Degradable dendrimers divergently synthesized *via* click chemistry†

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Large degradable dendrimers (MW > 30 kDa) were synthesized in a divergent manner utilizing a novel 1,3,5-triazaadamantane (TAA) monomer that can degrade under acidic conditions.

The considerable impact of dendrimers on the field of nanotechnology can be traced to their easily tailored synthesis with predictable size, shape, and functionality.[1] Dendrimers have been used to prepare organic nanoparticles[2] and nanotubes,[3] as well as being used for molecular printboards[4] and drug delivery vehicles.[5] Recent interest has focused on dendrimers that degrade in a controlled fashion,[6] particularly *via* hydrolysis with an eye toward biological applications.[5b] Many hydrolytically labile dendrimers are known,[7] but to our knowledge none that have at each branch point a degradable unit with tunable hydrolysis kinetics. Herein, we report a facile method to prepare dendrimers containing a degradable 1,3,5-triazaadamantane (TAA) at each branch point.

We recently introduced the TAA unit as a stable aminal that undergoes pH dependent hydrolysis to give tris(amino-methyl)-ethane and substituted benzaldehydes used for its synthesis (Fig. 1).[8] Contrary to many other degradable materials such as polyesters, TAAs are stable under basic conditions but hydrolyze rapidly under acidic conditions to give basic by-products. Similar to substituted acetals[9] and *N*-ethoxybenzylimidazoles,[10] alteration of the aromatic ring substitution pattern affects the rate of TAA degradation.

Recent methods of dendrimer synthesis have enabled the rapid construction of macromolecules with an increased amount of structural complexity.[11] The copper catalyzed cycloaddition of azides with alkynes (CuAAC)[12] popularized as "click chemistry" has become widely used as a result of its functional group tolerance, high conversion rate, and mild reaction conditions. Using an iterative, divergent approach,[13a] we synthesized dendrimers comprising degradable monomer **5** with this method.

Synthesis of monomer **5** began by propargylation of TAA **1**[14] followed by acid hydrolysis to afford the desired tris amine salt **2** (Scheme 1). Benzaldehyde **4** was synthesized by activation of **3**[15] using DCC–NHS followed by amide formation with 2-(2-chloroethoxy)ethylamine hydrochloride (ESI†) and acetal hydrolysis. Condensation of **2** with **4** produced the desired triazaadamantane in multigram quantities with no evidence of side reaction between the amino and chloro groups during the course of the reaction.[16] The half life of this monomer is expected to be comparable to the previously reported analog containing an ester substituent.[8]

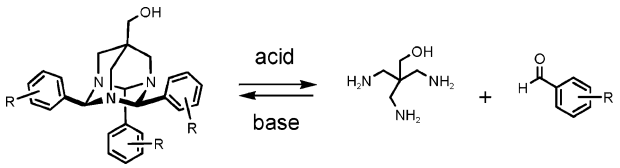
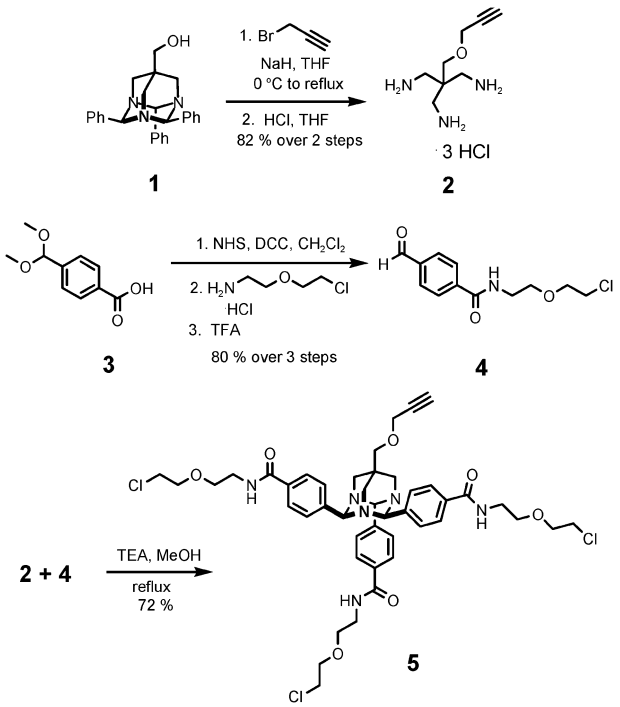


Fig. 1 Substituted TAA formation and degradation.



