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Hydrogen bonding in macrocyclic receptor systems

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The interactions of macrocyclic polyethers with alkali and alkaline earth cations have been well studied and much about their chemistry is now well understood. Less well examined or comprehended are hydrogen bond interactions. A combination of ion selective electrode binding constant determination techniques and fast atom bombardment mass spectrometry are brought to bear on this problem. It is found that all-oxygen crown ethers and their derivatives exhibit quite different complexation behaviour with ammonium salts than do their various azacrown counterparts.

INTRODUCTION

Hydrogen bond interactions are among nature's best known, most important, and ubiquitous interactions.[1] Among natural feeble forces,[2] these low energy interactions are responsible in part for the assembly and stabilization of a vast variety of huge structures including proteins and dimeric ribonucleic and deoxyribonucleic acids. Hydrogen bond interactions have served as the basis for a multiplicity of clever and novel receptor systems.[3] Among the earliest receptor systems that made use of directed hydrogen bond interactions are the crown ethers.[4] These macrocyclic polyether structures utilize a 'tripod' of N-H...X interactions (X = O,N) to stabilize host-guest complexes or supramolecular assemblies. In the latter case, the early work of Cram[5] and a considerable effort by others[6] has been based upon this 'tripod' notion. Indeed, several solid state structure studies have shown that this tripod does, in fact, form and that stable complexes result. We have previously used ammonium cation complexation to macrocyclic crown ethers as the basis of certain molecular boxes and their complexes.[7] In this work, diaza-18-crown-6 was the basic structural unit. In an effort to extend these studies, we developed a convenient preparation for triaza-18-crown-6,[8] first reported by Lehn and coworkers,[9] in the expectation that formation of three N-H...N hydrogen bonds, which Lehn has suggested are stronger than the corresponding N-H...O bonds,[10] would lead to greater complexation strength, organization, and selectivity. We report here the results of those studies and additional work on ammonium ion interactions.

RESULTS AND DISCUSSION

Hydrogen bonding strengths

Stryer, in his text on biochemistry,[11] presents a Table in which the following bond lengths are quoted: O-H...O, 2.70 Å; O-H...N, 2.88 Å; N-H...O, 3.04 Å; N^+-H...O, 2.93 Å; and N-H...N, 3.10 Å. It seems reasonable to suppose that hydrogen bond strength and bond length correlate. Indeed, the fact that the ammonium N^+-H...O bond is 0.1 Å shorter than the corresponding neutral N-H...O bond appears to confirm this intuition. On the other hand, it seems reasonable to think that the symmetrical N-H...N bond would be more stable than the corresponding N-H...O bond which must be asymmetrical. Pimentel and McClellan, in their classic work on the hydrogen bond,[12] presented average hydrogen bond distances for N-H...O and N-H...N bonds. They found that the average H-bond distance for ammonium salt donors to oxygen acceptors (41 data) was 2.88 ± 0.13 Å. They reported 'all' N-H...N distances (37 data) as 3.10 ± 0.13 Å. Wallwork[13] refined these data showing that for NH_n^+ donors, the donor-acceptor distances were as follows: 2.92 Å to N, 2.86 Å to O, and 3.00 Å to NH_n. In a more recent study, Kuleshova and Zorkii[14] have accumulated approximately 1000 bond length values with the

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following result. They report N–H...O has an average bond distance of 2.89 Å (883 data) and N–H...N has an average length of 2.98 Å (114 data). These two data sets (the former is a subset of the latter) seem to be in reasonable agreement.

Jeffrey and Saenger state (ref 1, p. 114) that "there is no evidence of a quantitative relationship between the O–H and H...O bond lengths and O...O distances." On p. 51 of the same volume, they further assert that, "There is no direct experimental relationship between hydrogen-bond lengths and hydrogen-bond strengths. It seems axiomatic that stronger hydrogen bonds will have shorter bond lengths than weaker bonds. It is certainly true that the very strong bonds as a class have shorter bond lengths than the moderate or weak bonds formed between biological molecules. However, ... the correlation is not straightforward." It thus seems that the assertion of Lehn and our own expectations, although reasonable and intuitive, may be misapprehensions.

