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Identification of diamine linkers with differing reactivity and their application in the synthesis of melamine dendrimers

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Abstract

Diamine linkers for the synthesis of dendrimers based on melamine were identified using competition reactions. The relative reactivity of the surveyed cyclic monoamines varies by 40 times, expanding the previously identified series to an overall relative reactivity range of 320 times. Azetidine is 40 times more reactive than the cyclic, nine-membered ring ($C_8H_{17}N$), and 320 times more reactive than benzylamine. Reactivity differences are attributed to pK_a values and sterics. Diamines incorporating these groups are useful linkers that can be employed in dendrimer synthesis. Specifically, the nucleophilicity of the individual amine groups comprising 3-aminoazetidine, 3-aminopyrrolidine, and 4-aminopiperidine varies by 100 times, 70 times, and 20 times, respectively. These linkers are incorporated into a generation three dendrimer.

Our group has invested significant energies in the synthesis of dendrimers based on triazines, also referred to as dendrimers based on melamine deriving from our use of diamine linkers.[1,2] Our early targets commonly incorporated *p*-aminobenzylamine because of the significant differences in the reactivity of the amines of this group. That is, during a convergent synthesis, protecting group manipulations and functional group interconversions could be avoided because the benzylic amine would react preferentially (essentially exclusively) with the monochlorotriazine dendron being elaborated.[1,3–7] The low stability of these aniline derivatives required reasonable, but additional, care on handling. While the use of distilled solvents and inert atmospheres is uncommon, nor is the requirement for refrigerated storage of intermediates, we recognized that these precautions could impact the broader acceptance of these materials.

The low cost and high reactivity of piperazine soon made it a linking diamine of choice for our investigations. However, when using piperazine, dimerization of monochlorotriazines was observed under non-ideal reaction conditions that were usually attributed to concentration, rate of addition, ineffective stirring or lack thereof, temperature of addition and the magnitude of stoichiometric excess.[4,8–18] Reactions with either *p*-aminobenzylamine or piperazine could be readily followed by NMR. The shift of the benzylic protons on reaction with the monochlorotriazine dendron or the desymmetrization of methylene groups of the piperazine group was diagnostic. Unfortunately, detecting dimeric sideproducts by NMR proves difficult due to signal degeneracy between the desired asymmetric monoamine and the symmetric dimer.

The wealth of commercially available diamines led us to conduct a rational survey of reactivity. Our goal was to identify diamine linkers with the reactivity differences displayed in *p*-aminobenzylamine without the disadvantages previously described. Our original study examined a range of primary and secondary amines including the cyclic amines piperidine and two piperazine derivatives (**A**–**F**, Fig. 1).[1] From these studies, aminomethylpiperidine emerged as a diamine linker of choice and was used extensively.[1,2,7,9,15–17,19,20] Using competition experiments, the

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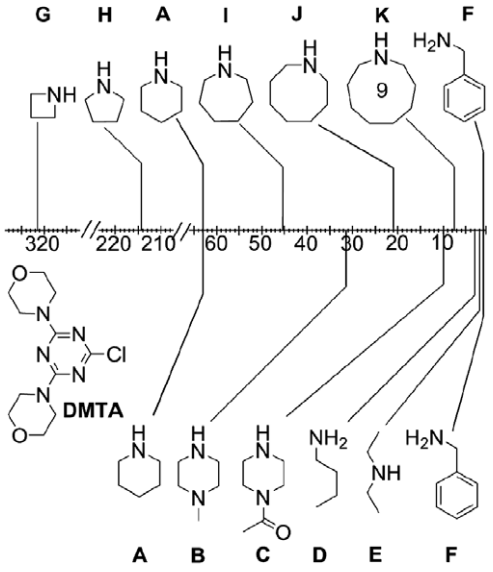


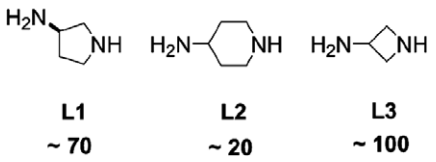
Fig. 1. Relative reactivity map for the substitution of monochlorotriazines. The reactivity difference between consecutive amines is shown on the scale.

relative reactivity difference measured for the cyclic secondary amine and primary amine of aminomethylpiperidine is ~20 times. Theoretically, 5% of the product formed might derive from the reaction of the monochlorotriazine dendron with the primary amine instead of the desired secondary amine. This population difference approaches the limit of detection by NMR spectroscopy, and accordingly the efforts described here were undertaken to identify other suitable diamine linkers. These amines are identified as **G**–**K** in Figure 1.

To establish relative reactivity of different monoamines, reactions were conducted by treating 1 equiv of a monochlorotriazine, **DMTA**, with 3 equiv of two competing amines chosen from **G**–**K** at room temperature (Supplementary data). The reactivity map was obtained by determining the product ratios using ^{1}H NMR after the disappearance of **DMTA**. These values for individual competition studies are consistent multiplicatively across the range of amines within experimental error. Protons α to the amine generally appeared downfield from those of the free amines, and provided convenient signals for measuring product distributions. Inclusion of **A** and **F** allows us to compare this new series to the existing series.

The data show that as the ring size decreases, the reactivity of the amine increases.[21] The pK_a of the conjugate acids of most reactive amines (**G**, **H**, and **A**) is 11.3, while the pK_a of the conjugate acids of less reactive amines (**I**–**K**) is 10.8.[22,23] Sterics can be used to rationalize the difference in reactivity within these subgroups.

