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Synthesis and Self-Assembly of Supramolecular Dendritic "Bow-Ties": Effect of Peripheral Functionality on Association Constants

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Self-assembled polyester dendritic bow-ties with various peripheral groups were prepared, and their association constants were measured by ^{1}H NMR in $CDCl_3$. The two complementary dendrons were prepared by attachment of either a bis(adamantylurea) or a glycinylurea to the focal point of the dendron. The parent self-assembled system with benzylidene acetals on one periphery and isopropylidene acetals on the other had an association constant of 520 M^{-1}. Upon deprotection of one dendron, the association constant is increased by more than an order of magnitude as the solubility of the hydroxyl-terminated dendron in $CDCl_3$ is decreased. In contrast, attachment of tri(ethylene oxide) units to the periphery of one dendron lowers the association constant by almost an order of magnitude. The causes of these relatively large changes in complex strength are discussed in terms of solubility, steric effects, competitive hydrogen bonding, and the structure of the dendritic scaffold.

Introduction

In recent years, the application of dendritic structures has expanded to include a diverse array of fields including drug delivery,[1] diagnostics,[2] catalysis,[3] and photo- or electroactive materials.[4] Despite the great advances in synthetic methods for preparing dendrimers,[5] one of the major challenges to their widespread application remains the large amount of synthetic effort required to attain well-defined, high molecular weight, functional dendritic structures. Therefore, inspired by nature's ability to gather relatively simple components into larger, more complex assemblies, researchers have sought to make use of the tool of molecular recognition to assemble dendritic architectures more efficiently.

Thus far, a range of noncovalent interactions have been exploited for the preparation of self-assembled dendrimers. The hydrogen bond mediated assembly, as first introduced by Zimmerman and co-workers, consisted of Fréchet-type benzyl ether dendrons with two isophthalic acid units at their focal point[6] but has since expanded to include other units such as naphthyridine,[7] ureidodeazapterin,[8] melamine, cyanuric acid,[9] and DNA oligomers[10] at the focal point. Metal-templated assemblies have also been investigated, such as those based on a Ru(II)−terpyridine system,[11] an iron−sulfur core,[12] or the complexation of lanthanide ions by carboxylic acids.[13]

(1) (a) Liu, M.; Fréchet, J. M. J. *Pharm. Sci. Technol. Today* **1999**, *2*, 393−401. (b) Malik, N.; Wiwattanapatapee, R.; Klopsch, R.; Lorenz, K.; Frey, H.; Weener, J. W.; Meijer, E. W.; Paulus, W.; Duncan, R. *J. Controlled Release* **2000**, *65*, 133−148. (c) Esfand, R.; Tomalia, D. A. *Drug Discovery Today* **2001**, *6*, 427−436. (d) Padilla De Jesús, O. L.; Ihre, H. R.; Gagne, L.; Fréchet, J. M. J.; Szoka, F. C. J. *Bioconjugate Chem.* **2002**, *13*, 453−461. (e) Gillies, E.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 1640−1641.

(2) (a) Stiriba, S.-E.; Frey, H.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 1329−1334. (b) Krause, W.; Hackmann-Schlichter, N.; Maier, F. K.; Müller, R. *Top. Curr. Chem.* **2000**, *210*, 261−308.

(3) (a) Liang, C. O.; Helms, B.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 2524−2525. (b) Hecht, S.; Fréchet J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6959−6960. (c) Piotti, M. E.; Rivera, F.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9471−9472. (d) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74−91. (e) Twyman, L. J.; King, A. S.; Martin, I. K. *Chem. Soc. Rev.* **2002**, *31*, 69−82. (f) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991−3023.

(4) (a) Freeman, A. W.; Koene, S. C.; Malenfant, P. R. L.; Thompson, M. E.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 12385−12386. (b) Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286−296. (c) Cameron, C. S.; Gorman, C. B. *Avd. Funct. Mater.* **2002**, *12*, 17−20. (d) Juris, A.; Venturi, M.; Ceroni, P.; Balzani, V.; Campagna, S.; Serroni, S. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1−32. (e) Adronov, A.; Fréchet, J. M. J. *Chem. Commun.* **2000**, 1701−1710. (f) Jiang, D.-L.; Aida, T. *J. Am. Chem. Soc.* **1998**, *120*, 10895. (g) Devadoss, C.; Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 9635−9644.

(5) (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3867. (b) Janssen, H. M.; Meijer, E. W. *Mater. Sci. Technol.* **1999**, *20*, 403−458. (c) Hawker, C. J. *Adv. Polym. Sci.* **1999**, *147*, 113−160. (d) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647. (e) Hawker, C.; Fréchet, J. M. J. *J. Chem Soc., Chem. Commun.* **1990**, 1010−1013.

(6) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098.

(7) Zimmerman, S. C.; Wang, Y.; Bharathi, P.; Moore, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 2172−2173.

(8) Corbin, P. S.; Lawless, L. J.; Li, Z.; Ma, Y.; Witmer, M. J.; Zimmerman, S. C. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 5099−5104.

(9) Freeman, A. W.; Vreekamp, R. H.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 138−139.

(10) Goh, S. L.; Francis, M. B.; Fréchet, J. M. J. *Chem. Commun.* **2002**, 2954−2955.

(11) Newkome, G. R.; He, E. F.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689−1746.

(12) Gorman, C. B.; Smith, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 9342−9343.

(13) Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286−296.

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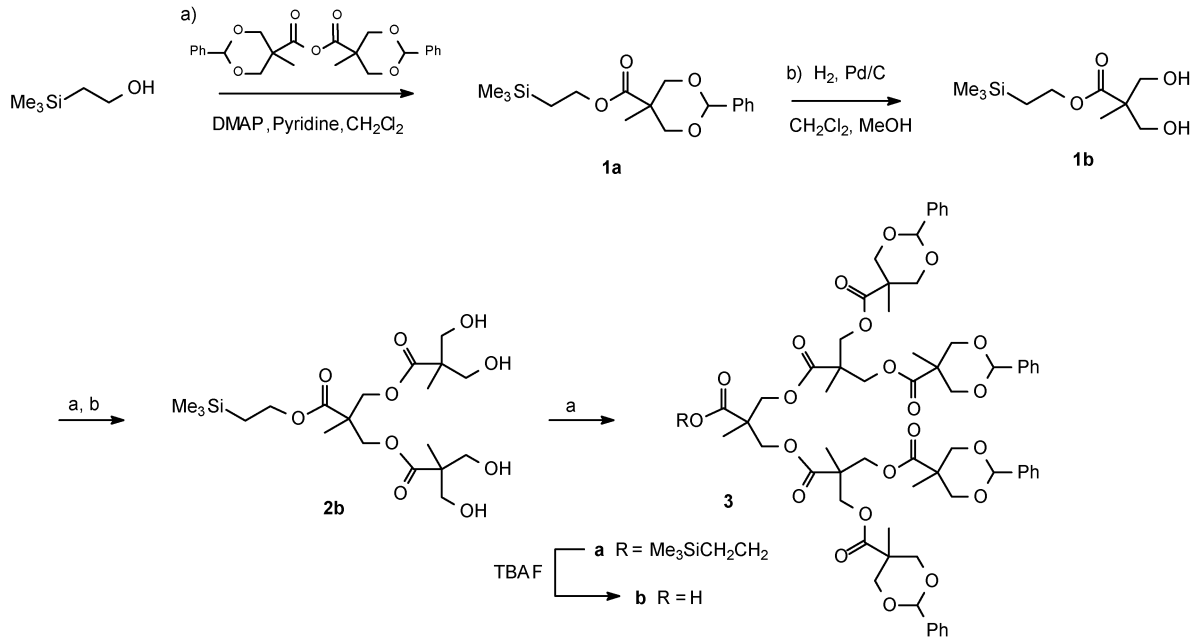
SCHEME 1



