

demonstrate that the E2-central transition state can be shifted toward the E1 borderline by utilizing a better leaving group and a weaker base.

Experimental Section

Reagents. Benzylidenemethylamines (**2**) and benzylmethylamines were available from previous work.⁶⁻⁸ Arylsulfonyl peroxides were prepared by known methods.^{22,23} *N*-(Arylsulfonyl)-*N*-benzylmethylamines (**1**) were prepared from arylsulfonyl peroxides and benzylmethylamines in EtOAc according to the procedure of Hoffman.^{9,10}

Kinetic Studies of Eliminations from 1. Base-promoted eliminations from **1** were followed by using a Cary 17D or Pye Unicam SP 500UV spectrophotometer with thermostated cuvette holders. Reactions were followed under pseudo-first-order conditions employing at least a tenfold excess of base. The solution of MeONa-MeOH (3.0 mL) was placed in a quartz cuvette and allowed to equilibrate in the cuvette compartment for 20 min. The cuvette was removed and 6 μ L of the freshly prepared solution of **1** in EtOAc was injected with a microsyringe. The cuvette was quickly shaken and returned to the cuvette compartment. The increase of absorption at the λ_{\max} for **2** with time was monitored. Plots of $-\ln [(A - A_0)/(A - A_0)]$ vs time were linear over at least 2 half-lives of the reaction. The slope was the pseudo-first-order rate constant, k_{obsd} . Values of k_{obsd} were determined at several base concentrations. Plots of k_{obsd} vs [MeONa] were straight lines passing through the origin. The

second-order rate constants were obtained from the slope.

Product Studies of Eliminations from 1. For reactions of **1** with MeONa-MeOH, the yields of **2** determined by the absorbance of infinity samples from the kinetic reactions were 60-90% based upon the starting arylsulfonyl peroxide.

The product of reaction of **1g** with MeONa-MeOH was identified by using more concentrated solutions. *N*-(Phenylsulfonyl)-*N*-benzylmethylamine (**1g**) was prepared by reaction of 0.37 mmol of phenylsulfonyl peroxide and 1.3 mmol of benzylmethylamine in 5 mL of EtOAc at -78 °C. The elimination reaction was conducted by adding 3.8 mL of 1.9 M MeONa-MeOH to the solution of **1g** and stirring for several hours at -78 °C. The solvent was removed in vacuo and the residue was extracted with diethyl ether. The diethyl ether extract was dried over MgSO₄, *m*-nitrotoluene (internal standard) was added, and the mixture was analyzed with a Hewlett-Packard Model HP 5890A gas chromatograph equipped with an HP 5970B mass-selective detector on a SE-54 cross-linked fused-silica capillary column (0.2 mm \times 16 m) with temperature programming from 90-300 °C.²² The products were benzaldehyde (9.4%), **2** (15.0%), benzylmethylamine (58.1%), and *N*-acetyl-*N*-benzylmethylamine (17.5%). Control experiments established that the benzaldehyde and *N*-acetyl-*N*-benzylmethylamine were the products from the hydrolysis of **2** and the reaction of benzylmethylamine with EtOAc, respectively, under the reaction conditions. Since an excess amount of benzylmethylamine was utilized in the preparation of **1**, the yield of elimination product (benzaldehyde + **2**) was calculated based on the starting peroxide. The yield was 85.6%.

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Complexation of Neutral Molecules by Preorganized Macrocyclic Hosts¹

Peter D. J. Grootenhuys,[†] Johan van Eerden,[‡] Pieter J. Dijkstra,[†] Sybolt Harkema,[‡] and David N. Reinhoudt^{**†}

Contribution from the Laboratories of Organic Chemistry and Chemical Physics, University of Twente, 7500 AE Enschede, The Netherlands. Received May 14, 1987

Abstract: The complexation of functionalized hemispherands **1-4**, rigid ligands in which more than half of the binding sites are preorganized, with a neutral guest, viz. malononitrile, has been studied. The thermodynamic parameters of the complexation of these ligands with malononitrile were determined in CDCl₃ and C₆D₆. The binding free energies ($-\Delta G^\circ = 1.2-2.7$ kcal/mol) were relatively favorable when compared with the stabilities of the corresponding complexes of flexible crown ethers. X-ray studies of the free (**2** and **4**) and complex (**1a**, **2**, and **4**) hemispherands revealed that both the methoxy oxygen atoms and the heteroatoms of the polyether chain are involved in the hydrogen bonding of the guest. The less organized ligand **1b** does not use the anisole binding sites of the terphenyl moiety according to X-ray studies. The ligands with the smallest conformational changes upon complexation generally form the strongest complexes. Molecular mechanics calculations of the free hosts confirm the different conformational flexibilities of the various macrocycles. Carbon-13 T_1 relaxation time studies of the free and complexed hemispherands clearly showed that the mobilities of the carbon-13 nuclei hardly decrease upon complexation, indicating that the host molecules are well preorganized.

In the past 2 decades many macrocyclic hosts capable of complexing cationic guests have been synthesized. Some guidelines can be derived by examining the thermodynamic parameters of the complex formation, and this has stimulated the rational design of host systems with defined properties. The so-called *principle of preorganization*, which states that "the smaller the changes in organization of host and guest, the stronger the binding", was first formulated by Cram.² The spherands,³ a class of compounds with extremely selective and strong binding properties for Li⁺ and

Na⁺ cations, are good examples of ligands based on this principle. However, the rather small cavities in these host molecules are not suited for the complexation of larger, polyfunctional guests. We are interested in the selective complexation of *neutral molecules*

(1) Part of this work appeared in preliminary form: van Eerden, J.; Grootenhuys, P. D. J.; Dijkstra, P. J.; van Staveren, C. J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1986**, *51*, 3918-3920.

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[†]Laboratory of Organic Chemistry.

[‡]Laboratory of Chemical Physics.

such as urea,⁴ alcohols,⁵ formaldehyde, and other small polar molecules.

