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Binding Features of Molecular Clips Derived from Diphenylglycoluril

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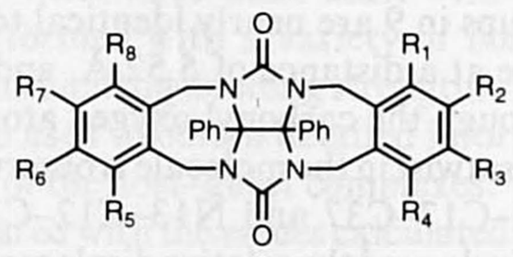
Abstract: The structure and binding properties of a series of receptor molecules based on the building block diphenylglycoluril are described. These receptors bind dihydroxy-substituted aromatic guests in chloroform solution by means of hydrogen bonding and π–π stacking interactions. IR difference spectroscopy shows that the hydrogen bonds are formed between the OH groups of the guest molecule and the π-electrons of the urea carbonyl groups present in the receptor. The structure of the complexes was further investigated by comparing the complexation-induced shifts in the ^{1}H NMR spectra with the calculated shifts for a number of geometries of the host–guest complexes. These data demonstrate that the guest molecules are clamped within the cavity of the receptor.

Introduction

Hydrogen bonding and π–π interactions are dominant forces in the aggregation of neutral molecules in nonaqueous solvents. In this regard they are valuable tools in the engineering of supramolecular assemblies. Exploring the potentialities of these interactions in order to attain strong and selective binding is currently an area of intense interest in host–guest chemistry. Rebek[1] and Hamilton[2] have shown that a single aromatic surface can significantly improve the complexation of a guest in a hydrogen-bonding receptor. Whitlock,[3] Zimmerman,[4] and others[5] have synthesized host molecules that are capable of binding neutral aromatic guests between two aromatic surfaces with or without the aid of hydrogen bonding.

In our research group we are designing hosts with the specific purpose of using them in the development of synzymes. These are supramolecular devices that combine the functions of recognition and catalysis. As part of this program we have developed molecular clip **1**, based on the concave molecule



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diphenylglycoluril.[6] Compound **1** has a well-defined geometry due to the rigidity the fused rings confer on the molecule. It contains a cleft of the proper dimensions to accommodate an aromatic molecule. The aromatic walls of the cleft and the two urea carbonyl groups at its base are expected to endow the clip with a high degree of specificity for guests that bind by π–π stacking and which are able to form two simultaneous hydrogen bonds.

We report here in detail on the binding properties of **1** and present an analysis of factors that determine the specificity of hosts of type **1** for dihydroxy-substituted aromatic guests.

Results

Synthesis. In order to evaluate the binding properties of **1**, we synthesized a number of derivatives, starting from **2a** or **3** (see Chart I for structures **2–9**) and the appropriate aromatic compound. Most of these syntheses have already been described elsewhere.[7] In this section the syntheses of **4**, **5**, **7**, and **8** are presented.

Compound **4**, which has two methoxy groups on one cavity wall and none on the other, was synthesized by partial reaction of the tetrachloro compound **3** with benzene, using $AlCl_3$ as a catalyst. The remaining chloromethyl groups of **3** were converted into cyclic ether groups by refluxing with 6 N aqueous HCl. The resulting mixture was then treated with dimethoxybenzene in Ac_2O/TFA to yield **4**, and the side products **6a** and **6c**, from which **4** could be isolated in 17% yield by column chromatography.

Having four electron-donating substituents on each cavity wall, **6c** is very susceptible to attack by electrophiles, which makes this compound a very convenient starting compound for the synthesis of further derivatives of **1**.

Compounds **7** were synthesized by reaction of **6c** with 2 equiv of Br_2 in CH_2Cl_2 with $AlCl_3$ as a catalyst. After purification by column chromatography the product was obtained as a mixture of the diastereomers **7a** and **7b**, which could be separated into the racemate and the meso compound, by column chromatography using ethyl acetate/hexane as the eluent. Assignment of the diastereomers was possible with the help of ^{13}C-NMR. The meso diastereomer showed two peaks in the carbonyl region, at 157.49 and 157.25 ppm, and the racemate only one at 157.38 ppm. For the complexation studies the racemate was used.

The dinitro compound **8** was synthesized by reaction of **6c** with 2 equiv of concentrated nitric acid in acetic anhydride. In this

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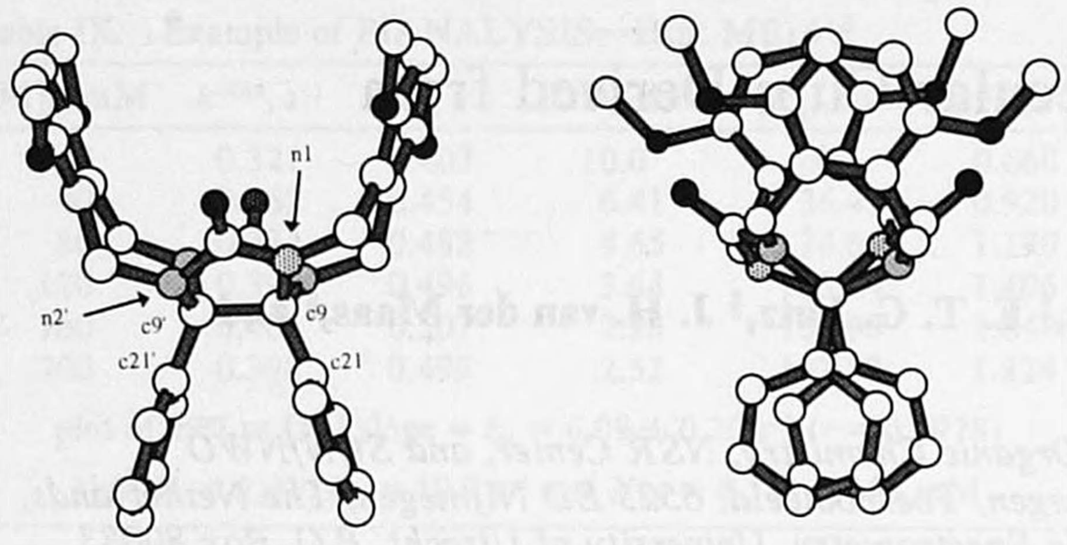


Figure 1. X-ray structure of **6c**. Hydrogen atoms have been omitted for clarity.

