# Experimental Evidence for Alkali Metal Cation−π Interactions

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The interaction of alkali metal ions with arenes such as benzene or substituted benzenes has been documented in a variety of ways. This paper reviews the experimental evidence that has been accumulated to document the cation-π interaction that occurs between arenes and, particularly the ions sodium and potassium.

## 1. Introduction

The frameworks of organic structures are defined by covalent bonds. Single, double, and triple bonds between carbon, nitrogen, oxygen, sulfur, and a few other elements characterize many millions of organic compounds. Although covalent bonds define the structures in a critical way, chemical properties and reactivity are often influenced profoundly by much weaker forces. The best known of noncovalent interactions is undoubtedly hydrogen bonding[1] but such feeble forces as electrostatic interactions, ionic interactions, van der Waals forces, and the hydrophobic interaction[2] are known to be important in chemistry and biology. A particularly intriguing noncovalent interaction that has been increasingly recognized during the past two decades, the cation−π interaction,[3] is the focus of this review. In the discussion that follows, we will focus on experimental approaches to identifying and assessing the alkali metal cation−π interaction. Our interest in experimental studies does not diminish in any way the importance of the numerous computational studies that have been reported but enough ''solid'' evidence has now been accumulated that the interaction can be documented by using a variety of experimental approaches.

### 1.1 The Cation−π Interaction

The cation−π interaction is fundamentally an electrostatic interaction between a positively charged species (a cation) and the electrons that make up one or more π bonds. In principle, the cation may be any 'onium species. The interaction of carbocations with double bonds, triple bonds, and arenes has been a mainstay of physical organic chemistry for much of the last 100 years. Numerous rearrangements, rate accelerations, and examples of anchimeric assistance have been accounted for by the proximity of a cation and a double bond. The interaction between metal

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**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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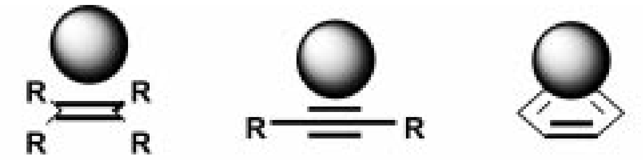
cations and arenes was thrust dramatically into the chemical arena at midcentury with the discovery of ferrocene. Innumerable examples of transition-metal−π or transition-metal−arene interactions have been found and studied since; of course these are predominantly covalent. The importance of ammonium-ion cation−π interactions was recognized more recently and has been of greatest interest within the biochemical community. Although alkali-metal cation−π interactions are potentially as important to biology as are ammonium ion−π interactions, experimental evidence for them has been almost nonexistent until very recently.

Three typical cation−π interactions are shown in the structures below. At the left and center are cation−double bond and cation−triple bond interactions. These are similar except that the triple bond is essentially cylindrically symmetrical whereas the p orbitals of the double bond are perpendicular to the carbon framework. Intuitively, a cation is expected to position itself directly above the middle of the π bond or the center of the benzene ring.



### 1.2 Ammonium−π Interactions

Although alkali-metal cation−π interactions are the main focus of this review, the field received enormous encouragement from success in identifying ammonium−π interactions. The ammonium−π contact is not only of the same fundamental type that is discussed here but more experimental work has been done on it. Indeed, a substantial body of experimental evidence exists concerning the attraction of an ammonium cation to a π bond.

In 1985, Deakyne and Meot-Ner[4] demonstrated by gas phase studies that the ammonium cation could interact favorably with olefins and substituted benzenes. At almost the same time, Burley and Petsko[5] reported the results of their survey of 33 high-resolution protein crystal structures. They noted a tendency for positively charged amine side chains to be positioned over the π face of aromatic residues. They coined the term ‘‘amino−aromatic’’ interaction, which they proposed contributed to protein stability. The analytical approach to identifying ammonium−π interactions in protein crystal structures has been extended in work undertaken by the groups of Thornton[6] and, more recently, Dougherty.[7]

In the realm of supramolecular chemistry, several research groups have reported cyclophanes, calixarenes, and other host molecules that bind quaternary amines in cavities having extensive π surfaces. Notable among these efforts are contributions by Collet,[8] Dougherty,[9] Lehn,[10] Mandolini,[11] Schneider,[12] Roelens,[13] Schwabacher,[14] and Shinkai.[15] These synthetic receptor molecules provided strong evidence that the ammonium cation−π interaction is a substantial force that may contribute significantly to molecular recognition.

In biological systems, the potential importance of ammonium cation−π interactions to molecular recognition processes has also been noted.[16] Quaternary ammonium−π contacts involving choline are also apparent in the solid-state structures of acetylcholine esterase[17] (an acetylcholine binding enzyme) and McPC603[18] (an antibody). A similar interaction has been inferred for the binding of acetylcholine by the acetylcholine receptor.[19] The evidence presented above suggests that the ammonium−π interaction is not only favorable, but can be a significant noncovalent force that is utilized by biological systems.

### 1.3 Silver Cation−π Interactions

Silver ion has long been known as a rearrangement catalyst, for example opening cubane to cuneane[20] or [3.1.1]bicyclooctane into cycloheptadiene.[21] Silver cation interacts readily with strained and unsaturated hydrocarbons at sites of π-electron richness. The ability of silver cation to complex olefins was demonstrated many years ago in several crystal structure studies. Complexes of silver with bullvalene,[22] (*E*)-cyclodecene,[23] and geijerene[24] were all reported in the late 1960s. Spectroscopic studies using $^{13}$C NMR verified these interactions in solution.[25] In recent work, evidence has accumulated for the interaction of $Ag^+$ with fullerenes[26] and calixarenes.[27]

Silver is clearly related to the alkali metals by virtue of its monovalency. Unlike such alkali metals as $Na^+$ and $K^+$, it is reactive and virtually absent from biological systems. Still, its ability to form π complexes is both suggestive and encouraging.

### 1.4 Theoretical Evidence for Cation−π Interactions

Theoretical (computational) methods have been extensively used to investigate cation−π interactions. A great deal of attention has been focused on the interaction between ammonium ions and benzene, phenol, and indole. These three residues are particularly important because they represent the side chains of three aromatic amino acids, phenylalanine (Phe, F), tyrosine (Tyr, Y), and tryptophan (Trp, W). The parent aromatic compound (e.g. benzene for Phe) is generally used to model the amino acid side chain.[28] Semi-empirical methods have been used to assess the binding of ligands to the acetylcholine receptor.[29] The interaction of ammonium ions with artificial cyclophane hosts was also recently modeled.[30]

Theoretical investigations of the cation−π interaction are not the focus of this review but a brief summary of the effort is presented here for perspective. An important paper that appeared in 1976 described work by Apeloig, Schleyer, Binkley, Pople, and Jorgensen whose calculations showed that dilithioacetylene preferred a π-bridged structure rather than a linear one.[31] Most of the theoretical efforts undertaken prior to 1997 are discussed in reference 3.

