Qualifying Exam Question from Dr. Bau

One normally thinks of π-aromatic systems as nonpolar, hydrophobic entities, and cations as polar and hydrophilic. Thus, one would naturally expect that π-systems would repel cations, anions and other charged species. However, in recent years, Dougherty and other researchers have been arguing that, contrary to intuitive expectations, cations and π-systems actually attract each other, and moreover they claim that the strength on this interaction is surprisingly large in many chemical and biological systems [see *Science*, **271**, 163 (1996)].

       Critically comment on this subject and summarize the evidence in support of the existence of cation-π interactions. Is this claim generally accepted? Are there opposing points of view, and if so what is the evidence supporting the opposing point of view? Finally, give us your opinion. Let us know what you think, and why.

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The cation-π interaction has become recognized as an increasingly important non-covalent intermolecular force, especially in the realm of biology. For many years though, this interaction was suggested by gas phase studies[1] and computational analyses.[2] It was not until recently that supporting evidence in the condensed phases, both in solution and in the solid state, was brought into the light.

The major proponent of the cation-π interaction cause is Dennis A. Dougherty, who has written several reviews on the subject in recent years.[3,4] He states that the reason benzene is generally considered nonpolar is because it lacks a permanent dipole moment. It does though have a quadrupole moment of considerable magnitude.[5] Benzene and other π-aromatic systems have permanent, non-spherical charge distributions that can interact through electrostatic forces with opposing charges. Cation-π interactions are said to be very important in studies of protein binding pockets, in which many aromatic amino acid residues are located where positively charged species are bound or interact in some fashion.

One of the better examples of cation-π interactions in the solid state is the macrocyclic polyethers made by Gokel *et al.*,[6] the most interesting of which are shown in Figure 1. They synthesized 4,13-diaza-18-crown-6 receptor molecules that are related to the amino acids phenylalanine, tyrosine, and tryptophan. Crystal structures were obtained for the free receptors, except for the phenylalanine analog, which showed that the sidearms of the molecule were turned away from the macrocycle. Crystal structures of the receptors exposed to potassium iodide were also obtained. The bound receptors feature a potassium held by the crown ether with each of the sidearms extended up and over the cation with the arenes close enough to interact strongly with K^+. An interesting

observation was found in the indole system. The potassium is sandwiched between the

pyrrole subunit rather than the indole's benzene ring of each indole. In computational

studies, the predicted result was that potassium was sandwiched between the indole's

benzene rings, meaning that the benzene part was a better π-donor. Another important

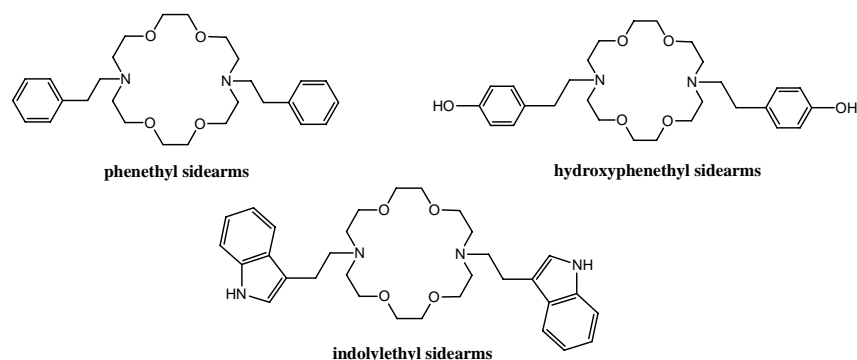point is the discrepancy between physical reality and computational studies.

phenethyl sidearms

hydroxyphenethyl sidearms

indolylethyl sidearms

Figure 1. Analogs of 4,13-diaza-18-crown-6.

In order to verify that the bound structures were due to electronic issues and not

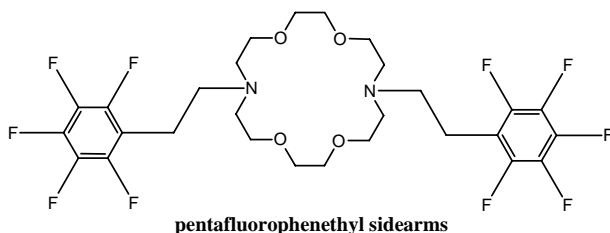just crystal packing forces, they made a decafluoromacrocycle (Figure 2). As they had

pentafluorophenethyl sidearms

Figure 2. Structure of decafluoromacrocycle.

hoped, when this macrocycle was complexed with KI, the pentafluorophenyl rings do not

participate in binding to the K^+. Thus, the π-donor effect of the arene electrons

determined the orientation of the sidearms. The bound structures of all of the

macrocycles are shown in Figure 3. In an earlier paper on the same structures by Gokel,

he states that one of his motivations was the lingering concern about whether the mass

