Two Chiral [1.1.1]Orthocyclophane Units Bridged by Three Biacetylene Units as a Host Which Binds Medium-Sized Organic Guests[1,2]

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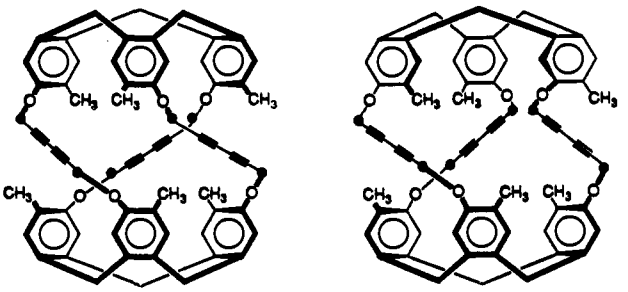
Abstract: A new chiral system, (±)-**1**, has been designed, synthesized, and found to bind the following molecules at −20 °C in $(CCl_3)_2CO$ with $-\Delta G°$ values (kcal mol^{-1}) as follows: $CHCl_3$, 5.7; $(CH_3)_3COH$, 4.9; cubane, 4.2; CH_2Cl_2, 4.8; propylene oxide, 4.4. Hosts (±)-**1** and *meso*-**1** were synthesized by a route possessing two key reactions. In the first, 3 mol of



(±)-**1** *meso*-**1**

4-bromo-3-methoxybenzyl alcohol (**2**) condensed (P_2O_5, Et_2O) to give the crown form of [1.1.1]orthocyclophane (**3**) (40%), which by conventional reactions was converted to the tris(propargyl ether) **6** (62% overall). Oxidative shell closure with $Cu(OAc)_2$, pyridine, and O_2 produced (±)-**1** (4%) and *meso*-**1** (2%) in which two rigid [1.1.1]orthocyclophane units were coupled through three $OCH_2C{\equiv}CC{\equiv}CCH_2O$ bridging groups. The crystal structures of the two hosts were determined. That of (±)-**1** possesses D_3 symmetry in which one [1.1.1]orthocyclophane unit is rotated with respect to the other about its C_3 axis by 120° so that the bridging units lie along the rims of the saucer-shaped capping units augmenting their depth, providing rim-to-rim hydrogen-to-oxygen contacts and closing the portals connecting the inner and outer phases. In the crystal structure of *meso*-**1**, a similar rotation was only 60°, and the two [1.1.1]orthocyclophane units do not have a common axis. The rims of the two substituted [1.1.1]orthocyclophane units in *meso*-**1** do not possess as complementary a relationship to one another as do those in its chiral isomer. The presence of guests in the cavity of (±)-**1** dissolved in $(CCl_3)_2CO$ as solvent was detected by the 2.50–4.24 ppm upfield shifts of the guests' proton signals in their ^1H NMR spectra. Benzene and $CHCl_2CHCl_2$ in the same solvent undergo bound-to-free guest exchange rapidly on the ^1H NMR time scale at 21 °C. At −20 °C, the activation free energy for decomplexation of (±)-**1**·C_6H_6 is ≈12 kcal mol^{-1}. At 21 °C, K_a of association is on the order of 10^3 M^{-1}. The K_a value for (±)-**1** binding $CHCl_2CHCl_2$ at 21 °C is between 10 and 100 M^{-1}. Within limits, the cavity size appears adaptable by bridging-unit folding to accommodate the steric requirements of the guest.

The origin of the problem addressed in this paper is found in the rigidly spherical, conceptual structure I (see Chart I), whose interior in CPK molecular models is large enough to incarcerate a large number of simple organic compounds. Notice that I is composed of 12 benzene rings joined to one another through 24 methylene groups by substitution in each case in the 1,2,4,5-positions. The shell of carcerand I is composed of eight [1.1.1]orthocyclophane (II) and of six [1.1.1.1]metacyclophane (III) units. The molecule is viewed in Ia down a C_3 axis of a near [1.1.1]orthocyclophane substructure, whereas in Ib the molecule is viewed down a C_4 axis of a near and artificialy expanded [1.1.1.1]metacyclophane unit.

A literature search revealed that simple syntheses of both types of units had been reported. Condensation of veratrole with CH_2O in acid produced cyclotriveratrylene (IV),[3] from which we prepared a series of cavitands.[4] Condensation of resorcinol with CH_3CHO (acid catalyst) produced compound V,[5] from whose analogues and derivatives we have prepared a variety of cavitands,[6] carcerands,[7] and hemicarcerands.[8]

These facts taken in sum encouraged us to design and synthesize (±)-**1** and *meso*-**1** and to study the binding properties of these hosts. The simple synthesis of IV also aided Collet et al. to design and synthesize the cryptophanes VI–VIII and to examine their binding properties.[9] The rigidity of the biacetylene unit coupled with the successful ring and shell closures by oxidative coupling of acetylene to give biacetylenes[10] led us to adopt $OCH_2C{\equiv}C$-

(1) Host–Guest Complexation 59.

(2) We warmly thank the USPHS for NIH Grant GM 12640.

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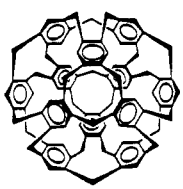
Chart I



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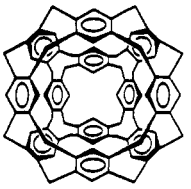
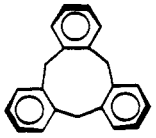


Ib



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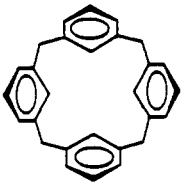

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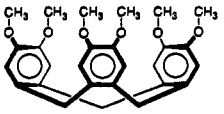
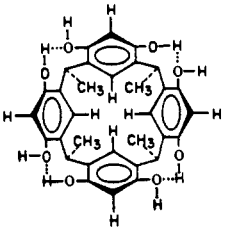
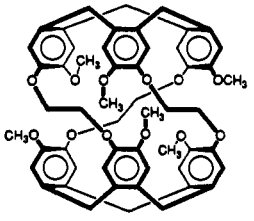


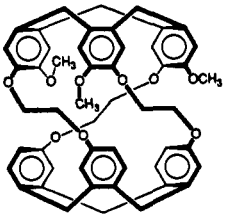
IV



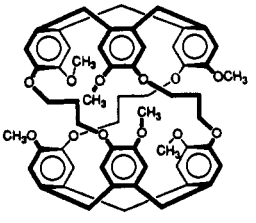
V



VI



VII



VIII

$C{\equiv}CCH_2O$ as our bridging units.

Molecular model examination of (±)-**1** suggested that the molecule possesses D_3 symmetry and an enforced cavity of variable size, depending on the conformations of the three $OCH_2C{\equiv}C$-$C{\equiv}CCH_2O$ bridging groups. At one extreme conformation, the axes of the three linear $CH_2C{\equiv}CC{\equiv}CCH_2$ groups run north and south if the [1.1.1]orthocyclophane units are designated as the polar caps of the globe-shaped molecule. This conformation is complementary to the tris(acetylacetonides) of many of the elements of the periodic table, which possess the shape of a three-bladed propeller with D_3 symmetry. In models, the three blades of such guests occupy the three portals in the hemicarceplex. At the other extreme conformation, the axes of the three $CH_2C{\equiv}CC{\equiv}CCH_2$ groups (in one enantiomer) run southeast to northwest (or vice versa) and pack along the rims of the northern and southern polar caps, thereby essentially closing the portals to create a spherical cavity roughly complementary to $CHCl_3$ or $(CH_3)_3COH$.