Recent work has continued to focus on two major issues. First, calculated binding energies have been compared to data obtained from experimental gas-phase measurements. The 6-31G** level of ab initio theory has been generally successful in reproducing the gas-phase experimental results.[32] Binding strengths for various cations follow the expected electrostatic sequence. Thus, $Li^+$ is calculated to have the strongest attraction for benzene and the binding energy between cation and arene decreases as the atomic number of the cation increases. Theoretical data for the $Cs^+$−benzene complex have recently been reported[33] and the effect of polarization terms on cation−π binding energy continues to be investigated.[34] Based on the work of Kollman,[35] molecular mechanics methods with empirical correction terms have been assessed.[36] The alkali metal selectivity of a hypothetical ''collarene'' was also calculated.[37]

Optimized binding geometries have been calculated for several cation−π pairs. Theoretical methods have consistently shown that the geometry-optimized $Na^+$−benzene complex is a sixfold symmetric complex, in which the cation resides over the centroid of the ring. Small molecule crystal structures generally agree with this result (see section 3.1). Recent work extended these calculations to larger aromatic systems, such as naphthalene.[38,39] The heterocyclic system indole provides an interesting test of these calculations. The predicted energy minimum for $Na^+$ is that in which the cation is positioned above the six-membered (benzene) ring of indole.[39−41] Recent experimental data for the $Na^+$−indole complex have shown the unexpected result of coordination by the five-membered, nitrogen-containing ring of indole (see section 5).

## 2. Gas-Phase Studies

The extensive computational studies alluded to and described above are generally performed for the gas phase. This review is focused on experimental results, however, and some of the earliest studies were also conducted in the gas phase. The seminal contribution to this area was the work of Sunner, Nishizawa, and Kebarle that was reported in 1981.[42] They examined the gas-phase equilibrium,

$$K^+B_{n-1} + B \rightleftarrows K^+B_n,$$

in which B represents benzene. The ionization chamber of a mass spectrometer was configured to contain a platinum gauze filament, painted with a potassium salt, capable of thermionic emission. Experiments were done using low pressures of benzene or benzene mixed with methane. Thermodynamic data were obtained by using the van't Hoff method. The experimentally determined enthalpy ($\Delta H$) for the reaction shown above is −19.2 kcal/mol (−80.2 kJ/mol). The related process,

$$K^+W + W \rightleftarrows K^+W \text{ (W = water)},$$

gives a value for $\Delta H$ of −17.9 kcal/mol (−74.9 kJ/mol).[43]

A related equilibrium reaction, namely

$$K^+W_xB_y + W \rightleftarrows K^+W_{x-1}B_{y+1} + B,$$

was also studied by this method. Van't Hoff plots of the benzene−water exchange equilibrium were again used to obtain thermodynamic parameters. Using the data from the latter study, a corrected value for $\Delta H$ of −18.3 kcal/mol (−76.6 kJ/mol) was obtained for the reaction $K^+ + B \rightleftarrows K^+B$. In the authors' own words, the fact that $-\Delta H$ for $K^+B$ is greater than for $K^+W$ ''is surprising.'' Indeed, these results continue to surprise simply because the magnitude of this interaction is so substantial. It must not be overlooked that these results are for the gas phase where competition with bulk water is not an issue. Still, the interaction is substantial by any assessment.

In more recent work using high-pressure mass spectrometry, Guo, Purnell, and Castleman[44] analyzed the equilibrium

$$Na^+ + \text{benzene} \rightleftarrows Na^+\text{(benzene)}.$$

As in the studies by Kebarle et al., the van't Hoff method was used to obtain thermochemical parameters (Table 1). The enthalpy ($-\Delta H$) found for the equilibrium shown was 28.0±0.1 kcal/mol (117.2 kJ/mol). This value seems reasonable compared to the value of about 18 kcal/mol (75.3 kJ/mol) found for a similar association between $K^+$ and benzene. The latter cation is larger but bears the same charge so its charge density and thus its electrostatic interaction with the benzene π system is expected to be less.

Table 1. Bonding energies for $Na^+$ and $K^+$

| Interaction | $-\Delta H$ (kcal/mol) | Ref. |
|---|---|---|
| $Na^+ + C_6H_6$ | 28.0±0.1 | [44] |
| $Na^+ + H_2O$ | 24.0 | [44] |
| $Na^+ + HOCH_3$ | 26.6 | [44] |
| $K^+ + C_6H_6$ | 18.3 | [42] |
| $K^+ + H_2O$ | 17.9 | [42] |

The importance of these observations can hardly be overstated. Both $Na^+$ and $K^+$ are by far, the most common metal cations found in biological systems. Their interactions with the aromatic sidechains of amino acids such as tryptophan, tyrosine, and phenylalanine are of great potential importance. Such interactions within the low-polarity environment of a phospholipid bilayer or a folded protein do not require competition with bulk water and therefore may be very influential.

Lisy and co-workers[45,46] have used a combination of mass spectrometry and vibrational spectroscopy to assess the interactions of $Na^+$ and $K^+$ with water and benzene. Clusters are formed by generating $K^+$ ions thermionically and allowing the molecular beam to interact with a mixture of benzene, water, and argon. Clusters of the type $K^+(\text{benzene})_n(\text{water})_m$ were detected in which $m + n = 3-6$. The authors concluded that $K^+$ preferred to bind benzene over water.[45] In very recent work, it has been shown that $K^+$ interacts with an aromatic complex even in an aqueous environment, whereas $Na^+$ cation does not.[46]

The selectivity of the $Na^+/K^+$ interaction with benzene and water is of intrinsic interest but it may also be relevant to biological problems. Several years ago, Dougherty and co-workers advanced a hypothesis to account for $K^+$ over $Na^+$ selectivity of certain cation channels. The ''Shaker'' potassium-conducting channel of *Drosophila melanogaster* has a tyrosine present (a GYG sequence) in the so-called signature sequence. It was suggested that the aromatic side chain of tyrosine ($CH_2C_6H_4OH$) might interact with and stabilize a transient $K^+$. The hypothesis was attractive because it accounted for the fact that a larger cation is selected over a smaller cation in what is generally regarded as a rigid pore. Theoretical calculations showed that benzene could compete effectively with water in the solvation sphere of $K^+$ and thus stabilize the cation and strip it of some of its hydration shell. The stronger interaction of $Na^+$ with water prevented this and the fully hydrated $Na^+$ cation remained too large to enter the pore. Heginbotham and MacKinnon used site-directed mutagenesis to remove the tyrosine hydroxy group. The tyrosine to phenylalanine (Y→F) mutation altered selectivity even though the arene was still present.[47] The recent crystal structure of the KscA channel of *Streptomyces lividans* shows that the tyrosine hydroxy group is playing an organizational role.[48]

Cumulatively, the studies described in this section are extremely important because they demonstrate cation−π interactions experimentally. Of course, the gas phase is a low-polarity environment but so are the interiors of many proteins and bilayer membranes. Unfortunately, these gas-phase techniques, by their very nature, cannot give detailed structural information.

