# Cation-π Interactions in Chemistry and Biology: A New View of Benzene, Phe, Tyr, and Trp

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Cations bind to the π face of an aromatic structure through a surprisingly strong, noncovalent force termed the cation-π interaction. The magnitude and generality of the effect have been established by gas-phase measurements and by studies of model receptors in aqueous media. To first order, the interaction can be considered an electrostatic attraction between a positive charge and the quadrupole moment of the aromatic. A great deal of direct and circumstantial evidence indicates that cation-π interactions are important in a variety of proteins that bind cationic ligands or substrates. In this context, the amino acids phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp) can be viewed as polar, yet hydrophobic, residues.

Noncovalent intermolecular forces play a major role in determining the structures of biological macromolecules and in mediating processes such as receptor-ligand interactions, enzyme-substrate binding, and antigen-antibody recognition. Although the hydrophobic effect, hydrogen bonding, and ion pair (salt bridge) interactions have been extensively studied and discussed, there is another important but generally underappreciated noncovalent binding force. Cations, from simple ions like $Li^+$ to more complex organic structures like acetylcholine (ACh), are strongly attracted to the π face of benzene and other aromatic structures (Fig. 1). Several features distinguish this cation-π interaction from other noncovalent binding forces and make it especially well suited to novel types of biological binding.

An overview of research efforts from my labs and many other groups is presented here that delineates the scope and importance of cation-π interactions. Fundamental gas-phase ion studies have led to a model for the physical origin of the effect and suggest a new way of looking at benzene and other aromatic systems. Studies of organic model systems, coupled with a wide range of results from structural biology, have established the relevance of cation-π interactions to biological recognition through interactions with aromatic side chains from the amino acids Phe, Tyr, and Trp.

Most important, not only can a binding site made up of aromatic rings bind cations, it also can compete with the highly favorable solvation of an ion provided by an aqueous medium. Hence, binding sites can be created that are in one sense polar (in that they are able to bind ions) yet are overall hydrophobic (being composed of hydrocarbon units). This combination of properties is especially well suited to the interior of a protein or a cell membrane, environments in which cation binding by conventional ion pairing may not be feasible. To document such behavior, I briefly describe a number of biological structures in which cation-π interactions are known to be important. It is not my intention to present an exhaustive list of all possible cation-π interactions, but rather to describe some representative examples that illustrate this phenomenon.

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## The Fundamental Interaction: Gas-Phase Studies

Benzene is the prototype aromatic system and the starting point for understanding the side chains of Phe, Tyr, and Trp (*1*). Simple cations interact very strongly with benzene (Fig. 1), as demonstrated by gas-phase, ion-molecule binding studies (*2*). The magnitude of this interaction varies considerably with the nature of the ion, such that $Li^+$, $Na^+$, $K^+$, and $Rb^+$ show binding enthalpies of 38, 28, 19, and 16 kcal/mol, respectively (*2–6*). These very large affinities are competitive with the strongest known nonbonding interactions. The binding sequence is a classical electrostatic trend in which the smaller ions are more tightly bound. More complex cations also bind well to benzene; $NH_4^+$ and $N(CH_3)_4^+$ show binding enthalpies of 19 and 9 kcal/mol, respectively (*7*). What is the origin of such noncovalent interactions? Certainly, many effects are involved, and a complete quantitative analysis of a cation-π interaction would have to consider them all. However, a viable qualitative model can be developed by emphasizing very simple electrostatic effects.

Benzene is generally considered a nonpolar molecule because it does not have a permanent dipole moment. It does, however, have a quadrupole moment (Fig. 2) (*8*) that is quite substantial in magnitude (*9*). That is, benzene has a permanent, nonspherical charge distribution (Fig. 2) that is expected to interact with appropriately positioned charges through electrostatic forces. A convenient visualization tool is a plot of the electrostatic potential surface of the molecule (Fig. 2).

Chemists and biologists often invoke dipole moments to explain a large number of phenomena related to molecular recognition, especially in aqueous media; quadrupole moments are often not a major consideration (*10*). However, according to classical calculations that consider only electrostatics, a point charge is stabilized just as much by a model quadrupole similar in magnitude to that of benzene as it is by a model dipole similar in magnitude to that of water (*11, 12*). Does this imply that benzene should compete with water in binding simple ions? Yes, in the gas phase. Kebarle and co-workers showed as early as 1981 that the $K^+$-water interaction is worth 18 kcal/mol versus 19 kcal/mol for $K^+$-benzene (*2*). In the gas phase, a cation, given a choice between water (with its large dipole moment and oxygen lone pairs) and benzene (a "nonpolar" hydrocarbon), in fact chooses the hydrocarbon (*13*). If polarizability and dispersion forces were dominating the cation-π interaction, larger ions like $Rb^+$ or $N(CH_3)_4^+$ might be expected to bind bet-

