of **17** was excised by transformation to the bromides **18**, follow d by tin hydride reduction at 60 °C providing only **19**.[23] Fortunately each step of this reduction process occurred without loss of regio- or stereochemical integrity of the adjacent trisubstituted alkene.[24]

Finally the total synthesis was completed upon removal of the tetrahydropyranyl ether yielding **20** and manganese dioxide oxidation. After the conjugated aldehyde **21** was formed, a second allylic oxidation was initiated by in situ addition of 9-hydroxynonanoate methyl ester (1 equiv) with sodium cyanide and glacial acetic acid, affording nearly quantitative conversion to the methyl pseudomonate **22**.[25] Deprotection with boron chloride at −90 °C in methylene chloride (2 min) followed by treatment of the residue with 1 M lithium hydroxide in aqueous methanol (10 min for saponification of the methyl ester) and reacidification (HOAc) gave a 97% yield of synthetic (+)-pseudomonic acid C (**1c**), $[\alpha]^{24}_D$ +8.7° (*c* 0.3, $CHCl_3$), as confirmed by direct comparisons with the authentic natural metabolite.[26,27]

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(23) Reductions with *n*-Bu_3SnH at 100 °C also led to ring opening and further reduction of the THP ether.
(24) The high degree of stereocontrol for this two-step procedure is not general.
(25) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(26) Experimental details and all data for complete chemical characterizations will be forthcoming in the full account of this work.
(27) We wish to thank Professor Gary Keck (University of Utah) for generously providing samples of natural pseudomonic acids A and C.

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The Effect of Preorganization of Macrocyclic Hosts on the Complexation of Neutral Molecules

Summary: The contribution of preorganization to recognizing and binding *neutral* guest species is described. We found that hemispherands form relatively stable complexes with malononitrile. A substantial contribution to the free energy of complexation originates from the relief of electrostatic O···O repulsion which is present in the uncomplexed ligand.

Sir: Hemispherands[1] represent a class of ligands in which at least half of the binding sites are preorganized. In this paper we describe the contribution of preorganization to recognizing and binding *neutral* guest species. We found that hemispherands form relatively stable complexes with malononitrile. A substantial contribution to the free energy of complexation originates from the relief of electrostatic O···O repulsion which is present in the uncomplexed ligand.

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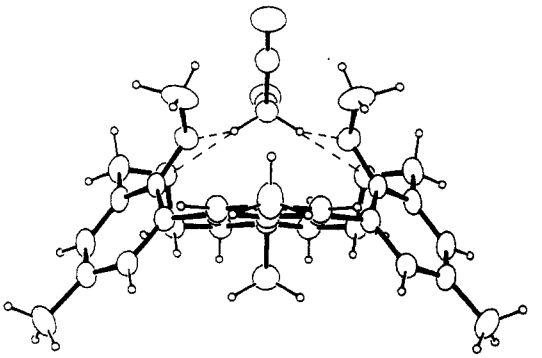
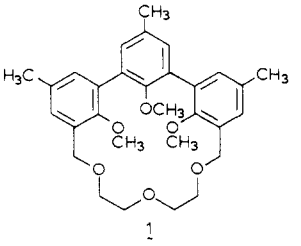


Figure 1. Front view of the structure of 1–malononitrile. Hydrogen bonds indicated by dashed lines: C···O distance range, 3.09–3.15 Å; C–H···O angle range, 129–149°.

Cram and co-workers have studied the complexation of a variety of hemispherands with alkali and substituted ammonium cations.[2] They found that hemispherand **1** exhibits a strong binding capacity toward a number of cations.[2]

We are currently interested in the selective complexation of neutral guests, e.g., urea,[3] nitromethane,[4a] and malononitrile,[4b] by macrocyclic hosts. In such complexes the guest is hydrogen-bonded to the receptor molecule. So far the investigations carried out in solution, using malononitrile as a probe for studying conformational properties of flexible ligands, have stressed the importance of a proper relative orientation of binding sites.[4b] Therefore, we studied ligands **1** and **2**, both designed according to the preorganization principle.[5] Hemispherand **1** was prepared according to Cram,[2a] and **2** was prepared from a highly prefunctionalized pyrylium salt,[6] in order to study the effect of different H-bond acceptor sites.



