Review Article

Solvent Effects in Molecular Recognition#

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Synthetic cyclophane receptors form stable and highly structured inclusion complexes with aromatic solutes in the liquid phase. The major host–guest interactions in these complexes are π–π-stacking and edge-to-face aromatic–aromatic interactions. Electron donor–acceptor (EDA) interactions control the relative stability of cyclophane–arene inclusion complexes in organic solvents. Generally, electron-deficient benzene and naphthalene derivatives form the most stable complexes with electron-rich cyclophanes. In water, however, unfavorable complexation-induced changes in the solvation of guest functional groups may entirely mask contibutions of EDA interactions to the relative complexation strength. Similarly, complexation-induced changes in the solvation of host substituents may also strongly affect the measurable complexation strength. The inclusion complexation of benzene derivatives in water is strongly exothermic, accompanied by an unfavorable entropic term. A large part of the favorable enthalpy change results from solvent-specific contributions. Negative heat capacity changes are measured for all inclusion complexes in water. Arene complexation occurs in solvents of all polarity. Binding free energy decreases from water to polar protic, to dipolar aprotic, and to apolar solvents and can be predicted in a linear free energy relationship with the empirical solvent polarity parameter $E_T(30)$. In all solvents, the formation of a pyrene–cyclophane inclusion complex is enthalpically driven. The exothermicity generally increases from apolar solvents, to dipolar aprotic solvents, to protic solvents. Strong dual isoequilibrium relationships correlate the thermodynamic parameters $\Delta G°$, $\Delta H°$, and $T\Delta S°$ for pyrene complexation in the different environments. Differential solvent interactions are responsible for these unprecedented compensation effects.

Solvent effects play a crucial role in any molecular recognition event in the liquid phase.[1,2] The choice of the correct solvent may lead to a considerable strengthening of a host–guest association; a less appropriate selection, however, may prevent complexation from occurring altogether. Water is the best solvent for inducing strong association between apolar binding partners, and this property is essential for sustaining all functions of life. In contrast, hydrogen bonding complexation by synthetic receptors has not yet been observed in the aqueous phase as a result of the competition between the water molecules and the solutes for the hydrogen bond donor and acceptor sites.

This account summarizes our comprehensive molecular recognition studies with synthetic cyclophane receptors.[2–5] This work was undertaken to advance the individual molecular level description of solvent effects on apolar host–guest associations. In the first section, the structural characteristics of the receptors and their inclusion complexes are described. The subsequent section analyzes whether weak intermolecular forces, e.g. aromatic–aromatic interactions,[6–13] can compete with solvent effects in determining relative host–guest association strength. This will be followed by a discussion of the thermodynamic quantities that characterize tight apolar complexation in aqueous solution. Finally, the relationship between apolar binding strength and solvent polarity is investigated in solvents which cover the entire polarity range.

Structures of tetraoxa[*n*.1.*n*.1]cyclophanes and their inclusion complexes with aromatic guests

In the productive binding conformation, the tetraoxa[*n*.1.*n*.1]paracyclophanes **1–5** adopt the shape of a rectangular cavity with four electron-rich aromatic rings as its walls. This is shown in Figs. 1 and 2 for the **2**·*p*-xylene complex.

The geometries in Figs. 1 and 2 were obtained from a conformational search which began by docking *p*-xylene into the cavity of **2** according to X-ray crystal structure analysis.[14] Low-energy conformations of the complex were generated using the AMBER force field and the BATCHMIN Monte Carlo search method included in MACRO-

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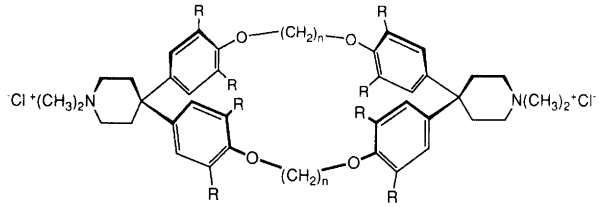


	n	R
1	3	H
2	3	OCH_3
3	4	H
4	4	CH_3
5	4	OCH_3

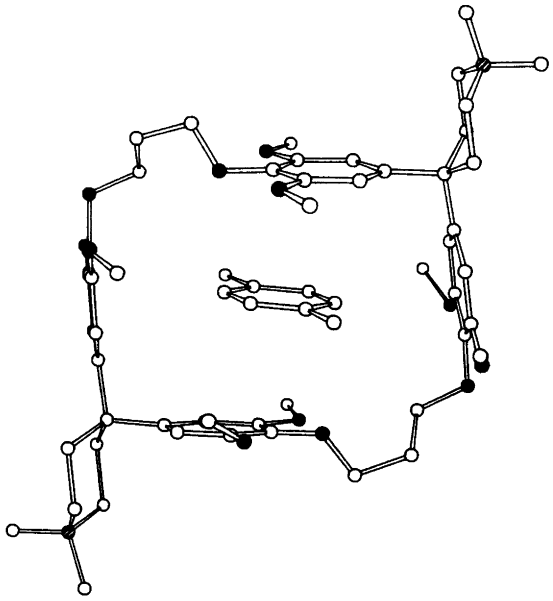


Fig. 1. Lowest-energy geometry of the *p*-xylene complex of the cyclophane **2**.

MODEL.[15] Starting from a total of 2500 gas phase complex conformations, a surface-area based solvation treatment[16] gave 109 structures within 1 kcal mol^{-1} of the lowest-energy conformer. After pattern recognition studies, 28 unique structures were identified out of the 109 conformers. Fig. 2A shows a superposition of the 28 conformations of the **2**·*p*-xylene complex. Fig. 2B shows a space-filling representation of the superposition of the 28 structures from which the guest has been removed to show clearly the tight molecular box which fits the size of a benzene ring.

Substituted aromatic substrates, e.g. 2,6-disubstituted naphthalenes and *para*-substituted benzene derivatives, that are complementary in size and shape to the cyclophanes **1–5**, generally prefer to adopt an axial-type inclusion geometry[17,18] (Scheme 1). This way, the highly solvated guest substituents are oriented into the solution, which minimizes any unfavorable desolvation in the complexes. The analysis of complexation-induced changes in the ^1H NMR chemical shifts reveals that guests encapsulated by **1–5** adopt the two orientations **A** and **B** (Scheme 2), which is in agreement with the previously discussed modeling studies (Figs. 1 and 2).

