Molecular Clips Based on Propanediurea. Exceptionally High Binding Affinities for Resorcinol Guests

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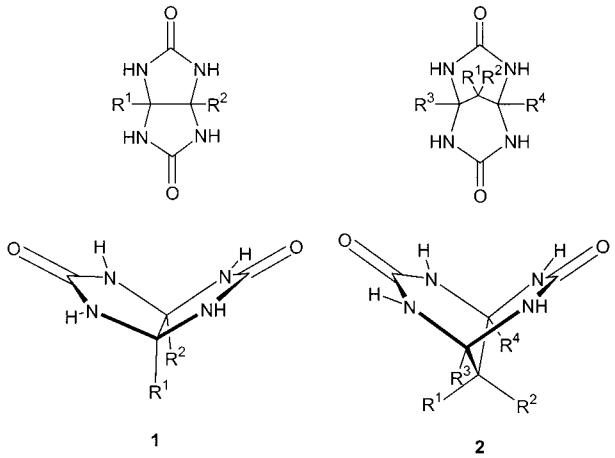
A series of new receptor molecules derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (propanediurea) is described. These molecules possess a cavity which is defined by two nearly parallel aromatic side walls positioned on top of a bis-urea framework. The resulting "U-shaped" clip molecules are ideal hosts for the complexation of flat aromatic guest molecules. The affinity of these new propanediurea based molecular clips for dihydroxybenzene derivatives is exceptionally high, with association constants up to $K_a = 2\ 400\ 000$ L mol^{-1}. Comparison of the binding mechanism of a variety of clip and half clip hosts, in conjunction with NMR, IR, and X-ray studies, has enabled the reason for this high binding to be elucidated. It is shown that subtle sub-angstrom changes in the geometry of the clip molecules have a great impact on their binding properties.

Introduction

The design and synthesis of host molecules for the binding of neutral guest molecules continues to be an area of interest in supramolecular chemistry.[1] Research in our laboratory has for some time been focused on the development of receptors derived from the concave molecule diphenylglycoluril (Chart 1, **1**, $R^1 = R^2 =$ Ph). These "U-shaped" clips bind dihydroxybenzenes by means of hydrogen bonding between the hydroxyl groups of the guest and the urea carbonyl groups of the host and by $\pi-\pi$ stacking interactions between the guest and the host side walls.[2] Other groups have synthesized and studied receptors having a similar U-shape, which are composed of linked aromatic residues.[3] Molecular clips with a large variety of side walls have been synthesized, and the supramolecular chemistry of these clips has been extensively studied.[2,4] Some effort has been directed toward modifying the glycoluril framework **1** of the hosts. The urea functionalities in **1** have been replaced by thiourea and guanidine groups,[5] and clips have been synthesized starting from dimethylglycoluril (**1,** $R^1 = R^2 =$ Me),[6] dipyridylglycoluril (**1**, $R^1 = R^2 =$ 2-pyridyl), and ditoluylglycoluril (**1**, $R^1 = R^2 =$ 4-toluyl), with subsequent functionalization of the toluyl groups.[7,8,9] As could be expected, these modifications did not significantly alter the overall shape of the clips. The binding properties changed considerably in the clips with guanidine and thiourea hydrogen bond acceptor sites, the guest binding affinities being higher in the former clips and much lower in the latter ones.[5] More recently clip molecules have been synthesized from bipyridylglycoluril (**1**, $R^1, R^2 =$ 2,2′-bipyridyl), which displayed slightly "squeezed" cavities, resulting in rather poor binding properties.[10] In a preliminary communication we recently published the synthesis and binding properties of a modified molecular clip

Chart 1



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[†] Department of Organic Chemistry.
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(9) Rebek's group has synthesized glycoluril derivatives with various groups R which have been used for the construction of molecular capsules: (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647. (b) Tokunaga, Y.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2656. (c) Szabo, T.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 6193.

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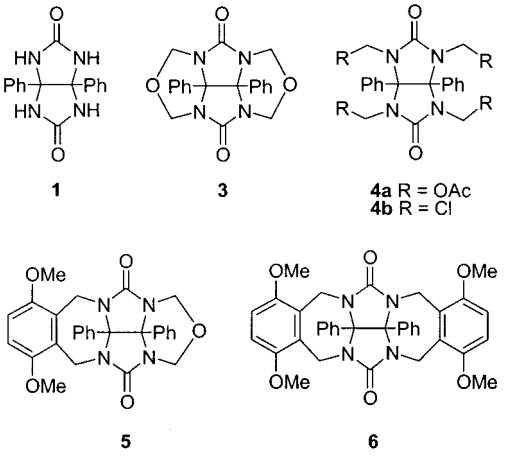
Chart 2



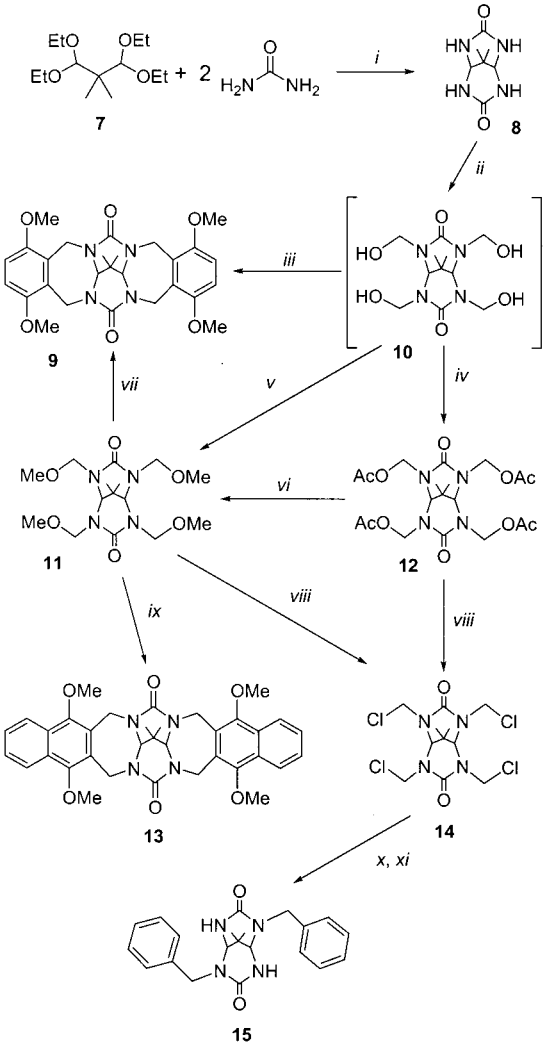
based on 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**2**, $R^1 = R^2 = Me$; $R^3 = R^4 = H$, dimethylpropanediurea).[11] Molecules of type **2** show strong similarities with diphenylglycoluril and were first described in 1908 ($R^{1,2} = H$ or Me; $R^{3,4} = Me$).[12] Both **1** and **2** possess a shallow cavity with two strong hydrogen bond acceptor sites. The ureido nitrogen atoms allow for functionalization of the framework. The main difference between **1** and **2**, which triggered us to synthesize and study clip molecules from the latter type, is the slightly sharper angle between the carbonyl groups in **2**. This structural feature results in a cavity that is somewhat deeper with the carbonyl oxygen atoms being closer together. A further reason to study **2** is the fact that the substituents R^3 and R^4 can be varied in order to influence the complexation properties of clips derived from this compound. The groups R^1 and R^2 allow for functionalization of the clips in a similar way as reported for **1**.[7,8,10] In addition, molecular modeling indicated that the side walls of clips derived from **2** would be more parallel than those of clips derived from **1**, which might enhance the $\pi-\pi$ stacking interactions between a bound guest and the host.

In this paper we give a full account of the synthesis, structure, and binding properties of a series of clip molecules derived from **2**, which show exceptionally high affinities for resorcinol derivatives.

Results and Discussion

Synthesis. Clip molecules derived from diphenylglycoluril are usually synthesized from the cyclic ether **3** (Chart 2).[2] This compound is readily available from the base catalyzed reaction of **1** ($R^1 = R^2 = Ph$) with formaldehyde, yielding tetra(hydroxymethyl)diphenylglycoluril, followed by acid catalyzed dehydration.[2] The reaction of formaldehyde with 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**8**) (Scheme 1), which was obtained by treating dimethylmalonaldehyde tetraethylacetal (**7**) with two molecules of urea, has been described in a patent.[13] Thus, **8** was reacted with paraformaldehyde in a slightly basic solution to give the tetra(hydroxymethyl) derivative **10**. A ring closed product

Scheme 1[a]



[a] Reagents and conditions. *i*: H_2O, H_2SO_4, 100 °C, 4 h, 90%. *ii*: H_2O, $(CH_2O)_n$, NaOH, 60 °C, 3 h. *iii*: H_2SO_4, 1,4-dimethoxybenzene, rt, 16 h, 23%. *iv*: Ac_2O, HCl, 100 °C, 30 min, 17%. *v*: MeOH, HCl, 50 °C, 2 h. *vi*: MeOH, HCl, rt, 16 h. *vii*: Ac_2O, TFA, 95 °C, 30 min, 1,4-dimethoxybenzene, 100 °C, 30 min, 78%. *viii*: CH_2Cl_2, $SOCl_2$, rt, 16 h. *ix*: Ac_2O, TFA, 1,4-dimethoxynaphthalene, 95 °C, 30 min, 58%. *x*: Benzene, $AlCl_3$, reflux, 16 h. *xi*: 6 M HCl, reflux, 30 min, 67%.

comparable to **3** could not be obtained, neither by heating with acid nor by using dehydrating agents such as triethyl orthoformate or molecular sieves. Since purification of **10** turned out to be difficult, this compound was used directly in the subsequent reaction with 1,4-dimethoxybenzene in sulfuric acid to afford clip molecule **9** in 23% yield. Alternatively, **10** can be transformed into the corresponding tetra(methoxymethyl) derivative **11** by stirring in methanol in the presence of HCl at 50 °C.[13] Compound **11** was reacted with 1,4-dimethoxybenzene in an amidoalkylation reaction in acetic anhydride/TFA to give clip molecule **9** in high yield. The intermediate in this reaction is the tetra(acetoxymethyl) derivative **12**. This compound could be obtained directly from **10** by heating with acetic anhydride/HCl. It was possible to transform **12** into **11** in high yield by stirring in methanol containing a trace of HCl. A clip molecule with 1,4-dimethoxynaphthalene walls (**13**) was prepared in reasonable yields by reaction of **11** with 1,4-dimethoxynaphthalene in acetic anhydride/TFA (Scheme 1).

