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Lariat Ether Receptor Systems Show Experimental Evidence for Alkali Metal Cation−π Interactions

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ABSTRACT

Cation−π interactions occur between cations and electron-rich species such as double bonds, triple bonds, and arenes. The π-electron system may be neutral or anionic, but the latter are less relevant to biology, at least so far as is currently known. Among the 20 essential amino acids, there are four aromatic residues. These are benzene, phenol, indole, and imidazole, on the side chains of phenylalanine, tyrosine, tryptophan, and histidine, respectively. Of these, imidazole is expected to be a σ-donor, and benzene, phenol, and indole are antipicated to serve as π-donors. Sodium and potassium are the most abundant cations in living systems. This Account describes an experimental system that has been developed to probe, especially by X-ray crystallography, the interactions that occur between Na^+ or K^+ and the neutral arenes of particular biological significance.

Introduction

Molecular recognition studies of the alkali metal cations lithium, sodium, potassium, rubidium, and cesium present an interesting challenge. Each of these cations is a featureless sphere, differentiated only by size. The outer orbital of group 1 cations is of the σ-type, so the cation's bonding exhibits none of the directionality present in transition elements. Each alkali metal cation possesses a single positive charge, so there is at least a difference in charge density—the smaller cations are more Lewis acidic than the larger ones. Indeed, the lithium cation is quite acidic, and numerous arene−lithium interactions have been documented. Here we focus primarily on sodium and potassium, as these are the most biologically abundant alkali metal cations.

The question of ion selectivity is critical to the study of ion channel transport. We have been involved for a decade in the development of membrane-spanning synthetic molecules that transport cations[1−5] through phospholipid bilayers. We have called this family of ion transporters "hydraphiles", and much of the work has recently been summarized.[6] These and related studies have interested us in weak, stabilizing forces of all types but particularly those that involve alkali metal cations.

Stabilizing Chemical Interactions

Several types of chemical interactions are widely acknowledged to have a significant influence on chemical structure. Clearly, the most important of these is the covalent bond, which constitutes the molecular framework of most compounds. Although covalent links define primary structure in all chemical systems, weaker or feeble forces play a profound "secondary" role. Hydrogen bonds, salt bridges, and van der Waals contacts are all weak interactions, but they have a profound cumulative effect on three-dimensional chemical structures.

The focus of this Account is none of these well-established interactions but rather the alkali metal cation−π interaction.[7] Alkali metal stabilization by π-systems has been studied in the gas phase and in a number of crystal structures. For the most part, solid-state structural evidence has involved charged (anionic) π-systems, and the bulk of these involve organometallic complexes or networks. A well-defined experimental vehicle has been needed so that cation−π interactions between alkali metal cations and biologically important neutral arenes could be systematically assessed.

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George Gokel was raised in Florida. He earned the B.S. at Tulane University and the Ph.D. in chemistry from the University of Southern California. After a two-year postdoctoral stay in the laboratory of Donald Cram at UCLA and a brief stint at DuPont's Central Research Department, he began an academic career. He has held faculty positions at The Pennsylvania State University, the University of Maryland, and the University of Miami. He is currently Director of the Bioorganic Chemistry Program and Professor in the Department of Molecular Biology and Pharmacology of the Washington University School of Medicine in St. Louis.

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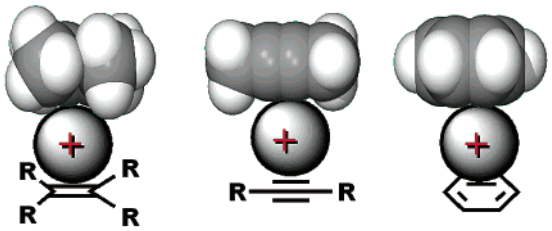


FIGURE 1. Space-filling molecular models of tetramethylethylene, 2-butyne, and benzene coordinating to an alkali metal cation.

Table 1. Gas-Phase Interaction Energies for Na^+ and K^+

interaction	$-\Delta H$ (kcal·mol^{-1})	method	ref
$Na^+ + C_6H_6$	28.0 ± 0.1	MS	9
$Na^+ + H_2O$	24.0	MS	9
$Na^+ + HOCH_3$	26.6	MS	9
$K^+ + C_6H_6$	18.3	MS/computation	8
$K^+ + H_2O$	17.9	MS/computation	8
$Na^+ + C_6H_6$	21.5	MS/computation	11
$Na^+ + C_6H_6$	21.8	MS/computation	12
$Na^+ + C_6H_6$	24.7−28.1	computation	13

Unsaturated Donor Groups

Three types of cation−π interactions are shown in Figure 1. Above each cation is shown a CPK rendering of the chemical formula drawn below it. The potential donors are double and triple bonds (left and center) and, at the right, a benzene ring.

The association of either Na^+ or K^+ with benzene is essentially an acid−base reaction. The cation−benzene interaction should be readily detectable by mass spectrometry; competing interactions are minimal in the gas phase at low pressure. Indeed, Kebarle and co-workers[8] conducted pioneering mass spectrometric experiments and demonstrated that the reaction $K^+ + C_6H_6 \rightarrow (C_6H_6{\cdot}K)^+$ had an enthalpy $-\Delta H = 18.3$ kcal·mol^{-1}. Analogous experiments revealed that the enthalpy of the corresponding reaction, $K^+ + H_2O \rightarrow (H_2O{\cdot}K)^+$, was essentially the same, i.e., 17.9 kcal·mol^{-1}. Subsequent calculations and experimental studies by Castleman and co-workers showed a similar relationship for the reactions of Na^+ with C_6H_6, with H_2O, or with CH_3OH.[9] The data are summarized in Table 1. Recent studies, some of which are summarized in Table 1, suggest that these values are too high.[10]

Calculations by Hay and co-workers using different programs and basis sets gave Na^+−C_6H_6 interaction energies in the 25−28 kcal·mol^{-1} range.[13] Interactions of Na^+ and K^+ have been assessed with amino acids as well.[14,15] In the bulk aqueous phase, for example, a benzene ring would not compete effectively with 6−8 water molecules.[16] Within the low-polarity insulator regime of a phospholipid bilayer or the interior of a globular protein, however, interactions of M^+ with the side chains of phenylalanine (benzene), tyrosine (phenol), or tryptophan (indole) could be substantial indeed.

