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Cation-π interactions in aromatics of biological and medicinal interest: Electrostatic potential surfaces as a useful qualitative guide

(aromatic amino acid/molecular recognition)

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ABSTRACT **The cation-π interaction is an important, general force for molecular recognition in biological receptors. Through the sidechains of aromatic amino acids, novel binding sites for cationic ligands such as acetylcholine can be constructed. We report here a number of calculations on prototypical cation-π systems, emphasizing structures of relevance to biological receptors and prototypical heterocycles of the type often of importance in medicinal chemistry. Trends in the data can be rationalized using a relatively simple model that emphasizes the electrostatic component of the cation-π interaction. In particular, plots of the electrostatic potential surfaces of the relevant aromatics provide useful guidelines for predicting cation-π interactions in new systems.**

In recent years, studies of model systems and the analysis of biological macromolecular structures have established the importance of the cation-π interaction as a force for molecular recognition in aqueous media (1). Appropriately designed cyclophane receptors serve as powerful, general hosts for quaternary ammonium, sulfonium, and guanidinium cations, in large part because of the cation-π interaction (2–4). In the gas phase, the binding of simple cations to benzene and related structures has been shown to be quite substantial, comparable even to cation-water interactions (5). In addition, a large amount of evidence has now been developed that establishes cation-π interactions as important in a number of biological binding sites for cations (1, 6, 7). Cation-π interactions have been considered in such diverse systems as acetylcholine receptors (nicotinic, muscarinic, and ACh esterase), K^+ channels, the cyclase enzymes of steroid biosynthesis, and enzymes that catalyze methylation reactions involving S-adenosylmethionine (1). Cation-π interactions have also been invoked to rationalize specific drug–receptor interactions (8–11).

A complete, quantitative description of the cation-π interaction can be obtained only by considering a number of fundamental, intermolecular forces such as charge-quadrupole, charge-dipole, charge-induced dipole, charge-transfer, dispersion forces, and hydrophobic forces. However, we have recently shown (12) that, for simple prototypical aromatic systems, the cation-π interaction is most strongly influenced by an electrostatic term, involving the interaction of the cation with the large, permanent quadrupole moment of the aromatic ring (1, 13, 14). Given this result, one should be able to qualitatively, and perhaps even semiquantitatively, evaluate new ring systems as potential cation binders by considering only the electrostatic surface of the aromatic.

In the current work, we put this model to a more extensive test. We provide quantitative, *ab initio* evaluations of the cation-π interaction for 17 structures, emphasizing structures of relevance to biological receptors and prototype heterocycles of the type often of importance in medicinal chemistry. We find that all the trends in this series are qualitatively reproduced by considering only the electrostatic potential energy surface of the aromatic in the absence of a cation, consistent with the electrostatic model. In addition, the current model successfully rationalizes observations concerning the relative frequency of different aromatic amino acids at biological cation-π sites. We also show that the major trends of the *ab initio* surfaces are reproduced using the much less costly AM1 method, greatly expanding the range of applicability of the method.

METHODS

We have performed a series of computational studies on the binding of the sodium cation (Na^+) to the prototype systems **1–17** of Fig. 1. *Ab initio* molecular orbital calculations were performed on the aromatic molecules and their 1:1 complexes with Na^+ using the GAUSSIAN 92 program package (15). Geometry optimization of all the molecules and complexes was carried out at the 6-31G** level (i.e., 6-31G**//6-31G**). In optimizing the complexes, the aromatic rings were not constrained to be planar. Although not the major emphasis of this work, we have also calculated binding energies for Na^+ to heteroatoms in the molecules where the heteroatoms bear a substantial negative charge.

