The Journal of
Organic
Chemistry

VOLUME 56, NUMBER 10 MAY 10, 1991

Communications

Binding of Dihydroxybenzenes in a Synthetic Molecular Clip. Effect of Hydrogen Bonding and π-Stacking

Rint P. Sijbesma, Arno P. M. Kentgens,† and Roeland J. M. Nolte*

Department of Organic Chemistry and SON/NWO HF-NMR Facility, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

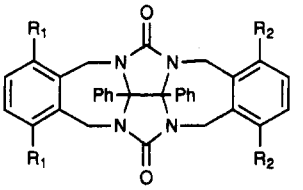
Received January 8, 1991 (Revised Manuscript Received March 11, 1991)

Summary: A synthetic host, which can easily be assembled starting from urea and benzil, selectively binds resorcinol by hydrogen bonding and π-stacking.

Exploring the potentialities of π-π interactions and hydrogen bonding 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,[4a,b] and others[5a,b] have synthesized host molecules that are capable of binding neutral aromatic guests between two aromatic surfaces with or without the aid of hydrogen bonding. We describe here a class of receptors (1) that bind dihydroxybenzenes by means of hydrogen bonds as well as π-π interactions.

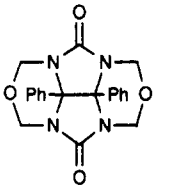
Compounds 1 were assembled from the cheap starting compounds urea and benzil by the following sequence of reactions: (i) condensation in the presence of acid to yield diphenylglycoluril (89%),[6] (ii) reaction of the latter compound with formaldehyde to give 2 (75%), (iii) acetylation with acetic anhydride and subsequent conversion of the tetraacetate into the tetrachloride 3 with thionylchloride (86%), and finally (iv) $SnCl_4$-catalyzed reaction of 3 with an appropriately substituted benzene (1a, 99%; 1b, 36%; 1c, 95%).[7]

Receptors 1 (Figure 1) contain a cleft that is defined by the central diphenylglycoluril unit and two *o*-xylylene walls. X-ray as well as molecular modeling studies show for 1c a minimum energy conformation in which these walls are at a relative angle of 27°.[8] The distance between the centers of the walls is 5.8 Å. These features enable the receptor to stabilise a complex with an aromatic molecule

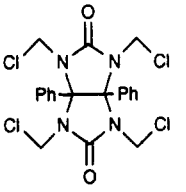


1

a R_1,R_2 = H
b R_1 = H, R_2 = OMe
c R_1,R_2 = OMe



2



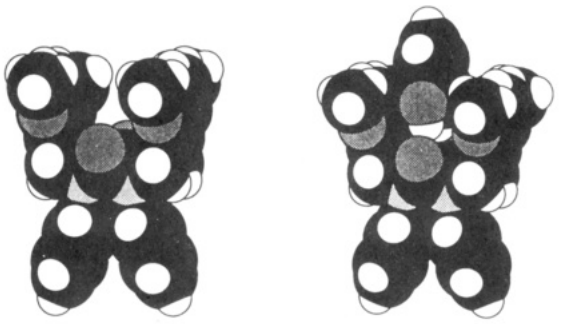
3

by π-π interactions. The carbonyl groups of the diphenylglycoluril unit are hydrogen bond acceptors: in-

†SON/NWO HF-NMR Facility.

(1) Rebek, R., Jr. *Angew. Chem.* **1990**, *102*, 261–272.
(2) Goswami, S.; Hamilton, A. D.; van Engen, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 3425–3426.
(3) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054–8055. Zimmerman, S. C.; van Zyl, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 7894–7896.
(4) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120–7121.
(5) (a) Harmata, M.; Barnes, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 5655–5657. (b) Diederich, F.; Ferguson, S. B. *Angew. Chem.* **1986**, *98*, 1127–1129.
(6) Butler, A. R.; Leitch, E. *J. Chem. Soc., Perkin Trans. 2* **1980**, 103–109.

0022-3263/91/1956-3199$02.50/0



a b

Figure 1. (a) Modeled structure of **1c**, based on an X-ray structure.[8] (b) Proposed structure of the complex of **1c** with resorcinol, based on Figure 1a and ^{1}H NMR data of the complex.

