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Interactions in Supramolecular Complexes Involving Arenes: Experimental Studies

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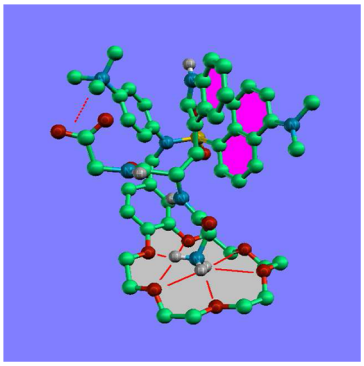

The process of learning by doing has fueled supramolecular chemistry and, more specifically, the understanding of noncovalent aromatic interactions in synthetic and natural systems. The preparation of new host molecules and the investigation of their complexations have produced many insights into significant noncovalent binding mechanisms. In this Account, we attempt to discuss significant binding contributions involving aromatic units and their practical applications. We use typical examples from our group and the literature, but this Account is not a comprehensive view of the field.

Other than systems with saturated frameworks, host compounds based on arenes offer better controlled conformations and active interactions with many guest molecules. Because of their fluorescent properties, larger aryl systems are particularly suitable for sensors. The noncovalent interactions observed with different supramolecular complexes can be compared and exploited for interactions with biopolymers such as nucleic acids. Complexes formed with cyclophanes have been a constant source of inspiration for understanding noncovalent forces and their use for the design of functional supramolecular systems. Other than cyclodextrins or ionophores, which occur in nature, arene-based macrocycles are synthetic and provide more opportunities for structural variations than other macrocycles. These derivatives allow researchers to study and to exploit an unusually broad variety of binding mechanisms in both aqueous and organic media.

Systematic analyses of complexes with different substituents and structures in solution, based also on flat aromatic systems such as porphyrins, can lead to a consistent picture of the noncovalent forces that dominate in these systems. These studies have elucidated attractive interactions between many heteroatoms and π systems including cyclopropanes . Through systematic analysis of the equilibrium measurements one can derive binding free energy increments for different interactions. The increments are usually additive and provide predictive tools for the design of new supramolecular systems, benchmarks for computational approaches, and an aid for drug design. In aqueous media, the major noncovalent forces between different aryl systems or between arenes and heteroatoms of larger polarizibility are dispersive, and hydrophobic forces play a minor role. In several examples, we show that electrostatic forces also contribute significantly if donor and acceptor groups show complimentarity.

In early investigations, researchers found cation$-\pi$ and, to a lesser degree, anion$-\pi$ interactions with several cyclophanes in systems where the host or the guest molecules bear charges in an orientation that facilitates contact between charged and aryl portions of the molecules. In supramolecular complexes, hydrogen bonding effects are usually only visible in apolar media, but very strong acceptors such as phenolate anions can also work in water. To facilitate potential applications, researchers have primarily developed water-soluble, arene-containing receptors through the implementation of permanent charges. Supramolecular complexes that mimic enzymes can also rely on aryl interactions. Examples in this Account illustrate that the conformation of host$-$guest complexes may differ significantly between the solid and solution state, and suitable spectroscopic methods are needed to observe and control these conformations.

1. Introduction

Noncovalent forces involving aryl systems play a significant role in natural and synthetic complexes; they have been aptly reviewed by Meyer, Diederich, et al.[1] and were put into the context of other possible binding mechanisms in supramolecular complexes.[2] Chemists have made an early effort to make artificial receptors effective in aqueous media, targeting systems of biomedical importance.[3] In this Account, we discuss how our group like others has tried over many years to understand and to use interactions with aryl compounds in supramolecular complexes. Particular attention is paid to interactions of heteroatoms with arenes, which can

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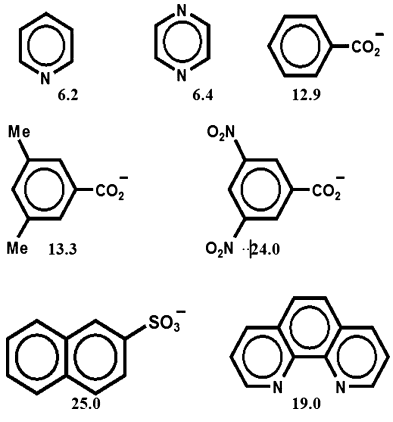
provide significant stabilization in corresponding associations. We stress the possibility to quantify noncovalent binding contributions in the form of free energy increments from equilibrium measurements, usually by titration in solution.[4]

2. Stacking and Dispersion Forces with Open Aromatic Host Compounds

Stacking has been recognized as a most important binding contribution in supramolecular structures involving arenes, but it involves different interaction mechanisms.[5] Stacking interactions have found many applications, including chemomechanical polymers.[6] Large and flat aromatic surfaces can serve as efficient host structures for aromatic targets. Systematic analyses of many complexes with porphyrin moieties, made water-soluble by either cationic or anionic substituents, allowed us to separate binding increments due to stacking from those due to ion pairing, assuming a constant ion pair contribution of $\Delta G_{ion} = 5$ kJ/mol per salt bridge;[7] this increment was found in hundreds of organic ion pair complexes at intermediate ionic strength.[2] Scheme 1 illustrates that complexes of tetrapyridinium porphyrin with phenyl-shaped substrates exhibit within ± 1.5 kJ/mol deviation a rather constant stacking contribution of 7.5 kJ/mol for a benzene ring, remarkably independent of the presence of heteroatoms in the π system and also of additional methyl groups; this as well as the negligible binding with saturated systems points to the absence of significant hydrophobic effects. The face-to-face stacking orientation between the porphyrin host and the aryls was secured by NMR data (Figure 1). The size dependence of stacking contributions is observed also with intercalators in double-stranded nucleic acids;[8] Figure 2 illustrates the similar stacking mechanism in both cases.

