Unique steric and geometry induced stoichiometries observed in the divergent synthesis of poly(ester-acrylate/amine) (PEA) dendrimers†‡

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This work describes the Michael addition of *unprotected*, *branched*, $(A)_x$-type acrylate monomers (*i.e.*, trimethylolpropane triacrylate (TMPTA); $x = 3$ or pentaerythritol tetraacrylate (PTA); $x = 4$) to various mono- and poly-alkyleneamine cores under mild conditions to produce (*core*: amine); $G = 1$; > *dendri*-poly(ester-acrylate)$_z$]; (PEA) type dendrimers in one step. Quite remarkably, this strategy did not necessitate *large excess reagent protocols* as required for traditional Tomalia-type poly(amidoamine) (PAMAM) dendrimer syntheses, yet produced relatively little oligomeric/polymeric side product. Ideal, mathematically predictable dendrimer structures were obtained in high yield with only modest excesses (*i.e.*, 4.0 moles of monomer/core-NH); whereas, at lower ratios (*i.e.*, 0.5–2.0 moles of monomer/core-NH), non-ideal, geometrically controlled dendrimers possessing, macrocyclic (looped) structures (*i.e.*, geometrically induced stoichiometry (GIS)) were formed when adequate reactivity space was available on the amine scaffolding. However, when amine core reaction sites became highly congested, one observed the formation of well defined, non-ideal dendrimers exhibiting sterically induced stoichiometries (SIS). It is postulated that Michael addition of these nanoscale (*i.e.*, 1–1.5 nm) branched $(A)_x$ monomers onto these sub-nanosized linear-α,ω-alkylenediamine or poly(alkyleneamine) scaffoldings produces a highly congested reaction environment even at this early generational state (*i.e.*, $G = 1$). The observed products appear to be influenced and directed by these consequential steric and geometric space constraints.

1 Introduction

Recent challenges advanced by the nanotechnology community[1,2] have placed a high priority on defining risk/benefit boundaries for some of the most widely utilized nano-building blocks, namely: *dendrons/dendrimers, metal nano clusters* (*quantum dots*), *nanotubes and fullerenes*.[3,4] More specifically, attention has been focused on gaining a deeper understanding of critical parameters such as: nano-structural toxicity,[5] nano-periodic properties/patterns[6–8] reactivities and stoichiometries.[9–11] Dendrons/dendrimers are regarded as one of the best defined synthetic nano-structural platforms available for direct use or as reactive intermediates for synthesizing higher nano-complexity. This is based on the ability to control nano-sizes, shapes and surface chemistries with a vast number of dendrimeric compositions.[12,13] Basic dendron/dendrimer compositions are synthetically accessible by many variations of either divergent or convergent strategies and are briefly overviewed in Fig. 1. Contemporary accounts of these strategies have been extensively reviewed elsewhere.[14–16] Convergent synthesis can generally be used to produce defect free structures up to some sterically limiting generational level. On the other hand, divergent strategies although more readily scalable, give more defects.

A unique feature of dendrimer synthesis is the ability to predict polyvalent, surface stoichiometries and molecular weights (Scheme 1).[9] Undesired reactions including cyclization

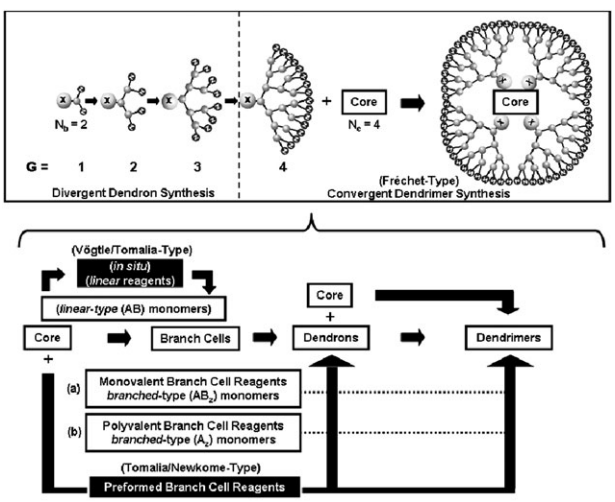

Fig. 1 Traditional divergent and convergent synthesis strategies to dendrons and dendrimers.

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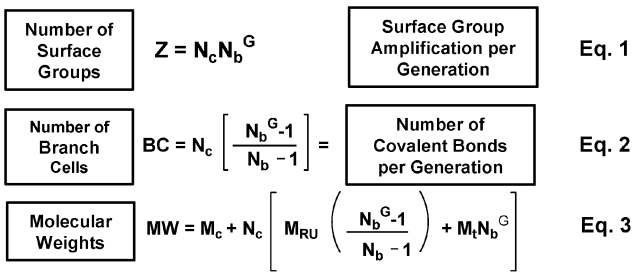


Scheme 1 In these equations, N_c and N_b are the core and branch functionalities (*i.e.*, multiplicities), respectively. In the case of eqn (1) (Z = theoretical number of terminal groups when: $N_c = 4$ and $N_b = 2$ for the dendrimer illustrated in Fig. 1); wherein, M_c, M_{RU} and M_t are molecular weights of the core, repeating unit and terminal surface groups, Z, respectively and G is the generation number (eqn (2) and (3)).

and steric inhibition of growth can lead to deviations from ideality.[17]

Products exhibiting suppressed valency and molecular mass defects driven by geometrically controlled, macrocycle formation have been referred to as possessing *geometrically induced stoichiometry* (*GIS*).[13,18] Similarly, non-ideal, suppressed terminal dendrimer valency derived from "constrained reaction space phenomena" on a polyvalent core or dendrimer surface has been referred to as exhibiting *sterically induced stoichiometry* (*SIS*).[12,19] These defects have been observed throughout the divergent synthesis of many compositionally diverse dendrimer families including *dendri*-poly(amidoamines).[9,20–25] Serious mass and stoichiometric deviations from theoretical values for typical [*core*: 1,2-diaminoethane]; (G = 1–10): {*dendri*-PAMAM(NH_2)$_z$} type dendrimers due to GIS effects are not observed until approximately generation = 4–5. In this series, more substantial mass and stoichiometry defects were noted beyond generation = 7, undoubtedly indicating both GIS effects and the substantial onset of de Gennes dense packing[26] or SIS behavior.[10,27] Other dendrimer families exhibiting such defects include: *dendri*-poly(propyleneimines),[16] *dendri*-poly(amides) (arborols),[28,29] *dendri*-poly(ethers),[30] *dendri*-poly(thioethers).[19] Understanding the causative rules and patterns that influence the pervasive occurrence of GIS and SIS effects in the synthesis of these and other diverse dendrimer compositional families is a critical step that must be taken in order to properly define dendrimer-based nano-reactivity and stoichiometry properties. Furthermore, there has been keen interest in the improvement of divergent synthesis strategies involving the use of reduced reaction times, unprotected monomers and enhanced amplification/stoichiometry advantages as recently reported by Majoral, Caminade and others.[31,32]

We now wish to report one of the first examples of a new divergent dendrimer synthesis (Fig. 1, route (b)) based on the Michael addition of an unprotected, $(A)_x$-type, preformed branch cell monomer[33] to a variety of aliphatic amine cores. Furthermore, unexpected inducement of both SIS and GIS effects were observed at the very first step (*i.e.*, core transformations to G = 1 level), while synthesizing a new family of poly(ester-acrylate/amine) (PEA) dendrimers. The first step in this novel iteration strategy involved dendronization[34] of various mono-alkylamines, *linear*-α,ω-alkylene diamine or poly(alkyleneamine) cores with nanoscale, *branched* acrylate monomers, $(A)_x$, such as trimethylolpropane triacrylate (TMPTA) (**1**) or pentaerythritol tetraacrylate (PTA) (**2**). This work will focus only on this first alkylation step. Dendronization involved Michael addition of the respective amine bearing cores to one or more acrylate moieties of the polyvalent branch cell reagent $(A)_x$. Monoalkyl amine cores produced either GIS-type, macrocyclic products, ideal dendronized cores or mixtures of these two architectures, depending on the ratio of branched acrylate monomer to amine core reaction sites. *Linear*-α,ω-alkylene diamine cores were examined beginning with more congested, 1,2-diaminoethane and then systematically extended up to less congested 1,12-diamimododecane. The more congested cores (*i.e.*, 1,2-diaminoethane and poly(alkyleneamines) were found to produce (SIS) type dendrimers, whereas, ideal, or GIS-type dendrimers were obtained with less congested *linear*-α,ω-alkylene diamines.

