



Solid-State Evidence for Alkali Metal to Arene π -Complexation

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Abstract

We report a variety of alkali metal cation- π interactions, documented by X-ray crystallography. These include interactions with the neutral arenes benzene, phenol, and indole. We also include structural results for lithium, sodium, potassium, rubidium, and cesium cation- π complexes in which the arene has enhanced electron richness owing to an adjacent or integral charge.

Introduction

Among the feeble forces that sustain supramolecular chemistry, hydrogen bond formation, van der Waals interactions, solvophobic effects and electrostatic interactions are the most prominent. The recognition of cation- π interactions is relatively recent – certainly within the past quarter century.

Two important contributions legitimized the cation- π interaction of arenes and alkali metal cations. The first was the pioneering work of Kebarle and coworkers [1], who showed that K^+ is complexed by benzene in the gas phase. These mass spectrometric experiments showed that the strength of the interaction (enthalpy) between K^+ and benzene was similar in magnitude to the interaction $K^+\cdot(OH_2)$. Of course, 6–8 molecules of water rather than just one typically hydrate K^+ . Similarly, the complexation of Na^+ by benzene shows a significant stabilization enthalpy [2]. As with K^+ , the stabilization of Na^+ by C_6H_6 , H_2O , or CH_3OH were all similar, at least as assessed by mass spectrometry.

The importance of a single water molecule would be greatest in the gas phase or in a very low polarity environment. The latter is often encountered in biological systems within the insulator regime of the ubiquitous phospholipid. Thus, the importance of cation- π interactions may be greatest in biological systems. Mass spectrometric studies conducted by Meot-Ner and Deakyne suggested that ammonium ions could also exhibit cation- π interactions [3]. Burley and Petsko surveyed the protein data bank and found that a significant number of lysine sidechains were near arenes [4]. At physiologic pH, the lysine ϵ -amine is protonated to form an alkyllammonium ion. The proximity of these

chains and the sidechains of such amino acids as phenylalanine (Phe), tyrosine (Tyr), or tryptophan (Trp), suggests that the ammonium- π interaction is important.

What was lacking until very recently, was clear solid state structural evidence for alkali metal, cation- π interactions. Solid-state data would provide the structural biologist and the chemist with distance and angle measurements that would better help to understand the phenomenon. The quest for such information intensified after the structure of acetylcholine esterase was determined. The solid state suggests that the acetylcholine esterase's active site recognizes the quaternary ammonium residue of acetylcholine through a π -electron rich pocket [5]. Another factor that stimulated interest in cation- π interactions was the postulate that K^+ -channel selectivity might be influenced thereby. This postulate was discounted by site directed mutagenesis in a natural K^+ -selective channel [6]. The role of the aromatic moieties became apparent when the solid state structure of the KcsA channel of *Streptomyces lividans* was reported [7].

In this article, we survey some of the solid-state structure data that have influenced thinking about the alkali metal cation- π interaction. We also include definitive structural evidence that confirms this interaction in the solid state.

Results and discussion

Alkali metal cations

The goal of our efforts in this area [8] has long been to demonstrate and understand the cation- π interaction between unsaturated organic residues and alkali metal cations such as sodium and potassium. Clearly, contacts between Na^+ or K^+ and double and triple bonds are of great

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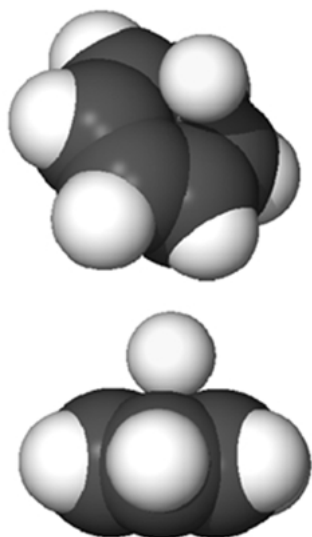


Figure 1. Two space-filling views of the cation- π interaction between benzene and sodium.

chemical interest. Of greater biological relevance, however, is the interaction of these ubiquitous ions with benzene, phenol, and indole, the sidearms of phenylalanine, tyrosine, and tryptophan. These three residues comprise >8% of amino acids in all known protein sequences.

