

Binding Features of Molecular Clips. Separation of the Effects of Hydrogen Bonding and π – π Interactions

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Abstract: The ability of clip shaped molecules based on the building block diphenylglycoluril to form complexes with dihydroxybenzene guest molecules has been studied in detail. The binding strength of these complexes can be varied over a wide range ($K_a \approx 0$ – 10^5 M⁻¹), by applying small modifications in the host or the guest molecule. It is found that the complexation is a combination of different effects, viz., hydrogen bonding, π – π stacking interactions, and a cavity effect.

Introduction

Molecular recognition continues to be a topic of great interest in supramolecular and biomimetic chemistry.^{1,2} Depending upon the function and the need of selectivity in the recognition process, several types of interactions can play a role. In aqueous solution the hydrophobic effect often is the main driving force for host–guest complex formation,³ which can lead to very high association constants for natural as well as synthetic systems. The selectivity of the binding can be improved if additional interactions are involved, such as hydrogen bonding, electrostatic interactions, van der Waals forces, and π – π stacking interactions. When these interactions are highly complementary and directional, the binding process will be completely selective as in the case of the mutual recognition of DNA base pairs, primarily by hydrogen bonding, which has served as an example for the design of many synthetic hosts capable of binding guests according to the same complementarity principles.⁴ The approach of using a combination of interactions is particularly

important for receptors in organic solvents, because here the hydrophobic effect is lacking. Rebek et al. have used this approach to develop host systems that can bind guests based on hydrogen bonding and π – π stacking.⁵ The latter interaction is possible because of the presence of an adjacent aromatic surface, which also induces a higher degree of preorganization. An even higher degree of preorganization is achieved with two aromatic surfaces adjacent to the hydrogen bonding site resulting in tweezer type receptor molecules, as synthesized by Zimmerman.⁶ Whitlock et al. have shown that by carefully tuning the cavity size, very high association constants in chloroform can be achieved.⁷

A general thorough understanding of the mechanism of complex formation in organic solvents is important for the future development of host–guest systems and supramolecular devices.⁸ Toward this goal we have been designing and studying receptor molecules based on diphenylglycoluril (DPG) which are capable of binding dihydroxybenzenes.^{9a} Clip molecule **1** has a preorganized cleft, which can bind a guest by hydrogen bonding and π – π stacking interactions. Clip molecule **2** is capable of complexing aromatic guests by π – π interactions only.¹⁰ To examine the binding forces in our host–guest complexes more precisely, we have synthesized a series of new receptor molecules based on the diphenylglycoluril building block.^{9b} Here we present binding studies and computational investigations, that allow us to more fully understand and quantify the contributions of the different intermolecular interactions that play a role in host–guest binding within these systems.

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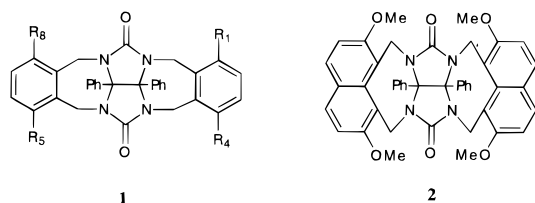
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Results and Discussion

Hydrogen Bonding, π - π Interactions, and Cavity Effects.

As depicted in Figure 1, clip molecules of type **1** contain a cleft with a cavity size of approximately 6.4 Å (center-to-center distance) which is ideal to bind flat aromatic guest molecules in between. From our earlier studies^{9a} it is known that the main binding interactions in the formation of complexes of dihydroxybenzenes with molecular clip **1a** in chloroform are (i) hydrogen bonding between the OH groups of the guest and the urea carbonyl functions of the host and (ii) π - π interactions between the aromatic surfaces of the guest and the host. It is of use to be able to manipulate the strength of complexation and to thoroughly understand the processes involved in binding. Toward this goal the complex formation between a series of new receptor molecules and guest molecules (Chart 1) were studied. The influence of the hydrogen bond donor (guest), the hydrogen bond acceptor (host), the presence and size of the cavity wall of the host, and the substituents on the host and guest upon binding will be discussed below. Binding affinities were calculated from ¹H NMR titrations experiments, which provide association constants (K_a 's) and complex induced shift (CIS) values, the latter being the maximum shift for a given proton of the host or guest, when the complex is completely formed. In addition IR studies and calculations have been performed.¹¹

Influence of the Hydrogen Bond Donor on Binding.

Previous binding studies with clip molecules and 1,2-dihydroxybenzene, 1,3-dihydroxybenzene, and, 2,7-dihydroxynaphthalene guest molecules have revealed that the C=O-H-O angle of the hydrogen bond has a substantial influence on the strength of this bond and hence on the association constant of the host-guest complex.^{9a} The strength of this hydrogen bond is also expected to be dependent upon the type of donor, e.g., it will decrease in the series 1,3-dihydroxybenzene > 1,3-diaminobenzene > 1,3-dithiohydroxybenzene. It has been reported by Abraham¹² that for complexes, purely based on hydrogen bonding, the strength is proportional to the hydrogen bond acidity of the donor. In line with this work, we measured the association constants of complexes between **1a** and the above mentioned guests and found that these constants drop with decreasing acidity of the guest molecule, *viz.*, from $K_a = 2600 \text{ M}^{-1}$ (1,3-dihydroxybenzene) to $K_a = 65 \text{ M}^{-1}$ (1,3-diaminobenzene) to $K_a \approx 0 \text{ M}^{-1}$ (1,3-dithiohydroxybenzene). The acidity of the OH groups of 1,3-dihydroxybenzenes can simply be varied by using different substituents on the 5-position of the guest molecule (Chart 1).¹³ The strength of the complexation with clip **1a** was found to change significantly when the substituent was varied (Table 1). 3,5-Dihydroxypentylbenzene

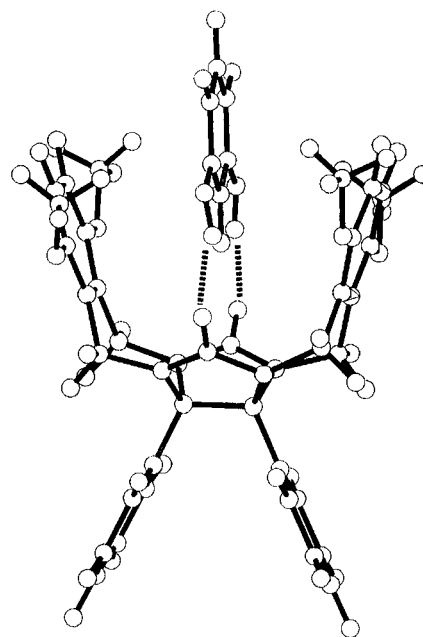


Figure 1. Binding of an 1,3-dihydroxybenzene guest molecule between the aromatic side-walls of clip **1a**, due to hydrogen bond formation and π - π stacking interactions.