2 Results and discussion

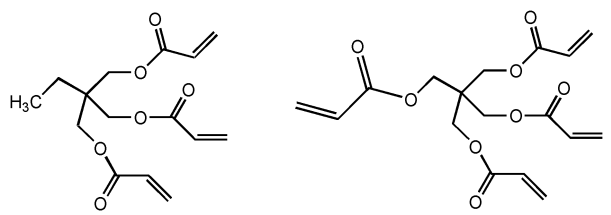
2.1 General

Nanoscale, tri- or tetra-branched acrylate monomers (*i.e.*, trimethylolpropane triacrylate (TMPTA), (**1**) or pentaerythritol tetraacrylate (PTA) (**2**); (*i.e.*, diameters = 1–1.5 nm by Corey–Pauling–Koltun (CPK) models) were utilized as Michael receptor reagents and combined with three different categories of nucleophilic amine cores, namely; (1) monoalkyl amines, (2) *linear*-α,ω- alkylene diamine or (3) poly(alkyleneamine) cores. In all cases, high yields of [*core*: amine]; (G = 1); {*dendri*-poly(ester/acrylate/amine)} dendrimers were obtained under very mild conditions, as ideal products or containing various dendron/macrocyclic looping levels. This divergent process did not require the usual large excesses of branched monomer reagent to avoid oligomer/polymer formation. However, the mole ratio of branched acrylate monomer/core-NH could generally be used to control the resulting dendronized product architectures. These architectures included (a) partially looped, GIS-type products, (b) missing dendron, SIS-type products or (c) ideally dendronized architectures based on original amine core (–NH) stoichiometry. These observations were made within a range of 0.5–4.0 molar ratios of *branched*-acrylate monomer/core amine –NH sites. Using higher monomer excesses (*i.e.*, 4 moles/core-NH) generally produced ideal dendrimer structures. However, using slight excesses (*i.e.*, 2.0 moles $(A)_x$/core-NH) generally yielded geometry controlled GIS-type products containing macrocyclic moieties. In other cases (*i.e.*, with more congested cores such as 1,2-diaminoethane (EDA), diethylenetriamine, (DETA) or tris(2-aminoethyl)amine, (TREN), only sterically induced stoichiometric, SIS-type, dendrimers were obtained throughout this range. These SIS type products possessed core reaction sites (*i.e.*, –NH) that were *sterically inaccessible to the nanoscale, branched acrylate monomer reagents, but accessible to small* (*sub-nano*) *sized reagent such as methylacrylate or phenylisothiocyanate*. These products were generally isolated by immiscible solvent extraction from methanol or column chromatography. They were characterized by size exclusion

chromatographic (*i.e.*, Sephadex column) workup, ^{1}H, ^{13}C NMR, FTIR, HPLC, MALDI-TOF mass spectrometry and certain diagnostic reagents/reactions to provide further confirmation of structure.

2.2 Branched acrylate monomer reagents

Two branched acrylate monomers, namely; trimethylolpropane triacrylate (TMPTA), (**1**) or pentaerythritol tetraacrylate (PTA) (**2**) were used in this study. Measurements made with Corey–Pauling–Koltun (CPK) models indicate the diameters of these structures vary between 1–1.5 nm. Michael addition of an amine core, –NH to the first acrylate group in each case produces a $G = 1$, branch cell with a multiplicity of $N_b = 2$ for TMPTA and an $N_b = 3$ for PTA. Therefore, exhaustive dendronization of monoalkylamine cores ($N_c = 2$) would be expected to produce an ideal didendron, dendrimer structure (*i.e.*, structure (**5**) or (**6**); Scheme 1). Exhaustive dendronization of α,ω-alkylenediamine cores ($N_c = 4$) would be expected to produce tetradendron, dendrimers. (*i.e.*, ideal products as in Scheme 3 structures (**10**) or (**11**). *Intra*molecular Michael addition of amine core functionality to more than one acrylate group on (**1**) or (**2**) (*i.e.*, GIS-type behavior) would be expected to yield looped, macrocycle moieties; whereas, similar *inter*-molecular reactions would be expected to produce polymers or gels. On the other hand, the introduction of branched acrylate monomers to produce a more sterically congested environment would be expected to yield SIS-type, dendron deficient products and architectures.

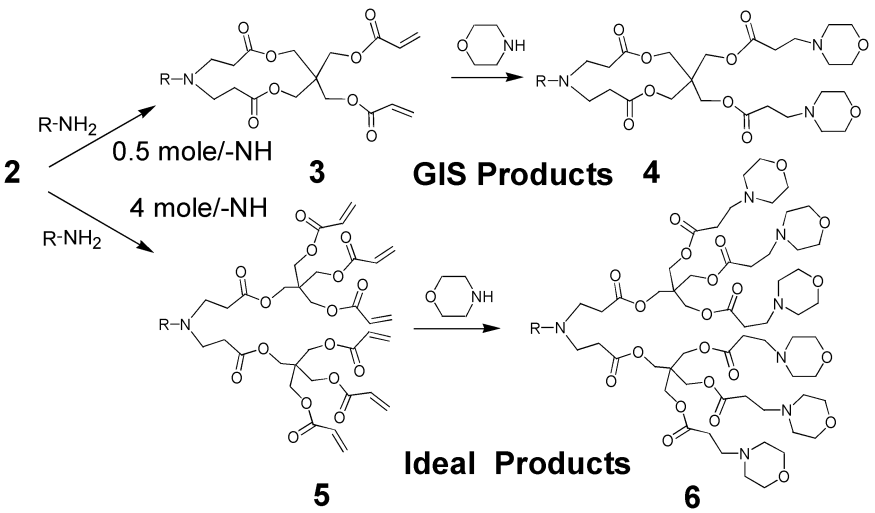


2.3 Monoalkylamine cores

Both short (C_5) and longer (C_{11}) monoalkyl amine cores were added to either less than stoichiometric amounts or modest excesses (*i.e.*, 0.5 to 4 moles $(A)_x$/core-NH) of the branched tri- or tetraacrylate monomers in methanol. A variety of dendronized products, depending on monomer excesses, were obtained as shown in Scheme 1. In the case of (C_5), 0.5 moles of (**1**) or (**2**)/core-NH produced a looped, macrocyclic-type monodendron product (**3**) in high yield. Using a 4 mole $(A)_x$/core-NH gave primarily an ideal didendron, dendrimer (**5**), whereas, a slightly lower excess of acrylate monomer (*i.e.*, 0.5 mole $(A)_x$/core-NH) produced mixtures of (**3**) and (**5**) (Scheme 2). This suggests that first order *intra*molecular looping reactions may become competitive under these conditions compared with second order, bimolecular reactions to produce ideal didendron dendrimers, if the excesses are reduced even slightly. All products were isolated by size exclusion column chromatography workup (*i.e.*, Sephadex column) and characterized by ^{1}H, ^{13}C-NMR, FTIR, HPLC, MALDI-TOF mass spectrometry (see Experimental section). Performing a ninhydrin test or allowing these products to react with smaller electrophilic reagents such as methyl acrylate or phenyl isothiocyanate indicated there were no detectable active hydrogens in these mono- and didendron products. In each case the acrylate terminated products were pacified to avoid acrylate polymerization by conversion into morpholine terminated products (**4**) and (**6**), respectively.

