Chapter 8

Supramolecular Assemblies Formed from a Heteroditopic Molecule Containing a Secondary Ammonium Ion and Crown Ether Moiety

8.1. Introduction

Efforts continue to be directed toward the spontaneous construction of ordered linear arrays through noncovalent bonds. The approach to achieve this goal is extended from the use of complementary homoditopic molecules[1-3] as described in the previous chapters 5, 6, and 7 to the use of a heteroditopic molecule.[4] In this chapter the synthesis and complexation studies of a heteroditopic molecule in which two complementary units, dibenzo-24-crown-8 (DB24C8) and dibenzylammonium hexafluorophosphate, are covalently connected are described. The use of a single building block of this type which is analogous to AB monomers in conventional polymerization reactions is advantageous because it guarantees the 1:1 stoichiometry between the complementary units required for the formation of supramolecular aggregates. The nature of the aggregates derived from the heteroditopic molecule was analyzed by ^{1}H NMR spectroscopy in solution and by mass spectroscopy (MALDI-TOF and FAB) in the gas phase.

8.2. Results and Discussion

8.2.1 Synthesis

Figure 8.1 shows the synthetic routes to the heteroditopic molecule **4**. A typical procedure involving removal of water from the reaction mixture to drive the equilibrium forward was utilized in the synthesis of the DB24C8 Schiff base derivative **2**, which was later reduced to secondary amine **3** with sodium borohydride in alcoholic solvent. The ^{1}H NMR spectrum of **3** (Figure 8.2) shows a characteristic singlet for the imine proton at 8.27 ppm. The electron withdrawing nature of the adjacent C=N linkage gives rise to a considerable downfield chemical shift of the resonance for the imine proton. A sharp singlet at 4.79 ppm for the benzylic protons gave an additional evidence for the successful formation of **3**. Two sharp singlets for the benzylic protons at 3.72 and 3.78

ppm and disappearance of the resonance for the imine proton in the ^{1}H NMR spectrum of **3** confirmed a successful reduction of **2**. The resulting amine **3** was subsequently acidified with 2M HCl solution and followed by ion exchange reaction to afford the secondary ammonium salt substituted DB24C8 **4**. As seen in the ^{1}H NMR spectrum (Figure 8.3) of ion exchanged salt **4** only the resonance for H_f is detected because the resonance for the other benzylic protons, H_g, totally overlaps with the resonance for H_α. The heteroditopic molecule is insoluble in halogenated solvents such as chloroform and methylene chloride and only slightly soluble in acetone and acetonitrile. Competitive solvents for hydrogen bonding interactions such as DMSO and water ready solubilize **4** at room temperature.

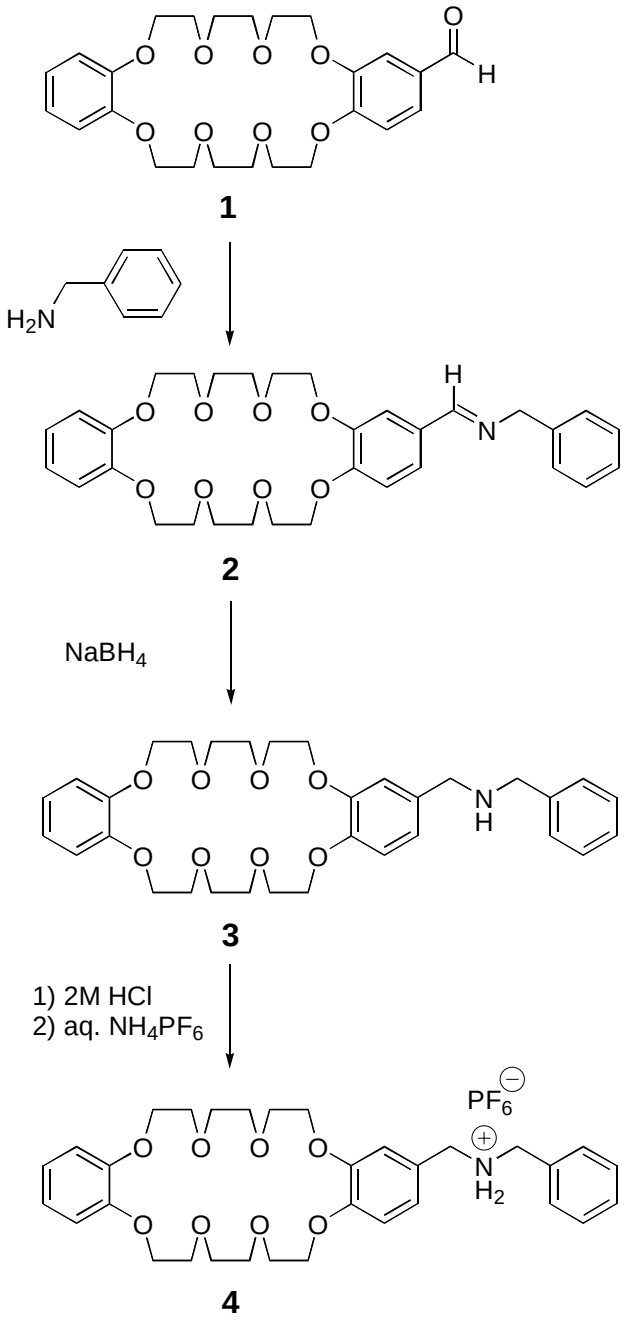

Figure 8.1. Outline of the synthesis of the heteroditopic molecule **4**.