Concerning the reliability of these calculations, estimates of the basis set superposition error (BSSE) were obtained by full counterpoise calculations for most of the complexes. Absolute BSSEs were found to be small (1.4–1.8 kcal/mol). More importantly in considering trends across a related series of compounds, ΔBSSE, the extent to which the BSSE preferentially stabilizes one complex versus another, was found to be negligible (<0.3 kcal/mol) for all comparisons here. Experimentally, the $-\Delta H$ for binding of Na^+ to benzene has been measured to be 28 kcal/mol (16), in good agreement with the calculated value of 27.1 (Fig. 1). Of course, the ΔE values calculated here are not strictly comparable to ΔH values measured experimentally, but the usual corrections for zero-point vibrational, rotational, and translational effects will be small, especially when comparing related structures, and will not significantly affect any conclusions drawn from the calculations. We have previously shown (3, 7) that MP2 corrections do not significantly alter the conclusions reached from such calculations. Also, we have previously shown (4) that using NH_4^+ in place of Na^+ does not alter any trends in data of this type. Therefore, these simpler model calculations are relevant to real experimental systems.

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Abbreviation: BSSE, basis set superposition error.

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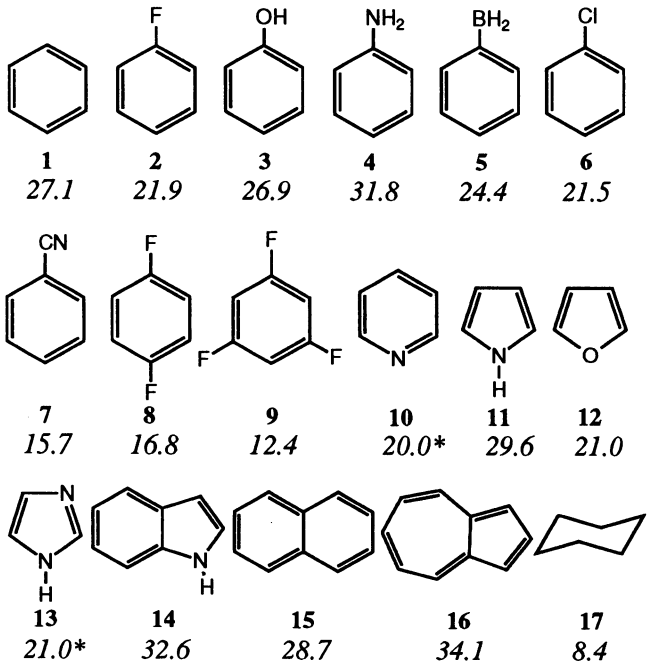

FIG. 1. Structures studied by the *ab initio* method. Binding energies (6-31G**//6-31G**, kcal/mol) are given for each structure. Energies marked with * are for cation-π complexes that are not true energy minima (see text).

Electrostatic potential surfaces of the aromatic rings were generated by mapping 6-31G** electrostatic potentials onto surfaces of molecular electron density (0.002 electron/Å (3)) and color-coding, using the program SPARTAN (17). In all surfaces shown here, the potential energy values range from +25 kcal/mol to −25 kcal/mol, with red signifying a value greater than or equal to the maximum in negative potential and blue signifying a value greater than or equal to the maximum in positive potential. It should be remembered that in most structures, some regions of electrostatic potential (especially those associated with heteroatoms) lie beyond the ±25 kcal/mol range. This range was chosen to emphasize the variations in the aromatic region. Semiempirical AM1 calculations (18, 19) of the same surfaces were also performed to compare the two levels of theory.

RESULTS AND DISCUSSION

Quantitative Results. We have previously presented an extensive, quantitative analysis of the simple, substituted benzenes **1–5** and a few other structures (12). Briefly, we found that conventional, resonance-based intuitions about substituents are not relevant to the cation-π interaction. For example, note that phenol (**3**) is no better than benzene in cation-π interactions, even though phenol is much more reactive in electrophilic substitution. However, quantitative evaluation of the electrostatic component of the *ab initio* binding energy completely rationalized the trend in the data. The data also showed a rough correlation with σ_{meta}, a Hammet parameter that primarily evaluates the inductive effect of a substituent.

In the current work, our goal is to develop a simple model that is easily applicable to a broad range of systems. For this purpose we have considered the electrostatic potential surfaces of the uncomplexed, ground state aromatic ring. If such a model were viable, the molecule-ion complexes would not have to be evaluated. One would simply consider the isolated aromatic ring system, calculate its ground state wavefunction, and map the electrostatic surface. To test the reliability of this approach, we fully evaluated the complexes for structures **1–17** to provide quantitative benchmarks against which to evaluate the electrostatic potential surfaces.

