Aromatic Rings

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Aromatic Rings in Chemical and Biological Recognition: Energetics and Structures

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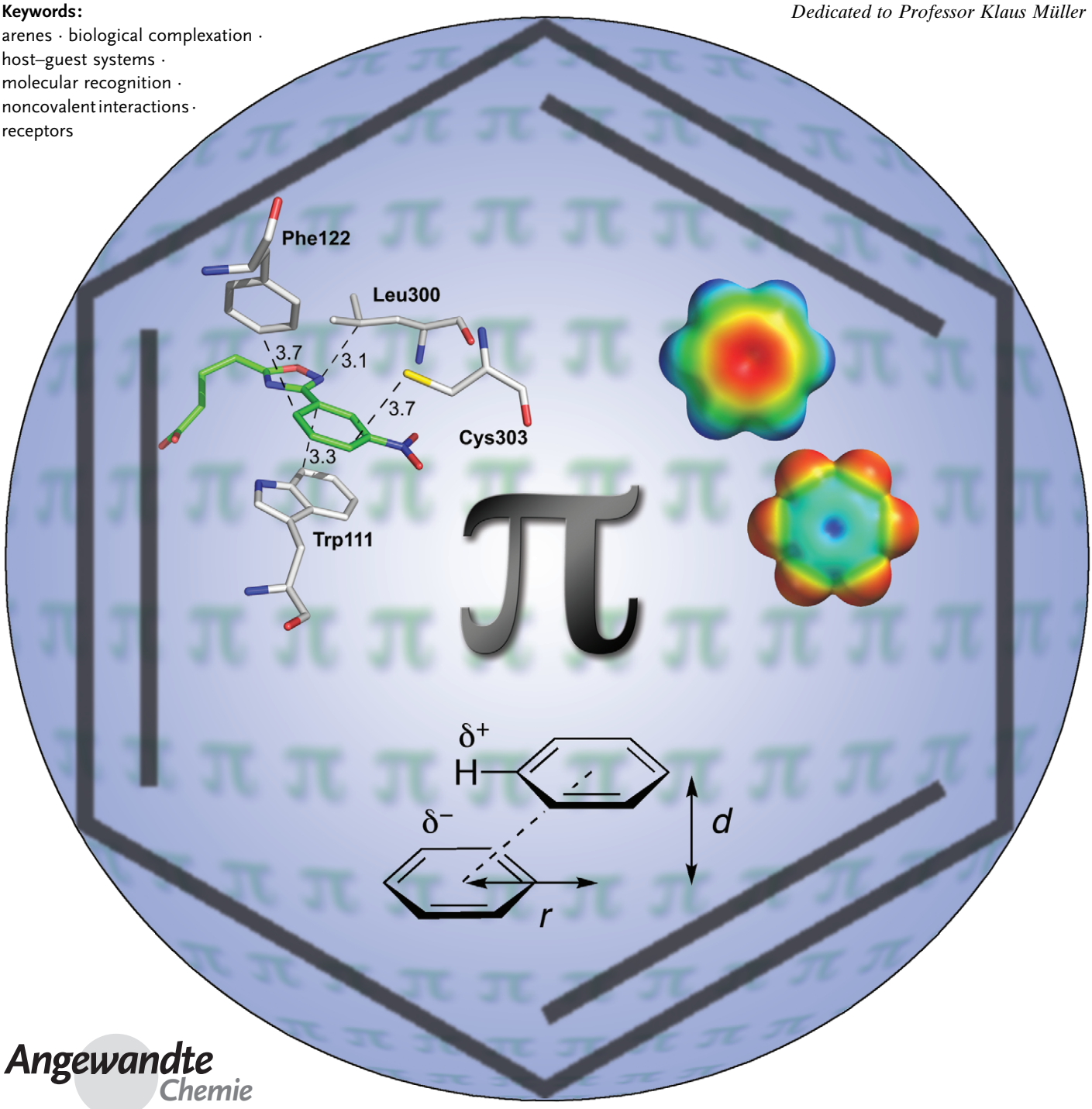
Dedicated to Professor Klaus Müller



This review describes a multidimensional treatment of molecular recognition phenomena involving aromatic rings in chemical and biological systems. It summarizes new results reported since the appearance of an earlier review in 2003 in host–guest chemistry, biological affinity assays and biostructural analysis, data base mining in the Cambridge Structural Database (CSD) and the Protein Data Bank (PDB), and advanced computational studies. Topics addressed are arene–arene, perfluoroarene–arene, S···aromatic, cation–π, and anion–π interactions, as well as hydrogen bonding to π systems. The generated knowledge benefits, in particular, structure-based hit-to-lead development and lead optimization both in the pharmaceutical and in the crop protection industry. It equally facilitates the development of new advanced materials and supramolecular systems, and should inspire further utilization of interactions with aromatic rings to control the stereochemical outcome of synthetic transformations.

From the Contents

1. Introduction

Noncovalent inter- and intramolecular interactions involving aromatic rings are ubiquitous in chemical and biological processes. We analyzed the different types of interactions with aromatic rings, in terms of their abundance, energetics, and geometric preferences, in a review in 2003.[1] Since then, much progress has been made both experimentally and theoretically, thus mandating the writing of a follow-up review to update the broad, interested readership. The aim of this article is to analyze and summarize the latest computational and experimental developments towards the understanding and application of noncovalent interactions with aromatic rings, with a focus on their quantification in solution using biological and model systems. The various sections generally start with a short summary of important results and trends discussed in the previous review, and subsequently move on to the new findings reported since 2003. Some sections also contain a brief overview of the application of aromatic interactions as a controlling element in organic synthesis.

The review begins with arene–arene interactions (Section 2), a topic of enormous interest in the literature. Therefore, we had to restrict ourselves in the discussion and examples presented. Special attention is given to substituent effects, which have increasingly been the focus of theoretical and experimental reports. Section 3 discusses interactions between arenes and perfluoroarenes, thereby highlighting the utility of the arene–perfluoroarene synthon in crystal engineering and as a selectivity-controlling element in organic synthesis. Hydrogen bonding to π surfaces is the topic of the shorter Section 4. Section 5 describes new insights into sulfur–arene interactions, a subject that was reviewed comprehensively in the earlier article. Numerous new studies have appeared on cation–π interactions using biological and model systems, as well as theoretical calculations (Section 6). Finally, Section 7 discusses anion–π interactions that were not covered in the earlier article but have seen extensive, ongoing investigations in the recent years.

2. Arene–Arene Interactions

Interactions between aromatic rings are abundant in chemical and biological systems, and span from molecular recognition to self-assembly, and to catalysis and transport.[1] All three geometries of the benzene dimer, parallel-displaced, T-shaped edge-to-face, and eclipsed face-to-face (Figures 1 a–c), were modeled at high levels of theory and found to be

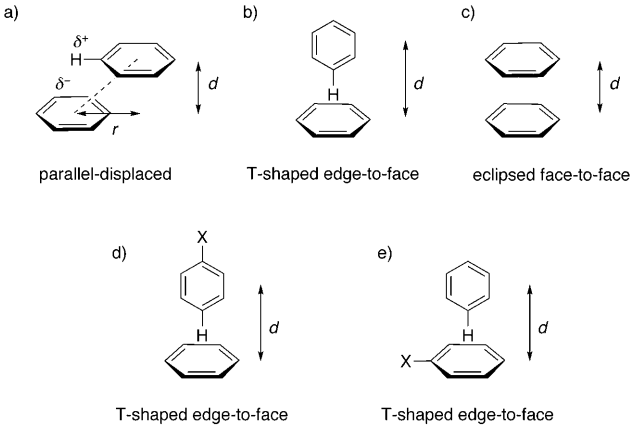


Figure 1. a–c) Interaction geometries of the benzene dimer. d,e) Substituent effects on arene–arene interactions.

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attractive in nature with a preference for the parallel-displaced and T-shaped geometries. Such preference has been observed during mining of both the CSD and PDB, and this holds also for investigations in the gas phase and in solution.[1] Quantifications in model systems, which included first investigations of substituent effects on arene–arene interactions (Figures 1 d,e), provided free enthalpy increments ($\Delta\Delta G$) down to about -1 kcal mol^{-1} for these interactions. Stacking between aromatic heterocycles frequently occurs in the eclipsed face-to-face geometry, especially when there is a favorable superimposition of the δ^+ and δ^- polarized atoms in the interacting partners. Arenes and heteroarenes also undergo stacking and edge-to-face interactions with extended hydrogen-bonding arrays.

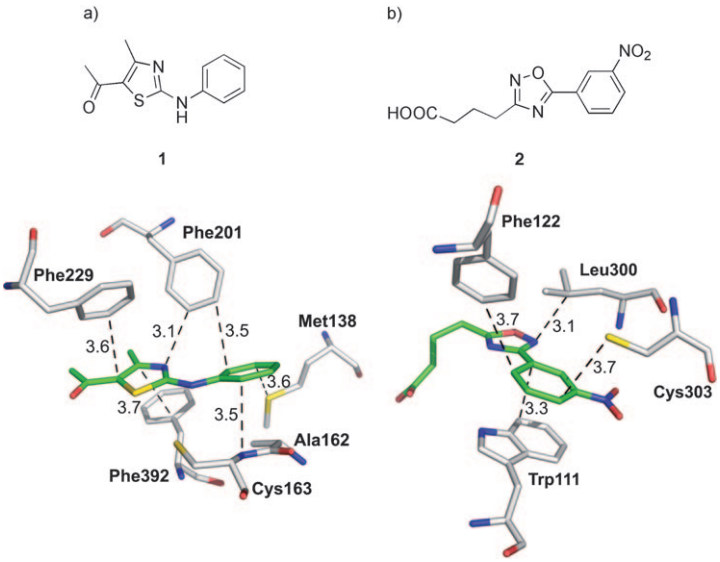

Figure 2. a) Inhibitor **1** bound to the active site of KAS (resolution 1.35 Å, PDB code: 2VBA) showing heavy-atom distances typical of arene–arene interactions.[4] b) Complexation of inhibitor **2** by aldose reductase (resolution: 1.43 Å, PDB code: 2IKG).[6a] Distances in Å. Color code: gray $C_{protein}$, green C_{ligand}, red O, blue N, yellow S.

2.1. Biological Systems

Interactions between aromatic and heteroaromatic rings are major contributors to protein structure and protein–ligand complexation[2] and are determinants in nucleic acid structures, as evident from the base-pair stacking in duplex DNA.[3] A plethora of new examples for arene–arene interactions in biological systems have been revealed in X-ray and NMR structures of protein–ligand complexes, and two examples are shown in Figure 2.

The crystal structure of ligand **1** bound to β-ketoacyl-acyl carrier protein synthase (KAS) revealed parallel-displaced stacking interactions (Figure 2 a) between the aminothiazole moiety and the side chain of Phe392.[4] This interaction rigidifies the conformation of Phe392 as compared to the apoenzyme. In addition, the phenyl moiety of the inhibitor undergoes stacking interactions with the backbone amide of Ala162/Cys163, engages in S···aromatic interactions with Met138, and displays edge-to-face contacts with the side chain of Phe201. The intermolecular heavy atom distances seen in this structure are highly characteristic of aromatic interactions, which usually occur at C···C distances between 3.4 and 3.8 Å.[1,5]

Klebe and co-workers solved two X-ray co-crystal structures of aldose reductase inhibitors (Figure 2 b),[6] which featured favorable π–π stacking interactions between the aromatic inhibitor and the side chain of Trp111 with shortest carbon–carbon distance between aromatic rings of 3.3 Å. Isothermal titration calorimetry (ITC) measurements revealed a strong enthalpic driving force ($\Delta G° = -8.4$ kcal mol^{-1}, $\Delta H° = -6.1$ kcal mol^{-1}, $T\Delta S° = 2.3$ kcal mol^{-1}) for the binding of the *m*-nitrophenyl-bearing inhibitor **2**, which is electrostatically complementary to the electron-rich indole ring. Removal of the nitro group reduces the affinity by one order of magnitude.

Aromatic π–π interactions not only determine biological structures but also modulate the physical properties of residues at enzyme active sites. In Cu^{II}-containing redox metalloproteins, the stacking of a Cu^{II}-coordinated His imidazole with a Phe side chain in the second coordination sphere affects the properties of the imidazole ring, such as its pK_a value, the reduction potential E_m of the metal center, and the electron-transfer (ET) properties of the protein.[7] Intra-

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molecular stacking between a phenyl ring and the pyridine ring of a nicotinamide derivative increases the basicity of the pyridine N atom by about 0.5 pK_a units.[8]

Finally, π–π interactions play a prominent role in adenine recognition by kinases[9] and in protein–protein[10] and RNA–protein interactions.[11]

2.2. Calculations

Theoretical studies on π–π interactions have been summarized in a review,[12] and new calculations have appeared on their cooperative interplay with other intermolecular interactions,[13] substituent effects,[14] and the effects of transition-metal coordination.[15] Additionally, numerous calculations on aromatic–aromatic interactions of different homo- and heterodimers have been reported,[16] such as for benzene,[17] toluene,[18] nitrobenzene,[19] pyridine,[20] azulene,[21] triphenylene,[22] coronene,[23] DNA bases,[24] porphine,[25] aromatic amino acids,[26] and others.[27]

Coupled cluster calculations by Tsuzuki et al. had shown the most stable geometries of the benzene dimer to be parallel-displaced and T-shaped, with CCSD(T) interaction energies of −2.48 and −2.46 kcal mol^{-1}, respectively, whereas the face-to-face complex is less stable (−1.48 kcal mol^{-1}), yet still a minimum on the energy hypersurface.[1,28] The major contribution to the interaction energy arises from dispersion,[29] underlining the importance of including electron correlation corrections into the calculation of arene–arene interactions. The efforts made to overcome the inability of density functional theory (DFT) methods to account for dispersion were recently reviewed by Grimme et al.[30] According to Grimme,[31] π–π stacking interactions are a particular type of electron correlation (dispersion) effect acting in large unsaturated systems when they are in close proximity to each other, and for systems with ≤ 10 carbon atoms there is little theoretical evidence for a special role of the π orbitals. The term "π–π stacking" should therefore be viewed as a convenient geometrical descriptor for the interaction mode in unsaturated molecules.

Substituent effects on aromatic interactions have been intensively investigated in recent years, mostly using coupled cluster theory. Sinnokrot and Sherrill found all monosubstituted benzene–benzene dimers in the face-to-face geometry to be more stable than the corresponding nonsubstituted benzene dimer, independent of the electron-donating or electron-withdrawing character of the substituent.[32] Similar results were reported by Hobza, Kim, and co-workers.[14a] For the edge-to-face geometry,[33] both increases and decreases of the interaction energies were found depending on the substituent. An electron-withdrawing substituent in the *para* position of the edge component (Figure 1 d) enhances the stability of the T-shaped substituted benzene–benzene dimer, with $\Delta\Delta E$ down to about −0.7 kcal mol^{-1} for X = CN or NO_2. In contrast, an electron-donating substituent, such as OH or NH_2, in this position leads to a small destabilization of the dimer. Substitution of the face component by an electron-accepting substituent (Figure 1 e) is destabilizing, whereas the introduction of a face-donor substituent stabilizes the dimer. For all geometries, dispersion and exchange repulsion were found to be more important than electrostatics in determining the total binding energies of the dimers.[33a] According to Hobza, Kim, and co-workers, dispersion energy is dominant in the aromatic interactions, albeit largely cancelled out by the exchange-repulsion terms. However, electrostatic energy is the governing force for conformational and substituent effects.[14a]

Recently, through-space effects have been increasingly taken into consideration in explaining substituent effects. Arnstein and Sherrill found contributions from direct interactions of the substituents on one ring with the neighboring ring to affect parallel-displaced π–π interactions.[34] Such direct interactions were also reported by Wheeler and Houk for the substituted benzene–benzene face-to-face dimer.[35] In agreement with previous calculations,[32] they found interaction energies of all substituted dimers to be more attractive than that of the benzene dimer. The π–π stacking interaction energies correlated with the Hammett substituent constants σ_m and were attributed to direct electrostatic interactions between the substituent and the unsubstituted ring, with the stabilization also involving dispersion interactions.

Extending their investigations to the two types of T-shaped monosubstituted benzene–benzene dimers (edge- or face-ring-substituted, Figure 1 d,e),[36] Wheeler and Houk again obtained a correlation between interaction energy and Hammett constant σ_m, in agreement with the previous calculations.[33] Direct interactions, such as those between the local dipoles induced by the substituents and the other ring, account for a large part of the substituent effects. Additionally, in the edge-ring-substituted dimers (Figure 1 d), changes in the partial charges on the interacting edge-hydrogen atoms and corresponding changes in their attractive electrostatic interaction with the face ring also make an important contribution.

Recently, Wheeler and Houk developed a more general picture for the dominance of through-space effects of substituents over their effect on the aryl π system.[37] They proposed that substituents on aromatic rings do not significantly change the local π-electron density of the arene, but only their electrostatic potential (ESP). They state that strictly speaking the terminology "electron rich" and "electron poor" is not appropriate for substituted arenes, since the

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main difference is in the charge distribution and not in the local π-electron density.

Arenes bearing multiple substituents have also been investigated by second-order perturbation theory.[38] All substituted face-to-face dimers were more stable than the benzene dimer, with additive substituent effects in all cases except for geometries with substituents aligned on top of each other. For T-shaped dimers, the picture was more complex, but taking the Hammett constants and polarizabilities into account, a model predicting the effect of multiple substitution could be developed.

Wang and Hobza calculated the binding energies of benzene with different six-membered N-heteroarenes and found the interaction to strengthen with increasing number of nitrogen atoms.[39] The major part of the interaction energy originates from dispersion; the electrostatic component was counterbalanced by a large unfavorable exchange-repulsion term. The most-stable geometries were parallel-displaced and T-shaped edge-to-face. Recently, advances in the calculations of stacking interactions between nucleobases were reviewed by Hobza and co-workers.[24c] Calculations showed the π–π stacking between bases in DNA and RNA/DNA double helices to significantly enhance their hydrogen-bonding ability.[40] The largest contribution to complex stabilization was found to arise from dispersion rather than electrostatic interactions. Stacking between aromatic amino acid side chains and nucleobases has also been extensively investigated in computational studies.[41]

2.3. A Versatile Synthon for Crystal Engineering

Arene–arene dimers represent an important supramolecular synthon,[42] which is abundantly used in crystal engineering, in the design of liquid crystals and advanced materials, and in many other applications.[43] While parallels between molecular recognition in the solid state and in solution exist, crystal packing can be governed by additional factors such as shape, space filling, and crystallization conditions.[1,44] Several crystallographic studies report strong deformations of aromatic systems to enable favorable π–π interactions.[45] Generally, interplanar distances between 3.4 and 3.6 Å are observed for parallel-stacked arenes.[1,5] Arene–arene interactions are frequently combined with other directional interactions, such as hydrogen bonding, to generate new architectures for supramolecular materials.[46] The interaction strength in liquid crystals, arranged in columnar architectures, can be adjusted by lateral substituents on the aromatic cores.[47] The enclathration of aromatic guests into crystal pores shaped by aromatic molecules has also been further documented.[48]

2.4. Model Studies

Arene–arene interactions are widely employed in the formation of different supramolecular architectures, such as rotaxanes and catenanes. Given the abundance of these attractive systems, the reader is referred to pertinent reviews.[49] Extensive investigations on aromatic-guest-binding by cyclophanes,[50] self-assembled cyclophanes,[51] and elegant three-dimensional cages self-assembled by transition-metal coordination,[52] have also been continued. Curved π systems, such as fullerenes and bowls, undergo favorable concave–convex π–π stacking complexation with carbon nanorings,[53] but also a variety of other hosts such as cyclotriveratrylene with tetrathiafulvalene arms[54] and calix[6]arenes with built-in triptycene moieties.[55] The focus of this Section is on recent model systems that have been studied in solution to achieve an experimental quantification of individual arene–arene interactions.

