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dissolved in 20 mL of THF is slowly added within 1 h to a well-stirred suspension of SmCp2 (10 mmol) in THF (150 mL) at -20 °C. A brown suspension is obtained. A solution of 4.16 mmol of aldehyde in 5 mL of THF is quickly added. The reaction mixture turns immediately yellow. After 2 h, the solution is stirred for 20 min. A suspension of SmCp2 (10 mmol) in THF (150 mL) at -20 °C. A brown suspension is obtained. A solution of 4.16 mmol of aldehyde in 5 mL of THF is quickly added. The reaction mixture turns immediately yellow. After 2 h, the solution is stirred for 20 min.

Note Added in Proof: We recently found that benzoyl chloride gives 3 mainly when quenching is performed in anaerobic conditions. Benzil 2 has been therefore produced by very fast air oxidation of precursor ene diol prior to tautomerization to 3 (for a similar observation, see: Duhamel, L.; et al. Tetrahedron Lett. 1983, 24, 4209).
Dihydroxybenzene Binding in Synthetic Molecular Clefts

Table I. Association Constants, Calculated Saturation Shifts of the Probe Signals in the Receptor \( [\Delta \sigma] \), and Free Energies of Complexation for Complexes of Receptor 1a with DHB’s in CDCl\(_3\) at 298 ± 2 K

<table>
<thead>
<tr>
<th>entry</th>
<th>DHB</th>
<th>( K_a \times 10^n )</th>
<th>( \Delta \sigma_{ppm} )</th>
<th>( -\Delta G^\circ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAT</td>
<td>7.0</td>
<td>0.50</td>
<td>10.5 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>4,5-Br2-CAT</td>
<td>12.3</td>
<td>0.34</td>
<td>17.6 ± 0.2</td>
</tr>
<tr>
<td>3</td>
<td>RES</td>
<td>29</td>
<td>0.51</td>
<td>19.7 ± 0.1</td>
</tr>
<tr>
<td>4</td>
<td>HQ</td>
<td>6.5</td>
<td>0.64</td>
<td>16.0 ± 0.2</td>
</tr>
<tr>
<td>5</td>
<td>2-Cl-HQ</td>
<td>15.6</td>
<td>0.48</td>
<td>18.0 ± 0.2</td>
</tr>
<tr>
<td>6</td>
<td>2-Br-HQ</td>
<td>18</td>
<td>0.48</td>
<td>18.5 ± 0.1</td>
</tr>
<tr>
<td>7</td>
<td>2,3-Cl2-HQ</td>
<td>7.2b</td>
<td>0.56</td>
<td>16.3 ± 0.2</td>
</tr>
<tr>
<td>8</td>
<td>2,5-Cl2-HQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>2,3-Br2-HQ</td>
<td>14</td>
<td>0.51</td>
<td>17.9 ± 0.1</td>
</tr>
<tr>
<td>9</td>
<td>2,5-Br2-HQ</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2,3-CN2-HQ</td>
<td>3000d</td>
<td>0.47</td>
<td>31.2 ± 1.0</td>
</tr>
</tbody>
</table>

*Estimated error in \( K_a \), 4%, unless otherwise indicated. 
*Induced shifts too low to determine \( K_a \). 
*This value was determined by a solid-liquid (CDCl\(_3\)) extraction experiment (see Experimental Section), estimated error in \( K_a \), 50%.

Results and Discussion

Complexation of various DHB’s by receptors 1a and 1b was investigated with \(^1H\) NMR spectroscopy in CDCl\(_3\). Upon titrating the receptor with a DHB, the signals of the cavity wall protons shift upward. Titrating a DHB with one of the receptors leads to an upward shift of the DHB aromatic proton signals, whereas the signals of the OH protons shift downward. These shifts indicate that the guest molecules are bound inside the cavities of 1a and 1b, with the OH groups forming hydrogen bonds with the receptor. Downfield shifts and a broadening of the signals of the \( \text{OH} \) protons in the bridges of the receptor suggest that the nitrogen atoms are involved in hydrogen bonding, although hydrogen bonding with the carbonyl groups cannot be excluded, in particular in the case of complexation of resorcinol. Association constants \( (K_a) \) and saturation shift values of the host signals were calculated with the aid of a computer program. Excellent fits were obtained assuming that only 1:1 complexation takes place. Binding constants for 1a with the three isomeric DHB’s (Table I, entries 1, 3, and 4) decrease in the order resorcinol > dihydroquinone > catechol. The low \( K_a \) of catechol is probably due to the presence of an intramolecular hydrogen bond in this molecule. In order to form two hydrogen bonds with the receptor, this intramolecular hydrogen bond has to be broken. Consequently, the gain in free energy upon complexation of catechol in 1a is much lower than upon complexation of the other two DHB’s. The \( \Delta H^\circ \) and \( \Delta S^\circ \) values for the formation of the complex of 1a with catechol were determined by evaluating the binding constants at four different temperatures. These values are \( \Delta H^\circ = -22.0 \pm 0.1 \text{ kJ} \text{ mol}^{-1} \) and \( \Delta S^\circ = -36 \pm 3 \text{ J} \text{ mol}^{-1} \text{ K}^{-1} \), suggesting that the complexation is enthalpy driven.

