electron-withdrawing inductive effect.[46]

Four compounds were investigated and found to have values of k_{inh} that were too small to be measurable in our system; these compounds are listed in Table I but not Table II. Menadione, a quinone, does not behave as an antioxidant in our system; quinones typically are good scavengers of carbon-centered radicals but not of peroxyl radicals.[47] Aminopyrine is a tertiary amine; although sometimes referred to as an antioxidant, it would not be expected to scavenge peroxyl radicals, and it has no activity in our system. Ibuprofen is a benzylacetic acid derivative and also would not be expected to be an antioxidant. We tested it since nonsteroidal antiinflammatory compounds that are inhibitors of prostaglandin synthase often are found to be antioxidants; however, ibuprofen, which is a very effective antiinflammatory drug, has no detectable antioxidant properties in our system. This implies that using antioxidant effectiveness as a screening technique for antiinflammatory drugs has limitations. β-Carotene also has an inhibitor constant that is too small to measure in our system. This result is in agreement with the results of Burton and Ingold,[48] who have shown that β-carotene is quite effective at low oxygen tensions but less so at higher oxygen tensions in their chlorobenzene-methyl linoleate system. Our linoleic acid-aqueous system, of course, is fully oxygenated, and we find that β-carotene has a very low effectiveness as an antioxidant.

Acknowledgment. We are very grateful to both Dr. Keith Ingold and to Professor Ross Barclay for extremely helpful suggestions and comments on a preliminary draft of this manuscript. We also thank Dr. Barclay for providing a preprint copy of his manuscript reporting k_p values for linoleic acid in SDS micelles at 30 °C and the private communication of his unpublished value at 37 °C. Dr. Ingold provided generous gifts of the three tocopherol analogues. Dr. Graham Burton was very helpful during the building of our pressure transducer apparatus. Dr. John Cosgrove measured the value of k_d for ABAP in the micellar system. We are grateful to the Eisai Co., Hoffmann-La Roche, Dow Chemical Co., and the Upjohn Co. for generous samples of their chemical compounds. This work was supported in part by a grant from the NIH and a contract from the National Foundation for Cancer Research.

(46) Ingold, K. V., private communication.
(47) Walling, C. *Free Radicals in Solution*; Wiley: New York, 1957.
(48) Burton, G. W.; Ingold, K. U. *Science (Washington, D.C.)* **1984**, *224*, 569-573.

Host-Guest Complexation. 46. Cavitands as Open Molecular Vessels Form Solvates[1,2]

Donald J. Cram,* Stefan Karbach, Hye-Eun Kim, Carolyn B. Knobler, Emily F. Maverick, John L. Ericson, and Roger C. Helgeson

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received August 10, 1987*

Abstract: The syntheses, physical properties, and crystal structures of a series of cavitands of general structure I are described. The four methyl groups act as "feet" to support "bowls" whose depths and shapes vary with the character of the R substituents (H, CH_3, Br, and I) and whose curvatures vary with the number of methylenes in the O to O bridges (n = 1-3). These compounds all possess enforced concave surfaces of molecular dimensions (cavitands) and form solvates with simple guest molecules, most of which are complementary to their cavities, such as CH_2Cl_2, $CHCl_3$, SO_2, CH_3CN, $C_6H_5CH_3$, $(CH_2)_6$, and C_6H_6. Nine crystal structures of inclusion complexes have been determined that illustrate a variety of differently shaped bowls and different host-guest contacts. Three examples of compound I are reported in which only three of the four sets of adjacent oxygens are bridged. These compounds provide starting materials for a variety of more elaborate cavitands into which binding and catalyzing functional groups might be incorporated.

Structural recognition in complexation depends directly on stereoelectronic complementarity between surfaces common to hosts and guests in their complexes.[3] At one extreme, complexes contain partners, which are completely organized for complexation *prior* to their becoming paired (preorganized).[4] At the other extreme, complexes are derived from conformationally mobile hosts and guests. In the usual intermediate or latter cases, those molecular parts of each partner that bind one another are very likely to be rigid and relatively free of conformational degrees of freedom once complexed. *Thus most host-guest complexes are more rigid than their hosts and guests taken separately.*

This generalization particularly applies to complexation in solution in which host, guest, and complex are all solvated. Complexes present less surface for solvent contacts than hosts and guests taken separately. Therefore, complexes are less solvated than their uncomplexed partners taken in sum. Even with highly preorganized hosts and guests, rotational degrees of freedom exist for their solvating molecules. Thus desolvation accompanying complexation represents an exchange of increased rigidity of the binding partners for more degrees of freedom for those solvent molecules that are liberated.

In an attempt to eliminate some of the cancelling effects that compose structural recognition in complexation, we have increasingly studied hosts that are highly preorganized for complexation. In this investigation we sought a series of compounds that fulfill the following criteria. (1) The compounds should be cavitands containing *enforced concave surfaces of molecular dimensions*.[5,6] (2) The dimensions should be subject to design.

(1) We warmly thank the National Science Foundation for Grant CHE 81-09532, which helped support this work.
(2) This paper is dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.
(3) (a) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564-2571. (b) Weber, D. E.; Vögtle, F. In *Topics in Current Chemistry, Host Guest Complex Chemistry I*; Springer Verlag: Berlin, 1981; Vol. 98, pp 1-42.
(4) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057.
(5) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826-5828.

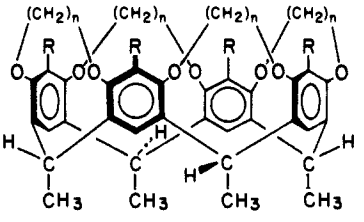
0002-7863/88/1510-2229$01.50/0

Table I. Media and Results of Multiple Bridging Reactions

reactants			products							
			four bridges				three bridges			
R of phenol	$X(CH_2)_nX$	medium	compd no.	*n* of $(CH_2)_n$	yield, %	solvate	compd no.	*n* of $(CH_2)_n$	yield, %	solvate
H	$BrCH_2Cl$	DMSO–DMF, K_2CO_3	**5**	1	23	CH_2Cl_2				
CH_3	$BrCH_2Cl$	DMA, K_2CO_3	**6**	1	63	none				
Br	$BrCH_2Cl$	DMSO, Cs_2CO_3	**7**	1	55	$CHCl_3$	**12**	1	11	$CH_3C{\equiv}N$
CH_3	$TsOCH_2CH_2OTs$	DMA, K_2CO_3	**9**	2	43	CH_2Cl_2				
Br	$TsOCH_2CH_2OTs$	DMSO, Cs_2CO_3	**10**	2	35	H_2O	**13**	2	30	CH_2Cl_2
CH_3	$TsO(CH_2)_3OTs$	DMA, K_2CO_3	**11**	3	16	CH_2Cl_2				
Br	$TsO(CH_2)_3OTs$	DMSO, Cs_2CO_3	**12**	3	50	H_2O	**15**	3	27	CH_2Cl_2

(3) The compounds should be easy to prepare in quantity. (4) The gross frameworks of the cavitands should be stable to reaction conditions that allow a variety of functional groups to be introduced that focus on the cavity. (5) The solubility of the cavitands should be manipulable by introduction at positions remote from the cavity of multiple groups that render the substances soluble in solvents ranging from water to hydrocarbons.

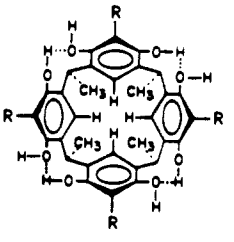
The generalized cavitand I, in which the character of R and the value of *n* can be systematically varied, has been found to satisfy criteria 1–4. A description of how criterion 5 is satisfied by substitution of the four methyl "feet" of structure I by a variety of other groups is reserved for a future paper in this series.



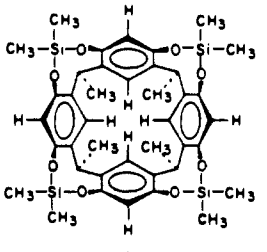
I:R is H, CH_3, Br or I; n is 1, 2 or 3

Results and Discussion

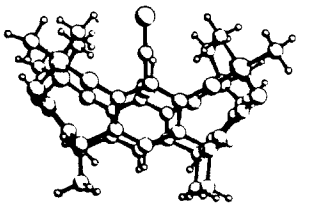
Syntheses. Octols **1–3** served as the starting materials for the cavitands reported here. Compound **1**[7] is easy to prepare from acetaldehyde and resorcinol on a large scale (73% in our hands). Its configuration was rigorously established for the first time from the crystal structure of its tetrasilyl derivative **4**.[8] Other authors,[9] using ^1H NMR spectral comparisons, have concluded that its configuration resembles that of the more stable of the two diastereomers obtained from *p*-bromobenzaldehyde and resorcinol, whose octabutyrate ester was shown by crystal-structure determination to possess the all-cis configuration.[10] The conformational equilibrium of the all-cis stereoisomer derived from benzaldehyde and resorcinol and the acid-catalyzed isomerization of the cis–trans–trans stereoisomer to the more stable all-cis stereoisomer have been reported by Högberg.[11] Compound **1** also appears to be conformationally mobile and to be the most thermodynamically stable of the several stereoisomers initially formed in the cyclooligomerization reaction.



1, R = H
2, R = CH_3
3, R = Br



4



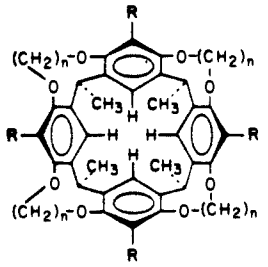
4·CS_2

Treatment of 2-methylresorcinol with acetaldehyde likewise provided the all-cis stereoisomer **2** (57%), whose configuration was demonstrated by crystal structure determination of a derivative (see next section). The greater stability of the all-cis diastereomers in the three systems so far reported appears to be associated with the uninterrupted chain of hydrogen bonds formable in the all-cis isomers but not with the other isomers.[11] Octol **1** readily underwent bromination with *N*-bromosuccinimide (NBS) in 2-butanone to give the tetrabromide **3** (80%).

