Rigidly Hollow Hosts That Encapsulate Small Molecules†,[1,2]

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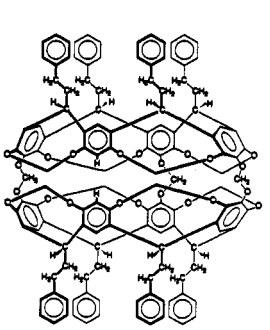
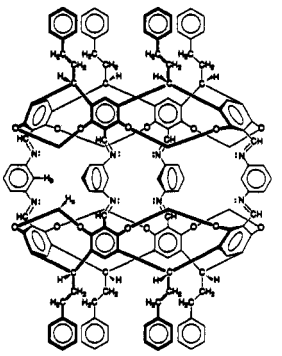
New chiral host systems **1** and **2** possessing C_3 symmetry have been designed and synthesized. Molecular models of **1** and **2** indicate they contain small enforced cavities and three portals complementary to small molecules. The crystal structure of **1**·2CH_3CN shows one molecule of CH_3CN is encapsulated and the second exists as a solvate. A crystal structure of **2**·2CH_3OH shows one CH_3OH molecule is encapsulated and a second serves as a solvate. A crystal structure of **2**·CH_2Cl_2 shows the host to be empty and that the CH_2Cl_2 acts as a solvate to provide (by disorder) a C_3 pattern about the C_3 axis of the host. In $CDCl_3$ solutions ($CDCl_3$ is too large to occupy its cavity), **1** complexed O_2, N_2, H_2O, and CO_2 readily and reversibly (^1H NMR spectra), particularly at low temperatures. In $CDCl_3$ solution, **1** binds CH_3OH with K_a = 10 M^{-1}, $\Delta G°_{295}$ = −1.4 kcal mol^{-1}, $\Delta H \simeq$ −6.6 kcal mol^{-1}, and $\Delta S \simeq$ −18 cal mol^{-1} K^{-1}. It also binds CH_3CN, but much more weakly. Triamine **2** in $CDCl_3$ binds O_2, N_2, and H_2O weakly and CH_3OH with a K_a = 47 M^{-1}, $\Delta G°_{295}$ = −2.3 kcal mol^{-1}, $\Delta H \simeq$ −8.5 kcal mol^{-1}, and $\Delta S \simeq$ −21 cal mol^{-1} K^{-1}. This host binds CH_3CN at 295 K with a K_a in the range of 1–10 M^{-1}, and CH_3CH_2OH with a K_a <5 M^{-1}. The ^1H NMR signals of the guest's CH_2 group of **2**·CH_3CH_2OH indicate the protons to be diastereotopic. The half-life for decomplexation of **2**·CH_3CH_2OH was about 40 min at 25 °C.

Previous papers in this series reported the syntheses and binding properties of two hosts (I, II) which when heated in solution in the presence of large excesses of guests of the right size and shape gave characterizable complexes.[3-5] For example, I heated in pyridine gave I·C_5H_5N, II heated in tripyridyl phosphoramide solutions of adamantane, of ferrocene, or of [2.2]paracyclophane gave II·adamantane, II·ferrocene, and II·[2.2]paracyclophane, respectively. The steric barrier to decomplexation of these incarcerated guests we term *constrictive binding*. In extreme cases, such as that of II·ruthenocene, it must be the dominant contributor to the activation energy for decomplexation ($\Delta G^‡ \sim$ 28 kcal mol^{-1}).[4] A similar compound, III, is more conformationally mobile. The northern hemisphere can rotate with respect to the southern around its C_3 axis to give the lowest energy conformation, which is also the most compact, with the biacetylene bridging units folded to form the torrid zone of the sphere-shaped host.[5] This host bound cubane in $Cl_3CCOCCl_3$, and the decomplexation rates were fast on the human but slow on the NMR time scale. Lacking among these hosts is one that is essentially rigid, but complementary to only small guests.

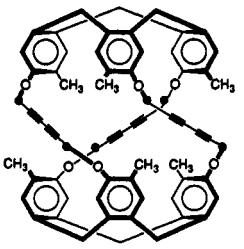
This paper reports the synthesis, crystal structures, and binding properties of new hosts **1** and **2**, which in Corey–Pauling–Koltun (CPK) molecular models possess enforced cavities and three portals complementary to two or three heavy-atom molecules. These hosts are much more rigid than III and therefore should show higher structural recognition in their complexation characteristics. We wished to test this preconception by estimating the association constants of **1** and **2** with O_2 and N_2 and to compare them with those of I. The volume of the inner phase of I is too large to share much common surface with guests as small as O_2 or N_2, whereas the enforced inner phases of **1** and **2** have volumes much more complementary to those of O_2 and N_2. Compound **2** bears a structural resemblance to host IV of Collet, Lehn et al.,[6] which is conformtionally flexible enough to fill much of its own cavity and has much larger portals than **2**. This host was shown to bind $CH_3NH_3^+$ in halogenated solvents.[6]



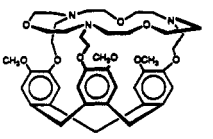
I



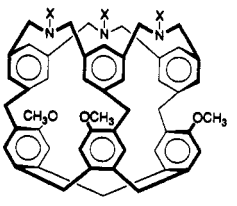
II



III



IV



1, X = OTs

2, X = H

Results and Discussion

Syntheses. The syntheses of **1** and **2** involved known diol **3**[7] as starting material, which was methylated with NaH–CH_3I to give **4** (93%). This material was metalated with *n*-BuLi, and the organometallic produced was for-

† This paper is dedicated to Professor Kurt Schaffner on the occasion of his 60th birthday.

(1) Host–Guest Complexation. 60.
(2) The authors thank the U.S. Public Health Service for supporting Grant GM-12640.
(3) (a) Tanner, M. E.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 1659–1660. (b) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717–7727.
(4) Quan, M. L. C.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2754–2755.
(5) Cram, D. J.; Tanner, M. E.; Keipert, S. J.; Knobler, C. B. *J. Am. Chem. Soc.*, in press.

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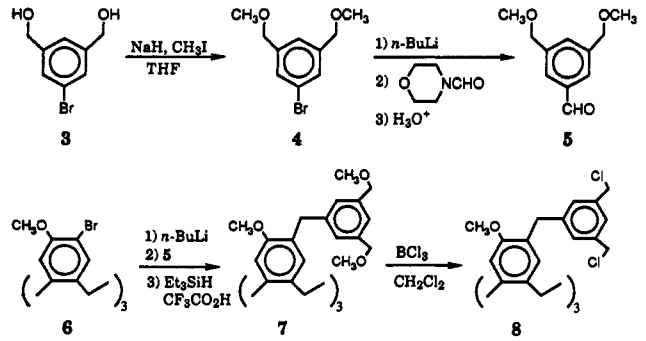
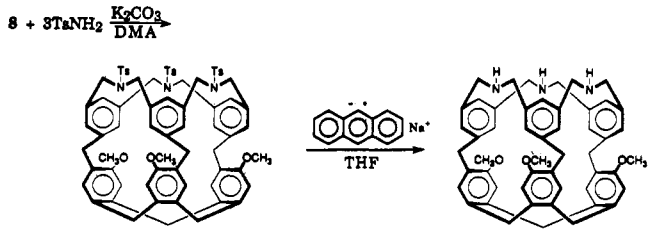
mylated with *N*-formylmorpholine to provide aldehyde **5** (67%). Chiral tris-bromide **6**, available from an earlier investigation,[5] was trimetalated with *n*-BuLi, and the tris-metalated material at −78 °C was treated with aldehyde **5** to give a diastereomeric mixture of triols. This material was not isolated, but reduced with Et_3SiH–CF_3CO_2H–CH_2Cl_2 to provide **7** in 66% yield for the two steps. This hexabenzyl ether **7** was converted to the corresponding hexabenzyl chloride **8** (75%) by treatment with BCl_3–CH_2Cl_2.