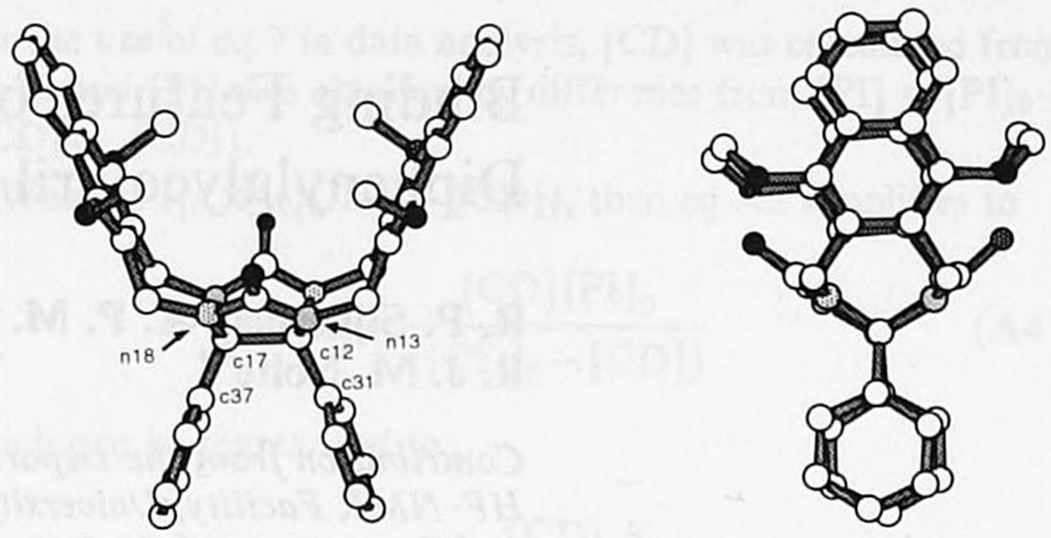
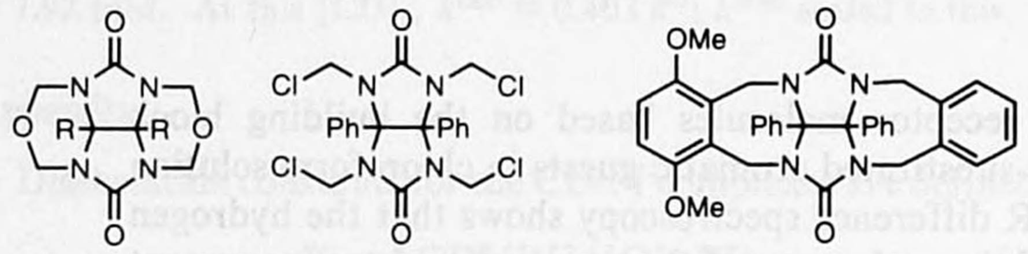
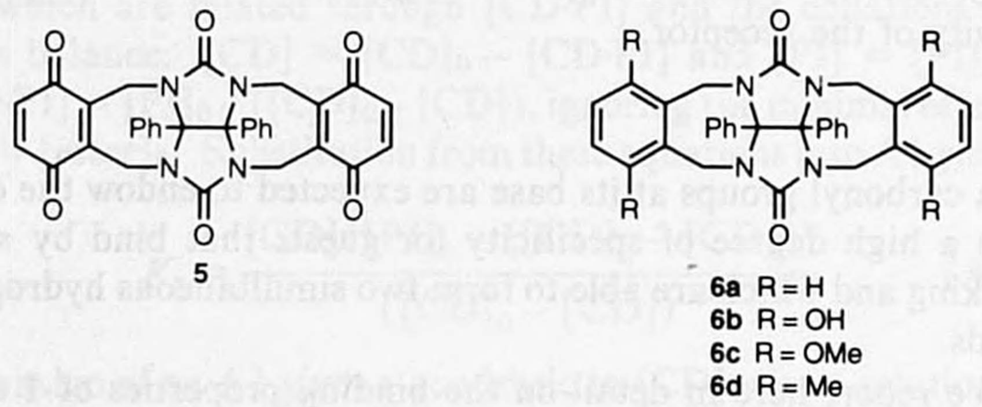
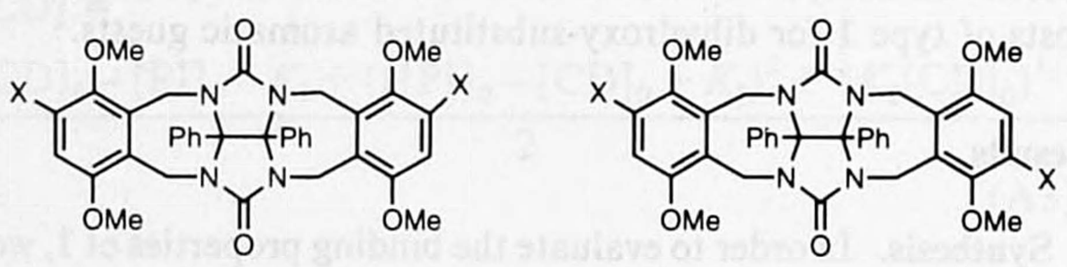


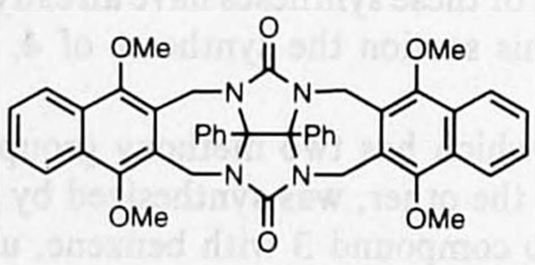
Figure 2. X-ray structure of **9**. Hydrogen atoms have been omitted for clarity.

Chart I









case we were not able to separate the diastereomers and consequently the mixture was used in the complexation studies.

The bright-red compound **5** was prepared from **6b** by aerial oxidation in DMSO solution using Cu_2Cl_2 as a catalyst.[8]

X-ray Structures. The presence of the basic structural features in hosts **1** that allow these molecules to function as molecular receptors for dihydroxybenzenes (viz. two carbonyl groups at the base of a cleft which is flanked by two *o*-xylylene moieties) had previously been established by the X-ray structure of **6b**.[9] The X-ray structures of **6c**[10] and **9**,[11] determined recently, provide more detailed information on the geometries of these compounds, in particular with regard to their remarkable difference in complexation behavior (*vide infra*).

Just as in the X-ray structure of **6b**, there is a noticeable twist in the diphenylglycoluril part of **6c** (Figure 1). The dihedral angle C21–C9–C9′–C21′ is 22°, the same value as in **6b**. The dihedral angle N1–C9–C9′–N2′ is 18° (17° in **6b**). The twist is most strikingly visible in the dimethoxybenzene walls of the cavity. It is most convenient to express the distortion in the molecule as the relative displacement of the centers of the benzene rings along the axis through the carbonyl oxygen atoms. In **6c** this displacement is 1.11 Å, as compared to 1.09 Å in **6b**. The two dimethoxybenzene moieties define a tapering cavity, the best planes through the cavity walls being at a relative angle of 39.5°, with the centers of the benzene rings 6.67 Å apart.

The carbonyl groups of the glycoluril moiety, which are the hydrogen-bonding acceptor sites, are at an angle of 39° with the axis through the carbonyl oxygen atoms. The latter atoms are 5.52 Å apart, which is almost the same value as in **6b**. In the complexation experiments with aromatic guests, which are described in this paper, **2a** is used as a reference receptor. Compound **2** has hydrogen- bonding acceptor sites but no cavity. In **2b**, the dimethyl analog of **2a** of which the crystal structure has been published recently,[12] the distance between the carbonyl oxygen atoms is shorter (4.98 Å) than that in **6c**, and the carbonyl groups are at a larger angle with the axis through the carbonyl oxygen atoms (57.2°). The origin of the differences between these rigid structures lies in the size of the rings flanking the glycoluril units. Whereas in **6c** a C4 fragment is linking the two ureido nitrogen atoms, in **2b** these atoms are spanned by a shorter C–O–C bridge. The effect is a folding of the glycoluril moiety in **2b** to bring the nitrogen atoms closer together.

The methoxy groups in **6c** significantly deviate from the least-squares planes of the benzene carbon atoms of the cavity walls. They are rotated 29.3° and 9.5° out of these planes and point inward.

There are striking similarities as well as differences between the structures of **6c** and **9** (Figure 2). The relative positions of the carbonyl groups in **9** are nearly identical to those in **6c**. The oxygen atoms are at a distance of 5.52 Å, and the C=O angle with the axis through the carbonyl oxygen atoms is 37.5°. In **9** however, much less twist in the molecule is observed. The dihedral angles C31–C12–C17–C37 and N13–C12–C17–N18 are 6.6° and 4.8°, respectively, and the relative displacement of the centers of the benzene rings in the naphthalene moieties that are connected to the glycoluril part of the molecule is just 0.2 Å. The naphthalene walls in this molecule are at a much larger relative angle (53°) and are farther apart (6.95 Å) than the walls in **6c**. The methoxy groups of **9** are almost at perpendicular angles (83.5° and 85°) to the naphthalene rings, and there are intramolecular contacts between the methyl groups and the carbonyl oxygen atoms, (shortest methyl carbon to carbonyl oxygen distance is 3.21 Å) indicative of C–H···O bonding.[13]

Complexation Studies. Addition of a dihydroxy-substituted aromatic guest, such as resorcinol, to a solution of one of the hosts **1** caused the NMR signals of the aromatic protons of the guest and the signals of the cavity wall protons of the host to shift upfield, whereas the proton signals of the OH groups moved downfield. These shifts indicate that complexes are formed,