The quantitative data are summarized in Fig. 1. The geometries of the various complexes are as anticipated, with the Na^+ lying over the center (or the approximate center in lower symmetry aromatics) of the ring. Concerning binding energies in simple systems, an amino group as in aniline (**4**) strongly enhances the cation-π interaction, while electron withdrawing groups such as F and CN are deactivating. Especially impressive is the deactivating influence of CN.

To some extent, the trends in the more complex systems (**10–16**) are conventional. Pyridine (**10**) is deactivated, pyrrole (**11**) is activated. However, furan (**12**), even though it is much more reactive toward electrophiles, is significantly poorer than benzene at cation-π interactions, an effect that has been noted before and substantiated by cyclophane binding studies (4). On going from pyrrole to imidazole (**13**) one sees a large drop in cation-π binding. Indole (**14**) is, as expected, strongly binding. Perhaps surprisingly, the optimized indole complex (19) places the Na^+ over the C_6 ring, rather than the pyrrole, suggesting that, in cation-π binding, indole is better thought of as a derivative of aniline rather than pyrrole (see below). Naphthalene (**15**) is slightly better than benzene, and the preferred geometry places the Na^+ over the center of one ring (C_s symmetry), rather than the overall molecular center. The C_{2v} complex, however, is only 2.2 kcal/mol less stable, and, at this level of theory, it represents the transition state for the interconversion of the C_s forms. Azulene (**16**) presents quite a potent cation-π binding site, and, as expected, the cation is centered on the five-membered ring. Finally, cyclohexane (**17**) is included as a structure of comparable size but with no significant electrostatic binding [near zero quadrupole moment (20)]. It is a very weak binder. Note that if polarizability were the dominant factor in establishing the magnitude of a cation-π interaction, one might have expected cyclohexane to outperform benzene, since it is known to be more polarizable than benzene (20, 21). Of course, this is not the case, emphasizing the importance of the electrostatic term.

All the calculations reported here refer to a gas-phase environment, as is appropriate for evaluating the fundamental nature of the cation-π interaction. In most instances, though, cation-π interactions have been invoked in solution. Certainly, in considering the differences among various *cations* in cation-π interactions, solvation–desolvation arguments are of paramount importance (7). However, in the current study the ion is held constant. Thus, we expect that in considering cation-π interactions, differential solvation-desolvation effects among the various aromatics will be small, and so the calculations will be of value to investigators designing new systems.

In compounds **2–4**, **7**, **10**, and **13**, the heteroatom also bears a substantial amount of negative charge (see below), and binding of the cation to the heteroatom is possible. Although not the primary focus of the current work, we will briefly consider these structures here. Binding Na^+ to the heteroatom of **2–4**, **7**, **10**, and **13**, is worth 22.3, 27.4, 33.2, 36.5, 33.4, and 39.5 kcal/mol, respectively. For **2–4**, heteroatom binding is competitive with, and generally slightly better than, cation-π binding. For **7**, **10**, and **13**, the heteroatom site is much more strongly binding, and in the cases of **10** and **13**, only the binding to the nitrogen represents a true minimum on the 6-31G** potential energy surface. The binding energies for cation-π complexes of **10** and **13** were obtained by forcing the Na^+ to stay over the π system, and so must be considered approximate.

The relevance of these heteroatom-based cation binding sites will depend on the particular system, and more importantly on the context of the binding event. Of course, these alternative binding modes would be extremely relevant in the gas phase. In solution, however, solvation issues would now be critical. This is because one would expect the penalty for

desolvating the heteroatoms to be much more severe than for the aromatic, and so the cation-π site should compete more effectively with the heteroatom site in solution. In biological structures, one would expect some control over the orientation of an aromatic group, whether it is part of a protein structure or part of a substrate or drug that is targeted to a protein binding site. The precise positioning of an aromatic may control whether cation-π or heteroatom binding is preferred. Finally, with an organic cation such as tetramethylammonium or acetylcholine, one can anticipate that the cation-π binding geometry would lead to more favorable van der Waals and hydrophobic contributions to binding.