The three conformationally mobile octols, **1–3**, were converted to bowl-shaped cavitands by fourfold ring closures, which introduced methylene or polymethylene bridges anchored by the four sets of proximate oxygens. Molecular model (CPK) examination indicates that only the all-cis isomer in its C_{4v} conformation places these oxygens close enough to one another to be bridged by chains as short as those containing one to three carbons. Thus these reactions by themselves demonstrate the configurations of **1–3**. Table I reports the media and results of the multiple ring-closing reactions carried out under moderately high dilution conditions. Generally, higher yields were obtained from phenols with R = CH_3 or Br than with R = H, probably because steric depression of intermolecular reaction rates leading to noncyclic oligomers was greater than that of their intramolecular counterparts leading to ring closure. The use of $BrCH_2Cl$ to introduce methylene groups into the phenols gave better yields of the cavitands than either CH_2I_2 or CH_2Br_2. From the reaction conditions and times required for consumption of starting material, we conclude that **1** > **2** ≫ **3** in reaction rates with alkylating agents.

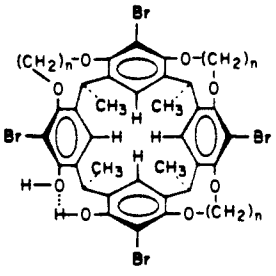
The ring closures leading to cavitands **5–8** involved formation of four eight-membered cycles. Those leading to cavitands **9** and **10** provided four new nine-membered cycles, and those that gave **11** and **12** generated four new 10-membered cycles. Higher temperatures and longer reaction times were required as the cycle sizes increased. No yield patterns as a function of cycle size are visible in the results. Generally, DMSO–Cs_2CO_3 provided the best reaction medium.[12]

(6) Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177–1183.
(7) Niederl, J. B.; Vogel, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 2512–2514.
(8) Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575.
(9) Schneider, H.-J.; Güttes, D.; Schneider, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647–649.
(10) (a) Erdtman, H.; Högberg, S.; Abrahamsson, S.; Nilsson, B. *Tetrahedron Lett.* **1968**, 1679–1682. (b) Nilsson, B. *Acta Chem. Scand.* **1968**, *22*, 747. (c) Palmer, K. J.; Wong, R. Y.; Jurd, L.; Stevens, K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 847–852.
(11) (a) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500. (b) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050.



5, R = H, n = 1; **6**, R = CH_3, n = 1
7, R = Br, n = 1; **8**, R = I, n = 1
9, R = CH_2, n = 2; **10**, R = Br, n = 2
11, R = CH_3, n = 3; **12**, R = Br, n = 3

When R = Br, introduction of the fourth bridge occurred more slowly than the other three, so that diphenols **13–15** containing only three bridges were obtained either as byproducts or as major products, depending on the amounts of $X(CH_2)_nX$ employed.

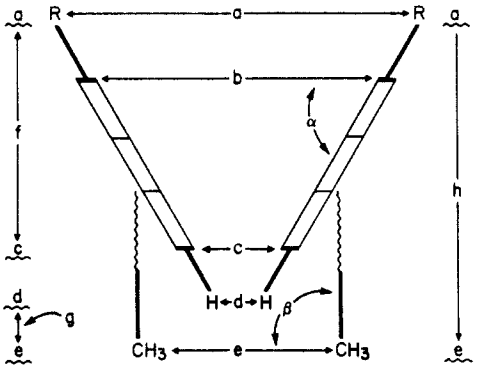


13, n = 1
14, n = 2
15, n = 2

This rate difference probably reflects an incremental increase in the rigidity of the cavitands with addition of each bridge. Molecular models (CPK) indicate that tribridged phenols **13–15** provide much less conformational adaptability to accommodate the geometric requirements of linear SN_2 transition states than do the mono- or dibridged intermediate phenols. The first bridge introduced blocks the ring-inverting conformational interconversions characteristic of the free phenols and their noncyclic derivatives. Preliminary results indicate that practical amounts of monobridged and the two dibridged analogues of the starting phenols can be obtained by proper manipulation of reaction conditions. Access to such compounds and to **13–15** is very welcome since they provide useful starting materials for syntheses of a variety of desired cavitands containing different kinds of bridges and substituents in the same molecule. The tetraiodo cavitand **8** was prepared by tetralithiating **1** and treating the organometallic with I_2 (40%). This conversion is a prototype for others in which a variety of functional groups can be introduced into these cavitands.[13]

Crystal Structures of the Cavitands. Nine crystal structures of solvates of cavitands **5–10** and **15** were determined. All of these are inclusion complexes, but some involve solvent molecules packed between the inclusion complexes. Their compositions are as follows: **5**·CH_2Cl_2, **6**·CH_3CN, **6**·$(CH_2)_6$·C_6H_6, **7**·$CHCl_3$, **8**·$CH_3C_6H_5$, **9**·$(CH_2)_6$, **9**·C_6H_6·C_6H_6, **10**·CH_2Cl_2, and **15**·CH_2Cl_2. The distances and angles relevant to the shapes of their cavities are listed in Table II and defined in general drawing **16**.

These cavitands are all generally conical, with the cone supported on a square framework of four methyl "feet" located at the bottom in drawings **16** and I. The nearly closed bases of their cavities are defined by a 16-member [1.1.1.1]metacyclophane macroring. The open tops are defined by [*m.m.m.m*]metacyclophane macrorings containing eight oxygens and from 24 to



16

32 ring members (the ring of **15** is incomplete). Charts I–III contains side and top (bottom for **6**·CH_3CN, **7**·$CHCl_3$, and **15**·CH_2Cl_2) stereoviews of their crystal structures along with identifying line structures.

Molecular model examination of all of these cavitands except **15** suggest they could contain C_4 axes. Only **6**·CH_3CN contains this symmetry element. The cavitand parts of the other crystal structures have approximate C_2 axes, particularly those containing the OCH_2O bridges. One measure of the extents to which the cavitands depart from having C_4 axes is indicated by how much the two diagonal distances for *a*, *b*, *c*, *d*, and *e* differ from one another in each host (see **16** for definitions). For example, the two *a* values for **5** are 9.11 and 8.96 Å, a difference of 0.15 Å, which is 1.7% of the average of the two *a* values. The percent differences of *a* for the other solvates are as follows: **6**·CH_3CN, 0%; **6**·$(CH_2)_6$·C_6H_6, 1.4%; **7**·$CHCl_3$, 4.9%; **8**·$CH_3C_6H_5$, 1.6%; **9**·$(CH_2)_6$, 21.4%; **9**·C_6H_6·C_6H_6, 22.6%; **10**·CH_2Cl_2, 24.7%; and **15**·CH_2Cl_2, 49.8%. Interestingly, the crystal structure of **15**·CH_2Cl_2 is "disordered" to provide a crystallographic C_2 axis. The $ArOCH_2CH_2CH_2OAr$ and ArOH·O(H)Ar types of bridges appear interchangeable in their positions in the lattice. Because of the lack of electron density associated with the one hydrogen-bonded bridge, its interspersion with $O(CH_2)_3O$ bridges detracted only in a minor way from our ability to place these atoms in their crystal structures. Molecular models of **15** indicate that the two types of bridges can provide similar ArO to ArO spans. A mixture of **12** and **15** cocrystallizes to give what to the eye appears to be homogeneous material. To insure that the crystal structure was actually performed on **15** and not on **12** or a mixture, the single crystal that had been used in the structure determination was submitted to TLC and found indeed to be **15**.

Aside from the guest solvates, the hosts with 24-membered-ring rims (one methylene per bridge) deviate from having C_4 axes by 2 ± 2%. The hosts with 28-membered-ring rims (two methylenes per bridge) deviate by 23 ± 2% from having C_4 axes by elongating their rims in one dimension and narrowing them in another. This effect is accentuated more in the host of **15** with a pseudo-32-membered-ring top. Thus planes *a–e* (see **16**) are essentially square in the rigid hosts **5–8**, but rectangular in **9** and **10**, and more markedly so in **15**. This effect is accentuated in plane *a* defined by R groups, but is less visible in plane *e* defined by the methyl feet. Thus in **5–8**, deviation of plane *e* from having a C_4 axis is 2 ± 2%, in **9** and **10** it grows to 4 ± 1%, and in **15** it still is only 8%. Other evidence for the relative rigidity of the supporting structure of the bowls is found in the averaged low value of 0.03 ± 0.05 Å by which the methyl carbons of the "feet" deviate from coplanarity, the largest deviation being observed for **7**·$CHCl_3$ (±0.08 Å). A third measure of the pedestal-like rigidity of the bowl support structure is the proximity of the CH_3–C axis being perpendicular to the best plane of the methyl feet (*e*). For hosts **5–10**, β_{av} = 87.4 ± 2.6° (β measures this parameter), while β = 83.8° for **15**.