Although the solid-state structures of a number of adducts between macrocyclic hosts and neutral guests have been published,⁶ until recently, quantitative data about the complexation in solution were not available. Therefore, we have systematically studied the thermodynamic stabilities of complexes of a variety of macrocyclic polyethers and different neutral guests, i.e., nitromethane, malononitrile, and acetonitrile.^{7,8} X-ray studies have shown that in these complexes H bonds between the ligand and the CH-acidic guests are present. One of the most stable complexes in C₆D₆ is the 18-crown-6-malononitrile (1:1) complex with a binding free energy of -3.2 kcal/mol at 298 K. This is still relatively low in comparison with the stabilities of the corresponding complexes with charged guests such as alkylammonium cations (-ΔG° = 5.3-7.8 kcal/mol, C₆H₆).⁹ From the available data we concluded that a macroring of 18 ring atoms, the absence of intraannular interactions in the uncomplexed macrocycle, and the presence of additional binding sites in the ligand favorably increase the overall stability of the complexes formed.⁷

Ligands in which a part of the cavity is rigid and preorganized can in principle act as host molecules for a larger variety of guests, i.e., not only small centrosymmetrical Li⁺ and Na⁺ cations but also polyfunctional cations or even neutral molecules. Hemispherands, receptor molecules in which at least half of the binding sites are preorganized, form complexes with alkali metal and alkylammonium cations.¹⁰ X-ray analysis of a complex between host **1a** and *t*-BuNH₃ClO₄ has revealed that one bifurcated and two linear H bonds are formed between the host and guest.^{10b} The binding free energy at 298 K amounts to -7.68 kcal/mol (CDCl₃).^{10a} The ability to act as an H bond acceptor in combination with the favorable binding free energies observed for various complexes of the hemispherands with charged electrophilic guests prompted us to explore the complexing properties of these ligands toward neutral molecules. Although in the literature several examples of host molecules are reported in which rigid building blocks are combined with more flexible parts, the complexation of such hosts with neutral guests has received little attention. Complexes of the very rigid cavitands^{11a} with CS₂ were studied by Cram et al., and they reported binding free energies at 298

Table I. Thermodynamic Parameters^{a,b} for 1:1 Complexation of the Hemispherands (**1-4**) with Malononitrile at 298 K

hemi-spherand	solvent							
	C ₆ D ₆				CDCl ₃			
	K ₁₁	ΔH°	TΔS°	ΔG°	K ₁₁	ΔH°	TΔS°	ΔG°
1a	31	-8.1	-6.1	-2.0	28	-8.4	-6.4	-2.0
1b	16	-6.2	-4.5	-1.7	15	-1.8	-0.2	-1.6
2	31	-3.9	-1.9	-2.0	104	-3.9	-1.2	-2.7
3	38	-5.7	-3.5	-2.2	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>
4	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	8	-4.7	-3.5	-1.2

^aK₁₁ in L/mol; ΔH°, TΔS°, and ΔG° in kcal/mol. ^bAccuracy: ±10%. ^cChemical shift difference too small to obtain reliable results.

K in apolar solvents¹² of approximately +1 kcal/mol.^{11b} Recently, very stable complexes of other spherical hosts, cryptophanes, with neutral guests have been described by Collet and co-workers.^{13a} These cryptophanes form complexes with chloroform and dichloromethane with binding free energies at 298 K up to -3.7 kcal/mol in 1,1,2,2-tetrachloroethane.^{13b} Unfortunately, until now only one X-ray study (of a 1:1 cryptophane-CH₂Cl₂ complex) has been published.^{13c} Therefore, the nature of the associative forces in complexes of cavitands and cryptophanes remains unclear, but most likely desolvation plays an important role, so the complexation might be entropy driven. In contrast, several crystallographic studies have been performed on the inclusion of acetone, toluene, and other neutral guests by calixarenes; however, quantitative data for the obviously very weak association with uncharged guests in solution are lacking so far.¹⁴

In this paper we report the results of a quantitative study of the complexation of several functionalized hemispherands with malononitrile. The reasons for studying malononitrile as the guest molecule are twofold. First, most of the thermodynamic data on the complexation with flexible macrocyclic polyethers are available for this neutral guest, which makes a comparison possible and meaningful. Second, the ability of malononitrile to act as a ¹H NMR probe can be used for the facile determination of the thermodynamic data.⁷

In order to study the role of the preorganization of the host on the complexation process, the structures of uncomplexed hemispherands and of the complexes of the same hemispherands with malononitrile were determined by single-crystal X-ray diffractometry. Conformations of the uncomplexed ligands were generated by the molecular mechanics method¹⁵ so that the geometries and corresponding steric energies of both the free and the complexed ligands could be compared. We have also carried out carbon-13 NMR longitudinal (¹³C T₁) relaxation time measurements of the free and the complexed species in order to obtain quantitative information about the conformational changes upon complexation in solution. The results of these various methods agree quite well and give a detailed overall picture of the complexation of the preorganized hemispherands with malononitrile.

Results

Thermodynamic Parameters of the Complexation. The ¹H NMR chemical shift of malononitrile in the presence of a receptor molecule depends essentially on the ratio free:complexed malononitrile in the NMR tube. When an excess host is present and the association constant of the complex is sufficiently large so that more than 99.9% of the guest is complexed, considerable downfield shifts of the malononitrile protons up to 1.4 ppm are observed. In all experiments within the temperature range 240-320 K we

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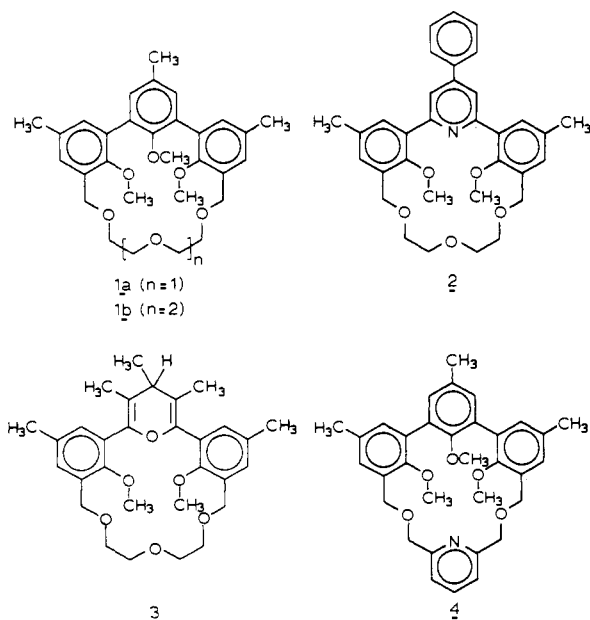
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Table II. Short Nonbonded Distances and Hydrogen Bonds in the Crystal Structures of the Malononitrile Complexes of Ligands **1a**, **1b**, **2**, and **4**^a

ligand	A	distance D···A, Å	distance H···A, Å	angle D-H···A, deg
1a	O1	3.08		
	O4 ^b	3.09	2.19	149
	O8 ^b	3.15	2.42	129
1b	O1	3.29	2.60	122
	O4	3.41	2.39	165
	O8	3.29		
	O26	3.38		
	O34	3.29	2.53	133
2	O1	3.04	2.66	106
	O4	3.07	2.26	147
	O8	3.28	2.55	138
	O29	3.35	2.68	130
	O37	3.21	2.34	154
4	N1	3.40	2.69	133
	O4	3.35		
	O8	3.24	2.50	123
	O26	3.23	2.61	114
	O34	3.16		

^aD = hydrogen bond donor atom (malononitrile C(H₂) atom), A = acceptor (heteroatom of ligand). Criteria: distances D···A maximum 3.50 Å, H···A maximum 2.75 Å. ^bOccurs twice due to crystallographic mirror plane.

observed fast exchange between the free and complexed malononitrile. By determining the chemical shifts of a series of samples in which the host:guest ratio was varied, we calculated the association constants of the host-guest complexes with a computer program that iteratively minimizes the sum of the squares of the differences between the experimentally observed and the theoretically derived chemical shift of malononitrile.⁷ Indications for complex stoichiometries other than 1:1 were absent. By performing the measurements at four temperatures we derived both the enthalpy and entropy of complexation. In Table I the thermodynamic parameters are given for the 1:1 complexation of the hemispherands **1a**,^{10a} **1b**,^{10b} **2**,^{10c} **3**,^{10d} and **4**^{10d} with malononitrile.