SCHEME 1. Complexation of *meso*-Tetrapyridinium Porphyrin and Aromatic Substrates, Experimental Binding Free Energies in Water (ΔG_t in kJ/mol), and Stacking Contribution ($\Delta G_{stack} = \Delta G_t - \Delta G_{ion}$, with $\Delta G_{ion} =$ 5 kJ/mol per Salt Bridge)



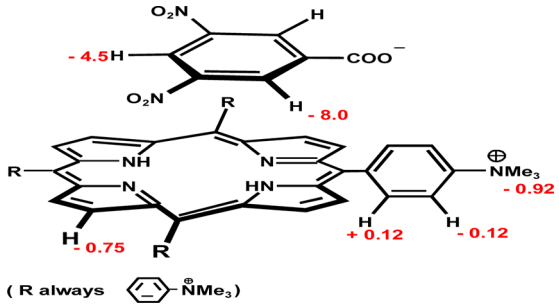


FIGURE 1. Model of porphyrin stacked with dinitrobenzoate. Complexation induced NMR shifts [ppm, for 100% complexation] indicate face-to-face orientation.[7,9]

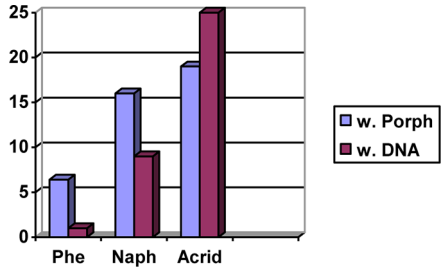


FIGURE 2. Stacking contributions with phenyl, napthtyl, and acridyl derivatives in complexation with porphyrins and with ds-DNA; ΔG (kJ/mol), if applicable after deduction of ion pair contribution (5 kJ/mol); see text and refs 7 and 8.

The affinity toward the porphyrin moiety is significantly increased not only with larger π systems but in particular also by the presence of substituents such as nitro groups. Systematic comparison of complexation energies of porpyrins with substituted benzoates and other heteroatom-containing ligands reveals a fairly linear dependence on the polarizibility of the corresponding substances (Figure 3); this supports dispersion effects as dominant important contributions.[9] Obviously, such heteroatom interactions with arenes can significantly stabilize corresponding associations; for example, two nitro groups are worth almost a benzene unit in stacking energy. In line with the π character of its C–C bonds, even cyclopropane, which has been measured in the form of its carboxylic acid, exhibits significant attraction with $\Delta\Delta G =$ 1.65 kJ/mol, not too far from $\Delta\Delta G = 2.4$ kJ/mol for a vinyl substitutent.

Figure 4 illustrates application of stacking for sequence-selective fluorimetric sensing of peptides. A receptor with a crown ether for complexation of the peptide $^{+}NH_3$ terminus at one end and a peralkylammonium group at the other for binding the COO^{-} terminus is equipped with a dansyl unit L at a fixed position along a spacer. The dansyl unit can stack with amino acid side groups R such as phenyl in phenylalanine in the right sequence position;[10] this leads

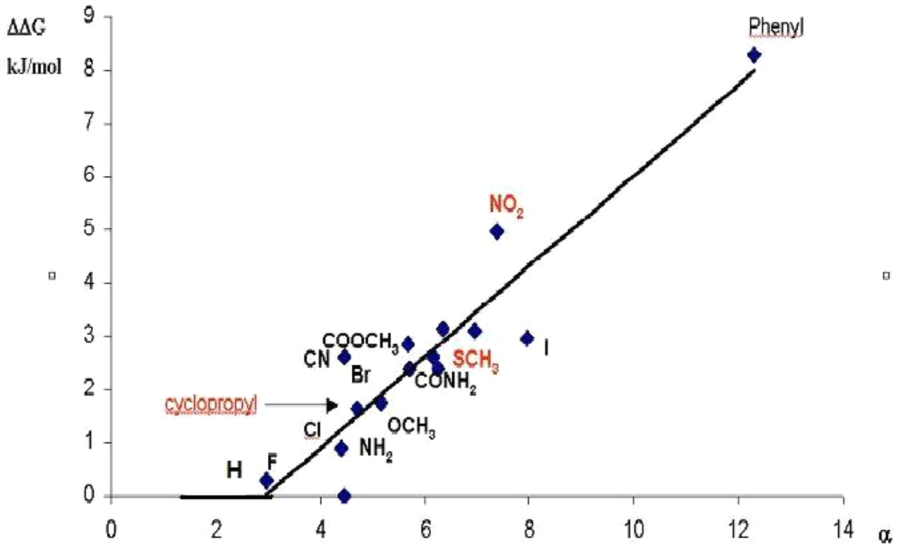


FIGURE 3. Correlation of free binding energies, $\Delta\Delta G$ (from porphyrin complex measurements), and molar polarizibilities, α, of corresponding methyl derivatives, CH_3-R.[2]

