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Dispersive Interactions in Solution Complexes

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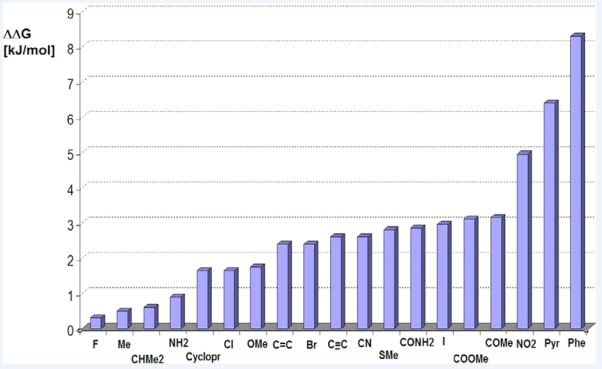
CONSPECTUS: Dispersive interactions are known to play a major role in molecular associations in the gas phase and in the solid state. In solution, however, their significance has been disputed in recent years on the basis of several arguments. A major problem until now has been the separation of dispersive and hydrophobic effects, which are both maximized in water due the low polarizability of this most important medium. Analyses of complexes between porphyrins and systematically varied substrates in water have allowed us to discriminate dispersive from hydrophobic effects, as the latter turned out to be negligible for complexations with flat surfaces such as porphyrins. Also, for the first time, it has become possible to obtain binding free energy increments $\Delta\Delta G$ for a multitude of organic residues including halogen, amide, amino, ether, carbonyl, ester, nitro, sulfur, unsatured, and cyclopropane groups, which turned out to be additive. Binding contributions for saturated residues are unmeasurably small, with $\Delta\Delta G > 1$ kJ/mol, but they increase to, e.g., $\Delta\Delta G = 5$ kJ/mol for a nitro group, a value not far from, e.g., that of a stacking pyridine ring. Stacking interactions of heteroarenes with porphyrins depend essentially on the size of the arenes, in line with polarizabilities, and seem to be rather independent of the position of nitrogen within the rings.



Measurements of halogen derivatives indicate that complexes with porphyrins, cyclodextrins, and pillarenes as hosts in different media consistently show increasing stability from fluorine to iodine as the substituent. This, and the observed sequence with other substrates, is in line with the expected increase in dispersive forces with increasing polarizability. Induced dipoles, which also would increase with polarizability, can be ruled out as providing the driving source in view of the data with halides: the observed stability sequence is opposite the change of electronegativity from fluorine to iodine. The same holds for the solvent effect observed in ethanol−water mixtures.

Dispersive contributions vary not only with the polarizability of the used media but also with the interacting receptor sites; it has been shown that for cucurbiturils the polarizability inside the cavity is extremely low, which also explains why hydrophobic effects are maximized with these hosts. Complexations with other known host compounds, however, such as those between cryptands or cavitands with, e.g., noble gases, bear the signature of dominating dispersive forces. Some recent examples illustrate that such van der Waals forces can also play an important role in complexations with proteins. Again, a clue for this is the increase in ΔG for inhibitor binding by 7 kJ/mol for, e.g., a bromine in comparison to a fluorine derivative.

1. INTRODUCTION

London dispersive interactions, which, in the classical description, are those between fluctuating dipoles, play an indisputably large role in the solid state.[1] In crystalline alkanes, where the heat of sublimation provide a measure of intermolecular interactions, the sublimation energies amount to up to, e.g., 52 kJ/mol for *n*-hexane.[2] Dispersive interactions can also dominate in the gas phase, where they find application in sensing and separation techniques.[3] They also play an important role in micelles,[4] membranes,[5] and many biologically important aggregates.

