

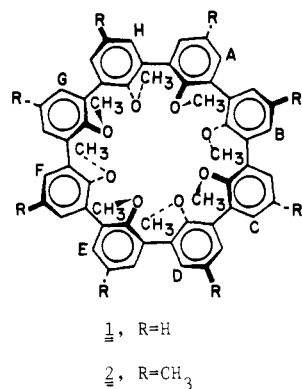
Host-Guest Complexation. 44. CavitanDs and Caviplexes Composed of Eight Anisyl Groups¹

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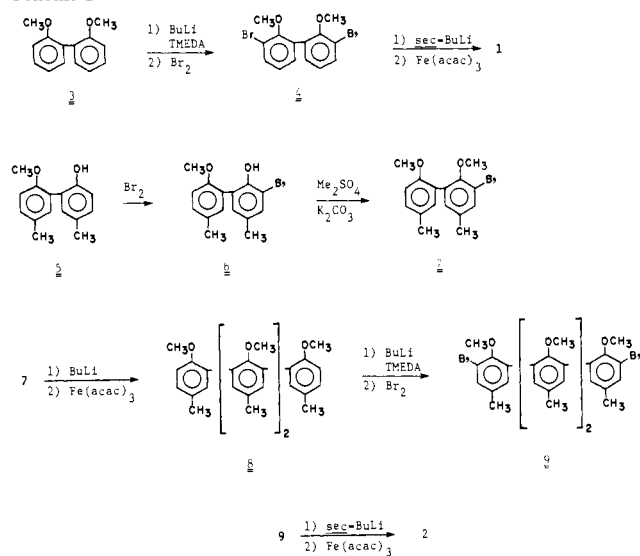
Abstract: The syntheses, crystal structures, and binding properties of cavitanDs **1** and **2** are reported. Macrocycle **1** is composed of eight anisyl units bonded to one another in their 2,6-positions ((C₆H₃OCH₃)₈) and was prepared in 1.4% yield by Fe(acac)₃ oxidation of the dilithium organometallic formed by treatment of 3,3'-dibromo-2,2'-dimethoxy-1,1'-biphenyl (**4**) with *n*-BuLi. Macrocycle **2** is composed of eight 4-methylanisyl units bonded to one another in their 2,6-positions ((CH₃C₆H₂OCH₃)₈). It was prepared by Fe(acac)₃ oxidation of the dilithium organometallic formed by treatment of 3,3''-dibromo-2,2',2''-tetramethoxy-5,5',5'',5'''-tetramethylquaterphenyl (**9**) with *sec*-butyllithium. The yield was maximal at 4.7% when the ring closure was carried out in the presence of CsBr. The crystal structures of **1**, **2**, and 2·C₂H₅OH reveal that each of the eight oxygens is anti to its two neighboring oxygens to provide an (up-down)₄ conformational arrangement. In **1**, four of the methyls attached to the oxygens are turned inward (those on rings A, B, E, and F), and four are turned outward (those on rings C, D, G, and H). The resulting cavity is small and egg-shaped, with one half lined with methyls and the other half with oxygen's unshared electron pairs. In **2**, two of the methyls attached to oxygens are turned inward (those on rings A and E), and six are turned outward (those on rings B, C, D, F, G, and H). Additionally, a para methyl carbon of an adjacent host is located 3.3–3.5 Å from the oxygens of rings B, D, F, and H. The cavity of **2** is larger than that of **1** and is shaped like a tangerine, with one quarter lined with methyls and three quarters lined with oxygen's unshared electron pairs. In 2·C₂H₅OH, three of the methyls attached to oxygens are turned inward (those on rings A, E, and H) and the other five are turned outward. The C₂H₅OH molecule is external to the cavity and overlies ring E, and its hydroxyl hydrogen bonds the oxygen of ring E. The crystal structure of 2·CsClO₄ shows the Cs⁺ guest to be ligated by the eight oxygens located at the apices of a square antiprism. The squares are 2 Å apart and have sides ranging from 4.3 to 4.7 Å. An oxygen from ClO₄⁻ completes the coordination about Cs⁺. The free energies were determined at 25 °C in CDCl₃ saturated with D₂O for **1** and **2** binding the picrate salts of Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺, NH₄⁺, CH₃NH₃⁺, and *t*-BuNH₃⁺. The -ΔG° values are maximal for **1** and **2** complexing Cs⁺ (11.8 and 13.9 kcal mol⁻¹, respectively) and minimal for **1** and **2** complexing *t*-BuNH₃⁺ (3.2 and 4.0 kcal mol⁻¹, respectively). The relationships between structure and binding are discussed in terms of the principle of preorganization.

Examination of CPK molecular models of compounds **1** and **2** indicates that their metacyclophane arrangement of the benzene rings provides an enforced cavity whose size and shape vary with the conformational organizations of the methoxyl groups. The



collective bulk of the methoxyl groups is accommodated without apparent strain only in conformations in which each of the eight oxygens is anti to its nearest two neighbors, to provide an enforced (up-down)₄ arrangement of the eight oxygens. The methyl of each methoxyl group can either converge on or diverge from the cavity. If all methyl groups point inward, they contact one another to form a cylindrical cavity complementary to a model of diacetylene guest. With all methyl groups pointing outward, the cavity is lined with the sixteen electron pairs of the eight oxygens. At maximum aryl-aryl dihedral angle, the resulting cavity is complementary to chair cyclohexane, or a well-worn tennis ball. At minimum aryl-aryl dihedral angle, the cavity is complementary to a sphere slightly larger than the Cs⁺ ion. The many different

Scheme I



combinations of methyl groups pointing inward or outward provide a variety of differently shaped cavities whose surfaces are defined by combinations of oxygen's unshared electron pairs and the hydrogens of companion methoxyl groups. Thus **1** and **2** contain enforced cavities (cavitanDs)^{2,3} whose sizes, shapes, and electronic character are adaptable within limits to the demands of potential guests. This paper reports the syntheses of **1** and **2**, the crystal structures of **1**, **2**, 2·C₂H₅OH, and 2·CsClO₄, and the binding properties of **1** and **2**.

(1) We thank the National Science Foundation for Grant NSF CHE 84-19994 for support of this research.

