An NMR Study of the Supramolecular Chemistry of Modified Poly(propyleneimine) Dendrimers

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ABSTRACT: The supramolecular chemistry of the third generation poly(propyleneimine) dendrimers (**1**) having adamantylurea end groups was investigated using multidimensional NMR on a 750 MHz spectrometer. A stable complex (**3**) is formed when **1** is combined with cyanobiphenyl guest molecules (**2**) having glycinylurea type end groups. Proton connectivities were obtained from 2D $^{1}H-^{1}H$ TOCSY experiment. The ^{13}C and ^{1}H resonances were correlated from the 2D $^{1}H-^{13}C$ gHSQC experiment. Spatial proximity of the host−guest molecules was determined from a 2D $^{1}H-^{1}H$ NOESY experiment. Evidence of the specific binding interactions responsible for the stable complex of **1** with **2** was obtained from $^{1}H-^{1}H$ interactions determined from the NOESY spectrum.

Introduction

Dendrimers are hyperbranched polymers having a treelike structure around a central core. Since their first synthesis reported by Vögtle,[1] dendrimers have drawn widespread attention among all fields of science.[2] Unlike the linear polymers which have a molecular weight distribution, dendrimers are monodisperse in nature. This is achieved by careful control of reactions during their preparation in a stepwise manner, either from the core to the periphery (divergent) or from the periphery to the core (convergent). Because of their highly branched ordered structures, dendrimers tend to form spherical shapes resulting in lower viscosity solutions, high solubility, and higher reactivity compared to those of their linear counterparts. The unique combination of physical and chemical properties of dendrimers makes them suitable for a variety of applications such as nanoreactors, binary information storage systems, magnetic resonance imaging (MRI) contrasting agents, light-emitting diodes (LED), enzyme mimics, etc.

Owing to their globular shape and dense packing at the periphery, they can be used in supramolecular chemistry as hosts to bind small guest molecules. Supramolecular chemistry arises due to intermolecular interactions between two or more entities not covalently linked with each other. Maciejewski[3] first predicted the use of dendrimers for encapsulating guest molecules. The presence of cavities similar to the active sites of the enzymes makes dendrimers suitable for encapsulating guest molecule.

Keeping this use in mind, chemists have tailor-made molecules that can selectively bind substrate (guest) molecules. End group modification is the most commonly used approach for making dendrimer suitable as host molecules. Poly(propyleneimine) dendrimers were modified by attaching adamantylurea as end groups,[4] and the resulting dendrimer was used to bind guests having polar glycinyl urea fragments at the end of a long relatively nonpolar structure. These structures are good candidates for supramolecular building blocks as the bulky adamantyl groups stabilize a globular dendrimer shape. Knowledge of the specific host−guest interactions responsible for the formation of stable host−guest complexes is key to the rational design and assembly of many useful supramolecular structures.

Nuclear magnetic resonance (NMR) is one of the most powerful and versatile techniques for studying complex organic structures. The usefulness of NMR comes from the fact that it can distinguish between each types of nuclei within a molecule on the basis of their chemical environments. One-dimensional (1D) NMR along with other techniques such as mass spectrometry (MS) was used to obtain structural information on dendrimers.[5] The dispersion of the NMR spectrum into a second and third frequency axis in 2D and 3D NMR experiments has opened new avenues for the use of NMR spectroscopy.[6] The increase in dispersion through the use of additional dimensions can provide a wealth of information on complex supramolecular structures and interactions. Chai et al.[7] have used multidimensional NMR experiments to study intra- and intermolecular interactions among dendrimers and to study solvent−dendrimer interaction. In this work we have used 1D and 2D NMR techniques to investigate the supramolecular host−guest interactions of modified poly(propyleneimine) dendrimer **1** and guest **2**.

Experimental Section

Preparation of Dendrimer−Guest Complex. A detailed description of the preparation of the host (**1**) and guest (**2**) molecules was given in ref 4.

The host−guest complex was prepared by dissolving 15 mg of the host dendrimer (3.3×10^{-6} mol) in approximately 10 mL of chloroform together with 10.5 mg of the guest (2.65×10^{-5} mol) so that the host:guest ratio was 1:8. The mixture was sonicated at 30 °C until a clear solution was obtained. The solvent was removed in vacuo, and approximately 15 mg of the mixture was dissolved in about 0.7 mL of $CDCl_3$ for spectral analysis. Proton NMR at 750 MHz was consistent with data previously published.

