

# Structural Features of Solid-State Calix[4]arene in the Cone Conformation

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A statistical analysis of cone-shaped calix[4]arene structural features derived from the Cambridge Structural Database is presented. The mean, standard deviation and range of values for lengths, angles, and dihedrals for the monomers and for the macrocyclic assembly as a whole are provided. A comparison of native, near-native, and derivatized calix[4]arenes is made. Semiempirical molecular orbital theories and empirical force field calculations, both in gas and solution phase, are inconsistent with experimentally known conformer populations of a tetramethyl ether derivative of *p*-tert-butylcalix[4]arene. A reason for the inability of these computational methods to give correct answers is given, and extreme caution is urged when using these tools to predict calixarene structure and energy.

## I. Introduction

Calixarenes are cyclic oligomers of derivatized benzenes usually linked by *m*-methylene units.<sup>1</sup> Since their discovery they have been recognized as having structural attributes, both geometric and electronic, that are conducive to guest-host complexation.<sup>2</sup> Their ease of synthesis allows for synthetic modification of both upper and lower rims, and a recent emphasis in the field of calixarene chemistry has been on derivatizing these important macrocycles.<sup>3</sup>

The topological features of calixarenes have been likened to the cyclodextrins, and ongoing studies of inclusion of ions and small organic molecules within their cavities have been undertaken with the intention of exploiting this phenomenon for a variety of targeted effects. While the guest-host complexation of native, underivatized calixarenes is uneventful, it is becoming widely recognized that the calixarenes offer an easily constructed substructure onto which other units may be built to elicit important physicochemical responses, one example being as a material for nonlinear optics.<sup>4</sup> The basic structural features of these architecturally important cup-shaped macrocycles are clearly key elements for future design purposes.

In an earlier paper we presented a detailed analysis of cyclodextrins,<sup>5</sup> cyclic oligomers of  $\alpha$ -D-glucose, that similarly serve as an architectural foundation for synthetic modification for guest-host complexation. In that paper we provided an assessment of monomeric and macrocyclic features for all known crystal structures along with a computational analysis of their conformations. Because cyclodextrins and calixarenes have much in common we present here information on calix[4]arenes culled from the Cambridge Structural Database (CSD). The focus of this study is on those calix[4]arenes with cone conformations because they are most amenable to guest-host complexation and because there are a large number of these shapes (in contrast to other conformations) allowing for a good qualitative assessment of their structure. Also presented is an evaluation of the predictive ability of several popular empirical force fields and semiempirical molecular orbital programs that have been used by organic chemists to compute the structures and energies of calixarenes. It will be shown that most of these methods fail to correctly predict experimentally determined conformer populations and that caution must be used when implementing these theoretical tools for structure prediction.

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(1) Recent reviews include: (a) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1989, Vol. 1. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vincens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Böhmer, V.; McKervey, M. A. *Chem. Unserer Zeit* 1991, 195.

(2) Several citations after those discussed in ref 1 include: (a) Arnaud-Neu, F.; Böhmer, V.; Guerra, L.; McKervey, M. A.; Paulus, E. F.; Rodriguez, Z.; Schwing-Weill, M.-J.; Tabatabai, M.; Vogt, W. *J. Phys. Org. Chem.* 1992, 5, 471. (b) Schwing-Weill, M.-J.; Arnaud-Neu, F.; McKervey, M. A. *Ibid.* pp 496-501. (c) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Chem. Lett.* 1992, 755. (d) Arnaud-Neu, F. et al. *J. Chem. Soc., Perkin Trans. 2* 1992, 1119. (e) McCarrick, M.; Wu, B.; Harris, S. J.; Diamond, D.; Barrett, G.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* 1992, 1287. (f) Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Ungaro, R. *Ibid.* pp 1291. (g) Barrett, G.; Böhmer, V. et al. *J. Chem. Soc., Perkin Trans. 2* 1992, 1595.

(3) Several citations after those discussed in ref 1 include: (a) Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* 1991, 56(1), 301. (b) Nagasaki, T.; Sisido, K.; Arimura, T. and Shinkai, S. *Tetrahedron*, 1992, 48(5), 797. (c) Moran, J.K.; Roundhill, D. M. *Inorg. Chem.* 1992, 31(21), 4213. (d) van Loon, J.-D.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* 1992, 33(35), 5125. (e) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* 1992, 114(26), 10573. (f) Neri, P.; Pappalardo, S. *J. Org. Chem.* 1993, 58(5), 1048. (g) Asfari, Z.; Vicens, J.; Weiss, J. *Tetrahedron Lett.* 1993, 36(4), 627.

## II. Experimental Section

Structures were obtained from the 1992 CSD.<sup>6</sup> Of the 86 hits, 68 were calix[4]arenes, the rest being higher homologs. In this dataset three had no coordinates, four had incomplete coordinates with bad structures, and one was disordered. They were thus removed. Also removed were all calix[4]arenes linked as dimers (usually by metals) as well as those coordinated to metals. Further deleted were calix[4]arenes in conformations other than cone, leaving a working set of 29 crystal structures. These structures were partitioned into three categories: native structures, near-native structures, and derivatized structures. Native structures are pure, cone calix[4]arenes with four OH groups on the lower rim. Near-native structures contain simple functionality on the lower rim like ethers and esters, but not metals or lower rim

(4) Kelderman, E.; Derhaeg, L.; Heesink, G. J. T.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* 1992, 31(8), 1075.

(5) Lipkowitz, K. B.; Green, K.; Yang, J.-A. *Chirality*, 1992, 4, 205.

