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Supramolecular Chemistry

Binding Mechanisms in Supramolecular Complexes

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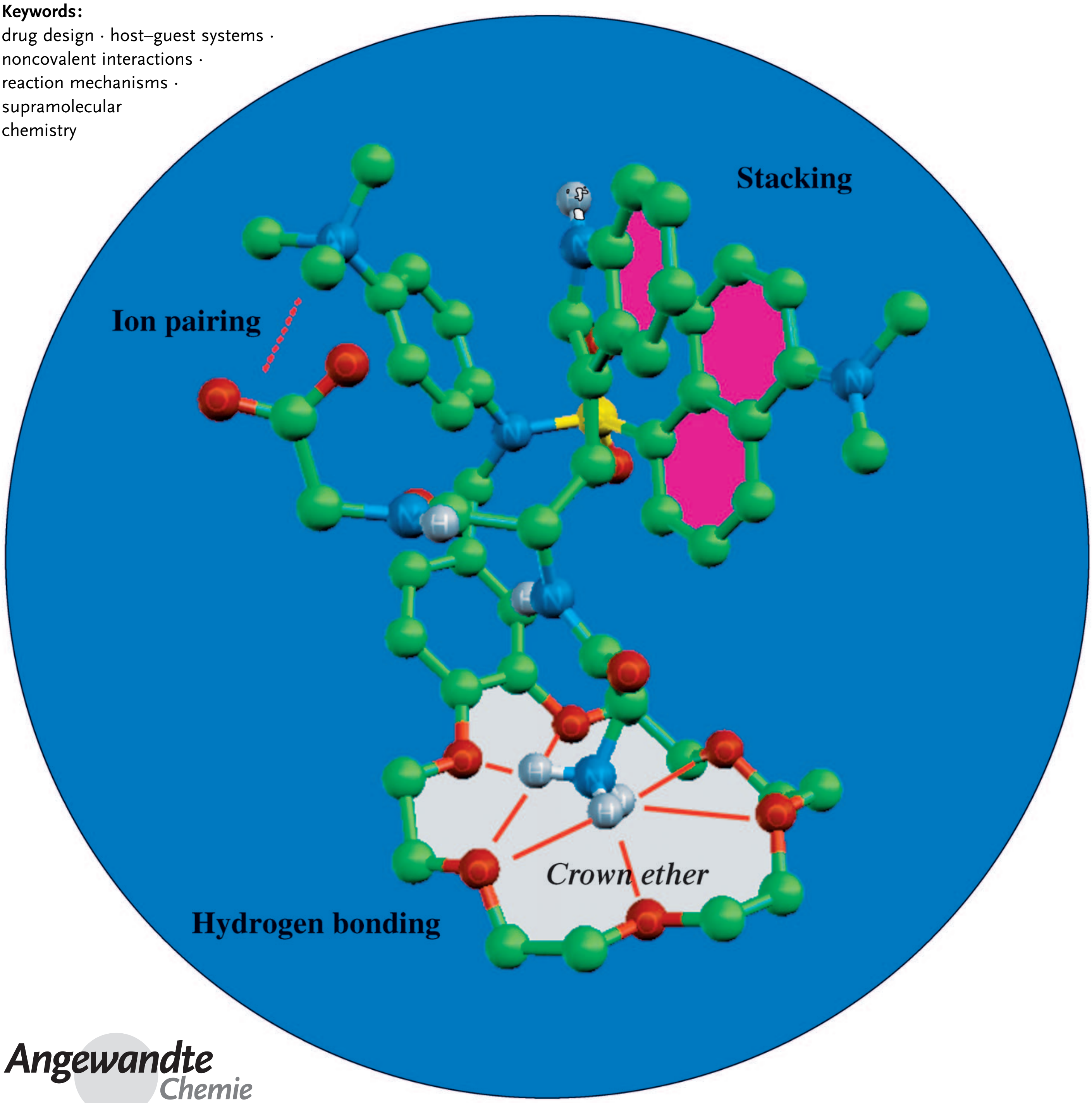

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Supramolecular chemistry has expanded dramatically in recent years both in terms of potential applications and in its relevance to analogous biological systems. The formation and function of supramolecular complexes occur through a multiplicity of often difficult to differentiate noncovalent forces. The aim of this Review is to describe the crucial interaction mechanisms in context, and thus classify the entire subject. In most cases, organic host–guest complexes have been selected as examples, but biologically relevant problems are also considered. An understanding and quantification of intermolecular interactions is of importance both for the rational planning of new supramolecular systems, including intelligent materials, as well as for developing new biologically active agents.

From the Contents

> “*Comprendre, c'est distinguer*”
> (Descartes)

1. Introduction—Efficient Noncovalent Interactions

With courageous simplification, one might assert that the chemistry of the last century was largely the chemistry of covalent bonding, whereas that of the present century is more likely to be the chemistry of noncovalent binding. The intelligent utilization of interactions between molecules is increasingly merging with the formerly dominant synthesis and characterization of highly complex structures. It is no coincidence that these interactions are the basis of all biological systems, whose efficiency will long continue to surpass that of synthetic systems by orders of magnitude. Supramolecular chemistry has begun to achieve, aided by targeted interactions between pre-programmed bonding centers, complex functions in highly organized molecular systems. In addition to monographs,[1] including many dealing with specific host–guest complexes,[2] a number of reviews are available on this subject, mainly devoted to specialized topics,[3] including some with an emphasis on mechanistic aspects.[4] In other reviews, the primary focus is on systems of biological or medicinal interest.[5] An understanding and precise description of interactions between organic molecules, particularly in the condensed phase, is still in its infancy,[6] although the theoretical foundations have long been known.[7]

The mechanisms of molecular recognition between organic molecules are the central theme of the present Review, whose purpose is to contribute to a systematization of the rapidly developing field of supramolecular chemistry. Even though the formation and function of most supramolecular complexes rests on several simultaneously applicable mechanisms, an attempt will be made at classification according to dominant interactions. Following a discussion of the principles of the formation of supramolecular complexes and their quantitative characterization, prototypical examples will be used to illustrate the most important binding mechanisms in order of increasing complexity, starting with ion pairs and Coulombic forces, and ending with dispersive and hydrophobic interactions. Information regarding the significance and most recent applications of intermolecular interactions have been consigned to an appendix for reasons of space.

1.1. The Chelate Effect—“Multivalency” in Synthetic and Biological Systems

Additive interactions involving a multitude of binding centers in reversibly formed complexes can lead to binding strengths approaching those of covalent bonds. This principle, long familiar to inorganic chemists, is traditionally referred to as the chelate effect; however, it has more recently also been termed “multivalency”. The formation of the supramolecular complexes considered here presupposes a satisfactory geo-

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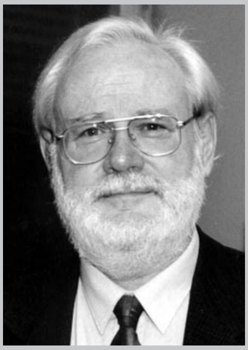
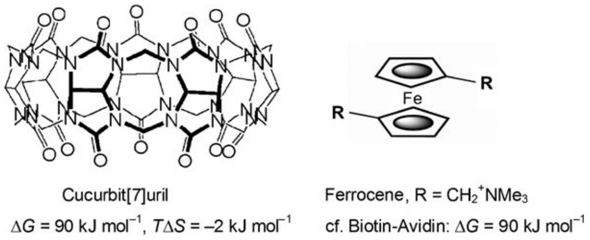
metric fit between the host and guest molecules. With many receptors, this is achieved by a macrocyclic structure. The nature of the so-called macrocyclic effect is still not entirely clear,[8] but its magnitude can nevertheless be assigned in a consistent way through the quantitative analysis of structure–property relationships based on a sufficient number of experimental values.[9] Numerous examples will be used to show that, in the sense of the chelate effect, the overall binding energy ΔG in supramolecular complexes is determined in general by the additivity of individual contributions to the free energy $\Delta\Delta G$. Additivity is observed much less often for the underlying ΔH and $T\Delta S$ contributions; thus, the chelate effect itself cannot be explained in a straightforward way on the basis of either entropy or enthalpy effects.[10]

Examples of **high affinity** in synthetic complexes include complexes of azacrown ethers with triphosphates ($\lg K = 11$ in water),[11] or a cryptaspheraplex with Cs^+ ions (extraction into chloroform with $\Delta G = 90\,\mathrm{kJ\,mol^{-1}}$).[12] Host compounds derived from cyclodextrins and calixarenes bind with porphyrin derivatives in water through multiple interactions with $\lg K > 9$.[13] Ditopic biscyclodextrins exhibit binding constants as high as 4×10^7, with enthalpy increases of up to $90\,\mathrm{kJ\,mol^{-1}}$. These effects may, however, be reduced by entropy penalties $T\Delta S$ of as much as $47\,\mathrm{kJ\,mol^{-1}}$.[14] Multiple interactions make it possible for the synthetic tris-vancomycin derivative shown in Scheme S1 in the Supporting Information to associate with a cell-wall tripeptide with $\lg K = 17$.[15] This complex is thus orders of magnitude more stable than the biotin–streptavidin complex found in nature, which is considered to be unique in its strength.[16] The combination of a ditopic crown ether with a bisammonium–C_{60} adduct in dichloromethane makes it possible, through multiple hydrogen bonds, to achieve binding constants that exceed 10^6.[17] Molecular rosette capsules composed of three calix[4]arene–melamine and six diethylbarbiturate units and held together by hydrogen bonds form complexes with electron-rich anthraquinones in chloroform with K values as high as $10^{10}\,\mathrm{M^{-1}}$, which are attributable in part to stacking of an electrostatic nature.[18] Readily accessible macrocyclic host compounds such as cucurbit[n]uril bind α,ω-alkyldiammonium salts with high affinity in water under acidic conditions,[19] for example, spermine with up to $K = 10^{10}\,\mathrm{M^{-1}}$ and adamantane–ammonium derivatives with $K > 10^{12}\,\mathrm{M^{-1}}$. [20] A ferrocene derivative with two alkylammonium groups R gives a complex with cucurbit[7]uril with $K = 3 \times 10^{15}\,\mathrm{M^{-1}}$, a strength comparable to that of the biotin–streptavidin complex, with $\Delta H = (90 \pm 1)\,\mathrm{kJ\,mol^{-1}}$. This latter system simultaneously displays an extraordinarily small entropy penalty, where $T\Delta S$ approaches zero (Scheme 1).[21]



Hans-Jörg Schneider became Professor of Organic Chemistry at the Universität des Saarlandes in 1972. His early research concentrated on conformational analysis, strain-reactivity relationships, NMR spectroscopy, and selective functionalization of hydrocarbons. He later became involved in mechanisms of molecular recognition, enzyme and receptor analogues, DNA interactions, and artificial esterases and nucleases. Most recently his major interest has been on molecular recognition in chemomechanical polymers. He has published more than 250 papers, and been (co)author and editor of several books on supramolecular topics.



Scheme 1. A cucurbituril–ferrocene complex with a similarly high affinity value as the biotin–avidin complex.

The fact that **high selectivity** can also be achieved with synthetic host compounds is illustrated, for example, by a calixarene/crown ether combination that is better at discriminating between potassium and sodium ions than is the natural ionophore valinomycin.[22] The examples cited illustrate how the chelate effect, through simultaneous involvement of multiple and complementary binding sites, can lead to highly efficient molecular associations. Nature also provides examples of multivalent[23] interactions in the form of extremely stable antibody–antigen pairs or also carbohydrate–protein complexes.[24] These latter interactions play a pivotal role in glycobiology.[25–27]

1.2. Increases in Affinity and Sensitivity Beyond the Chelate Effect: Cooperativity, Allosteric Systems, Co-complexation, Dendimers, and Compartmentalization

On closer inspection of literature examples, the magic word "multivalency" represents a new term for the long-familiar chelate effect. Multivalency is not to be confused with cooperativity, which refers to mutual intensification or weakening of binding centers.[28] Both nature and synthetic chemists have discovered ways to strengthen additive interactions between binding centers. These include positively cooperative allosteric systems, in which occupation of one binding center increases the affinity at a second center through conformative coupling within the host molecule.[29] The readily achievable rigidity of the conformational interaction means that the strength of such a coupling can be significantly greater for a synthetic allosteric host than for proteins, which are characterized by relatively high flexibility. Thus, complexation constants for lipophilic dyes in model receptors become measurable only in the presence of metal ions, which lead to formation of a cavity (see Scheme S2 in the Supporting Information).[30,31] By contrast, even strongly cooperative enzymes generally show significant levels of affinity in the presence of a single partner alone.[32]

Positive cooperativity is also the distinguishing feature of heteroditopic host compounds, which provide binding centers for two guest molecules that develop mutual attractive forces through co-complexation (see Scheme S3 in the Supporting Information). In particular, this principle is employed with great success in the complexation of ion pairs.[33] The combination of a crown ether (see Scheme S3 in the Supporting Information) with an amide bridge, for example, leads in the presence of KCl to a complexation constant that is up to a 300-fold increase relative to complexation with potassium tetraphenyl borate, since only the chloride anion fits in the bridge.[34] Peralkylammonium tosylates can, in a similar fashion, be complexed more selectively than other ammonium salts with bridged calixarenes.[35] Heteroditopic calix[4]diquinone/crown ether host compounds show especially strong cooperative binding with ion pairs; thus, NaCl, for example, binds about 60 times more strongly than NaI.[36] In a dimeric calixarene containing guanosine (G), a G quartet binds the cation of an ion pair, while the NH protons also present bind the anion.[37] Conversely, tightly associated molecules, including proteins, can also be separated through complexation (see Scheme S3 in the Supporting Information).

One possibility for increasing the affinity, which is largely overlooked, relates to the notion that more binding centers might be introduced into the host compound than are required for utilization of all the centers present in the guest molecule (Figure 1). For example, providing excess binding centers for the complexation of sugar derivatives with carboxylate anions results in affinity increases that exceed the corresponding statistical advantage (see Scheme S4 in the Supporting Information).[38] For similar reasons, the presence of six chlorine atoms in lindane, each of which by itself constitutes a very weak hydrogen-bond acceptor, leads to phenol binding to lindane as tightly as to a strongly basic amine.[39] Moreover, a significant increase in the binding constant is observed when parts of a guest compound protrude out of the cavity of a cyclophane host, thereby leading to the availability of more contacts than are directly usable.[40]

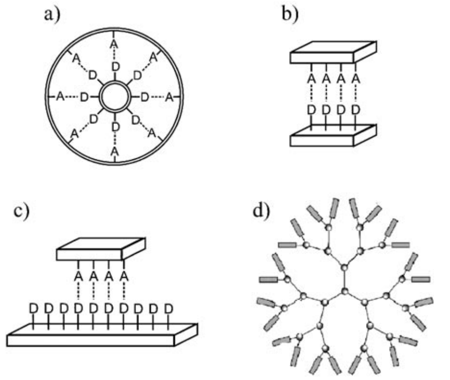


Figure 1. Complexes with an even (a, b) and an odd number of binding centers (c), as well as a dendrimer (d) with 12 external binding centers. Reprinted with permission from Ref. [38].

Dendrimers provide the opportunity for introducing an especially large number of binding centers into a single homogeneous host molecule. This in turn can result in a substantial increase in affinity with respect to a single guest molecule, but which may be diminished by steric screening effects and by self-association.[41] Interactions within and at the periphery of a dendrimer can also be altered by the inclusion of guest molecules.[42] The increase in affinity with dendrimers can be useful in numerous biological applications, including targeted transport and the release of active agents.[43] The presence of multiple binding centers for fullerenes in appropriate dendrimers results, for example, in substantial increases in the binding constants for the complex, even in cases where a 1:1 stoichiometry has been confirmed.[44] In the case of lactose dendrimers, a nearly 1000-fold increase in affinity relative to the monomer has been found with an octamer,[45] and observed inhibition constants for lectins are up to 2000 times greater compared to the corresponding monomeric sugars with a related 16-mer. [46] Anionic dendrimers bind dopamine more strongly by orders of magnitude than the analogous monomeric benzoate.[47] These examples show that observed increases in binding affinity do not require the assumption of unique dendrimer or cluster effects,[25c] or of special cooperativities. It should be noted that the derivation of thermodynamically unambiguous affinity parameters in complexes with multiple binding centers, especially common to biopolymers, demands a number of parameters or variable interaction coefficients.[48] In the case of complex stoichiometries other than the often merely assumed 1:1 composition, the efficiency of an association can be quantified with the aid of an affinity index BC_{50}, which, analogous to an IC_{50} value, specifies the required concentration of the major partner to ensure 50% complexation.[49]

Compartmentalization: One possibility——although rarely considered——for improving not the affinity, but rather the sensitivity, and thus, for example, the detection limit for a guest-molecule analyte in highly dilute medium is compartmentalization of the host–guest system. Figure 2 illustrates how occupation of every binding center requires fewer guest molecules in a small compartment than would be the case with a larger compartment.[50] This effect has been described and quantified only once—in the context of the miniaturization of sensors.[51] It is important to note, however, that the guest molecule to be detected, even in a dilute solution, must be bound as completely as possible inside the compartments. In other words, the achievable sensitivity is once again limited by affinity. Scheme S5 in the Supporting Information illustrates, with the example of a chemomechanical polymer gel, how reducing the size of gel particles containing the binding centers dramatically increases the response sensitivity.[52] In the same way, the noncovalent binding of concavalin molecules on the surface of saccharide-

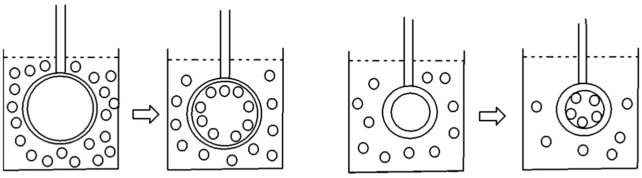


Figure 2. Increase in the sensitivity through compartmentalization. Reprinted with permission from Ref. [38].

containing polydiacetylene vesicles results in a colorimetric reaction which increases significantly in the case of smaller vesicles. This effect has also been attributed to complete occupation of the smaller particles, even at a low analyte concentration.[53]

2. Extensions of the Lock-and-Key Principle and the Additivity of Interactions

2.1. Induced Fit and Strain Effects

The lock-and-key principle, discussed in countless monographs and reviews, describes the necessary geometric fit between host and guest molecules. This principle can be modeled relatively easily by force-field simulations. Such simulations are also suited to establishing how much strain needs to be tolerated within a molecule during the formation of the complex through deformation of the most stable conformations. An "induced fit" is nearly always to be expected. The extent to which this can lower the resulting association energy can be understood through examples from coordination chemistry. Thus, metal ions with a small radius show a greater affinity for 1,3-diaminopropane than for 1,2-diaminoethane, whereas larger ions behave in the opposite way. The explanation for this effect is the differing torsional-angle (Pitzer) strains in the resulting metallacyclohexanes or -pentanes, respectively.[54] The necessary creation of *gauche* interactions in the course of the complexation results in an open-chain tetramine that binds copper(II) ions a factor of 10^{10} less strongly than does the corresponding macrocycle.[54a] In a complex of potassium ions with the crown compound [18]crown-5, only 1/6 fewer oxygen atoms are present as potential acceptor centers than in the complex with [18]crown-6, but the binding constant with [18]crown-6 is decreased by far more than 1/6. This is a result of steric hindrance from substitution of an O atom with a CH_2 group.[55] Introducing a methyl group on the nitrogen atom in the case, for example, of a K^+ complex with 1,5-diazacrown-6 leads to a 1000-fold increase in the association constant, since in the absence of steric interaction from the methyl group the free electron pair on the N atom is not directed toward the K^+ ion.[56] This is an example of a stereoelectronic effect often not captured by force fields. Extensive conformational changes in the host and guest are also observed in organic host–guest complexes. An example is the inclusion of steroids in cyclodextrins.[57]

2.2. Entropy Contributions

The build-up of high-enthalpy interactions leads in general to substantial entropy penalties. In cyclic receptors these may increase further through additional restrictions on mobility that accompany formation of the complex.[58] Conversely, interaction in and with proteins can be improved by the introduction of covalent bonds, thereby limiting the mobility.[59] However, with exact-fit cavities, which can still admit a minimum number of solvent molecules (Section 10), entropy penalties may be small relative to the corresponding gain in enthalpy. An example is the cucurbit[7]uril complex cited in Section 1.1 (Scheme 1).[21] Entropy contributions in formation of the complex are often difficult to quantify;[60] moreover, in contrast to enthalpy factors, they are also temperature dependent, which can even lead to a change in mechanism. Since ΔS, but not ΔH, is dependent on the standard conditions or mass units selected, the complex formed between benzene and β-cyclodextrin, for example, shows under the standard conditions of 1 M $\Delta H = -19.2\,\mathrm{kJ\,mol^{-1}}$, a negative contribution from $\Delta S = -15$ e.u, but actually a positive value of $\Delta S = +18$ on the basis of mole fractions.[61] A decrease in entropy is almost always observed on formation of synthetic host–guest complexes under standard conditions, whereas positive $T\Delta S$ contributions are sometimes found as well with protein complexes.[62] Only the formation of salt bridges is generally driven by entropy, while this is certainly not the case with so-called hydrophobic interactions, contrary to common assumption (Sections 9 and 10).

Enthalpy-entropy compensations should generally be anticipated with noncovalent complexes. A strong enthalpic interaction between multiple binding centers, as characterized by a large enthalpy advantage, normally leads to greater limitations on degrees of freedom, and thus to greater losses of entropy.[5c,63–65] Positive cooperativity between binding centers means greater binding strength, and is usually characterized by enthalpic advantages and entropic penalties; the converse holds for negative cooperativities.[66] Enthalpy-entropy compensations are intuitively enlightening, but they cannot be justified theoretically and, because of the relationship between the non-independent parameters $T\Delta S$ and ΔH, may simply be an experimental artifact.[67] Conclusions have been drawn about changes in mobility within a complex, as well as about degrees of desolvation from the slope and abscissa in a correlation between ΔH and $T\Delta S$.[68] On the other hand, little or indeed no predictive power is attributed to such correlations in regard to the nature of supramolecular complexes—they have even been described as phantoms.[69]

Translational degrees of freedom suffer a loss of about $150\,\mathrm{J\,mol^{-1}\,K^{-1}}$ if medium-sized molecules (M_r ca. 100) approach each other.[70] The associated cost in free energy can be estimated at $5–6\,\mathrm{kJ\,mol^{-1}}$.[71] Losses in translational entropy are greater in the gaseous state than in solution, but experimental values vary considerably. Thus, the measured value for methanol with triethylamine in the gas phase is $-81\,\mathrm{J\,mol^{-1}\,K^{-1}}$, for example, and in CCl_4 solution $-39\,\mathrm{J\,mol^{-1}\,K^{-1}}$; for *p*-xylene with tetracyanoethylene in the gas phase $-65\,\mathrm{J\,mol^{-1}\,K^{-1}}$, but in CH_2Cl_2 solution $-31\,\mathrm{J\,mol^{-1}\,K^{-1}}$. The literature provides values with even greater divergence.[72] In a typical host–guest complex involving multiple binding centers, the free energy costs related to the association of two molecules need be paid only once: namely, with the first interaction. With octa- to decavalent carbohydrate-toxin inhibitors, multiple interactions at the ends of the molecules lead to increasingly smaller entropy penalties, and to affinities in the subnanomolar range.[73] Diminished and constant entropy penalties explain the additivity of ΔG values generally observed in the formation of supramolecular complexes. The frequent compensation of $T\Delta S$ and ΔH contributions noted above also plays a role in the additivity of ΔG values. Noncovalent bonds arising during the formation of a complex result in positive contributions to **vibrational entropy**. These usually also lead to a characteristic increase in the heat capacity. Particularly in protic solvents, however, solvation effects account for the major part, by far, of the entropy differences in the formation of the complex; the formation of ion pairs in water is almost exclusively entropy driven (Section 4).

The literature discusses values of 13–20,[70] 4,[74] 1.5–6[75,76] or, depending on the nature of the barrier, 0–15 J $\text{mol}^{-1}\,\text{K}^{-1}$[77] for losses in degrees of **rotational freedom** suffered for each single bond affected during the course of the complexation. Non-quantum mechanical estimates of entropy losses in the presence of single bonds can lead to misleading results as a consequence of variability in rotational barriers.[78]

Experimental data derived from supramolecular complexes with differing numbers of single bonds show surprisingly small losses suffered through the presence of single bonds—both in systems based on hydrogen bonds[79] and ones with the formation of ion pairs.[80] The free energy of complexation ΔG_{cplx} (Figure 3) decreases as the number n of single bonds increases, but the loss is nevertheless small since $\Delta\Delta G = 0.5$–$1.3\ \text{kJ}\,\text{mol}^{-1}$ per single bond. Similar values have been observed in studies with artificial peptide β-pleated sheets[81] and in other studies as well.[82] One might expect that greater restrictions in degrees of freedom would result from stronger complexes. Nevertheless, measurements on nickel or copper complexes with conformationally pre-fixed 1,2-diaminocyclohexane or alternatively with freely mobile ethylenediamine, for example,[83] also show only $\Delta\Delta G = 1.5\ \text{kJ}\,\text{mol}^{-1}$, although here the ΔG_{cplx} values lie at 45 and 65 $\text{kJ}\,\text{mol}^{-1}$, respectively. Apparently, the presence of flexible regions in host–guest complexes is less of a disadvantage than previously supposed. Indeed, open-chain podands often display binding properties comparable to those of the largely conformationally fixed crown ethers.[84] This also has significance for the synthesis of new receptors or ligands. Biological systems such as proteins, which often show very strong noncovalent interactions, are constructed from fragments which, as is the case with amino acids, for example, include at least two single bonds each.