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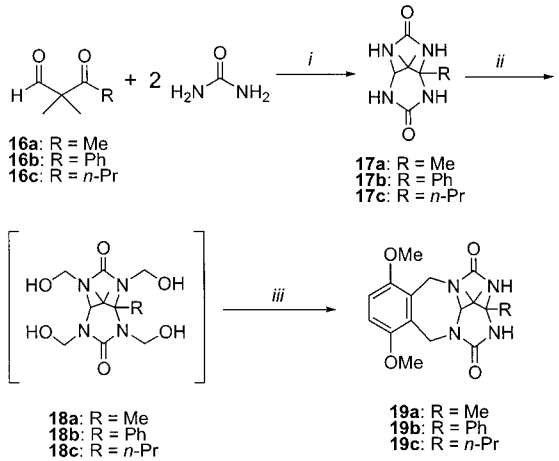
(11) Jansen, R. J.; Rowan, A. E.; de Gelder, R.; Scheeren, H. W.; Nolte, R. J. M. *Chem. Commun.* **1998**, 121.
(12) De Haan, T. *Recl. Trav. Chim. Pays-Bas* **1908**, *27*, 162.
(13) Petersen, H.; Steimmig, A.; Schönleben, W.; Bille, H. Ger. Patent 2011703, 1971; *Chem. Abstr.* **1972**, *76*, 60867s.

Scheme 2[a]

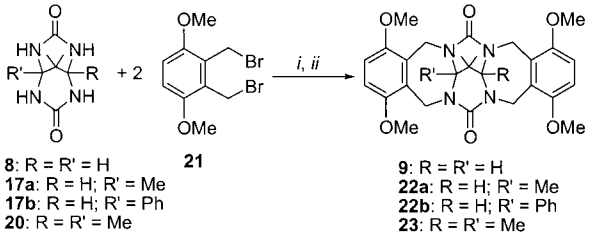


[a] Reagents and conditions. *i*: Toluene, TFA, reflux, 4 h, ~95%. *ii*: H_2O, CH_3CN, $(CH_2O)_n$, NaOH, 60 °C, 3 h. *iii*: H_2SO_4, 1,4-dimethoxybenzene, rt, 16 h, ~25%.

The tetra(methoxymethyl) and tetra(acetoxymethyl) substituted propanediurea compounds **11** and **12** did not react with unactivated aromatic molecules such as benzene. To synthesize a clip molecule with benzene side walls as has been described for clips of type **1**, we changed these substituents into chlorines, thus creating better leaving groups.[14] This could be accomplished by reacting **11** or **12** with $SOCl_2$ at room temperature, giving the tetra(chloromethyl) derivative **14** in high yield (Scheme 1). The reaction of **14** with benzene in the presence of $AlCl_3$, as has been described for **4b**,[14] afforded however 2,6-dibenzyl-9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]-nonane-3,7-dione **15** as the sole product. Apparently, when one of the chloromethyl groups on one side of **14** has reacted, the remaining chloromethyl group is not reactive enough to give the bis-substituted benzene derivative. In the subsequent hydrolytic workup the remaining chloromethyl group is converted back to a hydroxymethyl group, which loses formaldehyde to give the free HNC(O) function (Scheme 1).[15]

An obvious way of preparing clip molecules functionalized at R^3 or R^4 (see **2**, Chart 1) seemed to be by starting from 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione derivatives **17**. These compounds have been synthesized by heating 2,2-dimethyl-3-oxoaldehydes **16** with urea.[16] We found that reaction of compounds **16** with 2 equiv of urea in toluene at reflux temperature in the presence of TFA as a catalyst with azeotropic removal of water produced compounds **17** in very high yield (over 90%). The reaction product is virtually insoluble in most solvents and precipitates from the reaction mixture. Washing with various solvents and subsequent drying yielded a material of high purity. Reaction of compounds **17** with paraformaldehyde in the presence of base,[13] followed by reaction with 1,4-dimethoxybenzene in sulfuric acid, yielded exclusively "half clip" compounds **19** (Scheme 2). Apparently, the hydroxymethyl groups at the side of **18** where R is located are either not sufficiently

Scheme 3[a]



[a] Reagents and conditions. *i*: DMSO, NaH, rt, 24 h. *ii:* **21**, rt, 16 h, ~30%.

stable under the reaction conditions or are sterically blocked for reaction, leading to deformylation instead of substitution.[15]

When 1,5,9,9-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.1]-nonane-3,7-dione **20** was subjected to the reaction conditions described above, no clip molecule could be isolated. To access clip molecules derived from 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-diones substituted at the 1 and 5 positions of the skeleton (**17a,b** and **20**), we developed a different synthetic route (Scheme 3). Compounds **17a,b** and **20** were treated with NaH and 1,4-dimethoxy-2,3-bis(bromomethyl)benzene (**21**) to give clip molecules **22a**, **22b**, and **23** in moderate yields. Compound **21** was obtained either by benzylic bromination of 1,4-dimethoxy-2,3-dimethylbenzene with NBS or in two steps by reduction of 3,6-dimethoxyphthalic anhydride with $LiAlH_4$ followed by treatment with PBr_3. When 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**8**) was subjected to the reaction conditions described above, clip molecule **9** could be obtained analogously in 20% yield.

Structure and Binding Properties. The binding affinities of the new host molecules **9**, **22a**, and **23** for a number of hydroxybenzene derivatives (**24** and **25**) were measured by NMR titration experiments in $CDCl_3$ using the aromatic wall protons of the host and the aromatic protons of the guest as probes.[18,19] To allow for reliable comparisons of the binding energies of different clips, we preferred to use competition experiments as opposed to standard titration techniques to determine association constants (see Experimental Section). The results are summarized in Table 1. Of all the hosts studied, compound **9** has the highest affinity for resorcinol derivatives (K_a values up to 2.4×10^6 L mol^{-1}). If a methyl substituent is present at the 1-position of the clip (**22a**) the association constants drop slightly (approximately 10% ($\Delta\Delta G \approx 0.3$ kJ mol^{-1})). If methyl substituents are present at both the 1 and 5 positions (clip **23**), the measured K_a values are approximately 30% ($\Delta\Delta G \approx 0.9$ kJ mol^{-1}) lower than those of the parent compound

(14) (a) Sijbesma, R. P.; Kentgens, A. P. M.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3199. (b) Sijbesma, R. P.; Nolte, R. J. M.; *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 643.

(15) The acid hydrolysis of hydroxymethylene ureas to yield formaldehyde and the corresponding urea compound has been described: (a) Nordhøy, F.; Ugelstad, J. *Acta Chem. Scand.* **1959**, *13*, 864. (b) Petersen, H. *Textile Res. J.* **1971**, 239.

(16) Spänig, H.; Schönleben, W. Belg. Patent 645094, 1963; *Chem. Abstr.* **1965**, *63*, 13299f.

(17) The observed $\Delta\Delta G$ values are very small, but we believe that they are indicative of a change in the structure of the binding pocket. Most competition experiments were carried out in duplo and where possible compared with direct binding measurements. Wilcox et al. have shown that self-association of one of the components significantly reduces the accuracy of a titration experiment: Wilcox, C. S.; Adrian, J. C., Jr.; Webb, T. H.; Zawacki, F. J. *J. Am. Chem. Soc.* **1992**, *114*, 10189. The self-association of the resorcinol guests and the clips was therefore investigated but was found to be too small to be measured.

(18) Sijbesma, R. P.; Kentgens, A. P. M.; Lutz, E. T. G.; Van der Maas, J. H.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1993**, *115*, 8999.