(6) Cambridge Structural Database, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

Table I. CSD Reference Codes and Agreement Factors for Structures Used in This Study

	refcode	*rfact	
native	CUPWAL	0.073	
	DACLUO	0.090	
	DACMAV	0.070	
	JABWEO	not given	
	near-native	DAKSEN10	0.106
		DOGGAH	0.120
		DUTBUP	0.056
		FAZKEW	0.101
		FAZKEW10	not given
		FEHXOF	0.094
derivatized	FEHXOF10	0.094	
	KEVXIS	0.064	
	KEVXOY	0.067	
	KEYVAL	0.072	
	KEYVAL	0.072	
	SEKBEP	0.078	
	SIWTEX	0.097	
	VIRXAV	0.071	
	GACCUI	0.054	
	KEBPEM	0.150	
	KEBPOW	0.150	
	KEBPUC	0.075	
	SAFJEO	0.050	
	SAFJEO10	0.050	
	SAFJIS	0.054	
	VIKUR	0.156	
	VAZJAH	0.088	
VIBPIF	0.068		
SEZCIJ	0.050		

bridges connecting one monomer to another. Both native and near-native calixarenes contain only H, Me or t-Bu groups on the upper rim. Derivatized calixarenes are the same as the near-native ones except that the upper rim contains para substituents other than H, Me, or t-Bu. Most of these groups are sulfonates, but other functionalities like halogens and nitro groups exist. Table I lists the CSD reference codes and the crystallographic agreement factor, *R*. It is to be noted that several of these have more than one calixarene molecule per unit cell. Finally, we point out that many calixarene structures, including some calix[4]arenes in the cone form, are of solvates. We did not attempt to delete these from the dataset. Indeed, our purpose here is to examine the allowed deformations these macrocycles can undergo by using the crystal lattice as a perturbation. This provides some (limited) information about the calixarene's potential energy surface that we wish to compare with theory in a later part of this paper.

The empirical force fields used for computational analysis were MM2, AMBER and OPLSA as implemented in MacroModel V3.5<sup>7</sup> and CHARMM as implemented in Quanta/CHARMM.<sup>8</sup> The semiempirical molecular orbital programs used were MOPAC,<sup>9</sup> AMPAC,<sup>10</sup> and AMSOL.<sup>11</sup>

For all molecular mechanics calculations no cutoffs of any kind were used. The dielectric of the medium was set to 1.5, and the structures were optimized with a truncated Newton-Raphson minimizer until the gradient root mean square  $\leq 0.1$  kJ/Å mol in MacroModel and with the adopted basis Newton Raphson minimizer in CHARMM. Conformer searching was carried out with the MULTIC search strategies of Lipton and Still.<sup>12</sup> The lowest energy structures found this way were further minimized as above and used as input for the semiempirical molecular orbital methods. Full geometry optimizations relaxing all internal degrees of freedom were then carried out with the AM1 and PM3 Hamiltonians using the keyword "precise" as recommended by

Table II. Monomer Bond Lengths (Å) for Cone Calix[4]arenes

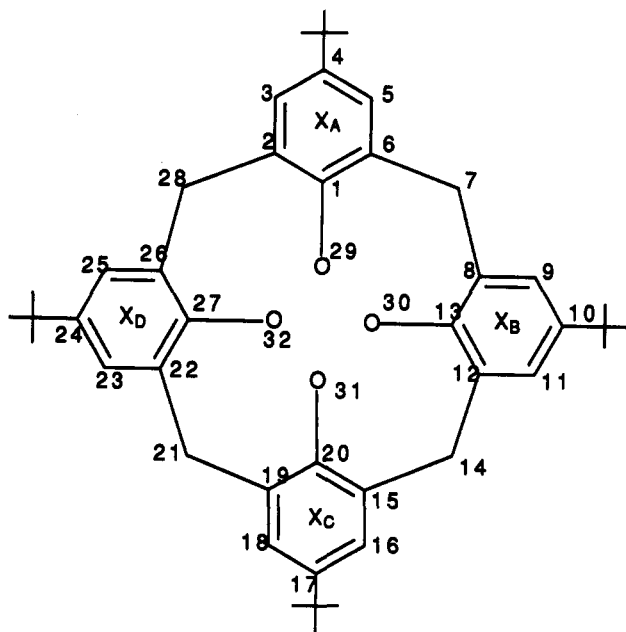
	low value	high value	avg	stand. devn
bond length C1–O29				
native	1.31	1.42	1.378	0.031
near-native	1.37	1.42	1.394	0.017
derivatized	1.21	1.41	1.339	0.052
all	1.21	1.42	1.373	0.042
bond length C6–C7				
native	1.50	1.58	1.527	0.024
near-native	1.48	1.59	1.519	0.018
derivatized	1.47	1.54	1.520	0.011
all	1.47	1.59	1.521	0.018

Boyd.<sup>13</sup> All molecules were assumed to exist as neutral, ground state singlets.

The solvated conformations were computed by using the lowest energy structures above. The GBSA method of Still<sup>14</sup> in MacroModel and AMSOL was used. Full geometry optimizations could be accomplished with the empirical force fields but not with AMSOL which was too slow (1 month of a MIPS 4000 chip in a SGI workstation did not give an optimized structure). Consequently, the AMSOL solvated structures refer to the lowest energy gas-phase structures that were held fixed in the solvation calculations.

### III. Results and Discussion

**A. Crystallographic Analysis.**<sup>15</sup> The numbering scheme of the calix[4]arenes used here is given below. In this report we consider the monomeric features first followed by the macrocyclic features.



**1. Monomeric Features. i. Distances.** Two monomeric features of interest are the O–Ar (e.g., O<sub>29</sub>–C<sub>1</sub>) and CH<sub>2</sub>–Ar (e.g., C<sub>6</sub>–C<sub>7</sub>) bond lengths. Table II contains the lowest observed value, the highest observed value, the average value, and the standard deviations (SD) for these lengths according to the calixarene's classification as native, near-native, or derivatized macrocycle. The av-

(7) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* 1990, 11(4), 440.

(8) Molecular Simulations Inc., 200 Fifth Avenue, Waltham, MA 02154.

(9) Stewart, J. J. P. *QCPE Bull.* 1990, 455, MOPAC 6.0.

(10) AMPAC as implemented in AMSOL (ref 11) was used.

(11) Cramer, C. J.; Lynch, G. C.; Truhlar, D. G. *QCPE Bull.* 1993, 13(1), 606, AMSOL 3.0.1.

(12) Lipton, M.; Still, W. C. *J. Comput. Chem.* 1988, 9(4), 343.

(13) Boyd, D. B.; Smith, D. W.; Stewart, J. J. P.; Wimmer, E. *J. Comput. Chem.* 1988, 9, 387.

(14) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* 1990, 112, 6127.

(15) Analyses of conformations of calix[4]arenes in the solid state exist. See: Perrin, M.; Oehler, D. Reference 1b, pp 65–85. Andreotti, G. D.; Uguzzoli, F. Reference 1b pp 87–123.