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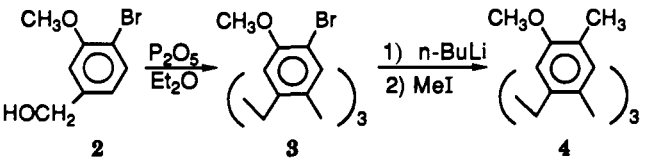
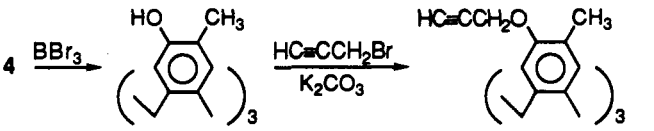
Results

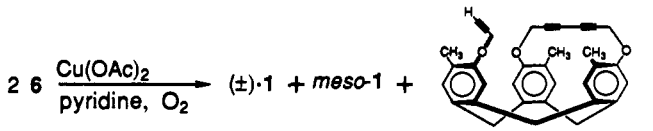
Syntheses. Our synthesis employed 4-bromo-3-methoxybenzyl alcohol[11] (**2**) as starting material, treatment of which with P_2O_5 and Et_2O gave the cyclotribenzylene compound **3** in 40% yield.[12]



2 **3** **4**



5 **6**



7

The bromine in **2** acts as a group that protects the 4-position from alkylation by benzyl cations during the conversion of **2** to **3**, on the one hand, and introduces synthetic flexibility into further reactions of **3**, on the other. In the synthesis leading to **1**, tribromide **3** was lithiated and the tris(organometallic) produced was quenched with methyl iodide to give **4** (83%). This material was demethylated with BBr_3 in CH_2Cl_2 to give tris(phenol) **5** (86%), which, when alkylated with propargyl bromide and K_2CO_3, produced the tris(acetylenic ether) **6** (88%).

The final shell closure by coupling of the two tris(acetylenic) half-shells was achieved with anhydrous cupric acetate in pyridine at 60 °C. The conditions of this reaction were crucial to the production of even the low yields of 4% (±)-**1** and 2% *meso*-**1** that were isolated. Under anaerobic (argon-degassed) conditions, no **1** was formed although excess copper(II) was employed. Conflicting reports as to the need for the presence of dioxygen have appeared.[10b,c] When run at 85 °C, the reaction gave a trace of intramolecularly coupled product, **7**, which was characterized only by its ^1H NMR and mass spectra. The highest and most reproducible yields of **1** were obtained when excess $Cu(OAc)_2$ was rapidly added to a 3 mM solution of **6** in oxygen-saturated pyridine at 60 °C. After 10 min at this temperature, the reaction mixture was quenched by pouring it into water. Although both (±)-**1** and *meso*-**1** were readily soluble in halogenated hydrocarbons, they exhibited different chromatographic behaviors. In TLC on silica gel with 1:1 CCl_4/CH_2Cl_2, (±)-**1** had an R_f value of 0.49, whereas *meso*-**1** gave $R_f = 0.29$.

Crystal Structure. The identities of the two diastereomers were determined by X-ray crystal structure studies. Appropriate

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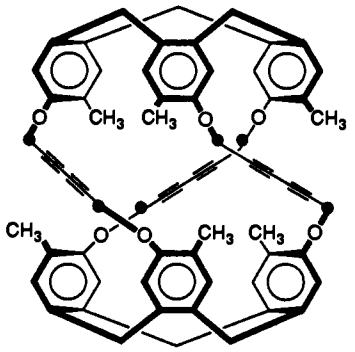
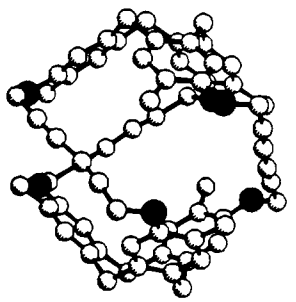
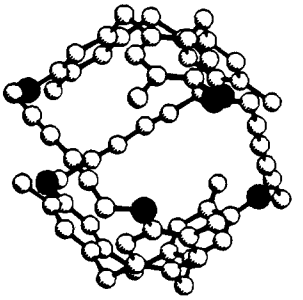
(12) (a) The synthesis of this compound was briefly mentioned in the literature: Cram, D. J. *Science* **1983**, *219*, 1177–1183. (b) Keipert, S. J. Ph.D. Thesis, University of California, Los Angeles, 1985. (c) An independent synthesis of this molecule by a similar procedure has been reported: Canceill, J.; Collet A. *Nouv. J. Chim.* **1986**, *10*, 17–23.

Chart II

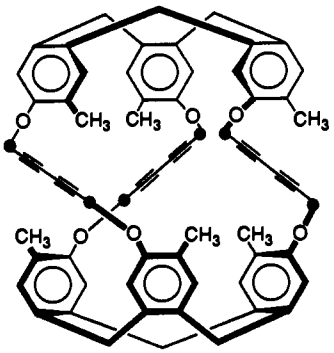
Line drawings **Stereoviews of crystal structures**

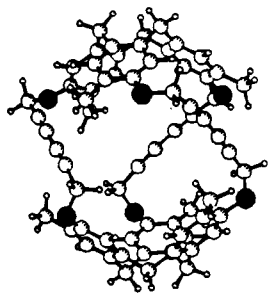


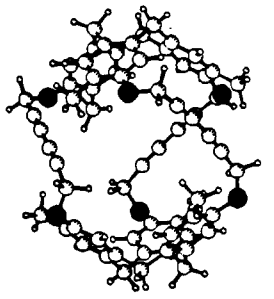




(±)-1 (top rotated 120°)







***meso*-1 (top rotated 60°)**

crystals of (±)-**1** were grown from CH_2Cl_2, and the X-ray structure was refined to $R = 0.126$. The X-ray structure of crystals of *meso*-**1** grown from $C_6H_{14}/CHCl_3/EtOH$ was refined to $R = 0.102$. In both crystal structures, solvents of crystallization were too disordered to locate well, although the interior of *meso*-**1** was clearly occupied by disordered $CHCl_3$ and that of (±)-**1** was occupied by disordered CH_2Cl_2. Chart II depicts stereoviews of the two crystal structures (oxygens are darkened, and disordered halocarbons are omitted) with line drawings of the isomers.

The most notable feature of the structures is the fact that the northern hemisphere is rotated around the polar axis relative to the southern hemisphere, but to extents which differ for the two diastereomers. For (±)-**1**, this rotation of 120° produces a compact spherical shape with the linear-bridging groups lying along the rims of the two polar caps. In CPK molecular models, this rotated conformation closes the three wide portals found in the nonrotated or "open" conformation and minimizes the internal volume of the hemicarcerand. The rotated or "closed" conformation appears strain-free and produces many more hydrogen-to-oxygen and hydrogen-to-triple bond contacts than the nonrotated conformation. The D_3 symmetry of (±)-**1** is beautifully visible in both the open and closed structures, the open structure possessing a sufficiently large cavity to accommodate molecules as large as $Fe(acac)_3$ (22 heavy atoms) and the closed structure being only large enough for nearly spherical molecules such as $CHCl_3$ (4 heavy atoms).