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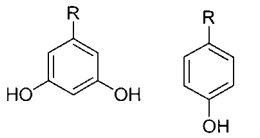
Chart 3



24 **25**

a: R = Me
b: R = H
c: R = OMe
d: R = Cl
e: R = CN

a: R = OMe
b: R = H
c: R = Cl
d: R = CN
e: R = NO_2

Table 1. Association Constants (K_a in L mol^{-1}) and (in brackets) Free Energies of Binding (kJ mol^{-1}) of Various Combinations of Clip Compounds and Substituted Resorcinol and Phenol Guest Compounds[a]

	host			
guest	**9**	**22a**	**23**	**6**[b]
24a[c]	13 000 (−23.5)	9 500 (−22.7)	8 800 (−22.5)	1 900 (−18.7)
24b[c]	31 000 (−25.6)	25 000 (−25.1)	22 600 (−24.8)	2 600 (−19.5)
24c[c]	34 000 (−25.8)	33 100 (−25.8)	23 500 (−24.9)	4 400 (−20.8)
24d[d]	280 000 (−31.1)	270 000 (−31.0)	200 000 (−30.2)	16 000 (−24.0)
24e[e]	2 400 000 (−36.4)	2 200 000 (−36.2)	1 600 000 (−35.4)	100 000 (−28.5)
25a[d]	23 (−7.8)	*f*	16 (−6.9)	20 (−7.4)
25b[d]	22 (−7.7)	*f*	18 (−7.2)	29 (−8.3)
25c[d]	180 (−12.9)	*f*	160 (−12.6)	80 (−10.9)
25d[c]	2000 (−18.8)	*f*	1450 (−18.0)	415 (−14.9)
25e[c]	4400 (−20.8)	*f*	2000 (−18.8)	1200 (−17.6)

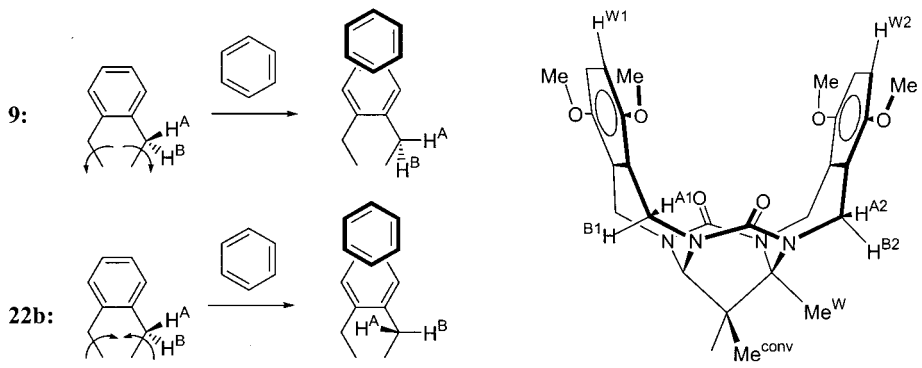
[a] The association constants were determined at 298 K in $CDCl_3$. [b] Values taken from ref 4. [c] Approximate error 20%. [d] Approximate error 30%. [e] Approximate error 40%. [f] Not determined.

without these substituents (**9**).[17] Molecular modeling indicates that the methyl substituent directly under the side wall of the clip "locks" this wall in a position which is slightly bent out due to van der Waals contacts with the xylylene methylene protons. Once the side wall is locked it is unable to adopt the optimal geometry for guest binding, which results in a lower binding constant. In the case of clip **22a**, the decreased flexibility of one of the side walls can largely be compensated for by the other side wall, which is still flexible. This results in only a small decrease in binding affinity. When both side walls are "locked", however, as is the case for clip **23**, the binding constant decreases slightly more because no adjustment is possible. Additional evidence for this hypothesis comes from the NMR titration data. The resonances due to the *o*-xylylene protons of the different clip molecules shift upon the addition of a guest molecule (see Table 2). Such a shift was not observed for host molecules of type **6**. It indicates that the side walls of the clip undergo a conformational change upon binding of a guest (induced fit, see Figure 1). For clip **9** the complexation induced shifts ($\Delta\delta_{max}$, CIS) were considerably larger than for clip **23**. Due to its asymmetry, clip **22a** has two sets of signals for the *o*-xylylene protons: one set for the protons on the "methyl side" and one set for the protons on the "hydrogen side". As expected, one set showed large shifts, as in clip **9**, and one set showed relatively minor shifts, as in clip **23**. The same trend was observed for the clip side wall protons. A shift of $\Delta\delta$ −0.60 ppm was observed for the flexible clip **9**, and a slightly smaller shift of $\Delta\delta$ −0.44 ppm for the rigid clip. The aromatic wall protons of clip **22a** showed shifts of $\Delta\delta$ −0.53 and −0.49 ppm, respectively. The observed $\Delta\delta$'s indicate that upon binding of resorcinol, the side walls of clip **9** move closer to the guest. As a result of this, the aromatic protons of the host experience a shielding effect caused by the guest. This effect is more pronounced when the distance between the side wall protons and the aromatic ring of the guest is smaller. This leads to slight differences in shift: $\Delta\delta$ −0.60 ppm for **9**, $\Delta\delta$ −0.44 ppm for **23**, and two values between these extremes for **22a**. The difference in binding affinity for resorcinol derivatives, as found for clips **9** and **23**, is mainly due to a difference in flexibility of the cavity side walls. As can be seen in Table 1, the difference in $\Delta G°$ is a steady 0.9 ± 0.1 kJ mol^{-1} for all resorcinol derivatives bound in **9** and **23**. Since the position of the carbonyl groups with respect to the cavity walls is expected to be the same in **9** and **23**, differences in hydrogen bonding cannot account for the observed differences in binding affinities. This assumption has been validated by determining the binding affinities of clips **9** and **23** for a number of 4-substituted phenol derivatives (**25a**−**e**, Table 1). In this case, only one hydrogen bond can be formed, which is optimal in all clip molecules. Any observed differences in binding energies must be caused by the cavity side walls. Since the binding affinities of **9** and **23** for **25** are relatively low, the $\Delta\Delta G°$ values could not be determined as accurately as in the case of the resorcinol guests. The average difference in $\Delta G°$ values between **9** and **23** again was found to be approximately 0.9 kJ mol^{-1}. Noteworthy in this respect are also the CIS values of the aromatic wall protons of the clip molecules, which are a measure of the position of the guest with respect to the cavity side walls. These values are higher for clip molecule **9** than for clip **23**. For example, with 4-nitrophenol (**25e**) as a guest the CIS values are −0.66 and −0.48 ppm for hosts **9** and **23**, respectively. This suggests that for the former host the distance between the aromatic side walls and the guest in the complex is smaller than for the latter host.

From the above data it is clear that binding of guests in clip molecules **9** and **22a**, and to a much lesser extent in clip molecule **23** takes place via an induced fit mechanism (see Figure 1). Increased flexibility of the host, and thus a greater ability to adopt its conformation to a guest bound in its cavity, results in a higher binding constant. With a strongly binding guest (5-cyanoresorcinol, **24e**), association constants of up to 2.4×10^6 L mol^{-1} can be reached.

To find additional support for the mechanism of guest binding, we solved the X-ray structures of clips **9**, **22a**, and **22b**. The structure of **9** has been published in the preliminary communication.[11] Single crystals from **22a** were obtained by the vapor diffusion technique using chloroform/acetone as the solvent and diethyl ether as the precipitant. Single crystals of **22b** were obtained by the liquid diffusion procedure using dichloromethane as the solvent and hexane/acetone as the precipitant. Despite repeated attempts, single crystals suitable for X-ray analysis could not be obtained for clip molecule **23**. The structures of clips **9** and **22a** turned out to be very similar (Figure 2a,b). Both form dimers in the solid state, with the wall of one clip molecule being buried in the cavity of another clip. Clip molecule **22b** on the contrary did

Table 2. Chemical Shifts of Selected Protons in Free Clip Molecules 9, 22a, 22b, and 23 and Complex Induced Shift (CIS) Values (ppm, in parentheses) of These Protons in Host−Guest Complexes of the Clips with Resorcinol in $CDCl_3$ at 298 K[a,b]



	$H^{W1,2}$			$H^{A1,2}$			$H^{B1,2}$		Me^W	Me^{conv}
9	6.74 (−0.60)			5.42 (+0.45)			3.91 (−0.28)[c]		*d*	1.35 (+0.16)
22a	6.72 (−0.53)	6.63 (−0.49)	5.55 (+0.31)	5.95 (+0.06)	3.85 (−0.19)		3.87 (+0.01)		1.71 (+0.09)	1.33 (+0.13)
23	6.63 (−0.44)			6.05 (−0.04)			3.93 (+0.05)		1.82 (+0.10)	1.34 (+0.12)
22b	6.66 (−0.45)	6.53 (−0.43)	5.54 (+0.43)	5.42 (+0.14)	3.81 (−0.10)		3.90 (+0.28)[c]		*d*	1.06 (+0.15)

[a] See structural depiction (above right). [b] A "−" sign denotes an upfield shift and a "+" sign denotes a downfield shift. [c] On binding of a resorcinol guest molecule the xylylene protons H^{A2} and H^{B2} of clips **9** and **22b** change positions as depicted in the above left illustration. [d] Proton is not present in the molecule.