The variation in the O–O distances with *n* in the ArO-$(CH_2)_n$OAr bridges provides a good measure of the "relative openness" of the cavity on its rim. In **5–8**, in which *n* = 1, this distance is nearly constant at 2.34 ± 0.04 Å. The orbitals of the

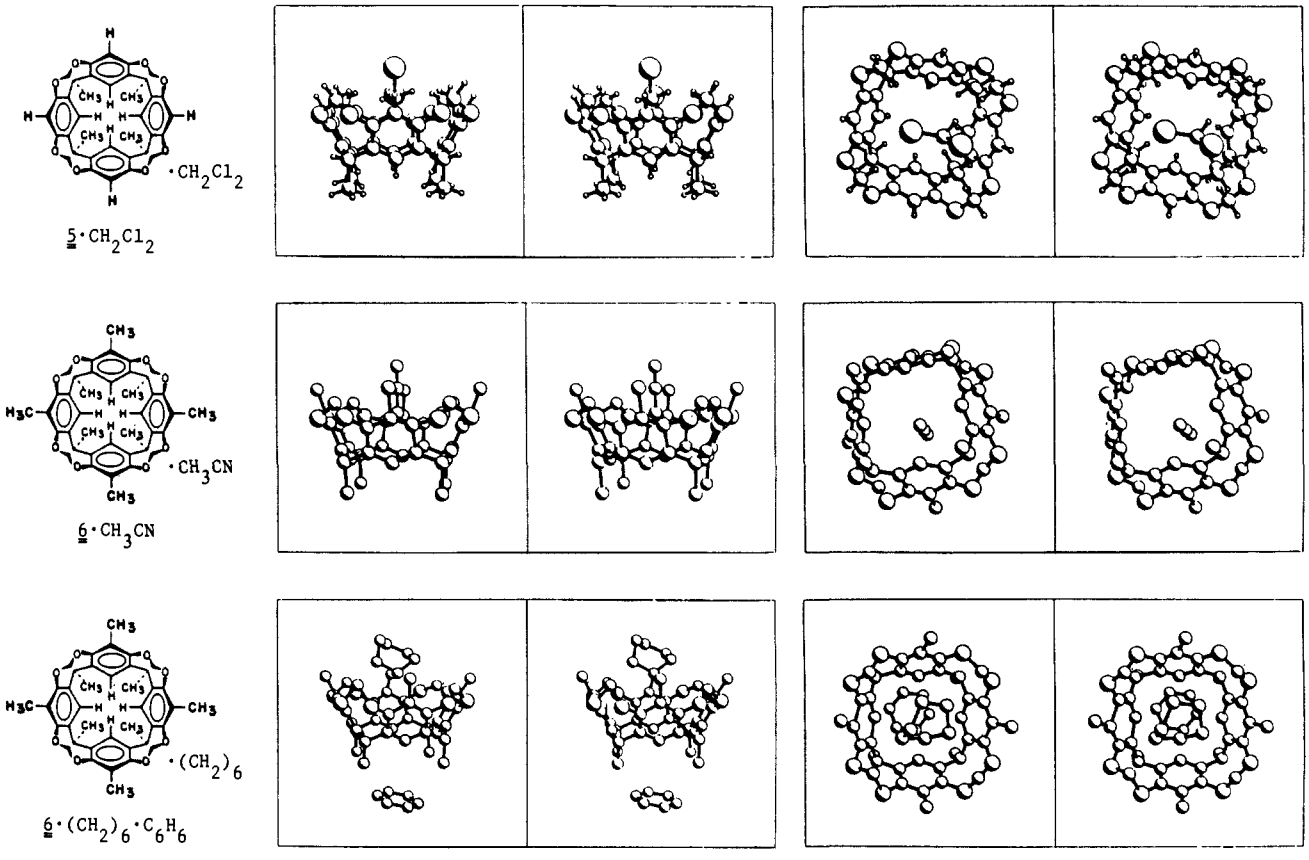
(12) Piepers, D.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 383–384.
(13) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575–2576.

Table II. Distances and Angles Relevant to the Shapes of Cavities of Cavitands[a]

compd no. solvate	5 CH_2Cl_2	6 CH_3CN	6 $(CH_2)_6$–C_6H_6	7 $CHCl_3$	8 $CH_3C_6H_5$	9 $(CH_2)_6$	9 C_6H_6–C_6H_6	10 CH_2Cl_2	15 CH_2Cl_2
distances (Å) between									
R···R diagonal of plane *a* (*a*)	9.11, 8.96	9.09	9.50, 9.63	9.34, 9.81	10.07, 9.91	9.75, 12.09	9.68, 12.15	9.77, 12.53	8.16, 13.57
$(R···R)_{av}$ for *a*	9.04	9.09	9.56	9.58	9.99	10.92	10.92	11.15	10.86
R out of plane *a*	±0.01	0.00	±0.04	±0.06	±0.01	±0.50	±0.52	±0.57	±1.18
C···C diagonal of plane *b* (*b*)	8.03, 7.89	7.93	8.01, 8.00	8.00, 7.83	7.92, 7.90	8.04, 9.52	7.98, 9.54	7.79, 9.43	6.94, 10.03
$(C···C)_{av}$ for *b*	7.96	7.93	8.00	7.92	7.91	8.78	8.76	8.61	8.48
C out of plane *b*	±0.01	0.00	±0.02	±0.02	±0.01	±0.28	±0.28	±0.27	±0.62
C···C diagonal of *c* (*c*)	5.25, 5.27	5.31	5.17, 5.26	5.25, 5.23	5.28, 5.24	5.06, 5.10	5.06, 5.10	5.02, 5.17	5.08, 5.28
$(C···C)_{av}$ for *c*	5.26	5.31	5.22	5.24	5.26	5.08	5.07	5.10	5.18
C out of plane *c*	±0.00	0.00	±0.02	±0.02	±0.01	±0.05	±0.05	±0.02	0.02
H···H diagonal of plane *d* (*d*)	4.18, 4.20	4.33	4.32, 4.12	4.29, 4.26	4.25, 4.18	3.34, 3.93	3.47, 4.10	3.50, 3.89	3.58, 4.50
$(H···H)_{av}$ for *d*	4.19	4.33	4.22	4.28	4.22	3.64	3.78	3.70	4.04
H out of plane *d*	±0.01	0.00	±0.01	±0.02	±0.01	±0.20	±0.19	±0.14	±0.24
$CH_3···CH_3$ diagonal of plane *e* (*e*)	7.10, 7.32	7.06	7.14, 7.15	7.34, 7.02	7.24, 7.04	6.91, 7.20	6.90, 7.26	7.04, 7.24	6.89, 7.47
$(CH_3···CH_3)_{av}$ for *e*	7.21	7.06	7.14	7.18	7.14	7.06	7.08	7.14	7.18
CH_3 out of plane *e*	±0.03	0.00	±0.02	±0.08	±0.07	±0.01	±0.00	±0.03	±0.03
plane *a* to *c* (*f*)	3.34	3.90	3.81	4.15	4.21	3.18	3.09	3.33	3.15
plane *d* to *e* (*g*)	0.64	0.77	0.70	0.67	0.62	0.88	0.89	0.87	0.86
plane *a* to *e* (*h*)	4.95	5.53	5.36	5.69	5.76	4.74	4.80	5.0	4.74
near O···O	2.39, 2.36	2.30	2.32, 2.34	2.33, 2.42	2.36, 2.37	3.01, 2.95	2.98, 2.88	2.96, 2.88	3.29, 3.02
	2.38, 2.38		2.32, 2.32	2.34, 2.31	2.34, 2.35	2.98, 2.93	2.97, 2.89	2.83, 2.87	
near $(O···O)_{av}$	2.38	2.30	2.32	2.35	2.36	2.97	2.93	2.91	3.16
angles (deg) between									
planes *a* and *c*	0.4	0	2.8	0.5	1.1	0.1	0.4	0.5	0
planes *d* and *e*	0.6	0.00	1.5	1.0	0.4	0.2	0.1	0.6	0
planes *a* and *e*	0.5	0.00	1.1	0.7	1.1	0.2	0.4	1.2	0
planes benzene and *b* (*α*)	61.6, 61.2	62.8	59.1, 60.1	60.9, 62.8	61.9, 60.7	58.5, 37.8	59.6, 38.4	58.9, 38.5	69.7, 28.2
	61.4, 59.2		61.1, 61.0	59.9, 61.0	60.5, 61.9	57.3, 38.1	58.78 39.3	60.0, 39.7	69.7, 28.2
$(\alpha)_{av}$	60.85	62.8	60.3	61.2	61.2	47.9	49.0	49.3	49.0
plane *e* to CH_3C (*β*)	88.6, 89.5	90	86.0, 87.2	85.8, 85.2	86.5, 89.1	87.3, 85.7	87.5, 84.3	87.6, 86.8	84.0, 83.6
	88.7, 88.5		85.3, 86.3	87.7, 86.3	87.0, 88.3	86.4, 86.0	86.4, 85.6	89.0, 88.4	
$(\beta)_{av}$	88.8	90	86.3	86.2	87.7	86.4	86.0	88.0	83.8
dihedral OCCO (*γ*)						64.0, 62.4	63.1, 65.3	62.6, 59.3	
						61.4, 68.8	59.0, 68.4	61.9, 62.3	
$(\gamma)_{av}$						64.2	63.4	61.5	

[a] Planes *a*–*e* are defined as the best planes in general diagram **16** of the following: *a*, four R groups; *b*, four aryl carbons bonded to R groups; *c*, four aryl carbons bonded to hydrogen; *d*, four aryl hydrogens; *e*, four aryl methyls. Distances *a*–*e* (Å) refer to atoms in planes most distant from one another in the respective *a*–*e* planes. Distances *f*–*h* are those between best planes. Structure **16** in the text explicitly defines the distances and angles.