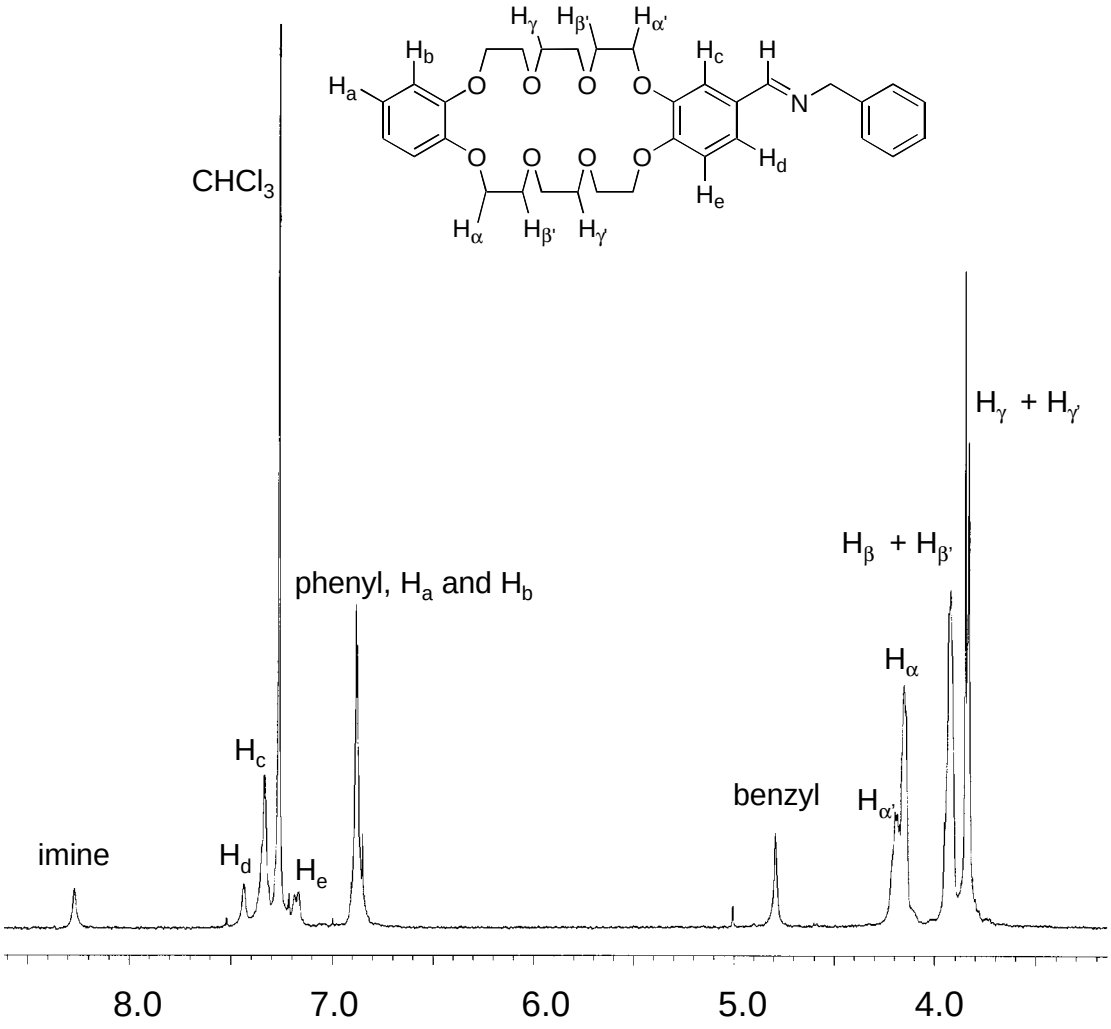

Figure 8.2. The ^{1}H NMR spectrum of **2** (400 MHz, chloroform-*d*, 22°C).

