Communications to the Editor

Analysis of Amidinium Guest Complexation by Comparison of Two Classes of Dendrimer Hosts Containing a Hydrogen Bonding Unit at the Core

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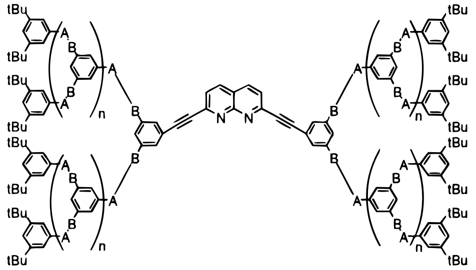
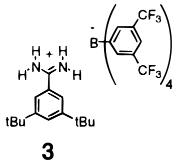
Dendrimers are attracting increasing attention because of their unique, highly branched structures, novel properties, and availability through iterative synthesis.[1] At the same time, remarkably little is known about the three-dimensional structure and the interior nanoenvironment of dendrimers. For example, there remains considerable debate about whether the point of maximum density resides at the core or the surface,[2] and little is known about the porosity, flexibility and interior polarity of dendrimers.

We recently reported that hydrogen bonding units at the core of dendrimers can be used to control their aggregation.[3] Herein we report the ability of two classes of dendritic hosts with naphthyridine units at their cores (**1a**−**d**, **2a**−**d**) to hydrogen bond complementary benzamidinium guests **3** and **4**. Because hydrogen bond strengths depend on solvent polarity, the guest molecule serves as a sensitive probe of the dendrimer's internal accessibility and polarity. This study provides one of the first direct comparisons of properties of two distinct classes of dendrimers and broadly assesses the suitability of this class of polymers to site-specifically complex small molecules within their interiors via hydrogen bonding.[4]



1a : n = 0, A-B = CH_2-O
1b : n = 1, A-B = CH_2-O
1c : n = 2, A-B = CH_2-O
1d : n = 3, A-B = CH_2-O
2a : n = 0, A-B = C≡C
2b : n = 1, A-B = C≡C
2c : n = 2, A-B = C≡C
2d : n = 3, A-B = C≡C



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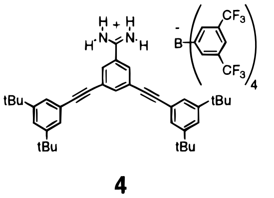

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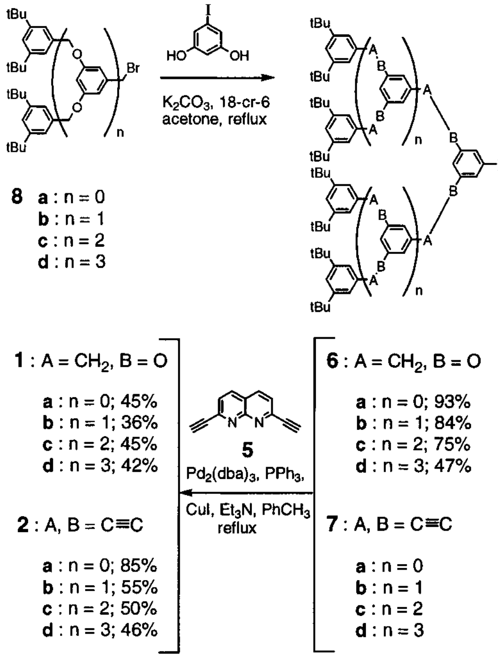
Dendrimers **1** and **2** differ only in the two atoms connecting the aryl groups. The OCH_2 groups in **1** are polar (vide supra) and flexible, whereas the phenyl acetylene units are apolar and likely make **2** quite porous. Hosts **1** and **2** and guests **3** and **4** were synthesized in straightforward fashion[5] (Scheme 1), the latter from readily available phenyl acetylene based dendrons[6] or arylphenyl ether dendrons.[7] Compounds **3** and **4** were used as their tetrakis[3,5-bis(trifluoromethyl)phenyl]borate salts to enhance their solubility in organic solvents.[8]

Scheme 1



The association constants (K_{assoc}) were too high in chloroform-*d* to determine accurately by ^1H NMR, therefore most of the studies were performed in 10% acetonitrile-d_3/chloroform-*d*. The stoichiometry of all host−guest complexes was determined to be 1:1 by Job analysis. This finding, combined with the substantial downfield shifts (>1 ppm) of the benzamidinium NH_2 groups upon complexation, and the lack of any complexation between **3** and **9**, indicates that binding is driven by specific hydrogen bond pairing at the naphthyridine core.

