Chapter 10

Effect of Substituents on the Formation of Pseudorotaxanes from Dialkylammonium Ions and Dibenzo-24-crown-8

10.1. Introduction

Stoddart's discovery of the approach to synthesize pseudorotaxanes from dialkylammonium salts and dibenzo-24-crown-8 (DB24C8) stands out as a landmark in the field of supramolecular chemistry.[1,2] As discussed in chapter 1, these pseudorotaxanes are stabilized primarily by hydrogen bonding, occasionally supplemented with weaker π-π stacking interactions. This approach has been exploited to spontaneously create large entities such as dendrimers,[3] linear arrays,[4-6] and polypseudorotaxanes.[7,8]

Examination of CPK molecular models revealed that the phenyl groups at the termini of dibenzylammonium salt are relatively bulky compared to the cavity size of DB24C8. We were therefore curious to study the effect of substituents purposely placed on the phenyl rings of dibenzylammonium salts on the formation of pseudorotaxanes. In this chapter we describe the syntheses of a pair of substituted dibenzylammonium salts and their complexation behavior toward DB24C8 in solution.

10.2. Results and Discussion

10.2.1. Synthesis

The synthetic routes to the dialkylammonium salts **5a** and **5b** are depicted in Figure 10.1. First, the new diimines **3a** and **3b** were formed by the reaction of methyl or methoxy substituted primary amine **2** and the corresponding substituted aldehyde **1** with simultaneous removal of water. **3a** and **3b** were isolated as liquids in 81 and 96% yields, respectively. **3a** was purified by vacuum distillation (at 112-114^{o}C @0.08 mmHg) after the solvent was rotary evaporated from the reaction mixture. However, **3b** was only washed with hexanes and the product was used in the following step without further purification. The resonances for the imine protons in **3a** and **3b** emerge as singlets at 8.67 and 8.81 ppm, respectively, in the ^{1}H NMR spectra. A dramatic downfield shift of

the imine proton signal is explained in terms of the electron withdrawing nature of N=C linkage. Integration of these resonances in each spectrum accounts for one proton. These spectroscopic observations are in good agreement with the structures of **3a** and **3b**. Further spectroscopic evidence for the formation of **3a** came from a sharp singlet observed for the benzylic protons at 4.83 ppm and two sharp singlets side by side for the methyl groups on the phenyl rings at 2.50 and 2.39 ppm. In the case of **3b**, the ^{1}H NMR spectrum exhibits a singlet, integrated for two protons, for the benzylic protons at 4.83 ppm and three singlets for the methoxy groups on the phenyl rings at 3.85, 3.83, and 3.80 ppm.

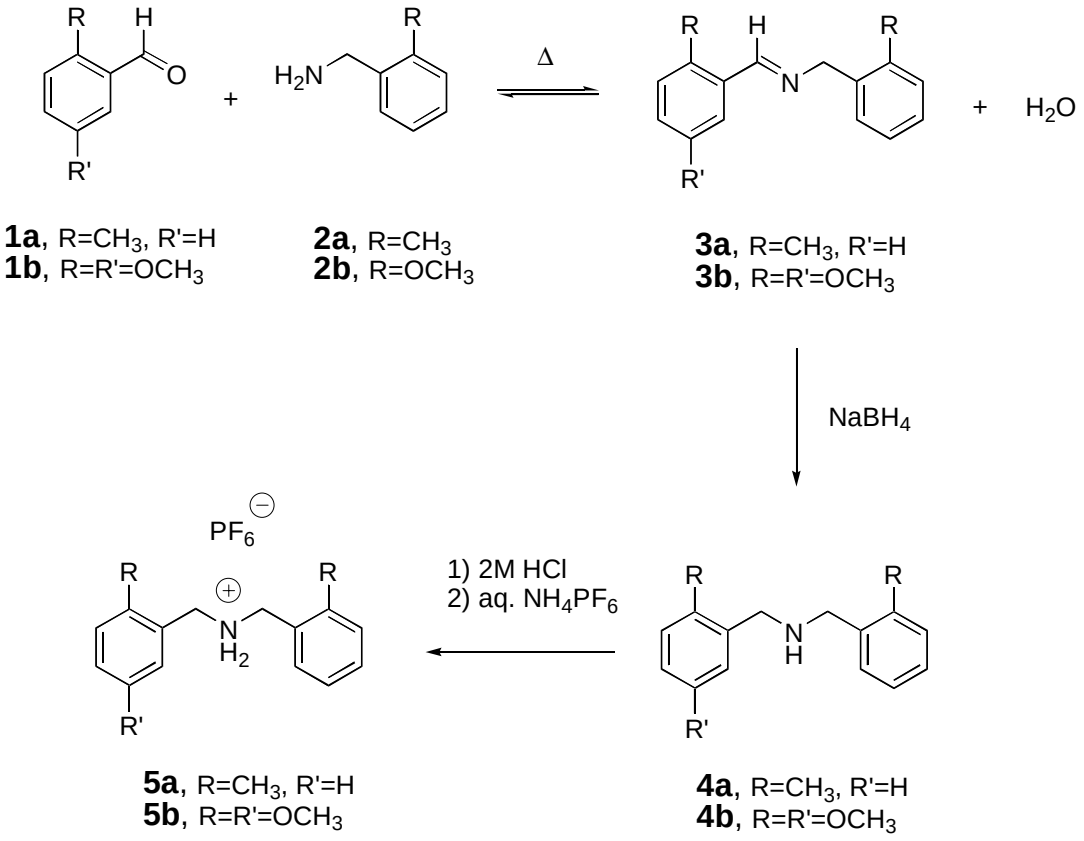


Figure 10.1. Syntheses of the dialkylammonium salts **5a** and **5b**.