Although our interest is in the two most common alkali metal cations, Na^+ and K^+ , the family of alkali metal ions actually comprises 5 common members: Li^+ , Na^+ , K^+ , Rb^+ , and Cs^+ . Their ionic radii increase from lithium to cesium as follows: Li (~ 0.7 Å), Na (0.97 Å), K (1.33 Å), Rb (1.47 Å), and Cs (1.66 Å). All are spheres lacking structural features or directionality because they use the s orbital for bonding.

Our strategy in the present work was to examine the Cambridge Crystallographic Database (CSD) to determine what structures showed evidence for cation- π interactions. The distance parameter for the first search was set to 3.5 Å for the separation of the cation and the centroid of an aromatic ring. Using this restriction, more than 300 hits were obtained. It is clear that many of the structures in this group cannot be classified as examples of cation- π interaction as illustrated in Figure 1 because the interactions between the alkali metal and the arene are not symmetrical. In other words, the cation is closer to one or a few of the atoms in the aromatic ring and the line passing through the cation and the centroid of the ring forms an acute angle with the plane of the ring.

Arene complexes of lithium

The lithium cation is the smallest alkali metal ion and it is the most acidic. It is expected to behave, in many ways, as a proton does. Although it is not the ion of greatest interest in the present context, it is worth noting that it clearly forms cation- π complexes of exactly the type schematized in Figure 1. Among the many examples of solid-state structures containing lithium cation, three examples clearly show its

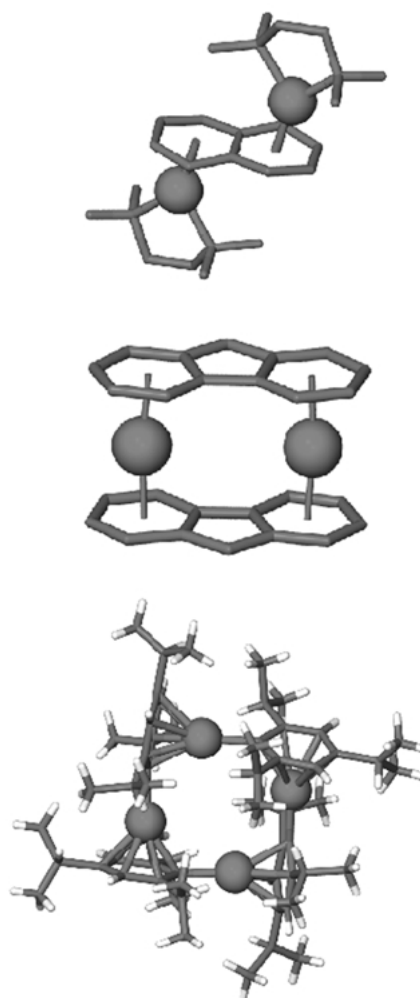


Figure 2. Structures of lithium complexes, top NAPLIM, middle: GITNEC, and bottom: LEFSEU.

π -binding modes. In all cases, the structures are of neutral lithium salts.

Figure 2 (top) shows one of the earliest cation- π complex structures. Stucky and coworkers reported the structure of dark purple dilithium naphthalenide (CSD code: NAPLIM) [9]. The anion was generated by treatment of 1,4-dihydronaphthalene with butyllithium. The lithium ions are present on opposite sides of the naphthalenide and stabilized by interaction with tetramethylethylenediamine. The lithium ions are ~ 2 Å from the benzene ring centroids and make an angle with it of $\sim 85^\circ$. An “ideal” contact would be at an angle of 90° . The van der Waals thickness of a benzene ring is ~ 3.5 Å and the ionic radius for Li^+ is ~ 0.7 Å. The sum ($1.75 + 0.7$) is 2.45 Å, significantly greater than the observed distance. Of course, the benzene ring is charged and the strength of the cation- π contact is expected to be correspondingly stronger.

