FEATURE ARTICLE

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The aromatic sidechains of amino acids as neutral donor groups for alkali metal cations

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An aromatic residue that can serve as a pi-donor occurs in all known protein sequences about one out of every 11 amino acids. Benzene, phenol, and indole, the sidechains of phenylalanine, tyrosine, and tryptophan, are particularly important in protein structure. Solid state structures confirm the interactions of these neutral arenes, along with double and triple bonds, with sodium and potassium cations.

When Sutor suggested more than four decades ago[1] that C–H hydrogen bonds were a weak but significant force, neither the chemical nor the biological community showed much interest. Some forty years later, it is clear that these interactions are significant and general.[2] Alkali metal cation–pi interactions are similar in the sense that there is ample evidence for them, but their significance is currently neither fully recognized nor appreciated. Evidence for this phenomenon has, until quite recently, been largely limited to mass spectrometric[3–6] and computational data.[7–11] Important as these approaches are, the near absence of solid state structural information has made it difficult to visualize and analyze cation–pi interactions involving alkali metal cations. During the past several years, we have undertaken a program to demonstrate that such interactions occur between alkali metal cations and neutral arenes such as benzene, phenol, and indole. These are the three potentially donating aromatic sidechains that occur among the 20 so-called essential amino acids.

Before discussing the relevance of these interactions to biology, it is important to acknowledge that cation–pi interactions have been known for many years in several contexts. In particular, numerous examples are available in organometallic complexes. To our knowledge, essentially all of these involve transition metal cations and arenes that are either anions or part of a negatively charged system. Early examples of alkali metal complexes with arenes include dilithium naphthalenide dianion[12] and the solid state structures of $KBPh_4$[13] and $RbBPh_4$.[14]

George Gokel was born in New York City but moved as a child to Florida where he grew up. He studied chemistry at Tulane University in New Orleans and earned a doctorate in chemistry at the University of Southern California in Los Angeles. After post-doctoral work with Donald Cram at UCLA and a short stint at the DuPont Chemical Co., Dr Gokel began his academic career. He has held positions in chemistry departments at Pennsylvania State University, the University of Maryland, and the University of Miami. He is currently Professor in the Department of Molecular Biology and Pharmacology and Director of the Program in Chemical Biology at the Washington University School of Medicine in St. Louis. He holds a joint appointment in the Department of Chemistry.

The arenes in proteins are not charged. The pK_a of the tyrosine hydroxyl is about 10, so it is not ionized at physiologic pH. Likewise, tryptophan's indole nitrogen is too weakly basic to be protonated at pH 7.2. Further, the reduction of an arene (such as the benzene ring of phenylalanine) to an anion would be difficult to achieve under biological conditions.

Our efforts and this discussion are confined to alkali metal cations and to the four essential amino acids that possess sidechains terminated by arenes. These are histidine (His, H, arene = imidazole), phenylalanine (Phe, F, arene = benzene), tyrosine (Tyr, Y, arene = phenol), and tryptophan (Trp, W, arene = indole). When we began our studies, we presumed that cation binding by the imidazole residue of histidine would involve sigma donation from a ring nitrogen atom to a cation. Imidazole is known to be electron deficient and the nitrogen atoms certainly coordinate to such metals as Zn(II) in this fashion. It was surprising to us that definitive structural information was not available in the Cambridge Structural Database to confirm this expectation.

Cation–pi interactions between alkali metal ions and arenes are expected to exhibit their greatest effect in a nonpolar environment. This could be in the gas phase, deep inside a protein, or within the hydrocarbon regime of a phospholipid bilayer membrane. The latter is more relevant to biology but harder to study than the gas phase. Like hydrogen bonds, individual cation–pi interactions may be weak. The occurrence of Phe, Tyr, and Trp in all known protein sequences is about 8.5%. Thus, a protein having 250 amino acid residues could have 20 or so cation–pi interactions. Even if each interaction amounted to only a few kilocalories, twenty such interactions would be a significant structural force.