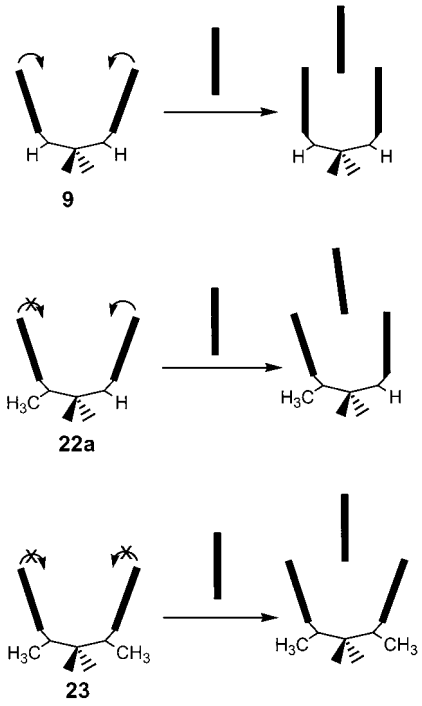


Figure 1. Schematic representation of the formation of host−guest complexes from host molecules **9**, **22a**, and **23** and resorcinol.

not pack in this geometry (Figure 2c). This suggests that filling up the cavity of this clip molecule is energetically unfavorable. The X-ray structure of **22b** indicates that the side walls of this clip are in a more parallel orientation than the side walls of clip **9**. The distance between the centers of the aromatic side walls of clip **22b** is 4.84 Å, as opposed to 6.43 and 6.50 Å for clips **9** and **22a**, respectively. Since the minimum energy contact distance between two parallel π systems is 3.42 Å, a cavity with a size two times this distance (6.84 Å) is ideal for binding of an aromatic guest.[19a] It is therefore evident that on binding of a guest (or the side wall of a second clip molecule), the walls of **22b** are forced to bend outward. This is hampered by the phenyl group under one of these side walls. This will result in a higher barrier for guest binding. This explanation is validated by the results of the binding constant determinations. The association constant of clip **22b** with resorcinol (**24b**) was measured to be 2800 L mol^{-1}, which is only 9% of the value measured for clip **9** (K_a = 31 000 L mol^{-1}). For 5-chlororesorcinol (**24d**) the binding constant was 25 000 L mol^{-1}, again 9% of the value measured for clip **9** (K_a = 280 000 L mol^{-1}). The NMR spectra recorded during the determination of the binding constants for **22b** showed some interesting features. The pattern of the proton signals for the phenyl group under the cavity wall of **22b** changed considerably upon addition of a guest to the solution, in line with the idea that a guest bound in the cavity forces the side walls to bend outward. The side wall directly above the phenyl group when forced outward restricts the free rotation of this phenyl group, resulting in a splitting of the signals in the NMR spectrum. In Table 2 the CIS values of some of the protons of clip **22b** with resorcinol as a guest as well as the chemical shifts of these protons in the uncomplexed state are listed. Upon complexation of a guest the side walls bend away, pushing the xylylene CH_2 B2 protons out of the shielding region of one of these side walls and the phenyl group. As a consequence a downfield shift of +0.28 ppm results. In the case of clip molecule **9** the side walls bend inward upon complexation of a guest, moving the xylylene CH_2 B2 protons in their shielding zones. This results in an upfield shift of −0.28 ppm (see also drawing in note of Table 2).

Clip molecules of type **9** have a considerably higher affinity for resorcinol derivatives than clip molecules of type **6** (Table 1). One of the reasons for this increased

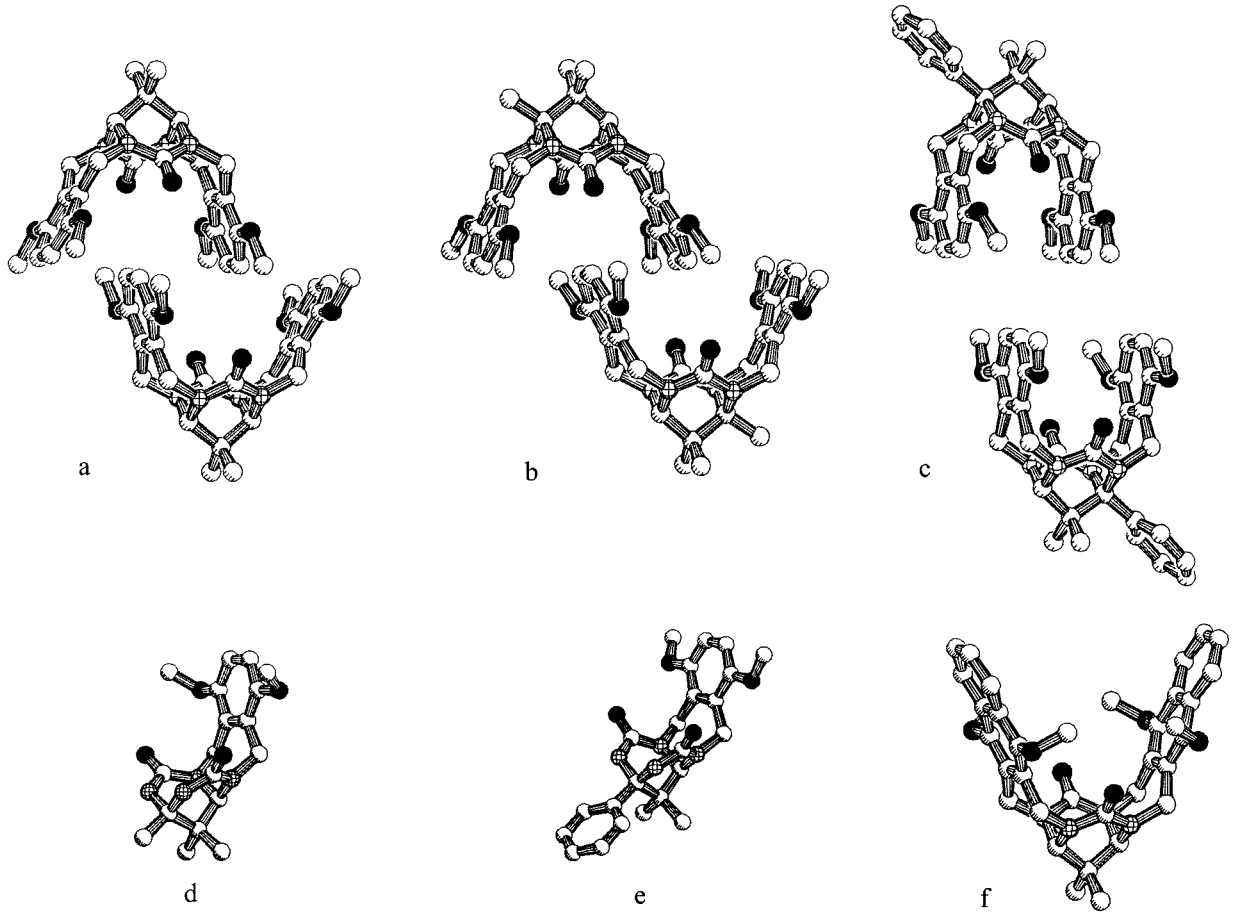


Figure 2. Crystal structures of different host molecules: (a) **9**; (b) **22a**; (c) **22b**; (d) **19a**; (e) **19b**; (f) **13**. The drawings were made using the PLUTON program.[27]

affinity is the flexibility of the side walls in the former molecules. Hosts **6** are quite rigid molecules; their xylylene CH_2 protons exhibit no CIS upon binding of a guest. The same ridigity is observed for clip molecule **23**, which otherwise has the same structure as clip **9**. The CIS values of the side wall aromatic protons in the case of resorcinol as the guest are −0.60 ppm for the flexible clip **9** and −0.44 and −0.45 ppm for the rigid clips **23** and **6**, respectively. This suggests that in complexes of resorcinol with the latter two clips, the position of the guest with respect to the side walls is similar; the geometry is considerably different for the flexible clip **9**.

For clips of type **6** it has been shown that the major contribution to guest binding comes from hydrogen bonding.[4] To investigate the relative importance of hydrogen bonding in clip **9**, we plotted the binding free energies of guests **24a**−**e** in **9** and **6** as a function of the Hammett [σ_m(R)] parameter of the substituent R of the guest (Figure 3). The plot reveals a linear correlation, for both clip **6** and **9**. This increase in binding as the σ_m increases is the result of both an increase in the hydrogen bonding interaction and as well as an increase in the $\pi-\pi$ stacking as the polarization of the guest increases. The slopes of the plots also indicate that binding of resorcinol derivatives in clip **9** is more sensitive to the substituent on the guest than binding in clip **6**. The increase in sensitivity of host **9** over host **6** can be attributed to two factors, namely, a greater sensitivity of the hydrogen bonding in host **9**[4] and the induced fit mechanism that operates upon guest binding to **9**. As a result of the induced fit mechanism the $\pi-\pi$ interaction is stronger

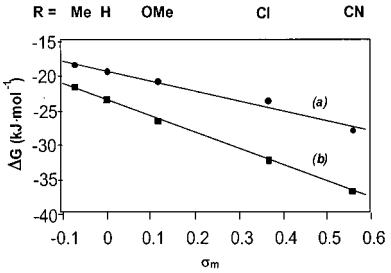


Figure 3. Binding free energies of guests **24a**−**e** in clips **6** (a) and **9** (b) as a function of the Hammett parameter (σ_m (R)) of the substituent R in the guest.

for the more polarized guests and hence the gradient is larger for **9** than for **6** (Figure 3).