2.4 *Linear*-α,ω-alkylenediamine cores

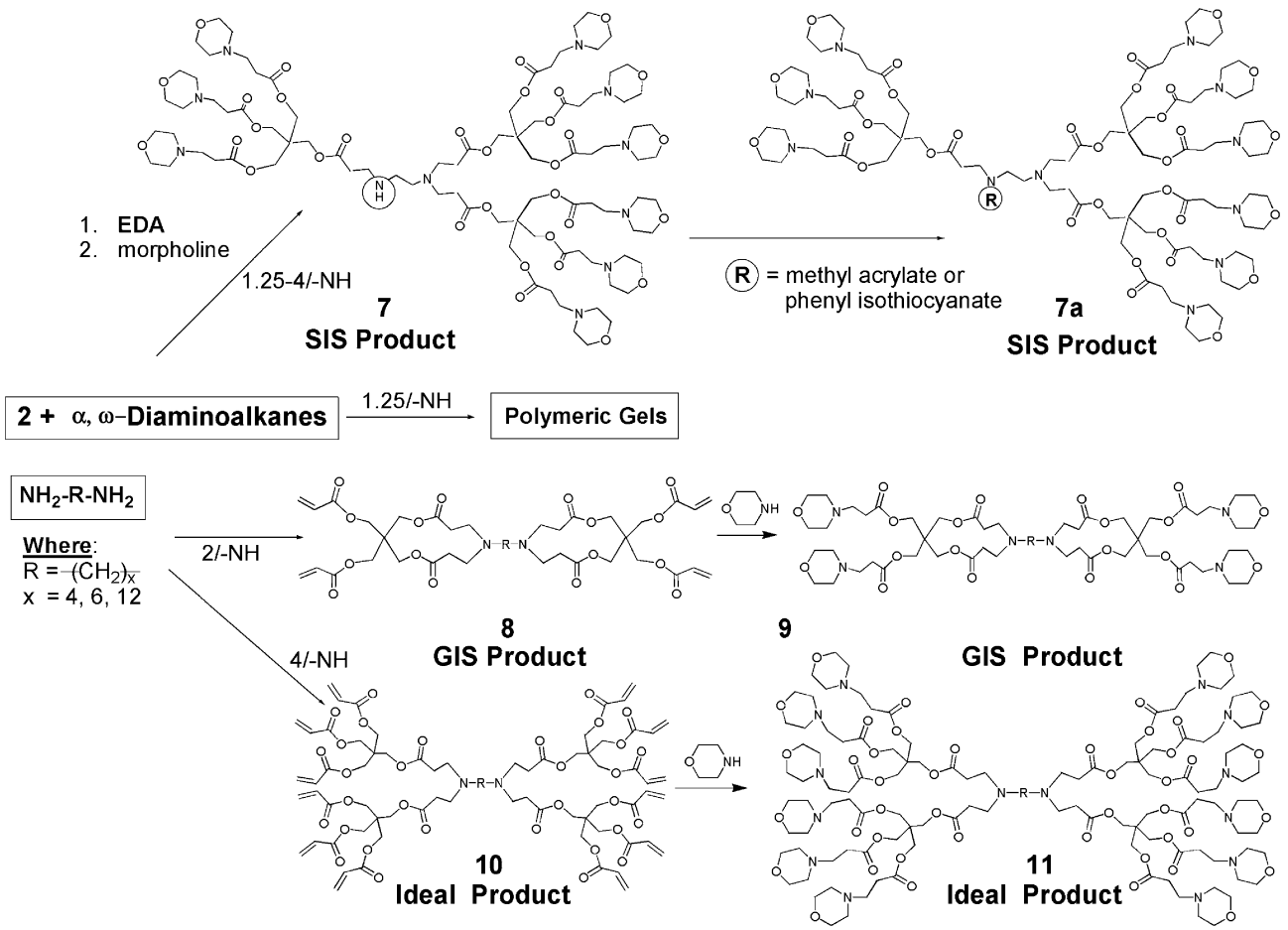
Linear-α,ω-alkylenediamine cores possessing from 2–12 methylene spacer linkages were added to slight or modest excesses of the branched TMPTA (**1**) or PTA (**2**) reagents in methanol, (*i.e.*, 1.25–4 moles $(A)_x$/core-NH). A range of different products was obtained as a function of the acrylate/core-NH and the (–NH) congestion level of the amine core. Using a low $(A)_x$/–NH ratio of 1.25 produced polymeric/gel like products from all of the *linear*-α,ω-alkylenediamine cores *with the exception of* 1,2-*diaminoethane*. For example, reducing the core spacer linkage to two methylene groups, (*i.e.*, 1,2-diaminoethane) under identical conditions, gave very high yields of tridendron adduct (**7**)[33] using either TMPTA (**1**) or PTA (**2**) (Scheme 3). Using branched acrylate monomer TMPTA (**1**) in concentration ranges from 1.25– 4.0 moles/–NH produced high yields of only the SIS type; [*core*: 1,2-diaminoethane; ($G = 1$); {*dendri*-poly(ester-(acrylate)$_9$} dendrimer in one step. The 1,2-diaminoethane core also yielded a tridendron, [*core*: 1,2-diaminoethane]; ($G = 1$); {*dendri*-poly(ester-(acrylate)$_{12}$)} dendrimer (**7**) with PTA (**2**) under identical conditions (Scheme 3). These crude reaction products were isolated from a slight excess of acrylate reagent, as a colorless oil, by solvent phase separation from methanol and further purified with size exclusion column chromatography (*i.e.*, Sephadex). One could increase the $(A)_x$/NH mole ratio to 2.0 and 4.0, respectively, with the 1,2-diaminoethane core and consistently produce the tridendron, SIS-type; [*core*: 1,2-diaminoethane]; ($G = 1$); {*dendri*- poly(ester(morpholine)$_{9/12}$)} dendrimer product (**7**) in very high yield. Using branched acrylate monomers (**1**) or (**2**) in concentration ranges from 1.25–4.0 moles/core-NH, produced high yields of only the tridendron-type adduct (**7**) as determined by material balance, MALDI-TOF mass spectrometry and NMR (Fig. 2). These observations were contrary to those reported by Xu *et al.*[33] In all cases a *positive* ninhydrin test was noted, indicating the presence of an active amine hydrogen supporting a sub-stoichiometric SIS dendron defined type tridendron product. Presumably such a core-NH was not sterically accessible to the nano-sized *branched* acrylate reagents (**1**) or (**2**) to give exhaustively alkylated, ideal tetra-dendron dendrimers under these conditions. Further confirmation of the SIS-type products was garnered by subsequent reaction of the presumed tridendron adducts with methyl acrylate or phenyl isothiocyanate. In each case the expected products, (**7a**), were formed by the reaction of core amine hydrogens which appear to be accessible only to these small, sub-nanoscale reagents, as determined by ^{1}H, ^{13}C NMR and a negative ninhydrin test. As a control, 1,2-diaminoethane was combined with sub-



Scheme 2

nanoscale, *linear* methyl acrylate monomer under identical conditions to give a quantitative yield of the tetra-adduct.

Simply increasing the $(A)_x$/–NH mole ratio to 2.0 for the less congested diamine cores (*i.e.*, butane, hexane and dodecane) gave (GIS) type, looped-didendron, products (**8**) and (**9**) rather than polymeric gels. However, increasing the $(A)_x$/NH mole ratio to 4.0 produced high yields of ideal, tetradendron, dendrimers analogous to (**10**), *i.e.*, [*core*: diamine]; (G = 1); {*dendri*-poly(ester-acrylate)$_{12}$} dendrimer type products in all cases with the exception of 1,2-diaminoethane. Both the