3a and **3b** were then reduced with sodium borohydride in methanol to the corresponding secondary dialklyamines **4a** and **4b** in 99 and 91% yield, respectively. The ^{1}H NMR spectrum of new compound **4a** shows the disappearance of the imine signals and the appearance of a new singlet, integrating for four protons, for the benzylic

protons. A sharp singlet at 2.34 ppm corresponds to the signal for the methyl groups. Similarly, a sharp singlet was observed 3.82 ppm for the benzylic protons in the ^{1}H NMR spectrum of new compound **4b**. Since the benzyl protons of **4b** are nonequivalent, two singlets are presumably overlapped. Three singlets for the three non-equivalent methoxy groups of **4b** were also observed.

The dialkylamines **4a** and **4b** were acidified with 2M HCl followed by an ion exchange reaction to afford the corresponding dialkylammonium salts **5a** and **5b** in 92 and 94% yield, respectively. The ^{1}H NMR spectra of new compounds **5a** and **5b** (Figures 10.2 and 10.3, respectively) reveal significant downfield signal shifts for the benzylic protons due to the newly formed adjacent NH_2^+ sites. **5a** is sparingly soluble in halogenated solvents such as chloroform and methylene chloride. In contrast, **5b** showed excellent solubility in such chlorinated solvents.

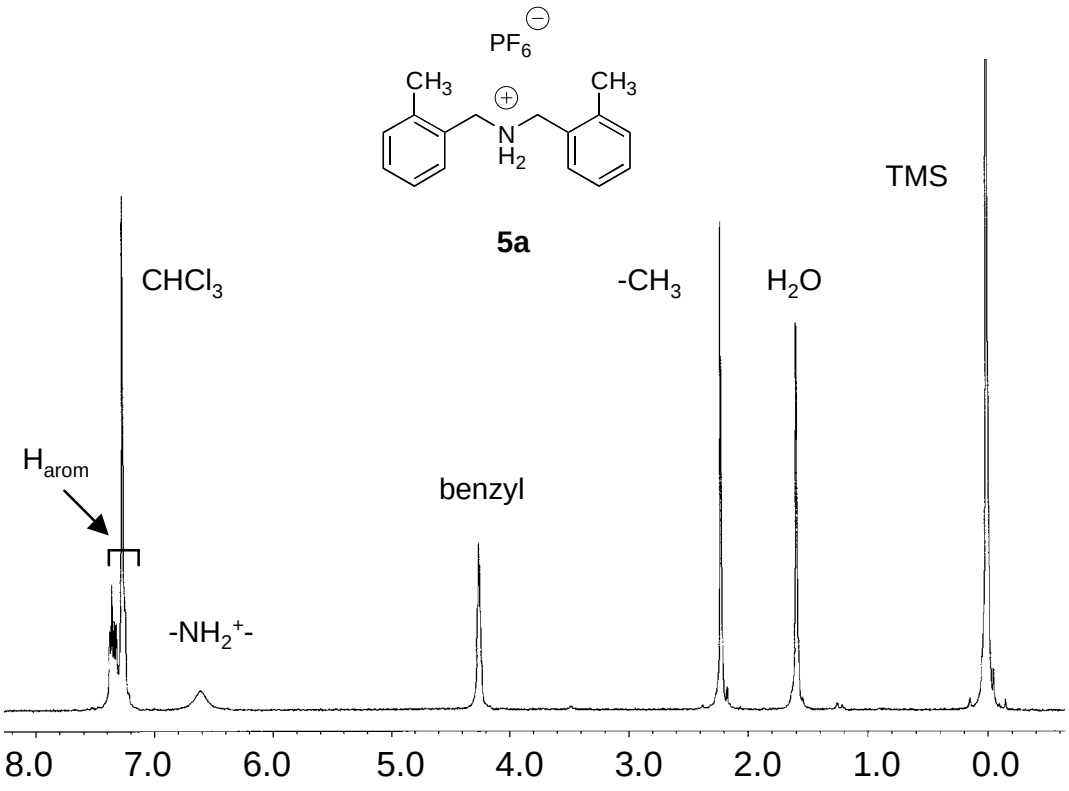


Figure 10.2. The ^{1}H NMR spectrum of **5a** (400 MHz, chloroform-*d*, 22^{o}C).