In solution, dispersive effects are like all intermolecular interactions weakened by competing interaction of the solute with the bulk solvent, particularly if this exhibits a large polarizability. As a medium, water has by far the smallest polarizability, with the exception of perfluorinated solvents; this allows the largest intermolecular dispersive forces to occur in that medium. At the same time, solvophobic interactions are maximized in water, which differ enormously between various receptor molecules[6] and must be distinguished from van der Waals contributions. As stated recently, the role of dispersion interactions in supramolecular complexation processes is still widely debated.[7] The aim of the present Account is primarily to elucidate with experimental results the significance and the size of dispersive forces in solution complexes. For theoretical evaluations of dispersive forces, which by far exceed experimental investigations, we can refer here only to recent reviews[8,9] and papers aiming mostly at associations in the gas state or in crystals.[1,10,11]

2. DISPERSION INTERACTIONS IN SOLUTION: INSIGNIFICANT ?

Several arguments were brought forward against a significant role of dispersive interactions in condensed media.[7,12] One argument

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is based on the Kirkwood−Slater equation, which describes dispersive forces as a function of the polarizability α and the number N of outer electrons, which, in each case, is referenced to interacting atoms i and j with distance r_{ij}. Corresponding calculations predict the same dispersive contribution for, e.g., fluorine and chlorine due to cancelation between an increase of polarizability α and the simultaneous increasing size of an atom.[13] However, the electron cloud of larger atoms is easier to deform, so a rigid-body description using the r_{ij}^{-6} term for the atom-to-atom distance becomes inappropriate. Furthermore, it has been argued that van der Waals interactions are a simple function of molecular surface area, independent of atom type:[7] the almost identical intermolecular contact surface areas of a solute in the free and complexed states could mean that for nonpolar liquids the contribution of van der Waals interactions would be similar in the solvent and inside the complex. However, the polarizability of commonly used nonpolar solvents varies considerably. In line with this, the cohesive energy density of solvents varies from, e.g., 50 to over 500 J cm^{-3} and correlates with intermolecular free energy changes observed with a molecular balance.[17] Furthermore, the polarizability of a receptor's interior can differ significantly from one host to the other, with a minimum value observed for cucurbiturils;[14] Figure 1 illustrates

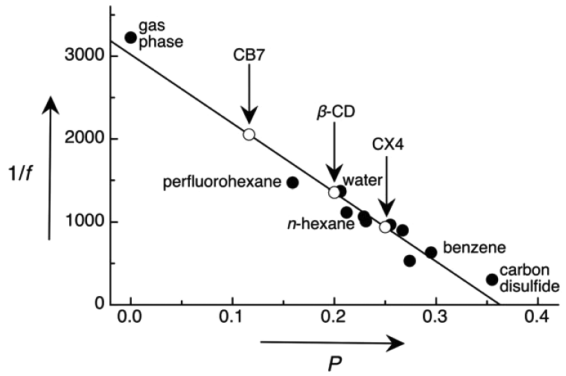

Figure 1. Polarizability differences. Linear correlation of the inverse oscillator strength of the indicator 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO) and the polarizability of the environment; see ref 14. CB7, cucurbit[7]uril; β-CD, β- cyclodextrin; CX4, p-sulfonatocalix[4]-arene. Reproduced with permission from ref 15. Copyright 2011 VCH Wiley.

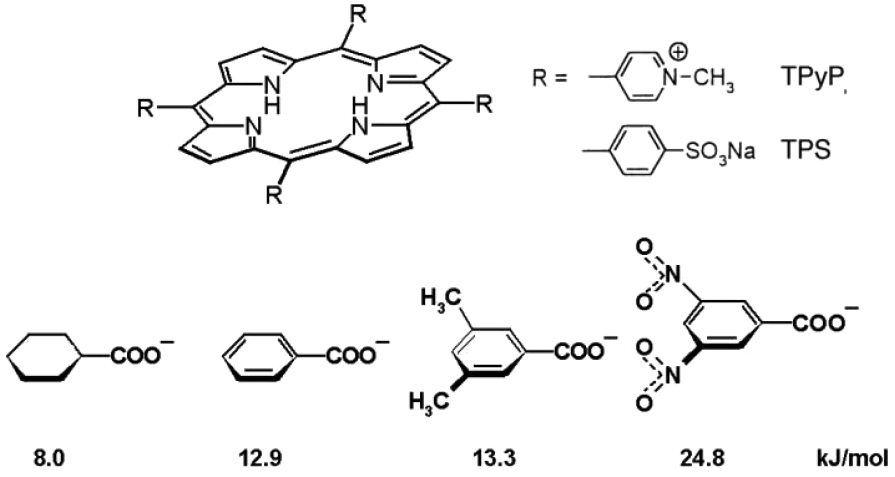

Figure 2. Complexation of porphyrins with cationic or anionic substituents R in the *meso* position (**TPyP** or **TPS**) in water, demonstrating the absence of measurable hydrophobic dispersive binding contributions and the presence of large dispersive binding contributions (ΔG values in kJ/mol for complexation with TPyP in water).