In contrast, in the crystal structure of *meso*-**1**, the rotation of the northern hemisphere relative to the southern is only 60°, which in CPK models is about as closed a conformation as can be adopted by this molecule. There is also a displacement of one hemisphere with respect to the other, so they do not share a common axis. The resulting cavity is approximately ellipsoidal in shape, and the shell surface contains many small holes in the torrid and temperate zones of the globe. Possibly, the conformational differences in (±)-**1** and *meso*-**1** are due to the inclusion of guests with different steric requirements, for example, CH_2Cl_2 for (±)-**1** and $CHCl_3$ for *meso*-**1**. This is unlikely, since CPK models of (±)-**1** and *meso*-**1** can both easily accommodate $CHCl_3$ models in their minimum-cavity conformations. More likely, the difference in minimum cavity sizes arises from the differences in symmetry properties of the isomers. When two like enantiomers are bridged as in (+)- or (−)-**1**, rotation of the northern hemisphere around the C_3 axis allows the three bridges to move concertedly in the same circular direction. When two opposite enantiomers are bridged as in *meso*-**1**, a similar rotation causes two bridges to move in the same circular direction but the third in the opposite direction, which leads to noncomplementary and therefore looser packing of the CH_3 and C≡CC≡C moieties. The resulting larger surface of the meso isomer compared to the (±) isomer is probably why the meso isomer elutes more slowly in TLC.

Characterization of the Hemicarceplexes. When (±)-**1** dissolved in CH_2Cl_2 was precipitated by addition of EtOH and the product dried at 95 °C under vacuum, complex (±)-**1**·CH_2Cl_2 was formed. Elemental analyses and an ^1H NMR spectrum of the material suggested that the guest was inside the host and the host:guest ratio was 1:1. Extended heating of this complex above 130 °C under high vacuum failed to liberate the guest but gradually led to chemical decomposition. When **1**·CH_2Cl_2 was dissolved in $C_6H_5CH_3$ and the solvent removed under vacuum, **1**·$C_6H_5CH_3$ (1:1) was obtained (^1H NMR). $C_6H_5CH_3$ could not be removed from this solid by heating it at 130 °C under high vacuum. Free carcerand (±)-**1** was finally obtained by digesting **1**·CH_2Cl_2 as a solid in refluxing CH_3CN and drying the resulting **1**·CH_3CN at 100 °C under vacuum for 24 h. The smaller CH_3CN molecules appear to replace the larger CH_2Cl_2 molecules (operation of the mass law) and then in turn have a sufficiently low activation energy to be thermally removed from the resulting solid. In contrast, when *meso*-**1** was precipitated from CH_2Cl_2 by the addition of excess CH_3OH, the included CH_2Cl_2 was removed from the solid precipitate by heating it for 100 h at only 60 °C. Two effects

are probably operative that explain this difference: (1) CH_2Cl_2 is more complementary to the interior of (±)-**1** than to that of *meso*-**1**; (2) the cavity openings of *meso*-**1** are larger than those of (±)-**1**.

The ^1H NMR spectra of (±)-**1** and *meso*-**1** in $CDCl_3$ at 25 °C were very similar. In CPK molecular models, rotations of the northern vs the southern hemispheres can occur either clockwise or counterclockwise to give different diastereomers. Cooling to −65 °C of the $CDCl_3$ solutions of (±)-**1** and *meso*-**1** produced no noticeable broadening or loss of symmetry of the ^1H NMR spectral peaks. Either such rotational conformers are rapidly equilibrating on the ^1H NMR time scale, or more likely, the conformations shown in Chart II for the isomers are much more stable than alternative conformations. The FAB MS of (±)-**1** gave m/e = 943 (M^+, 10%), while that of *meso*-**1** gave m/e = 943 (M^+, 100%).

Choice of Solvent for Complexation Studies. Since much of the interior of (±)-**1** is lined with its six phenyl groups, we anticipated that complexation of guests would be detectable by substantial upfield shifts of their protons. A solvent was needed which was itself free of protons, which would be too large to easily enter the cavity of (±)-**1**, and which would dissolve both host and guest. Hexachloroacetone was the solvent of choice. In CPK models, this solvent could enter the cavity of the host only in the latter's most extended form and could remain in the interior only when the rotation of the hemispheres with respect to one another was ≤60°, thus losing the rim-to-rim attractions presumed to stabilize the crystal structure of (±)-**1** (Chart II).

Accordingly, $(CCl_3)_2CO$ was purified by repeated recrystallizations from pentane at −78 °C followed by distillation under reduced pressure through a Vigreux column. This material exhibited only three peaks in its ^1H NMR spectrum (a coaxial insert containing $CDCl_3$ was used as reference), two broad signals at δ 4.2 and 1.2 and a sharp singlet at δ 2.3. Irradiation of the δ 4.2 peak causes the δ 1.2 peak to disappear, which suggests they are due to the hydroxyl protons of $(CCl_3)_2C(OH)_2$ and free water, respectively, which are exchanging slowly on the NMR time scale but rapidly with respect to their relaxation rates. Quantitative hydration of $(CCl_3)_2CO$ occurs only in the presence of bases such as $(CH_3)_2SO$,[13] which stabilize the *gem*-diol by hydrogen bonding. In the present study, addition of $(CH_3)_2SO$ at concentrations as low as 30 mM resulted in dramatic downfield shifts as great as 2.5 ppm of the δ 4.2 signal. Cooling of the solvent to −20 °C caused the δ 4.2 and 1.2 peaks to broaden and shift downfield to δ 4.4 and 1.4–1.8, respectively. The nature of the δ 2.3 signal is not clear. Its integral indicates a 0.5 mM concentration of protons. The peak neither shifted nor broadened in the presence of host, which indicated that the latter did not interfere with the binding properties in any way.

Diederich[14] et al. have demonstrated that the empirical solvent polarity parameter, E_T[15] (which correlates linearly with Kosower's Z values[16]), provides linear free energy relationships for the changes in free energies of binding of pyrene by a cyclophane host with changes in solvent. Since $(CCl_3)_2CO$ appears to react rapidly with Reichart's dye,[15] we used Kosower's dye (reaction is slower) to determine the Z value for $(CCl_3)_2CO$ of 76.9 kcal mol^{-1}. This value reflects the very polar nature of this solvent and indicates its polarity lies between that of 1-butanol (Z = 77.7 kcal mol^{-1}) and that of acetonitrile (Z = 71.3 kcal mol^{-1}). Thus $(CCl_3)_2CO$ as solvent should provide relatively good solvophobic driving forces for apolar guests.

Guests Strongly Bound by (±)-1. Free hemicarcerand (±)-**1** is soluble in $(CCl_3)_2CO$ to the extent of about 3 mg/mL, whereas for **1**·$CHCl_3$ the solubility is greater than 15 mg/mL. Since complexes in general are more soluble than free hosts, a quick solubility test provides an indication of whether binding occurs. Unambiguous evidence for binding was obtained from 500-MHz ^1H NMR spectral studies.

Table I. Chemical Shifts in ^1H NMR Spectra (500 MHz) at −20 °C in $(CCl_3)_2CO$ with (±)-**1** as Host

guest structure		δ free guest	δ bound guest	Δδ
		3.79	1.01	2.79
$CHCl_3$		7.20	2.96	4.24
$(CH_3)_3COH$	CH_3	1.08	−1.96	3.04
	OH	none[a]	−3.07	
CH_2Cl_2		5.20	1.21	3.99
$H_2C(O)CH—CH_3$	CH_3	1.10	−2.13	3.23
	CH_2	2.46	−0.42, −0.46	2.88, 2.92
		2.16	−1.61, −1.66	3.77, 3.82
	CH	2.71	−1.29	4.00
C_6H_6		7.12	≈4.6	≈2.5

[a] Hydroxyl protons rapidly exchange with solvent protons.