Chart I



unshared electron pairs of the oxygens diverge from the cavity, and the hydrogens of the single CH_2 groups point upward–inward and upward–outward in pairs. In **9** and **10**, in which $n = 2$, the O–O distance is 2.93 ± 0.08 Å (three structures). Again, the orbitals of the unshared electron pairs on the oxygens diverge from the cavity, and the atoms of the CH_2CH_2 groups point generally

Chart II

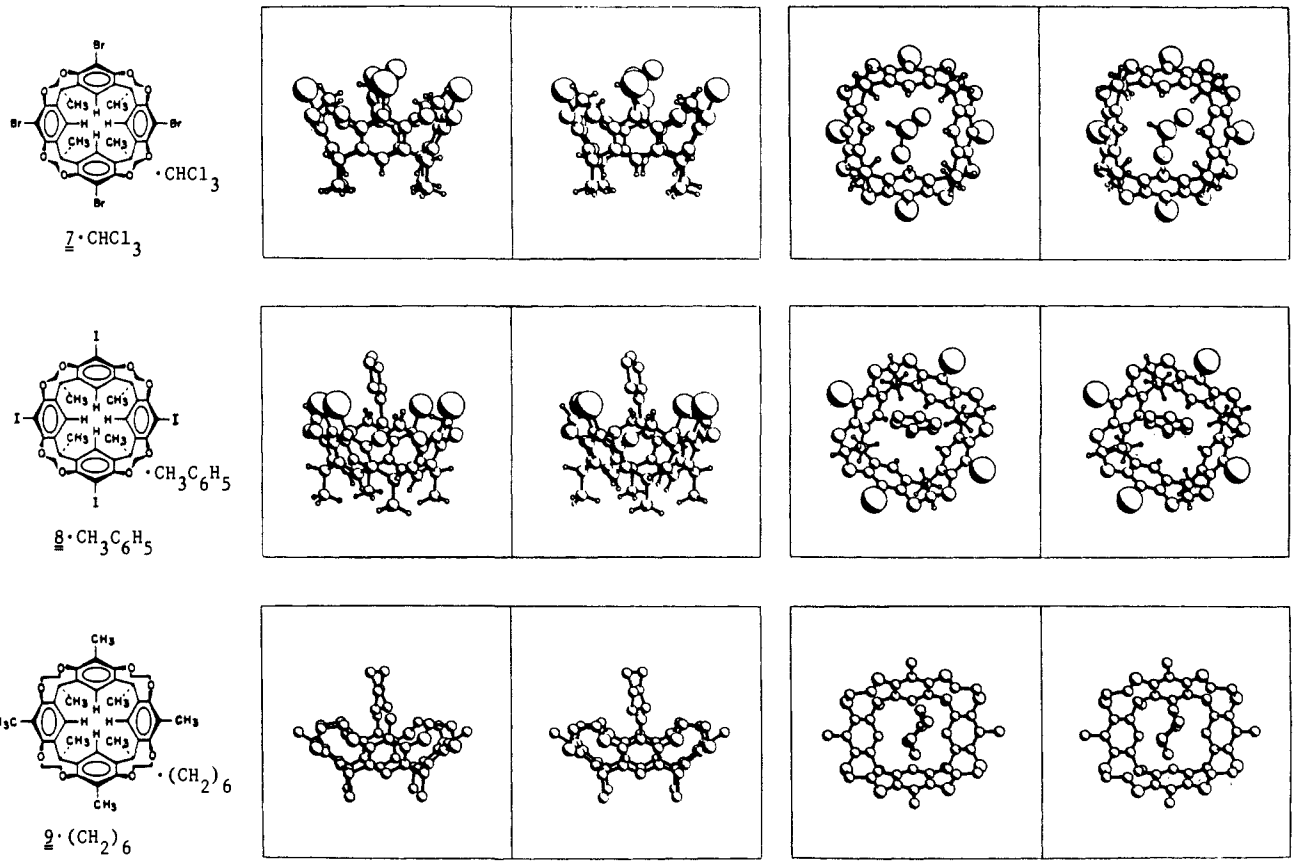
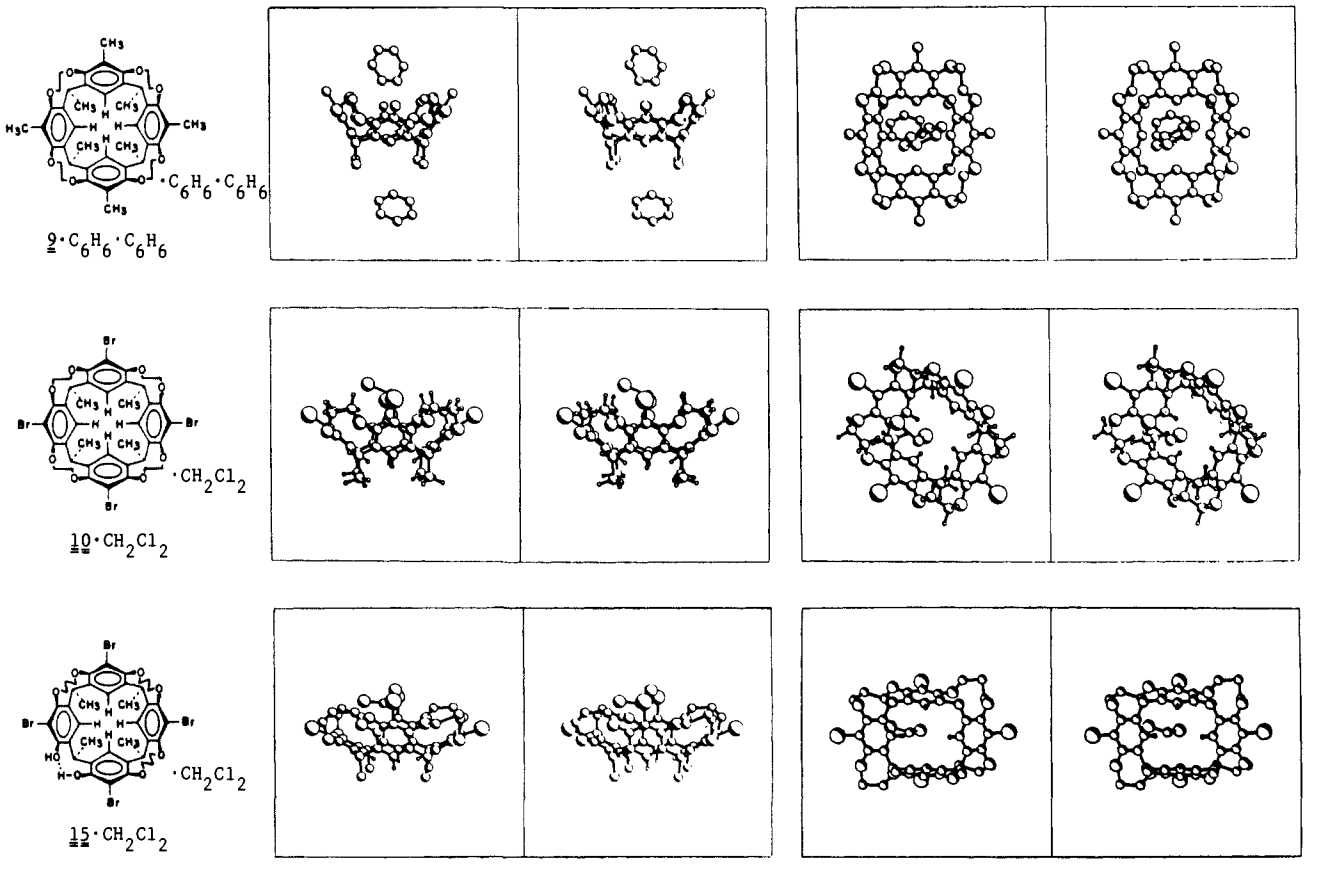


Chart III



upward to increase the depth of the cavity. In **15**, in which n = 3, the O–O distance is 3.16 ± 0.14 Å, to provide an even more open cavity. Of the eight oxygens, the orbitals of the unshared electron pairs on six of the oxygens diverge from the cavity, and the atoms of the $CH_2CH_2CH_2$ module are generally oriented outward, resulting in little increase in the depth of the cavity. The

orbitals of the other two oxygens turn inward. The dihedral angles (γ) of the OCH_2CH_2O bridges in **8** and **9** are 63 ± 4°, indicating the presence of little torsional strain. In the stereoviews of **15**·CH_2Cl_2, the $CH_2CH_2CH_2$ groups appear to be nicely staggered to produce little torsional strain.

Since linking two of these cavitands at their rims through the four R groups of I leads to carcerands,[13] the interesting question arises about the sizes of the pores that might allow entrance to (or egress from) the interiors of closed-surface hosts composed of these cavitand parts. The largest openings in the surfaces of **5–10** and **15** are between the methyl feet, which themselves provide a cylindrical opening of about 3.5-Å diameter. The pores are further narrowed by the four aryl hydrogens that define plane *d* in the general drawing, **16**. The $(H\cdots H)_{av}$ diagonal distance *d* across the plane provides a measure of the opening. As expected from model examination, *d* varies with the value of *n* in the bridges as follows: for **5–8** (five structures), d_{av} = 4.25 ± 0.07 Å, to provide a pore diameter of about 3.2 Å; for **9** and **10** (three structures), d_{av} = 3.71 ± 0.07 Å, to give a pore diameter of about 2.6 Å; for **15**, d_{av} = 4.04 Å, to provide a pore diameter of about 3.0 Å. Few molecules or ions are small enough to pass through these openings.

The cavity diameters at the rims of the hosts are roughly measured by the values of *a*, which equal the R···R diagonal *across* the plane *a*. This distance varies both with *n* and the character of the R substituents as follows. In **5–8** with *n* = 1, R = H provides a_{av} = 9.04 Å, to give a rim diameter of about 8 Å; R = CH_3, a_{av} = 9.32 Å, to give a rim diameter of about 7.1 Å; R = Br, a_{av} = 9.58 Å, to give a rim diameter of about 7.3 Å; R = I, a_{av} = 9.99 Å, to provide a rim diameter of about 7.4 Å. In **9** and **10** with *n* = 2, R = CH_3 provides a_{av} of 10.92 Å, to give a rim diameter of about 8.7 Å; R = Br provides a_{av} of 11.15 Å and a rim diameter of about 8.9 Å. In **15** with *n* = 3 and R = Br, a_{av} = 10.86 Å to provide a rim diameter of about 8.6 Å. That this parameter varies so little reflects the only minor effect that the values of n have on the proximate O···O distances.

The cavity depths are best measured by the distance *f* from plane *a*, defined by the R groups to plane *c*, defined by the lower carbons of the four aryls (see drawing **16**). These f_{av} values vary with the values of *n* and the nature of the R group. Cavitands **5–8** with *n* = 1 provide f_{av} values as follows: R = H, 3.34 Å; R = CH_3, 3.86 Å; R = Br, 4.15 Å; R = I, 4.21 Å. Cavitands **9** and **10** with *n* = 2 provide f_{av} values of 3.14 Å for R = CH_3 and 3.33 Å for R = Br. Host **15** with *n* = 3 and R = Br gives an f_{av} value of 3.15 Å. Thus the cavity depths increase somewhat with increases in Ar–R bond lengths, but decrease with increasing values of *n*, as expected.