Hydrophobic interactions have been exploited to prepare dendrimers based on a bis(adamantane) core and two dendrons with cyclodextrin units at the focal point.[14] A self-assembled pseudorotaxane was prepared on the basis of cation-π interactions,[15] and $\pi-\pi$ stacking interactions have been used to assemble benzyl ether dendrons into well-defined structures such as cubes or cylinders.[16]

Although several studies have investigated the effect of dendrimer generation on the strength of complex association,[6,7,17,18] to our knowledge there has not been any systematic study of the effect of peripheral functionality at a given generation on the association constant. We have recently been interested in dendritic bow-ties bearing orthogonal surface functionality because of their potential for attachment of complementary surface groups to each side of the bow-tie and have recently reported the covalent synthesis of such structures.[19] In addition to providing a more "convergent" route to such structures, it was recognized that self-assembled dendritic bow-ties would be an ideal scaffold for a study of the effect of peripheral functionality on the association strength. It was hoped that it would be possible to adjust the strength of the bow-tie complex by simply altering the solubility of an individual dendron or introducing flexible groups on the dendrimer periphery, while maintaining a constant generation.

In this article, we report the noncovalent synthesis of polyester dendritic bow-ties based on 2,2-bis(hydroxymethyl)propionic acid using the complementary bis(adamantylurea)−glycinylurea system, developed by Meijer and co-workers, at the focal point of the bow-tie.[20] This system was chosen since it is not self-complementary and therefore has the potential to bring together two orthogonally functionalized dendrons. In addition, the association constant is in a range expected to be appropriate for study by convenient ^{1}H NMR methods.[21] The synthesis of the parent dendrons having isopropylidene or benzylidene acetals on the periphery is described, as well as their attachment to the focal point adamantylurea or glycinylurea units. The peripheral groups of the parent dendrons were altered to provide new dendrons, and these were assembled in various combinations to provide several different complexes. The association constants for complex formation were measured by ^{1}H NMR, and the effect of the changes in peripheral functionality on the association constants was examined.

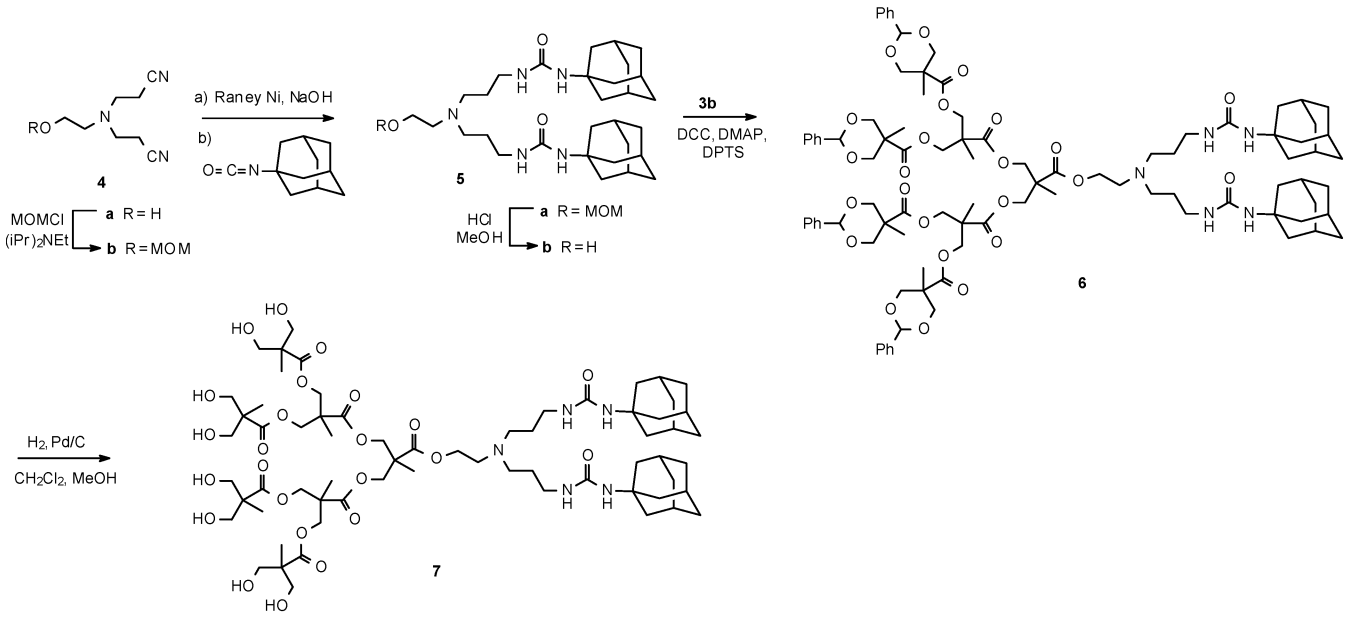
Results and Discussion

Synthesis. In this article, the dendrons are named using the following shorthand notation: (peripheral group)$_m$-[G-n]-(focal point group)$_p$, where m is the number of peripheral groups, n is the dendron generation, and p is the number of focal point groups.

The (benzylidene)$_4$-[G-3]-COOH **3b** was synthesized divergently as shown in Scheme 1 using a recently reported anhydride coupling method.[22] A trimethylsilylethyl ester was chosen as the protecting group for the focal point acid. Therefore, trimethylsilylethanol was coupled with the previously reported benzylidene-2,2-bis-

(14) Newkome, G. R.; Godínez, L. A.; Moorefield, C. N. *Chem. Commun.* **1998**, 1821−1822.
(15) Gibson, H. W.; Yamaguchi, N.; Hamilton, L.; Jones, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 4653−4665.
(16) Percec, V.; Cho, W.-D.; Ungar, G.; Yeardley, D. J. P. *J. Am. Chem. Soc.* **2001**, *123*, 1302−1315.
(17) Cardona, C. M.; Alvarez, J.; Kaifer, A. E.; McCarley, T. D.; Pandey, S.; Baker, G. A.; Bonzagni, N. J.; Bright, F. V. *J. Am. Chem. Soc.* **2000**, *122*, 6139−6144.
(18) Smith, D. K.; Diederich, F. *Chem. Commun.* **1998**, 2501−2502.
(19) Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, 14137−14146.
(20) Baars, M. W. P. L.; Karlsson, A. J.; Sorokin, V.; de Waal, B. F. W.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4262−4265. Baars, M. W. P. L.; Meijer, E. W. *Top. Curr. Chem.* **2000**, *210*, 131−182.
(21) Fielding, L. *Tetrahedron* **2000**, *56*, 6151−6170.
(22) Ihre, H.; Padilla De Jesús, O. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5908−5917.

