Chapter 3

The Construction of Novel 1:3 Supramolecular Complex Formed from a Homotritopic Molecule and DB24C8 as a Core Architecture for Self-Assembling Dendrimers

3.1. Introduction

The beauty and efficiency of self-assembling processes are results of association of complementary units through noncovalent bonding interactions (hydrogen bonding, electrostatic, hydrophobic-hydrophilic, π-π stacking interactions, etc.) leading to thermodynamically stable suprastructures. Such self-assembling phenomena build up the fundamental frameworks of well-known biological suprastructures, *e.g.*, the tobacco mosaic virus (TMV) and DNA.[1-4] It is a great challenge for synthetic chemists to mimic such methodology to design and prepare highly ordered supramolecular architectures. Stoddart and his coworkers have successfully employed the complexation of dialkylammonium salts with dibenzo-24-crown-8 (DB24C8) to spontaneously self-assemble several supramolecular architectures.[5,6] The versatile nature of this self-assembling approach inspired us to create a core architecture for dendritic materials whose potential utility has caused a significant surge of interest in the last decade.[7-9]

The main building block (**4**)[10] for the core architecture has three arms extending from the central benzene ring (Figure 3.1). Each arm contains a dialkylammonium salt moiety that is capable of binding with DB24C8 to form the 1:3 complex (**2**) (Figure 3.2). In this chapter, we describe the construction of **5** from the homotritopic molecule **4** and DB24C8 in solution. The structural integrity of **5** was demonstrated by ^{1}H NMR spectroscopy and mass spectrometry.

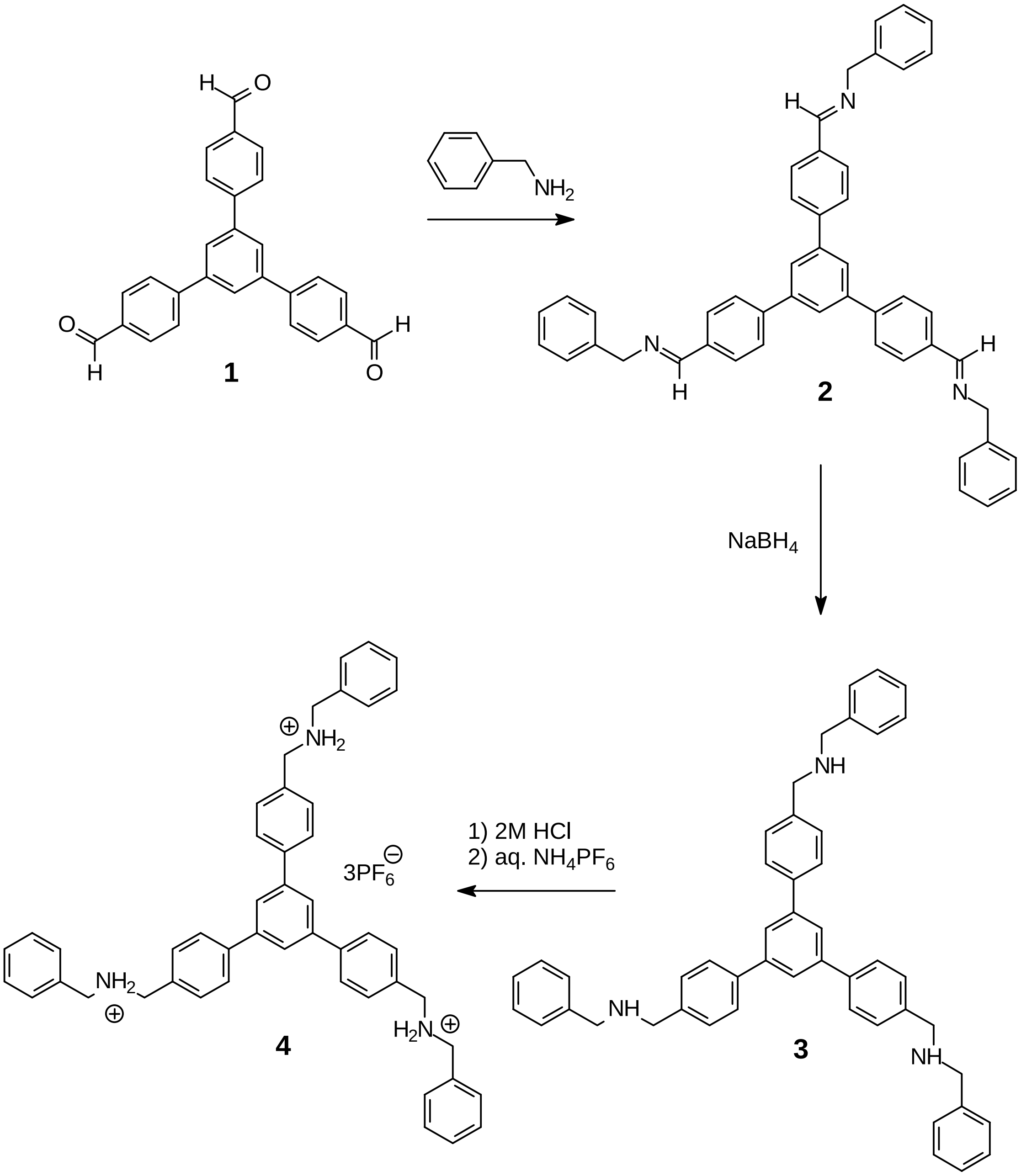


Figure 3.1. Synthesis of **4**.