## 3. Crystal Structures

The controversy over the function of the so-called GYG selectivity sequence and the success of synthetic channel compounds generally[49] inspired Murayama and Aoki to search for cation−π interactions between $K^+$ and the aromatic rings of calix[6]arene.[50] Close contacts are clearly observed in these structures between $K^+$ and certain aromatic carbon atoms of the phenolic residues. For example, calix[6]arene itself forms a pentahydrated dipotassium complex. One of the $K^+$ ions makes two contacts with arene carbon atoms at a distance of about 3.35 A. Other carbon atoms in the same ring, however, are approximately between 3.6 and 4.0 A away. A similar situation is observed in structures of $K^+$ complexing calix[4]arene having additional substituents.[51] Thus, the cation−π interaction in this system is not symmetrical about the arene's centroid as predicted by the numerous theoretical studies cited above.

In an early and under-appreciated paper, Atwood reported solid-state evidence for symmetrical $K^+$− and $Cs^+$−arene contacts in systems that also contained complex aluminum compounds.[52] In half a dozen structures, the contacts between the arene centroid and $K^+$ cation were found to be in the 3.3−3.6 A range, with most being between 3.3 and 3.5 A. In one case, a $K^+$ cation was bound in the center of dibenzo-18-crown-6. The complex was solvated by a benzene ring disposed directly over $K^+$ as shown in Figure 1. The interaction was apparently strong enough to pull $K^+$ towards it and 0.3 A out of the mean plane of macroring donors. A number of other small-molecule structures show clear indications of alkali metal−arene cation−π contacts. These are discussed in the next section.

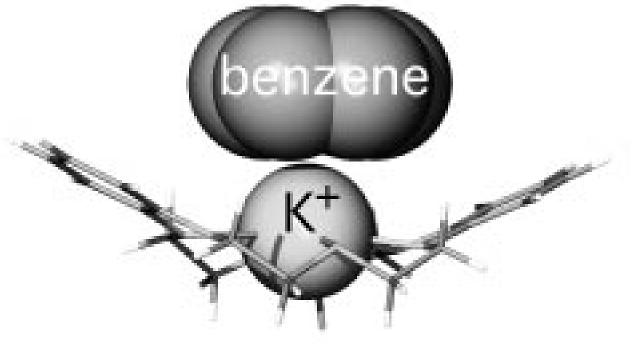


Figure 1. Fragment from the solid-state structure of a dibenzo-18-crown-6 potassium complex; a benzene molecule (dark gray) is positioned above the $K^+$ (light gray); the crown ether is shown as a tube model; coordinates taken from CSD entry BACTUU10[52b]

### 3.1 Small-Molecule Crystal Structures

The Cambridge Structural Database (CSD) of small-molecule crystal structures is a rich source of experimental information for cation−π interactions involving alkali metal cations. Some of the examples include aromatics that are, like the cyclopentadienyl ligand in ferrocene, also organic anions.

Other cases include inorganic anions that contain aromatic rings, such as tetraphenyl borate. One of the earlier examples of a cation−π interaction from the CSD is the simple salt $K^+BPh_4^-$. The solid-state structure, Figure 2, shows that the potassium cation is in close contact with the phenyl rings of the anion.[53] Although $K^+BPh_4^-$ is an elegant example, such cation−anion complexes will not be discussed further here. Cation−π interactions surely play a role in the coordination of the alkali metals in these cases but the cation−anion attraction is also an important consideration. We have also intentionally avoided discussion of cation−π complexes that are formed as part of a transition or other heavy-metal complex. We highlight a few examples of alkali metal cations that are coordinated by neutral aromatics.

One recent example of an unanticipated $Na^+$−π interaction comes from a cluster of six sodium cations coordinated by bridging triphenylsilylthiolates.[54] The hexameric aggregate contains two molecules of toluene, one of which is in contact with an $Na^+$. The coordination environment is shown in Figure 3. An additional noteworthy example was recently reported of benzene and toluene trapped in the crystal lattice of alkali metal−carborane anion salts.[55] In the latter case, the authors noted that the alkali metals are found in the expected geometry, with the contact distance approximated by the van der Waals radii.

Several other examples of trapped solvent molecules forming a cation−π complex with a $K^+$ ion have recently been reported. In addition to the work cited above from Michl,[55] three closely related silicon anions have been shown to coordinate potassium cations such that benzene or toluene is included in the crystal lattice.[56] In these cases,

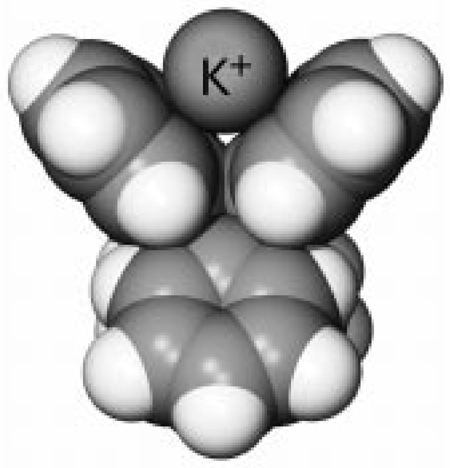


Figure 2. Solid-state structure of $KBPh_4$; a neighboring tetraphenyl borate also participates in the coordination of the $K^+$ cation (light gray) but is not shown for clarity; coordinates taken from CSD entry KTPHEB[53]

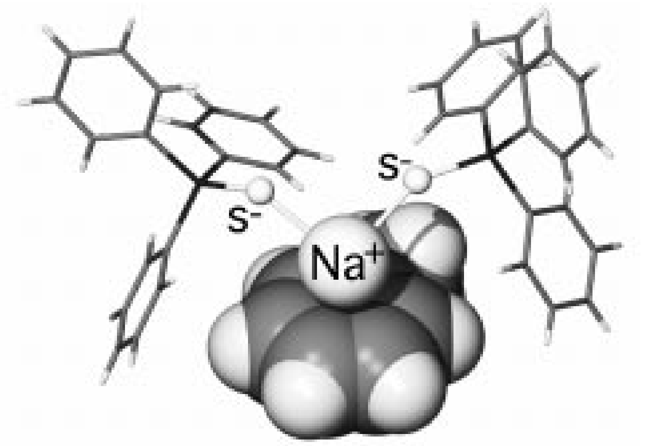


Figure 3. Fragment of the solid-state structure of $[(NaSSiPh_3)_6(toluene)_2]$; the sodium ion (large light gray sphere) is coordinated by two thiolate ions (sulfur atoms are shown as small light gray spheres) and one molecule of toluene; coordinates taken from CSD entry PEQNOO[54]

the $K^+$ is in very close contact with the arenes ($K^+$−centroid distances of 3.0−3.2 A).

