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‘One-pot’ sequential deprotection/functionalisation of linear-dendritic hybrid polymers using a xanthate mediated thiol/Michael addition.

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Thiol-Michael addition chemistry is a powerful tool for the preparation of functional materials. In this first report of xanthate-functional linear-dendritic polymer hybrids, the preparation of four generations of xanthate-functionalised dendron atom transfer radical polymerisation macroinitiators is described using an orthogonal chemical strategy. The controlled polymerisation of tertiary butyl methacrylate is demonstrated to high conversion and without interference from the xanthate surface groups. Modification of the peripheral xanthate groups of dendrons at the hybrid polymer chain-end has been studied using a one-pot deprotection/functionalisation strategy and a range of commercially available and bespoke acrylate monomers to form complex polymer architectures from feedstock polymers, differing in the number of modified end groups and the surface chemistry of the dendron chain end.

Introduction

Over the past decade, synthetic approaches using “click” chemistry concepts have aided the preparation of a huge variety of functional materials for a range of applications, including a particular emphasis on drug delivery.[1] Of the many click reactions typically used, the copper-catalysed azide-alkyne click (CuAAC) reaction is arguably the most reported, since it is high yielding, efficient, requires facile conditions and the subsequent purification steps are relatively straightforward. Highlights of using this chemistry have included the preparation of functional dendrimers,[2,3,4,5] post modification of linear polymers,[6] orthogonal post modification of polymers,[7,8] preparation of dendronised polymers,[9,10] and post modification of linear-dendritic hybrids.[11]

Although efficient and highly useful, CuAAC chemistry has two specific limitations. Firstly, azides are hazardous and considerable care is required during the preparation and use of azide functional compounds, especially low molecular weight materials and when using multi-gram scales.[12] Secondly, copper catalysts are required to be removed to very low residual levels if the synthesised materials are required for biological systems as copper presents inherent toxicity.[13,14] Neither of these issues are insurmountable, however, the formation of triazole groups is a necessary byproduct of azide-alkyne reactions and this may not be desirable within a target product.

Thiol-derived click chemistries have also become widely reported and share many of the “click” benefits of CuAAC chemistry, but with without some of the inherent safety concerns.[15] Early reports focussed on using radical thiol-ene chemistry to prepare functional polymers[16] with reported benefits in the synthesis of dendrimers.[17] Despite not requiring a metal catalyst, radical-radical coupling and disulfide bond formation have been highlighted as frequent problems when using thiol-ene chemistry leading to unwanted side reactions.[18]

Thiol-Michael addition chemistry has also been studied as an example of click chemistry. As an option, it provides benefits due to the lack of radicals used and proceeds through a conjugate addition reaction with an activated monomer, such as an acrylate or an acrylamide.[19,20] Focus on the optimal conditions for these types of reaction has shown that minute quantities of catalyst in a variety of different solvents is all that is required to generate very high yields and pure compounds.[21,22] Unfortunately, thiol-based chemistries present their own inherent drawbacks mainly derive from the manipulation of thiol functional compounds which are pungent, sensitive to oxidation and commercially limited to a relatively small range of simple molecules.

Xanthate groups have been utilised for many years as protecting groups for thiols in conventional organic chemistry, in reversible addition fragmentation chain transfer (RAFT) polymerisations,[23,24] as protected thiols during atom transfer radical polymerisation (ATRP) and as protected thiols in the ligand exchange of gold nanoparticles.[25]

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Recent reports from our group have exploited xanthates in the preparation of "masked" thiol-functional dendrimers based on the AB_2 monomer 2,2-bis(methoxy)propionic acid (bis-MPA);[26] providing flexible chemistry options that allow one-pot deprotection/functionalisation thiol- Michael addition strategies onto dendrimer surfaces using a range of acrylate substrates. This approach avoids the direct manipulation of noxious thiol compounds, and the highly limits the potential for oxidative disulfide formation since xanthate formation involved the use of commercially available xanthate salts and the final deprotection/functionalisation reactions were conducted in a one-pot manner using the same amine catalyst. No free thiol-functional compounds are handled experimentally and libraries of functional dendrimers were able to be prepared from initial samples of xanthate-functional materials.

Here we aim to extend the versatility of this strategy through the synthesis of four generations of xanthate peripheral functional dendritic macroinitiators capable of initiating ATRP polymerisation from their focal point chemistry. Dendron macroinitiator syntheses (MW > 4000 g/mol) have been considerably facilitated by the introduction of a new xanthate functional anhydride building block, enabling increased yields and easier purification than our previous report.

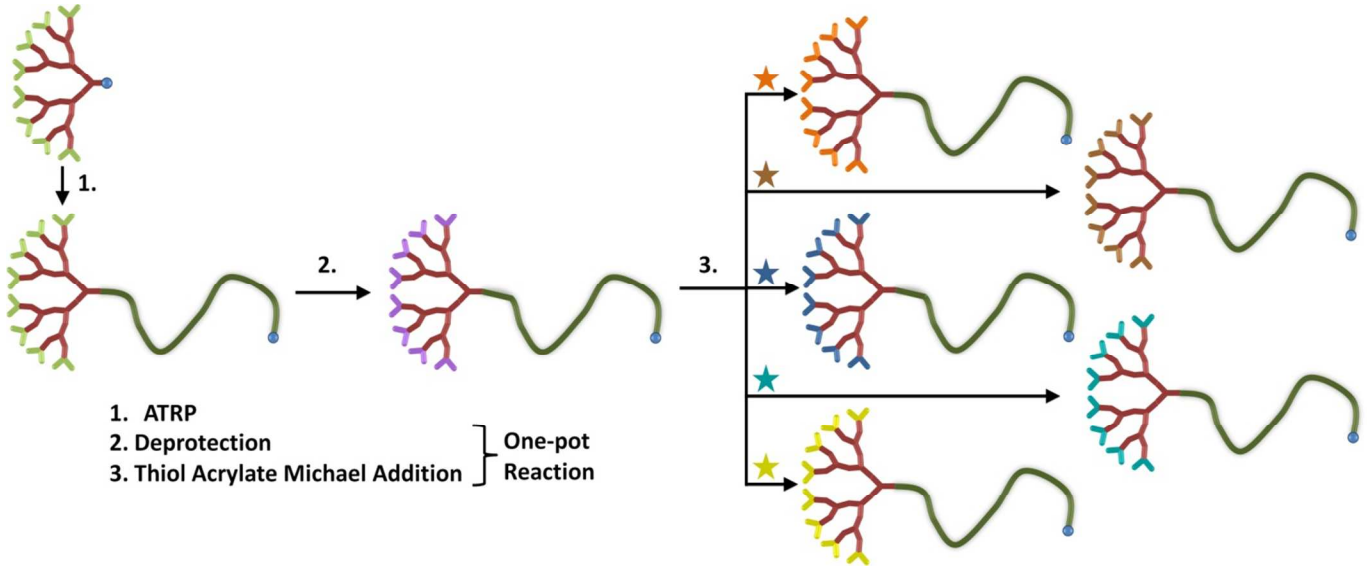


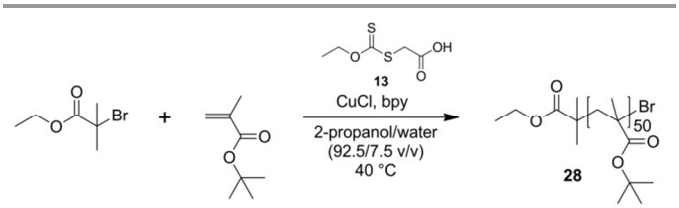
Figure 1. Schematic representation of a linear-dendritic hybrid polymer library synthesis bearing a generation four xanthate-functional dendron: 1) polymerisation from the dendron macroinitiator focal point by ATRP, and the one pot functionalisation strategy incorporating the stepwise 2) deprotection of the xanthate functionality and 3) thiol Michael addition using a range of functional acrylate molecules (shown as coloured stars).