Electron-withdrawing substituents in the guest have a positive effect on the binding. This is apparent when the binding constants of 4,5-dibromocatechol and of 2,3-dicyanodihydroquinone are compared with the binding constants of the parent DHB’s (Table I, entries 1, 2, 4 and 11). The OH groups of the DHB’s with electron-withdrawing substituents can form stronger hydrogen bonds than those of the unsubstituted DHB’s. In case of the complex of 1a and 2,3-dicyanodihydroquinone this leads to an association constant of \( 3 \times 10^6 \text{ M}^{-1} \). This is one of the highest binding constants reported for a complex between a synthetic receptor and a neutral guest in an organic solvent.

It is more difficult to explain the differences in the \( K_a \) values of the halogen-substituted dihydroquinones because several factors influence the binding of these guests. Introduction of a halogen substituent increases the hydrogen-bond acidity of the OH groups, but at the same time OH groups ortho to a halogen substituent become partly intramolecularly hydrogen bonded. If only one halogen substituent is present, the OH group meta to this halogen forms a stronger hydrogen bond with the receptor than the OH group of dihydroquinone itself. The hydrogen bond of the ortho OH group with the receptor will be about as strong as in dihydroquinone, due to the opposing effects of electron withdrawal and intramolecular hydrogen bonding. The net effect of the introduction of one halogen substituent, therefore, is an increase of the association constant. Upon introducing a second halogen atom, both OH groups become intramolecularly hydrogen bonded.

For the 2,3-dihalogeno-substituted dihydroquinones, the association constants fall between those of the corresponding monosubstituted dihydroquinones and of dihydroquinone itself. If there are substituents on each side of the dihydroquinone ring (as in 2,5-dichlorodihydroquinone), binding is sterically inhibited; the substituents are too large to allow the guest to enter the cavity deeply enough to form two hydrogen bonds with the receptor. With these guests, complexation-induced shifts fall below the limit of detection, and the binding constants for complexation in the cavity are very small. Compound 1a thus is able to dis-


criminate strongly between isomeric DHB's (Table I, entries 7–10).

In Table II the complexation properties of the four receptors la–d for catechol, resorcinol, and dihydroquinone are compared. Receptor 1b binds dihydroquinone much more strongly than 1a, while binding of resorcinol and catechol is weaker. This altered preference is probably caused by the presence of intramolecular hydrogen bonds between the NH groups and the urea carbonyl groups in receptor 1b.10 CPK models suggest that these hydrogen bonds keep the nitrogen atoms at a fixed position, with their free electron pairs pointing into the cavity (Figure 1). The distance between these electron pairs is ideally suited for making two hydrogen bonds with dihydroquinone. The stronger binding of dihydroquinone by 1b than by 1a is an example of Cram's "principle of preorganisation,"11 which states that hosts having low conformational freedom lose less entropy upon complexation of a guest, and hence bind stronger and more selectively.

Receptors 1c and 1d were designed to achieve selective binding of catechol and catechol derivatives such as dopamine. In 1c and 1d the nitrogen atoms in the bridges are at the appropriate distance to form two hydrogen bonds with the catechol OH groups. Because the DHB's cannot enter the cavities of receptors 1a, 1b, or 1c, the association constants in diethyl ether are low. Therefore, the binding constants of these receptors were determined by means of competition experiments with host 1a. For reasons that are not yet clear to us, host 1c binds all investigated DHB's very weakly. Receptor 1d, however, is a much better binder of catechol than hosts 1a and 1b. When going from 1b to 1d the association constant increases by a factor of 12.5. For resorcinol this increase is only by a factor of 1.6, whereas for dihydroquinone even a 10-fold decrease in binding constant is observed. With 4,5-dibromocatechol, 1d forms a 1:1 complex that precipitates from solution.

In summary, our experiments indicate that receptor molecules 1 display strong binding properties for dihydroxybenzenes. Furthermore, we have shown that it is possible to tune the binding preference of these receptors by altering the geometry of the binding sites.