SCHEME 2



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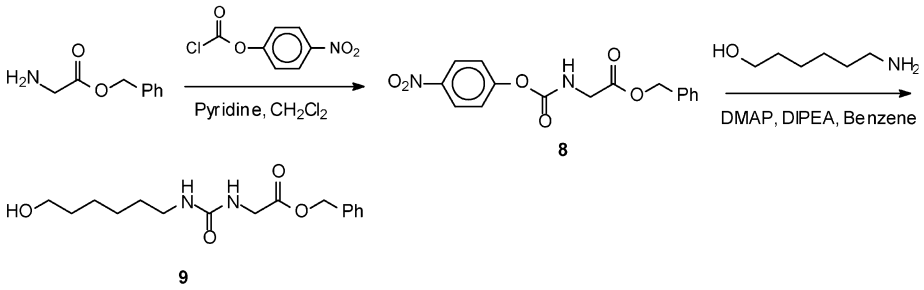

(oxymethyl)propionic anhydride,[22] in the presence of DMAP and pyridine, to provide the benzylidene-[G-1]-trimethylsilylethyl ester **1a**. The benzylidene acetal protecting group was then removed by catalytic hydrogenolysis using Pd/C as catalyst to provide the $(HO)_2$-[G-1]-trimethylsilylethyl ester **1b**. The coupling and deprotection procedures were repeated again to give the $(HO)_4$-[G-2]-trimethylsilylethyl ester **2b**, and one more coupling to the anhydride provided the $(benzylidene)_4$-[G-3]-trimethylsilylethyl ester **3a**. The trimethylsilylethyl ester protecting group was removed using tetrabutylammonium fluoride (TBAF), yielding the acid **3b** with four peripheral benzylidene acetals.

To synthesize the adamantylurea moiety, the previously reported dinitrile **4a**[23] was protected as the MOM ether **4b** as shown in Scheme 2, and then the nitrile groups were reduced to amines using Raney nickel under basic conditions. Without further purification, the amine groups were reacted with adamantyl isocyanate to form the bis(adamantylurea) compound **5a**. The MOM protecting group was then removed under acidic conditions to provide the alcohol **5b**, which could be coupled to **3b** using DCC, in the presence of DMAP and 4-dimethylaminopyridinium *p*-toluenesulfonate (DPTS) to provide the parent dendron **6**. The periphery of **6** could be converted from benzylidene acetals to hydroxyls by hydrogenolysis to give **7**.

The glycinylurea moiety was prepared as shown in Scheme 3. Benzyl glycinate was reacted with 4-nitrophenyl chloroformate, yielding *N*-(4-nitrophenyloxycarbonyl)benzyl glycinate **8**. This carbamate was then reacted with 1,6-aminohexanol to provide **9**, with the desired urea moiety and a hydroxyl handle for coupling to the dendron. The $(isopropylidene)_4$-[G-3]-COOH **10**,[24] was coupled to **9** using DCC as shown in Scheme 4, providing **11a**, and the benzyl ester protecting group was removed to give the second parent dendron **11b**. Removal of the isopropylidene acetals on the periphery of **11b** was accomplished using ceric ammonium nitrate (CAN),[25] to provide the hydroxyl-terminated dendron **13**.

Oligo(ethylene oxide) units could be introduced to the periphery of the dendron by first removing the isopropylidene acetals from the benzyl ester **11a** using the CAN method to provide **13**, followed by coupling with the acid-functionalized triglyme **14**, prepared as previously reported,[26] to give **15a**. Finally, the benzyl ester protecting

(23) Bell, J. A.; Kenworthy, C. *Synthesis* **1971**, 650−652.

(24) Würsch, A.; Möller, M.; Glauser, T.; Lim, L. S.; Voytek, S. B.; Hedrick, J. L. *Macromolecules* **2001**, *34*, 6601−6615.

(25) Marko, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207−3209.

(26) Ihre, H.; Padilla De Jesús, O. L.; Szoka, F. C. J.; Fréchet, J. M. J. *Bioconjugate Chem.* **2002**, *13*, 433−452.

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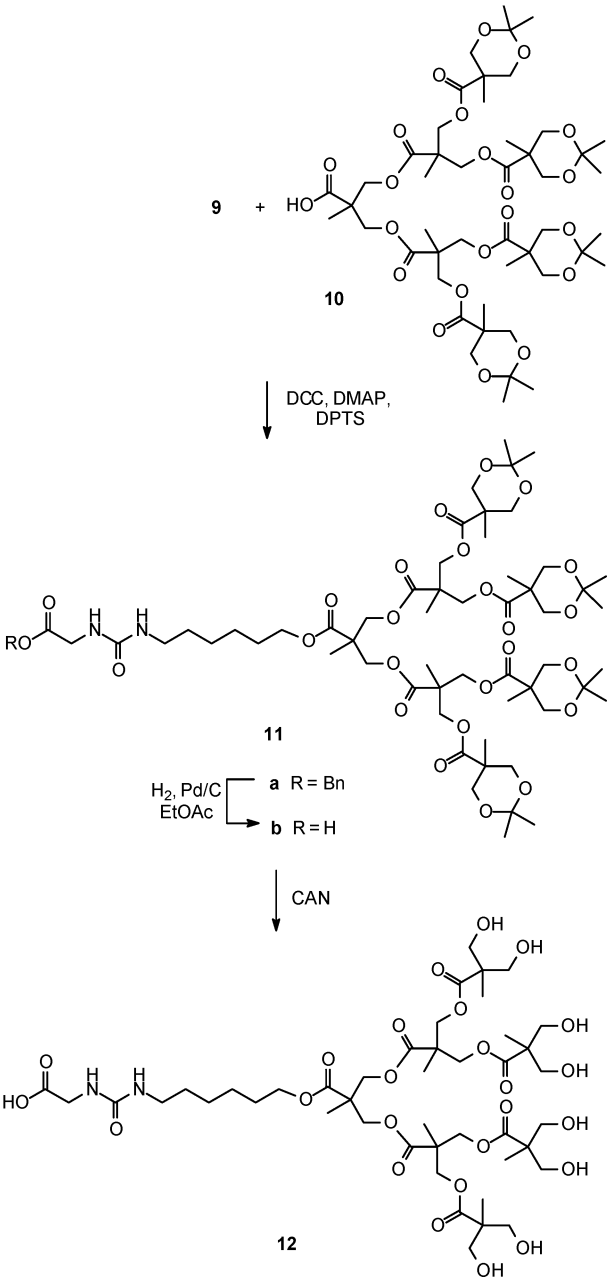

