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Substituent effects in the binding of bis(4-fluorobenzyl)ammonium ions by dianilino[24]crown-8

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Abstract—A series of *para*-substituted dianilino[24]crown-8 (DA24C8) macrocycles were synthesized and their ability to form host–guest complexes with bis(4-fluorobenzyl)ammonium ions (DFA^+) were investigated. Although these crown ethers contain weakly hydrogen bonding aniline motifs, they do bind DFA^+ in $CDCl_3/CD_3NO_2$ solution, presumably in a pseudorotaxane-like manner. A plot of the values of the relative binding strengths ($\log[K_a(R)/K_a(H)]$) versus the Hammett substituent constants σ^+ of the groups at the *para*-position of the aniline units suggests that a linear free energy correlation exists for this self-assembly process. The strength of the binding between the crown ether and the thread-like ion can be fine-tuned over a narrow range by judicious choice of the substituting groups.

The binding between dibenzo[24]crown-8 (DB24C8) and various dibenzylammonium ions (DBA^+) has been investigated extensively for almost a decade.[1] The favorable [N^+–H···O] and [N^+–C–H···O] hydrogen bonding interactions between the ammonium ion and the ether motifs of the macrocycle result in the interpenetration of the DBA^+ ion into the cavity of the DB24C8 macroring to form a 1:1 pseudorotaxane[2] complex. To date, the geometry of this inclusion complex and the strong noncovalent interactions between DB24C8 and DBA^+ units have led to efficient syntheses of many interlocked molecular compounds, such as catenanes and rotaxanes.[3] DB24C8 cannot be substituted simply in a symmetrical manner, however, and this feature is one that complicates stereochemical matters when it comes to building intricate interlocked molecules from mono- or bifunctional DB24C8 macrocycles.[4] To overcome this problem, other symmetrical crown ethers, such as bis-*m*-phenylene-[26]crown-8 (BMP26C8)[5] and dipyrido[24]-crown-8 (DP24C8),[6] have been synthesized and investigated as alternative host molecules (Fig. 1).

An additional issue to address in preparing molecular shuttles and molecular switches[7] based on these species is that the strong binding interactions between the components can results in high activation energies and corresponding slow rates of switching,[8] which could be drawbacks for their eventual use in high-speed devices. Using components that bind less strongly would overcome this problem, albeit at the expense of low yields for their molecular assembly. Thus, in making high-speed, symmetrical, machine-like molecules it would be useful to be able to adjust the strength of the hydrogen bonding interactions *after* assembly of the interlocked

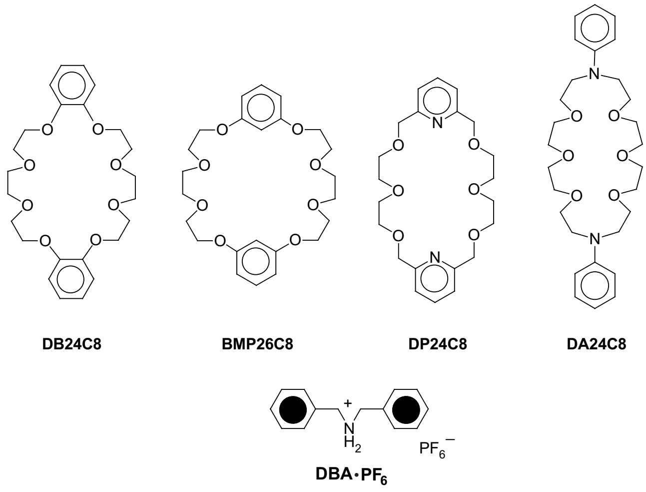

Figure 1. Some crown ethers that bind to the thread-like DBA^+ ion.

Keywords: crown ethers; pseudorotaxanes; linear free energy correlation.

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molecules. From this point of view, using the crown ether dianilino[24]crown-8 (DA24C8)[9] and its D_{2h}-symmetrical substituted derivatives in the synthesis of interlocked molecules may be a solution to these problems. The binding behavior between DA24C8 and DBA^+ has not been reported so far, but we expected that it would be reasonably strong because of the presence of six aliphatic ether oxygen atoms and two aniline nitrogen atoms (cf. DB24C8, which has four aliphatic (strong) and four aromatic (weak) ether oxygen atoms) in the crown ether that are capable of accepting hydrogen bonds. Although we expected the aniline nitrogen atoms to be quite weak hydrogen bond acceptors, because their lone pairs of electrons are positioned perpendicular to the mean plane of the macrocycle rather than within it,[10] their basicity can be increased by positioning electron-donating groups at their *para*-positions,[11] which would enhance the strength of binding between the crown ether and DBA^+ ions. Thus, a crown ether with strongly electron-donating groups could be used in the synthesis of an interlocked molecule, which is then modified with electron-withdrawing groups that decrease the energy barrier for translation of the macrocyclic ring. As a first step toward such controllable molecular devices, in this paper we report the syntheses of a series of *para*-substituted DA24C8 macrocycles and investigate their binding to bis(4-fluorobenzyl)ammonium hexafluorophosphate ($DFA{\cdot}PF_6$).