Table II. Complexation by (±)·**1** of Guests in $(CCl_3)_2CO$ at −20 °C

guest structure	K_a, M^{-1} (±50%)	$-\Delta G°_{253}$, kcal mol^{-1} (±0.4)
 [a]	4000	4.2
$CHCl_3$[a]	77000	5.7
$(CH_3)_3COH$[a]	16000	4.9
CH_2Cl_2[b]	13000	4.8
$H_2C(O)CH—CH_3$[b]	6000	4.4

[a] Values determined directly. [b] Values determined by competition study.

Solutions of free host and guest were prepared in $(CCl_3)_3CO$, and the spectra were run with a coaxial insert containing $CDCl_3$ for locking purposes. The chemical shifts are reported relative to external residual $CHCl_3$ set at δ 7.26. The three guests most studied were cubane, $(CH_3)_3COH$, and $CHCl_3$. Each ambient-temperature ^1H NMR spectrum provided two very broad sets of guest peaks, which represent the bound and free forms of the guest in slow exchange with one another on the ^1H NMR time scale. At −20 °C, these signals were sharp and easily integrated. For each guest, the proton signals of bound material were shifted upfield several parts per million compared to those of the free guest (see Table I). At room temperature, the signals of the free host are sharp. Shifts in the resonances of the host upon complexation were small (0–0.18 ppm), and at −20 °C, the "free-host" signals were much broader than those of the complexed host. The dynamic relationship between bound- and free-guest peaks were unambiguously demonstrated through saturation-transfer experiments.[18] Irradiation of the free-guest signals caused the bound·guest signals to disappear, indicating that the decomplexation rate is larger than the rate of relaxation of the guest protons. When the solutions were heated, the two kinds of guest signals coalesced to give T_c values of approximately 40, 50, and 60 °C for $CHCl_3$, cubane, and $(CH_3)_3COH$, respectively. The use of the coalescence temperature method for the two exchanging signals indicates that $\Delta G^{\ddagger}_{T_c}$ for decomplexation is ≈13–14 kcal mol^{-1} for these complexes.[18]

The association constants for (±)-**1** in $(CCl_3)_2CO$ complexing cubane, $CHCl_3$, and $(CH_3)_3COH$ were determined at −20 °C from the integrals of the free and complexed guests. The concentrations of host and guest were varied to keep the amount of complexed guest between 62 and 80%. The inherently large ^1H NMR integration errors (about ±10% at the lowest concentrations) indicate the association constants (K_a) of Table II to be accurate only to

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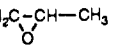
(17) Craik, D. J.; Higgins, K. A. *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 22, pp 72–76.

(18) Atta-ur-Rahman. *Nuclear Magnetic Resonance*; Springer-Verlag: New York, 1986; pp 131–133.

Table III. Complexation by (±)-**1** of Guests in $(CCl_3)_2CO$ at −20 °C (Competition Experiments)

guest G	guest G′	K_a/K_a' obsd	K_a/K_a' calcd[a]	K_a, M^{-1} calcd[b]
$CHCl_3$	$(CH_3)_3COH$	3.5	4.8	
$CHCl_3$		21	19	
$(CH_3)_3COH$		5.4	4	
CH_2Cl_2		3.2		13 000
	$CHCl_3$	0.077		6 000

[a] Ratio determined from data in Table II. [b] Value determined from K_a' in Table II.

±50% and the $-\Delta G°_{253}$ values to ±0.4 kcal mol^{-1}. Attempts to work at higher dilution to achieve higher accuracy were frustrated by unsolved problems associated with obtaining purer $(CCl_3)_2CO$. The narrow temperature range within which sharp signals could be observed ($(CCl_3)_2CO$ freezes at −23 °C) prohibited determination of the entropic and enthalpic components of the binding free energy.

Experiments were conducted in which two different guests (G and G′) competed for the same host, H ((±)-**1**). Such an approach provides ratios of association constants (K_a/K_a') and has the advantages that the absolute concentrations of neither host nor guest need to be known and that higher concentrations of guests can be employed. Equation 1 relates the ratio K_a/K_a' to the

$$\frac{K_a}{K_a'} = \frac{[HG][G']}{[HG'][G]} = \frac{(G_b)(G_f')}{(G_b')(G_f)} \quad (1)$$

measurable integrals of the first free guest (G_f), the first bound guest (G_b), the second free guest (G_f'), and the second bound guest (G_b'). As an example, $CHCl_3$ was found to bind (±)-**1**, 3.5 times more strongly than $(CH_3)_3COH$, which compares reasonably well with the ratio of association constants of 4.8 obtained by direct measurement.

The association constants for CH_2Cl_2 and propylene oxide were measured by competition studies. Both guests are somewhat smaller in cross section than the previous three, and their signals were still slightly broadened at −20 °C, indicating that the barrier to decomplexation is lower. When pitted against cubane, CH_2Cl_2 was the more strongly bound guest by a factor of 3.2. Table III records the K_a and free energy values obtained by competition experiments.

An interesting aspect of the complexation of propylene oxide by (±)-**1** is that both host and guest are chiral and two diastereomeric complexes should be formed when they are mixed. Each diastereomeric complex should have its own ^1H NMR spectrum, and by integration of their peaks, their relative concentrations might be determined. The spectrum of a mixture of $(CCl_3)_2CO$ 3 mM in (±)-**1** and 7 mM in (±)-propylene oxide was recorded at −20 °C. Under these conditions, the host is fully complexed. The bound-guest signals were all shifted upfield of δ 0, and saturation-transfer experiments revealed their corresponding "unbound" signals (Table I).[17] The somewhat broadened signals due to the bound-methyl and -methine signals prevented differentiation between the diastereomeric complexes (all coupling information in both bound- and free-guest signals was lost due to the dynamics of this system). The signals of the bound-methylene protons were both doubled. The "free" peak at δ 2.46 becomes two peaks at δ −0.42 and −0.46 upon complexation. The "free" peak at δ 2.16 becomes two peaks at δ −1.61 and −1.66. This corresponds to differences of 22.0 and 25.0 Hz, respectively, for the chemical shifts of the methylene protons in the two diastereomeric complexes. Integration of these signals revealed that the two diastereomeric complexes at equilibrium were present in equal concentrations within experimental error. This is hardly surprising. Model examination of **1**·propylene oxide indicates that the guest is only very loosely held in the cavity, even in its most compact conformation.

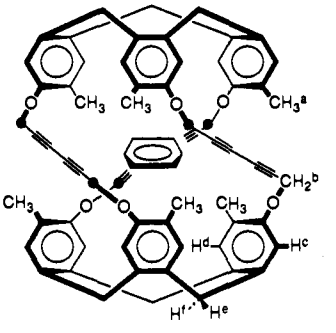
Table IV. Chemical Shifts of (±)·**1** in the 500-MHz ^1H NMR Spectrum of (±)-**1**·C_6H_6 in $(CCl_3)_2CO$ at 21 °C

host protons[a]	δ (±)-**1**	δ (±)-**1**·C_6H_6	Δδ
CH_3^a	1.91	2.04	+0.13
CH_2^b	4.57, 4.46	4.71, 4.50	+0.14, +0.4
Ar H^c	6.48	6.30	−0.18
Ar H^d	6.80	6.61	−0.19
Ar_2 CH^e	3.24	3.00	−0.24
Ar_2 CH^f	4.40	4.10	−0.30

[a] Protons are labeled in structure **8**.