Waters extensively investigated arene–arene interactions in both peptide α-helices and β-hairpin peptides in aqueous buffers.[56] The additional stabilization of α helices by interactions between neighboring pairs (Phe–Phe, Phe–4,4′-biphenylalanine, and Phe–perfluorophenylalanine (F_5-Phe)) amounts to $\Delta\Delta G = -0.1$ to -0.8 kcal mol^{-1}, with the Phe–Phe interaction providing the largest stabilization.[56d] In β hairpins, the Phe–Phe interaction was found to be more stabilizing than Glu–Lys salt bridges.[56b,57]

A similar β-hairpin system (Figure 3a) containing two Trp and two Lys residues was found to bind adenosine-5′-triphosphate (ATP) through a combination of electrostatic

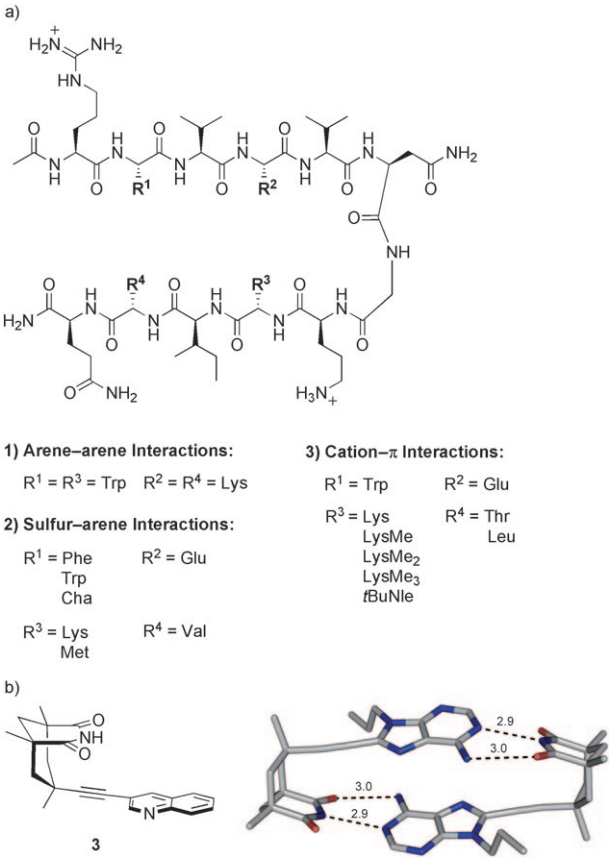


Figure 3. a) β-Hairpin peptides designed to investigate and quantify interactions of aromatic rings.[56a,185,217b] Cha = cyclohexylalanine, *t*BuNle = *tert*-butyl norleucine. b) Receptors to investigate adenine interactions in solution and in the solid state (CCDC-234433).[58] Distances in Å. Color code: gray C, red O, blue N.

interactions between the phosphates and the positively charged Lys residues, and π–π stacking interactions of the adenine moiety with the Trp side chains.[56a] Using fluorescence spectroscopy, the binding affinity of ATP was determined in acetate buffer ($K_a = 5800\,M^{-1}$, $\Delta G = -5.1$ kcal mol^{-1}; $T = 298$ K), with contributions of -1.8 kcal mol^{-1} from the aromatic interactions. By using fluorescence quenching, the association constant of flavine mononucleotide (FMN) complexation was determined to be $K_a = 2200\,M^{-1}$ in acetate buffer ($\Delta G = -4.6$ kcal mol^{-1}; $T = 298$ K), with a contribution of -3.4 kcal mol^{-1} from the flavine–Trp interaction.[56c]

The Rebek imide-type receptor **3** (Figure 3b; left) bearing a quinoline platform formed a complex with 9-ethyladenine with $\Delta G° = -2.8$ kcal mol^{-1} in $CDCl_3$ ($K_a = 121\,M^{-1}$, $T = 295$ K), of which -0.8 kcal mol^{-1} was attributed to the aromatic stacking between adenine and quinoline.[58] The receptor with an ethynyladenine platform formed supramolecular dimers in the solid state and in solution, with a dimerization constant of $K_{dim} \geq 10^4\,M^{-1}$ in $CDCl_3$ at 295 K (Figure 3b; right).

Molecular balances have been intensively studied to quantify noncovalent interactions[59] and, in particular, arene–arene contacts. Shimizu and co-workers studied aromatic parallel-displaced interactions with molecular balance **4**, wherein the phenyl ring of the ether arm is forced to undergo parallel-displaced stacking interactions with the arene platform in the folded conformation (Figure 4a).[60] By evaluating the ratio of the folded and unfolded conformations using ^{1}H NMR spectroscopy at 298 K in $CDCl_3$, the phenyl–phenanthrene interaction in folded **4** was quantified as $\Delta G = -0.84$ kcal mol^{-1}, and the interaction with a pyrene platform as -1.01 kcal mol^{-1}.[60a] The preference for folding was enhanced with increasing solvent polarity, going from benzene to acetonitrile, and correlated well with the solvent polarity parameter $E_T(30)$.[61]

In a study of 2,4-substituted xylopyranosides by ^{1}H NMR spectroscopy in $CDCl_3$, the stacking interaction of two pyrene substituents was found to stabilize the $^1C_4$ conformation, wherein both pyrene substituents are axial, by -1.7 kcal mol^{-1}.[62] The interaction was cancelled out in the presence of polar solvents, such as CD_3OD or $(CD_3)_2SO$.

We investigated substituent effects on the aromatic edge-to-face interactions by determining the folding equilibria of variously substituted Tröger base-derived molecular torsion balances[63] in C_6D_6 and $CDCl_3$ (Figure 4b).[64] The energetics determined for the two types of balances, **5** with an unsubstituted edge ring and **6** with a CF_3-substituted one, varied drastically. For **5**, similar folding preferences, independent of the nature of the face-ring substituent, were measured.[64a,c] In the CF_3-substituted torsion balance **6**, the interacting edge proton is much more positively polarized and the interaction with the unsubstituted face component becomes enhanced by $\Delta\Delta G = -0.4$ kcal mol^{-1} (C_6D_6). Interestingly, a strong dependence of the folding preference on the nature of the face-ring substituent was now observed and an excellent correlation between the free enthalpy of folding ΔG and the Hammett constant σ_m of the face substituent was found in both C_6D_6 and $CDCl_3$ (Figure 4b). The values for the free enthalpies of folding ΔG of the conformers, attributed to

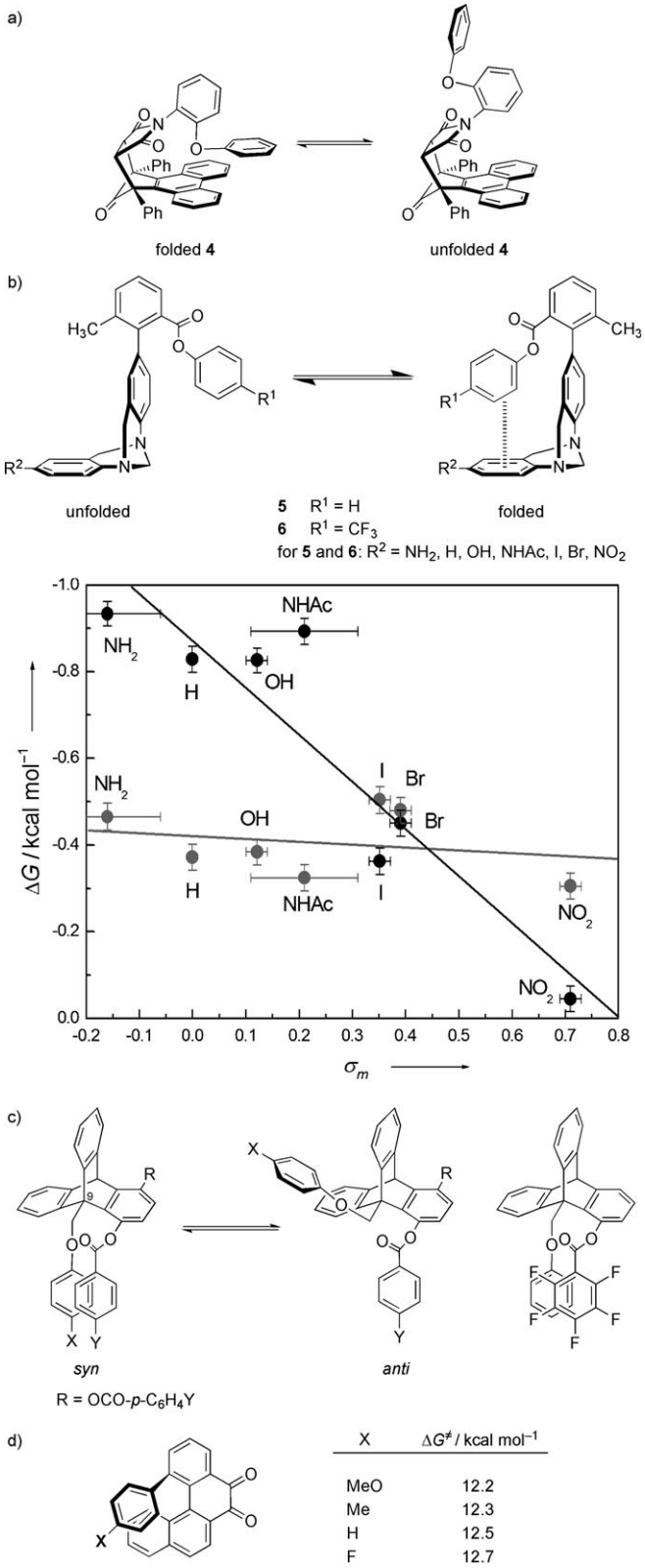


Figure 4. a–d) Molecular balances to investigate and quantify arene–arene interactions.[60a, 64c, 69a,b, 70, 142a] The graph in Figure 4b shows the experimental free enthalpies of folding in C_6D_6 for **5** and **6** as a function of face-ring substitution.[63c] The deviating data points for NHAc substituents are due to additional orthogonal C–F···C=O interactions in the folded conformation. Color code: gray **5**, black **6**.

the strength of the edge-to-face interaction, ranged from −0.05 ($R^1 = CF_3$, $R^2 = NO_2$) to −0.93 kcal mol^{-1} ($R^1 = CF_3$, $R^2 = NH_2$) in C_6D_6, and −0.08 ($R^1 = H$, $R^2 = NHAc$) to −0.65 kcal mol^{-1} ($R^1 = CF_3$, $R^2 = NHAc$) in $CDCl_3$. Based on the analysis introduced by Kim and co-workers,[33b] the substituent effects were explained by a dominant contribution of dispersion interactions to the total free enthalpy of interaction, with electrostatic and exchange-repulsion forces counterbalancing each other. The similar behavior in both solvents contradicts earlier predictions by Cockroft and Hunter[65] that were based on a simple electrostatic solvation model.[66] Overall, the observed substituent effects are in good agreement with the results discussed above from theoretical calculations by Kim,[33b] Sherrill,[33a] and Houk.[36]

Since the pioneering work by Ōki,[67] triptycene derivatives[68] have been established as useful molecular balances to investigate intramolecular noncovalent interactions. Gung and co-workers employed these systems to study parallel-displaced stacking interactions between variously *para*-substituted arenes.[69] By taking advantage of the slow rotation about the C9−CH_2 bond, the ratio of the folded *syn* and unfolded *anti* conformer was determined by low-temperature ^{1}H NMR spectroscopy in $CDCl_3$ (Figure 4c). Attractive interactions were found when both X and Y substituents were electron-withdrawing groups, or when one was an electron-donating group and the other an electron-withdrawing substituent.[69a,b] In $CDCl_3$, the free enthalpy of folding, $\Delta G°_{anti \rightarrow syn}$, ranged from +0.20 (X = Y = Me, Figure 4c) to ≤ -1.65 kcal mol^{-1} (X = NMe_2, MeO, CF_3; Y-phenyl: 3,5-dinitrophenyl). Stronger interactions were found when Y-C_6H_4 was replaced with N-heterocyclic aromatic rings.[69c] In agreement with theoretical predictions,[39] the free enthalpies of folding, $\Delta G°$, ranged from −0.16 (X = NMe_2, Y-phenyl: 4-pyridyl) to −0.91 kcal mol^{-1} (X = NMe_2, Y-phenyl: 6-pyrimidyl) in $CDCl_3$.

Cozzi, Siegel, and co-workers studied parallel-displaced π–π stacking using two series of benzophenanthrene model systems bearing a *para*-substituted phenyl ring (Figure 4d) and determined the differences in the barrier of rotation about the biaryl bond upon varying the substituent using variable temperature (VT) ^{1}H NMR spectroscopy in [D_8]THF.[70] Analogous to their previous 1,8-diarylnaphthalene model system,[71] the barrier $\Delta G^{\neq}$ increased in both series upon moving from electron-donating to electron-withdrawing substituents, thus howing an excellent correlation with the Hammett constants σ_p and emphasizing the role of polar π effects.

Chemical double-mutant cycles are a powerful tool for the dissection and quantification of noncovalent interactions in solution.[72] They were popularized first by Hunter and co-workers who applied their supramolecular zipper complexes to investigate substituent effects on aromatic stacking interactions (Figure 5, see also Section 6).[73] In $CDCl_3$, the aromatic stacking interaction energies $\Delta\Delta G$ ranged from +0.4 to −0.8 kcal mol^{-1} depending upon the substituents on the aromatic rings ($T = 298$ K). Whereas the major trends of the stacking energies could be explained by electrostatics, a simple ESP surface model was unable to sufficiently describe the substituent effects. This was mainly attributed to direct through-space interactions of the substituents.

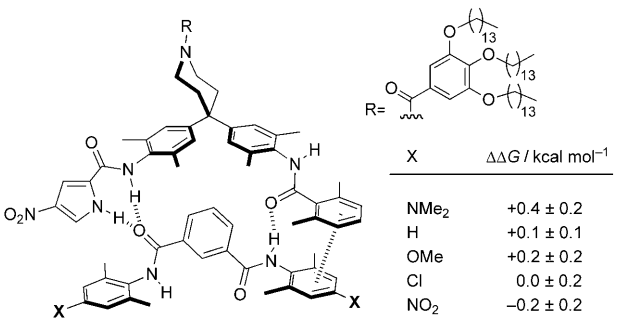
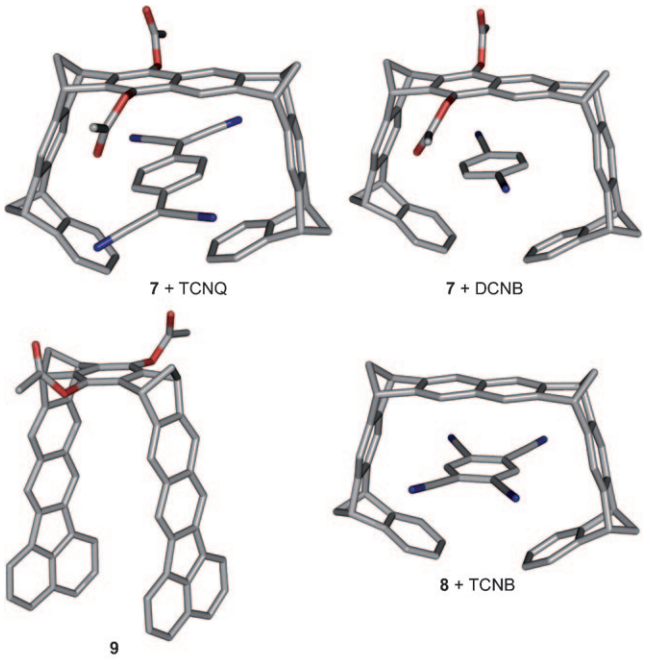


Figure 5. A supramolecular zipper complex to investigate substituent effects on aromatic stacking interactions in chemical double-mutant cycles.[73]

Among the various molecular tweezers and clips that have been prepared for guest complexation,[74] the rigid preorganized systems by Klärner and co-workers, such as **7**–**9**, have been the most rewarding in yielding quantitative insights into molecular recognition in aromatic host environments (Figure 6).[75]

These systems preferentially bind neutral electron-deficient aromatic guests through aromatic π–π stacking and edge-to-face interactions, but also cationic guests (see Section 6). Complexation occurs in organic solvents such as $CDCl_3$ and, in the case of appropriately functionalized tweezers, also in water. The structures of the complexes in solution were deduced from ^{1}H NMR spectroscopic measurements, which also yielded thermodynamic and kinetic quantities for the host–guest complexation steps. The proposed complex geometries in solution were confirmed in the solid state by a large number of X-ray crystal structures (Figure 6).[75f] ESP surfaces have been particularly useful in explaining and visualizing the driving force for binding: the highly negative ESP surface inside the cavity of the clips and tweezers enables favorable polar interactions with encapsulated electron-deficient guests.[75a,b] No complex formation was detected with electron-rich arenes.[75d] Dispersion and C−H···π interactions are also operative in these systems, and allow for high structural variation by extension of the aromatic sidewalls, as illustrated in Figure 6 by the benzo[*k*]-fluoranthene-bearing clip **9**.[75g]

A plethora of examples for applications of arene–arene interactions to the structure and function of supramolecular systems, and their utilization in polymer chemistry and chromatography have been reported since the publication of the first review.[1] Selected examples are self-assembled π stacks[76] of functional dyes such as bis(merocyanine) tweezers,[77] naphthalene and perylene diimide dyes with alternating electron-donor and electron-acceptor character,[78] bis(velcrand)s consisting of quinoxaline-bridged, biphenyl-linked resorcin[4]arenes,[79] hexakis(*para*-substituted-phenylethynyl)triindoles,[80] glycoluril-based molecular clips,[81] and self-assembled coordination cages.[82] Similarly, the investigations of π stacking to porphyrins and porphyrinoids exceed the scope of this review. However, it should be



Host	Guest	K_a / M^{-1}	T / K	Solvent
7	DCNB	110	298	$CDCl_3$
	TCNB[b]	7.3×10^5	298	$CHCl_3$
8	TCNQ	$> 10^5$	294	$CDCl_3$
	TCNB	$> 10^5$	294	$CDCl_3$
9	TCNQ	580	298	$CDCl_3$
	TCNB	920	298	$CDCl_3$
	TNF[a]	3.3×10^5	298	$CHCl_3$

[a] by spectrophotometric titration
[b] by spectrofluorimetric titration

DCNB = 1,4-dicyanobenzene
TCNB = 1,2,4,5-tetracyanobenzene
TCNQ = tetracyanoquinodimethane
TNF = 9-dicyanomethylene-2,4,7-trinitrofluorene

Figure 6. Molecular tweezers and clips complex electron-deficient arenes with high binding affinity (CCDC-222267, 222268, 618377, 682029).[75a,g] Color code: gray C, red O, blue N.

pointed out that an N-confused Zn^{II} porphyrin, bearing a pendant phenyl group, assembles through N-to-Zn ligation into a trimeric structure featuring a benzene trimer array of the phenyl rings.[83] In comparison to the nonphenylated analogue, the aromatic interactions between the three benzene rings in edge-to-face orientation stabilized the trimer by $\Delta\Delta G = -2.6\ \text{kcal mol}^{-1}$ with a stabilization enthalpy increment of $\Delta\Delta H \approx -1.3\ \text{kcal mol}^{-1}$ per interaction site at 298 K, as shown by VT ^{1}H NMR studies in a mixture of $[D_8]$toluene and $[D_5]$pyridine.