Scheme 3

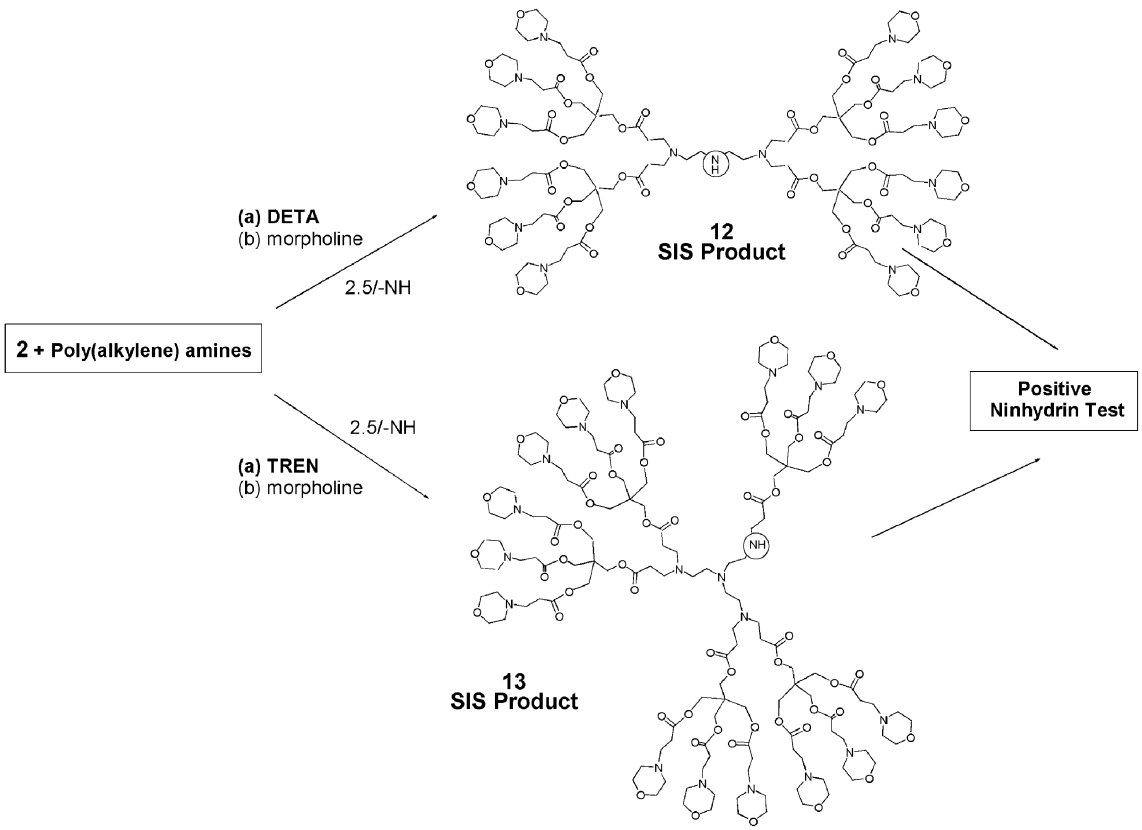
presumed GIS-type looped products (**8**) and (**9**) as well as the exhaustively alkylated, ideal dendrimers (**10**) and (**11**) tested negative when exposed to ninhydrin. All these acrylate terminated dendrimers, *i.e.*, (**8**) and (**10**) were predisposed to undergo polymerization if stored unprotected at room temperature. However, by shielding from exposure to light with aluminum foil, samples could be stored for short intervals at low temperature. Room temperature, shelf-stable products were readily obtained by Michael addition of a nucleophilic agent such as morpholine, to give the [*core*: diamine]; (G = 1); {*dendri*-poly(ester-morpholine)$_{12}$)} dendrimers, (**11**). These more stable products could be further purified by size exclusion column chromatography and were characterized by ^{1}H, ^{13}C NMR, FTIR, HPLC, PAGE and MALDI-TOF mass spectrometry (see Experimental section). Characterization studies indicated that a variety of SIS, GIS as well as ideal products were obtained and were dependent on the number of methylene linkages between the reactive –NH sites, as well as the mole ratio of branched acrylate reagent (**1**) or (**2**)/core-NH.

2.5 Poly(alkyleneamine) cores

Several poly(alkyleneamine) cores, namely; diethylenetriamine (DETA) or tris(2-aminoethyl)amine (TREN) in methanol were added to a stoichiometric excess of (TMPTA) (**1**) or tetraacrylate (PTA) (**2**), (*i.e.*, 2.5 mole (A)$_x$/core-NH). In each case, products were isolated and immediately converted into morpholine terminated derivatives. Both (**1**) and (**2**) gave SIS-type products with these cores, based on MALDI-TOF analyses. Reaction of (**2**) with DETA and TREN gave tetradendron (**12**) and pentadendron (**13**) dendrimers, respectively. These products are each one dendron deficient from ideal structures and should possess one active hydrogen. Although the exact position of the active hydrogen in (**12**) was not determined, both (**12**) and (**13**) were found to be ninhydrin positive, thus supporting SIS derived products. Further confirmation of the SIS-type products was garnered by subsequent reactions with methyl acrylate or phenyl isothiocyanate to give expected products, as determined by ^{1}H and ^{13}C NMR, thus supporting active hydrogen structures (Scheme 4).

2.6 Dendronization patterns

It is apparent from an examination of patterns displayed in Table 1 that the mole ratios of un-protected, branched acrylate monomers to amine core are critical for obtaining well defined dendronized products, whether they are GIS, SIS or ideal types. Sub-stoichiometric to slight excesses of (A)$_4$ to core-NH tend to favor multi-bodied polymerization/oligomerization events, especially when these Michael addition reactions are attempted on linear α,ω-alkylenediamines and poly(alkylene)amines. Surprisingly, the congested 1,2-diaminoethane core appears to be an exception in that a SIS-type product is obtained even at monomer excesses as low as 1.0–1.2 moles/–NH. This suggests that a unique nano-steric environment may be directing the formation of this SIS product. Interestingly, these SIS-type products persist for this congested amine core even at much higher mole ratios of monomer (*e.g.* 2.0–4.0 moles/–NH). On the other hand, uncongested monoalkyl amines produce high yields of GIS products at sub-



Scheme 4

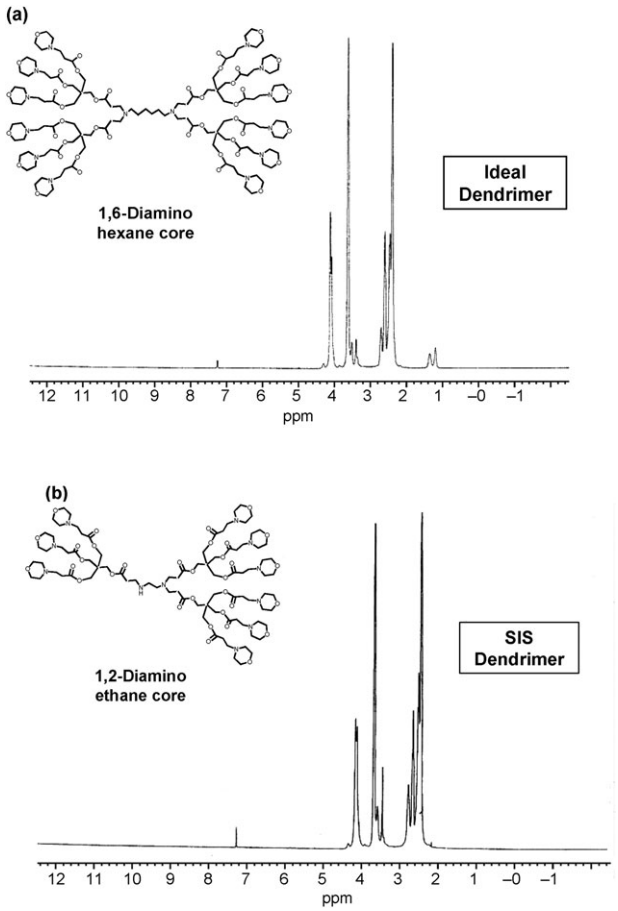


Fig. 2 (a–b). Proton NMR spectra obtained for an ideal, tetradendron product obtained from (a) reaction of PTA with an uncongested amine core (*i.e.*, 1,6-diaminohexane) and (b) reaction of PTA with a congested amine core (*i.e.*, 1,2-diaminoethane) to produce an (SIS)-type, tridendron product.

stoichiometric levels and ideal, didendron products at higher excesses (*i.e.* 4.0 moles/–NH). Furthermore, it should be noted that good yields of GIS-type products may be obtained with linear-α,ω-alkylenediamines at moderate excesses with the formation of ideal dendrimer products at higher excesses (*i.e.*, 4.0 moles/–NH). Finally, it is interesting to observe that more highly congested poly(alkylene)amines, such as DETA and TREN continue to yield SIS-type products even at the highest monomer excesses examined (*i.e.*, 4.0 moles/–NH). In any case, the monomer excesses required to produce oligomer/polymer free dendrimeric products with $(A)_4$ type acrylates are far less than are required to produce traditional *dendri*-poly (amidoamine) (PAMAM) dendrimers with *linear*-acrylate monomers.[35]

2.7 Product characterization

The degree of dendronization observed as a function of congested/uncongested amine cores (*i.e.* 1,2-diaminoethane *vs.* 1,6-diaminohexane) was readily appraised by ^{1}H NMR analysis and integration of certain diagnostic proton signals. Fig. 2(a) illustrates a typical proton spectrum for an uncongested amine core (*i.e.*, 1,6-diaminohexane) which yields an ideal, tetradendron product resulting from Michael addition at all four active amine hydrogens. Integration of signals at δ 1.21 and 1.38 ppm assigned to the eight interior protons of the hexane core *vs.* four protons α to the morpholine ether moiety at δ 3.62 ppm were observed in a ratio that supported a 1 : 4 adduct. This integral ratio supports the proposed ideal tetradendron structure. In contrast, Fig. 2(b) illustrates that by similar analysis of ethane core protons at δ 3.42 ppm *vs.* morpholine proton signals at δ 3.62 ppm were observed in a ratio that supported a 1 : 3 adduct. This supports the proposed SIS-type, tridendron product, wherein Michael addition occurred at only three of the possible four active hydrogens. Furthermore, mass balances reported in the experimental section also corroborate this conclusion. Presumably, this is due to steric effects presented by the tridendron adduct against the nanoscale, branched acrylate monomers. In both cases, additional evidence supporting the respective structures was obtained by MALDI-TOF, PAGE and SEC analyses. In the case of the (SIS) dendrimer, (**7**), ninhydrin tests as well as diagnostic reactions with sub-nanoscale sized reagents produce (**7a**) and supported this structure as described earlier.