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Table I. Complexation Induced Shift (CIS) Values (in ppm) of Host and Guest in the Complexes of Hosts with Catechol, Resorcinol, and 2,7-Dihydroxynaphthalene

	guest	
host	catechol	resorcinol
2a	cat: 1.63 (OH)	res: 1.59 (OH)
4	host: 0.22 (ArH);[a] 0.22 (Me)	host: 0.48 (ArH)
5		host: 0.49 (ArH)
6a	cat: 0.1 (ArH);[b] 2.15 (OH)	res: 1.6 (OH); 2.27 (H2); 0.3 (H4,6)
6c	host: 0.31 (ArH); 0.28 (Me)	host: 0.47 (ArH) res: 2.71 (H2); 0.30 (H5); 0.42 (H4,6)
6d	host: 0.22 (ArH); 0.07 (Me) cat: 0.25 (ArH);[b] 1.61 (OH)	host: 0.43 (ArH)
7a		host: 0.45 (ArH); 0.17 (OMe)
8a,b		host: 0.32 (ArH)
9		res: 1.6 (OH) res: 0 (ArH); >0.7 (OH)

host	guest: 2,7-dihydroxynaphthalene
6c	1.59 (H1,8); 0.16 (H3,6); 0.24 (H4,5)

[a] The proton signals of the dimethoxybenzene wall were monitored. [b] Signals of catechol protons coincide.

Table II. Association Constants of Host **6c** with Aromatic Compounds in $CDCl_3$ (T = 298 ± 2 K)

guest	K_a (M^{-1})
catechol	60
resorcinol	2600; 3000[a]
4,6-dibromoresorcinol	5600; 4250;[a] 5600[b]
2,7-dihydroxynaphthalene	7100[b]

[a] Determined in a liquid–liquid extraction experiment. [b] Determined in a competition experiment with resorcinol.

involving hydrogen bonds between the OH groups of the guest and the carbonyl groups of the host. Furthermore, they suggest that the aromatic moiety of the guest is wedged in between the walls of the cavity. Only one signal was observed for the free and bound forms of host and guest, implying that the exchange process is fast on the NMR time scale.

A titration in which the shift is monitored as a function of the concentrations of host and guest allowed the calculation of association constants and complexation induced shift (CIS) values. In some cases a competitive method was used to evaluate relative association constants, or a liquid–liquid extraction was used. The theory and methodology for the determination of association constants by ^{1}H-NMR have been dealt with elsewhere.[14] Titrations were performed with a variety of hosts and guests to study the factors influencing binding strength. The experimental CIS values can be used to obtain detailed information about the precise geometry of the host–guest complexes. To this end these values were compared with the values calculated with a theoretical model for the shifts induced by the aromatic moieties in host and guest *(vide infra)*. The results of the NMR titrations are summarized in Tables I–III.

Infrared spectroscopy was used to investigate hydrogen bonding between hosts **1** and hydroxy-substituted guests. The host carbonyl stretching vibration as well as the OH stretching vibration band of the guest is influenced by hydrogen bonding. It is well-known that the shape and position of these bands can provide detailed information on the nature of the hydrogen bonds in the complexes. Problems caused by interfering bands could for the most part be solved by applying difference spectroscopy. The solubility of some of the host compounds was too low in the noncompeting solvent CCl_4. In these cases $CHCl_3$ or $CDCl_3$ was used. IR spectra of the pure hosts and some glycoluril derivatives were recorded in solid KBr and, if possible, in solution. The peak maxima of the host compounds in the carbonyl stretching region

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Table III. Association Constants (M^{-1}, Error in Parentheses) of Hosts with Catechol and Resorcinol in $CDCl_3$ (T = 298 ± 2 K)

	guest	
host	catechol	resorcinol
2a	14(5)	25(10)
4	40(12)	580(80)
5		30(15)
6a	80(6)	200(20)
6c	60(10)	2600(400)
6d	60(10)	450(50)
7a		280(25)
8a,b		230(25)
9	<5	<5

Table IV. Values of Carbonyl Stretching Frequencies (cm^{-1}) in Host Compounds

	ν C=O	
host	KBr	solution
2a	1758, 1746, 1741, 1728	1765, 1743[a]
2b	1727	
6c	1732, 1712	1720, 1703[b]
6d	1722, 1706	1725, 1708;[a] 1715, 1701[b]
10a	1686	
10b	1715, 1690, 1677	
11		1704, 1688;[b] 1735, 1723[c]

[a] In CCl_4. [b] In $CHCl_3$. [c] In hexane.

Table V. Differences in OH Stretching Frequencies (cm^{-1}) between Complexes and Free Guests[a]

guest	host	solvent	$\Delta\nu$ OH[b]
phenol	**2a**	$CHCl_3$	148, 192
	6d	CCl_4	210, 260
	12	CCl_4	146, 222
resorcinol	**6c**	$CHCl_3$	233
	6d	$CDCl_3$	204
	12	CCl_4	132, 228
catechol	**6d**	CCl_4	23,[c] 280[d]
2,7-dihydroxynaphthalene	**2a**	CCl_4	128, 228
	6d	CCl_4	200

[a] The C=O stretching frequencies of the carbonyl group in the hosts move 18–25 cm^{-1} to lower wavenumbers upon complex formation. [b] Bands move to lower wavenumbers upon hydrogen bonding. [c] Intramolecular hydrogen bond. [d] Intermolecular hydrogen bond.

are listed in Table IV. Table V and Figures 3 and 4 show the effects of complexation on the OH bands of the guest.

Discussion

Structure of Host–Guest Complexes. A. Infrared spectroscopy. First we will discuss the effect of complexation on the position of the carbonyl stretching vibration of the host. One difficulty is that in some free hosts ν C=O proves to be split into at least two bands (Table IV). This splitting is probably caused by coupling of the C=O vibration via the C—N stretching vibration. Support for this explanation is found in the Raman spectra of our compounds, which displayed reversed relative intensities as compared to the IR spectra.

IR spectra of compounds **2a**, **6c**, and **6d** mixed with phenol, catechol, or resorcinol in CCl_4 or $CHCl_3$ all show a ν C=O at 18–25 cm^{-1} lower wavenumber than that for the most intense ν C=O in the free host. This indicates that the carbonyl groups in the complexes are involved in hydrogen bonding. The $\Delta\nu$ values are in good agreement with values reported in the literature for hydrogen- bonded complexes of other urea derivatives with phenols.[15]

Additional information on the structure of the complexes can be obtained from the change in the OH stretching vibration of complexed guests. The difference IR spectrum of a mixture of