Scheme 1 Synthesis of TAA monomer **5**.

Dendrimer synthesis began by reacting three equivalents of monomer with tri-azide core **6** (ESI†) (Scheme 2). Because of the high solubility of monomer **5** in dichloromethane, the procedure reported by Lee *et al.*was used and was found to be highly effective.[17] Azide displacement of terminal chloro groups produced azide-terminated dendrimer **8**. This process was repeated to produce second and third generation dendrimers **9–11**. Because of the high molecular weight of monomer **5** (MW = 884) and overall high reaction yields, large dendrimers can be synthesized rapidly in this fashion.

Table 1 summarizes the characterization data. Dendrimers were characterized by IR spectroscopy, MALDI-TOF MS, and analytical GPC. NMR was not useful because multiple

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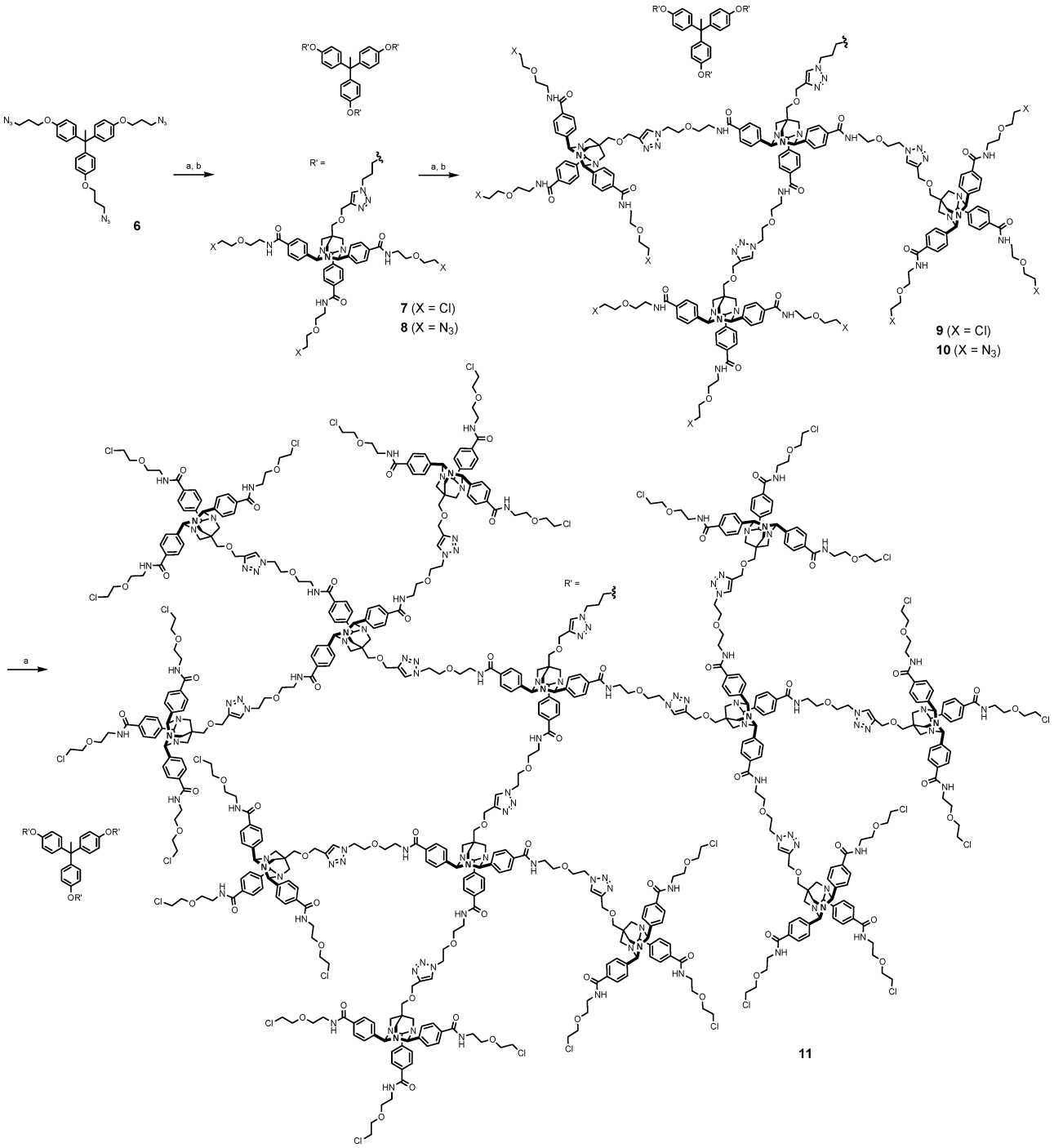

Scheme 2 Dendrimer synthesis: (a) **5**, $CuSO_4$, NaAsc, CH_2Cl_2–H_2O; (b) NaN_3, DMF, 100 °C (see Table 1 for yields).