The macroinitiators were used to prepare linear dendritic hybrids of varying generation, and importantly kinetics and model experiments were performed to ensure that the presence of xanthate functionalisation does not lead to loss of control during ATRP. Finally, the materials were subject to one-pot deprotection and Thiol Michael addition functionalisation with five different commercially acrylate monomers demonstrating the ease, flexibility and synthetic control over surface group chemistry using this synthetic methodology, Figure 1. We envisage this to be a highly useful tool for the preparation of complex functional macromolecules.

Results and Discussion

Model Reaction

Recent reports have shown that the presence of xanthate functionalities do not inhibit or retard control radical polymerisation or induce chain transfer.[23,24] To establish a lack of xanthate interference within our proposed reactions, a model polymerisation of tertiary butyl methacrylate (*t*-BuMA) was performed in the presence of the previously reported xanthate functional acid **13**,[26] and the commercially available ATRP initiator ethyl 2-bromoisobutyrate (EBiB) in alcoholic/aqueous media at 40 °C employing a CuCl/2,2'-bypridine (bpy) catalytic system, Scheme 1.



Scheme 1. Model ATRP of *t*-butyl methacrylate with ethyl 2-bromoisobutyrate (EBiB) in the presence of the acid functional xanthate moiety 2-((ethoxycarbonothioyl)thio)acetic acid (**13**).

Monomer conversion reached >99% after 16 hours at 40°C, as determined by the disappearance of methacrylate vinyl signals

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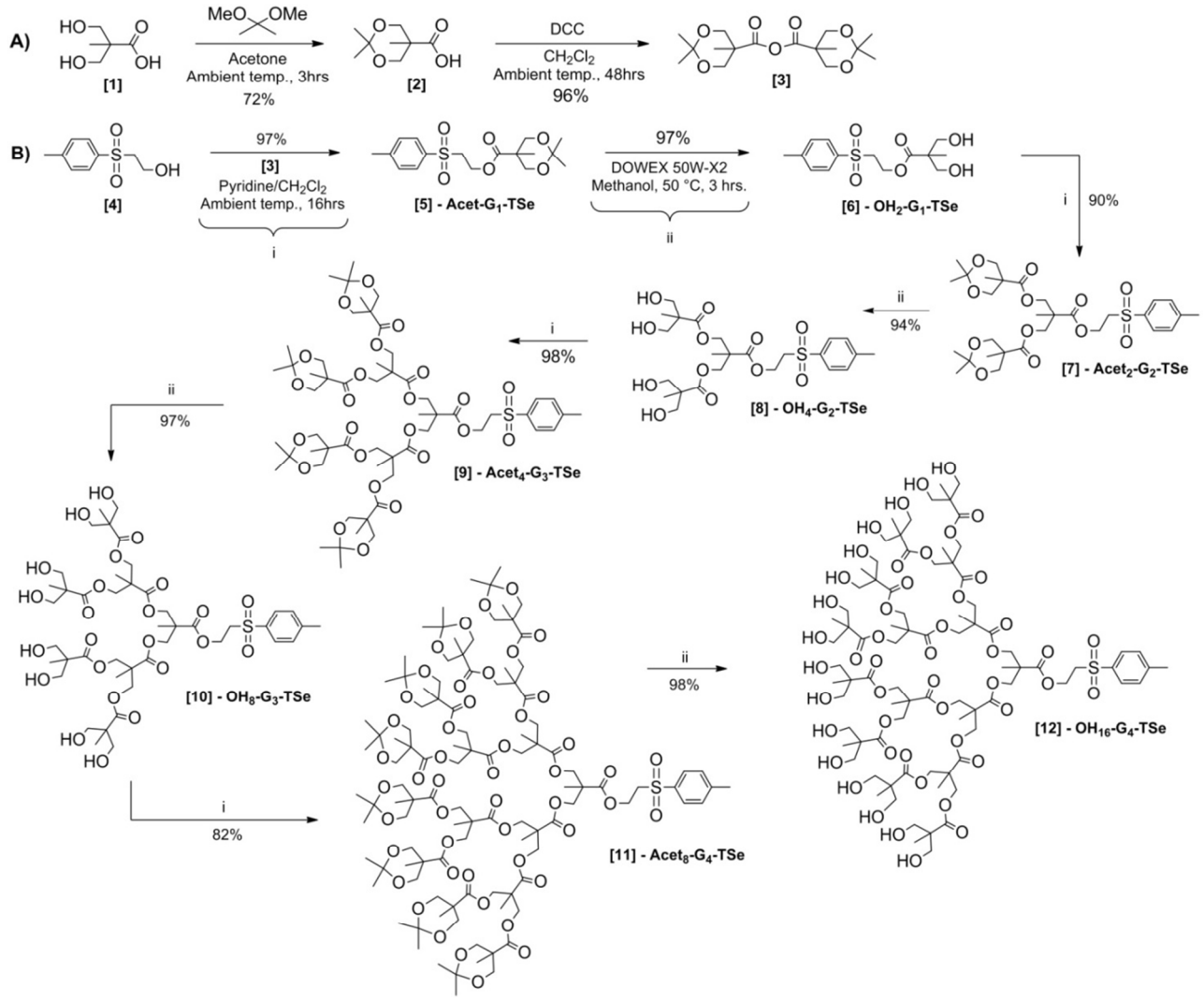
using ^{1}H nuclear magnetic resonance (NMR) spectroscopy. Following purification requiring a neutral alumina column to remove the catalytic system and two precipitations into cold *n*-hexane, no evidence of the characteristic xanthate resonance (δ = 4.65 ppm) was observed (see electronic supporting information (ESI) Figure S1A+B). Triple detection size exclusion chromatography (SEC) displayed a monomodal molecular weight distribution (ESI Figure S2) a number average molecular weight (M_n) of 7900 g/mol (target M_n = 7100 g/mol) and weight average molecular weight (M_w) of 12300 g/mol, resulting in a broader than expected dispersity (Đ) of 1.56 but suggesting no reaction inhibition or termination.



Scheme 2. Synthesis of four generations of polyester dendrons: A) Preparation of isopropylidene-2,2-bis(oxymethyl)propionic anhydride, **3**; B) Divergent synthesis of four generations of hydroxyl terminated dendrons **6**, **8**, **10** and **12**.