The binding free energy at 298 K of most of the hemispherand-malononitrile complexes is less than -2.0 kcal/mol, indicating that, in general, hemispherands act as good ligands for malononitrile. The strongest association is observed for host **2** in CDCl₃, ΔG° = -2.7 kcal/mol.

X-ray Crystallography. The crystal structures of the uncomplexed ligand **4** and the malononitrile complexes of **1a**, **1b**, **2**, and **4** were determined by X-ray diffraction. The structures of **1a**,¹⁶

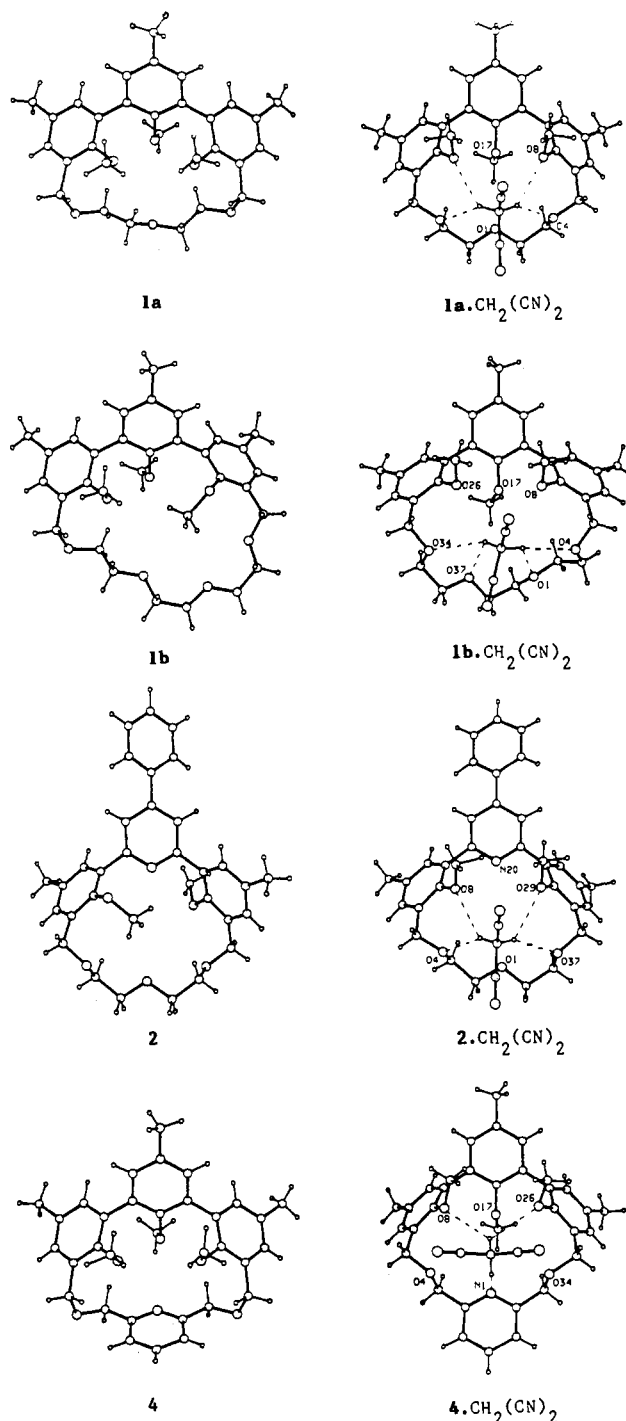


Figure 1. Views of the crystal structures of the ligands **1a**, **1b**, **2**, and **4** and their malononitrile complexes. H bonds are indicated by dashed lines; the atom numbering of the heteroatoms of the complexed hosts is shown.

1b,^{10f} and **2**^{10f} are included in the discussion in order to complete the comparison of the structures of the four uncomplexed hemispherands **1a**, **1b**, **2**, and **4** and their malononitrile complexes. In Figure 1 a view of the structures is given. The hydrogen-bonding parameters for the hemispherand-malononitrile complexes are collected in Table II. Data on the hemispherand units are given in Table III.

The structures of the free and complexed hosts show several interesting features. First, in some cases the flanking methoxy groups in the free hosts diverge from the cavity (**1a** and **4**) and in other cases they converge toward the cavity (**1b** and **2**). In the

Table III. Hemispherand Dimensions in the Crystal Structures of the Ligands **1a**, **1b**, **2**, and **4** and Their Malononitrile Complexes: Distances (Å) between the Flanking Methoxy and Adjacent Ether Oxygens (OArCH₂O), between the Flanking and Central Methoxy Oxygens (OArArO), and between the Two Flanking Methoxy Oxygens (OArArArO) and Displacements (Å) of Methoxy Oxygens out of the Plane of the Attached Aryl and Aryl-Aryl Dihedrals (Deg)^a

	1a	1a-CH₂(CN)₂^b	1b	1b-CH₂(CN)₂	2	2-CH₂(CN)₂	4	4-CH₂(CN)₂
OArCH ₂ O	2.71/3.59 ^c	3.02	3.29	3.16	2.97	2.94	3.59	2.99
	3.55	3.02	3.51	3.21	3.15	3.08	3.72	3.08
OArArO (OArPyrN)	2.84	2.86	2.94	2.82	2.88	2.94	2.89	2.80
	2.85	2.86	3.63	2.88	2.97	3.08	2.96	2.93
OArArArO (OArPyrArO)	3.56	3.98	4.49	3.78	4.98	3.84	3.62	4.17
displacement of methoxy O's	0.02	0.18	0.07	0.12	0.14	0.01	0.05	0.12
out of plane of	0.04	0.01	0.02	0.11			0.06	0.06
attached aryl	0.06	0.18	0.11	0.12	0.19	0.15	0.07	0.14
aryl-aryl (pyridyl) dihedral	56	57	60	52	47	48	59	58
	60	57	82	53	54	59	61	60

^aIn **2** the central anisyl is replaced by a pyridyl group. ^bEqual values due to crystallographic mirror plane. ^cTwo values due to positional disorder of the ether oxygen.

latter case the cavity is occupied partly by one methyl group, and upon complexation extensive conformational reorganizations are expected to occur. A related phenomenon was observed earlier in the X-ray structure of an expanded hemispherand.^{10c} The reorganizations needed are observed in the corresponding malononitrile complexes where all anisyl methoxy groups are oriented away from the cavity. The general tendency of hosts to fill their own cavities by adopting appropriate conformations, the so-called self-complexation,¹⁷ can also be observed in the orientation of the methylene H atoms of the free hemispherands. In the structures of the uncomplexed hosts **1-4** at least one polyether H atom is pointing toward the cavity, whereas in the complexed macrocycles all polyether H atoms are pointing away from the cavity.

