Chapter IV

Secondary Ammonium Salts

IV.1. Introduction

Several secondary ammonium salts with hexafluorophosphate counterions were synthesized. To study the complexation behavior of these salts in solution with the crown ethers discussed in **Chapter II** it was necessary to make the salts as soluble as possible in organic solvents, specifically non-polar solvents such as chloroform. The hexafluorophosphate anion was chosen as the counterion because the ion pairing is not as tight as in the chloride salts, for instance, and, therefore, they are more soluble. Both mono- and diammonium salts were synthesized.

IV.2. Results and Discussions

The secondary ammonium salts were either synthesized from their respective amines or via a multi-step reaction sequence. The multi-step reaction sequence began with the condensation reaction of an amine with an aldehyde to give an imine. The imine was subsequently reduced to the amine, which was acidified to the chloride salt. Ion exchange gave the desired hexafluorophosphate salts.

IV.2.1 Monoammonium Hexafluorophosphate Salts

1. Dibenzyl- and Di-*n*-butylammonium Hexafluorophosphates

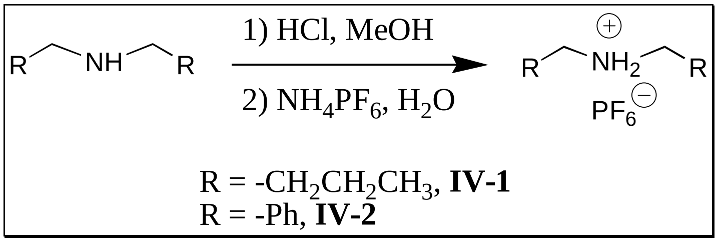

Figure IV-1. Synthesis of dibenzyl- (**IV-1**) and di-*n*-butyl- (**IV-2**) ammonium hexafluorophosphates.

Both dibenzyl- (**IV-1**) and di-*n*-butyl- (**IV-2**) ammonium hexafluorophosphate were synthesized in two steps from their respective amines (**Figure IV-1**). The amines were first acidified using hydrochloric acid in water. Ion exchange was then performed by addition of a saturated aqueous solution of ammonium hexafluorophosphate until precipitation of the desired salt occurred. Both products were isolated as white solids. The yields for **IV-1** and **IV-2** were 87.8 and 43.9 %, respectively. The relative lower yield for **IV-2** is probably due to its slight solubility in hot water, which was used to purify the product.

2. Diphenethylammonium Hexafluorophosphate

The synthesis of diphenethylammonium hexafluorophosphate (**IV-8**, **Figure IV-2**) required more reaction steps than the above mono-ammonium salts. The first step involved the condensation of phenylacetaldehyde (**IV-3**) and phenethylamine (**IV-4**) using *p*-toluenesulfonic acid as a catalyst to give the Schiff base N-phenethylidene-phenethylamine (**IV-5**). This product was not isolated, but was used directly for the next step where the Shiff base was reduced using sodium borohydride to give the diphenethyl amine (**IV-6**), which was not isolated. The third step involved the direct acidification of the amine using 2M HCl which gave diphenethylammonium hydrochloride (**IV-7**). This product was isolated as a white solid but a yield was not determined. The last step was the ion exchange using ammonium hexafluorophosphate. The product was obtained in an overall yield of 72.3 %. It must be noted that the synthesis must be done in one day without isolation of the non-salt products due to the instability of the Schiff base **IV-5**[1] and amine **IV-6**. Also, the desired product, **IV-8**, must be stored below room temperature to prevent decomposition.