Electrostatic Potential Surfaces. The primary goal of the present work is to provide a simple tool for anticipating cation-π interactions, without resorting to a full *ab initio* calculation for each system under consideration. Previous experience (4) and the finding that the electrostatic component of the total binding energy faithfully mirrors the trend in the full binding energy (12) suggested that simple inspection of the electrostatic potential surfaces of the aromatic systems would be valuable in this regard. We now report that this is so.

Fig. 2 shows the *ab initio* electrostatic potential surfaces for structures **1–17**. Recall that red codes for regions of relatively negative electrostatic potential, while blue codes for positive potential. Recall also that some regions, especially those associated with heteroatoms, are "off scale" in this representation. Focusing on the aromatic ring regions, there is remarkable agreement between expectations based on the electrostatic potential surfaces and the quantitative binding results of Fig. 1. The trend in cation-π binding strengths of the simple benzenes—**4** > **1** ≈ **3** > **5** > **2** > **6** > **8** > **7** > **9**—is well-reproduced. Most strikingly, the electrostatic potential surfaces predict that phenol should be quite comparable to benzene, as is observed.

Phenol serves to nicely illustrate the difference between electrostatic potential surface analysis and conventional aromatic substituent effects, which are generally based on reactivity. Clearly, as far as the electrostatic potential surface is concerned, the σ-withdrawing and π-donating properties of the phenolic group roughly cancel, and so phenol is comparable to benzene. In considering reactivity, one is evaluating a substituent's ability to stabilize a transition state, and resonance issues become much more important than inductive effects. A general conclusion from the present study is that cation-π interactions generally reflect "ground state" properties of the aromatic.

The predictive success of the electrostatic potential surfaces continues with the heterocycles **10–14**. The very weak binding of pyridine and the very strong binding of pyrrole are clearly indicated. Imidazole is an interesting case. In the *ab initio* calculations the π complex was not a true minimum. In addition, binding to the iminic nitrogen is much preferred to binding to the π system. The electrostatic potential surface of **13** provides a rationalization. Unlike pyrrole, for which there is a clear peak in the negative electrostatic potential over the π system, there is no such π binding site in **13**. Placing a cation anywhere over the π system of **13** will inevitably lead to the end-on nitrogen complex.

The electrostatic potential surface of indole (**14**) is also interesting. It much more nearly resembles that of aniline than that of pyrrole. The most negative electrostatic potential is over the C_6 ring, consistent with the preferred geometry of the complex. Thus, from the standpoint of the electrostatic potential surface, indole is much more like an ethenoaniline than a benzopyrrole.

Another interesting system is azulene (**16**). The large polarization of the π system is clearly evident. The strong binding of Na^+ and its position over the 5-ring are nicely anticipated by the electrostatic potential surface.

The unique properties of oxygen are again evident in the electrostatic potential surface for furan. A system that is much more reactive in electrophilic substitution is now much less