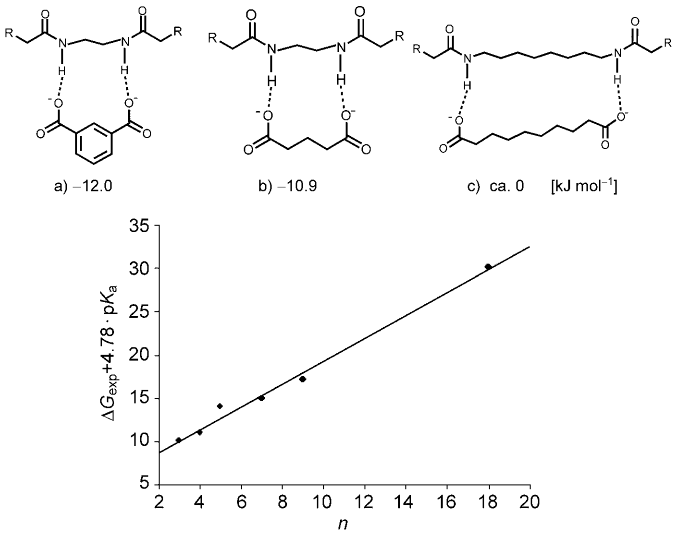


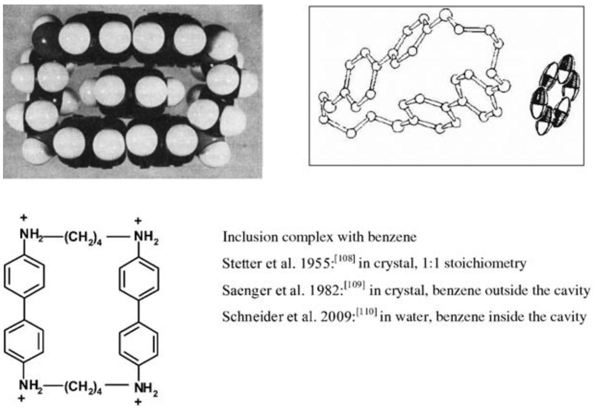
Figure 3. Effect of rotatable single bonds on complexing energy ΔG, with examples of hydrogen bond asociates as a function of the number n of rotatable single bonds in the related partner molecules. The first data point corresponds to structure (a), the last to structure (c). The slope suggests a penalty of only 1.3 $\text{kJ}\,\text{mol}^{-1}$ per single bond (measurements in chloroform; complexation energy ΔG in $\text{kJ}\,\text{mol}^{-1}$). Reprinted from Ref. [79] with permission.

3. The Quantification of Noncovalent Interactions; Methods and Applications

3.1. Analytical Methods

Energy values for intermolecular forces are accessible through the determination of equilibrium constants K and the corresponding association energies ΔG between molecules in the condensed phase or in the gaseous state.[85] The use of immobilized receptors allows surface plasmon resonance (SPR) investigations not only for the rapid measurement of equilibrium constants for a large number of ligands, but can also afford kinetic data.[86] The quantification of bond strengths on immobilized surfaces is possible through derivation of an effective concentration or molarity, as introduced previously for quantifying the effectivity of enzymes or for ring-closing reactions.[87] The effective concentration of a monovalent component in solution is that concentration which is enough to cause bonding with a reaction partner. In the case of a host–guest complex on a surface, this refers to the concentration of free, unoccupied surface centers relative to those that have already reacted with guest molecules, and which within a given volume are bound to the surface through a flexible linker.[88]

Reliable ΔH and ΔS values can be obtained only through calorimetric measurements. Moreover, only these also permit the determination of ΔH values at a sufficient number of different temperatures, and thus also allow determination of heat capacities ΔC_p. The derivation of thermodynamic parameters from the temperature dependence of equilibrium constants according to the van't Hoff method often leads to errors.[89] Measurements in the gas phase have become possible even for high-molecular-weight supramolecular complexes using so-called soft ionization techniques such as electrospray ionization (ESI) or matrix-assisted laser desorption/ionization (MALDI).[90] Under some circumstances, competition and kinetic experiments permit thermodynamic data to be established in this way without interference from solvent effects. The validity of mass spectrometric methods can be limited by a preference for ionic complexes and by the appearance of nonspecific associations, as through extracavity binding with cyclodextrins.[91] For example, complexes of proteins with carbohydrates show, under some circumstances, nonspecific interactions in the gaseous state that differ significantly from those observed in solution.[92] Nevertheless, especially with simpler metal complexes, basic thermodynamic data can be obtained that permit the differentiation of interfering solvent effects (see, for example, Section 6). Mass spectrometric methods also facilitate effective chiral discrimination in the gas phase.[93] Direct measurement of intermolecular interactions by force-spectroscopic methods (AFM)[94] have recently been extended to measuring the dissociation of molecules outside of a host matrix. Disruption forces ranging from $F = 39$ to 102 pN have been measured for five β-cyclodextrin complexes with $\Delta G = 9.6$–27.6 kJ mol^{-1} in water. The relationship between F and the corresponding ΔG values in solution can be derived numerically, and a correlation is observed, albeit with a considerable amount of error with respect to the forces (see Figure S3 in the Supporting Information).[95]. Through the use of host monolayers of cavitands at high dilution, a force sensor (cantilever), equipped with ammonium ions as guest molecules, displays a statistically distributed deviation which requires regression analysis.[96]



Inclusion complex with benzene

Stetter et al. 1955:[108] in crystal, 1:1 stoichiometry

Saenger et al. 1982:[109] in crystal, benzene outside the cavity

Schneider et al. 2009:[110] in water, benzene inside the cavity

Figure 4. Historically the oldest illustration of an organic inclusion complex with a macrocycle: Is the guest molecule benzene inside or outside the cavity? Reprinted from Refs. [108–110] with permission.

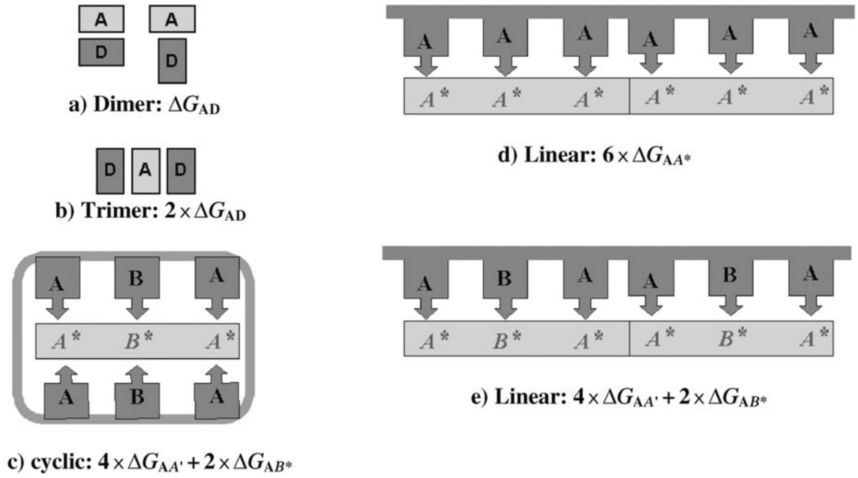
3.2. Mode of Complexation: Multiple Complexes, Intra- and Extracavitational Binding

One complication in the assignment of individual interactions arises from the occurrence of multiple conformations within a single complex, which is not always easy to establish.[97] The same applies to the simultaneous formation of multiple complexes, as observed, for example, with calixarenes[98] and very commonly with cyclodextrins.[99] Computer-based evaluation, including with commercially available programs, permits not only nonlinear fits of binding isotherms, which are generally less error prone, but also the treatment of stoichiometries beyond simple 1:1 complexes. An interpretation of thermodynamic data is not sensible in the absence of substantiated assumptions regarding the underlying structures; noncovalent interactions often do not appear in the expected places. For example, distinguishing intra- and extracavitational complexes of calixarenes[100] is not always easy.[101] In the crystalline state, in particular, it is not unusual to discover guest molecules both inside and outside a cavity, as for example with calix[4]arenes in the cone conformation.[102] In the cases of transition-metal derivatives[100d] (Section 6.2) and polymeric networks[103] of calixarenes the interactions often involve the aromatic exterior, and not a cavity. Noncovalent interactions both inside and outside the calixarene cavity constitute the basis for new materials resembling clathrates;[104–106] this also applies to cryptophanes.[107] A historically noteworthy example is the complex of benzene with a benzidinocyclophane. This first known case of a presumed intracavity inclusion complex was reported on the basis of the 1:1 stoichiometry found in the crystalline state.[108] X-ray analysis later showed the benzene in fact to be outside the cavity.[109]However, a very recent NMR analysis has indeed revealed intracavity inclusion in aqueous solution (Figure 4).[110]

Hydrophilic guest molecules bind with cyclodextrins preferentially outside the cavity, but still strongly enough for NMR analysis.[111] Similar external complexation is observed with phenols, whereas fluorinated derivatives bind within the cavity.[112] Consistent with such findings, equivalent or often even better results are obtained in chromatographic separations using open-chain cyclodextrin analogues rather than with cyclodextrin itself.[113] In the complexation of metal ions, an initially unexpected binding outside the cavity is sometimes observed in solution. Thus, upon dissolution in water, the Eu^{3+} ion from a crystalline [222]cryptand complex wanders out of the cavity into the solution.[114] NMR investigations[115] and molecular dynamics simulations[116] of similar complexes also indicate that outer-sphere binding occurs.[117] The mobility of a guest molecule within a cavity can be so limited that in the presence of two binding centers in the guest, two orientations will arise as a result of different interactions with the two complementary centers in the host cavity, a phenomenon that can be observed by NMR spectroscopy (Section 10).

3.3. Quantification of Binding Contributions in Solution

Figure 5 illustrates the routes so far taken toward the quantification of noncovalent interactions in solution. Numerous methods are available for determining binding constants, including of organic complexes,[1,118] but often not all the possibilities are utilized. Thus, through variation of the reaction medium (Section 10),[119] such as the proportion of organic solvent, it can almost always be arranged for an association constant to fall within the desired range for a specific method. By this means, particularly when a binary solvent mixture is used, it becomes possible to extrapolate to conditions unattainable experimentally.[120] Through competition measurements with, for example, substrates that fluoresce, interactions can be studied for which no directly measurable spectroscopic change occurs because of the corresponding association. Weak interactions can be analyzed especially effectively with “intramolecular balances”,[122] which take advantage of shifts in conformational equilibria as a consequence of differing noncovalent forces in the conformers. Such systems at the same time offer the advantage of a better defined geometry.



a) Dimer: ΔG_{AD}

b) Trimer: $2\times\Delta G_{AD}$

c) cyclic: $4\times\Delta G_{AA'}+2\times\Delta G_{AB*}$

d) Linear: $6\times\Delta G_{AA*}$

e) Linear: $4\times\Delta G_{AA'}+2\times\Delta G_{AB*}$

Figure 5. Interactions in simple molecular associations (a, b), in a macrocyclic complex (c), as well as in linear homo- and heterotopic host–guest complexes (d, e).

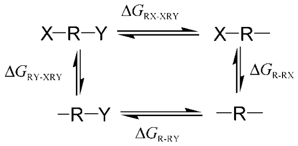
3.3.1. Analyses with Molecules containing One or More Binding Centers

In the simplest case one can determine association energies between two molecules when each has only a single binding center. Such energy values for donor–acceptor interactions can be found in easily overlooked databases, built from over 10000 individual measurements.[122] At the heart of these are association constants—often established through vibrational spectroscopy-—for simple alcohols, amines, etc., in the gas phase or, more often, in carbon tetrachloride or chloroform solution. The factors α and β introduced for polar interactions in Section 7.1, particularly with respect to hydrogen-bond donors and acceptors, can be derived from this data collection. These in turn, despite isolated discrepancies, also provide a generally consistent picture for, among other things, solvent effects (Section 10). The α and β factors can to some extent be correlated with calculated atomic charges or electrostatic potentials.[123] Analyses with simple molecules have various limitations; however, the associations are often so weak that high substrate concentrations must be used, which in turn necessarily alter the reaction medium during the course of the titration. For the same reason, a spectroscopic analysis of the underlying complex structure is more difficult to accomplish than with stronger supramolecular complexes, in which there is also significantly better ordering of the associated species. With simple molecular associates, not only can different orientations increasingly arise, but so can different stoichiometries (Figure 5, cases a and b). Moreover, the entropy contribution with simple associates is considerably higher than with supramolecular systems, for which a loss in degrees of translational freedom during the course of establishing a noncovalent bond need not be paid repeatedly for every interaction.

Attempts are often made to obtain, using few measurements, generally valid increments for interactions between specific functions from changes in equilibria accompanying variations in individual host–guest complexes. However, a reliable derivation of noncovalent interaction energies requires the analysis of a larger number of different systems than does, for example, obtaining substituent or reaction constants of the Hammett or Taft type. If in the case of a well-defined change, such as acidity or reactivity, data are required from about ten different systems, for example, then even more data are necessary with the multiplicity of forces and geometries typical of noncovalent complexes. Host–guest compounds can be prepared in a targeted way so as to juxtapose a multitude of functions against complementary groups. A relatively high degree of order and conformational stability can be assured with an increasing number of individual interactions both in macrocyclic and open-chain systems (Figure 5, cases c, d, e). At the same time, however, one must take into account that both negative and positive cooperativity may occur between neighboring binding centers, thus weakening as well as strengthening the interaction. An optimal geometric fit can be assured by computer-assisted molecular modeling design, and corroborated experimentally, generally by NMR spectroscopic methods. By variation of parts of the molecules it becomes possible to study the complexes in most diverse media. If the energy contributions of individual interactions are additive, then data obtained from homotopic host and guest molecules (Figure 5, cases c and d) with increasing numbers n of similar interactions in the complex will show a linear relationship between experimentally determined association energies ΔG and n. The slope of the best-fit line then serves as a reliable measure of the value $\Delta\Delta G_{xy}$ of a single interaction between functions x and y. Numerous analyses of this type have shown the expected additive behavior (for example, Figure S1 in the Supporting Information), and provided $\Delta\Delta G_{xy}$ values for many interactions, not only of significance for biological studies but also for materials.[4c,d] Complexes with varied interactions (Figure 5, case e) can be described similarly with additive increments through multilinear regression (Figure S2 in the Supporting Information). Analyses offering greater certainty are possible, however, if one of the interactions can be established through independent studies with homogeneous complexes.[124]

3.3.2. Analyses with Molecules containing Mutated Binding Centers

In analyses involving so-called mutations, one or two of the interacting functions present is exchanged, and a contribution from one of the interacting pairs is determined by calculating a difference. This procedure is employed in particular with protein complexes, in which “site-specific” mutants are readily accessible by gene technology.[125] As indicated in Scheme 2, differences in the ΔG values are measured between mutants with a uniform basic skeleton (or protein) R bearing active groups X, Y, or no such group. If X



Scheme 2. Determination of intramolecular interactions from changes in the position of equilibrium between double mutants XRY, XR, RY, and R.

and Y do not themselves interact and the geometric orientation remains constant, then a mutation from XRY to RY should lead to the same ΔG difference as from XR to R. This in turn should lead to the desired intermolecular interaction:

$$\Delta\Delta G = \Delta G_{\text{RY-XRY}} - \Delta G_{\text{R-XR}} = \Delta G_{\text{RX-XRY}} - \Delta G_{\text{R-RY}}.$$

The advantage of a so-called double-mutant experiment of this type is that instead of the binding energies themselves, their *changes* are utilized to obtain increments in the binding energy $\Delta\Delta G$. Problems arise through possible changes in the geometry, and from secondary interactions.[126] Such discrepancies show up, for example, in the determination of contributions from hydrogen bonds on the basis of single-point mutations. Thus, the exchange of a single amide group for an ester group in complexes of vancomycin with a mutated peptidoglycan lowered the equilibrium constant by a factor of 1000.[127] The problems can be even greater when starting with a relatively simple host–guest complex whose geometry allows significantly more degrees of freedom than a protein complex; the latter is conformationally better fixed as a result of a multitude of interactions. The potential error in the analyses is illustrated, for example, by a value derived from "mutated" host–guest complexes[128] for hydrogen bonds of the amide type, for which a value in chloroform of $\Delta\Delta G = 2.8\,\text{kJ}\,\text{mol}^{-1}$ was derived, whereas determinations with more than 70 other complexes (Section 7) gave $\Delta\Delta G = 5$–$7\,\text{kJ}\,\text{mol}^{-1}$ per hydrogen bridge.[129] The analysis of more than 70 protein complexes also produced $\Delta\Delta G$ values of about $5\,\text{kJ}\,\text{mol}^{-1}$.[130]

3.4. LFER and QSPR/QSAR Experiments, Analyses with Protein Complexes

A wide array of affinity data are available for complexes of proteins, usually enzymes, and active substances because of the medicinal implications.[131] If the structure of the binding center (perhaps varied by mutation) is known, then interactions between complementary functions can be determined. The so-called energy-scoring functions[132–134] accessible in this way play a promising role in the rational development of drugs. These functions are based on studies of, for example, 80[130] or even 170[135] different complexes, with strengths between $\lg K = 2$ and 11. Adaptable parameters are employed, and include several examples, such as the number and geometry of hydrogen bonds and ionic interactions, the electrostatic potential and number of water molecules at the binding center, the extent of lipophilic contact surfaces, specific interactions between aromatic compounds, and the flexibility of the ligands.[136] Association constants calculated in this way for 82 protein complexes of known 3D structure, for example, show for a training set alone an error of approximately an order of magnitude (Figure S4A in the Supporting Information). Complexes not included in the training set are of course associated with even greater deviations (Figure S4B in the Supporting Information). The limitations of this method are defined not only by the possible secondary interactions mentioned in Section 3.1.2, including changes in geometry[137] and the local environment with respect, for example, to polarity, but also by the difficulty of describing certain noncovalent forces, such as dispersive interactions, and also variations of the medium.

The additivity of individual interactions[138] was demonstrated quite early on through quantitative structure–property relationships (QSPR).[139] In the case of interactions involving host–guest complexes and biological systems these are more commonly referred to as quantitative structure–activity relations (QSAR).[140] As a rule, one generally uses the largest possible set of experimental data as the so-called training set, sometimes supported by new "data-mining" methods.[141,142] Structures of complexes from databases (for example, the Brookhaven Protein Data Base (pdb) or the Cambridge Structural Database (CSD))[143] may be used, as well as, more recently, collections of affinity data,[131,144] which are also applicable to protein–protein interactions.[145] In addition, or alternatively, structures can be simulated with force-field methods. Satisfactory linear correlations between observed and calculated complexation energies are often obtained with the help of appropriate algorithms that reflect the relationship between molecular fragments and properties, and also more recently by using neuronal networks.[146,147] In the absence of structural data—an especially common situation with biopolymers—structural information can also be developed from a sufficiently large number of experimental affinities. In three-dimensional QSAR procedures (3D-QSAR),[148,149] interaction surfaces of the receptors are described with the aid of potentials, for example, for hydrogen bonds, which are complementary to ligands that can be well characterized. The process of preparing electrostatic potential surfaces in this way, especially with protein/active-substance complexes, is known as comparative molecular field analysis (CoMFA);[150]. With programs such as GRID,[151] surfaces are "felt" in computer simulations by, for example, hydrophobic or hydrophilic test molecules.[152] Combinatorial syntheses that take advantage of dynamic libraries[153] (for an example see Scheme S6 in the Supporting Information) increase the amount of experimentally accessible data by orders of magnitude; this technique is also being used more and more for the exploration of intermolecular forces.[154] A comprehensive analysis of a great many complexes with biopolymers gave, for the "best" ligands, a rough correlation with the increasing number of non-hydrogen atoms, thereby leading to an affinity of about $6\,\text{kJ}\,\text{mol}^{-1}$ per heavy atom with ligands that were not too large.[155] ΔG values for the interactions in lectin–sugar complexes could be rather precisely reproduced within a training set, even in the absence of explicit entropy factors, in most cases to $\pm 1\,\text{kJ}\,\text{mol}^{-1}$. Suitably scaled values for polar and nonpolar hydrogen bonds were used together with Lennard-Jones as well as desolvation potentials and new docking routines.[156] Phenomenological procedures can also be based on parameters that have no direct connection with physically defined interactions.[157] Here again, calculated and experimental affinities correlate well in data comparisons for which the calibration is based on the utilized parameters themselves.

Classic linear free energy relationships rely on the comparison of numerous pieces of experimental data with independent parameters, such as for electron withdrawal or donation of organic functional groups, which can normally be associated with specific mechanisms. Thus, complexation constants for crown ether and cryptand complexes in protic solvents can be described using "substituent" parameters[158] derived from measurements of hydrogen-bond associates (Section 7) in carbon tetrachloride (Figure S5 in the Supporting Information; for examples, see Section 5.1 etc).[122] Linear free energy relationships of the Hammett type can lead not only to satisfying predictability, but also give insight into dominant mechanisms, at least if—with respect, for example, to homologous compounds—a comparable sort of bonding predominates. Commonly used parameters are based on hydrophobic or lipophilic contributions, and stem from distribution coefficients between water and lipophilic media (Sections 9 and 10). Other parameters reflect the capacity for forming hydrogen bridges, and can also reproduce solvent effects or distribution coefficients.[159] Within a particular series of compounds, significant correlations also appear with simple Hammett substituent constants, which document the electrostatic nature of intermolecular forces.[160] Of less predictive value are multiparameter correlations,[161] which under some circumstances actually end up being consistent with every conceivable binding mechanism. The widespread applicability of cyclodextrins has resulted in a particularly large number of their complexes having been studied (Section 9), and the corresponding stabilization energies ΔG analyzed with the aid of SAR methods,[162] sometimes with up to nine parameters.[163] For complexes of β-cyclodextrins with 48 active agents of medicinal interest, a linear correlation with four parameters produced a correlation coefficient r of 0.78 ($F = 16.7\,\%$); with five parameters and a cubic term $r = 0.834$ ($F = 19.2\,\%$) was achieved. The weights of individual terms can give some indication of the relevant mechanisms. The large number of parameters required with most QSAR/QSPR analyses, and the considerable correlation of numerous parameters among themselves—where most of them are not mutually orthogonal—complicates an unambiguous identification of individual interactions, let alone their quantification.

3.5. Correlations Based on Structural Analyses

The incomparably precise structural analyses available from single crystals serves as the classic basis for evaluating noncovalent interactions in terms of geometric requirements. However, with supramolecular complexes this approach carries with it especially great demands.[164] In the crystalline state, geometric conditions for efficient interactions can be very precisely defined, and then incorporated into the development of new materials[165] and new active agents.[166] A statistically significant number of examples of a particular geometric environmental relationship in the crystalline state offers valuable clues regarding intermolecular interactions,[167] even in the absence of values for the underlying energies. The computer program IsoStar was developed on the basis of the particularly comprehensive Cambridge Structural Database and supplemented by ab initio calculations. This method supplies typical geometric parameters for noncovalent interactions between about 250 chemical functions.[168]

Noncovalent forces can develop more freely in solution or in the gas phase than is possible in the solid state because of the constraints of periodicity and optimal lattice energies. Thus, even the newest methods of predicting crystal structures still lead frequently to a variety of packings and structures.[169] Lattice energies are responsible for the fact, for example, that the critical spacings for van der Waals interactions in crystals can be as much as 0.4 A greater than the sums of ideal van der Waals distances.[170] Similarly with weak hydrogen bonds, normal geometric distance and angle criteria are applicable only with strict limitations.[171] Occasionally unusually small distances are observed, such as with CH···O contacts, which tend to suggest repulsive interactions.[172]

NMR analyses of both small molecules and proteins in solution have revealed significant deviations from the crystal structures. Typical cases have been treated above in Section 3.2 in the context of extra- and intracavity inclusion. In general, it must be taken into account that, particularly with weak interactions, a solid structure is determined by countless interactions with functional groups apart from the single interaction of interest, especially if the molecule in question is large and/or exerts other strong interactions. A relevant example involves hydrogen bonds with covalently bonded fluorine as an acceptor (Section 7.5), which can be readily determined in solution but are scarcely detectable in the crystalline state. Despite these limitations, even weaker interactions are sometimes readily recognized from crystal-structure attributes. Dimerization constants for peptides correlate to some extent with distances between the donor and acceptor units as established by X-ray diffraction with crystals, as well as by NMR spectroscopy in solution.[173] Several modifications sometimes arise with single crystals, which might, for example, offer clues to alternative hydrogen-bond geometries.[174]

3.6. Theoretical Methods/Computer Simulations

Quantum chemical evaluation of intermolecular associations has witnessed enormous progress of late through the expansion of basis sets and the inclusion of electron correlation and polarization effects by using Møller–Plesset (MP) methods, particularly since it is now possible to compute even large systems more economically by DFT methods.[175–178] Errors arising from uncritical application of B3LYP functionals in particular in the course of DFT calculations have been described repeatedly, as have their correction, especially by the inclusion of correlation interactions.[179] In the past, DFT calculations have often done an inadequate job of capturing especially weak interactions. Newer, more effective approaches take into account only the total spin density and its derivatives rather than explicit orbitals, but provide relatively precise geometries and binding energies for the corresponding complexes, even with otherwise difficult to access dispersive interactions.[180] The advantage of quantum mechanical methods over molecular mechanics (MM) approaches based on classical force fields is that they do not require empirical parameterization and they also provide information regarding spin density/charge distribution, NMR shifts, etc. The fact that major problems remain—for example, in the computation of simple hydrogen-bond associates—is illustrated by the considerable differences in the experimental data in a recent report on the association of nucleobases and similar derivatives in chloroform,[181] even when explicit attention was given to solvent molecules. The description of localizable single interactions can be improved with the aid of inverse force-constant ("compliance") matrices.[182]

Molecular mechanics approximations for complex systems with many electrons are not only more economical, they have the further advantage of capturing more simply and more clearly the pairwise interactions of special importance in the understanding and development of host–guest complexes.[183] Complexation energies can be predicted from a combination of potential energies obtained through force-field calculations, solvation descriptions based on electrostatic models with inclusion of hydrophobic contacts corresponding to surfaces (Sections 9 and 10), and explicit consideration of entropy contributions from solvation as well as rotational, translational, and vibrational effects.[184] Examples include the association of cyclodextrins with benzene, resorcinol, fluorobiprofen, and naproxen, albeit only to within $\pm 3.5\,\mathrm{kJ\,mol^{-1}}$.[185] More recently, force fields have been used effectively to describe complexes of transition metals.[186] It is essential to recognize in such simulations, however, that the choice of the underlying force-field parameters is arbitrary within wide bounds, and requires calibration with test sets and thereby adaptation to experimental data from the structurally most commonly utilized systems. Thus, adjustment of the dielectric constants, which are important for electrostatics, from the often employed value $\varepsilon = 2$ to $\varepsilon = 4$, for example, results in reducing the ΔG_{Coul} value by half. Even more uncertain can be the estimation of hydrophobic contributions arising from contact surfaces between the interacting parts of molecules, for which very widely divergent values are utilized (Section 9). Free energy perturbation (FEP) methods[187] permit explicit inclusion of solvent molecules and require no supplementary entropy terms. Here atomic coordinates are generated by using molecular dynamic (MD) or Monte Carlo (MC) methods, and the Newtonian equations of motion are applied to each atom, albeit in a very time-consuming approach. Again, the accuracy of the parameterization for the individual interactions is the limiting factor. FEP and MD methods have been used to simulate, for example, steroid–antibody complexes in an aqueous box with deviations of $\pm 5\,\mathrm{kJ\,mol^{-1}}$.[188]

4. Formation of Ion Pairs/Salt Bridges

4.1. Ion Pairs in Water; Quantification, Salt and Solvent Effects

Just as with biologically important complexes, ion pairs or salt bridges play a major role in supramolecular complexes, especially in an aqueous environment. In the case of enzymes this also applies to interactions at the active center.[125,189] Such interactions can, for example, block undesirable associations of the proteins, as shown mainly in model experiments with peptides.[190] Salt bridges between macrocycles such as calixarenes with opposing charges make possible the formation of stable molecular capsules (Section 10.3). The complexation of nucleotides, saccharic acids, peptides,[191] etc. usually relies primarily on the formation of an ion pair involving carboxylate and phosphate groups,[192] particularly with host compounds such as polyamines,[193] azoniacyclophanes,[2c] and aminocyclodextrins.[194] Guanidinium groups have proven to be particularly versatile, lending themselves to good geometric fixation in polycyclic rings. At the same time, they provide oriented hydrogen-bond donors and, in contrast to amines, retain their positive charges even at high pH values.[195] In the case of phosphonate-containing receptors frequently used for complexing amino acids, peptides, neurotransmitters, etc., advantage is taken of the increase in binding strength with charge.[196] The negatively charged grooves in nucleic acids represent the point of attack not only, for example, for countless antibiotics, but also for polyamines; the charge and its compensation by various cations thereby also has an influence on the conformation of the double helix.[197] Analogous to synthetic host–guest complexes,[4c,d] these associations show a remarkably linear correlation between the binding strength and the number of possible interactions, here between the ammonium and phosphate centers of the ligand and receptor (Figure S6A in the Supporting Information).