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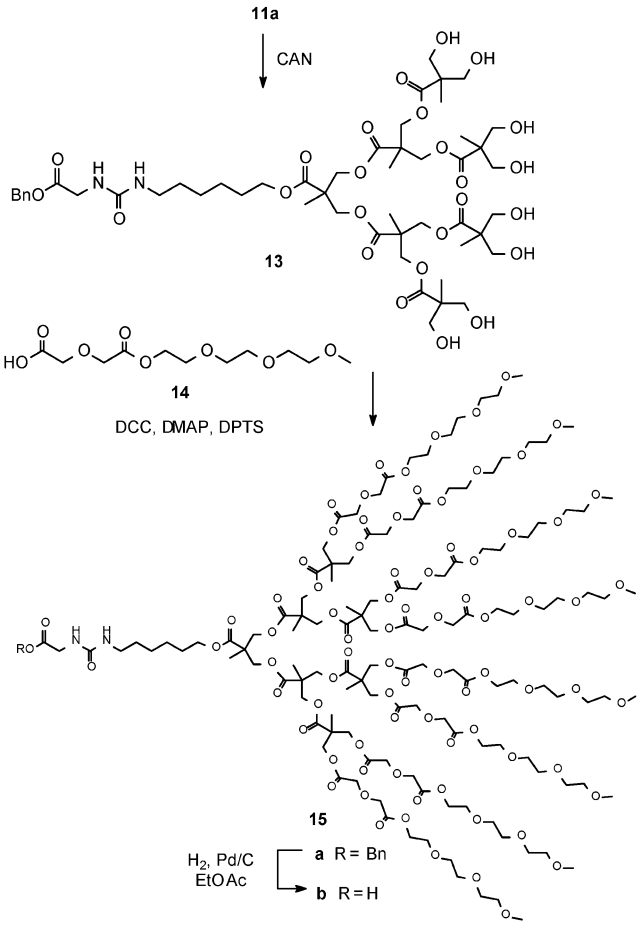

group was removed by catalytic hydrogenolysis to yield the acid **15b**.

Complex Formation. The parent complex **[6·11b]** was formed by dissolving equimolar amounts of compounds **6** and **11b** in dry $CDCl_3$. A comparison of the ^1H NMR spectra of **6** and **11b** with that of a 51 mM solution of complex **[6·11b]** (Figure 1) shows that there is a downfield shift for the adamantylurea hydrogen atoms from δ 4.64 and 5.32 to δ 5.09 and 5.64, as well as a significant broadening for these signals. The methylene protons adjacent to the tertiary amine also shift downfield from δ 2.37 and 2.53 to δ 2.67 and 2.78, consistent with protonation of the amine. These results are in agreement with those reported by Meijer.[20] Somewhat unexpectedly, the signals corresponding to the protons on the urea group of **11b** shift upfield upon complexation. This may be a result of the dendrimer environment.

The dependence of chemical shift on complex concentration is shown in Figure 2 for all signals but that of proton 1, which was too broad to measure accurately at lower concentrations. Using the appropriate curve-fitting procedure,[27] the association constant (K_a) for complex **[6·11b]** was determined to be (520 ± 90) M^{-1}. To provide an accurate comparison between complexes, all association constants are reported based on the signal for the methylene protons 6 as assigned in Figure 1, since the association constant varies somewhat depending on the proton investigated. This signal was chosen since it is the only one that remains unobstructed by other peaks throughout the titration experiment for all complexes.

Effect of Peripheral Group on Complex Formation. To study the effect of end groups on the association constant of the two-component system, complex formation was attempted using the deprotected dendron **7** with dendron **11b**, leading to complex **[7·11b]**. It was anticipated that the reduced solubility of **7** in $CDCl_3$ would enhance the strength of complex association. Indeed the K_a of complex **[7·11b]** was found to be (6800 ± 2900) M^{-1}, an increase of more than an order of magnitude. It is believed that this enhancement is due to a greater decrease in free energy when the relatively insoluble dendron **7** forms the soluble complex in comparison to the free energy decrease when both dendrons are already

(27) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry*; Schneider, H. J., Durr, H., Eds.; VCH: New York, 1991; pp 123−143.

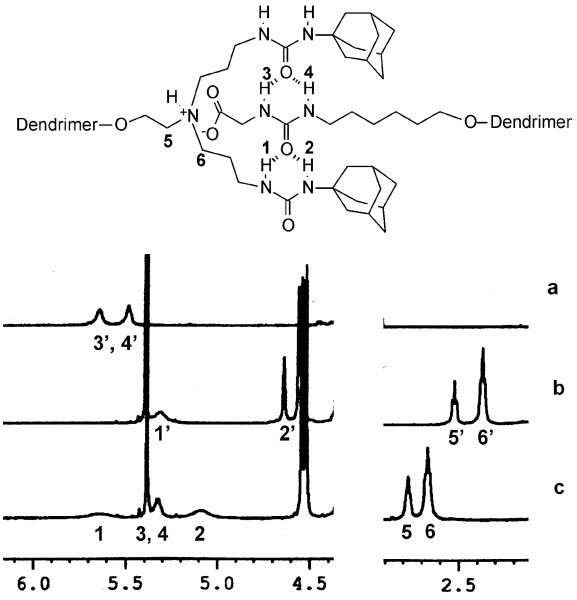

FIGURE 1. ^{1}H NMR spectra (500 MHz) of (a) **11b**, (b) **6**, and (c) **6**·11b (51 mM) in $CDCl_3$. Proton assignments are given, where *n*′ refers to the proton in the uncomplexed species.

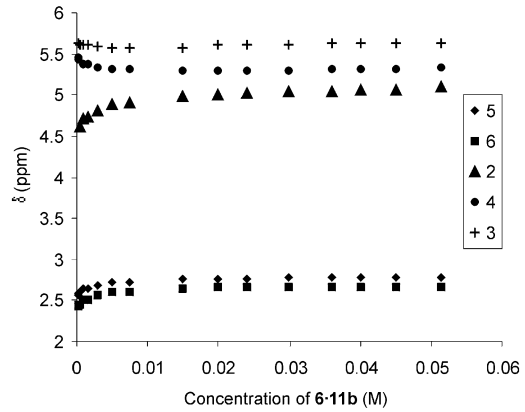

FIGURE 2. The dependence on concentration of the chemical shift of the methylene protons adjacent to the tertiary amine and the urea protons of complex **[6·11b]**.

readily soluble. A somewhat similar effect has also been observed in the formation of a supramolecular dendrimer where the core by itself is insoluble in $CDCl_3$ prior to complexation of the dendritic arms.[15] In this study, however, the enhancement is remarkable because the insoluble hydroxyl groups are not at the protected core of the complex but rather at the periphery.

When attempts were made to combine the fully deprotected dendron **12** with **6** in $CDCl_3$, no complex formation was observed. ^{1}H NMR analysis of the mixture showed that **6** had dissolved in the $CDCl_3$ while **12** remained fully insoluble. This failure to form the desired complex may be due to the extremely low solubility of **12** in $CDCl_3$ or to the lack of solubility of the resulting complex. Although **7** and **12** have the same peripheral groups, the more hydrophobic focal point of **7** may help to raise its solubility in $CDCl_3$ just enough to enable formation of the soluble complex.