In 1985, Meot-Ner and Deakyne demonstrated (gas-phase, mass spectrometric studies) that the ammonium cation could interact favorably with π-systems such as substituted benzenes.[17] At about the same time, Burley and Petsko surveyed the Protein Data Bank (PDB) for ammonium cation−π interactions.[18] Their conclusion was that protonated lysine or cationic arginine was stabilized by proximity to the electron-rich side chains of phenylalanine, tryptophan, or tyrosine.

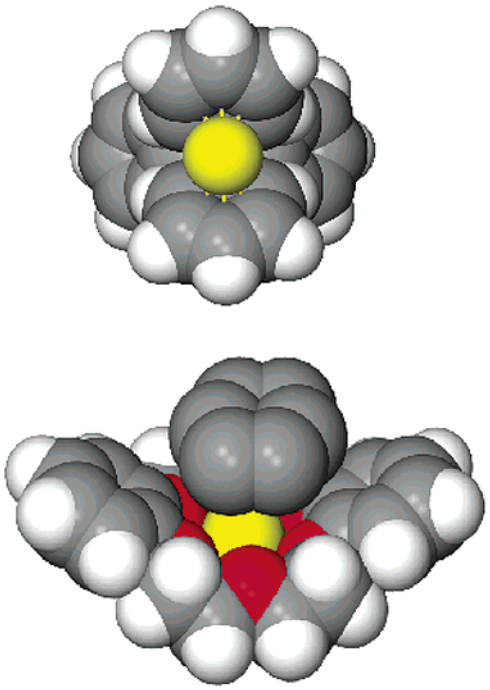


FIGURE 2. Solid-state structures of $KB(C_6H_5)_4$ (top) and a benzene-coordinated dibenzo-18-crown-6·potassium complex (bottom).

Some solid-state information was also available in the same time frame. Figure 2 shows two crystal structures relevant to the present discussion. The structure of potassium tetraphenylborate (top view, CPK representation) is shown in the upper panel.[19] It is interesting to note that a structure of the $RbBPh_4$ complex was reported as early as 1962.[20] The potassium cation in the $KBPh_4$ complex[19] is clearly nestled in a "V"-shaped space created by adjacent benzene rings. In one sense, the potassium cation is located exactly where it should be for an optimal cation−π interaction. On the other hand, considering steric issues and site occupancies, one might ask, where else would the cation reside?

The lower panel of Figure 2 shows the solid-state structure of a K^+ complex of dibenzo-18-crown-6 reported by Atwood and co-workers.[21] Benzene occupies the apical position, and no anion is present in its coordination sphere. Typically, dibenzo-18-crown-6·potassium complexes are planar. In this case, potassium is pulled 0.3 Å out of the donor group plane by the axial arene. This is an important structure because the benzene ring involved in complexation is neutral, i.e., it is not part of a delocalized anion that increases its donicity. The report[21] was focused on bonding modes for the dioxygen ligand, and the significance of this structure in the present context has largely been overlooked.

In addition to the examples cited, we noted above that a number of solid-state structures have been reported in which there is clear evidence of cation−π contacts. Most

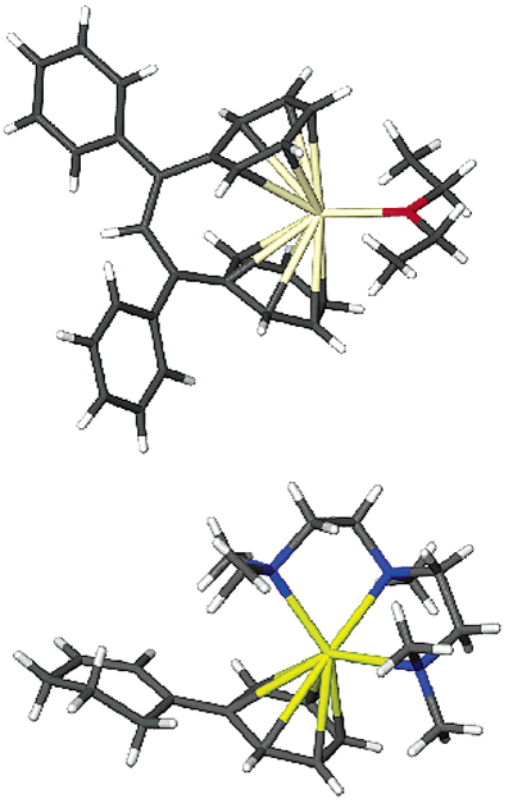


FIGURE 3. Structures involving benzene coordination in which the arene is part of an extended anionic system.

of these occur with Li^+, an ion, and/or with anionic π-systems. Lithium cation is less abundant in vivo than is Na^+. Still, examples of arene$-\pi$ interactions with ions such as Na^+ are known. For example, a gallium mesitylide complex shows multiple π-contacts with Na^+.[22] The sodium ion is not centrosymmetric in this case, and the arene carbon-to-Na^+ contacts are generally in the range 3.1−3.4 Å. A Mn/Na mixed metal complex involving a sodium−arene contact has also been reported.[23]

Four other solid-state structures show short Na^+−arene interactions in which the cation clearly forms a π-complex. In the first case, three of the aromatic rings of 9,9′-bis(anthracene) are in contact with sodium ions.[24] Each cation is further stabilized by complexation with tetramethylethylenediamine (TMEDA). The three Na^+−arene interactions, two of which occur on opposite sides of the same arene, show Na···C distances of <2.8 Å. A second example involves a tetraphenyltetracene in which four Na^+ ions interact with the arenes and are further stabilized by contact with two THF molecules each.[25] In this case, sodium is close to the arene and positioned over the center of the aromatic ring. The THF molecules are disordered.

The two clearest examples of cation$-\pi$ contact between Na^+ and an arene involve benzene rings conjugated to deprotonated olefins. The sodium salt of 1,1,3,3-tetraphenylpropenide forms a complex in which two of the benzene rings sandwich Na^+ at a distance of ∼3 Å and an angle of ∼65° (upper panel of Figure 3).[26] In this case, a molecule of diethyl ether is also in sodium's coordination sphere. An excellent example may be found in a solid-state structure involving 1-phenylcyclohexene (lower panel of Figure 3).[27] The sodium cation of the allyl anion is positioned directly over the aromatic centroid, and all Na···C(arene) contacts are <2.8 Å. Sodium ion is further complexed by the tridentate ligand $Me_2NCH_2CH_2N(CH_3)CH_2CH_2NMe_2$.

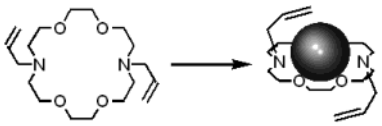


FIGURE 4. Proposed cation complexation by diallyldiaza-18-crown-6 based on known lariat ether complexes.