The middle panel of Figure 2 shows the solid state structure of fluorenyllithium (CSD: GITNEC). The compound was prepared by addition of butyllithium to a toluene solution of fluorene. The red-orange lithium complex was obtained by crystallization from either benzene or toluene. The structure is a sandwich in which a Li^+ ion is in contact

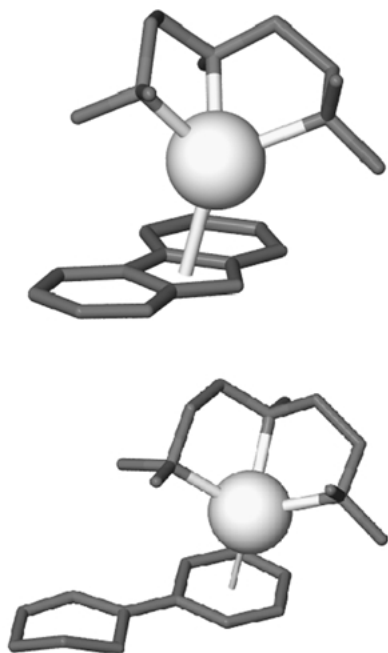


Figure 3. Structures of sodium complexes, top: VOKPUG, bottom: VIYDUC.

with each benzene ring. As in the naphthalenide structure, the distance between Li^+ and the fluorenyl anion (1.951 Å and 1.957 Å) is about 2.0 Å. The line from the middle of each centroid through Li^+ is 174.65°, or nearly straight. The angle of the centroid with the plane of the benzene ring is 88.9°, or nearly the theoretical value. Unlike the naphthalenide case, no other residue interacts with the cation, suggesting that this intimate contact is sufficient for stabilization.

A tetrameric structure of lithium 1,3,5-tris(isopropyl)benzenide (CSD: LEFSEU) is shown in the bottom panel of Figure 2. It was prepared by treatment of 1-bromo-2,4,6-tris(isopropyl)benzene with butyllithium in hexane. The tetrameric product was isolated as colorless crystals [10]. In the solid state, each lithium ion shares a σ -bond to the benzene ring and is π -complexed by an adjacent arene. This leads to a square, tetrameric arrangement. The imaginary line connecting the centroid of one ring through Li^+ to a second benzene ring is nearly straight ($\sim 172^\circ$). The $\text{sp}^2\text{-Li}$ bond is ~ 2.1 Å as expected but the Li-centroid distance is a short 1.86 Å and the axis of the interaction is essentially perpendicular to the benzene ring plane (90.72°).

Arene complexes of sodium cation

The solid-state structures of two sodium-arene complexes are shown in Figure 3. The top panel shows a sodium fluorenyl complex in which sodium is π -complexed to the 5-membered ring (CSD: VOKPUG). The bottom panel shows a complex between sodium and the anion of cyclohexenylbenzene (CSD: VIDYUC).

The sodium fluorenyl complex was isolated as orange crystals from the reaction of *n*-butylsodium with fluorene in the presence of pentamethyldiethylenetriamine [11]. In

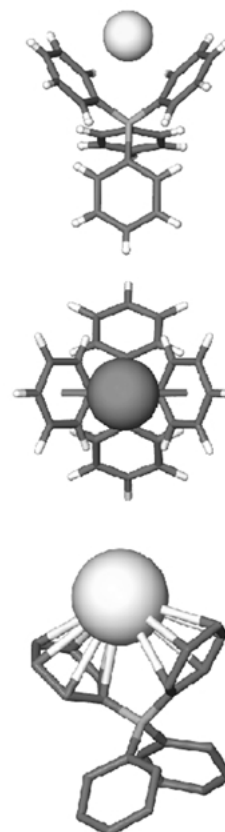


Figure 4. Structures of Na^+ (ZZUPI01, top), K^+ (KTPHEB, center) and Rb^+ (RBPBOR, bottom) salts of $\text{B}(\text{C}_6\text{H}_5)_4^-$.