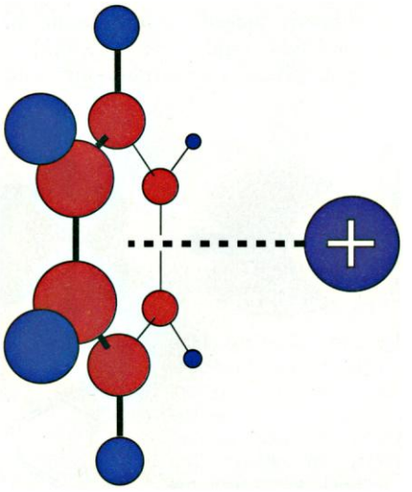

**Fig. 1.** The cation-π interaction, showing a generic positive charge interacting with benzene (hydrogens are blue, carbons red). The interaction geometry along the sixfold axis is consistent with a large number of calculated structures for such species (*2, 4, 7*).

ter, but in fact $Li^+$ is most tightly bound, consistent with the greater importance of electrostatics (*14–17*).

Perhaps, then, the term cation-π should be abandoned, and we should talk simply of ion-quadrupole interactions. This viewpoint is not advisable for two reasons. First, electrostatics are only part, albeit a major part, of the story. Modern theory clearly indicates that cation-π interactions cannot be quantitatively modeled unless additional terms, such as induced dipoles, polarizabilities, dispersion forces, and charge transfer, are included (*18*). Second, the term ion-quadrupole has very specific implications with regard to the distance dependence of the interaction. The stabilization energy of an ion-quadrupole interaction is expected to drop off as $1/r^3$, where $r$ is the distance between the ion and the quadrupole. However, the cation-π interaction definitely does not show such a distance dependence (*19*) but rather exhibits a $1/r^n$ dependence, with $n < 2$ (*20*), that more closely resembles a Coulombic ($1/r$) interaction. As such, the more descriptive term cation-π is a better way to identify the stabilizing interaction between a positive charge and the π face of an aromatic system, with the understanding that electrostatic interactions with the quadrupole charge distribution of the aromatic are of prime importance. Interest in electrostatic interactions has increased in recent years (*21*), especially with regard to biological macromolecules (*22*). In such structures, the quadrupole moment of aromatics could contribute to the electrostatic picture, and this should be accounted for in high-resolution studies.

If benzene can bind positive charges, then it should also bind partial positive charges, that is, molecules with highly polarized bonds. Indeed, polar molecules like $H_2O$ and $NH_3$ bind to benzene (*23*). As expected, these interactions are much weaker than a full cation-π interaction; $H_2O$ and $NH_3$ show binding energies to benzene of 1.8 and 1.4 kcal/mol, respectively. Similarly, the well-known T-shaped geometry of the benzene dimer must have a substantial electrostatic component (*24*). These weaker interactions are quite interesting and important, but are not the major focus of this work.

## Model Studies in Aqueous Media

In the early 1980s, my group initiated studies of a series of water-soluble "hosts," cyclophane molecules that were intended to mimic the binding properties of biological receptors (Fig. 3) (*25*). On the basis of earlier studies that suggested that aromatics were especially well suited to hydrophobic binding, aromatic rings were used to define the "walls" of the host (*25*, *26*). These cyclophane structures bind quaternary ammonium compounds with unexpectedly high affinities. Quantitative studies showed that a major factor in the binding was the favorable interaction between the positive charge of the "guest" molecule and the electron-rich aromatic faces of the walls of the host (Fig. 3). A number of other artificial receptor systems that bind cations through cation-π interactions have since been observed (*27*).

The most important feature of this work was that the binding of cations occurred in aqueous media. That is, these simple receptors could pull a cation out of water and into a hydrophobic, nominally nonpolar environment. Recall that in aqueous media, noncovalent interactions must compete with the substantial solvation energy of ions and polar groups. This "desolvation penalty" is the reason why surface-exposed hydrogen bonds and ion pairs often contribute very little to protein stability in water (*28*); the energy gain from forming a hydrogen bond or ion pair between two polar groups is not enough to compensate for the loss of solvation energy of the two groups. The desolvation penalty can be paid by the energy of protein folding, which can remove the polar groups from exposure to water. Even very weak interactions can be important in this context. Such compensation is not possible, however, with the much smaller artificial receptors of Fig. 3. Our results thus suggested that the magnitude of the cation-π interaction could be quite substantial in favorable systems, and that the interaction may function in the aqueous medium of a living cell.