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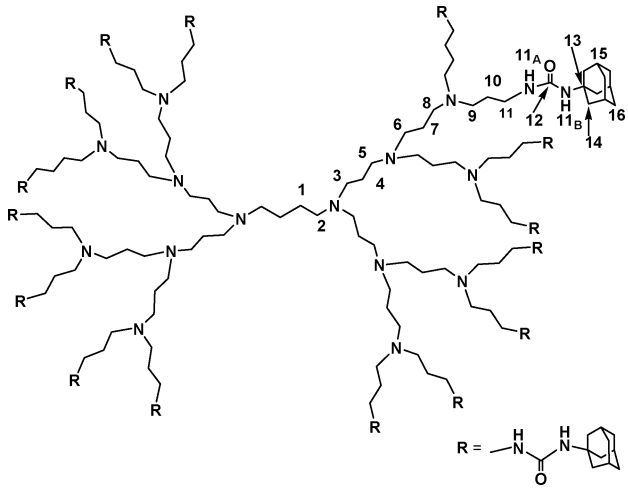

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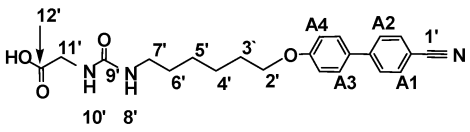

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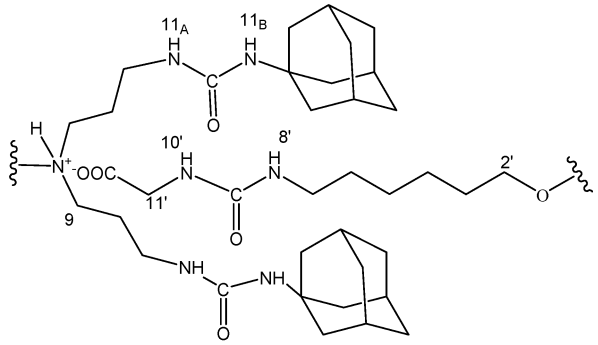
2D NOESY NMR. The 2D $^1H-^1H$ NOESY[8] (nuclear Overhauser enhancement spectroscopy) spectrum of **1** was obtained using a 5 mm switchable probe on an INOVA 400 spectrometer. The experimental parameters were a $\pi/2$ pulse of 7.7 μs, a mixing time of 0.4 s, 16 transients per increment, and 1024 increments. The NOESY experiment on the complex was performed on a Varian INOVA 750 MHz instrument, equipped with a Nalorac H/C/N 5 mm triple-resonance PFG probe using a 9.3 μs $\pi/2$ pulse, 1 s relaxation delay, 6.1 kHz spectral window, 0.1 s mixing time, and 0.1 s acquisition time; 16 transients were averaged for each of 2 × 256 increments using the States[9] method of phase sensitive detection in the f1 dimension. Processing was done with sinebell and shifted sinebell weighting functions and zero-filling to a 2048 × 1024 data matrix before Fourier transformation.

2D TOCSY NMR. The 2D $^1H-^1H$ TOCSY[10] (total correlation spectroscopy) experiment was performed on the complex of **1** and **2** using the same 750 MHz spectrometer. The spectrum was collected using a $\pi/2$ pulse width of 11 μs, a relaxation delay of 3 s, 6.1 kHz spectral window, and 0.17 s acquisition time; a spin-lock pulse was applied for a period of 0.1 s with a spin-lock field of 10.6 kHz with MLEV-16 modulation; 16 transients were averaged for each of the 2 × 256 increments using the States method[9] of phase sensitive detection. Sinebell and shifted sinebell weighting functions were used for processing, and the data were zero-filled to a 4096 × 1024 data matrix before Fourier transformation.

2D gHSQC NMR. A gradient-assisted HSQC[11] (gHSQC) experiment was performed on the host−guest complex, with the same INOVA 750 MHz instrument configuration, using 9.3 μs (^1H) and 16 μs (^{13}C) $\pi/2$ pulses, 1 s relaxation delay, 8 kHz spectral width in ^1H dimension, 15.8 kHz in the ^{13}C dimension, and 0.083 s acquisition time with ^{13}C GARP decoupling; eight transients were averaged for each of 2 × 512 increments using the States[9] method of phase sensitive detection in the f1 dimension. Processing was done with sinebell and shifted sinebell weighting functions and zero-filling to a 2048 × 2048 data matrix before Fourier transformation. A delay of $1/[2^1J_{CH}]$ (where $^1J_{CH} = 140$ Hz) was used to optimize the intensity of cross-peaks from one bond $^{13}C-^1H$ correlations; for coherence selection, gradients were applied for 2 and 1 ms with gradient strengths of 0.2 and 0.1 T/m, respectively.