The binding of resorcinol in the cavity molecules described here is due to three factors, namely hydrogen bonding between the phenolic OH groups and the urea carbonyl groups, $\pi-\pi$ stacking interactions between the guest and the cavity walls, and a cavity effect.[4] By comparing the binding affinities of resorcinol with hosts **3**, **5**, **6**, **9**, **19c**, and **26** (Figure 4), the individual importance of these factors can be determined, both for the glycoluril based host−guest system (A) and for the propanediurea based system (B). This additive approach, however, is more a qualitative than a quantitative analysis. The comparaison of the different host−guest binding energies gives only an indication that the binding increases and cannot be directly attributed to one specific interaction because the sum of the different components is always less than the whole, as has been demonstrated by

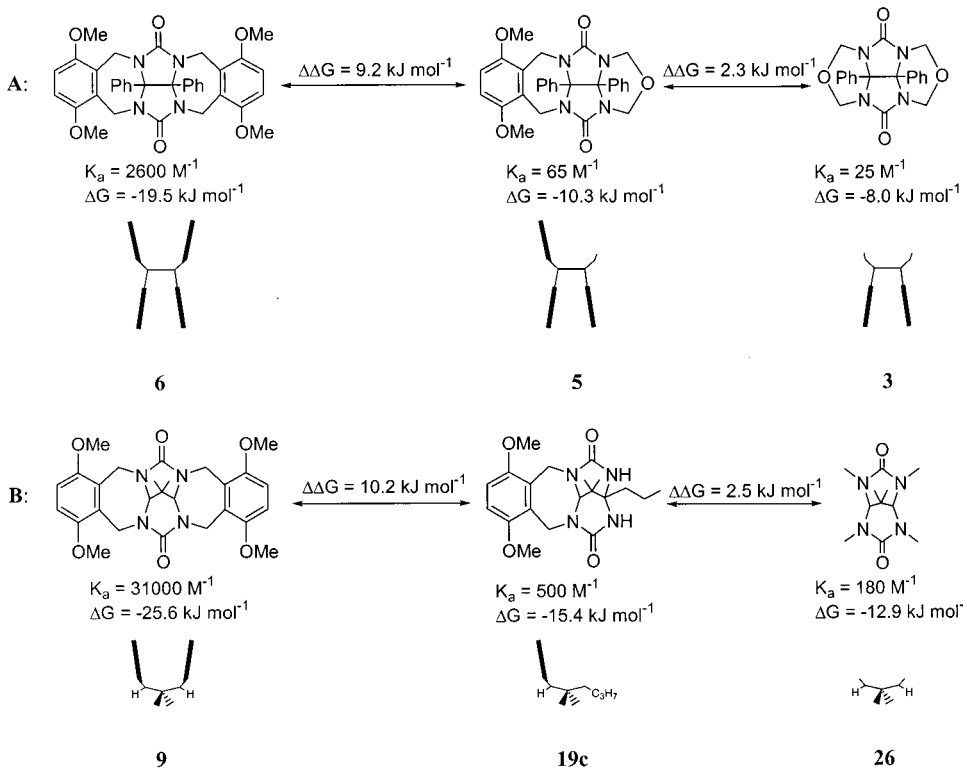


Figure 4. Association constants and Gibbs free energies of binding of resorcinol in clips, half clips, and frameworks of type **3** and of type **26** and schematic structures of the clips, half clips, and frameworks.

Jencks.[22] Half clip **19c** was used instead of **19a** for solubility reasons; the binding affinities of the two half clips are supposed to be comparable. The structures of hosts **19a** and **19b** were established by X-ray structure determinations (Figure 2d,e). The shapes of the different hosts are represented schematically in Figure 4.

Receptors **3** and **26** can bind resorcinol on the basis of hydrogen bonding only (see eqs 1a and 1b, respectively). In receptors **5** and **19c** the binding is a result of hydrogen bonding and $\pi-\pi$ stacking interactions of one side wall with the resorcinol guest (see eqs 2a and 2b, respectively). By subtracting the values in eqs 2a and 2b from the values in equations (1a) and (1b) the energy involved in $\pi-\pi$ stacking interactions of one side wall with the resorcinol guest can be calculated (see eqs 4a and 4b. In the case of receptor molecules **6** and **9** the interaction energy is made up of hydrogen bonding, twice the $\pi-\pi$ stacking interaction of the guest with one cavity wall, and the cavity effect (see eqs 3a and 3b). The energy attributable to the cavity effect can be calculated by subtracting twice the values in eqs 4a and 4b and the values in eqs 1a and 1b from the values in eqs 3a and 3b (see eqs 5a and 5b). It should be noted that the hydrogen bonding energy upon binding to **3** and **26** has a significant unfavorable entropic component. Hence subtracting eq 1 from eq 2 overestimates the contribution of one $\pi-\pi$ interaction; the relative values are more an indication of the enthalpy of the $\pi-\pi$ interaction rather than the free energy. However, one can say that the relative effect of adding one wall and then a second is the same for both cavities.

receptor **3**: (hydrogen bonding)
$$-\Delta G = 8.0 \text{ kJ mol}^{-1} \quad (1a)$$

receptor **26**: (hydrogen bonding)
$$-\Delta G = 12.9 \text{ kJ mol}^{-1} \quad (1b)$$

receptor **5**: (hydrogen bonding + 1 × $\pi-\pi$ interaction)
$$-\Delta G = 10.3 \text{ kJ mol}^{-1} \quad (2a)$$

receptor **19c**: (hydrogen bonding + 1 × $\pi-\pi$ interaction)
$$-\Delta G = 15.4 \text{ kJ mol}^{-1} \quad (2b)$$

receptor **6**: (hydrogen bonding + 2 × $\pi-\pi$ interaction + cavity effect)
$$-\Delta G = 19.5 \text{ kJ mol}^{-1} \quad (3a)$$

receptor **9**: (hydrogen bonding + 2 × $\pi-\pi$ interaction + cavity effect)
$$-\Delta G = 25.6 \text{ kJ mol}^{-1} \quad (3b)$$

1 × $\pi-\pi$ stacking interaction (host−guest system A)
$$-\Delta G = 2.3 \text{ kJ mol}^{-1} \quad (4a)$$

1 × $\pi-\pi$ stacking interaction (host−guest system B)
$$-\Delta G = 2.5 \text{ kJ mol}^{-1} \quad (4b)$$

cavity effect (host−guest system A)
$$-\Delta G = 6.9 \text{ kJ mol}^{-1} \quad (5a)$$

cavity effect (host−guest system B)
$$-\Delta G = 7.7 \text{ kJ mol}^{-1} \quad (5b)$$

($-\Delta G$ for binding in a clip molecule (eqs 3a and b) minus 2($-\Delta G$) for $\pi-\pi$ interaction (eqs 4a and b) minus $-\Delta G$ for hydrogen bonding (eqs 1a and b))

(20) Hadži, D.; Bratos, S. In *The Hydrogen Bond*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland Publishing Company: Amsterdam, 1976; Vol. II, pp 565−611.
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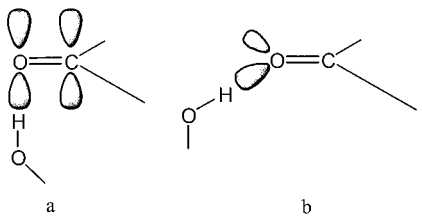

Figure 5. Hydrogen bonding of a phenolic OH group to a carbonyl group: (a) to the π-electrons; (b) to the n-electrons.

By comparing eqs 1a−5a with eqs 1b−5b the following conclusions can be drawn with respect to the differences in binding affinity of resorcinol in clip molecules **6** and **9**: (i) the difference in binding energies is mainly due to hydrogen bonding effects which are stronger for the propanediurea framework than for the glycoluril framework ($\Delta\Delta G$ = 4.9 kJ mol^{-1}, see eqs 1a and 1b); (ii) the $\pi-\pi$ stacking interactions are approximately equal (see eqs 4a and 4b); (iii) the cavity effects are approximately equal (see eqs 5a and 5b).

It is clear from the above analysis that the difference in hydrogen bonding is the major factor governing the increase in binding affinity for resorcinol derivatives of clip **9** compared to clip **6**. Therefore, we decided to investigate differences in hydrogen bond geometry between both host−guest complexes. A hydrogen bond with the oxygen atom of a carbonyl group can be formed with either the π-electrons (Figure 5a) or with the n-electrons (Figure 5b). It was shown previously that in clip molecules derived from glycoluril, resorcinol forms hydrogen bonds with the π-electrons. The reason for this is that resorcinol that is being bound in the cavity prefers to form hydrogen bonds with *both* carbonyl groups of the clip molecule, which leads to geometrical constraints.[18] To investigate the importance of the hydrogen bonds in more detail we monitored the length of the hydrogen bonds between these clips and several guests by means of IR spectroscopy. For compounds with comparable structural features the frequency difference between the OH vibration in the free state and in the hydrogen bonded state is a measure of the length of the hydrogen bond.[20] Experiments carried out with receptor **3** have shown that the length of the hydrogen bonds is independent of the guest and consequently of the energy involved in hydrogen bonding.[4] In the case of clip molecules of type **6** the length is dependent on the type of guest because the binding geometry is a compromise between optimum hydrogen bonding and optimum $\pi-\pi$ interactions: guests that form strong hydrogen bonds are pulled into the cavity in order to optimize hydrogen bonding, whereas guests that form weaker hydrogen bonds are pushed out in order to optimize $\pi-\pi$ stacking. IR spectra of chloroform solutions of mixtures of guests and hosts showed two absorptions for the OH vibration: one for the free species and one for the hydrogen bonded complex. The difference between these values can thus be determined easily. The measured OH vibration differences ($\Delta\nu$) were observed to be equal for clip molecules **6** and **9** for each guest. For example, for resorcinol (**24b**) $\Delta\nu$ = 233 cm^{-1} with clip **6**, and $\Delta\nu$ = 239 cm^{-1} with clip **9**. For cyanoresorcinol (**24e**) $\Delta\nu$ values of 301 and 302 cm^{-1} were measured. (The $\Delta\nu$ is larger for the latter guest because the hydrogen bond is shorter and stronger.) This indicates that for a specific guest the hydrogen bonds between the hydroxy groups and the carbonyl oxygen atoms of the clip have almost exactly the same length in the complexes with both clip molecules. At a first glance this observed similarity seems to be contradictory to the observed differences in guest binding strength. An additional important parameter in binding of resorcinol, however, is the distance between the oxygen atoms of the carbonyl groups of the host molecules which determines the geometry of the hydrogen bond. This distance, as determined from the X-ray structures, is 5.2 Å for clip **9**[10] and 5.5 Å for clip **6**.[14] If one assumes that the hydrogen bonds are linear and have an O−H−O distance of 2.7 Å,[21] the optimal distance between the carbonyl oxygen atoms for binding of resorcinol is 3.9 Å. Although both **9** and **6** do not approach this value, the former clip molecule still is better suited for resorcinol binding than the latter clip molecule, in line with the measured binding constants. To prove this concept the binding of 2,7-dihydroxynaphthalene was studied. For this guest the optimal distance between the carbonyl oxygen atoms is larger, viz 6.3 Å. This means that host **6** should have a higher affinity for this guest than host **9** (see Figure 6). This could indeed be confirmed by NMR titration experiments. Host **9** binds 2,7-dihydroxynaphthalene with an association constant of K_a = 2300 ± 200 L mol^{-1}, whereas for host **6** the association constant is K_a = 7100 ± 500 L mol^{-1}.[18] We also measured the binding affinities of **9** and **6** for catechol. The association constants amounted to K_a = 130 ± 15 L mol^{-1} and K_a = 60 ± 10 L mol^{-1}, respectively. These low numbers indicate that the two clips are not very well equipped to complex this guest. Catechol forms an intramolecular hydrogen bond that needs to be broken to allow formation of two hydrogen bonds between this guest and the urea carbonyl groups of the clips. Nevertheless, clip **9** is better suited than clip **6** to match the hydrogen bond donor sites of catechol, in line with the ideas presented above.