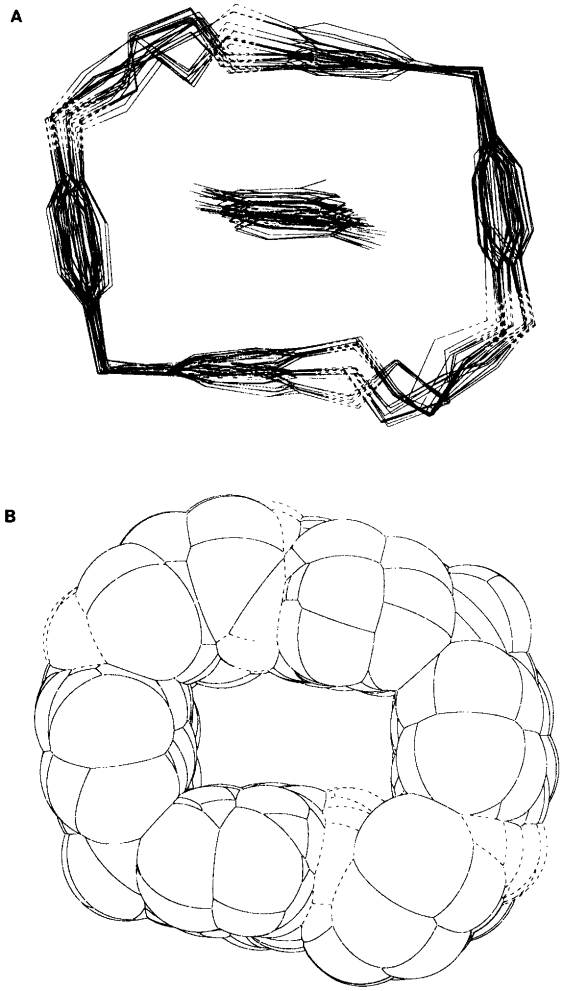
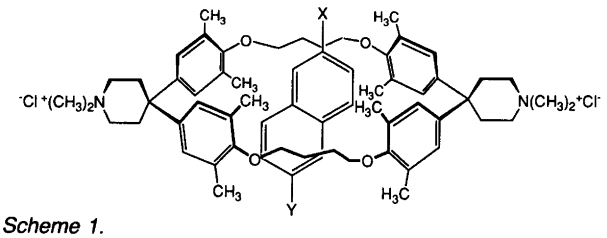
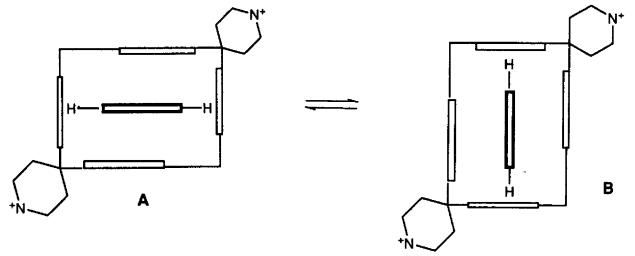


Fig. 2. (A) Superposition of 28 host–guest conformers within 1 kcal mol^{-1} of the lowest energy geometry of the *p*-xylene complex of the cyclophane **2**. The two different orientations of *p*-xylene in the cavity of **2** are shown. (B) Space-filling model of the 28 lowest energy conformations. To show the tight molecular box-shaped binding site, the *p*-xylene guest has been removed from the cavity. In both representations A and B, the methoxy groups and the piperidinium rings are omitted for clarity.



Scheme 1.



Scheme 2.

In the series of equally sized cyclophanes **3–5**, the octamethyl host **4** is the best binder followed by the octamethoxy host **5** and then by the unsubstituted cyclophane **3**.[19] This sequence, which is observed in all complexation studies in protic solvents, shows that cavity depth (**3** < **4** < **5**) is not the only factor determining association strength. The methoxy groups deepen the cavity making **5** a better binder than **3**. However, it appears that hydrogen bonding between the methoxy groups and the solvent molecules provides favorable solvation to parts of the cavity, thus reducing the solvophobic forces for apolar binding. The absence of such favorable interactions between the solvent and the octamethyl derivative gives the cavity of **4** the most apolar character, and such an environment promotes the strongest apolar complexation in protic solvents.

Solvent effects versus electron donor–acceptor interactions

The role of aromatic–aromatic interactions, and in particular electron donor–acceptor (EDA) interactions in stabilizing synthetic host–guest complexes has attracted considerable interest in recent theoretical and experimental molecular recognition studies.[6–13,20–24] We became interested in the question of whether, in polar protic environments, weak intermolecular forces, such as EDA interactions, compete with solvent effects in determining relative host–guest association strength.[25] It was found that in polar protic solvents and, especially in water, solvophobic forces provide a very large favorable contribution to the free energy of apolar binding.[26,27] In addition, specific changes in the solvation of functional groups of either host or guest during the complexation process dramatically influence binding strength.[19,28]

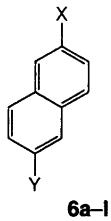
For these studies, we chose cyclophanes **1–5** as the hosts and a variety of neutral 2,6-disubstituted naphthalene and *para*-disubstituted benzene derivatives with different electronic properties as the guests. According to an EDA model, electron-poor guests should form more stable complexes with these electron-rich cyclophanes compared with electron-rich guests. In complexes adopting the geometries **A** and **B** (Scheme 2), two electrostatic interactions are similarly affected by changes in the electronic properties of the guest. Both the attractive π–π stacking ring interactions and the dipolar edge-to-face interactions should become more energetically favorable with increasing electron affinity of the guest. The edge-to-face interactions are strengthened by an increasing positive polarization of the guest hydrogen atoms that are oriented into the π-electron clouds of the electron-rich benzene rings of the hosts. Similarly, favorable π–π stacking interactions increase when the guest becomes more electron-accepting. These two components of EDA interactions in our complexes cannot be analyzed separately.

Our studies with host **4** and the 2,6-disubstituted naphthalenes **6a–i** revealed that in $(CD_3)_2SO$ and CD_3OD (Table 1), electronic host–guest complementarity generally defines relative complexation strength.[17,25] The electron-rich cyclophane forms the most stable complexes with the electron-deficient substrates **6g–i**, whereas considerably less stable complexes are formed by the electron-rich derivatives **6a–c**. The complexes of substrates containing one donor and one acceptor substituent (**6d–f**) demonstrate intermediate stability.