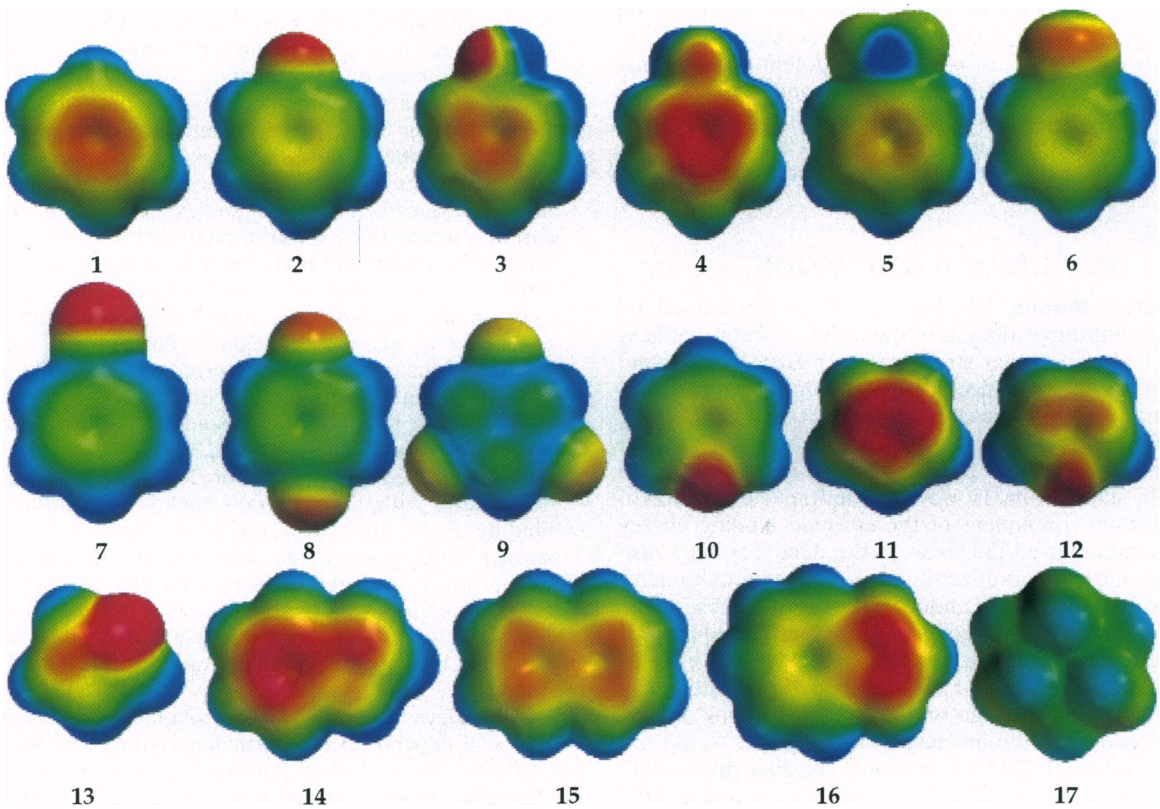

FIG. 2. *Ab initio* electrostatic potential surfaces for **1–17**. Structures are arranged and oriented as in Fig. 1.

effective than benzene in cation-π binding. The electrostatic potential surface clearly shows that now the σ-withdrawing properties of the oxygen overwhelm the π-donating, and the ring is deactivated. Again, the ground state wavefunction correctly predicts the cation-π binding ability.

The results for furan and other heterocycles also serve to emphasize the important contributions of polarized X—H bonds to the cation-π interaction. In benzene, a crucial factor is the greater electronegativity of sp^2 C relative to H, which produces substantial C^-—H^+ bond dipoles. The quadrupole of benzene can be viewed as the sum of these six local dipoles. Removing one of these dipoles, as in converting benzene to pyridine, diminishes the quadrupole accordingly, and this should contribute to a weakening of the cation-π interaction. Similar effects are evident with furan and imidazole. Also, on going from furan to pyrrole, one introduces a strong N—H dipole, accounting for the potent cation binding site in pyrrole.

Biological Relevance: Phe, Tyr, Trp, and His. A major concern of our research has been the extent to which nature uses aromatic residues to fashion cation binding sites in proteins (1). Certainly, Phe, Tyr, and Trp are present at a number of cation binding sites, as we have extensively documented elsewhere. Based on our observations, it appears that the various aromatic sidechains do not appear with equal frequency at potential cation-π sites. Trp is always especially prominent, especially considering that, in general, it is the least frequently used amino acid (22). Tyr is used almost as much as Trp and certainly more frequently than Phe. Phe is used sometimes at cation-π sites, but His never is.

The results described here nicely rationalize these observations. Trp (modeled by indole, **14**) is clearly the best-suited amino acid for a cation-π binding site. His (imidazole, **13**), on the other hand, is the worst, and in fact its electrostatic potential surface and the *ab initio* binding studies suggest it may not be at all viable for cation-π binding. In addition, a His can be protonated at physiological pH, which would obliterate any chance of contributing to cation binding. Of course, the heteroatom binding site of His could serve as a cation binding site in an appropriate protein structure.