Guests That Rapidly Exchange with (±)-1·G. Benzene and $CHCl_2CHCl_2$ are examples of guests which undergo exchange with (±)-**1**·G rapidly on the ^1H NMR time scale in $(CCl_3)_2CO$ at available temperatures. A solution 2.1 mM in (±)-**1** and 1.5 mM in C_6H_6 at 21 °C provides a 500-MHz ^1H NMR spectrum with a broad benzene proton signal centered at δ 5.6. This represents an exchange-averaged resonance which is moved upfield from its unbound position of δ 7.07. When the sample was heated, the guest signal sharpened and moved downfield (e.g., to δ 6.18 at 61 °C), indicating that complexation is enthalpically favored and entropically disfavored. Cooling the sample caused the signal to further broaden until it reached T_c at ~5 °C. Spectra taken with excess C_6H_6 at −20 °C showed the beginning of very broad peaks at δ 7.12 and 4.6, which represent the free and bound C_6H_6 in slow exchange on the ^1H NMR time scale. These values were used to estimate that $\Delta G^{\ddagger}_{278} \approx 12$ kcal mol^{-1} for decomplexation.[18]

Interesting and informative shifts in the host's ^1H NMR signals that were due to the guest were observed in the spectrum of (±)-**1**·C_6H_6. Guest saturation of host was readily achieved by using a $(CCl_3)_2CO$ solution containing several equivalents of C_6H_6 per equivalent of (±)-**1**. All of the protons positioned near the equator of the host (CH_3^a and $CH_2^bC{\equiv}C$) are shifted somewhat downfield relative to those of the free host, whereas those of the temperate and polar regions (Ar H^c, Ar H^d and Ar_2 CH^e, Ar_2 CH^f) are shifted upfield (Table IV). These shifts strongly suggest that the bound C_6H_6 lies in a plane perpendicular to the C_3 axis of the host, as formulated in **8**. Protons above or below the plane



8

of the bound C_6H_6 lie in the shielding cone, whereas those close to the plane are deshielded. The ^1H NMR spectrum of a solution of $(CCl_3)_2CO$ 2.1 mM in (±)-**1** and 1.5 mM in C_6H_6 at 21 °C gave a doublet at δ 3.11 for H^e (free (±)-**1** gives δ 3.24 and (±)-**1**·C_6H_6 gives δ 3.00), which indicates the host is about 54% bound. Thus the association constant is approximately 10^3 M^{-1} at 21 °C. Similar studies with toluene as a potential guest failed to produce evidence of complexation, although dissolution of (±)-**1** in toluene followed by solvent evaporation produces (±)-**1**·$nC_6H_5CH_3$, which is stable to 130 °C under high vacuum.

Dynamic behavior was exhibited by (±)-**1** binding $CHCl_2CHCl_2$ in $(CCl_3)_2CO$. At 25 °C, the 500-MHz ^1H NMR spectrum of the solution of host and guest gave its guest signal as a broad, averaged peak shifted upfield from its unbound position at δ 5.80. At lower temperatures, the signal broadened until coalescence

occurred at approximately −5 °C. The slow-exchange spectrum was not accessible due to the solvent freezing point of −23 °C. A rough estimate of the K_a value at 21 °C was made by following the small shifts of Ar H^c of the host (see host of **8**) when guest was added.

To an approximately 4 mM solution of host was added $CHCl_2CHCl_2$ in increments whose amounts were measured by integrations. The δ of H^c (see **8**) at 6.48 ppm in the absence of guest was plotted (nine points) against the equivalents of guest present. Saturation binding did not occur until >100 equiv of guest/equiv of host had been added, at which δ at H^c had moved to 6.40 ppm. Upon the addition of roughly 4 equiv, 50% of the maximum shift had occurred, which indicates K_a is on the order of 10–100 M^{-1} at 21 °C.

Nonbinding Properties of *meso*-1. The ^1H NMR spectrum of $(CCl_3)_2CO$, 5 mM in both *meso*-**1** and cubane, showed no signs of complexation from −20 to +40 °C. Host and guest signals were unchanged from those of the separate components. Addition of even ≈50 equiv of cubane did not affect the chemical shifts of the host peaks. Similarly, the addition of ≈50 equiv of CH_2Cl_2 to a 1.3 mM solution of *meso*-**1** produced no detectable shifts in the host's spectrum.

Discussion

The results demonstrate that apolar guests of appropriate size and shape are readily and strongly complexed by (±)-**1** but not by *meso*-**1** in $(CCl_3)_2CO$ as solvent. The question arises as to whether this solvent is complexed by either of these two hosts. Molecular model (CPK) examination indicates that complexes (±)-**1**·$(CCl_3)_2CO$ and *meso*-**1**·$(CCl_3)_2CO$ can be made only when the three bridging $CH_2C{\equiv}CC{\equiv}CCH_2$ groups are in their most extended form, one in which their three axes are close to being parallel to one another and to the polar axes of the two hosts. When solutions of "free (±)-**1**" are dissolved in $(CCl_3)_2CO$, the ^1H NMR host signals broaden when the solution is cooled to −20 °C, possibly indicating the onset of coalescence between fast and slow guest exchange on the spectral time scale. Evidence against a fully desolvated cavity at 25 °C is found in the sharpness of the ^1H NMR signals of the host at this temperature. Results of research with other aryl-lined cavities that are known to be fully desolvated show broadening effects due to the binding of small amounts of dissolved paramagnetic dioxygen.[8]

The results demonstrate that (±)-**1** binds appropriately sized and shaped guests with free energies at 253 K that range from −4.2 for cubane to −5.7 kcal mol^{-1} for $CHCl_3$ (Table II). Molecular model examination of (±)-**1**·G provides a good correlation between the binding free energies and the complementarity of the guest and host in its *most closed conformation*, one which maximizes rim-to-rim contacts, minimizes cavity volume, and provides a near-spherical cavity, as in the crystal structure of (±)-**1**·G. The guests bind (±)-**1** at −20 °C in the following decreasing order: $CHCl_3$ > $(CH_3)_3COH$ > CH_2Cl_2 > propylene oxide > cubane. At 21 °C, C_6H_6 is more strongly bound than $CHCl_2CHCl_2$. Chloroform in models of (±)-**1**·$CHCl_3$ provides the largest common surface between host and guest without any rotational constraint of host vs guest, unlike the model of (±)-**1**·$(CH_3)_3COH$, whose OH group fits better in the equatorial rather than in the polar caps of the host. Dichloromethane in models of (±)-**1**·CH_2Cl_2 "rattles" when shaken, and thus the cavity is a mixture of vacuum and guest. Propylene oxide in its (±) complex is presumably a little misshapen for the cavity except when the best plane of the guest corresponds to the best equatorial plane of the host. Such an arrangement is compatible with the Δδ values of Table I, which decrease on average in the order CH > CH_2 > CH_3, which measures their tendency to occupy the polar regions of the cavity. No CPK models for cubane are available, but those of cyclobutadiene fit into the closed form of models of (±)-**1** in such a way which suggests that, in order for cubane to fit into the cavity, the cavity would have to elongate slightly around its C_3 axis, disengaging some of the rim-to-rim close contacts. While models of C_6H_6 fit into the cavity of models of (±)-**1** in its closed form, this guest has relatively few close contacts in the polar regions of the host. For models of $CHCl_2CHCl_2$ to fit into the cavity of models of (±)-**1**, the latter must elongate along its C_3 axis by more than is observed for models of (±)-**1**·cubane.