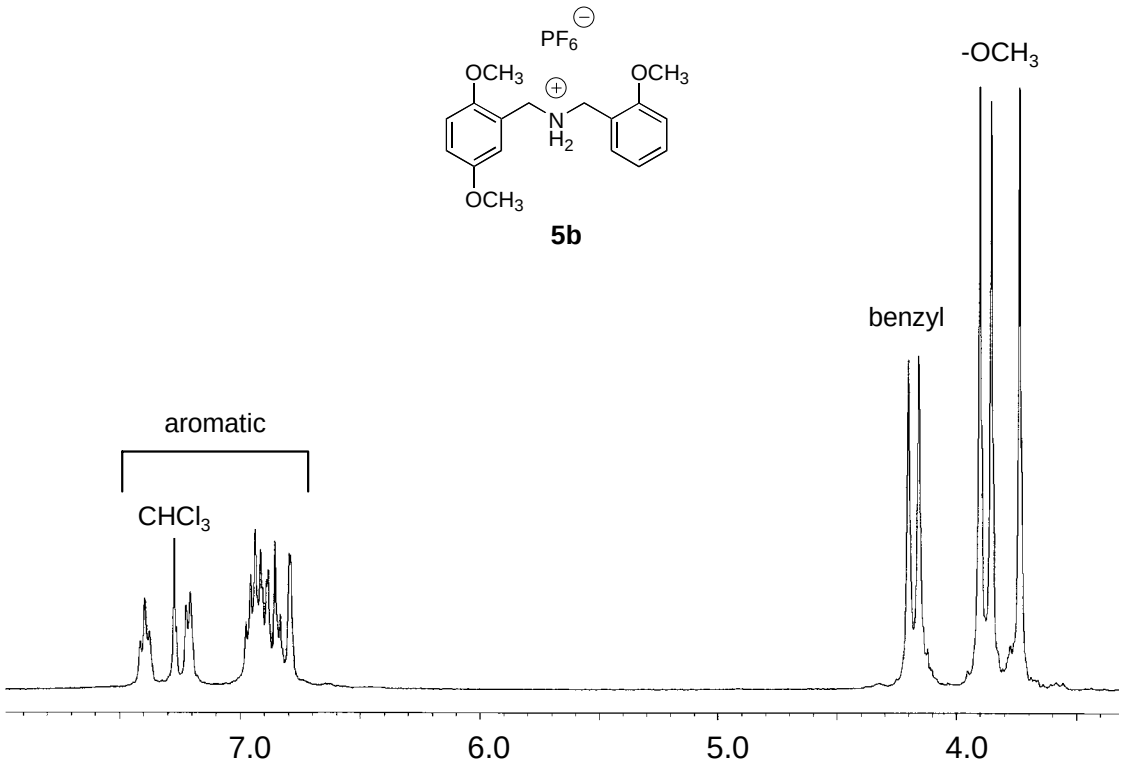


Figure 10.3. The ^{1}H NMR spectrum of **5a** (400 MHz, chloroform-*d*, 22^{o}C).

10.2.2. Complexation studies in solution

The complexation between the dialkylammonium salts and DB24C8 in solution was investigated by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of equimolar solutions of **5a** and DB24C8 (2.0 x 10^{-2} M each in acetone-d_6) (Figure 10.4b) exhibits two sets of signals for the pseudorotaxane formed from **5a** and DB24C8 and uncomplexed **5a**, indicating slow association and dissociation between the two component on the ^{1}H NMR time scale.[1,2] For a comparison purpose, the ^{1}H NMR spectrum of an equimolar solution of dibenzylammonium hexafluorophosphate **6** and DB24C8 (2.0 x 10^{-2} M each in acetone-d_6) was recorded (Figure 10.5b). The signals for the pseudorotaxane complexes display similar trends in chemical shifts (Tables 1 and 2). The signals for the benzylic, H_α, and H_β protons of the corresponding pseudorotaxane all show significant downfield chemical shifts. The large chemical shift changes ($\Delta\delta$) were observed for the benzylic protons in the 1:1 pseudorotaxane formed between **5a** and DB24C8 and **6** and DB24C8, -0.172 and -0.120 ppm, respectively. Presumably, the

benzylic protons of **5a** and **6** in the pseudorotaxane complexes are positioned in the deshielded region of the benzene ring.