3 Conclusions

We report a versatile new strategy for the dendronization[34] of amine bearing scaffoldings (cores) under very mild conditions without the need for "protect–deprotect" protocols. This strategy involves the Michael addition of nanoscale, branched

Table 1 An overview of patterns associated with (GIS), (SIS) and ideal dendrimer structures as a function of amine cores and mole ratios of branched acrylate $(A)_4$ to core-NH

	Mole ratio of branched $(A)_4$ to core-NH			
	0.5	1.0–1.25	2.0–2.5	4.0
Monoalkylamines ($R–NH_2$)				
$R = CH_3(CH_2)_x–$ (x = 4, 10)	(**3**), (**4**) (GIS)	(**3**), (**4**) (GIS)	—	—
	—	(**5**), (**6**) (Ideal)	—	(**5**), (**6**) (Ideal)
Linear-α,ω-alkylenediamines ($NH_2–R–NH_2$)				
$R = –(CH_2)_x–$ (x = 2)	—	(**7**) (SIS)	(**7**) (SIS)	(**7**) (SIS)
$R = –(CH_2)_x–$ (x = 4, 6, 12)	Polymer/gel	Polymer/gel	(**8**), (**9**) (GIS)	(**10**), (**11**) (Ideal)
Poly(alkylene)amines				
$HN[(CH_2)_2NH_2]_2$ (DETA)	Polymer/gel	Polymer/gel	—	(**12**) (SIS)
$N[(CH_2)_2NH_2]_3$ (TREN)	Polymer/gel	Polymer/gel	—	(**13**) (SIS)

acrylate monomers to produce [*core*: amine]; (G = 1); {*dendri*-poly(ester/acrylate/amine)} type dendrimers in one step. The versatility of this approach has been demonstrated with three categories of amine cores, namely; (a) monoalkylamines, (b) *linear*-α,ω-alkylenediamine and (c) poly(alkyleneamines). Explicit examples of steric (SIS) and geometric (GIS) controlled dendronization events were observed in the transformation of the amine cores to the G = 1 stage. Ideal, dendronized products (dendrimers) were obtained when modest excesses of acrylate monomer (*i.e.*, 4.0 moles (A_x)/core-NH) were reacted with uncongested amine scaffoldings. Reducing the monomer excesses produced either polymeric gels or dendron deficient products that exhibited geometrically induced stoichiometries (GIS). These GIS-type products (macrocycles) were derived from intramolecular, looping events and in many cases were favored over intermolecular polymerization events. This appears to be due to the more congested nano-environment created by Michael addition of the nanoscale, branched monomer adducts. Using more congested amine scaffolding (*i.e.*, 1,2-diaminoethane, *etc.*) invariably led to steric controlled products that exhibited sterically induced stoichiometries (SIS). These SIS-type products were generally missing one or more dendrons compared to that expected for an ideally dendronized substrate. Although we report only dendrimer growth to G = 1, higher generation constructions are possible and will be reported later. The object of this work was to focus on the rich array of SIS, GIS and ideal dendrimer structures that are possible by merely controlling core design and unprotected $(A)_x$/core-NH mole ratios in this first transformation. It will be interesting to understand the extent and nature of these effects during higher generation dendrimer iterations, which are in progress and will be reported in due course.

4 Experimental

4.1 General methods and materials

Methanol (99.8%, Aldrich), amylamine (99%, Aldrich), pentaerythritol tetraacrylate (Aldrich), trimethylolopropane triacrylate (Aldrich), morpholine (99+%, Aldrich), 1,2-diaminoethane (99.5+%, Aldrich), 1,4-diaminobutane (Aldrich), 1,6-hexanediamine (99.5+%, Aldrich), 1,12-diaminododecane (97%, Fluka). All solvents and chemicals purchased from Aldrich were used as obtained. Deionized water (18.2 MΩ) was made using the Millipore DI water system. All thermometers were used without calibration. Silica gel 60, particle size 0.040–0.063 mm, 230–400 mesh ASTM was obtained from EM Sciences. Sephadex was purchased from Amersham Biosciences. Thin layer chromatography (TLC) was performed using Whatman Adsorption plates, 60 Å silica gel, 250 mm layer thickness. The ^{1}H and ^{13}C NMR spectra were obtained using a Bruker WM 360 SF instrument. MALDI-TOF mass spectrometry was performed on a Bruker Autoflex-LRF Mass Spectrometer. HPLC spectra were measured using a Perkin Elmer (Series 200). GPC spectra were obtained by a Waters 1515 instrument. Poly(acrylamide) gel electrophoresis was performed on a homogeneous (15%) gel at acidic condition. UV-Vis spectra were measured using a Hewlett Packard model 8543 and software made by Agilent Technologies. FT-IR spectra were measured using Nicolet, MAGNA-IR-560.

4.2 Monoalkyl amine cores

Dendronization of amyl amine with PTA (2) (0.5 mole of PTA/core NH) and subsequent terminal conversion with morpholine; (3) and (4). Pentaerythritol tertraacrylate, (**2**), (3.52 g, 10 mmol) was dissolved in methanol (5.0 mL) and cooled to 4 °C with an ice–water bath. A solution of amyl amine (872 mg, 10 mmol in 10 mL methanol) was added during a period of 5 min. After addition, reaction was stirred at 4 °C for 30 min, warmed to room temperature and stirred in the dark overnight. A layer of oil phased out at the bottom of flask. MALDI-TOF: calc. for $C_{22}H_{33}NO_8$ (looped monodendron), (**3**), 439.50, found, 440.13 (M + H), 472.19 (M + K). A solution of morpholine (4.18 g, 48 mmol, in methanol (10 mL) was added to the reaction mixture while cooled to 4 °C. After addition, the mixture was allowed to warm to room temperature and stirred overnight. Solvent was removed to give the crude product as a clear oil. 0.8 g of the crude was purified by Sephadex G (LH-20) column using methanol as solvent. Fractions 6–18 were combined for final characterization.

MALDI-TOF: calc. for $C_{30}H_{51}N_3O_{10}$ (looped, monodendron), (**4**), 613.74; found, 631.32 (M + Na) 647.40 (M + K) and some other minor higher mass peaks.

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 0.91 (t, J = 7.2 Hz, 3H, $-CH_3$), 1.2–1.5 (m, 6H, $-CH_2CH_2CH_2-$), 2.43 (m, 8H), 2.56 (m, 8H), 2.65 (m, 8H), 3.55–3.61 (m, 8H), 4.23 (m, 8H). Integration of core and dendron signals supported the looped, monodendron structures (**4**).

^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 13.30, 22.49, 26.56, 29.52, 31.14, 31.45, 31.88, 49.11, 50.91, 53.33, 53.62, 53.91, 53.94, 61.15, 62.05, 66.47, 173.17, 173.58.

Dendronization of amylamine with pentaerythritol tetraacrylate (1.0 mole PTA/NH) and pacified with morpholine. Pentaerythritol tetraacrylate (7.05 g, 20 mmol) was dissolved in methanol (10 mL) and cooled to 4 °C with an ice–water bath. The solution of amyl amine (872 mg, 10 mmol in 10 mL methanol) was added during a period of 5 min. After addition, the reaction was stirred at 4 °C for 30 min, allowed to warm to room temperature and stirred in the dark overnight. MALDI-TOF: calc. for $C_{22}H_{33}NO_8$ (looped, monodendron), 439.50, found, 440.13 (M + H), 472.19 (M + K), structure (**3**). $C_{39}H_{53}NO_{16}$ (ideal, didendron dendrimer) 791.84, found, 792.41 (M + H), structure (**5**).

A solution of morpholine (8.36 g, 96 mmol, in methanol (10 mL) was added to the reaction mixture after cooling to 4 °C. The mixture was allowed to warm to room temperature and stirred overnight. Solvent was removed to give 0.8 g of crude product as a clear oil which was purified by Sephadex G (LH-20) column using methanol as the solvent. Fractions 6–18 were combined for final characterization.