To add steric bulk to dendron **11b**, an acid-functionalized tri(ethylene oxide) moiety was attached to each of its eight hydroxyl groups. This increases the molecular weight of the dendron from 1190 g/mol for **11b** to 3129 g/mol for **15b** and also increases the solubility of the dendron in highly polar media including water. A review of the literature shows that the dendrimer generation for a number of supramolecular dendrimer systems has had little or no effect on the complex stability,[7,18,28] whereas in others it has either enhanced or decreased the stability of the desired complex considerably.[6,17] In this system, the combination of the tri(ethylene oxide) substituted dendron **15b** with **6** leads to complex **[6·15b]**, with a considerably lower K_a amounting only to (70 ± 9) M^{-1} versus (520 ± 90) M^{-1} for the parent complex **[6·11b]**. Initially this result was somewhat surprising considering that the tri(ethylene oxide) groups are located far from the focal point. In addition, covalent systems of the same polyester backbone can be readily prepared from higher generation dendrons with as many as 32 tri(ethylene oxide) groups on the periphery.[26] However, closer inspection of this particular system reveals possible explanations for the observed effect. First, in comparison to other systems where the dendrimer core and backbone are relatively rigid, the polyester backbone and focal point functionality of **15b** are quite flexible. This may allow for considerable backfolding of the dendrimer backbone and tri(ethylene oxide) groups toward the focal point of the dendron, thus sterically hindering complex formation. In addition, a weak association of the oxygens of the tri(ethylene oxide) moieties with the urea hydrogens of the core group may lower the association constant by competition with dendron **6** for hydrogen bonding.

To verify the effects observed in the previous complexes, **15b** was combined with the hydroxyl terminated dendron **7** to form complex **[7·15b]**. The K_a for this system was found to be (1000 ± 300) M^{-1}, an enhancement again of more than an order of magnitude over the value measured for complex **[6·15b]**, verifying the effect of the hydroxyl functionalized periphery of **7**. The effect of the peripheral tri(ethylene oxide) groups is confirmed by the 7-fold decrease in K_a for **[7·15b]** relative to **[7·11b]**. In fact, the K_a value for **[7·15b]** is very close to the predicted value of 965 M^{-1} based on a 13-fold increase relative to the parent system due to the hydroxyl periphery and a 7-fold decrease resulting from the tri(ethylene oxide) groups observed for the previous complexes. Therefore, the combination of dendrons **7** and **15b** provides a confirmation of both the solubility and end group effects.

Conclusion

The first noncovalent synthesis of a polyester dendritic bow-tie based on the monomer 2,2-bis(hydroxymethyl)propionic acid was reported. This system was used to demonstrate that changes in peripheral functionality of the dendrimer have a profound effect on the association constant. Dendrimers therefore offer a convenient scaffold to study the effect of various properties such as solubility, steric hindrance, and competitive hydrogen bonding on the strength of complex formation. The

(28) Wang, Y.; Zeng, F.; Zimmerman, S. C. *Tetrahedron Lett.* **1997**, *38*, 5459−5462.

information obtained from these systems can be very useful for the future design of self-assembling systems. In particular, future work will focus on the use of knowledge gained from this system for the synthesis of well-defined, noncovalent dendritic structures with higher association constants. In addition, in the future we hope to use such concepts for the formation of supramolecular dendrimers in polar protic solvents such as water.

Experimental Section

Benzylidene-[G-1]-trimethylsilylethyl Ester (1a) and Representative Esterification Procedure. Trimethylsilylethanol (1.4 mL, 1.0 equiv, 9.7 mmol) and DMAP (0.29 g, 0.24 equiv, 2.3 mmol) were dissolved in 60 mL of CH_2Cl_2, and 10 mL of pyridine was added. Benzylidene-2,2-bis(oxymethyl)-propionic anhydride (5.0 g, 12 mmol, 1.2 equiv), prepared as previously reported,[20] was added, and the reaction mixture was stirred at room temperature overnight. The excess anhydride was quenched by stirring the reaction mixture with 5 mL of a 1:1 pyridine/water solution overnight. The organic phase was diluted with CH_2Cl_2 and washed with 1 M $NaHSO_4$, 10% Na_2CO_3, and saturated brine. The organic layer was dried and evaporated to give 2.91 g (92%) of **1a** as a white solid. Mp: 55−56 °C. IR (film from CH_2Cl_2): 1730. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 9H), 1.03 (s, 3H), 1.06−1.08 (m, 2H), 3.64 (d, 2H, J = 11.5), 4.28−4.31 (m, 2H), 4.67 (d, 2H, J = 11.5), 5.45 (s, 1H), 7.33−7.34 (m, 3H), 7.44−7.46 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.1, 17.5, 18.1, 42.5, 63.7, 73.8, 102.0, 126.5, 128.4, 129.2, 138.1, 174.4. MS calcd $[M + Li]^+$ ($C_{17}H_{26}LiO_4Si$): 329.1760. Found: (FABHR) 329.1753. Anal. Calcd for $C_{17}H_{26}O_4Si$: C, 63.32; H, 8.13. Found: C, 63.48; H, 8.02.

$(HO)_2$-[G-1]-trimethylsilylethyl Ester (1b) and Representative Benzylidene Deprotection Procedure. Compound **1a** (0.95 g, 3.0 mmol) was dissolved in 10 mL of CH_2Cl_2 and diluted with 10 mL of methanol, and 95 mg of 10% w/w Pd/C was added. The apparatus for catalytic hydrogenolysis was evacuated and filled with H_2 three times. After vigorous stirring overnight the catalyst was filtered off in a glass filter and was carefully washed with methanol. The filtrate was evaporated to give 0.66 g (96%) of **1b** as a white solid. Mp: 53−55 °C. IR (film from CH_2Cl_2): 3330, 1720. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 9H), 0.99−1.03 (m, 2H), 1.04 (s, 3H), 3.04 (br s, 2H), 3.68 (dd, 2H, J = 11.2, 4.2), 3.87 (dd, 2H, J = 11.1, 4.4), 4.21−4.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −1.3, 17.3, 17.5, 49.2, 63.7, 68.4, 176.4. MS calcd $[M + H]^+$ ($C_{10}H_{23}O_4Si$): 235.1365. Found: (HRFAB) 235.1356. Anal. Calcd for $C_{10}H_{22}O_4Si$: C, 51.25; H, 9.46. Found: C, 51.33; H, 9.37.