Synthesis of xanthate-functional dendritic macroinitiators

The target high molecular weight dendritic molecules required both peripheral functionalisation and focal point modification to produce xanthate-functional ATRP macroinitiators. The AB_2 bis-MPA monomer was chosen for the dendritic scaffold synthesis, due to its low toxicity, ease of preparation and reported compatibility with ATRP.[29] Dendrons of generations one to four (G_1-G_4) were synthesised by a divergent growth approach, Scheme 2. The focal point protecting group, *p*-toluene sulfonyl ether ester (TSe) was utilised, since the conditions for its removal in later synthesis have been shown not to be complicated by the presence of xanthate groups.[26] In our initial report of one-pot thiol Michael addition chemistry, we used the benzylidene protected bis-MPA anhydride building block[31] to synthesise the dendritic scaffold, but were limited to repetitive small scale reactions since the hydrogenation step to regenerate the 1,3-diol periphery utilises a Parr pressure reaction vessel.

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Here we adopted the well-established acetonide protected bis-MPA anhydride **3**,[28] Scheme 2A, whereby the acetonide protecting groups can be cleaved using acidic DOWEX 50W-X2 resin on a multigram scale without degradation of the dendritic ester backbone.

Anhydride monomer **3** was prepared using literature procedures by protecting the diol functionality of bis-MPA with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of *p*-toluene sulfonic acid.[28] The resulting acetonide protected bis-MPA was self-condensed using N,N-dicyclohexyl-carbodiimide (DCC) to generate the anhydride **3** in 96% recovered yield.

The anhydride **3** was used to prepare a range of dendritic macromolecules (**5-12**) up to the G_4 hydroxyl functional dendron **12**, Scheme 2B, by a two stage divergent growth approach resulting in each consecutive generation. The growth step was achieved by reacting each hydroxyl group with 1.3-1.5 equivalents of anhydride monomer **3**, 0.2 equivalents of DMAP and 5 equivalents of pyridine (per hydroxyl group) in a 1:3 ratio of Pyridine:CH_2Cl_2 (v/v). After stirring for 16 hours at ambient temperature, the reaction was quenched with water, diluted with CH_2Cl_2 and washed with acid (1M $NaHSO_4$), base (1M $NaHCO_3$) and brine. The first generation dendron, Acet-G_1-TSe, **5**, was synthesised in 97% recovered yield with confirmation by electrospray mass spectrometry (ESI-MS) with $[MNa]^+$ and $[MK]^+$ adducts at 379.1 Da and 395.1 Da respectively. ^1H and ^{13}C NMR analysis (Figures S3-S5) was also used to confirm the structures.

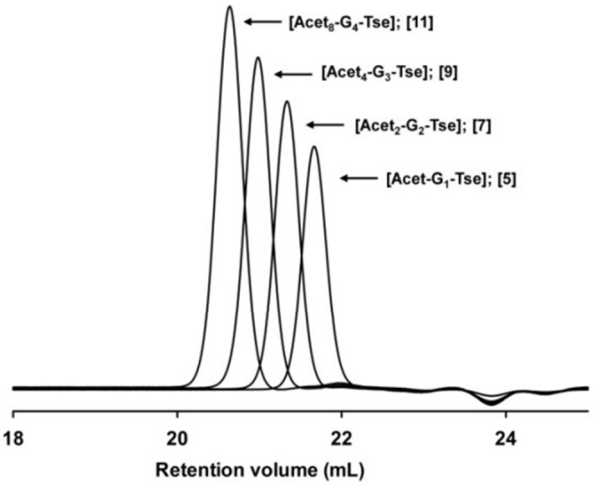

Figure 2. Overlay of SEC chromatograms (refractive index) from four generations of acetonide protected dendrons.

Removal of the acetonide protecting groups was achieved by dissolving the materials in methanol, warming to 50 °C, adding DOWEX-X2 resin, and leaving the mixture to stir for 3 hours. The progress of the reactions was monitored using thin-layer chromatography (TLC), and led to high recovered yields for each material. The first generation dendron, OH_2-G_1-TSe, **6**, was formed in 97% yield and was equally confirmed using ESI-MS ($[MH]^+$, $[MNa]^+$ and $[MK]^+$ = 317.1, 339.1 and 355.1 Da respectively, Figure S8). No trace of degradation of the TSe protecting group was observed by ^1H, ^{13}C NMR or mass spectrometry (Figures S6-S8). Macromolecules **7-12**, Scheme 2B, required column chromatography after each growth step to remove the lower molecular weight impurities with structural integrity confirmed by ^1H and ^{13}C NMR and ESI-MS or time-of-flight matrix assisted laser desorption ionisation (MALDI-TOF) mass spectrometry (Figures S9-S26). Dendritic macromolecules **5**, **7**, **9** and **11** were also studied using triple detection SEC (Figure 2) and individual monomodal chromatograms were observed, highlighting the purity of each structure. Despite the low resolution nature of mass determination using SEC, the M_w values correlated well with the expected increasing overall molar mass of the materials and values of Đ were < 1.4, mainly due to broadening on the column (**5** M_w (SEC) = 410 g/mol, Đ = 1.28; **7** M_w (SEC) = 610 g/mol, Đ = 1.37; **9** M_w (SEC) = 1165 g/mol, Đ = 1.30; **11** M_w (SEC) = 2295 g/mol, Đ = 1.24).

We recently reported xanthate functionalisation of dendritic macromolecules using the xanthate acid building block **13**, Scheme 3A, using DCC/DPTS chemistry.[26] For the lower generation hydroxyl-functional dendrons, OH_2-G_1-TSe, **6**, and, OH_4-G_2-TSe, **8**, xanthate functional dendrons Xan_2-G_1-TSe, **15**, and Xan_4-G_2-TSe, **16**, were prepared by using these reported methods, resulting in recovered yields of 84% and 88% respectively. For higher generation materials, Xan_8-G_3-TSe, **17**, and Xan_{16}-G4-TSe, **18**, it was found that using **13** with DCC/DPTS resulted in partially functionalised xanthate dendrons that were extremely difficult to separate from their fully functionalised counterparts by liquid chromatography. The solubilities of hydroxyl-functional dendrons OH_8-G_3-TSe, **10**, and OH_{16}-G_4-TSe, **12** were extremely poor in CH_2Cl_2 and required considerable dilution for total solubility; a possible explanation for incomplete acylations. Changing the esterification strategy from DCC/DTPS to anhydride chemistry solved these problems. Xanthate acid **13** was dehydrated with DCC in CH_2Cl_2 at ambient temperature for 24 hours to prepare the anhydride monomer **14** in 99% recovered yield, Scheme 3A. Reaction completion was determined by ^{13}C NMR spectroscopy with the appearance of the anhydride carbonyl carbon resonance at 163 ppm and the disappearance of the acid carbonyl signal at 174 ppm (Figure S28). Pyridine was used as both a catalyst and co-solvent (1:2 v/v mixture with CH_2Cl_2) during the anhydride couplings and was found to be an excellent solvent for OH_8-G_3-TSe, **10**, and OH_{16}-G_4-TSe, **12**. By dissolving the hydroxyl dendron OH_8-G_3-TSe, **10**, or OH_{16}-G_4-TSe, **12** in pyridine, cooling the mixture in an ice bath and adding the anhydride **14** in CH_2Cl_2 to the solution, the reaction was free from precipitation or solubility issues. Final purification by liquid chromatography generated the xanthate functionalised dendrons Xan_8-G_3-TSe, **17**, and Xan_{16}-G4-TSe, **18**, in 75% and 76% recovered yield respectively. Confirmation of the target molecule synthesis was achieved by ^1H and ^{13}C NMR spectroscopy and MALDI-TOF mass spectrometry; **17**, $[MNa]^+$ = 2331.42 Da and **18**, $[MNa]^+$ = 4555.85 Da (Figures S31 and S34).