Lariat Ethers as a Vehicle for Studying Cation$-\pi$ Interactions

Although the efforts cited above are important and revealing, most are complicated by the question of charge. Even in the $KBPh_4$ case,[19] each arene possesses partial negative charge because it is part of the tetraphenylborate anion. This is so for the organometallic networks noted above and for the anion of cyclohexenylbenzene shown in Figure 3.

Our intent was to design a system in which the molecules would have a "choice" about the types of interactions they could exhibit. In the late 1970s, we developed a class of compounds that we dubbed *lariat ethers*.[28] These compounds are crown ethers having flexible sidearms that can augment complexation of a ring-bound cation. As with other crown ethers, the primary interaction with the cation occurs between it and the macrocycle.[29] If the sidearm is appropriately positioned, it can reinforce the binding. The result is a three-dimensional array of complexing donor groups in a flexible receptor system.[30] In developing the chemistry of the lariat ethers, we obtained both solution and solid-state evidence for sidearm participation in a variety of complexes.[31]

We felt that a cation$-\pi$ contact would be convincing if the donor groups on these flexible sidearms interacted with a ring-bound cation. Our plan was thus to bind a cation within the macroring and give alkene-, alkyne-, or arene-terminated sidearms the opportunity to provide the ion with axial solvation. A schematic of the expected alkene−donor structure, based on the known ether-sidearmed complex, is illustrated in Figure 4.

Diaza-18-crown-6 (**1**) was substituted at both nitrogen atoms by propyl (**2**), allyl (**3**), or propargyl (**4**) sidearms. Solution binding of both Na^+ and K^+ and solid-state studies were conducted on macrocycles **2**−**4**. The three compounds functioned as complexing agents, but no enhancement in efficacy could be documented as sidearm π-donicity increased. In addition, X-ray crystal structures were obtained for complexes of **3** and **4**, but no evidence of sidearm participation was found.[32] Solid-state structures of *N*,*N*′-dibenzyl-4,13-diaza-18-crown-6 (**5**), the synthetic precursor to **1**, likewise showed no sidearm participation.[31]

A particularly disappointing result was obtained with the alkyne-sidearmed derivative of **1**. The complex of

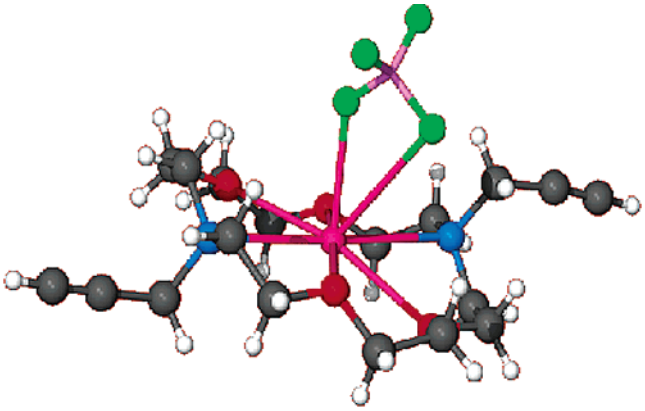
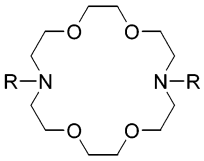


FIGURE 5. Solid-state structure of bis(propargyl)diaza-18-crown-6 complexing KBF_4. The sidearms are not involved in the cation complexation.



1, R = H
2, R = $CH_2CH_2CH_3$
3, R = $CH_2CH{=}CH_2$
4, R = $CH_2C{\equiv}CH$
5, R = CH_2Ph
6, R = CH_2CH_2Ph
7, R = $CH_2CH_2C_6H_4OH$
8, R = CH_2CH_2-indolyl
9, R = $CH_2CH_2C_6F_5$

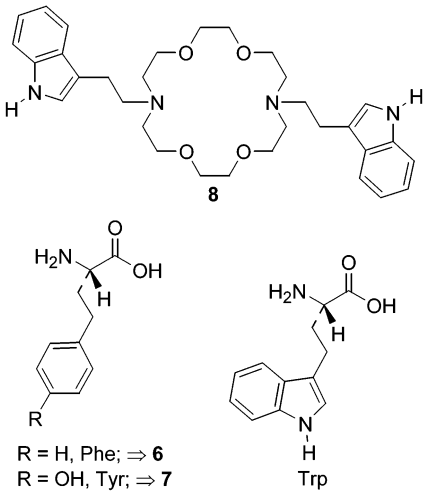
propargyl-sidearmed **4** and KBF_4 was isolated, and its structure was determined. Tetrafluoroborate (BF_4^-) was chosen as counterion because its poor donicity was expected to favor sidearm interaction with the ring-bound cation. Complex **4**·KBF_4 is shown in Figure 5. Clearly, the sidearms are turned away from the macrocycle-complexed cation, and two of the four fluorines are in contact with the cation. The complex may be described as a bifurcated hexagonal pyramid. Because of these disappointing results, our effort in this area lay fallow for some years.

The Cation−π Interaction and Cation Channels

In the early 1990s, speculation about the mechanism by which potassium channels select the larger cation rather than the smaller sodium ion renewed our interest in the cation−π problem. Kumpf and Dougherty offered the clever proposal that cation−π interactions within the channel were responsible for K^+ selectivity.[33] An experimental study reported by MacKinnon and co-workers disproved this hypothesis,[34] but our interest was piqued. By this time, we were actively developing our synthetic hydraphile channels,[6,35] and further exploration of the cation−π issue as a fundamental phenomenon of biological relevance[36,37] appeared to merit effort.

Design Features for the Receptor System

Because of our interest in organic chemical models of biological phenomena, the renewal of our cation−π work focused on amino acid side chains. None of the 20 common amino acids possess either an olefin or alkyne subunit. Four amino acids have aromatic side chains. The side chain of histidine (His, H) is imidazole. This is an aromatic residue, but it is relatively electron poor. Moreover, its interactions with cations are typically of the σ-donor type. We therefore focused attention on phenylalanine (Phe, F), tyrosine (Tyr, Y), and tryptophan (Trp, W). Their side chains are respectively benzene, phenol, and indole. All three of these residues are π-rich. Calculations[10,38−40] show that the π-donicities are in the order indole > phenol > benzene.