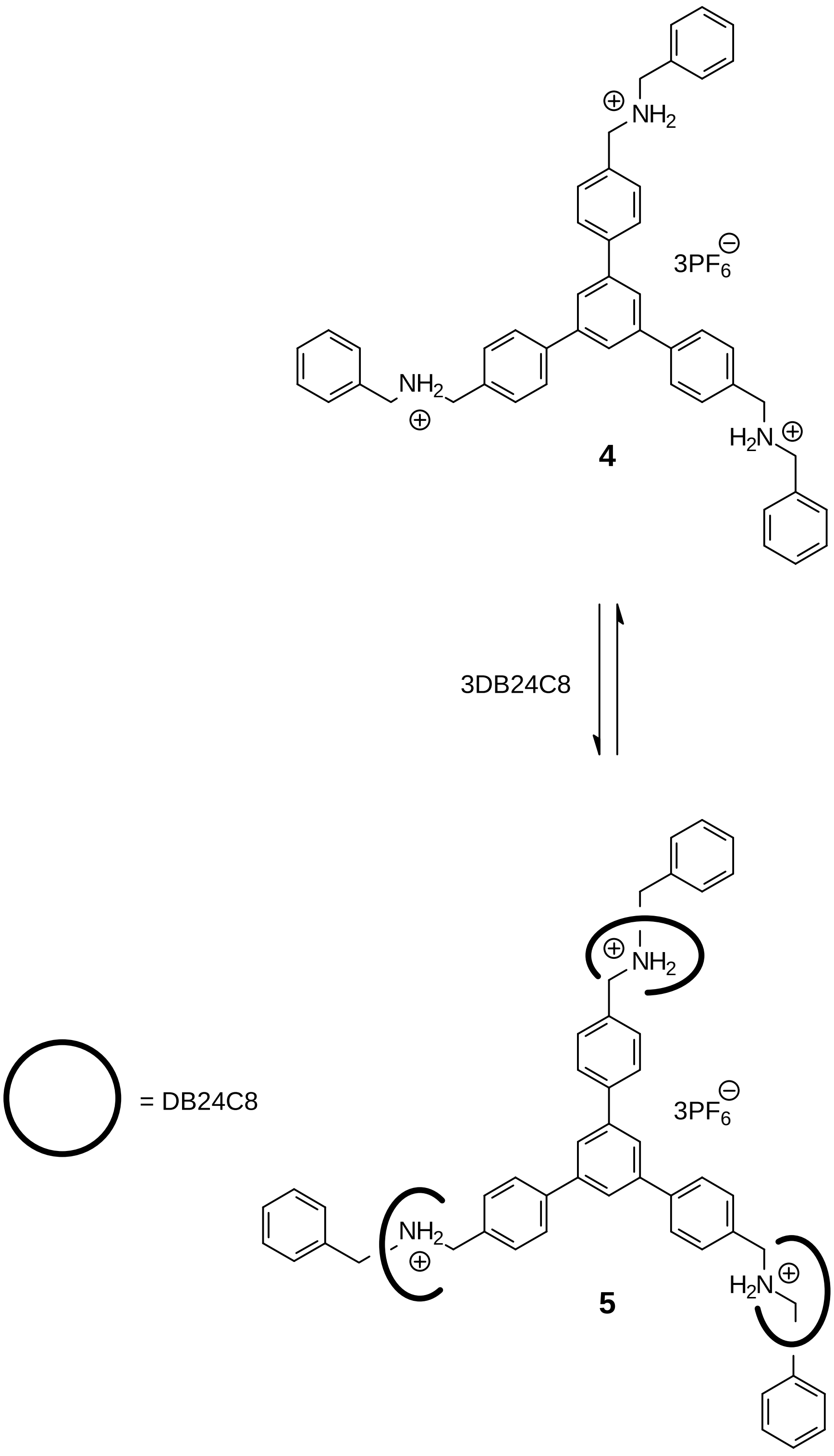


Figure 3.2. Construction of the 1:3 complex (**5**).

3.2. Results and Discussion

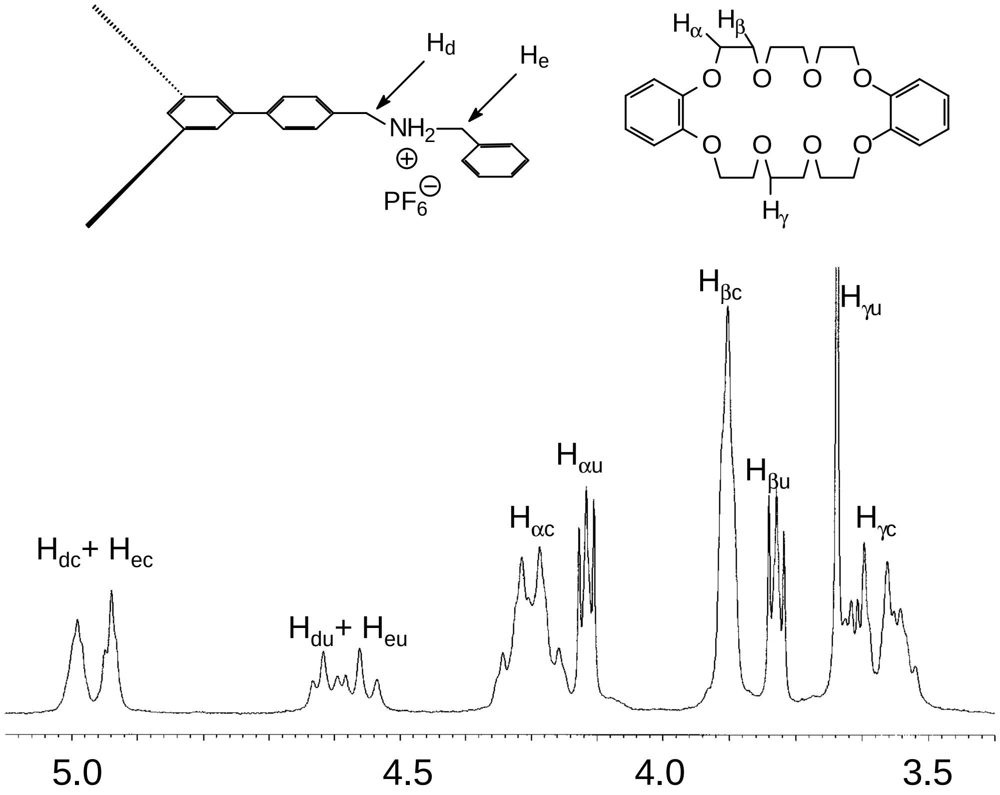
3.2.1. Synthesis

1,3,5-Tris(*p*-formylphenyl)benzene (**1**)[11] was refluxed with benzylamine in a mixture of toluene and DMAC to give **2**. The ^{1}H NMR spectrum **2** showed a typical signal for the imine proton at 8.47 ppm. **2** was then reduced to **3** using sodium borohydride. The ^{1}H NMR spectrum of **3** showed two singlets corresponding to the two nonequivalent benzyl protons at 3.86 and 3.88 ppm. Acidification of **3** with 2M HCl, followed by ion exchange afforded the homotritopic molecule **4**. The two singlets for the benzyl protons were significantly shifted downfield due to the cation formation. **4** exhibited good solubility in acetone and acetonitrile but not in halogenated solvents such as chloroform and methylene chloride.

CPK molecular modeling of the 1:3 complex (**5**) revealed that all three ammonium salt moieties in **4** are apart from one another, enabling the complete complexation with DB24C8 to form **5**.

3.2.2. Complexation studies in solution

The aliphatic region of ^{1}H NMR spectrum of a solution of the homotritopic molecule **4** and DB24C8 in acetone-d_6 (1.0 x 10^{-2} M/3.0 x 10^{-2} M) shows four different sets of signals for free DB24C8, complexed DB24C8, free ammonium salt moiety, and complexed ammonium salt moiety (Figure 3.3). This is attributed to slow association and dissociation between **4** and DB24C8 on the ^{1}H NMR time scale. The signal assignments were made with the aid of the COSY spectrum (Figure 3.4). The signals for $H_{\alpha c}$ and $H_{\beta c}$ shifted downfield from those for $H_{\alpha u}$ and $H_{\beta u}$ by 0.072 and 0.070 ppm, respectively. In contrast, the signal for $H_{\gamma c}$ shifted upfield and emerged as a broad multiplet. The signal pattern changes observed for $H_{\alpha c}$, $H_{\beta c}$, and $H_{\gamma c}$ can be understood easily. As illustrated in Figure 3.5 when DB24C8 is complexed with the ammonium salt moiety, there are six nonequivalent ethyleneoxy protons for complexed DB24C8. For example, as illustrated in Figure 3.5 at the α position of complexed DB24C8 there are two nonequivalent protons, *i.e.*, $H_{\alpha 1c}$ and $H_{\alpha 2c}$, due to the two neighboring arms. Similarly, $H_{\beta 1c}$, $H_{\beta 2c}$, $H_{\gamma 1c}$, and $H_{\gamma 2c}$ are not in the same environment.



c=complexed, u=uncomplexed

Figure 3.3. The aliphatic region of ^{1}H NMR spectrum of solutions of **4** and DB24C8 (1.0 x 10^{-2}/3.0 x 10^{-2} M) (400 MHz, acetone-d_6, 22^{o}C).