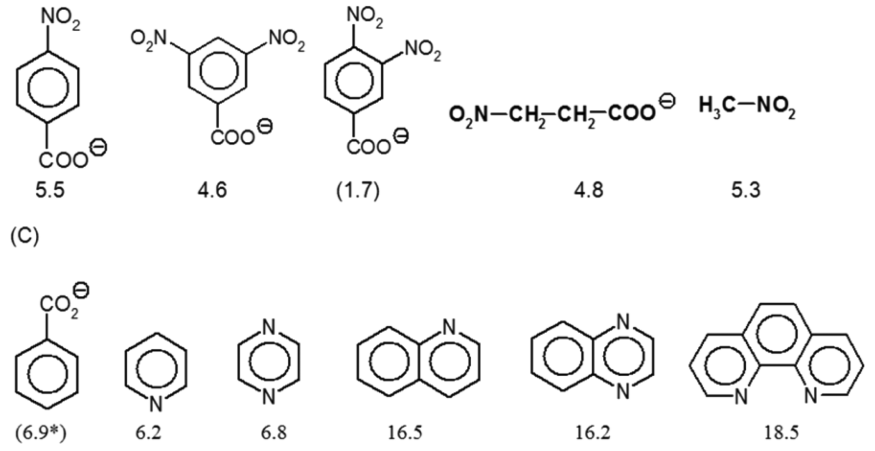

Figure 3. Additive $\Delta\Delta G_X$ increments in **TPyP** complexes for nitro substituents as an example and stacking ΔG values of heterocycles. Where applicable, ΔG = 5 kJ/mol is subtracted from the total ΔG_{PhX} for ion pair contributions of the parent acid (all ΔG values are in kJ/mol).

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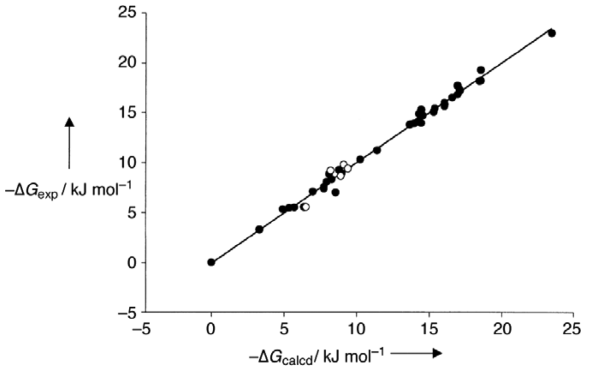

Figure 4. Additivity of $\Delta\Delta G_X$ increments: calculated versus measured complexation energies for 50 different complexes with porphyrins **TPyP** or **TPS** (see Figure 2); correlation slope m = 1.007, coefficient r = 0.996; filled circles, complexes with **TPyP**; open circles, complexes with **TPS**. Reproduced with permission from ref 16. Copyright 2002 VCH Wiley.

the large difference between different media and the inside of several host compounds.[15]

3. SEPARATION OF DISPERSIVE AND HYDROPHOBIC EFFECTS: EXPERIMENTAL DATA FOR VAN DER WAALS BINDING CONTRIBUTIONS OF DIFFERENT GROUPS

The fundamental problem of distinguishing solvophobic from dispersive effects has been solved for the first time by measurements with complexes of water-soluble porphyrins and a large variety of guest molecules.[16] The examples shown in Figure 2 demonstrate that in such associations between flat surfaces alkyl groups contribute binding energies below the error limit of 1 to 2 kJ/mol per methylene group, even though alkanes are expected to exhibit much larger hydrophobic effects than those of more water-soluble polar compounds. The barely measurable binding effects of alkane groups in water was recently confirmed by investigation with a molecular balance.[17] In

