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Polyvalent Interactions in Unnatural Recognition Processes

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The synthesis of two cluster compounds, one containing six secondary dialkylammonium ion centers and the other possessing six benzo-*m*-phenylene[25]crown-8 (BMP25C8) macrocycles, both appended to hexakis(thiophenyl)benzene cores, is described. The binding of these clusters with complementary mono- and divalent ligands is investigated with NMR spectroscopy to probe polyvalency in these unnatural recognition systems. The ability of the two different families of clusters to bind complementary monovalent ligands is compared with that of the monovalent receptor pair, namely the dibenzylammonium ion and BMP25C8. This comparison is made possible by determining an average association constant (K_{AVE}) for the binding of each recognition site on the cluster with the corresponding monovalent ligand. We have found that the clustering of recognition sites together in one molecule is detrimental to their individual abilities to bind monovalent ligands. In the case of the polyvalent interaction between the hexakisBMP25C8 cluster and divalent dialkylammonium ions, an association constant, K_{POLY}, was calculated from the value of K_{AVE} determined for the complexation of the individual component recognition sites. This polyvalent interaction is significantly stronger than that associated with the averaged monovalent interactions.

Introduction

In natural systems it has been observed[1] that the binding interactions between multivalent clusters of receptors and substrates can be extremely strong, even though individually these ligands bind only weakly to each other. An example of this concept of employing polyvalent interactions between species is the phenomenon known[2] as the "glycoside cluster effect", in which the relatively low binding affinity exhibited between single carbohydrate ligands and lectins is overcome by the clustering together of these ligands. These clusters of carbohydrate ligands show enhanced binding affinities to lectins and are involved in many important biological processes by which cells, bacteria, and viruses recognize one another. The two most important mechanisms[3] that are responsible for this enhancement in the binding affinity between carbohydrate clusters and lectins are (i) statistical effects and (ii) the chelate effect. Statistical effects can express themselves in a cluster presenting a high local concentration of, for example, carbohydrate ligands, which may lead to lower dissociation rates and hence stronger binding with a lectin. In the case of the chelate effect, the multiple binding moieties in a carbohydrate ligand can bind cooperatively to the lectin, leading to a strong interaction. Chemists[4] are starting to employ this concept of polyvalency in the synthesis of artificial receptors and ligands. There have been a number of striking examples[5] of multi- and polyvalent ligands—designed either rationally or randomly—that

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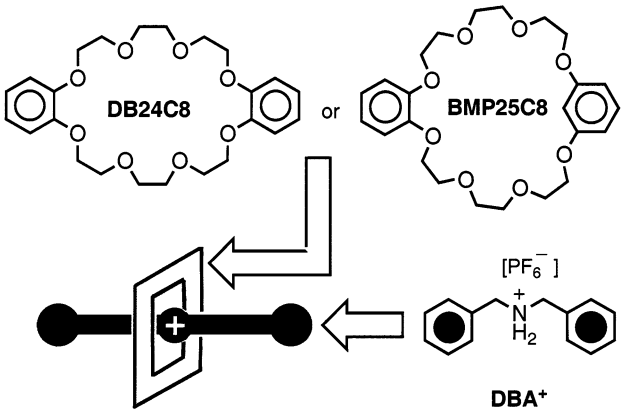

FIGURE 1. Dibenzylammonium ions (DBA^+) form complexes possessing pseudorotaxane superstructures with the crown ethers dibenzo[24]crown-8 (DB24C8) and bis-*m*-phenylene[25]-crown-8 (BMP25C8).

show promising inhibitory behavior toward toxins, viruses, and bacteria.

The complexation (Figure 1) between dibenzylammonium (DBA^+) cations and dibenzo[24]crown-8 (DB24C8) or benzo-*m*-phenylene[25]crown-8 (BMP25C8) derivatives is an example of an extensively studied[6−9] monovalent interaction. Although there are examples[10,11] where this binding interaction is enhanced by the clustering together of multiple copies of this recognition motif, they are few in number. The clustering of binding sites (Figure 2) in the tris(dialkylammonium) salt **1**·3PF_6 and the tris(crown ether) **2** results[10] in an extremely stable complex being formed when the two are mixed. The value[12] for the association constant (K_a) between **1**·3PF_6 and **2** is greater

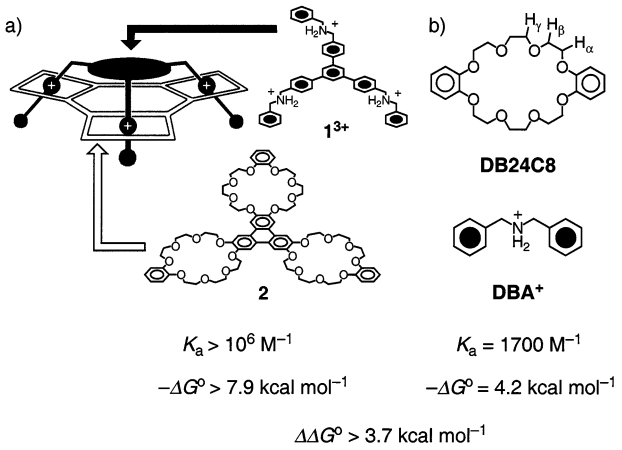

FIGURE 2. The binding in $CDCl_3/CD_3CN$ (1:1) of (a) the trisammonium salt **1**·3PF_6 and tris(crown ether) **2** is considerably stronger than the corresponding monovalent interaction between (b) DB24C8 and DBA^+.

than 10^6 M^{-1} in $CDCl_3/CD_3CN$ (1:1), a K_a value that corresponds to a free energy of binding ($-\Delta G°$) of more than 7.9 kcal mol^{-1}. For the corresponding monovalent interaction between DB24C8 and the DBA^+ ion in the same solvent mixture, an association constant of 1700 M^{-1} has been determined.[6b] This value of K_a corresponds to a free energy of binding of 4.2 kcal mol^{-1}. Thus, the polyvalent interaction between the two trivalent species is in excess of 3.7 kcal mol^{-1} more favorable than the

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corresponding monovalent interaction. It has also been observed[11] that cyclodextrin clusters bearing seven DB24C8 or seven BMP25C8 rings bind monovalent dialkylammonium salts more weakly than does DB24C8 or BMP25C8, respectively. It was found, however, that the strength of binding of these clusters to a divalent bis(dialkylammonium) salt is much stronger than the interactions between the corresponding monovalent species. That is to say, these crown ether clusters show reduced binding toward monovalent ionic species, but enhanced binding to multivalent ionic compounds, relative to the strength of the parent monovalent systems. To understand better these phenomena, we have investigated the binding of other multivalent clusters bearing crown ether and dialkylammonium ion recognition sites with monovalent and divalent ligands.

As the recognition system involves the interaction of multiply charged species, our observations may also be of relevance to the self-assembly of other systems, e.g., the self-assembly of block copolymer micelles via the aggregation of multiply charged amphiphilic block copolymers.[13] Recent developments in this vast field of research include the development of polyelectrolyte copolymers, which have potential for use as drug-delivering microgels.[14]

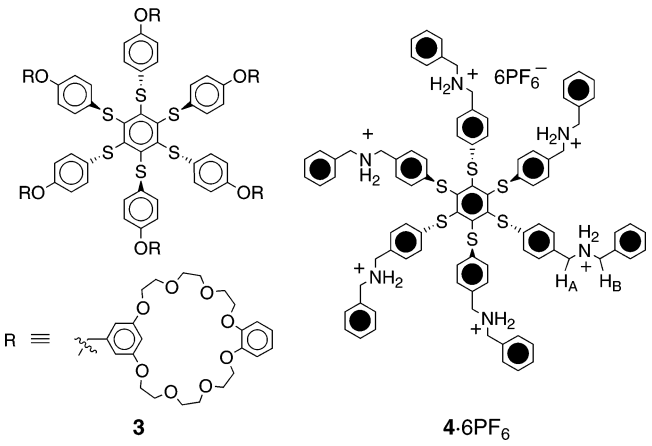

FIGURE 3. The clusters **3** and **4**·6PF_6, which present six crown ether rings and six dialkylammonium ion centers, respectively.

This paper describes the synthesis of two multivalent such clusters (Figure 3), one bearing six crown ether rings (**3**), and the other possessing six secondary dialkylammonium ion centers (**4**·6PF_6). We have probed the binding of these clusters to complementary monovalent and polyvalent ligands by NMR spectroscopy to evaluate the contributions of statistical and chelate effects to polyvalent interactions in such unnatural recognition systems. A hexakis(phenylthio)benzene core was employed in the clusters since (i) it can be readily synthesized and (ii) the recognition sites attached to this core are spatially arranged in a precise manner with a large degree of directionality and symmetry. Hexakis(phenylthio)benzene derivatives usually possess, in both the solid state[15] and in solution,[16] conformations in which neighboring substituents of the benzenoid core point in opposite directions—that is to say, the thiophenyl substituents on the 1,3,5-positions of the central aromatic ring point in one direction with respect to the plane of the central benzenoid core and those on the 2,4,6-positions point in the opposite direction.