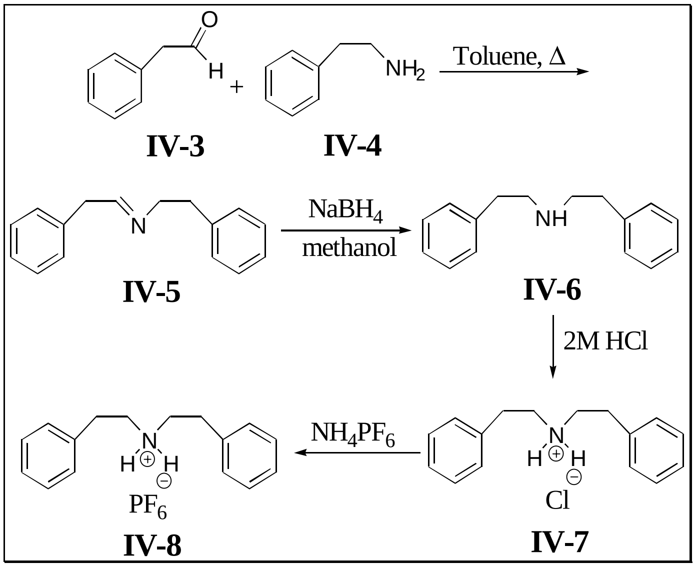

Figure IV-2. Synthesis of diphenethylammonium hexafluorophosphate (**IV-8**)

IV.2.2 Diammonium Bishexafluorophosphate Salts

1. N,N’-Dibenzyl-*m*- and *p*-xylylenediammonium Bishexafluorophosphates

Both diammonium bishexafluorophosphate salts, N,N’-dibenzyl-*m*-xylylenediammonium bishexafluorophosphate, **IV-17**, and N,N’-dibenzyl-*p*-xylylenediammonium bishexafluorophosphate, **IV-19**, were synthesized in four steps (**Figure IV-3**). The syntheses were conducted in a manner similar to that for the monoammonium salts discussed above. Benzaldehyde, **IV-9**, was reacted with the appropriate primary diamine to give the bis(Schiff bases) which were then reduced to their corresponding amines, which were then acidified to their chloride salts. Ion exchange using ammonium hexafluorophosphate resulted in the production of the desired bishexafluorophosphates **IV-17** and **IV-19**. The overall yields for the two products were 60.0 and 67.5 %, respectively.

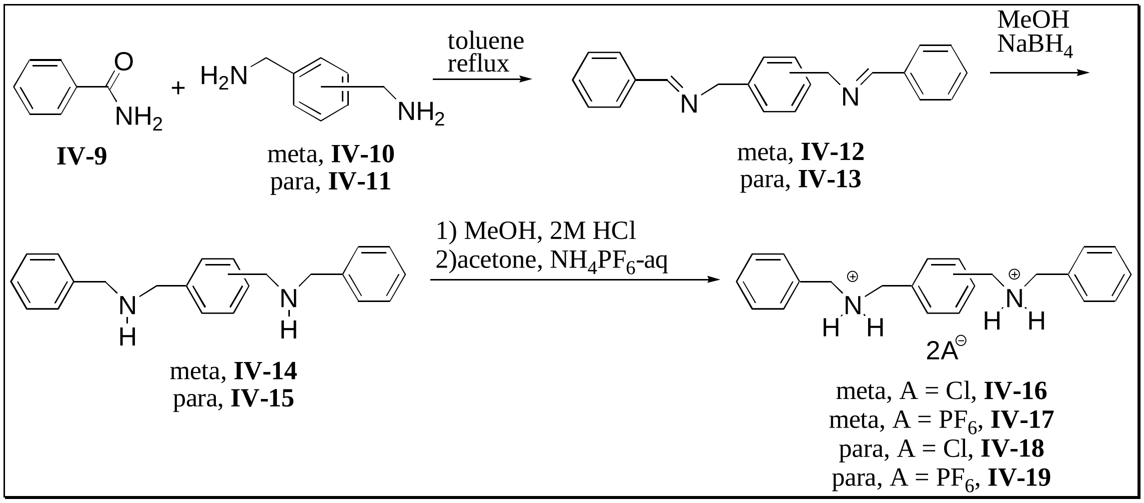

Figure IV-3. Synthesis of diammonium salts.

2. Deuterated N,N'-Dibenzyl-*m*- and *p*-xylylenediammonium Bishexafluorophosphates

To elucidate the peak assignments in the NMRs for the complexes formed from dibenzo-24-crown-8 and **IV-17** and **IV-19**, partially deuterated analogs of **IV-17** and **IV-19** were synthesized (**Figure IV-4**). Their complexation behavior with dibenzo-24-crown-8 will be discussed in **Chapter V**.