Kebarle and coworkers made the first definitive observation of an alkali metal cation–pi interaction[15] more than 20 years ago. They demonstrated by mass spectrometric methods that the complex of K^+ with benzene was similar in stability to the interaction of K^+ with a molecule of methanol ($[CH_3OH{\cdot}K]^+$). Later work by Castleman showed corresponding results for Na^+.[16] Other efforts were underway at about the same time. Meot-Ner and Deakyne used mass spectrometric methods to explore the cation–pi interaction between arenes and 'onium ions.[17] Burley and Petsko searched the Protein Data Bank (PDB) in an effort to identify close contacts between 'onium ions and aromatic sidechains.[18]

Our development of the lariat ether compounds[19] led us to consider whether arenes in the sidearms could provide intramolecular solvation to a ring-bound cation. Sadly, we were unaware at the time of Atwood's strongly suggestive structure of a $K^+{\cdot}$dibenzo-18-crown-6 in which a molecule of benzene provided axial solvation to the cation.[20] We prepared macrocycles that had double bonds, triple bonds, or arenes in the sidearms and determined their solution complexation constants

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and solid state structures. In no case was definitive evidence obtained for a cation–pi interaction.[21] It was there that our effort lay until the early 1990's.

The goal of the studies

A question of interest to the biological community is how protein channels achieve their remarkable cation selectivity. In 1993, Dougherty proposed that K^+ transport selectivity might result from cation–pi interactions in the selectivity filter of a potassium channel.[22] The following year, Mackinnon and coworkers showed that it is the tyrosine hydroxyl groups rather than the arene *per se* in potassium channels that are important for selectivity.[23] Mackinnon's pioneering crystal structure determination of the KcsA channel protein has verified the latter conclusions.[24]

Even if cation–pi interactions do not determine ion selectivity in channels, they can certainly influence other processes. Our challenge was to obtain structural evidence as this is inherently more tangible than the results of gas phase studies or calculations. We felt that such an endeavor was of critical importance and value because it would provide the basis for evaluating potential cation–pi interactions that were observed under less ideal conditions. Structural information such as bond distances and angles is not obtained from mass spectrometric experiments. Computational studies are important and suggestive but reach conclusions based on the best currently available force fields.

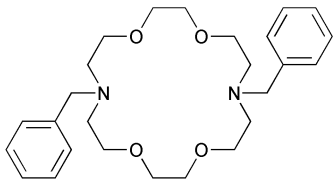
Our goal was to design and to prepare receptor molecules that would afford us clear and unequivocal solid state structural evidence for cation–pi interactions between neutral arenes and the alkali metal ions sodium and potassium. As noted above, we limited our efforts to these two cations because they are by far the most common in biological systems. At the outset, we anticipated extending our efforts to divalent calcium but this was a more distant vision. We restricted our initial studies to benzene, phenol, and indole – the arene termini of phenylalanine, tyrosine, and tryptophan, respectively. Some information was obtained concerning histidine's imidazole and this is discussed briefly below.

The experimental design and the synthetic receptor system

We recognized that salts such as NaCl do not crystallize from benzene, so a key question was how to develop a system that could interact with Na^+ or K^+. Carboxylic acids certainly do so and the carboxylate sidechains of aspartic and glutamic acids are well known to contact and to solvate metallic cations. We were concerned that carboxylates would be the dominant donors in any receptor containing them and that they would overwhelm pi-interactions.