Scheme 1 depicts the route we used to synthesize the substituted DA24C8 macrocycles **6a–d**. Reactions of excess *p*-substituted anilines **1a–d** with the bistosylate **2** afforded diamines **3a–d**. The diamines **3a–d** were then reacted with tetraethyleneglycoyl dichloride[12] in dry toluene under conditions of high dilution to give the macrocyclic lactams **5a–d**, which were subsequently reduced smoothly by borane in THF into the corresponding substituted DA24C8 macrocycles **6a–d**. The overall yields of these synthetic procedures, from anilines **1a–d** to crown ethers **6a–d**, are between 18% and 33%. Crown ether **6e** was synthesized in 78% yield from crown ether **6d** by a palladium-catalyzed amination.[13]

When a ^1H NMR spectrum was obtained from a solution (20 mM) of both the crown ether **6a** and dibenzylammonium hexafluorophosphate ($DBA{\cdot}PF_6$) in CD_3CN at 298 K, we observed no significant movement of any of the signals in the spectrum relative to the spectra of the individual components. This result suggests that the degree of binding between crown ether **6a** and thread-like ion DBA^+ is negligible in CD_3CN at 298 K. To enhance the hydrogen bonding strength, we changed the solvent to a 2:1 mixture of $CDCl_3$ and CD_3NO_2[14] and replaced $DBA{\cdot}PF_6$ with the more-soluble $DFA{\cdot}PF_6$. Thus, when $DFA{\cdot}PF_6$ and the crown ether **6a** were mixed together (20 mM) in $CDCl_3/CD_3NO_2$ (2:1), we observed the appearance of additional broad signals in the ^1H NMR spectrum recorded at 298 K. To monitor the complexation more conveniently, we cooled the solution to 223 K. At this temperature, more than half of the components in the solution were complexed (Fig. 2).

Upon complexation, the signal of the methylene protons of $DFA{\cdot}PF_6$ that are adjacent to the NH_2^+ unit is shifted downfield by 0.49 ppm, relative to its signal when uncomplexed, to 4.46 ppm. The broad signal at 3.25–3.60 ppm, which represents the resonances of the ethylene protons of the crown ether **6a**, is split upon complexation into four signals at 3.16, 3.41, 3.50 and

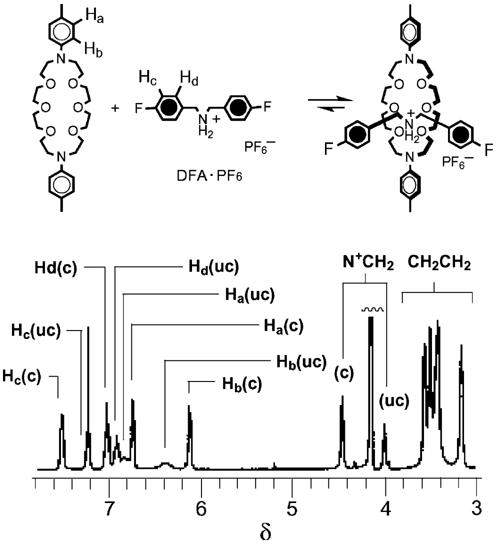
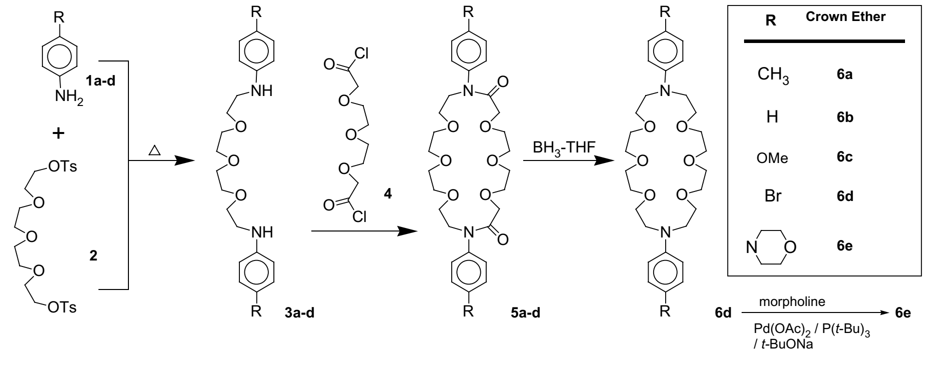