Table I. Association Constants (M^{-1})[a] of Compounds 1a–c and 2 with Resorcinol (Res) and Catechol (Cat) in $CDCl_3$ at 298 ± 2 K

	guest	
host	Res	Cat
1a	200 (20)	80 (6)
1b	580 (80)	40 (12)
1c	2600 (400)	60 (10)
2	25 (10)	14 (5)

[a] Standard deviations in parentheses.

frared measurements on mixtures of **1** and resorcinol in CCl_4 or $CHCl_3$ show that these groups are involved in hydrogen bonding with the guest.[9]

Upon addition of **1** to a solution of a dihydroxybenzene in $CDCl_3$, the ^{1}H NMR signals of the cavity wall protons of the host and the aromatic protons of the guest shift upfield, whereas the signals of the hydroxylic protons of the guest shift downfield. Fitting of the binding curves[10] obtained in titrations afforded the binding constants of **1a–c** and **2** with the guests shown in Table I. In a titration with hydroquinone, which cannot form two hydrogen bonds with one molecule of **1**, very small shifts were observed in the host as well as in the guest. Thus, this guest is not bound in the cavity of **1**. K_a's for catechol in hosts **1a–c** are in the range of 40–80 M^{-1}. These binding constants are higher than the K_a of this guest in **2** by a factor of roughly 5, showing the effect of π-π stacking with the cavity walls. The K_a's of the complexes of the hosts with catechol are generally lower than the K_a's of the complexes with resorcinol. This is, among other reasons, caused by the presence of an intramolecular hydrogen bond in catechol that must be disrupted in order to form two hydrogen bonds with the host. The K_a's of the hosts with resorcinol also show that hydrogen bonding as well as π-π interactions play a role in the binding of this guest in **1a–c**. Compound **2**, which can form two hydrogen bonds with resorcinol, but has no capability of stabilizing the complex by π-π interactions, binds resorcinol with a K_a of only 25 M^{-1}. For compound **1a** the binding constant has increased to 200 M^{-1}, while for **1c**, the K_a is as high as 2600 M^{-1}. The complex between **1b** and resorcinol has an intermediate K_a of 580 M^{-1}. The origin of the higher K_a values observed for **1b** and **1c** is not clear yet, but we presume that the ether oxygen atoms in the latter host molecules are involved in hydrogen bonding with the guest, or that they strengthen the hydrogen bonds of the guest with the carbonyl groups of the host by reducing the interaction of these groups with solvent molecules. To ascertain that resorcinol is indeed bound in the cleft of the receptor, we compared the experimentally determined induced ^{1}H

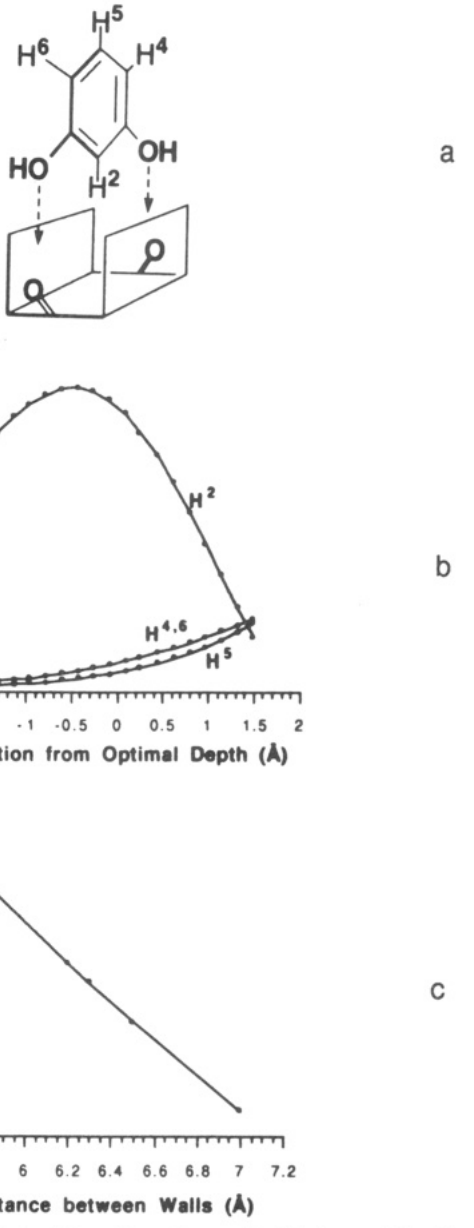


Figure 2. (a) Mode of insertion of resorcinol in **1c** used for the ^{1}H NMR shift calculations. (b) Calculated induced ^{1}H NMR shifts of the protons of resorcinol as a function of the depth of insertion in the cleft of **1c**. At the optimal depth of insertion the distance between the carbonyl oxygen atoms of **1c** and the phenolic oxygen atoms of resorcinol is 2.72 Å. (c) Calculated induced ^{1}H NMR shifts of proton H^2 of resorcinol in the complex with **1c** as a function of the distance between the centers of the *o*-xylylene walls.