Jeffrey and Saenger have also noted that "Bond energies are derived from thermochemical data such as virial coefficients, heats of fusion, and transport properties such as viscosity, thermal conductivity, and spectroscopic data. Hydrogen-bond lengths come solely from diffraction experiments, with the exception of a few complexes of simple molecules which are stable in the gas phase and can be studied by microwave spectroscopy."

It has been pointed out by Cram, Goldberg, and others, that two interactions can occur between a crown ether and a bound ammonium cation. The first is formation of three N–H...O bonds. The second is the pole–dipole interaction that is possible between the three remaining oxygen atoms and the quaternary ammonium nitrogen atom (> O: → N$^+$). Goldberg[15] has presented a Figure like the one shown in Figure 2 below to describe these two interactions. In the top portion of the Figure, the distances are given as 3.1 Å and 2.1 Å for the O → N contact and the N–H to O distance, respectively. When the typical N–H bond distance of ~1 Å is added to the 2.1 Å quoted, the two distances are identical.

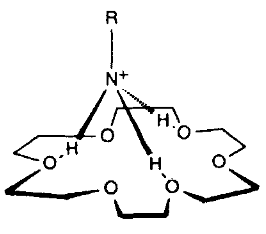

Figure 1 Tripod hydrogen bonding between ammonium ion and 18-crown-6.

Ammonium ion complexes

The symmetry of the 18-crown-6·NH_4^+ complex is obvious from a study of molecular models. Solid state structures of both the ammonium chloride[16] and bromide[17] complexes with 18-crown-6 have been reported and confirm this symmetry. In neither case, however, do the hydrogen atoms seem to have been located by direct methods although in both cases electron density in appropriate positions appears to have been observed. Indeed, it is interesting to note that in very few cases have the hydrogen atoms been located in these complexes. The lack of direct evidence for N–H...N interactions is even more dramatic in the case of azacrowns.

The classic case of azacrown–ammonium ion complexation was the low temperature (113 K) study conducted by Maverick, Grossenbacher, and Trueblood.[18] In this investigation, the *t*-butylammonium complex of pyrido-18-crown-6 was examined. Three hydrogen bonds were observed; one of them was a N–H...N hydrogen bond to pyridine as the H-bond acceptor. The bond length for this interaction was 2.10 Å and the two N–H...O bonds exhibited distances of 2.10 Å and 2.20 Å. The conformation about the C–N bond was *gauche*, as expected. The structure is illustrated in schematic form in Figure 4. To our knowledge, this is the only solid state structure in which any N–H...N hydrogen bonds in an ammonium–azacrown ether complex have ever been reported. In other cases, it appears that the hydrogen positions are guessed to be in reasonable positions or inferred from the substituents on R–NH_3^+ which are expected (see Fig 4) to show the *gauche* conformation about the N–C bond. An excellent example of this is the recent report of Zhu, Izatt,

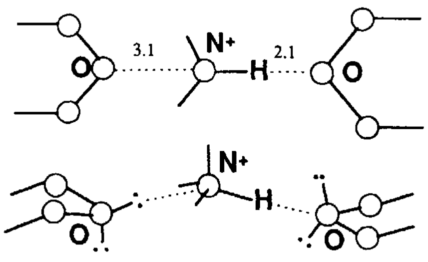

Figure 2 N–H...O vs. O → N$^+$ interactions.

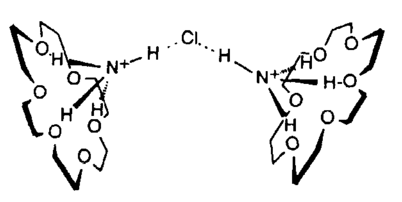

Figure 3 Schematic representation of 18-crown-6·NH_4^+ complex.

Bradshaw and Dalley.[19] In this investigation, "all of the non-hydrogen atoms were located in the E map", and "Positions for the hydrogens bonded to the nitrogen of the cation were taken from a difference map. During the refinement, these hydrogens were fixed to ride on the nitrogen and their isotropic thermal parameters were refined." This is an especially interesting case because the complex is between benzylammonium cation and the same pyrido-crown studied by Trueblood and coworkers. The focus of this inquiry was whether or not a π-interaction between pyridine and phenyl stabilizes the complex with pyrido-18-crown-6 (**2**) or diketopyrido-18-crown-6 (**3**).