^{1}H NMR (CD_3OD, 300 MHz, δ ppm) 0.95 (t, J = 7.2 Hz, 3H, $-CH_3$), 1.22–1.57 (m, 6H, $-CH_2CH_2CH_2-$), 2.45 (m), 2.57 (m), 2.68 (m), 3.55–3.71 (m), 4.22 (m).

^{13}C NMR (CD_3OD, 75 MHz, δ ppm) 13.33, 22.59, 26.54, 29.43, 31.67, 31.23, 49.33, 50.34, 53.37, 53.67, 53.02, 53.43, 61.12, 62.93, 66.73, 173.22, 173.61.

Dendronization of amylamine with pentaerythritol tetraacrylate (4 moles PTA/core-NH) and subsequently quenched with morpholine. Pentaerythritol tertraacrylate (7.05 g, 20 mmol) was dissolved in methanol (10 mL) and cooled to 4 °C with an ice–water bath. The solution of amylamine (218 mg, 2.5 mmol in 5 mL methanol) was added during a period of 5 min. After addition, the reaction was stirred at 4 °C for 30 min, allowed to warm to room temperature and then stirred at room temperature in the dark overnight. MALDI-TOF: calc. for $C_{39}H_{53}NO_{16}$, structure (**5**), 791.84, found, 792.40 (M + H).

A solution of morpholine (8.36 g, 96 mmol) in methanol (10 mL) was added to the reaction mixture after cooling to 4 °C. The mixture was allowed to warm to room temperature and stirred overnight. Then solvent was removed to give the 0.8 g of crude product as a clear oil which was purified by Sephadex G (LH-20) column using methanol as solvent. Fractions of 8–16 were combined for final characterization.

MALDI-TOF: calc. for $C_{63}H_{107}N_7O_{22}$, structure (**6**), 1314.56, found, 1314.78 (M + H), and some other higher unidentified peaks.

^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 0.877 (t, J = 7.5 Hz, 3H, –CH_3), 1.21–1.39 (m, 6H, –$CH_2CH_2CH_2$–), 2.43 (m, 24H), 2.50 (m, 16H), 2.63 (m, 16H), 3.66 (m, 24H), 4.14 (m, 16H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm) 14.31, 22.82, 26.95, 29.79, 32.22, 34.74, 49.16, 53.63, 54.10, 54.29, 62.14, 62.63, 67.06, 171.92, 172.02, 172.28.

Dendronization of undecylamine with pentaerythritol tetraacrylate (1.0 mole PTA/core-NH) quenched with morpholine. Pentaerythritol tertraacrylate (6.42 g, 18.2 mmol) was dissolved in methanol (10 mL) and cooled to 4 °C with an ice–water bath. A solution of undecylamine (1.56 mg, 9.1 mmol in 10 mL methanol) was added over a period of 5 min. After addition, the reaction was stirred at 4 °C for 30 min and allowed to warm to room temperature and then stirred overnight protected from light. MALDI-TOF: calc. for $C_{28}H_{45}NO_8$ (looped, monodendron), (**3**), 523.66, found, 524.28 (M + H), 556.33 (M + K). $C_{45}H_{65}NO_{16}$ (ideal, didendron), (**5**), 875.99, found, 876.51 (M + H).

A solution of morpholine (7.61 g, 87.4 mmol) in methanol (10 mL) was added to the reaction mixture while cooling at 4 °C. After addition, the mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed to give the crude product as a clear oil, 14.2 g (95%).

4.3 Linear-α,ω-diaminoalkane cores (congested)

Preparation of [*core*: 1,2-diaminoethane]; (G = 1); *dendri* {$CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_3$; (1.25 equivalents PTA per NH). To a 50 ml round bottom flask with a stir bar was added pentaerythritol tetraacrylate (PTA) (17.6 g, 0.50 mmol) and 15 ml MeOH cooled to ~4 °C. 1,2-Diaminoethane (600 mg, 10 mmol) in 10 mL MeOH was added over about 5 min. This mixture was stirred at 30 °C for 18 h. The crude reaction product was cooled to 20 °C and poured into 150 g of stirred methanol. A clear/cloudy product layer phased out by allowing the mixture to stand without stirring for 1 h. The methanol layer was decanted and this process was repeated two more times. A clear, viscous product residue was devolatilized at high vacuum for 3 h while protecting from light, using aluminum foil, to give 9 g (95% based on a tridendron product). A MALDI-TOF mass spectrum of this product exhibited indicated a major peak at 1117 amu (M + H) supporting the tridendron product which has a theoretical MW = 1116 amu, structure (**7**).

Conversion of [*core*: 1,2-diaminoethane]; (G = 1); *dendri* {$CH_2CH_2CO_2CH_2C(CH_2OCO_2CH{=}CH_2)_3\}_3$ to the morpholine adduct. To a 100 mL round bottom flask containing a stir bar was added the [*core*: 1,2-diaminoethane]; (G = 1); {*dendri*-poly(acrylate)$_9$} dendrimer, (9 g, 8.1 mmol, 73 mmol acrylate) in 20 g MeOH and the resulting mixture was cooled to ~4 °C. To this mixture was added dropwise over ~5 min to morpholine (9.5 g, 110 mmol, 1.5 moles per acrylate) in 20 g MeOH at 25 °C. This mixture was stirred at 4 °C for 30 min then at room temperature for 18 h. The volatiles were removed on a rotary evaporator followed by high vacuum to give 19 g of crude material. This crude material was mixed with 150 mL MeOH and heated to ~60 °C to make the solution homogeneous. Allowing this solution to cool to room temperature over ~4 h, caused a clear, oily product to phase out as an immiscible layer. This process was repeated two more times to produce a morpholine free product that weighted, 16 g (92% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (br s, 36 H), 2.47–2.50 (br s, 30 H), 2.60–2.62 (br s, 18 H), 2.73 (br s, 13H), 3.41 (br s, 4 H), 3.54 (br s, 6H), 3.63 (br s, 36 H), 3.8–4.2 (br m, 29 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.22, 42.65, 44.00, 49.48, 53.61, 54.09, 54.26, 62.09, 62.60, 66.84, 66.93, 67.02, 171.90, 172.10, 172.20.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Reaction of [*core*: 1,2-diaminoethane]; (G = 1); *dendri* {$CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_3$; morpholine terminated adduct with methyl acrylate. To a 10 mL round bottom flask with a stir bar was added poly(ester-amine) dendrimer, (G = 1) 1,2-diaminoethane core, morpholine terminated adduct (150 mg, 7.9×10^{-5} mol) and 2 g MeOH. To this mixture was added methyl acrylate (50 mg, 5.8×10^{-4} mol, 6 moles). The flask was sealed with a polypropylene cap and heated at 40 °C for 24 h. This mixture was cooled and evacuated on a rotary evaporator followed by high vacuum at 40 °C for 4 h to give 158 mg material.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (br s, 36 H), 2.46–2.56 (br s, 30 H), 2.58–2.67 (br s, 18 H), 2.72 (br s, 13H), 3.39 (br s, 4 H), 3.53 (br s, 6H), 3.63 (br s, 36 H), 3.98–4.2 (br m, 29 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.04, 32.18, 42.51, 42.63, 43.81, 43.97, 49.69, 51.88, 53.58, 54.07, 54.23, 62.08, 62.58, 66.91, 63.08, 66.89, 66.99, 67.08, 171.89, 171.96, 172.22.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Reaction of [*core*: 1,2-diaminoethane]; (G = 1); *dendri* {$CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_3$; morpholine terminated adduct with phenyl isothiocyanate. To a 10 mL round bottom flask with a stir bar was added poly(ester-amine) dendrimer, (G = 1), 1,2 diaminoethane core, morpholine terminated adduct (200 mg, 1.0×10^{-4} mol) and 2 g methylene chloride. To this mixture was added phenyl isothiocyanate (50