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Table I. Binding Free Energies ($-\Delta G^\circ$) and Association Constants (K_a) of Hosts for Picrate Salt Guests at 25 °C in CDCl_3 Saturated with D_2O

guest	host					
	1		2		10	
	$-\Delta G^\circ$, kcal mol $^{-1}$	K_a , mol $^{-1}$	$-\Delta G^\circ$, kcal mol $^{-1}$	K_a , mol $^{-1}$	$-\Delta G^\circ$, kcal mol $^{-1}$	K_a , mol $^{-1}$
Li^+	6.9	1.13×10^5	8.3	1.20×10^6	5.4	9.01×10^3
Na^+	8.6	1.90×10^6	10.1	2.49×10^7	6.1	2.93×10^4
K^+	7.6	3.68×10^5	8.9	3.30×10^6	5.4	9.01×10^3
Rb^+	9.4	7.66×10^6	10.4	4.13×10^7	6.6	6.82×10^4
Cs^+	11.8	4.38×10^8	13.9	1.51×10^{10}	8.2	1.01×10^6
NH_4^+	8.5	1.69×10^6	9.1	4.62×10^6	6.3	4.11×10^4
CH_3NH_3^+	7.7	4.36×10^5	9.0	3.90×10^6	6.0	2.48×10^4
$t\text{-BuNH}_3^+$	3.2	2.21×10^2	4.0	8.50×10^2	3.4	3.09×10^2
av	8.0		9.2		5.9	

Table II. Geometric Parameters in Crystal Structures of Cavitands **1**, **2**, and **2**· $\text{C}_2\text{H}_5\text{OH}$ and Caviplex **2**· CsClO_4

		12	14	16	18
Ar-Ar dihedral angle, deg	average	73.3	79	71	65
	range	59–88	62–90	50–89	58.5–74
tilt angle of Ar's from best plane, ^a deg	average	45	43	40	36
	range	24–69	18–61	21–62	28–42
Ar-O-CH ₃ bond angle, deg	average	116.7	113.9	113.9	113.0
	range	113.1–125.0	112.0–116.3	111.6–117.7	110.2–115.4
no. of CH ₃ 's turned in		4	3	3	0
no. of O's bent in ^b		1	3	0	3
O distances bent from Ar plane, Å	CH ₃ in (av)	0.13 (4 bent out)	0.07 (2 bent out)	0.17 (3 bent out)	none
	CH ₃ out (av)	0.06 (3 bent out)	0.04 (3 bent out)	0.10 (5 bent in)	0.055 (3 bent in)
		0.04 (1 bent in)	0.03 (3 bent in)	none bent out	0.051 (5 bent out)
8 O distances from mean plane, ^c Å	average	1.21	1.14	1.14	0.99
	range	0.98–1.54	0.95–1.30	0.82–1.28	0.94–1.03
O to opposite O distance, Å	average	6.83	6.58	6.66	6.19
	range	6.46–7.24	6.43–6.74	6.45–7.24	6.05–6.25
distance (C to C, Å) in and opposite CH ₃ 's	average	4.32	3.82	3.65	
	range	3.92–4.73	3.82	3.65	
10 Cs-O distances, Å	average				3.24
	range				3.18–3.28

^a Defined by carbons of Ar-Ar linkages. ^b Bent inward from plane of attached aryl. ^c Mean plane of all eight oxygens.

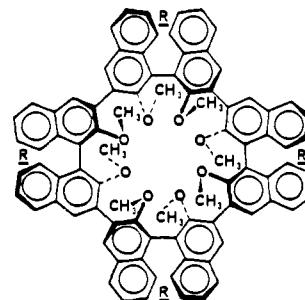
Results

Syntheses (Scheme I). Dimetalation of **3**⁴ with BuLi in the presence of tetramethylethylenediamine (TMEDA) and bromination of the organometallic produced dibromide **4** (24%). This material was metalated with *sec*-BuLi, and the organometallic generated was oxidized with Fe(acac)₃ in refluxing benzene under high dilution conditions to produce cavitand **1** (1.4%). The ¹H NMR and ¹³C NMR spectra of cavitand **1** indicated the presence of only one kind of C₆H₃OCH₃ unit at room temperature in CDCl₃.

Phenol **5**⁵ was brominated to give **6** (93%), methylation of which produced **7** (97%). This monobromide was metalated with BuLi, and the organometallic obtained was oxidized with Fe(acac)₃ to provide quateraryl compound **8** (70%). Lithiation of **8** with BuLi-TMEDA and bromination of the resulting bisorganometallic gave the quateraryl dibromide, **9** (78%). This compound was doubly metalated with *sec*-BuLi, and the resulting material was oxidized with Fe(acac)₃ in refluxing benzene under high dilution conditions to produce cavitand **2** (2.9%). When carried out under the same conditions except that the reaction mixture (THF-benzene) was saturated with dry CsBr, the yield increased to 4.7%. This experiment was inspired by the fact that Kellogg⁶ had observed many macroring closures to go with much higher yields in the presence of Cs⁺, and that **2** binds Cs⁺ better than the other ions (see later section). The ¹H NMR and ¹³C NMR spectra of cavitand **2** in CDCl₃ at room temperature indicated the presence of only one kind of *p*-CH₃C₆H₂OCH₃ unit.

Binding Free Energies. The binding free energies ($-\Delta G^\circ$ values) and K_a values (association constants) were determined for **1** and

2 complexing at 25 °C the picrate salts of Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺, NH₄⁺, CH₃NH₃⁺, and *t*-BuNH₃⁺ in CDCl₃ saturated with D₂O. These salts dissolved in D₂O were extracted into CDCl₃ in the absence and presence of the cavitands, utilizing the techniques already described.⁷ Each $-\Delta G^\circ$ value represents the average of at least two determinations that differed by less than 0.3 kcal mol⁻¹ from one another. The values for **1** were determined by two different experimentalists working with different preparations of materials. Suitable ¹H NMR experiments demonstrated that only 1:1 complexes were formed between **1** and **2** as hosts and CsClO₄ as guest. Extractions, complexations, and equilibrations were instantaneous on the human time scale. Decomplexations were slow on the ¹H NMR time scale at room temperature, so complexed and uncomplexed host could be observed simultaneously. Table I lists the $-\Delta G^\circ$ and K_a values. Those for related chiral host **10**⁸ are included for comparison purposes.



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(4) *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, 1982; p 674.