### 3.2 Proteins, DNA, and RNA

In biomolecules, such alkali-metal cation interactions with π systems are barely documented. The three amino acids that can most reasonably serve as π donors in proteins are phenylalanine, tryptophan, and tyrosine. The amino acid histidine is also aromatic but its donor nitrogen is typically protonated under physiological conditions. To the best of our knowledge, there is only one example known in proteins of $Na^+$ interacting with an aromatic ring. In a recent structure of hen egg white lysozyme, an $Na^+$ is positioned over the aromatic face of a tryptophan side chain (indole).[57] Remarkably, this $Na^+$-binding site is exposed to the aqueous environment and the chemical function of the site is currently unknown.

The coordination of a $Cs^+$ cation by aromatic residues has been documented in three protein crystal structures: rhodanese,[58] glutamine synthetase,[59] and methylamine dehydrogenase.[60] The role of this binding site in rhodanese is unclear. However, in the structures of glutamine synthetase and methylamine dehydrogenase (see Figure 4) the $Cs^+$ cation was used as a heavy-atom replacement by the crystallographers to locate the putative binding site of an $NH_4^+$ cation. Ammonium is a substrate for glutamine synthetase and a product formed by methylamine dehydrogenase (see Figure 4). The heterocyclic bases of DNA and RNA are also aromatic. Recent evidence indicates that the alkaline-earth metal $Mg^{2+}$ can interact with the π face of these heterocycles in some cases.[61]

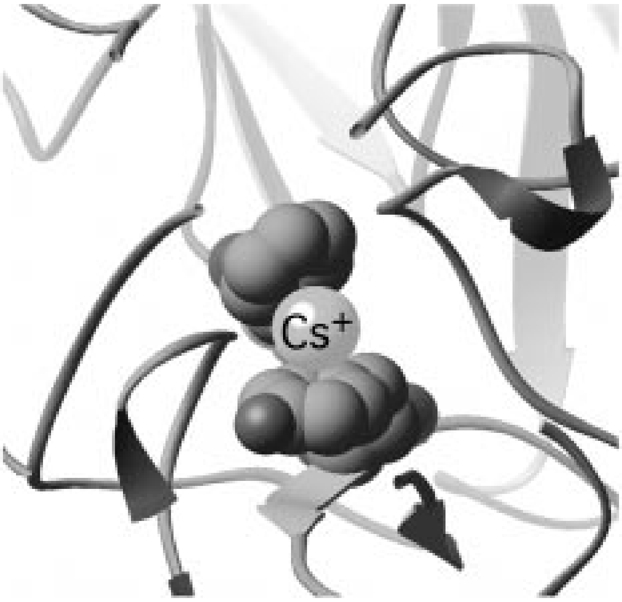


Figure 4. The active site of methylamine dehydrogenase; the $Cs^+$ ion (light gray sphere) is coordinated by the aromatic side chains of a phenylalanine and a tyrosine; coordinates kindly provided by Prof. F. S. Mathews

Two problems encountered in the biological arena are the resolution of solid-state structures and the structural models used. In some cases, the resolution of the structure is too poor to clearly identify $Na^+$, which has a diameter of about 2 A and only 10 electrons. Further, water (which also has 10 electrons) interactions, rather than non-covalent contacts with cations, are often modeled when either might be possible. As noted by Woehl and Dunn,[62] ‘‘it has proven rather difficult to characterize the three-dimensional structures of the metal sites for $Na^+$ and $K^+$ in proteins because of the similarities in the X-ray scattering factors of these ions to water and hydronium ion (ten electrons). ... With refined, reasonably high resolution structures, it has been possible to locate the metal-ion binding sites for $Na^+$ and $K^+$ in a few proteins.’’ As the number and resolution of crystal structures of biological molecules increases, we anticipate that many more such interactions will be observed.

## 4. Zeolites

As early as 1968, cation−π interactions were identified by using infrared spectroscopy between zeolites and adsorbed arenes such as benzene and toluene.[63] A study by Bezus and co-workers[64] described differential interactions of ethane and ethylene adsorbed in X-zeolites. The measurement of adsorption isotherms revealed not only the binding energies for the putative cation−π interaction but suggested a charge density correlation for the interactions.[65] Primet and co-workers studied benzene adsorbed into zeolites by using a combination of UV and IR spectroscopy.[66] Evidence was obtained for a direct interaction between the arene and cations such as $Na^+$ and $Ca^{2+}$. A key conclusion was that a strong interaction between the cation and benzene occurred but that the arene's molecular structure was preserved. This finding is in agreement with current thinking about the energies of cation−π interactions but no energetic data were reported in this study.

In very recent work,[67] quite close contacts were reported for the interaction of xylene with $Cs^+$. The ionic radius for $Cs^+$ is 1.66 Å and the half-thickness of an arene is approximately 1.7 Å. Thus, the van der Waals contact is expected to give a $Cs^+$−arene distance of approximately 3.4 Å. The six $Cs^+$−arene carbon contacts were reported to be in the range 2.75−3.11 Å making the cation−π contact very close indeed. Hashimoto and co-workers reported a fluorescence study of anthracene adsorbed into zeolites.[68] They also report calculated interactions between $Na^+$ and anthracene using the 6-31G(d) and 6-311(2d,p) basis sets for their calculations. The authors state that the ''optimal structure of a complex, $Na^+$(anthracene) has the Na atom on the $C_{2v}$ axis above the center of the anthracene molecule. The optimized distance between the $Na^+$ ion and the center of the anthracene is 0.233 nm.'' The ionic radius for $Na^+$ is near 1.0 Å making the cation−π contact less than the 2.7 Å by summing the distances. Of course, the presence of these systems within constraining cages may also play a role in these interactions.

## 5. Our Experimental Evidence

The discovery of ''crown ethers'' by Pedersen[69] and the cryptands by Lehn[70] permitted a general study of the properties of alkali-metal cations and their interactions with various donor groups. The alkali-metal cation family comprises group I in the periodic table: lithium, sodium, potassium, rubidium, cesium, and francium. These cations all possess a single positive charge but differ in size. Essentially, they are featureless spheres. The highest occupied orbital of the parent metal in each case is the spherical s orbital. They therefore exhibit none of the orientation-specific binding associated with various heavy metals and their numerous oxidation states.