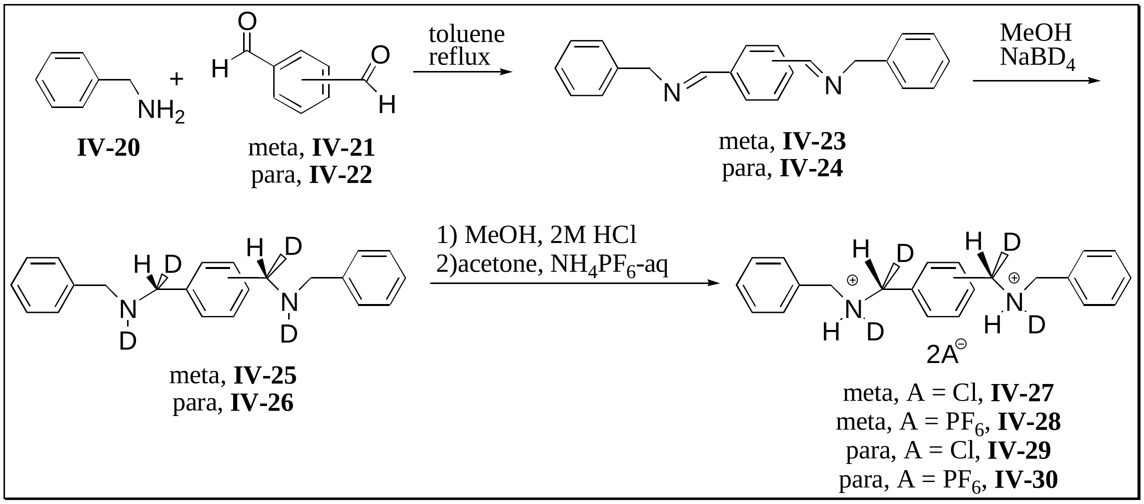

Figure IV-4. Synthesis of partially deuterated diammonium salts.

The first step of the syntheses was different from that of the undeuterated analogs. Here the appropriate diamines were condensed with benzaldehyde and this resulted in the two Schiff Bases **IV-23** and **IV-24**. These products were not characterized, but used directly for the reduction step. Sodium borodeuteride was used instead of sodium borohydride to give the partially deuterated amines **IV-25** and **IV-26**. Acidification of the amines followed by the ion exchange using ammonium hexafluorophosphate resulted in the desired products **IV-28** and **IV-30**. The yields were 50.7 and 20.0 %, respectively.

IV.3 Conclusions

Several monoammonium and diammonium salts of the hexafluorophosphate variety were synthesized including two partially deuterated diammonium bis(hexafluorophosphate) salts. These salts were synthesized as potential linear components for the formation of pseudorotaxanes. Their complexation behavior with crown ethers and cryptands will be discussed in the following chapter.

IV.4 Experimental

Chemical Reagents and Measurements

All chemicals were reagent grade and used directly as received from Aldrich except where specified. All solvents were HPLC or GC grade. Melting points were taken in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Varian spectrometer with tetramethylsilane as an internal standard. The following abbreviations have been used in describing NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), br s (broad singlet), br t (broad triplet), dd (doublet of doublets), and m (multiplet). Elemental Analyses were performed by Atlantic Microlabs of Norcross, GA. IR were obtained on a Perkin-Elmer spectrometer using KBr pellets.

1. Di-*n*-butylammonium hexafluorophosphate (IV-1): Di-*n*-butyl amine (10.0 g, 77.4 mmole) was placed in a 3-neck round bottom flask equipped with a reflux condenser and a magnetic stir bar. The flask was placed in an ice bath and 20 ml of DI water was added. To the stirring solution 250 ml of 2M HCl was added dropwise. This resulting solution was stirred for 24h. The solvent was removed to afford a white solid. The solid was suspended in 150 ml of DI water. Upon heating, the solid dissolved. Ammonium hexafluorophosphate (~ 13 g) was then added until precipitation ceased. The white solid was filtered and dried in the open air overnight. Yield = 19.11 g (87.8 %). mp = 260 °C (dec) (lit.[2] = 245 °C). ^{1}H NMR (400 MHz, CD_3CN, ambient T), δ (ppm): 6.29 (br t, 2H), 2.95 (m, 6H), 1.36 (h, J = 7.2 Hz , 4H), 1.59 (p, J = 7.2 Hz, 4H), 0.93 (t, J = 7.2 Hz, 4H). ^{13}C NMR (100 MHz, CD_3CN, ambient T), δ (ppm): 13.7, 20.2, 28.6, 49.0 (4 peaks as required).