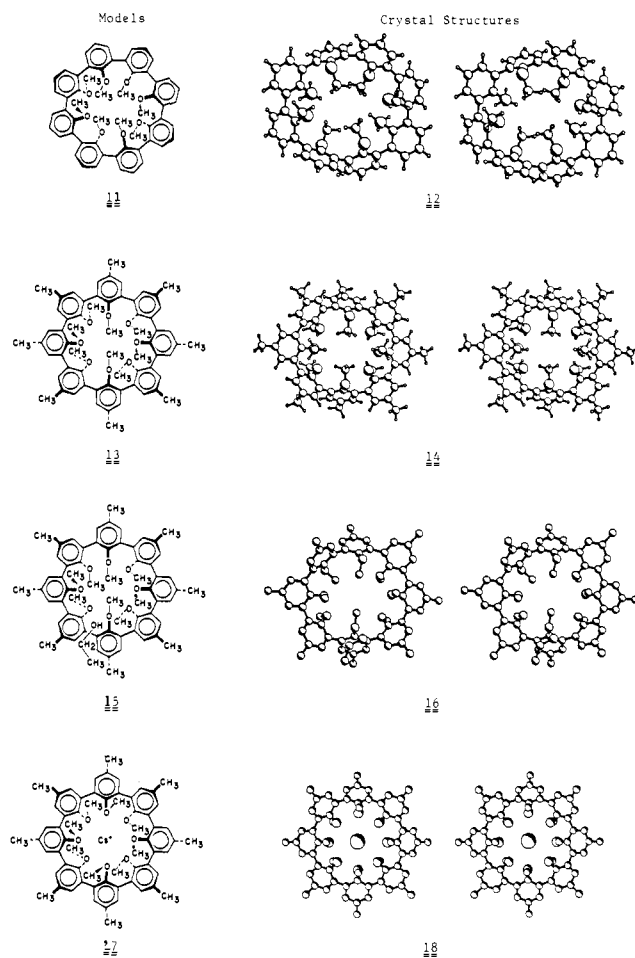
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Chart I



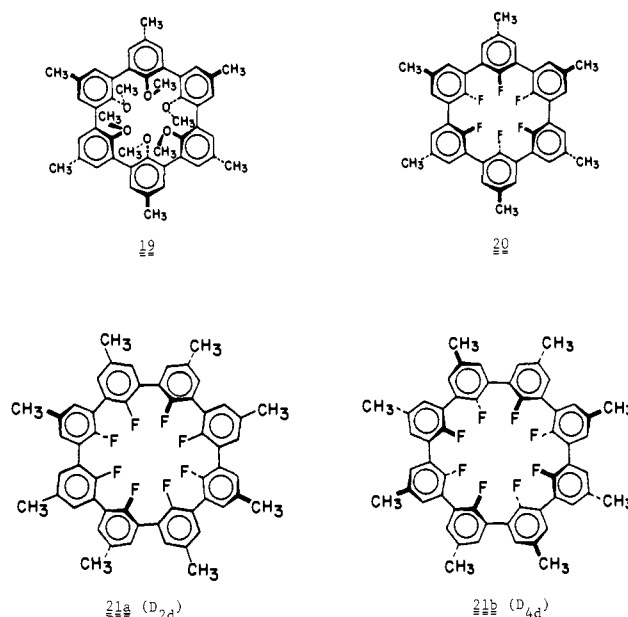
Crystal Structures. Cavitands **1**, **2**, and $2 \cdot \text{C}_2\text{H}_5\text{OH}$ and caviplex $2 \cdot \text{CsClO}_4$ formed single crystals suitable for X-ray analysis to provide *R* values of 0.063 (296 K), 0.09 (113 K), 0.096 (115 K), and 0.10 (115 K), respectively. Table II lists relevant bond angles and distances. Chart I compares drawings based on CPK model examination of **1**, **2**, $2 \cdot \text{C}_2\text{H}_5\text{OH}$, and $2 \cdot \text{Cs}^+$ (**11**, **13**, **15**, and **17**) with stereoviews based on crystal structures (**12**, **14**, **16**, and **18**, respectively).

Discussion

Effects of Added Salts on Ring-Closure Yields. In attempts to increase the yields in the oxidative coupling of dibromide **9** to give **2**, the oxidizing medium (THF–benzene) was saturated with added dry salts of the alkali metals. The yields were as follows: LiBr, 2.9%; NaBr, 0%; KBr, 3.3%; RbBr, 4.5%; CsBr, 4.7%. With the exception of the experiment with NaBr, the trend in yield correlates with the ionic diameters of the cations, which are as follows:¹⁰ Li^+ , 1.20 Å; Na^+ , 1.90 Å; K^+ , 2.66 Å; Rb^+ , 2.96 Å; Cs^+ , 3.38 Å. These experiments suggest that some sort of templating effect is operative, possibly for both polymer and macrocycle formation. The results provide yet another example of the presence of Cs^+ ion enhancing yield in formation of macrocyclic systems.⁶

Structures of Hosts. Comparisons of the conformations of rigid spherand **19**¹¹ and cavitands **1**, **2**, and **20**¹² are instructive. The crystal structures of spherand **19** and spheraplexes $19 \cdot \text{Li}^+$ and

$19 \cdot \text{Na}^+$ are conformationally very similar to one another.¹¹ The



geometric requirements for attaching six methoxyl groups to the 18-membered carbocyclic ring in **19** ensures that the oxygens are octahedrally arranged about an empty cavity and that all six methyl groups point outward away from the cavity. The crystal structure of host **20**, in which six fluorines are substituted for the six methoxyls for **19**, provides a similar octahedral arrangement of heteroatoms. Thus the bulk of the methyl groups turned outward is *not needed* to organize the arrangement of oxygens in **16**. In contrast, a comparison of the conformations of cavitands **1** and **2** with that of **21** indicates that the bulk of the methyl groups of the methoxyls is *needed* to provide the square, antiprismatic arrangement of oxygens attached to the 24-membered carbocycle of **1** and **2**. Thus the octafluoro analogue **21** exists in the conformation drawn in **21a** (D_{2d} symmetry, ^{19}F NMR) rather than in the square, antiprismatic conformation **21b** (D_{4d} symmetry). In contrast, **1** and **2** have NMR spectra consistent with having the square-prismatic arrangement of oxygens found in drawings **11**, **13**, **15**, and **17** and in crystal structures **12**, **14**, **16**, and **18**. Molecular models (CPK) of **1** or **2** in the conformation resembling **21a**, although assemblable, are compressed and strained due to the spatial requirements of the eight methyls attached to the oxygens. The preference for conformation **21a** over **21b** possibly reflects the lower cavity volume and more favorable C–F dipole–dipole interactions in the former conformation.