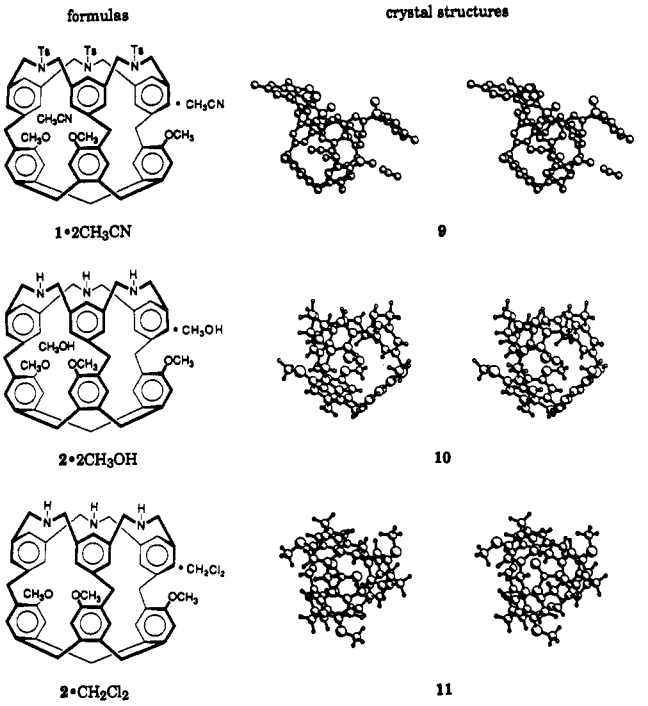


The shell closure was accomplished by the slow addition of a solution of **8** and 3 equiv of *p*-toluenesulfonamide ($TsNH_2$) in $(CH_3)_2NCOCH_3$ to K_2CO_3–$(CH_3)_2NCOCH_3$ at 65 °C. The tris-*N*-tosylamide **1** was produced in 10% yield. Substitution of Cs_2CO_3 for K_2CO_3 did not affect this yield. When conducted at room temperature, no shell-closed product was isolated. The modest yield observed for the shell closure may be due to intermolecular reactions of 2 mol of **8** with the tosylamide anions to produce diaza[3.3]metacyclophanes leading to higher oligomers through further reaction. In this connection, the analogous cyclization of 1,3-bis(bromomethyl)benzene with tosylamide led to dimer 2,11-bistosylaza[3.3]metacyclophane in 53% yield, with no mention being made of the formation of trimer.[8] The tosyl groups of **1** were removed by reduction with sodium anthracenide in tetrahydrofuran[9] at 0 °C to give **2** (65%).



Crystal Structures. Chart I provides stereoviews of the crystal structures of hosts **1**·2CH_3CN (**9**), **2**·2CH_3OH (**10**), and **2**·CH_2Cl_2 (**11**). Crystals of **1**·2CH_3CN were grown from CH_3CN–CH_2Cl_2, and its structure was refined to R = 0.122. Two molecules of CH_3CN were present in the crystal, one located in the host's cavity (partial occupancy) and oriented perpendicular to the host's pseudo C_3 axis. The other mole of CH_3CN was present as a solvate (external to the cavity). The tosyl group's variation in orientation destroyed the intrinsic C_3 symmetry of host **1**.

Chart I. Crystal Structures of Hemicarcerand and Hemicarceplexes



Crystals of **2**·2CH_3OH were grown from hexane–CH_2Cl_2–CH_3OH, and crystal structure **10** was refined to give R = 0.124. A molecule of CH_3OH is located inside the host's cavity, there being three equivalent positions, each enjoying one-third occupation. A second CH_3OH is located outside of the cavity as a solvate in a position remote from the observer. The crystal structure of **2**·CH_2Cl_2 was refined to R = 0.18. Crystals were grown from hexane–CH_2Cl_2. In stereoview **11** of **2**·CH_2Cl_2, the observer is looking down the C_3 molecular axis of the crystal with the [1.1.1]orthocyclophane unit nearest the eye. The CH_2Cl_2 present is outside of the cavity in a position remote from the observer, and it provides (by disorder) a C_3 pattern about the C_3 axis of the host. Pseudo-hydrogen bonding of CH_2Cl_2 to strong acceptors has been observed previously with highly preorganized systems,[10] but is absent in **2**·CH_2Cl_2.

The striking feature of the two crystal structures involving **2** is that the host structures are virtually identical, even though one contains a guest (**10**) and the other (**11**) does not contain any identifiable guest. The unshared electron pairs and the hydrogens attached to the three nitrogens are directed away from the interior of the cavity. *These crystal structures demonstrate that the host's organization is not dependent on occupancy of its cavity.*

Complexation by Host 1 of N_2, H_2O, and CO_2. Examination of molecular models of **1** and **2** and of typical ^1H NMR solvents indicates the hosts' cavities to be much too small to accommodate $CDCl_3$ or CD_2Cl_2. Thus, dissolution of **1** or **2** in such solvents is tantamount to dissolving holes in liquids, providing other very small solute molecules are absent. We first examined the question of whether the ubiquitous small molecules O_2, N_2, H_2O, and CO_2 complex **1** dissolved in $CDCl_3$. Accordingly, an 8 mM solution of **1** in $CDCl_3$ in an NMR tube was degassed by repeated freeze–evacuate–thaw cycles and its 500-MHz ^1H NMR spectrum was taken at 21 and −40 °C. Similar 8 mM solutions saturated with N_2 (5.6 mM)[11] or with O_2 (11.5

(6) Canceill, J.; Collet, A.; Gabard, J.; Kotzyba-Hibert, F.; Lehn, J.-M. *Helv. Chim. Acta* **1982**, *65*, 1894–1897.
(7) Sherrod, S. A.; da Costa, R. L.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565–1577.
(8) Bottino, F.; Di Grazia, M.; Finacchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521–3529.
(9) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204–6210.
(10) Doxsee, K. M.; Feigel, M.; Stewart, K. D.; Canary, J. W.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 3098–3107, Figure 6.

