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# Journal Name

## COMMUNICATION

# The First Peripherally Masked Thiol Dendrimers: A Facile and Highly Efficient Functionalization Strategy of Polyester Dendrimers via One-Pot Xanthate Deprotection/Thiol-Acrylate Michael Addition Reactions.

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**Introducing multiple reactive functional groups at the periphery of dendrimer materials presents considerable challenges if the functionality is able to self-react. An efficient and facile approach to introducing masked thiols at the surface of polyester dendrimers is presented. One-pot, deprotection/thiol-acrylate Michael addition from the xanthate-functional dendritic substrates (generation zero to two) has been achieved for the first time, with high efficiency demonstrated using three acrylates of varying chemistry and avoiding disulfide formation.**

The continually increasingly interest in 'click' reactions has extended to a wide range of demonstrated approaches. Application has been reported across chemical biology,[1] light activated syntheses,[2] drug discovery[3] and materials chemistry.[4] Since the early reports of the application of copper-catalysed azide-alkyne click (CuAAC) in the formation of dendronised polymers,[5] CuAAC has been used to readily funtionalise dendrimers, via reaction at surface alkyne groups,[6] or to synthesise dendrimers directly and without the need for protection/deprotection strategies.[7] Reports of the synthesis of a 6th generation dendrimer in a single day[8] are testament to the flexibility and versatility of such reactions.

Thiol-ene and thiol-yne "click" reactions have also attracted considerable interest in polymer and dendrimer chemistry. Thiol-acrylate reactions have particular benefits as they provide high yields, do not generate byproducts, require no transition metal catalyst or radical initiation and proceed in a wide variety of solvents.[4] Recent reports have described sequential thiol-ene/thiol-yne reactions,[9] to form octafunctional low generation dendritic polymers with multiple stereocentres, and thiol-acrylate Michael addition to introduce hydroxyl functionality during the intermediate steps of divergent dendrimer growth.[10] Iterative triacrylate/dithiol reaction, to form dendrimers that may be surface functionalized with a range of monofunctional thiols (e.g. thiol functional polyethylene glycol), has also been studied,[11] however, this approach utilizes very high reagent excesses, reminiscent of early divergent PAMAM dendrimer reports; >10 fold molar excess of DL-dithiothreitol (DTT) was used to form a $G_0$ trithiol and an approximately 50-fold molar excess of DTT was used to generated the $G_2$ dendrimer containing 12 thiol functional groups.

Despite the interest in thiol-acrylate Michael addition, the authors are unaware of reports of dendrimer syntheses that solely locate thiols at the periphery of the molecule to provide stable, multi-functional thiol-terminated dendrimers for post functionalisation; in the large majority of reports, monothiols are reacted with multi-acrylate functional dendrimers, possibly due to the wide range of commercially available monothiol substrates. Thiols have the potential to oxidize and form disulfide and this has been utilized to generate thiol functionality at the core of polyester dendrons,[12,13] after reduction of disulfide core molecules, facilitating 'Janus' dendrimer synthesis. In these cases a single thiol is present at the focal point but multiple thiols at the periphery of dendrons is also not reported within the current literature. Here, we report a versatile and efficient strategy for the placement of protected thiol groups, in the form of xanthates, at the surface of polyester dendrons, the formation of ideally branched dendrimers and the one-pot deprotection/thiol-acrylate Michael addition to introduce diverse chemistry at the dendrimer surface.

Recently, xanthate groups have been used as chain transfer agents in reversible-addition fragmentation-chain transfer (RAFT) controlled polymerizations,[14] as protected thiols during atom transfer radical polymerization and RAFT[15a-b] and as protected thiols in the ligand exchange of gold nanoparticles.[16] We chose to employ S-alkyl-O-ethyl xanthate esters as thiol protecting groups in the synthesis of thiol terminated dendrons and dendrimers, Scheme 1. Deprotection can be easily achieved under very mild conditions using a simple alkylamine[15a-b] and, since alkylamines are known catalysts for thiol-Michael addition reactions,[17a-c] deprotection and functionalisation can be conducted in a simple one-pot manner, crucially avoiding disulfide formation.