In CPK models of **1** and **2**, rotations about the oxygen–aryl bonds appear to have activation energy barriers low enough for equilibrations of conformers to occur very rapidly on the ^1H NMR time scale at attainable temperatures. In models, conformer **11**, with four opposing methyl groups turned inward, conformer **13**, with two opposing methyl groups turned inward, and conformer **15**, with three opposing methyl groups turned inward, all appear to be as free of strain and compression as the conformer drawn for **1** and **2**, in which all methyls attached to oxygen are turned outward. Other conformers with more than four inward-turned methyls appear to be substantially more strained than **11**, **13**, or **15**. Conformers **11**, **13**, and **15** have much smaller cavities than conformers **1** and **2**. The cavity in crystal structure **12** is oblong and complementary in CPK models to models of triatomic molecules such as $\text{HC}\equiv\text{N}$ or HONH_2 , being about 4 Å long, about 2.5 Å wide, and about 4 Å deep. The cavity in the crystal structure **14** in CPK models is large enough to embrace single molecules of simple solvents such as CH_3CN , CH_2Cl_2 , or $\text{CH}_3\text{CH}_2\text{OH}$ without strain. The cavity of **16** in models is between those of **12** and **14** in size. Although the cavity of **15** is nearly large enough to *host* the molecule of $\text{CH}_3\text{CH}_2\text{OH}$ found in its crystal structure, this potential guest is external to the cavity. It overlies ring E in **15**, and its hydroxyl hydrogen bonds the oxygen

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of ring E, whose unshared electron pairs are turned outward. The fact that differing numbers of methyl groups are turned inward in **12** (4), **14** (2), **16** (3), and **18** (0) indicates that the macrocyclic system imposes little intrinsic driving force for dominance of a single conformation.

The geometric parameters of Table II for crystal structures **12**, **14**, **16**, and **18** provide further interesting comparisons. The benzene rings in these macrocyclic hosts are planar, the maximum deviation in each of the four structures of a carbon from its C₆ plane being 0.02 Å. In **19**, **19**·Li⁺, and **19**·Na⁺ the benzene rings are not planar. The average aryl-aryl dihedral angles in free hosts **12**, **14**, and **16** are respectively 73.3°, 79°, and 71°, which decreases to 65° in caviplex **18**. The average angles of tilt of the aryl groups from the carbocycles best plane (defined by the carbons of the Ar-Ar linkages) are respectively 45°, 43°, and 40° in **12**, **14**, and **16**, decreasing to 36° in caviplex **18**. Thus **12**, **14**, and **16** resemble one another in dispositions of their aryl groups in spite of differences in the partial occupancy of their cavities. In **12**, the four inward-turned methyl groups provide both a floor and a roof for a cavity of reduced dimensions, whereas in **14**, the two inward-turned methyl groups provide a roof to a cavity which is somewhat inefficiently filled by the intermolecular packing of a *p*-CH₃C₆H₂ of an adjacent molecule into it from the floor side (not shown in **14**). Comparisons of the distance parameters for **12**, **14**, and **16** also indicate that aside from the differences in placement of the methyls of the methoxyls, the general locations of the aryls and oxygens resemble one another. For example, the average distances of the eight oxygens from their mean plane are 1.21 Å in **12**, 1.14 Å in **14**, and 1.14 Å in **16**, but the value decreases to 0.99 Å in **18**. The average distances between the inward-turned and opposite methyl carbons are 4.32 Å in **12**, 3.82 Å in **14**, and 3.65 Å in **16**. The average O-O distance in **12** is 6.83 Å, in **14** is 6.58 Å, in **16** is 6.66 Å, but in **18** it decreases to 6.19 Å.

The oxygens are bent out of the planes of their attached aryl groups in directions which only partially correlate with the locations of their attached methyl groups. Thus **12** has four inward-turned methyls whose oxygens are bent outward an average of 0.13 Å, **14** has two inward-turned methyls whose oxygens are bent outward an average of 0.07 Å, and **16** has three inward-turned methyls whose oxygens are bent outward an average of 0.17 Å. However, in **12**, **14**, **16**, and **18**, the oxygens bound to outward-turned methyls appear capable of bending either inward or outward by average values of between 0.03 and 0.10 Å (see Table II).

Most of the above comparisons indicate that complexation of **1** or **2** with Cs⁺ causes some host reorganization. Thus the inward-turned methyl groups are driven outward, and the square antiprism defined by the oxygens in **1** and **2** shrinks to better complement the diameter of the Cs⁺ guest. In **18**, each Cs⁺ is ligated by the eight oxygens of the macrocycle and by two additional oxygens provided by two ClO₄⁻ groups. These ClO₄⁻ groups are not shown in **18**. One is located directly above and the other directly below the Cs⁺ in **18**. These Cs⁺...O distances are 3.20 and 3.32 Å, comparable to the average Cs⁺-O distance of 3.25 Å (range 3.18-3.27 Å) for the other eight ligands. The Cs⁺ ion is well centered, being only 0.02 Å from the mean plane of the eight oxygens of the host. The overall average Cs⁺ to oxygen distance for all ten oxygens is 3.25 Å. If the standard covalently bound oxygen diameter of 2.80 Å is assumed,¹⁰ the diameter of Cs⁺ in **18** becomes 3.70 Å, 0.30 Å in excess of the more usual diameter of 3.40 Å.¹⁰ Surprisingly, only three of the eight oxygens are bent outward from the planes of their attached aryls (average of 0.055 Å), the other five being bent inward (average of 0.51 Å). The eight oxygens in **18** are located at the apices of a square antiprism. The squares are in planes separated by 2 Å and have sides ranging from 4.3 to 4.7 Å.

These four crystal structures taken in sum indicate that although **1** and **2** are largely preorganized for binding Cs⁺ with respect to the gross locations of its oxygens, the methyl groups are not preorganized, and the oxygens are capable of hydrogen bonding solvent (e.g., as in **2**·C₂H₅OH). Thus these hosts are neither as

ideally nor as completely preorganized as is spherand **19** for binding Na⁺ or Li⁺.