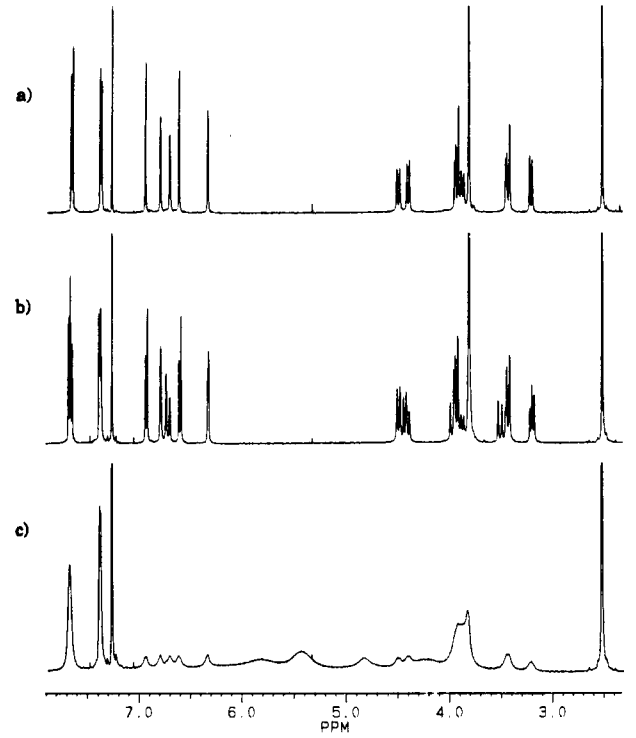


Figure 1. ^1H NMR of 8 mM solution of 1 in $CDCl_3$ (−40 °C): spectrum a, degassed; spectrum b, N_2 saturated; spectrum c, O_2 saturated.

mM)[12] were prepared, and their spectra were also taken at the two temperatures. Figure 1 records the spectra taken at −40 °C.

The host peaks in the degassed sample of 1 remained sharp upon cooling, and only minor changes in their chemical shifts were visible. At 21 °C, the degassed and N_2-saturated solutions gave very similar ^1H NMR spectra with sharp peaks, but when cooled to −40 °C, a new set of host peaks grew into the spectrum of the N_2-saturated sample with chemical shifts slightly different from those of free 1 (Figure 1). The only peaks unaffected by the presence of N_2 were those due to the tosyl methyl protons (δ 2.50) and the orthocyclophanes' methylene protons (δ 4.48 and 3.42), both of which are either remote from or oriented away from the cavity, and from any of its four portals. The new signals that appear at −40 °C appear to be due to $1{\cdot}N_2$, whose N_2 occupies the cavity. At −10 °C the signals of $1{\cdot}N_2$ are broadened, which indicates the barrier to decomplexation is greater than 14 kcal mol^{-1} at this temperature.[13] At −3, −28, and −40 °C, the amounts of host in the form of $1{\cdot}N_2$ measured by proton integration were 30, 50, and 60%, respectively. Thus, the K_a values for association at these temperatures are on the order of 10^2 M^{-1}, the binding being entropically disfavored. The similarity of the spectrum of 1 in $CDCl_3$ and in $CDCl_3$ saturated with N_2 at 21 °C is attributed to the small amount of $1{\cdot}N_2$ (10%) present at this temperature, and to the probability that the decomplexation rate is approaching the coalescence point between fast and slow guest exchange on the ^1H NMR time scale.

In the ^1H NMR spectrum of the O_2-saturated solution of 1 in $CDCl_3$ taken at 21 °C, the host peaks of protons close to the cavity are greatly broadened due to complexation of paramagnetic O_2. Only the peaks of the tosyl groups were relatively unaffected (see Figure A of supplementary material). When the solution was cooled to −40 °C (see Figure 1) new sets of peaks appeared, attributed to $1{\cdot}O_2$ that is decomplexing slowly on the ^1H NMR time scale. These new peaks are first observed at −3 °C, indicating that $\Delta G^{\ddagger}$ for decomplexation is close to the ~14 kcal mol^{-1} observed for $1{\cdot}N_2$. The new signals attributed to $1{\cdot}O_2$ are very broad, are shifted several ppm from those of the free host resonances, and at −40 °C appear at δ 5.80, 5.45, 4.85, and 4.20. These signals have been broadened and shifted so dramatically at −40 °C that they are not assigned. The extent of this effect should be strongly dependent on the distance away from, and the orientation of the guest protons with respect to, the bound triplet dioxygen molecule.[14] The signals of the *free* host are still quite broad at this temperature but appear at the same chemical shifts as those of the degassed samples of 1. The appearance of the spectrum of the mixture of $1{\cdot}O_2$ and 1 at −40 °C (Figure 1) is consistent with a K_a value of about 10^2 M^{-1}, with the complexation process being entropically disfavored. The spectrum taken at 21 °C appears to be strongly affected by the small fraction of the host present as $1{\cdot}O_2$, which is rapidly exchanging with free host on the ^1H NMR time scale. The peak broadening in the spectrum of $1{\cdot}O_2$ is probably due to both scalar coupling and dipole–dipole interactions between the proximate proton nuclei and the unpaired electrons of triplet oxygen.[14] Paramagnetic effects due to complexation of O_2 have also been observed in the bowl-shaped cavitands[15] and spherical hemicarcerands.[3] Such broadening occurs without deliberate addition of O_2 and provides a general indicator for the presence of an unfilled cavity of molecular dimensions.

Evidence for the complexation of H_2O by 1 in $CDCl_3$ was also observed in the 500-MHz ^1H NMR spectra. The incremental addition of solid 1 to an NMR tube containing $CDCl_3$ caused the position of the residual water peak at its normal place at δ 1.54 to shift upfield as far as δ 1.37 at 8.2 mM host concentration. This shift is attributed to the inclusion of a small amount of water within the aryl-lined cavity, which is exchanging rapidly on the ^1H NMR time scale with uncomplexed water. A solution of *N,N*-dibenzyl-*p*-toluenesulfonamide[16] in $CDCl_3$ did not show this effect, which demonstrates that the polar sulfonamide groups of the host taken alone are not responsible for the shifts. When a degassed sample of 1 in $CDCl_3$ (8.2 mM) was cooled to −28 °C, the adventitious water proton peak shifted further upfield ($\Delta\delta$ = 1.28 ppm) and broadened dramatically, suggesting that the water binding by 1 is entropically disfavored. The water peak broadened enough to disappear into the base line when the solution was cooled to −40 °C. The slowly exchanging state could not be reached due to the solution freezing at lower temperatures. When a sample of the solvent was cooled from 21 to −28 °C, δ for the water shifted only from δ 1.54 to 1.68 at −28 °C, and the peak remained sharp.

