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The Cation–π Interaction

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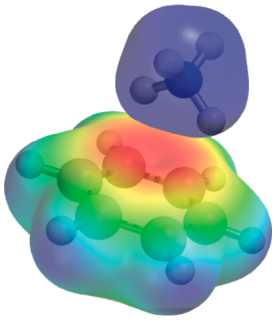

The chemistry community now recognizes the cation–π interaction as a major force for molecular recognition, joining the hydrophobic effect, the hydrogen bond, and the ion pair in determining macromolecular structure and drug–receptor interactions. This *Account* provides the author's perspective on the intellectual origins and fundamental nature of the cation–π interaction.

Early studies on cyclophanes established that water-soluble, cationic molecules would forego aqueous solvation to enter a hydrophobic cavity if that cavity was lined with π systems. Important gas phase studies established the fundamental nature of the cation–π interaction. The strength of the cation–π interaction (Li^+ binds to benzene with 38 kcal/mol of binding energy; NH_4^+ with 19 kcal/mol) distinguishes it from the weaker polar–π interactions observed in the benzene dimer or water–benzene complexes. In addition to the substantial intrinsic strength of the cation–π interaction in gas phase studies, the cation–π interaction remains energetically significant in aqueous media and under biological conditions. Many studies have shown that cation–π interactions can enhance binding energies by 2–5 kcal/mol, making them competitive with hydrogen bonds and ion pairs in drug–receptor and protein–protein interactions.

As with other noncovalent interactions involving aromatic systems, the cation–π interaction includes a substantial electrostatic component. The six (four) $C^{\delta-}$–$H^{\delta+}$ bond dipoles of a molecule like benzene (ethylene) combine to produce a region of negative electrostatic potential on the face of the π system. Simple electrostatics facilitate a natural attraction of cations to the surface. The trend for (gas phase) binding energies is $Li^+ > Na^+ > K^+ > Rb^+$: as the ion gets larger the charge is dispersed over a larger sphere and binding interactions weaken, a classical electrostatic effect. On other hand, polarizability does not define these interactions. Cyclohexane is more polarizable than benzene but a decidedly poorer cation binder.

Many studies have documented cation–π interactions in protein structures, where lysine or arginine side chains interact with phenylalanine, tyrosine, or tryptophan. In addition, countless studies have established the importance of the cation–π interaction in a range of biological processes. Our work has focused on molecular neurobiology, and we have shown that neurotransmitters generally use a cation–π interaction to bind to their receptors. We have also shown that many drug–receptor interactions involve cation–π interactions. A cation–π interaction plays a critical role in the binding of nicotine to ACh receptors in the brain, an especially significant case. Other researchers have established important cation–π interactions in the recognition of the "histone code," in terpene biosynthesis, in chemical catalysis, and in many other systems.

A Brief (Personal) History of the Cation–π Interaction

In 1981, Kebarle showed that K^+ binds to benzene with a $-\Delta H°$ of 19 kcal/mol, and K^+ binds to water with a $-\Delta H°$ of 18 kcal/mol.[1] An ion, naked in the gas phase and desperate for solvation, choosing between water with its lone pairs and large dipole moment and a hydrocarbon, chooses the hydrocarbon. Kebarle's analysis emphasized the electrostatic ion–quadrupole interaction to benzene and also the ion-induced dipole interaction.

The impact of these seminal observations emerged gradually on many fronts, but ultimately, gas phase data of this sort best reveal the essential nature of the cation–π interaction. Later, more advanced gas phase studies confirmed the preference of K^+ for benzene over water.[2,3] Many other ions and π systems have been studied,[4,5] with

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key $-\Delta H°$ values being 28 kcal/mol for Na^+ and a remarkable 38 kcal/mol for Li^+ binding to benzene. Binding energies to ethylene have also been determined (Li^+, 19 kcal/mol; Na^+, 12 kcal/mol, etc.).[6] In 1985, Meot-Ner and Deakyne published work that would prove to be especially relevant, showing that NH_4^+ and alkylammoniums including Me_4N^+ also bind well to benzene in the gas phase.[7,8] As noted above, these very large intrinsic binding energies set the cation–π interaction apart from other interactions involving π systems and lead to significant binding energies in solution and in biological systems.