The only slightly puzzling result is Tyr versus Phe. Our data clearly say that phenol and benzene are equally effective at cation-π binding, and so provide no obvious reason why Tyr should be preferred. We have argued in the past that Tyr is preferred because proteins can use the OH to position the ring properly (1). The cation-π interaction is quite directional, as one must have the face, not the edge, of the aromatic in contact with the cation.

An additional possibility is that the interaction of a hydrogen bond-acceptor with the phenolic hydroxyl would not only position the Tyr, but would also have an effect on the cation-π interaction. Electrostatic reasoning suggests that such an interaction would enhance the cation-π interaction. To study this effect, we considered the system phenol-formamide, Fig. 3. The distance and the angles between the oxygen on formamide and the phenolic hydroxyl were chosen according to published values for hydrogen bond networks in analogous systems (23). First we calculated the 6-31G** electrostatic potential surface of this system, Fig. 3. It is clear that the interaction of a hydrogen bond acceptor with phenol greatly increases the negative electrostatic potential on the aromatic ring. This means that the cation-π interaction in such a system will be stronger than for an isolated phenol. These predictions were confirmed by an *ab initio* binding energy calculation. Considering the system depicted in Fig. 3, we placed a sodium ion on the phenol-formamide complex at the optimized position calculated for phenol and performed a HF 6-31G** single point energy calculation of the binding energy. The resulting

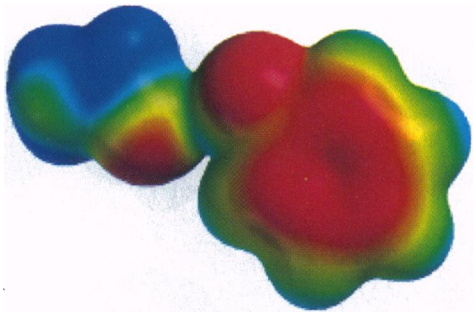

FIG. 3. *Ab initio* electrostatic potential surface of the phenol-formamide complex. The hydrogen bond points back away from the viewer, from the phenol oxygen to the carbonyl oxygen of the formamide. The aromatic ring should be compared with the electrostatic potential surface for benzene in Fig. 2.

value was 9.2 kcal/mol higher‡ than the binding energy of sodium to simple phenol (24).

In this light, one can postulate why Tyr appears to be preferred over Phe. A hydrogen bond to the phenolic OH of Tyr could help position the ring properly. In addition, such a hydrogen bond would greatly enhance the extent to which the Tyr can contribute to cation binding through cation-π interactions. Of course, the exact interplay of these and other factors will depend on the exact protein structure under consideration. Still, we consider it remarkable that such simple considerations can rationalize a significant body of biostructural data.

AM1 Results. The above results provide a compelling case that *ab initio*, 6-31G** electrostatic potential surfaces lead to reliable predictions of cation-π binding ability for various aromatic ring systems. Anticipating that others may wish to apply this approach to other, more complicated systems, we wished to establish whether electrostatic potential surfaces derived from a lower level of theory that could more readily be applied to larger systems would still be useful. As such, we calculated electrostatic potential surfaces for compounds **1-17** using the AM1 semi-empirical method (18), some results of which are shown in Fig. 4. Note that AM1 is not very successful at reproducing *ab initio* binding energies for systems of this type (19). It is therefore surprising, but gratifying to see that in almost all regards the AM1 electrostatic potential surfaces represent very good approximations to the *ab initio* surfaces. We show only representative structures from the full set of 17 studied, but the performance of the method is consistent throughout the series.