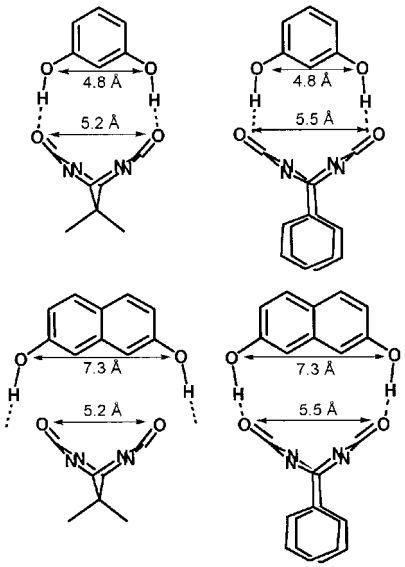

Figure 6. Hydrogen bonding interactions between the guest molecules resorcinol (top) and 2,7-dihydroxynaphthalene (bottom) and host molecules of **9** (left) and **6** (right). For clarity, only the frameworks with the hydrogen bonding sites of the host molecules are shown.

It has been previously shown that resorcinol binds in an asymmetric geometry in a clip that possesses only one hydrogen bond acceptor group.[4] It is assumed that in clips with two hydrogen bond acceptor groups resorcinol

cannot form two perfect hydrogen bonds simultaneously because of the geometry of the host carbonyl groups. We postulate given the experimental evidence that in hosts of type **9** the hydrogen bond geometry is closer to the optimum than for hosts of type **6** and hence stronger hydrogen bonding occurs. It is quite remarkable how such slight changes in geometry can induce such significant increases in binding.

Conclusions

The synthesis of a series of new receptors derived from propanediurea has been presented. These molecules are U-shaped and show a high affinity for resorcinol derivatives. The binding properties of these hosts have been studied in detail and have been compared to those of previously developed clip molecules derived from diphenylglycoluril. The enhanced binding properties of the new hosts can be accounted for by the smaller distance between the hydrogen bond acceptor sites in these clip molecules. Although the differences in geometry are subangstrom (~0.3 Å), the effect on the binding properties is very large, highlighting the necessity for host−guest complementarity. It was found that the affinity of the propanediurea receptors for resorcinol can be fine-tuned by introducing substituents under the side walls of the molecules.

The very high binding affinities of the new hosts (K_a up to 2 400 000 L mol^{-1}) can be used in the construction of supramolecular aggregates. Work in this direction is in progress.

Experimental Section

General. Thionyl chloride was distilled prior to use. Sodium hydride was a commercially available 60% suspension in mineral oil. Benzene, diethyl ether, and THF were distilled under nitrogen from sodium benzophenone ketyl. Carbon tetrachloride was dried on molecular sieves (4 Å). All other solvents and chemicals were commercially available materials and were used as received. Merck silica gel (60H) was used for column chromatography. Melting points were determined on a Jeneval polarization microscope THMS 600 hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1720-X spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument with $(CH_3)_4Si$ as the internal standard (δ 0.00 ppm) for the ^{1}H spectra and $CDCl_3$ as the internal standard (δ 77.0 ppm) for the ^{13}C spectra. Abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were recorded on a VG 7070E instrument. Elemental analyses was determined with a Carbo Erba EA 1108 instrument.

Compounds. The syntheses of compounds **3**,[14] **6**,[14] and **5**[23] have been reported elsewhere. 1,4-Dimethoxynaphthalene and 1,4-dimethoxy-2,3-dimethylbenzene were prepared by methylation of 1,4-dihydroxynaphthalene and 2,3-dimethylhydroquinone, respectively, using dimethyl sulfate and KOH as reagents. Compounds **8**,[24] **11**,[13] **20**,[12] **26**,[25] and 3,6-dimethoxyphthalic anhydride[26] were prepared according to literature procedures.

Compound 9. (A) From **8**. A mixture of 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**8**) (0.380 g, 2.07 mmol), water (0.9 mL), 3 drops of an aqueous 1 N NaOH solution, and paraformaldehyde (0.250 g, 8.33 mmol) were stirred at 60 °C for 3 h. The resulting clear solution was neutralized by bubbling CO_2 through it for a few minutes. The solution was concentrated in vacuo, yielding impure **10** (0.602 g). A solution of 1,4-dimethoxybenzene (1.38 g, 10.0 mmol) in 16 mL of concentrated sulfuric acid was then added and the mixture was stirred for 16 h at room temperature. The resulting solution was poured onto 200 g of crushed ice, made basic with a concentrated aqueous NaOH solution, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed once with water (50 mL) and dried (Na_2SO_4). The solution was concentrated in vacuo, and the resulting yellowish powder was purified through a short column (EtOH/CH_2Cl_2, 2:98 v/v) yielding **9** as a white powder (0.242 g, 0.476 mmol, 23%). (B) From **11**. To a mixture of TFA (1 mL) and acetic anhydride (1 mL) was added **11** (400 mg, 1.11 mmol). The resulting suspension was heated at 95 °C for 30 min. Then 1,4-dimethoxybenzene (337 mg, 2.44 mmol) was added and the resulting solution was heated at 100 °C for 30 min. The reaction mixture was cooled on ice and 6 mL of methanol was cautiously added. The precipitate was filtered off, washed with cold methanol, and dried in vacuo, yielding **9** as a white powder (439 mg, 0.864 mmol, 78%). (C) From **8** and **21**. In 50 mL of degassed DMSO were suspended **8** (331 mg, 1.80 mmol) and NaH (191 mg, 7.96 mmol), and the mixture was stirred under a nitrogen atmosphere at room temperature for 24 h. Then, **21** (1.20 g, 3.70 mmol) was added, and the reaction mixture was stirred for another 16 h at room temperature. The resulting solution was poured onto 150 g of crushed ice. The resulting precipitate was filtered off, washed with water and ethanol, and purified by column chromatography (EtOH/CH_2Cl_2, 2:98 v/v) yielding **9** as a white powder (183 mg, 0.360 mmol, 20%). An analytically pure sample was obtained by recrystallization from MeOH/$CHCl_3$. Crystals suitable for X-ray analysis were obtained by slow diffusion of diethyl ether in a CH_2Cl_2 solution of the compound: mp 348 °C subl; EIMS *m*/*z* 508 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, s), 3.78 (12H, s), 3.90 (4H, d, J = 15.2 Hz), 4.32 (2H, s), 5.42 (4H, d, J = 15.2 Hz), 6.74 (4H, s); ^{13}C NMR ($CDCl_3$) δ 23.04, 32.18, 44.73, 57.44, 79.10, 112.57, 128.31, 151.85, 154.42; IR (KBr) ν = 1638, 1659 cm^{-1} (C=O). Anal. Calcd for $C_{28}H_{36}4O_7$ (**9**·MeOH): C, 62.21; H, 6.71; N, 10.36. Found: C, 62.21; H, 6.66; N, 10.28.

Compound 12. Paraformaldehyde (1.86 g, 62.0 mmol) was dissolved by heating in 7.5 mL water containing 5 drops of an aqueous 2 N NaOH solution. Then, 9,9-dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**8**) (2.85 g, 15.5 mmol) was added, and the mixture was heated at 60 °C until it became clear. The resulting solution was stirred for 30 min at room temperature and was neutralized by bubbling CO_2 through it for a few minutes. The solution was concentrated in vacuo and 25 mL of acetic anhydride, and 5 drops of aqueous concentrated HCl was added. The mixture was stirred at 100 °C for 30 min and poured onto 300 g of crushed ice. The solution was neutralized with aqueous NaOH and extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was washed with water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was passed through a short column (EtOH/CH_2Cl_2, 2:98 v/v). The first fraction was collected and recrystallized twice from 1-propanol, yielding white crystalline **12** (1.25 g, 2.65 mmol, 17%): mp 164−166 °C; EIMS *m*/*z* 267 (100), 442 [M − 2CH_3]$^+$; ^{1}H NMR ($CDCl_3$) δ 1.12 (6H, s), 2.09 (12H, s), 4.98 (2H, s), 5.44 (4H, d, J = 10.8 Hz), 5.54 (4H, d, J = 10.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.27, 21.82, 31.73, 72.02, 152.41, 171.61; IR (KBr)R ν = 1669, 1745 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{28}4O_{10}$: C, 48.30; H, 5.97; N, 11.86. Found: C, 48.50; H, 5.94; N, 11.69.