this case, as well as in the example shown in the lower panel of Figure 3, Na^+ is further stabilized by ligation with $(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ (PMDTA). In both complexes, the $\text{Na}^+\text{-N}$ distances with diethylenetriamine PMDTA are all about 2.45 Å and the N-Na-N angle is $75\text{--}76^\circ$.

The ionic radius of Na^+ is near 1 Å. Any contact between an arene and Na^+ that is closer than about 2.7 Å is within the van der Waals contact distance. In the sodium fluorenyl complex, the distance from Na^+ to the aromatic centroid (central ring of the fluorenyl anion) is 2.56 Å. As the figure is drawn, the axis from Na^+ to the arene appears acute but the average of the five contact angles is near 90° .

1-Phenylcyclohexenyl sodium, shown in the lower panel of Figure 3, was prepared by metalation of 1-phenylcyclohexene with *n*-butylsodium in hexane and benzene in the presence of PMDTA. The complex is violet in color [12]. The structure is similar in many respects to that of the sodium fluorenyl structure described above. Sodium shows an even closer aromatic contact, however, at a distance of only 2.46 Å. The authors note that the six $\text{Na}^+\text{-C}$ distances range from 2.70 Å to 2.96 Å. Thus, the centroid axis is not perpendicular to the arene but it is not far from it. One point to note is that the cyclohexenyl ring is slightly ($\sim 8^\circ$) out of planarity with the benzene ring.

A comparison of Na^+ , K^+ , and Rb^+ salts of tetraphenylborate

As noted above, Na^+ , K^+ , and Rb^+ are featureless spheres that exhibit little directionality in their binding modes. A salt such as KBPh_4 is overall neutral but the negative charge of the anion is distributed over the four aromatic rings. This charge should make each of the benzene rings a stronger donor for an alkali metal cation than would be benzene itself. The examples shown in Figures 2 and 3 all involve charged arenes that should show a greater affinity for a cation.

The solid-state structures of NaBPh_4 (CSD: ZZZUPI01), KBPh_4 (KTPHEB), and RbBPh_4 (RBPBOR) are shown in the three panels of Figure 4. The latter structure is one of the earliest, if not the earliest, alkali metal π -arene complexes, dating from 1962 [13]. The tetraphenylborate anion is tetrahedral and Rb^+ is symmetrically placed between two of the facing rings at a distance of 3.17 Å. The centroid-Rb-centroid angle is 91.5°. The Rb^+ ion is in further contact with two rings from an adjacent molecule creating an extended chain in which all cations contact four arenes.

The middle panel of Figure 4 shows the crystal structure of KBPh_4 , reported by Hoffmann and Weiss in 1974 [14]. The essential features of the complex are similar to the Rb^+ complex although the authors did not cite the RbBPh_4 structure in their report. Like the Na^+ and Rb^+ complexes, it is a neutral salt in which the cation occupies a cleft within the anion. The K^+ position may be due to electrostatic or steric interactions or both. Although the contact between K^+ and either benzene ring is at a distance of 2.986 Å, the centroid to K^+ angles are 84.79° on one side and 95.01° on the other.

The structure of NaBPh_4 , shown in the top panel of Figure 4, is an unpublished result obtained from the Cambridge Crystallographic Database (ZZZPI01). The general features are similar to those of the related salts shown in the same figure. Because the anion is rigid, the smaller Na^+ ion is not closer to each aromatic than is K^+ , but stands between them at a distance of 3.03 Å. The centroid-Na-centroid angle is $\sim 99^\circ$. Whether or not this suggests a space-occupying model for understanding these complexes is open to speculation.