Note that the important issue here is not the exact appearance of any single AM1 surface in comparison to its *ab initio* counterpart. Rather, it is the variations in electrostatic potential surfaces within the AM1 series that are important. For example, the AM1 surface of benzene is noticeably different from the *ab initio* surface, with the semi-empirical surface showing generally smaller variation in electrostatic potential. However, this effect persists in the other simply-substituted systems, and so comparisons among the AM1 surfaces are useful. There are some qualitative differences between some AM1 and *ab initio* surfaces, but in all instances one would reach the same general conclusions about trends in cation-π binding energies by consulting either the *ab initio* or AM1 surfaces. Thus, while we would advocate using 6-31G** surfaces when possible, in more complex systems for which *ab initio* calculations may not be feasible, it appears that AM1 can provide a useful guideline.

‡A significant fraction of this extra stabilization (≈5.8 kcal/mol) comes from the long-range interaction of the Na^+ with the dipole of the formamide.

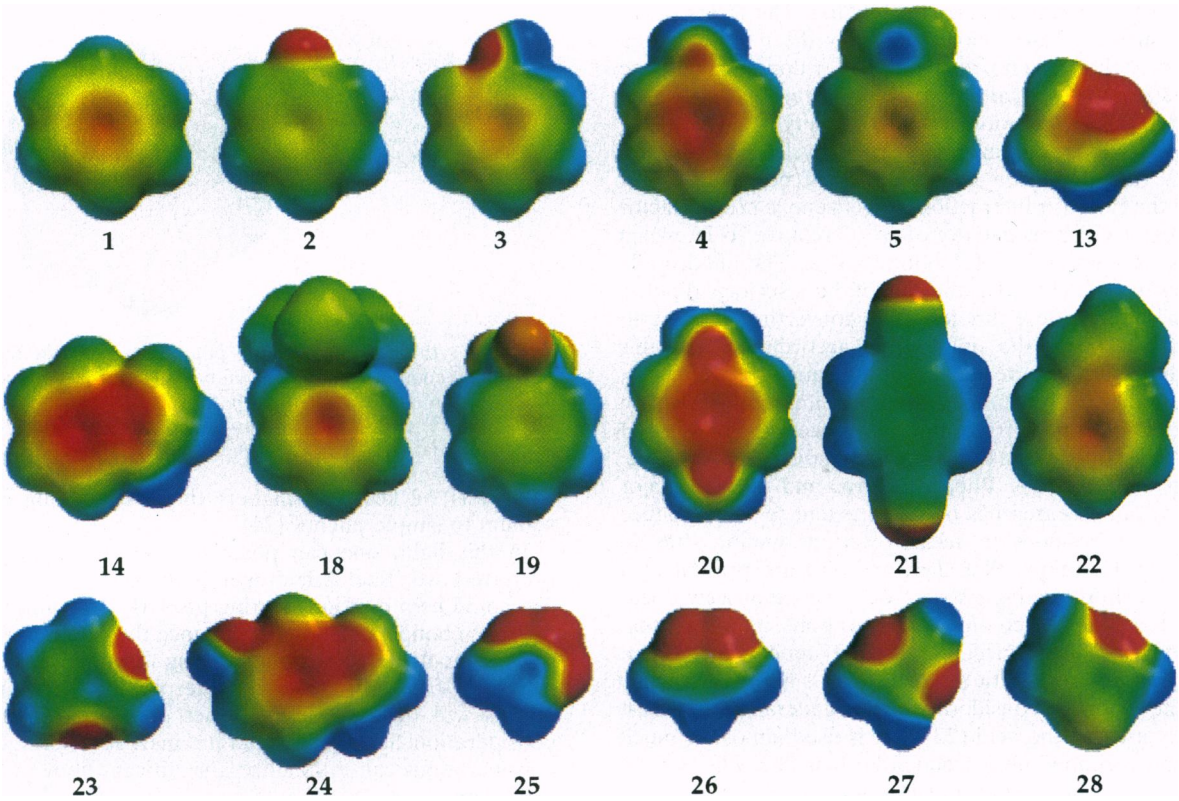

FIG. 4. AM1 electrostatic potential surfaces for selected structures.