In 1982 (unaware of Kebarle's work), we initiated a program to develop fully synthetic molecules that were water-soluble and had well-defined hydrophobic binding sites. Inspired by work on cyclodextrins and early studies of simple cyclophanes, we designed a series of cyclophanes, typified by structure **1** in Figure 1.[9] The ethenoanthracene unit of **1** enforced a rigid, concave aromatic surface and clearly separated the solubility-inducing carboxylates from the hydrophobic binding site. They also introduced chirality; **1** has D_2 point group symmetry. At the same time, François Diederich used similar principles to design and synthesize cyclophanes based on a diphenylmethane with a spirocyclic ammonium group for solubility.[10]

Both groups found that such cyclophanes could pull very hydrophobic molecules like pyrene out of water and into the hydrophobic cavity. Diederich went on to perform a series of important experiments on the role of solvent in such complexation[11] and used the spirocyclic cyclophanes as a platform to develop novel catalysts and to learn much about molecular recognition.

While binding pyrene was interesting, we viewed its interaction with **1** more as solvent repulsion than molecular recognition. We thus sought guest molecules that were substantially water-soluble but that could be coaxed out of water and into the binding site. Recalling that many phase transfer catalysts, molecules that are comfortable at the organic–water interface, are quaternary ammonium compounds, we thought that perhaps a quat would be a good starting point. On the basis of sophisticated modeling strategies (i.e., hand-held space-filling (CPK) models), we settled on adamantyltrimethylammonium, ATMA. Indeed, ATMA binds very well to **1** with $-\Delta G° = 6.7$ kcal/mol and $K_D = 12\ \mu$M.[12] The very distinctive NMR shifts induced by binding (a big advantage of working with cyclophanes) established a binding geometry just as predicted by the CPK models. These were impressive binding numbers for a freely soluble guest, and our 1986 paper on the subject

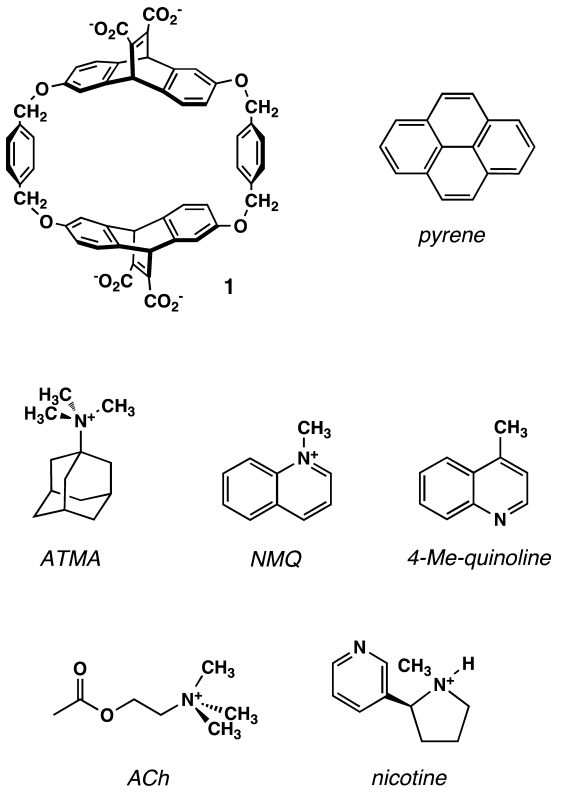

FIGURE 1. Structures discussed in text.

focused on the fact that ATMA was water-soluble and also not a flat aromatic compound, unique results for cyclophane binding at the time.

Based on the ATMA results, we considered other "quaternized" guests. We found that **1** bound many compounds of this sort, an especially favorable case being *N*-methylquinolinium (NMQ, Figure 1), which showed $-\Delta G° = 8.4$ kcal/mol and $K_D = 600$ nM in aqueous media. We were amazed to see that 4-methylquinoline, which is almost identical to NMQ in size, shape, and hydrophobic surface area but is, of course, neutral and hydrophobic, was a *much weaker* binder ($-\Delta G° = 5.9$ kcal/mol; $K_D = 47\ \mu$M). At this point, we realized that the positive charge was playing an important role in recognition.