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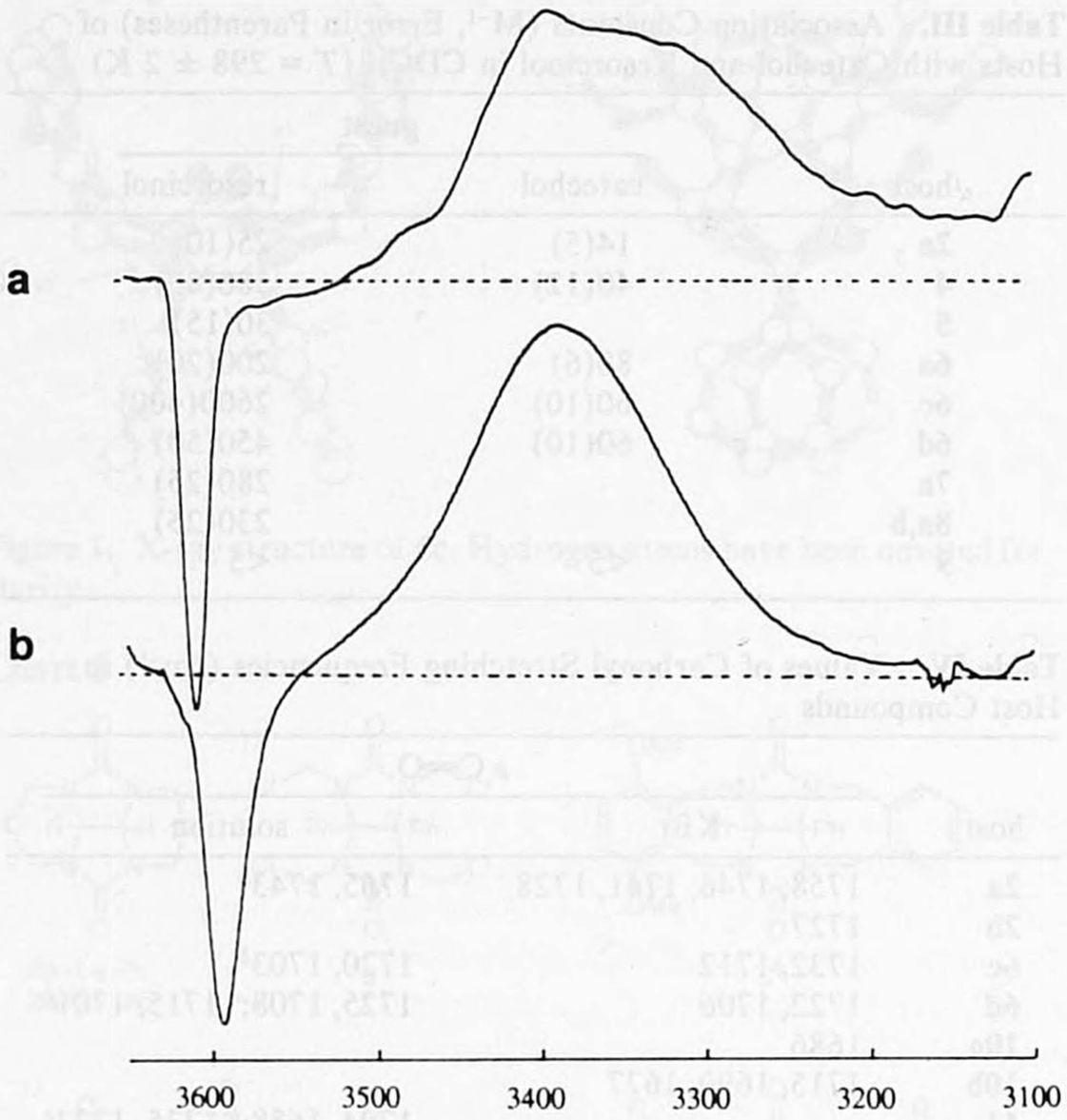


Figure 3. Difference IR spectrum of (a) a mixture of phenol and **6d** in CCl_4 and of (b) a mixture of resorcinol and **6d** in CCl_4.

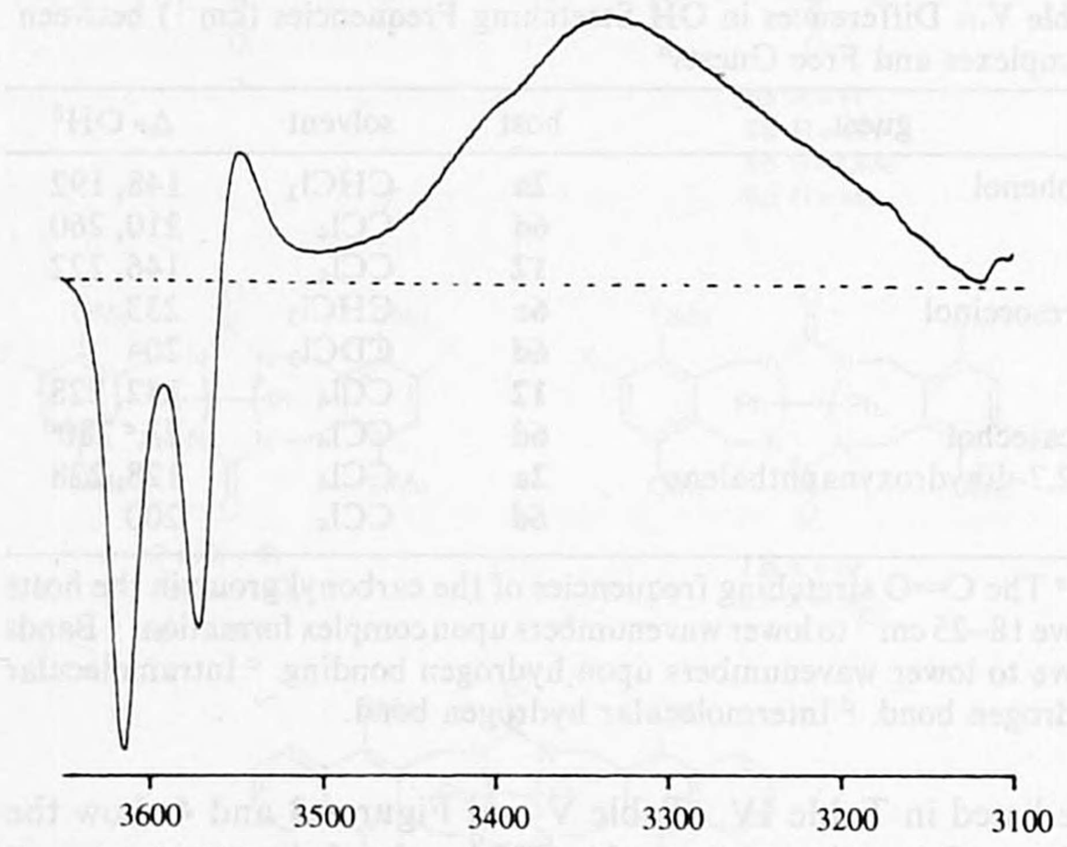
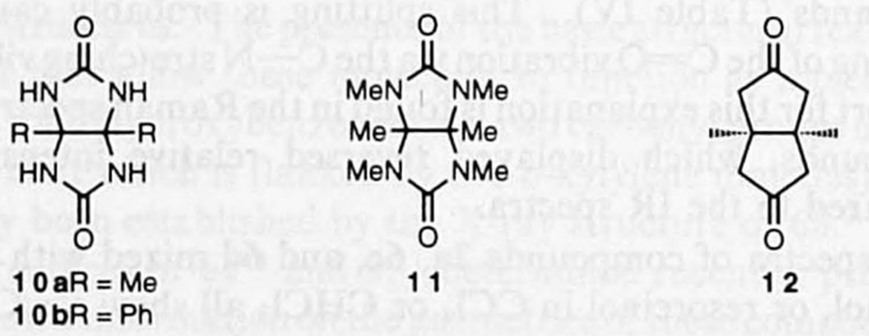


Figure 4. Difference spectrum of a mixture of catechol and **6d** in CCl_4.

phenol and **6d** shows two overlapping hydrogen-bonded OH bands at 3401 and 3351 cm^{-1} (Figure 3a). None of these bands are due to self-associated phenol,[16] as we checked separately. Both resorcinol and phenol show the same effect in the complex with diketone **12**. Very remarkably, the complex of **6d** with resorcinol



10a R = Me
10b R = Ph

11 **12**

shows a single symmetrical band in the hydrogen-bonded OH region (Figure 3b). It is known that phenols form two types of complexes with the carbonyl groups of ketones and related compounds.[17,18] In one type the OH group is in the direction of the n-electrons of the ketone, whereas in the other type it is directed toward the π-electrons (Figure 5). The band with the smaller

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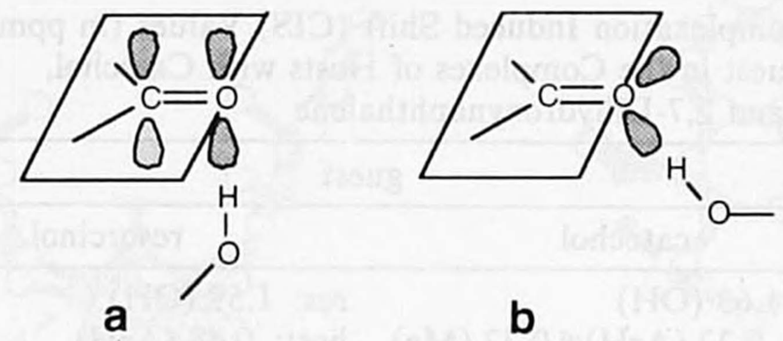

Figure 5. The two modes of hydrogen bonding with a carbonyl group: (a) with theπ-electrons of the carbonyl group; (b) with the n-electrons of the carbonyl group.