New techniques have appeared and provide novel insight: Using high-resolution neutron diffraction in conjunction with H/D isotopic labeling, the structures of benzene and toluene in the liquid phase were deciphered. For benzene, the coordination number in the nearest neighbor shell was found to be approximately 12 molecules,[84] which happens to be the coordination number in crystalline orthorhombic benzene.[1] At distances between the ring centroids less than 5 Å, a preference for parallel-displaced π–π contacts is observed, whereas perpendicular Y-shaped geometries, with two hydrogen atoms directed at the neighboring aromatic ring, dominate at separations greater than 5 Å.[84] Atomic force microscopy (AFM) has been used to address the π–π stacking energetics of pyrene and perylene at the single-molecule level.[85]

2.5. C–H···π Interactions

C–H···π interactions are ubiquitous in chemistry and biology. Their nature and occurrence are fully documented on the homepage of Nishio,[86] which features a database with publications on C–H···π interactions, and the reader is referred to this valuable resource which is complemented by reviews.[87] Therefore, these interactions are only briefly discussed here. C–H···π describes interactions of a non-aromatic C–H moiety with an aromatic ring and should not be confused with edge-to-face interactions between two aromatic rings.

High-level calculations (CCSD(T)) of C–H···π interactions have been performed,[88] involving the complexes of benzene with different small molecules.[89] The C–H···π interaction is weak: for the benzene–methane complex, its energy in the gas phase was calculated to be −1.5 kcal mol^{-1}.[88] Characteristic of the C–H···π interaction is a large favorable dispersion component and a small electrostatic contribution, resulting in very weak directionality. Activated C–H···π contacts, such as those of benzene with acetylene or chloroform, are considerably more favorable in terms of stabilization energy, partly because of the enhanced acidity of the interacting C–H, but mainly because of the increased dispersion originating from the polarizable substituents. Tsuzuki and Fujii compared C–H···π contacts with hydrogen bonds (e.g. O–H···π, N–H···π) and showed that the origin of the interaction is not the same and thus, the C–H···π contacts cannot be considered hydrogen bonds.[88] Dispersion is the main contributor to the C–H···π interaction, whereas hydrogen bonding is mainly governed by electrostatics. Presently, C–H···π interactions can be characterized in proteins directly by NMR spectroscopy at atomic resolution.[90]

Davis and co-workers obtained a long-awaited breakthrough in the development of synthetic receptors for saccharide recognition in aqueous solution.[91] They developed cage-type host systems which not only undergo lateral hydrogen bonding with the encapsulated sugar, but also sandwich the guest between two aromatic biphenyl or *m*-terphenyl moieties, as shown in Figure 7a for the selective cellobiose receptor **10**.[92] The activated C–H units of the complexed saccharide undergo efficient C–H···π interactions with the aromatic surfaces, the key to the formation of stable 1:1 complexes with association constants approaching $1000\ \text{M}^{-1}$ in water in the best cases. Potency and selectivity of these synthetic lectins are similar to those measured for their biological counterparts, which also utilize C–H···π interactions with aromatic amino acid side chains for complexation. Notably, the importance of these interactions for carbohydrate recognition had long been proposed by Lemieux[93] and had been revealed in the elegant crystallographic work by Quiocho and co-workers.[94]

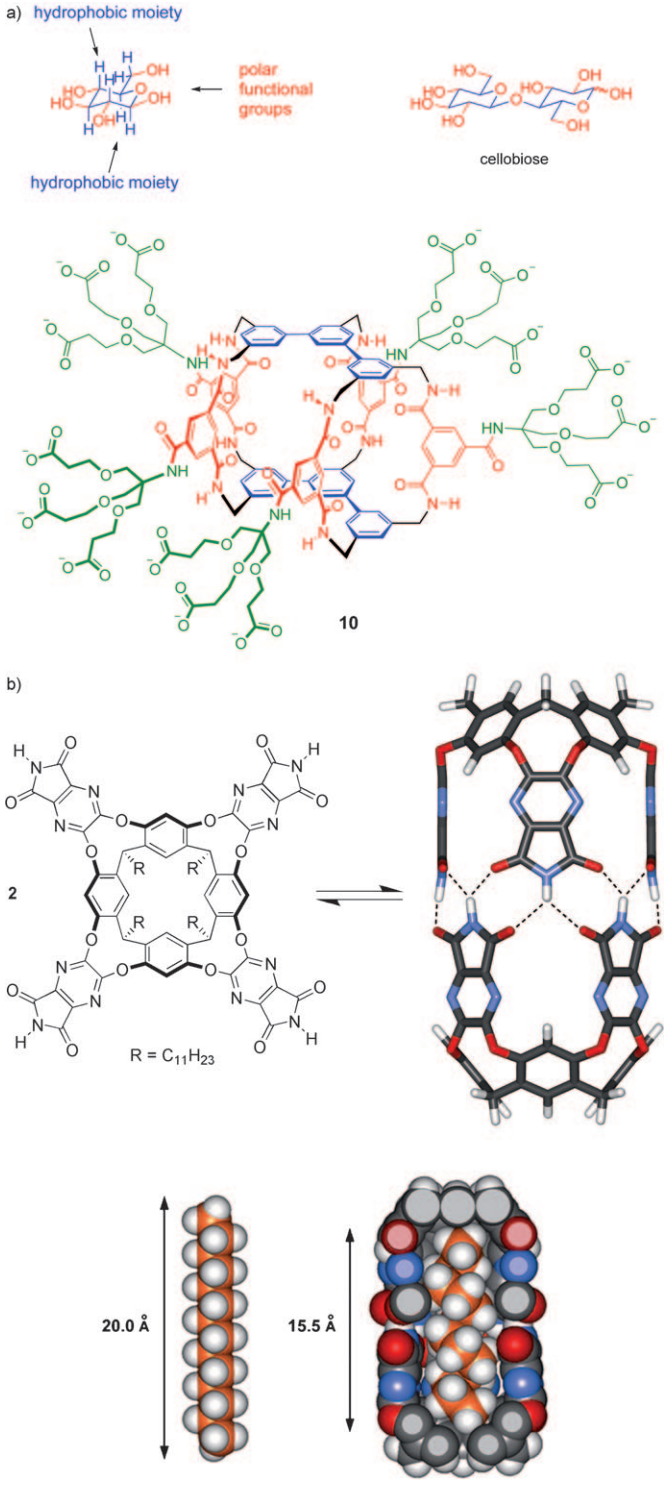


Figure 7. a) The lectin mimic **10** selectively binds cellobiose in water because of complementary hydrophilic and hydrophobic moieties.[92] b) Top: A tetraimide cavitand forms a dimer with a 15.5 Å long void.[97b] Bottom: *n*-Decane binds in the all-*anti* conformation, but the larger *n*-tetradecane is forced into *cis* conformation to fit into the void. The *cis* strain is compensated by C–H···π interactions. Color code: gray $C_{cavitand}$, orange C_{ligand}, red O, blue N.

Waters and co-workers investigated C–H···π interactions in a β-hairpin system.[95] For carbohydrate–π interactions they determined stabilization free enthalpies ($\Delta\Delta G°$) of −0.5 to −0.8 kcal mol^{-1} in aqueous solution, depending on the nature of the interacting arene and carbohydrate.[96]

Rebek and co-workers studied the conformational preferences of long-chain alkanes[97] enclosed in the confined space of cavitands[98] and self-assembled capsules[99] (Figure 7b). Numerous tight C–H···π interactions stabilize these complexes, and the alkane ^{1}H NMR resonances appear strongly and differentially upfield shifted. For optimal space occupancy and to avoid exposure to water, alkyl chains can fold into helical conformations when binding in water to the cavitands. In the capsules, they fold into helices if the length of the inner space is not sufficient for adopting the more stable all-antiperiplanar conformation.

As a final example, Martín and co-workers achieved chiral recognition of amino acid derivatives with an optically active synthetic receptor in $CDCl_3$ utilizing C–H···π interactions as the major discriminating force between the two diastereoisomeric complexes.[100] A single C–H···π interaction from the optically active host to one enantiomer of a Trp guest was quantified in a double-mutant cycle to amount to $\Delta\Delta G = -0.98$ kcal mol^{-1} (298 K, $CDCl_3$), thereby accounting for about 70% of the chiral discrimination.

2.6. Arene–Arene Interactions in Organic Synthesis

Arene–arene interactions can play a significant role in organic synthesis as documented in several reviews.[101] Earlier work had provided evidence for an important role of aromatic edge-to-face interactions in enantioselective reductions.[102] The interactions have been proposed to influence the yield and/or selectivity of different reaction types: intra- and intermolecular photochemical reactions,[103] allylic oxidations,[104] ruthenium-catalyzed transfer hydrogenations,[105] titanium-catalyzed oxidations of sulfides,[106] and others.[107] Two examples (Figure 8) illustrate these advances.

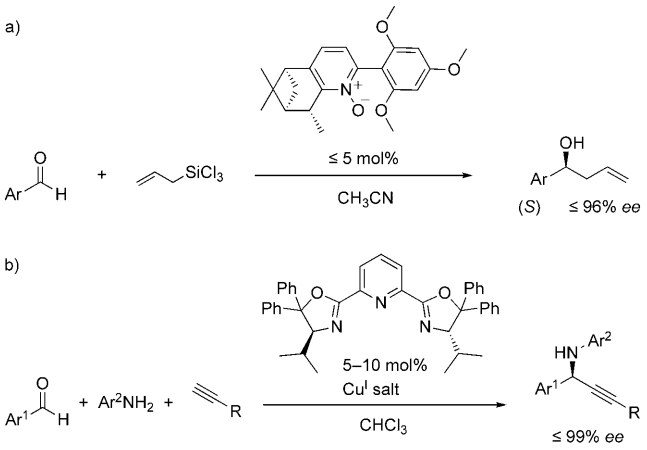


Figure 8. High enantioselectivity employing π–π interactions was achieved a) for the allylation of aromatic aldehydes with chiral pyridine-type *N*-oxides,[108b] and b) for the three-component synthesis of propargylamines.[109]

In asymmetric allylation of aromatic and heteroaromatic aldehydes, enhanced reaction rates and enantioselectivities were observed for electron-deficient benzaldehydes, in comparison to phenyl or electron-donor-substituted aldehydes, when performing the reaction with a methoxynaphthalene-bearing isoquinoline *N*-oxide catalyst.[108] This points to a role of arene–arene interactions between the reacting aldehyde and the catalyst. Additionally, the loss of selectivity when exchanging the solvent from CH_2Cl_2 to CH_3CN supports the role of π–π interactions in the transformation. Enantioselectivity was further enhanced using an electron-rich trimethoxyphenyl *N*-oxide catalyst (Figure 8a).

π–π Stacking interactions have been proposed to influence the stereochemical outcome in the synthesis of aromatic propargylamines (Figure 8b).[109] A chiral Cu^I complex with a pyridine bis(oxazoline) ligand was found to catalyze the reaction of aromatic aldehydes with amines and alkynes to give propargylamines with high yield and enantioselectivity. In the postulated transition state, the ligand complexes the substrate in a manner which enables two edge-to-face and one π–π stacking interaction, thus blocking one face from the attack of the copper acetylide.

3. Perfluoroarene–Arene Interactions

Perfluorobenzene forms 1:1 co-crystals with benzene.[110] The melting point of the co-crystals (297 K) is significantly higher compared to that of the single crystals of either perfluorobenzene or benzene (about 278 K for both). In crystals of neat benzene or neat hexafluorobenzene, edge-to-face orientations of the aromatic rings are prevalent. In contrast, parallel stacking of alternating perfluorobenzene–benzene rings is characteristic of the co-crystals, thus resulting in a columnar arrangement. A negative deviation from Raoult's law indicates attractive interactions.[111] The interplane distance between the aromatic rings ranges from 3.4 to 3.8 Å.

Quadrupole moments differ strikingly between perfluorobenzene ($+32\times10^{-40}\,C\,m^2$) and benzene ($-29\times10^{-40}\,C\,m^2$).[112] Interestingly, 1,3,5-trifluorobenzene displays almost no quadrupole moment ($+3\times10^{-4}\,°C\,m^2$). ESP surfaces are shown in Figure 9. The columnar perfluorobenzene–benzene co-crystal packing is the result of an optimization of quadrupole–quadrupole, dispersion, and C–H···F–C interactions, and has been discussed in various reviews.[1,28,113] According to calculations, the strength of the C_6H_6–C_6F_6 interaction is in the range of -3.7 to $-5.6\,kcal\,mol^{-1}$.[114] Interaction free enthalpies from -0.2 to $-1.0\,kcal\,mol^{-1}$ were measured in solution for different perfluoroarene–arene assemblies in chemical[115] and recently also biological environments.[116]

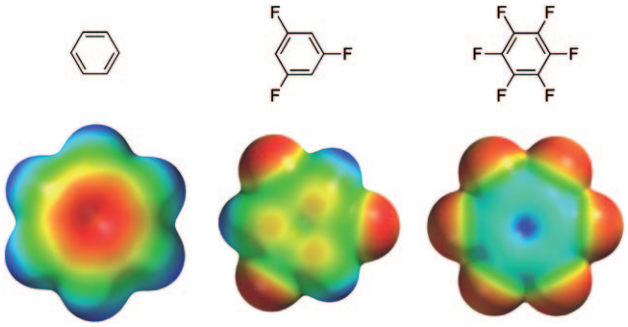


Figure 9. ESP surfaces of C_6H_6, 1,3,5-$C_6H_3F_3$, and C_6F_6 (Spartan, B3LYP/6-31G(d)).

3.1. Perfluoroarene–Arene Pairs: Versatile Supramolecular Synthons for Crystal Engineering

The dimeric perfluoroarene–arene parallel stacking motif has found wide application as a supramolecular synthon[42a] in crystal engineering.[1,111,113b,c,117] Alternate stacking frequently extends into infinite columnar structures. The synthon can assemble in a binary mixture of molecules, one with an unsubstituted and one with a fluorinated aromatic ring (e.g. C_6H_6 and C_6F_6). More frequently, however, both arene and perfluoroarene moieties are connected by appropriate linkers within a single molecular species, which self-assembles as a result of the formation of the synthon.

In addition to the stacking interactions, crystals featuring supramolecular perfluoroarene–arene synthons are stabilized by abundant C–H···F–C contacts. The hydrogen-bonding nature of these contacts remains under debate.[113a,d,118] Of course, molecular shape is another determining factor of the packing geometry.[111]

The synthon has been applied to the design of crystals lacking other strong directional interactions,[119] such as hydrogen bonds, in conjunction with additional directional interactions,[120] and in crystals of metal–organic complexes.[121]

Important lessons can be learned from this large body of work, which shows great structural diversity. While many crystal structures are largely dominated by strong directional interactions such as hydrogen bonding or metal coordination, perfluoroarene–arene stacking contributes even in the presence of these. This is illustrated in Figure 10 by the transition-metal complex **11**, which forms long rods, and by the binary pentafluorobenzoic acid-diphenylacetylene system, which crystallizes in a "brick-wall" motif. In the absence of directional interactions, perfluoroarene–arene interactions become dominant. In binary mixtures, arene–perfluoroarene complexes usually form with 1:1 stoichiometry, but also 2:1 complexes are sometimes obtained.[119e] Important in the design of crystal structures is the general shape of the molecule: the linkers connecting arene and perfluoroarene moieties,[119f,h,i,m] as well as other attached substituents[119j] strongly influence the crystal packing. Molecules containing more than two aromatic moieties can undergo combinations of parallel-stacked perfluoroarene–arene interactions and edge-to-face arene–arene interactions, thereby resulting in greater complexity and spatial arrangement in three dimensions.[119g]

Various applications for this supramolecular synthon are emerging. Flexible coordination networks can display guest-dependent structures.[121i] Müllen and co-workers developed a

concave polycyclic aromatic hydrocarbon host which incorporates C_6F_6 as a guest in the crystal structure.[122] Chiral binol (1,1′-binaphthalene-2,2′-diol) derivatives with one or two fluorinated six-membered rings were used to obtain homochiral coiled columns in crystals.[119l] The perfluoroarene–arene synthon has been utilized in crystalline chromophores for electronic and optoelectronic applications.[117] Perfluoroarene–arene interactions were also investigated by scanning tunneling microscopy (STM) on metal surfaces.[123]

3.2. Reaction Control and Catalysis

Frauenrath and co-workers employed perfluoroarene–arene interactions in topochemical polymerizations of buta-1,3-diynes to poly(diacetylene) in the crystalline phase.[124] The supramolecular synthon aligns the diacetylene moieties of the monomers in proper geometry for polymerization under UV irradiation. Crystalline monomers lacking the synthon, and hence the required spatial arrangement, did not polymerize.

Examples of the control of catalytic processes by intermolecular interactions are emerging. The regioselectivity of the copper-free 1,3-dipolar cycloaddition of alkynes with azides was ensured using perfluoroarene–arene interactions.[125] The synthon was also employed in ring-closing metathesis to enhance the yield of macrocyclizations to form cyclophanes in CH_2Cl_2 or toluene (Figure 11).[126] The pentafluorophenyl residue in **12** shields one side of the aromatic ring by undergoing intramolecular perfluoroarene–arene interactions. This forces the two 1-hexenyl substituents to reside on the opposite side and enables the reaction to **13**. In the absence of the C_6F_5 residue, mixtures of dimer and oligomers were obtained. The required perfluoroarene–arene interactions remained effective even at elevated temperatures ($\leq 110\,^{\circ}C$) and in the presence of a competitive solvent, such as toluene.