(Benzylidene)$_4$-[G-3]-COOH (3b). Compound **3a** (1.6 g, 1.3 mmol) was dissolved in 40 mL of dry THF, and 2.5 mL of a 1 M tetrabutylammonium fluoride solution in THF was added. The reaction mixture was stirred at room temperature for 1 h, then diluted with 100 mL of EtOAc, and washed with 1 M $NaHSO_4$ and then acidic brine. The organic phase was dried and evaporated to give 1.4 g (91%) of **3b** as a white glass. IR (film from CH_2Cl_2): 3210, 1740. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 12H), 1.02 (s, 3H), 1.19 (s, 6H), 3.58 (d, 8H, J = 11.0), 4.04 (d, 2H, J = 11.0), 4.12 (d, 2H, J = 11.0), 4.28−4.38 (m, 8H), 4.57 (d, 8H, J = 11.0), 5.40 (s, 4H), 7.28−7.30 (m, 12H), 7.39−7.44 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 17.8, 17.9, 42.7, 46.3, 46.9, 65.5, 66.3, 73.5, 101.9, 126.3, 128.3, 129.1, 137.7, 171.9, 173.25, 173.32. MS calcd $[M + Na]^+$ ($C_{63}H_{74}NaO_{22}$): 1206.2. Found: (MALDI-TOF) 1206.3. Anal. Calcd for $C_{63}H_{74}O_{22}$: C, 63.89; 6.30. Found: C, 64.05; H, 6.33.

***N*,*N*-Bis(2-cyanoethyl)-ethanolamine Methoxymethyl Ether (4b).** The alcohol **4a** (1.0 g, 6.0 mmol, 1.0 equiv) was dissolved in THF (40 mL), and (^{i}Pr)$_2$NEt (10 mL, 60 mmol, 10 equiv) was added. The solution was cooled to 0 °C, and then distilled chloromethyl methyl ether (2.9 mL, 36 mmol, 6 equiv) was added. The reaction mixture was stirred at 0 °C for 1 h and then overnight at room temperature. The reaction mixture was poured over 200 mL of ice and extracted with CH_2Cl_2. The aqueous phase was adjusted to pH 12 with concentrated NaOH and then extracted with CH_2Cl_2. The organic phase was dried and evaporated to provide 1.2 g (93%) of **4b** as a yellow oil. IR (film from CH_2Cl_2): 2247. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (t, 4H, J = 6.8), 2.81 (t, 2H, J = 5.4), 2.95 (t, 4H, J = 6.8), 3.35 (s, 3H), 3.59 (t, 2H, J = 5.4), 4.60 (s, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 17.3, 50.6, 53.3, 55.6, 66.6, 96.9, 118.8. MS calcd $[M + H]^+$ ($C_{10}H_{18}N_3O_2$): 212.1399. Found: (HRFAB) 212.1405. Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.49; H, 8.32; N, 19.54.

Bis(adamantylurea) Methoxymethyl Ether (5a). Compound **4b** (0.40 g, 1.9 mmol) was dissolved in 5 mL of 95% EtOH containing 0.28 g of NaOH. Raney nickel (0.2 g) was added as a slurry in water, and the reaction mixture was stirred under a hydrogen atmosphere at 50 psi overnight. The reaction mixture was carefully filtered through a glass filter, and the catalyst was washed with EtOH. The filtrate was concentrated, and the resulting residue was taken up in 10 mL of water. Saturated NaOH was added until the amine began to oil out, and the mixture was extracted with $CHCl_3$ until no more amine appeared in the $CHCl_3$ extract by TLC. The organic layers were dried and evaporated to provide 0.23 g of the diamine. Without further purification, the diamine (0.23 g) was dissolved in 5 mL of CH_2Cl_2, and adamantyl isocyanate (0.57 g, 3.2 mmol) was added. The reaction mixture was stirred at room temperature overnight and then evaporated. The product was purified by column chromatography using EtOAc/MeOH (80/20) to afford 0.52 g (48% overall) of **5a** as a colorless glass. IR (film from CH_2Cl_2): 3342, 1630, 1562. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58−1.65 (m, 16H), 1.93−1.97 (m, 12H), 2.01−2.40 (m, 6H), 2.47 (t, 4H, J = 6.2), 2.59 (t, 2H, J = 5.7), 3.17 (t, 4H, J = 6.2), 3.36 (s, 3H), 3.61 (t, 2H, J = 5.7), 4.63 (s, 2H), 4.66 (s, 2H), 5.58 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.3, 29.8, 36.7, 39.0, 42.8, 50.8, 52.7, 53.3, 55.7, 65.8, 96.8, 158.1. MS calcd $[M + H]^+$ ($C_{32}H_{56}N_5O_4$): 574.4332. Found: (HRFAB) 574.4324. Anal. Calcd for $C_{32}H_{55}N_5O_4$: C, 66.98; H, 9.66; N, 12.21. Found: C, 66.66; H, 9.67; N, 12.04.

Bis(adamantylurea) Alcohol (5b). Compound **5a** (0.10 g, 0.17 mmol) was dissolved in 10 mL of MeOH, and several drops of HCl were added. The solution was heated at 60 °C for 6 h, then cooled, and quenched with NEt_3. The solution was concentrated to low volume, and the resulting residue was taken up in CH_2Cl_2 and washed with 0.1 M NaOH. The organic phase was dried and evaporated to give 90 mg (98%) of **5b** as a white solid. Mp > 190 °C. IR (film from CH_2Cl_2): 3330, 1633, 1560. ^{1}H NMR (500 MHz, $CDCl_3$): 1.50−1.72 (m, 16H), 1.81−1.97 (m, 12H), 2.02 (br s, 6H), 2.41 (t, 4H, J = 7.1), 2.47 (t, 2H, J = 6.0), 3.21 (t, 4H, J = 6.9), 3.61 (t, 2H, J = 6.0), 5.17 (s, 2), 5.96 (s, 2). ^{13}C NMR (125 MHz, $CDCl_3$): 27.4, 29.8, 36.7, 38.4, 42.7, 50.6, 52.2, 56.2, 58.5, 158.9. MS calcd $[M + H]^+$ ($C_{30}H_{52}N_5O_3$): 530.4070. Found: (HRFAB) 530.4072. Anal. Calcd for $C_{30}H_{51}N_5O_3$: C, 68.01; H, 9.70; N, 13.22. Found: C, 68.18; H, 9.50; N, 12.88.

(Benzylidene)$_4$-[G-3]-(adamantylurea)$_2$ (6). The alcohol **5b** (0.10 mg, 0.19 mmol, 1.0 equiv) and the acid **3b** (0.34 g, 0.29 mmol, 1.5 equiv) were dissolved in 10 mL of CH_2Cl_2. DMAP (4.6 mg, 38 μmol, 0.20 equiv) and 4-dimethylaminopyridinium *p*-toluenesulfonate (DPTS) (12 mg, 38 μmol, 0.20 equiv) were added, followed by DCC (78 mg, 0.38 mmol, 2.0 equiv), and the reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. The reaction mixture was filtered to remove the dicyclohexylurea (DCU) byproduct, and the filtrate was concentrated. The product was purified by column chromatography using a solvent gradient from EtOAc/MeOH (90/10) to EtOAc/MeOH (80/20) to afford 0.32 g (71%) of **6** as a colorless glass. IR (film from CH_2Cl_2): 3350, 1742, 1640. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 12H), 1.03 (s, 3H), 1.21 (s, 6H), 1.50−1.54 (m, 4H), 1.62 (s, 12H), 1.90 (s, 12H), 1.20 (s, 6H), 2.37 (t, 4H, J = 5.8), 2.53 (t, 2H, J