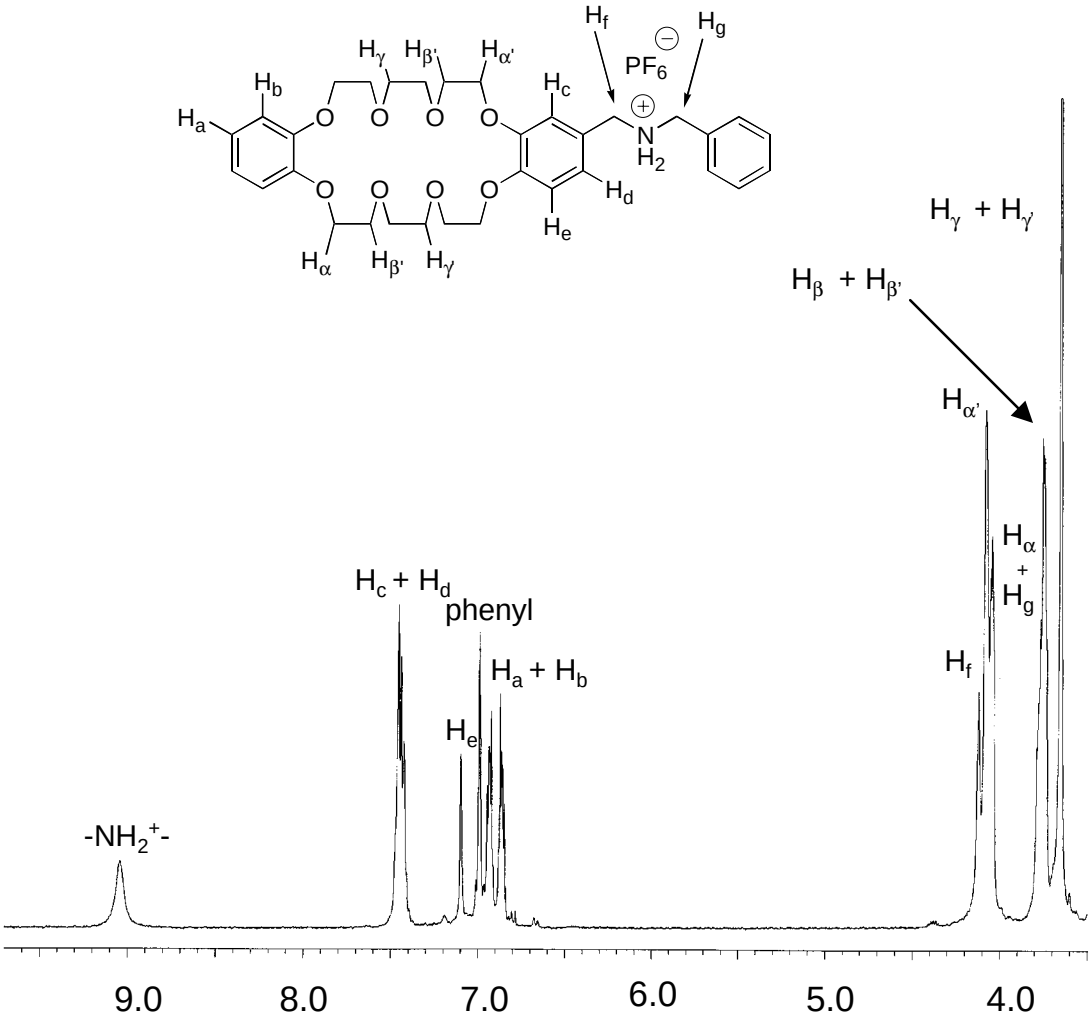

Figure 8.3. The ^{1}H NMR spectrum of **4** (400 MHz, DMSO-d_6, 22°C).

8.2.2. Complextion studies by ^{1}H NMR spectroscopy

Figure 8.4 illustrates the general approach to create linear arrays **5** from the heteroditopic molecule **4**. The complexation studies of **4** in solution by ^{1}H NMR spectroscopy encountered difficulties due to the poor solubility exhibited by the heteroditopic molecule in non-polar solvents where the association between the complementary units is ideally high. Thus, the complexation of **4** was studied in more polar solvents (acetone and acetonitrile) in order to enhance the solubility of **4**. However, it should be noted that the solubility of **4** was limited even in these solvents. For example, 10 mL of acetone-d_6 failed to completely dissolve 0.5 mmol of **4** to make a 5.0 x 10^{-2} M solution. As observed for other systems involving complementary units of

DB24C8 and dibenzylammonium salt moieties,[5-7] the ^{1}H NMR spectrum of a 2.0 x 10^{-2} M solution of **4** in acetone-d_6 (Figure 8.5) revealed two sets of signals (*i.e.*, complexed and uncomplexed **4**) based on the argument of slow exchange on the ^{1}H NMR time scale. However, the complete signal assignments for complexed and uncomplexed moieties of **4** in the ^{1}H NMR spectra was not straightforward. The signals in the aromatic region could not be assigned properly due to their severe overlaps. The complication of the ^{1}H NMR spectra resulted from two reasons: 1) There may be more than two types of supramolecular structures formed in solution, namely linear chains **5** and cyclic species **6**. In other words, the chemical shifts of the signals for **6** may be unique from those in **5**, giving rise to two sets of signals. Similar spectroscopic observations were made with the complementary homoditopic molecules discussed in the previous chapters 5, 6, and 7. 2) The precise chemical shifts of the signals for uncomplexed **4** are unknown in acetone-d_6 because the complementary moieties in **4** spontaneously associate in such solvent to form **5** and/or **6**.

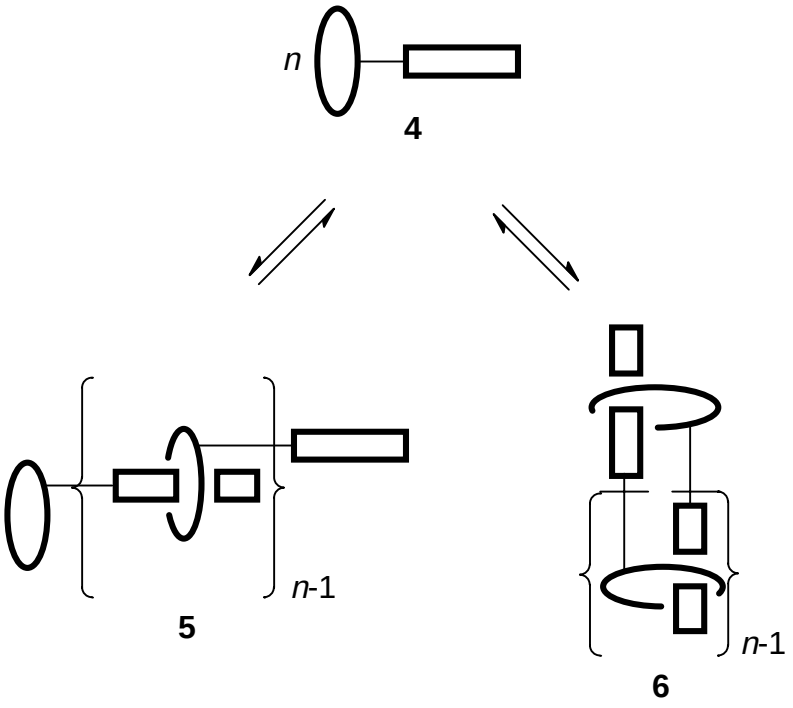

Figure 8.4. Cartoon representations of the formation of linear arrays **5** and cyclic species **6** by self-assembly of **4**.