Arene complexes of potassium cation

The three complexes described above, like their predecessors, all involve “anionic” arenes. In cases such as sodium fluorene, it is obvious. The presence of the charge in the BPh_4^- anion may be more subtle but it is clearly present. The structure shown in Figure 5 (CSD: BACTUU10) is one of the earliest, if not the earliest, neutral cation- π complex.

A related case may be found in the structure of potassium *t*-butylphenylphosphide (CSD: PEBROD). The compound dimerizes to form a parallelogram of P and K atoms. Both phosphorus atoms are attached to *t*-butyl and phenyl groups. Each potassium may formally be considered to be attached to three residues. One of the potassium cations is solvated by *N*-methylimidazole. The “divalent” potassium cation is near the adjacent benzene ring which constitutes the third ligand. The benzene ring makes two close C–K contacts of

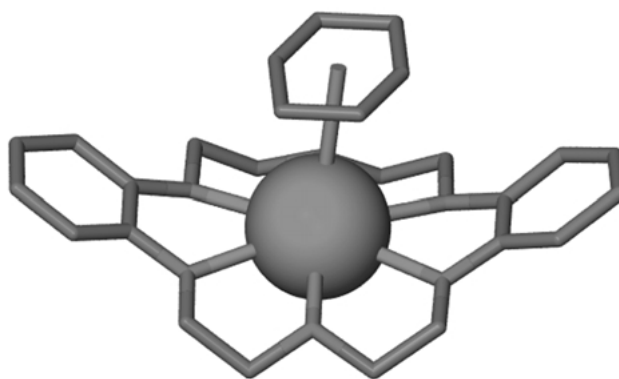


Figure 5. Structure of the potassium dibenzo-18-crown complex (BACTUU10) in which neutral benzene solvates the apical position of the hexagonal pyramid.

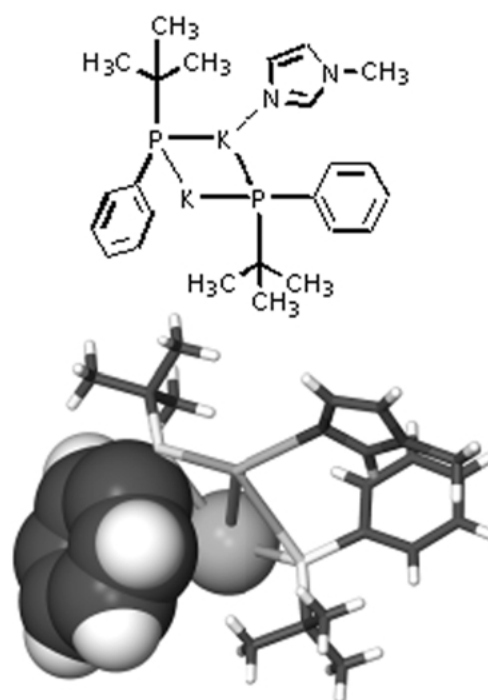


Figure 6. Structure of a π -bound K^+ complex of a phosphide anion (CSD: PEBROD).

3.020 Å and 3.151 Å with K^+ . A third carbon is more distant but is also in contact with K^+ (3.466 Å). The remaining three benzene ring carbon atoms are 3.679 Å, 3.950 Å, and 4.066 Å making a stabilization role for them dubious. In any event, K^+ in the complex shown in Figure 6 is certainly not stabilized by a centroid interaction as illustrated in Figure 1.

Other structures are intrinsically interesting but are not fully relevant to our purposes: for instance, in some cases the anionic nature of the molecule containing the aromatic ring augments its electron-rich character thus compromising the study of the pure cation- π interaction. Other forces are clearly playing a relevant role. It is unclear why the cation assumes that specific position in the crystal.