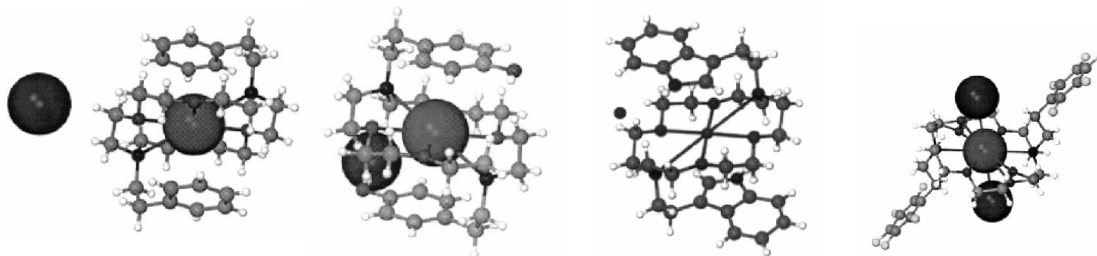spectral work in cation-π interactions accurately represented the situation outside of the

gas phase.[7]

Figure 3. Bound polyether receptors; arene groups are phenyl, hydroxyphenyl, indolyl, and pentafluorophenyl, going from left to right.

Few studies of the cation-π interaction seem concerned with what and where the

anion is. In recent work by Bartoli and Roelens,[8] they found that an adequate description

of the cation-π interaction in solution must take into account that the host-guest complex

is a three-partner system in which the actual cation-π interaction is substantially

modulated by the attraction exerted on the cation by the anion through a charge

polarization mechanism. They saw that weaker cation-π binding may reflect stronger

cation-anion attraction and vice versa.

In a computational study by Tsuzuki *et al.*,[9] they state that induction (polarization)

and electrostatic interactions are the major source of the attraction in Li^+, Na^+, and K^+ / π-

complexes, with induction being a significant contributor. Ma and Dougherty said that

electrostatic interactions played the major role and polarizability was not the defining

feature of the cation-π interaction.[10]

Cation-π interactions were postulated to determine the specificity of potassium

protein channels by Dougherty.[11] This hypothesis was tested by MacKinnon and

coworkers.[12] By means of site directed mutagenesis, they exchanged the tyrosine to

phenylalanine, keeping an arene group in the same position. Potassium selectivity was lost in the channel. The cation-π hypothesis was discounted.

An X-ray crystal structure of $K^+ B(C_6H_5)_4^-$ (Figure 4) is supposed to suggest a cation-π interaction with an alkali metal atom.[13] The K^+ is nestled between two phenyl rings of its anion, as well as two more phenyl rings of an adjacent anion. While appearing to be bound by four benzenes, it can be argued that the potassium is getting as close to the anion as it can get, and that the potassium is filling a void space rather than being complexed with the aryl groups.[14]
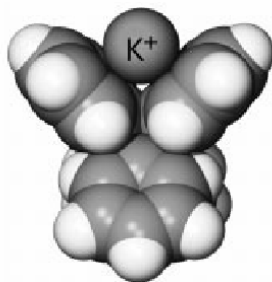

Figure 4. Crystal structure of $K^+ B(C_6H_5)_4^-$.

The cation-π interactions in the groove leading to the binding pocket of the acetylcholine receptor allows for stabilization as acetylcholine travels from the aqueous environment to the receptor site, where it is bound by polar amino acids.[15]

An *ab initio* study[16] suggests that cation-π interactions fall along the continuum of σ - π bondings of various types of electrophilic (cationic) acceptors with arene donors that were initially identified by Mulliken as charge-transfer. The formation of a π-complex precedes the formation of a σ-complex in the mechanism for electrophilic aromatic substitution (EAS), as shown in Figure 5.[17] Based on detailed studies of benzylations of benzene – toluene mixtures, Olah *et al.*[18] proposed that the transition states of these reactions displayed characteristics that ranged from weak π-complexes to
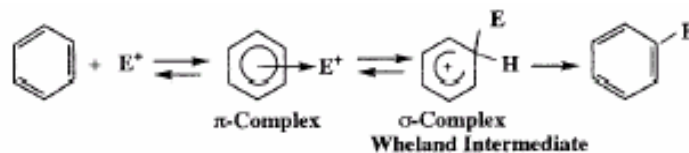
Figure 5. Mechanism for EAS.

strong σ-complexes. A set of X-ray crystallographic studies of metal ion complexes with hexakis(methoxymethyl)benzene confirms this continuum idea by finding potassium in a π-complex, and rubidium and cesium in σ-complexes.[19]

I think that cation-π interactions do exist, but they are only beginning to be understood. Like Gokel, I would be quite leery of their existence if the only proof was due to just mass spectrometry and computational studies. I think Gokel's work with his 18-crown-6 derivatives were convincing. Also, I can see how cations would be attracted to the quadrupolar nature of the arenes.

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