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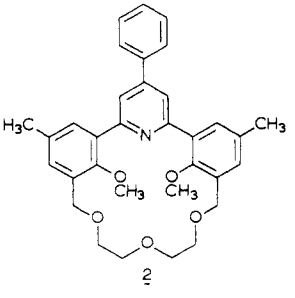

2

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Table I. Thermodynamic Parameters[a,b] for 1:1 Complexation of Hemispherands 1 and 2 with Malononitrile at 298 K

	solvent							
	C_6D_6				$CDCl_3$			
ligand	K_{11}	$\Delta H°$	$T\Delta S°$	$\Delta G°$	K_{11}	$\Delta H°$	$T\Delta S°$	$\Delta G°$
1	31	-8.1	-6.1	-2.0	28	-8.4	-6.4	-2.0
2	31	-3.9	-1.9	-2.0	104	-3.9	-1.2	-2.7

[a] K_{11} in L/mol; $\Delta H°$, $T\Delta S°$, and $\Delta G°$ in kcal/mol. [b] Accuracy: ±10%.

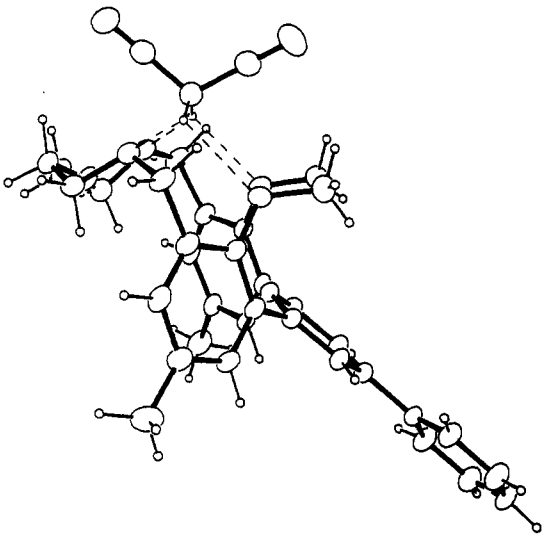

Figure 2. Side view of the structure of 2–malononitrile. Hydrogen bonds indicated by dashed lines: C···O distance range, 3.07–3.35 Å; C–H···O angle range: 129–154°; pyridine–phenyl dihedral angle, 16.3°.

The structures of $1{\cdot}CH_2(CN)_2$ and $2{\cdot}CH_2(CN)_2$ were determined by single-crystal X-ray diffractometry[7,8] on suitable crystals, prepared by slow evaporation of equimolar solutions of malononitrile and the ligands in diethyl ether. Both complexes show a very similar host–guest interaction, which is illustrated by the front view of $1{\cdot}CH_2(CN)_2$ (Figure 1) and the side view of $2{\cdot}CH_2(CN)_2$ (Figure 2), respectively.

Host 1 has a nearly identical geometry in its complexes with $CH_2(CN)_2$ and with t-$BuNH_3ClO_4$,[2b] in terms of O···O distances, aryl–aryl dihedrals, and deviations from planarity of the anisole moieties. On the other hand the H bonding between host 1 and its guest is rather different in the two complexes: two bifurcated, nonlinear H bonds with $CH_2(CN)_2$ vs. one bifurcated and two linear H bonds with t-$BuNH_3$. The deformations of the aryls and the polyether bridge upon complexation have been discussed extensively by Cram and co-workers[1,2b] by comparison of solid-state X-ray data of the free and complexed ligand. Combination of their data with ours suggests that the mere presence of NH_3^+ or acidic CH_2 hydrogens in the cavity of the host relieves the repulsion between the oxygen lone pairs. This is confirmed by the thermodynamic data of complexation.

In order to study the conformational changes of the ligands upon complexation in solution, we determined thermodynamic parameters of the association with malononitrile, using variable temperature ^1H NMR techniques[4a] (Table I). The following conclusions can be drawn.

First, hemispherands, compared to flexible crown ethers, form relatively stable complexes with malononitrile at 298 K in apolar solvents, with binding free energies ranging from -2.0 to -2.7 kcal·mol^{-1}. The $-\Delta G°$ values are rather large for complexes between neutral species in organic solvents when compared to the data reported by Cram et al.[9] for the inclusion of CS_2 at 300 K by a cavitand in $CDCl_3$ (ΔG = +0.91 kcal·mol^{-1}) and in C_6D_6 (ΔG = +1.02 kcal·mol^{-1}).

