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.

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

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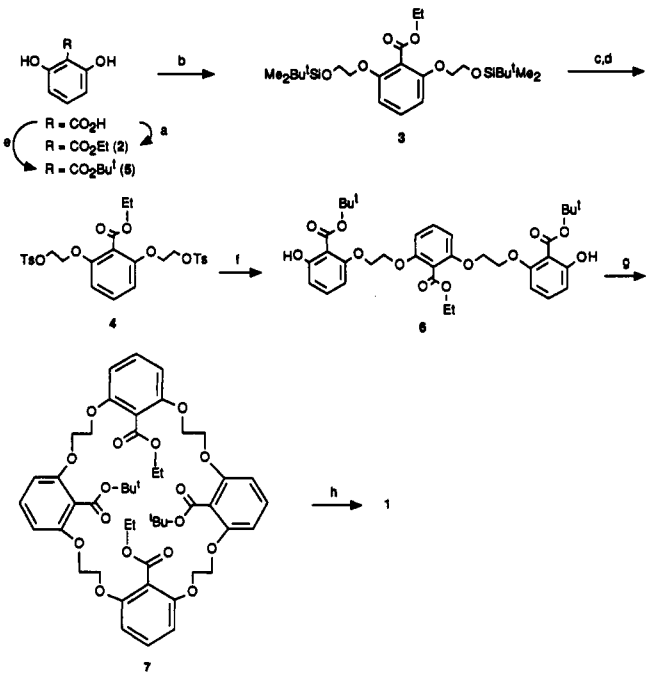
Summary: Hemiacetal cleavage catalyst 1 was designed, synthesized, and shown to be effective in promoting glycolaldehyde dimer dissociation and tetramethylglucose mutarotation.

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%.

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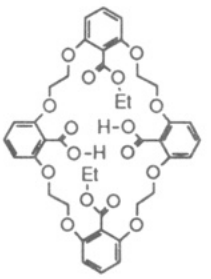


1

In comparison with Rebek's systems in which carboxyl functions are constrained to be in a convergent conformation, our new structure (1) is conformationally much more mobile. Molecular modeling studies show that 1 has many accessible low-energy conformations with various degrees of carboxyl group convergence (the lowest energy ones in the gas phase and in chloroform are shown in Figure 1).[7] However, although the carboxyl groups of 1 are not rigidly oriented in space, they can be easily organized by interaction (hydrogen bonding) between catalyst (1) and substrate.[8]

A straightforward synthesis of 1 is outlined in Scheme I (overall yield ca. 19–20%). Commercially available 2,6-dihydroxybenzoic acid was transformed in a few, high-yield steps into fragments 4 and 6, ready for macrocyclization. Cs_2CO_3 mediated reaction under high dilution and slow addition conditions[9] gave the 28-membered ring 7 as the only nonpolymeric product in 45% yield.[10]

In the gas phase

In chloroform

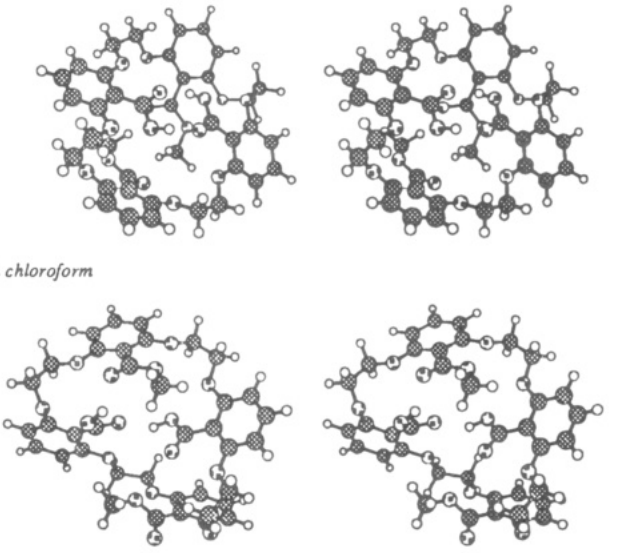


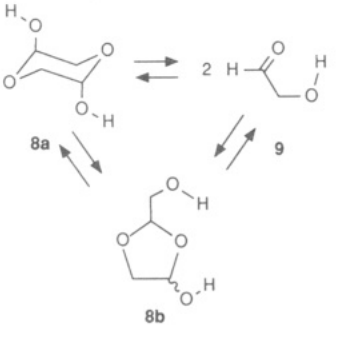
Figure 1. Stereoviews of the lowest energy conformers of 1 (methyl ester instead of ethyl ester) in the gas phase (top picture) and in chloroform (bottom picture). For details on the minimization, see ref 7.