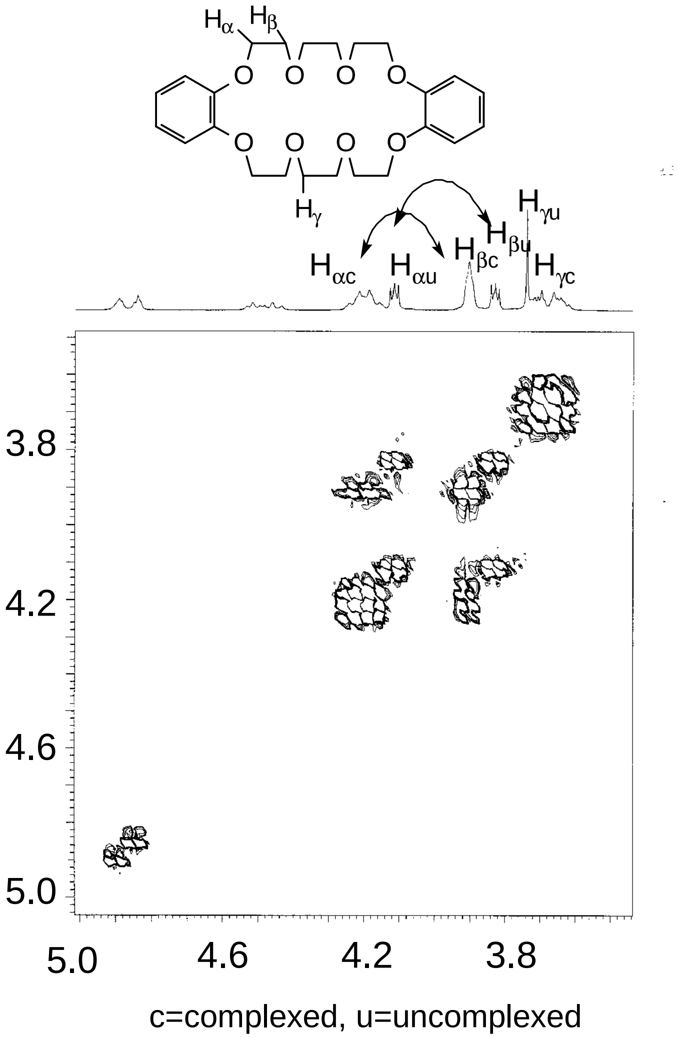


Figure 3.4. The aliphatic region of the COSY spectrum of solutions of **4** and DB24C8 ($1.0 \times 10^{-2}/3.0 \times 10^{-2}$ M) (400 MHz, acetone-d_6, 22°C).

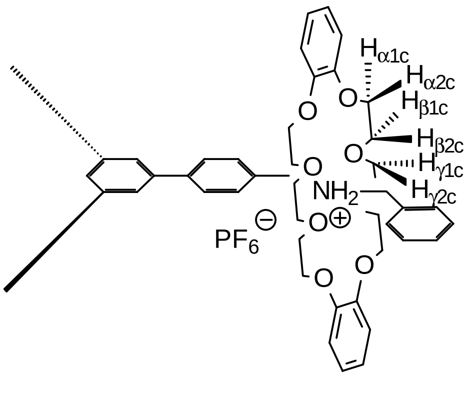


Figure 3.5. Representation of the complexation site between the ammonium salt moiety of **4** and DB24C8.

Figure 3.6 shows the aromatic region of the ^1H NMR spectrum of a solution of **4** and DB24C8 (1.0 x 10^{-2}/3.0 x 10^{-2} M). In addition, the COSY spectrum (Figure 3.7) was obtained to assign the peaks properly. The coupling interactions are depicted in Figure 3.7, showing the footsteps for the complete signal assignment. The signal for the internal 2,4,6-protons of the core benzene ring, H_{au}, appeared at 7.98 ppm and the signal for H_{ac} shifted upfield to 7.66 ppm after complexation. Presumably, the H_{ac} protons are situated in the shielded region of the catechol unit of complexed DB24C8 in **5**, resulting in a significant upfield chemical shift for H_{ac}. The intensity of the signal for H_{au} gradually decreased with increased concentration of DB24C8 and eventually disappeared when 9 equivalents of DB24C8 was added. In contrast, the intensity of the signal for H_{ac} showed a steady increase as the concentration of DB24C8 was increased.

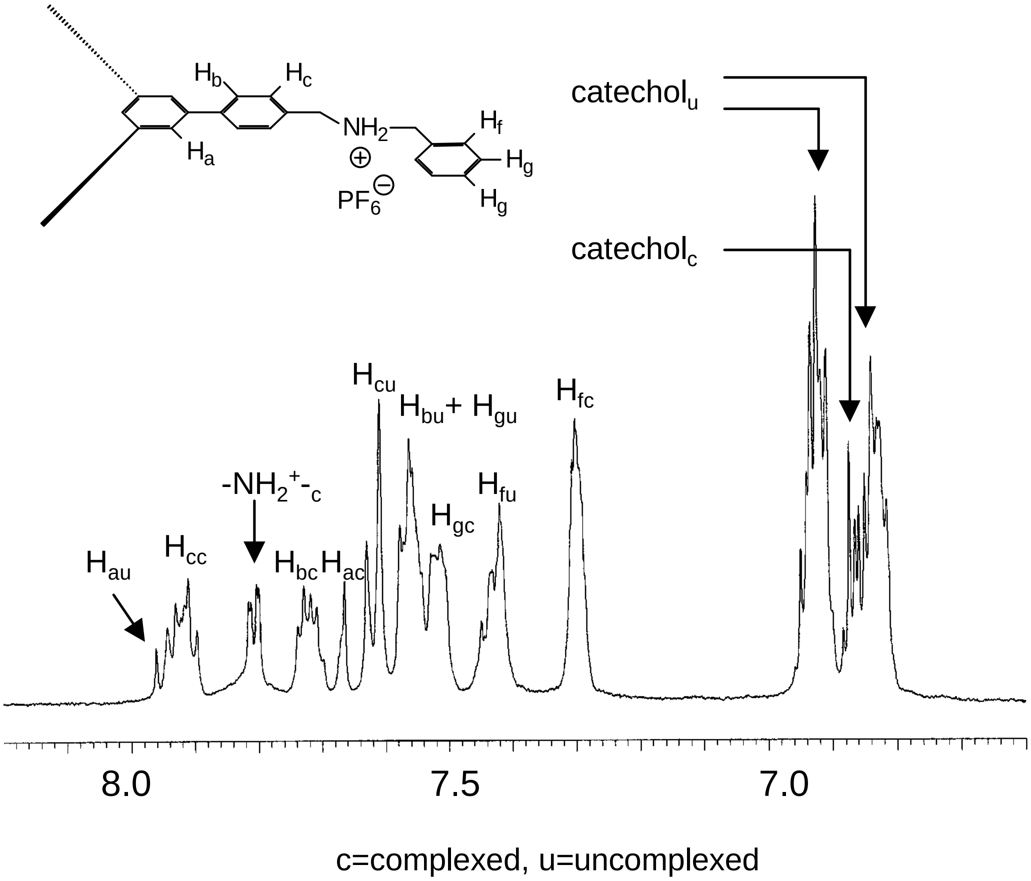


Figure 3.6. The aromatic region ^1H NMR spectrum of solutions of **4** and DB24C8 (1.0 x 10^{-2}/3.0 x 10^{-2} M) (400 MHz, acetone-d_6, 22°C).