Correlation of Structure with Binding. The patterns of -ΔG° values for **1**, **2**, and **10** binding the picrate salts of the alkali metal ions in CDCl₃ (saturated with D₂O) each provide the order Cs⁺ > Rb⁺ > Na⁺ > K⁺ > Li⁺ (Table I). As expected, Cs⁺ is the most complementary to the cavities of the hosts, being bound by 2.4, 3.5, and 1.6 kcal mol⁻¹ more strongly than Rb⁺ by **1**, **2**, and **10**, respectively. The respective K_a^{Cs}/K_a^{Rb} ratios for **1**, **2**, and **10** are 57, 366, and 14. Although the standard ionic diameter of K⁺ (2.66 Å) is substantially higher than that of Na⁺ (1.90 Å), the latter is better bound than the former by **1**, **2**, and **10** by 1.0, 1.2, and 0.7 kcal mol⁻¹, respectively. Furthermore, Na⁺ is more strongly bound than Li⁺ by **1**, **2**, and **10**, the respective Δ(-ΔG°) values being 1.7, 1.8, and 0.7 kcal mol⁻¹.

Molecular model examination indicates that the cavities of **1** and **2** with all methyls pointing outward are complementary to up to 4 mol of H₂O hydrogen bonded to alternate anisyl units and (or) to each other. Spheres the diameter of Li⁺ (1.20 Å) or Na⁺ (1.90 Å) can nest in the cavity by displacing 1 mol of H₂O and can be ligated without strain by the oxygens of three methoxyl oxygens. A sphere the diameter of Na⁺ can additionally be ligated by two of (up to) three nesting waters, whereas that of Li⁺ can be ligated by only one of these. A sphere the diameter of K⁺ (2.66 Å) to nest in the cavity must displace two nesting waters. It can be ligated without strain by three of the methoxy oxygens and the oxygens of up to two remaining waters. Thus in effect, the ions compete with water for the cavity, which undoubtedly scavenges water from the medium (chloroform saturated with water). Sodium appears to get into this anisole-water structure with lower energy than either Li⁺ or K⁺.

In models of **1** and **2**, NH₄⁺ can nest in the cavity along with two waters, CH₃NH₃⁺ can nest only with one, and *t*-BuNH₃⁺ can only form a perching complex on a cavity containing two water molecules. The -Δ(ΔG°) values for **1**, **2**, and **10** favor NH₄⁺ over CH₃NH₃⁺ by only 0.8, 0.1, and 0.3 kcal mol⁻¹, respectively, whereas they favor CH₃NH₃⁺ over *t*-BuNH₃⁺ respectively by 4.2, 5.0, and 2.6 kcal mol⁻¹. Thus **2** complexes CH₃NH₃⁺ by a factor of 27 500 more strongly than *t*-BuNH₃⁺ (ratio of K_a values). This is the largest structural recognition factor we have observed involving these two alkylammonium ions.⁹

Comparisons of the general binding power of the three hosts show that **2** > **1** > **10**, the respective -ΔG°_{av} values being 9.2, 8.0, and 5.9 kcal mol⁻¹. This correlates roughly with the Hammett linear free energy σ values of -0.17 for the *p*-methyl group, 0 for *p*-hydrogen, and +0.17 for a 3,4-(CH₃)₂ (benzo) group.¹³ Comparison of the -ΔG° values for **1** and **2** binding Cs⁺ (11.8 vs 13.9 kcal mol⁻¹, respectively) indicates that substitution of each para hydrogen by a methyl group increases the binding by about 0.25 kcal mol⁻¹. Similar inductive effects have been observed to influence the binding of aryldiazonium guests by 18-crown-6¹⁴ and alkali metal cations by the benzocorands.¹⁵

When arranged according to their binding power toward their most complementary anions, the following order is observed: spherands > cryptaspherands > cryptands > hemispherands > corands > podands.⁹ This order correlates with the degree of preorganization of the systems for binding guests and for inhibiting the binding of solvent.⁹ Cavitands **1** and **2** are comparable to the hemispherands¹⁶ in their binding power. Although the eight oxygens of **1** and **2** are better preorganized for binding than the oxygens of the hemispherands, they are less preorganized to inhibit solvation by water than are the hemispherands. Both of these aspects of preorganization are important to binding.

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Experimental Section

General. Tetrahydrofuran (THF) and Et₂O were distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled twice from CaH₂. Benzene was distilled from LiAlH₄. Other solvents were dried over 3-Å molecular sieves. Ferric acetylacetonate was dried at 100 °C under vacuum prior to use. Column chromatography was performed on silica gel 60 (E. Merck, particle size 0.063–0.200 nm, 70–230 mesh ASTM). Thin-layer chromatography was performed on silica gel precoated plastic sheets (E. Merck, thickness 0.2 mm). Preparative thin-layer chromatography was conducted on 2-mm silica gel 60 plates (E. Merck). Gel permeation chromatography was performed on a 20 ft × 0.375 in. (o.d.) column that was packed with Styragel (200 g, Waters Associates, 100 Å) with CH₂Cl₂ as the mobile phase and flow rates of 4 mL min⁻¹. Analytical high-pressure liquid chromatography was conducted on an Altex 110 A chromatograph with a Partasil PXS 10 column. Melting points were measured on either a Mel-Temp or Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were observed on a Bruker WP-200 spectrometer (200 MHz) in CDCl₃ unless otherwise stated. All chemical shifts are reported in parts per million, using TMS as a reference unless otherwise stated. Carbon-13 NMR spectra were taken at 50.29 MHz on the same spectrometer. Mass spectra were taken on an AEI Model MS 9 spectrometer at 70 eV. FAB mass spectra were obtained on an AEI MS 902 spectrometer with 6-kV atomic beam energy.