Table 1. Binding Free Energy Increments[a]

substituent R	α CH_3-R	ΔG (kJ/mol)	n
$-CH_3$	4.47	<0.5	4
$-CH(CH_3)_2$		0.6	1
$-CH{=}CH_2$	6.26	2.4	6
$-C{\equiv}C-$	6.18	2.6	1
−cyclopropyl		1.65	2
−phenyl	12.3	8.3	6
−pyridyl		6.4	5
−F	2.97	0.3	3
−Cl	4.72	1.65	5
−Br	5.7	2.4	4
−I	7.97	2.95	3
$-NH_2$	4.0−4.7	0.9	1
$-OCH_3$	5.16	1.75	3
$-COOCH_3$	6.94	3.1	1
$-COCH_3$	6.35	3.15	1
$-SCH_3$		2.8	1
−CN	4.45	2.6	2
$-NO_2$	7.37	4.95	5
$-CONH_2$	5.67	2.85	5

[a] $\Delta\Delta G$ (kJ/mol) of different groups R and molecular polarizability α of corresponding methyl derivatives CH_3-R. Binding contributions $\Delta\Delta G$ of functional groups R in complexes with porphyrins **TPyP** or **TPS** (see Figure 2; n, number of underlying systems/observables; polarizabilities α of MeR compounds in [10^{-24} cm^3][23]).

contrast, hydrophobic contributions can be quite large in complexes with receptors containing cavities: the release of high-energy water molecules inside such cavities[6] is essentially responsible for very high affinities, e.g., in cucurbituril complexes.

On the basis of measurements with a variety of substituted compounds, consistent $\Delta\Delta G$ increments with negligible deviations were obtained. For instance, $\Delta\Delta G$ values for a single nitro group in nitromethane, 2-nitropropionic acid, and different nitrobenzoic acids were in the narrow range of (5 ± 0.5) kJ/mol

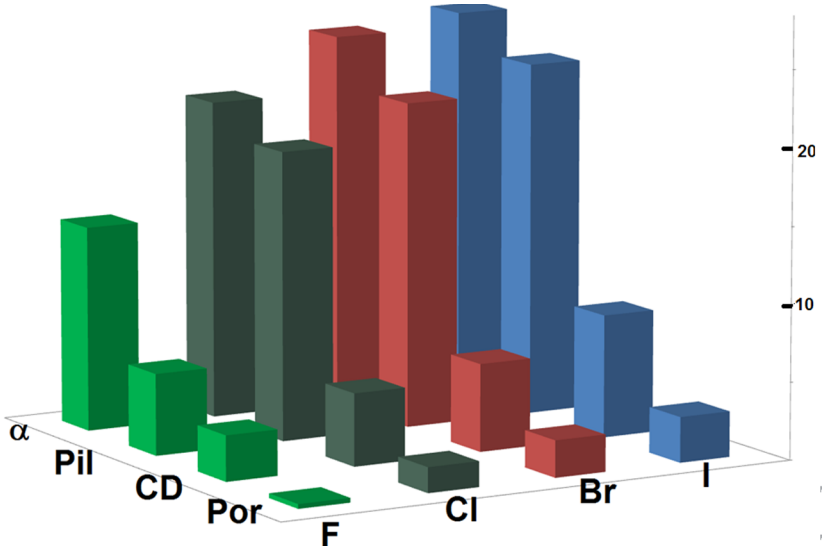

Figure 5. Affinities (ΔG in kJ/mol) of halogen derivatives with porphyrins (Por; $\Delta\Delta G$ increments, Table 1), α-cyclodextrin[20] (CD), and pillarene[21] (Pil) and polarizabilities α (relative values) of corresponding compounds MeR.

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as the average from all four measured systems (Figure 3). *o*-Dinitrobenzoic acid deviates from this due to steric hindrance between neighboring nitro groups, which prohibits the flat-to-flat interaction that is visible in NMR spectra of the other complexes. Very similar free energy increments were observed for complexes with the negatively charged porphyrin **TPS** and ligands bearing a positive charge (Figure 4). Noticeably, even the cyclopropane carboxylic acid exhibits a larger affinity than, e.g., butanoic acid, which reflects the sp^2 character of cyclopropane bonds with a correspondingly larger polarizability (overview, Table 1). The observed large binding contribution with thio-derivatives is in line with the known importance of sulfur$-\pi$ interactions in proteins; our $\Delta\Delta G$ = 2.8 kJ/mol value from interactions with the large porphyrin moiety **TPyP**[16] is not far from the interaction between methionine and smaller aryls such as phenylalanin or tryptophane observed with peptide hairpins, up to −2.1 kJ/mol, as determined by double mutant cycles.[18] Large and additive binding contributions by amide functions are also visible in complexes of oligoglycins with a porphyrin host.[19]