Table III. Monomer Bond Angles (deg) for Cone Calix[4]arenes

	low value	high value	avg	stand. devn
bond angle O29-C1-C6				
native	117.8	123.7	119.6	1.4
near-native	115.6	122.7	118.9	1.7
derivatized	116.3	121.6	119.7	1.5
all	115.6	123.7	119.3	1.6
bond angle C1-C6-C7				
native	117.0	123.5	121.4	1.6
near-native	118.0	124.7	121.9	1.5
derivatized	116.3	124.9	120.6	1.6
all	116.3	124.9	121.4	1.7
bond angle C6-C7-C8				
native	106.0	113.0	111.4	2.3
near-native	108.0	115.7	111.4	1.9
derivatized	107.9	115.0	111.8	2.1
all	106.0	115.7	111.5	2.0

average O-Ar length for native calix[4]arenes is 1.38 Å. One would anticipate a narrow distribution of these seemingly invariant bond lengths, but in fact one finds lengths anywhere from 1.31 to 1.42 Å. The O-Ar length for near-native calix[4]arenes is 1.39 Å, indicating elongation due to change in functionality from phenol to, e.g., ether and ester, with a much narrower range of lengths. The derivatized calixarenes (this set has substitution on the upper rim) have the shortest O-Ar average length of 1.34 Å with a broad distribution of values ranging from 1.21 to 1.41 Å. This broad distribution reflects the through conjugation of the para substituents which include electron-donating halogens and electron-withdrawing nitro groups, but mainly (~73% of this subset) sulfonates. The average O-Ar length for all calixarenes is 1.37 Å with SD = 0.042. The O-Ar lengths of this entire set span the range from 1.21 to 1.42 Å which is a broader range than one would first expect but consistent with through-conjugation of para substituents along with influences due to modification of the phenol functionality to ethers, esters, and so on. Histograms of all these distributions are in the supplementary material.

The CH<sub>2</sub>-Ar bond lengths are also surprisingly variable. For the pure, native calix[4]arenes the average value is 1.53 Å. This distribution is somewhat misleading because it actually is a bimodal distribution with one grouping centered around 1.52 Å and the other, smaller set, at 1.57 Å. The native calixarenes display the largest standard deviation in CH<sub>2</sub>-Ar lengths, but this reflects the small number of samples rather than the actual range of lengths (1.50–1.58 Å). The complete set of all calixarenes has an average CH<sub>2</sub>-Ar length of 1.52 Å with lengths from 1.47 to 1.59 Å. This is a substantial range of values for the CH<sub>2</sub>-Ar monomer length indicating that, in a collective mode, one may be able to substantially expand the interior of the macrocycle ring cavity upon guest inclusion.

**ii. Bond Angles.** Three monomer bond angles are considered: O-C<sub>Ar</sub>-C<sub>Ar</sub>, C<sub>Ar</sub>-C<sub>Ar</sub>-CH<sub>2</sub>, and C<sub>Ar</sub>-CH<sub>2</sub>-C<sub>Ar</sub>. These values, partitioned into their classification as native, near-native, or derivatized systems, are given in Table III. The O-C<sub>Ar</sub>-C<sub>Ar</sub> bond angle for the native calixarenes is on average 119.6°. The average value for the near-native subset is 118.9°. The average angle for the derivatized subset is 119.7°. For the entire set of calixarenes the average angle is 119.3° with values ranging from 115.6° to 123.5°. Hence, one finds an average O-C<sub>Ar</sub>-C<sub>Ar</sub> near the expected 120° for an sp<sup>2</sup> carbon with a modest range of values possible.

Table IV. Monomer Dihedral Angles (deg) for Cone Calix[4]arenes

	low value	high value	avg	stand. devn
dihedral angle O29-C1-C6-C7				
native	-5.2	+5.6	0.3	4.0
near-native	-9.4	+8.9	-0.3	5.0
derivatized	-9.2	+16.2	0.2	5.3
all	-9.2	+16.2	0.0	4.9
dihedral angle C1-C2-C3-C4				
native	-5.7	+5.6	0.0	2.2
near-native	-8.0	+6.9	0.0	2.9
derivatized	-11.2	+14.7	0.0	3.3
all	-11.2	+14.7	0.0	2.9

The external bond angles, e.g., C<sub>1</sub>-C<sub>6</sub>-C<sub>7</sub>, for the native calixarenes is 121.4°. The average angle for the near-native species is 121.9°. The derivatized species has an average value of 120.6°, and the entire collection has an average angle of 121.4° (SD = 1.68) with values ranging from 116.3° to 124.9°.

The C<sub>Ar</sub>-CH<sub>2</sub>-C<sub>Ar</sub>, e.g., C<sub>6</sub>-C<sub>7</sub>-C<sub>8</sub>, average bond angle for the native structures is 111.4° with values ranging from a compressed tetrahedral bond angle of 106.0° to an extended value of 113.0°. The near-native calixarene average is 111.4° with values from 108.0° to 115.7°. The derivatized calixarene average is 111.8° with a range from 107.9° to 115.0°, and for the entire set of calixarenes the average bond angle is 111.5° (SD = 2.03) with values ranging from 106.0° to 115.7°.

**iii. Dihedral Angles.** Two dihedral angles of the monomers were considered: O-C<sub>Ar</sub>-C<sub>Ar</sub>-CH<sub>2</sub> and C<sub>Ar</sub>-C<sub>Ar</sub>-C<sub>Ar</sub>-C<sub>Ar</sub>. These results are given in Table IV. For the O-C<sub>Ar</sub>-C<sub>Ar</sub>-CH<sub>2</sub> dihedral angles, e.g., O<sub>29</sub>-C<sub>1</sub>-C<sub>6</sub>-C<sub>7</sub>, native calixarenes have an average of 0.3° with values ranging from -5° to +6°. For the near-native calixarenes the average dihedral angle is -0.3° with a range from -9° to +9°. The average value for the derivatized subset is 0.2° with a range from -9° to +16°, and for all the calixarenes the average is 0.0° with values ranging from -9° to +16°. Hence, while one may find that on average the O-C<sub>Ar</sub>-C<sub>Ar</sub>-CH<sub>2</sub> torsion angle is planar, at any given time it can assume a wide range of values.