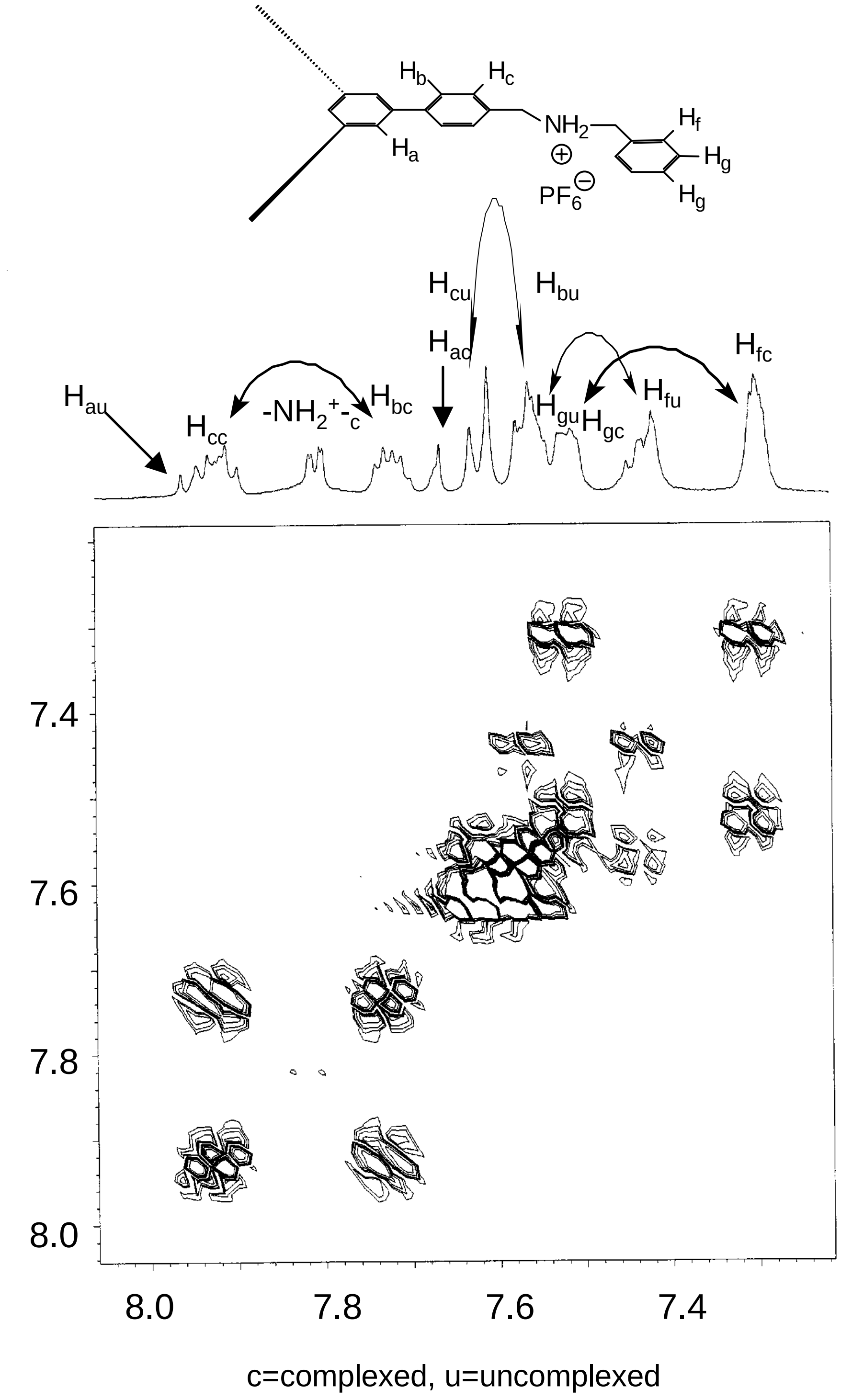


Figure 3.7. The aromatic region of the COSY spectrum of solutions of **4** and DB24C8 ($1.0 \times 10^{-2}/3.0 \times 10^{-2}$ M) (400 MHz, acetone-d_6, 22°C).

The most intriguing observation in the ^{1}H NMR spectra of solutions of **4** and DB24C8 is perhaps the behavior of the signals for H_{du} and H_{eu} (Figure 3.8). Two sharp singlets corresponding to H_{du} and H_{eu} shifted upfield and disintegrated into broader multiplets with increasing concentration of DB24C8 and eventually disappeared with 9 equivalents of DB24C8. The complication of the signals for H_{du} and H_{eu} is probably due to the existence of the 1:1 and 1:2 complexes. As illustrated in Figure 3.9 when one of the arms is occupied with DB24C8, the two initially equivalent H_e protons and the two H_d protons become non-equivalent (diastereotopic), meaning that there is a total of four nonequivalent benzyl protons, H_{d1u}, H_{d2u}, H_{e1u}, and H_{e2u}. When two of the arms are complexed with DB24C8, the two H_{du} protons and two H_{eu} protons are equivalent as shown in Figure 3.10. The gradual upfield signal shifts observed for H_{du} and H_{eu} are the result of the increased concentration of PF_6^- ion with respect to uncomplexed ammonium salt moiety, *i.e.*, ion pairing. The association constant (K_a) for the 1:3 complex was estimated to be 2.1 x 10^7 M^{-3} in actone-d_6 from the integration of the complexed and uncomplexed signals in the relevant ^{1}H NMR spectra and the expression K_a=[1:3 complex]/[**4**]$\cdot$[DB24C8]^3.