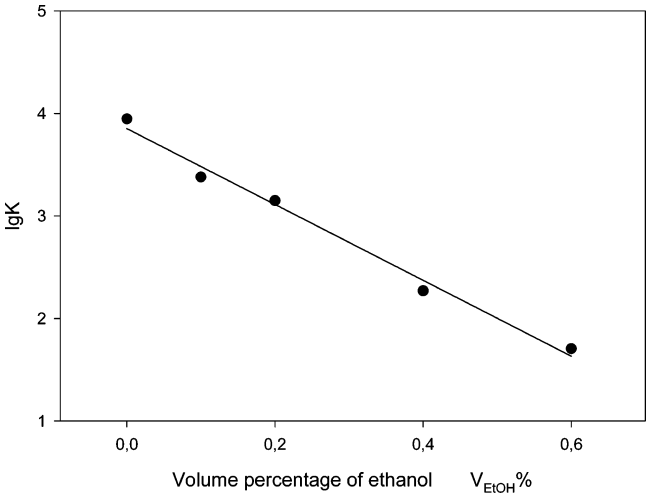

Figure 6. Solvent effect: association constants (log K) of 3,5-dinitrobenzoate with **TPyP** in water/ethanol.

4. DISPERSION FORCES AS THE ORIGIN OF THE OBSERVED INTERACTIONS

How can we identify the binding mechanisms involved in the porphyrin complexes? First, one can be sure that the binding of all ligands with heterosubstituents is not due to solvophobic effects, as even alkanes show no significant binding. Second, electrostatic contributions can be ruled out on the basis of the data observed with halogen derivatives. The affinities increase distinctly from fluorine to iodine as substituent not only with porphyrin complexes but also with cyclodextrin[20] and pillarene complexes,[21] in line with the increase in polarizability (Figure 5). Polar interactions would predict the opposite, in view of the different halogen electronegativities. Noticeably, for cyclodextrin complexes, the increase of ΔG from F to I is also opposite the order expected for a polar interaction between the halogen and the C−H bonds inside cyclodextrin. Furthermore, the π surface of the porphyrins bears a negative partial charge, favoring association with ligands bearing positive partial charges, which is not seen in the experiments. In particular, with noble gas complexes (see Section 5), polar contributions can be excluded.

Polarizability seems to be the decisive factor, with an increase in the order F < Cl < Br < I. This is supported by a rough correlation between binding contributions of different groups R as a function of molecular polarizabilities α of MeR,[22] although the correlation shows considerable scatter due to neglecting the varying distance between the binding partners. The decrease in the binding constants with increasing ethanol content in aqueous mixtures (Figure 6) also is at variance with electrostatic binding, as this is expected to show an inverse dependence.

5. STACKING AND DISPERSIVE INTERACTIONS IN SELECTED SUPRAMOLECULAR COMPLEXES

Many supramolecular complexes show a signature of dispersive binding contributions, particularly if aryl parts are involved, such as for fullerenes with an exceptionally high polarizability.[24] In contrast to what is often believed,[25] dispersive and not electrostatic effects seem to be the major stabilizing factor in $\pi-\pi$ and C−H$-\pi$ interactions.[26] Substituent effects in π stacking can be explained solely in terms of direct interactions with the substituents.[27] Experiments with torsional balances including arene interactions seem to correlate with Hammett substituent constants; this was taken as another evidence for electrostatic interactions instead of van der Waals effects in C−H$-\pi$ interactions.[28] However, recent analyses, also based on experiments with torsion balances, indicate that the binding variations in these systems originate from direct local interactions between the substituent and the arenes.[29]