The xanthate functional carboxylic acid **[3]**, Scheme 1A, was prepared on a 50g scale by reacting bromoacetic acid **[2]** in acetone at ambient temperature with potassium ethyl xanthogenate **[1]**, a cheap and commercially available reagent. After filtration and simple water washings to remove the salt byproduct, the product was confirmed by ^{1}H and ^{13}C nuclear magnetic spectroscopy (NMR) using characteristic signals such as the triplet at 1.43 ppm, quartet at 4.66 ppm (^{1}H NMR) and xanthate carbonyl at 212 ppm (^{13}C NMR;

see Figures S1-S2). The approach was initially evaluated using a model reaction, allowing for evaluation and optimization of the conditions for the one-pot xanthate deprotection/thiol-acrylate Michael addition. A low molecular weight generation zero (G$_0$) xanthate terminated polyester dendrimer was synthesized by the reaction of [3] with triethanolamine (TEA), using conventional N,N′-dicyclohexyl-carbodiimide (DCC) esterification chemistry (see Scheme S1). Confirmation of the trifunctional xanthate product [Xan$_3$-G$_0$] was obtained by ^{1}H and ^{13}C NMR and electrospray ionisation mass spectrometry (ESI-MS; MNa$^+$ = 658.0 Da), (see Table 1 and Figures S3-S6). Deprotection and thiol-acrylate Michael addition was studied in THF in the presence of *n*-butylamine. *n*-Butylamine is reported to deprotect thiols, through reaction with xanthates to form dithiocarbamates, and is also known to generate the strongly nucleophilic thiolate anion, through reaction with the released thiols, which is able to undergo direct conjugate addition with acrylate monomers.
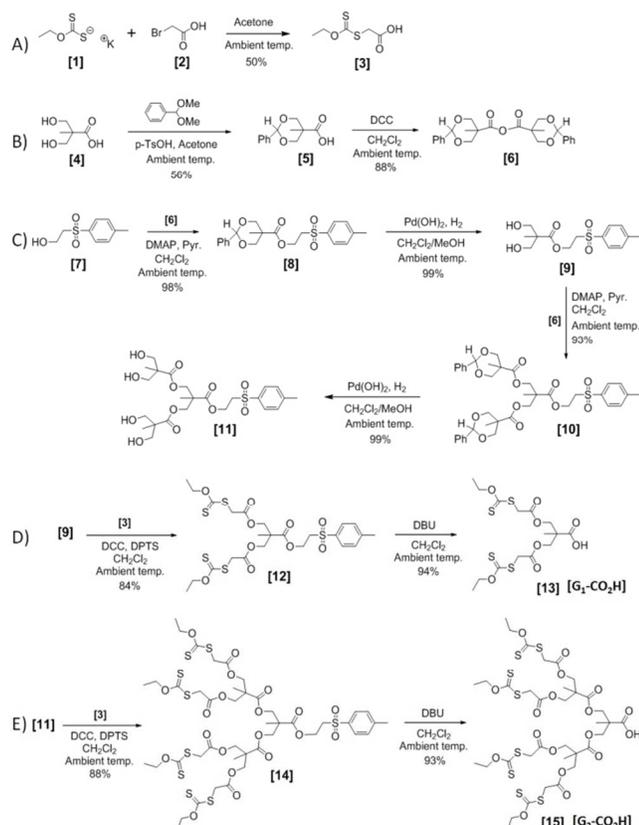


**Scheme 1.** Synthesis of xanthate functional dendrons. A) formation of a xanthate functional carboxylic acid motif [3]; B) Synthesis of a protected 2,2-bismethylolpropionic acid anhydride [6]; C) Synthesis of core-protected hydroxyl-functional G$_1$ [9] and G$_2$ [11] dendrons; D) Surface functionalisation and focal point deprotection to form **G$_1$-CO$_2$H**; E) Surface functionalisation and focal point deprotection to form **G$_2$-CO$_2$H**.

Monitoring of the deprotection of [Xan$_3$-G$_0$] using thin layer chromatography and ^{1}H NMR (see Figure S7) indicated considerable deprotection in 30 minutes (91 %) and near complete removal of the xanthate groups after 1.5 hours at ambient temperature. Addition of benzyl acrylate to the vessel in a near stoichiometric ratio generated the Michael adduct [Bz$_3$-G$_0$] after 18 hrs at ambient temperature in 93% yield. Confirmation was obtained by ESI-MS (MNa$^+$ = 880.2 Da), gel permeation chromatography (GPC), ^{1}H and ^{13}C NMR (See Figures S8-11). As expected, total loss of the characteristic O-ethyl

xanthate carbonyl at 212 ppm (^{13}C NMR) was observed, and the appearance of new proton and carbon environments in the ^{1}H and ^{13}C spectra were seen for the Michael adduct.