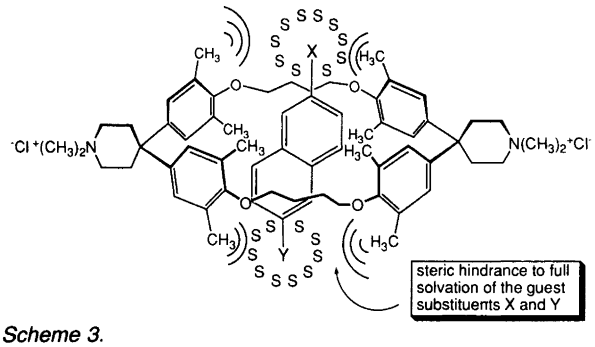
In sharp contrast, the acceptor–acceptor guests **6j–l** form complexes with stabilities that deviate strongly from those expected based solely on the EDA model. The amide functionalities of the guests undergo favorable multiple hydrogen bonding to the solvent, resulting in large stable solvation shells.[17] It is reasonable to assume that during complexation both the apolar cavity walls and, to a greater

Table 1. Association constants K_a and free energies of formation $\Delta G°$ for complexes of cyclophane **4** with 2,6-disubstituted naphthalene guests in CD_3OD, T = 303 K.

Guest	X	Y	K_a/ l mol^{-1}	$\Delta G°$/ kcal mol^{-1}
Donor–donor guests				
6a	OH	OH	23 ± 5	−1.90 ± 0.16
6b	NH_2	NH_2	27 ± 5	−1.97 ± 0.11
6c	OCH_3	OCH_3	53 ± 5	−2.39 ± 0.06
Donor–acceptor guests				
6d	NH_2	NO_2	105 ± 15	−2.79 ± 0.09
6e	OCH_3	NO_2	111 ± 10	−2.83 ± 0.05
6f	OCH_3	CN	119 ± 10	−2.88 ± 0.06
Acceptor–acceptor guests				
6g	$COOCH_3$	$COOCH_3$	188 ± 10	−3.15 ± 0.03
6h	NO_2	NO_2	216 ± 15	−3.24 ± 0.05
6i	CN	CN	272 ± 15	−3.38 ± 0.04
6j	$CONEt_2$	$CONEt_2$	< 10	> −1.3
6k	$CONH_2$	$CONH_2$	29 ± 5	−2.07 ± 0.16
6l	SO_2NH_2	SO_2NH_2	40 ± 5	−2.22 ± 0.08



6a–l



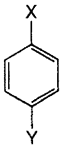
Scheme 3.

extent, the eight methyl groups of **4** interfere with an intact solvation shell of the amide residues (Scheme 3). These amide moieties are better solvated in the bulk than in the inclusion complexes and, therefore, the overall measurable complexation strength is reduced by a loss in solvation energy.

These specific substituent solvation effects are particularly pronounced in water and can lead to a complexation strength very different from that expected from considerations of attractive host–guest binding forces or the strong solvophobic driving forces in this solvent.[17] Electronic host–guest complementarity controls the relative association strength in aqueous solution only if substituent desolvation energies are approximately equivalent for the various solutes being compared. We found that the relative stabilities of the complexes between receptor **1** and *para*-disubstituted benzene derivatives in water is governed by EDA interactions (Table 2).[3,17] This host does not bear

Table 2. Association constants K_a and free energies of complexation $\Delta G°$ for complexes of cyclophane **1** with 1,4-disubstituted benzene derivatives in D_2O, T = 293 K.

Guest	X	Y	K_a/ l mol^{-1}	$\Delta G°$/ kcal mol^{-1}
Donor–donor guests				
7a	NH_2	NH_2	< 10	< 1.3
7d	CH_3	CH_3	< 85	< 2.6
7e	OCH_3	OCH_3	< 85	< 2.6
Donor–acceptor guests				
7g	CH_3	CN	420 ± 100	−3.5 ± 0.2
7f	OH	NO_2	600 ± 100	−3.7 ± 0.2
7h	CH_3	NO_2	600 ± 100	−3.7 ± 0.2
Acceptor–acceptor guests				
7i	NO_2	NO_2	1340 ± 200	−4.2 ± 0.1
7j	CN	CN	1520 ± 150	−4.3 ± 0.1
7k	$COOCH_3$	$COOCH_3$	1920 ± 200	−4.4 ± 0.1



7a–k

hindering substituents at the four aromatic rings which could interfere with full solvation of the guest functional groups in the complexes. In contrast, binding of benzene derivatives by cyclophanes **2** and **5** (Table 3) in water is

Table 3. Association constants K_a and free energies of complexation $\Delta G°$ at 293 K for complexes of cyclophane **5** with 1,4-disubstituted benzene derivatives in D_2O. Also shown are the solubilities of the guests in water as well as their Hansch partition coefficients log $P_{octanol}$.

	Guest		K_a/l mol^{-1}	$\Delta G°$/kcal mol^{-1}	Solubility[a] /mol l^{-1}	log $P_{octanol}$[b]
	X	Y				
Donor–donor guests						
7a	NH_2	NH_2	$(3.6 \pm 0.4) \times 10^2$	−3.43 ± 0.07	3.4×10^{-1}	−0.33[c]
7b	OH	OH	$(5.6 \pm 0.4) \times 10^2$	−3.69 ± 0.05	5.1×10^{-1}	0.59
7c	CH_3	OH	$(3.2 \pm 0.4) \times 10^3$	−4.71 ± 0.09	1.8×10^{-1}	1.94
7d	CH_3	CH_3	$(9.3 \pm 0.5) \times 10^3$	−5.33 ± 0.04	1.9×10^{-3}	3.15
7e	OCH_3	OCH_3	$(1.0 \pm 0.05) \times 10^4$	−5.38 ± 0.03	5.8×10^{-3}	2.09[c]
Donor–acceptor guests						
7f	OH	NO_2	$(2.3 \pm 0.3) \times 10^4$	−5.86 ± 0.08	9.5×10^{-2}	1.91
7g	CH_3	CN	$(3.0 \pm 0.3) \times 10^4$	−6.01 ± 0.07	1.2×10^{-3}	2.06[c]
7h	CH_3	NO_2	$(3.0 \pm 0.3) \times 10^4$	−6.01 ± 0.07	2.6×10^{-3}	2.42
Acceptor–acceptor guests						
7i	NO_2	NO_2	$(7.8 \pm 0.5) \times 10^3$	−5.22 ± 0.04	4.4×10^{-4}	1.46
7j	CN	CN	$(7.8 \pm 0.6) \times 10^3$	−5.23 ± 0.05	1.0×10^{-3}	0.99[c]
7k	$COOCH_3$	$COOCH_3$	$(1.2 \pm 0.2) \times 10^5$	−6.81 ± 0.09	2.8×10^{-4}	2.11[c]

[a]Temperatures for solubility measurements: 288 K (**7b**), 298 K (**7d**); all others at 293 K. [b]Ref. 32. [c]Calculated log $P_{octanol}$ values; others are experimental values from Ref. 32.