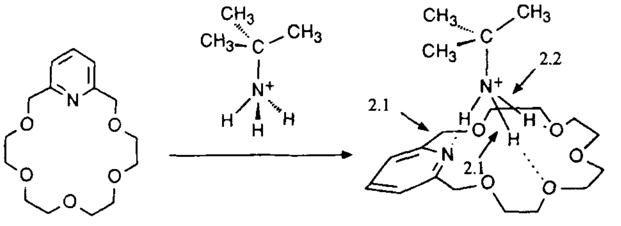

Figure 4 Schematic representation of complex between pyrido-18-crown-6 and *t*-butylammonium cation.

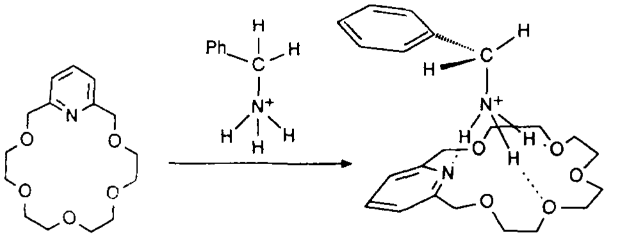

Figure 5 Schematic representation of complex between pyrido-18-crown-6 and benzylammonium cation.

Solution binding data for ammonium ion complexes. The question of complexation between ammonium ions and an all-aliphatic crown is more difficult to resolve. There is certainly no doubt that such complexes form. Indeed, a decade ago, we used ammonium cation complexation strengths to demonstrate sidearm participation in lariat ether complexation in the solution phase.[20] To our knowledge, no ammonium ion complexes of aliphatic azacrowns, save that described by Lehn for spherand,[6b] have been reported. Solution phase data for ammonium cation complexes have been obtained for a variety of structures. These are summarized in Table 1. The question was whether triaza-18-crown-6 derivatives[21] were much better ammonium cation binders than 18-crown-6 or derivatives thereof. Lehn reported that in 90% methanol solution, the binding constants (log K_S) for 18-crown-6 and trimethyltriaza-18-crown-6 were 4.07 and 4.81 respectively. This quite strong binding constant led us to develop ammonium cation binders having flexible sensor sidearms. The structures we developed failed to exhibit the selectivity we had hoped to observe. We thus measured the ammonium complexation constants for 18-crown-6, trimethyltriaza-18-crown-6, and hexamethylhexaza-18-crown-6 under similar conditions using ion-selective electrode methods in anhydrous methanol. Our results were as follows: 18-crown-6, 4.08; trimethyltriaza-18-crown-6, 4.97; hexamethylhexaza-18-crown-6, 3.79. In contrast to the results Lehn obtained, however, we observed the

Table 1 Ammonium ion complexation

Compound number	Compound identity	Cation	*log K_S (This work)*		*log K_S (Other work)*		
			100% MeOH	*90% MeOH*	*100% MeOH*	*90% MeOH*	*Reference*
1	18-Crown-6	Na^+	4.35	3.73	–	3.51	
1	18-Crown-6	K^+	6.08	5.28	–	5.23	
1	18-Crown-6	NH_4^+	4.08	–	4.27	4.07	32
1	18-Crown-6	$CH_3NH_3^+$	–	3.43	4.25	3.32	32
1	18-Crown-6	$CH_3CH_2N_3^+$	–	–	3.99	3.20	10
2	Pyrido-18-crown-6	NH_4^+	–	–	–	3.35	18
2	Pyrido-18-crown-6	$PhCH_2NH_3^+$	–	–	–	3.78	18
3	Diketopyrido-18-crown-6	NH_4^+	–	–	–	2.60	18
3	Diketopyrido-18-crown-6	$PhCH_2NH_3^+$	–	–	–	2.68	18
4	Dimethyldiaza-18-crown-6	NH_4^+	2.99	–	–	–	
5	Trimethyltriaza-18-crown-6	Na^+	–	<1.5	–	<1.5	
5	Trimethyltriaza-18-crown-6	K^+	4.36	3.21	–	3.78	
5	Trimethyltriaza-18-crown-6	NH_4^+	4.97	–	–	–	
5	Trimethyltriaza-18-crown-6	$CH_3NH_3^+$	–	3.98	–	4.81	10
5	Trimethyltriaza-18-crown-6	$CH_3CH_2NH_3^+$	–	3.83	–	4.49	10
6	Hexamethylhexaaza-18-crown-6	K^+	2.01	–	–	–	
6	Hexamethylhexaaza-18-crown-6	NH_4^+	3.79	–	–	–	