The classic description of ion-pair associations follows from the Born model cycle, and both the Bjerrum Equation [Eq. (1)] and the simpler Fuoss Equation [Eq. (2)] use the parameters Q and a, which mainly characterize possible distances between the ions,[2b,198]) the dielectic constants ε, and the permanent charges z_{A} and z_{B} of the anion and cation.

$$K = (4\pi N/1000)(z_{\mathrm{A}}\, z_{\mathrm{B}}\, e^2/\varepsilon\, k\, T)^3\, Q(b) \tag{1}$$

$$\lg K = -2.6 + 3 \lg a + 243\, z_{\mathrm{A}}\, z_{\mathrm{B}}/\varepsilon\, a \tag{2}$$

Solvation effects can also be described through empirical force fields[199] by using FEP methods (Section 3.4), but these require specific potentials for the charge/water interaction.[200] Figure S6B in the Supporting Information shows that the interaction energy can be described to a good approximation as a linear function of the product of the charges $z_{\mathrm{A}}\, z_{\mathrm{B}}$ for over 200 ion pairs. Apparently, any differences in the magnitude, charge distribution, and polarizability of the very different ions involved have an almost negligible influence on the association energy. Accordingly, an astonishingly uniform correlation was found between $\lg K$ and the number of possible salt bridges for a large number of organic host–guest complexes with, for example, phenolate, sulfate, and carboxylate anchor groups.[4c,d,124] The resulting additive value of 5–8 kJ per mol and bridge at frequently employed ionic strengths is also found in the study of numerous inorganic ion pairs ($\Delta G = (6.2 \pm 0.4)\,\mathrm{kJ\,mol^{-1}}$), as well as organic ion pairs ($7.5 \pm 0.3\,\mathrm{kJ\,mol^{-1}}$).[201] The consequences of inexact geometric fit between the host and guest molecules, especially with salt bridges, are less severe than often assumed. Thus, the association constant K for an ion pair with α,ω-dianions decreases only from $K = 170\,\mathrm{M}^{-1}$ to $K = 72\,\mathrm{M}^{-1}$ when the separation varies between 9.3 and 6.0 A.[202]

The change in the stability of an ion pair as a function of total ionic strength I for the medium, particularly with inorganic complexes, has been investigated thoroughly,[203] and can be described by the Debye–Hückel Equation [Eq. (3)]:

$$\lg K = \lg K_0 + m\sqrt{I}/(1+\sqrt{I}) \qquad (3)$$

Experiments with organic host–guest complexes[120] show that the influence of added salts can be estimated accurately by the Debye–Hückel Equation, where the slope of a linear correlation with, for example, $m = 4 \pm 0.6$ for 2+2 combinations (dianion + dication) comes close to the predicted theoretical value. This is surprising as the host–guest complexes examined—containing, for example, azoniacyclophanes and calix-like resorcinarenes—present very different and anisotropic geometries. In every case, the systems investigated were ones in which an optimal fit was assured between the corresponding positively and negatively charged centers. The examples shown in Figure 6 also take into account ionic strengths generated by the host–guest ions themselves, without the addition of extra salts. They show that linear relationships also exist with ion pairs in which the distance between the charges within the partners differs greatly.[204] Thus, pair **1** gives the values $\lg K_0 = 2.85$ and $m = 4.6$, and for pair **2** $\lg K_0 = 2.21$ and $m = 3.9$. The number n of freely rotating single bonds in pair **1** is $n = 6$, and for pair **2** $n = 13$. Similar to the hydrogen-bonded complexes cited in Section 2, a linear correlation was again observed between $\lg K$ and n, and once more there was only a small influence of the presence of single bonds that are free to rotate (here only $\Delta\Delta G = 0.5$ kJ per single bond and mol).

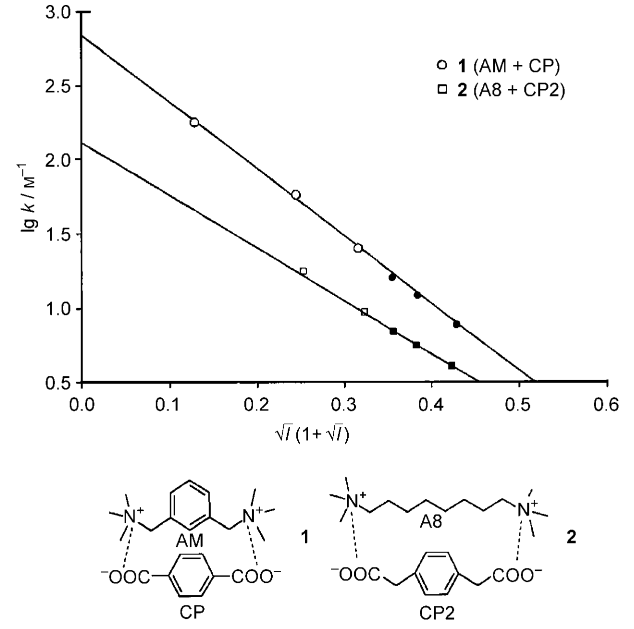


Figure 6. Debye–Hückel correlation between association constants (as lg*K*) and ionic strength *I* of the medium for two ion pairs with differing distance between the charge carriers. Reprinted from Ref. [204] with permission.

The relationship between the number of possible salt bridges and the stability of an ionic association is the basis of many host–guest complexes. Figure 7 illustrates the dependence of the binding strength on protonation, and thus on the pH value of the medium, with a macrocyclic polyamine used as the host compound.[4e,203] The anions **3**–**7** all bear the same triple negative charge. The differences in the observed affinity are due to differences in satisfactory geometric fits in the complexes. The fits improve with increasing protonation, and thus with binding strength, as one would expect on the basis of an affinity–selectivity relationship.[4e] With ionizable groups, the efficiency of forming ion pairs—as well as hydrogen bonds—depends on the p*K* values of the partners, which may change during the formation of a complex. The same is true with biologically important salt bridges: the p*K* values of amino groups in aminoglycosides varies as a function of the interaction with RNA from 5.7, to 6.1, or up to 6.7.[205] In addition to 1:1 cation/anion associates, complexes with higher

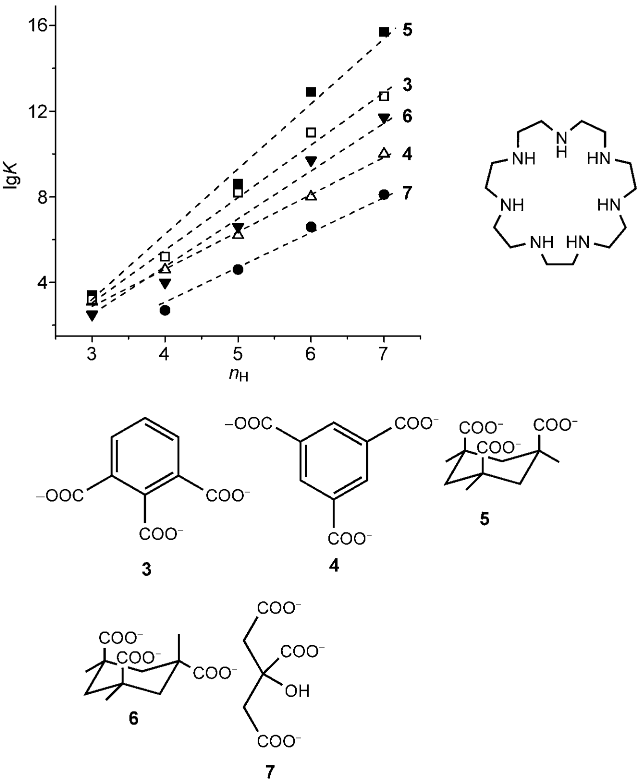


Figure 7. Binding strength (as lg*K*) for anions **3**–**7** with a macrocyclic amine as a function of the degree of protonation (n_H) of the host compound. Reprinted from Ref. [4e] with permission.

stoichiometries are often observed because of self-association of the ions. These processes, too, are entropy driven. As a consequence, dilution of one component can lead to the formation of higher molecular complexes.[206]

Solvent effects play an important role with ion pairs. Among other ways, these can be described on the basis of the Poisson Equation,[207] and in the simplest case also with the dielectric constants ε of the Bjerrum or Fuoss Equation. To date solvent effects have been investigated experimentally primarily with inorganic associates. Figure 8 shows that despite specific solvation effects, for example with DMSO or MeCN, there exists a roughly linear correlation with $1/\varepsilon$. The association constant increases with Et_4NBr from roughly $2\,\text{M}^{-1}$ in water to $1350\,\text{M}^{-1}$ in butanol, with Bu_4NBr from 3 to $900\,\text{M}^{-1}$, and with Bu_4NI from 5 to $1200\,\text{M}^{-1}$. The solvation is stronger for smaller ions with high charge density; hence—at least partial–-desolvation during complex formation requires more energy. This leads in the case of halides in protic media, for example, to an increase in the stability of ion pairs in the order $I^- > Br^- > Cl^-$, whereas the difference for Me_4NHal in water amounts only to a factor of 2 in K. As anticipated, the order is reversed in weakly solvating media such as DMSO ($I^- < Br^- < Cl^-$), again with only small differences. On the other hand, in the gas phase[208] the much larger differences reported in Table S1 in the Supporting Information are found, with decreasing ΔG values in the order $F^- < Cl^- < Br^-$. Contact ion pairs of especially high stability are formed in media that result in little or no solvation.[209] In such an environment, the separation of ion pairs can become so difficult that it interferes with the formation, for example, of rotaxanes from crown ethers and ammonium derivatives.[210] Tetra-*n*-butylammonium cyanide in water displays an association constant of $K = 10\,\text{M}^{-1}$. Astonishingly, in DMSO it is smaller, with $K = 2\,\text{M}^{-1}$, whereas in THF $K = 6\times10^4\,\text{M}^{-1}$, and the formation of higher aggregates is observed.[211]

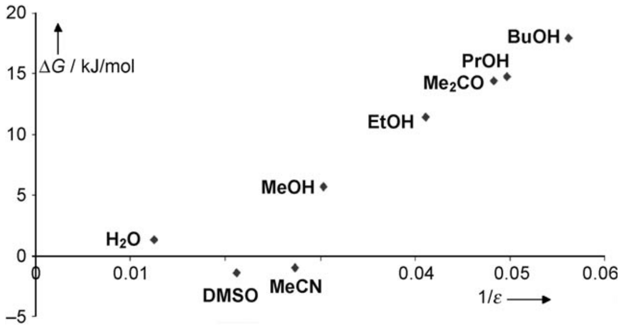


Figure 8. Solvent effects with ion pairs. Association energies ΔG [kJ mol^{-1}] of Et_4NBr as a function of $1/\varepsilon$ in various solvents.

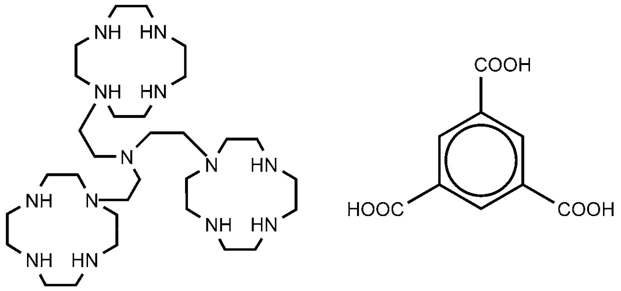
Only in the gas phase is the thermodynamics of ion-pair formation determined exclusively by enthalpy. This is as would be anticipated on the basis of a simple Coulomb interaction, which increases as the radius of the cation and anion decreases (Table S1 in the Supporting Information). Entropy contributions have a destabilizing effect, albeit of relatively small magnitude. The relationship is precisely the reverse for salt bridges with host–guest complexes in protic solvents. In water, the most commonly employed medium, the driving force is almost entirely an entropy increase, and often an endothermic reaction is even observed (Table 1).[201] The reasons for the dominant entropy contributions have been thoroughly discussed elsewhere;[2b,198] in the Bjerrum and Fuoss Equations they result from the derivation of K as a function of temperature. The decisive factor is that dielectric shielding by the solvent decreases rapidly with increasing temperature as a consequence of increasing ionic motion, thereby resulting in a decreased alignment of the solvent molecules. The entropy of solvent–ion interactions, as predetermined by the temperature dependence of ε, becomes more positive (stabilizing) the closer the ions in a pair approach one another. This effect is stronger in water than in any other medium because of its especially high ε value.

Table 1: Thermodynamic values in water (all in kJ mol^{-1}; extrapolated to $I = 0$) for complexes of amines (fully protonated) with the citrate trianion $^-OOCH_2COH(COO^-)CH_2COO^-$.[201]

Amine	n[a]	ΔH	$T\Delta S$	ΔG
$H_2N\text{-}(CH_2)_2\text{-}NH_2$	2	0.9	21	20.4
$H_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_3NH_2$	3	−0.9	23	23.6
$H_2N\text{-}(CH_2)_3\text{-}NH(CH_2)_4NH(CH_2)_3NH_2$	4	5.5	39	33.7

[a] Number of charges in the amine.

The examples in Scheme 3 illustrate as a function of the pH value, and thus extent of ionization, how either hydrogen bonds or formation of an ion pair will dominate. Only the latter, which arisies at high pH values with carboxylates, is exclusively entropy driven.[212]

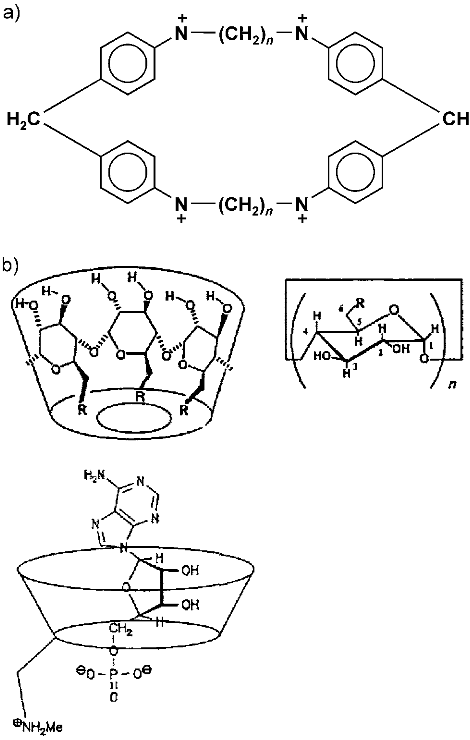


pH 3: $\Delta H = -50$, $T\Delta S = -10$ kJ mol^{-1}
pH 7: $\Delta H = 0$, $T\Delta S = 40$ kJ mol^{-1}

Scheme 3. Example of a change in the binding mechanism as a result of changing the pH value.[212]

4.2. Ion Pairs, with the Participation of Other Binding Mechanisms

Salt bridges often play a role in the formation of a complex simultaneously with other binding mechanisms. The various contributions can be quantified with complexes of positively charged receptors such as an azoniacyclophane (Scheme 4, Table 2):[213] doubly negatively charged nucleo-



Scheme 4. Host compounds for nucleotides with salt bridges as well as additional interactions: a) azoniacyclophane CP66 ($n=6$); b) heptaamino-β-cyclodextrin ($R=NH_2$) with adenosine monophosphate (AMP).

tides show values of $\Delta G_{XP}=17.5$–$19.5\ kJ\,mol^{-1}$; the corresponding electrically neutral nucleosides form complexes with $\Delta G_X=7$–$10\ kJ\,mol^{-1}$ (Table 2). The difference $\Delta\Delta G=\Delta G_{XP}-\Delta G_X$ is a constant $(10\pm 2)\ kJ\,mol^{-1}$, which is consistent with the presence in each case of two salt bridges between a host ammonium center and a guest phosphate ion. As shown above, one would anticipate here $(5\pm 1)\ kJ\,mol^{-1}$ per bridge. As expected, the affinity of nucleotides for positively charged receptors such as an azoniacyclophane increases sharply with the charge of the anion (Table 2). Cation–π interactions between nucleobases and host ammonium centers provide a further binding contribution of 7–10 kJ mol^{-1}, with a modest base selectivity. The constants rise to as much as 1×10^6[214] with the sevenfold charged heptaamino-β-cyclodextrin.[194] Additional interactions arising from inclusion of the ribose unit, and to some extent also the nucleobase, are apparent in the corresponding variations in the K values (Scheme 4). NOE experiments confirm that the ribose unit, not the nucleobase, is enclosed in the cyclodextrin cavity. Ribophosphate binds with 34 kJ mol^{-1}, phosphate with 20 kJ mol^{-1}, and ribose with 8 kJ mol^{-1}. The corresponding binding contribution for the sugar unit of about 10 kJ mol^{-1} could be the result of dispersive CH···CH interactions within the cavity, and in part also from hydrogen bonds on the edge of the cyclodextrin.

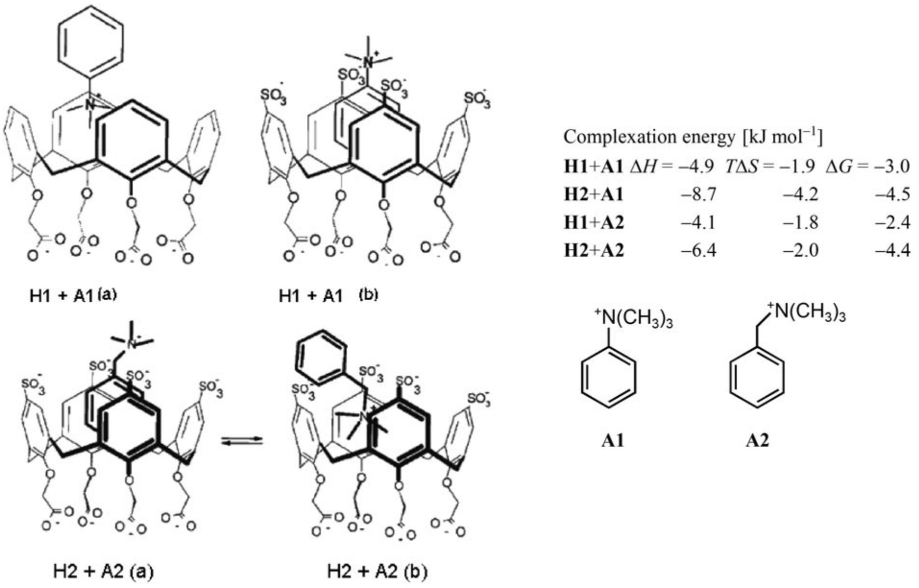
Table 2: Association constants ($K\times 10^3\ M^{-1}$, in water) of nucleosides and nucleotides with a cyclophane.[a]

X=	A	G	U	C	T
nucleoside X	0.05/–	0.01	0.01	0.015	–
XMP	1.9/*126*	0.5/*40*	0.85/*20*	0.93/*87*	1.21
XDP	11.5/–	–	-	–	–
XTP	36.0/*3290*	–	–	–	–

[a] In italics: association constants with heptaamino-β-cyclodextrin.

Cation and stacking interactions play a role in addition to salt bridges in complexes of the anionic calixarene compounds **H1** and **H2**, which are fixed in a cone conformation, with aromatic amines such as **A1** and **A2** in water (Scheme 5).[215] NMR analyses reveal that in the case of **H1**+**A1** the orientation **a** dominates as a result of the prevailing $^+NMe_3$–π interaction, whereas in **H2**+**A2** the supplementary SO_3^-–$^+NMe_3$ salt bridge leads to the phenyl rings being included in the cavity with simultaneous aryl–aryl stacking (conformation **b**). The reduced role of the salt bridges expresses itself here by exothermic and entropic penalties.

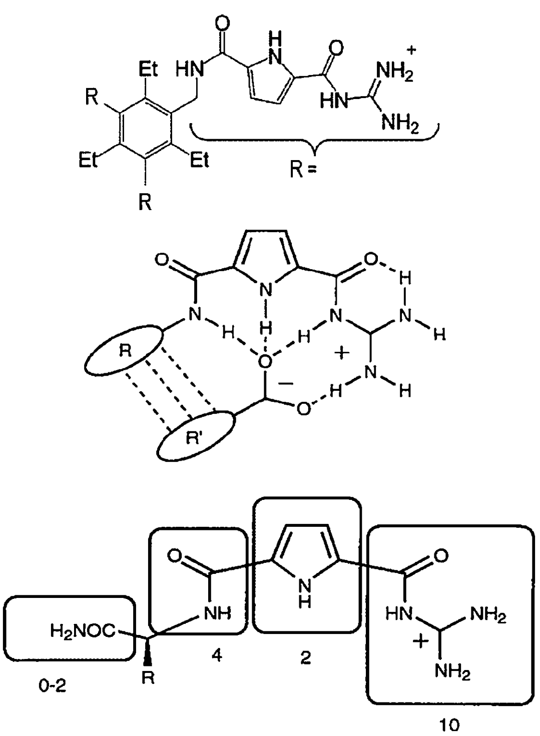
A combination of salt bridges and van der Waals forces can be utilized in calixarene capsules (Section 10) to bind ammonium derivatives in the upper part, and neutral guest molecules such as imidazolidine-2-one in the lower part (Scheme S7 in the Supporting Information).[216] Similar associates form from polyamino- and polysulfanato-β-cyclodextrin.[217] The triple positive charge on the guanidinium unit in one receptor (Scheme 6) produces large binding constants in



Complexation energy [kJ mol^{-1}]

	ΔH	$T\Delta S$	ΔG
H1+A1	−4.9	−1.9	−3.0
H2+A1	−8.7	−4.2	−4.5
H1+A2	−4.1	−1.8	−2.4
H2+A2	−6.4	−2.0	−4.4

Scheme 5. Complexes of anionic calixarene compounds with aromatic amines.

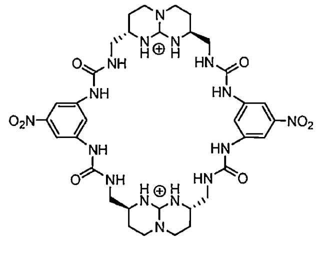


Scheme 6. Binding contributions in complexes with guanidiniocarbonylpyrrole receptors; the numbers 0–2, 4, 2, and 10 designate, for the individual interactions (stacking, hydrogen bonds, and ion pairs), the asociated ΔG values (in kJ mol^{-1}) of the complex with Ac-Ala-O$^-$.[220]

water with the citrate anion ($K = 10^5\,\text{M}^{-1}$) or with methylphosphate (at pH 4, $K = 12500\,\text{M}^{-1}$).[218] The *K* values with sugar phosphate anions are double those with methylphosphate. This, and a rather modest selectivity relative to three isomeric sugars, has been interpreted as a consequence of extra hydrogen bonds.[219] A comparison of association constants for a guanidinocarbonyl pyrrol receptor with various amino acid derivatives permits the ordering of the various binding contributions in the complex. For Ac-Ala-O$^-$ ($K = 1600\,\text{M}^{-1}$ in water) the contributions noted in Scheme 6 are observed with up to 4 kJ mol^{-1} for hydrogen bonds and 10 kJ mol^{-1} for the primarily effective double salt bridges.[220]

4.3. Ion Pairs in Non-aqueous Solvents

Complexes of calix[4]arene derivatives with both amino acids and peptides in methanol show association constants ranging from 3000 to $45000\,\text{M}^{-1}$, arising largely from Δ*H* contributions and with entropy factors appearing to be largely cancelled out by $\Delta H - T\Delta S$ compensation.[221] The complexation is actually dominated by interaction between the protonated N termini of the amino acids and the phosphoryl groups on the calixarene. However, the stability of the complexes nevertheless correlates with the lipophilic character of the amino acid side chains, consistent with a solvophobic contribution even in methanol. Pyridinium units on the edges of the calix[4]arenes can serve as selective receptors for α,ω-dicarboxylates. Malonate, citrate, etc. show *K* values of about $3000\,\text{M}^{-1}$ in DMSO, while in MeCN the constants rise to about $60000\,\text{M}^{-1}$.[222] The association of a macrocycle containing two guanidinium units (Scheme 7) in acetonitrile shows that the remarkable enantiodifferentiation can, even in an aprotic solvent, be largely due to an entropy preference for one of the ion pairs.[223] Hydrogen bonds can also contribute in the less competitive solvent acetonitrile selected in this study.