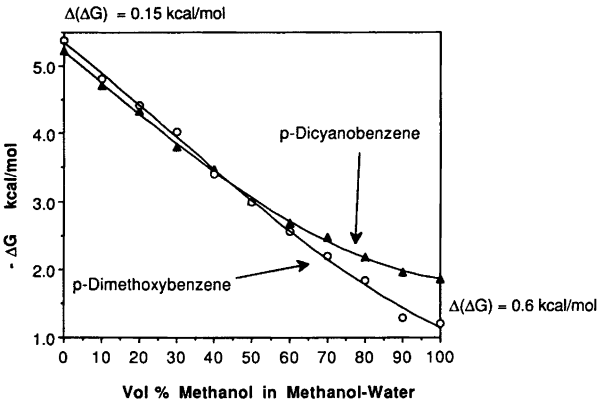


Fig. 3. Free energy of formation of the **5**·1,4-dicyanobenzene and **5**·1,4-dimethoxybenzene complexes in D_2O–CD_3OD mixtures.

largely dominated by solvent effects which complicates the binding analysis.[17,29] The methoxy substituents of these hosts interfere with the solvation of the guest functional groups in the complex, and this undoubtedly represents an important factor in the relative complexation strength. Solvophobic driving forces are important, although we did not find a strong general correlation between host–guest association strength and the solubility[30,31] or the Hansch partition coefficient[32] log $P_{octanol}$ of the guests; both are measures for the solvent affinity of the guests. However, an interesting trend is apparent in the group of donor–donor guests. Here, the substrates with the lowest solubilities and the largest positive log $P_{octanol}$ values, both indicators of poor solute–solvent interactions, form the strongest complexes. Other factors, difficult to analyze, are specific favorable interactions, e.g. hydrogen bonding, or unfavorable interactions between the methoxy groups of the host and the guest functionalities.

Interestingly, all three complexes between **2** or **5** with dipolar donor–acceptor substituted guests (**7f–h**) are quite stable despite the high solubility of these solutes. This observation provides evidence for a significant contribution of dipole-induced dipole interactions to the association strength.

The fact that solvent effects which mask contributions of EDA interactions are much more pronounced in water than in methanol is clearly shown by studies in binary water–methanol mixtures (Fig. 3).[17,19,33] In pure D_2O, the complex between 1,4-dicyanobenzene (**7j**) and **5** is 0.15 kcal mol^{-1} less stable than the complex of 1,4-dimethoxybenzene (**7e**). However, with increasing methanol content in the binary mixture, the complex with the electron-accepting guest **7j** gains in relative stability and, in pure CD_3OD, is stabilized by 0.6 kcal mol^{-1} compared with the complex of **7e** which has a lower electronic complementarity.

Thermodynamics of cyclophane–arene inclusion complexation in water

A calorimetric study was performed in order to obtain accurate enthalpic values for the complexation between **5** and the *para*-disubstituted benzene derivatives **7b–k** in water.[27] By combining these values with the change in free energy[29] according to Gibb's free energy equation, the change in entropy was determined. We found that all inclusion processes were strongly exothermic, accompanied by an unfavorable entropic term (Table 4). The stability of the same complexes with similar geometry in methanol is much less favorable, and this is largely due to a strong reduction in the enthalpic driving force. We have previously identified (i) more favorable changes in solvent cohesive interactions and (ii) a larger gain in dispersion interactions as two factors responsible for the stronger enthalpic driving force for apolar complexation in water compared with methanol and other solvents.[19,26,29] A literature survey showed that many biotic and abiotic complexation processes of small molecules are characterized by thermodynamic characteristics similar to those shown for the benzene complexes of cyclophane **5**. Tight binding of apolar aromatic solutes in hydrophobic pockets of enzymes and antibodies,[34] in the cavity of cyclodextrins,[35] and in the narrow AT-rich regions of the DNA minor groove[36] are all enthalpy-driven processes.

Table 4. Thermodynamic characteristics from variable-temperature ^1H NMR titrations and calorimetry for the formation of complexes between cyclophane **5** and 1,4-disubstituted benzene guests in water and methanol.

Guest	^1H NMR	Calorimetry[a]		
	$\Delta G°_{293\ K}$[b]/ kcal mol^{-1}	$\Delta H°_{293\ K}$/ kcal mol^{-1}	$\Delta C_p°$[c]/ cal mol^{-1} K^{-1}	$T\Delta S°_{293\ K}$/ kcal mol^{-1}
Complexes in D_2O or H_2O[d]				
7k	−6.81	−11.8	−60	−5.0
7h	−6.01	−8.1	−50	−2.1
7g	−6.01	−8.1	−70	−2.1
7f	−5.86	−10.5	−130 ± 20	−4.6
7e	−5.38	−10.0	−20	−4.6
7d	−5.33	−7.2	−20	−1.9
7j	−5.23	−10.3	−30	−5.1
7i	−5.22	−9.8	−40	−4.6
7c	−4.71	−10.6	−110 ± 50	−5.9
7b	−3.69	−10.3	−60	−6.6
Complexes in CD_3OD or CH_3OH[e]				
7j	−1.86	−4.2 ± 1.5[f]		−2.4
7e	−1.20	−3.7		−2.5

[a]Calorimetric enthalpic data have an uncertainty of ±0.2 kcal mol^{-1}. [b]Free energies of complexation have an uncertainty of ±0.07 kcal mol^{-1} for complexes in D_2O and ±0.17 kcal mol^{-1} for complexes in CD_3OD. [c]Approximate numbers, except for **7c** and **7f** due to strong temperature dependence of $\Delta C_p°$ (Ref. 41). [d]^1H NMR data in D_2O, calorimetry in H_2O. [e]^1H NMR data in CD_3OD, calorimetry in CH_3OH. [f]From van't Hoff analysis of ^1H NMR data.