Unequivocal evidence for dispersive interactions is seen in cryptand complexes with noble gases and small organic compounds; in addition, maximum complexation in organic solvents is observed when the guest is in optimal contact with the surface of the host's inner cavity.[30] In aqueous solution, the presence of high-energy water inside the cryptand cavity[6] can also contribute to large binding constants, but the similar constants found in nonpolar solvents can be explained only by dispersive forces. It has been shown that cryptand **1** (n = 2), which has a spherical cavity of 81.5 A^3, binds chloroform (volume 72 A^3) with an occupancy factor of 0.886, corresponding to a closely packed crystal.[31] The large binding enthalpy of ΔH = −34 kJ/mol with ΔS = −67 J/(mol K) is comparable with the heat and entropy of crystallization of organic compounds. The same cryptand **1** (n = 2) binds xenon with a binding constant of $K = 3.9 \times 10^3$ M^{-1} in 1,1,2,2-tetrachloroethane. With a water-soluble triacetate-functionalized cryptophane derivative, a much higher affinity for xenon is observed (K = 33 000 M^{-1}).[32] Part of this dramatic increase can be ascribed to a hydrophobic effect of high-energy water[6] inside the cryptophane. With larger solvents such as 1,2-dichlorobenzene, a much higher association constant of $K = 2.6 \times 10^4$ M^{-1} between the cryptophane **1** (n = 3) and even chloroform was observed.[33]

Cavitand **2**, derived from an imidazole-containing cyclopeptide connected to a triphenylphosphane oxide unit, binds chloroform in a very slow process with $K = 1.4 \times 10^5$ M^{-1} in $C_2D_2Cl_4$ as solvent.[34] The extraordinarily high binding constant, which is about 100 times larger than the one with cryptand **1**, is due to the optimal fit of trihalomethanes to the trigonal bipyramidal cavity so that a multitude of dispersion interactions between the trihalomethanes and the cavity atoms is possible. An imploded cryptophane structure is observed in the absence of the cavity-filling ligand chloroform.

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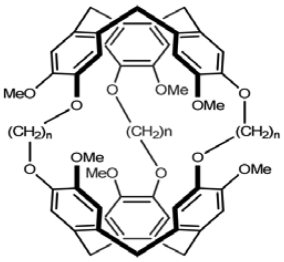

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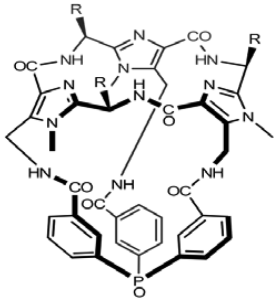

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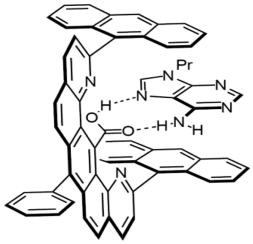

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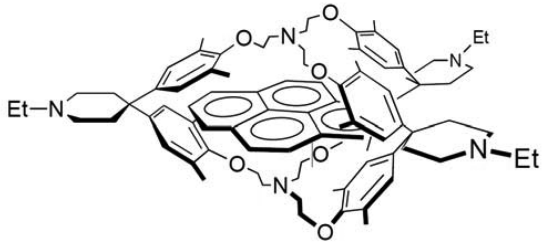

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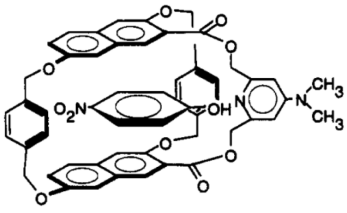


5

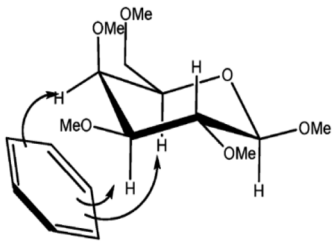
Stacking

Stacking between aromatic moieties is an often reported binding motif in supramolecular complexes, in which dispersive effects also dominate in solution; corresponding conclusions that also include edge-to-face orientations have been aptly reviewed.[35] Interactions of heteroarenes with porphyrins in water depend essentially on the size of the arenes, in line with their polarizabilities, and are rather independent of the presence or location of nitrogen within the rings.[36] The predominance of van der Waals over polar interactions is evident from the same affinities of nucleosides and nucleotides with some porphyrin receptors in spite of their positive charge.[37] The tweezer **3** represents an early example for stacking even in the polarizable medium chlorofom: the complexation with adenine exhibits, e.g., ΔG = 24 kJ/mol, and a comparison with the complex between adenine and butyric acid shows, for hydrogen bonding, ΔG = 13 kJ/mol, so the net stacking contribution amounts to about 12 kJ/mol.[38] Sizeable affinities were observed for complex **4**, ranging from 5 kJ/mol in CS_2 to 33 kJ/mol in trifluoroethanol; the dominating enthalpic contributions, obtained with calorimetry, were correlated with the solvent polarity and reflect both nonclassical solvophobic and dispersive contributions.[35] Complex **5** binds in chloroform *p*-nitrophenol with $K = 4 \times 10^5$ M^{-1}, an affinity much higher than expected for hydrogen bonding alone.[39]