Results and Discussion

It is proposed that the host molecules **1** can bind the guests **2** through a combination of electrostatic and H-bonding interactions**.** At this moment it is still unclear which interaction is the predominant one, but it is clear that the combination of interactions enhances binding to the dendrimer. As a result of the bulky adamantylurea end groups, each pair of dendritic arms can act as a scaffold to hold one guest molecule. Since a third generation dendrimer has a total of 16 arms, in theory eight guest molecules (**2**) can adhere to one host molecule. The proposed binding scheme is



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The primary objective of this research was to determine the nature of interaction between **1** and **2** in solution. Before looking at any specific interaction, structural characterization was performed by NMR, and unambiguous resonance assignments were obtained. Since the 1D proton spectrum had overlapping resonances, 2D experiments like $^1H-^1H$ TOCSY to identify the methylene resonances of complex **3**. 1D resonance assignments of uncomplexed **2** were not obtained, as it was not soluble in chloroform. The 1D ^{13}C spectrum of **3** was insufficient for complete resonance assignments. So carbon resonances having directly attached protons were identified from 2D $^1H-^{13}C$ gHSQC experiment. After obtaining all the necessary resonance assignments, the through-space $^1H-^1H$ interactions between **1** and **2** in complex **3** were identified with a NOESY experiment. The NOESY data confirmed the proposed structure of the complex.

The 1D ^1H spectra of **1** and **3**, shown in parts a and b of Figure 1, respectively, can be used to confirm the structures of the dendrimer and the host−guest complex. In the ^1H spectrum the resonance at 1.41 ppm is from H_1, while the broad hump at 1.58 ppm contains resonances from H_4, H_7, and H_{10}. Resonances from the equivalent terminal adamantyl groups (H_{16}, H_{14}, and H_{15}) appear at 1.67, 1.98, and 2.04 ppm, respectively. Resonances from all those protons that are two bonds away from the tertiary nitrogens (H_2, H_3, H_5, H_6, H_8, and H_9) appear at 2.39 ppm. The peak at 3.12 ppm is from the α-methylene of the adamantylurea group (H_{11}). In the ^1H spectrum of the complex (Figure 1b) many additional resonances appear as a result of incorporating the cyanobiphenyl guest (**2**) into the system. In the downfield region of the spectrum four doublets appear from the biphenyl moiety of the guest. There are three distinct resonances in the urea proton region at 6.31 (H_{11A}), 6.17 ($H_{8'}/H_{10'}$), and 5.64 ppm (H_{11B}). The triplet at 3.94 ppm is from the methylene group attached to the oxygen atom in the guest ($H_{2'}$). The singlet upfield

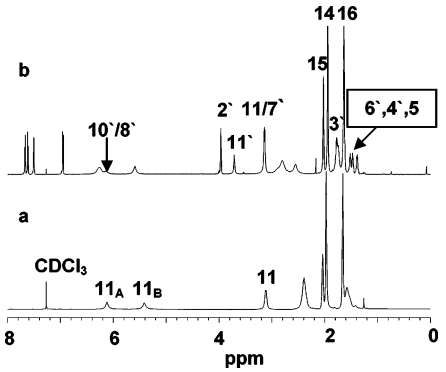

Figure 1. 1D proton spectra of dendrimer **1** (a) and complex **3** (b).

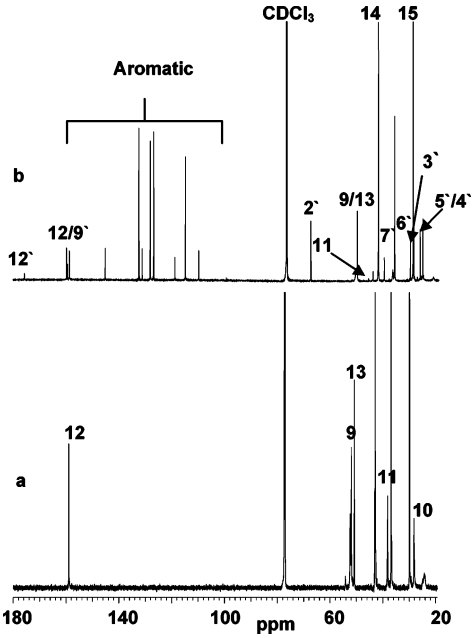

Figure 2. 188.6 MHz ^{13}C spectrum of the dendrimer **1** (a) and complex **3** (b).