The next dihedral angle considered is the C<sub>Ar</sub>-C<sub>Ar</sub>-C<sub>Ar</sub>-C<sub>Ar</sub>, e.g., C<sub>1</sub>-C<sub>2</sub>-C<sub>3</sub>-C<sub>4</sub> (Table IV). It is well established that benzenes are on average planar but they can be substantially distorted. Indeed, we recently pointed out that benzene is far less rigid than one assumes; torsional distortions around the aromatic C=C bonds in benzene (up to 15°) are virtually indistinguishable from twisting around the C-C bonds in cyclohexane.<sup>16</sup> For the native calixarenes one finds the average benzene ring dihedral angle to be 0.0° with a range from -6° to +6°. For the near-native subset the average dihedral angle is also zero with a range from -8° to +7°. For the derivatized calixarenes the average is also zero but the range is from -11° to +15°, and for all calixarenes one finds the average benzene dihedral angle to be zero with a wide range from -11° to +15°.

It is recognized that stretching force constants are larger than bending force constants which in turn are larger than torsional force constants. Hence, stretching deformations will be smaller than bending deformations which in turn are smaller than torsional deformations. This shows up,

(16) Lipkowitz, K. B.; Peterson, M. A. *J. Comput. Chem.* 1993, 14(1), 121.

as anticipated, in the aforementioned results. What is surprising, however, is how wide a range some of these monomer structural features can adopt indicating that, in a collective mode, the calixarenes are more flexible than one would anticipate. Although the average bond lengths, bond angles, and dihedral values are near their normal, strainfree values, they can substantially change to accommodate a guest.

**2. Macrocyclic Features.** The macrocycle's structure is most relevant for guest-host complexation and for design purposes. Their structural features have embedded in them the combination of monomeric structural features described above in addition to other degrees of freedom. The monomers are more flexible than anticipated, and the macrocycle, as an entity, can use the monomer distortion modes to amplify its ability to distort. In this section we consider distances, angles, and dihedrals as above, but not of contiguous atoms. We consider two types of interatomic distances and angles. The first we call "neighbor" interactions exemplified by ring A interacting with ring B, ring B with ring C and so on. The second type we call "diagonal" interactions exemplified by ring A interacting with ring C. These reflect transannular aspects of the calixarene conformations. At the outset one anticipates, especially because of the soft hinging motions of the  $\text{CH}_2\text{-Ar-CH}_2$  moieties, wide-ranging structural distributions. These soft mode hinging distortions are most responsible for the inherent calixarene flexibility.

**i. Distances.** Four distances are evaluated: the O-O distance, the  $\text{CH}_2\text{-CH}_2$  distance, the Ar-Ar centroid distance and the  $\text{C}_{\text{Ar}}\text{-C}_{\text{Ar}}$  upper rim distances; each as a neighbor and diagonal pair. These results are summarized in Table V. The oxygen-oxygen neighbor distances, e.g.,  $\text{O}_{29}\text{-O}_{30}$ ,  $\text{O}_{30}\text{-O}_{31}$  etc., are on average 2.65 Å for the native calixarenes. As anticipated, due to hydrogen bonding at the lower rim, a narrow distribution of O-O lengths exists (SD = 0.01). All neighboring O-O atoms are within 2.61–2.66 Å. For the diagonal, cross-ring distances one finds an average of 3.74 Å. The range of diagonal O-O distances is between 3.4 and 4.0 Å reflecting other distortion modes of the calixarenes. For the near-native calixarenes the neighbor O-O distance average is 3.04 Å while the average diagonal distance is 4.20 Å. Removing the phenolic hydrogens thus destroys the well-defined cup shape leading to wide amplitude flexing motions of the monomers. For the derivatized calixarenes the O-O neighbor average distance is 2.87 Å. The O-O average distance for diagonal oxygens in the derivatized subset is 4.08 Å. For all calixarenes the average neighboring O-O distance is 2.92 Å (SD = 0.362) with distances ranging from 2.4 to 4.6 Å, and for the diagonal O-O average distance one finds a value of 4.04 Å (SD = 0.687) with values ranging from 3.0 to 5.7 Å. Evidently, there is a wide amplitude canting motion of the aromatic rings into or out of the macrocyclic cavity much like that found in cyclodextrins.

The equatorial belt of linker methylene groups provides some information about the "breathing" motion of the macrocycle. Unlike the O-O distances that reflect aryl ring cantings around their benzylic hinges, the  $\text{CH}_2$  distances reflect mostly angular distortions, bond lengthenings or contractions, and some twisting motions of the entire macrocycle. The average neighbor  $\text{CH}_2\text{-CH}_2$  distance for native calixarenes is 5.10 Å. The average diagonal  $\text{CH}_2\text{-CH}_2$  distance is 7.21 Å. For near-native calixarenes the average neighbor  $\text{CH}_2\text{-CH}_2$  distance is 5.09 Å and the

Table V. Macrocyclic Distances (Å) for Cone Calix[4]arenes

	low value	high value	avg	stand. devn
029-030 neighbor length				
native	2.61	2.66	2.65	0.01
near-native	2.35	3.97	3.04	0.24
derivatized	2.50	4.62	2.87	0.50
all	2.35	4.62	2.92	0.36
029-031 diagonal length				
native	3.41	4.02	3.74	0.16
near-native	3.05	5.37	4.20	0.81
derivatized	3.16	5.72	3.96	0.61
all	3.05	5.72	4.04	0.69
C7-C14 neighbor length				
native	5.08	5.16	5.10	0.03
near-native	5.03	5.23	5.09	0.05
derivatized	5.05	5.15	5.10	0.02
all	5.03	5.23	5.09	0.04
C7-C21 diagonal length				
native	7.18	7.30	7.21	0.04
near-native	7.01	7.50	7.19	0.10
derivatized	7.05	7.36	7.20	0.09
all	7.01	7.50	7.20	0.09
$x_A\text{-}x_B$ neighbor length				
native	4.77	4.86	4.82	0.02
near-native	4.55	5.05	4.72	0.12
derivatized	4.54	4.99	4.80	0.11
all	4.54	5.05	4.76	0.11
$x_A\text{-}x_C$ diagonal length				
native	6.34	7.30	6.81	0.26
near-native	5.34	7.69	6.59	0.85
derivatized	5.58	7.44	6.70	0.49
all	5.34	7.69	6.66	0.67
C4-C10 neighbor length				
native	5.88	6.07	5.99	0.05
near-native	5.39	6.34	5.74	0.24
derivatized	5.28	7.19	5.98	0.38
all	5.28	7.19	5.86	0.30
C4-C17 diagonal length				
native	7.54	9.34	8.45	0.49
near-native	5.42	10.04	7.86	1.68
derivatized	5.86	9.64	8.19	1.01
all	5.42	10.04	8.07	1.34

average diagonal  $\text{CH}_2\text{-CH}_2$  distance is 7.19 Å. For the derivatized calixarenes the average neighboring  $\text{CH}_2\text{-CH}_2$  distance is 5.10 Å and the diagonal  $\text{CH}_2\text{-CH}_2$  distance is 7.20 Å. For all calixarenes the average neighbor  $\text{CH}_2\text{-CH}_2$  distance is 5.09 Å (SD = 0.041) with distances ranging from 5.03 to 5.24 Å, and the average diagonal distance is 7.20 Å (SD = 0.090) with distances ranging from 7.0 to 7.5 Å. Although the methylene distances can vary 0.2 Å between neighbors and 0.5 Å transannularly, this belt of linker atoms is far less easily distorted than the aforementioned O-O distances. Clearly, then, guest-host complexation will induce macroring openings or closures by canting the aromatic rings into or out of the cavity rather than from "breathing" distortions of what appears to be a relatively inflexible belt of linker groups.

