Selectivity in supramolecular host–guest complexes†

Hans-Jörg Schneider*[a] and Anatoly K. Yatsimirsky*[b]

The background of possible selectivity–affinity correlations and their limitations is reviewed, with typical crown ether and cryptand complexes, ionic associations, hydrogen bonded complexes and complexes driven by van der Waals, stacking or hydrophobic interactions, with some additional topics including associations based on metal coordination as supplementary material. This *tutorial review* is addressed to students and researchers interested in molecular recognition, and relates to the design of sensors, of discriminators for separation processes, of supramolecular devices and of drug compounds. A theoretical analysis of selectivity in supramolecular host–guest complexes, defined as a difference in binding free energies for structurally related guests, as a function of total binding free energy shows that for certain types of intermolecular interactions one may observe a correlation between selectivity and affinity. Such correlation fails however if the selectivity is due to additional interactions at a secondary binding sites, which is expected in complexes with anisotropic guest molecules. Several clear examples of theoretically expected selectivity–affinity correlations are found. The influence of reaction conditions on the experimentally observed selectivity, defined as a difference in complexation degrees with different guests in the presence of added receptor, is illustrated. The importance of often neglected solvent effects on selectivity is exemplified with ionophore and hydrogen bonded complexes.
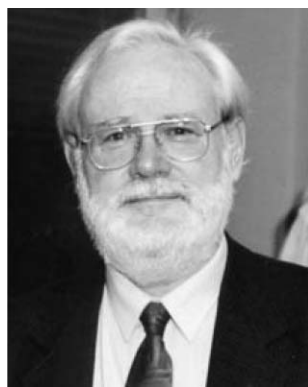
1 Introduction/aims/scope

High selectivity is a hallmark of biological receptors, and has always been a most important aim of synthetic supramolecular chemistry.[1] At the same time high affinity, which ensures high sensitivity for a chosen analyte or reagent, is an equally significant goal. The importance of possible correlations between affinity and selectivity has only recently been emphasized,[2] and will be a major focus of the present review, as well as the consequences of multivalency in supramolecular complexes. The underlying principles are relatively well understood for complexation of metal ions,[3] although questions regarding *e.g.* the role of enthalpic *vs.* entropic contributions remain open. Aspects of selectivity in metal complex formation related to strain and stress induced by complexation as well as to fit and misfit between interacting components have been already reviewed.[4] In this review we will discuss typical examples of host–guest complexes, arranged according

[a]*FR Organische Chemie, Universität des Saarlandes, D 66041 Saarbrücken, Germany. E-mail: ch12hs@rz.uni-sb.de*
[b]*Facultad de Química, Universidad Nacional Autónoma de México, 04510 México D.F., México. E-mail: anatoli@servidor.unam.mx*
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Hans-Jörg Schneider studied in Munich, Berlin and Tübingen, where he obtained his PhD degree in 1967. After two years as postdoctoral researcher at the Univ. of California, San Diego he worked on his habilitation and in 1972 became Professor at the Universität des Saarlandes. His research concerned stereochemistry, mechanisms of organic reactions, NMR spectroscopy, and later supramolecular chemistry, including receptor and enzyme mimics, more recently also molecular recognition in chemomechanical polymers. He is the author of 250 publications, including several monographs and book contributions.

Hans-Jörg Schneider

Anatoly K. Yatsimirsky has obtained PhD and DrSc degrees from Moscow State University, where he was Professor until 1992. Since 1992 he has been a Professor of the National Autonomous University of Mexico. His research interests are in bio-organic chemistry and metal complex catalysis. He is the author of 160 publications including a monograph on supramolecular chemistry and book contributions.

Anatoly K. Yatsimirsky

to their interaction mechanism. Space limitations do not allow us to discuss many other approaches to highly selective and strong associations, in particular on the basis of metal coordination complexes[5] (for more examples and illustrations see ESI†).

The mechanistic basis for a most selective molecular recognition poses many problems, which will be addressed in the present review. In traditional supramolecular chemistry selectivity is characterized by the hole-size fitting concept;[1] which, however, requires significant modifications. As has been shown in particular with coordination complexes an optimal affinity is reached if bonds between transition metal ions and the donor functions are formed with a minimum of strain energy.[3,4] Another limitation is that due to solvation and likely entropic factors a higher binding constant is often observed if the guest molecule enjoys more freedom, and occupies only part of the space inside a host cavity.[6] The design of suitable host geometries can be significantly supported by calculational approaches.[7] The until now scarcely investigated dependence of selectivity on the reaction medium will be another focus of this review as well as the often overlooked fact, that in complexes where protonation plays a significant role, the experimentally observed selectivity depends on the pH used in the competitive recognition experiments. A few examples will serve to illustrate co-operativity effects in allosteric and co-complexation systems. The strong dependence of selectivity on the nature of the underlying non-covalent forces will be highlighted with host–guest complexes from the literature. It is hoped, that the overview will help not only the rational design of highly selective synthetic receptors, but also support the understanding of biological systems. Although the selectivity aspect is always considered in reviews and monographs on supramolecular chemistry, it rarely has been a subject of a special discussion.[8] The obvious importance of this aspect for the design of sensors, of discriminators for separation processes, of many supramolecular devices and last not least of drug compounds justifies an attempt to highlight the basic principles and possible new approaches in this area.

2 Some theoretical considerations on affinity–selectivity correlations and their limitation

For reaction of a receptor R with either ligand X or ligand Y, with equilibrium constants K_{RX} and K_{RY} one can write the familiar expressions (1) and (2)

$$K_{RX} = \exp(-\Delta G_{RX}/RT) \qquad (1)$$

$$K_{RY} = \exp(-\Delta G_{RY}/RT) \qquad (2)$$

The selectivity now can be expressed by eqn (3).

$$K_{RX}/K_{RY} = \exp[(\Delta G_{RY} - \Delta G_{RX})/RT] \qquad (3)$$

Since with larger absolute values of interaction free energies one also may expect to observe larger differences between them, in most general terms one may expect increased selectivity with increased affinity. However, this depends also

on the way in which a change in receptor or ligand structure or a change in reaction conditions affects the ΔG values. For several types of intermolecular interactions the binding free energy (or log K) can be expressed as a product of certain physicochemical properties (P) of receptor R and ligand L, eqn (4).

$$\Delta G_{RL} = aP_R P_L + b \qquad (4)$$

This is true for ionic association, where P_R and P_L are charges of receptor and ligand, for hydrogen bonding, where P_R and P_L are e.g. acidity and basicity parameters of H-donor and H-acceptor groups of receptor and ligand molecules, and in a more complicated form for Lewis acid–base (metal–ligand) interactions. Combining eqn (3) and (4) one obtains following expressions for selectivity.

$$\Delta G_{RY} - \Delta G_{RX} = aP_R(P_Y - P_X) \qquad (5)$$

$$K_{RX}/K_{RY} = \exp[aP_R(P_Y - P_X)/RT] \qquad (6)$$

Obviously, for a given pair of ligands X and Y the ratio of binding constants will increase for receptors possessing larger P_R values and larger affinity to both ligands.

Most synthetic and biological receptors are polydentate; the total binding free energy then is usually the sum of single interaction energies. This additivity principle has been shown to be valid for large number of supramolecular complexes including ion pairing, hydrogen bonds and van der Waals forces as intermolecular binding contributions, provided of course that the interacting functions are in a geometrically matching position.[9] An important particular case of this situation is involvement of a number n of the same type of interactions provided by a multidentate receptor for binding of a given ligand. In this case one obtains the following expression for ΔG_{RL}:

$$\Delta G_{RL} = n\Delta\Delta G_i \qquad (7)$$

where $\Delta\Delta G_i$ is the pairwise binding free energy increment. Obviously these increments will be different for ligands X and Y, so one obtains for the free energy difference and for the ratio of binding constants expressions (8) and (9) respectively.

$$\Delta G_{RY} - \Delta G_{RX} = n(\Delta\Delta G_{iY} - \Delta\Delta G_{iX}) \qquad (8)$$

$$K_{RX}/K_{RY} = \exp[n(\Delta\Delta G_{iY} - \Delta\Delta G_{iX})/RT] \qquad (9)$$

Since n is a property of the receptor R, eqn (8) and (9) apparently are similar to (5) and (6), and predict an increase in selectivity by multivalency on the basis of a total binding free energy increase.

Almost perfect correlations between selectivity and affinity in terms of eqn (8) and (9) can be seen for example in simple coordination complexes with linear polyamine ligands, Fig. 1.