Biscoe and Breslow reported the selective reduction of diketones in water with $LiC_6F_5BH_3$.[127] Favorable intermolecular interactions of the C_6F_5 moiety with the aromatic substituents of the substrate increased the rate of reduction of an aromatic over an aliphatic keto group. A selectivity of up to 91:9 was obtained in D_2O. A beneficial effect of the perfluoroarene–arene interactions on the enantioselectivity of a Ti(TADDOLato)-catalyzed sulfenylation of β-ketoesters with PhSeCl was found by Jereb and Togni.[128] The reaction of a perfluoroarene substrate took place with 72% *ee*, which is in slight contrast to the 62% *ee* obtained with nonfluorinated arenes. An asymmetric photocyclization of an achiral diarylethene, assisted by perfluoroarene–arene interactions, was achieved in the solid state.[129] Co-crystallization with achiral octafluoronaphthalene resulted in a chiral crystalline environment which enabled the transformation to occur in a highly enantioselective fashion (>99% *ee*). In contrast, a racemic mixture was obtained in solution.

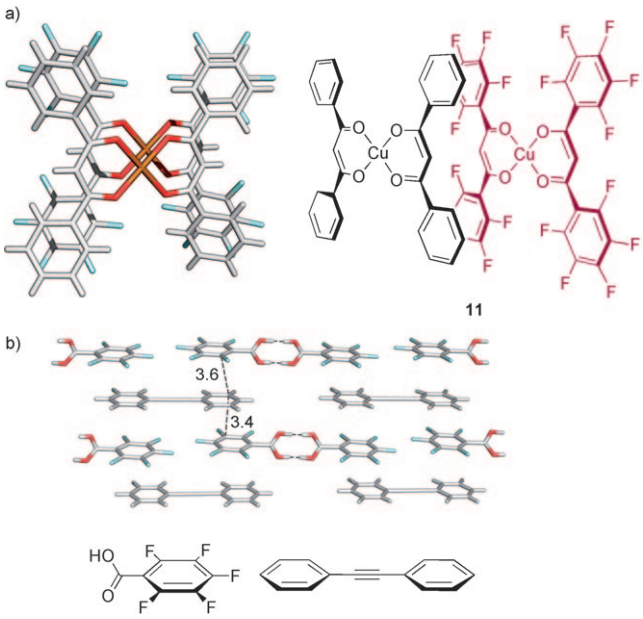


Figure 10. a) Perfluorophenyl–phenyl interactions govern the crystal packing of **11** to afford long rods (CCDC-650334),[121h] and b) to generate a "brick-wall" motif in 1:1 crystals of diphenylacetylene and pentafluorobenzoic acid (CCDC-205458).[120a] Distances in Å. Color code: gray C, turquoise F, red O, orange Cu.

3.3. Computational Studies

Tsuzuki et al. investigated the most important geometries of the C_6F_6–C_6H_6 dimer using CCSD(T) methods (Figure 12).[130] The most favorable one is the parallel-displaced geometry ($\Delta E = -5.38\,kcal\,mol^{-1}$), followed by the face-to-face geometry ($\Delta E = -5.07\,kcal\,mol^{-1}$), with interplanar distances of 3.6 and 3.5 Å, respectively. The T-shaped geometries, however, are much less stable (−1.74 and $-0.88\,kcal\,mol^{-1}$) mainly as a result of reduced dispersion interactions and an unfavorable electrostatic term. Dispersion interactions make the major stabilizing contributions to all four geometries. The directionality of the interaction is determined by both dispersion and electrostatic terms, the latter including also the quadrupole interaction term.[131]

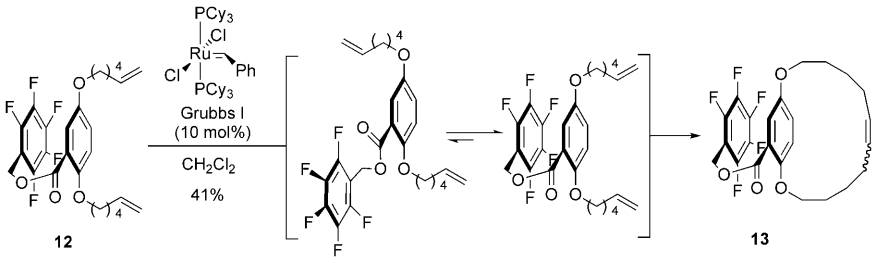
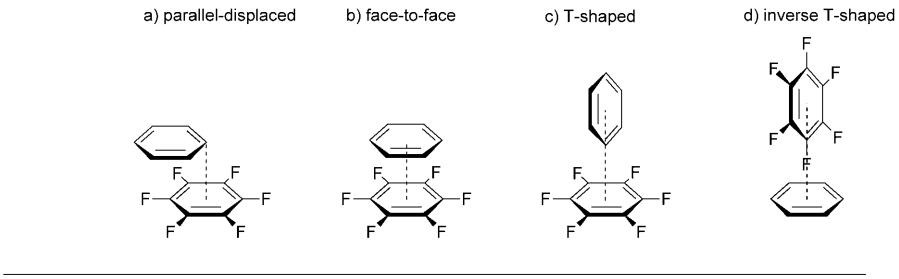


Figure 11. Enhancement in cyclophane yield in ring-closing metathesis mediated by the pentafluorophenyl–phenyl interaction.[126a]

Other studies revealed the dominant role of dispersion in perfluoroarene–arene interactions.[119i,132] At present, it seems that a dominant effect of quadrupole interactions can be ruled out.

Substituent effects (X = CN, F, H, Me, NH_2, NMe_2) on C_6H_5X–C_6F_6 complexes were investigated by using up to the MPs(full)/aug-cc-pVDZ level of theory.[133] Parallel-displaced dimer geometries were found to be more stable than those in the face-to-face geometry.[133a] In particular, the stability increased when the substituent was located on top of the C_6F_6 ring. The highest stability was calculated for X = NMe_2, and attributed to a charge-transfer effect.[133a,134]



	a) parallel-displaced	b) face-to-face	c) T-shaped	d) inverse T-shaped
d [Å] =	3.6	3.5	5.0	6.0
ΔE [kcal mol^{-1}] =	−5.38	−5.07	−1.74	−0.88

Figure 12. Geometries of hexafluorobenzene–benzene dimers, their distances, and CCSD(T) interaction energies.[130]

3.4. Biological Systems

The effects of organofluorine on binding efficacy and selectivity in protein–ligand complexation are currently being intensively investigated,[135] and in this context, the molecular recognition properties of perfluorophenyl rings in ligands bound to biological receptors are explored.[136] Analysis of the results and establishment of structure–activity relationships (SARs) may however be complicated by the fact that the attractive interactions of a perfluorinated ring on a ligand with the side chains of aromatic amino acids might be masked by unfavorable interactions when some of the fluorine substituents point into an electron-rich environment of the surrounding protein.

The effect of the -C_6F_5 moiety on the secondary structure of peptoids, oligomers of N-substituted glycines, was investigated by NMR and CD spectroscopy in CH_3CN.[137] Constructs with alternating phenyl and pentafluorophenyl side chains were prepared to investigate whether their stacking would lead to distinct conformational preferences. Incorporation of C_6F_5 substituents enforced helicity in the peptoids, in contrast to the usually preferred threaded loop conformations.

The effects of Phe→F_5-Phe mutations on the folding of a 35-residue protein, the chicken villin headpiece subdomain (cVHP), which folds into a discrete tertiary structure with helical motifs, was investigated by Gellman and co-workers.[138] A total of seven mutants were prepared involving three spatially interacting Phe rings (Phe6, Phe10, and Phe17), but only the mutation of Phe10 resulted in a greater stabilizing effect on the protein fold compared to the wild-type ($\Delta G_{fold} = -2.5$ kcal mol^{-1}). The other mutations had either no effect or even destabilized the protein ($\Delta\Delta G$ up to $+0.8$ kcal mol^{-1}), thus underlining the necessity of the right interaction geometry and avoiding repulsive contacts.

The stacking interactions of two phenyl–pentafluorophenyl pairs were studied within the homodimeric de novo protein α_2D, which forms a three-helix bundle in water (Figure 13).[116a] Phe→F_5-Phe mutants were synthesized, and the folding of monomers into homodimers was studied by fluorescence resonance energy transfer (FRET), NMR spectroscopy, and thermal denaturation studies. A chemical double-mutant cycle revealed that each phenyl–pentafluorophenyl pair contributes down to $\Delta\Delta G = (-1.0 \pm 0.3)$ kcal mol^{-1} to the stability of the dimer.

The C_6H_5–C_6F_5 synthon has also been introduced into nucleic acids.[139] Notably, nucleobases interact differently with arenes and perfluoroarenes.[140] Thus, 9-ethyladenine binds better to a synthetic receptor (analogous to **3** in Figure 3) by stacking on a naphthyl ring ($\Delta G = -2.49$ kcal mol^{-1}) rather than on a perfluoronaphthyl ring ($\Delta G = -1.88$ kcal mol^{-1}).

3.5. Model Systems

The energetics of the perfluoroarene–arene synthon in solution[141] have been investigated in a number of model studies. Gung and co-workers prepared a triptycene-based molecular torsion balance (Figure 4c), which in the folded *syn* conformation undergoes near face-to-face C_6H_5–C_6F_5 interactions that are absent in the *anti* conformation.[142] The *syn* conformation is particularly preferred if the two stacking rings have opposite polarity. Thus, with the *p*-NMe_2-substituted phenoxy ring and a pendant $C_6F_5CO_2$ moiety, $\Delta G_{anti\rightarrow}$

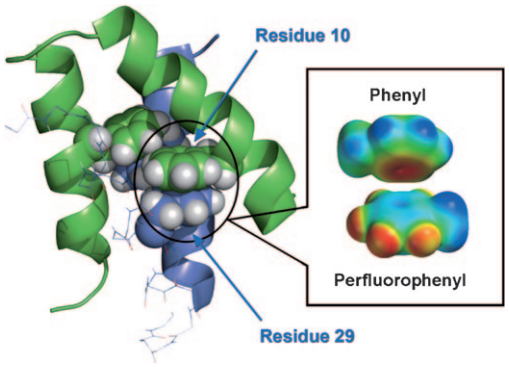
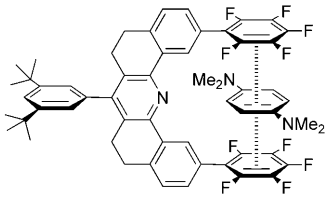


Figure 13. Three-helix bundle structure of the designed homodimeric protein α_2D with stacked Phe and F_5-Phe rings in positions 10 and 29, respectively (PDB code: 1QP6).[116a]

$_{syn} = -0.99$ kcal mol^{-1} was measured in $CDCl_3$ (293 K). If the number of F atoms in the benzoate ester is decreased stepwise from $C_6F_5CO_2$ to $C_6H_4FCO_2$ ($\Delta G_{anti \rightarrow syn} = +0.72$ kcal mol^{-1}), the driving force for folding is reduced and the *anti* conformation preferred.

Perfluoroarene–arene interactions were also studied by Hunter and co-workers in double-mutant cycles using molecular zipper complexes (Figure 5).[73,143] Free enthalpy increments $\Delta\Delta G$ for the stacking interaction with a C_6F_5 ring were determined by ^{1}H NMR spectroscopy in $CDCl_3$ (293 K) and revealed substituent effects opposite to those seen in the stacking to a nonfluorinated phenyl ring. Electron-rich arenes prefer stacking with the C_6F_5 ring and changes in $\Delta\Delta G$ from -0.76 (p-NMe_2) to $+0.05$ kcal mol^{-1} (p-NO_2) were observed.

The molecular tweezer **14** (Figure 14) was investigated for its ability to sandwich aromatic guests between two C_6F_5 rings.[144] ^{1}H NMR titrations showed that the more electron rich the intercalated arene, the higher the complex stability: *N*,*N*,*N*′,*N*′-tetramethylphenylene-1,4-diamine was bound the strongest with $\Delta G = -1.1$ kcal mol^{-1} (THF, 300 K).



14

Figure 14. Molecular tweezer for the complexation of electron-rich aromatic guests.[144a]

4. Hydrogen Bonding to Aromatic Systems

Hydrogen bonding is a broad phenomenon with bond energies spanning from 0.2 to 40 kcal mol^{-1},[145] and with the average free enthalpy contribution $\Delta\Delta G$ from a traditional neutral hydrogen bond in aqueous solution contributing as much as -1.5 kcal mol^{-1}.[146] The hydrogen bonds to a π system are rather weak in their incremental free enthalpy contribution. Numerous experimental and theoretical studies have been devoted to clarifying the interaction energies and geometries of these π-hydrogen bonds,[147] some of which will be discussed in the following.

N–H···π and O–H···π interactions regularly occur in proteins; in a PDB search of 592 protein crystal structures, Steiner and Koellner found one aromatic amino acid out of eleven to be π-hydrogen-bond accepting in general, and one out of six tryptophans, which is the most potent acceptor.[148] These weak hydrogen bonds can also influence the conformation of molecules.[87b] Commonly, the distance between the hydrogen-bond donor atom and the centroid of the aromatic ring is 3.2–3.8 Å,[148] as seen for example in the case of cyclic aniline trimers.[149]

Hydrogen-bonding contacts between the N–H of amino and amide groups and the side chains of aromatic amino acids contribute significantly to protein stability and to protein–ligand binding.[150] The N–H···π interactions between amides and aromatic amino acids have been investigated with peptide model systems,[151] and identified, for example, in the case of inhibitors binding to Chk1 kinase,[152] where the aromatic ring of the inhibitor ($K_i = 26$ nM) undergoes N–H···π interactions with the amide NH of Ser147/Asp148 (Figure 15).[153]

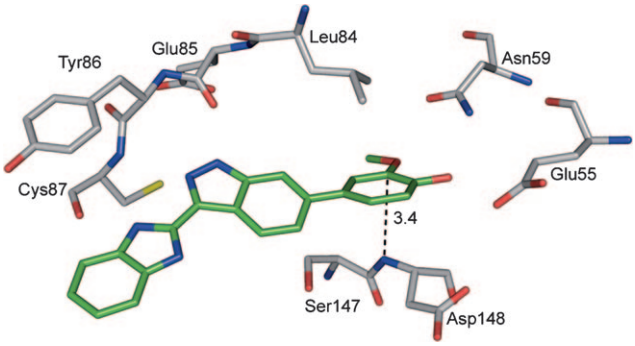


Figure 15. N–H···π hydrogen bond between Ser147/Asp148 of Chk1 kinase and the phenyl moiety of the inhibitor (resolution: 2.60 Å, PDB code: 2C3K).[153] Distances in Å. Color code: gray $C_{protein}$, green C_{ligand}, red O, blue N, yellow S.

4.1. Physical and Theoretical Aspects

Several calculations have been performed on the geometry and strength of O–H···π and N–H···π interactions.[13e,16a,154] For O–H···π interactions of water with benzene, the water molecule is located above the center of the aromatic ring in the most stable geometry, with one hydrogen atom pointing towards the center of the ring (Figure 16a).[28] This monodentate binding geometry was found to be more stable than the bidentate one. Similar results were obtained for ammonia with benzene (Figure 16b): the monodentate binding geometry was preferred compared to the bi- and tridentate ones, and the ammonia molecule resided most preferably above the center of the aromatic ring.

Ab initio studies by Tsuzuki et al. showed that the interaction between benzene and ammonia or water has a significant dispersion component, with directionality being mainly controlled by electrostatic interactions.[155] The interaction energy of the water–benzene complex was higher than that of the ammonia–benzene complex (-3.17 versus -2.22 kcal mol^{-1}). For formamide, the most stable geometry was the T-shaped N–H···π hydrogen-bonded one, with calculated binding energies as low as -4.0 kcal mol^{-1} (Fig-

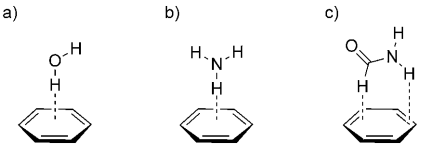


Figure 16. The most stable interaction geometries for a) the O–H···π interaction of water with benzene, b) the N–H···π interaction of ammonia with benzene, and c) the interaction of formamide with benzene.[28]

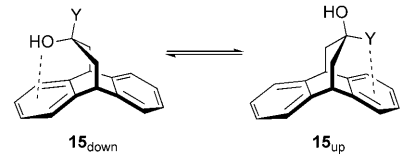
ure 16c).[28,156] For *N*-methylformamide, a stabilization energy of around −5.0 kcal mol^{-1} was predicted for both stacked and T-shaped geometries on the CCSD(T)/CBS level of theory.[157] Solvation by water was found to weaken the O–H···π and N–H···π interaction by 1–2 kcal mol^{-1}.[158]

4.2. Energetic Aspects from Experimental Studies

The energetic aspects of N–H···π and O–H···π interactions have been investigated with different methods and model systems,[159] and a few of them are discussed in the following. Zheng et al. used two-dimensional (2D) IR vibrational echo spectroscopy to investigate the binding of phenol to *p*-xylene, benzene, and bromobenzene.[160] Electronic-structure calculations determined the gas-phase binding mode of the phenol–benzene complex to consist of O–H···π and edge-to-face interactions. The dissociation time constant τ_d for the complexes shortens upon moving from electron-donating to electron-withdrawing substituents on the arene ring that interacts with the phenol. The bond enthalpies $\Delta H°$, determined by measuring the temperature dependence of the complexation equilibria by IR absorption, were −2.23 kcal mol^{-1}, −1.67 kcal mol^{-1}, and −1.21 kcal mol^{-1} for the phenol–*p*-xylene, phenol–benzene, and phenol–bromobenzene complexes, respectively. The stabilization enthalpy of the indole–benzene complex was determined as −5.2 kcal mol^{-1} by mass-analyzed threshold ionization experiments, and computational studies on the CCSD(T) level of theory supported the N–H···π interaction geometry of the complex.[161]

Hughes and Waters investigated the effect of acylation of the Lys side chain upon the interaction with Trp in a β-hairpin system using double-mutant cycles, and found similar interaction energies for Lys–Trp and LysAc–Trp, that is, −0.30 and −0.34 kcal mol^{-1}, respectively.[162] In NMR studies in D_2O (pH 4.0, 50 mM [D_3]NaOAc) at 298 K, the upfield shift of the amide proton of LysAc is indicative of interactions with the aromatic ring of Trp.