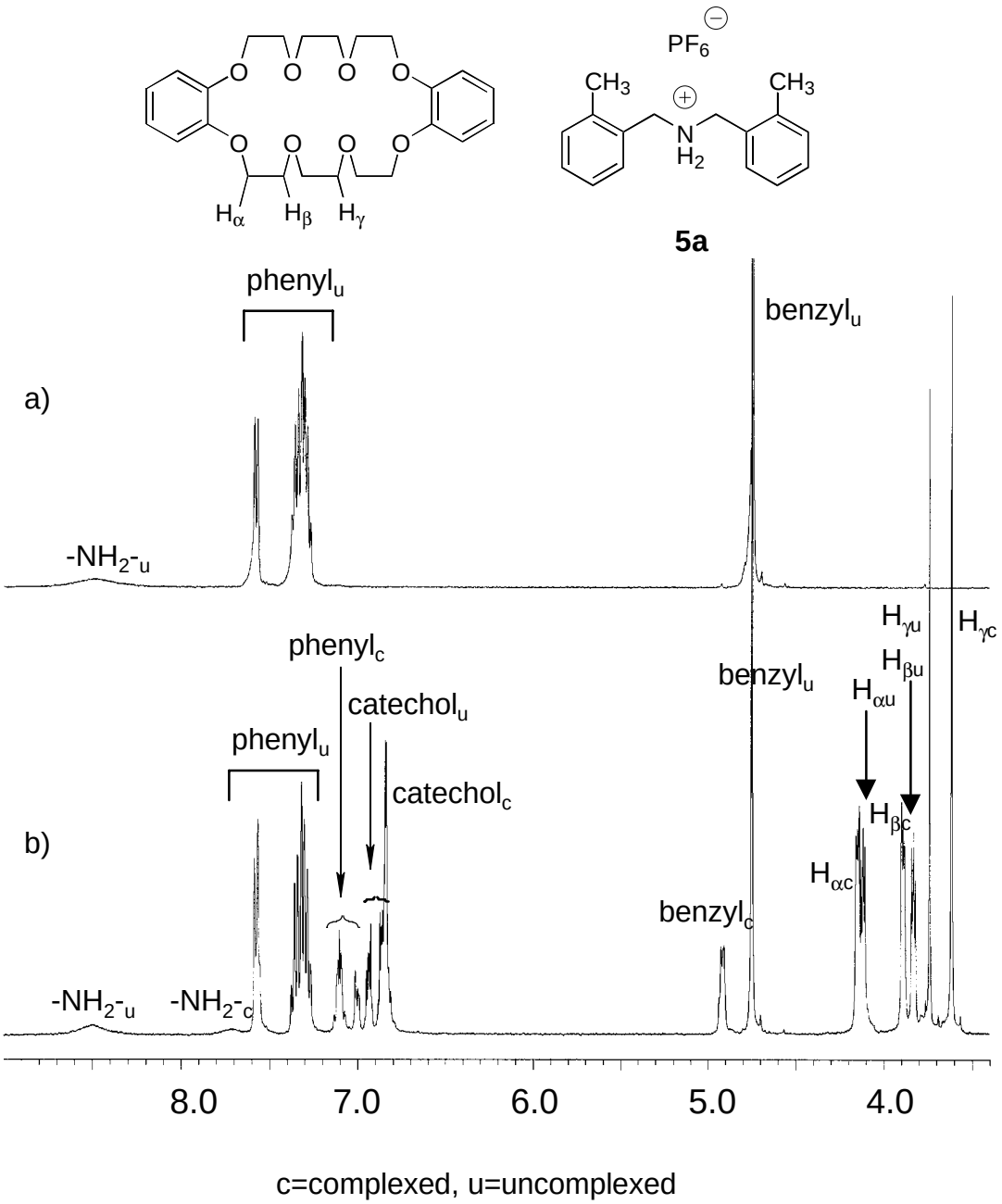


Figure 10.4. The stacked ^{1}H NMR spectra of a) a 2.0 x 10^{-2} M solution of **5a** and b) an equimolar solution of **5a** and DB24C8 (2.0 x 10^{-2} M each) (400 MHz, acetone-d_6, 22^{o}C).

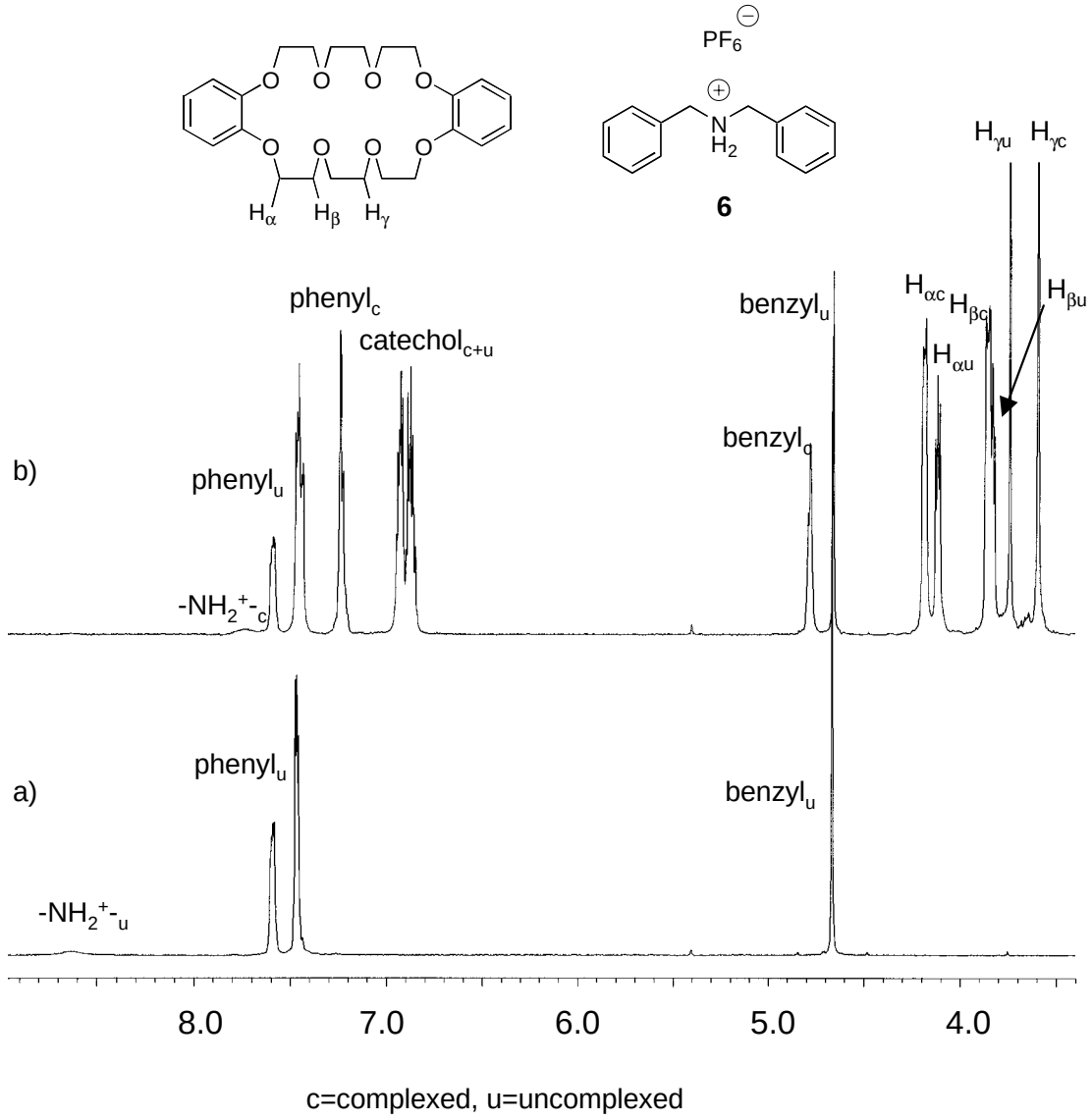


Figure 10.5. The stacked ^{1}H NMR spectra of a) a 2.0 x 10^{-2} M solution of **6** and b) an equimolar solution of **6** and DB24C8 (2.0 x 10^{-2} M each) (400 MHz, acetone-d_6, 22^{o}C).