Complex in MeCN with

L-Tartrate	$H = -40.5$	$T\Delta S = -3.5$	$\Delta G = -37.0$ kJ mol^{-1}
D-Tartrate	$H = -45.0$	$T\Delta S = -11.0$	$\Delta G = -33.9$

Scheme 7. Entropy-dependant differentiation of diastereomeric ion pairs in an aprotic medium (MeCN).[223]

5. Electrostatic Interactions

Attractive forces between opposing permanent charges constitute the basis for most noncovalent bonds in supramolecular complexes. Most ion pairs, hydrogen bonds, and ion–π interactions have their origin here as well, but these are treated in separate sections of their own because of their importance. Theoretical analyses of electrostatic complexes have become possible particularly as a result of further developments in the classical Poisson–Boltzmann approach.[224]

5.1. Ion–Polypole Interactions

Numerous supramolecular complexes owe their stability and function to electrostatic forces between a permanent charge and partner molecules with an opposing *partial charge*, and the partial charge may be further increased by polarization. Such host–guest associations are often referred to as donor–acceptor complexes, although electrons are never, and charges only rarely, transferred. In most cases, charge–transfer interactions also contribute little to stability (Section 9). The complexation of alkali-metal and alkaline-earth cations by crown ethers and related compounds is based on an attraction between the ion and the free electron pairs on a heteroatom in the ligand.[225] Polar contributions in the formation of intermolecular complexes can be verified through Hammett analyses, such as in the association of Na, K, and Tl ions with substituted macrocycles (Figure 9).[226] Complexes of *p-tert*-butylcalix[4]arene esters with alkali-metal ions show linear Hammett correlations with substituents , which alter the electron density at the C=O group.[227]

As noted in Section 3.2, the donating effect of heteroatoms in ionophores can also be quantified by using polarity

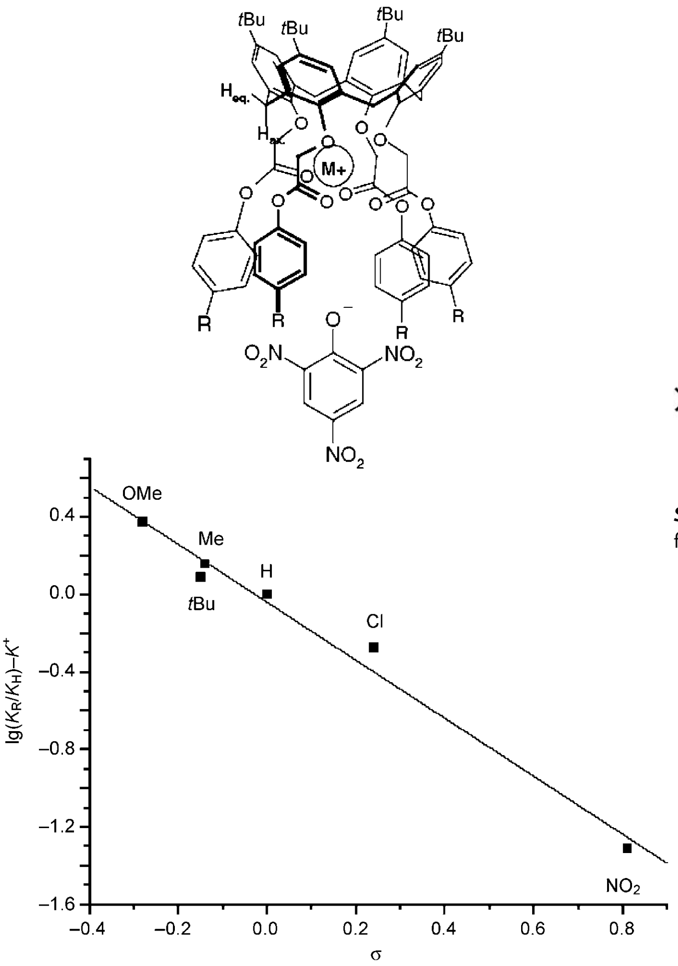
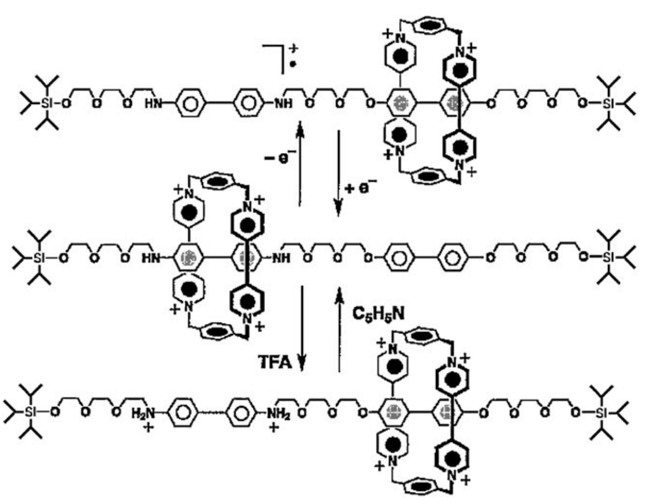


Figure 9. Complex of a *p-tert*-butylcalix[4]arene ester with potassium picrate, and Hammett correlation with the extraction constant (as lg *K*) from H_2O to CH_2Cl_2. Reprinted from Ref. [227] with permission.

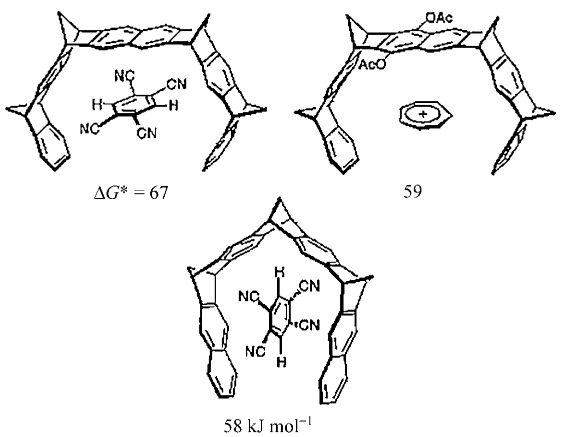
parameters such as α or β;[122] these describe the stability of crown ether and cryptand complexes quite successfully (Figure S5 in the Supporting Information).[158] With azacrown ethers, for example, the orientation of the lone pair of electrons on the nitrogen atom toward the cation is decisive.[228] As would be expected for electrostatic interactions, the formation of complexes between crown ethers or related compounds and cations is determined largely by the free enthalpy ΔH, while entropy effects, in contrast to the situation with ion pairs, usually play a minor role.[2a,229] The formation and function of rotaxanes and catananes from cyclophanes and axis molecules[230] is determined largely by electrostatic interactions. In the classical models of molecular machines, the attraction between an electron-rich aminoaryl "station" and an electron-deficient cyclophane, for example, is replaced by repulsion upon protonation of the aminoaryl station (Scheme 8).[231] This leads to rapid and reversible mechanical motion of the cyclophane "shuttle" between the stations. Instead of through changes in the pH value, a corresponding electron transfer can also be achieved photochemically or with redox reagents.[232] Cyclodextrins also form rotaxanes[233] which are more stable with bipyridinium axes, for example,



Scheme 8. A rotaxane shuttle based on Coulomb forces. Reprinted from Ref. [231] with permission. TFA = trifluoroacetic acid.

than with the corresponding reduced neutral bipyridine. This also opens the way here for redox switching. Redox reactions of tetrathiafulvalene (TTF) components[234] allows the corresponding catenanes also to be switched in an analogous way through charge transfer (Scheme S8 in the Supporting Information). The electron-rich tetra-TTF-calix[4]pyrrole proves also to be a suitable receptor for fullerenes and for electron-deficient, neutral guest molecules.[235]

The inner faces of concave-shaped aromatic cleft or tweezer compounds are characterized, relative to the convex exterior, by a greatly increased partial negative charge.[236] This leads to effective complexation of electron-deficient guests (Scheme 9). The stability of such complexes in chloroform increases with the electron deficit of the guest molecule, dominated by enthalpy gains and influenced only minimally by entropy contributions. The negative electrostatic potential surfaces, confirmed by MO calculations, permit, for example, the effective complexation of NAD^+.[237]



Scheme 9. Complexes of electron-rich cleft or tweezer compounds with electron-deficient guest molecules; activation energies of the exchange ΔG^* in $CDCl_3$.[236]

The complexation of (protonated) amines in cucurbituril macrocycles[238] (CBs; Scheme 1) is largely attributable to ion–dipole interactions, as evidenced, for example, from the stability order with *n*-pentane derivatives (Scheme S9 in the Supporting Information).[239] Binding enthalpies determine the affinity differences. Stability-reducing $T\Delta S$ contributions differ less, and may even be smaller with the stronger complexes.[21] Depending on the generally acidic reaction conditions, urea carbonyl groups of the CB portals are bound in the presence of salts to metal ions. These are displaced during complexation by protonated amines, but nevertheless act in a co-complexing way with alcohols. Polar groups such as O, S, or N atoms within the alkyldiamine chain decrease the stability of the complexes, because the cucurbituril cavity itself is hydrophobic.[240]

Solvent effects with crown ether complexes[241] are difficult to treat theoretically because, among other reasons, the ion solvation shell is still partially present in the complex.[242] Numerous empirical solvent parameters have been employed, including Gutman donor numbers,[243] quantities for the polarity,[244a] permittivity,[244b] solvation strength,[244c] and Kirkwood parameters.[244d] A satisfactory description would include consideration of individual energy contributions for the solvation of both the cation and the ligand. Experimental values for ΔH and $T\Delta S$ as well as ΔG contributions for the transfer from water to methanol vary according to the metal ion, which also remains in contact with the solvent in cryptands.[245] Figure S7 in the Supporting Information shows an acceptable correlation of $\lg K$ with a) with the free energy of transfer ΔG_t of K^+ from water into various solvents for the complex of [18]crown-6 with potassium ions, as well as b) the Gutman donor values for the medium.[246]

5.2. Interactions between Electronically Neutral Polar Groups

Multipolar interactions between electronically neutral polar groups make a significant contribution to the formation of many intermolecular associations, although by themselves these are relatively weak, often overshadowed by other forces, and sometimes competitively masked by solvents.[3d,247] Such weak interactions are thus largely ascertained through systematic analyses of crystal structures. Thus, the interactions in $C{=}X\cdots Y$ systems such as $C{=}O/O = C$, $C{=}O/CN$, $C{=}O/NO_2$, and $C{=}O/RF$ are often detected on the basis of intermolecular distances that fall short of the sum of van der Waals radii, usually in combination with a $C{=}X\cdots Y$ contact angle close to 90°. As expected, interactions of $C{=}O$ and $C{=}N$ dipoles with halogens (Hal) are characterized at a statistically significant level by an orthogonal arrangement of the Hal atom above the $C{=}X$ dipole, with a preference for the partially negatively charged halogen to approach at the electrophilic end of the dipole. Analogous orthogonal positioning is also frequently observed between neighboring $C{=}O$ groups, in which case, however, electrostatically equally favorable antiparallel dispositions are also found.[248] Such antiparallel orientations also prove dominant between highly polar $C{-}F$ groups in crystal structures. Interactions with the other less strongly polar but more polarizable $C{-}Hal$ units are also accompanied by more orthogonal arrangements. In this case, the stronger dispersive interactions (Section 8) often contribute to other intermolecular forces outlined only briefly here. These have increasingly also been structurally characterized in proteins and in their complexes with active agents,[3d] where those particularly with halogens play a role that was only recently recognized.[249] According to MP2 calculations, however, interactions between chalcogen atoms are largely dominated by van der Waals forces; electrostatic effects should play a role only between sp^3-hybridized oxygen atoms.[250]

The so-called **halogen bond** between a Lewis base **B** and a halogen molecule **XY** arises, similar to the analogous hydrogen bond, to a large degree from electrostatic attraction,[251] with a smaller contribution from polarization of the dihalogen bond.[252] Gas-phase studies in conjunction with theoretical analyses[251] have shown that the geometry of the halogen bond is similar to that of the hydrogen bond. This has been confirmed by systematic analysis of a great many sets of crystal-structure data.[253] In this study, a correlation emerged between a decrease in the $Y\cdots X$ distance and an increase in the $Y\cdots X$ distance, as well as a relationship between changes in the distance and either Lewis base strength or association energies, for example, of complexes with I_2^-. Bispyridylethane forms in the presence of 1,4-diiodtetrafluorcyclohexane and hydroquinone crystals with the former: Hal-N contributions are stronger than hydrogen bonds.[254] Iodine in particular can develop a partial positive charge in conjunction with electron-withdrawing substituents, such as in the case of iodoperfluorohexane, which can lead to electrostatic attraction to electron pairs on nitrogen atoms. Such $N\cdots I$ interactions have also been observed in liquid crystals, where color shifts have been interpreted as indicative of weak charge-transfer contributions.[255] The quantification of dipolar interaction energies is often based on MO calculations,[256] which confirm the preponderant electrostatic interactions. Since electrostatic effects play a role with free electron pairs, they can be represented explicitly in ab initio calculations, including hydrogen bonds, and then implemented in force fields.[257] The propanone dimer shows a significant preference for an antiparallel arrangement in the gas phase, with $-22\ \mathrm{kJ\,mol^{-1}}$,[248] while other calculations for the $C{=}O\cdots C{=}O$ interaction give significantly smaller values,[258] such as about $-6\ \mathrm{kJ\,mol^{-1}}$.[259] With the aid of the molecular torsion balance shown in Figure S8 in the Supporting Information it proved possible to obtain—albeit approximate—enthalpy values $\Delta G_{\mathrm{CF\cdots NCO}}$ for the interaction between an orthogonal $C{-}F$ bond dipole and an acetamido group.[260]

Many **stacking interactions** between aromatic compounds (Section 8) are also due to electrostatic attraction when the π systems involved present opposing partial charges.[261] This applies also to possible changes in the electron-density distribution caused by substituents, which may under some circumstances be reproduced with appropriate force fields.[262] Such polar effects presumably also contribute to the stability of complexes of anthracene-containing cleft compounds[263] and nucleobases through electron-deficient heterocycles. It was postulated on the basis of a double-mutant cycle (Figure S9 in the Supporting Information) that the influence of the aromatic substituents corresponds at least semiquantitatively to calculated changes in the surface potentials. However, the differences in experimental complexation energies fall within the relatively narrow range of $+1.5$ to $-3.2\ \text{kJ mol}^{-1}$. This finding together with the also conformationally possible direct interaction between the substituents and phenyl nuclei lying opposite leads to uncertainties. The observed trends (Figure S9 in the Supporting Information) nevertheless show the anticipated stronger complexation with decreasing electron density in the substituted aromatic compound.

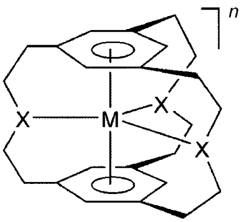
Perfluorinated aromatic compounds result in enhanced stabilization in supramolecular complexes through electrostatic attraction between electron-deficient and electron-rich aromatic compounds, and in some circumstances also through hydrogen bonds with the (aryl)C−F bonds.[264] According to MP2/6–31G** calculations, the interaction between perfluoroarenes and benzene in the gaseous state amounts to about 20–30 kJ mol^{-1},[265] with the forces being mainly electrostatic.[266] In contrast to non- or minimally fluorinated aromatic compounds, which crystallize preferentially in a V-shaped arrangement, the electrostatic interaction between unsubstituted and highly fluorinated aromatic compounds results largely in a face-to-face stacking.[267,268] Intramolecular interactions between variously substituted aromatic rings in face-to-face arrangements have been investigated by employing, for example, triptycene models, where more precise energy values were derived by using a molecular torsion balance.[269] Compounds with highly electron-deficient rings (for example, with pentafluorobenzoate) exhibited consistently higher attractive forces regardless of the nature of the other aryl residue. Values of $\Delta H = -7.7\ \text{kJ mol}^{-1}$ and $T\Delta S = 4 \pm 1.5$ were obtained for $Me_2NC_6H_4$ and C_6F_5CO groups. With respect to perfluorbenzoate (C_6F_5CO), the order of attraction is $MeNC_6H_4 > Me_3C_6H_2 > Me_2C_6H_3 > MeC_6H_4 > MeOC_6H_4 > C_6H_5 > O_2NC_6H_4$, which is in agreement with the donor capacities of the groups. Consistent with electrostatic forces, the complexing power of sulfonatocalixarenes with substituted phenyl derivatives in water is dependent not on the hydrophobicity of the molecule, but is instead a linear function of Hammett substituent constants σ_p (Figure S10 in the Supporting Information).[270] It was concluded from double-mutant analyses with cleft complexes which contained either phenyl (Ph−H) or perfluorophenyl (Ph−F) units that electron-donating substituents X on complementarily arranged phenyl groups promoted stacking interactions. These are repulsive for phenyl (Ph−H; for example, for $X = NMe_2$ $\Delta\Delta G = 1.5\ \text{kJ mol}^{-1}$ in $CDCl_3$) and, as expected, attractive for perfluorophenyl (Ph−F; for example, for $X = NMe_2$ $\Delta\Delta G = -3.2\ \text{kJ mol}^{-1}$). However, an attraction, albeit a weaker one, is observed with a perfluorophenyl unit when $X = NO_2$ ($\Delta\Delta G = -1.0$ or $-0.2\ \text{kJ mol}^{-1}$).[271] Analogous studies with complementary phenyl units that contain alternate electron-withdrawing and electron-donating substituents showed for $X = NO_2$ and $Y = NMe_2$, for example, attractive contributions of $\Delta\Delta G = -4.5\ \text{kJ mol}^{-1}$.[272] One problem with these systems is the possibility that the substituent X not only alters the electron densities of the aromatic compounds, but also interacts with them directly. Moreover, the limitations already noted in Section 3.1 with respect to possible structural changes need to be considered in the application of such mutant cycles.

6. Cation– and Anion–π Interactions

6.1. Cation–π Complexes

The complexation of aromatic partner molecules with cations[273] has mainly been documented for organic host–guest complexes. The aggregation behavior of micelles containing aromatic groups was early on attributed to interactions with the peralkylammonium groups they contained;[274] this was proven for the corresponding naphthyl derivatives by NMR and absorption spectroscopy.[275] Cation–π interactions in particular have been discussed in review articles[273] and also in monographs,[1] so here only a brief overview is given. The partial negative charge of the π cloud of the aromatic compounds, compensated by positively inclined hydrogen atoms, can be depicted as a quadrupole; this leads to a steeper dependence of the attraction on the cation–π distance than would be the case with a simple pole–pole interaction. That the strength of the metal ion–π bond can exceed even that of cation hydration was proven quite early on in the gaseous state with mass spectrometry and ion cyclotron resonance.[276] Thus, ΔG values for $Li^+\cdots C_6H_6$ are 124, for $Li^+\cdots H_2O$ 114,[277] for $^+NMe_4\cdots C_6H_6$ 14, and for $^+NMe_4\cdots H_2O$ 10 kJ mol^{-1}.[278] The binding strength of, for example, benzene for ions decreases in the order $Li > Na > K \gg NMe_4$[273,279] as a consequence of a reduced electrostatic attraction as the charge density decreases. However, calculations on the interaction of Na^+ with benzene, as with ethylene, show an electrostatic share of only about 60 %; the remainder is thus due largely to a dipole in the π system induced by the cation.[273] DFT calculations with calix[4]arenes as host compounds indicate that the conformation is altered significantly by the metal ion, and that the ions are not situated precisely in centroid positions over the phenyl rings in the way a simplified model of a quadrupole interaction would predict. Especially with larger cations, such as K^+ or Ag^+, dispersive interactions contribute significantly, as suggested by ab initio simulations with various π systems as partners.[280] The interaction between phenyl and pyridinium groups varies considerably depending on the orientation of the rings.[281]

Smaller cyclophanes complex metal ions well through the cation–π effect, with a selectivity determined by the geometric fit between the cavity and cation. Spherand **8** binds Ag^+ and Ga^+ ions preferentially,[282] whereas cyclophane **9** has an optimal cavity for Cs^+ ions.[283] The importance of a preorganized cavity for optimal cation–π interactions is evident with cyclophane **10**: only if a basketlike arrangement of the phenyl rings is stabilized with a polyoxyethylene bridge ($n = 1$ or $n = 2$) are K values of $40\ \text{M}^{-1}$ observed with Me_4N^+ picrate, even in the competitive solvent chloroform.[284] In cyclindrophanes with heteroatoms X in the cavity (X = NH, O, or S), interaction with these heteroatoms also contributes



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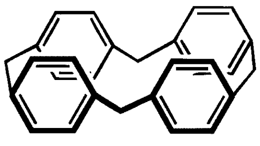

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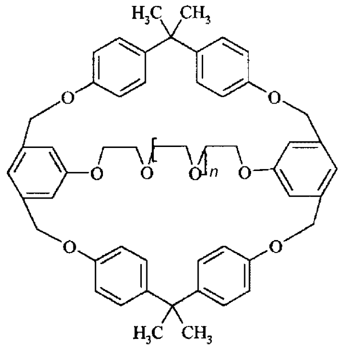

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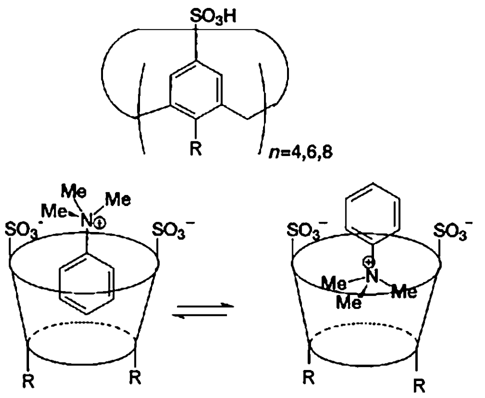
significantly to the complexation of, for example, Ag or Cu ions.[285]

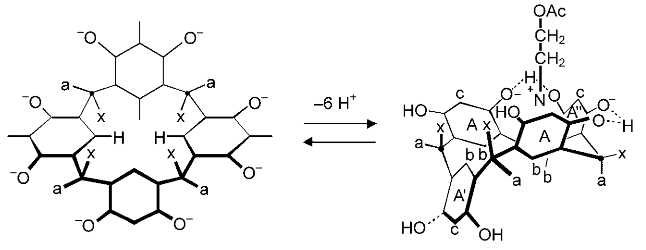
The complexation of larger cyclophanes (Scheme S10 in the Supporting Information), discussed extensively in Ref. [273], is mechanistically very informative. Binding energies for the water-soluble complexes with quinoline and its N-methylated derivative differ by 10 kJ mol^{-1}; this difference is attributable largely to the $^{+}$N···phenyl interaction, since in chloroform (with R = COOMe), contrary to expectation, only the positively charged—and thus more hydrophilic—guest molecule binds to any measurable extent. Similar results are obtained with azoniacyclophanes, which in water (with X = $^{+}$NMe$_3$) unexpectedly bind naphthalene more effectively than the saturated and, therefore, more lipophilic derivative (Scheme S10 in the Supporting Information). The number n of possible pairwise $^{+}$N···aryl interactions is for both macrocycles approximately four; therefore, the contribution for a single $^{+}$NMe$_3$–π interaction would be roughly 2 kJ mol^{-1}. This agrees to a first approximation with the value obtained experimentally for simple ion pairs, in which the number m of aromatic compounds was varied systematically. If the association energies of the corresponding ion pairs are plotted against the number m, the correlation shown in Scheme S11 in the Supporting Information is obtained after subtraction of 5 kJ mol^{-1} per salt bridge in each case (Section 4). The association constants increase from about $K = 100\,\text{M}^{-1}$ for $m = 0$ through $K = 180\,\text{M}^{-1}$ for $m = 2$ to $K = 700\,\text{M}^{-1}$ for $m = 4$. Individual complexes fall outside the linear correlation because of differences in their conformations, as shown by force-field simulations. The energy contributions in excess of those from salt bridges can be attributed not to hydrophobic factors, but instead to a large degree to cation–π contributions: hydrophobic contributions should be larger with saturated partner molecules (Scheme S11 in the Supporting Information), rather than smaller, as is observed. Moreover, the association constants tend to increase in the presence of organic solvents rather than decrease. The correlation leads to a mean value of $\Delta\Delta G = 1.5$ kJ mol^{-1} for a phenyl–$^{+}$NMe$_3$ interaction,[124] a value consistent with the macrocyclic systems described above. The solvent plays an at first unexpected role in cation–π interactions: in water, an only slightly polarizable medium, complexes with cationic substrates are especially stable, even though they are more hydrophilic and must be at least partially desolvated. In organic media such as chloroform, however, electronically neutral aromatic host compounds can also be used.[286]

Calixarenes and similar resorcinarenes in the cone conformation present multiple phenyl groups in a concave arrangement, which predestines them for interaction with cations.[287] Thus, such host compounds bind ammonium derivatives in water; however, salt bridges with anionic groups can render a contribution to the host molecule that is not easy to distinguish. This applies also to other host compounds that were made water soluble with anionic substituents and able to bind acetylcholine and similar cationic substrates very effectively.[288] Calixarenes with four sulfonic acid groups complex ammonium derivatives such as acetylcholine with K values that can exceed $10^5\,\text{M}^{-1}$, with salt bridges making significant contributions.[289] Scheme 10 illustrates how the pH value controls the mode of complexation with a calixarene.[287] Apparently, the presence of phenolate instead of phenol groups increases the polarizability and electronegativity of the electron cloud, so that interaction of the $^{+}$NMe$_3$ group with the surrounding aromatic rings increases. The association constants of calix[4]arene derivatives with anilinium guest molecules are around $K = 5600\,\text{M}^{-1}$. The value of ΔH amounts here to -6.2 kJ mol^{-1}; the considerable entropy contribution of $T\Delta S = -3.6$ kJ mol^{-1} indicates a salt bridge as a significant element in the binding.



Scheme 10. Calixarene–anilinium complexes: at pH 0.4 (R = OH), inclusion of the phenyl ring dominates for $n = 4$; at pH 7.3 (R = O$^-$) the complex with a cation–π interaction is also visible in the NMR spectrum.[287]

In the case of resorcinarene **11**, the transformation from an open conformation **A**, mandated by repulsion of the phenolate groups, to a half-closed conformation **B** is achieved by lowering the pH value.[290] Form **B** puts three phenyl rings in a favorable position for interaction with, for example, the $^{+}$NMe$_3$ group of acetylcholine. Although the negative charge

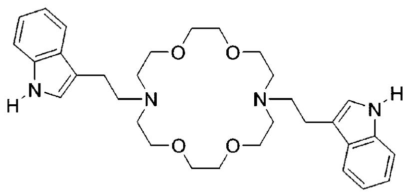


11A **11B**

in **B** is considerably less than in the fully deprotonated ring, the acetylcholine cation binds only with dianion **B** rather than octaanion **A**. The cation–π interaction can also be utilized here for shifting conformations through addition or removal of a guest molecule instead of pH change.

Binding constants with aromatic host compounds are determined not only by the cation, but also by the complementary anion. Thus, association constants K of a calixarene crown ether with tetramethylammonium salts in chloroform show a dramatic dependence on the anion: $K = 30\,\mathrm{M}^{-1}$ is observed tosylate, $100\,\mathrm{M}^{-1}$ for chloride, $390\,\mathrm{M}^{-1}$ for trifluoroacetate, and $2200\,\mathrm{M}^{-1}$ for picrate.[291] The at least partially essential separation of ion pairs requires considerable energy, particularly in aprotic solvents. Calculations on model complexes with benzene and tetramethylammonium formate show that the charge distribution in larger cations is also strongly influenced by the anion.[292] Another factor influencing anion binding is the size of the cavity, which is often too small to simultaneously accommodate a larger anion. The high affinity of picrate relative to tosylate shows, however, that interaction of the anion with aromatic rings of the calixarene *outside* the cavity plays a decisive role. More recent studies on complexes of this sort document that, besides cation–π interactions, interactions with the polyoxyethylene units also make a contribution, albeit a small one.[293] A simple quantification of the anion effect could possibly be obtained by changing the lipophilicities of the salts. Figure S11 in the Supporting Information illustrates that—with the exception of sulfonates—host–guest affinities do indeed decrease in an approximately linear way as the solubility of the salts in chloroform increases.[294] Experiments with dialkyltrichlorostannates as larger anions show that the charge distribution of the anion plays a key role. This can be computed by using DFT methods as electrostatic potentials (EP) at the ion pair surface that is in contact with the π surface of the receptor. The various complexation constants for $^{+}NMe_4$ salts were described well in this way, although again with the exception of sulfonates (Figure S11 in the Supporting Information).[294] As demonstrated by van't Hoff analyses, binding in these complexes is driven exclusively by enthalpy, with opposing $T\Delta S$ effects. This illustrates again the electrostatic character of the cation–π interactions in aprotic solvents.