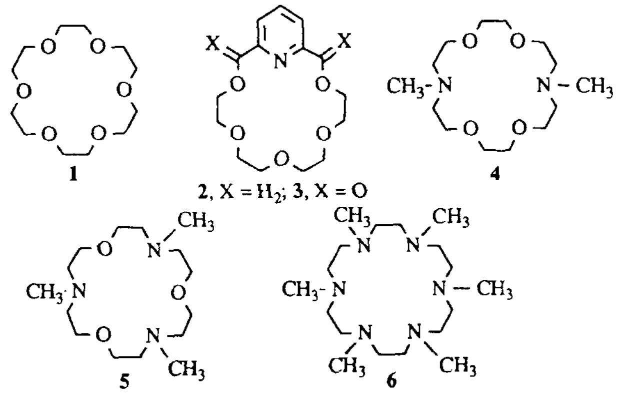

Figure 6 Compounds 1–6.

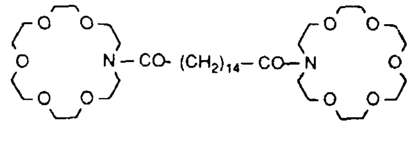

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Figure 7 Compound 7.

following $CH_3NH_3^+$ constants (log K_S) under conditions (90% methanol:10% water) which attempted to duplicate his: 18-crown-6, 3.73 and trimethyltriaza-18-crown-6, 3.98.

These limited comparisons substantiate the trends reported by Lehn but the magnitudes we observe are somewhat lower. It is interesting to note however, that the combination of three N–H...N hydrogen bonds and three $O: \rightarrow N^+$ pole–dipole interactions appear to make trimethyltriaza-18-crown-6 an especially good complexing agent for ammonium salts.

Assessment of ammonium cation complexation by fast atom bombardment mass spectrometry (FABMS). The FABMS technique is an appealing method to use in determining the complexation behaviour of crown ether systems because it is sensitive, reliable, and requires a relatively small sample. Indeed, we[22] and others[23] have previously demonstrated the potential importance of this emerging methodology. We decided to study complexation between ammonium ions and a systematically varied series of crown and azacrown ethers in order to determine if any difference in binding behaviour was apparent as a result of nitrogen for oxygen substitution in the macro-ring. The compounds studied are shown in Figure 7. An important principle of FABMS, as applied to complexation, is that the spectrum observed reflects the phenomena that occur in solution. All spectra were obtained in *m*-nitrobenzyl alcohol, a compound not identical to methanol but not unlike it. The FAB spectra of 18-crown-6 in the presence of NH_4^+ or $CH_3CH_2NH_3^+$ contain ions consistent with the complex $[18\text{-crown-}6\cdot NH_4]^+$ or $[18\text{-crown-}6\cdot CH_3CH_2NH_3]^+$. The FAB spectra of trimethyltriaza-18-crown-6 showed quite different behaviour. In this case, the $[\text{triazacrown}\cdot H]^+$ ion dominated the spectrum. Notwithstanding, the ammonium ion complexes were detected in the spectrum. For example, when trimethyltriaza-18-crown-6 and ethylammonium chloride were mixed with *m*-nitrobenzyl alcohol, an ion was observed at m/z 349 which corresponds to $[\text{crown}\cdot CH_3CH_2NH_3]^+$. One might conclude from this that proton transfer is more energetically favoured in the azacrown case than in the all-oxygen crown systems. Proton transfer is obviously expected to be favoured when nitrogen, rather than oxygen, is the base. In principle, at least, complexation could still occur between the protonated azacrown and the neutral amine, but we did not observe it.