of the $H_{2'}$ resonance at 3.82 ppm is the resonance $H_{11'}$. The broad hump at 3.16 ppm contains proton resonances of the outermost methylene group on the dendritic arm attached to the adamantylurea group (H_{11}) along with the $H_{7'}$ resonance of the guest. This is confirmed from the TOCSY and NOESY spectra. The broad peak at 3 ppm is attributed to H_9 along with some impurities. The downfield shift of H_9 is consistent with the protonation of the adjacent tertiary nitrogen by the introduction of carboxylic acid from the guest as suggested in the previous study of this system.[4] The positions of the three adamantyl resonances (H_{14}, H_{15}, and H_{16}) remain almost the same in the complex. All three of the adamantyl resonances appear as singlets due to the fact that the dihedral angles between the adamantyl protons are not suitable to produce resolvable *J*-coupling. The resonances at 1.76, 1.51, 1.46, and 1.38 ppm are the remaining methylene spacers of the guest molecule.

Owing to the greater dispersion of the ^{13}C chemical shifts, the resonances of some fragments that are not resolved in the ^1H spectrum are separated in Figure 2a. The resonances from C_4 and C_7 are at 24.37 ppm, but C_{10} appears slightly downfield at 28.2 ppm. The small peak at 24.93 ppm is the resonance from C_1. Four types

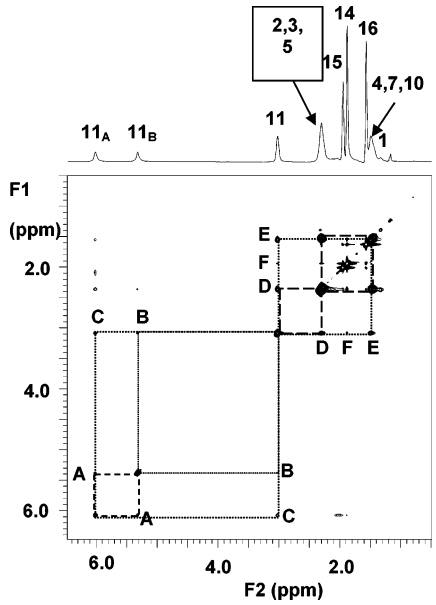

Figure 3. 400 MHz NOESY spectrum of dendrimer **1**.

of adamantyl carbon resonances appear at 29.97 (C_{15}), 36.89 (C_{16}), 43.02 (C_{14}), and 50.86 ppm (C_{13}). The resonance of C_{11} is at 38.25 ppm. Other resonances are resolved at 51.95 (C_9), 52.45 (C_3, C_5, C_6, and C_8) and 159.02 ppm (C_{12}). The ^{13}C spectrum of the complex **3** in Figure 2b clearly shows all the aliphatic carbon resonances of the host **2**. The downfield resonance at 68.17 ppm is from $C_{2'}$ while the peak at 44.85 ppm is the resonance of $C_{11'}$.The rest of the resonances of the methylene protons of the aliphatic spacer in **2** appear at 40.57 ($C_{7'}$), 30.78 ($C_{6'}$), 29.44 ($C_{3'}$), 27.08 ($C_{5'}$) and 26.14 ppm ($C_{4'}$).

The $^1H-^1H$ NOESY spectrum (Figure 3) of the dendrimer confirms some of the assignments made by simple inspection of the 1D proton spectrum. The urea protons (11_A and 11_B), apart from showing cross-peaks between each other's resonances (cross-peaks A), exhibit cross-peaks B and C with the resonances of the adjacent methylene protons (H_{11}). Also, the H_{11} resonances show correlations with the resonances of H_9 and H_{10}, cross-peaks D and E, respectively. Interestingly, the presence of cross-peak F, between H_{11} and H_{14} resonances, indicates that the neighboring arms are in close proximity to each other as intra-arm $H_{11}-H_{14}$ is only possible in the highly unfavorable s-cis/s-cis conformation about the two C−N bonds of the urea moiety.

The $^1H-^1H$ TOCSY spectrum of the complex (Figure 4) shows cross-peaks among the resonances of all the protons belonging to the same spin system, and is very helpful in identifying resonances from long sequences of coupled protons. The resonances of the aliphatic spacers in the guest molecules ($H_{2'}-H_{7'}$) can be distinguished from other proton resonances by the TOCSY spectrum. As expected from the structure, the $H_{2'}$ resonance shows TOCSY correlations with the resonances from the rest of the methylene spacers. Similarly, the $H_{7'}$ resonance also yields cross-peaks with the resonances other protons within the ^1H spin system of its spacer. Also, the adamantyl protons (H_{14}, H_{15}, and H_{16}) yield strong TOCSY cross-peaks, even though *J*-couplings among these protons' resonances are not resolved in the ^1H 1D spectrum. The most interesting cross-peaks are A and B, which correlate the resonances