Intramolecular O–H···π interactions were investigated by following the conformational equilibria of disubstituted dibenzobicyclo[3.2.2]nonanes by ^{1}H NMR spectroscopy in $CDCl_3$ at 298 K (Figure 17, see also Section 5).[163] Alcohols **15a** and **15b** bearing an alkyl substituent point the proton of the hydroxy group preferably towards the aromatic ring



15$_{down}$ **15**$_{up}$

Compound	Y	ratio$_{down/up}$	$\Delta G°$ / kcal mol^{-1}
15a	Me	94:6	−1.9
15b	*n*Bu	94:6	−1.9
15c	H	7:93	+1.5

Figure 17. Conformational equilibrium of the functionalized dibenzobicyclo[3.2.2]nonane model system to explore the strength of O–H···π interactions.[163]

($\Delta G° = -1.9$ kcal mol^{-1}), whereas in the secondary alcohol **15c**, the hydroxy group is directed towards the solvent because of its larger size in comparison to the hydrogen atom. In a follow-up study, the O–H···π interaction was compared with the N–H···π interaction by replacing the hydroxy group in **15a** with an amino group, and the O–H···π interaction was found to be 1 kcal mol^{-1} more stable in $CDCl_3$ at 298 K.[164]

5. Sulfur–Arene Interactions

The nature of sulfur–arene interactions has been explored in a number of studies, which have been extensively reviewed.[1,165] In protein environments, Met is as likely as Phe and Trp to be located in close proximity to Trp, and about 50% of the contacts occur with the face of the aromatic ring.[165f,166] Figure 18 shows the most important interaction geometries for the side chains of Met (Figure 18a) and Cys

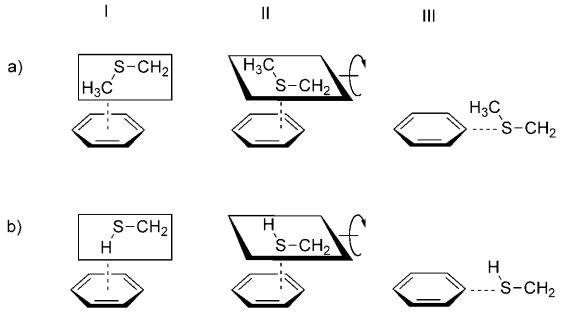


Figure 18. Geometries for Met–arene and Cys–arene interactions in proteins: The arrows indicate the variation of the angles between the aromatic ring plane and the planes through the Me-S-CH_2 and H-S-CH_2 fragments.

(Figure 18b) with aromatic rings. For Met side chains, the location atop the face, with S at a distance of less than 4 Å to the aromatic ring carbon atoms, is as abundant as the location at the edge of the ring.[165f] In contrast, a CSD search revealed a preference of C-S-C fragments for the edge of aromatic rings (Figure 18a.III) in small molecules.[165d] In a computational study, the side chain of Cys was shown to interact preferentially with the aromatic face, thus establishing a S–H···π contact (Figure 18b.I).[165e] However, PDB searches showed that Cys in proteins largely interacts through geometry shown in Figure 18b.II [165f] because of its strong preference (82% of all Cys) to act as a conventional hydrogen-bond donor to O or N.[165e] Additionally, 90% of Cys residues in proteins are present in the disulfide form, cystine.[167] Some studies also report a preference for the geometry, shown in Figure 18b.III, in proteins.[165e,168] Consequently, the expression "sulfur–arene interaction" can be regarded as an oversimplification,[1] as it can be divided into more specific interaction modes: S···π, S–H···π, S–C–H···π, and C–H···S interactions.[56d]

Sulfur–arene interactions are largely dispersive in nature, although the geometry of the association might be affected by electrostatics. A consensus from previous investigations of

biological and model systems quantifies the incremental binding free enthalpy ($\Delta\Delta G$) for this interaction to range from -0.5 to -1.0 kcal mol^{-1}.[1,56d]

5.1. Biostructural Analysis

A most notable feature of sulfur–arene interactions is the abundance of Met side chains interacting with the adenine moiety, as shown by a Relibase[169] search in the PDB for ATP in kinases and other enzyme-bound adenine-bearing cofactors, such as *S*-adenosylmethionine[170] (SAM; Figure 19). Met side chains also participate in the binding of other nucleobases and analogues,[171] and heteroaromatic substitutes of adenine from ATP in small-molecule kinase inhibitors in particular.

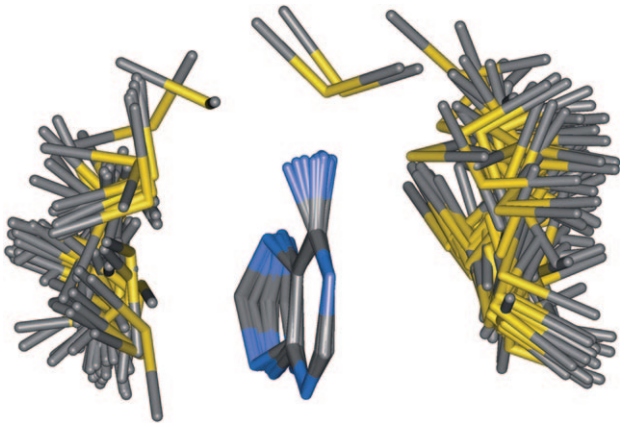


Figure 19. Superimposition of 225 Met side chains in close proximity to adenine extracted from 129 crystal structures from the PDB. Distances up to 4.2 Å were found from the NH_2-bearing carbon atom in position 6 to the sulfur atom. The search was performed using Relibase + 3.0.1.[169] Color code: gray C, blue N, yellow S.

Several PDB searches have appeared in the literature in recent years. Chakrabarti and co-workers investigated the environment of divalent sulfur in proteins (Figure 20).[167,172] The extracted sulfur–arene interactions are most frequent at distances of 3.6–4.3 Å (closest atom–atom contact), with a maximum occurrence at 3.9 Å. In all the geometries, the sulfur atom is displaced from the center ($\theta = 30$–$90°$), apparently enabling more favorable interactions with the aryl ring. The antibonding σ* orbitals of the S–C bonds tend to be directed towards the π-electron cloud, whereas the sulfur lone pairs preferentially orient towards the partially positively charged (δ^+) rim of the arene.

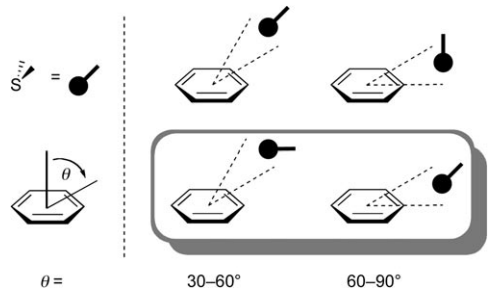


Figure 20. Preferred interaction geometries for Met and Cys with aromatic rings (Phe, Tyr, Trp, and His) as extracted from the PDB.[172] The framed geometries appear more frequently than the ones shown on the top.

Another PDB study concludes that Met side chains are often in proximity to a π donor (ca. 22%), such as aromatic rings but also amides.[173] Interestingly, the authors observed very frequent C–H···S contacts (ca. 40%), thus indicating a strong tendency of Met to undergo dispersive interactions. Cys side chains often display contacts to π donors (ca. 30%) and to C–H fragments (ca. 20%). Thus, the higher ratio of π to C–H contacts for Cys as compared to Met indicates a preference for S–H···π hydrogen-bonding type interactions over dispersion.

The following crystallographic examples, which were selected from a large collection[174] for sulfur–arene interactions in protein–ligand complexes, especially highlight the impact of the interactions on ligand-binding affinity and selectivity. Carell and co-workers obtained a crystal structure of a cisplatin lesion in DNA polymerase η (Figure 21 a).[175] The side chain of Met74 in the polymerase is embedded into a box shaped by three nucleobases that contribute significantly to the stabilization of the folded geometry of the lesion, thus further inhibiting the movement of the polymerase along the DNA chain.

The structure of a complex between the p53 transactivation domain and the pleckstrin homology domain of transcription factor b1 (Tfb1) was solved by NMR spectroscopy (Figure 21 b).[176] The Trp side chain of p53 at the interface of the proteins undergoes S–arene interactions with Met59 of Tfb1. The activity decreased by a factor of 12 upon mutation of Met59 to Ala.

The X-ray co-crystal structures of the ligand-dependent transcription factors peroxisome proliferator activated receptor-γ (PPARγ) and -α (PPARα) were obtained (Figure 21 c).[177] The structures show that the selectivity of the inhibitor **16** (EC_{50}(PPARα) = 0.03 μM; EC_{50}(PPARγ) = 0.21 μM) can be partly rationalized by additional S–H···π interactions with Cys276 in PPARα.

5.2. Computational Studies

H_2S–arene interactions with different arenes such as benzene,[168,178] naphthalene,[154e] azulene,[179] polycyclic aromatic hydrocarbons (PAHs),[180] indole,[181] and other heterocycles,[178b] have been preferentially addressed in recent computational work. Various computational methods and force fields have been applied to calculate the interaction energies. Most studies conclude that the interaction is largely dispersive.[154e,178b,179,181] Electrostatic contributions also play a role[178a] and are of the same magnitude in both H_2S–arene and H_2O–arene complexes; dispersion, however, is much stronger in the former.[181] Calculations that account for the strong dispersive contribution of the interaction provide the best results. In the most favored interaction geometry of

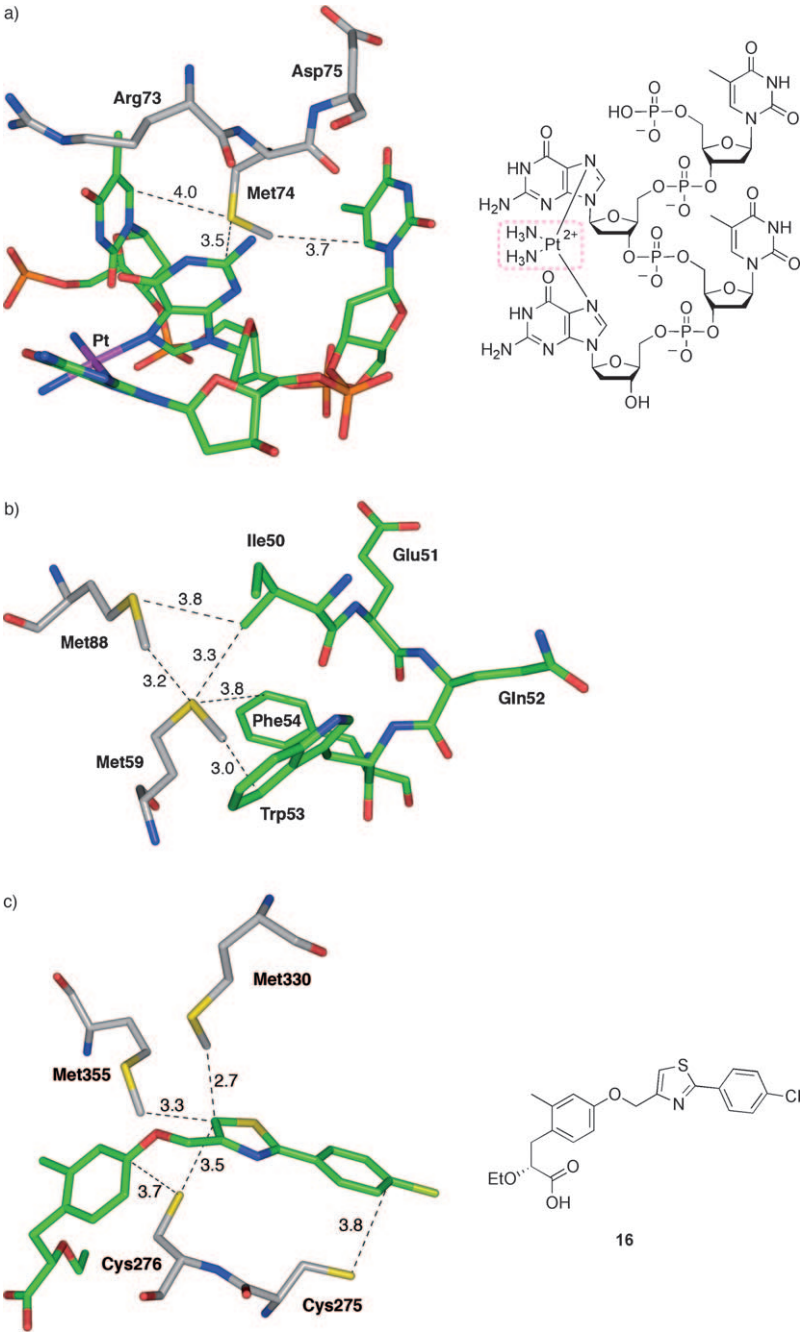


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Figure 21. a) X-ray crystal structure of a cisplatin DNA lesion (**GTG**T) bound to DNA polymerase η (PDB code: 2WTF).[175] b) The binding of a fragment of p53 to the pleckstrin homology domain of Tfb1 (PDB code: 2GS0).[176] c) Inhibitor **16** bound to PPAR (PDB code: 3FEI).[177] Distances in Å. Color code: gray $C_{protein}$, green $C_{DNA/p53/ligand}$, red O, blue N, yellow S, orange P, magenta Pt.

H_2S–benzene, sulfur is situated over the centroid of the aromatic ring with the hydrogen atoms pointed towards the plane (Figure 22a),[168] but desymmetrization of the geometry by a displacement of the sulfur is also found.[182] The H_2S–benzene complex is not strictly C_{2V} symmetric but one hydrogen atom of H_2S is pointing more towards the aromatic plane (tilted by about 30°), thus resulting in a C_s geometry and suggesting that C_{2V} symmetry is a second-order saddle point rather than a minimum. The calculated interaction energies of the H_2S–arene complexes are mostly in the range of −0.7 to −2.8 kcal mol^{-1} for benzene derivatives, but can be up to −5.2 kcal mol^{-1} for circumcoronene ($C_{96}H_{24}$), a polycyclic aromatic hydrocarbon. Generally, the larger and the more electron rich the arene system, the stronger the interaction energies.

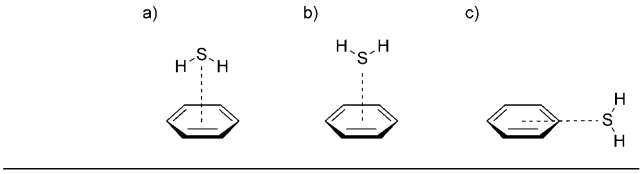
Only very few new computational investigations were reported on interactions mimicking the biologically important Met–arene contacts.[168,178b,183] They confirm the earlier findings summarized in the previous review.[1] In view of the substantial energetic contribution of dispersion interactions in complexes such as Me_2S–arene, meaningful computations require methods capable of treating these properly.

5.3. Model Systems

New investigations of model systems confirm the energetic gains from sulfur–arene interactions ($\Delta\Delta G$ between −0.5 and −1.0 kcal mol^{-1}) that were extracted from previous work.[1]

Motherwell, Hunter, and co-workers studied an intramolecular S–arene interaction in $CDCl_3$ using a molecular torsion balance (Figure 23; see also Figure 17).[163] The equilibrium between the conformers of **17** undergoing either CH_2O–π or CH_2S–π interactions is 24:76, which translates into a free enthalpy difference of −0.7 kcal mol^{-1} (T = 293 K). To appreciate this value, it is important to consider that only the S/O atoms participate in the interaction and that the geometry is highly restricted. Nevertheless, this study shows that the aromatic ring interacts preferentially with the sulfur rather than oxygen atom, most probably because of the large difference in polarizability (for S, 3.0×10^{-24} cm^3; for O, 0.63×10^{-24} cm^3).[184]

Waters and co-workers used a β-hairpin system (see Figure 3a in Section 2) to evaluate the energetics of S–arene interactions.[185] The interactions of the side chains of Phe, Trp, and cyclohexylalanine (Cha) with the side chain of Met within the hairpin were evaluated in aqueous solution using a double-mutant cycle. The Met–Phe interaction stabilizes the β-hairpin by −0.3 kcal mol^{-1} (T = 298 K). The same value was observed for the Met–Trp interaction, but Met more favorably interacts with Cha (−0.5 kcal mol^{-1}). In this hairpin system, cycloalkyl moieties are apparently better interaction partners for Met than aromatic rings. The authors concluded that the S–arene interaction is largely based on the high polarizability of the sulfur atom, in accordance with most other work.[1]



	a)	b)	c)
d [Å] =	3.8	3.6	5.5
ΔE [kcal mol^{-1}] =	−2.64	−1.12	−0.74

Figure 22. Calculated distances and interaction energies for three local minima of the H_2S···arene complex on the CCSD(T)/aug-cc-pVTZ level.[168]

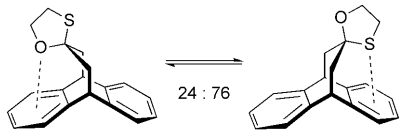


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Figure 23. Molecular balance to investigate S···aromatic interactions.[163]

Recently, selenium–arene[186] and tellurium–arene interactions have also been proposed.[187] Also, the lowering of the oxidation potential of an aromatic ring as a consequence of sulfur–arene interactions has been reported.[188]

6. Cation–π Interactions

The cation–π interaction is abundant in nature. Model studies, pioneered by Dougherty and co-workers, have made seminal contributions to understanding the way nature exploits this interaction to bind biologically relevant molecules.[189] Investigations of numerous model systems and synthetic receptors for onium ion recognition have shown the strength of the cation binding to be proportional to the number of aromatic rings, and the incremental free enthalpy contribution $\Delta\Delta G$ to reach values of 0.5 kcal mol^{-1} per aromatic ring.[1] However, energetic quantification studies in biological systems still remain scarce.

In nature, the binding site of ligands bearing ammonium residues often consists of aromatic amino acid side chains, as in the uptake of ammonium ions by an ammonia transport channel (PDB code: 1U7G),[190] in the binding of the positively charged 7-methylguanosine ring in the human nuclear cap-binding complex (Figure 24a),[191] in the complexation of trimethyllysine ($LysMe_3$) of histone H3K4me3 in the aromatic box of the BPTF PHD finger of the nucleosome remodeling factor NURF (Figure 24b),[192] and in the encapsulation of *N*,*N*,*N*-trimethylglycine in the aromatic box formed by three Trp side chains of periplasmic ligand-binding protein ProX (Figure 24c).[193]

While electrostatic attraction between the π system and the cation has been established as the main contributing force to the interaction,[189d] recent calculations have shown induction to play a significant role as well.[28] Using the ESP CHELPG method (ElectroStatic Potential Charges from

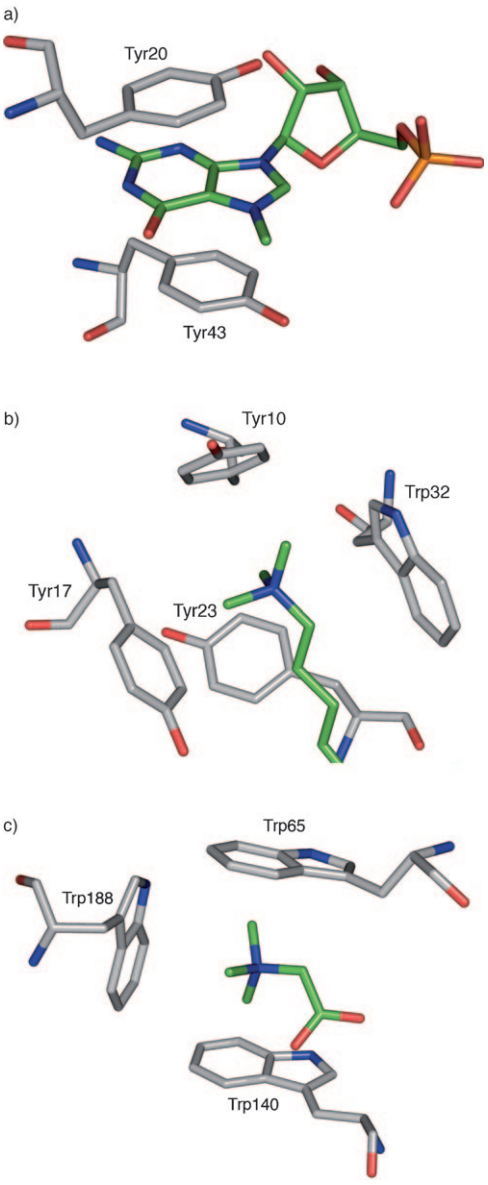


Figure 24. Binding of a) the positively charged 7-methylguanosine ring in the human nuclear cap-binding complex (PDB code: 1H2T),[191] b) *N*,*N*,*N*-trimethylated Lys of histone H3K4me3 in the aromatic pocket of BPTF PHD finger (PDB code: 2F6J),[192] and c) *N*,*N*,*N*-trimethylglycine bound in the aromatic box formed by three Trp residues of periplasmic ligand-binding protein ProX (PDB code: 1R9L).[193] Color code: gray $C_{protein}$, green C_{ligand}, red O, blue N, yellow S, orange P.