(**G1**), which has a slightly electron releasing substituent, has a $K_a = 1500 \text{ M}^{-1}$ and a binding free energy $\Delta G_b = -18.1 \text{ kJ/mol}$ which is about 10 kJ/mol lower than that of 3,5-dihydroxycyanobenzene (**G8**, $K_a = 10^5 \text{ M}^{-1}$, $\Delta G_b = -28.5 \text{ kJ/mol}$) which contains an electron withdrawing substituent. A plot of the binding energy as a function of the Hammett constant ($\sigma_m(R)$) of the substituent of the guest, which in turn is related to the acidity of the OH groups, gives a good linear correlation (see Supporting Information, Figure S2). An identical binding study was carried out with substituted phenols as guest molecules. In the case of these guests only one hydrogen bond can be formed with the urea carbonyls of the host. As seen for the 1,3-dihydroxybenzene derivatives an increase in binding was observed as the substituent became more electron withdrawing (Table 2). The binding strength of the phenolic guests, however, was found to be less dependent upon the substituent than the binding strength of the 1,3-dihydroxybenzene guests (the gradients in the Hammett plots being -10.0 and -14.7, respectively (see Supporting Information, Figure S2)). This is a result of the fact that in the former case the substituent on the guest changes the strength of only one hydrogen bond, whereas in the latter case it changes the strength of two bonds.

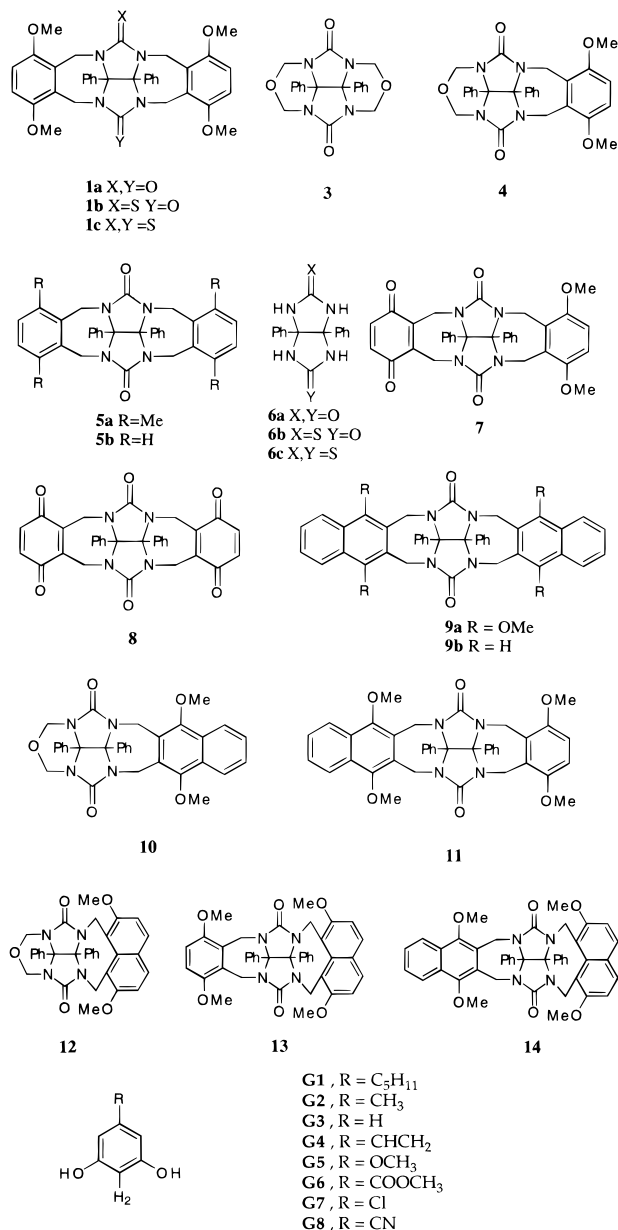
Influence of the Hydrogen Bond Acceptor on Binding. If one or two of the carbonyl oxygen atoms of **1a** were replaced by sulfur atoms (**1b** and **1c**, respectively), which are known to be very poor hydrogen bond acceptors,¹² the observed complexes formed with 1,3-dihydroxybenzenes were found to be much weaker (Table 1). Again, however, a linear correlation was found, between the Hammett constant and the strength of binding (see Figure 2a). Examination of the plots for each series revealed that the average binding strength in clip **1b**, which possesses one carbonyl and one thiocarbonyl group, is not exactly midway between those in **1a** and **1c**. This is due to the fact that when only one hydrogen bond is formed, a more optimal geometry is possible, resulting in a stronger bond (the single OH-O hydrogen bond in the complexes formed with **1b** is stronger than each of the hydrogen bonds formed with

(11) Some clip molecules formed dimers by self-complexation in solution, which is a possible competition for the guest complexation. The self-complexation constants in general were so low that the guest complexation was not influenced. It was not necessary, therefore, to take this self-complexation into account in the calculations of the association constants. A more detailed study concerning interactions between clip molecules in solution and the solid state will be published in a separate paper.³⁰

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Chart 1



1a). The optimal geometry of complexation to two carbonyl functions apparently is slightly different from that to one carbonyl function. This was confirmed by measuring the ¹H NMR CIS values of the different side-wall protons of clip **1b**, which indicated that the guest is unsymmetrically bound within the cleft and shifted toward the single carbonyl group (see Figure 3). This offset geometry is in line with molecular mechanics calculations which we carried out on **1b** and the guest **G6**.¹⁴ The slope of the plot of the binding free energy (ΔG_b) versus the Hammett constant ($\sigma_m(R)$) decreased when the two carbonyl groups of the clip were replaced by thiocarbonyl groups but was not zero. As will be shown below, the contribution of hydrogen bonding to the binding can be neglected in the case of complexation in clip **1c**. In this host, binding is solely based upon interactions between the aromatic walls of the cleft and the aromatic guest.

Influence of the Cavity Wall on Binding. The substituent effects observed for the binding of guests in clip **1c** suggests that other factors than hydrogen bonding are influenced when

the substituent on the guest is changed. The electron density on the aromatic ring of the guest, and hence the interaction of this ring with the π -systems of the walls of the host, is also dependent upon the guest substituent. To examine the factors involved in the π - π interactions, binding affinities of the guests were measured with clip molecules possessing no, one or two cavity walls (**3**, **4**, **1a**, Figure 4).