Aliphatic polyester chemistry based on the AB$_2$ monomer 2,2-bismethylolpropionic acid (bis-MPA) was chosen for dendrimer scaffold synthesis as it was ideally suited to the chosen functionalisation strategy.[18a] Generation one and two dendrons were synthesized using a divergent growth approach, Scheme 1B-E. Initially, the hydroxyl groups of bis-MPA were protected as previously reported using benzaldehyde dimethyl acetal to form [5], which was self-condensed with DCC in CH$_2$Cl$_2$ to form the symmetrical anhydride [6] in 88% yield on an 85 g scale. Several strategies have been reported for the protection of the focal carboxylic acid of the bis-MPA derived dendrons and initially a benzyl ester[18b] was utilized, however, studies of the protecting group removal showed considerable poisoning of the palladium catalyst by the sulfur atoms within the xanthate moieties. Use of a *p*-toluene-sulfonyl ether ester has been reported previously[19a] and incorporation and removal using the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was shown to not be complicated by the presence of the xanthate groups.

Table 1. Analysis of dendrimers before and after Michael addition

| Dendrimer; Entry # | $M_{calc.}$ (Da) | ESI-MS [MH$^+$] $M_{obs.}$ (Da) | MALDI-TOF [MNa$^+$] $M_{obs.}$ (Da) | GPC $M_n$ (Da) | $M_w$ (Da) | Đ |
|---|---|---|---|---|---|---|
| [Xan$_3$-G$_0$];[16] | 635.1 | 636.1 | - | 890 | 1400 | 1.57 |
| [Bz$_3$-G$_0$];[17] | 857.3 | 858.3 | - | 1095 | 1350 | 1.23 |
| [Xan$_6$-G$_1$];[18] | 1469.1 | 1470.1 | 1492.2 | 1540 | 1795 | 1.16 |
| [Bz$_6$-G$_1$];[19] | 1913.6 | - | 1936.8 | 2145 | 2320 | 1.08 |
| [Am$_6$-G$_1$];[20] | 1799.7 | - | 1823.1 | 2400 | 2795 | 1.16 |
| [OEG$_6$-G$_1$];[21] | 3834* | - | 3858* | 3830 | 4345 | 1.14 |
| [Xan$_{12}$-G$_2$];[22] | 3137.3 | - | 3161.0 | 4100 | 4485 | 1.09 |
| [Bz$_{12}$-G$_2$];[23] | 4026.1 | - | 4049.7 | 4230 | 4530 | 1.07 |
| [Am$_{12}$-G$_2$];[24] | 3798.5 | - | 3822.2 | 5855 | 6275 | 1.07 |
| [OEG$_{12}$-G$_2$]; [25] | 7868* | - | 7897* | 8585 | 9795 | 1.14 |

*Nominal Molecular weights due to polymer modification

Xanthate-functional dendron synthesis was therefore accomplished by reacting *p*-toluene sulfonyl ethanol (TSe) with the anhydride monomer [6] in the presence of pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP) at ambient temperature for 16 hrs, Scheme 1C. After quenching of the excess anhydride with water, the crude product [8] was isolated in 98% yield. Benzylidene protecting groups were readily removed using Pd(OH)$_2$ under H$_2$ (10 bar) in a 1:1 mixture of CH$_2$Cl$_2$ and methanol to form [9]. Repetition of these steps led to the synthesis of the second generation hydroxyl-terminated dendron [11] with yields of >90% at each stage. The structures were fully characterized by ^{1}H and ^{13}C NMR and GPC. The addition of xanthate functionality was simply carried out through the reaction of [9] and [11] with [3] in the presence of DCC and a catalytic amount of 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) in CH$_2$Cl$_2$, Scheme 1D&E. DPTS was chosen for this step to reduce urea side reactions which are favoured at high pH; no trace of the urea side product was observed when DPTS was used. Following purification, confirmation of the target molecules [12] and [14] was obtained using ESI-MS (MNa$^+$ = 663.0 Da) and matrix assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry (MNa$^+$ = 1219.1 Da) respectively (see Figures S12-17). Complete removal of the Tse protecting group was achieved using an excess of DBU after 12 hrs at ambient temperature. Precipitation

of the reactions into *n*-hexane resulted in the two dendrons **G₁-CO₂H [13]** and **G₂-CO₂H [15]**. Confirmation by ESI-MS and MALDI-TOF also confirmed the loss of 182.0 Da from both the original masses of **[12]** and **[14]**, (see Figures S18-23)