= 5.7), 3.07 (t, 4H, J = 6.3), 3.58 (dd, 8H, J = 11.6, 3.5), 4.00−4.13 (m, 6H), 4.32−4.37 (m, 8H), 4.54 (dd, 8H, J = 11.6, 4.2), 4.64 (s, 2H), 5.32 (s, 2H), 5.40 (s, 4H), 7.29−7.32 (m, 12H), 7.37−7.39 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 17.78, 17.81, 27.7, 29.7, 36.6, 38.0, 42.6, 42.7, 46.6, 47.0, 50.6, 51.7, 51.9, 63.5, 65.3, 66.1, 73.6, 101.9, 126.3, 128.3, 129.1, 137.9, 158.04, 172.0, 172.3, 173.4. MS calcd $[M + Na]^+$ ($C_{93}H_{123}N_5NaO_{24}$): 1717.9. Found: (MALDI-TOF) 1719.1. Anal. Calcd for $C_{93}H_{123}N_5O_{24}$: C, 65.93; H, 7.31; N, 4.31. Found: C, 65.74; H, 7.27; N, 4.18.

***N*-(4-Nitrophenyloxycarbonyl)benzyl Glycinate (8).** Benzyl glycinate (0.62 g, 3.8 mmol, 1.0 equiv), prepared as previously reported[29] was dissolved in 4 mL of 1:1 CH_2Cl_2/pyridine and was added dropwise to a solution of 4-nitrophenyl chloroformate (2.3 g, 11 mmol, 3 equiv) in 20 mL of CH_2Cl_2 at 0 °C. After 10 min, the solution was diluted with CH_2Cl_2 and washed with 1 M $NaHSO_4$ and brine. The organic phase was evaporated, and the product was purified by column chromatography using CH_2Cl_2/hexane (90/10) to elute with excess 4-nitrophenyl chloroformate, followed by CH_2Cl_2 to elute the product. The fractions containing product were combined and washed with 2% Na_2CO_3 to remove 4-nitrophenol. The organic phase was dried and evaporated to provide 0.81 g (65%) of **8** as a white solid. Mp: 111−112 °C. IR (film from CH_2Cl_2): 3315, 3080, 1747, 1714, 1520. ^{1}H NMR (500 MHz, $CDCl_3$): 4.10 (d, 2H, J = 6.2), 5.21 (s, 2H), 5.91 (t, 3H, J = 5.6), 7.26−7.29 (m, 2H), 7.33−7.37 (m, 5H), 8.17−8.21 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 43.0, 67.6, 122.1, 125.2, 128.5, 128.8, 128.8, 135.1, 145.0, 153.4, 155.8, 169.5. MS calcd $[M + H]^+$ ($C_{16}H_{15}N_2O_6$): 331.0930. Found: (HRFAB) 331.0936. Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.21; H, 4.27; N, 8.49. Found: C, 58.48; H, 4.09; N, 8.66.

[3-(6-Hydroxyhexyl)ureido]acetic Acid Benzyl Ester (9). To a solution of **8** (0.79 g, 2.4 mmol, 1.0 equiv) in 10 mL of benzene were added 1,6-aminohexanol (0.34 g, 2.9 mmol, 1.2 equiv), DMAP (88 mg, 0.72 mmol, 0.30 equiv), and diisopropylethylamine (0.46 g, 3.6 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 30 min, diluted with 50 mL of CH_2Cl_2, and washed with 1 M $NaHSO_4$, 2% Na_2CO_3, and saturated brine. The organic phase was dried and evaporated to give 0.61 g (86%) of **9** as a white solid. Mp: 75−77 °C. IR (film from CH_2Cl_2): 3350, 1740, 1648, 1580. ^{1}H NMR (500 MHz, $CDCl_3$): 1.27−1.37 (m, 4H), 1.43−1.54 (m, 4H), 2.71 (s, 1H), 3.11−3.15 (m, 2H), 3.56−3.58 (m, 2H), 3.99 (d, 2H, J = 6.0), 5.13 (s, 2H), 5.35 (t, 3H, J = 5.5), 5.57 (t, 3H, J = 5.55), 7.29−7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 25.4, 26.5, 30.2, 32.6, 40.4, 42.4, 62.6, 67.1, 128.4, 128.6, 128.8, 135.5, 158.7, 171.7. MS calcd $[M + H]^+$ ($C_{16}H_{25}N_2O_4$): 309.1814. Found: (HRFAB) 309.1820. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.34; H, 7.85; N, 9.08. Found: C, 62.12; H, 8.05; N, 9.08.

(Isopropylidene)$_4$-[G-3]-glycinylurea Benzyl Ester (11a). The alcohol **9** (0.14 g, 0.48 mmol, 1.0 equiv) and acid **10**[24] (0.72 g, 0.72 mmol, 1.5 equiv) were dissolved in 10 mL of CH_2Cl_2. DMAP (12 mg, 96 μmol, 0.20 equiv) and DPTS (30 mg, 96 μmol, 0.20 equiv) were added, followed by DCC (0.20 g, 0.96 mmol, 2.0 equiv), and the reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. The reaction was filtered to remove the dicyclohexylurea (DCU) byproduct, and the filtrate was concentrated. The product was purified by column chromatography using a solvent gradient from EtOAc/Hex (60/40) to EtOAc/Hex (80/20) to afford 0.55 g (91%) of **11a** as a colorless glass. IR (film from CH_2Cl_2): 3400, 1753, 1686, 1656, 1562. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (s, 12H), 1.27 (s, 3H), 1.28 (s, 6H), 1.34 (s, 12H), 1.34−1.38 (m, 4H), 1.41 (s, 12H), 1.45−1.49 (m, 2H), 1.60−1.67 (m, 2H), 3.17−3.21 (m, 2H), 3.62 (dd, 8H, J = 11.8, 2.4), 4.00 (d, 2H, J = 5.5), 4.11−4.16 (m, 10H), 4.20−4.34 (m, 12H), 5.14 (s, 2H), 5.35 (t, 1H, J = 5.5), 5.51 (t, 1H, J = 5.6), 7.30−7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 17.6, 17.7, 18.4, 21.6, 25.5, 25.7, 26.4, 28.4, 30.0, 40.2, 42.1, 42.2, 46.6, 46.9, 65.0, 65.5, 66.0, 66.1, 66.7, 98.1, 128.2, 128.3, 128.6, 135.6, 158.3, 171.2, 171.9, 172.1, 173.6. MS calcd $[M + Na]^+$ ($C_{63}H_{96}NaN_2O_{25}$): 1304.4. Found: (MALDI-TOF) 1305.2. Anal. Calcd for $C_{63}H_{69}NaN_2O_{25}$: C, 59.05; H, 7.55; N, 2.19. Found: C, 59.33; H, 7.58; N, 2.19.