Table I. Dissociation (eq 1) in $CDCl_3$ at 25 °C

catalyst	ratio catalyst–substrate	ca. $t_{1/2}$,[a] h	ca. $t_{25\%}$,[a] h	ref
none	–	72.1		*b*
benzoic acid	1:5	30.8		*b*
glutaric acid	1:20.8	22.0		*b*
2-pyridone	1:20	12.0		*b*
divergent Rebek's acid	1:16.7	12.0		*b*
convergent Rebek's acid	1:400	12.0 min		*b*
none	–		30.0	*c*
benzoic acid	1:5		14.0	*c*
2-pyridone	1:20		7.5	*c*
1	1:400		2.5	*c*

[a] See footnote 12. [b] Reference 6. [c] This paper. The initial concentration of 8a was 5×10^{-3} in all reactions.

As a substrate for our catalyst we chose glycolaldehyde dimer **8a**, since its dissociation to the monomer **9** (eq 1) has been studied in detail by other workers with a number of catalysts,[6] thus allowing direct comparison of the various systems. In $CDCl_3$ the reaction follows a complex kinetic



(1)

8a 9 8b

(4) For the development of this notion in macrocyclic contexts, see: (a) Newcomb, M.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6405. (b) Bell, T. W.; Cheng, P. G.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5185. (c) Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* **1988**, *110*, 4071. (d) For other leading references in this field, see: Askew, B. C. *Tetrahedron Lett.* **1990**, *31*, 4245–48 and references therein.

(5) 1 was designed by using CPK models, taking into account synthetic accessibility, and with provision made for solubility in nonpolar organic solvents, whose use was intended to foster hydrogen bonding as the basis for recognition and catalysis.

(6) Wolfe, J.; Nemeth, D.; Costero, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 983–984 and references therein.

(7) Details on the modeling studies. (a) In the gas phase: 39 conformers were found within 2.0 kcal mol^{-1} of the lowest energy one (included). The first 28 conformers (within 1.7 kcal mol^{-1} of the lowest energy one) have the same carboxyl group arrangement as shown in Figure 1 (doubly hydrogen-bonded 8-membered ring; O—H···O distance = 1.75 Å). Conformers with relative energies ≥ 1.8 kcal mol^{-1} have various different carboxyl group orientations. Usage-directed Still–Chang–Guida torsional Monte Carlo method (see: Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379), as a part of BATCHMIN 3.1 molecular mechanics program, was used for the conformational search on a Silicon Graphics Iris workstation. (b) In chloroform: the previous 39 conformers were minimized in chloroform using the GB/SA model included in BATCHMIN (see: Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127). In the lowest energy one (shown in Figure 1), the doubly hydrogen-bonded 8-membered ring is disrupted. The doubly hydrogen-bonded 8-membered ring feature is retained in other conformers, e.g. in the second lowest energy one (relative energy +0.15 kcal mol^{-1}). (c) BATCHMIN is part of the MacroModel molecular modeling program: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. We thank Professor Clark Still (Columbia University) for a copy of MacroModel and helpful advice on its use.

(8) The carboxyl group of 1 should be easily accessible for intermolecular, syn oriented hydrogen bonding with an external substrate, since the intramolecular H-bonding with the ortho oxygen atoms, although forming a 6-membered ring, would be anti-oriented and therefore highly disfavored. In fact, hydrogen bonds between a carboxyl group (hydroxyl hydrogen) and a substrate strongly prefer the syn orientation. The preference for syn versus anti often dominates over any preference for intramolecular versus intermolecular, see: (a) Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169–176. (b) Gandour, R. D.; Nabulsi, N. A. R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1990**, *112*, 7816–17. For other cases or exceptions, see: (c) Dutton, P. J.; Fronczek, F. R.; Fyles, T. M.; Gandour, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 8984–8985. (d) Nowich, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902–8906.

(9) van Keulen, B. J.; Kellog, R. M.; Piepers, O. *J. Chem. Soc., Chem. Commun.* **1979**, 285–6. Dijkstra, G.; Kruizinga, W. H.; Kellog, R. M. *J. Org. Chem.* **1987**, *52*, 4230–34. Kaptein, B.; Barf, G.; Kellog, R. M.; Van Bolhuis, F. *J. Org. Chem.* **1990**, *55*, 1890–1901.