In all complexes malononitrile is H bonded to heteroatoms of the hemispherands. Hosts **1a** and **2** form bifurcated H bonds to the flanking anisole methoxy groups and to the adjacent polyether oxygen atoms. A different H-bonding scheme was reported for the complex of **1a** with the *tert*-butylammonium cation.^{10d} This complex is structured by three H bonds, two of them between the N-H's and the benzylic oxygen atoms, and one bifurcated H bond from N-H to the two flanking methoxy oxygen atoms. In the case of **1b** only the (more basic) heteroatoms of the flexible polyether chain are involved in the binding. In the complex of host **4** the malononitrile molecule has adopted a position in which the pyridine moiety in the polyether bridge acts as a H-bond acceptor together with the two flanking methoxy groups. Therefore, in this complex the guest is rotated almost 90° around its C₂ axis compared with the orientation of malononitrile in the other complexes.

Molecular Mechanics. Since the X-ray structures of the free and complexed hemispherands showed relevant conformational differences with regard to the position of the methoxy groups that can converge toward or diverge from the cavity, we wanted a quantitative comparison of several conformations. Molecular mechanics calculations,¹⁵ which yield detailed information on molecular geometries and the corresponding relative steric energies of conformations, have been used before in studies on rigid hosts, e.g., spherands¹⁸ and cryptands.¹⁹ We were interested in the effect of the ring size and the variation of the rigid unit and therefore the ligands **1a**, **1b**, and **2** were studied. Using molecular graphics in combination with the dihedral driver option of the MMP2 force field,²⁰ we generated a number of starting geometries for the free hosts. After the energy minimization relatively few (<10) low-energy conformations remained. Data on a number of low-energy

Table IV. Contributions (kcal/mol) to the Steric Energy of Several Conformations of the Hemispherands **1a**, **1b**, and **2** As Calculated by Molecular Mechanics (MMP2)^a

ligand	conf ^b	bnd	vdW	tor	dip	tot
1a	+d-d+d	13.1	17.6	-18.0	1.0	13.7 ^c
	+d-d+d	10.6	19.6	-20.5	5.6	15.3 ^d
	+d-c+d	13.5	17.9	-18.5	2.9	15.8
	+d-d+c	14.4	18.9	-18.9	2.3	16.7
1b	+d-d+d	13.6	22.5	-7.5	1.8	30.4
	+d-d+c	13.4	19.6	-23.3	1.3	11.0 ^c
	+d-c+d	13.1	21.2	-22.0	3.2	15.5
	+d-c+c	15.8	20.0	-20.5	1.8	17.1
2	+d-d+d	12.3	20.9	-20.1	5.8	18.9 ^d
	+c-c+c	18.2	19.9	-15.1	1.1	24.1
	+d-c	15.0	24.4	-13.4	2.0	28.0 ^c
	+d+d	12.2	24.7	-14.8	7.0	29.2 ^d
	+d+c	15.7	25.7	-14.0	2.4	29.8
	+d-d	12.9	26.9	-12.1	4.9	32.6

^aIn the MMP2 force field^{15,31} the total steric energy (tot) is a summation of energies belonging to several terms associated with bonding interactions (bnd), van der Waals interactions (vdW), torsion energy (tor), and dipole-dipole interactions (dip). ^bAbbreviations used for describing the conformation of the rigid moiety: d = diverging OCH₃ group, c = converging OCH₃ group, + = OCH₃ group above plane through polyether ring, - = OCH₃ group beneath plane through polyether ring. ^cConformation as in the crystal structure of the free ligand. ^dConformation as in the crystal structure of the complexed ligand.

conformations of the ligands **1a**, **1b**, and **2** are summarized in Table IV.

Although we did not scan the entire conformational space of the hosts and the calculations were performed on isolated "gas-phase" molecules, Table IV shows some interesting results. In all cases the conformation of the free ligand observed in the solid state resembles the calculated conformation with the lowest steric energy. It is noteworthy that the number of conformations that could be generated was rather low. This is in contrast with molecular mechanics studies carried out for more flexible ligands such as 18-crown-6. Uiterwijk et al. have shown that there are at least 190 conformations possible for this ligand within a steric energy range of 20 kcal/mol.²¹ Apparently, the hemispherands are conformationally much more rigid.

The conformations all possess alternating anisole units with the exception of the +d+d-d conformation²² of ligand **1a**. This "DL" isomer was assembled earlier by Cram and co-workers on the basis of Corey-Pauling-Koltun (CPK) model studies,^{10a} but from Table IV it is clear that the corresponding energy is very high and it is not likely to occur in solution.

Finally, it is noted that the conformations of the complexed hemispherands appear to be of a higher steric energy than the conformations of the corresponding uncomplexed ligands, due to

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(22) See Table IV for an explanation of the codes for conformations.

Table V. Carbon-13 T_1 Relaxation Times^a (s) and Chemical Shifts (ppm) of the Free Hemispherands (1-4) and the Corresponding Malononitrile Complexes (CDCl₃, 293 K)^{b,c}

group	1a		1b		2		3		4	
	f	c	f	c	f	c	f	c	f	c
OCH ₃ flanking										
T_1	2.24	2.36	2.56	2.02	2.18	1.90	2.68	2.50	2.61	2.15
δ	60.9	62.0	61.6	61.7	62.7	62.1	61.7	61.3	60.4	61.9
OCH ₃ central										
T_1	1.89	1.64	1.89	1.97	na	na	na	na	2.04	1.65
δ	59.9	59.9	60.2	60.1	na	na	na	na	59.6	59.6
OCH ₂ Ar										
T_1	0.55	nd	0.46	0.47	0.44	0.30	0.37	0.27	0.41	0.5
δ	68.4	68.0	68.6	68.2	68.4	68.6	67.6	68.0	69.2	70.5
OCH ₂										
T_1	0.62	nd	0.71	0.52	0.38	0.29	0.36	0.24	0.5	0.7
δ	69.6	69.8	68.7	69.0	69.7	70.0	69.3	69.6	66.2	69.1
	69.7	69.9	69.7	70.1	70.3	70.2	70.2	70.1	69.3	70.8
			70.6	70.2						

^a Estimated standard deviation: 10%. ^b The chemical shifts of the complexes were obtained by using the samples from the T_1 determinations. ^c Abbreviations used: f = free macrocycle, c = complex with malononitrile (1:1), na = not applicable, nd = not determined.

the relatively unfavorable dipole energy term of the former ones. However, in the malononitrile complexes the electrostatic repulsion between the heteroatom lone pairs will be compensated to a large extent by the interactions of these H-bond acceptors with the (partially positively charged) malononitrile protons. This will lower the steric energy of the conformations as found in the complexed hemispherands.

