Supramolecular chemistry of flexible, dendritic-based structures employing molecular recognition

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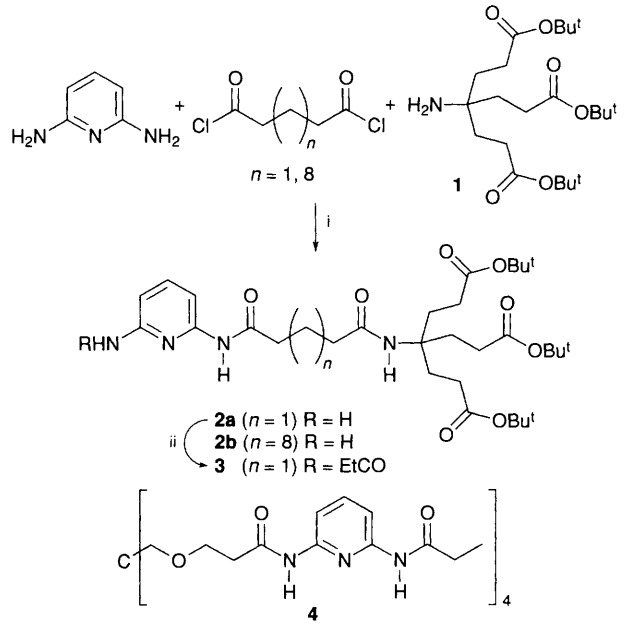
Molecular recognition of glutarimide using 2,6-diamidopyridine units incorporated into dendritic building blocks is examined.

Reports of non-covalent associations and molecular recognition for the formation of 'self-assembling dendrimers'[1] and other 'interactive' structures[2–5] provided the impetus to construct sites capable of molecular recognition[6] within a dendritic[7] framework. We herein report the incorporation of 2,6-diamidopyridine moieties into dendritic mesomolecules and examine their ability to form hydrogen bonded complexes with imide groups.

Preparation of early generation polypyridino dendrimers was facilitated by employing high-dilution conditions for the connection of three structural components (Scheme 1). Addition of one equivalent of aminotris(*tert*-butyl ester)[7] **1** and diisopropylethylamine to glutaryl dichloride or dodecanedioyl dichloride, followed by addition of excess 2,6-diaminopyridine yielded (35–40%) the extended dendrons **2a** and **2b**, respectively. Arylamine protons (NH_2) were observed (^1H NMR) at δ 4.56, while the amide proton signals occurred at δ 6.09 [$NH_{(Alk)}$] and 8.46 [$NH_{(Ar)}$]. Nearly identical ^1H and ^{13}C NMR spectra were recorded for the related elongated amino triester **2b**.

Arylamine **2a** was subsequently acylated *via* reaction with propionyl chloride to give the diamidopyridine triester **3**. Tetrakisdiamidopyridine **4** was then constructed by the treatment of a poly(acid chloride) **5** (Scheme 2) with 2-amino-6-*N*-propionoylpyridine.