8

R = H, Phe; ⇒ **6**
R = OH, Tyr; ⇒ **7**
Trp

Our design for compounds **6**−**8** was modified only slightly compared to the receptors prepared a decade earlier. The macrocycle was expected to bind Na^+ or K^+ as a hexacoordinate ring. The π-donors were positioned two carbons from the flexible, invertable nitrogen atoms so that they could adopt the energetically most favorable structural positions. It was hoped that ring complexation of the cation would be augmented by axial, π-type "sandwich" complexation with the arenes. The flexibility of the receptor systems was confirmed by an examination of CPK models and by Monte Carlo simulations on the sidearms.[41] The receptor molecules were typically prepared by alkylation of diaza-18-crown-6 by the appropriate halide (X) of the form XCH_2CH_2arene. The resulting compounds were fully characterized in the chemical sense.[41]

Receptors Having Indole-Terminated Sidearms as Tryptophan Side Chain Mimics

The structures of indolylethyl-substituted **1**, i.e., **8**, and its KI complex, i.e., **8**·KI, are shown at the top and bottom of Figure 6, respectively.[42] Uncomplexed macrocycle **8** exhibits a typical "parallelogram" conformation, clearly apparent in the upper panel. In this structure, the $-CH_2-CH_2-$ units are generally in the gauche conformation. Two methylene groups on opposite sides of the ring are in the anti conformation and are turned inward to fill the macrocycle's central void. Notably, the sidearms and their attached arenes are turned away from the macroring.

In the KI complex, the conformation of **8** changes

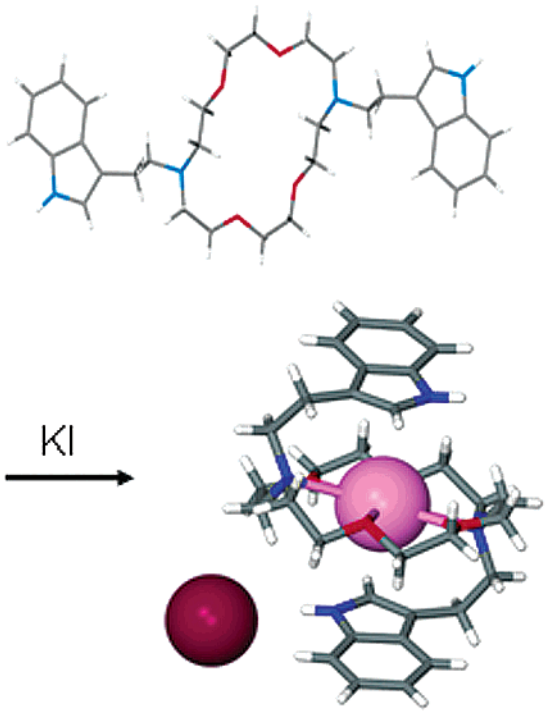


FIGURE 6. Solid-state structures of indolylethyl-sidearmed **8** and its KI complex. The latter is shown larger.

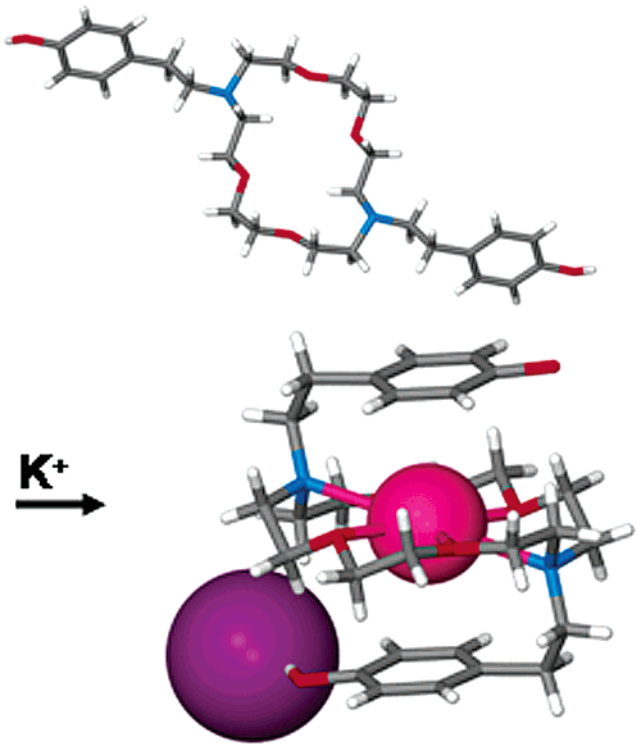


FIGURE 7. Solid-state structures of **7** (top) and **7**·KI (bottom). The latter is shown larger.

significantly.[42] The macrocycle itself adopts an approximately D_{3d} conformation so that all of the ring donors can interact directly with K^+. The nitrogen-attached sidearms rearrange from the extended conformation to afford a sandwich-type structure in which the pyrrolo (five-membered ring) is closest to K^+. The iodide anion, an excellent donor, is excluded from the solvation sphere and is H-bonded to one of the indole NH groups. It should be noted that the indole units are tilted and do not form what might be called a "flat sandwich" of the type known for ferrocene.

Results such as those shown in Figure 6 always make us question whether the interactions are "real" or are due exclusively to crystal packing forces. Compound **8** was studied by NMR spectroscopy in CD_3COCD_3 solution, a moderately polar solvent. Nuclear Overhauser effects were observed in the absence of cation, suggesting that the sidearms were positioned in the extended conformation observed for unbound **8** in the solid state. When an equivalent of sodium was added, however, the observed NOEs suggested that **8** was complexed and had adopted the sandwich conformation. A titration experiment (incremental addition of salt to **8**) showed that the most affected proton in the spectrum was attached to the pyrrolo C-2 carbon atom. In the solid state, it is that carbon atom that is nearest to the bound cation. It is interesting to note that a nearly identical complex structure was observed for **8** when either Na^+ or K^+ was the cation and when I^-, SCN^-, or PF_6^- was the anion.[41]

It may seem surprising that iodide anion does not directly contact the cation in complexes of **8**. This would certainly be reasonable because the anion's full negative charge is expected to strongly favor proximity to the cation. The significance of the cation$-\pi$ interaction as a stabilizing force is emphasized by the exclusion of anions from the cation's solvation sphere.[41]

Phenol-Terminated Sidearms as Tyrosine Side Chain Mimics

The side chain of the amino acid tyrosine is *p*-phenol. Receptors **7** and **8** are identical except that the terminal arenes are phenol and indole, respectively.[43] In both cases, the arene is attached at the position found in the amino acid. Solid-state structures were obtained for both unbound receptor **7** and its potassium iodide complex, **7**·KI. The structures are shown in Figure 7.