Second, for ligand 1 the enthalpic contribution to the free energy of complexation is much larger than for 2. This can be explained in terms of a more significant relief of electrostatic repulsion in 1 upon complexation, which therefore might be an important contribution to the overall $\Delta H°$.

We have also carried out molecular mechanics (MM2)[10] calculations, which show that 1 is more preorganized than 2. For 1 the major minima in the potential energy surface, the "meso" and "DL" isomers,[2a] differ by 10 kcal·mol^{-1} in steric energy, the meso isomer being the global minimum. In the case of ligand 2 at least three minima can be calculated with much smaller steric energy differences, due to the large conformational freedom of the methoxy groups and increased rotations around the pyridine–anisole bonds.

Further support for the validity of this explanation is found in ^{13}C NMR T_1 relaxation time studies[11] in solution, which indicate that the T_1 of the outer OCH_3 groups of 1 increases from 2.24 to 2.36 s upon complexation with malononitrile, whereas in 2 the T_1 decreases from 2.18 to 1.92 s. This means that the mobility of the outer OCH_3 groups *increases* upon complexation in the case of ligand 1. Usually the reverse is observed for the mobilities of binding sites, i.e., a freezing of the atoms involved, upon complexation. This is illustrated by the reduced flexibility, after complexation of 2 with malononitrile, of the polyether ^{13}C atoms for which T_1(uncomplexed)/T_1(complexed) = ±1.2. For 18-crown-6 this ratio is 2.9,[12] which clearly shows the effect of preorganization.

(7) $C_{30}H_{36}O_6{\cdot}C_3H_2N_2{\cdot}C_4H_{10}O$, monoclinic, space group $C2/m$, a = 19.431 (5) Å, b = 14.925 (5) Å, c = 13.798 (2) Å, β = 125.30 (1)°, V = 3266 (3) Å^3, Z = 4, D_c = 1.29 g·cm^{-3}, μ(Mo Kα) = 0.8 cm^{-1}. Measured 2993 unique reflections ($3° < \theta < 25°$), T = 150 K. Structure solved by direct methods. Full-matrix least-squares refinement of 1882 observed reflections ($F_o^2 > 3\sigma(F_o^2)$). Final R = 4.0%, R_w = 4.3%, $w = 4F_o^2/\sigma^2(F_o^2)$, 320 variables. The asymmetric unit contains one-half hemispherand, the other half being generated by the crystallographic mirror plane, and a malononitrile, lying in this plane. The structure exhibits some disorder. The C atoms of the two outer methoxy groups were refined on two partly occupied positions (only majority positions shown in Figure 1). The occupancy of a solvent molecule diethyl ether, which was found to be disordered around the twofold axis, was refined to 0.60.

(8) $C_{33}H_{35}NO_5{\cdot}C_3H_2N_2$, monoclinic, space group $P2_1/c$, a = 17.292 (1) Å, b = 9.180 (1) Å, c = 21.191 (2) Å, β = 108.32 (1)°, V = 3193 (1) Å^3, Z = 4, D_c = 1.23 g·cm^{-3}, μ(Mo Kα) = 0.8 cm^{-1}. Measured 5615 unique reflections ($3° < \theta < 25°$), T = 148 K. Solution by direct methods. Refinement of 3722 observed reflections to final R = 3.6%, R_w = 4.7%, 573 variables. Disorder: one methoxy carbon refined on two partly occupied positions, one methyl rotationally disordered (not shown in Figure 2). The structure has approximate mirror symmetry, excluding the phenyl ring. All calculations were done with the *Structure Determination Package* (B. A. Frenz and Associates Inc., College Station, TX, and Enraf Nonius, Delft, 1983).

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Third, an enthalpy–entropy compensation effect[4b,13] is observed for the complexes measured, resulting in $\Delta G°$ values of the same magnitude. Due to a relatively favorable $T\Delta S°$, the stability of **2**·$CH_2(CN)_2$ in $CDCl_3$ is enlarged. This might be rationalized by assuming that **2** is specifically solvated by a D-bonded $CDCl_3$ molecule, which is released during complexation: an entropically favorable process.