A particularly intriguing example is the interaction of K^+ with the arenes of a calix[4]arene structure (CSD: YEYSIE) in which all four arenes are substituted by *t*-butyl and *N*, *N*-

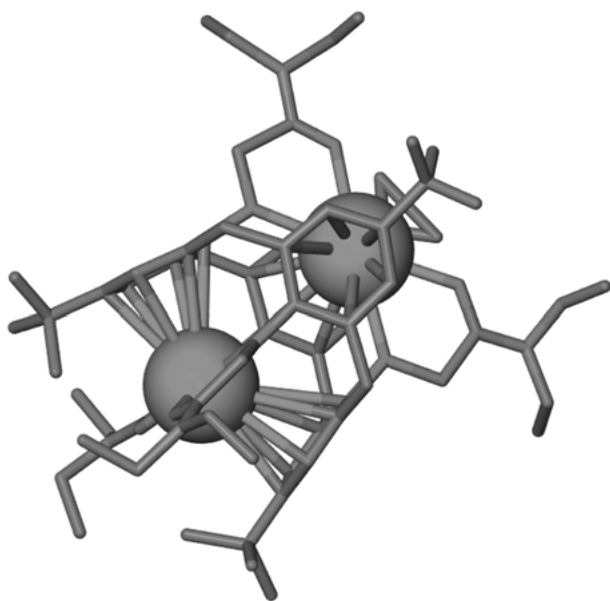


Figure 7. A calix[4]arene that encompasses two K^+ cations within it (CSD: YEYSIE).

diethylamido groups. The KI_3 complex (anion not shown) is pictured in Figure 7. The complex is in the 1,3-alternate conformation. The bound K^+ is coordinated by six residues. These include two of the four arenes in each case. The cation- π interaction is augmented in each case by two phenolic ether oxygens and two amido carbonyl groups. The four $K^+ \cdots$ centroid distances are 3.010 Å and 3.063, 3.070, and 3.110 Å.

This is an interesting structure and there is no doubt that K^+ π -contacts occur. Both the K^+ -centroid distances and the exclusion of I_3^- from the solvation sphere support this conclusion. It is hard to see what else the two phenolic benzene rings would do, given the structural constraints. This may be a digression into the philosophical realm but the most convincing examples of cation- π interactions must surely be those that are observed in conformationally flexible systems and where charges in the donor do not direct the ions.

Arene complexes of cesium cation

An intriguing example involving Cs^+ rather than either Na^+ or K^+ is the structure of cesium 2,6-diisopropylphenoxide (CSD: SUDXAQ). In the structure shown in the top panel of Figure 8, it appears that the Cs^+ ion is complexed only by the π -system and that the phenoxide anion is not involved. Of course, the fact that the phenol is ionized increases the electron density in the π -system and enhances the likelihood that π -complexation will occur.

The actual complexation pattern can only be appreciated by looking beyond the single structural unit. In the lower panel of Figure 8, two molecules are illustrated. In this case, the hydrogen atoms have been eliminated and the framework is shown in the ball and stick representation. The two Cs^+ ions and one of the oxygen atoms are shown in the space-filling metaphor. It is clear in this illustration that the oxygen anion of the top phenoxide is a critical donor for the Cs^+ ion

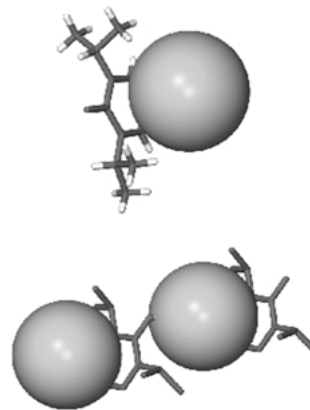


Figure 8. A cesium phenoxide salt in which both σ - and π -interactions with cation are in evidence (CSD: SUDXAQ).

of the bottom complex. Indeed, this polymeric interaction extends infinitely throughout the crystal.