In contrast to these results, it is interesting to note that when the tertiary nitrogen of the macro-ring was replaced by amidic nitrogen (i.e. $>N\text{–}CH_2\text{–} \rightarrow >N\text{–}CO\text{–}$, compound **7**), enhanced ammonium ion complexation (formation of $[\text{crown}\cdot RNH_3]^+$) was observed. This is somewhat unexpected as the basicity of the amine nitrogen is greater than the amidic nitrogen. One would thus anticipate that complexation between ammonium salt and amine would be greater than between ammonium salt and amide.

The FABMS method offered an experimental means of studying a long-standing interest of ours. Little is known about the precise magnitudes of lipophilic–lipophilic (van der Waals) interactions[24] between or among, for example, hydrocarbon chains. Our interest in fatty acid binding and acylating proteins[25] led us to construct the bis(steroidal) crown ether shown in Figure 8 as compound **9**. Our expectation was that in a moderately polar solvent such as *m*-nitrobenzyl alcohol, binding of an alkylammonium salt, $CH_3(CH_2)_nNH_3^+$, should occur by the 'tripod' mechanism.

When a 1:1:1 mixture of ethylammonium ($CH_3CH_2NH_3^+$), nonylammonium $[CH_3(CH_2)_8$-

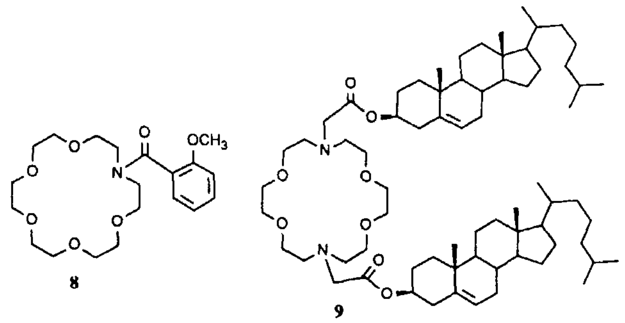

Figure 8 Compounds **8** and **9**.

NH_3^+], and tetradecylammonium [$CH_3(CH_2)_{13}$-NH_3^+] chlorides was added to 18-crown-6 in *m*-nitrobenzyl alcohol and subjected to FABMS analysis, the spectrum was very simple and dominated by a base peak (*m/z* 478) that corresponded to [18-crown-6·tetradecylammonium]$^+$. An ion having approximately half the base peak's intensity was observed at *m/z* 408 and corresponded to [18-crown-6·nonylammonium]$^+$. The ion corresponding to [18-crown-6·ethylammonium]$^+$ that should have been observed at *m/z* 310 either did not occur or was too small to be identified under these conditions.

Considering that these ammonium salts should be surface active, the longer alkyl chains are expected to dominate the gas liquid interface of the FAB matrix. It is therefore reasonable to assume that the formation of complexes should be in the order tetradecyl > nonyl > ethyl, as observed.

A quite different observation was made when trimethyltriaza-18-crown-6 was subjected to the same mixture of ammonium salts and experimental conditions described above. In this case, the only ion observed in the spectrum having an intensity greater than 10% was *m/z* 304 (100%). This base peak corresponds to the protonated molecular ion [trimethyltriaza-18-crown-6·H]$^+$. In the molecular mass range 350–1000 kDa, no peak at all was evident above the baseline noise. Nevertheless, a several-hundred-fold amplification of the signal in this region revealed several peaks. The base peak of this newly amplified region was observed at *m/z* 517 and corresponded to [trimethyltriaza-18-crown-6·tetradecylammonium]$^+$. An ion noted at *m/z* 447 had an intensity of *ca.* 50% and corresponded to [trimethyltriaza-18-crown-6·nonylammonium]$^+$. An ion at *m/z* 347, [trimethyltriaza-18-crown-6·ethylammonium]$^+$, could be identified among other ions in this greatly amplified region but it was, as before, not a dominant ion.