Results and Discussion

Synthesis of the Hexakis(phenylthio)benzene Clusters. Hexakis(phenylthio)benzene derivatives can be synthesized[17] readily by substituting the fluorine atoms on hexafluorobenzene with aromatic thiolate ions in aprotic, polar solvents, such as 1,3-dimethylimidazolidin-2-one (DMI). This reaction proceeds well at room temperature, generally requiring only a few hours to reach completion.

Synthesis of the Hexakis(crown ether) Cluster. The hexakisBMP25C8 cluster **3** was synthesized as outlined in Scheme 1. We employed a divergent strategy, first preparing the hexathiobenzene core and then attaching the crown ether appendages to the periphery of this core. Hexakis(*p*-methoxyphenylthio)benzene[16] (**5**) was obtained by reacting the thiolate anion of *p*-methoxythiophenol and hexafluorobenzene in DMI. This compound was demethylated by using boron tribromide to afford hexakis(*p*-hydroxyphenylthio)benzene (**6**). The BMP25C8 derivative **8** was prepared by macrocyclization, under high dilution conditions, between the commercially available 3,5-dihydroxybenzyl alcohol and the bistosylate[11] **7**. This crown ether was reacted subsequently with methanesulfonyl chloride to afford the mesylate **9**. Hexakis(*p*-hydroxyphenylthio)benzene (**6**) was then reacted with the BMP25C8 derivative **9** in MeCN, in the presence of K_2CO_3 and [18]crown-6, to produce a good yield of the hexakisBMP25C8 cluster **3**.

Synthesis of the Dialkylammonium Cluster. The hexakis(dialkylammonium) cluster **4**·6PF_6 was synthesized (Scheme 2) starting from the commercially available 4-methylthiobenzaldehyde. The starting material was converted to the dialdehyde disulfide **11**, employing a procedure similar to that reported in the literature.[18] First, the thioether was oxidized to the sulfoxide **10** with *m*-chloroperoxybenzoic acid (mCPBA) at 0 °C to avoid over-oxidation. After purification by column chromatography, the sulfoxide **10** was subjected to a Pummerer rearrangement with trifluoroacetic anhydride, followed by hydrolysis with a mixture of methanol and triethy-

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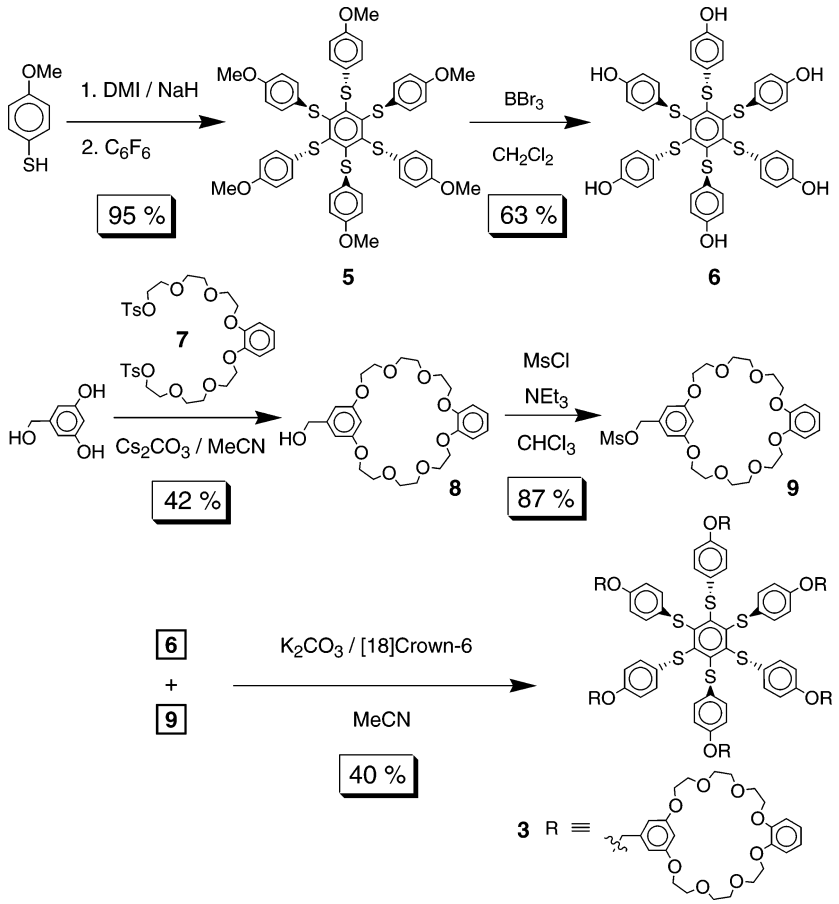
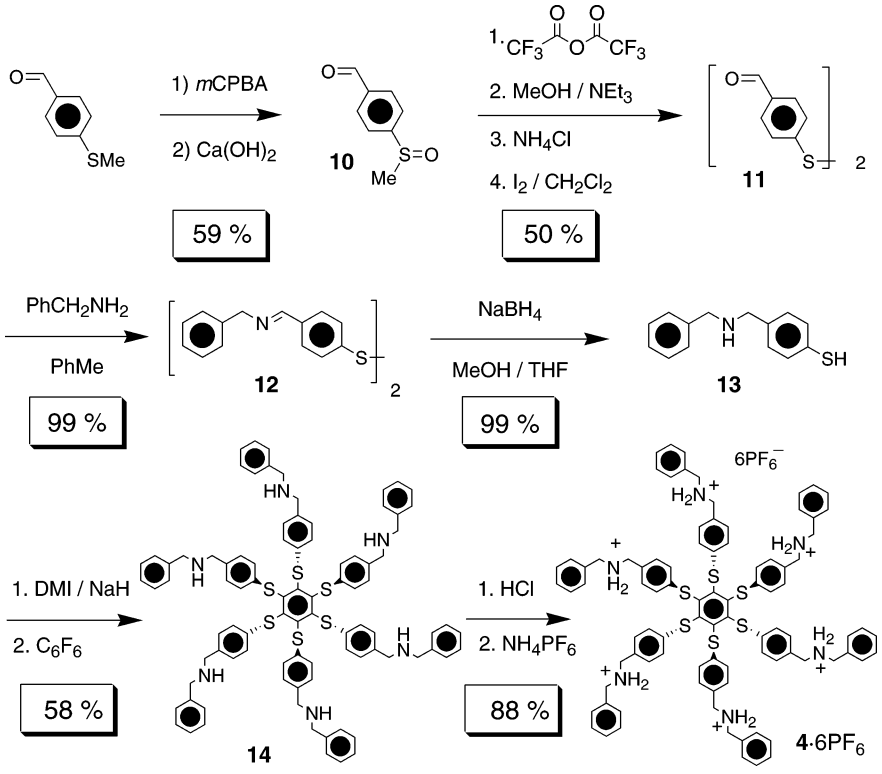
SCHEME 1. The Synthesis of the HexakisBMP25C8 Cluster 3



SCHEME 2. The Synthesis of the Hexakis(dialkylammonium ion) Cluster 4·6PF$_6$



lamine to afford the corresponding thiol-bearing benzaldehyde. For ease of characterization and use, this thiol was oxidized, using iodine, to form the disulfide **11**. The dialdehyde disulfide **11** was condensed with benzylamine

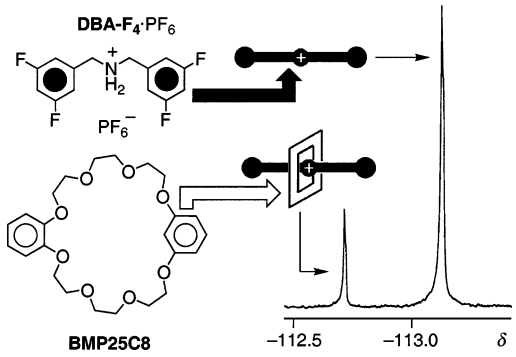


FIGURE 4. Partial ^{19}F NMR spectrum [376 MHz, CD_2Cl_2/CD_3CN (1:1), 300 K] of an equimolar solution of BMP25C8 and DBA-F_4·PF_6.

to yield the diimine disulfide **12**. In one step, the imino and disulfide groups were reduced by using sodium borohydride to afford the thiol **13**. Sodium hydride was employed to form the thiolate anion from the thiol **13**. This thiolate anion was then reacted, in DMI, with hexafluorobenzene at room temperature to give the hexaamine **14**. The structure was confirmed by its ^{13}C NMR spectrum, which exhibited only one signal corresponding to the carbon atoms of the thiobenzene core at a characteristic[16] chemical shift of 148 ppm. The hexaamine **14** was protonated with concentrated hydrochloric acid to give the hexakis-hydrochloride salt. Counterion exchange with ammonium hexafluorophosphate afforded the desired hexakis(dialkylammonium) hexakis(hexafluorophosphate) salt **4**·6PF_6 as a yellow solid.

Studying Statistical Effects in the Binding of Cluster Compounds with Monovalent Ligands. To investigate the importance of statistical effects in the interactions of multivalent crown ethers and multivalent dialkylammonium salts with their respective ligands, we studied their strength of binding with complementary monovalent species. If statistical effects play an important role in the polyvalent binding of these systems, an increase in the strength of complexation of the individual binding moieties with monovalent species would be expected.