Owing to the availability of the crowns, the cryptands, the cavitands, and other remarkable molecules, the study of alkali-metal cations has been extensive during the last quarter century. The potentially important interactions with the π electrons of double bonds, triple bonds, and aromatic rings have remained sparse, in large measure because of the difficulty of addressing the interaction experimentally. Our own efforts in this area were initiated nearly 20 years ago but the experimental success was very limited. Remarkably, simple extensions of those original ideas have now led to a number of useful experimental results in this area.

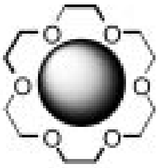
### 5.1 Lariat Ethers

Pedersen's crown ethers are two-dimensional, donor-containing macrocycles. Their inward-turned donor groups permit a spherical cation to be surrounded, solvated, and thus stabilized. Although the structural diversity of crown ethers is enormous,[71] crowns are essentially two-dimensional cation binders. Because access to the crown's ''hole'' is unhindered from above and below, the rates of cation binding and release are generally high.[72] The complexation of cations by ''host'' or ''receptor'' compounds is expressed by the equation: $\text{host} + M^+ \rightleftarrows [\text{host} \cdot M]^+$. The equilibrium constant for this process is usually designated $K_S$, and is the ratio of the binding or complexation rate $k_1$ over the release or decomplexation rate, $k_{-1}$, i.e., $K_S = k_1/k_{-1}$.

$$\text{receptor} + M^+ \underset{k_{\text{release}}}{\overset{k_{\text{complex}}}{\rightleftharpoons}} \text{complex}$$

Cryptands differ from crown ethers by the addition of a third donor group strand. The cryptand host molecules are shaped like an elongated sphere and typically complex a cation by including the cation within the three-dimensional structure. Since the cation is surrounded in three dimensions by the receptor, entry and egress of the cation is generally slower than for related crown ether/cation combinations.[73] The loss of dynamics, however, is compensated by enhanced cation selectivity. The two-dimensional crown ethers exhibit better dynamics but poorer cation selectivities under comparable conditions.

The issue of binding and release dynamics takes on an additional dimension when considered in terms of transmembrane conveyance.[74] Conduction of a cation across a membrane requires at least three distinct variables. The first is binding of the cation on the external surface of the membrane. For this step, strong binding, good selectivity, and good complexation dynamics are ideal. Within the low-polarity regime of the membrane, only the magnitude of the equilibrium constant is important. At the opposite surface of the membrane, release dynamics are critical or the cation's journey from the opposite surface of the membrane will have been in vain. In the late 1970s, we considered how one might mimic the effectiveness of the mitochondrial potassium transporter valinomycin.[75] The solid-state structure of valinomycin showed that the apparently too-large macrocycle (36-membered) folds into a ''tennis-ball seam''[76] arrangement around $K^+$.[77] This envelops the cation but the open structure of the unbound host affords good binding dynamics. We therefore developed a family of compounds in which the third strand of the cryptand was not covalently bound to the two-dimensional crown. This afforded the possibility of good dynamics and selectivity. Because we envisioned these compounds as being lasso-shaped and we imagined their complexation as a ‘‘rope-and-tie’’ sequence, we called the compounds ‘‘lariat ethers.’’[78] A substantial body of information concerning these compounds now bears out the original design concepts.[79] Examples of the three host systems are shown as **1**, **2**, and **3**, in each case binding a K$^+$ cation as it is known to be held within the receptor structure.



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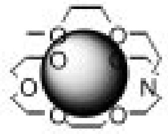

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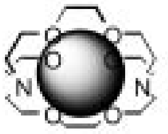

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### 5.2 Classes of Lariat Ethers

Lariat ethers are subject to the same hypervariability as are the crowns and cryptands. They may be modified by altering the ring size, the sidearm, or the donor groups. In addition, the number and position of the sidearms may be varied to afford complexation that is either cryptand-like (sidearms *syn*) or crown-like (sidearms *anti*). Solid-state structural studies have confirmed both complexation modes as shown in Figure 5.

Although we have explored attaching sidearms to carbon atoms in the macrocyclic ring, the bulk of our effort has used nitrogen as a connector or pivot atom. Because nitrogen is stereochemically invertable, the N-pivot receptors are achiral. The addition of a second arm required a means to designate its presence. Using the Latin word *bracchium* (arm), we coined the term BiBLE for ‘‘bibracchial lariat ether.’’

### 5.3 Lariat Ethers Having Olefinic Sidearms

Studies of one- and two-armed lariat ethers with a variety of cations persuaded us that bibracchial (two-armed) lariat ethers would be appropriate to study alkali metal−olefin interactions. We anticipated that the alkali-metal cation would be bound within the crown ring more or less symmetrically. Counterions could fill the apical void but the axial positions might also be filled by π donors on suitably placed sidearms. Our hope was that if sidearm participation could not be demonstrated unequivocally using X-ray structural methods, we might still be able to infer π-donor interactions from binding-constant studies in solution.