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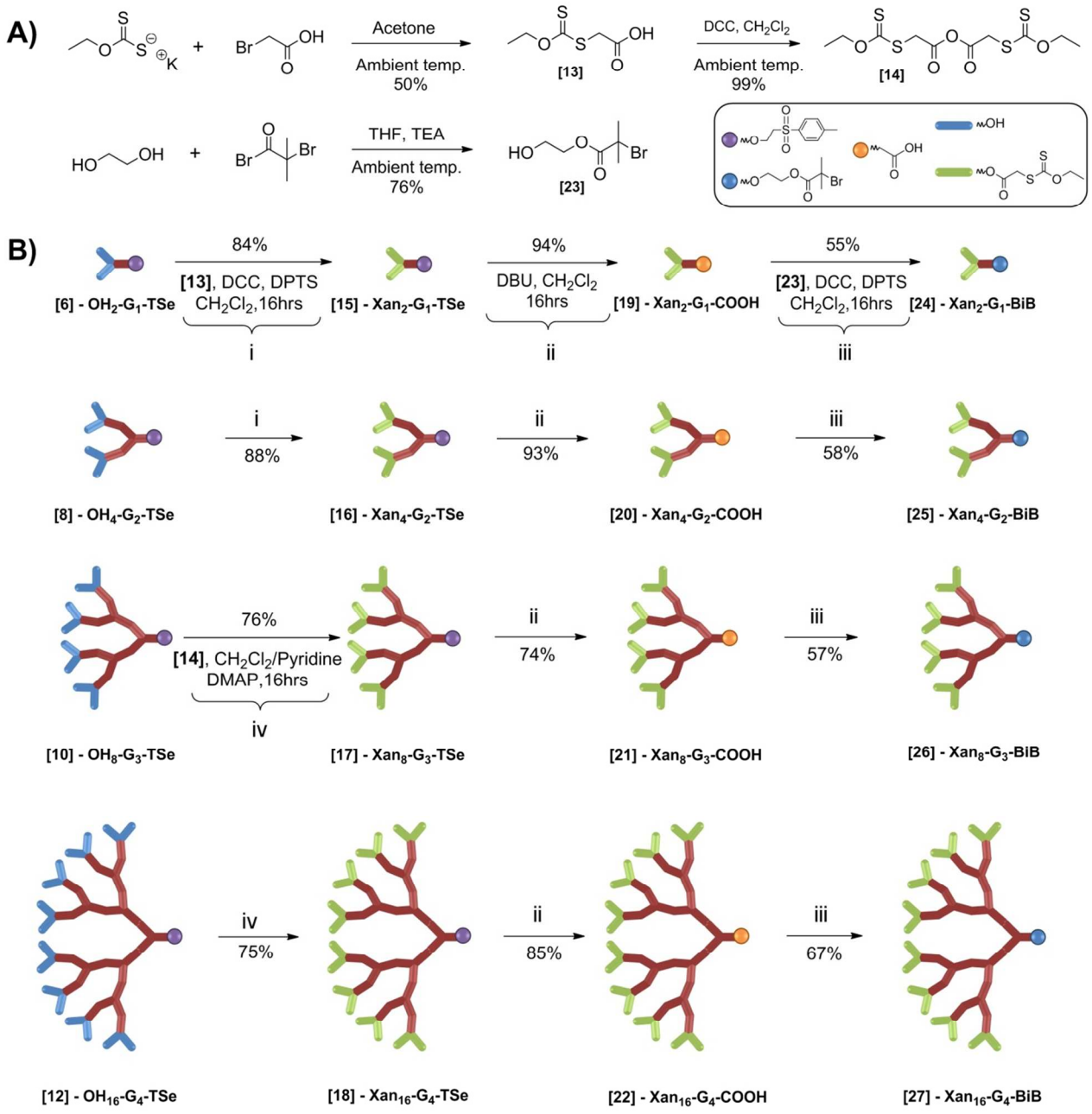
Complete removal of the TSe focal point protection from each of the xanthate-functional dendrons **15** - **18**, was achieved using 1.3 equivalents of the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) after 16 hours at ambient temperature. Analysis of the purified products by ESI-MS or MALDI-TOF indicated the expected loss of 182.0 g/mol; e.g., Xan_8-G_3-TSe, **17**, $[MNa]^+$ = 2331.42 Da Xan_8-G_3-COOH, **21**; $[MNa]^+$ = 2149.10 Da and Xan_{16}-G_3-COOH, **22**, $[MK]^+$ = 4393.83 Da (Figures S37 and S40).



Scheme 3. Surface and focal point functionalisation of xanthate-functional dendron ATRP macroinitiators: A) Synthesis of the xanthate functional anhydride **14**, and 2-hydroxyethyl-2-bromoisobutyrate, **23**; B) Schematic synthetic strategy for xanthate-functional dendron macronitiators to the fourth generation (**24**, **25**, **26** and **27**).

ATRP has been used previously to form linear-dendritic hybrids and new complex branched architectures[29] including the recently reported hyperbranched polydendrons,[30] therefore the focal point acid functionality of dendrons **19-22** were reacted with 2-hydroxyethyl 2-bromoisobutyrate, **23**, using DCC/DPTS, to form four generations of dendritic ATRP

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macroinitiators, **24**-**27**, in relatively high recovered yields (55-76%). **23** was synthesised by reacting 2-bromoisobutyrate bromide with an excess of ethylene glycol, Scheme 3A, using reported procedures.[32]

Purification of the macroinitiators was achieved using a combination of aqueous acid and base washes and automated liquid chromatography. Characterisation of each initiator using ^{1}H NMR spectroscopy indicated the appearance of a sharp singlet at approximately 1.90 ppm, for the resonances of the two symmetrical methyl groups of the bromoisobutyrate moiety, and an additional integral of four methylene protons at approximately 4.40 ppm introduced during reaction with **23** (Figures: S44, S47, S50, S53). ^{13}C NMR was also useful for characterisation of the first three generations of initiators (**24-26)**, indicating the loss of the acid carbonyl resonance at approximately 173 ppm, and the subsequent formation of a new ester carbonyl resonance at approximately 172 ppm (Figures: S45, S48 and S51). Neither the acid nor ester carbonyl could not be readily observed for the fourth generation macroinitiator, **27** (Figure S54), presumably due the reduced mobility of the macromolecule, however, MALDI-TOF and ESI-MS confirmed the expected $[MNa]^+$ adducts in all cases (Figures 3, S46, S49, S52, S55).