The lariat ethers, sidearmed crown ether compounds that we developed two decades ago,[19a] were still the obvious candidate for these studies. Our plan was that the Na^+ or K^+ cations would be bound in a macrocycle and the pi-donor residues, placed on the sidearms, would interact axially. A macrocycle candidate would be *N*,*N*′-disubstituted-4,13-diaza-18-crown-6 derivatives. The placement of the arenes on the sidechain was obviously critical as no one had reported pi-complex formation from *N*,*N*′-dibenzyl-4,13-diaza-18-crown-6. Dibenzyldiaza-18-crown-6 is the key precursor in accessing the family of two-armed diazacrowns.[25] A study of CPK molecular models revealed that the arenes of 2-phenylethyl sidechains attached to nitrogen should be ideally situated if the anticipated pi-interaction was to occur.

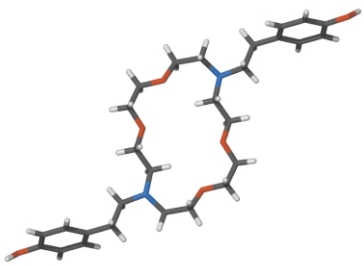
We had extensive experience with the lariat ethers[19b] and the desired receptor compounds were readily brought to hand. Two



Dibenzyldiaza-18-crown-6

approaches were used. In one, dibenzyldiaza-18-crown-6 was deprotected (hydrogenolyzed) to diaza-18-crown-6. Sidearms were then added to the diazamacrocycle (step b in Scheme 1). In the other, the desired sidearm was incorporated as the primary amine, $ArCH_2CH_2NH_2$, using a single-step cyclization method we developed previously (step a).[26] The compounds are shown as **1–3** in Scheme 1. An alternative procedure involving acylation and reduction was used to produce **4** (step c).

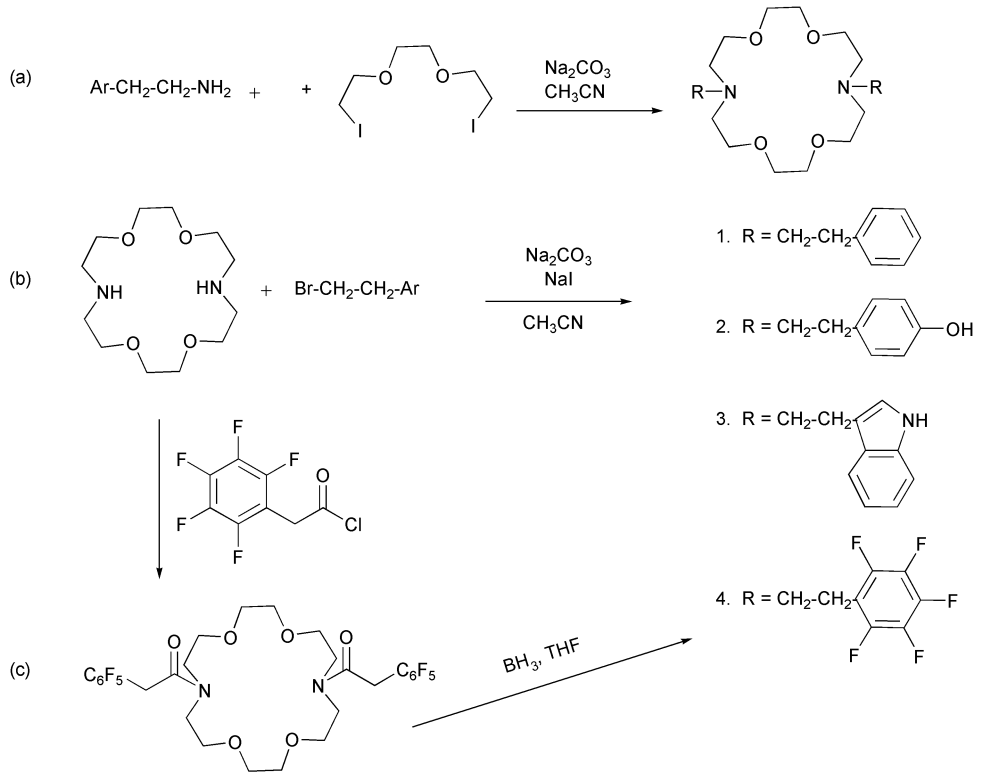
Once the appropriate synthetic receptors were in hand, it remained only to form complexes with various salts, crystallize them, and obtain their solid state structures. Compounds **2–4** were solid and could be studied in the absence of any salt. In all three cases, the crown showed the typical "parallelogram" conformation in which the macroring is essentially open and the two sidearms are turned away from the ring. The arenes were as distant from each other as possible.[27] The structure of uncomplexed **2** is shown.