Binding between the Hexakis(crown ether) Cluster and Monovalent Ligands. To investigate how the clustering of the crown ether moieties in the hexakis-BMP25C8 cluster **3** might affect the strength of the binding to secondary dialkylammonium ions of each moiety, we studied the complexation between this cluster and bis(3,5-difluorobenzyl)ammonium hexafluorophosphate salt DBA-F_4·PF_6. The dialkylammonium salt DBA-F_4·PF_6 is known[7e] to complex with BMP25C8 with an association constant of 25 M^{-1} in CD_3CN. In this binding process, the rate of exchange[19] between the free and complexed species is slow on the ^{19}F NMR time scale at 376 MHz. As a result, the ^{19}F NMR spectrum of a solution of BMP25C8 and DBA-F_4·PF_6 reveals (Figure 4) two resonances that correspond to the fluoro substituents of the dialkylammonium ion. The relatively downfield resonance (−112.7 ppm) corresponds to the fluorine atoms of the [BMP25C8·DBA-F_4][PF_6] complex and the more upfield one (−113.1 ppm) to the free DBA-F_4^+ ion. Hence, by comparing the ratio of the integrals of these two resonances, the relative concentrations of the complexed and free species can be calculated and, thus, a value for the binding constant (K_a) between the two components can be determined.

^{19}F NMR spectra of solutions of the hexakisBMP25C8 cluster **3** and DBA-F_4·PF_6 reveal (Figure 5) a signal (−113.1 ppm) corresponding to the fluorine atoms in free DBA-F_4^+ ions and a set of overlapping signals (−112.4 to −112.6 ppm) corresponding to fluorine atoms of bound DBA-F_4^+ ions. These overlapping signals presumably correspond to fluorine atoms of the inclusion complexes, ranging from [2]- through to [7]pseudorotaxanes, formed between the hexakis(crown ether) and the cation. Although assigning these signals to the different [*n*]-pseudorotaxane species is not an easy task, the total concentration of complexed and uncomplexed DBA-F_4^+ ions can be determined readily by integration of the spectrum. An average association constant (K_{AVE}) for the complexation can be calculated from these concentrations. This average association constant[11] is defined as a measure of the strength of the binding interactions between a single crown ether moiety and a single secondary dialkylammonium moiety. This quantity can be defined as

$$K_{AVE} = \frac{[\text{complexed } NH_2^+ \text{ centers}]}{[\text{uncomplexed } NH_2^+ \text{ centers}][\text{uncomplexed crown ether units}]} \quad (1)$$

We define an "NH_2^+ center" as a single secondary dialkylammonium ion center within a compound containing one or more of these centers, and a "crown ether unit" as a single crown ether moiety within a compound containing one or more of these moieties.

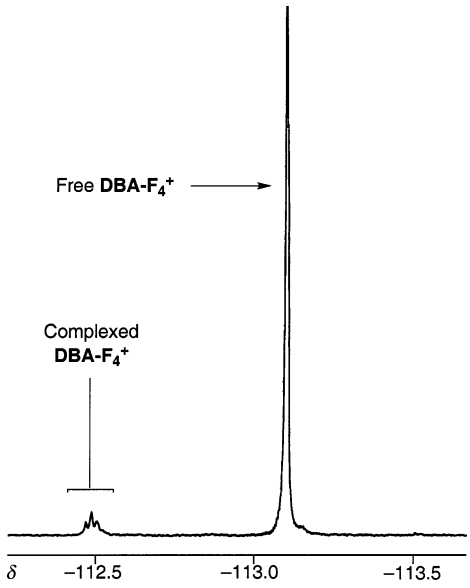


FIGURE 5. Partial ^{19}F NMR spectrum [376 MHz, CD_2Cl_2/CD_3CN (1:1), 300 K] of a solution of the hexakisBMP25C8 cluster **3** and DBA-F_4·PF_6.

(19) In the interaction with the DBA^+ ion, the rate of exchange between complexed and uncomplexed BMP25C8 species is neither slow nor fast on the NMR spectroscopic time scale at 300−600 MHz. ^1H and ^{19}F NMR spectra containing broad resonances result from this phenomenon and, hence, the value of K_a cannot be determined easily by the single-point method.

Historically, the determination of an association constant for the binding of a dibenzylammonium cation by a DB24C8 receptor, undergoing slow exchange on the NMR time scale, has been performed by the single-point method. Indeed, since the complexation of dialkylammonium cations by macrocyclic polyethers was first reported,[6a,20] many papers have utilized the single-point method to determine association constants. Gibson et al. has published[9h,21] recently a more sophisticated analysis for the complexation of ionic guests by neutral receptors. This analysis takes into account the ion-pairing equilibrium between the guest cation and its associated counterion. The effects of this equilibrium can manifest themselves in concentration-dependent fluctuations in the apparent K_a values, and their more sophisticated equilibrium treatment takes this observation into account. Our attempts to reanalyze our data from the experiments presented here, utilizing the method described by Gibson et al., resulted in very limited success—only the simplest experiments involving the complexation of a monocationic guest by a monovalent crown ether afforded sensible values for K_a. When the treatment was applied to experimental data from our own systems involving polyvalent recognition, spurious results were obtained. Consequently, we have analyzed our own experimental data using the method described[6b,7a,b,11,22] previously by our own research group, one that is based firmly upon the tried-and-tested single-point method for the determination of K_a.

For a system in which there are two monovalent ligands present that bind together in a 1:1 stoichiometry (e.g., BMP25C8 and DBA-F_4·PF_6), K_{AVE} is simply the standard association constant (i.e., K_a). In a system where there are multivalent species present, however, K_{AVE} is the association constant for each crown ether/dialkylammonium ion binding interaction viewed independently from each other. Thus, by comparing the values of K_{AVE} for the binding of DBA-F_4·PF_6 with (i) BMP25C8 and (ii) the hexakisBMP25C8 cluster **3**, the effect of clustering the crown ether moieties on their binding of DBA-F_4^+ ions can be determined. First, to determine an accurate value of K_{AVE} for the binding between BMP25C8 and DBA-F_4·PF_6, ^{19}F NMR spectra were obtained for a series of solutions of the two species in CD_3CN/CD_2Cl_2 (1:1). In each solution, the concentration of BMP25C8 was held constant at 3.0 mM, while the concentration of DBA-F_4·PF_6 was varied from 1.0 to 15.1 mM. From each of these spectra, a value for K_{AVE} was determined by using the single-point method.[6,11] A binding isotherm,[23] based on a 1:1 model for this system, was constructed (Figure 6) by plotting ([complex]/[crown ether moieties]$_{TOT}$) against [free NH_2^+ centers]. This binding isotherm could then be compared with others to obtain a qualitative assessment of binding strength of the individual crown ethers to the dialkylammonium ion centers. The mean of the values of K_{AVE} for the individual data points was calculated to be 116 ± 35 M^{-1}, a value that corresponds to a mean free energy change, $\Delta G°_{AVE}$, of −2.8 ± 0.2 kcal mol^{-1}.

A similar set of ^{19}F NMR titration experiments were undertaken in CD_3CN/CD_2Cl_2 (1:1) between the hexakis-BMP25C8 cluster **3** and DBA-F_4·PF_6. In these experiments, the concentration of **3** was held constant at 0.5 mM, i.e., the concentration of crown ether sites corresponded to 3.0 mM, just as was the case in the titration experiments between BMP25C8 and DBA-F_4·PF_6. The concentration of the salt was varied from 1.01 to 12.12 mM. From the relative integrals of all the resonances corresponding to complexed DBA-F_4^+ ions and the free DBA-F_4^+ ions, we determined the concentrations of complexed NH_2^+ centers. From these experiments, a binding isotherm was plotted (Figure 6) and a mean value of K_{AVE} was calculated to be 48 ± 14 M^{-1}, which corresponds to a mean $\Delta G°_{AVE}$ of −2.3 ± 0.2 kcal mol^{-1}. It should also be noted from the separate data points that the individual values of K_{AVE}, between the hexakis-BMP25C8 cluster **3** and DBA-F_4^+ ions, decrease as the concentration of the salt is increased.

From the comparison of the binding isotherms and the mean values of the K_{AVE}, it is apparent that BMP25C8

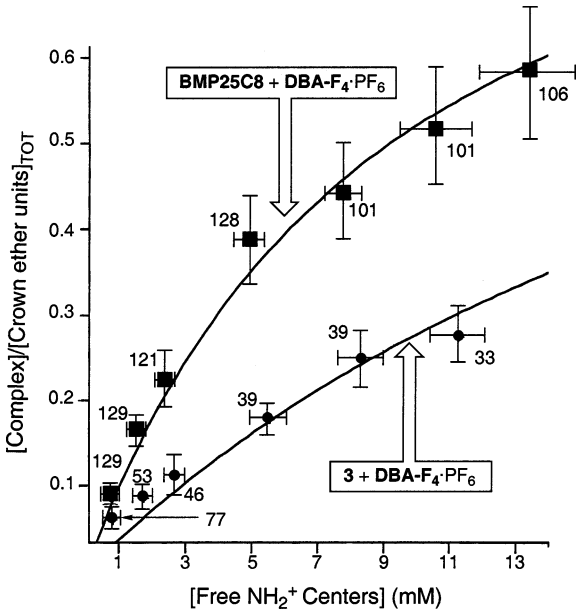


FIGURE 6. "Best-fit" binding isotherms for the complexation between BMP25C8 and DBA-F_4·PF_6 (■) and the complexation between the hexakisBMP25C8 cluster **3** and DBA-F_4·PF_6 (●). Next to each data point is displayed the value of K_{AVE} (M^{-1}; errors ±30%) determined by using the single-point method. The values on the *y*-axis represent the measured concentration of complexed DBA-F_4^+ ions divided by the total concentration of crown ether moieties. The values on the *x*-axis represent the concentration of free DBA-F_4^+ ions in solution. Error bars on each data point are set at 10% and 14% for the *x*- and *y*-axes, respectively, and reflect experimental errors in the weight and volume of the samples and in the integration of peaks in spectra.