$\Delta\nu$ OH is assigned to the OH groups hydrogen bonded with the π-electrons. Phenol, which interacts with only one of the carbonyl groups of **6d** or **12**, has the possibility to form both kinds of complexes. Resorcinol, on the other hand, forms hydrogen bonds with both carbonyl groups. In the complex with **6d** it is confined to the cleft of the host. Therefore its OH groups favor interaction with the π-electrons of the carbonyl groups for geometric reasons. The value of $\Delta\nu$ OH in this complex (204 cm^{-1}) is similar to the smaller value of $\Delta\nu$ OH in the complex of phenol with **6d** (210 cm^{-1}). The infrared spectrum of the complex of 2,7-dihydroxynaphthalene with **6d** also shows only one band in the hydrogen bonded OH region, with a $\Delta\nu$ OH of 200 cm^{-1}, almost the same value as in the complex of resorcinol with this host. This value suggests that in the complex of **6d** with 2,7-dihydroxynaphthalene hydrogen bonds are also formed with the π-electrons of the carbonyl groups. In the complexes of phenol and 2,7-dihydroxynaphthalene with **2a**, more than one band is present in the OH stretching region, but in these complexes additional hydrogen bonds with the ether oxygen atoms complicate assignment of the bands.

Free catechol in CCl_4 solution has one of the OH groups intramolecularly hydrogen bonded to the other OH group. This gives rise to two OH stretching vibrations in the IR spectrum. We observed these vibrations at 3615 and 3570 cm^{-1} (literature values are 3611 and 3558 cm^{-1} [19]). Upon addition of **6d** to a solution of catechol, both bands decrease in intensity to almost the same degree (Figure 4), and new bands arise at 3547 and 3332 cm^{-1}. The band at 3547 cm^{-1} is probably due to the intramolecularly hydrogen-bonded OH group in the complex and the band at 3332 cm^{-1} due to the intermolecular hydrogen bond. Table V shows that $\Delta\nu$ OH of the intermolecular hydrogen bond is larger in the complex with catechol than in the complexes with resorcinol and phenol. A similar observation has been reported for 1:1 hydrogen-bonded complexes of catechol with Bu_2S, THF, and DMSO.[20] It is known that an OH group acting as an acceptor becomes more acidic. As a result a strengthening of the intermolecular hydrogen bond in the complex may occur.[21] A complex in which the intramolecular hydrogen bond in catechol has been disrupted in favor of a double intermolecular hydrogen bond with the carbonyl groups of the host cannot be excluded but seems energetically less likely.

B. NMR. Chemically Induced Shift Values. We have investigated the geometry of the complexes of resorcinol, catechol, and 2,7-dihydroxynaphthalene by comparing the experimentally determined shift values with values that can be calculated using Johnson and Bovey's quantitative ring current model.[22-24] To this end a computer program was developed that uses the positions of the protons and the centers of the aromatic rings in a host–

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(23) For a different approach based on quantum mechanical shift calculations, see: Haigh, C. W.; Mallion, R. B. *Org,. Magn. Reson.* **1972**, *4*, 203. Fukazawa, Y.; Ogata, K.; Usui, S. *J. Am. Chem. Soc.* **1988**, *110*, 8692.
(24) The Bovey–Johnson ring current model has been used before to explain NMR shifts in inclusion complexes; e.g. see: Odashima, K.; Itai, A.; Litaka, Y.; Arata, Y.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4373.

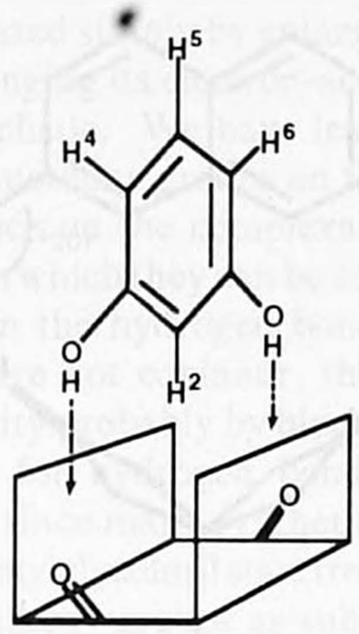

Figure 6. Mode of insertion of resorcinol in the cavity of **6c** as used for the ^{1}H NMR shift calculations.

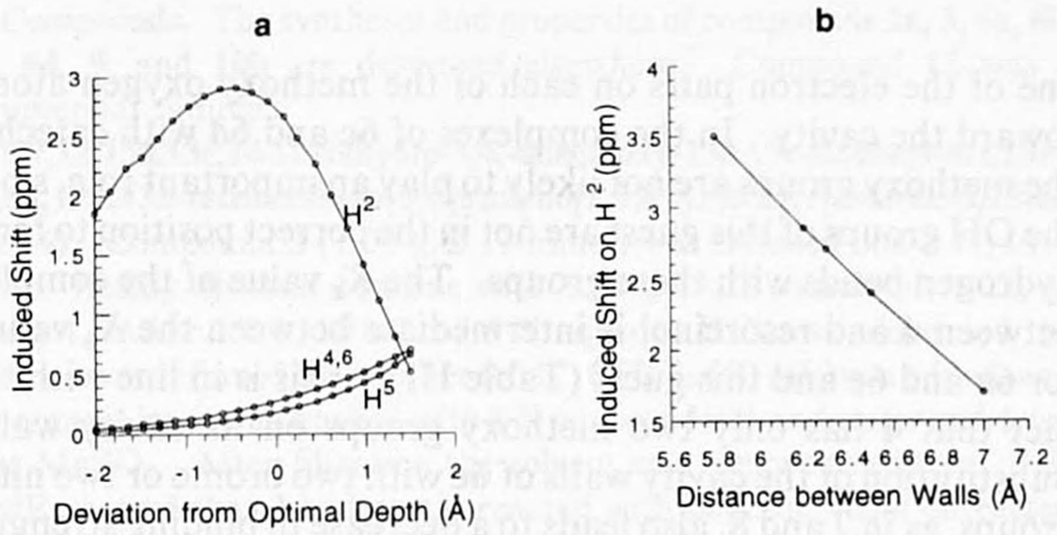

Figure 7. (a) Calculated CIS values of the protons of resorcinol as a function of the depth of insertion in the cleft of **6c** with a cavity-wall distance of 6.3 Å. (b) Calculated CIS values of proton H2 of resorcinol in the complex with **6c** as a function of the distance between the cavity walls.

guest complex to calculate the shielding effect of the aromatic rings on the protons.

The CIS values of the aromatic protons of resorcinol and of the cavity-wall protons of the receptors were calculated for various depths of insertion of the resorcinol molecule into the cleft of the receptor and for a number of cavity-wall distances. The resorcinol molecule was lowered into the cavity with its OH groups pointing toward the carbonyl groups (Figure 6) and was moved in a plane defined by the C_2 axis and the carbonyl oxygen atoms of the host. The CIS values are plotted as a function of the depth of insertion of the resorcinol molecule in Figure 7a and as a function of the distance between the walls in Figure 7b. If we assume that the optimal insertion depth is the one corresponding with an O–H···O hydrogen-bonding distance of 2.72 Å (the average distance of O–H···O hydrogen bonds in a number of crystal structures[25]), the measured CIS value of H2 (2.71 ppm) is best reproduced with a wall to wall distance of 6.3 Å, as opposed to a wall to wall distance of 6.67 Å in the crystal structure of **6c** (Figure 7b and Table I). The carbon atoms at the rim of the cavity of **6c**, which are the carbon atoms in closest contact with the resorcinol molecule (Figure 8), are 6.8 Å apart if the cavity-wall centers are separated by 6.3 Å. In a complex with this host geometry, the distance between the resorcinol C2 atom and each of the cavity walls is 3.4 Å. Thus, at this site, the cavity walls are in van der Waals contact with the resorcinol molecule.