The conformation observed for unbound **7** is, like that of free **8**, the typical "parallelogram" arrangement for two-armed (bibracchial) lariat ethers. As above, two of the methylene groups are turned inward, and the sidearms are in extended conformations in which the two arenes are as remote from each other as possible. The structures in both panels of Figure 8 are shown in the tube metaphor, except for KI, which is shown in a space-filling representation.[43]

Reaction of **7** with KI affords **7**·KI, a complex in which the six ring donors are turned inward to form the equatorial belt of the potassium ion's solvation sphere. The apical positions are occupied by the two benzene rings, which form a sandwich with the spherical potassium. The organization of these two arenes is obvious from the bottom panel of Figure 7. The aromatic centroids are positioned directly over and under K^+, although the parallel arenes are offset ~9° from the approximate plane of the macrocycle. The iodide counterion is in a position

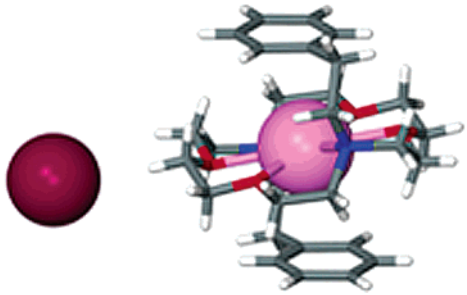


FIGURE 8. The KI complex of phenylethyl-sidearmed **6**.

similar to that observed for **8**·KI. Iodide is hydrogen bonded by one of the phenol hydroxyl groups just as the anion interacted with the indolyl NH of **8**. Again, K^+ is eight-coordinate if the arene's π-system is counted as a single donor. Iodide is excluded from the solvation sphere and is at a distance of ~7 Å. The comparable distance in **8**·KI is ~6 Å. In the NaI complex of **8** (i.e., **8**·NaI, not shown), the Na↔I distance is also ~6 Å.[41]

Benzene-Terminated Sidearms as Phenylalanine Side Chain Mimics

The receptor terminated by benzene rings, compound **6**, was isolated as an oil. As a result, it was impossible to obtain an ambient temperature X-ray structure of this molecule. When **6** was treated with KI, the solid complex **6**·KI formed, and we obtained its crystal structure.[44] The complex is shown in Figure 8 in the tube metaphor, except for K^+ and I^-, which are shown as van der Waals spheres. As in the tyrosine-sidearmed complex, K^+ is sandwiched essentially in the center of two benzene rings. A line drawn through the center of K^+ intersects both benzene rings in their centers. Moreover, the iodide anion, which is excluded from the solvation sphere, is in approximately the same position as it lies in the KI complex of **7**. The K↔I distance is 7.27 Å, slightly longer but similar to that in **7**·KI.

The similarity in the structures of **6**·KI and **7**·KI was at once gratifying and troubling. The clear sandwich structures observed for complexes of **6**, **7**, and **8** made exclusion of the iodide counterion seem reasonable. Moreover, the iodide ion was never closer to the cation than 6 Å, too far for any significant interaction to occur. In complexes of **7** and **8**, however, the "excluded" iodide was stabilized by interaction with a sidearm H-bond donor. Such a possibility was lacking in **6**·KI, but the K↔I distance was similar in **6**·KI and **7**·KI, as was the approximate anion position. We were concerned that crystal packing or other extrinsic forces rather than the electronic interaction we sought to probe were controlling the sidearm position.

Reversing the Electronic Effect: Pentafluorophenyl-Substituted Sidearms

Our concern about possible packing forces could be resolved experimentally. Benzene is an electron-rich π-donor system. Hexafluorobenzene is similar in size and shape to benzene but is electron poor. Figure 9 shows benzene and hexafluorobenzene in the CPK representation. Electrostatic surfaces have been calculated for each by using the commercially available software package Spartan. The CPK representation shows that the hydrogens (radius 1.1 Å) and fluorines (1.35 Å) differ little in spatial requirements. It seemed reasonable to assume that the arenes would adopt similar conformations if the solid-state structures were dominated by packing, rather than electronic, forces.

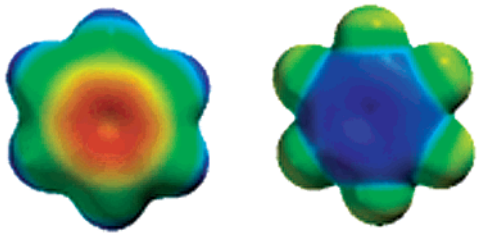


FIGURE 9. Electrostatic potential surfaces for benzene and hexafluorobenzene calculated using the commercial software Spartan.

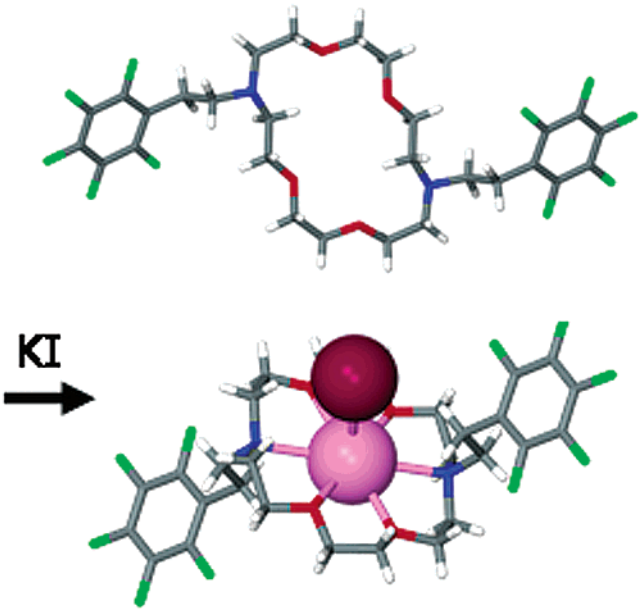


FIGURE 10. Solid-state structures of pentafluorophenylethyl-sidearmed **9** and its KI complex.

The electrostatic surfaces of the two arenes show red (benzene) and blue (hexafluorobenzene, right of figure) centers. The computational program renders areas of high electron density as red and low electron density as blue. A sandwich-type solid-state structure similar to that obtained for **8**·KI would strongly suggest that the results obtained for **6** and **7** were artifacts of the experimental method. It seemed more likely to us, however, that a nonsandwiched crown ether complex would form. We expected K^+ to be bound in the center of the macroring and to be coordinated by the ring donors and iodide anion. The sidearms, which offer no stabilization in this case, should be turned away from the cation.