An important limitation of a selectivity–affinity correlation stems from the often valid situation, that a host provides for a primary interaction site which may secure a high affinity to the guest through the binding to a complementary guest
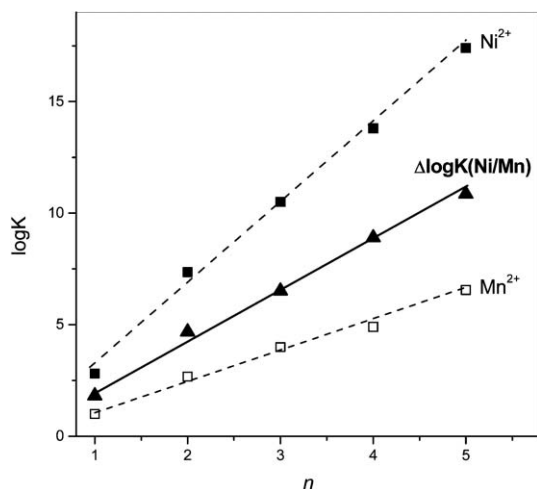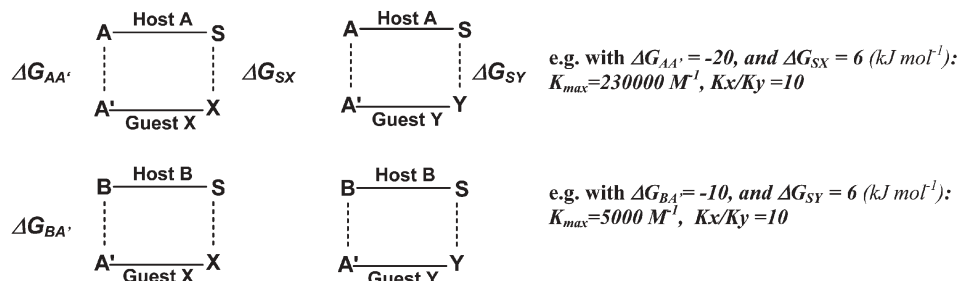
Fig. 1 Logarithms of stability constants of Mn^{2+} and Ni^{2+} complexes with linear polyamine ligands $H_2N(CH_2CH_2NH)_{n-1}H$ as a function of total number n of nitrogen donor atoms. As n increases from 1 to 5 the selectivity of binding of Ni^{2+} over Mn^{2+} increases in terms of K_{Ni}/K_{Mn} by nine orders of magnitude.
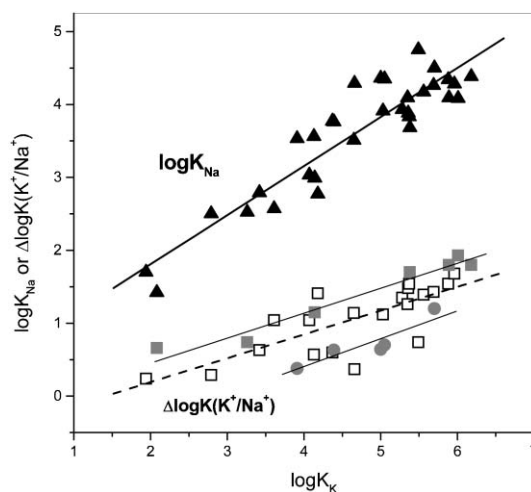

Fig. 2 Correlations between logarithms of stability constants of complexes of 18-C-6 derivatives with Na^+ and K^+ in methanol at 25 °C. Solid triangles – stability constants for Na^+ vs. K^+; open and grey symbols – differences in log K values for these cations, grey squares – only aliphatic derivatives, grey circles – only benzo-crowns. Experimental data from ref. 10.

interaction site A', and a second, often geometrically distant site S, which secures the selectivity. Scheme 1 illustrates that if two guest molecules guest X and guest Y feel with primary host site A or B different interaction energies $\Delta G_{AA'}$ and $\Delta G_{BA'}$, but the same ΔG_{SY} at the discrimination site S, that the selectivity ratio K_X/K_Y can be the same, even if the total binding constants may differ enormously. Many host systems used for the discrimination of anisotropic guest molecules do make use of at least two different interaction sites, for which reason we can expect mostly for simple isotropic systems such as metal cations or halide anions a linear correlation between selectivity and affinity of complexation.

3 Crown ether and cryptand complexes: hole size fitting and other effects

The theoretically expected simultaneous increase of selectivity and affinity is rarely seen in quantitative terms with receptors of variable structures, but can be often observed in limited series of structurally similar hosts, as will be illustrated below. We start these analyses with the historically oldest supramolecular complexes between alkali cations and crown ethers or cryptands.
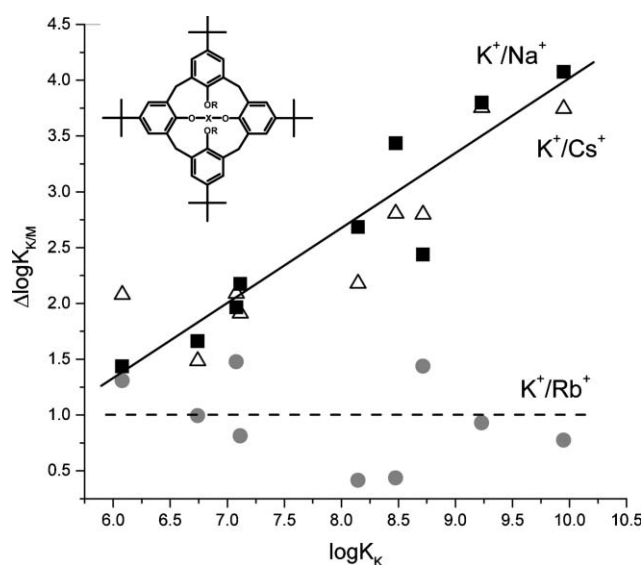
Fig. 2 (solid triangles) shows the linear correlation between the formation free energies of complexes with K^+ against those with Na^+ for 32 ionophores derivatives of 18-C-6 in MeOH taken from ref. 10 The slope 0.67 $\pm$ 0.05 ($R = 0.918$) of the correlation reflects just the intrinsic affinity differences between these cations with any receptor. In gas phase associations[11] between parent cation acceptor molecules both the ΔG values for Na^+ and K^+ associations and the differences $\Delta\Delta G$ between them are much larger due to the absence of competing solvents. Thus, dimethyl ether with K^+ shows $-\Delta G = 50$ kJ mol^{-1}, with Na^+ 74 kJ mol^{-1} ($\Delta\Delta G = 24$ kJ mol^{-1}); for dimethyl ethylene glycol the values are for K^+ 90, for Na^+ 133 kJ mol^{-1} ($\Delta\Delta G = 44$ kJ mol^{-1}; ΔG data are mostly calculated from published[11] ΔH and ΔS values). This emphasizes the theoretically expected effect of large total binding free energy on the selectivity. In the condensed phase the difference is by orders of magnitude smaller, and is reversed (see Section 9: Solvent effects).

The ΔG variations in crown ether and cryptand complexes are due to differences in the electron donor capacity C_D of the heteroatoms, which can be characterized by measurements of related hydrogen bond associations. It has been shown that

Scheme 1 Host–guest complexes with separate binding sites for high affinity (A–A' or B–A') and for selectivity (S–X or S–Y). The same selectivity will be observed with either large total binding constants (upper case), or smaller binding constants (lower case).

Fig. 3 Selectivity $\Delta \log K$ with calixarene-crown ether complexes ($X = CH_2CH_2(OCH_2CH_2)_n$ $n = 3$ or 4, R = Me, Et, n-C_3H_7, i-C_3H_7 or $CH_2C_6H_5$), for K^+ $vs.$ Na^+ (squares), for K^+ $vs.$ Cs^+ (triangles), and for K^+ $vs.$ Rb^+ (circles); experimental data from ref. 12.

e.g. the stability of K^+ complexes with all such ionophores correlate with the sum $\sum C_D$ with very little scatter.[9a] From this point of view one may expect the K^+/Na^+ selectivity to correlate with affinity, *e.g.* expressed as $\log K_K$. Indeed, such correlation exists (dashed line in Fig. 2, slope 0.33 ± 0.05, $R = 0.747$); if one chooses series of more closely related ligands, *e.g.* only aliphatic derivatives (grey squares) or only benzo-derivatives (grey circles) the correlations become much less scattered. On the other hand an attempt to correlate results for crown ethers of different sizes and in different media did not show any tendency of increased selectivity for hosts with higher affinities (see ESI†).

A fairly linear correlation between selectivity and affinity is observed with structurally related calixarene-based ionophores.[12] These hosts show approximately constant discrimination factor of 10 between the best fitting cations K^+ and Rb^+ (dashed line in Fig. 3), but one observes the theoretically expected linear correlation for complexation selectivity of K^+ $vs.$ the smaller Na^+ and larger Cs^+ ions (solid line in Fig. 3).

4 Ion pairs in aqueous medium

4.1 Selectivity by charge differences

It has been demonstrated that equilibrium constants for a large number of ionic association reactions in water can be satisfactorily fitted to the eqn (10) where z_R and z_L are total charges of R and L[13]

$$\log K_{RL} = az_R z_L + b \tag{10}$$

Parameters a and b vary for different types of charged species, *e.g.* they are different for inorganic anions and carboxylates, but within a series of given chemical species eqn (10) provides a reasonably good correlation. Alternatively
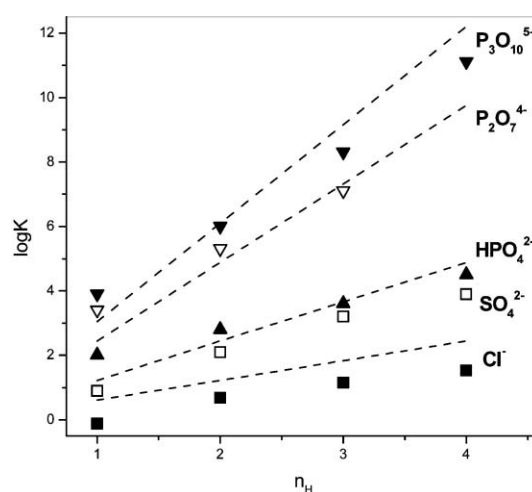
Fig. 4 Logarithms of binding constants of different anions to protonated forms of spermine in water at zero ionic strength;[13] n_H is the number of protons bound to spermine; dashed lines are theoretical profiles calculated in accordance with eqn (10) for anion charges 1, 2, 4 and 5.

the free energy of association can be estimated by multiplication of a constant binding increment of -5.5 kJ mol^{-1} (at ionic strength 0.1 M) by the number of all pairwise ionic contacts between R and L.[9a] The expression for selectivity which follows from eqn (10) and (5) takes the form of eqn (11).

$$\Delta \log K_{RL} = az_R(z_Y - z_X) \tag{11}$$

This provides perhaps the simplest case of selectivity when ions of different charges can be differentiated by Coulombic interaction with oppositely charged receptor, where the degree of differentiation increases with the increase in receptor charge. Obviously, ions of similar charge ($z_Y = z_X$) are not expected to be discriminated in this way.