In 1987, we submitted a paper on NMQ and other cationic guests, which showed that it was specifically the aromatic rings of the cyclophane that were recognizing the positive charge. While the paper was under review, the accomplished protein crystallographer Greg Petsko visited Caltech, and I asked him if he had ever seen anything like this. Of course, he responded yes and pointed us to the 1986 Burley–Petsko paper on the "amino–aromatic" interaction.[13] In responding to referee's comments concerning our NMQ paper, we added references to the Burley–Petsko

paper (and Meot-Ner), and we termed the effect an "ion–dipole" interaction.[14]

The amino–aromatic interaction evolved from seminal observations of Perutz, who in 1986 noticed in a protein crystal structure that the amide NHs of an asparagine were in close contact with the face of a benzene ring, an arrangement "suggestive of a hydrogen bond".[15] Pertuz and Levitt followed up on this with a paper entitled *Aromatic Rings as Hydrogen Bond Acceptors*,[16] which further documented attractive interactions between polarized bonds and the face of an aromatic ring.

At the suggestion of Perutz, Petsko and Burley launched a search for similar interactions in protein crystal structures.[13] They evaluated 33 high-resolution structures (the PDB has grown a bit since then!) looking to see whether an NH group from the side chains of asparagine, glutamine, histidine, arginine, or lysine had a propensity to be near the face of the aromatic ring of phenylalanine, tyrosin, or tryptophan. Such a tendency was found, and the authors favored the electrostatic interpretation of Meot-Ner and Kebarle.

Subsequent analysis of protein crystal structures by Thornton established that amino–aromatic interactions in which an NH points into the face of an aromatic ring are, in fact, "remarkably rare".[17] In most instances, an sp^2 NH that is near an aromatic is stacked, and the NHs make conventional hydrogen bonds. Nevertheless, the work of Petsko and Burley played a key role in alerting the structural biology community to potential polar interactions involving aromatic rings. In hindsight, we suspect that one factor that could have compromised the Burley/Petsko analysis was the aggregation of data involving the neutral side chains of asparagine and glutamine with data involving the cationic side chains of arginine and lysine. Asparagine and glutamine can only make polar–π interactions, while arginine and lysine can participate in much stronger cation–π interactions.

Meanwhile, we were now in full "quat-binding" mode with our cyclophane receptors, and we published scores of binding constants, establishing that **1** was a general receptor for $RNMe_3^+$ compounds, alkylated quinolines, and other heterocycles, sulfonium compounds, guanidinium compounds, and so on.[18,19] We also showed that **1** would catalyze the Menschutkin reaction of methyl iodide with quinoline to make NMQ[20,21] and the reverse reaction (conceptually), the dealkylation of sulfonium compounds by strong nucleophiles.[20]

By 1990, we realized that "ion–dipole" was not really an appropriate descriptor for the effects we were seeing, and we proposed the term "cation–π interaction".[21,22] This served to distinguish the binding of full ions from the weaker binding of neutral polar molecules. Also, since ethylene binds cations through the same mechanism and since aromaticity is certainly not the defining feature of the binding interaction, we felt that "π" was preferable to "aromatic".

With **1** established as a general binding site for $RNMe_3^+$ compounds, we asked whether there were any biologically important molecules of this sort. It was not hard to find acetylcholine (ACh), the longest-known, best-studied neurotransmitter. We showed that **1** bound ACh well, and in 1990, based on that observation and a survey of the limited information then available on ACh binding sites, we predicted that ACh would bind to proteins through a cation–π interaction.[23] One year later, Sussman and Silman published the first crystal structure of a protein that binds ACh, the acetylcholine esterase.[24] It was literally textbook knowledge at the time that the esterase contained an "anionic subsite" that binds the positive charge of ACh. However, there was no such anion in the esterase structure, and instead the quat of ACh sits directly on the face of the indole ring of a conserved tryptophan. There was proof that Nature used a cation–π interaction to bind an important small molecule.

We became obsessed with the notion that Nature would use the cation–π interaction to bind ACh and perhaps other cationic guests, and we were especially intrigued with the role the cation–π interaction might play in neurobiology. We read and learned a great deal about the state of molecular neurobiology in the early 1990s, greatly aided by my colleague Henry Lester in Caltech's biology division. This ultimately lead to the fruitful and ongoing collaboration with Professor Lester involving unnatural amino acids that has provided some of the most compelling evidence for cation–π interactions; more about that later.