The parameter α is defined as the angle between the best plane of a benzene and best plane, *b*, defined by the four aryl carbons bonded to R groups (see **16**). The α_{av} values provide a measure of how fast the aryls converge on one another in passing from the open to the constricted end of the cone. These α_{av} values are essentially the same for **5–8**, where *n* = 1 at 61.3 ± 1.5°. For **9**, **10**, and **15**, α_{av} values are also nearly the same at 48.8 ± 0.9°, even though *n* = 2 for **9** and **10** and *n* = 3 for **15**. The latter value is probably limited by steric and bond-angle constraints associated with the relatively rigid base of the cone.

Comparisons of the crystal structures of **6**·CH_3CN with **6**·$(CH_2)_6$·C_6H_6 and of **9**·$(CH_2)_6$ with **9**·C_6H_6·C_6H_6 provide answers to how much the structures of the hosts are dependent on those of the guests. As expected, the dependency is minor but interesting. For example, the CH_3CN guest in **6**·CH_3CN leaves the host with a C_4 axis, whereas the $(CH_2)_6$ guest of **6** slightly elongates the rim in one dimension and narrows it in a second. The differences between the host structures of **9**·$(CH_2)_6$·C_6H_6 and **9**·C_6H_6·C_6H_6 are negligible, probably because both guests are too large to deeply penetrate into the cavity of the host.

Host–Guest Structural Relationships. The three-dimensional views of the crystalline caviplexes provide a qualitative impression of the degrees of complementarity between host and guest. In **5**·CH_2Cl_2, the CH_2Cl moiety of the guest lies largely in the open end of the cavity, and the other Cl protrudes from the rim. In **6**·CH_3CN, the CH_3C penetrates deeply enough into the cavity to bring the tops of the OCH_2O hydrogens nearly level to the N atom of the guest. The dipoles of host and guest probably cancel one another more in this arrangement than in an alternative one in which the N is deep in the cavity. In **6**·$(CH_2)_6$·C_6H_6, the two hydrogens and carbon (CCH_2C) of a *boat* cyclohexane penetrate the top of the cavity. Boat cyclohexanes are rarely encountered in organic chemistry without additional bridges or substituents. In effect, the host appears to play the role usually played by bulky substituents that force a boat conformation on cyclohexane. The benzene ring appears to contact the four methyl feet, with its C_6 axis not far from being coincident with the best C_4 axis of the host. In **7**·$CHCl_3$, one Cl deeply penetrates the cavity, while the remaining $CHCl_2$ group lies partially in the wide opening at the top of the bowl. In **8**·$CH_3C_6H_5$, the CH_3C atoms lie fully in, and the 2,6 carbons and hydrogens partially in the cavity. The axis of the CH_3–C bond of the guest appears to be nearly coincident with the near C_2 axis of the host.

In **9**·$(CH_2)_6$·C_6H_6 a *chair*-cyclohexane edge lies across the face of the mouth in the smaller dimension of the flattened cone so that only two equatorial hydrogens penetrate the cavity. This structure exemplifies a highly noncomplementary relationship between host and guest and probably is an artifact of the intermolecular packing forces of the crystal. In **9**·C_6H_6·C_6H_6, only two ortho hydrogens of the benzene pseudoguest penetrate the cavity. The structure of **10**·CH_2Cl_2 exemplifies a much more complementary host–guest relationship. One Cl group deeply penetrates the cavity, and the other Cl and its attached carbon lie in the entrance to the flattened cone distributed along the longer dimension of the host.

In **15**·CH_2Cl_2, one Cl of the guest penetrates deeply the cavity of the host, and the two hydrogens are well within the cavity. The remaining C–Cl bond axis is oriented along the longer dimension of the flattened cone and the two atoms occupy the cavity entrance in a moderately complementary and compact host–guest arrangement. The aryl hydrogens that constrict the opening at the base of the cone are clearly visible in this structure.

Caviplexes **5**·CH_2Cl_2, **7**·$CHCl_3$, **10**·CH_2Cl_2, and **15**·CH_2Cl_2 provide interesting comparisons. One chlorine of **7**·$CHCl_3$, **10**·CH_2Cl_2, and **15**·CH_2Cl_2 lies deep in the cavity in such a way that the C–Cl dipole of the guest is aligned to complement the Br–C dipoles of the host. The elongation of the cone opening in one dimension and narrowing in the other brings the compensating dipoles closer together in these three caviplexes. This effect is most pronounced in **15**, the most flexible host. The absence of C–Br dipoles in **5**·CH_2Cl_2 correlates with the absence of a chlorine inserted deeply into the cavity of **5**. Although given ample opportunity to form crystalline inclusion complexes with CH_2Cl_2 or $CHCl_3$, **6** and **8** (in which R is CH_3 instead of Br) failed to provide them.

Conclusions

This study indicates that cavitands of varying dimensions containing a variety of substituents can be designed with the aid of CPK molecular models and then readily prepared. Nine crystal structures demonstrate the general conformity between expectation and realization regarding their structures. Either three or four bridges of varying lengths can be used to rigidify the bowl-shaped cavities. All nine crystal structures proved to be inclusion complexes, but they vary greatly in the areas of the surfaces common to host and guest. Complementarity was high when the guests were CH_3CN, $C_6H_5CH_3$, CH_2Cl_2, and $CHCl_3$ and low when the guests were C_6H_6 or $(CH_2)_6$. The hosts with single-carbon methylene bridges were nearly rigid. Those with two or three carbons in their methylene bridges exercised their flexibility to accommodate the dipole–dipole interactions between host and guest. The rims of the bowls varied considerably in their deviation from having a C_4 axis, but all possessed at least near C_2 axes. The support structures at the bases of the bowls were much more rigid and came much closer to having C_4 axes. The portals at the bases of the bowls were small enough to allow only very small ions or molecules to pass through their surfaces. All cones were

"supported on four methyl feet". We believe these cavitands of well-defined geometry and ready availability will provide starting points for the syntheses of a variety of important compounds.

Experimental Section

General Procedures. Tetrahydrofuran and Et_2O were distilled under N_2 from sodium benzophenone ketyl, CH_2Cl_2 was distilled and redistilled from CaH_2 when dryness was required, and benzene was distilled from $LiAlH_4$. Dimethylformamide (DMF) and dimethylacetamide (DMA) were allowed to stand over 3-Å molecular sieves activated by heating to 360 °C for 5 h and cooling in a dessicator. Dimethyl sulfoxide (DMSO) was stirred with activated alumina for 2 h, refluxed over CaO for 4 h under Ar, cooled and stirred (12 h) with CaH_2, and finally distilled at 43–45 °C (0.1 mm). All reactions were conducted under an Ar atmosphere. Column chromatography was performed with silica gel 60 (E. M. Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). Preparative thin-layer chromatography employed 2-mm silica gel plates (E. M. Merck, 60 F_{254}). Thin-layer chromatography was conducted on plastic-backed, precoated silica gel plates (E. M. Merck F_{254}, 0.2-mm thickness). Dry columns were packed with silica gel (E. M. Merck 60 F_{254}). Crystals for crystal-structure determination were prepared by slow evaporation of their solutions. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Mass spectra were recorded on a Kratos AE-1 Model MS-9 double-focusing spectrometer at 16 or 70 eV at inlet temperatures indicated, and FAB MS were determined on a ZAB SE instrument. Proton NMR spectra were recorded at 200 MHz on a Bruker WP-200 spectrometer. Chemical shifts refer to $SiMe_4$ as an internal standard.

2,8,14,20-Tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol Stereoisomer (1). Method A. Resorcinol (342 g or 3.11 mol) was dissolved in 620 mL of water, 620 mL of ethanol, and 310 mL of 37% aqueous HCl. To this stirred solution was added slowly 137.1 g of CH_3CHO. Immediately after the addition was complete, the reaction was cooled in a water bath to control the exotherm. The reaction mixture was then maintained at 80 °C for 16 h, and the yellow needles that separated were collected and washed with cold 1:1 ethanol–water until the washings were light yellow to give material dried at 80 °C at 10^{-1} Torr for 30 h (310 g, 73%). The physical properties of this compound corresponded to those reported,[7] and the material was suitable for use in subsequent reactions.

2,5,8,11,14,17,20,23-Octamethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol Stereoisomer (2). Application of method A to 10.28 g (0.08 mol) of 2-methylresorcinol (Aldrich) in 100 mL of ethanol, 100 mL of water, 50 mL of concentrated aqueous HCl, and 3.60 g (0.08 mol) of acetaldehyde (addition time, 5 min) gave, after standing at room temperature in air and isolation, 7.0 g (75%) of **2**, mp 220–225 °C: ^{1}H NMR ($(CD_3)_2SO$) δ 1.70 (d, 12 H, CH_3CH), 2.00 (s, 12 H, Ar CH_3), 4.46 (q, 4 H, CH_3CH), 7.41 (s, 4 H, ArH), 8.70 (s, 8 H, OH); MS (16 eV, 300 °C), *m/z* 600 (M^+). Anal. Calcd for $C_{36}H_{40}O_8 \cdot {}^3/_2H_2O$: C, 68.90; H, 6.86. Found: C, 69.12; H, 6.80.

5,11,17,23-Tetrabromo-2,8,14,20-tetramethylpentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaene Stereoisomer (3). To a stirred orange solution of crude **1** (25.80 g, 474 mmol) in 600 mL of 2-butanone was added 67.5 g (379 mmol) of *N*-bromosuccinimide (freshly recrystallized from 500 mL of boiling water) in portions. After 10 min, the product started to crystallize. The mixture was stirred for 4 h, and the product was collected and washed with hot CH_2Cl_2 and dried under vacuum at 100 °C to give 32.59 g (80%) of **3** as a white solid. A sample was recrystallized from 1:5 DMF–CH_2Cl_2 to give mp >360 °C dec: ^{1}H NMR ($(CD_3)_2SO$) δ 1.58 (d, 12 H, CH_3CH), 4.63 (q, 4 H, CH_3CH), 6.80 (s, 4 H, Ar H), 8.37 (s, 8 H, OH); MS (70 eV, 300 °C), no M^+ observed. Anal. Calcd for $C_{32}H_{28}O_8Br_4$: C, 44.49; H, 3.28. Found: C, 44.76; H, 3.28.