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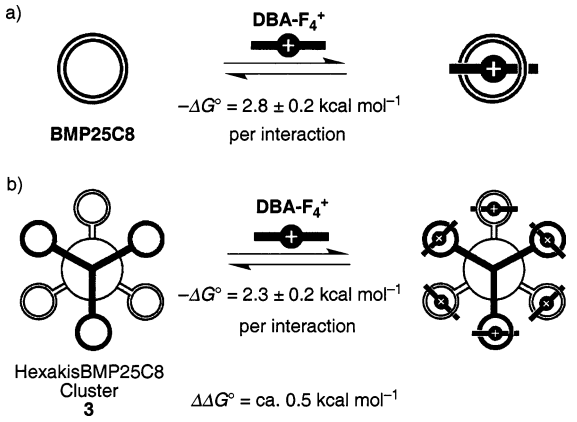

FIGURE 7. A comparison of the free energy of binding between (a) BMP25C8 and DBA-F_4·PF_6 and (b) the hexakis-BMP25C8 cluster **3** and DBA-F_4·PF_6.

is a better host for DBA-F_4^+ ions than is the hexa-BMP25C8 cluster **3**. Indeed, the crown ether rings of the hexakisBMP25C8 cluster seem to bind (Figure 7) the dialkylammonium thread DBA-F_4^+ about 0.5 kcal mol^{-1} less effectively.[24] Hence, the clustering of the crown ether rings has a detrimental effect on their ability to bind monovalent secondary dialkylammonium ions. This effect is probably a consequence of unfavorable electronic and steric factors. A hexakis(crown ether) cluster that binds a single dialkylammonium ion will possess a single positive charge. Any additional binding between the remaining free crown ether macrocycles in the 1:1 complex and other dialkylammonium ions will have to overcome the electrostatic repulsion between this positively charged complex and the approaching unbound dialkylammonium ions. Steric hindrance from each bound cation and its associated anion is also expected to inhibit further binding between the hexakis(crown ether) cluster and dialkylammonium ions. Both effects are detrimental to binding and they will increase in significance as the cluster binds further dialkylammonium ions. This increased repulsion of DBA-F_4 cations may be the reason for the decrease in the observed K_{AVE} for hexaBMP25C8 cluster **3** as the concentration of the dialkylammonium ion increases. At low concentrations of cations, lower order complexes (i.e., [2]- and [3]pseudorotaxanes) are all that can be expected to form and, since these complexes are not expected to suffer the steric and electronic effects to the degree that the higher order complexes do, the value of K_{AVE} is relatively high. At higher concentrations of dialkylammonium ions, higher order [n]pseudorotaxanes are inhibited from forming, and so these complexes having lower binding affinities for dialkylammonium ions will cause the value of K_{AVE} to decrease.

Gibson and co-workers[25] have also observed a similar phenomenon between DBA$^+$ ions and polymethacrylates bearing DB24C8 appendages. They found that the values of K_{AVE} for the binding of these polymers with DBA$^+$ ions were lower than those for the binding of DB24C8 with DBA$^+$ ions, at the same concentrations of crown ether rings, by a factor of between 2 and 30. The values of K_{AVE} for those polymer/DBA$^+$ interactions also decrease with increasing dialkylammonium ion concentration.

In the cases of BMP25C8 and hexaBMP25C8 **3** binding with DBA-F_4^+, the general trend is a decrease in K_{AVE} as the concentration of the ammonium ions increases. This general decrease is probably a consequence of ion pairing between the ammonium ion and its hexafluorophosphate anion, a situation that consequently diverges the system away from ideal behavior. Research by Gibson and co-workers[9h] has explored this phenomenon with a variety of counterions, with the hexaflurophosphate anion exhibiting the weakest ion pairing with dibenzylammonium cations. The use of hexafluorophosphate as a counterion in our own experiments helps to minimize ion-pairing effects, as does the relatively narrow concentration range over which these experiments are performed. Indeed, the relatively narrow range of experimentally determined K_{AVE} values (129 to 106 M^{-1} and from 77 to 33 M^{-1}: Figure 6) supports the idea that although our system exhibits ion-pairing effects, they do not affect significantly the validity of the conclusions.

Binding between the Hexakis(dialkylammonium) Cluster and Dibenzo[24]crown-8. The binding of the hexakis(dialkylammonium) cluster **4**·6PF_6 with DB24C8 was investigated (Figures 8 and 9) to discover how the clustering of six NH_2^+ centers in a single species affects each unit's ability to bind to crown ethers. If a value for K_{AVE} is determined for the binding between these two species, then this value can be compared to that found[6,22e] for the complexation between DBA$^+$ and DB24C8. Thus, a similar comparison can be made between these two

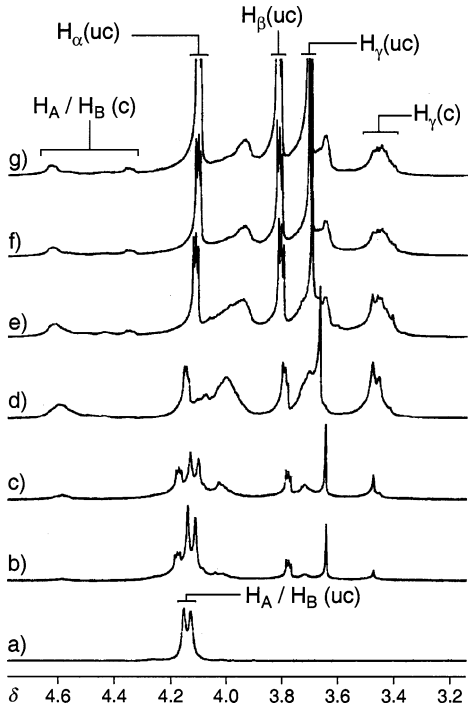

FIGURE 8. ^{1}H NMR spectra [500 MHz, CD_2Cl_2/CD_3CN (1:1), 300 K] of a mixture of **4**·6PF_6 and DB24C8. The concentration of **4**·6PF_6 is 4.88 mM, while the concentration of DB24C8 is (a) 0.00, (b) 2.32, (c) 5.04, (d) 14.8, (e) 29.2, (f) 44.9 , and (g) 59.9 mM. For peak labeling, see Figures 2 and 3.

(24) We have observed a similar effect in the binding of (i) a β-cyclodextrin-based heptakisBMP25C8 derivative and (ii) BMP25C8 with DBA-F_4·PF_6 in CD_3CN. The cluster compound binds this ion less effectively by ca. 0.4 kcal mol^{-1}. See ref 11.

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systems as was made above for the corresponding binding of the hexakisBMP25C8 cluster **3** and BMP25C8 with DBA-F_4^+ ions. To establish a value of K_{AVE} and a binding isotherm between DBA·PF_6 and DB24C8, ^{1}H NMR spectra were obtained for a series of CD_3CN/CD_2Cl_2 (1:1) solutions of DBA·PF_6 and DB24C8. In these experiments, the concentration of DBA·PF_6 was held constant at 29.3 mM, while the concentration of DB24C8 was varied from 3 to 58 mM. The relative amount of free and complexed DB24C8 was determined by comparing the integrals for the resonances of the γ-OCH_2 protons (Figure 8) in the bound and unbound states of the crown ether. For the individual data points, a binding isotherm was constructed (Figure 9), values of K_{AVE} were determined, and a mean value for K_{AVE} of 478 ± 143 M^{-1} was calculated.[26] This value of K_{AVE} corresponds to a mean value for $\Delta G°_{AVE}$ of −3.7 ± 0.2 kcal mol^{-1}.