The amide (**8**) that forms from aza-18-crown-6 and *o*-anisic acid is lariat-like[26] in the sense that a sidearm containing the *o*-methoxyphenyl group is present on the macro-ring nitrogen. In this case, however, the nitrogen is amidic and thus less basic and less flexible than the saturated counterpart. When mixed with the three ammonium salts (see above) the FAB spectrum was again quite simple. The dominant ion, corresponding to [crown·H]$^+$ was observed at *m/z* 398. No other ion was observed with an intensity greater than 15% of this base peak. As in the previous case, however, the signal in the 400–1000 kDa mass region was greatly amplified. Ions corresponding to the [crown·RNH_3]$^+$ complexes were again observed and ion intensities were in the order C_{14} (*m/z* 611, 100%) > C_9 (*m/z* 541, 55%) > C_2 (*m/z* 443, 10%).

The alpha (bottom) surface of a steroid is an almost planar array of C–H (hydrocarbon) groups. We thought that a bibracchial lariat ether having two steroid-containing sidearms could form a U-shaped complex with a long chain alkylammonium salt. We presumed that the most stable arrangement for the complex would be for a tripod interaction to occur between RNH_3^+ and the crown. The ammonium salt's hydrocarbon chain would then align with the two steroid alpha surfaces for hydrophobic contact stabilization. It was expected that as *n* increased from 1 to 8 to 13 (i.e. the sequence ethyl, nonyl, tetradecyl) that the complex ions corresponding to [crown·RNH_3]$^+$ would become increasingly intense. The base peak in the FAB spectrum was observed at *m/z* 1120 and corresponded to the protonated molecular ion. No ion having an intensity greater than 5% of the base peak was observed in the mass range 1150–1900 kDa. As in previous experiments in this series, the latter mass range signal was greatly amplified. In contrast to all previous observations, no series of complexes, albeit weak, could be identified. Clearly, the proton transfer mechanism is important in this azacrown system, as it was the azacrown systems reported above. Even so, we cannot account for the steroid exhibiting entirely different behaviour to its simpler relatives. A speculative explanation is that the large steroid arms sterically hinder approach of the ammonium salt to such an extent that complexation is energetically not feasible.

Construction of molecular boxes using ammonium salt binding interactions. We have previously reported studies using adenine- and thymine-substituted bibracchial lariat ethers as subunits for the assembly of molecular boxes.[6] The notion underlying that effort was that the organizing (hydrogen-bond dimerization) ability of nucleotide bases combined with crown-ammonium cation interactions might lead to discrete structures having a high degree of order – all the result of simple hydrogen bond interactions. We found that in aqueous solution, two 4,13-diaza-18-crown-6 derivatives having either thymines or adenines at the ends of short hydrocarbon tethers did, in fact, aggregate. Determination of the association constants in aqueous solution by vapour pressure osmometry was useful but problematic. Although measurement of box formation itself is not difficult, the presence of a diammonium salt and its attendant charge make use of osmometry uncertain, as the calibration coefficients for charged and uncharged species differ.

In the process of developing molecular boxes based upon the system described above, we had occasion to synthesize a diaza-18-crown-6 derivative in which one nitrogen bore an ethylene sidechain terminating in an adenine residue. On the other nitrogen, a propyl

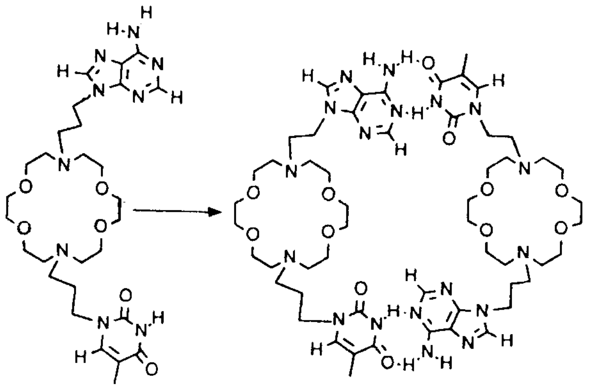

Figure 9 Formation of a 'DNA box' from **A–O–T**.