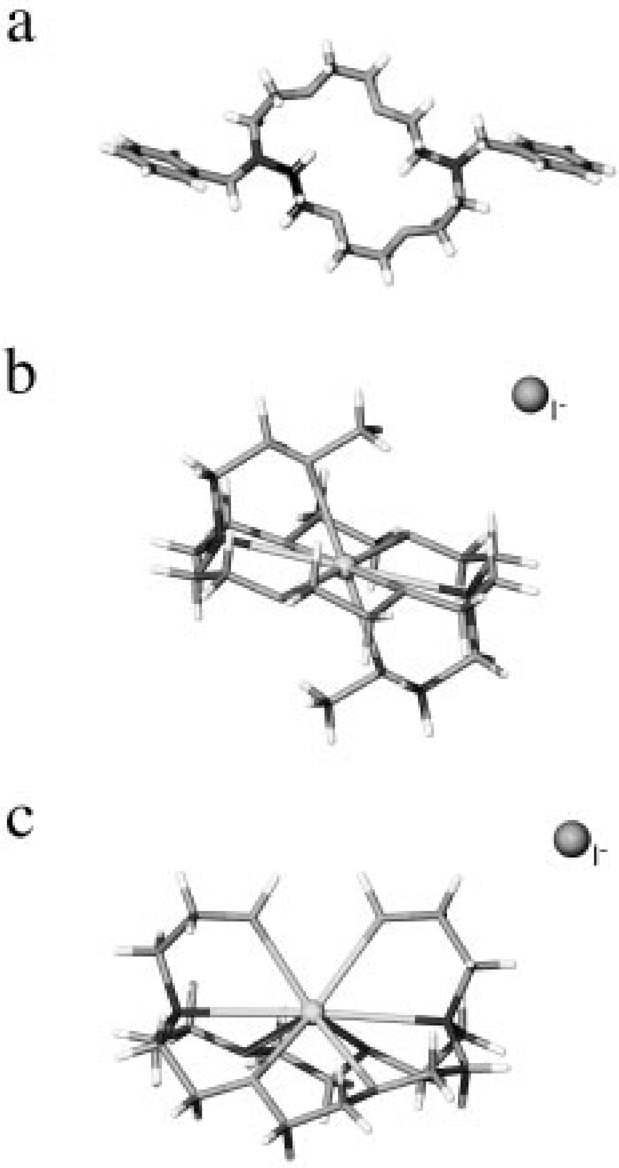


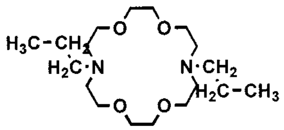
Figure 5. The crystal structures of three BiBLEs; (a) the unbound structure of **8**;[81] (b) the *anti* KI complex of *N*,*N*′-bis(2-hydroxyethyl)-1,10-diaza-18-crown-6;[83c] (c) the *syn* KI complex of *N*,*N*′-bis(2-methoxyethyl)-1,10-diaza-18-crown-6[83c]

### 5.4 Ligand Syntheses

We decided to use 4,13-diaza-18-crown-6 derivatives in the initial studies. The 18-membered ring is of a size suitable to accommodate either Na$^+$ or K$^+$. Moreover, the two, symmetrically disposed nitrogen atoms would permit attachment of identical sidearms that could complex in the fashion indicated above. The initial target structures are shown as compounds **4−7**. The sidearms are *n*-propyl (**4**),[80] allyl (**5**),[23] propargyl (**6**),[23] and cyanomethyl (**7**).[81] All four compounds have three-atom, linear chains and **4−6** increase in relative unsaturation at the distal terminus of the sidearm. The sidearms of **6** and **7** are isosters although the latter differs in the terminal atom and dipole.

### 5.5 Cation-Binding Studies

The ability of compounds **4−6** to bind Na$^+$ or K$^+$ was assessed by use of ion-selective electrode (ISE)[82] binding studies. By maintaining ring size and sidearm length within the series and varying the extent of unsaturation, we felt the presence of increased cation−π interactions would be manifested in an increase in binding constants. The first results we obtained were encouraging if not exciting. The



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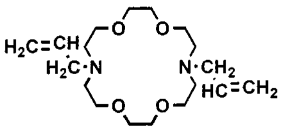

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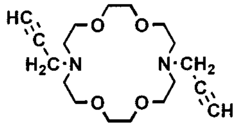

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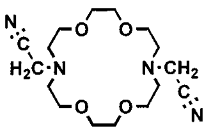

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sodium binding constants (log $K_S$), measured at 25 °C in anhydrous methanol, were 2.86 (**4**), 3.04 (**5**), and 3.61 (**6**). These values are logarithms and correspond to equilibrium-binding constants as follows: 725 (**4**), 1100 (**5**), and 4100 (**6**).

We surmised that the ca. 1.5-fold increase from **4** to **5** resulted from an interaction of the ring-bound cation with the π electrons of the double bond. We interpreted the ca. four fold increase in binding observed for **6** compared to **5** to be due to the symmetry of the triple bond. Thus, all sidearm orientations in which the triple bond could reach the cation would afford stabilization whereas the double bond of **5** was directional. An identical series of measurements of $K^+$ binding constants showed a similar trend. The experimentally determined $K^+$ binding constants (log $K_S$) were 3.77 (**4**), 4.04 (**5**), and 4.99 (**6**). The log $K_S$ values correspond to equilibrium constants of 5900, 11000, and 98000. The $K^+$ binding constants were uniformly higher than those observed for the same receptors with $Na^+$, as expected. As before, the increase in binding from **5** to **6** (ca. nine fold) was greater than the enhancement from **4** to **5** (ca. 1.9-fold). The data seemed both reasonable and internally consistent.

### 5.6 Crystal Structures of BiBLEs whose Sidearms Contain Double or Triple Bonds

An intensive effort was undertaken to obtain X-ray crystal structures for these complexes. We felt that such data would not only be conclusive, but the structures would give information about the directionality of the interaction. In collaboration with Fronczek and Gandour,[83] we obtained the solid-state structures of several bibracchial lariat ethers and their alkali-metal complexes. We felt that the best chance of observing a cation−π interaction with an alkali metal was with *N*,*N′*-bis(propargyl)-4,13-diaza-18-crown-6 (**6**). Two structures of **6** were obtained: **6**·KSCN and **6**·4 $H_2O$.[23] In the former, $K^+$ was bound in the center of the macrocycle, but the sidearms were extended from the ring and not interacting with the cation. In the latter case, water was H-bonded to the macrocycle oxygen atoms but no evidence of interaction with the sidearms, again extended, was observed.

### 5.7 Thermodynamic Measurements

The apparent conflict between the solution binding constants and the solid-state data might have been due to crystal-packing forces that prevented formation of the expected complexes. We felt we could obtain confirmation of the π interaction by demonstrating a systematic increase in the enthalpic contribution to complexation. Izatt, Christensen, and their co-workers have assembled a substantial database in this area that could be used for comparison.[6][84] We therefore undertook an assessment of the thermodynamic parameters by using the van't Hoff relationship.[85] The so-called van't Hoff isochore or van't Hoff equation is $d \ln K/dT = \Delta H/RT^2$. A plot of ln $K_S$ vs. $1/T$ (in Kelvin) gives a plot having a slope of $-\Delta H/R$ and an intercept of $\Delta S/R$. In a typical analysis, the equilibrium constant ($K_S$) is plotted (ordinate) vs. inverse temperature (abscissa). In our studies, the equilibrium complexation constants were determined at temperatures in the range of 15−40 °C.

We obtained the results shown in Table 2 for $Na^+$ and $K^+$ complexation of **4−7**. No cation−π interaction is expected for compound **4**. To the extent that such an interaction occurs, $\Delta H$ is expected to be greater for **6** (triple bond) than for **5**. The relationship of $\Delta H$ between **7** [cyanomethyl ($-CH_2C{\equiv}N$:) sidearms] and **6** [propargyl ($-CH_2C{\equiv}CH$) sidearms] was unclear. Cyanomethyl is isosteric with propargyl but the sidearms differ in overall dipole and the nucleophilicity of the distal terminus. The cyanomethyl sidearm is expected to be a better σ donor owing to the electron pair present on the nitrogen atom.