The same hosts can also function as catalysts for certain types of organic reactions (*29*). Such hosts accelerate reactions that involve the creation of a positive charge and reactions in which a positive charge is formally destroyed. These findings suggested that the polarizability component of the cation-π interaction plays a more prominent role in catalysis (*29*). As discussed below, these observations also may be of considerable importance for certain types of biological catalysis.

## Cation-π Interactions in Biological Structures

The gas-phase and model studies paint a remarkable picture of benzene. It can provide a potent binding site for cations, one that under favorable conditions can even compete with an aqueous environment. Yet benzene is a hydrophobic structure, and it is more likely to be found in the interior of a protein or embedded in a membrane. In proteins, the usual cation-binding structures are the side chains of Asp and Glu. These contain carboxylic acids that are expected

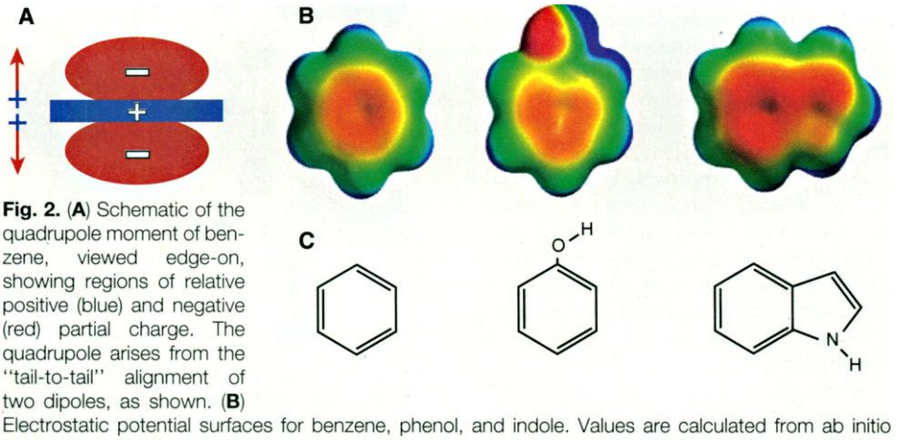


**Fig. 2.** (**A**) Schematic of the quadrupole moment of benzene, viewed edge-on, showing regions of relative positive (blue) and negative (red) partial charge. The quadrupole arises from the "tail-to-tail" alignment of two dipoles, as shown. (**B**) Electrostatic potential surfaces for benzene, phenol, and indole. Values are calculated from ab initio 6-31G** calculations [see (*26*) for details] and are color-coded from red (−25 kcal/mol) to purple (+25 kcal/mol). (**C**) Structures of benzene, phenol, and indole, the aromatic components of Phe, Tyr, and Trp, respectively.

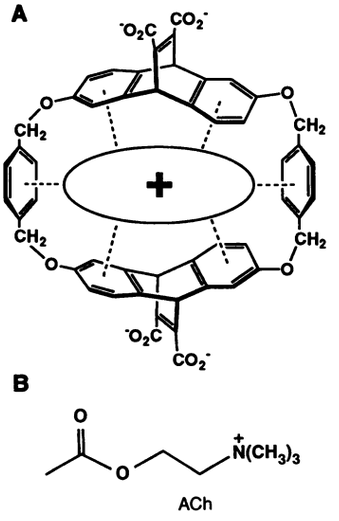


**Fig. 3.** (**A**) Water-soluble cyclophane host binding a generic cationic guest. (**B**) Structure of ACh, a strong-binding guest.

to ionize to anionic carboxylates in an aqueous environment. However, it is not obvious that a carboxylic acid will be ionized when it is not exposed to water. Here, nature might need a different kind of cation-binding site, a "hydrophobic anion," for which the obvious candidates are the side chains of Phe, Tyr, and Trp (Fig. 2) (*2*).

Other researchers have also considered nontraditional roles for aromatic residues in protein structures. In 1986, Perutz *et al.* documented a "hydrogen bond" from an amide NH to a benzene ring of a bound drug (*30*). Burley and Petsko described the "amino-aromatic" interaction, which they based on a statistical tendency of side chain NH groups to be positioned near aromatic residues, and provided a lucid analysis of other "weakly polar" interactions (*31*). More recent work suggests that amino-aromatic interactions involving NH groups from the neutral side chains of Asn and Gln may not be very substantial contributors to protein stability (*32*). This result is perhaps not surprising, given the relatively weak intrinsic attraction of $NH_3$ to benzene in the gas phase. On the other hand, amino-aromatic interactions of the cationic Lys and Arg side chains are examples of the more general cation-π interaction and should be energetically significant. In fact, for an Arg-aromatic interaction, a stacked geometry (guanidinium group of Arg parallel to the plane of the aromatic) is also quite favorable (*33*), which indicates that the charge of the residue is more important than the presence of NH groups.