Systematic analyses of crystal structures show that a favorable orientation for cation–π interactions appears frequently in proteins, for example with arginine side chains over the indole ring of tryptophan.[295] Similar interactions are found, for example, in the Na^+–phenylalanine complex in the gas phase.[296] A receptor with association constants for histidine as high as $K = 10^4\,\mathrm{M}^{-1}$ in methanol has been synthesized by taking advantage, among other things, of imidazolium–phenyl interactions.[297] NMR spectroscopic analyses show the significance of cation–π interactions in the folding of peptides.[298] Model studies with lariat ethers of the type **12** have demonstrated the possibility of a role for cation–π interactions in transport through membrane channels:[299] Both in the crystalline state and in methanol solution, the indole side rings move from an open conformation to one that is closed only in the presence of K^+ ions. In this arrangement the cation is enclosed by both the crown ether and the indole unit.



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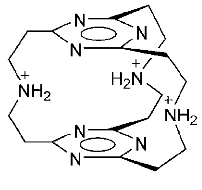

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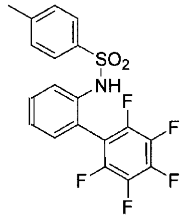

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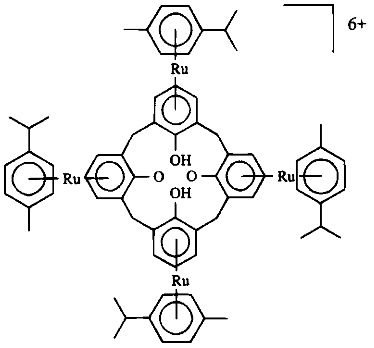
6.2. Anion–π Interactions

Apart from the case of CH···anion hydrogen bonds (Section 7), attractive electrostatic forces between anions and π systems should by nature develop only with electron-deficient arenes. Such complexes have only recently been extensively studied, and review articles have recently been published.[300] A quadrupole with an electrostatic attraction for anions can be present in heterocycles, or it can be achieved with substituents. Ab initio calculations show that trifluorotriazine, 1,3,5-trinitrobenzene, and 1,3,5-trifluorobenzene, for example, have a largely electrostatic attraction for chloride anions, whereas a polarization of the π system induced by the anion makes a significant contribution in s-triazine.[301,302] The interactions are depicted rather well by calculating electrostatic potential surfaces.[303] Ab initio calculations on perfluoro derivatives of numerous aromatic compounds indicate, as well as electrostatic effects, contributions also attributable to polarization and dispersion effects,[304] a result consistent with analyses for a series of other π systems.[305] More recent calculations on associations based on fluorinated aromatic compounds and anions support hydrogen bonds involving (aryl)C–H bonds.[306] Simulations of benzene–formate associations as models for analogous amino acid interactions, along with crystal structures, show a preference for the formation of hydrogen bonds between C–H bonds and the anion for aromatic compounds that are not electron deficient.[307] According to ab initio calculations, cylindrophanes such as **13**, in which two electron-deficient heteroarenes are bound by aminoalkyl bridges, should bind fluoride anions especially effectively through formation of an ion pair with the protonated nitrogen unit and also through an anion–π interaction, with a definite preference for chloride.[308]

In comparison to the almost redundant theoretical studies regarding anion–π associates, there have so far been only relatively few experimental reports on such complexes. Investigations with aromatic ion pairs[124] (see Figure S2 in the Supporting Information), as well as with diphenylmethane and diphenylethane derivatives bearing alternate positive and negative charges,[309] have given evidence for the first time of anion–π attraction, and provided a ΔG value of about 1.5 $\mathrm{kJ\,mol^{-1}}$ per interaction in water. Weak complexes ($K =$ 1 to 10 $\mathrm{M^{-1}}$) of a series of electron-deficient molecules with bromide anions were analyzed—as $\mathrm{Prop_4NBr}$ salts—in acetonitrile; charge-transfer bands were observed, whose maxima correlated linearly with the reduction potentials of the π acceptors (Figure S12 in the Supporting Information).[310] The flexible host compound **14** complexes halide anions in chloroform, as predicted from electron-density calculations and supported by crystal-structure analysis, with $K = 20–30\,\mathrm{M^{-1}}$. In the absence of fluorine substituents, there was no detectable anion binding, as expected.[311]

Sufficient electron deficit can be produced in the π system if the aromatic ring is flanked by a cation on the side opposite to the anionic complexation, as shown by MO calculations[312] and by metal complexes such as **15**. According to X-ray structure analyses, halide anions are present in the center of the cavity of such a calixarene. Association constants of $K = 550\,\mathrm{M^{-1}}$ for $\mathrm{Cl^-}$, $K = 130\,\mathrm{M^{-1}}$ for $\mathrm{Br^-}$, and $K = 50\,\mathrm{M^{-1}}$ for $\mathrm{I^-}$ with **15** in water have been found, which reflect the decreasing charge densities of the anions. For steric reasons, anions such as $\mathrm{OAc^-}$ show no detectable association.[313] The sixfold metalated cryptand **16** (Cp* = cyclopentadiene) complexes triflate ($\mathrm{CF_3SO_3^-}$) in $\mathrm{CD_3NO_2}$ with $K = 3\times10^4\,\mathrm{M^{-1}}$, but with only $K = 10\,\mathrm{M^{-1}}$ in $\mathrm{CD_2Cl_2}$.[314] This difference has been interpreted as being due to the reduced solvating power of the less-polar medium $\mathrm{CD_2Cl_2}$, but it might also be related to steric limitations for entry of the solvent into the cavity (Section 10).



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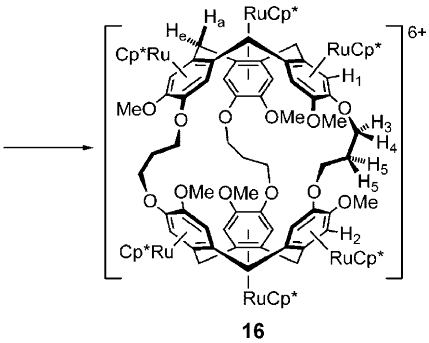

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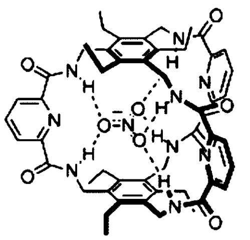
7. Hydrogen Bonds

7.1. Fundamentals

The interaction between on the one hand donor and acceptor atoms D and A bearing partial negative charges and on the other of a proton located between A and D has been treated in numerous monographs[171,315] and review articles,[316] also in regard to supramolecular complexes,[317], including metal compounds,[318] and in the context of drug design.[319] For this reason, only principles important for organic host–guest complexes will be considered here, with so-called weak hydrogen bonds at the forefront. Stronger hydrogen bonds possess increasing covalent character, and show a tendency toward more cooperative effects through mutual polarization of the groups.[320] In weaker complexes, the electrostatic aspect dominates, including in many situations involving ionic partners.[321] This explains the relatively high degree of tolerance in the relationship between the bond strength and geometry of the D···H···A arrangement. Optimal attraction would theoretically be expected for a linear D···H···A bridge, and indeed, of all the noncovalent interactions, hydrogen bonding is the one with the most pronounced directionality. Analyses based on the Cambridge Structure Databank show that with heteroatoms as acceptors there is a preference for the hydrogen bond to point toward the lone pairs of electrons, albeit with a dependence on the environment.[168] Computation allows explicit partial charges to be assigned to the lone electron pairs.[257] Hydrogen bonds involving hydroxy compounds show critical dependence not only on the distance, but also on the orientation of the electron pairs on the oxygen atoms.[322] Molecular mechanics force fields often show deficits in the simulation of hydrogen bonds, particularly with respect to orientation effects.[323] Numerous papers also document the existence of attractive interactions with aromatic compounds—as if they were weak bases (Section 7.6). MP2 calculations indicate relatively strong, barrier-free OH–π as well as ArH–π hydrogen bonds in the gas phase.[324] The frequency shifts that appear in IR spectra with weak R–H bridges can be correlated with changes in the R–H bond lengths.[325]

The directionality of hydrogen bonds makes them among the most important instruments for selective molecular recognition. Classic examples include synthetic receptors such as **17** for the selective complexation of nitrate.[326] In



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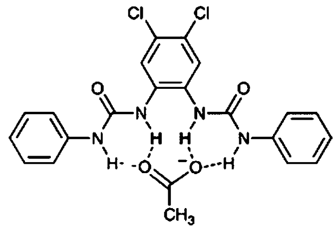

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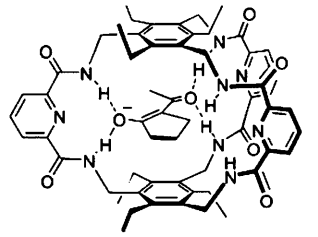

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DMSO, carboxylates are bound in **18** with $K > 10^3\,\text{M}^{-1}$, but sulfates or halides with only $K < 50\,\text{M}^{-1}$.[327] Hydrogen bonds can lead to complexation of enolates, as in **19**, so strong that the acidities of the corresponding 1,3-dicarbonyl compounds drop by up to three p*K* units.[328]

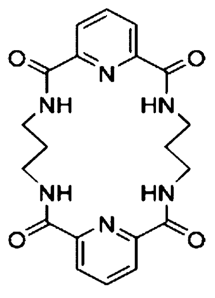
Amides or groups similar to amides can be built into a host–guest complex in large numbers to generate strong complexes, despite the individual interactions being weak. The prime example of achieving even femtomolar stability through chelation is the complex formed between biotin and streptavidin, often exploited in biotechnological applications. At least five bridges involving the biotin–urea unit participate, and according to recent calculations[329] there is also a positive cooperativity. This latter effect comes largely through induced polarization of the biotin–urea unit, a finding confirmed by analyses of streptavidin double mutants.[330]

Particularly strong bridges have been described as low barrier hydrogen bonds (LBHB) and correspond to about 130 kJ mol^{-1} in the gas phase; here the p*K* values for D and A are numerically equally large. Barriers to proton transfer can disappear because of the resulting symmetrical potentials. One consequence of this is an especially short D···A distance: instead of O-(H)-O ≈ 2.8 Å, for example, one finds ≈ 2.3 Å and there is a simultaneous characteristic downfield NMR shift of more than 16 ppm for the bridging H atom.[315] A further indication is the low deshielding in the NMR spectrum for an LBHB deuterium ion compared to the H$^+$ ion, which is more likely to tunnel because of its lower mass. The existence of the LBHB effect has not been proven unequivocally, but has been shown to be applicable to certain enzymes.[331] Neutron and electron diffraction experiments in combination with ab initio calculations on benzoylacetone as a model suggest an LBHB which, similar to other strong hydrogen bonds, is stabilized by covalent contributions.[332]

Weak hydrogen bonds have energies of 5 to 20 kJ mol^{-1}, and can be characterized by DFT methods as electrostatic hard–hard interactions, whereas in the sense of the HSAB principle, stronger ones (15–150 kJ mol^{-1}) constitute soft–soft combinations.[333] The strength of an individual bridge can be correlated with the basicity of the acceptor and the acidity of the donor, although dispersive effects also play a role, especially in the presence of alkyl substituents.[334] Mean-value increments that describe the strength of numerous D and A groups have been obtained from equilibrium experiments with thousands of associations[122] (Section 3.1). The equilibrium constants are obtained multiplicatively as $\lg K_{\text{calcd}} = f_1\,\alpha\beta + f_2$, where f_1 and f_2 are constants that are dependant upon the reference solvent employed ($CHCl_3$ or CCl_4). Table S2 in the Supporting Information provides the corresponding donor and acceptor strengths for frequently encountered structural elements. As noted in Section 3.1, these can serve in the planning of synthetic receptors based on hydrogen bonds, but also, for example, of ionophores and other complexes based on electrostatic effects (see Figure S5 in the Supporting Information).

7.2. Hydrogen Bonds for Complexing Anions with Amides and Derivatives

Numerous host compounds for the selective complexation of anions are based on the formation of hydrogen bonds with the NH donor groups of amides[335] or their derivatives, for example with urea groups.[336] Thioamides provide even stronger interactions, as do thioureas,[337] where MO calculations indicate that such groups should represent good donors but poor acceptors for hydrogen bonds.[338] The precise-fit embedding of functions of this sort into cyclic systems leads to receptors that selectively complex anions even in competitive solvents. In addition to macrocyclic lactams[339] such as **20**, cyclic peptides have proven especially effective; for example, **21** binds sulfate 20 times more strongly than it does chloride, even in aqueous medium (D_2O/MeOD = 80:20).[340] Electron-withdrawing substituents considerably strengthen hydrogen bonds in aryl urea derivatives, for example; this finding is consistent with the corresponding substituent constants and with computed electron densities.[341] Typical complexation energies and their additivity will be illustrated next on the basis of simple systems.



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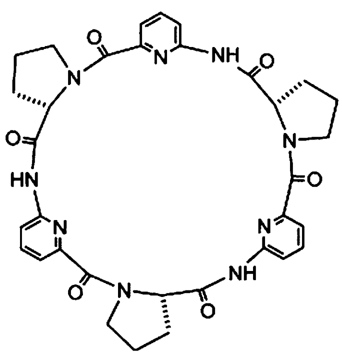
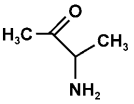
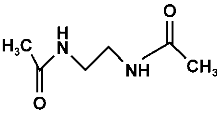
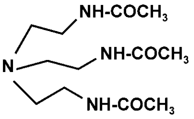
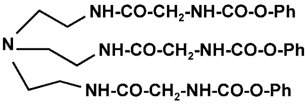
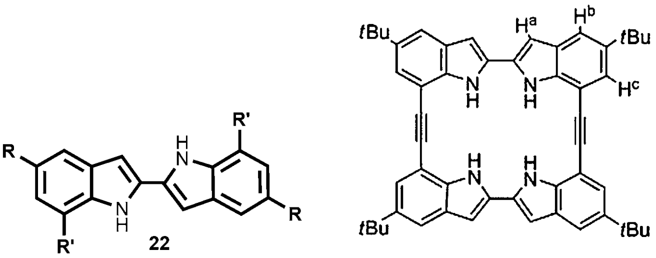


21

The host compounds shown in Table 3 for complexing halide anions in an aprotic solvent have different structures and conformations;[342] nevertheless, they demonstrate that association energies are to a large extent dependent only on the number *n* of possible RCONH···anion interactions. Mean values for a single interaction turn out for RCONH···chloride to be $\Delta\Delta G = (5 \pm 1.5)$ kJ mol^{-1} and for RCONH···bromide to be $\Delta\Delta G = (3.5 \pm 1.5)$ kJ mol^{-1}. The weaker complexation of halide anions in the order F > Cl > Br > I is a consequence of decreasing charge density, and is evident in the corresponding gas-phase affinities.[343] These are found, for example, to be 80 for the association of F^- with methanol, 42 for Cl^-, 36 for Br^-, and 19 for I^- (ΔG values in kJ mol^{-1}). The difference $\Delta\Delta G$ in the binding energies for the guest molecules increases as the number *n* of interactions increases.[4e] Thus, for example, the selectivity as a ratio of the association constants K_{Cl}/K_{Br} for the examples cited in Table 3 increases from 1.25:1 for acetamide to 9.8:1 with a hexaamide. The examples reveal that relatively high selectivity can be achieved with a sufficient number of interactions based on hydrogen bonds, even with simply constructed, acyclic receptors.[344] Improved preorientation of the acceptor functions, as achieved with urea groups in a steroid framework,[345] often provides little gain in selectivity; thus, by this strategy a maximal K_{Cl}/K_{Br} ratio of 9:1 was also found. Considerably higher affinities and selectivities are attainable by positioning as many donor functions as possible in a single precisely fitting cavity, as shown with macrocyclic indole derivatives (Scheme 11).[346] It is true that pyrrole and indole derivatives have lower NH acidity[347] than, for example, urea, but they can still be effectively employed for anion complexation.[348] The complexation of calix[5]pyrrole with alkylammonium chlorides in DMSO is relatively weak, with $\Delta G = 17$ kJ mol^{-1}, and driven mainly by entropy, since $T\Delta S = +9.5$ kJ mol^{-1}; by contrast, astonishingly similar values of $\Delta G = 25$–29 kJ mol^{-1} are found in MeCN, $MeNO_2$, and CH_2Cl_2. Furthermore, the equilibria are driven by enthalpy and there is a dependence on the cation chosen.[349]

Table 3: Complexation of halide anions in chloroform with open-chain host compounds.

	n	ΔG (Cl) [kJ mol^{-1}]	ΔG (Br) [kJ mol^{-1}]
	1	5.7	4.6
	2	11.6	7.2
	3	14.2	12.0
	6	18.2	12.6



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$K = 9\times10^2$ M^{-1}
$K_{Cl}/K_{Br} = 6$

23

$K = 2\times10^6$ M^{-1} in MeCN
$K_{Cl}/K_{Br} = 780$ in MeCN

Scheme 11. Increase in effectivity through macrocyclic arrangement of donor functions for anion binding.[345]

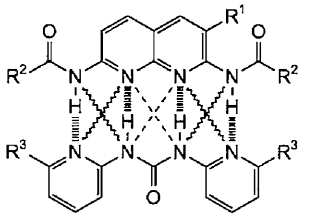
7.3. Interactions in the Presence of Multiple D/A Functions

With many hydrogen bonds, entities arise in which D/A functions are located close to one another, and bridges can be strengthened or weakened. This is especially the case when the D and A functions are located on the same side, that is, less with normally *transoid* amides than with lactams, and above all with nucleobases and their analogues. This was discovered quite early on with Watson–Crick base pairs: an association energy of 8.5 kJ mol^{-1} is observed for the A-T combination by using appropriate model compounds, but for the G-C pair the association energy is 24.5 kJ mol^{-1}, even though the difference resides only in either two (for A-T) or three (for G-C) bonds (Scheme S12 in the Supporting Information). The reason for the particularly low stability of AT lies in repulsion between two A or two D groups situated diagonally opposite each other.[350] This repulsion occurs only once with the G-C pair, and the adjacent DD or AA dipoles lead simultaneously in this case to increased attraction. Based on NMR analysis of deuterium isotope effects, however, the N1···N3 hydrogen bonds in the A:U base pairs of RNA are stronger than the corresponding A:T pairings in DNA,[351] contrary to results from ab initio calculations.[352]

The total energy of such combinations can be expressed as a function of the number *m*, *n*, or *o* of individual interactions [Eq. (4)]:[129e]

$$\Delta G = m\,\Delta G_p + n\,\Delta G_{AA} - o\,\Delta G_{AD} \qquad (4)$$

The analysis of 58 combinations similar to nucleobases in chloroform showed that the total energy can be precisely represented within ± 1.8 kJ mol^{-1} by a value of $\Delta G_p = 7.9$ kJ mol^{-1} for the attractive primary interaction between oppositely situated NHC=O and C=ONH groups, and an astonishingly consistent value of 2.9 kJ mol^{-1} for all secondary ΔG_{AA}, ΔG_{DD}, and ΔG_{AD} values. Here, the AA and DD combinations are treated as positive, and the AD or DA combinations as negative. The fact that no statistically significant numerical differences exist between the attractive quantities ΔG_{AA} or ΔG_{DD} on the one hand and the repulsive quantities ΔG_{AD} or ΔG_{AD} on the other is consistent with Coulomb forces being the source of the secondary interactions, which should be numerically equal in the two cases by virtue of identical partial charges and geometric positioning. Deviations from the increments are to be anticipated if the acidity or basicity of the groups involved changes considerably. This was observed, for example, with various DDA-D·AADA heterodimers.[353] Generally speaking, additivity appears to be better preserved with stronger associations. These also are recognizable through stronger complex-induced NMR (CIS) shifts in the NMR spectra for the NH protons involved (Scheme 12).[354] The presence of multiple bridges can also lead to increased rigidity and hindrance of optimal contacts.[355]



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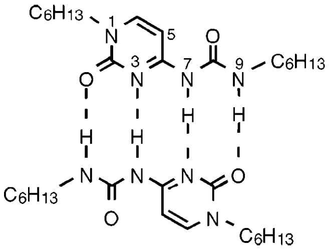
Scheme 12. Example of a DAAD-ADDA complex **24** ($R^3 = H$; $R^1 = CN$): a) without any steric hindrance ($R^2 = n$-butyl) and b) with steric hindrance ($R^2 = tert$-butyl). The association energies ΔG are at (a): 18.6 and (b) 9.4 kJ mol^{-1} (calculated: 17.9 kJ mol^{-1}). The complex-induced shifts (CIS) in the NMR spectra of the NH protons are in (a) 3.7–4.4 ppm and (b) 0.8–1.5 ppm.[353]

Homogeneous combinations such as AA–DD are evidently favored energetically. These can be realized synthetically (examples: **25**–**28**),[356] and used to develop new types of polymers.[357] Nucleic acids themselves represent building blocks for the construction of higher molecular weight associates through numerous D–A combinations,[358] as well as for the development of new materials through self-association.[359] The production of nanoscale materials from DNA double strands and the corresponding quadruplexes also rests on such complementary hydrogen bonds.[360] Such D–A arrays are particularly well-suited to the noncovalent binding of fullerenes to electron-donor units in redox- or photoactivatable systems.[361]

Derivatives of cytosine[362] or guanidine[363] such as **25** and **26** are to some extent free of unfavorable tautomeric forms, and dimerize in chloroform with $K > 10^7\,\text{M}^{-1}$. The problem of an undesirable self-association of one component can be overcome with the DAAD combination of 1,8-naphthyridines and guanosine.[364] An especially high affinity with $K = 10^9\,\text{M}^{-1}$ is achieved with the DADDAD-ADAADA combination **27**.[365] With concavely formed receptors, such as **28**,[366] it becomes possible to reach high affinities with a relatively small guest molecule.

Alternating DA-AD combinations stabilize parallel β-strand conformations of peptide models such as **29** (R: amino acid side chain).[367] NMR spectroscopy has verified the structure of both a foldamer[368] with intramolecular bridges around a -$(CH_2)_3$- "handle", as well as the resulting dimer with intermolecular bonds. The dimerization constant in chloroform has been estimated to be $K > 10^6\,\text{M}^{-1}$. Such interactions are also typical for peptides, which play a role in Alzheimer and prion syndromes. Comparable foldamers have been characterized for numerous antiparallel as well as parallel so-called hairpins.[369]



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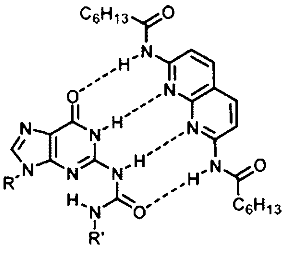
AADD–DDAA with $K > 10^7$ M^{-1}



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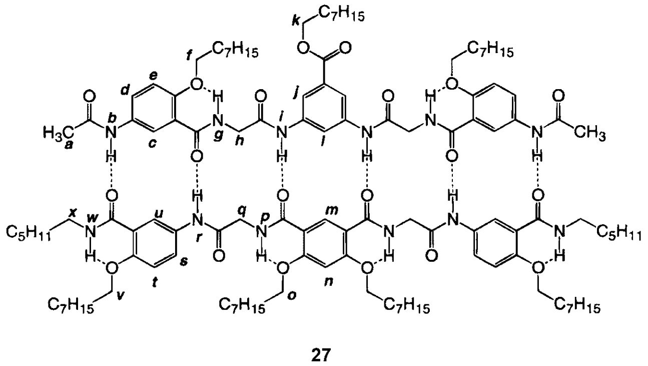
DAAD–ADDA with $K = 5\text{x}10^7$ M^{-1}



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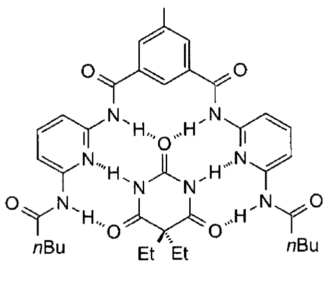
DADDAD–ADAADA with $K = 10^9$ M^{-1}



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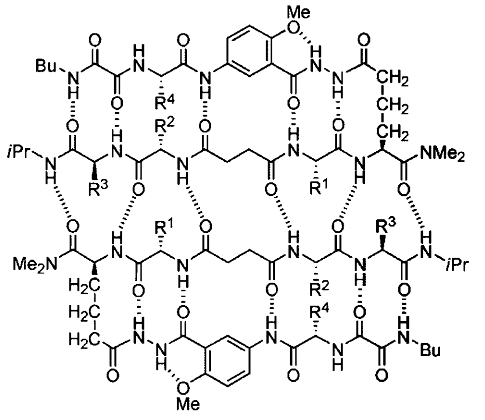

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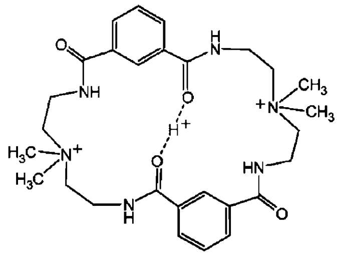

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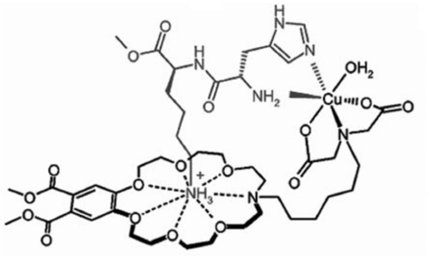
Multiple hydrogen bonds can be used in the construction of macrocyclic capsules,[370] as in the case of a porphyrin derivative[371] (Scheme S13 in the Supporting Information; see also Section 10). An example of the binding of a cation through an amide group is provided by the macrocycle **30**. This complexes a proton in its center—despite two permanent positive charges in the host—through double hydrogen bonds with the carbonamide group.[372] Relative to normal O-(H)-O distances (ca. 2.8 Å), a shortening to 2.45 Å and a simultaneous lengthening of the amide C=O separation from its normal 1.24 Å to 1.27 Å has been found crystallographically. This can be regarded as an indication of an LBHB bridge.