Table 10.1. Chemical shifts (δ) in acetone-d_6 at 22°C for **5a** (2.0 x10^{-2} M), DB24C8 (2.0x 10^{-2} M), and the 1:1 complex (2.0 x 10^{-2} M each)

proton signal	**5a**	DB24C8	1:1 complex	$\Delta\delta$
-CH_3	2.418	-	2.420	-0.002
benzyl	4.744	-	4.916	-0.172
phenyl	7.317	-	7.112	+0.205
	7.576	-	7.005	+0.571
NH_2^+	8.520	-	7.718	+0.802
H_α	-	4.116	4.148	-0.032
H_β	-	3.830	3.889	-0.059
H_γ	-	3.739	3.614	+0.125
catechol	-	6.862	6.840	+0.022
	-	6.938	6.840	+0.098

Table 10.2. Chemical shifts (δ) in acetone-d_6 at 22°C for **6** (2.0 x10^{-2} M), DB24C8 (2.0x 10^{-2} M), and the 1:1 complex (2.0 x 10^{-2} M each)

proton signal	**6**	DB24C8	1:1 complex	$\Delta\delta$
benzyl	4.665	-	4.785	-0.120
phenyl	7.456	-	7.231	+0.225
	7.593	-	7.435	+0.158
NH_2^+	8.627	-	7.740	+0.887
H_α	-	4.116	4.184	-0.068
H_β	-	3.830	3.856	-0.026
H_γ	-	3.739	3.593	+0.146
catechol	-	6.862	overlapped	-
	-	6.938	overlapped	-

CPK models of **5a** and DB24C8 showed that a substantial force is required for the phenyl ring of **5a** to penetrate through the cavity of DB24C8 to achieve the 1:1 pseudorotaxane geometry because of the methyl substituents on the phenyl rings of **5a**. Since the concentrations of each species are known from Figure 10.4b, the association constant (K_a) can be derived from the expression of K_a=[**5a**:DB24C8]/[free **5a**][free DB24C8]. As predicted by the molecular modeling study, a significantly lower K_a value was obtained for the formation of the 1:1 pseudorotaxane from **5a** and DB24C8 relative to that from **6** and DB24C8 (90 vs. 360 M^{-1}). The free energy of complexation (ΔG) between **5a** and DB24C8 was calculated to be 2.6 kcal/mol at 22°C from the K_a value using the equation of ΔG=-RTln$K$ where R is the gas constant, T is the absolute temperature in kelvin (K).

Interestingly, the ^{1}H NMR spectra of equimolar solutions of **5a** and DB24C8 (2.0 x 10^{-2} M each in chloroform-*d*) are time dependent (Figure 10.6). The spectrum recorded 20 hours after the two equimolar solutions were mixed (Figure 10.6b) is considerably different from the spectrum obtained immediately after mixing (Figure 10.6a). The signals for $H_{\alpha u}$ and $H_{\beta u}$ protons of free DB24C8 at 4.175 and 3.933 ppm, respectively, are weak in intensity in Figure 10.6a but strong in Figure 10.6b. Similarly, the signal for the benzylic protons of the pseudorotaxane in Figure 10.6a is more intense compared to that in Figure 10.6b. However, no significant changes were observed in the spectra recorded after 40 and 73 hours (Figures 10.6c and d, respectively). These observations led us to believe that DB24C8 was predominately associated with **5a** to form the pseudorotaxane-like structure for at least 10 minutes after the equimolar chloroform solutions were combined. However, the equilibrium was somewhat shifted back to the individual components after 10 minutes. At this moment, we do not have any constructive explanations for these puzzling phenomena.