The viability of AM1 electrostatic potential surfaces makes it a simple task to survey a large number of aromatic systems for potential cation-π binding ability. To illustrate this point, we provide AM1 surfaces for a number of additional structures. The new structures are shown in Fig. 5, and the electrostatic potential surfaces in Fig. 4. A striking contrast is diamino- vs. dicyanobenzene (**20** vs. **21**), showing the roughly additive effect of substituents. Introducing multiple heteroatoms as in **23–28** can have dramatic effects on the electrostatic potential surfaces. The important point is that it is a fairly trivial matter to generate an AM1 surface for almost any structural unit of interest, suggesting that this approach will be of value in the design of molecules of chemical and pharmaceutical interest.

A Word of Caution. A primary goal of this work is to make the case that electrostatic potential surfaces can provide very valuable guidelines for understanding and even predicting important phenomena in molecular recognition. However, it must be remembered that the electrostatic potential surfaces provide only qualitative guidelines. In this regard, it may be of value to explicitly note a few potential pitfalls of the method.

It is always important to compare any new electrostatic potential surface to some reference surface. Different surfaces may be presented in different ways. For example, if we plotted a range of ± 20 kcal/mol (3) rather than ± 25 kcal/mol, all the images would change. However, relative to the benzene image, all the changes would be in the same direction, although they may be "damped out" if too broad or too narrow of a range is chosen. Also, not all surfaces will be centered on zero. For example, in studying a series of organic cations, one would see positive potential over the entire molecular surface, and it is variation in that positive potential that would be of interest. In such a case, a range from, for example, +25 to +50 kcal/mol may be more appropriate. However, then a green/yellow color would not correspond to a zero electrostatic potential, as it does here. Note also that solvation is expected to play a much larger role with ionic structures, diminishing the usefulness of these gas phase electrostatic potential surfaces. Even the definition of a molecular "surface" is somewhat arbitrary, depending on the electron density cutoff used (or on the choice of van der Waals radii). In addition, there will always be some amount of "image processing" with such pictures, depending on the ways in which the image was captured, manipulated, printed, etc. Thus, one should always print a reference structure, processed in exactly the same way, for comparison. For studies of cation-π interactions, benzene is an obvious choice.

Finally, it remains to be determined to what extent electrostatic potential surfaces will be useful semiquantitative indicators of other types of interactions of relevance to molecular recognition. We have performed here extensive, calculations on cation-π interactions that establish the viability of a predominantly electrostatic model. Only when this is the case can electrostatic potential surfaces be expected to be of value. In

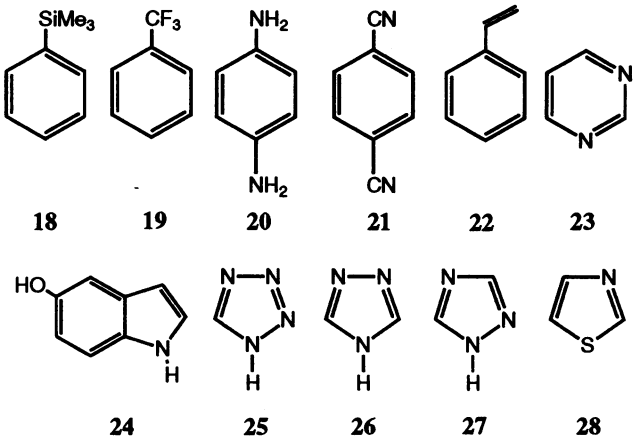

FIG. 5. Structures studied by the AM1 method only.

other systems, new types of interactions may become more important.

CONCLUSIONS

Quantitative evaluation of 17 different cation-π complexes reveals the fundamental nature of this important noncovalent binding interaction. Changes in binding energy do not strictly follow conventional aromatic substituent patterns, but instead are most strongly influenced by electrostatic forces. The quantitative results provide a rationalization of observations concerning the roles of the various aromatic amino acids in defining biological cation-π binding sites.

Consistent with the electrostatic model, simple inspection of the electrostatic potential surfaces of the isolated aromatic rings provides a qualitative guideline to cation-π binding sites. Both *ab initio* methods and the more generally applicable semi-empirical method AM1 are useful in this regard, making it a simple matter to predict the cation-π binding ability of new ring systems.

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