Electrostatic Potentials Generalized), the atomic partial charges of the tetramethylammonium (TMA) cation were calculated as +0.28 for N, −0.30 for C, and +0.16 for H.[194] Hence, the contribution of the positively polarized C–H bonds interacting with the negatively polarized π system through C–H···π interactions should also be taken into consideration.[195]

The key review by Ma and Dougherty[189d] has been followed up by more recent accounts, mainly from the point of view of computational studies.[28,196] Further examples of the cation–π interaction in biology, in particular in neuro-

sciences,[197] emerge constantly,[193,198] and the importance of investigations on model systems[199] for the quantification of the interactions has been underscored. Cation–π interactions have also been exploited in ligand design,[200] de novo peptide design,[201] and as a controlling element in organic synthesis.[202]

6.1. Information from Protein and Small-Molecule Crystal Structure Analyses

Cation–π interactions at biological interfaces were investigated in a series of PDB searches. To elucidate the importance of cation–π interactions in protein–DNA binding, 62 X-ray crystal structures of protein–DNA complexes were analyzed,[203] with 45 showing cation–π contacts. Arg–π interactions were found more often than Lys–π contacts. The Arg side chain was observed to interact preferentially with Phe and Tyr rather than with Trp. Purine nucleobases undergo stronger cation–π interactions with their five-membered ring rather than with their six-membered rings. Computed interaction energies varied from −2.4 to −9.9 kcal mol^{-1}, the average being −5.0 and −4.3 kcal mol^{-1} for Arg and Lys, respectively.[203a]

In another investigation, 52 protein–DNA complexes were considered.[204] In 37 of these complexes the cation–π/hydrogen-bond stair motif[205] was observed, which involves the cation–π interaction of a DNA nucleobase with Arg or Lys simultaneously hydrogen bonded to another nucleobase.

A search for cation–π interactions between adenine and either Arg or Lys in ATP-binding proteins revealed that such contacts existed in 40 out of 68 adenylate–protein complexes, thus underlining their importance for adenine binding by proteins.[206]

Since Arg is an important residue at protein–protein interfaces, a total of 734 crystal structures featuring such interfaces were analyzed to investigate the role of cation–π pairs in protein–protein interactions (PPIs).[207] Nearly half of the protein complexes and 30% of the homodimers featured at least one such interfacial pair. Arg–Tyr interactions were found to be the most abundant (43%) out of the possible cation–π pairs. The interaction involving Arg was calculated to contribute on average −3.3 kcal mol^{-1} of electrostatic free energy of binding. In over 60% of the cases, the cation–π contact was accompanied by hydrogen bonding of Arg to residues on the second interacting protein. Coplanar arrangement of the guanidinium group with the arene is favored (53%) over orthogonal and oblique geometries.

Metal cation–π interactions have attracted increasing attention, and Sastry and co-workers performed a search in the CSD and PDB.[13c] The interactions of alkali- and alkaline-earth metal cations with two aromatic rings are at least as abundant as those with only one ring. In the former, the cation–π contact induces the cooperative strengthening of the π–π interaction of the two aromatic rings. In proteins, parallel-displaced and T-shaped geometries of the two rings seem to be preferred, wherein the metal cation resides above the center of one ring (the face ring in the edge-to-face geometry). For interactions with one aromatic ring, calculations have shown that off-axis configurations can also be favorable, although to a minor extent.[208] Computational analyses identify double-decker face-to-face complexes as the most stable ones.[13c] Further study of the interplay of cation–π and π–π interactions is clearly worthwhile, and MP2 calculations, complemented by experimental analysis by Frontera, Deyà, and co-workers have already provided additional evidence of substantial positive cooperativity between the two types of interactions.[209]

The crystal structure of thermoalkalophilic T1 lipase revealed a Na^+···Phe interaction at an average C···Na^+ distance of 3.3 Å.[210] In the CSD, nine complexes involving contacts between phenyl rings and K^+ showed an average interaction distance of 3.3 Å, whereas two complexes involving Na^+ displayed a distance of 2.8 Å. Calculations on the Na^+···Phe interaction in the structure of T1 lipase revealed a large gain, both in enthalpy and entropy, in the binding of the cation to the protein.[211]

The reader is referred to additional examples of cation–π interactions in X-ray crystal structures in biological systems,[212] small-molecule crystals,[213] and host–guest complexes,[46a,214] which were reported in the last years.

6.2. Energetic Quantifications in Biological Environments

Waters and co-workers investigated the recognition of $LysMe_3$ with a β-hairpin peptide model system (Figure 3a).[215] In the hairpin system, the interaction of Trp with $LysMe_3$ is stronger than with its purely aliphatic counterpart, *tert*-butyl norleucine (*t*BuNle). The interaction energies are (−1.0 ± 0.1) kcal mol^{-1} for $LysMe_3$–Trp, and (−0.6 ± 0.1) kcal mol^{-1} for *t*BuNle–Trp (D_2O/[D_3]acetate buffer). Thermal denaturation studies revealed the interaction with $LysMe_3$ to be entropy driven with a negligible enthalpic contribution, whereas the binding of *t*BuNle showed unfavorable enthalpy and a greatly enhanced favorable entropy of folding. In the case of the binding of mutated H3 (methylated histone 3) peptides to the HP1 chromodomain,[216] the $LysMe_3$-bearing H3 peptide was shown to bind with much higher affinity (K_d = 10 μM) than the *t*BuNle-bearing peptide (K_d = 310 μM) in a fluorescence polarization assay in buffer solution at 288 K.

Methylation of Lys in histones is an epigenetic modification, which is critical in gene expression. Patel and co-workers showed by NMR, calorimetric, and surface plasmon resonance (SPR) studies that the binding of histone H3K4 to the aromatic pocket of the BPTF PHD finger is enhanced by increasing the degree of the Lys side chain methylation (Figure 24b).[192]

Waters and co-workers studied the effect of methylation on the cation–π interaction in their β-hairpin system (Figure 3a).[217] Methylation increased the stability of the hairpin by $\Delta\Delta G = -0.3$ kcal mol^{-1} (Lys–Trp), −0.5 kcal mol^{-1} (LysMe–Trp), −0.7 kcal mol^{-1} ($LysMe_2$–Trp), and −1.0 kcal mol^{-1} ($LysMe_3$–Trp) (all within ±0.1 kcal mol^{-1}; T = 298 K), as evaluated with double-mutant cycles in buffer solution.[217b] With each methylation, the folding entropy became more favorable, whereas the enthalpic driving force was reduced. Both asymmetric and symmetric dimethylation of Arg were

shown to stabilize the hairpin by $\Delta\Delta G = (-1.0 \pm 0.1)$ kcal mol^{-1}.[217d] Similar binding enhancements upon Lys methylation were observed by the same group using a synthetic Dougherty-type cyclophane host with disulfide bridges;[218] the cyclophanes were obtained using a dynamic combinatorial library approach.[219]

We identified the enzyme factor Xa to bind quaternary ammonium ions effectively in the S4 pocket,[220] which constitutes an aromatic box that consists of the three side chains of Tyr99, Phe174, and Trp215. The tricyclic trimethylammonium-bearing inhibitor (±)-**18**, with a phenylamidinium moiety targeting the S1 pocket of the enzyme, binds to factor Xa with an inhibitory constant of $K_i = 0.28$ μM, whereas the neutral *tert*-butyl inhibitor (±)-**19** has a much lower affinity ($K_i = 29$ μM; Figure 25a). The quaternary ammonium ion binds efficiently to the S4 pocket, and the N^+/C replacement shows that cation–π interactions contribute $\Delta\Delta G = -2.8$ kcal mol^{-1} to the free enthalpy of binding, that is, approximately 0.9 kcal mol^{-1} per aromatic ring ($T = 298$ K).

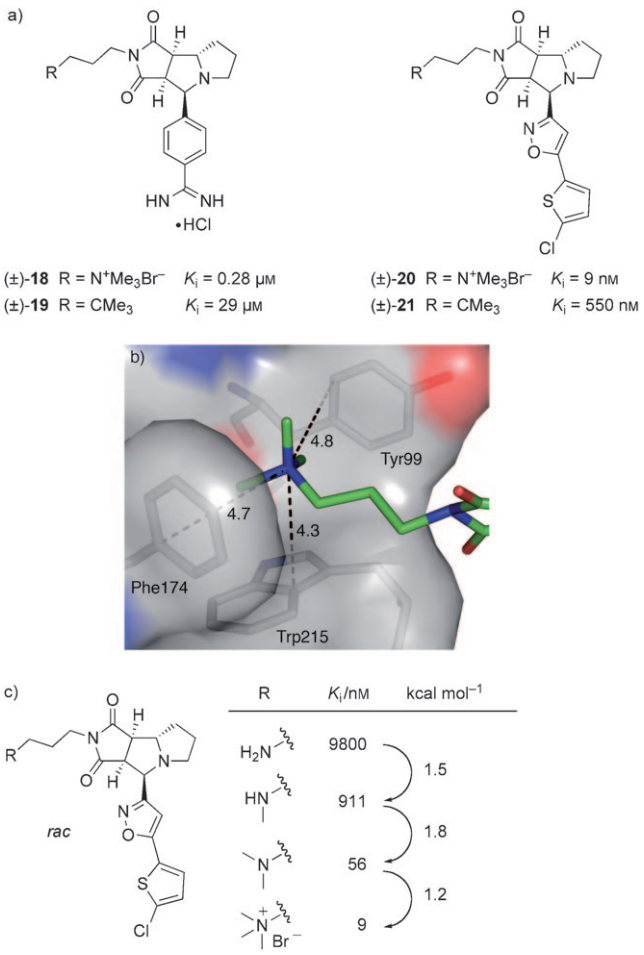


Figure 25. a) Inhibitors for the investigation of cation–π interactions in the S4 pocket of factor Xa.[220,221] b) Incorporation of the Me_3N^+ center of (3a*S*,4*R*,8a*S*,8b*R*)-**20** in the S4 pocket of factor Xa (PDB code: 2JKH).[221] c) Binding affinity to factor Xa strongly increases from primary to the quaternary ammonium ligand. Under the conditions of the biological assay at pH 7.8, the amines are fully protonated. Distances in Å. Color code: gray $C_{protein}$, green C_{ligand}, red O, blue N.

The ligand system was subsequently redesigned to enhance the binding affinity (Figure 25a).[221] The cationic ligand (±)-**20** with a neutral isoxazolyl chlorothiophenyl needle occupying the S1 pocket was highly potent ($K_i = 9$ nM), whereas the *tert*-butyl analogue (±)-**21** only bound with an affinity of $K_i = 550$ nM, thus resulting in a free-enthalpy increment for the cation–π interaction of $\Delta\Delta G = -2.5$ kcal mol^{-1} and 0.8 kcal mol^{-1} per aromatic ring. These data confirm that the cation–π interaction is one of the strongest driving forces in biological complexation processes. The X-ray crystal structures of (±)-**18** (PDB code: 2BOK) and (±)-**20** (Figure 25b; PDB code: 2JKH) complexed with factor Xa revealed that, in both structures, the onium ion resides at nearly identical positions within the S4 pocket. The cationic center is located approximately in the middle of the aromatic box, on the intersection of the normals passing through the centroids of the aromatic rings.

The strength of cation–π interactions at the active site of factor Xa depends strongly on the degree of ammonium ion methylation, and the binding affinity increases with each methylation from $K_i = 9800$ nM (H_3N^+-), to $K_i = 911$ nM (H_2MeN^+-), to $K_i = 56$ nM (HMe_2N^+-), and to $K_i = 9$ nM (Me_3N^+-, (±)-**20**; Figure 25c). The increment in free binding enthalpy of $\Delta\Delta G = -1.2$ to -1.8 kcal mol^{-1} per methylation amounts to a gain of -0.4 to -0.6 kcal mol^{-1} per aromatic ring. The improved fit of the ammonium substituent into the aromatic box of the S4 pocket, and the decreasing costs of ligand desolvation account for this enhancement in affinity upon stepwise methylation. Whereas quaternary ammonium ions do not cross biological membranes, tertiary ions may do so after deprotonation: the good affinity of the tertiary amine ligand ($K_i = 56$ nM) suggests the applicability of mildly basic *tert*-amines as suitable substituents that, in the nonprotonated form, can cross the membrane and in the protonated form undergo strong cation–π interactions in the S4 pocket of factor Xa. Basic tertiary amine residues are indeed popular to fill this site as revealed in a PDB search.[220]

The weak binding of the primary ammonium inhibitor leads us to discard a true cation–π interaction between aromatic side chains and Lys in the absence of a counteranion.[222] Presumably, Lys rather interacts with the aromatic rings through C–H···π interactions with its side chain, as proposed by Gallivan and Dougherty,[223] whereas the primary ammonium center turns away from the aromatic ring to benefit from solvation.

Cation–π interactions are critical in many recognition processes involving neuroreceptors containing binding pockets lined by aromatic amino acid side chains for binding substrates such as nicotine, serotonin (5-hydroxytryptamine), dopamine, acetylcholine (ACh), or GABA (γ-aminobutyric acid). This was revealed in remarkable collaborative work by the Dougherty and Lester groups.[224] One elegant way to probe these interactions is to introduce nonnatural aromatic amino acids, which have increasingly fluorinated aromatic rings, to the receptors. Fluorine substitution reduces the electron density of the aromatic rings and cation binding weakens, as evaluated in electrophysiological measurements. This strategy was used to probe and identify cation–π interactions at the $GABA_A$[224b] and $GABA_C$[224a] receptor

binding sites, at the dopamine binding site of the D2 receptor of a G-protein coupled receptor (GPCR),[224c] and at the nicotinic ACh α4β2 brain receptor binding site.[224d] As an example, mutation of β_2Tyr97 in the $GABA_A$ receptor into the corresponding increasingly fluorinated Tyr derivatives caused an approximately 20-fold increase in the EC_{50} value with each additional fluorine substituent, which is indicative of weakened cation–π interactions in the binding of GABA.[224b]

6.3. Model Systems

Numerous synthetic host systems have been found to complex quaternary ammonium[225] and pyridinium ions[226] in organic and aqueous media. In a reversed mode, a cationic *N*-methylquinolinium receptor was found to bind 9-ethyladenine in $(CDCl_2)_2$ at 295 K more strongly ($\Delta\Delta G = -0.6$ kcal mol^{-1}) than the corresponding quinoline-based receptor (Figure 3b), which is not capable of undergoing cation–π interactions.[140]

Resorcin[4]arene-based cavitands and capsules bind organic cations in aqueous solution[227] and organic solvents.[228] In CH_3OH, Ballester and Sarmentero observed a resorcin[4]arene cavitand to complex choline with an affinity of $K_a = (3.2 \pm 0.9 \times 10^5)\,M^{-1}$ ($T = 298$ K).[229]

As a result of their electron-rich nature, pyrogallol[4]arenes complex larger cations, such as tetramethylphosphonium, even more strongly than the corresponding resorcin[4]arene hosts.[230] In ITC studies in ethanolic solution ($T =$ 298 K), the pyrogallol[4]arene host **22** (Figure 26a) was observed to complex L-carnitine [$K_a = (18000 \pm 1000)\,M^{-1}$] with much higher affinity than betaine [$K_a = (3200 \pm 100)\,M^{-1}$], choline [$K_a = (3400 \pm 200)\,M^{-1}$], and ACh [$K_a = (6100 \pm 200)\,M^{-1}$].[225c] The binding of all these guests is enthalpy driven and accompanied by a slight entropic loss. In addition to cation–π interactions, hydrogen bonding contributes to the binding affinity.

Rebek and co-workers synthesized the resorcin[4]arene-based receptor **23** (Figure 26b), which binds choline and ACh in water ($T = 298$ K) with high affinity (by ITC: K_a(choline) = $(25900 \pm 700)\,M^{-1}$, K_a(ACh) = $(14600 \pm 1200)\,M^{-1}$).[231] The ITC experiments showed a significant enthalpic contribution to guest complexation. Cavitands of this type have also been shown to accelerate in their interior the aminolysis of *p*-nitrophenyl choline carbonate with propylamine to give the corresponding carbamate,[232] and when functionalized at the rim by a Zn/salen complex, the acylation of choline to ACh.[233]

Rim-extended resorcinarene cavitands by Atwood and Szumna (Figure 26c), such as **24a**, were found to selectively encapsulate TMA salts as ion pairs in $CDCl_3$ and in crystals.[234] The cation is bound within the resorcin[4]arene bowl, whereas the anion interacts with the amide N–H groups at the rim, thereby sealing the cavitand. The addition of methanol, which competes with the counteranion for the N–H recognition sites, resulted in the cation being encapsulated by **24a** and the anion being released into the solvent.[234a] Further extension of the cavity with additional phenyl substituents, as in **24b**, allowed capsular ion-pair binding even in the presence of methanol, as found in X-ray crystal structures.[234b] Spherical halide anions were bound with remarkable selectivity; an affinity order of $I^- > Br^- > Cl^-$ was found in ion extraction experiments.