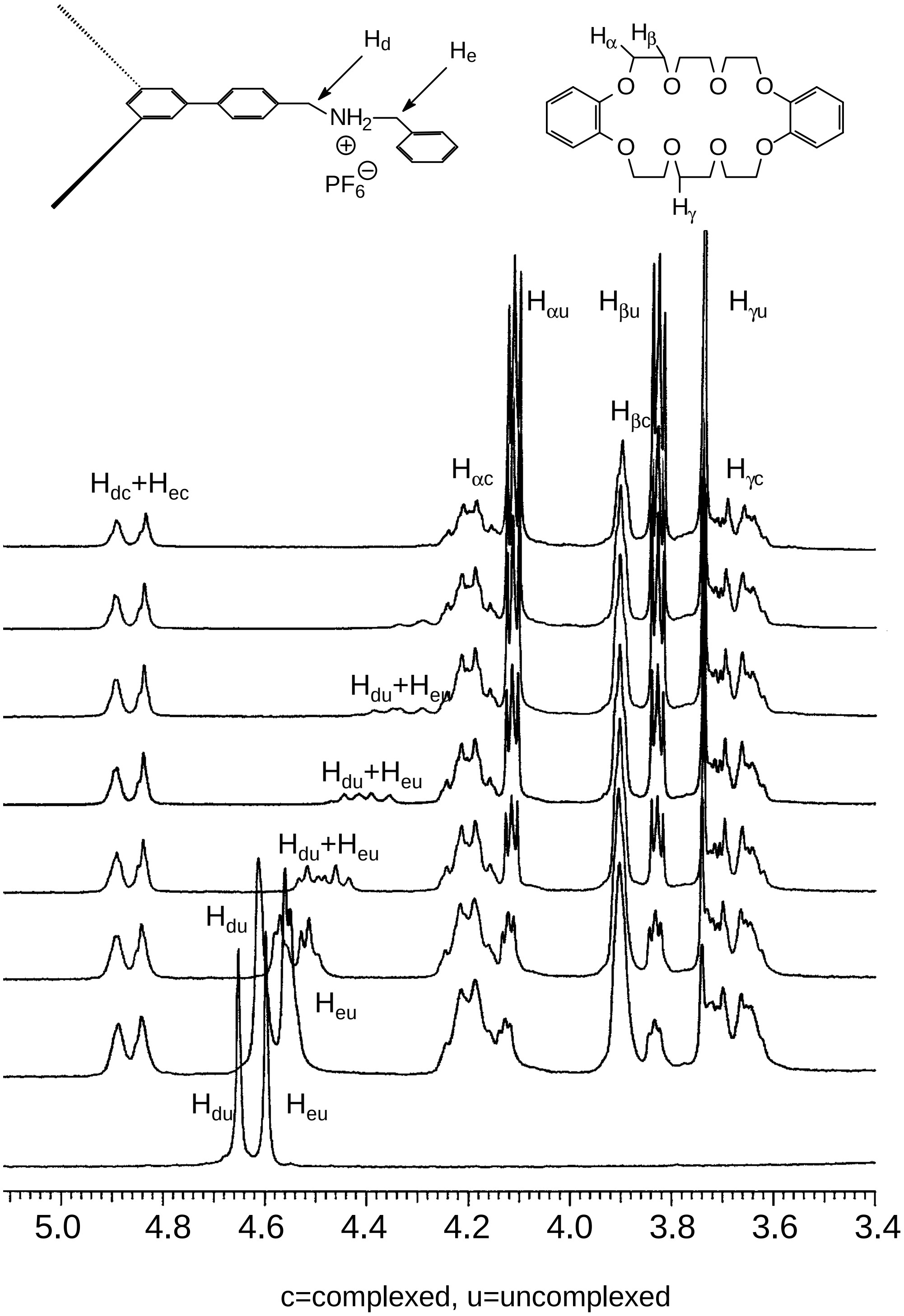


Figure 3.8. The stacked ^{1}H NMR spectra of a 1.0 x 10^{-2} M solution of **4** mixed with a) 0, b) 1.0 x 10^{-2}, c) 2.0 x 10^{-2}, d) 3.0 x 10^{-2}, e) 4.0 x 10^{-2}, f) 5.0 x 10^{-2}, g) 6.0 x 10^{-2}, and h) 9.0 x 10^{-2} M solution of DB24C8 (400 MHz, acetone-d_6, 22^{o}C).

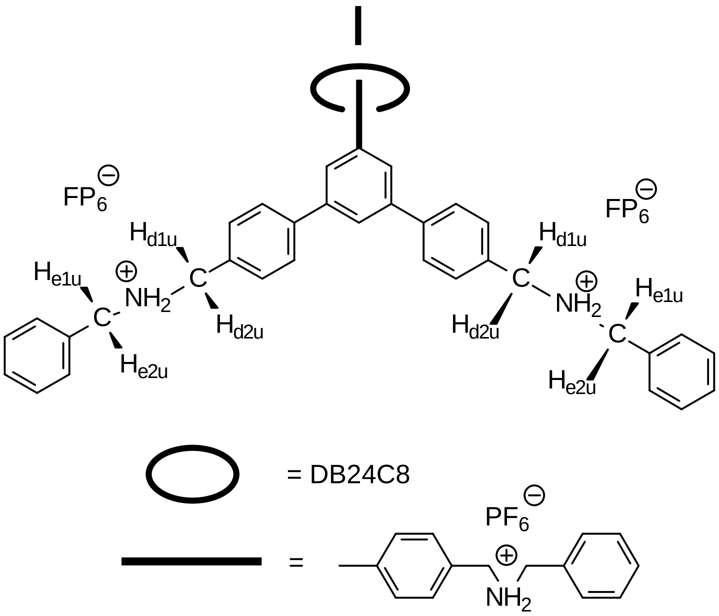


Figure 3.9. Representation of the H_{du} and H_{eu} protons in the 1:1 complex.

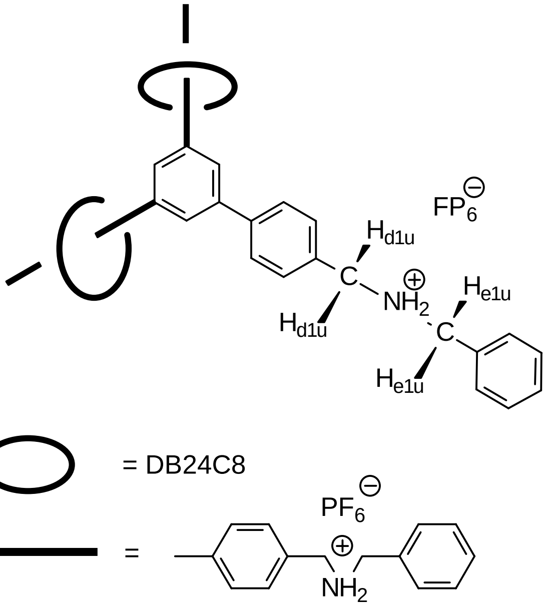


Figure 3.10. Representation of the H_{du} and H_{eu} protons in the 1:2 complex.

To gain further insight into the signal pattern changes observed for H_{du} and H_{eu} in the ^{1}H NMR spectra of solutions of **4** and DB24C8, one of the benzyl protons in the homotritopic molecule was deuterated to afford **9** and the ^{1}H NMR spectra of **9** and

DB24C8 were recorded in acetone-d_6. The synthetic approach employed is shown in Figure 3.11.