3,3'-Dibromo-2,2'-dimethoxy-1,1'-biphenyl (4). To 30.5 mL (202 mmol) of TMEDA in 550 mL of dry ether at 25 °C was added 209 mmol of *n*-BuLi in hexane. The mixture was stirred for 10 min, and 19.06 (89 mmol) of 2,2'-dimethoxy-1,1'-biphenyl (3)⁴ was added. The reaction was stirred at 25 °C for 2.5 h and then cooled to -78 °C. To this mixture was added a solution of 30 mL (586 mmol) of P₂O₅-dried bromine in 35 mL of dry pentane. The reaction was maintained at -78 °C for 5 min, allowed to warm slowly to 25 °C, and quenched with 500 mL of aqueous Na₂SO₃ solution (saturated). The mixture was partitioned between 500 mL of water and 1500 mL of CHCl₃. The organic layer was washed with 500 mL of water, dried over MgSO₄, and concentrated under vacuum. The dark residue was flash chromatographed (SiO₂, 25 × 8.5 cm, cyclohexane → 5% benzene/cyclohexane) to give **4** as a viscous, yellow oil. Crystallization of this material from CH₂Cl₂/heptane provided pure product as large, colorless crystals (7.90 g, 24%): mp 84.5–86.5 °C; ¹H NMR δ 3.55 (s, 3 H, OCH₃), 7.03 (t, 1 H, ArH₃, *J* = 7.8 Hz), 7.28 (d of d, 1 H, ArH₆, *J*_o = 7.6 Hz, *J*_m = 1.6 Hz), 7.58 (d of d, 1 H, ArH₄, *J*_o = 7.9 Hz, *J*_m = 1.6 Hz); MS *m/z* 374 (56), 372 (100), M⁺ (⁷⁹Br) 370 (58). Anal. Calcd for C₁₄H₁₂Br₂O₂: C, 45.20; H, 3.25; Br, 42.95. Found: C, 45.24; H, 3.28; Br, 42.96.

41,42,43,44,45,46,47,48-Octamethoxynonacyclo[35.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}.1^{27,31}.1^{32,36}]octatetraconta-1(41),2,4,6(48),7,9,11(47),12,14,16(46),17,19,21(45),22,24,26(44),27,29,31(43),32,34,36(42),37,39-tetracosane (1). To a solution of 12.20 g (32.79 mmol) of dibromide **4** in 300 mL of THF at -78 °C was added 104 mmol of *sec*-BuLi in cyclohexane. After stirring at -78 °C for 15 min, the dilithiate mixture was transferred via cannula into a refluxing solution of 51.1 g (147 mmol) of Fe(acac)₃ in 7.5 L of benzene. The reaction was refluxed for 4 h and then stirred at 25 °C for 1 day. To the reaction mixture were added with vigorous stirring 500 mL of aqueous HCl (concentrated) and 500 mL of water. Benzene was removed by distillation under vacuum, leaving a deep red aqueous layer. The aqueous mixture was filtered, and the collected solid was washed well with water and dried under vacuum. The reaction flask was washed with water and dried under vacuum. The solid which adhered to the walls was dissolved in CH₂Cl₂, which was subsequently removed under reduced pressure, leaving a brownish foam. This foam was combined with the dried collected solid. The solid material was triturated with 150 mL of boiling ether and filtered. The mother liquor was concentrated under vacuum. The residue was chromatographed (medium pressure, silica gel, 45%–55% (by volume) Et₂O/CH₂Cl₂) to afford the crude cycle, which was then recrystallized from CH₂Cl₂/acetone to give pure **1** as fine, white needles (97 mg, 0.114 mmol, 1.4%): mp 348–350 °C; ¹H NMR δ 3.14 (s, 3 H, OCH₃), 7.14–7.34 (m, 3 H, ArH); ¹³C NMR δ 59.80 (OCH₃), 122.90 (aromatic CH, para to OCH₃), 130.29 (aromatic CH, meta to OCH₃), 132.94 (aromatic C, ortho to OCH₃), 156.20 (aromatic C, attached to OCH₃); MS *m/z* 850 (20), 849 (44), M⁺ 848 (100). Anal. Calcd for C₅₆H₄₈O₈: C, 79.23; H, 5.70. Found: C, 79.16; H, 5.65.

2'-Methoxy-3-bromo-5,5'-dimethyl-1,1'-biphenyl-2-ol (6). To a solution of 1 g (4.4 mmol) of **5** in 10 mL of CHCl₃ was added dropwise a solution of 0.74 g (4.5 mmol) of bromine in 5 mL of CHCl₃ until the red color persisted after 0.5 h of stirring. Then 100 mL of CH₂Cl₂ was added, and the solution was washed with three 100-mL aliquots of aqueous NaHSO₃ solution and two 50-mL aliquots of water. The organic layer was dried (MgSO₄) and concentrated to dryness under reduced pressure. The solid was dissolved in hot hexane and cooled to -20 °C

to yield fluffy white crystals which were filtered, washed with hexane, and dried to give 1.2 g (89–96%); mp 123–123.5 °C; ¹H NMR δ 2.30 (s, 3 H, ArCH₃), 2.336 (s, 3 H, ArCH₃), 3.850 (s, 3 H, OCH₃), 6.340 (s, 1 H, OH), 6.47–7.35 (m, 5 H, ArH); MS *m/z* 309 (10), 308 (64), M⁺ 307 (14), M⁺ 306 (75). Anal. Calcd for C₁₅H₁₅O₂Br: C, 58.65; H, 4.92. Found: C, 58.58; H, 4.79.

3-Bromo-2,2'-dimethoxy-5,5'-dimethyl-1,1'-biphenyl (7). To a stirred mixture of 5 g (16.2 mmol) of **6** and 3.4 g (24.6 mmol) of K₂CO₃ in 250 mL of acetone was added 2.3 mL (24.6 mmol) of (CH₃)₂SO₄. After 24 h of stirring at 25 °C, 10 mL of concentrated NH₄OH was added to the mixture, which was then stirred for an additional 2 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between 200 mL of EtOAc and 100 mL of water. The organic layer was washed with 100 mL of water and 100 mL of brine and dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was submitted to flash chromatography on 100 g of silica gel with 1:1 (by volume) CH₂Cl₂/cyclohexane as the mobile phase (*R*_f 0.46 on TLC) to yield 5.03 g (97–98%) of **7** as a clear oil (dried at 80 °C under vacuum): ¹H NMR δ 2.303 (s, 6 H, ArCH₃), 3.471 (s, 3 H, OCH₃), 3.752 (s, 3 H, OCH₃), 6.85–7.36 (m, 5H, ArH); MS (190 °C) *m/z* 323 (11), 322 (M⁺, 73), 320 (13). Anal. Calcd for C₁₆H₁₇O₂Br: C, 59.83; H, 5.33. Found: C, 59.96; H, 5.39.