Table V. Rim-to-Rim Close Distances (van der Waals + 0.20 Å, or Less) in the Crystal Structure of ±·**1**·G Due to Twist

type	no.	type	no.	type	no.
O···HCH_2—	11	C···CH_3—	9	C···HCHO	2
O···CH_3—	5	C···H of Ar	22	O···O	1
C···HCH_2—	22	C···C of Ar	16[a]		

[a] 2.48 Å.

Molecular models of the above guests also fit into the much larger cavity of a model of *meso*-**1**, which is sterically unable to bring its rims together. Thus it seems likely that *meso*-**1** in its open (extended) form complexes the $(CCl_3)_2CO$ solvent molecules to the exclusion of smaller dissolved molecules whose volumes are too small to be complementary to the minimum size of *meso*-**1**. This interpretation attributes the strong binding of (±)-**1** and weak binding of *meso*-**1** to the rim-to-rim attractions in (±)-**1** and their absence in *meso*-**1**. In the host's crystal structure ((±)-**1**·G, guest disordered), there are a total of 88 atom-to-atom close distances (van der Waals + 0.20 Å, or less) created by the 120° twist around the polar axis of the northern relative to the southern hemisphere. Table V lists their numbers and types. Many of these must provide enthalpic attractive forces that act in concert with the usual host–guest dipole–dipole attractions, as well as with the entropic driving force of avoiding the collection of small volumes of empty space between solvent molecules and merging them to produce hollow hosts.[7,8]

Interesting comparisons can be made between the binding properties of (±)-**1**, in $(CCl_3)_2CO$ and those of Collet's host VIII dissolved in $CDCl_2CDCl_2$.[9e] Both (±)-**1** and VIII seem to be the most complementary to a guest the size and shape of $CHCl_3$, indicating their cavities possess similar dimensions. The number of atoms in each of the three $O(CH_2)_3O$ bridges connecting the two [1.1.1]orthocyclophane units in VIII is 5, whereas the number in (±)-**1** ($OCH_2C{\equiv}CC{\equiv}CCH_2O$) is 8. Unlike the five-atom bridges in VIII which are conformationally mobile, the enforced linearity of the $CH_2C{\equiv}CC{\equiv}CCH_2$ unit greatly reduces its conformational mobility. The crystal structure of VIII·$CHCl_3$ shows that its northern polar cap is rotated 60° with respect to the southern polar cap, which minimizes the dimensions of the cavity and maximizes its rim-to-rim interactions.[9e] The crystal structure of (±)-**1**·G likewise minimizes the dimensions of its cavity, but the rotation of its two caps with respect to one another is 120°. When the association constant of VIII binding $CHCl_3$ in $CDCl_2CDCl_2$ as solvent is calculated at −20 °C from its reported ΔH and ΔS values,[9e] a K_a = 4300 M^{-1} is obtained, which corresponds to $\Delta G°_{253}$ = −4.2 kcal mol^{-1}. This compares with K_a = 77 000 M^{-1} for (±)-**1** binding $CHCl_3$ in $(CCl_3)_2CO$ at −20 °C, or $\Delta G°_{253}$ = −5.7. Molecular models (CPK) of VIII in its extended conformations seem to be more complementary to $CDCl_2CDCl_2$ than does (±)-**1** in its open form to $(CCl_3)_2CO$. This may be the source of the difference between the two systems.

Benzene and $CHCl_2CHCl_2$ undergo more rapid guest exchange with (±)·**1**·G than the other guests examined. The slot-shaped cross section of benzene is more complementary to the roughly

slot-shaped portals of partially opened forms of (±)-**1** than are the cross sections of the more spherical guests. Thus the rates of complexation and decomplexation are expected to be faster for benzene than for $CHCl_3$, $(CH_3)_3COH$, or cubane. The fast rate of exchange with $CHCl_2CHCl_2$ is accounted for by the inability of the two rims to contact each other in models of (±)-**1**·$CHCl_2CHCl_2$, thus bringing the structure and free energy of the complex closer to those for the transition state for complexation–decomplexation.

Interestingly, the barriers to decomplexation are larger for complexes of VIII than for those of (±)-**1**. For example, $\Delta G^{\ddagger}_{300} \approx 17$ kcal mol^{-1} for VIII·$CHCl_3$,[19] whereas that for (±)-**1**·$CHCl_3$ is ≈13 kcal mol^{-1}. This may reflect the greater length and degree of folding of the $OCH_2C{\equiv}CC{\equiv}CCH_2O$ bridges in (±)-**1** vs those of the $O(CH_2)_3O$ bridges in VIII. Possibly, many of the rim-to-rim contacts are maintained in the transition state for complexation–decomplexation, only one of the three portals having to open to allow entrance or egress of guests. This presumption appears feasible in CPK models of (±)-**1** with $CHCl_3$ only half-incarcerated.

Summary

Two new diastereomerically related hosts (**1**) have been designed and synthesized, and their (±) and meso configurations have been assigned by crystal structure determinations. The crystal structure of (±)-**1** shows the molecule assumes a compact structure with a near-spherical cavity complementary to small molecules such as $CHCl_3$, $(CH_3)_3COH$, CH_2Cl_2, cubane, propylene oxide, and benzene. In $(CCl_3)_2CO$ as solvent, these molecules are bound by (±)-**1** with binding free energies that range from <4 to 5.7 kcal mol^{-1}. The decomplexation activation free energies for these complexes are in the 12–14 kcal mol^{-1} range. The crystal structure of *meso*-**1** possesses a considerably larger cavity which is ellipsoidal in shape. In $(CCl_3)_2CO$ as solvent, *meso*-**1** fails to complex the above guests, possibly because it binds solvent better than does (±)-**1**.

Experimental Section

General Procedures. All chemicals were reagent grade and were used as received unless otherwise specified. All reactions were conducted under an atmosphere of argon unless otherwise noted. Tetrahydrofuran was freshly distilled from sodium benzophenone ketal prior to use.

The ^{1}H NMR spectra were recorded on a Bruker AF-200 or AM-500 spectrometer at 200.1 or 500.1 MHz, respectively. All NMR spectra are referenced to tetramethylsilane as an internal standard at 0.00 ppm, unless otherwise noted. Electron impact mass spectra were recorded on a Kratos AE·1 Model MS·9 spectrometer. FAB mass spectra were determined on a ZAB SE instrument. All melting points were determined on a Thomas·Hoover apparatus and are uncorrected. Gravity chromatography was performed on E. Merck silica gel 60 (70–230 mesh). Silica thin·layer chromatography was done on E. Merck glass-backed plates (silica gel 60, F_{254}, 0.25 mm).