ATRP of *t*-butyl methacrylate using xanthate-functionalised dendritic macroinitiators

The CuCl/2,2'-bipyridyl catalyst mediated ATRP of *t*-BuMA was studied using the xanthate functional macroinitiators since the resulting polymer backbone and pendant tertiary methyl groups are all visible via ^{1}H NMR with resonances between approximately 0.8-2.2 ppm and do not overlap with resonances for the xanthate peripheral groups. This enabled the use of NMR to monitor the progress and success of the targeted thiol-Michael addition 'click' chemistry. Polymerisation of ^{t}BuMA using, Xan_2-G_1-BiB, **24**, and Xan_4-G_2-BiB **25**, were initially conducted in a mixture of 2-propanol/water (92.5/7.5 v/v) at 40 °C following our model reaction (Table 1, sample **28**) and previously reported conditions.[33] Conversions reached >90% after 7 hours, and Đ values remained low (<1.4) with both initiator (Table 1, samples **29** and **30**). Analysis of the resulting linear-dendritic hybrids **29** and **30** by SEC and ^{1}H NMR also showed a good correlation with theoretical molecular weights (Table 1). Kinetic studies indicated a constant concentration of active radicals, through a linear semi-logarithmic plot *vs.* time, and a linear relationship with increasing M_n *vs.* conversion was also observed (Figures S56 and S57).

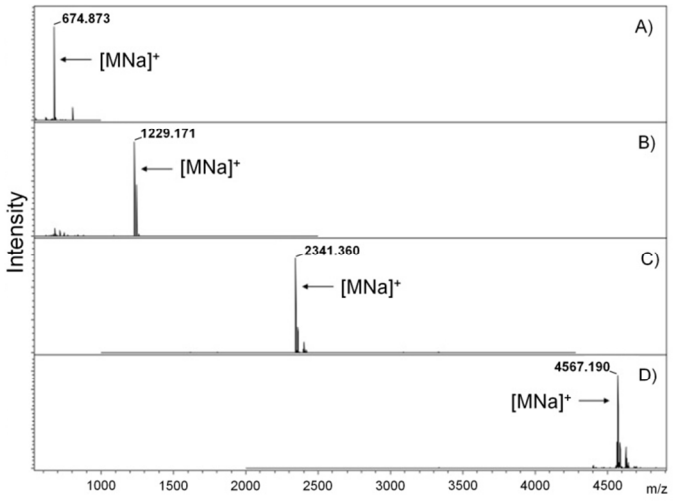

Figure 3. Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) spectra confirming synthesis of xanthate-functional dendritic initiators; A) Xan_2-G_1-BiB **24**, (MNa^+ = 674.87 Da); B) Xan_4-G_2-BiB **25**, (MNa^+ = 1229.17 Da); C) Xan_8-G_3-BiB (26), (MNa^+ = 2341.36 Da); D) Xan_{16}-G_4-BiB **27**, (MNa^+ = 4567.19 Da).

The third and fourth generation initiators, Xan_8-G_3-BiB, **26**, and Xan_{16}-G_4-BiB, **27**, were insoluble in the isopropanol/water mixture employed in the initial polymerisations. Various commonly used ATRP solvents were studied to establish conditions to solubilise these macroinitiators, including methanol (insoluble), 2-propanol 100% (insoluble), ethanol 100% (insoluble) and water 100% (insoluble). Acetone was found to solubilise all four generations of initiators **24**-**27**, and was used as an alternative to the isopropanol/water mixture, with all polymerisations using the CuCl/bpy catalytic system as previously, but at a temperature of 50 °C. Kinetic studies revealed that the polymerisations were found to be much slower with either **24** or **25** relative to the isopropanol/water mixture used previously (Figures 4, S58 and S59).

Table 1. Characterisation of xanthate-functional linear-dendritic polymer hybrids synthesised by G_1-G_4 xanthate-functional macroinitiated ATRP of *t*-butyl methacrylate.

Target polymer;	Sample	Time (h)	Conv (%)	Theoretical M_n (g/mol)	SEC[c] M_n (g/mol)	SEC M_w (g/mol)	SEC Đ	SEC dn/dc	Calc DP_n SEC	Calc DP_n ^{1}H NMR
EBiB -p(*t*-$BuMA_{50}$)[a]	**28**	16	99+	7100	7900	12300	1.56	0.0764	56	-
Xan_2-G_1p(*t*-$BuMA_{50}$)[a]	**29**	7	92	7141	8730	11920	1.37	0.0764	57	59
Xan_4-G_2p(*t*-$BuMA_{50}$)[a]	**30**	6	94	7819	9900	13415	1.36	0.0754	61	48
Xan_2-G_1p(*t*-$BuMA_{50}$)[b]	**31**	24	99+	7141	11800	15200	1.29	0.0764	79	60
Xan_4-G_2p(*t*-$BuMA_{50}$)[b]	**32**	24	98	7819	15300	19100	1.25	0.0754	99	49
Xan_8-G_3p(*t*-$BuMA_{50}$)[b]	**33**	28	95	9087	15000	17000	1.13	0.0776	89	76
Xan_{16}-G_4p(*t*-$BuMA_{50}$)[b]	**34**	29	99+	11542	29000	33000	1.14	0.0712	172	87

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[a]IPA/H_2O (92.5/7.5 v/v), 50 wt%, 40°C; [CuCl];[Bpy];[^{t}BuMA] = [1];[2];[50]. [b]Acetone, 50 wt%, 50°C; [CuCl];[Bpy];[^{t}BuMA] = [1];[2];[50]. [c]THF containing 2% TEA (v/v)

Despite the slower polymerisations, all polymerisations using the four generations of initiators showed kinetics that indicated controlled radical polymerisation under these conditions, (Figures 3, S58, S59, S60 and S61).