In searching for examples of cation-π interactions in biology, we have not emphasized contributions to protein folding, where the desolvation energy has been prepaid. As discussed above, under these conditions even very weak interactions can appear to be important. Rather, more demanding tests of the cation-π interaction have been sought. Can aromatic residues in a protein pull a cationic substrate out of water and into a nominally hydrophobic environment, as was seen for our hosts?

Our model studies had shown that synthetic receptors can bind the cationic neurotransmitter ACh (Fig. 3) with an affinity comparable to that of natural receptors (*34*), and thus ACh receptors provided a natural starting point. Our analysis of the then available evidence concerning a number of natural ACh-binding sites, in conjunction with the crystal structure of the phosphocholine-binding antibody McPC603 (*35*), led us to explicitly propose in 1990 that the binding of ACh would be mediated by cation-π interactions rather than by conventional interactions of the quaternary ammonium cation with carboxylate anions (*34*). Since that time, cation-π interactions have been demonstrated, or at least proposed, in a large number of protein structures, including systems other than ACh-binding sites; several such systems are described below. Note that the presence of cation-π interactions in a given binding site does not rule out a role for conventional (ion pair) interactions in these systems; in fact, there is good evidence for the coexistence of the two types of interaction in our synthetic receptors as well as in the McPC603 structure (*34, 35*) and in many of the systems discussed below.

*Acetylcholine esterase.* Less than a year after our proposal, Sussman *et al.* reported the first determination of the molecular structure for a natural ACh-binding site, that of ACh esterase (*36*). This structure includes 14 highly conserved aromatic residues that define a large portion of the ACh-binding site and an "aromatic gorge," a ~20 Å cleft that leads from the surface of the enzyme to the active site. On the basis of this structure, Sussman *et al.* concluded that the classical anionic subsite is in fact misnamed, and that the trimethylammonium group is bound primarily by aromatic residues, most especially a Trp. This study provided compelling structural evidence for the importance of cation-π interactions. Further studies of ACh esterase have confirmed and expanded on these initial conclusions, and the well-known "peripheral anionic site" has also been identified as a Trp.

Although Trp is a relatively uncommon residue, it appears to be especially prominent at cation-π sites, as in ACh esterase and other structures discussed below. The electrostatic potential maps in Fig. 2 suggest a possible reason: Indole provides a much larger, much more intense region of negative electrostatic potential than does benzene or phenol, and thus it constitutes a more attractive cation-binding site. It also appears that Tyr is more prominent than Phe at cation-π sites. Although the binding capabilities of the aromatic rings of the two residues are very similar, the oxygen of Tyr provides a second site of highly negative electrostatic potential (Fig. 2), which could also contribute to cation binding through electrostatic interactions (*37*). Of course, the OH of Tyr (and the NH of Trp) can also perform other functions not available to Phe.

*Nicotinic acetylcholine receptor (nAChR).* Some of the strongest support for cation-π interactions at ACh-binding sites comes from studies of the nAChR. Even without an x-ray structure, the evidence for a key role for aromatic residues at the ACh-binding site, and hence for the possible involvement of a cation-π interaction, is very strong (*38–41*). The photoaffinity labeling studies of Changeux and co-workers (*39*) established an important role for aromatic residues at the binding site, and a number of later studies confirmed and expanded on these findings. At least six, and perhaps as many as eight, aromatic residues (all Tyr or Trp) on three discontinuous segments of the protein are now known to be at or near the agonist-binding site (Fig. 4). This impressive cluster of aromatics would seem to mandate a relatively hydrophobic binding site and perhaps would make cation-π interactions almost unavoidable (*41*). A number of studies also implicate aromatic residues in binding bungarotoxin and related inhibitors of the nAChR through a highly conserved Arg of the toxin.