1,21,23,25-Tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis-[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocin Stereoisomer (5). To a mixture, stirred at 30 °C under Ar, of 3.5 L of dry DMSO and 307 g (2.38 mol) of finely ground dry K_2CO_3 were added over 4 days by syringe pump 109 g (0.2 mol) of dried octol **1** and 100 mL (1.1 mol) of CH_2ClBr dissolved in 300 mL of dry DMF. The mixture was stirred for an additional day at 30 °C under Ar and poured into 6 L of 2 M aqueous NaCl. The mixture was agitated for 1 h, and the fine precipitate that separated was filtered and washed with water. This material was suspended in 2 L of CH_2Cl_2, stirred for 5 h, and filtered. The residue was suspended in 1 L of 10% acetone in CH_2Cl_2 and filtered. The combined organic layers were washed with 300 mL of aqueous 2 N NaOH and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The residue was washed through a 40 × 3 cm column of 10–60-μm silica gel with CH_2Cl_2. If the eluates were still brown, the product was again chromatographed at medium pressure through silica gel. The eluate was evaporated to a volume of 200 mL and diluted with 300 mL of EtOH. The product that crystallized at 0 °C was collected, washed with cold CH_2Cl_2, and dried at 70 °C and 10^{-1} Torr to give, after drying, 28.0 g (23%) of **1**·CH_2Cl_2. The CH_2Cl_2 was removed by repeated evaporation of $CHCl_3$ from solutions of **5** to give **1**, mp > 360 °C: TLC R_f 0.15 (SiO_2–CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 12 H, CH_3CH, *J* = 7.4 Hz, 4.44 (d, 4 H, inner of CH_2, *J* = 7.2 Hz), 4.96 (q, 4 H, CH_3CH, *J* = 7.4 Hz), 5.75 (d, 4 H, outer of CH_2, *J* = 7.2 Hz), 6.47 (s, 4 H, 2-Ar *H*), 7.25 (s, 4 H, 5-Ar *H*); MS (70 eV), *m/z* 592 (M^+). Anal. Calcd for $C_{36}H_{32}O_8$: C, 72.86; H, 5.44. Found: C, 72.72; H, 5.36. Anal. Calcd for $C_{36}H_{32}O_8 \cdot CH_2Cl_2$: C, 65.58; H, 5.05. Found: C, 65.49; H, 4.92.

To test the ability of **5** to form insoluble complexes with other small solvent molecules, a saturated solution of **5** in $CHCl_3$ was prepared and diluted by a like volume of $CHCl_3$. To different aliquots of this solution were added (as drops or bubbles) possible small molecular guests. Evidence of complex formation was the precipitation of crystals, which were observed with CH_3CN, CH_2Cl_2, and SO_2. Complexes were not observed for CH_3OH, CS_2, HC≡CH, CO_2, CH_3I, and I_2. The complex with CH_3CN gave an IR spectral C≡N stretch at 2244.5 cm^{-1} (FT-IR MX1, Nicolet), that with SO_2 gave bands at 1325.0 and 1140.83 cm^{-1}. Anal. Calcd for $C_{36}H_{32}O_8 \cdot SO_2$: C, 65.84; H, 4.92. Found: C, 65.59; H, 4.82.

1,7,11,15,21,23,25,28-Octamethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]-bis[1,3]benzodioxocin Stereoisomer (6). A mixture of dry **2** (0 70 g, 1.17 mmol), CH_2BrCl (1.23 g, 9.53 mmol), and K_2CO_3 (5.00 g, 36.18 mmol) in 120 mL of dry DMA was stirred under Ar for 3 days. The mixture was cooled and filtered through Celite, and the filtrate was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water and brine, and dried ($MgSO_4$). The solvent was evaporated under vacuum to give product that was purified by silica gel chromatography with CH_2Cl_2 as the mobile phase to give 0.49 g (63%) of **6**, a small sample of which was recrystallized from 1:1 CH_2Cl_2–CH_3CN (or 1:1 benzene–cyclohexane) to give mp >360 °C: ^{1}H NMR ($CDCl_3$) δ 1.73 (d, 12 H, CH_3CH), 2.00 (s, 12 H, Ar CH_3), 4.29 (d, 4 H, inner of CH_2), 5.20 (q, 4 H, CH_3CH), 5.92 (d, 4 H, outer of CH_2), 7.14 (s, 4 H, Ar H); MS (70 eV, 320 °C), *m/z* 648 (M^+). Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.07; H, 6.37. Found: C, 74.15; H, 6.28.

7,11,15,28-Tetrabromo-1,21,23,25-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzodioxocin Stereoisomer (7) and 4,8,12,16-Tetrabromo-20,22,24,25-tetramethyl-2,18-methano-20*H*,22*H*,24*H*-dibenzo[*d*,*d*′][1,3]dioxocino[5,4-*i*:7,8-*i*]bis[1,3]-benzodioxocin-3,17-diol Stereoisomer (13). A mixture of dry octol **3** (1.00 g, 1.16 mmol), Cs_2CO_3 (6.06 g, 18.60 mmol), and CH_2BrCl (1.23 g, 9.53 mmol) in 50 mL of dry DMSO was stirred under Ar at 60–70 °C for 24 h. The mixture was cooled and filtered through Celite, and the solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (30 mL), and the solution was washed with water and brine and dried ($MgSO_4$). The solvent was evaporated under vacuum to give a yellow solid, which was a mixture of two compounds by TLC. This material was chromatographed on silica gel with CH_2Cl_2 as the mobile phase to give first **7** (0.62 g, 55%) followed by **13** (0.12 g, 11%). A small sample of **7** was recrystallized from 1:1 CH_2Cl_2–hexane, mp ≥360 °C: ^{1}H NMR ($CDCl_3$) δ 1.81 (d, 12 H, CH_3CH), 4.40 (d, 4 H, inner of CH_2), 5.10 (q, 4 H, CH_3CH), 6.00 (d, 4 H, outer of CH_2), 7.26 (s, 4 H, Ar H); MS (70 eV, 330 °C), *m/z* 908 (M^+). Anal. Calcd for $C_{36}H_{28}O_8Br_4$: C, 47.60; H, 3.10. Found: C, 47.63; H, 3.01.

A small sample of **13** after recrystallization from CH_2Cl_2–CH_3CN gave mp 335–340 °C dec: ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 3 H, CH_3), 1.78 (d, 6 H, CH_3), 1.84 (d, 3 H, CH_3), 4.34 (d, 1 H, inner of CH_2), 4.42 (d, 2 H, inner of CH_2), 4.67 (q, 1 H, CH), 5.08 (q, 3 H, CH), 5.94 (d, 1 H, outer of CH_2), 5.99 (d, 2 H, outer of CH_2), 7.19 (s, 2 H, Ar H), 7.30 (s, 2 H, Ar H); MS (70 eV, 250 °C), *m/z* 896 (M^+). Anal. Calcd for $C_{35}H_{28}Br_4O_8 \cdot CH_3CN$: C, 47.39; H, 3.31. Found: C, 47.09; H, 3.63.

7,11,15,28-Tetraiodo-1,21,23,25-tetramethyl-2,20:3,19-dimetheno-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]-bis[1,3]benzodioxocin Stereoisomer (8). Before lithiating **5**, it was important to drive off reactive solvents (such as CH_2Cl_2) entrapped in its crystal lattice. This was most easily accomplished by distilling benzene and THF from solutions of **5** through a Vigreux column. Vacuum alone or vacuum with modest heating did not suffice. To a solution of 745 mg of **5** in 100 mL of dry Et_2O stirred under Ar at 0 °C was added 11 mL of 1.8 M phenyllithium in 70% cyclohexane–30% ether (19.8 mmol) by syringe. The reaction mixture was allowed to warm to 25 °C and was stirred for 2 days. It was then cooled in a dry ice–acetone bath, and 5.5 g of iodine was added as a solid. The mixture was warmed to 25 °C, the solvent was evaporated, the residue was dissolved in CH_2Cl_2, and the solution was filtered through 70 cm^3 of SiO_2 in a sintered-glass funnel. The silica pad was rinsed with 150 mL of CH_2Cl_2. The solvent was

evaporated from the filtrates to give a dark solid. This material was triturated with 10 mL of acetone to give **8** as a pale solid, which was one spot by TLC (SiO_2 eluted with 1:1 hexane–CH_2Cl_2, R_f 0.3), weight 596 mg (40%). A small sample was recrystallized from toluene, mp >360 °C, to give crystal structure quality **8**·$C_6H_5CH_3$. An analytical sample of **8** was prepared by recrystallization from CS_2 and drying under high vacuum for 12 h at 80 °C and 10 h at 178 °C: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 12 H, $CHCH_3$, J = 7.6 Hz), 4.33 (d, 4 H, inner of CH_2, J = 8.0), 5.07 (q, 4 H, $CHCH_3$ J = 7.6), 5.98 (d, 4 H, outer of CH_2, J = 8.0 Hz), 7.20 (s, 4 H, Ar H); MS (70 eV, 330 °C), m/z 1096 (M^+). Anal. Calcd for $C_{36}H_{28}O_8I_4$: C, 39.44; H, 2.57. Found: C, 39.21; H, 2.78.