Fig. 4 shows the experimental results for ion association of five inorganic anions with differently protonated forms of spermine, which follow eqn (10) with $a = 0.612$ and $b = 0$ (dashed lines). As expected, the separation between binding constants for *e.g.* tripolyphosphate pentaanion and hydrogenphosphate dianion increases from $\Delta \log K = 1.9$ to 6.6 on going from monoprotonated to tetraprotonated spermine (the $\Delta \log K$ values predicted from eqn (11) are 1.8 and 7.3, respectively).

4.2 Shape selectivity and dependence of experimentally observed selectivity on pH and on concentrations

Classical examples for selective binding due to shape differences between spherical and non-spherical anions, or between dicarboxylic acids of varying length, mainly due to Lehn *et al*, can be found in recent books[1] and reviews, particularly on anion complexation.[14]

In spite of low directionality of charge-charge interactions, significant shape selectivity can be observed in recognition of ionic compounds in sufficiently rigid systems. The results for recognition of a series of tricarboxylates **1–5** by protonated forms of the macrocycle **6** illustrate this point.[15]
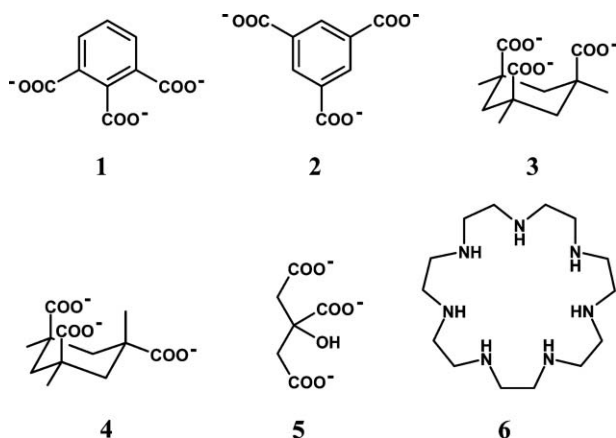
Fig. 5 shows the logarithms of stability constants for complexes of trianions with increasingly more protonated forms of the macrocycle. Plots are roughly linear with positive slopes, but for a given degree of protonation of the macrocycle the constants are significantly different in spite of the similar charge of all guest anions. Binding of all rigid anions is stronger than that of the flexible citrate (**5**) and the discrimination between anions becomes more pronounced on increase in the macrocycle charge, again in accordance with expected selectivity–affinity correlation.

Molecular modeling confirmed that the shape selectivity arises here from different degree of matching between carboxylate and ammonium groups. Several other systems for selective ion pairing with isomeric polycarboxylates based on the same principle have been reported.[15]

Further search for a more efficient receptor for citrate (**5**) lead to development of a C_3-symmetric tricationic host **7**, which binds citrate with log $K_{assoc} \approx 5$ in water, but lacks the shape selectivity and does not discriminate rigid and flexible guests: binding constants for trianions **1**, **3** and **5** decrease in the order **1** > **5** > **3**, but vary just within a factor of three.[16]

Discrimination of polyatomic anions such as carboxylates, phosphates, sulfate *etc.* in water is usually achieved by hosts with complementary and geometrically matching cationic functions as illustrated by a recent example of recognition of anions by a dicopper complex of cryptand **8**, $[Cu_2^{II}(8)]^{4+}$, Fig. 6.[17] Although in this case the cationic sites are created by a transition metal ion, affinities of anions do not follow stability constants of their Cu(II) complexes. Also, basicity, shape and size of anions are not important factors. The best correlation is observed with the "bite length" of anions defined as a distance between two terminal donor atoms of the anion. Anions with bite length, which fits the distance between two Cu(II) ions in axial positions of the cryptand in its most stable conformation show the highest affinities.
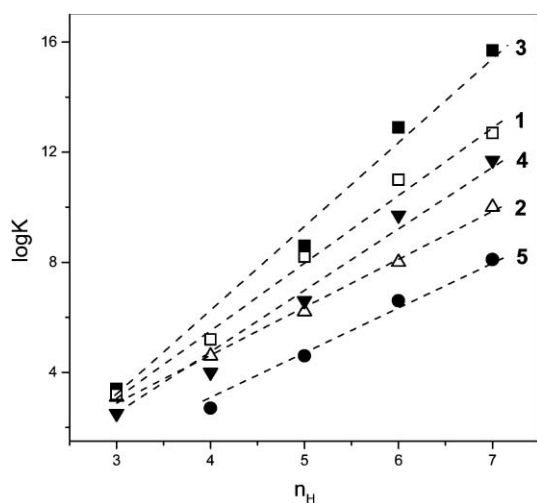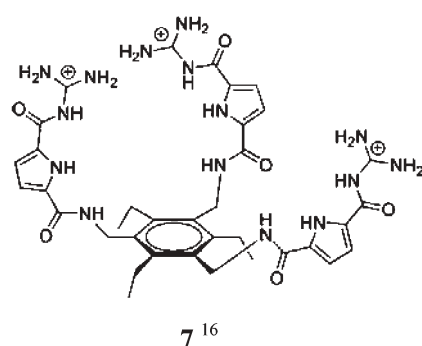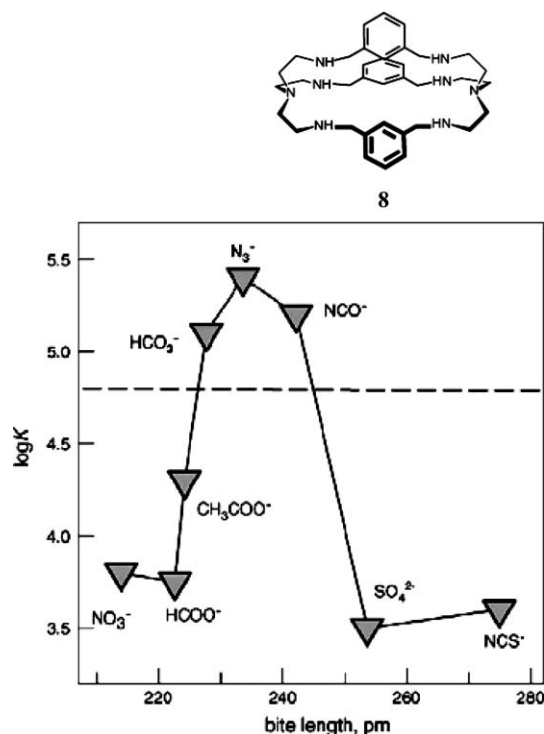

Fig. 5 Logarithms of stability constants (25 °C, 0.15 M NaClO₄) for complexes of trianions **1–5** with protonated forms of **6** vs. number of protons n_H bound to the macrocycle.[15]

Fig. 6 Selectivity of anion binding by cryptate $[Cu_2^{II}(8)]^{4+}$ in water.[17] Reprinted from V. Amendola, M. Bonizzoni, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, F. Sancenón and A. Taglietti, *Coord. Chem. Rev.*, **250**, 1451, Some guidelines for the design of anion receptors, Copyright (2006), with permission from Elsevier.

9 [14d]
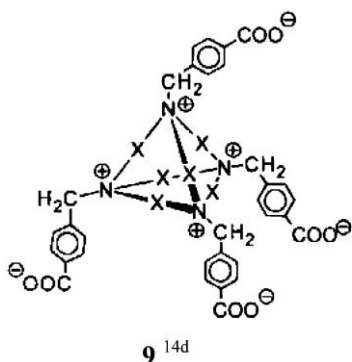
The confined space in macrocyclic hosts such as **9** (X = (CH$_2$)$_n$, n = 6 or 8) lead to stable complexes with halides and with cyanide (K [in M^{-1}] Cl = 270; Br = 2150; I = 6500) in water, where bromide and iodide binding is enthalpically driven.[14d]

Selective complexation of natural carbohydrates poses particular problems,[18] as hydrogen bonding is very weak in water and needs help by ion pairing. In 30% water in DMSO glucuronic acid **10a** binds with the host **7** with K_{assoc} = 480 M^{-1}, the isomeric galacturonic acid **10b** binds three times stronger; with sugar phosphates instead of carboxylate the associations become much stronger, but any selectivity disappears.[16b]

10a   **10b**
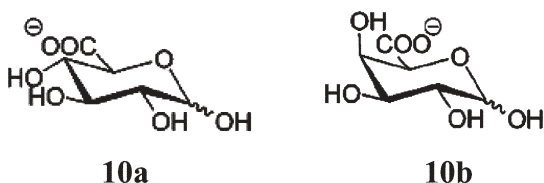
An interesting aspect related to systems as discussed above is the question of the experimentally observed selectivity in terms of actual proportion of complexed to uncomplexed substrate or analyte as a function of pH and of host concentrations. We will first address the influence of pH on actual affinities, which plays a significant role if the charge of either cation or anion, or of both, depend on the degree of protonation. Results in Fig. 5 show that the binding constants for *e.g.* isomers **3** and **4** differ by two to four orders of magnitude and those for **4** surpass those for citrate by the same factor starting from pentaprotonated macrocycle. However, this does not mean that the fractions of bound anions at a given pH will differ by the same factors because all three anions have different basicities (pK_a of the monoprotonated forms of anions **3–5** equal 7.3, 6.9 and 5.4, respectively) and in the acid medium necessary for the macrocycle protonation each anion will be protonated to a different degree. A better parameter is the so-called apparent or conditional stability constant K_{app} defined in terms of total bound and free concentrations of components (A is the anion and R is the macrocyclic receptor):[15]

$$K_{app} = \frac{\sum [H_{i+j}RA]}{(\sum [H_iA])(\sum [H_jR])} \quad (12)$$

The calculated values of K_{app} for anions **3–5** are plotted *vs.* pH in Fig. 7.[19] Under conditions when the complexation
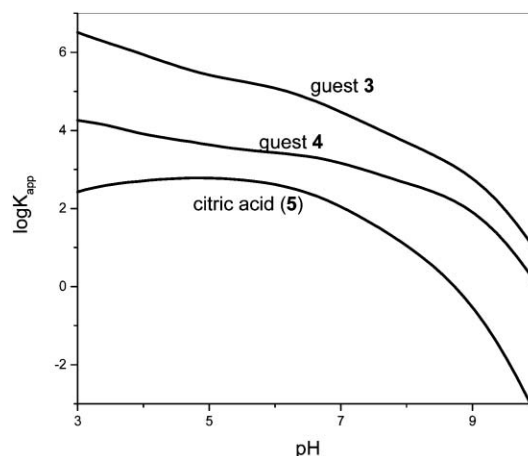