A 500-MHz spectrum (−28 °C) of a 7 mM solution of 1 in $CDCl_3$ saturated with CO_2 showed that the host was almost completely complexed. Only very weak signals due to the free host were observed. The high solubility of CO_2

(11) Battino, R., Ed. *IUPAC Solubility Data Series*; Pergamon Press: Oxford, 1982; Vol. 10; pp 232–233.
(12) Battino, R., Ed. *IUPAC Solubility Data Series*; Pergamon Press: Oxford, 1981; Vol. 7; p 452.
(13) This conclusion is based on the observation that signals separated by 40 Hz are below the coalescence temperature. Atta-ur-Raman *Nuclear Magnetic Resonance*; Springer-Verlag: New York, 1986; pp 131–133.
(14) Shaw, D. *Fourier Transform N.M.R. Spectroscopy*; Elsevier Scientific: Amsterdam, 1976; pp 207–214 and 311–318.
(15) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575.
(16) This compound was prepared by the reaction of *p*-toluenesulfonamide with benzyl chloride in refluxing acetone containing K_2CO_3. The product was isolated by silica gel chromatography and characterized by ^1H NMR only.

in $CDCl_3$ accounts for the extent of the complexation.[17] The position of the slightly broadened adventitious water peak at δ 1.62 is consistent with this interpretation.

Complexation of 1 with CH_3OH and CH_3CN. The shielding effects on the proton signals in the ^1H NMR (500-MHz) spectra of bound CH_3OH were particularly large. A $CDCl_3$ solution that was 8.7 mM in 1 and 99 mM in CH_3OH was degassed and sealed. The ^1H NMR spectrum at 22 °C (Figure B of supplementary material) shows that two sets of host and guest signals are present, indicating that binding-partner exchange was slow on the ^1H NMR time scale. The methyl signal of bound CH_3OH appears as a doublet at δ −2.00 (J = 5.6 Hz) and its hydroxyl as a quartet at δ −4.57 (J = 5.6 Hz). These two sets of signals are moved upfield by $\Delta\delta$ 5.48 and 5.64 ppm, respectively. The unbound CH_3OH signals appear as singlets because of exchange decoupling which occurs when the OH protons are exchanging with other protons in solution (adventitious H_2O) at a rate greater than 2.2 times the coupling constant.[18] The observed coupling in the bound CH_3OH indicates that this rate has been lowered to less than 12 s^{-1} due to its location within the cavity. Molecular model examination of $1{\cdot}CH_3OH$ indicates that both the CH_3 and OH protons are pressed against the faces of the aryl groups, which accounts for the large shifts upfield of their NMR signals.

Proton integration indicated that 49% of the host is complexed, which provides K_a = 10 M^{-1} (±25%) and $\Delta G°_{295}$ = −1.4 kcal mol^{-1} (±0.2).[19] Proton integration of the adventitious water present indicated its concentration to be ~33 mM. However, the small shifts in the position of its ^1H NMR signal suggest it is only weakly bound and should not materially affect the calculations. The binding of CH_3OH by 1 increased as the temperature was decreased. A linear five-point plot of $\Delta G°$ against temperature (K) over the temperature range from −16 to 37 °C provided estimates of ΔH = −6.6 kcal mol^{-1} and ΔS = −18 cal mol^{-1} K^{-1}.

Host 1 was found to be only a very weak binder of CH_3CN. A 500-MHz ^1H NMR spectrum at −28 °C of a degassed $CDCl_3$ solution 3 mM in 1 and 120 mM in CH_3CN displayed a weak signal at δ −3.29 ppm, which provides a $\Delta\delta$ value of 5.33 ppm shift for the guest's CH_3 group. Proton integrations indicated that less than 5% of the host contained guest. The extent of complexation did not change over a 24-hour period, indicating that equilibrium had been reached. The observation of partial occupancy of the cavity of 1 by CH_3CN in crystal structure **9** is attributed to the very high concentration of guest present during crystallization.

Complexation by Host 2 of Small Molecules. The 500-MHz ^1H NMR spectrum of a solution of triamine host 2 in $CDCl_3$ indicates that this host's cavity like that of 1 is empty. Figure 2 contains the spectra of an 8 mM solution of host in degassed, in N_2-saturated, and in O_2-saturated $CDCl_3$ at 21 °C. The broadening of some host signals in the spectrum of 2 in N_2-saturated $CDCl_3$ is due to the exchange between bound and free host at a rate close to that producing coalescence. At −28 °C, the exchange between bound and free host became slow on the ^1H NMR time scale, with 2 being approximately 60% complexed. Thus, 2 is a slightly stronger binder of N_2 than 1, which under the same conditions was only 50% complexed.

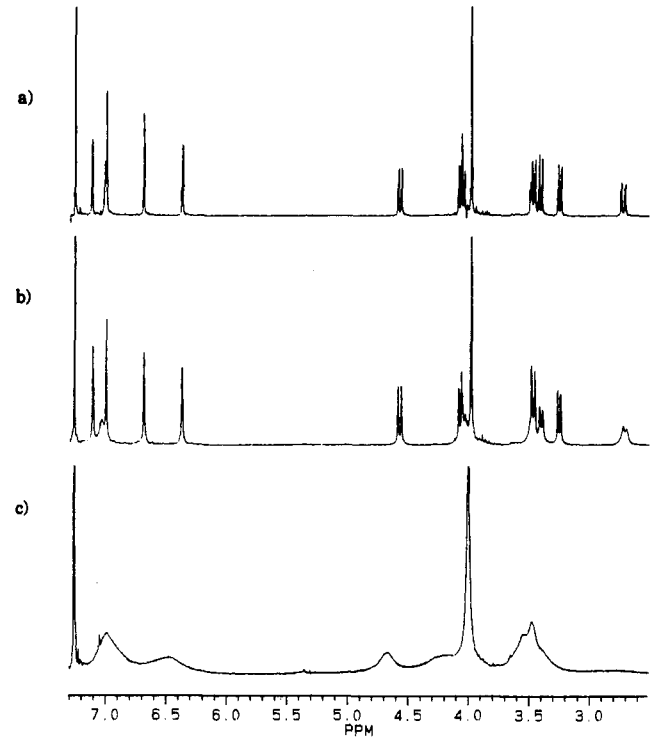


Figure 2. ^1H NMR of 8 mM solution of 2 in $CDCl_3$ (21 °C): spectrum a, degassed; spectrum b, N_2 saturated; spectrum c, O_2 saturated.

The presence of O_2 in the O_2-saturated $CDCl_3$ spectrum of 2 caused extreme broadening of the host's proton signals (Figure 2). When this solution was cooled, very broad signals appeared between δ 4 and 6, due to the formation of $1{\cdot}O_2$. The adventitious water proton signal was uninformative since it was in fast exchange with the amine protons of the host.

The ^1H NMR spectrum at 22 °C was taken of a degassed solution of $CDCl_3$ which was 8.0 mM in 2 and 40 mM in CH_3OH (Figure C of supplementary material). The CH_3 group of the $2{\cdot}CH_3OH$ appears as a sharp singlet at δ −1.67 ($\Delta\delta$ = 5.15), indicating tht free CH_3OH exchange with $2{\cdot}CH_3OH$ is slow on the ^1H NMR time scale and that the guest is firmly lodged within the cavity abutting the faces of the shielding aryl groups. The hydroxyl proton of the bound guest was not located, indicating that it is rapidly exchanging its protons with unbound CH_3OH. Such exchange might occur by a proton relay mechanism via the three amino groups, or by direct hydrogen bonding with external CH_3OH through the three side portals, which are much larger than the end portal centered on the C_3 axis.