**G₁-CO₂H [13]** and **G₂-CO₂H [15]** were both employed to form the first and second generation xanthate functional dendrimers utilizing triethanolamine as the core, and DCC/DPTS chemistry, shown in Scheme 2 (see Schemes S2-3). Purification in both cases was achieved using automated liquid chromatography resulting in the first generation dendrimer **[Xan₆-G₁] [18]** (MALDI-TOF: MNa⁺ = 1492.20 Da) in 65% yield and the second generation dendrimer **[Xan₁₂-G₂] [22]** (MALDI-TOF: MH⁺ = 3138.0 Da, MNa⁺ = 3161.0 Da) with a yield of 58%, Table 1 (see Figures S24-30).
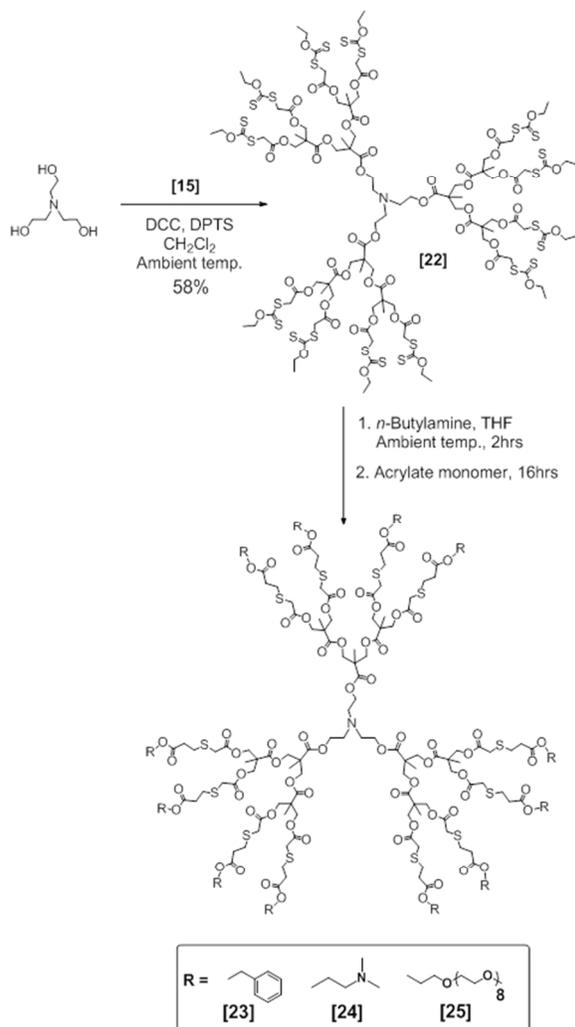


**Scheme 2.** Synthesis of **[Xan₁₂-G₂]** xanthate functional dendrimer and subsequent one-pot deprotection/thiol Michael addition with various acrylates.

It is interesting to note the isotopic distributions of the xanthate terminated materials. Sulfur has four stable isotopes ($^{32}$S, $^{33}$S, $^{34}$S, $^{36}$S; relative abundance (%) 95.02:0.75:4.21:0.02) and, as each xanthate group contains two sulfur atoms, 12 sulfur atoms are present in **[Xan₆-G₁]** and 24 in **[Xan₁₂-G₂]**. The mass spectra therefore display a broad isotopic distribution (Figures 1A-B), however, in addition masses that were increasing by multiples of 16 Da were observed in both ESI-MS and MALDI-TOF analyses (see Figures S26 & 30). Oxidation of xanthates has been reported, resulting in addition of oxygen at the non-thiocarbonyl sulfur

atoms[20] and we assume this occurs during ionization within the different mass spectrometers.