This study shows that partially preorganized ligands such as hemispherands are capable of complexing neutral molecules. The relatively small conformational reorganizations, combined with the relief of repulsive interactions in the free ligands, both upon complexation, give thermodynamically stable complexes.

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Supplementary Material Available: Listings of positional and thermal parameters of the two structures (12 pages). Ordering information is given on any current masthead page.

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Additions and Corrections

James A. Franz,* Mikhail S. Alnajjar, Russell D. Barrows, David L. Kaisaki, Donald M. Camaioni, and Naushadali K. Suleman. Reactions of the 2-Allylbenzyl Radical: Relative and Absolute Rate Constants for Abstraction of Hydrogen Atom from Thiophenol, Dicyclohexylphosphine, Phenols, and Arylalkyl Donors.

Page 1454. The following three tables (Tables V–VII) should appear in the text on page 1454.

Table V. Predicted and Observed Isotope Content in 2-Allyltoluene Obtained from Reactions of 2-Allylbenzyl Radical with Diphenylmethane-d_2 (Method A)

		2AT label, % d_1	
temp, °C	k_H/k_D	predctd[a,b]	obsd[b]
190	5.5	95.2	99.5
180	5.9	94.9	100
160	6.6	94.3	99
140	7.8	93.4	97
120	9.0	92.4	96

[a] Percent label in donor, $f_D = 0.991$. [b] % $d_1 = f_D/(f_D + (1 - f_D)k_H/k_D)$, with $E' = 0$ in eq 6c. Estimated error, ±5%.

Table VI. Isotope Effects and Distribution of Hydrogen and Deuterium by Source in 2AT from the Reaction of 2-Allylbenzyl Radical with Fluorene-d_2

	$k_{abs(H)}/k_{abs(D)}$		label content of 2AT		
	method	method			
temp, °C	A[a]	B[b]	% d_1[c]	% $d_{0,res}$[d]	% $d_{0,E}$[e]
190.0	5.01	5.12	84 (83.6)	14.9 (13.7)[f]	1.5 (2.7)[f]
179.5	5.32	5.32	84 (83.1)	15.4 (14.1)[f]	1.6 (2.8)[f]
160.6	5.60	5.71	81 (82.1)	16.3 (14.9)[f]	1.6 (3.0)[f]
138.5	6.15	6.26	79 (81.1)	17.6 (16.0)[f]	1.3 (2.9)[f]
120.0	6.70	6.80	82 (80.2)	19.0 (17.1)[f]	0.9 (2.7)[f]

[a] Calcd using eq 5b and 6b. [b] Calcd using 6a and 6b. [c] Experimentally determined value of % d_1 in 2AT, remainder d_0. Values in parentheses are least-squares values of experimental values vs. T(°C) used to calculate $k_{re}/k_{abs(D)}$ in eq 6a. [d] Percent of 2AT formed by abstraction of residual hydrogen in donor cmpd, calcd from eq 6d, with $g = 1$. [e] Percent of 2AT formed by disproportionation or abstraction from impurities, calcd using eq 6e, with $g = 1$. [f] Calcd from eq 6d and 6e with $g = 1/\exp(0.1875 \times 204/T(K))$.

Table VII. Relative Arrhenius Parameters,[a] Reaction Enthalpies, and Isotope Effects for Abstraction from Donors

				k_H/k_D		
donor	A_H/A_D[a]	$E_D - E_H$, kcal/mol	$-\Delta H°$, kcal/mol[b]	25 °C	120 °C	190 °C
p-xylene	0.29 ± 0.11	2.96 ± 0.16	0	43[c]	12.7	7.2
diphenylmethane	0.33 ± 0.13	2.57 ± 0.40	8	26[c]	9.0	5.5
fluorene	0.98 ± 0.65	1.42 ± 0.38	11	12[c]	6.8	5.1

[a] Errors are at the 95% confidence interval. [b] Enthalpies of reaction for benzyl + donor, using the following BDE values: toluene, 89; xylene, 89; diphenylmethane, 81; and fluorene, 78. [c] Extrapolated values.