The next distance considered is that between centroids of the aromatic rings (Table V). These centroids, X, are the centers of the benzene rings defined by the six carbon atoms of each ring. There are, thus, four centroids, one for each ring:  $X_A, X_B, X_C, X_D$ . For native calixarenes the average distance between neighboring centroids, e.g.,  $X_A\text{-}X_B, X_B\text{-}X_C$ , etc., is 4.82 Å. The distance between diagonal centroids, e.g.,  $X_A\text{-}X_C$ , is 6.81 Å. For the near-native set the average neighboring centroid distance is 4.72 Å and the average diagonal centroid distances is 6.59 Å. For the

derivatized set the average neighbor centroid is 4.80 Å and the diagonal average is 6.70 Å. For all calixarenes the average distance of neighboring centroids is 4.76 Å (SD = 0.114) with values ranging from 4.5 Å to 5.1 Å. The average distance for the diagonal centroids is 6.66 Å (SD = 0.671) with values ranging from 5.3 to 7.7 Å. It should be kept in mind, for those who are interested in these dimensions for guest-host complexation studies, that the centroids described here are in the mean plane of the benzene rings; aromatic  $\pi$  electrons are above and below these centroids preventing close approach by guest molecules.

Finally, to complement the lower rim dimensions we consider the upper rim dimensions of these cuplike molecules. For the pure calixarenes the average  $C_{Ar}-C_{Ar}$  neighbor distance, e.g.,  $C_4-C_{10}$ ,  $C_{10}-C_{17}$  etc., is 5.99 Å. The diagonal distance for the pure calixarenes is 8.45 Å. For the near-native calixarenes the average upper rim  $C_{Ar}-C_{Ar}$  neighboring distance is 5.74 Å and the diagonal average is 7.86 Å. For the derivatized set of calixarenes, the average upper rim  $C_{Ar}-C_{Ar}$  neighbor distance is 5.98 Å and the diagonal average distance is 8.19 Å. For all calixarenes, the average upper rim  $C_{Ar}-C_{Ar}$  neighbor distance is 5.86 Å (SD = 0.304) with distances ranging from 5.3 to 7.2 Å while the average diagonal distance is 8.07 Å (SD = 1.337) with values ranging from 5.4 to 10 Å. Again, as found for the O-O distances, we find substantial canting of the aromatic rings about their benzylic hinges which are controlling the gap of both upper and lower rims. The positions of the methylene linker groups and the centroids of the aromatic rings are more rigidly fixed in space. The average transannular (diagonal) upper rim diameter of  $\sim 8.07$  Å is nearly twice as large as the transannular lower rim O-O distance of 4.04 Å. Even without the network of hydrogen bonds holding the lower rim intact, these molecules, as a class of macrocyclic hosts, do have chalice or cuplike shapes in the solid state.

**ii. Angles.** In this section we examine deviations calix[4]arenes have from 4-fold symmetry. For symmetrically substituted calix[4]arenes, measured over a long time scale as, for example, by NMR spectroscopy, 4-fold symmetry is expected. On a shorter time scale, or at any given instant, the macrocycle need not have 4-fold symmetry but may have 2-fold or no symmetry at all. One of the questions being answered in this section is: how symmetric are the calix[4]arenes? To evaluate this we consider the four O-O-O angles on the lower rim, the four  $CH_2-CH_2-CH_2$  angles of the equatorial belt of linker atoms, and the four upper rim  $C_{Ar}-C_{Ar}-C_{Ar}$  angles, all of which should be 90° for a perfect, 4-fold symmetric macrocycle. We also consider the angles made between the planes of adjacent benzene rings. The reader is to be cognizant of the fact that most of the calix[4]arenes in our datasets are not symmetrically substituted. Nonetheless, the following distributions provide information concerning the desymmetrization of the macrocycle. Results are summarized in Table VI.

For the native calixarenes the average O-O-O angle, e.g.,  $O_{29}-O_{30}-O_{31}$ , is 89.9°. On average, then, one would say calix[4]arenes have 4-fold symmetry. However, the range of O-O-O angles is from 80° to 99°. Hence, at any given instant the native calixarene may be distorted 10°. For near-native calixarenes the average O-O-O angle is 89.3°. Again, one would argue that on average the calixarenes have 4-fold symmetry but in reality the structures are usually quite distorted with values ranging

Table VI. Macrocyclic Angles (deg) for Cone Calix[4]arenes

	low value	high value	avg	stand. devn
Angle $O_{29}-O_{30}-O_{31}$				
native	80.3	98.8	89.9	4.8
near-native	59.8	119.3	89.3	20.5
derivatized	63.9	118.6	88.6	13.8
all	59.8	119.3	89.1	16.5
angle $C_7-C_{14}-C_{21}$				
native	89.2	90.1	90.0	0.2
near-native	87.2	92.7	89.9	1.2
derivatized	87.5	92.4	89.9	1.4
all	87.2	92.7	89.9	1.2
angle $C_4-C_{10}-C_{17}$				
native	89.0	101.8	90.7	5.3
near-native	55.0	120.1	88.4	23.0
derivatized	48.6	110.4	87.2	13.7
all	48.6	120.1	88.4	18.1

from 60° to 120°. The same arguments hold for derivatized calixarenes with an average O-O-O angle of 88.6 and values ranging from 60° to 120°. The average O-O-O angle for all calixarenes is 89.1° (SD = 16.45) with angles ranging from 60° to 120°. The very large standard deviations for all but the native calixarenes indicate that the twisting motion capable of distorting the macrocycle from 4-fold symmetry is a relatively low energy process.