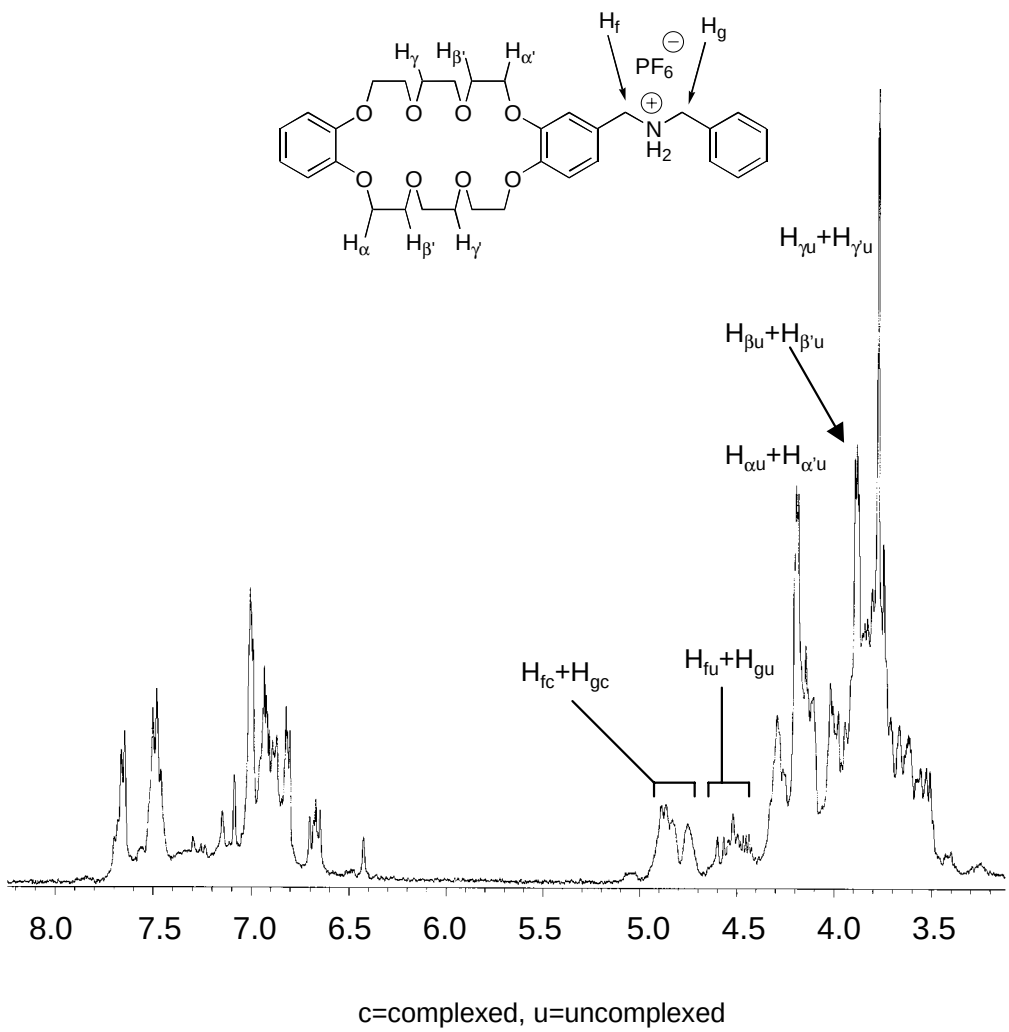

Figure 8.5. The ^{1}H NMR spectrum of **4** (400 MHz, acetone-d_6, 22°C).

Equilibria of self-assembling systems such as the one described above are under thermodynamic control.[8] This means that the equilibrium constants (K) in these systems are related to the thermodynamic function of the Gibbs free energy change, ΔG^o, at equilibrium as follows; $\Delta G^o = -RT\ln K$ where R is the gas constant, T is the absolute temperature in Kelvins (K). This equation predicts that the more negative ΔG^o is, the higher the K value is. ΔG^o is also related to the change in enthalpy (ΔH^o) and in entropy (ΔS^o) as follows; $\Delta G^o = \Delta H^o - T\Delta S^o$. This equation predicts that ΔG^o is more negative at lower T in any system that is under thermodynamic control. Thus, these equations collectively predict that lowering T increases the K value. To demonstrate this experimentally the ^{1}H NMR spectra of equimolar solutions of DB24C8 and

dibenzylammonium hexafluorophosphate (2.0 x 10^{-2} M in acetone-d_6) were recorded at different temperatures (Figure 8.6). As the solution temperature is lowered the signals for uncomplexed species gradually become less intense and those for the 1:1 complex become more intense, indicating that the *K* value is greater at lower temperatures (Table 8.1). ΔH and ΔS values were determined to be –6.7 kcal mol^{-1} and –11 cal mol^{-1} K^{-1}, respectively.

Table 8.1. Association constants (*K*) for the 1:1 complex in acetone-d_6 at different temperatures.