10,15-Dihydro-2,7,12-tribromo-3,8,13-trimethoxy-5*H*·tribenzo[*a*,*d*,·*g*]cyclononene (3). To a rapidly stirred mixture of 40 g of P_2O_5 suspended in 400 mL of dry ether was slowly added 20 g (92 mmol) of 4·bromo·3-methoxybenzyl alcohol (**2**).[11] The mixture was warmed to reflux temperature, the stirring was stopped, and the mixture was refluxed for 2 days. The ether was evaporated, the residue was triturated with CH_2Cl_2, and the extract was filtered through a bed of silica gel in a large, coarse-fritted glass funnel. The silica gel was rinsed with additional CH_2Cl_2 until the eluent was colorless. The CH_2Cl_2 was evaporated to the point where a saturated solution was obtained, and then the solution was poured into 2 L of ether. Fine white crystals formed on cooling to 0 °C overnight and were removed by filtration through a medium glass frit, rinsed with ether, and dried at 10^{-5} Torr. This gave 7.25 g of **3** (40%): mp 296 °C; ^{1}H NMR (500 MHz, $CDCl_3$; see **8** for proton labels) δ 7.50 (s, 3 H, Ar H^c), 6.84 (s, 3 H, Ar H$_b$^{d}), 4.64 (d, 3 H, Ar$_2$ CH$_2$^{f}, J = 14 Hz), 3.86 (s, 9 H, OCH_3), 3.57 (d, 3 H, Ar$_2$ CH$_2$^{e} H, J = 14 Hz); ^{13}C NMR (50 MHz, CD_2Cl_2) δ 155.3, 140.3, 134.7, 132.8, 113.8, 110.3, 56.8, 36.3; MS m/e 594, 596, 598, 600 (M^+ with 3 Br). Anal. Calcd for $C_{24}H_{21}Br_3$: C, 48.27; H, 3.54; Br, 40.10. Found: C, 48.42; H, 3.43; Br, 40.21.

(19) Calculated from the values $\Delta G^{\ddagger}_{300}$(complexation) = −13.3 kcal/mol and ΔG_{300} = −3.7 kcal/mol as reported in ref 9e.

5*H*-Tribenzo[*a*,*d*,*g*]cyclononene, 10,15-Dihydro-2,7,12-trimethyl-3,8,13-trimethoxy- (4). To 800 mL of dry THF under argon was added 4.2 g (7.0 mmol) of **3**. The mixture was gently warmed to dissolve the starting material and then cooled to −78 °C in a dry ice/acetone bath. Addition of 30 mmol of *n*-butyllithium (2.2 M in hexanes) caused the tris(aryllithiate) to form as a white precipitate. The mixture was stirred for 10 min, and then the reaction was quenched by the addition of 2.5 mL (40 mmol) of CH_3I. The cold bath was removed, and the mixture was allowed to warm to 25 °C, during which time the precipitate disappeared. The THF was evaporated under vacuum, and the residue was extracted with CH_2Cl_2 and water. The CH_2Cl_2 layer was dried over $MgSO_4$ and evaporated to dryness. Compound **4** was then isolated by silica gel chromatography (1:1 CH_2Cl_2/hexanes) and dried at 110 °C under vacuum. This gave 2.4 g (83%) of **4** as a white powder: mp 214–217 °C; ^{1}H NMR (500 MHz, $CDCl_3$; see **8** for proton labels) δ 2.11 (s, 9 H, Ar CH_3), 3.58 (d, 3 H, H^e, J = 13.6 Hz), 3.79 (s, 9 H, Ar OCH_3), 4.75 (d, 3 H, H^f, J = 13.6 Hz), 6.78 (s, 3 H, Ar H^c), 7.09 (s, 3 H, Ar H^d); MS (16 eV, 130 °C) m/e 402 (M^+, 100%). Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.55; H, 7.42.

5*H*-Tribenzo[*a*,*d*,*g*]cyclononene, 10,15-Dihydro-2,7,12-trimethyl-3,8,13-trihydroxy- (5). To a solution of 2.15 g (5.3 mmol) of **4** in 100 mL of CH_2Cl_2 was added 2 mL (21 mmol) of BBr_3. A gray precipitate immediately formed and gradually redissolved. The mixture was allowed to stir under argon at 25 °C for 3 h. The reaction was quenched by the gradual addition of excess (20 mL) CH_3OH. The solvent was evaporated under reduced pressure, and 100 mL of CH_3OH was added; subsequent evaporation under reduced pressure removed trimethyl borate as a methanol azeotrope. The resulting solid was dissolved in 100 mL of EtOAc, and 30 g of silica gel was added. The EtOAc was then removed in vacuo. The silica-gel·adsorbed sample was dry·loaded onto a 200·g silica gel column and eluted with 9:1 CH_2Cl_2/EtOAc. This gave 1.65 g of compound **5** (86%) as a white solid after drying at 110 °C under vacuum: dec >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6; see **8** for proton labels) δ 2.00 (s, 9 H, Ar CH_3), 3.34 (d, 3 H, H^e, J = 13.4 Hz), 4.58 (d, 3 H, H^f, J = 13.4 Hz), 6.73 (s, 3 H, Ar H^c), 6.95 (s, 3 H, Ar H^d); MS (16 eV, 200 °C) m/e 360 (M^+, 100%). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.97; H, 6.68.

5*H*-Tribenzo[*a*,*d*,*g*]cyclononene, 10,15-Dihydro-2,7,12-trimethyl-3,8,13-tris(2-propynyloxy)- (6). To a solution of 1.55 g (4.3 mmol) of **5** in 100 mL of $(CH_3)_2CO$ were added 3 g of K_2CO_3 (22 mmol) and 22 mmol of propargyl bromide (2.5 mL of 80% solution in toluene). This mixture was refluxed for 12 h. The $(CH_3)_2CO$ was evaporated under vacuum, and the residue was extracted with CH_2Cl_2 and water. The CH_2Cl_2 layer was dried with $MgSO_4$ and evaporated to dryness. Purification by silica gel chromatography (7:3 CH_2Cl_2/hexanes) and drying at 100 °C under vacuum gave 1.80 g (88%) of **6** as a white solid: mp 186–189 °C; ^{1}H NMR (500 MHz, $CDCl_3$; see **8** for proton labels) δ 2.11 (s, 9 H, Ar CH_3), 2.47 (t, 3 H, CCH, J = 2.4 Hz), 3.59 (d, 3 H, H^e, J = 13.6 Hz), 4.68 (m, 6 H, OCH_2), 4.75 (d, 3 H, H^f, J = 13.6 Hz), 6.93 (s, 3 H, Ar H^c), 7.14 (s, 3 H, Ar H^d); MS (16 eV, 125 °C) m/e 475 (M^+, 100%). Anal. Calcd for $C_{33}H_{30}O_3$: C, 83.52; H, 6.37. Found: C, 83.33; H, 6.25.

3,26-(Epoxy[2,4]hexadiynoxy)-6,9:29,32-dietheno-7,44:21,30-dimethano-18,22:41,45-dimetheno-22*H*,45*H*-dibenzo[*n*,*i*$_1$][1,8,22,29]tetraoxacyclodotetracontin, 12,13,14,15,35,36,37,38-Octadehydro-5,11,16,23,28,34,39,46-octahydro-2,19,25,42,49,61-hexamethyl- ((±)-1); 3,26-(Epoxy[2,4]hexadiynoxy)-6,9:29,32-dietheno-7,44:21,30-dimethano-18,22:41,45-dimetheno-22*H*,45*H*-dibenzo[*n*,*i*$_1$][1,8,22,29]tetraoxacyclodotetracontin, 12,13,14,15,35,36,37,38-Octadehydro-5,11,16,23,28,34,39,46-octahydro-2,19,25,42,49,61-hexamethyl- (*meso*-1). A vigorous stream of O_2 was bubbled through 600 mL of freshly distilled (from CaH_2) pyridine at 60 °C for 15 min. To this was added 15 g (83 mmol) of $Cu(OAc)_2$ (previously prepared by refluxing the monohydrate in acetic anhydride for 12 h, removing the solvent in vacuo, and drying at 100 °C under high vacuum). Gradually, 2.6 g (5.5 mmol) of **6** was added as a solid over 5 min. The mixture was stirred for an additional 5 min under an atmosphere of oxygen. The mixture was then poured hot into 2 L of water. The resulting precipitate was collected by filtration. Silica gel chromatography (1:1 CH_2Cl_2/CCl_4) provided (±)-**1**. Changing the eluent to 7:3 CH_2Cl_2/CCl_4 provided crude *meso*-**1**. Recrystallization of (±)-**1** from CH_2Cl_2/EtOH provided 135 mg (4%) of analytically pure (±)-**1**·$2CH_2Cl_2$ as X·ray-quality light yellow cubes. Dissolution of this material in CH_2Cl_2 followed by rapid precipitation by the addition of excess EtOH and drying at 95 °C (24 h) under high vacuum produced material which analyzed correctly for (±)-**1**·CH_2Cl_2. In both cases, the solvent molecules could not be driven from the solid with prolonged heating above 130 °C (the host appeared to slowly decompose at these temperatures). In order to obtain free (±)-**1**, the material was digested in refluxing CH_3CN for 48 h under argon. The insoluble host was collected by filtration and dried at 115 °C for 24 h