For the host–guest complexes with catechol, less information is available than for the complexes with resorcinol because there are no proton signals in the host or the guest that shift strongly. Another complication is that all aromatic protons of free catechol have approximately the same shift. Calculations were performed in which the catechol molecule was lowered vertically into the host, with its OH groups pointing toward the carbonyl groups. The optimal insertion depth was considered to be the one with the OH groups at the hydrogen-bonding distance of the carbonyl groups. The calculated induced shift of the aromatic protons of catechol is 0.36 for H3,6 and 0.15 for H4,5, as compared to an

(25) Wallwork, C. S. *Acta Crystallogr.* **1962**, *15*, 758.

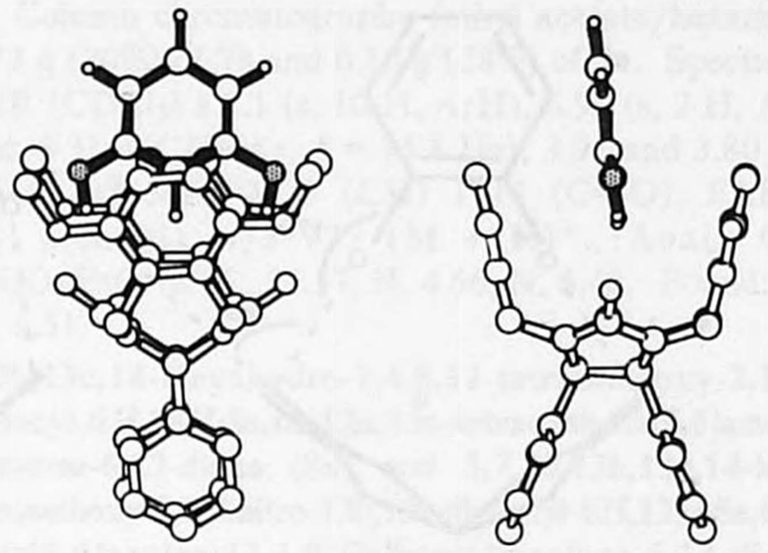

Figure 8. (a, left) Side view of the complex between resorcinol and **6c** based on NMR data. Hydrogen atoms of the host have been omitted for clarity. (b, right) Front view of the same complex. Methoxy groups and hydrogen atoms of the host have been omitted for clarity.

experimental CIS value of 0.25 ppm in the complex with **6d**. The calculated shift on the cavity-wall protons is 0.49 ppm whereas the experimentally observed value is 0.31 ppm in the complex with **6c** and 0.22 pm in the complex with **6d** (Table I). Consequently the calculations indicate that catechol is bound inside the cavities of hosts **1**, but because of the small CIS values no conclusions can be drawn as to the precise mode of complexation of this guest.

The CIS values of 2,7-dihydroxynaphthalene have been calculated in a host structure with a cavity-wall distance of 6.3 Å. Excellent agreement between calculated and experimental CIS values is obtained, when it is assumed that the guest is complexed symmetrically and simultaneously forms two hydrogen bonds with the carbonyl groups of the host. The calculated values are 1.53 ppm for H1,8, 0.18 ppm for H3,6, and 0.22 ppm for H4,5. The experimental values are 1.59, 0.16, and 0.24 ppm, respectively (Table I).

Factors Determining Complex Stability. A. Electronic and Geometric Features of the Guest. Table II shows that the binding strength of the host–guest complex is strongly influenced by the type of substituent on the guest. Electron-withdrawing substituents increase the acidity of the OH groups of the guest, causing the association constants to be higher. When bromo substituents are introduced in the aromatic nucleus, the K_a increases from 2600 M^{-1}, for the complex of **6c** with resorcinol, to 5600 M^{-1}, for the complex with dibromoresorcinol.

The three dihydroxy-substituted aromatic compounds catechol, resorcinol, and 2,7-dihydroxynaphthalene show a remarkable difference in K_a, viz. 60 M^{-1} for catechol, 2600 M^{-1} for resorcinol, and 7100 M^{-1} for 2,7-dihydroxynaphthalene. Apart from differences in π–π stacking interactions, which are difficult to quantify, the major cause for these different K_a values resides in the relative geometry of the phenolic OH groups of these guests. In catechol, the OH groups are 2.72 Å apart. One of these groups forms an intramolecular hydrogen bond with the ortho oxygen atom. This hydrogen bond has to be disrupted before two simultaneous hydrogen bonds with the carbonyl groups of the host can be formed. The evidence from IR experiments on the complex between **6d** and catechol is in favor of the preservation of the intramolecular hydrogen bond in this complex. If this indeed is the case, the complex is stabilized by only one hydrogen bond, and consequently the association constant is low. However, if there are two intermolecular hydrogen bonds in the complexes with catechol, the short distance between the two OH groups will force these hydrogen bonds to have an unfavorable geometry. Assuming that the hydrogen bonds are linear[26] and have an O···O distance of 2.7 Å, then the COH angle in the cathechol complexes must be 179°, instead of the normal 109° (Figure 9a). The disruption of the intramolecular hydrogen bond and the nonideal geometry of the hydrogen bonds will cause the K_a's of the cathechol

(26) Olovsson, I.; Jönsson, P.-G. In *The Hydrogen Bond*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North Holland Publishing Company: Amsterdam, New York, Oxford, 1976; Vol. II, Chapter 8, pp 393–456.

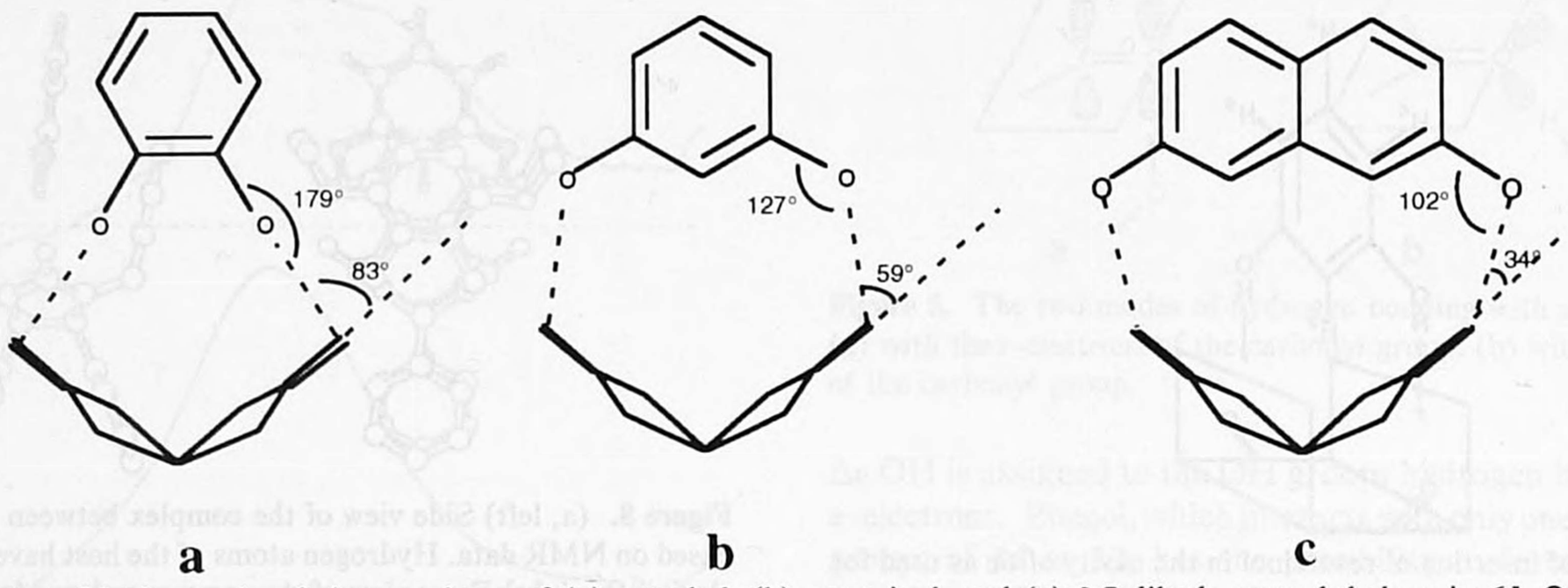

Figure 9. Geometry of hydrogen bonds in complexes of (a) catechol, (b) resorcinol, and (c) 2,7-dihydroxynaphthalene in **6d**. Only the glycoluril framework of **6d** has been drawn.

complexes to be lower than those of the other host–guest complexes (Tables II and III). For complexation of resorcinol, no intramolecular hydrogen bond needs to be disrupted and the distance between the OH groups is more favorable. The COH angle in symmetrically complexed resorcinol is 127°. This is closer to the optimal angle of 109° than that in the complex of catechol.