Temperature (^oC)	*K* (M^{-1})
+22	$3.8x10^2$
0	$1.3x10^3$
-20	$2.7x10^3$
-30	$3.1x10^3$
-40	$6.6x10^3$
-50	$2.3x10^4$
-60	$3.3x10^5$

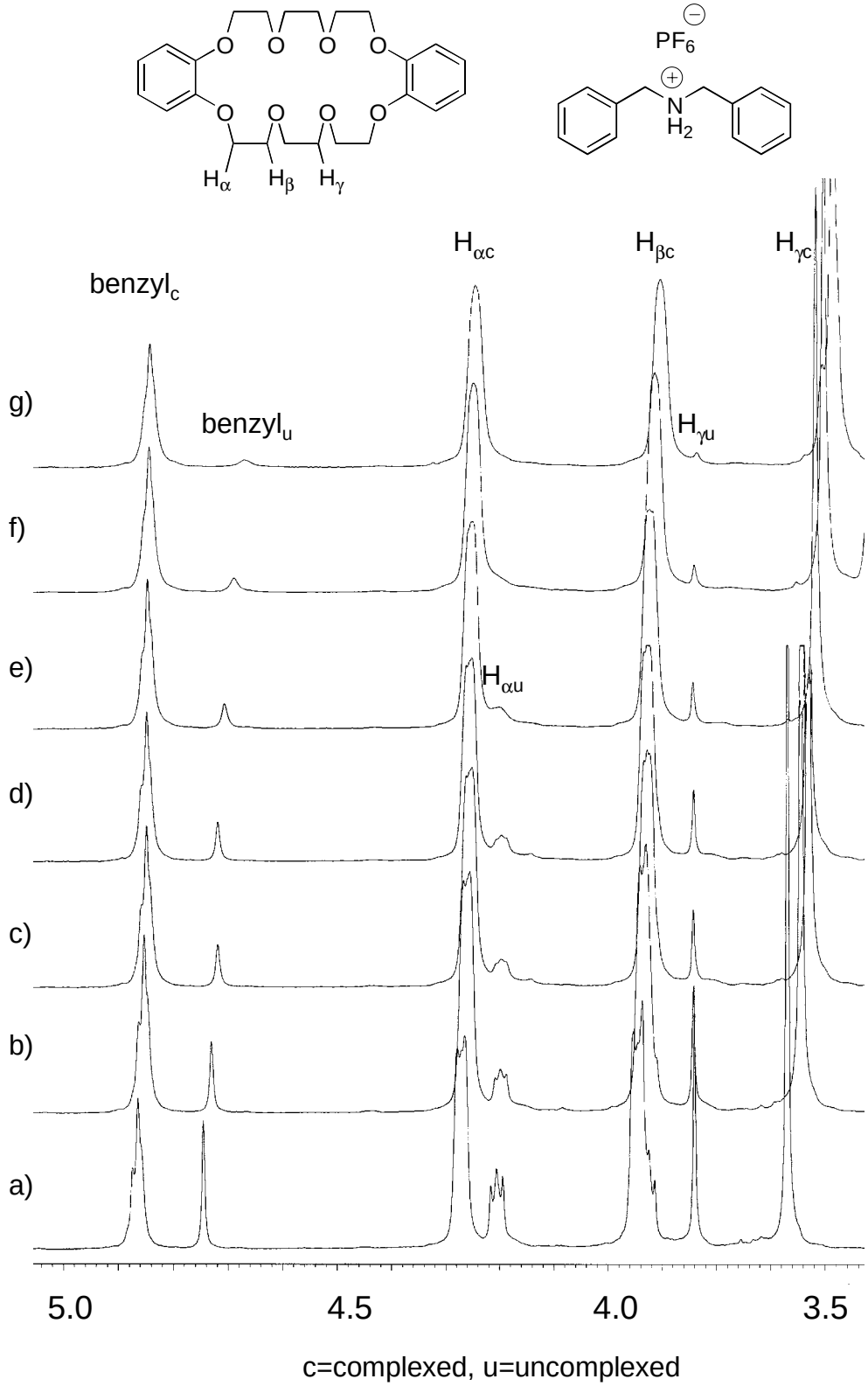

Figure 8.6. The stacked variable-temperature ^{1}H NMR spectra of equimolar solutions of DB24C8 and dibenzylammonium salt at a) 22, b) 0, c) –20, d) –30, e) –40, f) –50, and g) –60°C (2.0 x 10^{-2} M each, 400 MHz, acetone-d_6).

Thus, the next logical experiment to perform was variable temperature ^{1}H NMR spectroscopy on **4**. We speculated that it might be possible to detect the signals for the end group of the linear arrays in the ^{1}H NMR spectra by adjusting the solution temperatures. Figure 8.7 shows the stacked ^{1}H NMR spectra of a solution of the heteroditopic molecule **4** at various temperatures. As seen in Figure 8.7 no significant spectroscopic change is noted even at slightly below the freezing temperature of the solvent at which the association constant is presumably the highest. At 22°C the peaks at 4.20, 3.86 and 3.75 ppm are tentatively assigned as the signals for H_α, H_β, and H_γ, respectively, of the uncomplexed crown ether moiety by referring to the ^{1}H NMR spectrum of **3** (in acetone-d_6) which only displayed one set of signals. A pair of multiple peaks in the region of 4.90-4.75 ppm may be corresponding to the signals for the benzylic protons of the complexed ammonium salt moiety, while a couple of multiple peaks between 4.60 and 4.40 ppm are probably due to the signals for the benzylic protons of the uncomplexed ammonium salt moiety. The ^{1}H NMR spectra recorded in acetonitrile-d_3 showed similar results. Because the complexation studies of **4** in solution by ^{1}H NMR spectroscopy are not feasible, mass spectroscopy was used to characterize the supramolecular structure formed from **4**.