2. Dibenzylammonium hexafluorophosphate (IV-2): 2 M HCl (250 mL) was added to dibenzylamine (4.93 g, 25 mmole). Immediately a white precipitate was observed. The solution was stirred for 4 hours at room temperature. The water was removed and the white solid was redissolved in 100 mL of water. The white precipitate dissolved upon heating. A saturated aqueous solution of ammonium hexafluorophosphate was added to the hot water solution until precipitation ceased. The precipitate was filtered and washed with hot water. The white solid was recrystallized twice in water and dried overnight. Yield = 3.77 g (43.9 %). Mp = 207.1-209.1 ^{o}C (lit.[2] = 192-193 ^{o}C). ^{1}H NMR (400 MHz, CD_3CN, ambient T), δ (ppm): 7.47 (m, 10H), 7.0 (br s, 2H), 2.24 (s, 4H).

3. Diphenethylammonium hexafluorophosphate (IV-8): A solution of phenylacetaldehyde (**IV-3**, 5.38g, 44.8 mmol) and phenethylamine (**VI-4**, 5.45 g, 45.0 mmol) and ~75 mL of toluene was heated at reflux with a Dean-Stark trap for 2 h and then cooled to rt. The solvent was removed by rotoevaporation to give a yellow oil. The oil was dissolved in CH_3OH (100 mL) and $NaBH_4$ (1.7g, 44.8 mmol) was added over 1h. The resulting suspension was heated to reflux and maintained for 15 min. Deionized (DI) H_2O (100 mL) was then added. The solvent was removed by rotoevaporation and another 100 mL of DI H_2O was added at ~ 0 ^{o}C. A tacky, yellow oil was observed and the H_2O was decanted. CH_3OH (25 mL) was added to the oil followed by 2M HCl (250 mL) at ~ 0 ^{o}C. The resulting solution was stirred for 2 h. A yellow oil was observed in the bottom of the flask. The CH_3OH/H_2O layer was decanted. The solvents were removed by rotoevaporation to give a yellow solid. MP = 264.8 - 266.2 (lit.[3] Mp = 265 - 266 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T) δ (ppm): 7.26 (m, 10H), 2.94 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6, ambient T) δ (ppm): 137.6, 128.7, 126.8, 40.0, 33.0. The chloride salt was stirred in hot H_2O and solid NH_4PF_6 was added until precipitation ceased. The white precipitate was filtered and then dried in a desiccator. Yield = 12.08 g (72.3 %), mp = 155 ^{o}C (sublimes). ^{1}H NMR (400 MHz, CD_3CN, ambient T) δ (ppm): 7.31 (m, 10H), 3.23(t, J = 8.4 Hz, 8H), 2.94 (t, J = 8.4 Hz, 8H). ^{13}C NMR (100 MHz, DMSO-d_6, ambient T) δ (ppm): 136.9, 128.6, 126.8, 47.7, 31.5. IR: 3030, 2930, 2797, 2432, 1753, 1590, 841, 752, 690, 564, 488 cm^{-1}.