Fig. 7 Calculated values of K_{app} (see eqn (12)) for anions **3–5** and host **6** *vs.* pH.
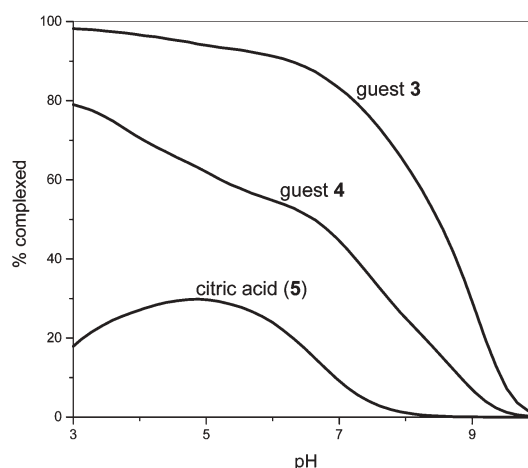

Fig. 8 Percentage of the bound guest to **6** *vs.* pH at total concentrations of guest and the macrocycle 1 mM.

degree is directly proportional to the binding constant the selectivity is just the ratio of K_{app}, *e.g.* at pH 4 the selectivity for **3** *vs.* **4** is 100, and for **3** *vs.* **5** it is 1500.

It is often overlooked that the *concentrations* used in an experiment always influences the actual proportion of complexed to free analyte. The complexation degree generally is not directly proportional to the binding constant. Under conditions of low concentrations, where such proportionality does exist, one finds only a small fraction of the bound ligand, which will then reduce the determination sensitivity of the analyte. Fig. 8 shows the pH-profiles of the complexation degree for 1 mM solutions of the same three anions in the presence of 1 mM **6**, which is a sufficiently high receptor concentration for nearly quantitative binding of **3** at low pH. Evidently the real discrimination is significantly poorer than one would expect on basis of K_{app} because other anions also are bound to the receptor by 20–70%.

5 Ion pairs in non-aqueous medium

The implementation of ionic sites into organic residues allows one to obtain in non-aqueous media larger affinities, which,

| Anion	Host 11a³⁺, log K	Host 11b³⁺ logK
F⁻	6.2	5.0
Cl⁻	3.2	>7
Br⁻	2.5	6.6
NO₃⁻	2.6	5.6
I⁻	<2	4.5
AcO⁻	4.7	4.4

Scheme 2 Anion complexes in acetonitrile.[14b] (For F⁻ and AcO⁻ anions log *K* values only for the 1 : 1 complexes are shown here, see text).

however, do not necessarily lead to higher selectivities. The cationic receptors **11a,b**, Scheme 2, show a moderate preference for chloride over bromide. The more basic anions F⁻ and CH₃COO⁻, when present in excess, induce deprotonation of the pyrrole NH groups, and also therefore lead to equilibria with other stoichiometries than 1 : 1. Since the larger Cl⁻ anion can in contrast to the small F⁻ anion approach all three cationic residues the trifurcate host **11b** is exceptional by its distinct preference for chloride over fluoride.[14b]

12 [20]   **13** [21]
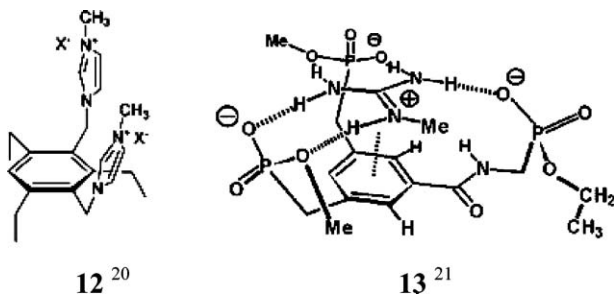
Ion pairing with the imidazolinium host **12** leads in DMSO to the surprisingly large value of K_{Cl}/K_{Br} >74, with $K = 740$ M⁻¹ for Cl⁻.[20] The guanidinium receptor **13** uses three phosphonate acceptor groups to bind with high selectivity *e.g.* the side group of arginin.[21]

Ditopic receptors can make use of additional interactions between two different guest compounds entrapped in a host, which in particular with binding of salts leads to increased selectivity (Scheme 3)[14,22] Thus, the host **14** binds Na⁺ and K⁺ as tetraphenylborates in DMSO with similar affinities (5 and 8 M⁻¹, respectively), but addition of Bu₄NCl increases binding constant for K⁺ to 340 M⁻¹, and that for Na⁺ only to 25 M⁻¹ creating a more than 10-fold differentiation between the

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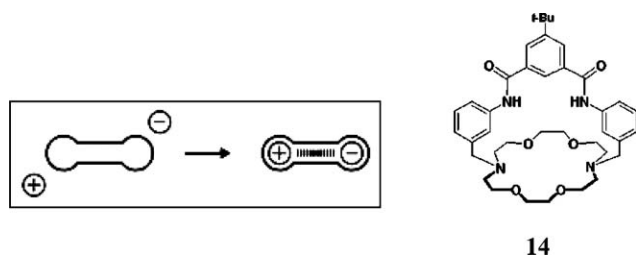
Scheme 3 Example of a ditopic receptor for ionic compounds.[22d]

cations.[22d] The reason for this effect is that the smaller chloride fits into the receptor cavity, providing additional electrostatic attraction to the cation, but the effect is much smaller for sodium because binding of this cation changes the conformation of azacrown in such way that oxygen atoms of the macrocycle approach the chloride creating significant ion–dipole repulsion.

6 Hydrogen bonded complexes

Interactions between species possessing H-donor D and H-acceptor A sites can be described quantitatively in terms of eqn (9) or (10) derived for CCl₄ solutions.[23]

$$\Delta G_{RL} = 2.43 C_A C_D + 5.70 \qquad (13)$$

$$\log K_{RL} = 7.354\alpha_2^H \beta_2^H - 1.094 \qquad (14)$$

If receptor is *e.g.* a proton donor the selectivity for ligands with proton acceptor sites will be given by eqn (15) or (16).

$$\Delta\Delta G_{RL} = 2.43 C_D(R)\{C_A(X) - C_B(Y)\} \qquad (15)$$

$$\Delta\log K_{RL} = 7.354\alpha_2^H(R)\{\beta_2^H(X) - \beta_2^H(Y)\} \qquad (16)$$

Thus discrimination between basic ligands will increase on going from receptor bearing an aliphatic OH group ($\alpha_2^H = 0.4$) to receptor bearing a carboxyl group ($\alpha_2^H = 0.6$) by a factor of 1.5 in terms of $\Delta\log K_{RL}$ according to eqn (16).

Donor groups such as amides, ureas *etc* allow to construct host compounds in which affinity and selectivity can be controlled by the number of interactions and the size of the host cavity, analogous to the ionic complexes in aqueous media which we discussed above. In addition, hydrogen bonds distinguish themselves from other non-covalent interactions by their pronounced directionality.[24] For a systematic comparison of selectivity and affinities, and later of solvent effects, we first concentrate on the complexation of halide anions, which as guests are free from directional restrictions, and for which sufficient literature data are available.[14] Also, we restrict the analysis on associations with electroneutral host structures. Simultaneous ionic interactions render the mechanistic interpretation more complex, and generally also lead to smaller selectivity than those based on hydrogen bonding alone.

Open-chain hydrogen bond donor arrays provide synthetically simple yet often already selective host compounds for anions. The examples shown in Scheme 4[25] support the notion that selectivity increases with affinity, due to the increased number *n* of interactions.