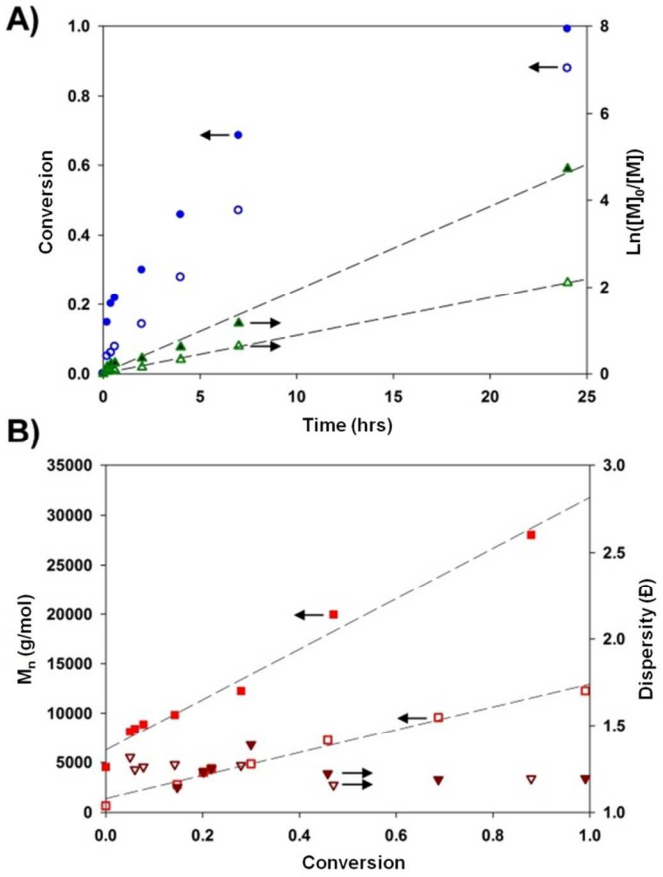

Figure 4. Representative kinetic studies of copper-catalysed ATRP of *t*-butyl methacrylate in acetone using xanthate-functional dendron macroinitiators: A) Conversion *vs.* time and corresponding semi-logarithmic plots for polymerisations initiated with either Xan_2-G_1-BiB, **24** (closed blue circles and closed green triangles) or Xan_{16}-G_4-BiB, **27** (open blue circles and open green triangles) - dotted lines represent linear regression of the semi-logarithmic plot; B) M_n (SEC) *vs.* conversion and dispersity *vs.* conversion plots using Xan_2-G_1-BiB, **24** (open red squares and closed brown triangles) and Xan_{16}-G_4-BiB, **27** (closed red squares and open brown triangles) - dotted lines represent the linear regression of the M_n (SEC) *vs.* conversion plots.

The ATRP reactions using initiator Xan_8-G_3-BiB, **26**, reached 95% conversion in 28 hours, (Table 1, sample **33**) whilst Xan_{16}-G_4-BiB, **27**, polymerisations reached 99+% conversion in 29 hours (Table 1, **34**). Analysis of the resulting linear-dendritic hybrids by triple detection SEC showed excellent Đ values (<1.2), but a loss of M_n targeting. This discrepancy with targeted M_n was found to increase with increasing macroinitiator generation (Table 1, samples **31**-**34**) and is probably due to the increased steric constraints at the initiating site and subsequent issues with initiator efficiency leading to fewer successful initiation events and higher than expected molecular weights; evidence of residual initiator was found by SEC in samples **30**, **32**, **33** and **34**, initiated by the second to fourth generation macroinitiators. ^{1}H NMR analysis of the linear-dendritic hybrid materials **29**-**34** revealed the characteristic signal present for the CH_2 environment adjacent to the xanthate thio-carbonyl group at 4.50 ppm, also indicating the successful maintenance of this functionality at the periphery of the dendritic segment of the hybrid polymers (Figures S62-S65).

One-pot xanthate deprotection thiol-Michael addition 'click' functionalisation of linear-dendritic polymer hybrids

The presence of the xanthate peripheral functional groups within the linear-dendritic polymer hybrids presents the opportunity to use the synthesised materials as modifiable substrates to create a range of functionalised complex architectures through simple one-pot xanthate deprotection, followed by thiol-Michael addition using a range of acrylate monomers.

Five commercially available acrylate monomers and one novel acrylate were chosen to demonstrate the versatility of the chemistry, Figure 5. This range of acrylates allowed an array of different functionalities to be introduced including hydrophilic, hydrophobic and polymeric groups. The preparation of a morpholino functional monomer, **41**, from morpholio propan-2-ol **40**, Figure 5B, was achieved by reaction of acryloyl chloride in the presence of triethylamine (TEA) and a catalytic amount of DMAP resulting in a recovered yield of 74% after purification; ^{1}H and ^{13}C NMR spectroscopy confirmed success of the synthesis (Figures S66 and S67). Since acrylate monomers are relatively stable they can be prepared on large scales, and are not potentially explosive, unlike azide based monomers frequently used in conjunction with alkyne/azide click reactions.

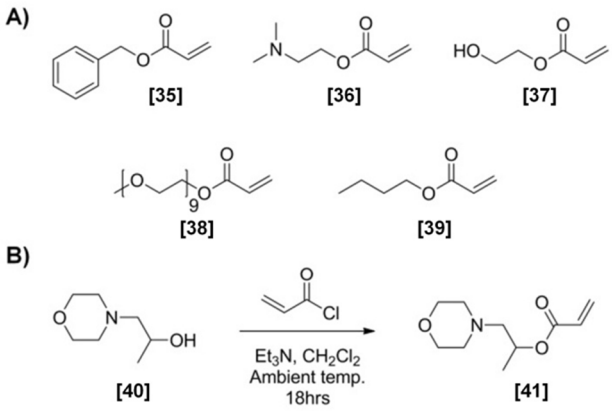

Figure 5. Acrylate functional monomers studied. A) Commercially available monomers; Benzyl acrylate (Bzy), **35**; 2-(Dimethylamino)ethyl acrylate (Am), **36**; [2-Hydroxyethyl acrylate (Hydx), **37**; Oligo(ethylene glycol) monomethyl ether acrylate (M_n = 480 g/mol) (OEG), **38**; Butyl acrylate (Butyl), **39**. B) Synthesised morpholino propanoyl acrylate (Morph), **41**.