We end this section by bringing the history full circle. The Burley–Pestko analysis was crucial to our work, but in the end it did not settle the question of the role (if any) of cation–π interactions in protein structures. In 1999, we revisited this question, making two key methodological changes.[25] First, we considered only cationic side chains and thus evaluated solely Arg/Lys···Phe/Tyr/Trp. Also, while most statistical analyses of protein structure employ a geometry-based criterion, we chose not to do so. Instead we developed an energy-based criterion, evaluating all possible cation–π interactions to determine whether they make a significant energetic contribution to protein stability. We evaluated 593 high-resolution, nonhomologous protein

structures and found that there is 1 cation–π interaction for every 77 residues in the Protein Data Bank. That means there are over 500 000 cation–π interactions in the PDB today. Remarkably, 25% of all tryptophan residues experience an energetically significant cation–π interaction to an arginine or lysine of the protein. The program CAPTURE can perform these energy-based evaluations for any pdb file, and it is available on the web (capture.caltech.edu). Other statistical analyses have appeared, including one that shows that cation–π interactions are especially prominent at protein–protein interfaces, with half of protein complexes and one-third of homodimers containing at least one intermolecular cation–π interaction.[26]

The Electrostatic Model

The electrostatic model originally proposed by Kebarle has come to be accepted as defining the fundamental nature of the cation–π interaction. A general electrostatic model for interactions involving π systems was championed in early work by Hunter and Sanders.[27] For the cation–π interaction, we do not mean to imply that other forces such as dispersion and ion-induced dipole interactions do not contribute to the binding energy to significant degrees. It is simply that analysis of possible electrostatic interactions generally provides excellent guidance when considering a potential cation–π interaction. For example, we used computational studies to show that, across a series of simple π systems, 100% of the *variation* in binding energy resulted from variation in the electrostatic component of the interaction, when Na^+ was the probe cation.[28] We also suggested that simple electrostatic potential surfaces of the π system provided good, qualitative guidance as to the potential strength and geometry of a cation–π interaction.[19,29] More recent, more advanced calculations have led to new views as to how substituents on a π system impact a cation–π interaction, but electrostatics still play a key role.[30]

We noted above how a region of negative electrostatic potential is created above simple π systems by the C–H bond dipoles, which in turn arise because sp^2 carbon is more electronegative than hydrogen. In simple high-symmetry molecules, the bond dipoles lead to a molecular quadrupole moment, which can also serve as a useful guide to predicting cation–π interactions.

Given this analysis, perhaps we should substitute the term "ion–quadrupole interaction" for cation–π interaction. However, this would ignore the other factors such as dispersion and ion-induced dipole interactions that can be

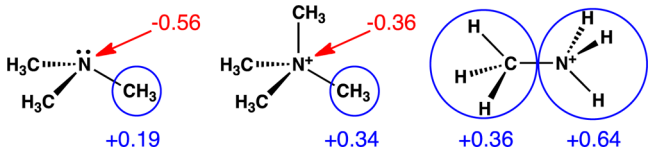

FIGURE 2. Charge distributions in representative structures. HF-6-31G**, natural charge distributions.

significant contributors to the binding energy. More importantly, the term ion–quadrupole implies a very specific distance dependence, and the cation–π interaction does not follow that distance dependence. The distance dependence of the cation–π interaction is in fact relatively shallow, so moving a cation slightly away from its optimal position (van der Waals contact) is not energetically costly.[31]

We noted above how larger ions produce a weaker cation–π interaction; Rb^+ is a weaker binder than Li^+, a classical electrostatic effect. In this light, the binding energies for NH_4^+ and NMe_4^+, 19 and 9 kcal/mol, fit right in. K^+ and ammonium have the same cation–π binding energies, and they have similar ionic radii; they have essentially the same hydration energies; and in biology, ammonium can often pass through K^+-selective channels. To first order, tetramethylammonium is just a bigger ion, and so its binding energy is weaker. Of course, a tetramethylammonium ion is more polarizable than Li^+, so polarization effects will contribute more to the binding energy. But overall, the electrostatic model provides excellent guidance. We see no value in terms like "NH–π" and "CH–π" for ammonium systems; they are just cation–π interactions.

Speaking of tetramethylammonium, despite over 20 years of discussing the cation–π interaction, there is still an aspect of it that is not fully appreciated by most biologists and by many chemists. Consider trimethylamine (Figure 2). There are many ways to partition charges in molecules, and without getting into a debate as to the merits of each, all agree that the nitrogen carries a partial negative charge and the methyls (actually the hydrogens on the methyls) carry compensating positive charges. Nitrogen is more electronegative than carbon. Now consider tetramethylammonium. We teach freshmen that the + charge on N is a *formal charge*. It does not mean that the N is charged. The physics of the universe did not change when we alkylated the N; nitrogen is still more electronegative than carbon. In tetramethylammonium, *the positive charge is on the methyl groups* (Figure 2). When a quaternary ammonium like ACh makes a cation–π interaction, it is because the methyl groups contact the π system.