Solvent-cohesive interactions, which are the basis of the nonclassical enthalpic hydrophobic effect, also rely to a large degree on dispersive interactions between solvent molecules, which are liberated upon complex formation; similar solvent-dependent driving forces have recently been identified with a molecular balance.[17]

C−H−π Interactions

C−H−π interactions are essentially dispersive in nature and bear the hallmark of enthalpy-dominated contributions, as corroborated also by *ab initio* calculations.[40] They play a significant role in protein−carbohydrate complexation, where axial C−H bonds of, e.g., pyranoses interact with aromatic amino acid residues.[41] The interaction of various pyranosides with excess benzene, as a model, has been found by calorimetry to exhibit up to ΔH = 132 kJ/mol; corresponding NMR analyses have indicated that arrangements such as **6** are typical, with three C−H bonds in contact with a benzene moiety.[42] Host **7** exhibits, with water as the medium, a remarkable binding constant of K = 56 M^{-1} for glucose, again essentially by C−H−π interactions.[43] Related to this, thermal denaturation studies with a 12-residue peptide containing tryptophane and a glucose side group in different positions indicated that folding of the hairpin was enthalpically favorable with ΔH = 25 kJ/mol and entropically unfavorable with ΔS = 70 J/(mol K), with a total of ΔG = 3.5 kJ/mol for a glucose−Trp interaction.[44]



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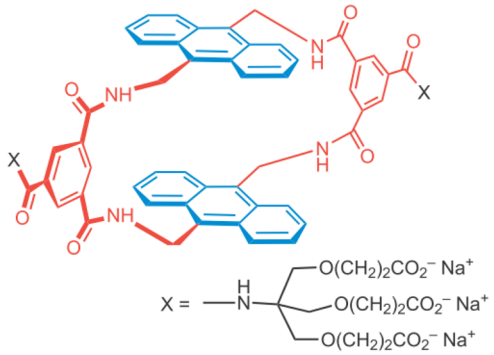

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Heteroatoms

Heteroatoms also interact with arenes by dispersive forces, primarily as a function of their polarizability. A search in the

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Cambridge Structural Database in combination with *ab initio* calculations indicated that interactions with halogens are primarily electrostatic but that there are also dispersive and charge-transfer contributions, with short halogen−oxygen distances in proteins and nucleic acids, especially for the highly polarizable iodine.[45] S−H groups interact stronger than O−H or N−H groups, in line with the larger polarizability; in addition, S−H groups can form more easily the even more active thiolate anion. Corresponding examples, which highlight polar and van der Waals contributions in artificial and biological complexes, have been aptly reviewed.[35] *Ab initio* calculations for complexes of methanethiol, as a model, for cysteine with an aromatic ring predicted a dispersive S−Ar contribution of around 10 kJ/mol.[46]

6. SELECTED PROTEIN COMPLEXES WITH DISPERSIVE INTERACTIONS

In enzymes, the sulfur atom in methionine side chains often interacts with adenine substrates or with cofactors such as ATP. The complex of a protein synthase and an aminothiazole inhibitor, with a binding affinity of 25 μM, shows not only a dispersive S···aryl interaction with methionine (Met138) but also stacking between the inhibitor phenyl ring with the backbone amide groups of Ala162 and Cys163.[35b,47] As illustrated in Figure 7, not only sulfur but also amide groups