These macrocyclic distortions are also reflected in the  $CH_2-CH_2-CH_2$  angles but to a lesser extent (Table VI). For native calixarenes the average  $CH_2-CH_2-CH_2$  angle is 90° with a range from 89° to 90°. For near-native calixarenes the average angle is 89.9° with values ranging from 87° to 93°. For derivatized calixarenes the average is 89.9° with values ranging from 87° to 92°. For all calixarenes, the average  $CH_2-CH_2-CH_2$  angle is 89.9° (SD = 1.19) with values spanning the range from 87° to 93°. This distribution is a normal distribution centered near 90°, and, being narrow in range indicates that the distortions from 4-fold symmetry are not originating from the methylenes which appear to be quite rigid linker groups attempting to enforce 4-fold symmetry.

The upper rim  $C_{Ar}-C_{Ar}-C_{Ar}$  angles defined by, e.g.,  $C_4-C_{10}-C_{17}$  are, like the lower rim, near 90° but have a large variation in their values. For native calixarenes the  $C_{Ar}-C_{Ar}-C_{Ar}$  average is 90.7° with values from 89° to 102°. For near-native calixarenes the average is 88.4° with values in the range from 55° to 120°. For derivatized calixarenes the average is 87.2° with values ranging from 49° to 110°. For all calixarenes the average upper rim angle is 88.4° (SD = 18.14) with angles from 49° to 120°. Hence, we find that the lower and upper rims of calix[4]arenes are on average almost 90° but have low-energy twisting motions that easily allow wide amplitude distortions from 4-fold symmetry. The equatorial methylenes, in contrast, are not easily distorted from 4-fold symmetry. Groups that enforce twisting in only one direction would make these macrocycles asymmetric and capable, ideally, of chiral recognition during guest-host binding.

The final measure of deviation from 4-fold symmetry is the angle made between neighboring benzene planes. To do this we define a least-squares plane fit to the six carbons of each of the four benzenes in each calixarene. Hence, the plane of ring A is  $P_A$ , that in ring B is  $P_B$ , etc. The angles  $P_A-P_B-P_C$ ,  $P_B-P_C-P_D$ , and so on are then measured. For the native calixarenes the average is 85.3° (SD = 19.35). However, the distribution is not a normal

**Table VII. Macrocyclic Dihedral Angles (deg) for Cone Calix[4]arenes**

	low value	high value	avg	stand. devn
dihedral angle C7-C14-C21-C28				
native	0.0	0.7	0.2	0.3
near-native	-6.0	3.7	-2.0	3.1
derivatized	-3.0	6.8	2.8	4.3
all	-6.0	6.8	-0.1	3.9
dihedral angle $x_A-x_B-x_C-x_D$				
native	-8.6	0.0	-2.2	4.3
near-native	-19.2	17.0	0.8	13.0
derivatized	-7.4	41.3	5.9	15.6
all	-19.2	41.3	2.0	12.9

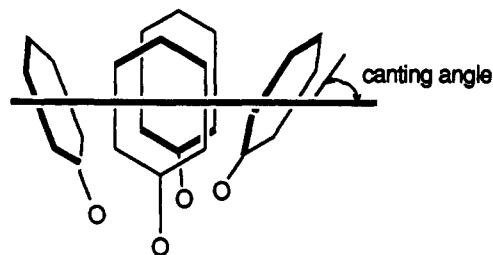
one. Rather, it is bimodal with one maximum centered at  $\sim 68^\circ$  and the other at  $108^\circ$ . For the near-native calixarenes a more normal distribution exists with an average interplane angle of  $88.8^\circ$  (SD = 9.47) with values from  $65^\circ$  to  $105^\circ$ . For derivatized calixarenes the average is  $89.7^\circ$  (SD = 16.67) with values ranging from  $60^\circ$  to  $110^\circ$ . For all calixarenes the average interplanar angle is  $88.5^\circ$  (SD = 14.02) with values ranging from  $60^\circ$  to  $110^\circ$ . Again, at any given time these macrocycles do not have 4-fold symmetry, and they are easy to distort with deviations up to  $80^\circ$ .

**iii. Dihedrals.** Three macrocyclic dihedral angles of interest are the dihedral angles made by the near-planar  $\text{CH}_2$  groups (Table VII), the dihedral angles made by the centroids of the four benzene rings (Table VII) and the dihedral angles between the mean plane of the four  $\text{CH}_2$  groups with the benzene ring planes. This latter measure is an indication of how far the benzenes are canted out of the macrocycle's interior.

The  $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$  dihedral angle for a perfectly planar array of methylene linker units making up the equator of the macrocycle is zero. For native calix[4]arenes the average dihedral angle is  $0.2^\circ$  with no values larger than  $\pm 1^\circ$ . For near-native calixarenes the average is  $-2.0^\circ$  with values ranging from  $-6^\circ$  to  $+4^\circ$ . For derivatized calixarenes the average is  $2.8^\circ$  with values ranging from  $-3^\circ$  to  $+7^\circ$ . For all calixarenes the average  $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$  dihedral angle is  $-0.1^\circ$  (SD = 3.86) with values ranging from  $-6^\circ$  to  $+7^\circ$ . Thus, the equatorial belt of linker  $\text{CH}_2$  groups are on average close to planarity but are capable of undergoing distortions of ca.  $\pm 7^\circ$ .

The next descriptor we consider is the dihedral angle between the centroids of each aromatic ring (Table VII). The centroids are the mean position between the six carbons of each aromatic ring as described earlier. For native calixarenes the average value is  $-2.2^\circ$  with values ranging from  $-9^\circ$  to zero. At first one might wonder why this dihedral is not zero as was found for the methylenes described above. The reason is that the position of the centroids reflects some information about ring canting (that will be described below). This dihedral angle thus is not redundant with the methylene descriptor above. For near-native calixarenes the average dihedral of benzene centroids is  $0.8^\circ$  with values ranging from  $-19^\circ$  to  $+17^\circ$ . For derivatized calixarenes the average is  $5.9^\circ$  with values ranging from  $-7^\circ$  to  $+41^\circ$ . For all calixarenes the average dihedral of the four benzene centroids is  $2.0^\circ$  (SD = 12.92) with values ranging from  $-19^\circ$  to  $+41^\circ$ . Again, these dihedral angles reflect, somewhat, ruffling of the macrocycle from planarity like the  $\text{CH}_2$  dihedrals described above, but they contain information about monomeric benzene ring cantings described below.