What about a more typical biological cation, such as the RNH_3^+ groups seen in lysine or the neurotransmitters GABA, serotonin, dopamine, etc.? Certainly, the $-NH_3^+$ group carries a very significant charge, but the adjacent CH_2 group carries a charge comparable to that of the methyls of tetramethylammonium (Figure 2). Thus, cations like these can make a cation–π interaction two ways: with the ammonium group or with the carbon next to the ammonium. In the Protein Data Bank, we see lysine engaging in both kinds of interactions, with the interaction to carbon actually being more common.[25]

The Magnitude of the Cation–π Interaction

How much can a cation–π interaction contribute to the binding of a drug or the stabilization of a protein? This is a challenging question for any weak, noncovalent interaction, as the value depends strongly on the choice of reference state and the context within which the measurement is made. Several studies of model systems have addressed this question, as summarized in recent reviews;[32−34] here we focus on studies of proteins binding a drug or substrate. In a series of insightful experiments, Diederich quantitatively evaluated cation–π interactions for drugs binding in the aromatic-rich S4-pocket of factor Xa. It was determined that the cation–π interaction increased binding by 2.8 kcal/mol.[35] This is similar to what we had earlier seen in the binding of NMQ vs 4-methylquinoline to cyclophane **1**.[14] A similar strategy was employed by Schultz, comparing the binding of a sulfonium ion vs the (neutral) carbon analogue to a cluster of aromatics in staphylococcal nuclease.[36] The cation–π interaction was considered to contribute 2.6 kcal/mol to the binding interaction. Based on these and other studies, Diederich concluded that "the cation–π interaction is one of the strongest driving forces in biological complexation processes".[33]

Another way to quantitate a cation–π interaction is to compare tryptophan to 4,5,6,7-tetrafluorotryptophan (F_4-Trp) when binding a cationic drug in a protein binding site. In F_4-Trp, the electrostatic component of the cation–π interaction has been completely removed, while other structural features are intact (phenylalanine vs 3,4,5-triflourophenylalanine (F_3-Phe) provides a similar comparison for phenylalanine or tyrosine systems).[37,38] In this comparison, solvation effects are minimized because the drug is not changed, and we are considering solely the difference in binding when the cation–π interaction is or is not present (or actually, the electrostatic component of the cation–π interaction). We have measured this ratio for over 30 binding interactions of small molecules to proteins. For the prototype quat, ACh, the F_4-Trp to tryptophan ratio ranges from 50 to 500 across several different proteins, with the latter value corresponding to a $-\Delta G^\circ$ of 3.7 kcal/mol. For other drug–receptor combinations, larger values have been measured, with the largest ratio that we have seen being over 10 000 for glycine binding to its cognate receptor, corresponding to a $-\Delta G^\circ$ of 5.5 kcal/mol. All these data indicate that the cation–π interaction can contribute greatly to drug binding, making it easily competitive with other noncovalent binding forces.

Cation–π Interactions in Neurobiology

As noted above, our cyclophane work naturally led us to the neurotransmitter ACh. We became convinced that Nature would use a cation–π interaction to bind ACh and perhaps other cations, but we were unsure how to prove it. Crystallography is great, but simply seeing a contact in a crystal structure gives no sense of the energetic contribution of the interaction. Also, our interest had migrated to neuroscience, and in the early 1990s, there were no structures of the large, complex integral membrane proteins that play the central role in neurobiology. We needed a different strategy.

In 1995, through a large collaborative effort, *in vitro* methodology developed by Schultz was adapted to achieve the first site-specific incorporation of an unnatural amino acid into proteins expressed in a living cell.[39] The cell was not *Escherichia coli* or yeast, but a vertebrate cell, the *Xenopus laevis* oocyte. The complex proteins of the mammalian nervous system are generally not amenable to expression in bacteria or yeast; a vertebrate cell is required. Since the receptors of interest to us were ion channels, the powerful tools of electrophysiology could be brought to bear. In collaboration with Henry Lester, we could now bring the methodology and mindset of physical organic chemistry to the complex receptors and ion channels of neuroscience.