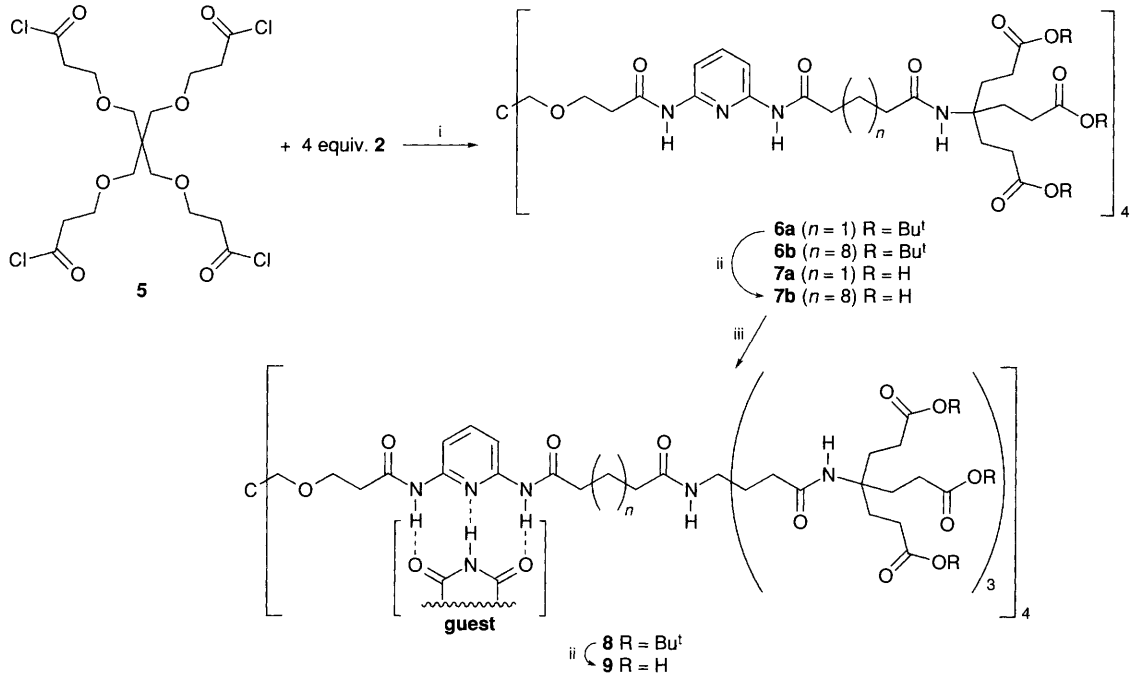
Scheme 1 Three-component reaction for the preparation of building blocks possessing a hydrogen-bonding, molecular recognition site. *Reagents and conditions*: i, THF, $EtPr^i_2N$, 0–25 °C, 24 h; ii, ClCOEt, THF, Et_3N.

Acylation of four equivalents of the triester **2a** with tetrahedral core[7] **5** provided the first tier, tetrapyridine dodecaester **6a** (Scheme 2). Supporting ^{13}C NMR resonance's included four C=O absorptions and five distinct aromatic peaks [δ 109.4, 109.6 ($C_{3,5}$), 140.4 (C_4), 149.5 and 149.7 ($C_{2,6}$)] suggesting a 'polar gradient' proceeding from the central carbon to the periphery. Reaction of amine **2b** (4 equiv.) with the core **5** gave the corresponding extended dodecaester **6b** as supported by similar ^1H and ^{13}C NMR spectra observed for **6a**.

Synthesis of a second generation polypyridine dendrimer was effected by deprotection of 12-ester **6a** to give dodecaacid **7a** as evidenced by the disappearance of peaks attributed to the *tert*-butyl ester moieties followed by reaction with amine **1** (12 equiv.) to afford 36-ester **8**. Support for the conversion includes the appearance of ^{13}C NMR signals at δ 57.4 and 80.5 corresponding to the new branching C_4°s and *tert*-butyl C_4°s, respectively. Heteroaromatic peaks appeared as broadened absorptions. The ^1H NMR spectrum recorded the expected signals as well as two broadened resonances at δ 8.95 and 9.12 (pyridine carboxamide protons). Treatment of the 36-ester **6** with formic acid gave the water soluble 36-acid **7**. Conversion of the more lipophilic dodecaester **6b** to the corresponding 12-acid **7b** (HCO_2H) proceeded smoothly; however, repeated attempts to prepare the second tier, 36-ester *via* the DCC–1-HBT acid-amine coupling were unsuccessful.