(7) Structures of all new compounds were fully supported by spectral and analytical data. Details will be published in a full paper. Compound **1b** was synthesized in two steps from **3** by reaction with benzene and subsequent reaction with 1,4-dimethoxybenzene.

(8) (a) Molecular mechanics: Allingers Molecular Mechanics program MM2, cf.: Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *13*, 395. The crystal structure of the analogue of **1c** with OH groups instead of OMe groups was used to generate the starting geometry for calculations: Smeets, J. W. H.; Sijbesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928. (b) The crystal structure of **1c** has recently been elucidated: Beurskens, P. T.; Beurskens, G.; Sijbesma, R. P.; Nolte, R. J. M., to be published.

(9) For example: $\Delta\nu$(C═O) = −20 cm^{-1}; $\Delta\nu$(O—H) = −233 cm^{-1} for the formation of the complex between **1c** and resorcinol in $CHCl_3$.

(10) (a) Granot, J. *J. Magn. Reson.* **1983**, *55*, 216–224. (b) de Boer, J. A. A.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J.; de Jong, F. *J. Am. Chem. Soc.* **1982**, *104*, 4073–4076.

NMR shifts for resorcinol in the complex with 1c ($\Delta\delta$ = 2.7 ppm for H-2, $\Delta\delta$ = 0.42 ppm for H-4 and H-6, and $\Delta\delta$ = 0.30 ppm for H-5) with values that can be calculated for any complex geometry with the model of Johnson and Bovey.[11] If the resorcinol molecule is lowered vertically into the cavity along the plane through the carbonyl groups, with the OH groups pointing toward the carbonyl oxygen atoms (Figure 2a), induced shifts on the resorcinol protons can be plotted as a function of the depth of insertion into the cleft. If the carbonyl oxygen and the phenolic oxygen are at hydrogen bonding distance (≈2.72 Å),[12] the calculated induced shifts on H-4,6 and H-5 agree quite well with the measured shifts. The calculated shift of H-2, however, is significantly larger than the experimental value. In the complex this proton is situated above the centers of the cavity walls, and therefore its shift is very sensitive to small changes in complex geometry. When the structure of 1c is modeled with the distance between the centers of the *o*-xylylene walls of the cavity constrained to a larger value, viz 6.3 Å, and the resultant structure is used in a calculation of induced shifts, the calculated and experimentally derived shifts of H-2 are in much better agreement (Figure 2, parts b and c). These results allow us to conclude that binding of resorcinol in the cleft proceeds via an induced fit mechanism.

Recently, Hunter and Sanders have published work that gives insight into the relative orientations hosts and guests may have that are favored by π-π interactions.[13] They predict a favorable interaction for the offset and tilted geometry we find in our complex. We are currently investigating the influence of substituents on the walls of the cleft to gain a deeper understanding of the forces that determine the strength of binding interactions in these kinds of host–guest complexes.

Acknowledgment. Mr. B. Lutz is gratefully acknowledged for doing the IR experiments.

(11) Johnson, C. S., Jr.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012–1014.
(12) Wallwork, C. S. *Acta Cryst.* **1962**, *15*, 758–759.
(13) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.