7.4. Crown Ether Amine Complexes; Solvent Effects

Oxygen atoms in crown ethers and related ligands also serve as hydrogen-bond acceptors. With [18]crown-6, for example, each oxygen atom can be involved in either one or two such bridges. Recent IR analyses in conjunction with HF/MP2 calculations show linear single bridges for the complex with H_3O^+,[373] but the presence of a new type of LBHB bridge has also been suggested.[374] Consistent with an electrostatic binding mechanism, the binding strength of *p*-substituted anilino crown ethers with bis(4-fluorobenzyl)ammonium ions correlates with Hammett σ substituent constants.[375] Calculations on various basis sets with inclusion of electron correlation (MP2) also show contributions from induced charge displacements.[376]

Among the most important applications of hydrogen bonds in crown ethers are stereoselective complexations, especially enantioselective ones,[377] as well as systems that are switchable, either photochemically or with pH changes.[378] The binding of protonated amines to crown ethers is commonly employed for selective complex formation in, for example, the formation of rotaxanes,[379] or also in combination with, for example, metal centers,[380] as in **31**.[381] Receptor **32** also takes advantage of the formation of hydrogen bonds between crown ethers and the N termini of peptides. Supplemental stacking with the phenyl group of the tripeptide Gly-Gly-Phe results in a binding strength of $\lg K = 4.4$ in water.[382]



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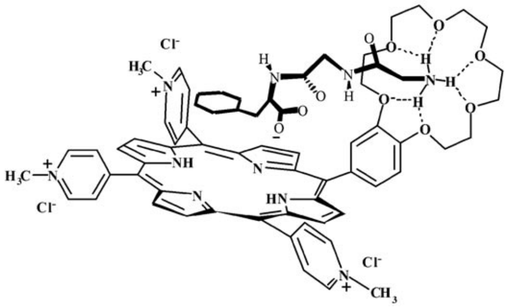

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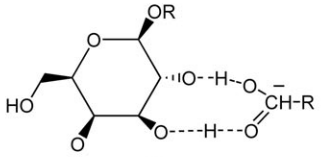
Hydrogen bonds are especially sensitive to media that can function as both a donor and an acceptor. Hydrogen bonds are, therefore, detectable in water only with relatively strong complexes or when there is the simultaneous action of other mechanisms, such as a metal interaction (see **31**). Exothermic reactions are found for complexes of dicarboxylates with urea derivatives in DMSO, with $T\Delta S$ values near zero. In aqueous solution, on the other hand, bisguanidinium receptors and dicarboxylates tend instead to show endothermic associations as the methanol content increases; the entropic advantages have been explained by increasing release of solvent molecules at the binding center.[383]

The factors[122] α and β, cited above, can serve as **solvent parameters**, and provide donor and acceptor strengths for competitive solvents.[384] Ab initio/DFT calculations suggest, however, that binding strengths seldom correlate with the pK values of proton donors.[385] Figure S13 in the Supporting Information shows, on the other hand, that the $\lg K$ values of crown ether complexes with ammonium ions are a relatively linear function of the basicity parameter β of the solvent.[386] These crown ether associations are dominated by enthalpy contributions, with $T\Delta S$ penalties only half as large.[385] By using newly derived α and β factors, a linear correlation was found for an associate consisting of perfluoro-*tert*-butanol and tri-*n*-butylphosphine oxide as shown in Figure S14 in the Supporting Information when the α_s and β_s values for the corresponding medium were subtracted from the α and β values of the substrates employed.[387] The low scatter is a consequence of the special α_s and β_s values used here, which were obtained with the same substrates as for the correlation itself.

7.5. Weak Donors and Acceptors; Complexation of Carbohydrates

Weak D or A groups can form useful complexes through combination with complementary stronger groups. Benzene, for example, associates with water in the gas phase with a stability of about 10 kJ mol^{-1},[388] in agreement with ab initio calculations for OH–π and NH_3–π complexes. Significant dispersive contributions were also found here.[389] The formation of hydrogen bonds between CONH groups and aromatic groups in chloroform led to a cyclophane showing association constants with diamides that were increased by a factor of 10^4 relative to guest molecules lacking the acidic NH group.[390] The interaction between the guest NH protons and the host phenyl ring in this case is also apparent from crystallography. It should be noted, however, that the increased basicity of the carbonyl group in an amide also plays a role (Scheme S14 in the Supporting Information).

The hydroxy groups of **carbohydrates** can be made to complex in a simple way only in noncompetitive media.[391] The *O*-alkyl glycosides used for this purpose can be bound selectively, for example, through the phenolic groups of resorcinarenes in solvents such as chloroform.[392] In water, for example, glucose binds to a resorcinarene if the phenolic group of the latter is deprotonated, thus making it a better acceptor. In addition, C–H bridges then also become effective with the more strongly negatively charged π system.[393] The notoriously weak hydroxy group donors can generally be induced to react more efficiently with anionic acceptors. With a cholaphane, for example, fluoride anions can be complexed selectively in chloroform through OH···F hydrogen bonds.[394] Vicinal OH groups of sugar molecules bind preferentially with bi- or polydentate anions such as carboxylate and phosphate,[395] but only in aprotic solvents. The effectivity increases in accordance with charge density in the order iodide < bromide < chloride < fluoride, culminating with the double bridge that is possible with, for example, benzoate, which binds 1-alkylgalactosides (alkyl-R′ = $C_{12}H_{25}$) in chloroform with $K = 10^3\,\text{M}^{-1}$ (**33**). This relatively high affinity is attributable again, as presented in Section 1.2 (Scheme S4 in the Supporting Information), to the availability of an excess of OH donor groups relative to acceptor groups. The simultaneous effect of two phosphonate groups in **34** allows 1-octylpyranosides to bind in acetonitrile with $K \approx 3 \times 10^4\,\text{M}^{-1}$.[396] The fluorescent probe **35** binds *O*-octylglucoses in chloroform through four hydrogen bonds with $K = 2 \times 10^4\,\text{M}^{-1}$ and galactoses with $K = 6 \times 10^3\,\text{M}^{-1}$, where different Cotton effects are observed.[397]



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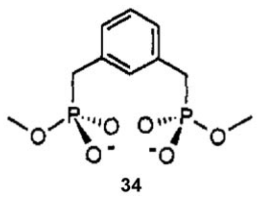

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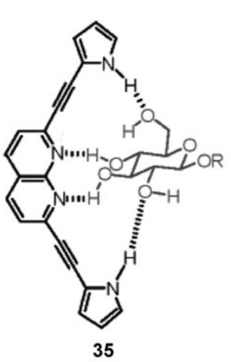

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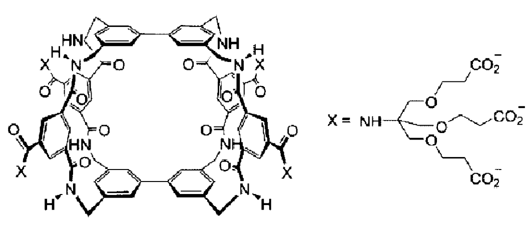
Phenolic groups in a macrocycle are well-suited to accepting *O*-octyl disaccharides, which bind even in the competitive solvent MeCN/MeOH (88:12) with $K = 10^4\,\text{M}^{-1}$ (Scheme S15a in the Supporting Information).[398] The chiral binaphthyl units also allow a differentiation of enantiomers.[399] In metalloporphyrins (Scheme S15b in the Supporting Information), the Lewis acidic zinc center in combination with hydrogen bonds to side groups leads to an affinity of, for example, 21.5 kJ mol^{-1} for the α anomer, and 25.6 kJ mol^{-1} for the β anomer.[400]

Weak interactions with saturated hydroxy compounds pose a special challenge in the development of synthetic receptors for carbohydrates in the natural medium water.[401,402] In protein–carbohydrate complexes, hydrogen bonds in more hydrophobic cavities play a role in addition to that of hydrophobic interactions.[403] Model calculations and also IR analyses show not only OH–aryl hydrogen bonds but also largely dispersive CH–aryl interactions as significant factors for binding of carbohydrates by proteins.[404] Higher affinities can be achieved with synthetic receptors in competitive solvents if supplementary ion-pair binding is present, as for example with saccharic acids[219] or aminoglycosides.[405] From calorimetric measurements at least, α-cyclodextrin complexes with monosaccharides in water with $\Delta G = 7$–12 kJ mol^{-1}, where entropic factors quite remarkably play a nearly exclusive role.[406]

The construction of more complex guest molecules, such as **36**, also permits competition for neutral sugars with water and leads in combination with CH–π interactions and particularly the numerous carboxylate groups to binding constants of $K = 10\,\text{M}^{-1}$ with glucose and $K = 17\,\text{M}^{-1}$ with cellobiose.[402a] Host molecule **37** demonstrates that, with proper choice and topological arrangement of the binding elements, even effective acyclic receptors can be designed for sugars.[407] High constants can be attained in an aprotic medium with glucopyranoside through multiple hydrogen bonds; furthermore, the constants show a difference of a factor of 6 between the anomers. Even an unprotected dissacharide displays significant binding in water, with CH–π interactions with the aromatic parts of the receptors contributing. The association constants fall by an order of magnitude when the receptor lacks carboxy groups, thus underscoring the significance of hydrogen bonds. Lipophilic interactions are largely responsible for the remarkably high association constants of sandwich receptors consisting of two bridged porphyrin units, which range in water from $K \approx 10^3\,\text{M}^{-1}$ for glucose to nearly $10^5\,\text{M}^{-1}$ for maltotriose; here, too, anomers differ markedly.[408] Shifts in the IR absorptions of the receptor amide groups indicate the involvement of hydrogen bonds.



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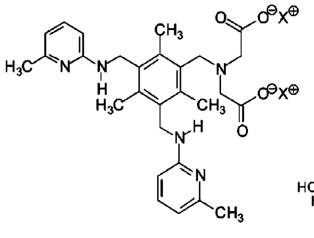

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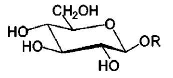
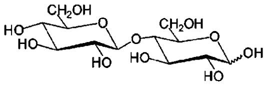


R=C_8H_{17} in $CDCl_3$: K=1.2X10^5 M^{-1}

R=CH_3 in H_2O: K=2 M^{-1}



K=300 M^{-1} (in H_2O)

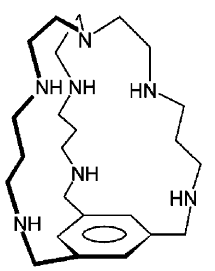
Covalently bonded halogens are especially weak acceptors. On a pK_{HB} scale based on equilibrium measurements in CCl_4, RHal values are found to range from 0.0 (Hal = F) to −0.4 (Hal = I). In contrast, all normal acceptors are characterized by distinctively positive values that range, for example, from over +2.1 for amines to +6.0 for amine oxides.[409] As early as 1962 it was shown through association studies of phenol with cyclohexyl halides in carbon tetrachloride that, in contrast to the so-called Badger–Bauer correlation between IR frequencies and bond enthalpies, free binding energy decreases in the order RF > RCl > RBr > RI, where a value of $\Delta G = 13\,\text{kJ mol}^{-1}$ was obtained for RF.[410] More recent studies of associations of *p*-fluorophenol with, for example, cyclopentyl halides RHal in CCl_4 as solvent yielded ΔG values (in kJ mol^{-1}) for RF of 5.4 (ΔH 10.5), for RCl 3.6 (ΔH 3.6), for RBr 3.7 (ΔH 7.1), and for RI 3.7 (ΔH 5.2), where enthalpy values were established by the van't Hoff method.[411] Similar relative values, always with ΔH–ΔS compensation, have also been observed for other alkyl halides, with ΔG values for fluoroadamantane, for example, reaching as high as 7.5 kJ mol^{-1}.

The applicability of RF groups as possible receptors has attracted special attention, as a consequence, among other factors, of their presence in numerous pharmaceuticals[412] and solid materials.[413] There is also interest in the context of the perfect suitability of a fluorotoluene nucleoside as a thymine replacement for completely error-free incorporation into double-stranded DNA.[414,415] Hydrogen bonds have been postulated for, among other things, fluorine-containing active agents,[416] although generally regarded negatively on the basis of MO calculations.[417] Associations seem to exist in the gas phase between H-C-C-F fragments from fluorobenzene and water or methanol.[418] A systematic comparision of cryptand–ammonium ion complexes with CH and with CF groups in the host cavity indicated that CF···HN hydrogen bonds are either absent or very weak.[419] In contrast to the spectroscopically established equilibria alluded to above with fluorophenol, for example, numerous authors have concluded that there are weak or barely detectable bridges when CF is the acceptor,[420] unlike the case of coordination with metal ions.[421] Analysis of 5947 CF fragments in crystal structures led to only 37 structures (that is, 0.6 %) that exhibit small CF···HX (X = O, N) distances.[422] However, a study of fluorine-containing ligands in the Protein Data Bank showed that up to 18 % of them displayed geometries characteristic of hydrogen bonds.[423] In agreement with earlier results,[424] the bridge seems to be stronger with aliphatic than with aromatic fluorine compounds. In numerous crystal structures, H–X distances are found to decrease in the order RI > RBr > RCl > RF, which replicates the increasing strength of the donors involved, where exceptions are observed for OH as the donor.[425] Evidently, hydrogen bonds with covalently bonded fluorine are unambiguously measurable in solution, but too weak relative to many crystal lattice interactions to prevail in the solid state.

7.6. Bridges involving C–H Bonds

C–H bonds are especially weak donors, but they play a previously underrated role in the structure of crystals and, as only recently recognized, also in solution and in biological systems. Various reviews[426] are available on the subject, so here only a few characteristic systems are considered. Structural analyses of nucleic acids and proteins often show distinctly short CH···O contacts.[427] The CH···O bridges typically display H–O distances of 2.1 to 2.5 Å and C–(H) distances of 3.1–3.5 Å. Weak bridges of this sort depend largely on Coulomb forces, so the C-H-O arrangements are mostly linear, and the effect is actually more far-reaching than with stronger bridges.[428]

CH–π bridges with anions as acceptors are, according to MO calculations[429,430] on model complexes, quite significant, and are also visible in crystal structures.[425] Complexation enthalpies of chloride anions in the gas phase range from 15 kJ mol^{-1} for methane to about 80 kJ mol^{-1} for pyrrole, consistent with DFT calculations.[431] DFT calculations also confirm that binding strengths, especially the electrostatic portions, increase with electron-withdrawing substituents on the aromatic rings.[432] Azide CH groups support anion binding in dipyrrolyl-1,3-propanedione–BF_2 complexes.[433] Simultaneously operative N–H and C–H bridges lead to a strong and selective binding of fluoride anions with the macrocyclic azacyclophane **38**. Larger anions tend instead to experience repulsion because of the π-electron cloud of the receptor, and are more weakly complexed.[434] A cavity with four imidazolium and four pyrene units binds the nucleotide GTP through both N–H and C–H bridges.[435] Stabilizing contributions from CH groups have also been established for other anion receptors.[436] The C–H acidity of the pyrazole ring in **39** suffices to bind tetrabutylammonium chloride in



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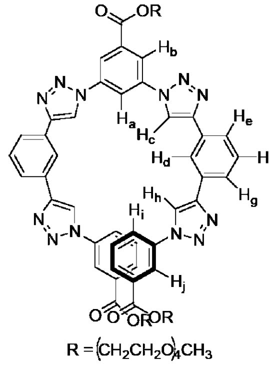

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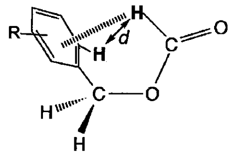
acetone with $K = 1.7 \times 10^4\,\text{M}^{-1}$, and at the same time the C–H protons involved experience a deshielding of about 1.5 ppm in the NMR spectra.[437]

C–H bridges with aromatic compounds[438] as acceptors clearly represent the weakest complexes imaginable, and calculations indicate a significant contribution from dispersive interactions.[439] According to ab initio calculations, alkane C–H bonds interact with aromatic rings exclusively through dispersive mechanisms,[440] which should actually also be significant in the case of the stronger associations with ammonia or water.[441] Even cyclopropane can, similar to an olefin, function as a weakly acidic C–H donor and as a weak π acceptor.[442] Quantum chemical calculations on associates with π systems as acceptors—mostly with benzene dimers (Scheme S16 in the Supporting Information),[443,444] but also, for example, of ethylene with H_2O, NH_3, and HF[445]—show in general significant dispersive contributions, and thus require large basis sets and MP methods for taking into consideration electron correlation. Numerous improvements have been suggested.[446] It has been concluded from ab initio calculations that the interaction of aromatic rings and sp^2 CH bonds displays little of the character of typical hydrogen bonds,[447] a finding that recent calculations and IR analyses appear, however, to contradict.[448] According to 6-31 + G** calculations with the inclusion of electron correlation (with MP2), bridges of OH or NH donors with aromatic amino acids are weak, and decrease in the order Trp > His > Tyr ≈ Phe, although protonated His represents a sufficiently strong donor.[449] Ab initio calculations were used for the refinement of force fields for such CH–π interactions.[450] Simulations of the interaction of formamide and benzene as a model for interactions in proteins, by using various large basis sets and MP2 methods, testify to the fact that here a role is played not only by the NH group of the amides but by the entire RCONHR dipole. Interaction energies of 12–17 $\text{kJ}\,\text{mol}^{-1}$ were calculated for roughly 100 of 500 protein crystal structures with phenyl–amide contacts.[451]

The classic case of benzene dimers (Scheme S16 in the Supporting Information) as an edge-to-face hydrogen bond was found in numerous theoretical and experimental studies to be the preferred geometry, although the energy difference relative to a face-to-face conformation (Section 8) appears to be very small.[446] Substituents and heteroatoms can strongly influence the conformations,[452] and this usually involves mainly direct interactions of the substituents with an aromatic ring lying opposite.[453] The benzene–benzene association is very weak, with $K \approx 1\,\text{M}^{-1}$ in water,[443a] so intramolecular interactions are often necessarily used as models. The electrostatic mechanism of the CH–π interaction is apparent in Hammett correlations, obtained from NOE experiments with substituted phenyl derivatives **40**: here linear relationships were found throughout between NOE enhancements and the substituent constants σ, always with a negative reaction constant ρ.[454] The rotational barriers for 1,8-diarylnaphthalene increase with the number of fluorine substituents on a phenyl ring, since the reduced electron density leads to a more positive charge for the aromatic quadrupole, and thus to more stable face-to-face stacking of aryl residues in the ground state (Section 8).[455,456] The adduct of the CH acidic trifluoromethane with benzene has been characterized by vibration spectroscopy as well as through ab initio calculations.[457]



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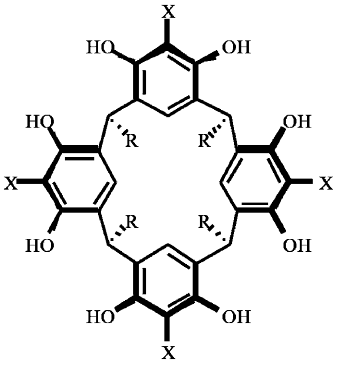

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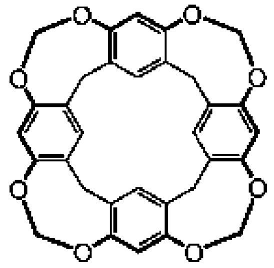

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The weakness of the CH–π interaction makes it difficult to demonstrate it unambiguously with supramolecular complexes in solution. The binding constants K of a calix[4]arene tetrasulfonate **41** ($R = SO_3^-$, $X = H$) with substituted ammonium ions R'_4N^+ increase from $K \approx 1\,\text{M}^{-1}$ for $R' = H$ to $K = 160\,\text{M}^{-1}$ for $R' = \text{Me}$.[458] This is attributable to increasing hydrogen bonding with the $^+$N-C-H protons, which are known to actually bear the charges in alkylammonium ions. Gas-phase MS experiments show that anions are tightly bound through converging C–H hydrogen bonds in electrically neutral cavities such as **42**.[459] Although dispersive components contribute with CH–π interactions, the observed dependence of the rotamer equilibria on substituents on the phenyl ring suggests a hydrogen bond that is largely stabilized electrostatically.[460] In many crystal structures,[461] including in transition-metal complexes[462] and poorly soluble diastereomeric salts,[463] CH–π distances below the sum of the van der Waals radii are often found. The same is true of inclusion compounds of fullerenes.[464] Clathrates typically contain aromatic compounds, often with significant CH–π contacts, and this also applies to numerous rotaxanes and catenanes.[438c]

Measurement of conformer equilibria by using a so-called internal balance (see Section 5.2) in chloroform gave an increment of 1.0 $\mathrm{kJ\,mol^{-1}}$ for the edge-to-face interaction, although also an improbable even higher value for the interaction of a phenyl ring with a *tert*-butyl group.[121a] The strength of an *intramolecular* CH–π interaction was calculated from conformer equilibrium studies with a cyclophane to be 35 $\mathrm{kJ\,mol^{-1}}$.[465] Analyses with double-mutant cycles gave $(1.4\pm0.8)\,\mathrm{kJ\,mol^{-1}}$ for the intermolecular aryl–aryl interaction in chloroform.[466a] More recent analyses based on 7,7-diphenylnorbornanes rather than the more-flexible diphenylcyclohexanes produced sevenfold smaller values ($\Delta G=(-0.2\pm0.6)\,\mathrm{kJ\,mol^{-1}}$) for the edge-to-face interaction, which were attributed to small entropic penalties.[466b] The combination of the weak acceptor benzene and an equally weak CH donor necessarily leads to increments that are difficult to measure. Uncertainties stem from the solvents, which can lead to differing degrees of solvation; furthermore, there are hard to estimate conformational differences between the partners upon which the interactions are based. Reliable values should be accessible from determination of a large number of equilibria or analyses in the gas phase.

Hydrophobic effects (Section 9) contribute significantly to carbohydrate interactions in aqueous media.[467] On the other hand, corresponding crystal-structure analyses show particularly small CH–π separations in some cases.[468] According to MP2/6-31G(d,p) calculations, carbohydrates can enter into significant interactions with aromatic compounds, ones that are to some extent dispersive.[469] Thermodynamic and NMR spectroscopic analyses of saccharide modifications with aromatic groups show that the interaction enthalpy increases as the size of the aromatic group increases, and decreasing with the fluorine substitution in the aryl residue.[470]

8. Dispersive and Stacking Interactions

8.1. Fundamentals

Dispersive interactions, which in the classic London–Eisenschitz interpretation are due to attraction between fluctuating dipoles, result according to MO concepts from electron correlation. Despite their relative weakness among the van der Waals forces, they play a major role in a multitude of supramolecular complexes. Even if often overshadowed by electrostatic effects, it is wrong to designate them, as is occasionally postulated,[4b] as negligible. In complexes involving active receptors, the sum of the lipophilic interactions often plays an even greater role than such polar effects as hydrogen bonds.[471] Van der Waals forces make a significant contribution to the conformation and binding behavior of biopolymers,[470,472] especially in the interior of proteins[473] and with their folding,[125] as well as, for example, in the intercalation of aromatic compounds in nucleic acids.[474] High-affinity ligands for prion proteins and, for example, their tyrosine units consist, among other things, of triazine derivatives with multiple anthracene residues.[475] Protein–nucleic acid interactions are regarded as being determined more by van der Waals contacts than by hydrogen bonds.[476] Dispersive effects are involved also in carbohydrate binding in proteins,[403,477] as well as in the binding of alcohols to proteins.[478]

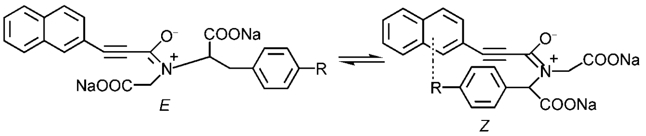
As already noted in Sections 3.4 and 7.7 in the discussion on benzene dimers, calculations involving van der Waals complexes entail the use of large basis sets, and for electron correlation or polarization effects, elaborate MP methods. The Slater–Kirkwood Equation [Eq. (5)] describes dispersive interaction energy in classical terms as a function of the polarizability α and the number N of outer electrons, in each case with reference to the interacting atoms i and j in the separation $\boldsymbol{r}_{ij}$:

$$E=[\alpha_i\,\alpha_j\,\boldsymbol{r}_{ij}^{-6}]/[(\alpha_i N_i)^{1/2}+(\alpha_j N_j)^{1/2}] \tag{5}$$

Thus, dispersive forces apparently increase from top to bottom within a group of elements in the periodic table. However, in Equation (5) the contact surfaces between interacting parts of the molecule are described by seemingly hard van der Waals radii $\boldsymbol{r}$, even though easily polarizable electron clouds can be deformed so as to favor an optimal contact. As a consequence, interaction energies for fluorine and chlorine, for example, erroneously appear equally large when calculated according to the Slater–Kirkwood Equation,[4b] which is in flagrant contradiction of experimental results (Sections 8.3 and 8.7)

Even the structures of cyclophanes as host molecules are determined partially by dispersive interactions.[479] The simulation of cryptophane complexes with CH_2Cl_2, $CHCl_3$, and CCl_4 in the gas phase, as well as in chloroform, using the usual force fields leads only after reparameterization to a correct sequence for the experimentally observed stabilities.[480] Stacking between π systems is considered here as well, although it is almost always determined in part by electrostatic forces. The voluminous literature on benzene dimers has already been mentioned in Section 7.5 in the context of edge-to-face hydrogen bonds, including the influence of substituents. In face-to-face complexes, aryl units are necessarily displaced from each other (Scheme S16 in the Supporting Information), since in this way Coulomb repulsions between the associated π-electron clouds are reduced, and attractive interactions become possible with the positively charged H atoms of the CH groups. For similar reasons, electrostatic interactions between hetero substituents lead generally to a preference for conformation (b2) in Scheme S6 of the Supporting Information.

The usually weak stacking interactions can be quantified relatively well through the position of the E–Z equilibrium in an appropriately substituted amide (Scheme 13).[481] For R = H in water (D_2O), the same advantage is observed for the E conformation, with the same small $\Delta G_{E/Z}$ difference as in $CDCl_3$. When R = phenyl, contact now becomes possible with the naphthyl residue lying opposite, thus causing the Z isomer to be preferred. With R = cyclohexyl, a *smaller* preference for



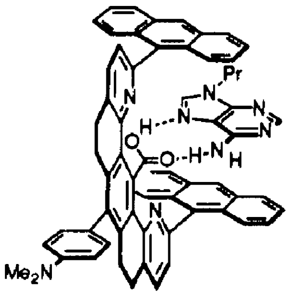
Scheme 13. Intramolecular stacking interactions of naphthyl units with aromatic substituents R.

the Z conformation is actually found in water, which rules out a hydrophobic interaction as the driving force. Dispersive interactions are also apparent, since there is the same preference for the *Z* form with R = pyridyl, pyrimidyl, or quinuclidine. However, the differences of $-\Delta G_{E/Z} = 0.43$ versus $0.79\,\text{kJ}\,\text{mol}^{-1}$ for R = phenyl or R = pyrimidyl are relatively small, and may also be influenced by polar effects. Stacking between aryl units increases with the polarity of the solvent.[482]

8.2. Typical Host–Guest Complexes, Charge Transfer Interactions

As presented in Section 5.2, many stacking complexes are based on Coulomb forces.[483] Such complexes are characteristically a combination of electron-poor and electron-rich units.