(HO)$_8$-[G-3]-glycinylurea (12). Compound **11b** (75 mg, 63 μmol, 1.0 equiv) was dissolved in 2 mL of CH_3CN and was diluted with 1 mL of 20 mM pH 7.0 borate buffer. CAN (5.5 mg, 10 μmol, 0.16 equiv) was added, and the reaction mixture was heated at 50 °C for 2 h. After cooling the reaction mixture was partitioned between THF and 0.1 M $NaHSO_4$ in saturated brine. The organic phase was washed with another portion of the acidic brine, dried, and evaporated. The product was purified by passing over a silica plug, using first EtOAc/MeOH (90/10), followed by EtOAC/MeOH (80/20) to provide 55 mg (85%) of **12** as a colorless glass. IR (film from THF): 3390, 1735, 1726, 1584. ^{1}H NMR (500 MHz, MeOD): 1.15 (s, 12H), 1.29 (s, 6H), 1.30 (s, 3H), 1.37−1.41 (m, 4H), 1.48−1.51 (m, 2H), 1.68−1.71 (m, 2H), 3.14 (t, 2H, J = 7.0), 3.60 (d, 8H, J = 10.7), 3.68 (dd, 8H, J = 10.9, 2.6), 3.72 (d, 2H, J = 9.9), 4.16 (t, 2H, J = 6.6), 4.23−4.33 (m, 12H). ^{13}C NMR (125 MHz, MeOD): 17.5, 18.3, 18.4, 27.0, 27.7, 29.8, 31.3, 41.2, 45.2, 48.1, 48.2, 51.9, 65.9, 66.3, 66.8, 67.5, 161.3, 173.9, 174.2, 176.1. MS calcd $[M + Na]^+$ ($C_{44}H_{74}NaN_2O_{25}$): 1054.1. Found: (MALDI-TOF) 1053.9.

(HO)$_8$-[G-3]-glycinylurea Benzyl Ester (13). The ester **11a** (0.18 g, 0.14 mmol, 1.0 equiv) was dissolved in 2 mL of CH_3CN and was diluted with 1 mL of 20 mM pH 7.0 borate buffer. CAN (12 mg, 22 μmol, 0.16 equiv) was added, and the reaction mixture was heated at 50 °C for 2 h. After cooling, the reaction mixture was partitioned between THF and saturated brine. The organic phase was washed with another portion of brine, dried, and evaporated. The product was purified by passing it over a silica plug, using first EtOAc/MeOH (90/10), followed by EtOAC/MeOH (80/20) to provide 0.13 g (85%) of **13** as a colorless glass. IR (film from THF): 3400, 1737, 1660, 1572. ^{1}H NMR (400 MHz, MeOD): 1.15 (s, 12H), 1.29 (s, 6H), 1.30 (s, 3H), 1.37−1.42 (m, 4H), 1.47−1.53 (m, 2H), 1.65−1.71 (m, 2H), 3.12−3.17 (m, 2H), 3.60 (d, 8H, J = 10.9), 3.69 (dd, 8H, J = 10.9, 2.1), 3.92 (s, 2H), 4.16 (t, 2H, J = 6.6), 4.25 (dd, 4H, J = 11.0, 2.2), 4.29−4.34 (m, 8H), 5.17 (s, 2H), 7.31−7.39 (m, 5H). ^{13}C NMR (100 MHz, MeOD): 17.5, 18.3, 18.4, 26.9, 27.6, 29.7, 31.2, 41.1, 43.0, 48.0, 51.9, 65.9, 66.3, 66.8, 67.4, 67.8, 129.35, 129.40, 129.7, 137.4, 161.1, 172.7, 173.9, 174.1, 176.0. MS calcd $[M + Na]^+$ ($C_{51}H_{80}NaN_2O_{25}$): 1144.2. Found: (MALDI-TOF) 1144.7. Anal. Calcd for $C_{51}H_{80}N_2O_{25}$: C, 54.63; H, 7.19; N, 2.50. Found: C, 54.46; H, 7.48; N, 2.44.

Oligo(ethylene oxide)-[G-3]-gylcinylurea Benzyl Ester (15a). Compound **13** (79 mg, 70 μmol, 1.0 equiv) was dissolved in 2 mL of DMF and was diluted with 4 mL of CH_2Cl_2. The acid **14** (0.32 g, 1.1 mmol, 16 equiv), prepared as previously reported,[26] was added, followed by DCC (0.29 g, 1.4 mmol, 20 equiv), DMAP (28 mg, 0.23 mmol, 3.2 equiv), and DPTS (72 mg, 0.23 mmol, 3.2 equiv). The reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere and then was filtered to remove DCU. The filtrate was diluted with EtOAc and washed with saturated brine. The organic phase was dried and evaporated. The resulting residue was purified by column chromatography using a solvent gradient from EtOAc/Hex (75/25) to CH_2Cl_2/MeOH (50/50), yielding 0.14 g (63%) of **15a** as a colorless glass. IR (film from CH_2Cl_2): 3400, 1752, 1685, 1550. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 18H), 1.19 (s, 3H), 1.23−1.31 (m, 4H), 1.34−1.43 (m, 2H), 1.51−1.59 (m, 2H), 3.03 (m, 2H), 3.28 (s, 24H), 3.44−3.46 (m, 16H), 3.50−3.56 (m, 48H), 3.60−3.66 (m, 20H), 3.90 (d, 2H, J = 6), 4.02 (t, 2H, J = 8.0), 4.14−4.22 (m, 72H), 5.05 (s, 2H), 5.25 (s, 1H), 5.40 (s, 1H), 7.24−7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.4, 17.7, 25.6, 26.3, 28.3, 30.1, 40.0, 42.0, 46.3, 46.5, 46.6, 58.9, 63.9, 65.2, 65.3, 65.5, 66.3, 66.5, 67.7, 67.8, 68.8, 70.42, 70.44, 71.8, 128.1, 128.2, 128.5, 135.5, 158.1, 169.2, 169.6,

(29) Gray, C. J.; Quibell, M.; Jiang, K.-L.; Baggett, N. *Synthesis* **1991**, *2*, 141−147.

171.2, 171.3, 171.5, 171.9. MS calcd $[M + Na]^+$ ($C_{139}H_{224}NaN_2O_{81}$): 3242.3. Found: (MALDI-TOF) 3242.9. Anal. Calcd for $C_{139}H_{224}N_2O_{81}$: C, 51.86; H, 7.01; N, 0.87. Found: C, 51.67; H, 6.91; N, 0.89.

General Procedure for Complex Formation and Determination of Association Constants by ^{1}H NMR. Complexes were formed by combining the complementary amine and acid in a 1:1 molar ratio in dry $CDCl_3$. Association constants were determined by ^{1}H NMR at 500 MHz in $CDCl_3$ using the dilution protocol[27] over a concentration range from ~60 to ~ 0.2 mM.

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Supporting Information Available: General experimental procedures and materials; procedures for preparation of compounds **2a**, **2b**, **3a**, **4a**, **7**, **11b**, and **15b**; and ^{1}H NMR spectrum of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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