Carbon-13 NMR Longitudinal Relaxation Time Measurements.

Previously we have used ¹³C T_1 values of free and complexed hosts in order to study the conformational reorganizations of hosts upon complexation.^{17a} Recently, we applied this method to three series of uncomplexed functionalized crown ethers that show self-complexation phenomena.^{17b} In order to investigate the conformational changes in the hemispherands upon complexation with malononitrile in solution, the T_1 values of the carbon-13 nuclei of the various OCH₃ and OCH₂ units in the free and complexed ligands were measured (Table V). Since the nuclear Overhauser effects for these protonated carbons are all between 2.7 and 3.0, the relaxation process proceeds mainly by the dipole-dipole (DD) mechanism and therefore the T_1 values reflect the mobilities of the observed nuclei.²³ An increased molecular motion lowers the efficiency of DD interactions and lengthens the T_1 value.²⁴ Upon complexation the T_1 values of the ¹³C nuclei decrease in nearly all cases, indicating that the flexibilities of several parts of the hosts are reduced upon complexation; this in agreement with other complexation studies on various ligands.¹⁷ However, in host 1a the T_1 value of the flanking methoxy groups increases upon complexation from 2.24 to 2.36 s. This would mean that the mobilities of the methoxy groups which act as H-bond acceptors in the 1a-CH₂(CN)₂ complex increase upon complexation.

For the free and complexed ligands the T_1 values of the central methoxy groups are lower than the corresponding values of the flanking methoxy groups. Apparently, the mobilities of the central methoxy groups are lower than the mobilities of the flanking methoxy groups. This effect is also reflected in the chemical shifts of the methoxy substituents (vide infra).

Discussion

Thermodynamics of the Complexation. The negative binding free energies in Table I clearly indicate the formation of complexes of hemispherands with malononitrile in apolar solvents. Although the structural variation in the hosts is not so large as in our earlier complexation studies with crown ethers, we feel that the incorporation of rigid moieties such as teranisyl units into hosts is favorable for the complexation of neutral guests.

A close look at the data in Table I reveals that also for these complexes an enthalpy-entropy compensation effect is observed: differences in the ΔH° are to a large extent compensated for by the $T\Delta S^\circ$ term so that the resulting effect on the ΔG° is relatively small. The apparent exception is host 2, which shows a relatively favorable complexation entropy term. This might be due to the release of a CDCl₃ molecule, D bonded to the pyridine nitrogen in the free host, upon complexation. In analogy with the literature^{7b,25} the data fit well a linear relation $T\Delta S^\circ = A(\Delta H^\circ) + B$, with, for these hemispherands, $A = 0.99$ and $B = 1.86$ kcal/mol ($n = 8$, $r = 0.99$). The corresponding values that we have found for the complexation of crown ethers with malononitrile are $A = 0.84$ and $B = 0.7$ kcal/mol.^{7b} Since the number of data in the present study is relatively small, care should be taken when the differences are interpreted. However, the value of B seems to be significantly larger for the hemispherands in comparison to the crown ethers. This would indicate that the desolvation of the neutral guest is more important for the complexation by more rigid ligands. Inoue and Hakushi found the same trend for the complexation of the cations by crown ethers and cryptands, where B amounts to 2.4 and 4.0 kcal/mol, respectively.²⁵

Comparison of the complexation data of the 18- and 21-membered hosts 1a and 1b shows that also for preorganized ligands the optimal ring size for the complexation of malononitrile is 18 ring atoms. In agreement with this observation the H bonds in the crystal structure of the 1a-CH₂(CN)₂ complex are shorter (and stronger) than for the corresponding 1b-CH₂(CN)₂ complex (vide infra). Another point of interest is the large difference in the magnitude of the ΔH° and $T\Delta S^\circ$ terms of 1b in C₆D₆ (-6.2 and -4.5, respectively) and CDCl₃ (-1.8 and -0.2, respectively). This difference might be rationalized by assuming the formation of a structured CDCl₃ complex which dissociates upon complexation with malononitrile. Compared with hosts 1a and 2 the 21-membered ligand is not well preorganized and the binding is relatively small. Therefore the magnitudes of both the ΔH° and $T\Delta S^\circ$ terms are relatively small.

Hydrogen Bonding. From the data on H bonding in the hemispherand-malononitrile complexes (Table II) several important aspects will be discussed. First, the interactions between the malononitrile CH₂ group and the hemispherand heteroatoms can be described as weak H bonds,²⁶ considering the rather long nonbonded distances: 3.1-3.4 Å for donor-acceptor and 2.2-2.7 Å for proton-acceptor distances. Similar values have been reported for the crystalline complexes of malononitrile with 18-crown-6²⁷ and 2,6-pyridino-18-crown-6.^{7b}

Second, most interactions can be described as strongly nonlinear H bonds, with the angle subtended at the hydrogen between 120°

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(24) Assuming that the extreme narrowing condition is fulfilled, which is reasonable for the molecules under study. See ref 23.

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Table VI. Occurrence of Conformational Changes in Several Functional Moieties of Hemispherands **1a**, **1b**, **2**, and **4** upon Malononitrile Complexation Observed in the Crystalline State

hemispherand	moiety		
	polyether bridge	methoxy group	aryl-aryl dihedral
1a	yes	no	no
1b	yes	yes	no
2	yes	yes	yes
4	yes	no	no

and 150°. The reason for this nonlinearity is twofold. In the complexes most H bonds are bifurcated; i.e., two nonlinear interactions are preferred over one linear. Steric constraints also render H bonds nonlinear: the distance between two hemispherand heteroatoms involved in linear H bonds to the malononitrile hydrogens should approximate 5 Å, whereas the distance between the flanking methoxy oxygens in the ligands **1a**, **1b**, and **2**, hydrogen bonded to malononitrile, is 3.8–4.0 Å (Table III).