4. N,N'-dibenzylidene-*m*-xylylenediamine (IV-12): Benzaldehyde (**IV-9**, 13.5g, 127.2 mmole) was placed in a three-neck round bottom flask equipped with a Dean-Stark apparatus containing 100 mL of toluene. *m*-Xylylenediamine (**VI-10**, 8.66g, 63.6 mmole) was then added dropwise to the stirring solution at RT. The solution was then heated to reflux. The reaction was complete when no more water was collected in the Dean-Stark apparatus. After removal of the solvent a slightly yellow oil was observed. Trituration with hexanes gave a powdery white solid. Recrystallization was done from hexanes/ethyl acetate. Yield = 17.39 (87.5 %). Mp = 66.2 - 66.7 °C (Lit.[4] = 67 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T), δ (ppm): 8.39 (s, 2H), 7.78 (m, 4H), 7.41 (m, 6H), 7.31 (m, 2H), 7.24 (m, 2H), 4.82 (s, 4H). ^{13}C NMR (100 MHz), δ (ppm): 162.0, 139.5, 137.1, 130.7, 128.7, 128.6, 128.3, 127.6, 126.7, 65.0 (10 peaks as required).

5. N,N'-dibenzyl-*m*-xylylenediamine (IV-14): IV-12 (17.0g, 54.4 mmole) was added to a two-neck round bottom flask containing 175 mL of MeOH and a magnetic stir bar. The flask was equipped with a condenser and heated to 40 °C with stirring. $NaBH_4$ (4.12g, 108.8 mmoles) was added slowly over a 1h period. The resulting mixture was stirred under reflux for 15 min. Upon cooling the mixture was diluted with DI water (200 mL). A yellow-white oil settled out. Chloroform was added to the flask and the two-layered solution was then transferred to a separatory funnel. The chloroform layer was collected and the water layer was washed two times (100 mL) with chloroform. After removal of the organic solvent a yellow oil was obtained. After trituration with hexanes and cooling in the freezer a solid formed. The solid was filtered and dried in an oven overnight at 65 °C. Yield = 14.05 g (82.2 %). Mp = 31.3 - 32.6 °C (Lit.[5] = 33.5 - 34.8 °C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 7.27 (m, 14H), 3.79 (s, 4H), 3.80 (s, 4H), 1.61 (br s, 2H). ^{13}C NMR (100 MHz), δ (ppm): 140.4, 140.2, 128.3, 128.3, 128.1, 127.8, 126.8, 126.7, 53.2, 53.1 (10 peaks as required).

6. N,N'-dibenzyl-*m*-xylylenediammonium dichloride (IV-16): IV-14 (14.0g, 44.2 mmole) was dissolved in ~60 mL of MeOH and placed in a 500 mL three-neck round bottom flask equipped with a condenser. The flask was placed in an ice bath. 200 mL of a 2M solution of HCl was then added slowly. After the first 100 mL a white precipitate was observed. Upon complete addition of the acidic solution the magnetic stir bar was unable to stir. The solvent was removed and the white powder was dried under vacuum at 65°C for 14h. Yield = 17.06 g (99.0 %). Mp = 217.6 - 222.6 °C (Mp for perchlorate salt[6] = 217 - 218 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 9.83 (br s, 4H), 7.71 (m, 1H), 7.64 (dd, J = 0.8, 4.6 Hz, 2H), 7.60 (m, 4H), 7.50 (t, J = 7.6 Hz, 1H), 7.42 (m, 6H), 4.16 (s, 8H). ^{13}C NMR (100 MHz), δ (ppm): 132.4, 132.1, 131.9, 130.9, 130.3, 129.1, 128.7, 49.9, 49.7 (9 peaks).

7. N,N'-dibenzyl-*m*-xylylenediammonium bis(hexafluorophosphate) (IV-18): IV-16 (16.11g, 41.4 mmole) was dissolved in hot DI water (~300 mL). A saturated aqueous solution of ammonium hexafluorophosphate was then added slowly until precipitation ceased. The solid was filtered and washed with DI water. White needles were obtained. The needles were dried under vacuum at ~65 °C for 14h. Yield = 16.20 g (84.4 %). Mp = 216.3-219.5 °C. (lit. Mp for diperchlorate salt[6] = 217 - 218 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 9.26 (bs, 4H), 7.57 (m, 3H), 7.46 (m, 11H), 4.19 (s, 4H), 4.18 (s, 4H). ^{13}C NMR (100 MHz), δ (ppm): 132.5, 132.1, 132.0, 131.1, 130.4, 129.7, 129.6, 129.2, 50.6, 50.27 (10 peaks as required).