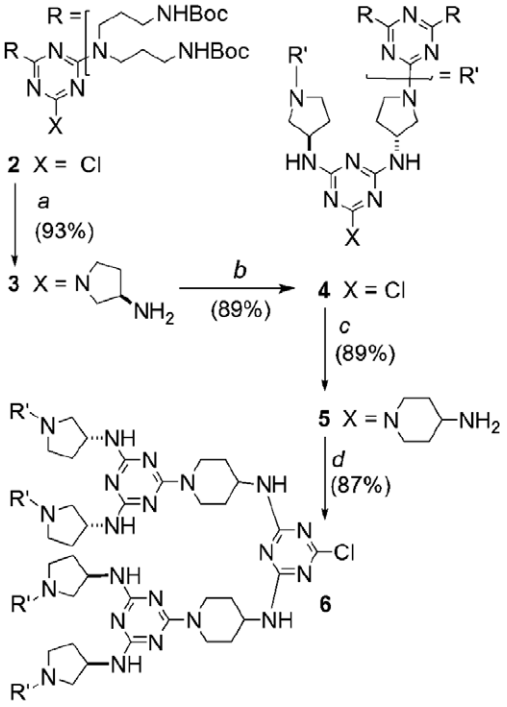
From these data, we identified new diamine linkers based on three criteria. First, a minimum reactivity difference of ~20 times between the amines should reduce dimer formation. Second, one or more unique ^{1}H NMR signals should facilitate characterization. Third, the diamine



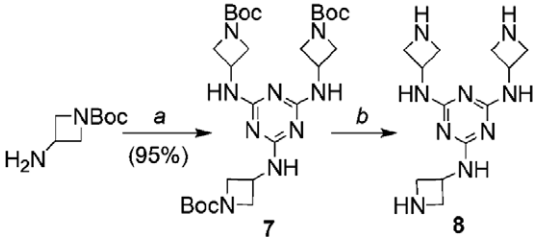
Scheme 1. Three new diamine linker with the relative reactivity difference of the diamines indicated.

should be commercially available or accessible in a minimal number of steps. Diamine linkers **L1**–**L3** (Scheme 1) were chosen because they meet the criteria and are commercially available. A single enantiomer of 3-aminopyrrolidine is commercially available. These linkers were then evaluated by preparing dendrimer **1** as a proof-of-concept.

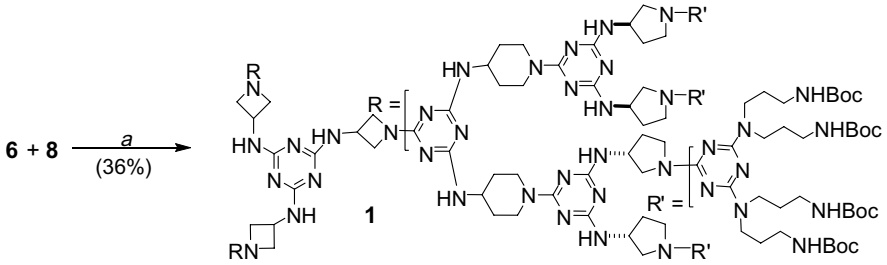
Scheme 2 shows the convergent strategy used to synthesize dendrimer **1**. Following selective protection of the primary amines of 3,3′-diaminodipropylamine with BOC–



Scheme 2. Synthesis of G3 dendron **6**. Reagents and conditions: (a) THF, rt, overnight; (b) THF, cyanuric chloride, Hunig's base (DIPEA), 40 °C, overnight; (c) THF, rt, overnight; (d) THF, cyanuric chloride, Hunig's base (DIPEA), 40 °C, 2d.



Scheme 3. Synthesis of the core, **8**. Reagents and conditions: (a) THF, cyanuric chloride, Hunig's base (DIPEA), 70 °C, 7d; (b) (1:1) TFA/DCM, rt, overnight.



Scheme 4. Synthesis of **1**. Reagents and conditions: (a) THF, BEMP resin, 70 °C, 7d.

ON, treatment with cyanuric chloride affords monochlorotriazine **2**. Intermediate **2** is treated with an excess of **L1** to produce **3**. In an iterative fashion, the synthesis continues with the reaction of cyanuric chloride to form **4**, then **L2** to generate **5**. Cyanuric chloride treated with a slight excess of **5** gives **6**. While iteration with 3-aminoazetidine progresses the sequence, sterics precludes trimerization with a cyanuric chloride core.

Instead, a less sterically encumbered core, **8**, is synthesized by treating cyanuric chloride with **L3** followed by deprotection (Scheme 3). This strategy affords a highly reactive core possessing three azetidine groups, which upon reaction with a large excess of **6** (Scheme 4). The reported yield of 36% represents the amount of material obtained in pure form after extensive chromatography, and is not a reflection of an unsuccessful reaction. Indeed, we estimate conversion to product occurred in >80%.

In conclusion, we foresee that each linker offers interesting features that could be exploited in future work. Aminoazetidine (**L1**) offers a highly reactive and sterically unencumbered amine that might find use in situations where piperidine-type amines are unreactive or react sluggishly. Aminopyrrolidine (**L2**) offers opportunities to explore chiral environments in these dendrimers. Aminopiperidine (**L3**) offers an inexpensive linker that aligns with our current reliance on aminomethylpiperidine groups. In addition, these linkers convey spectroscopically unique signatures to different regions of the dendrimer architecture; an effect only rarely observed in related architectures.[24–29] The use of these signals to probe the conformation of **1** will appear shortly.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.056.

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