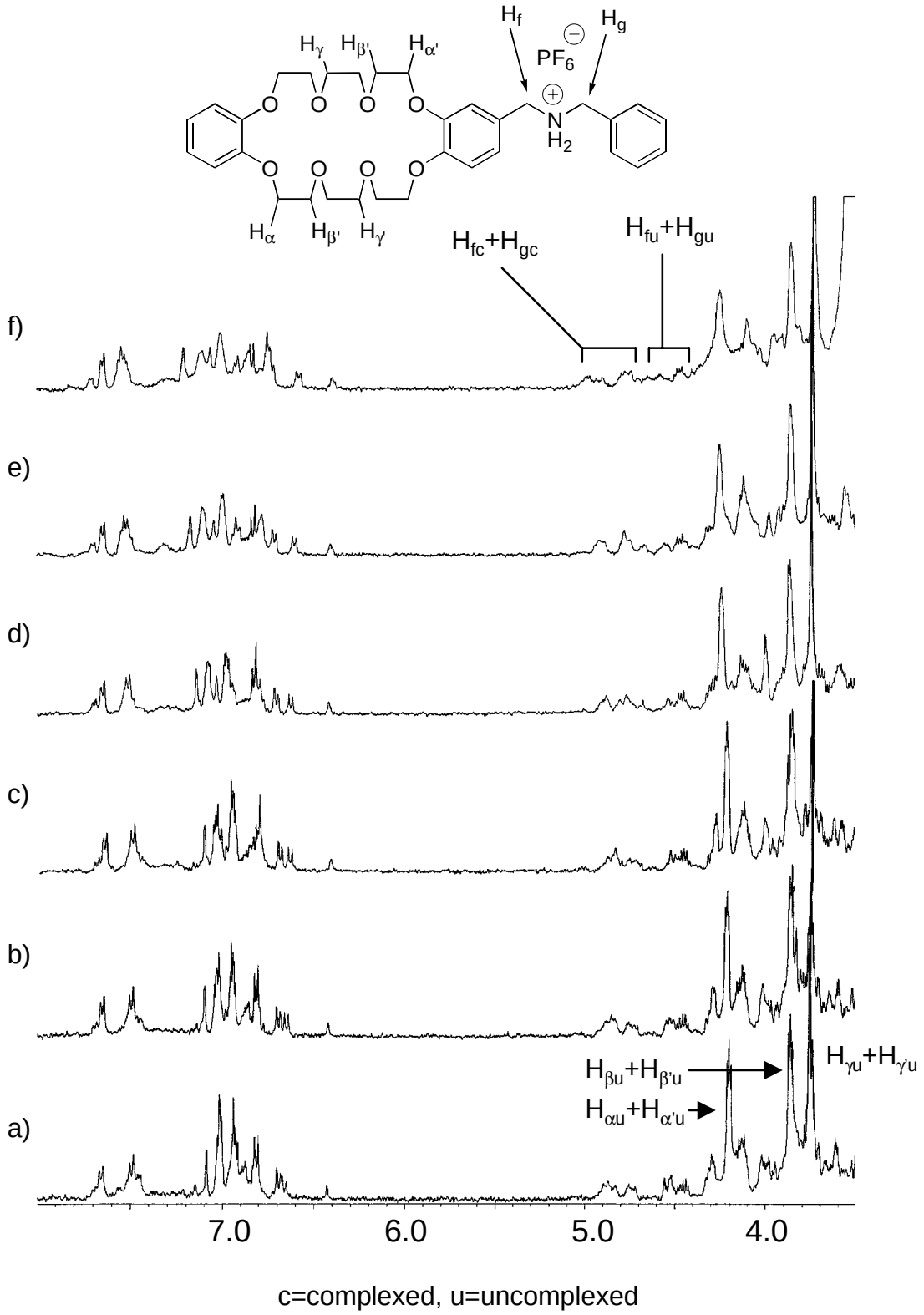

Figure 8.7. The stacked variable-temperature ^{1}H NMR spectra of a 2.0 x 10^{-2} M solution of **4** at a) 22, b) 10, c) 0, d) –20, e) –40, and f) –60°C (400 MHz, acetone-d_6).

8.2.3. Mass spectrometry

The solid state sample, prepared by slow evaporation of a chloroform/acetonitrile (1/1 v/v) solution of **4**, was first analyzed by matrix assisted laser desorption ionization (MALDI). The mass spectrum (Figure 8.8) revealed a peak at *m*/*z*=1137 g/mol, indicating the formation of dimeric supermolecules in the gas phase after loss of one PF_6^- counter ion and HPF_6. The base peak observed at *m*/*z*=1017 g/mol corresponds to dimer after loss of the benzylamine fragment, one PF_6^- counter ion and HPF_6. However, there was no evidence of oligomeric or polymeric aggregates in the mass spectrum. We believe that fragmentation (dissociation) of the aggregates might have been caused by the laser beam during ionization. Therefore, the same sample was analyzed by fast-atom bombardment mass spectrometry (FABMS) which offers a soft ionization. The FAB mass spectrum was dominated by the peaks at *m*/*z*=1283 and 1137g/mol corresponding to dimeric aggregates after loss of one and two PF_6^- counter ions, respectively. Unlike the MALDI spectrum, the FAB mass spectrum indicated the existence of the higher aggregates. The peaks at m/z=2710 and 2443 g/mol correspond to the tetrameric aggretates after loss of one and three PF_6^- counter ions. The peak for the trimeric aggregates after loss of two PF_6^- counter ions were observed at *m*/*z*=1848 g/mol.