To describe how far into or out of the macrocycle cavity the aromatic ring is tilted, we define a mean plane formed by the four  $\text{CH}_2$  groups. The angles between the mean plane of each benzene with the mean plane of the methylenes is  $90^\circ$  if each aromatic ring is perpendicular to the mean plane of the macrocycle. For a cup shape,



the lower rim is canted into the cavity and the upper rim outward. This makes an upper rim angle  $< 90^\circ$  if the upper rim is canted outward and  $> 90^\circ$  if it is tilted inward. This measure of ring tilting with respect to the mean plane of the linking  $\text{CH}_2$  groups is the complement of the inclination,  $\delta$ , described by Perrin and Oehler.<sup>17</sup>

For native calixarenes the average canting angle is  $54.4^\circ$  (SD = 5.72) with values ranging from  $40^\circ$  to  $60^\circ$ . Even for native calix[4]arenes, presumed to be fairly rigid due to lower rim hydrogen bonding, this seems like a substantial amount of flexing, but this should be expected because twisting around the benzylic bonds giving rise to this deformation is a low-energy conformational process. The major force keeping the bottom of the cavity closely knit together is the intermonomer hydrogen bonds. Removal of these H-bonds should allow one to see larger flexing motions. Indeed, the average cant angle for the near-native calixarenes, void of H-bonding on the lower rim (dispersion, dipole stacking, electrostatic forces, etc. of course remain), is  $63.0^\circ$  (SD = 20.82) with values ranging from  $20^\circ$  to  $100^\circ$ . Such a wide distribution indicates this twisting motion to be very "soft". One finds examples where some rings are nearly parallel to the mean plane of the macrocycle while others have the upper rim tilted somewhat into the cavity. For derivatized calixarenes the average cant angle is  $59^\circ$  with values ranging from  $25^\circ$  to  $105^\circ$ . For all calix[4]arenes studied, the average canting of the aromatic rings with respect to the mean plane of the macrocycle is  $60.2^\circ$  (SD = 18.07) with values spanning the wide range from  $20^\circ$  to  $105^\circ$ .

#### IV. Computational Analysis

At the outset of this study we intended to make comparisons between conformational features of calix[4]arenes in the solid state with modern computational tools. Assessing crystal structures of calixarenes, as above, provides limited information about these molecules' potential energy surface. In contrast, computational methods allow one to explore the entire potential energy surface, assuming they are valid methods.

Only cone-shaped calix[4]arenes in the solid state were considered above. Here we examine the relative energies of the cone, partial cone, and 1,2- and 1,3-alternate conformations of a native calixarene and a near-native calixarene which have been computed with molecular mechanics and quantum mechanics at the semiempirical

(17) See pp 74-75 in ref 1b.



Table VIII. Relative Energies (kJ/mol) of Native *p*-*tert*-Butylcalix[4]arene in the Gas Phase

force field	cone	partial cone	1,2-alternate	1,3-alternate
MM2	0.0	61.7	80.3	99.9
AMBER	0.0	41.9	49.5	41.7
OPLSA	0.0	82.0	96.7	81.2
CHARMm	309.1	0.0	68.5	120.1
MOPAC6 AM1	0.0	23.0	35.1	45.1
MOPAC6 PM3	0.0	48.7	53.8	35.8
AMPAC AM1	0.0	33.7	41.8	50.6
AMPAC PM3	0.0	8.5	51.5	31.7

level of theory. A significant number of scientists have used these computational tools to predict calixarene shape and stability.<sup>18</sup> We ask: how reliable, and hence valid, are these computational techniques when applied to calixarenes?

Both the native calixarene and near-native calixarene have *tert*-butyl groups on each aromatic ring on the upper rim. The native calixarene has -OH groups on the lower rim, while the near-native calixarene has -OMe groups on the lower rim. For each major conformer, i.e., cone, partial cone, and 1,3- and 1,2-alternate, only the lowest energy structure is reported. The other conformations due to the other rotameric states of the OH and OMe groups are omitted from discussion. The conformer searches were done with MacroModel using MM2, AMBER, and the OPLS-Amber force fields. The lowest energy MM2 structures were used as input to Quanta/CHARMm, MOPAC, AMPAC, and AMSOL. These structures were then optimized with those programs. The relative energies for the native *p*-*tert*-butylcalix[4]arene in the gas phase are given in Table VIII while those for the tetramethyl ether are given in Table IX.

With the exception of Quanta/CHARMm, all methods indicate the cone conformer to be most stable. Why this program failed so miserably is not understood by us; the optimized structure has nearly 4-fold symmetry like the other structures computed by the other force fields but

Table IX. Relative Energies (kJ/mol) of the Tetramethyl Ether of *p*-*tert*-Butylcalix[4]arene in the Gas Phase

force field	cone	partial cone	1,2-alternate	1,3-alternate
MM2	15.1	15.1	31.0	0.0
AMBER	10.5	10.6	37.8	0.0
OPLSA	24.9	25.2	63.1	0.0
CHARMm	317.7	0.0	68.1	142.0
MOPAC6 AM1	66.0	0.0	20.3	18.9
MOPAC6 PM3	59.8	0.0	23.1	8.5
AMPAC AM1	97.2	107.2	116.2	0.0
AMPAC PM3	0.0	2.4	30.1	23.8

Table X. Relative Energies (kJ/mol) of Native *p*-*tert*-Butylcalix[4]arene in H<sub>2</sub>O Continuum Solvent

method	cone	partial cone	1,2-alternate	1,3-alternate
MM2	0.0	43.1	58.0	61.4
AMBER	0.0	28.5	39.1	27.7
OPLSA	0.0	60.1	75.3	61.7
AMSOL	0.0	40.3	45.8	56.2

Table XI. Relative Energies (kJ/mol) of the Tetramethyl Ether of *p*-*tert*-Butylcalix[4]arene in H<sub>2</sub>O Continuum Solvent

method	cone	partial cone	1,2-alternate	1,3-alternate
MM2	17.1	17.1	34.7	0.0
AMBER	10.7	10.9	34.0	0.0
OPLSA	20.5	21.1	51.7	0.0
AMSOL	101.4	110.7	117.0	0.0

the very high energy is perplexing. Earlier versions of this program had flawed parameter sets as noted by Reinhoudt.<sup>18h</sup> Accordingly, we dismiss the results from this program. Experimentally, the cone conformer is found exclusively for native calixarenes. The relative energies of the other conformers are not known experimentally. The results in Table VIII give conflicting results where most of the computational methods indicate the partial cone to be the second most stable conformation but some indicate the 1,3-alternate to be second most stable.