The K_{assoc} were measured for complexes between hosts **1** and **2** and guests **3** and **4** by using a ^1H NMR dilution method[9] (Table 1). In each case, the complexation was fast on the ^1H NMR time scale.[10] To further assess the role of the dendritic substituents in the binding process, a K_{assoc} value was measured for the complex

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(1) Recent reviews: (a) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681−1712. (b) Xu, Z.; Kyan, B.; Moore, J. S. In *Advances in Dendritic Macromolecules*; Newkome, G. R., Ed.; JAI: Greenwich, 1994; Vol. 1, pp 69−104. (c) Dvornic, P. R.; Tomalia, D. A. *Curr. Opin. Colloid Interfac. Sci.* **1996**, *1*, 221−235. (d) Fréchet J. M. J.; Hawker, C. J.; Wooley, K. L. *J. Macromol. Sci. Pure Appl. Chem.* **1994**, A31, 1627−1645. (e) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Syntheses, Perspectives;* VCH: Weinheim, 1996.

(2) (a) de Gennes, P. G.; Hervet, H. *J. Phys.* **1983**, *44*, L351-L360. (b) Metzler, A. D.; Tirrell, D. A.; Jones, A. A.; Inglefield, P. T. *Macromolecules* **1992**, *25*, 4549−4552. (c) Murat, M.; Grest, G. S. *Macromolecules* **1996**, *29*, 1278−1285. (d) Naylor, A. M.; Goddard, W. A., III; Kiefer, G. E.; Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339−2341. (e) Boris, D.; Rubinstein, M. *Macromolecules* **1996**, *29*, 7251−7260. (f) Wooley, K. L.; Klug, C. A.; Tasaki, K.; Schaefer, J. *J. Am. Chem. Soc.* **1997**, *119*, 53−58.

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

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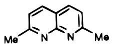
formed between **3** and **4** and 2,7-dimethylnaphthyridine (**10**). Although diyne **5** was a more appropriate control compound, it exhibited insufficient solubility for study. Most striking is the fact that the K_{assoc} are nearly identical for the eight different **1·3** and **2·3** complexes and for the control complex **10·3** (Table 1). The maximum $\Delta\Delta G°$ for the **1·3** and **2·3** complexes, $\leq$0.3 kcal mol^{-1}, is likely within experimental error. Thus, the size of the dendrimer and its chemical nature only marginally alter complex stability. With the larger guest **4**, the higher generation dendritic hosts bind more weakly, reflecting the increased steric demands for complexation.

Table 1. Summary of Binding Constants between Dendritic Hosts and Guests **3** and **4** in Mixtures of CD_3CN and $CDCl_3$[a]

	guest							
	3						**4**	
	5% CD_3CN		10% CD_3CN		15% CD_3CN		10% CD_3CN	
host	K_a (M^{-1})	$-\Delta G°$ (kcal/mol)	K_a (M^{-1})	$-\Delta G°$ (kcal/mol)	K_a (M^{-1})	$-\Delta G°$ (kcal/mol)	K_a (M^{-1})	$-\Delta G°$ (kcal/mol)
10	6520	5.1	1860	4.4	960	4.0	2610	4.6
1a	3020	4.7	940	4.0	490	3.6	1100	4.1
1b			810	3.9			790	3.9
1c			780	3.9			560	3.7
1d	3580	4.8	800	3.9	380	3.5	390	3.5
2a	4260	4.9	1400	4.2	610	3.7	2040	4.4
2b			1290	4.2			1370	4.2
2c			1030	4.0			1080	4.1
2d	2680	4.6	820	3.9	340	3.4	520	3.6

[a] At 293 K. Method: ^{1}H NMR dilution of a 1:1 host−guest complex.[9] Saturation ranges are between 10 and 80%. Binding constants are averages of triplicate runs that were within ±15%.