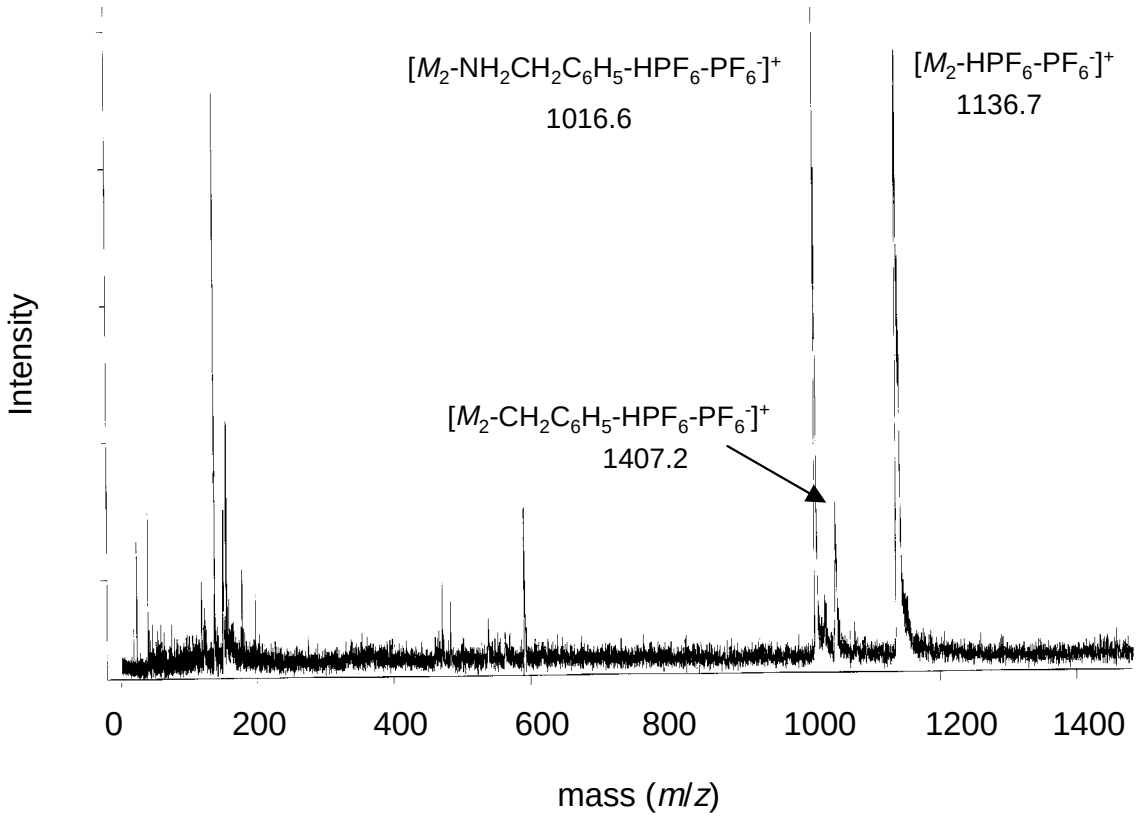

Figure 8.8. The MALDI spectrum of the solid sample prepared from **4**.

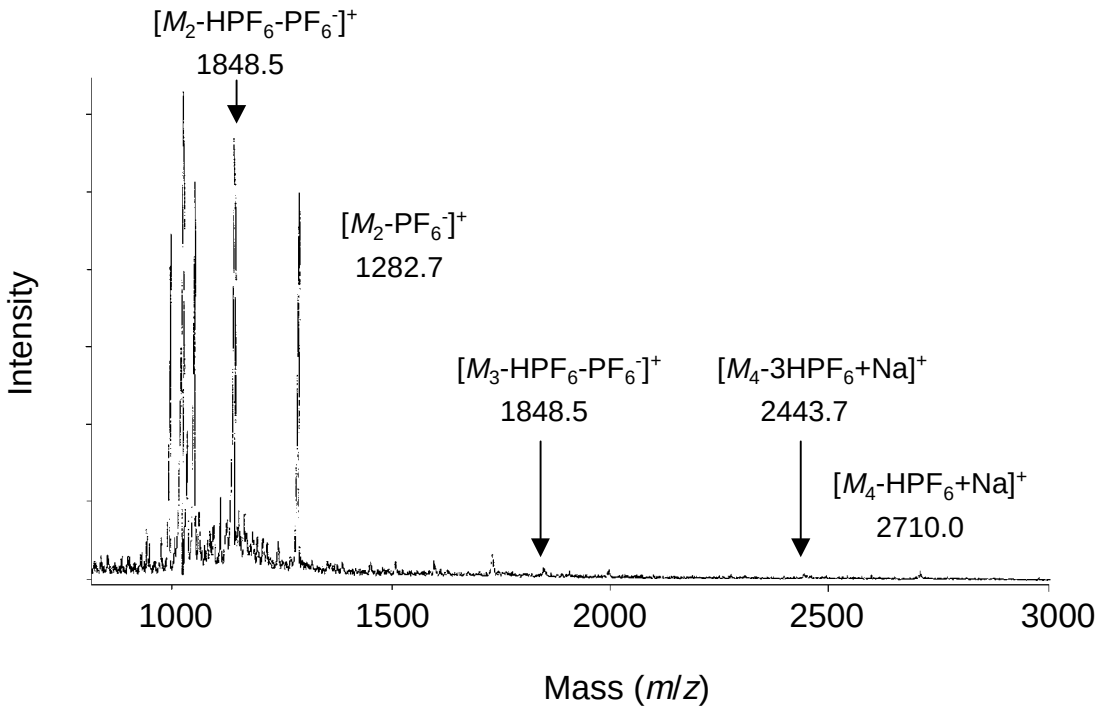

Figure 8.9. The FAB mass spectrum of the solid sample prepared from **4**.