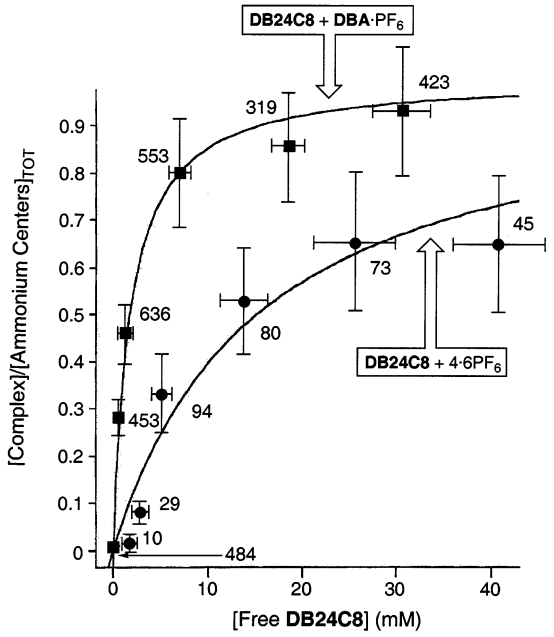

FIGURE 9. "Best-fit" binding isotherms for the complexation between DB24C8 and DBA·PF_6 (■) and the complexation between DB24C8 and the hexakis(dialkylammonium) cluster **4**·6PF_6 (●). Next to each data point is displayed the value of K_{AVE} (M^{-1}; errors ±60%) determined by using the single-point method. The values on the *y*-axis represent the measured concentration of complexed DB24C8 divided by the total concentration of dialkylammonium ion centers (error in *y*-axis for upper isotherm: 14%; lower isotherm: 28%). The values on the *x*-axis represent the concentration of free DB24C8 in solution (error in upper isotherm 10%, lower isotherm 20%).

To draw a comparison between the complexation of DB24C8 with DBA^+ ions and the cluster **4**·6PF_6, ^{1}H NMR spectra were obtained (Figure 8) for a series of solutions of **4**·6PF_6 and DB24C8 in CD_3CN/CD_2Cl_2 (1:1). In these solutions, the concentration of the hexakis(dialkylammonium) cluster **4**·6PF_6 was held constant at 4.88 mM, i.e., the concentration of NH_2^+ centers is 29.3 mM. The concentrations of DB24C8 in these solutions were varied from 0 to 59.9 mM. The ^{1}H NMR spectra of the mixture of the two compounds become increasingly complicated on addition of increasing amounts of DB24C8. As the concentration of DB24C8 is increased, the intensities of the resonances corresponding to the protons in the uncomplexed dialkylammonium ion sites decrease and new resonances appear for the protons of the complexed species. As there are many geometries possible for the higher order complexes, exact assignments to particular species are not possible. In the region of the ^{1}H NMR spectra representing signals of the aliphatic protons (3.2−4.8 ppm), however, it is possible to assign some of the resonances to protons in the complexed and uncomplexed species. As the concentration of DB24C8 is increased, the signals for the benzylic methylene protons adjacent to the NH_2^+ centers—namely H_A and H_B (see Figure 3 for their assignment)—in the complexed DBA^+ ions appear in a characteristic region[22e] (4.3−4.6 ppm) of the spectrum. Also, the resonances corresponding to the α-, β-, and γ-OCH_2 protons (see Figure 2 for their assignment) in the free and the complexed states of DB24C8 are observed. By comparing the integrals of the resonances corresponding to the γ-OCH_2 protons in the bound DB24C8 macrocycles and the β-OCH_2 protons in the uncomplexed DB24C8 rings, the relative concentrations of DB24C8 in the free and complexed states were determined.

From the data obtained from these ^{1}H NMR spectra, a binding isotherm was plotted (Figure 9) and a mean value for K_{AVE} of 55 ± 33 M^{-1} was determined. This value of K_{AVE} corresponds to a mean $\Delta G°_{AVE}$ of −2.4 ± 0.5 kcal mol^{-1}. Since the individual values of K_{AVE} vary considerably with the concentration of DB24C8, a large error is assumed for the mean value of K_{AVE}.[27] At a DB24C8 concentration of 2.3 mM, the observed value of K_{AVE} is 10 M^{-1} while at a concentration of 14.8 mM, the value of K_{AVE} is 94 M^{-1}. This change in the observed value of the association constant is large and is probably outside the error limits of the experiment. At low concentrations (2.3−14.8 mM) of DB24C8, the observed values of K_{AVE} increase quite dramatically upon increasing the concentration of the crown ether. At higher concentrations (14.8−59.9 mM), however, the observed values of K_{AVE} decrease as the concentration of DB24C8 increases. This latter observation can be explained by unfavorable steric interactions between crown ethers bound to the same hexakisammonium cluster. The increase, however, in the value of K_{AVE} upon increasing the concentration of DB24C8 (between 2.3 and 14.8 mM) is not easy to rationalize.[28] It is possible that it is a result of experimental error in determining integrated values of signals at low concentrations.[29]

From a comparison of the binding isotherms and the mean free energy changes (Figure 10) upon complexation, the DBA^+ moieties in the hexakis(dialkylammonium) cluster seem to bind DB24C8 ca. 1.3 kcal mol^{-1} less effectively than does DBA·PF_6. This reduction in the

(26) Because of difficulties in integrating these spectra, we believe that the error limits are large. Additionally, there is probably some divergence from the ideal 1:1 binding isotherm because the δ values of some of the signals shift upon addition of increasing amounts of the crown ether. This divergence from the ideal behavior could be a consequence of competing equilibria, such as, for example, ion pairing between the dialkylammonium cation and its hexafluorophosphate anion.

(27) We assume an error of ±60% for values of K_a, which results primarily from an assumed error of 10% in integrating signals in these complicated NMR spectra.

strength of complexation is probably a consequence of unfavorable steric interactions between crown ethers bound to the same hexakis(dialkylammonium) cluster. Also, the three dialkylammonium ion sites on each face of the cluster may form a cavity that could bind favorably with a hexafluorophosphate anion, producing an interaction that could compete with the binding of the crown ethers.[30] Taken together, these factors support the view that the strength of binding between DB24C8 and the hexakis(dialkylammonium) cluster **4**·6PF_6 is expected to be lower than that between DB24C8 and DBA^+ ions in the same solvent.

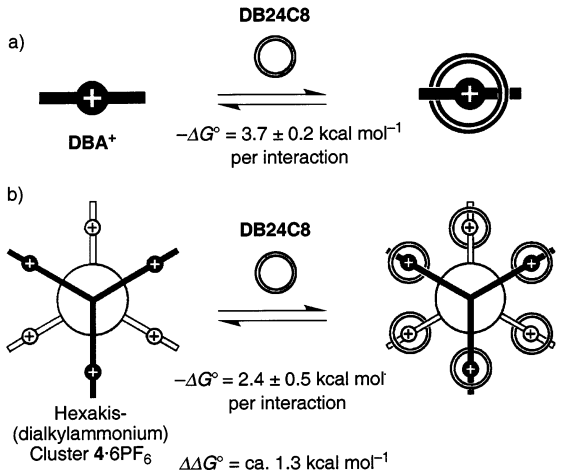

FIGURE 10. A comparison of the free energy of binding between (a) DBA^+ and DB24C8 and (b) the hexakis(dialkylammonium) cluster **4**·6PF_6 and DB24C8.

Thus, in both cases, clustering the crown ether rings or dialkylammonium ion recognition sites reduces the individual strength of binding of these moieties toward complementary monovalent ligands. Thus, it seems that steric and electronic factors play a more important role in the binding of these clusters than do statistical effects.

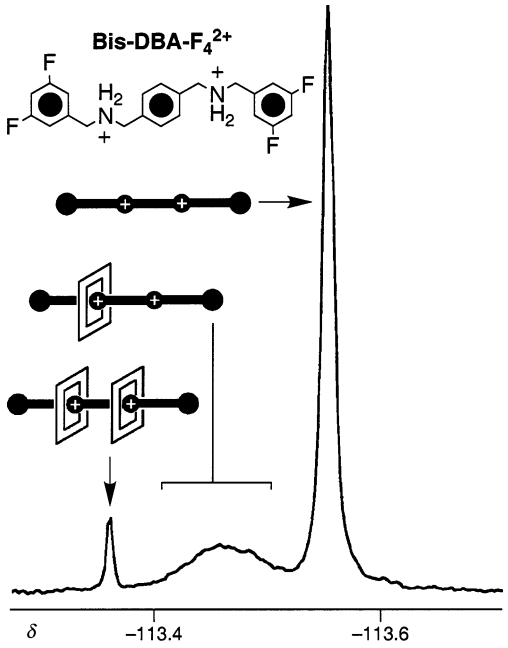

FIGURE 11. Partial ^{19}F NMR spectrum [376 MHz, CD_2Cl_2/CD_3CN (1:3), 300 K] of an equimolar solution of BMP25C8 and bis-DBA-F_4·PF_6.

Study of Chelate Effects in the Binding of the Hexakis(crown ether) Cluster with Mono- and Bis-(dialkylammonium) Ions. To study the contribution of chelate effects to multivalent interactions, we investigated the binding of the bis(dialkylammonium) ion[11] bis-DBA-F_4·2PF_6 (Figure 11) to the hexakisBMP25C8 cluster **3** and BMP25C8. An ^{19}F NMR spectrum of a solution of the bis(dialkylammonium) salt bis-DBA-F_4·2PF_6 and BMP25C8 displays (Figure 11) three resonances. These resonances are a sharp singlet (−113.55 ppm) corresponding to unbound bis-DBA-F_4^{2+} ions, a broad signal[31] centered on −113.45 ppm, corresponding to the 1:1 complex, and another sharp singlet (−113.36 ppm), corresponding to the 2:1 complex. From the integrals associated with these resonances, it is possible to determine the concentrations of each species and hence a value for K_{AVE} can be calculated by using eq 1. Hence, from a set of ^{19}F NMR titration experiments[32] in CD_3CN/CD_2Cl_2 (3:1) with the concentration of BMP25C8 held at a constant 6.0 mM and the concentration of salt varied from 0 to 8 mM, a binding isotherm was plotted (Figure 12) and a mean value for K_{AVE} of 48 ± 14 M^{-1} was determined.[33] This value of K_{AVE} corresponds to a mean value for $\Delta G°_{AVE}$ of −2.3 ± 0.2 kcal mol^{-1}.