*Muscarinic acetylcholine receptor (mAChR) and other G protein–coupled receptors (GPCRs).* The mAChR is a member of the much stud-

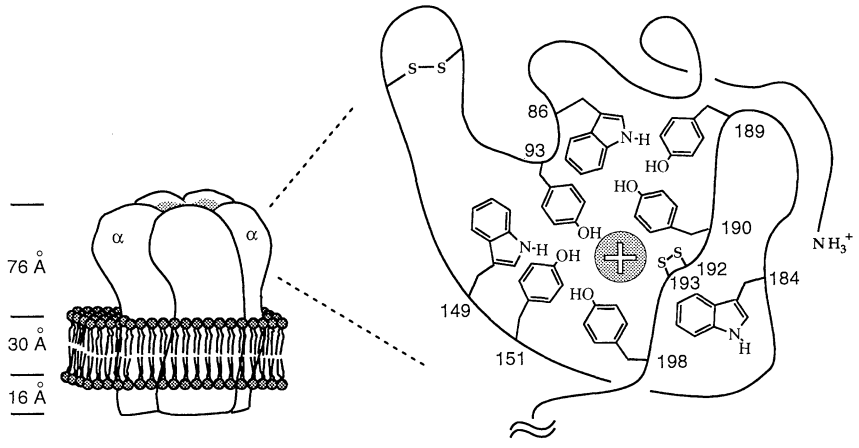


**Fig. 4.** Highly schematic view of the nAChR. Left: Overall structure, derived from Unwin (*40*). Right: Expanded view of the $NH_2$-terminal region of the α subunit, the primary location of the agonist-binding site. The illustrated Tyr and Trp residues have been shown to be near the agonist site (+) by means of affinity labeling (residues 86, 93, 149, 151, 190, and 198), mutagenesis (93, 190, and 198), nuclear magnetic resonance (nuclear Overhauser enhancement) (184), or interactions with toxin antagonists (189). Residues 86, 93, 149, 151, 190, and 198 (Torpedo numbering) are very highly conserved, whereas 184 and 189 are aromatic in roughly 50% of the known sequences. At least one aromatic on a non-α subunit has also been implicated in binding. This scheme is adapted from Changeux and co-workers (*39*).

ied class of GPCRs that also includes receptors for a wide range of cationic amines such as dopamine, epinephrine, and serotonin, as well as a large number of peptidic ligands such as bradykinin and tachykinin (*42*). Although no high-resolution structure is available, a number of models for these "seven-helix" receptors have been built, starting from the low-resolution structure for bacteriorhodopsin. For example, Hibert *et al.* found that the cationic group of ACh, dopamine, or serotonin is involved in an ion pair with a carboxylate. However, "the most striking feature which is common to all cationic neurotransmitter GPCR is the presence of a cluster of conserved aromatic residues which encages the ammonium-aspartate ion pair" (*43*, p. 3458; see also *44*). A cation-$\pi$ interaction was explicitly proposed to be important in the binding. Other computational models for the mAChR (*45*) and the D2 dopamine receptor (*46*) also indicate a possible role for cation-$\pi$ interactions.

Given the results for ACh esterase and the nAChR, it is perhaps not surprising that the mAChR also uses aromatic residues for binding the quaternary ammonium group of ACh. However, the GPCR models go further, proposing a similar binding motif for the relatively more hydrophilic (*34*), protonated primary amines, $RNH_3^+$. Validation of these models would establish that the cation-$\pi$ interaction can be effective not only on relatively hydrophobic quaternary ammonium compounds such as ACh, but also on more hydrophilic cations.

*$K^+$ channels: ion selectivity*. A unique feature of aromatics is their combination of two properties that are usually considered mutually exclusive: ion binding and hydrophobicity. As such, it seemed natural to emphasize quaternary ammonium compounds such as ACh, which, although still quite well solvated by water (*34*), are certainly less hydrophilic than ions such as $Na^+$ or $K^+$. For these simpler ions, it might be anticipated that the desolvation penalty for removing the ion from water to a hydrophobic binding site would be too great.

For these reasons, serious consideration of cation-$\pi$ interactions with such ions did not begin until the Shaker channel, a voltage-gated $K^+$ channel, was cloned and sequenced (*47*). These channels display considerable selectivity (perhaps as great as 1000:1) for $K^+$ over ions such as $Na^+$. Many $K^+$ channels have now been sequenced, and a clear trend has emerged: Across a wide range of structures, the pore region—a short segment of the protein that is primarily responsible for ion selectivity—contains a highly conserved Gly-Tyr-Gly sequence. If the Gly-Tyr-Gly sequence is present, the channel is $K^+$ selective; if it is absent, the channel is not highly selective (*48*). These channels are generally tetramers, and so there are four copies of the triad in the ion channel.