In the case of **3** the binding can only be based upon hydrogen bonding. In the case of **4** this hydrogen bonding can be assisted by a single π - π interaction between the guest and one side-wall and in the case of **1a** by π - π interactions with two side-walls. From the X-ray structures of **1a**, **3**, and **4** (Figure 4) it is clear that there are no geometric differences in the diphenylglycoluril framework of the three molecules. Any difference in the binding properties between **1a** and **4**, therefore, must be a result of the specific cleft-shape of **1a**. The results of the binding studies with molecules **3**, **4**, and **1a** and different guests are summarized in Tables 1–3. In general the binding constants of guest molecules to host **4** are only slightly higher than those to molecule **3**. A Hammett plot of the data shows that the slope of the curve of the binding free energy versus the Hammett σ_m constant for complexation to compound **4** is larger (–12.5) than that for complexation to compound **3** (–6.3) (see Figure 2b). From this result we may conclude that there is a π - π interaction between the guest molecule and the side-wall of **4**, since binding to **4** is much more substituent dependent than the binding to **3**. Comparison of these data with those obtained for clip **1a** clearly reveals that the addition of a second side-wall to the host, which result in the formation of a cleft, significantly increases the association constants. Zimmerman has observed a similar increase in binding for his molecular tweezers⁶ when a second aromatic surface is added. In the case of the receptor with only one side-wall (**4**) the favorable enthalpic effect of the interaction of the side-wall with the guest is cancelled out by the loss in translational and rotational entropy. These entropy effects are already accounted for when the second wall is added (**1a**). A guest bound to receptor **1a** has an extra π -stacking interaction which is free from loss in entropy, resulting in a higher binding constant. Whitlock,⁷ Cram,¹⁷ and Collet¹⁸ all have shown that the “snugness” of fit between the host and guest plays a significant role in the binding. The better the fit, the larger the van der Waals contact. Collet¹⁸ and Still¹⁹ have observed an additional solvation effect for their cavity containing hosts. In solvents that fitted poorly within the cavities, the binding constants of the host–guest complexes were significantly higher. In our case, chloroform molecules are too big to solvate the cavity, and upon complexation of the guest the cleft is favorably filled. The overall complex is much better solvated than the two individual components. In summary, we propose that when a second wall is added to our host molecule, the following effects play a role: (i) the second π - π interaction is free from entropy losses, (ii) a larger van der Waals contact between the host and the guest molecule is possible as a result of the guest being sandwiched between the two aromatic side-walls of the host, and (iii) a favorable solvation effect arises because the cavity is too small to be solvated by solvent molecules. The combined features (i) and (iii) can be described as “the cavity effect”. This effect together with (ii) makes that **1a** is a better receptor molecule than **4**.

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Table 1. Association Constants (M^{-1}) and Binding Free Energies (kJ/mol) Measured for Complexes between Host Molecules Containing Different Hydrogen Bond Acceptors Sites and Various 1,3-Dihydroxybenzene Guest Molecules^a

guest	host 1a			host 1b			host 1c		
	K_a	ΔG	CIS ^b	K_a	ΔG	CIS ^b	K_a	ΔG	CIS ^b
G1	1500 (200)	-18.1 (0.2)	-2.45	<i>c</i>	<i>c</i>	<i>c</i>	74 (15)	-10.7 (0.7)	-1.79
G2	1900 (75)	-18.7 (0.1)	-2.48	450 (40)	-15.1 (0.2)	-2.40	56 (10)	-9.8 (0.4)	-1.79
G3	2600 (200)	-19.5 (0.2)	-2.61	750 (100)	-16.4 (0.3)	-2.40	51 (4)	-9.7 (0.2)	-2.10
G4	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	86 (5)	-11.0 (0.1)	-2.16
G5	4400 (300)	-20.8 (0.2)	-2.56	1300 (230)	-17.8 (0.5)	-2.30	82 (15)	-10.9 (0.5)	-1.95
G6	16500 (2000)	-24.1 (0.3)	-2.75	2500 (200)	-19.4 (0.2)	-2.76	177 (12)	-12.8 (0.2)	-2.32
G7	16000 (2000)	-24.0 (0.3)	-2.82	3500 (180)	-20.2 (0.1)	-2.67	225 (15)	-13.4 (0.2)	-2.52
G8	1×10^5 (5×10^4)	-28.5 (2.2)	-2.95	<i>c</i>	<i>c</i>	<i>c</i>	772 (75)	-16.5 (0.2)	-2.46

^a In chloroform. Errors are given in parentheses. ^b Complexation induced shift (CIS) values for the H² proton of the guest molecules. ^c Not determined.

Table 2. Association Constants Measured for Receptor **1a** and Different Substituted Phenols^a

guest	K_a (M^{-1})	ΔG (kJ/mol)
4-methoxyphenol	20 (15)	-7.4
3-methylphenol	15 (10)	-6.7
phenol	29 (5)	-8.3
4-chlorophenol	80 (10)	-10.8
methyl-3-hydroxybenzoate	160 (15)	-12.6
4-cyanophenol	415 (50)	-14.9
4-nitrophenol	1200 (60)	-17.6

^a In chloroform. Errors are given in parentheses.

Effects of Substituents on the Cavity Wall. As outlined above the electron density on the aromatic ring of the guest influences the π - π interaction between the host and the guest. In a similar manner substituents on the aromatic walls of the host can affect this π - π interaction. In order to investigate this effect in more detail the binding affinities of clips **5a** and **5b**, having different substituents on the aromatic wall, were measured and compared to **1a**. The results for different guest molecules are presented Table 3. (See Supporting Information, Figure S3). Changing the methoxy groups of clip **1a** for methyl groups (**5a**) decreases the binding strength significantly. The clip molecule with unsubstituted benzene rings as side-walls (**5b**) has an even lower affinity for the dihydroxybenzene guest molecules. These differences are mainly due to changes in the strength of the π - π interactions and the size of the cavity. A stronger π - π interaction between the host and the guest results in a larger dependency of the ΔG of binding on the Hammett parameter $\sigma_m(R)$, giving a larger slope for **1a** compared to **5a** and **5b** in the plot of the binding free energy versus $\sigma_m(R)$ (see Supporting Information, Figure S3). The "cavity effect" will also be slightly different for clips **1a**, **5a**, and **5b**, since the size of the cavity increases when the substituents on the side-walls are larger. It should be noted that the side-wall substituent may also change the solvation of the urea carbonyl groups and in this way affect the binding affinity, but since the difference in the hydrogen bonding properties between **1a** and **3** is small, this effect is not expected to contribute significantly.

Separation of the Factors Determining the Binding Affinities. The results of the binding studies allow us to estimate what contribution each of the different interactions has on the binding of 1,3-dihydroxybenzene guests in the clip molecules. This can be done by examining the fitted curves of the binding free energy versus the Hammett constant $\sigma_m(R)$ for the different clips (eqs 1-5). Assuming that hydrogen bonding to the

thiocarbonyl groups of the clips has a negligible contribution to the binding,²⁰ eq 1 for clip **1c** gives the contribution of the two walls to the binding free energy. Eq 2 obtained for clip molecule **3** describes the contribution of the hydrogen bonding to this energy (it is assumed that there is no difference in solvation of the carbonyl groups in **1a** and **3**). The sum of eqs 1 and 2 (see eq 3) must be equal to the equation for binding to clip molecule **1a** (eq 4). It can be seen that a good agreement is obtained, given the errors in the experiments (estimated errors are approximately 1 kJ/mol).

clip **1c** ($2 \times \pi$ - π interaction + cavity effect)

$$-\Delta G = 10.4 + 9.1\sigma \text{ (kJ/mol)} \quad (1)$$

clip **3** (hydrogen bonding)

$$-\Delta G = 7.8 + 6.3\sigma \text{ (kJ/mol)} \quad (2)$$

eq (1) + (2)

$$-\Delta G = 18.2 + 15.4\sigma \text{ (kJ/mol)} \quad (3)$$

clip **1a**

$$-\Delta G = 19.3 + 14.7\sigma \text{ (kJ/mol)} \quad (4)$$

clip **4** - clip **3** ($1 \times \pi$ - π interaction)

$$-\Delta G = 2.5 + 6.3\sigma \text{ (kJ/mol)} \quad (5)$$

Since molecule **4** has only one aromatic wall and hence does not possess a cavity, the π - π interaction energy for one wall can be obtained by subtracting the equation for **3** from the one for **4**, giving eq 5. The cavity effect, which can be considered to be independent of the substituent of the guest, can then be estimated by subtracting twice the π - π interaction of one wall (eq 5) and the hydrogen bond contribution (eq 2) from the equation for **1a**. This gives a value of approximately 6 kJ/mol. This cavity effect is only a minor part of the binding and is significant only when both the π - π interactions and hydrogen bonding interactions are small.