Numerous complexes of **1–3**[28] were obtained. These involved both Na^+ and K^+ cations in combination with such anions as I^-, BF_4^-, PF_6^-, SCN^-, and BPh_4^-. Numerous crown ether complexes are known.[29] Typically, the cation is surrounded and complexed by the macroring donors to form a symmetrical and nearly planar array. The cation's two apical positions are unoccupied when a crown is of about the right size to provide meridional solvation. Generally, the axial voids are filled either by a counterion (anion), water, or solvent. When water is present, it is often bound, in turn, to an anion. The crown complexes may organize within the crystal in such a way that two complexes in an infinite chain share the apical anion.

Chemical intuition suggested that the absence of a cation–pi interaction would be apparent from two structural features. First, the sidearms would be turned away from each other and extended from the macroring. Second, anions or solvent molecules would fill the apical positions. Cation–pi interactions would be indicated by a sidearm conformation in which the arene, rather than the anion, contacted the cation. In the latter case, the anion would be excluded from the cation's solvation sphere. The structures illustrated in Fig. 1 for compounds **1–3** clearly show a potassium cation surrounded by four oxygen, two nitrogen, and two arene donors. The large iodide anion is clearly excluded from the solvation sphere. In the complexes **2**·KI and **3**·KI,[30] there is an H-bond interaction between the anion and the arene. In **2** it involves the tyrosine hydroxyl group and in **3** it is the indolyl NH that serves as the H-bond donor.

The similarity between the KI complexes of **1** and **2** concerned us. There is no H-bond stabilization of the iodide anion and yet it is positioned similarly in the two complexes. If the iodide was thus oriented as a result of crystal packing or other lattice forces, then perhaps the sidearms were arranged in



Scheme 1

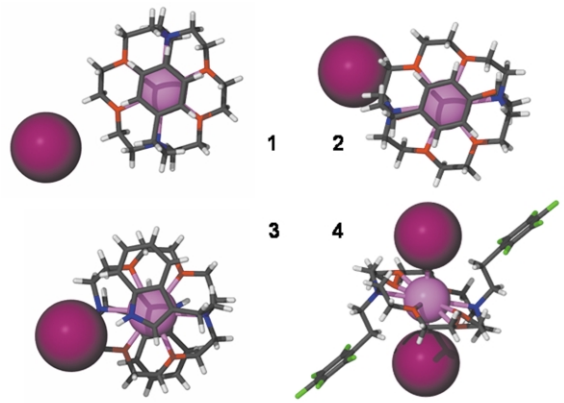


Fig. 1 Solid state structures of two-armed receptors complexing KI. Upper left, **1**·KI; upper right, **2**·KI; lower left, **3**·KI; and lower right, **4**·KI.

what appeared to be a pi-complexing conformation as a result of the same forces. An experimental test was devised. The phenyl groups of **1** were replaced by pentafluorophenyl residues.[31] In all other respects, the receptor molecules remained identical. The presence of fluorines instead of hydrogens was not a major perturbation sterically but was expected to exhibit a significant electronic effect.