In a symmetrical complex with 2,7-dihydroxynaphthalene, the COH angle is 102°. In this complex the hydrogen bond is 34° out of the plane of the urea segments. The geometric requirements for hydrogen bonding with the π-electrons of a carbonyl group are not known, so it is not possible to analyze whether this angle with the plane of the urea segments is less favorable than that in the complexes with resorcinol or catechol, in which these values are 59° and 83°, respectively. The similarity of the value of $\Delta\nu$ OH in the complexes of **6d** with 2,7-dihydroxynaphthalene and resorcinol indicates that the strength of the hydrogen bonds is approximately the same. The higher K_a of the former complex must therefore be caused by more favorable $\pi-\pi$ stacking interactions.

B. Effects of Variations in the Host. One of the objectives of our study was to investigate the contribution of $\pi-\pi$ interactions to binding in our host–guest complexes. Table III shows some remarkable differences in K_a values of the complexes of resorcinol with different receptor molecules. The complex of resorcinol with **2a** can only be stabilized by hydrogen bonds. It has a relatively low association constant of 25 M^{-1}. Providing the receptor with two *p*-quinone walls as in **5** has little effect on the K_a. Apparently, there are no strong attractive interactions between these *p*-quinone moieties and a resorcinol molecule, which is remarkable. The complexes of resorcinol with receptors containing benzene rings as cavity walls, however, display much higher K_a values. Changing the cavity walls from quinone moieties in **5** to benzene rings in **6a** leads to an eightfold increase in K_a. A similar feature is observed for catechol (Table III). The increased binding of resorcinol and catechol in the hosts with aromatic cavity walls as compared to **5** is contrary to expectation. The observed offset geometry of the host–guest complexes however is in accordance with theory.[27] Calculations of the forces stabilizing the complexes of **6** with resorcinol are currently in progress.[28]

Going from **6a** to **6d** and **6c**, the K_a for resorcinol increases from 200 to 450 and 2600 M^{-1}, respectively. This trend is not repeated in the complexes of **6c** and **6d** with catechol, for which guest binding is somewhat weaker than that in **6a**. We believe that in both **6c** and **6d** the methoxy and methyl substituents strengthen the hydrogen bonds of resorcinol with the carbonyl groups by reducing the interaction of these groups with solvent molecules. Another possibility is that the oxygen atoms of the methoxy groups in **6c** are involved in hydrogen bonding. Methoxy groups in aromatic molecules have a preference for being in the plane of the aromatic ring.[29] In **6c** this conformation would direct one of the electron pairs on each of the methoxy oxygen atoms toward the cavity. In the complexes of **6c** and **6d** with catechol the methoxy groups are not likely to play an important role, since the OH groups of this guest are not in the correct position to form hydrogen bonds with these groups. The K_a value of the complex between **4** and resorcinol is intermediate between the K_a values for **6a** and **6c** and this guest (Table III). This is in line with the fact that **4** has only two methoxy groups on its cavity walls. Substitution of the cavity walls of **6c** with two bromo or two nitro groups, as in **7** and **8**, also leads to a decrease in binding strength. These substituents force two of the methoxy groups to rotate out of the plane of the cavity walls, causing them either to point inward, blocking the carbonyl groups completely, or to point outward, in which case the electron pairs of the oxygen atoms are less favorably oriented for hydrogen bonding with resorcinol.

Compound **9** is a host with dimethoxynaphthalene cavity walls. It shows quite different complexation behavior when compared to the other hosts. Although the OH proton signals of resorcinol shift upon titration with **9**, its aromatic proton signals are not influenced at all. These results indicate that hydrogen bonds are formed between host and guest but the guest is not bound inside the cavity of **9**. It is interesting to see in the X-ray structure of **9** that all four methoxy groups are pointing into the cleft. From an examination of CPK models, it is clear that if one of the methoxy groups is pointing into the cleft, the π-electrons of the carbonyl group on that side of the molecule will be blocked for hydrogen bonding with dihydroxybenzene. If the crystal structure of **9** reflects the conformational preference of the methoxy groups in solution, the low K_a of **9** with catechol and resorcinol (Table III) is caused by the complete blocking of both carbonyl groups for hydrogen bonding with a guest in the cavity. Another factor that may be responsible for the absence of binding is the different π-electron density at the point where **9** makes contact with the guest molecule.

Conclusions

The expectation that hosts of type **1** are good receptors for dihydroxybenzene derivatives has turned out to be correct. The guests are bound in the cavity of all hosts except **9**, as could be shown by comparison of calculated and experimental CIS values.

Although the carbonyl groups of the glycoluril moieties do not point into the cavity of the hosts, they nevertheless are quite efficient binding sites, as they allow the formation of hydrogen bonds via their π-electron system.

The stabilizing effect of $\pi-\pi$ interactions was established by comparing the binding properties of the different host compounds and was confirmed by the results of the CIS calculations on the complexes with resorcinol. These calculations show that, upon binding, the cavity walls move closer together to within van der Waals distance of the guest. Our initial assumption that binding

(27) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.
(28) Hunter, C. A.; Sijbesma, R. P.; Nolte, R. J. M. Unpublished results.
(29) Spellmeyer, D. C.; Grootenhuis, P. D. J.; Miller, M. D.; Kuyper, L.F.; Kollman, P. A. *J. Phys. Chem.* **1990**, *94*, 4483 and references cited therein.

strength can be increased simply by enlarging the surface of the cavity walls or by changing its electron-accepting properties has proven to be too simplistic. We have learned that the conformational features of methoxy groups on the cavity walls have a quintessential influence on the complexation properties of the host. In compounds in which they can be coplanar with the cavity walls, they strengthen the hydrogen bonds. In compounds in which these groups are not coplanar, they completely inhibit binding inside the cavity probably by blocking the π-electrons of the carbonyl groups for hydrogen bonding. This feature is especially important, since many synthetic routes to derivatives of hosts based on diphenylglycoluril start from **6c** and consequently contain methoxy or alkoxy groups as substituents.

Experimental Section

Compounds. The syntheses and properties of compounds **2a, 3, 6a, 6b, 6c, 6d, 9,** and **10b** are described elsewhere.[7] Compound **12** was a commercial sample.