Figure 2. Partial ^1H NMR spectrum [400 MHz, $CDCl_3/CD_3NO_2$ (2:1), 223 K] of an equimolar mixture (20 mM) of **6a** and $DFA{\cdot}PF_6$, which demonstrates that uncomplexed (uc) and complexed (c) species equilibrate with one another slowly on this NMR spectroscopy timescale.



Scheme 1. Syntheses of the DA24C8 derivatives.

3.56 ppm, respectively. In the mixture, the signals of the aromatic protons of **6a** exist in two distinct groups: sharp complexed and broad uncomplexed signals. These signals are consistent with the notion that **6a** and DFA·PF_6 form a pseudorotaxane-like complex in $CDCl_3/CD_3NO_2$, with possible [N^+–H···O] and [N^+–H···N] hydrogen bonding interactions. The fast-atom bombardment (FAB) mass spectrum recorded on an equimolar mixture of **6a** and DFA·PF_6 reveals a peak at *m/z* 765 corresponding to the 1:1 complex having lost its PF_6^- ion.

We could not accurately determine the association constant for this assembly by ^{1}H NMR spectroscopy using the single-point method[15] at either 223 or 298 K because of difficulty in integrating the broad and, in some cases, overlapping signals; instead, the binding constant was elucidated at 298 K using ^{19}F NMR spectroscopy.[4b] As expected, a solution (20 mM) of a mixture of the salt DFA·PF_6 and the crown ether **6a** gave an ^{19}F NMR spectrum at 298 K having sharp and distinguishable signals (Fig. 3). The signals appearing at −112.94 and −111.23 ppm were assigned to the uncomplexed and complexed DFA$^+$ ions, respectively, based on a literature precedent.[4b,16] By integration of these signals, the association constant for pseudorotaxane formation between DFA·PF_6 and **6a** was calculated to be 15 M^{-1} at 298 K. We used this method to determine the association constants for the complexes formed between DFA·PF_6 and the other substituted DA24C8 crown ethers;[17] Table 1 lists the values of the association constants and their derived free energies of association. We note that among these crown ethers, it is macrocycle **6e**, which bears the most-strongly electron-donating substituents (morpholine units) on its aniline rings, that binds most strongly to DFA·PF_6; the crown ether with the most-electron-withdrawing bromine substituents (**6d**) is the weakest binder. The values of $\Delta H°$ and $\Delta S°$ of each complexation process were obtained from the intercept and slope, respectively, of the straight line in the plot of $\Delta G°$ versus T, which was obtained from the variable-temperature NMR spectroscopy experiments. The negative values of $\Delta H°$ and $\Delta S°$ in each case suggest that these complexation events are enthalpy-driven processes. A linear free energy correlation has been reported in the supramolecular complexation between DB24C8 and variety of *meta*- and *para*-substituted DBA$^+$ ions.[15b] The electronic nature of the substituents on the DBA$^+$ unit affects the NH_2^+ center's ability to donate a hydrogen bond and the ability to form π–π stacking interactions between the substituted benzyl unit and the catechol ring of the DB24C8 macrocycle. From Table 1, it is clear that the strength of the binding between DA24C8 derivatives and DFA$^+$ ions is related to the electronic nature of the substituents on the aniline units of the macrocycles. To examine whether a linear free energy correlation exists in this case or not, the relative association constants ($\log[K_a(R)/K_a(H)]$) for pseudorotaxane formation between the fluoro-substituted salt DFA·PF_6 and the substituted crown ethers were plotted against the substituent constant (σ^+).[18] A straight line is the result (Fig. 4), which suggests that a linear free energy correlation does exist for this supramolecular complexation event. The slope of the straight line, which corresponds to the value of for the complexation process, is ca. −0.28. The linear tendency implies that the binding strength between DFA$^+$ and other substituted DA24C8 macrocycles may be closely estimated simply by knowing the value of σ^+ of the substitutents.