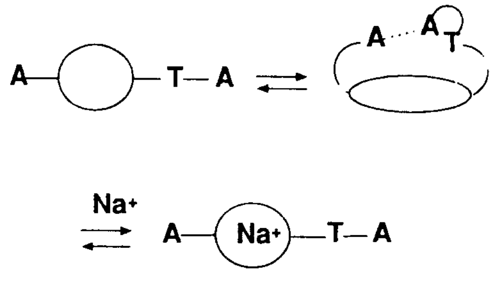

Figure 10 **A–O–T–A** compound.

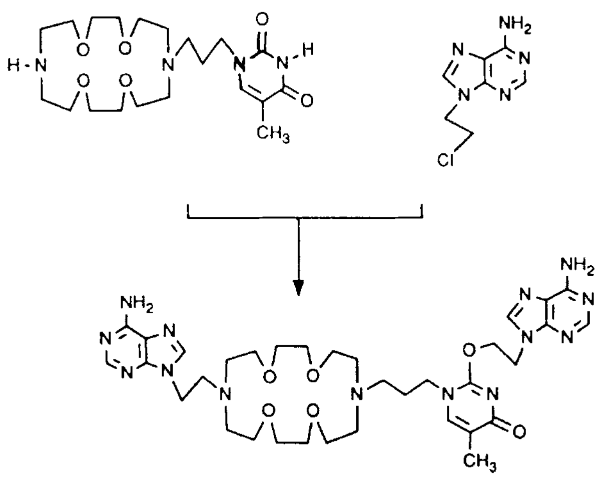

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Figure 11 Preparation of compound **10**.

sidechain terminated in a thymine which was, in turn, attached to another adenine. We have referred to this compound as **A–O–T–A**, in which **A** is adenine, **T** is thymine, and **O** represents the diaza-18-crown-6 residue (Fig 10).

Extensive studies involving COSY and NOESY spectroscopy led us to the conclusion that a structure as represented in Figure 11 exists in chloroform solution and that the entire complex system is organized by a combination of π-stacking (adenine/thymine) and a single Hoogsteen hydrogen bond between transannular adenines.[6b] We think that such systems will be useful in probing the organization of otherwise complicated systems.

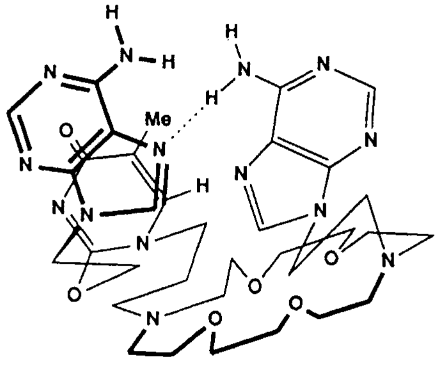

Figure 12 A self-organizing lariat ether derivative based upon nucleotide bases.

It is interesting to note that addition of an equivalent of $Na^+PPh_4^+$ completely collapses this self-organized system, apparently by sodium complexation between the macro-ring and the cation. Such an interaction is expected to be stronger than the combination of π-stacking and the single hydrogen bond in this case.

CONCLUSION

We undertook this study originally because our observations of binding strength upon which we had based certain preliminary receptor designs did not match literature values. In the process, we considered the question of whether ammonium ions bind more strongly to nitrogen or oxygen in a macro-ring having both atoms. Our conclusion is that the combination of N–H...N hydrogen bonds plus O → N dipolar interactions provides a special stabilization for trimethyltriaza-18-crown-6 complexes of ammonium cation. The question of crown–ammonium ion interactions is further complicated by results obtained using the FAB method. This shows the expected complexation between RNH_3^+ and all-oxygen crowns, but proton transfer appears to dominate when nitrogen is present in the macro-ring. Further studies to clarify this latter novel finding are underway.