The solid state structures of **1**·KI and **4**·KI are strikingly different. In both cases, the K^+ cation is embedded within the macroring but the sidearm arrangements could not be more different. Complex **1**·KI is shown in Fig. 1 in a top view that makes clear the near perfect alignment of the two sidearm benzene rings above and below the ring-bound K^+ ion. As noted above, the iodide ion is excluded from the solvation sphere. In **4**·KI, the sidearms are turned away and are essentially opposite each other. Neither is near the ring-bound cation. The positions above and below the cation are both occupied by iodide ions in what constitutes an infinite ···K–I–K–I··· chain within the crystal. This is precisely the result that one would expect if the sidechain arenes were incapable of the appropriate Lewis base donor interaction. It is not unreasonable that complexes such as **1**·KI and **2**·KI, which are similar in size and shape, would crystallize in a similar arrangement. If crystal packing forces were the only variable, one would expect **4**·KI to be similar, if not identical.

Smaller macrorings and single sidearms

Early in the studies that are recounted here, a reviewer raised a question about the receptor systems **1–4**. The reviewer objected to publication on the grounds that the positive results for **1–3** were really a complex artifact of the receptor system. This referee was unconvinced by the negative result with **4**. This critic was particularly uncomfortable with the structural result obtained for indole derivative **3**·KI. A number of computational studies predicted that the benzene ring of indole would be the key donor in pi-complexation. Fig. 1 shows clearly that it is the 5-membered pyrrolo ring, rather than the benzo unit, that serves this function. In contrast to the reviewer's discomfort, we inferred from this experimental observation that the indole sidechain of tryptophan is likely a flexible and versatile pi-donor. We also felt that valuable as computational studies are, an experimental observation is at least as valid.

Fortunately for us, the criticism described above came at a time when we had already begun to explore variations in the receptor systems and their complexes. An obvious question is whether or not receptor **1** will form a similar complex with sodium cation. If so, will the smaller sodium cation also form a stable pi-complex when only one arene is present on a single sidearm? What if the single sidearm is attached to a 15-membered macrocycle? The relevant compounds are **5–7**, which have an arene at the terminus of a single, 2-carbon sidechain. Three solid state structures that address the question of how these compounds complex alkali metal cations are shown in Fig. 2.

The complex between *N*-(2-phenylethyl)-aza-18-crown-6 (**5**) and KI is shown in two views at the top of Fig. 2. Unlike the complex of KI with two-armed **1**, both apical positions cannot

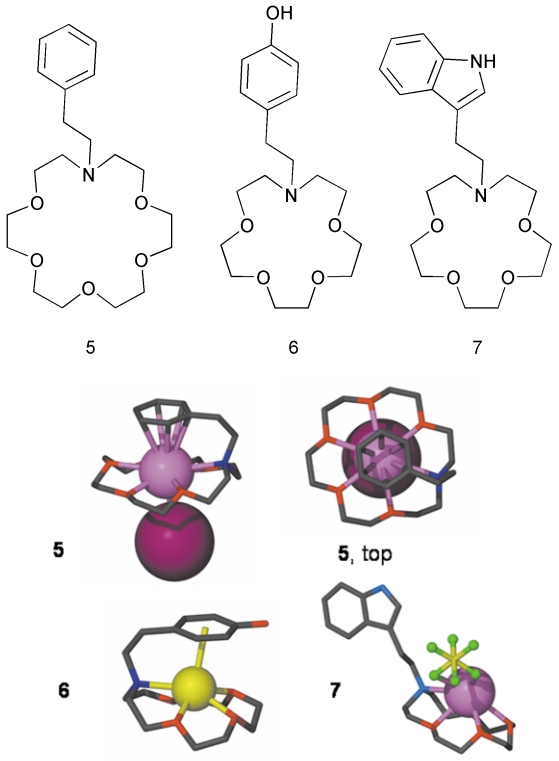


Fig. 2 Solid state structures of single-armed receptor complexes. Upper left and right panels, **5**·KI; lower left, **6**·$NaBPh_4$; and lower right, **7**·KPF_6.

be occupied by arenes in the same molecule. One possibility is the formation of an extended system such as shown for **4** in Fig. 1 but this is not observed. Instead, one apex is occupied by the attached arene and the other apex is satisfied by iodide anion. This result is consistent with the known complexation behavior of 18-crown-6 lariat ethers and with the observations discussed above.