(10) Compound 7: FAB MS 714 (100), 889 (M + H, 12), 911 (M + Na, 20); ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (6 H, t, J = 7.0 Hz), 1.28 (18 H, s), 4.10 (4 H, q, J = 7.0 Hz), 4.31 (16 H, br s), 6.55 (8 H, d, J = 7.7 Hz), 7.18 (2 H, t, J = 7.7 Hz), 7.22 (2 H, t, J = 7.7 Hz). Found: C, 64.78; H, 6.41. Calcd for $C_{48}H_{56}O_{16}$: C, 64.85; H, 6.35.

Table II. TMG Mutarotation at 25 °C

catalyst	ratio catalyst–substrate	ca. $t_{1/2}$, h	solvent	ref
2-pyridone	1:1100	9.0	benzene	*a*, *b*
benzoic acid	1:1100	4.5	benzene	*a*, *b*
1	1:1100	51 min	benzene	*a*
benzoic acid	1:1100	7.5	$CHCl_3$	*a*
1	1:1100	2.5	$CHCl_3$	*a*
2-pyridone	1:1673	13.0	benzene	*a*, *b*
2-pyridone	1:3351	22.9	benzene	*a*, *b*
benzoic acid	1:2166	13.3	benzene	*a*, *b*
1	1:2334	2.3	benzene	*a*

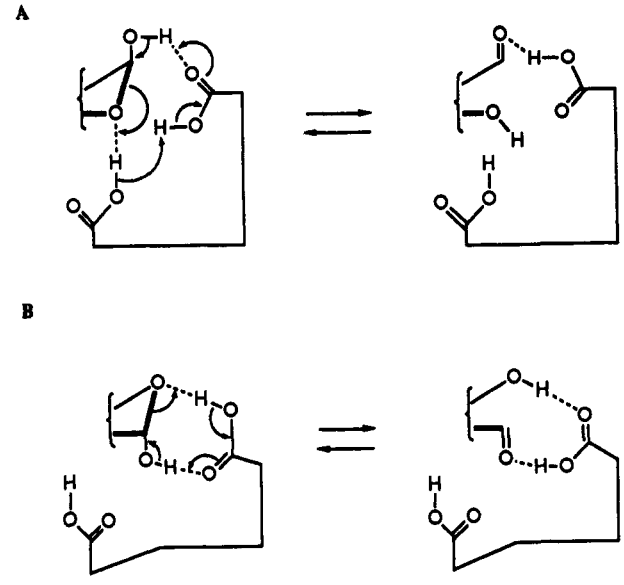
[a] This paper. TMG with $[\alpha]_D^{25} = 117°$ (benzene, *c* 2.0) was prepared according to ref 14g. TMG concentration was 0.085 M in all experiments. [b] Reference 14f.

law, which involves: (a) initial formation (up to a 60% of the reaction mixture) and then slower consumption of the dioxolane isomer **8b** toward a steady-state concentration (ca. 30% of the reaction mixture); (b) consumption of dimer **8a** from 100% to traces (ca. 2%) of the reaction mixture; (c) formation of monomer **9** from 0% up to a steady-state concentration (ca. 70% of the reaction mixture).[11] When the concentration of the various species is approximately **8a**:**8b**:**9** 2:30:68, which corresponds to 51–52% completion of the dissociation reaction, the reaction can be considered at a stationary state. As a meaningful kinetic parameter we therefore defined $t_{25\%}$ as the time when the dissociation reaction is 25% completed, i.e. aldehyde **9** concentration is 40% of the mixture.[12] In $CDCl_3$, dissociation in the absence of catalyst is slow ($t_{25\%}$ = 30 h; $t_{52\%}$ = ca. 3 days).[12,13] Compounds such as 2-pyridone and carboxylic acids, which are known as tetramethylglucose mutarotation catalysts[14] and as bifunctional catalysts for various reactions,[15] are quite sluggish in promoting this dissociation reaction (Table I).