8. N,N'-dibenzylidene-*p*-xylylenediamine (IV-13): Benzaldehyde (**IV-9**, 5.09 g, 48.0 mmole) was placed in a three-neck round bottom flask equipped with a Dean-Stark apparatus containing 200 mL of toluene. *p*-Xylylenediamine (**IV-11**, 3.27 g, 24.0 mmole) was then added dropwise to the stirring solution at RT. The solution was then heated at reflux for 2h. The reaction was complete when no more water was collected in the Dean-Stark apparatus. After removal of the solvent a slightly yellow solid was observed. Recrystallization was done from hexanes/ethyl acetate. Yield = 7.34 g (97.9 %). Mp = 90.5 - 91.7 °C (lit.[6] = 89.2 - 91.6 ^{o}C). ^{1}H NMR (400 MHz, DMSO-d_6, ambient T), δ (ppm): 8.50 (s, 2H), 7.78 (m, 4H), 7.46 (m, 6H), 7.32 (s, 4H), 4.78 (s, 2H), 4.77 (s, 2H). ^{13}C NMR (100 MHz), δ (ppm): 162.1, 138.6, 136.5, 131.2, 129.11, 128.4, 128.4, 64.18 (8 peaks as required).

9. N,N'-dibenzyl-*p*-xylylenediammonium bis(hexafluorophosphate) (IV-19): **IV-13** (6.00 g, 19.2 mmole) was added to a two-neck round bottom flask containing 50 mL of methanol (HPLC grade) and a magnetic stir bar. The flask was equipped with a condenser and heated to 40 °C. $NaBH_4$ (3.80 g, 0.10 moles) was added slowly over a 1h period. The resulting mixture was stirred under reflux for 8h. Upon cooling the solvent was removed and the residue was suspended in DI water (30 ml) and extracted with methylene chloride (4x10 ml). The water layer was concentrated and the resulting white solid was filtered and washed with water. The solid was dried in a vacuum oven. 7.22 g was obtained. The solid was insoluble in DMSO and did not melt when heated to 350 °C. The white solid (6.47 g, 16.6 mmole) was suspended in 100 ml of acetone and stirred with a magnetic stir bar. A saturated solution of NH_4PF_6 was then added (~7 g). The resulting white solid suspension was filtered and washed with acetone. The solvent was removed to afford a white solid. Yield = 68.9 % (6.05 g). Mp = 261.2 - 263.6 ^{o}C (lit.[7] = 238 (dec.) ^{o}C). ^{1}H NMR (400 MHz, CD_3CN, ambient T), δ (ppm): 7.51 (s, 10H), 7.45 (s, 4H), 4.23 (s, 4H), 4.21 (s, 4H). ^{13}C NMR (100 MHz), δ (ppm): 133.1, 131.7, 131.5, 131.2, 130.7, 130.11, 52.31, 51.56 (8 peaks as required).

10. N,N'-Dibenzyl-*m*-xylylenediammonium-d$_4$ bis(hexafluorophosphate) (IV-28): A solution of benzylamine (**IV-20**, 3.84 g, 23.0 mmol) and isophthaldehyde (**IV-21**, 1.54 g, 11.5 mmol) was heated at reflux in toluene (50 ml) with stirring in a Dean-Stark apparatus overnight. Upon cooling, the solvent was removed using a rotoevaporator to give 1,3-bis(benzyliminomethyl)benzene (**IV-23**) as a solid. The solid was dissolved in MeOH (50 ml) and $NaBD_4$ (2.00 g, 47.8 mmol) was added slowly to the reaction mixture. The reaction mixture was heated at reflux for 8 h. Upon cooling, concentrated HCl was added (pH < 2). After rotoevaporation of the solvent a solid was obtained. The solid was extracted using water (30 ml) and CH_2Cl_2 (2 x 50 ml). The combined extracts were washed with a 5% solution of $NaHCO_3$ (2 x 60 ml) and water (50 ml) and then dried with $MgSO_4$. The organic solvent was removed by rotoevaporation to give 1,3-bis(benzlyaminomethyl)benzene-d_2 (**IV-25**) as a colorless solid. The solid was dissolved in MeOH (50 ml) and concentrated HCl was added (pH < 2), and the reaction mixture was stirred for 1 h. Removal of the solvent by rotoevaporation gave a colorless solid, which was suspended in acetone (50 ml). A saturated solution of NH_4PF_6 in water was added until dissolution occurred. Removal of the solvent by rotoevaporation gave a white solid. The solid was washed with water and dried under vacuum. Yield = 50.7 % (3.57 g). Mp = 214.9 - 216.9 °C. ^{1}H NMR (400 MHz, CD_3CN, ambient T) δ (ppm): 7.83 (br s, 2H), 7.73 (m, 1H), 7.67 (m, 3H), 7.60 (m, 10H), 4.34 (m, 6H); ^{13}C NMR (100 MHz) δ (ppm): 133.3, 132.4, 132.2, 131.4, 131.2, 130.8, 130.7, 130.1, 52.2, 51.2 (10 carbons as expected).