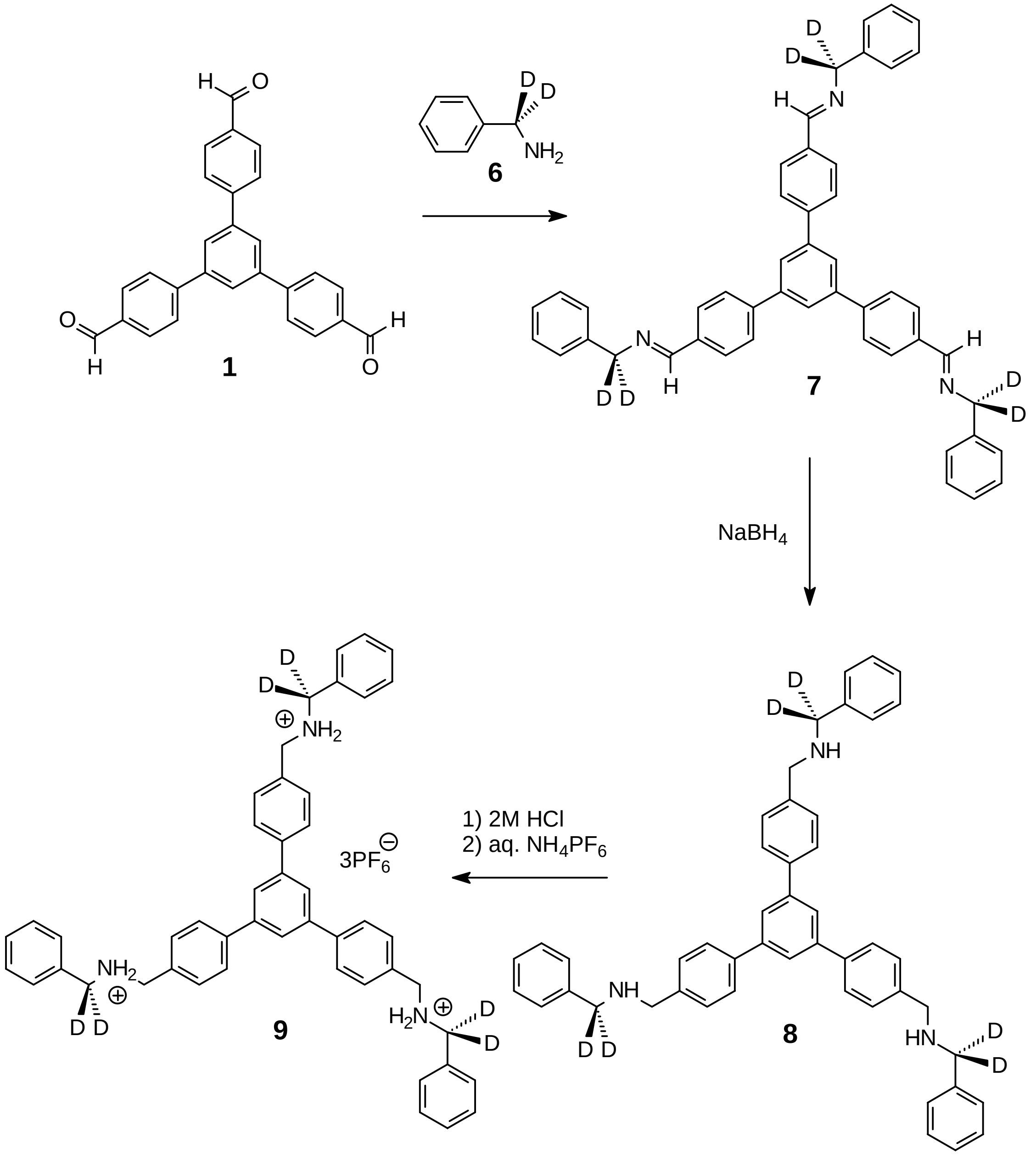


Figure 3.11. Synthesis of the deuterated homotritopic molecule **9**.

The ^{1}H NMR spectrum of **9** in acetone-d_6 (Figure 3.12b) revealed that the signal for the H_d proton is significantly shifted downfield with respect to that of **4** (Figure 3.12a). We believe that this downfield shift is due to the position of the PF_6^- counter ion in **9**. The ^{1}H NMR spectrum of solutions of **9** and DB24C8 (*e.g.*, Figure 3.13d) indicated four sets of signals corresponding to free DB24C8, complexed DB24C8, free ammonium salt moiety, and complexed ammonium salt moiety. Surprisingly, the signal for H_{du} did not shift upfield or change its shape with increased concentration of DB24C8 as we observed with **4** and DB24C8. The association constant (K_a) for the 1:3 complex of **9** and DB24C8 was calculated to be 1.7 x 10^{6} M^{-3} in actone-d_6 at 22°C. A slightly lower association constant for the 1:3 complex of **9** and DB24C8 compared to that of **4** and DB24C8 is presumably due to less acidic deuterium of ammonium salt moieties in **9**. At this moment, we are not able to rationalize the spectroscopic discrepancy between the deuterated and undeuterated systems.

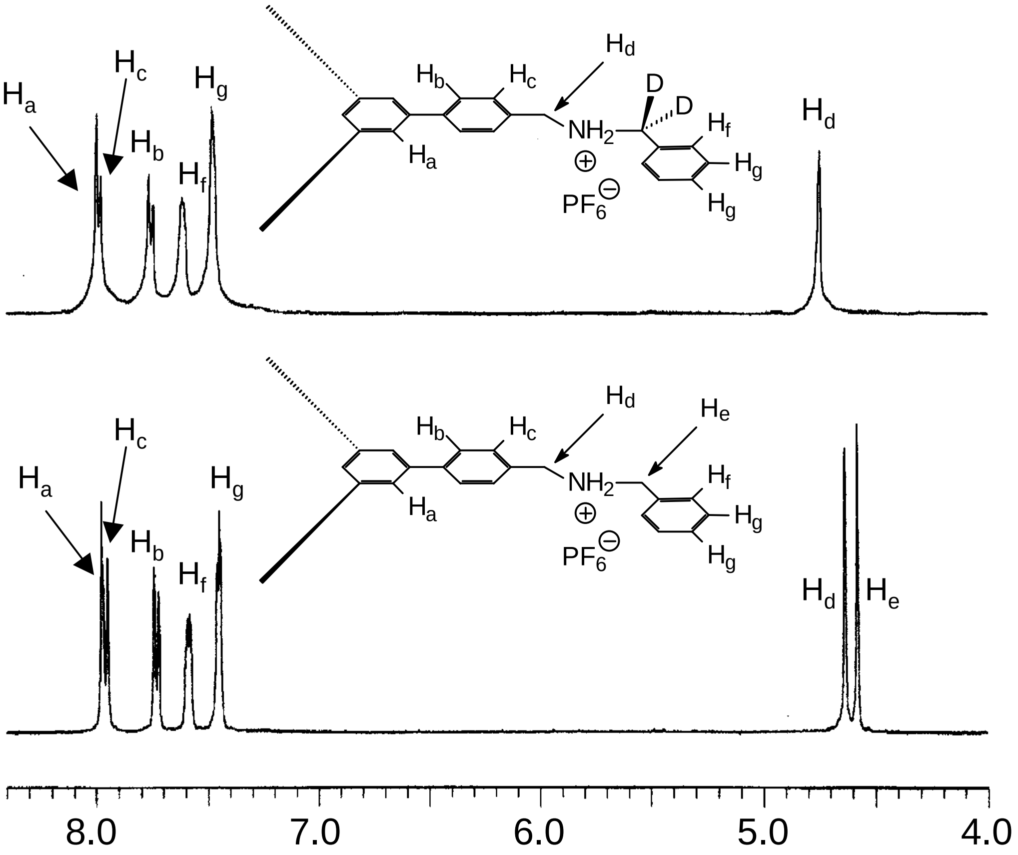


Figure 3.12. The ^{1}H NMR spectra of a 1.0 x 10^{-2} M solution of a) **4** and b) **9** (400 MHz, acetone-d_6, 22°C).