The contact between K^+ and the sidearm benzene ring is ~3.1 Å and the arene is essentially perpendicular to a line dropped from its centroid to the cation.[32] The top view of this complex is shown in the upper right panel of Fig. 2. The arene, the cation, the anion, and the macroring appear as four approximately concentric rings. A coordinated potassium cation has a radius of ~1.5 Å. The half-thickness of a benzene ring is ~1.7 Å. Taken together, they exceed the observed K-arene distance in this complex. The inference is that the arene is tightly coordinated to the ring-bound cation.

A very similar structural arrangement is apparent in the Na^+ complex of **6**. The macrocycle is the smaller *N*-(2-(4-hydroxyphenyl)ethyl)-aza-15-crown-5 (**6**) which complements the smaller cation.[33] The anion in this case is Ph_4B^- and is not shown. The anion is present in the crystal lattice but it does not contact the **6**·Na^+ complex. Further, the aromatic hydroxyl group is H-bonded to a water molecule that is not shown in this figure. The arene deviates by about 10° from being perpendicular to a line dropped from it to the cation. The Na^+-arene distance is ~2.8 Å. The sum of an arene thickness and the radius of Na^+ is (1.7 + 1.1) = 2.8 Å suggesting that in this case the interaction is a strong one as well.

The situation shown in the lower right panel of Fig. 2 is interesting. The macrocycle is *N*-(2-(3-indolyl)ethyl)-aza-15-crown-5 (**7**).[34] The KPF_6 complex of **7** is illustrated. In this case, the larger K^+ cation was mated with a 15-membered macroring. The arene was positioned at the end of an ethylene chain as in both **5** and **6**. In the case of **7**·KPF_6, the sidearm arene did not serve as a donor group. Instead, the apical position is occupied by two of the six fluorine atoms contributed by what is generally regarded as a poorly donating anion. Two of the four remaining fluorine atoms serve as donors for an adjacent complex.[34] The complex shown is part of a dimer structure linked by the PF_6 anion.

N-(2-Phenylethyl)-aza-15-crown-5 forms a stable complex with $NaBPh_4$ in which the arene is an apical donor (structure not shown).[33] Crystallization of various Na^+ salts and either *N*-benzylaza-15-crown-5 or *N*-(3-phenylpropyl)-aza-15-crown-5 produced solid complexes but in no case was evidence obtained for a cation–pi interaction. A final note is that no complex exhibiting a cation–pi interaction was obtained with any of the receptors used in these studies with any calcium salt.[35]

Histidine, the fourth essential aromatic amino acid

The importance of histidine in a variety of specialized coordinating roles can hardly be overstated. Its interactions with transition metal ions in metalloenzymes are well established. Moreover, it plays a critical role in catalysis in the family of enzymes known as the serine proteases. In both of these applications, it is the heterocycle's nitrogen atoms that play specific roles either as donors or Lewis bases or both. Imidazole is not regarded as an electron-rich aromatic and we therefore did not expect it to function as a pi-donor as we did for the sidechains of phenylalanine, tyrosine, or tryptophan. Remarkably, there was little structural evidence to confirm this expectation.

We prepared compound **8**, *N*-(2-imidazolylethyl)-aza-15-crown-5, by treating histamine dihydrochloride with tetraethylene glycol dimesylate in the presence of base. Crystallization of the lariat ether in the presence of $NaBPh_4$ afforded the lariat ether complex but the imidazole–cation contact clearly involved a sigma-, rather than pi-, interaction (Fig. 3).[33]

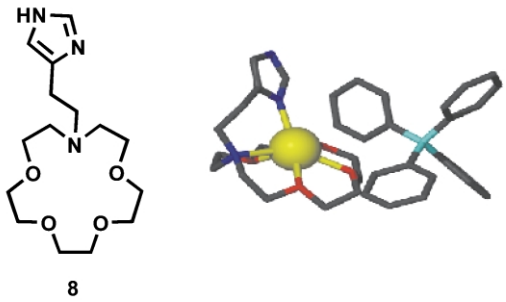


Fig. 3 Structure of **8** and its complex with $NaBPh_4$.