Whereas tight apolar complexation in water is often characterized by the thermodynamic characteristics discussed above (large negative change in enthalpy and negative change in entropy), different quantities (positive change in entropy and close to zero enthalpic change) are measured for the formation of micelles and membranes.[37] Clearly, apolar binding and other association processes in water may be either enthalpically or entropically driven. Unfortunately, in the past, hydrophobic binding has often been seen uniquely as an entropically driven process. Characterizing apolar binding processes in water as being hydrophobic is acceptable as long as no specific thermodynamic quantities are implied.

The calorimetric method provides a way of directly measuring the heat capacity changes $\Delta C_p^\circ = (\partial \Delta H^\circ / \partial T)_p$[38] that accompany the complexation between **5** and the benzene substrates. Table 4 shows that all inclusion processes in water are characterized by negative heat capacity changes.[27] With values of -20 to -130 cal mol^{-1} K^{-1}, their magnitudes are in the ranges expected from previous work on cyclodextrin[39] and cyclophane[40] inclusion complexation.

The magnitude of ΔC_p° depends strongly on the nature of the guest. The largest negative values (-110 to -130 cal mol^{-1} K^{-1}) are obtained for dipolar guests with a hydroxy group [*p*-nitrophenol (**7f**) and *p*-cresol (**7c**)].[41] In contrast, smaller ΔC_p° values (-20 to -40 cal mol^{-1} K^{-1}) are measured for the non-protic, symmetrical guests *p*-xylene (**7d**), 1,4-dimethoxy- (**7e**), 1,4-dinitro- (**7i**), and 1,4-dicyano-benzene (**7j**) (Table 4).[27] A negative change in the heat capacity occurs when the difference in enthalpy ΔH° between the state of the solvated free host and guest and the state of the solvated complex increases with temperature (Fig. 4). Our data suggest that changes in solvation of the free solutes are the main factor determining ΔC_p° in these experiments. Guests with a strong molecular dipole and a hydrogen bonding group interact strongly with their solvent cage. When the temperature is raised, this interaction becomes weaker and the enthalpy of the state of solvated free solute rises. Assuming that the host–guest complex is more rigid and less temperature-labile than the guest–solvent cage assembly, the state of the solvated complex is not raised as much with increasing temperature, and therefore, a larger negative ΔH° value is measured with increasing temperature (Fig. 4).

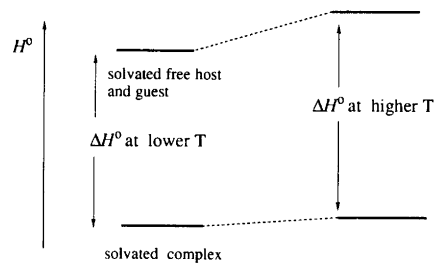


Fig. 4. Diagram to illustrate the temperature-dependent changes in complexation enthalpy which result in negative changes in the heat capacity ΔC_p°.

Solvent dependency of the enthalpic driving force for apolar complexation

Apolar arene complexation is not limited to water or alcohols but occurs in solvents of all polarity.[26,42,43] However, a dramatic solvent dependence was observed for the stability of the pyrene complex **8**.[26] Upon changing from water, the most polar, to carbon disulfide, the least polar of 18 solvents, complexation free energies decrease from $\Delta G^\circ = -9.4$ kcal mol^{-1} to $\Delta G^\circ = -1.3$ kcal mol^{-1} (Table 5). Apolar binding strength increases regularly from apolar to dipolar aprotic solvents, to polar protic solvents, and to water. Both ^{1}H NMR spectroscopy and optical titrations were needed to determine the association constants K_a covering this wide range between ca. 10 l mol^{-1} and ca. 10^7 l mol^{-1}.[26,42] Fig. 5 shows the electronic absorption and emission titrations used to determine the stability of the complex **8** in ethanol. The K_a values obtained from both titrations (2.5×10^4 and 2.4×10^4 l mol^{-1}, respectively, at 303 K) are in excellent agreement. In the absorption titration, several isosbestic points indicate the exclusive formation of a 1 : 1 complex. A strong linear free energy relationship exists between the free energy of formation of complex **8** and the solvent polarity parameter $E_T(30)$ of the various solvents including water (Fig. 6).[44] Strong correlations between $E_T(30)$ and binding free energies in related host-guest systems have also been found for binary aqueous solvent mixtures.[17,19,33]

To answer the important question about the nature of the driving force of complexation which strengthens with increasing solvent polarity, we determined, in a calorimetric study, the thermodynamic characteristics for the formation of complex **8** in a total of 12 solvents of different polarity.[27,45] Table 6 shows that the formation of **8** is enthalpically driven in all solvents, and complexation entropies are unfavorable except in benzene and *N,N*-dimethylacetamide (DMA).[27] Complexation in alcohols exhibits the largest exothermicity and, in general, the enthalpic driving force decreases from polar protic solvents, to dipolar aprotic solvents, and to apolar solvents. Correspondingly, the complexation entropy becomes increasingly less favorable as the exothermicity increases, resulting in a strong isoequilibrium relationship.

Table 6 clearly shows that the enthalpic and entropic terms can differ dramatically for complexation in solvents in which similar binding free energies are measured. For example, the free energies of formation of **8** in the three dipolar aprotic solvents acetone, $(CD_3)_2SO$ and DMA differ only by 0.5 kcal mol^{-1}. Binding in the first two solvents is strongly enthalpically driven ($\Delta H^\circ \approx -6.5$ kcal mol^{-1}) and entropically unfavorable ($T\Delta S^\circ \approx -2.4$ kcal mol^{-1}). In contrast, the enthalpic driving force for binding in DMA is more than 4 kcal mol^{-1} smaller, and inclusion in this solvent is characterized by both favorable enthalpic ($\Delta H^\circ = -2.0$ kcal mol^{-1}) and entropic ($T\Delta S^\circ = +2.4$ kcal mol^{-1}) contributions of similar magnitude.

In these studies, the important question remains of

Table 5. Association constants K_a (l mol^{-1}) and free energies of formation $\Delta G°$ (kcal mol^{-1}) for complex **8** in eighteen solvents of different polarity as expressed by $E_T(30)$ values (kcal mol^{-1}), T = 303 K.