The data shown in Table 2 for compounds **4−6** were surprising. The cation binding constants had increased regularly for both $Na^+$ and $K^+$. We expected this to be confirmed by a similar increase in $\Delta H$. Such a trend was, in fact, observed for sodium complexation. The pattern was not confirmed for the $K^+$ case for which the magnitude of $\Delta H$ varies in the order **5** > **4** > **6** rather than **6** > **5** > **4**. The data to this point conflicted. Cation−π interactions seemed to be confirmed by the $Na^+$ and $K^+$ binding constants and by the increase in $\Delta H$ for the $Na^+$ series with increasing π donicity. No confirmation was found, however, in the $\Delta H$ data for the $K^+$ series and the solid-state structures failed to corroborate the interaction.

A further test was clearly required. Compound **7** was thus prepared and its binding constants determined with both $Na^+$ and $K^+$. Thermodynamic parameters were established, as before, by using the van't Hoff method. In both the $Na^+$ and $K^+$ cases, $\Delta H$ was at or near the maximum in the series. In contrast, the binding constants were at or near the bottom of each series. As before, we were unable to confirm π-sidearm cooperation in the solid state. These conflicting results were more a lesson in the need for thorough analysis of binding phenomena than any confirmation of cation−π interactions, although there were tantalizing hints in the data. There the matter lay for a number of years.

### 5.8 Cation−Arene π Interactions

During the early to mid-1990s, there was a renaissance of interest in cation−π interactions, mostly focused on the potential interactions of the sidechains of phenylalanine, tyrosine, and tryptophan. The aromatic residues in question

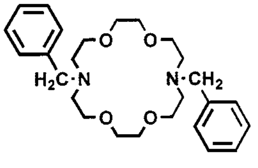
Table 2. Equilibrium constants and thermodynamics of cation-binding affinities

| No. | Sidearm | log $K_S$ [a] $Na^+$ | $K^+$ | Sodium cation $\Delta H$ | $T\Delta S$ | Potassium cation $\Delta H$ | $T\Delta S$ |
|---|---|---|---|---|---|---|---|
| − | 18-Crown-6 | 4.34 | 6.09 | −7.40±0.11 | −1.50±0.09 | −11.3±0.02 | −3.03±0.04 |
| **4** | $CH_2CH_2CH_3$ | 2.86 | 3.77 | −2.82±0.05 | 1.08±0.04 | −6.28±0.27 | −1.14±0.30 |
| **5** | $CH_2CH=CH_2$ | 3.04 | 4.04 | −3.56±0.23 | 0.59±0.20 | −7.34±0.02 | −1.84±0.01 |
| **6** | $CH_2-C\equiv CH$ | 3.61 | 4.99 | −4.97±0.04 | −0.05±0.12 | −4.97±0.04 | −0.05±0.12 |
| **7** | $CH_2-C\equiv N$: | 2.69 | 3.91 | −4.87±0.08 | −1.20±0.10 | −9.54±0.11 | −4.21±0.09 |

[a] In anhydrous $CH_3OH$ at 15−41 °C as described in reference 29. log $K_S$ values in $M^{-1}$, enthalpy values in kcal/mol; entropies in eu.

are benzene, phenol, and indole, respectively. As noted above, calculations conducted in a number of different groups predicted that π-donor strength would decrease in the order Trp > Tyr ≈ Phe. Prior to our own work, no small-molecule crystal structures were reported that demonstrated cation−π coordination of alkali metals by indole, the sidechain of tryptophan. This is in spite of theoretical calculations suggesting that indole is a more potent cation−π donor than benzene (phenylalanine) or phenol (tyrosine). With respect to ammonium−tryptophan interactions, recent statistical and energetic analysis suggests that in proteins, up to 25% percent of all tryptophans are involved in cation−π interactions.[7] A second prediction for the indolyl system was that the benzene, rather than the pyrrole, ring of indole would be in the closest contact with either $Na^+$ or $K^+$.

We had previously prepared and studied *N*,*N*′-dibenzyl-4,13-diaza-18-crown-6 (**8**)[23,86] and had seen no evidence for cation−π interactions in that BiBLE system either. We considered the calculations that predicted the strongest cation−π interaction in the Phe, Tyr, Trp series to occur with tryptophan. We constructed CPK molecular models and positioned indole apically above and below the ring-bound cation so that the benzene ring, the site predicted to have the maximal interaction, would be directly over the cation. We selected a 2-carbon sidechain so that indole could be attached to the macrocycle in the arene's 3-position as it is in the amino acid and still enjoy the comfortable fit apparent in the molecular models.



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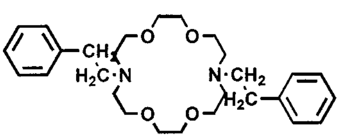

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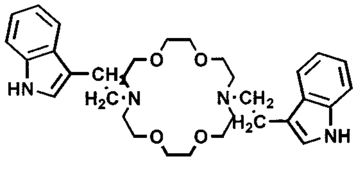

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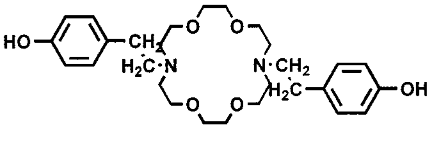

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Using a similar overall strategy, we prepared three new 4,13-diaza-18-crown-6 derivatives to which were attached the phenylethyl (**9**), hydroxyphenylethyl (**10**),[87] and indolylethyl (**11**)[88] sidearms. These compounds were prepared by using one of two basic approaches. In the first instance, 4,13-diaza-18-crown-6 was alkylated using the incipient sidearm as an electrophile. Alternately, the previously reported,[85] single-step synthesis was employed. In the latter case, a primary aliphatic amine, $R-NH_2$ in which R is the incipient sidearm, is treated with triethylene glycol diiodide in the presence of sodium carbonate and acetonitrile. A lengthier but ultimately better-yielding, two-step process was sometimes employed.[22]

### 5.9 Solid-State Structural Data

Compounds **10**[86] and **11**[87] were crystallized in the absence of any salt and in the presence of various alkali-metal salts. Figure 6 shows some of the results of these studies. In panel a, compound **10** is shown in the tube metaphor unbound (left side) and bound to $Na^+$ at the right-hand side. The figure was constructed from the experimentally determined coordinates for the crystals in each case. The structure of **10** is as expected. The macrocycle is in a typical unbound conformation in which methylene groups on opposite sides of the macrocycle turn inward. The sidearms are extended from the macrocycle's *pseudo-para*-nitrogen atoms. The ethylene sidechains are in the *antiperiplanar* conformation. No cation is present in the crystal and no sidearm interaction is observed.