Due to the intrinsic hydrogen bonds acceptor strength decreasing from fluoride to iodide, even a simple donor molecule such as methanol shows in absence of competing solvent molecules already large selectivity in the gas phase, with $K_{Cl}/K_{Br} = 17$ ($K_{Cl} = 2.6 \times 10^7$ M⁻¹), or $K_{Br}/K_I = 56$ ($K_{Br} = 1.3 \times 10^6$ M⁻¹).[11]
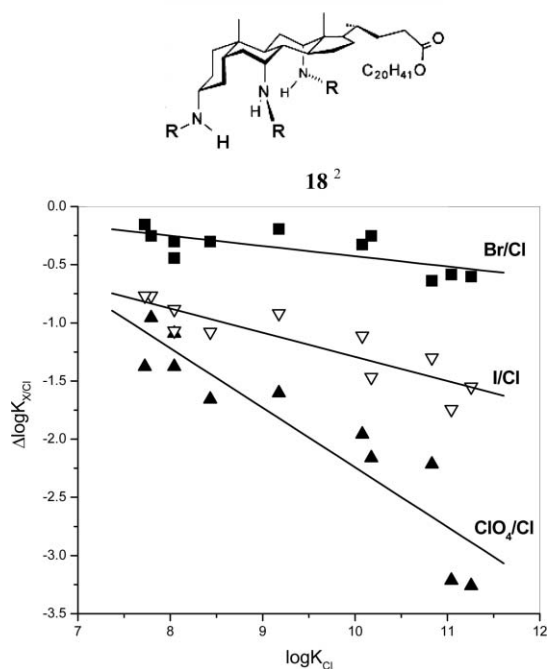
Steroid skeletons allow to mount hydrogen bond donor functions such as urea in highly organized manner, **18**, which lead to high affinity with many anions, with *K* values of up to 10^{11} M⁻¹ (for chloride, in chloroform).[2] However, the highest selectivity was with $K_{Cl}/K_{Br} = 9$ just in the range of that with

K_{Cl}/K_{Br} 1.25   2.45   9.5 in CDCl$_3$

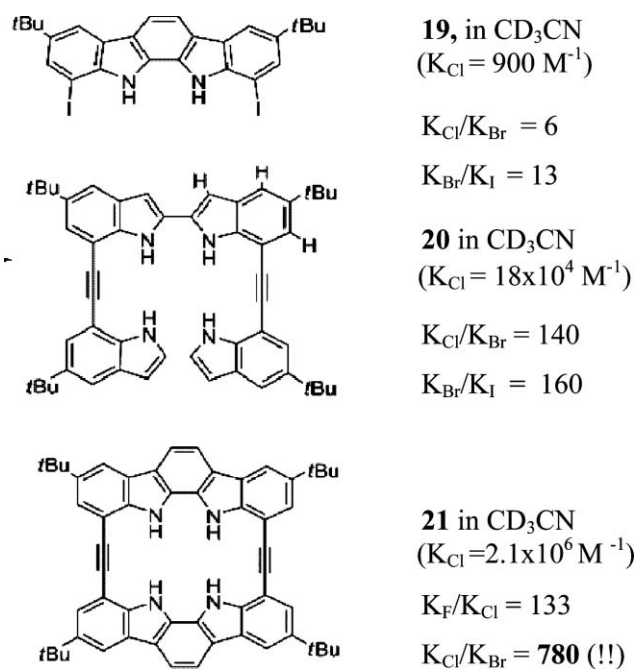$-\Delta G$ for Cl$^-$ 6   14   18   kJ/mol
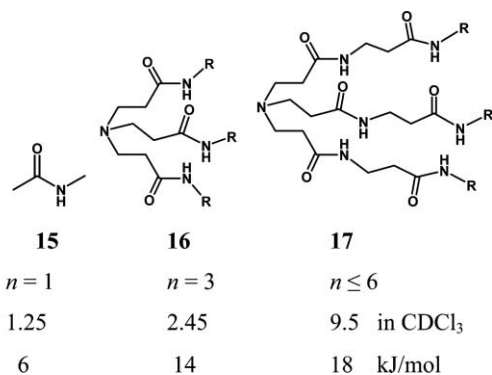
Scheme 4 Open-chain hosts for halide recognition by hydrogen bonding.[25]

the simple flexible host in Scheme 4, and was in fact observed with a system of smaller affinity (K around 10^8 M^{-1}). If one analyzes all binding constants with such steroid-based urea hosts, omitting one where an ester group is used instead of urea, one finds, however, correlations between affinity and selectivities, which are satisfactorily linear, with larger slopes for pairs of anions more distant in their basicities, *e.g.* the slope for ClO$_4$$^-$/Cl$^-$ is 0.51 compared to 0.088 for Br$^-$/Cl$^-$ (Fig. 9). With non-symmetrical anions such as acetate or ethanesulfonate there is no general correlation, likely due to steric effects (see ESI†).

Anion receptors containing indole as hydrogen bond donors show selectivities, which simultaneously with the affinity are increased with a increasing number of donor sites, and culminate if the maximum of four donor units are within a sterically very constrained cavity, Scheme 5.[26] This is illustrated with a series of host compounds; the last one being exhibiting very high binding constant with fluoride

18[2]

Fig. 9 Selectivity of anion recognition by receptor **18**[2] in chloroform.

19, in CD$_3$CN
(K_{Cl} = 900 M^{-1})

K_{Cl}/K_{Br} = 6

K_{Br}/K_I = 13

20 in CD$_3$CN
(K_{Cl} = 18x10^4 M^{-1})

K_{Cl}/K_{Br} = 140

K_{Br}/K_I = 160

21 in CD$_3$CN
(K_{Cl} = 2.1x10^6 M^{-1})

K_F/K_{Cl} = 133

K_{Cl}/K_{Br} = **780** (!!)

Scheme 5 Halide anion complexation with indole-containing hosts.[26]

(K = 5.6 × 10^8 M^{-1} in MeCN). High selectivities with these hosts are also retained in polar media such as acetone (see Section 9 on Solvent effects).

If complexation is supported by *e.g.* electrostatic interactions, hydrogen bonding can also be used in aqueous medium for selective recognition of peptides with the host **22**, as shown in Scheme 6.[27]

As seen already with the last example in Scheme 5 *macrocyclic cavities* allow a significant selectivity increase. This is also true if the cavity is so large, that large ions such as iodide are with **23** preferred over those with higher charge density, in contrast to the usual sequence (Scheme 7).[28]

Smaller cavities such as in calix[4]pyrroles **24** show the expected preference for small ions, *e.g.* K_F/K_{Cl} = 50, or K_{Cl}/K_{Br} = 35 in dichloromethane[29] (Scheme 8). It should be noted that in acetonitrile, however, a much smaller $K_{F/Cl}$ = 1.8 was reported.[30] Calorimetric measurements of such complexes brought partially conflicting results, depending in some cases also on the mode of addition. The corresponding
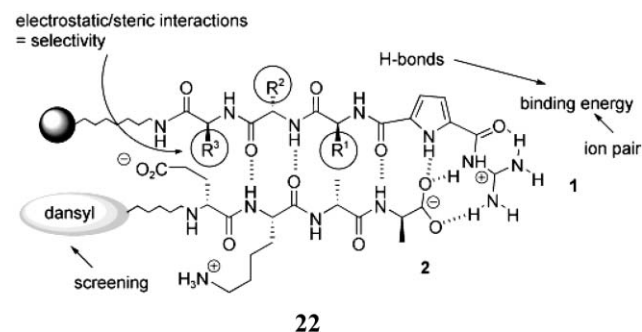
Scheme 6 Simultaneous use of hydrogen bonds and electrostatic interactions with host **22** for peptide recognition.[27] Reprinted from C. Schmuck, D. Rupprecht, and W. Wienand, *Chem.–Eur. J.* 2006, **12**, 9186. Copyright (2006), with permission from Wiley.
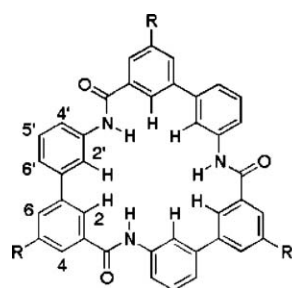
23, in CDCl₃ + 2% DMSO:

$K_I = 1.3 \times 10^5 \text{ M}^{-1}$

$K_I/K_{Cl} = 15$

$K_{NO3}/K_{Cl} = 5; \quad K_{TsO}/K_{Cl} = 3$

Scheme 7 A large macrocycle with a reversed selectivity between iodide and chloride.[28]

thio-derivatives **25**,[31] which have been studied in detail with respect to solvent effects (see below) exhibit the expected, although moderate selectivities. Macrocyclic tetraamides (**26**, Scheme 8) yielded with *e.g.* $K_{Cl}/K_{Br} \approx 13$ a remarkable selectivity even in the more competitive solvent DMSO.[32]

The macrocyclic peptide **27** represents a rare case of anion complexation by pure hydrogen bonding in water, with preference for iodide and in particular for sulfate; both 1 : 1 and 2 : 1 complexes were observed and characterized by *e.g.* NMR spectroscopy.[33]

27[33]
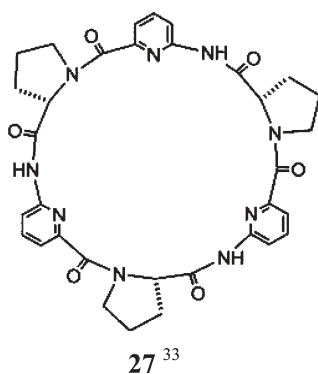
in D₂O:MeOD (80:20)

K_1 values (M⁻¹): Cl⁻: 5; Br⁻: 16; I⁻: 23; SO₄²⁻: 96

The *directionality* of hydrogen bonds is the basis for systems which discriminate *e.g.* spherical anions from *e.g.* carboxylate, can be illustrated with the bis-urea host **23**, well suited to discriminate carboxylates from other anions.[34]
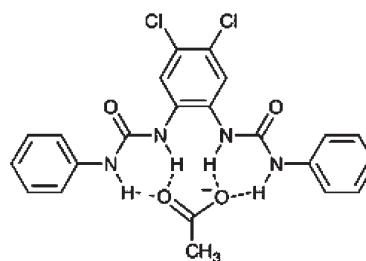
28,[34] in DMSO:

RCOO⁻ : K > 10³ M⁻¹

H₂PO₄⁻ : K = 730 M⁻¹

HSO₄⁻, Hal⁻ : K < 50 M⁻¹

With the macrocyclic host **23** binding equilibria with HSO₄⁻ and H₂PO₄⁻ were even slow on the NMR time scale.[28] Guanidinium groups (**29**) serve the same purpose, but also show favorable interactions with *e.g.* phosphate or sulfate.[14,35] Three converging hydrogen bonds are used in the complex **30** for selective binding of nitrate anions.[35] Multiple hydrogen bonds lead with a boron-complex to binding constants with phosphate exceeding those with *e.g.* carboxylate by a factor over 100.[36]
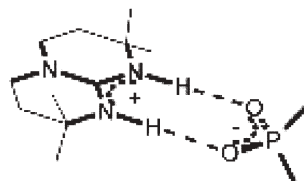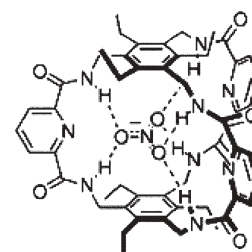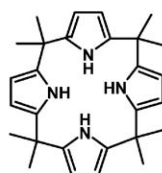
29   **30**[35]