The negative value of ρ suggests that the fluoro-substituted salt DFA·PF_6 favors complexation with DA24C8 macrocycles bearing strongly electron-donating

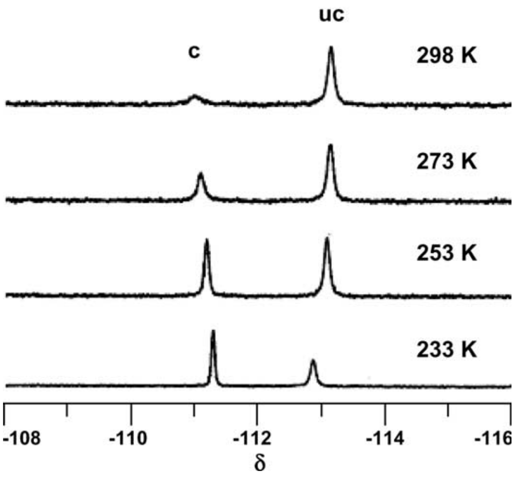


Figure 3. Partial variable-temperature ^{19}F NMR spectra [376 MHz, $CDCl_3/CD_3NO_2$ (2:1)] of an equimolar mixture (20 mM) of **6a** and DFA·PF_6.

Table 1. Stability constants[a] (K_a) and derived thermodynamic data for the complexation of substituted DA24C8 macrocycles and DFA·PF_6

Crown ether	K_a (M^{-1})[a]	$-\Delta G°$ (kcal mol^{-1})[b]	$\Delta H°$ (kcal mol^{-1})[c]	$\Delta S°$ (cal mol^{-1} K^{-1})[c]
6a	15	1.60	−4.7 ± 0.7	−10.7 ± 2.8
6b	11	1.42	−4.3 ± 0.5	−10.3 ± 2.0
6c	16	1.64	−6.3 ± 0.8	−15.5 ± 2.8
6d	8	1.23	−4.0 ± 0.4	−9.2 ± 1.7
6e	30[d]	2.02	−8.8 ± 1.1	−22.7 ± 4.0

[a] Stability constants (K_a) were obtained as outlined in Ref. 15 based on the ^{19}F NMR spectra in $CDCl_3/CD_3NO_2$ (2:1) at 298 K (error ⩽ 15%).

[b] The free energy of complexation ($-\Delta G°$) was calculated from each value of K_a using the equation $-\Delta G° = RT \ln K_a$.

[c] The values of $\Delta H°$ and $\Delta S°$ were obtained from the intercept and slope of the straight line in the plot of $\Delta G°$ versus T using the relationship $\Delta G° = \Delta H° - T\Delta S°$.

[d] The samples were prepared by dissolving freshly prepared **6e** in the degassed deuterated solvent: they were then kept in the dark to minimize any possible photooxidation.

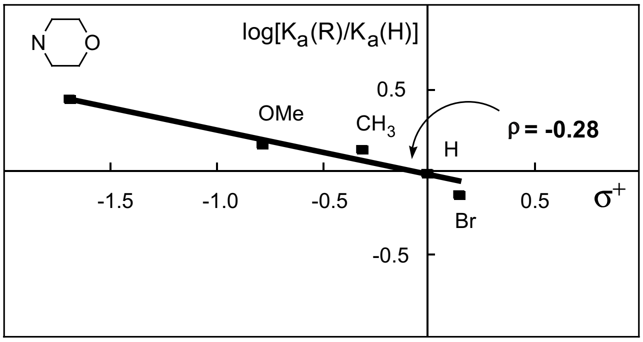


Figure 4. Hammett correlation between $\log[K_a(R)/K_a(H)]$ and σ^+ in $CDCl_3/CD_3NO_2$ (2:1) at 298 K. The slope of the straight line obtained corresponds to the supramolecular reaction constant (ρ).

substitutents. The small value of ρ implies that it is possible to modify the binding affinity between the crown ether and the thread-like ion over a reasonable range by controlling the electronic properties of the substitutents on the aniline ring, but that the magnitude of this change in the association constant is not dramatic. Since a simple oxidation reaction can readily convert the electron-donating methyl groups of macrocycle **6a** into more-electron-withdrawing formyl groups, and that an amination reaction can translate the macrocycle **6d** into a fourfold stronger binder (**6e**), it seems reasonable to expect that judicious choice of the substituent on the crown ether, coupled with a suitable post-assembly modification, would allow the preparation of speed-controllable machine-like molecules.

We have synthesized a series of DA24C8 derivatives and demonstrated that their affinity for binding with DFA$^+$ ions can be fine-tuned by judicious choice of substituents. We are now trying to assemble this recognition system into a [2]rotaxane through dynamic imine formation.[19]

Acknowledgements

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