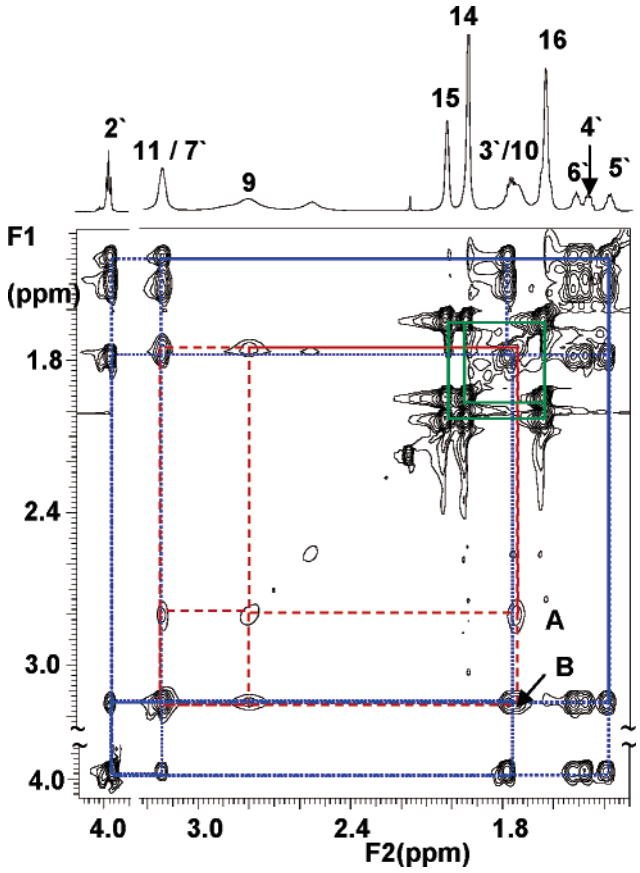

Figure 4. 750 MHz $^{1}H-^{1}H$ TOCSY spectrum of complex **3**.

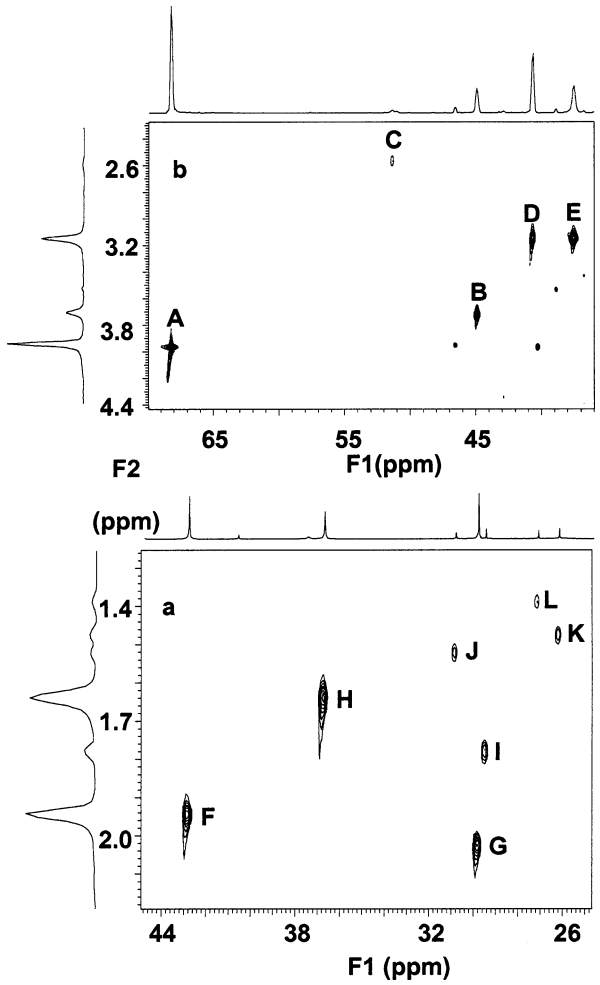

Figure 5. 750 MHz $^{13}C-^{1}H$ gHSQC spectrum of the complex **3**: upfield region (a) and downfield region (b).

of H_9 and H_{11} with H_{10}, confirming their assignments. Therefore, both H_9 and H_{10} are shifted downfield upon complexation of guest, consistent with protonation of the amine nitrogen next to H_9.