Third, information on preferences of malononitrile for H-bond acceptors can be obtained from the H-bonding patterns in the hemispherand-malononitrile complexes. In **1a**·CH₂(CN)₂ two ether and two methoxy oxygens act as H-bond acceptors, whereas in **1b**·CH₂(CN)₂, upon extending the polyether bridge with one ethyleneoxy unit, all four ether and no methoxy oxygens take part in the H bonding. This preference for ether oxygens is confirmed by the H-bonding parameters for **1a**·CH₂(CN)₂ and **2**·CH₂(CN)₂ in Table II: the H bonds with the relatively more basic ether oxygens are shorter and more linear than those with methoxy oxygens. Comparison of the structures of **1a**·CH₂(CN)₂ and **4**·CH₂(CN)₂ reveals a clear preference for the pyridyl nitrogen as an H-bond acceptor,^{7b,28} although the parameters of **4**·CH₂(CN)₂ in Table II and the unfavorable ΔG° of complexation suggest rather weak interactions, probably due to steric hindrance between the malononitrile CN groups and hemispherand oxygens (distances 3.0–3.1 Å). The pyridyl nitrogen in **2**·CH₂(CN)₂ cannot take part in the H bonding, because it is buried deep in the cavity, shielded by the flanking methoxy groups.

Preorganization. The degree of preorganization of the hemispherands **1a**, **1b**, **2**, and **4** with respect to malononitrile complexation is summarized in Table VI. The data indicate that upon complexation conformational changes occur in several parts of the hemispherands. Hemispherand **1a** is preorganized to a large extent; only the conformation of the flexible polyether bridge changes to facilitate cooperative H bonding of malononitrile with the ether and methoxy oxygens. Extension of the polyether bridge results in a decreased preorganization for ligand **1b**. One of the methoxy groups partly fills the macrocyclic cavity; this means that prior to malononitrile complexation it has to change its orientation and diverge from the cavity. In **2** the absence of the central methoxy group results in a relative decrease of preorganization: the flanking methoxy groups can adjust their orientation, and rotation around the aryl-aryl bonds is also possible. In **4** the polyether bridge is more rigid than in **1a**, but still a conformational change occurs: the angle between the 2,6-pyridyl substituent in the polyether bridge and the central anisole moiety changes from 90° to 15° upon complexation with malononitrile.

From the data of Table III we can evaluate the effect of malononitrile complexation on the hemispherand dimensions. First, large changes due to reorganization upon complexation (Table VI) are observed, e.g., in the distance between the flanking methoxy oxygens for **1b** and **2** and in the aryl-aryl dihedral for **1b**. Second, more subtle effects, due to the H-bonding interactions, are observed. Hemispherands **1a** and **4**, which show no substantial reorganization of the teranisol unit, exhibit an increased distance between the flanking methoxy oxygens. The displacement of the methoxy oxygens out of the plane of their attached aryl, a measure of the deformation of the anisyl group, increases upon complex-

ation, except for **2**, which has already a large deformation of the anisyl units in the uncomplexed ligand. This increase in deformation has also been observed in the complex of **1a** with *tert*-butylammonium perchlorate.^{3a} It is probably related to the steric constraints imposed by the hydrogen bonding. The aryl-aryl dihedrals show no large changes upon complexation, except for one dihedral in **1b**. Of the complexed hemispherands, **1b** and **2** have a slightly more planar configuration, i.e., smaller dihedrals, than **1a** and **4**, reflecting the larger conformational freedom and relative lack of preorganization of **1b** and **2**.

¹H NMR spectral changes (CDCl₃) observed for the hemispherands **1–4** upon complexation with malononitrile are consistent with changes observed in the crystal structures of the free and complexed ligands. The chemical shifts follow the trend as found for **1a** upon complexation with *t*-BuNH₃⁺. The signal for the central methoxy protons in **1a**·CH₂(CN)₂ is at δ 2.49, whereas the values for **1a** and **1a**·*t*-BuNH₃⁺ are δ 2.56 and 2.20, respectively.^{10a} The smaller chemical shift differences in **1a**·CH₂(CN)₂ compared with **1a**·*t*-BuNH₃⁺ are in agreement with the weaker association in the first-mentioned complex. As seen from the X-ray structure of **1b**·CH₂(CN)₂ only coordination to the polyether bridge occurs. This is reflected in the ¹H NMR spectra, which show almost identical chemical shifts in **1b** and **1b**·CH₂(CN)₂. Only small changes for the ethylene protons, appearing as a multiplet, were observed. For the conformationally more mobile host **2** the spectra of the free ligand and the malononitrile complex show very small differences. The methoxy hydrogen atoms show a downfield shift of 0.04 ppm, corresponding to the shift differences of these protons in all hemispherands upon complexation. The flexibility of **2** is reflected in the singlet observed for the benzylic protons compared to the AB system as found in **1a**. Fast ring inversion on the ¹H NMR time scale can only be inhibited by complexing **2** with Na⁺ and K⁺,^{10f} but not with malononitrile, obviously due to a fast exchange of malononitrile in solution. Only minor chemical shift differences were observed for **4** and **4**·CH₂(CN)₂. The central methoxy protons are found at δ 2.68 in **4** and at δ 2.65 in **4**·CH₂(CN)₂, which is in agreement with the weak association found.

The carbon-13 T₁ measurements provide information on the preorganization prior to complexation in solution. The individual differences between the hemispherands are interesting but the varying molecular weights and solvation of the hosts make a quantitative interpretation difficult. Therefore, we will focus on the most pronounced effects.

From Table V it is clear that the T₁ values of the OCH₂ and OCH₃ carbons generally decrease upon complexation. The decrease is rather small when compared to the decrease of the T₁ value of the OCH₂ carbons of 18-crown-6 upon complexation with malononitrile from 1.98 to 0.69 s as reported recently by Knöchel and co-workers.^{6d} In the case of the preorganized host **1a** even an increase of the T₁ values of the flanking methoxy carbons is observed upon complexation, which means that the mobilities of these methoxy groups increase. This must be due to the partial release of conformational strain in host **1a** upon complexation. The conformational strain is caused by the strong electrostatic repulsion between the oxygen lone pairs. This is a definite proof that also in solution the hemispherands are far more preorganized than the simple crown ethers.

Another interesting fact is the decrease in preorganization of the flanking methoxy groups going from host **1a** to **1b**, in agreement with the crystal structure data.

For the hosts with both central and flanking methoxy groups the T₁ value of the central OCH₃ is always smaller than the one for the flanking OCH₃ groups. Apparently, the central methoxy group is less mobile than the flanking methoxy groups. This result is confirmed by the molecular mechanics calculations on host **1a**. For this host we used the dihedral driver option of the MMP2 program in order to systematically rotate around the C–O and the O–Ar bonds and optimize the rest of the structure. It appeared that the minima in the potential energy surface as a function of the two dihedrals were much steeper for the central than for the flanking methoxy groups.