Reinhoudt's group has demonstrated that for the tetramethyl ether of *p*-*tert*-butylcalix[4]arene the partial cone is the thermodynamically most stable conformation followed, in order of decreasing stability, by the 1,2-alternate, the cone, and then the 1,3-alternate conformers.<sup>18h</sup> In their paper they found, using Quanta/CHARMm (with presumably the corrected set of parameters as we are using) that the most stable conformer is the 1,3-alternate. Experimentally, the 1,3-alternate is least stable. We find, in Table IX, that Quanta/CHARMm predicts the partial cone to be most stable, consonant with experiment, but the other conformers are not consistent with experiment. Indeed, from Table IX we find that none of the computational methods were able to reproduce experiment. Since these gas phase energies are being compared with solution-phase NMR results (typically recorded in CDCl<sub>3</sub>, DMSO, etc.) we thought it reasonable to compute the energies of these structures in solvent using continuum models. Solvents parameterized in MacroModel include CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. AMSOL is parameterized only for H<sub>2</sub>O. Fully optimized MM2, AMBER, and OPLSA structures were found using MacroModel. Single point calculations were done for AMSOL (see Experimental Section). The results of our calculations on the native calixarene is given for water in Table X and for methylene chloride in Table XII. The results for the tetramethyl ether in water is given in Table XI and Table XIII has the energies computed in CH<sub>2</sub>Cl<sub>2</sub>.

Using continuum solvation models we found that none of the computational methods were congruent with

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**Table XII. Relative Energies (kJ/mol) of *p*-tert-Butylcalix[4]arene in CH<sub>2</sub>Cl<sub>2</sub> Continuum Solvent**

force field	cone	partial cone	1,2-alternate	1,3-alternate
MM2	0.0	50.1	72.3	83.4
AMBER	0.0	38.0	47.6	43.2
OPLSA	0.0	82.6	94.6	90.0

**Table XIII. Relative Energies (kJ/mol) of the Tetramethyl Ether of *p*-tert-Butylcalix[4]arene in CH<sub>2</sub>Cl<sub>2</sub> Continuum Solvent**

force field	cone	partial cone	1,2-alternate	1,3-alternate
MM2	10.7	10.7	23.2	0.0
AMBER	0.0	0.0	30.7	1.1
OPLSA	21.3	21.4	57.3	0.0

experiment. The reason for the poor performance of these programs may be attributed to several factors. The energies reported in these tables are enthalpy differences that are being compared to free energy differences experimentally. Even if one assumes significant entropy of mixing terms which, parenthetically, are usually offset by counterbalancing entropies of symmetry number, the differences between the computed energies still seem too large.

The reason for such poor agreement with experiment is, in our opinion, because of a complete breakdown in the parameterization of these empirical and semiempirical schemes. The conformations of these macrocycles are very sensitive to long range attractive interactions. Most of the atom-atom stabilizing interactions come from non-bonded interactions of one monomer sensing neighbor and transannular monomers. Most molecular mechanics programs have been heavily parameterized to reproduce intramolecular conformations, e.g., chair vs boat cyclohexanes rather than intermolecular features. The monomer-monomer interactions in calixarenes are, effectively, intermolecular in nature. Hence, much of the controlling interactions in calixarenes are from long range dispersion forces that are notoriously ill-behaved with single determinant wavefunctions, even at the semiempirical level, and are not well treated by molecular mechanics because they have not been adequately parameterized for weak, intermolecular complexes. Thus, we find these methods to be ineffective and unreliable computational tools for predicting calixarene conformer stability. We caution others to refrain from placing too much significance in such computed energies.

### Summary

Cone-shaped calix[4]arenes were extracted from the Cambridge Structural Database for structural analysis. Distributions of monomeric and macrocyclic degrees of freedom were evaluated in a way that allows one to compare subsets of native, near-native, and derivatized calix[4]arenes. Monomer features assessed include a variety of bond lengths, bond angles, and dihedral angles. The substantial range of CH<sub>2</sub>-C<sub>Ar</sub> linker distances indicates

that in a collective mode the interior of the macrocycle may substantially expand upon guest inclusion. Adding to this is the observation that the four aromatic rings are, on average, planar but can undergo wide amplitude puckering distortions.

Macrocyclic features examined include a variety of nonbonded lengths, angles, and dihedrals. The equatorial belt of methylene groups holding the macrocycle together is relatively rigid. "Breathing" of the macrocycle's cavity originates primarily from aromatic ring tilting motions. The average upper rim dimensions of cone calix[4]arenes are nearly twice as large as the lower rim dimensions indicative of true chalice topographies. The O-O-O, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>, and C<sub>Ar</sub>-C<sub>Ar</sub>-C<sub>Ar</sub> angles are, on average, nearly 4-fold symmetric, but wide amplitude twisting motions of the macrocycle are easy to induce. The four linker methylene groups are nearly planar with some limited ruffling motion from planarity. The largest macrocyclic deformation arises from aromatic rings canting into or out of the macrocycle's interior. The average dihedral angle between the mean plane of the methylene linker groups and the benzene rings is 62° with values spanning the range from 20° to 105°. This twisting originates from the soft hinging mode of the C<sub>Ar</sub>-CH<sub>2</sub> benzylic bonds which in turn define the shape of the chalice. The average values reported here along with the range of values for lengths, angles, and dihedrals for both monomeric and macrocyclic features of these cup-shaped molecules are of value to those who intend to use these molecules for guest-host complexation studies or for further architectural modification to elicit a physicochemical response.

Finally, a comparison of semiempirical molecular orbital Hamiltonians and various force fields in gas and solution phase show very poor agreement (amongst themselves and with experiment) when used to determine the relative energies of cone, partial cone, and 1,2- and 1,3-alternate conformations. The complex interplay of long range nonbonded interactions giving rise to the conformational states of calixarenes are not well treated by these methods. It is advised that one use extreme caution when implementing such tools to predict structures and energies of calixarenes.

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**Supplementary Material Available:** Histogram plots of the distributions described in this paper, with plots for native calixarenes, near-native calixarenes, derivatized calixarenes, native plus near-native calixarene, and all calixarenes for each structural degree of freedom (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.