**Experimental Section**

Compounds 1a–d were synthesized according to procedures described previously by us.4 The physical properties of 1a and 1b have been published.4 Those of 1c and 1d are as follows:

1,6,3,4-Bis[3,3',6,6'-bis(4-acetylcatechyl)-1,7-dioxahexamethylene]-1,2-xylylene tetrabromo-3,6a,6a-diphenylimidazol[4,5-d]imidazol-2,5(1H,3H)-dione (1c).

This compound was purified by column chromatography (silica gel, eluent CHCl3/MeOH): yield 73%; mp >200 °C dec; IR (KBr) 3080–2980 (ArH), 1705 (C==O), 1150–1050 (COC); 1H NMR (CDCl3) δ 7.40 (m, 10 H, ArH), 7.11 (m, 10 H, ArH), 6.84 (s, 4 H, ArH), 5.45 and 3.65 (2 d, 8 H, NCH2Ar, J = 15.4 Hz), 3.70 (m, 12 H, OCH2CH2, NCH2Ar), 3.45 and 3.02 (m, 8 H, NCH2CH3); FAB-MS (m/z 881 (M + H)+). Anal. Calcd for C52H45N10O6H2O: C, 72.14; H, 6.05; N, 9.35. Found: C, 72.62; H, 5.95; N, 9.34.

1,6,3,4-Bis[3,3',6,6'-bis(4-acetyl-1,7-dioxahexamethylene)-1,2-xylylene] tetrabromo-3,6a,6a-diphenylimidazol[4,5-d]imidazol-2,5(1H,3H)-dione (1d).

This compound was purified by column chromatography (silica gel, eluent CHCl3/BuOH/Et3N): yield 95%; mp >200 °C dec; IR (KBr) 3310 (NH), 1705 (C==O), 1150–1050 (COC); 1H NMR (CDCl3) δ 7.10–7.17 (m, 10 H, ArH), 6.62 (s, 4 H, ArH), 5.50 and 3.65 (2 d, 8 H, NCH2Ar, J = 15.4 Hz), 4.31 and 4.23 (2 m, 2 H, NCH2Ar), 3.45 and 3.02 (2 m, 2 H, NCH2CH3), 3.05 and 2.93 (2 m, 8 H, NCH2CH3). 2.40 (s, 2 H, NH); FAB-MS (m/z 701 (M + H)+).

Dihydroxybenzenes. Dihydroquinone, catechol, resorcinol, and 2,3-dicyanodihydroquinone were commercial products. Brominated dihydroquinones were reaction products of dihydroquinone with bromine in CCl4 and separation of the products by careful column chromatography with EtoAc/n-hexane as eluent. Chlorinated dihydroquinones were obtained by reaction of dihydroquinones with SOCl2 in diethyl ether.14 The products were separated by column chromatography (CHCl3/MeOH). 4,5-Dibromocatechol was prepared by bromination of catechol with bromine in CHCl3. All dihydroxybenzenes were further purified by repeated recrystallization or sublimation at reduced pressure. Purity was checked by comparison of the melting points with literature values.15,16

1H NMR Titrations. The protocol of Granot was followed as compound solubility and spectrometer sensitivity allowed.8 Each titration was carried out with 10 different samples. These samples were prepared from stock solutions of the receptor and the substrate in CDCl3. The concentration of the component of which the 1H NMR signal was monitored was roughly kept constant. The amount of the other component was varied from 0 to 8 equiv. CDCl3 was added to adjust the total volume of each sample to approximately 0.6 mL. Errors in association constants were evaluated from the difference between Ka values in independent titrations and the average Ka values, as well as from the confidence limits on single determinations found with the curve-fitting routine.12

Association constants of 1c and 1d were determined from competition experiments with 1a. To a solution of 1a and a DHB one of these hosts was added and the shifts of the signals of 1a were monitored.

Due to the insolubility of 2,3-dicyanodihydroquinone in CDCl3, the association constant for the complex between 1a and 1d was determined by a solid-liquid (CDCl3) extraction experiment conforming to the literature.13 In order to estimate the reliability of this procedure, a similar solid-liquid extraction was also carried out with dihydroquinone. This experiment gave a Ka of 1.2 × 109 M−1 which is in the same range as the value found with the titration method (6.5 × 109 M−1, see Table I). As a further check the Ka values of dihydroquinone and 2,3-dicyanodihydroquinone were also determined by 1H NMR titrations in a solvent mixture in which both guests are soluble, viz. CDCl3/acetonitrile, 4:1, v/v.

These values are 12 M−1 and 4.2 × 109 M−1, respectively. Assuming the ratio of association constants to be independent of solvent, one calculates a value of 2.3 × 109 M−1 for the Ka of 1a with dicyanodihydroquinone in CDCl3. This value is very similar to the one obtained by the solid liquid extraction method (Ka = 3 × 109, Table I).