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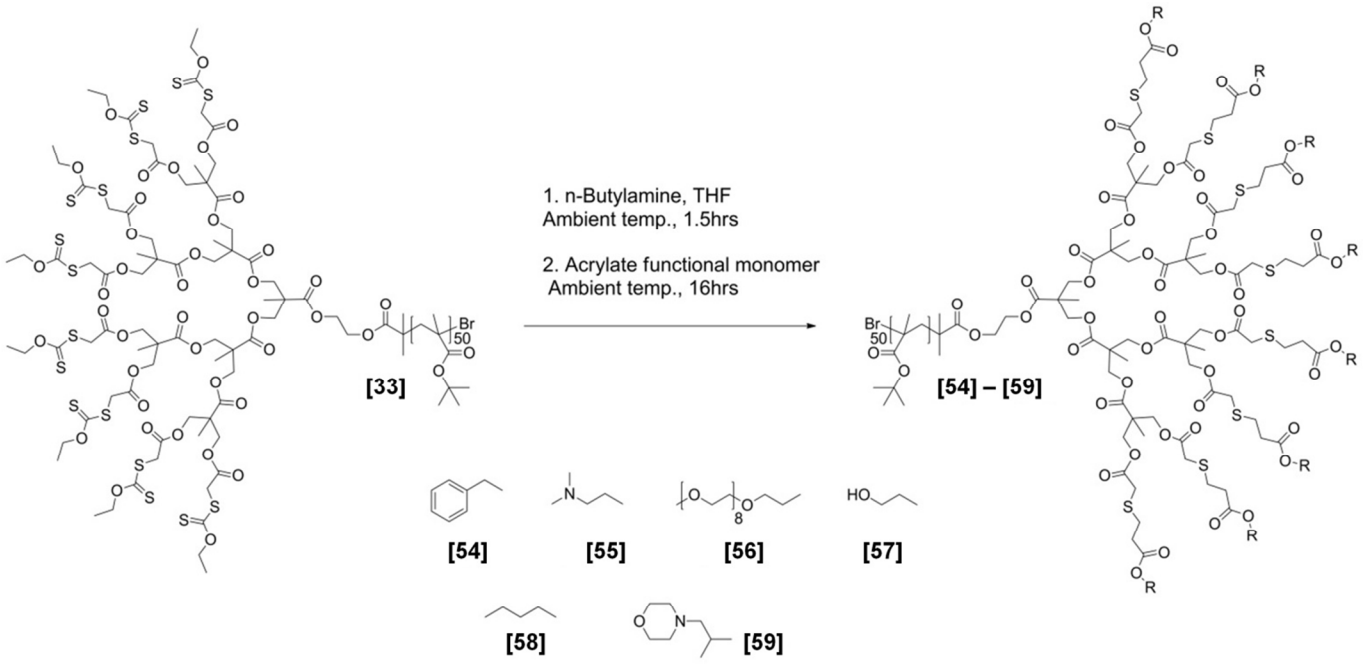
Recent reports of polymers with pendant xanthate groups have shown that complete removal of the xanthate functionality and subsequent thiol generation can result under mild conditions using a 2.5 molar excess of *n*-butylamine at ambient temperature after dissolution of the polymers into THF.[24] Similarly, we recently demonstrated that ideal dendrimers, produced using the bis-MPA scaffold and surface-functionalised with xanthates, can be peripherally modified using the same one-pot mild conditions followed by Michael addition with a range of acrylates and without degradation of the polyester framework.[26] Following these procedures, each of the four dendritic hybrids (**29**, **30**, **33** and **34**) was dissolved in anhydrous THF (10 wt%) and bubbled rigorously with nitrogen for a period of approximately 10 minutes to remove any residual oxygen from the vessel. Polymers **29** and **30** were chosen over **31** and **32** due to their M_n values more closely correlating to targeted molecular weights. Following degassing, a 2.5 molar excess of *n*-butyl amine per xanthate surface group was added to the solution, and the reaction left stirring at ambient temperature for 1.5 hours. After *in situ* deprotection, the range of chosen acrylates (**35-39** and **41**) was added to the same vessel in a 5 molar excess per thiol and without isolation of the thiol-functional linear-dendritic hybrid, Scheme 4. The reactions were left to stir at ambient temperature overnight and purified by direct precipitation into cold *n*-hexane. In cases where unreacted acrylate could still be observed after precipitation (^{1}H NMR spectroscopy) the materials were further purified under high vacuum and freeze dried. Specific care was required when using acrylate **38**, and samples were diluted with THF and subjected to dialysis against a THF/water mixture (80/20 v/v).



Scheme 4. One-pot deprotection/thiol Michael addition modification of the linear-dendritic hybrid polymer bearing the third generation xanthate-functional dendron, **31**, using various acrylates.

Each functionalised linear-dendritic hybrid was analysed by SEC and ^{1}H NMR spectroscopy (Table 2, S68 – S87) to study the success of the functionalisation and the effect of the Michael addition to sample molecular weights and Đ. For each modification, the conversion of surface groups was found to exceed 99% (Figures S68 to S87). Characteristic changes from the spectra of each initial xanthate linear-dendritic hybrid were readily observable in modified materials; for example the functionalisation of the linear-dendritic hybrid bearing the third generation xanthate-functional dendron with oligo(ethylene glycol) methyl ether acrylate (OEG, M_n = 480 g/mol) is shown in Figure 5, with comparison to the starting xanthate functional material, **33**. The total loss of the quartet signal at 4.60 ppm, corresponding to the methylene environment adjacent to the outer methyl of the ethyl xanthate moiety, indicated successful removal of the xanthate moieties with subsequent generation of the corresponding highly reactive thiol end groups. Clearly, this was not observed during the reaction as samples were not taken and direct acrylate addition was utilised to allow the thiol-Michael addition. A noticeable shift in the singlet corresponding to the methylene environment situated between the xanthate and the outer ester group was observed, shifting from approximately 3.90 ppm before deprotection, **33**, Figure 6, to approximately 3.30 ppm after deprotection and Michael addition, **56**, Figure 5. In the case presented in Figure 6, a strong resonance corresponding to the introduction of the oligo(ethylene glycol) chain signals was observed between 3.30 and 3.80 ppm, but different acrylate-specific signals were

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observed for each surface modification. In each case, two new methylene triplet resonances between 2.60 and 2.80 ppm were observed, corresponding to the addition of the thiol to the acrylate double bond and the formation of the functionalised product.

Table 2. SEC analysis of linear-dendritic hybrids after Michael addition

Target polymer	Sample	SEC[a]		
		M_n (g/mol)	M_w (g/mol)	Đ
Bzy_2-G_1p($tBuMA_{50}$)	**42**	10277	13212	1.29
Am_2-G_1p($tBuMA_{50}$)	**43**	11995	15347	1.28
OEG_2-G_1p($tBuMA_{50}$)	**44**	11192	14713	1.32
$Hydx_2$-G_1p($tBuMA_{50}$)	**45**	9857	12786	1.30
$Butyl_2$-G_1p($tBuMA_{50}$)	**46**	11861	15086	1.27
$Morph_2$-G_1p($tBuMA_{50}$)	**47**	13734	17360	1.26
Bzy_4-G_2p($tBuMA_{50}$)	**48**	11906	14800	1.24
Am_4-G_2p($tBuMA_{50}$)	**49**	12242	16069	1.31
OEG_4-G_2p($tBuMA_{50}$)	**50**	14073	17867	1.27
$Hydx_4$-G_2p($tBuMA_{50}$)	**51**	11095	15766	1.42
$Butyl_4$-G_2p($tBuMA_{50}$)	**52**	13731	17617	1.28
$Morph_4$-G_2p($tBuMA_{50}$)[b]	**53**	27552	45587	1.67
Bzy_8-G_3p($tBuMA_{50}$)	**54**	15524	17908	1.17
Am_8-G_3p($tBuMA_{50}$)[c]	**55**	20099	54207	2.70
OEG_8-G_3p($tBuMA_{50}$)	**56**	21766	26544	1.22
$Hydx_8$-G_3p($tBuMA_{50}$)	**57**	13983	17958	1.28
$Butyl_8$-G_3p($tBuMA_{50}$)	**58**	14574	18446	1.27
$Morph_8$-G_3p($tBuMA_{50}$)[d]	**59**	20013	38298	1.91
Bzy_{16}-G_4p($tBuMA_{50}$)	**60**	28961	33624	1.16
$Morph_{16}$-G_4p($tBuMA_{50}$)[e]	**61**	48816	526639	10.8

[a]THF containing 2% TEA (v/v); [b]Nominal theoretical M_n = 10350 g/mol; [c]Nominal theoretical M_n = 15450 g/mol; [d]Nominal theoretical M_n = 15900 g/mol; [e]Nominal theoretical M_n = 30100 g/mol

Analysis of the functionalised products using SEC generally resulted in observed molecular weights higher than their parent starting materials and, in most cases, no dramatic changes in Đ values, Tables 2. Not surprisingly, the most noticeable increase in molecular weight resulted from hybrids functionalised with OEG chains at each initial xanthate site.