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Table VII. Crystal Data and Data Collection Parameters

	1a-CH ₂ (CN) ₂	1b-CH ₂ (CN) ₂	2-CH ₂ (CN) ₂	4	4-CH ₂ (CN) ₂
formula	C ₃₇ H ₄₈ N ₂ O ₇ ^a	C ₃₅ H ₄₂ N ₂ O ₇	C ₃₆ H ₃₇ N ₃ O ₅	C ₃₃ H ₃₅ N ₃ O ₅	C ₃₆ H ₃₇ N ₃ O ₅
fw	632.80	602.73	591.71	525.65	591.71
lattice type	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	C2/m	P2 ₁ /n	P2 ₁ /c	P2 ₁ /c	C2/c
T, K	150	194	148	293	146
cell dimensions					
a, Å	19.431 (5)	11.285 (4)	17.292 (1)	12.589 (5)	27.648 (10)
b, Å	14.925 (5)	14.056 (4)	9.180 (1)	14.032 (6)	12.255 (3)
c, Å	13.798 (2)	20.798 (6)	21.191 (2)	17.213 (4)	19.067 (5)
β, deg	125.30 (1)	92.23 (2)	108.32 (1)	107.00 (4)	100.64 (2)
V, Å ³	3266 (3)	3297 (3)	3193 (1)	2908 (4)	6349 (6)
Z	4	4	4	4	8
D _c , g·cm ⁻³	1.29	1.21	1.23	1.20	1.24
F(000)	1360	1288	1256	1120	2514
μ, mm ⁻¹	0.08	0.08	0.08	0.07	0.08
θ range, deg	3–25	3–22.5	3–25	3–25	3–25
no. of unique reflections					
measd	2993	4281	5615	5106	5563
obsd	1882	1918	3722	2983	3029
no. of variables	320	406	573	460	398
R, %	4.0	5.0	3.6	3.4	7.3
R _w , %	4.3	7.7	4.7	4.9	9.4
weighting factor p	0.03	0.08	0.05	0.07	0.08
extinction g (×10 ⁻⁷)	6.3 (10)	0.4 (10)	3.8 (4)	6.3 (7)	7.6 (8)

^a Contains a diethyl ether solvent molecule, disordered around the twofold axis; occupancy refined to 0.60.

Conformational Flexibility of the Free Hosts. Since some of the free hemispherands show a tendency to fill part of their cavity with a converging methyl group (1b and 2), we decided to study this self-complexation phenomenon using molecular mechanics. In Table IV the calculated conformations of hosts 1a, 1b, and 2 with both converging and diverging methoxy groups are given. In general, the electrostatic contribution to the steric energy is decreased by a converging position of a methoxy group, but the torsion and bonding terms become mostly less favorable.

The conformations that are found in the complexed hosts possess a large dipole contribution to the steric energy. In the case of complexation with a guest, the electrostatic repulsion will be reduced and the total steric energy will be much more favorable. This is most clearly observed for hosts 1a and 2: if the dipole term would be halved the "complexed" conformation would become the lowest in energy (see Table IV). For the 21-membered ligand 1b the situation is more complicated. Here the steric energy of the conformation of the complexed ligand seems to be high in comparison to the conformation of the free host. The conformations with converging methoxy groups are energetically relatively favorable in this rather flexible ligand due to the favorable bonding and torsion terms. In the malononitrile complex the +d-d+d conformation remains relatively high in energy and therefore one should not expect a thermodynamically very stable complex. This is in full agreement with the experimental data (vide infra).

Conclusions

In this contribution both experimental solid-state and solution data together with data from calculations on isolated molecules result in a rather detailed picture of the free and complexed hemispherands. In most cases the results from the various techniques and methods agree very well.

Hemispherands form thermodynamically relatively stable complexes with malononitrile molecules. In the complexes the malononitrile is H bonded to the heteroatoms of the hemispherands. The rigidity of the (functionalized) teranisyl moieties is responsible for the preorganization of the host prior to complexation. Although hemispherands may not be the ideal receptor molecules for malononitrile, the reduced conformational flexibility of these hosts in comparison to crown ethers is favorable for the complexation of neutral molecules.

We are now extending our studies toward the combination of rigid (teranisyl) moieties with several calixarenes. In the resulting compounds, the so-called calixaspherands, a cavity in which a high

electrostatic repulsion is present is in close proximity to a larger hydrophobic cavity. Such compounds could act as excellent hosts for both charged and uncharged species.

Experimental Section

¹H NMR and ¹³C NMR spectra were recorded on a Bruker WP-80 apparatus equipped with a B-VT-1000 temperature accessory and an N.M.C. 1280 spectrometer, respectively, with Me₄Si as an internal standard. Malononitrile was recrystallized from CHCl₃ before use. CDCl₃ was Merck 99 atom % and C₆D₆ was Janssen Chimica 99 atom %. Elemental analyses were carried out in the Laboratory of Analytical Chemistry under the supervision of Mr. W. Lengton.

Materials. Hemispherands 1a,^{10a} 1b,^{10b} 2,^{10c} 3,^{10d} and 4^{10d} were prepared by known methods.

Crystalline Compounds. The crystals of the CH₂(CN)₂ complexes for the X-ray structure determinations were prepared by slow evaporation of the solvent of hemispherand/malononitrile solutions in diethyl ether. ¹H NMR spectra were recorded on solutions of the hemispherand-malononitrile (1:1) complexes.

1a-CH₂(CN)₂: ¹H NMR δ 7.25 (s, 2 H, ArH), 7.05 (s, 4 H, ArH), 4.90 (AB, J = 11.7 Hz, 2 H, ArCH₂), 4.29 (AB, J = 11.7 Hz, 2 H, ArCH₂), 3.60–3.35 (m, 8 H, OCH₂CH₂O), 3.42 (s, 6 H, OCH₃), 4.20 (s, 2 H, CH₂(CN)₂), 2.49 (s, 3 H, OCH₃), 2.45 (s, 3 H, CH₃), 2.32 (s, 6 H, CH₃). Anal. Calcd for C₃₀H₃₆O₆·CH₂(CN)₂·0.6O (CH₂CH₃)₂: C, 70.49; H, 7.35; N, 4.64. Found: C, 70.71; H, 7.14; N, 4.07.

1b-CH₂(CN)₂: ¹H NMR δ 7.14 (s, 2 H, ArH), 7.08 (s, 4 H, ArH), 4.84 (AB, J = 10.7 Hz, 2 H, ArCH₂), 4.21 (AB, J = 10.7 Hz, 2 H, ArCH₂), 3.60 (s, 6 H, OCH₃), 3.6 (s, 2 H, CH₂(CN)₂), 3.55–3.17 (m, 12 H, OCH₂CH₂O), 2.87 (s, 3 H, OCH₃), 2.39 (s, 3 H, CH₃), 2.32 (s, 6 H, CH₃). Anal. Calcd for C₃₅H₄₂N₂O₇: C, 69.74; H, 7.02; N, 4.65. Found: C, 69.52; H, 7.03; N, 4.49.