The 2D $^{1}H-^{13}C$ gHSQC spectrum (Figure 5a,b) correlates the resonances of the protons with those of directly attached carbons. Since the carbon resonances are more disperse, it is easier to distinguish some of the resonances having very similar ^{1}H resonance frequencies. The proton resonances of the first and last methylene groups of the guest ($H_{2'}$ and $H_{11'}$) are within 0.15 ppm, but the ^{13}C peaks are well separated. Cross-peaks A and B in Figure 5b are the gHSQC correlations of C−H fragments 2′ and 11′, respectively. The low-intensity cross-peak C is from the methylene fragment 9 in **1**. The downfield shift of H_9 as a result of protonation of the adjacent methylene is evident from this spectrum. The adamantyl resonances can be readily identified from the gHSQC spectrum. The resonances of $H_{7'}$ and H_{11} are very close to each other, but they can be distinguished by the help of the gHSQC spectrum. From the analysis of the ^{13}C spectrum of **1** in Figure 2a, it is known that C_{11} appears near 37 ppm, so cross-peak E is the one bond correlation of the fragment $C_{11}-H_{11}$ while D is that of $C_{7'}-H_{7'}$. This is in accordance with the interpretation of the $^{1}H-^{1}H$ TOCSY data described above. In Figure 5a, the proton resonance at 1.62 ppm (H_{16}) is correlated with 36.69 ppm in the ^{13}C chemical shift dimension; therefore, the resonance of C_{16} is at 36.69 ppm (cross-peak H). Similarly, the two other gHSQC correlations F and G can be attributed to C_{14} and C_{15}, respectively. Cross-peaks I, J, K, and L are the gHSQC correlations of the C−H fragments of the inner methylenes 3′, 6′, 4′, and 5′, respectively. The gHSQC spectrum establishes the assignments of most of the resonances in the upfield region of the ^{13}C spectrum (Figure 2b) of complex **3**. The resonance assignments are summarized in Table 1.

Segments from the NOESY spectrum of **3** (Figures 6 and 7) are most important in this study as they reveal the specific H−H interactions associated with complexation between the host and the guest. Figure 6 shows the NOE interactions of the protons bound to nitrogen atoms in **3**. The resonances of urea type N−H protons in the dendrimer (H_{11A} and H_{11B}) apart from showing cross-peaks among themselves (B) also exhibit cross-peaks with the resonances of the other N−H protons (A and C). The only other urea type groups present in the system are the N−H protons ($H_{10'}$ and $H_{8'}$) situated at the acidic end of the guest molecules. This is consistent with the close proximity of urea type protons **1** and **2**. However, this is not unequivocal evidence as the cross-peaks could be produced by chemical exchange of the amide protons.

The urea proton resonances of **1** also exhibit cross-peaks (D and E) with the resonances of the methylene group situated in between the acidic and urea moiety of the guest ($H_{11'}$). This is definitive evidence for a binding model having the carboxylic acid end groups of the guest molecules encapsulated within pockets near the surface of the dendritic host, as they are correlations between nonexchangeable protons on the host and guest molecules. Cross-peaks F and G are consistent with

Table 1. Resonance Assignments of 1 and 2 in Complexed and Uncomplexed States[a]

		uncomplexed		complexed	
molecule	atom no.	δ_C	δ_H	δ_C	δ_H
1	1	24.93	1.41		
	2	54.52	2.39		2.56
	3	52.45	2.39		2.56
	4	24.37	1.58		1.75
	5	52.45	2.39		2.56
	6	52.45	2.39		2.56
	7	24.37	1.58		1.75
	8	52.45	2.39		2.56
	9	51.95	2.39	51.36	2.8
	10	28.2	1.58		1.76
	11	38.41	3.12	37.42	3.14
	11A		6.12		6.27
	11B		5.41		5.59
	12	159.02		159.89	
	13	50.86		50.72	
	14	43.02	1.98	42.79	1.94
	15	29.97	2.04	29.76	2.02
	16	36.89	1.67	36.69	1.64
2	1′			119.02	
	2′			68.17	3.96
	3′			29.44	1.78
	4′			26.14	1.47
	5′			27.08	1.38
	6′			30.78	1.52
	7′			40.57	3.14
	8′				6.14
	9′			159.54	
	10′				6.14
	11′			44.85	3.71
	12′			175.72	

[a] Uncomplexed **2** data are not available due to its poor solubility in $CDCl_3$.

intermolecular interactions between H_9 and H_{10}, respectively, of **1** and urea protons ($H_{8'}$ and $H_{10'}$) of **2**. However, it is important to realize that these cross-peaks among N−H protons might also arise from chemical exchange.