By using *p*-sulfonatocalix[4]arene as a host in water ($T =$ 298 K), Hof and co-workers observed an increase in the binding affinity of Lys and Arg upon methylation by using ^{1}H NMR spectroscopy.[235] $LysMe_3$ ($K_a = (37000 \pm 18000)\,M^{-1}$) binds 70-fold stronger than its nonmethylated

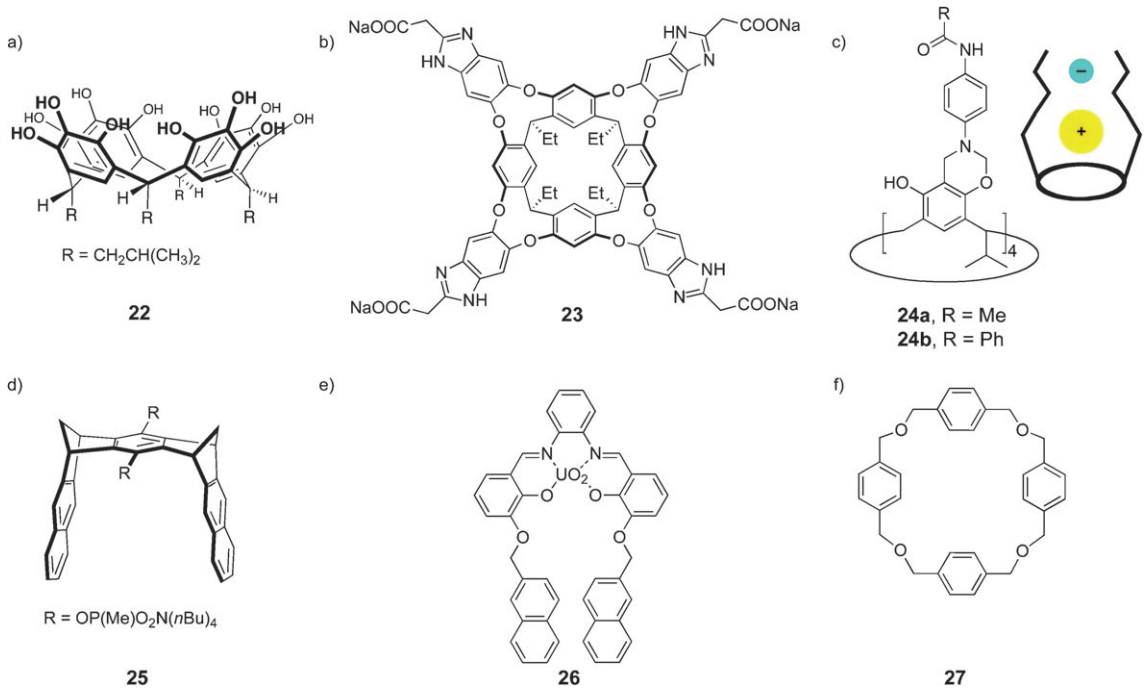


Figure 26. Host molecules shown to complex guests through cation–π interactions.[225c,231,234b,237,241,245]

counterpart ($K_a = (520 \pm 300)\,M^{-1}$). ITC studies showed a strong enthalpic driving force and a smaller favorable entropic component for the complexation, with the enthalpic component increasing significantly with each methylation ($\Delta\Delta H$: LysMe→$LysMe_2$: -0.8 kcal mol^{-1}; $LysMe_2$→$LysMe_3$: -0.5 kcal mol^{-1}, for similar studies in biological environment, see Section 6.2).[235a]

The highly preorganized molecular clips and tweezers, introduced by Klärner and co-workers, also recognize organic cations in addition to electron-deficient aromatic guests.[75a] The electron-rich cavities of these aromatic host molecules, such as **25** (Figure 26d), have been shown to bind Lys and Arg in water,[236] as well as a variety of N-alkylpyridinium guests,[237] such as NAD^+,[237,238] and even sulfonium guests such as SAM.[239] The positively charged moiety of the guests was shown to bind in the aromatic cavity by ^{1}H NMR titration studies. Additionally, clip and tweezer molecules were shown to inhibit alcohol dehydrogenase by binding either to NAD^+ or to Lys residues on the surface of the enzyme.[240]

Uranyl-salophen-based receptors, such as **26** (Figure 26e), form complexes with TMA and tetrabutylammonium (TBA) salts in chloroform.[241] X-ray analysis confirmed that the uranyl ion coordinates to the counteranion which undergoes ion pairing with the quaternary ammonium ion. The latter interacts favorably with the aromatic pendants (naphthalene rings in **26**) of the receptor. The receptor complexes ACh with an affinity of $K_a = 42\,000\,M^{-1}$ (298 K). The binding affinity of TBA^+X^- increases with the hardness of the counteranion in the order I^- ($K_a = 190\,M^{-1}$) < Br^- ($K_a = 1200\,M^{-1}$) < Cl^- ($K_a = 23\,000\,M^{-1}$), thus indicating that the major energetic contribution to the binding arises from the coordination of the anion to the hard metal ion center.[242]

6.4. Parameters Affecting Cation–π Interactions

A number of investigations with synthetic receptors have addressed specifically the influence of counteranions on cation–π interactions. This is a relevant issue particularly in lower-polarity environments, where the cation is ion paired with the counteranion, resulting in a more complex three-component (cation, anion, arene) recognition process.[1]

Counteranion effects were studied with chemical double-mutant cycles by Hunter and co-workers, using their molecular zipper complex (for the structure, see Figure 5 in Section 2),[243] in which the interacting *N*-methylpyridinium ion is held in close proximity to a substituted phenyl ring. They confirmed the previously determined increment for the cation–π interaction to be $\Delta\Delta G = -0.6$ kcal mol^{-1} ($CDCl_3$, $T = 300$ K) in the absence of either strong donor or acceptor substituents on the phenyl ring. In agreement with theoretical calculations,[244] the cation–π interactions in this system were found to be independent of the nature of the counteranion (BPh_4^-, PF_6^-, I^-).[243b] However, the opportunity of the anions to interact with other binding sites in the system makes an unambiguous clarification of counteranion effects on cation–π interactions in the molecular zipper system complicated.

Roelens and co-workers prepared tetraether cyclophane **27** (Figure 26f),[245] which is a better receptor in $CDCl_3$ (296 K) for TMA salts than the previously reported macrocyclic tetraester derivative.[246] Receptor **27** does not feature any competing counteranion binding sites. As with the tetraester, large differences in the binding affinity of the salt to **27** were observed upon changing the counterion. Upon complexation of salts with anions of high charge density, such as chloride, a large loss in cation–π binding affinity was observed (for TMA^+Cl^-, $K_a = 165\,M^{-1}$) as compared to salts with softer anions, such as dimethyltrichlorostannate ($K_a = 1004\,M^{-1}$). The investigations with the cyclophanes show that electrostatic inhibition is a constant for each anion and can be predicted by calculating the ion-pair electrostatic potential (EP): the higher the EP, the more stable the cation–cyclophane complex. However, in the context of cation–π-mediated binding of tight ion pairs by conformationally rigid hosts, the results might be affected by steric hindrance in the case of large anions.

Solvation effects on the cation–π interaction were studied on a model protein by double-mutant cycles, where the interaction between a buried Trp and partly solvated Lys, Arg, and His were investigated.[247] The Trp–Lys interaction accounted for $\Delta\Delta G = (-0.73 \pm 0.08)$ kcal mol^{-1}, Trp–Arg for $\Delta\Delta G = (-0.71 \pm 0.06)$ kcal mol^{-1}, and Trp–His (protonated) for $\Delta\Delta G = (-0.48 \pm 0.08)$ kcal mol^{-1}. Upon reconstruction of the protein by shuffling the order of the amino acids, the investigated Trp–Lys pair becomes much more solvent exposed. As a result, the strength of the interaction strongly decreases, resulting in an interaction energy of $\Delta\Delta G = +0.15$ kcal mol^{-1}. This suggests that solvent-exposed cation–π interactions are destabilizing or weak at best.

Theoretical calculations were performed on the effects of solvation on the cation–π interaction between Li^+, K^+, or Mg^{2+} and benzene.[248] Solvation of the cation was found to decrease the interaction with the π system, whereas the interaction energy increases with solvation of the aromatic ring.

According to CCSD(T) calculations, the major contribution to the interaction energy of *N*-methylpyridinium cations with a π system stems from electrostatics and induction, qualifying the interaction as a cation–π interaction.[20b] Interactions between an *N*-methylpyridinium cation and phenyl rings in the backbone of oligo(arylene-ethynylene)s increase the folding stability of oligomers in acetonitrile by about $\Delta\Delta G = -1.8$ kcal mol^{-1} as compared to the corresponding non-*N*-methylated analogues.[249] However, the interpretation of this energetic stabilization might be more complicated, as the relationship between the folding stability and oligomer length is yet to be precisely determined. Furthermore, remarkable substituent effects warrant further investigation: the foldamer stability increases when the *N*-methylpyridinium ring bears electron-donating *para* substituents, whereas electron-accepting groups have a destabilizing effect.[250]

6.5. Metal Cation–π Interactions

Even though alkali metal ions can form complexes with aromatic molecules in the gas phase with very high affinity,[251]

in aqueous solution the binding is weak and experimental results are scarce. As a result of the large desolvation penalty, Na^+ and K^+ cations are rarely bound to proteins through cation–π interactions.[252] Gokel and co-workers have extensively reviewed[253] cation–π interactions of alkali metal ions which can be established not only in crystals, but also in solution, when the cation is bound to crown ethers and sandwiched between pendant phenol or indole moieties. Recently, they also analyzed cation–π interactions between tetraphenylborate and alkali metal cations.[254] Other reviews surveyed transition-metal cation–π interactions in the gas phase,[255] and cation–π interactions of metal ions coordinated to aromatic ligands.[256]

The binding of Cs^+ to *p*-sulfonatocalix[4]arene was observed by ^{133}Cs diffusion NMR spectroscopy[257] to have a binding affinity of $K_a = (22 \pm 9)\,M^{-1}$ in aqueous solution, which is in very good agreement with the values found by ^1H NMR titration[257] and microcalorimetric[258] techniques. Microcalorimetric studies of different metal ions binding to *p*-sulfonatocalix[4]arene in water showed that while Na^+ and Ag^+ do not seem to form complexes with the host in water, K^+, Rb^+, and Cs^+ do.[258] In contrast to divalent and trivalent cations, binding is weak and enthalpy driven, thus suggesting that monovalent cations bind inside the aromatic cavity because of the favorable cation–π interactions. Binding strength in water (pH 2; 298 K) varies from $\Delta G = (-0.6 \pm 0.05)$ kcal mol^{-1} to $\Delta G = (-1.6 \pm 0.02)$ kcal mol^{-1} for K^+ and Cs^+, respectively.

By using X-ray crystallography and ^1H NMR titration studies in acetone, acetonitrile, and chloroform, crown-ether-bridged resorcin[4]arenes were observed to bind alkali metals, particularly Cs^+, within the aromatic cavity through cation–π interactions.[259] Pyrogallol[4]arenes have been shown by X-ray crystallography to act as receptors for alkali metal cations, namely K^+, Cs^+, and Rb^+, as well.[260]

Ca^{2+}–indole interactions were investigated using ^{13}C NMR and CD spectroscopy in the context of the development of a Trp-based fluorescent chemosensor for the metal ion (Figure 27a).[261] The chemosensor binds Ca^{2+} ions with its ethylenediaminetetraacetate-derived (EDTA) central core in aqueous buffer selectively over other alkali and alkali-earth metal ions. NMR studies suggest that the bound ion additionally interacts with both indole rings of the chemosensor system.

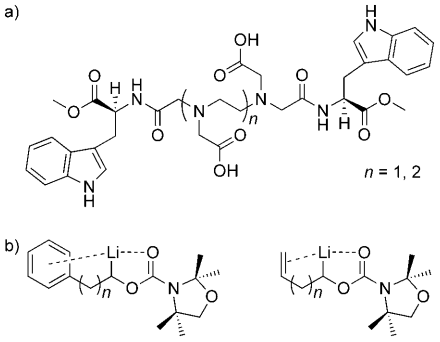


Figure 27. a) The fluorescent chemosensor binds Ca^{2+} ions selectively in aqueous buffer.[261] b) Organolithium–π interactions were quantified through Sn–Li exchange equilibria.[262]

The quantification of organolithium–π interactions was possible through Sn–Li exchange equilibria (Figure 27b).[262] When the organolithium center was able to form a pseudo-four- or a pseudo-five-membered chelate with a phenyl ring or a carbon–carbon double bond, the stabilizing effect resulting from the cation–π interactions was between $\Delta\Delta G = -1.5$ and -2.2 kcal mol^{-1} for phenyl and $\Delta\Delta G = -1.3$ and -1.7 kcal mol^{-1} for the double bond.

Additional evidence for the binding of alkali metal cations to double bonds was found in trimethylsilylated allyl complexes.[263] In X-ray crystal structures, Li^+, Na^+, and K^+ are situated between three allyl bonds with distances suggesting cation–π interactions (for Li^+, some σ-bonding is involved). Calculations predict that the interaction decreases in the order $Li^+ > Na^+ > K^+$.

6.6. Cation–π Interactions in Organic Synthesis

Despite its high occurrence in many areas of chemistry and biology, the cation–π interaction has been rarely utilized in organic synthesis thus far. In their early studies, Dougherty and co-workers observed rate enhancements of the alkylation of quinoline derivatives to the corresponding quinolinium salts when performing the reaction in the presence of a cyclophane host, which stabilizes the positively charged transition state of the transformation through cation–π interactions.[264] More recently, Yamada reviewed intramolecular cation–π interactions employed in organic synthesis, focusing mainly on N-substituted pyridinium–π interactions.[202] A series of interesting reports have appeared since then.

Cation–π interactions were found to influence the regiochemical outcome of an intramolecular Schmidt reaction of 2-azidoalkyl ketones in dichloromethane.[265] A typically disfavored pathway becomes preferred through cation–π interactions between the intermediate diazonium cation and an aromatic substituent. An increase in selectivity was found when the aromatic ring was substituted with electron-donating groups; a decrease was found with electron-withdrawing groups.

In photochemistry, the interaction has been used to influence the regiochemistry of [2+2] photodimerization of styrylpyridinium salts,[266] also complexed with cyclodextrin and cucurbituril hosts.[267] Favorable cation–π interactions between pyridinium and phenyl induce good yields of the *syn*-head-to-tail product in acidic media.[266] Higher selectivity was obtained with phenyl rings bearing electron-donating substituents, whereas electron-withdrawing substituents led to a loss of selectivity.

The interaction has also been exploited in the design of an asymmetric Diels–Alder catalyst,[268] which influences stereoselectivity by a proposed intramolecular Cu^{2+} cation–π interaction.[269] Chiral pyridinium and quinolinium salts with tethered phenyl rings were allylated regio- and enantioselectively because of the cation–π interaction between the rings.[270] The *N*-methylquinolinium ring in one of the starting materials was shown to lie parallel to the phenyl ring at an interplanar distance of 3.4 Å by X-ray crystallography.

Pyridinium salts have also been used in enantioselective cyclopropanation reactions.[271]

Very recently, cation–π interactions were reported to enable intramolecular olefin metathesis reactions: macrocyclization products were obtained in 45–90% yield when *N*-methylquinolinium salt added as a conformational control element, whereas no product formation was observed in the absence of the salt (for similar observations with perfluoroarenes, see Section 3.2).[272] As a result of the cation–π interaction between the quinolinium and the arene of the starting material, one side of the aromatic ring is shielded, and the substituents are forced into an orientation where the metathesis reaction can occur. In the same manner, the quinolinium controlling element also enabled intramolecular Glaser–Hay coupling reactions with yields around 40%.

7. Anion–π Interactions

Anion–π interactions have raised growing interest in recent years with reports ranging from observations in crystals to extensive computational investigations, and first energetic quantification studies in solution are now also appearing. Accordingly, a number of comprehensive reviews has been published over the past few years.[273] Herein, we will concentrate on anion–π interactions with neutral π systems; the numerous studies on systems with positively charged or metal-coordinated aromatic rings are beyond the scope of this broader review article.

Anion–π interactions are mostly observed with electron-deficient aromatic rings, such as triazines[274] and perfluoroarenes.[275] The interaction rarely occurs in biological systems, since the electron-rich aromatic amino acid side chains avoid negative charges in close proximity to their π clouds. Egli and Sarkhel state that these kinds of interactions are scarcely found in nature because Phe, Tyr, and Trp cannot be positively polarized.[276] This, however, is not the case for nucleobases, and more anion–π interactions can be expected to occur with these π systems. Accordingly, a PDB search revealed that aromatic amino acids interact with the side chains of Asp and Glu preferentially through binding at the ring edge, with an interplanar angle of 0°.[277]

An anion can interact with a π system through four different modes (Figure 28): a) hydrogen bonding, b) noncovalent anion–π interactions, where the anion resides above the center of the aromatic ring, c) strongly covalent σ interactions, and d) weakly covalent σ interactions, where the anion is located outside the periphery of the π system.[273c,278] Hay and Bryantsev emphasize that, depending on the type of anion and the π system, binding motifs (a), (c), and (d) should also be taken into consideration in addition to the noncovalent anion–π interaction (b).[273c] In the gas phase, hexafluorobenzene was observed to bind chloride,[279] bromide, and iodide largely through electrostatic interactions,[280] whereas fluoride was found to form a covalent bond.[281] Benzene rings with fewer fluorine substitutents, however, were shown to bind Cl^- and I^- through ionic hydrogen bonds to the arene protons.[282] By IR spectroscopy, bromide and iodide were observed to form weakly covalent σ complexes with 1,3,5-trinitrobenzene in the gas phase, whereas OH^- forms a covalent bond with the aromatic ring.[283] In general, nucleophilic anions (F^-, CN^-, RO^-) preferably form strong σ complexes with electron-deficient arenes, charge-diffuse anions (ClO_4^-, BF_4^-, PF_6^-) form noncovalent anion–π complexes, and charge-dense anions (Cl^-, Br^-, NO_3^-) form both weak σ complexes, favored with more electron-deficient arenes, and noncovalent anion–π complexes.[273c]

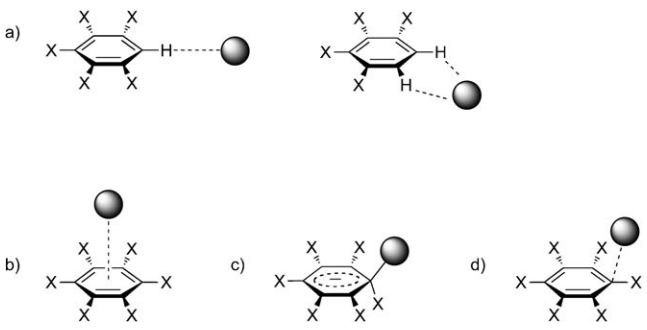


Figure 28. The interaction types of anions with π systems:[278] a) C–H hydrogen bonding; b) noncovalent anion–π interaction; c) strongly covalent σ interaction; d) weakly covalent σ interaction.

The major contributions to the anion–π interaction arise from electrostatics and polarization, but dispersion contributes as well.[28,273b,e,275b,284] The electrostatic component correlates with the magnitude of the electric quadrupole moment Q_{ZZ} of the aromatic ring.[273b] Although the binding energy of the anion–π interaction is not only electrostatic, trends can be predicted using only the electrostatic term. Accordingly, the binding energy decreases with the increase of the ionic radius of the anion. For aromatics with a large positive Q_{ZZ} value, such as hexafluorobenzene, electrostatics dominate the anion–π interaction, but as Q_{ZZ} diminishes, polarization energy becomes more important.