mg, 5.8×10^{-4} mol, 6 moles). The reaction was stirred at room temperature for 24 h, devolatilized on a rotary evaporator followed by high vacuum at 40 °C for 1 h to give 250 mg material. This crude product was warmed in 2 g MeOH to give a clear solution. Cooling the solution to 25 °C caused an immiscible layer to phase out. This procedure was repeated three times to yield an oily product which was devolatilized at 40 °C for 3 h to give 220 mg of product. This material, according to NMR analysis, was consistent with a thiourea structure that would be expected by reaction with an amine core possessing an active hydrogen.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (br s, 36 H), 2.47–2.58 (br s, 30 H), 2.60–2.70 (br s, 18 H), 2.74 (br s, 13H), 3.42 (br s, 4 H), 3.54 (br s, 6H), 3.63 (br s, 36 H), 3.8–4.2 (br m, 29 H), 7.15–7.36 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.21, 42.65, 44.00, 49.67, 53.93, 53.60, 54.08, 54.25, 62.07, 62.62, 63.09, 66.99, 125.96, 127.53, 128.76, 129.76, 171.91, 171.96, 172.27.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1596, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Preparation of [*core*: 1,2-diaminoethane |; (*G* = 1); *dendri* $\{CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_3$; (4 moles PTA per NH) and conversion to the morpholine terminated adduct. To a 50 ml round bottom flask equipped with a stir bar was added pentaerythritol tetraacrylate (PTA) (18.7 g, 53.1 mmol) in 15 ml MeOH and cooled to ~4 °C. 1,2-Diaminoethane (200 mg, 3.3 mmol) in 10 mL MeOH was added over a 5 min period. This mixture was stirred at 30 °C for 18 h. This mixture was cooled to 4 °C and added dropwise to morpholine (27 g, 318 mmol, 1.5 moles per acrylate) in 10 g MeOH, followed by stirring at room temperature for 24 h under N_2. The volatiles were removed with a rotary evaporator, followed by high vacuum to give 37.5 g of crude material. An aliquot of this mixture (836 mg) was purified using a Sephadex LH-20 column (void volume 105 mL) in MeOH taking 40 × 3 mL fractions. Product was collected in fractions 1–18 to give 140 mg (5.7 g product, 90% yield, as the (3 : 1), tridendron adduct).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (br s, 36 H), 2.47–2.50 (br s, 30 H), 2.60–2.62 (br s, 18 H), 2.73 (br s, 13H), 3.41 (br s, H), 3.53 (br s, 6H), 3.63 (br s, 36 H), 3.8–4.2 (br m, 29 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.21, 42.65, 44.00, 49.48, 53.59, 54.09, 54.25, 62.08, 62.60, 66.91, 67.00, 171.85, 171.96, 172.22.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

4.4 Linear-α,ω-diaminoalkane cores (less congested)

Preparation of [*core*: 1,4-diaminobutane]; (*G* = 1); *dendri* $\{CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_4$ (2 moles PTA per NH) and conversion to morpholine terminated adduct. To a 50 mL round bottom flask containing a stir bar was added pentaerythritol tetraacrylate (PTA) (11.7 g, 32 mmol, 2 moles per NH) and 10 mL MeOH. To this mixture cooled to 4 °C was added 1,4-diaminobutane (365 mg, 4.1 mmol) in 5 mL MeOH. This reaction mixture was stirred at 25 °C for 18 h under N_2. After cooling to ~15 °C, morpholine (17 g, 195 mmol, 1.5 moles per acrylate) was added dropwise over ~5 min into 40 mL stirred MeOH containing cooled at 4 °C. This mixture was stirred for 18 h at room temperature. This mixture was devolatilized with a rotary evaporator followed by high vacuum for 3–5 h to give 24.53 g crude material. An aliquot (897 mg) was purified on a Sephadex LH-20 column (void volume 105 mL) in methanol taking 30 × 3 mL fractions. A TLC (MeOH) indicated the product was in fractions 5–23. These collected fractions were stripped of volatiles to a constant weight to give 140 mg (4.3 g, 93% yield for a didendron adduct, MW = 1140).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (br s, 4 H), 2.38 (br s, 36 H), 2.45–2.50 (br s, 30 H), 2.59 (br m, 18 H), 2.69 (br m, 13H), 3.39 (br s, 4 H), 3.52 (br s, 6H), 3.60 (br s, 36 H), 3.9–4.2 (br m, 29 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 24.84, 32.19, 42.60, 43.07, 43.80, 44.96, 49.15, 49.30, 53.57, 54. 06, 54.24, 62.09, 62.59, 63.08, 66.79, 66.89, 67.00, 171.90, 172.10, 172.20.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Preparation of [*core*: 1,12-diaminododecane]; (*G* = 1); *dendri* $\{CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_4$, (2 moles PTA per NH) and conversion to morpholine terminated adduct. To a 50 mL round bottom flask containing a stir bar was added pentaerythritol tetraacrylate (PTA) (17.6 g, 50 mmol, 2.2 moles per NH) and 10 mL MeOH. To this mixture cooled at 4 °C was added 1,12-diaminododecane (1.16 g, 5.8 mmol) in 20 mL MeOH. This mixture was stirred at 25 °C for 18 h under N_2. This mixture was added dropwise over ~5 min to a mixture of 40 g MeOH containing morpholine (26 g, 300 mmol, 1.5 moles), cooled to 4 °C. This mixture was stirred at room temperature for 18 h, devolatilized on a rotary evaporator followed by submission to high vacuum for 3–5 h to give 37.5 g. An aliquot (1.0 g) was purified on a Sephadex LH-20 column (void volume 105 mL) in methanol taking 30 × 3 mL fractions. A TLC (MeOH) indicated the product eluded in fractions 1–16. These collected fractions were stripped of volatiles to a constant weight to give 146 mg (5.5 g, 99% yield) of the didendron adduct containing two loops, with theoretical MW = 1252.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (br s, 14 H), 1.38 (br s, 4 H), 2.40 (br s, 24 H), 2.41–2.55 (br s, 18 H), 2.55–2.65 (br s, 10 H), 2.68–2.78 (br s, 6H), 3.39 (br s, 4 H), 3.52 (br s, 2 H), 3.62 (br s, 24 H), 4.0–4.2 (br s, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 27.76, 29.94, 32.20, 42.46, 42.60, 43.08, 44.03, 49.07, 49.18, 49.39, 53.58, 54.068, 54.26, 62.09, 62.59, 63.07, 67.00, 171.86, 172.16, 172.21, 172.53.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Preparation of [*core*: 1,6-diaminohexane]; (*G* = 1); *dendri* $\{CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_4$, (4 moles PTA per NH) and conversion to morpholine terminated adduct. To a 50 mL round bottom flask equipped with a stir bar was added pentaerythritol tetraacrylate (PTA) (18.2 g, 51.7 mmol) and 10 mL MeOH. 1,6-Diaminohexane (400 mg, 3.4 mmol) in 10 mL MeOH was added to this mixture which had been cooled to 4 °C. This reaction mixture was stirred at 25 °C for 18 h under N_2. After cooling to ~15 °C this reaction mixture

was added dropwise over ~5 min into a stirred morpholine solution (27 g, 310 mmol, 1.5 moles per acrylate) in 40 mL MeOH cooled at 4 °C. This reaction mixture was stirred for 19 h at room temperature, devolatilized on a rotary evaporator, followed by submission to high vacuum for 3–5 h to give 36 g crude material. An aliquot (1.0 g) was purified on a Sephadex LH-20 column (void volume 105 mL) in methanol taking 30 × 3 mL fractions. A TLC (MeOH) indicated the product eluded in fractions 1–16. These collected fractions were stripped of volatiles to a constant weight giving 250 mg (9 g, 97% yield of the tetra-dendron adduct).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (br s, 4 H), 1.37 (br s, 4H), 2.41 (br s, 48 H), 2.46–2.7 (br m, 64 H), 3.40 (br s, 4H), 3.52 (br s, 4H), 3.63 (br s, 48 H), 4.0–4.2 (br s, 32 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 27.64, 32.22, 42.61, 43.10, 44.02, 49.05, 53.60, 54.09, 54.27, 62.10, 62.60, 66.92, 67.02, 171.88, 172.22.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