For additional examples and informations see ESI.†

7 Complexes with electrostatic, stacking and van der Waals interactions

Analytes of biological importance are becoming an increasingly important target for selective supramolecular complexations. Usually they are confined to an aqueous surrounding,

24[29]

in CD₃CN	in CD₂Cl₂
$K_{Cl} = 2 \times 10^5 \text{ M}^{-1}$	$K_{Cl} = 3.5 \times 10^4 \text{ M}^{-1}$
$K_F/K_{Cl} = 31$	$K_F/K_{Cl} = 50$
$K_{Cl}/K_{Br} = 11$	$K_{Cl}/K_{Br} = 35$
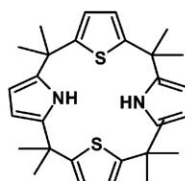
25[31]

in CD₃CN (ΔG_{Cl}=-23.7 kJ/mol)

$K_F/K_{Cl} = 9$

$K_{Cl}/K_{Br} = 5$
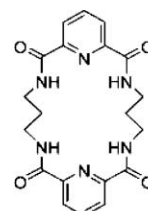
26[32]

in DMSO (!):

$K_{Cl} = 1930 \text{ M}^{-1}$

$K_{Cl}/K_{Br} = 13$

Scheme 8 Macrocyclic hosts for anion recognition by hydrogen bonding.
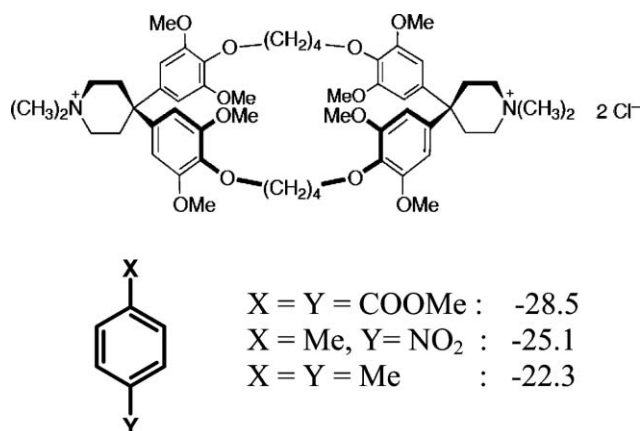
Scheme 9 Complexation free energies ΔG (in water, kJ mol^{-1}) with an electron-rich cyclophane.[37]

Scheme 10 Selectivity of the tweezer host for N/C-protected amino acids; K_a values in buffered aqueous solution.[39] Reprinted from M. Fokkens, T. Schrader and F.-G. Klärner, *J. Am. Chem. Soc.*, 2005, **127**, 14415, A Molecular Tweezer for Lysine and Arginine, Copyright (2005), with permission from The American Chemical Society.

where hydrophobic forces can also contribute. Most often these associations comprise aromatic units;[37] their stacking or edge-to-face binding modes can involve Coulombic, cation–π and dispersive interactions. As a rule it is difficult to exactly separate for such supramolecular associations specific binding mechanisms; for this reason and for practical considerations we will treat the selectivity aspects for corresponding complexes together in one section. Our major aim is to illustrate how different kinds of such interactions can be used for selective complexations.

An electron rich cyclophane host shows only moderate selectivity of *e.g.* phenyl derivatives with different substituents, for which both by electrostatic stacking face-to-face as well as edge-to-face are responsible (Scheme 9).[37] Noticeably, the selectivity in terms of enthalpy differences $\Delta\Delta H$ is much more pronounced than that in $\Delta\Delta G$, which are to large degree compensated by adverse entropic contributions. In such cases one can expect higher selectivities at higher temperature, due to the $T\Delta S$ term, which shows at room temperature already differences of up to $\Delta(T\Delta S) = 13$ kJ mol^{-1}.

Fully aromatic clefts or tweezers (Scheme 10) can serve by predominantly electrostatic forces as hosts only for electron-deficient neutral and cationic substrates.[38] This is due to the quite negative partial charge on the concave side of these hydrocarbons. An application of this type of interaction for selective binding of lysine and arginine in water was reported by using a phosphonate appended dianionic tweezer.[39]

All of the above-mentioned mechanisms can lead to affinity increase with the contact surface between host and guest. Selectivity with respect to the size of *e.g.* an aromatic guest
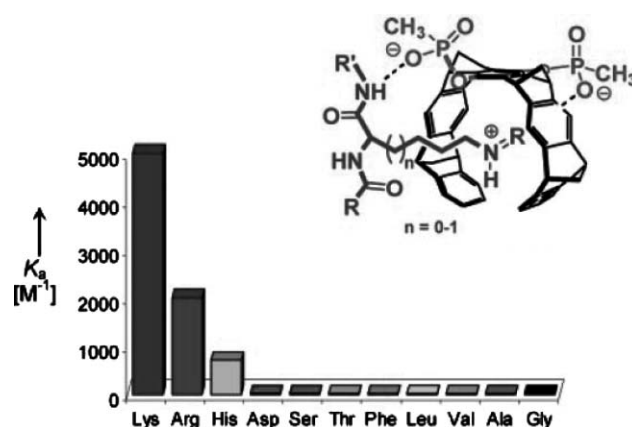
molecule can therefore be achieved not only by inclusion in geometrically matching host cavities, but simply also by interaction with a flat host surface, as illustrated with affinity difference in associations with water-soluble porphyrins (Scheme 11).[40]

In contrast to the negligible influence of heteroatoms as part of a π-system (Scheme 11) heteroatoms can be distinguished better if they are in substituents at other molecules, as illustrated in Scheme 12, again with simple porphyrin complexes. Here binding constants between *e.g.* *p*-halogeno and *p*-nitro benzoates differ by a factors of up to about 10, and obviously reflect the influence of polarizability on dispersive interactions. Regioisomers with heterosubstituents either in *m*- or *p*-position cannot be distinguished, whereas those in *o*-position lead to steric distortions and thus to affinity changes. Contributions of aliphatic groups here are obviously negligible, but can be sizeable in complexes dominated by hydrophobic interactions such as cyclodextrins (see below).

The selective recognition of amino acids and peptides is of significance for many applications; ion pairing provides a increasingly used way for the distinction of basic and acidic amino acid residues,[42] whereas hydrogen bonding can essentially used only in non-aqueous media with protected amino acids. Dispersive interactions are of major significance for the distinction of lipophilic amino acids, as illustrated in Scheme 13 with a sequence-selective host for tripeptides. The placement of the stacking unit **RH** in the host, which is also

TPPy $-\Delta G_{assoc}$:   6.2   6.4   16.7   16.1   19.0
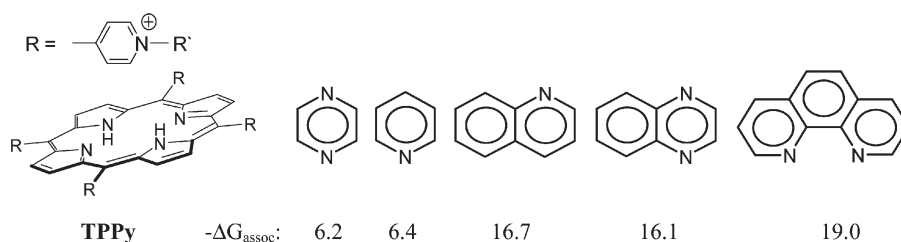
Scheme 11 Free energies of associations ($-\Delta G$, kJ mol^{-1}, in water) of a cationic water-soluble porphyrin (**TPPy**) with aromatic guest molecules of increasing size.[40]
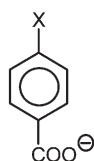
X =	H	Me	CH=CH$_2$	F	Cl	Br	I	NO$_2$
TPPy	13.8	13.8	16.0	13.9	15.1	15.8	16.55	19.3
α-CD	6.5	4.8		6.5	12.7			ca. 15*

* literature values of K$_{assoc}$ vary between 70 and 360 M^{-1}

Scheme 12 Free energies of associations $-\Delta G$ (kJ mol^{-1}, in water) between the large π-surface of porphyrin **TPPy**[40](see Scheme 11), or α-cyclodextrin (α-CD) and anions of benzoic acids with different substituents; values with α-CD from ref. 41.
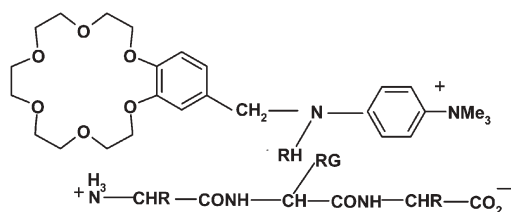
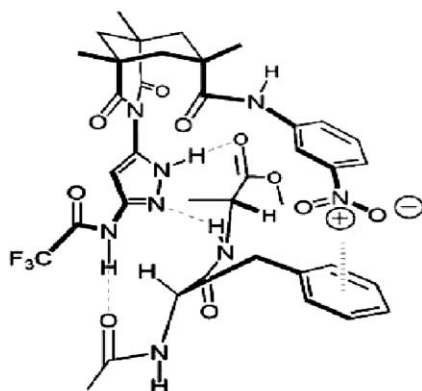| Tripeptide	RG	$-\Delta G$ (kJ mol^{-1})
Gly-Gly-Gly	H	13.2
Gly-Ala-Gly	Me	15.6
Gly-Leu-Gly	CHMe$_2$	16.7
Gly-Phe-Gly	Ph	18.3
Gly-Trp-Gly	Indole	19.0