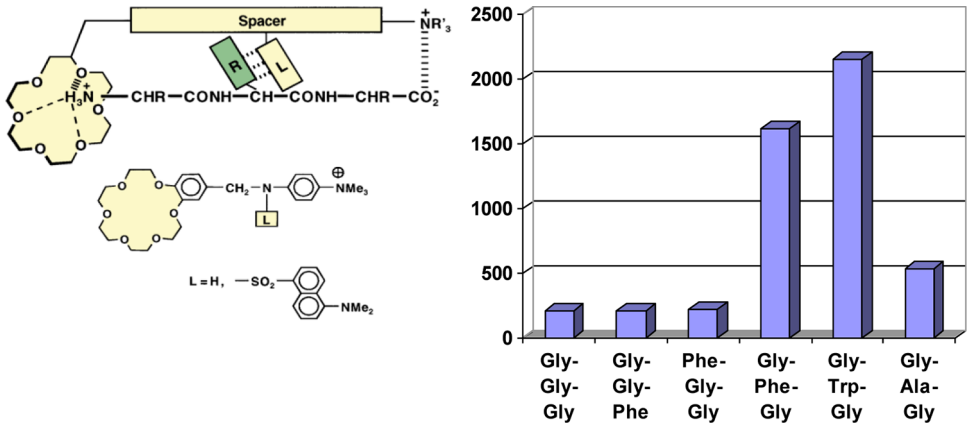
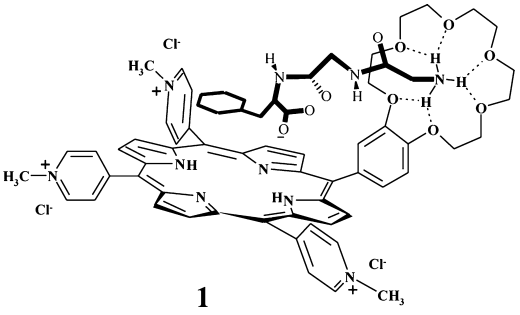


FIGURE 4. Length- and sequence-selective peptide recognition with stacking between a dansyl reporter unit L and an amino acid side group R, in water; binding constants in M^{-1}.[10]



1

FIGURE 5. Stacking between a porphyrin host **1** and aromatic side chain of peptides (simplified structure).[11]

to a restored fluorescence emission due to the removal of the quenching effect by the unoccupied electron lone pairs at the crown ether.

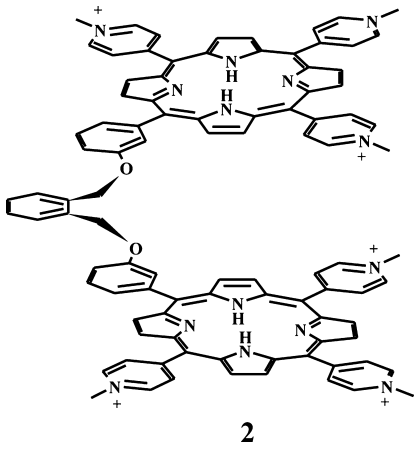


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FIGURE 6. A porphyrin cleft, **2**, with dominant stacking interactions, able to complex nucleotides and nucleosides with similar affinities.[14]

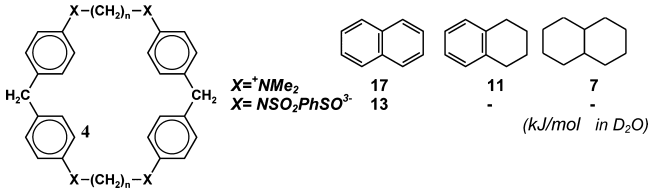


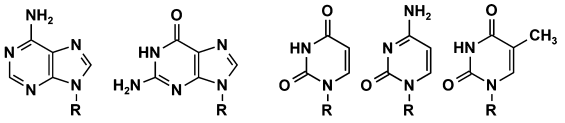
FIGURE 7. Cyclophane **4** (CP*nn*, $n = 6$) and binding affinities with different guest molecules of similar shape in water.[17]

Another example (Figure 5) relies on the stacking between a porphyrin host and again the aromatic side chain of peptides with a crown ether at the host securing complexation of the peptide $^{+}NH_3$ terminus.[11] The binding can be measured by the UV change of the P-450 band and is, for example, 100 times stronger for Gly-Phe than Gly-Gly.

An obvious way to increase affinities is to provide in tweezer or cleft molecules more than one stacking unit in a receptor. After the early investigations of this strategy,[12] many molecular tweezers have been developed, which can also be dominated, for example, by electrostatic interactions[13] (see section 4). The cleft shown in Figure 6 shows strong binding not only to nucleotides but also to electroneutral nucleosides with similar affinities.[14] Here stacking by double inclusion is so strong that additional ion pairing plays only a small role. The observed log K values were 4.6 for adenosine, 3.35 for thymidine, and 5.42 for cytidine, thus exhibing only moderate base selectivity, which is typical also for intercalation into double-stranded nucleic acids. Similar small base selectivities were observed with other nucleotide receptors;[15] only a bisintercaland exhibits slightly larger selectivities with trinucleotides, with log $K = 6.8$ for UTP, log $K = 5.4$ for ATP, and log $K = 4.4$ for UTP, for example.[15]