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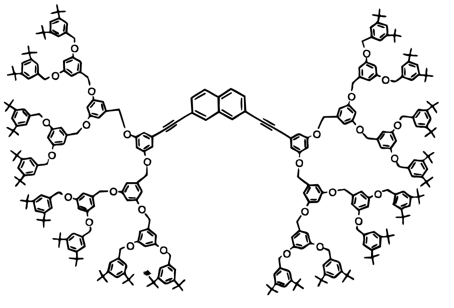

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Binding studies of **1a**,**d** and **2a**,**d** with guest **3** were performed in 5% and 15% acetonitrile-d_3/chloroform-d to gain additional insight into the role of the solvent and dendrimer substituents in controlling the nanoenvironment at the core. A plot of complexation energy vs solvent composition is shown in Figure 1. The four dendrimers exhibit similar $\Delta G°$ values in each solvent mixture ($\Delta\Delta G° \leq 0.3$ kcal mol^{-1}), and each shows a similar response to change in solvent polarity. All the results combined suggest that the environment at the naphthyridine core of both types of dendritic hosts is either apolar or controlled by the solvent even in the largest dendritic hosts (**1d**, **2d**). Using a spectrophotometric method, Hawker and Fréchet[11a] reported that the local polarizability parameter at the core of arylbenzyl ether dendrimers is very high and comparable to that of very polar solvents such as DMF. The K_{assoc} value for the **3·10** complex is <3 M^{-1} in dimethylformamide-d_7 and ca. 200 M^{-1} in acetone-d_6. Hydrogen bond strengths measure a different component of solvent polarity than π^*, but whatever the polarity the current results show that the dendrimer exerts a negligible influence on the core nanoenvironment even in **1d** and **2d**.

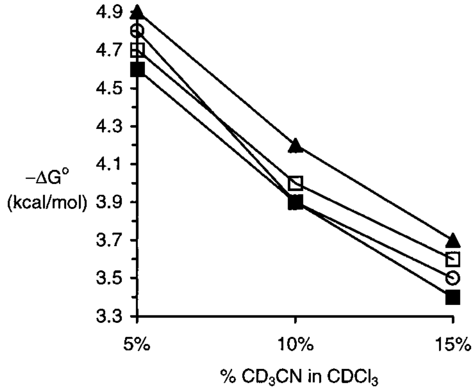

Figure 1. Plot of complexation energy as a function of solvent polarity. Complexes with **3**: □, **1a**; ○, **1d**; ▲, **2a**; ■, **2d**.

In conclusion, dendritic naphthyridine hosts with molecular weights up to the 10 kD range are capable of binding a simple benzamidinium guest via specific hydrogen bonding interactions at their core. The fast on−off rates, high complex stability, relative insensitivity of complexation strength to the dendrimer size and nature, and the similar response to solvent polarity suggest that these hosts are highly porous.

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Supporting Information Available: Experimental and spectral details for each of the compounds in this study (11 pages). See any current masthead page for ordering information and Web access instructions.

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Wallimann, P.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1996**, *79*, 779−788. (f) Stevelmans, S.; van Hest, J. C. M.; Jansen, J. F. G. A.; van Boxtel, D. A. F. J.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 7398−7399.

(5) Dendritic hosts **1** and **2** were shown to be pure and to have the assigned structure by ^{1}H and ^{13}C NMR, size exclusion chromatography, and matrix assisted laser desorption ionization mass spectrometry (MALDI). Compounds **1a**−**d**, **2a**−**d**, **3**, and **4** each gave an acceptable elemental analysis. Further details of the preparation and characterization of all compounds in this study can be found in the Supporting Information.

(6) Bharathi, P.; Patel, U.; Kawaguchi, T.; Pesak, D. J.; Moore, J. S. *Macromolecules* **1995**, *28*, 5955−5963 and references therein.

(7) Hawker, C. J.; Fréchet J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647. Hawker, C. J.; Fréchet J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2459−2469.

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(9) Wilcox, C. S. *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.: VCH: New York, 1991; 123−143.

(10) Diederich reported broadened resonances for hydrophobic guests bound by a water soluble "dendrophane" whose molecular weight is smaller than **1d** and **2d** (ref 11b) and a steroid binding dendrophane that shows fast binding on the NMR time scale for all generations (ref 4e).

(11) (a) This study used a spectrophotometric probe at the dendrimer core. Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375−4376. See also: (b) Mattei, S.; Seiler, P.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1995**, *78*, 1904−1912. (c) Jiang, D. L.; Aida, T. *J. Chem. Soc., Chem. Commun.* **1996**, 1523−1524.