5,7,12,13b,13c,14-Hexahydro-1,4,-dimethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (4). Compound **3** (1.03 g, 2.11 mmol) was refluxed under N_2 in10 mL of freshly distilled benzene with 1.23 g (9.25 mmol) of $AlCl_3$ as catalyst. After 1.5 h, 10 mL of 6 N aqueous HCl was added and the mixture was refluxed for another 0.5 h. $CHCl_3$ (50 mL)was added, and the organic layer was washed with 6 N aqueous HCl, and water and dried over $MgSO_4$. After filtration the solvent was removed in vacuo. ^{1}H-NMR showed that **3** had partly reacted with benzene. The unreacted chloromethyl groups had formed cyclic oxapropyl groups, giving a mixture of compounds, which could not be separated by column chromatography. A sample (0.44 g) of this mixture was dissolved in 1 mL of acetic anhydride and 1.5 mL of trifluoroacetic acid. *p*-Dimethoxybenzene (0.33 g, 2.39 mmol) was added, and the mixture was heated at 90 °C for 20 min. Hereafter 4 mL of methanol was added to decompose the acetic anhydride, followed by 25 mL of $CHCl_3$. The solution was washed twice with 1 N aqueous NaOH, and the solvent was removed in vacuo. By careful chromatography ($CHCl_3$/methanol, 199:1 v/v), 0.200 g (15% based on *p*-dimethoxybenzene) of **4** could be separated from the other two products, **6a** and **6c**. ^{1}H NMR ($CDCl_3$) δ 7.1 (m, 12 H, ArH), 6.66 (s, 2 H, ArH), 5.60, 4.85, 4.22 and 3.73 (4d, 8 H, NC*H*HAr, J = 15.8 Hz), 3.75 (s, 6 H, OCH_3); FAB-MS (*m*-nitrobenzyl alcohol) m/z 559 $(M + H)^+$. Anal. Calcd for $C_{34}H_{30}N_4O_4 \cdot 0.5CH_2Cl_2$: C, 68.94; H, 5.20; N, 9.32. Found: C, 68.49; H, 5.05; N, 9.1.

5,7,12,13b,13c,14-Hexahydro-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene. (5). Compound **6b** (0.37 g, 0.66 mmol) was dissolved in 10 mL of DMSO. Cu_2Cl_2 (50 mg) and 0.5 mL of pyridine were added, and air was bubbled through the mixture for 2 h. The red solution was poured into 100 mL of 1 N aqueous HCl, and the resulting suspension was extracted with 50 mL of $CHCl_3$. The $CHCl_3$ layer was washed twice with 5% aqueous NH_3, dried, and concentrated in vacuo to yield 0.275 g (75%) of **5**. A sample was recrystallized from acetic acid for analysis. ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 10 H, ArH), 6.80 (s, 4 H, CH), 5.53 and 3.71 (2d, 8 H, NC*H*HC, J = 15.8 Hz); FAB-MS (*m*-nitrobenzyl alcohol) m/z 559 $(M + H)^+$. Anal. Calcd for $C_{32}H_{22}N_4O_6 \cdot 0.65CH_3CO_2H$: C, 66.93; H, 4.15; N, 9.38. Found: C, 67.0; H, 3.92; N, 9.44.

2,9-Dibromo-5,7,12,13b,13c,14-hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (7a) and 2,10-Dibromo-5,7,12,13b,13c,14-hexahydro-1,4,8,11-tetramethoxy-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (7b). Compound **6c** (0.31 g, 0.2 mmol), $AlCl_3$ (35 mg),and Br_2 (0.32 g) were stirred for 24 h in 10 mL of CH_2Cl_2. The reaction mixture was filtered, and the filtrate was washed twice with aqueous $NaHSO_3$ and evaporated to dryness. Column chromatography (ethyl acetate/hexane, 1:2 v/v) yielded 0.073 g (20%) of **7b** and 0.10 g (28%) of **7a.** Spectral data for **7b**: ^{1}H NMR ($CDCl_3$) δ 7.1 (s, 10 H, ArH), 6.95 (s, 2 H, ArH), 5.93 and 3.68 (2d, 8 H, NC*H*HAr, J = 15.8 Hz), 3.95 and 3.80 (2s, 12 H, OCH_3); IR (KBr) 3062–2828 (CH) 1718 (C=O); FAB-MS (*m*-nitrobenzyl alcohol) m/z 777 $(M + H)^+$. Anal. Calcd for $C_{36}H_{32}Br_2N_4O_6 \cdot EtOAc$: C, 55.57; H, 4.66; N, 6.48. Found: C, 55.24; H, 4.54; N, 6.51.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetramethoxy-2,10-dinitro-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (8a) and 5,7,12,13b,13c,14-hexahydro-1,4,8,11-tetramethoxy-2,9-dinitro-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,13a-tetraazabenz[5,6]azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (8b). Compound **6c** (0.65 g, 1.05 mmol) was stirred in a solution of 0.5 mL of 65% HNO_3 in 3 mL of acetic anhydride. After 16 h, 15 mL of methanol was added to destroy the acetic anhydride. Thereafter 25 mL of $CHCl_3$ was added, and the solution was washed twice with 1 N aqueous NaOH. The solvent was removed in vacuo. After purification by column chromatography ($CHCl_3$/CH_3OH, 99:1 v/v), 0.446 g (60%) of **8** (mixture of diastereomers) was obtained. ^{1}H NMR ($CDCl_3$) δ 7.15 (m, 12 H, ArH), 5.64, 5.54, 3.82 and 3.73 (4d, 8 H, NC*H*HAr, J = 15.8 Hz), 3.99 and 3.86 (s, 12 H, OMe); FAB-MS (*m*-nitrobenzyl alcohol) m/z 709 $(M + H)^+$. Anal. Calcd for $C_{36}H_{32}N_6O_{10} \cdot 0.5CH_2Cl_2$: C, 58.36; H, 4.43; N, 11.19. Found: C, 58.17; H, 4.30; N, 10.91.

Tetrahydro-3a,6a-dimethylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (10a). This compound was prepared from urea and butanedione according to a literature procedure.[30]

1,3,4,6-Tetramethyltetrahydro-3a,6a-dimethylimidazo[4,5-*d*]imidazole- 2,5(1*H*,3*H*)-dione (11). This compound was prepared by methylation of **10a** with dimethyl sulfate in DMSO. IR (hexane) 1735, 1723 (C=O) (lit.[31] 1735, 1715); ^{1}H-NMR ($CDCl_3$) δ 2.90 (s, 12 H, NCH_3), 1.48 (s, 6 H, CH_3).

Bromination of Resorcinol. Resorcinol (1.1 g, 10 mmol) was suspended in 30 mL of $CHCl_3$, and 3.2 g of Br_2 (20 mmol) in 10 mL of $CHCl_3$ was added over 1 h. The solvent was evaporated, and the mixture was purified by column chromatography ($CHCl_3$/CH_3OH, 97:3 v/v). Two products were isolated: 0.25 g (9%) of **2,4-dibromo-1,3-benzenediol (a)** and 1.93 g (72%) of **4,6-dibromo-1,3-benzenediol (b): (a)** ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1 H, H5), 6.57 (d, 1 H, H6), 5.69 (br, s, 2 H, OH); **(b)** ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H, H5), 6.74 (s, 1 H, H2), 5.48 (br, s, 2 H, OH). A sample of **b** was purified further by sublimation for use in the titration experiments.

Binding Experiments. The ^{1}H-NMR shift titrations, the ^{1}H-NMR competition experiments, and the liquid–liquid extractions were performed as was described elsewhere.[14]

Infrared Experiments. FT-IR spectra were recorded on a Perkin Elmer 1800 FT-IR spectrophotometer with a DTGS detector; resolution was 2.0 or 4.0 cm^{-1}; the apodization was weak. For each spectrum 50–400 scans were taken. The interferometer was flushed with nitrogen, and the sample compartment was dried with molecular sieves. The CCl_4 and $CHCl_3$ solutions were measured in 2-mm CaF_2 and/or 10-mm Infrasil cells. KBr pellets (1 mg of sample per 300 mg of KBr) were pressed at 60 bar/mm^2. The accuracy of the wavenumbers is 1 cm^{-1} for sharp peaks and 3 cm^{-1} for broader bands. The concentration of the dihydroxybenzenes and the hosts was $<10^{-2}$ M. Difference spectra were measured versus reference host solutions, where the positive absorbance values indicate the formation of a complex and the negative signals are indicative for the amount of host converted into the complexed form.

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(31) Suvurova, L. I.; Eres'ko, V. A.; Epishina, L. V.; Lebedev, O. V.; Khmel'nitskii, L. I.; Novikov, S. S.; Povstyanoi, M. V.; Krylov, V. D.; Korotkova, G. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 1306; *Chem. Abstr.* **1979**, *91*, 140829f.