3. Interactions in Water-Soluble Cyclophanes

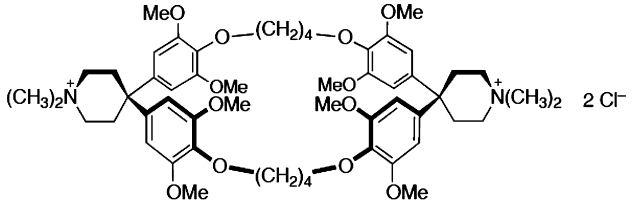
In their early investigations, Koga et al.[16] noticed that an increase of the hydrophobic area in the cavity greatly enhances the stability of the complex. However, systematic studies of cyclophanes such as **4** with either positive or negative charges in the host showed distinctly smaller affinities with aliphatic guest molecules (Figure 7), clearly speaking against a primarily hydrophobic mechanism and for a special attraction between cationic centers in the host and aryl moieties in the guest (see section 5).[17] The cyclophane **4** has a size suitable for naphthalene-shaped guest molecules, as visible by computer-aided molecular modeling; intracavity complexation was secured by shielding data in the NMR spectra.[18] Nevertheless, solvent effect studies in mixed aqueous media showed that the observed association constants correlate better with hydrophobicity



for R =					
ribose	10	≈ 6.5	≈ 6	≈ 7	-
ribose-OPO$_2^{2\theta}$	19.3	15.9	17.3	18.3	17.6

FIGURE 8. Complexation free energies (kJ/mol, in water) of nucleotides and nucleosides with **4** (CP*nn*, X = $^{+}NMe_3$).

parameters of the solvent than with polarity parameters.[19] However, if one tries to correlate complexations of, for instance, pyrene with Diederich's cyclophane **5** in all possible solvents, including very unpolar media, good results are obtained with the Dimroth–Reichhardt E_T polarity parameters, with enthalpy as the major driving force, as established by calorimetry.[1] Generally dispersion effects and the cohesive nature of the media seem to dominate solvent effects with aryl complexations.[1] That electrostatic forces play an important role is visible in the increased affinities of electron-poor benzene guest molecules with the electron-rich host **5**; the observed ΔG values increase with benzene substituents X and Y from 22.3 kJ/mol for X = Y = Me to 25.1 kJ/mol for X = Me and Y = NO_2 to 28.5 kJ/mol for X = Y = COOMe.[1]



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Cyclophanes such as **4** (X = $^{+}NMe_3$) lend themselves for the complexation of nucleobases and exhibit a remarkably similar binding energy difference between nucleotides and nucleosides[20] (Figure 8). The binding free energies show a rather constant difference of 10 ± 1 kJ/mol . This agrees well with the presence of two salt bridges between the doubly charged phosphate and one +N corner of the cyclophane, using the above-mentioned constant free energy increment of 5 ± 1 kJ/mol per single bridge[2,21] (at zero ionic strength, this value increases to up to 8 kJ/mol[22]). NMR spectra in combination with force field calculations agree with a total immersion of the nucleobases within the cavity and a contact between one +N center and the sugar phosphate group. Apart from the stronger adenine association, the nucleobases exhibit only small binding differences, in line with the small variations between the binding of different heterocycles with, for instance, porphyrins (see section 2).

TABLE 1. Melting Point Changes, ΔT_m [°C], induced by cyclophanes CP*nn* (**4**, X = $^+NMe_2$) on DNA and RNA Models[a]

CP*nn* (**4**, X = $^+NMe_2$)	ds-DNA [poly(dAdT)]	ds-RNA [poly(AU)]
CP33	30	27
CP44	36	14
CP55	28	6
CP66	27	−6

[a]Performed in MES buffer at a ratio of 0.2 mol of CP*nn* per mol of nucleic acid phosphate.

With nucleic acids, cyclophanes of the type **4** (X = $^+NMe_2$) show an unexpected behavior.[23] Basic groove binders, for example, the antibiotic neomycin, distinctly stabilize double-stranded RNA (with poly(AU), the melting point increase amounts to $\Delta T_m = 33$ °C), whereas ds-DNA is barely affected (neomycin with poly(dAdT), $\Delta T_m = 1$ °C). The conformationally rather rigid cyclophanes **4** (X = $^+NMe_2$) exhibits stabilization with the DNA model poly(dAdT) as well as with calf-thymus DNA, visible also by spectroscopic methods. In contrast, with the RNA (poly(AU)) smaller ΔT_m values are observed with the smaller macrocycles CP33, CP44, and CP55. With CP66, an exceptional destabilization of RNA occurs (Table 1). Modeling studies show that the phosphates in the RNA groove match the cationic ammonium centers of the macrocycle less well than did those in the larger B-DNA groove. The smaller RNA groove then prefers intracavity inclusion of a nucleobase with concomitant base flipping, resulting in unwinding of the RNA helix.

Unwinding of the double helix can also be achieved with another principle, based on cleft-like diphenyl compounds, which do not intercalate into double strands but exhibit attractive stacking with single-stranded units. As a result, such ligands act like an artificial helicase.[24] The effect is particularly strong with *p*-chlorophenyl derivatives, which destabilize ds calf-thymus DNA with a ΔT_m decrease of −28 °C, for example. Chlorine, as discussed in section 2, can exert favorable interactions with π systems; it has a diameter similar to a nucleobase and therefore may well enhance intercalation. In a related analysis, the Cambridge crystal data file showed in 10.502 out of 72.738 chlorine- and arene-containing structures the chlorine in closer proximity to the π surface than to arene C−H bonds.[25]