ΔH and ΔS of Binding. The thermodynamic parameters ΔH and ΔS for the binding of the guest 1,3-dihydroxybenzene in a series of clips were determined by ¹H NMR titrations. The results are presented in Table 5. It can be concluded that the binding is enthalpy driven. Examination of the values reveals

(20) In a forthcoming paper it will be shown that clip **1b** binds with approximately the same affinity as a clip in which one carbonyl group is reduced to a CH₂ group. This is additional proof for the fact that the thiocarbonyl groups are not involved in hydrogen bonding. Gieling, G.; Scheeren, H.; Nolte, R. J. M. To be published.

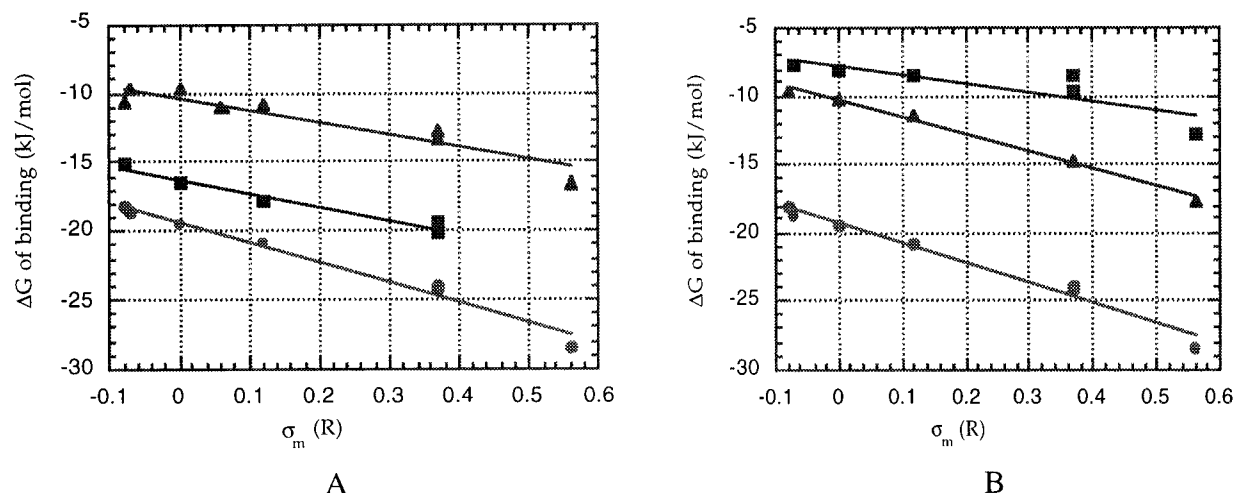


Figure 2. Binding free energies of various guest molecules (see Table 1) in clip molecules containing different hydrogen bond acceptors sites (Figure A; **1a**, ●; **1b**, ■; **1c**, ▲) and a different number of side-walls (Figure B; **1a**, ●; **3**, ■; **4**, ▲) plotted as a function of the Hammett constant (σ_m (R)) of the guest substituent (R).

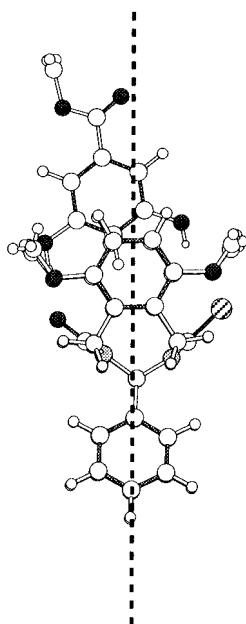


Figure 3. Binding geometry of guest molecule **G6** in clip **1b**, as determined by molecular mechanics calculations (CHARMm Force Field) which is in agreement with the experimentally determined CIS values.

that on going from clip **1a** to **1c**, both ΔH and ΔS decrease by a factor of 2, which is in line with the linear relation between ΔH and ΔS reported in the literature for hydrogen bond formation.²¹ The increases in ΔH and ΔS for binding to **1a** as compared to **4** are both quite large, as expected, indicating that the cavity effect involved in the binding to **1a** consists of both an enthalpic as well as an entropic term.

The ΔS value for binding in **1a** is approximately zero in the solvent mixture acetonitrile/chloroform (1:10, v/v) (Table 4), and the binding is determined by a small negative enthalpy factor only. This is because acetonitrile solvent molecules are small enough to fit into the cleft of **1a**, resulting in a better solvation of the cleft and hence in a smaller cavity effect.

Geometry of the Complexes. From the ^1H NMR experiments the complex induced shift (CIS) values can be determined, which are the differences in chemical shifts between the fully bound and the unbound species. A computer program was

written, based on the Johnson and Bovey tables, which calculates using ring current shifts, the approximate CIS values of certain protons in the host–guest complex.^{9a,22,23} The CIS values for the H2 proton of the 1,3-dihydroxybenzene guest molecules were calculated to increase if the guests are bound more deeply in the cleft of the clips. The CIS values also increased if the side-walls of the clip are positioned closer together. Using this program and the experimentally obtained CIS values, the insertion depth of the guest within the cavity of the clip was calculated. The general trend for all clips of type **1** was that guest molecules with more electron rich aromatic rings are bound less deeply within the cleft of the host molecule. The maximum difference in binding depth for the different guests was 0.3–0.4 Å for clip **1a**. In the case of clip **1c** a similar variation in binding depth was observed. The guests, however, were generally bound more deeply in clip **1a** than in **1c**, which resulted in a smaller variation of the CIS values for complexes with the former host. In clip **1c** the binding is based on π – π interactions and the cavity effect, whereas in clip **1a** hydrogen bonding is also a very important factor. The results obtained with **1a** and **1c** suggest that the optimal distance for π – π interaction is further out of the cavity than the optimal distance for hydrogen bonding. Thus, when a guest is bound in clip **1a** the hydrogen bonds are pulling it inside the cleft. In order to achieve an optimum π – π interaction the cavity walls are pushing the guest slightly out of the cavity. The resulting complex geometry with the host is a compromise between these two forces.

The complexes formed between the different 1,3-dihydroxybenzenes and the clip molecules were also studied by IR spectroscopy measurements in CHCl_3 solution. In an earlier study we showed that the hydrogen bonds of the guest are directed toward the π electrons of the urea carbonyl functions.^{9a} In the present study we looked at the influence of the guest substituent on the difference in the OH stretching frequency of the bound and the unbound guest ($\Delta\nu = \nu_{\text{unbound}} - \nu_{\text{bound}}$; (see Supporting Information, Figure S4)). In the case of molecule **3**, which binds substrates by means of hydrogen bonds exclusively, the OH stretching frequency was only very slightly substituent dependent²⁴ ($\Delta\nu = 162 - 174 \text{ cm}^{-1}$). This suggests that a stronger hydrogen bond to the urea carbonyl functions, as observed for guests with an electron withdrawing group, does

(22) Johnson, C. S., Jr.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.