**[Xan₆-G₁]** was treated with *n*-butylamine with near total deprotection (TLC) within 1.5 hrs as seen in the model reactions. Three acrylate monomers, benzyl acrylate, 2-(dimethylamino)ethyl acrylate (DMAEA) and oligo(ethylene glycol) methyl ether acrylate (OEGA₉), with a number average degree of polymerization = 9 monomer units (number average molecular weight (Mn) = 480 Da), were selected to react with the thiol-terminated dendrimer and were added at near stoichiometric concentrations with respect to thiols. The benzyl functionalised first generation dendrimer, **[Bz₆-G₁]**, was recovered in 92% yield and was confirmed by $^1$H and $^{13}$C NMR and MALDI-TOF analysis (MNa⁺ = 1936.8 Da, Table 1). Functionalisation with DMAEA, forming **[Am₆-G₁]**, was also readily confirmed by $^1$H and $^{13}$C NMR and MALDI-TOF analysis. OEGA₉ generated the expected broad distribution of signals within the MALDI-TOF analysis due to the distribution of the oligo(ethylene glycol) side chain lengths. Individual masses were confirmed as relating to fully functionalised dendrimer **[OEG₆-G₁]** and GPC analysis showed a complete shift to higher molecular weight whilst maintaining low dispersity (Đ) values, Table 1 and Figure 1.
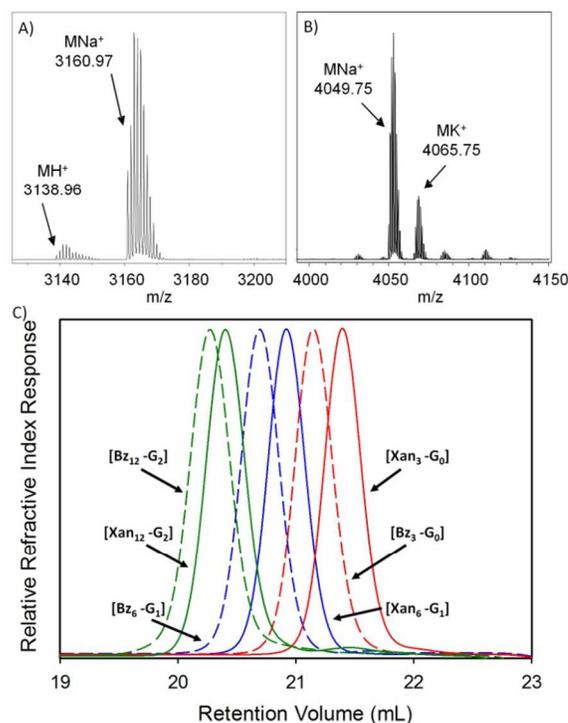


**Figure 1.** Analysis of xanthate functional dendrimers before and after one-pot deprotection/thiol-Michael addition with benzyl acrylate. MALDI-TOF mass spectra of A) **[Xan₁₂-G₂]**, **[22]**, and B) **[Bz₁₂-G₂]**, **[23]**. C) Overlays of the GPC chromatograms of the three dendrimer generations before (solid lines) and after (dashed lines) reaction.

The ability to fully functionalise using the sterically challenging oligomeric acrylate is testament to the efficiency of the strategy (see Figures S31-43). **[Xan₁₂-G₂]** was treated in an identical manner with near stochiometric amounts of the three acrylates, Scheme 2, also resulting in fully functionalised materials as determined by $^1$H and $^{13}$C NMR, GPC and MALDI-TOF analysis (Table 1; see Figures S44-56). In some cases, signals were observed within the mass spectra that indicated oxidation of the thio-ether groups, generated after Michael addition, to sulfoxides (see Figures S33, 37, 46 & 51);

again, this has been reported[21] and is believed to occur during analysis.

The GPC chromatograms of the **[Xan$_3$-G$_0$]**, **[Xan$_6$-G$_1$]** and **[Xan$_{12}$-G$_2$]** along with the corresponding **[Bz$_3$-G$_0$]**, **[Bz$_6$-G$_1$]** and **[Bz$_{12}$-G$_2$]** modified dendrimers are shown in Figure 1C, highlighting the efficiency of the one-pot reaction and the purity of the resultants products. An attempt to increase the number of carbons within **[3]** to allow additional spacing between the xanthate units and the ester carbonyl at the periphery of the dendrimers (by replacing bromoacetic with bromopropionic acid) was successful until the removal of the TSe protecting group at the focal point of the xanthate dendron. The conditions used during TSe removal also resulted in elimination of the xanthate functionality, subsequent double bond formation and the generation of acrylate functional peripheral groups. This was readily observed within the $^1$H NMR and mass spectral analyses (see Figures S57-58). This elimination reaction may have further application in site-specific acrylate functionality placement in functional materials.

In conclusion, the first xanthate surface functional dendrons and dendrimers are presented that undergo a facile deprotection and surface functionalisation. From three generations of polyester dendrimers a further seven materials with hydrophilic, hydrophobic and polymeric surface groups were readily generated through ambient temperature one-pot reactions. The approach uses a new xanthate functional carboxylic acid that offers opportunities to place stable xanthates into materials across a range of chemical strategies, enabling the reactivity of thiols without the direct handling of these reactive and noxious chemicals.

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### Notes and references

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