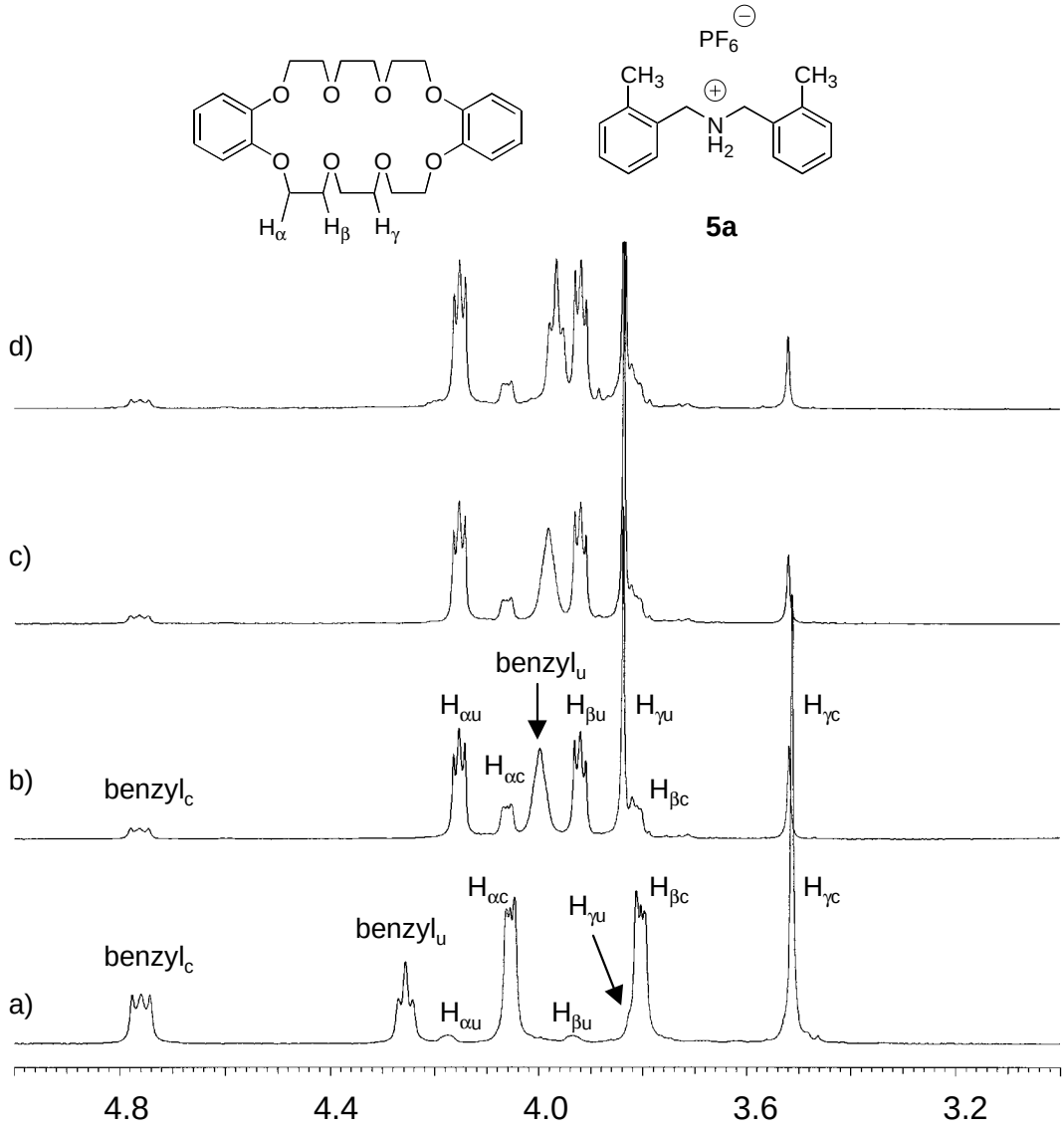
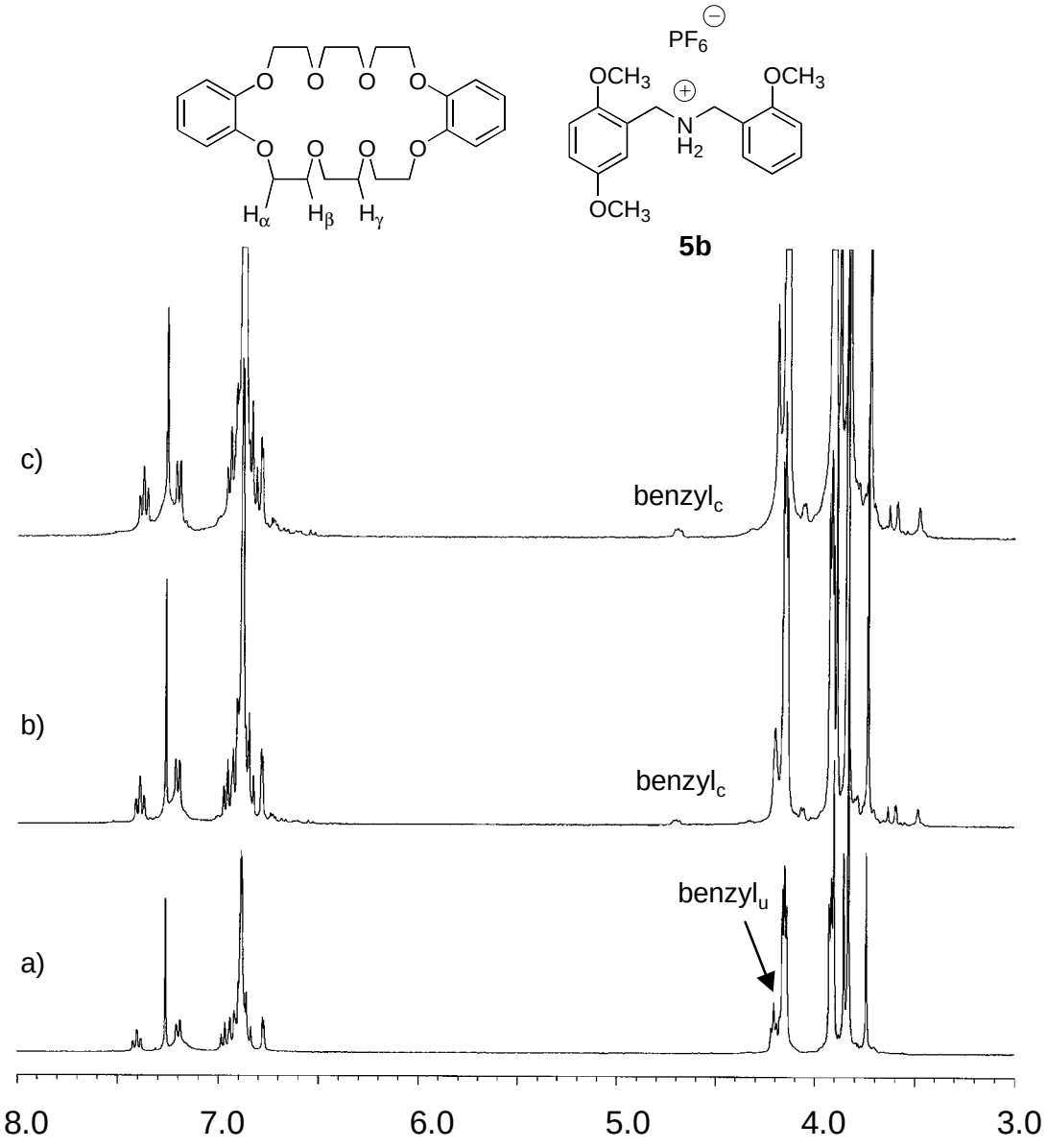


Figure 10.6. The stacked ^{1}H NMR spectra of equimolar solutions of **5a** and DB24C8 (2.0 x 10^{-2} M each) recorded after a) 10min, b) 20 hours, c) 40 hours, and d) 73 hours (400 MHz, chloroform-*d*, 22^{o}C).