Tweezer molecules such as **43** and **44** complex nucleobases through stacking interactions, and also through hydrogen bonds with carboxy groups of the host compound. Complexation energies ΔG of 13 and $12\,\text{kJ}\,\text{mol}^{-1}$ were found for the pyrimidine bases cytidine and uridine in chloroform, whereas the larger purine base adenosine gave a value of $24\,\text{kJ}\,\text{mol}^{-1}$, and guanosine $20\,\text{kJ}\,\text{mol}^{-1}$.[484] The contribution of the hydrogen bond can be determined through comparison with the binding energy, for example, of 9-propyladenine with butyric acid ($\Delta G = 13\,\text{kJ}\,\text{mol}^{-1}$). In the case of the tweezer, a value $\Delta G = 25\,\text{kJ}\,\text{mol}^{-1}$ is observed, which leads to a stacking contribution for the adenine ring of about $12\,\text{kJ}\,\text{mol}^{-1}$. The cleft molecule **44** contains no carboxy groups but nevertheless binds larger electron-deficient aromatic compounds such as trinitrofluorenone ($\Delta G = 12.5\,\text{kJ}\,\text{mol}^{-1}$, in $CDCl_3$); however, with dinitrofluorenone the value sinks to $10\,\text{kJ}\,\text{mol}^{-1}$.[485] This finding makes it clear that the electrostatic attraction between electron-rich and electron-poor aromatic rings does indeed play a role (Section 5.2). Nevertheless, the large contribution of dispersive forces is underscored by the fact that considerable complexation energies are still found with not particularly electron-rich anthracene host compounds, and that they are determined in general by the size of the facing guest aromatic compound. In a similar way, in complexes supported by hydrogen bonds, adenine is bound by anthryl groups with $K = 70\,\text{M}^{-1}$, whereas the presence of a phenyl group leads only to $K = 2\,\text{M}^{-1}$.[486]



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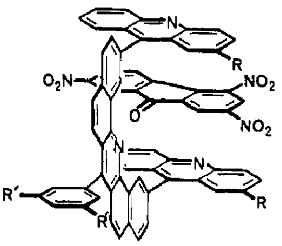
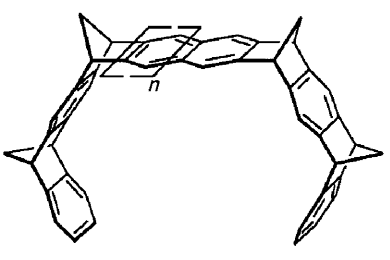
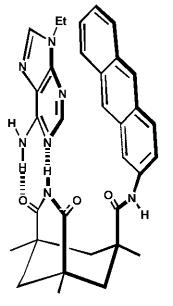


44

As presented in Section 5.2, it is a characteristic feature of cleft molecules such as **45** that the π system facing the guest molecule possesses a significant partial negative charge, through which electrostatic effects are more strongly pronounced. Thus, the following typical association constants are found for *para*-disubstituted benzene derivatives $C_6H_4R_2$: for R = OAc $K = 10\,\text{M}^{-1}$, for R = NO_2 $K = 45\,\text{M}^{-1}$, and for R = CN $K = 110\,\text{M}^{-1}$ (in $CDCl_3$).[487]



45, *n*=1



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It was shown in a classic study that with complexes held together by hydrogen bonds, such as **46**, a stability maximum is reached with anthracene substituents. The complexation energy decreases with naphthyl, phenyl, and methyl substituents by $\Delta\Delta G = (1.85 \pm 0.15)\,\text{kJ}\,\text{mol}^{-1}$ (in chloroform as solvent) for each phenyl unit.[488]

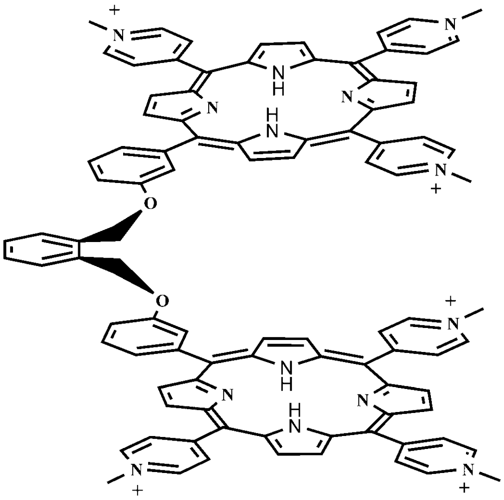
The association of electron-poor and electron-rich compounds is often ascribed to **charge-transfer** (CT) interactions.[489] Such CT complexes are characterized by transfer from the HOMO of an electron-rich component into the LUMO of an electron-deficient molecule, and by the corresponding UV/Vis bands. Typical CT complexes are usually so weak that they can be studied only in concentrated solution, and thus only with poor accuracy. For example, the strong acceptor trinitrobenzene displays a value of only $\Delta G = 4.5\,\text{kJ}\,\text{mol}^{-1}$ with the donor hexamethylbenzene in CCl_4, and with toluene it falls to barely measurable levels.[490]

8.3. Porphyrin Complexes

Stacking interactions of porphyrins play an important role, for example, in the development of new materials.[491] Fullerenes can be complexed effectively with porphyrins,[492] calixarenes, and many other aromatic host compounds.[493] Attraction between the π systems of photochemically activatable dyads, which contain a fullerene as an electron donor attached through a flexible bridge to a porphyrin,[494] leads to an environment conducive to electron transfer.[495] The interaction between fullerene and porphyrin leads in the corresponding complexes to an increase of the association constants by several orders of magnitude.[496] Porphyrin tetramers can bind fullerenes such as C_{60} with association constants of about 6×10^3, even in the competitive solvent toluene.[497]

Water-soluble porphyrins usually bear positively or negatively charged substituents in the meso positions, and show both polar and lipophilic interactions.[498] The dimerization of [4-(N-methyl)pyridinium]porphyrins is characterized by large and negative ΔH and ΔS values, which suggests the dominance of dispersive mechanisms.[499] The especially stable 1:2 complexes consisting of two heptakis-tri-O-methyl-β- cyclodextrins and porphyrins with ionic meso substituents are characterized by similar thermodynamic values, where polarization of the electrically neutral CD is regarded as a significant factor.[500]

The porphyrin derivative **47** shows surprisingly similar complexation constants for multiply charged nucleotides and electroneutral nucleosides. For example, with adenosine one observes a value of $\lg K=4.8$, and with ATP $\lg K=4.5$ (in water, 0.3 M buffer). The preponderant dispersive character can also explain the scarcely differing affinities ($\Delta\lg K=\pm 0.3$) of nucleosides and nucleotides derived from A, G, C, and T.[501] Similarly, the bis(phenanthridinium) receptor **48** again binds nucleotides and nucleosides with comparable strength ($\lg K=5$–6);[502] a dependence of affinity on the charge of the nucleotide is not observed with either **47** nor **48**: despite the presence of charges, which have no influence.



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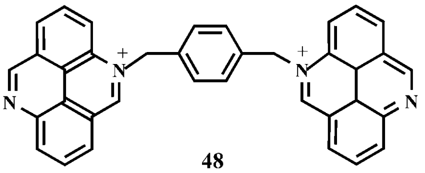
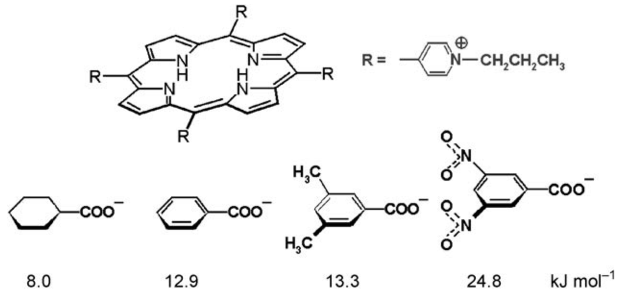


48

8.4. Dispersive or Solvophobic Interactions?

Distinguishing between solvophobic and dispersive interactions is always problematic, but especially with water as the solvent. With lipophilic molecules, both hydrophobic and dispersive mechanisms are the strongest interactions in water. Analysis of various porphyrin complexes in water has made it possible to differentiate definitively between hydrophobic and van der Waals contributions (Scheme 14). Remarkably, the affinity of cyclohexane carboxylate is actually weaker than that of the less hydrophobic, but nearly isosteric benzoate anion; moreover, two methyl substituents, for example, contribute almost nothing to an increase in the binding strength. This means that hydrophobic contributions are negligibly small with complexes of this sort, which facilitates developing a scale of binding contributions for various hetero groups by comparing affinities of different substrates. Systematic comparison of numerous mono- and disubstituted benzoic acids shows that substituent contributions are largely additive, and that the resulting values are transferable as well to aliphatic systems. With aromatic compounds, the presence of a nitro group leads to a contribution of $\Delta\Delta G=5\,\text{kJ mol}^{-1}$ (Scheme 14). Nitromethane binds with $5.3\,\text{kJ mol}^{-1}$; in the case of 3-nitropropionic acid, the nitro group increases the affinity by about $4.8\,\text{kJ mol}^{-1}$ (Section 8.8).

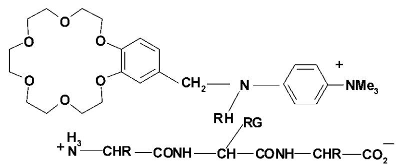


Scheme 14. Complexation energies of selected substrates with tetrapyridiumporphyrin TPPyP.

8.5. Stacking of Peptides

The folding of peptides is determined largely by interactions between aromatic amino acid side chains.[503] According to model studies, peptides in the form of β sheets (Scheme S17 in the Supporting Information)—at least in apolar media—are present largely in the homochiral conformation, which permits stacking between the amino acid residues R.[504] Heterochiral arrangements are preferred with basic amino acids, for example with polylysine,[505] as is to be expected because of repulsion between ionic groups in a homochiral form. A contribution of about $2\,\text{kJ mol}^{-1}$ has been derived with hairpin models for the Phe-Phe intrastrand interaction.[506] However, analyses with model oligopeptides containing phenylalanine and cyclohexylalanine in the side chain showed no preference for combinations with neighboring Phe-Phe units.[507]

The interaction between amino acid side chains RG and aromatic units RH in a synthetic host compound (Scheme 15)



Tripeptide	RG	–ΔG [kJ mol^{-1}]
Gly-Gly-Gly	H	13.2
Gly-Ala-Gly	Me	15.6
Gly-Leu-Gly	CHMe$_2$	16.7
Gly-Phe-Gly	CH$_2$Ph	18.3
Gly-Trp-Gly	Indole	19.0

Scheme 15. Side-chain interactions of peptides with a dansyl group RH of a synthetic receptor.

provides an effective basis for sequence-selective recognition of peptides.[508] The primary bond of the peptide $^+$NH$_3$ terminus with the crown ether, and the salt bridge between peptide-COO$^-$ and host $^+$NMe$_3$ groups, gives an association constant for Gly-Gly-Gly in water of 210 KM^{-1}; a tenfold higher value of $K = 2150\,\text{M}^{-1}$ is obtained with Gly-Trp-Gly. Aliphatic residues RH, such as in Ala, Val, and Leu, despite their greater lipophilicity, result in a lower affinity than Phe or Trp, which again points to dispersive stacking as a significant mechanism. Aromatic guest molecules[509] such as dihydroxynaphthalene or also methylviologen complex simultaneously in the large cavity of cucurbit[8]uril in aqueous solution. The concurrent interaction of cucurbit[8]uril and methylviologen permits a remarkable discrimination between different amino acids and peptides, again with a preference for aromatic amino acids (Scheme S18 in the Supporting Information).[510] The affinity for tryptophan is 8 times less than that for phenylalanine, and even 19 times less in the case of tyrosine. If charge-transfer interactions were decisive, the reverse should be found, namely a greater affinity for the electron-rich tyrosine. Thus, the determining factors here are also the dispersive force between aromatic units, together with simultaneously operative ion-pair binding, particularly in the case of peptides with N-terminal tryptophan. The formation of rotaxanes and other supramolecular complexes with cucurbit[8]uril is often ascribed to charge-transfer interactions,[511] although it is usually better explained through electrostatic effects. The association of protonated amines in cucurbituril is consistent with dominating van der Waals forces, determined largely by ΔH values, which with linear alkyl amines increase up to a chain length of C$_5$, with increments of up to 9.6 kJ mol^{-1} per methylene group.[512] The inclusion of chiral amines in cucurbit[7]uril also comes about through enthalpy advantages, which with phenylalanine-containing dipeptides, for example, can amount to as much as 37 kJ mol^{-1}, always with small $T\Delta S$ values.[513] A nitro group on a phenyl residue increases the association constant by an order of magnitude through additional stacking (Scheme S18 in the Supporting Information),[514] consistent with the observations above regarding porphyrin complexes (Scheme 14).

8.6. Calixarene Complexes

Calixarene complexes[100] often exhibit not only polar interactions but also van der Waals interactions, which are characterized, for example, by a dominance of enthalpic rather than entropic factors (Sections 4.2 and 4.3). Similar to the results shown in Scheme 3 (Section 4.1), a complex of calix[4]arene tetrasulfonate with 2,6-dimethylpyridine at pH 7, with $\Delta H = 48$ kJ mol^{-1} and $T\Delta S = 26$ kJ mol^{-1}, shows features of van der Waals forces and CH hydrogen bonds, whereas at pH 2, with $\Delta H = 39$ kJ mol^{-1} and $T\Delta S = 14$ kJ mol^{-1}, the entropic penalties are reduced due to the stronger polar contributions.[515] A reduced affinity is observed on inclusion of electron-rich substrates in calixarenes, but a larger affinity is found with electron-deficient substrates. This is an indication that an electrostatic mechanism predominates here.[516] Complexes of sulfonatocalix[4]-arenes with 2,2- as well as 4,4-dipyridinium salts in water are determined largely by enthalpy advantages, not as with salt bridges by entropy advantages, evidence again of van der Waals interactions.[517] Deuterium NMR relaxation studies of solid calixarene complexes with chloroform as the guest show an unusually high mobility of the guest molecule, which is regarded as an indication of dispersive interactions.[518]

Fullerene–calixarene interactions are characterized above all by gains in enthalpy ΔH; the corresponding losses in entropy $T\Delta S$ represent only about one-fourth of the ΔH gain, which can be explained by the round, largely dispersively bound and mobile "buckyballs".[519] Calixarenes and related host compounds complex the electron-deficient fullerenes as a function of cavity size, and are thus well suited for the separation of such guest molecules.[520] Calixarenes based on naphthalene instead of phenyl rings are predestined by their increased aromatic surface for complexation with fullerenes.[521] With bridged biscalix[5]arenes, the presence of two calix units causes an increase in association constants with fullerenes by about 40-fold relative to the complex with a monocalixarene (Scheme S19 in the Supporting Information) and reaches a value of $K = 10^5\,\text{M}^{-1}$ with C$_{70}$, with minor differences in solvents such as benzene, toluene, or CS$_2$.[522] Resorcin[4]arene barely binds C$_{70}$ at all in water, but C$_{60}$ well.[523] Analysis of the charge-transfer bands showed that very little charge transfer occurs in the ground state. The complexation of fullerenes by peralkoxy-substituted calixarenes in solvents such as CCl$_4$ is characterized by charge-transfer bands showing charge-transfer transition energies that correlate with the electron affinities of the acceptors.[524] Consistent with a largely dispersive binding mechanism, the affinity of C$_{60}$ for substituted calyx[5]arenes increases with increasing polarizability both of the substituents and the solvent (Scheme S20 in the Supporting Information).[525]

Corannulenes possess a concave structure, which is a good fit with fullerenes (Scheme S21 in the Supporting Information); furthermore, similar to tweezer guest compounds,[236] they have a negative partial charge on the concave surface. Therefore, association constants are observed with the electron-deficient fullerenes that, in the case of C$_{60}$ with suitably substituted corannulenes in, for example, CS$_2$, extend up to $K = 1300\,\text{M}^{-1}$.[526] Association constants as high as $K =$

$10^7\,\text{M}^{-1}$ are attained for macrocyclic bisporphyrins with C_{70}, for example. Metalation of the porphyrins causes significant increases only in the case of rhodium (Scheme S22 in the Supporting Information).[527] Apart from calixarenes, cyclophanes and cyclodextrins have also been used for the complexation of fullerenes.[528,529] Complexations achieved in this way, including in water, take advantage not only of dispersive but also hydrophobic forces. Even simple, often heterocyclic donors such as thiafulvalene form fullerene complexes, at least in the solid state.[530] Ab initio calculations on porphyrin–fullerene complexes indicate that electrostatic forces constitute roughly half of the interaction; metalation of the porphyrins results in the electrostatic part increasing, but is nevertheless limited by increased Pauli repulsion.[531]

8.7. Dispersive Effects with Heteroatoms

The often underestimated[4c] influence of heteroatoms on dispersive interactions can be quantified with the aid of the porphyrin complexes described in Section 8.4 (Scheme 14, Table S3 in the Supporting Information). This dispersive contribution clearly increases, as expected, with polarizability, although at the same time the van der Waals distances also increase.[532] A comparison with known polarizabilities (Figure 10) reveals a nearly linear relationship. The contribution of a nitro group approaches that of a phenyl group, and suggests the use of such substituents as a way of increasing weak interactions (Scheme S18b in the Supporting Information). It is worth noting the high value of the SMe group relative to that of the OMe group, which has biological relevance.[125] The contribution of the cyclopropyl unit reflects the fact that the three-membered ring has more olefinic than aliphatic character. That the increments for dispersive contributions of individual functions, obtained by averaging, are transferable and additive is documented by the fact that all experimentally determined equilibrium constants agree with them perfectly (Scheme S23, Figure S15 in the Supporting information).[532]

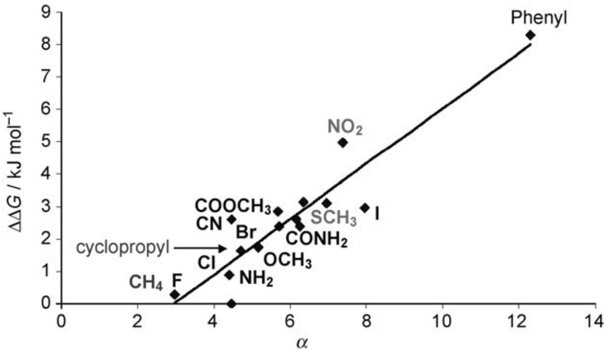


Figure 10. Correlation between binding-energy increments $\Delta\Delta G$ (from measurements of porphyrin complexes) and molar polarizabilities α of the corresponding methyl compounds CH_3R.

Heteroatom dispersive interactions can also develop with π systems, as shown in complexes of porphyrins with heteroatom-containing guest molecules. If steric restrictions cause an electronegative heteroatom to be located over the center of a phenyl group, repulsion would be anticipated from the partial negative charge of the π system. It has been concluded from experiments with a double-mutant cycle that repulsion between a CX_3 group and a phenyl ring, for example, increases from $1.2\,\text{kJ mol}^{-1}$ for X = Br, to $1.5\,\text{kJ mol}^{-1}$ for X = Cl, and up to $2.8\,\text{kJ mol}^{-1}$ for X = F; however, the assumed error is $\pm 1\,\text{kJ mol}^{-1}$, and the position of the CX_3 group can vary from one system to another.[533] Above all, the solvent $CDCl_3$ will in any case mask van der Waals interactions because of its high polarizability; compared to the CX_3 group of the substrate, it is after all present in great excess. An attractive interaction between C–Hal groups and aromatic rings, as manifested in porphyrin complexes, is possible if the halogen is not centrally located above the π system, but still is in contact with the polarizable π-electron cloud. Analysis of 20000 crystal structures containing halogen and aryl groups at appropriate distances from each other, and avoiding a position over the center of the π system, led to only a few hundred of the structures in an arrangement compatible with a dispersive interaction. The rest were characterized by geometries suggesting hydrogen bonds with the aryl–CH linkages.[534] Contacts between C–Cl and aryl groups were found, for example, in triptycene derivatives,[535] as well as, for example, in a calix[6]pyrrole/trichloroethanol complex.[536] Interactions of halogen atoms with aromatic systems were identified mostly in solids;[537] however, these are often dependent upon electrostatic effects (Section 5.2). In the case of contacts between C–Br groups and halide anions, most of the crystal structures resemble those with hydrogen bonds.[538] However, the easily polarizable iodo groups in particular often show contacts that fall below the sum of the van der Waals radii.[539] The introduction of bromo substituents into quinolinium guest compounds increases the affinity for cyclophane guest molecules in aqueous medium by about $1\,\text{kJ mol}^{-1}$.[540] The previously discussed dispersive interactions of oxygen and especially of sulfur groups can be quantified by measuring rotamer equilibria for triptycene derivatives, in which contact is possible between the alkoxy chains and phenyl groups substituted at the 9-position (Scheme S24 in the Supporting Information).[541] A preference is observed for the *syn* conformation with aromatic compounds that are not electron deficient, even in the readily polarizable solvent chloroform. Electrostatic effects (Section 6.2) lead in the presence of electron-withdrawing substituents X to a strengthening of the *syn* conformation, and electron-donating substituents to its weakening.

9. Solvophobic/Hydrophobic Interactions, Cyclodextrin Complexes

9.1. Fundamentals

The solvent-assisted association of lipophilic molecules or their components is especially pronounced in water. Hydrophobic interactions play a major role, particularly with biologically important interactions, but also with many biomimetic synthetic complexes. There are already a number of monographs devoted to such interactions,[542–544] and hundreds of review articles, only a few of which are cited here.[545–547] The significance of the hydrophobic effect for reactions in water,[548] particularly for the development of synthetic receptors, has been treated in separate reviews.[549] It becomes possible, with a suitable rotaxane, for example, to initiate a mechanical motion by changing from a hydrophobic to a hydrophilic medium.[232b] The significance of dispersive[550] or also hydrophobic effects in peptide–peptide interactions has already been discussed in Section 8, and it plays an important role in protein structures.[125,551] Association of cationic lipids with DNA is, as expected, favored entropically, and it tends to be endothermic, as lipophilic contributions are characterized by negative changes in the heat capacity.[552]

The structure and dynamics of water are the key to understanding hydrophobic effects, and once again it will suffice to reference the existing literature.[541–548,553] Recently, MD simulations and also experimental results have led to a refined picture of the structure of water, characterized by one to two stronger hydrogen bonds and additional weaker ones per H_2O molecule, rather than the conceivable maximum of four.[554] MD simulations and HF-MO calculations indicate that one water molecule is surrounded on average by 2.8 others.[555] According to femtosecond IR and MD analyses, water molecules not connected by hydrogen bonds play almost no role.[556] The temperature-dependence of the hydrophobic effect, which in hot water leads to a positive entropy on dissolution of a nonpolar substance, has been explained with hydrogen-bonding models.[557] According to X-ray spectroscopic analyses, and consistent with neutron-diffraction results, warming above room temperature causes a change in the coordination number of the water molecule from four to only two.[558] The ratio of ΔH to ΔS appears to be temperature-dependent in the folding of proteins; at room temperature the entropic contribution predominates.[559] The hydration of small, hard substrates leads theoretically to small fluctuation disturbances in the water structure, with energies largely determined by entropy. In contrast, with larger substrates, even in the subnanometer region, association and cavity formation in water is dominated by enthalpy, and is best described by the interaction between surfaces exposed to solvent,[560] or in some circumstances better by the number of interacting C–H bonds.[561]

Solvophobic forces are much stronger in water than in any other solvent, since solvation of a substrate requires, on the one hand, a particularly large number of solvent molecules, a consequence of the small size of the water molecule, and on the other hand because the solvent molecules are especially heavily structured through hydrogen bonds. The classical Frank–Evans model describes the hydrophobic effect as an entropic advantage during the association of lipophilic substrates, which arises through the release of water molecules. The solvation of lipophilic surfaces in water is presumed to lead to increased ordering of the solvation sphere. After the gathering together of two or more substrate molecules, less water molecules are required for the resulting aggregate than were previously necessary. The Frank–Evans principle has recently become controversial, since, among other things, the thermodynamics of the transfer of lipophilic substrates into water can also be explained with the aid of the scaled-particle theory (SPT) without the assumption of any special water structure.[562] Neutron diffraction experiments also argue against the formation of higher-order water structures in the presence of nonpolar substrates,[563] consistent with more recent simulations.[564,565] Other descriptions have been proposed to resolve inconsistencies in the thermodynamic characterization.[566] It has been emphasized that one consequence is that the number of hydrogen bonds in bulk water plays a less significant role than their directionality.[567] A negative enthalpic contribution to the hydrophobic effect has been postulated for the rare gases and for alkanes, but by contrast a positive one for aromatic compounds, increasing with the size of the hydrocarbon. A definite indication of a hydrophobic effect is the change in the heat capacity ΔC_p, which increases with hydration of nonpolar substrates and decreases with polar ones.[568]

Entropy-driven associations with ion pairs are indeed found experimentally with ion pairs (Section 4), but surprisingly seldom, even with cyclodextrin complexes, for which hydrophobic driving forces have often been assumed. A hydrophobic effect dominated by enthalpy advantages, described as **nonclassical**,[569] occurs when water molecules are set free by the gathering of substrate molecules in a large cavity, and then able to form hydrogen bonds among themselves. The resulting gain can be quantified in terms of the cohesion forces of the solvent γ, as expressed in the surface tension.[570] The number of possible bridges per water molecule is limited by solvation of nonpolar surfaces, especially in cavities such as those of cyclodextrins.[571] The release of such energy-rich water molecules, also localizable around peptides,[572] thus results also in a gain in enthalpy. Both the entropic effect and the hydrophobic effect arising from enthalpic factors increase with the surface area ΔA that after association is no longer exposed to water. The resulting free energy ΔG_{hp} won by the release of water molecules can therefore be described by Equation (6).

$$\Delta G_{hp} = \text{const}\,\gamma\,\Delta A \tag{6}$$

In simulations frequently employed, however, γ values for water differ considerably: from 100 to 500 $\text{J mol}^{-1}\,\text{Å}^{-2}$.[1d] Experiments with 50 different aromatic compounds produced an average value of 430 $\text{J mol}^{-1}\,\text{Å}^{-2}$, nearly independent of the presence of heteroatoms.[573] However, more recent analyses have produced a value of 200 $\text{J mol}^{-1}\,\text{Å}^{-2}$.[574] The simultaneous presence of other and cooperative interactions can result in the values obtained from transfer measurements with hydrocarbons being considerably larger.[575] Thermodynamic measurements on the transfer of a nonpolar substrate from the gaseous state or out of a nonpolar solvent, such as hexane, into water provide a direct measure of the hydrophobic effect. The increment for a single CH_2 group in linear hydrocarbons is $\Delta\Delta G = 3.85$, $\Delta\Delta H = 2.75\ \text{kJ mol}^{-1}$, and for a CH_3 group $\Delta\Delta G = 8.4$, $\Delta\Delta H$–5.4 and $T\Delta\Delta S = -13.8\ \text{kJ mol}^{-1}$; that is, the increment for a CH_3 group is an entropy-dominated effect.[576] Parameters exist for the hydrophobicity of amino acids that in part differ greatly, as the corresponding enthalpic contributions were derived from dilution experiments.[577]