Integrations of the three methylene doublets located at δ 3.05 in the ^1H NMR spectrum of $2{\cdot}CH_3OH$ and at δ 2.72 in that of free 2 were used to determine the degree of complexation. At 22 °C, 62% of the host was complexed, which corresponds to K_a = 47 M^{-1} (±25%) and $\Delta G°_{295}$ = −2.3 (±0.2) kcal mol^{-1}.[19] A linear plot of $\Delta G°_T$ against T provided estimates of $\Delta H°$ = −8.5 kcal mol^{-1} and $\Delta S°$ = −21 cal mol^{-1} K^{-1}. These values may be slightly low due to competition of CH_3OH with adventitious H_2O for cavity occupation. Exploratory studies indicated that addition of excess CF_3CO_2D to a $CDCl_3$ solution of 2 and CH_3OH did not dramatically affect the binding equilibrium. The protonated form of the host was still soluble.

Qualitative binding studies indicated that CH_3CN is bound by 2 with a K_a value in the range of 1–10 M^{-1}. The singlet for the CH_3 protons of $2{\cdot}CH_3CN$ was observed at δ −2.81 ($\Delta\delta$ = 4.81) in the 500-MHz ^1H NMR spectrum of a solution of 2 and CH_3CN in $CDCl_3$ at 22 °C. The binding

(17) Gjaldbæk, J. *Chr. Acta. Chem. Scand.* **1953**, *7*, 537–544.
(18) Sanders, K. M.; Hunter, B. K. *Modern NMR Spectroscopy. A Guide for Chemists*; Oxford University Press: Oxford, 1987; Chapter 7.
(19) Errors based on an estimated 10% uncertainty in the values of the proton integration.

in 2·CH_3CN is considerably stronger than that in 1·CH_3CN. The crystal structure of 1·CH_3CN indicates that the sulfonamide nitrogen is sp^2 hybridized and that this effect coupled with the steric requirements of the Ts groups in 1 imposes conformational constraints on the $ArCH_2NTsCH_2Ar$ moieties, which draw the aryl groups closer together and decrease the cavity size of 1 as compared to that of 2.

Host 2 weakly binds CH_3CH_2OH in $CDCl_3$ ($K_a < 5\ M^{-1}$). In the presence of a large excess of CH_3CH_2OH in $CDCl_3$, bound guest's ^1H NMR signals are observed upfield of $(CH_3)_4Si$. The guest's CH_2 protons are diastereotopic due to their residence in the cavity of a chiral host. They appear as multiplets at δ −0.88 ($\Delta\delta$ = 4.60) and δ −1.12 ($\Delta\delta$ 4.84). The methyl group appears as a triplet at δ −3.67 ($\Delta\delta$ = 4.91). Irradiation of the methyl signal caused the CH_2 signals to collapse into two doublets. The hydroxyl proton's signal was not observed due to rapid proton exchange between bound and unbound EtOH.

In attempts to prepare 2·EtOH, an 8 mM solution of 2 in neat EtOH was stirred for 1 week at room temperature, the solvent was evaporated in vacuo without heating, and the resulting solid was dissolved in $CDCl_3$ for immediate ^1H NMR spectral examination. The spectrum showed that approximately 10% of the host contained EtOH. By following the decrease in the value of the integrals of the bound EtOH at 22 °C, a half-life of 40 min was measured. Thus, although 2 is only a very weak binder of EtOH, the decomplexation rate for 2·EtOH is on the human time scale, indicating that the complexation rate is also slow. Molecular models of 2·EtOH can be easily assembled, but this guest can be forced out through the side portals only with some difficulty. Thus, 2·EtOH once formed appears to be held together not only by the usual contact forces, but also by weak constrictive binding,[3,4] which must be overcome for dissociation to occur. This behavior of 2·EtOH contrasts with that of 2·CH_3OH, which at room temperature formed and dissociated instantaneously on the human time scale and was much more stable than 2·EtOH. Thus, 2 shows structural recognition of both a thermodynamic and kinetic variety.

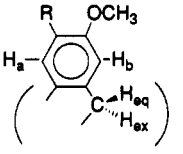
The binding constants, K_a, for host I binding N_2 and O_2 at 22 °C were about 180 and 40 M^{-1}, of the same order of magnitude as 1 binding these molecules ($\sim 10^2\ M^{-1}$). Thus, the fact that the total volume of the cavity of I is many times that of 1 or 2 appears not to have an overriding influence on the binding constants toward these small molecules.

Summary

Two new chiral hosts (1 and 2) have been synthesized that contain small enforced cavities that are roughly spherical in shape. The molecules possess C_3 symmetry, three side portals of cross sections smaller than that of the cavity, and a much smaller portal centered on the C_3 axis. Crystal structures of 1·2CH_3CN (9), 2·2CH_3OH (10), and 2·CH_2Cl_2 (11) correspond to expectations based on CPK molecular model examination. In 9 the cavity is occupied by one CH_3CN guest, 10 contains an encapsulated CH_3OH, and 11 an *empty* cavity, the CH_2Cl_2 (solvate) being too large to enter or to lodge in the cavity. In $CDCl_3$ as solvent (much too large to be encapsulated), 1 was found to bind N_2 and O_2 at −40 °C with K_a values on the order of $10^2\ M^{-1}$ (same order of magnitude as I binding N_2 and O_2), and the $\Delta G^{\ddagger}_{283}$ for decomplexation of 1·N_2 and 1·O_2 was ~14 kcal mol^{-1}. Qualitative experiments showed that H_2O was more weakly bound and that 1·CO_2 was readily formable. Binding of all of these guests was enthalpically favored and entropically disfavored. Methanol was bound by 1 with $\Delta G°_{295} = -1.4$ kcal mol^{-1}, $\Delta H° \sim -6.6$ kcal mol^{-1}, and $\Delta S° \sim -18$ kcal $mol^{-1}\ K^{-1}$. Acetonitrile was much more weakly complexed. Host 2 in $CDCl_3$ bound N_2, O_2, H_2O, and CH_3CN comparably well to 1, and CH_3OH with $\Delta G°_{295} = -2.3$ kcal mol^{-1}, $\Delta H° \sim -8.5$ kcal mol^{-1}, and $\Delta S° \sim -21$ kcal $mol^{-1}\ K^{-1}$. Host 2 binds CH_3CH_2OH more weakly than CH_3OH, but unlike 2·CH_3OH, 2·CH_3CH_2OH decomplexes at a rate which is on the human time scale at room temperature, due to constrictive binding forces that must be overcome during decomplexation. A diagnostic test for hosts with enforced cavities being empty in solvents too large to be complexed is the broadening of host signals due to complexation of small amounts of dissolved paramagnetic oxygen. This study demonstrates that hosts can be prepared which show high kinetic and thermodynamic structural recognition in complexation between CH_3OH and CH_3CH_2OH.