EXPERIMENTAL SECTION

^1H-NMR spectra were recorded on a Varian XR-400 NMR Spectrometer or on a Hitachi Perkin-Elmer R-600 High Resolution NMR Spectrometer in $CDCl_3$ solvents and are reported in ppm (δ) downfield from internal $(CH_3)_4Si$. ^{13}C-NMR were recorded on a JEOL FX90Q or Varian XL-400 NMR Spectrometer or as noted above. Infrared spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer and were calibrated against the 1601 cm^{-1} bond of polystyrene. Optical rotations were measured on a Perkin-Elmer Model 241 Polarimeter in a glass microcell (100 mm path length, 1 ml volume) with a Na gas discharge lamp as the light source. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic analyses were performed on aluminium oxide 60 F-254 neutral (Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with activated aluminium ocide (MCB 80-235 mesh, chromatographic grade, AX 611) or with Kieselgel 60 (70–230 mesh). Chromatotron chromatography was performed on a Harrison Research Model 7924 Chromatotron with 2 mm thick circular plates prepared from Kieselgel 60 PF-254. Gas chromatographic analyses were conducted on a Hewlett-Packard model 5720 gas chromatograph equipped with a flame ionization detector and a 5 ft. × 0.25 in. column packed with 1.5% OV-101 on 100/120 mesh Chromosorb G. Helium was used as the carrier gas, and the flow rate was *ca.* 60 ml/min.

All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best grade commercially available and were distilled, recrystallized or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Combustion analyses were performed by Atlantic Microlab Inc, Atlanta, GA, and are reported as percentages.

FAB spectra were recorded on a VG TRIO 2 by using a 6–8 KeV Xe primary beam and a *m*-nitrobenzyl alcohol matrix. The spectra reported herein were peak averaged over four scans. In a typical experiment, *m*-nitrobenzyl alcohol (*1 μl*), *1 μl* of a 50 mM lariat ether solution ($CHCl_3$), and 1 μl of a 50 mM aqueous solution of metal chloride were carefully mixed on the FAB probe.

Cation binding constants were measured in absolute MeOH at 25.0 ± 1.0°C using a Corning 476210 electrode and an Orion model 701A 'ionalyzer' meter according to the method of Frensdorff[27] as described in detail.[28] Values for the equilibrium constants are reported as log K_S.

Compounds **1**–**6** are known, 18-Crown-6, **1**, and hexamethylhexaaza-18-crown-6, **6**, were purchased from the Aldrich Chemical Company. Pyridine crowns **2** and **3** were reported in references 18 and 19, respectively. Dimethyldiaza-18-crown-6, **4**, and trimethyltriaza-18-crown-6, **5**, were reported by Lehn and Vierling.[10] A discussion of the family of compounds including **7** has recently been reported.[29]

Aza-18-crown-6 *o*-anisamide, **8**, was prepared as described previously.[30]

(bis-Dihydrocholesteryl-[*N*,*N*-(1,4,10,13-tetraoxa-7,16-diazacyclooctadecane)-]-bis-acetate

Dihydrocholesteryl chloroacetate[31] (1.86 g, 4.0 mmol), diaza-18-crown-6 (0.50 g, 1.9 mmol), Na_2CO_3 (0.81 g, 7.6 mmol), and KI (64 mg, 0.4 mmol) were heated in butyronitrile (50 ml) at reflux (115°C) while stirring for 48 h. The mixture was cooled to room temperature, filtered, and concentrated under vacuum. The residue was redissolved in methylene chloride (50 ml), washed with water (2 × 25 ml), brine (25 ml), and dried ($MgSO_4$). Chromatography over a short column (silica gel 60, 0–3% methanol/methylene chloride) afforded the title compound as a white solid [m.p. 117–118°C after recrystallization from ethyl acetate in 31% yield (0.67 g)]. ^1H-NMR (400 MHz); 0.65 (s, 6H, C_{18}-steroid), 0.81–1.98 (m, 92H, steroid), 2.95 (t, 8H, $(O{-}CCH_2)_2$ N), 3.46 (s, 4H, NCH_2CO), 3.61 (broad s, 16H, $(OCH_2{-}C)_2N$, 4.72 ppm (m, 2H, C_3-steroid). IR (KBr): 2940 (s), 2880 (s), 1730 (s) cm^{-1}. $[\alpha]_S^{25} + 11.2$ (c = 2 in $CHCl_3$). Analysis calculated from $C_{70}H_{122}N_2O_8$: C, 75.09; H, 10.98. Found: C, 75.16; H, 10.97.

The preparation of compound **10** is described in reference 7b.

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