and the progress of the reaction was monitored by TLC. After completion of the

reaction, the mixture was diluted with H_2O (100 ml) and extracted with ether (3 × 200 ml). The combined extracts were washed with H_2O (6 × 150 ml), brine (2 × 150 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give dimethyl 5-(allyloxy)isophthalate (5.61 g, 95%) as a colorless solid used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (t, J = 1.4 Hz, 1H); 7.76 (d, J = 1.4 Hz, 2H); 6.10–6.00 (m, 1H); 5.44 (dq, J = 17.2 Hz, J = 1.5 Hz, 1H); 5.32 (dq, J = 10.5 Hz, J = 1.3 Hz, 1H); 4.62 (dt, J = 5.2 Hz, J = 1.5 Hz, 2H); 3.93 (s, 6H). ^{13}C NMR (100.6 MHz): δ 166.1, 158.6, 132.4, 131.8, 123.1, 120.1, 118.2, 69.2, 52.4.

Typical Claisen rearrangement procedure: synthesis of dimethyl 4-allyl-5-hydroxyisophthalate.[13] A solution of dimethyl 5-(allyloxy)isophthalate (2.50 g, 10.0 mmol, 1 equiv.) in *o*-dichlorobenzene (13 ml) was refluxed under nitrogen for 44 h. The progress of the reaction was followed by TLC analysis. Part of the solvent was removed under high vacuum until precipitation started. Following the crystallization the solid was filtered and dried in vacuum to give dimethyl 4-allyl-5-hydroxyisophthalate (2.13 g, 84%) as a colorless solid used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 1.7 Hz, 1H); 7.64 (d, J = 1.7 Hz, 1H); 6.07–5.97 (m, 1H); 5.47 (s, 1H); 5.14–5.07 (m, 2H); 3.92 (s, 3H); 3.91 (s, 3H); 3.82 (dt, J = 6.0 Hz, J = 1.6 Hz, 2H). ^{13}C NMR (100.6 MHz): δ 167.4, 166.1, 155.0, 135.3, 132.1, 131.8, 129.2, 124.1, 119.7, 116.4, 52.4, 31.2.

MS (ESI): Calcd for $C_{13}H_{13}O_5$ (M − H) 249.1, found 249.1.

Synthesis of dimethyl 4-allyl-5-(allyloxy)isophthalate. Dimethyl 4-allyl-5-(allyloxy)isophthalate was prepared from dimethyl 4-allyl-5-hydroxyisophthalate (5 g, 20.0 mmol, 1 equiv.) under *O*-allylation reaction conditions, using allyl bromide (3.46 ml, 40.0 mmol, 2 equiv.) and K_2CO_3 (4.14 g, 30.0 mmol, 1.5 equiv.) in dry DMF (44 ml). The product was characterized and used without further purification (5.24 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 1.5 Hz, 1H); 7.62 (d, J = 1.4 Hz, 1H); 6.09–5.90 (m, 2H); 5.43 (dq, J = 17.3 Hz, J = 1.6 Hz, 1H); 5.29 (dq, J = 10.6 Hz, J = 1.4 Hz, 1H); 5.03–4.95 (m, 2H); 4.61 (dt, J = 5.0, J = 1.6, 2H); 3.91 (s, 3H); 3.89 (s, 3H); 3.81 (dt, J = 6.2 Hz, J = 1.5 Hz, 2H). ^{13}C NMR (100.6 MHz): δ 167.4, 166.2, 156.8, 135.8, 135.5, 132.5, 131.6, 128.7, 123.7, 117.6, 115.2, 69.4, 52.2, 30.8.

Synthesis of dimethyl 4,6-diallyl-5-hydroxyisophthalate (1). The product **1** was prepared from dimethyl 4-allyl-5-(allyloxy) isophthalate (5 g, 17.2 mmol, 1 equiv.) under Claisen rearrangement reaction conditions, but the reaction was completed in 17 h. The crude material was purified by column chromatography on a silica gel (5 : 95 EtOAc–hexanes) to give the pure product (4.9 g, 97%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H); 6.06–5.96 (m, 2H); 5.52 (s, 1H); 5.14–5.07 (m, 4H); 3.89 (s, 6H); 3.83 (dt, J = 6.0 Hz, J = 1.6 Hz, 4H). ^{13}C NMR (100.6 MHz): δ 167.3, 154.3, 135.5, 131.0, 129.2, 124.9, 116.3, 52.2, 31.5.