Run	Solvent	K_a/l mol^{-1}	$\Delta G°$/kcal mol^{-1}	$E_T(30)$/kcal mol^{-1}
1	Water–1 % Me_2SO [a]	6.0×10^6	−9.4	63.0
2	2,2,2-Trifluoroethanol–1 % Me_2SO	4.2×10^5	−7.8	59.4
3	Ethylene glycol–10 % Me_2SO	1.8×10^5	−7.3	55.9
4	Methanol	4.4×10^4	−6.4	55.5
5	Formamide–10 % Me_2SO	3.0×10^4	−6.2	55.2
6	Ethanol	2.5×10^4	−6.1	51.9
7	*N*-Methylacetamide–10 % Me_2SO	1.5×10^4	−5.8	52.1
8	*N*-Methylformamide–10 % Me_2SO	4.8×10^3	−5.1	54.0
9	Acetone	1.2×10^3	−4.3	42.2
10	*N,N*-Dimethylacetamide–10 % Me_2SO-d_6	1.1×10^3	−4.2	43.0
11	Dimethyl sulfoxide-d_6 [b]	6.9×10^2	−3.9	45.0
12	*N,N*-Dimethylformamide-d_7–10 % Me_2SO-d_6	1.6×10^2	−3.0	43.7
13	*N,N*-Dimethylformamide-d_7	1.5×10^2	−2.9	43.8
14	Dichloromethane-d_2	1.2×10^2	−2.9	41.4
15	Tetrahydrofuran-d_8	8.4×10^1	−2.7	37.4
16	Chloroform-d_1	4.3×10^1	−2.3	39.1
17	Benzene-d_6	1.2×10^1	−1.5	34.5
18	Carbon disulfide	9×10^0	−1.3	32.6

[a]The aqueous solution contains [Na_2CO_3] = 10^{-3} mol l^{-1} to prevent protonation of the pentamine host. [b]H/D solvent isotope effects are below the error in K_a.

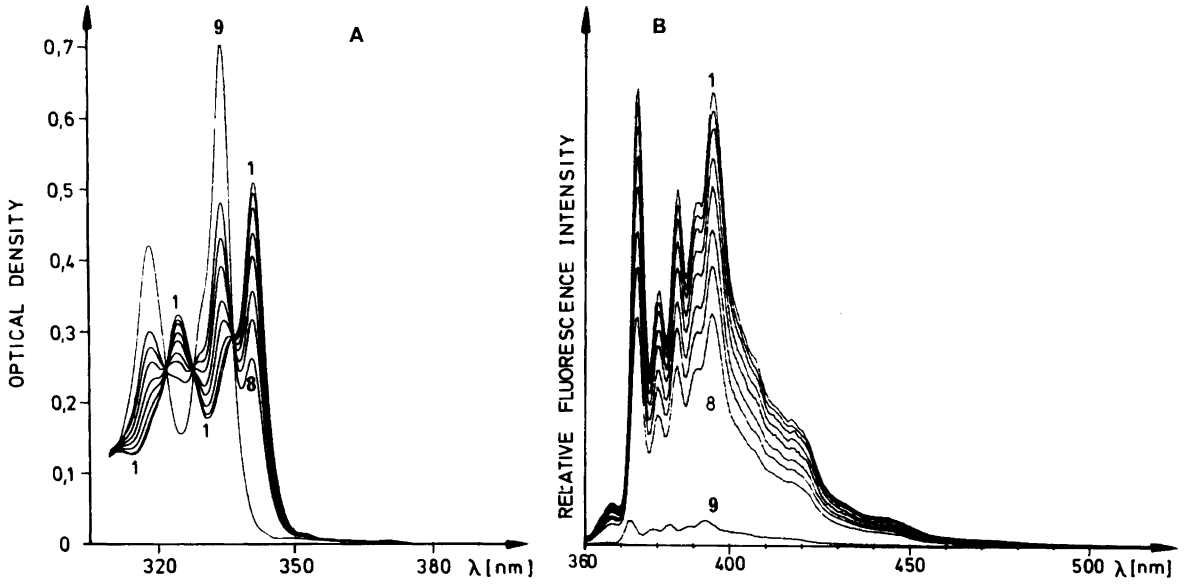
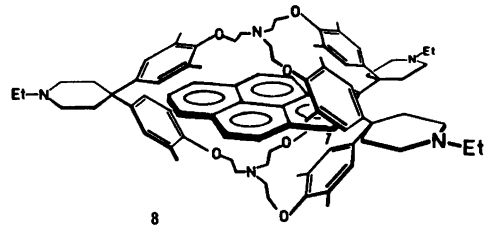


Fig. 5. Electronic absorption (A) and emission (B) titrations to determine the association constant of complex **8** in ethanol (T = 303 K). The absorption titration was evaluated at λ = 341 nm, d = 5 cm; the emission titration was evaluated at λ_{exc} = 341 nm and λ_{em} = 395 nm. In both titrations, the total guest concentration [G_o] is 2.99×10^{-6} mol l^{-1}, and the total host concentration [H_o] is the following from spectrum 1 to spectrum 9: 3.00, 2.41, 1.80, 1.20, 0.90, 0.60, 0.45, 0.30, and 0×10^{-4} mol l^{-1}.



whether desolvation prior to host–guest complexation is exothermic in some solvents and endothermic in others or whether solvent effects are always endothermic with the least unfavorable enthalpic solvent effects occurring in water and other polar protic solvents. The answer to this question lies in the accurate determination of the enthalpy change for the inclusion of the guest into the host. This important quantity might be measured experimentally by

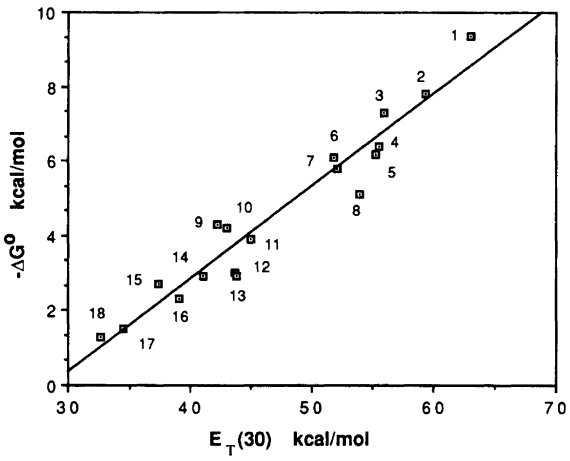


Fig. 6. Dependence of the free energy of formation $-\Delta G°$ (kcal mol^{-1}) of complex **8** (T = 303 K) on the solvent polarity as expressed by $E_T(30)$ values (kcal mol^{-1}). The numbers in the graph refer to the entries shown in Table 5.