An additional advantage of preparing pentafluorophenyl-sidearmed receptor **9** was that it solidified. We obtained the crystal structure that is shown at the top of Figure 10.[44] It is essentially identical to the structures

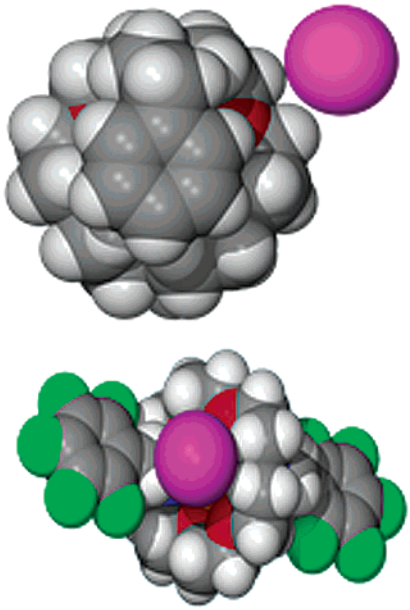


FIGURE 11. Top views of the solid-state structures of **6** (upper panel) and **9**.

observed for unbound **7** and **8** and to the structure expected for **6**. This gave us additional confidence that the presence of the pentafluoro residues would not introduce a new and unexpected variable into this equation.

The solid-state structure of **9**·KI is shown in the lower panel of Figure 10. Potassium cation, the lighter sphere, is located at the center of the macroring, forming a classical crown complex. Iodide anion is in direct contact with it. The structure shown suggests a hexagonal pyramid as the coordination geometry. In fact, an examination of the extended structure shows that the complexes are stacked one above the next. This arrangement comprises an infinite chain of ~K···I···K···I~ contacts such that each K^+ is in a hexagonal bipyramidal arrangement.

The striking difference in molecular organization is apparent in the structures shown in Figure 11. These are top views of receptors **6** and **9**, each complexing KI. The receptors are nearly isosteres, but only benzene serves as a π-donor. The top panel clearly shows the total encapsulation of the cation and the complete exclusion of the anion. In contrast, the bottom panel shows the intimate contact between anion and cation, while the sidearms and arenes of **9** remain extraneous to binding.

Biological Significance

The arene/sidearm combinations studied were chosen because they correspond to the side chains of the three essential amino acids that can serve as π-donors.[45,46] A statistical distribution of the 20 essential amino acids would mean that each occurs about 5% of the time. By that criterion, phenylalanine, tryptophan, and tyrosine are relatively rare. Their occurrence in all known protein sequences is phenylalanine 3.9%, tyrosine 3.2%, and tryptophan 1.3%. A protein having 250 amino acids (about 30 kDa) could possess as many as 21 cation$-\pi$ interactions. The present work shows that cation$-\pi$ interactions between alkali metals and benzene, phenol, and indole are possible. Indeed, they are most probable in a low-polarity environment such as the interior of a membrane or globular protein, where hydration forces are minimized.

Figure 12 shows space-filling representations of **8**·KI, **7**·KI, and **6**·KI side by side.[41] Clearly, the arenes in the KI complexes of **6** and **7** are nearly parallel. The arenes of **8**·KI, shown at the left, are distinctly tilted. We were concerned about the tilt but also by the fact that indole is calculated to be most electron rich near the center of the benzo, rather than the pyrrolo, subcyclic unit. Molecular models suggest that the indole ring is too large to penetrate the macrocycle's hole. The pyrrolo subunit is smaller and can approach the cation more closely. Thus, although electronically weaker, the pyrrolo subunit is sterically preferable.

The importance of these observations is that the flexible sidearms adapt to achieve the most effective stabilization arrangement. It is well known that the strengths of hydrogen bonds are greatest when the interactions are short and linear. The solid-state structures of enzyme active sites typically show an array of interactions including salt bridges, hydrophobic contacts, and hydrogen bonds. The H-bonds are often bifurcated or even trifurcated, but they still contribute to the overall stabilization of the structural arrangement. The experimental result observed for indolyl-sidearmed **8**·KI shows that structural adjustments may also be possible in natural systems when alkali metal cation$-\pi$ interactions are observed.

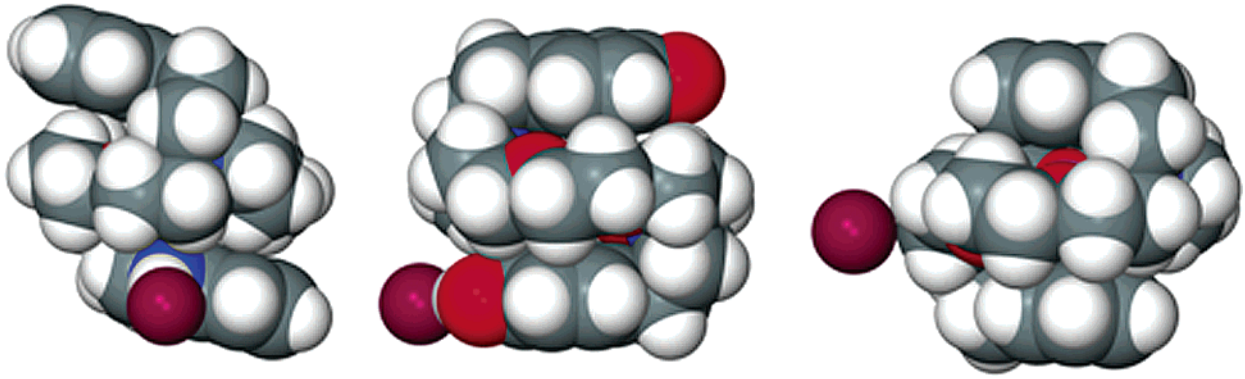


FIGURE 12. Side views of the solid-state structures of (left to right) **8**·KI, **7**·KI, and **6**·KI.

The focus of this Account is the interaction between neutral π-donors of biological relevance and alkali metal cations. Such studies are nominally limited to benzene, phenol, and indole, the side chains of phenylalanine, tyrosine, and tryptophan. It is worth noting, however, that the lariat ether receptors can be extended to include double and triple bond donors. Thus, we have recently shown that diaza-18-crown-6 macrocycles bearing CH_2-$CH_2CH{=}CH_2$ and $CH_2CH_2C{\equiv}CH$ sidearms can complex alkali metals using double[47] and triple bonds[48] as donors.