Scheme 13 The use of lipophilic interactions for sequence-selective discrimination of neutral amino acid residues in peptides in water.[43]

Guest	K, M^{-1}
Trp-Gly-Gly	1.3×10^5
Gly-Trp-Gly	2.1×10^4
Gly-Gly-Trp	3.1×10^3
Trp	4.3×10^4
Phe	5.3×10^3
Tyr	2.2×10^3
His	no binding observed

Scheme 14 Recognition of N-terminal tryptophan by formation of a ternary complex with cucurbit[8]uril and methyl viologen.[45]
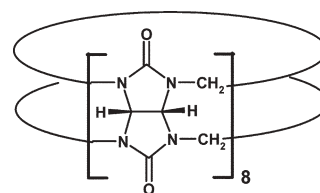
length-selective, allows a favourable binding contribution only if the complementary amino acid with a side chain **RG** is in the center position of the peptide, other positions are discriminated by up to ten times smaller binding constants.[43]

The selective binding of aromatic peptide residues can be improved by implementation of a nitro group into the host **31** which in line with the dispersive effects discussed above enhances the affinity constant by a power of magnitude.[44]
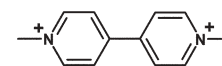
The mechanism of recognition involves formation of ternary complexes (**Q8**–**MV**–guest) held together by a combined action of electrostatic interactions of terminal peptide ammonium groups or free amino acid with carbonyl groups of Q8 as well as the face-to-face interaction of indole ring with the included MV dication. The receptor binds aromatic amino acids with a clear preference for tryptophan and also recognizes peptides with N-terminal tryptophan.

31 [44]
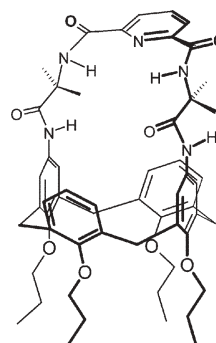
in acetone-D$_6$; K in 10^4 [M^{-1}]

CH$_3$COO$^-$:	1.05
C$_6$H$_5$COO$^-$:	4.01
N-Ac-Gly-COO$^-$:	0.62
N-Ac-*L* Ala -COO$^-$:	0.49
N-Ac-*D* Ala -COO$^-$:	0.57
N-Ac-*L* Phe-COO$^-$:	0.79
N-Ac-*D*-Phe -COO$^-$:	1.05

32 [46]

High affinity together with significant selectivity for recognition of N-terminal tryptophan in water was achieved by using as a host cucurbit[8]uril (**Q8**) in combination with methyl viologen (**MV**), Scheme 14.[45]

The macrocyclic peptidocalix[4]arene **32** exhibits significant selectivity for aryl- over alkyl carboxylates due to π–π-stacking interactions. In addition, the presence of chiral amino acids in the host leads to moderate enantioselectivity with N-protected amino acids as guest molecules.[46] Solubility reasons prevent the use of water as solvent, where larger selectivity can be expected.

8 Hydrophobically driven cyclodextrin complexes

Cyclodextrin complexes are considered to be typical examples of hydrophobically driven associations, although it is known that depending particularly on the polarizability of the guest molecule dispersive interactions can dominate. As an example we shall consider the binding of alcohols to cyclodextrins. As shown in Fig. 10 there is a good correlation of log K values for linear 1-alcohols *vs.* number n of carbon atoms, reflecting a constant binding increment per methylene group and the generally higher affinity with the smaller and hence better size-fitting α-cyclodextrin. The selectivity of binding of alcohols with different chain length is approximately constant for both cyclodextrins with K increasing by a factor of three on addition of each methylene group to an alcohol. Changing the shape of the guest *e.g.* by using *tert*-BuOH instead of *n*-BuOH strongly affects the binding (Fig. 10): with the larger β-CD the fit becomes better and K increases by a factor of 20, but with smaller α-CD the fit is poorer and K even decreases by a factor of 2.5.

Typically the cyclodextrin is modified by attaching of a signaling *e.g.* fluorescent moiety, like *e.g.* in structure **33**,[47] to convert it to a sensor. Such modification of course may affect the binding. The open triangles in Fig. 10 show the binding constants of the same 1-alcohols to **33**. Evidently the affinity is strongly reduced by the modification (the effect attributed to the steric hindrance), however, the slope of log K *vs. n* is the same, as one would expect for this type of interaction. So, the modified cyclodextrin provides the same selectivity in spite of reduced affinity.

33 [47]
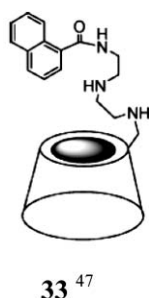
More perfect biological receptors often provide larger binding increments per methylene and therefore may afford a better selectivity. As an example, Fig. 10 shows the binding constants for a series of 1-alcohols to a major urinary protein MUP-1.[48] The binding increment here is twice as that with cyclodextrins: K increases by a factor of 7 per additional methylene group. Also the absolute values of binding constants are *ca.* two orders of magnitude larger, thus providing another example of increased selectivity with increased affinity.

9 Solvent effects

According to eqn (3) any solvent leading to smaller affinity of complexation should lead to a decrease of selectivity, as smaller ΔG values would be reflected in concomitantly smaller free energy difference $\Delta\Delta G$. Therefore quantitative correlations between affinity and solvent properties should be helpful for the prediction of selectivity, which may be enhanced by
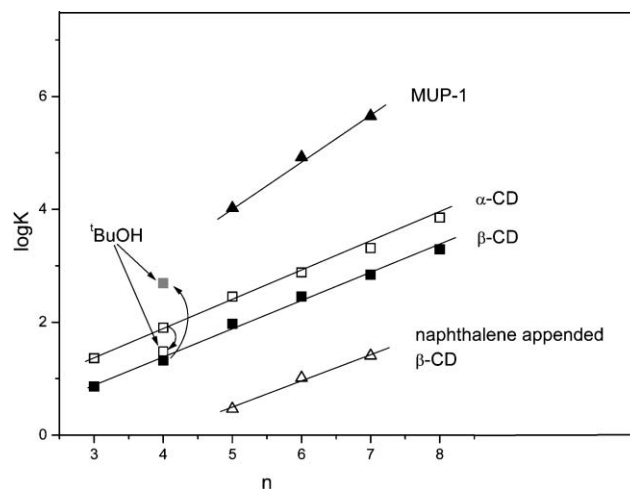
Fig. 10 Logarithms of binding constants of 1-alcohols to α- and β-cyclodextrin (open and solid squares respectively), to naphthalene appended β-CD **33** (open triangles) and to the MUP-1 protein (solid triangles). Grey symbols show the binding constants for *tert*-butanol.

proper choice of a solvent. Unfortunately, the influence of the reaction medium on supramolecular equilibria is often difficult to quantify.

9.1 Solvent effects on ionophore complexes

With ion complexes and electroneutral ligands one can expect the major variation from solvation or desolvation of the most polar partner. Indeed, it has been realized since long time ago that the hole-size peak selectivity of metal ion complexation by crown ethers and related ligands is observed to the great extent due to the cation solvation effect. For complexation between potassium salts and 18-crown-6 in 14 different solvents one observes a linear correlation (with $R \approx 0.95$) of ΔG with standard Gibbs transfer energies $\Delta G°_t$ of the metal ion from water to the given solvent.[9a] Comparison with some other cations and ligands, including [222]cryptand, also revealed, that the complexation constant changes are essentially a linear function of the cation desolvation free energies. Less meaningful correlations ($R \approx 0.9$) are obtained with values characterizing the electron donor capacity of the solvent. Parameters characterizing the solvent polarity, such as E_T, are extremely poor descriptors ($R = 0.3$). Reaction enthalpies ΔH vary much more than ΔG, for instance from 12 kJ mol^{-1} (in MeCN) to 68 kJ mol^{-1} (in Me$_2$CHOH), without meaningful correlations to any known solvent properties.[9a]

Both theoretical calculations[49] and experimental gas-phase measurements[50] show that in the absence of a solvent the affinity of cations to crown ethers of different sizes always parallels the cation charge density, *i.e.* the highest affinity is always observed for Li$^+$ among alkali metal ions and for Mg^{2+} among alkaline-earth cations. Recent measurements of stability constants for alkali metal ions in poorly solvating nitromethane indeed show the expected order Na$^+$ > K$^+$ > Rb$^+$ > Cs$^+$ regardless of the macrocycle size.[51]

As expected, measurements in different solvents usually show a decreased affinity in more polar solvents due to stronger solvation of metal ions. This in principle may lead to
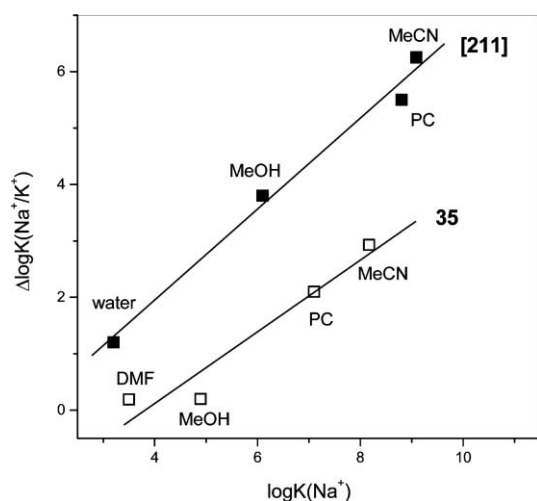
Fig. 11 Correlations between differences in log K values for complexation of Na$^+$ and K$^+$ with [211]cryptand (solid squares) or with lariat ether **34** (open squares) and log K for Na$^+$ in different solvents.

an observation of affinity-selectivity correlation, which indeed can be found in several cases, *e.g.*. for complexation of alkali metal ions with [221]cryptand (data from ref. 10) and with a bibrachial lariat ether **34**,[52] see Fig. 11.