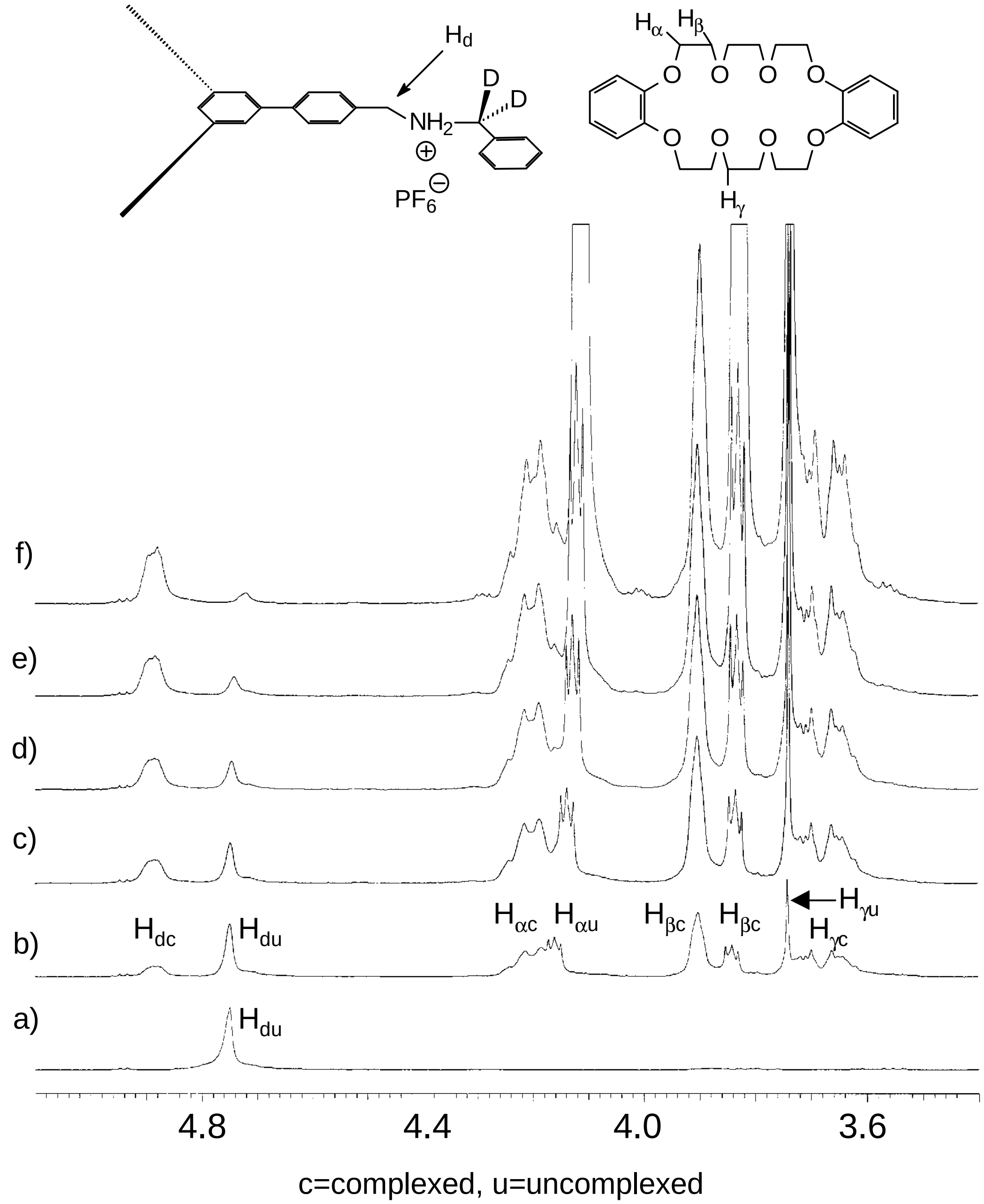


Figure 3.13. The stacked ^{1}H NMR spectra of a 1.0 x 10^{-2} M solution of **9** mixed with a) 0, b) 1.0 x 10^{-2}, c) 2.0 x 10^{-2}, d) 3.0 x 10^{-2}, e) 4.0 x 10^{-2}, and f) 9.0 x 10^{-2} solution of DB24C8 (400 MHz, acetone-d_6, 22°C).

Fast atom bombardment mass spectrometry (FABMS) confirmed the formation of the 1:3 complex. The sample for FABMS was prepared by slow evaporation of a solution of **4** and DB24C8 in chloroform at room temperature. The spectrum was recorded in the positive ion mode using 3-NBA (*meta*-nitrobenzyl alcohol) as the matrix.

The FABMS spectrum (Figure 3.14) exhibited a peak at *m*/*z*=2300.5 corresponding to the molecular ion of the 1:3 complex after the loss of a PF_6^- counter ion. The peak at *m*/*z*=1707.8 arises from the 1:2 complex with only one PF_6^- counter ion. The signals for the 1:1 complex both intact (*m*/*z*=1258.6) and after loss of PF_6^- (*m*/*z*=1112.6) were also observed.

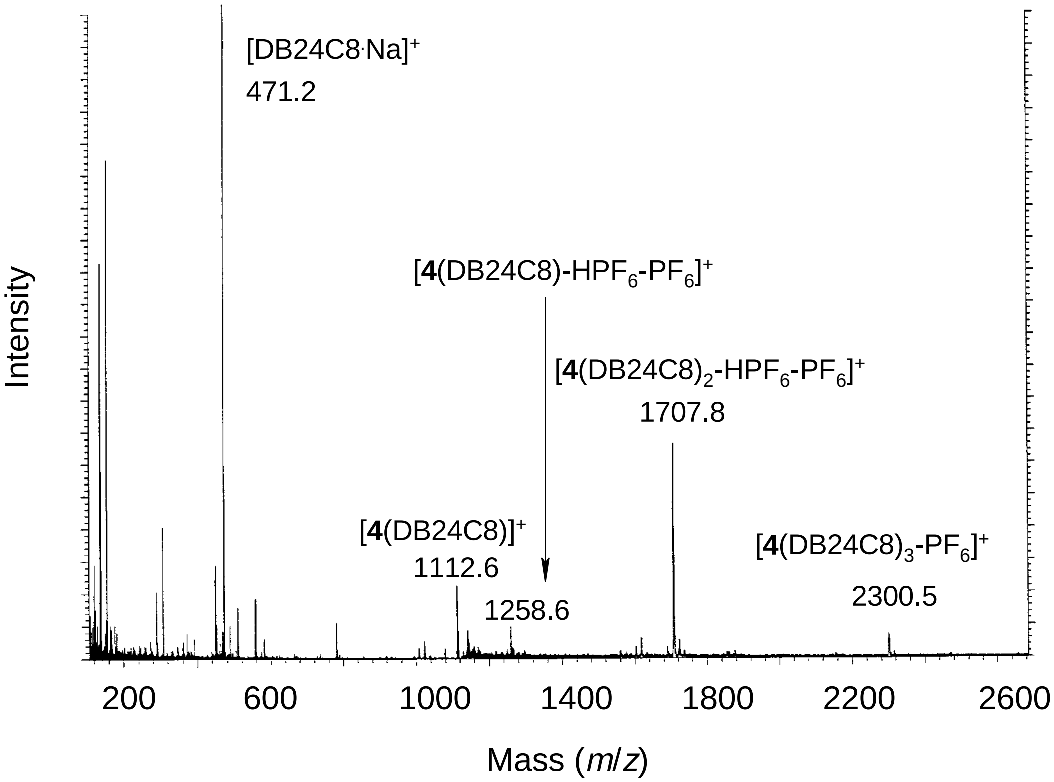


Figure 3.14. The FAB mass spectrum of the 1:3 complex.

3.3. Conclusion

The construction of a new class of pseudorotaxane architecture using simple molecular recognition of the homotritopic molecule **4** and DB24C8 was demonstrated in both solution and the gas phase. In chapter 4 we will describe the construction of self-assembling dendrimers utilizing the 1:3 complex as their core architecture.