tions bind to podands, glymes, crown ethers, and cryptands.[50]

An isoequilibrium relationship holds for the complexation of various *para*-substituted benzene derivatives by cyclophane **5** (Table 4) with an α value of 1.14 (T_{iso} = 257 K) having a linear correlation coefficient of R = 0.86.[27] A strong correlation with α = 0.72 (T_{iso} = 421 K) and R = 0.954 was also revealed when the enthalpy of formation of the pyrene complex **8** in solvents of different polarity (Table 6) was plotted against the complexation entropy (Fig. 7, solid line). More surprisingly, plots of $\Delta H°$ and $T\Delta S°$ against $\Delta G°$ (Figs. 8 and 9) yielded graphs that showed the existence of two isoequilibrium relationships which are separated by the binding strength. The first six solvents in Table 6 fall on one line (A), and the weaker binding solvents comprise the second line B. The dual isoequilibrium relationship seen in the plots correlating the free energy with the complexation enthalpy and entropy should also be expressed in the plot of enthalpy against

Table 6. Enthalpic ($\Delta H°$) and entropic ($T\Delta S°$) contributions to the free energies of formation $\Delta G°$ of complex **8** in solvents of different polarity.

Run	Solvent	$\Delta G°$/kcal mol^{-1} [a]	$\Delta H°$/kcal mol^{-1}	$T\Delta S°$/kcal mol^{-1}
1	2,2,2-Trifluoroethanol	−7.8 ± 0.1	−20.0 ± 0.2	−12.2 ± 0.2
2	Methanol	−6.4 ± 0.1	−12.0 ± 0.2	−5.6 ± 0.2
3	Ethanol	−6.1 ± 0.1	−11.0 ± 0.2	−4.9 ± 0.2
4	*N*-Methylacetamide	−5.8 ± 0.1	−9.0 ± 0.2	−3.2 ± 0.2
5	*N*-Methylformamide	−5.1 ± 0.1	−5.6 ± 0.1	−0.5 ± 0.1
6	*N,N*-Dimethylacetamide [b]	−4.4 ± 0.1	−2.0 ± 0.4	+2.4 ± 0.4
7	Acetone	−4.3 ± 0.1	−6.6 ± 0.4	−2.3 ± 0.4
8	Dimethyl sulfoxide	−3.9 ± 0.2	−6.4 ± 0.2	−2.5 ± 0.2
9	*N,N*-Dimethylformamide	−2.9 ± 0.2	−3.7 ± 0.2	−0.8 ± 0.2
10	Tetrahydrofuran	−2.7 ± 0.2	−3.0 ± 0.2	−0.3 ± 0.2
11	Chloroform	−2.3 ± 0.2	−3.1 ± 0.2	−0.8 ± 0.2
12	Benzene	−1.5 ± 0.2	−0.8 ± 0.2	+0.7 ± 0.2

[a]The $\Delta G°$ values in runs 8–12 were obtained in deuteriated solvents, whereas all calorimetric data result from protonated solvents. The amounts of 1 % (v/v) Me_2SO (in run 1) and 10 % (v/v) Me_2SO (in runs 4 and 5) were co-solvents in binding titrations to determine $\Delta G°$ which introduces a non-determined minor error into the concentrations used to transform measured heats into enthalpies. [b]$\Delta G°$ value from calorimetric titration.

studying directly gas-phase complexation. Alternatively, a van't Hoff analysis on the temperature dependence of gas phase association constants obtained computationally by double annihilation techniques in free energy perturbational theory would yield this enthalpic term.[1,46]

Isoequilibrium relationships in apolar complexation

A linear relationship between $\Delta H°$ and $\Delta S°$ commonly known as an isokinetic (isoequilibrium) relationship[47] has been observed in many processes including host–guest complexation.[35b,c,48,49] The slope of the line in the plot of $T\Delta S°$ against $\Delta H°$ is defined as the α parameter, and the β parameter represents the slope when $\Delta H°$ is plotted against $\Delta S°$. The α parameter has been used in host–guest studies to reflect the amount of reorganization required when cavity entropy change. Indeed, a reinvestigation of the plot of the complexation enthalpy against entropy revealed the two sets of solvents (dotted lines in Fig. 7). A literature survey of solvent dependences in host–guest complexation and transport phenomena shows that linear relationships between thermodynamic parameters do exist in some systems, but usually only between $\Delta H°$ and $\Delta S°$ or between $\Delta H°$ and $\Delta G°$.[47-49] Precedence for the strong dual isoequilibrium relationships is found in studies by Tagaki *et al.*[51] These researchers observed a dual isoequilibrium relationship dependent upon the binding free energies in their studies of alcohol complexation with α- and β-cyclodextrins.

To explain the isoequilibrium relationships of the pyrene complex **8** in solvents of different polarity, it is important to consider that, according to ^{1}H NMR analysis, a very similar

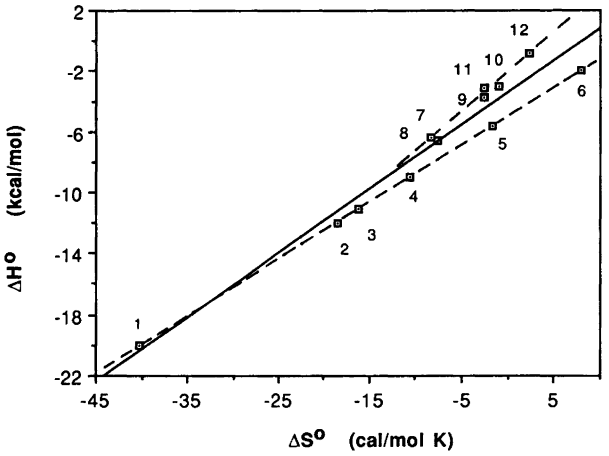


Fig. 7. Solid line: isoequilibrium relationship (R = 0.954) between the enthalpy ($\Delta H°$) and the entropy ($\Delta S°$) for the formation of complex **8** at T = 303 K in various solvents. For the numbering of the solvents, see Table 6. Dotted lines: dual isoequilibrium relationships revealing two sets of solvents. The linear correlation coefficients are R = 1.00 for the solvents 1–6 having the larger free energies and R = 0.979 for the other six solvents.