8.3. Conclusions

Although the extra sets of signals emerged in the ^{1}H NMR spectra of **4** were indicative of complexation between the complementary moieties of **4**, the detailed analysis of solution behavior was not accomplished primarily due to the complexity of the ^{1}H NMR spectra. In addition, the poor solubility of **4** in noncompetitive solvents would prevent the formation of high aggregates of **5** and/or **6**. Nevertheless, the FAB mass spectrum showed the existence of as high as tetrameric aggregates in the gas phase. While this research was in progress, Stoddart and his coworkers reported the X-ray structure of dimeric complex from the same heteroditopic molecule.[9] In that report, they state that it is extremely difficult to overcome the entropic penalty associated with high aggregates of **5** and **6**. However, we realize that high concentration is required for systems with the association constants in the range of 10-10^3 M^{-1} such as **4** in order to obtain large aggregates in solution. In chapter 11, we describe the construction of linear arrays from an analogous heteroditopic molecule containing paraquat and bis-*m*-phenyl-32-crown-10 moieties, which shows much improved solubility in noncompetitive solvents.

8.4. Experimental

The solvents were used as received. Melting points were taken on a Mel-Temp II melting point apparatus and are uncorrected. The 400 MHz ^{1}H NMR spectra were recorded on a Varian Unity with tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to denote splitting patterns: s (singlet), d (doublet), t (triplet), and m (multiplet). Elemental analyses were obtained from Atlantic Microlab, Norcross, GA. Mass spectra were provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

4-Benzyliminomethyldibenzo-24-crown-8 (2). To a 50 mL round bottom flask equipped with a Dean-Stark trap, condenser and nitrogen bubbler were added 4-formyldibenzo-24-crown-8 (185 mg, 0.39 mmol), benzylamine (53.2 mg, 0.50 mmol, 1.2 equiv.) and toluene (25 mL) and the mixture was refluxed for 24 h. Upon completion of

the reaction the solvent was rotary evaporated to give a yellow liquid, which was subsequently recrystallized from dry ethanol to afford an off-white solid (53.2 mg, 41% yield), mp 78-79°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.83 (8H, m), 3.92 (8H, m), 4.15 - 4.19 (8H, m), 4.79 (2H, s), 6.85-7.44 (12H, m), and 8.27 (1H, s). LRESI: *m*/*z*=588 [*M*+Na]$^+$; HRMALDI: calcd for [*M*+H]$^+$ $C_{32}H_{40}O_8N$ 566.2754, found 556.2746.

4-(*N*-benzylaminomethyl)dibenzo-24-crown-8 (3). To a 25 mL round bottom flask equipped with a magnetic stirrer and nitrogen bubbler were added the Schiff base (19.6 mg, 0.035 mmol) and methanol (6 mL) and the solution was warmed to 40°C. To this were added small portions of $NaBH_4$ (2.6 mg, 0.069 mmol) and the reaction mixture was refluxed for 8 h. Upon completion of the reaction the solvent was stripped off with a rotary evaporator to give a white solid which was suspended in H_2O and extracted with chloroform twice. The organic layers were combined and dried over $MgSO_4$. Upon removal of the solvent the product was isolated as a clear liquid (16.2 mg, 82% yield). ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.72 (2H, s), 3.78 (2H, s), 3.83 (8H, m), 3.92 (8H, m), 4.15 (8H, m), and 6.82-7.33 (12H, m).

4-(*N*-benzylammoniomethyl)dibenzyo-24-crown-8 hexafluorophosphate (4). To a 10 mL round bottom flask equipped with a magnetic stirrer were added the amine **3** (14.2 mg, 0.029 mmol), 2M HCl (3 mL) and methanol (5 mL) and the reaction mixture was vigorously stirred for 3 h at reflux. At the end of the reaction the solvents were removed *in vacuo* to give an off-white solid which was redissolved in H_2O and an aqueous solution of NH_4PF_6 added until no further precipitation was observed. The precipitate was filtered and isolated as an off-white solid (8.1 mg, 40% yield), mp 222-225°C (lit. mp decomp. 210°C). ^{1}H NMR (400 MHz, DMSO-d_6, 22°C): δ=3.32 (8H, m), 3.65 (8H, m), 3.75-3.79 (4H, m), 4.03-4.08 (4H, m and 2H, s), 4.12 (2H, s), 6.85-7.45 (12H, m), and 9.04 (2H, s). LRESI: *m*/*z*=568 [*M*-PF_6]$^+$; HRMALDI: calcd for [*M*-HPF_6+Na]$^+$ $C_{32}H_{41}O_8NNa$ 590.2730, found 590.2738.

8.5. References

1)Yamaguchi, N.; Gibson, H. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 143-147.

2)Yamaguchi, N.; Gibson, H. W. *J. Chem. Soc., Chem. Commun.* **1999**, 789-790.

3)Yamaguchi, N.; Gibson, H. W. *Am. Chem. Soc. Div. Polym. Mater. Sci. Eng.* **1999**, *80*, 217-218.

4)Ashton, P. R.; Baxter, I.; Cantrill, S. J.; Fyfe, M. C. T.; Glink, P. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1294-1297.

5)Ashton, P. R.; Campbell, P. J.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; Williams, D. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1865-1869.

6)Ashton, P. R.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Schiavo, C.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 709-728.

7)Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393-401.

8)Bruice, P. Y. *Organic Chemistry*; Prentice Hall: New Jersey, 1995.

9)Ashton, P. R.; Baxter, I.; Cantrill, S. J.; Fyfe, M. C. T.; Glink, P. T.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1294-1297.