This trend led Heginbotham and MacKinnon to propose (*49*) that perhaps cation-$\pi$ interactions are responsible for establishing ion selectivity in $K^+$ channels (*50*). To test this proposal, Kumpf and Dougherty performed a theoretical study of the interaction of simple cations with benzene, both in the gas phase and in water (*4*). As noted above, the gas-phase binding sequence is $Li^+ > Na^+ > K^+ > Rb^+$. However, in water a dramatic reordering is seen, and the affinity of a cation-$\pi$ site follows the order $K^+ > Rb^+ \gg Na^+, Li^+$; this is qualitatively the same sequence seen in $K^+$-selective channels. Although the smaller ions have a greater affinity for benzene in the gas phase, they are also much better solvated by water. The trade-off between these two opposing forces causes the cation-$\pi$ interaction to peak naturally at $K^+$ in water. Although the absolute binding energies of these ions in water may not be large, tight binding is not desirable in ion channels; high ion flux is important, and selectivity must arise from interactions that are inherently weak. Further work will be required to determine whether $K^+$ channels do, in fact, use a cation-$\pi$ mechanism to achieve ion selectivity (*51*), but the calculations establish that it is physically plausible.

*$K^+$ channels: tetraethylammonium (TEA) blockade*. MacKinnon and co-workers had earlier established that cation-$\pi$ interactions are likely important in another feature of voltage-gated $K^+$ channels: blockade by the organic cation TEA (*49*, *52*). At a particular site at the mouth of the pore, TEA-sensitive channels have a Tyr, whereas TEA-insensitive channels have a nonaromatic residue such as Thr. TEA-insensitive channels can be made TEA-sensitive by simply introducing tyrosines at the key site, and the free energy of TEA interaction depends linearly on the number of tyrosines present.

*$Na^+$ channels: toxin blockade*. Several recent studies indicate that aromatic residues play a key role in the interaction of cationic groups of toxins such as tetrodotoxin (TTX) and saxitoxin with $Na^+$ channels (*53*). A Tyr that is present in toxin-sensitive brain channels but is absent in toxin-insensitive cardiac channels plays a critical role in toxin binding. Similarly, a crucial Trp is present in a TTX-sensitive skeletal muscle channel but is absent in a TTX-insensitive cardiac form.

*S-Adenosylmethionine (SAM)*. Our synthetic receptors can act as catalysts for the transfer of a methyl group from a sulfonium compound to a nucleophile. Such a reaction is very common in nature, where the alkylating agent is SAM (also known as AdoMet) (Fig. 5). The nucleophiles in these reactions can be any of a broad range of structures, including nucleic acids, proteins, sugars, and C=C bonds of steroids and lipids (*54*). The similarity of our model reactions to those of Fig. 5 led us to propose that cation-$\pi$ interactions might be important in reactions involving SAM (*29*).

Subsequently, the crystal structure of a cytosine-DNA methyltransferase was reported (*55*). It reveals a van der Waals contact between the S-$CH_3$ unit of SAM and the $\pi$ face of a Trp residue, in a favorable alignment for catalysis assisted by cation-$\pi$ interactions (Fig. 5) (*56*). In addition, a recent analysis of many methyltrans-

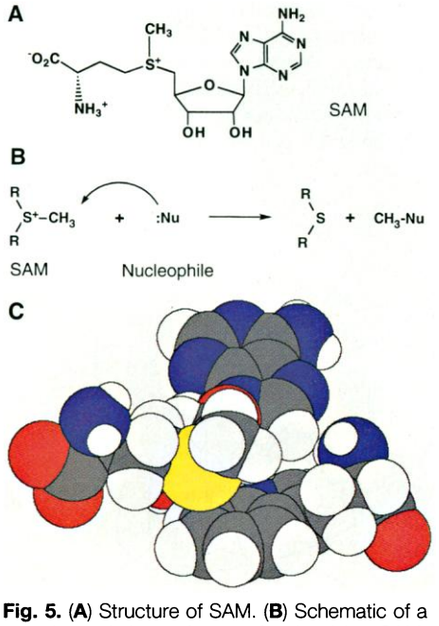


**Fig. 5.** (**A**) Structure of SAM. (**B**) Schematic of a generic methyl transfer reaction involving SAM. (**C**) Space-filling representation of SAM bound to the DNA methyltransferase. The SAM lies on top of $Trp^{41}$ from the protein, with the methyl group projecting forward. Color code: sulfur, yellow; carbon, gray; nitrogen, blue; hydrogen, white; oxygen, red. Coordinates are taken directly from the Brookhaven Protein Data Bank file 1hmy (*55*).