A few years later, we had our tool for discovering cation–π interactions. We noted above that fluorine is deactivating for a cation–π interaction.[28] Importantly, progressive fluorination has an additive effect on the cation–π binding ability of the ring. With the unnatural amino acid methodology, we could take any phenylalanine, tyrosine, or tryptophan and replace it with the monofluoro-, difluoro-, trifluoro-, etc. derivatives. Remarkably, for specific residues at the binding sites of many proteins, we see a linear correlation between the attenuation of the potential

cation–π binding ability of the residue by fluorination and the function of the receptor or binding of an appropriate ligand. We mentioned above the tryptophan to F_4-Trp comparison. We only would consider such a comparison if it is part of a full linear "fluorination plot".

Our first linear fluorination plot was for a particular tryptophan of the nicotinic acetylcholine receptor (nAChR), the prototype neurotransmitter-gated ion channel.[40] ACh is the natural ligand, but the receptor is also activated by nicotine and similar compounds. The nAChR is the parent of a family of so-called pentameric receptors that includes receptors for serotonin, GABA (γ-aminobutyric acid), and glycine, and we obtained linear fluorination plots for all of these.[41] The 2011 crystal structure of another member of the family, GluCl,[42] clearly shows a cation–π interaction to the agonist, glutamate.

The cation–π interaction also plays a critical role in nicotine addiction, which begins when nicotine binds to and activates nAChRs in the brain. However, nAChRs are also found at the neuromuscular junction; every voluntary muscle movement begins with ACh being released from a nerve and activating a nAChR in the muscle. Why then, do smokers not twitch, or worse? It turns out that the cation–π interaction between the receptor and nicotine is strong for receptors found in the brain but weak or nonexistent for receptors at the neuromuscular junction, even though the critical tryptophan residue is present in all receptors.[43] The difference can be traced to a single residue that actually lies outside the agonist binding site. When it is a glycine, nicotine cannot make the cation–π interaction and so is a weak activator of the receptor. With any other amino acid at this site (it is lysine in brain receptors), nicotine makes the cation–π interaction and is potent. In fact, some people have a mutation at this site of the nAChRs of their neuromuscular junction, and they suffer from a myasthenic syndrome.[44]

It's Not Just Quats

While our cyclophane work emphasized alkylated cations and our first biological studies were on ACh, there is ample evidence that all types of cations can participate in cation–π interactions under biologically relevant conditions. In our own work, we have seen strong cation–π interactions for many other types of structures, including serotonin, GABA, glycine, nicotine, epibatidine, varenicline (Chantix), ondansetron (Zofran), granisetron (Kytril), tetrodotoxin, lidocaine, and others. And, of course, the over 500 000 cation–π interactions in the PDB mentioned above have lysine or arginine as the cation, not quats.

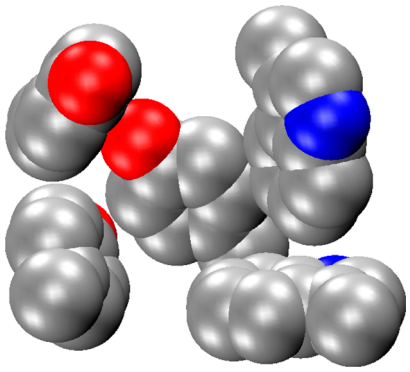

FIGURE 3. The aromatic box from AChBP (pdb file 1I9B).

Even small metal ions can experience cation–π interactions. Select well-documented examples include a Na^+–phenylalanine complex in T1 lipase, which has been observed structurally and characterized by MD simulations,[45] Ca^{2+} blockade of a Na^+ channel,[46] a strong cation–π interaction between a tryptophan ring and Cu^{1+} in the CusF protein,[47] and many examples of simple metals or cationic amino acids binding to the bases of nucleic acids.[48] Synthetic systems that combine a crown ether and a π system provide excellent binding sites for alkali metal cations.[49]

The Aromatic Box

When we designed cyclophane **1**, we certainly were not mimicking any biological receptor. However, it turns out there is a recurring motif in structural biology that is similar to **1** and related molecules. This motif has been termed the "aromatic box", and perhaps the best example brings us back to the ACh receptor. In 2001, the ACh binding proteins (AChBPs), small, soluble proteins that are 20–25% homologous to the agonist-binding domain of nAChRs, were described.[50] The tryptophan that we had identified by fluorination of the nAChR three years earlier[40] was indeed at the agonist binding site, and this tryptophan makes a cation–π interaction to ligands bound to the AChBPs.