Summary and Conclusions

Numerous feeble forces are now recognized as important that were not thought to be at all significant even 10 years ago. Notable among these is the C−H hydrogen bond[49,50] that has achieved respectability during the past decade.[51] Cation−π interactions have been observed a number of times, particularly in solid-state structures of organometallic complexes. Although computational and mass spectrometric evidence for this phenomenon has been obtained, definitive solid-state evidence has been lacking. The lariat ether model systems are especially appropriate to this problem because the flexible sidearms can compete with the counteranion or not, as appropriate to the system.

Future studies in molecular recognition and supramolecular chemistry must include cation−π interactions in the panoply of feeble forces. The consequences of this interaction are potentially profound for biology. Currently, "extra" electron density corresponding to 10 electrons is routinely assigned to water molecules in the absence of other models. As the quality of protein structures continues to increase, it may be possible to distinguish these 10-electron signals as water or sodium cation. At present, this electron density can be considered in electronic terms as possibly revealing cation−π interactions. Sodium is ubiquitous, and the possibilities for complexation by the sidearms of phenylalanine, tryptophan, and/or tyrosine are abundant.

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References

(1) Doyle, D. A.; Cabral, J. M.; Pfuetzner, R. A.; Kuo, A.; Gulbis, J. M.; Cohen, S. L.; Chait, B. T.; MacKinnon, R. The structure of the potassium channel: molecular basis of K^+ conduction and selectivity. *Science* **1998**, *280*, 69−77.

(2) MacKinnon, R.; Cohen, S. L.; Kuo, A.; Lee, A.; Chait, B. T. Structural conservation in prokaryotic and eukaryotic potassium channels. *Science* **1998**, *280*, 106−109.

(3) Roux, B.; MacKinnon, R. The cavity and pore helices in the KcsA K^+ channel: electrostatic stabilization of monovalent cations. *Science* **1999**, *285*, 100−102.

(4) Morais-Cabral, J. H.; Zhou, Y.; MacKinnon, R. Energetic optimization of ion conduction bythe K^+ selectivity filter. *Nature* **2001**, *414*, 37−42.

(5) Zhou, Y.; Morais-Cabral, J. H.; Kaufman, A.; MacKinnon, R. Chemistry of ion coordination and hydration revealed by a K^+ channel−Fab complex at 2.0 Å resolution. *Nature* **2001**, *414*, 43−48.

(6) Gokel, G. W. Hydraphiles: Design, Synthesis, and Analysis of a Family of Synthetic, Cation-Conducting Channels. *Chem. Commun.* **2000**, 1−9.

(7) Ma, J. C.; Dougherty, D. A. The cation−π Interaction. *Chem. Rev.* **1997**, *97*, 1303−1324.

(8) Sunner, J.; Nishizawa, K.; Kebarle, P. Ion−solvent interactions in the gas phase. The potassium ion and benzene. *J. Phys. Chem.* **1981**, *85*, 1814−1820.

(9) Guo, B. C.; Purnell, J. W.; Castleman, A. W., Jr. The clustering reactions of benzene with sodium and lead ions. *Chem. Phys. Lett.* **1990**, *168*, 155−160.

(10) Ryzhov, V.; Dunbar, R. C.; Cerda, B.; Wesdemiotis, C. Cation-pi Effects in the Complexation of Na^+ and K^+ with Phe, Tyr, and Trp in the Gas Phase. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 1037−1046.

(11) Armentrout, P. B.; Rodgers, M. T. An Absolute Sodium Cation Affinity Scale: Threshold Collision-Induced Dissociation Experiments and ab Initio Theory. *J. Phys. Chem. A* **2000**, *104*, 2238−2247.

(12) Hoyau, S.; Norman, K.; McMahon, T. B.; Ohanessian, G. A Quantitative Basis for a Scale of Na^+ Affinities of Organic and Small Biological Molecules in the Gas Phase. *J. Am. Chem. Soc.* **1999**, *121*, 8864−8875.

(13) Hay, B. P.; Nicholas, J. B.; Feller, D. Novel binding modes in tetramethoxycalix[4]arene: implications for ligand design. *J. Am. Chem. Soc.* **2000**, *122*, 10083−10089.

(14) Gapeev, A.; Dunbar, R. C. Cation−π interactions and the gas-phase thermochemistry of the Na^+/phenylalanine complex. *J. Am. Chem. Soc.* **2001**, *123*, 8360−8365.

(15) Siu, F. M.; Ma, N. L.; Tsang, C. W. Cation−π interactions in sodiated phenylalanine in the charge-solvated or zwitterionic form? *J. Am. Chem. Soc.* **2001**, *123*, 3397−3398.

(16) Shannon, R. D. Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides. *Acta Crystallogr., Sect. A* **1976**, *A32*, 751−767.

(17) Meot-Ner, M.; Deakyne, C. A. Unconventional ionic hydrogen bonds. 2. $NH^+{\cdots}\pi$. Complexes of onium ions with olefins and benzene derivatives. *J. Am. Chem. Soc.* **1985**, *107*, 474−479.

(18) Burley, S. K.; Petsko, G. A. Amino-aromatic interactions in proteins. *FEBS Lett.* **1986**, *203*, 139−143.

(19) Hoffmann, K.; Weiss, E. Ueber metall-alkyl- und -aryl-verbindungen. XVI. Die krystallstructuren von kaliumtetraphenylborat, K[B(C6H5)4] und tetramethylammonium-tetraphenylborat, [N(CH3)4][B(C6H5)4]. *J. Organomet. Chem.* **1974**, *67*, 221−228.

(20) Ozol, Y.; Vimba, S.; Levins, A. Crystal structure of $RbBPh_4$ (RBPBOR). *Krystallografiya* **1962**, *7*, 362.

(21) Hrncir, D. C.; Rogers, R. D.; Atwood, J. L., "New Bonding Mode for a Bridging Dioxygen Ligand: The Crystal and Molecular Structure of [K·dibenzo-18-crown-6][$Al_2Me_6O_2$]·$2C_6H_6$," *J. Am. Chem. Soc.* **1981**, *103*, 4277−4278.

(22) Wehmschulte, R. J.; Power, P. P. Multiple Ga−Ga Bonding Character in Na[Ga($GaTrip_2$)$_3$], and a Comparison with Neutral Ga($GaTrip_2$)$_3$ (Trip=2,4,6-^{i}Pr$_3$C$_6$H$_2$). *Angew. Chem., Int. Ed.* **1998**, *37*, 3152−3154.

(23) Franceschi, F.; Hesschenbrouck, J.; Solari, E.; Floriani, C.; Re, N.; Rizzoli, C.; Chiesi-Villa, A. The reactivity of dibenzotetramethyltetraaza[14]annulene−Mn(2): functionalisation of manganese in a macrocyclic environment. *J. Chem. Soc., Dalton Trans.* **2000**, 593−604.