The size of the terminal aryl groups of **5b** was slightly increased relative to that of **5a** by attaching two methoxy groups on one end and one on the other. According to CPK models, total insertion of **5b** intoDB24C8 is virtually impossible even from the end with one methoxy substituent. This observation appears to be valid as the ^{1}H NMR spectrum of an equimolar solution of **5b** and DB24C8 (2.0 x 10^{-2} M each in chloroform-*d*) recorded 5 minutes after the equimolar solutions were mixed (Figure 10.7a) shows no sign of the

pseudorotaxane formation. Therefore, the equimolar solution was warmed to 53^{o}C and stirred in a sealed NMR tube to give thermal energy required for the formation of the pseudorotaxane. This technique is analogous to the "slippage method" using paraquat derivatives and bis-*p*-phenylene-34-crown-10 (BPP34C10) developed in the laboratories of Stoddart.[9,10] Indeed, the ^{1}H NMR spectrum taken after 6 days at 53^{o}C (Figures 10.7b) revealed the signal at 4.70 ppm corresponding to the benzylic protons for the psudorotaxane complex and the equilibrium was finally established after 11 days. Integration ratios of the signals for the benzylic protons of the pseudorotaxane to those in uncomplexed **5b** were determined to be 7 to 93 and 8 to 92 after 6 and 11 days, respectively, by using the deconvolution technique. The association constant (K_a) was calculated to be 5 M^{-1} using the expression of K_a=[**5b**:DB24C8]/[free **5b**][free DB24C8]. These observations suggest that the activation energy required for DB24C8 to slip over the methoxy substituents of **5b** to form the pseudorotaxane is difficult to surmount.



c=complexed, u=uncomplexed

Figure 10.7. The stacked ^{1}H NMR spectra of an equimolar solution of **5b** and DB24C8 (2.0 x 10^{-2} M each) recorded after a) 5 min. at 22^{o}C, b) 6 days at 53^{o}C, and c) 11 days at 53^{o}C (400 MHz, chloroform-*d*).

10.2.3. X-ray crystallography

Single crystals suitable for X-ray analysis were prepared by vapor diffusion of hexane into a 1:1 solution of **5a** and DB24C8 in chloroform (1.0 x 10^{-2} M each). The solid state structure of the pseudorotaxane is shown in Figure 10.8. Both NH_2^+

hydrogens participate in a total of four hydrogen bonding interactions with the oxygen atoms of DB24C8. There is an additional stabilization by π-π stacking interaction between one of the two electron rich catechol units of DB24C8 and the somewhat electron deficient phenyl ring of **5a**. The conformations adopted by both **5a** and DB24C8 are reminiscent of the crystal structure of the pseudorotaxane between **6** and DB24C8 reported in the literature.[1,2]

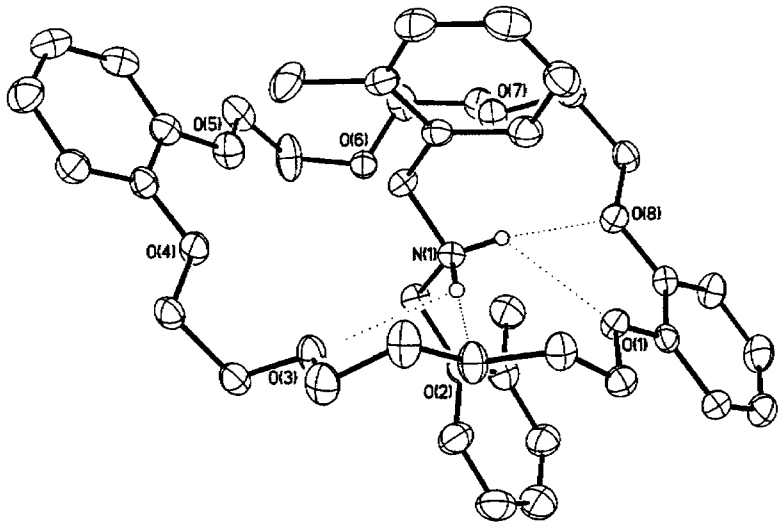


Figure 10.8. The pseudrorotaxane complex formed from **5a** and DB24C8.

10.3. Conclusions

By subtle changes made on the substituents of terminal phenyl groups of the dibenzylammonium salt, a significant change was observed for the complexation of **5a** and **5b** with DB24C8 in solution compared to the model system of **6** and DB24C8. The association constant (K_a) for the pseudorotaxane formed from **5a** and DB24C8 in acetone-d_6 is four-fold smaller than that for less bulky **6** and DB24C8. Another study showed that the slightly larger trimethoxy substituted dialkylammonium salt **5b** only allowed 8% of DB24C8 to slip over to form the pseudorotaxane like structure at 53°C.