Computational and solid state experiments

The importance of computational methods in modern chemical and biological sciences can hardly be overstated. They are limited, of course, by the capabilities of the equipment used and by the force fields employed. The latter derive from chemical principles and from experimental results. Notwithstanding the insights calculations can provide, whatever information is obtained from a computational experiment must be considered with respect to the input. Solid state data are reassuring but also constitute a "best fit" situation. This is especially so for protein structures that are solved by model building rather than by direct methods.

When we obtained the solid state structure for **3**·KI, we found that the two pyrrole subunits of indole sandwiched the cation. Computational studies showed clearly that the benzene ring was the more electron rich subunit of indole. Studies with molecular models convinced us that there was no steric restriction, but clearly the calculations and the experimental results were not in accord.

We were able to prove the versatility of indole's pi-basicity by preparing the isomer of **3** in which the 2-carbon sidechain was attached at indole's 5-position rather than at the natural 3-position. In this study,[36] we prepared both the 15- and 18-membered macrocycles in which the ethylene sidearms were terminated by either 3- or 5-indoles. Solid state structures were obtained with Na^+ cation for both 15-membered rings and with K^+ for both 18-membered lariat ethers (Fig. 4). All four single-armed compounds formed complexes in which pi-stabilization of the ring-bound cation was obvious. When the arene was connected to the "natural" 3-position, the pyrrole residue served as the pi-donor. In contrast, the benzene ring was the pi-donor when the lariat ether's sidechain was attached at the 5-position.

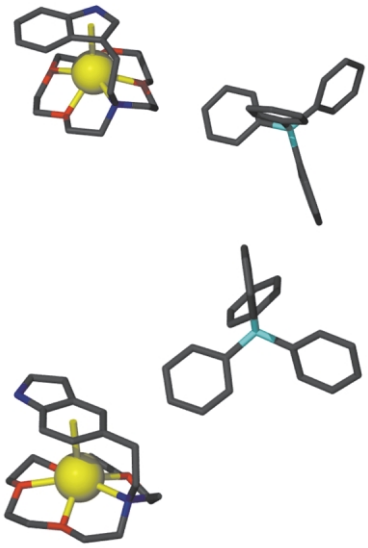


Fig. 4 Structures of $NaBPh_4$ complexes of *N*-(2-indolylethyl)-aza-15-crown-5, in which the ethylene sidearm is attached either at the 3- (top) or 5-position.

These observations strongly reinforce our view that tryptophan's indole is a versatile pi-donor. So far as is known, the indole residue is always attached at the 3-position in proteins but the sidechain is flexible. It should not be disturbing that the calculations and experiments do not agree. The experimental data simply reveal a greater versatility than was recognized by the computational studies.

Solution phase studies of cation–pi interactions

A concern is often expressed that gas phase studies are unrealistic because the solvation forces present in the liquid phase are not present. A similar argument has been made about computational studies. The question has also been raised about how realistic are the structures of single entities in an ordered crystal compared to a complex solution environment. Here the issue is crystal packing forces and a preference for interactions and conformations that lead to stable crystals rather than certain chemistry. These concerns are clearly valid as cautionary notes. The results obtained here and indeed, by all methods, should be considered in the light of current understanding but appreciated for what novel chemistry they may reveal.