Diacid **1** is a quite effective catalyst for this reaction: a 0.0125 mM:5 mM catalyst:substrate ratio (1:400) is enough to convert **8** → **9** (25% completion) within 2.5 h.[16] The rate acceleration is remarkably higher than that imparted by the benzoic acid (ca. 5–6 times faster with 80 times less catalyst). **1** is 25–30 times less efficient than Rebek's convergent diacid,[6] which is rigidly preorganized to fit the substrate within the cleft.[3b]

Another benchmark for a hemiacetal cleavage catalyst is tetramethylglucose (TMG) mutarotation.[14] For example, Rebek's convergent diacid is specifically suited to the dissociation of **8**, but shows no activity with TMG, i.e. a nonproductive binding was observed.[6] Diacid **1** is about 10 times more efficient than 2-pyridone and 5 times more efficient than benzoic acid as catalyst for TMG mutarotation in benzene (Table II). Two mechanisms can be proposed for binding and catalysis of glycolaldehyde–dimer dissociation and TMG mutarotation (Scheme II). According to mechanism B, concerted bifunctional catalysis via doubly hydrogen bonded 8-membered ring is likely to involve protonation of the equatorial lone pair of the ethereal oxygen.[17] Alternatively (mechanism A), the axial lone pair is protonated with consequent reduction of the anomeric effect and weakening of the endocyclic C–O bond.

Scheme II. Proposed Mechanisms for Binding and Catalysis of Glycoaldehyde–Dimer Dissociation and Tetramethylglucose (TMG) Mutarotation[a]



[a] A (axial catalysis): the axial lone pair is protonated with consequent reduction of the anomeric effect and weakening of the endocyclic C–O bond. B (equatorial catalysis): concerted bifunctional catalysis via doubly hydrogen bonded 8-membered ring.

Although the rate accelerations in both **8** dissociation and TMG mutarotation are small, these data show that catalyst **1** is relatively substrate insensitive. Our present efforts are directed toward the construction of systems that are more effective while retaining substrate generality.

Acknowledgment. We are grateful for financial support from the Commission of the European Communities [Grant SC1*.0324.C(JR)]. We are also pleased to acknowledge Dr. Anna Bernardi for helpful commentary.

(11) Dimer **8a** is ≥95% diaxial (J_{gem} = 11.7 Hz; J_{ax-eq} = 3.34 Hz; J_{eq-eq} = 2.23 Hz in $CDCl_3$), while **8b** is a 1:1 mixture of two stereoisomers: (i) $CDCl_3$, δ OH 2.9 (m, 2 H); CH_2OH 3.7–3.8 (m, 2 H); HC*H*O 3.81 (dd, 1 H, *J* = 8.9, 4.0 Hz); HC*H*O 4.20 (dd, 1 H, *J* = 8.9, 4.5 Hz); OCHO 5.35 (m, 1 H); OC*H*OH 5.73 (dd, 1 H, *J* = 4.0, 4.5 Hz). (ii) OH 2.9 (m, 2 H); CH_2OH 3.7–3.8 (m, 2 H); HC*H*O 3.90 (dd, 1 H, *J* = 9.0, 3.9 Hz); HC*H*O 4.05 (d, 1 H, *J* = 9.0 Hz); OCHO 5.35 (m, 1 H); OC*H*OH 5.55 (d, 1 H, *J* = 3.9 Hz).

(12) $t_{25\%}$ roughly corresponds to the time when half of the dissociation reaction from time zero (0%) to the stationary state (51–52%) has been completed. $t_{52\%}$ roughly correspond (≥) to the $t_{1/2}$ values given in ref 6.

(13) These results were obtained under carefully controlled conditions. $CDCl_3$ was passed through alumina under dry nitrogen, and freshly prepared $CDCl_3$ solutions were kept in the dark under dry nitrogen. Using these conditions the results were reproducible. Using $CDCl_3$ possibly contaminated by trace amounts of one of the solvent decomposition products (e.g. phosgene, chlorine, DCl), or by traces of water, which is known to catalyse the reaction (see: Stassinopoulou, C. I.; Zioudrou, C. *Tetrahedron* **1972**, *28*, 1257–1263), erratic results were obtained. The presence of contaminants caused irreproducible rate accelerations. For example, the ratio between dioxolane isomer **8b** and **8a** ranged from ca. 1:3 after 1 h (purified $CDCl_3$) to ca. 7:1 after 1 h (nonpurified $CDCl_3$).

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(16) The initial concentration of **8a** was 5 × 10^{-3} M in all reactions. In the reactions catalyzed by **1**, dimer **8a** was rapidly consumed with formation of **8b** and **9**. At 25% completion time ($t_{25\%}$) the distribution was approximately **8a**:**8b**:**9** = 11:49:40.

(17) For theoretical studies on two-hydrogen transfer reactions, see: Svensson, P.; Bergman, N.-A.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* **1990**, 862–863 and references therein.