(24) Bock, H.; Havlas, Z.; Hather, D. Tris(tetramethylethylenediaminesodium)-9,9-bianthryl-The Salt of a pi-Hydrocabon Radical Trianion with Three Na^+- -C-pi Contacts to One Molecular Half. *Angew. Chem., Int. Ed.* **1998**, *37*, 502−504.

(25) Bock, H.; Gharagozloo-Hubmann, K.; Nather, C.; Nagel, N.; Havlas, Z. [{Na^+(THF)$_2$}$_4$(rubrene)]: Crystalization and Structure Determination of a Contact-Ion Quintuple for the First Pi-Hydrocarbon Tetraanion. *Angew. Chem., Int. Ed.* **1996**, *35*, 631−632.

(26) Bock, H.; Ruppet, K.; Havlas, Z.; Fenske, D. Tetraphenylallysodium diethyl Ether: A Contact Ion Pair with an Intramolecular Na^+-sandwich. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1042−1044.

(27) Corbelin, S.; Kopf, J.; Lorenzen, P. N.; Weiss, E. Phenylsodium compounds with eta^3-allyl or eta^6-phenyl coordination. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 825−826.

(28) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. Lariat Ethers. Synthesis and Cation Binding Properties of Macrocyclic Polyethers Possessing Axially Disposed Secondary Donor Groups. *J. Chem. Soc., Chem. Commun.* **1980**, 1053−1054.

(29) Gokel, G. W. Lariat Ethers: From Simple Sidearms to Supramolecular System. *Chem. Soc. Rev.* **1992**, *21*, 39−47.

(30) Gokel, G. W.; Schall, O. F. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon: Oxford, 1996; Vol. 1, pp 97−152.

(31) Gandour, R. D.; Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Schultz, R. A.; White, B. D.; Arnold, K. A.; Mazzocchi, D.; Miller, S. R.; Gokel, G. W. Solid-State Structural Chemistry of Lariat Ether and BiBLE Cation Complexes: Metal Ion Identity and Coordination Number Determine Cavity Size. *J. Am. Chem. Soc.* **1986**, *108*, 4078−4088.

(32) Arnold, K. A.; Viscariello, A. M.; Kim, M.; Gandour, R. D.; Fronczek, F. R.; Gokel, G. W. N,N′-bis(Substituted)-4,13-diaza-18-crown-6 derivatives having pi-donor-group-sidearms: correlation of thermodynamics and solid-state structures. *Tetrahedron Lett.* **1988**, 3025−3028.
(33) Kumpf, R. A.; Dougherty, D. A. A mechanism for ion selectivity in potassium channels: computational studies of cation-pi interactions. *Science* **1993**, *261*, 1708−1710.
(34) Heginbotham, L.; Lu, Z.; Abramson, T.; MacKinnon, R. Mutations in the K^+ channel signature sequence. *Biophys. J.* **1994**, *66*, 1061−1067.
(35) Murillo, O.; Watanabe, S.; Nakano, A.; Gokel, G. W. Synthetic models for transmembrane channels: Structural variations that alter cation flux. *J. Am. Chem. Soc.* **1995**, *117*, 7665−7679.
(36) Dougherty, D. Cation-pi interactions in chemistry and biology. A new view of benzene, Phe, Tyr, and Trp. *Science* **1996**, *271*, 1163−1168.
(37) Gallivan, J. P.; Dougherty, D. A. Cation-pi interactions in structural biology. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459−9464.
(38) Mecozzi, S.; West, A. P., Jr.; Dougherty, D. A. Cation−π interactions in simple aromatics: electrostatics provide a predictive tool. *J. Am. Chem. Soc.* **1996**, *118*, 2307−2308.
(39) Wouters, J. Use of theoretical descriptors to characterize cation-pi binding sites in (macro)molecules. *J. Comput. Chem.* **2000**, *21*, 847−855.
(40) Ryzhov, V.; Dunbar, R. C. Interactions of phenol and indole with metal ions in the gas phase: Models for Tyr and Trp side-chain binding. *J. Am. Chem. Soc.* **1999**, *121*, 2259−2268.
(41) Meadows, E. S.; De Wall, S. L.; Barbour, L. J.; Gokel, G. W. Alkali Metal Cation−π Interactions Observed by Using a Lariat Ether Model System. *J. Am. Chem. Soc.* **2001**, *123*, 3092−3107.
(42) De Wall, S. L.; Meadows, E. S.; Barbour, L. J.; Gokel, G. W. Solution and Solid State Evidence for Alkali Metal, Cation−π Interactions with Indole, The Side Chain of Tryptophan. *J. Am. Chem. Soc.* **1999**, *121*, 5613−5614.
(43) De Wall, S. L.; Barbour, L. J.; Gokel, G. W. Cation−π complexation of potassium cation with the phenolic side chain of tyrosine. *J. Am. Chem. Soc.* **1999**, *121*, 8405−8406.
(44) De Wall, S. L.; Meadows, E. S.; Barbour, L. J.; Gokel, G. W. Synthetic receptors as models for alkali metal cation-*pi* binding sites in proteins. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6271−6276.
(45) Wouters, J. Cation-p (Na^+-Trp) interactions in the crystal structure of tetragonal lysozyme. *Protein Sci.* **1998**, *7*, 2472−2475.
(46) Wouters, J.; Maes, D. Identification of a potential metal cation-pi binding site in the structure of a thermophilic Bacillus stearothermophilus triosephosphate isomerase mutant. *Acta Crystallogr.* **2000**, *D56*, 1201−1203.
(47) Hu, J.; Barbour, L. J.; Gokel, G. W. Solid state evidence for pi-complexation of sodium cation by carbon-carbon double bonds. *Chem. Commun.* **2001**, 1858−1859.
(48) Hu, J.; Barbour, L. J.; Gokel, G. W. Solid-state evidence for π-complexation of potassium cation by a carbon−carbon triple bond. *J. Am. Chem. Soc.* **2001**, *123*, 9486−9487.
(49) Desiraju, G. R. The C−H···O hydrogen bond in crystals: What is it? *Acc. Chem. Res.* **1991**, *24*, 290−296.
(50) Desiraju, G. R. The C−H···O hydrogen bond. Structural implications and supramolecular design. *Acc. Chem. Res.* **1996**, *29*, 441−449.
(51) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/Pi Interaction: Evidence, Nature, and Consequences*; Wiley-VCH: New York, 1998.

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