(28) Ion pairing between the ammonium cluster and the hexafluorophosphate anion may contribute to the changes in values of K_{AVE}. At lower concentrations of the crown ethers, lower order complexes are formed, which may weaken ion-pairing interactions between the hexacationic host and the counterions, thus increasing the apparent K_{AVE}. The weakening of the ion-pairing interaction upon binding of the cationic centers could be a consequence of a bound cationic center having a more dispersed positive charge than an unbound one. This charge dispersal would result in reduced electrostatic charges between the hexacation and any anions. This changing strength of ion pairing may be a component of the effect of clustering multivalent cationic receptors.

(29) The Weber rule of thumb (see, for instance: Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. in *Comprehensive Supramolecular Chemistry*; Davies, J. E., Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 8, pp 425−482) states that accurate association constants can be obtained only at total concentrations of host and guest at which the minor component in the system is between 20% and 80% complexed. It may appear at first glance that some of the data in the lower isotherm of Figure 9 (i.e., those with values of K_a of 10 and 29 M^{-1}) fall outside of the Weber range. In actual fact, these data represent a situation in which ca. 23% and 44%, respectively, of the crown ether—the minor component—is complexed, and so the derived values of K_a seem to be valid from the viewpoint of the Weber rule.

(30) We have observed such interactions between dialkylammonium ions and hexafluorophosphate anions (usually [C−H···F] hydrogen bonds) in many solid-state structures of similar host−guest systems. See, for example: Ashton, P. R.; Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 12514−12524.

(31) This signal is broad presumably because the crown ether moiety shuttles back and forth between the two NH_2^+ centers of the bis-(dialkylammonium) ion at a rate commensurate with that of the NMR time scale at 376 MHz. That is to say, the crown ether exists in discrete "bound" and "unbound" states (i.e., slow exchange) because its rate of passage over the 3,5-difluorophenyl units is slow, but within the 1:1 complex, the crown ether has less of a steric barrier for shuttling between the binding sites. This lower shuttling barrier, however, is not low enough to cause this process to be fast on the NMR time scale, and so at 376 MHz the two termini of the bis(dialkylammonium) ion are somewhat nonequivalent and, hence, their signals are broad.

(32) A ratio of 3:1 for CD_3CN/CD_2Cl_2 was used as the solvent mixture in these experiments because the bisammonium salt bis-DBA-F_4·2PF_6 does not have the required solubility in CD_3CN/CD_2Cl_2 (1:1) solvent mixture.

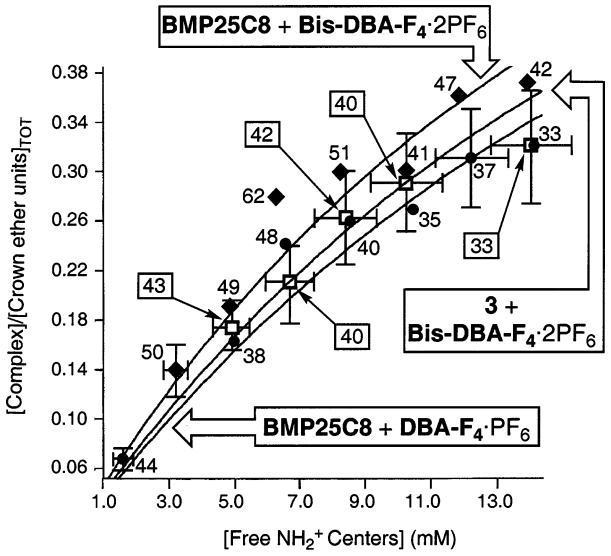

FIGURE 12. "Best-fit" binding isotherms for the complexation between BMP25C8 and bis-DBA-F_4·$2PF_6$ (◆), the complexation between the hexakisBMP25C8 cluster **3** and DBA-F_4·$2PF_6$ (□), and the complexation between BMP25C8 and DBA-F_4·PF_6 (●). The values on the *y*-axis represent the measured concentrations of complexed DB24C8 divided by the total concentration of dialkylammonium ion centers (errors ±14%). The values on the *x*-axis represent the concentration of free NH_2^+ centers in solution (errors ±10%). Some error bars have been omitted for the sake of clarity.

The ^{19}F NMR spectrum of a solution of bis-DBA-F_4·$2PF_6$ and the hexakisBMP25C8 cluster **3** in CD_3CN/CD_2Cl_2 (3:1) displays (Figure 13) a sharp resonance (−113.30 ppm), corresponding to the fluorine atoms associated with free NH_2^+ centers of the bis-DBA-F_4^{2+} ions, and a complicated set of overlapping signals in the range −112.8 to −113.2 ppm that corresponds to fluorine atoms of these dications having complexed NH_2^+ centers. Once again, some of the signals most likely represent fluorine atoms of the dication existing in 1:1 and 2:1 complexes, i.e., there is a broad signal centered at −113.1 ppm, which suggests complexes displaying shuttling, and sharp signals between −112.8 and −113.0 ppm, which suggest [3]pseudorotaxane-like states. By comparing the integrals of the two main sets of resonances (i.e., total complexed and total uncomplexed), the concentrations of complexed and free NH_2^+ centers were determined and values for K_{AVE} were calculated with eq 1. Hence, from a set of ^{19}F NMR titration experiments in CD_3CN/CD_2Cl_2 (3:1) with the concentration of the BMP25C8 cluster **3** held constant (1.0 mM) and the concentration of salt varied from 0 to 8 mM, a binding isotherm was plotted (Figure 12) and a mean value for K_{AVE} of 39 ± 12 M^{-1} was determined. This value of K_{AVE} corresponds to a mean value for $\Delta G°_{AVE}$ of −2.2 ± 0.2 kcal mol^{-1}.

For comparison, a binding isotherm was plotted (Figure 12) and the mean values for K_{AVE} and $\Delta G°_{AVE}$ were found for the binding of BMP25C8 with DBA-F_4·PF_6 over a similar range of concentrations in this solvent system [CD_3CN/CD_2Cl_2 (3:1)].[34] A mean value for K_{AVE} of 39 ± 12 M^{-1} was calculated, which corresponds to a mean value for $\Delta G°_{AVE}$ of −2.2 ± 0.2 kcal mol^{-1}. From a comparison of the binding isotherms and the mean values for $\Delta G°_{AVE}$, it appears that the strength of binding between individual crown ether moieties and NH_2^+ centers in these three binding systems differs only marginally.[35,36]

(33) The corresponding value of K_{AVE} has been calculated in CD_3CN to be slightly lower, as expected for a more polar solvent, at 30 ± 9 M^{-1} ($\Delta G°_{AVE}$ = −1.8 ± 0.2 kcal mol^{-1}). See ref 11.

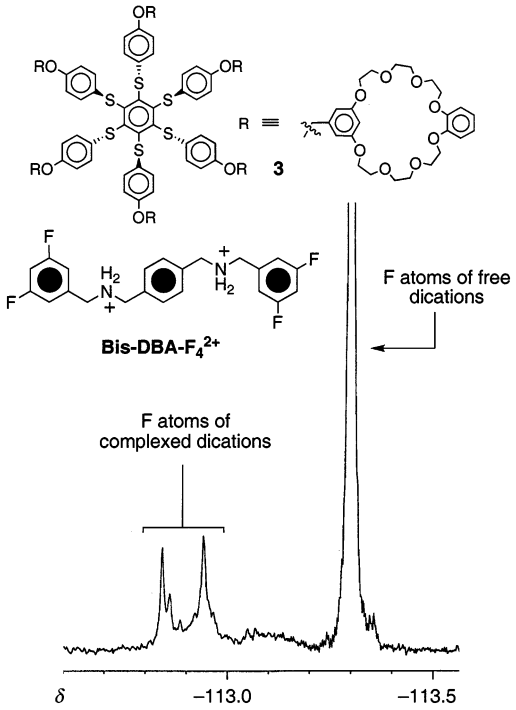

FIGURE 13. Partial ^{19}F NMR spectrum [376 MHz, CD_2Cl_2/CD_3CN (1:3), 300 K] of an equimolar solution of the hexakis-BMP25C8 cluster **3** and bis-DBA-F_4·$2PF_6$.

Calculating Multivalent Binding Affinities. For the binding between the hexakisBMP25C8 cluster **3** and the bis(dialkylammonium) salt bis-DBA-F_4·$2PF_6$, a binding constant (K_{POLY}),[1,11] which corresponds to the binding constant in the complexation of 1 equiv of bis-DBA-F_4^{2+} ions with 1 equiv of the hexakisBMP25C8 cluster **3** to afford the 1:1 complex, can be determined from the mean value of K_{AVE}.