Synthesis of dimethyl 5-hydroxy-4,6-dipropylisophthalate (2). Pd/C (5%) was carefully added to the stirred solution of phenol **1** (2.20 g, 7.6 mmol, 1 equiv.) in MeOH, in a flask with an attached valve-equipped hydrogen-filled balloon. The mixture was stirred under hydrogen for 4 h at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered and washed with MeOH. The filtrate and washings were combined and the solvent was evaporated to yield the pure product as a colorless solid (2.10 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H); 5.07 (s, 1H); 3.89 (s, 6H); 2.97–2.93 (m, 4H); 1.67–1.57 (m, 4H); 1.02 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.6 MHz): δ 167.5, 152.8, 133.5, 128.3, 124.8, 52.1, 29.1, 23.0, 14.4.

MS (ESI): Calcd for $C_{16}H_{21}O_5$ (M − H) 293.1, found 293.1.

Solid phase synthesis

Typical procedure for nucleophilic substitution: synthesis of G1(dipropyl-CO_2Me). K_2CO_3 (0.56 g, 4.1 mmol, 3 equiv.), **2** (1.99 g, 6.8 mmol, 5 equiv.), TBAI (0.75 g, 2.0 mmol, 1.5 equiv.) and 18-crown-6 ether (0.11 g, 0.4 mmol, 0.3 equiv.) were added to a suspension of Wang bromo polystyrene resin (1.50 g, 1.4 mmol, 0.90 mmol g^{-1}, 1 equiv.) in DMF (12 ml). The suspension was heated to 60 °C for 3 days. The resin was washed with DMF–water, DMF, THF–water, THF, $CHCl_3$ and then dried under vacuum. Yield 100%, loading 0.76 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 165.1, 156.5, 113.2, 74.0, 49.6, 28.0, 23.1, 12.8. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.93 (s, 1H); 4.01 (s, 6H); 2.95–2.91 (m, 4H); 1.67–1.59 (m, 4H); 1.01 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 170.9, 152.9, 134.8, 128.1, 125.4, 53.3, 29.4, 23.0, 13.9.

Typical procedure for reduction: synthesis of G1(dipropyl-CH_2OH). $LiBH_4$ (12.11 ml, 24.2 mmol, 20 equiv., 2 M solution in THF) and $B(OMe)_3$ (0.14 ml, 1.2 mmol, 1 equiv.) were added to a suspension of the resin **G1(dipropyl-CO_2Me)** (1.60 g, 1.2 mmol, 0.76 mmol g^{-1}, 1 equiv.) in THF (5 ml). The mixture was heated to 40 °C for 24 h. The resin was washed with an aqueous solution of ammonium chloride–THF, ethanolamine–THF, DMF, THF–water, THF, $CHCl_3$ and then dried under vacuum. Yield 83%, loading 0.65 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 113.2, 74.5, 60.6, 27.4, 22.9, 13.1. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.11 (s, 1H); 5.44 (s, 4H); 2.72–2.68 (m, 4H); 1.67–1.57 (m, 4H); 1.05 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 152.3, 131.1, 130.2, 126.0, 68.6, 29.0, 23.2, 13.9.

Typical procedure for chlorodehydroxylation: synthesis of G1(dipropyl-CH_2Cl). Hexachloroethane (2.32 g, 9.8 mmol, 10 equiv.) and triphenylphosphine (2.57 g, 9.8 mmol, 10 equiv.) were added to a suspension of the resin **G1(dipropyl-CH_2OH)** (1.51 g, 0.98 mmol, 0.65 mmol g^{-1}, 1 equiv.) in THF (12 ml). The suspension was mixed at room temperature overnight. The resin was washed with THF–H_2O, THF, $CHCl_3$ and then dried under vacuum. Yield 80%, loading 0.50 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 113.2, 74.0, 42.3, 27.6, 22.7, 12.8. Following TFA-induced cleavage:

^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.07 (s, 1H); 4.62 (s, 4H); 2.76–2.72 (m, 4H); 1.69–1.59 (m, 4H); 1.06 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 151.8, 134.9, 129.7, 126.0, 44.3, 28.8, 23.4, 14.0.