Our goal was, if possible, to extend the computational results of others and our own solid state results to the solution phase. We therefore dissolved bis(indole) receptor **3** in CD_3COCD_3, a solvent of intermediate polarity that has often been used in complexation studies. We found from NMR experiments that nuclear Overhauser effects suggested a conformation for **3** essentially identical to that observed for the free receptor in the solid state. When an equivalent of NaI was added, the NOE results were consistent with the complex conformation identified in the solid state and shown in Fig. 1. A further study involved titration of the receptor with NaI. It was found that the proton attached to C-2 (the pyrrole residue) was shifted more than any other proton and it was shifted upfield, consistent with a cation–pi interaction.[28]

Beyond the essential amino acids

Life is dominated by the 20 essential amino acids, but hundreds of other amino acids occur in nature. We therefore felt it was reasonable to ask if the pi-complexing ability of phenylalanine, tyrosine, and tryptophan analogs could extend to other pi-systems. The obvious candidate is the simple double bond, which is ubiquitous in bilayer membrane systems. The triple bond, although less common, is also of obvious interest. We will note but not discuss these studies at length in this Feature because our focus here is the common amino acid sidechains.

It is worth recording that pi-interactions involving isolated double[37] and triple bonds[38] with sodium and potassium cations have been documented by using the lariat ether receptor system. Although numerous examples of olefin and acetylene interactions with various metals have been reported, we limit ourselves here to neutral double[37] and triple bonds[38] interacting with alkali metal cations. The two complexes illustrated in Fig. 5 show essentially the same behavior that was observed for the arene complexes. We infer from this that when alkali metal cations are present in a biological milieu, simple double bonds may interact with them to organize or stabilize the system. Such interactions are undoubtedly modest and will likely be dismissed by some readers. It should be noted, though, that C–H hydrogen bonding was not given much attention when Sutor suggested it, although numerous studies[2] now confirm it.

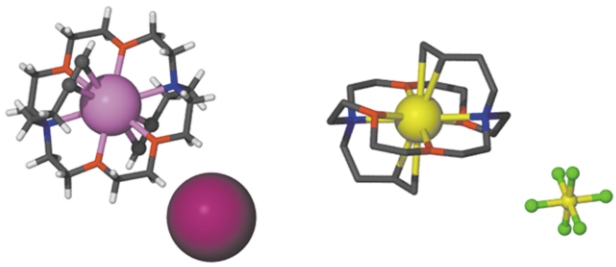


Fig. 5 Solid state structures of diaza-18-crown-6 derivatives having (left) $CH_2CH_2C{\equiv}CH$ and (right) $CH_2CH_2CH{=}CH_2$ sidechains. The complexed salts are (left) KI and $NaPF_6$.

Conclusions and extension to biological systems

The combination of studies by numerous groups that include computational, gas phase, solution phase, and solid state studies establishes beyond any doubt that cation–pi interactions can occur with biologically relevant metal cations and arenes. The studies are broader than this single conclusion but the lesson is clear as it currently relates to biology. The strengths of these interactions and how they are altered by dielectric or by the proximity of other donors that bifurcate the interaction all remain unknown. Conclusive evidence that such interactions can occur strongly implies that they do occur. There is no doubt that numerous cation–pi interactions will be revealed in biological systems as the resolution of crystal structures continues to improve and as deliberate searches are made for ions such as sodium that may previously have been identified as water.

For the supramolecular chemist, cation–pi interactions represent an additional feeble force that must be quantified and understood. Once such issues as the strength of interaction, the

preferred orientations, steric constraints, *etc.* are all identified, cation–pi interactions will enter the supramolecular chemist's toolbox. Equally important, though, the detailed understanding of such interactions will be critical for the biologist who will be thinking about exactly the same chemistry but in a different context.

Acknowledgments

Support of this project over a number of years by the NIH, NSF, and currently by the PRF is gratefully acknowledged. Many talented coworkers, whose names appear on the papers cited herein, have contributed to the success of this project. This effort could not have achieved the current level of success without close collaboration with Professor Leonard J. Barbour.

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