The average free energy change for an individual interaction is defined as

$$\Delta G°_{AVE} = -RT \ln K_{AVE} \quad (2)$$

The free energy of binding between two multivalent systems that have *N* individual component interactions between them can be estimated as the sum of these component interactions:

$$\Delta G°_{POLY} = N\Delta G°_{AVE} \quad (3)$$

This equation can be expressed in terms of association constants K_{POLY} and K_{AVE} as follows:

$$K_{POLY} = (K_{AVE})^N \quad (4)$$

Thus, a value of K_{POLY} can be calculated for the binding between one Bis-DBA-F_4^{2+} dication and one hexakis-

(34) Recall that we had calculated this association constant in CD_3CN/CD_2Cl_2 solution (1:1) to be 116 ± 35 M^{-1}. See Table 1, entry 3.

TABLE 1. Values of Mean K_{AVE} and Mean $\Delta G°_{AVE}$ for the Interactions between Various Crown Ether Hosts and Dialkylammonium Guests at 300 K

entry	host	guest	solvent	K_{AVE} (M^{-1})	$\Delta G°_{AVE}$ (kcal mol^{-1})
1[a]	BMP25C8	DBA-F_4·PF_6	CD_3CN	25	−1.9
2[b]	BMP25C8	DBA-F_4·PF_6	CD_3CN	20 ± 6	−1.8 ± 0.2
3	BMP25C8	DBA-F_4·PF_6	CD_3CN/CD_2Cl_2, 1:1	116 ± 35	−2.8 ± 0.2
4	BMP25C8	DBA-F_4·PF_6	CD_3CN/CD_2Cl_2, 3:1	39 ± 12	−2.2 ± 0.2
5[b]	BMP25C8	bis-DBA-F_4·$2PF_6$	CD_3CN	30 ± 6	−1.8 ± 0.2
6	BMP25C8	bis-DBA-F_4·$2PF_6$	CD_3CN/CD_2Cl_2, 3:1	48 ± 14	−2.3 ± 0.2
7	**3**	DBA-F_4·PF_6	CD_3CN/CD_2Cl_2, 1:1	48 ± 14	−2.3 ± 0.2
8[c]	**3**	bis-DBA-F_4·$2PF_6$	CD_3CN/CD_2Cl_2, 3:1	39 ± 12	−2.2 ± 0.2
9[d]	DB24C8	DBA·PF_6	CD_3CN	420	−3.6
10	DB24C8	DBA·PF_6	CD_3CN/CD_2Cl_2, 1:1	478 ± 143	−3.7 ± 0.2
11	DB24C8	**4**·$6PF_6$	CD_3CN/CD_2Cl_2, 1:1	55 ± 33	−2.4 ± 0.5

[a] Values taken from ref 7e. [b] Values taken from ref 11. [c] The value of K_{POLY} for this interaction is 1500 ± 1100 M^{-1} ($\Delta G°_{POLY}$ = 4.4 ± 0.5 kcal mol^{-1}). [d] Value taken from ref 6a.

BMP25C8 cluster **3**. When these two species bind together, there are two individual component interactions (i.e., $N = 2$) because when one dication is complexed by one cluster, two NH_2^+ centers are bound. Hence, K_{POLY} is calculated to be 1500 ± 1100 M^{-1} [i.e., $(39 \pm 12)^2$] in CD_3CN/CD_2Cl_2 (3:1), which corresponds to a value for $\Delta G°_{POLY}$ of −4.4 ± 0.5 kcal mol^{-1}. The corresponding monovalent interaction between BMP25C8 with DBA-F_4·PF_6 has a value of K_a, coincidentally, of 39 M^{-1} in CD_3CN/CD_2Cl_2 (3:1). Hence, the strength of interaction between the two species acting multivalently is significantly stronger than the component interactions between any of the structurally similar monovalent species examined in this study. This increased strength of binding between polyvalent species indicates that strong chelate effects in multivalent systems can overcome adverse electronic and steric effects. Table 1 summarizes the binding constants obtained in this study.

Conclusions

We have synthesized two cluster compounds, one containing six BMP25C8 rings and the other possessing six dialkylammonium ion centers attached to a hexakis-(thiophenyl)benzene core. The clustering of the crown ether rings and the NH_2^+ centers in these compounds is detrimental to the strengths of binding by the individual crown ethers or NH_2^+ centers to monovalent ligands (compare entries 3 and 7, and 10 and 11, in Table 1). In the case of the binding between DB24C8 and the hexakis-(dialkylammonium) cluster **4**·$6PF_6$, the reduction in binding strength is likely a consequence of unfavorable steric interactions between adjacent crown ether units bound to the same core unit. In addition to steric factors, electronic repulsion between two or more dialkylammonium cations reduces the strengths of binding of DBA-F_4^+ ions to the hexakisBMP25C8 cluster **3**. These results demonstrate that, in the case of these simple receptors and ligands, any potential for enhanced binding expected from statistical effects is overwhelmed by unfavorable electronic and steric factors, when considering the binding of monovalent species to a complementary multivalent cluster. Although the clustering of binding sites reduces the strength of binding of the hexakisBMP25C8 cluster to monovalent cations ($\Delta G°_{AVE}$ = ca. −2.3 kcal mol^{-1}) relative to the monovalent species ($\Delta G°_{AVE}$ = −2.8 kcal mol^{-1}), it increases the strength of the binding of the cluster to multivalent species, such as the bis-(dialkylammonium) ion Bis-DBA-F_4^{2+} ($\Delta G°_{POLY}$ = ca. −4.4 kcal mol^{-1}), in similar solvents. This result demonstrates the large influence that chelate effects can have in the binding of two polyvalent species. This study demonstrates that multivalency can be employed effectively in unnatural systems and emphasizes the importance of understanding the mechanisms through which it occurs. By borrowing the concepts of multi- and polyvalency from the natural world, chemists can solve problems caused by monovalent species interacting only relatively weakly by clustering many such ligands together to obtain strong interactions between polyvalent versions of the same species.[1,4,5] Although this and other related[10,11] studies provide some clues as to how chemists can use multivalency in designing strongly binding systems, optimizing the components in the systems—recognition centers, core units, and linkers—remains a challenge still to be met.

Experimental Section

Hexakis(4-methoxyphenylthio)benzene (5). NaH (1.0 g, 43 mmol) was suspended in degassed 1,3-dimethyl-2-imidazolidinone (10 mL). The suspension was again degassed and cooled to 0 °C, and then 4-methoxythiophenol (1.8 g, 13 mmol) was added carefully. The reaction mixture was placed under an Ar atmosphere and hexafluorobenzene (134 mg, 0.7 mmol) was added. The mixture was stirred under Ar for 6 h at room temperature, during which time a yellow suspension formed. This suspension was partitioned between H_2O (100 mL) and PhMe (100 mL). The organic layer was then washed with H_2O (10 × 100 mL) and dried (Na_2SO_4) and the solvent was removed in vacuo to give a yellow oil. EtOH (5 mL) was added to this yellow oil and after 1 h a yellow solid had formed. The yellow solid was filtered off and washed with EtOH to afford the title compound **5** (0.65 g, 95%). Mp 158−161 °C; FAB-MS *m/z* 906 $[M]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 18H), 6.67 (d, J = 8 Hz, 12H), 6.89 (d, J = 8 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.1, 114.3, 128.5, 130.8, 147.6, 158.2. Anal.

(35) In an earlier study, we found that a cluster of seven BMP25C8 units appended to a β-cyclodextrin core exhibits a significantly higher value of K_{AVE} (59 ± 18 M^{-1}) toward bis-DBA-F_4^{2+} than did BMP25C8 itself (20 ± 9 M^{-1}). See ref 11.

(36) With this divalent cationic salt, we would expect ion pairing to play a role in binding behavior. However, given that the values of K_{AVE} vary slightly (62 to 42 M^{-1} for BMP25C8 with bis-DBA-F_4·$2PF_6$ and 43 to 33 M^{-1} for **3** with bis-DBA-F_4·$2PF_6$), this effect does not change the conclusion that the binding strength of these systems differs only marginally.

Calcd for $C_{48}H_{42}O_6S_6$: C, 63.55; H, 4.67; S, 21.21. Found: C, 63.49; H, 4.68; S, 21.18.

Hexakis(4-hydroxyphenylthio)benzene (6). A solution of BBr_3 in CH_2Cl_2 (1 M, 7.9 mL, 7.9 mmol) was added over 30 min to a solution of hexakis(4-methoxyphenylthio)benzene (**5**) (0.22 g, 0.24 mmol) in dry CH_2Cl_2 under Ar at −78 °C. The solution was then warmed to room temperature and stirred under Ar overnight. H_2O (10 mL) was added carefully to the reaction mixture and then EtOAc (20 mL) was also added. The organic phase was washed with H_2O (35 mL) and saturated aqueous NaCl (35 mL) and dried ($MgSO_4$), and then the solvent was evaporated in vacuo to give a yellow solid. This solid was subjected to column chromatography (SiO_2; EtOAc/PhMe, 1:1 to 3:1) to afford the title compound **6** as a yellow solid (0.10 g, 63%). Mp 240 °C dec; FAB-MS *m*/*z* 822 $[M]^+$; ^{1}H NMR (500 MHz, CD_3COCD_3) δ 6.73 (d, J = 8 Hz, 12H), 6.88 (d, J = 8 Hz, 12H), 8.52 (s, 6H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 115.9, 127.3, 130.7, 147.6, 156.2. Anal. Calcd for $C_{42}H_{30}O_6S_6$: C, 61.29; H, 3.67; S, 23.38. Found: C, 61.15; H, 3.68; S, 23.15.