4. Electrostatic Donor−Acceptor and CT interactions

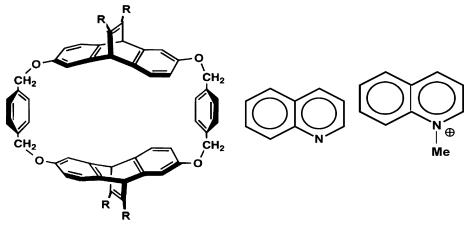
The molecular tweezers and clips described by Klärner et al.[13] (see article by Klärner et al.[13d] in this issue) complex electron-poor arenes in chloroform with affinities reaching, for example, from 10 kJ/mol for dicyanobenzene to over 28 kJ/mol with tetracyanobenzene; the electrostatic potential surfaces of these tweezers were shown by *ab initio* calculations to be strongly negative at the concave inside, pointing to dominating electrostatic forces for the complexation, as suggested also by the earlier findings of Diederich et al.[1] (see section 3). The presence of CT bands can by no means be taken as evidence for charge transfer as the driving force for complexation, as it is sometimes implied.[13b,26] Typical charge-transfer complexes such as that of trinitrobenzene with hexamethyl benzene are actually quite weak, with only $\Delta G = 4.5$ kJ/mol in CCl_4.[27]

The donor−acceptor systems, which are the basis of the well-known molecular machines by the Stoddart group, are based on, for instance, cyclobis(paraquat-*p*-phenylene) as π-accepting tetracationic cyclophanes and hydroquinone, 1,5-dioxynaphthalene, or tetrathiafulvalene units as donor. They always exhibit in acetonitrile and similar solvents strong CT signals; nevertheless the observed affinities, reaching up to 4 kJ/mol, are attributed to electrostatic attraction between donor and acceptor.[28] Related studies by Siegel et al. based on correlations with polar substituent constants clearly exhibit dominating electrostatic and dispersive, but not CT, interactions for stacking.[29] The rather strong cyclophane complexes with nitrophenol studied by Whitlock et al.[45] in apolar solvents also showed no indication of charge transfer. Similarly, stacking between nucleobases is generally attributed to dominating dispersive interactions.[30]

5. Cation−π Interactions

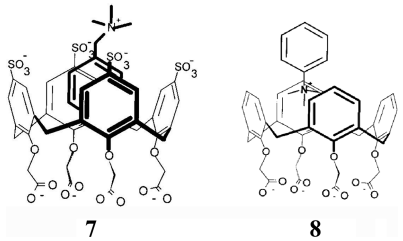
In 1988, several groups independently reported on stabilization effects of cationic centers interacting with aromatic moieties in cyclophanes. This was then recognized as one of the most important noncovalent forces in many supramolecular systems,[31] although gas phase studies have quantified previously corresponding binding energies between metal cations and, for instance, benzene.[32] *Ab initio* calculations of Na cation complexes with substituted aryl rings suggest that the electrostatic potential above the π center determines the strength of the cation−π interaction, primarily via inductive effects.[33] Other computations indicate for substituent effects generally quite variable contributions of both through-bond and through-space effects.[34] Wheeler and Houk, however, concluded that substituent effects in such complexes arise primarily from direct through-space interactions with the substituents.[35] Dougherty et al. demonstrated first that the presence of a ^+N cationic center in the guest molecule **6** leads to a distinct affinity increase in complexation with the cyclophane (Figure 9).[36]

In 1988, we recognized that special ion−π interactions must be responsible for the stabilization of complexes with cyclophanes such as **4** bearing positive charges, which can interact directly with enclosed aromatic guest molecules.



6 G1 G2

FIGURE 9. Cyclophane **6** complexes exhibiting cation$-\pi$ interactions. ΔG for R = COO^- is 22 kJ/mol with **G1** and 32 kJ/mol with **G2** in D_2O; for R = COOMe with **G1**, ΔG = 14.5 kJ/mol in $CDCl_3$.



7 8

FIGURE 10. Complexes of calixarenes with either dominating $^+N-\pi$ or ion pair interactions, see text.

The clue was the large affinity increase with the number of π electrons in the guest; in addition association constants with host systems in which the ^+N charge is missing are significantly diminished.[17,37] Figure 7 illustrates typical examples. For the same reason estrogens insert into the cavity with the aromatic A ring and not with the more hydrophobic saturated parts.[38] A comparison of organic ion pairs containing a variable number of arenes exhibit, after deduction of the ubiquitous increment of 5 kJ/mol for each salt bridge, a correlation with the number of arenes, leading to an increment of about 2 kJ/mol for each ion$-$aryl interaction.[21] That cation$-\pi$ effects in addition to smaller hydrophobic forces dominate such complexations is not contradicted by the observed dependence of the solvent hydrophobicity parameters, because organic solvents will always diminish the dispersion effects of water, which has a lower polarizibility than any other medium.[1,3] Remarkably, the same increment of about 2 kJ/mol for each cation$-\pi$ interaction was found even in chloroform for complexations of several aromatic hosts with acetylcholine and tetramethylammonium chloride.[39]

Calixarenes and the related resorcarenes also show clear manifestation of cation$-\pi$ effects. A tetrasulfonato calixarene **7** binds, for instance, benzylammonium cation with a NMR-proven orientation of the phenyl residue inside the cavity.[40] In contrast, the calix **8** without anionic groups at the upper rim binds anilinium ions with the phenyl ring outside and the ^+N center inside the cavity, due to the then predominating cation$-\pi$ effect (Figure 10). Remarkably, the different mechanisms are also reflected by the thermodynamic values: with **7** ($T\Delta S$ = 19 and ΔH = 4.9 kJ/mol), one finds a distinct entropic contribution typical for salt bridge contributions, whereas with **8** ($T\Delta S$ = 4.2 and ΔH = 8.7 kJ/mol), the enthalpic cation$-\pi$ interaction plays a greater role.