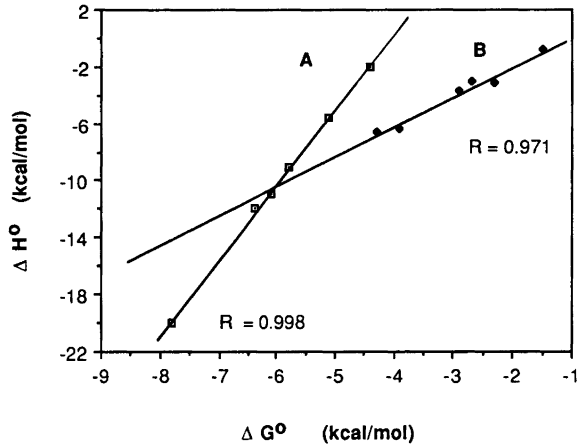


Fig. 8. Dual isoequilibrium relationship between the enthalpy ($\Delta H°$) and the free energy ($\Delta G°$) for the formation of complex **8** at T = 303 K in various solvents. The solvents on lines A and B correspond to those in runs 1–6 and 7–12 in Table 6, respectively.

tight and highly structured complex forms in all environments. Therefore, the enthalpic term for the intrinsic host–guest interactions should be of a similarly favorable magnitude in all solvents. Correspondingly, the entropic component associated with the tight host–guest complexation step must be strongly unfavorable in all solvents. However, the complexation entropy varies from strongly unfavorable in polar protic solvents to near zero values in apolar solvents, partially compensating an enthalpic term which becomes gradually less favorable upon changing from polar protic, to dipolar aprotic, and to aprotic solvents (Table 6). From these considerations, it is obvious that the compensatory

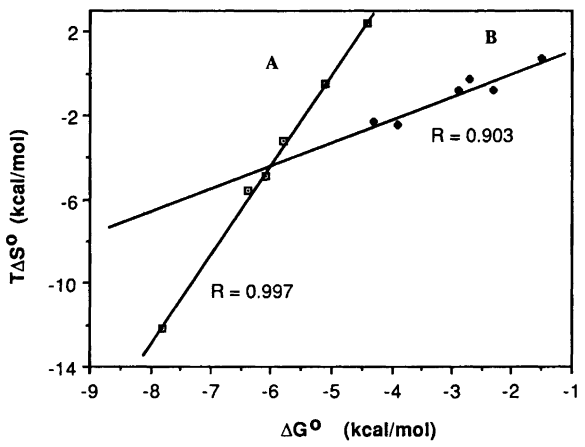


Fig. 9. Dual isoequilibrium relationship between the entropy ($T\Delta S°$) and the free energy ($\Delta G°$) for the formation of complex **8** at T = 303 K in various solvents. The solvents on lines A and B correspond to those in runs 1–6 and 7–12 in Table 6, respectively.

relationship originates from differences in solvent interactions rather than from changes in the host–guest relationship.

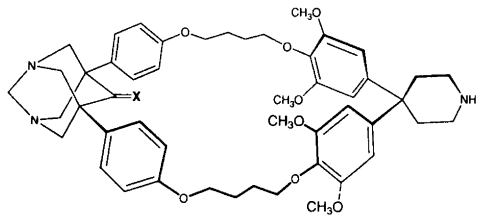
The separation of the solvents into two isoequilibrium relationships also appears to originate from differences in solvent interactions. Line A has an α value of 0.81 which means that the entropic change plays, expectedly, a larger role for these solvents as compared with the solvents comprising line B with a smaller α value of 0.55. The strongest binding solvents on line A are all hydrogen bonding solvents with the exception of dimethylacetamide (DMA). Plots of the acceptor number AN[52] of these solvents, including DMA, versus each one of the three thermodynamic quantities ($\Delta G°$, $\Delta H°$, and $T\Delta S°$) for the formation of **8** show strong correlations in each case ($R > 0.91$). The location of DMA together with hydrogen bonding solvents on line A rather than on line B together with the other aprotic solvents is surprising at first. However, with its particularly large dipole moment and very high potential for strong dispersion interactions, the cohesive interactions in DMA possibly are more comparable to those of polar protic than aprotic solvents. There is precedence in the literature for the additional unique behavior and properties of DMA, as compared with the other formamide solvents and related compounds.[53]

Solvation of host substituents determines complexation strength

In the preceding section on EDA interactions, it was demonstrated that complexation-induced changes in the solvation of guest substituents may have a large effect on the measurable host–guest association strength in the liquid phase. At the end of this short review, the effect of such changes in substituent solvation will be further highlighted by a study performed with a novel host system.[54] Cyclo-

Table 7. Association constants K_a and free energies of formation $\Delta G°$ for complexes of cyclophanes **9–11** with 6-cyano-2-naphthol in D_2O–DCl–CD_3OD (57.5 : 2.5 : 40 vol%), T = 293 K.

Cyclophane	K_a/l mol^{-1}	$\Delta G°$/kcal mol^{-1}
9	210	−3.1
10	40	−2.2
11	no measurable complexation	



9 X = H_2
10 X = O
11 X = H, OH

phanes **9–11** possess large cavity binding sites into which functional groups converge. The cavity in these macrocycles is sufficiently large to accommodate naphthalene substrates independent of the nature of the convergent substituent X. However, in D_2O–DCl–CD_3OD (57.5 : 2.5 : 40; vol%) at T = 293 K, the three macrocycles differ strongly in their receptor properties. Whereas the methylene derivative **9** forms a moderately stable complex with 6-cyano-2-naphthol, the carbonyl compound **10** binds only weakly, and no complexation is observed with the hydroxy derivative **11**. We explain the difference in binding free energy of more than 3 kcal mol^{-1} by the solvation of the functional groups on **9–11**. Whereas the methylene derivative **9** provides an apolar binding site suitable for naphthalene incorporation, the functional groups on **10** and **11** lead to a more favorably solvated cavity, therefore reducing the solvophobic driving forces for complexation. Upon incorporation of naphthalene into the cavity of **10** and **11**, the hydroxy and the carbonyl groups lose some of their favorable solvation which apparently costs either some or all of the binding free energy, respectively.

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