Table 1 Characterization data for dendrimers **7–11**

Compound	Generation	Periphery	TAAs	Yield (%)	GPC PDI	Theoretical mass/g mol^{-1}	MALDI mass/g mol^{-1}
7	1	9 (–Cl)	3	86	1.01	3207.2	3208.4
8	1	9 (–N_3)	3	93	1.02	3266.5	3266.4
9	2	27 (–Cl)	12	93	1.04	11224.3	11227.4
10	2	27 (–N_3)	12	96	1.06	11402.4	11407.2
11	3	81 (–Cl)	39	56	1.38	35279.6	35279.1

diastereomers[16] led to broad, uninformative spectra. IR spectroscopy conveniently monitored the presence and absence of the azide stretch band at *ca.* 2100 cm^{-1} (Fig. 2a). This peak completely disappeared after reaction with monomer **5** for each generation. MALDI-TOF MS confirmed product by showing mass peaks in good agreement with the

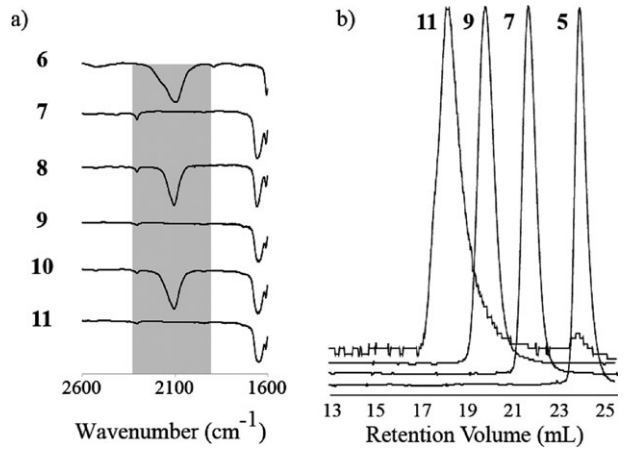

Fig. 2 (a) Azide region of IR spectra of core and dendrimers; (b) GPC traces of monomer and dendrimers.

calculated values (ESI†). Analytical GPC showed narrow, symmetric peaks characteristic of perfect dendrimers (Fig. 2b). The characterization showed complete conversion of all reactions for the first two dendrimer generations. Imperfections resulting from incomplete conversion, which are a common occurrence when synthesizing dendrimers divergently, were only seen in product **11** in which 27 reactions per molecule were needed. Only the trace for dendrimer **11** shows evidence of incomplete monomer attachment as evidenced by a shoulder at higher retention times.

Addition of HCl to a solution of compound **9** in THF–MeOH confirmed that the dendrimers were fully degradable. The by-products, which were analyzed by ^{1}H NMR and mass spectrometry, corresponded to the aldehyde groups from the periphery of the dendrimer, the aldehyde groups from the interior of the dendrimer, and the core. Amounts and ratios of compounds were in good agreement with the calculated values (ESI†).

In conclusion, dendrimers were synthesized from a degradable 1,3,5-triazaadamantane (TAA) monomer. The largest contains 39 TAA molecules, displays 81 functional groups on its periphery, and has a molecular weight above 35 kDa. Although a divergent strategy was used, a remarkably high conversion was observed for several generations. The method demonstrated here allows the synthesis of dendrimers that contain TAA groups throughout the entire structure. Because an iterative strategy is used, it should be possible to incorporate TAA monomers with different degradation rates thus allowing for the creation of generation dependent degradable dendrimers possessing both spatial and temporal control of degradation. After appropriate surface modification that would enable water solubility, these materials may be useful for biological applications such as drug and/or gene delivery because TAAs are stable under physiological conditions and labile under relevant acidic conditions such as those found in endosomal compartments, tumor tissues, and sites of inflammation.[18]

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