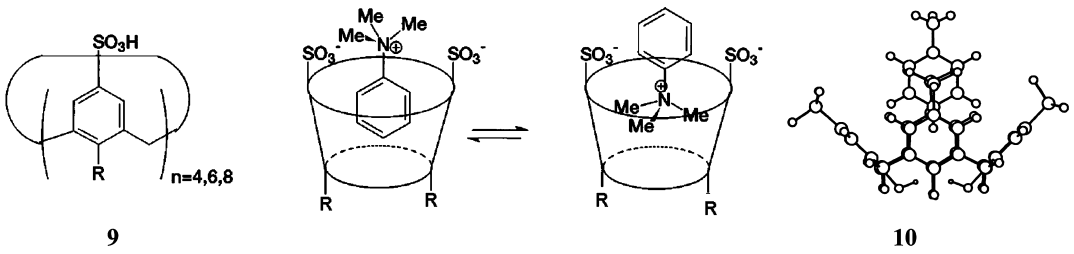
Similarly the orientation of insertion can depend on the applied pH (figure 11).[41] At pH 0.4 (R = OH), the strong ion pairing leads to dominating contact ion pairing; at higher pH, the phenolic groups are deprotonated (R = O^-), leading to a π moiety with partial negative charge and higher polarizibility. This then enlarges the $^+N-\pi$ attraction with a concomitant inverted orientation.

6. Anion$-\pi$ Interactions

In contrast to interactions of π systems with cations those with anions have received only later attention, in most cases restricted to aryl derivatives bearing electron-withdrawing substituents or heteroaromatic rings; in these, electrostatic forces between the then more electron-deficient π center and the anions secure for electrostatic reasons larger binding constants.[42] Recent calculations, however, predict for the interaction of anions and substituted arenes like for those with cations (see above) mostly direct interactions between the anion and the substituents, although for chloride$-$arene complexes an excellent correlation with computed electrostatic potentials was observed.[43] The first and still rare observation of anion complexations with unactivated π systems have been observed with host$-$guest complexes, in which the negative charge is, also according to NMR analyses, in perpendicular contact with the π surface, such as in tetrasulfonato calixarene complex **10** with toluene as guest.[37] As with related open dibenzylbenzene$-$diphenylethane combinations, the measured complexation energies amount to 2 kJ/mol per anion$-\pi$ pair in water.[37]

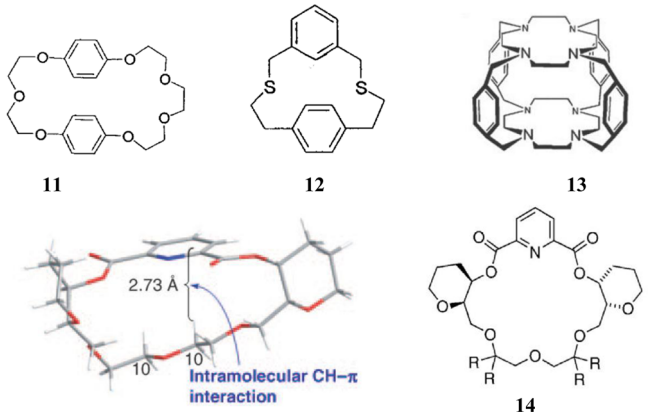
7. Hydrogen Bonding

In aqueous media, hydrogen bonds are usually too weak, but in aprotic solvents, even inherently weak hydrogen bonds like those between arenes as donor or acceptor are well documented.[44] Whitlock et al. prepared a series of host molecules complexing hydrogen bond donors in nonpolar media, mostly with nitrophenol as guest in nonpolar solvents.[45] Stoddart et al. noticed already in 1987 in crystals of aromatic crown ethers **11** an intramolecular edge-to-face interaction between the opposing rings.[46] Kim et al.[47] and Gellman et al.[48] have shown in thiacyclophanes such as **12** in the solid state edge-to-face CH$-\pi$ interactions, also with



9 10

FIGURE 11. Complexation of tetrasulfonato calixarene (**9**, $n = 4$, R = OH or R = O^-) with anilinium salts, with a pH-dependent orientation, and the complex **10** with toluene with host **9** (R = H).



11 12 13 14

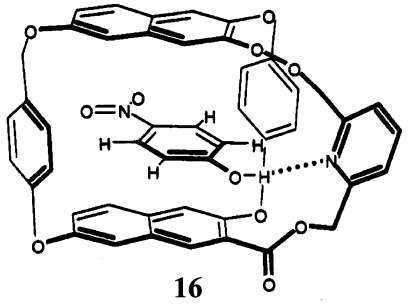
FIGURE 12. Intermolecular CH–π interaction in a pyridine-containing macrocycle **14**, from ref 50.

evidence in aprotic solvents by NMR. Recently a ball-shaped cyclophane of cyclene **13** was studied using NMR and computational methods, exhibiting substantial stabilization through CH–π interactions.[49]

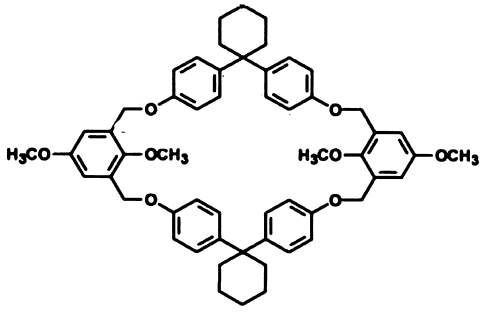
The pyridine-containing macrocycle **14** showed promising enantioselectivity for O-protected amino acids bearing aromatic side chains.[50] NMR data indicated the absence of a face-to-face interaction between the aromatic side chain and the host pyridine unit but in accordance with the crystal structure showed an intramolecular C–H$\cdots\pi$ bridge (Figure 12). NOESY spectra suggested the presence of an intermolecular CH–π interaction between one host proton and the aromatic side chain of tryptophan as a major factor for the observed enantioselectivity.