Acceleration of Hemiacetal Cleavage through Hydrogen Bonding: A New Synthetic Catalyst with Balanced Conformational Flexibility and Preorganization

Cesare Gennari,* Francesco Molinari, Marcella Bartoletti, Umberto Piarulli, and Donatella Potenza

Dipartimento di Chimica Organica e Industriale, Università di Milano, Centro C.N.R. Sostanze Organiche Naturali, via Venezian 21, 20133 Milano, Italy

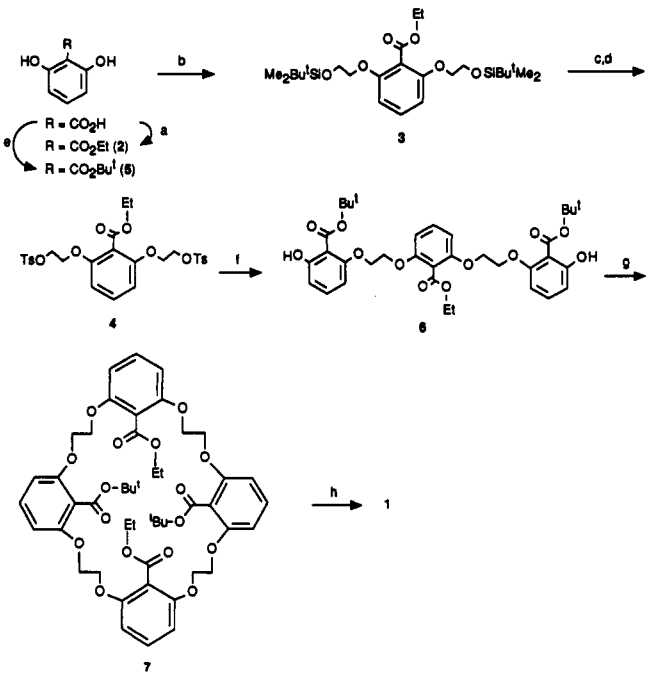
Received January 11, 1991

Summary: Hemiacetal cleavage catalyst 1 was designed, synthesized, and shown to be effective in promoting glycolaldehyde dimer dissociation and tetramethylglucose mutarotation.

The design of synthetic molecules that mimic elements of enzyme catalysis is of great interest.[1] The ultimate goal in model systems would be to recognize transition states better than ground states through noncovalent interactions.[2] Models should also possess an optimum balance between conformational flexibility and preorganization[3a,b] in order to be tailored for a reaction class rather than for a single particular substrate.

Inspired by the cleftlike molecules introduced by Rebek and co-workers featuring convergence of useful functional groups, particularly carboxylic acids,[1e,4] we designed[5] and synthesized diacid 1 for catalysis of hemiacetal cleavage.[6]

Scheme I.[a] **Synthesis of 1**



[a] Reagents: (a) EtOH, H_2SO_4, reflux;[15b] 65%; (b) 2, $Me_2Bu^tSiO(CH_2)_2OTs$, Cs_2CO_3, DMF, 50 °C; 85%; (c) *n*-Bu_4NF, THF, 25 °C; 99%; (d) TsCl, CH_2Cl_2, Et_3N, 4-DMAP cat.; 96%; (e) *N,N*-dimethylformamide di-*tert*-butyl acetal, benzene, reflux;[15b] 65%; (f) excess 5, Cs_2CO_3, DMF, 60 °C; 60%; (g) 4, Cs_2CO_3, DMF, 70 °C, slow addition;[9] 45%; (h) CF_3CO_2H, CH_2Cl_2, 0 °C; 90%.

(1) For recent reviews, see: (a) Tabushi, I. *Tetrahedron* **1984**, *40*, 269–292. (b) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112. (c) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386. (d) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009–1020. (e) Rebek, J., Jr. *Science* (Washington, D.C.) **1987**, *235*, 1478–1484; *Pure Appl. Chem.* **1989**, *61*, 1517–1522; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255. Among recent leading references to this rapidly growing field, see: (f) Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 5972. (g) Koga, K.; Sasaki, S. *Pure Appl. Chem.* **1988**, *60*, 539. (h) Menger, F. M.; Ladika, M. *J. Org. Chem.* **1990**, *55*, 3006–7. (i) Tecilla, P.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1232–34. (j) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *27*, 915–18. (k) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1990**, *112*, 8024–8034. (l) A number of other highly relevant papers are assembled in the following: *Enzyme Mechanisms*; Page, M. I., Williams, A., Eds.; Royal Society of Chemistry: London, 1987.
(2) Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375; *Nature* **1948**, *161*, 707–709. For a recent discussion, see: Kraut, J. *Science (Washington, D.C.)* **1988**, *242*, 533–540.
(3) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–57. (b) A flexible (adjustable) system which is at least as good as a related rigid (preorganized) one for binding 9-ethyladenine, was recently described, see: Tjivikua, T.; Deslongchamps, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8408–8414.

0022-3263/91/1956-3201$02.50/0