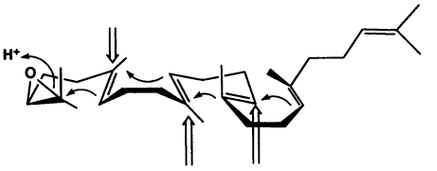

**Fig. 6.** Schematic of the cyclization of squalene epoxide. Single arrows designate electron flow, such that positive charge develops at the opposite end of any double bond from which an arrow emanates. Double arrows suggest sites in the enzyme that guide the cyclization process—anions in the original proposal, aromatics in the more recent models. Drawing adapted from Johnson *et al.* (*58*).

ferase sequences reveals a conserved motif that is "unusually rich" in aromatic residues and has been proposed to be involved in binding SAM (57).

*Steroid biosynthesis.* The cationic cyclization of squalene is a crucial step in steroid biosynthesis (Fig. 6). A key concept in this field is the Johnson *et al.* model (58), which proposes a number of anionic sites in the cyclase enzyme that guide cation generation and thus formation of the proper ring system. However, a carbocation in close proximity to a carboxylate might be expected to react irreversibly to form an ester. Alternatively, the quadrupole moment of an aromatic ring could readily guide cation formation without providing such a reactive site. Also, because the substrate (squalene epoxide) is quite hydrophobic, the active site would be expected to be hydrophobic.

The first sequences of cyclase enzymes have only recently been reported (59). These structures, too, are unusually rich in aromatic residues, and two groups of researchers have explicitly proposed that cation-π interactions may be important in squalene cyclizations. In such a model, aromatic residues play the role of the anions in the Johnson *et al.* mechanism. Consistent with this notion is the appearance of a recurring sequence in the cyclase enzymes, termed the QW motif, that could provide the key aromatic residues.

*Other examples.* Shifts in the p$K_a$'s ($K_a$, acid constant) of residues can be expected when cation-π interactions are possible. Mutagenesis studies of barnase established that the protonated form of a His can be preferentially stabilized by an adjacent aromatic residue as the result of cation-π interactions (60). The order of the effect is Trp > Tyr > Phe, exactly as expected for a cation-π interaction (Fig. 2). In the Src homology 2 (SH2) domain of the *v-src* oncogene, the aromatic group of a bound phosphotyrosine interacts with the side chains of Arg and Lys residues, which indicates important cation-π interactions (61). In T cell receptor–peptide contacts, aromatic residues can serve the same function as (anionic) glutamate in recognizing a Lys, and cation-π interactions are invoked (62). Phospholipase $A_2$, in its binding region, shows a high similarity to the McPC603 antibody, and thus cation-π interactions play an important role in binding (63). In a more general sense, modern analysis of protein structures by Karlin and co-workers clearly establishes the unique role of aromatics and the importance of cation-π interactions (64). Finally, on a more speculative note, it seems possible that the tendency of aromatic residues from integral membrane proteins to cluster near the surface of the membrane (65) could reflect, in part, cation-π interactions between the aromatic ring and the choline head groups of the lipid.

## Conclusions

A number of lines of evidence establish that aromatic systems interact strongly with cations. Although many effects are involved, to first order this cation-π interaction can be considered an electrostatic effect that involves the quadrupole moment of the aromatic. What is perhaps most surprising, yet is firmly established by studies of model systems, is that energetically, the cation-π interaction can compete with full aqueous solvation in binding cations. This suggests that proteins might also use cation-π interactions to bind cationic substrates. There is now compelling evidence that nature does adopt such a strategy. Several crystal structures clearly demonstrate van der Waals contacts between cationic substrates and aromatic residues. Also, a great deal of circumstantial evidence places aromatic residues in the active regions of a number of proteins that interact with cations. Although the implications of some of the examples described above might be debatable, the weight of evidence indicates that cation-π interactions are among the many noncovalent forces that contribute to biological structures.

These results lead to a new view of aromatics in general and of the aromatic amino acids Phe, Tyr, and Trp in particular. Although these structures are certainly hydrophobic, they are also highly polar—quadrupolar, however, not dipolar. This unusual combination of properties facilitates the creation of biological recognition sites that are capable of binding polar cationic substrates strongly and selectively, yet are compatible with a hydrophobic environment (66). Studies of new systems and reexaminations of earlier systems will likely provide further evidence for the importance of cation-π interactions in biological structures.