2,2',2'',2'''-Tetramethoxy-5,5',5'',5'''-tetramethyl-1,1':3,1'':3',1'''-quaterphenyl (8). To a very dry mixture stirred under argon at -78 °C of dried **7** (11.6 g, 36.1 mmol) in 90 mL of freshly distilled THF was added 18.9 mL of a 2.1 M BuLi solution in hexane (39.8 mmol). The solution was stirred for 10 min at -78 °C and was transferred via a double-ended hollow needle into a solution stirred under argon at 25 °C composed of 14.7 g (42 mmol) of dried Fe(acac)₃ in 150 mL of dried, freshly distilled THF. The resulting mixture was stirred 12 h during which a heavy precipitate formed. The THF was evaporated under reduced pressure and the residue was dissolved in 500 mL of EtOAc. This solution was washed with three 300-mL portions of 2 N aqueous HCl (the last aqueous layer was colorless), 300 mL of water, and 300 mL of brine. The organic layer was dried (MgSO₄) and evaporated to dryness under reduced pressure. The residue was crystallized from 50 mL of hexane at -20 °C to yield after washing and drying 6.3 g (68–72%) of white crystals: mp 128–129 °C; ¹H NMR δ 2.309 (s, 6 H, ArCH₃), 2.337 (s, 6 H, ArCH₃), 3.288 (s, 6 H, OCH₃), 3.752 (s, 6 H, OCH₃), 6.83–7.17 (m, 10 H, ArH); MS (130 °C) *m/z* 483 (33), 482 (M⁺, 100). Anal. Calcd for C₃₂H₃₄O₄: C, 79.64; H, 7.10. Found: C, 79.59; H, 7.04.

3,3''-Dibromo-2,2',2'',2'''-tetramethoxy-5,5',5'',5'''-tetramethyl-quaterphenyl (9). To a solution stirred at 25 °C under dry argon of 1.0 g (2.07 mmol) of dry **8** in 30 mL of freshly distilled (dry) Et₂O was added 0.66 g (2.3 mmol) of dry TMEDA followed by 2.2 mL of 2.1 M BuLi in hexane (4.6 mmol). The suspension was stirred at 25 °C for 3 h and cooled to -78 °C, and a solution of 640 μL (41 mmol) of P₂O₅-dried Br₂ in 10 mL of dry pentane was added dropwise. The solution was allowed to warm to 25 °C, stirred for 12 h, and then poured slowly into 100 mL of water saturated with NaHSO₃. The mixture was shaken with 100 mL of EtOAc, and the organic phase was washed with two 100-mL portions of water saturated with NaHSO₃, two 50-mL portions of water, and 50 mL of brine. The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was flash chromatographed on 75 g of silica gel with 5:95 (by volume) Et₂O/(CH₂)₆ as the mobile phase (*R*_f of **8**, 0.08; *R*_f of monobromo impurity, 0.21; *R*_f of **9**, 0.33 on TLC) to give after evaporation and drying (80 °C at high vacuum) of the appropriate fraction 1.04 g (78%) of **9** as a clear oil; ¹H NMR δ 2.315 (s, 6 H, ArCH₃), 2.351 (s, 6 H, ArCH₃), 3.294 (s, 6 H, OCH₃), 3.551 (s, 6 H, OCH₃), 7.10–7.41 (m, 8 H, ArH); MS (250 °C) *m/z* 643 (14), 642 (M⁺, 56), 641 (33), 640 (100). Anal. Calcd for C₃₂H₃₂Br₂O₄: C, 60.02; H, 5.04. Found: C, 59.95; H, 5.20.

41,42,43,44,45,46,47,48-Octamethoxy-4,9,14,19,24,29,34,39-octamethoxynonacyclo[35.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}.1^{27,31}.1^{32,36}]octatetraconta-1(41),2,4,6(48),7,9,11(47),12,14,16(46),17,19,21(45),22,24,26(44),27,29,31(43),32,34,36(42),37,39-tetracosane (2). Method A. Dibromide **9** was dried as a viscous oil for 10 h at 85 °C under high vacuum, cooled, and weighed. A stirring bar was added to a 0.846-g (1.32 mmol) sample of **9**, and the material was dried an additional 10 h. The flask was capped and flushed with argon. Freshly distilled THF (25 mL) was added, and the solution was cooled to -78 °C under dry argon. A solution of 2.7 mL of *sec*-butyllithium (1.45 M in cyclohexane, 3.92 mmol) was added, and the metalated mixture was stirred for 10 min. This solution was cannulated into a refluxing and very dry solution of 1.97 g (5.31 mmol) of Fe(acac)₃ stirred under dry argon, followed by a 10-mL rinse of freshly distilled THF. The reaction was refluxed for 1 h and stirred at 25 °C for 10 h. Benzene was removed under reduced pressure, and the solid was partitioned between 300 mL of EtOAc and 200 mL of 2 N hydrochloric acid. The organic layer was washed with

200-mL portions of 2 N hydrochloric acid until the aqueous layer was colorless. It was also washed once with 200 mL of H₂O and once with 200 mL of brine. The organic layer was dried (MgSO₄) and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ and gel chromatographed in two portions. Fractions from 180–245 mL of CH₂Cl₂ contained product. Solvent was removed from these fractions under reduced pressure. The residue was purified by preparative TLC (SiO₂, 1:1 EtOAc/CH₂Cl₂). The product (30.5 mg, 0.0318 mmol, 4.8%) was extracted from the silica with EtOAc and isolated by removal of solvent under reduced pressure. The white, crystalline solid **2** (18.1 mg, 0.0189 mmol, 2.9%) was obtained by recrystallization from 2 mL of CH₂Cl₂ and 4 mL of EtOH; mp >360 °C; ¹H NMR δ 2.353 (s, 3 H, ArCH₃), 3.104 (s, 3 H, ArOCH₃), 7.099 (s, 2 H, ArH); ¹³C NMR δ 20.767, 59.773, 130.578, 131.987, 132.637, 153.873; MS *m/z* 974 (14), 962 (24), 961 (66), 960 (M⁺, 100). Anal. Calcd for C₆₄H₆₄O₈: C, 79.97; H, 6.71. Found: C, 79.89; H, 6.78. Crystals of **2** suitable for crystal structure determination were grown by slow evaporation of a 1:1 (by volume) CH₂Cl₂/EtOH solution. Crystals of **2**·EtOH suitable for crystal structure determination were grown by slow evaporation of a 1:1 (by volume) CHCl₃/EtOH solution.