Experimental Section

General. All chemicals were reagent grade and used as received unless otherwise specified. All reactions were conducted under an atmosphere of argon. THF was freshly distilled from sodium benzophenone ketyl prior to use. DMA was dried by storage for at least 72 h over activated (24 h, 320 °C) 3 Å molecular sieves and was degassed under high vacuum immediately before use. The ^1H NMR spectra were recorded at 360 and 500 MHz, respectively. All ^1H NMR spectra are referenced to residual $CHCl_3$ at 7.26 ppm. All melting points were determined in open capillaries and are uncorrected. Gravity chromatography was performed on E. Merck silica gel 60 (70–230 mesh). TLC was done on E. Merck glass-backed plates (silica gel 60, F_{254}, 0.25 mm). Silica gel (E. Merck) of 230–400 mesh was used in the preparation of the reversed-phase support.[20] Reversed-phase TLC was performed using glass-backed octadecylsilane-bonded plates, 0.2 mm thickness, from Whatman. General structure 12 provides proton labels used in the assigning of chemical shifts to the hydrogens of the new compounds described herein.



12

1-Bromo-3,5-bis(methoxymethyl)benzene (4). To 8.9 g (0.37 mol) of NaH (prepared oil-free by rinsing with pentane) in 1 L of dry THF was added a solution of 20 g (92 mmol) of diol 3 in 25 mL of dry THF. After the solution was stirred for 15 min, 50 mL (0.80 mol) of CH_3I was added. This mixture was stirred at 25 °C for 12 h. The reaction was quenched by the addition of 5 mL of H_2O, and the solvent was removed in vacuo. The residue was extracted with Et_2O and water, and the organic layer was dried ($MgSO_4$) and evaporated to produce 22 g of a yellowish oil. Distillation of the oil at 0.1 Torr and 75 °C gave 21 g (93%) of 4 as a colorless liquid: ^1H NMR (360 MHz, $CDCl_3$) δ 3.39 (s, 6 H, OCH_3), 4.42 (s, 4 H, CH_2), 7.22 (s, 1 H, ArH), 7.41 (s, 2 H, ArH); MS (16 eV, 150 °C) 246 (M^+ (^{81}Br), 75) 244 (M^+ (^{79}Br), 78), 165 (M^+ − Br, 100). Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.34; Br, 32.60. Found: C, 49.18; H, 5.44; Br, 32.48.

3,5-Bis(methoxymethyl)benzaldehyde (5). A solution of 6 g (25 mmol) of 4 in 500 mL of dry THF under argon was cooled to −78 °C in a dry ice–acetone bath. To this mixture was added 27 mmol of *n*-butyllithium (14.2 mL of a 1.9 M solution in hexanes). After the mixture stirred for 2 min, 3 mL (30 mmol) of 4-formylmorpholine was added, and the mixture was allowed to warm to 25 °C. The mixture was acidified by the addition of 10 mL of a 3.5 N aqueous solution of HCl, and the solvent was removed in vacuo. The residue was extracted with pentane and water, and the organic layer was dried over $MgSO_4$ and evaporated.

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This gave 3.2 g (67%) of **5** as a light yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.43 (s, 6 H, OCH_3), 4.53 (s, 4 H, CH_2), 7.60 (s, 1 H, ArH), 7.79 (s, 2 H, ArH), 10.03 (s, 1 H, CHO); MS (16 ev, 90 °C) 194 (M^+, 100). For analytical purposes, a small amount of material was further purified by Kugelrohr distillation. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.94; H, 7.27.

2,7,12-Tris[[3,5-bis(methoxymethyl)phenyl]methyl]-10,15-dihydro-3,8,13-trimethoxy-5*H*-tribenzo[*a*,*d*,*g*]cyclononene Racemate (7). A solution of 2.8 g (4.7 mmol) of racemic **6** in 500 mL of dry THF under argon was cooled to −78 °C in a dry ice–acetone bath. To this was added 15 mmol of *n*-butyllithium (7.8 mL of a 1.9 M solution in hexanes). A white precipitate immediately formed. After the mixture had stirred for 5 min, a solution of 3.1 g (16 mmol) of aldehyde **5** in 25 mL of dry THF was added. The precipitate persisted upon warming the mixture to 25 °C. The addition of 2 mL of 2 N HCl gave a clear, colorless solution. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and evaporated to give 5 g of an off-white foam. This material was dissolved in 300 mL of CH_2Cl_2 and 21 mL (0.13 mol) of Et_3SiH, and 10 mL (0.13 mol) of CF_3CO_2H acid was added. After being stirred at ~25 °C for 2 h, the reaction mixture was quenched by the addition of 16 g (0.15 mol) of solid Na_2CO_3 followed by 100 mL of water. This mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. Silica gel chromatography of the solution (15:85 EtOAc–CH_2Cl_2) of the product provided 2.75 g (66%) of **7** as a white solid: mp 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (s, 18 H, CH_2OMe), 3.50 (d, 3 H, Heq, J = 13.6 Hz), 3.64 (s, 9 H, $ArOCH_3$), 3.77 (d, 3 H, $ArCH_2Ar$, J = 15.2 Hz), 3.89 (d, 3 H, $ArCH_2Ar$, J = 15.2 Hz), 4.38 (s, 12 H, CH_2OMe), 4.68 (d, 3 H, Hax, J = 13.5 Hz), 6.60 (s, 3 H, ArHb), 6.94 (s, 3 H, ArHa), 7.06 (s, 6 H, ArH), 7.13 (s, 3 H, ArH); MS (xenon FAB, NOBA matrix) m/e 895 (M^+, 23). Anal. Calcd for $C_{57}H_{66}O_9$: C, 76.48; H, 7.34. Found: C, 76.31; H, 7.34.

2,7,12-Tris[[3,5-bis(chloromethyl)phenyl]methyl]-10,15-dihydro-3,8,13-trimethoxy-5*H*-tribenzo[*a*,*d*,*g*]cyclononene Racemate (8). To 2.7 g (3 mmol) of **7** in 100 mL of CH_2Cl_2 was added 20 mmol of BCl_3 (20 mL of a 1.0 M solution in CH_2Cl_2). This mixture was stirred at 25 °C for 15 min and then quenched by the gradual addition of 20 mL of MeOH. The solvent was evaporated under reduced pressure. Methanol (100 mL) was added and then evaporated under reduced pressure to remove $(CH_3O)_3B$ as a methanol azeotrope. This procedure was repeated two more times. The resulting solid was run through a plug of silica gel with $CHCl_3$ as eluent to give 2.1 g (75%) of **8** as a white solid: mp dec above 230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (d, 3 H, Heq, J = 13.5 Hz), 3.65 (s, 9 H, $ArOCH_3$), 3.83 (s, 6 H, $ArCH_2Ar$), 4.50 (s, 12 H, CH_2Cl), 4.72 (d, 3 H, Hax, J = 13.5 Hz), 6.64 (s, 3 H, ArHb), 6.98 (s, 3 H, ArHa), 7.14 (s, 6 H, ArH), 7.23 (s, 3 H, Ar-H); MS (xenon FAB, NOBA matrix) complex isotope pattern centered at m/e 923 (M^+ + 1, 100). Anal. Calcd for $C_{51}H_{48}Cl_6O_3$: C, 66.46; H, 5.25. Found: C, 66.53; H, 5.24.