## REFERENCES AND NOTES


1. The introduction of several heteroatoms (as, for example, in histidine or the ring systems of the nucleic acids) leads to new types of interactions and complicates the analysis. Certainly, however, electrostatic interactions of the type described here will remain important.
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4. R. A. Kumpf and D. A. Dougherty, *Science* **261**, 1708 (1993).
5. The interaction of transition metals with benzene, as in bis(benzene)chromium or the $Ag^+$ complexes of arenes or olefins (6), is qualitatively different and is not considered here. Note also that the cation-π interaction should apply to simpler π systems, such as those in olefins and alkynes.
6. For lead references, see J. Gross, G. Harder, F. Vogtle, H. Stephan, K. Gloe, *Angew. Chem. Int. Ed. Engl.* **34**, 481 (1995).
7. C. A. Deakyne and M. Meot-Ner (Mautner), *J. Am. Chem. Soc.* **107**, 474 (1985); M. Meot-Ner (Mautner) and C. A. Deakyne, *ibid.*, p. 469.
8. A quadrupole moment can be thought of as two dipole moments aligned in such a way that there is no net dipole. This can be achieved by the "tail-to-tail" arrangement of Fig. 2, or by placing two dipoles side by side, with one facing "north" and the other "south."
9. G. R. Dennis and G. L. D. Ritchie, *J. Phys. Chem.* **95**, 656 (1991).
10. See, however, J. H. Williams, *Acc. Chem. Res.* **26**, 593 (1993).
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12. The multipole expansion series (pole, dipole, quadrupole, octupole . . . ) is not a perturbation series. That is, there is no reason to expect, a priori, that an ion-quadrupole interaction will always be weaker than an ion-dipole interaction, especially at the short interaction distances considered here.
13. These findings naturally do not imply that ionic structures should be more soluble in benzene than in water. The gas-phase data consider only the first solvation shell of the ion. In bulk water, a great deal of the solvation energy comes from longer range, continuum (Born) solvation, provided by water's large dielectric constant. Such forces are negligible in benzene.
14. The other major factor in the cation-π interaction is most likely an induced dipole that arises in the aromatic in response to the nearby charge. If this were the dominating factor, polarizability should be of major importance. However, benzene is not an especially polarizable molecule, and in fact the in-plane polarizability is greater than the out-of-plane polarizability (15). Cyclohexane is more polarizable than benzene (16), but it is a decidedly weaker cation binder (17). As such, induced dipole arguments do not lead to straightforward rationalizations of the observations. On the other hand, the quadrupole moment of cyclohexane (16) is much smaller than that of benzene (9), consistent with observations.
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# Quantum Engineering of Optical Nonlinearities

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Second-order optical nonlinearities in materials are of paramount importance for optical wavelength conversion techniques, which are the basis of new high-resolution spectroscopic tools. Semiconductor technology now makes it possible to design and fabricate artificially asymmetric quantum structures in which optical nonlinearities can be calculated and optimized from first principles. Extremely large second-order susceptibilities can be obtained in these asymmetric quantum wells. Moreover, properties such as double resonance enhancement or electric field control will open the way to new devices, such as fully solid-state optical parametric oscillators.

When light is incident on matter, the bound electrons vibrate in the electromagnetic field. While moving under the electromagnetic force, the electrons generate a synchronous polarization field, which interferes with the original field. At low amplitude, this generated field is proportional to the exciting one, and the interference between the driving field and the generated one is the origin of the linear properties of light in matter, such as those described by the optical index of refraction. If the potential that binds the electrons in the material is asymmetric in space, the electron orbits will be distorted relative to the symmetric case, that is, elongated in the direction of the more confining part of the potential. The distorted electron orbits will then generate harmonic polarization waves (*1–3*). For instance, a wave at radial frequency $\omega$ will generate a wave at frequency $2\omega$: This is called second-harmonic generation (SHG) and is widely used in the field of nonlinear optics. If we assume a time ($t$)-varying electromagnetic field of amplitude $E$ polarized along the $z$ axis ($E_z e^{-i\omega t}\mathbf{e}_z$), the generated SHG polarization $P_x^{2\omega}(t)$ along the $x$ axis $\mathbf{e}_x$ is related to the fundamental electromagnetic field through the relation

$$P_x^{2\omega}(t) = \frac{\varepsilon_0}{2}\chi_{xzz}^{(2)}E_z^2 e^{-2i\omega t} + \text{c.c.} \qquad (1)$$

where $\varepsilon_0$ is the vacuum permittivity, $\chi_{xzz}^{(2)}$ is the second-order optical susceptibility coefficient for SHG in this polarization configuration, and c.c. is the complex conjugate of the first term (*4*).

The required asymmetry of the electron binding potential is present in naturally

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