5,6,10,11,15,16,20,21-Octahydro-1,8,13,18,25,27,29,32-octamethyl-2,24:3,23-dimetheno-1*H*,25*H*,27*H*,29*H*-bis[1,4]dioxonino[6,5-*j*:6′,5′-*j*′]benzo[1,2-*e*:5,4-*e*′]bis[1,4]benzodioxonin Stereoisomer (9). To a mixture, stirred under Ar at 100 °C, of 5.00 g (36.1 mmol) of dry K_2CO_3 (finely ground), 80 mL of dry DMA, and 1.00 g (1.67 mmol) of dry **2** was added 4.93 g (13.32 mmol) of $TsOCH_2CH_2OTs$. The mixture was stirred at 100 °C for 3 days, cooled to 25 °C, and filtered through Celite, and the filtrate was evaporated under vacuum. The residue was shaken with water and CH_2Cl_2, and the water layer was twice extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried ($MgSO_4$). The solution was evaporated to 10 mL, which was filtered through silica gel to give pure **9** as a white powder, weight 0.50 g (43%). A small sample was recrystallized from 1:1 CH_2Cl_2–cyclohexane, mp 330 °C dec: ^{1}H NMR ($CDCl_3$) δ 1.65 (d, 12 H, CH_3CH), 2.18 (s, 12 H, Ar CH_3), 3.4–3.6 (m, 8 H, inner of CH_2CH_2), 4.2–4.4 (m, 8 H, outer of CH_2CH_2, AA′XX′ system), 5.44 (q, 4 H, CH_3CH), 7.36 (s, 4 H, ArH); MS (70 eV, 260 °C), m/z 704 (M^+). Anal. Calcd for $C_{44}H_{48}O_8$·0.5CH_2Cl_2: C, 71.54; H, 6.56. Found: C, 71.57; H, 6.94.

8,13,18,32-Tetrabromo-5,6,10,11,15,16,20,21-octahydro-1,25,27,29-tetramethyl-2,24:3,23-dimetheno-1*H*,25*H*,27*H*,29*H*-bis[1,4]dioxonino-[6,5-*j*:6′,5′-*j*′]benzo[1,2-*e*:5,4-*e*′]bis[1,4]benzodioxonin Stereoisomer (10) and 4,9,14,19-Tetrabromo-23,25,27,28-tetramethyl-2,21-methano-23*H*,25*H*,27*H*-dibenzo[*e*,*e*′][1,4]dioxonino[6,5-*j*:8,9-*j*′]bis[1,4]benzodioxonin-3,20-diol Stereoisomer (14). A mixture of dry **3** (1.00 g, 1.16 mmol), $TsOCH_2CH_2OTs$ (3.55 g, 9.60 mmol), Cs_2CO_3 (6.06 g, 18.60 mmol), and 50 mL of dry DMSO was stirred under Ar at 60–65 °C for 24 h and cooled to 25 °C. The mixture was filtered through Celite, and the filtrate was evaporated under vacuum. The mixture was shaken with $CHCl_3$ and water, and the water layer was twice extracted with $CHCl_3$. The combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated under vacuum to give a yellow solid, which was chromatographed on silica gel with CH_2Cl_2 as the mobile phase to give first **10** (0.40 g, 35%) and then **14** (0.35 g, 30%). On TLC (silica gel, CH_2Cl_2), **10** gave R_f 0.39 and **14** gave R_f 0.16. A small sample of **10** was recrystallized from 1:1 benzene–hexane, or 1:1 CH_2Cl_2–hexane, mp >360 °C: ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 12 H, CH_3CH), 3.7–3.9 (m, 8 H, inner of CH_2CH_2, half of AA′XX′), 4.4–4.6 (m, 8 H, outer of CH_2CH_2, half of AA′XX′), 5.50 (q, 4 H, CH_3CH), 7.39 (s, 4 H, ArH); MS (16 eV, 330 °C), m/z 964 (M^+). Anal. Calcd for $C_{40}H_{36}Br_4O_8$·0.5H_2O: C, 49.33; H, 3.80. Found: C, 49.25; H, 3.99. A small sample of **14** was recrystallized from 1:1 CH_2Cl_2–hexane, mp 315–320 °C dec: ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 3 H, CH_3CH), 1.70 (d, 6 H, CH_3CH), 1.80 (d, 3 H, CH_3CH), 3.64–4.02 (m, 6 H, inner of CH_2CH_2), 4.35–4.62 (m, 6 H, outer of CH_2CH_2), 4.70 (q, 1 H, CH_3CH), 5.48 (q, 3 H, CH_3CH), 7.34 (s, 2 H, Ar H), 7.37 (s, 2 H, Ar H); MS (70 eV, 250 °C), m/z 938 (M^+). Anal. Calcd for $C_{38}H_{34}Br_4O_8$·0.5CH_2Cl_2·1.0H_2O: C, 46.27; H, 3.71. Found: C, 46.05; H, 3.83.

6,7,12,13,18,19,24,25-Octahydro-1,9,15,21,29,31,33,36-octamethyl-2,28:3,27-dimetheno-1*H*,5*H*,11*H*,17*H*,23*H*,29*H*,31*H*,33*H*-bis[1,5]dioxecino[7,6-*k*:7′,6′-*k*′]benzo[1,2-*f*:5,4-*f*′]bis[1,5]benzodioxecin Stereoisomer (11). A mixture of solvate-free **2** (1.00 g, 1.67 mmol), dry pulverized K_2CO_3 (7.50 g, 36.2 mmol), 100 mL of dry DMA, and $TsO(CH_2)_3OTs$ (5.10 g, 13.3 mmol) was stirred under Ar at 95 °C for 20 h. The mixture was cooled and filtered through Celite, and the filtrate was evaporated under vacuum. The residue was dissolved in $CHCl_3$, and the organic layer was washed with water and brine and dried ($MgSO_4$). The solution was evaporated to ~5 mL and filtered through silica gel with CH_2Cl_2 as the mobile phase to give 0.20 g (16%) of **11** as a white solid. A small sample was recrystallized from 1:1 $CHCl_3$–cyclohexane, mp >360 °C: ^{1}H NMR ($CDCl_3$) δ 1.57 (d, 12 H, CH_3CH), 1.80–2.1 (m, 4 H, inner of CCH_2C), 2.17 (s, 12 H, Ar CH_3), 2.2–2.4 (m, 4 H, outer of CCH_2C), 3.80 (m, 8 H, inner of CH_2CCH_2), 4.44 (m, 8 H, outer of CH_2CCH_2), 5.18 (q, 4 H, CH_3CH), 7.16 (s, 4 H, Ar H); MS (70 eV, 300 °C), m/z 760 (M^+). Anal. Calcd for $C_{48}H_{56}O_8$·$CHCl_3$: C, 66.85; H, 6.53. Found: C, 66.73; H, 6.59.

9,15,21,36-Tetrabromo-6,7,12,13,18,19,24,25-octahydro-1,29,31,33-tetramethyl-2,28:3,27-dimetheno-1*H*,5*H*,11*H*,17*H*,23*H*,29*H*,31*H*,33*H*-bis[1,5]dioxecino[7,6-*k*:7′,6′-*k*′]benzo[1,2-*f*:5,4-*f*′]bis[1,5]benzodioxecin Stereoisomer (12). A mixture of solvate-free **3** (1.00 g, 1.16 mmol), $TsO(CH_2)_3OTs$ (3.69 g, 9.60 mmol), and Cs_2CO_3 (6.06 g, 18.60 mmol) in dry DMSO (50 mL) was stirred at 65–75 °C for 4 days. The mixture was cooled to 25 °C and filtered through Celite, and the solvent was evaporated under vacuum. The residue was shaken with $CHCl_3$ and water, the organic layer was washed with water, and the combined aqueous layers were extracted with $CHCl_3$. The combined $CHCl_3$ layers were twice washed with water and once with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2 as the mobile phase to give 0.59 g (50%) of **12** as a white powder. A small sample was recrystallized from 1:1 hexane–CH_2Cl_2, mp >360 °C: ^{1}H NMR ($CDCl_3$) δ 1.57 (d, 12 H, CH_3CH), 2.00–2.40 (m, 8 H, CCH_2C), 4.05 (m, 8 H, inner of CH_2CCH_2), 4.65 (m, 8 H, outer of CH_2CCH_2), 5.10 (q, 4 H, CH_3CH), 7.07 (s, 4 H, Ar H); MS (70 eV, 300 °C), m/z 1020 (M^+). Anal. Calcd for $C_{44}H_{44}Br_4O_8$·0.5CH_2Cl_2: C, 50.28; H, 4.27. Found: C, 50.47; H, 4.34.

4,10,16,22-Tetrabromo-26,28,30,31-tetramethyl-2,24-methano-26*H*,28*H*,30*H*-dibenzo[*f*,*f*′][1,5]dioxecino[7,6-*k*:9,10-*k*′]bis[1,5]benzodioxecin-3,23-diol Stereoisomer (15). To a mixture of 11.4 g (13 mmol) of dry **3** and 20.6 g (54 mmol) of $TsO(CH_2)_3OTs$ in 475 mL of dry DMSO stirred under Ar at 25 °C was added 50 g (153 mmol) of Cs_2CO_3. The suspension was stirred for 52 °C for 47 h, cooled to 25 °C, diluted with 500 mL of CH_2Cl_2, and filtered. The filtrate was shaken with 1 L of 5% aqueous NaCl, the layers were separated, and the organic layer was extracted with three 1-L portions of 5% aqueous NaCl and dried. The solvent was evaporated under vacuum to 40 mL, and the solution was added to a 600-g column of silica gel prepared in CH_2Cl_2. Elution of the column with CH_2Cl_2 gave 0.15 g (1%) of **12** followed after empty fractions by 3.5 g (27%) of **15** as a white solid, a small sample of which was recrystallized from CH_2Cl_2, mp >300 °C: ^{1}H NMR ($CDCl_3$) δ 1.55–1.67 (m, 12 H, CH_3CH), 1.92–2.43 (m, 6 H, CCH_2C), 3.92–4.10 (m, 6 H, inner of CH_2CCH_2), 4.52–4.74 (m, 6 H, outer of CH_2CCH_2), 4.98–5.14 (m, 4 H, CH_3CH), 7.07 (s, 2 H, Ar H), and 7.09 (s, 2 H, Ar H); MS-FAB (*m*-$NO_2C_6H_4CH_2OH$ matrix), m/z 980 (M^+). Anal. Calcd for $C_{41}H_{40}Br_4O_8$: C, 50.23; H, 4.11. Found: C, 50.16; H, 4.04.