1,13,14,21,22,34-Hexahydro-30,36,48-trimethoxy-13,21,44-tris[(4-methylphenyl)sulfonyl]-6*H*,12*H*,20*H*,28*H*-2,5-etheno-9,25-[(methanimino)methano]-3,32:17,37-dimethano-7,11:15,19:23,27:29,33-tetrametheno-13,21-benodiazacyclohexatriacontine Racemate (1). A solution of 400 mg (0.43 mmol) of **8** and 220 mg (1.28 mmol) of *p*-toluenesulfonamide (recrystallized from EtOH) in 60 mL of dry DMA was added over 12 h (via syringe pump) to a mixture of 5 g (36 mmol) of K_2CO_3 and 500 mL of dry DMA at 55 °C. The temperature was then raised to 75 °C, and stirring was continued for an additional 12 h. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$ and evaporated. Silica gel chromatography (97.5:2.5 CH_2Cl_2–EtOAc) gave 80 mg of fairly pure product. Recrystallization of this material from ethanol/CH_2Cl_2 and drying at 190 °C under vacuum gave 55 mg of **1** (10%) as white crystals: mp > 300 °C; ^{1}H NMR (500 MHz, degassed $CDCl_3$) δ 2.49 (s, 9 H, $ArCH_3$), 3.21 (d, 3 H, CH_2, J = 12.2 Hz), 3.41 (d, 3 H, Heq, J = 13.6 Hz), 3.46 (d, 3 H, CH_2, J = 18.0 Hz), 3.84 (s, 9 H, OCH_3), 3.97 (d, 3 H, CH_2, J = 12.2 Hz), 4.01 (d, 3 H, CH_2, J = 17.9 Hz), 4.03 (d, 3 H, CH_2, J = 12.7 Hz), 4.29 (d, 3 H, CH_2, J = 12.8 Hz), 4.50 (d, 3 H, Hax, J = 13.4 Hz), 6.35 (s, 3 H, ArH), 6.59 (s, 3 H, ArH), 6.62 (s, 3 H, ArH), 6.84 (s, 3 H, ArH), 6.92 (s, 3 H, ArH), 7.34 (d, 6 H, tosyl ArH, J = 8.2 Hz), 7.66 (d, 6 H, tosyl ArH, J = 8.3 Hz). MS (xenon FAB, NOBA matrix) m/e 1215 (M^+, 100). Anal. Calcd for $C_{72}H_{69}N_3O_9S_3$: C, 71.09; H, 5.72. Found: C, 70.94; H, 5.77.

1,13,14,21,22,34-Hexahydro-30,36,48-trimethoxy-6*H*,12*H*,20*H*,28*H*-2,5-etheno-9,25-[(methanimino)methano]-3,32:17,37-dimethano-7,11:15,19:23,27:29,33-tetrametheno-13,21-benodiazacyclohexatriacontine Racemate (2). A 0.1 M stock solution of sodium anthracenide was prepared by dissolving 1 g (5.6 mmol) of anthracene (recrystallized from EtOH) and 115 mg of sodium metal (5 mmol) in 50 mL of dry THF under argon. After stirring for 2 h, dissolution was complete, and a dark blue color persisted. To 50 mL of dry THF was added 100 mg (0.082 mmol) of **1**. This was cooled to 0 °C, and 8.5 mL (0.85 mmol) of the anthracenide solution was added. This was stirred for 2 min and quenched by the addition of 2 mL of saturated NaCl solution. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 and water. The organic layer was dried over Na_2SO_4 and concentrated to a volume of 25 mL. Dry HCl gas was bubbled through this solution for 1 min, causing the tris-hydrochloride salt to precipitate. The solids were collected by filtration and washed with CH_2Cl_2. This material was freely soluble in water. The solids were added to 50 mL of a 0.5 M solution of Na_2CO_3, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to give 55 mg of a yellow solid. The solid was redissolved in CH_2Cl_2, preabsorbed on 0.6 g of reversed-phase silica gel, and flash chromatographed through an additional 6 g of this support (1:4.5:4.5 triethylamine/H_2O/acetone containing 3 g NaBr per 100 mL). The fractions corresponding to product were collected, and the solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 and dilute aqueous Na_2CO_3. The organic layer was dried over Na_2SO_4 and concentrated to 20 mL. This mixture was poured into 100 mL of pentane, and the resulting precipitate was collected by filtration. Drying of the solid at 190 °C under vacuum produced 40 mg (65%) of **2** as a light yellow solid: mp >300 °C; ^{1}H NMR (500 MHz, degassed $CDCl_3$) δ 2.72 (d, 3 H, CH_2, J = 15.7 Hz), 3.25 (d, 3 H, CH_2, J = 12.2 Hz), 3.41 (d, 3 H, CH_2, J = 12.5 Hz), 3.47 (d, 3 H, Heq, J = 13.5 Hz), 3.47 (d, 3 H, CH_2, J = 16.1 Hz), 3.98 (s, 9 H, OCH_3), 4.05 (d, 3 H, CH_2, J = 11.7 Hz), 4.07 (d, 3 H, CH_2, J = 11.8 Hz), 4.57 (d, 3 H, Hax, J = 13.4 Hz), 6.37 (s, 3 H, ArHb), 6.69 (s, 3 H, ArHa), 7.00 (s, 3 H, ArH), 7.01 (s, 3 H, ArH), 7.12 (s, 3 H, ArH). MS (xenon FAB, NOBA matrix) m/e 754 (M^+ + 1, 100). Anal. Calcd for $C_{51}H_{51}N_3O_3\cdot H_2O$: C, 79.35; H, 6.92. Found: C, 79.21; H, 7.16.

Complexation Studies. Solutions for quantitative studies were prepared in volumetric glassware. All studies were performed on a 500-MHz spectrometer. The temperature of the probe was calibrated using the difference in chemical shifts between the two peaks of methanol (below 295 K) or ethylene glycol (above 295 K). All degassed samples were prepared by freezing the sample in liquid nitrogen, evacuating to 0.1 Torr, and thawing. This was repeated three times, and on the final cycle the NMR tube was sealed prior to thawing. Oxygen- and nitrogen-saturated samples were prepared by bubbling a vigorous stream of the gas through the NMR sample for a minimum of 10 min immediately before collecting the data. Additional solvent was added to the tubes prior to saturating to compensate for solvent loss due to evaporation.