Synthesis of G2(dipropyl-CO_2Me)

We proceeded as for the synthesis of **G1(dipropyl-CO_2Me)** but used the following quantities: K_2CO_3 (0.35 g, 2.5 mmol, 5 equiv.), **2** (1.17 g, 4.0 mmol, 8 equiv.), TBAI (0.46 g, 1.3 mmol, 2.5 equiv.) and 18-crown-6 ether (79.24 mg, 0.3 mmol, 0.6 equiv.), and **G1(dipropyl-CH_2Cl)** (1.00 g, 0.5 mmol, 0.50 mmol g^{-1}, 1 equiv.) in DMF (10 ml). Yield 100%, loading 0.40 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 165.0, 155.7, 140.9, 113.1, 73.7, 72.5, 49.7, 28.0, 23.3, 12.8. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.95 (s, 2H); 7.12 (s, 1H); 5.45 (s, 4H); 4.03 (s, 12H); 2.97–2.93 (m, 8H); 2.72–2.68 (m, 4H); 1.68–1.57 (m, 12H); 1.07–1.00 (m, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 171.3, 153.0, 152.3, 135.1, 131.0, 130.1, 128.2, 125.8, 125.6, 68.5, 53.4, 29.5, 29.0, 23.1, 13.9, 13.8.

MS (MALDI): Calcd for $C_{46}H_{62}O_{11}Na$ (M + Na) 813.4, found 813.4; calcd for $C_{46}H_{62}O_{11}K$ (M + K) 829.4, found 829.4.

Synthesis of G2(dipropyl-CH_2OH)

We proceeded as for the synthesis of **G1(dipropyl-CH_2OH)** but for 48 h, using the following quantities: $LiBH_4$ (8.19 ml, 16.4 mmol, 40 equiv., 2 M solution in THF), $B(OMe)_3$ (93.01 µl, 0.8 mmol, 2 equiv.) and the resin **G2(dipropyl-CO_2Me)** (1.05 g, 0.4 mmol, 0.39 mmol g^{-1}, 1 equiv.) in THF (5 ml). Yield 88%, loading 0.35 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.8 MHz, C_6D_6): δ 75.7, 61.1, 28.2, 24.0, 13.0. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.12 (s, 3H); 5.45 (s, 12H); 2.72–2.68 (m, 12H); 1.67–1.57 (m, 12H); 1.05 (t, J = 7.2 Hz, 18H). ^{13}C NMR (100.8 MHz, $CDCl_3$–TFA 1 : 1): δ 152.3, 131.0, 130.1, 125.9, 68.6, 28.9, 23.2, 13.9.

Synthesis of G2(dipropyl-CH_2Cl)

We proceeded as for the synthesis of **G1(dipropyl-CH_2Cl)** but for 48 h, using the following quantities: hexachloroethane (1.62 g, 6.9 mmol, 20 equiv.), triphenylphosphine (1.80 g, 6.9 mmol, 20 equiv.) and the resin **G2(dipropyl-CH_2OH)** (0.98 g, 0.3 mmol, 0.35 mmol g^{-1}, 1 equiv.) in THF (8 ml). Yield 100%, loading 0.34 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 155.4, 134.5, 133.4, 113.0, 73.7, 72.0, 42.1, 27.5, 22.9, 13.1. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.12 (s, 1H); 7.08 (s, 2H); 5.45 (s, 4H); 4.62 (s, 8H); 2.92–2.62 (m, 12H); 1.82–1.59 (m, 12H); 1.19–1.02 (m, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 152.3, 151.9, 135.1, 131.4, 130.4, 129.9, 126.4, 126.3, 68.8, 44.4, 29.1, 28.9, 23.5, 23.4, 14.1, 13.9.

Synthesis of G2(2H/dipropyl-CO_2Me)

K_2CO_3 (0.03 g, 0.2 mmol, 5 equiv.), **2** (0.10 g, 0.3 mmol, 8 equiv.), TBAI (0.04 g, 0.1 mmol, 2.5 equiv.) and 18-crown-6 ether (6.73 mg, 0.03 mmol, 0.6 equiv.) were added to a suspension of **G1(CH$_2$Cl)** resin[10c] (0.15 g, 0.04 mmol, 0.28 mmol g^{-1}, 1 equiv.) in DMF (1.5 ml). The suspension was heated to 60 °C for 3 days. The resin was washed with DMF–water, DMF, THF–water, THF, $CHCl_3$ and then dried under vacuum. Yield 100%, loading 0.25 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 165.1, 156.4, 140.7, 111.2, 113.1, 73.9, 68.1, 49.7, 28.0, 23.2, 12.8. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 8.18 (s, 2H); 7.33 (s, 1H); 7.12 (s, 2H); 4.93 (s, 4H); 4.04 (s, 12H); 3.06–3.02 (m, 8H); 1.66–1.56 (m, 8H); 0.97 (t, J = 7.3 Hz, 12H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 171.5, 156.9, 154.6, 143.8, 139.7, 130.1, 128.9, 120.0, 114.5, 76.2, 53.7, 30.2, 25.0, 14.0.