Compound 13. Prepared as described for **9**, method B, from **11** (116 mg, 0.322 mmol) and 1,4-dimethoxynaphthalene (140 mg, 0.745 mmol) yielding **13** as a white powder (113 mg, 0.186 mmol, 58%). An analytically pure sample was obtained by slow diffusion of diethyl ether in a dichloromethane solution of the compound to give **13** as white needles. Crystals suitable for

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X-ray analysis were prepared by slow diffusion of hexane in a CH_2Cl_2 solution of the compound: mp 326−328 °C; EIMS *m/z* 608 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.45 (6H, s), 4.03 (12H, s), 4.05 (4H, d, J = 15.6 Hz), 4.42 (2H, s), 5.77 (4H, d, J = 15.6 Hz), 7.43−7.47 (4H, m), 7.99−8.02 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.01, 32.01, 46.47, 62.64, 79.80, 123.05, 126.28, 127.13, 128.34, 150.38, 154.18; IR (KBr) ν = 1663 cm^{-1} (C═O). Anal. Calcd for $C_{36}H_{38}4O_6Cl_2$ (**13**.CH_2Cl_2): C, 62.41; H, 5.53; N, 8.09. Found: C, 62.27; H, 5.48; N, 8.04.

Compound 14. (A) From **12**. A solution of **12** (321 mg, 0.680 mmol) in 2.5 mL of thionyl chloride was stirred under a nitrogen atmosphere for 16 h at room temperature. The solvent was removed in vacuo yielding **14** as a white, very hygroscopic powder (255 mg, 0.675 mmol, 99%). (B) From **11**. A solution of **11** (1.00 g, 2.78 mmol) in a mixture of CH_2Cl_2 (4 mL), thionyl chloride (9 mL), and one drop of water was stirred under a nitrogen atmosphere for 16 h at room temperature. Diethyl ether (40 mL) was added, and the reaction mixure was cooled to 0 °C. The mixture was filtered, and the residue was washed with dry diethyl ether. The resulting white solid was redissolved in dry CH_2Cl_2 and filtered. The solvent was removed in vacuo yielding **14** as a white powder (0.950 g, 2.51 mmol, 90%): FAB-MS *m/z* 329 [M- CH_2Cl]$^+$ (100); ^{1}H NMR ($CDCl_3$) δ 1.28 (6H, s), 4.65 (2H, s), 5.35 (4H, d, J = 10.7 Hz), 5.67 (4H, d, J = 10.7 Hz); ^{13}C NMR ($CDCl_3$) δ 22.16, 31.73, 58.95, 75.62, 149.66. Due to the instability of the compound, no reproducible elemental analysis could be obtained.

Compound 15. A mixture of **14** (399 mg, 1.06 mmol), $AlCl_3$ (920 mg, 6.89 mmol), and 6 mL of dry benzene was refluxed under a nitrogen atmosphere for 16 h. The reaction mixture was allowed to cool to room temperature, and an aqueous 6 N HCl solution (20 mL) was added. The resulting mixture was refluxed for 30 min, cooled, and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with aqueous 2 N NaOH (50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting brown powder was washed with diethyl ether to give (±)-**15** as a white powder (260 mg, 713 mmol, 67%). A sample was recrystallized for elemental analysis by slow diffusion of diethyl ether in a CH_2Cl_2/MeOH solution of the compound, giving pure **15** as white crystals: mp 305−306 °C; EIMS *m/z* 365 [M+H]$^+$ (100); ^{1}H NMR ($CDCl_3$) δ 1.08 (6H, s), 3.91 (2H, d, J = 3.9 Hz), 4.23 (2H, d, J = 15 1 Hz), 4.98 (2H d, J = 15.0 Hz), 5.63 (2H, d, J = 3.6 Hz), 7.27−7.37 (10H, m); ^{13}C NMR ($CDCl_3$) δ 22.55, 31.74, 48.76, 68.74, 127.87, 128.51, 128.85, 137.03, 153.81; IR (KBr) ν = 1650, 1672 cm^{-1} (C═O). Anal. Calcd for $C_{21}H_{24}4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.39; H, 6.60; N, 15.23.

Compound 17a. To toluene (90 mL) were added **16a** (2.41 g, 21.1 mmol), urea (2.54 g, 42.3 mmol), and TFA (2 mL). The mixture was refluxed in an inert atmosphere for 4 h with azeotropic removal of water. Subsequently it was cooled and filtered. The precipitate was washed with ethanol and dried in vacuo, yielding 3.93 g (19.8 mmol, 94%) of **17a** as a white powder. Recrystallization from boiling water (~1 g L^{-1}) provided white crystals.

Compounds 17b. Prepared as described for **17a** starting from **16b** (8.00 g, 48.8 mmol) and urea (5.86 g, 97.7 mmol). Yield 11.8 g (45.4 mmol, 93%) of **17b** as a white powder. Crystalline material was obtained by recrystallization from boiling water.

Compounds 17c. Prepared as described for **17a** starting from **16c** (2.75 g, 19.4 mmol) and urea (2.40 g, 40.0 mmol). Yield 4.35 g (19.2 mmol, 99%) of **17c** as a white powder. Crystalline material was obtained by recrystallization from boiling water.

Compound 19a. In a mixture of acetonitrile (7 mL) and water (2 mL) were suspended **17a** (213 mg, 1.08 mmol) and paraformaldehyde (230 mg, 7.67 mmol). Two drops of an aqueous 2 N NaOH solution were added and the mixture was stirred for 16 h at 60 °C. The resulting solution was cooled and CO_2 was bubbled through it for a few minutes. The solvent was removed in vacuo and 1,4-dimethoxybenzene (1.01 g, 7.31 mmol) in concentrated sulfuric acid (12 mL) was added. The reaction mixture was stirred for 16 h at room temperature. The resulting solution was poured onto 100 g of crushed ice, neutralized with a concentrated aqueous solution of NaOH and $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo yielding **19a** as a white powder (78 mg, 0.22 mmol, 20%). Crystals suitable for X-ray analysis were prepared by slow diffusion of diethyl ether in a MeOH/$CHCl_3$ solution of the compound: mp 320−322 °C dec; EIMS *m/z* 360 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, s), 1.30 (6H, s), 3.72 (2H, d, J = 15.5 Hz), 3.86 (s, 6H), 4.41 (1H, s), 4.90 (2H, s), 5.82 (2H, d, J = 15.5 Hz), 6.82 (2H, s); ^{13}C NMR ($CDCl_3$:MeOD-*d*4 4:1): δ 19.43, 20.35, 34.72, 44.08, 56.77, 69.08, 81.25, 112.14, 128.05, 151.40, 154.92; IR (KBr) ν = 1631, 1676 cm^{-1} (C═O). Anal. Calcd for $C_{19}H_{28}4O_5$ (**19a**.MeOH): C, 58.15; H, 7.19; N, 14.28. Found: C, 58.16; H, 7.13; N, 14.10.

Compound 19b. Prepared as decribed for **19a** from **17b** (1.42 g, 5.46 mmol), paraformaldehyde (660 mg, 22 mmol), and 1,4-dimethoxybenzene (3.0 g, 22 mmol). The crude product was purified through a short column (EtOH/CH_2Cl_2, 5:95 v/v) yielding **19b** (580 mg, 1.41 mmol, 26%). Crystals suitable for X-ray analysis were prepared by slow diffusion of hexane in a MeOH/CH_2Cl_2 solution of the compound, followed by slow evaporation: mp 333−334 °C; EIMS *m/z* 422 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.15 (6H, s), 3.78 (2H, d, J = 15.4 Hz), 3.89 (6H, s), 4.49 (1H, s), 5.20 (2H, s), 5.8 (2H, d, J = 15.4 Hz), 6.85 (2H, s), 7.40−7.58 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.29, 36.52, 44.54, 57.38, 74.88, 81.90, 112.76, 127.78, 128.35, 128.57, 129.32, 151.79, 154.71; IR (KBr) ν = 1636, 1644, 1674 cm^{-1} (C═O). Anal. Calcd for $C_{24}H_{28}4O_4Cl_2$ (**19b**.CH_2Cl_2): C, 56.90; H, 5.58; N, 11.07. Found: C, 56.88; H, 5.48; N, 11.18.

Compound 19c. Prepared as decribed for **19a** from **17c** (501 mg, 2.22 mmol), paraformaldehyde (273 mg, 9.10 mmol), and 1,4-dimethoxybenzene (790 mg, 5.72 mmol). Yield (210 mg, 0.54 mmol, 24%) **19c** as a white powder: mp 322 °C dec; EIMS *m/z* 388 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.1 Hz), 1.23−1.34 (8H, m), 1.57−1.63 (2H, m), 3.72 (2H, d, J = 15.4 Hz), 3.86 (6H, s), 4.38 (1H, s), 5.04 (2H, s), 5.82 (2H, d, J = 15.4 Hz), 6.82 (2H, s); ^{13}C NMR ($CDCl_3$) δ 14.23, 14.44, 20.79, 34.65, 35.69, 44.26, 57.34, 70.71, 81.69, 112.63, 128.38, 151.68, 154.19; IR (KBr) ν = 1646, 1675 cm^{-1} (C═O). Anal. Calcd for $C_{21}H_{30}4O_4Cl_2$ (**19c**·CH_2Cl_2): C, 53.28; H, 6.39; N, 11.83. Found: C, 53.40; H, 6.21; N, 11.89.