(23) It should be noted that the same features which are responsible for a difference in association constants may also alter the aromatic ring current. Hence the calculations are only approximate.

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Table 3. Association Constants (M^{-1}) and Binding Free Energies (kJ/mol) for Host Molecules **3**, **4**, **5a**, and **5b**^a

guest	host 3			host 4			host 5a			host 5b		
	K_a	ΔG	CIS ^c	K_a	ΔG	CIS ^b	K_a	ΔG	CIS ^b	K_a	ΔG	CIS ^b
G1	23 (5)	-7.8 (0.4)	1.47	50 (10)	-9.7 (0.5)	-0.96	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>
G2	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	290 (30)	-14.1 (0.3)	-2.63	74 (15)	-10.7 (0.5)	-1.97
G3	25 (10)	-8.0 (1.2)	1.59	65 (10)	-10.3 (0.4)	-1.09	360 (20)	-14.6 (0.1)	-2.93	175 (15)	-12.8 (0.2)	-2.33
G4	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	<i>d</i>	670 (30)	-16.1 (0.1)	-2.85	215 (20)	-13.3 (0.2)	-2.41
G5	32 (12)	-8.6 (1.1)	1.51	105 (15)	-11.5 (0.4)	-1.20	510 (20)	-15.4 (0.1)	-2.84	195 (20)	-13.1 (0.3)	-2.37
G6	30 (15)	-8.4 (1.7)	1.72	<i>d</i>	<i>d</i>	<i>d</i>	1600 (250)	-18.3 (1.3)	-3.41	475 (30)	-15.3 (0.2)	-2.97
G7	52 (20)	-9.8 (1.2)	1.85	385 (25)	-14.7 (0.2)	-1.24	2400 (200)	-19.3 (0.2)	-3.02	850 (50)	-16.7 (0.2)	-2.88
G8	175 (30)	-12.8 (0.5)	1.88	1250 (100)	-17.7 (0.2)	-1.34	<i>d</i>	<i>d</i>	<i>d</i>	3500 (400)	-20.2 (0.3)	-3.07

^a In chloroform. Errors are given in parentheses. ^b Complexation induced shift (CIS) values for the H² proton of the guest molecules. ^c CIS values for the OH protons of the guest molecules. ^d Not determined.

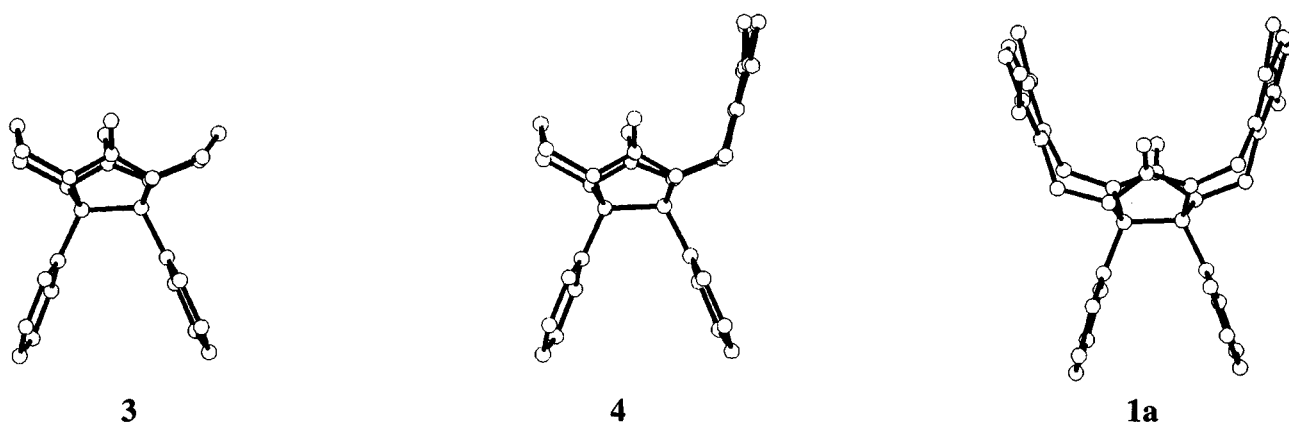


Figure 4. X-ray structures showing the difference between a clip-shaped molecule **1a** and molecules in which binding is based upon hydrogen bonding only (**3**) and hydrogen bonding assisted by an aromatic moiety (**4**). Hydrogens have been omitted for clarity. The X-ray structures of **3** and **1a** have been published;^{9a,15} that of **4** will be published elsewhere.¹⁶

Table 4. ΔH and ΔS of Binding for Complexes between 1-Methoxy-3,5-dihydroxybenzene (**G5**) and Different Clip Molecules^a

	1a	1a ^b	1c	4	7
ΔH (kJ/mol)	-38 ± 10	-10 ± 3	-20 ± 5	-17 ± 5	-31 ± 8
ΔS (J/mol·K)	-63 ± 30	0.6 ± 7	-31 ± 18	-27 ± 10	-53 ± 30

^a Determined in chloroform. ^b In chloroform/acetonitrile (10:1 v/v). At six different temperatures (270, 280, 298, 305, 318 and 328K).

Table 5. Association Constants (M^{-1}) of Olivetol in Clips with Different Side-Walls^a

clip	K_a (M^{-1})	ΔG (KJ/mol)	clip	K_a (M^{-1})	ΔG (KJ/mol)
1a	1500 (300) ^b	-18.1	11	55 (20) ^b	-9.9
2	1400 (100) ^c	-17.9	12	20 (10) ^c	-7.4
9a	<1 (5) ^b		13	1060 (100) ^c	-17.2
9b ^d	70 (20) ^b	-10.5	14	90 (10) ^c	-11.1
10	<1 (5) ^b				

^a In chloroform. Errors are given in parentheses. ^b Association constants were determined by following the chemical shift of the side-wall protons as a function of the guest concentration. ^c Association constants were determined by integration of the signals of the different conformers.

not result in a larger difference in OH stretching frequency. For clip molecules **1a**, **1b**, **5a**, and **5b**, the differences in OH stretching frequencies varied significantly (e.g., $\Delta\nu = 225$ –301 cm^{-1} for clip **1a**). This can be explained in terms of hydrogen bond length. This length will be optimal for complexes formed with **3**, since in this case hydrogen bonding is the only force holding the complex together, and this length does not vary significantly for the different substrate molecules.