The stronger hydrogen bonds involving phenolic groups in calixarenes have long been known to play a decisive role in forming a molecular cavity.[51] Urea groups at the upper rim of calixarene **15** provide for stronger hydrogen bonding, either intramolecular with a pinched cone conformation in $CDCl_3$ or intermolecular to anions. Ethyl ester groups at the lower rim can act as selective receptors for Na ions; addition of Na ions converts the pinched cone conformation to a symmetrical cone (Figure 13). As a result, the system performs as a bifunctional receptor with positive heterotropic allostery, capable of binding hydrophilic salts MX (M = Na, K; X = Cl, Br, I) in apolar solvents.[52]

Intermolecular hydrogen bonds between host and guest molecules are usually observed only with stronger donor or acceptor units. The complex **16** described by Whitlock et al. in chloroform, however, seems to exhibit not only a stronger interaction between the phenolic guest group and the N atom of the host pyridine but also other edge–face hydrogen bonds.[53] Cocrystallization of the cyclophane **17** with picoline and lutidine isomers revealed in the solid state a strong selectivity concentration dependence, based only on weak CH–N and CH–O hydrogen bonds as visible in the X-ray-derived structures.[54]



16



17

With the resorcarene **19** bearing eight phenolic groups (Figure 14), a combination of hydrogen bonding and electrostatic interactions leads to a molecular switch, which can be triggered either by guest uptake and release or by pH changes.[55] At high pH, the macrocycle assumes a chairlike conformation due to the repulsion of the fully deprotonated OH groups; lowering the pH or uptake of, for instance,

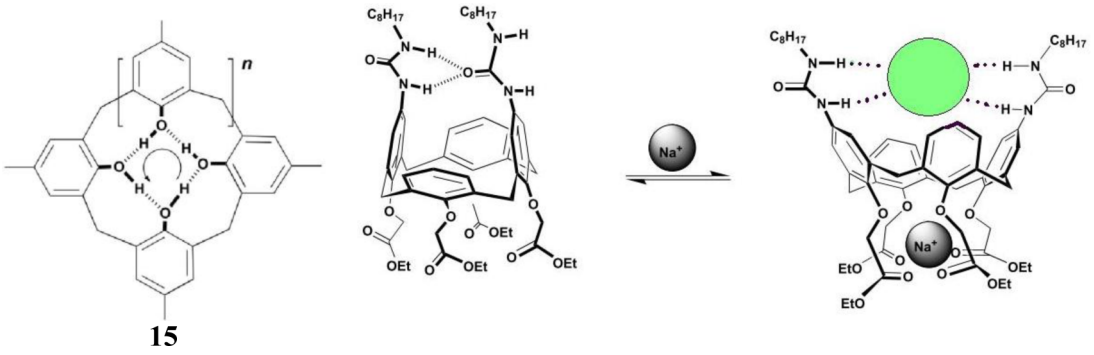


FIGURE 13. (left) Hydrogen bonds at the bottom of calixarenes; (right) an allosteric bifunctional calixarene; the hydrogen bonds between the urea units are free to take up an anion only if the metal ion is incorporated at the bottom.

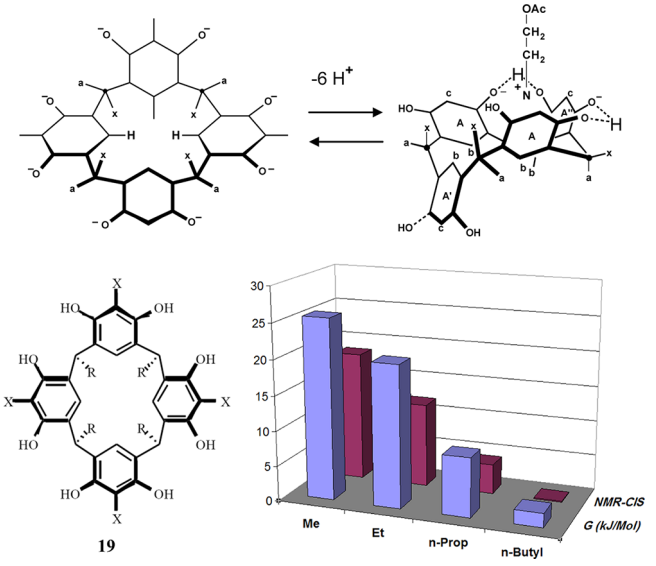


FIGURE 14. Resorcarene **19** bearing eight phenolic groups with conformation changes triggered either by guest uptake and release or by pH changes and binding free energies, ΔG (blue, in kJ/mol), of peralkylammonium salts (R_4NBr, with R = Me, Et, n-Prop, n-Butyl) and corresponding complexation-induced NMR shifts (red) on the ^+N-CH protons (for better visibility in 10 × ppm units).