Compound 22a. Prepared as described for **9** (method C) from **17a** (554 mg, 2.80 mmol) and **21** (1.95 mg, 6.02 mmol). The crude product was purified by column chromatography (EtOH/CH_2Cl_2 2/98 v/v) yielding **22a** as a white powder (366 mg, 0.700 mmol, 25%). Crystals suitable for X-ray analysis were prepared by the vapor diffusion technique using acetone/$CHCl_3$ as the solvent and diethyl ether as the precipitant: mp 352−353 °C subl; EIMS *m/z* 522 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, s), 1.71 (3H, s), 3.74 (6H, s), 3.77 (6H, s), 3.85 (2H, d, J = 15.2 Hz), 3.87 (2H, d, J = 17.1 Hz), 4.27 (1H, s), 5.55 (2H, d, J = 15.2 Hz), 5.97 (2H, d, J = 17.2 Hz), 6.63 (2H, s), 6.72 (2H, s); ^{13}C NMR ($CDCl_3$) δ 18.30, 22.62, 35.23, 39.35, 45.24, 56.85, 57.34, 82.14, 110.38, 112.36, 128.51, 129.38, 151.58, 151.74, 154.29; IR (KBr) ν = 1624, 1652 cm^{-1} (C═O). Anal. Calcd for $C_{29}H_{35}4O_6Cl_3$ (**22a**·$CHCl_3$): C, 54.26; H, 5.50; N, 8.73. Found: C, 54.44; H, 5.44; N, 8.62.

Compound 22b. Prepared as described for **9** (method C) from **17b** (350 mg, 1.35 mmol) and **21** (923 mg, 2.85 mmol). The crude product was purified through a short column (MeOH/CH_2Cl_2 2/98 v/v) yielding **22b** as a white powder (245 mg, 0.419 mmol, 30%). An analytically pure sample was obtained by liquid diffusion using CH_2Cl_2 as the solvent and diethyl ether as the precipitant. Crystals suitable for X-ray analysis were prepared by slow diffusion of hexane/acetone in a CH_2Cl_2 solution of the compound: mp >350 °C; EIMS *m/z* 584 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.06 (6H, s), 3.73 (6H, s), 3.77 (6H, s), 3.81 (2H, d, J = 15.0 Hz), 3.89 (2H, d, J = 15.2 Hz), 4.35 (1H, s), 5.42 (2H, d, J = 15.2 Hz), 5.54 (2H, d, J = 15.0 Hz), 6.53 (2H, s), 6.66 (2H, s), 7.27−7.43 (5H, m); ^{13}C NMR ($CDCl_3$) δ 23.03, 36.63, 41.76, 45.00, 57.39, 57,73, 79.49, 84.58, 112.00, 112.84, 127.84, 128.14, 128.59, 128.82, 129.61, 135.55, 151.92, 155.65; IR (KBr) ν = 1654, 1675 cm^{-1} (C═O).

Anal. Calcd for $C_{33}H_{36}4O_6$: C, 67.79; H, 6.21; N, 9.58. Found: C, 67.91; H, 6.26; N, 9.42.

Compound 23. Prepared as described for **9** (method C) from **20** (326 mg, 1.54 mmol) and **21** (1.02 g, 3.15 mmol). The crude product was recrystallized from $CHCl_3$/EtOH yielding **23** as a white crystalline solid (234 mg, 0.436 mmol, 28%): mp 340−341 °C subl; EIMS *m*/*z* 536 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, s), 1.83 (6H, s), 3.73 (12H, s), 3.93 (4H, d, J = 17.4 Hz), 6.04 (4H, d, J = 17.2 Hz), 6.59 (4H, s); ^{13}C NMR: δ 19.02, 20.96, 39.21, 40.06, 56.74, 74.22, 110.20, 129.35, 151.51, 154.44; IR (KBr) ν = 1652 cm^{-1} (C=O). Anal. Calcd for $C_{30}H_{37}$-$4O_6Cl_3$ (**23**·$CHCl_3$): C, 54.93; H, 5.68; N, 8.54. Found: C, 54.98; H, 5.69; N, 8.48.

1,4-Dimethoxy-2,3-bis-(hydroxymethyl)benzene. To a cooled suspension of $LiAlH_4$ (4 g, 0.11 mol) in THF (250 mL) was slowly added a suspension of 3,6-dimethoxyphthalic anhydride (2.0 g, 9.6 mmol) in THF (300 mL). The reaction mixture was refluxed for 48 h in an inert atmosphere. The mixture was cooled on ice, and water was added dropwise until evolution of hydrogen stopped. Water (200 mL) was added, and the mixture was extracted with $CHCl_3$ (4 × 100 mL). The combined organic layers were washed with water (150 mL), dried ($MgSO_4$), and concentrated in vacuo, yielding the crude product. Recrystallization from toluene/methanol gave a white crystalline solid (1.58 g, 7.98 mmol, 83%): mp 145 °C; EIMS *m*/*z* 198 M^+ (100); ^{1}H NMR ($CDCl_3$) δ 2.87 (2H, s), 3.81 (6H, s), 4.82 (4H, s), 6.83 (2H, s); ^{13}C NMR: δ 56.15, 56.42, 111.04, 129.45, 151.81. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.70; H, 7.02.

1,4-Dimethoxy-2,3-bis-(bromomethyl)benzene (21). (A) From 1,4-dimethoxy-2,3-dimethylbenzene. A mixture of *N*-bromosuccinimide (4.98 g, 28 mmol), 1,4-dimethoxy-2,3-dimethylbenzene (2.32 g, 14 mmol), and 50 mL of dry CCl_4 was irradiated with a 200 W lamp at reflux temperature in a nitrogen atmosphere for 1 h. The solution was cooled to room temperature, filtered, and concentrated in vacuo yielding **21** as a white powder (4.36 g, 13.5 mmol, 96%). (B) From 1,4-dimethoxy-2,3-bis-(hydroxymethyl)benzene. To a cooled suspension of 1,4-dimethoxy-2,3-bis-(hydroxymethyl)benzene (6.26 g, 31.6 mmol) in 200 mL of dry diethyl ether was slowly added a solution of PBr_3 (20 g, 74 mmol) in diethyl ether (10 mL). The suspension was then refluxed for 2 h and allowed to cool to room temperature. The mixture was cautiously poured onto 200 g of crushed ice and extracted with diethyl ether (3 × 250 mL). The combined organic layers were washed with water (50 mL), dried (Na_2SO_4), and concentrated in vacuo yielding **21** as a white powder (9.97 g, 30.8 mmol, 97%). An analytically pure sample was prepared by crystallization from toluene: mp 149 °C; EIMS *m*/*z* 164 $[M - 2Br]^+$ (100), 324 M^+; ^{1}H NMR ($CDCl_3$) δ 3.86 (6H, s), 4.74 (4H, s), 6.84 (2H, s); ^{13}C NMR ($CDCl_3$) δ 23.92, 56.24, 112.12, 126.37, 151.74. Anal. Calcd for $C_{10}H_{12}O_2Br_2$: C, 37.19; H, 3.43. Found: C, 37.19; H, 3.58.

Binding Experiments.[17] The association constants of complexes with all guests except **24d**,**e** were determined by ^{1}H NMR shift titrations at 298 K on a Bruker AM-300 instrument with $(CH_3)_4Si$ as the internal standard, using fresh $CDCl_3$, predried on molecular sieves (4 Å). The concentration of the fixed component was approximately 0.5 mM when K_a values were greater than 2000 M^{-1}, 4 mM when K_a values were smaller than 250 M^{-1}, and K_a^{-1} in other cases. The concentration of the other component was varied between the concentration of the fixed component and 10 times this value (or 15 times for K_a values lower than 150). Since for guest **24c** very high binding constants were measured, these values were double-checked in competition experiments with **24b**. For complexes with guests **24d**,**e** no accurate values could be obtained from ^{1}H NMR shift titrations since the binding constants are too large to be measured by this technique. Therefore binding constants of clips with guests **24d** and **24e** were determined in competition experiments with **24c** and **24d**, respectively. For comparison of binding properties of clips **9** and **22a** and clips **9** and **23** we also used competition experiments. For competition experiments a 1 mM solution of a guest (or host) was prepared. This solution was used to prepare a solution containing 1 mM guest (or host) and 1 mM host A (or guest A) and a solution containing 1 mM guest (or host) and 1 mM host B (or guest B). Aliquots of these two solutions were mixed to a total volume of 0.6 mL and measured. Due to the experimental setup of the competition experiments, the *relative* association constant K_{rel} can be determined very accurately. Generally the error margins are smaller than 5%.[19b] This method is therefore very useful when comparing the affinity of two hosts for a certain guest molecule. If this affinity is similar, comparison of the binding constants determined by standard titrations is impossible because of the relatively large error margins. Direct competition experiments do allow for reliable comparison.

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Supporting Information Available: X-ray structural information on **9**, **13**, **19a**, **19b**, **22a**, and **22b** (PDF) and ORTEP drawings of these structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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