Crystal Structure. Compound **5**·CH_2Cl_2 crystallizes in small, colorless, irregularly shaped fragments from CH_2Cl_2 in the monoclinic system $C2/c$. Unit cell dimensions are as follows: a = 19.759 (6), b = 8.164 (2), and c = 40.008 (6) Å; β = 107.48 (2)°; v = 6156 Å^3; Z = 8. The crystal was examined on a Syntex $P\bar{1}$ diffractometer, Mo Kα radiation, at 115 K. The structure was determined by direct methods. Refinement of 526 parameters (4803 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently = 0.057. Compound **6**·CH_3CN crystallizes from CH_2Cl_2–$(CH_2)_6$–CH_3CN as clear, colorless prisms in the tetragonal space group $P4$. Unit cell dimensions are as follows: a = 16.009 (2) and c = 8.1205 (9) Å; V = 2089 Å^3; Z = 2 (eight quarter molecules). The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 128 K. The structure was determined by direct methods. Refinement of 122 parameters (1050 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.16. There are two unrelated but similar host–guest complexes in the crystal and an additional interstitial CH_3CN.

Compound **6**·$(CH_2)_6$·C_6H_6 crystallizes from benzene–cyclohexane as colorless prisms in the orthorhombic system $P2_12_12_1$. Unit cell dimensions are as follows: a = 12.334 (2), b = 15.415 (2), and c = 22.588 (4) Å; V = 4285 Å^3; Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 128 K. The structure was determined by direct methods. Refinement of 269 parameters (1922 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.15. A benzene molecule is also present in the crystal.

Compound **7**·$CHCl_3$ crystallizes from $CHCl_3$ as colorless prismatic needles in the triclinic system $P\bar{1}$. Unit cell dimensions are as follows: a = 12.193 (5), b = 18.910 (8), and c = 20.471 (10) Å; α = 113.56 (3), β = 105.25 (4), and γ = 93.16 (3)°; V = 4105 Å; Z = 4. The crystal was examined on a Syntex $P\bar{1}$ diffractometer, Mo Kα radiation, at 295 K. The structure was determined by direct methods. Refinement of 472 parameters (4296 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.12. There are two similar but crystallographically unrelated cavitands in the crystal and a highly disordered, as yet uncharacterized, solvent molecule.

Compound **8**·$CH_3C_6H_5$ crystallizes in small, colorless, irregularly shaped fragments from CCl_4–CS_2–toluene in the triclinic system $P\bar{1}$. Unit cell dimensions are as follows: a = 11.799 (2), b = 13.096 (2), and c = 17.755 (3) Å; α = 79.678 (4), β = 79.795 (5), and γ = 66.141 (4)°; V = 2476 Å^3; Z = 2. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 295 K. The structure was determined by heavy-atom methods. Refinement of 309 parameters (6831 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently = 0.061. The unit cell contains seven molecules of toluene. Except for the two that are complexed, toluene is disordered.

Compound **9**·C_6H_6·C_6H_6 crystallizes from CH_2Cl_2–$(CH_2)_6$–C_6H_6 as clear, colorless prisms in the monoclinic space group $P2_1/n$. Unit cell dimensions are as follows: a = 14.642 (2), b = 21.505 (3), and c = 15.777 (2) Å; β = 90.140 (4)°; V = 4978 Å^3; Z = 4. The crystal was examined on a HUBER diffractometer, Mo Kα radiation, at 298 K. The structure was determined by direct methods. Refinement of 317 parameters (3016 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.14. Only one of the two benzene molecules is complexed.

Compound **9**·$(CH_2)_6$·$(CH_2)_6$ crystallizes from cyclohexane as colorless blades in the monoclinic system $P2_1/n$. Unit cell dimensions are as follows: 14.518 (4), b = 21.242 (5), and c = 15.586 (4) Å; β = 90.21-(1)°; V = 4819 Å^3; Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 298 K. The structure was determined by direct methods. Refinement of 257 parameters (2123 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.13. An uncomplexed, as well as complexed, cyclohexane molecule is present in the crystal.

Compound **10**·CH_2Cl_2·CH_2Cl_2 crystallizes from CH_2Cl_2 as colorless thin blades in the orthorhombic system $Pna2_1$. Unit cell dimensions are as follows: a = 22.847 (4), b = 21.500 (4), and c = 8.865 (2) Å; V = 4355 Å^3; Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 295 K. The structure was determined by direct methods. Refinement of 358 parameters (2501 reflections with $F > \sigma(F)$) has an agreement value, R, currently at 0.11. Only one of the two CH_2Cl_2 molecules is involved in host–guest complexation.

Compound **15**·CH_2Cl_2 crystallizes from CH_2Cl_2 as colorless thin platelets in the orthorhombic system *Pnna*. Unit cell dimensions are as follows: a = 8.762 (4), b 20.072 (8), and c = 24.260 (9) Å; V = 4299 Å^3; Z = 4 (eight half molecules related by a twofold axis). The crystal was examined on a modified Picker FACS-1 diffractometer Mo Kα radiation, at 298 K. The structure was determined by heavy-atom methods. Refinement of 151 parameters (1648 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.10. The propylene bridges are disordered. Full details will be published elsewhere.

Synthesis of Optically Pure α-Amino Acids via Salts of α-Amino-β-propiolactone

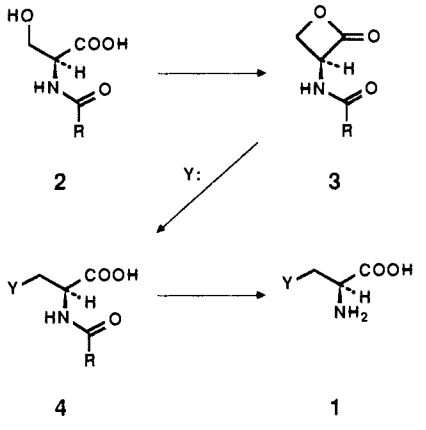
Lee D. Arnold, Robert G. May, and John C. Vederas*

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received August 14, 1987*

Abstract: Treatment with trifluoroacetic acid of *N*-(*tert*-butoxycarbonyl)-L-serine β-lactone (**3a**) (available by Mitsunobu cyclization of the corresponding N-protected serine derivative **2**, R = O-*t*-Bu) produces 3-amino-2-oxetanone as its trifluoroacetate salt **5**. Addition of 1 equiv of *p*-toluenesulfonic acid to the reaction mixture affords the corresponding stable tosylate salt **6**, which can be stored indefinitely. The salts **5** and **6** are attacked at the β-carbon by a variety of nucleophiles (e.g., RSH, Me_2S, CF_3COO^-, HPO_4^{2-}, Cl^-, CN^-, pyrazole, N_3^-) to give unprotected, optically pure (2*S*)-α-amino acids **1** in 77–96% isolated yield. The ring openings can be done in a variety of organic solvents (e.g., DMF, trifluoroacetic acid, MeCN) or in water at pH 5.0–5.5, depending on the nucleophile.

The biological importance[1] and synthetic utility[2,3] of α-amino acids **1** continue to stimulate development of new routes to these compounds. Most recent approaches rely on stereospecific construction of one or more bonds to the α-carbon,[4] but several very practical methods attach a side chain to a preexisting chiral α-amino acid derivative.[5,6] Recently we reported syntheses of amino acids that employ ring-opening of N-protected β-lactones

Scheme I



(1) (a) Barrett, G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) Bender, D. A. *Amino Acid Metabolism*; Wiley: Chichester, U.K. 1985. (c) Davies, J. S. *Amino Acids and Peptides*; Chapman and Hall: London, 1985.

(2) For reviews, see: (a) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165–246. (b) Ottenheijm, H. C. J. *Chimia* **1985**, *39*, 89–98.

(3) For some recent examples, see: (a) Renaud, P.; Seebach, D. *Angew. Chem.* **1986**, *98*, 836–838. (b) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320–5327. (c) West, J. B.; Wong, C. H. *J. Org. Chem.* **1986**, *51*, 2728–2735. (d) Schöllkopf, U.; Kuehnle, W.; Egert, E.; Dyrbusch, M. *Angew. Chem.* **1987**, *99*, 480–482. (e) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492.

(4) For a few recent examples, see: (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104. (b) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041–6043. (c) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395. (d) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397. (e) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, 6397–6399. (f) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (g) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406. (h) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243–5252. (i) Mulzer, J.; Angermann, A.; Schubert, B.; Seilz, C. *J. Org. Chem.* **1986**, *51*, 5294–5299. (j) McIntosh, J.; Leavitt, R. K. *Tetrahedron Lett.* **1986**, *27*, 3839–3842. (k) Ojima, I.; Chen, H. J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 625–626. (l) Schöllkopf, U.; Toelle, R.; Egert, E.; Nieger, M. *Liebigs Ann. Chem.* **1987**, 399–405. (m) Johnson, C. R.; Imamoto, T. *J. Org. Chem.* **1987**, *52*, 2170–2174. (n) Polt, R.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1930–1936.

(5) For leading references, see: (a) Nakajima, K.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1565–1566. (b) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095–1098. (c) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855–5858. (d) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 256–257. (e) Barlos, K.; Mamos, P.; Papaioannou, D. Sanida, C.; Antonopoulos, C. *J. Chem. Soc., Chem. Commun.* **1986**, 1258–1259. (f) Bajgrowicz, J. A.; El Hallaoui, A.; Jaqueir, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843. (g) Nagasawa, T.; Yamada, H. *Appl. Biochem. Biotechnol.* **1986**, *13*, 147–165. (h) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153–155.

0002-7863/88/1510-2237$01.50/0