Method B. Method B was similar to method A except that a KBr-THF slurry was prepared and used as the reaction medium as follows. A 1.95-g (50.0 mmol) sample of potassium metal was rinsed three times with dry toluene and then with freshly distilled dry THF, and the metal was added to 35 mL of freshly distilled THF. A 3.75-g (20.0 mmol) sample of 1,2-dibromoethane was added. The mixture was sonicated for 15 h under argon. The resulting slurry of KBr and THF was cannulated into a flask containing 0.726 g (1.13 mmol) of dry **9**. The reaction was conducted as outlined in method A. From 1.80 g (4.85 mmol) of Fe(acac)₃ and 2.6 mL (1.45 M in cyclohexane, 3.77 mmol) of *sec*-butyllithium, 28.4 mg (0.0296 mmol, 5.2%) and 18.9 mg (0.0197 mmol, 3.0%) of **2** were obtained before and after final recrystallization, respectively. The product had physical properties identical with those obtained from **2** prepared by method A.

Method C. Method C resembled method A except that a RbBr-THF slurry was used as the reaction medium. A 3.2-g (19.3 mmol) sample of RbBr was dried at 135 °C for 16 h under high vacuum. This material was transferred to the coupling apparatus as a slurry by repeated cannulation using freshly distilled benzene. A 1.78-g (4.80 mmol) portion of Fe(acac)₃ was then added and the reaction was conducted as indicated in method A. A 0.768-g (1.20 mmol) sample of **9** gave 42.1 mg (0.0438 mmol, 7.3%) of **2** prior to recrystallization and 13.6 mg (0.0142 mmol, 2.4%) following recrystallization. The product had physical properties identical with those of the sample prepared by method A.

2·CsClO₄. To a solution of 5.0 mg (5.21 mmol) of **2** in 1.0 mL of CDCl₃ was added 0.021 mL of a 0.262 M solution of CsClO₄ in (C-D₃)₂SO. The resulting solution gave the following ¹H NMR spectrum: δ 2.405 (s, 3 H, ArCH₃), 3.206 (s, 3 H, ArOCH₃), 7.092 (s, 2 H, ArH).

Crystals of **2**·CsClO₄ suitable for X-ray crystal structure determination were prepared by slow evaporation of 1:1 (by volume) CH₂Cl₂/EtOH solution of the complex.

Determination of Association Constants and Free Energies of Complexation. The technique has been described in detail.^{7,17} The initial host and guest concentrations were 0.015 M for **1** and **2** except when Rb⁺ and Cs⁺ served as guests, in which case 0.001 M concentrations were used.

Crystal Structure Determinations. Compound **1** crystallizes in small colorless platelets from CDCl₃ in the triclinic system *P* $\bar{1}$. Unit cell dimensions are as follows: *a* = 7.924 (2) Å, *b* = 11.433 (3) Å, *c* = 25.541 (6) Å, α = 79.12 (2)°, β = 83.61 (2)°, γ = 87.60 (2)°, *V* = 2258 Å³, *Z* = 2. The crystal was examined on a Syntex P1 diffractometer, Mo Kα radiation, at 296 K. The structure was determined by direct methods. Refinement of 757 parameters (2863 reflections with *I* > 3σ(*I*)) has an agreement value, *R*, currently at 0.063. Compound **2**·CH₂Cl₂ crystallizes from CHCl₃/C₂H₅OH as clear, colorless, multifaceted crystals in the monoclinic space group *P*2₁/*n*. Unit cell dimensions are as follows: *a* = 14.936 (4) Å, *b* = 15.088 (4) Å, *c* = 25.727 (6) Å, β = 92.44 (2)°, *V* = 5792 Å³, *Z* = 4. The crystal was examined on a Syntex P1 diffractometer, Cu Kα radiation, at 113 K. The structure was determined by direct methods. Refinement of 325 parameters (4857 reflections with *I* > 3σ(*I*)) has an agreement value, *R*, currently at 0.089. The CH₂Cl₂ solvent is disordered. Compound **2**·C₂H₅OH crystallizes from ethanol as colorless prisms in the monoclinic system *P*2₁/*n*. Unit cell dimensions are as follows: *a* = 14.117 (6) Å, *b* = 27.796 (9) Å, *c* = 14.845 (4) Å, β = 94.29 (3)°, *V* = 5809 Å³, *Z* = 4. The crystal was examined on a Syntex P1 diffractometer, Cu Kα radiation, at 115 K. The structure was determined by direct methods. Refinement of 673 parameters (7589 reflections with *I* > 1.5σ(*I*)) has an agreement value, *R*, currently at 0.096. The ethyl fragment of the ethanol solvent is disordered. Ethanol is hydrogen bonded to one of the O binding sites of the host. Compound **2**·CsClO₄·CH₂Cl₂ crystallizes from CH₂Cl₂/C₂H₅OH as small colorless prismatic needles in the orthorhombic system *Pnam*. Unit cell dimensions are as follows: *a* = 17.088 (5) Å, *b* = 19.691 (6) Å, *c* = 20.392 (6) Å, *V* = 6861 Å³, *Z* = 4 (8 half-molecules related by *m*). The crystal was examined on a Syntex P1 diffractometer, Mo Kα radiation, at 115 K. The structure was determined by direct methods. Refinement of 258 parameters (3064 reflections with *I* > 2σ(*I*)) has an agreement value, *R*, currently at 0.10. Full details will be published elsewhere.

Registry No. **1**, 110569-94-3; **2**, 110569-95-4; **2**·C₂H₅OH, 110570-01-9; **2**·CsClO₄, 110570-03-1; **2**·CH₂Cl₂, 110589-06-5; **3**, 4877-93-4; **4**, 110569-96-5; **5**, 24046-10-4; **6**, 110569-97-6; **7**, 110569-98-7; **8**, 110569-99-8; **9**, 110570-00-8; Fe(acac)₃, 14024-18-1.

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