When aromatic side-walls are involved in binding, π – π effects influence the depth of binding. An electron releasing group on the dihydroxybenzene guest forces the molecule to be bound slightly further outside the cleft, which makes the distance between the OH function and the urea carbonyl function longer. This results in a smaller $\Delta\nu$ for the OH stretching frequency between the bound and unbound species. In the case of clips **5a** and **5b** the π – π interaction was observed to be smaller, resulting in smaller binding constants, which is also reflected in a smaller difference in the OH stretching frequency ($\Delta\nu = 194$ –245 cm^{-1} for clip **5a** and $\Delta\nu = 223$ –283 cm^{-1} for clip **5b**). Remarkably, the variation in $\Delta\nu$ values for complexes with molecule **4** ($\Delta\nu = 191$ –266 cm^{-1}) were similar to those found for clip **1a**. This suggests that for a clip with one side-wall the complex geometry alters in the same way as for a clip with two side-walls. This is in agreement with the above calculated contribution of one wall to the π – π interaction energy and the relatively large difference in CIS value for the different complexes formed with **4**. Clip **1b** also showed a large variation in the OH stretching frequencies. The results for this compound, however, cannot be compared directly with the other clips, since the guests in **1b** are bound unsymmetrically and are shifted toward the oxygen carbonyl function. In addition, the influence

(24) Stymme et al. have found a much stronger substituent dependency of the OH stretching frequency for substituted phenols which were complexed to dimethylacetamide. The OH bond in these complexes, however, was directed to the n-electrons and not toward the π electrons which is the case in our complexes. Stymme, B.; Stymme, H.; Wettermark, G. *J. Am. Chem. Soc.* **1973**, *95*, 3490.

of the substrate substituent on the π - π interaction will be different in **1b**, since the location of the guest between the two aromatic surfaces is different than that in clip **1a**. One can conclude, however, that the one hydrogen bond formed in **1b** varies in a similar way to the two bonds formed in **1a** ($\Delta\nu = 216$ – 267 cm^{-1} for clip **1b**).

Calculations. We performed computational studies on the host-guest complexes using the semiempirical method AM1.²⁵ The interaction energies were calculated by subtracting the energies of the host and guest from the minimum complex energy. The results for a series of host-guest combinations (hosts **1a**, **1b**, **1c**, **5a**, **5b**, and guests **G1**–**G5**) revealed a linear correlation between the interaction energy and the Hammett σ_m -(*R*) substituent of the guest (see Supporting Information, Table S1 and Figure S5). In line with the experiments, the clip molecules containing thiocarbonyl groups were calculated to have a lower affinity for the substrates than the clip molecules having carbonyl groups. (The calculated interaction energies of the different complexes were larger than the experimentally observed free energies of binding, since no entropy factors or solvent effect were taken into account in the calculations.)

The calculated geometry of the different complexes followed the same trend as that observed experimentally. The more electron withdrawing the substituent on the guest, the deeper it is bound in the cleft. The calculated minimum energy geometry for the complex between **1b** and 1,3-dihydroxybenzene was also in agreement with the experimental results in that the substrate was calculated to bind in the cavity in a nonsymmetrical manner, shifted toward the oxygen atom of the carbonyl group of the DPG framework (see Figure 3).

We also used a simpler model to calculate the interactions between the aromatic rings of the clip and the guests. The model of Hunter and Sanders has proven to be useful in predicting the geometric features of interacting aromatic rings.²⁶ The interaction energy between the aromatic guests and the two side-walls of the clips were calculated using the geometries obtained from the previously discussed experimental and computational results. For different guest molecules and different types of clip side-walls the interaction energies were calculated as a function of the guest binding depth (see Supporting Information, Figure S6). A number of trends could be predicted using this model, which were in full agreement with the experimental data. The more electron deficient the aromatic ring of the guest is, the smaller the repulsive electrostatic interaction between the walls and the guest becomes resulting in a larger overall interaction energy with the electron rich side-walls. In the case that the repulsive electrostatic interaction decreases, the optimum π - π interaction is calculated to be located more deeply within the cavity. The bigger the side-wall is (compounds **1a** and **5a** versus **5b**), the more favorable the interaction is between the aromatic rings. The dominant force in the π - π interaction is the large van der Waals attraction. This attractive force is large but relatively insensitive to the host-guest geometry. The electrostatic repulsive interaction, however, is very geometry dependent and dominates the complexation geometry. The overall geometry of the complex is a compromise between these two forces. When the guest molecules become more electron deficient, the electrostatic repulsion decreases, whilst the van der Waals attraction remains constant. As a result the calculated minimum in the energy versus binding depth plot moves to a geometry in which the

guest is bound deeper in the cleft, which is in line with experimental results (see Supporting Information).

Variation of the Aromatic Side-Wall To Increase the π - π Interaction. It was of interest to investigate whether the guest binding could be fine-tuned by using more electron deficient side-walls on the host in order to decrease the electrostatic repulsion or by using larger aromatic surfaces in order to increase the van der Waals attraction. In the following, both approaches will be discussed.

Binding to Benzoquinone-Walled Clips. Benzoquinone is known to form strong donor-acceptor complexes with dihydroxybenzenes.²⁷ In order to increase the host-guest binding affinities by reducing the electrostatic repulsion, clip molecules with benzoquinone side-walls were synthesized (compounds **7** and **8**). Surprisingly, it was found that the binding of 1,3-dihydroxybenzenes to clips **7** and **8** was significantly lower than that to clip **1a**. The association constants of the complexes with olivetol (**G1**) dropped from $K_a = 1500\text{ M}^{-1}$ to $K_a = 465\text{ M}^{-1}$ to $K_a = 85\text{ M}^{-1}$, when going from two 1,4-dimethoxybenzene (DMB) side-walls (**1a**) to one 1,4-DMB wall and one benzoquinone wall (**7**) to two benzoquinone side-walls (**8**). The interaction between the electron rich olivetol guest and the electron poor benzoquinone is less favorable than the interaction between the electron rich 1,4-DMB and olivetol, which is remarkable. Calculations using the Hunter and Sanders model²⁶ suggested that the geometries of the complexes formed between the benzoquinone clips and olivetol, which are defined by the formation of two hydrogen bonds with the carbonyl groups of the DPG framework, are not optimal for large favorable π - π interactions. According to these calculations the electrostatic repulsion between the side-walls and the aromatic guest decreases, as is expected, but the van der Waals attraction also decreases. The latter effect is larger than the former one, resulting in an overall decrease in π - π interaction and consequently in a lower binding constant. The calculations, however, predict a smaller decrease (only 1 kJ/mol) in binding than that experimentally observed (3.5 kJ/mol). This difference could be due to a solvation effect. This is also reflected in the thermodynamic parameters ΔH and ΔS for clip **7** compared with those for clip **1a** (Table 5). A decrease in both enthalpy and entropy was observed for clip **7**, which suggests that a combination of a smaller π - π interaction between the host and the guest, together with a change in entropy effects results in an overall lower binding constant.