When **10** crystallized in the presence of NaI or KI, the crystal structure data revealed almost identical structural arrangements. The structure of the complex shows the cation in the center of the macrocyclic ring. The latter is in the expected $D_{3d}$ conformation. The sidearms are turned inward toward the macrocycle and one indole group is positioned above and the other below the macrocycle.

The conformation of the unbound macrocycle is typical of that observed for 2-armed lariat ethers. One methylene group on each ''side'' of the ring is turned inward to help fill the molecular void. The sidearms are extended from the ring and the ethylene unit is in a *gauche* conformation. The more interesting result is shown at the right of Figure 6a. When NaI is present, the two sidearms fold so that the arenes are above and below ring-bound $Na^+$. The two arenes

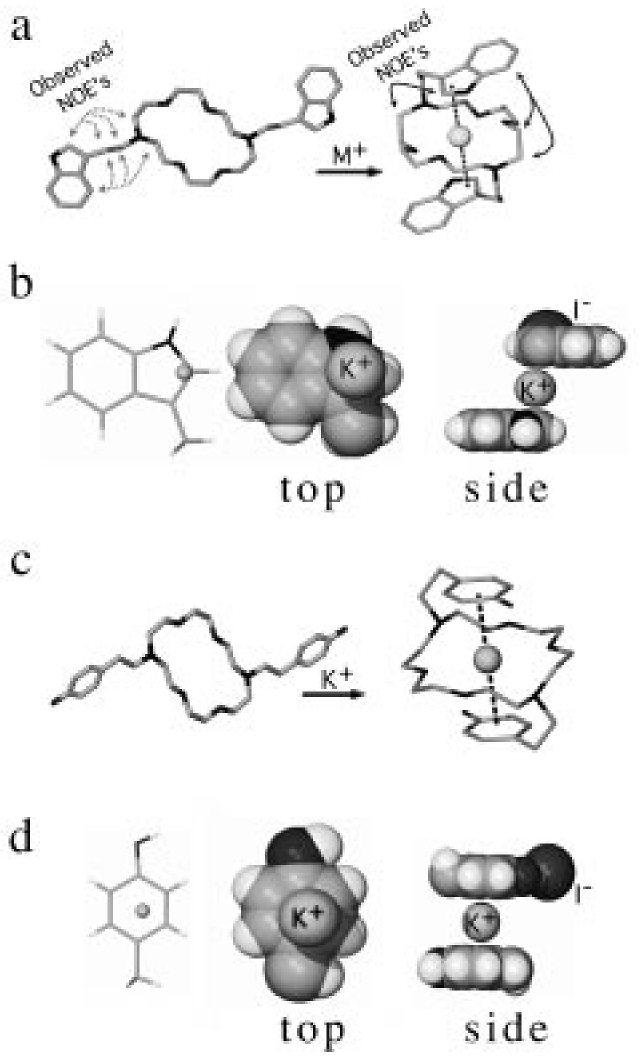

Figure 6. (a) Structure of **10** in the absence and presence of NaI (reprinted with permission of *J. Am. Chem. Soc.*); (b) left and center, top views (tube and CPK) of the cation−π binding interaction between $Na^+$ and indole, right side view of the sandwich complex; (c) structure of **11** in the absence and presence of KI; (d) left and center, top views (tube and CPK) of the cation−π binding interaction between $K^+$ and phenol, right side view of the sandwich complex

are parallel to each other and comprise a sandwich complex of the sodium cation. This confirms in the solid state that an arene (indole) can form a π complex with an alkali-metal cation. Such interactions are, of course, well known in the organometallic literature. Indeed, such compounds as ferrocene[89] and dibenzenechromium[90] are archetypes for entire families of such structures. The observation of cation−π interactions by X-ray crystallographic methods, however, is an important milestone in alkali-metal ion chemistry. We note that compound **10** was also studied in acetone solution by NMR methods in the presence and absence of NaI. Nuclear Overhauser effect interactions were identified as indicated in Figure 6 (panel a). This confirms that the sidearms participate in binding in solution as well as in the solid state.

Panel b illustrates the structural relationship between indole and the ring-bound cation. As noted above, theoretical calculations have consistently concluded that the benzene, rather than the pyrrole, ring would be the preferred donor. In fact, the cation is closest to C-2 of indole as is apparent from both the tube and CPK representations. The sandwich structure is shown at the right of panel b. The large sphere shown in the back of and adjacent to the upper indole group is the iodide ion. The crystal structure shows that iodide is hydrogen-bonded to the indole NH. This is especially interesting because iodide is charged and would be expected to compete effectively with indole as an auxiliary donor group. A nearly identical structure was observed for **10** · KI.[86]

Panel c provides the same type of information about **11** that is shown for **10** in panel a. Each part of the equation was obtained by a separate crystal-structure analysis. The figures are drawn in an analogous fashion to emphasize the similarity in structures. As for **10**, unbound **11** shows a typical "rectangular" conformation for the macrocycle. The sidearms are turned away from the macrocycle and the ethylene spacer chains are in the *antiperiplanar* arrangement. When **11** is complexed by $K^+$, a sandwich complex forms with the cation in the center of the macrocycle and the center of the sandwich. The orientation of the cation and the arene are shown in two views (top and side). Why the experimentally observed coordination position of the indole ring differs from the theoretical predictions is currently unclear but it may be due, in part, to a steric interaction between the arene and the macrocycle. Some details of the interactions observed in **10**·$K^+$ and **11**·$K^+$ are recorded in Table 3. Note that the heteroatom−donor and cation−π distances are either identical or virtually the same in these two KI complexes.

## 6. Conclusions

The long-standing problem of characterizing alkali-metal cation−π interactions is finally yielding to experimental effort. Theoretical calculations have certainly been encouraging. The results of mass-spectral work have always been clear but there was a lingering concern about whether these results accurately represented the situation outside the gas phase. The present results show conclusively that such interactions occur and that the bonding parameters are largely as expected. A challenge that remains as this article is written is to understand a discrepancy between experiment and calculation. Theoretical treatments predict that indole

Table 3. Structural information for $K^+$−arene π complexes

| Complex | Interaction | Distance [Å] |
|---|---|---|
| **10** · KI[a] | O−K average | 2.70±0.06 |
| | N−K average | 3.06 |
| | K→centroid | 3.45 |
| **11** · KI[b] | O−K average | 2.70±0.06 |
| | N−K average | 3.04 |
| | K→centroid | 3.44 |

[a] Data from ref.[86] − [b] Data from ref.[87]

should bind to an alkali metal with the benzo centroid but all of the crystal structures obtained in our laboratory show that the pyrrolo subunit is the donor group. We and others are undertaking additional experiments and calculations in an attempt to better document and understand the phenomenon of alkali-metal cation−$\pi$ interactions.

## Acknowledgments

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