4.5 Poly(alkyleneamine) cores

Preparation of [*core*: diethylenetriamine]; (G = 1); *dendri*-{$CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_4$, (2.8 moles per NH) and conversion to morpholine terminated adduct. To a 50 ml round bottom flask with a stir bar was added pentaerythritol tetraacrylate (PTA) (6 g, 0.17 mmol, 2.8 moles per NH) and 15 ml MeOH cooled at ~4 °C was added diethylenetriamine (DETA) (119 mg, 1.2 mmol) in 10 mL MeOH over 5 min. This mixture was stirred at 25 °C for 18 h. This mixture was added dropwise over ~5 min to a mixture of 40 g MeOH containing morpholine (9 g, 103 mmol, 1.5 moles per acrylate) cooled to 4 °C. This resulting mixture was stirred at room temperature for 18 h. This mixture was devolatilized with a rotary evaporator, followed by high vacuum for 3 h to give 24 g. An aliquot of this mixture (900 mg) was purified using a Sephadex LH-20 column (void volume 105 mL) in MeOH taking 30 × 3 mL fractions. A TLC (MeOH) indicated the desired product was present in fractions 1–16. These fractions were devolatilized to a constant weight giving 180 mg (2.6 g, *i.e.*, 84% yield, based on a (4 : 1), tetradendron adduct. This product gave a positive ninhydrin test indicating the presence of an active core amine hydrogen.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (br s, 48 H), 2.46 (br m, 28 H), 2.60 (br m, 22 H), 2.72 (br s, 10 H), 3.39 (br s, 6 H), 33.53 (br s, 6 H), 3.62 (br s, 48 H), 4.10, br m, 32 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.20, 42.62, 43.20, 43.99, 49.62, 53.58, 54.07, 54.24, 62.08, 62.58, 63.07, 67.00, 171.89, 172.23.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

Preparation of [*core*: tris(2-aminoethyl)amine]; (G = 1); *dendri*-{$CH_2CH_2CO_2CH_2C(CH_2CO_2CH{=}CH_2)_3\}_4$ (2.5 moles per NH) and conversion to morpholine terminated adduct. To a 50 ml round bottom flask with a stir bar was added pentaerythritol tetraacrylate (PTA) (7.44 g, 0.21 mmol, 2.5 moles per NH) and 15 ml MeOH cooled at ~4 °C was added tris(2-aminoethyl)amine (EDA) (200 mg, 1.36 mmol) in 10 mL MeOH over about 5 min. The resulting mixture was stirred at 25 °C for 18 h. This mixture was added dropwise over 5 min to a mixture of 40 g MeOH containing morpholine (11 g, 126 mmol, 1.5 moles per acrylate) cooled at 4 °C and stirred at 25 °C for 18 h. The volatiles were removed using a rotary evaporator and high vacuum for 4 h to give 14.6 g of crude material. An aliquot of this material was purified using a Sephadex LH-20 column (void volume 105 mL) in MeOH taking 30 × 3 mL fractions. A TLC (MeOH) indicated the desired product eluded in fractions 1–16. These collected fractions were evacuated to a constant weight to give 220 mg (3.6 g, 95% yield based on a (5 : 1) pentadendron adduct, structure (**13**). This product gave a positive ninhydrin test indicating the presence of an active core amine hydrogen.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (br s, 60 H), 2.49 (br s, 55 H), 2.61 (br m, 28 H), 2.73 (br s, 15 H), 3.40 (br m, 8 H), 3.52 (br m, 10 H), 3.62 (br s, 60 H), 4.10 (br m, 41 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.20, 42.62, 43.21, 43.96, 49.65, 51.87, 53.59, 54.07, 54.42, 62.09, 62.58, 63.07, 66.91, 67.01, 171.90, 171.98, 172.24.

FTIR (neat) ν_{max} 2956, 2818, 1738, 1449, 1252, 1117, 1054, 1011, 859 cm^{-1}.

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References

1 *EPA, Final Nanotechnology White Paper* http://www.epa.gov/osa/nanotech.htm, February 15, 2007.
2 O. Renn and M. C. Roco, *J. Nanopart. Res.*, 2006, **8**, 153–191.
3 D. A. Tomalia, *Chem. Today*, 2005, **23**, 52–55.
4 D. A. Tomalia, *Mater. Today*, 2005, (March), 34–46.
5 V. L. Colvin, *Nat. Biotechnol.*, 2003, **21**, 1166–1170.
6 I. Amato, *Chem. Eng. News*, 2006, **84**, 45–46.
7 E. V. Shevchenko, D. V. Talapin, N. A. Kotov, S. O'Brien and C. B. Murray, *Nature*, 2006, **439**, 55–59.
8 E. V. Shevchenko, D. V. Talapin, C. B. Murray and S. O'Brien, *J. Am. Chem. Soc.*, 2006, **128**, 3620–3637.
9 D. A. Tomalia, *Prog. Polym. Sci.*, 2005, **30**, 294–324.
10 D. A. Tomalia, H. M. Brothers II, L. T. Piehler, H. D. Durst and D. R. Swanson, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 5081–5087.
11 G. A. DeVries, M. Brunnbauer, Y. Hu, A. M. Jackson, B. Long, B. T. Neltner, O. Uzun, B. H. Wunsch and F. Stellacci, *Science*, 2007, **315**, 358–361.
12 D. A. Tomalia, A. M. Naylor and W. A. Goddard III, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 138–175.
13 J. M. J. Fréchet and D. A. Tomalia, *Dendrimers and Other Dendritic Polymers*, Wiley, Chichester, 2001.
14 D. Astruc and F. Chardac, *Chem. Rev.*, 2001, **101**, 2991.
15 D. Astruc, *Pure Appl. Chem.*, 2003, **75**, 461–481.
16 A. W. Bosman, H. M. Janssen and E. W. Meijer, *Chem. Rev.*, 1999, **99**, 1665–1688.
17 J. Peterson, V. Allikmaa, J. Subbi, T. Pehk and M. Lopp, *Eur. Polym. J.*, 2003, **39**, 33–42.
18 D. A. Tomalia and H. D. Durst, in *Supramolecular Chemistry I—Directed Synthesis and Molecular Recognition*, ed. E. W. Weber, Springer Verlag, Berlin–Heidelberg, 1993, pp. 193–313.

19 M. K. Lothian-Tomalia, D. M. Hedstrand and D. A. Tomalia, *Tetrahedron*, 1997, **53**, 15495–15513.
20 P. R. Dvornic and D. A. Tomalia, *Macromol. Symp.*, 1995, **98**, 403–428.
21 D. A. Tomalia, *Aldrichimica Acta*, 1993, **26**(4), 91–101.
22 D. A. Tomalia, *Adv. Mater.*, 1994, **6**, 529–539.
23 D. A. Tomalia, *Aldrichimica Acta*, 2004, **37**, 39–57.
24 B. L. Schwartz, A. L. Rockwood, R. D. Smith, D. A. Tomalia and R. Spindler, *Rapid Commun. Mass Spectrom.*, 1995, **9**, 1552–1555.
25 P. B. Smith, S. J. Martin, M. J. Hall and D. A. Tomalia, in *Applied Polymer Analysis Characterization*, ed. J. Mitchell, Jr., Hanser Publishers, Munich, 1987, pp. 357–385.
26 P. G. de Gennes and H. J. Hervet, *J. Phys., Lett.*, 1983, **44**, 351–360.
27 D. A. Tomalia and J. M. J. Fréchet, in *Dendrimers and Other Dendritic Polymers*, ed. J. M. J. Frechet and D. A. Tomalia, Wiley, Chichester, 2001, pp. 3–44.
28 G. R. Newkome, C. N. Moorfield and F. Vögtle, *Dendritic Molecules*, VCH, Weinheim, 1996.
29 G. R. Newkome, Z.-Q. Yao, G. R. Baker and V. K. Gupta, *J. Org. Chem.*, 1985, **50**, 2003–2004.
30 A. B. Padias, H. K. Hall, Jr, D. A. Tomalia and J. R. McConnell, *J. Org. Chem.*, 1987, **52**, 5305–5312.
31 V. Maraval, J. Pyzowski, A.-M. Caminade and J.-P. Majoral, *J. Org. Chem.*, 2003, **68**, 6043–6046.
32 L. Brauge, G. Magro, A.-M. Caminade and J.-P. Majoral, *J. Am. Chem. Soc.*, 2001, **123**, 6698–6699.
33 D.-M. Xu, K.-D. Zhang and X.-L. Zhu, *J. Appl. Polym. Sci.* 2004, **92**, 1018–1022. These authors report the formation of only an ideal, tetradendron, dendrimer as the sole product when using 1,2-diaminoethane as a core with trimethylopropane triacrylate (TMPTA). In our hands we obtained only the tridendron, dendrimer (SIS) product using the same core with (TMPTA) or PTA under identical conditions as well as under a variety of other conditions as described in the Experimental section.
34 A.-D. Schluter and P. J. Rabe, *Angew. Chem., Int. Ed.*, 2000, **39**, 865–883.
35 D. A. Tomalia, in *Polymer Chemistry—A Practical Approach*, ed. F. J. Davis, Oxford University Press, Oxford, UK, 2004, ch. 7, pp. 188–199.