Binding to Clips with Large Aromatic Side-Walls. In order to enlarge the van der Waals contact and hence to increase the binding between host and guest, we synthesized clip molecules with naphthalene side-walls. The naphthalene rings were connected at the 2,3 position (compounds **9**, **10**, and **11**), resulting in "high" side-walls and at the 1,8 position (compounds **2**, **12**, **13**, and **14** *vide infra*) resulting in "broad" side-walls. Clip **9a** appeared to be unable to bind 1,3-dihydroxybenzene, which was thought to be due to the methoxy groups blocking the cleft.^{9a} The binding properties of the unsubstituted naphthalene derivative (clip **9b**) were, therefore, studied. The X-ray structures of **9a** and **9b** showed that apart from the presence or absence of the methoxy groups the cavities of the compounds were similar

(Figure 5). In **9a** the methoxy groups indeed point toward the cleft, which prevent the carbonyl functions from forming a hydrogen bond with a guest. If the presence of the methoxy groups are the only reason for the inability of **9a** to bind dihydroxybenzenes, then **9b** was expected to bind these guest molecules more strongly. Clip **9b** indeed was able to bind

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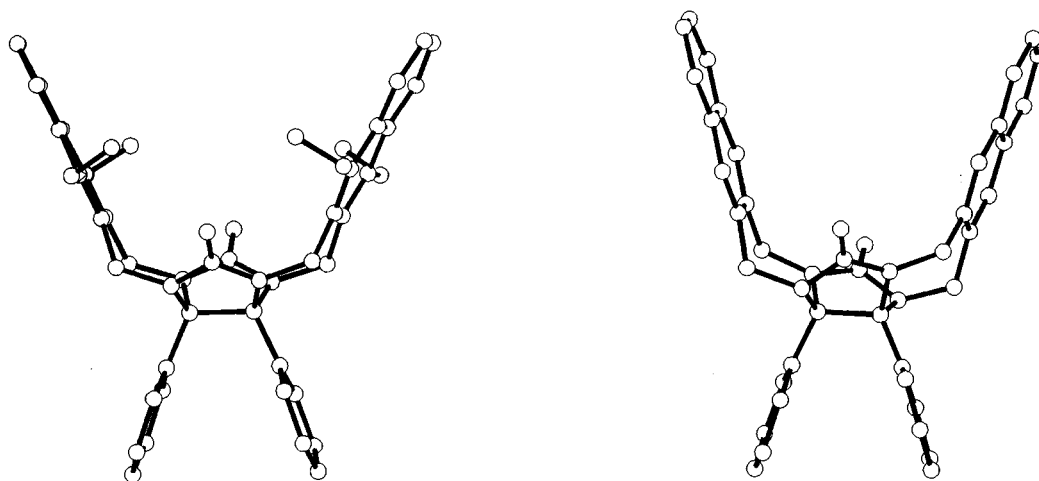


Figure 5. X-ray structures of **9a**^{9a} and **9b**.³² Hydrogen atoms have been omitted for clarity.

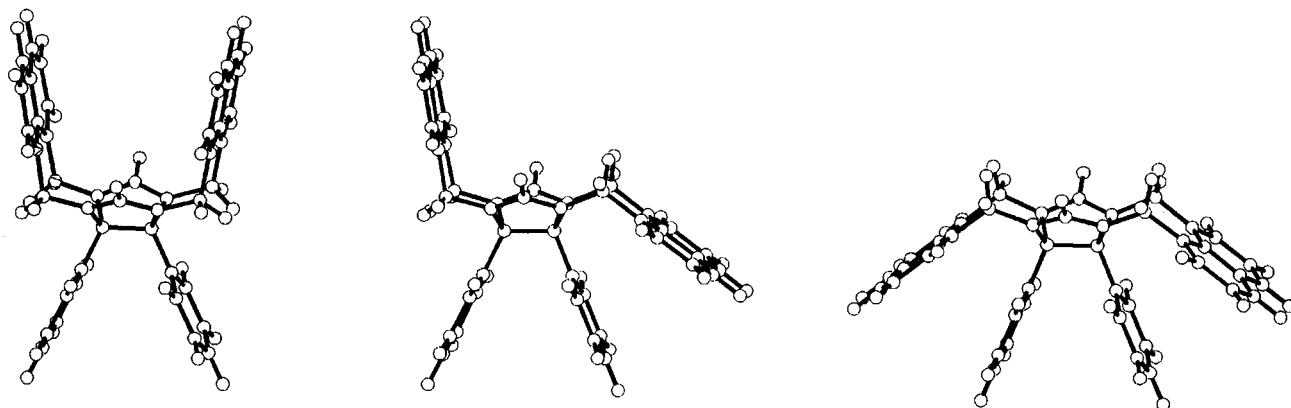


Figure 6. The three conformations of clip **2** which interconvert slowly on the NMR time scale (left *anti-anti* (*aa*); middle *anti-syn* (*as*); and right *syn-syn* (*ss*)).

resorcinol; however, the association constant was low ($K_a = 70 \text{ M}^{-1}$, Table 7). Remarkably, **9b** binds the guest less strongly than the benzene-walled clip **5b** ($K_a = 175 \text{ M}^{-1}$, Table 4). Apparently, the enlarged π -system in the former compound is disadvantageous for host-guest complexation. This result suggests that the inability of **9a** to bind guest molecules is not only solely due to steric hindrance of the methoxy groups but also to an unfavorable π - π interaction. Calculations using the Hunter and Sanders model confirmed that there is indeed a very large electrostatic repulsion (27.5 kJ/mol) between the naphthalene moiety and the aromatic ring of the guest when the latter is forced into the cleft in order to form hydrogen bonds with the urea carbonyl functions. The advantage of a larger van der Waals surface (−25 kJ/mol) is cancelled out by a larger electrostatic repulsion between the guest and the naphthalene side-walls. If the methoxy groups are removed, the electron density on the side-walls is smaller, and the repulsion is partially reduced which enables **9b** to weakly bind dihydroxybenzenes. Comparison of the binding of olivetol to **3** and **4** with that to the naphthyl analogue of the latter compound (**10**) also reveals the negative influence of systematically enlarging the aromatic π -surface. The binding to **4** ($K_a = 50 \text{ M}^{-1}$, Table 3) is somewhat higher than to **3** ($K_a = 23 \text{ M}^{-1}$, Table 3) as discussed before. Enlarging the side-wall with a larger π surface, i.e., the naphthalene moiety in **10**, decreases the binding dramatically ($K_a(\text{10}) < 1 \text{ M}^{-1}$, Table 5). This is in line with the trend found for **4**, **1a**, and **9a** and the above mentioned calculations which predict an unfavorable electrostatic interaction between the large naphthalene surface and the aromatic ring of the guest. Rebek et al. studied the binding of 9-ethyladenine to receptor molecules based on Kemp's acid having different assisting π surfaces.^{5a,28}

They found a correlation between the binding energy and the size of the π surface. In their case each additional benzene increased the binding energy by a 1.6 kJ/mol. Although their and our approaches are the same, *viz.*, binding based on hydrogen bonding which is assisted by a side-wall for stacking interactions, the results are opposite. This shows clearly that each new host-guest system has to be analyzed carefully.