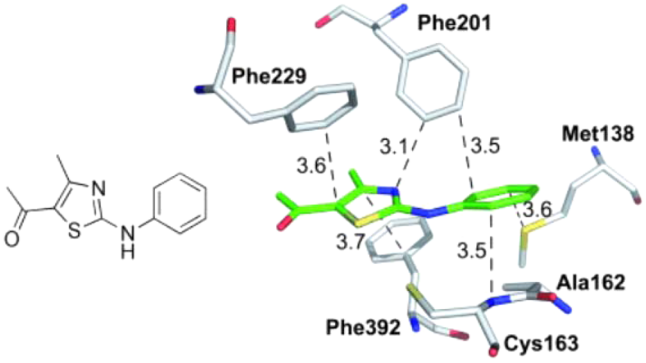

Figure 7. Example of multiple interactions with a dominant dispersive nature in a protein inhibitor complex (see text). Green parts indicate inhibitor thiazole and phenyl rings; typical distances are given in angstroms[35b] (based on X-ray structure,[47] resolution 1.35 Å, PDB code: 2VBA). Reproduced with permission from ref 35b. Copyright 2011 VCH Wiley.

exhibit large interactions with π sytems (as with porphyrins; see above) due to their increased polarizability.

Complexes of a serine protease factor and different phenylacetamide derivatives with a halogen R′ at the *para* position showed, in comparison to that when R′ = H, inhibition with a gain of 10.5 kJ/mol for R′ = Br and R = Cl but only 3.5 kJ/mol for R′ = F; the X-ray-structure shows the interaction of a chloro atom with the tyrosine aryl moiety (Figure 8).[48] Both *ab initio* calculations at the MP2/aug-cc-pVDZ level and results of CSD searches showed the absence of directional orientation, which indicates that dispersive forces are dominant and not an electrostatic binding contribution.

Thermal unfolding studies with an α-hairpin peptide bearing an N-terminal phenylalanine and halogen substituents on an opposing phenyl ring indicated an increasing stabilization of the hairpin, in the order F (0.5) < Cl (1.42) < Br (1.97) < I (2.26) (all $\Delta\Delta G$ values are in kJ/mol). The correlation with the halogen

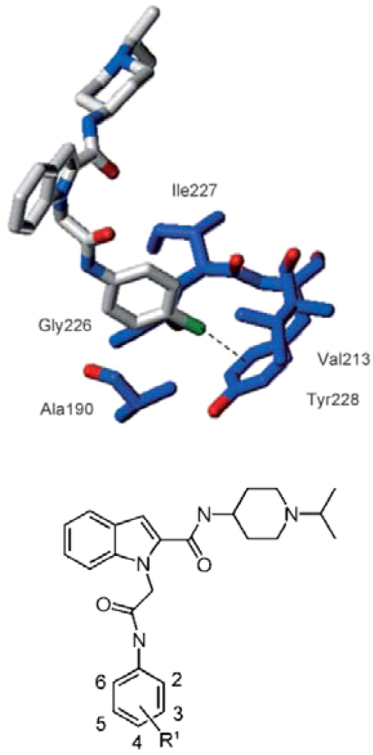

Figure 8. Dispersive interaction of an inhibitor's chloro atom with tyrosine's aryl moiety. Gray parts indicate inhibitor rings.[48] Reproduced with permission from ref 48. Copyright 2009 VCH Wiley.

polarizability and the enthalpic driving force, determined by the van't Hoff method, was regarded as evidence for a dominating dispersive force, although a C−H−Hal hydrogen-bonding alternative to the Hal−π interaction could not be excluded.[49]

7. CONCLUSIONS AND OUTLOOK

With the exception of pure alkanes, dispersive interactions represent perhaps the most frequent noncovalent binding force in organic complexes in solution, particularly in water. Experimental results unequivocally demonstrate the importance of intermolecular dispersive effects also in solution; opposite views were shown to be based on questionable arguments. At the same time, dispersive forces are quite difficult to describe through rigorous computation; significant progress has been made by using terms that take care of electron correlation on the basis of empirical data. Identification of such van der Waals contributions requires their separation from hydrophobic interactions, which are also maximized in water. Distinction from polar forces can be supported by structural characterization, including the directionality of the interaction. More experimental studies are needed before one can reach a firm general basis for deriving corresponding interaction energy contributions; in the future, these could provide general group contribution scales, as are available for hydrogen bonds.[50] Such experimentally secured data in the form of scoring functions can play a significant role in the understanding of biological assemblies and in the design of new receptors or of biologically active compounds. In the future, analyses of solvent effects will be of help here; the different polarizabilities of the medium and of the receptor cavity should also be evaluated. Complexes where both partners have an increased polarizability should lead to particularly stabilized host−guest assemblies.

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