Further evidence for complexation is evident from intermolecular NOESY interactions between nonexchangeable protons, shown in the expansion of the 1.3−4.1 ppm region from the NOESY spectrum (Figure 7). This spectrum is expanded to clearly distinguish the closely spaced cross-peaks from one another. Cross-peaks A, B, and C arise from the close proximity of $H_{11'}$ of **2** and the peripheral methylene protons H_{11}, H_{10}, and H_9 of the dendrimer, respectively. In this orientation, the methylene group at the polar end of the aliphatic spacer of **2** (i.e., $H_{7'}$), should approach the adamantly protons of **1**. This intermolecular interaction is confirmed by NOESY cross-peaks D, E, and F between the resonance of $H_{7'}$ and the resonances of H_{14}, H_{15}, and H_{16}, respectively. Similarly, cross-peak G is evidence for the proximity of H_{14} and $H_{6'}$.

Cross-peaks in this figure, from intramolecular NOE interactions, also support some of the resonance assignments made above. For example, cross-peaks I and H originate from the NOE interactions of H_{10} with H_9 and H_{11}, respectively, consistent with the previous assertion that H_{10} is shifted downfield in the complex. Similarly, cross-peaks J and K from the methylene spacers of the guest confirm that one of these methylene resonances is around 3.15 ppm ($H_{7'}$). Intramolecular NOESY cross-peaks M and N result from interactions between H_{15}−H_{16} and between H_{14}−H_{16}, respectively. Finally, cross-peaks L, O, and P result from the interactions among the aliphatic spacers of **2**. Cross-peak L is the only NOE

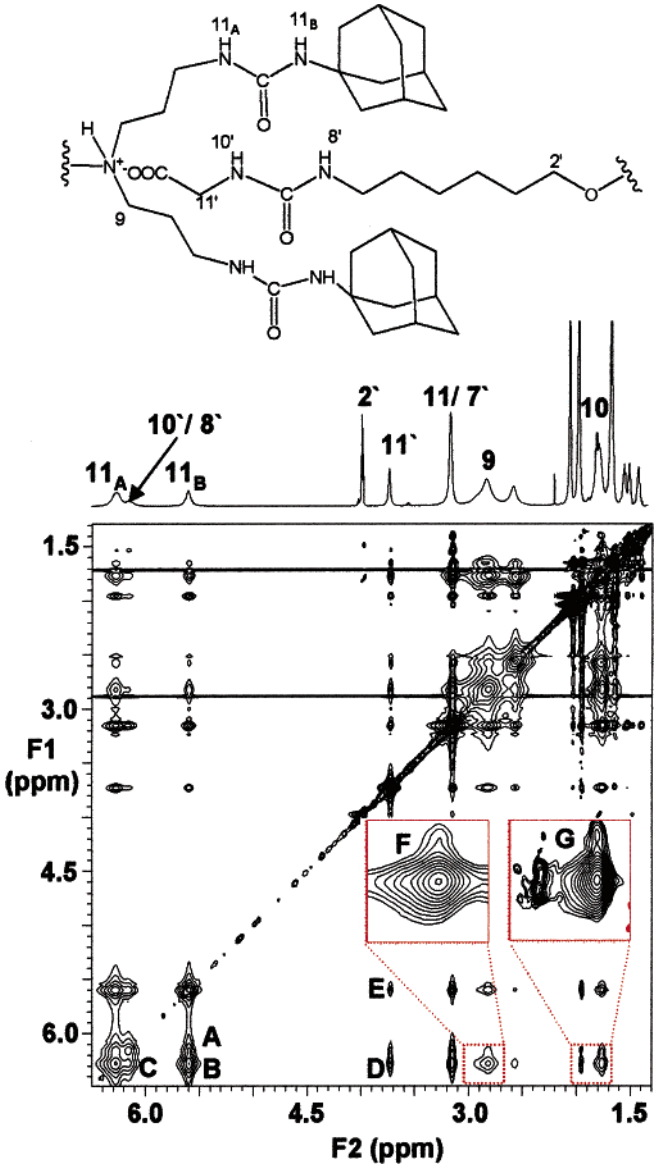

Figure 6. 750 MHz $^1H-^1H$ NOESY spectrum of complex **3**.

interaction of $H_{2'}$, and hence it must be the interaction with the protons on next methylene group in the chain, i.e., $H_{3'}$. The $H_{3'}$ resonance exhibits two other NOESY cross-peaks O and P, of which O is more intense. Cross-peak O is due to interaction with the neighboring methylene $H_{4'}$, while the less intense cross-peak P arises from the interaction of $H_{3'}$ and $H_{5'}$.