A surprising observation, however, was borne out across the functionalisation reactions carried out on linear-dendritic hybrids containing G_2-G_4 dendrons; when using tertiary amine-functional acrylates, significantly higher than expected molecular weight increases were observed with corresponding increases in Đ. Even when using the hybrid polymer containing the G_1 dendron, the attempted introduction of morpholino end groups led to the highest observed molecular weights, although the dispersity remained consistent with the parent materials (Table 2, sample **47**). In the G_2-dendron containing series, the morpholino functionalisation led not only to higher molecular weights but also a marked increase in dispersity. Whilst attempting the same modifications with the G_3–dendron containing hybrids, the introduction of either dimethyl amino or morpholino functionality led to large increases in dispersity, predominantly driven by much higher M_w values than the other samples. Due to a lack of sample, only the benzyl and morpholino modification of G_4-dendron containing hybrids was attempted with maintenance of dispersity and molecular weights during reactions with benzyl acrylate and large increases in dispersity (Đ > 10), M_n and M_w (values > 520 kg/mol) when reacting with the morpholino acrylate **41**.

The observed behaviour was rationalised as potentially occurring by either issues with the SEC column interaction which became more readily observed at higher generations, or the presence of an unexpected side reaction leading to reaction between the increasingly end-functional materials; this last possibility being more likely than a strong interaction with the SEC column. The side reaction may also be a retardation of the the thiol-Michael addition in the presence of the amine functionality leading to disulfide bond formation between end – functional structures; this would be expected to be more pronounced at high dendron generation and requires further study.

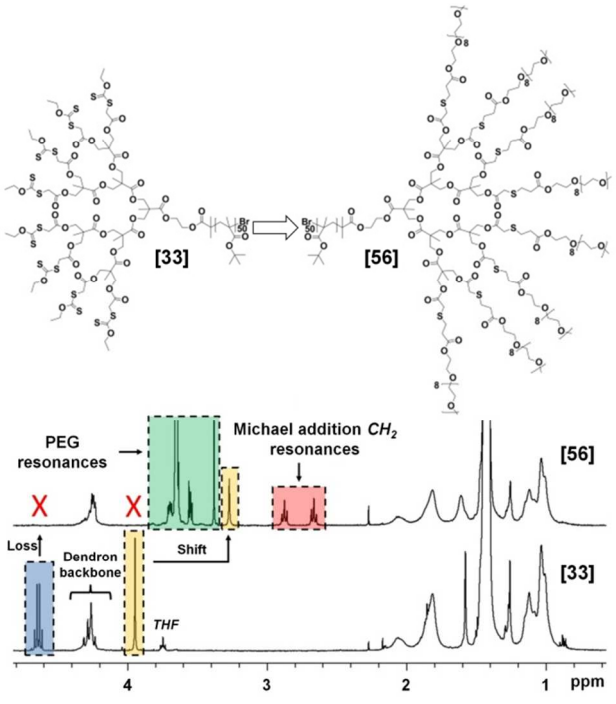

Figure 6. ^{1}H NMR spectra of the starting material, **33**, and product, **56**, after the one-pot deprotection of the linear-dendritic hybrid polymer bearing the third generation xanthate-functional dendron and subsequent thiol/Michael addition with oligo(ethylene glycol) methyl ether acrylate (OEG, M_n = 480 g/mol).

Conclusions

The synthesis of a new family of xanthate functional dendritic macroinitiators to the fourth generation has been achieved using a bis-MPA polyester backbone. The materials were produced in high recovered yields as a result of a new xanthate anhydride building block, and characterised to establish the synthetic success and purity. Each dendron has benefitted from the orthogonality of the synthesis strategy, employing peripheral and focal point protection/deprotection approaches that allow accurate manipulation and functional group control during multiple site specific esterification reactions. Although

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anhydride coupling is not highly mass efficient, scale-up may benefit from recycling of the eliminated acid by-product; no attempts were made to achieve this within the current study. The macroinitiators can be used to promote controlled radical polymerisation of *t*-BuMA under ATRP conditions to produce a new range of linear-dendritic hybrid polymers and the one-pot deprotection, thiol-Michael addition, previously demonstrated for ideal dendrimers, was shown to be effective at the chain end of the hybrid polymers. A library of twenty different surface functional linear-dendritic hybrid polymers was readily generated in very high yields from just four initial polymers, however, tertiary amine functional acrylates were shown to require further optimisation to avoid side reactions. This methodology has implications for many future material synthesis strategies where the direct manipulation of thiols is to be avoided and high yielding functionalisation is required. It also has implications for the search for accelerated, high yielding one-pot reactions to enable materials and chemical innovation; a target for highlighted by the recent surge of interest in 'click' chemistries.[34] Our current work is focussed on using this chemistry to synthesise materials with site specific functionalisation for potential drug delivery applications.

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Notes and references

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Electronic Supplementary Information (ESI) available: Materials, experimental procedures and characterization data with assignments. See DOI: 10.1039/c000000x/

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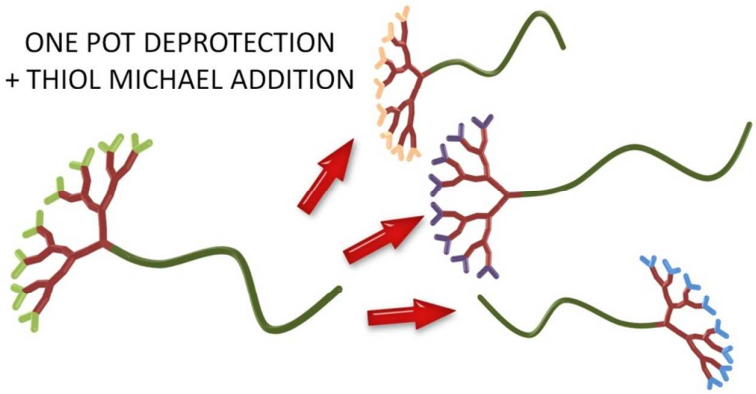
Graphical Abstract

‘One-pot’ sequential deprotection/functionalisation of linear-dendritic hybrid polymers using a xanthate mediated thiol/Michael addition.

Sam E. R. Auty,[a] Oliver C. J. Andrén,[b] Michael Malkoch,[b] and Steven P. Rannard[a*]

An orthogonal synthesis strategy has been employed to produce a range of dendritic macroinitiators bearing xanthate surface functionaliy. After atom transfer radical polyemrisation, the resulting linear-dendritic hybrid polymers undergo a highly efficient one-pot deprotection to thiols and subsequent acrylate Michael addition to allow formation of a library of functionalised materials.



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