Synthesis of G2(dipropyl/2H-CO_2Me)

LiH (3.18 mg, 0.4 mmol, 10 equiv.), dimethyl 5-hydroxyisophthalate (0.17 g, 0.8 mmol, 20 equiv.) and TBAI (0.09 g, 0.2 mmol, 6 equiv.) were added to a suspension of **G1(dipropyl-CH_2Cl)** resin (0.10 g, 0.04 mmol, 0.40 mmol g^{-1}, 1 equiv.) in DMF (1 ml). The suspension was heated to 60 °C for 2 days. The resin was washed with DMF–water, DMF, THF–water, THF, $CHCl_3$ and then dried under vacuum. Yield 100%, loading 0.35 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 163.8, 157.2, 130.5, 121.5, 118.2, 113.2, 73.8, 66.8, 50.0, 27.6, 22.6, 12.8. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 8.35 (t, J = 1.4, 2H); 7.87 (d, J = 1.5, 4H); 7.12 (s, 1H); 5.45 (s, 4H); 4.06 (s, 12H); 2.72–2.68 (m, 4H); 1.67–1.57 (m, 4H); 1.05 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 166.3, 156.3, 152.2, 137.0, 131.8, 126.4, 122.8, 120.8, 63.3, 52.5, 28.2, 23.2, 14.4.

MS (MALDI): Calcd for $C_{34}H_{38}O_{11}Na$ (M + Na) 645.2, found 645.2; calcd for $C_{34}H_{38}O_{11}K$ (M + K) 661.2, found 661.2.

Synthesis of G3(dipropyl-CO_2Me)

We proceeded as for the synthesis of **G1(dipropyl-CO_2Me)** but used the following quantities: K_2CO_3 (0.23 g, 1.6 mmol, 8 equiv.), **2** (0.84 g, 2.9 mmol, 14 equiv.), TBAI (0.34 g, 0.9 mmol, 4.5 equiv.) and 18-crown-6 ether (46.02 mg, 0.2 mmol, 0.85 equiv.), and **G2(dipropyl-CH_2Cl)** (0.50 g, 0.20 mmol, 0.40 mmol g^{-1}, 1 equiv.) in DMF (4 ml). Yield 100%, loading 0.29 mmol g^{-1}.

Partial gel-phase ^{13}C NMR (100.6 MHz, C_6D_6): δ 165.1, 155.7, 140.9, 132.4, 113.3, 72.5, 49.7, 28.1, 23.3, 12.8. Following TFA-induced cleavage: ^{1}H NMR (400 MHz, $CDCl_3$–TFA 1 : 1): δ 7.92 (s, 4H); 7.07 (s, 3H); 5.41 (s, 12H); 4.00 (s, 24H); 2.94–2.90 (m, 16H); 2.69–2.65 (m, 12H); 1.66–1.55 (m, 28H); 1.05–0.99 (m, 42H). ^{13}C NMR (100.6 MHz, $CDCl_3$–TFA 1 : 1): δ 171.4, 153.0, 152.3, 135.1, 130.9, 130.1, 128.5, 125.8, 125.7, 68.5, 53.5, 29.6, 28.9, 23.1, 13.9, 13.8.

MS (MALDI): Calcd for $C_{106}H_{142}O_{23}Na$ (M + Na) 1807.0, found 1807.0; calcd for $C_{106}H_{142}O_{23}K$ (M + K) 1823.0, found 1823.0.

Conclusion

In conclusion, we developed new sterically congested building blocks for the synthesis of polyether dendritic molecules and demonstrated the solid-phase assembly of up to third-generation dendrons, incorporating these branched modules. The increased electron density of the aromatic rings of the new monomers destabilizes the bonds, connecting them in the dendritic framework. Accordingly, these dendrons exhibit clean acidolytic disassembly into monomeric units. Although the dendrons reported in this paper require relatively high acidity of the medium in order to undergo complete degradation, the study of the principles of such acidolytic decomposition may be of importance in the future for design of functional dendritic constructs, for instance in the field of drug delivery.[19]

Acknowledgements

This research was supported by Grant No. 955/10 from the Israel Science Foundation and Grant No. 2008193 from the United States–Israel Binational Science Foundation (BSF).

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