A designed receptor to examine cation- π interactions

As noted above, more than 300 structures are known in which there is some evidence for a cation- π contact. Our interest was to see if we could obtain clear evidence for arene-cation interactions that could not reasonably be attributed to (1) the presence of a charge or charges in the system, (2) accidental overlap of the cation and π -system, or (3) interstitial packing of an arene.

Our long experience with lariat ether compounds suggested that they might be applicable in this context. The macrocycle could readily complex either Na^+ or K^+ . The traditional polyether sidearms were known to provide axial solvation to the ring-bound cation. The theory was then that replacement of the ether donors by appropriately situated arenes could lead to a receptor molecule suitable for this purpose. It would be essential for the sidearms to be long enough to place the centroid in the axial positions of a hexagonal bipyramid. The sidearms would also require attachment at nitrogen atoms to maximize their flexibility.

Because of our interest in the biological context, our thinking was largely restricted to the cations Na^+ and K^+ . Likewise, the three arenes of greatest interest were benzene, phenol, and indole. As noted in the Introduction, these are the sidechains of phenylalanine, tyrosine, and tryptophan. An occurrence of 8% for these amino acids means that in a protein having 250 residues, more than 20 cation- π interactions are possible. Even in cases in which the interaction is non-optimal, some stabilizing contact occurs or a space-filling requirement is met and, in either case, its importance has long been neglected.

We thus prepared three receptors having the general structure $ArCH_2CH_2\langle N18N\rangle CH_2CH_2Ar$ in which the arene is benzene (**1**, terminus of the phenylalanine side-chain), phenol (**2**, tyrosine), and indole (**3**, tryptophan). These receptors have the ability to bind a cation in the center of the macrocycle. The sidearms, which are uncharged, may or may not then participate in complexation. If complexes

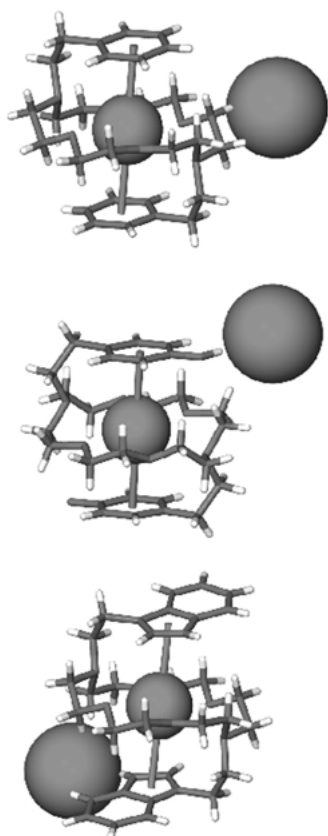
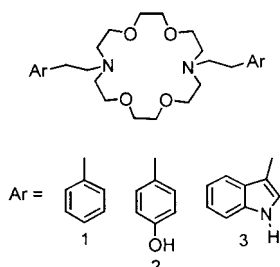


Figure 9. A comparison of three diaza-18-crown-6 receptors having arenes at the termini of 2-carbon chains: (top) benzene, (middle) phenol, and (bottom) indole.

form, the arenes will occupy the otherwise empty apical positions.

All three of these compounds were found to form stable complexes with Na^+ and K^+ . The three structures in which K^+ is the bound cation are shown in Figure 9 in the tube format except for K^+ and I^- which are represented in the CPK metaphor. In all three structures, the cation is bound within the macrocyclic ring and the sidechain arenes complete the solvation sphere. In all cases, the charged anion is not in contact with the cation even though the stabilization provided by such an interaction should be substantial.