The AChBP structure also revealed a remarkable structural motif. Five highly conserved residues, three tyrosines and two tryptophans, form an "aromatic box" that defines much of the agonist binding site and binds the cationic moiety of ACh and other small molecules (Figure 3). It is conserved across the pentameric receptor family, and all natural agonists make a cation–π interaction, although different drug–receptor pairs can use different members of the box. In addition, some agonists make cation–π interactions with

more than one member of the box (always two residues that are quite near each other). The aromatic box is very accommodating to a positive charge.

More remarkably, the aromatic box has shown up in other completely unrelated proteins. Many examples have been documented in recent reviews.[32,33,35] In a very recent example, another protein that binds ACh, the M2 G-protein coupled receptor (GPCR), has been shown to possess an aromatic box, in what has been termed a "striking example of convergent evolution".[51]

Other Examples

In an Account like this, it is neither possible nor appropriate to present a comprehensive catalogue of examples of cation–π interactions. There are thorough discussions elsewhere,[4,31−33,52] and new examples are appearing literally every week; we apologize to the authors of many beautiful examples that space limitations prevent us from mentioning. Here we present a few examples that are especially compelling.

Cation–π interactions and an aromatic box have been clearly established to play an important role in the critical process of recognizing posttranslational modifications of chromatin proteins that contribute to the "histone code" that regulates gene expression. Exposed lysine residues on histone proteins H3 and H4 are methylated to form both trimethyllysine ($RCH_2NMe_3^+$) and dimethyllysine ($RCH_2NHMe_2^+$) structures. A "common and striking feature of methyllysine reader domains is the positioning of the methylammonium moiety within an aromatic cage consisting of two to four aromatic residues".[53] Clever studies by Waters showed that a t-butyl group cannot substitute for the $-NMe_3^+$ group, establishing that it is a cation–π interaction, not a hydrophobic effect, that is controlling this key interaction.[54]

It has been appreciated for some time that the (cationic) 7-methylguanosine that caps the 5′ end of eukaryotic mRNAs is bound by various initiation factors through cation–π interactions. Beautiful crystal structures reveal a sandwich of two aromatic amino acids from the protein around the methyl-G.[55,56]

Cation–π interactions are a ubiquitous feature in terpene cyclases, the enzymes responsible for the formation of steroids and countless other ring systems via cationic cyclization of polyisoprenoid substrates. Many structural studies find multiple aromatic amino acids at active sites, and these π systems stabilize specific high-energy carbocation intermediates, guiding the cyclization to form the desired product.[57] Fluorinated phenylalanine derivatives have been incorporated into a squalene–hopene cyclase, providing clear evidence of the catalytic importance of the cation–π interaction.[58]

In plants, the photoreceptor UVR8 responds to UV–B light (280–315 nm) by triggering the expression of more than 100 genes. The protein in its inactive form is a homodimer. Critical arginines at the dimer interface make elaborate cation–π interactions with surrounding tryptophans, including two tryptophans that together serve as the UV sensor. Absorption of UV light by these tryptophans disrupts the cation–π interactions; this in turn disrupts *inter*subunit ion pairs involving the arginines, destabilizing the dimer. The dimer dissociates, and this initiates the signaling process.[59,60]

Many examples of chemical catalysis that exploit cation–π interactions have been reported. For example, Jacobsen has developed organocatalysts for two bioinspired reactions: cationic polycyclizations[61] and a Claisen rearrangement.[62] In both cases a key cation–π interaction is necessary for optimal yields and enantioselectivities.

Conclusion

The cation–π interaction is now appreciated to be an important factor in molecular recognition and catalysis in chemistry and biology. We hope this Account has provided some sense of the nature and origins of the cation–π interaction, as well as its impact across broad areas of chemistry and biology.

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BIOGRAPHICAL INFORMATION

Dennis Dougherty received his B.S. and M.S. degrees from Bucknell University and his Ph.D. from Princeton University, and he did postdoctoral work at Yale University. He is currently Professor of Chemistry at Caltech.

FOOTNOTES

The authors declare no competing financial interest.

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