Conclusions

High field 2D-NMR (750 MHz) provides the necessary dispersion to resolve all the resonances in the supramolecular assembly **3**. Complete resonance assignments of the host **1** and guest **2** fragments in the complex **3** have been made. NOESY data provided information about close approach of specific structure fragments on the host and guest molecules in the supramolecular assembly. These intermolecular interactions support a specific binding model for the formation of a stable host−guest complex. The dispersion in the 750 MHz NOESY spectrum is better than data presented in earlier work[4] with this complex, permitting the identification of many specific NOE interactions between the dendrimer and the cyanobiphenyl guest. Overall, the

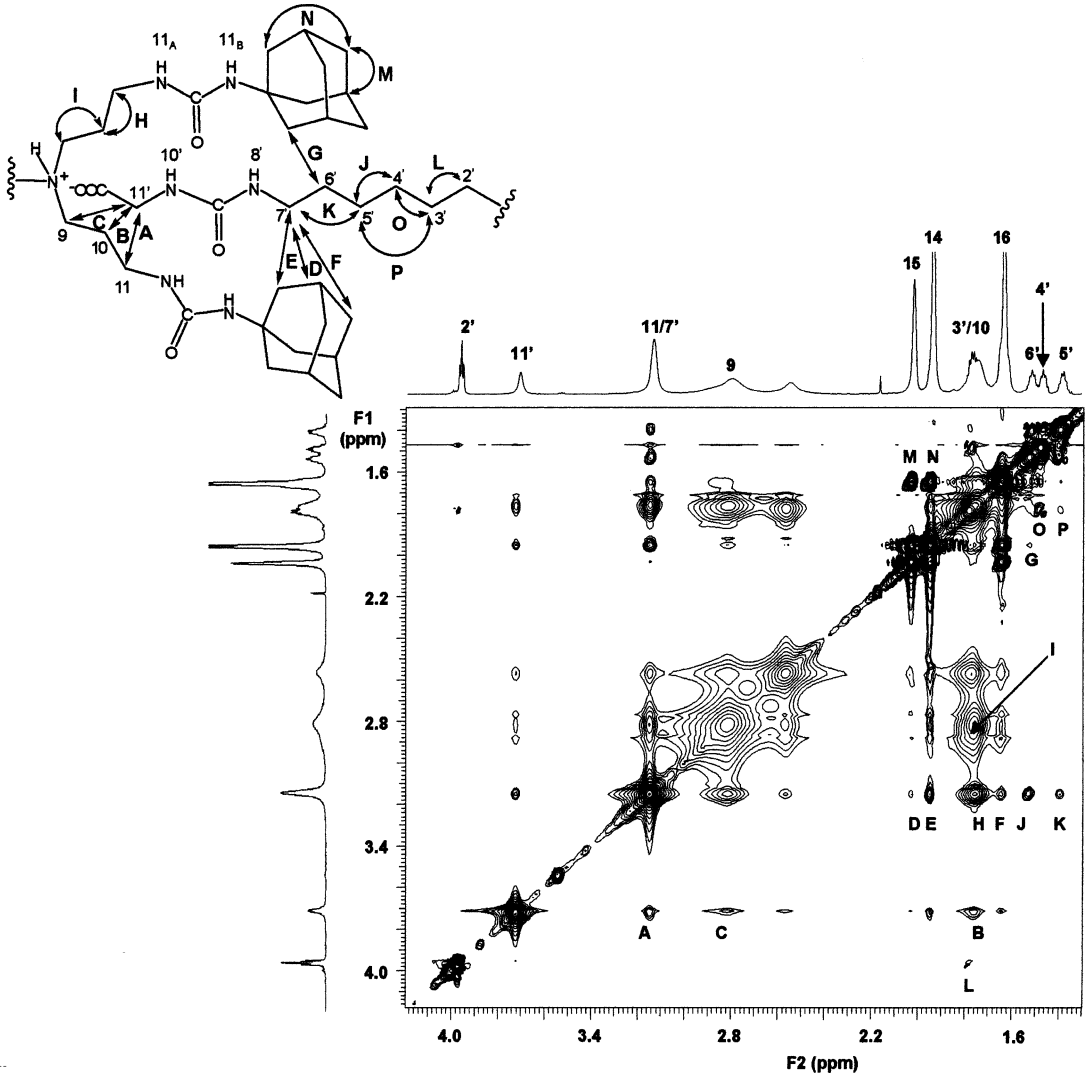

Figure 7. Expansion of the high field region from the 750 MHz $^1H-^1H$ NOESY spectrum of complex **3**.

NOESY data presented support the conclusions of previous work and give further evidence and insight into the host−guest interaction.

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