2a-CH₂(CN)₂: ¹H NMR δ 7.85–7.46 (m, 5 H, C₆H₅), 7.70 (s, 2 H, pyridine H), 7.21 (d, 2 H, ArH), 7.07 (d, 2 H, ArH), 4.55 (s, 4 H, ArCH₂), 3.78 (s, 2 H, CH₂(CN)₂), 3.52 (s, 14 H, OCH₃ and OCH₂CH₂O), 2.33 (s, 6 H, CH₃). Anal. Calcd for C₃₆H₃₇N₃O₅: C, 73.08; H, 6.30; N, 7.10. Found: C, 73.24; H, 6.54; N, 7.06.

3-CH₂(CN)₂: ¹H NMR δ 7.03 (s, 2 H, ArH), 6.96 (s, 2 H, ArH), 4.44 (s, 4 H, ArCH₂), 3.70 (s, 6 H, OCH₃), 3.51 (s, 2 H, CH₂(CN)₂), 3.36 (bs, 8 H, OCH₂CH₂O), 2.97 (q, J = 6.5 Hz, 1 H, pyran H), 2.28 (s, 6 H, ArCH₃), 1.77 (s, 6 H, pyran CH₃), 1.31 (d, J = 6.5 Hz, 3 H, pyran CH₃). Suitable crystals for X-ray and elemental analyses could not be obtained.

4-CH₂(CN)₂: ¹H NMR δ 7.61 (m, 1 H, pyridine H), 7.26–7.06 (m, 8 H, ArH and pyridine H), 5.13 (AB, J = 11.7 Hz, 2 H, ArCH₂), 4.49 (AB, J = 11.7 Hz, 2 H, ArCH₂), 4.54 (AB, J = 14.0 Hz, 2 H, pyridine CH₂), 4.32 (AB, J = 14.0 Hz, 2 H, pyridine CH₂), 3.65 (s, 2 H, CH₂(CN)₂), 3.11 (s, 6 H, OCH₃), 2.65 (s, 3 H, center OCH₃), 2.40 (s, 3 H, center CH₃), 2.34 (s, 6 H, CH₃). Anal. Calcd for C₃₃H₃₅O₃N·1.3CH₂(CN)₂: C, 72.47; H, 6.20; N, 8.24. Found: C, 72.48; H, 6.32; N, 8.14.

Determination of Association Constants. The determination of the association constants was carried out at four temperatures in the range 240–320 K using nine samples with varying host/guest ratios. The sample-dependent chemical shift of malononitrile was used to iteratively calculate the association constant by the method of de Boer et al.⁷

X-ray Crystallography. X-ray diffraction measurements were performed on a Philips PW1100 or an Enraf-Nonius CAD4 diffractometer, both using graphite-monochromated Mo K α radiation. Crystal data and data collection parameters are in Table VII. Lattice parameters were determined by least-squares from 20 to 25 centered reflections. Intensities were measured in the $\omega/2\theta$ scan mode and corrected for the decay of three control reflections, measured every hour, and for Lorentz-polarization, but not for absorption.

The structures were solved by direct methods²⁹ and refined with full-matrix least-squares. Reflections with $F_o^2 > 3\sigma(F_o^2)$ were considered to be observed and were included in the refinement (on F). Weights were calculated as $w = 4F_o^2/\sigma^2(F_o^2)$; $\sigma^2(F_o^2) = \sigma^2(I) + (pF_o^2)^2$, with $\sigma(I)$ based on counting statistics and p an instability factor obtained from plots of F_o vs weighted error. The malononitrile hydrogens were located on difference Fourier maps and included in the refinement. Due to disorder of methyl groups in some of the structures, not all hemispherand hydrogens could be located. Depending on data quality and data/parameter ratio these hydrogens were included in the refinement or put in calculated positions (C–H distance 0.96 Å) and treated as riding on their parent C atoms ($B_{iso}(H) = 1.2B_{eq}(C)$). The structure of **1a**·CH₂(CN)₂ contains a diethyl ether solvent molecule, which is disordered around a twofold axis; no hydrogens were taken into account. Details concerning the treatment of hydrogens and positional disorder are available as supplementary material.

Parameters refined were the overall scale factor, isotropic extinction parameter g (correction of F_c with $(1 + gI_c)^{-1}$), positional and anisotropic thermal parameters for non-H atoms, positional and isotropic thermal parameters for H atoms (if included), and occupancy factors for positionally disordered atoms. Refinement converged with a shift/error ratio less than unity for all variables, except occasionally for disordered atoms. Final difference Fourier maps showed no significant features. All calculations were done by using SDP.³⁰

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T_1 Measurements. The T_1 values were determined by inversion-recovery methods. The experimental details were published previously.¹⁷ For the determinations concerning the complexes a fivefold excess of malononitrile was added to make sure that more than 99% of the host was in its complexed form. The concentration of the host varied between 0.05 and 0.1 M.

Molecular Mechanics. Calculations were carried out with Allinger's MMP2 program³¹ (based on QCPE programs 395 and 400) as incorporated in the CHEMX suite.²⁰ All parameters were standard. The error in the relative steric energies is assumed to be less than 1 kcal/mol. For ligand **1a** the calculations were also carried out with the parameters belonging to the AMBER force field.³² The same order and approximately the same differences for the steric energies of the various conformations were obtained.

Starting conformations for the energy minimizations were obtained by both molecular graphics methods and X-ray coordinates. In order to scan the conformational space the dihedral driver³³ from the MMP2 program was used for the central and flanking methoxy groups of host **1a**.

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Supplementary Material Available: Tables of coordinates and anisotropic thermal parameters of non-H atoms, coordinates and isotropic thermal parameters of H atoms, bond distances and angles, and selected torsion angles for the five crystal structures (25 pages). Ordering information is given on any current masthead page.

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Kinetics and Deuterium Kinetic Isotope Effects for the Thermal [1,7] Sigmatropic Rearrangements of *cis,cis*-1,3,5-Octatriene

John E. Baldwin* and V. Prakash Reddy

Contribution from the Department of Chemistry, Syracuse University, Syracuse, New York 13244. Received June 8, 1987

Abstract: Thermal isomerizations of *cis,cis*-1,3,5-octatriene at 60–111 °C occur with activation parameters $\log A = 9.1$ and $E_a = 21.3$ (to *cis,cis,cis*-2,4,6-octatriene) and $E_a = 20.2$ kcal mol⁻¹ (to *cis,cis,trans*-2,4,6-octatriene). Primary deuterium kinetic isotope effects for these [1,7] sigmatropic shifts are found to be 6.4–7.7 and not markedly temperature dependent, indicative of a linear or nearly linear C7–H–C1 geometry in the transition-state structure.

Thermal [1,7] sigmatropic migrations of hydrogen have been well recognized and theoretically codified for more than 20 years.¹ From the pioneering experimental studies on compounds related to calciferol² to the recent demonstration of antarafacial stereo-

chemistry across the heptatrienyl unit for the [1,7] hydrogen shifts shown by *cis*-isotachysterol analogues,³ investigations have typically been concerned with rearrangements shown by comparatively large molecules. Quantitative kinetic and stereochemical work on

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