acetylcholine inverts the systems due to formation either of phenolic O···H···O hydrogen bonds or of $^+N-\pi$ attraction, which thus functions also as element of an allosterically controlled proton pump, which is triggered by cationic guest molecules. The p*K* values of the phenolic groups are lower for the removal of the first protons in comparison to resorcinol but significantly higher for removal of the remaining protons, which are involved in hydrogen bonds. The binding constants reach $K = 50\,000\ M^{-1}$ for acetylcholine, in the range expected for the presence of four salt bridges. Tetralkyl ammonium salts (R_4NBr, with R = Me, Et, n-Prop, n-Butyl) exhibit a steep dependence of ΔG on the separation between the ^+N center and the anionic phenolate; the distance dependence can be correlated with a simple Coulomb equation, yielding a dielectric constant of $\varepsilon = 32$. The corresponding complexation induced (CIS) NMR shifts on the ^+N-CH protons decrease in the same way as ΔG; the observed CIS values are due to the ring current of the arenes and agree with an orientation of the ^+N center above the upper rim of the macrocycle. This is also borne out by computer modeling, meaning that cation$-\pi$ interactions play only a minor role here even with ^+NMe guest molecules. Ditopic amines such as $Me_3N-(CH_2)_n-NMe_3$ form strong trimeric complexes.

8. Catalytic Cyclophanes

The complexation of hydrophobic compounds in cyclophanes, in particular of stacking aromatic guest molecules, have led to early attempts to use such systems as catalysts.[56] Breslow et al. extended their strategies for selective functionalization based on cyclodextrin complexes to cyclophanes bearing, for example, manganese−porphyrin units, also with the hope of better stability against self-oxidation of the catalyst.[57] Diederich et al. have used their oxacyclophane **5** as a basis for several enzyme mimics, with covalent implementation of suitable functions as cofactors.[58] Dougherty et al. introduced substituents of an increasing polarizibility into the cyclophane **6**, and found that the k_{cat}/k_{un} ratios, not the complexation constants, increased in the order Me < OMe < Cl < Br, pointing to a stabilization of transition states by dispersion effects.[59] Lack of space allows us only to mention here some examples from our laboratory. The hydrolysis of bis(*p*-nitrophenyl) phosphate, which is a compound used as model of warfare agents such as VX, soman, etc., is enhanced by up to 2 orders of magnitude, and total accelerations of about 10^7 by introduction of aromatic substituents at the N atoms of a ethylenediamine of Cu(II) complex **20** have been observed.[60]

Inclusion in a host that is not further derivatized such as **4** (X = NMe_2) can exhibit large effects not only on reaction

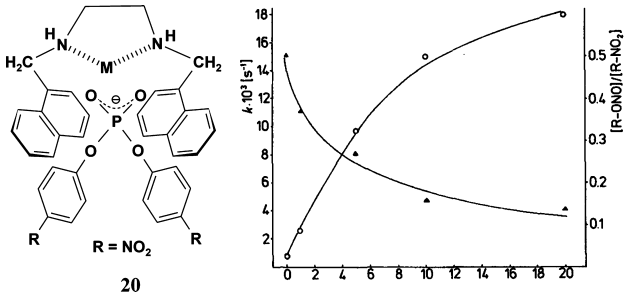


FIGURE 15. Catalysis of a substitution reaction with the cyclophane **4**, rate acceleration, and product change.

kinetics but also on product composition. Thus, 2-bromomethyl naphthalene reacts in the presence of the host with the ambident nitrite anion with a dramatic change from the predominating nitric acid ester to the nitro compound formation; this can be explained by an increase of the S_N2-type substitution by the anion, which assembles at the $^+$N corner of the cyclophane, and thus to an increased attack at the softer nitrogen atom instead of the oxygen atom of the ambident anion (Figure 15).[61] Analyses of the saturation profile furnish a Michaelis–Menten constant of 4.1 L/mol and an efficiency of $k_{cat}/k_{un} = 30$.

9. Conclusions

Studies of synthetic complexes with arenes as part of host or of guest moieties have provided already significant insight into the nature of relevant noncovalent interactions, including those occurring in biological systems. Such empirical analyses are based mostly on thermodynamic measurements in solution; they should be accompanied by securing the underlying structures by spectroscopic methods. Quantification of the interactions must be secured by measuring a sufficiently large number of equilibria in order to derive meaningful data; separation of the different interaction mechanisms is possible by systematic comparison of complexes with different kind and number of interactions sites. Solvent effects can shed light on the dominant binding forces and by extrapolation allow prediction of complexations in media that are not accessible experimentally. The virtually unlimited number and variations of synthetic host–guest complexes should in the future provide a firmer and more detailed basis for the understanding also of biologically important interactions, for the comparison with computational predictions, and for the design of drugs and of new supramolecular systems for many technological applications.

BIOGRAPHICAL INFORMATION

Hans-Jörg Schneider is professor *em.* of organic chemistry at the Universität des Saarlandes, where he was appointed in 1972. He studied in Tübingen, Munich, and Berlin (TU), and obtained his Ph.D. in 1967 in the group of Michael Hanack in Tübingen. In 1967–1969, he was Postgraduate Research Fellow at the University of California, San Diego, with Prof. R.C. Fahey and in 1969–1971 with Walter Hückel at Tübingen University. He published more than 260 papers and is author, coauthor, and editor of several books and many invited reviews. His research interests included conformational analysis, NMR spectroscopy, mechanisms of molecular recognition, new enzyme and receptor analogs, and artificial nucleases, esterases, and helicases. More recently, his group developed chemomechanical polymers with supramolecular binding sites.

FOOTNOTES

The authors declare no competing financial interest.

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