under high vacuum. This produced (±)-**1** which exhibited a very clear ^{1}H NMR spectrum (no CH_2Cl_2 present) but which analyzed 0.5% low in carbon. This material was used in the binding studies: dec >300 °C; ^{1}H NMR (500 MHz, $CDCl_3$; see **8** for proton labels) δ 2.19 (s, 18 H, Ar CH_3), 3.49 (d, 6 H, H^e, J = 13.6 Hz), 4.65 (d, 6 H, H^f, J = 13.5 Hz), 4.66 (d, 6 H, CH_2, J = 16.6 Hz), 4.83 (d, 6 H, CH_2, J = 16.6 Hz), 6.70 (s, 6 H, Ar H^c), 7.05 (s, 6 H, Ar H^d); MS (Xenon FAB, NOBA matrix) m/e 943 (M^+, 10%). Anal. Calcd for $C_{66}H_{54}O_6 \cdot 2CH_2Cl_2$: C, 73.38; H, 5.49. Found: C, 73.37; H, 5.24. Calcd for $C_{66}H_{54}O_6 \cdot CH_2Cl_2$: C, 78.28; H, 5.49. Found: C, 78.58; H, 5.43. Anal. Calcd for $C_{66}H_{54}O_6$: C, 84.05; H, 5.77. Found: C, 83.55; H, 5.61.

The crude *meso*-**1** was chromatographed (6.5:3.5 CH_2Cl_2/CCl_4) a second time, producing 45 mg (2%) of *meso*-**1** as a white powder. Recrystallization from $MeOH/CH_2Cl_2$ gave 32 mg of *meso*-**1** as thin, long crystals. X-ray-quality crystals were grown from $CHCl_3$/hexanes: dec >300 °C; ^{1}H NMR (500 MHz, $CDCl_3$; see **8** for proton labels) δ 2.17 (s, 18 H, Ar CH_3), 3.53 (d, 6 H, H^e, J = 13.7 Hz), 4.55 (d, 6 H, CH_2, J = 16.3 Hz), 4.67 (d, 6 H, H^f, J = 13.6 Hz), 4.79 (d, 6 H, CH_2, J = 16.3 Hz), 6.78 (s, 6 H, Ar H^c), 7.07 (s, 6 H, Ar H^d); MS (Xenon FAB, NOBA matrix) m/e 943 (M^+, 100%). Anal. Calcd for $C_{66}H_{54}O_6$: C, 84.05; H, 5.77. Found (sample dried 48 h under high vacuum, 55 °C): C, 83.54; H, 6.06.

Hexachloroacetone Purification. Reagent grade $(CCl_3)_2CO$ (70 mL, Aldrich Chemical Co.) was dissolved in 250 mL of pentane in a 500-mL flask equipped with a drying tube. This was cooled to −78 °C in a dry ice/acetone bath. The pentane was decanted from the resulting large white crystals. This process was repeated three more times. The recrystallized $(CCl_3)_2CO$ was passed through filter paper, and the residual pentane was removed in vacuo. The resulting liquid was distilled through a Vigreux column (~40 Torr, 110 °C) to produce 35 mL of $(CCl_3)_2CO$ of suitable purity for use in the binding studies. This solvent purified in this manner contains very little water and must be stored in a desiccator to prevent it from absorbing atmospheric moisture.

Complexation Studies. Solutions were prepared in volumetric glassware using solvent purified as indicated above. All studies were performed on a 500-MHz spectrometer. The temperature of the probe was calibrated using the differences in chemical shifts between the two peaks of methanol as a standard. A coaxial insert containing "100 atom %" $CDCl_3$ (Aldrich Chemical Co.) was employed for locking purposes. All chemical shifts in $(CCl_3)_2CO$ are reported relative to the external, residual $CHCl_3$ set to 7.26 ppm.

Crystal Structure Data. Compound (±)-**1** crystallizes from CH_2Cl_2/C_2H_5OH as colorless parallelepipeds in the orthorhombic system *Pbca*. Unit cell dimensions are as follows: a = 20.493 (3) Å, b = 26.341 (3) Å, c = 21.568 (3) Å, V = 11 643 Å^3, Z = 8. The crystal was examined on a modified Syntex P$\bar{1}$ diffractometer (Cu Kα radiation) at 25 °C. The structure was determined by direct methods. Refinement of 347 parameters (2034 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.126.

Compound *meso*-**1** crystallizes from $CHCl_3$/hexanes as colorless parallelepipeds in the triclinic system P$\bar{1}$. Unit cell dimensions are as follows: a = 11.767 (2) Å, b = 13.874 (2) Å, c = 20.069 (3) Å, α = 95.736 (5)°, β = 102.525 (5)°, γ = 111.157 (4)°, V = 2930 Å^3, Z = 2. The crystal was examined on a modified Syntex P$\bar{1}$ diffractometer (Cu Kα radiation) at 25 °C. The structure was determined by direct methods. Refinement of 367 + 77 parameters (2 blocks, 3848 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.102.

Further crystallographic details will be published elsewhere.

Cyclopropanation of Unactivated 1,3-Dienes by Fischer Carbene Complexes

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Abstract: Though Fischer carbene complexes do not, in general, react with unactivated alkenes, Fischer carbene complexes of molybdenum and chromium have been found to readily monocyclopropanate many simple 1,3-dienes in good-to-excellent yields, with high levels of chemo-, regio-, and stereoselectivity. A mechanism involving the intermediacy of an η^1-alkyl, η^3-allyl complex is proposed to account for this selectivity.

Introduction

Since their initial preparation in the early 1960s, Fischer carbene complexes have been widely investigated, and a variety of novel and synthetically useful transformations have been developed.[1] Some of the earliest studies of their reactivity focused on reactions with substituted alkenes. Fischer and co-workers demonstrated that alkenes with either electron-donating[2] or electron-withdrawing[3] substituents were readily cyclopropanated by phenylmethoxycarbene complexes of chromium, molybdenum, and tungsten. These findings have led to a variety of more recent investigations of the reactivity of Fischer carbene complexes with both electron-rich and electron-poor olefins.[4]

Studies of intramolecular cyclopropanation reactions with Fischer carbene complexes have shown much less reliance on the presence of donor or acceptor substituents on the alkene component.[5] Though occasionally complicated by competing olefin

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