A previous binding study¹⁰ of 1,3-dihydroxybenzene with **2**, a clip with two 2,7-dimethoxynaphthalene (2,7-DMN) side-walls, failed due to precipitation of the complex; however, the better solubility of the complex between **2** and olivetol (**G1**) allowed us to study the effect of a broad aromatic side-wall (Table 5). When the naphthalene moiety is attached at the 1,8 position, the geometry of the π - π interaction is altered, and the electrostatic repulsive component will be significantly reduced. A complication is that the connection between the side-wall and the glycoluril framework in **2** is no longer a seven-membered ring but an eight-membered ring. This results in a side-wall which flips slowly on the NMR time scale from an *anti* to a *syn* orientation with respect to the phenyl rings on the convex side of the DPG framework (Figure 6). Clip **2** therefore can adopt three conformations *anti-anti* (*aa*), *anti-syn* (*as*), and *syn-syn* (*ss*). In chloroform these ratios are 2.7, 88.8, and 8.5%, respectively.¹⁰ Molecules with only one 1,8-connected naphthalene side-wall (compounds **12**–**14** Chart 2) consequently have two conformations in solution, *viz.*, *anti* and *syn*.^{8b} The association constants for binding of guests to the *aa* or *anti* conformers were calculated by determining the conformer ratio of the host as a function of the guest concentration, assuming that the clips do not bind guest molecules in the other

conformers.¹⁰ This assumption is justified, since monowalled clips **12**, **4**, and **10** showed a very low affinity toward guest molecules. As can be seen in Table 5 the binding affinities of olivetol toward clip molecules containing 2,7-DMN side-walls are in the same range as those to clip molecules with 1,4-dimethoxybenzene (1,4-DMB) side-walls. Different factors, however, play a role in the binding to these two type of clips. The van der Waals interaction between the aromatic ring of the guest and the naphthalene moiety is much larger. Other effects cancel out this favorable effect which results in an overall similar binding strength for an 1,4-DMB and a 2,7-DMN side-wall. Calculations using the Hunter and Sanders model confirmed that there is a large van der Waals attraction (−22.5 kJ/mol) without a significantly larger electrostatic repulsion (10 kJ/mol) between the 1,8-connected naphthalene side-walls and the ring of the guest, as compared to the 2,3-connected naphthalenes **9a** and **9b**. Comparison between the binding affinities of clip **1a** and **13** (Table 5) indicate that the substitution of one 1,4-DMB wall by a 2,7-DMN wall reduces the binding. Replacing the second 1,4-DMB wall by another 2,7-DMN wall (from **13** to **2**) slightly increases the binding. These small effects are probably due to a slightly different complex geometry, and the “cavity effect” when the side-wall is enlarged. From the X-ray structures of **2** and **12** it is known that these clip molecules have slightly different distances and angles between the carbonyl oxygen atoms which in turn has an influence on the hydrogen bond formation between the host and the guest. More detailed studies of clip molecules which adopt different conformations are discussed in a separate paper.³⁰

Conclusions

Analysis of complexes between a variety of clip molecules and guests by ¹H NMR and IR spectroscopy, in combination with theoretical calculations, has enabled us to get detailed insight into the binding mechanism of aromatic molecules in cleft-type host molecules. The complexation strength between clip molecules of type **1** and 1,3-dihydroxybenzenes is a combination of a “cavity effect”, hydrogen bonding, and π – π stacking interactions between the host and the guest. The cavity effect, which is a result of an entropy effect and a solvation effect, is responsible for approximately 6 kJ/mol of the binding energy. The large difference in binding affinity toward dihydroxybenzene guest molecules observed for the mono-side-walled clip **4** and clip molecule **1a** is mainly based on this effect. The hydrogen bond formation between the OH groups of the guest and the urea carbonyl functions of the glycoluril framework as well as the π – π interactions are dependent upon the type of substituent on the guest molecule. The contribution of the hydrogen bonding to the binding energy is given by the eq $-\Delta G = 8 + 6\sigma$ (kJ/mol). The π – π interaction between one aromatic 1,4-dimethoxybenzene side-wall and the aromatic guest contributes to the overall binding energy $-\Delta G = 2.5 + 6\sigma$ (kJ/mol). This interaction is based on an attractive van der Waals force and a repulsive electrostatic force, the latter being the dominant factor in determining the geometry of the complex. The electrostatic repulsion pushes the guest out of the cavity of the clip, whereas the hydrogen bonding pulls it into the cleft. The effect of enlarging the aromatic side-walls by using naphthalene rings, in order to increase the van der Waals attraction and in turn to obtain higher association constants, was more complex than expected. When the naphthalene wall is pointing upwards (1,4-DMN) the electrostatic repulsion between

host and guest significantly increases, cancelling out the increase in van der Waals attraction. In the case of the 1,8-connected side-wall (2,7-DMN) a larger van der Waals attraction is combined with only a slight increase in electrostatic repulsion between the host and the guest. This does not result, however, in larger association constants because the clip molecule can adopt different conformations. It has been shown that the binding strength of complexes between our clips and aromatic guests can span a wide range ($K_a \approx 0$ – 10^5 M^{−1}), by simply applying small modifications in the host or the guest molecule. This ability to vary the binding strength will be used in future applications of these systems.

Experimental Section

The syntheses of compounds **1a**, **5a**, **5b**, **3**, **8**, and **9a** have been described elsewhere.^{9a} The syntheses of **1b** and **1c**²⁰ and the syntheses of **5**, **7**, **9b**, **10**, **11**, **12**, **13**, and **14** are described in a separate paper.^{9b} The hydroxy and dihydroxybenzene guest molecules were commercially available products except for chloro-3,5-dihydroxybenzene, which was synthesized as described in the literature.³¹ CDCl₃ was dried on P₂O₅ and distilled before use. Binding constants were determined by ¹H NMR titration experiments on Bruker AM 500, AM 400, and AM 200 instruments, using optimal concentrations to minimize errors in the fit procedure, see ref 9a.

IR spectra were recorded on a Perkin Elmer FTIR 1720-X spectrometer, with a resolution of 2.0 cm^{−1}. For each spectrum 64 scans were taken. The interferometer was flushed with nitrogen.

Calculations. Calculations were performed on Silicon Graphics Challenge and Silicon Graphics Indigo II work stations. For the calculations using the Hunter and Sanders model the following procedure was used: the aromatic structures were generated with the Sybyl program and optimized by calculations with the MOPAC program. The charges and coordinates were taken from the output file of this program. By using the keyword PI in MOPAC the final density matrix was split into π and σ contributions. The π densities at the diagonal of the density matrix were used as the π charges above and below the plane of the aromatic molecule in the calculations using the Hunter and Sanders model. For comparison the interaction between two 1,4-dimethoxybenzene molecules was also calculated with this model using the π densities extracted from the z-orbitals. The differences between the two calculations were small, and only significant when the distance between the aromatic surface was small at direct overlap. This is a result of the larger π densities in the oxygen atoms, used during this calculation. Energy surfaces were calculated, using an electrostatic and a van der Waals potential, by stepwise changing the x and y coordinates of one of the two surfaces. For the energy profiles shown (Figure S6, Supporting Information) the following procedure was used: a guest molecule was placed between two side-walls at the distance of minimum energy calculated with AM1. The interaction energy was then calculated as function of the x coordinate (binding depth). The AM1 calculations were carried out as follows: the complex and the free components were minimized, and the interaction energies were calculated by subtracting the heats of formation of the free components from the heat of formation of the complex.

Acknowledgment. We thank Prof. J. H. van der Maas and Mr. B. Lutz for discussions concerning the IR data and the CAOS-CAMM center for use of their computer facilities.

Supporting Information Available: Table S1 and Figures S2–S6 (6 pages). See any current masthead page for ordering and Internet access instructions.

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