Free barbituric acid, which is only sparingly soluble in CD_3CN, exhibits a very broad downfield absorption for the imide moieties; whereas, it is freely soluble to the limit of complementary complexation in the presence of the bis-amidopyridine dendrimers. (No discernable change in the ^1H NMR spectrum of a third tier, non-amidopyridine-constructed dendrimer in the presence of barbituric acid was observed.) Chemical shift changes for the complexed diamidopyridine NH moieties, even in this competing solvent, corresponded to *ca.* 0.1 ppm for both generation dendrimers. Spectra obtained using the second tier dendrimer **8**, at 60 °C, recorded upfield amide absorptions at δ 8.75; comparison of the chemical shifts of these protons (δ 9.05) in the guest free dendrimer suggests internal hydrogen-bonding in the free host. Thus, accounting for self association, the Δδ of the amide peak, when complexed, corresponds to 0.3 to 0.4 ppm.

^1H NMR titration experiments (in $CDCl_3$) for the determination of host (**3**, **4** and **6a**)–guest hydrogen-bonding association constants employed glutarimide primarily due to its 1 : 1 docking potential (unsubstituted barbituric can complicate data interpretation due to 2 : 1 complex formation). Host solutions were titrated with known amounts of the glutarimide guest.† Chemical shift changes of the monopyridine's (**3**) carboxamide protons (a maximum of 0.5 and 0.7 ppm downfield for each NH) were plotted *vs.* imide concentration. Apparent association constants of K_a = 62.1 and K_a = 66.6 were determined for each NH. Titration using glutarimide and tetrapyridine core **4** gave a maximum shift of 0.7 ppm for each pyridinecarboxamide NH;



Scheme 2 Construction of first and second tier utilitarian dendrimers possessing four 2,6-diamidopyridine units. *Reagents*: i, THF, $EtPr^i_2N$, 0–25 °C, 12 h; ii, HCO_2H, 35 °C, 18 h; iii, aminotriester **1**, DCC, 1-HBT, DMF, 25 °C, 12 h.

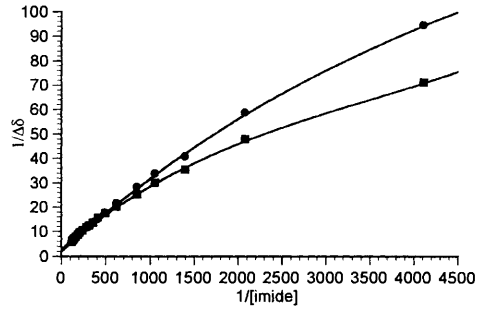


Fig. 1 ^{1}H NMR titration data plotted for the determination of glutarimide : dendrimer **6a** hydrogen-bonding association constants (■ NH, ● N′H′)

K_a = 69.8 and 69.9. Constants derived from these experiments are also comparable with reported values for similar hosts–guest complexes.[2,8] Fig. 1 represents the titration of glutarimide with the first generation, tetra(bisamidopyridine) dendrimer **6a**. The change in pyridinecarboxamide proton shift upon final titration with glutarimide corresponds to 0.1 and 0.2 ppm for each NH. The magnitude of these shifts corresponds well with that observed for the barbituric acid guest and further supports the postulated self association. A curved correlation suggests a more complicated guest–host relationship than in the previous examples or the formation of higher order aggregates.[9] Other factors potentially affecting this relationship and the resulting weak associations as indicated by the small NH chemical shifts [complexation of 3′-azido-3′-deoxythimidine (AZT) exhibited more pronounced downfield shifts of the participating protons[10]] include inefficient donor–acceptor alignment, the potential for host self-association, and the availability of additional complexation sites (*i.e.* CONH and CO_2R moieties; K_a *ca.* 46 dm^3 mol^{-1}).[8] However, these findings support specific host–guest(s) interactions; although, additional coordination sites might weakly compete for the guest(s). Dynamic guest(s) migration is envisioned.

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Footnote

† Titrations were performed at 25 °C using $CDCl_3$ as the solvent. Host concentrations were maintained constant (concentrations: [**3**] = 0.0015 mol dm^{-3}, [**4**] = 0.0020 mol dm^{-3}, and [**6a**] = 0.00075 mol dm^{-3}) and were titrated with aliquots of glutarimide–host solutions (glutarimide stock concentrations: 0.026, 0.049 and 0.025 mol dm^{-3}, for **3**, **4** and **6a**, respectively).

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