10.4. Experimental

The solvents were used as received. Melting points were taken on a Mel-Temp II 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).

***o*-(2-Methylbenzylideneaminomethyl)toluene (3a).** To a 100 mL round bottom flask equipped with a Dean-Stark trap, condenser and magnetic stirrer were added 2-methylbenzylamine (**2a**) (1.52 g, 12.5 mmol), *o*-tolualdehyde (**1a**) (1.50 g, 12.5 mmol) and toluene (25 mL). The reaction mixture was stirred and refluxed for 24 h. After the solvent was rotary evaporated, the resulting yellow liquid was vacuum distilled (at 112-114^{o}C @0.08 mmHg) to afford a slightly yellowish liquid (2.25 g, 81% yield), used without purification. ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=2.39 (3H, s), 2.50 (3H, s), 4.83 (2H, s), 7.17-7.32 (7H, m), 9.73 (1H, d, J = 7.2 Hz) and 8.67 (1H, s).

Bis(2-methylbenzyl)amine (4a). To a 50 mL round bottom flask equipped with a magnetic stirrer were added **3a** (1.37 g, 6.14 mmol) and methanol (25 mL). Small portions of sodium borohydride (0.465 g, 12.3 mmol) were added slowly to the methanol solution. The reaction mixture was then refluxed for 12 h. Upon completion of the reaction the solvent was removed *in vacuo* to give a white solid which was suspended in H_2O and extracted with $CHCl_3$ twice. The organic layers were combined, dried over $MgSO_4$ and concentrated to afford a clear liquid (1.37 g, 99% yield), used without purification. ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=2.34 (6H, s), 3.83 (4H, s), 7.16 (6H, m), and 7.33 (2H, m).

Bis(2-methylbenzyl)ammonium hexafluorophosphate (5a). To a 100 mL round bottom flask equipped with a magnetic stirrer were added **4a** and 2M HCl (25 mL). The mixture was stirred for 30 min. and the white precipitate was filtered and washed with cold H_2O. This solid was dissolved in hot water and the solution was cooled to 0°C. To this was added an aqueous solution of NH_4PF_6 until no further precipitation was observed. The precipitate was filtered and recrystallized from H_2O to afford a white solid (0.8672 g, 92% yield), mp 178-180^{o}C. ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=2.22 (6H, s), 4.25 (4H, s), 6.61 (2H, s), and 7.24-7.37 (8H, m). LRESI: m/z=226 [M-PF_6]$^{+}$;

HRMALDI: calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{20}N$ 226.1596, found 226.1588.

***o*-(2,5-Methoxybenzylideneaminomethyl)toluene (3b).** To a 50 mL round bottom flask equipped with a Dean-Stark trap, condenser and magnetic stirrer was added a solution of 2,5-dimethoxy benzaldehyde (**1b**) (1.86 g, 11.1 mmol) in toluene (15 mL). To this mixture were added 2-methyoxybenzylamine (**2b**) and toluene (5 mL) and the reaction mixture was brought to reflux and stirred for 8 h. Upon completion of the reaction the solvent was rotary evaporated to give the crude product, which was then washed with hexanes to afford a yellow liquid (3.02 g, 96% yield). This product was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ=3.80 (3H, s), 3.83 (3H, s), 3.85 (3H, s) 4.83 (2H, s), 6.85-7.31 (6H, m), 7.58 (1H, d, J = 3.2 Hz), and 8.81 (1H, s).

***o*-(2,5-Methoxybenzylaminemethyl)toluene (4b).** To a 25 mL round bottom flask equipped with a condenser and magnetic stirrer were added **3b** (2.52 g, 8.83 mmol) and MeOH (10 mL). To this were added small portions of $NaBH_4$ (0.67 g, 17.7 mmol) and the reaction mixture was refluxed for 18 h. Upon completion of the reaction the solvent was stripped off *in vacuo* and the resulting yellow gummy material was suspended in H_2O and extracted with $CHCl_3$ twice. The organic layers were combined and dried over $MgSO_4$. After removal of the solvent a yellow liquid was isolated as the product (2.32 g, 92% yield). This product was used in the next step without further purification. ^{1}H NMR (400 MHz, chloroform-*d*, 22^{o}C): δ= 3.77 (6H, s), 3.80 (3H, s), 3.82 (4H, s), and 6.72-7.29 (7H, m).

***o*-(2,5-Methoxybenzylammoniummethyl)toluene hexafluorophosphate (5b).** To a 100 round bottom flask equipped with a magnetic stirrer were added **4b** (1.82 g, 6.34 mmol) and 2M HCl (20 mL) and the reaction mixture was stirred at room temperature for 2 h. At this point the amine **4b** was still phase separated from the aqueous solution. A small amount of MeOH was added to obtain a homogeneous solution and the reaction mixture was then refluxed for 24 h. The solvent was removed by rotary evaporator and the resulting yellow liquid was dissolved in H_2O and aq. NH_4PF_6 was added until no further precipitation was observed. The solvent was decanted and the precipitate, a

yellow liquid, was recrystallized from water to give yellow crystals (2.59 g, 94% yield), mp 145-147°C. ^{1}H NMR (400 MHz, chloroform-*d*, 22°C): δ=3.74 (3H, m), 3.86 (3H, s), 3.90 (3H, s) 4.16 (2H, s), 4.20 (2H, s), and 6.79-7.41 (7H, m). LRESI: *m*/*z*=288 [*M*-PF_6]$^+$; HRMALDI: calcd for [*M*-PF_6]$^+$ $C_{17}H_{22}N$ 288.1600, found 288.1612.

10.5. References

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