Recent results on solvent effects on cation and anion recognition with large polyfunctional receptors point to importance of co-complexation of solvent molecules with guests for affinity and selectivity.

Studies on the cation binding by a calixarene **35**[53] in four solvents (MeCN, MeOH, DMF and propylene carbonate (PC)) show that in MeOH and DMF one observes the binding of only two cations, Ag$^+$ and Hg^{2+}, surprisingly with inversed selectivity ($K_{Ag} \gg K_{Hg}$ in MeOH, but $K_{Hg} > K_{Ag}$ in DMF). However in MeCN the receptor binds a large number of cations (Li$^+$, Na$^+$, Ag$^+$, Ca^{2+}, Pb^{2+}, Hg^{2+} and Cu^{2+}) with strongly increased affinity to Hg^{2+}, but decreased affinity to Ag$^+$ as compared to MeOH and DMF. This stronger binding in MeCN cannot be attributed just to lower donor number (DN) of this solvent because in PC, which is even less donor solvent, receptor **35** does not bind cations at all. It has been shown that inclusion of a MeCN molecule in the cavity formed by aromatic rings of **35** causes an allosteric effect inducing a widening of the cavity formed by polar chains where metal ion binding occurs; this makes possible complexation of a large number of cations in this solvent.

Another example of co-complexation with a solvent molecule strongly affecting the selectivity was observed in recognition of anions by a porphyrinic receptor **36**.[54] The binding of chloride and dihydrogenphosphate was studied in two solvents, DMSO and CH$_2$Cl$_2$. In DMSO, $K_{Cl} > 10^5$ M^{-1} and $K_{H_2PO_4} = 1.4 \times 10^3$ M^{-1}, but in CH$_2$Cl$_2$, the affinity to chloride goes down ($K_{Cl} = 1.5 \times 10^3$ M^{-1}) while that to dihydrogenphosphate goes up ($K_{H_2PO_4} = 1.8 \times 10^4$ M^{-1}), thus inverting the selectivity. Addition of DMSO to CH$_2$Cl$_2$ improves binding of chloride. Although the fact of binding of a DMSO molecule to the receptor was confirmed independently by X-ray crystallography, the role of this bound molecule remains rather obscure. Changes in anion solvation also can contribute to the inverted selectivity: the protic hydrogenphosphate should be better solvated in the proton acceptor DMSO than in CH$_2$Cl$_2$; this may reduce the affinity in the former solvent, but chloride should be better solvated in more proton donor CH$_2$Cl$_2$ than in aprotic DMSO, and therefore show lower affinity with the former solvent.

Binding constants of 18C6 with protonated amines in water, 2-propanol, *tert*-butyl alcohol, *n*-octanol, DMF, DMSO, pyridine and HMPT have been found to vary by factors of up to 1000; the solvent effects can be described with values characterizing the electron donor capacity of the solvent. Although no linear dependence of the difference $\Delta \log K$ between benzylammonium and anilinium chloride on the total affinity was observed, somewhat larger $\Delta \log K$ values were found with less competing solvents.[55]

9.2 Solvent effects on hydrogen bonded complexes

In complexation based on hydrogen bonds the selectivity is generally larger in solvents with smaller donor or acceptor capacities, although a linear correlation between affinity and selectivity is rarely seen. Jeong *et al.* have recently carried out a systematic study of solvent effects on binding constants of halide anions with open chain indole-donor ligands **19** and **20** (see Scheme 5).[26] The data (see Tables S1 and S2 in ESI†) demonstrate impressively how a suitable choice of the solvent allows to optimize selectivities, reaching with the simple bisindole host **19** *e.g.* $K_{Cl}/K_{Br} = 6$ in MeCN, or 16 in THF. With the still conformationally flexible tetraindole **20** not only the affinities are significantly increased (see above), but the selectivities reach peak values of $K_{Cl}/K_{Br} = 140$ in MeCN, or 120 even in the polar medium acetone. For K_{Br}/K_I the peak values are 2300, now in CD$_2$Cl$_2$, or 1900, surprisingly again in acetone. The binding constants, which do not correlate with

**34** [52]   **35** [53]   **36** [54]
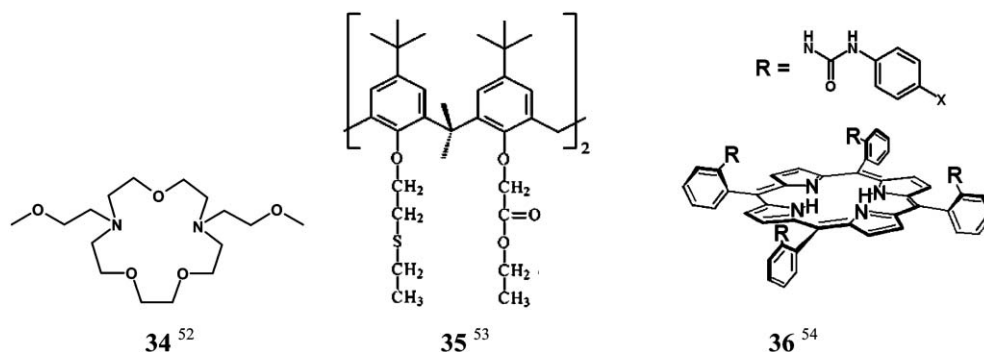
any known solvent property parameters, show the expected increased selectivities comparing the bisindole with tetraindole as host (see section Hydrogen bonded complexes), but the correlation between affinity and selectivity is much less clear in the comparison of different reaction media. In particular, high selectivities are observed in acetone, which due to its polarity does not lead to particular strong complexation. That specific solvation effects play a more important role than just the change of total affinity with the solvent is also seen in halide anion complexation with diphenylurea as ligand (see Table S3 in ESI†), where again a peak selectivity of $K_{Cl}/K_{Br} = 15$ is reached in acetone.

A significant change in relative affinity of protic and aprotic anions to a bicyclic polypeptide antibiotic thiostrepton was observed on going from DMSO to chloroform.[56] In DMSO, affinities follow the order of increased basicity of anions (F⁻ = AcO⁻ ≫ H₂PO₄⁻, Cl⁻, Br⁻, HSO₄⁻), but in chloroform the pattern is more complex: Cl⁻ = HSO₄⁻ > F⁻ > AcO⁻ > Br⁻ > H₂PO₄⁻. The strongly increased affinity to HSO₄⁻ is attributed to its ability to bind to the host as a proton donor.

10 Chiral recognition: an outlook

Since the classical use of binaphthyl crown ethers **38** for the discrimination of enantiomeric amino acid derivatives by Cram and co-workers,[57] hundreds of investigations have addressed selective recognition of chiral substrates;[58] it is out of the scope of the present review to discuss any examples in detail. Significant progress has been made by coupling discriminating chiral units to primary recognition sites, in line with Scheme 1. With a host such as **39** aromatic amino acids can be bound selectively by a combination of ion pairing to the guanidinium residue, of hydrogen binding to the crown ether, and of π–π stacking to the naphthyl units.[59]

38 [57]   **39** [59]
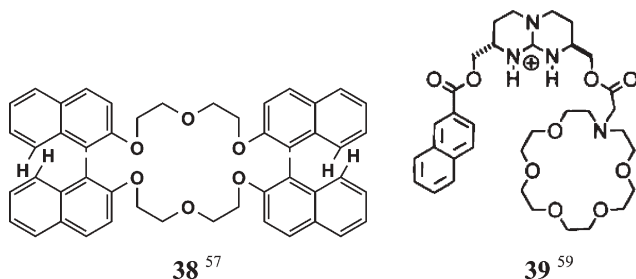
It should be noticed that for the chiral recognition site a binding free energy difference $\Delta\Delta G$ of e.g. 10 kJ mol⁻¹ between association with one over the other isomer is sufficient to reach a selectivity ratio around 100, whereas the primary binding site, e.g. a crown ether or a guanidinium unit, may contribute much higher binding energy; in consequence, the correlation between selectivity and total affinity can completely break down for such cases. For additional examples and information see ESI.†

11 Conclusions

The design of a selective receptor usually is focused on complementarity of interacting host and guest sites, pre-organization and choosing of a proper interaction type (e.g. stacking interactions for selective binding of aromatic vs. aliphatic guests). However, since the selectivity is a balance of numerous aspects affecting the binding, the influence of such factors as solvent effects or secondary, both attractive and repulsive, interactions cannot be underestimated. The situation becomes even more complicated if one considers a real experimentally observed selectivity in terms of different complexation degrees under chosen conditions rather than the simple ratio of binding constants.

If only one type of interaction mode prevails one can expect to see a general correlation between selectivity and total affinity. Both selectivity and affinity can gain from multi-valency by augmentation of the number of binding sites, even in poorly preorganized flexible receptors. One may consider selectivity–affinity correlations as an analog of the once popular reactivity–selectivity principle, which nowadays is often criticized for lack of generality and an absence of a firm theoretical basis.[60] As we saw, however, the selectivity–affinity correlation can be justified theoretically for certain types of interactions and its limitations also can be predicted satisfactorily. The role of secondary interaction sites for discrimination between different analytes is the most important limitation of linear affinity–selectivity correlations. On the other hand, the introduction of such secondary interaction sites holds much promise for the development of highly selective supramolecular hosts, where a primary interaction site can simultaneously and independently provide for high affinities.

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