11. N,N'-Dibenzyl-*p*-xylylenediammonium-d_4 bis(hexafluorophosphate) (IV-30) A solution of **IV-20** (3.84 g, 23.0 mmol) and terephthaldehyde (**IV-22**, 1.54 g, 11.5 mmol) was heated at reflux in toluene (100 ml) with stirring in a Dean-Stark apparatus overnight. Upon cooling, the solvent was removed using a rotoevaporator to give 1,4-bis(benzyliminomethyl)benzene (**IV-24**) as a solid. The solid was dissolved in MeOH (50 ml) and $NaBD_4$ (2.00 g, 47.8 mmol) was added slowly to the reaction mixture. The reaction mixture was heated at reflux for 8 h. Upon cooling concentrated HCl was added (pH < 2). After rotoevaporation of the solvent a solid was obtained. The solid was extracted using water (30 ml) and CH_2Cl_2 (2 x 50 ml). The combined extracts were washed with a 5% solution of $NaHCO_3$ (2 x 60 ml) and water (50 ml) and then dried with $MgSO_4$. The solvent was removed by rotoevaporation to give 1,4-bis(benzlyaminomethyl)benzene-d_2 (**IV-26**) as a colorless solid. The solid was dissolved in MeOH (50 ml) and concentrated HCl was added (pH < 2), and the reaction mixture was stirred for 1 h. Removal of the solvent by rotoevaporation gave a colorless solid, which was suspended in acetone (50 ml). A saturated solution of NH_4PF_6 in water was added until dissolution occurred. Removal of the solvent by rotoevaporation gave a white solid. The solid was washed with water and dried under vacuum. Yield = 20.0 % (1.57 g). Mp = 258.4 - 260.1 ^{o}C. ^{1}H NMR (400 MHz, CD_3CN, ambient T) δ (ppm): 7.52 – 7.48 (m, 4H), 7.47 – 7.43 (m, 10H), 4.20 (br s, 2H), 4.20 (s, 4H); ^{13}C NMR (100 MHz) δ (ppm): 133.0, 131.7, 131.5, 131.1, 130.7, 130.1, 52.2, 51.2 (8 carbons as expected).

IV.5 References

1) Bellas, M.; Suschitzky, H. J. *J. Chem. Soc.* **1966**, 189.
2) Mohamed, K.; Padma, D. K.; Kalbankeri, R. G.; Murthy, A. R. *Indian J. Chem. Sect. A* **1985**, *24*, 195-198.
3) Yates, P.; Giles, R. G. F.; Farnum, D. G. *Can. J. Chem* **1969**, *47*, 3997.
4) Ruggli; Leupin; Dahn *Helv. Chim. Acta.* **1947**, *30,* 1845.
5) Rikagaku, K.; Sewa, D. ; Rikagaku, K.; Sewa, D., Ed.: Japan, 1977.
6) Ruggli, P.; Leupin, E.; Dahn, H. *Helv. Chim. Acta* **1947**, *30*, 1845.
7) Ashton, P. R.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Schiavo, C.; Stoddart, J. F.; Tasker, P. A.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*.