Hexa(benzo-*m*-phenylene[25]crown-8) Cluster (3). A solution of mesylate **9** (1.1 g, 1.98 mmol) in dry MeCN (7.5 mL) was added to a hot suspension of hexakis(4-hydroxyphenylthio)benzene (**6**) (90 mg, 0.11 mmol), K_2CO_3 (270 mg, 1.98 mmol), and [18]crown-6 (29 mg, 0.11 mmol) in dry MeCN (7.5 mL) under Ar. The reaction mixture was heated under reflux overnight. After the reaction mixture had cooled to room temperature, it was partitioned between EtOAc (40 mL) and H_2O (40 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting yellow oil was subjected to HPLC (reverse phase C18 silica; MeCN/H_2O, 1:1 to 1:0 over 30 min, then MeCN, 10 min) to yield the title compound **3** as a yellow oil (0.16 g, 40%). MALDI-TOF-MS *m*/*z* 3069 $[M + Na]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67−3.71 (m, 48H), 3.77−3.80 (m, 24H), 3.82−3.85 (m, 24H), 4.09−4.14 (m, 48H), 4.88 (s, 12H), 6.51 (d, J = 2 Hz, 12H), 6.62 (t, J = 2 Hz, 6H), 6.72 (d, J = 8 Hz, 12H), 6.86−6.90 (m, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.0, 68.9, 69.7, 69.8, 70.8, 70.9, 101.9, 106.7, 115.1, 115.3, 121.6, 128.8, 130.7, 138.8, 147.3, 148.9, 157.5, 160.1.

4-(Methanesulfinyl)benzaldehyde (10). 3-Chloroperoxybenzoic acid (13.0 g, 75 mmol) was added portionwise to a solution of 4-(methylthio)benzaldehyde (11.4 g, 75 mmol) in $CHCl_3$ (200 mL) at 0 °C. The suspension was then stirred at 0 °C for 90 min. After the solution was warmed to room temperature, $Ca(OH)_2$ (8.3 g, 110 mmol) was added and the suspension was stirred for a period of 30 min before being filtered. The solvent was removed from the filtrate in vacuo, leaving a white solid. This solid was subjected to column chromatography (SiO_2; CH_2Cl_2/EtOAc, 1:0 to 1:1) to yield the title compound **10** as a white solid (7.5 g, 59%). Mp 85−86 °C (lit.[37] mp 81−82 °C); EI-MS *m*/*z* 169 $[M]^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.77 (s, 3H), 7.81 (d, J = 8 Hz, 2H), 8.06 (d, J = 8 Hz, 2H), 10.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.7, 124.2, 130.4, 138.1, 152.4, 191.1. Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06. Found: C, 56.98; H, 4.68; S, 19.07.

4,4′-Dithiobis(benzaldehyde) (11). 4-(Methanesulfinyl)-benzaldehyde (**10**) (8.1 g, 48 mmol) was heated under reflux in freshly distilled trifluoroacetic acid anhydride (100 mL) under Ar for 15 min. The solvent was then removed in vacuo and an ice-cooled mixture of NEt_3 (100 mL) and MeOH (100 mL) was added carefully to the resulting residue. The solvent was removed in vacuo from the resulting solution to afford a yellow residue. This residue was partitioned between $CHCl_3$ (100 mL) and saturated aqueous NH_4Cl (100 mL), and the aqueous phase was washed with $CHCl_3$ (100 mL). The organic fractions were combined and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give a yellow oil. The oil was dissolved in CH_2Cl_2 (100 mL) and I_2 (12.2 g, 48 mmol) was added. This mixture was stirred for a period of 4 h then washed with 1 M $Na_2S_2O_3$ (100 mL) and dried ($MgSO_4$), and then the solvent was evaporated in vacuo. The resulting yellow solid was subjected to column chromatography (SiO_2; PhMe) to afford the title compound **11** as a white solid (3.3 g, 50%). Mp 98−103 °C; EI-MS *m*/*z* 274 $[M]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8 Hz, 4H), 7.82 (d, J = 8 Hz, 4H), 9.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.3, 130.4, 135.1, 143.8, 191.0. Anal. Calcd for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; S, 23.38. Found: C, 60.94; H, 3.61; S, 23.18.

4,4′-Dithiobis(benzylidenebenzylamine) (12). A solution of 4,4′-dithiobis(benzaldehyde) (**11**) (3.0 g, 10.9 mmol) and benzylamine (2.3 g, 21.8 mmol) in PhMe (200 mL) was heated overnight under reflux in a Dean−Stark apparatus. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure to afford the title compound **12** as a yellow solid (4.9 g, 99%). FAB-MS *m*/*z* 453 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (s, 4H), 7.10−7.50 (m, 10H), 7.52 (d, J = 8 Hz, 4H), 7.71 (d, J = 8 Hz, 4H), 8.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.0, 127.0, 127.1, 128.0, 128.5, 128.9, 135.1, 139.1, 139.6, 160.9.

4-(Benzylaminomethyl)thiophenol (13). $NaBH_4$ (2.1 g, 55 mmol) was added portionwise over 40 min to a solution of 4,4′-dithiobis(benzylidenebenzylamine) (**12**) (4.9 g, 10.9 mmol) in degassed dry MeOH (50 mL) and degassed dry THF (50 mL) under Ar. The reaction mixture was stirred overnight. The solvents were then evaporated and the resulting yellow residue was partitioned between degassed CH_2Cl_2 (50 mL) and degassed H_2O (50 mL). The aqueous layer was washed with degassed CH_2Cl_2 (50 mL). The organic layers were combined and dried ($MgSO_4$) under Ar, and then the solvent was evaporated in vacuo to afford the title compound **13** as a yellow oil (4.9 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78−3.81 (m, 4H), 7.24−7.34 (m, 7H), 7.45 (d, J = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.5, 53.0, 126.9, 128.0, 128.3, 128.7, 131.0, 133.1, 139.5, 140.3.

Hexakis[4-(benzylaminomethyl)phenylthio]benzene (14). 4-(Benzylaminomethyl)thiobenzene (**13**) (4.9 g, 10.7 mmol) was dissolved in degassed 1,3-dimethyl-2-imidazolidinone (10 mL). This solution was then degassed further with a stream of Ar. NaH (0.8 g, 33 mmol) was added portionwise. After each portion of NaH had been added, the reaction mixture was carefully degassed under vacuum. The reaction mixture was then placed under an Ar atmosphere and hexafluorobenzene (0.11 g, 0.6 mmol) was added. The reaction mixture was stirred under Ar for 3 d before being partitioned between PhMe (100 mL) and H_2O (100 mL). The aqueous layer was separated and washed with PhMe (100 mL). The organic layers were combined and washed with H_2O (5 × 100 mL). The solvent was removed in vacuo to give a dark orange oil. This oil was subjected to column chromatography (SiO_2; CH_2Cl_2/THF/NEt_3, 99:0:1 to 90:9:1 to 50:50:1) to afford the title compound **14** as a yellow oil (0.51 g, 58%). FAB-MS *m*/*z* 1440 $[M]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (s, 12H), 3.78 (s, 12H), 6.93 (d, J = 8 Hz, 12H), 7.16 (d, J = 8 Hz, 12H), 7.28−7.37 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.4, 53.0, 126.9, 128.0, 128.1, 128.3, 128.6, 136.0, 138.1, 139.9, 147.7.

Hexakis[4-(benzylammoniomethyl)phenylthio]benzene Hexakis(hexafluorophosphate) (4·6PF$_6$). Hexakis-[4-(benzylaminomethyl)phenylthio]benzene (**14**) (87 mg, 0.6 mmol) was dissolved in THF (2 mL). MeOH (10 mL) was added to this solution to form a cloudy suspension and then concentrated HCl (2 mL) was added. The reaction mixture was stirred overnight to form a yellow precipitate, which was filtered off, washed with THF (5 mL), and then dissolved in hot H_2O (50 mL). Saturated aqueous NH_4PF_6 (1 mL) was added to this solution and the yellow suspension that formed was extracted with $MeNO_2$ (50 mL). The organic phase was washed with H_2O (2 × 40 mL) and dried (Na_2SO_4), and then the solvent was evaporated in vacuo to afford the title compound **4**·6PF_6 as a yellow solid (0.12 g, 88%). Mp 150 °C dec; ES-MS *m*/*z* 941 $[M - HPF_6 - 2PF_6]^{2+}$; ^{1}H NMR (400 MHz, CD_3CN) δ 4.08 (s, 12H), 4.12 (s, 12H), 6.99 (d, J = 8 Hz, 12H), 7.33 (d, J = 8 Hz, 12H),

(37) Creary, X.; Mersheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 1110−1114.

7.40−7.50 (m, 30H); ^{13}C NMR (125 MHz, CD_3CN) δ 50.5, 51.1, 127.3, 128.4, 129.0, 129.7, 130.1, 130.2, 131.1, 139.0, 147.5.

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**·6PF_6, **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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