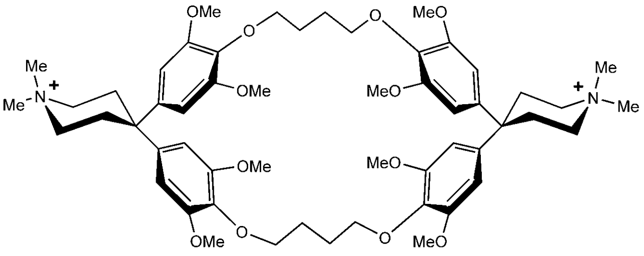
The distribution coefficient P for a substance between water and a lipophilic phase such as n-octanol is normally used as a parameter for hydrophobicity.[578] The free energy of transfer from a hydrocarbon into water is taken as the corresponding thermodynamic function. For alkanes, this is approximately a function of the size of the substrate.[575] The influence of substituents can be generalized as π_X through comparison of P values with standard substrates, and has been tabulated for a great many substituents [Eq. (7)].[579]

$$\pi_X = \log(P_{RX}/P_{RH}) \quad (7)$$

9.2. Synthetic Complexes in which Solvophobic Interactions are Dominant

Examples of solvent-driven complexations in media other than water are rare. Bisporphyrins bound to calixarenes show association constants for C_{60} that range from $\lg K = 4.4$ in toluene to $\lg K = 6.6$ in cyclohexane, where the differences are largely enthalpic in nature. Complexation strengths show an inverse correlation with fullerene solubility in toluene/acetonitrile mixtures (Scheme S25 in the Supporting Information), which points to desolvation of the guest molecules as the driving force for complexation.[580]

Complexes with cyclophanes, calixarenes, and resorcinarenes are often based on lipophilic forces and supplementary interactions such as hydrogen bonds.[100,581] The affinity of lipophilic substrates for lipophilic cavities reaches a maximum in aqueous medium, and in the sense of the nonclassical hydrophobic effect cited above, largely through enthalpic factors. This becomes especially clear (Table S4 in the Supporting Information) in the binding, for example, of pyrene in an electroneutral cavity (**49**; for the solvent dependency see Section 10). Similar characteristics are found in the corresponding complexations with substituted phenyl derivatives, which show values in water of $\Delta G = -15$ to -28 kJ mol^{-1} and of $T\Delta S = -8$ to -28 kJ mol^{-1}.[582]



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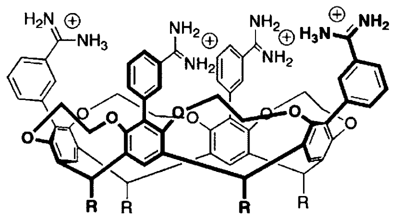
Often the various binding mechanisms first become clear with calorimetric data. Thus, in the complexation of a resorcarene tetrasulfonate in water, one finds for Me_4N^+ $\Delta G = 14$ kJ mol^{-1} and $\Delta H = 5$ kJ mol^{-1}, and for p-NO_2-C_6H_4-$CH_2{}^+NMe_3$ the same ΔG value, but $\Delta H = 23$ kJ mol^{-1}: the nitro group results in increased attraction with the electron-rich aromatic guest, but with a loss of mobility and thus entropy, which, in the binding of Me_4N^+ results, in contrast, in a positive hydrophobic contribution.[583] The complexation of uracil derivatives with calixarene derivatives in aqueous media correlates with the surface in the partner molecule that is exposed to solvent.[584] A cavitand binds substrates such as cyclohexanone or hydroxymethyladamantane largely through entropy gains, with values of $\Delta H = -8$ to -17 kJ mol^{-1} and $T\Delta S = 12$ to 23 kJ mol^{-1}.[585] More often, however, entropy penalties are found, such as with the self-association of a lipophilic tweezer compound.[586]

Cavitands and carcerands often enclose molecules without any special interaction with the guest.[587] Such cage or container compounds (see also Section 10) permit the stabilization of kinetically unstable molecules such as cyclobutadienes or arynes.[588] These can be made water soluble through the introduction of ionic groups (such as in **50**),[589] and bind, for example, nucleotides, besides through ion-pair bridges, largely through hydrophobic interactions, with enthalpic contributions dominant.[590] Cavitands such as **51** form dimers in water which complex, for example, an androsterone with an association constant of $K = 10^8$ M^{-1}, both consequences of strong hydrophobic effects.[591] Similar complexes are accessible by using phosphorylated calixarenes.[592] Hydrophobic forces in conjunction with CH hydrogen bonds in the case of guest molecules such as naphthalene, p-xylene, or ferrocene lead to association constants with hemicarcerand **52** that can exceed 10^8 M^{-1}.[593] Simple resorcarenes such as **53** with lipophilic substituents such as $R = (CH_2)_5CH_3$ complex in water and even diethyl ether with $\Delta G = 10$ kJ mol^{-1}, or n-phenylpropanol with $\Delta G = 16$ kJ mol^{-1}.[594]

Both the enthalpy and entropy values for encapsulation appear to be positive in protic solvents, which shows that solvent molecules are set free by such complexation. The capsules supported by hydrogen bonds also become stronger, even in protic media, as the stability of substrate binding within the cavity increases. Instead of hydrogen bonds as the driving force for the formation of more-closed cavities, coordination with metal ions can also be used, for example, in the case of pyridyl-substituted cavitands. The solvent effects in the much more stable complexes of this sort are naturally much weaker. However, the addition of trimethylamine destabilizes such complexes through competitive interaction, whereas the corresponding platinum capsules are inert to this latter effect.[595]

9.3. Cyclodextrin Complexes

Complexation with cyclodextrins[596] constitutes probably the most important aspect of supramolecular chemistry from an economic standpoint.[597] Its application in the development of new systems for molecular recognition or, for example, for rotaxanes,[233,598] as drug carriers,[599] or for guiding reactions,[600] including in derivativized form,[601] has been extensively documented. As already noted, a hydrophobic effect is usually assumed to be an important driving force for the formation of a complex, although most of the



$R = -CH_2CH_2CH_2(OCH_2CH_2)_4CH_3$

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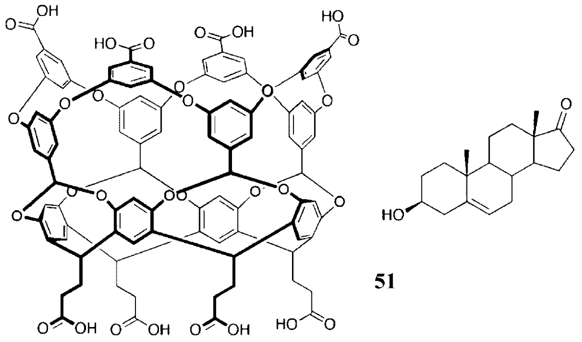

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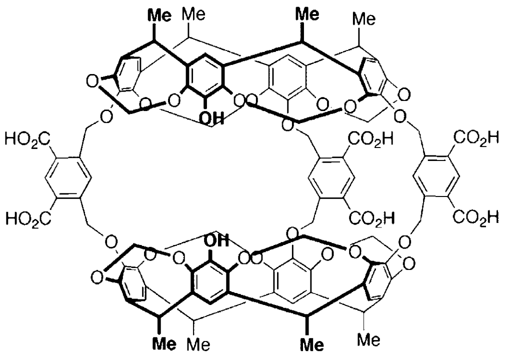

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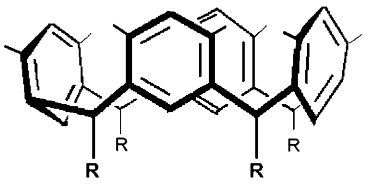


53, $R{=}(CH_2)_5CH_3$: 8 OH groups

vast number of experimental studies[602] document an entropic contribution much less often than an enthalpic one. X-ray structural analyses show two, six to seven, and about twelve water molecules in the cavities of α-CD, β-CD, and γ-CD, respectively,[603] which is in agreement, for example, with Monte Carlo simulations.[604] Complexation leads, nevertheless, to disruption of water associations outside the cavity. Dominant enthalpic contributions have also been observed with complexes of host molecules containing three cyclodextrin units.[605] The hydrophobicity of the cyclodextrin cavity is a consequence of the fact that the interior side is occupied by axial C–H bonds of the glucose units. For differing estimates of the hydrophobicity within the cavity as well, see the cited references.[595,596,603,606]

Van der Waals and polar interactions are often assumed to be significant factors, based also on the results of recent simulations.[607] It must be taken into account in the interpretation of thermodynamic values that cyclodextrins have a tendency to form nontrivial 1:1 complexes,[608] and that, as already mentioned in Section 3.2,[91] contrary to expectation, the substrate often binds outside the cavity.[609] With predominantly hydrophobic forces it is also found by "offering" guest molecules that bear groups of varying size, that the groups that bind inside the cavity are specifically those that do not fill it,[610] but instead leave room for water molecules (see also Section 10). The application of NMR spectroscopic methods can help verify the conformation of the complex in solution;[611] this is particularly easy in the case of aromatic guest molecules.

As already mentioned in Section 3.4, energies calculated using force fields with inclusion of hydrophobic contacts corresponding to the solvent-contact surface permit computation of complexation energies,[183,185] including for the association of cyclodextrins. Numerous theoretical studies discuss computations with respect to such complexes, including MD and MO methods.[183,185,606] In the simplest case, the affinities of lipophilic guest molecules can be correlated with their hydrophobicity parameters, as illustrated by the example of the complexation of pyrocatechols with aminocyclodextrins (Figure S16 in the Supporting Information).[612] Complexations of hydrocarbons, especially with the larger capacity γ-cyclodextrins, show strongly negative ΔC_p values (with the consequence of a strong temperature dependence on ΔH). This is in accordance with the transfer of alkanes from the gaseous state into water as discussed above, together with negligibly small enthalpy contributions, consistent with a classical hydrophobic effect dominated by entropy (Table S5 in the Supporting Information).[613] Inclusion in the smaller α-cyclodextrin, on the other hand, permits dispersive interactions as well, and is largely determined by enthalpy, with substantial entropy penalties. This effect becomes more pronounced the higher the polarizability and electron density of the guest molecule, as shown, for example, by experiments with *p*-nitrophenolate anions.[601,614] Entropic contributions become dominant with less polarizable or hydrophobic substrates, as in the complexation of amino acids.[615]

The affinity of homologous alcohols and carboxylic acids $CH_3(CH_2)_nX$ for α-cyclodextrin shows a straightforward relationship between n and ΔG or $\ln K$; a similar situation also exists for ΔH and ΔS [Eq. (8)]:[616]

$$\ln K = -0.375 + 1.19\,n \tag{8a}$$

$$\Delta H\ [\mathrm{kJ\,mol^{-1}}] = 5.13 - 3.83\,n \tag{8b}$$

$$\Delta S\ [\mathrm{J\,mol^{-1}\,K^{-1}}] = 14.1 - 3.0\,n \tag{8c}$$

From the linear correlations it follows for alcohols that for a single methylene group $\Delta\Delta G = -3.0$, with $\Delta\Delta H = -3.83$ and $T\Delta\Delta S = -0.83$ (in each case in kJ mol^{-1}), which are in relatively good agreement with corresponding values for the gas–water transfer of, for example, hexane. The increments are similar for carboxylic acids (with β-cyclodextrin $\Delta\Delta G = -3.3\ \text{kJ mol}^{-1}$), always with strongly negative ΔC_p values. A similar increment of $\Delta\Delta G = -2.3\ \text{kJ mol}^{-1}$ was found with a series of alkanones and hydroxypropyl-β-cyclodextrin.[617] It must be taken into account that the ΔG and ΔH values are dependent on whether they refer, as usual, to molar concentrations or to mol fractions (Table S5 in the Supporting Information), and that here the ΔH values are particularly temperature dependent. The presence of polar groups in the guest molecules leads to a decrease in the hydrophobic part. This applies particularly to ionic groups whose hydrophilicity P values are as high as those from five or six hydroxy groups together. Thus, for complexes with α-cyclodextrin the $\lg K$ value for phenol falls from 2.1 to 1.2 after deprotonation, and that for aniline after protonation from 1.75 to 0.36. Ionic groups are much more strongly hydrated than neutral ones, and they complex more weakly. Thus, formation of a complex leads to a shift in the dissociation equilibrium toward the neutral form, and both acids and bases appear to be weaker.

Cyclodextrin complexes with amino acids, peptides, nucleotides, and nucleosides: There are numerous reports of the application of cyclodextrins for complexation of biologically important substrates. Of interest here is their use in peptide delivery systems,[618] or for nucleotides as "gene vectors".[619] The aggregation of peptides typical in Alzheimer's disease can be inhibited by persubstituted aminocyclodextrins.[620] The utilization of modified cyclodextrins[621] with additional substituents, usually in the form of amino groups, has been particularly successful, where the hydrophobic contribution is reduced in favor of polar binding forces. In this way, a higher enantio- or diastereoselectivity can also be achieved with amino acids and peptides or with chiral amines.[622] A domination of enthalpic driving forces is characteristic of hydrophobic interactions; for example, in the complexation of protected dipeptides with native γ-CD these can reach $-68\ \text{kJ mol}^{-1}$, generally with opposing entropy penalties of the same order of magnitude.[623] With benzyloxycarbonyl derivatives, the aryl ring of the protecting group is usually found inside the CD cavity,[624] but this changes with aromatic amino acids such as Ala-Tyr.[625] Relatively strong complexes of native di- and tripeptides with monoamino-β-CDs are observed only in the presence of lipophilic amino acid residues, which, according to NMR analysis, dip into the cavity. Selectivity is largely lost with the use of heptaamino-β-CD because of the dominance of salt bridges.[626] The association constants of nucleotides with aminocyclodextrins can exceed $K = 10^6\ \text{M}^{-1}$, with complexes stabilized largely by salt bridges with heptaamino-β-CD, for example. If the association constants are reduced, as with monoamino-β-CD, then a preference of roughly an order of magnitude is found for the larger purine derivatives AMP or GMP relative to UMP or CMP, a result consistent with stronger hydrophobic contributions.[194] Complexes of bis(guanidinium)tetrakis-β-cyclodextrin and adenosine phosphate reach affinities comparable to those of heptaamino-β-CD and ATP.[627]

10. Solvent Effects, Container Molecules

10.1. General Description

The influence of the medium on the formation of a complex also reflects the binding mechanism,[628] and has, therefore, already been treated in preceding sections. Here only a few general principles and applications with specific supramolecular associations are discussed. The dependence of host–guest equilibria can also be correlated with the dependence of distribution coefficients for individual compounds in selected solvents, as mentioned in Section 9. Various equations have been suggested to this end,[629] including in the form of Equation (9):[630]

$$SP = c + eE + sS + aA + bB + vV \tag{9}$$

This equation contains the variable SP, which may, for example, be $\lg K$ or the distribution coefficent P. The parameters describe characteristics of the compound (solute): E the molar refractivity, with a coefficient e, which contains the dispersive interaction between substrate and solvent; S a measure of the dipolarity and polarizability of the compound, where s measures the corresponding interaction with the solvent; A and B are the acceptor and donor constants of the compound, respectively, as discussed in Section 7.1, where a and b are the corresponding characteristics of the solvent; and V is a function of the energy of the solvent–solvent interaction, which is interrupted by introduction of the substrate. The description of the distribution equilibrium for ion pairs can be well defined thermodynamically, as can that for electrically neutral substrates.[631] It must be noted with solvent mixtures that the polarity parameter, for example, may show a *discontinuous* dependence on the proportions of the various solvents if there is mutual reinforcement or reduction of the polarity.[632] Solvation parameters that in application of the Kirkwood–Buff equation for binary mixtures characterize the local interaction between, for example, water and cosolvent, also fail to show a continuous course as a function of the composition.[633]

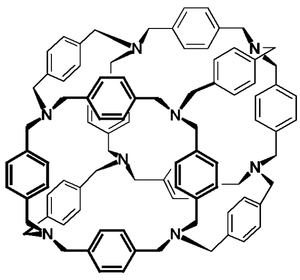
10.2. Solvent Effects with Supramolecular Complexes—Empirical Correlations

A commonly employed description of the influence of the solvent on the formation of a complex makes use of polarity parameters[628a] such as E_T,[628] which in principle should be limited to polar interactions. In fact, one nevertheless often finds linear relationships between complexation energies ΔG or $\lg K$ values and the E_T parameters of the solvents, as in Figure S17 in the Supporting Information for the host compound **49**, mentioned in Section 9, and pyrene as the guest molecule.[581] Apparently the strength of the complex increases with the polarity of the medium and decreases with its polarizability. This points to a nonclassical solvophobic character of the binding, consistent with the observed largely enthalpic driving force (Section 9). However, in contrast to the ΔG values, the ΔH values display considerable scatter in a correlation with E_T parameters.

If not polar but, for example, hydrophobic interactions dominate, less satisfactory relationships should be anticipated with the polarity parameters of the medium. Indeed, for various supramolecular complexes there exist significantly better linear correlations with solvophobicity parameters SP of the medium, obtained from transfer energies of hydrocarbons in various media,[634] rather than with polarity parameters such as E_T (Figure S18 in the Supporting Information).[120] Figure S13[581] in the Supporting Information shows that complexation in water is also described by the polarity parameter E_T, even though polar interactions should be weakened here. The reason is that, in water, both the dispersive and hydrophobic forces reach their optimum level, simultaneously with maximum polarity of the solvent. All the parameters shift in the same direction with a change in solvent. This typical parameter intercorrelation complicates the task of drawing conclusions about the binding mechanism, especially when a multiparameter set must be applied, as in the case of Equation (9). Nevertheless, the value of a systematic investigation of solvent effects is often underestimated. It generally makes it possible at least to rule out mechanistic alternatives. Thus, an increase in association constants with water content argues unambiguously against a dominance of ion-pair binding or electrostatic effects in general, and for dispersive or hydrophobic binding (and vice versa). Moreover, empirical correlations permit extrapolation to complexes for which direct measurements in a particular solvent are ruled out on methodological grounds, for reasons of insufficient solubility, for example, or because the affinities are too large or too small. If the ΔG values for cyclodextrin complexes are plotted against the mole fraction of cosolvent in mixtures of water and an organic cosolvent, a correlation is obtained with an initial slope m that is dependent upon the polarity or the hydrophobicity of the cosolvent. However, surprising discontinuities sometimes appear in a comparison of initial slopes m with $\lg P$ values for the cosolvent (Figure S19 in the Supporting Information). These have been interpreted such that some solvents occupy the cavity if their polarities are similar to or smaller than that of the cavity itself.[595]

10.3. Molecular Containers and Capsules

The medium within a cavity can differ considerably from the external environment. Polarity parameters can be ascertained, for example, from differences in the fluorescence emission I of dyes such as 8-anilino-1-naphthalenesulfonic acid (ANS), which can be observed, for example, inside cage compound **54**.[635] Comparison of the corresponding fluorescence emission I in various solvents permits the cavity E_T values to be arranged in order, which as expected show increases with increasing protonation of the interior side of the cage. By using this approach and diphenylamine as the fluorescent dye, an E_T value of 88 was ascertained for α-cyclodextrin, a value similar to that of ethanol.[636] However, the fluorescence emission also depends significantly on the orientation of the dye, not simply on the polarity of the surroundings.[637]



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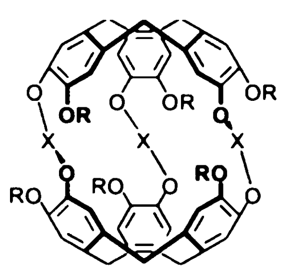

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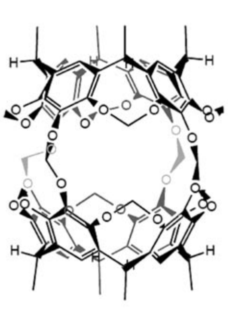
In a cycloveratrylene such as **55**, the formation of complexes with small guest molecules is possible if either the solvent molecules are definitely too large for the available portals or a solvent similar to water would be unfavorable inside the hydrophobic cavity.[638] Thus, **55** ($X = (CH_2)_3$, $R = OCH_3$) in tetrachloroethane as the solvent complexes $CHCl_3$ with $\Delta G = -15.5\ \mathrm{kJ\,mol^{-1}}$ and $\Delta H = -25\ \mathrm{kJ\,mol^{-1}}$; CH_2Cl_2 binds with $\Delta G = 12\ \mathrm{kJ\,mol^{-1}}$, but with a ΔH value of only $+4\ \mathrm{kJ\,mol^{-1}}$ (endothermic); thus, inclusion of the smaller guest molecule is entropically dominated.[639] The water-soluble derivative **55** ($R = CH_2COOH$) complexes tetramethylammonium chloride in water in a smaller cavity ($X = (CH_2)_3$) with $\Delta G = -15\ \mathrm{kJ\,mol^{-1}}$, but in a larger one ($X = (CH_2)_5$) with $-20\ \mathrm{kJ\,mol^{-1}}$, although here the cavity is so large that it can still accept additional solvent molecules. The observation that, contrary to the principle of a best possible fit between host and guest, optimal binding strength is often achieved only in the presence of a sufficient number of solvating molecules could be quantified for the first time in experiments with closed molecular capsules and carceplexes such as **56**–**58**.[640] A comparison of the cavity volume with the volumes of enclosed guest molecules showed that, on average, only $(55 \pm 10)\,\%$ of the cavity is occupied by guest molecules. In the presence of special interactions such as hydrogen bonds between the enclosed molecules, the packing coefficient may rise to about 70 %. Similar packing coefficients of 55 %, in a variance from the simple lock-and-key principle, were found with the particularly stable cucurbituryl complexes mentioned in Section 1.[21]

Guest molecules in the form of capsules can be created, as with **58**, through hydrogen bonds[641] or, as with **59**, through formation of an ion pair[642] between parts of molecules with concave shapes. Capsules arising through the formation of fourfold salt bridges bind, for example, quinuclidinium salts in water primarily through hydrophobic forces. In capsule cavities,[643] as well as in carcerands,[644] guest molecules can appear with differing orientations relative to each other. Normally unstable conformations of, for example, flexible alkanes, can thus become fixed in such cavities.[645]

Special solvent effects are to be anticipated when complexation takes place only, or largely, in dimer cages,



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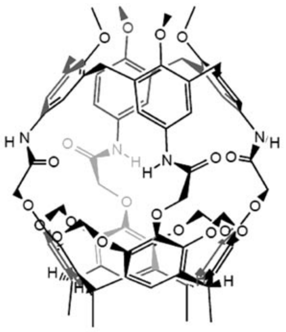

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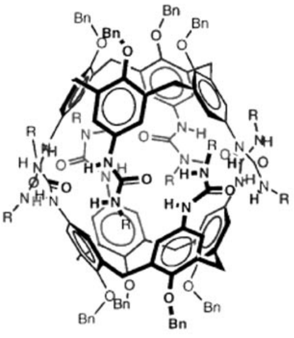

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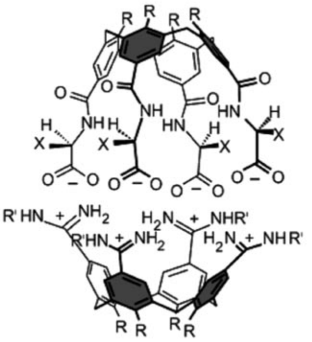

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the formation of which occurs, for example, through hydrogen bonds. Familiar examples include capsules obtained from resorcinarenes, the stability of which declines with an increasing ability of the solvent to form hydrogen bonds.[639,640a] Nevertheless, macrocycles derived from, for example, aldehydes and pyrogallol form dimers with trapped ammonium derivatives even in aqueous acetonitrile; exchange arising through opening and reclosing of the capsules is slow on the NMR time scale. The influence of solvent on capsule formation decreases, as is to be expected, if the guest molecules involved bind especially well within the cavity.[646] The formation of noncovalently bound capsules is favored by the template effect of solvents such as benzene, first through stabilization of a concave conformation and then through inclusion of two benzene molecules in a dimeric capsule (Scheme S26 in the Supporting Information).[647]

Strong influences of the solvent on the formation of supramolecular complexes are to be anticipated if the medium stabilizes alternative conformations of the host compound, which either bind guest molecules or release them again. The classic example of this is the so-called container molecules first described as early as 1982 and based on resorcinarene cavities.[648] These can assume conformations either of a closed vase or an open "kite", where only the former, for example, is able through hydrophobic effects to bind lipophilic guest molecules (Scheme S27 in the Supporting Information). Transition from the vase to the open form requires 40–60 $\mathrm{kJ\,mol^{-1}}$.[649] Temperature reduction leads to a preference for the open form, which can be explained through the higher enthalpy of solvation of this form because of its larger surface area. For the same reason, polar solvents are able to stabilize open conformations to such an extent that in protic media no vase form and no supramolecular complex formation is detectable.[650] Resorcin[4]arene cavitands with four quinoxaline or pyrazine units display conformations that are switchable not only by temperature and solvent, but which can also be governed by the addition of acids or metal ions. Hydrogen bonds with the nitrogen atoms of the heterocycles favor, for steric reasons, the open form. A corresponding shift to the open form correlates with acidity parameters of the medium.[587,651] By attaching larger side groups to such containers it becomes possible, again controllable by the medium, for length differences to arise between the ends of the molecules of from 7 Å to 70 Å (Scheme S27 in the Supporting Information). Such expansions and contractions are of interest with respect, among other things, to artificial muscles.[652]

11. Future Prospects

Supramolecular systems will in the future dominate many fields of chemistry, where the diversity of possible applications will increasingly demand large and complex associates. Modern synthetic, analytical, and also theoretical methods will considerably accelerate the development of such systems, as well as of biologically active materials. It is to be hoped that host–guest complexes prepared in the future, often with considerable effort, will be increasingly examined by using rigorous physical methods, including the way they function in a variety of media. Thermodynamic values acquired for complex formation should always be supplemented by characterization of the underlying structures. The necessary wide diversity of intermolecular interactions in highly complex systems poses heavy demands with respect to clarifying the underlying mechanisms. Meeting these demands is both an intellectual challenge and the key to countless new applications.

The publications cited in the text from my research group in Saarbrücken would have been unimaginable without the engaged contribution of a vast number of diplom and doctoral candidates, as well as visiting scientists. They have my thanks for their tireless and critical cooperative efforts. The DFG, the Fonds der Chemischen Industrie, the VW-Stiftung, INTAS, and the Alexander von Humboldt-Stiftung supported our research over the course of decades.

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