3.4. Experimental

Tetrahydrofuran (THF) was distilled from Na and benzophenone. Pyridine and hexanes were stirred with CaH_2 overnight and distilled. All other solvents were used as received. The 400 MHz ^{1}H NMR spectra were recorded on a Varian Unity with tetramethylsilane (TMS) as an internal standard. The IR spectra were taken on a Nicolet Impact 400 infrared spectrometer using pulverized KBr as the medium. Elemental analyses were obtained from Atlantic Microlab, Norcross, GA. Mass spectra were provided by the Nebraska Center for Mass Spectrometry, Lincoln, Nebraska. 1,3,5-tris(*p*-formylphenyl)benzene (**1**) was prepared using the literature protocols.[11,12]

1,3,5-Tris[*p*-(benzyliminomethyl)phenyl]benzene (2).[10] To a 250 mL three neck round bottom flask equipped with a mechanical stirrer and a Dean-Stark trap were added **1** (263 mg, 0.673 mmol), benzylamine (238 mg, 2.22 mmol), and a mixture of toluene and DMAC (80 mL/20 mL). The reaction mixture was stirred and refluxed for 2 days. The solvent was evaporated and the resulting yellow solid was dissolved in THF and precipitated into dry hexane twice. The product was recrystallized from hexane to afford plate-like, slightly yellow crystals (310 mg, 74%), mp 173-178^{o}C. ^{1}H NMR (400 MHz, chloroform-*d*$_6$, 22^{o}C): δ=4.87 (s, 6H), 7.27 (m, 6H), 7.36 (m, 9H), 7.81 (d, 6H, J = 8.4 Hz), 7.84 (s, 3H), 7.91 (d, 6H, J = 8.4 Hz), and 8.47 (s, 3H). LRFAB: m/z=658 $[M]^+$. Anal. calcd for $C_{48}H_{39}N_3$: C, 87.64; H, 5.98; N, 6.31, found: C, 87.52; H, 6.03; N, 6.31.

1,3,5-Tris[*p*-(benzylaminomethyl)phenyl]benzene (3).[10] To a 100 mL one neck round bottom flask were added **2** (127 mg, 0.193 mmol) and MeOH (30 mL). $NaBH_4$ (42.8 mg, 1.16 mmol) was added portionwise to the suspension over a period of 20 min and the reaction mixture was refluxed for 15 h, cooled and diluted with 5 mL of H_2O. The white solid obtained after evaporation of the solvent was suspended in H_2O and extracted with CH_2Cl_2 (10 mL x 2). The organic layers were combined and concentrated to give a colorless liquid (70.9 mg, 55% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.86 (s, 6H) 3.88 (s, 6H), 7.27 (m, 6H), 7.36 (m, 9H), 7.46 (d, 6H, J = 8.4 Hz) 7.67 (d, 6H, J = 8.4 Hz), and 7.77 (s, 3H).

1,3,5-Tris[*p*-(benzylammoniomethyl)phenyl]benzene Tris(hexafluorophosphate) (4). To a 25 mL one neck round bottom flask was added **3** (70.9 mg, 0.108 mmol) and 2M HCl (2 mL). The solution was stirred at 25°C for 10 h. The solvent was rotary evaporated to afford a white solid, which was dissolved in H_2O (65 mL). To this solution was added aq. NH_4PF_6 at 0°C. Soon after the addition the mixture became cloudy and it was further stirred for 1 h and placed in a centrifuge to isolate a white solid, which was then recrystallized from H_2O to afford a white solid (52.0 mg, 90% yield), mp 226-227°C (lit.[10] mp decomp 139°C). ^{1}H NMR (400 MHz, acetone-d_6, 22°C): δ=4.58 (s, 6H), 4.64 (s, 6H), 7.45 (m, 9H), 7.58 (m, 6H), 7.73 (d, 6H, J = 8.4 Hz), 7.96 (d, 6H, J = 8.4 Hz), and 7.80 (s, 3H). LRFAB: m/z=810 $[M\text{-}HPF_6\text{-}PF_6]^+$, 664 $[M\text{-}2HPF_6\text{-}PF_6]^+$. Anal. calcd for $C_{48}H_{48}N_3P_3F_{18}$: C, 52.32; H, 4.39; N, 3.81, found: C, 52.44; H, 4.43; N, 3.83.

6. To a 500 mL round bottom flask equipped with a magnetic stirrer and N_2 Inlet were added benzonitrile (2.58 g, 25.0 mmol), $LiAlD_4$ (1.0 M ether solution, 25 mL, 25 mmol), and anhydrous diethyl ether (200 mL) and the reaction mixture was stirred for 12h. Ethyl acetate was added to quench the reaction and the solvent was evaporated to give a white solid, which was suspended in H_2O and extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, and concentrated to give a brown liquid, which was vacuum distilled at 38-39°C @0.5 mmHg (lit.[13] bp 75-76°C @15 mmHg) to afford a colorless liquid (0.34 g, 13% yield). ^{1}H NMR (400 MHz, chloroform-d, 22°C): δ=7.23-7.36 (5H, m).

7. To a 250 mL three neck round bottom flask equipped with a mechanical stirrer and a Dean-Stark trap were added **1** (100 mg, 0.257 mmol), **6** (101 mg, 0.923 mmol), and a mixture of toluene and DMAC (30 mL/10 mL). The reaction mixture was stirred and refluxed for 2 days. The solvent was evaporated and the resulting yellow solid was dissolved in THF and precipitated into dry hexane twice. The product was recrystallized from hexane to afford a yellow solid (33 mg, 20%), mp 160-163°C. ^{1}H NMR (400 MHz, chloroform-d_6, 22°C): δ=7.27-7.30 (m, 6H), 7.36-7.38 (m, 9H), 7.76 (d, 6H, J = 8.4 Hz), 7.88 (s,3H), 7.92 (d, 6H, J = 8.4 Hz), and 8.46 (s, 3H). LRFAB: m/z=664.3 $[M]^+$. HRFAB: calcd for $[M]^+$ $C_{48}H_{34}N_3D_6$: 664.3599, found 664.3567.

8. To a 100 mL one neck round bottom flask were added **2** (33.2 mg, 0.050 mmol) and MeOH (5 mL). $NaBH_4$ (18.9 mg, 0.500 mmol) was added protionwise to the suspension over a period of 5 min and the reaction mixture was refluxed for 12 h, cooled and diluted with 5 mL of H_2O. The white solid obtained after evaporation of the solvent was suspended in H_2O and extracted with CH_2Cl_2 (10 mL x 2). The organic layers were combined and concentrated to give a yellow liquid (24 mg, 72% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.87 (s, 6H), 7.28-7.30 (m, 6H), 7.33-7.40 (m, 9H), 7.46 (d, 6H, J = 8.4 Hz) 7.66 (d, 6H, J = 8.4 Hz), and 7.75 (s, 3H). LRFAB: m/z=670.3 $[M+H]^+$. HRFAB: calcd for $[M]^+$ $C_{48}H_{40}N_3D_6$: 670.4068, found 670.4042.

9. To a 25 mL one neck round bottom flask were added **3** (20 mg, 0.030 mmol), MeOH (10 mL), and 2M HCl (5 mL). The solution was stirred at 25°C for 10 h. The solvent was rotary evaporated to afford a white solid, which was dissolved in H_2O (65 mL). To this solution was added aq. NH_4PF_6 at 0°C until no further precipitation was observed. The precipitate was filtered and recrystallized from H_2O to afford a slightly yellowish solid (17.2 mg, 64% yield), mp decomp 210°C. ^{1}H NMR (400 MHz, acetone-d_6, 22°C): d=4.58 (s, 6H), 4.64 (s, 6H), 7.45 (m, 9H), 7.58 (m, 6H), 7.73 (d, 6H, J = 8.4 Hz), 7.96 (d, 6H, J = 8.4 Hz), and 7.80 (s, 3H). LRFAB: m/z=816.3 $[M\text{-}HPF_6\text{-}PF_6]^+$, 670.3 $[M\text{-}2HPF_6\text{-}PF_6]^+$.

3.5. References

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