The structure of phenol-sidearmed **2** is typical [15]. The macrocycle is in the D_{3d} arrangement typical of potassium-crown complexes. The two arenes form a sandwich above and below the equatorial belt of the macrocycle. The excluded iodide anion is H-bonded to the phenolic hydroxyl group. An almost identical arrangement is apparent in the benzene-sidearmed complex of **1** [16]. Remarkably, the

iodide counterion, which is also excluded from the solvation sphere, is not H-bonded but occupies a position similar to that observed in the phenol complex. In both cases, the arene is centered above and below the ring-bound cation.

A different situation was observed in the tryptophan-sidearmed K^+ complex of **3** [17]. Theory predicts that the benzo, rather than the pyrrolo, subcyclic unit is the better coordinating site for a cation. We clearly observe coordination of the cation nearest to the indole C-2 carbon. This is the case in the solid state and was confirmed by NMR studies conducted in acetone solution [18]. We believe that this difference between experiment and theory is a steric issue. The smaller pyrrolo unit may be a poorer donor than benzo in the π -sense, but it can get closer to the cation. The net stabilization is, of course, a combination of donicity and distance.

In summary, cation- π interactions involving neutral donors are an important force in supramolecular chemistry. They occur with arenes that comprise the sidechains of nearly 10% of natural amino acids and probably contribute in a major way to the stability of certain protein structures. When structural biologists begin to look specifically for such interactions, many examples of these contacts will no doubt be documented.

Acknowledgements

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References

1. J. Sunner, K. Nishizawa, and P. Kebarle: *J. Phys. Chem.* **85**, 1814 (1981).
2. B. C. Guo, J. W. Purnell, and A. W. Castleman Jr.: *Chem. Phys. Letters* **168**, 155 (1990).
3. M. Meot-Ner and C. A. Deakynne: *J. Am. Chem. Soc.* **107**, 474 (1985).
4. S. K. Burley and G. A. Petsko: *FEBS* **203**, 139 (1986).
5. J. L. Sussman, M. Harel, F. Frolow, C. Oefner, A. Goldman, L. Toker, and I. Silman: *Science* **253**, 872 (1991).
6. L. Heginbotham, Z. Lu, T. Abramson, and R. MacKinnon: *Biophys. J.* **66**, 1061 (1994).
7. R. MacKinnon, S. L. Cohen, A. Kuo, A. Lee, and B. T. Chait: *Science* **280**, 106 (1998).
8. K. A. Arnold, A. M. Viscariello, M. Kim, R. D. Gandour, F. R. Fronczek, and G. W. Gokel: *Tetrahedron Lett.* **3025** (1988).
9. J. J. Brooks, W. Rhine, and G. D. Stucky: *J. Am. Chem. Soc.* **94**, 7346 (1972).
10. K. Ruhlandt-Senge, J. J. Ellison, R. J. Wehmschulte, F. Pauer, and P. Power: *J. Am. Chem. Soc.* **115**, 11353 (1993).
11. S. Corbelin, J. Kopf, and E. Weiss: *Chem. Ber.* 2417 (1991).
12. S. Corbelin, J. Kopf, P. N. Lorenzen, and E. Weiss: *Angew. Chem. Int. Ed. Engl.* **30**, 825 (1991).
13. Y. Ozol, S. Vimba, and A. Levins: *Krystallografiya* **7**, 362 (1962).
14. K. Hoffmann and E. Weiss: *J. Organomet. Chem.* **67**, 221 (1974).
15. S. L. De Wall, L. J. Barbour, and G. W. Gokel: *J. Am. Chem. Soc.* **117**, 8405 (1995).
16. S. L. De Wall, E. S. Meadows, L. J. Barbour, and G. W. Gokel: *Proc. Natl. Acad. Sci. USA* **97**, 6271 (2000).
17. S. L. De Wall, E. S. Meadows, L. J. Barbour, and G. W. Gokel: *J. Am. Chem. Soc.* **121**, 5613 (1999).
18. E. S. Meadows, S. L. De Wall, L. J. Barbour, and G. W. Gokel: *J. Am. Chem. Soc.* **123**, 3092 (2001).