7.1. Computational Studies

In 1997, Alkorta et al. calculated several small electron-donating molecules to interact favorably with hexafluorobenzene, and found 53 examples in 30 crystal structures in the CSD of this kind of interaction.[275a] A few years later, Gallivan and Dougherty showed by CP-MP2 calculations that water can bind to hexafluorobenzene with the lone pair of the oxygen atom pointing towards the center of the ring with a binding energy of −2.1 kcal mol^{-1}.[285] In 2002, Alkorta et al. performed MP2 calculations for complexes of different anions (halides, CN^-, etc.) with perfluoroaromatics, and found large interaction energies ranging from −11.4 to −18.7 kcal mol^{-1}.[284a] Similar calculations were done by Ballester, Deyà, and co-workers on C_6F_6 and different anions, revealing that the strength of the anion–π interaction, with interaction energies ranging from −26.6 to −8.2 kcal mol^{-1}, is comparable to that calculated for the cation–π interaction.[275b] In a CSD search, they identified 1944 hits for noncovalent π–interactions between lone pair electrons and perfluorobenzene derivatives, 27 of which were interactions of anions. At the same time, Mascal et al. published MP2 calculations on

triazine and trifluorotriazine in complex with Cl^-, F^-, and N_3^-. They located minima for anion–centroid bonding, but also for σ complexes, π stacking (N_3^-), and hydrogen-bonding geometries.[286] For F^-, a strongly covalent binding mode (Figure 28c) has been observed in many calculation studies,[275b,278,284a,286,287] in agreement with the covalent bonding of F^- to hexafluorobenzene observed in the gas phase.[281] However, calculations showed that increasing solvation of the anion drives the binding preferably towards the geometries with more anion–π character (Figure 28b,d).[288]

For halides interacting with π systems, calculations have suggested off-center geometries (Figure 28d) to be more relevant than the interaction geometry with the centroid of the ring (Figure 28b).[278] Of the 30 halide–arene complexes found in the CSD, only five showed the halide residing closer to the centroid than to the ring carbon atoms. These off-center geometries have been shown to have significant charge-transfer character, which is inconsistent with the definition of the noncovalent anion–π interaction. This was also evident in solution studies by Kochi and co-workers, who observed a color change induced by the addition of halide to a solution of electron-deficient arenes.[289] In addition, the Mulliken correlation of the oxidation potential of the anion with the energy of the charge-transfer absorption band further supports this finding.

Since then, numerous calculations have emerged on anions in complex with various aromatic systems,[284b,287,290] and on the cooperativity of the anion–π interaction with other noncovalent interactions.[209b,c,291] The total interaction energies of anion–π complexes have been calculated to be comparable[284b] or smaller[28] than those of cation–π complexes: because of the greater size of anions compared to cations, the interaction partners have to be further apart from each other, resulting in reduced electrostatic interaction. Both cation–π and anion–π interactions strongly depend on the magnitude of the quadrupole moment and molecular polarizability of the aromatic ring. Thus, in complexes with π systems having negligible Q_{ZZ} values, the strength of the cation–π and anion–π interaction is expected to be similar.[290b] Electrostatics and induction energy make the largest contributions to the total interaction energy, but, unlike for cation–π complexes, dispersion energy contributes substantially to the anion–π interaction, becoming as important as electrostatics and induction for complexes with organic anions.[284b] Characteristic of the anion–π interaction is also a substantial exchange-repulsion energy. DFT methods should be used with caution in theoretical characterization of anion–π interactions, since in most cases they do not account for dispersion forces.[273c]

The binding energies were calculated to increase proportionally with the number of electron-deficient aromatic rings interacting with the anion: the 1:2 Cl^-/Br^-···(trifluorotriazine)$_2$ complexes showed a binding energy of approximately two times that of the 1:1 complex, and three times that for 1:3 complexes.[292] Additionally, simultaneous contacts of the aromatic system with a cation from the opposite side of the ring were calculated to enable anion–π interactions with electron-rich aromatics,[293] and to lead to further stabilization of the complex.[294]

7.2. Structural Evidence

Numerous X-ray crystal structures have been published in which the arene of the anion–π complex is charged,[295] or coordinated to an ionic metal center.[279,291a,296–298] The latter interaction mode has been successfully used in crystal engineering and self-assembly of networks.[299] Metal coordination has been shown to greatly enhance the anion–π binding ability of heterocyclic aromatic rings.[300] A CSD search for five-membered metal-coordinated aromatic rings gave 126 hits in 111 crystal structures for the anion–π interaction.[301] To date, examples of the anion–π interaction with charge-neutral or noncoordinated arenes remain rare; some examples, however, have been found in X-ray crystal structures of for example, perfluorinated arenes,[275c,302] cyanuric acids,[303] and others.[304]

Hay and Custelcean searched the CSD for anion–π contacts with criteria that would only identify hits belonging to the category of pure anion–π interactions (Figure 28b): the geometries should closely resemble the ones predicted by calculations, the π system should be charge neutral, the anion should be over the center of the π system, and the contacts of the anion to the arene ring atoms should be shorter than the sum of the van der Waals radii.[305] Using very restrictive search criteria (d(Cl^-···C-all six ring carbon atoms) ≤ 3.37 Å; $\theta = 90 \pm 10°$), no convincing examples of the Cl^-–π interaction were found. The Cl^- ion showed a significant preference for undergoing C–H···Cl^- hydrogen bonding on the periphery of the arene (Figure 28a).

Reedijk, Gamez, and co-workers performed a CSD search for anion–π interactions with six-membered heteroaromatic rings bearing nitrogen, phosphorus, boron, or silicon atoms.[306] For halides, 77 anion–π contacts were found with N-heteroaromatic rings at distances from the anion to the center of the aromatic ring below the sum of the van der Waals radii. Additional examples of anion–π contacts were found for anions consisting of two to six atoms. In nearly all cases, the interaction was accompanied by hydrogen bonding to the anion.

Kochi and co-workers studied anion–π interactions by growing molecular wires from different electron-deficient arenes and polyatomic anions.[295h,307] The crystallographic data show that for various anion–π interactions the distance between the anion and the closest carbon atom of the arene is 2–13% shorter than the sum of the van der Waals radii.[307]

The interaction mode, as seen in the X-ray crystal structures, of different halides with a pentafluorophenyl system (Figure 29a) varied with the cationic substituent on the ring: in the primary ammonium-substituted complex **28a**, the anion was found to interact mainly through hydrogen bonding, in the iminium complex **28b** the anion interacted with only one carbon atom of the aromatic ring, and in the amidinium salt complex **28c** the anion had simultaneous contacts with either two or all six aromatic carbon atoms.[302a] The binding of Cl^- and Br^- was also observed in the X-ray crystal structures of a tripodal amine receptor **29** (Figure 29b), where, in addition to hydrogen bonding, the anions undergo interactions with the carbon atoms of the perfluorinated arenes (3.48–3.85 Å for Cl^-, 3.29–3.43 Å for

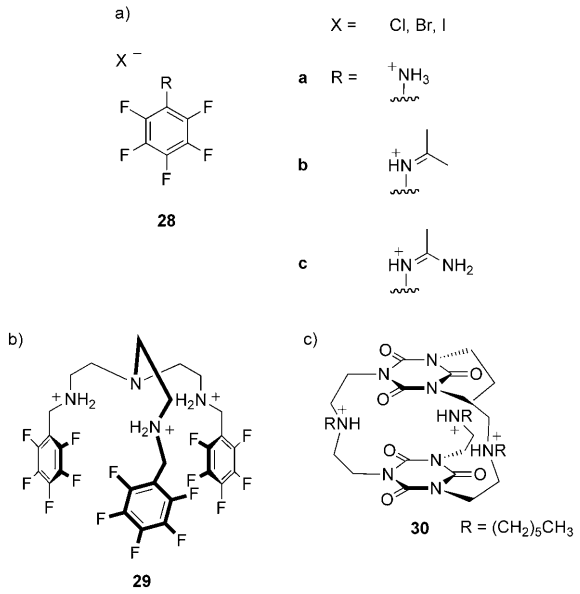
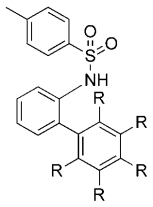


Figure 29. a) By varying the substituent R of receptor **28**, different binding modes of halides were observed.[302a] b) The pentafluorophenyl-substituted receptor **29** binds Cl^- and Br^- through a combination of hydrogen-bonding and anion–π interactions.[308] c) Cylindrophane **30** was shown by X-ray crystallography to bind F^- inside the cavity through hydrogen-bonding and anion–π interactions.[309b]

Br^-).[308] In ^1H NMR titration studies in $(CD_3)_2SO$, higher binding constants were observed for the fluorinated receptor **29** in comparison with its nonfluorinated counterpart, thus suggesting a contribution from anion–π interactions to the binding of the halides.

Mascal et al. have prepared the cyanuric-acid-based cylindrophane **30** predicted to bind fluoride ions selectively (Figure 29c).[309] In addition to ESI-MS methods, the binding of F^- was observed by X-ray crystallography, wherein the anion is located in the middle of the cavity undergoing hydrogen-bonding interactions to the ammonium moieties on the walls of the cavity and anion–π interactions to the sandwiching cyanuric acid moieties.



31a R = F
31b R = H

Figure 30. The pentafluorophenyl-bearing receptor **31a** binds halides in $CDCl_3$ with modest affinity, whereas the phenyl-substituted **31b** does not.[310]

7.3. Studies on Model Systems

The binding of different halides to receptor **31a,b** was observed by ^1H NMR titration experiments in $CDCl_3$ (Figure 30): while Cl^-, Br^-, and I^- all showed moderate association constants for the interaction with the perfluorinated receptor **31a** (T = 298 K, K_a = 30, 20, and 34 M^{-1}, respectively), no measurable binding constants were detected for phenyl-substituted **31b**.[310] Enhanced binding to **31a** is explained by a combination of anion–π and hydrogen-bonding interactions. The sulfonamide N–H of **31a** is more acidic compared to that of **31b**, and the lower pK_a value should strengthen ionic hydrogen bonding to the anion. However, the nearly equal binding affinity of **31a** for Cl^-, Br^-, and I^- suggests that anion–π interactions with the C_6F_5 ring are also contributing. Interactions of halide anions with electron-deficient rings have also been observed in a modified porphyrin system,[311] with tripodal receptors,[312] and a triazine-containing cage molecule.[313] Very recently, anion–π interactions of F^- with an electron-rich arene were reported for a tripodal cage molecule.[314]

In view of the physiological relevance of biological chloride ion channels,[315] the transport of Cl^- has been intensively addressed by model systems.[316] Matile and co-workers have prepared and extensively studied a series of anion–π slides, which transport halide anions with varying selectivity across lipid bilayers through a presumed multiion hopping mechanism.[317] The slides consist of two electron-deficient oligonaphthalenediimide rods (Figure 31), the length of which roughly matches the thickness of standard lipid bilayer membranes.[317d] The activity and the selectivity of the slides could be tuned by varying the substituents at both ends of the rods.[317b,d] If the two bilayer-spanning rods are bridged (Figure 31), a more shape-persistent channel is obtained, which shows enhanced selectivity but reduced activity, possibly because of the proximity of the rods to

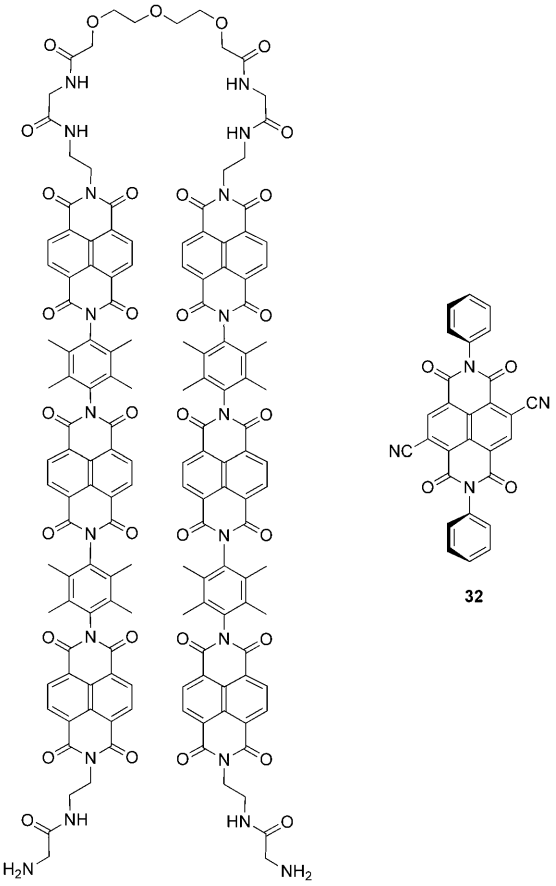
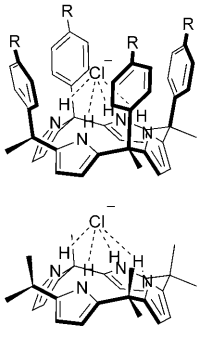


Figure 31. Anion–π slides.[317b,e] Left: Bridging electron-deficient oligonaphthalenediimide rods enhances the selectivity of anion transport. Right: Less-crowded, more-electron-deficient rods such as **32** were found to be highly active in transport assays.

each other.[317b] The activity of the channels is highest if one end bears charged primary ammonium centers, but becomes reduced if charges are placed on both termini of the channel. Recently, a thorough study was reported on the anion binding properties of the rods and simple capped naphthalenediimide fragments using tandem mass spectrometry and transmembrane transport investigations.[317e] Significant enhancement in activity was found when the steric crowdedness was reduced and the naphthalenediimide moieties rendered more electron-accepting through cyano substitution, as in **32**. Selectivity for Cl^- over Br^- and I^-, and for NO_3^- over AcO^- was observed with this simple cyano-substituted naphthalenediimide. The compound also showed high activity in transport assays.

Ballester and co-workers have quantified the anion–π interaction of Cl^- in complex with a series of tetraaryl calix[4]pyrrole hosts in acetonitrile by ^1H NMR titrations and ITC (Figure 32).[318] Encapsulation of the anion was also shown by X-ray crystallography.[319] While the anion benefits from the slightly converging pyrrolic N–H moieties and undergoes ionic hydrogen bonding,[320] evidence of anion–π interactions was obtained when the *para* substituents on the four aromatic walls were systematically varied. Upon moving from the electron-donating methoxy to the electron-withdrawing nitro substituent, the overall free enthalpy of binding was estimated to become enhanced by about $-4.3\ kcal\,mol^{-1}$, approximately $-1.1\ kcal\,mol^{-1}$ per aromatic ring.[318] However, comparing the free enthalpy of complexation to that of the nonsubstituted octamethyl calix[4]pyrrole host **33**, the $Cl^-\cdots\pi$ interaction was actually repulsive in all cases except for the nitro-substituted system ($\Delta\Delta G = -0.1\ kcal\,mol^{-1}$). The experimental interaction free enthalpies correlate with the Hammett constants σ_p of the substituents indicating that $Cl^-\cdots\pi$ interactions are dominated by electrostatic effects.

For the association of F^- to a capsular host, resulting from Re^I-assisted self-assembly of 2,2′-bipyridine and a tris(3-pyridyl)triazine ligand, the binding constant K_a (CH_3CN, $T = 293\ K$) was determined to be $5.3 \times 10^3\ M^{-1}$ by evaluation of the changes in the absorption and emission spectra upon addition of the anion.[321] The stability of the complex was attributed to anion–π interactions with the surrounding aromatic rings, especially with the triazine ring, and the proposed inclusion geometry was supported by the crystal structure obtained with an encapsulated PF_6^- anion.



R	ΔG / kcal mol^{-1}	ΔΔG[a] / kcal mol^{-1}
OMe	–2.9	1.0
H	–3.1	0.9
COOMe	–4.1	0.7
Br	–4.8	0.5
CN	–6.2	0.1
NO_2	–7.2	–0.1

33 ΔG = –6.9 kcal mol^{-1}

Figure 32. Calix[4]pyrrole host to quantify anion–π interactions in acetonitrile at 298 K.[318] The anion–π interaction was found to be repulsive, as compared to **33**, in all cases, except for the *para*-nitro-substituted host. [a] $\Delta\Delta G = (\Delta G - \Delta G_{33})/4$.

Calculations and X-ray crystallography have shown the anion–π interaction with electron-deficient aromatic rings to be relevant, especially if the heteroatoms of the rings are coordinated to a metal ion. First convincing quantifications in model systems have appeared, and the interaction has been probed in an organic transformation.[322] The examples in crystal engineering show that the interaction can be successfully exploited in structural design. Evidence for occurrence in biological systems awaits to be unraveled,[323] in particular involving electron-deficient protonated nucleobases and related electron-deficient heterocycles, as suggested by Egli and Sarkhel.[276]

8. Summary

This review once more illustrates the unique strength of a multidimensional approach towards deciphering and quantifying molecular recognition events. The combination of model system studies with biostructural and biological affinity analysis, database mining in the CSD and the PDB, and increasingly reliable, high-level computational predictions provides exceptional, in-depth insight into intermolecular forces that cannot be reached by analyzing the results generated by one of these strategies only. Importantly, biological and chemical studies nicely converge in their conclusions with respect to the free enthalpy that can be gained from interactions with individual rings. This reiterates that the same molecular recognition principles are effective in both chemical and biological environments. Interestingly, arene–arene, perfluoroarene–arene, S···aromatic, and cation–π interactions all contribute as low as $\Delta\Delta G\ -1.0\ kcal\,mol^{-1}$ per aromatic ring to host–guest and protein–ligand binding, with more to be gained with increasing number of aromatic rings. Thus, quaternary ammonium ion binding in the S4 pocket of factor Xa, lined by Trp, Tyr, and Phe side chains contributes $\Delta\Delta G = -2.5$ to $-2.8\ kcal\,mol^{-1}$ to the binding free enthalpy. Arene–arene interactions and increasingly cation–π interactions are by far the most intensively studied and understood, but quantification and use of perfluoroarene–arene and S···arene interactions, as well as of hydrogen bonding to π surfaces have also seen much progress. Compared to the first review seven years ago, anion–π interactions have attracted strong theoretical and experimental interest and have therefore become the content of an entire section in this account. Also, inter- and intramolecular interactions involving aromatic rings are increasingly finding application in organic synthesis to control the stereochemical outcome of transformations, as illustrated in many sections of this review.

Where are some of the frontiers for future work? Substituent effects on arene–arene interactions are poorly investigated in solution study, and theoretical predictions have clearly moved ahead of experiment. Quantifications of perfluoroarene–arene interactions in model systems are still rare. This also holds for S···arene interactions, which have

been identified and quantified in biological studies but not as much in model systems. Since cationic substrates, such as ACh, are essential constituents of neurochemical processes and Lys methylation in histones is relevant to epigenetic gene regulation, it can be expected that investigation of cation–π interactions in biological environments will be further expanded. Anion–π interactions, which, like so many other molecular recognition processes such as halogen bonding, was first identified in crystal packings, became the subject of extensive theoretical studies, and recently first quantifications in solution studies have been described. It is predictable that biological examples will follow in the near future.

This in-depth analysis of interactions with aromatic rings fertilizes medicinal chemistry, materials science, crystal engineering, and organic synthesis. New exciting studies will certainly keep shedding light on the aromatic interactions in the future.

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