Crystal Structure Determinations. Compound **1**·2CH_3CN crystallized from CH_2Cl_2/CH_3CN as colorless parallelepipeds in the triclinic system $P\bar{1}$. Unit cell dimensions are as follows: a = 11.710 (2) Å, b = 11.809 (2) Å, c = 28.075 (4) Å, α = 96.930 (3)°, β = 93.594 (3)°, γ = 119.334 (3)°, V = 3327 Å^3, Z = 2. The crystal was examined on a modified Syntex $P\bar{1}$ diffractometer, Cu$K\alpha$ radiation, at 25 °C. The structure was determined by direct methods. Refinement of 387 + 28 parameters (2 blocks, 5753 reflections with $I > 3\sigma(I)$ has an agreement value, R, currently at 0.122.

Compound **2**·CH_2Cl_2 crystallized from CH_2Cl_2/hexane as colorless parallelepipeds in the rhombohedral system $R\bar{3}$. Unit cell dimensions are as follows: a = 17.054 (4) Å, γ = 49.68 (1)°, V = 2650 Å^3 (rhombohedral cell), a = 14.301 (3) Å, c = 44.65 (1) Å, V = 7950 Å^3 (hexagonal cell), Z = 6($^1/_3$ molecule in the asymmetric unit). The crystal was examined on a Huber diffractometer, Mo$K\alpha$ radiation, at 25 °C. The structure was de-

termined by direct methods. Refinement of 105 parameters (1019 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.182. We believe this relatively high value is at least partly attributable to the high degree of disorder in these crystals.

Compound $2{\cdot}CH_3OH$ crystallized from $CH_3OH/CHCl_3$ as colorless parallelepipeds in the rhombohedral system $R\bar{3}$. Unit cell dimensions are as follows: a = 17.090 (2) Å, γ = 49.33 (1)°, V = 2637 Å^3 (rhombohedral cell), a = 14.262 (2) Å, c = 44.914 (6) Å, V = 7912 Å^3 (hexagonal cell), Z = 6 ($^1/_3$ molecule in the asymmetric unit). The crystal was examined on a Syntex $P\bar{1}$ diffractometer, CuKα radiation, at 25 °C. The structure was determined by direct methods. Refinement of 118 parameters (1233 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.124.

Complete crystallographic details are provided in the supplementary material.

Registry No. 1, 137334-67-9; $1{\cdot}N_2$, 137334-76-0; $1{\cdot}O_2$, 137334-77-1; $1{\cdot}H_2O$, 137334-78-2; $1{\cdot}CO_2$, 137362-96-0; 1·MeOH, 137334-79-3; 2, 137334-68-0; $2{\cdot}N_2$, 137334-80-6; $2{\cdot}O_2$, 137334-81-7; 2·MeCN, 137334-82-8; 2·EtOH, 137334-83-9; 3, 51760-22-6; 4, 137334-69-1; 5, 137334-70-4; 6, 137432-38-3; 7, 137334-71-5; 8, 137334-72-6; 9, 137334-73-7; 10, 137334-74-8; 11, 137334-75-9; $TsNH_2$, 70-55-3; BCl_3, 10294-34-5; sodium anthracenide, 12261-48-2; *N*-formylmorpholine, 4394-85-8.

Supplementary Material Available: Figures A, B, and C as ^{1}H NMR spectra; listings of crystallographic experimental conditions, Figures 1s, 2s, and 3s, of the three host molecules characterized by X-ray diffraction studies, positional and thermal parameters, and interatomic distances and angles for $1{\cdot}2CH_3CN$, $2{\cdot}CH_3OH$, and $2{\cdot}CH_2Cl_2$ (33 pages). Ordering information is given on any current masthead page.

Ring-Opening Reactions of α-Stannyl Epoxides with Metal Hydrides and Organocuprates

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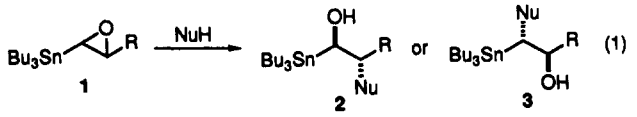
α-Epoxyorganostannanes are attacked by metal hydride reagents (DIBAL-H, $LiAlH_4$, REDAL) and Me_2CuLi at the carbon atom proximal to the tin atom and directly at the tin atom. For example, tributyl(epoxyethyl)stannane (5) reacts with DIBAL-H to give a mixture of 2-(tributylstannyl)ethanol (7) and tributyltin hydride. Reaction of 5 with Me_2CuLi affords predominantly 2-(tributylstannyl)propan-1-ol (8) and some Bu_3SnMe. Similarly, 3-(tributylstannyl)oxiranemethanol (10) reacts with REDAL and Me_2CuLi to provide products of nucleophilic attack at C-3. Cleavage occurs with inversion of stereochemistry. Tributyl(3,4-epoxybutyl)stannane (21) reacts with $LiAlH_4$ to give secondary alcohol 22 as the sole product.

While the nucleophilic opening of α-epoxyorganosilanes has been reasonably well-documented,[1] the literature contains no detailed reports of such reactions with the corresponding stannanes. In fact, α-epoxyorganostannanes do not seem to have been the subject of much attention.[2] In connection with our work with α-alkoxyorganostannanes,[3] it was of interest to study the regioselectivity of the nucleophilic ring opening of α-epoxyorganostannanes. In particular, we wished to ascertain whether ring opening of 1 would afford α-hydroxystannanes 2 (which could be converted into synthetically useful α-alkoxyorganostannanes) or β-hydroxystannanes 3 (eq 1). Our findings in this area are reported below.

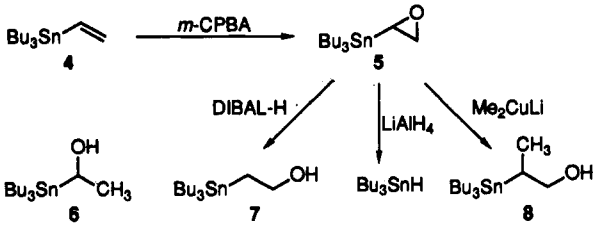


Results and Discussion

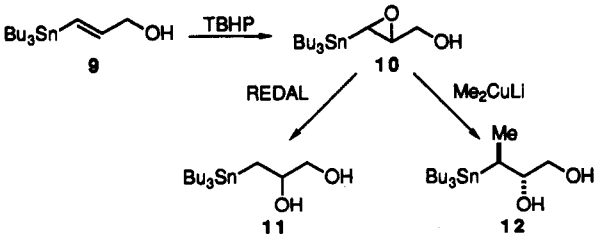
The epoxide derived from tributylvinylstannane (4) has been prepared previously in low yield (12%) by treatment of 4 with *m*-CPBA in benzene.[4] A simple change in solvent dramatically improved the yield of 5: When vinylstannane 4 was allowed to react with *m*-CPBA in $CHCl_3$, epoxide 5 was isolated in reasonable yield (67%) after column chromatography.

There appear to be no reports of studies on nucleophilic openings of 5.[5] When 5 was treated with DIBAL-H at low

Scheme I



Scheme II



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(4) Ayrey, G.; Parsonage, J. R.; Poller, R. C. *J. Organomet. Chem.* **1973**, *56*, 193.

(5) Reaction of 4 with a magnesio cuprate was reported in footnote 11 of: Matsubara, S.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 5857.

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